

Université de Montréal

**Application de la stratégie de séparation de phase à la  
synthèse de macrocycles complexes et développement  
d'une réaction de thioalcynylation pour la synthèse de  
macrocycles sulfurés**

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## Résumé

Les réactions de macrocyclisation sont souvent difficiles à réaliser du point de vue expérimental, puisque la dilution élevée nécessaire requiert un montage encombrant et la purification du mélange est souvent complexe en raison d'une mauvaise sélectivité de cyclisation. Ces raisons peuvent compliquer la planification des voies de synthèse, ce qui dissuade souvent les chimistes d'utiliser les macrocycles pour différentes applications. Dans les dernières années, notre groupe de recherche a développé une méthode nommée stratégie de séparation de phase. Il s'agit d'un nouveau protocole permettant de faire des réactions de macrocyclisation de façon monotope et dans un milieu beaucoup plus concentré, tout en évitant les réactions parasites d'oligomérisation, facilitant ainsi la purification des macrocycles obtenus.

Cette thèse décrit le développement et l'application de stratégies permettant de surmonter les défis liés aux réactions de macrocyclisation. Dans la première partie de la thèse, le protocole de la stratégie de séparation de phase a pu être utilisé pour la synthèse de squelettes macrocycliques complexes, comme celui du produit naturel ivorenolide A (Chapitre 4) et celui de l'anti-viral vaniprevir (Chapitre 6). Ce protocole a permis de réaliser l'étape de macrocyclisation dans un milieu réactionnel 120 fois plus concentré, tout en maintenant un niveau de sélectivité de macrocyclisation élevé.

Dans la deuxième partie de la thèse, le développement d'une nouvelle synthèse d'acétylures de soufre catalysée par un complexe de cuivre a permis la synthèse d'une librairie de macrocycles peptidiques (Chapitre 8). L'incorporation du motif acétylure de soufre a aussi permis la diversification de ce dernier afin de greffer plusieurs étiquettes bioactives. Pour terminer, l'étendue de la réaction intermoléculaire de la nouvelle réaction de formation de thioalcynes a été explorée (Chapitre 9). Ceci a permis la synthèse d'alcynes disubstitués par des hétéroatomes ainsi que la fonctionnalisation de peptides contenant une cystéine non protégée. Des études mécanistiques expérimentales et computationnelles de la nouvelle méthode de synthèse de thioalcynes ont aussi été réalisées.

**Mots-clés** : macrocyclisation, macrocycle, séparation de phase, Glaser-Hay, acétylure de soufre, cuivre



## Abstract

Macrocyclization reactions can be problematic due to poor selectivity of cyclization versus oligomerization. As such, difficult purification of complex mixtures and/or the use of complex and cumbersome experimental setups are often necessary. The drawbacks can complicate synthetic pathways and deter chemists from exploring the unique chemical space of macrocycles. Our group has developed a new macrocyclization strategy called phase separation strategy, a protocol enabling one-pot macrocyclization reactions at much higher concentration.

In the present thesis, the challenges associated with macrocyclization reactions are tackled by the development and the application of new strategies. First, the phase separation strategy protocol was used to synthesize the backbone of complex macrocycles like the natural product ivorenolide A (Chapter 4) and the antiviral vaniprevir (Chapter 6). With the use of the phase separation strategy protocol, macrocyclization reactions were performed at concentrations 120 times higher than traditional protocols while maintaining a high level of macrocyclization selectivity.

Second, the development of a new copper-catalyzed synthesis of alkynyl sulfides for the synthesis of a macrocyclic peptide library is described (Chapter 8). The macrocyclic peptides were also tagged with several biomarkers by diversification of the resulting alkynyl sulfide motif. Finally, the scope of the intermolecular copper-catalyzed reaction was explored (Chapter 9). Using the method, bis-heteroatom substituted alkynes were synthesized and modification of unprotected cysteine sidechains was possible. Furthermore, the mechanistic reaction pathway of the new alkynyl sulfide synthesis was studied experimentally and computationally.

**Keywords** : macrocyclization, macrocycle, phase separation, Glaser-Hay, alkynyl sulfide, copper

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## Liste des abréviations

4CzIPN	2,4,5,6-Tétra(9H-carbazol-9-yl)isophthalonitrile
9-BBN	9-Borabicyclo[3.3.1]nonane
$\alpha$	Alpha
$\beta$	Beta
$\pi$	Pi
$\mu$	Mu
$\mu$	Microlitre
$\eta$	Êta
$\sigma$	Sigma
$\delta$	Déplacement chimique
$\omega$	Omega
$\mu\text{w}$	Micro-onde (irradiation)
Å	Angström
Ac	Acétyl
AC	Agent de couplage
acc	Acide 1-Aminocyclopropane-1-carboxylique
ADN	Acide désoxyribonucléique
ARN	Acide ribonucléique
Alk	Alkyl
aq	Aqueux
atm	Atmosphère (pression)
bathophen	Bathophénanthroline
bpy	2,2'-Bipyridine
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
br	“Broad”
brsm	Basé sur le matériel de départ récupéré (based on recovered starting materials)
Bu	Butyl
C	Celsius
cat	Quantité catalytique
CBz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
cm	Centimètre
cod	1,5-Cyclooctadiène
CuAAC	<i>Copper-catalyzed azide-alkyne cycloaddition</i>
Cy	Cyclohexyl
d	Jour
d	Doublet
D	Dextrogyre
DABCO	1,4-Diazabicyclo[2.2.2]octane
D-A	Diels-Alder
dba	Dibenzylidèneacétone
DBU	1,8-diazabicyclo[5.4.0]undéc-7-ène

DCE	1,2-Dichloroéthane
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichlorométhane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Azodicarboxylate de diéthyle
DEL/LED	Diode Électroluminescente
DFT	<i>Density-Functional Theory</i>
DIAD	Azodicarboxylate de diisopropyle
DIBAL-H	Hydruure de diisobutylaluminium
DIPA	N,N-Diisopropylamine
DIPEA	N,N-Diisopropyléthylamine
DIPP	2,6-Diisopropylphényl
DMAP	4-Diméthylaminopyridine
DMF	N,N-Diméthylformamide
dmphen	2,9-Diméthyl-1,10-phénanthroline
DMSO	Diméthylsulfoxyde
dppe	Diphénylphosphineéthane
dppf	Diphénylphosphineferrocène
dppm	Diphénylphosphinéméthane
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
E	Électrophile
ee	Excès énantiomérique
<i>E</i>	Entgegen (opposé)
EBX	Éthynylbenziodoxolone
EDC	1-Éthyl-3-(3-diméthylaminopropyl)carbodiimide
Ent	Énantionère
Et	Éthyl
Equiv.	Équivalents
ESI	Spectrométrie de masse par ionisation électronébuleuse
FLT3	Fms-like tyrosine kinase 3
Fmoc	Fluorénylméthoxycarbone
g	Gramme
GEA	Groupement électroattracteur
G-I	Catalyseur de Grubbs 1 <sup>ère</sup> génération
G-II	Catalyseur de Grubbs 2 <sup>ième</sup> génération
GH-I	Catalyseur de Grubbs-Hoveyda 1 <sup>ère</sup> génération
GH-II	Catalyseur de Grubbs-Hoveyda 2 <sup>ième</sup> génération
Glyme/DME	1,2-diméthoxyéthane
GLP-1R	Récepteur du glucagon-like peptide-1
GP	Groupement partant
h	Heures
HATU	Hexafluorophosphate de (diméthylamino)-N,N-diméthyl(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)méthaniminium
Hz	Hertz
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole

HOPO	1-Hydroxy-2-pyridone
HPLC	Chromatographie liquide à haute pression
HRMS	Spectrométrie de masse haute résolution
CI <sub>50</sub>	Concentration inhibitrice médiane
<i>i</i> -Pr	Isopropyl
IrAAC	<i>Iridium-catalyzed azide-alkyne cycloaddition</i>
IUPAC	Union Internationale de Chimie Pure et Appliquée
<i>J</i>	Constante de couplage
JAK2	Janus kinase 2
<i>k</i>	Constante de vitesse
K	Kelvin
kcal	Kilocalorie
L	Litre
<i>L</i>	Lévogyre
LDA	Diisopropylamidure de lithium
<i>m/z</i>	Masse sur charge
<i>m</i>	Multiplet
<i>m</i>	meta
<i>m</i> CPBA	Acide métachloroperbenzoïque
Me	Méthyl
Mes	2,4,6-Triméthylphényl
mg	Milligramme
MHz	Mégahertz
min	Minutes
mL	Millilitre
mm	Milimètre
mM	Millimolaire
mmol	Millimole
MM	Masse moléculaire moyenne
MNBA	Anhydride 2-Méthyl-6-nitrobenzoïque
mol	Mole
MOM	Méthoxyméthyl
mp	Point de fusion
MS	Spectrométrie de masse
MTBE	Méthyl <i>tert</i> -butyl éther
<i>n</i>	Néo
NBS	N-bromosuccinimide
NHC	Carbène N-hétérocyclique
ng	Nanogramme
nm	Nanomètre
nM	Nanomolaire
NMP	N-méthyl-2-pyrrolidone
NS3	Protéine non-structurale 3
NS4A	Protéine non-structurale 4A
Nuc	Nucléophile
<i>o</i>	ortho

<i>p</i>	para
PCC	Pyridinium chlorochromate
PEG	Poly(éthylène) glycol
pH	Potentiel hydrogène
Ph	Phényl
Phe	Phénylalanine
phen	1,10-Phénanthroline
PhMe	Toluène
phth	Phtalimide
pKa	Constante de dissociation d'acide sur échelle logarithmique
PMB	<i>p</i> -Méthoxybenzyl
PPG	Poly(propylène) glycol
ppm	Partie par million
psi	Livre-force par pouce carré
pTsOH	Acide <i>para</i> -Toluènesulfonique
q	Quadruplet
rac	Racémique
rt	Température ambiante
RMN	Résonance Magnétique Nucléaire
s	Singulet
s	Seconde
SAR	Relation Structure-Activité
SMAC	<i>Second mitochondria-derived activator of caspases</i>
S <sub>N</sub> 2	Substitution Nucléophile bimoléculaire
SSP	Stratégie de séparation de phase
<i>t</i>	<i>tert</i>
t	Triplet
T	Température
TBA	Tétrabutylammonium
TBS	<i>tert</i> -Butyldiméthylsilyl
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ène
TBDPS	<i>tert</i> -Butyldiphénylsilyl
<i>t</i> -Bu	<i>tert</i> -Butyl
TC	Thiophène-2-carboxylate
terpy	2,2';6',2"-Terpyridine
TES	Triéthylsilyl
TFA	Acide Trifluoroacétique
TFE	2,2,2-Trifluoroéthanol
THF	Tétrahydrofurane
TIPS	Triisopropylsilyl
TLC	Chromatographie sur couche mince
TMEDA	N,N,N',N'-Tétraméthyléthylènediamine
TMG	1,1,3,3-Tétraméthylguanidine
tmphen	3,4,7,8-Tétraméthyl-1,10-phénanthroline
TMS	Triméthylsilyl
TOF	<i>Time-of-flight</i>



tol	Tolyl
Trt	Triphénylméthyl
Ts	Toluenèsulfonyl
UV	Ultraviolet
v	Vitesse
VHC/HCV	Virus de l'Hépatite C
Vis	Visible
wt	Poids
Xantphos	4,5-Bis(diphénylphosphino)-9,9-diméthylxanthène
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphényle
Z	Zusammen (ensemble)
°	Degrée
%	Pourcentage
$\Delta G$	Énergie libre de Gibbs
$\Delta H$	Enthalpie
$\Delta S$	Entropie
‡	État de transition

*“The meeting of two personalities is like the contact of two chemical substances: If there is any reaction, both are transformed.”*

*- C.G. Jung*

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# Chapitre 1. Les macrocycles

Le domaine de la chimie est parsemé de molécules cycliques. Dans le cas des molécules possédant un cycle contenant de trois à six atomes, telles que le cyclopropane (**1.1**), elles sont considérées comme ayant un petit cycle. Pour les molécules dont le cycle comprend de sept à onze atomes, comme l'azépine (**1.2**), on parle plutôt de moyens cycles. Les « macrocycles », quant à eux constituent les molécules qui contiennent un agencement d'atomes formant un cycle de douze chaîons (atomes) et plus<sup>1</sup>. Un exemple bien connu de cette dernière classe de molécules est l'érythromycine A (**1.3**), un antibiotique naturel ayant une activité antimicrobienne comparable à la pénicilline (Figure 1.1). Comme il est possible de le constater, l'augmentation du nombre de chaîons d'un cycle permet intrinsèquement d'augmenter sa complexité fonctionnelle et spatiale. Ceci fait donc des macrocycles une plateforme intéressante pour le développement de molécules biologiquement actives.

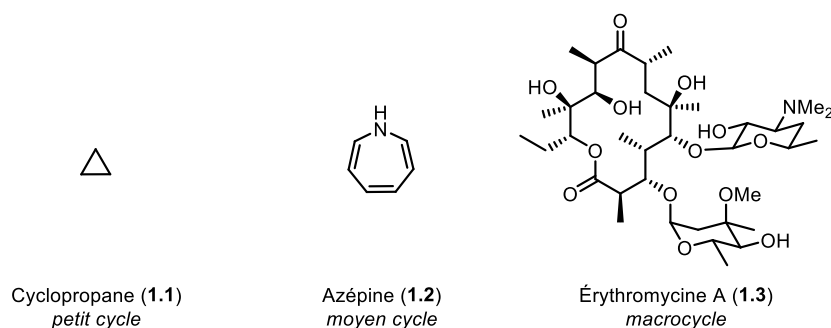


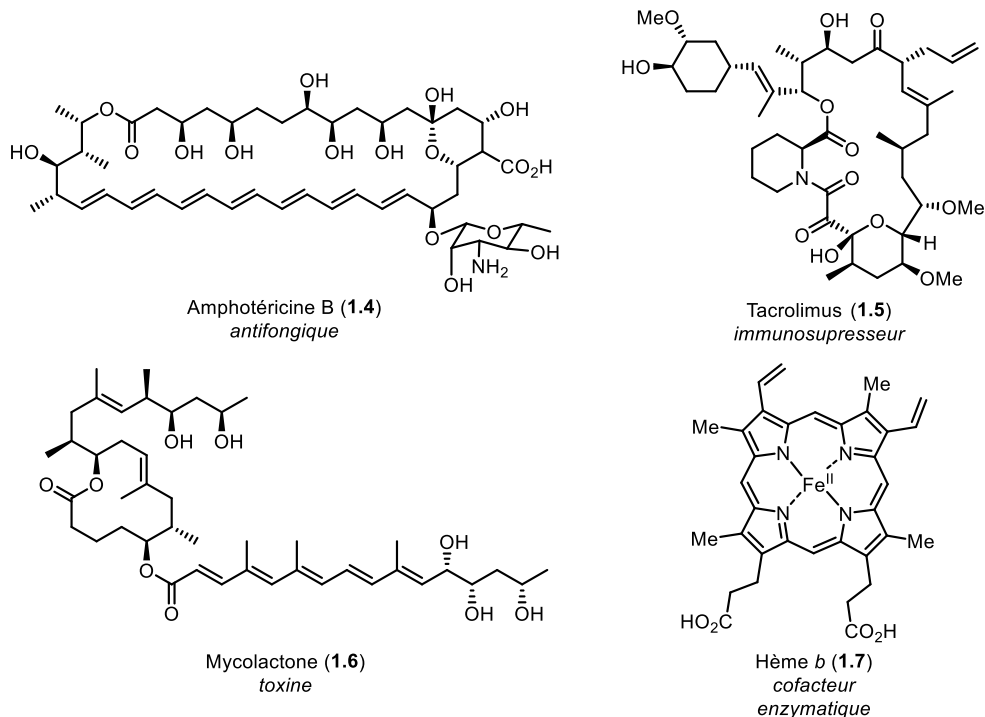
Figure 1.1 Exemples de molécules cycliques

## 1.1 L'omniprésence des macrocycles en chimie

### 1.1.1 Les macrocycles dans la nature

Depuis des milliers d'années, les produits naturels sont utilisés par les différentes cultures mondiales pour traiter les infections et les maladies. On considère comme étant un produit naturel tout composé chimique originalement synthétisé par un organisme vivant<sup>2</sup>. Parmi ces molécules, environ 20 % possèdent un motif macrocyclique dont la majorité est composée de 14, 16 ou 18 chaîons<sup>3</sup>. La plupart des macrocycles naturels sont des macrolactones (esters macrocycliques) ou macrolactames (amides macrocycliques). Les macrolides sont des macrolactones appartenant à la famille des polycétides et possédant

généralement des propriétés thérapeutiques. L'antibiotique, érythromycine A (**1.3**), mentionné plus tôt fait partie de cette famille. On y retrouve également l'amphotéricine B (**1.4**), un antifongique faisant partie de la liste des médicaments essentiels de l'Organisation mondiale de la santé<sup>4</sup> ainsi que le tacrolimus (**1.5**), un immunosuppresseur utilisé lors de la transplantation d'organe afin de prévenir le rejet des allogreffes (même espèce, individus différents). Par contre, il existe également des macrolides ayant des effets néfastes pour l'humain. Par exemple, la mycolactone (**1.6**) est une toxine responsable des ulcères de Buruli, une infection causant la nécrose de la peau. Les macrocycles naturels ne sont pas tous des macrolactones ou des macrolactames; certains macrocycles sont composés d'unités pyrrole ou pyrroline. Retrouvés dans les systèmes biologiques, ces macrocycles sont souvent liés à un atome métallique (fer, magnésium, cobalt, etc.) et jouent le rôle de cofacteur enzymatique. Des exemples communs comprennent l'hème *b* (**1.7**) de l'hémoglobine (porphyrine), les chlorophylles (chlorine) et la vitamine B<sub>12</sub> (corrine) (Figure 1.2).



**Figure 1.2** Exemples de macrocycles naturels biologiquement actifs

Par leur complexité, les macrocycles posent un défi synthétique de taille, notamment pour l'étape de fermeture de cycle<sup>5</sup>. Historiquement, la sélectivité de la macrocyclisation était l'un des principaux obstacles lors de la réalisation d'une synthèse totale d'un produit naturel



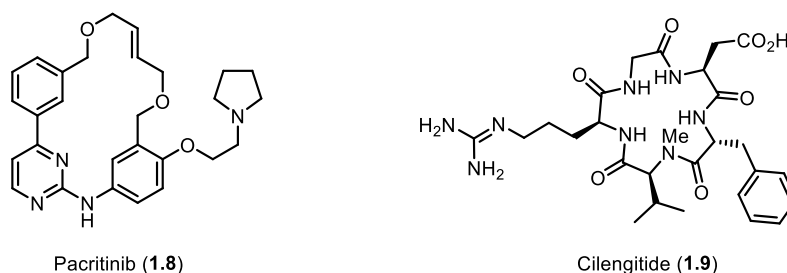
macrocyclique. Ceci a mené certains grands chercheurs comme E. J. Corey à innover en développant de nouvelles stratégies (réactions) de macrocyclisation<sup>6</sup>. Afin de surmonter le défi synthétique des macrocycles, d'autres chercheurs utilisent plutôt une approche semi-synthétique. Ceci consiste à extraire un composé issu d'une biosynthèse (i.e. microbienne) et de le modifier afin d'augmenter son activité biologique et sa stabilité. Un exemple de composé semi-synthétique est la clarithromycine (érythromycine 6-O méthylé), un antibiotique issu de la modification de l'érythromycine A (**1.3**)<sup>7</sup>. En tenant compte de la difficulté de la synthèse totale de l'érythromycine A (50 étapes, rendement global de 0.006%)<sup>8</sup>, la commercialisation d'un de ces dérivés sans processus semi-synthétique serait purement inimaginable. Malgré tout, les propriétés médicinales des composés naturels macrocycliques contrebalancent le défi synthétique, ce qui les rend particulièrement attrayants pour l'industrie pharmaceutique.

### 1.1.2 Les macrocycles dans l'industrie pharmaceutique

En chimie médicinale, l'identification de médicaments oralement actifs passe normalement par une série de critères, dont les règles de Lipinski<sup>9</sup>. Ces règles stipulent que le médicament doit 1) avoir au plus 5 donneurs de ponts hydrogène, 2) avoir au plus 10 accepteurs de ponts hydrogène, 3) avoir une masse moléculaire inférieure à 500 g/mol et 4) avoir un coefficient de partition (log P) inférieur à 5. Cependant, de façon générale, les médicaments macrocycliques ne respectent pas certaines de ces règles, notamment celle faisant référence à la masse moléculaire. Pourtant, les candidats macrocycliques possèdent plusieurs propriétés physicochimiques et pharmacocinétiques très intéressantes, comme une bonne solubilité, lipophilicité et stabilité métabolique, menant à une bonne biodisponibilité orale<sup>10</sup>.

Par conséquent, il y a eu l'apparition de nouveaux critères additionnels pour l'identification de médicaments tels qu'avoir une surface polaire inférieure à 140 Å<sup>2</sup> et une limite de 10 liaisons avec liberté de rotation (règles de Veber), ce qui favorise la classe des macrocycles<sup>11</sup>. En effet, la contrainte conformationnelle des macrocycles est un paradoxe. D'une part, les macrocycles ont la flexibilité nécessaire pour bien interagir avec un site actif dynamique et d'autre part, la rigidité structurelle des macrocycles permet de réduire le coût entropique associé à l'adoption d'une conformation bioactive<sup>12</sup>.

Grâce à leur grande surface de contact, les macrocycles sont efficaces pour inhiber les interactions protéine-protéine. Parmi ces candidats, on retrouve notamment le pacritinib (**1.8**), un inhibiteur des kinases JAK2/FLT3 actuellement en phase clinique III aux États-Unis pour le traitement de la myélofibrose primitive (Figure 1.3)<sup>13</sup>. Les macrocycles peptidiques sont aussi très efficaces comme inhibiteur des interactions protéine-protéine. Le cyclopeptide cilengitide (**1.9**) est un composé anti-angiogénique permettant le ralentissement de la croissance des tumeurs malignes et ainsi atténuer le développement des métastases<sup>14</sup>.



**Figure 1.3** Exemples de macrocycles synthétiques

En dépit de leur potentiel pharmaceutique élevé, les macrocycles restent une classe de candidats peu étudiée, principalement à cause des difficultés liées à leur synthèse. En effet, l'étape de macrocyclisation est souvent problématique et les solutions existantes ne peuvent pas toujours être appliquées à une production industrielle. De plus, la synthèse de macrocycles tend à être plutôt linéaire, ce qui pose également un problème au niveau de l'élaboration de bibliothèques moléculaires pour une étude de structure-activité (*SAR*) ou pour un criblage à haut débit. Pour pallier cet obstacle, plusieurs technologies ont été développées comme la synthèse parallèle<sup>15</sup>, la synthèse par programmation d'ADN<sup>16</sup> ou la synthèse chimioenzymatique<sup>17</sup>.

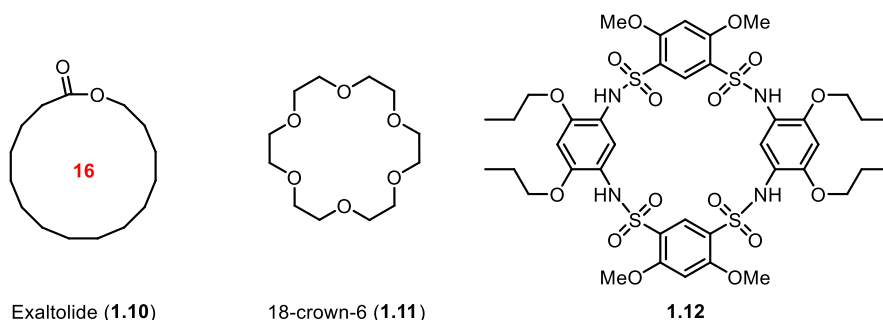
### 1.1.3 Les macrocycles dans d'autres domaines

Outre l'industrie pharmaceutique, celle des cosmétiques, mais aussi la chimie supramoléculaire et le domaine des matériaux tirent profit des macrocycles (Figure 1.4). La chimie des cosmétiques, aussi appelée la « chimie des arômes » utilise des molécules appelées musc, une classe de molécules odorantes retrouvées dans la nature. Une certaine proportion de ces molécules est constituée de macrocycles comme l'Exaltolide® (**1.10**) qui possède un seuil de détection olfactive de 2.1 ng/L<sub>air</sub><sup>18</sup>. Ce type de macrocycles se retrouve maintenant dans

plusieurs objets de la vie quotidienne comme les parfums, les savons et les shampoings. Ils sont produits annuellement sur une échelle allant jusqu'à 1000 tonnes métriques<sup>19</sup>.

En chimie supramoléculaire, les macrocycles sont présents dans une panoplie d'applications comme le développement de systèmes hôtes-invités<sup>20</sup> et même des machines moléculaires<sup>21</sup>. Le prix Nobel de chimie en 1987 a été attribué à trois chercheurs, soit Donald Cram, Jean-Marie Lehn et Charles Pedersen pour le développement de molécules dont leur structure permet des interactions hautement sélectives. Un exemple de ces molécules est l'éther couronne *18-crown-6* (**1.11**) découvert par Charles Pedersen. Ce polymère d'éthylène glycol macrocyclique fait des interactions très spécifiques avec le cation potassium ( $K^+$ ).

Il existe aussi des macrocycles importants dans le domaine de la chimie des matériaux comme les macrocycles à structure persistante (*shape-persistent macrocycles*)<sup>22</sup>. Des composés comme le macrocycle **1.12** peuvent être utilisés pour créer des assemblages nanotubulaires et ainsi créer des structures poreuses à l'échelle nanoscopique<sup>23</sup>.



**Figure 1.4** Structures de macrocycles utilisés dans divers domaines de la chimie

## 1.2 Défis synthétiques liés à la synthèse des macrocycles

Bien que le potentiel des macrocycles soit reconnu par la communauté scientifique, l'obstacle majeur à leur utilisation provient de la difficulté à les synthétiser. En effet, le comportement des réactions de macrocyclisation n'est pas aussi prévisible que celui des réactions intermoléculaires. Plusieurs aspects comme les contraintes thermodynamiques (entropie et enthalpie) ainsi que les contraintes conformationnelles sont directement responsables de ce phénomène<sup>24</sup>.

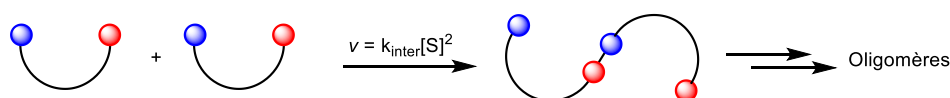
## 1.2.1 Aspects cinétiques et thermodynamiques des réactions de macrocyclisation

Dès les années 1920-1930, des chercheurs comme Ruzicka<sup>25</sup> et Ziegler<sup>26</sup> ont observé que les réactions de macrocyclisation étaient directement en compétition avec les réactions d'oligomérisation. Ils ont également observé que la concentration de la réaction pouvait avoir un impact sur la sélectivité pour la formation de macrocycles. Dans une réaction de macrocyclisation typique, les deux groupements réactionnels impliqués dans la réaction se retrouvent sur le même substrat de départ. Pour la réaction intramoléculaire (Figure 1.5A), il s'agit d'une réaction de premier ordre puisqu'une seule molécule est impliquée dans la formation du macrocycle. Pour la réaction intermoléculaire (Figure 1.5B), deux molécules de substrat sont impliquées pour la formation du dimère, menant ainsi à une réaction de deuxième ordre. Ainsi, une diminution de la concentration du substrat dans le milieu réactionnel affecte davantage la réaction intermoléculaire que la réaction de macrocyclisation, ce qui favorise la synthèse du macrocycle.

A) Réaction intramoléculaire

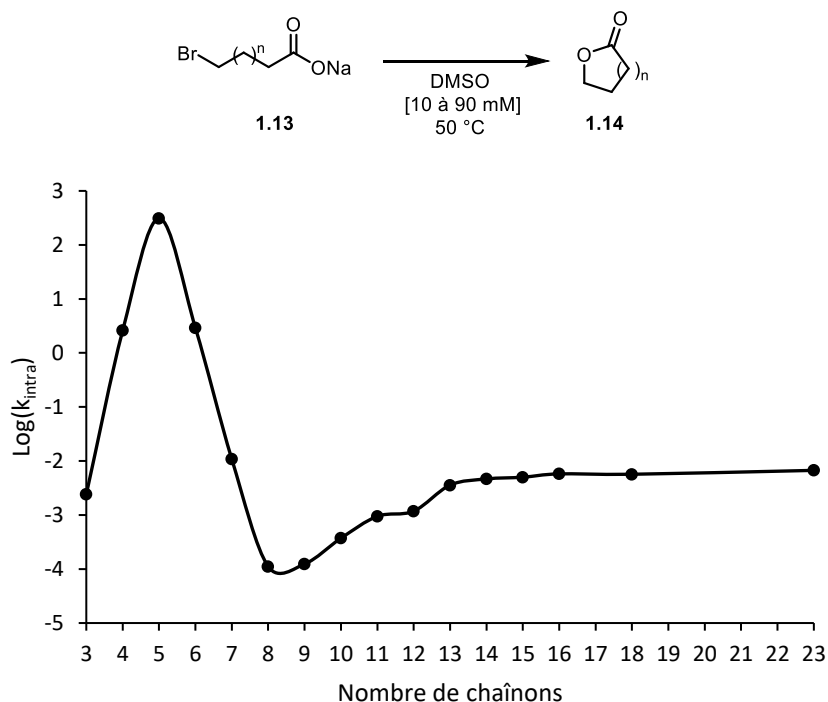


B) Réaction intermoléculaire



**Figure 1.5** Vitesse de réaction pour des réactions intra- et intermoléculaire

Dans les années 1970, des chimistes ont étudié la cinétique de la fermeture de cycle de chaînes  $\omega$ -bromocarboxylate de sodium **1.13** par réaction  $S_N2$  pour former une série de lactones **1.14** allant de 3 à 23 chaînons (Figure 1.6)<sup>27</sup>. Cette étude a établi que les formations de cycles à 4, 5 et 6 étaient les plus rapides, que les vitesses de formation des cycles de 8 à 12 étaient les plus lentes, et étonnamment, qu'un plateau est atteint à partir d'un nombre de 13 chaînons et plus.



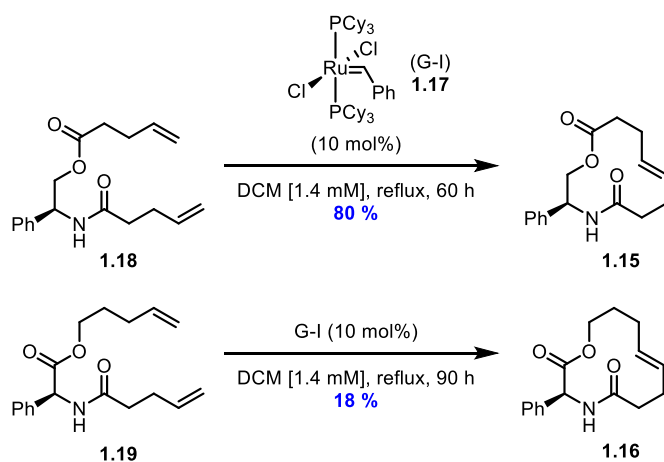
**Figure 1.6** Vitesse de fermeture de cycle lors de la formation de lactones de différentes tailles

Pour expliquer ce phénomène, il faut se tourner vers les aspects thermodynamiques d'une réaction de cyclisation. La vitesse de fermeture de cycle dépend de l'énergie de l'état de transition intermédiaire entre la forme « linéaire » du substrat initial et la forme « cyclique » du substrat final ainsi que la probabilité que les deux groupements fonctionnels se rencontrent. L'énergie de l'état de transition est composée d'un facteur entropique et d'un facteur enthalpique ( $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ ). La probabilité que les deux groupements fonctionnels se rencontrent diminue avec l'augmentation de la longueur de chaîne à cause de l'augmentation du nombre de degrés de liberté de mouvement de la chaîne. Afin de former le macrocycle, il faut donc qu'il y est une diminution de la liberté de mouvement dans l'état de transition menant à un facteur entropique ( $\Delta S^\ddagger$ ) négatif. Pour ce qui est du facteur enthalpique de l'état de transition ( $\Delta H^\ddagger$ ), il représente trois types de tensions de cycle : 1) la tension de torsion, appelée tension de Pitzer, correspond à l'opposition des forces de liaison causée par leur décalage; 2) la tension de Baeyer correspond à la déformation des angles de liaison et 3) la tension de Prelog, ou transannulaire, correspond aux interactions répulsives entre les atomes de part et d'autre du cycle<sup>28</sup>. Ces types de tension deviennent moins importants avec

l'augmentation de la longueur de chaîne, mais sont particulièrement présents dans les cycles de 8 à 12, ce qui explique la diminution significative de la vitesse de formation de cycle pour les cycles moyens (8-12). En résumé, la vitesse de cyclisation est dictée par les tensions de cycle (contribution plus importante pour les cycles de moins de 12 chaînons) et par le nombre de degré de liberté (contribution plus importante pour les cycles de plus de 12 chaînons).

## 1.2.2 Contraintes conformationnelles pour la macrocyclisation

Les aspects thermodynamiques et cinétiques présentés à la section précédente ont été étudiés sur des substrats conformationnellement non biaisés, soit des chaînes aliphatiques saturées. En revanche, les réactions de macrocyclisation impliquent généralement des substrats ayant une plus grande complexité au sein du squelette cyclique, ce qui peut mener à une contrainte supplémentaire pour l'adoption de la conformation optimale lors de la fermeture de cycle<sup>29</sup>. Un exemple typique est la formation des lactones **1.15** et **1.16** par macrocyclisation par métathèse d'oléfines (Schéma 1.1). En présence de 10 mol% du complexe de ruthénium Grubbs de 1<sup>ère</sup> génération (G-I) (**1.17**) dans un milieu très dilué de dichlorométhane (1.4 mM) à reflux, la lactone **1.15** a pu être formée à 80 % à partir du diène **1.18** tandis que la transformation du diène **1.19** n'a donné que 18 % de la lactone **1.16**. Quoique structurellement très similaires, une analyse par diffraction des rayons X de ces deux diènes a établi que la position de l'ester du diène **1.19** ne permet pas l'adoption d'une conformation propice à la cyclisation, contrairement à son homologue **1.18**<sup>30</sup>.



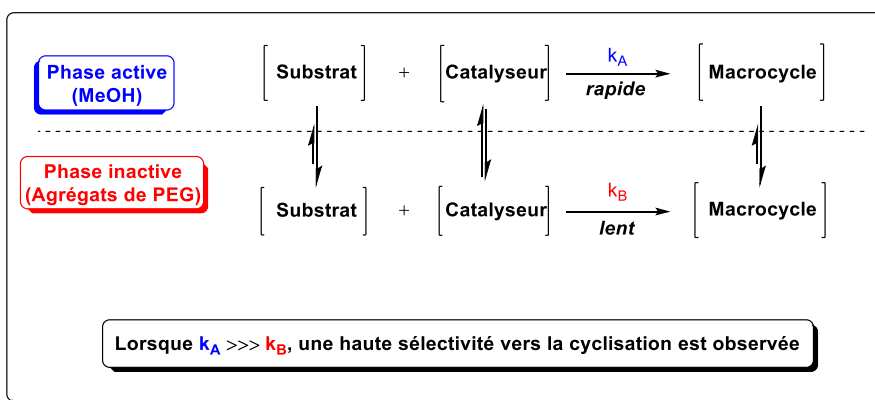
**Schéma 1.1** Effet d'une contrainte conformationnelle sur la macrocyclisation de lactones par métathèse d'oléfines

Au fil des années, plusieurs stratégies de contrôle conformationnel ont été développées afin d'améliorer les réactions de macrocyclisation<sup>31</sup>. La pré-organisation de substrats linéaires par coordination à des métaux<sup>32</sup> ou par ponts hydrogène<sup>33</sup> est largement exploitée pour la synthèse de macrocycles, notamment pour la synthèse d'éthers couronne<sup>34</sup>. Des auxiliaires covalents ou ioniques ont aussi été utilisés pour augmenter l'efficacité de certaines réactions de macrocyclisation<sup>35</sup>. Enfin, une autre stratégie permettant d'augmenter la vitesse de fermeture de cycle est l'effet Thorpe-Ingold ou *gem*-diméthyle<sup>36</sup>. Beesley, Ingold et Thorpe ont démontré que la présence de deux substituants méthyle sur un atome de carbone influence l'orientation des liaisons adjacentes menant à une conformation éclipsée (normalement décalée), ce qui est bénéfique pour une réaction de cyclisation. Il s'agit d'un effet local efficace pour les petits et moyens cycles, mais qui est plutôt inefficace pour les cycles de plus grandes tailles<sup>37</sup>.

### 1.2.3 Solutions traditionnelles pour les réactions de macrocyclisation

Tel que mentionné précédemment, l'effet de la concentration lors d'une réaction de macrocyclisation a plus d'impact sur la réaction parasitaire d'oligomérisation que sur la réaction de fermeture de cycle. Par conséquent, les réactions de macrocyclisation sont normalement effectuées dans un milieu très dilué. Bien que cette stratégie soit viable pour la synthèse à petite échelle, l'utilisation d'une grande quantité de solvant pose des problèmes majeurs sur les plans économique et environnemental, ainsi qu'au niveau de la sécurité d'opération. Il y a donc eu un développement de stratégies alternatives afin d'éviter l'utilisation d'une dilution élevée. Une première technique est d'effectuer l'addition lente du substrat linéaire au mélange réactionnel plus concentré de sorte que la concentration locale du substrat dans le milieu réactionnel soit très faible; il est alors question de pseudo-dilution. L'addition lente est souvent réalisée à l'aide d'un pousse-seringue mécanique qui permet un contrôle précis et constant sur la vitesse d'ajout. Une deuxième technique est la synthèse sur support solide<sup>38</sup>. L'immobilisation du substrat linéaire ou d'un réactif/catalyseur sur une matrice inerte crée une réactivité locale (pseudo-dilution) qui permet généralement la limitation de la formation d'oligomères. Cependant, l'utilisation de cette dernière stratégie semble être limitée à la synthèse de peptides cycliques<sup>39</sup>.

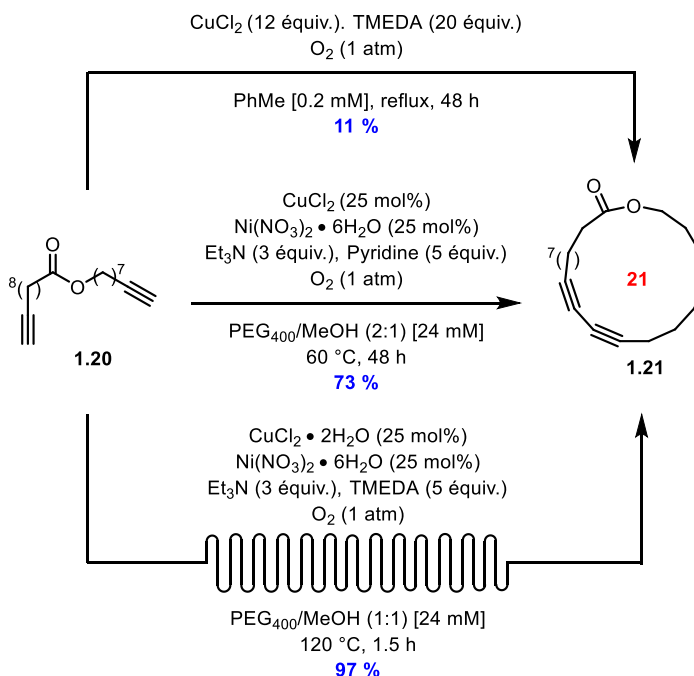
En 2011, notre groupe de recherche a développé une nouvelle stratégie permettant d'effectuer des réactions de macrocyclisation sans avoir recours à l'utilisation d'addition lente ni de dilution élevée. Cette méthode porte le nom de stratégie de séparation de phase (SSP) et exploite les propriétés d'agrégation d'un co-solvant de poly(éthylène) glycol (PEG) dans un solvant hydrophile formant ainsi un système biphasique<sup>40</sup>. La SSP consiste en une phase « active », où la vitesse de la réaction est rapide, et une phase « inactive », où la vitesse de réaction est très lente. Le fonctionnement de la SSP repose sur deux principes généraux, soit 1) la préférence de résidence du substrat linéaire dans la phase inactive (agrégats de PEG) et 2) la vitesse de réaction dans la phase active doit être grandement supérieure à la vitesse de diffusion du substrat linéaire de la phase inactive vers la phase active (Figure 1.7).



**Figure 1.7** Représentation schématique de la stratégie de séparation de phase

La stratégie de séparation de phase a été développée en utilisant le couplage de Glaser-Hay comme réaction modèle, soit le couplage entre deux alcynes terminaux catalysé par un complexe de cuivre<sup>41</sup>. Dans des conditions traditionnelles d'addition lente et de dilution élevée, l'introduction du diyne **1.20** dans un large excès du système catalytique CuCl/TMEDA à une très faible concentration de 0.2 mM dans le toluène à reflux produit le macrocycle **1.21** dans un faible rendement de 11% (Schéma 1.2). Heureusement, en utilisant les conditions de la SSP, soit 25 mol% de CuCl<sub>2</sub>·2H<sub>2</sub>O/Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O en présence de pyridine dans un mélange PEG<sub>400</sub>/MeOH (2 :1) à une concentration de 24 mM, le même produit peut être obtenu dans un rendement de 73%.





**Schéma 1.2** Stratégie de séparation de phase pour la synthèse de macrocycles par couplage de Glaser-Hay

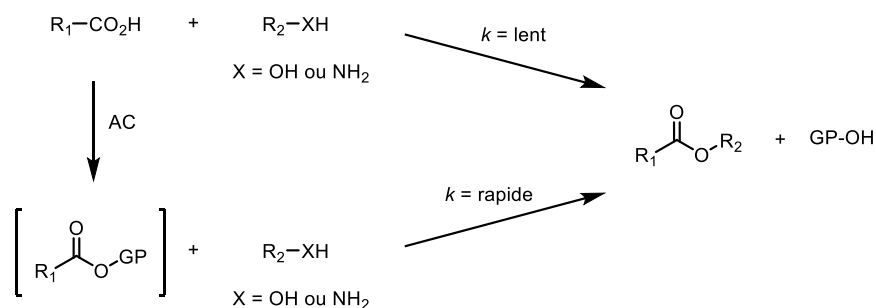
Ensuite, le temps réactionnel a pu être réduit significativement (1 h – 6 h au lieu de 48 h) en utilisant un chauffage par micro-ondes<sup>42</sup>, alors qu’une étude de l’influence de la structure du co-solvant de PEG a permis de réduire la charge catalytique à 2.5 mol% de [Cu]/[Ni], tout en maintenant une grande réactivité et sélectivité<sup>43</sup>. Par la suite, la SSP a fait un pas de plus vers l’obtention d’une méthode de macrocyclisation durable par son adaptation à la chimie en débit continu, offrant ainsi une plateforme pour la synthèse de macrocycles sur une échelle de grammes<sup>44</sup>. Finalement, il a été démontré que la macrocyclisation par SSP était aussi applicable à d’autres types de réaction comme la formation de triazoles par cycloaddition 1,3-dipolaire de Huisgen catalysée par un complexe de cuivre<sup>45</sup> et la formation de macrocycles par métathèse<sup>46</sup>.

## 1.3 Méthodes courantes de macrocyclisation

### 1.3.1 Macrolactonisation et Macrolactamisation

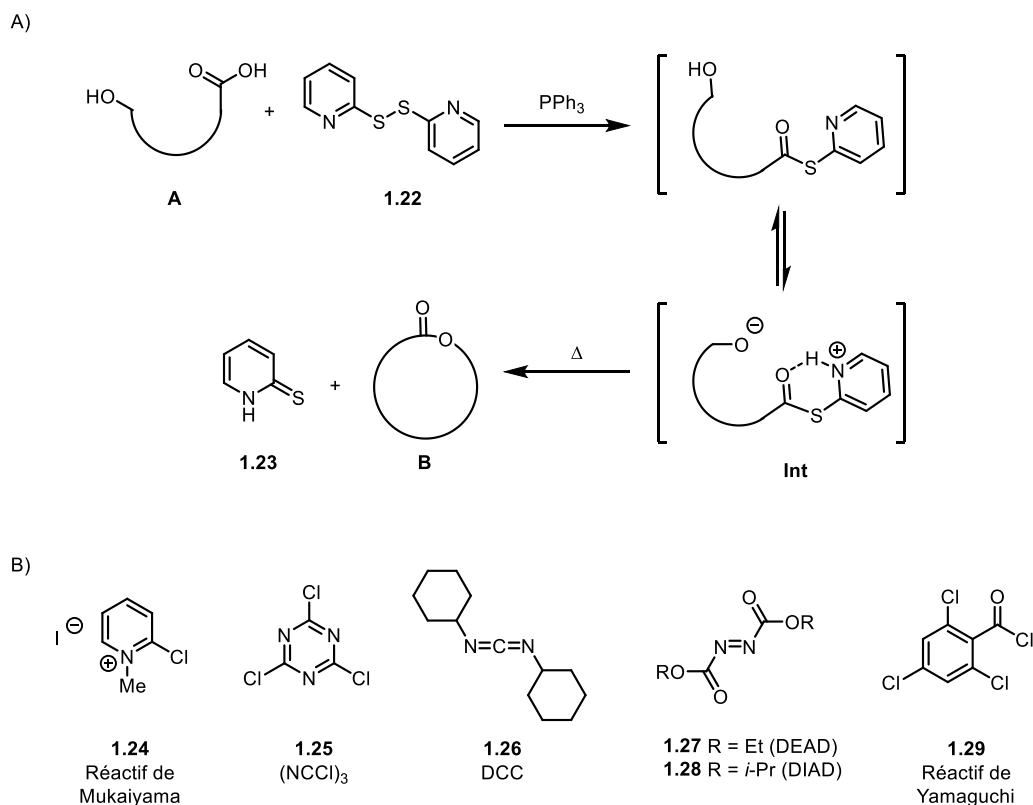
Les macrolactones et les macrolactames constituent la grande majorité des macrocycles biologiquement actifs. Depuis les 50 dernières années, plusieurs méthodes ont été

développées afin de perfectionner l'étape clé de macrocyclisation<sup>47</sup>. Ces différentes réactions reposent essentiellement sur la même stratégie, soit l'utilisation d'agents de couplage (AC). En effet, les réactions d'estérification et d'amidation sont cinétiquement très lentes en absence de catalyseur. Le rôle de l'agent de couplage est d'abord d'activer l'acide carboxylique afin de former un meilleur électrophile et permettre l'attaque du nucléophile (alcool ou amine). L'agent de couplage sert également de bon groupement partant (GP), rendant le couplage thermodynamiquement favorable (Figure 1.8).



**Figure 1.8** Utilisation d'un agent de couplage lors des réactions d'estérification et d'amidation

La première réaction de macrocyclisation efficace a été publiée en 1974 par Corey et Nicolaou<sup>48</sup>. La stratégie était d'activer la fonctionnalité acide carboxylique du substrat linéaire (**A**) avec du disulfure de 2,2'-dipyridine (**1.22**) et de la triphénylphosphine (PPh<sub>3</sub>) afin de former un motif thio-ester (**Int**). Ce dernier est très électrophile et la présence de l'hétérocycle permet le rapprochement de la fonctionnalité hydroxyle menant à la formation éventuelle de la macrolactone (**B**) avec le départ de la 2-pyridinethione (**1.23**) (Figure 1.9A).

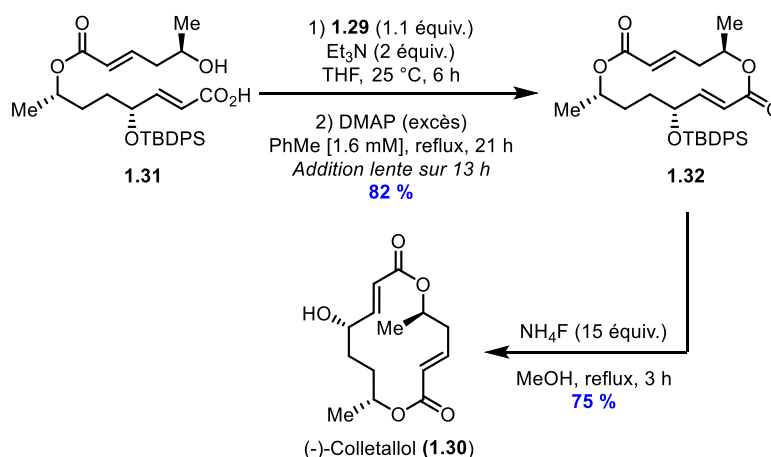


**Figure 1.9** Macrolactonisation de Corey-Nicolaou (A) et structures de divers agents de couplage (B)

Suivant la publication de la macrolactonisation de Corey-Nicolaou, plusieurs autres chercheurs ont développé des méthodes similaires applicables à la macrocyclisation. Mukaiyama<sup>49</sup> a utilisé l'iodure de 1-méthyl-2-chloropyridinium (**1.24**) comme agent de couplage, tandis que Venkataraman<sup>50</sup> a opté pour le chlorure cyanurique (NCCl)<sub>3</sub> (**1.25**). Keck et Boden<sup>51</sup> ont adapté les conditions de l'estérification de Steglich en utilisant le *N,N'*-dicyclohexylcarbodiimide (DCC) (**1.26**) en présence de 4-diméthylaminopyridine (DMAP) et la réaction de Mitsunobu, impliquant un réactif de type azodicarboxylate (DEAD (**1.27**) ou DIAD (**1.28**)), a également été utilisée pour la synthèse de macrolactones (Figure 1.9B)<sup>52</sup>.

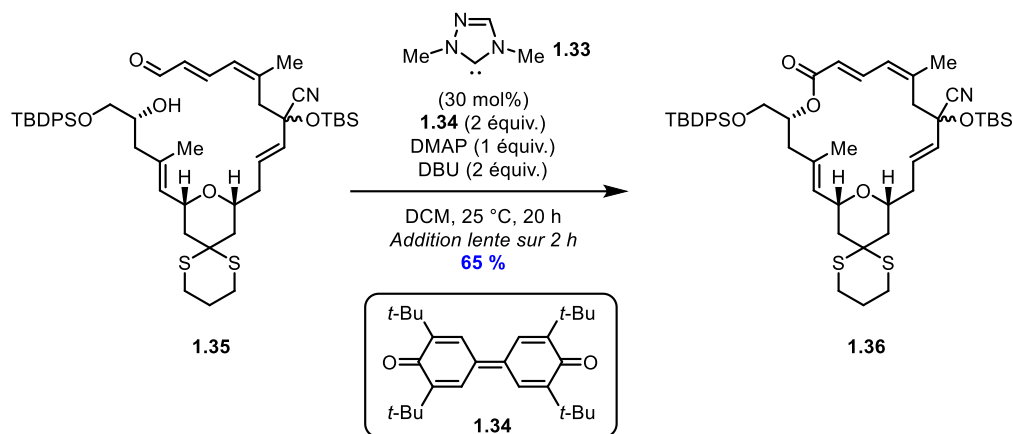
Toutefois, l'agent de couplage pour les réactions de macrolactonisation le plus utilisé dans la littérature est sans aucun doute le chlorure de 2,4,6-trichlorobenzoyl (**1.29**), aussi connu sous le nom de réactif de Yamaguchi<sup>53</sup>. Cet agent de couplage réagit avec l'acide carboxylique pour former *in situ* un anhydride mixte. La présence des trois atomes de chlore permet ensuite une attaque sélective d'un agent de transfert d'acyle comme le DMAP sur le

carbonyle le moins encombré, soit celui du substrat, tout en augmentant l'efficacité du groupement partant par effet inductif électronique. La réaction de macrolactonisation de Yamaguchi a été utilisée dans de nombreuses synthèses totales de macrolactones, notamment dans la synthèse de (-)-colletalol (**1.30**) réalisée par Kumar en 2016 (Schéma 1.3)<sup>54</sup>. Les auteurs ont fait la synthèse du précurseur linéaire **1.31** contenant une fonction acide carboxylique et une fonction hydroxyle (*seco*-acide) avant de le soumettre dans des conditions de macrolactonisation de Yamaguchi. L'anhydride mixte a d'abord été préformé avant d'être ajouté goutte-à-goutte sur une période de 13 h à une solution très diluée (1,6 mM) de DMAP dans le toluène à reflux. Ce protocole a permis aux auteurs d'obtenir la macrolactone **1.32**, qui a ensuite été transformée en (-)-colletalol (**1.30**) par la déprotection du groupement silylé.



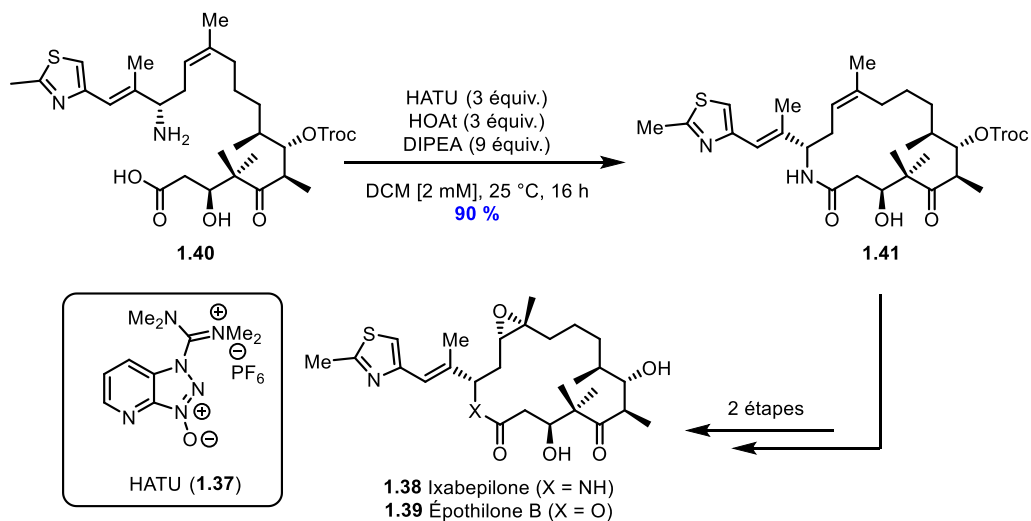
**Schéma 1.3** Macrolactonisation de Yamaguchi dans la synthèse de (-)-colletalol

Un désavantage majeur des réactions de macrolactonisation présentées précédemment est l'utilisation d'une quantité stœchiométrique de l'agent de couplage. Plus récemment, des méthodes catalytiques<sup>55</sup> ont été développées par White<sup>56</sup> (Pd), Breit<sup>57</sup> (Rh), Dai<sup>58</sup> (Pd) et Collins<sup>59</sup> (Hf) qui ont utilisé des catalyseurs à base de métaux de transition pour effectuer l'étape de macrocyclisation. De son côté, Hong<sup>60</sup> a plutôt utilisé le carbène *N*-hétérocyclique (NHC) **1.33** en présence de la diphénoquinone **1.34** pour réaliser la macrocyclisation oxydative de l'aldéhyde **1.35** en macrolactone **1.36** (Schéma 1.4).



**Schéma 1.4** Macrocyclisation oxydative catalysée par un carbène *N*-hétérocyclique

Suivant la même stratégie de synthèse des macrolactones, les macrolactames ont aussi besoin d'une activation de la fonctionnalité électrophile pour être formées. En revanche, comme elles sont souvent des peptides cycliques, ce sont plutôt des agents de couplage peptidique qui sont employés, quoique les composés présentés à la figure 1.9 puissent aussi être utilisés<sup>61</sup>. L'hydrochlorure de 1-(3-diméthylaminopropyl)-3-éthylcarbodiimide (EDC·HCl) et le sel d'uronium HATU (**1.37**) sont ceux qui sont le plus utilisés et, puisque les acides aminés sont sujet à racémiser lorsque la cinétique de couplage est lente (souvent le cas pour des réactions de macrocyclisation), des agents de transfert d'acyle comme le 1-hydroxy-7-azabenzotriazole (HOAt) sont aussi utilisés pour limiter la racémisation. Cette stratégie a été utilisée par Danishefsky dans la synthèse totale de l'ixabepilone (**1.38**), un analogue azoté synthétique du produit naturel épothilone B (**1.39**)<sup>62</sup>. En combinant l'agent de couplage HATU avec l'agent de transfert d'acyle HOAt, les auteurs ont pu effectuer la macrocyclisation de l'acide aminé **1.40** pour former la macrolactame **1.41** avec 90 % de rendement et rétention de la pureté énantiomérique (Schéma 1.5).

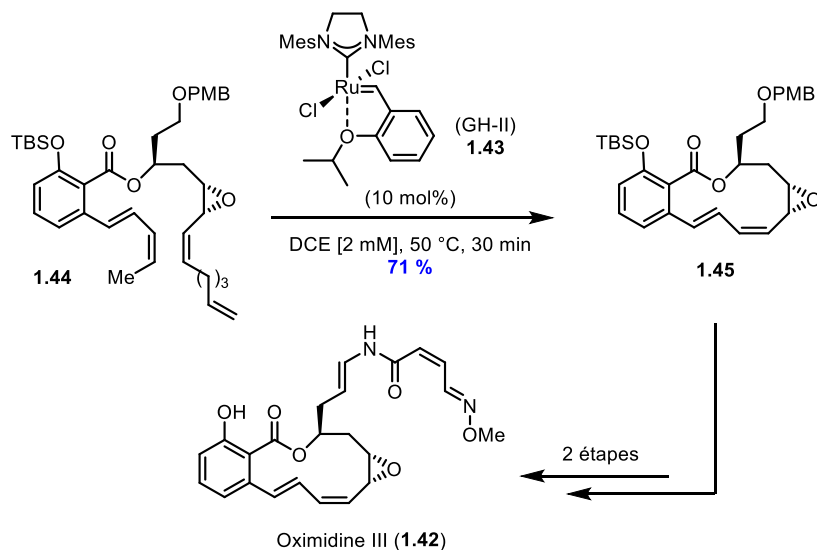


**Schéma 1.5** Synthèse totale de l'ixabépilone par macrolactamisation

### 1.3.2 Formation de liens C-C

La formation de liens carbone-carbone est une stratégie assez répandue pour la synthèse de macrocycles. Il existe bien entendu des versions macrocycliques des réactions communes comme l'oléfination de Horner-Emmons-Wadsworth<sup>63</sup> ou bien de Julia-Kocienski<sup>64</sup>, mais ces réactions ont été largement surpassées par le développement de stratégies catalytiques comme les couplages catalysés par un complexe de palladium<sup>65</sup> ou de cuivre<sup>66</sup>. Une autre réaction catalytique largement utilisée pour la synthèse de macrocycles est la réaction de métathèse d'oléfines<sup>67</sup>. En effet, cette dernière est très avantageuse considérant les nombreux catalyseurs possibles ainsi que les groupements fonctionnels qui sont tolérés.

La macrocyclisation par métathèse d'oléfines a fait ses preuves pour la synthèse de produits naturels<sup>68</sup> de même que dans le domaine pharmaceutique<sup>69</sup>. Un exemple typique de l'application de cette méthode est la synthèse du produit naturel oximidine III (**1.42**) par Porco et ses collègues<sup>70</sup>. En utilisant 10 mol% du catalyseur de Grubbs-Hoveyda de 2<sup>ème</sup> génération (GH-II) (**1.43**), les auteurs ont effectué la cyclisation du diène **1.44** pour former le macrocycle **1.45** avec 71 % de rendement et une stéréosélectivité parfaite pour l'alcène formé (100 % Z) (Schéma 1.6).



**Schéma 1.6** Synthèse totale de l'oximidine III par macrocyclisation par métathèse d'oléfines

## 1.4 Conclusion

Les macrocycles, autant naturels que synthétiques, sont des composés importants pour plusieurs sphères de la chimie. Leur utilisation reste toutefois limitée du fait qu'ils ne sont pas faciles d'accès, et que la sélectivité pour la macrocyclisation par rapport à l'oligomérisation soit difficile à contrôler. Nonobstant le développement des stratégies permettant une sélectivité intramoléculaire comme l'addition lente et la dilution élevée, des méthodes économiquement viables et bénignes pour l'environnement sont souhaitables<sup>71</sup>. La présente thèse portera sur l'application d'une stratégie de macrocyclisation à concentration élevée par couplage de Glaser-Hay pour la synthèse d'un produit naturel et d'un médicament (Chapitre 2 - 6) et du développement d'une réaction de thioalcynylation catalysée par un complexe de cuivre (I) pour la construction de macrocycles soufrés (Chapitre 7 – 9).

## 1.5 Bibliographie

- McNaught, A. D.; Wilkinson, A. IUPAC. Compendium of Chemical Terminology, 2<sup>nd</sup> ed. (the "Gold Book"). Blackwell Scientific Publications: Oxford, **2014**; p 870.
- All Natural, éditorial, *Nat. Chem. Biol.* **2007**, *3*, 351.
- Frank, A. T.; Farina, N. S.; Sawwan, N.; Wauchope, O. R.; Qi, M.; Brzostowska, E. M.; Chan, W.; Grasso, F. W.; Haberfield, P.; Greer, A. *Molec. Divers.* **2007**, *11*, 115-118.

4. World Health Organization Model List of Essential Medicines, 21<sup>st</sup> List, 2019. Geneva: World Health Organization; 2019.
5. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44 – 122.
6. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614 - 5616.
7. Kumazawa, K.; Yagisawa, M. *J. Infect. Chemother.* **2002**, *8*, 125 – 133.
8. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne L. J.; Card P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobels, K.; Gals, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210 – 3213., *J. Am. Chem. Soc.* **1981**, *103*, 3213 – 3215., *J. Am. Chem. Soc.* **1981**, *103*, 3215 – 3217.
9. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3 - 26.
10. Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608 – 624.
11. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615 – 2623.
12. Mallinson, J.; Collins, I. *Future Med. Chem.* **2012**, *4*, 1409 – 1438.
13. William, A. D.; Lee, A. C.-H.; Blanchard, S. P.; Poulsen, A.; Teo, E. L.; Nagaraj, H.; Tan, E.; Chen, D.; Williams, M.; Sun, E. T.; Goh, K. C.; Ong, W. C.; Goh, S. K.; Hart, S.; Jayaraman, R.; Pasha, M. K.; Ethirajulu, K.; Wood, J. M.; Dymock, B. W. *J. Med. Chem.* **2011**, *54*, 4638 – 4658.
14. Dechantsreiter, M. A.; Planker, E.; Matha, B.; Lohof, E.; Hölzemann, G.; Jonczyk, A.; Goodman, S. L.; Kessler, H. *J. Med. Chem.* **1999**, *42*, 3033 – 3040.
15. Marsault, E.; Hoveyda, M. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vézina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Déziel, R.; Peeters, T.; Fraser, G. L. *J. Med. Chem.* **2006**, *49*, 7190 – 7197.
16. Gartner, Z. J.; Tse, B. N.; Grubina, R.; Doyon, J. B.; Snyder, T. M.; Liu, D. R. *Science* **2004**, *305*, 1601-1605.
17. Kohli, R. M.; Burke, M. D.; Tao, J.; Walsh, C. T. *J. Am. Chem. Soc.* **2003**, *125*, 7160 – 7161.
18. Kraft, P. *Chemistry and Technology of Flavors and Fragrances*, Blackwell Publishing Ltd, **2009**.



19. Belsito, D.; Bickers, D.; Bruze, M.; Calow, P.; Dagli, M. L.; Fryer, A. D.; Greim, H.; Miyachi, H.; Saurat, J. H.; Sipes, I. G. *Food Chem. Toxicol.* **2011**, *49*, S219 – S241.
20. Zhou, Y.; Jie, K.; Zhao, R.; Huang, F. *Adv. Mater.* **2019**, *32*, 1904824 (<https://doi.org/10.1002/adma.201904824>)
21. Bruns C. J.; Stoddart, J. F. *Acc. Chem. Res.* **2014**, *47*, 2186 – 2199.
22. Zhang, W.; Moore, J. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 4416 – 4439.
23. He, L.; An, Y.; Yuan, L.; Feng, W.; Li, M.; Zhang, D.; Yamato, K.; Zheng, C.; Zeng, X. C.; Gong B. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10850 – 10855.
24. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95 - 102.
25. Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* **1926**, *9*, 249 - 264.
26. Ziegler, K.; Eberle, H.; Ohlinger, H. *Justus Liebigs Ann. Chem.* **1933**, *504*, 94 - 130.
27. Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1977**, *99*, 6308 - 6312.
28. Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637 - 1648.
29. Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, *2005*, 1949 - 1964.
30. Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648 - 10649.
31. White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 509 – 524.
32. Lavendomme, R.; Ronson, T. K.; Nitschke, J. R. *J. Am. Chem. Soc.* **2019**, *141*, 12147 – 12158.
33. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606 - 9614.
34. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017 – 7036.
35. (a) El-azizi, Y.; Schmitzer, A.; Collins, S. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 968 - 973.  
(b) El-Azizi, Y.; Zakarian, J. E.; Bouillierand, L.; Schmitzer, A. R.; Collins, S. K. *Adv. Synth. Catal.* **2008**, *350*, 2219 - 2225.
36. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080 - 1106.
37. Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, L. *J. Org. Chem.* **1979**, *44*, 1258 - 1261.
38. Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev.* **2015**, *115*, 8736 – 8834.
39. Früchtel, J. S.; Jung, G. *Angew. Chem. Int. Ed.* **1996**, *35*, 17 - 42.
40. Bédard, A.-C.; Collins, S. K. *Chem. Eur. J.* **2013**, *19*, 2108-2113.
41. Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976-19981.
42. Bédard, A.-C.; Collins, S. K. *Chem. Commun.* **2012**, *48*, 6420-6422.
43. Bédard, A.-C.; Collins, S. K. *ACS Catal.* **2013**, *3*, 773-782.
44. Bédard, A.-C.; Régnier, S.; Collins, S. K. *Green Chem.* **2013**, *15*, 1962-1966.

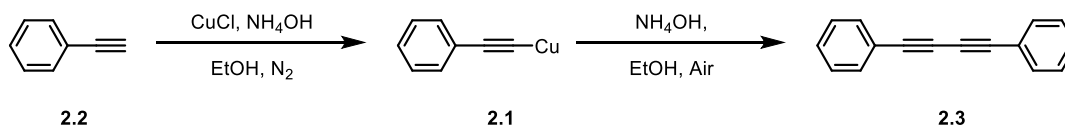
45. (a) Bédard, A.-C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 5286-5289. (b) Bédard, A.-C.; Santandrea, J.; Collins, S. K. *J. Flow Chem.* **2015**, *5*, 142-144.
46. Raymond, M.; Holtz-Mulholland, M.; Collins, S. K. *Chem. Eur. J.* **2014**, *20*, 12763–12767.
47. Yu X.; Sun, D. *Molecules* **2013**, *18*, 6230 – 6268.
48. (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614 – 5616. (b) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, *17*, 3409 – 3412.
49. Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, *5*, 49 – 50.
50. Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893 – 1896.
51. Boden E. P. Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394 - 2395.
52. Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551 – 2651.
53. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993.
54. Vandana Kauloorkar, S.; Kumar, P. *RSC Adv.* **2016**, *6*, 63607 – 63612.
55. Li, Y.; Yin, X.; Dai, M. *Nat. Prod. Rep.* **2017**, *34*, 1185 – 1192.
56. Fraunhoffer, K. J.; Prabakaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032 - 9033.
57. Lumbroso, A.; Abermil N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789 - 793.
58. Bai, Y.; Dexter D. C.; Dai, M. *J. Angew. Chem., Int. Ed.* **2014**, *53*, 6519 - 6522.
59. de Léséleuc, M.; Collins, S. K. *ACS Catal.* **2015**, *5*, 1462 – 1467.
60. Lee, K.; Kim H.; Hong, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5735 - 5738.
61. Montalbetti, C. A. G. N.; Falque V. *Tetrahedron* **2005**, *61*, 10827 – 10852.
62. Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J.; Chou T. C.; Guan, Y. *J. Org. Chem.* **2001**, *66*, 4369 – 4378.
63. (a) Larsen, B. J.; Sun, Z.; Nagorny, P. *Org. Lett.* **2013**, *15*, 2998 – 3001. (b) Ando, K.; Narumiya, K.; Takada, H.; Teruya, T. *Org. Lett.* **2010**, *12*, 1460 – 1463.
64. Chatterjee, B.; Bera, S.; Mondal, D. *Tetrahedron: Asymmetry* **2014**, *25*, 1 – 55.
65. Ronson, T. O.; Taylor, R. J. K.; Fairlamb, I. J. S. *Tetrahedron* **2015**, *71*, 989 – 1009.
66. (a) Santandrea, J.; Bédard, A.-C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 3892 – 3895. (b) Bogdan, A. R.; James, K. *Chem. Eur. J.* **2010**, *16*, 14506 – 14512.
67. Vanderwal, C. D.; Atwood, B. R. *Aldrichimica Acta* **2017**, *50*, 17 – 27.
68. Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*. WILEY-VCH Verlag GmbH & Co. KGaA : Weinheim, **2010**.
69. Yu, M.; Lou, S.; Gonzalez-Bobes, F. *Org. Process Res. Dev.* **2018**, *22*, 918 – 946.

70. Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, Jr., J. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3601 – 3605.
71. Santandrea, J.; Bédard, A.-C.; de Léséleuc, M.; Raymond, M. Collins, S. K. *Alternative Strategies for the Construction of Macrocycles*. John Wiley & Sons, Inc.: Hoboken, **2017**.

## Chapitre 2. La réaction de couplage de Glaser-Hay

### 2.1 Origine et évolution

En 1869, un chimiste allemand du nom de Carl Glaser travaillait sur la formation de phénylacétylure de cuivre (I) (**2.1**) à partir de phénylacétylène (**2.2**) et de chlorure de cuivre (I) (CuCl) lorsqu'il a observé la réactivité de ces derniers en présence d'air ambiant dans une solution alcoolique d'ammoniac<sup>1</sup> (Figure 2.1). Le produit formé a été identifié comme étant le 1,4-diphénylbutadiyne (**2.3**), résultant de la formation d'un nouveau lien C<sub>sp</sub>-C<sub>sp</sub>. Cette observation a été très importante dans le domaine de la chimie organométallique et porte maintenant le nom de couplage de Glaser. Cependant, mise à part son utilisation pour la synthèse de l'indigo par Baeyer en 1882<sup>2</sup>, les conditions initiales développées par Glaser ont été peu utilisées dans la littérature. Une des raisons majeures est la nécessité d'isoler l'acétylure de cuivre (I), une classe de composés potentiellement explosifs.

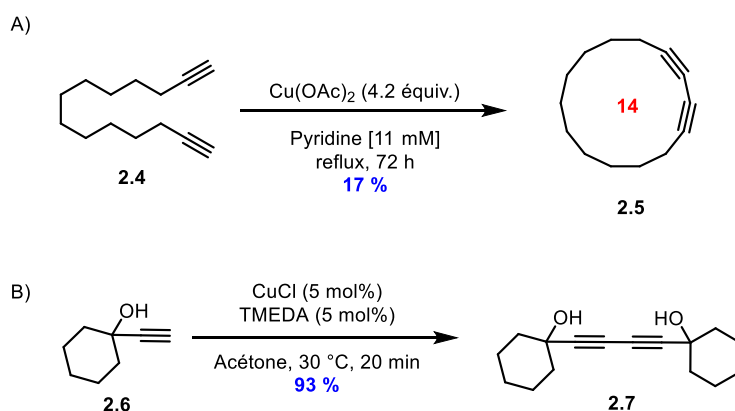


**Figure 2.1** Couplage oxydatif de Glaser

Il aura fallu près de 90 ans avant que les chercheurs Eglinton et Galbraith apportent une des premières modifications importantes au couplage de Glaser, soit l'utilisation d'une quantité sur-stœchiométrique d'acétate de cuivre (II) (Cu(OAc)<sub>2</sub>) en présence de pyridine dans le méthanol<sup>3</sup>. Quoique très similaire aux conditions originales de Glaser, ce nouveau protocole permettait le couplage oxydatif en formant *in situ* l'acétylure de cuivre, évitant du fait même son isolement problématique. Avec ces nouvelles conditions réactionnelles, Eglinton et son collègue ont synthétisé les premiers macrocycles comprenant un motif 1,3-butadiyne<sup>4</sup>. Par exemple, dans des conditions de dilution élevée (11 mM), le diyne **2.4** a pu être transformé en macrocycle **2.5** lorsqu'il réagit avec un excès de complexe de cuivre (II) (Schéma 2.1A).

Le grand désavantage des conditions d'Eglinton est l'utilisation d'une quantité stœchiométrique en cuivre. Cependant, ce problème a rapidement été résolu en 1962 lorsque Hay publia une version catalytique du couplage de Glaser<sup>5</sup>. L'utilisation d'une amine tertiaire,

comme le ligand bidenté *N,N,N',N'*-tétraméthyléthylènediamine (TMEDA), rend l'acétylure de cuivre formé très soluble dans la plupart des solvants organiques. Ceci a pour effet d'augmenter considérablement la vitesse de la réaction, de favoriser la purification, tout en ayant des conditions beaucoup plus douces. Pour ces raisons, l'utilisation de ces conditions réactionnelles est désormais très répandue dans la littérature et est maintenant connu sous le nom de réaction de couplage de Glaser-Hay<sup>6</sup>. Un exemple typique est la dimérisation du 1-éthynylcyclohexanol (**2.6**). En faisant réagir cet alcyne terminal avec 5 mol% du système catalytique CuCl/TMEDA, le dimère **2.7** est obtenu dans un rendement de 93 % en seulement 20 minutes (Schéma 2.1B).



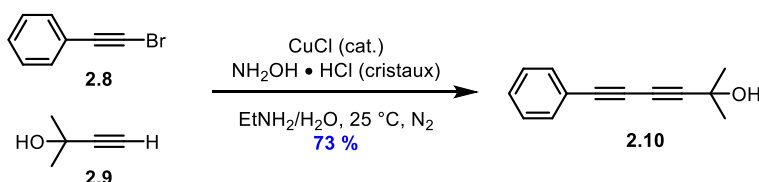
**Schéma 2.1** Modifications d'Eglinton (A) et de Hay (B) au couplage de Glaser

Depuis la découverte de Hay, plusieurs méthodes ont été développées pour la synthèse du motif 1,3-butadiyne par dimérisation d'alcynes terminaux ou substitués<sup>7</sup>. Il a été montré que plusieurs dérivés d'acétylure pouvaient subir un couplage oxydatif en présence de métaux comme le cuivre, le palladium ou le manganèse<sup>8</sup>. Parmi ces dérivés d'acétylure, on retrouve les dérivés silylés<sup>9</sup>, les borates<sup>10</sup> et trifluoroborates<sup>11</sup>, les organomagnésiens<sup>12</sup> et les organotelluriens<sup>13</sup>. Certains chercheurs ont également exploré différents agents oxydants pour remplacer l'oxygène moléculaire, comme le *N*-bromosuccinimide (NBS)<sup>14</sup> ou bien l'iode moléculaire (I<sub>2</sub>)<sup>15</sup>. Finalement, certains homocouplages réductifs ont été développés, impliquant soit des halogénures d'alcynes<sup>16</sup> ou tout simplement des alcynes terminaux en présence d'un catalyseur de cobalt et de poudre de zinc comme réducteur<sup>17</sup>.

## 2.2 Défis de synthèse des 1,3-diynes asymétriques

Le couplage de Glaser-Hay est probablement la méthode synthétique la plus pratique et directe pour la formation de 1,3-diynes symétriques. En revanche, la synthèse de 1,3-diynes asymétriques représente un défi de taille. Il a été observé que le pKa des protons alcyoniques a un effet important sur la vitesse de la réaction de couplage de Glaser-Hay<sup>5</sup>. Ainsi, si les partenaires de couplage ne sont pas assez similaires, un mélange statistique est obtenu et l'utilisation d'un excès du partenaire le moins réactif est souvent nécessaire afin de forcer la formation du produit d'hétérocouplage.

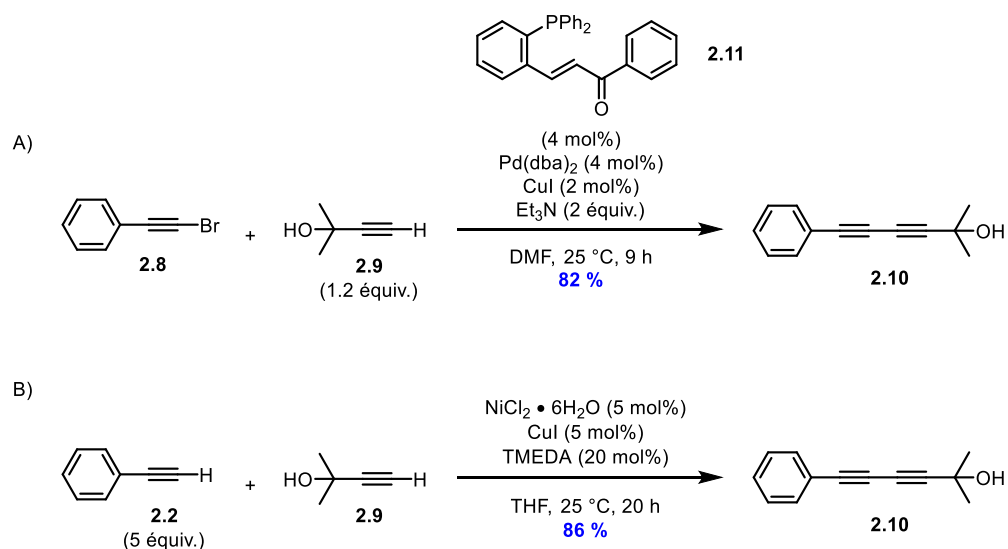
Pour relever ce défi synthétique, plusieurs méthodes visant à favoriser l'hétérocouplage sélectif pour la formation de 1,3-diynes asymétriques ont été développées<sup>18</sup>. Une première stratégie révolutionnaire a été rapportée en 1955 et est connu sous le nom de couplage de Cadiot-Chodkiewicz<sup>19</sup>. Il s'agit du couplage entre un halogénoalcyne **2.8** et un alcyne terminal **2.9** dans un milieu réducteur de cuivre (I) pour former le diyne **2.10** (Schéma 2.2). L'ajout d'hydroxylamine permet de maintenir un milieu réducteur, empêchant la source de cuivre d'atteindre un état d'oxydation de +2. De plus, la réaction doit se dérouler sous une atmosphère anaérobie, sans quoi la réaction de Glaser pourrait se produire et former le produit d'homocouplage de l'alcyne terminal.



**Schéma 2.2** Couplage de Cadiot-Chodkiewicz

Le principal désavantage du couplage de Cadiot-Chodkiewicz est la nécessité de préfonctionnaliser un des deux partenaires de couplage (formation de l'halogénoalcyne). En général, la transformation de l'alcyne terminal en halogénoalcyne se fait assez facilement en utilisant du NBS et du nitrate d'argent<sup>20</sup>. Toutefois, la stabilité de certains halogénoalcynes peut poser un problème lors d'une synthèse multi-étape. Il n'en demeure pas moins qu'il s'agit d'une méthode qui a été très utilisée dans la synthèse de produits naturels et autres poly-yne d'intérêt<sup>21</sup>.

Dans les dernières années, plusieurs travaux ont été publiés sur la formation de motifs 1,3-diynes asymétriques par le couplage d'alcynes. En 2008, Lei et ses collègues ont développé une variante du couplage de Cadiot-Chodkiewicz par l'addition d'un co-catalyseur de palladium (0) et d'un ligand bidenté phosphinoalcène (**2.11**)<sup>22</sup>. En utilisant ce nouveau système catalytique, le diyne **2.10** a pu être obtenu dans un rendement isolé de 82 % et une sélectivité de 92 % par rapport à la formation des produits d'homocouplage (Schéma 2.3A). Cependant, cette méthode utilisait encore un halogénoalcyne comme substrat. L'année suivante, le groupe de Lei a donc développé un autre système catalytique qui permettait la formation sélective de 1,3-diynes asymétriques à partir d'alcynes terminaux (Schéma 2.3B)<sup>23</sup>. Cette fois-ci, c'est un co-catalyseur de nickel (II) qui a été utilisé, permettant la formation du diyne **2.10** dans des conditions aérobiques douces. Toutefois, l'utilisation d'un excès du partenaire le plus réactif était nécessaire afin de maintenir une sélectivité satisfaisante.

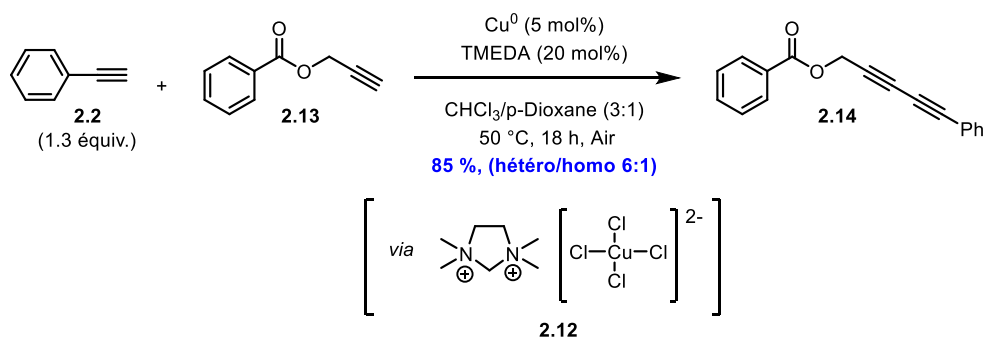


**Schéma 2.3** Travaux de Lei sur le développement d'hétérocouplages co-catalysés par un complexe de palladium (A) et de nickel (B)

En 2014, d'autres méthodes impliquant un catalyseur de cuivre sont apparues dans la littérature. D'abord, Ranu et ses collègues ont développé des nanoparticules composées de cuivre et de fer ( $\text{CuFe}_2\text{O}_4$ ) permettant le couplage entre des halogénoalcynes et des esters boroniques alcyniques afin de former une série de diynes asymétriques<sup>24</sup>. Les auteurs ont démontré une recyclabilité (jusqu'à 10 cycles) des nanoparticules, mais la méthode est limitée aux dérivés d'esters boroniques aryles.

Ensuite, le groupe de Young a opté pour une stratégie différente, soit l'immobilisation d'un des substrats sur un support solide. En utilisant des conditions traditionnelles de Glaser-Hay, les auteurs ont pu synthétiser une vaste librairie d'alcools et d'amines propargyliques à partir d'alcynes terminaux avec de bons rendements<sup>25</sup>. Cependant, cette technique comprend des désavantages évidents comme des étapes réactionnelles supplémentaires pour charger et cliver le substrat du support solide ainsi que l'utilisation d'un large excès du substrat secondaire (10 équiv.).

Enfin en 2016, Yin a découvert de nouvelles conditions sélectives pour la formation de 1,3-diynes asymétriques<sup>26</sup>. Il a observé qu'en chauffant une source de cuivre métallique en présence de TMEDA dans un mélange de chloroforme et de 1,4-dioxane, un précipité jaune se formait, correspondant au complexe de cuivre **2.12**. La particularité de ce complexe est qu'il permet une bonne sélectivité pour la formation de diynes asymétriques à partir d'alcynes terminaux électroniquement très différents. Par exemple, lorsque le dérivé d'acide benzoïque **2.13** est soumis dans les conditions réactionnelles avec du phénylacétylène (**2.2**), 85 % du diyne **2.14** est formé selon une sélectivité de 6 : 1 par rapport aux produits d'homocouplage (Schéma 2.4). Les détails mécanistiques ne sont pas élucidés, mais les auteurs ont postulé que l'efficacité du catalyseur en faveur de l'hétérocouplage provient d'une saturation électronique causée par les atomes de chlore, empêchant la coordination aux alcynes pauvres en électrons tout en favorisant l'échange de ligands avec ceux riches en électrons.

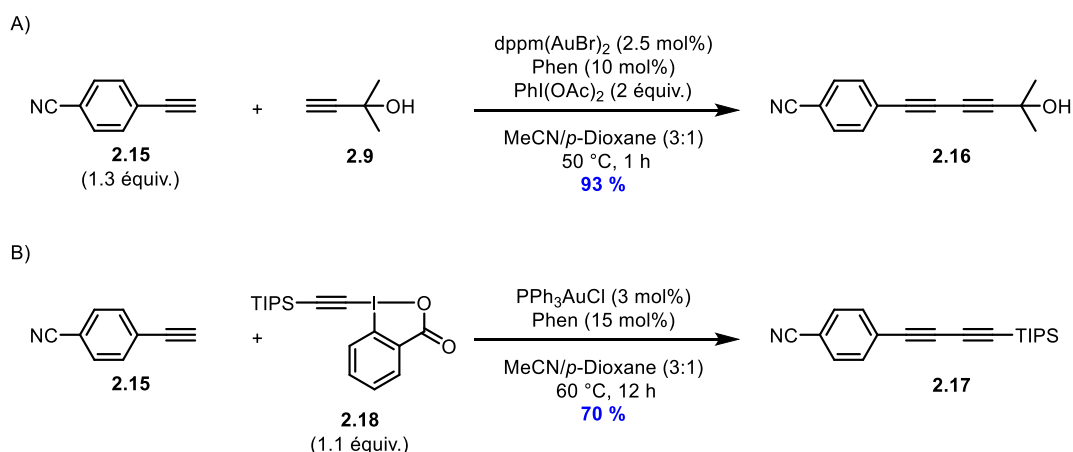


**Schéma 2.4** Formation sélective de 1,3-diynes asymétriques catalysée par un complexe de cuivre

L'usage de catalyseurs de cuivre pour la formation de diynes asymétriques n'est pas exclusif. En 2014, Shi et ses collègues ont montré que l'or peut aussi servir de catalyseur



sélectif pour l'hétérocouplage d'alcynes terminaux<sup>27</sup>. En utilisant le dimère d'or  $\text{dppm}(\text{AuBr})_2$  comme catalyseur et une quantité stœchiométrique d'oxydant  $(\text{PhI}(\text{OAc})_2)$ , un mélange 1.3 : 1 des alcynes **2.15** et **2.9** a pu être couplé pour former le diyne **2.16** avec 93 % de rendement (Schéma 2.5A). Plus récemment, Patil a aussi utilisé un catalyseur d'or ( $\text{PPh}_3\text{AuCl}$ ) pour coupler des alcynes terminaux avec des réactifs de type éthynylbenziodoxolone (EBX)<sup>28</sup>. Dans ces conditions, le diyne **2.17** a pu être obtenu sélectivement à partir de l'alcyne terminal **2.15** et du réactif **2.18** (Schéma 2.5B). Ingénieusement, aucun oxydant externe n'est nécessaire puisque le réactif EBX sert à la fois de substrat activé et d'oxydant. Toutefois, ce double rôle limite grandement l'étendue de la réaction (efficacité acceptable seulement pour les dérivés d'EBX silylés).



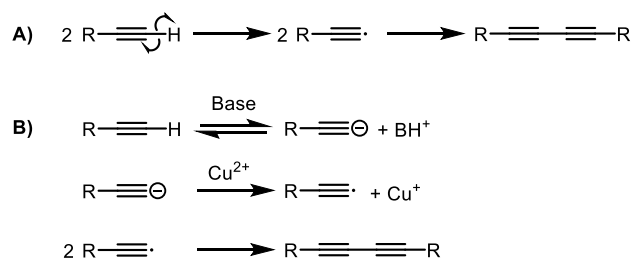
**Schéma 2.5** Formation sélective de 1,3-diyne asymétriques catalysée à l'or par Shi (A) et Patil (B)

## 2.3 Mécanisme du couplage de Glaser-Hay

### 2.3.1 Études expérimentales

Les hypothèses mécanistiques de la réaction de Glaser-Hay ont beaucoup changé au fil des ans. D'un côté, il s'agit d'une très vieille réaction et la compréhension de la chimie d'aujourd'hui est beaucoup plus avancée qu'il y a 150 ans. D'un autre côté, la réaction de Glaser a subi plusieurs modifications au niveau de ses conditions réactionnelles depuis sa découverte, causant nécessairement un changement évident au niveau mécanistique.

Le premier postulat mécanistique du couplage de Glaser a été fait en 1936 par Zalkind et Fundyler, stipulant qu'un clivage homolytique du lien C-H alcyne produirait un acétylène radicalaire et le produit de couplage serait obtenu par recombinaison radicalaire (Figure 2.2A)<sup>29</sup>. Un des problèmes majeurs de ce mécanisme est l'omission du rôle de l'atome de cuivre ainsi que des additifs. Ce mécanisme a tout de même été accepté pendant une vingtaine d'année, jusqu'à ce que Klebanski et ses collègues effectuent des expériences cinétiques et identifient le rôle des ions cuivrique ( $\text{Cu}^{2+}$ ) comme étant l'agent oxydant<sup>30</sup>. De plus, ils ont observé que la vitesse de la réaction était accélérée en milieu basique et qu'il y avait une dépendance du pKa du proton alcyne sur la vitesse réactionnelle (réaction plus rapide avec un proton alcyne plus acide). Klebanski propose donc que le mécanisme passe d'abord par une étape de déprotonation réversible suivie d'une oxydation de l'acétylure par l'atome de cuivre pour enfin former le 1,3-diène par recombinaison radicalaire (Figure 2.2B).

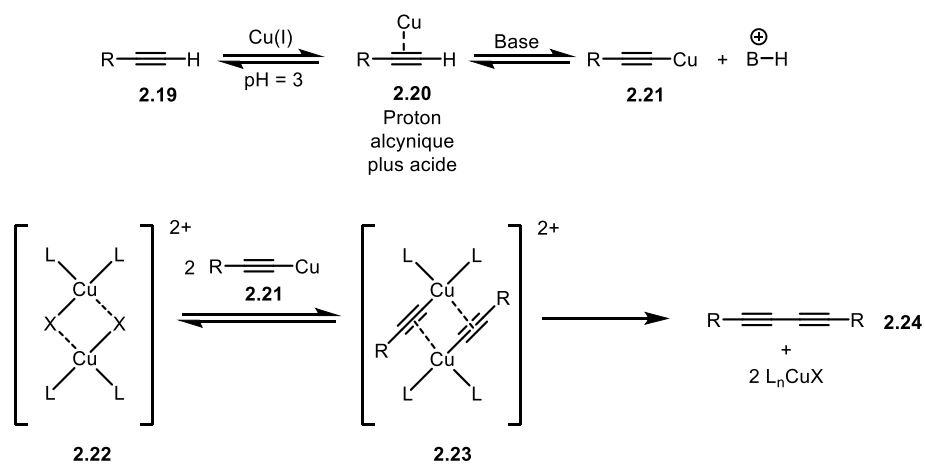


**Figure 2.2** Mécanismes proposés par Zalkind (A) et Klebinski (B)

Quelques années plus tard, Clifford et Waters ont découvert l'importance des ions  $\text{Cu}^+$  et proposent pour la première fois l'implication d'un acétylure de cuivre<sup>31</sup>. L'idée de la formation d'acétylure de cuivre suivie d'une recombinaison radicalaire a été appuyée par Eglinton. Dans la publication de ses travaux sur la synthèse de macrocycles par couplage oxydatif au cuivre, Eglinton met en doute l'existence d'un sel de cuivre cyclique et donc soutient la formation du produit final par recombinaison radicalaire issue de la décomposition des complexes de cuivre formés<sup>4</sup>.

En 1964, l'hypothèse mécanistique du couplage de Glaser a pris un tournant drastique lorsque Bohlmann réfuta complètement l'idée d'un mécanisme radicalaire<sup>32</sup>. En effet, il a rationalisé que si l'obtention du produit de couplage était le résultat d'une recombinaison radicalaire, le mélange de deux alcynes terminaux différents donnerait un mélange statistique

de 2 : 1 : 1 pour le produit d'hétérocouplage et des produits d'homocouplage respectivement. En mélangeant deux alcynes assez différents électroniquement, il a observé que l'alcyne le plus activé réagissait rapidement pour donner presque exclusivement le produit d'homocouplage (> 99%) avec seulement des traces de produit d'hétérocouplage (< 1%). En revanche, en utilisant deux alcynes électroniquement semblables, une plus grande proportion du produit d'hétérocouplage (39%) a été observée. La sélectivité de la première expérience ne pouvant être expliquée par le mécanisme radicalaire, Bohlmann a conclu que le couplage des alcynes terminaux devait nécessairement passer par la formation de complexes de cuivre. Bohlmann a aussi démontré que le cuivre jouait un rôle important dans l'étape de déprotonation. Comme Klebanski et Clifford, il a observé que plus le milieu réactionnel était basique, plus la réaction était rapide. Cependant, en milieu acide (pH = 3), l'ajout d'un sel de cuivre (I) permettait tout de même la déprotonation de l'alcyne terminal **2.19**. Il a donc posé comme hypothèse que les ions cuivreux formaient un complexe  $\pi$  avec la liaison triple (**2.20**), ce qui rendrait le proton alcyinique plus acide et permettrait la formation d'acétylure de cuivre **2.21** (Figure 2.3). À partir de ces observations, Bohlmann a proposé un mécanisme général dans lequel il y aurait la formation d'un complexe dimérique d'acétylures de cuivre **2.23**.



**Figure 2.3** Formation d'un complexe dimérique d'acétylures de cuivre proposé par Bohlmann

Finalement, Fedenok *et al.* ont confirmé qu'il y avait bel et bien un lien entre l'acidité du proton alcyinique et la vitesse de la réaction de couplage<sup>33</sup>. Ils ont étudié la cinétique de la

réaction de plusieurs phénylacétylènes substitués en position *para* et ont observé une corrélation entre la constante  $\sigma$  d'Hammett et la vitesse réactionnelle.

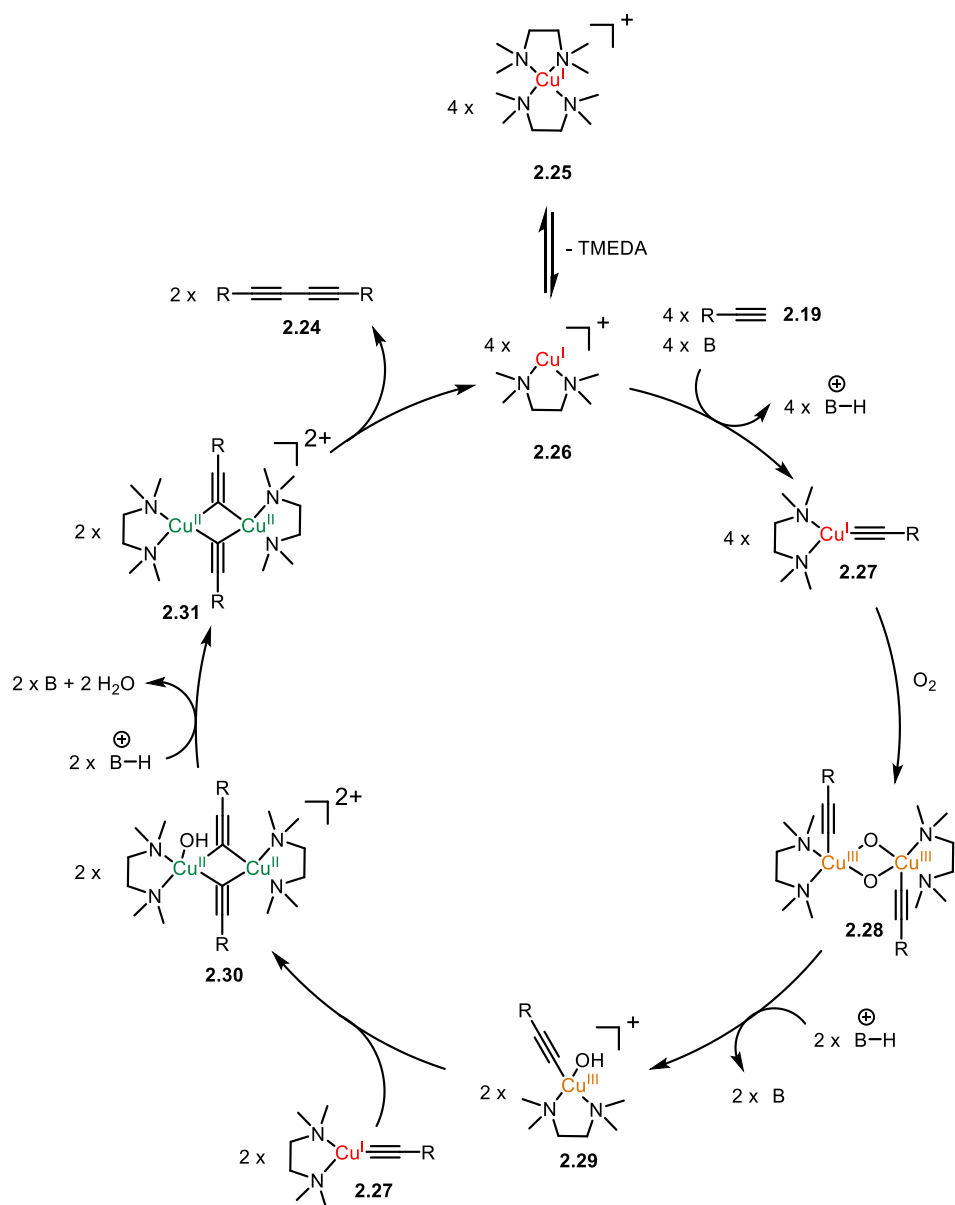
Les études expérimentales du mécanisme de la réaction de Glaser sont difficiles à réaliser puisque la réaction est assez rapide et difficile à étudier, par exemple, par RMN  $^1\text{H}$  à cause du caractère paramagnétique de certains complexes de cuivre intermédiaires. Certaines expériences de RMN  $^{13}\text{C}$  ou bien de spectroscopie UV-Vis ont été réalisées<sup>34</sup>, mais la réaction semble s'adapter aux différentes conditions et fonctionne quasiment dans tous les cas. Malgré plusieurs efforts expérimentaux pour élucider le mécanisme de la réaction de Glaser, celle-ci reste encore bien mal comprise. Le mécanisme semble s'avérer beaucoup plus complexe que ce qui était imaginé à l'origine par Zalkind, Klebanski et Clifford, mais tous ces travaux ont permis d'établir avec certitude trois aspects importants de cette réaction: 1) l'obtention du produit de couplage ne passe pas par une simple recombinaison de radicaux; 2) la vitesse réactionnelle dépend grandement de l'acidité du proton alcyne et les atomes de cuivre aident à la déprotonation via une complexation  $\pi$ ; 3) les ions  $\text{Cu}^+$  et  $\text{Cu}^{2+}$  jouent tous les deux un rôle dans la réaction et forment possiblement des complexes de cuivres dimériques comportant des acétylures.

### 2.3.2 Études computationnelles

Depuis plusieurs années, les études computationnelles évoluent de plus en plus et deviennent des outils intéressants pour l'étude de mécanismes réactionnels complexes comme celui de la réaction de Glaser-Hay. Deux études mécanistiques, utilisant une approche DFT (*Density Functional Theory*), ont été réalisées dans les dernières années. Les études de Fomine<sup>35</sup> et de Maseras<sup>36</sup> sont basées sur le mécanisme de Bohlmann et essaient d'expliquer, par un mécanisme complet, les observations expérimentales obtenues par le passé, soit l'indifférence de la nature de l'oxydant et la dépendance de l'acidité du proton alcyne sur la vitesse réactionnelle (Figure 2.4).

Dans les conditions réactionnelles, il y a généralement un excès du ligand TMEDA par rapport à la source de cuivre. Comme le TMEDA est un excellent ligand, il y a formation d'un complexe stable **2.25** qui est cependant inactif. À la suite de la perte d'un ligand, le complexe cationique **2.26** peut effectuer la cupration de l'alcyne terminal pour former l'acétylure de

cuivre **2.27**. Une partie des acétylures de cuivre **2.27** est ensuite oxydée par l'oxygène moléculaire afin de former le complexe dimérique bis( $\mu$ -oxo)- $\sigma$ -diacétylure de cuivre (III) **2.28**. Des complexes de cuivre similaires ont déjà été isolés et caractérisés par diffraction des rayons X<sup>37</sup>. La protonation du dimère de cuivre (III) enclenche sa décomposition en hydroxy- $\sigma$ -acétylure de cuivre (III) **2.29**. À ce stade du mécanisme, le complexe de cuivre (III) **2.29** et le complexe de cuivre (I) **2.27** formé précédemment participeraient à une réaction rédox dans laquelle le complexe bimétallique de cuivre (II) **2.30** serait obtenu. La protonation du ligand hydroxyle suivie de la perte d'une molécule d'eau donnerait le complexe **2.31**. Ce type de complexe Cu(II)<sub>2</sub>( $\mu$ -C $\equiv$ CR)<sub>2</sub> a déjà été observé par Yamaguchi et ses collègues par l'usage de diverses techniques analytiques<sup>38</sup>. Ces chercheurs ont également observé que la quantité molaire d'eau formée était proportionnelle à la quantité molaire du produit de couplage. Finalement, une élimination réductrice du complexe bimétallique de cuivre (II) **2.31** donnerait le produit de couplage **2.24**, tout en reformant le complexe initial de cuivre (I) **2.26**.

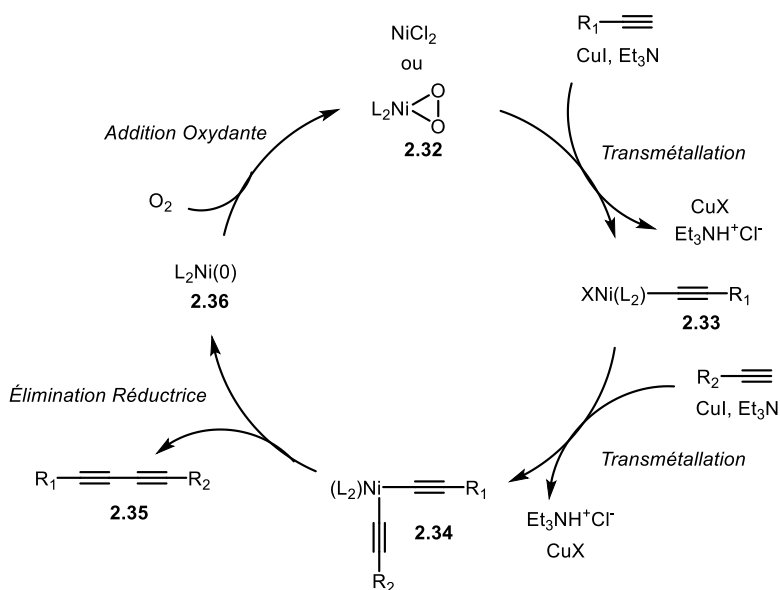


**Figure 2.4** Mécanisme du couplage de Glaser-Hay basé sur l'étude DFT de Maseras

Le bilan global de la transformation d'alcynes terminaux en 1,3-diynes serait la consommation d'une molécule d'oxygène et la production de molécules d'eau. Selon les calculs de Maseras, le couplage serait exergonique de -56,9 kcal/mol, et la formation de l'acétylure de cuivre (I) **2.27** serait l'étape limitante (17,5 kcal/mol). Ces données respectent les observations faites par les données expérimentales quant aux vitesses relatives des différents alcynes terminaux, à l'absence d'effet notable de la nature de l'oxydant et aux conditions douces associées à la réaction de Glaser-Hay.

### 2.3.3 Couplage de Glaser-Hay co-catalysé par un complexe de nickel

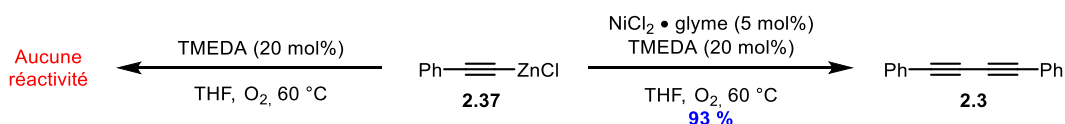
Pour les cas mécanistiques discutés précédemment, les systèmes étaient constitués d'un seul catalyseur de cuivre. Dans un système de co-catalyse avec un complexe de nickel, le mécanisme doit nécessairement être bien différent. Le mécanisme proposé par Lei (Figure 2.5)<sup>39</sup> ressemble grandement à un mécanisme classique de couplage au palladium<sup>40</sup>. Les premières étapes du mécanisme seraient deux étapes consécutives de transmétallation entre l'espèce de nickel(II) **2.32** et les acétylures **2.19** de cuivre formés *in situ* pour générer un complexe bis- $\sigma$ -acétylure de nickel(II) **2.34**. Ensuite, une étape d'élimination réductrice donnerait le 1,3-diyne asymétrique **2.35** ainsi que le complexe de nickel(0) **2.36**. Ce dernier réagirait rapidement avec l'oxygène présent en solution pour former le complexe ( $\eta^2$ -peroxo)Ni(II) **2.32** qui pourrait à son tour participer dans des étapes de transmétallation. En effet, il a déjà été observé que le nickel(0) pouvait former rapidement des complexes ( $\eta^2$ -peroxo)Ni(II) lorsqu'il se retrouve en présence d'oxygène<sup>41</sup>.



**Figure 2.5** Mécanisme proposé pour l'hétérocouplage oxydatif d'alcynes terminaux co-catalysé par un complexe de nickel

Par le biais d'expériences mécanistiques, le groupe de Lei a pu confirmer le rôle précis du nickel. Pour ce faire, les auteurs ont préformé un acétylure de zinc(II) (**2.37**), un intermédiaire stable qui ne produit pas, à lui seul, de composé 1,3-diyne **2.3**. En revanche, lorsque cet acétylure de zinc **2.37** est mis en présence de nickel(II), le produit de couplage est

obtenu à 93 %, confirmant les étapes de transmétallation des acétylures vers l'atome de nickel suivies d'une élimination réductrice (Schéma 2.6). Ils ont aussi observé que l'ajout du co-catalyseur de nickel(II) augmentait significativement la vitesse réactionnelle, soit de près d'un facteur de quatre. Ceci reflèterait une meilleure capacité du nickel à participer dans une étape d'élimination réductrice comparativement aux catalyseurs de cuivre. Finalement, les auteurs ont mesuré que le ratio molaire entre la consommation d'oxygène et la production du produit de couplage était de 1 : 1, un ratio qui était de 1 : 2 dans le cas de la catalyse uniquement au cuivre. Ceci s'explique par le fait que l'oxydation du nickel par l'oxygène s'effectue sur un seul atome métallique contrairement à la catalyse avec un complexe de cuivre où les deux atomes du dimère de cuivre doivent être oxydés.



**Schéma 2.6** Démonstration de la participation du nickel dans les étapes de transmétallation et d'élimination réductrice

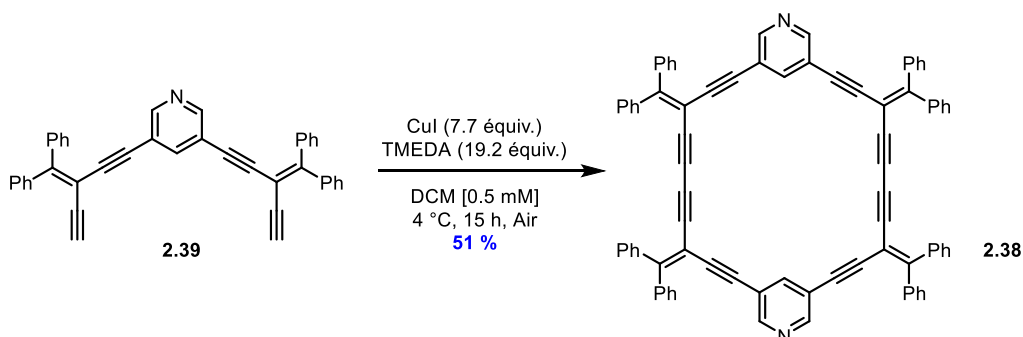
## 2.4 Applications du couplage de Glaser-Hay

La dimérisation oxydative d'alcynes terminaux est une réaction très intéressante puisqu'il s'agit de la voie synthétique la plus directe et efficace pour la synthèse de motifs 1,3-diynes conjugués<sup>42</sup>. La simple idée d'utiliser une approche catalytique avec un complexe de cuivre tout en ne produisant que des molécules d'eau comme sous-produit stœchiométrique a suscité l'intérêt de la communauté scientifique<sup>43</sup>.

Toutefois, l'application de la réaction de couplage de Glaser-Hay n'a que très peu été utilisée dans le domaine de la synthèse totale à cause de son manque de sélectivité pour la formation de motifs 1,3-diynes asymétriques. En effet, il est rare de retrouver des produits naturels issus d'une dimérisation symétrique d'alcynes terminaux. Par conséquent, la communauté de chimistes organiciens s'est plutôt tournée vers des conditions de couplage plus sélectives comme le couplage de Cadiot-Chodkiewicz<sup>40</sup>. Cependant, la réaction de Glaser-Hay a connu du succès dans d'autres sphères de la chimie, notamment dans le domaine de la chimie supramoléculaire et la chimie des matériaux. Par exemple, Tykwinski a utilisé le couplage de Glaser-Hay pour la synthèse du pyridinophane **2.38** par dimérisation du



précurseur **2.39** (Schéma 2.7)<sup>44</sup>. Ce type de macrocycle à structure permanente peut être utilisé comme ligand analogue à la 4,4'-bipyridine pour la construction de systèmes auto-assemblés.



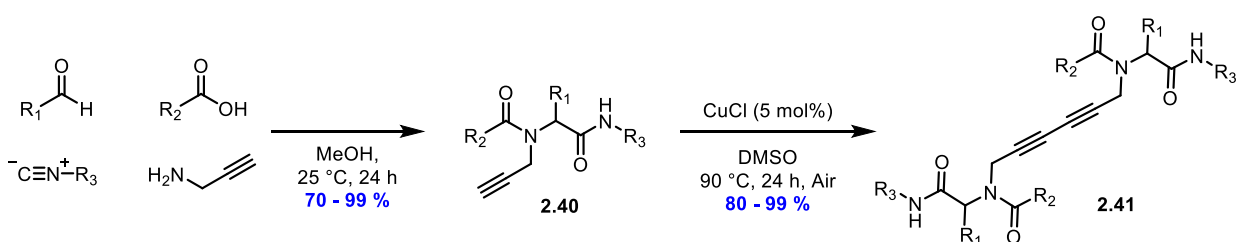
**Schéma 2.7** Synthèse de pyridinophanes par couplage oxydatif d'alcynes terminaux

La réaction de Glaser-Hay a aussi été utilisée pour la formation de paracyclophanes. En effet, Tschierske a rapporté la synthèse de cristaux liquides macrocycliques contenant un motif 1,3-diène synthétisé par une version macrocyclique de la réaction de Glaser-Hay<sup>45</sup>. Plus récemment, notre groupe de recherche a également utilisé ce couplage oxydatif pour effectuer la synthèse de paracyclophanes contenant le motif 1,3-diène dans leur chaîne *ansa*<sup>46</sup>.

L'application du couplage de Glaser-Hay a également été exploitée dans le domaine de la biochimie. Il est connu que le motif 1,3-diène possède une intensité Raman assez importante. Cette propriété a été exploitée par Sodeoka et ses collègues afin de fonctionnaliser de petites molécules d'intérêt et d'étudier par imagerie Raman leur mouvement dans des cellules vivantes<sup>47</sup>. En 2003, le groupe de Matsuda a utilisé le couplage oxydatif de Glaser-Hay afin de modifier des oligodésoxynucléotides supportés directement sur la colonne utilisée lors de leur synthèse automatisée<sup>48</sup>. Plus récemment, Dawson et ses collègues ont développé un protocole robuste de type Glaser-Hay pour la modification de peptides agonistes du récepteur GLP-1R<sup>49</sup>. Ces deux méthodes ont permis aux auteurs l'incorporation d'étiquettes (*tag*) intéressantes pour des études biologiques comme les étiquettes d'affinité (Biotine), de fluorophores (ombelliférone ou fluorescéine) et de PEGylation.

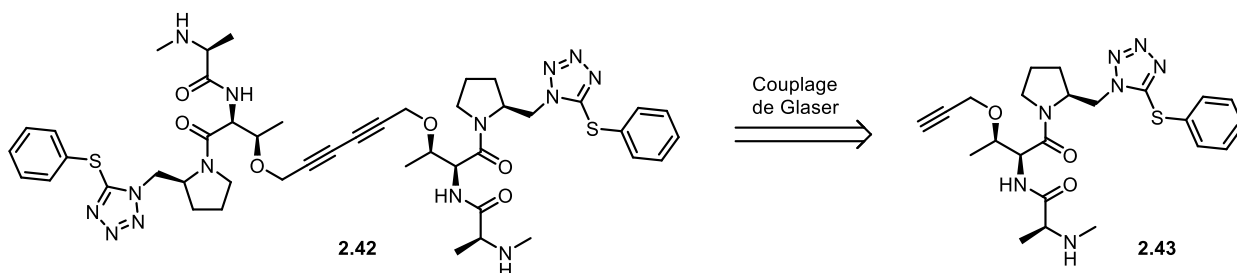
Le couplage oxydatif d'alcynes terminaux a également été utilisé afin de rigidifier des tétrapeptides macrocycliques substitués avec des alcynes terminaux<sup>50</sup>. Il a été établi que l'étape de fermeture de cycle avec la réaction de Glaser pouvait être réalisée en solution sur le peptide libre (68 % de rendement) ou directement sur le support solide utilisé pour la synthèse

du précurseur (90 % de rendement). Finalement, Wessjohann a synthétisé une série de composés antibactériens par des réactions séquentielles d'Ugi et de Glaser (Schéma 2.8)<sup>51</sup>. Dans une première étape, une série d'aldéhydes, d'acides carboxyliques, d'isocyanures sont mélangés en présence d'amines propargyliques afin de former des peptoïdes (**2.40**) portant un alcyne terminal (70 – 99 %). Ensuite, ces peptoïdes subissent une homodimérisation dans des conditions aérobiques et catalytiques de cuivre (80 – 99 %). Dans une étude biologique, les auteurs ont démontré que certains de ces dimères (**2.41**) permettaient d'inhiber en partie la croissance d'une souche de bactérie (*Bacillus subtilis*).



**Schéma 2.8** Formation de dimères peptoïdes antibactériens par réactions séquentielles d'Ugi et de Glaser

L'effet biologique du motif 1,3-diène a également été observé en 2004 par Harran<sup>52</sup>. Dans cette étude, les auteurs ont identifié le composé **2.42** qui a la propriété de mimer la complexation de la protéine *Smac* à divers inhibiteurs de l'enzyme *caspase*, l'enzyme responsable de l'apoptose des cellules humaines cancéreuses (Figure 2.6). La particularité de ce composé dimérique est l'inactivité totale de son monomère **2.43** (même en excès), montrant l'importance biologique du motif 1,3-diène dans ce système.



**Figure 2.6** Structures du mime protéique dimérique **2.42** et son monomère inactif **2.43**

## 2.5 Conclusion

Le couplage de Glaser a beaucoup évolué depuis sa découverte il y a 150 ans. Les contributions d'Eglinton et de Hay ont permis d'élaborer des protocoles robustes et sécuritaires pour la formation de liens carbone-carbone par couplage oxydatif d'alcynes terminaux. Bien que les détails mécanistiques restent encore à être élucidés, la réaction de couplage de Glaser (et toutes ses variantes) a été appliquée dans plusieurs sphères de la chimie pour la synthèse et la fonctionnalisation de molécules d'intérêt par le biais de la construction du motif 1,3-diyne.

## 2.6 Bibliographie

1. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422 – 424. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, 154, 137 - 171.
2. Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1882**, 15, 50 – 56.
3. Eglinton, G; Galbraith, A. R. *Chem. Ind.* **1956**, 737 – 738.
4. Eglinton, G; Galbraith, A. R. *J. Chem. Soc.* **1959**, 889 – 896.
5. Hay, A. S. *J. Org. Chem.* **1962**, 27, 3320 – 3321.
6. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, 39, 2632 – 2657.
7. Sindhu, K. S.; Anilkumar, G. *RSC Adv.* **2014**, 4, 27867 - 27887.
8. Shi, W.; Lei, A. *Tetrahedron Lett.* **2014**, 55, 2763 – 2772.
9. Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, 65, 1780 – 1787.
10. Oh, C. H.; Reddy, V. R. *Tetrahedron Lett.* **2004**, 45, 5221 – 5224.
11. Paixão, M. W.; Weber, M.; Bragad, A. L.; de Azeredod, J. B.; Deobaldd, A. M.; Stefani, H. A. *Tetrahedron Lett.* **2008**, 49, 2366 – 2370.
12. Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, 129, 13788 – 13789.
13. Singh, F. V.; Amaral, M. F. Z. J.; Stefani, H. A. *Tetrahedron Lett.* **2009**, 50, 2636 – 2639.
14. Li, L.; Wang, J.; Zhang, G.; Liu, Q. *Tetrahedron Lett.* **2009**, 50, 4033 – 4036.
15. Li, D.; Yin, K.; Li, J.; Jia, X. *Tetrahedron Lett.* **2008**, 49, 5918 – 5919.
16. (a) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, 68, 7085 – 7087. (b) Chen, Z.; Jiang, H.; Wang, A.; Yang, S. *J. Org. Chem.* **2010**, 75, 6700 – 6703.
17. Hilt, G.; Hengst, C.; Arndt, M. *Synthesis* **2009**, 395 – 398.

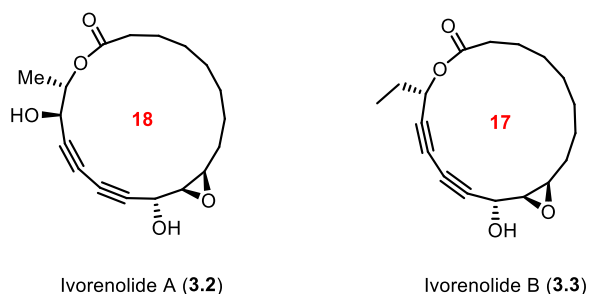
18. Shi, W.; Lei, A. *Tetrahedron Lett.* **2014**, *55*, 2763 – 2772.
19. Chodkiewicz, W.; Cadiot, P. *C. R. Hebd. Séances Acad. Sci.* **1955**, *241*, 1055 - 1057.
20. Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* **2006**, *128*, 8336 - 8340.
21. Sindhu, K. S.; Thankachan, A. P.; Sajitha P. S.; Anilkumar, G. *Org. Biomol. Chem.* **2015**, *13*, 6891- 6905.
22. (a) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 14713 – 14720. (b) Weng, Y.; Cheng, B.; He, C.; Lei, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 9547 - 9551.
23. Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2008**, *11*, 709 - 712.
24. Ahammed, S.; Kundu, D.; Ranu B. C. *J. Org. Chem.* **2014**, *79*, 7391 – 7398.
25. Tripp, V. T.; Lampkowski, J. S.; Tyler, R.; Young, D. D. *ACS Comb. Sci.* **2014**, *16*, 164 – 167.
26. Su, L.; Dong, J.; Liu, L.; Sun, M.; Qiu, R.; Zhou, Y.; Yin, S.-F. *J. Am. Chem. Soc.* **2016**, *138*, 12348 – 12351.
27. Peng, H.; Xi, Y.; Ronaghi, N.; Dong, B.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2014**, *136*, 13174 – 13177.
28. Banerjee, S.; Patil, N. T. *Chem. Commun.* **2017**, *53*, 7937 – 7940.
29. Zalkind, Y. S.; Fundyler, F. B., *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 128 - 130.
30. Klebanski, A. L.; Grachev, I. V.; Kuznetsova, O. M., *J. Gen. Chem. USSR* **1957**, *27*, 3008 - 3013.
31. Clifford, A. A.; Waters, W. A., *J. Chem. Soc.* **1963**, 3056 - 3062.
32. Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G., *Chem. Ber.* **1964**, *97*, 794 - 800.
33. Fedenok, L. G.; Berdnikov, V. M.; Shvartsberg, M. S., *J. Org. Chem. USSR* **1974**, *10*, 934 - 936.
34. Vilhelmsen, M. H.; Jensen, J.; Tortzen, C. G.; Nielsen, M. B., *Eur. J. Org. Chem.* **2013**, 701.
35. Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S., *Tetrahedron* **2002**, *58*, 6741 - 6747.
36. Jover, J.; Spuhler, P.; Zhao, L.; McArdleb, C.; Maseras, F., *Catal. Sci. Technol.* **2014**, *4*, 4200 - 4209.
37. (a) Aboellella, N. W.; Lewis, E. A.; Reynolds, A. M.; Brennessel, W. W.; Cramer, C. J.; Tolman, W. B., *J. Am. Chem. Soc.* **2002**, *124*, 10660 - 10661; (b) Fujisawa, K.; Tanaka, M.; Moro-oka, Y.; Kitajima, N., *J. Am. Chem. Soc.* **1994**, *116*, 12079 - 12080. (c) Kang, P.; Bobyr, E.; Dustman, J.; Hodgson, K. O.; Hedman, B.; Solomon, E. I.; Stack, T. D. P., *Inorg. Chem.* **2010**, *49*, 11030 - 11038; (d) Spencer, D. J. E.; Aboellella, N. W.; Reynolds, A. M.; Holland, P. L.; Tolman, W. B., *J. Am. Chem. Soc.* **2002**, *124*, 2108 - 2109.
38. Yamaguchi, K.; Kamata, K.; Yamaguchi, S.; Kotani, M.; Mizuno, N., *J. Catal.* **2008**, *258*, 121 - 130.

39. Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709 – 712.
40. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085.
41. (a) Kieber-Emmons, M.; Riordan, C. G., *Acc. Chem. Res.* **2007**, *40*, 618 - 625. (b) Lanci, M. P.; Brinkley, D. W.; Stone, K. L.; Smirnov, V. V.; Roth, J. P., *Angew. Chem. Int. Ed.* **2005**, *44*, 7273 - 7276.
42. Lumb, J.-P. *The Oxidative Dimerization of Acetylenes and Related Reactions: Synthesis and Applications of Conjugated 1,3-Diynes*. WILEY-VCH Verlag GmbH & Co. KGaA : Weinheim, **2014**.
43. Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234 – 6458.
44. Campbell, K.; McDonald, R.; Branda, N. R.; Tykwinski, R. R. *Org. Lett.* **2001**, *3*, 1045 – 1048.
45. Hegmann, T.; Neumann, B.; Wolf, R.; Tschierske, C. *J. Mater. Chem.* **2005**, *15*, 1025 – 1034.
46. Bolduc, P.; Jacques, A.; Collins, S. K. *J. Am. Chem. Soc.* **2010**, *132*, 12790 - 12791.
47. Yamakoshi, H.; Dodo, K.; Palonpon, A.; Ando, J.; Fujita, K.; Kawata, S.; Sodeoka, M. *J. Am. Chem. Soc.* **2012**, *134*, 20681 - 20689.
48. Minakawa, N.; Ono, Y.; Matsuda, A. *J. Am. Chem. Soc.* **2003**, *125*, 11545 – 11552.
49. Silvestri, A. P.; Cistrone, P. A.; Dawson, P. E. *Angew. Chem. Int. Ed.* **2017**, *56*, 10438 – 10442.
50. Verlinden, S.; Geudens, N.; Martins, J. C.; Tourwe, D.; Ballet, S.; Verniest, G. *Org. Biomol. Chem.* **2015**, *13*, 9398 – 9404.
51. Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. *Beilstein J. Org. Chem.* **2015**, *11*, 25 – 30.
52. Li, L.; Thomas, R. M.; Suzuki, H.; De Brabander, J. K.; Wang, X.; Harran, P. G. *Science* **2004**, *305*, 1471 – 1474.



### 3.1 Découverte et synthèse des ivorenolides A et B par Yue

De 2012 à 2014, un groupe de chercheurs chinois a extrait de l'écorce du tronc de l'acajou d'Afrique (*Khaya ivorensis*) une nouvelle classe de molécules montrant une activité cytotoxique, anti-inflammatoire et anti-malariale. Parmi cet extrait, ils ont isolé deux nouvelles molécules naturelles, soit les ivorenolides A (**3.2**)<sup>5</sup> et B (**3.3**)<sup>6</sup> (Figure 3.2). L'ivorenolide A (**3.2**) est une macrolactone de 18 chaînons possédant cinq stéréocentres. Cette dernière présente également des effets immunosuppresseurs intéressants (CI<sub>50</sub> = 4,80 μM) face à la prolifération des lymphocytes T via l'inhibition de la glycoprotéine concanavaleine A (ConA). Pour sa part, l'ivorenolide B (**3.3**) est une macrolactone de 17 atomes avec quatre centres stéréogéniques. Une caractéristique particulière de ces nouvelles molécules est qu'il s'agit des premiers composés macrocycliques naturels possédant un système conjugué de type 1,3-butadiyne.

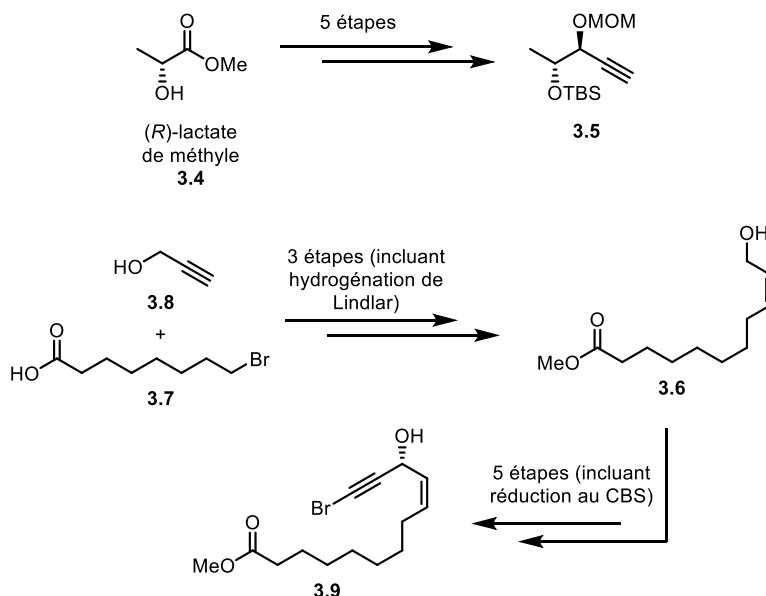


**Figure 3.2** Structures des ivorenolides A et B

#### 3.1.1 Synthèse totale de l'énantiomère non naturel de l'ivorenolide A

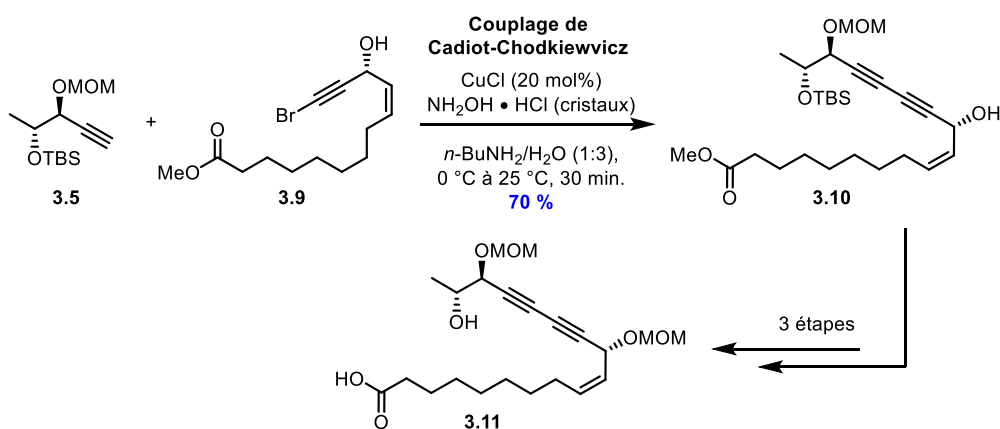
Yue et ses collègues<sup>5</sup> ont élucidé la structure d'ivorenolide A (**3.2**) en utilisant diverses techniques d'analyse telles que la spectroscopie de diffraction des rayons X et la spectroscopie RMN. Toutefois, ces techniques analytiques n'ont pas permis de déterminer la stéréochimie absolue du produit naturel. Ils se sont donc tournés vers la synthèse totale pour y parvenir. Il s'agit d'une synthèse convergente de deux fragments en 12 étapes linéaires (22 % de rendement global) débutant par la transformation du chiron (*R*)-lactate de méthyle (**3.4**) en alcyne terminal **3.5** par une série de réactions de protection et une alcynylation stéréosélective. Parallèlement, les auteurs ont construit la chaîne aliphatique **3.6** comprenant un alcène *Z* obtenu par hydrogénation catalytique de Lindlar à partir de l'acide 8-bromooctanoïque (**3.7**) et de l'alcool propargylique (**3.8**). Une série de modifications, incluant une réduction au CBS-

oxazaborolidine, a été faite pour finalement obtenir la chaîne **3.9** possédant un bromoalcyne (Figure 3.3).



**Figure 3.3** Premières étapes de la synthèse de l'énantiomère d'ivorenolide A par Yue

Un couplage de Cadiot-Chodkiewicz catalysé par un complexe de cuivre (I) en milieu réducteur a ensuite permis de former le motif 1,3-butadiyne à partir de l'alcyne terminal **3.5** et du bromoalcyne **3.9**. Le précurseur linéaire, le *seco*-acide **3.11**, a ainsi été obtenu à la suite de manipulations de groupements protecteurs (Schéma 3.1).

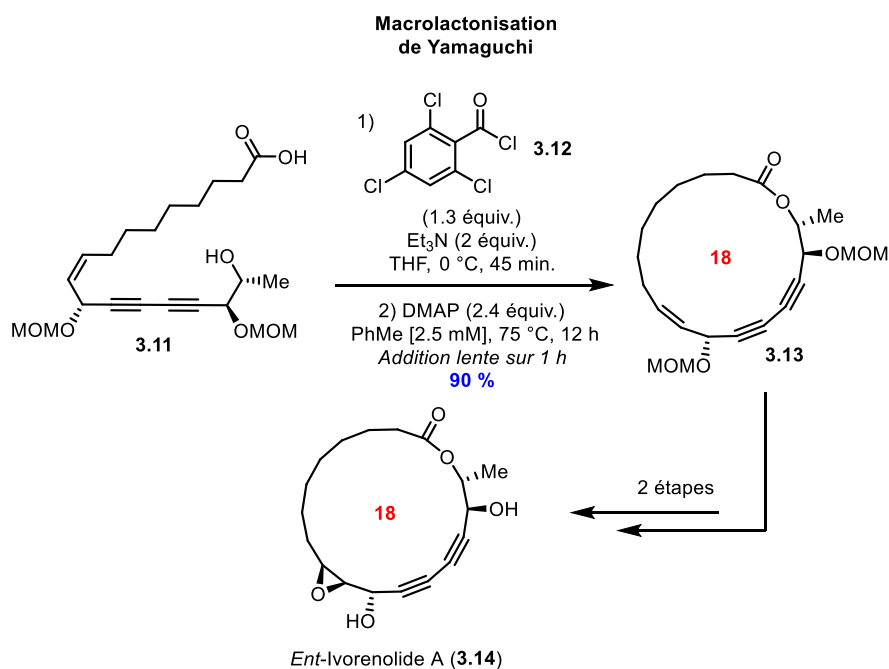


**Schéma 3.1** Couplage de Cadiot-Chodkiewicz et formation du *seco*-acide **3.11**

L'étape clé de fermeture de cycle a finalement été réalisée selon le protocole de macrocyclisation de Yamaguchi (Schéma 3.2). Ce protocole consiste à faire réagir le *seco*-



acide **3.11** avec le chlorure de 2,4,6-trichlorobenzyle (**3.12**) en présence de Et<sub>3</sub>N afin de former *in situ* un anhydride mixte. Une addition lente de ce dernier à un mélange très dilué (2.5 mM) de DMAP/PhMe permet d'obtenir le macrocycle **3.13** avec un rendement de 90 %. Une fois les dernières étapes de la synthèse complétées, soit la déprotection des alcools propargyliques et une époxydation au *m*-CPBA, les auteurs ont déterminé analytiquement que le produit final obtenu était en fait l'énantiomère non-naturel **3.14** de l'ivorenolide A (**3.2**). Étonnamment, ils ont observé que le produit synthétique possédait une activité immunosuppressive plus importante que le produit naturel.



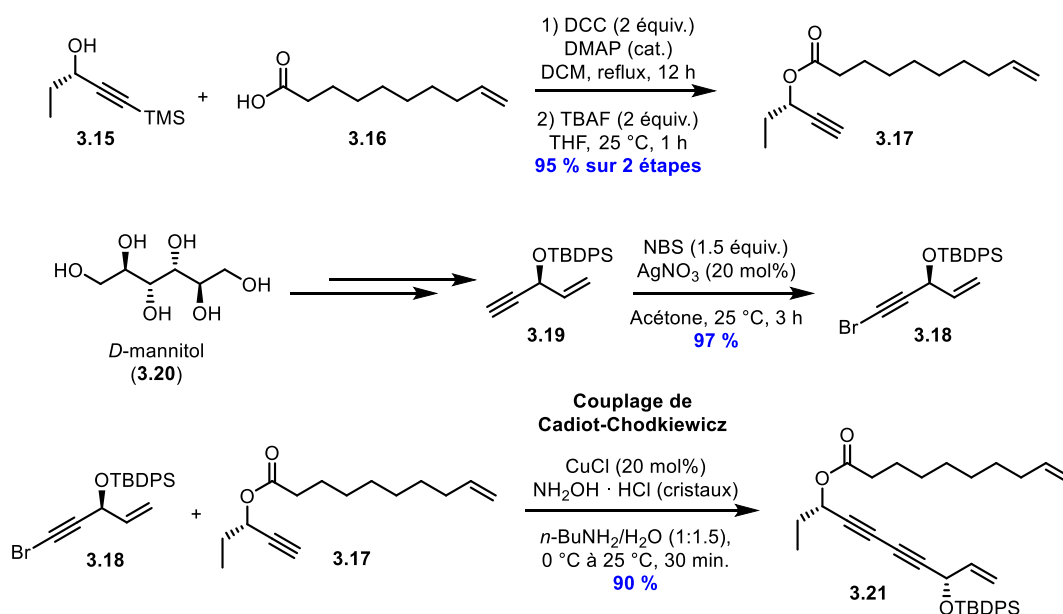
**Schéma 3.2** Macrocyclisation par macrolactonisation de Yamaguchi et dernières étapes de la synthèse de Yue

### 3.1.2 Synthèse totale de l'ivorenolide B

Le groupe de Yue a rapporté la première synthèse totale de l'ivorenolide B (**3.3**) en 2014<sup>6</sup>. Contrairement à leur synthèse de l'énantiomère non naturel de l'ivorenolide A (**3.14**), l'étape de fermeture de cycle n'a pas été faite par une réaction typique de macrolactonisation, mais plutôt par la formation d'un nouveau lien carbone-carbone via une réaction de métathèse croisée d'oléfines macrocyclique.

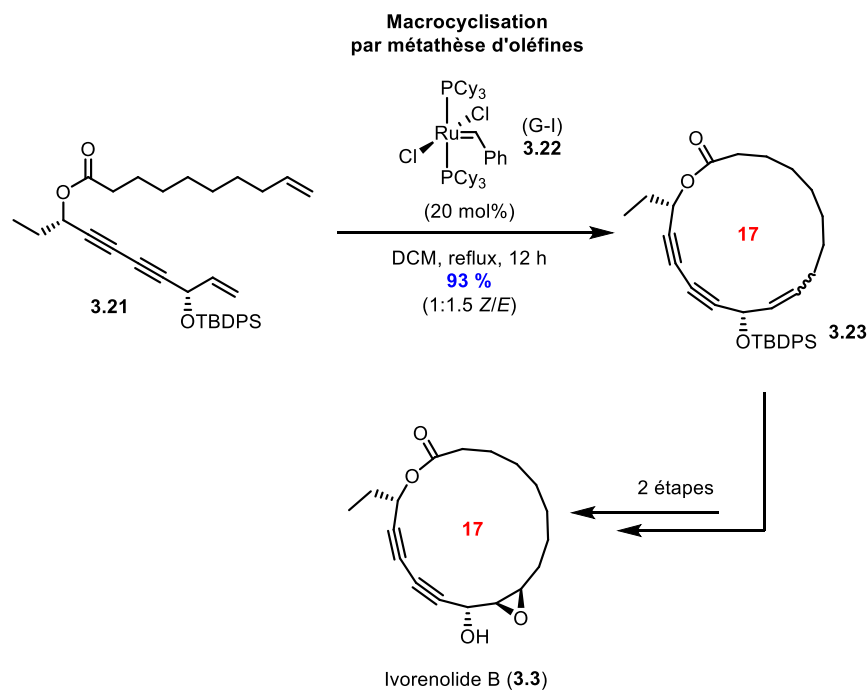
Leur synthèse démarre avec le couplage de l'alcool **3.15**<sup>7</sup> et de l'acide 9-décénoïque (**3.16**) par une estérification de Steglich (DCC, DMAP), suivi par la déprotection du groupement TMS

pour donner l'alcyne terminal **3.17** (Schéma 3.3). Parallèlement, le bromoalcyne **3.18** est préparé par la bromation de l'alcyne **3.19** (obtenu en plusieurs étapes à partir du *D*-mannitol (**3.20**))<sup>8</sup>. Selon la même stratégie utilisée pour la synthèse de l'énantiomère non naturel de l'ivorenolide A (**3.14**), le motif 1,3-butadiyne a été obtenu par un couplage de Cadiot-Chodkiewicz pour donner le précurseur linéaire **3.21** possédant deux alcènes terminaux.



**Schéma 3.3** Synthèse du diène linéaire **3.21** par couplage de Cadiot-Chodkiewicz

Une fois le diène **3.21** en main, les auteurs ont réalisé l'étape de fermeture de cycle par métathèse catalysée par le complexe de ruthénium Grubbs 1<sup>ère</sup> génération (G-I) (**3.22**). Pour ce faire, les deux réactifs ont été mélangés dans un milieu très dilué de DCM (1 mM) à reflux pour donner le macrocycle désiré **3.23** avec un excellent rendement de 93 % et un mélange 1 : 1,5 d'isomères *Z/E*. (Schéma 3.4). Après une séparation des diastéréoisomères ainsi que des étapes d'époxydation et de déprotection, l'ivorenolide B (**3.3**) a été obtenu en seulement 6 étapes avec un rendement global de 26 %, ce qui représente une nette amélioration comparativement à leur synthèse précédente de l'énantiomère non naturel de l'ivorenolide A (**3.14**).



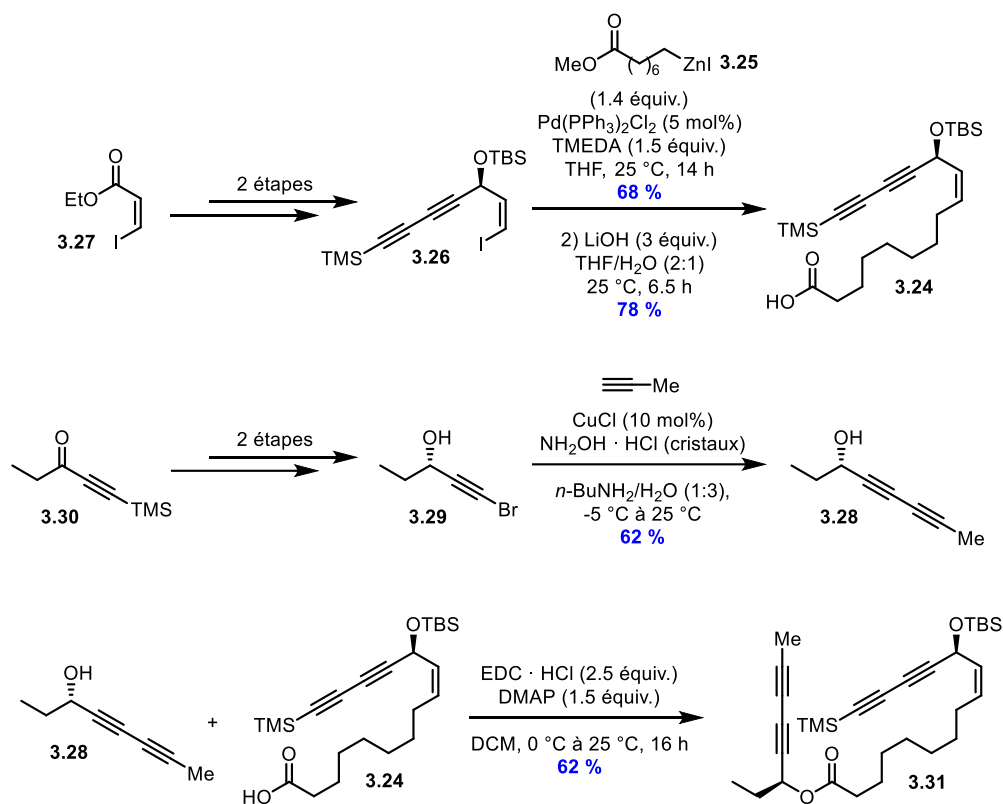
**Schéma 3.4** Macrocyclisation par métathèse d'oléfines et dernières étapes de la synthèse de l'ivorenolide B (3.3) par Yue

### 3.2 Synthèse totale de l'ivorenolide B par Fürstner

En 2015, durant nos travaux sur la synthèse de l'ivorenolide A (3.2), deux nouvelles synthèses de molécules appartenant à la famille des ivorenolides ont vu le jour dans la littérature, soit la première synthèse totale de l'ivorenolide A (3.2) par le groupe de Yadav<sup>9</sup> (voir Chapitre 3.3.1) ainsi que la synthèse totale de l'ivorenolide B (3.3) par le groupe de Fürstner<sup>10</sup>. Cette dernière est la première synthèse de la famille des ivorenolides qui implique la formation du motif 1,3-butadiyne au cours de l'étape de macrocyclisation.

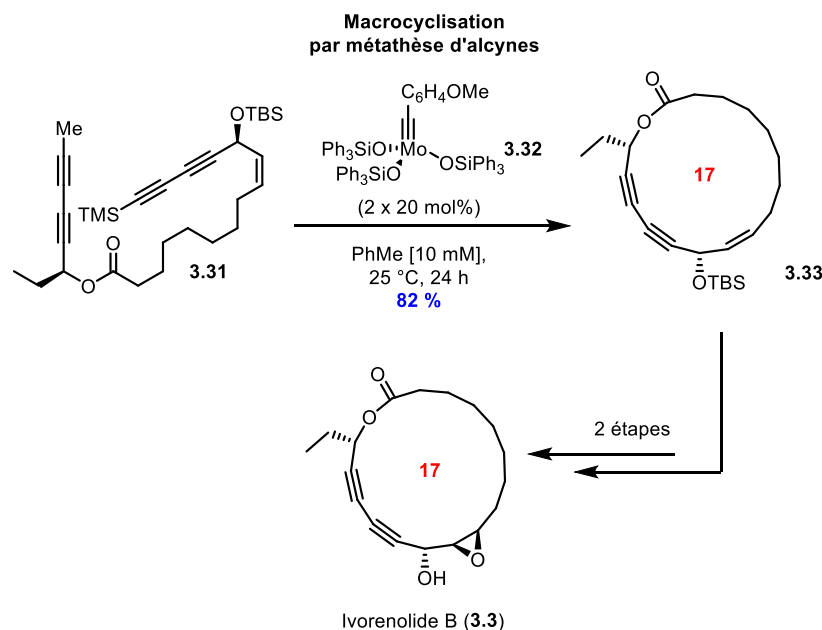
Pour ce faire, les auteurs ont dû réaliser la synthèse d'un précurseur linéaire 3.24 possédant deux motifs 1,3-butadiyne asymétriques issus de deux fragments différents. Le premier est obtenu par couplage de Negishi entre l'iodozincique 3.25 et l'iodovinyle 3.26, ce dernier étant obtenu en deux étapes par une alcynylation énantiosélective, à partir de l'iodovinyle 3.27 (Schéma 3.5). Le deuxième fragment 1,3-diyne 3.28 est obtenu par un couplage de Cadiot-Chodkiewicz entre le prop-2-yne et le bromoalcyne 3.29, obtenu à partir de la cétone 3.30 par réduction asymétrique de Noyori, puis bromation. Finalement, le

couplage de ces deux fragments a été réalisé par une estérification utilisant le EDC comme agent de couplage pour former le tétrayne linéaire **3.31**.



**Schéma 3.5** Synthèse du tétrayne linéaire **3.31**

Une fois le précurseur linéaire obtenu, le groupe de Fürstner a utilisé leur protocole de macrocyclisation par métathèse croisée d'alcynes pour effectuer l'étape de fermeture de cycle (Schéma 3.6). Cette réaction s'effectue en présence du catalyseur d'alkylidyne de molybdène **3.32** en milieu relativement dilué (10 mM) de toluène anhydre. Puisqu'il s'agit d'un complexe susceptible de dégrader en milieu réactionnel (présence d'eau, d'oxygène et sensibilité face aux sous-produits formés), deux portions de 20 mol% ont été nécessaires pour réagir complètement le tétrayne **3.31**. Avec cette procédure, le macrocycle **3.33** a été obtenu dans un rendement de 82 %. Les dernières étapes de déprotection et d'époxydation ont permis de compléter la synthèse de l'ivorenolide B (**3.3**) en 9 étapes linéaires avec un rendement global de 12 %.

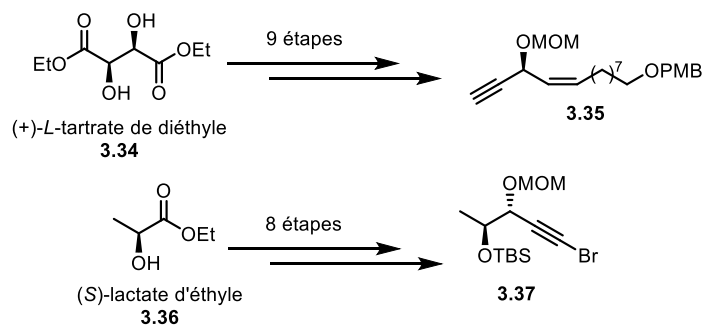


**Schéma 3.6** Macrocyclisation par métathèse d'alcynes et dernières étapes de la synthèse de l'ivorenolide B (**3.3**) par Fürstner

### 3.3 Synthèses de la famille des ivorenolides par Yadav

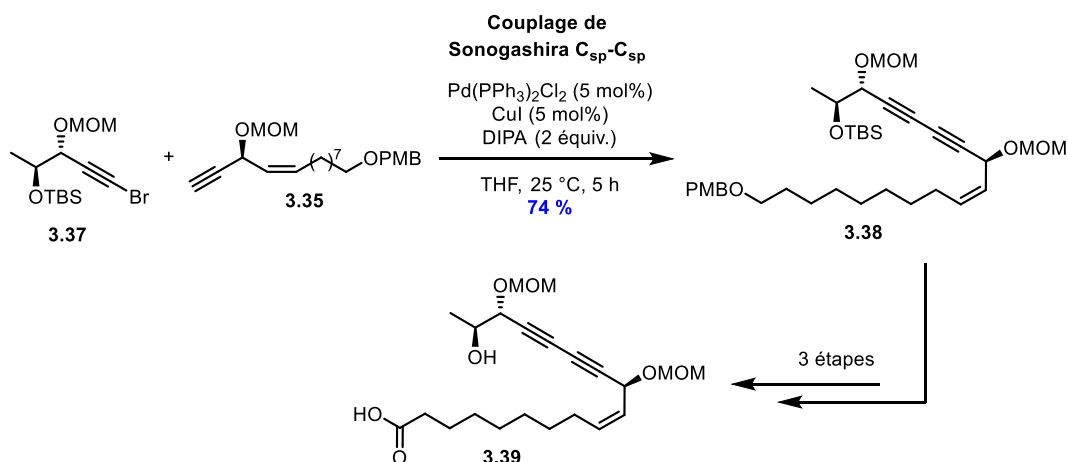
#### 3.3.1 Première synthèse totale de l'ivorenolide A

La première synthèse totale de l'ivorenolide A (**3.2**) a été réalisée en 2015 par le groupe de Yadav<sup>9</sup>. Il s'agit d'une synthèse convergente de deux fragments couplés ensemble pour former le motif 1,3-butadiyne. Pour la synthèse du premier fragment, le (+)-*L*-tartrate de diéthyle (**3.34**) a été converti en alcyne terminal **3.35** par une série de 9 étapes. Parmi ces transformations, une oléfination de Wittig a permis d'obtenir l'alcène de géométrie *Z* et une réaction d'élimination induite par une base, développée dans le groupe de Yadav<sup>11</sup>, a permis d'obtenir l'alcool propargylique chiral **3.35** (Figure 3.4). Pour la synthèse du deuxième fragment, le (*S*)-lactate d'éthyle (**3.36**) a été converti en alcool propargylique chiral **3.37** en 8 étapes, en utilisant la même stratégie de synthèse que pour le fragment précédent.



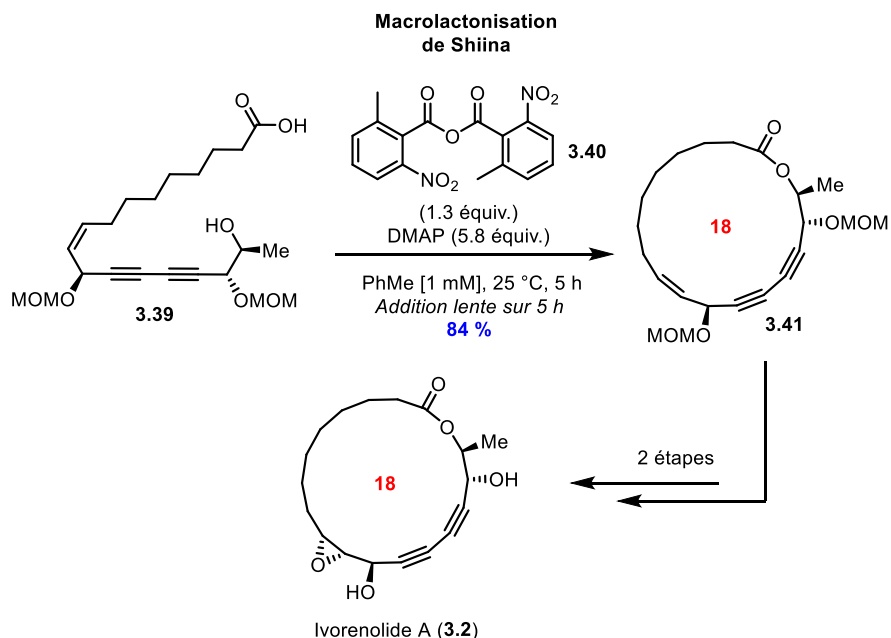
**Figure 3.4** Premieres \u00e9tapes de la synth\u00e8se de l'ivorenolide A (**3.2**) par Yadav

Une fois les deux fragments obtenus, un couplage de Sonogashira  $C_{sp}\text{-}C_{sp}$  a \u00e9t\u00e9 r\u00e9alis\u00e9 afin de former le compos\u00e9 **3.38** poss\u00e9dant le motif 1,3-butadiyne pr\u00e9sent dans le produit final. Des \u00e9tapes subs\u00e9quentes de d\u00e9protection et d'oxydation ont permis de former le *seco*-acide **3.39** (Sch\u00e9ma 3.7).



**Sch\u00e9ma 3.7** Couplage de Sonogashira  $C_{sp}\text{-}C_{sp}$  et formation du *seco*-acide **3.39**

Similairement \u00e0 la synth\u00e8se de Yue, le groupe de Yadav a effectu\u00e9 l'\u00e9tape de macrocyclisation en employant une strat\u00e9gie de macrolactonisation utilisant un agent de couplage st\u00e9chiom\u00e9trique. Cependant, cette fois-ci, les auteurs ont utilis\u00e9 le protocole de Shiina, soit l'emploi de l'anhydride 2-m\u00e9thyl-6-nitrobenzo\u00efque (MNBA) (**3.40**). \u00c0 la suite d'une addition lente du *seco*-acide **3.39** sur 5 h \u00e0 un m\u00e9lange de MNBA/DMAP dans un milieu tr\u00e8s dilu\u00e9 (1 mM) de tolu\u00e8ne, le macrocycle **3.41** a \u00e9t\u00e9 obtenu avec un rendement de 84 %. Finalement, les \u00e9tapes traditionnelles de d\u00e9protection et d'\u00e9poxydation concluent la premi\u00e8re synth\u00e8se totale de l'\u00e9nantiom\u00e8re naturel d'ivorenolide A (**3.2**) en 16 \u00e9tapes lin\u00e9aires avec un rendement global de 13 % (Sch\u00e9ma 3.8).

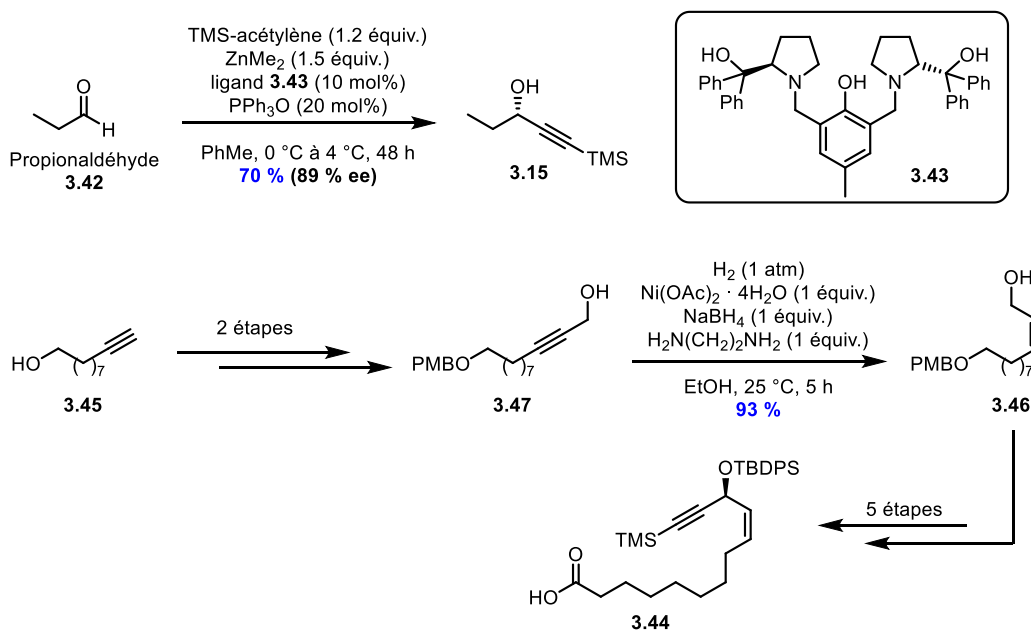


**Schéma 3.8** Macrocyclisation par macrolactonisation de Shiina et dernières étapes de la synthèse de l'ivoenolide A (3.2) par Yadav

### 3.3.2 Synthèse totale de l'ivoenolide B

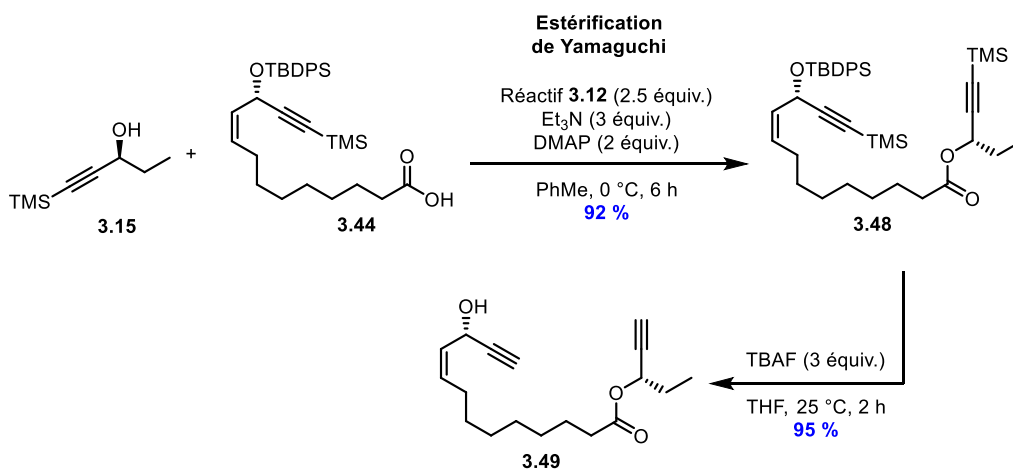
La synthèse totale de l'ivoenolide B (3.3) la plus récente a été effectuée par le groupe de Yadav en 2018. Inspiré par nos travaux sur l'ivoenolide A<sup>12</sup> (3.2) ainsi que ceux du groupe de Fürstner sur l'ivoenolide B<sup>10</sup> (3.3), le groupe de Yadav a développé une méthode de macrocyclisation de Glaser-Hay par catalyse synergique à l'or et au cuivre.

Pour ce faire, deux fragments ont été synthétisés (Schéma 3.9). Le premier fragment (3.15) a été obtenu par l'alcynylation énantiosélective du propionaldéhyde (3.42) en présence de diméthylzinc et du ligand chiral (*R,R*)-prophenol 3.43. Suivant la même stratégie, le deuxième fragment (3.44) a été obtenu en 8 étapes à partir du déc-9-yn-1-ol (3.45). Le motif alcène *Z* (3.46) a été introduit par hydrogénation partielle stéréosélective de l'alcyne interne 3.47 en présence d'un catalyseur de nickel. Finalement, la fonction acide carboxylique du fragment 3.44 a ensuite été obtenue à la suite d'une série d'étapes d'oxydation et de déprotection.



**Schéma 3.9** Premières étapes de la synthèse de l'ivorenolide B (**3.3**) par Yadav

L'intermédiaire **3.48** a été obtenu par le couplage des deux fragments **3.15** et **3.44** par une estérification intermoléculaire utilisant l'agent de couplage de Yamaguchi, suivie par la déprotection des groupements protecteurs silylés pour donner le diyne **3.49** (Schéma 3.10).

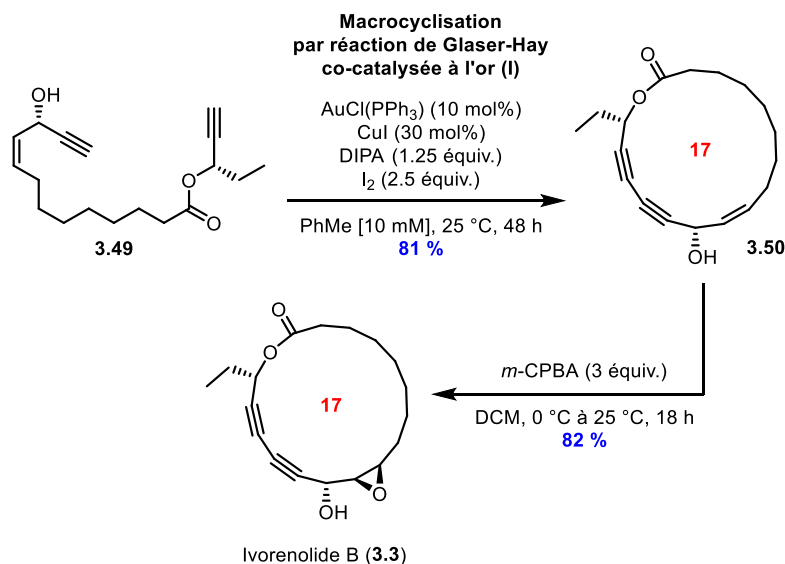


**Schéma 3.10** Convergence de la synthèse vers le diyne **3.49**

Tel que mentionné, l'étape de macrocyclisation a été faite par une réaction de Glaser-Hay légèrement modifiée (Schéma 3.11). En effet, le groupe de Yadav a utilisé un co-catalyseur d'or (I) ainsi qu'un oxydant stœchiométrique, soit l'iode moléculaire (I<sub>2</sub>) en présence d'iodure de cuivre et d'un ligand aminé, soit la diisopropylamine (DIPA). Ces



modifications correspondent à une stratégie similaire aux modifications apportées par le groupe de Lei en 2008 <sup>13</sup>, soit utiliser un co-catalyseur de nickel pour faciliter l'élimination réductrice en présence d'un oxydant. Le rôle du catalyseur de cuivre/DIPA est de former des acétylures de cuivre en solution. Cet intermédiaire peut ensuite faire une transmétallation oxydative avec le complexe d'or pour former un complexe d'acétylure d'or (III). Cet intermédiaire peut enfin faire une élimination réductrice pour former le composé diyne et régénérer le catalyseur d'or (I). Suivant cette stratégie, le groupe de Yadav a pu obtenir le macrocycle **3.50** avec un rendement de 67 %. Encore une fois, l'étape de macrocyclisation a été réalisée dans un milieu relativement dilué (10 mM) et a requis un long temps de réaction (48 h). Une dernière étape d'époxydation leur a permis de terminer la synthèse d'ivorenolide B (**3.3**) (12 étapes, rendement global de 31 %)



**Schéma 3.11** Macrocyclisation par réaction de Glaser-Hay co-catalysée à l'or (I) et dernière étape de la synthèse de l'ivorenolide B (**3.3**) par Yadav

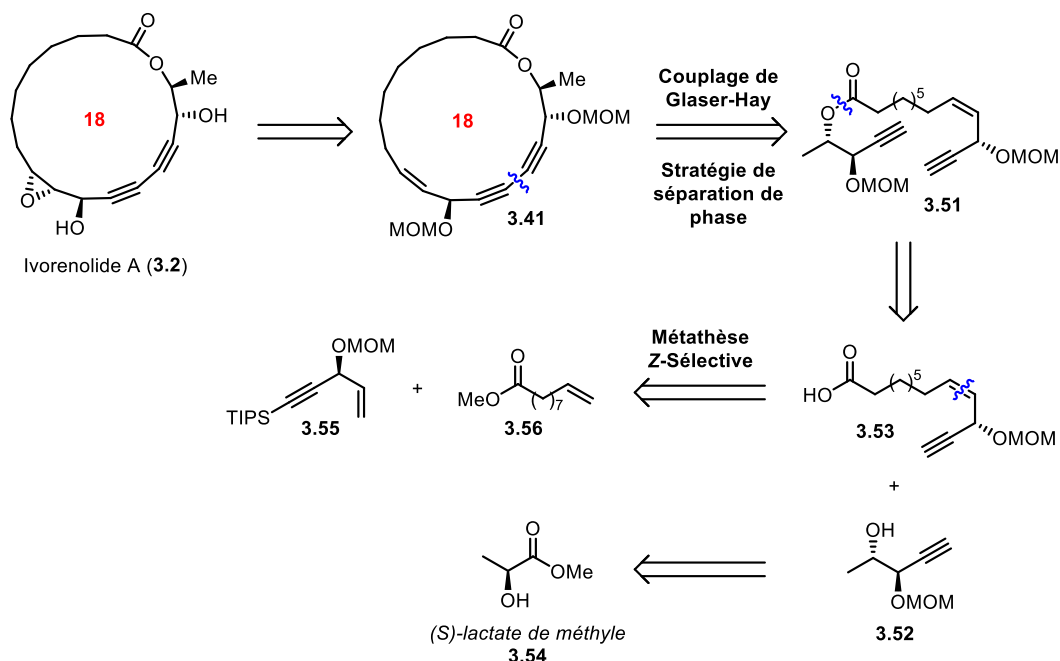
### 3.4 Analyse rétrosynthétique de la synthèse de l'ivorenolide A :

#### Macrocyclisation par réaction de Glaser-Hay

Avec le développement du protocole de macrocyclisation à concentration élevée par réaction de Glaser-Hay développé dans notre groupe de recherche, son application pour la synthèse d'un macrocycle avec une plus grande complexité semblait nécessaire. Avec la découverte du premier produit naturel possédant un motif 1,3-butadiyne, la synthèse de l'ivorenolide A était

un projet logique. Cependant, plusieurs incertitudes planaient quant à la possibilité de racémisation des alcools propargyliques lors de la réaction de macrocyclisation ainsi qu'à l'encombrement stérique pouvant être occasionné par les groupements protecteurs adjacents. De plus, les méthodes existantes posaient un défi synthétique pour la préparation des macrocycles complexes à l'échelle du gramme. La combinaison de la stratégie de séparation de phase et de la chimie en débit continu pouvait potentiellement être la clé pour relever ce défi. Afin de répondre à ces questions, une synthèse de l'ivorenolide A a été envisagée. En analysant les synthèses de Yue et de Yadav, on pouvait imaginer que le macrocycle **3.41** pouvait être obtenu en appliquant notre protocole de macrocyclisation de Glaser-Hay à partir du diyne linéaire **3.51** (Figure 3.5). Ce dernier pouvait, quant à lui, être obtenu à partir du couplage de deux fragments, soit l'alcool propargylique **3.52** et la chaîne alcynique **3.53**. Le fragment alcool **3.52** pouvait facilement être obtenu à partir du chiron (*S*)-lactate de méthyle (**3.54**) qui est commercialement disponible et peu dispendieux. Pour sa part, la chaîne alcynique **3.53** pouvait être formée par une réaction de métathèse stéréosélective à partir de deux synthons connus de la littérature, soit les alcènes terminaux **3.55** et **3.56**. En résumé, les buts du projet étaient :

- 1) Évaluer la performance de la réaction de Glaser-Hay en présence de centres chiraux, d'un encombrement stérique au niveau des fonctions alcynes et la tolérance à certains groupements protecteurs.
- 2) Appliquer la stratégie de séparation de phase pour la synthèse d'un macrocycle complexe comme l'ivorenolide A.
- 3) Démontrer la montée en échelle (*scale up*) d'un macrocycle par l'exploitation des avantages de la stratégie de séparation de phase et de la chimie en débit continu.



**Figure 3.5** Analyse rétrosynthétique pour la synthèse de l'ivorenolide A par macrocyclisation de Glaser-Hay

### 3.5 Bibliographie

1. <https://www.cihi.ca/fr/transplantations-dorganes-au-canada-statistiques-annuelles-du-drcito-2018> (consulté le 13 aout 2019)
2. 2017 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 2006-2017. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI.
3. Matsuda, S.; Koyasu, S. *Immunopharmacology* **2000**, *47*, 119-125.
4. Naesens, M.; Kuypers, D. R. J.; Sarwal, M. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 481-508.
5. Zhang, B.; Wang, Y.; Yang, S. P.; Zhou, Y.; Wu, W. B.; Tang, W.; Zuo, J. P.; Li, Y.; Yue, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 20605-20608.
6. Wang, Y.; Liu, Q. F.; Xue, J. J.; Zhou, Y.; Yu, H. C.; Yang, S. P.; Zhang, B.; Zuo, J. P.; Li, Y.; Yue, J. M. *Org. Lett.* **2014**, *16*, 2062-2065.
7. Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 12432-12440.
8. Ghosh, S.; Pradhan, T. K. *Synlett* **2007**, *15*, 2433-2435.
9. Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; Kumar, S. R.; Yadav, J. S. *Org. Lett.* **2015**, *17*, 979-981.

10. Ungeheuer, F.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 11387 – 11392.
11. Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033-7046.
12. de Léséleuc, M.; Godin, É.; Parisien-Collette, S.; Lévesque, A.; Collins, S. K. *J. Org. Chem.* **2016**, *81*, 6750 – 6756.
13. Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709-712.

## Chapitre 4. Catalytic Macrocyclization Strategies Using Continuous Flow: Formal Total Synthesis of Ivorenolide A.

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### Contributions :

- Mylène de Léséleuc a participé à la mise en œuvre des expériences, dans la synthèse du fragment « acide », notamment dans l'optimisation de la réaction de métathèse, et a participé à la rédaction du manuscrit concernant la partie expérimentale.
- Éric Godin a participé à la mise en œuvre des expériences, a fait la synthèse de toute la molécule, a fait les études de macrocyclisation et a participé à la rédaction du manuscrit concernant la partie expérimentale.
- Shawn Parisien-Collette a optimisé les trois premières étapes de la synthèse du fragment « alcool ».
- Alexandre Lévesque a participé à l'étude de macrocyclisation du substrat modèle en chimie en débit continu
- Shawn K. Collins a participé à la mise en œuvre des expériences et à l'écriture du manuscrit.

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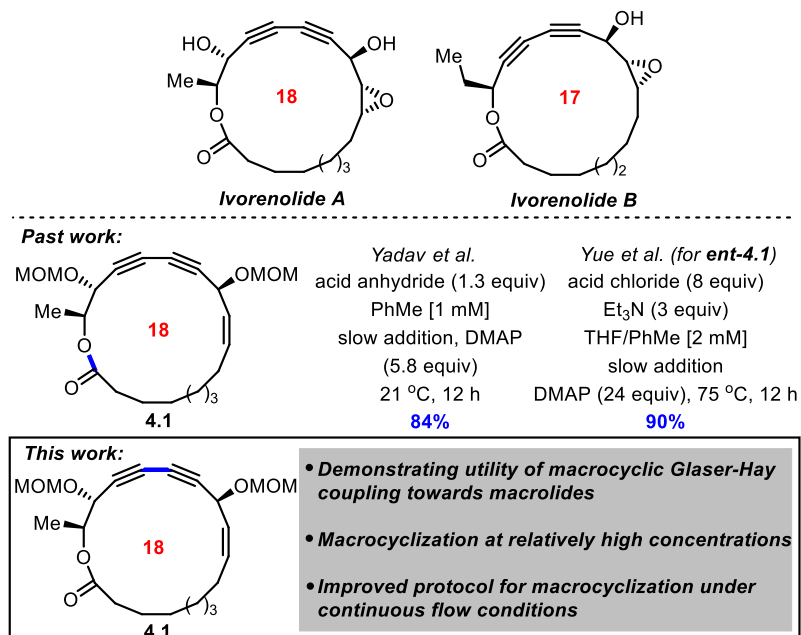
## 4.1 Abstract

A formal total synthesis of ivorenolide A has been accomplished employing a Z-selective olefin cross metathesis and a macrocyclic Glaser-Hay coupling as key steps. The macrocyclization protocol employed a phase separation/continuous flow manifold whose advantages include catalysis, fast reaction times, high concentrations and facile scale-up.

## 4.2 Introduction

Macrolides are a family of macrocyclic natural products having a wide array of biological activities.<sup>1</sup> From a synthetic perspective, several methods have evolved as the most popular candidates for macrocyclization. Macrolactonization<sup>2</sup> via stoichiometric activation of seco-acids, such as the Yamaguchi protocol,<sup>3</sup> is without a doubt the most popular method for constructing the ester motif of macrolides. Another common synthetic route to form macrocycles involves carbon-carbon bond formation via transition metal catalysis, usually using olefin metathesis or cross-coupling strategies.<sup>4</sup> Despite the utility displayed by the above transformations, the macrocyclizations are usually performed at low concentration, and rely upon slow addition techniques. Consequently, scale-up of the target macrocycles becomes problematic,<sup>5</sup> which is disappointing when promising biological activity is observed. The ivorenolides A<sup>6</sup> and B<sup>7</sup> are a unique class of macrolides which possess 1,3-diyne motifs isolated from the stem bark of *K. ivorensis* (Figure 4.1). Their immunosuppressive activities make them attractive targets for medicinal chemistry investigations given the need for new immunosuppressants with improved therapeutic profiles. Total syntheses of both the natural and unnatural enantiomers of ivorenolide A have appeared in the literature, each exploiting a macrolactonization employing stoichiometric activation strategies and high dilution and/or slow addition as the key macrocyclization step (Figure 4.1).<sup>6,8</sup> As such, the development of alternative methods for macrocyclization that would employ catalysis, high concentrations and facilitate scale-up would be highly desirable.<sup>9</sup> Our group has put forth an alternative strategy for the synthesis of macrocycles via Glaser-Hay coupling using a “phase separation” strategy.<sup>10</sup> The protocol was shown to exploit aggregation effects caused by mixtures of poly(ethylene)glycol (PEG) co-solvents.<sup>11</sup> During the development of the “phase separation” technology, it was apparent that the substrate scope explored to date was limited, and did not

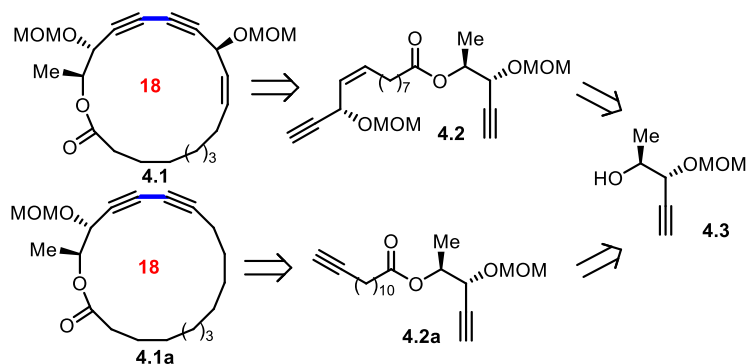
address the influence of chiral centers, steric hindrance about the alkyne reaction centers or tolerance to common protecting groups. In addition, no investigation of the feasibility of scale-up of complex macrocycles at the gram scale had been demonstrated. To respond to the aforementioned questions, the formal total synthesis of ivorenolide A by application of the “phase separation” strategy under continuous flow techniques is described herein (Figure 4.1).



**Figure 4.1** Macrocyclization strategies via continuous flow towards ivorenolide A

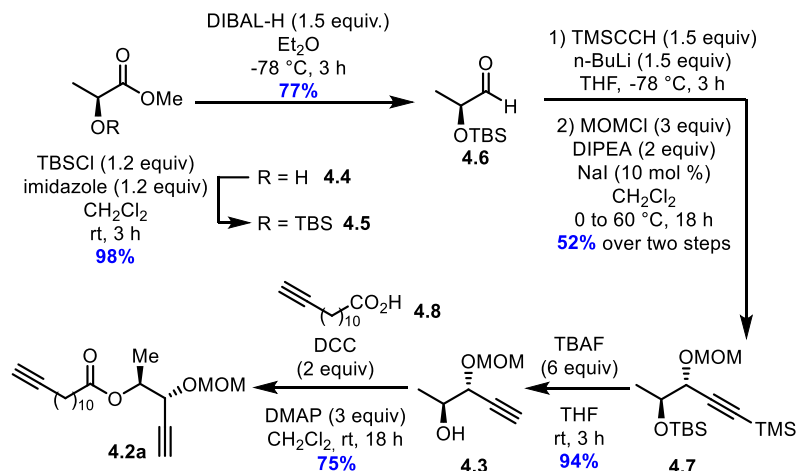
### 4.3 Results/Discussion

The retrosynthetic analysis for the development of a phase separation/continuous flow macrocyclization towards the synthesis of ivorenolide A aimed to prepare the 18-membered macrolactone **4.1** intermediate, which was previously prepared by Yadav<sup>12</sup> and Yue<sup>6</sup> as well as a simplified model **4.1a** (Figure 4.2). Envisioning the macrocyclization event arising from Glaser-Hay coupling of two terminal alkynes, the linear precursor **4.2** was selected as a target for the formation of macrocycle **4.1**, while the macrocyclization of the model 18-membered macrolactone **4.1a** was also imagined arising from Glaser-Hay coupling of linear precursor **4.2a**. Each ester (**4.2** and **4.2a**) could be prepared from esterification of the alcohol **4.3** with a corresponding carboxylic acid derivative.



**Figure 4.2** Retrosynthetic analysis towards the macrocyclic core of ivorenolide A (**4.2**→**4.1**) and a simplified model (**4.2a**→**4.1a**)

The synthesis of alkynyl alcohol **4.3** commenced from TBS-protected (*S*)-methyl lactate (Scheme 4.1). Reduction of the ester **4.5** to the corresponding aldehyde **4.6** using DIBAL-H and addition of the organolithium derived from trimethylsilyl acetylene afforded solely the desired diastereomer. Subsequent MOM-protection afforded the fully protected alkyne **4.7** in 52% yield over two steps. Removal of both silyl protecting groups provided **4.3** in 94% yield. Esterification of alcohol **4.3** using DCC/DMAP conditions with known carboxylic acid **4.8** provided the macrocyclization precursor **4.2a** in 75% yield.

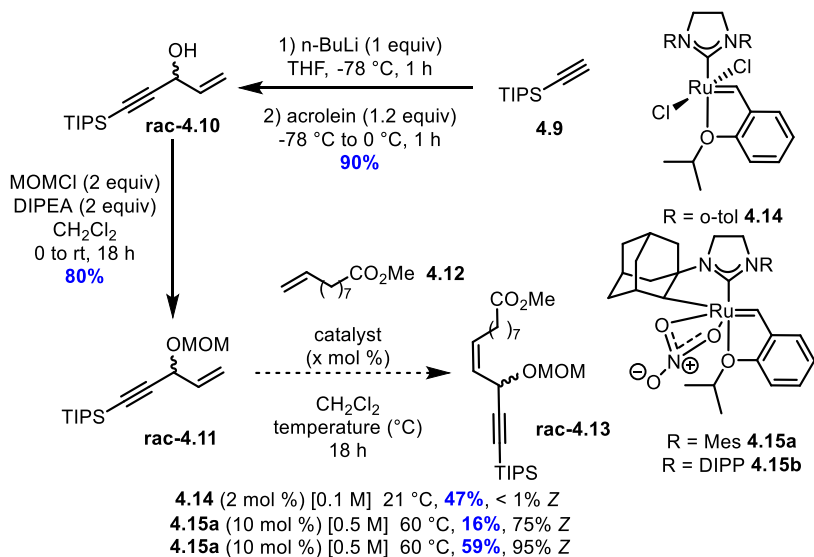


**Scheme 4.1** Synthesis of alcohol **4.3** and diene **4.2a** analysis towards the macrocyclic core of ivorenolide A (**4.2**→**4.1**) and a simplified model (**4.2a**→**4.1a**)

The carboxylic alkynyl synthon **4.2** required for the synthesis of macrocycle **4.1** was then envisioned arising from a *Z*-selective cross metathesis process.<sup>13</sup> The MOM-protected substrate **rac-4.11** could be prepared in two steps via alkylation of acrolein and subsequent



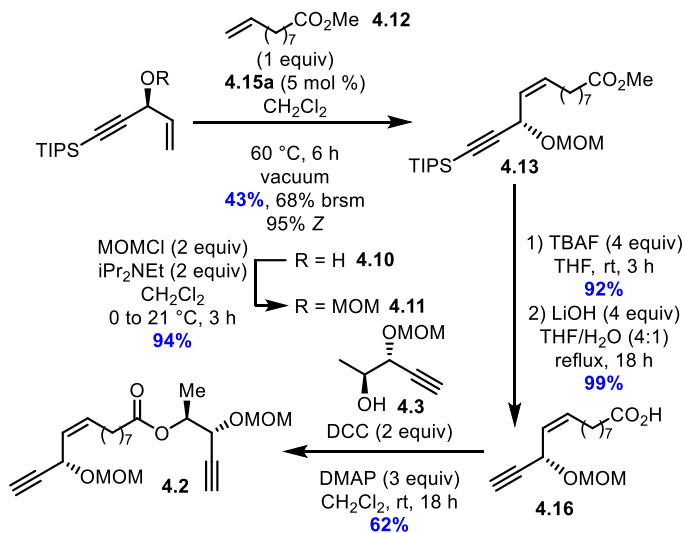
protection from MOMCl. To test the synthetic route, several cross metathesis reactions were evaluated on the racemic, MOM-protected secondary alcohol **rac-4.11** (Scheme 4.2)



**Scheme 4.2** Optimization of a *Z*-selective cross metathesis to prepare racemic **4.13**

Cross metathesis was first evaluated with 1.0 equivalent of methyl ester **4.12** at room temperature using the Stewart-Grubbs catalyst **4.14**.<sup>14</sup> The desired product **rac-4.13** was obtained in 47% yield and isolated as the pure *E*-isomer. Next, two Ru-based *Z*-selective catalysts were evaluated, each having a different NHC in which the *N*-aryl substituent differed.<sup>15</sup> After a brief survey of reaction conditions,<sup>16</sup> it was found that the DIPP-bearing catalyst **4.15b** at 10 mol%, 60 °C and at [0.5 M] afforded a 59% yield of the desired olefin **rac-4.13**, in excellent *Z*-selectivity (95% *Z*). Cross metathesis using the mesityl catalyst **4.15a**<sup>17</sup> was not as selective (75% *Z*). With optimized conditions for the cross metathesis procedure in hand, the synthesis of the enantioenriched carboxylic acid **4.16** was undertaken (Scheme 4.3). First the enantiomerically pure alcohol **4.10** could be obtained via a previously reported CBS reduction, or via diastereomeric resolution.<sup>18</sup> The alcohol **4.10** was protected as its MOM ether **4.11** in 94% yield and subsequently subjected to *Z*-selective cross metathesis. To improve reproducibility at larger scales, an applied vacuum was used for removing ethylene.<sup>19</sup> Consequently, the yield and selectivity of the reaction remained reproducible at 43% (68% based on recovered starting material) and >95% *Z* with a shorter reaction time (6 h vs. 18 h). With enantiopure olefin **4.13** in hand, desilylation was performed using TBAF to provide the corresponding terminal alkyne in 92% yield (Scheme 4.3). Saponification of the

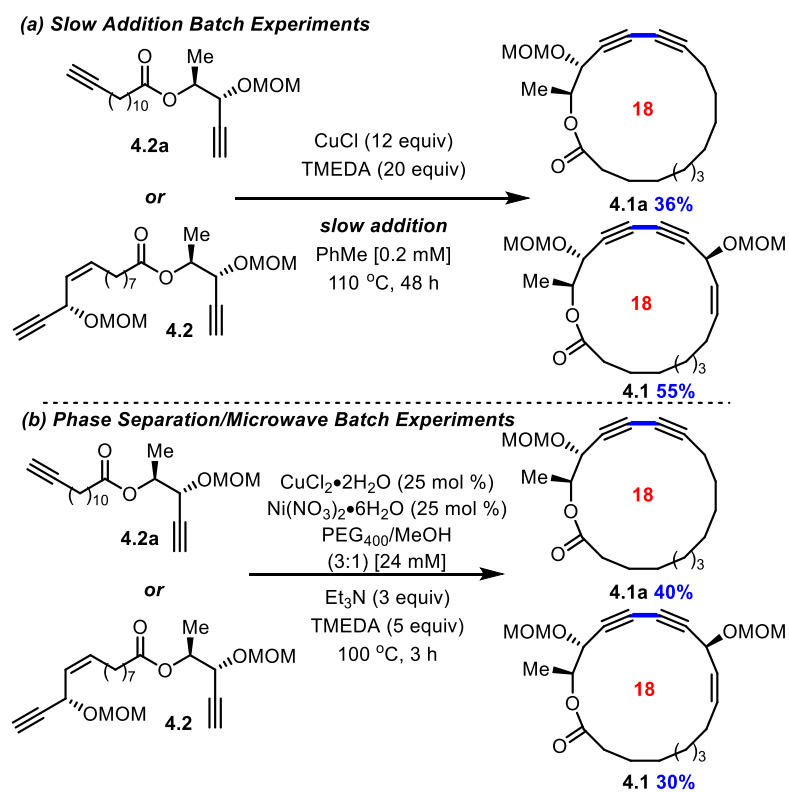
ester afforded the carboxylic acid **4.16** in 99% yield. Esterification of acid **4.16** with secondary alcohol **4.3** was promoted by reaction with DCC and DMAP to provide the desired compound **4.2** in 62% yield.



**Scheme 4.3** Synthesis of linear precursor **4.2** for macrocyclization to form the macrocyclic core of ivorenolide A

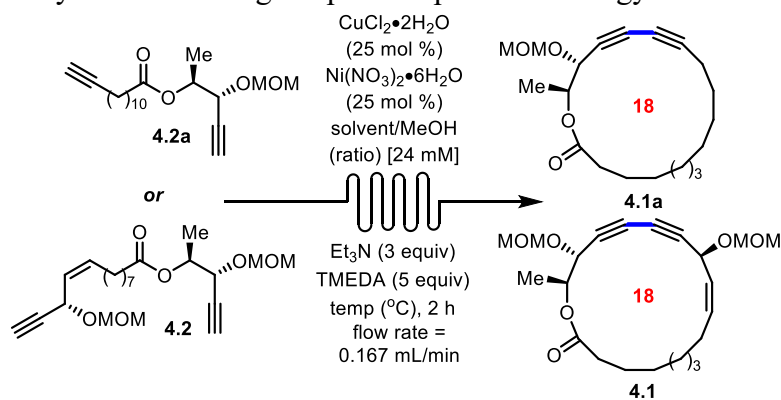
With both key linear precursors in hand, attempted macrocyclization was performed first using the simplified model **4.2a** (Scheme 4.4). As such, the bis-alkyne **4.2a** was cyclized under slow addition conditions, using super-stoichiometric amounts of CuCl (12 equiv.) and ligand (TMEDA, 20 equiv.) in refluxing toluene. Slow addition was performed over 36 h and the refluxing reaction mixture (final concentration 0.2 mM) was left to stir for another 12 h to promote conversion of all the starting material **4.2a**. Macrocycle **4.1a** was isolated following silica gel chromatography in 36% yield. When identical reaction conditions were used to cyclize the more complex macrocyclization precursor **4.2**, the yield of the desired macrocycle **4.1** was higher at 55%. Next, the macrocyclization precursors were subjected to phase separation conditions at ~120 times the concentration employing reaction conditions previously developed for cyclization under microwave heating.<sup>20</sup> For the cyclization of **4.2a**, a 40% yield of macrocycle **4.1a** was isolated. Similar yields (30%) were also observed using the linear precursor **4.1**. Each bis-alkyne was observed to be sensitive to the basic conditions of the protocol for macrocyclization and it was hoped that the precise control over temperature/reaction time using continuous flow would be advantageous.<sup>21</sup> For the model precursor **4.2a**, macrocyclizations under continuous flow conditions<sup>22</sup> were evaluated with

different ratios of PEG solvent to MeOH (Table 1.1). Based upon previous work,<sup>23</sup> residence times of 1-2 h were selected for study. Consequently, a low flow rate (0.167 mL/min) combined with a 20 mL reactor volume were necessary (two 10 mL reactor coils were connected in series). In addition, since higher ratios of PEG<sub>400</sub>/MeOH typically provide higher selectivity for macrocyclization versus oligomerization, albeit with longer reaction times, the optimization of the macrocyclization was conducted with a 2 h residence time. When precursor **4.2a** was cyclized at 120 °C, with a residence time of 2 h in PEG<sub>400</sub>/MeOH (1:1) a 30% yield of macrocycle **4.1a** was isolated. Efforts to boost yields through increasing the ratio of PEG<sub>400</sub>/MeOH to 4:1 resulted in lower yields, and a ratio of PEG<sub>400</sub>/MeOH (8:1) required longer reaction times (4 h). Switching the solvent from PEG<sub>400</sub> to PPG<sub>425</sub>, a poly(propylene)glycol solvent previously demonstrated to be efficient in “phase separation”-type macrocyclizations, provided the best yield of macrocycle **4.1a** (38-40% yield).



**Scheme 4.4** Macrocyclizations under slow addition conditions (a) and macrocyclizations under phase separation/microwave heating (b) to form macrocycles **4.1** and **4.1a**

To demonstrate the feasibility of using the “phase separation” strategy alongside continuous flow for large scale preparation of macrolide type macrocycles, the macrocyclization (**4.2a**→**4.1a**) was repeated at gram scale and provided identical yields to what was observed at smaller scales (50-150 mg). Gram scale cyclization of diyne **4.2a** required 120 mL of the PPG<sub>425</sub>:MeOH (2:1) solvent mixture, while the equivalent slow addition experiment would have required >14 L of PhMe. When a similar set of conditions were used for the macrocyclization of precursor **4.2** possessing the additional *Z*-olefin and propargylic stereocenter, the best conditions surveyed utilized 120 °C, with a residence time of 2 h in PEG<sub>400</sub>/MeOH (1:1) for a 52% yield of macrocycle **4.1**. The higher yield of macrocycle **4.1** (52%) versus the model macrocycle **4.1a** under similar reaction conditions could be explained by the effects of the additional *cis*-olefin and stereocenter in the respective precursor **4.2** versus **4.2a**. The addition of the olefin and hydroxyl motifs could promote a conformational bias to help bring the alkyne functionalities closer to one another.<sup>24</sup> Consequently, the use of the phase separation/continuous flow conditions for the preparation of the ivorenolide macrocycle **4.1** provided several advantages to using a traditional slow addition type strategy. In addition to providing a similar yield (55 vs 52% of **4.1**), reaction under the phase separation/continuous flow manifold were catalytic as opposed to using superstoichiometric quantities of ligand and metal source, the reaction time was significantly shortened (48 vs 2 h) and the concentration was greater by more than two orders of magnitude (0.2 vs 24 mM).

**Table 4.1** Macrocyclizations using the phase separation strategy in continuous flow

	PEG solvent	Ratio (PEG:MeOH)	Temp. ( $^\circ\text{C}$ )	Yield (%) <sup>a</sup>
macrocyclization <b>4.2a</b> → <b>4.1a</b>				
1	PEG <sub>400</sub>	1:1	120	30 (<5)
2	PEG <sub>400</sub>	2:1	120	26 (<5)
3	PEG <sub>400</sub>	4:1	120	19 (24)
4	PEG <sub>400</sub>	8:1	120	14 (18) <sup>b</sup>
5	PPG <sub>425</sub>	2:1	120	38-40 <sup>c</sup>
macrocyclization <b>4.2</b> → <b>4.1</b>				
6	PEG <sub>400</sub>	1:1	120	52 (0)
7	PEG <sub>400</sub>	2:1	120	37 (<5)
8	PEG <sub>400</sub>	4:1	100	27 (30)

<sup>a</sup> Yields following chromatography. Recovered starting material in parentheses. <sup>b</sup> 4 h reaction time. <sup>c</sup> Reactions performed at 80 or 100  $^\circ\text{C}$  afforded similar yields with small amounts of unreacted **4.2a**. For ease of purification, the reaction was kept at 120  $^\circ\text{C}$ . Ring sizes in red.

## 4.4 Conclusions

In summary, a formal total synthesis of ivorenolide A has been accomplished using a macrocyclic catalytic oxidative coupling of terminal alkynes and a *Z*-selective cross metathesis as key steps. Macrocyclization has been demonstrated employing a phase

separation/continuous flow method that is applicable to complex macrolides bearing chiral centers, steric hindrance about the alkynes and common protecting groups. The macrocyclization also described for the first time that continuous flow protocols allows for much more facile scale-up that would be highly problematic using high dilution strategies or microwave heating. The phase separation strategy produced good yields of the desired macrocycles employing catalysis in place of stoichiometric reagents, faster reaction times than the corresponding batch reactions and at concentrations ~120X greater than the slow addition strategy. Given the rarity of macrocyclizations performed under continuous flow, and the importance of macrocycles in both natural product synthesis and medicinal chemistry, the use of the phase separation/continuous flow method would be expected to have significant impact.

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**Supporting Information.** Characterization data for all new compounds and optimization data for the *Z*-selective metathesis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## 4.5 Bibliographie

1. (a) Napolitano, J. G.; Daranas, A. H.; Norte, M.; Fernandez, J. J. in *Advances in Anticancer Agents in Medicinal Chemistry* (Prudhomme, M. Ed.) Betham Science Publishers, 2013. (b) Xie, J.; Bogliotti, N. *Chem. Rev.* **2014**, *114*, 7678-7739.
2. Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2013**, *113*, PR1-PR40.
3. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

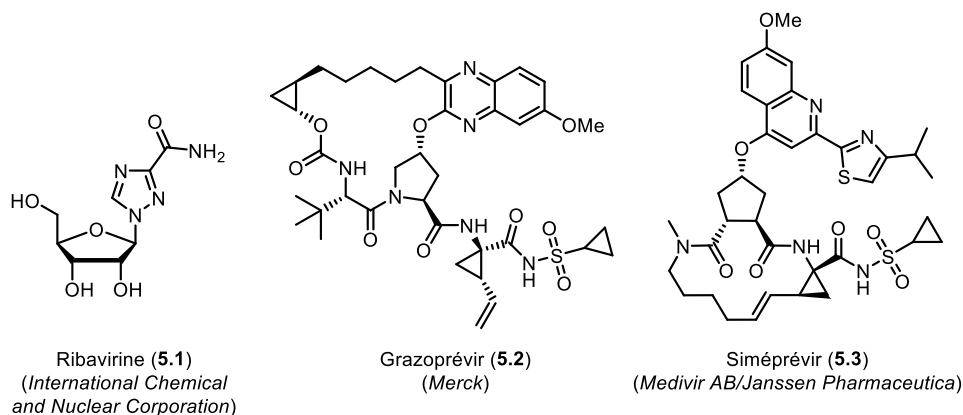
4. (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490-4527. (b) Stang, E. M.; White, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2094–2097. (c) Dieckmann, M.; Rudolph, S.; Dreisigacker, S.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10782-10788.
5. (a) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303-1306. (b) Gallou, F.; Saim, S.; Koenig, K. J.; Bochniak, D.; Horhota, S. T.; Yee, N. K.; Senanayake, C. H. *Org. Proc. Res. Dev.* **2006**, *10*, 937-940.
6. Zhang, B.; Wang, Y.; Yang, S. P.; Zhou, Y.; Wu, W. B.; Tang, W.; Zuo, J. P.; Li, Y.; Yue, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 20605-20608.
7. Wang, Y.; Liu, Q.-F.; Xue, J.-J.; Zhou, Y.; Yu, H.-C.; Yang, S.-P.; Zhang, B.; Zuo, J.-P.; Li, Y.; Yue, J.-M. *Org. Lett.* **2014**, *16*, 2062-2065.
8. Ivorenolide B see: Ungeheuer, F.; Furstner, A. *Chem. Eur. J.* **2015**, *21*, 11387-11392.
9. Examples of macrocyclization at high concentrations: (a) Collins, J. C.; Farley, K. A.; Limberakis, C.; Liras, S.; Price, D.; James, K. *J. Org. Chem.* **2012**, *77*, 11079-11090. (b) Wei, X.; Shu, C.; Haddad, N.; Zeng, X.; Patel, N. D.; Tan, Z.; Liu, J.; Lee, H.; Shen, S.; Campbell, S.; Varsolona, R. J.; Busacca, C. A.; Hossain, A.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2013**, *15*, 1016-1019. (c) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112-6114.
10. Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976-19981.
11. (a) Bédard, A.-C.; Collins, S. K. *Chem. Eur. J.* **2013**, *19*, 2108-2113. (b) Bédard, A.-C.; Collins, S. K. *ACS Catal.* **2013**, *3*, 773-782.
12. Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; Kumar R, S.; Yadav, J. S. *Org. Lett.* **2015**, *17*, 979–981.
13. (a) Werrel, S.; Walker, J. C. L.; Donohoe, T. J. *Tetrahedron Lett.* **2015**, *56*, 5261-5268. (b) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186. (c) Quigley, B. L. Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501–506. (d) Herbert, M. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 5018 – 5024. (e) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461-466.
14. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

15. Mangold, S. L.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 12469-12478.
16. See Supporting Information for details.
17. Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525-8527.
18. Mann, T. J.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8395-8400. An alternative route via diastereomeric separation was also used. See Experimental Section.
19. Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88-93.
20. Bedard, A.-C.; Collins, S. K. *Chem. Commun.* **2012**, *48*, 6420-6422.
21. (a) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2-25. (b) Ley, S. V.; Fitzpatrick, D. E.; Myers, R. M.; Battilocchio, C.; Ingham, R. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10122-10136. (c) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849-8869. (d) Kim, H.; Min, K.-I.; Inoue, K.; Im, D. J.; Kim, D.-P.; Yoshida, J.-i. *Science* **2016**, *352*, 691-694.
22. Continuous flow macrocyclizations see: (a) Salvador, C. E. M.; Pieber, B.; Neu, P. M.; Torvisco, A.; Kleber Z. Andrade, C.; Kappe, C. O. *J. Org. Chem.* **2015**, *80*, 4590-4602. (b) Bogdan, A. R.; Jerome, S. V.; Houk, K. N.; James, K. *J. Am. Chem. Soc.* **2012**, *134*, 2127-2138. (c) Skowerski, K.; Wierzbicka, C.; Grela, K. *Curr. Org. Chem.* **2013**, *17*, 2740-2748.
23. Bédard, A.-C.; Régnier, S.; Collins, S. K. *Green Chem.* **2013**, *15*, 1962-1966.
24. Liau, B. B.; Gnanadesikan, V.; Corey, E. J. *Org. Lett.* **2008**, *10*, 1055-1057.



## Chapitre 5. Introduction à l'antiviral vaniprévir

Le virus de l'hépatite C (VHC) est un petit virus d'ARN (environ 60 nm) qui cause une maladie du foie. La maladie causée par ce virus transmissible par le sang est responsable de la majorité des cancers du foie. En 2009, il était estimé que 3% de la population mondiale était porteur du VHC, mais cette valeur a grandement diminué pour atteindre 1% en 2015<sup>1</sup>. La cause de cette diminution est l'apparition de médicaments efficaces pour le traitement du virus. La grande majorité des médicaments contre le VHC ciblent la protéase NS3/4A du virus, une enzyme qui joue un rôle important dans sa réplication. Le traitement classique contre le VHC est une combinaison de l'antiviral ribavirine (**5.1**) et d'un dérivé pégylé d'interféron (protéine produite par des cellules du système immunitaire). Cependant, ce traitement cause plusieurs effets secondaires<sup>2</sup>. Plus récemment, plusieurs médicaments efficaces causant des effets secondaires moindres ont été commercialisés comme le grazoprévir (**5.2**) (2018) et le siméprévir (**5.3**) (2013) (Figure 5.1).



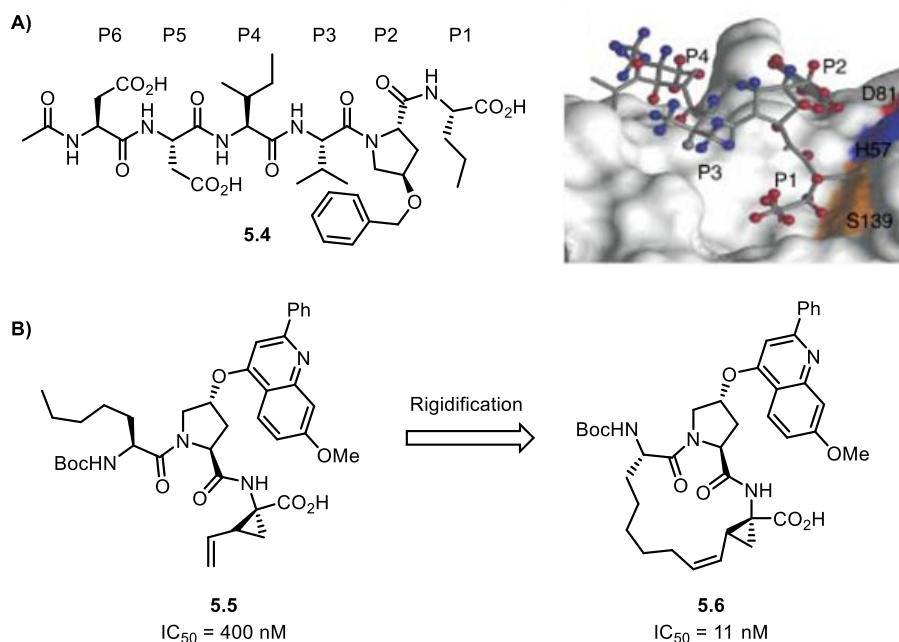
**Figure 5.1** Structure des antiviraux ribavirine (**5.1**), grazoprévir (**5.2**) et siméprévir (**5.3**)

### 5.1 Découverte des antiviraux macrocycliques

Au début des années 2000, un groupe de chimistes de Boehringer Ingelheim (Laval, Québec, Canada) a mené des études RMN afin d'étudier l'interaction de l'inhibiteur hexapeptide **5.4** avec la protéase NS3 (en absence du co-facteur NS4A)<sup>3</sup>. La modélisation de l'interaction du substrat avec le site actif a permis aux auteurs d'identifier les fonctionnalités non nécessaires et de rationaliser le design d'une nouvelle classe d'inhibiteurs adoptant la

bonne conformation pour maximiser l'interaction. Par leurs observations, ils ont déterminé que les résidus P4, P5 et P6 se situaient à l'extérieur du site actif et qu'un mélange de conformères *cis/trans* de l'amide P2-P3 était présent. Les auteurs ont donc rationalisé qu'un pont aliphatique reliant les résidus P1 et P3 permettrait de rigidifier la conformation du lien amide en position *trans*.

Leurs travaux d'optimisation structurelle ont été effectués à partir du médicament prototype **5.5**<sup>4</sup>. En rigidifiant la structure afin d'obtenir le macrocycle **5.6**, les auteurs ont observé une augmentation significative de l'activité inhibitrice du médicament ( $IC_{50} = 400$  nM (**5.5**) à 11 nM (**5.6**)) (Figure 5.2).

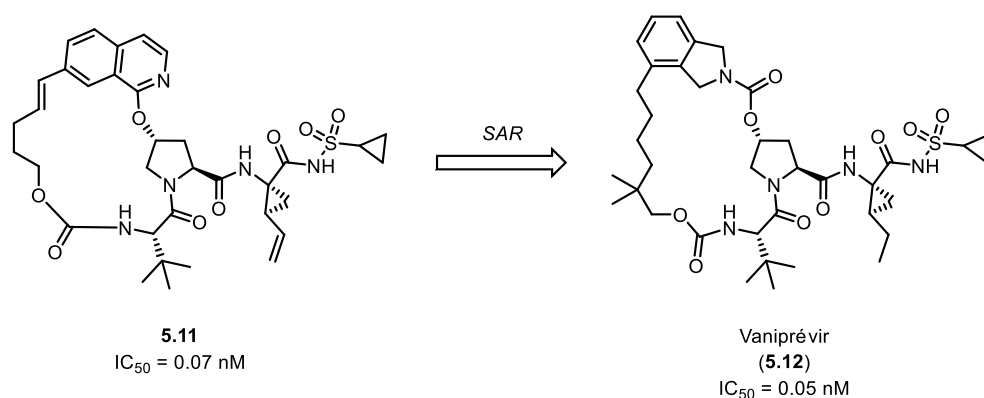


**Figure 5.2** Modélisation de l'interaction entre l'hexapeptide **5.4** et l'enzyme NS3 (A) et Augmentation de l'activité inhibitrice par rigidification de la conformation de **5.5** en macrocycle **5.6** (B). Image reproduite avec l'autorisation de John Wiley and Sons

La découverte de cette nouvelle classe d'antiviraux macrocycliques a poussé les auteurs à effectuer une étude de relation structure-activité (*SAR*)<sup>5</sup>. Après quelques modifications, notamment au niveau de l'hétérocycle et du groupement protecteur carbamate, le médicament pionnier BILN 2061 (**5.7**) a vu le jour. Tout au long du développement de BILN 2061 (**5.7**), l'étape de fermeture de cycle a été réalisée par une réaction de métathèse d'oléfines transformant le diène **5.8** en macrocycle **5.9** utilisant le catalyseur de Grubbs-



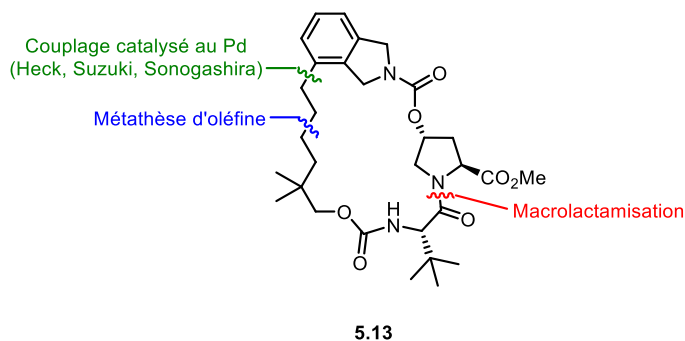
cette étude computationnelle ont permis à l'équipe d'identifier le candidat macrocyclique **5.11**. Ce macrocycle structurellement très similaire à BILN 2061 (**5.7**) possède toutefois une activité environ 4 fois plus grande, soit une  $IC_{50}$  de 0.07 nM (0.3 nM pour **5.7**). Sa particularité est la connexion du macrocycle. En effet, le macrocycle **5.11** est connecté entre les positions P2 et P4 tandis qu'il était connecté entre P1 et P3 dans le cas de BILN 2061 (**5.7**). Par la suite, une étude *SAR* a permis d'identifier un composé légèrement supérieur, soit le vaniprévir (MK-7009) (**5.12**) (Figure 5.3)<sup>9</sup>.



**Figure 5.3** Structures du macrocycle prototype **5.11** et du vaniprévir (**5.12**)

Contrairement aux autres candidats de l'étude structure-activité, le vaniprévir (**5.12**) possédait non seulement une activité antivirale accrue, mais aussi de bonnes propriétés pharmacocinétiques et une excellente sélectivité vis-à-vis diverses protéases humaines<sup>10</sup>. Ceci a donc permis à ce composé biologiquement actif d'entrer rapidement en phase clinique<sup>11</sup>.

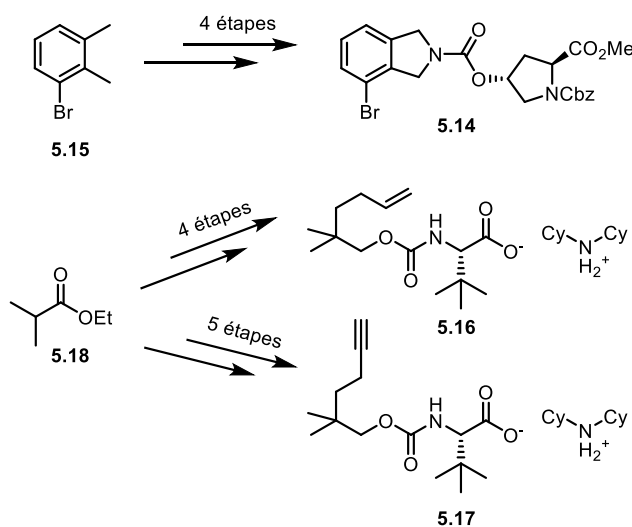
Les phases cliniques I, II et III nécessitent une quantité de produits beaucoup plus importante que les premiers tests *in vitro*. De ce fait, de nouvelles stratégies de synthèse ont été envisagées, afin que la préparation de ces composés soit sécuritaire, non nuisible pour l'environnement et économiquement viable pour la synthèse manufacturière. Les chimistes de la compagnie pharmaceutique Merck ont donc exploré plusieurs voies de synthèse pour la construction du cœur macrocyclique du vaniprévir (**5.13**) (Figure 5.4).



**Figure 5.4** Déconnexions étudiées pour la construction du cœur macrocyclique du vaniprévir (**5.13**) par Merck

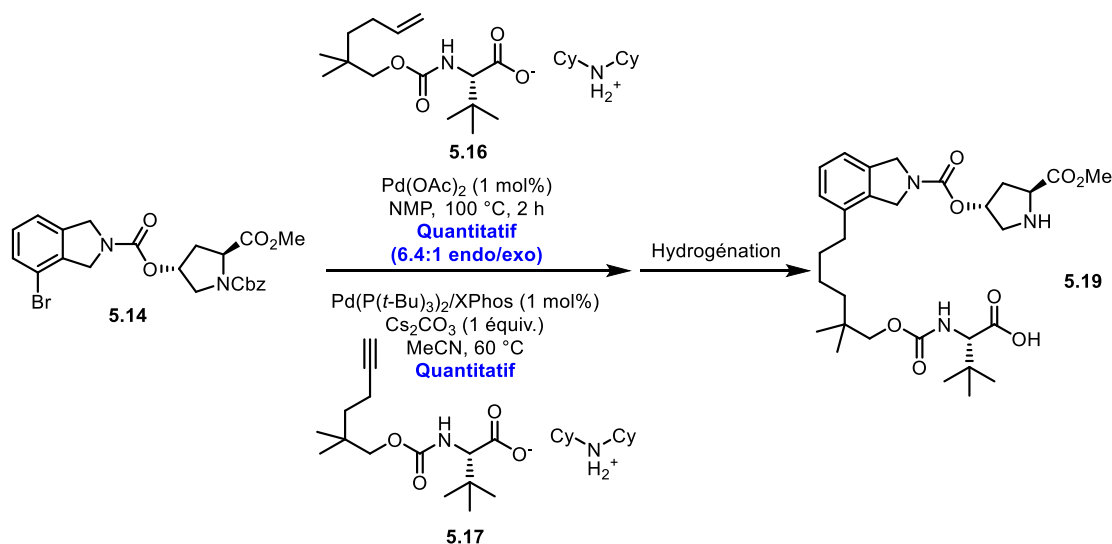
### 5.2.2 Synthèse du vaniprévir par macrolactamisation

Une première voie de synthèse envisagée par Merck a été d'employer une réaction de macrolactamisation comme étape de fermeture de cycle<sup>12</sup>. Pour s'y prendre, l'équipe a construit deux fragments qu'ils ont couplés ensemble selon deux stratégies de couplage catalysé par un complexe de palladium, soit les couplages de Heck et de Sonogashira. Le premier fragment carbamate **5.14** possédant les motifs isoindoline et hydroxyproline a pu être obtenu en quatre étapes à partir du 3-bromo-*o*-xylène (**5.15**). Ce fragment universel a pu être utilisé pour les deux stratégies de couplage au palladium. Pour ce qui est des seconds fragments carbamate **5.16** et **5.17**, ils ont été synthétisés selon une même stratégie à partir de l'isobutyrate d'éthyle (**5.18**) (Figure 5.5).



**Figure 5.5** Synthèse des fragments nécessaires pour les couplages de Heck et de Sonogashira

Une fois tous les fragments en main, ils ont pu être joints à l'aide des conditions de couplage de Heck ou de Sonogashira. Une étape d'hydrogénation subséquente permet l'obtention du même composé, soit le précurseur linéaire **5.19** (Schéma 5.2). Il est également possible d'apprécier la déprotection simultanée du groupement protecteur carboxybenzyle (Cbz) judicieusement sélectionné.

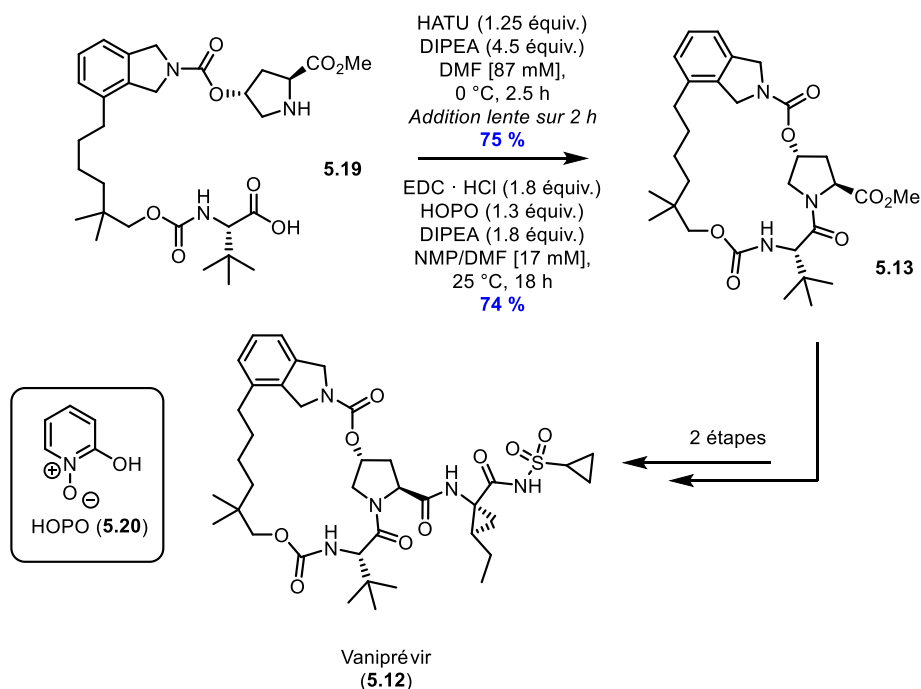


**Schéma 5.2** Couplages de Heck et de Sonogashira pour la synthèse du précurseur linéaire **5.19**

Après une étude des conditions réactionnelles optimales, la voie de synthèse impliquant le couplage de Heck a été sélectionnée. Malgré un rendement plus faible à cause de la formation du sous-produit *exo*, la voie de synthèse nécessite une étape réactionnelle de moins. De plus, l'absence de ligand pour cette réaction de couplage réduit significativement le coût lié à cette synthèse.

Finalement, l'étape de fermeture de cycle par une réaction de couplage peptidique a été étudiée en détails. Divers agents de couplage et additifs ont été criblés afin d'identifier les conditions optimales pour l'obtention du cœur macrocyclique du vaniprévir **5.13**. L'utilisation de l'agent de couplage HATU et celle du couple EDC/HOPO (**5.20**) ont été étudiés (Schéma 5.3). On observe une très bonne réactivité (100 % conversion en moins de 5 min) avec l'agent de couplage HATU, alors qu'un temps réactionnel beaucoup plus long (12 h) est nécessaire avec le couple EDC/HOPO. Comme la cinétique de la réaction de macrolactamisation impliquant HATU était très rapide, une addition lente du substrat au mélange réactionnel a

permis d'effectuer la réaction à une concentration finale de 87 mM (50 g/L), tout en maintenant un bon rendement de 75 %. Pour le couple EDC/HOPO, la stratégie d'addition lente n'a pas été fructueuse et la macrocyclisation n'a pu qu'être effectuée à une concentration de 17 mM (10 g/L) avec un rendement de 74 %. Malgré l'efficacité supérieure des conditions de HATU, le coût d'utilisation d'une plus grande quantité de solvant pour EDC/HOPO a été jugé économiquement plus avantageux que l'utilisation d'un agent de couplage plus efficace, mais dispendieux, comme HATU. Une fois la synthèse du cœur macrocyclique complétée, deux étapes simples de saponification et de couplage de la chaîne latérale ont permis l'achèvement d'une voie de synthèse du vaniprévir (**5.12**) avec un rendement global de 20%. Cette synthèse économiquement viable, a pu être utilisée pour soutenir les besoins des phases cliniques.

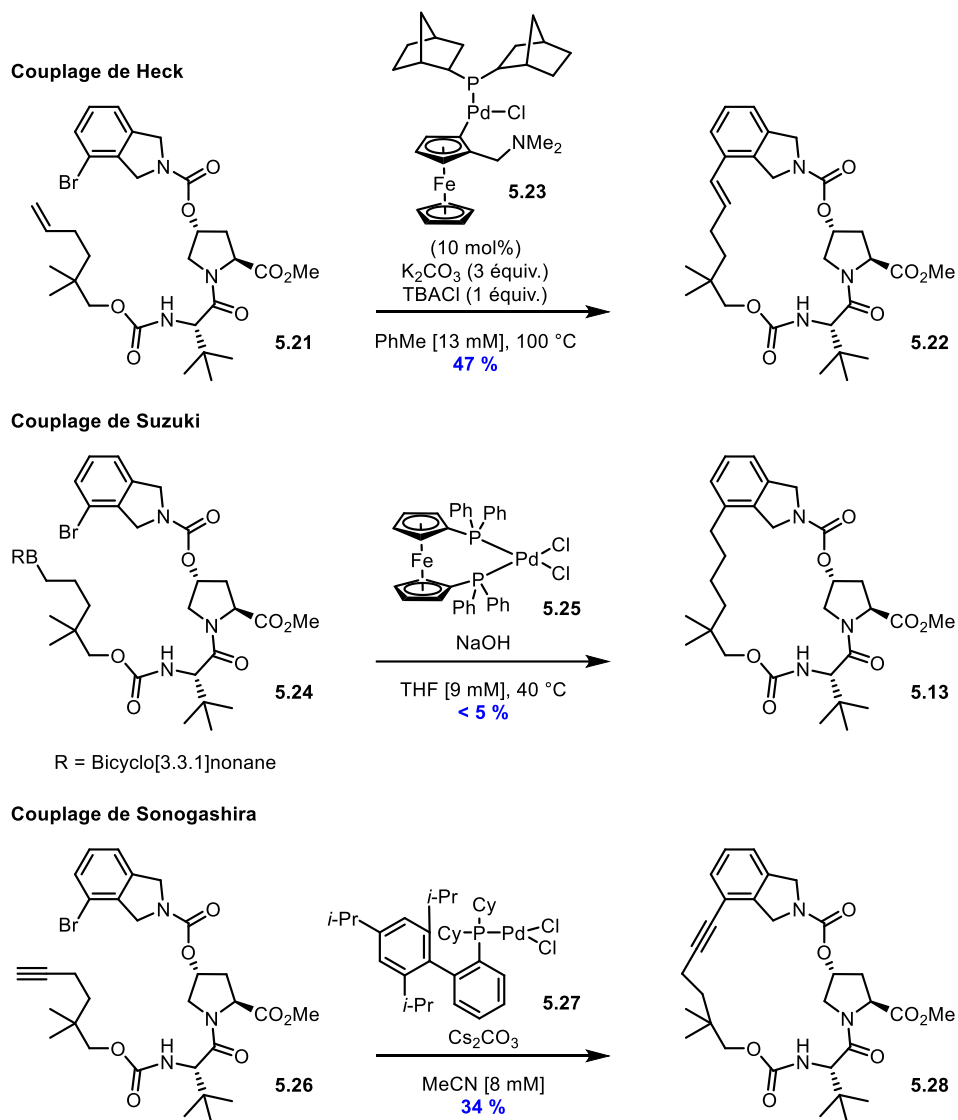


**Schéma 5.3** Construction du cœur macrocyclique du vaniprévir **5.13** par réaction de macrolactamisation.

### **5.2.3 Synthèse du vaniprévir par une réaction de couplage utilisant un catalyseur de palladium**

La synthèse du vaniprévir présentée dans la section précédente emploie une étape de macrolactamisation utilisant un agent de couplage pour la fermeture de cycle. Un des désavantages majeurs de ce type de réaction est l'utilisation d'une quantité stœchiométrique de réactifs générant, par le fait même, une quantité stœchiométrique de sous-produits. Une voie de synthèse ayant recours à une réaction catalytique serait donc idéale. Dans la même étude ayant menée à la voie de synthèse par macrolactamisation, les auteurs ont également étudié différentes approches catalytiques pour l'étape de macrocyclisation<sup>12</sup>. Au total, trois approches catalytiques employant un catalyseur de palladium ont été explorées, soit les réactions de couplage de Heck, de Suzuki et de Sonogashira (Schéma 5.4).





**Schéma 5.4** Tentatives de macrocyclisation par couplage de Heck, Suzuki et Sonogashira

Le couplage de Heck intramoléculaire du précurseur **5.21** a d'abord donné des résultats intéressants. Il a été possible d'obtenir le macrocycle **5.22** avec un rendement de 47 % en utilisant un catalyseur très complexe de palladium contenant un ligand ferrocényle et un ligand dinorbonylphosphine (**5.23**). Cependant, des conditions de dilution élevées (13 mM) étaient nécessaires et des réactions secondaires d'oligomérisation, de débromation et de formation du produit de couplage *exo* ont été observées.

Les auteurs ont ensuite tenté d'obtenir le macrocycle par couplage de Suzuki intramoléculaire. Pour ce faire, l'alcène **5.21** utilisé pour la macrocyclisation par couplage de Heck a été transformé en adduit de 9-BBN **5.24**. À partir de ce dernier, et en utilisant le catalyseur PdCl<sub>2</sub>(dppf) (**5.25**), le macrocycle **5.13** n'a été formé qu'à l'état de trace, malgré l'utilisation d'une dilution élevée (9 mM).

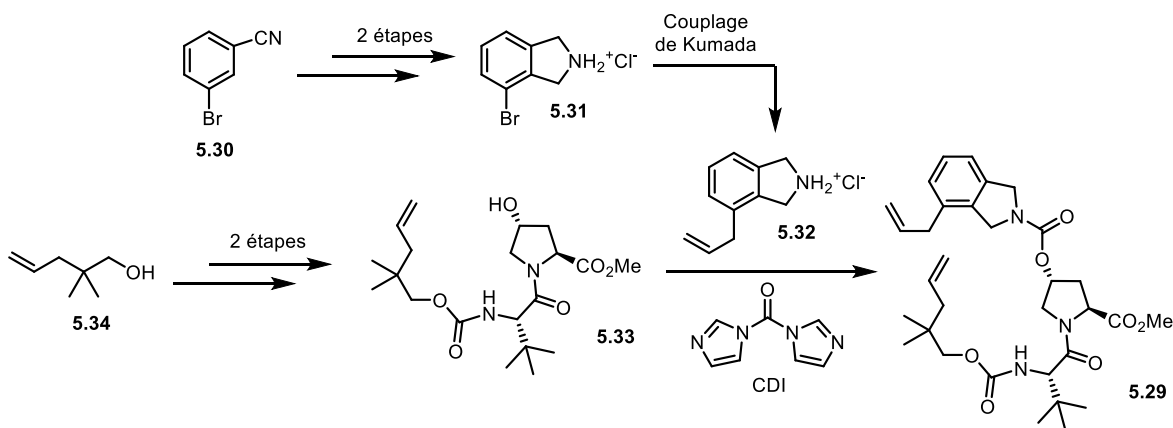
Finalement, une macrocyclisation par couplage de Sonogashira a été envisagée. À partir du précurseur linéaire **5.26** contenant un alcyne terminal, les auteurs ont utilisé le catalyseur PdCl<sub>2</sub>(XPhos) (**5.27**) dans l'acétonitrile (8 mM) pour obtenir un faible rendement de 34 % du macrocycle **5.28**, en plus d'une quantité non négligeable d'oligomères.

Ces trois tentatives de macrocyclisation catalysées par un complexe palladium démontrent bien le défi synthétique de cette étape clé. Une cinétique trop lente dans des conditions très diluées mène à une dégradation du système catalytique tandis qu'une cinétique trop rapide mène à la formation de sous-produits oligomériques.

#### **5.2.4 Synthèse du vaniprévir par métathèse d'oléfines**

Au début de l'étude de macrocyclisation du vaniprévir réalisée par l'équipe de Merck, une autre voie de synthèse catalytique a été brièvement étudiée. Il s'agit d'une macrocyclisation par métathèse d'oléfines catalysée par un complexe de ruthénium, une stratégie qui a initialement servi pour la synthèse du vaniprévir lors de sa découverte<sup>9</sup>. Toutefois, malgré son efficacité remarquable (rendements de 91 – 98 %), des conditions de dilution (<3 mM) et une charge catalytique (10 - 30 mol%) très élevées étaient primordiales; de plus, toutes les tentatives afin d'améliorer les conditions réactionnelles ont mené à une baisse du rendement.

Avec la progression du médicament en phase clinique, la compagnie Merck a décidé de retravailler sur la voie de macrocyclisation par métathèse d'oléfines<sup>13</sup>. En utilisant cette réaction chimique, le macrocycle peut être construit de trois façons possibles : 1) un couplage styryle/homoallyle, 2) un couplage allyle/allyle ou bien 3) un couplage homoallyle/vinyle. Pour des raisons économiques et de facilité de synthèse, l'option allyle/allyle a été sélectionnée. La synthèse du précurseur linéaire **5.29** suit essentiellement la même stratégie développée précédemment, à l'exception du motif isoindoline. Afin d'installer le groupement allyle nécessaire pour l'étape de métathèse d'oléfines, un couplage de Kumada a été utilisé afin de former l'isoindoline **5.32** (Figure 5.6). Parallèlement, l'autre fragment alcène **5.33** a été synthétisé en deux étapes à partir de l'alcool **5.34**. Enfin, les deux fragments ont pu être couplés en utilisant du carbonyldiimidazole (CDI) pour former le diène **5.29**.

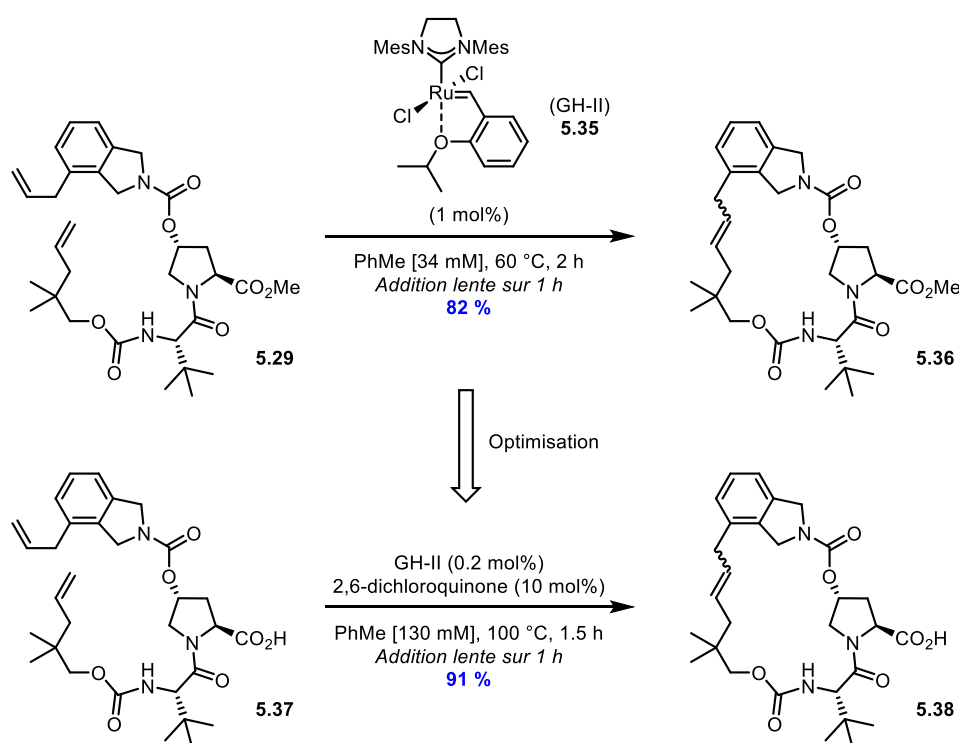


**Figure 5.6** Synthèse du diène linéaire **5.29**

Une fois le précurseur linéaire **5.29** en main, les chercheurs ont tenté de résoudre les problèmes rencontrés lors du développement du médicament, soit les problèmes de dilution et de charge catalytique très élevées. Ils ont rapidement découvert qu'une addition lente simultanée du diène **5.29** et de 1 mol% du catalyseur GH-II (**5.35**) à une concentration de 34 mM permettait d'obtenir le macrocycle **5.36** dans un rendement de 82%. En augmentant la concentration, les chercheurs ont observé l'apparition d'un sous-produit macrocyclique à 19 chaînons. Ce sous-produit est formé à la suite de la cyclisation d'un précurseur linéaire dont l'un des groupements alcènes a subi une isomérisation causée par la présence d'un hydrure de ruthénium. En effet, il est connu que les catalyseurs de métathèse d'oléfines peuvent dégrader dans les milieux réactionnels pour former ce type d'hydrure<sup>14</sup>. Pour empêcher leur formation,

les chercheurs ont ajouté un additif (2,6-dichloroquinone) afin de piéger les hydrures de ruthénium formés.

Il a également été observé que la pureté du diène **5.29** jouait un rôle majeur dans l'efficacité de la réaction de métathèse. Les chercheurs ont donc opté pour le diène **5.37**, un acide carboxylique pouvant être purifié par cristallisation. Avec toutes ces modifications, les conditions réactionnelles finales de l'étape de macrocyclisation par métathèse d'oléfines impliquent seulement 0.2 mol% du catalyseur GH-II à une concentration de 130 mM pour donner le macrocycle **5.38** dans un rendement de 91 % (Schéma 5.5).



**Schéma 5.5** Synthèse du cœur macrocyclique du vaniprévir par macrocyclisation par métathèse d'oléfines

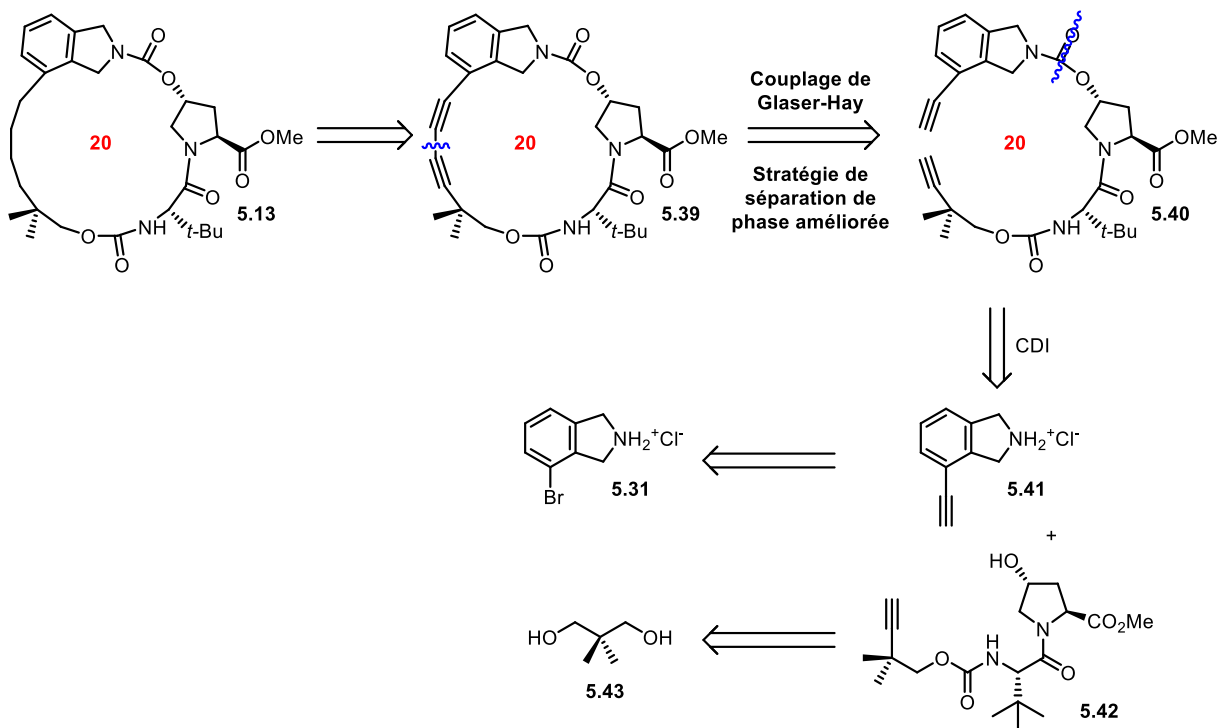
### 5.3 Analyse rétrosynthétique de la synthèse du vaniprévir : Macrocyclisation par réaction de Glaser-Hay à concentration élevée

À la suite du succès de l'application de la stratégie de séparation de phase pour la synthèse du macrocycle complexe ivorenolide A, notre groupe avait le désir de développer

davantage l'efficacité de ce protocole. En effet, notre protocole d'origine permettait la synthèse de macrocycles à une concentration d'environ 30 mM, ce qui était considéré comme étant relativement concentré. Toutefois, comme il a été démontré dans ce chapitre, la viabilité économique de la synthèse de macrocycles dans le domaine de la chimie médicinale requiert plutôt des réactions se déroulant à des concentrations supérieures à 100 mM. Il s'agit donc d'un défi de taille puisque cet ordre de grandeur de concentration est normalement utilisé pour des réactions intermoléculaires et donc, le contrôle de la macrocyclisation par rapport à l'oligomérisation est d'autant plus difficile.

Pour s'attaquer à ce problème, nous avons posé comme hypothèse que diminuer davantage la vitesse de diffusion du substrat linéaire de la phase apolaire inactive (PEG) vers la phase polaire active (MeOH) permettrait d'effectuer la réaction dans un milieu nettement plus concentré (>100 mM). Nous estimions que ce résultat pouvait être atteint par l'utilisation d'un co-solvant de poly(éthylène) glycol dendritique, un motif ayant démontré un plus lent relargage de médicaments comparativement à son homologue linéaire<sup>15</sup>. Afin d'évaluer l'efficacité du protocole amélioré dans un contexte de chimie médicinale, la synthèse du cœur macrocyclique du vaniprévir **5.13** a été envisagée. L'application du nouveau protocole de macrocyclisation de Glaser-Hay à concentration élevée permettrait d'obtenir le macrocycle **5.39** à partir du diyne linéaire **5.40** (Figure 5.7). Pour la synthèse du précurseur linéaire, une approche convergente a été planifiée. En utilisant le réactif CDI, le motif carbamate reliant les fragments isoindoline **5.41** et alcool **5.42** a pu être construit. La synthèse de ces derniers a pu être faite à partir du sel d'hydrochlorure de 3-bromoisoindoline (**5.31**), commercialement disponible, et du 2,2-diméthylpropane-1,3-diol (**5.43**) respectivement. En résumé, les buts du projet étaient :

- 1) Améliorer le système de séparation de phase afin de permettre une macrocyclisation dans un milieu très concentré (>100 mM).
- 2) Appliquer le nouveau système de séparation de phase à la synthèse d'un macrocycle complexe d'intérêt pharmaceutique, comme le cœur macrocyclique du vaniprévir.



**Figure 5.7** Analyse rétrosynthétique pour la synthèse du cœur macrocyclique **5.13** du vaniprévir par macrocyclisation de Glaser-Hay à haute concentration.

## 5.4 Bibliographie

1. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
2. Guide de médication de Rebetol (Capsule de Ribavirine), Merck [https://www.merck.com/product/usa/pi\\_circulars/r/rebetol/rebetol\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/r/rebetol/rebetol_pi.pdf) (consulté le 5 septembre 2019)
3. Tsantrizos, Y. S.; Bolger, G.; Bonneau, P.; Cameron, D. R.; Goudreau, N.; Kukolj, G.; LaPlante, S. R.; Llinàs-Brunet, M.; Nar, H.; Lamarre, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1356-1360.
4. Goudreau, N.; Cameron, D. R.; Bonneau, P.; Gorys, V.; Plouffe, C.; Poirier, M.; Lamarre, D.; Llinàs-Brunet, M. *J. Med. Chem.* **2004**, *47*, 123-132.
5. Llinàs-Brunet, M.; Bailey, M. D.; Bolger, G.; Brochu, C.; Faucher, A.-M.; Ferland, J.-M.; Garneau, M.; Ghiro, E.; Gorys, V.; Grand-Maître, C.; Halmos, T.; Lapeyre-Paquette, N.; Liard, F.; Poirier, M.; Rhéaume, M.; Tsantrizos, Y. S.; Lamarre, D. *J. Med. Chem.* **2004**, *47*, 1605-1608.
6. (a) Tsantrizos, Y. S.; Cameron, D. R.; Faucher, A.-M.; Ghiro, E.; Goudreau, N.; Halmos, T.; Llinàs-Brunet, M. 2000, *Macrocyclic Peptides Active Against the Hepatitis C Virus*. PTC International Application [Boehringer Ingelheim (Canada) Ltd.]

- WO 00/59929** (b) Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiron, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinàs-Brunet, M. *Org. Lett.* **2004**, *6*, 2901-2904.
7. Yee, N. K.; Farina, V.; Houppis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson M. *J. Org. Chem.* **2006**, *71*, 7133-7145.
  8. Liverton, N. J.; Holloway, M. K.; McCauley, J. A.; Rudd, M. T.; Butcher, J. W.; Carroll, S. S.; DiMuzio, J.; Fandozzi, C.; Gilbert, K. F.; Mao, S.-S.; McIntyre, C. J.; Nguyen, K. T.; Romano, J. J.; Stahlhut, M.; Wan, B.-L.; Olsen, D. B.; Vacca, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4607-4609.
  9. McCauley, J. A.; McIntyre, C. J.; Rudd, M. T.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Gilbert, K. F.; Bush, K. J.; Holloway, M. K.; Swestock, J.; Wan, B.-L.; Carroll, S. S.; DiMuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S.-S.; Stahlhut, M. W.; Fandozzi, C. M.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *J. Med. Chem.* **2010**, *53*, 2443-2463.
  10. Liverton, N. J.; Carroll, S. S.; DiMuzio, J.; Fandozzi, C.; Graham, D. J.; Hazuda, D.; Holloway, M. K.; Ludmerer, S. W.; McCauley, J. A.; McIntyre, C. J.; Olsen, D. B.; Rudd, M. T.; Stahlhut, M.; Vacca, J. P. *Antimicrob. Agents Chemother.* **2010**, *54*, 305-311.
  11. Manns, M. P.; Gane, E.; Rodriguez-Torres, M.; Stoehr, A.; Yeh, C.-T.; Marcellin, P.; Wiedmann, R. T.; Hwang, P. M.; Caro, L.; Barnard, R. J. O.; Lee, A. W. *Hepatology* **2012**, *56*, 884-893.
  12. Song, Z. J.; Tellers, D. M.; Journet, M.; Kuethe, J. T.; Lieberman, D.; Humphrey, G.; Zhang, F.; Peng, Z.; Waters, M. S.; Zewge, D.; Nolting, A.; Zhao, D.; Reamer, R. A.; Dormer, P. G.; Belyk, K. M.; Davies, I. W.; Devine, P. N.; Tschaen, D. M. *J. Org. Chem.* **2011**, *76*, 7804-7815.
  13. Kong, J.; Chen, C.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820-3828.
  14. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160-17161.
  15. Thakur, S.; Kesharwani, P.; Tekade, R. K.; Jain, N. K. *Polymer* **2015**, *59*, 67-92.

# Chapitre 6. Phase Separation Macrocyclization in a Complex Pharmaceutical Setting: Application toward the Synthesis of Vaniprevir

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*J. Org. Chem.* **2017**, *82*, 7576-7582

## Contributions :

- Éric Godin a participé à la mise en œuvre des expériences, a fait la synthèse de toute la molécule, a fait les études de macrocyclisation concernant le vaniprevir et a participé à la rédaction du manuscrit concernant la partie expérimentale.
- Anne-Catherine Bédard a participé à la mise en œuvre des expériences, a exploré une première voie synthétique concernant le vaniprevir, a fait les études de macrocyclisation du modèle.
- Michaël Raymond a participé à l'exploration d'une voie de synthèse préliminaire du fragment isoindoline et a réalisé les mesures de tension de surface.
- Shawn K. Collins a participé à la mise en œuvre des expériences et à l'écriture du manuscrit.

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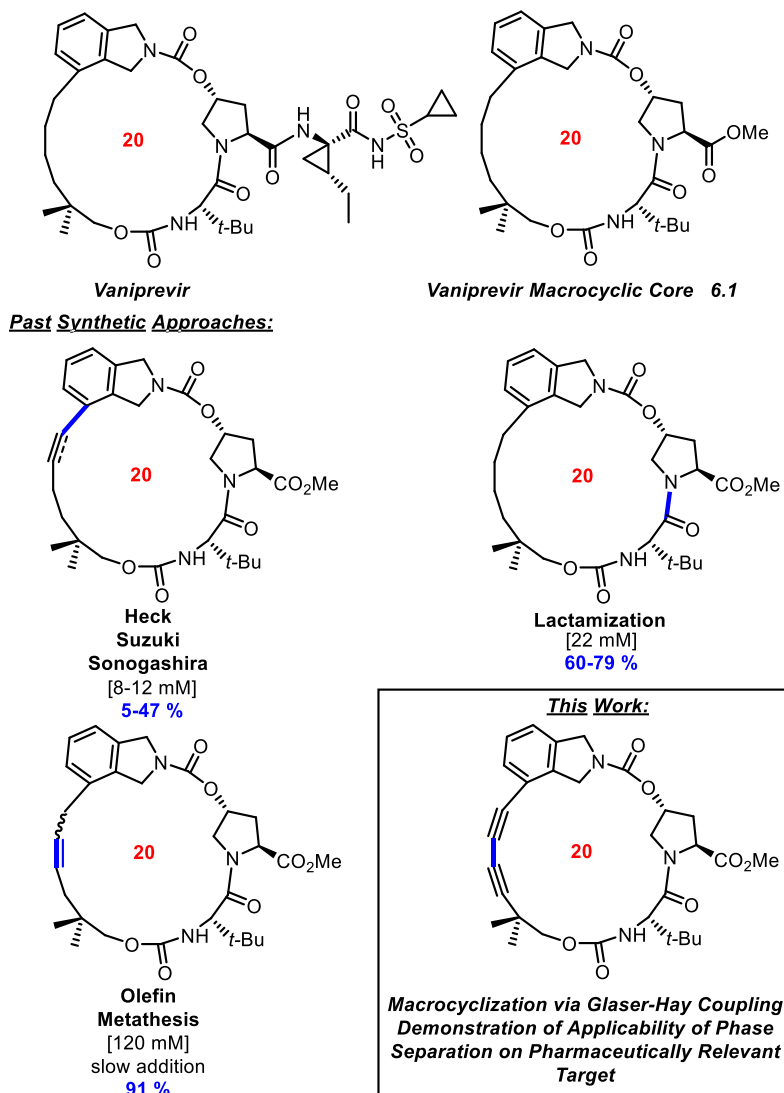
## 6.1 Abstract

A phase separation/continuous flow strategy employing an oxidative Glaser-Hay coupling of alkynes has been applied towards the synthesis of the macrocyclic core of complex pharmaceutical vaniprevir. The phase separation/continuous flow strategy afforded similar yields at 100-500 times the concentration and at shorter reaction times than common slow addition/high dilution techniques. In addition, dendritic PEG co-solvents were employed in the phase separation strategy for the first time and shown to allow productive macrocyclization at concentrations up to 200 mM.

## 6.2 Introduction

The macrocycle chemotype has made significant contributions to drug discovery due to unique properties that can allow for scanning of new chemical space.<sup>1</sup> Consequently, the interest in macrocycles in drug discovery has experienced significant growth in the past decade.<sup>2</sup> Terrett and co-workers have highlighted that current macrocyclic drugs are almost exclusively derived from naturally occurring macrocycles, with modifications typically occurring only at specific positions.<sup>3</sup> Synthetic macrocycles have come to represent a growing class of drug candidates, yet their diversity remains limited by the number of robust synthetic techniques amenable to library generation.<sup>4</sup> One of the major obstacles to any macrocycle synthesis involves surmounting the difficult ring closing event. Indeed, Terrett and co-workers also stated, “The only residual difficulty in macrocycle synthesis is finding conditions that allow good yields of cyclized materials from acyclic precursors... For single compounds, this is usually achieved by resorting to the use of large reaction volumes and low reactant concentrations; conditions that were devised many years ago.”<sup>3</sup> A representative example of the difficulty of optimizing a macrocyclization protocol was shown in the synthesis of the macrocyclic core of vaniprevir, a macrocyclic hepatitis C virus (HCV) NS3/4A protease inhibitor developed by Merck & Co. which was recently approved for treating hepatitis C in 2014 in Japan (Figure 6.1).<sup>5</sup> A macrolactamization protocol provided encouraging yields, but suffered from the use of stoichiometric reagents, while many catalytic cross-coupling routes provided undesirable yields. An olefin metathesis route proved optimal and could be conducted with low catalyst loading (0.2 mol %) at a concentration of 120 mM, although slow

addition techniques were employed. Our group has reported a phase separation strategy as a novel macrocyclization strategy permitting catalytic transformations at relatively high concentrations.<sup>6</sup> The ability to control dilution effects rests upon the ability of poly(ethylene)glycol (PEG) co-solvents to form lipophilic aggregates in solution with an accompanying hydrophilic solvent, whereby the aggregates preferentially solubilize organic substrates. Slow diffusion of a linear precursor out of a PEG aggregate into the MeOH co-solvent and subsequent cyclization is believed to mimic slow addition conditions. Through judicious control of the ratio of PEG:MeOH, the diffusion of the linear precursor can be controlled to optimize the preference for macrocyclization versus oligomerization. In general, higher ratios of PEG:MeOH (2:1→8:1) allow for macrocyclization processes to be conducted at much higher concentrations all the while affording higher yields.

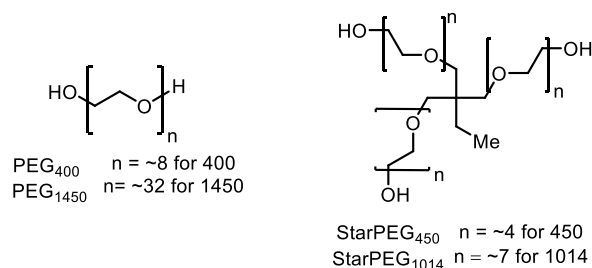


**Figure 6.1** Macrocyclization strategies towards vaniprevir

Consequently, the phase separation strategy represents an effort to apply the principles of sustainability to macrocyclization chemistry.<sup>7</sup> The phase separation strategy has recently been exploited by Itami and co-workers for the synthesis of thiophene-based macrocycles for materials science applications,<sup>8</sup> however no demonstrations of the utility of the phase separation strategy towards medicinal chemistry have been reported. Herein we report on the application of a phase separation strategy employing the rarely-exploited Glaser-Hay coupling for the synthesis of a complex pharmaceutical target.

## 6.3 Results/Discussion

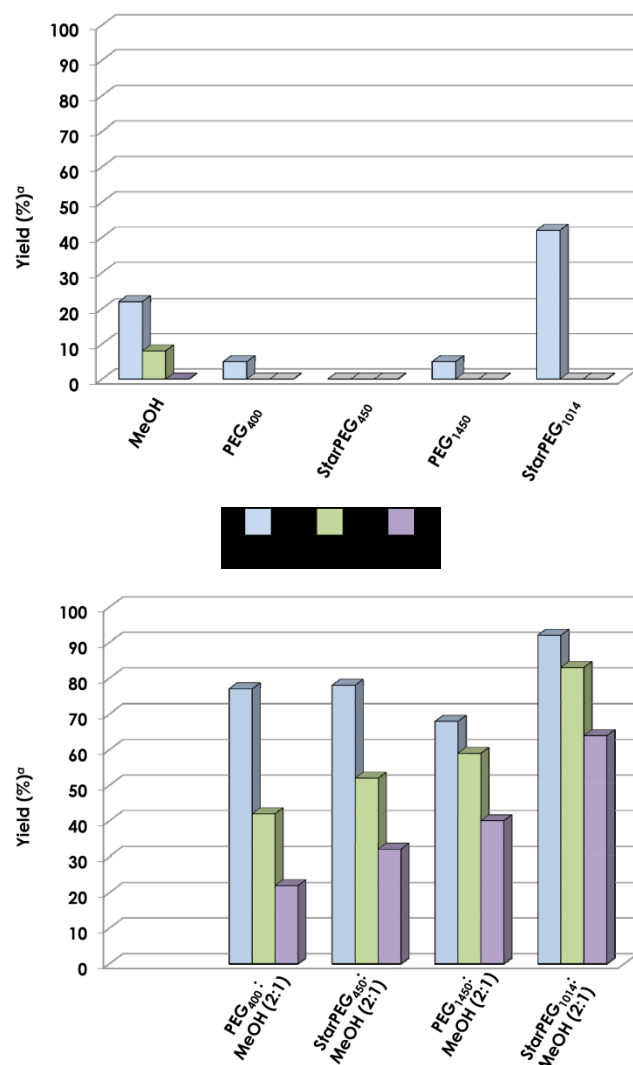
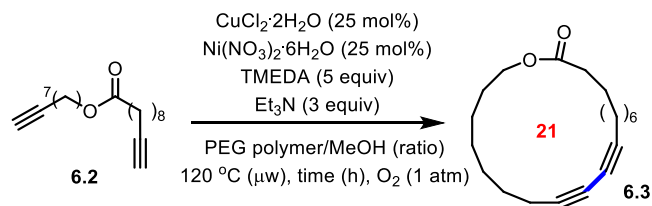
*Exploration of different PEG co-solvents for macrocyclization via phase separation.* The phase separation strategy relies upon the ability of PEG co-solvents to form lipophilic aggregates in MeOH solutions. Aggregation can be confirmed via surface tension measurements.<sup>9</sup> It has been shown that the structural characteristics of the PEG co-solvent can affect both its aggregation behaviour as well as catalysis.<sup>10</sup> For example, hydroxyl-terminated PEGs are important for inducing aggregation in MeOH and the ability to observe high macrocyclization efficiency. More lipophilic solvents, such as longer chain PEGs, or poly(propylene)glycol (PPG) solvents, allow for catalysis at lower catalyst loadings.



**Figure 6.2** PEG co-solvents for study in a “phase separation” macrocyclization process

The macrocyclization investigations via Glaser-Hay coupling were to be conducted using reaction conditions previously developed by our group,<sup>6</sup> which exploit a Ni-based co-catalyst to accelerate the rate of oxidative coupling,<sup>11</sup> under microwave heating. Based upon previous reports,<sup>6</sup> PEG<sub>400</sub> and PEG<sub>1450</sub> were selected to be evaluated in the macrocyclization to form the core of vaniprevir (Figure 6.2). In addition, branched dendritic or “StarPEG” polymers were also explored for the first time in macrocyclizations via phase separation (Figure 6.2). Dendritic PEGs exhibit low cytotoxicities and have found use in drug delivery applications.<sup>12</sup> In addition, StarPEGs are known to have an enhanced ability to encapsulate hydrophilic and hydrophobic guests as well as sustained release in aqueous media,<sup>13</sup> properties which would also be highly beneficial for developing a phase separation macrocyclization process. Two StarPEGs were chosen for study with average molecular weights of 450 and 1014 g·mol<sup>-1</sup>. The StarPEGs were selected so that their behavior could be compared to linear PEGs that had similar average molecular weights (400 and 1450 respectively). Surface tension measurements demonstrated that StarPEGs exhibit aggregation behaviour in MeOH similar to

the other PEG co-solvents: aggregation occurred in ratios of 1:1 up to 8:1 StarPEG:MeOH.<sup>14</sup> Before exploring the macrocyclization of the vaniprevir precursor, preliminary studies were performed in batch to compare the ability of the selected PEG polymers to control dilution effects at concentrations of 24, 100 and 200 mM (Figure 6.3).<sup>15</sup> The macrocyclization of model bis-alkyne **6.2** was chosen for initial investigations as its aliphatic structure is relatively free of structural biases which could influence its ability to undergo macrocyclization. Control reactions in either pure MeOH or pure PEG solvent are important for establishing whether phase separation is proving beneficial to the macrocyclization process. Control macrocyclizations (**6.2**→**6.3**, Figure 6.3 *top*) performed in pure MeOH showed low yields of macrocycle **6.3** at 24 mM (22 %) and only traces could be observed at either 100 or 200 mM. Control reactions performed in 100% PEG<sub>400</sub>, StarPEG<sub>450</sub>, or PEG<sub>1450</sub>, at 24 mM, all afforded yields of macrocycle **6.3** below 5 %. In sum, the control reactions all establish that phase separation provided by the mixtures of PEG co-solvent:MeOH is beneficial. An exception was the macrocyclization in StarPEG<sub>1014</sub>, where the yield of **6.3** was 43 %, implicating that for phase separation to be successful in the dendritic PEG system, yields of **6.3** would have to exceed 43 %. Also of note: macrocyclization in 100% PEG at 100 or 200 mM was not possible due to limited solubility of the catalysts and/or bis-alkyne **6.2**. The first macrocyclizations in PEG polymer:MeOH mixtures were performed at 24 mM at a ratio of 2:1 PEG polymer:MeOH, which had previously been shown to provide high yields of products (Figure 6.3 *bottom*). When macrocyclization was carried out in previously reported 2:1 PEG<sub>400</sub>:MeOH mixture, the yield of **6.3** was 77 %, and a similar yield of 78 % was obtained for the analogous 2:1 StarPEG<sub>450</sub>/MeOH. When using the linear 2:1 PEG<sub>1450</sub>:MeOH mixture the yield of **6.3** was 68 %, but increased dramatically in 2:1 StarPEG<sub>1014</sub>:MeOH to afford a 91% yield of macrocycle **6.3**.

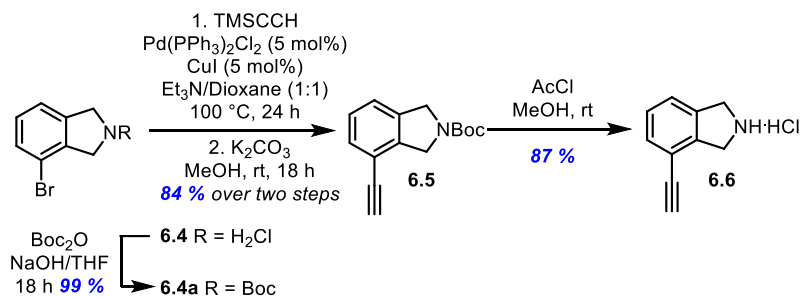


**Figure 6.3** Effect of solvent and concentration on macrocyclization (6.2→6.3)

*Top:* In pure MeOH, linear PEG and StarPEG solvents. *Bottom:* Solvent mixtures of linear PEGs and StarPEGs in MeOH. Macrocyclizations were performed at 24 mM (blue, 6 h), 100 mM (green, 8 h) and 200 mM (purple, 8 h). <sup>a</sup> All entries represent isolated yields following silica gel chromatography. Ring size indicated in red.

Next, macrocyclization was performed at concentrations of 100 and 200 mM with 8 h reaction times, as the preliminary results demonstrated that macrocyclizations in the StarPEG solvents often proceeded slower. When macrocyclization was carried out in previously reported 2:1 PEG<sub>400</sub>:MeOH mixture, yields of **6.3** dropped from 77 % (24 mM) to 22 % when the concentration was pushed to 200 mM. Reactions performed in the analogous 2:1 StarPEG<sub>450</sub>/MeOH mixture, provided slightly higher yields, however at the target 200 mM concentration, only 32 % of **6.3** could be isolated. Further improvements were observed when PEG polymers with higher average molecular weights were used as co-solvents. In the linear 2:1 PEG<sub>1450</sub>:MeOH mixture, the initial yield of **6.3** at 24 mM was only 68 %, however the yield dropped much less appreciably when the macrocyclization was performed at 200 mM (40 % of **6.3**). Finally, the best PEG polymer mixture surveyed was the 2:1 StarPEG<sub>1014</sub>:MeOH, where at 24 mM a 91% yield of macrocycle **6.3** was isolated and at 200 mM a 64 % yield was obtained.

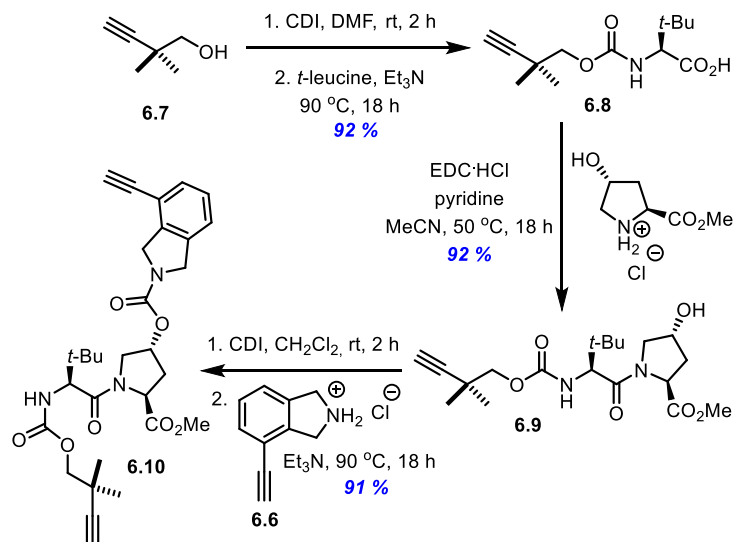
*Synthesis of the bis-alkynyl macrocyclization precursor.* The exploration of using a phase separation strategy employing a Glaser-Hay coupling began with the synthesis of the required alkynyl building block isoindoline **6.6** (Scheme 6.1).



**Scheme 6.1** Synthesis of isoindoline **6.6**

The isoindoline **6.6** could be prepared from the commercially available bromide **6.4** via Boc-protection, Sonogashira coupling and deprotection of the trimethylsilyl- and Boc-protecting groups. The remaining peptidic portion of the macrocyclic precursor **6.10** was prepared from the known alkynyl alcohol **6.7**,<sup>16</sup> which was converted to the carbamate **6.8** in 92 % yield using CDI and *tert*-leucine (Scheme 6.2). The following amide linkage was formed

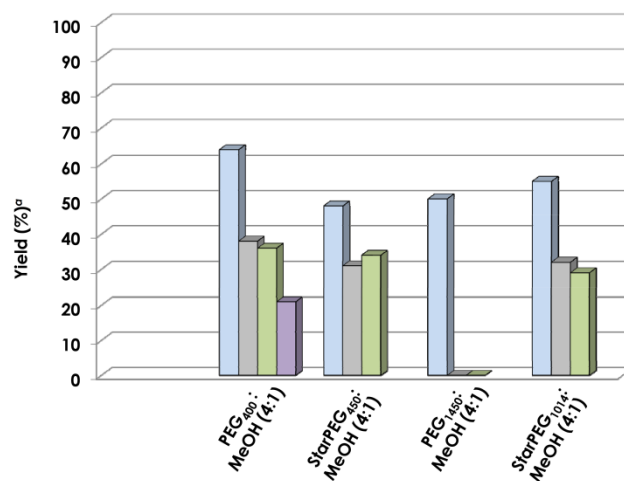
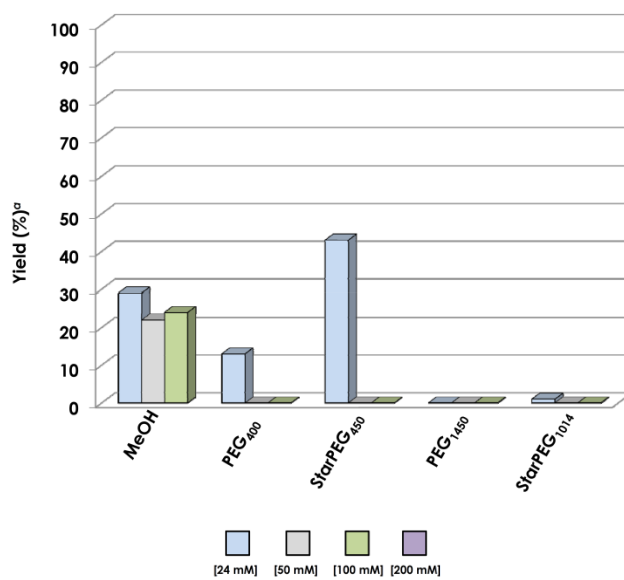
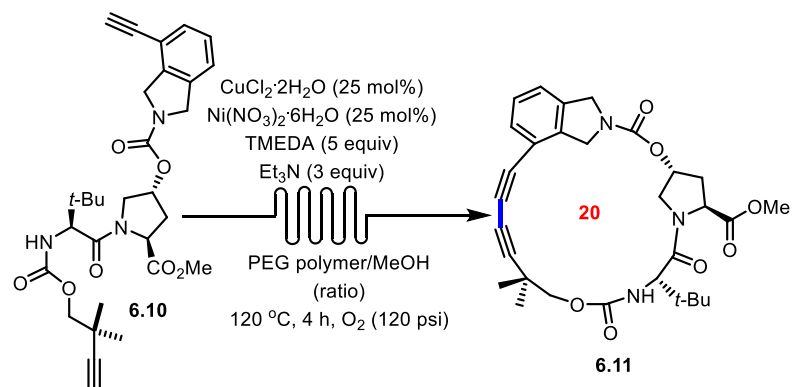
via coupling of the methyl ester of hydroxy-proline to afford the dipeptide **6.9** in 92 % yield. Lastly, a CDI-mediated coupling with the isoindoline **6.6** afforded the desired macrocyclization precursor **6.10** in 91 % yield.



**Scheme 6.2** Synthesis of an acyclic diyne precursor **6.10**

*Exploration of different PEG co-solvents for macrocyclization towards the core of vaniprevir.* Following the survey of different PEG:MeOH solvent mixtures for the macrocyclization of the model bis-alkyne **6.2**, a similar survey was undertaken for the cyclization of bis-alkyne **6.10** towards the macrocyclic core of vaniprevir **6.11**. With the goal of maximizing the efficiency of the process, it was decided to explore continuous flow methods for macrocyclization (**6.10**→**6.11**).<sup>17</sup>





**Figure 6.4** Effect of solvent and concentration on macrocyclization (6.10→6.11)

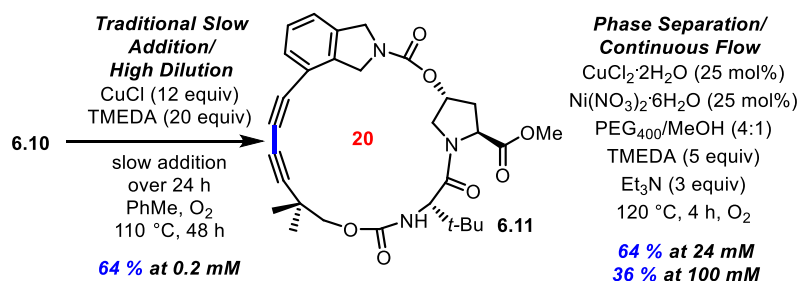
*Top:* In pure MeOH, linear PEG and StarPEG solvents. *Bottom:* Solvent mixtures of linear PEGs and StarPEGs in MeOH. Macrocyclizations were performed at 24 mM (blue), 50 mM

(grey), 100 mM (green) and 200 mM (purple). <sup>a</sup> All entries represent isolated yields following silica gel chromatography. Ring size indicated in red.

It had already been demonstrated that the phase separation strategy for macrocyclization was amendable to continuous flow and that the associated efficient energy and mass transfer resulted in improved reactions times and yields.<sup>18</sup> As such, the macrocyclization of bis-alkyne **6.10** was performed by injecting the entire reaction mixture into a flow system consisting of two stainless steel reactors in series heated to 120 °C. As the Glaser-Hay reaction is an oxidative process, the first of the reactors was a tube-in-tube reactor equipped to saturate the reaction mixture with oxygen.<sup>19</sup> It is important to note that the bis-alkyne **6.10** is structurally much more complex than the model bis-alkyne **6.2**. It is difficult to predict a priori whether the additional functionalization in **6.10** creates a bias towards productive macrocyclization, or undesired dimer- or oligomerization.<sup>20</sup> The first macrocyclizations (**6.10**→**6.11**) investigated were control reactions performed in 100% MeOH at three different concentrations (Figure 6.4, *top*). The macrocyclization at 24 mM afforded low yields (29 % of **6.11**) and slightly lower yields were obtained at 50 mM (22 %) and 100 mM (24 %).<sup>21</sup> Next, a second set of control reactions were performed whereby macrocyclization was conducted in 100% PEG at 24 mM. For macrocyclization in PEG<sub>400</sub>, the isolated yield of macrocycle **6.11** was low (13 %), but for the analogous dendritic StarPEG<sub>450</sub>, the yield was again much greater (43 % of **6.11**), demonstrating the increased reactivity observed with more lipophilic PEG solvents. In contrast, macrocyclizations were very inefficient when using higher molecular weights PEGs. The linear PEG<sub>1450</sub> is a solid at room temperature, making the reaction under flow conditions difficult to perform. While for the dendritic StarPEG<sub>1014</sub>, a liquid at room temperature, only trace amounts of the macrocycle **6.11** could be isolated. Unfortunately, macrocyclizations at 100 mM could not be performed due to problematic solubility of substrates and/or catalysts in the neat PEG solvents.

Next, the macrocyclization was investigated in the PEG:MeOH mixtures (Figure 6.4, *bottom*). Given the higher yields observed with StarPEG<sub>1014</sub> obtained in the macrocyclization of the simple model macrocycle **6.11**, the first cyclization towards the vaniprevir core **6.11** was investigated in 2:1 StarPEG<sub>1014</sub>:MeOH (24 mM).<sup>14</sup> When **6.10** was subjected to

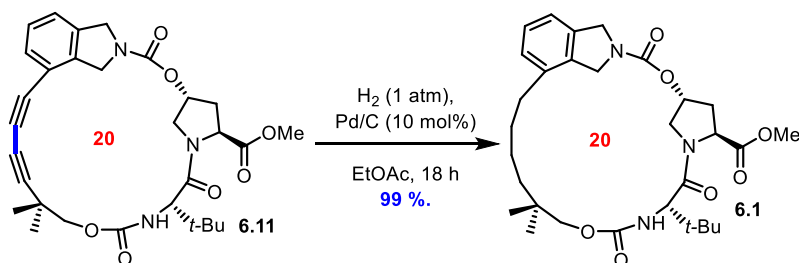
macrocyclization in 2:1 StarPEG<sub>1014</sub>:MeOH, only a 31% yield of macrocycle **6.11** was obtained with complete conversion of the starting bis-alkyne **6.10**. Reasoning that a better preference for macrocyclization could be obtained at higher PEG:MeOH ratios, the macrocyclizations of bis-alkyne **6.10** were conducted at 4:1 StarPEG<sub>1014</sub>:MeOH which afforded a yield of 55 % of **6.11**. Increasing or decreasing the ratio of PEG:MeOH did not improve the conversion to a significant degree,<sup>22</sup> and a ratio of 4:1 PEG polymer:MeOH was used for all further investigations. When comparing StarPEG<sub>1014</sub> to the linear analogue PEG<sub>1450</sub>, it was found that the yield of macrocycle **6.11** was slightly lower (50%) at 4:1 PEG<sub>1450</sub>:MeOH. A lower molecular weight StarPEG<sub>450</sub> also gave a comparable yield of **6.11** (48 % at 4:1 StarPEG<sub>450</sub>:MeOH). However, the best yield of **6.11** at 24 mM was with a 4:1 mixture of PEG<sub>400</sub>:MeOH (64 %).<sup>23</sup> Next, attempts were made to increase the concentration of the reaction to both 50 and 100 mM. After surveying 4:1 mixtures of PEG<sub>400</sub>, StarPEG<sub>450</sub> and StarPEG<sub>1014</sub> with MeOH, the best yield at either concentration was obtained with 4:1 PEG<sub>400</sub>:MeOH (38 % of macrocycle **6.11** at 50 mM and 36 % of macrocycle **6.11** at 100 mM).<sup>24</sup>



**Scheme 6.3** Comparing slow addition/high dilution and phase separation/continuous flow strategies towards the vaniprevir core **6.11**

In an effort to compare the phase separation/continuous flow protocol to common slow addition/high dilution strategies, the bis-alkyne **6.10** was cyclized at low concentration (0.2 mM) (Scheme 6.3). Excess copper/ligand was used to promote macrocyclization in 64% yield of **6.11** with a reasonable reaction time (48 h).<sup>25</sup> Consequently, the phase separation/continuous flow strategy provided similar yields at concentrations greater than 100 times that of slow addition/high dilution strategies. In addition, the former could promote macrocyclization at 36 % yield at up to 500 times greater concentrations. The macrocyclic

diyne **6.11** could be hydrogenated to afford the same macrocyclic intermediate **6.1** obtained by the Merck research team (Scheme 6.4).



**Scheme 6.4** Completing the synthesis of the vaniprevir core **6.1**

## 6.4 Conclusions

In summary, the phase separation strategy has been applied for the first time to macrocyclization of a complex pharmaceutical target, the macrocyclic core of vaniprevir. The phase separation strategy demonstrated good functional group tolerance to the nitrogen-based heterocycles, dipeptides and carbamates embedded within the structure of vaniprevir and provided good yields of the desired macrocyclic core **6.11** (55-64 %) using either PEG<sub>400</sub>:MeOH or newly explored StarPEG<sub>1014</sub>:MeOH. In addition, the macrocyclization demonstrates the utility of the Glaser-Hay oxidative coupling of alkynes for macrocyclization of pharmaceuticals. Macrocyclization towards the core of vaniprevir could be conducted at 100 mM using linear or dendritic PEG co-solvents. A “simpler” macrocyclization on an unbiased substrate could be conducted at 200 mM in good yields (64 % of **6.3**) using the newly explored dendritic PEGs as co-solvents. As a number of other synthetic processes rely upon controlling concentration effects,<sup>26</sup> it is possible that the new dendritic PEG/solvent mixtures could be used to improve such processes. It is also expected that as the interest in macrocycles in drug discovery continues to grow, so will the need for macrocyclization techniques that strive towards sustainability.

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continuous flow infrastructure. Ms. Vanessa Kairouz is thanked for assistance and valuable advice concerning continuous flow protocols. É. G., A.-C. B., and M. R. thank NSERC and the FRQNT for graduate scholarships.

**Supporting Information.** Surface tension measurements, macrocyclization data in tabular form and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

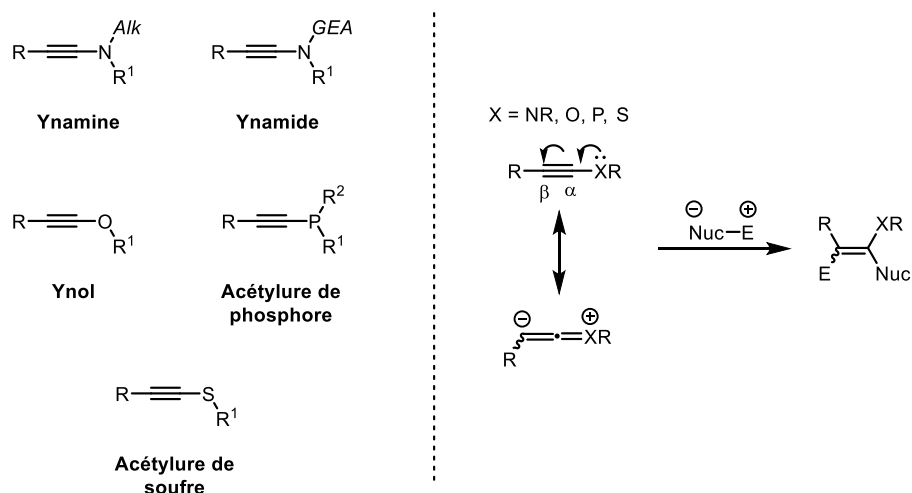
## 6.5 Bibliographie

1. (a) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767-9822. (b) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961-2004. (c) Matsuda, H.; Watanabe, S.; Yamamoto, K. *Chem. Biodiversity* **2004**, *1*, 1985-1991. (d) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2004**, *6*, 2989-2991. (e) Fehr, C.; Galindo, J.; Etter, O.; Thommen, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4523-4526.
2. For a chart illustrating the interest in macrocycles in both drug discovery and total synthesis through the relative number of citations, see the Supporting Information.
3. Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608-624.
4. (a) Seiple, I. B.; Zhang, Z.; Jakubec, P.; Langlois-Mercier, A.; Wright, P. M.; Hog, D. T.; Yabu, K.; Allu, S. R.; Fukuzaki, T.; Carlsen, P. N.; Kitamura, Y.; Zhou, X.; Condakes, M. L.; Szczypiński, F. T.; Green, W. D.; Myers, A. G. *Nature* **2016**, *533*, 338-345. (b) Nie, F.; Kunciw, D. L.; Wilcke, D.; Stokes, J. E.; Galloway, W. R. J. D.; Bartlett, S.; Sore, H. F.; Spring, D. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 11139-11143; (c) Collins, S.; Bartlett, S.; Nie, F.; Sore, H. F.; Spring, D. R. *Synthesis* **2016**, *48*, 1457-1473.
5. (a) Harper, S.; McCauley, J. A.; Rudd, M. T.; Ferrara, M.; DiFilippo, M.; Crescenzi, B.; Koch, U.; Petrocchi, A.; Holloway, M. K.; Butcher, J. W.; Romano, J. J.; Bush, K. J.; Gilbert, K. F.; McIntyre, C. J.; Nguyen, K. T.; Nizi, E.; Carroll, S. S.; Ludmerer, S. W.; Burlein, C.; DiMuzio, J. M.; Graham, D. J.; McHale, C. M.; Stahlhut, M. W.; Olsen, D. B.; Monteagudo, E.; Cianetti, S.; Giuliano, C.; Pucci, V.; Trainor, N.; Fandozzi, C. M.; Rowley, M.; Coleman, P. J.; Vacca, J. P.; Summa, V.; Liverton, N. J. *ACS Med. Chem. Lett.* **2012**, *3*, 332-336. (b) Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820-3828. (c) Ali, A.; Aydin, C.; Gildemeister, R.; Romano, K. P.; Cao, H.; Özen, A.; Soumana, D.; Newton, A.; Petropoulos, C. J.; Huang, W.; Schiffer, C. A. *ACS Chem. Biol.* **2013**, *8*, 1469-1478.
6. (a) Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976. (b) Bédard, A.-C.; Collins, S. K. *Chem. Commun.* **2012**, *48*, 6420-6422. (c) Bédard, A.-C.; Collins, S. K. *Chem. Eur-J.* **2013**, *19*, 2108-2113.
7. (a) Anastas, P. T. *ChemSusChem* **2009**, *2*, 391-392. (b) Horváth, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169-2173. (c) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521-527. (d) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1-6.

8. Ito, H.; Mitamura, Y.; Segawa, Y.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 159–163.
9. Surface tension measurements are well-precedented for the analysis of PEG aggregates, for examples see: (a) Dey, J.; Shrivastava, S. *Soft Matter* **2012**, *8*, 1305-1308. (b) Yang, S.-C.; Faller, R. *Langmuir* **2012**, *28*, 2275-2280. (c) Alam, M. S.; Mandal, A. B. *J. Mol. Liq.* **2012**, *168*, 75-79. PEG aggregates can also be analyzed by the use of UV and IR spectroscopy, see: (d) Froehlich, E.; Mandeville, J. S.; Arnold, D.; Kreplak, L.; Tajmir-Riahi, H. A. *Biomacromolecules* **2012**, *13*, 282-287. (e) Ouyang, C.; Chen, S.; Che, B.; Xue, G. *Colloids Surf., A* **2007**, *301*, 346-351.
10. Bédard, A.-C.; Collins, S. K. *ACS Catal.* **2013**, *3*, 773-782.
11. Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709-712.
12. Clinically approved PEGylated products: Adagen, Oncaspar, Doxil, PEGasys, PegIntron, Neulasta, Somavert, Macugen, Mircera, Cimzia, Sylatron. See: Mishraa, P.; Nayak, B.; Dey, R. K. *Asian J. Pharma. Sci.* **2016**, *11*, 337-348.
13. Thakur, S.; Kesharwani, P.; Tekade, R. K.; Jain, N. K. *Polymer* **2015**, *59*, 67-92.
14. See Supporting Information for details.
15. Note that all data are presented in tabular format in the Supporting Information.
16. For an alternative route to alkynyl alcohol **6.4** see: Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781-11790.
17. Previous reports have not shown any decrease in efficiency of the phase separation system in continuous flow. See reference 18 for details.
18. Bédard, A.-C.; Régnier, S.; Collins, S. K. *Green Chem.* **2013**, *15*, 1962-1966.
19. (a) Peterson, T. P. Polyzos, A.; O'Brien, M.; Ulven, T.; Baxendale, I. R.; Ley, S. V. *ChemSusChem* **2012**, *5*, 274-277. (b) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349–362.
20. For example, proline units are often found in macrocyclic scaffolds as they are known to promote  $\alpha$ -turn mimics and influence macrocyclization reactions. See: Chouhan, G.; James, K. *Org. Lett.* **2013**, *15*, 1206-1209. For an example of the structure of a linear precursor for macrocyclization being predisposed to macrocyclization by a certain mode of catalysis, while being unfavorable towards cyclization using an alternate mode of catalysis, See: Beckmann, H. S. G.; Nie, F.; Hagerman, C. E.; Johansson, H.; Tan, Y. S.; Wilcke, D.; Spring, D. R. *Nature Chem.* **2013**, *5*, 861-867.
21. It was not possible to identify a dimer formed from Glaser-Hay coupling of the more reactive aryl alkyne.
22. When the bis-alkyne **6.10** was subjected to macrocyclization in 2:1 StarPEG<sub>1014</sub>:MeOH, only a 31% yield of macrocycle **6.11** was obtained with complete conversion of the starting bis-alkyne **6.10**. See Supporting Information.
23. In continuous flow, a throughput of ~100 mg/d (24 mM) or ~230 mg/d (100 mM) is estimated.
24. Macrocyclization at 200 mM (4:1 PEG<sub>400</sub>:MeOH) afforded only 21 % of the desired macrocycle **6.11**.
25. Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81–130.
26. For an elegant example of phase separation used to minimize the concentration of hazardous intermediates, see: (a) Morandi, B.; Carreira, E. M. *Science* **2012**, *335*, 1471-1474. (b) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938-941.

## Chapitre 7. Introduction aux acétylures de soufre

La fonctionnalité alcyne ( $R-C\equiv C-R$ ) est un motif important en chimie organique. Un bon nombre de protocoles ont été développés pour les synthétiser ou les fonctionnaliser, faisant de ce motif un levier synthétique de choix dans la synthèse de molécules complexes<sup>1</sup>. Les alcynes substitués par un hétéroatome comme les ynamines/ynamides<sup>2</sup>, les ynols<sup>3</sup>, les acétylures de phosphore<sup>4</sup> et les acétylures de soufre (thioalcynes)<sup>5</sup> sont aussi très intéressants puisqu'ils permettent, par résonance, une polarisation sélective de la triple liaison (carbone  $\alpha$  électrophile; carbone  $\beta$  nucléophile). Par conséquent, il est possible de prédire leur réactivité, facilitant ainsi le développement de transformations régiosélectives (Figure 7.1).



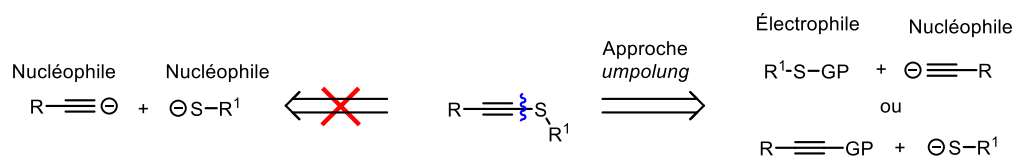
**Figure 7.1** Structure et réactivité des alcynes substitués par un hétéroatome

Ils existent encore peu d'applications synthétiques impliquant les ynamines et les ynols et ce du fait de leur instabilité. Cependant, l'ajout d'un groupement électroattracteur sur l'hétéroatome rendent les composés plus stables. Pour cette raison, il y a eu récemment un regain d'intérêt pour la synthèse et la diversification des ynamides<sup>6</sup>. L'étude des acétylures de soufre a également suscité l'intérêt, au cours de la dernière décennie, chez les chercheurs. Contrairement aux ynamines ou aux ynols, les acétylures de soufre sont très stables.

## 7.1 Synthèses des acétylures de soufre

Historiquement, la synthèse des premiers acétylures de soufre a été réalisée par la déshydrohalogénéation de  $\beta$ -bromovinyles de thioéther. Un désavantage majeur de cette approche est le nombre élevé d'étapes de synthèse nécessaires à partir du substrat thiol<sup>7</sup>.

Une approche plus directe pour la formation du lien C-S serait le couplage entre un thiol et un alcyne terminal. Cependant, ces deux fonctionnalités possèdent la même réactivité, puisqu'ils sont tous deux des nucléophiles (Figure 7.2). Ainsi, un couplage direct et sélectif entre ces deux fonctionnalités est *a priori* impossible. Afin de former un nouveau lien entre deux nucléophiles, une stratégie de renversement de polarité (*Umpolung*) peut être employée. Ceci consiste à transformer un composé nucléophile en composé électrophile par l'introduction d'un groupement partant. En utilisant cette approche, de nombreuses méthodes pour la synthèse de thioalcynes ont été développées dans les dernières années.

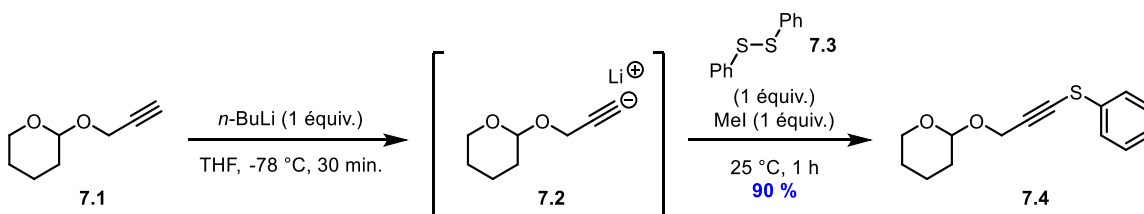


**Figure 7.2** Stratégie de renversement de polarité (*Umpolung*) pour la synthèse d'acétylure de soufre

### 7.1.1 Approches *Umpolung* du soufre

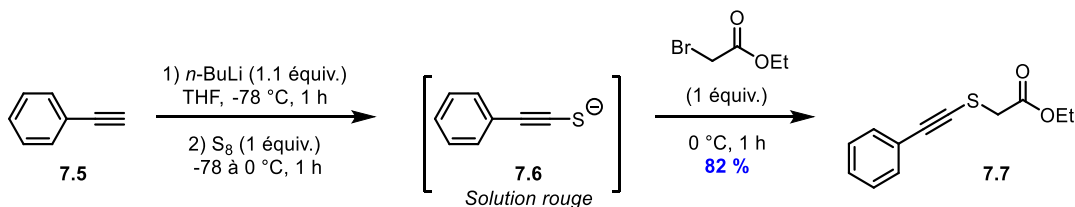
Une approche *umpolung* du soufre a été développée par MaGee et Kabanyane en 1992 dans laquelle ils ont utilisé des composés disulfures comme source électrophile de soufre<sup>8</sup>. Dans un premier temps, l'alcyne terminal **7.1** est déprotoné par du *n*-butyllithium afin de former un acétylure anionique **7.2**. Ce nucléophile peut ensuite réagir avec le disulfure **7.3** afin de former le produit de couplage **7.4** (Schéma 7.1). Dans le mélange réactionnel, les auteurs ajoutent également une quantité stœchiométrique d'iodure de méthyle afin de piéger le sous-produit thiolate libéré, évitant que ce dernier réagisse avec l'acétylure de soufre formé. De façon similaire, les dérivés bis-(5,5-diméthyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) de disulfure ont été utilisés pour la synthèse de thioalcynes asymétriques<sup>9</sup>.





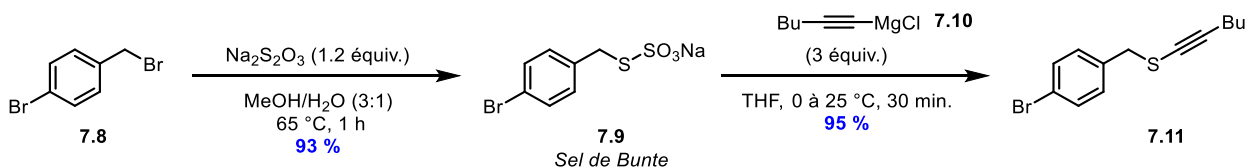
**Schéma 7.1** Synthèse d'un acétylure de soufre à partir d'un composé disulfure

Bien que ces méthodes soient efficaces, l'utilisation de disulfure nécessite la formation de ce dernier et génère un sous-produit gênant qui doit être neutralisé. Cette méthode n'est donc pas attrayante du point de vue de l'économie d'atomes. Une méthode alternative est l'utilisation du soufre élémentaire ( $S_8$ ) comme source électrophile de soufre. Cependant, au départ, cette méthode nécessitait l'isolement d'intermédiaires très réactifs<sup>10</sup>. Ce n'est qu'en 2012 que le groupe de Hu a développé un protocole monotope<sup>11</sup>. Similairement à l'approche de MaGee<sup>8</sup>, le phenylacétylène **7.5** est déprotoné avant de réagir avec le soufre élémentaire pour former un mélange réactionnel de couleur rouge foncé, une caractéristique de la formation de l'acétylure de thiolate **7.6** (Schéma 7.2). Finalement, ce dernier réagit avec un halogénoalcane pour former l'acétylure de soufre **7.7**.



**Schéma 7.2** Synthèse d'un acétylure de soufre à partir de soufre élémentaire

En 2014, des chercheurs de la compagnie Boehringer Ingelheim (Ridgefield, Connecticut, États-Unis) ont développé une nouvelle méthode pour la synthèse d'acétylures de soufre<sup>12</sup>. Celle-ci consiste à faire réagir le bromure d'alcane **7.8** avec du thiosulfate de sodium ( $Na_2S_2O_3$ ) afin de former un sel de *S*-alkylthiosulfate de sodium **7.9** (autrement nommé sel de Bunte) (Schéma 7.3). Comme les sels de *S*-alkylthiosulfate **7.9** sont connus pour réagir avec des nucléophiles et servir comme source électrophile de soufre<sup>13</sup>, les chercheurs ont utilisé différents réactifs de Grignard, dont l'organomagnésien **7.10** afin de former l'acétylure de soufre **7.11** dans un excellent rendement de 95%. Cette voie synthétique est très intéressante pour le secteur industriel puisque les sels de Bunte sont généralement des solides cristallins, facile à préparer et évitent l'utilisation de composés fortement odorants comme les thiols.



**Schéma 7.3** Synthèse d'un acétylure de soufre à partir d'un sel de *S*-alkylthiosulfate (sel de Bunte)

Au cours des 10 dernières années, plusieurs autres sources électrophiles de soufre ont été utilisées pour synthétiser des acétylures de soufre à partir d'acétylures anioniques (7.12). Zeni a utilisé les dérivés de bromothiols 7.13 pour faire la synthèse des 3-halo-4-chalcogen-2*H*-benzopyranes 7.14 via la formation d'acétylures de soufre (Schéma 7.4A)<sup>14</sup>. Cette approche a également permis la synthèse d'acétylures de sélénium et de tellure. Plus récemment, Zhang a rapporté la formation de thioalcynes 7.15 par le couplage d'alcynes terminaux et de séléno- ou thiocyanates 7.16 (Schéma 7.4B)<sup>15</sup>. Les auteurs proposent la génération *in situ* de composés disulfures suivie par l'attaque nucléophile de l'acétylure anionique. De son côté, Alcazaro a développé des sels de dibromothioimidazolium 7.17 permettant la synthèse éventuelle d'acétylures de soufre 7.18 (Schéma 7.4C)<sup>16</sup>. Cette méthode permet l'ajout subséquent de deux nucléophiles permettant de générer rapidement une grande librairie d'acétylures de soufre et de sélénium. Finalement, Gao et Zhou ont découvert un nouvel agent de transfert de thioalcynes, le *N*-alcynylthiophthalimide 7.19 (généralisé à partir du *N*-chlorothiophthalimide 7.20), permettant la synthèse de thioalcynes alkyles et aryles (Schéma 7.4D)<sup>17</sup>. Le réactif 7.19 est stable dans les conditions de pression et température ambiantes et peut être synthétisé sur une échelle de plusieurs grammes. Bien que plusieurs étapes soient nécessaires pour les synthétiser, contrairement aux réactifs de thioimidazolium 7.17, les *N*-alcynylthiophthalimide 7.19 peuvent réagir avec divers nucléophiles, notamment des acides arylboroniques et des β-cétoesters.

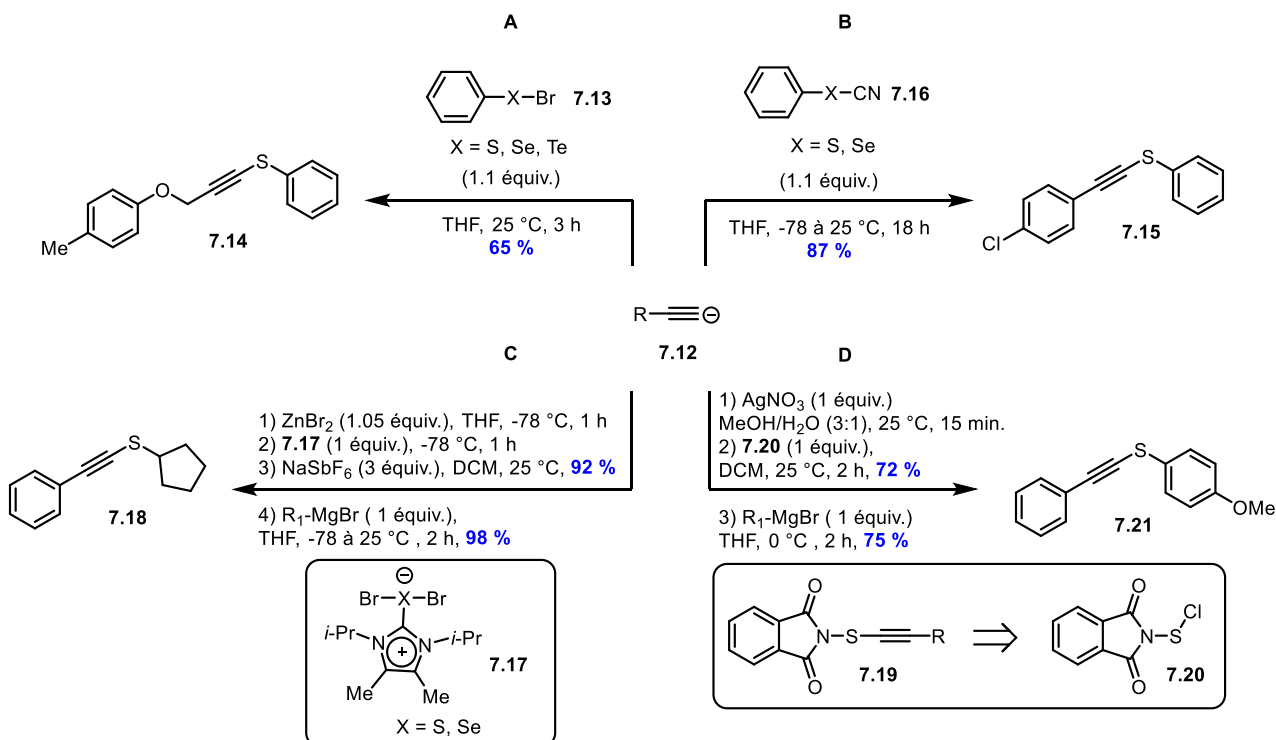
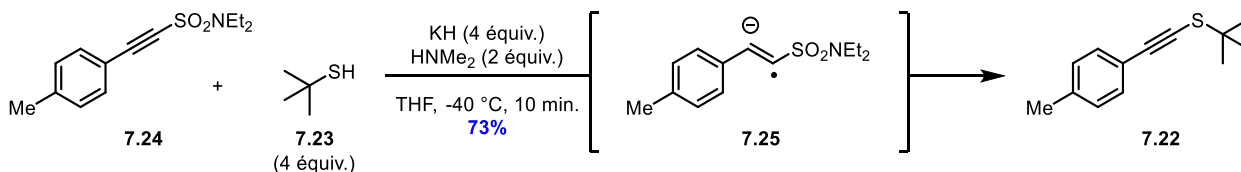


Schéma 7.4 Synthèses alternatives de thioalcyne à partir de sources électrophiles de soufre

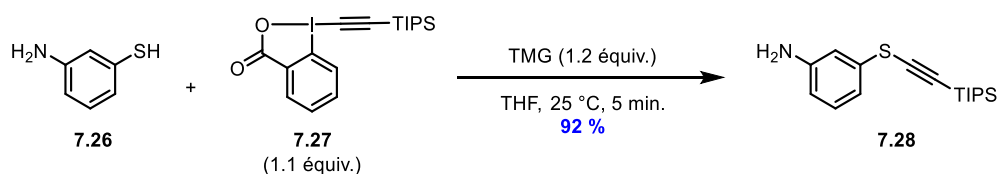
## 7.1.2 Approches *Umpolung* de l'alcyne

Les approches *umpolung* de l'alcyne ont été moins développées que celles du soufre. Néanmoins, quelques travaux à ce sujet ont été publiés au cours des dernières années. En 2012, le groupe de Wilden a développé une réaction de substitution d'alcyne sulfonamide par un anion *tert*-butanolate pour la synthèse de composés ynol<sup>18</sup>. Cette même stratégie a par la suite été adaptée pour la synthèse d'acétylures de soufre **7.22** en utilisant, dans ce cas-ci, l'anion *tert*-butylthiolate (*t*-BuS<sup>-</sup>) généré par déprotonation *tert*-butylthiol (**7.23**) avec de l'hydrure de potassium (Schéma 7.5)<sup>19</sup>. Le mécanisme proposé par les auteurs pour cette transformation serait de nature radicalaire. Le transfert d'un électron entre l'anion thiolate et l'alcyne sulfonamide **7.24** produirait un intermédiaire vinylique anionique radicalaire **7.25**. Une recombinaison avec le radical thiyl suivie de l'élimination *syn* du groupement partant sulfonamide formerait l'acétylure de soufre **7.22**. L'année suivante, le groupe de Wilden a publié une variante du couplage décrit précédemment en remplaçant l'alcyne sulfonamide par un chloroalcyne<sup>20</sup>.



**Schéma 7.5** Synthèse d'un acétylure de soufre à partir d'un alcyne sulfonamide

En 2013, le groupe de Waser a développé une approche générale et chimiosélective pour la synthèse d'acétylures de soufre en utilisant des composés de type trialkylsilyl-éthynylbenziodoxolone ( $R_3Si$ -EBX) comme source d'alcyne électrophile<sup>21</sup>. Par exemple, lorsque le thiol **7.26** est mis en présence du réactif **7.27** et de la base 1,1,3,3-tétraméthylguanidine (TMG), une conversion très rapide (5 min) a lieu pour former le thioalcyne silylé **7.28** dans un rendement de 92% (Schéma 7.6). La méthode est compatible avec plusieurs groupements fonctionnels et peut être utilisée pour fonctionnaliser l'acide aminé cystéine contenu dans des peptides.



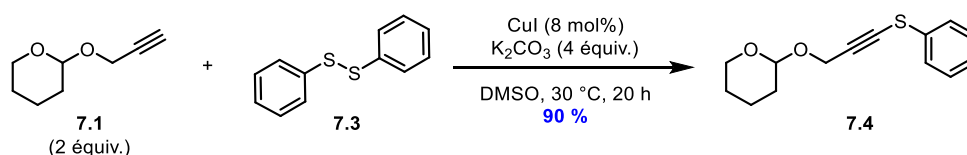
**Schéma 7.6** Synthèse d'un acétylure de soufre à partir d'éthynylbenziodoxolone

Le groupe de Waser a ensuite amélioré la méthode afin d'augmenter davantage l'étendue de la réaction<sup>22</sup>. Pour se faire, les auteurs ont utilisé une base plus forte, soit le 1,5,7-triazabicyclo[4.4.0]déc-5-ène (TBD), leur permettant l'utilisation de dérivés d'EBX comportant des substituants alkyle ou mésityle. Des études mécanistiques computationnelles ont révélé que la nature du dérivé d'EBX utilisé avait un impact direct sur la voie mécanistique<sup>23</sup>. Par exemple, les dérivés d'alcyne riches en électrons (-Me) favorisent une addition  $\beta$ , tandis que les dérivés d'alcyne déficients en électrons (-CO<sub>2</sub>Me) favorisent une addition  $\alpha$ .

### 7.1.3 Approches catalytiques

Jusqu'à présent, les réactions décrites font appel à la réactivité classique entre un composé électrophile et un composé nucléophile. Cependant, ce dernier est souvent généré par une déprotonation à l'aide d'une base forte. Ceci peut interférer avec certains groupements

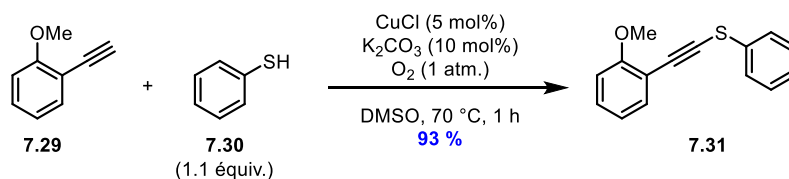
fonctionnels et limiter l'étendue de la réaction. Afin de pallier ce problème, il est possible d'utiliser un catalyseur de cuivre afin de générer *in situ* un acétylure de cuivre qui agit comme nucléophile non basique. En effet, l'utilisation de catalyseurs de cuivre pour la formation de liens C-S est un champ de recherche très actif dans la littérature<sup>24</sup>. Par exemple, Menezes et ses collègues ont démontré qu'un acétylure de cuivre, formé à partir de l'alcyne terminal **7.1** et d'une quantité catalytique d'iodure de cuivre (I) en présence d'une base relativement faible ( $K_2CO_3$ ), pouvait réagir avec le disulfure **7.3** pour former l'acétylure de soufre **7.4** (Schéma 7.7)<sup>25</sup>. Les auteurs ont également démontré qu'une telle approche pouvait être utilisée pour la synthèse d'acétylures de sélénium et de tellure.



**Schéma 7.7** Synthèse d'un acétylure de soufre catalysée par un complexe de cuivre à partir d'un alcyne terminal et d'un disulfure

Les additifs de cuivre sont très intéressants puisqu'ils peuvent augmenter la nucléophilie des alcynes terminaux, mais peuvent également augmenter l'électrophilie des disulfures. En effet, Menezes et Stefani ont utilisé de l'iodure de cuivre (I) pour réaliser le couplage entre un bromoalcyne et un disulfure<sup>26</sup>. Une stratégie similaire avait été développée par Shibasaki pour le couplage entre un disulfure et un alcyne terminal protégé par un groupement triméthylsilyle (TMS), un composé considéré comme peu nucléophile<sup>27</sup>. Ces deux méthodes nécessitent cependant une quantité stœchiométrique de l'additif de cuivre.

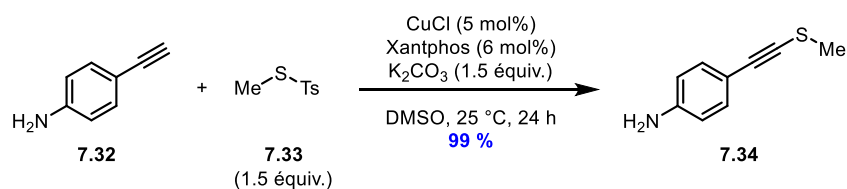
En 2013, le groupe de Rioux a développé une approche catalysée par un complexe cuivre pour le couplage direct entre un thiol et un alcyne terminal<sup>28</sup>. En utilisant une quantité catalytique de chlorure de cuivre (I) (5 mol%) et de carbonate de potassium (10 mol%), avec une atmosphère d'oxygène à 70 °C, l'alcyne terminal **7.29** et le thiol **7.30** ont pu être couplés pour former le thiolalcyne **7.31** dans un rendement de 93% (Schéma 7.8).



**Schéma 7.8** Synthèse directe d'un acétylure de soufre catalysée par un complexe de cuivre à partir d'un alcyne terminal et d'un thiol

Dans l'optique de réutiliser le catalyseur de cuivre, des chercheurs chinois ont immobilisé les atomes de cuivre sur un matériel mésoporeux, leur permettant ainsi de récupérer le catalyseur par une simple filtration une fois la réaction achevée<sup>29</sup>. Ce nouveau catalyseur hétérogène peut être réutilisé plus de 10 fois sans qu'une baisse d'efficacité ne soit observée (< 5%). Par ailleurs, des nanoparticules de cuivre ont aussi été utilisées pour le couplage d'alcynes terminaux avec des disulfures<sup>30</sup>.

En 2019, Hosoya a modifié l'approche de Rioux pour effectuer le couplage entre un alcyne terminal et un dérivé toluènethiosulfonate (R-STs)<sup>31</sup>. Les auteurs ont utilisé un système catalytique composé de CuI et du ligand Xantphos, leur permettant d'effectuer le couplage C-S dans des conditions plus douces (25 °C). Dans ces conditions, l'alcyne terminal **7.32** a pu réagir avec le réactif **7.33** pour former l'acétylure de soufre **7.34** avec un excellent rendement (Schéma 7.9). Ce nouveau système catalytique permet la synthèse d'acétylures de soufre présentant des substituants azotés (NH<sub>2</sub>, pyridine) ce qui était une limitation de la méthode de Rioux.

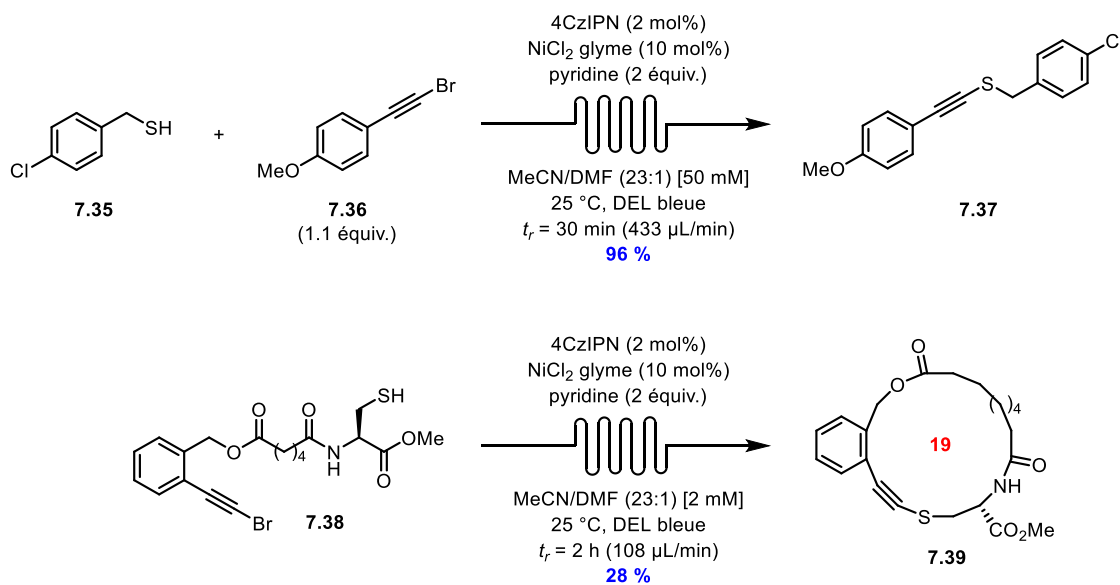


**Schéma 7.9** Synthèse d'un acétylure de soufre catalysée par un complexe de cuivre à partir d'un alcyne terminal et d'un dérivé toluènethiosulfonate

Le cuivre n'est pas le seul métal de transition qui peut être utilisé dans la synthèse d'acétylures de soufre. En effet, Alami et Messaoudi ont utilisé des catalyseurs de palladium pour alcyner des dérivés glycolisides<sup>32</sup>. Un système catalytique utilisant du nickel (0) a également été employé pour effectuer cette transformation<sup>33</sup>. Les avancées de la photochimie ont permis récemment le développement de plusieurs méthodes pour la synthèse de liaisons C-

S<sup>34</sup>. Parmi les stratégies photochimiques développées, la catalyse photorédox en tandem utilisant des complexes de ruthénium ou d'iridium avec un co-catalyseur de nickel s'est largement démarquée<sup>35</sup>.

En 2017, notre groupe de recherche a appliqué la photocatalyse en tandem pour la synthèse d'acétylures de soufre<sup>36</sup>. La réaction développée utilise une quantité catalytique du photocatalyseur organique 1,2,3,5-tétrakis(carbazol-9-yl)-4,6-dicyanobenzène (4CzIPN) et d'un catalyseur de nickel (II) en présence de pyridine, le tout irradié par une lumière bleue. Afin de favoriser la pénétration de la lumière dans le mélange réactionnel, la réaction a été effectuée à l'aide d'un montage de chimie en débit continu. Dans ces conditions, le thiol **7.35** peut être aisément couplé avec le bromoalcyne **7.36** pour former l'acétylure de soufre **7.37** dans un excellent rendement de 96% (Schéma 7.10). Cependant, la méthode ne pouvait être appliquée qu'à la transformation de bromoalcyne arylés puisque les substrats alkyles ne montraient aucune réactivité. Néanmoins, la réaction a pu être employée pour la synthèse du premier macrocycle contenant le motif thioalcyne (**7.39**).



**Schéma 7.10** Synthèse photochimique d'acétylures de soufre à partir de bromoalcyne et de thiols

## 7.2 Applications synthétiques des acétylures de soufre

### 7.2.1 Hydroadditions

Tout comme les alcynes, les thioalcyne peuvent participer à des réactions d'hydroaddition afin de former des thioéthers vinyliques polysubstitués. Entre autres, il est possible d'effectuer des réactions d'hydrosilylation<sup>37</sup>, d'hydrohalogénéation<sup>38</sup> et d'hydrozirconation<sup>39</sup>. Il est également possible de piéger l'intermédiaire formé avec un électrophile. Par exemple, Xu a réalisé la cupraboration catalytique du thioalcyne **7.40** pour former l'intermédiaire vinylique **7.41**, qui est immédiatement piégé par de l'iodure de méthyle pour donner le thioéther vinylique tétrasubstitué **7.42** avec un rendement de 93% (Schéma 7.11)<sup>40</sup>.

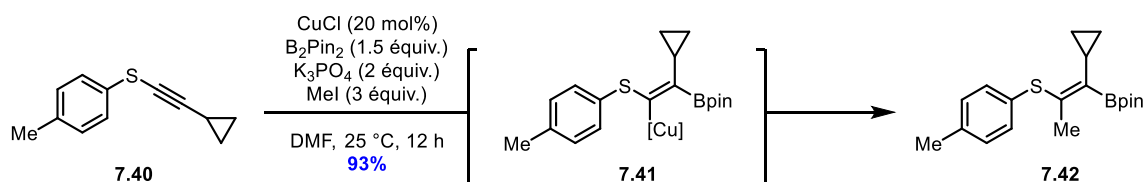
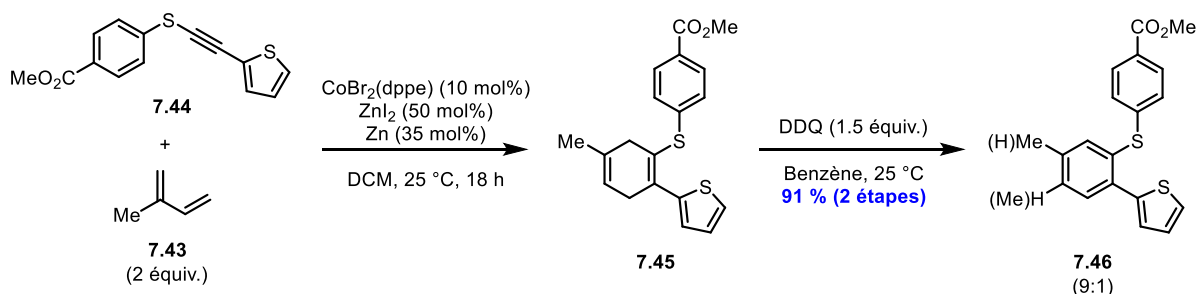


Schéma 7.11 Synthèse d'un thioéther vinylique par cupraboration de thioalcyne

### 7.2.2 Cycloadditions

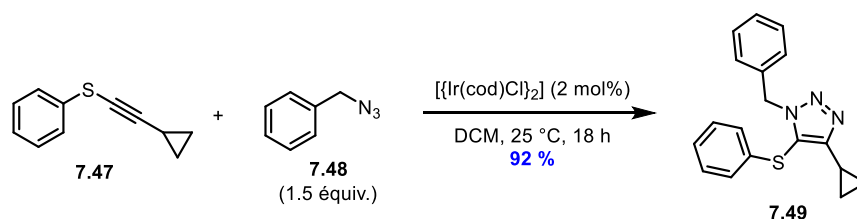
Les acétylures de soufre peuvent également participer à des réactions de cycloaddition. Il a été montré par Hilt que les thioalcyne peuvent agir comme diénophiles dans des réactions de cycloaddition [4+2] de Diels-Alder (D-A)<sup>41</sup>, de déhydro-D-A<sup>42</sup> ou même de hexadéhydro-D-A<sup>43</sup>. En effet, Hilt a démontré qu'en présence d'un catalyseur de cobalt et d'isoprène (**7.43**), le thioalcyne **7.44** est facilement converti en dihydrothiophényle **7.45** (91%) avec une bonne régiosélectivité (9 : 1). Une étape subséquente d'oxydation avec du DDQ peut être faite, donnant accès aux composés diarylthioéthers **7.46** (Schéma 7.12).





**Schéma 7.12** Synthèse de composés diarylthioéthers par cycloaddition [4+2] de Diels-Alder à partir d'acétylure de soufre

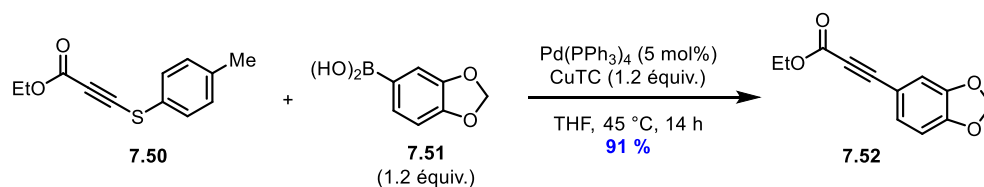
Les acétylures de soufre sont également de bons partenaires de couplage dans des réactions de cycloaddition thermique [2+2] pour former des cyclobutènes<sup>44</sup> ou des réactions de cycloaddition [2+2+2] pour former des pyrimidines<sup>45</sup>. Finalement, les thioalcyne sont aussi très efficaces dans les réactions de cycloaddition [3+2] de type 1,3-dipolaire de Huisgen. En utilisant un catalyseur de ruthénium<sup>46</sup> ou d'iridium<sup>47</sup>, l'acétylure de soufre **7.47** peut réagir avec l'azoture **7.48** afin de former exclusivement le régioisomère triazole 1,5-disubstitué **7.49** avec une excellente régiosélectivité (Schéma 7.13)<sup>48</sup>.



**Schéma 7.13** Synthèse d'un composé triazole soufré par cycloaddition 1,3-dipolaire de Huisgen à partir d'acétylure de soufre

### 7.2.3 Couplages croisés

Dans les bonnes conditions, les propriétés électroniques des acétylures de soufre peuvent être exploitées afin de réaliser des couplages croisés en présence de métaux de transition<sup>49</sup>. En effet, la partie soufrée du thioalcyne peut être vue comme un isostère d'halogène. Liebeskind a démontré que le thioalcyne **7.50** pouvait réagir avec l'acide boronique **7.51**, en présence d'un catalyseur de palladium et d'une source de carboxylate de cuivre, pour former l'alcyne interne **7.52** (Schéma 7.14). Cette méthode complémentaire à la réaction de Sonogashira peut être envisagée comme transformation orthogonale dans une synthèse multi-étapes.

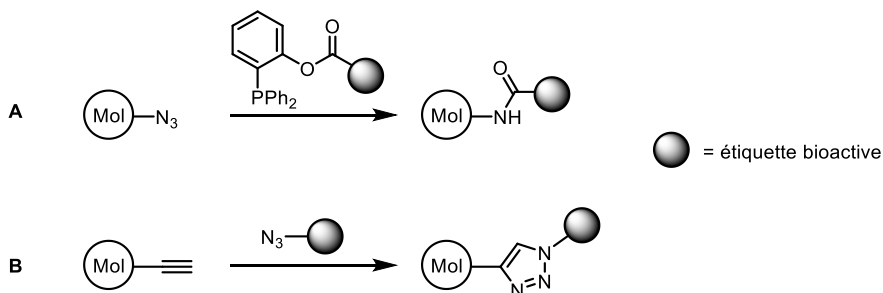


**Schéma 7.14** Formation d'un alcyne interne par couplage croisé entre un thioalcyne et un acide boronique

## 7.2.4 Bioconjugaison de la cystéine

La bioconjugaison est un concept important dans les domaines de la chimie médicinale et de la biochimie puisqu'elle permet d'améliorer l'efficacité des protéines et médicaments par l'ajout d'une étiquette bioactive<sup>51</sup>. De cette façon, il est possible d'augmenter le temps de demi-vie des molécules bioactives, leur rayon hydrodynamique, la précision de leur ciblage et bien plus encore<sup>52</sup>.

Il existe une panoplie de méthodes chimiques pour modifier les biomolécules<sup>53</sup>. Cependant, les méthodes classiques comme la ligation de Staudinger<sup>54</sup> (Figure 7.3A) ou la cycloaddition catalysée par un complexe de cuivre (CuAAC)<sup>55</sup> (Figure 7.3B) requièrent l'incorporation d'un alcyne ou d'un azote, deux éléments qui ne se retrouvent pas naturellement dans les peptides et les protéines.

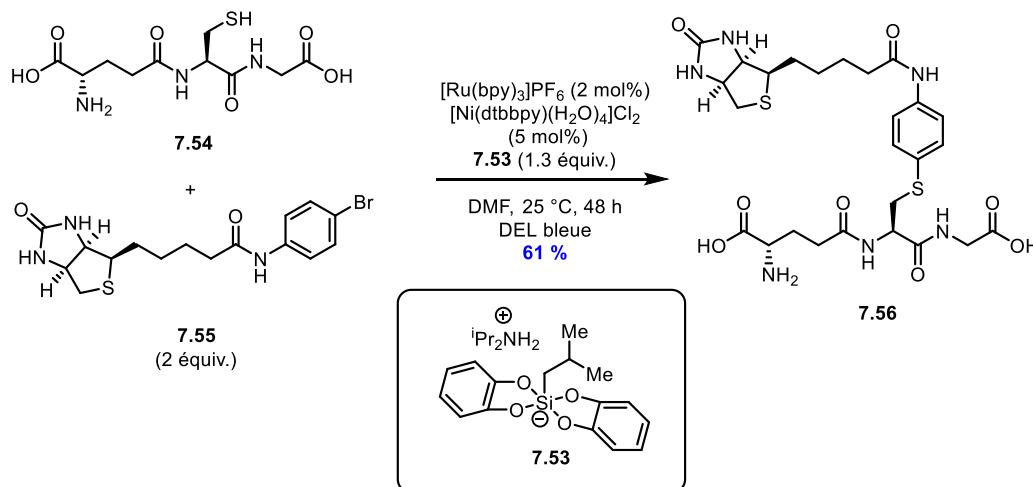


**Figure 7.3** Modification de biomolécules par ligation de Staudinger (A) et par CuAAC (B)

La bioconjugaison de thiols est une approche convoitée en chimie biologique et médicinale à cause de l'abondance de l'atome de soufre dans les médicaments ainsi que dans les peptides/protéines *via* l'acide aminé cystéine<sup>56</sup>. Au fil des ans, plusieurs méthodes ont été adaptées à la bioconjugaison de la cystéine. Parmi ces méthodes, les plus populaires sont l'attaque nucléophile de la fonction thiol sur un accepteur de Michael comme les dérivés de

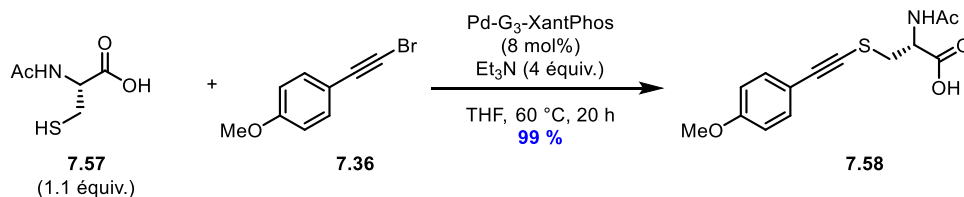
maléimide<sup>57</sup>, la formation d'un disulfure asymétrique<sup>58</sup>, ou bien la formation de thioéther par la réaction de thiol-ène<sup>59</sup>.

L'arylation de la cystéine est aussi une approche largement exploitée<sup>60</sup>. Récemment, Molander a démontré que la photocatalyse en tandem pouvait être utilisée pour fonctionnaliser la fonction thiol de biomolécules<sup>61</sup>. Par exemple, en irradiant avec une lumière bleue des quantités catalytiques des complexes  $[\text{Ru}(\text{bpy})_3]\text{PF}_6$  et  $[\text{Ni}(\text{dtbbpy})(\text{H}_2\text{O})_4]\text{Cl}_2$  ainsi que l'agent de transfert d'atome d'hydrogène **7.53**, l'arylation de la glutathione (**7.54**) a pu être réalisée afin d'instaurer différentes étiquettes bioactives (Schéma 7.15).



**Schéma 7.15** Biotination de la glutathione par arylation photochimique

Les acétylures de soufre ont également été utilisés pour modifier la fonction thiol de la cystéine. En 2016, Messaoudi a effectué l'alcynylation de biomolécules comme la cystéine **7.57** à partir du bromoalcyne **7.36** et du précatalyseur de palladium G<sub>3</sub>-XantPhos (Schéma 7.16)<sup>62</sup>. Cette méthode permet aussi l'arylation de la fonction thiol à partir de bromures d'aryle. Un fait à noter est que la formation des thioalcyne a été utilisée pour la bioconjugaison de biomolécules, mais la modification même du motif au sein de biomolécules reste encore à être explorée.



**Schéma 7.16** Formation d'un acétylure de soufre pour la bioconjugaison de la cystéine

## 7.3 Conclusion

Les acétylures de soufre sont une classe de molécules qui attire de plus en plus l'attention de la communauté chimique grâce à ses applications potentielles. Tel qu'illustré dans ce chapitre, les méthodes synthétiques existantes sont soit très restrictives au niveau de l'étendue de la réaction, soit elles requièrent une préfonctionnalisation relativement difficile d'un des deux partenaires de couplage. Le développement de nouvelles méthodes pourrait certainement permettre d'étudier de nouvelles applications du motif thioalcyne.

## 7.4 Buts du projet

L'utilisation des dérivés de réactif EBX développés par Waser est l'une des méthodes les plus efficaces pour la synthèse de thioalcyne<sup>21-22</sup>. Cependant, la synthèse du partenaire alcyne passe par sa préfonctionnalisation sous forme de dérivé d'EBX, ce qui peut devenir un défi synthétique lorsqu'il s'agit d'une molécule complexe, comme un précurseur macrocyclique. De plus, la méthode de Waser semble principalement fonctionner avec des alcyne alkyles et seulement un dérivé mésityle pour ce qui est des alcyne aryles. De façon complémentaire, la méthode photochimique développée dans notre groupe de recherche fonctionne bien lorsqu'il s'agit d'alcyne aryles, mais échoue pour les substrats alcyne alkyles<sup>36</sup>. Toutefois, la tolérance aux groupements fonctionnels et l'approche catalytique de la méthode photochimique était un bon point de départ pour le développement d'une méthode générale. Pour le développement de cette méthode, les points suivants ont été considérés :

- 1) La méthode devait être applicable tant aux substrats alkyles qu'aux substrats aryles
- 2) La méthode devait être tolérante à plusieurs groupements fonctionnels
- 3) La méthode devait se dérouler rapidement et dans des conditions douces
- 4) La méthode devait être efficace dans une grande plage de concentrations, permettant la synthèse de composés macrocycliques

Les prochains chapitres (8 et 9) porteront donc sur le développement d'une nouvelle méthode de synthèse de thioalcyne à partir de bromoalcyne et de thiols dans des conditions douces de catalyse avec des complexes de cuivre. Le chapitre 8 est un manuscrit décrivant le

développement de la méthode et son application pour la synthèse de composés macrocycliques. L'exploitation du motif thioalcyne à des fins de diversification y est aussi décrite. En ce qui concerne le chapitre 9, il s'agit d'un autre manuscrit dans lequel l'étendue de la réaction est explorée plus en détails. Il comporte aussi l'application de la méthode pour la bioconjugaison de cystéines, la synthèse d'alcyne disubstitués par des hétéroatomes ainsi qu'une étude mécanistique détaillée (données expérimentales et computationnelles).

## 7.5 Bibliographie

1. Trost, B. M.; Tracy, J. S. *Isr. J. Chem.* **2018**, *58*, 18 - 27.
2. (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064 – 5106; (b) Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimbürger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. *Chem. Lett.* **2016**, *45*, 574 – 585.
3. Minehan, T. G. *Acc. Chem. Res.* **2016**, *49*, 1168 - 1181.
4. Wang, T.; Chen, S.; Shao, A.; Gao, M.; Huang, Y.; Lei, A. *Org. Lett.* **2015**, *17*, 118 – 121.
5. Gray, V. J.; Wilden, J. D. *Org. Biomol. Chem.* **2016**, *14*, 9695 - 9711.
6. Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840 - 2859.
7. Arens, J. F.; Doornbos, T. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 481 - 486.
8. Kabanyane, S. T.; MaGee, D. I. *Can. J. Chem.* **1992**, *70*, 2758 – 2763.
9. Doroszuk, J.; Musiejuk, M.; Demkowicz, S.; Rachon, J.; Witt, D. *RSC Adv.* **2016**, *6*, 105449 - 105453.
10. Brandsma, L.; Wijers, H.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 583 – 584.
11. Zheng, W.; Zheng, F.; Hong, Y.; Hu, L. *Heteroat. Chem.* **2012**, *23*, 105 - 110.
12. Reeves, J. T.; Camara, K.; Han, Z. S.; Xu, Y.; Lee, H.; Busacca, C. A.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 1196 - 1199.
13. Distler, H. *Angew. Chem. Int. Ed.* **1967**, *6*, 544 – 553.
14. Godoi, B.; Sperança, A.; Back, D. F.; Brandão, R.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 3469-3477.
15. Yang, L.; Tian, Z.-Y.; Zhang, C.-P. *ChemistrySelect* **2019**, *4*, 311 – 315.
16. (a) Talavera, G.; Peña, J.; Alcarazo, M. *J. Am. Chem. Soc.* **2015**, *137*, 8704-8707. (b) Peña, J.; Talavera, G.; Waldecker, B.; Alcarazo, M. *Chem. Eur. J.* **2017**, *23*, 75-78.
17. Gao, W.-C.; Shang, Y.-Z.; Chang, H.-H.; Li, X.; Wei, W.-L.; Yu, X.-Z.; Zhou, R. *Org. Lett.* **2019**, *21*, 6021 – 6024.
18. Gray, V. J.; Slater, B.; Wilden, J. D. *Chem. Eur. J.* **2012**, *18*, 15582 – 15585.
19. Gray, V. J.; Cuthbertson, J.; Wilden, J. D. *J. Org. Chem.* **2014**, *79*, 5869 – 5874.
20. Chowdhury, R. M.; Wilden, J. D. *Org. Biomol. Chem.* **2015**, *13*, 5859 – 5861.
21. Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620 - 9623.
22. Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 16563 - 16573.
23. Wodrich, M. D.; Caramenti, P.; Waser, J. *Org. Lett.* **2016**, *18*, 60 - 63.

24. Sujatha, A.; Thomas, A. M.; Thankachan, A. P.; Anilkumar, G. *Arkivoc* **2015**, *1*, 1 - 28.
25. Bieber, L. W.; da Silva, M. F.; Menezes, P. H. *Tetrahedron Lett.* **2004**, *45*, 2735 – 2737.
26. Braga, A. L.; Reckziegel, A.; Menezes, P. H.; Stefani, H. A. *Tetrahedron Lett.* **1993**, *34*, 393 - 394.
27. Miyachi, N.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 1975 – 1976.
28. Yang, Y.; Dong, W.; Guo, Y.; Rioux, R. M. *Green Chem.* **2013**, *15*, 3170 – 3175.
29. Fang, Z.; He, W.; Cai, M.; Lin, Y.; Zhao, H. *Tetrahedron Lett.* **2015**, *56*, 6463 – 6467.
30. Mohan, B.; Hwang, S.; Woo, H.; Park, K. H. *Synthesis* **2015**, *47*, 3741 – 3745.
31. Kanemoto, K.; Yoshida, S.; Hosoya, T. *Org. Lett.* **2019**, *21*, 3172 – 3177.
32. (a) Brachet, E.; Brion, J. D.; Alami, M.; Messaoudi, S. *Adv. Synth. Catal.* **2013**, *355*, 2627 - 2636. (b) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J. D.; Alami, M.; Messaoudi, S. *Chem. Eur. J.* **2015**, *21*, 8375 - 8379.
33. Brachet, E.; Brion, J. D.; Alami, M.; Messaoudi, S. *Chem. Eur. J.* **2013**, *19*, 15276-15280.
34. (a) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587 – 2693. (b) Wimmer, A.; König, B. *Beilstein J. Org. Chem.* **2018**, *14*, 54–83.
35. (a) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760 - 1763. (b) Jouffroy, M.; Kelly, C. B.; Molander, G. A. *Org. Lett.* **2016**, *18*, 876 – 879.
36. Santandrea, J.; Minozzi, C.; Cruché, C.; Collins, S. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 12255 – 12259.
37. (a) Song, L. J.; Ding, S.; Wang, Y.; Zhang, X.; Wu, Y. D.; Sun, J. *J. Org. Chem.* **2016**, *81*, 6157 - 6164. (b) Fopp, C.; Isaac, K.; Romain, E.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Perez-Luna, A. *Synthesis* **2017**, *49*, 724 - 735; (c) Fopp, C.; Romain, E.; Isaac, K.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Perez-Luna, A. *Org. Lett.* **2016**, *18*, 2054 - 2057.
38. Bello, D.; O'Hagan, D. *Beilstein J. Org. Chem.* **2015**, *11*, 1902 - 1909.
39. (a) Zheng, W.; Hong, Y.; Wang, P.; Zheng, F.; Zhang, Y.; Wang, W. *Tetrahedron Lett.* **2013**, *54*, 3643 - 3646. (b) Kadikova, R. N.; Ramazanov, I. R.; Vyatkin, A. V.; Dzhemilev, U. M. *Synlett* **2018**, *29*, 1773–1775
40. Liu, S.; Zeng, X.; Xua, B. *Adv. Synth. Catal.* **2018**, *360*, 3249 – 3253.
41. Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624 – 630.
42. Shibata, T.; Sekine, A.; Mitake, A.; Kanyiva, K. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 15862 – 15865.
43. Pierson Smela, M.; Hoye, T. R. *Org. Lett.* **2018**, *20*, 5502 – 5505.
44. Riddell, N.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1934 - 1937.
45. Xie, L. G.; Niyomchon, S.; Mota, A. J.; Gonzalez, L.; Maulide, N. *Nat. Commun.* **2016**, *7*, 10914.
46. Destito, P.; Couceiro, J. R.; Faustino, H.; Lopez, F.; Mascarenas, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10766 - 10770.
47. Ding, S.; Jia, G.; Sun, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1877 - 1880.
48. Luo, Q.; Jia, G.; Sun, J.; Lin, Z. *J. Org. Chem.* **2014**, *79*, 11970 - 11980.
49. Yang, Z.; Chen, X.; Kong, W.; Xia, S.; Zheng, R.; Luo, F.; Zhu, G. *Org. Biomol. Chem.* **2013**, *11*, 2175 - 2185.
50. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91 - 93.
51. Farkaš, P.; Bystrický, S. *Chem. Pap.* **2010**, *64*, 683 – 695.
52. Gunnoo, S. B.; Madder, A. *Org. Biomol. Chem.* **2016**, *14*, 8002 – 8013.

53. McKay, C. S.; Finn, M. G. *Chem. Biol.* **2014**, *21*, 1075 – 1101.
54. (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007 - 2010. (b) Saxon, E.; Armstrong, J.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141 - 2143.
55. Li, L.; Zhang, Z. *Molecules* **2016**, *21*, 1393.
56. Minghao, F.; Bingqing, T.; Steven, H. L.; Xuefeng, J. *Curr. Top. Med. Chem.* **2016**, *16*, 1200 - 1216.
57. Ravasco, J. M. J. M.; Faustino, H.; Trindade, A.; Gois, P. M. P. *Chem. Eur. J.* **2019**, *25*, 43 – 59.
58. (a) van Kasteren, S. I.; Kramer, H. B.; Jensen, H. H.; Campbell, S. J.; Kirkpatrick, J.; Oldham, N. J.; Anthony, D. C.; Davis, B. G. *Nature*, **2007**, *446*, 1105 – 1109. (b) Davis, B.G.; Maughan, M. A. T.; Green, M. P.; Ullman, A.; Jones, J. B. *Tetrahedron: Asymmetry* **2000**, *11*, 245 – 262.
59. Grim, J. C.; Brown, T. E.; Aguado, B. A.; Chapnick, D. A.; Viert, A. L.; Liu, X.; Anseth, K. S. *ACS Cent. Sci.* **2018**, *4*, 909 – 916.
60. Zhang, C.; Vinogradova, E. V.; Spokoyny, A. M.; Buchwald, S. L.; Pentelute, B. L. *Angew. Chem. Int. Ed.* **2019**, *58*, 4810 – 4839.
61. Vara, B. A.; Li, X.; Berritt, S.; Walters, C. R.; Petersson E. J.; Molander, G. A. *Chem. Sci.* **2018**, *9*, 336 – 344.
62. Atto Al-Shuaeeb, R. A.; Kolodych, S.; Koniev, O.; Delacroix, S.; Erb, S.; Nicolaÿ, S.; Cintrat, J.-C.; Brion, J.-D.; Cianférani, S.; Alami, M.; Wagner, A.; Messaoudi, S. *Chem. Eur. J.* **2016**, *22*, 11365 – 11370.

## Chapitre 8. Synthesis and Diversification of Macrocyclic Alkynyl Sulfide

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*Manuscrit en préparation*

### Contributions :

- Éric Godin a participé à la mise en œuvre des expériences, a fait l'optimisation de la réaction de macrocyclisation, a fait la synthèse de quatre macrocycles et a participé à la rédaction du manuscrit et de la partie expérimentale.
- Sacha Nguyen Thanh a fait la synthèse des quatre macrocycles tripeptidiques.
- Javier Guerrero-Morales a fait les réactions de post-fonctionnalisation des macrocycles.
- Jeffrey Santandrea a fait la découverte et l'optimisation de la réaction intermoléculaire.
- Antoine Caron, Clémentine Minozzi, Noémie Beaucage, Bastien Rey, Mathieu Morency et Xavier Abel-Snape ont fait la synthèse de six macrocycles.
- Shawn K. Collins a participé à la mise en œuvre des expériences et à l'écriture du manuscrit.



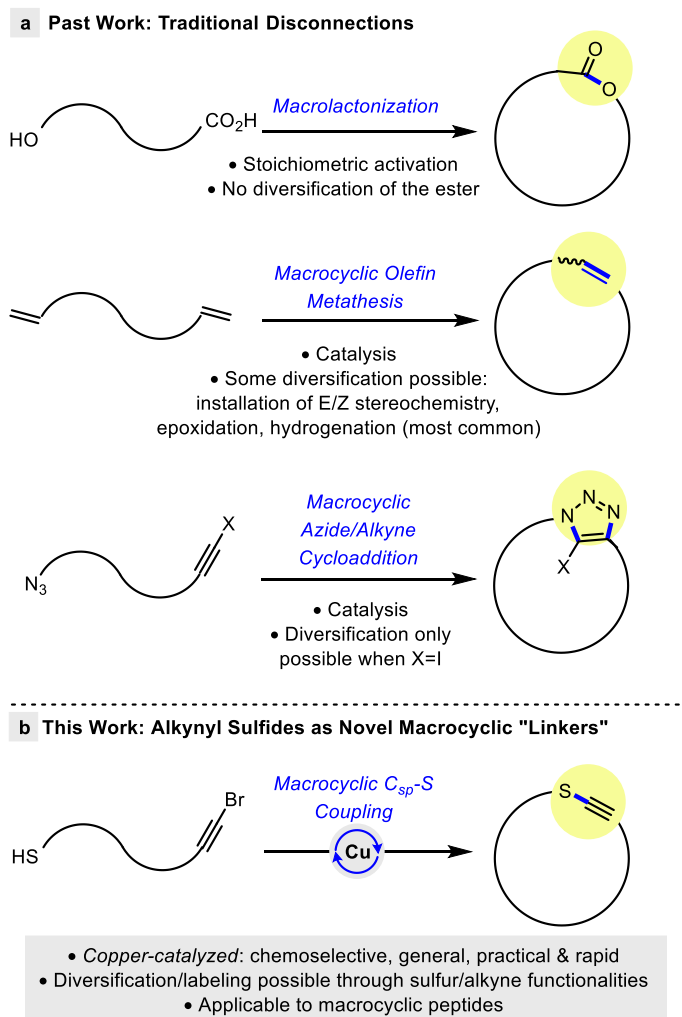
## 8.1 Abstract

The synthesis of rare macrocyclic alkynyl sulfides via a Cu-catalyzed C<sub>sp</sub>-S cross-coupling of thiols and bromoalkynes is presented. The catalytic protocol (Cu(MeCN)<sub>4</sub>PF<sub>6</sub>/dtbbpy) promotes chemoselective macrocyclization of peptides, dipeptides and tripeptides at ambient temperature (14 examples, 23→73 % yields). Importantly, incorporation of alkynyl sulfides as functionality opens new opportunities for diversification of macrocyclic frameworks through S-oxidation, halide addition and azide-alkyne cycloaddition chemistries to incorporate sulfones, halides or valuable fluorophore, biotin, PEG or farnesylated appendages (10 examples, 37→92 % yields).

## 8.2 Introduction

Macrocycles offer a unique topology within chemical space,<sup>1</sup> their structures can exist as both extended and flexible yet can retain remarkable conformational bias with appropriate functionality present. Current bioactive macrocyclic drugs are almost exclusively derived from natural products,<sup>2</sup> yet synthetic macrocycles represent a growing class of drug candidates. Retrosynthetically, a macrocyclic precursor typically contains a core from which extend appendages with functionality that when cyclized, is often referred to as the “linker”. Through the linker and macrocyclization, a conformation that is preferential for biological activity can be locked in, or alternatively, conformers exhibiting unwanted side effects can be locked out.<sup>3</sup> Consequently, the “linker” plays a critical role and is often modified systematically to examine its effects on activity. The most common linkers exploit well-known functional group manipulations (Figure 8.1). Macrolactonization<sup>4</sup> via stoichiometric activation of a *seco*-acid can be used to form ester-based linkers. Olefin metathesis<sup>5</sup> and copper-catalyzed azide-alkyne cycloaddition (CuAAC)<sup>6</sup> reactions are examples of catalytic processes that can be used to form macrocycles. In each of the above processes, the linker serves primarily to form the macrocycle, and no further diversification of the ring is envisioned. No functionalization of the esters is usually possible, most olefin metathesis macrocyclizations terminate with hydrogenolysis of the olefin and only in rare cases can the CuAAC be used to add further complexity to final cycle. The lack of utility of the linker is unfortunate, as it could be

exploited to add diverse pharmacophores, or to tag the macrocycle with useful appendages including fluorophores, poly(ethylene)glycol chains or affinity labels.



**Figure 8.1** Strategies for the synthesis of macrocycles

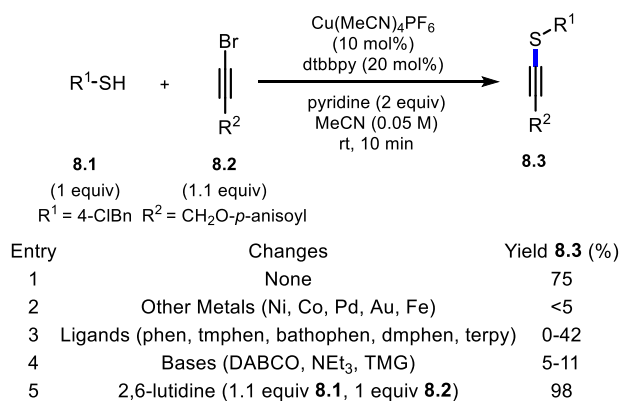
To develop new linker strategies for macrocyclization, the bond-forming event must create new functionality that has predictable reactivity patterns, and multiple avenues for diversification. Heteroatom-substituted alkynes are virtually unexplored as linkers for macrocyclization, despite possessing enhanced reactivity and predictable regioselectivity in their transformations when compared to common internal alkynes.<sup>7</sup> Alkynyl sulfides<sup>8</sup> are perhaps ideal for this purpose, as they possess suitable stability and are well known synthons for a variety of transformations.<sup>9</sup> In addition, the C<sub>sp</sub>-S motif is almost non-existent in macrocyclic scaffolds, and provides some measure of orthogonality with functionality

typically observed within natural products, heterocyclic chemistry and peptide science. Herein, we report on a novel Cu-catalyzed synthesis of alkynyl sulfides and application to the preparation of macrocyclic peptides.<sup>10</sup> The macrocyclization exhibits high chemoselectivity and occurs at ambient temperature. In addition, we disclose diversification of the alkynyl sulfide functionality through oxidations, halide additions or Ir-catalyzed azide-alkyne cycloadditions (IrAAC).

### 8.3 Results/Discussion

The interest in alkynyl sulfides has stimulated many different preparative methods. However, developing a method ideal for macrocyclization places certain restraints: the use of highly reactive and electrophilic alkynes based on dibenzothiophenium triflates or hypervalent iodine<sup>11</sup> might not be tolerant to the multi-step synthesis required to construct the precursors. Other methods such as catalytic metallaphotoredox approaches were limited to aryl alkynes.<sup>12</sup> where the majority of macrocyclization reactions take place from aliphatic-based substituents.<sup>13</sup> As such, our initial investigations into a new synthesis of alkynyl sulfides began with intermolecular screening involving the coupling of an alkyl thiol (4-chlorobenzyl thiol, 4-ClBnSH, **8.1**) with an alkyl-substituted bromoalkyne **8.2** as an electrophile.

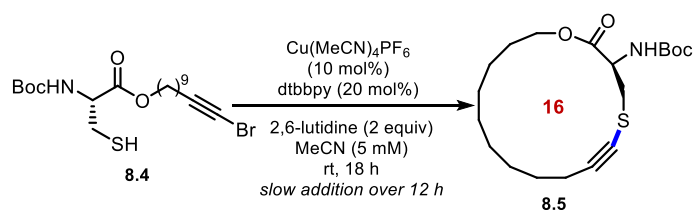
**Table 8.1** Optimization of a Cu-Catalyzed Coupling of an Alkyl-Substituted Bromoalkyne to Form an Alkynyl Sulfide<sup>[a]</sup>



<sup>[a]</sup> Yields determined by <sup>1</sup>H NMR spectroscopy using an internal standard. dtbbpy: 4,4'-di-tert-butyl-2,2'-dipyridyl, bpy: 2,2'-dipyridyl, phen: 1,10-phenanthroline tmphen: 3,4,7,8-tetramethyl-1,10-phenanthroline, bathophen: 4,7-diphenyl-1,10-phenanthroline, dmphen: 2,9-dimethyl-1,10-phenanthroline, terpy: 2,2':6',2''-terpyridine.

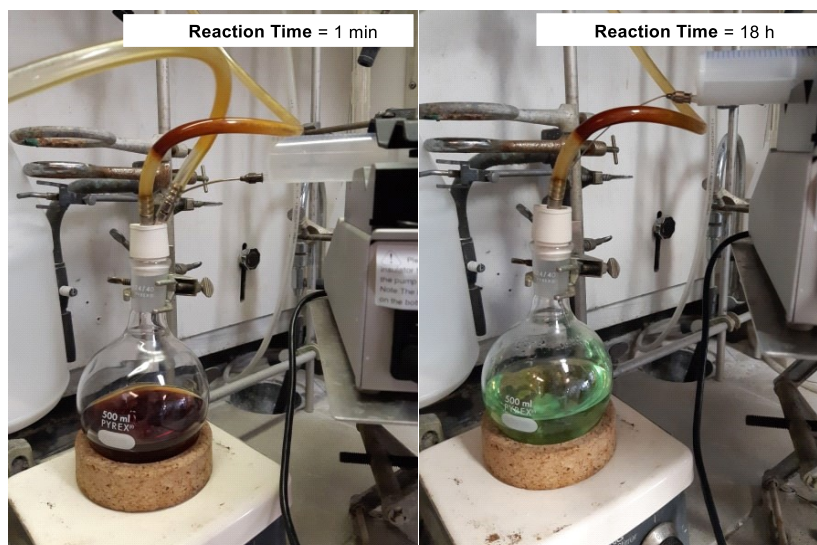
A wide range of diamine-type ligands, other alkynyl halides, and metal catalysts (Ni, Co, Pd, Au, and Fe) were surveyed to form the desired product **8.3** (Table 8.1). However, with Cu(MeCN)<sub>4</sub>PF<sub>6</sub> after only 10 min, total conversion of the thiol was observed and produced alkynyl sulfide **8.3** in 75 % yield. Further fine-tuning of the reaction parameters (a slight excess of the thiol, presence of an inert atmosphere, 2,6-lutidine as base) afforded **8.3** in 98 % yield.<sup>14</sup> To investigate whether the method was adaptable for macrocyclization, the cysteine-derived precursor **8.4** was prepared and submitted to the standard conditions, however low concentrations (5 mM) and slow addition of **8.4** over a 12 h period, followed by an additional 6 h of stirring were employed (Table 8.2). Gratifyingly, cyclization afforded the 16-membered ring **8.5** in 56 %. When the concentration was further decreased to 2.5 mM, or the catalyst loadings increased, no improvement in the isolated yield of macrocycle **8.5** was observed. Eliminating or reducing the time of the slow addition resulted in reduced yields of **8.5**. Furthermore, under the optimized conditions, the macrocyclization of **8.4** could be easily scaled to 500 mg scale affording an identical 56 % yield. The alkylation also provides a convenient visual indicator of completion of the reaction. Upon the start of the reaction, a deep red color is observed, while following completion, a light green color appears (Table 8.2).

**Table 8.2.** Optimization of a Cu-Catalyzed Coupling to form a Cysteine-Derived Macrocylic Alkynyl Sulfide<sup>[a]</sup>



Entry	Changes	Yield <b>8.5</b> (%)
1	none	56
2	[2.5 mM]	38
3	double the catalyst loadings	29
4	slow addition over 2 h	41
5	no slow addition	34

<sup>[a]</sup> Isolated yields. Ring size indicated in red.

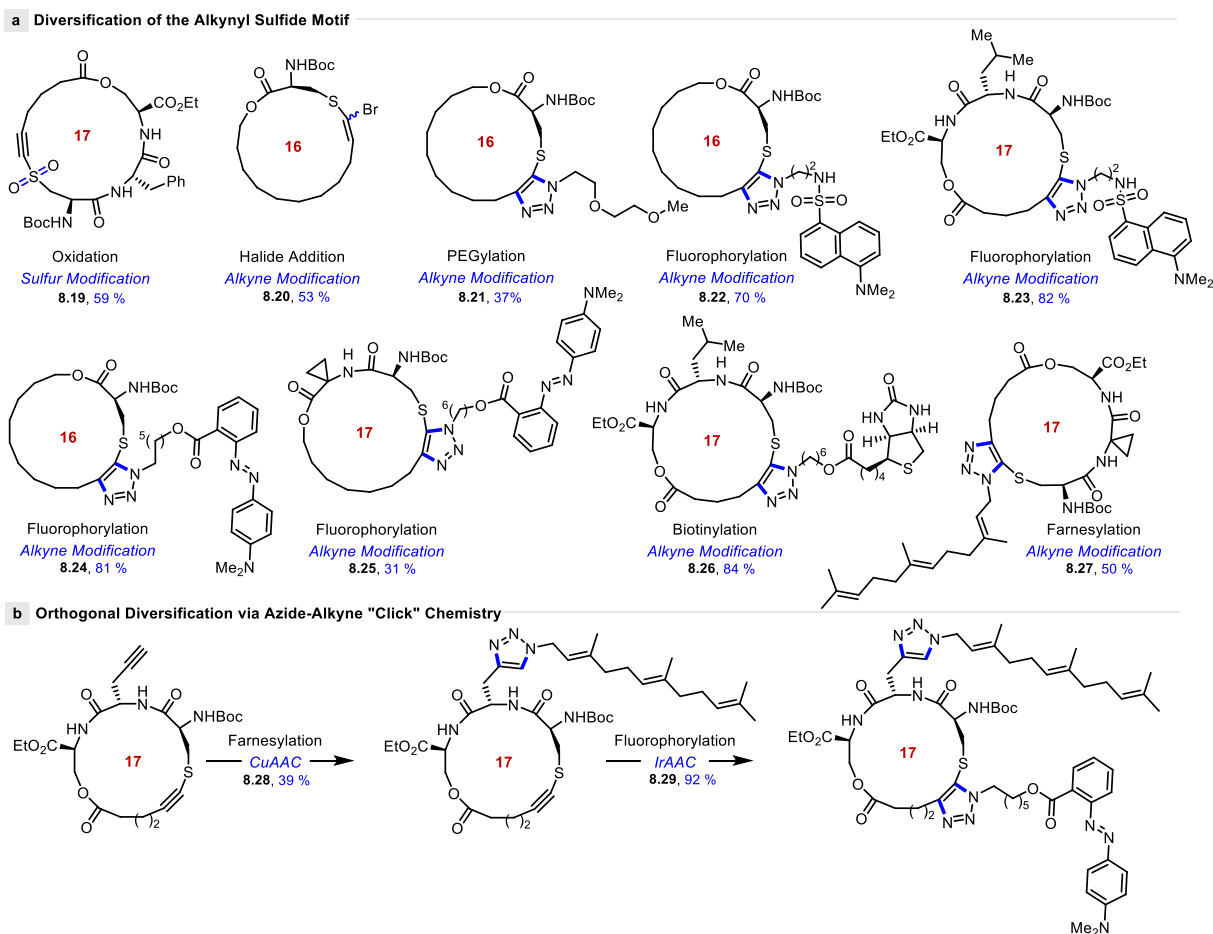


With optimized conditions in hand, the scope of  $\text{C}_{\text{sp}}\text{-S}$  coupling was first investigated with cysteine-derived macrocycles (Table 8.3). As mentioned previously, the macrocycles whereby the alkynyl bromide was connected via the ester functionality **8.5** was isolated in 56 % yield. Switching from Boc to Fmoc-protected cysteines was also found to be compatible with the reaction conditions (macrocycle **8.6**, 47 % yield). Next, an analogous macrocycle derived from cysteine in which the amide linkage was incorporated within the macrocyclic framework (**8.7**) was prepared, and could be obtained in 50 %. Macrocylic **8.8** derived from propargyl glycine could also be prepared in 52 % yield. A macrocycle **8.9** derived from the angiotensin-converting-enzyme-inhibitor captopril, was isolated in 67 % yield. Several dipeptide-derived

macrocycles were also prepared: a cysteine-phenylalanine derived macrocyclic alkynyl sulfide **8.10** was obtained in 35 % yield. Similarly, macrocyclic dipeptides having cysteine/isoleucine (**8.11**) or cysteine/acc (**8.12**) (1-aminocyclopropane-1-carboxylic acid) were smoothly prepared in 35 and 52 % yields respectively. A macrocyclic dipeptide having an unprotected terminal alkyne (cysteine/propargyl glycine) (**8.13**) was formed in 23% yield. Finally, a macrocyclic alkynyl sulfide derived from glycine and cysteine (**8.14**) was prepared in 73 % yield. Notably, the macrocycle incorporated an aromatic alkynyl sulfide that allowed comparison to other existing methods for C<sub>sp</sub>-S bond formation. When the macrocycle was formed using metallaphotoredox chemistry, the yield of **8.14** was notably lower (21 %), demonstrating the advantages of using the newly developed chemistry. Gratifyingly, X-ray crystallographic analysis also confirmed the connectivity of macrocycle **8.14**.<sup>15</sup> The Cu-catalyzed method could also prepare tripeptide macrocycles incorporating an alkynyl sulfide. An alkynyl bromide was installed on a serine residue and then used to form a series of tripeptides (Table 3c). The macrocycles incorporated other amino acids such as leucine, phenylalanine, acc and propargylglycine and were isolated in 55, 30, 30 and 58 % yields (**8.15**, **8.16**, **8.17** and **8.18** respectively).



cysteine-derived macrocycle **8.5** afforded the adduct **8.21** with an appended PEG chain (37 % yield). Interestingly, the incorporation of fluorophores onto the novel alkynyl sulfide macrocycles was also possible using IrACCs. The cysteine-derived macrocycle **8.5** and the tripeptide **8.15** underwent cycloaddition to afford dansyl-derived<sup>20</sup> macrocycles appended with the corresponding fluorophores (**8.22** and **8.23**, 70 and 82 % yields, respectively). The macrocycles could also be appended with a methyl red-derived fluorophore.<sup>21</sup>



**Figure 8.2** Diversification of macrocyclic alkynyl sulfides

Following IrACC, macrocycles **8.24** and **8.25** were isolated in 81 and 31 % yield respectively from the corresponding alkynyl sulfide peptides. Biotinylation was also possible and corresponding 17-membered macrocycle **8.26** was isolated in 84% yield. Farnesylation of the tripeptide **8.18** occurred in 50 % yield to afford the lipid-conjugate **8.27**. Importantly, the alkynyl sulfides reactivity patterns provides some orthogonality with the common CuAAC for



terminal alkynes.<sup>6a</sup> The tripeptide **8.17** could first undergo cycloaddition on the terminal alkyne of the propargyl glycine residue to install a farnesyl moiety without affecting the alkynyl sulfide “linker” (**8.28**, 39 %). Subsequent IrAAC then modified the macrocycle to include a methyl red fluorophore (**8.29**, 92 %).

## 8.4 Conclusions

In summary, a Cu-catalyzed C<sub>sp</sub>-S cross-coupling of thiols and bromoalkynes is presented as a new tool for constructing macrocyclic alkynyl sulfides. The protocol is operationally simple, employing a commercially available copper salt and ligand combination (Cu(MeCN)<sub>4</sub>PF<sub>6</sub>/dtbbpy), ambient temperature and conveniently includes a colorimetric indicator for reaction completion. Macrocyclic alkynyl sulfides are rare and their incorporation in macrocyclic peptides, dipeptides and tripeptides is notable given their importance in medicinal chemistry. The incorporation of an alkynyl sulfide adds an element of structural rigidity to the macrocycle skeletons. Importantly, there are ample avenues for diversification through oxidation to incorporate sulfones, halide addition, or via cycloaddition to add valuable fluorophore, biotin, PEG or farnesylated appendages. Functionalization of other terminal alkynes is possible in an orthogonal manner to the alkynyl sulfides, again provide a variety of options to modify cyclic peptide frameworks.

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**Keywords:** macrocycles • copper catalysis • alkynyl sulfides • peptides • cycloaddition

## 8.5 Bibliography

- 1) (a) C. J. Roxburgh, *Tetrahedron* **1995**, *51*, 9767-9822. (b) E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961-2004. (c) H. Matsuda, S. Watanabe, K. Yamamoto, *Chem. Biodiversity* **2004**, *1*, 1985-1991. (d) G. Rüedi, M. Nagel, H.-J. Hansen, *Org. Lett.* **2004**,

- 6, 2989-2991. (e) C. Fehr, J. Galindo, O. Etter, W. Thommen, *Angew. Chem.* **2002**, *114*, 4705-4708; *Angew. Chem., Int. Ed.* **2002**, *41*, 4523-4526.
- 2) E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608-624.
  - 3) Practical Medicinal Chemistry with Macrocycles, 1<sup>st</sup> ed.; E. Marsault, M. L. Peterson, Eds.; John Wiley & Sons, Inc.: Hoboken, 2017.
  - 4) For examples in Yamaguchi esterification see: a) A. Parenty, X. Moreau, J. M. Campagne, *Chem. Rev.* **2006**, *106*, 911-939. b) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993. c) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822-1830.
  - 5) a) D. Hughes, P. Wheeler, D. Ene, *Org. Process Res. Dev.* **2017**, *12*, 1938-1962. B) X. Yu, D. Sun, *Molecules* **2013**, *18*, 6230-6268.
  - 6) a) S. Jogula, B. Dasari, M. Khatravath, G. Chandrasekar, S. S. Kitambi, P. Arya, *Eur. J. Org. Chem.* **2013**, 5036-5040. b) M. A. Potopnyk, S. Jarosz, in *Click Chemistry in Glycoscience* (Eds.: Witczak, Z. J.; Bielski, R.) Wiley, 2013, 235-252. c) D. Kushwaha, P. Dwivedi, S. K. Kuanar, V. K. Tiwari, *Curr. Org. Synth.* **2013**, *10*, 90-135. d) A. R. Bogdan, S. V. Jerome, K. N. Houk, K. James, *J. Am. Chem. Soc.* **2012**, *134*, 2127-2138.
  - 7) a) T. G. Minehan, *Acc. Chem. Res.* **2016**, *49*, 1168-1181. b) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560-578. c) G. Evano, N. Blanchard, G. Compain, A. Coste, C. S. Demmer, W. Gati, C. Guissart, J. Heimburger, N. Henry, K. Jouvin, G. Karthikeyan, A. Laouiti, M. Lecomte, A. Martin-Mingot, B. Métayer, B. Michelet, A. Nitelet, C. Theunissen, S. Thibaudeau, J. Wang, M. Zarca, C. A. Zhang, *Chem. Lett.* **2016**, *45*, 574-585.
  - 8) a) W.-C. Gao, Y.-Z. Shang, H.-H. Chang, X. Li, W.-L. Wei, X.-Z. Yu, R. Zhou, *Org. Lett.* **2019**, *21*, 6021-6024. b) B. Waldecker, F. Kraft, C. Golz, M. Alcarazo, *Angew. Chem.* **2018**, *130*, 12718-12722; *Angew. Chem. Int. Ed.* **2018**, *57*, 12538-12542. c) J. Peña, G. Talavera, B. Waldecker, M. Alcarazo, *Chem. Eur. J.* **2017**, *23*, 75-78. d) F. Liu, W. Yi, *Org. Chem. Front.* **2018**, *5*, 428-433. e) Y. Yang, W. Dong, Y. Guo, R. M. Rioux, *Green Chem.* **2013**, *15*, 3170-3175. f) J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, H. Lee, C. A. Busacca, C. H. Senanayake, *Org. Lett.* **2014**, *16*, 1196-1199. g) E. Brachet, J. D. Brion, M. Alami, S. Messaoudi, *Adv. Synth. Catal.* **2013**, *355*, 2627-2636.
  - 9) a) [3+2] Cycloaddition: P. Destito, J. R. Couceiro, H. Faustino, F. López, J. L. Mascareñas, *Angew. Chem.* **2017**, *129*, 10906-10910; *Angew. Chem. Int. Ed.* **2017**, *56*, 10766-10770. b) [2+2+2] Cycloaddition: L. G. Xie, S. Niyomchon, A. J. Mota, L. González, N. Maulide, *Nat. Commun.* **2016**, *7*, 10914-10923. c) Annulation: Y.-Q. Zhang, X.-Q. Zhu, Y.-B. Chen, T.-D. Tan, M.-Y. Yang, L.-W. Ye, *Org. Lett.* **2018**, *20*, 7721-7725. d) R. J. Reddy, M. P. Ball-Jones, P. W. Davies, *Angew. Chem.* **2017**, *129*, 13495-13498; *Angew. Chem. Int. Ed.* **2017**, *56*, 13310-13313. e) Hydrosilylation: S. Ding, L. J. Song, Y. Wang, X. Zhang, L. W. Chung, Y. D. Wu, J. Sun, *Angew. Chem.* **2015**, *127*, 5724-5727; *Angew. Chem. Int. Ed.* **2015**, *54*, 5632-5635. f) 1,4-Chirality Transfer: D. Kaldre, B. Maryasin, D. Kaiser, O. Gajsek, L. González, N. Maulide, *Angew. Chem.* **2017**, *129*, 2248-2252; *Angew. Chem. Int. Ed.* **2017**, *56*, 2212-2215. g) Hydrohalogenation: D. Bello, D. O'Hagan, *Beilstein J. Org. Chem.* **2015**, *11*, 1902-1909. h) Hydroallylation: W. Kong, C. Che, L. Kong, G. Zhu, *Tetrahedron Lett.* **2015**, *56*, 2780-2782.

- 10) a) X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He, X. Qi, W. Shen, P. Liu, G. Chen, *Nat. Chem.* **2018**, *10*, 540-548. b) C. J. White, A. K. Yudin, *Nat. Chem.* **2011**, *3*, 509-524. c) C. Morrison, *Nat. Rev. Drug Discovery* **2018**, *17*, 531-533. d) A. Zorzi, K. Deyle, C. Heinis, *Curr. Opin. Chem. Biol.* **2017**, *38*, 24-29. e) H. Y. Lau, P. de Andrade, Y. Wu, D. R. Spring, *Chem. Soc. Rev.* **2015**, *44*, 91-102. f) J. Wu, J. Tang, H. Chen, Y. He, H. Wang, H. Yao, *Tetrahedron Lett.* **2018**, *59*, 325-333.
- 11) a) R. Frei, M. D. Wodrich, D. P. Hari, P.-A. Borin, C. Chauvier, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 16563-16573. b) R. Frei, J. Waser, *J. Am. Chem. Soc.* **2013**, *135*, 9620-9623.
- 12) J. Santandrea, C. Minozzi, C. Cruché, S. K. Collins, *Angew. Chem.* **2017**, *129*, 12423-12427; *Angew. Chem. Int. Ed.* **2017**, *56*, 12255-12259.
- 13) S. Zaretsky, A. K. Yudin, *Contemporary Macrocyclization Technologies in Practical Medicinal Chemistry with Macrocycles*, 1<sup>st</sup> ed.; E. Marsault, M. L. Peterson, Eds.; John Wiley & Sons, Inc.: Hoboken, 2017, p 1-24.
- 14) See Supporting Information for details.
- 15) CCDC 1968532 (**14**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)
- 16) S. Y. Woo, J. H. Kim, M. K. Moon, S.-H. Han, S. K. Yeon, J. W. Choi, B. K. Jang, H. J. Song, Y. G. Kang, J. W. Kim, J. Lee, D. J. Kim, O. Hwang, K. D. Park, *J. Med. Chem.* **2014**, *57*, 1473-1487.
- 17) D. Gao, T. G. Back, *Chem. Eur. J.* **2012**, *18*, 14828 – 14840.
- 18) A. A. H. A. Fuaad, F. Azmi, M. Skwarczynski, I. Toth, *Molecules* **2013**, *18*, 13148-13174. b) H. Li, R. Aneja, I. Chaiken, *Molecules* **2013**, *18*, 9797-9817.
- 19) Q. Luo, G. Jia, J. Sun, Z. Lin, *J. Org. Chem.* **2014**, *79*, 11970-11980.
- 20) a) L. Choulier, K. Enander, *Sensors* 2010, *10*, 3126–3144. b) C. Gros, B. Labouesse, *European J. Biochem.* **1969**, *7*, 463-470.
- 21) a) J. Beythien, P. D. White, *Tetrahedron Lett.* **2005**, *46*, 101-104. b) D. K. Das, P. Goswami, C. Barman, B. Das, *Environmental Engineering Research* **2012**, *17*, S75-S7

# Chapitre 9. General and Efficient Cu-Catalyzed C<sub>sp</sub>-S Coupling

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*Manuscrit en préparation*

## Contributions :

- Éric Godin a participé à la mise en œuvre des expériences, a fait la synthèse de vingt acétylures de soufre, a fait les expériences expérimentales pour l'étude mécanistique et a participé à la rédaction du manuscrit et de la partie expérimentale.
- Jeffrey Santandrea a participé à la mise en œuvre des expériences, a fait la synthèse de vingt-deux acétylures de soufre et a participé à la rédaction du manuscrit et de la partie expérimentale.
- Mathieu Morency a fait toutes les expériences computationnelles pour l'étude mécanistique.
- Radu I. Iftimie a supervisé les études mécanistiques et a participé à l'écriture du manuscrit.
- Shawn K. Collins a participé à la mise en œuvre des expériences et à l'écriture du manuscrit.

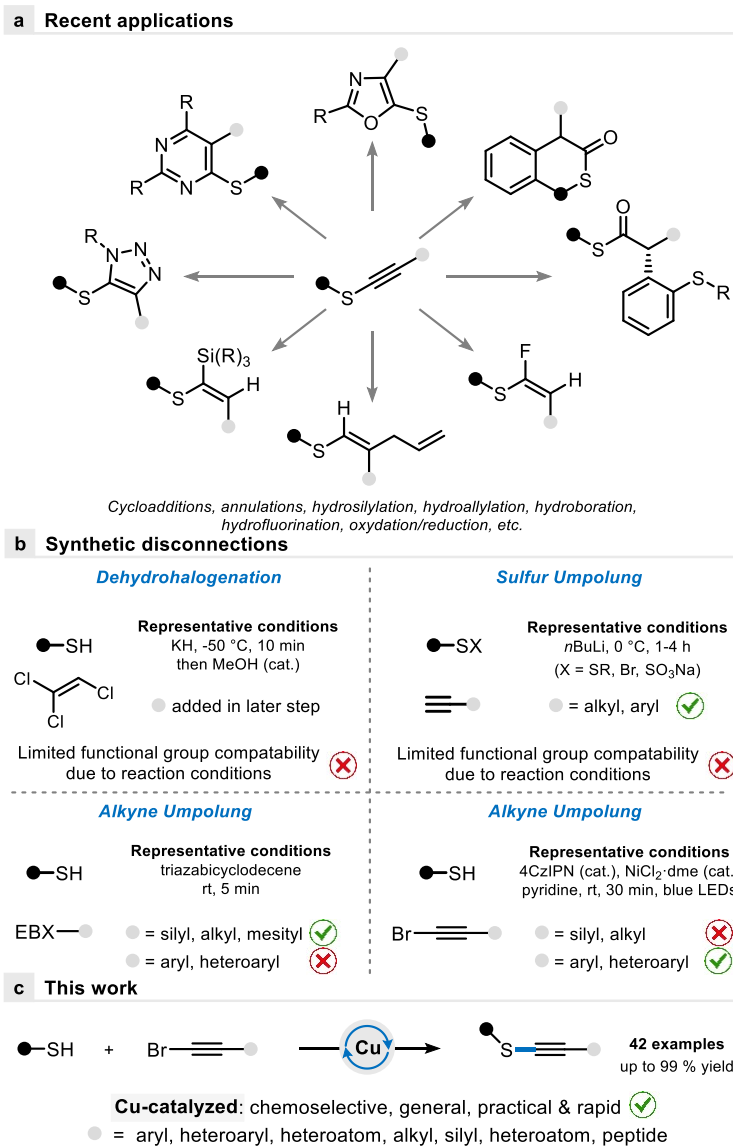
## 9.1 Abstract

Alkynyl sulfides are versatile heteroatom-substituted alkyne functional groups that combine predictive reactivity with ease of handling. However, current methods to access such compounds often depend on the tedious synthesis of preactivated reactants, apply harsh reaction conditions, and lack generality. Copper-catalyzed cross-coupling of thiols and bromoalkynes affords a mild, rapid and selective C<sub>sp</sub>-S coupling with broad scope, enabling the use of aryl-, alkyl- and silyl-substituted alkynyl coupling partners (42 total examples, 44-99 % yields). Importantly, the method enables the preparation of difficult-to-access bis-heteroatom-functionalized (*S,S*-, *S,P*- and *S,N*-) alkynes and new applications for the alkynyl sulfide motif as a tool for cysteine functionalization and labelling. Computational studies suggest that the mechanism of C<sub>sp</sub>-S bond formation involves two copper centers acting cooperatively to mediate cuprathiolation and subsequent rearrangement to form the desired alkynyl sulfide.

## 9.2 Introduction

Alkynes remain one of the most important and versatile building blocks in organic synthesis.<sup>1</sup> Their reactive  $\pi$ -system and predictive geometry enhances their utility in many diverse fields. Not surprisingly, alkynylation methods are of significant interest, and exhibit their own unique challenges. An example of existing challenges in alkynylation is in the synthesis of heteroatom-substituted alkynes. In comparison to aliphatic internal alkynes, heteroatom-substituted alkynes possess enhanced reactivity and predictable regioselectivity in their transformations.<sup>2</sup> Alkynyl sulfides are an important member of heteroatom-substituted alkynes because they mitigate predictive reactivity with ease of handling. Alkynyl sulfides have found application as synthons and substrates for a variety of transformations (Figure 9.1a).<sup>3</sup> As such, a number of methods have evolved for their synthesis (Figure 9.1b). The first synthesis of an alkynyl sulfide involved dehydrohalogenation to form the alkyne,<sup>4</sup> but more recent tactics involve umpolung strategies that form the C<sub>sp</sub>-S bond using either electrophilic sulfur or alkyne sources.<sup>5</sup> Amongst the latter, the use of ethynylbenziodoxolone (EBX) alkyne transfer reagents represents one of the more efficient methods for constructing alkynyl sulfides, but is not without its own limitations, particularly for the synthesis of alkynyl sulfides

from aryl alkynes.<sup>6</sup> Our own group recently disclosed a catalytic metallaphotoredox approach, which was highly efficient for the preparation of aromatic alkynyl sulfides, but failed with aliphatic alkyne coupling partners.<sup>7</sup> As such, the metallaphotoredox and EBX reagent methods are complimentary in nature with regards to their scope, but highlight the challenge of developing a universal catalytic strategy to alkynyl sulfides. Our group recently reported a new Cu-catalyzed protocol for the synthesis of alkynyl sulfides from alkyl alkynyl bromides and demonstrated its efficiency for forming complex peptidic macrocycles.<sup>8</sup> Herein, we report on a thorough examination of the scope of the intermolecular Cu-catalyzed synthesis of alkynyl sulfides from thiols and bromoalkynes that demonstrates broad functional-group and substrate tolerance (alkyl- and arylalkynes), and even further extends the scope to the synthesis of alkynylated peptides and bis-heteroatom-substituted alkynes (Figure 9.1c).



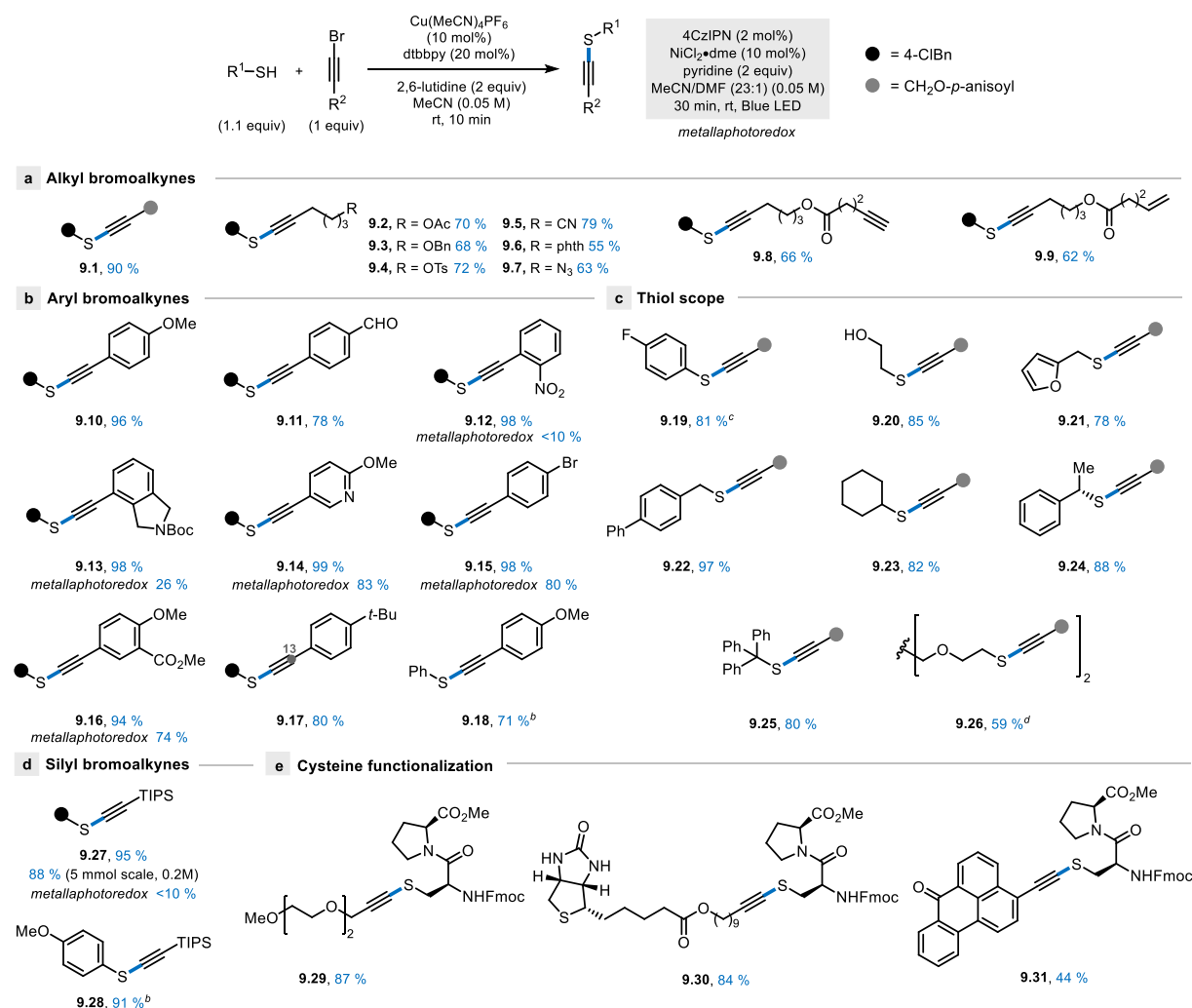
**Figure 9.1** Developing universal catalytic protocols for the synthesis of alkyne sulfides: Recent applications of alkyne sulfides as building blocks (a), synthetic disconnections toward alkyne sulfides (b) and unified alkyne umpolung strategy toward alkyne sulfides (c)

### 9.3 Results/Discussion

*Scope of the Cu-Catalyzed Synthesis of Alkynyl Sulfides.* The formation of alkynyl sulfides from alkynyl bromides and thiols utilized a catalytic system  $\text{Cu}(\text{MeCN})_4\text{PF}_6/\text{dtbbpy}/2,6\text{-lutidine}$  protocol that afforded a 90 % of the an alkynyl sulfide **9.1**. Intermolecular coupling took place at [50 mM] in approximately 10 min. Note that terminal alkynes did not afford the corresponding alkynyl sulfides, and other halogenated alkynes such as the chloro- and iodo-derivatives did not afford the desired product. The  $\text{C}_{\text{sp}}\text{-S}$  coupling was found to be compatible with various functional groups with regards to alkyl bromoalkyne partners (Table 9.1a). Alkyl-substituted alkynyl bromides having protected alcohols such as an acetate, benzyl or tosyl (**9.2**→**9.4**, 68-72 %), as well nitrile, phthalimide, azide, alkyne and alkene groups (**9.5**→**9.9**, 55-79 %). Next, the Cu-catalyzed protocol was evaluated with aromatic-substituted bromoalkynes (Table 9.1b).



**Table 9.1** Scope of the Cu-Catalyzed Formation of Alkynyl Sulfides: Intermolecular Cross-Coupling<sup>a</sup>



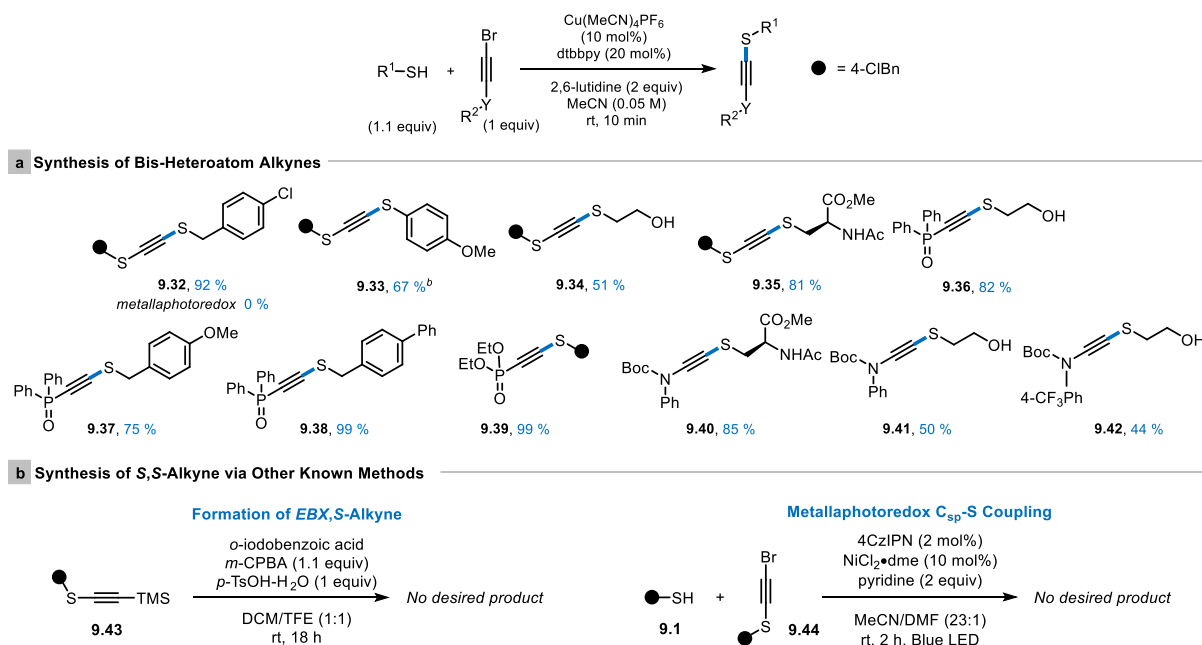
<sup>a</sup> Reactions performed on 0.25 mmol scale unless otherwise noted. Isolated yields. <sup>b</sup> Reaction time of 2 h. <sup>c</sup> Reaction performed in DMF instead of MeCN.

Coupling occurred in the presence of methoxy or aldehyde substituents to afford the desired alkynyl sulfides **9.10** and **9.11** in 96 and 78 % yields respectively. Importantly, aromatic alkynyl bromide substrates that were challenging or would not participate in the previously developed metallaphotoredox conditions were coupled in good yields using the Cu-catalyzed protocol. For example, preparation of an alkynyl sulfide bearing a nitro or isoindoline groups were not productive under the photochemical conditions (**9.12-9.13**, <10-26 % yield), but provided the corresponding alkynyl sulfides in 98 % yield under Cu-catalyzed conditions. Pyridine-, bromo- and salicylate-derived aromatic alkynyl bromides were also

tolerated and afforded the alkynyl sulfides in high yields (**9.14-9.16**, 94-99 %). A *t*-Bu-substituted alkynyl sulfide **9.17** was formed in 80 % yield bearing a <sup>13</sup>C-isotopic label. Finally, an aromatic thiol could also be coupled with an aromatic alkynyl bromide in good yield (71 % of **9.18**). It should be noted that coupling of aromatic thiols may require longer reaction times (10 min vs. 2 h) and solubility may require switching solvents (MeCN vs DMF). The coupling of both aliphatic and aryl thiols with alkyl-substituted bromoalkynes was also possible (Table 9.1c). A *p*-fluorophenolthiol also underwent coupling to afford the corresponding alkynyl sulfide **9.19** in 81 % yield. The thiol coupling partners derived from primary thiols such as 2-mercaptoethanol, 2-furanmethanethiol and 4-biphenylmethanethiol all afforded the corresponding alkynyl sulfides in good yields (**9.20**, 85 %; **9.21**, 78 %; **9.22**, 97 %). Secondary thiols including cyclohexanethiol and an enantioenriched benzylic thiol produced the respective alkynyl sulfides in high yields (**9.23** and **9.24**, 82 and 88 %). A tertiary thiol (TrtSH) provided **9.25** in good yield (80 %). The productive coupling with triphenylmethanethiol is again noteworthy, as the coupling of tertiary thiols failed with the previously developed metallaphotoredox conditions. In addition, a bis-coupling conducted using a bis-thiolated PEG-derivative afforded the desired alkynyl sulfide **9.26** in 59 % yield (77 % yield per coupling). Coupling of thiols to a TIPS-protected alkynyl bromide were also investigated (Table 9.1d) and the desired alkynyl sulfide **9.27** was isolated in 95 % yield and could be reproducibly scaled to 5 mmol scale with minimal loss of yield (88 %). Coupling of an aromatic thiol to afford **9.28** also occurred in good yield (91 %).<sup>9</sup> Cysteine conjugation is becoming a powerful tool for modifying the physical properties of peptides.<sup>10</sup> Recent examples of gold-<sup>10f</sup> and palladium-mediated<sup>10h-j</sup> methods demonstrate the potential to incorporate new motifs via covalent bonds while maintaining functional group tolerance and chemoselectivity. Given the catalytic and mild reaction conditions for the synthesis of alkynyl sulfides, it was reasoned that cysteine labelling should be possible (Table 9.1e). As such, a model dipeptide was submitted to the optimized reaction conditions in an attempt to incorporate a poly(ethylene)glycol (PEG)-like chain, an affinity tag and a fluorescent label. When the cysteine-containing dipeptide was treated with a corresponding PEG-appended alkynyl bromide, the corresponding alkynyl sulfide **9.29** was isolated in 87 % yield. Similarly, alkynyl sulfides bearing a biotin affinity tag (**9.30**) or a benzanthrone-based label (**9.31**) were prepared in 84 % and 44 % yield respectively. The latter result lower yield is due to the

problematic solubility of the organic dye. Considering the robustness of the copper-catalyzed protocol to other polar solvents (e.g. DMSO, MeOH), the above-mentioned labelling experiments illustrate the feasibility of incorporating alkynyl sulfides in more complex peptidic scaffolds.

**Table 9.2** Scope of the Cu-Catalyzed Formation of Alkynyl Sulfides: Bis-Heteroatom-Substituted Alkynes<sup>a</sup>

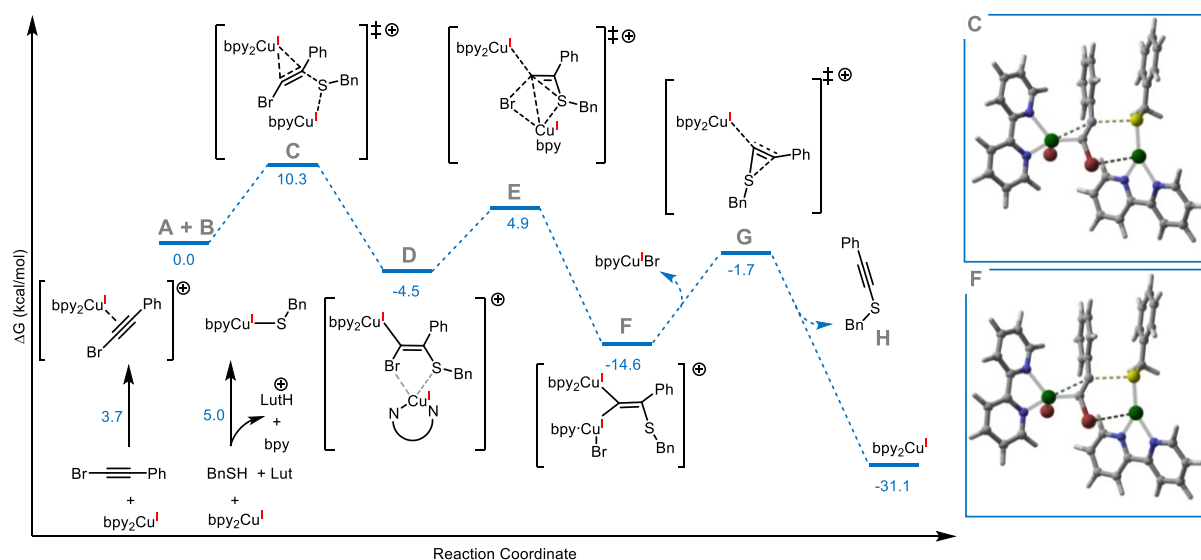


*Scope of the Cu-Catalyzed Synthesis of Alkynyl Sulfides: Bis-Heteroatom-Substituted Alkynes.* As the potential of heteroatom-substituted alkynes as synthons in organic chemistry continues to expand, it is curious that applications of other bis-heteroatom-substituted alkynes have not similarly been explored. Despite being known for more than half-a-century, there are comparatively few studies to understand and exploit such systems. The general syntheses of *S,S*-,<sup>11</sup> *S,P*- and *S,N*-disubstituted alkynes have remained almost unchanged since their initial discovery; i.e. anionic heteroatom nucleophiles which undergo addition onto electron-poor alkynes<sup>12</sup> possessing a suitable leaving group. To enable a new synthetic access to bis-heteroatom-substituted alkynes, the Cu-catalyzed protocol was first applied to *S,S*-alkynes<sup>13</sup> (Table 9.2a). The symmetrical *S,S*-alkyne **9.32** was prepared in 92 % yield under the optimized coupling conditions. Coupling of an aromatic thiol with a bromo-substituted alkynyl sulfide afforded **9.33** in 67 %, but required a 2 h reaction time. Other unsymmetrical alkynes such as

**9.34**, formed via coupling with 2-mercaptoethanol, or **9.35** from coupling with a protected cysteine derivative, afforded the corresponding *S,S*-alkynes in 51 and 81 % yield respectively. Other bis-heteroatom-substituted alkynes were also explored. The *S,P*-alkyne<sup>14</sup> **9.36** was isolated in 82 % yield from the coupling between a bromo-substituted alkynyl phosphine oxide and 2-mercaptoethanol. The *S,P*-alkynes **9.37** and **9.38** derived from 4-methoxybenzyl mercaptan and 4-phenylbenzyl mercaptan respectively were also obtained in good to excellent yields (75 and 99 % respectively). A phosphonate-derived alkynyl bromide afforded the *S,P*-alkyne **9.39** in 99 % yield. Additionally, three *S,N*-alkynes<sup>15</sup> were prepared: **9.40** was obtained in 85 % yield from coupling with an acetyl-protected cysteine derivative, while **9.41** was isolated in 50 % yield from coupling of the corresponding bromo-substituted ynamide with 2-mercaptoethanol. Similarly, a CF<sub>3</sub>-substituted bromo enamide underwent C<sub>sp</sub>-S coupling to afford the *S,N*-alkyne **9.42** in 44 % yield. Interestingly, while the Cu-catalyzed C<sub>sp</sub>-S coupling afforded the bis-heteroatom alkynes in good yields, other methods surveyed were not compatible (Table 9.2b). For example, when examining an umpolung strategy to form the C<sub>sp</sub>-S bond via an ethynylbenziodoxolone (EBX) alkyne transfer reagent,<sup>6</sup> the corresponding *EBX,S*-alkyne could not be isolated. In addition, a catalytic Ni-catalyzed metallaphotoredox approach for the preparation of alkynyl sulfides also failed to form an *S,S*-alkyne.

*Computational Analysis of the Cu-Catalyzed C-S Cross-Coupling.* While the mechanisms of Cu-catalyzed C-O and C-N bond-forming reactions have garnered significant attention, much less effort has been dedicated to elucidating the mechanisms of copper-catalyzed C-S bond-forming reactions.<sup>16</sup> Recent studies involving computation suggest some C-S bond forming reactions could proceed and halogen atom transfer pathways for halide activation, depending on the calculation method.<sup>17</sup> However, the alkynylation method developed herein proceeds in relatively short reaction times at ambient temperatures, which is in contrast to other reported methods which require longer reaction times and elevated temperatures (~24 h, ≥100 °C). However, the Cadiot-Chodkiewicz coupling is proposed to proceed via an OA/RE pathway with alkynyl bromides at room temperature.<sup>18</sup> The cross coupling of benzyl thiol and bromophenyl acetylene was evaluated computationally at the SMD(MeCN)-[M06/def2tzvp] level of theory (Figure 9.2). The combination of

Cu(MeCN)<sub>4</sub>PF<sub>6</sub>, BnSH and the strongly binding ancillary ligand, bpy, result in the formation of a  $\pi$ -complexed alkyne **A** and the Cu(I)-thiolato intermediate **B** would be generated.<sup>19</sup> Addition via transition state **C** involves both copper centers and results in intermediate **D**, in which a Cu(bpy) motif remains coordinated between the bromine and sulfur atoms. Rearrangement of **D** results in an exchange of the bromine for a copper center to form **F**. Fokin and co-workers suggested previously proposed similar stabilized dinuclear copper species as intermediates in the Cu(I)-catalyzed cycloaddition of azides and alkynes.<sup>20</sup> In addition, Toste and Houk previously calculated a *gem*-diauraalkene as an intermediate in the Au(I)-catalyzed rearrangement of allenynes to cross-conjugated trienes.<sup>21</sup> The short distance between the sulfur atom and  $\beta$ -carbon atom suggest that intermediate **F** can readily undergo rearrangement via loss of a (bpy)CuBr unit and 1,2-sulfur migration via transition state **G** to afford the desired alkynyl sulfide **H**. Analogous rearrangements were also proposed by Waser and co-workers in reactions involving EBX reagents with certain substitution patterns.<sup>22</sup>



**Figure 9.2** Computed Gibbs energy profile ( $\Delta G$  at 298.15 K) of the Cu-catalyzed formation of an alkynyl sulfide

Relative Gibbs energies are given in kcal mol<sup>-1</sup>. All calculations were performed at the SMD(MeCN)-[M06/def2tzvpp] level of theory and basis set.

## 9.4 Conclusions

The alkynylation of thiols has attracted increased attention, as the resulting alkynyl sulfides continue to find application as novel synthons. The copper-catalyzed cross-coupling of thiols and bromoalkynes presented herein is operationally simple, employing a commercially available copper salt and ligand combination ( $\text{Cu}(\text{MeCN})_4\text{PF}_6/\text{dtbbpy}$ ), ambient temperature and short reaction times (10 min). Notably, the protocol is the first to couple efficiently aryl-, alkyl-, silyl- and peptidic alkynyl coupling partners (42 total examples, 44-99 % yields). Importantly, the broad substrate scope, high reactivity and chemoselectivity of the method open the door to new applications of the alkynyl sulfide functional group. For example, the first catalytic synthesis of difficult-to-access bis-heteroatom (*S,S*-, *S,P*- and *S,N*-)-disubstituted alkynes is reported. The possibility to prepare the alkynes under mild conditions provides new opportunities to investigate their potential as synthons. In addition, cysteine functionalization was achieved and PEGylation, biotinylation and fluorescent-label tagging was demonstrated. The catalytic alkynylation of the dipeptide model is notable, as other recent transition-metal-based methods require stoichiometric quantities of reagents.<sup>10</sup> Computation investigations suggest that a di-copper intermediate may be present and alkynyl sulfide formation occurs via a 1,2-sulfur shift. Further computational investigations of the mechanism are currently underway and will be reported in due course

### ASSOCIATED CONTENT

Experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## 9.5 Bibliography

1. Trost, B. M.; Li, C.-J. *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*. Wiley-VCH, Weinheim, 2015.
2. (a) Minehan, T. G. Tandem Bond-Forming Reactions of 1-Alkynyl Ethers. *Acc. Chem. Res.* **2016**, *49*, 1168-118; (b) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. Ynamides in Ring Forming Transformations. *Acc. Chem. Res.* **2014**, *47*, 560-578; (c) Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. A Journey in the Chemistry of Ynamides: From Synthesis to Applications. *Chem. Lett.* **2016**, *45*, 574-585.
3. (a) [3+2] Cycloaddition: Destito, P.; Couceiro, J. R.; Faustino, H.; López, F.; Mascareñas, J. L. Ruthenium-Catalyzed Azide-Thioalkyne Cycloadditions in Aqueous Media: A Mild, Orthogonal, and Biocompatible Chemical Ligation. *Angew. Chem. Int. Ed.* **2017**, *56*, 10766-10770; (b) [2+2+2] Cycloaddition: Xie, L. G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. Metal-Free Intermolecular Formal Cycloadditions Enable an Orthogonal Access to Nitrogen Heterocycles. *Nat. Commun.* **2016**, *7*, 10914-10923; (c) Annulation: Zhang, Y.-Q.; Zhu, X.-Q.; Chen, Y.-B.; Tan, T.-D.; Yang, M.-Y.; Ye, L.-W. Synthesis of Isothiochroman-3-ones via Metal-Free Oxidative Cyclization of Alkynyl Thioethers. *Org. Lett.* **2018**, *20*, 7721-7725; (d) Annulation: Reddy, R. J.; Ball-Jones, M. P.; Davies, P. W. Alkynyl Thioethers in Gold-Catalyzed Annulations To Form Oxazoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 13310-13313; (e) Hydrosilylation: Ding, S.; Song, L. J.; Wang, Y.; Zhang, X.; Chung, L. W.; Wu, Y. D.; Sun, J. Highly Regio- and Stereoselective Hydrosilylation of Internal Thioalkynes under Mild Conditions. *Angew. Chem. Int. Ed.* **2015**, *54*, 5632-5635; (f) 1,4-Chirality Transfer: Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. An Asymmetric Redox Arylation: Chirality Transfer from Sulfur to Carbon through a Sulfonium [3,3]-Sigmatropic Rearrangement. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212-2215; (g) Hydrohalogenation: Bello, D.; O'Hagan, D. Lewis Acid-Promoted Hydrofluorination of Alkynyl Sulfides to Generate  $\alpha$ -Fluorovinyl Thioethers. *Beilstein J. Org. Chem.* **2015**, *11*, 1902-1909; (h) Hydroallylation: Kong, W.; Che, C.; Kong, L.; Zhu, G. Copper-Catalyzed Regio- and Stereoselective Hydroallylation of Thioalkynes with Allylboronates: A Facile and Convenient Synthesis of 1,4-Dienes. *Tetrahedron Lett.* **2015**, *56*, 2780-2782.

4. Arens, J. F.; Doornbos, T. The Chemistry of Acetylenic Ethers XVI. Acetylenic Thioethers. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 481-486.
5. (a) Gao, W.-C.; Shang, Y.-Z.; Chang, H.-H.; Li, X.; Wei, W.-L.; Yu, X.-Z.; Zhou, R. *N*-Alkynylthio Phthalimide: A Shelf-Stable Alkynylthio Transfer Reagent for the Synthesis of Alkynyl Thioethers. *Org. Lett.* **2019**, 10.1021/acs.orglett.9b02174; (b) Waldecker, B.; Kraft, F.; Golz, C.; Alcarazo, M. 5-(Alkynyl)dibenzothiophenium Triflates: Sulfur-Based Reagents for Electrophilic Alkynylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 12538-12542; (c) Liu, F.; Yi, W. A Thiol-Free Synthesis of Alkynyl Chalcogenides by the Copper-Catalyzed C–X (X = S, Se) Cross-Coupling of Alkynyl Carboxylic Acids with Bunte Salts. *Org. Chem. Front.* **2018**, *5*, 428-433; (d) Reeves, J. T.; Camara, K.; Han, Z. S.; Xu, Y.; Lee, H.; Busacca, C. A.; Senanayake, C. H. The Reaction of Grignard Reagents with Bunte Salts: A Thiol-Free Synthesis of Sulfides. *Org. Lett.* **2014**, *16*, 1196-1199; (e) Brachet, E.; Brion, J. D.; Alami, M.; Messaoudi, S. Stereoselective Palladium-Catalyzed Alkenylation and Alkynylation of Thioglycosides. *Adv. Synth. Catal.* **2013**, *355*, 2627-2636.
6. (a) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 16563-16573; (b) Frei, R.; Waser, J. A Highly Chemoselective and Practical Alkynylation of Thiols. *J. Am. Chem. Soc.* **2013**, *135*, 9620-9623.
7. Santandrea, J.; Minozzi, C.; Cruché, C.; Collins, S. K. Photochemical Dual-Catalytic Synthesis of Alkynyl Sulfides. *Angew. Chem. Int. Ed.* **2017**, *56*, 12255-12259.
8. Godin, É.; Nguyen Thanh, S.; Guerrero-Morales, J.; Santandrea, J.; Caron, A.; Minozzi, C.; Beaucage, N.; Rey, B.; Morency, M.; Abel-Snape, X.; Collins, S. K. Synthesis and Diversification of Macrocyclic Alkynyl Sulfide Peptides. *Angew. Chem., Int. Ed.* **2020**, *To be submitted*.
9. Coupling with thioacetic acid or benzene selenol were not successful.
10. (a) deGruyter, J. N.; Malins, L. R.; Baran, P. S. Residue-Specific Peptide Modification: A Chemist's Guide. *Biochemistry* **2017**, *56*, 3863-3873; (b) Zhang, C.; Welborn, M.; Zhu, T.; Yang, N. J.; Santos, M. S.; Voorhis, T. V.; Pentelute, B. L.  $\Pi$ -Clamp-mediated cysteine conjugation. *Nat. Chem.* **2016**, *8*, 120-128; (c) Henkel, M.; Röckendorf, N.; Frey, A. Selective and Efficient Cysteine Conjugation by Maleimides in the Presence of Phosphine Reductants. *Bioconjugate Chem.* **2016**, *27*, 2260-2265; (d) Cal, P. M. S. D.; Bernardes, G. J. L.; Gois, P. M. P. Cysteine-Selective Reactions for Antibody Conjugation. *Angew. Chem. Int. Ed.* **2014**, *53*, 10585-10587; (e) Canovas, C.; Moreau, M.; Bernhard, C.; Oudot, A.; Guillemin, M.; Denat, F.; Goncalves, V. Rapid Nickel(II)-Promoted Cysteine *S*-Arylation with Arylboronic Acids. *Angew. Chem. Int. Ed.* **2018**, *57*, 10646-10650; (f) Donnelly, D. P.; Dowgiallo, M. G.; Salisbury, J. P.; Aluri, K. C.; Iyengar, S.; Chaudhari, M.; Mathew, M.; Miele, I.; Auclair, J. R.; Lopez, S. A.; Manetsch, R.; Agar, J. N. Cyclic Thiosulfonates and Cyclic Disulfides Selectively Cross-Link Thiols While Avoiding Modification of Lone Thiols. *J. Am. Chem. Soc.* **2018**, *140*, 7377-7380; (g) Messina, M. S.; Stauber, J. M.; Waddington, M. A.; Rheingold, A. L.; Maynard, H. D.; Spokoyny, A. M. Organometallic Gold(III) Reagents for Cysteine Arylation. *J. Am. Chem. Soc.* **2018**, *140*, 7065-7069; (h) Bisseret, P.; Abdelkafi, H.; Blanchard, N. Aryl transition metal chemical warheads for protein bioconjugation. *Chem. Sci.* **2018**, *9*, 5132-5144; (i) Zhang, C.; Dai, P.; Vinogradov, A. A.; Gates, Z. P.; Pentelute, B. L. Arylation Chemistry



- for Bioconjugation. *Angew. Chem. Int. Ed.* **2018**, *57*, 6459-6463; (i) Kubota, K.; Dai, P.; Pentelute, B. L.; Buchwald, S. L. Palladium Oxidative Addition Complexes for Peptide and Protein Cross-linking. *J. Am. Chem. Soc.* **2018**, *140*, 3128-3133; (j) Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. Organometallic palladium reagents for cysteine bioconjugation. *Nature* **2015**, *526*, 687-691.
11. (a) Baganz, H.; Triebsch, W. 1,2-Bis-äthyl-mercapto-äthin. *Chem. Ber.* **1956**, *89*, 895-898; (b) Stang, P. J.; Zhdankin, V. V. Preparation and chemistry of PhI<sup>+</sup>C.tplbond.CI+Ph.cntdot.2-OTf, bis[phenyl]([(trifluoromethyl)sulfonyl]oxy]iodo]acetylene, a novel difunctional acetylene, bis(iodonium) species and a stable C2-transfer agent. *J. Am. Chem. Soc.* **1991**, *113*, 4571-4576; (d) Riera, A.; Cabré, F.; Moyano, A.; Pericás, M. A.; Santamaria, J. A broad scope highly efficient synthesis of bis(R-thio)acetylenes. *Tetrahedron Lett.* **1990**, *31*, 2169-2172; (e) Seidel, W. W.; Meel, M. J.; Schaffrath, M.; Pape, T. In Pursuit of an Acetylenedithiolate Synthesis. *Eur. J. Org. Chem.* **2007**, 3526-3532.
  12. Witulski, B.; Alayrac, C. Product Subclass 2: 1-Heteroatom-Functionalized 2-Haloacetylenes. In *Science of Synthesis, 24: Category 3, Compounds with Four and Three Carbon Heteroatom Bonds*; de Meijere, A., Schaumann, E., Eds.; Thieme: Stuttgart, 2006; pp 797-819.
  13. (a) Riera, A.; Marti, M.; Moyano, A.; Pericás, M. A.; Santamaria, J. Bis(*tert*-butylsulfonyl)acetylene: A highly reactive dienophile. *Tetrahedron Lett.* **1990**, *31*, 2173-2176; (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. Substituted Alkyne Synthesis under Nonbasic Conditions: Copper Carboxylate-Mediated, Palladium-Catalyzed Thioalkyne-Boronic Acid Cross-Coupling. *Org. Lett.* **2001**, *3*, 91-93; (c) Eller, C.; Kehr, G.; Daniliuc, C. G.; Fröhlich, R.; Erker, G. Facile 1,1-Carboboration Reactions of Acetylenic Thioethers. *Organometallics* **2013**, *32*, 384-386; (d) Seidel, W. W.; Meel, M. J.; Schallenberg, D.; Pape, T.; Villinger, A.; Michalik, D. Facile Formation of a Rhenium Allenylcarbene Complex with an Internal Dithioalkyne. *Eur. J. Inorg. Chem.* **2010**, 5523-5528; (e) Trofimov, B. A.; Myachina, G. F.; Rodionova, I. V.; Mal'kina, A. G.; Dorofeev, I. A.; Vakul'skaya, T. I.; Sinegovskaya, L. M.; Skotheim, T. A. Ethyedithiol-based polyeneoligosulfides as active cathode materials for lithium-sulfur batteries. *J. Appl. Polym. Sci.* **2008**, *107*, 784-787.
  14. Egorov, D. M.; Piterskaya, Y. L.; Dogadina, A. V.; Svintsitskaya, N. I. Reactions of 5-Substituted 1,3,4-Thiadiazole-2-thiones with Chloroacetylenephosphonates. *Tetrahedron Lett.* **2015**, *56*, 1552-1554.
  15. (a) Mansfield, S. J.; Campbell, C. D.; Jones, M. W.; Anderson, E. A. A Robust and Modular Synthesis of Ynamides. *Chem. Commun.* **2015**, *51*, 3316-3319; (b) Nakai, T.; Tanaka, K.; Setoi, H.; Ishikawa, N. A Convenient Preparation of Arylthioynamines. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3069-3070.
  16. Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper-Catalysed Ullmann Type Chemistry: From Mechanistic Aspects to Modern Development. *Chem. Soc. Rev.* **2014**, *43*, 3525-3555.
  17. (a) Zhang, S.-L.; Fan, H.-J. Theoretical Study on Copper-Catalyzed S-Arylation of Thiophenols with Aryl Halides: Evidence Supporting the LCu(I)-SPh Active Catalyst and Halogen Atom Transfer Mechanism. *Organometallics* **2013**, *32*, 4944-4951; (b) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K. W. An Air-Stable Copper Reagent for Nucleophilic Trifluoromethylthiolation of Aryl Halides.

- Angew. Chem. Int. Ed.* **2013**, *52*, 1548-1552.; (c) Andrada, D. M.; Soria-Castro, S. M.; Caminos, D. A.; Argüello, J. E.; Peñeñory, A. B. Understanding the Heteroatom Effect on the Ullmann Copper-Catalyzed Cross-Coupling of X-Arylation (X = NH, O, S) Mechanism. *Catalysts* **2017**, *7*, 388.
18. Sindhu, K.S.; Thankachan, A. P.; Sajitha, P. S.; Anilkumar, G. Recent developments and applications of the Cadiot-Chodkiewicz reaction. *Org. Biomol. Chem.* **2015**, *13*, 6891-905.
  19. (a) Chen, C.; Weng, Z.; Hartwig, J. F. Synthesis of Copper(I) Thiolate Complexes in the Thioetherification of Aryl Halides. *Organometallics* **2012**, *31*, 8031-8037; (b) Cheng, S.-W.; Tseng, M.-C.; Lii, K.-H.; Lee, C.-R.; Shyu, S.-G. Intermediates of Copper(I)-Catalyzed C-S Cross Coupling of Thiophenol with Aryl Halide by *in situ* ESI-MS Study. *Chem. Commun.* **2011**, *47*, 5599-5601.
  20. Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science* **2013**, *340*, 457-460.
  21. Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. Gold-Catalyzed Cycloisomerization of 1,5-Allenynes via Dual Activation of an Ene Reaction *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.
  22. Wodrich, M. D.; Caramenti, P.; Waser, J. Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents:  $\alpha$ - or  $\beta$ - $\pi$ -Addition? *Org. Lett.* **2016**, *18*, 60-63.

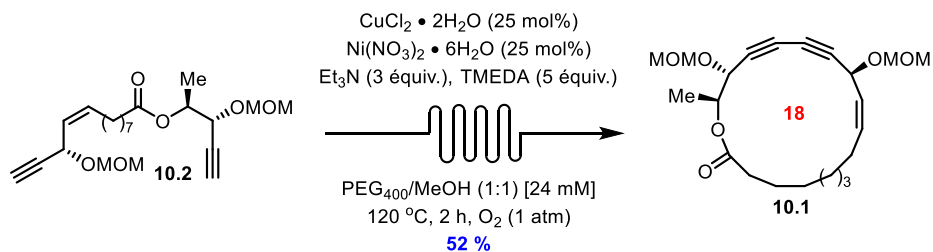
## Chapitre 10. Conclusions et perspectives

Cette présente thèse décrit d'abord l'application de la stratégie de séparation de phase (SSP) pour la synthèse formelle de macrocycles complexes comme le produit naturel ivorenolide A (Chapitre 4) ainsi que l'antiviral vaniprevir (Chapitre 6). Ensuite, une librairie de macrocycles peptidiques a été élaborée par le développement d'une nouvelle synthèse d'acétylures de soufre catalysée par un complexe de cuivre (Chapitre 8). Enfin, l'étendue de cette nouvelle méthode et son mécanisme ont été étudiés autant au niveau expérimental que computationnel (Chapitre 9).

### 10.1 Application de la stratégie de séparation de phase pour la synthèse de l'ivorenolide A et du vaniprevir

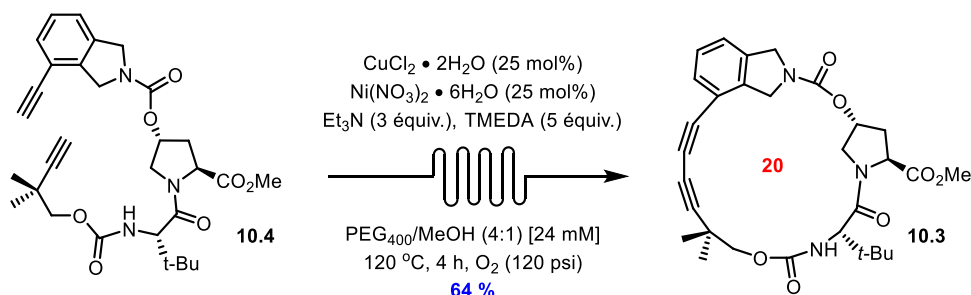
#### 10.1.1 Sommaire

La première partie de cette thèse visait l'application de la SSP développée dans notre groupe de recherche pour la synthèse de macrocycles complexes. Cette stratégie permet de réaliser l'étape de macrocyclisation à une concentration relativement élevée. La première cible pour tester l'efficacité de la SSP a été le produit naturel ivorenolide A (Chapitre 4)<sup>1</sup>. En utilisant cette méthode conjointement avec la chimie en débit continu, le précurseur synthétique macrocyclique de l'ivorenolide A **10.1** a pu être synthétisé par couplage oxydatif de Glaser-Hay (Schéma 10.1). La méthode s'est montrée robuste face à la présence de centres stéréogènes, de groupements protecteurs et d'encombrement stérique autour des alcynes terminaux. Dans des conditions catalytiques et à haute concentration (24 mM), le produit macrocyclique **10.1** a pu être obtenu dans un rendement de 52 %, un rendement similaire à celui obtenu dans des conditions traditionnelles d'addition lente et de haute dilution (0.2 mM).



**Schéma 10.1** Application de la stratégie de séparation de phase pour la synthèse de l'ivorenolide A

Par la suite, les limites de la méthode ont été une fois de plus explorées par la synthèse du cœur macrocyclique **10.3** du médicament vaniprévir (Chapitre 6)<sup>2</sup>. Le macrocycle d'intérêt pharmaceutique a été obtenu dans un rendement de 64 % à une concentration de cyclisation relativement élevée (24 mM) (Schéma 10.2). La présence d'un hétérocycle et des fonctionnalités carbamate et amide n'a pas affecté la réaction de macrocyclisation. De plus, l'utilisation d'un co-solvant de PEG dendritique (StarPEG<sub>1014</sub>) a permis de réaliser la macrocyclisation d'un substrat plus simple à une concentration très élevée (200 mM, 64 % de rendement).



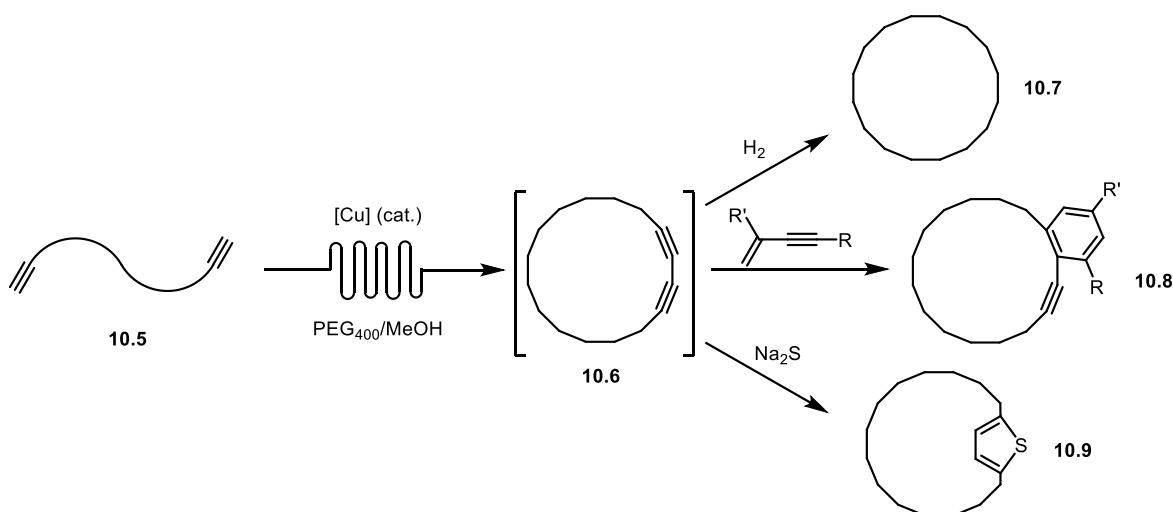
**Schéma 10.2** Application de la stratégie de séparation de phase pour la synthèse du vaniprévir

### 10.1.2 Travaux futurs

La diversification de la stratégie de séparation de phase a largement été explorée dans notre groupe de recherche. Il a été démontré que la SSP pouvait être appliquée à d'autres types de réaction comme la cycloaddition d'alcyne et d'azoture catalysée par un complexe de cuivre<sup>3</sup> ou la métathèse d'oléfine catalysée par un complexe de ruthénium<sup>4</sup>. Cependant, un des aspects qui reste inexploité est l'élaboration d'une librairie de macrocycles à partir de quelques squelettes macrocycliques communs cyclisés dans les conditions de la SSP. En effet, la

synthèse de macrocycles orientée sur la diversité a attiré beaucoup d'attention dans les dernières années<sup>5</sup>. Toutefois, les stratégies développées ont tendance à élaborer la diversité avant l'étape difficile de macrocyclisation, sans diversification subséquente une fois la fermeture de cycle accomplie.

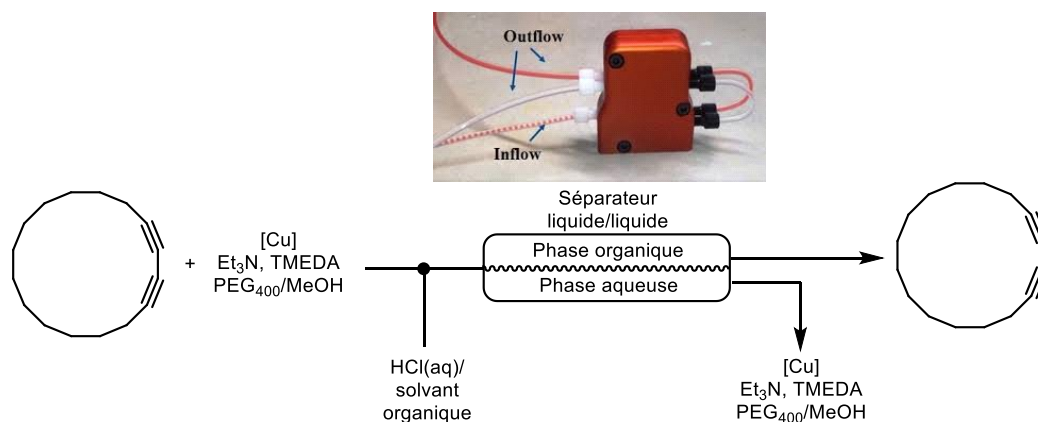
Pour se faire, un composé macrocyclique pourrait être synthétisé à l'aide de la SSP et de la chimie en débit continu afin de générer un intermédiaire qui agirait comme plateforme de diversification. Par exemple, un 1,3-diène linéaire **10.5** pourrait être cyclisé dans les conditions de couplage de Glaser-Hay afin de créer un intermédiaire macrocyclique **10.6** qui pourrait ensuite être transformé, sans isolation, en plusieurs dérivés dans une seconde réaction en ligne (Figure 10.1).



**Figure 10.1** Diversification de macrocycles générés par la stratégie de séparation de phase

Cette stratégie pourrait également être adaptée aux autres réactions pouvant être réalisées dans les conditions de SSP telles que les réactions de cycloaddition et de métathèse mentionnées plus tôt. Cependant, l'introduction d'une seconde réaction en ligne pose un défi majeur. En effet, les catalyseurs de cuivre et de nickel, le solvant protique méthanol ainsi que le caractère base de Lewis du co-solvant PEG peuvent être incompatibles avec les conditions réactionnelles subséquentes. Afin de remédier à ce problème, notre groupe a envisagé d'introduire une étape d'extraction liquide/liquide entre les deux étapes réactionnelles. Cette purification en ligne permettrait d'éliminer les solvants pouvant causer de l'interférence ainsi que les catalyseurs et sous-produits hydrophiles. Une telle purification est possible en utilisant

un séparateur de phase liquide/liquide Zaiput<sup>®</sup> adapté à la chimie en débit continu (Figure 10.2)<sup>6</sup>.



**Figure 10.2** Purification de l'intermédiaire macrocyclique par extraction en ligne (image tirée du site web de Zaiput Flow Technologies)

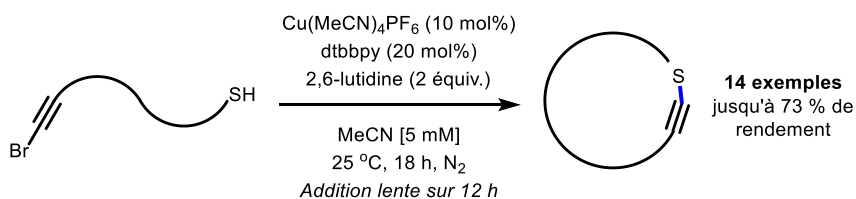
Pour conclure, le développement d'une méthode d'extraction permettrait l'utilisation de la SSP pour la génération d'intermédiaires macrocycliques qui pourraient ensuite être diversifiés par l'incorporation de réactions séquentielles, le tout dans un procédé en continu pouvant être facilement monté en échelle.

## 10.2 Développement d'une méthode générale catalysée par un complexe de cuivre pour la synthèse d'acétylures de soufre

### 10.2.1 Sommaire

La deuxième partie de cette thèse portait sur le développement d'une nouvelle réaction de couplage  $C_{sp}-S$  catalysée par un complexe de cuivre. Le couplage entre des bromoalcynes et des thiols a été réalisé à partir d'un sel de cuivre et d'un ligand disponible commercialement. Contrairement aux méthodes existantes, celle présentée est générale et a pu facilement être appliquée à la synthèse de composés macrocycliques (Chapitre 8)<sup>7</sup>. En tout, 14 exemples de mono-, di- et tripeptides macrocycliques incorporant un acétylure de soufre ont pu être synthétisés dans de bons rendements (23% - 73%) (Figure 10.3). De plus, l'incorporation du motif thioalcyne a permis de diversifier la librairie de macrocycles synthétisés, soit par l'oxydation de l'atome de soufre, l'halogénéation de l'alcyne ou en effectuant une réaction de cycloaddition avec un azoture. Par cette dernière modification,

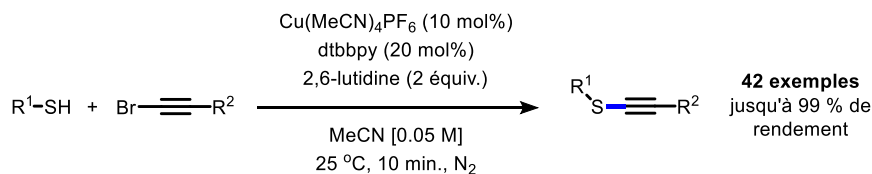
plusieurs biomarqueurs ont pu être greffés aux macrocycles, comme des fluorophores, une biotine, une chaîne farnésyle ou un acide aminé.



- **Catalyse au cuivre:** chimiosélectif, gén/ral et pratique
- Applicable à la synthèse de peptides macrocycliques
- Diversification et étiquetage possible par une fonctionnalisation du motif thioalcyne

**Figure 10.3** Synthèse de peptides macrocycliques par couplage C<sub>sp</sub>-S intramoléculaire catalysé par un complexe de cuivre

Par la suite, mes travaux ont porté sur l'exploration de l'étendue de la réaction intermoléculaire (Chapitre 9)<sup>8</sup>. En général, on observe une très bonne tolérance aux groupements fonctionnels dans la réaction de couplage C<sub>sp</sub>-S catalysée par un complexe de cuivre. Cette réaction permet d'accéder à des acétylures de soufre pour lesquels il n'existe pas de méthodes de synthèse alternatives (42 exemples, 44% - 99%) (Figure 10.4). Cette réaction a aussi permis la synthèse d'acétylures de soufre doublement substitués par des hétéroatomes. De plus, le couplage C<sub>sp</sub>-S a été appliqué à la fonctionnalisation d'une cystéine au sein d'un dipeptide afin d'y étiqueter divers biomarqueurs d'intérêt. Finalement, une étude de compétition et un marquage au carbone 13 (<sup>13</sup>C) ont été réalisés, en parallèle avec une étude computationnelle menée en collaboration avec le groupe du Pr. Ifimie afin de mieux comprendre le mécanisme de la réaction.

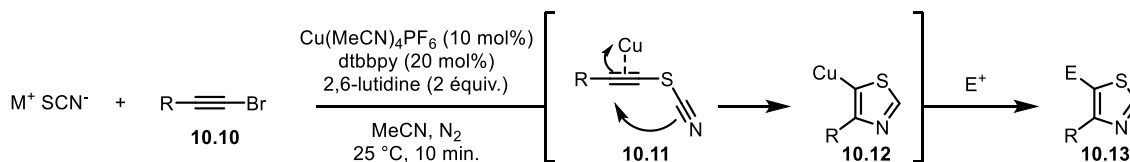


- **Catalyse au cuivre:** chimiosélectif, général, pratique et rapide
- Bonne tolérance aux groupements fonctionnels
- Applicable à la synthèse d'alcynes disubstitués (S,S), (N,S) et (P,S) et à l'étiquetage de cystéine

**Figure 10.4** Synthèse d'acétylures de soufre par couplage C<sub>sp</sub>-S intermoléculaire catalysé par un complexe de cuivre

## 10.2.2 Travaux futurs

La réaction de synthèse d'acétylures de soufre présentée dans cette thèse a été développée dans la dernière année de mon doctorat. De ce fait, plusieurs aspects liés à ce projet sont encore à explorer. Tout d'abord, seuls les composés soufrés de type thiol ont été utilisés. On pourrait toutefois imaginer d'utiliser d'autres types de composés soufrés, comme les thiocyanates. En effet, ces derniers permettraient la synthèse d'acétylures de thiocyanate<sup>9</sup>, une classe de composés intéressants, notamment pour la synthèse de thiazoles<sup>10</sup>. Dans un premier temps, un bromoalcyne **10.10** serait mis en présence d'ions thiocyanates ( $\text{SCN}^-$ ) et du système catalytique de cuivre ( $\text{Cu}(\text{MeCN})_4\text{PF}_6/\text{dtbbpy}/2,6\text{-lutidine}$ ) afin de former l'acétylure de thiocyanate **10.11** (Figure 10.5). Par la suite, la présence de cuivre en solution pourrait catalyser la cyclisation afin de former l'organocuivre **10.12**. Finalement, la protonation de l'intermédiaire ou le parachèvement avec un électrophile donnerait un composé thiazole **10.13**.



**Figure 10.5** Synthèse de thiazoles par une réaction en tandem de thioalcynylation catalysée par un complexe de cuivre suivie d'une cyclisation intramoléculaire

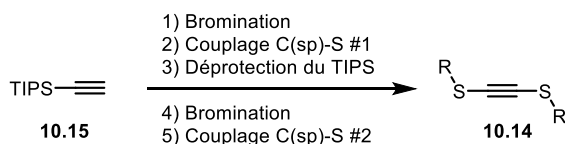
Alternativement, il pourrait être possible de réaliser la synthèse d'acétylures de soufre à partir d'autres halogénoalcyne. Des résultats computationnels préliminaires effectués par mon collègue Mathieu Morency du groupe du Pr. Iftimie suggèrent que la réaction de couplage catalysée par un complexe de cuivre pourrait être réalisée à partir de chloroalcyne en chauffant légèrement la réaction. En effet, la barrière d'activation calculée pour une telle transformation serait environ 3.1 kcal/mol plus haute qu'avec un bromoalcyne, ce qui correspondrait à une réaction chauffée à 64 °C pour un temps de réaction similaire de 10 min.

Un autre aspect du projet qui pourrait être amélioré est la synthèse des acétylures disubstitués par des atomes de soufre **10.14**. En effet, la voie synthétique suivie dans le cadre de ce projet comprenait cinq étapes à partir de l'éthynyltriisopropylsilane (**10.15**) (Figure 10.6). Toutefois, il serait imaginable d'obtenir ces composés en une seule étape à partir du

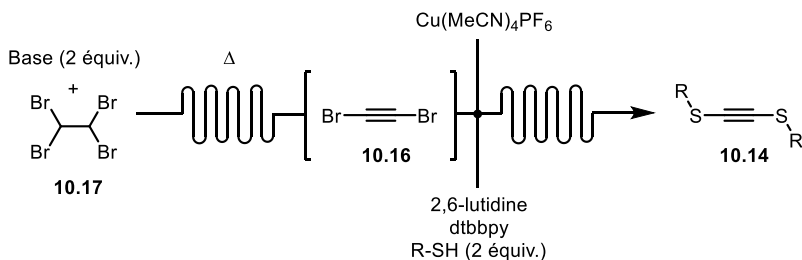


dibromoacétylène (**10.16**). Cependant, ce dernier est un liquide relativement instable et explosif dont l'isolement est problématique<sup>11</sup>. Tout comme la version chlorée, le dibromoacétylène (**10.16**) peut être généré *in situ* à partir du tétrabromoéthane (**10.17**) et d'une base par des réactions d'élimination. Afin de contrôler l'addition séquentielle des réactifs, la réaction pourrait être réalisée en chimie en débit continu. Tout d'abord, le dibromoacétylène (**10.16**) serait généré à partir du tétrabromoéthane (**10.17**). Par la suite, la réaction serait interceptée par un flux contenant, d'une part, la base 2,6-lutidine, le ligand dtbbpy et un thiol et, d'une autre part, le pré-catalyseur de cuivre (Figure 10.6). De plus, la chimie en débit continu permet d'avoir un excellent contrôle sur la stœchiométrie des réactifs ajoutés. Il serait donc possible d'avoir deux additions subséquentes de thiols différents afin de former des acétylures asymétriques disubstitués par des atomes de soufre.

Synthèse actuelle (4 étapes):

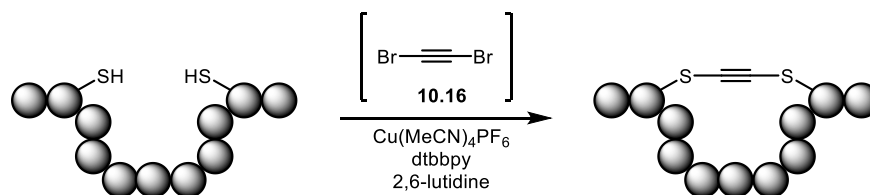


Synthèse envisagée (1 étape):



**Figure 10.6** Génération du dibromoacétylène en flux continu et synthèse directe d'acétylures disubstitués par des atomes de soufre

Une application intéressante de la stratégie développée serait dans le domaine de la rigidification conformationnelle de peptides. En effet, au cours des dernières années, ce champ de recherche a attiré l'attention de plusieurs chercheurs de renom tels que Pentelute<sup>12</sup>, Buchwald<sup>13</sup> et Derda<sup>14</sup>. Dans notre cas, le pont reliant les acides aminés cystéines du peptide serait tout simplement un motif acétylène, installé à partir du dibromoacétylène (**10.16**) généré *in situ* en débit continu à l'aide du système catalytique au cuivre (Figure 10.7).



**Figure 10.7** Rigidification de peptides par formation d'un pont acétylure disubstitué par des atomes de soufre

### 10.3 Bibliographie

- 1 de Léséleuc<sup>§</sup>, M.; Godin<sup>§</sup>, É.; Parisien-Collette, S.; Lévesque, A.; Collins, S. K. *J. Org. Chem.* **2016**, *81*, 6750 – 6756.
- 2 Godin, É.; Bédard, A.-C.; Raymond, M.; Collins, S. K. *J. Org. Chem.* **2017**, *82*, 7576 – 7582.
- 3 Bédard, A.-C.; Santandrea, J.; Collins, S. K. *J. Flow Chem.* **2015**, *5*, 142 - 144.
- 4 Raymond, M.; Holtz-Mulholland, M.; Collins, S. K. *Chem. Eur. J.* **2014**, *20*, 12763 – 12767.
- 5 Yi, S.; Varun, B. V.; Choi, Y.; Park, S. B. *Front. Chem.* **2018**, *6*, 507.
- 6 Zaiput, *Zaiput Flow Technologies* [<https://www.zaiput.com/product/liquid-liquid-gas-separators/>] (site consulté le 17 novembre 2019).
- 7 Godin, É.; Nguyen Thanh, S.; Guerrero-Morales, J.; Santandrea, J.; Caron, A.; Minozzi, C.; Beaucage, N.; Rey, B.; Morency, M.; Abel-Snape, X.; Collins, S. K. *Angew. Chem. Int. Ed.* **2020**, *Prêt à être soumis*.
- 8 Godin, É.<sup>§</sup>; Santandrea, J.<sup>§</sup>; Morency, M.; Ifimie, R. I.; Collins, S. K. *ACS Catal.* **2020**, *Manuscrit en préparation*.
- 9 (a) Fischer, D. R.; Williamson, B. L.; Stang, P. J. *Synlett* **1992**, *1992*, 535 – 536. (b) Takagi, K.; Takachi, H.; Sasaki, K. *J. Org. Chem.* **1995**, *60*, 6552 – 6556. (c) See, J. Y.; Zhao, Y. *Org. Lett.* **2018**, *20*, 7433 – 7436. (d) Li, M.; Song, W.; Dong, K.; Zheng, Y.; *Tetrahedron Lett.* **2019**, <https://doi.org/10.1016/j.tetlet.2019.151503>.
- 10 de Jong, R. L. P.; Meijer, J.; Sukhai, R. S.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 310 – 313.
- 11 Lemoult, M. *Bull. Soc. Chim. Fr.* **1905**, *3*, 194.
- 12 (a) Spokoyny, A. M.; Zou, Y.; Ling, J. J.; Yu, H.; Lin, Y. S.; Pentelute, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 5946 – 5949. (b) Zou, Y.; Spokoyny, A. M.; Zhang, C.; Simon, M. D.; Yu, H.; Lin, Y.-S.; Pentelute, B. L. *Org. Biomol. Chem.* **2013**, *12*, 566 – 573.
- 13 Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. *Nature* **2015**, *526*, 687 – 691. (b) Rojas, A. J.; Zhang, C.; Vinogradova, E. V.; Buchwald, N. H.; Reilly, J.; Pentelute, B. L.; Buchwald, S. L. *Chem. Sci.* **2017**, *8*, 4257 – 4263.

- 14 Kalhor-Monfared, S.; Jafari, M. R.; Patterson, J. T.; Kitov, P. I.; Dwyer, J. J.; Nuss, J. M.; Derda, R. *Chem. Sci.* **2016**, *7*, 3785 – 3790.

# Annexe 1. Procédures expérimentales et spectres RMN du

## Chapitre 4

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.<sup>1</sup> All chemical products obtained were reagent quality. Tridec-12-ynoic acid<sup>2</sup>, (±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne<sup>3</sup>, (3*S*)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne and Methyl dec-9-enoate<sup>4</sup> were prepared according to literature procedure. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated. Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>5</sup> and using silica gel (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator. Visualization of TLC plate was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR. NMR spectra were taken in deuterated CDCl<sub>3</sub> unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The acquisition parameters are shown on all spectra. The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), app t (apparent triplet), q (quartet), app quin (apparent quintet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment.

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<sup>1</sup> Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

<sup>2</sup> Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.*, **2012**, 3, 789-793.

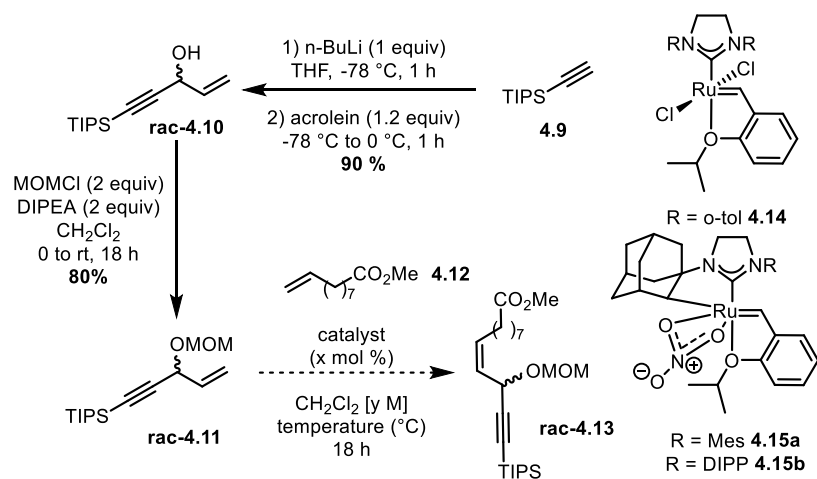
<sup>3</sup> Mann, T. J.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, 52, 8395-8400. An alternative route via diastereomeric separation was also used. See Experimental Section.

<sup>4</sup> Ranganathan, D.; Ranganathan, S.; Mehrotra, M. M. *Tetrahedron* **1980**, 36, 1869-1875.

<sup>5</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

## OPTIMIZATION OF A Z-SELECTIVE CROSS METATHESIS

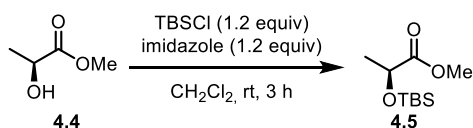
**Table 4.S1** Optimization of a Z-selective cross metathesis to prepare racemic **4.13**



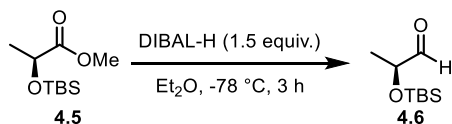
	Catalyst (mol %)	[M]	Temp. (°C)	Yield (%) <sup>a</sup>	% Z <sup>b</sup>
1	<b>4.14</b> (2)	0.1	21	47	< 1
2	<b>4.14</b> (2)	0.1	40	40	< 1
3	<b>4.15b</b> (2)	0.1	21	0	-
4	<b>4.15b</b> (5)	0.5	60	40	~98
5	<b>4.15b</b> (10)	0.5	60	59	95
6	<b>4.15a</b> (10)	0.5	60	16	75

<sup>a</sup> Yields following chromatography. <sup>b</sup> Determined by <sup>1</sup>H NMR Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-di-*iso*-propylphenyl.

## EXPERIMENTAL PROCEDURES



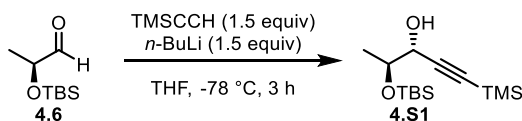
**Methyl (S)-2-((tert-Butyldimethylsilyl)oxy)propanoate (4.5).** TBSCl (8.68 g, 57.6 mmol, 1.2 equiv) and imidazole (3.92 g, 57.6 mmol, 1.2 equiv) were added to a solution of methyl (S)-2-hydroxypropanoate (**4.4**) (4.6 mL, 48.0 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) at 0 °C. The solution was stirred for 3 h at room temperature. Brine was then added, and the organic and aqueous layers were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×), and the combined organic phases were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (6% EtOAc in hexanes) was performed to afford the product as a colorless oil (10.27 g, 98%). Spectral data were in accordance with those previously reported in the literature.<sup>6</sup>



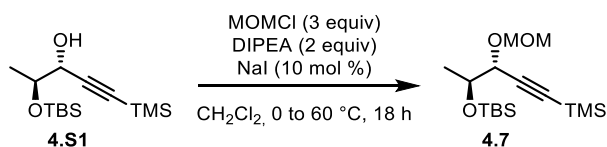
**(S)-2-((tert-Butyldimethylsilyl)oxy)propanal (4.6).** DIBAL-H 1 M in hexanes (20.0 mL, 20.0 mmol, 1.5 equiv) was added dropwise to a solution of methyl (S)-2-((tert-butyl)dimethylsilyloxy)propanoate (**4.5**) (2.92 g, 13.35 mmol, 1.0 equiv) in anhydrous Et<sub>2</sub>O (45 mL) at -78 °C and stirred for 3 h. The solution was then quenched with a solution of sodium and potassium tartrate, and the organic and aqueous layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3×). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (10% Et<sub>2</sub>O in hexanes) was performed to afford the product as a colorless oil (1.92 g, 77%). Spectral data were in accordance with those previously reported in the literature.<sup>7</sup>

<sup>6</sup> Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180–5182.

<sup>7</sup> Zhang, B.; Wang, Y.; Yang, S. P.; Zhou, Y.; Wu, W. B.; Tang, W.; Zuo, J. P.; Li, Y.; Yue, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 20605–20608.



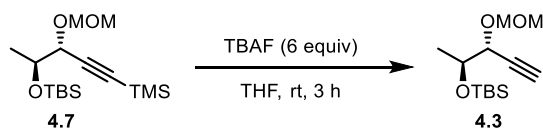
**(3R,4S)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (4.S1).** *n*-BuLi 1.35 M in hexanes (11.5 mL, 15.6 mmol, 1.5 equiv) was added dropwise to a solution of ethynyltrimethylsilane (2.2 mL, 15.6 mmol, 1.5 equiv) in anhydrous THF (23 mL) at  $-78\text{ }^{\circ}\text{C}$ . The solution was stirred for 2 h at  $0\text{ }^{\circ}\text{C}$ . (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (**4.6**) (1.96 g, 10.4 mmol, 1.0 equiv) was added to the solution at  $-78\text{ }^{\circ}\text{C}$  and stirred for an additional hour. The solution was then quenched with a solution of sodium and potassium tartrate. The resulting mixture was vigorously stirred for 2 h before Et<sub>2</sub>O (30 mL) was added to the mixture. The organic and aqueous layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 ×). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (100% Hexanes to 4% EtOAc in hexanes) was performed to afford exclusively the desired diastereoisomer as a white solid (1.55 g, 52%). Spectral data were in accordance with those previously reported in the literature.<sup>8</sup>



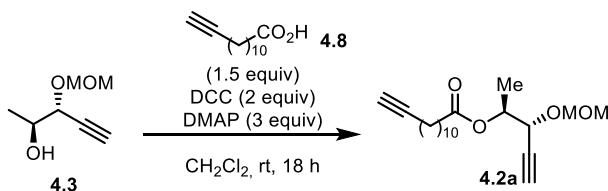
**(5R,6S)-6,8,8,9,9-Pentamethyl-5-((trimethylsilyl)ethynyl)2,4,7-trioxa-8-siladecane (4.7).** In a sealable tube, NaI (135 mg, 0.89 mmol, 10 mol %) was added to a solution of (3R,4S)-4-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (**4.S1**) (2.58 g, 8.9 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (90 mL). The solution was cooled to  $0\text{ }^{\circ}\text{C}$ , and *i*Pr<sub>2</sub>NEt (3.13 mL, 17.9 mmol, 2.0 equiv) and MOMCl (2.05 mL, 26.9 mmol, 3.0 equiv) were added. The mixture was stirred for 18 h at  $60\text{ }^{\circ}\text{C}$  and then quenched with water, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (100% Hexanes to 5% EtOAc in hexanes) was

<sup>8</sup> Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, 5, 3197–3199.

performed to afford the product as yellow oil (2.97 g, 99%). Spectral data were in accordance with those previously reported in the literature.<sup>9</sup>



**(2*S*,3*R*)-3-(Methoxymethoxy)pent-4-yn-2-ol (4.3).** TBAF (1 M in THF) (53.9 mL, 53.9 mmol, 6 equiv) was added to a solution of (5*R*,6*S*)-6,8,8,9,9-pentamethyl-5-((trimethylsilyl)ethynyl)-2,4,7-trioxa8-siladecane (**4.7**) (2.97 g, 9.0 mmol, 1.0 equiv) in anhydrous THF (45 mL) and stirred for 3 h at room temperature. The solution was then quenched with water, and the organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (30% EtOAc in hexanes) was performed to afford the product as a yellow oil (1.22 g, 94%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.96 (d, *J* = 8 Hz, 1H), 4.70 (d, *J* = 8 Hz, 1H), 4.31–4.29 (m, 1H), 3.98–3.95 (m, 1H), 3.42 (s, 3H), 2.50 (d, *J* = 2 Hz, 1H), 2.38 (bs, 1H) 1.31 (d, *J* = 4 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 94.4, 79.0, 75.8, 70.8, 69.1, 55.9, 18.1 ppm. HRMS (ESI+) *m/z* calculated for C<sub>7</sub>H<sub>12</sub>NaO<sub>3</sub> [M + Na]<sup>+</sup>: 167.0679; found: 167.0675.

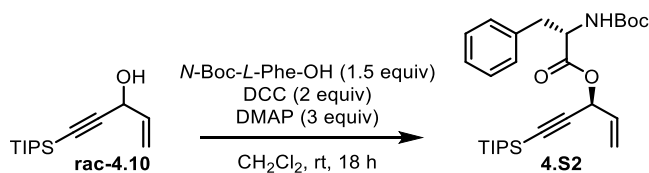


**(2*S*,3*R*)-3-(Methoxymethoxy)pent-4-yn-2-yl tridec-12-ynoate (4.2a).** DCC (946 mg, 4.6 mmol, 2 equiv), DMAP (840 mg, 6.9 mmol, 3 equiv), and (2*S*,3*R*)-3-(methoxymethoxy)pent-4-yn-2-ol (**4.3**) (331 mg, 2.3 mmol, 1 equiv) were added to a solution of tridec-12-ynoic acid (**4.8**) (723 mg, 3.4 mmol, 1.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h, and the precipitated urea was filtered. Silica gel was added to the filtrate, and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 10% EtOAc in hexanes) was performed to

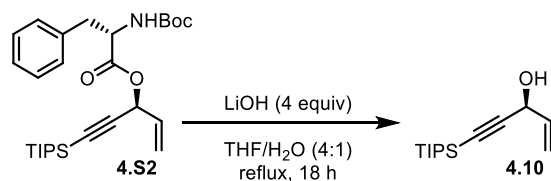
<sup>9</sup> Wang, Y.; Liu, Q.-F.; Xue, J.-J.; Zhou, Y.; Yu, H.-C.; Yang, S.-P.; Zhang, B.; Zuo, J.-P.; Li, Y.; Yue, J.-M. *Org. Lett.* **2014**, *16*, 2062–2065.



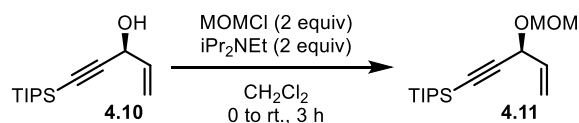
afford the product as a colorless oil (579 mg, 75%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.1–5.10 (m, 1H), 4.92 (d,  $J = 6.8$  Hz, 1H), 4.64 (d,  $J = 6.9$  Hz, 1H), 4.42 (dd,  $J = 4$  Hz, 2.1 Hz, 1H), 3.40 (s, 3H), 2.45 (d,  $J = 2.2$  Hz, 1H), 2.33 (t,  $J = 7.5$  Hz, 2H), 2.19 (td,  $J = 7.1$  Hz, 2.7 Hz, 2H), 1.95 (t,  $J = 2.7$  Hz, 1H), 1.65–1.61 (m, 2H), 1.56–1.49 (m, 2H), 1.40–1.28 (m, 15H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  173.1, 94.2, 84.8, 79.1, 75.0, 70.8, 68.0, 67.4, 55.7, 34.4, 29.40, 29.36, 29.2, 29.0 (2C), 28.7, 28.5, 24.9, 18.4, 15.1 ppm. HRMS (ESI+)  $m/z$  calculated for  $\text{C}_{20}\text{H}_{36}\text{NO}_4$  [ $\text{M} + \text{NH}_4$ ] $^+$ : 354.2639; found: 354.2648.



**(3S)-3-(*N*-Boc-*L*-phenylalanine)-5-(triisopropylsilyl)pent-1-en-4-yne (4.S2).** DCC (2.74 g, 13.3 mmol, 2 equiv), DMAP (2.43 g, 19.9 mmol, 3 equiv), and ( $\pm$ )-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne (**rac-4.10**) (1.58 g, 6.64 mmol, 1 equiv) were added to a solution of *N*-Boc-*L*-phenylalanine (2.64 g, 9.96 mmol, 1.5 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h, and the precipitated urea was filtered. Silica gel was added to the filtrate, and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 7%  $\text{Et}_2\text{O}$  in hexanes) was performed to separate the diastereomers and isolate **4.S2** as a colorless oil (923 mg, 29%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29–7.15 (m, 5H), 5.92 (d,  $J = 4.4$  Hz, 1H), 5.98–5.81 (m, 1H), 5.61 (d,  $J = 13.7$  Hz, 1H), 5.34 (d,  $J = 9.8$  Hz, 1H), 4.96 (d,  $J = 6.8$  Hz, 1H), 4.63 (d,  $J = 5.8$  Hz, 1H), 3.13–3.06 (m, 2H), 1.42 (s, 9H), 1.10–1.09 (m, 21 H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 155.0, 135.8, 132.5, 129.5, 129.4, 128.5, 127.0, 119.6, 119.4, 101.4, 89.7, 79.9, 65.6, 54.2, 37.9, 54.2, 37.9, 28.3, 18.5, 11.1 ppm. HRMS (ESI+)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{43}\text{NO}_4\text{SiNa}$  [ $\text{M} + \text{Na}$ ] $^+$ : 508.2854; found: 508.2865.

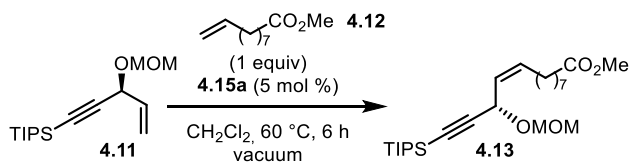


**(±)-3-Hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne (4.10).** The amino acid adduct (4.S2) (960 mg, 1.98 mmol, 1.0 equiv) was dissolved in THF (16 mL), then LiOH (190 mg, 7.92 mmol, 4.0 equiv) was added as an aqueous solution (4 mL). The reaction mixture was stirred at 65 °C for 18 h. The reaction was then cooled to room temperature, and HCl (1 M) was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 × 5 mL) was performed, and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the desired product as a white solid (421 mg, 89%). Spectral data were in accordance with those previously reported in the literature.<sup>10</sup>



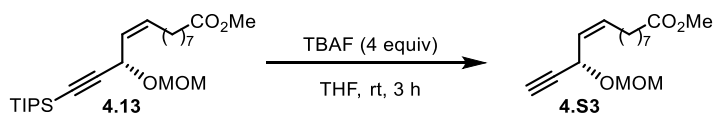
**(3S)-3-(Methoxymethoxy)-5-(triisopropylsilyl)pent-1-en-4-yne (4.11).** The alcohol (4.10) (1.50 g, 6.30 mmol, 1.00 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (31 mL). iPr<sub>2</sub>NEt (2.19 mL, 12.6 mmol, 2.00 equiv) was added to the solution. MOMCl (0.96 mL, 12.6 mmol, 2.00 equiv) was carefully added at 0 °C, and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by addition of water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL). The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Flash chromatography (5% Et<sub>2</sub>O in hexanes) was performed to obtain the product as a colorless oil (1.42 g, 80%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 5.94 (ddd, *J* = 17.0 Hz, 10.2 Hz, 5.5 Hz, 1H), 5.56 (dt, *J* = 17.0 Hz, 1.2 Hz, 1H), 5.28 (dt, *J* = 10.2 Hz, 1.2 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.90 (dt, *J* = 5.5 Hz, 1.2 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 3.41 (s, 3H), 1.10–1.03 (m, 21H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz) δ = 134.9, 117.7, 103.6, 93.7, 88.4, 66.7, 55.7, 18.6, 11.1 ppm; HRMS (ESI<sup>+</sup>) calculated for C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>SiNa [M + Na]<sup>+</sup>: 305.1907; found: 305.1907.31

<sup>10</sup> Mann, T. J.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8395–8400.



**Methyl (11*S*,9*Z*)-11-(Methoxymethoxy)-13-(triisopropylsilyl)tridec-9-en-12-ynoate (4.13).**

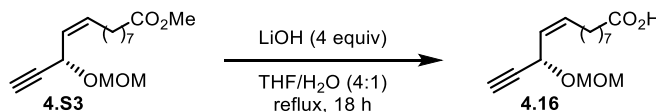
A flame-dried sealable tube was charged with CH<sub>2</sub>Cl<sub>2</sub> (2.75 mL), methyl dec-9-enoate (254 mg, 1.38 mmol, 1.00 equiv), and the ester (4.12) (390 mg, 1.38 mmol, 1.00 equiv). The catalyst (4.15b) (47 mg, 0.069 mmol, 0.05 equiv) was added, and the tube was sealed. The reaction mixture was allowed to stir for 3 h at 60 °C. A second equivalent of methyl dec-9-enoate (4.12) (254 mg, 1.38 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to stir for an additional 3 h. During the reaction time, the mixture was put under vacuum for 5 s every hour to eliminate the ethylene formed. After the mixture cooled down to room temperature, silica was added and the slurry was concentrated under reduced pressure. Flash chromatography (5 to 10% Et<sub>2</sub>O in hexanes) was performed to afford the product as a colorless oil (258 mg, 43% (68% BRSM), > 95:5 *Z/E*). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 5.64–5.52 (m, 2H), 5.14 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.17–2.11 (m, 2H), 1.66–1.60 (m, 2H), 1.42–1.29 (m, 8 H), 1.11– 1.05 (m, 21 H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz) δ = 174.2, 133.9, 127.1, 105.2, 93.3, 86.6 61.5, 55.6, 51.4, 34.1, 29.3, 29.11, 29.05, 29.03, 27.7, 24.9, 18.6. 11.1 ppm; HRMS (ESI<sup>+</sup>) calculated for C<sub>25</sub>H<sub>46</sub>O<sub>4</sub>SiNa [M + Na]<sup>+</sup>: 461.3058; found: 461.3063.



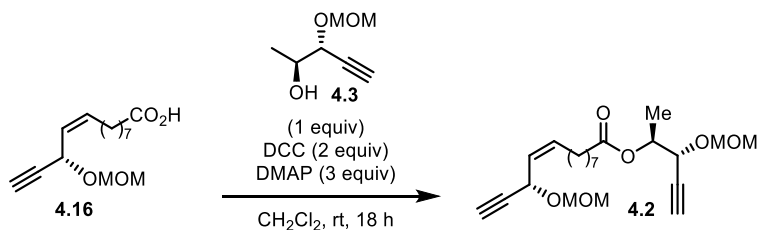
**Methyl (11*S*,9*Z*)-11-(Methoxymethoxy)tridec-9-en-12-ynoate (4.S3).**

The protected alkyne (4.13) (390 mg, 0.890 mmol, 1.00 equiv) and THF (2.67 mL) were added to a flame-dried roundbottom flask under N<sub>2</sub>. TBAF (1 M in THF, 1.78 mL, 1.78 mmol, 2.0 equiv) was slowly added, and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of H<sub>2</sub>O (2 mL) and extracted with Et<sub>2</sub>O (2 × 5 mL). The combined organic phases were washed with H<sub>2</sub>O (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Flash chromatography (5% to 10% EtOAc in hexanes) was performed to afford the product as a colorless oil (230 mg, 92%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ = 5.69–

5.62 (m, 1H), 5.54–5.48 (m, 1H), 5.13 (ddd,  $J = 8.8$  Hz, 2.1 Hz, 0.9 Hz, 1H), 4.85 (d,  $J = 6.9$  Hz, 1H), 4.63 (d,  $J = 6.9$  Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.48 (d,  $J = 2.1$  Hz, 1H), 2.30 (t,  $J = 7.5$  Hz, 2H), 2.16–2.10 (m, 2H), 1.66–1.58 (m, 2H), 1.43–1.29 (m, 8H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta = 174.2, 134.7, 126.4, 93.2, 81.8, 73.5, 60.5, 55.6, 51.4, 34.1, 29.2, 29.0$  (2C), 28.9, 27.5, 24.9 ppm; HRMS (ESI+) calculated for  $\text{C}_{16}\text{H}_{26}\text{O}_4\text{Na}$   $[\text{M} + \text{Na}]^+$ : 305.1723; found: 305.1715.

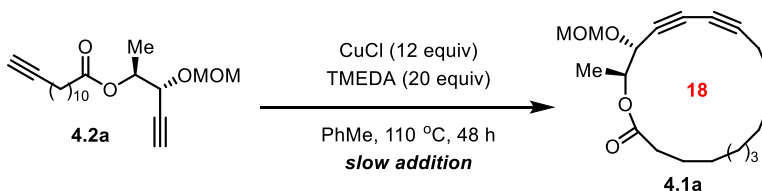


**(9Z,11S)-11-(Methoxymethoxy)tridec-9-en-12-ynoic Acid (4.16).** Methyl ester (4.S3) (251 mg, 0.890 mmol, 1.0 equiv) was dissolved in THF (4 mL), then LiOH (85 mg, 3.56 mmol, 4.0 equiv) was added as an aqueous solution (1 mL). The reaction mixture was stirred at 65 °C for 18 h. The reaction was then cooled to room temperature, and HCl (1 M) was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 × 5 mL) was performed, and the combined organic phases were washed with brine (15 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford the desired product as a low melting solid (238 mg, 99%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta = 5.66$  (dt,  $J = 10.6, 7.5$  Hz, 1H), 5.52 (m, 1H), 5.13 (dd,  $J = 8.8, 2.2$  Hz, 1H), 4.86 (d,  $J = 6.9$  Hz, 1H), 4.64 (d,  $J = 6.9$  Hz, 1H), 3.41 (s, 3H), 2.48 (d,  $J = 2.2$  Hz, 1H), 2.36 (t,  $J = 7.5$  Hz, 2H), 2.16–2.11 (m, 2H), 1.64–1.62 (m, 2H), 1.42–1.33 (m, 8H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta = 179.8, 134.6, 126.3, 93.1, 81.6, 73.5, 60.5, 55.5, 33.9, 29.1, 28.9, 28.8$  (2C), 27.4, 24.5 ppm; HRMS (ESI+) calculated for  $\text{C}_{15}\text{H}_{23}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 267.1602, found 267.1609.



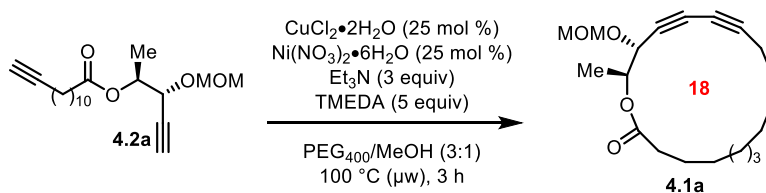
**(2S,3R)-3-(Methoxymethoxy)pent-4-yn-2-yl (S, Z)-11-(Methoxymethoxy)tridec-12-ynoate (4.2).** DCC (472 mg, 2.29 mmol, 2 equiv), DMAP (419 mg, 3.44 mmol, 3 equiv), and (2S,3R)-3-(methoxymethoxy)pent-4-yn-2-ol (4.3) (165 mg, 1.15 mmol, 1 equiv) were added to a solution of (9Z,11S)-11-(methoxymethoxy)tridec-9-en-12-ynoic acid (307 mg, 1.15 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (4 mL) and stirred for 18 h at room temperature. The solution was then

placed in the freezer for 12 h, and the precipitated urea was filtered. Silica gel was added to the filtrate, and the slurry was concentrated under reduced pressure. Flash chromatography (100% hexanes to 20% EtOAc in hexanes) was performed to afford the product as a colorless oil (282 mg, 62%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  = 5.65 (dt,  $J$  = 11 Hz, 7.3 Hz, 1H), 5.51 (t,  $J$  = 8.9 Hz, 1H), 5.14–5.09 (m, 2H), 4.92 (d,  $J$  = 6.9 Hz, 1H), 4.85 (d,  $J$  = 6.9 Hz, 1H), 4.63 (d,  $J$  = 6.9 Hz, 2H), 4.42 (dd,  $J$  = 3.8 Hz, 2.1 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.47 (dd,  $J$  = 9.9 Hz, 2.1 Hz, 2H), 2.33 (t,  $J$  = 7.5 Hz, 2H), 2.17–2.10 (m, 2H), 1.66–1.60 (m, 2H), 1.39–1.29 (m, 11H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  = 173.0, 134.7, 126.4, 94.2, 93.3, 81.8, 79.1, 75.0, 73.5, 70.8, 67.4, 55.6, 34.4, 29.2, 29.1, 29.0, 27.5, 24.9, 15.1 ppm; HRMS (ESI+)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{34}\text{NaO}_6$  [ $\text{M} + \text{Na}$ ] $^+$ : 417.2248; found: 417.2260.

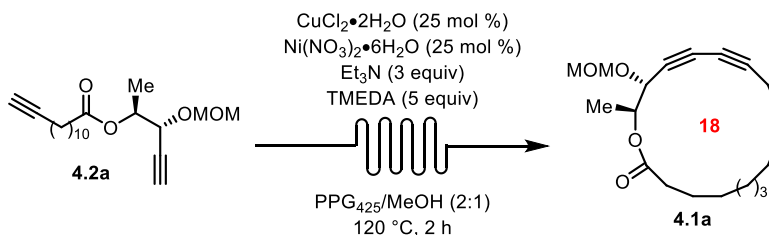


**(17*R*,18*S*)-17-(Methoxymethoxy)-18-methyloxacyclooctadeca-13,15-diyne-2-one (4.1a).**

*Slow Addition Procedure.* To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (154 mg, 1.56 mmol, 12 equiv) and TMEDA (0.4 mL, 2.6 mmol, 20 equiv) were added to PhMe (550 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of bis-alkyne **4.2a** (44 mg, 0.13 mmol, 1 equiv) in PhMe (50 mL) was slowly added over 36 h (0.023 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 12 h. The reaction was then cooled down to room temperature and concentrated under reduced pressure. Flash chromatography was performed (5% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil (15.6 mg, 36%).  $[\alpha]_{\text{D}}^{25} = -0.221$  ( $c = 0.0044$ , MeOH);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.04 (app quint,  $J = 6$  Hz, 1H), 4.93 (d,  $J = 9$  Hz, 1H), 4.61 (d,  $J = 6$  Hz, 1H), 4.30 (d,  $J = 6$  Hz, 1H), 3.38 (s, 3H), 2.36–2.31 (m, 4H), 1.74–1.67 (m, 4H), 1.37–1.26 (m, 15H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.8, 94.2, 81.0, 71.4, 71.0, 70.7, 69.0, 65.1, 55.9, 35.3, 29.7, 29.2, 28.4, 27.5, 26.8, 26.3, 25.7, 24.9, 18.8, 17.4 ppm. HRMS (ESI+)  $m/z$  calculated for  $\text{C}_{20}\text{H}_{30}\text{NaO}_4$  [ $\text{M} + \text{Na}$ ] $^+$ : 357.2036; found: 357.2029.



*Microwave Procedure:* In a microwave vial equipped with a stirring bar was dissolved the bis-alkyne **4.2a** (41 mg, 0.12 mmol, 1 equiv) in MeOH. To the mixture was added polyethylene glycol 400 (3.75 mL),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (5 mg, 0.03 mmol, 25 mol %), and  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (8.7 mg, 0.03 mmol, 25 mol %), and the mixture was stirred at room temperature for 30 s or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min, then TMEDA (0.09 mL, 0.6 mmol, 5 equiv) and  $\text{Et}_3\text{N}$  (0.05 mL, 0.36 mmol, 3 equiv) were added, and the mixture was stirred at room temperature for an additional 30 s. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil (16 mg, 40%).



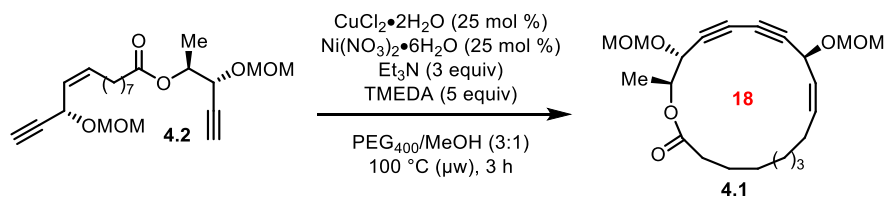
*Continuous Flow Procedure:* In a 200 mL pear-shaped flask equipped with a stirring bar,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (118 mg, 0.70 mmol, 25 mol %),  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (204 mg, 0.70 mmol, 25 mol %), TMEDA (2.07 mL, 13.9 mmol, 5 equiv), and  $\text{Et}_3\text{N}$  (1.16 mL, 8.34 mmol, 3 equiv) were dissolved in MeOH (20 mL) and the mixture was stirred at room temperature for 30 s or until the metals were solubilized. Poly(propylene glycol) 425 (77.2 mL) was added, and the mixture was stirred at room temperature for an additional 30 s. Bis-alkyne **4.2a** (935 mg, 2.78 mmol, 1 equiv) was dissolved in 18.6 mL of MeOH and then added to the solution. The reaction mixture was pumped into the flow reactor for a reaction time of 120 min ( $2 \times 10$  mL Stainless Steel reactors, with a temperature controlled 27 cm length section of tubing between reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction was conducted in a Vapourtec R4 reactor and an R2+ pumping module. The continuous flow setup is ended with two in-line back pressures regulators (Vapourtec 8 bar + IDEX 17 bar). Upon completion, the mixture

was extracted with EtOAc and washed with water, and the combined organic phases were washed with brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by chromatography (5 to 10% EtOAc in hexanes) to afford the desired product as a yellowish oil (353 mg, 38%).

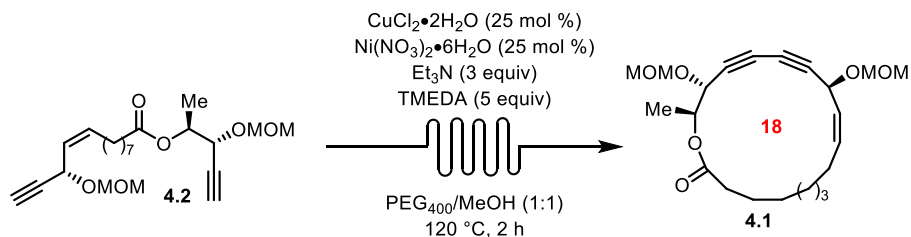


**(10Z,12S,17R,18S)-12,17-Di(methoxymethoxy)-18-methyloxacyclooctadec-10-ene-13,15-diyn-2-one (4.1).** *Slow Addition Procedure.* To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (119 mg, 1.2 mmol, 12 equiv) and TMEDA (0.3 mL, 2.0 mmol, 20 equiv) was added to PhMe (405 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of bis-alkyne **4.2** (40 mg, 0.10 mmol, 1 equiv) in PhMe (50 mL) was slowly added over 24 h (0.035 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 24 h. The reaction was then cooled down to room temperature and concentrated under reduced pressure. Flash chromatography was performed (5% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil (21.4 mg, 55%).  $[\alpha]_D^{25} = -62.1$  ( $c = 0.00145$ , MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.63–5.56 (td,  $J = 10.8, 5.5$  Hz, 1H), 5.49 (app t,  $J = 10.9$  Hz, 1H), 5.20 (d,  $J = 8$  Hz, 1H) 5.06–5.01 (m, 1H), 4.91 (d,  $J = 6.9$  Hz, 1H), 4.81 (d,  $J = 6.7$  Hz, 1H), 4.61 (t,  $J = 5.5$  Hz, 1H), 4.28 (d,  $J = 7.7$  Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.38–2.29 (m, 2H), 2.20– 2.06 (m, 2H), 1.73–1.57 (m, 4H), 1.39–1.29 (m, 9H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  172.8, 134.3, 126.5, 94.4, 93.6, 75.7, 70.6, 70.5, 69.5, 68.9, 61.5, 56.0, 55.7, 35.2, 29.7, 29.5, 29.4, 28.6, 28.5, 27.7, 25.4, 17.6 ppm. Spectral data were in accordance with those previously reported in the literature.<sup>11</sup>

<sup>11</sup> Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; Kumar, R. S.; Yadav, J. S. *Org. Lett.* **2015**, *17*, 979–981.



*Microwave Procedure:* In a microwave vial equipped with a stirring bar was dissolved bis-alkyne **4.2** (38 mg, 0.10 mmol, 1 equiv) in MeOH (1.05 mL). To the mixture were added polyethylene glycol 400 (3.15 mL),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (4.2 mg, 0.025 mmol, 25 mol %), and  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (7 mg, 0.025 mmol, 25 mol %), and the mixture was stirred at room temperature for 30 s or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min, then TMEDA (0.07 mL, 0.5 mmol, 5 equiv) and  $\text{Et}_3\text{N}$  (0.04 mL, 0.3 mmol, 3 equiv) were added, and the mixture was stirred at room temperature for an additional 30 s. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10% EtOAc in hexanes) to afford the desired product as a colorless oil (11.5 mg, 30%).



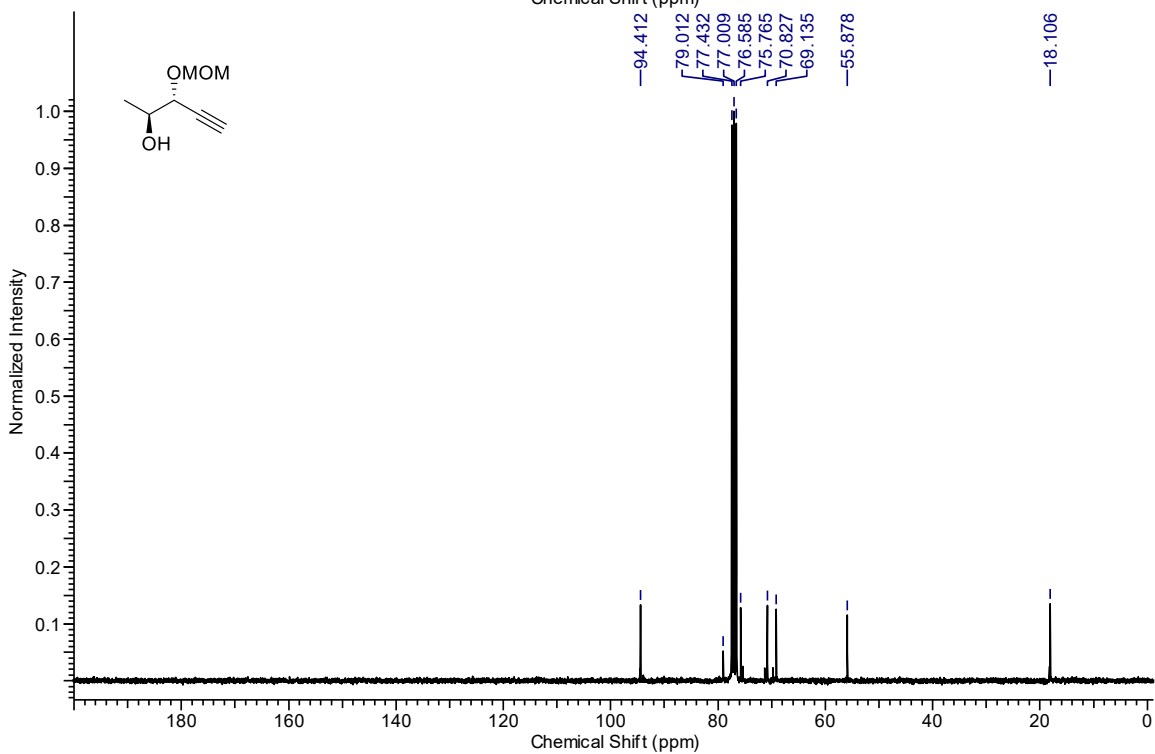
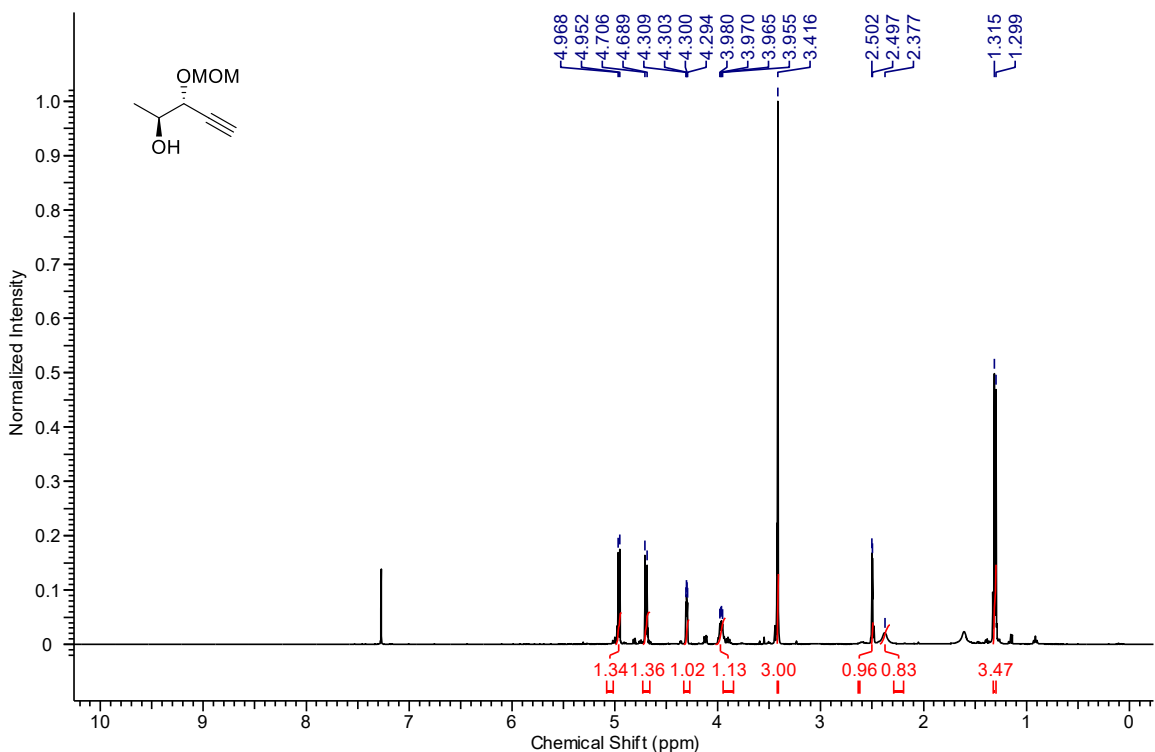
*Continuous Flow Procedure:* In a 20 mL-reaction vial equipped with a stirring bar,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (3 mg, 0.018 mmol) and  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (5.2 mg, 0.018 mmol) were dissolved in MeOH (1.5 mL) and the mixture was stirred at room temperature for 30 s or until the metals were solubilized. Polyethylene glycol 400 (1.5 mL), TMEDA (0.05 mL, 0.33 mmol), and  $\text{Et}_3\text{N}$  (0.03 mL, 0.22 mmol) were added, and the mixture was stirred at room temperature for an additional 30 s. Bis-alkyne **4.2** (19.9 mg, 0.051 mmol, 1 equiv) was mixed in 2 mL of the previous solution. The mixture was stirred at room temperature until everything was soluble and then taken into a syringe. The reaction mixture was injected using a 2 mL injection loop into the flow reactor for a reaction time of 120 min ( $2 \times 10$  mL Stainless Steel reactors, with a temperature controlled 27 cm length section of tubing between reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction was conducted in a Vapourtec R4 reactor and an R2+ pumping module. The continuous flow setup is ended with two in-line back pressures



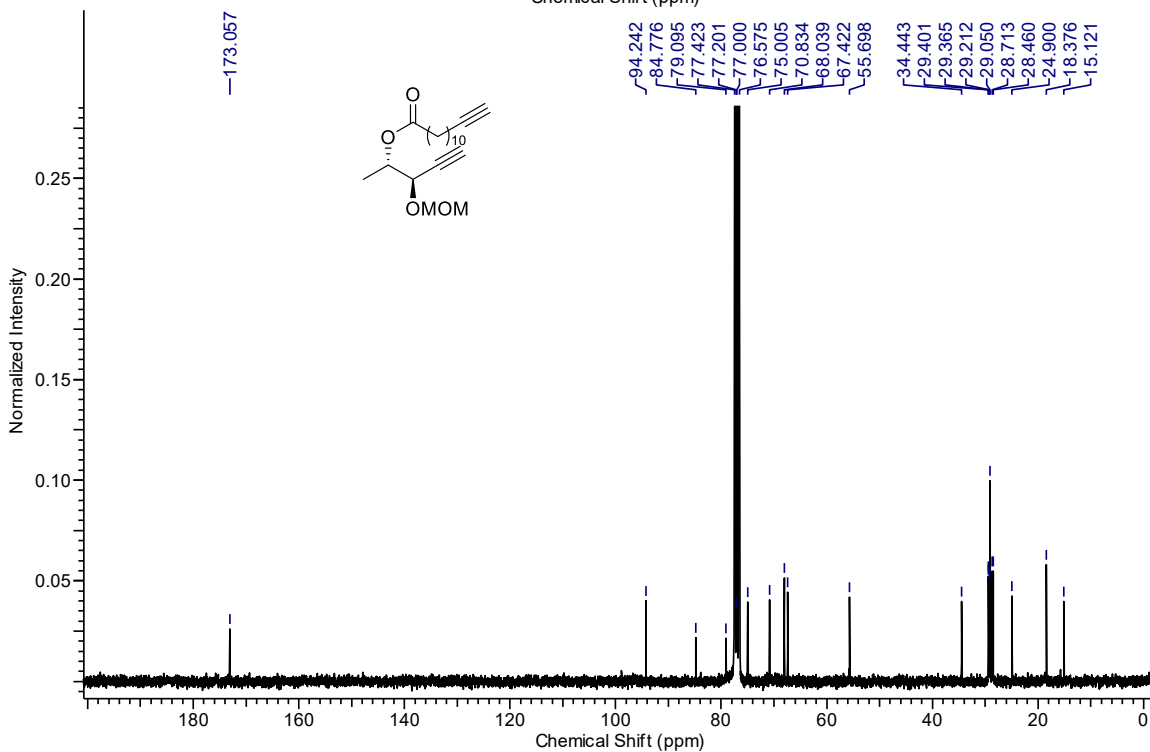
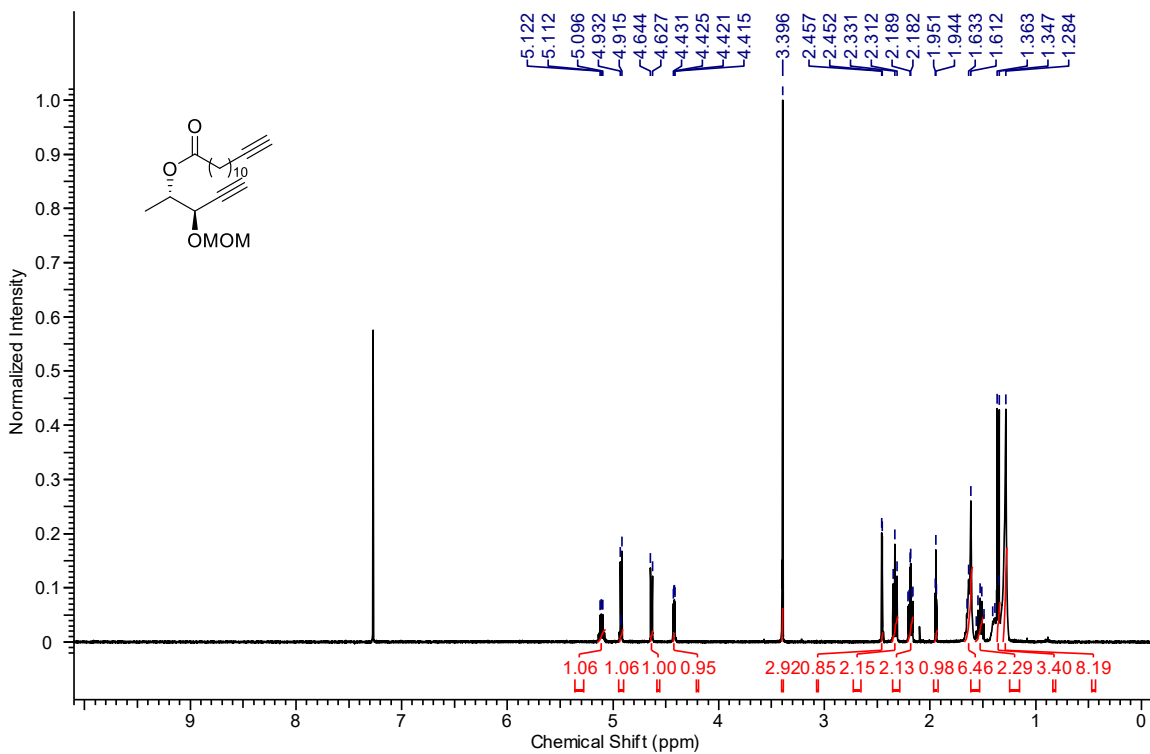
regulators (Vapourtec 8 bar + IDEX 17 bar). Upon completion, silica gel was added to the collection flask and the volatiles were removed under vacuum. The crude mixture was purified by chromatography (20% EtOAc in hexanes) to afford the desired product as a colorless oil (10.2 mg, 52%).

# SPECTRAL DATA FOR NEW COMPOUNDS

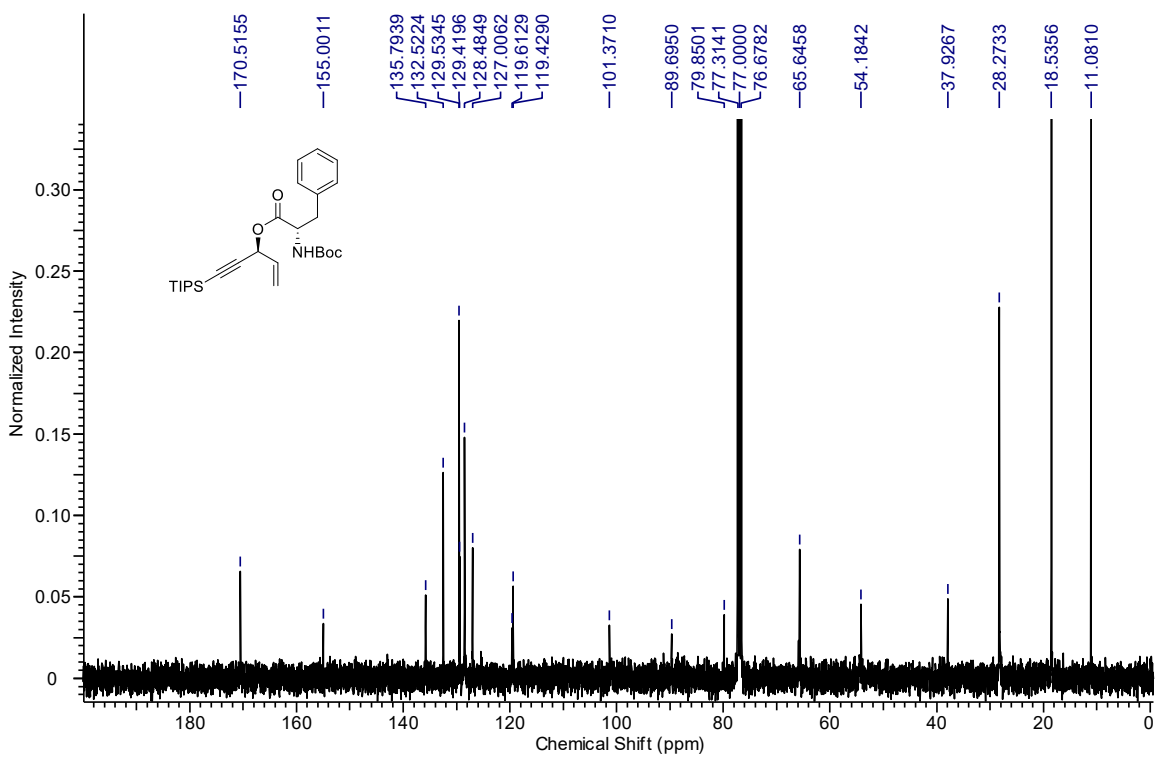
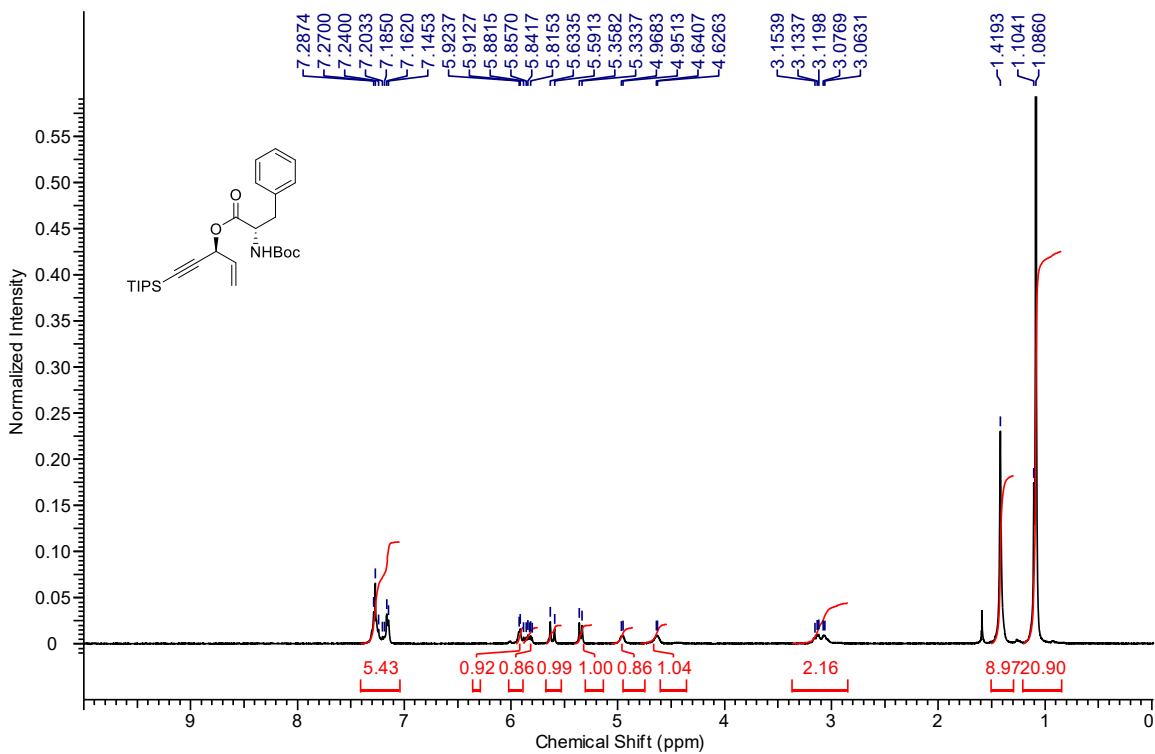
## MOLECULE 4.3



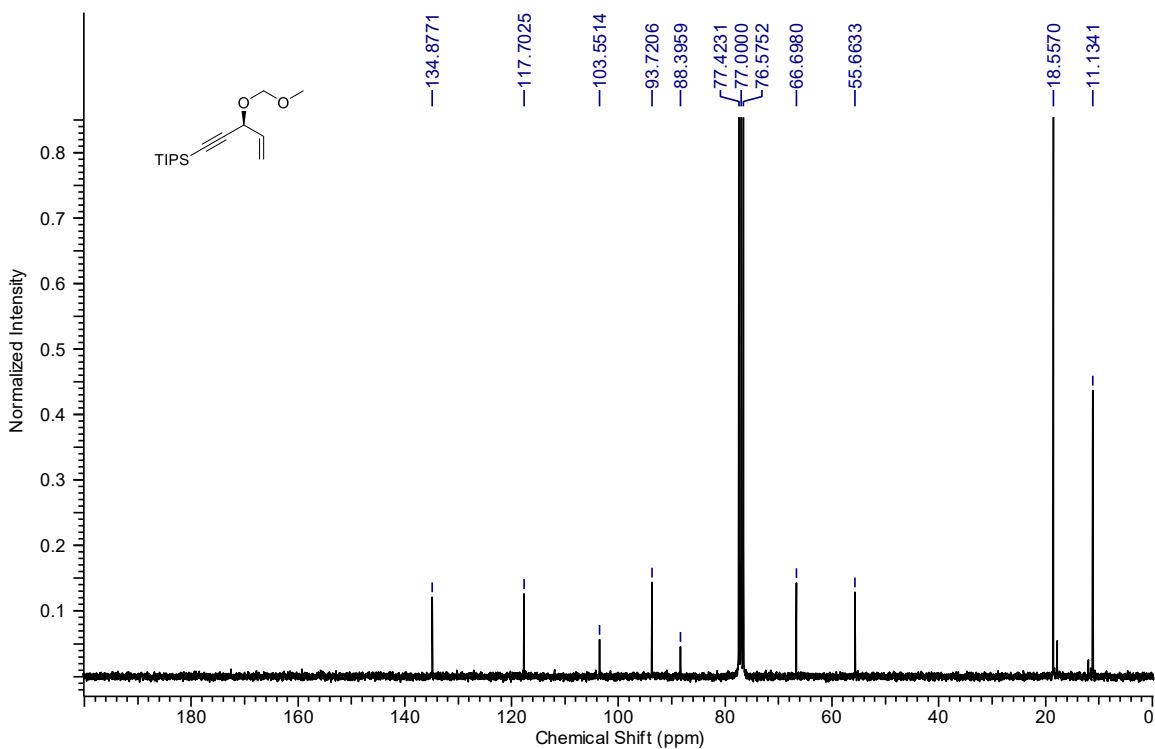
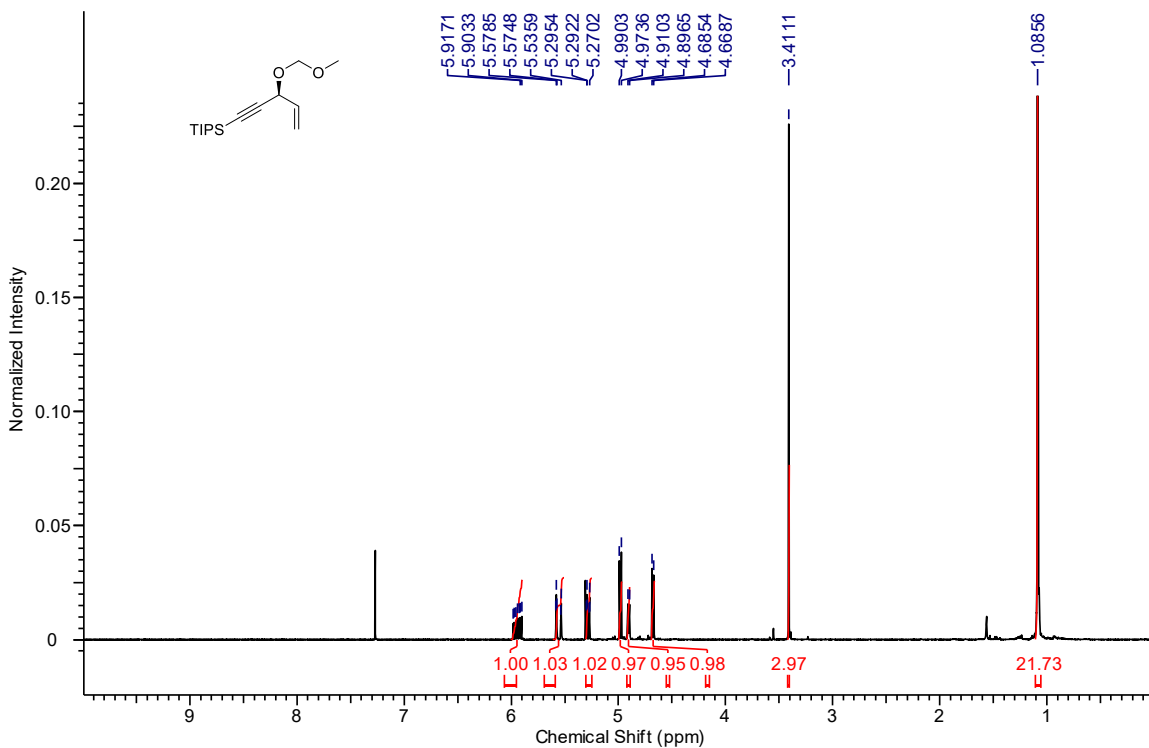
**MOLECULE 4.2a**



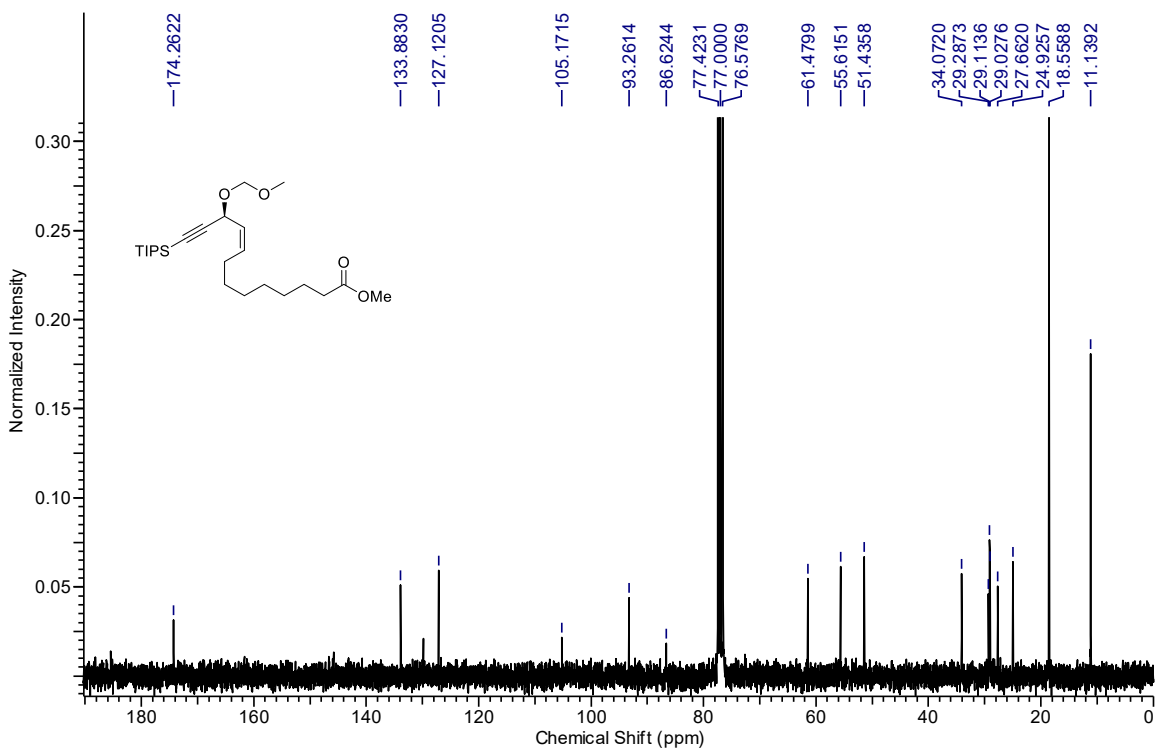
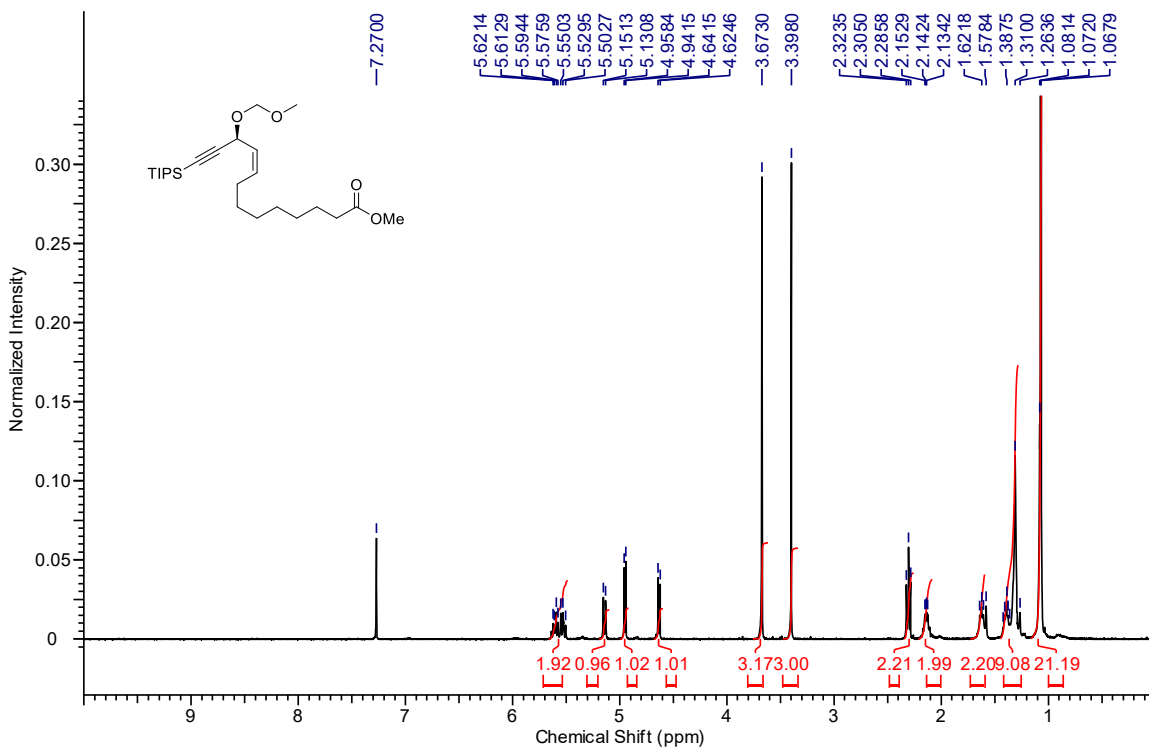
# MOLECULE 4.S2



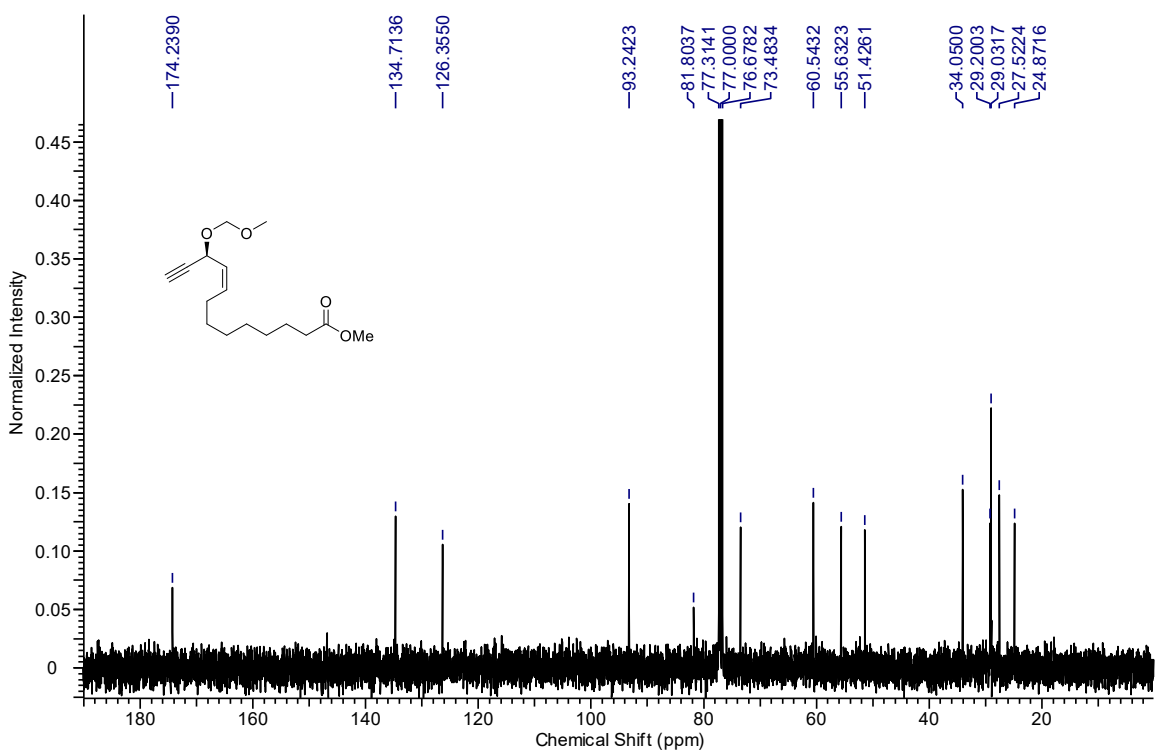
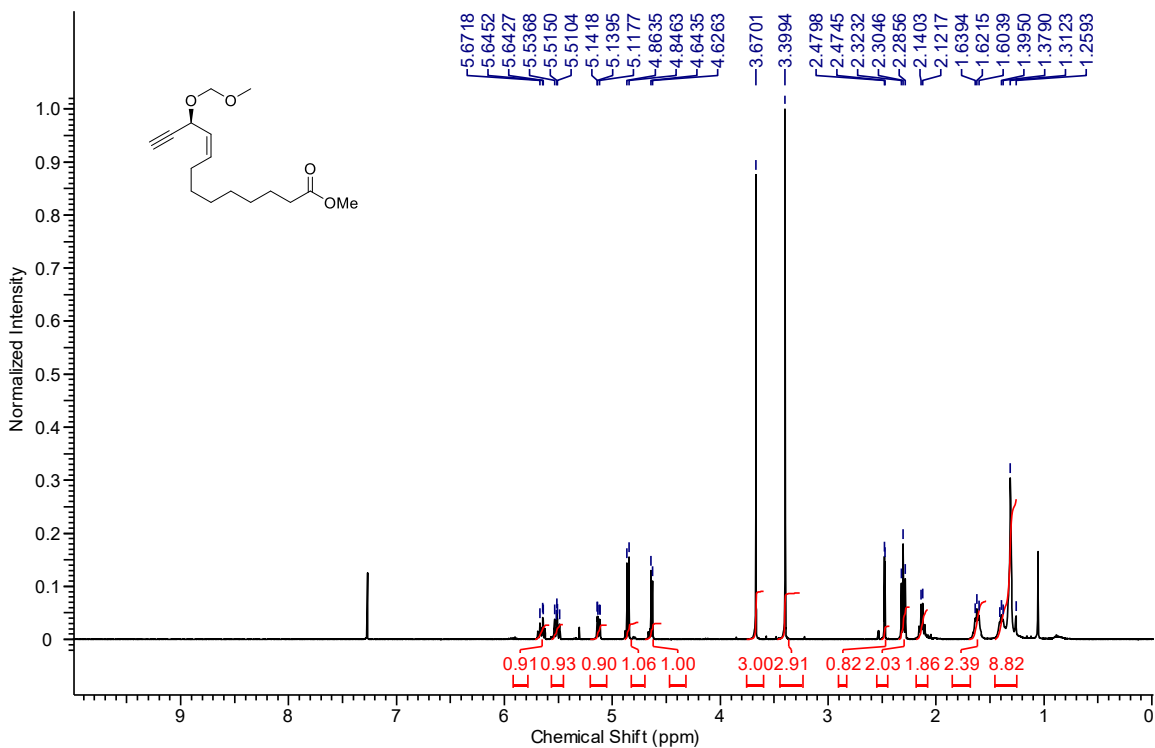
**MOLECULE 4.11**



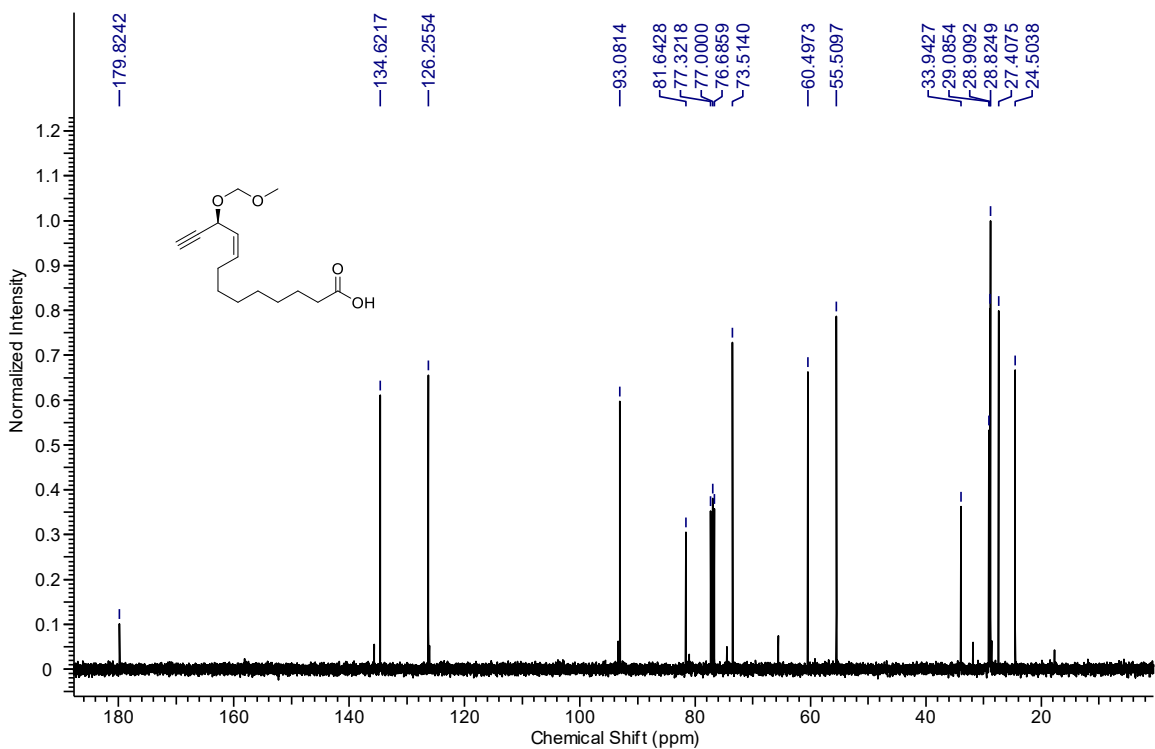
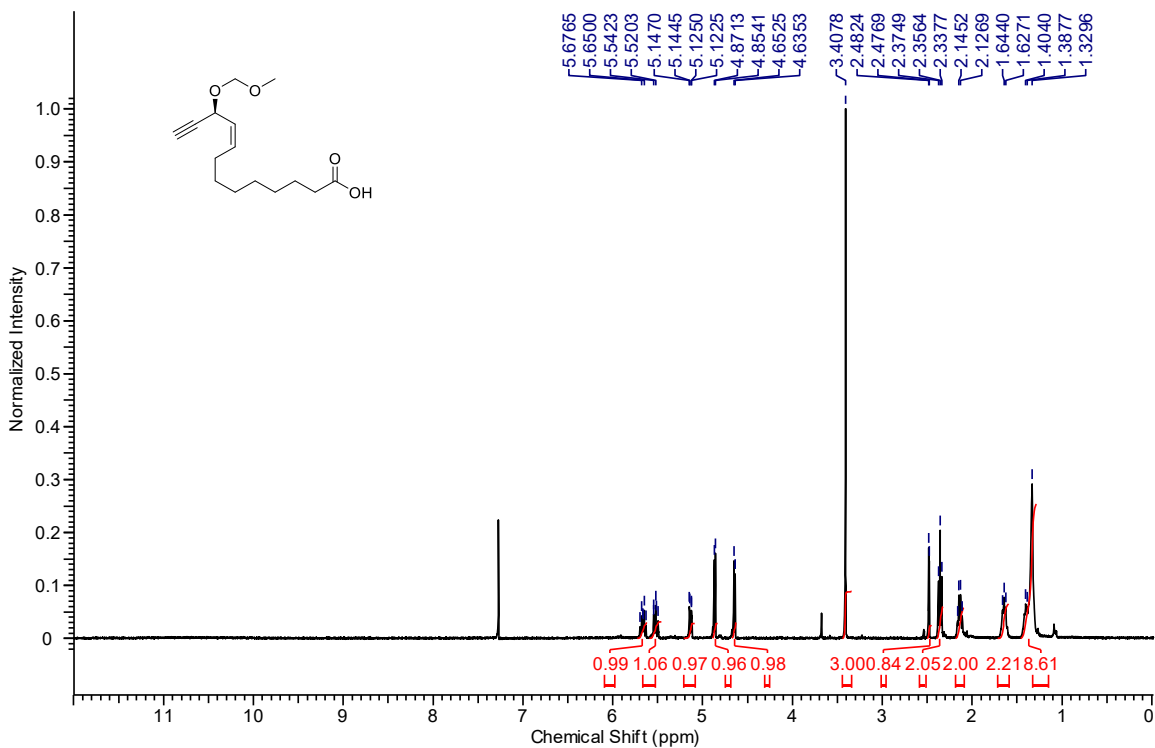
# MOLECULE 4.13



# MOLECULE 4.S3

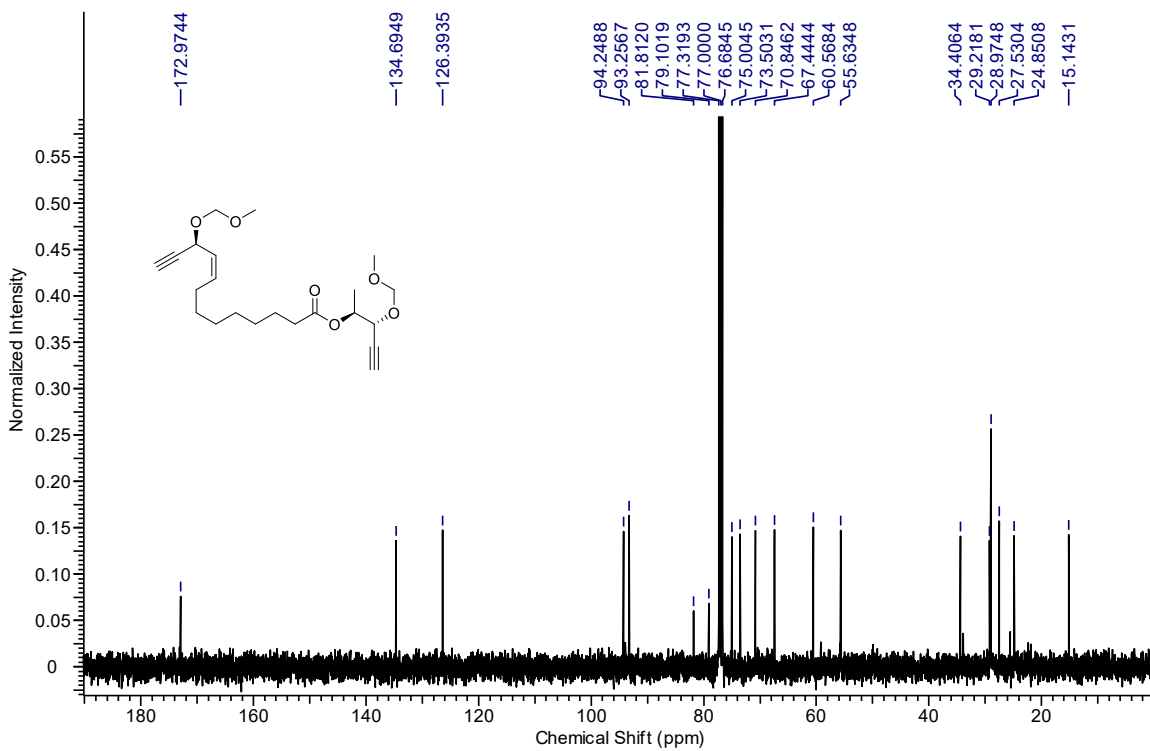
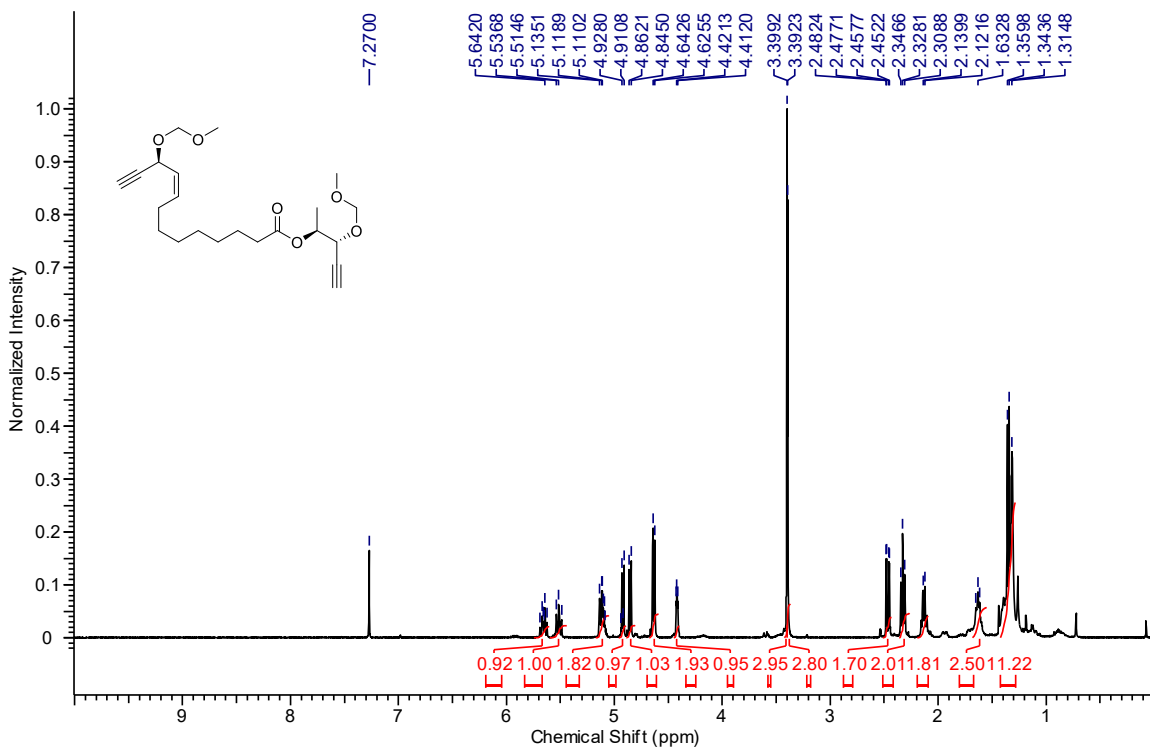


# MOLECULE 4.16

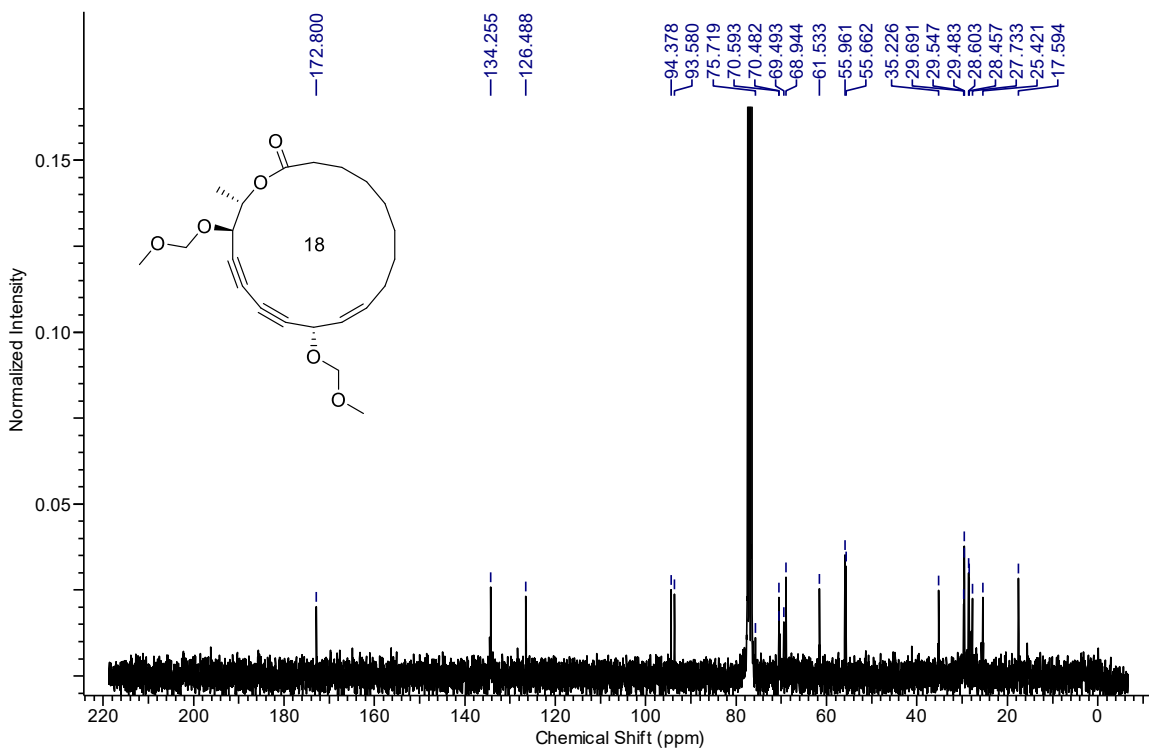
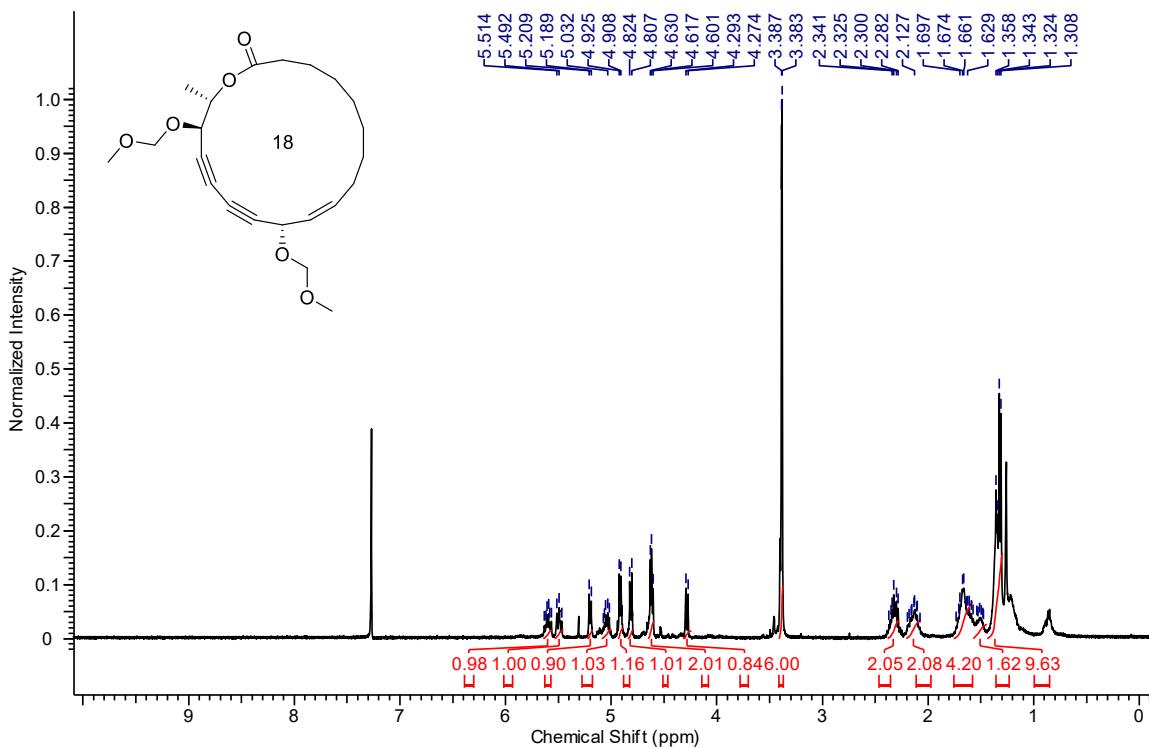




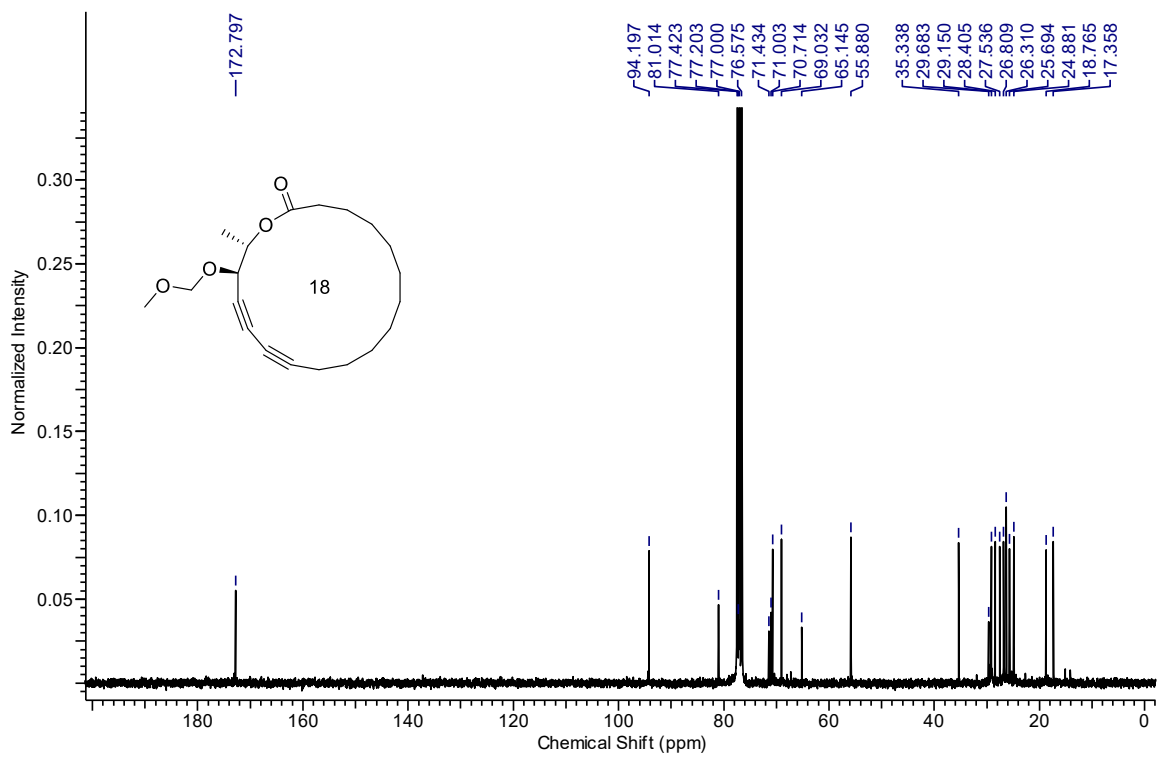
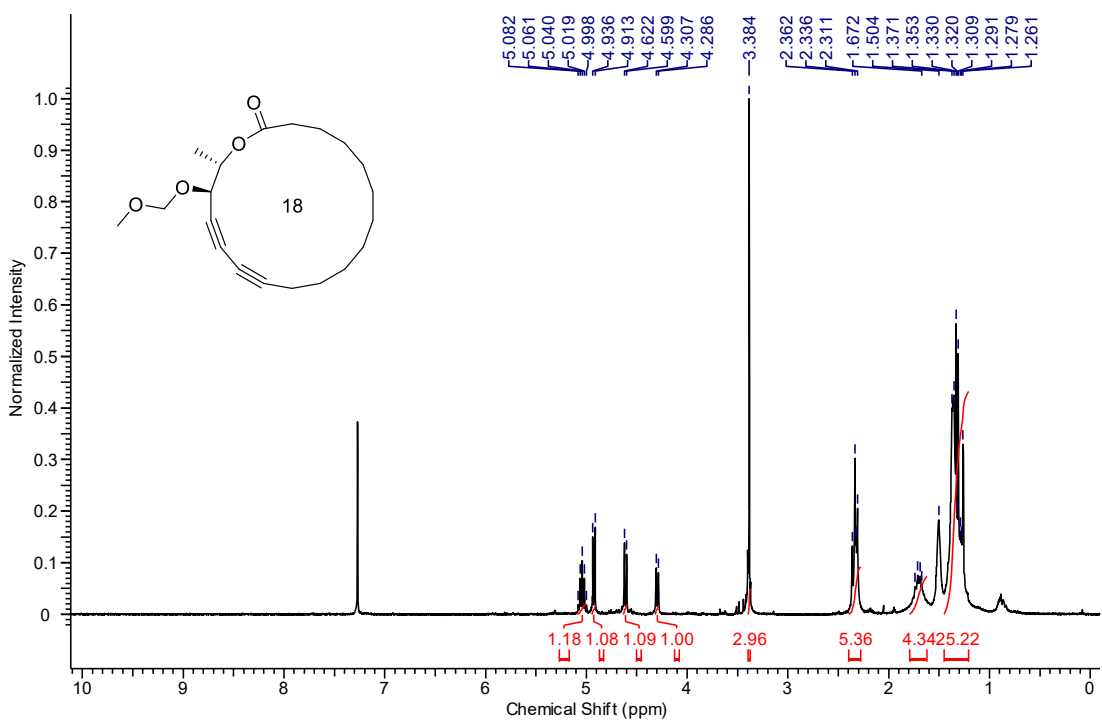
# MOLECULE 4.2



# MOLECULE 4.1



**MOLECULE 4.1a**



## Annexe 2. Procédures expérimentales et spectres RMN du Chapitre 6

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.<sup>12</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company or Alfa Aesar and were reagent quality. Technical solvents were obtained from VWR International Co. or ACP Chemicals Inc. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, Toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Bis alkyne **6.2**<sup>13</sup>, alcohol **6.7**<sup>14</sup> and hydroxyproline methyl ester<sup>15</sup> were synthesized according to literature. Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>16</sup> and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plate was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m

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<sup>12</sup> Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

<sup>13</sup> Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976-19981.

<sup>14</sup> Chen, G.-Q.; Zhang, X.-N.; Wei, Y.; Tang, X.-Y.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8492-8497.

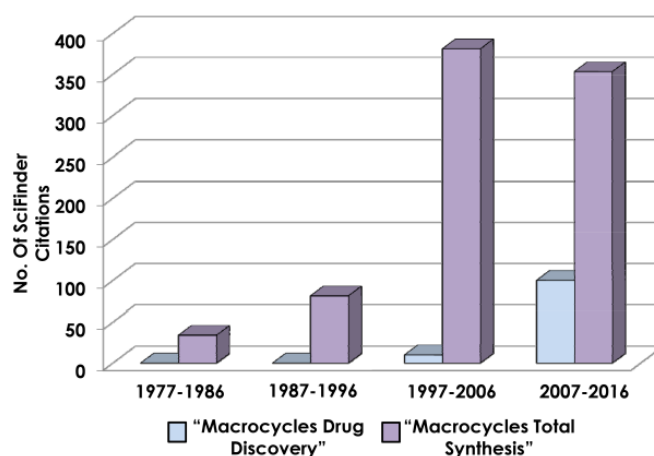
<sup>15</sup> Maison, W.; Arce, E.; Renold, P.; Kennedy, R. J.; Kemp, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 10245-10254.

<sup>16</sup> Still, W. C.; Kahn, M.; Mitra, A.J. *Org. Chem.* **1978**, *43*, 2923-2925.

(multiplet), br (broad); the list of couplings constants ( $J$ ) corresponds to the order of the multiplicity assignment. Mass spectrometric analyses for nominal masses were performed on a quadrupole analyzer, while high resolution masses were performed on a TOF analyzer.

### CHART ILLUSTRATING REPORTS OF MACROCYCLES IN DRUG DISCOVERY AND TOTAL SYNTHESIS

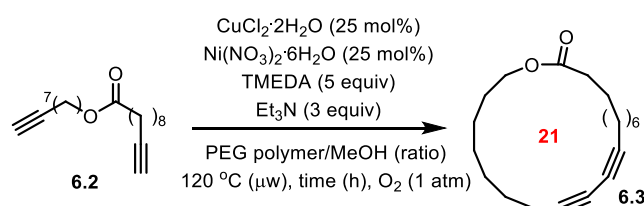
A recent Scifinder search for the term “macrocycles drug discovery” revealed that the number of citations remained low over a thirty year period (1977-2006), but has increased almost ten-fold in the past decade (Figure 6.S1, Scifinder Search May 16<sup>th</sup>, 2017). In parallel, a Scifinder search for the term “macrocycles total synthesis” revealed that interest in macrocycles has remained quite high amongst the synthetic community in the past twenty years.



**Figure 6.S1** Search of Scifinder citations for reports of macrocycles in drug discovery and total synthesis

## MODEL STUDIES AND SURFACE TENSION MEASUREMENTS OF NEW DENDRITIC PEG SOLVENTS

**Table 6.S1** Yields of macrocycle **6.3** employing a “phase separation” strategy: Comparison of solvent mixtures of linear PEGs and StarPEGs in MeOH



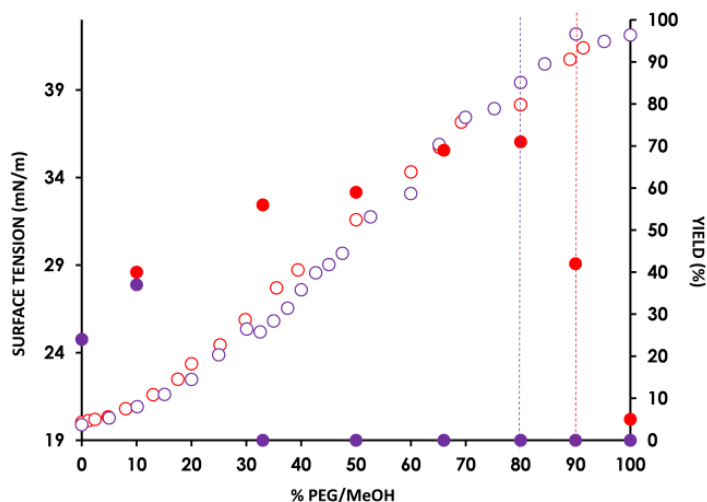
yield <b>6.3</b> (%) <sup>a</sup>						
	PEG			StarPEG		
% PEG/MeOH	190	400	1450	170	450	1014
0	24	24	24	24	24	24
10	40	44	46	37	43	53
33	56	54	53	0 <sup>b</sup>	74	80
50	59	62	61	0 <sup>b</sup>	77	81
66	69	75	68	0 <sup>b</sup>	78	92
80	71	77	55 <sup>b</sup>	0 <sup>b</sup>	75 <sup>b</sup>	85 <sup>b</sup>
90	42 <sup>b</sup>	56 <sup>b</sup>	45 <sup>b</sup>	0 <sup>b</sup>	58 <sup>b</sup>	64 <sup>b</sup>
100	5 <sup>b</sup>	5 <sup>b</sup>	5 <sup>b</sup>	0 <sup>b</sup>	33 <sup>b</sup>	42 <sup>b</sup>

<sup>a</sup> All compounds were isolated by silica gel flash chromatography. Unless otherwise stated, all remaining starting material **6.2** was oligomerized. <sup>b</sup> Remaining mass balance was recovered **6.2**.

The isolated yields of macrocycle **6.3** were then overlaid with plot of the surface tension experiments that were conducted at 60 °C (Figures 6.S2 and 6.S3).<sup>17</sup> Each figure indicates both the isolated yields of **6.3** (solid spheres) and the surface tension measurements (hollow spheres). In addition, each figure compares a StarPEG polymer (purple) and the

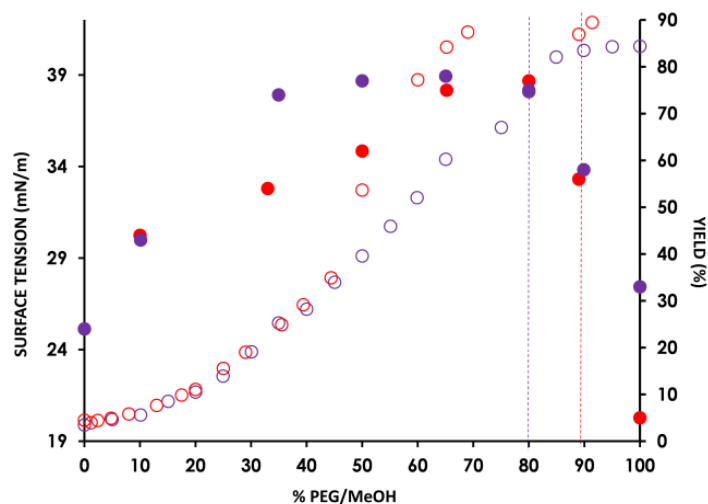
<sup>17</sup> The data shown in Table 6.S2 are reactions using microwave heating. Surface tension measurements were however recorded at 60 °C. Macrocyclization reactions performed with microwave heating provided similar yields to those conducted using traditional (oil bath) heating.

corresponding linear chain PEG (red) that has a similar average molecular weight. A dotted line is used to indicate the region at which high PEG/MeOH ratios exhibit catalyst inhibition resulting in the remaining mass balance being re-isolated bis-alkyne **6.2**. In general, the surface tension plots for all three solvent mixtures studied are relatively similar and displayed a non-linear increase in the surface tension between 100% MeOH and approximately 15-30% PEG/MeOH resulting in an S-shaped curve signaling the presence of aggregates in solution. Some differences include the comparison of the curves for PEG<sub>400</sub> and StarPEG<sub>450</sub>, where PEG<sub>400</sub> has a noticeably steeper curve and well-defined plateau. When comparing the surface tension curves of PEG<sub>1450</sub> and StarPEG<sub>1014</sub>, the latter has a well-defined S-shaped curve, since at PEG<sub>1450</sub> is a solid and does not completely solubilize at high PEG/MeOH ratios. Another difference between the macrocyclization behavior of **6.2**→**6.3** in either PEG or StarPEG/MeOH mixtures was the greater level of catalyst inhibition shown by the StarPEG mixtures (the purple dotted lines in Figures 6.S2 and 6.S3 indicate significant amounts of recovered bis-alkyne **6.2** at 80% StarPEG/MeOH).



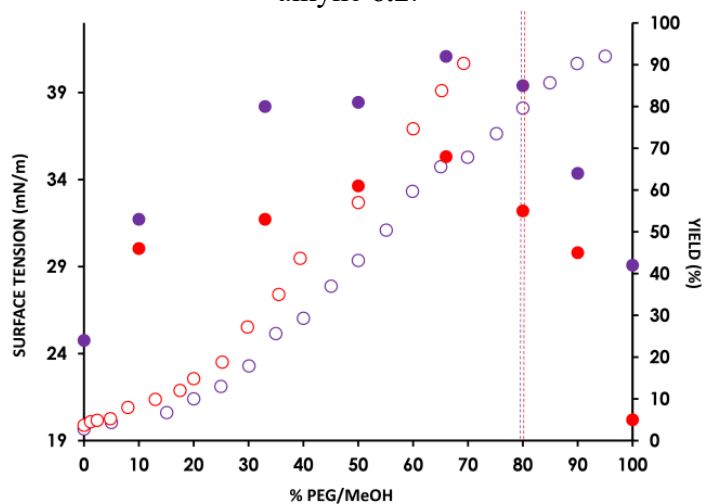
**Figure 6.S2** Effect of using StarPEG<sub>170</sub> polymer (purple) versus linear chain PEG<sub>195</sub> (red) when promoting macrocyclic Glaser-Hay coupling (**6.2**→**6.3**) at high concentration (24 mM)

Surface tension measurements (hollow spheres) and isolated yields (solid spheres) are plotted on the same figure. A dotted line is used to indicate the region at which high PEG/MeOH ratios exhibit catalyst inhibition resulting in the remaining mass balance being re-isolated bis-alkyne **6.2**.



**Figure 6.S3** Effect of using StarPEG<sub>450</sub> polymer (purple) versus linear chain PEG<sub>400</sub> (red) when promoting macrocyclic Glaser-Hay coupling (6.2→6.3) at high concentration (24 mM)

Surface tension measurements (hollow spheres) and isolated yields (solid spheres) are plotted on the same figure. A dotted line is used to indicate the region at which high PEG/MeOH ratios exhibit catalyst inhibition resulting in the remaining mass balance being re-isolated bis-alkyne 6.2.



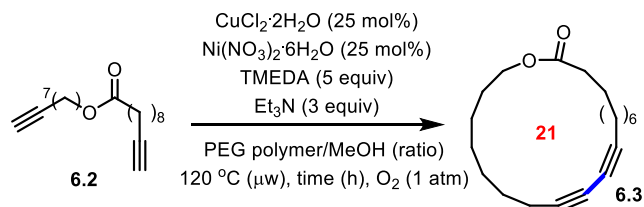
**Figure 6.S4** Effect of using StarPEG<sub>1014</sub> polymer (purple) versus linear chain PEG<sub>1450</sub> (red) when promoting macrocyclic Glaser-Hay coupling (6.2→6.3) at high concentration (24 mM)

Surface tension measurements (hollow spheres) and isolated yields (solid spheres) are plotted on the same figure. A dotted line is used to indicate the region at which high PEG/MeOH ratios exhibit catalyst inhibition resulting in the remaining mass balance being re-isolated bis-alkyne 6.2.



## TABULAR DATA FOR MACROCYCLIZATIONS

**Table 6.S2** Tabular data for the graphics shown in Figure 6.4 of the manuscript



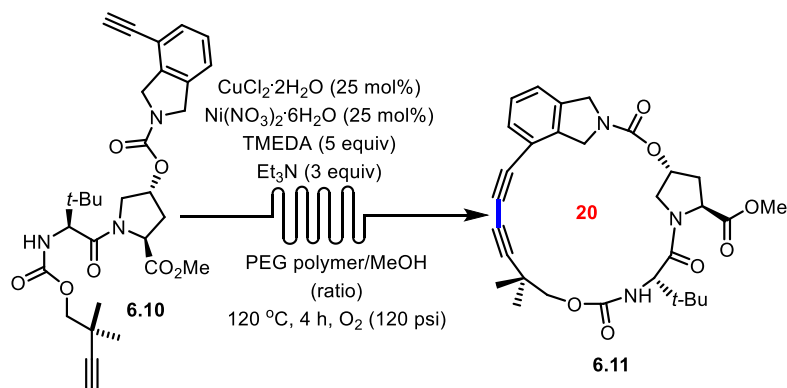
yield <b>6.3</b> (%) <sup>a</sup>					
[ <b>2</b> ] (mM)	100 % MeOH	100 % PEG <sub>400</sub>	100 % PEG <sub>450</sub>	100 % PEG <sub>1450</sub>	100 % PEG <sub>1014</sub>
24	22	5	0	5	42
100	8	0	0	0	0
200	0	0	0	0	0

<sup>a</sup> All compounds were isolated by silica gel flash chromatography.

yield <b>6.3</b> (%) <sup>a</sup>				
[ <b>2</b> ] (mM)	PEG <sub>400</sub> :MeOH (2:1)	StarPEG <sub>450</sub> :MeOH (2:1)	PEG <sub>1450</sub> :MeOH (2:1)	StarPEG <sub>1014</sub> :MeOH (2:1)
24	77	78	68	92
100	42	52	59	83
200	22	32	40	64

<sup>a</sup> All compounds were isolated by silica gel flash chromatography.

**Table 6.S3** Tabular data for the graphics shown in Figure 6.4 of the manuscript



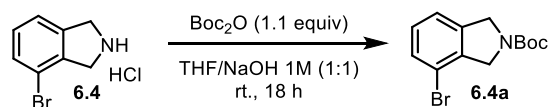
yield <b>6.11</b> (%) <sup>a</sup>					
[ <b>10</b> mM]	100 % MeOH	100 % PEG <sub>400</sub>	100 % PEG <sub>450</sub>	100 % PEG <sub>1450</sub>	100 % PEG <sub>1014</sub>
24	29	13	43	0	1
50	22	0	0	0	0
100	24	0	0	0	0

<sup>a</sup> All compounds were isolated by silica gel flash chromatography.

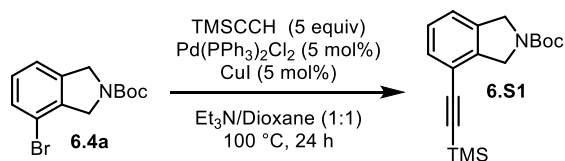
yield <b>6.11</b> (%) <sup>a</sup>				
[ <b>10</b> mM]	PEG <sub>400</sub> :MeOH	StarPEG <sub>450</sub> :MeOH	PEG <sub>1450</sub> :MeOH	StarPEG <sub>1014</sub> :MeOH
	(2:1)	(2:1)	(2:1)	(2:1)
24	64	48	50	55
50	38	31	0	32
100	36	34	0	29
200	21			

<sup>a</sup> All compounds were isolated by silica gel flash chromatography.

## EXPERIMENTAL PROCEDURES

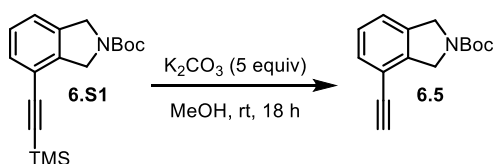


**tert-Butyl 4-bromoisindoline-2-carboxylate (6.4a):** To a solution of 4-bromoisindoline hydrochloride (**6.4**) (2.64 g, 11.2 mmol, 1 equiv) in NaOH 1M (26 mL) and THF (26 mL) was added Boc<sub>2</sub>O (2.71 g, 12.4 mmol, 1.1 equiv). The mixture was stirred 16 h at room temperature. EtOAc and H<sub>2</sub>O were added to the mixture and the layers were separated. The aqueous phase was extracted with EtOAc (2x). The organic phases were combined, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude solid (3.3 g, 99 %) was clean. *Note that rotamers are formed and can result in complex splitting patterns in the <sup>1</sup>H NMR, or can cause doubling of some peaks in the <sup>13</sup>C NMR spectrum. For clarity, all peaks are reported.* <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.39 (d, *J* = 8.6 Hz, 1 H), 7.24 - 7.08 (m, 2 H), 4.80 - 4.57 (m, 4 H), 1.58 - 1.45 (m, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ ppm = 154.3, 139.0, 138.8, 138.0, 137.9, 130.29, 130.25, 129.2, 129.1, 121.5, 121.3, 117.6, 117.3, 85.1, 80.0, 79.9, 53.5, 53.4, 53.2, 52.9, 28.5, 27.4; HRMS (ESI) *m/z* calculated for C<sub>13</sub>H<sub>16</sub>BrNO<sub>2</sub>Na [M+Na]<sup>+</sup>, 320.0257; found: 320.0265.

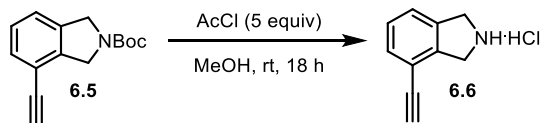


**tert-Butyl 4-((trimethylsilyl)ethynyl)isindoline-2-carboxylate (6.S1):** In a sealed tube, **6.4a** (167 mg, 0.56 mmol, 1 equiv) was dissolved in Et<sub>3</sub>N (1.5 mL) and 1,4-dioxane (1.5 mL). The solution was degassed with N<sub>2</sub> for 5 min. Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (39.3 mg, 0.056 mmol, 0.1 equiv) and CuI (5.3 mg, 0.028 mmol, 0.05 equiv) were added and the solution was degassed a second time with N<sub>2</sub> for 5 min. Ethynyltrimethylsilane (0.39 mL, 2.8 mmol, 5 equiv) was added and the mixture was stirred 24 h at 100 °C. Upon completion, the mixture was passed through a pad of Celite<sup>®</sup> and concentrated *in vacuo*. Purification by silica gel chromatography (3 % EtOAc/hexanes) gave the desired product (175 mg, 99 %) as an off-white solid. *Note that rotamers are formed and can result in complex splitting patterns in the <sup>1</sup>H NMR, or can cause doubling of some peaks in the <sup>13</sup>C NMR spectrum. For clarity, all peaks are reported.* <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.37 - 7.32 (m, 1 H), 7.25 - 7.15 (m, 2 H), 4.78 - 4.66 (m, 4 H), 1.54 - 1.50 (m, 9 H), 0.29 - 0.23 (m, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  ppm = 154.4, 140.3, 139.9, 137.2, 136.9, 130.2, 130.1, 127.4, 127.3, 122.8, 122.5, 118.3, 188.0, 102.0, 101.6, 98.8, 79.7, 79.7, 52.7, 52.4, 52.3, 52.1, 28.5, 28.4, -0.1; HRMS (ESI) m/z calculated for C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>SiNa [M+Na]<sup>+</sup>, 338.1548; found: 338.1547.

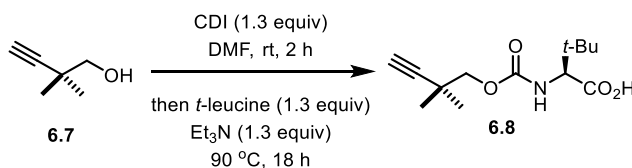


**tert-Butyl 4-ethynylisobutylisindoline-2-carboxylate (6.5):** To a solution of indoline **6.S1** (1.711 g, 5.43 mmol, 1 equiv) in MeOH (40 mL) was added K<sub>2</sub>CO<sub>3</sub> (3.75 g, 27.15 mmol, 5 equiv). The solution was stirred 18 h at room temperature. Upon completion by TLC, EtOAc and H<sub>2</sub>O were added and the layers were separated. The aqueous phase was extracted with EtOAc (2x). The organic phases were combined, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (2.5 % EtOAc/hexanes) gave the terminal alkyne (1.010 g, 84 %) as a white solid. *Note that rotamers are formed and can result in complex splitting patterns in the <sup>1</sup>H NMR, or can cause doubling of some peaks in the <sup>13</sup>C NMR spectrum. For clarity, all peaks are reported.* <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.40 - 7.35 (m, 1 H), 7.26 - 7.18 (m, 2 H), 4.78 - 4.66 (m, 4 H), 3.30 - 3.24 (m, 1 H), 1.55 - 1.51 (m, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  ppm = 154.4, 154.3, 140.4, 140.2, 137.5, 137.2, 130.8, 130.7, 127.5, 127.4, 123.2, 122.9, 117.2, 117.0, 81.3, 81.1, 80.7, 80.5, 79.8, 79.8, 52.7, 52.4, 52.2, 52.1, 28.5; HRMS (ESI) m/z calculated for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>, 266.1152; found: 266.1152.

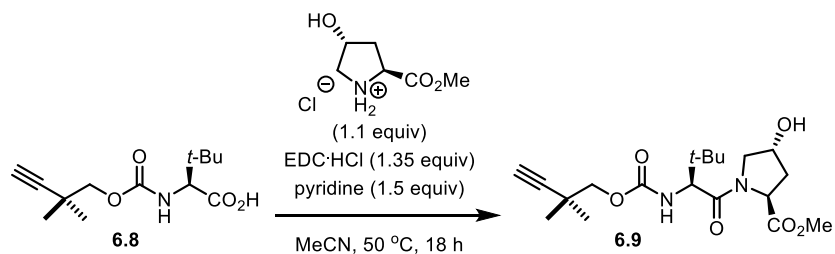


**4-Ethynylisobutylisindoline hydrochloride (6.6):** To a solution of isoindoline **6.5** (786 mg, 3.23 mmol, 1 equiv) in MeOH (15 ml), was added dropwise AcCl (0.86 ml, 16.17 mmol, 5 equiv) at 0 °C. The resulting mixture stirred for 18 h (or until completed by TLC) at room temperature. Et<sub>2</sub>O was added and a grey precipitate was formed and filtered, washed with Et<sub>2</sub>O (2x) and dried under vacuum to give the desired isoindoline salt as a grey powder (507

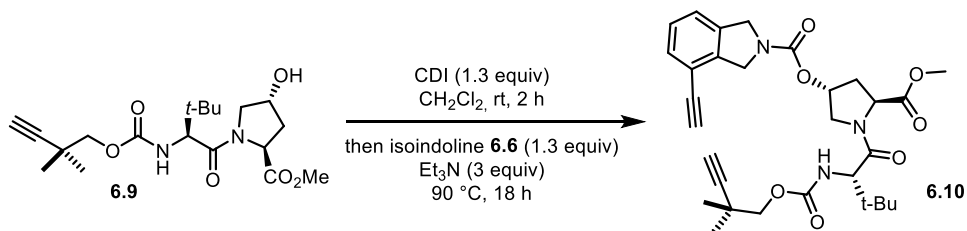
mg, 87 %).  $^1\text{H}$  NMR (400 MHz, MeOD- $d_4$ )  $\delta$  = 7.52 - 7.38 (m, 3 H), 4.70 - 4.66 (m, 4 H), 3.93 (s, 1 H);  $^{13}\text{C}$  NMR (100 MHz, MeOD- $d_4$ )  $\delta$  ppm = 138.3, 136.3, 133.3, 130.6, 124.7, 119.1, 84.5, 80.8, 52.7, 49.8; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{10}\text{H}_{10}\text{N}$   $[\text{M}+\text{H}]^+$ , 144.0812; found: 144.0808.



**(S)-2-((((2,2-Dimethylbut-3-yn-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid (6.8):** In a sealed tube, 2,2-dimethylbut-3-yn-1-ol (**6.7**) (1.84 g, 18.7 mmol, 1 equiv) and 1,1'-carbonyldiimidazole (3.96 g, 24.4 mmol, 1.3 equiv) were dissolved in DMF (20 mL). The mixture was stirred 2 h at room temperature. Then, *L-tert-leucine* (3.21 g, 24.4 mmol, 1.3 equiv) and  $\text{Et}_3\text{N}$  (3.74 mL, 26.3 mmol, 1.4 equiv) were added and the resulting mixture was warmed to 90 °C and stirred for 16 h. Then reaction was then cooled back to room temperature and MTBE and NaOH 0.5 M were added. The layers were separated and the organic layer was discarded. MTBE was added to the aqueous phase and the pH was adjusted to pH = 1 using HCl 6M. The layers were separated again. The organic phase was washed with brine, dried with  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude carboxylic acid (4.4 g, 92 %) was obtained as a sticky semi-solid.  $[\alpha]_{\text{D}}^{25} = 4.0$  ( $c = 0.0030$ , MeOH); *Note that rotamers are formed and can result in complex splitting patterns in the  $^1\text{H}$  NMR, or can cause doubling of some peaks in the  $^{13}\text{C}$  NMR spectrum. For clarity, all peaks are reported.*  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 11.22 (br. s., 1 H), 6.50 (d,  $J = 7.8$  Hz, 0.3 H), 5.43 (d,  $J = 9.5$  Hz, 0.7 H), 4.19 (d,  $J = 9.5$  Hz, 0.7 H), 4.05 - 3.90 (m, 2.3 H), 2.11 (s, 1 H), 1.22 (s, 6 H), 1.01 (s, 9 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm = 176.2, 157.0, 156.3, 88.7, 88.1, 72.8, 72.0, 69.1, 68.9, 63.2, 62.1, 34.6, 33.9, 31.7, 26.4, 25.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{13}\text{H}_{21}\text{NO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$ , 278.1365; found: 278.1363.

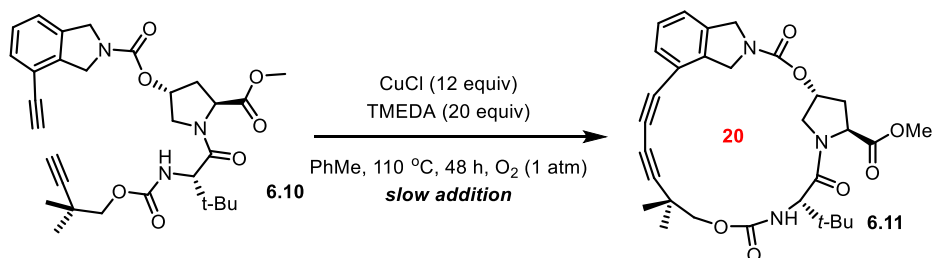


**Methyl (2S, 4R)-1-((S)-2-(((2,2-dimethylbut-3-yn-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylate (6.9):** Carboxylic acid (6.8) (1.03 g, 3.48 mmol, 1 equiv) was dissolved in MeCN (3 mL) at room temperature. *trans*-4-Hydroxy-*L*-proline methyl ester hydrochloride (695 mg, 3.83 mmol, 1.1 equiv) and pyridine (0.42 mL, 5.22 mmol, 1.5 equiv) were added to the stirring solution. EDC-HCl (900 mg, 4.70 mmol, 1.35 equiv) was added last and the mixture became bright yellow. The reaction was warmed to 50 °C and stirred 16 h. The crude mixture was cooled back to room temperature and PhMe and an aqueous solution of citric acid (15% wt) were added. The mixture was stirred for 5 min and the aqueous layer was discarded. Brine was added and the resulting mixture was stirred an additional 5 mins. The phases were separated and the organic phase was dried with MgSO<sub>4</sub> and concentrated *in vacuo*. The crude solid was azeotroped with PhMe and the clean alcohol was obtained as a colorless oil (1.23 g, 92 %).  $[\alpha]_{\text{D}}^{25} = -67.3$  ( $c = 0.0055$ , MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 5.49$  (d,  $J = 9.1$  Hz, 1 H), 4.69 (t,  $J = 8.7$  Hz, 1 H), 4.60 – 4.51 (m, 1 H), 4.27 (d,  $J = 8.9$  Hz, 1 H), 4.06 - 3.97 (m, 2 H), 3.93 - 3.85 (m, 1 H), 3.79 – 3.73 (m, 1 H), 3.75 (s, 3 H), 2.41 - 2.31 (m, 1 H), 2.13 (s, 1 H), 2.09 - 1.98 (m, 1 H), 1.24 (s, 6 H), 1.06 (s, 9 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  ppm = 172.4, 170.6, 156.4, 88.5, 71.8, 69.8, 69.0, 59.0, 57.7, 56.3, 52.0, 37.3, 35.8, 31.5, 26.0, 25.5; HRMS (ESI)  $m/z$  calculated for C<sub>19</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub> [M+H]<sup>+</sup>, 383.2184; found: 383.2182.



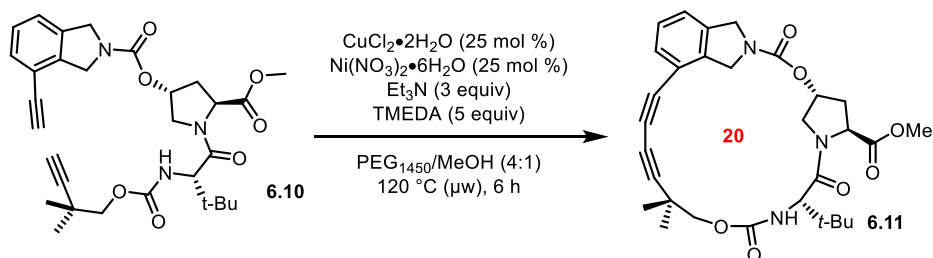
**(3R, 5S)-1-((S)-2-(((2,2-Dimethylbut-3-yn-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-ethynylisoindoline-2-carboxylate (**6.10**):**

Alcohol (**6.9**) (946 mg, 2.48 mmol, 1 equiv) and 1,1'-carbonyldiimidazole (CDI) (522 mg, 3.22 mmol, 1.3 equiv) were dissolved in dry DCM (12 mL). The mixture was stirred for 2 h at room temperature. Then, isoindoline (**6.6**) (579 mg, 3.22 mmol, 1.3 equiv) and Et<sub>3</sub>N (1,03 mL, 7,43 mmol, 3 equiv) were added and the resulting mixture was warmed to 50 °C and stirred for 18 h. Then the reaction was diluted with DCM and the phases were separated. The organic layer was washed with HCl 1 M (2x), NaHCO<sub>3</sub> sat. and brine. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purification by silica gel chromatography (40% EtOAc/hexanes) gave the desired bis-alkyne (1.25 g, 91 %) as a white solid. M.p.: 72,2 °C;  $[\alpha]_{\text{D}}^{25} = -14.8$  (c = 0.00135, MeOH); *Note that rotamers are formed and can result in complex splitting patterns in the <sup>1</sup>H NMR, or can cause doubling of some peaks in the <sup>13</sup>C NMR spectrum. For clarity, all peaks are reported.* <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.41 – 7.35 (m, 1H), 7.26 – 7.17 (m, 2H), 5.43 – 5.37 (m, 2H), 4.83 – 4.61 (m, 4H); 4.24 (d, *J* = 9.5 Hz, 1H), 4.20 (t, *J* = 12.5 Hz, 1H), 3.94 – 3.84 (m, 1H), 3.80 (d, *J* = 10.3 Hz, 1H), 3.77 – 3.75 (m, 3H), 3.55 – 3.46 (m, 1H), 3.32 – 3.27 (m, 1H), 2.55 – 2.48 (m, 1H), 2.26 – 2.18 (m, 1H), 2.06 (d, *J* = 7.5 Hz, 1H), 1.26 – 1.22 (m, 1H), 1.13 – 1.06 (m, 6H), 1.05 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ ppm = 172.0, 171.05, 171.00, 156.3, 153.8, 153.7, 139.8, 139.6, 136.9, 136.5, 131.0, 130.9, 127.71, 127.67, 123.1, 122.9, 117.3, 117.2, 88.8, 88.7, 81.9, 81.5, 80.4, 73.5, 71.68, 71.65, 68.73, 68.68, 59.2, 59.1, 57.9, 57.8, 54.03, 53.95, 53.0, 52.5, 52.3, 52.0, 35.4, 35.3, 35.0, 34.8, 31.5, 31.4, 26.2, 25.6, 25.5; HRMS (ESI) *m/z* calculated for C<sub>30</sub>H<sub>38</sub>N<sub>3</sub>O<sub>7</sub> [M+H]<sup>+</sup>, 552.2710; found: 552.2704.

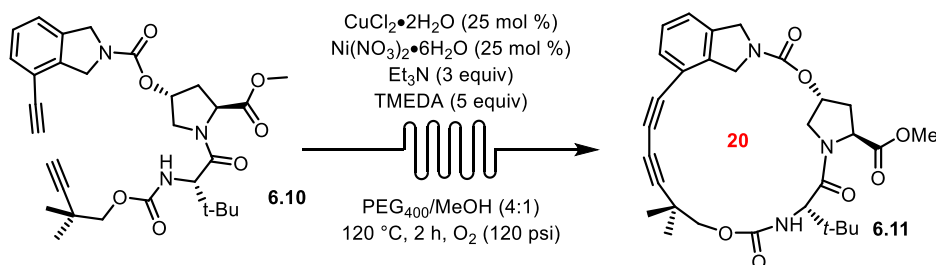


**Macrocycle (6.11).** *Slow Addition Procedure.* To a 1 L triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (119 mg, 1.2 mmol, 12 equiv) and TMEDA (0.3 mL, 2.0 mmol, 20 equiv) was added to PhMe (405 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of bis-alkyne **6.10** (55.2 mg, 0.1 mmol, 1 equiv) in PhMe (50 mL) was slowly added over 24 h (0.035 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 24 h. The reaction was then cooled down to room temperature and concentrated under reduced pressure. Flash chromatography was performed (40 → 60% EtOAc in hexanes) to afford the desired product as a white solid (35 mg, 64%). M.p. = 136.4 °C;  $[\alpha]_{\text{D}}^{25} = -32.0$  ( $c = 0.0020$ , MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 2H), 5.71 (d,  $J = 9.1$  Hz, 1H), 5.30 – 5.26 (m, 1H), 4.83 (d,  $J = 10.5$  Hz, 1H), 4.76 – 4.73 (m, 2H), 4.64 – 4.59 (m, 2H), 4.59 – 4.56 (m, 1H), 4.43 (d,  $J = 9.1$  Hz, 1H), 4.07 (dd,  $J = 11.8, 1.6$  Hz, 1H), 3.85 (dd,  $J = 11.7, 3.6$  Hz, 1H), 3.76 (s, 3H), 3.29 (d,  $J = 10.5$  Hz, 1H), 2.72 (qd,  $J = 7.3, 1.1$  Hz, 1H), 2.13 (qd,  $J = 10.9, 3.8$  Hz, 1H), 1.34 (s, 3H), 1.23 (s, 3H), 1.06 (s, 9H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 170.4, 155.3, 153.3, 144.4, 136.2, 129.4, 127.9, 123.1, 117.1, 89.6, 78.7, 74.3, 72.2, 71.4, 64.7, 59.4, 57.7, 53.8, 52.8, 52.3, 52.1, 37.2, 35.6, 33.1, 26.3, 25.4, 25.3 ppm. HRMS (ESI)  $m/z$  calculated for  $\text{C}_{30}\text{H}_{36}\text{N}_3\text{O}_7$   $[\text{M}+\text{H}]^+$ , 550.2565; found: 550.2549.





*Microwave Procedure:* In an open microwave vial equipped with a stirring bar, bis-alkyne **6.10** (26.5 mg, 0.048 mmol, 1 equiv),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2.0 mg, 0.012 mmol, 25 mol%) and  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (3.5 mg, 0.012 mmol, 25 mol%) were dissolved in MeOH (0.4 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Poly(ethylene) glycol 1450 (1.6 mL), TMEDA (0.035 mL, 0.24 mmol, 5 equiv.), and  $\text{Et}_3\text{N}$  (0.02 mL, 0.144 mmol, 3 equiv.) were added, and the mixture was stirred at room temperature for an additional 30 seconds. The vial was then sealed with a microwave cap. The reaction was warmed to 120 °C for 6 h. The crude mixture was purified by chromatography (40 → 60% EtOAc in hexanes) to afford the desired product as a white solid (13.7 mg, 50%).

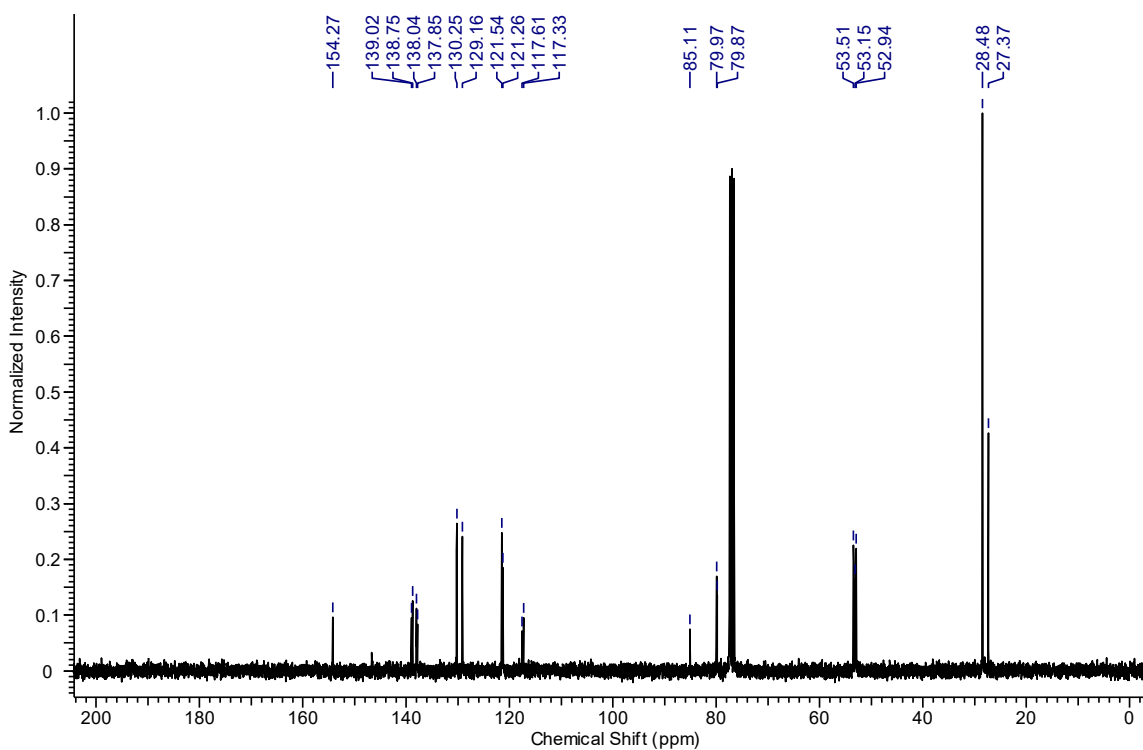
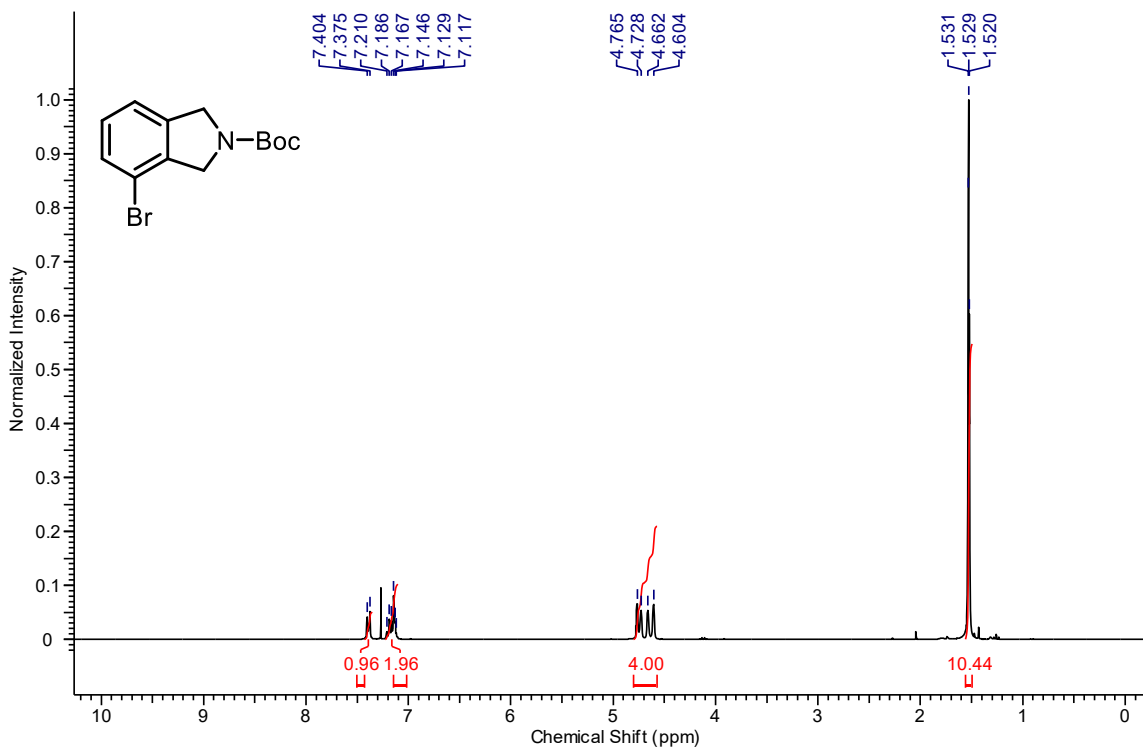


*Continuous Flow Procedure:* In a 4 mL-reaction vial equipped with a stirring bar, bis-alkyne **6.10** (24.4 mg, 0.048 mmol, 1 equiv),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2.0 mg, 0.012 mmol, 25 mol%) and  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (3.5 mg, 0.012 mmol, 25 mol%) were dissolved in MeOH (0.4 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. PEG co-solvent (1.6 mL), TMEDA (0.035 mL, 0.24 mmol, 5 equiv.), and  $\text{Et}_3\text{N}$  (0.02 mL, 0.144 mmol, 3 equiv.) were added, and the mixture was stirred at room temperature for an additional 30 seconds then taken up into a syringe. The reaction mixture was injected using a 2 mL injection loop into the flow reactor for a reaction time of 240 min (1 x 15 mL Stainless Steel reactor (tube-in-tube,  $\text{O}_2$  (120 psi)) and 1 x 10 mL Stainless Steel reactors with a 32 cm length section of Stainless Steel tubing between reactors) at a flow rate of 0.104 mL/min at 120 °C. The flow reaction was conducted in a Vapourtec R4 reactor and an R2+ pumping

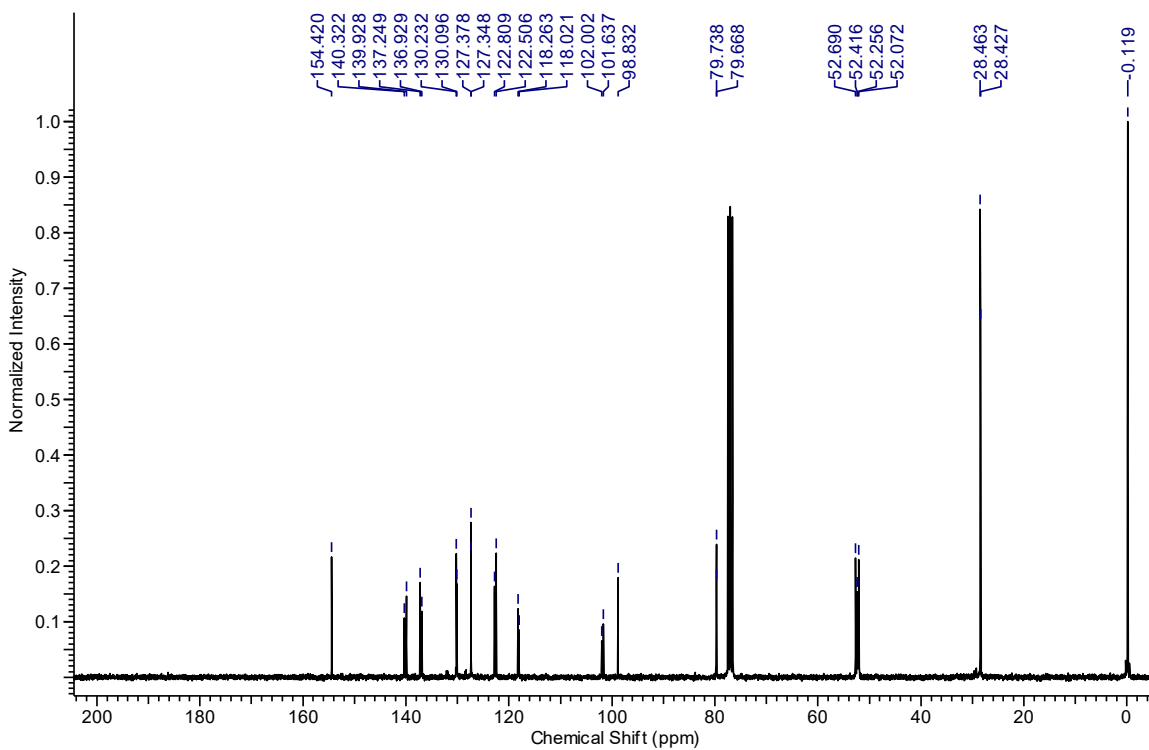
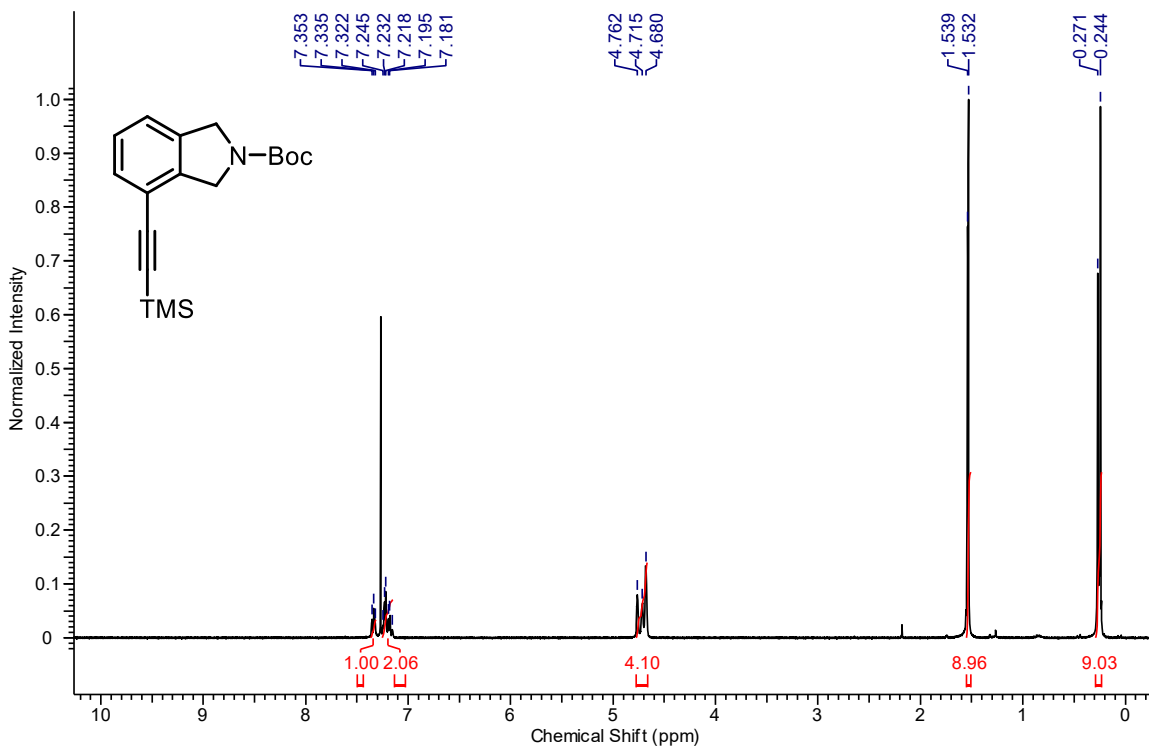
module. The continuous flow setup is ended with a back pressure regulator (IDEX 250 psi). Upon completion, silica gel was added to the collection flask and the volatiles were removed under vacuum. The crude mixture was purified by chromatography (40 → 60% EtOAc in hexanes) to afford the desired product as a white solid (15.5 mg, 64%).

# SPECTRAL DATA FOR NEW COMPOUNDS

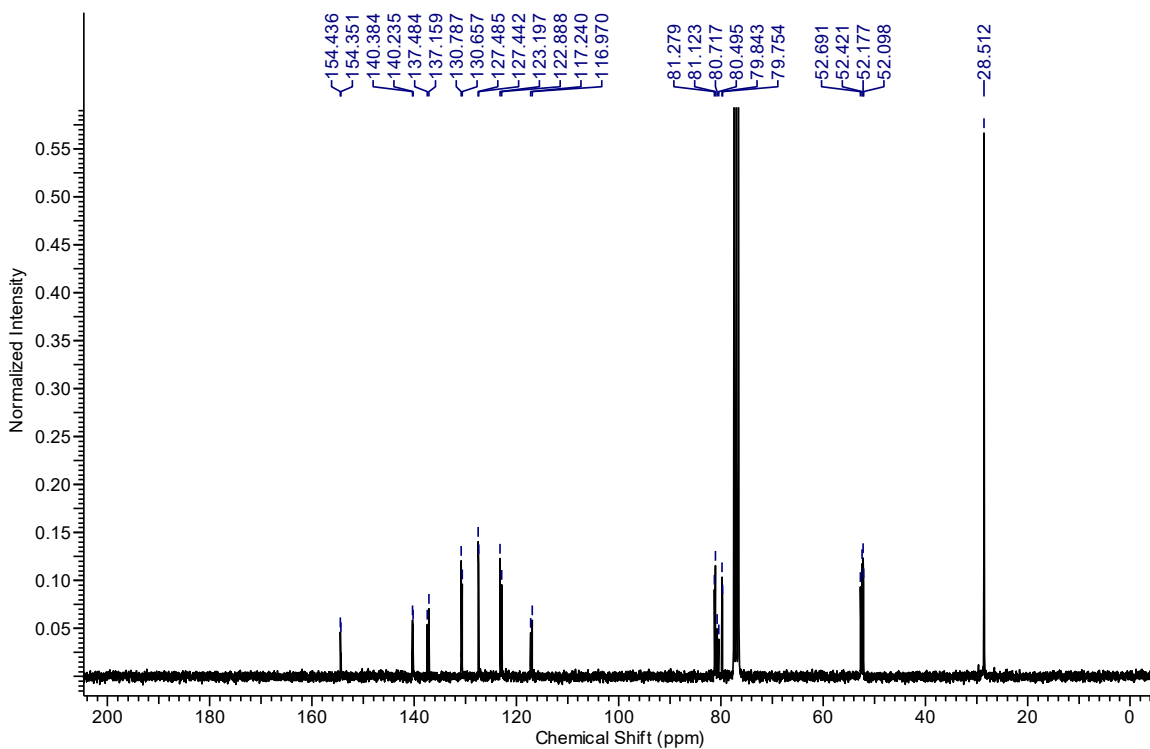
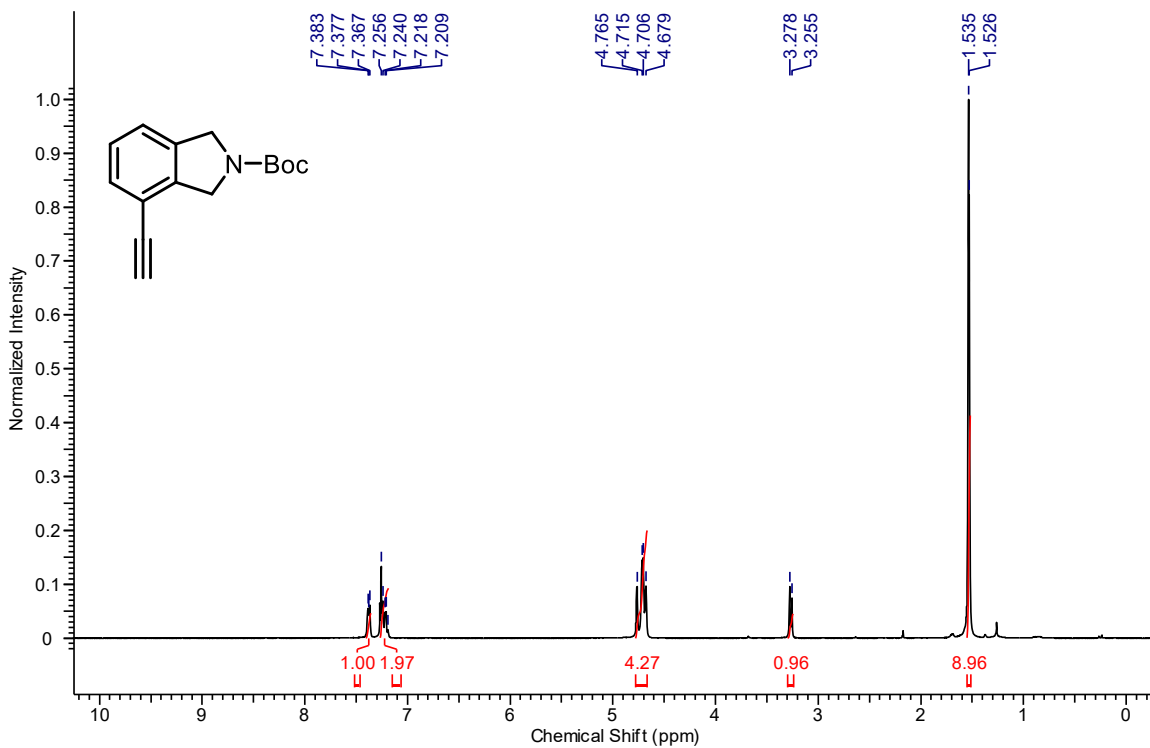
## MOLECULE 6.4a



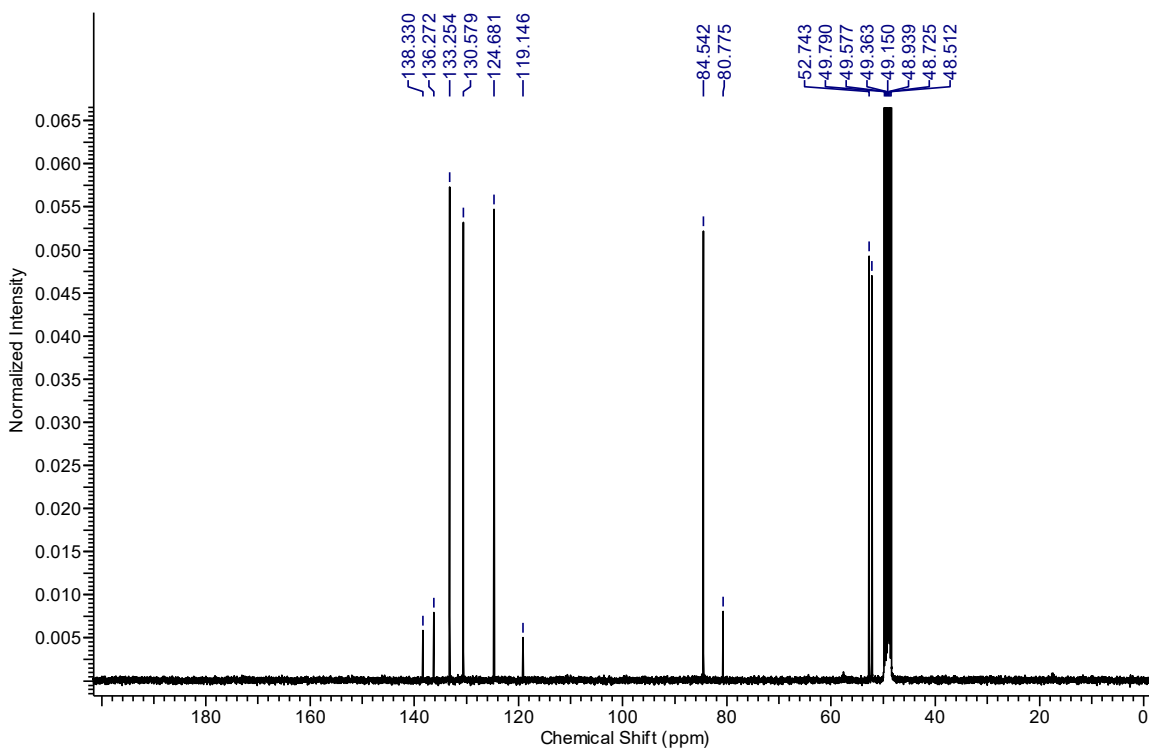
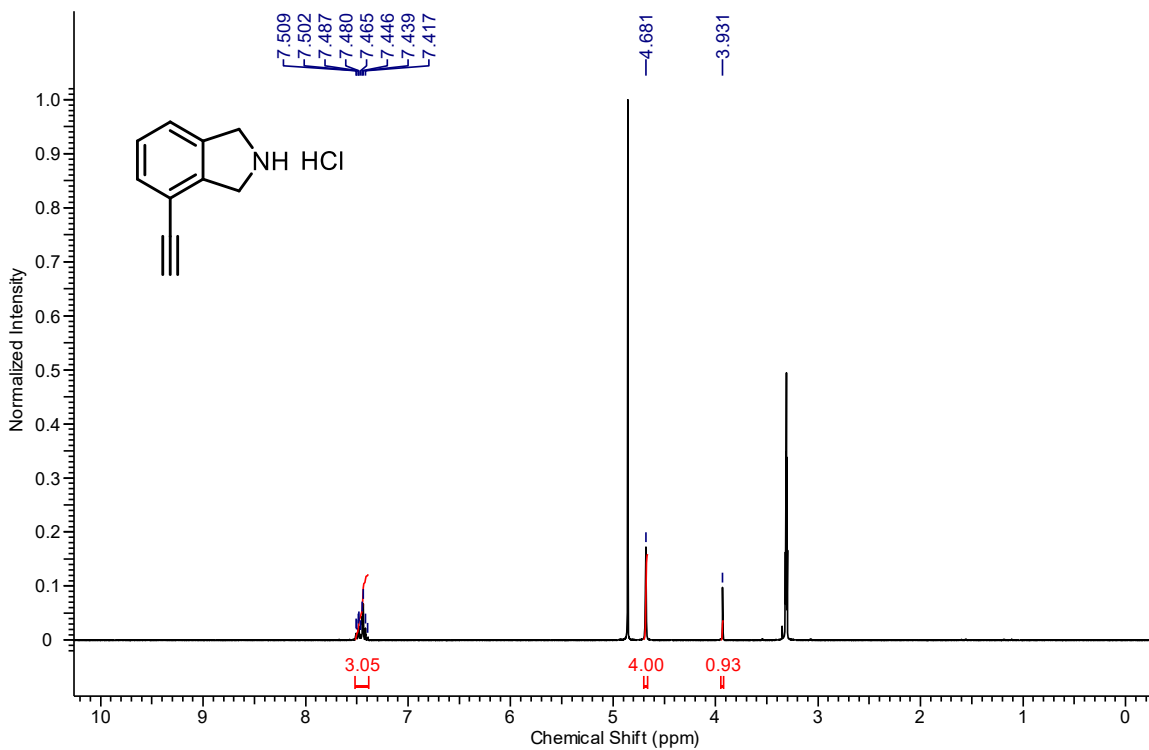
**MOLECULE 6.S1**



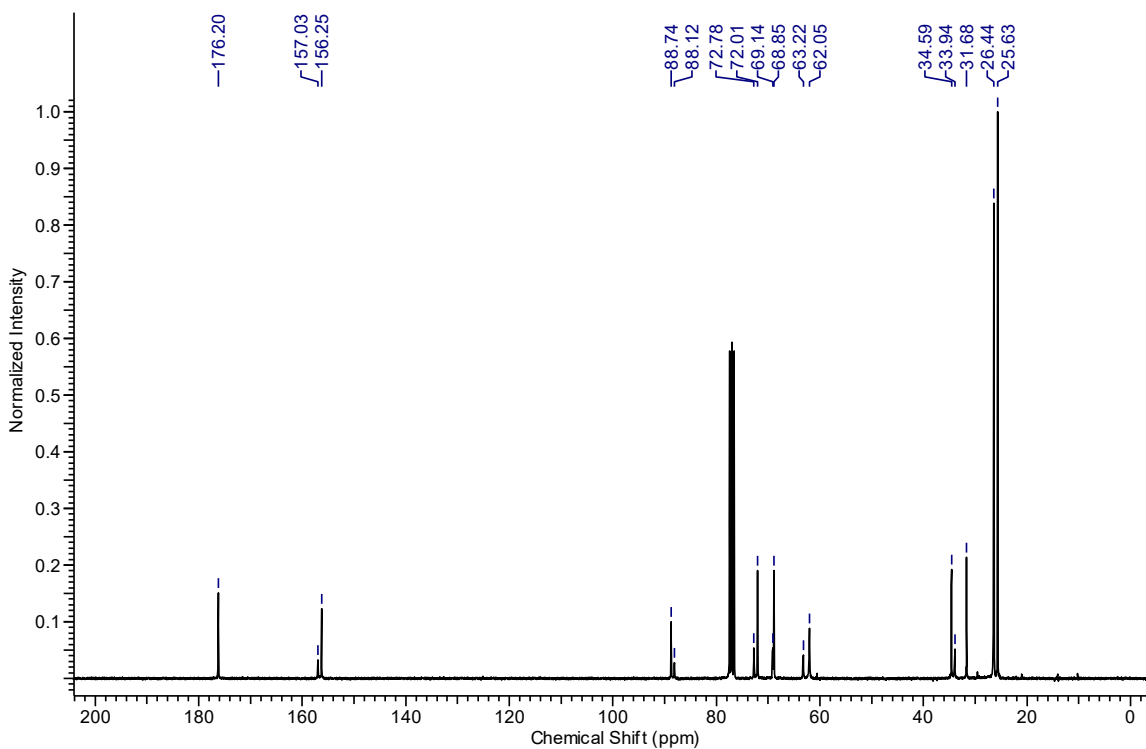
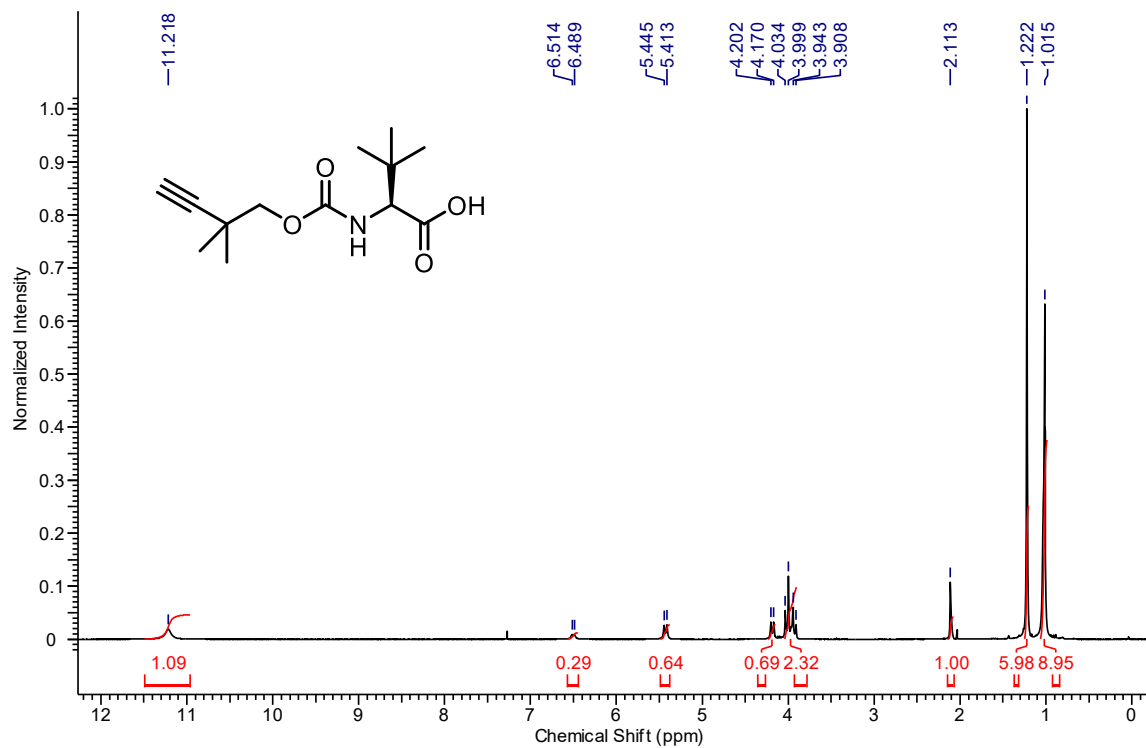
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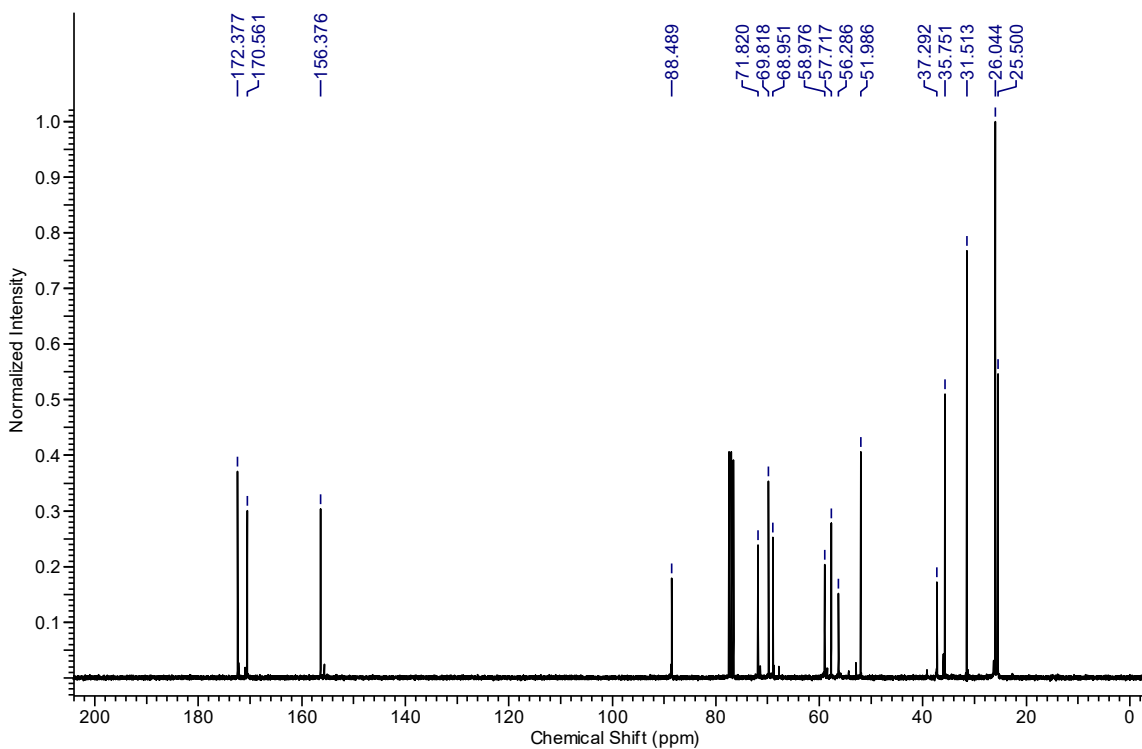
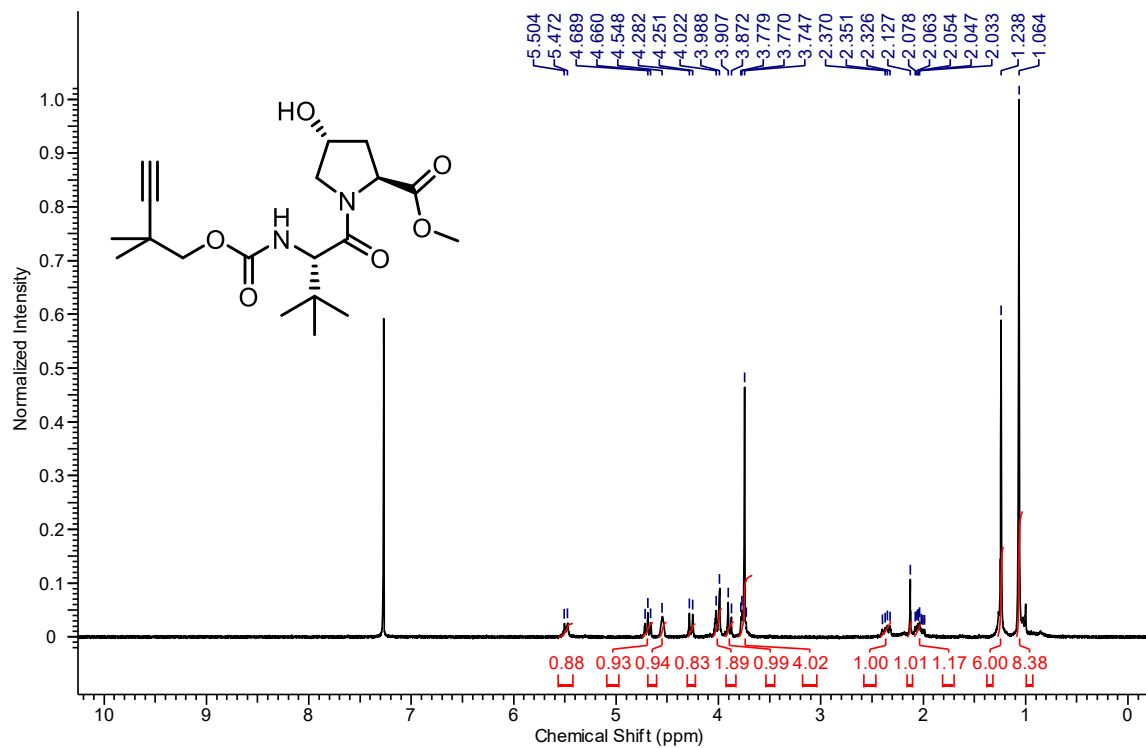
# MOLECULE 6.6



**MOLECULE 6.8**

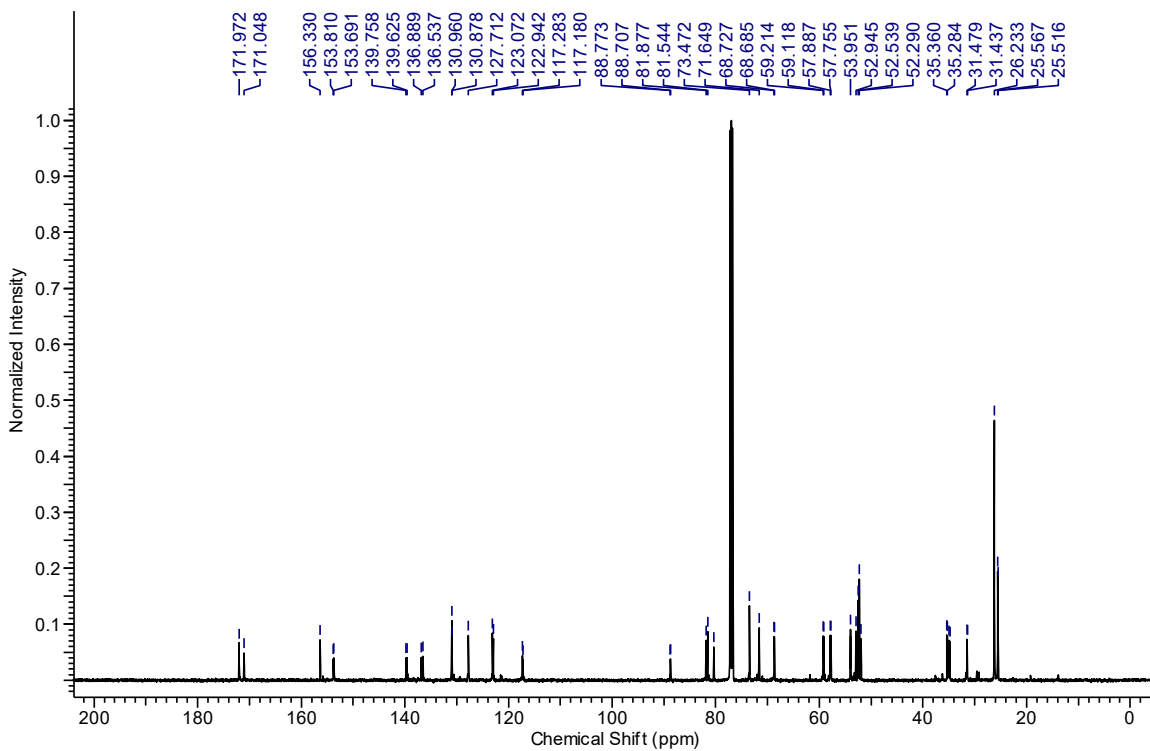
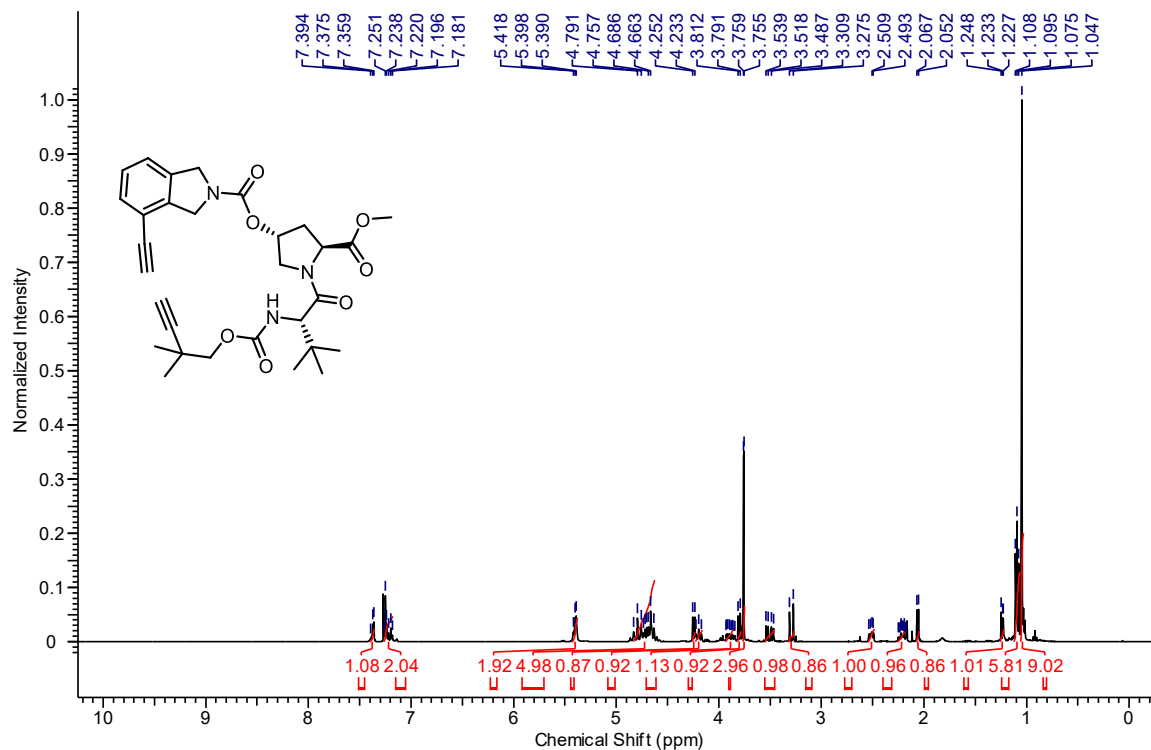


**MOLECULE 6.9**

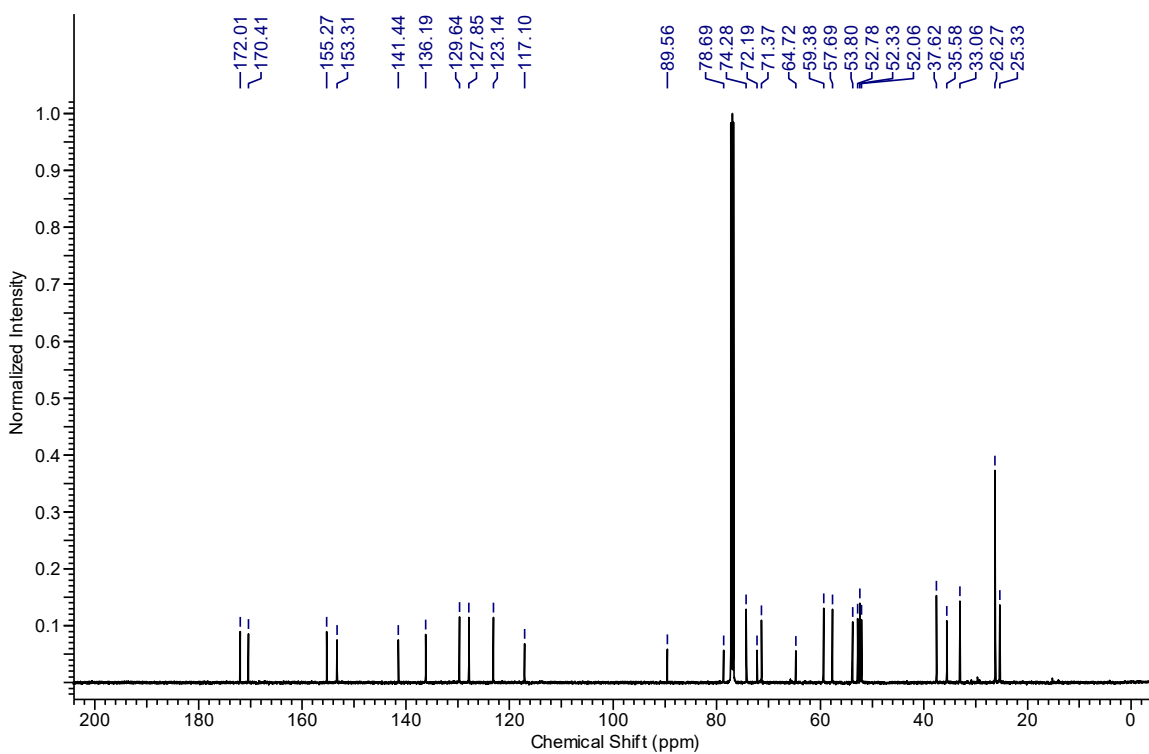
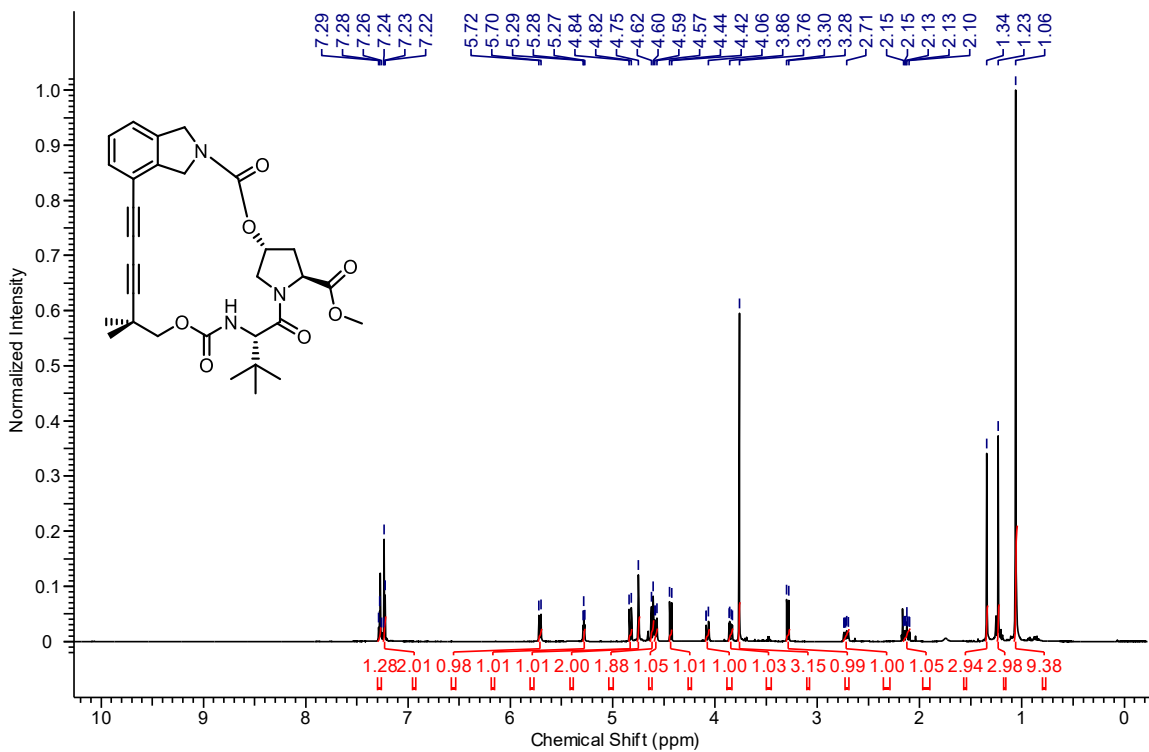




**MOLECULE 6.10**



# MOLECULE 6.11



## Annexe 3. Procédures expérimentales et spectres RMN du

### Chapitre 8

#### GENERAL:

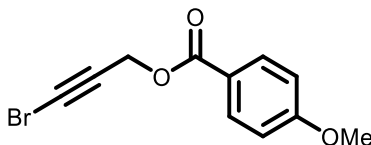
Reactions carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or flame dried and cooled under a stream of argon or nitrogen.<sup>18</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company, Alfa Aesar or Oakwood Chemicals, and were reagent quality. Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>19</sup> on silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plates was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR spectroscopy. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300, AV-400 and AV-500 instruments unless otherwise noted. Signals of solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectrometry (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal on an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

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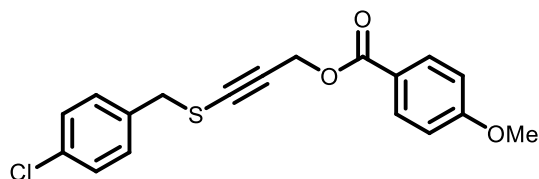
<sup>18</sup> Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

<sup>19</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494-1514.

## SYNTHESIS AND OPTIMIZATION OF INTERMOLECULAR ALKYNYL SULFIDE



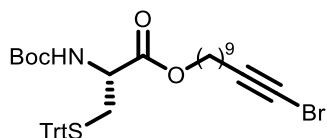
**3-Bromoprop-2-yn-1-yl 4-methoxybenzoate (8.2):** To a stirred solution of prop-2-yn-1-yl 4-methoxybenzoate<sup>20</sup> (1.78 g, 9.36 mmol, 1.0 equiv.) in acetone (47 mL, 0.2 M) were added AgNO<sub>3</sub> (0.318 g, 1.87 mmol, 20 mol%) and NBS (2.00 g, 11.2 mmol, 1.2 equiv.). The reaction was left to stir at room temperature for 30 min. Upon complete conversion (TLC), the reaction mixture was filtered on Celite<sup>®</sup> pad and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100 % hexanes → 5 % diethyl ether in hexanes), the desired product was obtained as a white solid (2.10 g, 83 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.03 (d, *J* = 9.0, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.92 (s, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 165.4, 163.7, 131.9, 121.7, 113.7, 74.4, 55.4, 53.0, 47.0; HRMS (ESI) *m/z* calculated for C<sub>11</sub>H<sub>10</sub>BrO<sub>3</sub> [M+H]<sup>+</sup> 268.9808; found 268.9806.



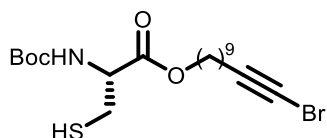
**3-((4-Chlorobenzyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (8.3):** A 118.5 mM solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (88 mg, 0.237 mmol) in acetonitrile (2 mL) was prepared under nitrogen. The solution was then sonicated under nitrogen until complete homogeneity was obtained. Bromoalkyne **8.2** (64 mg, 0.237 mmol, 1.0 equiv.), 4-chlorobenzenemethanethiol (0.034 mL, 0.261 mmol, 1.1 equiv.), dtbbpy (13 mg, 0.0474 mmol, 20 mol%) and 2,6-lutidine (0.055 mL, 0.474 mmol, 2.0 equiv.) were added to an 8 mL screw cap vial equipped with a stir bar. A septum was used to seal the vial and it was secured with parafilm. The vial was then purged with nitrogen for 2 minutes under vacuum. Afterwards, degassed acetonitrile (4.6 mL) was added to the vial under nitrogen. Once the vial was positioned onto a stir plate, the Cu(MeCN)<sub>4</sub>PF<sub>6</sub> solution (0.2 mL, 0.0237 mmol, 10 mol%) was added to the vial in one portion. The reaction mixture was stirred for 10 minutes. Upon completion of the reaction (TLC), concentration of the reaction mixture followed by purification by column chromatography on silica gel (100 % hexanes → 10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (74 mg, 90 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.02 (d, *J* = 9.0 Hz, 2H), 7.30-7.26 (m, 4H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.97 (s, 2H), 3.89 (s, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 165.6, 163.6, 135.0, 133.7, 131.8, 130.4, 128.7, 121.9, 113.7, 90.7, 77.2, 55.4, 53.1, 39.2; HRMS (ESI) *m/z* calculated for C<sub>18</sub>H<sub>16</sub>ClO<sub>3</sub>S [M+H]<sup>+</sup> 347.0503; found 347.0512.

## SYNTHESIS OF MACROCYCLIC ALKYNYL SULFIDES

<sup>20</sup> Wu, X.-F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, 1144-1147.

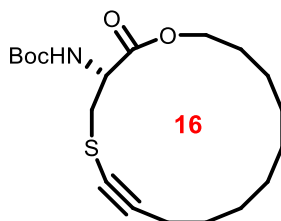


**11-Bromoundec-10-yn-1-yl *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteinate (8.S1):** 11-bromo-10-undecyn-1-ol<sup>21</sup> (890 mg, 3.60 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (2.24 g, 4.68 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (18 mL, 0.2 M). HOBt-H<sub>2</sub>O (730 mg, 5.40 mmol, 1.5 equiv), DIPEA (0.941 mL, 5.40 mmol, 1.5 equiv) and EDC-HCl (1.04 g, 5.40 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (2.13 g, 86 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.44-7.39 (m, 6H), 7.33-7.27 (m, 6H), 7.26-7.21 (m, 3H), 5.08 (d, *J* = 8.0 Hz, 1H), 4.36-4.27 (m, 1H), 4.12 (td, *J* = 6.5, 1.9 Hz, 2H), 2.68-2.53 (m, 2H), 2.21 (t, *J* = 7.0 Hz, 2H), 1.67-1.57 (m, 2H), 1.57-1.49 (m, 2H), 1.49-1.44 (m, 9H), 1.41-1.27 (m, 10H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 170.8, 154.9, 144.3, 129.4, 127.9, 126.8, 80.3, 79.8, 66.7, 65.6, 52.4, 37.5, 34.2, 29.2, 29.1, 28.9, 28.6, 28.4, 28.24, 28.16, 25.7, 19.6; HRMS (ESI) *m/z* calculated for C<sub>38</sub>H<sub>46</sub>BrNO<sub>4</sub>SNa [M+Na]<sup>+</sup> 714.2223; found 714.2229.

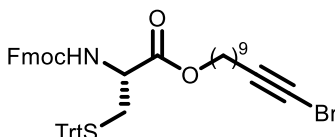


**11-Bromoundec-10-yn-1-yl (*tert*-butoxycarbonyl)-*L*-cysteinate (8.4):** Cysteine derivative **8.S1** (1.13 g, 1.63 mmol, 1 equiv) was added to a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (16.3 mL, 0.1 M) was then added followed by triethylsilane (1.30 mL, 8.16 mmol, 5 equiv). TFA (0.631 mL, 8.16 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. Upon completion (TLC), the reaction was quenched with triethylamine (0.6 mL). The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (5 % → 10 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (73 mg, 76 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 5.48-5.34 (m, 1H), 4.65-4.51 (m, 1H), 4.20-4.13 (m, 2H), 2.98 (dd, *J* = 8.8, 4.2 Hz, 2H), 2.20 (t, *J* = 6.9 Hz, 2H), 1.72-1.59 (m, 4H), 1.56-1.46 (m, 2H), 1.45 (s, 9H), 1.43-1.31 (m, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 170.4, 155.1, 80.4, 80.2, 66.0, 54.8, 37.5, 29.3, 29.1, 29.0, 28.7, 28.5, 28.3, 28.2, 27.4, 25.8, 19.7; HRMS (ESI) *m/z* calculated for C<sub>19</sub>H<sub>32</sub>BrNO<sub>4</sub>SNa [M+Na]<sup>+</sup> 472.1138; found 472.1128.

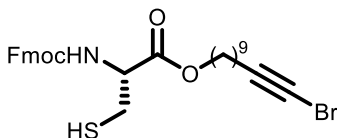
<sup>21</sup> Yamagishi, M.; Nishigai, K.; Ishii, A.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6471-6474.



**tert-Butyl (R)-(2-oxo-1-oxa-5-thiacyclohexadec-6-yn-3-yl)carbamate (8.5):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (8.6 mg, 0.032 mmol, 20 mol%) and 2,6-lutidine (0.037 mL, 0.32 mmol, 2 equiv). The flask was purged with nitrogen, then degassed acetonitrile (20 mL, 2/3 of total volume, 5 mM final concentration) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.2 mL, 0.016 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.4** (73 mg, 0.16 mmol, 1 equiv) was dissolved in degassed acetonitrile (12 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0167 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (10 % ethyl acetate in hexanes), the desired product was obtained as a white solid (32 mg, 56 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 5.43-5.28 (m, 1H), 4.70-4.58 (m, 1H), 4.34-4.25 (m, 1H), 4.25-4.16 (m, 1H), 3.31-3.20 (m, 1H), 2.97-2.84 (m, 1H), 2.40-2.33 (m, 2H), 1.79-1.65 (m, 2H), 1.58-1.47 (m, 6H), 1.46 (s, 9H), 1.45-1.38 (m, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 170.7, 155.1, 95.5, 80.2, 67.6, 65.9, 54.0, 38.0, 28.3, 27.9, 27.7, 27.4, 27.1, 26.8, 26.7, 25.5, 19.6; HRMS (ESI) m/z calculated for C<sub>19</sub>H<sub>31</sub>NO<sub>4</sub>SNa [M+Na]<sup>+</sup> 392.1866; found 392.1866.

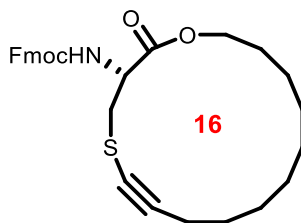


**3-Bromoprop-2-yn-1-yl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinate (8.S2):** 11-Bromo-10-undecyn-1-ol (1.14 g, 4.63 mmol, 1 equiv) and *N*-Fmoc-*S*-trityl-*L*-cysteine (3.52 g, 6.01 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (46 mL, 0.1 M). HOBt-H<sub>2</sub>O (750 mg, 5.55 mmol, 1.5 equiv), DIPEA (0.967 mL, 5.55 mmol, 1.5 equiv) and EDC-HCl (887 mg, 5.55 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 % → 20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (2.55 g, 69 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.78 (dd, *J* = 7.3, 3.1 Hz, 2H), 7.62 (dd, *J* = 7.2, 2.9 Hz, 2H), 7.45 – 7.38 (m, 8H), 7.35 – 7.28 (m, 6H), 7.27 – 7.19 (m, 5H), 5.28 (d, *J* = 8.3 Hz, 1H), 4.43 – 4.31 (m, 3H), 4.24 (t, *J* = 7.0 Hz, 1H), 4.12 (t, *J* = 6.7 Hz, 2H), 2.69 (dd, *J* = 12.3, 6.1 Hz, 1H), 2.62 (dd, *J* = 12.3, 4.6 Hz, 1H), 2.20 (t, *J* = 7.0 Hz, 2H), 1.66-1.57 (m, 2H), 1.54 - 1.45 (m, 2H), 1.40 - 1.23 (m, 10H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 170.6, 155.6, 144.3, 143.9, 143.7, 141.3, 129.5, 128.0, 127.7, 127.1, 126.9, 125.2, 120.0, 80.4, 67.1, 65.9, 52.9, 47.1, 37.5, 34.2, 29.3, 29.1, 29.0, 28.7, 28.5, 28.2, 25.8, 19.7. HRMS (ESI) m/z calculated for C<sub>48</sub>H<sub>48</sub>BrNO<sub>4</sub>SNa [M+Na]<sup>+</sup> 836.2378; found 836.2380.



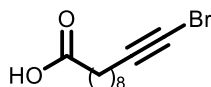
**3-Bromoprop-2-yn-1-yl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-cysteinate (8.S3):**

Cysteine derivative **8.S2** (190 mg, 0.233 mmol, 1 equiv) was added to a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $\text{CH}_2\text{Cl}_2$  (2.3 mL, 0.1 M) was then added followed by triisopropylsilane (0.77 mL, 1.17 mmol, 5 equiv). TFA (0.090 mL, 1.17 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. Upon completion (TLC), the crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (5 %  $\rightarrow$  10 % ethyl acetate in hexanes), the desired product was obtained as a sticky yellowish solid (73 mg, 76 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.78 (d,  $J$  = 7.6 Hz, 2H), 7.62 (d,  $J$  = 7.3 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.31 (m, 2H), 5.70 (d,  $J$  = 7.1 Hz, 2H), 4.70 – 4.63 (m, 1H), 4.48 – 4.37 (m, 2H), 4.30 – 4.13 (m, 3H), 3.07 – 2.98 (m, 2H), 2.20 (t,  $J$  = 7.0 Hz, 2H), 1.71 – 1.63 (m, 2H), 1.55 – 1.47 (m, 2H), 1.38 – 1.29 (m, 10H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.0, 155.6, 143.6, 141.3, 129.5, 127.8, 127.1, 125.1, 120.0, 80.4, 67.1, 66.1, 55.2, 47.2, 37.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.2, 25.8, 19.6. HRMS (ESI)  $m/z$  calculated for  $\text{C}_{29}\text{H}_{34}\text{BrNO}_4\text{SNa}$   $[\text{M}+\text{Na}]^+$  594.1288; found 594.1284.

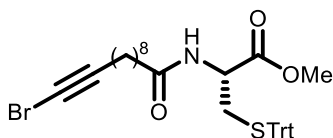


**(9H-Fluoren-9-yl)methyl (R)-(2-oxo-1-oxa-5-thiacyclohexadec-6-yn-3-yl)carbamate (8.6):**

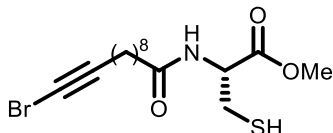
To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.6 mg, 0.035 mmol, 20 mol%) and 2,6-lutidine (0.041 mL, 0.35 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (48 mL, 2/3 of total volume, 2.5 mM final concentration) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (0.147 mL, 0.018 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S3** (101 mg, 0.18 mmol, 1 equiv) was dissolved in degassed acetonitrile (23 mL, 1/3 of total volume), transferred into a 60 mL syringe and added dropwise over 12 h using a syringe pump (0.0167 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (5 %  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a white solid (41 mg, 47 % yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.78 (d,  $J$  = 7.5 Hz, 2H), 7.62 (d,  $J$  = 7.4 Hz, 2H), 7.41 (dd,  $J$  = 7.0, 7.0 Hz, 2H), 7.33 (dd,  $J$  = 7.4, 7.4 Hz, 2H), 5.61 (d,  $J$  = 8.1 Hz, 2H), 4.81 – 4.70 (m, 1H), 4.49 – 4.41 (m, 2H), 4.34 – 4.20 (m, 3H), 3.33 (dd,  $J$  = 13.4, 3.7 Hz, 1H), 2.91 (dd,  $J$  = 13.2, 7.9 Hz, 1H), 2.45 – 2.27 (m, 2H), 1.80 – 1.63 (m, 2H), 1.58 – 1.35 (m, 12H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.4, 155.8, 143.7, 141.3, 127.7, 127.1, 125.1, 120.0, 95.8, 67.2, 67.1, 66.2, 54.0, 47.1, 38.0, 27.8, 27.7, 27.4, 27.1, 26.9, 26.7, 25.6, 19.5. HRMS (ESI)  $m/z$  calculated for  $\text{C}_{29}\text{H}_{34}\text{NO}_4\text{S}$   $[\text{M}+\text{H}]^+$  492.2194; found 492.2203.



**11-Bromo-10-undecynoic acid (8.S4):** To a stirred solution of 10-undecynoic acid (1.0 g, 5.49 mmol, 1.0 equiv) in acetone (27 mL, 0.2 M) were added AgNO<sub>3</sub> (187 mg, 1.10 mmol, 20 mol%) and NBS (1.47 g, 8.24 mmol, 1.2 equiv). The reaction was stirred at room temperature for 2 h. Upon complete conversion (TLC), the reaction mixture was filtered on Celite<sup>®</sup> pad and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20 % ethyl acetate in hexanes), the desired product was obtained as a white solid (1.40 g, 98 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 11.75 (bs, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 7.0 Hz, 2H), 1.68-1.58 (m, 2H), 1.55-1.45 (m, 2H), 1.42-1.24 (m, 8H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 180.5, 80.3, 37.5, 34.5, 29.0, 28.9, 28.8, 28.6, 28.2, 24.5, 19.6; HRMS (ESI) *m/z* calculated for C<sub>11</sub>H<sub>17</sub>BrO<sub>2</sub>Na [M+Na]<sup>+</sup> 283.0304; found 283.0303.



**Methyl *N*-(11-bromoundec-10-ynoyl)-*S*-trityl-*L*-cysteinate (8.S5):** 11-Bromo-10-undecynoic acid (200 mg, 0.77 mmol, 1 equiv), *S*-trityl-*L*-cysteine methyl ester hydrochloride<sup>22</sup> (378 mg, 1.0 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (7 mL, 0.1 M). HOBt-H<sub>2</sub>O (179 mg, 1.15 mmol, 1.5 equiv), DIPEA (0.2 mL, 1.15 mmol, 1.5 equiv) and EDC-HCl (221 mg, 1.15 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20 % → 30 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (384 mg, 80 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.42-7.38 (m, 6H), 7.32-7.27 (m, 6H), 7.26-7.21 (m, 3H), 5.93 (d, *J* = 7.8 Hz, 1H), 4.62 (dt, *J* = 7.8, 5.2 Hz, 1H), 3.72 (s, 3H), 2.67 (d, *J* = 5.2 Hz, 2H), 2.23-2.14 (m, 4H), 1.67-1.58 (m, 2H), 1.54-1.46 (m, 2H), 1.40-1.29 (m, 8H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.7, 171.0, 144.2, 129.4, 127.9, 126.8, 80.4, 66.8, 52.5, 50.9, 37.5, 36.3, 33.7, 29.1, 29.0, 28.8, 28.6, 28.1, 25.4, 19.6; HRMS (ESI) *m/z* calculated for C<sub>34</sub>H<sub>38</sub>BrNO<sub>3</sub>SNa [M+Na]<sup>+</sup> 642.1648; found 642.1616.

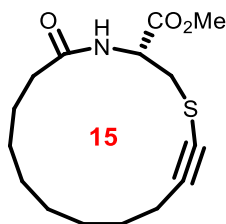


**Methyl (11-bromoundec-10-ynoyl)-*L*-cysteinate (8.S6):** Cysteine derivative **8.S5** (139 mg, 0.22 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.1M) was then added followed by triisopropylsilane (0.23 mL, 1.12 mmol, 5 equiv). TFA (0.08 mL, 1.12 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. The crude

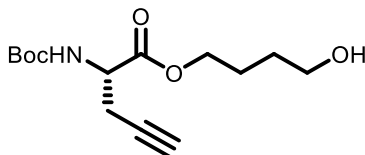
<sup>22</sup> Mays, J. R.; Restituyo, J. A.; Katzenberger, R. J.; Wassarman, D. A.; Rajski, S. R. *Tetrahedron Lett.* **2007**, *48*, 4579-4583.



product was concentrated under reduced pressure and purified by column chromatography on silica gel (30 % ethyl acetate in hexanes), the desired product was obtained as an amber oil (69 mg, 83 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.39-6.33 (m, 1 H), 4.91 (dt,  $J$  = 7.7, 4.0 Hz, 1H), 3.81 (s, 3H), 3.04 (dd,  $J$  = 3.9, 1.6 Hz, 1H), 3.02 (dd,  $J$  = 3.9, 1.6 Hz, 1H), 2.28 (t,  $J$  = 7.4 Hz, 2H), 2.20 (t,  $J$  = 7.0 Hz, 2H), 1.71-1.61 (m, 2H), 1.56-1.47 (m, 2H), 1.42-1.27 (m, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.1, 170.6, 80.4, 77.2, 53.4, 52.8, 37.5, 36.5, 29.1, 28.9, 28.7, 28.2, 26.9, 25.5, 19.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{25}\text{BrNO}_3\text{S}$   $[\text{M}+\text{H}]^+$  378.0738; found 378.0733.

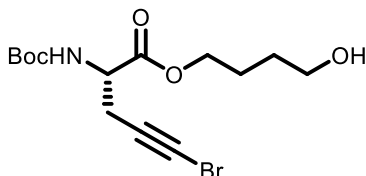


**Methyl (R)-5-oxo-1-thia-4-azacyclopentadec-14-yne-3-carboxylate (8.7):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.1 mg, 0.034 mmol, 20 mol%) and 2,6-lutidine (0.039 mL, 0.34 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (22.6 mL, 2/3 of total volume) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (0.2 mL, 0.017 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S6** (65 mg, 0.17 mmol, 1 equiv) was dissolved in degassed acetonitrile (11.3 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0157 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (30 %  $\rightarrow$  40 % ethyl acetate in hexanes), the desired product was obtained as a white solid (26 mg, 50 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.51 (d,  $J$  = 6.8 Hz, 1H), 5.07-5.00 (m, 1H), 3.77 (s, 3H), 3.27 (dd,  $J$  = 14.0, 5.2 Hz, 1H), 3.14 (dd,  $J$  = 14.0, 3.7 Hz, 1H), 2.41-2.24 (m, 4H), 1.85-1.73 (m, 1H), 1.68-1.58 (m, 1H), 1.51-1.36 (m, 10H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.2, 170.5, 95.1, 67.9, 52.7, 52.4, 37.9, 36.5, 26.7, 26.49, 26.46, 26.1, 25.5, 24.8, 19.4; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$  298.1471; found 298.1476.

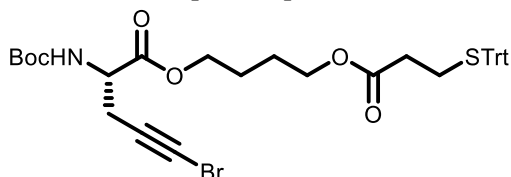


**4-Hydroxybutyl (S)-2-((tert-butoxycarbonyl)amino)pent-4-ynoate (8.S7):** Boc-*L*-propargylglycine (1 g, 4.69 mmol, 1 equiv) and 1,4-butanediol (1.04 mL, 11.7 mmol, 2.5 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (23 mL, 0.2 M). HOBt- $\text{H}_2\text{O}$  (751 mg, 7.03 mmol, 1.5 equiv), DIPEA (1.23 mL, 7.03 mmol, 1.5 equiv) and EDC-HCl (1.35 g, 7.03 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (40 %  $\rightarrow$  50 % ethyl acetate in hexanes) to give the desired product as a colorless oil (993 mg, 74 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.37 (d,  $J$  = 8.0 Hz, 1H), 4.49-4.40 (m, 1H), 4.30-4.15 (m, 2H), 3.67 (t,  $J$  = 6.4 Hz, 2H), 2.82-2.66 (m, 2H), 2.05 (t,

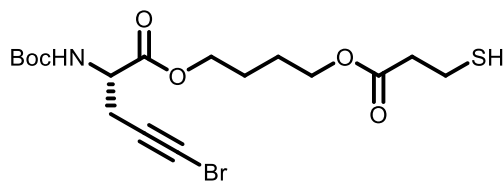
$J = 2.5$  Hz, 1H), 1.82-1.71 (m, 2H), 1.69-1.59 (m, 2H), 1.45 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 170.7, 155.1, 80.2, 78.5, 71.6, 65.5, 62.1, 51.9, 28.9, 28.2, 25.0, 22.8$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{23}\text{NO}_5\text{Na}$   $[\text{M}+\text{Na}]^+$  308.1468; found 308.1472.



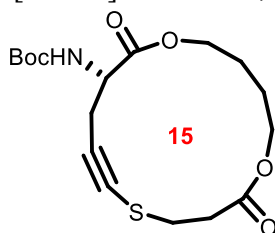
**4-Hydroxybutyl (*S*)-5-bromo-2-((*tert*-butoxycarbonyl)amino)pent-4-ynoate (8.S8):** To a stirred solution of propargylglycine derivative **8.S7** (697 mg, 2.44 mmol, 1.0 equiv) in acetone (12 mL, 0.2 M) were added  $\text{AgNO}_3$  (20.7 mg, 0.122 mmol, 5 mol%) and NBS (522 mg, 2.93 mmol, 1.2 equiv). The reaction was stirred at room temperature for 30 min. Upon complete conversion (TLC), the reaction mixture was filtered on Celite<sup>®</sup> pad and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (40 %  $\rightarrow$  50 % ethyl acetate in hexanes) to give the desired product as a colorless oil (736 mg, 83 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 5.35$  (d,  $J = 8.0$  Hz, 1H), 4.47-4.40 (m, 1H), 4.31-4.34 (m, 1H), 4.23-4.16 (m, 1H), 3.68 (t,  $J = 6.3$  Hz, 2H), 2.84-2.69 (m, 2H), 1.88-1.73 (m, 2H), 1.69-1.61 (m, 2H), 1.46 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 170.6, 155.0, 80.3, 74.7, 65.6, 62.2, 52.0, 41.7, 28.9, 28.3, 25.0, 24.1$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{22}\text{BrNO}_5\text{Na}$   $[\text{M}+\text{Na}]^+$  386.0574; found 386.0584.



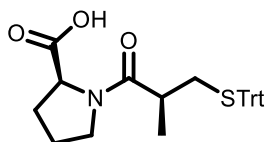
**4-((3-(Tritylthio)propanoyl)oxy)butyl (*S*)-5-bromo-2-((*tert*-butoxycarbonyl)amino)-pent-4-ynoate (8.S9):** Brominated propargylglycine derivative **8.S8** (736 mg, 2.02 mmol, 1 equiv), 3-(tritylthio)propionic acid (845 mg, 2.42 mmol, 1.2 equiv) were dissolved in  $\text{CH}_2\text{Cl}_2$  (18 mL, 0.1 M). DCC (625 mg, 3.03 mmol, 1.5 equiv) and DMAP (247 mg, 2.02 mmol, 1 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), the precipitated urea was filtered and filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 %  $\rightarrow$  20 % ethyl acetate in hexanes) to give the desired product as a sticky colorless oil (1.37 g, 98 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.46$ -7.40 (m, 6H), 7.32-7.27 (m, 6H), 7.25-7.19 (m, 3H), 5.32 (d,  $J = 8.0$  Hz, 1H), 4.49-4.40 (m, 1H), 4.29-4.20 (m, 1H), 4.20-4.11 (m, 1H), 4.07 (t,  $J = 5.7$  Hz, 2H), 2.83-2.68 (m, 2H), 2.46 (t,  $J = 7.2$  Hz, 2H), 2.25 (t,  $J = 7.2$  Hz, 2H), 1.74-1.66 (m, 4H), 1.47 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 171.8, 170.5, 155.0, 144.6, 129.5, 127.9, 126.7, 80.3, 74.7, 66.8, 65.2, 63.9, 52.0, 41.8, 33.5, 28.3, 26.9, 25.2, 25.1, 24.2$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{36}\text{H}_{40}\text{BrNO}_6\text{SNa}$   $[\text{M}+\text{Na}]^+$  716.1652; found 716.1659.



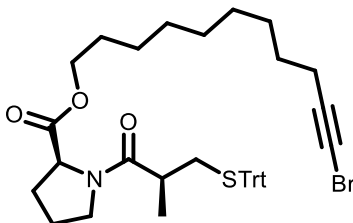
**4-((3-Mercaptopropanoyl)oxy)butyl (S)-5-bromo-2-((tert-butoxycarbonyl)amino)-pent-4-ynoate (8.S10):** Trityl-protected propargylglycine derivative **8.S9** (500 mg, 0.72 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $\text{CH}_2\text{Cl}_2$  (7.2 mL, 0.1M) was then added followed by triethylsilane (0.575 mL, 3.60 mmol, 5 equiv). TFA (0.276 mL, 3.60 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 30 min. Upon completion (TLC), the reaction was quenched with triethylamine (0.27 mL). The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (10 %  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (252 mg, 77 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.34 (d,  $J$  = 7.9 Hz, 1H), 4.51-4.40 (m, 1H), 4.33-4.23 (m, 1H), 4.22-4.10 (m, 3H), 2.84-2.73 (m, 4H), 2.66 (t,  $J$  = 6.6 Hz, 2H), 1.80-1.71 (m, 4H), 1.64 (t,  $J$  = 8.3 Hz, 1H), 1.46 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.6, 170.5, 155.0, 80.3, 74.7, 65.2, 64.0, 52.0, 41.8, 38.4, 28.2, 25.2, 25.1, 24.1, 19.7; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{26}\text{BrNO}_6\text{SNa}$   $[\text{M}+\text{Na}]^+$  474.0556; found 474.0553.



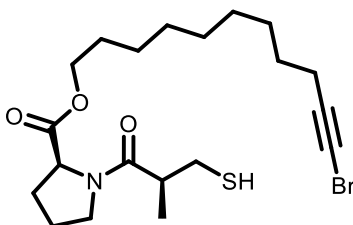
**tert-Butyl-(S)-(2,10-dioxo-1,11-dioxa-5-thiacyclopentadec-6-yn-9-yl)carbamate (8.8):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.1 mg, 0.0332 mmol, 20 mol%) and 2,6-lutidine (0.0386 mL, 0.332 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (22.1 mL, 2/3 of total volume) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (0.138 mL, 0.0166 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S10** (75 mg, 0.166 mmol, 1 equiv) was dissolved in degassed acetonitrile (11 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0153 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (20%  $\rightarrow$  30% ethyl acetate in hexanes), the macrocycle was obtained as a colorless sticky oil (32 mg, 52 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.39 (d,  $J$  = 8.0 Hz, 1H), 4.57-4.44 (m, 2H), 4.30-4.20 (m, 2H), 4.17-4.09 (m, 1H), 3.05-2.95 (m, 2H), 2.95-2.86 (m, 1H), 2.83-2.70 (m, 3H), 1.93-1.82 (m, 2H), 1.82-1.72 (m, 2H), 1.46 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.1, 170.7, 155.1, 89.8, 80.2, 71.2, 65.1, 64.6, 52.4, 34.4, 29.7, 28.3, 26.3, 25.2, 24.8; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{25}\text{NO}_6\text{SNa}$   $[\text{M}+\text{Na}]^+$  394.1295; found 394.1305.



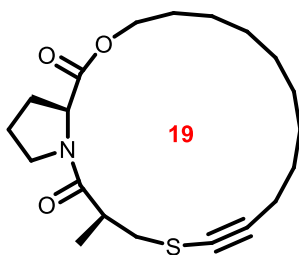
**(2-Methyl-3-(tritylthio)propanoyl)proline (8.S11):** A solution of ((*S*)-3-mercapto-2-methylpropanoyl)-*L*-proline (Captopril) (400 mg, 1.84 mmol, 1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise to a solution of triphenylmethyl chloride (513 mg, 1.84 mmol, 1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (9.2 mL, 0.2 M) and the reaction mixture was stirred 12 h at room temperature. Upon completion, the reaction mixture was extracted with NaOH 1M. The aqueous phase was acidified with HCl 1M and extracted with EtOAc. The organic phase was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The product was obtained as a white solid (724 mg, 86 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.48 – 7.37 (m, 6H), 7.34 – 7.23 (m, 6H), 7.23 – 7.16 (m, 3H), 4.42 – 4.19 (m, 1H), 3.35 – 3.20 (m, 1H), 3.20 – 3.04 (m, 1H), 2.74 – 2.61 (m, 1H), 2.22 – 2.00 (m, 3H), 2.00 – 1.84 (m, 2H), 1.82 – 1.67 (m, 1H), 1.00 – 0.80 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 174.7, 144.8, 129.6, 127.8, 126.6, 66.9, 47.2, 38.2, 35.0, 29.7, 28.5, 24.7, 16.9; HRMS (ESI) m/z calculated for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>SNa [M+Na]<sup>+</sup>: 482.1760; found: 482.1766.



**11-Bromoundec-10-yn-1-yl ((*S*)-2-methyl-3-(tritylthio)propanoyl)-*L*-prolinate (8.S12):** (2-Methyl-3-(tritylthio)propanoyl)proline (128 mg, 0.279 mmol, 1 equiv) and 11-bromoundec-10-yn-1-ol (69 mg, 0.279 mmol, 1 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (2.8 mL, 0.1 M). DIPEA (0.101 mL, 0.557 mmol, 2 equiv) and HATU (233 mg, 0.557 mmol, 2 equiv) were added and the mixture was left to stir at room temperature for 36 h. When the reaction was complete (TLC), distilled water was added and the phases were separated. The organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (30 % ethyl acetate in hexanes) to give the desired product as a white solid (145 mg, 76 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.47 – 7.36 (m, 6H), 7.32 – 7.24 (m, 6H), 7.24 – 7.17 (m, 3H), 4.45 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.13 – 4.01 (m, 2H), 3.44 – 3.35 (m, 1H), 3.32 – 3.24 (m, 1H), 2.74 (dd, *J* = 12.1, 7.2 Hz, 1H), 2.24 – 2.09 (m, 5H), 2.01 – 1.86 (m, 3H), 1.65 – 1.55 (m, 2H), 1.54 – 1.46 (m, 2H), 1.41 – 1.24 (m, 10H), 1.01 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 173.5, 172.3, 144.8, 129.6, 127.8, 126.5, 80.4, 66.8, 65.0, 58.6, 46.6, 38.1, 37.4, 34.9, 29.2, 29.1, 29.0, 28.9, 28.7, 28.5, 28.2, 25.7, 24.7, 19.6, 17.0; HRMS (ESI) m/z calculated for C<sub>39</sub>H<sub>46</sub>BrNO<sub>3</sub>SNa [M+Na]<sup>+</sup> 710.2274; found 710.2277.

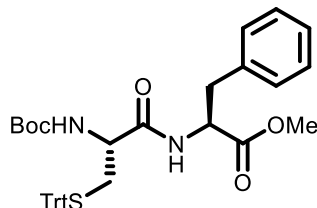


**11-Bromoundec-10-yn-1-yl ((S)-3-mercapto-2-methylpropanoyl)-L-prolinate (8.S13):** Trityl-protected Captopril derivative **8.S12** (145 mg, 0.21 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (2.1 mL, 0.1 M) was then added followed by triisopropylsilane (0.216 mL, 1.05 mmol, 5 equiv). TFA (0.081 mL, 1.055 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 18 h. Upon completion (TLC), the reaction was washed with saturated aqueous NaHCO<sub>3</sub> solution. The organic phase was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (25 % ethyl acetate in hexanes) to give the desired product as a white solid (59.4 mg, 63 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.55 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.71 – 3.63 (m, 2H), 2.98 – 2.88 (m, 1H), 2.83 – 2.73 (m, 1H), 2.44 (ddd, *J* = 14.6, 9.5, 5.0 Hz, 1H), 2.26 – 2.17 (m, 3H), 2.12 – 1.96 (m, 3H), 1.67 – 1.57 (m, 3H), 1.54 – 1.46 (m, 2H), 1.35 – 1.25 (m, 10H), 1.22 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 173.4, 172.3, 80.4, 65.1, 58.7, 46.9, 42.5, 37.4, 29.3, 29.13, 29.11, 28.9, 28.7, 28.5, 28.2, 27.6, 25.8, 24.8, 19.6, 17.0; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>33</sub>BrNO<sub>3</sub>S [M+H]<sup>+</sup> 446.1359; found: 446.1357.

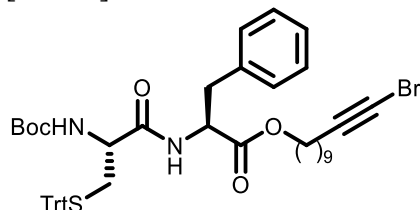


**(16S,21aS)-16-methyl-4,5,6,7,8,9,10,11,15,16,19,20,21,21a-tetradecahydro-1H,3H,17H-pyrrolo[2,1-c][1]oxa[8]thia[4]azacyclononadec-12-yne-1,17-dione (8.9):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.46 mg, 0.0345 mmol, 20 mol%) and 2,6-lutidine (0.0402 mL, 0.345 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (19.3 mL, 2/3 of total volume, 5 mM final concentration) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.144 mL, 0.0173 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S13** (77.1 mg, 0.173 mmol, 1 equiv) was dissolved in degassed acetonitrile (9.7 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0135 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (40% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (32 mg, 52 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.49 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.11 - 2.98 (m, 2H), 2.69 – 2.54 (m, 1H), 2.26 – 2.14 (m, 3H), 2.11 – 1.92 (m, 3H), 1.67 – 1.55 (m, 2H), 1.55 – 1.45 (m, 2H), 1.40 – 1.26 (m, 10H), 1.24 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 173.4, 172.3, 84.7, 80.4, 68.1, 65.1, 58.7, 46.9,

41.1, 37.6, 29.3, 29.10, 28.91, 28.7, 28.5, 28.2, 25.7, 24.7, 19.6, 16.9; HRMS (ESI)  $m/z$  calculated for  $C_{20}H_{32}NO_3S [M+H]^+$  366.2097; found 366.2084.

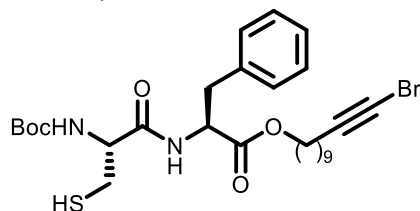


**Methyl *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteinyl-*L*-phenylalaninate (8.S14):** *N*-Boc-*S*-trityl-*L*-cysteine (200 mg, 0.43 mmol, 1 equiv), *L*-phenylalanine methyl ester hydrochloride (121 mg, 0.56 mmol, 1.3 equiv) were dissolved in dry  $CH_2Cl_2$  (4 mL, 0.1 M). HOBt- $H_2O$  (101 mg, 0.65 mmol, 1.5 equiv), DIPEA (0.11 mL, 0.65 mmol, 1.5 equiv) and EDC-HCl (124 mg, 0.65 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $CH_2Cl_2$ . The combined organic phases were washed with brine, dried ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (30 % ethyl acetate in hexanes), the desired product was obtained as a white solid (240 mg, 89 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.46-7.37 (m, 6H), 7.33-7.27 (m, 6H), 7.26-7.18 (m, 6H), 7.12-7.05 (m, 2H), 6.54-6.44 (m, 1H), 4.82-4.74 (m, 1H), 4.71-4.59 (m, 1H), 3.90-3.78 (m, 1H), 3.68 (s, 3H), 3.12 (dd,  $J$  = 13.9, 5.8 Hz, 1H), 3.06 (dd,  $J$  = 13.7, 6.0 Hz, 1H), 2.78-2.67 (m, 1H), 2.52 (dd,  $J$  = 13.0, 4.9 Hz, 1H), 1.41 (s, 9H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  = 171.3, 170.1, 144.4, 135.7, 129.5, 129.4, 128.5, 128.1, 127.0, 126.9, 67.2, 53.3, 53.2, 52.2, 37.8, 33.6, 29.7, 28.2; HRMS (ESI)  $m/z$  calculated for  $C_{37}H_{40}N_2O_5SNa [M+Na]^+$  647.2550; found 647.2560.

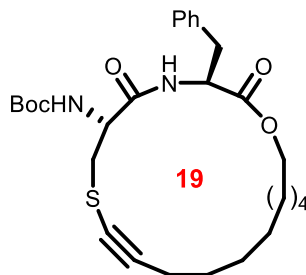


**11-Bromoundec-10-yn-1-yl *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteinyl-*L*-phenylalaninate (8.S15):** In a round bottom flask equipped with a stir bar, the dipeptide **8.S14** (240 mg, 0.38 mmol, 1 equiv) was dissolved in THF/MeOH (2:1) (1.5 mL, 0.25 M) and a solution of sodium hydroxide (30 mg, 0.76 mmol, 2 equiv) in  $H_2O$  (0.5 mL) was then added dropwise. The reaction mixture was stirred 2 h at room temperature. Upon complete conversion of the starting material (TLC), the crude reaction mixture was washed with HCl 1M and dichloromethane. The combined organic layers were washed with brine, dried with  $Na_2SO_4$  and concentrated under reduced pressure. The crude carboxylic acid was used directly in the next step without further purification. The crude dipeptide and 11-bromo-10-undecyn-1-ol (112 mg, 0.46 mmol, 1.3 equiv) were dissolved in dry  $CH_2Cl_2$  (3.5 mL, 0.1 M). HOBt- $H_2O$  (83 mg, 0.53 mmol, 1.5 equiv), DIPEA (0.09 mL, 0.53 mmol, 1.5 equiv) and EDC-HCl (102 mg, 0.53 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $CH_2Cl_2$ . The combined organic phases were washed with brine, dried ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (5 %  $\rightarrow$  20 % ethyl acetate in hexanes), the

desired product was obtained as a colorless oil (163 mg, 51 % yield over 2 steps).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.46-7.39 (m, 6H), 7.35-7.27 (m, 6H), 7.26-7.16 (m, 6H), 7.12-7.04 (m, 2H), 6.60-6.36 (m, 1H), 4.82-4.64 (m, 2H), 4.13-3.99 (m, 2H), 3.91-3.72 (m, 1H), 3.12-3.03 (m, 2H), 2.78-2.65 (m, 1H), 2.58-2.47 (m, 1H), 2.21 (t,  $J$  = 7.0 Hz, 2H), 1.60-1.47 (m, 4H), 1.41 (s, 9H), 1.34-1.23 (m, 10H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.0, 170.0, 155.2, 144.3, 135.6, 129.5, 129.3, 128.4, 128.0, 127.0, 126.9, 80.4, 67.2, 65.6, 53.8, 53.1, 37.9, 37.5, 33.9, 29.2, 29.1, 28.9, 28.7, 28.4, 28.22, 28.19, 25.7, 19.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{47}\text{H}_{55}\text{BrN}_2\text{O}_5\text{SNa}$  [ $\text{M}+\text{Na}$ ] $^+$  861.2907; found 861.2904.

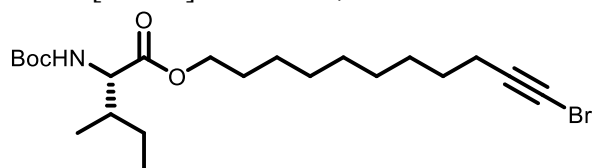


**11-Bromoundec-10-yn-1-yl (*tert*-butoxycarbonyl)-*L*-cysteinyl-*L*-phenylalaninate (8.S16):** Dipeptide **8.S15** (163 mg, 0.195 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $\text{CH}_2\text{Cl}_2$  (2 mL, 0.1M) was then added followed by triisopropylsilane (0.2 mL, 0.973 mmol, 5 equiv). TFA (0.075 mL, 0.973 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (80 mg, 69 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32-7.27 (m, 2H), 7.27-7.23 (m, 1H), 7.17-7.12 (m, 2H), 6.77-6.69 (m, 1H), 5.52-5.33 (m, 1H), 4.89-4.82 (m, 1H), 4.39-4.29 (m, 1H), 4.16-4.02 (m, 2H), 3.21-3.03 (m, 3H), 2.70-2.60 (m, 1H), 2.21 (t,  $J$  = 7.0 Hz, 2H), 1.65-1.56 (m, 2H), 1.55-1.48 (m, 2H), 1.47-1.44 (m, 9H), 1.42-1.34 (m, 2H), 1.29 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.2, 169.7, 155.3, 135.6, 129.3, 128.7, 127.2, 80.4, 65.8, 53.4, 53.2, 38.0, 37.9, 37.5, 29.7, 29.3, 29.1, 28.9, 28.7, 28.4, 28.25, 28.23, 25.8, 19.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{41}\text{BrN}_2\text{O}_5\text{SNa}$  [ $\text{M}+\text{Na}$ ] $^+$  619.1838; found 619.1812.



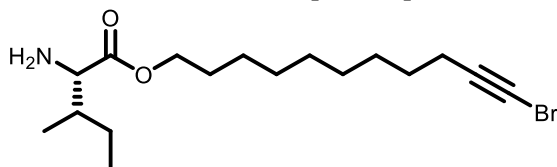
***tert*-Butyl ((3*S*,6*R*)-3-benzyl-2,5-dioxo-1-oxa-8-thia-4-azacyclononadec-9-yn-6-yl)carbamate (8.10):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (7.3 mg, 0.0268 mmol, 20 mol%) and 2,6-lutidine (0.031 mL, 0.268 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (18 mL, 2/3 of total volume, 5 mM final concentration) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (0.112 mL, 0.0134 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S16** (80 mg, 0.134 mmol, 1 equiv) was dissolved in degassed acetonitrile (9 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0124 mL/min) and the reaction mixture was stirred for a

total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (20 % ethyl acetate in hexanes), the desired product was obtained as a white solid (24 mg, 35 % yield). *Note that rotamers are formed and can result in complex splitting patterns in the  $^1\text{H}$  NMR, or can cause doubling of some peaks in the  $^{13}\text{C}$  NMR spectrum. For clarity, only major peaks are reported. Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are included in the final section of the Supporting Information.*  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.77-7.62 (m, 1H), 7.33-7.27 (m, 1H), 7.26-7.21 (m, 2H), 7.20-7.15 (m, 2H), 5.55-5.43 (m, 1H), 4.97-4.78 (m, 1H), 4.78-4.65 (m, 1H), 4.12-3.99 (m, 2H), 3.28-3.14 (m, 1H), 3.09-2.85 (m, 2H), 2.85-2.67 (m, 1H), 2.23-2.16 (m, 2H), 1.69-1.61 (m, 1H), 1.61-1.49 (m, 5H), 1.49-1.45 (m, 9H), 1.45-1.34 (m, 4H), 1.34-1.26 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.2, 169.9, 155.6, 136.1, 129.2, 128.5, 127.0, 80.4, 80.1, 68.1, 65.5, 54.2, 53.4, 45.6, 38.4, 37.5, 29.3, 29.1, 29.0, 28.7, 28.4, 28.2, 25.7, 19.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  539.2562; found 539.2550.



**11-Bromoundec-10-yn-1-yl 2-((tert-butoxycarbonyl)amino)-3-methylpentanoate (8.S17):**

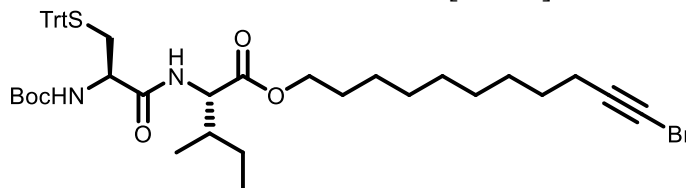
11-Bromoundec-10-yn-1-ol (200 mg, 0.809 mmol, 1.3 equiv) and Boc-*L*-isoleucine (144 mg, 0.622 mmol, 1 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (6 mL, 0.1 M). HOBt- $\text{H}_2\text{O}$  (126 mg, 0.934 mmol, 1.5 equiv), DIPEA (0.163 mL, 0.934 mmol, 1.5 equiv) and EDC-HCl (179 mg, 0.934 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 %  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a yellow oil (236 mg, 82 % yield).  $^1\text{H}$  RMN (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.04 (d,  $J$  = 8.4 Hz, 1H), 4.30 - 4.23 (m, 1H), 4.17 - 4.07 (m, 2H), 2.21 (t,  $J$  = 7.0 Hz, 2H), 1.91 - 1.82 (m, 1H), 1.70 - 1.60 (m, 2H), 1.58 - 1.47 (m, 2H), 1.45 (s, 9H), 1.40 - 1.28 (m, 11H), 0.96 - 0.90 (m, 6H);  $^{13}\text{C}$  RMN (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 172.2, 155.4, 80.1, 79.4, 64.9, 57.7, 37.9, 37.4, 29.1, 28.9, 28.8, 28.5, 28.4, 28.13, 28.07, 25.7, 24.9, 19.5, 15.3, 11.5; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{38}\text{BrNO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  482.1876; found 482.1895.



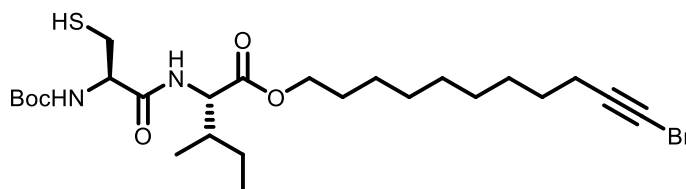
**11-Bromoundec-10-yn-1-yl 2-amino-3-methylpentanoate (8.S18):** Isoleucine derivative **8.S17** (337 mg, 0.936 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2/\text{TFA}$  (5:1) (9.4 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. Then, saturated aqueous  $\text{NaHCO}_3$  solution was slowly added and the phases were separated. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$  and the organic phases were combined, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give a yellow oil (315 mg, 93 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.83 (s, 2H), 4.28 - 4.14 (m, 2H), 4.05 - 3.95 (m, 1H), 2.21 (t,  $J$  = 7.1 Hz, 3H), 1.83 - 1.73 (m, 1H), 1.73 - 1.63 (m, 2H), 1.56 - 1.46 (m, 3H), 1.42 - 1.26 (m,



10H), 1.13 (d,  $J = 6.8$  Hz, 3H), 0.99 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 172.2, 80.3, 65.4, 58.1, 37.9, 37.4, 29.2, 29.0, 28.8, 28.6, 28.4, 28.1, 25.7, 25.1, 19.5, 15.3, 11.6$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{30}\text{BrNO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  360.1533; found 360.1531.

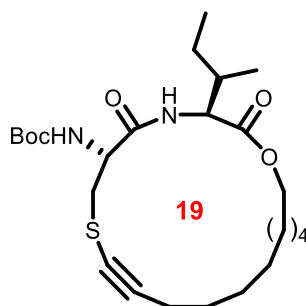


**11-Bromoundec-10-yn-1-yl-2-((tert-butoxycarbonyl)amino)-3-(tritylthio)-3-methylpentanoate (8.S19):** Isoleucine derivative **8.S18** (174 mg, 0.438 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (224 mg, 0.468 mmol, 1.1 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (4.4 mL, 0.1 M). HOBt- $\text{H}_2\text{O}$  (98 mg, 0.724 mmol, 1.5 equiv), DIPEA (0.126 mL, 0.724 mmol, 1.5 equiv) and EDC-HCl (139mg, 0.724 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 %  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a yellow oil (261 mg, 67 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.47 - 7.40$  (m, 6H), 7.33 - 7.27 (m, 6H), 7.26 - 7.20 (m, 3H), 6.65 (d,  $J = 6.0$  Hz, 1H), 4.77 (d,  $J = 5.9$  Hz, 1H), 4.49 (dd,  $J = 8.4, 5.1$  Hz, 1H), 4.15 - 4.03 (m, 2H), 3.87 - 3.78 (m, 1H), 2.77 (brs, 1H), 2.82 - 2.73 (m, 1H), 2.53 (dd,  $J = 13.0, 4.8$  Hz, 1H), 2.20 (t,  $J = 7.0$  Hz, 2H), 1.92 - 1.81 (m, 1H), 1.66 - 1.56 (m, 2H), 1.56 - 1.47 (m, 2H), 1.43 (s, 9H), 1.39 - 1.28 (m, 9H), 1.21 - 1.09 (m, 2H), 0.93 - 0.86 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.0, 169.9, 155.0, 144.1, 129.2, 127.7, 126.5, 80.0, 79.6, 66.8, 64.8, 60.0, 56.1, 53.1, 37.6, 37.4, 29.0, 28.7, 28.6, 28.3, 28.2, 27.90, 27.89, 25.5, 24.7, 19.3, 15.1, 11.2$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{44}\text{H}_{57}\text{BrN}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  827.30638; found 827.30715.



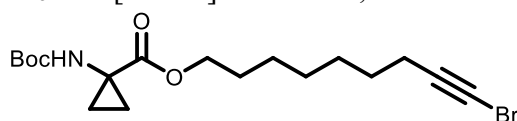
**11-Bromoundec-10-yn-1-yl-2-((tert-butoxycarbonyl)amino)-3-mercaptopropan-amido)-3-methylpentanoate (8.S20):** Cysteine derivative **8.S19** (135 mg, 0.168 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $\text{CH}_2\text{Cl}_2$  (1.7 mL, 0.1 M) was then added followed by triisopropylsilane (0.172 mL, 0.838 mmol, 5 equiv). TFA (0.064 mL, 0.838 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 5 h. Upon completion (TLC), the crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (5 %  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a yellow oil (21 mg, 22 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 6.83$  (d,  $J = 9.1$  Hz, 1H), 5.52 - 5.41 (m, 1H), 4.59 - 4.52 (m, 1H), 4.39 - 4.29 (m, 1H), 4.19 - 4.06 (m, 2H), 3.10 (ddd,  $J = 13.8, 7.8, 4.3$  Hz, 1H), 2.72 (ddd,  $J = 16.6, 10.2, 6.3$  Hz, 1H), 2.20 (t,  $J = 7.0$  Hz, 2H), 1.99 - 1.87 (m, 1H), 1.75 - 1.60 (m, 3H), 1.53-1.45 (m, 2H), 1.47 (s, 9H), 1.41 - 1.25 (m, 12H), 0.95 - 0.90 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.5, 169.9, 155.4, 80.6, 80.4,$

65.4, 56.7, 55.5, 37.8, 37.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.24, 28.24, 28.20, 25.8, 25.1, 19.6, 15.5, 11.6; HRMS (ESI)  $m/z$  calculated for  $C_{25}H_{43}BrN_2O_5SNa$   $[M+Na]^+$  585.1968; found 585.1974.



***tert*-Butyl-(3-(*sec*-butyl)-2,5-dioxo-1-oxa-814-thia-4-azacyclonadec-8-yn-6-yl)-**

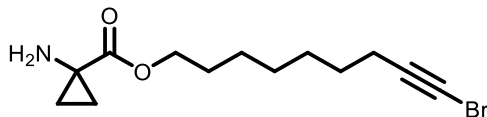
**carbamate (8.11):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (6 mg, 0.0222 mmol, 20 mol%) and 2,6-lutidine (0.0258 mL, 0.222 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (14.8 mL, 2/3 of total volume) was added. A solution of  $Cu(MeCN)_4PF_6$  (118.5 mM in MeCN) (0.0925 mL, 0.0111 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S20** (62.5 mg, 0.111 mmol, 1 equiv) was dissolved in degassed acetonitrile (7.4 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0103 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (10 → 20% ethyl acetate in hexanes), the macrocycle was obtained as a yellow oil (18.4 mg, 34 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 5.32 (d,  $J$  = 7.6 Hz, 1H), 4.58 (dd,  $J$  = 8.8, 5.3 Hz, 1H), 4.49 - 4.38 (m, 1H), 4.33 - 4.20 (m, 1H), 4.17 - 4.07 (m, 1H), 3.20 (dd,  $J$  = 13.7, 5.5 Hz, 1H), 2.95 - 2.85 (m, 1H), 2.40 - 2.31 (m, 2H), 2.01 - 1.89 (m, 1H), 1.72 - 1.63 (m, 3H), 1.55 - 1.50 (m, 3H), 1.49 (s, 9H), 1.46 - 1.28 (m, 12H), 1.24 - 1.16 (m, 2H), 0.94 (d,  $J$  = 7.0 Hz, 6H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 170.4, 169.8, 155.8, 95.8, 80.7, 65.2, 57.3, 53.9, 38.0, 35.6, 28.6, 28.3, 28.1, 27.7, 27.6, 27.53, 27.48, 25.9, 25.0, 19.7, 15.4, 11.5. HRMS (ESI)  $m/z$  calculated for  $C_{25}H_{42}N_2O_5SNa$   $[M+Na]^+$  505.2707; found 505.2711.



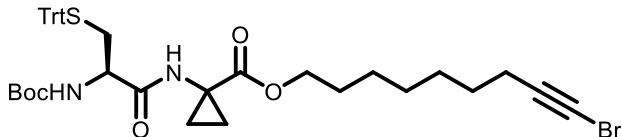
**9-Bromonon-8-yn-1-yl 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylate (8.S21):** 9-Bromonon-8-yn-1-ol<sup>23</sup> (404 mg, 1.84 mmol, 1 equiv), 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid (445 mg, 2.21 mmol, 1.2 equiv) were dissolved in  $CH_2Cl_2$  (18 mL, 0.1 M). DCC (457 mg, 2.21 mmol, 1.2 equiv) and DMAP (225 mg, 1.84 mmol, 1 equiv) were added and the mixture was left to stir at room temperature for 36 h. When the reaction was complete (TLC), the precipitated urea was filtered and filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20 % ethyl acetate in hexanes) to give the desired product as a yellow solid (660 mg, 89 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 5.18 (s, 1H), 4.05 (t,  $J$  = 6.5 Hz,

<sup>23</sup> Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. *J. Org. Chem.* **2013**, *78*, 3783-3801.

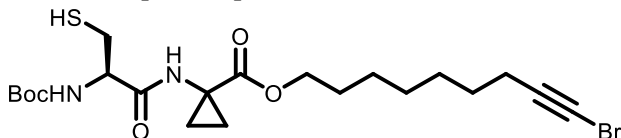
2H), 2.17 (t,  $J = 7.0$  Hz, 2H), 1.63 – 1.53 (m, 2H), 1.53 – 1.44 (m, 4H), 1.42 (s, 9H), 1.38 – 1.23 (m, 6H), 1.17 – 1.06 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 173.0, 155.9, 80.2, 79.8, 65.2, 37.5, 34.2, 28.6, 28.5, 28.5, 28.2, 28.1, 25.6, 19.5, 17.5$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{18}\text{H}_{28}\text{BrNO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  424.1094; found 424.1090.



**9-Bromonon-8-yn-1-yl 1-aminocyclopropane-1-carboxylate (8.S22):** Boc-protected amino acid **8.S21** (315 mg, 0.783 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2/\text{TFA}$  (5:1) (7.8 mL, 0.1 M) and the reaction was left to stir for 18 h at room temperature. Then, saturated aqueous  $\text{NaHCO}_3$  solution was slowly added and the phases were separated. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$  and the organic phases were combined, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (60 % acetone in hexanes) to give the desired product as a colorless oil (660 mg, 89 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 4.06$  (t,  $J = 6.7$  Hz, 2H), 2.20 (t,  $J = 7.0$  Hz, 2H), 2.04 (s, 2H), 1.57 - 1.65 (m, 2H), 1.46 - 1.55 (m, 2H), 1.30 - 1.43 (m, 6H), 1.25 - 1.29 (m, 2H), 0.97 - 1.02 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 176.5, 80.2, 65.0, 37.6, 35.6, 28.6, 28.51, 28.48, 28.1, 25.7, 19.5, 18.0$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{13}\text{H}_{21}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  302.0750; found 302.0762.

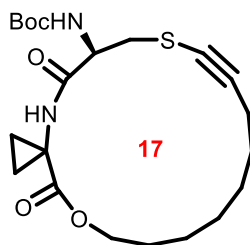


**9-Bromonon-8-yn-1-yl-1-(2-((tert-butoxycarbonyl)amino)-3-(tritylthio)propanamido)cyclopropane-1-carboxylate (8.S23):** *N*-Boc-*S*-trityl-*L*-cysteine (463 mg, 1 mmol, 1.3 equiv) and amino acid **8.S22** (232 mg, 0.77 mmol, 1 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (7.7 mL, 0.1 M). DIPEA (0.201 mL, 1.15 mmol, 1.5 equiv) and HATU (461 mg, 1.15 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), distilled water was added and the phases were separated. The organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20 % acetone in hexanes) to give the desired product as a white solid (453 mg, 79 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.18 - 7.48$  (m, 15H), 6.48 (br. s., 1H), 4.79 (br. s., 1H), 4.02 (t,  $J = 6.7$  Hz, 2H), 3.81 (br. s., 1H), 2.66 - 2.74 (m, 1H), 2.54 - 2.61 (m, 1H), 2.19 (t,  $J = 7.0$  Hz, 2H), 1.46 - 1.59 (m, 6H), 1.43 (s, 9H), 1.26 (s, 6H), 1.03 - 1.14 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta = 171.9, 171.4, 155.4, 144.4, 129.6, 128.1, 126.9, 80.3, 67.2, 65.4, 37.6, 33.7, 33.4, 28.6, 28.4, 28.3, 28.2, 25.6, 19.6, 17.5, 17.5$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{40}\text{H}_{47}\text{BrN}_2\text{O}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$  769.2281; found 739.2283.



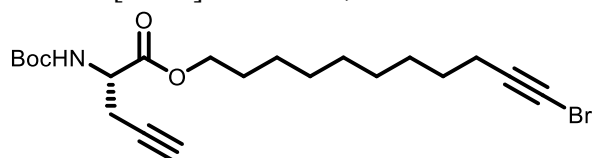
**4-((3-Mercaptopropanoyl)oxy)butyl-(*S*)-5-bromo-2-((tert-butoxycarbonyl)amino)-pent-4-ynoate (8.S24):** Trityl-protected dipeptide **8.S23** (305 mg, 0.41 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under

nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (4.1 mL, 0.1 M) was then added followed by triethylsilane (0.326 mL, 2.04 mmol, 5 equiv). TFA (0.158 mL, 2.04 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 30 min. Upon completion (TLC), the reaction was quenched with triethylamine (0.16 mL). The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (30 % ethyl acetate in hexanes), the desired product was obtained as a yellow oil (164 mg, 80 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.20 (brs, 1H), 5.56 - 5.63 (m, 1H), 4.31 (brs, 1H), 4.03 (t, *J* = 6.7 Hz, 2H), 2.97 - 3.08 (m, 1H), 2.67 - 2.77 (m, 1H), 2.17 (t, *J* = 7.0 Hz, 2H), 1.78 - 1.87 (m, 1H), 1.44 - 1.58 (m, 6H), 1.42 (s, 9H), 1.25 - 1.36 (m, 6H), 1.11 - 1.19 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 171.8, 171.3, 155.4, 80.2, 65.5, 60.3, 37.5, 33.5, 28.5, 28.3, 28.2, 28.0, 27.1, 25.5, 20.9, 19.5, 17.4, 17.2, 14.1; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>33</sub>BrN<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 527.1186; found 527.1163.



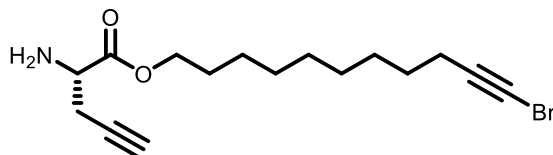
***tert*-butyl (5,19-Dioxo-18-oxa-8-thia-4-azaspiro[2.16]nonadec-9-yn-6-yl)carbamate (8.12):**

To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (10.8 mg, 0.0396 mmol, 20 mol%) and 2,6-lutidine (0.046 mL, 0.396 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (52.7 mL, 2/3 of total volume) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.165 mL, 0.0198 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S24** (100 mg, 0.198 mmol, 1 equiv) was dissolved in degassed acetonitrile (26.3 mL, 1/3 of total volume), transferred into a 60 mL syringe and added dropwise over 12 h using a syringe pump (0.0365 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (100% hexanes → 35% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (44 mg, 52 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.09 (brs, 1H), 5.18 (brs, 1H), 4.39 (ddd, *J* = 11.5, 7.8, 4.0 Hz, 1H), 4.20 - 4.05 (m, 2H), 3.42 (dd, *J* = 13.9, 2.9 Hz, 1H), 2.92 (dd, *J* = 12.9, 10.8 Hz, 1H), 2.39 (dd, *J* = 5.8, 5.8 Hz, 2H), 1.70 - 1.62 (m, 3H), 1.60 - 1.54 (m, 5H), 1.50 (s, 9H), 1.49 - 1.37 (m, 4H), 1.23 (ddd, *J* = 10.3, 7.5, 4.4 Hz, 1H), 1.16 (ddd, *J* = 10.3, 7.6, 4.3 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 172.2, 171.2, 156.0, 95.4, 81.0, 68.7, 65.7, 54.6, 37.0, 33.6, 28.32, 28.30, 28.2, 27.7, 27.0, 26.4, 19.6, 17.8, 17.5; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup> 425.2105; found 425.2104.

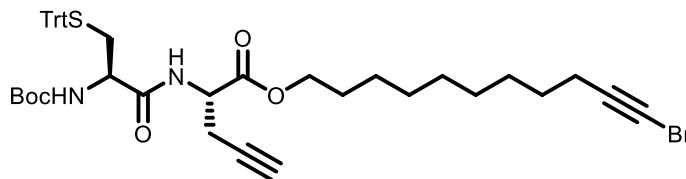


**11-Bromoundec-10-yn-1-yl (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-ynoate (8.S25):** 11-Bromoundec-10-yn-1-ol (929 mg, 3.76 mmol, 1.3 equiv) and Boc-*L*-2-propargylglycine (616 mg, 2.89 mmol, 1 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (29 mL, 0.1 M). HOBt-H<sub>2</sub>O (586 mg, 4.34 mmol, 1.5 equiv), DIPEA (0.755 mL, 4.34 mmol, 1.5 equiv) and EDC-HCl (673 mg, 4.34

mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 % → 20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (818 mg, 64 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 5.36 (d, *J* = 12.0 Hz, 1H), 4.46 - 4.45 (m, 1H), 4.20 - 4.12 (m, 2H), 2.80 - 2.70 (m, 2H), 2.21 (t, *J* = 5.2 Hz, 2H), 2.06 - 2.02 (m, 1H), 1.68 - 1.65 (m, 2H), 1.55 - 1.49 (m, 2H), 1.47 (s, 9H), 1.39 - 1.30 (m, 10H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 170.6, 155.1, 80.4, 80.1, 78.6, 71.5, 65.8, 60.4, 51.9, 37.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.3, 25.8, 22.9, 21.0, 19.7. HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>32</sub>BrNO<sub>4</sub>Na [M+Na]<sup>+</sup> 464.1407; found 464.1416.

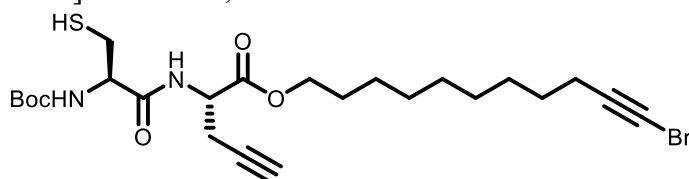


**11-Bromoundec-10-yn-1-yl (*S*)-2-aminopent-4-ynoate (8.S26):** Propargylglycine derivative **8.S25** (754 mg, 1.70 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/TFA (5:1) (17 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. Then, saturated aqueous NaHCO<sub>3</sub> solution was slowly added and the phases were separated. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the organic phases were combined, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a colorless oil (543 mg, 93 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.21-4.11 (m, 2H), 3.67 (brs, 1H), 2.70-2.61 (m, 2H), 2.22-2.19 (t, *J* = 6 Hz, 2H), 2.07-2.06 (t, *J* = 2 Hz, 1H), 1.68-1.63 (m, 2H), 1.54-1.48 (m, 2H), 1.39-1.27 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 174.1, 80.4, 79.5, 71.2, 65.5, 53.0, 37.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.2, 25.8, 25.0, 19.6; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>25</sub>BrNO<sub>2</sub> [M+H]<sup>+</sup> 342.1063; found 342.1076.

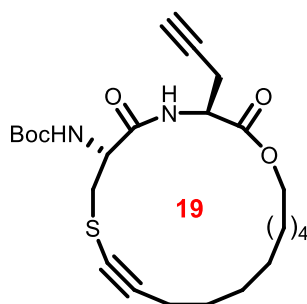


**11-Bromoundec-10-yn-1-yl (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(tritylthio)propanamido)pent-4-ynoate (8.S27):** Amine **8.S26** (475 mg, 1.39 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (663 mg, 1.39 mmol, 1 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (14 mL, 0.1 M). HOBt-H<sub>2</sub>O (281 mg, 2.08 mmol, 1.5 equiv), DIPEA (0.269 mL, 2.08 mmol, 1.5 equiv) and EDC-HCl (323 mg, 2.08 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (10 % → 20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (819 mg, 75 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.45 - 7.21 (m, 15H), 6.95 - 6.85 (m, 1H), 4.85 - 4.75 (m, 1H), 4.65 - 4.60 (m, 1H), 4.21 - 4.10 (m, 2H), 3.95 - 3.85 (m, 1H), 2.79 - 2.73 (m, 2H), 2.59 - 2.54 (m, 2H), 2.21 (t, *J* = 6.8 Hz, 2H), 1.94 (t, *J* = 2.0 Hz, 1H), 1.68 - 1.60 (m, 2H), 1.60 - 1.48 (m, 2H), 1.44 (s, 9H), 1.39 - 1.27 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 170.2,

169.8, 155.2, 144.3, 129.5, 128.0, 126.9, 80.8, 78.3, 71.5, 67.1, 65.0, 50.8, 37.5, 33.6, 29.3, 29.0, 28.9, 28.7, 28.4, 28.2, 28.2, 25.7, 22.3, 19.6; HRMS (ESI)  $m/z$  calculated for  $C_{43}H_{51}BrNO_5SNa [M+Na]^+$  809.2594; found 809.2580.

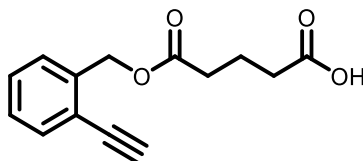


**11-bromoundec-10-yn-1-yl-(S)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-mercaptopropanamido)pent-4-ynoate (8.S28):** Cysteine derivative **8.S27** (819 mg, 1.04 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $CH_2Cl_2$  (10 mL, 0.1 M) was then added followed by triethylsilane (0.830 mL, 5.2 mmol, 5 equiv). TFA (0.402 mL, 5.2 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. Upon completion (TLC), the crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (100 % hexanes  $\rightarrow$  20 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (165 mg, 29 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.12 (brs, 1H), 5.51 (brs, 1H), 4.72 - 4.69 (m, 1H), 4.43 (brs, 1H) 4.26 - 4.10 (m, 2H), 3.17 - 3.11 (m, 1H), 2.88 - 2.73 (m, 2H), 2.21 (t,  $J$  = 6.0 Hz, 2H), 2.07 (t,  $J$  = 2.0 Hz, 1H), 1.70 - 1.63 (m, 2H), 1.54 - 1.47 (m, 12H), 1.39 - 1.28 (m, 10H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 169.9, 169.9, 155.3, 80.4, 78.2, 71.9, 66.2, 51.0, 29.3, 29.1, 28.9, 28.7, 28.5, 28.4, 28.3, 28.2, 27.1, 25.8, 25.7, 22.2, 19.6. HRMS (ESI)  $m/z$  calculated for  $C_{24}H_{37}BrNO_5SNa [M+Na]^+$  567.1499; found 567.1508.

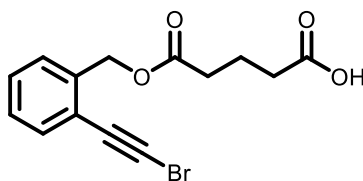


**tert-Butyl ((3S,6R)-2,5-dioxo-3-(prop-2-yn-1-yl)-1-oxa-8-thia-4-azacyclononadec-9-yn-6-yl)carbamate (8.13):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (13.2 mg, 0.0491 mmol, 20 mol%) and 2,6-lutidine (0.057 mL, 0.491 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (33 mL, 2/3 of total volume) was added. A solution of  $Cu(MeCN)_4PF_6$  (118.5 mM in MeCN) (0.207 mL, 0.0246 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S28** (135 mg, 0.246 mmol, 1 equiv) was dissolved in degassed acetonitrile (17 mL, 1/3 of total volume), transferred into a 24 mL syringe and added dropwise over 12 h using a syringe pump (0.0236 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (10  $\rightarrow$  35% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (26 mg, 23 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.70 (brs, 1H), 5.59 (brs, 1H), 4.78 - 4.71 (m, 2H), 4.21 - 4.11 (m, 2H), 3.11 - 3.06 (m, 2H), 2.85 - 2.74 (m, 2H), 2.21 (t,  $J$  = 6.0 Hz, 2H) 2.03 (t,  $J$  = 2.0 Hz, 1H), 1.67 - 1.61 (m, 2H), 1.53 - 1.47 (m, 11H), 1.39 - 1.26 (m, 10H);  $^{13}C$

NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.3, 169.9, 155.5, 80.4, 78.7, 71.5, 68.1, 66.0, 51.2, 37.5, 29.7, 29.3, 29.1, 29.0, 28.7, 28.5, 28.4, 28.2, 25.8, 19.6; HRMS (ESI)  $m/z$  calculated for C<sub>24</sub>H<sub>37</sub>BrNO<sub>5</sub>S [M+H]<sup>+</sup> 465.2418; found 465.2434.

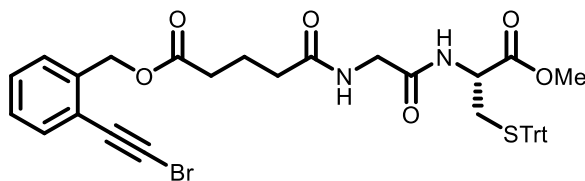


**5-((2-Ethynylbenzyl)oxy)-5-oxopentanoic acid (8.S29):** (2-Ethynylphenyl)methanol<sup>24</sup> (802 mg, 6.07 mmol, 1 equiv), glutaric acid (1.60 g, 12.1 mmol, 2.0 equiv) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (60 mL, 0.1 M). DCC (1.38 g, 6.68 mmol, 1.1 equiv) and DMAP (816 mg, 6.68 mmol, 1.1 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), the precipitated urea was filtered and filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100 % hexanes → 20 % ethyl acetate in hexanes), the desired product was obtained as a yellow solid (909 mg, 61 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.56-7.51 (m, 1H), 7.43-7.36 (m, 2H), 7.35-7.28 (m, 1H), 5.31 (s, 2H), 3.32 (s, 1H), 2.49 (t,  $J$  = 7.3 Hz, 2H), 2.46 (t,  $J$  = 7.3 Hz, 2H), 2.01 (tt,  $J$  = 7.2, 7.2 Hz, 2H), 2.07 (s, 3H), 1.69-1.61 (m, 2H), 1.56-1.49 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 177.7, 172.6, 138.0, 132.9, 129.0, 128.3, 128.1, 121.5, 82.1, 80.8, 64.6, 33.1, 32.7, 19.8; HRMS (ESI)  $m/z$  calculated for C<sub>14</sub>H<sub>14</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup> 269.0784; found 269.0794.

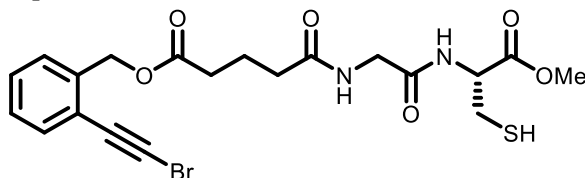


**5-((2-(Bromoethynyl)benzyl)oxy)-5-oxopentanoic acid (8.S30):** To a stirred solution of 5-((2-ethynylbenzyl)oxy)-5-oxopentanoic acid (169 mg, 0.69 mmol, 1.0 equiv) in acetone (3.5 mL, 0.2 M) were added AgNO<sub>3</sub> (23 mg, 0.14 mmol, 20 mol%) and NBS (146 mg, 0.82 mmol, 1.2 equiv). The reaction was left to stir at 60 °C for 30 min. Upon complete conversion (TLC), the reaction mixture was filtered on Celite<sup>®</sup> pad and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100 % hexanes → 5 % diethyl ether in hexanes), the desired product was obtained as a white solid (234 mg, 99 % yield). <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>)  $\delta$  = 7.53 (dd,  $J$  = 7.4, 0.9 Hz, 1H), 7.49 (ddd,  $J$  = 7.6, 1.8, 0.6 Hz, 1H), 7.44 (ddd,  $J$  = 7.2, 7.2, 1.5 Hz, 1H), 7.36 (ddd,  $J$  = 7.5, 7.5, 1.9 Hz, 1H), 5.26 (s, 2H), 2.49 (t,  $J$  = 7.4 Hz, 2H), 2.40 (t,  $J$  = 7.3 Hz, 2H), 1.92 (tt,  $J$  = 7.2, 7.2 Hz, 2H); <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>)  $\delta$  = 174.6, 173.5, 140.1, 133.9, 130.4, 129.8, 129.5, 123.0, 78.7, 65.1, 56.3, 34.0, 33.6, 21.4; HRMS (ESI)  $m/z$  calculated for C<sub>14</sub>H<sub>13</sub>BrO<sub>4</sub>Na [M+Na]<sup>+</sup> 346.9889; found 346.9889.

<sup>24</sup> Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877-8888.



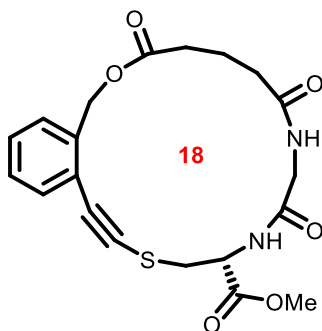
**2-(Bromoethynyl)benzyl (R)-5-((2-((1-methoxy-1-oxo-3-(tritylthio)propan-2-yl)amino)-2-oxoethyl)amino)-5-oxopentanoate (8.S31):** 5-((2-(bromoethynyl)benzyl)oxy)-5-oxopentanoic acid (88 mg, 0.26 mmol, 1 equiv), methyl *N*-glycyl-*S*-trityl-*L*-cysteinate<sup>25</sup> (157 mg, 0.29 mmol, 1.1 equiv) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.6 mL, 0.1 M). DCC (59 mg, 0.29 mmol, 1.1 equiv) and DMAP (35 mg, 0.29 mmol, 1.1 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), the precipitated urea was filtered and filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (50 % ethyl acetate in hexanes + 1 % acetic acid), the desired product was obtained as a brownish oil (97 mg, 50 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.48 (dd, *J* = 6.9, 1.0 Hz, 1H), 7.42-7.36 (m, 7H), 7.36-7.32 (m, 2H), 7.31-7.27 (m, 6H), 7.26-7.20 (m, 3H), 6.26 (d, *J* = 7.9 Hz, 1H), 6.21-6.16 (m, 1H), 5.26 (s, 2H), 4.55-4.47 (m, 1H), 3.89 (d, *J* = 5.1 Hz, 2H), 3.71 (s, 3H), 2.72 (ddd, *J* = 12.6, 12.6, 6.1 Hz, 1H), 2.64 (ddd, *J* = 12.6, 9.7, 4.8 Hz, 1H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.01 (tt, *J* = 7.1, 7.1 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 172.8, 172.4, 170.5, 168.4, 144.2, 138.2, 132.8, 129.5, 128.9, 128.4, 128.1, 128.0, 127.0, 122.0, 77.2, 67.1, 64.5, 54.6, 52.7, 51.2, 42.8, 35.0, 33.5, 33.2, 20.7; HRMS (ESI) *m/z* calculated for C<sub>39</sub>H<sub>37</sub>BrN<sub>2</sub>O<sub>6</sub>SNa [M+Na]<sup>+</sup> 763.1448; found 763.1455.



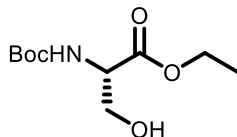
**2-(Bromoethynyl)benzyl (R)-5-((2-((3-mercapto-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-5-oxopentanoate (8.S32):** Dipeptide **8.S31** (61 mg, 0.082 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL, 0.1M) was then added followed by triisopropylsilane (0.08 mL, 0.41 mmol, 5 equiv). TFA (0.03 mL, 0.41 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 1 h. The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (50 % → 80 % ethyl acetate in hexanes), the desired product was obtained as a colorless oil (29 mg, 71 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.48 (d, *J* = 7.4 Hz, 1H), 7.39-7.34 (m, 2H), 7.31-7.28 (m, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.46-6.37 (m, 1H), 5.26 (s, 2H), 4.89-4.82 (m, 1H), 4.04-3.98 (m, 2H), 3.78 (s, 3H), 3.00 (dd, *J* = 8.8, 4.2 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.06-2.01 (m, 2H), 1.47 (t, *J* = 9.2 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.9, 170.2, 138.1, 132.8, 128.9, 128.4, 128.1, 122.0, 77.5, 64.5, 54.6, 53.7, 52.9, 43.2, 35.0, 33.2, 26.6, 20.7; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>23</sub>BrN<sub>2</sub>O<sub>6</sub>SNa [M+Na]<sup>+</sup> 521.0352; found 521.0361.

<sup>25</sup> Liu, X.; Suh, D.-Y.; Call, J.; Prestwich, G. D. *Bioconjugate Chem.* **2004**, *15*, 270-277.

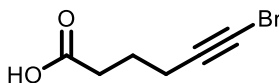




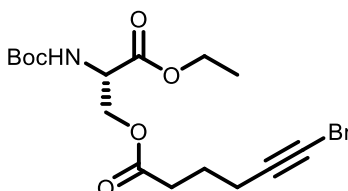
**Methyl 3,7,10-trioxo-4,5,6,7,10,11,12,13,15,16-decahydro-1*H*,3*H*,9*H*-8 $\lambda^2$ -benzo[*c*][1]oxa[7]thia[10,13]diazacyclooctadec-15-yne-12-carboxylate (8.14):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (4.9 mg, 0.018 mmol, 20 mol%) and 2,6-lutidine (0.021 mL, 0.18 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (12 mL, 2/3 of total volume, 5 mM final concentration) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.075 mL, 0.009 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S32** (45 mg, 0.09 mmol, 1 equiv) was dissolved in degassed acetonitrile (6 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0083 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (2.5 % → 5 % MeOH in dichloromethane), the desired product was obtained as a white solid (27 mg, 73 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.55 (d, *J* = 7.4 Hz, 1H), 7.49-7.39 (m, 2H), 7.38-7.30 (m, 2H), 5.96-5.87 (m, 1H), 5.32 (d, *J* = 11.7 Hz, 1H), 5.16 (t, *J* = 11.7 Hz, 1H), 4.88 (dt, *J* = 7.2, 5.1 Hz, 1H), 4.16 (dd, *J* = 16.8, 6.9 Hz, 1H), 3.72 (dd, *J* = 16.8, 5.9 Hz, 1H), 3.71 (s, 3H), 3.42-3.32 (m, 2H), 2.66-2.56 (m, 1H), 2.55-2.46 (m, 1H), 2.35-2.23 (m, 1H), 2.16-1.99 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.3, 173.0, 169.7, 169.3, 137.6, 132.1, 130.6, 129.0, 128.8, 123.5, 90.5, 83.4, 65.1, 52.9, 52.3, 43.6, 36.3, 34.5, 32.4, 21.0; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup> 419.1271; found 419.1283.



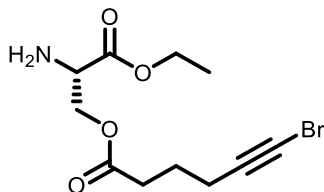
**Boc-*L*-Serine ethyl ester (8.S33):** In a round bottom flask, *L*-Serine ethyl ester (500 mg, 2.95 mmol, 1 equiv) was dissolved in water/ethyl acetate (1:1) (8.4 mL, 0.35 M). Boc<sub>2</sub>O (611 mg, 2.8 mmol, 1 equiv) was then added. The mixture was left to stir at room temperature before slowly adding potassium carbonate (611 mg, 4.42 mmol, 1.5 equiv). The flask was sealed with a Teflon septum and stirred at room temperature for 24 h. The phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The organic phases were combined, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to afford a colorless oil (523 mg, 76 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.55 (d, *J* = 7.4 Hz, 1H), 4.38-4.28 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.99-3.81 (m, 2H), 2.97 (s, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.9, 155.8, 80.2, 63.4, 61.7, 55.8, 28.2, 14.0; HRMS (ESI) *m/z* calculated for C<sub>10</sub>H<sub>19</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup> 256.1155; found 256.1160.



**6-Bromo-5-hexynoic acid (8.S34):** To a stirred solution of hex-5-ynoic acid (1.01 g, 9 mmol, 1 equiv) in acetone (4.5 mL, 0.2 M) were added AgNO<sub>3</sub> (306 mg, 1.8 mmol, 20 mol%) and NBS (1.92 g, 10.8 mmol, 1.2 equiv). The reaction was left to stir for 2 h. Upon complete conversion, water was added, and the mixture was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The organic phases were combined, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to afford a yellow oil (1.68 g, 98 %). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 11.76 (br s, 1H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.31 (t, *J* = 6.9 Hz, 2H), 1.88-1.81 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 179.7, 78.8, 39.0, 32.6, 23.1, 19.0; HRMS (ESI) *m/z* calculated for C<sub>6</sub>H<sub>7</sub>BrO<sub>2</sub> [M+H]<sup>+</sup> 190.9702; found 190.9699.

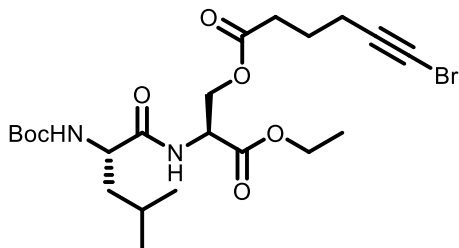


**(S)-2-((Boc)amino)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S35):** Boc-*L*-serine ethyl ester (2 g, 8.57 mmol, 1 equiv) and 6-bromo-5-hexynoic acid (2.13 g, 11.1 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (86 mL, 0.1 M). HOBt-H<sub>2</sub>O (1.74 g, 12.9 mmol, 1.5 equiv), DIPEA (2.24 mL, 12.9 mmol, 1.5 equiv) and EDC-HCl (2.47 g, 12.9 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the desired product as a colorless oil (2.52 g, 73 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.29 (d, *J* = 8.1 Hz, 1H), 4.60 – 4.52 (m, 1H), 4.47 (dd, *J* = 11.7, 3.4 Hz, 1H), 4.35 (dd, *J* = 11.1, 3.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.29 (t, *J* = 6.9 Hz, 2H), 1.87-1.78 (m, 2H), 1.47 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.4, 169.7, 155.1, 80.2, 78.9, 64.3, 61.9, 52.9, 38.9, 32.5, 28.2, 23.2, 19.0, 14.1; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>24</sub>BrNO<sub>6</sub>Na [M+Na]<sup>+</sup> 428.0679; found 428.0666.

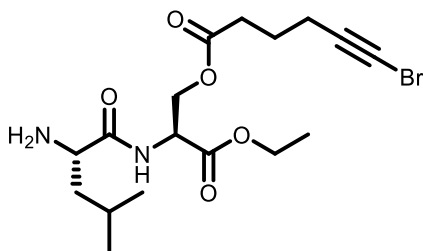


**(S)-2-Amino-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S36):** Serine derivative **8.S35** (1.70 g, 4.18 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/TFA (5:1) (42 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. Then, saturated aqueous NaHCO<sub>3</sub> solution (40 mL) was slowly added and the phases were separated. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the organic phases were combined, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a yellow oil (1.0 g, 78 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 6.76 (d, *J* = 7.6 Hz, 1H), 4.64 – 4.56 (m, 1H), 4.20 (qd, *J* = 7.2, 1.1 Hz, 1H), 3.95 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.85 (dd, *J* = 11.2, 3.5 Hz, 1H), 2.37 (t, *J* = 7.6 Hz, 2H),

2.27 (t,  $J = 6.9$  Hz, 2H), 1.89 – 1.77 (m, 2H), 1.27 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.8, 170.5, 79.1, 63.0, 61.8, 54.6, 38.7, 34.7, 23.8, 19.0, 14.0; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{11}\text{H}_{17}\text{BrNO}_4$   $[\text{M}+\text{H}]^+$  306.0336; found 306.0334.

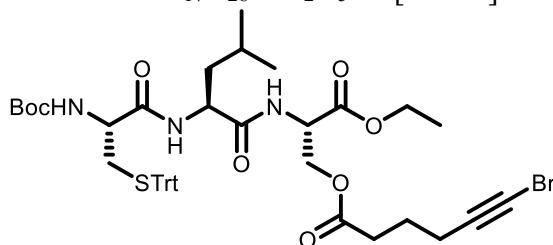


**Ethyl *O*-(5-bromopent-4-yn-1-yl)-*N*-((*tert*-butoxycarbonyl)-*L*-leucyl)-*L*-serinate (8.S37):** Deprotected serine derivative **8.S36** (1.00 g, 3.27 mmol, 1 equiv) and *N*-Boc-*L*-leucine (982 mg, 4.25 mmol, 1.3 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (33 mL, 0.1 M). HOBt- $\text{H}_2\text{O}$  (662 mg, 4.90 mmol, 1.5 equiv), DIPEA (0.853 mL, 4.90 mmol, 1.5 equiv) and EDC-HCl (939 mg, 4.90 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the desired product as a colorless oil (1.12 g, 66 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.80 (d,  $J = 7.0$  Hz, 1H), 4.92-4.84 (m, 1H), 4.82 (dt,  $J = 7.9, 3.4$  Hz, 1H), 4.49 (dd,  $J = 11.3, 3.9$  Hz, 1H), 4.38 (dd,  $J = 11.3, 3.5$  Hz, 1H), 4.24 (q,  $J = 7.2$  Hz, 2H), 4.19-4.11 (m, 1H), 2.45 (t,  $J = 7.3$  Hz, 2H), 2.29 (t,  $J = 6.9$  Hz, 2H), 1.87 – 1.78 (m, 2H), 1.74 - 1.68 (m, 2H), 1.54 – 1.48 (m, 1H), 1.46 (s, 9H), 1.30 (t,  $J = 7.0$  Hz, 3H), 0.99 – 0.94 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.4, 169.1, 155.5, 80.0, 78.9, 63.8, 62.0, 53.0, 51.6, 41.2, 38.9, 32.5, 28.2, 24.6, 23.2, 22.8, 21.9, 18.9, 14.0; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{35}\text{BrN}_2\text{O}_7\text{Na}$   $[\text{M}+\text{Na}]^+$  541.1520; found 541.1529.

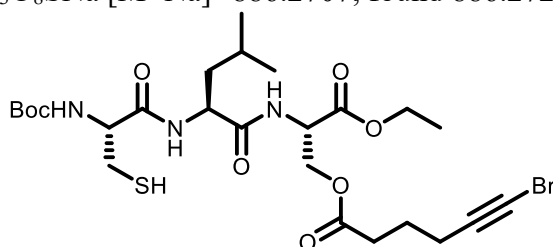


**Ethyl *N*-(*L*-leucyl)-*O*-(5-bromopent-4-yn-1-yl)-*L*-serinate (8.S38):** Dipeptide derivative **8.S37** (710 mg, 1.37 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2/\text{TFA}$  (5:1) (13.7 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. The reaction mixture was then concentrated to form an oil to which was added either pentane or diethyl ether to induce precipitation. The resulting solid was collected by filtration. Alternatively, following completion of the reaction, saturated aqueous  $\text{NaHCO}_3$  solution (40 mL) could be slowly added. The phases were separated and the aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$  and the organic phases were combined, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give a colorless oil (573 mg, 92%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.43 (d,  $J = 8.2$  Hz, 1H), 5.01 – 4.93 (m, 1H), 4.59 – 4.49 (m, 2H), 4.28 – 4.14 (m, 2H), 4.05 – 3.96 (m, 1H), 2.41 (t,  $J = 7.0$  Hz, 2H), 2.28 (t,  $J = 7.1$  Hz, 2H), 1.91 – 1.78 (m, 5H), 1.29 (t,  $J = 7.1$  Hz, 3H), 1.02 – 0.94 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$

172.9, 170.1, 168.3, 79.3, 66.2, 62.6, 51.6, 51.0, 39.3, 38.7, 34.4, 24.3, 24.1, 22.1, 21.5, 19.1, 13.9; HRMS (ESI)  $m/z$  calculated for  $C_{17}H_{28}BrN_2O_5Na$   $[M+Na]^+$  419.1176; found 419.1164.

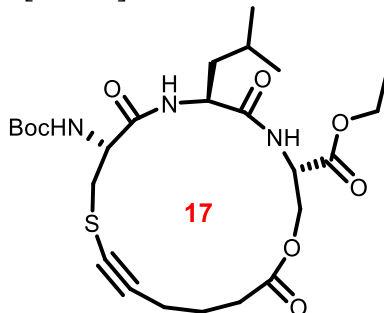


**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-9-isobutyl-2,2-dimethyl-4,7,10-trioxo-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S39):** Deprotected dipeptide **8.S38** (526 mg, 1.26 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (782 mg, 1.64 mmol, 1.3 equiv) were dissolved in dry  $CH_2Cl_2$  (13 mL, 0.1 M). HOBt- $H_2O$  (255 mg, 1.89 mmol, 1.5 equiv), DIPEA (0.329 mL, 1.89 mmol, 1.5 equiv) and EDC-HCl (362 mg, 1.89 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $CH_2Cl_2$ . The combined organic phases were washed with brine, dried ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the desired product as white solid (695 mg, 64 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.46- 7.40 (m, 6H), 7.33 – 7.27 (m, 6H), 7.26- 7.21 (m, 3H), 6.84 (d,  $J$  = 6.2 Hz, 1H), 6.40 (d,  $J$  = 7.7 Hz, 1H), 4.79 – 7.68 (m, 2H), 4.48 - 4.38 (m, 2H), 4.28 (dd,  $J$  = 11.3, 3.5 Hz, 1H), 4.20 (q,  $J$  = 7.0 Hz, 2H), 3.86 – 3.76 (m, 1H), 2.76 (dd,  $J$  = 12.5, 6.2 Hz, 1H), 2.55 (dd,  $J$  = 13.1, 5.3 Hz, 1H), 2.41 (td,  $J$  = 7.5, 1.5 Hz, 2H), 2.27 (t,  $J$  = 7.0 Hz, 3H), 1.86 - 1.75 (m, 2H), 1.73 – 1.59 (m, 2H), 1.42 (s, 9H), 1.28 (t,  $J$  = 7.1 Hz, 3H), 0.94 – 0.88 (m, 6H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  172.4, 171.3, 170.5, 168.9, 144.3, 129.5, 128.1, 126.9, 80.5, 79.0, 67.2, 63.6, 61.9, 53.6, 51.7, 51.5, 40.5, 38.9, 33.1, 32.5, 28.2, 24.5, 23.2, 23.0, 21.7, 19.0, 14.1; HRMS (ESI)  $m/z$  calculated for  $C_{44}H_{54}BrN_3O_8SNa$   $[M+Na]^+$  886.2707; found 886.2722.

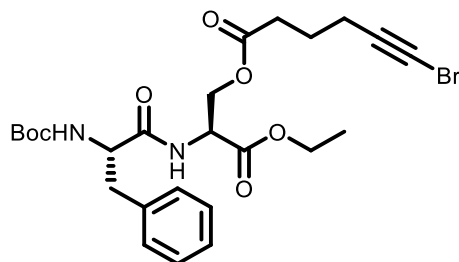


**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-9-isobutyl-6-((mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (8.S40):** Tripeptide **8.S39** (400 mg, 0.462 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $CH_2Cl_2$  (4.6 mL, 0.1M) was then added followed by triisopropylsilane (0.474 mL, 2.31 mmol, 5 equiv). TFA (0.179 mL, 2.31 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 2 h. The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to give a white solid (245 mg, 85 %).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 6.82 (d,  $J$  = 8.2 Hz, 1H), 6.68 (d,  $J$  = 7.2 Hz, 1H), 5.40 (d,  $J$  = 6.4 Hz, 1H), 4.80 (dt,  $J$  = 7.9, 3.7 Hz, 1H), 4.52 – 4.45 (m, 2H), 4.37 (dd,  $J$  = 11.3, 3.3 Hz, 1H) 4.34 – 4.30 (m, 1H), 4.24 (q,  $J$  = 7.2 Hz, 2H), 3.13 – 3.04 (m, 1H), 2.81

– 2.71 (m, 1H), 2.45 (td,  $J = 7.4, 1.3$  Hz, 2H), 2.29 (t,  $J = 6.7$  Hz, 2H), 1.87 – 1.78 (m, 2H), 1.77 – 1.56 (m, 3H), 1.47 (m, 10H), 1.29 (t,  $J = 7.1$  Hz, 3H), 0.99 – 0.92 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.5, 171.5, 170.3, 169.0, 155.4, 80.7, 79.0, 63.7, 62.1, 55.6, 51.9, 51.8, 40.8, 38.9, 32.5, 28.2, 26.6, 24.6, 23.2, 22.9, 21.8, 19.0, 14.0$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{25}\text{H}_{40}\text{BrN}_3\text{O}_8\text{SNa}$   $[\text{M}+\text{Na}]^+$  644.1612; found 644.1624.

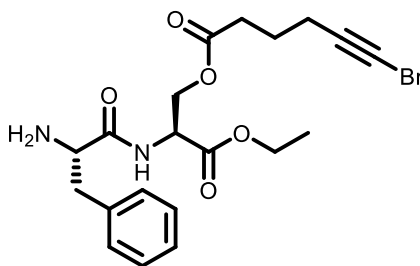


**Ethyl (3*S*,6*S*,9*R*)-9-((*tert*-butoxycarbonyl)amino)-6-isobutyl-5,8,17-trioxo-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.S15):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (8.80 mg, 0.0321 mmol, 20 mol%) and 2,6-lutidine (0.374 mL, 0.321 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (22 mL, 2/3 of total volume, 5 mM final concentration) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (136  $\mu\text{L}$ , 0.0161 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S40** (100 mg, 0.161 mmol, 1 equiv) was dissolved in degassed acetonitrile (10 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0138 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (15%  $\rightarrow$  30% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (47.5 mg, 55%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.11$  (d,  $J = 6.3$  Hz, 1H), 6.65 (d,  $J = 8.6$  Hz, 1H), 5.12 (d,  $J = 5.9$  Hz, 1H), 4.84 (dt,  $J = 7.7, 3.2$  Hz, 1H), 4.65 – 4.56 (m, 1H), 4.48 (dd,  $J = 11.2, 3.2$  Hz, 1H), 4.41 – 4.35 (m, 1H), 4.33 (dd,  $J = 11.4, 4.5$  Hz, 1H), 4.24 (q,  $J = 7.1$  Hz, 2H), 3.36 – 3.24 (m, 1H), 2.94 – 2.82 (m, 1H), 2.58 – 2.31 (m, 4H), 1.94 – 1.74 (m, 3H), 1.71 – 1.51 (m, 2H), 1.46 (m, 9H), 1.29 (t,  $J = 7.1$  Hz, 3H), 0.96 – 0.90 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.6, 171.2, 170.6, 168.7, 155.6, 94.4, 80.9, 68.4, 63.6, 62.0, 53.8, 51.7, 51.2, 39.6, 35.8, 32.0, 29.6, 28.1, 24.5, 22.8, 21.6, 19.0, 14.1$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{25}\text{H}_{39}\text{N}_3\text{O}_8\text{SNa}$   $[\text{M}+\text{Na}]^+$  564.2350; found 564.2364.

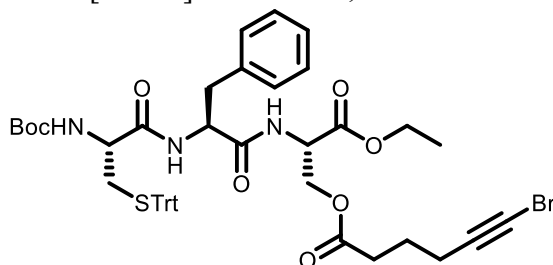


**(*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S41):** Deprotected serine derivative **8.S36** (143 mg, 0.49 mmol, 1 equiv) and *N*-Boc-*L*-phenylalanine (169 mg, 0.64 mmol, 1.3 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (5 mL, 0.1 M). HOBT- $\text{H}_2\text{O}$  (99 mg, 0.73 mmol, 1.5 equiv), DIPEA (0.128 mL, 0.73 mmol, 1.5 equiv) and EDC-HCl (141 mg, 0.73 mmol, 1.5 equiv) were added and the mixture

was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the desired product as a white solid (130 mg, 49 %) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33 – 7.28 (m, 2H), 7.27 – 7.19 (m, 3H), 6.69 (d, *J* = 7.4 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.80 – 4.72 (m, 1H), 4.43 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.33 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.09 (d, *J* = 6.6 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.27 (t, *J* = 6.9 Hz, 2H), 1.83 – 1.75 (m, 2H), 1.42 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.4, 171.2, 168.8, 155.3, 136.3, 129.3, 128.7, 127.0, 80.3, 78.9, 63.8, 62.1, 55.6, 51.7, 39.0, 38.2, 32.5, 28.2, 23.2, 19.0, 14.1; HRMS (ESI) *m/z* calculated for C<sub>25</sub>H<sub>33</sub>BrN<sub>2</sub>O<sub>7</sub>Na [M+Na]<sup>+</sup> 575.1363; found 575.1376.

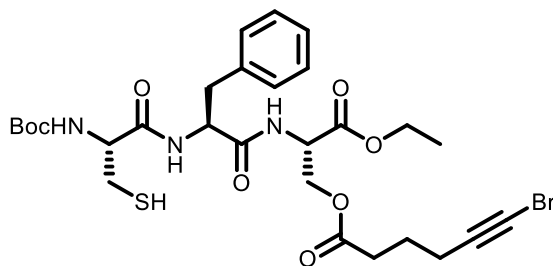


**(*S*)-2-((*S*)-2-Amino-3-phenylpropanamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S42):** Dipeptide derivative **8.S41** (500 mg, 0.93 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/TFA (5:1) (9.3 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. The reaction mixture was then concentrated to form an oil to which was added either pentane or diethyl ether to induce precipitation. The resulting solid was collected by filtration. Alternatively, following completion of the reaction, saturated aqueous NaHCO<sub>3</sub> solution (40 mL) could be slowly added. The phases were separated and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the organic phases were combined, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a colorless oil (400 mg, 98%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.39 – 7.29 (m, 3H), 7.25 – 7.18 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 4.87 – 4.76 (m, 1H), 4.53 – 4.36 (m, 2H), 4.25 (t, *J* = 6.6 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.35 – 3.18 (m, 2H), 2.37 – 2.20 (m, 4H), 1.87 – 1.73 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.8, 169.3, 168.0, 133.4, 129.21, 129.17, 128.1, 79.3, 65.9, 62.4, 54.1, 51.0, 38.7, 36.3, 34.4, 23.8, 19.0, 13.8; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>5</sub>Na [M+Na]<sup>+</sup> 475.08391; found 475.08448.

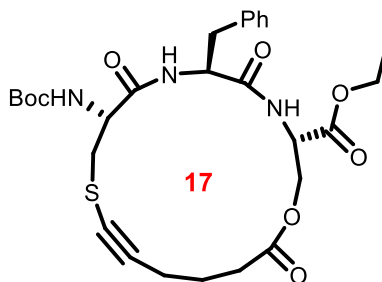


**Ethyl (6*R*,9*S*,12*S*)-9-benzyl-12-(((6-bromohex-5-ynoyl)oxy)methyl)-2,2-dimethyl-4,7,10-trioxo-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S43):** Deprotected dipeptide **8.S42** (80 mg, 0.18 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (113 mg, 0.24 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.1 M). HOBt-H<sub>2</sub>O (36.9 mg, 0.27

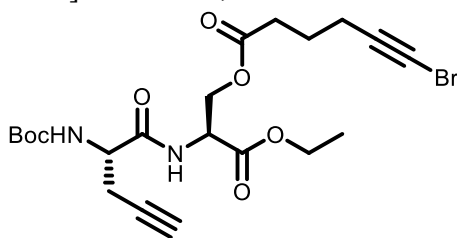
mmol, 1.5 equiv), DIPEA (0.047 mL, 0.27 mmol, 1.5 equiv) and EDC-HCl (52.4 mg, 0.27 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give the desired product as white solid (111 mg, 68 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.45 – 7.37 (m, 6H), 7.34 – 7.27 (m, 6H), 7.26 – 7.21 (m, 5H), 7.21 – 7.15 (m, 3H), 6.74 – 6.64 (m, 1H), 6.47 (d, *J* = 8.1 Hz, 1H), 4.70 – 4.61 (m, 2H), 4.54 (d, *J* = 5.6 Hz, 1H), 4.35 (dd, *J* = 11.4, 5.7 Hz, 1H), 4.24 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.68 (m, 1H), 3.15 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.03 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.57 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.37 (td, *J* = 7.5, 1.1 Hz, 2H), 2.26 (t, *J* = 7.0 Hz, 2H), 1.82 – 1.73 (m, 2H), 1.37 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.4, 170.2, 168.6, 155.4, 144.3, 136.1, 129.5, 129.3, 128.6, 128.1, 127.04, 126.96, 80.5, 79.0, 67.3, 63.5, 61.9, 53.8, 51.8, 38.9, 37.4, 33.3, 32.5, 31.9, 28.2, 23.2, 19.0, 14.1; C<sub>47</sub>H<sub>52</sub>BrN<sub>3</sub>O<sub>8</sub>Na [M+Na]<sup>+</sup> 920.2551; found 920.2578.



**Ethyl (6*R*,9*S*,12*S*)-9-benzyl-12-(((6-bromohex-5-ynoyl)oxy)methyl)-6-(mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (8.S44):** Tripeptide **8.S43** (300 mg, 0.334 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (3.3 mL, 0.1 M) was then added followed by triisopropylsilane (0.342 mL, 1.67 mmol, 5 equiv). TFA (0.128 mL, 1.67 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 2 h. The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to give a white solid (103 mg, 47 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.32 – 7.28 (m, 2H), 7.27 – 7.21 (m, 3H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.0 Hz, 1H), 5.36 – 5.28 (m, 1H), 4.79 – 4.71 (m, 2H), 4.43 (dd, *J* = 11.4, 4.0 Hz, 1H), 4.34 – 4.28 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.13 (d, *J* = 6.7 Hz, 2H), 3.11 – 3.03 (m, 1H), 2.72 – 2.62 (m, 1H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.84 – 1.74 (m, 2H), 1.45 (s, 9H), 1.40 – 1.35 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.4, 170.2, 169.9, 168.7, 155.3, 136.0, 129.3, 128.8, 127.2, 80.8, 79.0, 63.6, 62.1, 55.6, 54.3, 51.9, 39.0, 37.9, 32.5, 28.2, 26.7, 23.2, 19.0, 14.1; HRMS (ESI) *m/z* calculated for C<sub>28</sub>H<sub>38</sub>BrN<sub>3</sub>O<sub>8</sub>Na [M+Na]<sup>+</sup> 678.1455; found 678.1475.



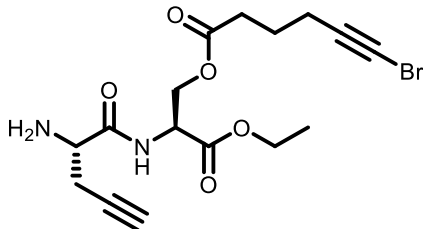
**Ethyl (3*S*,6*S*,9*R*)-6-benzyl-9-((*tert*-butoxycarbonyl)amino)-5,8,17-trioxo-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.16):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (8.34 mg, 0.0305 mmol, 20 mol%) and 2,6-lutidine (0.036 mL, 0.305 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (20 mL, 2/3 of total volume) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.13 mL, 0.0152 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S44** (100 mg, 0.152 mmol, 1 equiv) was dissolved in degassed acetonitrile (10 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0138 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (15% → 30% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (26 mg, 30%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33 – 7.27 (m, 2H), 7.26 – 7.21 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 5.14 – 5.04 (m, 1H), 4.91 – 4.82 (m, 2H), 4.46 – 4.37 (m, 2H), 4.31 – 4.19 (m, 3H), 3.25 – 3.06 (m, 3H), 2.91 – 2.80 (m, 1H), 2.52 – 2.42 (m, 1H), 2.41 – 2.32 (m, 1H), 2.31 – 2.21 (m, 2H), 1.83 – 1.71 (m, 2H), 1.46 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 172.5, 170.14, 170.10, 168.6, 155.4, 136.1, 129.5, 128.7, 127.0, 94.8, 80.9, 67.9, 63.6, 62.1, 53.7, 53.6, 51.7, 36.8, 35.5, 32.1, 28.2, 22.8, 18.9, 14.1; HRMS (ESI) *m/z* calculated for C<sub>28</sub>H<sub>38</sub>N<sub>3</sub>O<sub>8</sub>S [M+H]<sup>+</sup> 473.2374; found 473.2397.



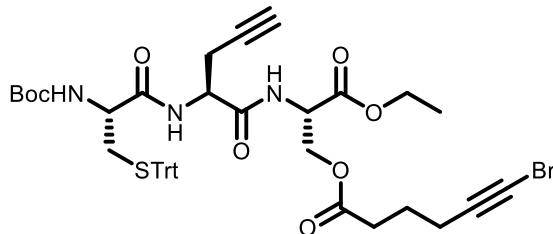
**(*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)pent-4-ynamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S45):** Deprotected serine derivative **8.S36** (520 mg, 1.7 mmol, 1 equiv) and *N*-Boc-*L*-propargylglycine (471 mg, 2.21 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (17 mL, 0.1 M). HOBt-H<sub>2</sub>O (344 mg, 2.55 mmol, 1.5 equiv), DIPEA (0.444 mL, 2.55 mmol, 1.5 equiv) and EDC-HCl (488 mg, 2.55 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to give the desired product as a white solid (558 mg, 66 %) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.09 (d, *J* = 7.0 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.85 – 4.76 (m, 1H), 4.46 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.38 (dd, *J* = 11.4, 3.5 Hz, 1H), 4.35 – 4.29 (m, 1H), 4.22 (q, *J* = 7.1 Hz,



2H), 2.79 (ddd,  $J = 16.7, 4.9, 2.1$  Hz, 1H), 2.61 (ddd,  $J = 17.0, 6.5, 2.3$  Hz, 1H), 2.42 (t,  $J = 7.4$  Hz, 2H), 2.27 (t,  $J = 6.9$  Hz, 2H), 2.10 (t,  $J = 2.6$  Hz, 1H), 1.85 – 1.75 (m, 2H), 1.46 (s, 9H), 1.28 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.3, 170.1, 168.8, 155.2, 80.5, 79.1, 78.8, 71.7, 63.6, 62.0, 52.7, 51.9, 39.0, 32.4, 28.1, 23.1, 22.2, 18.9, 14.0$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{21}\text{H}_{29}\text{BrN}_2\text{O}_7\text{Na}$   $[\text{M}+\text{Na}]^+$  523.1050; found 523.1041.

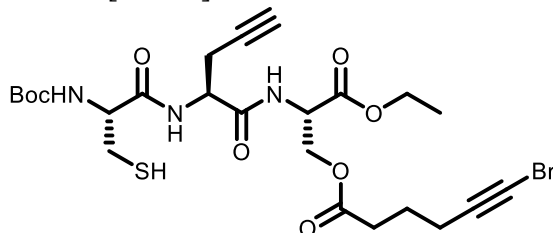


**(S)-2-((S)-2-Aminopent-4-ynamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S46):** Dipeptide derivative **8.S45** (558 mg, 1.11 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2/\text{TFA}$  (5:1) (11 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. The reaction mixture was then concentrated to form an oil to which was added either pentane or diethyl ether to induce precipitation. The resulting solid was collected by filtration. Alternatively, following completion of the reaction, saturated aqueous  $\text{NaHCO}_3$  solution (40 mL) could be slowly added. The phases were separated and the aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$  and the organic phases were combined, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give a colorless oil (402 mg, 90%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.94$  (d,  $J = 7.5$  Hz, 1H), 4.84 – 4.75 (m, 1H), 4.51 (dd,  $J = 11.3, 3.4$  Hz, 1H), 4.37 (dd,  $J = 11.5, 3.2$  Hz, 1H), 4.33 – 4.28 (m, 1H), 4.25 (q,  $J = 7.0$  Hz, 2H), 2.99 – 2.83 (m, 2H), 2.43 (t,  $J = 7.5$  Hz, 2H), 2.30 (s, 1H), 2.27 (t,  $J = 6.9$  Hz, 2H), 1.87 – 1.75 (m, 2H), 1.30 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.9, 168.6, 167.6, 79.0, 76.5, 74.1, 63.1, 62.4, 52.4, 51.6, 38.9, 32.5, 23.2, 21.3, 18.9, 14.0$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{16}\text{H}_{22}\text{BrN}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  401.0712; found 401.0708.

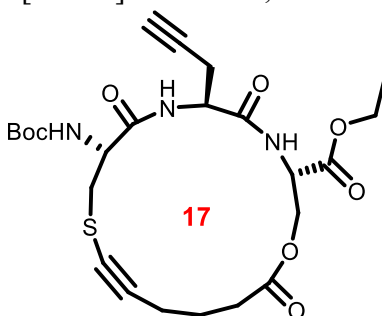


**Ethyl (6R,9S,12S)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-2,2-dimethyl-4,7,10-trioxo-9-(prop-2-yn-1-yl)-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S47):** The deprotected dipeptide **8.S46** (402 mg, 1.0 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (622 mg, 1.3 mmol, 1.3 equiv) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (10 mL, 0.1 M). HOBt- $\text{H}_2\text{O}$  (203 mg, 1.5 mmol, 1.5 equiv), DIPEA (0.262 mL, 1.5 mmol, 1.5 equiv) and EDC-HCl (288 mg, 1.5 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100% hexanes  $\rightarrow$  30% ethyl acetate in hexanes) to give the desired product as white solid (500 mg, 59 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.47 - 7.41$  (m, 6H), 7.34 – 7.28 (m, 6H), 7.26 – 7.21 (m, 3H), 7.12 (d,  $J = 6.7$  Hz, 1H), 6.81 (d,  $J = 6.9$  Hz, 1H), 4.78 – 4.70 (m, 2H), 4.58 – 4.50 (m, 1H), 4.40 (dd,  $J = 11.4, 4.8$  Hz, 1H), 4.33 (dd,  $J =$

= 11.3, 3.9 Hz, 1H), 4.21 (q,  $J = 7.1$  Hz, 2H), 3.87 – 3.78 (m, 1H), 2.84 (ddd,  $J = 17.7, 5.4, 2.8$  Hz, 1H), 2.80 – 2.72 (m, 1H), 2.64 (dd,  $J = 13.2, 5.1$  Hz, 1H), 2.56 (ddd,  $J = 16.9, 6.7, 2.7$  Hz, 1H), 2.42 (t,  $J = 7.5$  Hz, 2H), 2.27 (t,  $J = 7.0$  Hz, 2H), 2.06 – 2.01 (m, 1H), 1.85 – 1.75 (m, 2H), 1.65 – 1.58 (m, 3H), 1.42 (s, 9H), 1.28 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.3, 170.5, 169.4, 168.6, 155.5, 144.2, 129.4, 128.1, 126.9, 80.6, 79.0, 78.9, 71.9, 67.3, 63.4, 62.0, 53.7, 51.9, 51.4, 38.9, 33.2, 32.5, 28.2, 23.2, 21.6, 19.0, 14.0$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{43}\text{H}_{48}\text{BrN}_3\text{O}_8\text{SNa}$   $[\text{M}+\text{Na}]^+$  868.2238; found 868.2240.

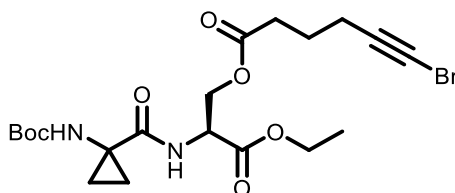


**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-6-(mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-9-(prop-2-yn-1-yl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S48):** Tripeptide **8.S47** (400 mg, 0.472 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry  $\text{CH}_2\text{Cl}_2$  (4.7 mL, 0.1 M) was then added followed by triethylsilane (0.377 mL, 2.36 mmol, 5 equiv). TFA (0.181 mL, 2.36 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 2 h. Upon completion (TLC), the reaction was quenched with triethylamine (0.2 mL). The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (100% hexanes  $\rightarrow$  35% ethyl acetate in hexanes) to give a colorless oil (121 mg, 42 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.18 - 7.06$  (m, 2H), 5.47 (d,  $J = 7.0$  Hz, 1H), 4.84 - 4.77 (m, 1H), 4.64 (dd,  $J = 13.6, 6.5$  Hz, 1H), 4.48 (dd,  $J = 11.4, 4.2$  Hz, 1H), 4.42 – 4.34 (m, 2H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.18 – 3.08 (m, 1H), 2.89 – 2.73 (m, 2H), 2.71 – 2.61 (m, 1H), 2.44 (t,  $J = 7.3$  Hz, 2H), 2.28 (t,  $J = 6.9$  Hz, 2H), 2.12 (t,  $J = 2.4$  Hz, 1H), 1.86– 1.77 (m, 2H), 1.66 (dd,  $J = 10.2, 7.7$  Hz, 1H), 1.46 (s, 9H), 1.29 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 172.5, 170.2, 169.2, 168.7, 155.4, 80.8, 79.0, 78.9, 72.1, 63.6, 62.2, 55.7, 52.1, 51.6, 39.0, 32.5, 28.2, 26.7, 23.2, 22.0, 19.0, 14.1$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{24}\text{H}_{34}\text{BrN}_3\text{O}_8\text{SNa}$   $[\text{M}+\text{Na}]^+$  626.1142; found 626.1163.

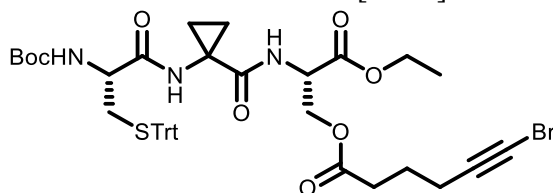


**Ethyl (3*S*,6*S*,9*R*)-9-((*tert*-butoxycarbonyl)amino)-5,8,17-trioxo-6-(prop-2-yn-1-yl)-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.17):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.1 mg, 0.0331 mmol, 20 mol%) and 2,6-lutidine (0.039 mL, 0.331 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (22 mL, 2/3 of total volume) was added. A solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (118.5 mM in MeCN) (0.14 mL, 0.0165 mmol, 10 mol%) was added to the mixture to afford a

red solution. The macrocyclic precursor **8.S48** (100 mg, 0.165 mmol, 1 equiv) was dissolved in degassed acetonitrile (11 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0153 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (100% hexanes → 35% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (16 mg, 30%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.25 (d, *J* = 6.7 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 4.93 – 4.86 (m, 1H), 4.83 – 4.73 (m, 1H), 4.55 – 4.45 (m, 2H), 4.34 (dd, *J* = 11.3, 4.8 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.23 – 3.13 (m, 1H), 2.98 – 2.87 (m, 2H), 2.66 (ddd, *J* = 16.8, 5.9, 2.6 Hz, 1H), 2.58 – 2.32 (m, 4H), 2.11 – 2.05 (m, 1H), 1.94 – 1.67 (m, 3H), 1.46 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.6, 170.4, 169.2, 168.5, 155.5, 94.8, 81.0, 79.0, 71.7, 67.8, 63.7, 62.1, 53.6, 51.8, 51.1, 35.5, 32.2, 28.2, 22.8, 21.2, 19.1, 14.1. HRMS (ESI) *m/z* calculated for C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>8</sub>SNa [M+Na]<sup>+</sup> 546.1881; found 546.1899.

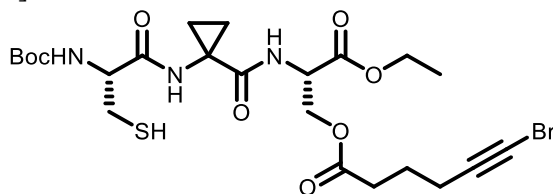


**(S)-2-(1-((*tert*-Butoxycarbonyl)amino)cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S49):** Deprotected serine derivative **8.S36** (520 mg, 1.70 mmol, 1 equiv) and 1-(Boc-amino)cyclopropanecarboxylic acid (444 mg, 2.21 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (17 mL, 0.1 M). HOBt-H<sub>2</sub>O (344 mg, 2.55 mmol, 1.5 equiv), DIPEA (0.444 mL, 2.55 mmol, 1.5 equiv) and EDC-HCl (488 mg, 2.55 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (15 % → 30 % ethyl acetate in hexanes) to give the desired product as a white solid (550 mg, 66 %) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.24 (d, *J* = 7.5 Hz, 1H), 5.23 (brs, 1H), 4.83 – 4.72 (m, 1H), 4.48 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.39 – 4.30 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.0 Hz, 2H), 1.84 – 1.74 (m, 2H), 1.58 – 1.50 (m, 2H), 1.45 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.4, 172.0, 169.2, 155.4, 80.6, 78.9, 63.9, 61.9, 52.1, 38.9, 35.3, 32.5, 28.1, 23.2, 19.0, 17.8, 14.1; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>30</sub>BrN<sub>2</sub>O<sub>7</sub> [M+H]<sup>+</sup> 511.1050; found 511.1041.

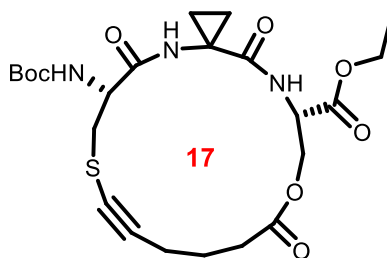


**(S)-2-(1-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-(tritylthio)propanamido)-cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S50):** Dipeptide derivative **8.S49** (90 mg, 0.18 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/TFA (5:1) (1.8 mL, 0.1 M) and the reaction was left to stir for 1 h at room temperature. Then, saturated aqueous NaHCO<sub>3</sub> solution (15 mL) was slowly added and the phases were separated. The aqueous phase was

extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the organic phases were combined, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give a colorless oil (72 mg, 97 %). The deprotected dipeptide (200 mg, 0.51 mmol, 1 equiv) and *N*-Boc-*S*-trityl-*L*-cysteine (319 mg, 0.67 mmol, 1.3 equiv) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5.1 mL, 0.1 M). HOBt-H<sub>2</sub>O (104 mg, 0.77 mmol, 1.5 equiv), DIPEA (0.179 mL, 0.77 mmol, 1.5 equiv) and EDC-HCl (148 mg, 0.77 mmol, 1.5 equiv) were added and the mixture was left to stir at room temperature for 18 h. When the reaction was complete (TLC), HCl 1M was added. The mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (15 % → 30 % ethyl acetate in hexanes) to give the desired product as white solid (280 mg, 65 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.45 – 7.41 (m, 6H), 7.34 – 7.28 (m, 6H), 7.26 – 7.22 (m, 3H), 6.47 (s, 1H), 4.87 – 4.81 (m, 1H), 4.75 – 4.66 (m, 1H), 4.40 – 4.34 (m, 1H), 4.30 (dd, *J* = 11.2, 5.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.55 (m, 1H), 2.75 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.60 (dd, *J* = 13.2, 5.1 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.28 – 2.22 (m, 2H), 1.84 – 1.75 (m, 2H), 1.74 – 1.68 (m, 1H), 1.59 – 1.55 (m, 1H), 1.43 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.03 – 0.83 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.8, 172.6, 171.3, 169.0, 155.8, 144.2, 129.5, 128.1, 127.0, 80.8, 79.2, 67.4, 63.4, 61.7, 54.2, 52.4, 38.8, 34.6, 32.6, 28.2, 23.2, 19.0, 17.5, 14.1; C<sub>42</sub>H<sub>48</sub>BrN<sub>3</sub>O<sub>8</sub>SNa [M+Na]<sup>+</sup> 856.2238; found 856.2255.

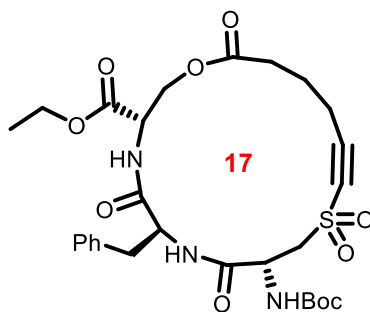


**(*S*)-2-(1-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-mercaptopropanamido)cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S51):** Tripeptide **8.S50** (250 mg, 0.30 mmol, 1 equiv) was added in a round bottom flask with a magnetic stirrer. The flask was sealed with a septum and put under nitrogen. Dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL, 0.1 M) was then added followed by triethylsilane (0.239 mL, 1.5 mmol, 5 equiv). TFA (0.115 mL, 1.5 mmol, 5 equiv) was then added and the reaction was left to stir at room temperature for 2 h. Upon completion (TLC), the reaction was quenched with triethylamine (0.2 mL). The crude product was concentrated under reduced pressure and purified by column chromatography on silica gel (100 % hexanes → 25 % ethyl acetate in hexanes) to give a white solid (103 mg, 47 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.38 (d, *J* = 7.8 Hz, 1H), 7.04 – 6.98 (m, 1H), 5.55 – 5.45 (m, 1H), 4.84 – 4.75 (m, 1H), 4.50 – 4.43 (m, 1H), 4.41 – 4.34 (m, 1H), 4.31 – 4.25 (m, 1H), 4.25 – 4.17 (m, 1H), 3.16 – 3.06 (m, 1H), 2.89 – 2.75 (m, 1H), 2.45 (t, *J* = 7.5 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 2H), 1.87 – 1.79 (m, 2H), 1.74 (dd, *J* = 9.7, 8.1 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.47 (s, 9H), 1.30 – 1.25 (m, 3H), 1.13 – 0.82 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.9, 171.4, 171.0, 169.2, 155.6, 81.1, 79.0, 63.8, 62.0, 56.1, 52.5, 38.9, 34.9, 32.7, 28.2, 26.5, 23.3, 19.0, 17.4, 14.1; HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>34</sub>BrN<sub>3</sub>O<sub>8</sub>SNa [M+Na]<sup>+</sup> 614.1142; found 614.1141.



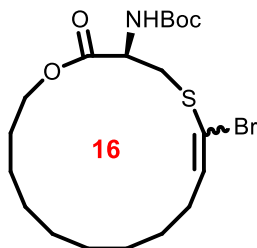
**Ethyl (6*R*,17*S*)-6-((*tert*-butoxycarbonyl)amino)-5,14,19-trioxo-15-oxa-8-thia-4,18-diazaspiro[2.16]nonadec-9-yne-17-carboxylate (8.18):** To a round bottom flask equipped with a magnetic stir bar were added dtbbpy (9.2 mg, 0.0338 mmol, 20 mol%) and 2,6-lutidine (0.039 mL, 0.338 mmol, 2 equiv). The flask was purged with nitrogen then degassed acetonitrile (22.7 mL, 2/3 of total volume) was added. A solution of Cu(MeCN)<sub>4</sub>PF<sub>6</sub> (118.5 mM in MeCN) (0.14 mL, 0.0168 mmol, 10 mol%) was added to the mixture to afford a red solution. The macrocyclic precursor **8.S51** (100 mg, 0.169 mmol, 1 equiv) was dissolved in degassed acetonitrile (11.3 mL, 1/3 of total volume), transferred into a 12 mL syringe and added dropwise over 12 h using a syringe pump (0.0157 mL/min) and the reaction mixture was stirred for a total of 18 h at room temperature. Concentration of the reaction mixture followed by purification by column chromatography on silica gel (15% → 35% ethyl acetate in hexanes), the macrocycle was obtained as a white solid (50 mg, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.52 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 5.68 (d, *J* = 8.1 Hz, 1H), 4.76 – 4.68 (m, 1H), 4.57 – 4.50 (m, 1H), 4.48 (dd, *J* = 11.6, 2.6 Hz, 1H), 4.43 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 12.6, 6.0 Hz, 1H), 2.98 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.50 – 2.38 (m, 3H), 1.95 – 1.85 (m, 2H), 1.70 – 1.62 (m, 1H), 1.60 – 1.52 (m, 1H), 1.47 (s, 9H), 1.30 – 1.24 (m, 4H), 1.20 – 1.01 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 173.3, 171.21, 171.19, 168.9, 155.9, 94.4, 81.2, 69.4, 64.7, 61.9, 54.9, 52.4, 35.8, 34.9, 32.6, 28.2, 22.6, 19.5, 17.4, 16.6, 14.1. HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>33</sub>N<sub>3</sub>O<sub>8</sub>SNa [M+Na]<sup>+</sup> 534.1881; found 534.1889.

## POST-FUNCTIONALIZATION OF PEPTIDE MACROCYCLES

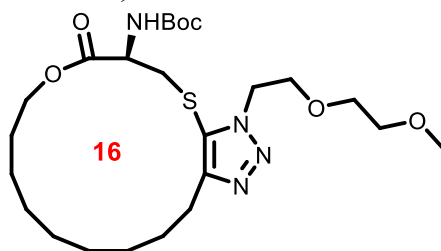


**Ethyl (3*S*,6*S*,9*R*)-6-benzyl-9-((*tert*-butoxycarbonyl)amino)-5,8,17-trioxo-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate 11,11-dioxide (8.19):** The thioalkyne **8.16** (16 mg, 0.028 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.56 mL, 0.05 M) and *m*CPBA (19.2 mg; 0.111 mmol, 4 equiv) was added. The mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (60 % ethyl acetate in hexanes) to give the desired

product as a white solid (10 mg, 59%). HRMS (ESI)  $m/z$  calculated for  $C_{28}H_{37}N_3O_{10}SNa$   $[M+Na]^+$  630.20919; found 630.21003.

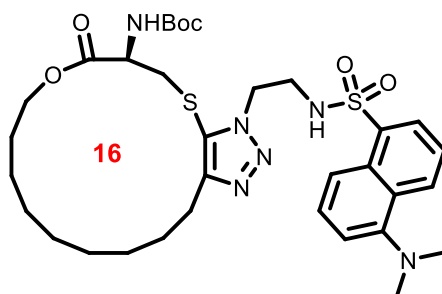


**tert-Butyl (R)-(6-bromo-2-oxo-1-oxa-5-thiacyclohexadec-6-en-3-yl)carbamate (8.20):** To a solution of thioalkyne **8.5** (36.0 mg, 0.0974 mmol, 1 equiv) in acetic acid (0.61 mL, 0.16 M) was added LiBr (84.6 mg, 0.974 mmol, 10 equiv). After stirring at room temperature for 18 h, the reaction mixture was quenched with water, extracted with ethyl acetate (3 x 10 mL), washed with brine, dried over  $Na_2SO_4$ , and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (10 % ethyl acetate in hexanes) to give the desired product as a yellow oil (43.9 mg, 53%, mixture of isomers).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 6.38 – 6.29 (m, 1H), 5.31 – 5.07 (m, 1H), 4.71 – 4.53 (m, 1H), 4.45 – 4.36 (m, 1H), 4.33 – 4.19 (m, 1H), 4.14 – 4.05 (m, 1H), 3.42 (dd,  $J$  = 13.0, 4.5 Hz, 1H), 3.23 (dd,  $J$  = 12.9, 4.4 Hz, 1H), 2.34 – 2.18 (m, 2H), 1.74 – 1.67 (m, 2H), 1.47 (s, 9H), 1.44 – 1.33 (m, 11H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 170.6, 154.9, 143.1, 115.4, 80.2, 66.0, 53.3, 37.2, 30.7, 28.3, 27.6, 26.8, 26.7, 26.5, 26.4, 25.8, 24.9. HRMS (ESI)  $m/z$  calculated for  $C_{19}H_{32}BrNO_4SNa$   $[M+Na]^+$  472.11276; found 472.11447.



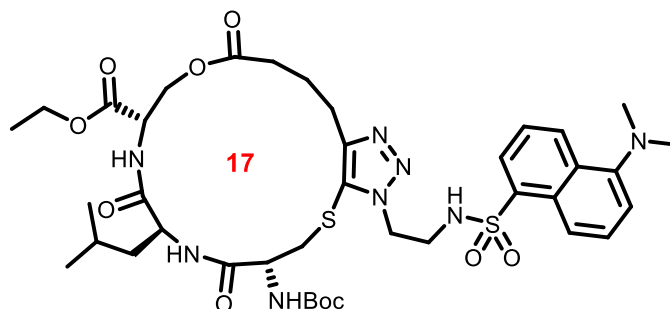
**tert-Butyl (R)-(3-(2-(2-methoxyethoxy)ethyl)-7-oxo-3,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-d][1,2,3]triazol-6-yl)carbamate (8.21):** In an flame-dried 2 mL vial was added the macrocycle **8.5** (37 mg, 0.1 mmol, 1 equiv), 1-azido-2-(2-methoxyethoxy)ethane<sup>26</sup> (14.5 mg, 0.1 mmol, 1 equiv) and dry  $CH_2Cl_2$  (0.85 mL, 0.056 M) under nitrogen. In a glove box,  $[Ir(cod)Cl]_2$  (3.4 mg, 0.005 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (10 % ethyl acetate in hexanes) to give the desired product as a white solid (19 mg, 37%).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 170.4, 155.3, 152.0, 126.4, 80.2, 71.5, 70.3, 69.8, 66.5, 58.8, 53.1, 47.8, 39.2, 28.3, 28.1, 27.4, 27.23, 27.20, 27.10, 27.06, 25.9, 24.5; HRMS (ESI)  $m/z$  calculated for  $C_{24}H_{43}N_4O_6S$   $[M+H]^+$  515.28978; found 515.28936.

<sup>26</sup> Yaniç, C.; Bredenkamp, M. W.; Jacobs, E. P.; Swart, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1381 – 1384.



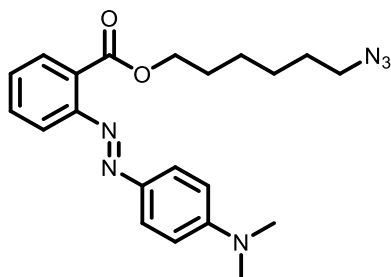
***tert*-Butyl (R)-(3-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethyl)-7-oxo-3,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-d][1,2,3]triazol-6-yl)carbamate (8.22)**: In an flame-dried 2 mL vial was added the thioalkyne **8.5** (37 mg, 0.1 mmol, 1 equiv), *N*-(2-azidoethyl)-5-(dimethylamino)naphthalene-1-sulfonamide<sup>27</sup> (31.9 mg, 0.1 mmol, 1 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (1.00 mL, 0.1 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (3.4 mg, 0.005 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (20 % ethyl acetate in hexanes) to give the desired product as a green oil (48 mg, 70%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 8.54 (d, *J* = 8.5 Hz, 1H), 8.26 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 5.88 (t, *J* = 5.7 Hz, 1H), 5.40 (d, *J* = 7.2 Hz, 1H), 4.45 – 4.36 (m, 2H), 4.31 – 4.25 (m, 1H), 4.10 – 4.04 (m, 1H), 3.57 – 3.44 (m, 2H), 3.12 (dd, *J* = 12.9, 4.6 Hz, 1H), 2.96 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.89 (s, 6H), 2.73 – 2.63 (m, 2H), 1.76 – 1.62 (m, 4H), 1.46 (s, 9H), 1.44 – 1.29 (m, 11H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 170.1, 155.3, 152.3, 151.9, 134.5, 130.6, 129.9, 129.6, 129.4, 128.5, 123.2, 118.2, 115.2, 80.8, 66.7, 53.3, 47.7, 45.4, 42.4, 39.2, 28.3, 27.9, 27.4, 27.1, 27.0, 26.9, 26.8, 25.6, 24.3; HRMS (ESI) *m/z* calculated for C<sub>33</sub>H<sub>48</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Na [M+Na]<sup>+</sup> 711.2969; found 711.29791.

<sup>27</sup> Inveraritya, I. A.; Hulme, A. N. *Org. Biomol. Chem.* **2007**, *5*, 636 - 643.

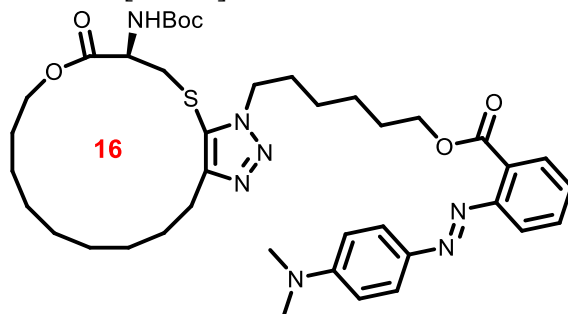


**Ethyl (6*R*,9*S*,12*S*)-6-((*tert*-butoxycarbonyl)amino)-3-(2-((5-(dimethylamino)naphthalen-1-sulfonamido)ethyl)-9-isobutyl-7,10,15-trioxo-6,7,8,9,10,11,12,13,15,16,17,18-dodecahydro-3*H*,5*H*-[1,2,3]triazolo[4,5-*l*][1]oxa[11]thia[4,7]diazacycloheptadecine-12-carboxylate (8.23):** In an flame-dried 2 mL vial was added the thioalkyne **8.15** (30.0 mg, 0.055 mmol, 1 equiv), *N*-(2-azidoethyl)-5-(dimethylamino)naphthalene-1-sulfonamide (19.5 mg, 0.061 mmol, 1.1 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL, 0.056 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (1.86 mg, 0.0028 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (60 % ethyl acetate in hexanes) to give the desired product as a green solid (39.7 mg, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.56 (d, *J* = 8.6 Hz, 1H), 8.22 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.53 (ddd, *J* = 10.7, 8.1, 8.1 Hz, 2H), 7.23 – 7.16 (m, 2H), 7.10 – 7.03 (m, 2H), 5.52 (d, *J* = 9.3 Hz, 1H), 4.78 – 4.72 (m, 1H), 4.65 – 4.57 (m, 2H), 4.52 – 4.45 (m, 2H), 4.45 – 4.39 (m, 1H), 4.30 – 4.25 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.73 (m, 2H), 3.41 – 3.36 (m, 1H), 3.33 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.07 (dd, *J* = 14.1, 8.9 Hz, 1H), 2.90 (s, 6H), 2.89 – 2.79 (m, 2H), 2.56 – 2.39 (m, 2H), 2.12 – 1.97 (m, 2H), 1.79 – 1.69 (m, 2H), 1.49 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.87 – 0.77 (m, 7H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 173.3, 171.3, 170.3, 168.9, 156.2, 152.0, 151.1, 134.2, 130.7, 129.9, 129.7, 129.4, 128.4, 127.2, 123.2, 118.5, 115.3, 81.1, 63.9, 62.0, 53.9, 52.4, 51.8, 47.7, 45.4, 42.7, 39.8, 39.6, 33.1, 29.3, 28.2, 24.6, 24.5, 23.0, 21.5, 14.1; HRMS (ESI) *m/z* calculated for C<sub>39</sub>H<sub>57</sub>N<sub>8</sub>O<sub>10</sub>S<sub>2</sub> [M+H]<sup>+</sup> 861.36336; found 861.36599.





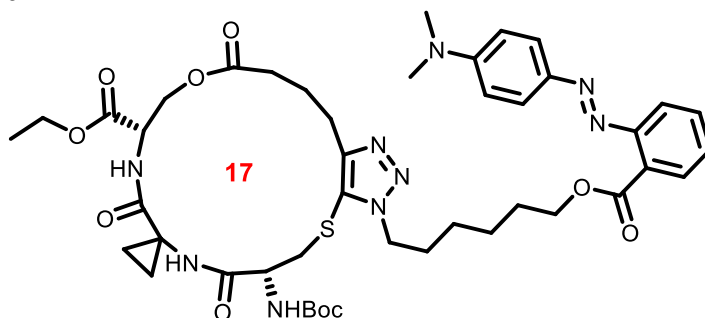
**6-Azidohexyl (*E*)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.S52):** To a round bottom flask equipped with a magnetic stir bar were added (*E*)-2-((4-(dimethylamino)phenyl)diazenyl)benzoic acid (400 mg, 1.49 mmol, 1 equiv), *N,N'*-dicyclohexylcarbodiimide (368 mg, 1.78 mmol, 1.20 equiv), 4-(dimethylamino)pyridine (218 mg, 1.78 mmol, 1.20 equiv) and 6-azidohexan-1-ol<sup>28</sup> (192 mg, 1.49 mmol, 1 equiv). The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7.43 mL, 0.2 M) and was left to stir at room temperature for 18 h. When the reaction was complete (TLC), the mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (30 % ethyl acetate in hexanes) to give the desired product as a red oil (310 mg, 53 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.86 (d, *J* = 9.2 Hz, 2H), 7.76 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.40 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.75 (d, *J* = 9.2 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 2H), 3.16 (d, *J* = 7.0 Hz, 2H), 3.10 (s, 6H), 1.71 – 1.61 (m, 2H), 1.52 – 1.43 (m, 2H), 1.37 – 1.27 (m, 4H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 168.4, 152.7, 152.5, 143.7, 131.6, 129.5, 128.19, 128.17, 125.4, 119.2, 111.3, 65.1, 62.7, 51.3, 40.2, 32.5, 28.8, 26.5, 25.3. HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>26</sub>N<sub>6</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 417.2010; found 417.2012.



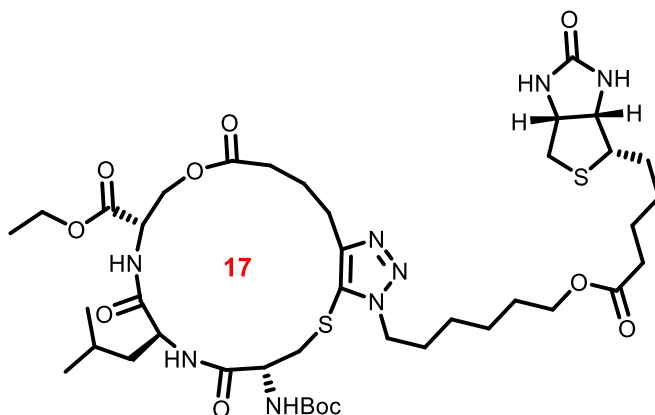
**(*R*)-6-(6-((*tert*-Butoxycarbonyl)amino)-7-oxo-6,7,10,11,12,13,14,15,16,17-decahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-*d*][1,2,3]triazol-3(9H)-yl)hexyl (*E*)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.24):** In a flame-dried 2 mL vial was added the thioalkyne **8.5** (26.2 mg, 0.071 mmol, 1 equiv), azide **8.S52** (28.0 mg, 0.071 mmol, 1 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (0.85 mL, 0.056 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (2.38 mg, 0.0036 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (60 % ethyl acetate in hexanes) to give the desired product as a red oil (44.0 mg, 81%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.85 (d, *J* = 9.1 Hz, 2H), 7.75 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (ddd, *J* = 8.1, 8.1, 1.3 Hz, 1H), 7.39 (ddd, *J* = 7.5,

<sup>28</sup> Mantovani, G.; Ladmiral, V.; Tao, L.; Haddleton, D. M. *Chem. Commun.* **2005**, 16, 2089 – 2091.

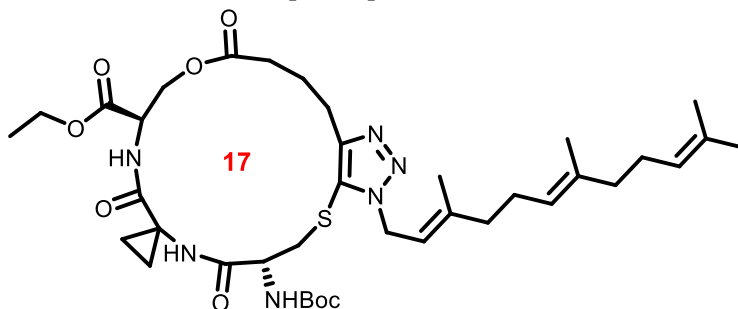
7.5, 1.2 Hz, 1H), 6.74 (d,  $J = 9.2$  Hz, 2H), 5.20 (d,  $J = 6.9$  Hz, 1H), 4.50 – 4.43 (m, 1H), 4.34 – 4.22 (m, 5H), 4.15 – 4.09 (m, 1H), 3.09 (s, 6H), 2.78 – 2.71 (m, 2H), 1.83 – 1.74 (m, 4H), 1.71 – 1.62 (m, 5H), 1.43 (s, 9H), 1.42 – 1.27 (m, 16H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 170.2, 168.3, 155.0, 152.7, 152.5, 152.1, 143.7, 131.6, 130.9, 129.5, 128.8, 128.2, 125.4, 119.2, 111.5, 80.5, 66.6, 65.1, 53.2, 48.3, 40.3, 39.2, 30.2, 28.6, 28.2, 28.0, 27.4, 27.1, 26.9, 26.8, 26.7, 26.2, 25.6, 25.5, 24.4$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{40}\text{H}_{58}\text{N}_6\text{O}_6\text{S}_2$   $[\text{M}+\text{H}]^+$  764.41638; found 764.41444.



**(R)-6-(6'-((tert-Butoxycarbonyl)amino)-7',10'-dioxo-5',6',7',8',13',14',15',16',17',18'-decahydro-10'H-spiro[cyclopropane-1,9'-[1,2,3]triazolo[4,5-i][1]oxa[8]thia[4]azacycloheptadecin]-3'(12'H)-yl)hexyl (E)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.25):** In an flame-dried 2 mL vial was added the macrocycle **8.18** (20 mg, 0.047 mmol, 1 equiv), azide **8.S52** (20.4 mg, 0.052 mmol, 1.2 equiv) and dry  $\text{CH}_2\text{Cl}_2$  (0.85 mL, 0.056 M) under nitrogen. In a glove box,  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (1.58 mg, 0.0024 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (60 % ethyl acetate in hexanes) to give the desired product as a red oil (12 mg, 31%).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 172.0, 171.5, 170.7, 168.5, 156.0, 152.7, 152.5, 152.0, 143.7, 131.7, 130.9, 129.5, 129.0, 128.8, 128.2, 125.4, 119.2, 111.4, 81.1, 66.1, 65.6, 65.1, 53.9, 48.2, 40.3, 38.8, 33.3, 30.2, 28.5, 28.3, 28.2, 28.1, 27.9, 27.4, 26.1, 25.5, 25.4, 24.9, 22.7, 18.2, 17.9, 14.1$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{42}\text{H}_{58}\text{N}_8\text{O}_7\text{SNa}$   $[\text{M}+\text{Na}]^+$  841.40414; found 841.4049.



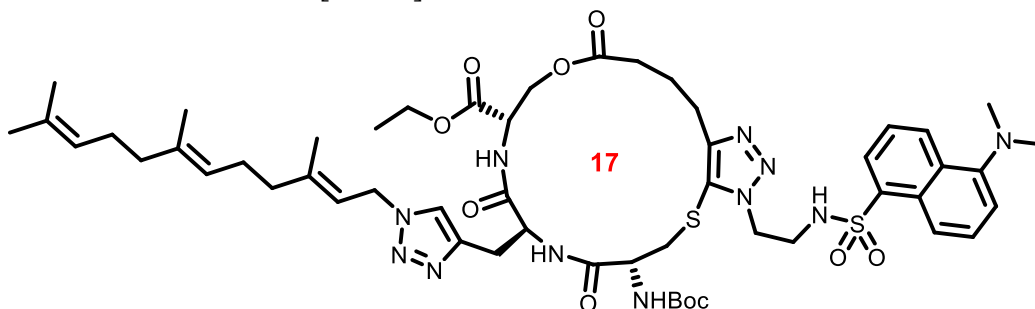
**Ethyl (6*R*,9*S*,12*S*)-6-((*tert*-butoxycarbonyl)amino)-9-isobutyl-7,10,15-trioxo-3-(6-((5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoyl)oxy)hexyl)-6,7,8,9,10,11,12,13,15,16,17,18-dodecahydro-3*H*,5*H*-[1,2,3]triazolo[4,5-*l*][1]oxa[11]thia[4,7]diazacycloheptadecine-12-carboxylate (8.26):** In an flame-dried 2 mL vial was added the thioalkyne **8.15** (29.0 mg, 0.054 mmol, 1 equiv), 6-azidohexyl 5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoate<sup>29</sup> (29.7 mg, 0.080 mmol, 1.5 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL, 0.054 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (1.80 mg, 0.0027 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (100 % acetone) to give the desired product as a brown solid (48.8 mg, 84%). HRMS (ESI) *m/z* calculated for C<sub>41</sub>H<sub>67</sub>N<sub>8</sub>O<sub>11</sub>S<sub>2</sub> [M+H]<sup>+</sup> 911.43652; found 911.43650.



**Ethyl (6'*R*,12'*R*)-6'-((*tert*-butoxycarbonyl)amino)-7',10',15'-trioxo-3'-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-5',6',7',8',10',11',12',13',15',16',17',18'-dodecahydro-3'*H*-spiro[cyclopropane-1,9'-[1,2,3]triazolo[4,5-*l*][1]oxa[11]thia[4,7]diazacycloheptadecine]-12'-carboxylate (8.27):** In an flame-dried 2 mL vial was added the thioalkyne **8.12** (40 mg, 0.078 mmol, 1 equiv), (2*E*,6*E*)-1-azido-3,7,11-trimethyldodeca-2,6,10-triene (29.0 mg, 0.117 mmol, 1.5 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 0.052 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (1.86 mg, 0.0028 mmol, 5 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel (50 % ethyl acetate in

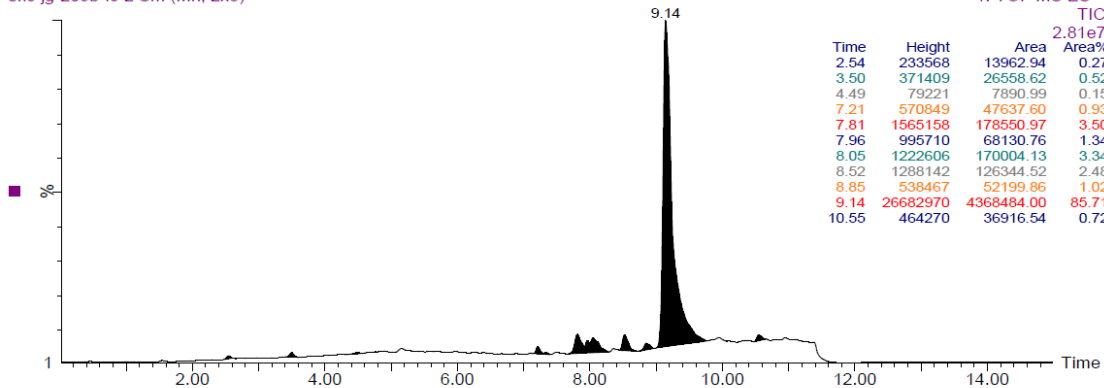
<sup>29</sup> Prasad, G.; Amoroso, J. W.; Borketey, L. S.; Schnarr, N. A. *Org. Biomol. Chem.* **2012**, *10*, 1992 – 2002.

CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product as a colorless oil (26.0 mg, 50%). HRMS (ESI) m/z calculated for C<sub>38</sub>H<sub>58</sub>N<sub>6</sub>O<sub>8</sub>SNa [M+Na]<sup>+</sup> 781.3929; found 781.39425.



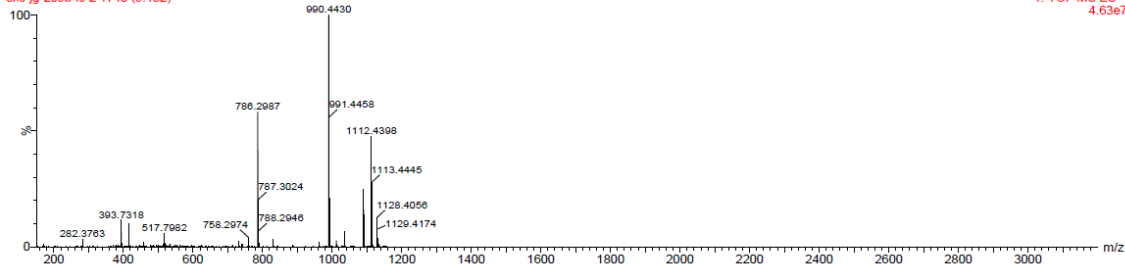
**Ethyl (6*R*,9*S*,12*S*)-6-((*tert*-butoxycarbonyl)amino)-3-(2-((5-(dimethylamino)naphthalen-1-sulfonamido)ethyl)-7,10,15-trioxo-9-((1-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-6,7,8,9,10,11,12,13,15,16,17,18-dodecahydro-3*H*,5*H*-[1,2,3]triazolo[4,5-*l*][1]oxa[11]thia[4,7]diazacycloheptadecine-12-carboxylate (8.29):** In a 2 mL vial, macrocyclic alkyne **8.17** (35.0 mg, 0.067 mmol, 1 equiv) and (2*E*,6*E*)-1-azido-3,7,11-trimethyldodeca-2,6,10-triene (18.2 mg, 0.074 mmol, 1.1 equiv) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.4 mL, 0.17 M). To the reaction mixture, were added CuSO<sub>4</sub>·5 H<sub>2</sub>O (3.2 mg, 0.020 mmol, 30 mol%) and a freshly prepared solution of sodium *L*-ascorbate (8.03 mg, 0.040 mmol, 60 mol%) in water (0.4 mL). The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), extracted with water (3×10 mL); dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude reaction mixture was added to a flame-dried 2 mL vial (20.0 mg, 0.026 mmol, 1 equiv) with *N*-(2-azidoethyl)-5-(dimethylamino)naphthalene-1-sulfonamide (16.6 mg, 0.052 mmol, 2 equiv) and dry CH<sub>2</sub>Cl<sub>2</sub> (1.00 mL, 0.026 M) under nitrogen. In a glove box, [Ir(cod)Cl]<sub>2</sub> (1.86 mg, 0.0028 mmol, 10 mol%) was added. The vial was removed from the glove box and the mixture was stirred at room temperature overnight. When the reaction was completed, the mixture was concentrated under reduced pressure. The crude reaction mixture was quickly purified by column chromatography on silica gel (70 % ethyl acetate in hexanes) to give the desired product as a green oil (26.0 mg, 85 % purity, 36 % over two steps). HRMS (ESI) m/z calculated for C<sub>53</sub>H<sub>75</sub>N<sub>11</sub>O<sub>10</sub>S<sub>2</sub>Na [M+Na]<sup>+</sup> 1112.5032; found 1112.50259.

skc-jg-209b-lc-2 Sm (Mn, 2x3)



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2.81e7

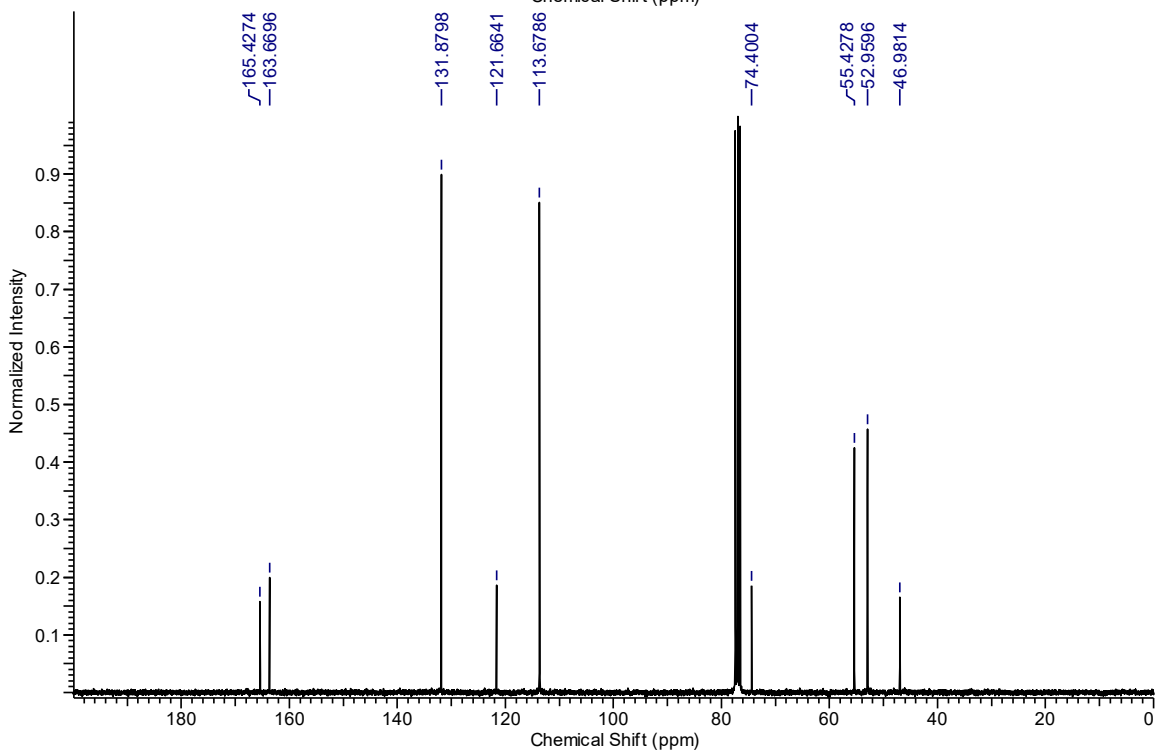
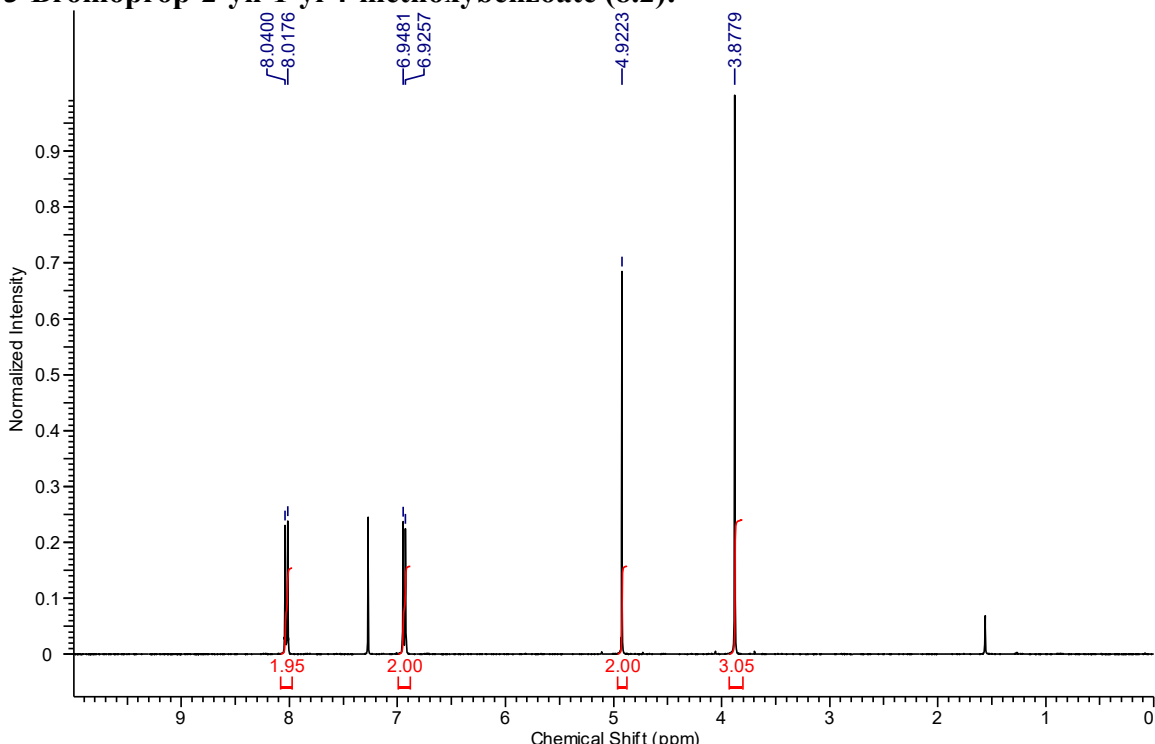
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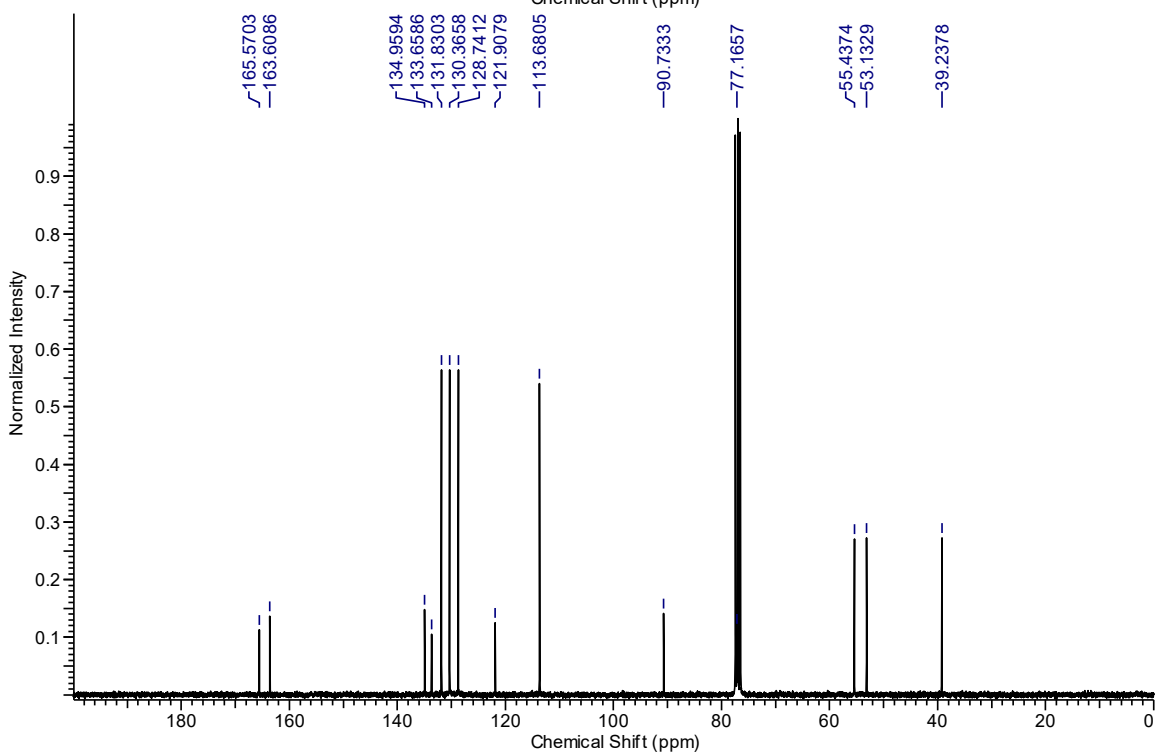
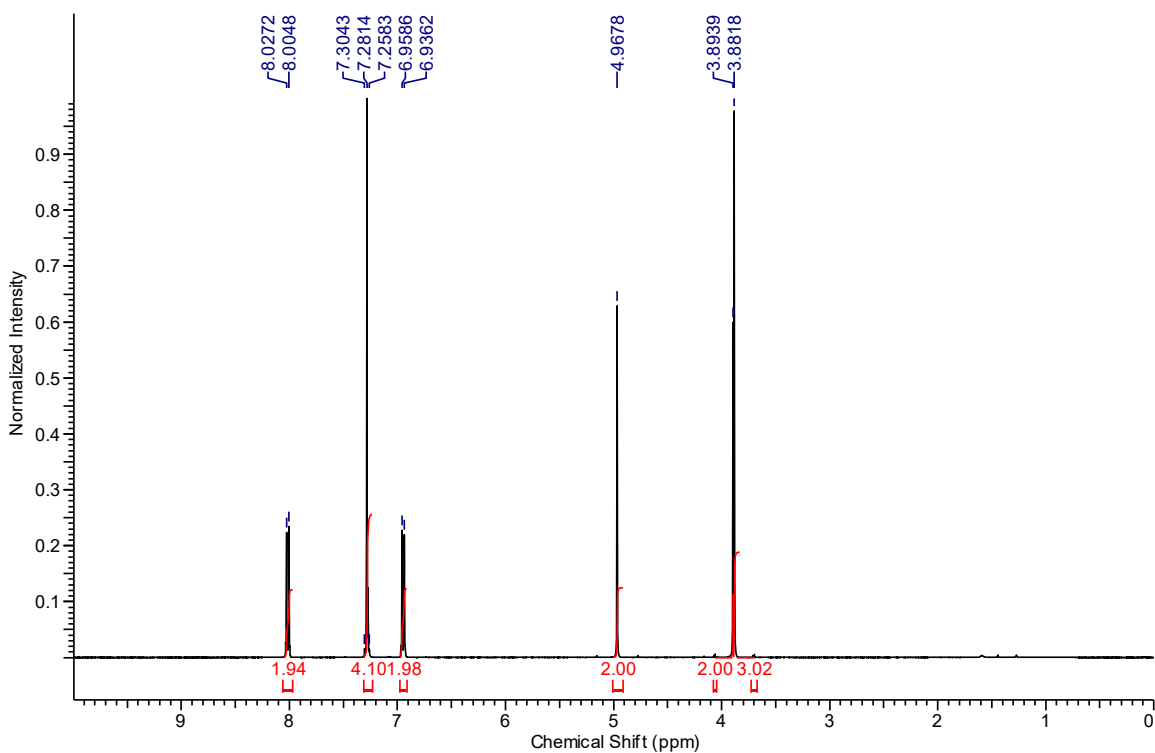
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4.63e7

# NMR DATA FOR ALL NEW COMPOUNDS

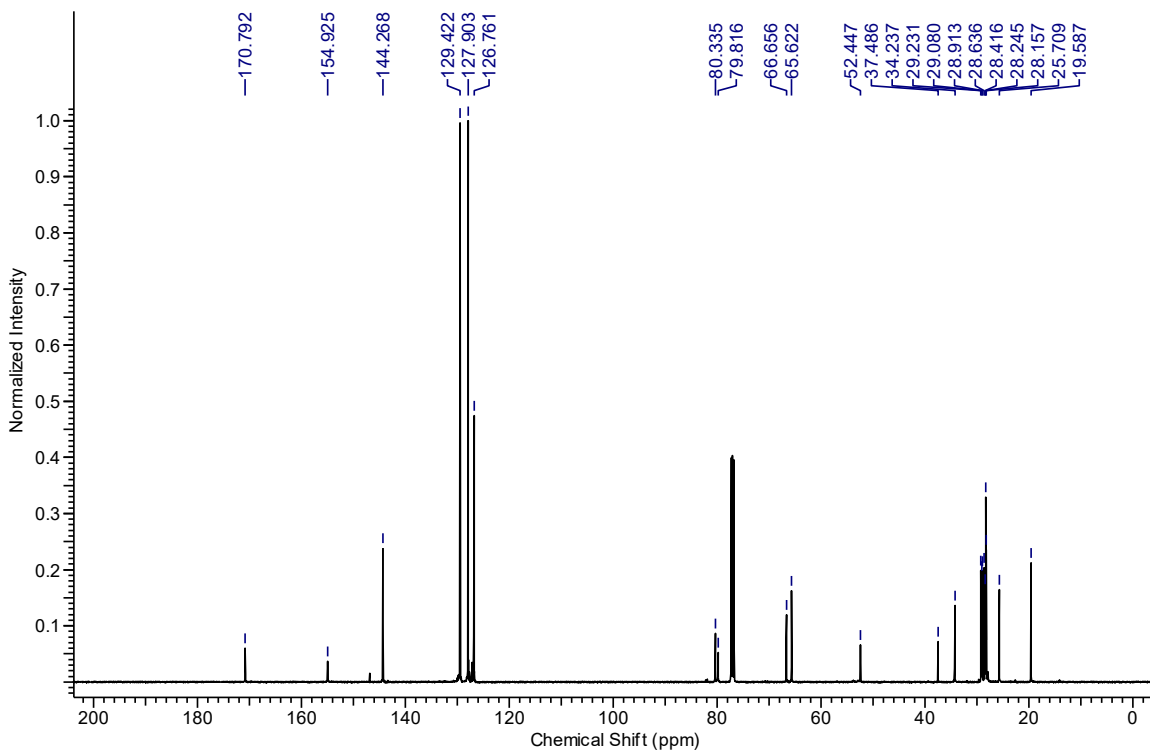
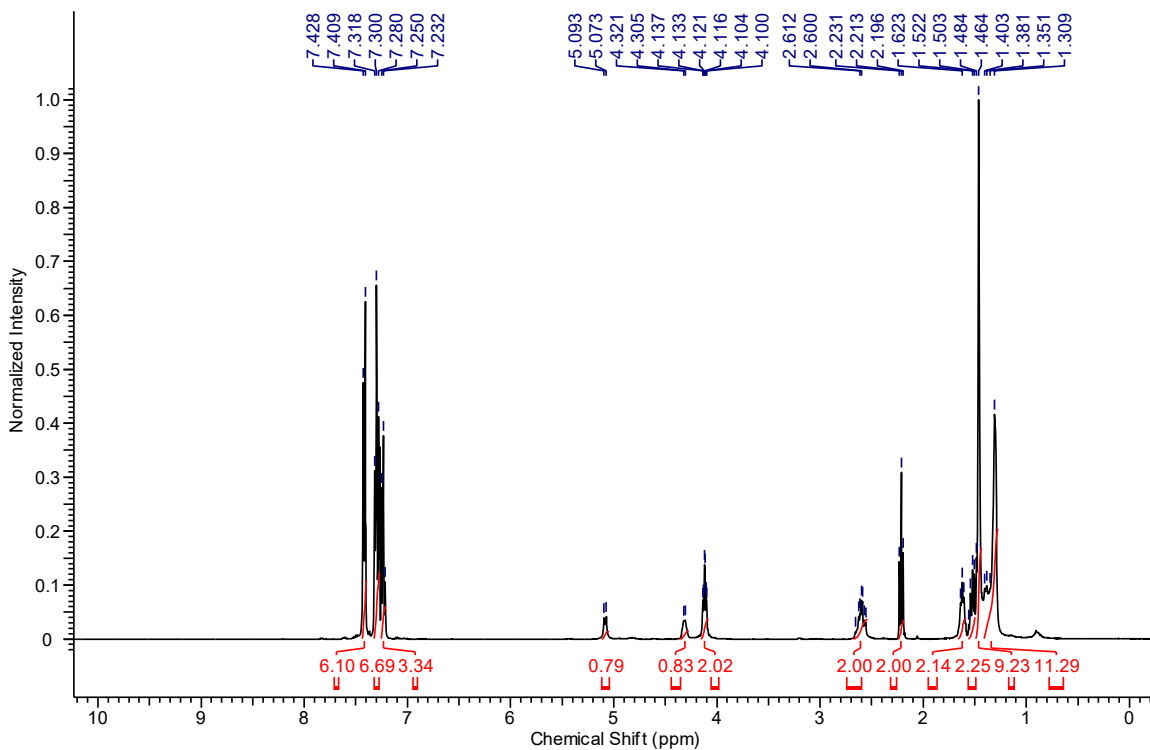
## 3-Bromoprop-2-yn-1-yl 4-methoxybenzoate (8.2):



**3-((4-Chlorobenzyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (8.3):**

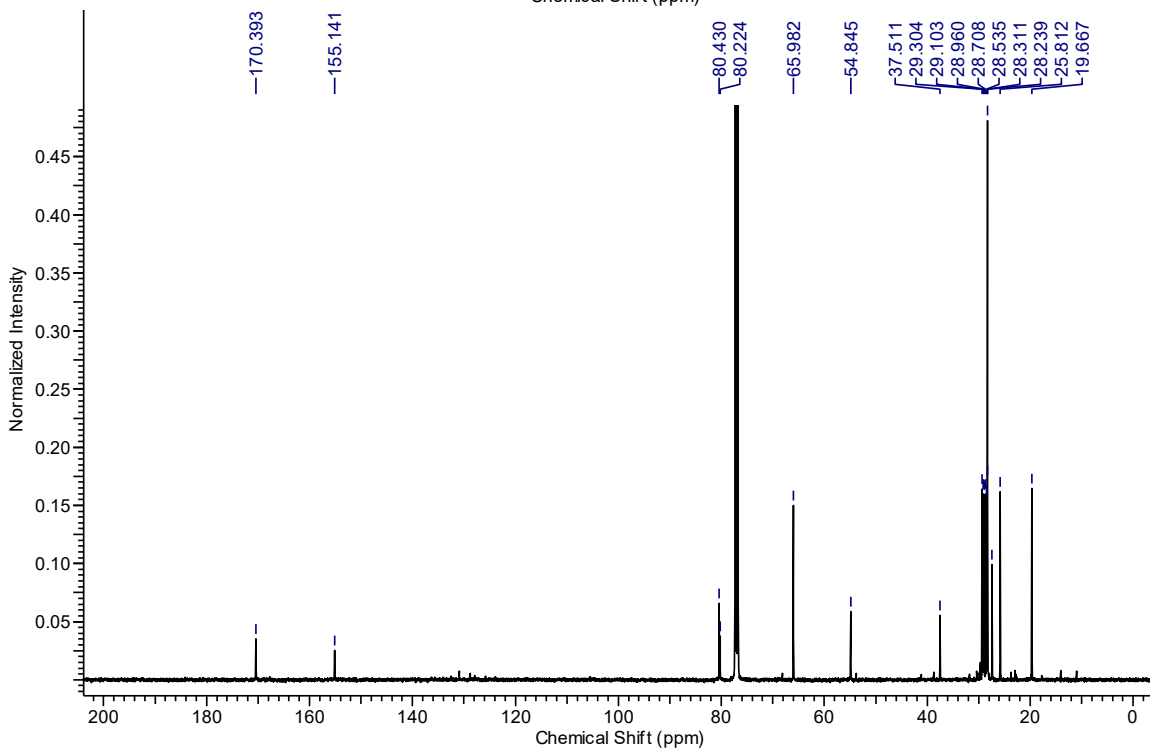
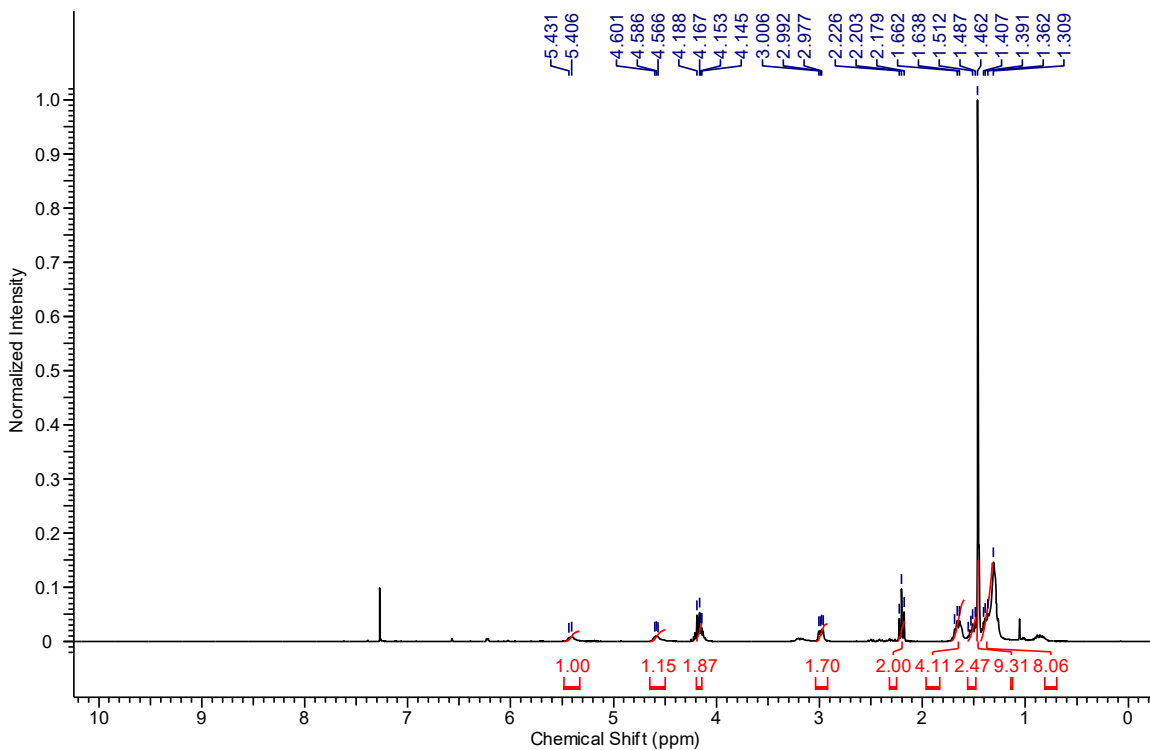


**11-Bromoundec-10-yn-1-yl *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteinate (8.S1):**

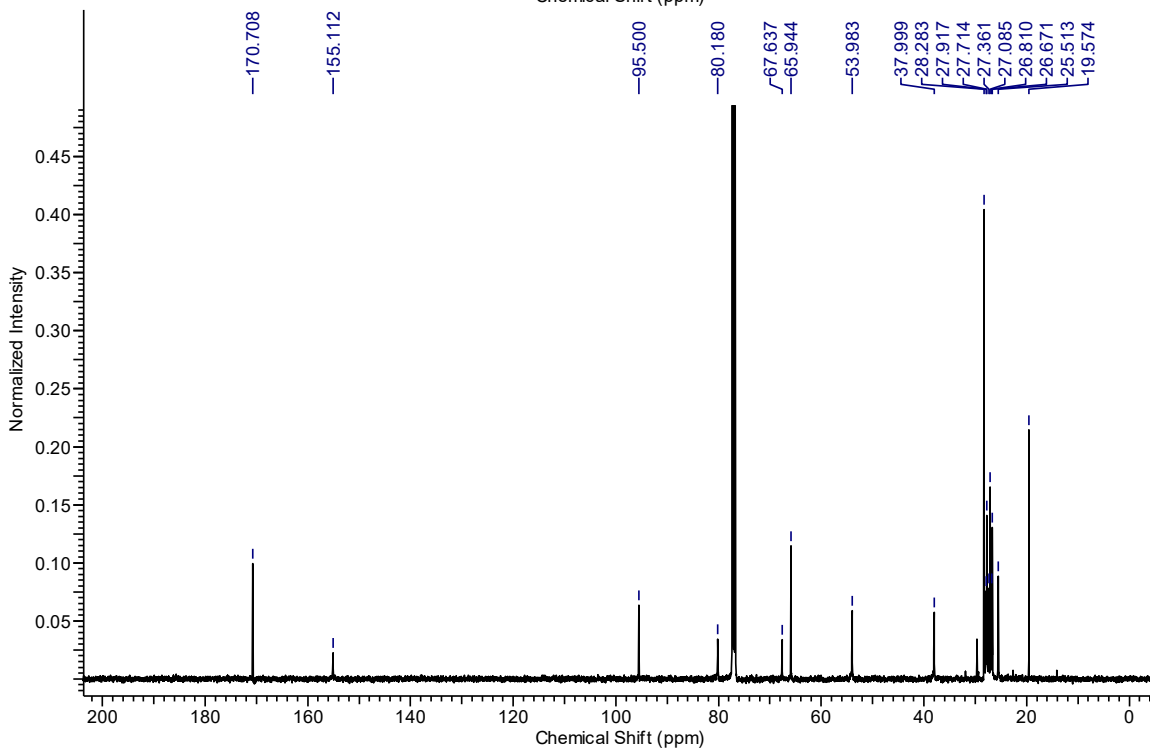
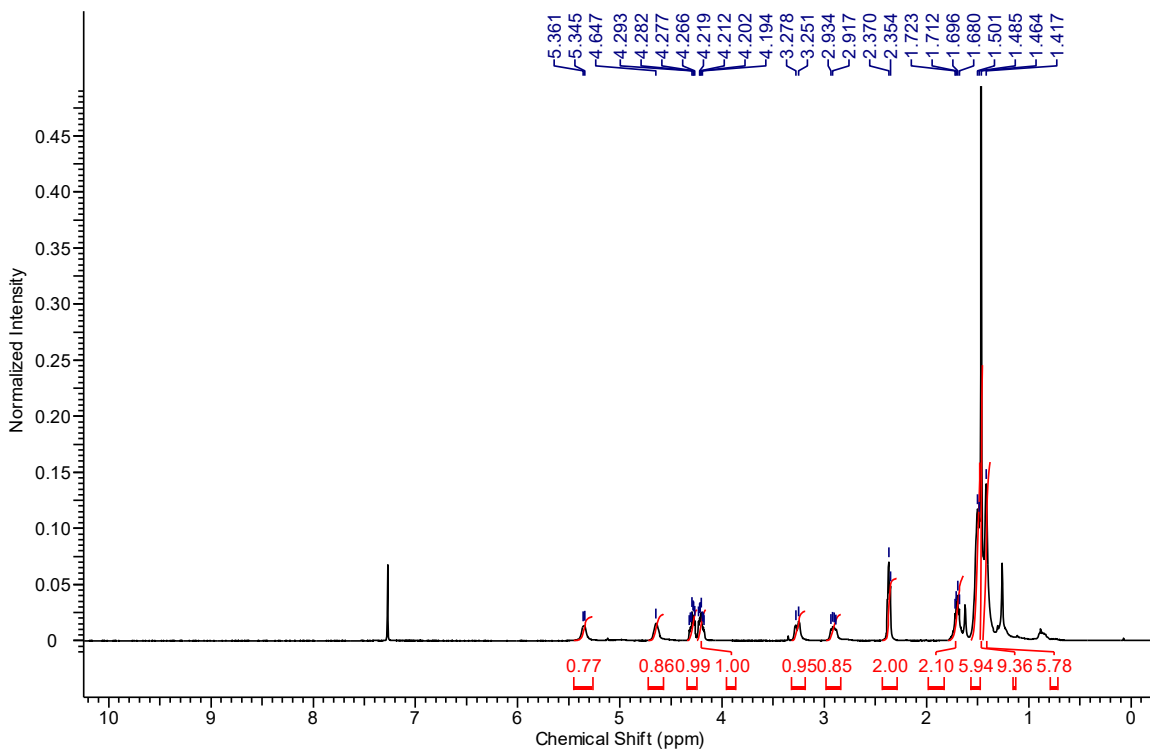




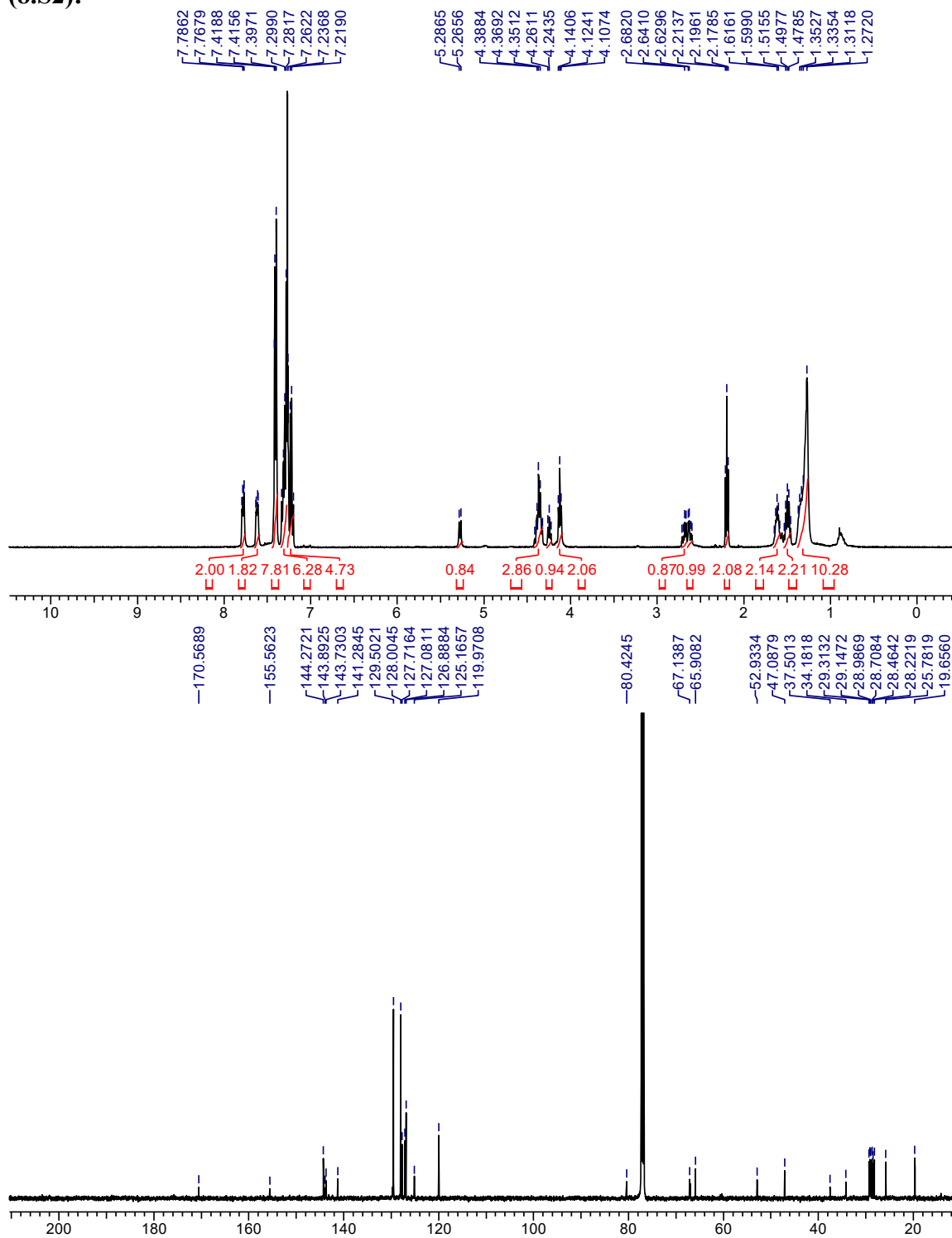
**11-Bromoundec-10-yn-1-yl (*tert*-butoxycarbonyl)-*L*-cysteinate (8.4):**



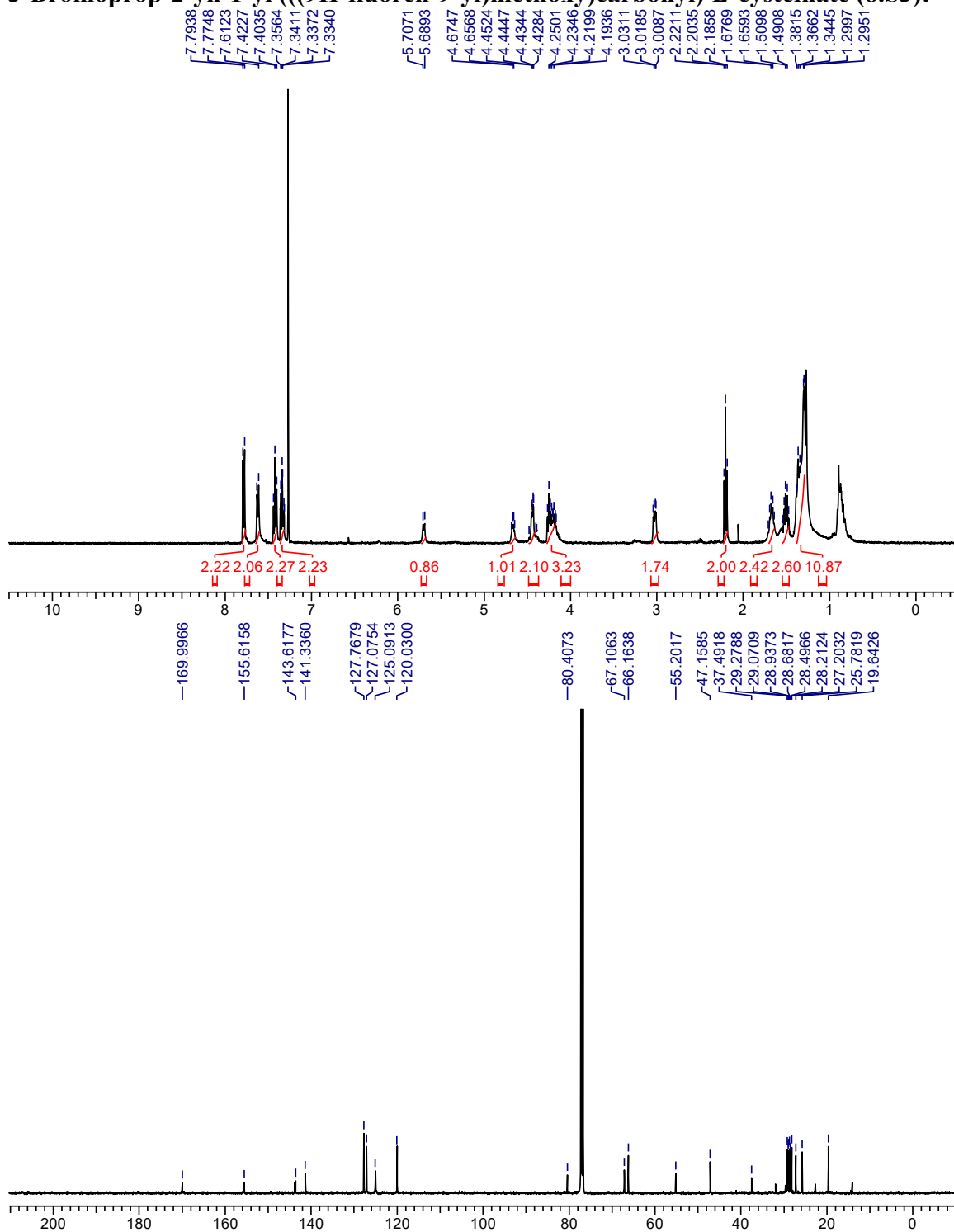
***Tert*-butyl (*R*)-(2-oxo-1-oxa-5-thiacyclohexadec-6-yn-3-yl)carbamate (8.5):**



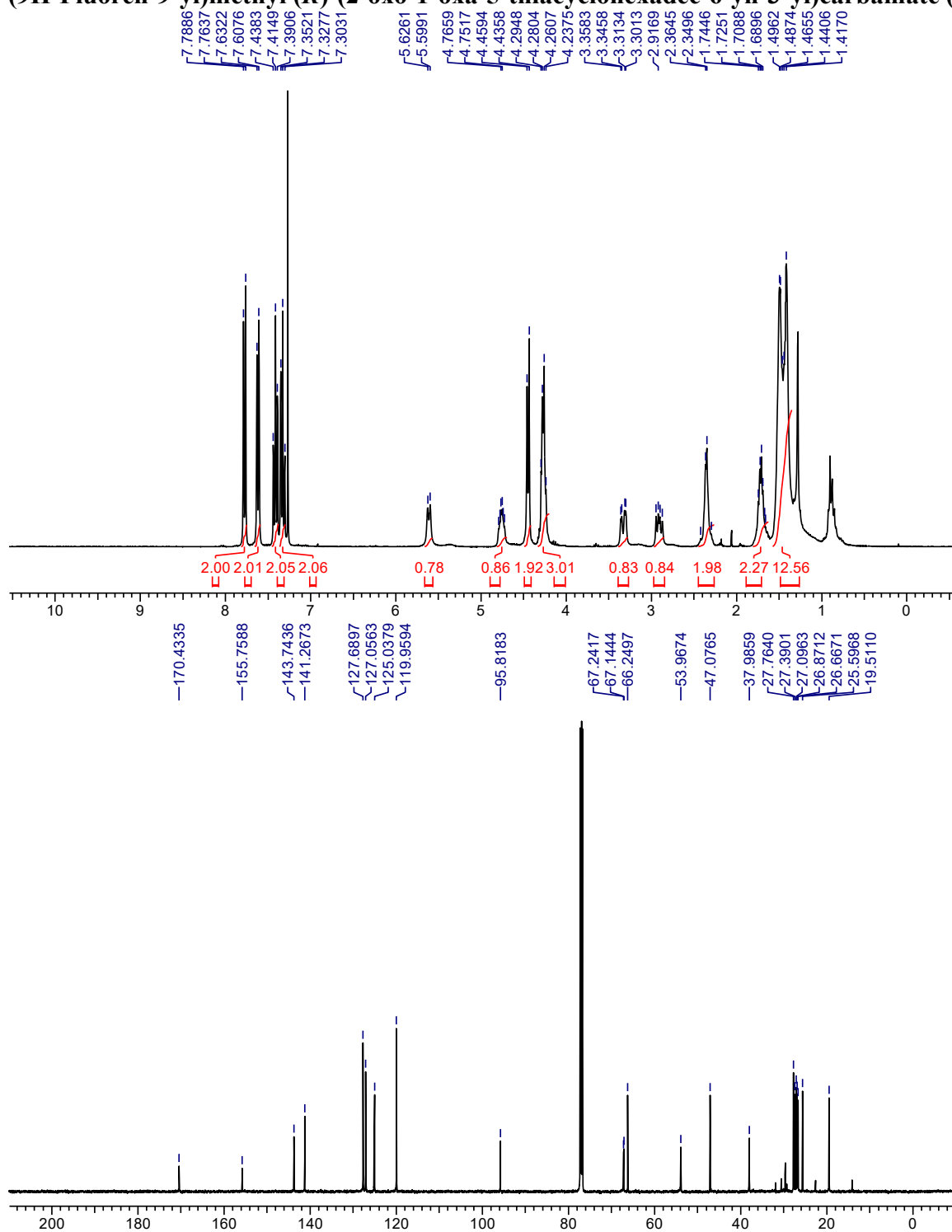
**3-Bromoprop-2-yn-1-yl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinate (8.S2):**



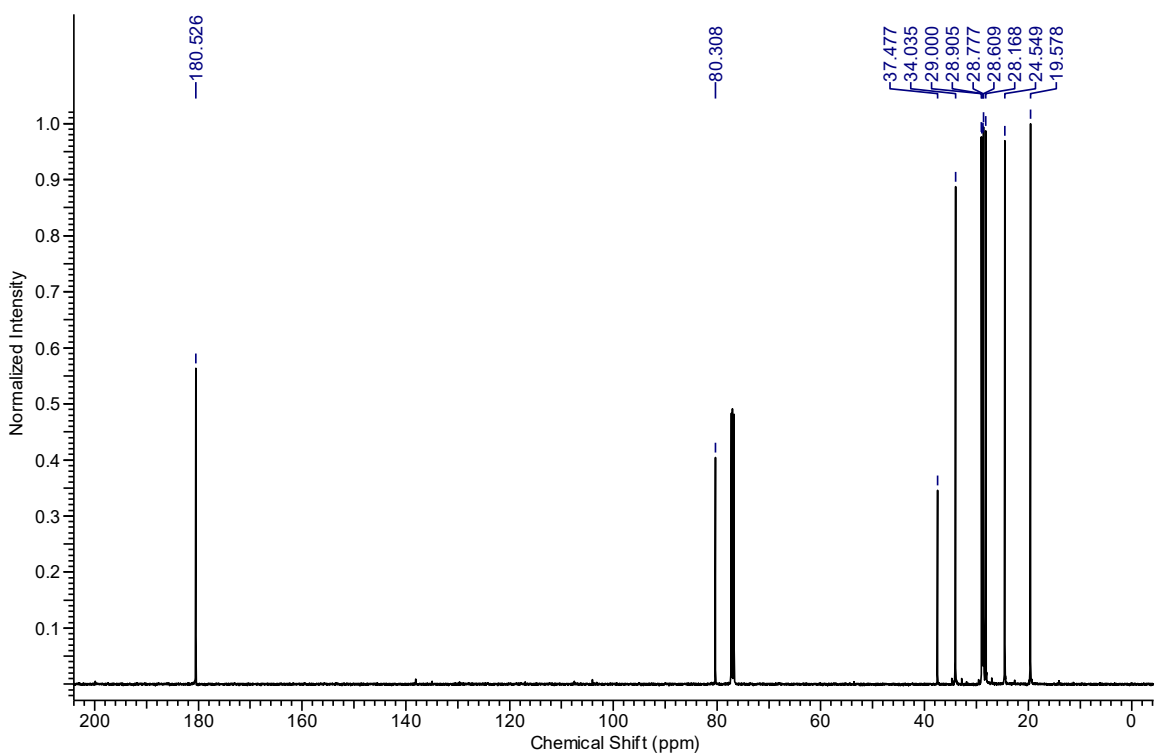
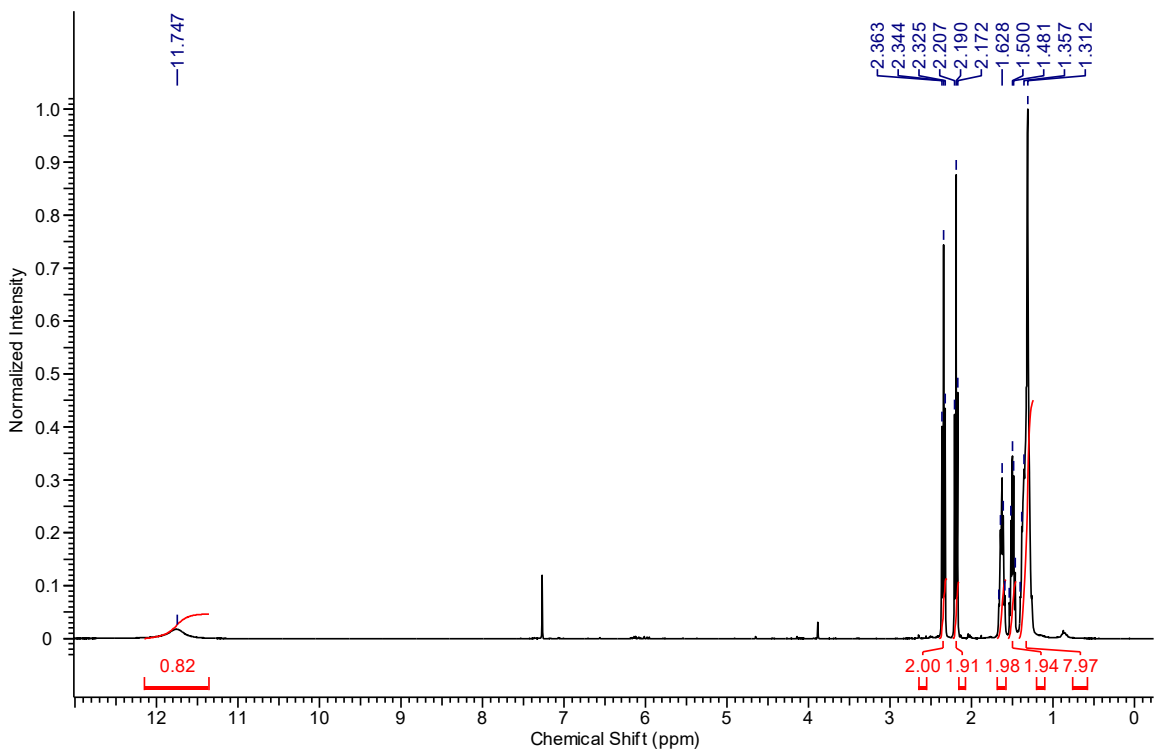
**3-Bromoprop-2-yn-1-yl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-cysteinate (8.S3):**



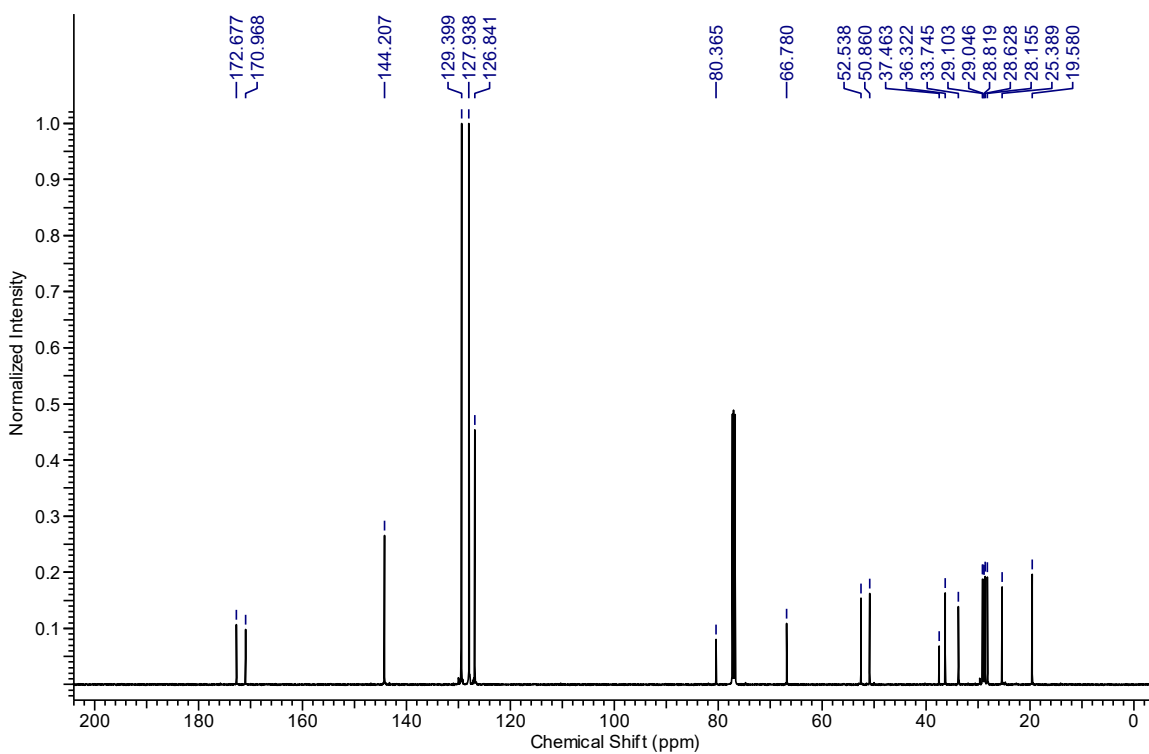
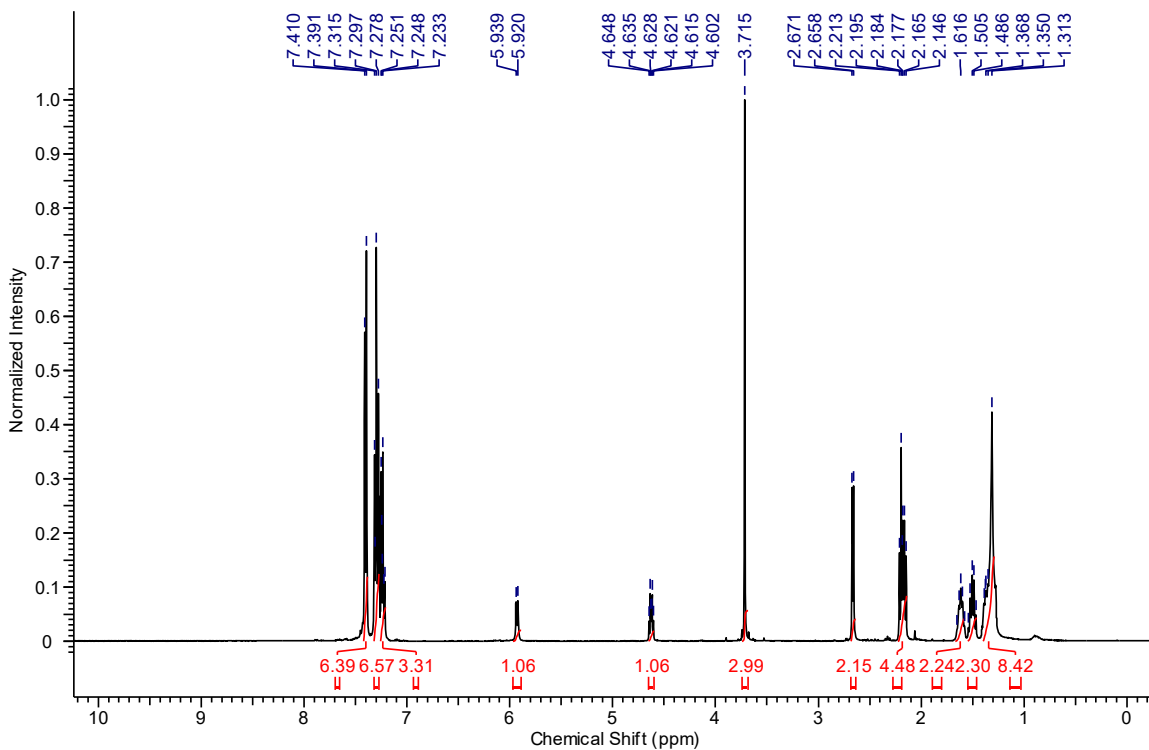
**(9H-Fluoren-9-yl)methyl (R)-(2-oxo-1-oxa-5-thiacyclohexadec-6-yn-3-yl)carbamate (8.6):**



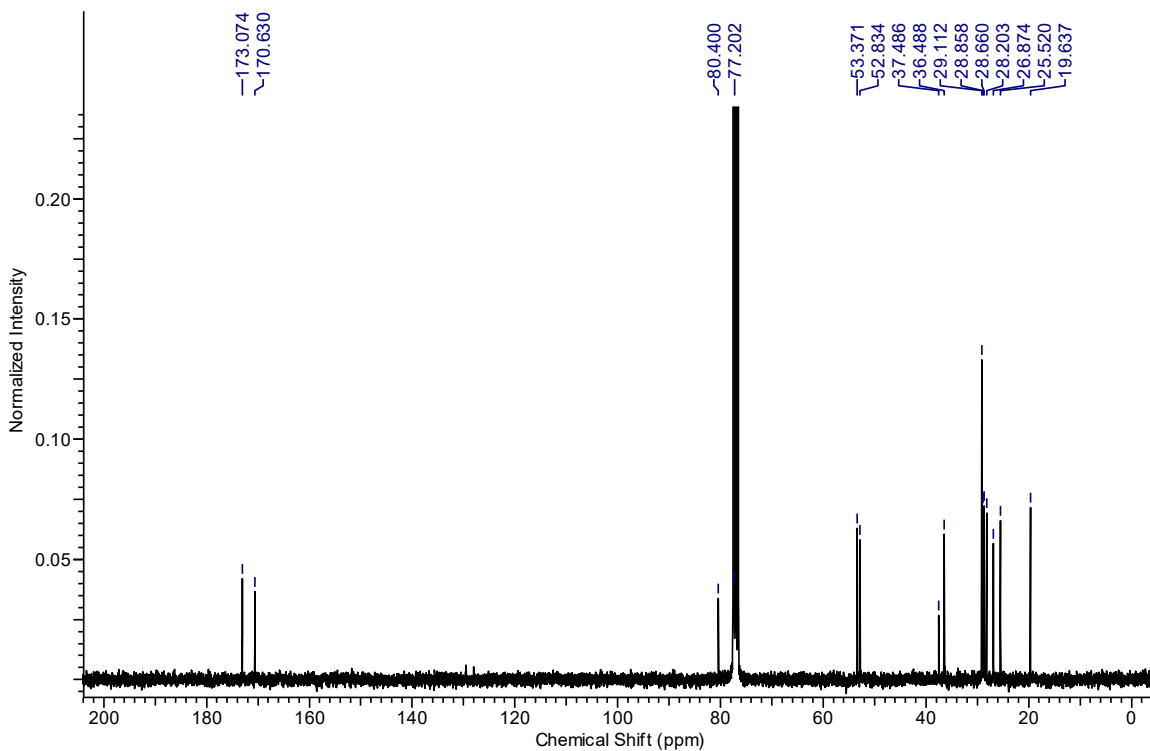
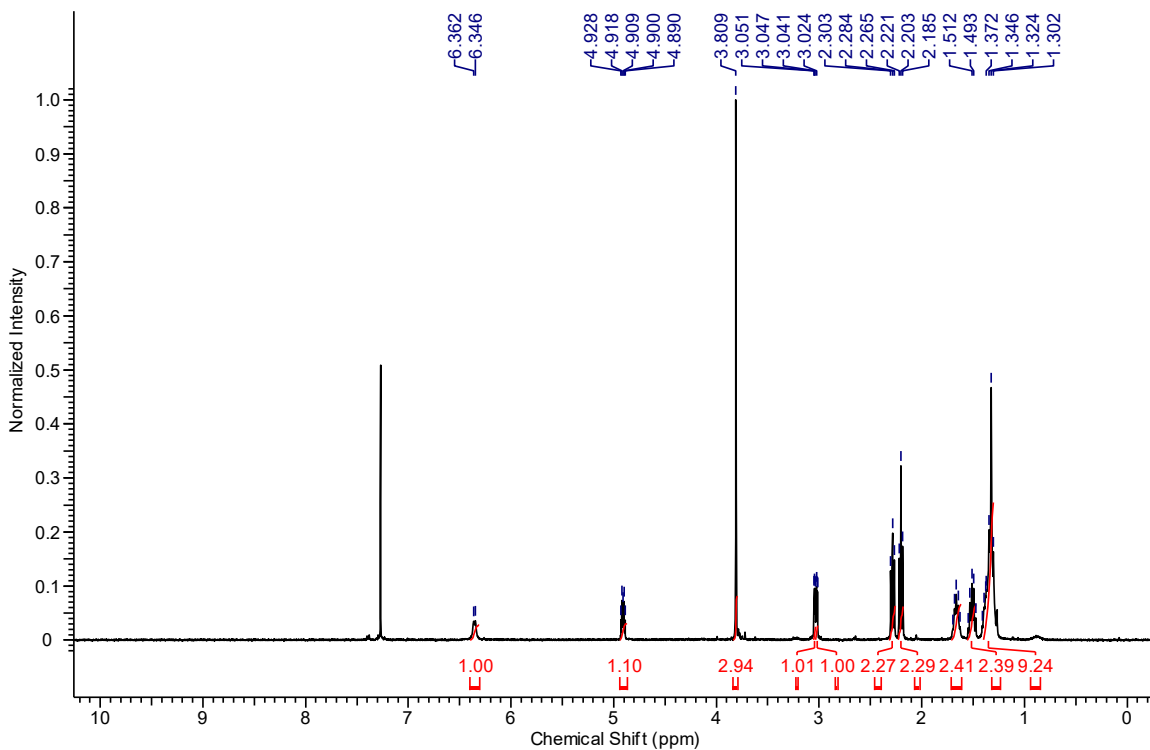
### 11-Bromo-10-undecynoic acid (8.S4):



**Methyl *N*-(11-bromoundec-10-ynoyl)-*S*-trityl-*L*-cysteinate (8.S5):**

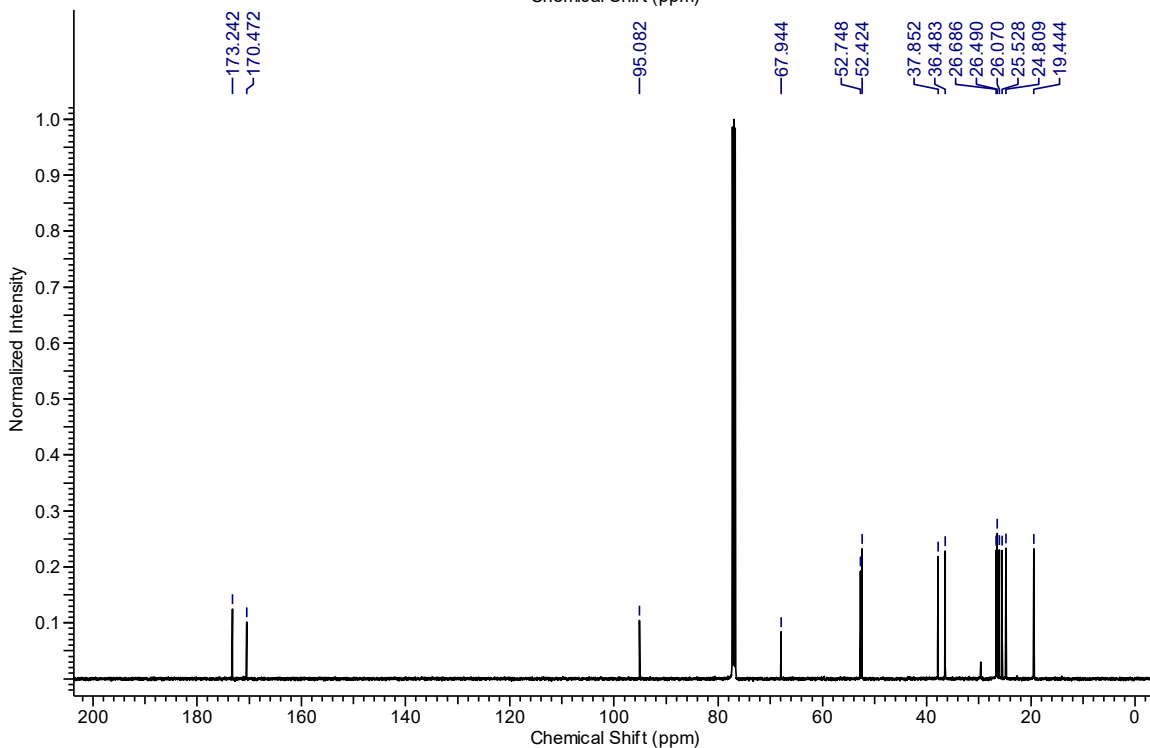
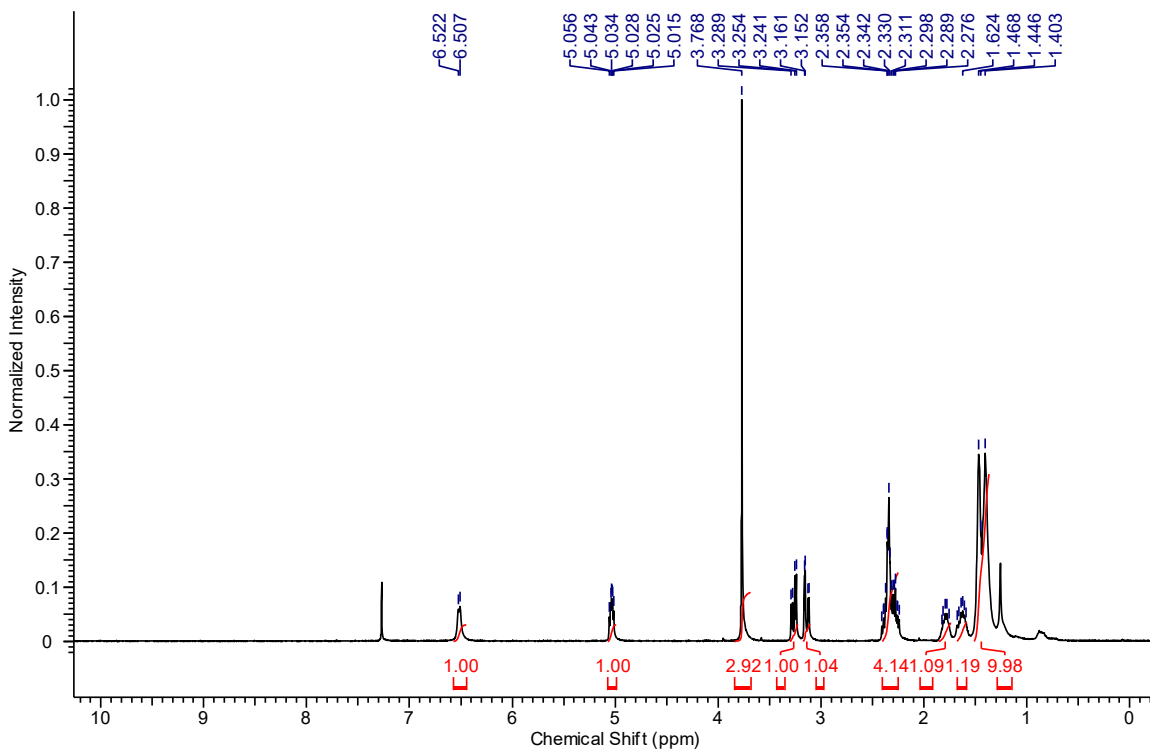


**Methyl (11-bromoundec-10-ynoyl)-L-cysteinate (8.S6):**

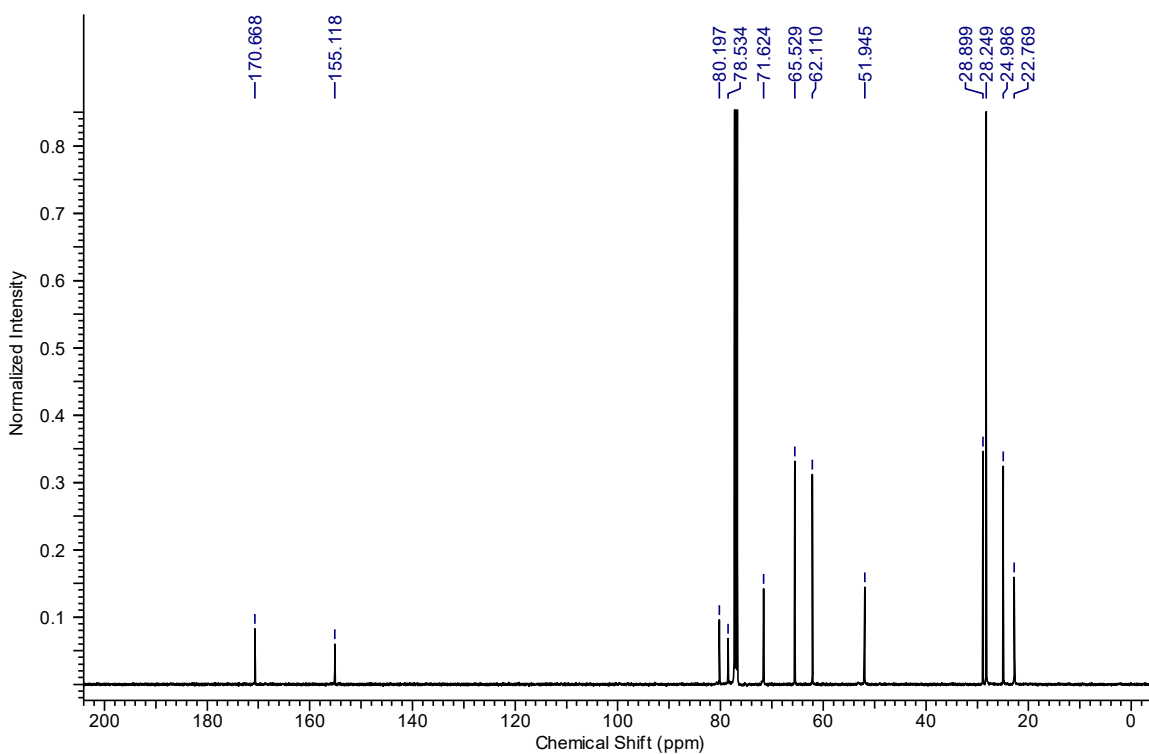
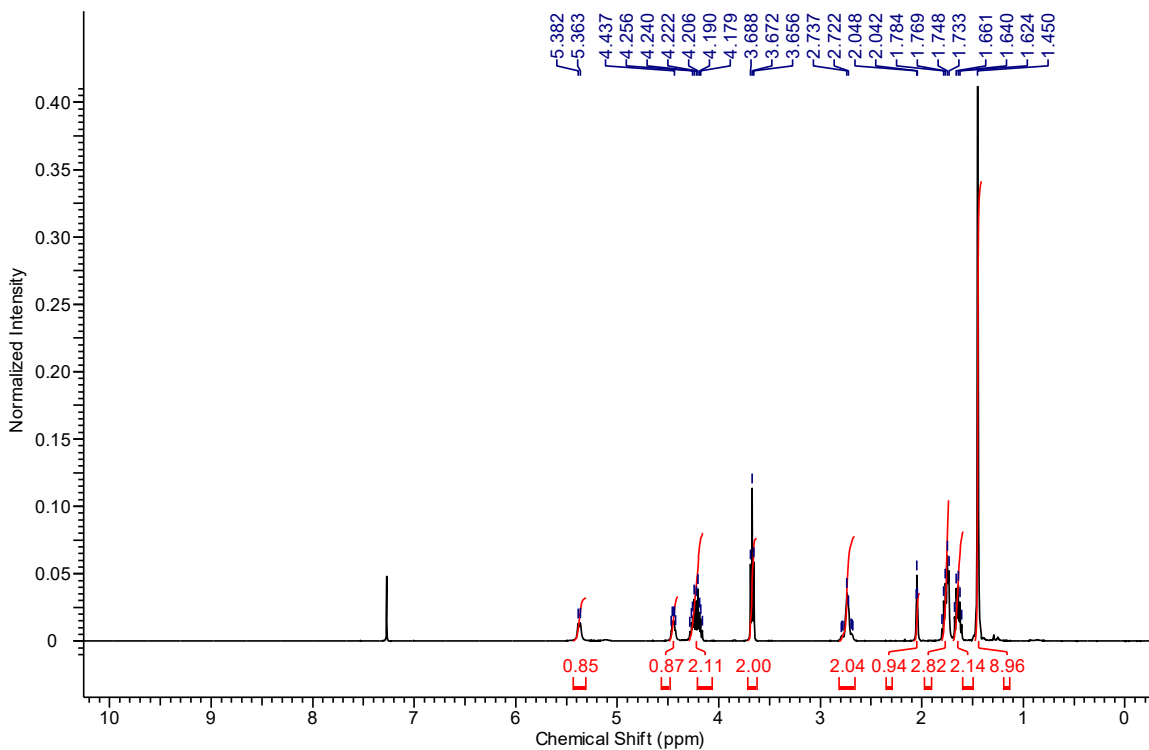




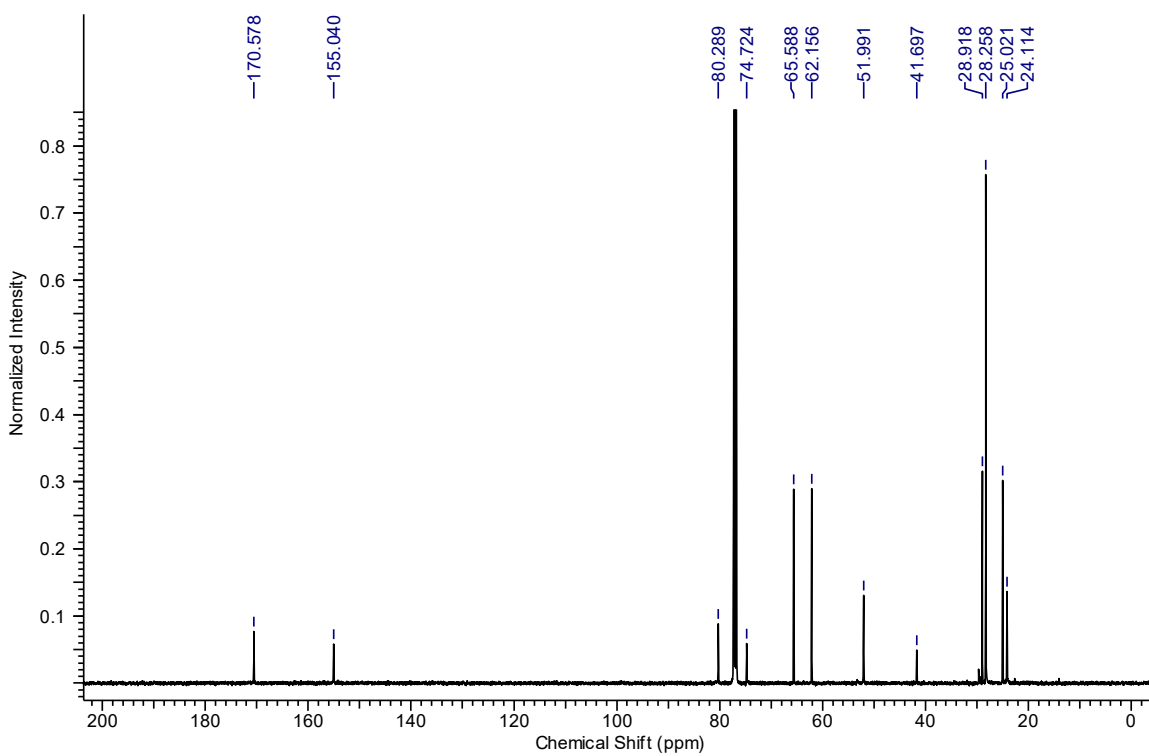
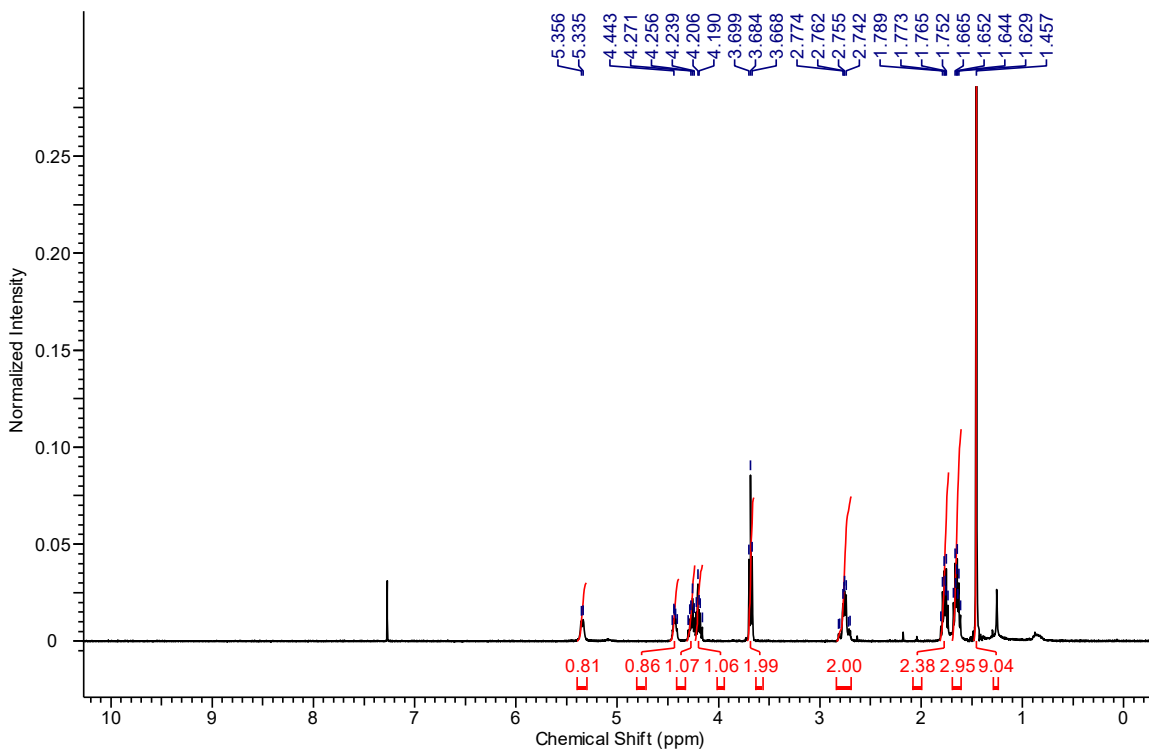
**Methyl (*R*)-5-oxo-1-thia-4-azacyclopentadec-14-yne-3-carboxylate (8.7):**



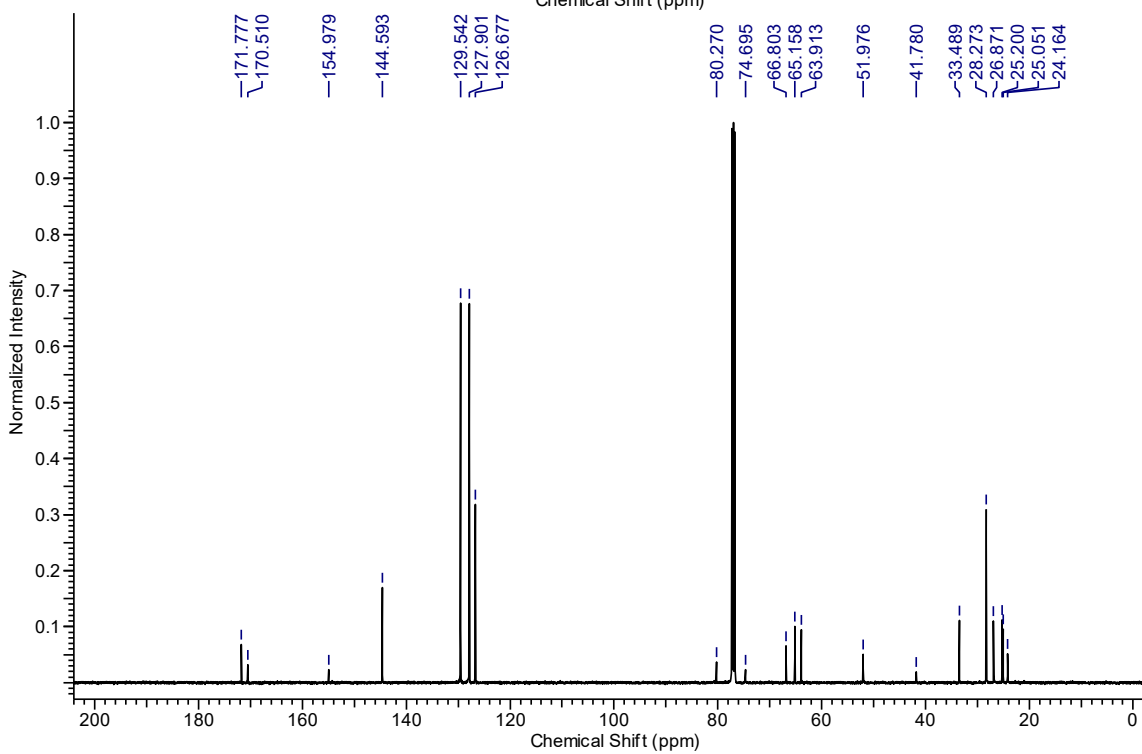
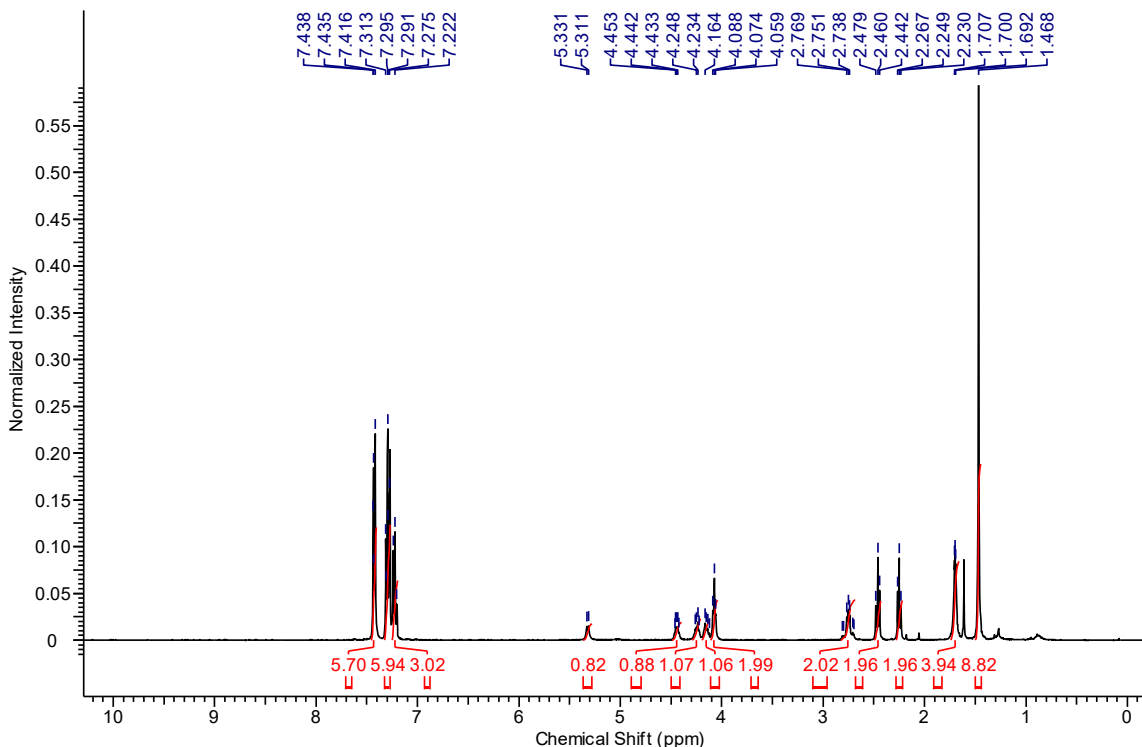
### 4-Hydroxybutyl (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-ynoate (8.S7)



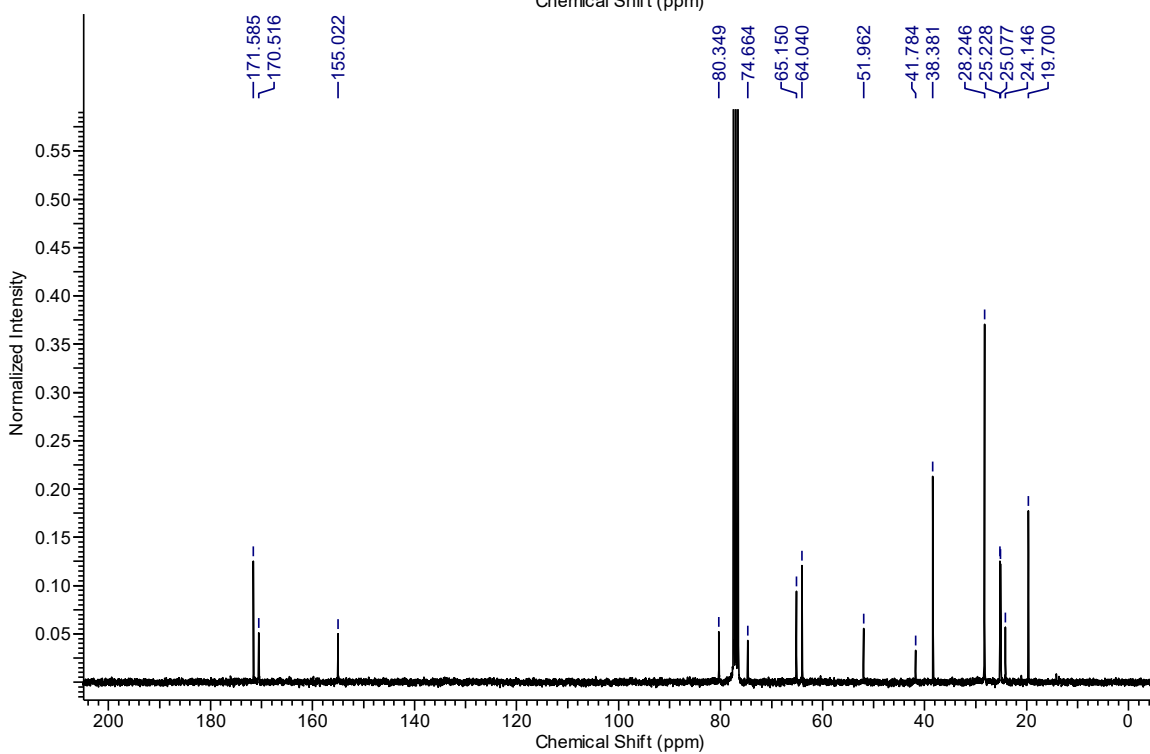
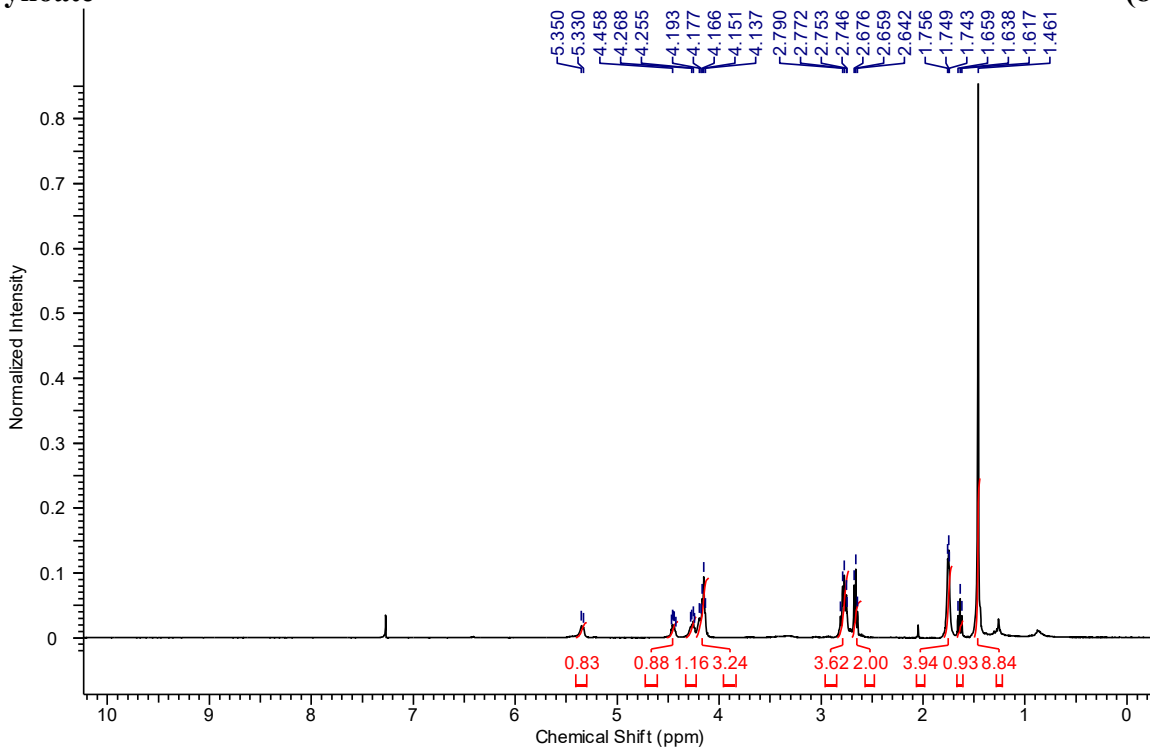
**4-Hydroxybutyl (S)-5-bromo-2-((tert-butoxycarbonyl)amino)pent-4-ynoate (8.S8)**



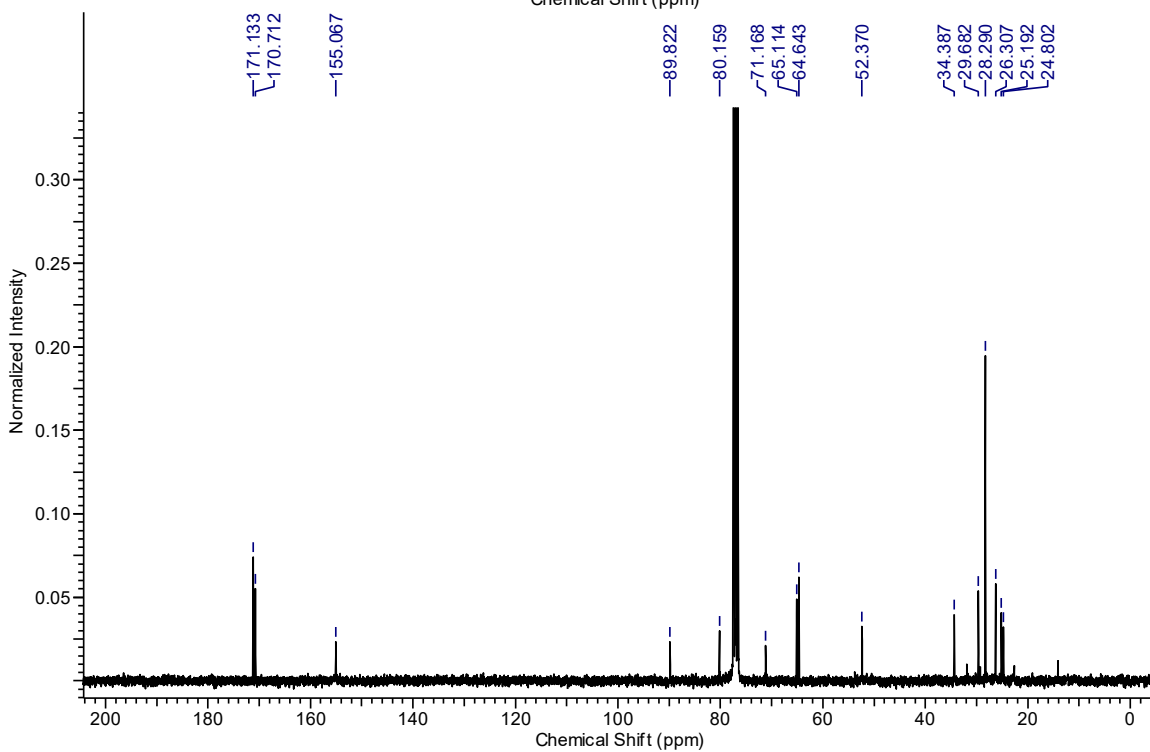
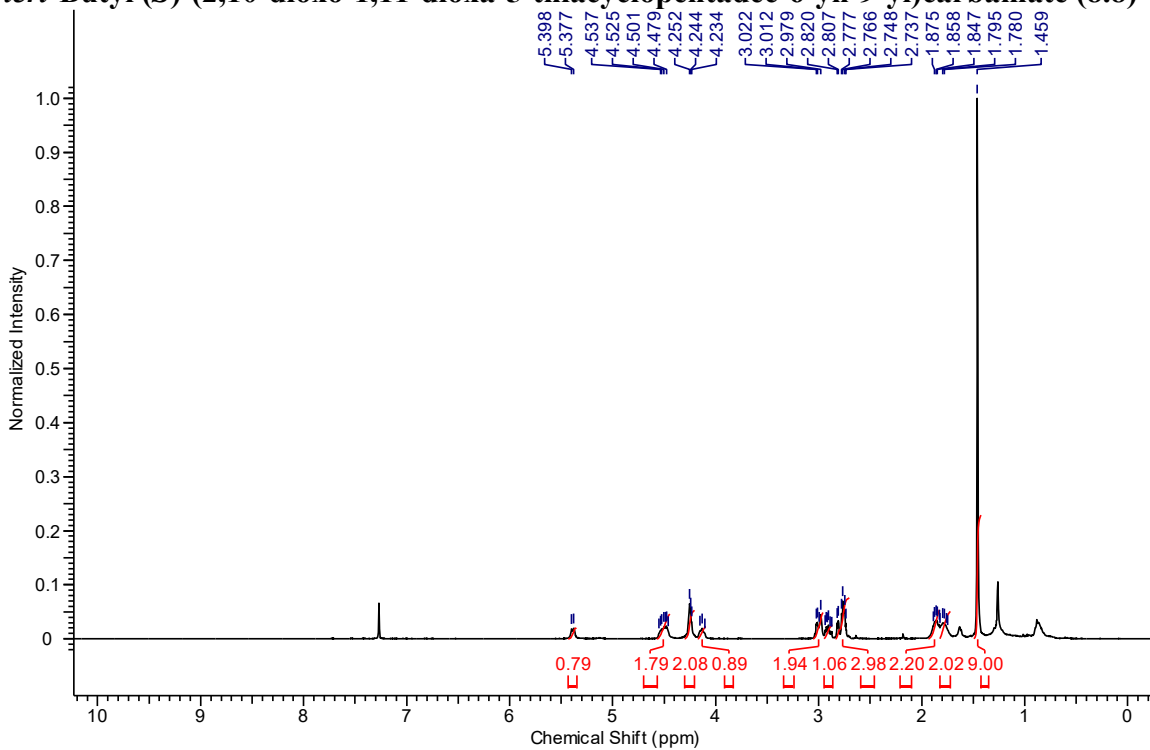
**4-((3-(Tritylthio)propanoyl)oxy)butyl (S)-5-bromo-2-((tert-butoxycarbonyl)amino)pent-4-ynoate (8.S9)**



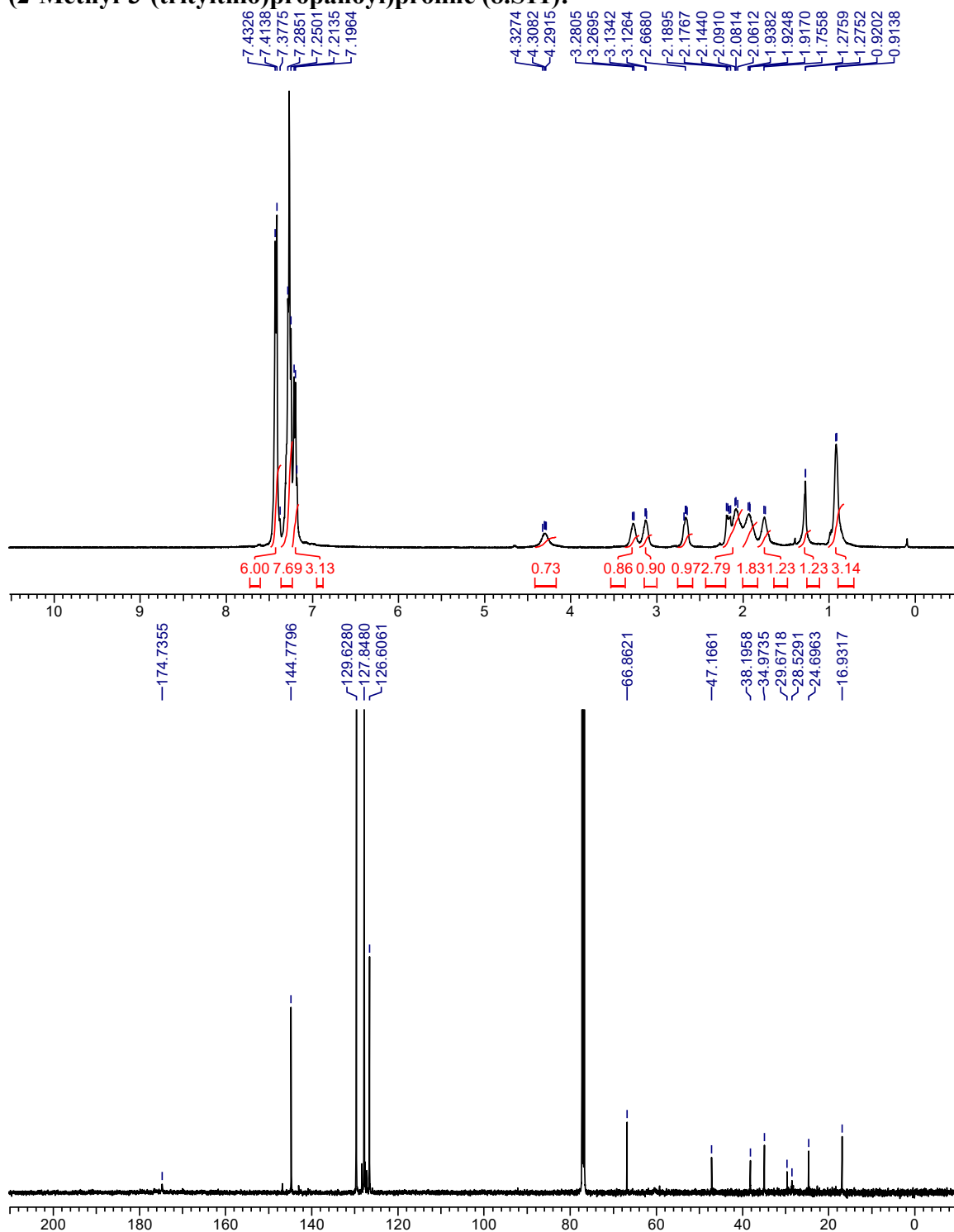
**4-((3-Mercaptopropanoyl)oxy)butyl (S)-5-bromo-2-((tert-butoxycarbonyl)-amino)pent-4-ynoate (8.S10)**



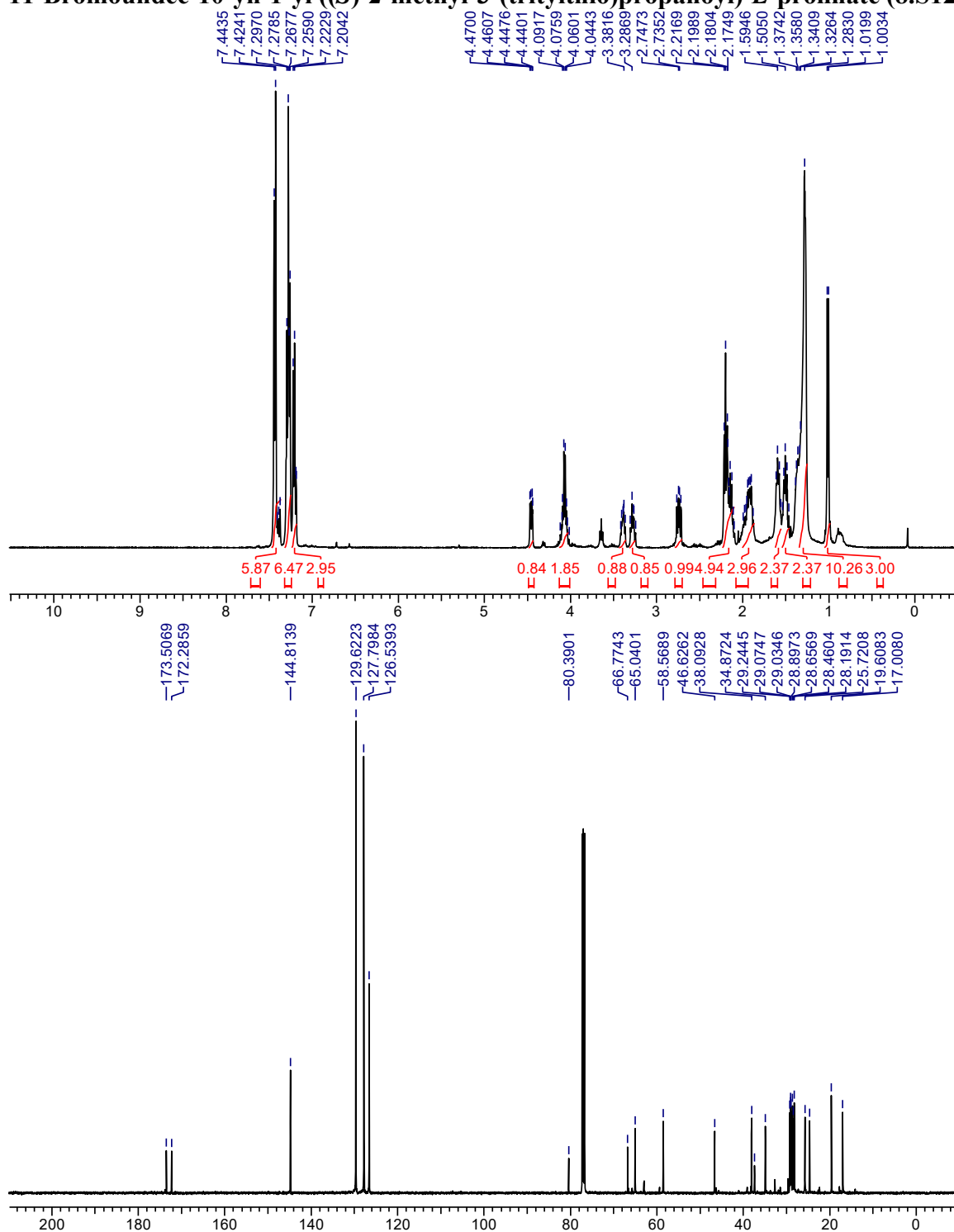
***tert*-Butyl (*S*)-(2,10-dioxo-1,11-dioxa-5-thiacyclopentadec-6-yn-9-yl)carbamate (8.8)**



**(2-Methyl-3-(tritylthio)propanoyl)proline (8.S11):**

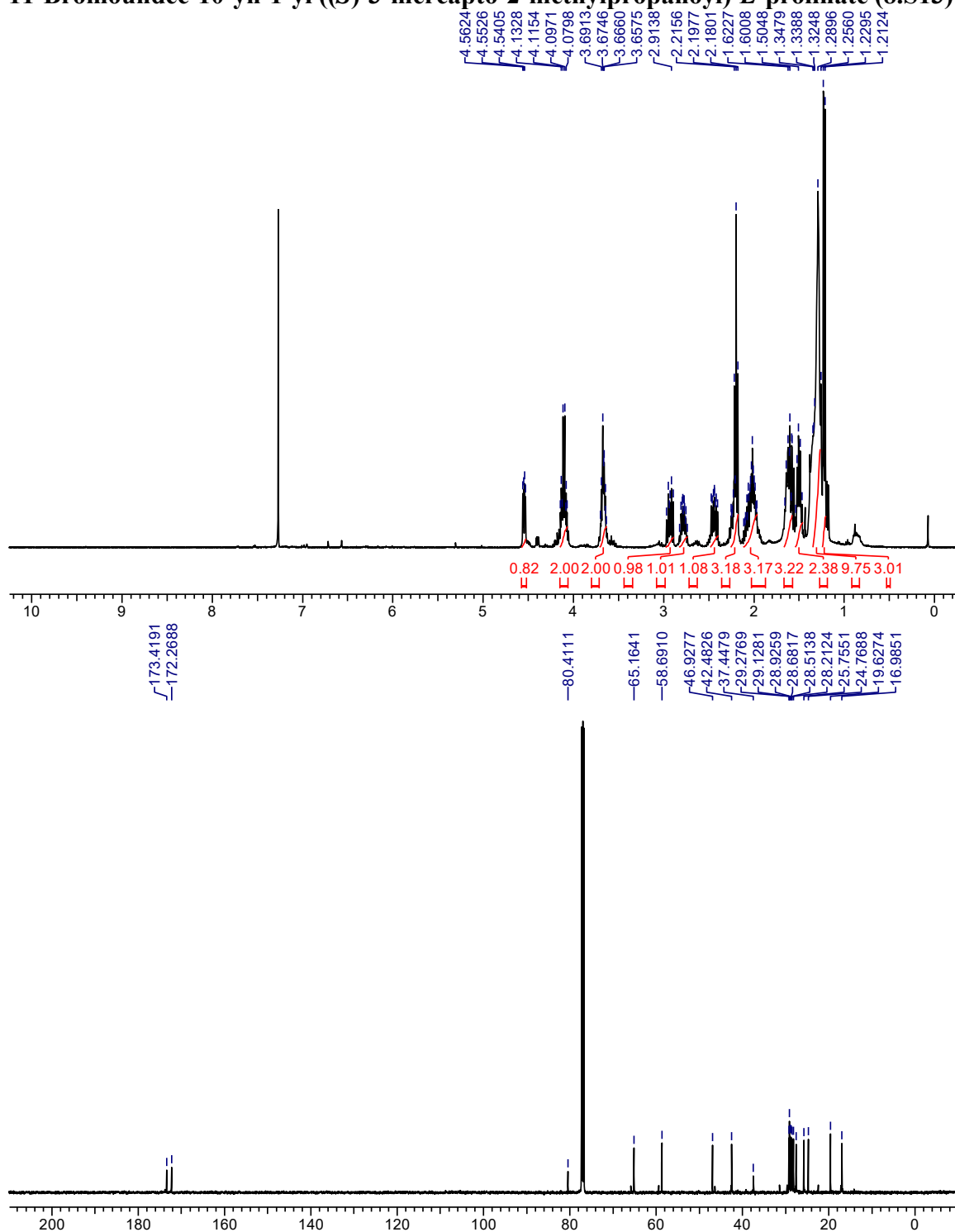


**11-Bromoundec-10-yn-1-yl ((S)-2-methyl-3-(tritylthio)propanoyl)-L-prolinate (8.S12):**

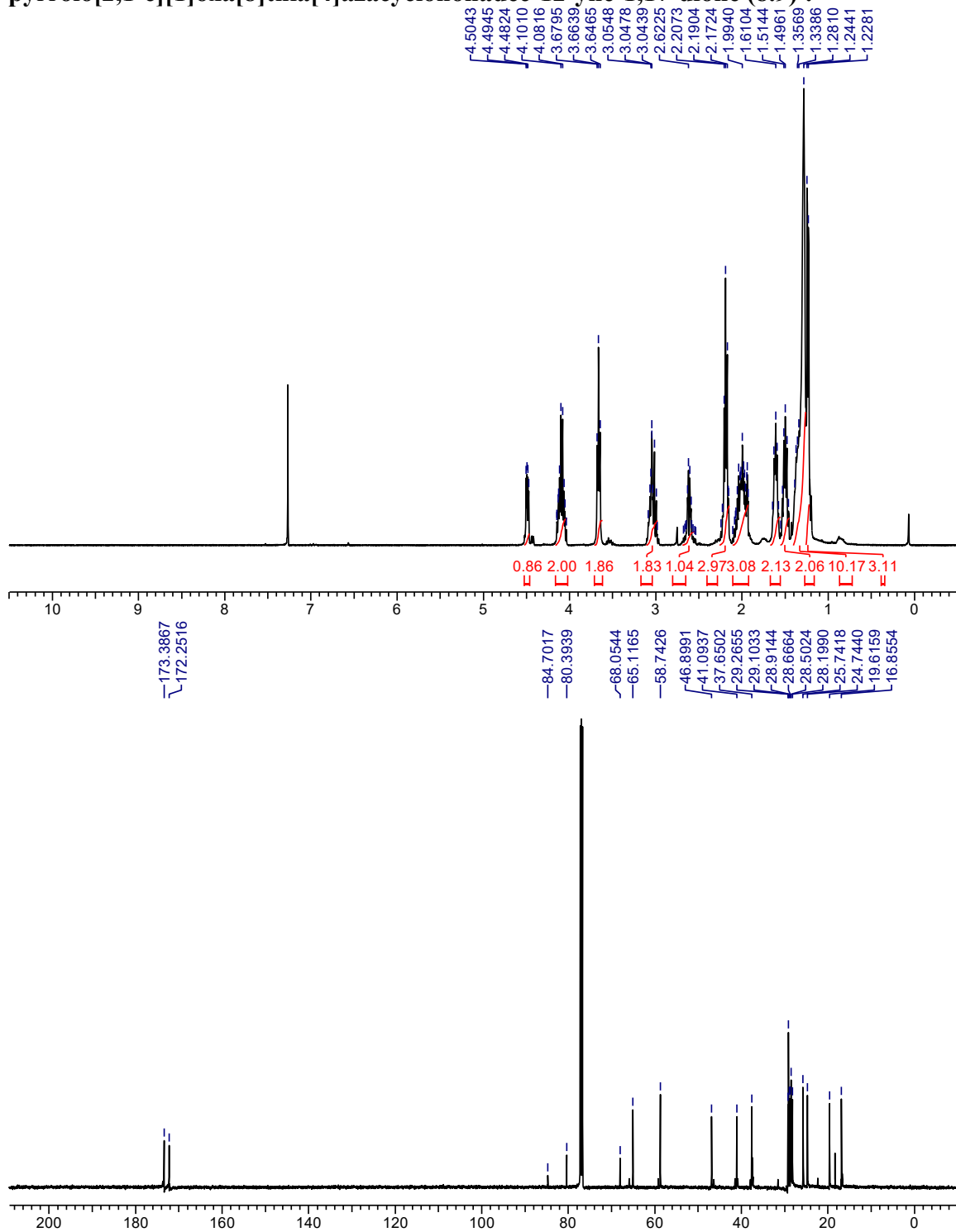




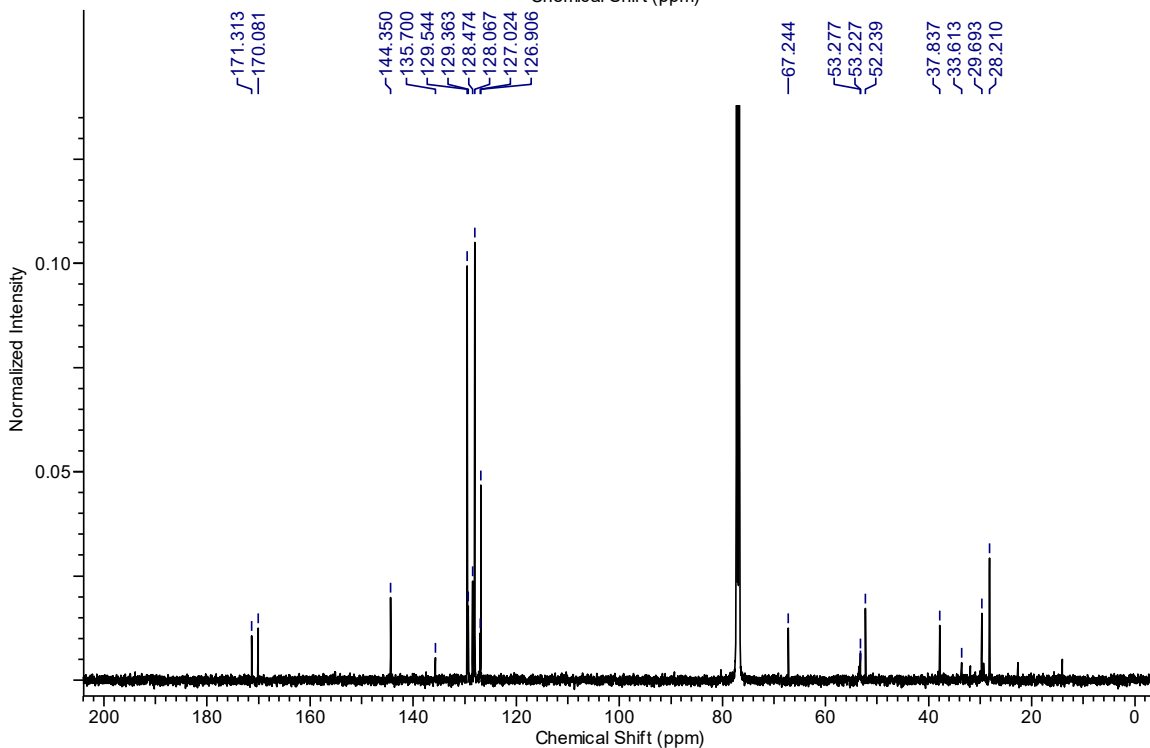
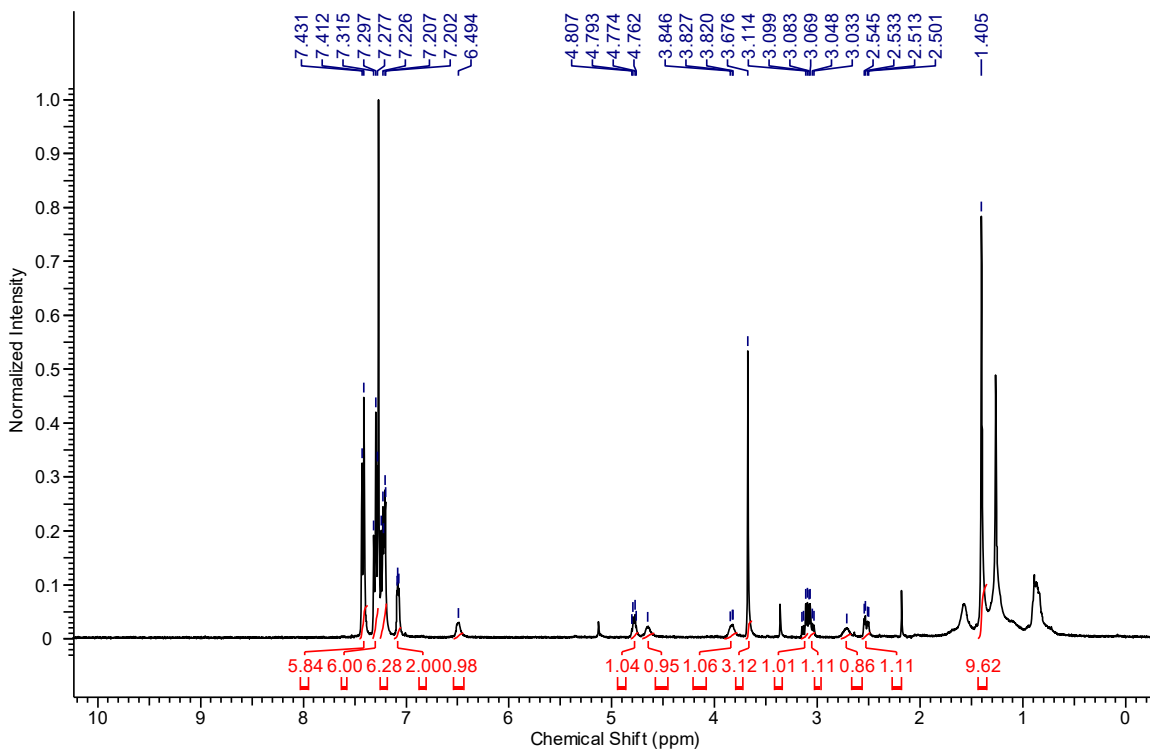
**11-Bromoundec-10-yn-1-yl ((S)-3-mercapto-2-methylpropanoyl)-L-prolinate (8.S13):**



**(16*S*,21*aS*)-16-methyl-4,5,6,7,8,9,10,11,15,16,19,20,21,21*a*-tetradecahydro-1*H*,3*H*,17*H*-pyrrolo[2,1-*c*][1]oxa[8]thia[4]azacyclonadec-12-yne-1,17-dione (8.9) :**

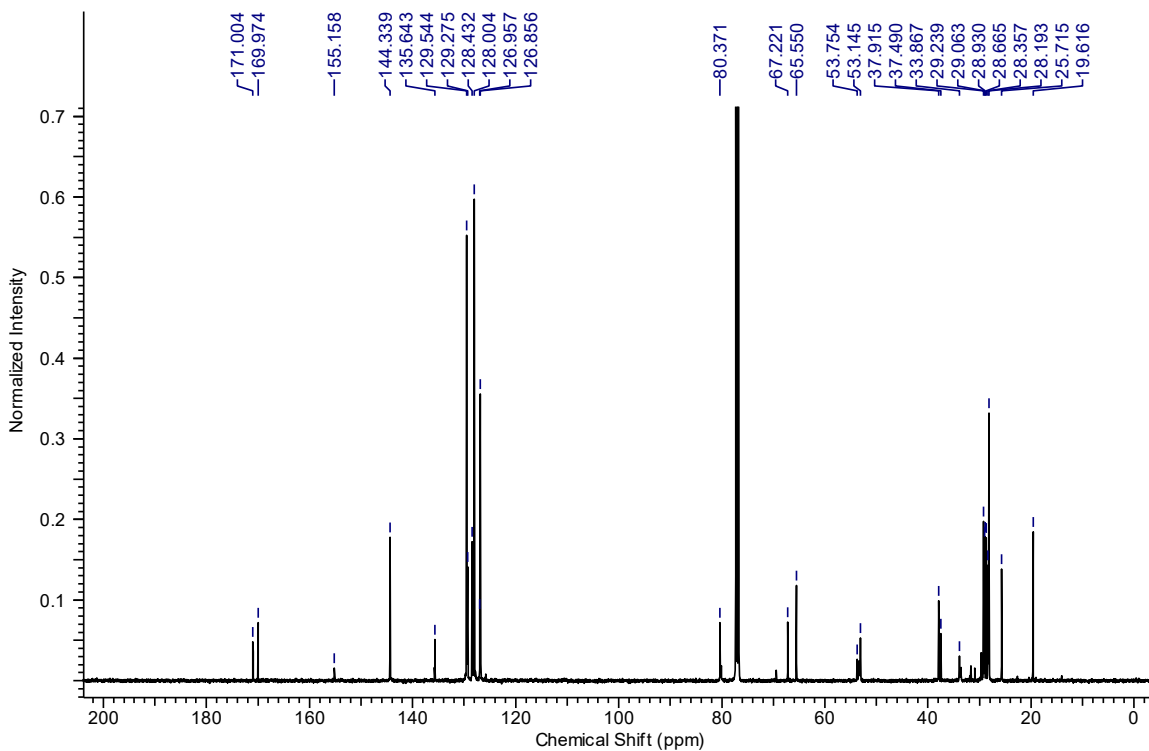
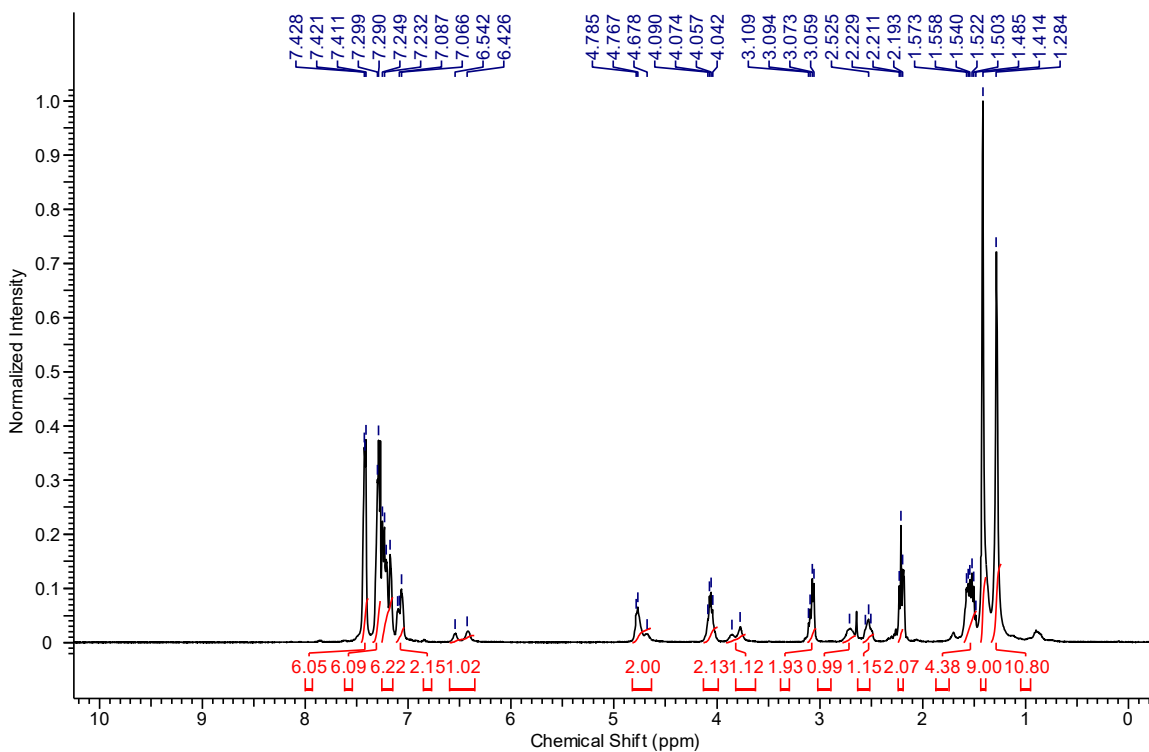


**Methyl *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteinyl-*L*-phenylalaninate (8.S14):**

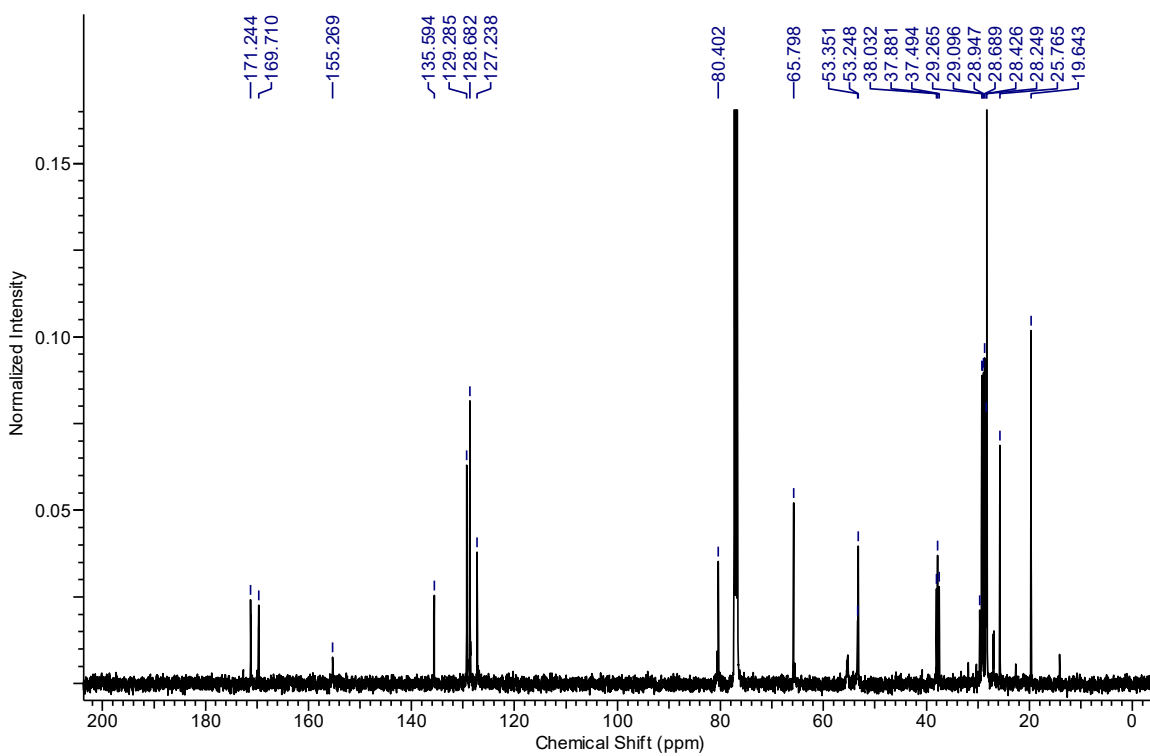
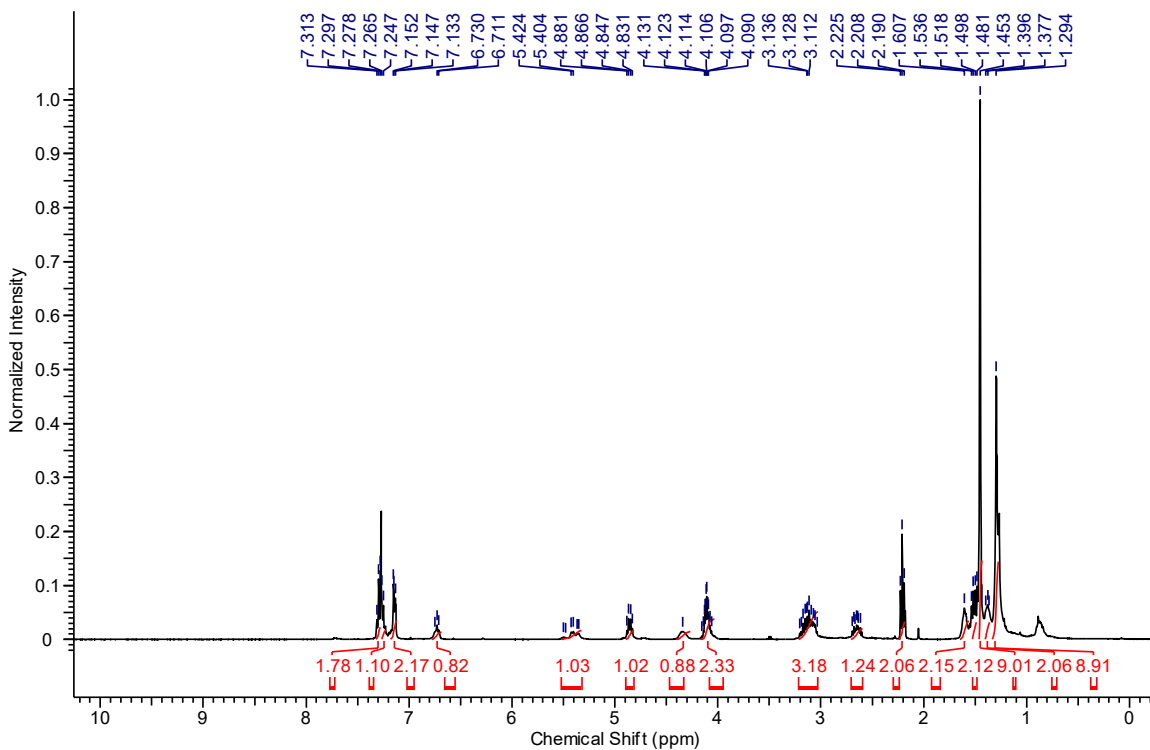


**11-Bromoundec-10-yn-1-yl  
phenylalaninate (8.S15):**

***N*-(*tert*-butoxycarbonyl)-*S*-trityl-*L*-cysteiny-*L*-  
phenylalaninate (8.S15):**



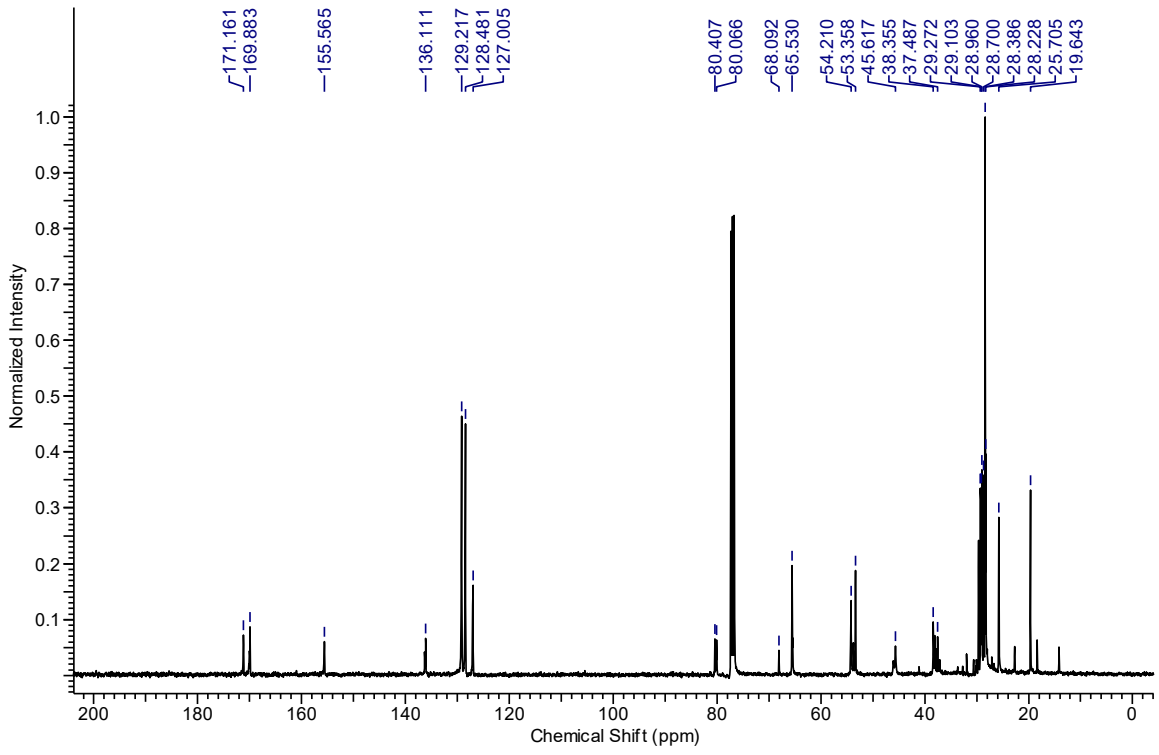
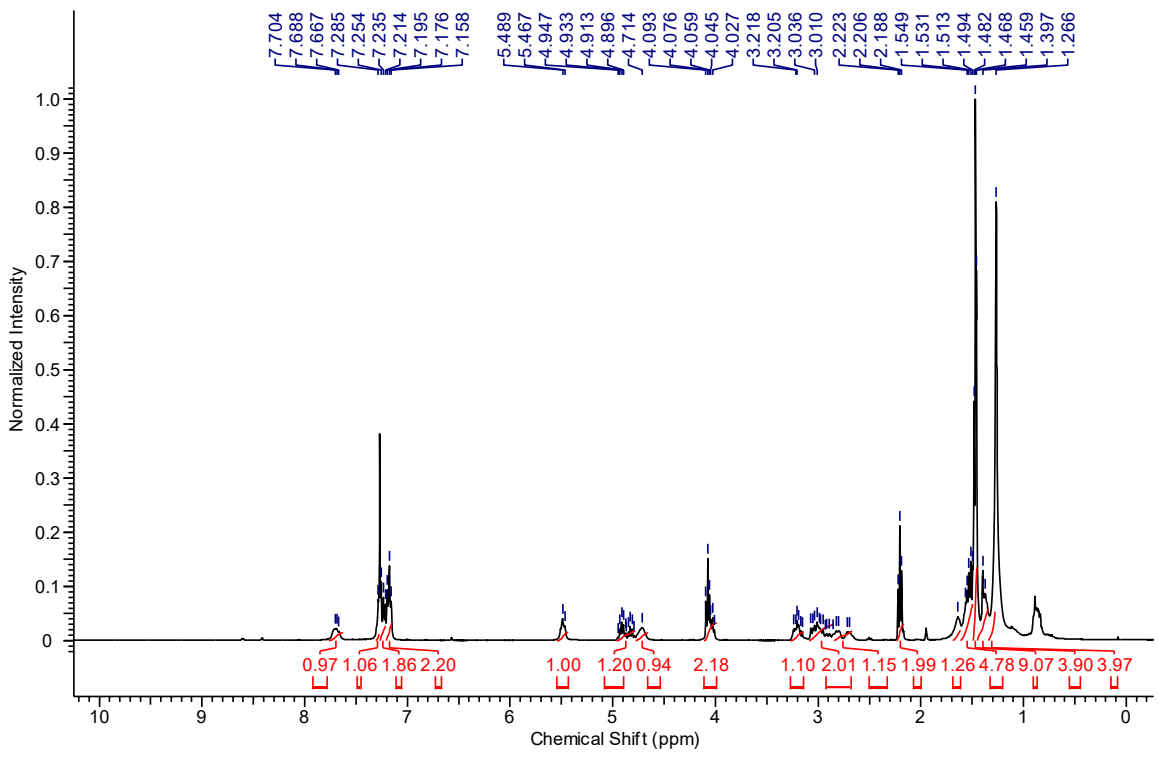
**11-Bromoundec-10-yn-1-yl (*tert*-butoxycarbonyl)-*L*-cysteinyl-*L*-phenylalaninate (8.S16):**



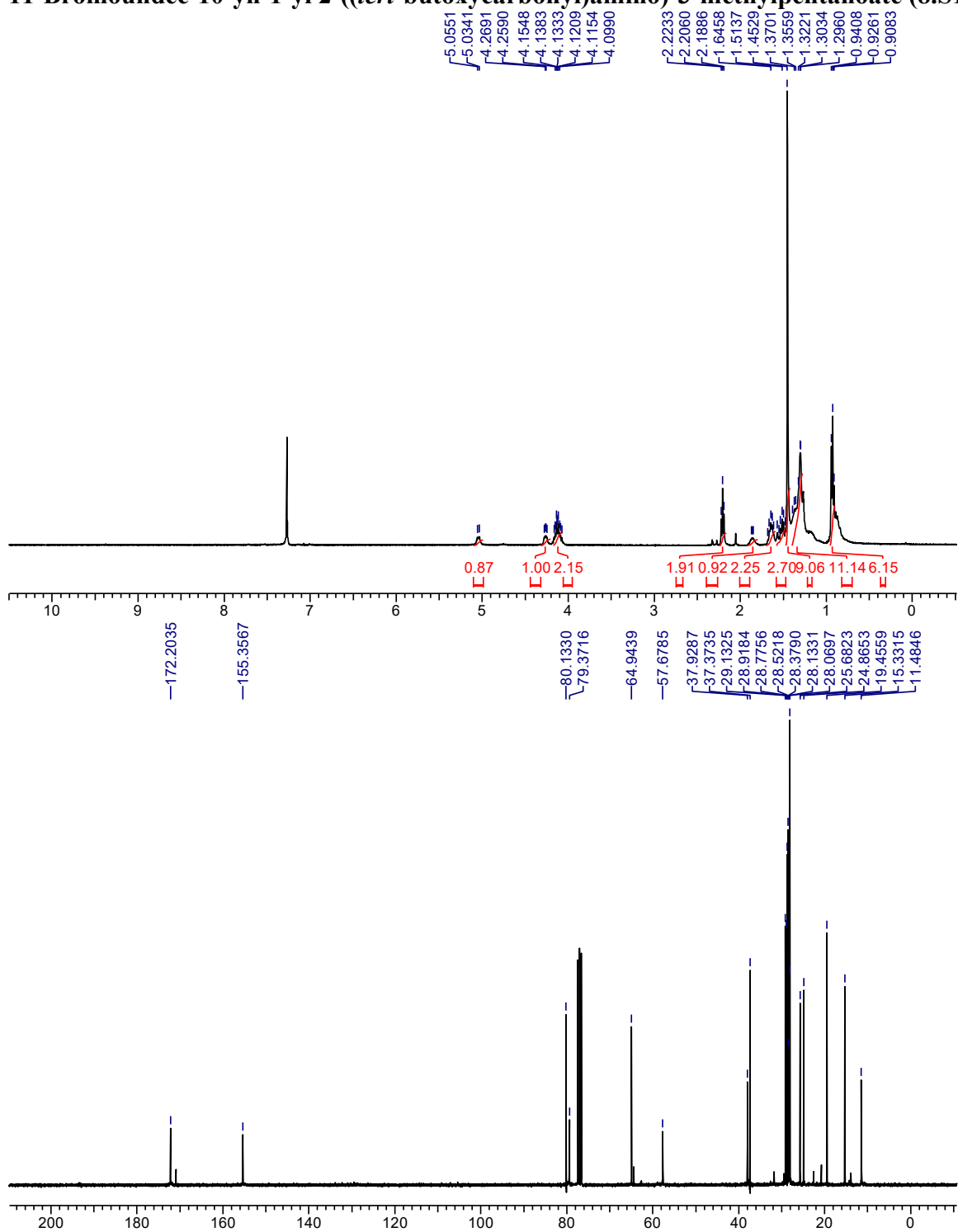
*tert*-Butyl

((3*S*,6*R*)-3-benzyl-2,5-dioxo-1-oxa-8-thia-4-azacyclonadec-9-yn-6-

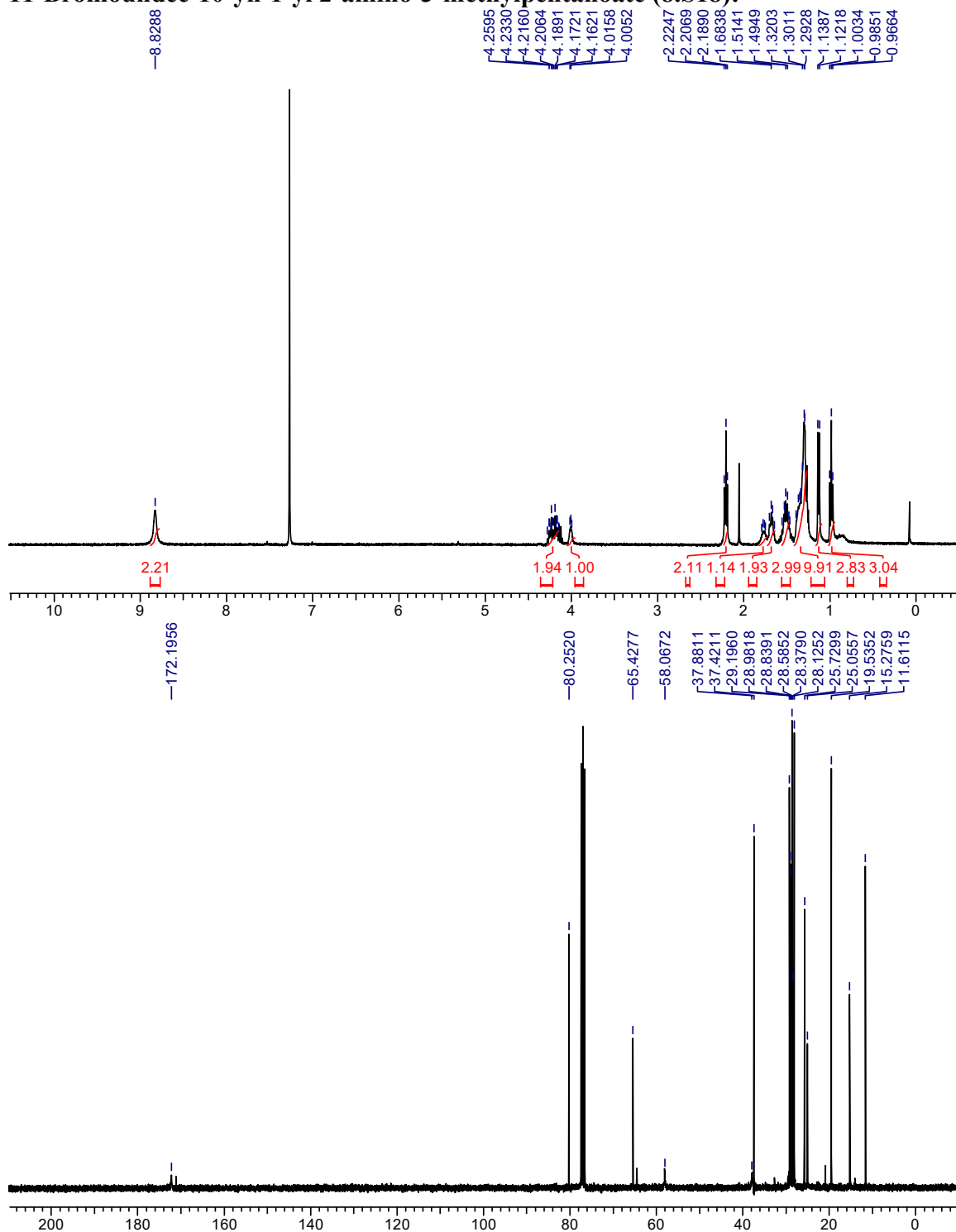
yl)carbamate (8.10):



**11-Bromoundec-10-yn-1-yl 2-((*tert*-butoxycarbonyl)amino)-3-methylpentanoate (8.S17):**



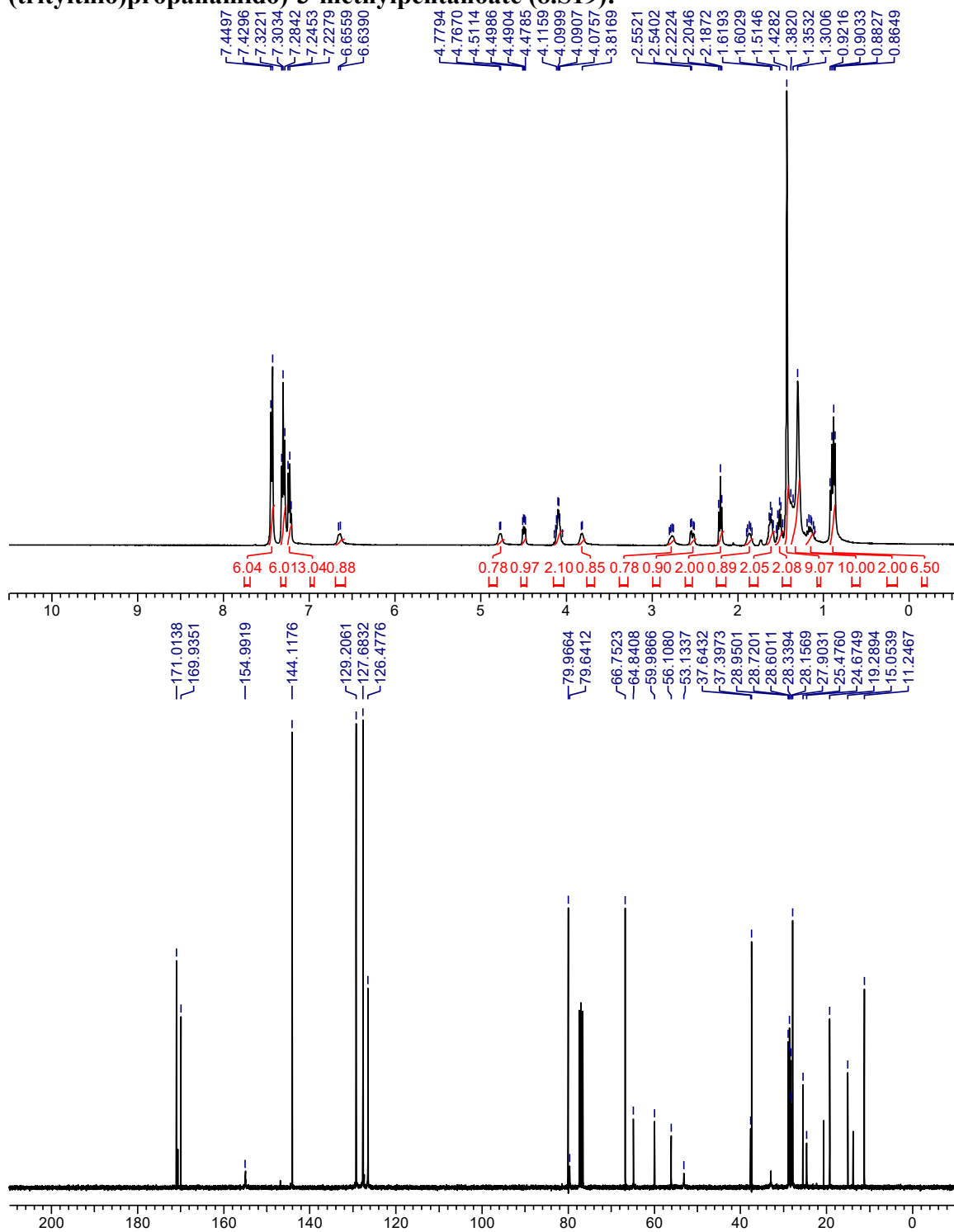
11-Bromoundec-10-yn-1-yl 2-amino-3-methylpentanoate (8.S18):



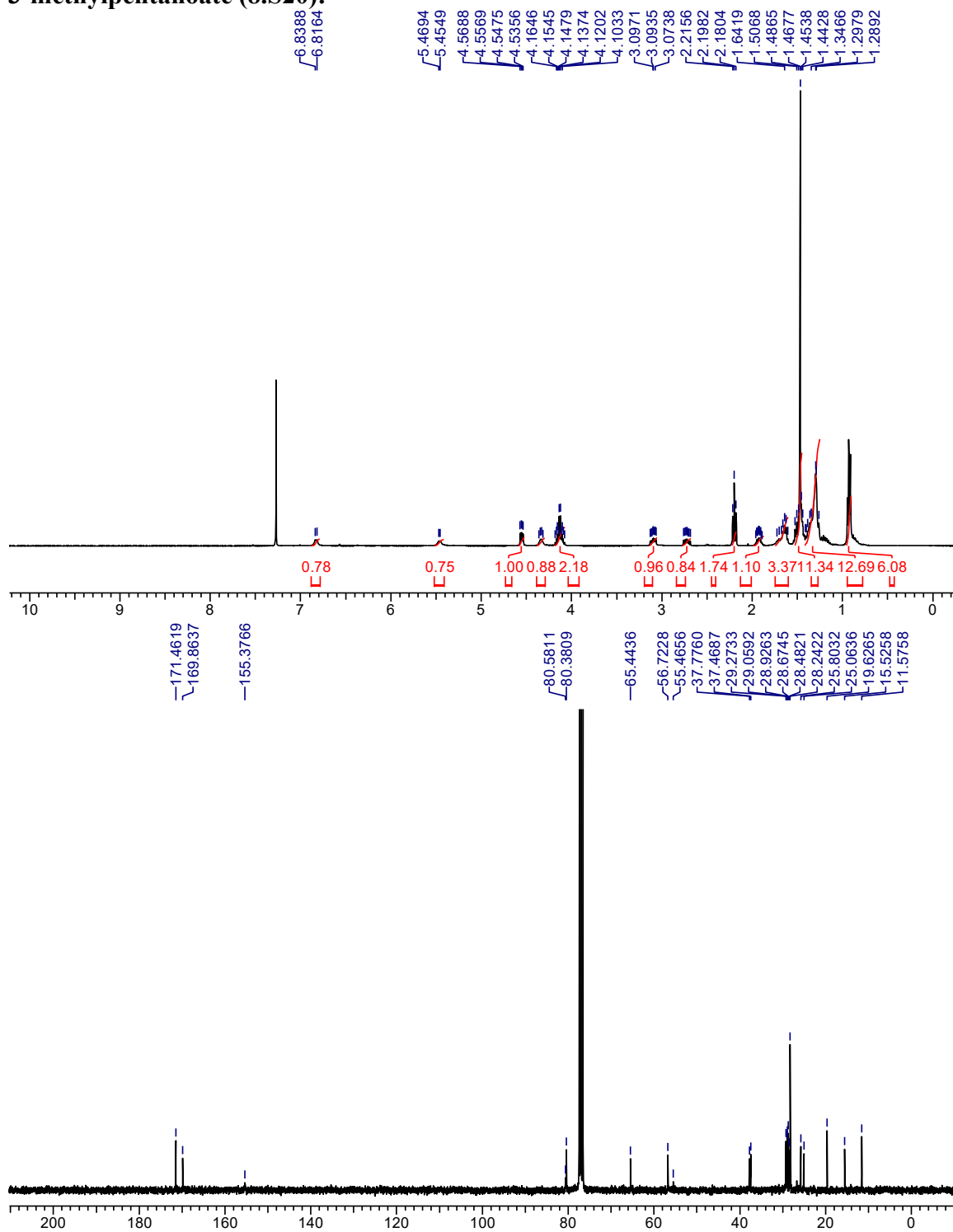


**11-Bromoundec-10-yn-1-yl  
(tritylthio)propanamido)-3-methylpentanoate (8.S19):**

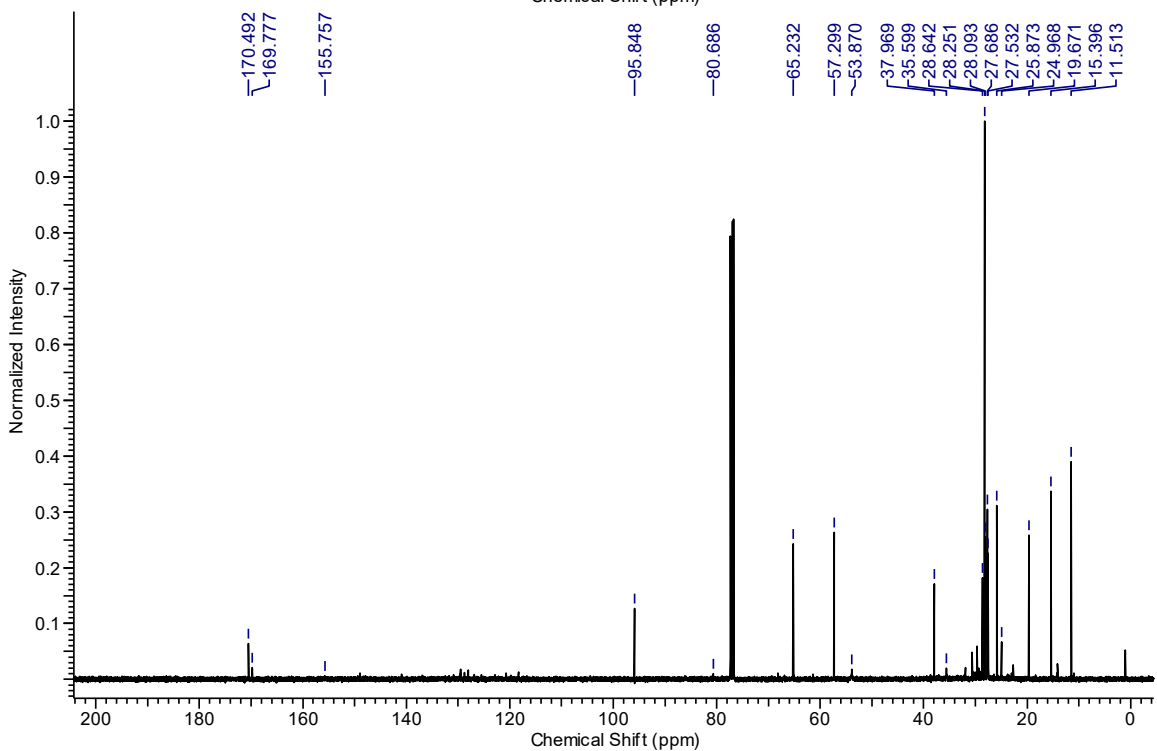
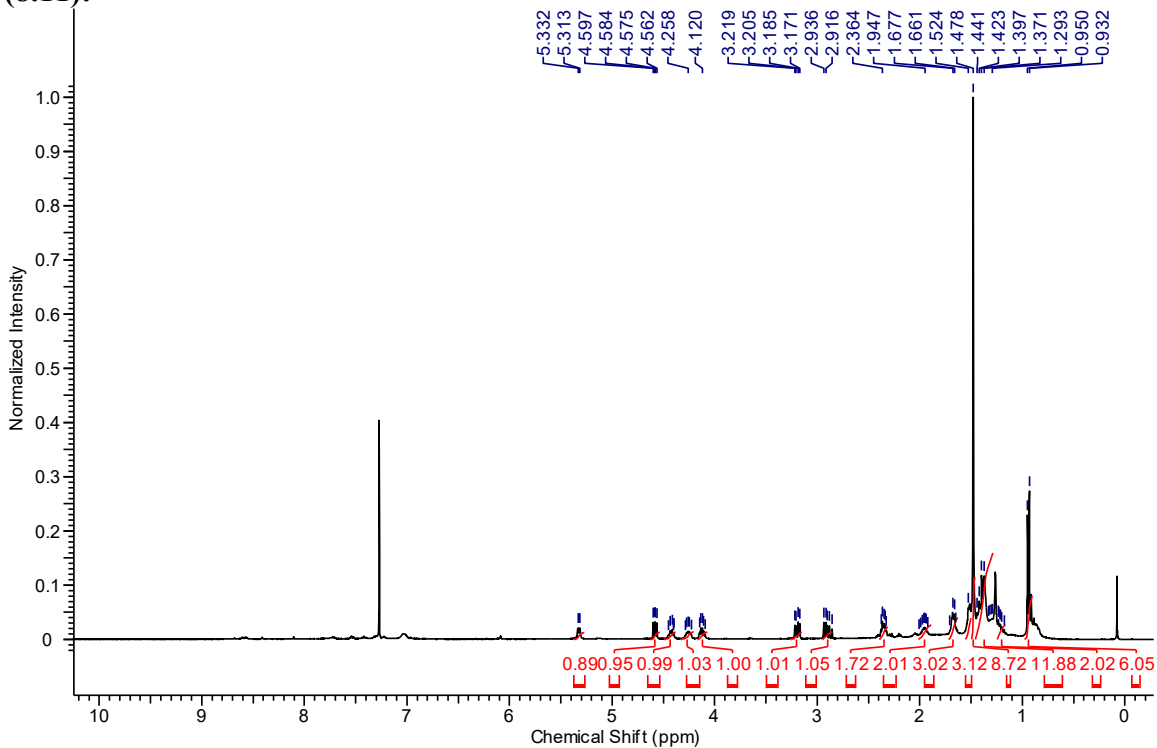
**2-(2-((*tert*-butoxycarbonyl)amino)-3-**



**11-Bromoundec-10-yn-1-yl 2-(2-((*tert*-butoxycarbonyl)amino)-3 mercaptopropanamido)-3-methylpentanoate (8.S20):**

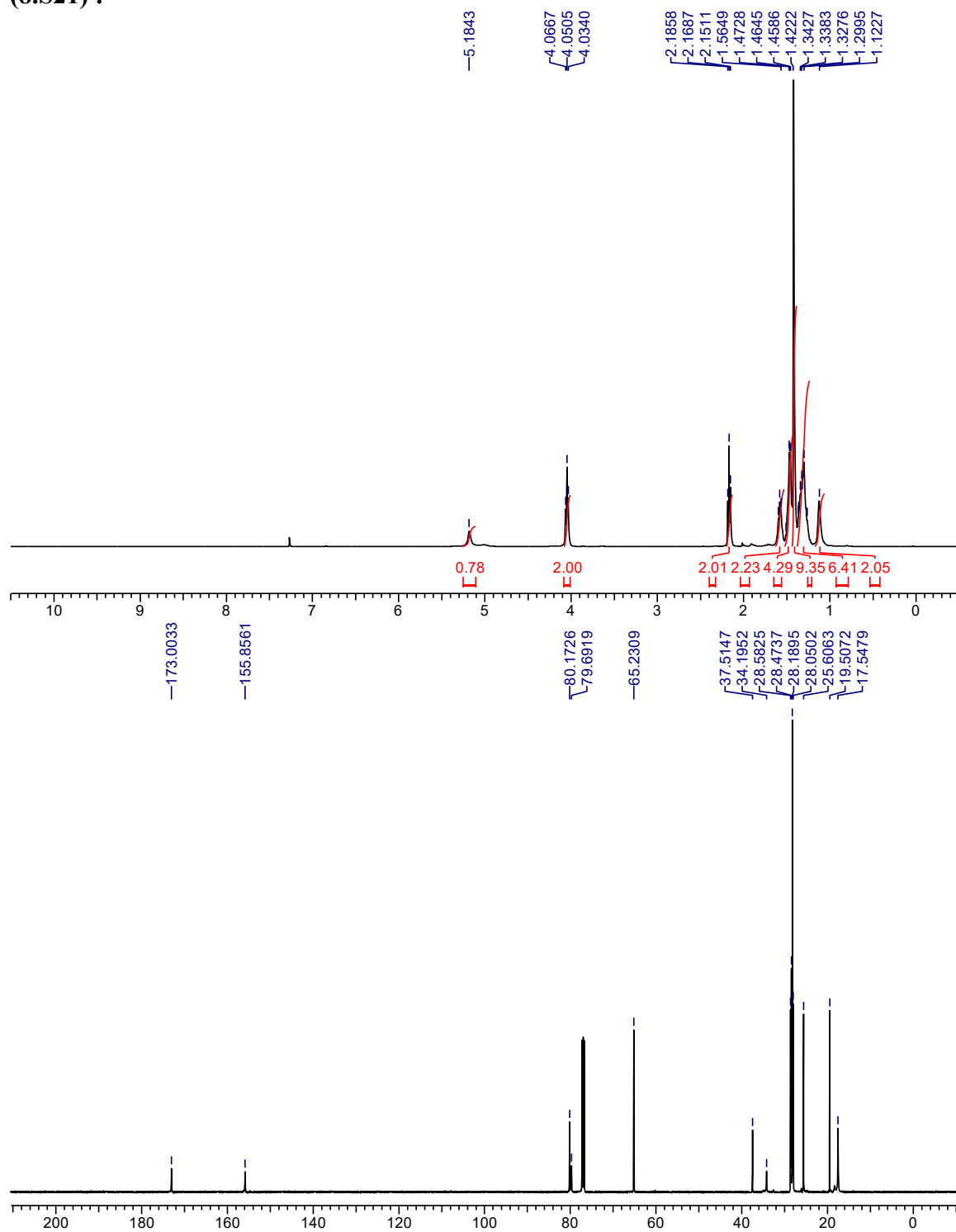


***tert*-butyl (3-(*sec*-butyl)-2,5-dioxo-1-oxa-8,14-thia-4-azacyclonadec-8-yn-6-yl)carbamate (8.11):**

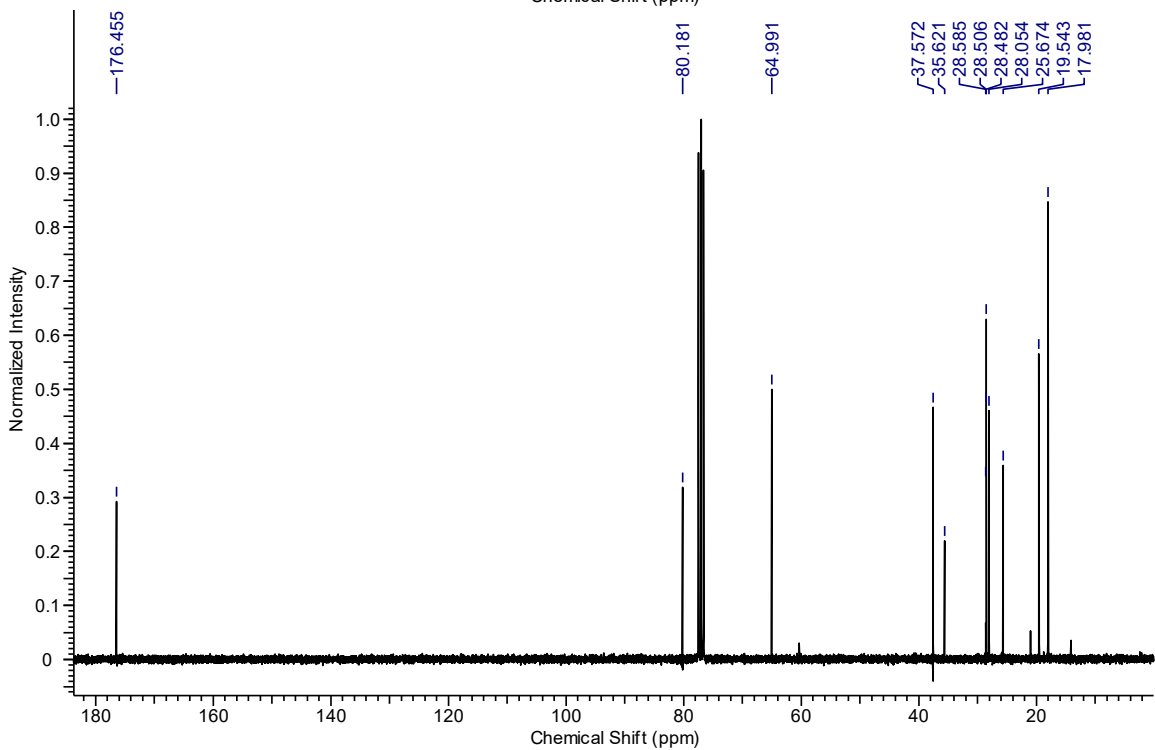
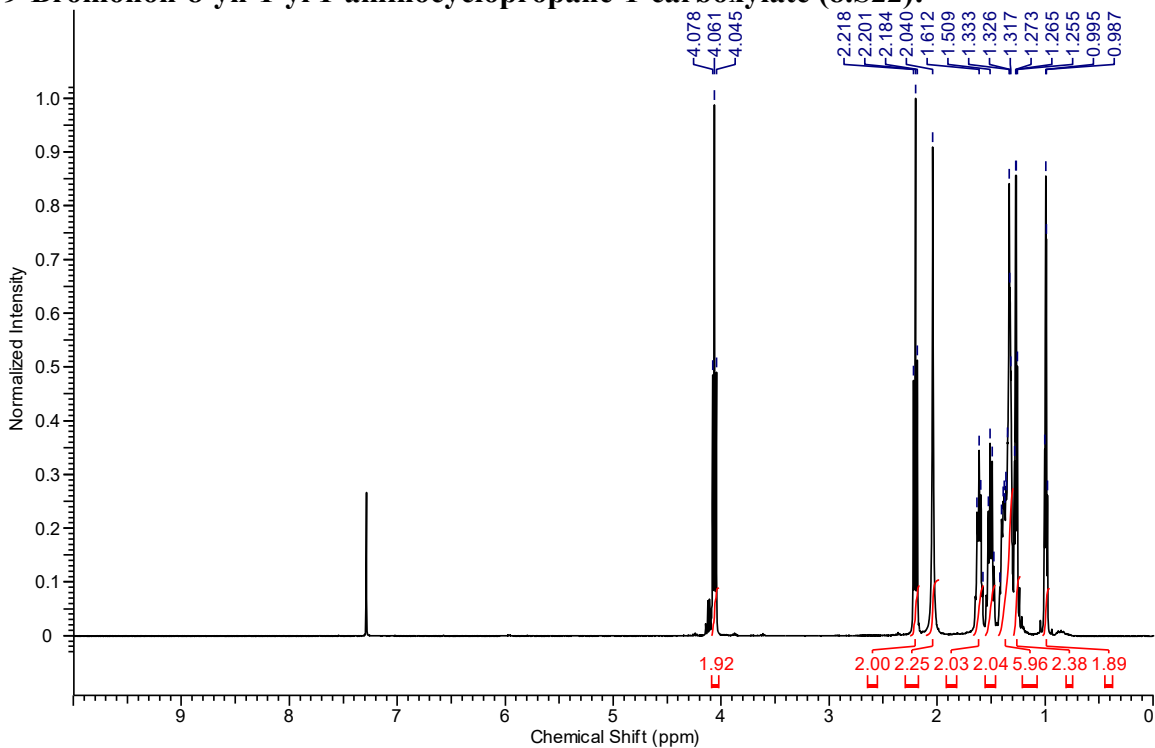


9-Bromonon-8-yn-1-yl  
(8.S21) :

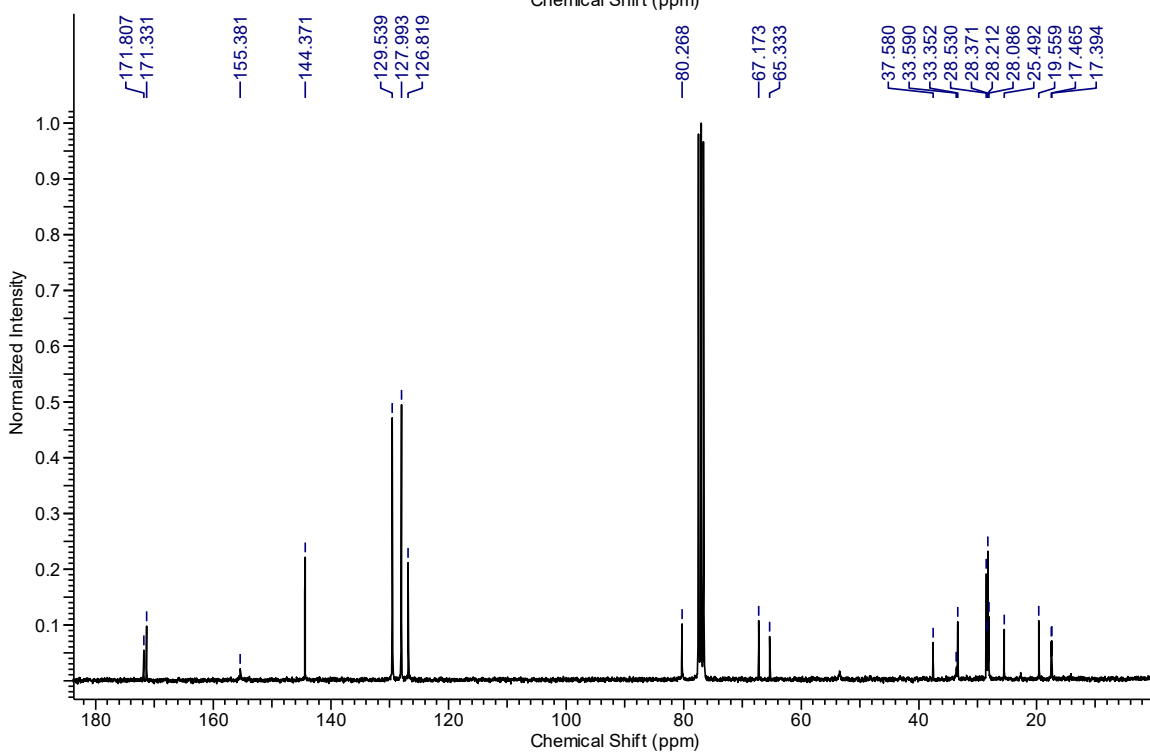
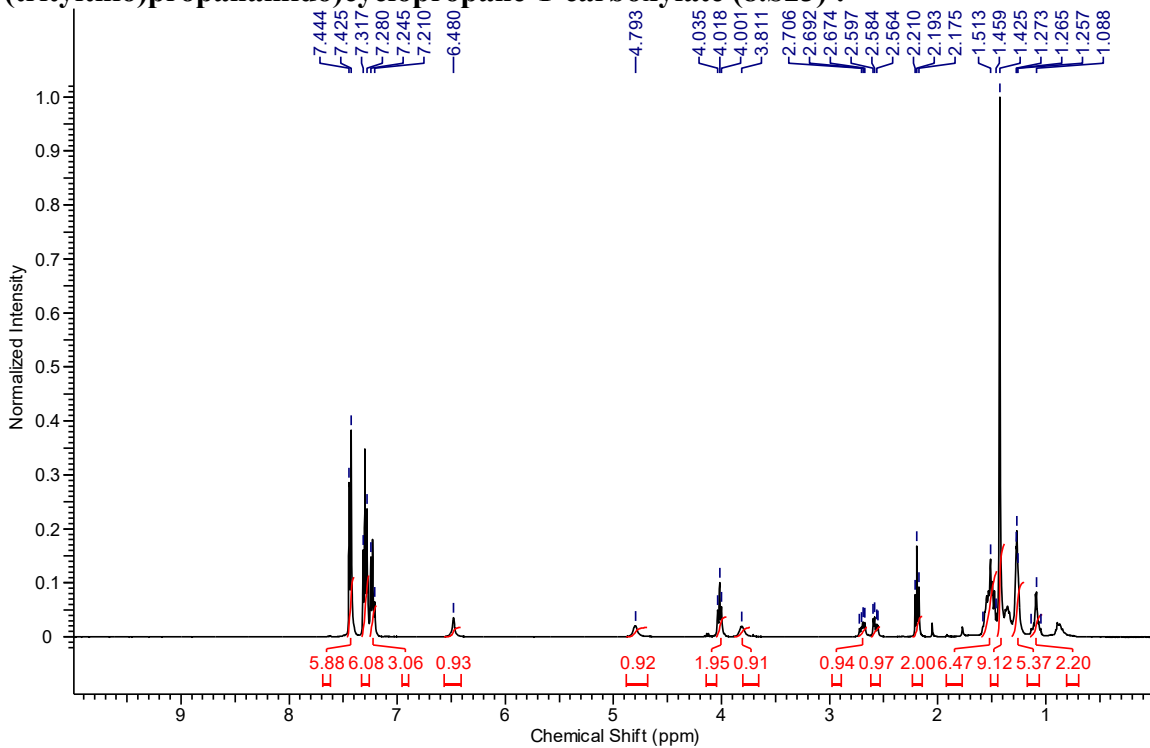
1-((tert-butoxycarbonyl)amino)cyclopropane-1-carboxylate



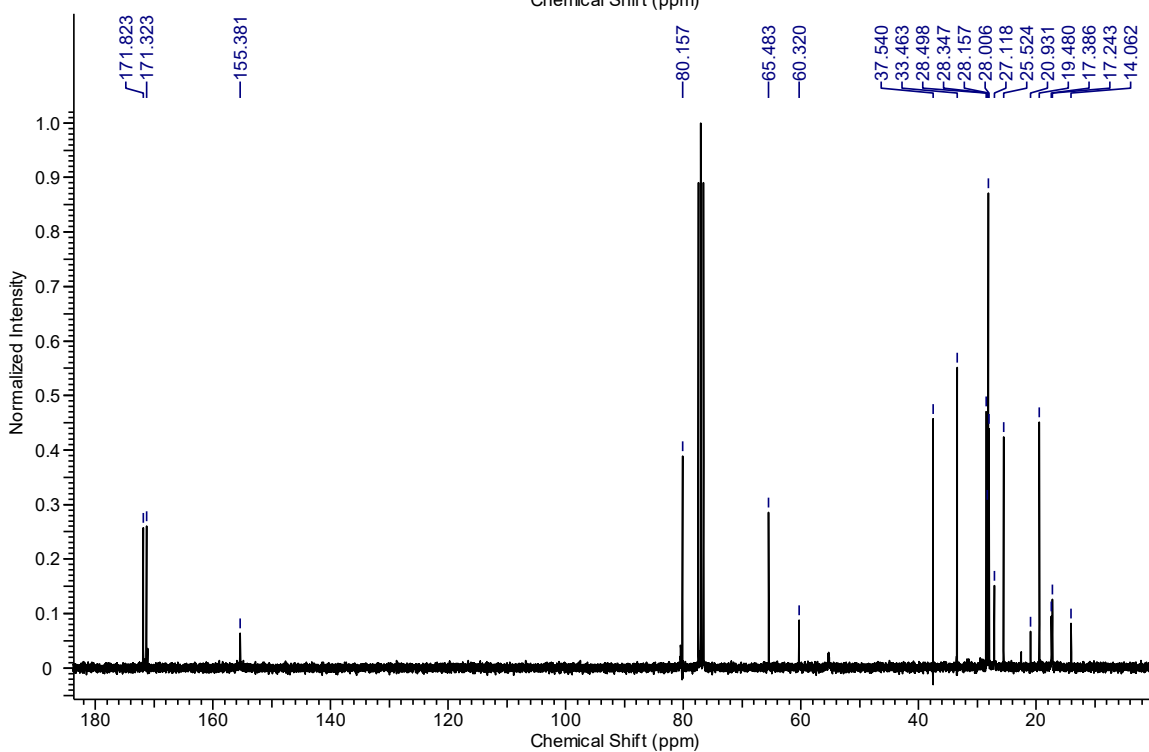
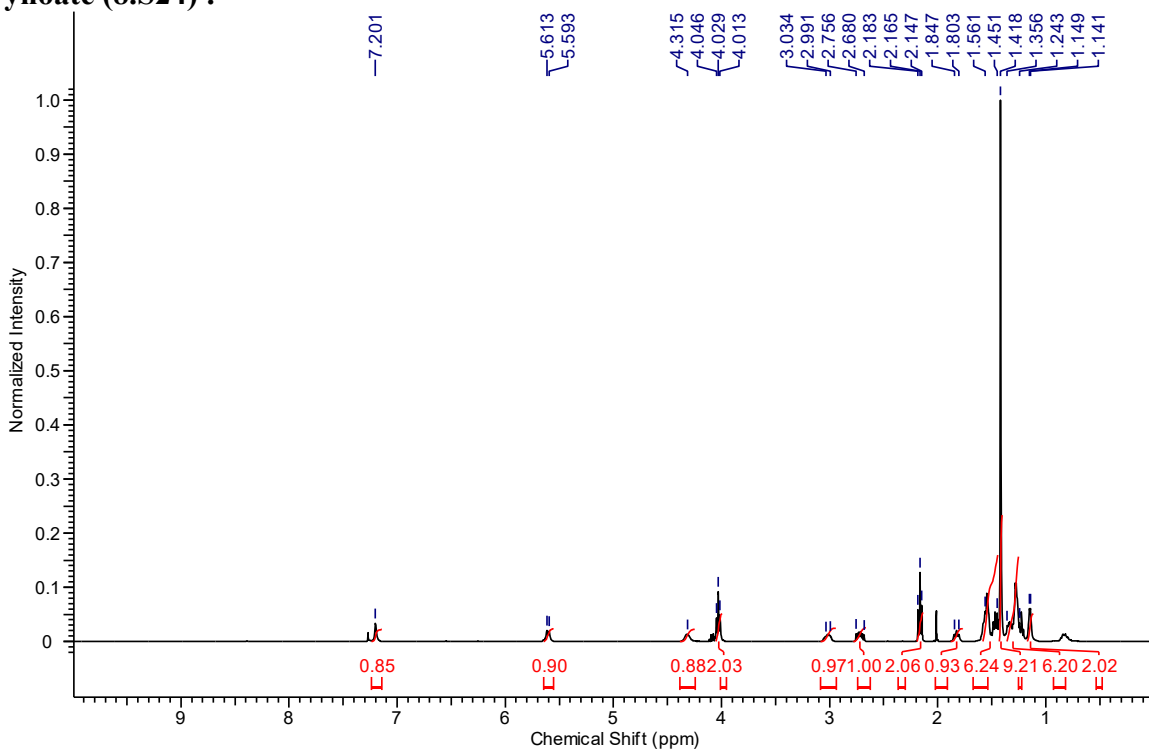
**9-Bromonon-8-yn-1-yl 1-aminocyclopropane-1-carboxylate (8.S22):**



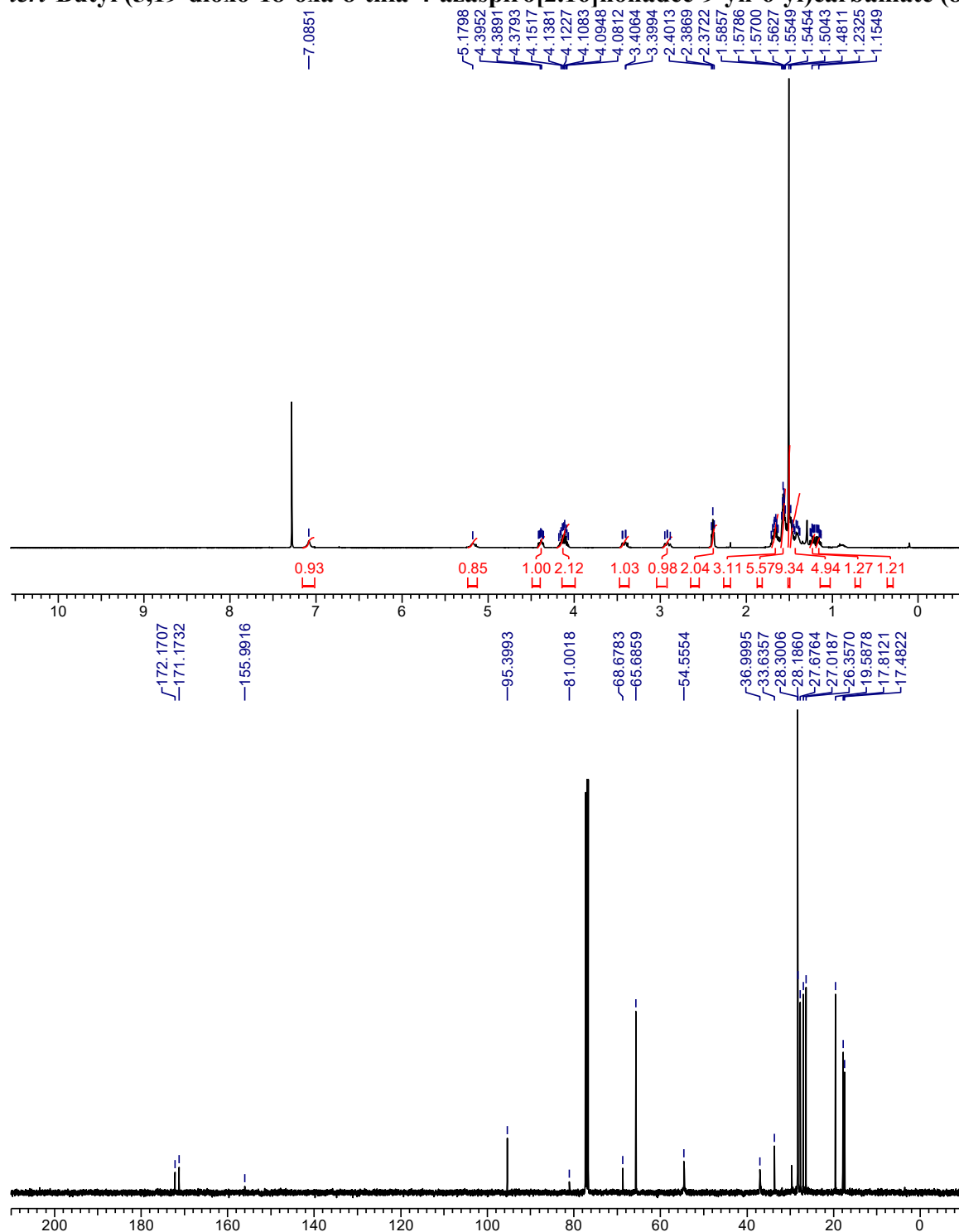
**9-Bromonon-8-yn-1-yl 1-(2-((*tert*-butoxycarbonyl)amino)-3-(tritylthio)propanamido)cyclopropane-1-carboxylate (8.S23) :**



**4-((3-Mercaptopropanoyl)oxy)butyl (S)-5-bromo-2-((tert-butoxycarbonyl)amino)pent-4-ynoate (8.S24) :**

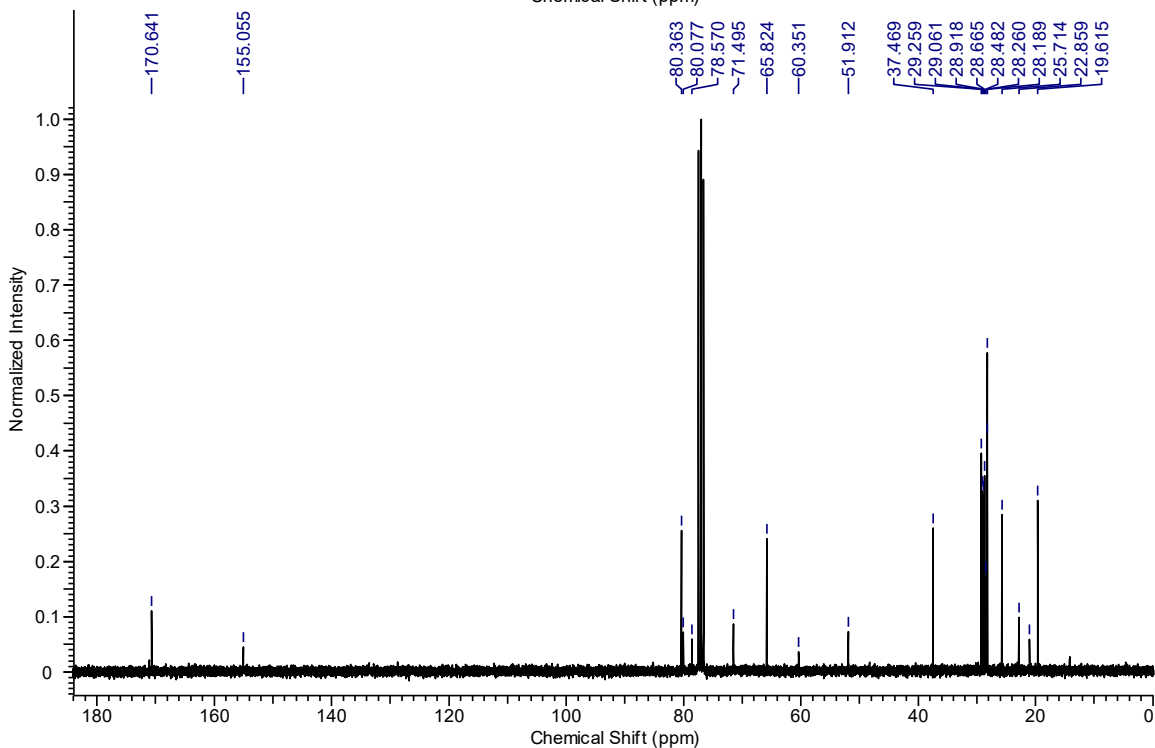
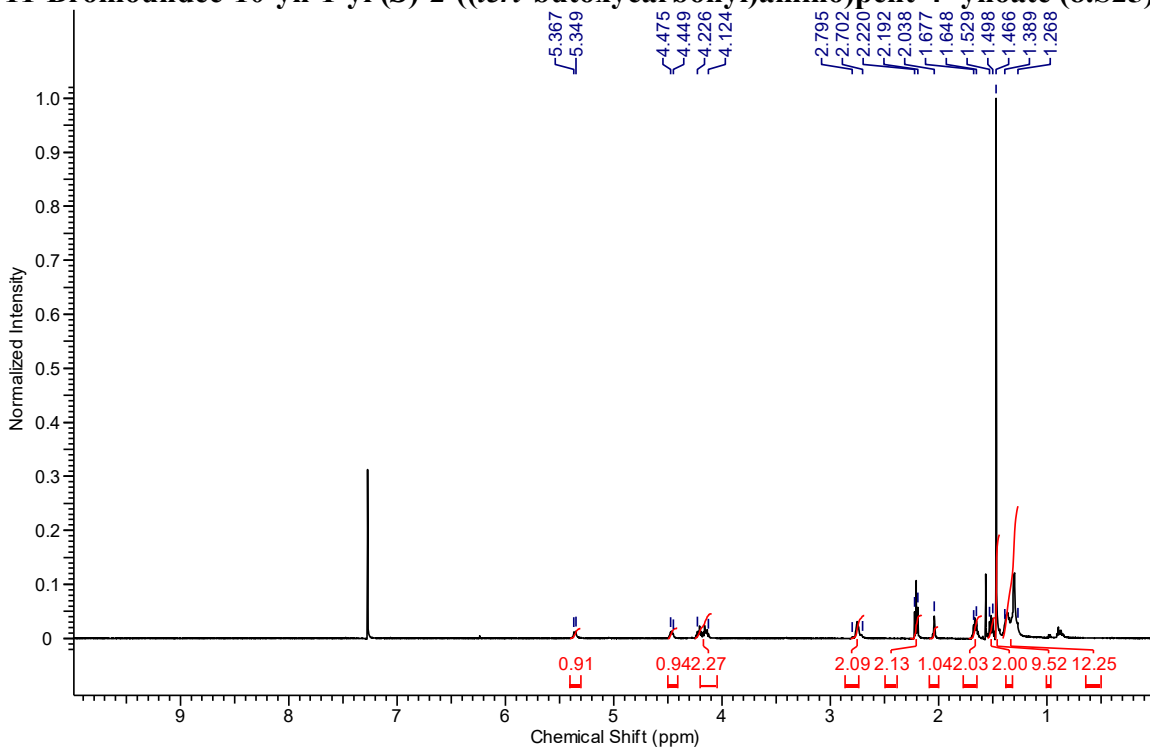


***tert*-Butyl (5,19-dioxo-18-oxa-8-thia-4-azaspiro[2.16]nonadec-9-yn-6-yl)carbamate (8.12):**

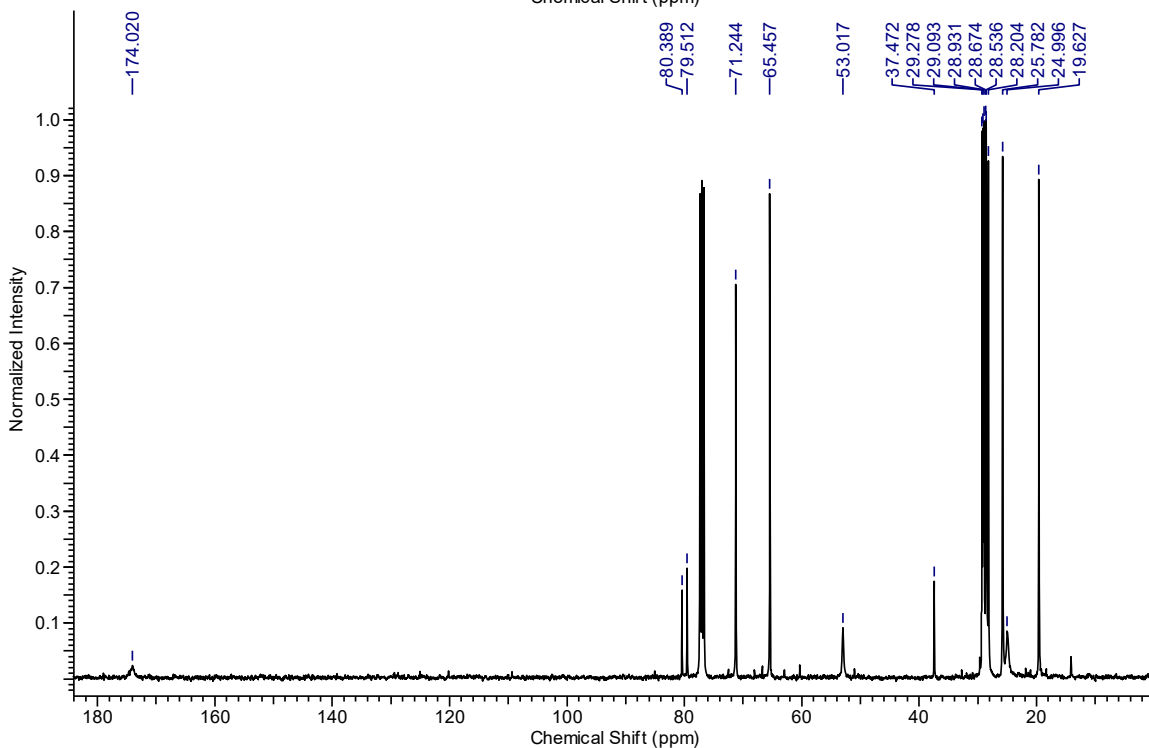
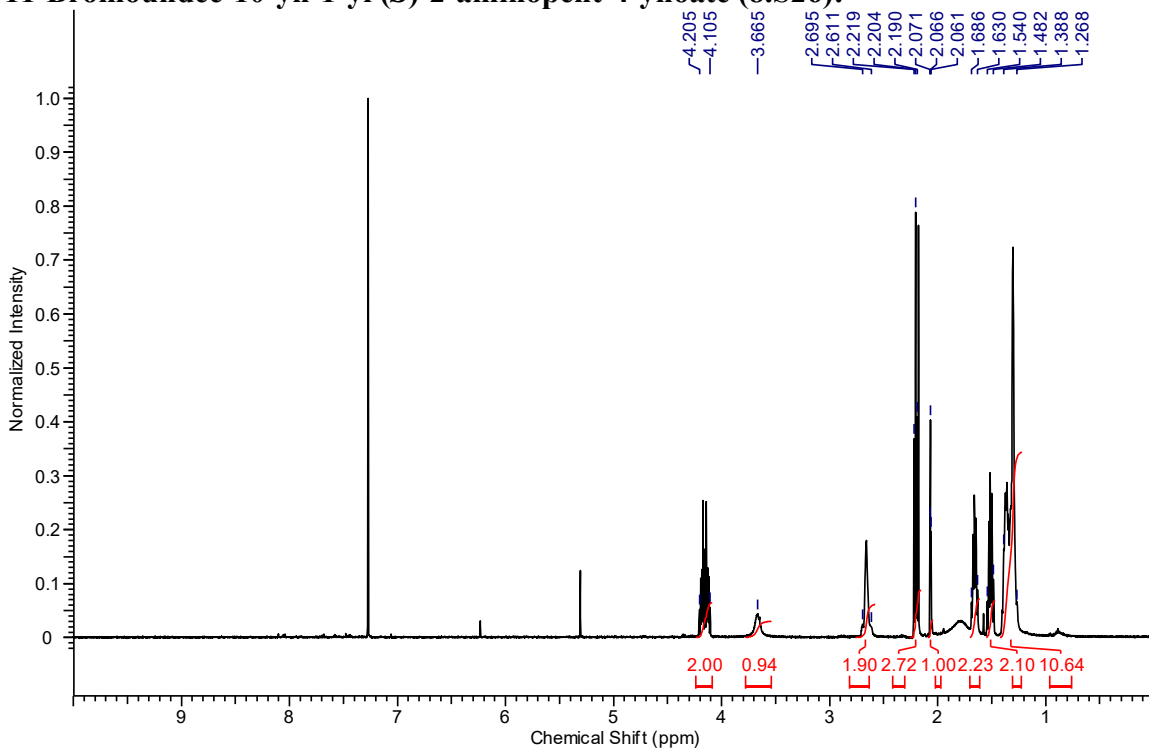




**11-Bromoundec-10-yn-1-yl (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-ynoate (8.S25):**



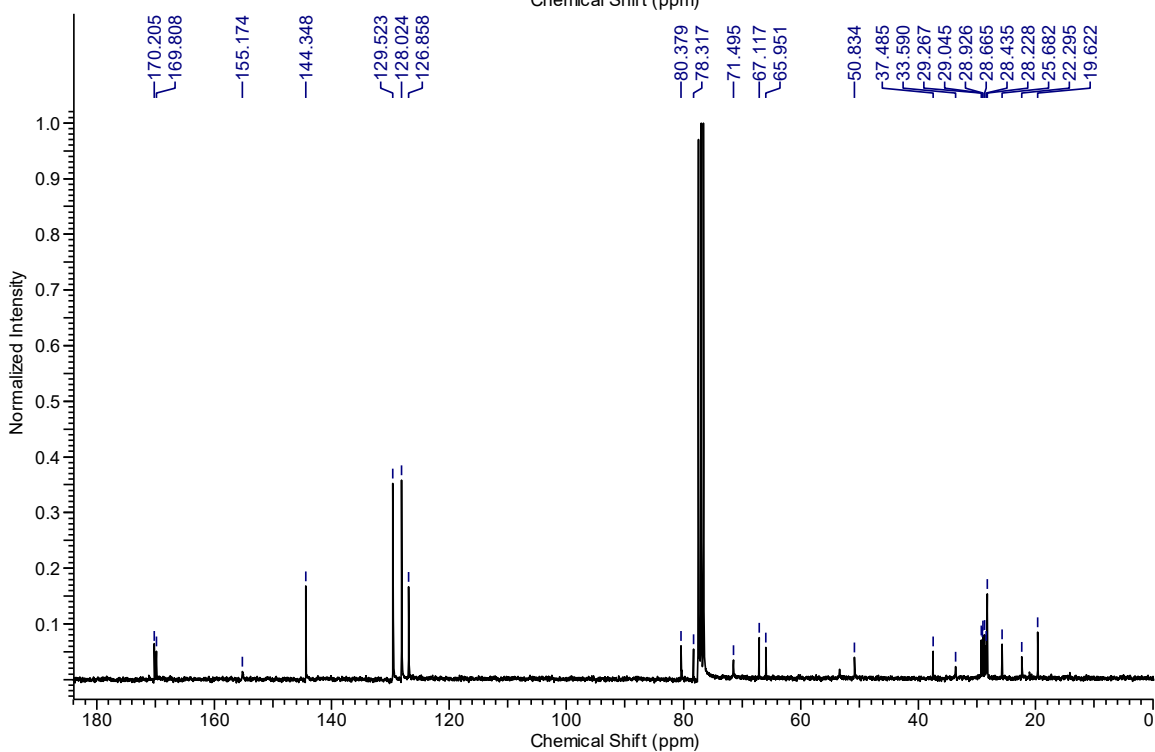
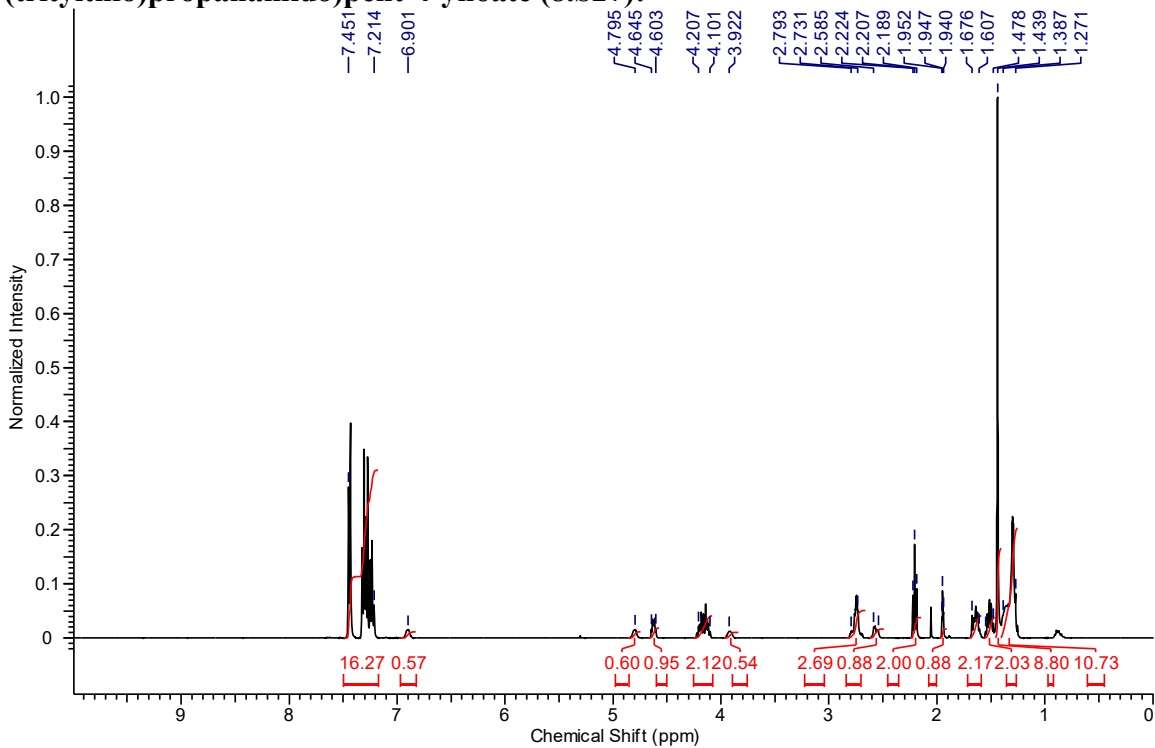
**11-Bromoundec-10-yn-1-yl (*S*)-2-aminopent-4-ynoate (8.S26):**



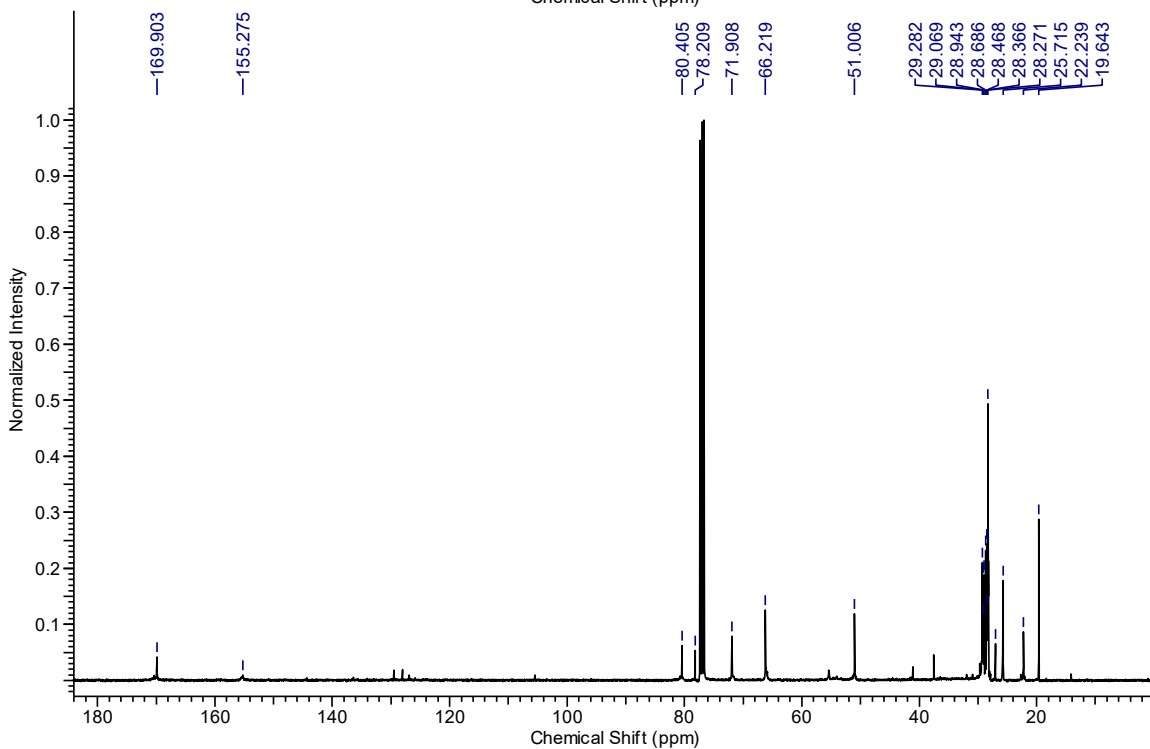
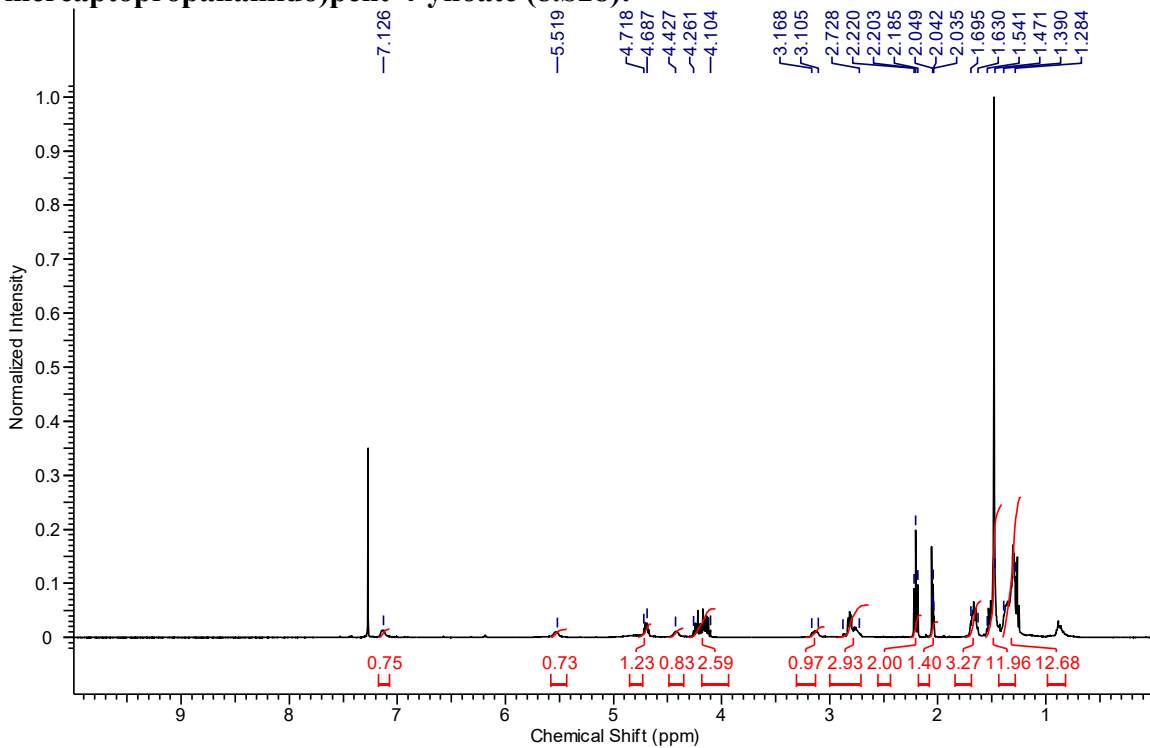
**11-bromoundec-10-yn-1-yl**

**(S)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-**

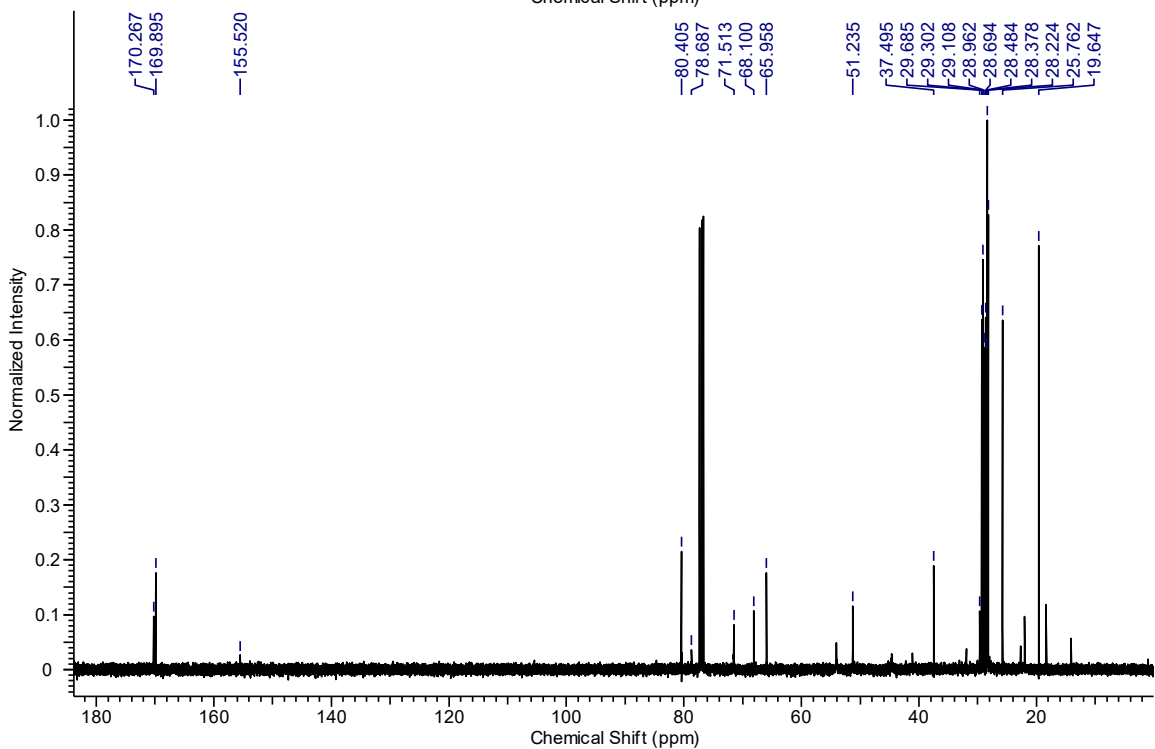
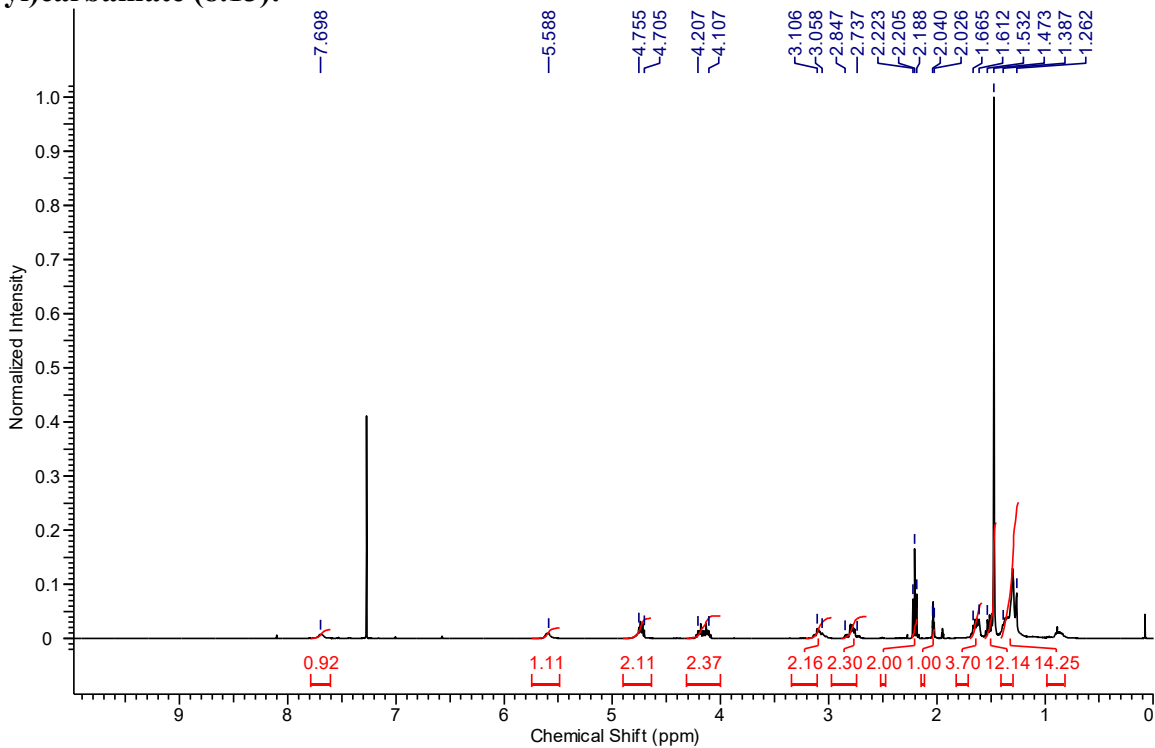
**(tritylthio)propanamido)pent-4-ynoate (8.S27):**



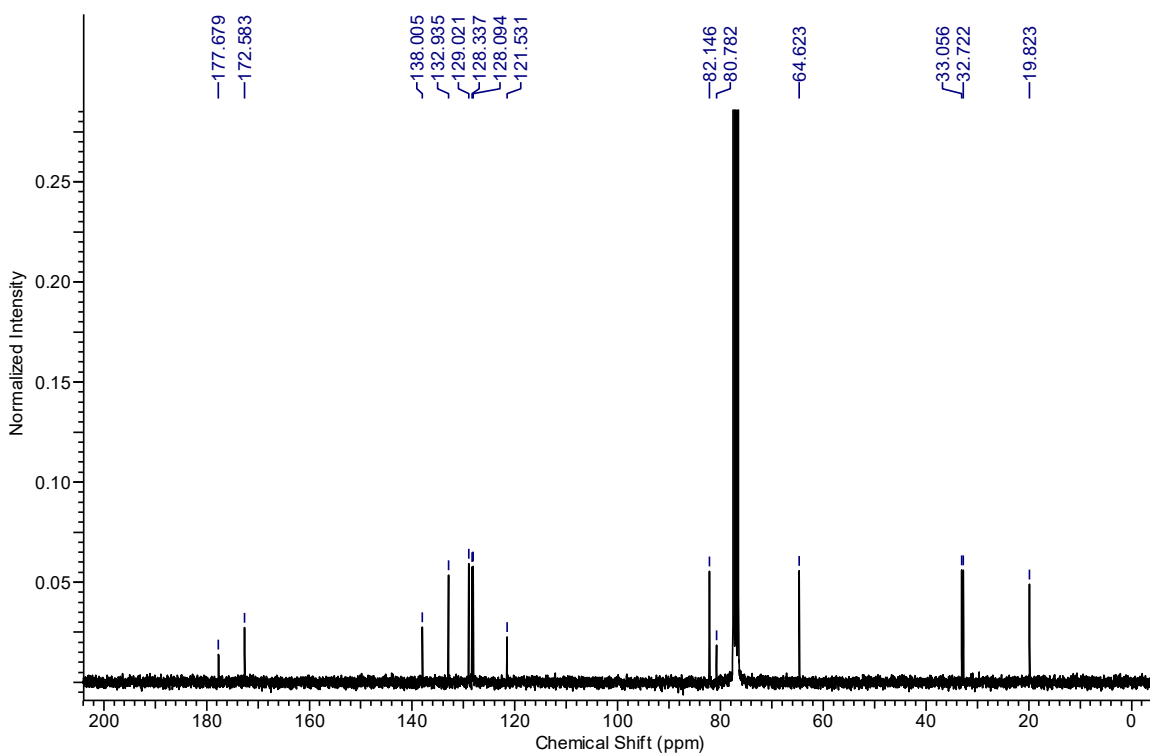
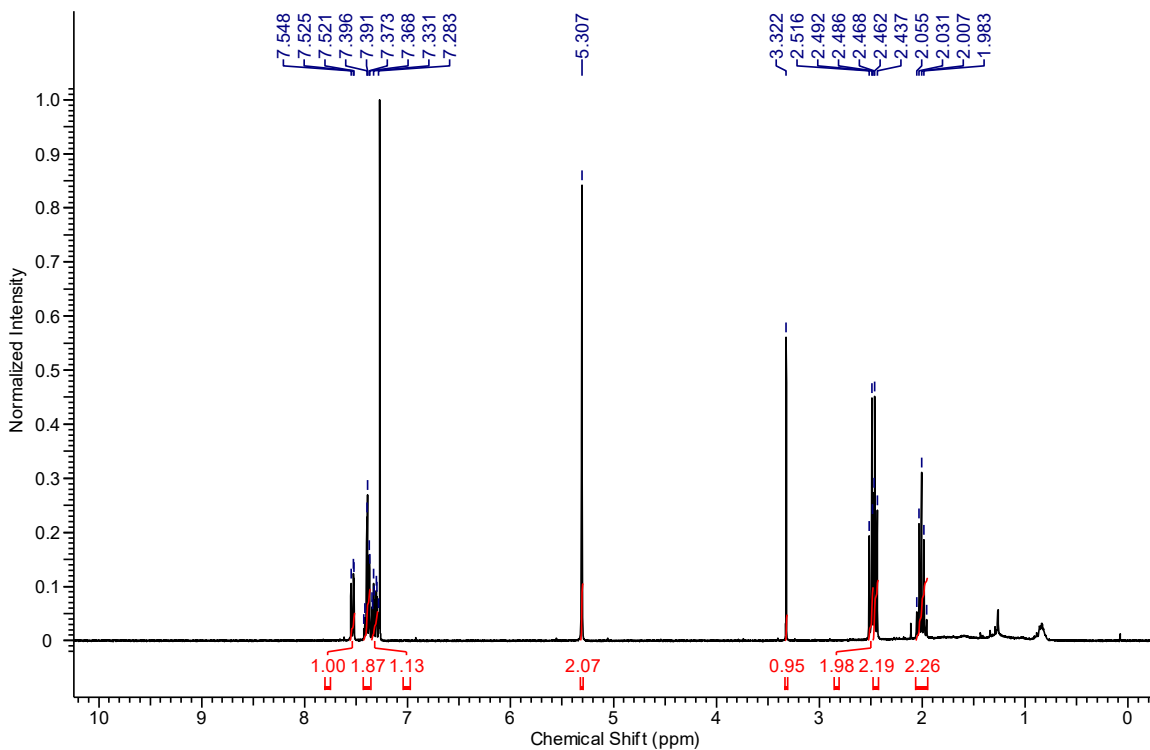
**11-bromoundec-10-yn-1-yl (S)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-mercaptopropanamido)pent-4-ynoate (8.S28):**



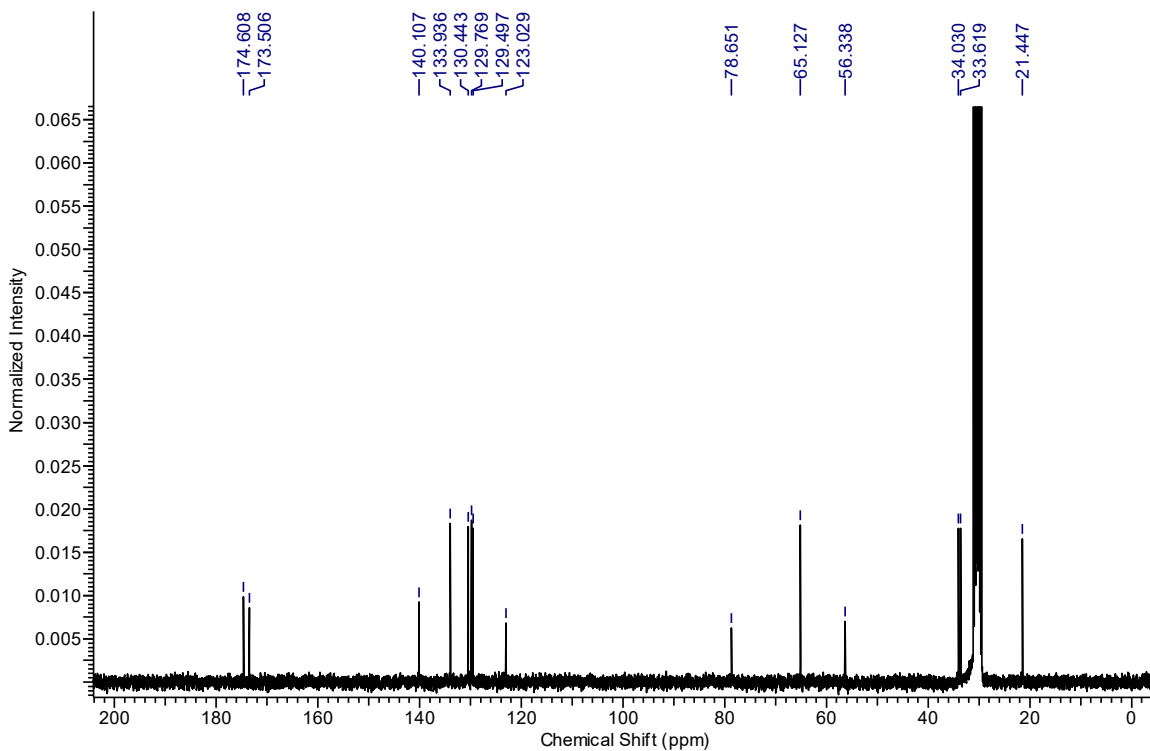
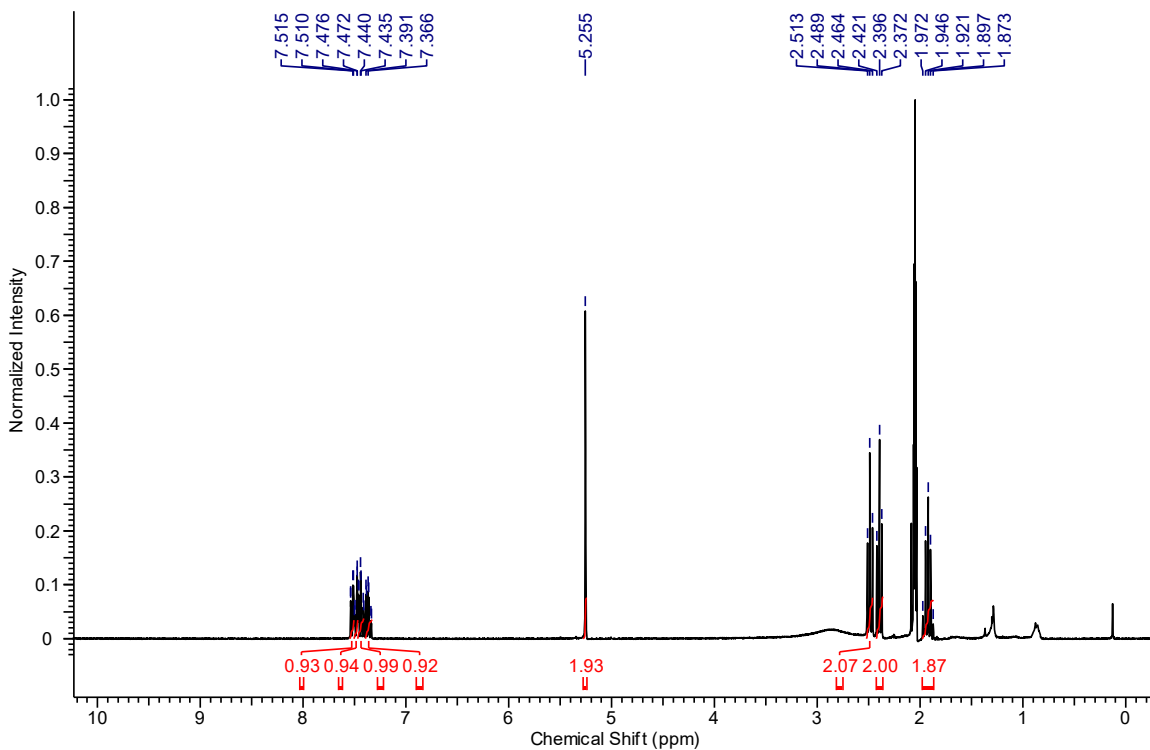
***tert*-Butyl ((3*S*,6*R*)-2,5-dioxo-3-(prop-2-yn-1-yl)-1-oxa-8-thia-4-azacyclonadec-9-yn-6-yl)carbamate (8.13):**



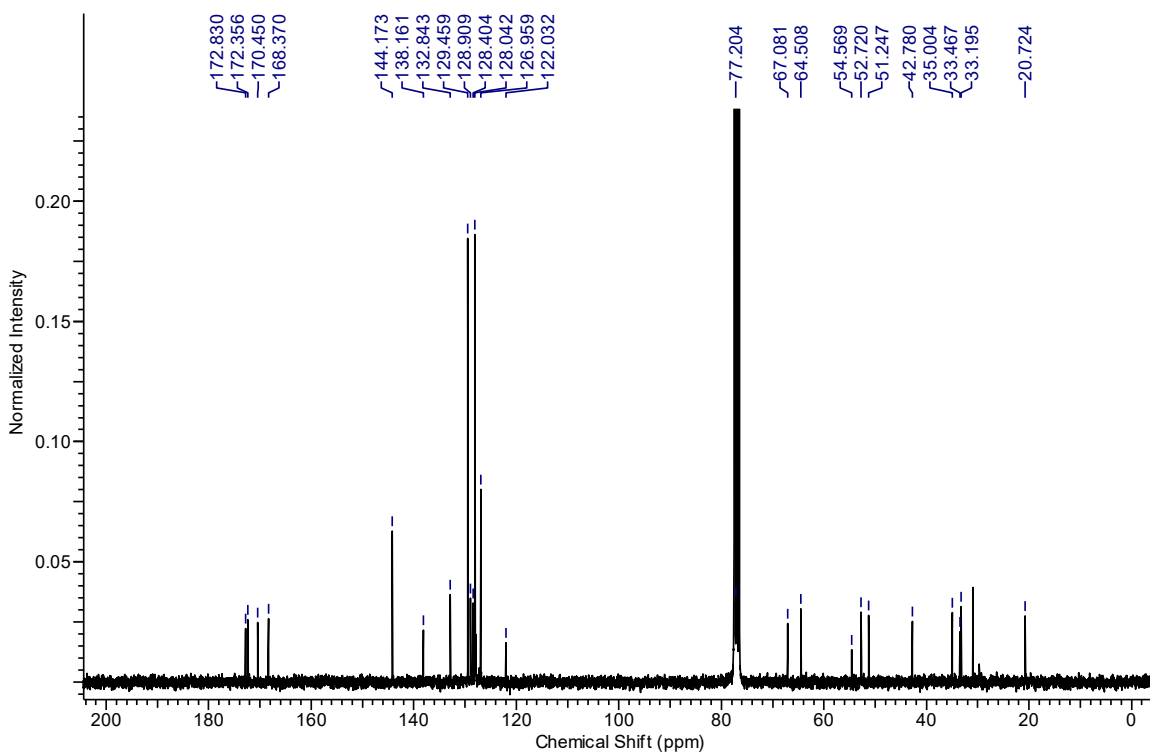
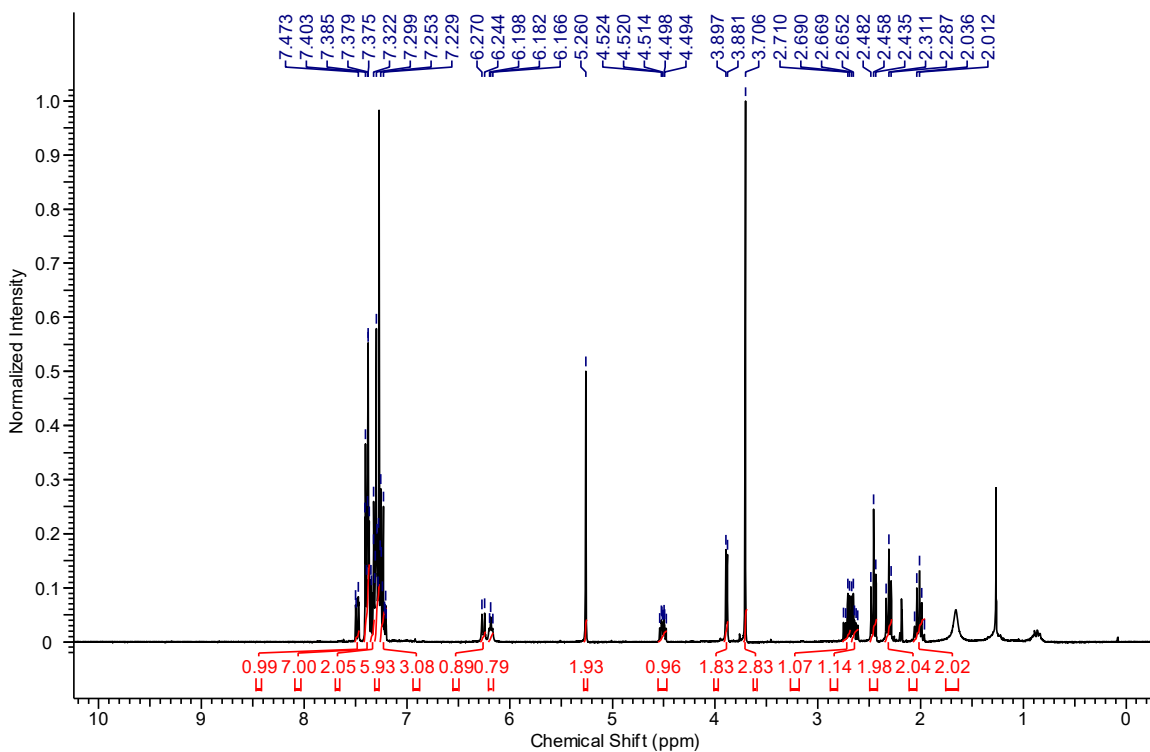
**5-((2-Ethynylbenzyl)oxy)-5-oxopentanoic acid (8.S29):**



5-((2-(Bromoethynyl)benzyl)oxy)-5-oxopentanoic acid (8.S30):

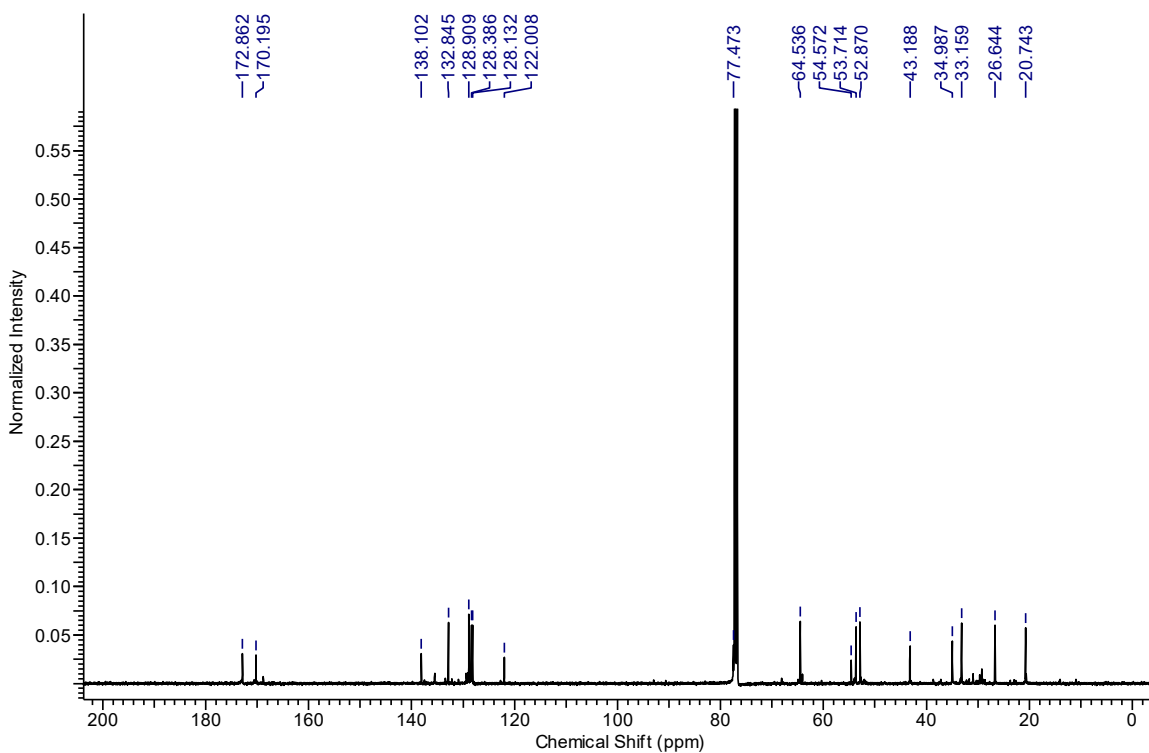
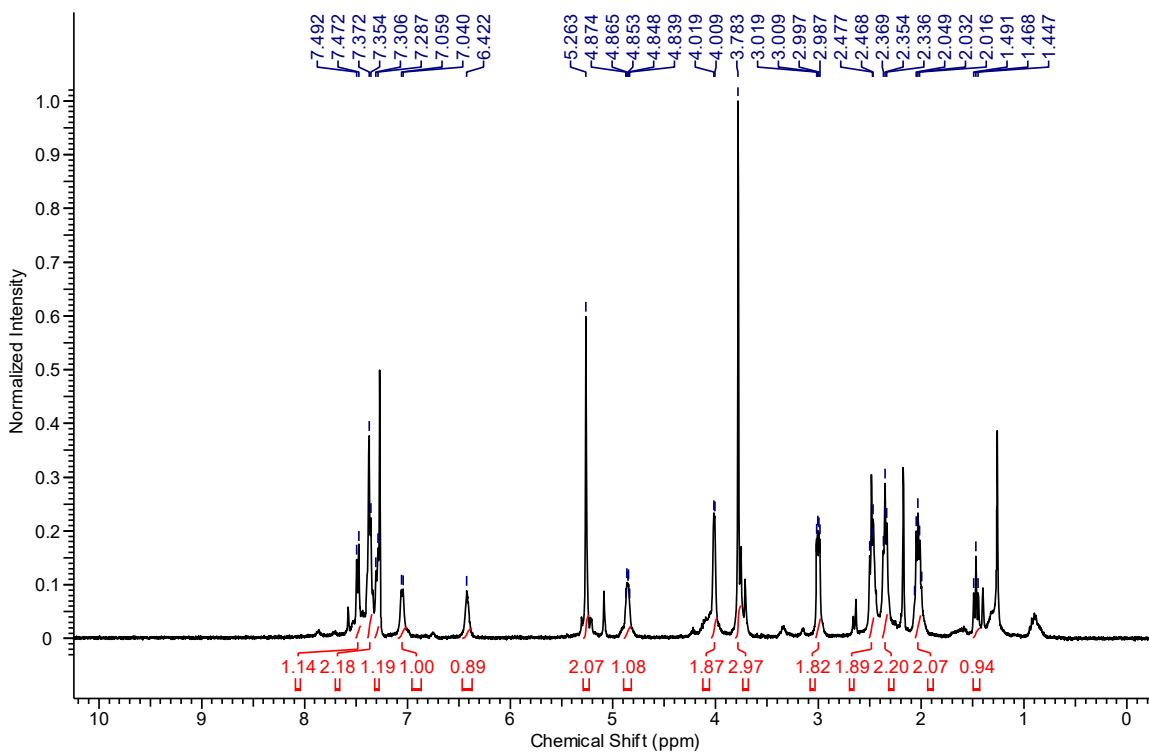


**2-(Bromoethynyl)benzyl (R)-5-((2-((1-methoxy-1-oxo-3-(tritylthio)propan-2-yl)amino)-2-oxoethyl)amino)-5-oxopentanoate (8.S31):**





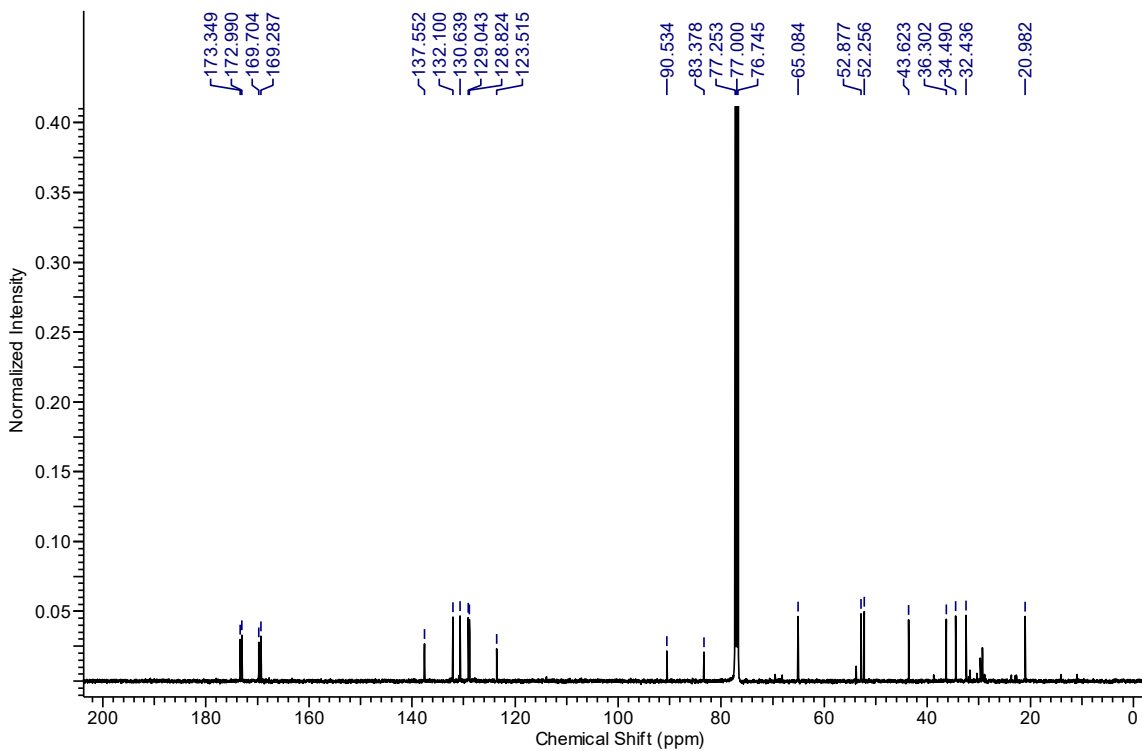
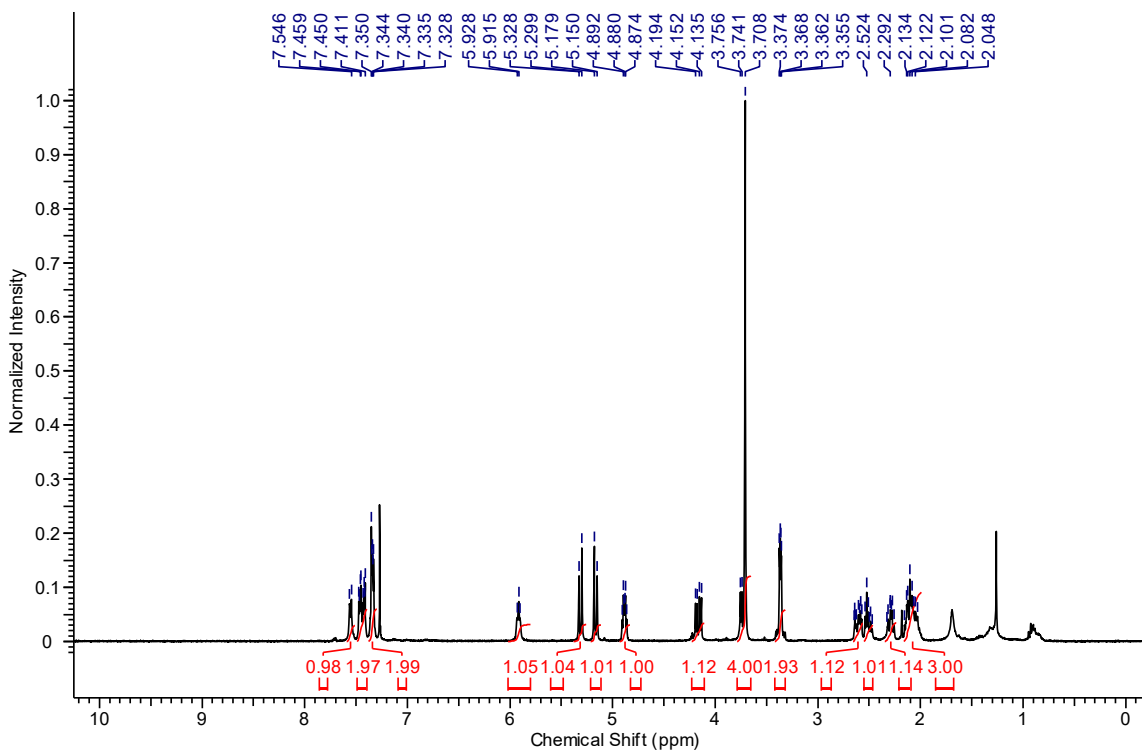
**2-(Bromoethynyl)benzyl (R)-5-((2-((3-mercapto-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-5-oxopentanoate (8.S32):**



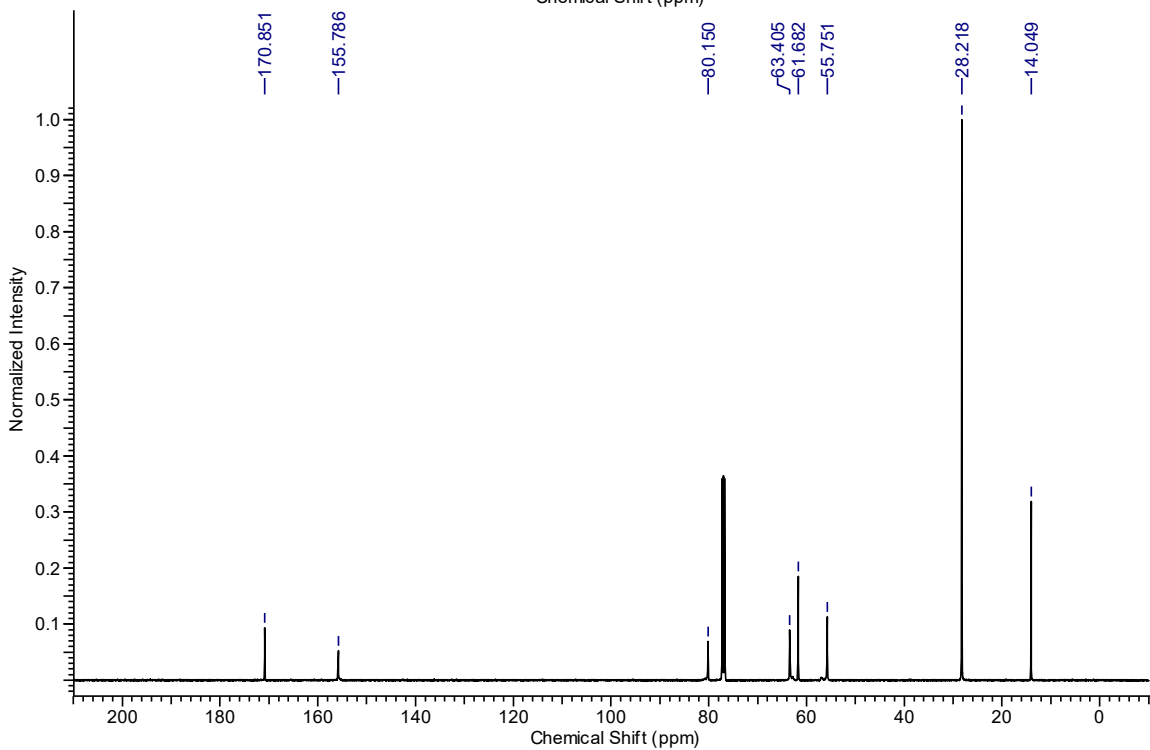
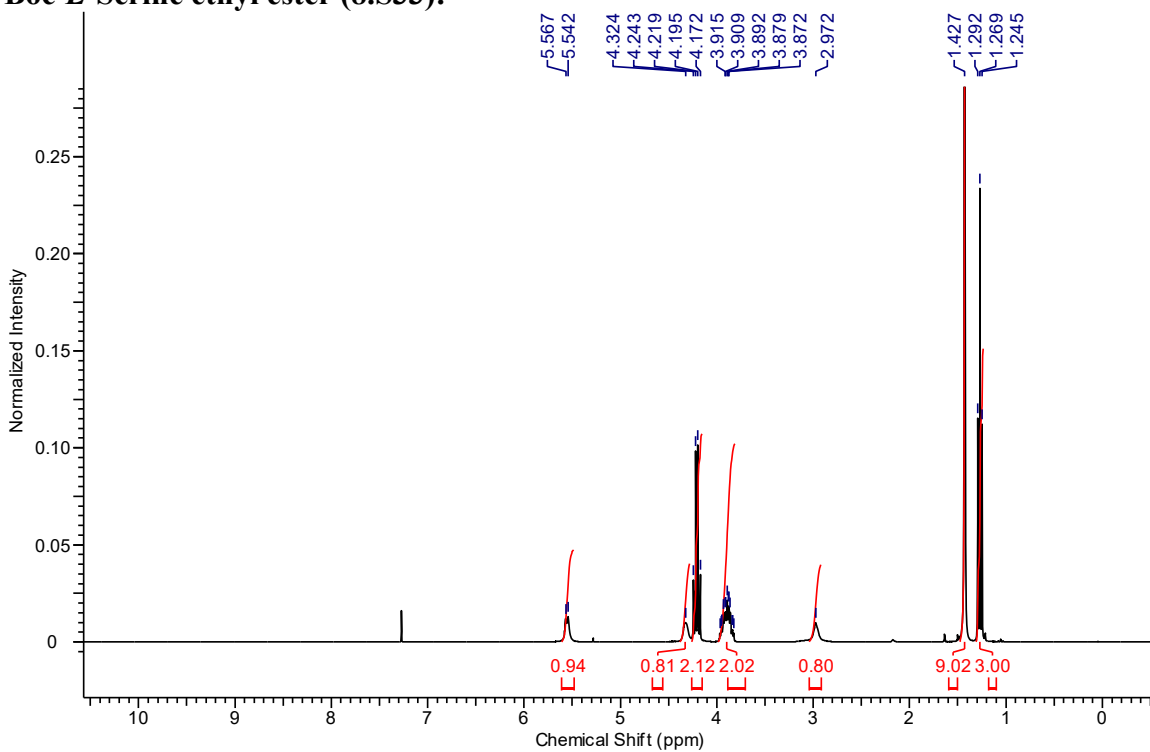
Methyl

3,7,10-trioxo-4,5,6,7,10,11,12,13,15,16-decahydro-1*H*,3*H*,9*H*-8 $\lambda^2$ -

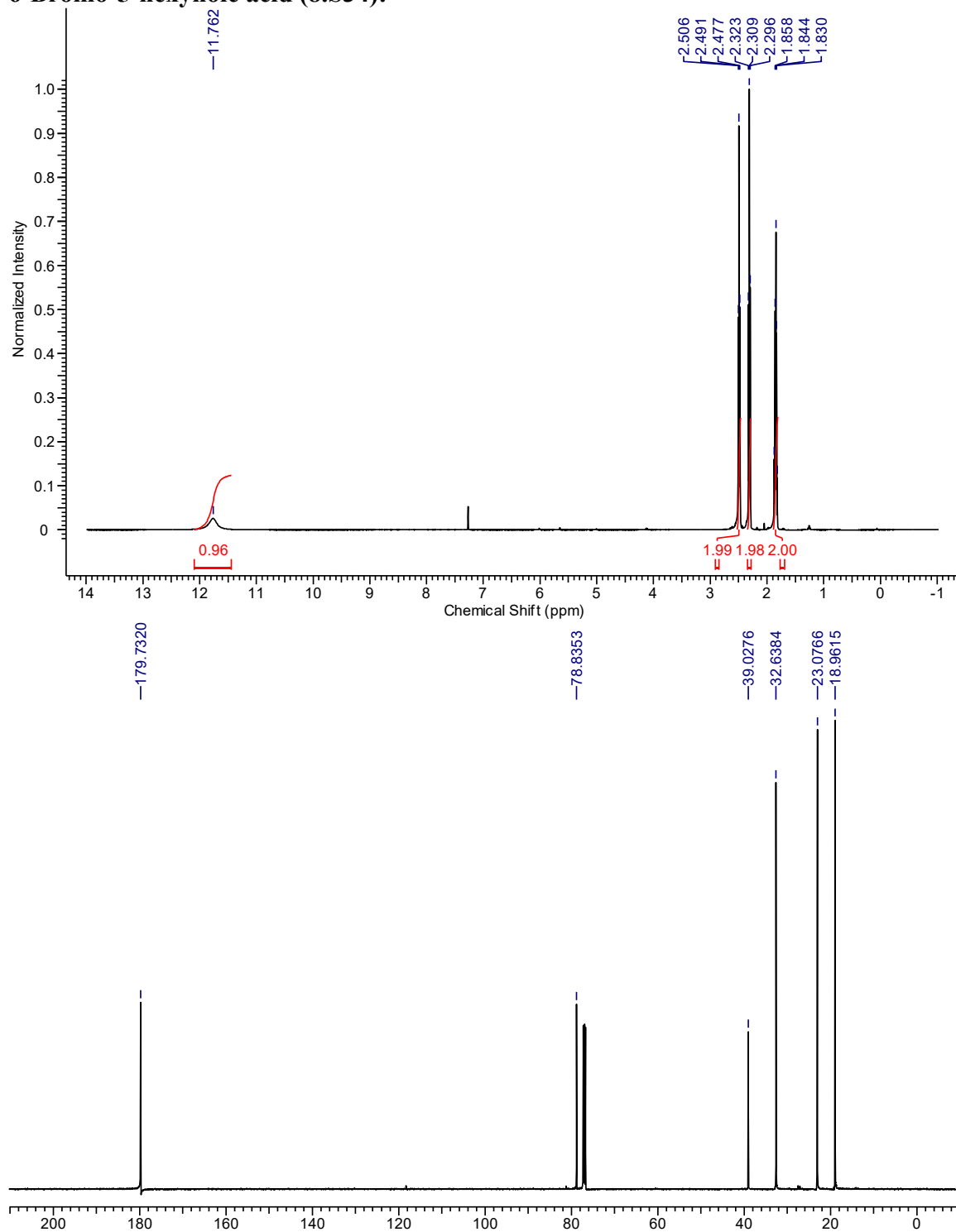
benzo[*c*][1]oxa[7]thia[10,13]diazacyclooctadec-15-yne-12-carboxylate (8.14):



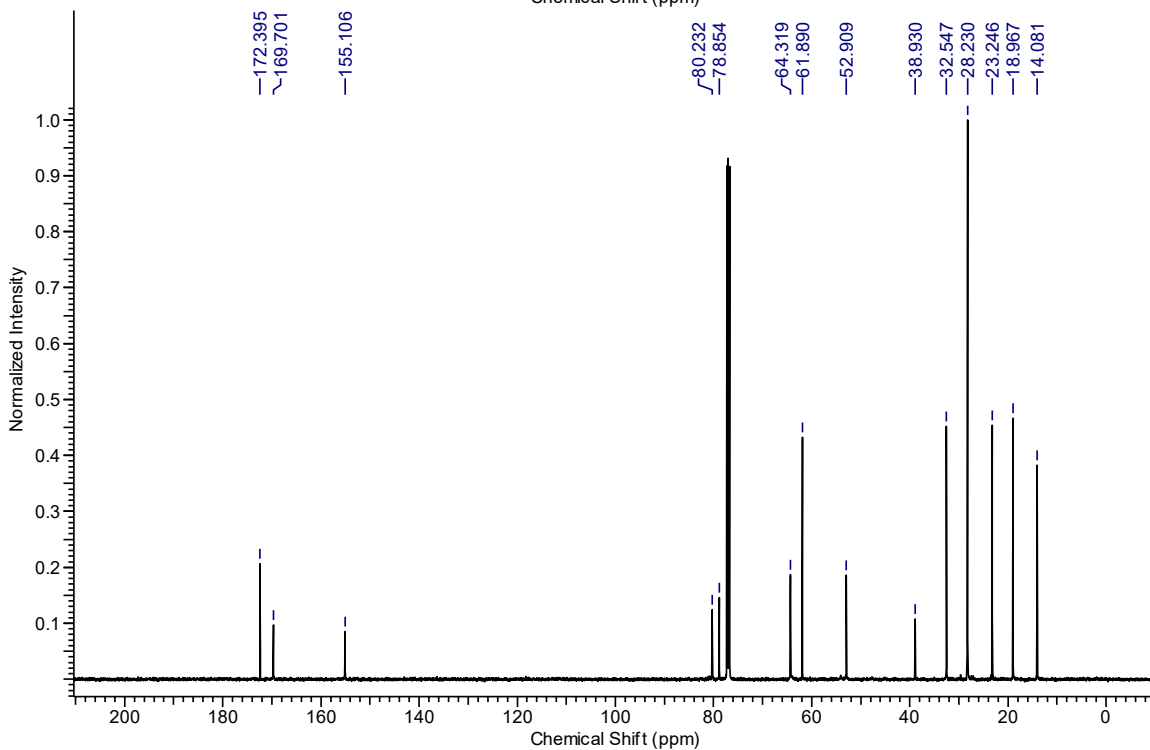
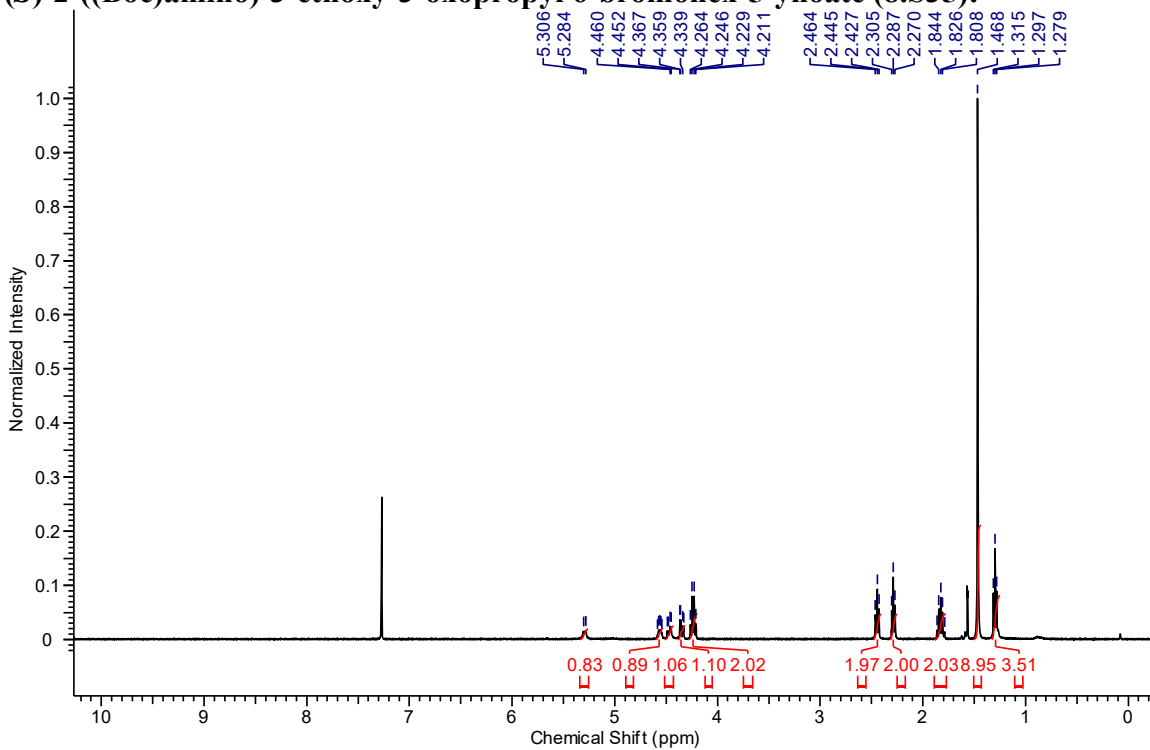
**Boc-L-Serine ethyl ester (8.S33):**



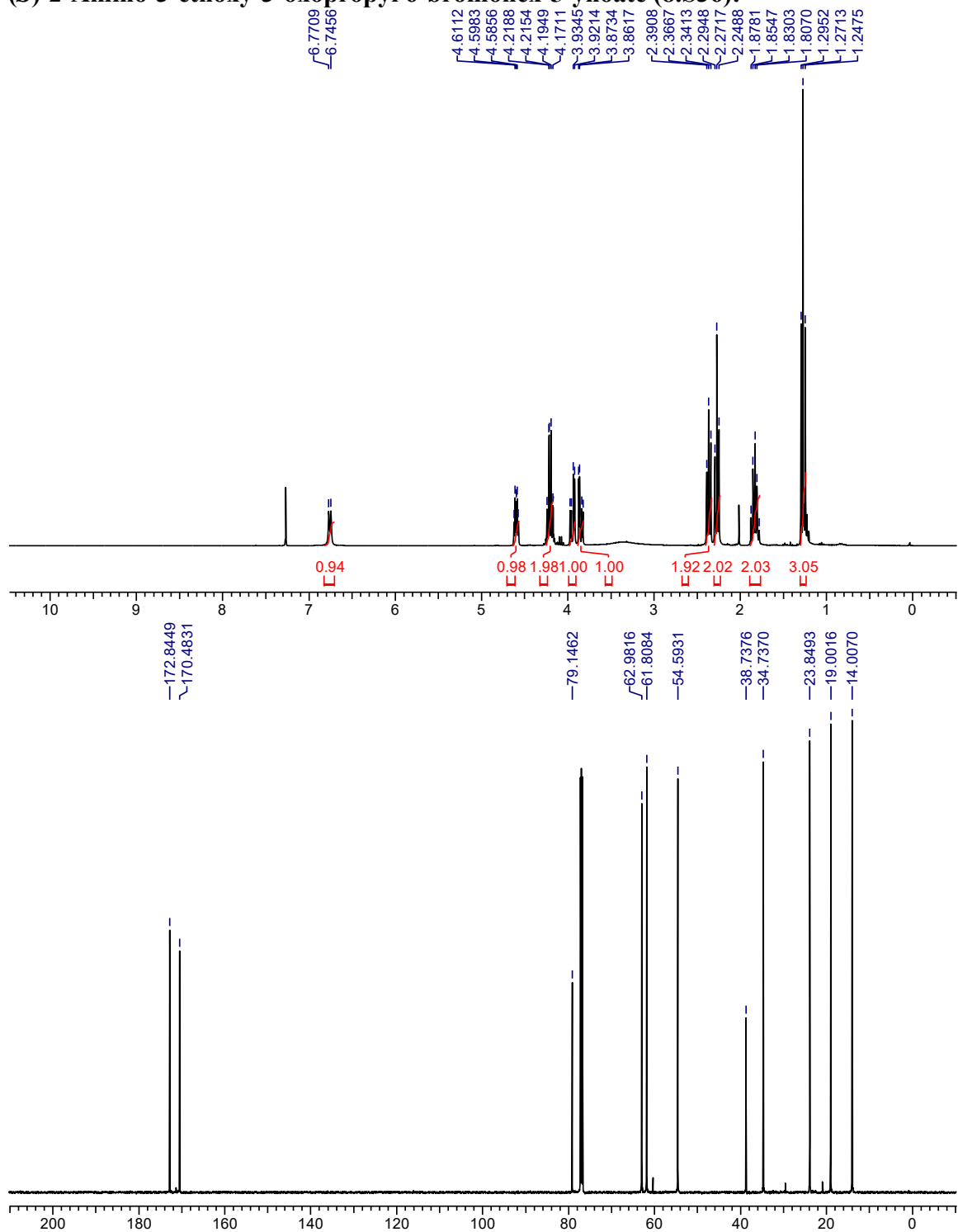
**6-Bromo-5-hexynoic acid (8.S34):**



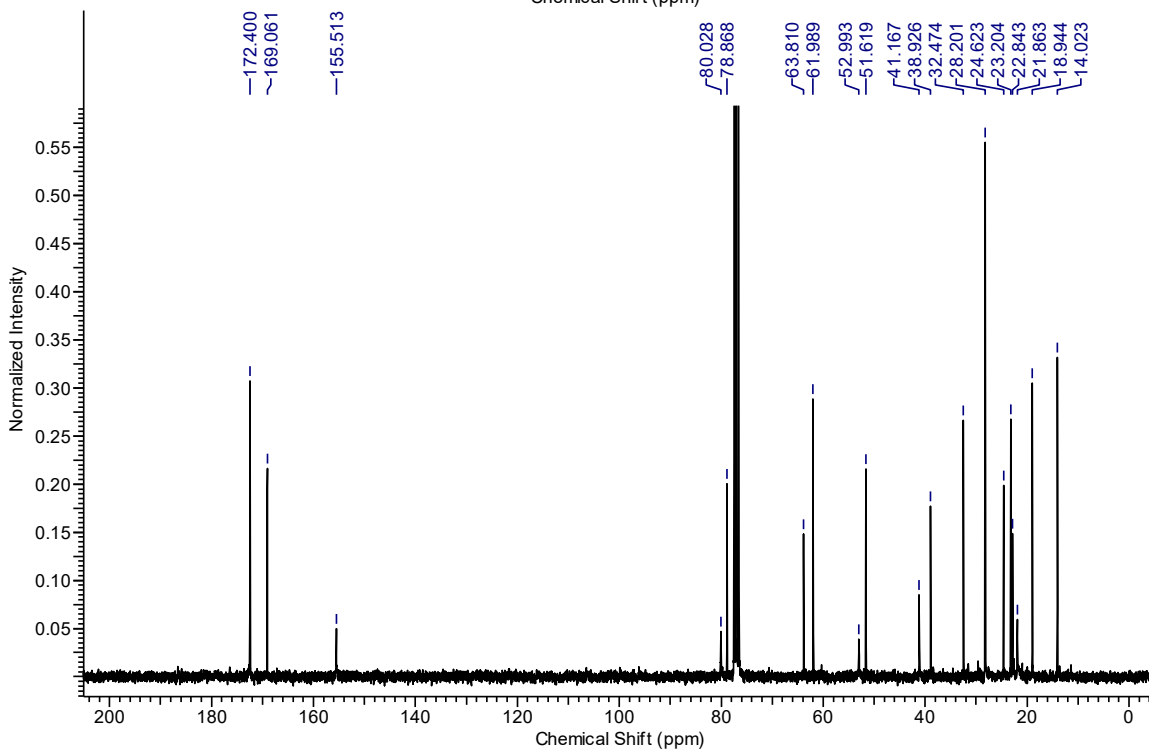
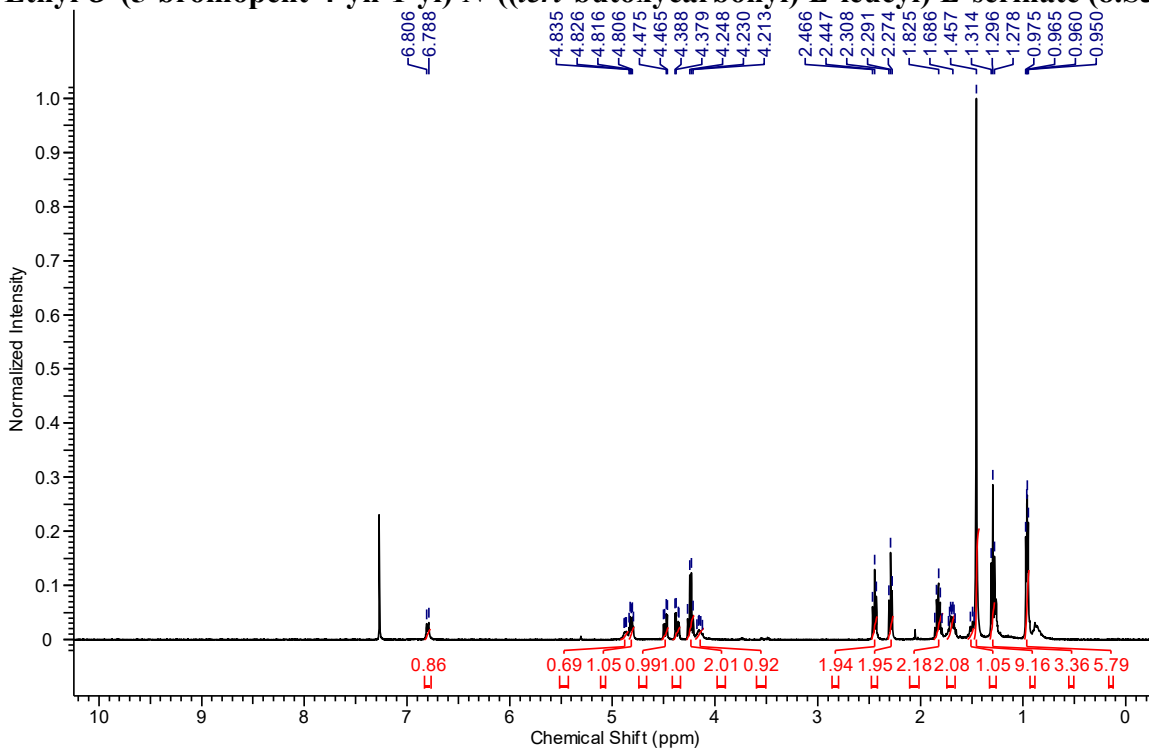
**(S)-2-((Boc)amino)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S35):**



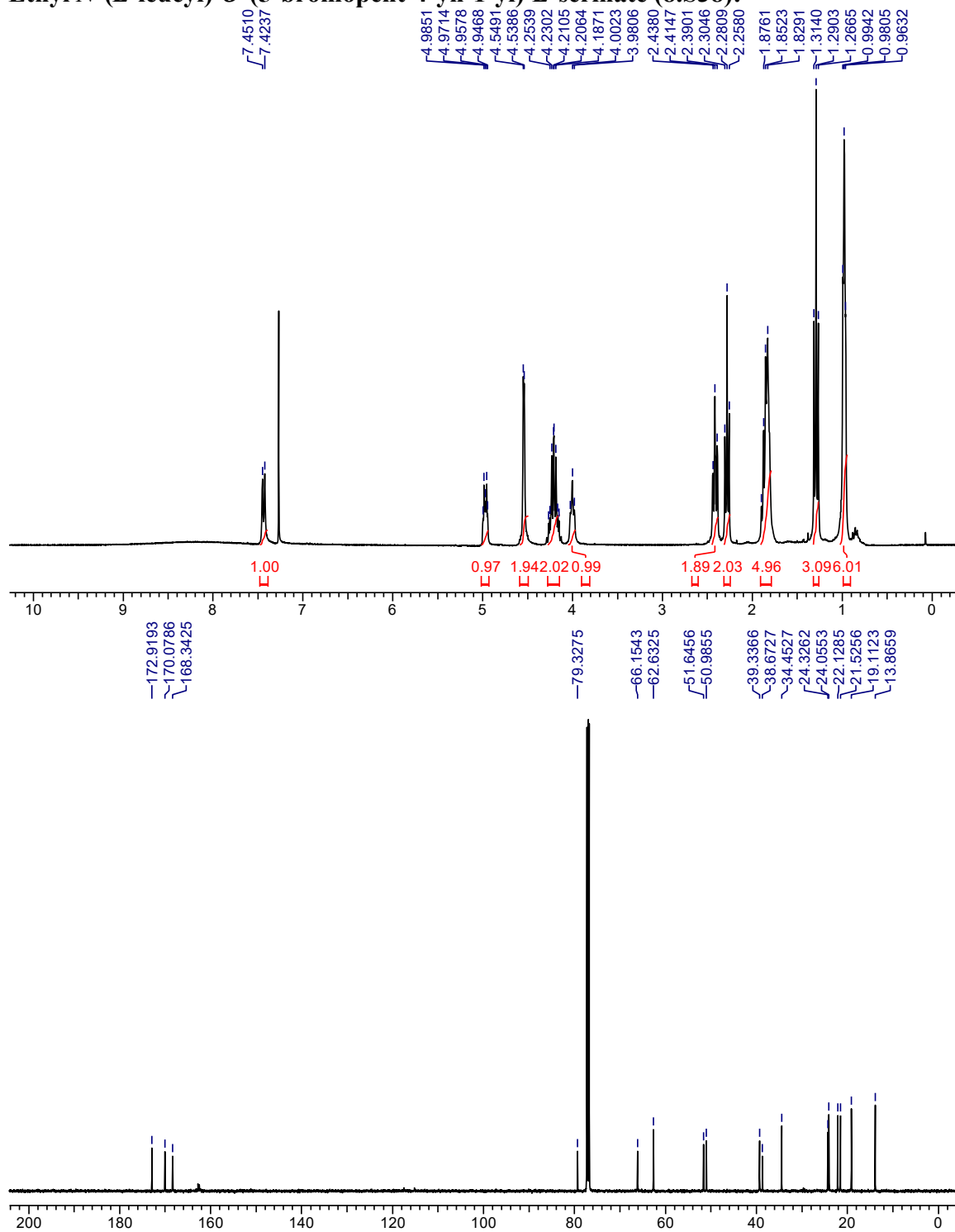
**(S)-2-Amino-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S36):**



**Ethyl *O*-(5-bromopent-4-yn-1-yl)-*N*-((*tert*-butoxycarbonyl)-*L*-leucyl)-*L*-serinate (8.S37):**

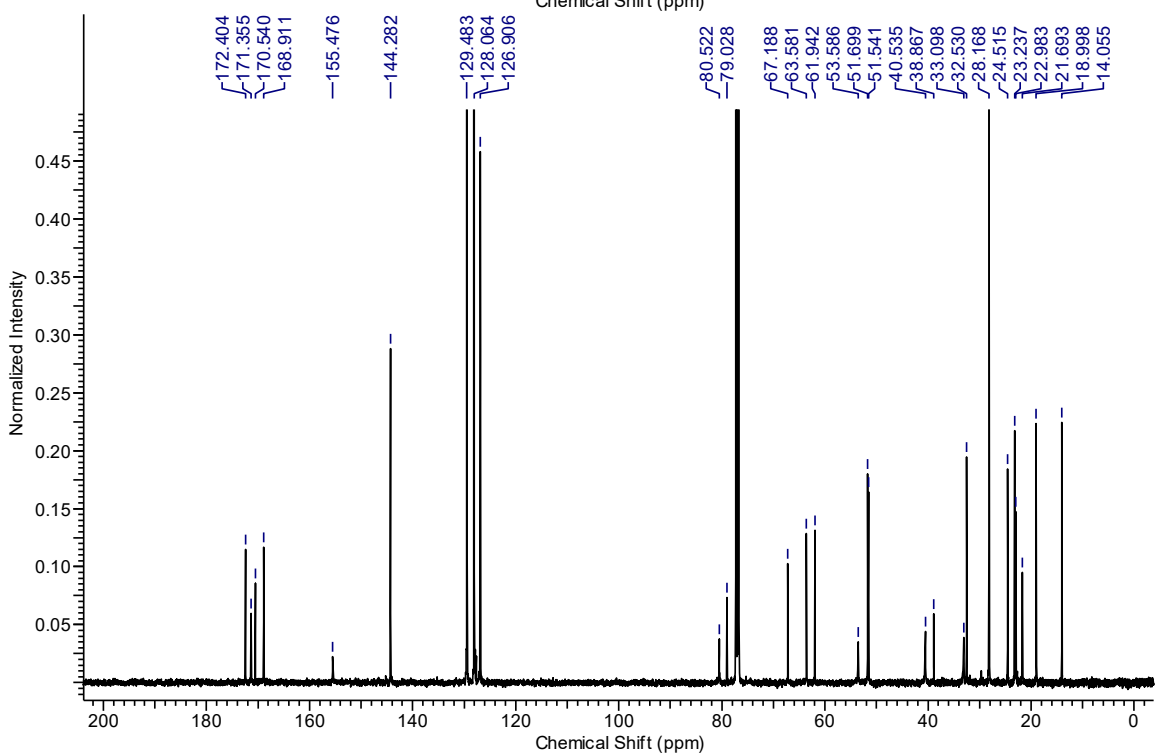
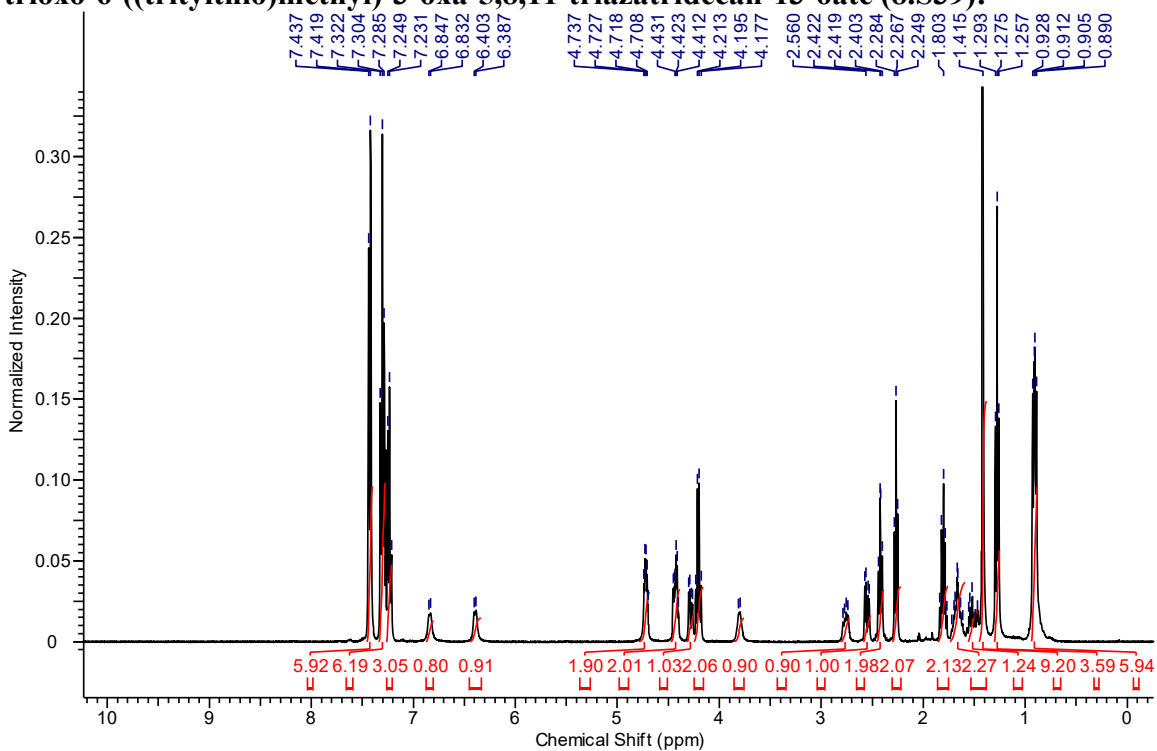


**Ethyl *N*-(*L*-leucyl)-*O*-(5-bromopent-4-yn-1-yl)-*L*-serinate (8.S38):**

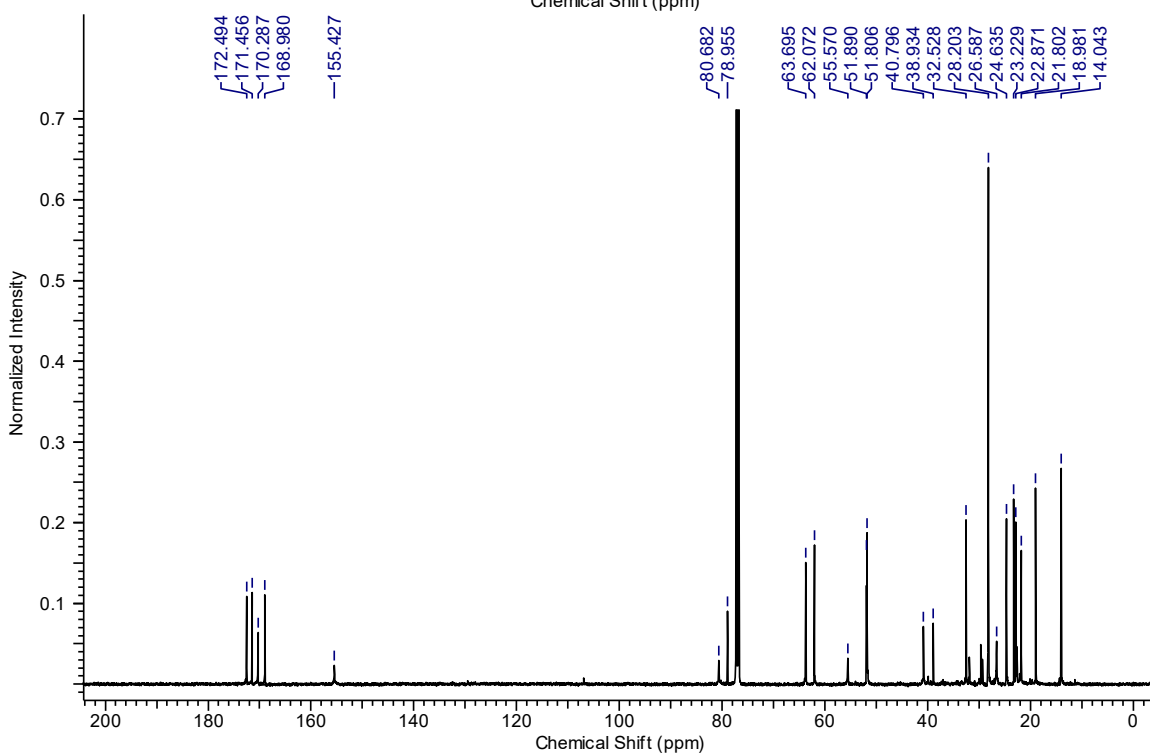
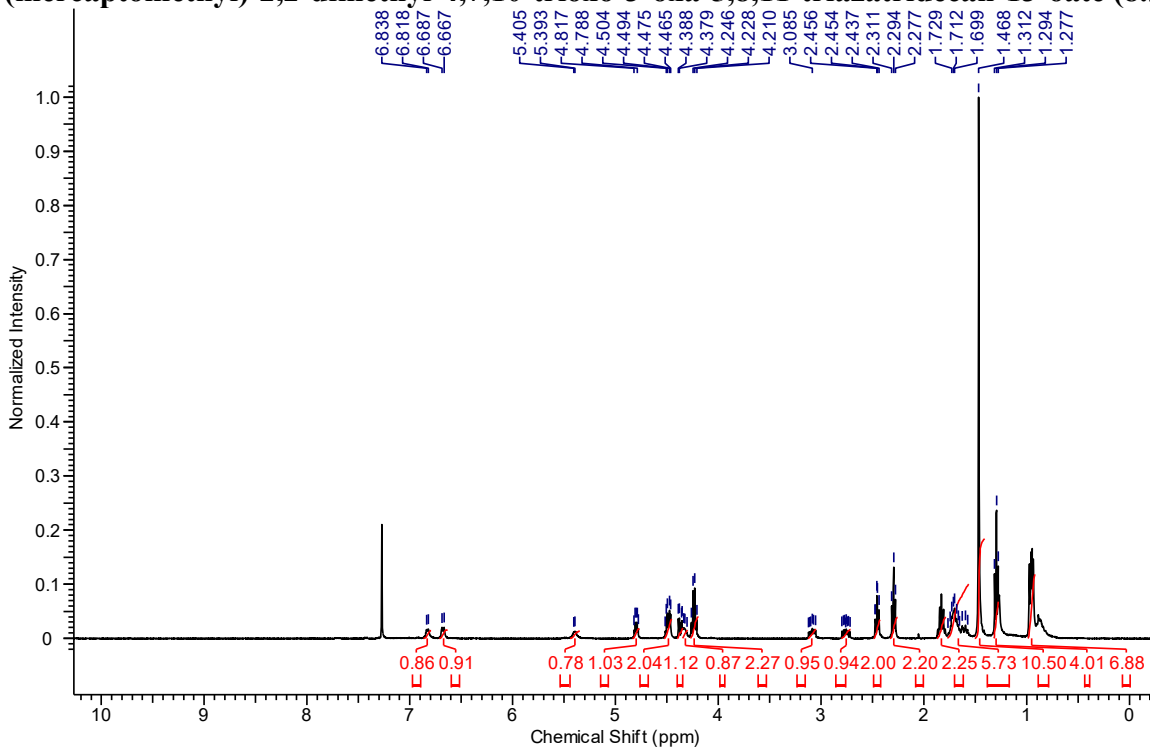




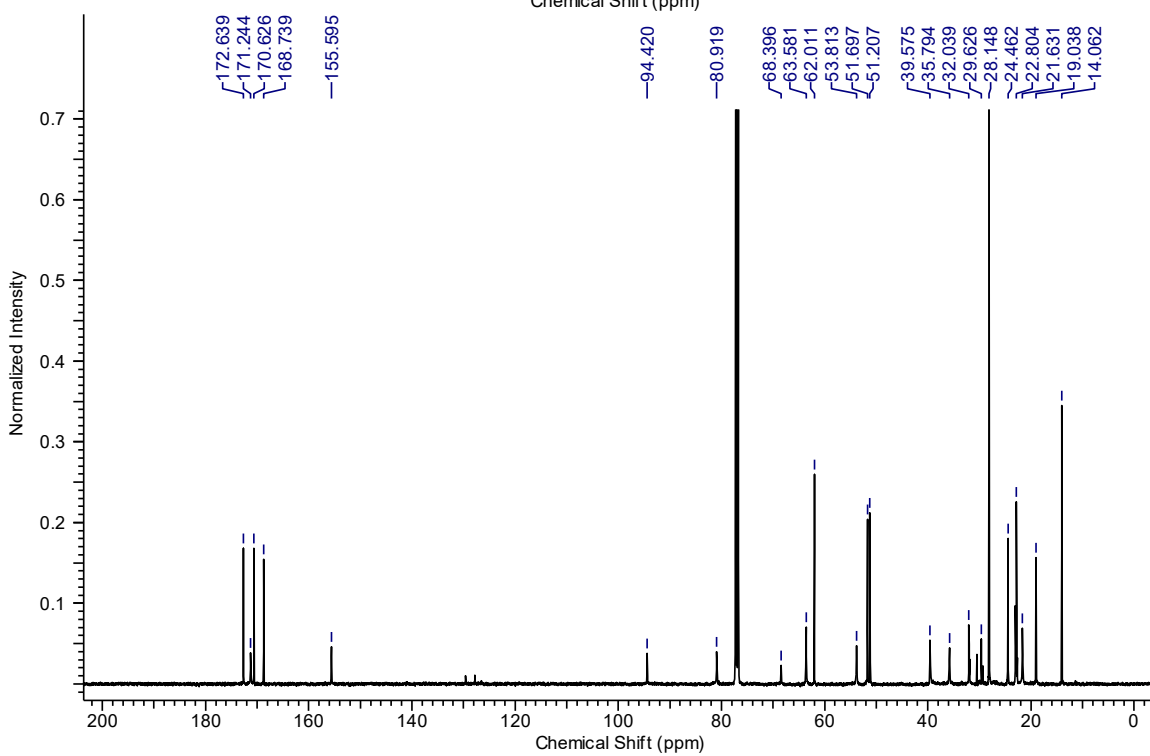
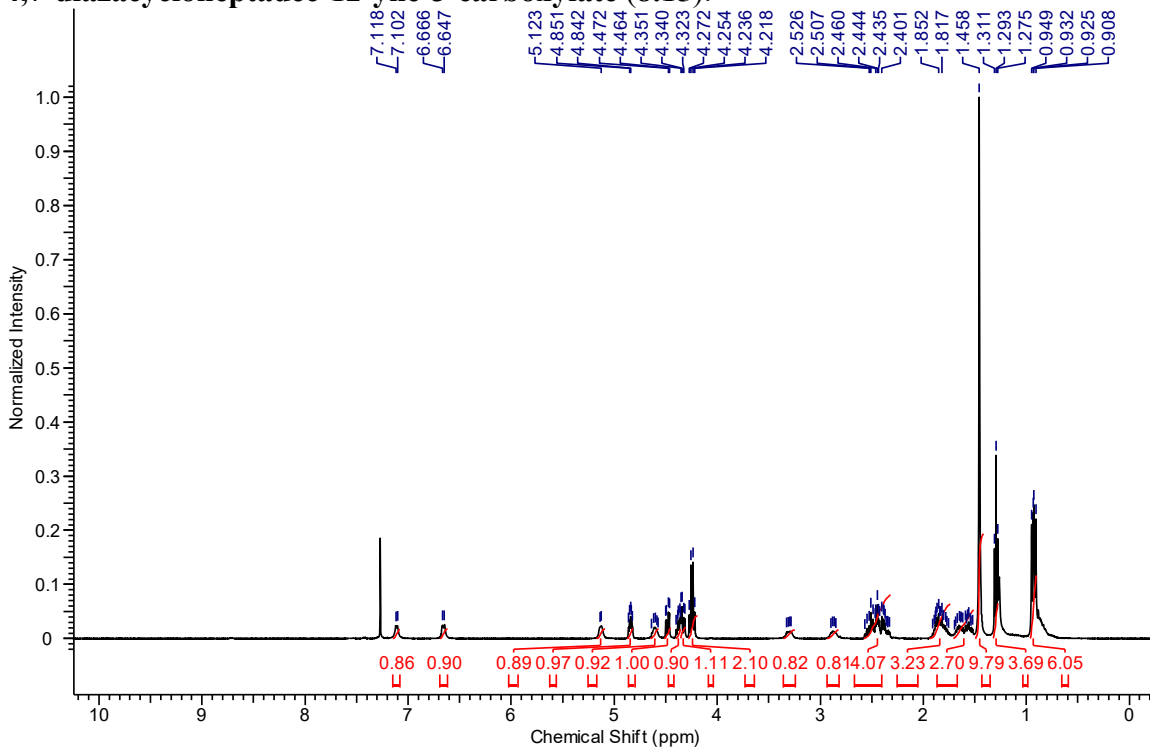
**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-9-isobutyl-2,2-dimethyl-4,7,10-trioxa-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S39):**



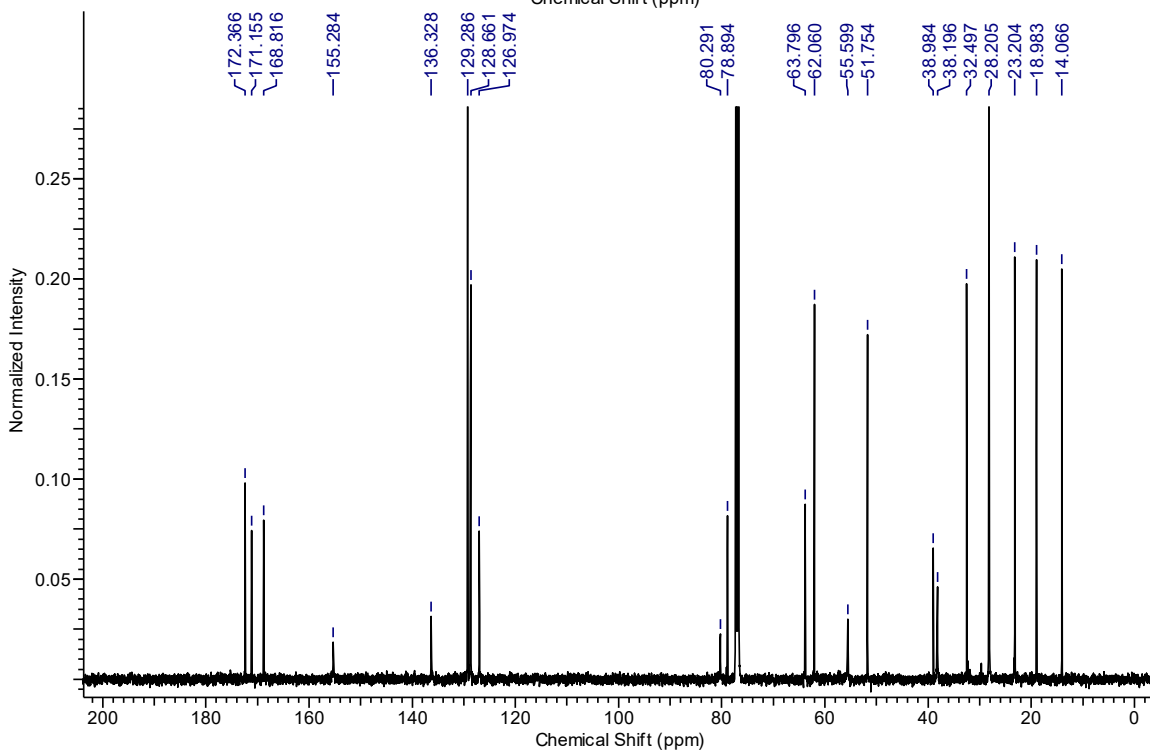
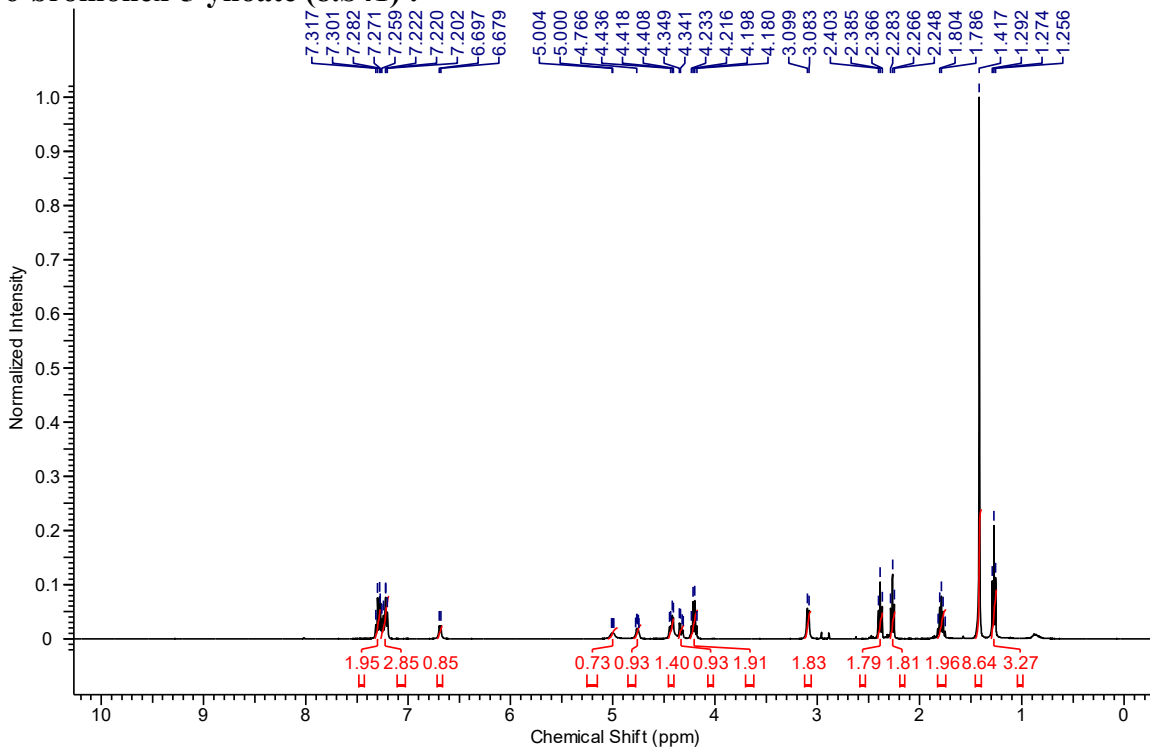
**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-9-isobutyl-6-(mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (8.S40):**



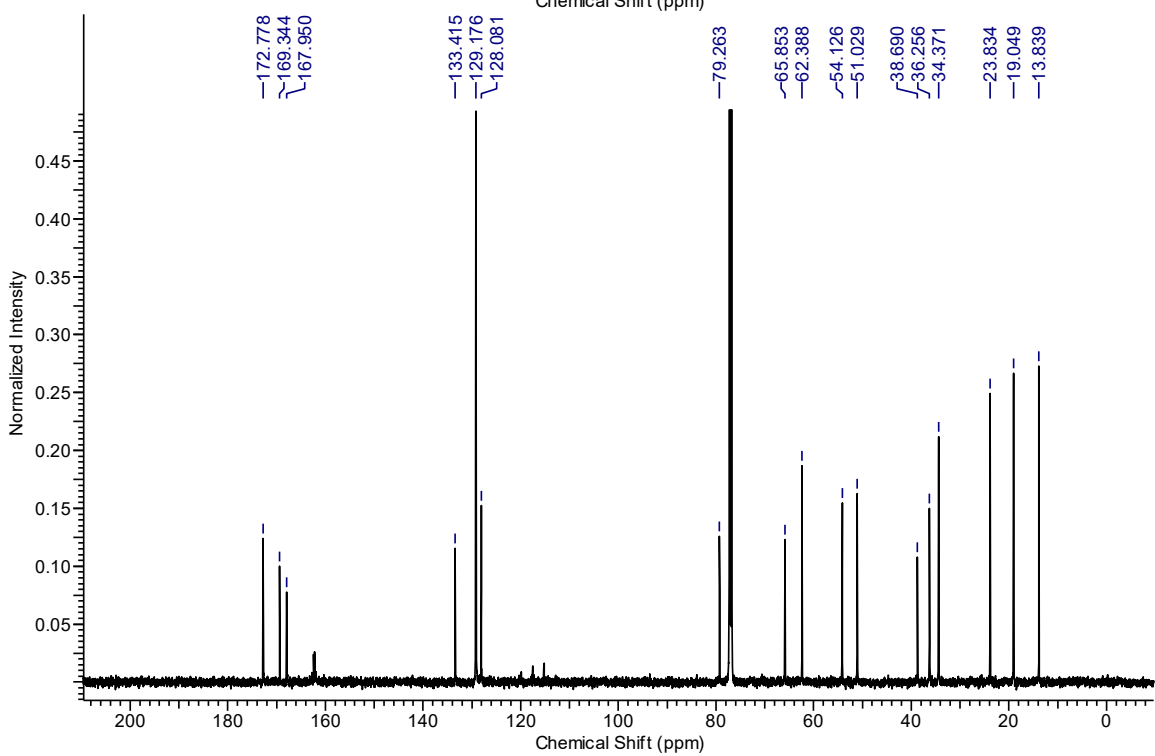
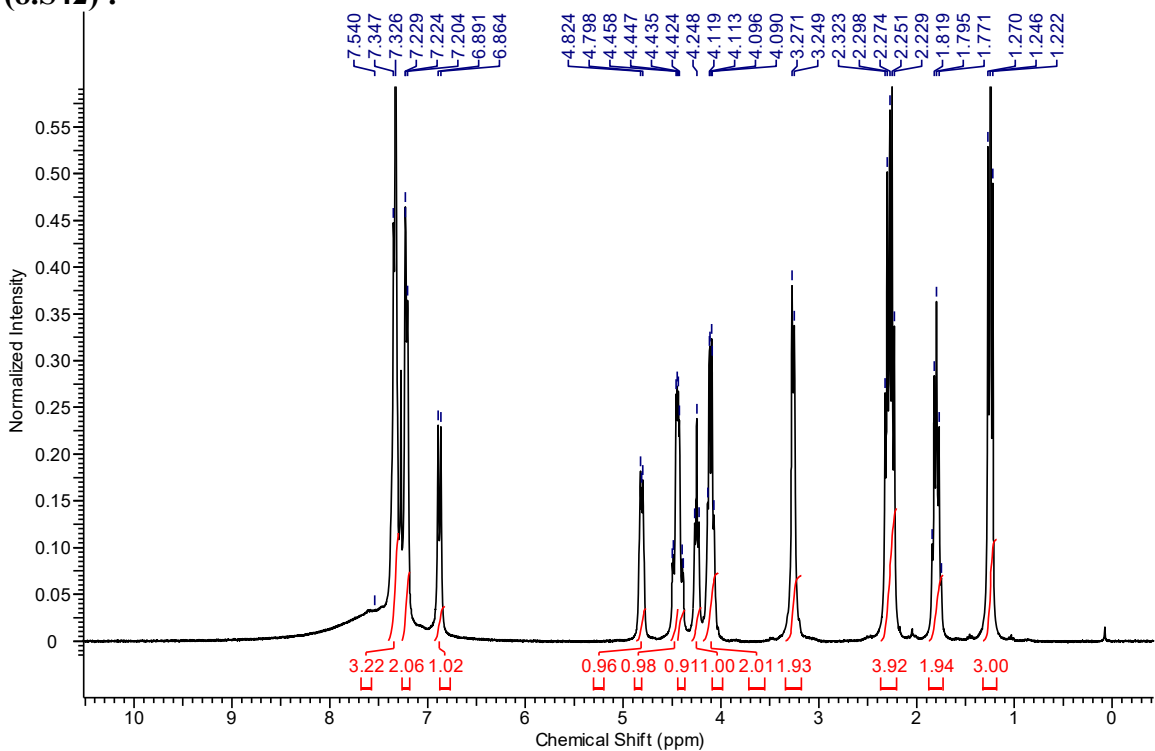
**Ethyl (3*S*,6*S*,9*R*)-9-((*tert*-butoxycarbonyl)amino)-6-isobutyl-5,8,17-trioxo-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.15):**



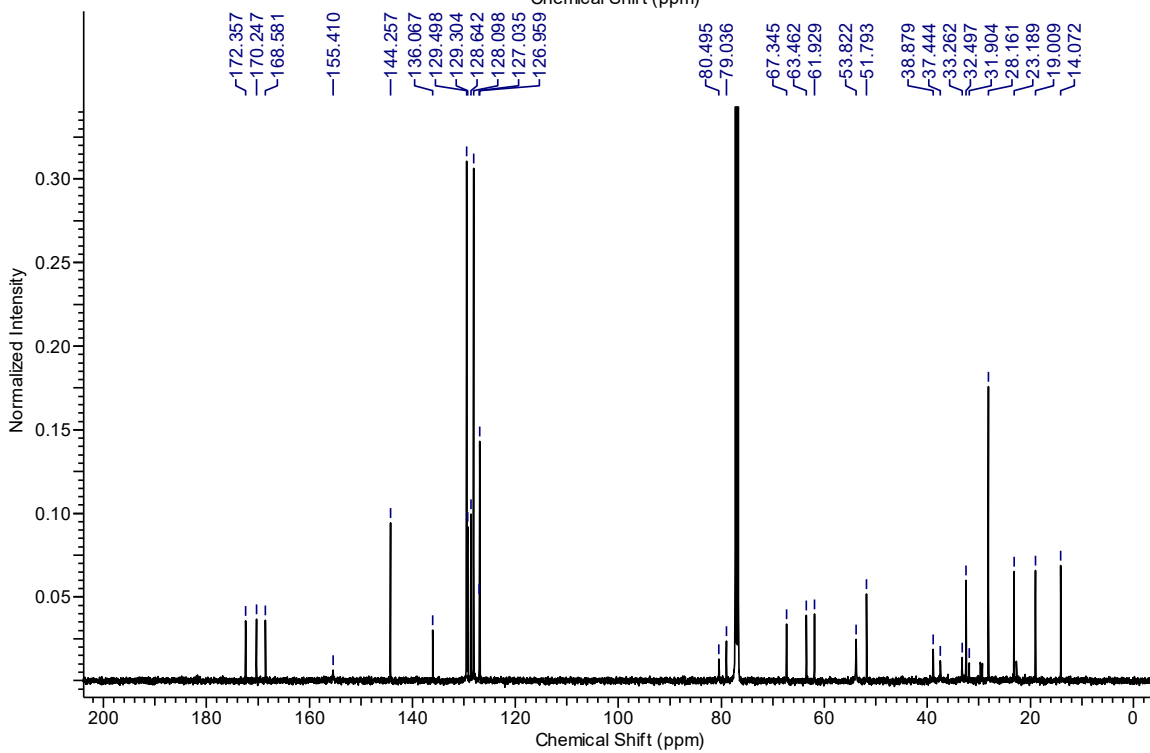
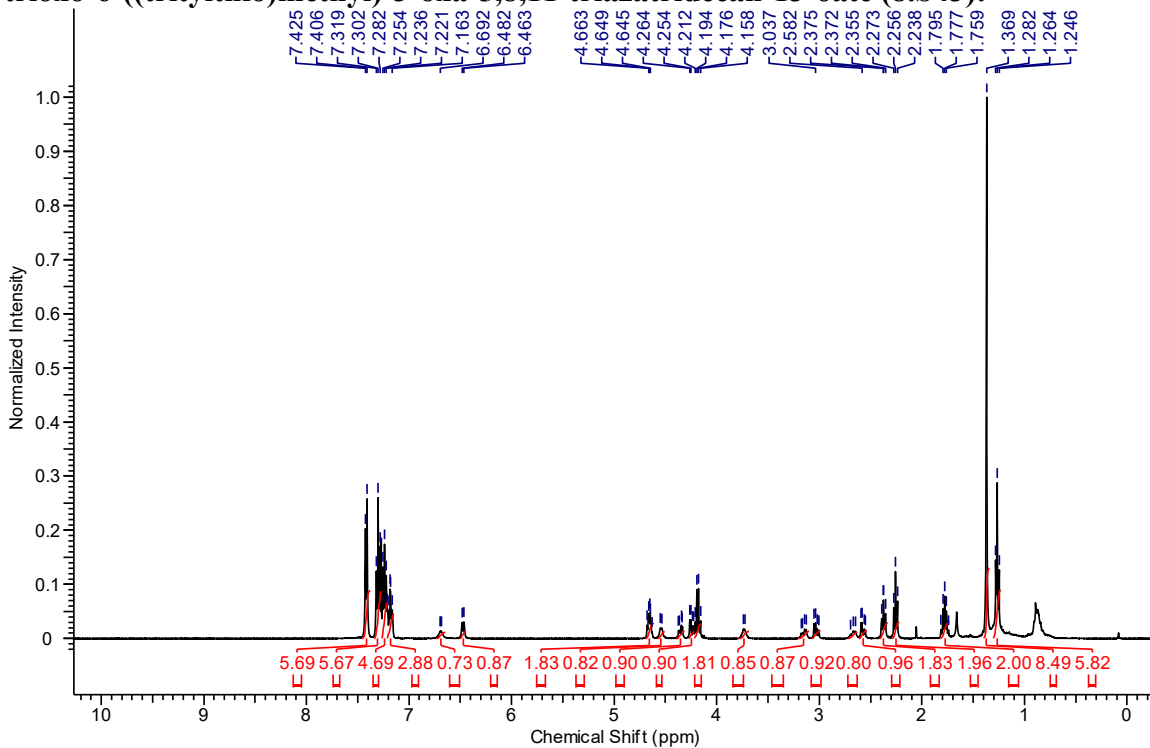
**(S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-ethoxy-3-oxopropyl  
6-bromohex-5-ynoate (8.S41) :**



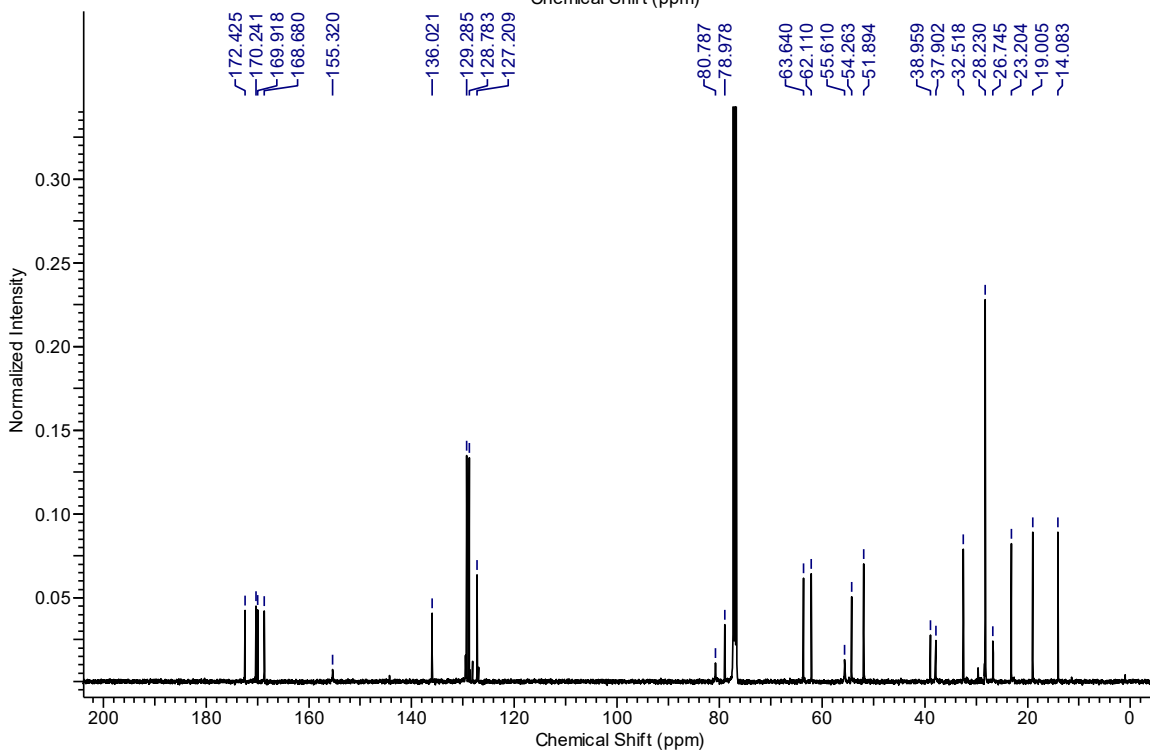
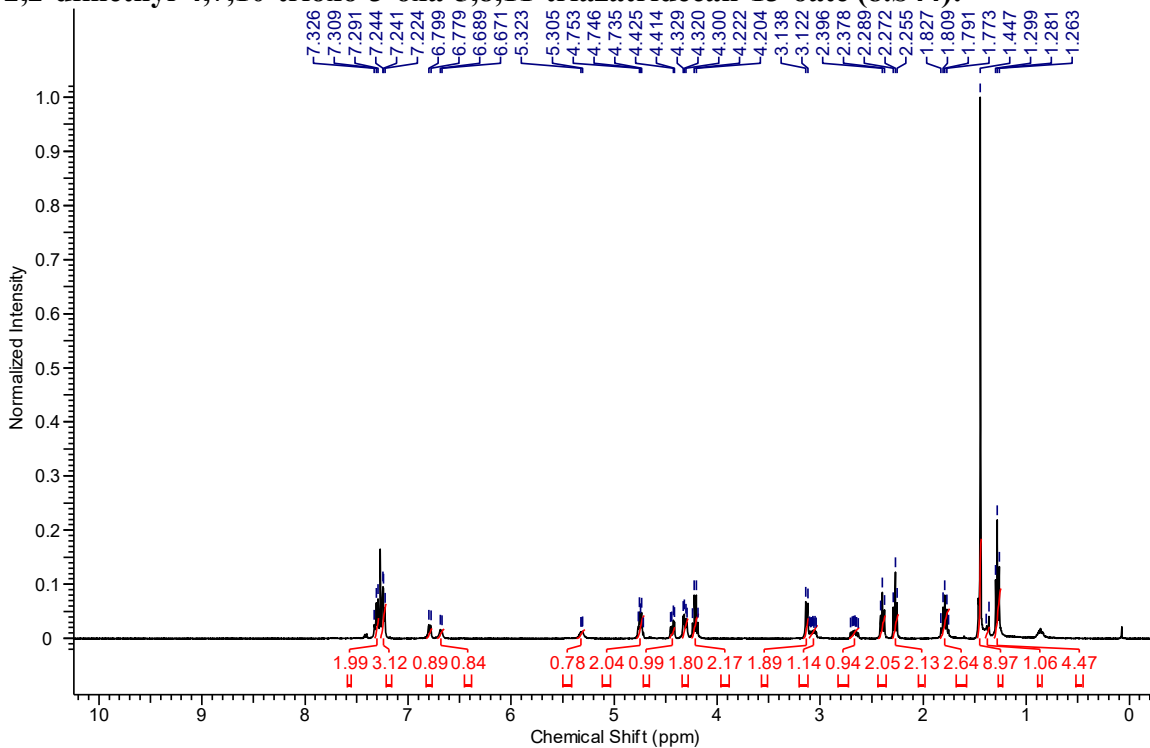
**(S)-2-((S)-2-amino-3-phenylpropanamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S42) :**



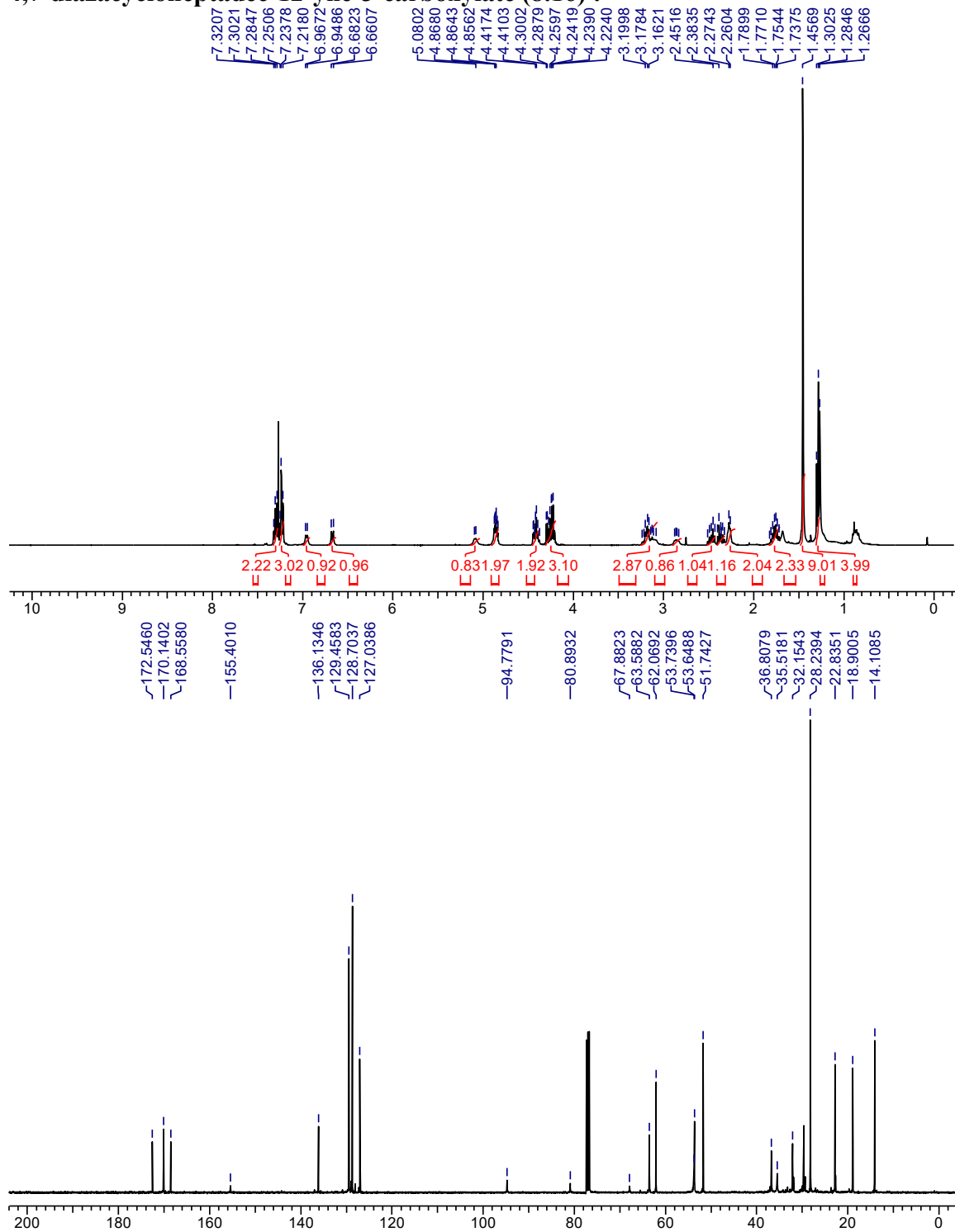
**Ethyl (6*R*,9*S*,12*S*)-9-benzyl-12-(((6-bromohex-5-ynoyl)oxy)methyl)-2,2-dimethyl-4,7,10-trioxo-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S43):**



**Ethyl (6*R*,9*S*,12*S*)-9-benzyl-12-(((6-bromohex-5-ynoyl)oxy)methyl)-6-(mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (8.S44):**



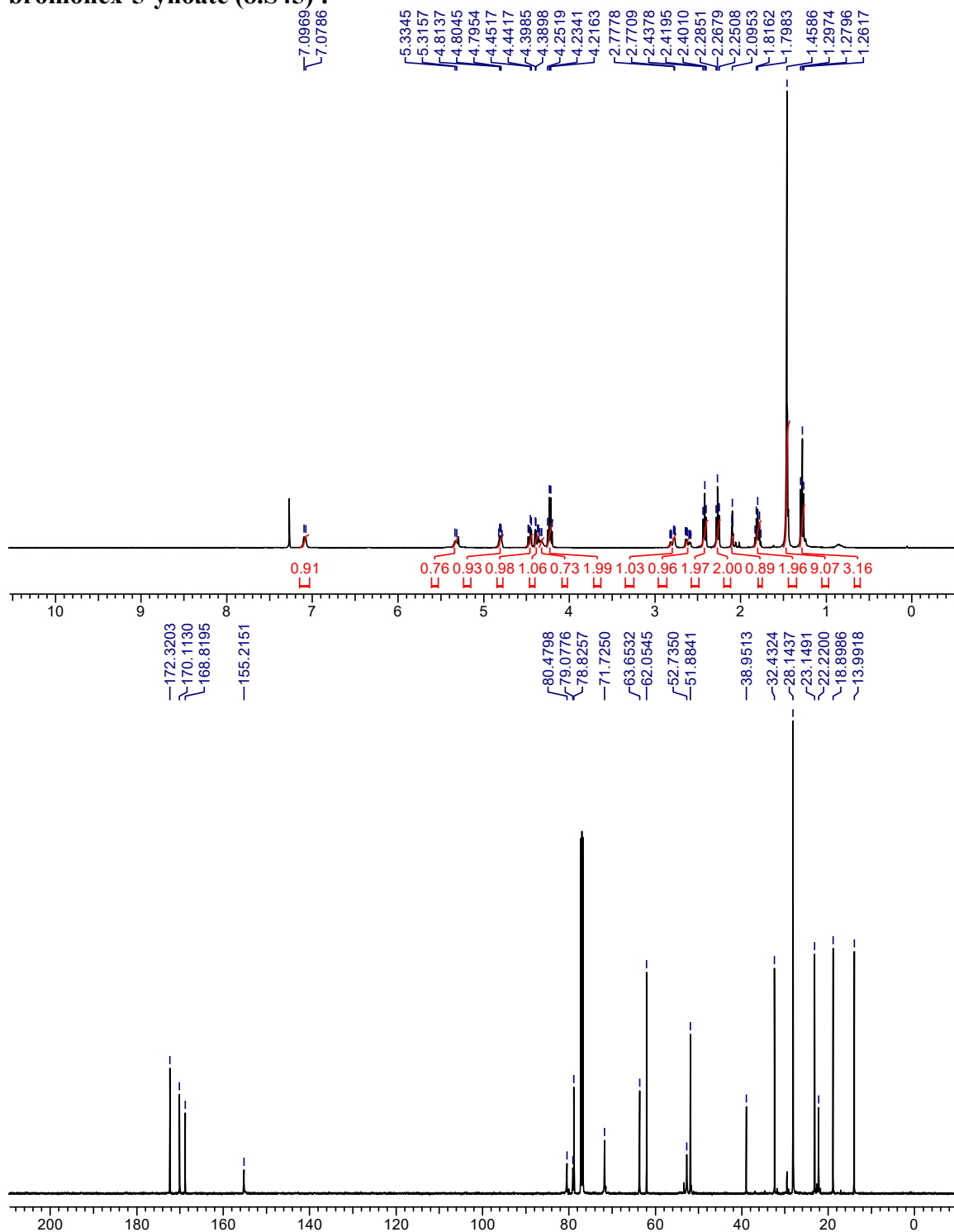
**Ethyl (3*S*,6*S*,9*R*)-6-benzyl-9-((*tert*-butoxycarbonyl)amino)-5,8,17-trioxo-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.16) :**



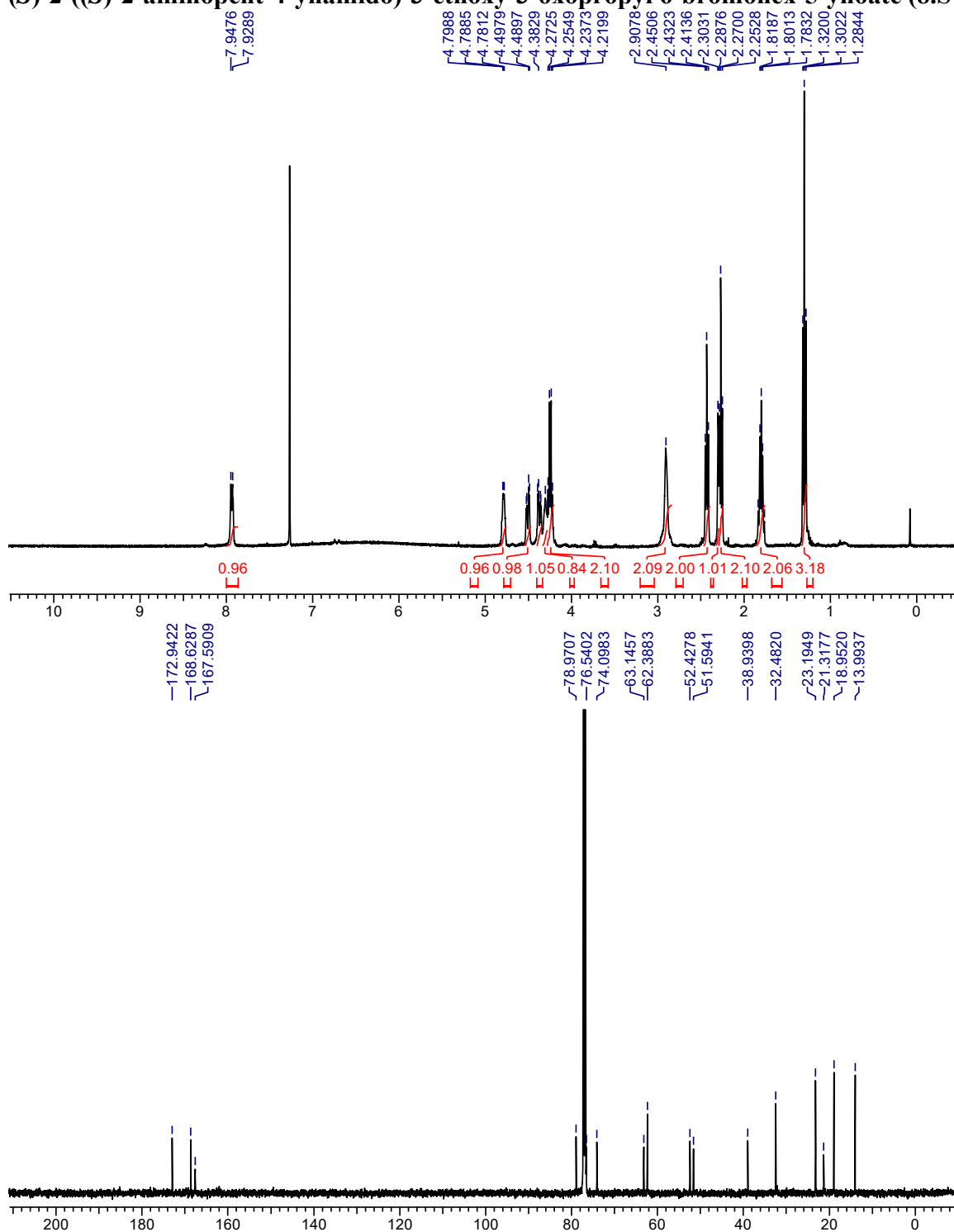


**(S)-2-((S)-2-((tert-Butoxycarbonyl)amino)pent-4-ynamido)-3-ethoxy-3-oxopropyl bromohex-5-ynoate (8.S45) :**

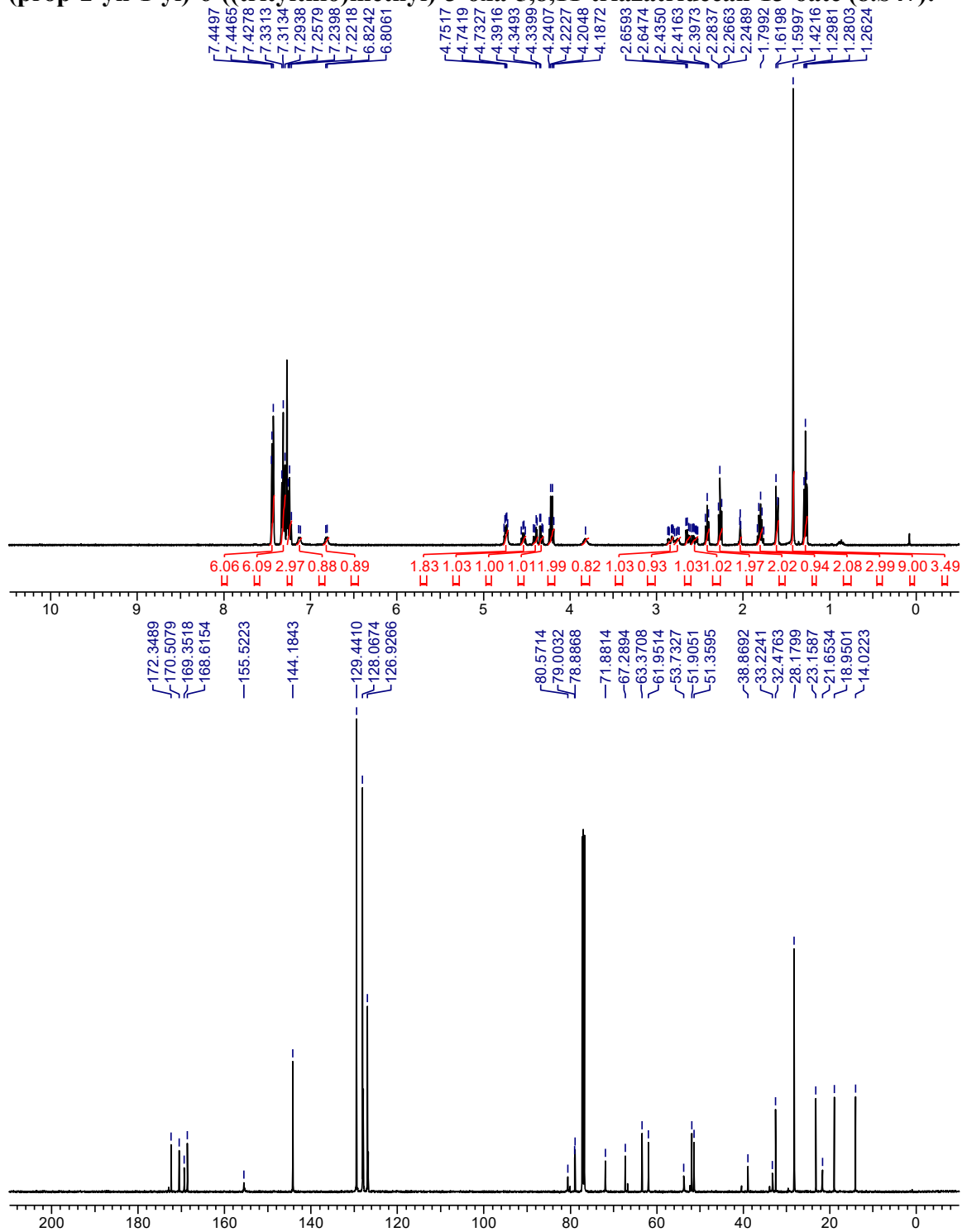
6-



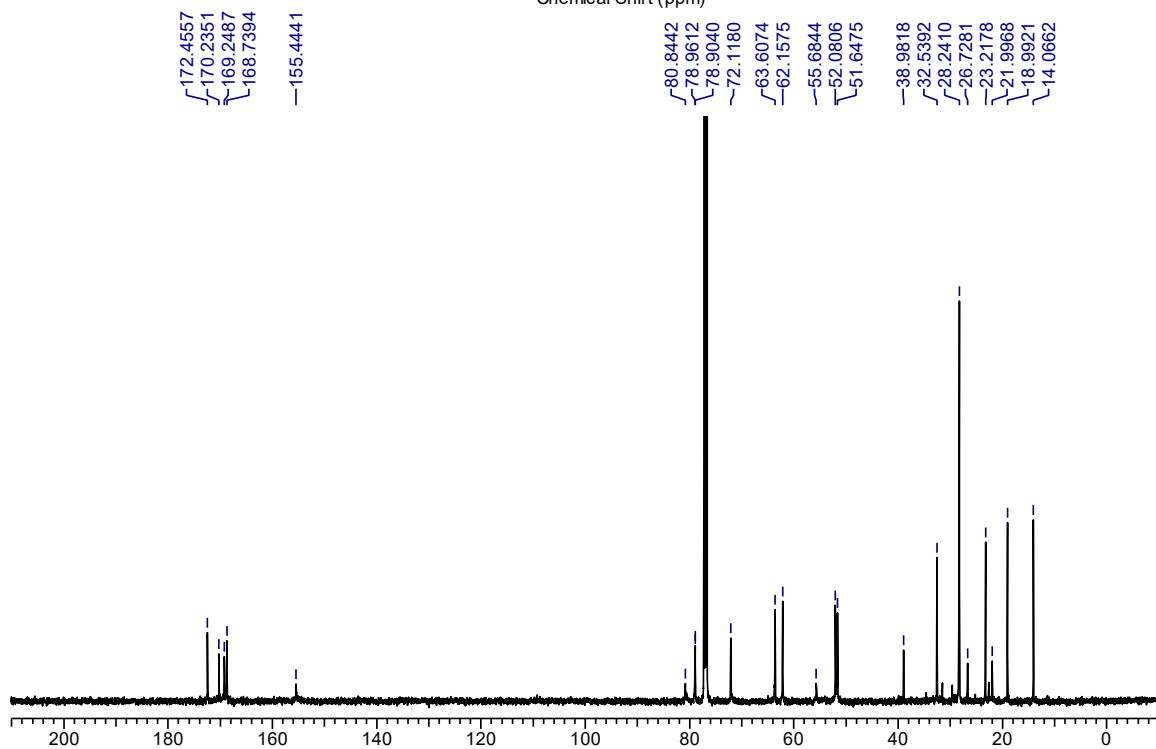
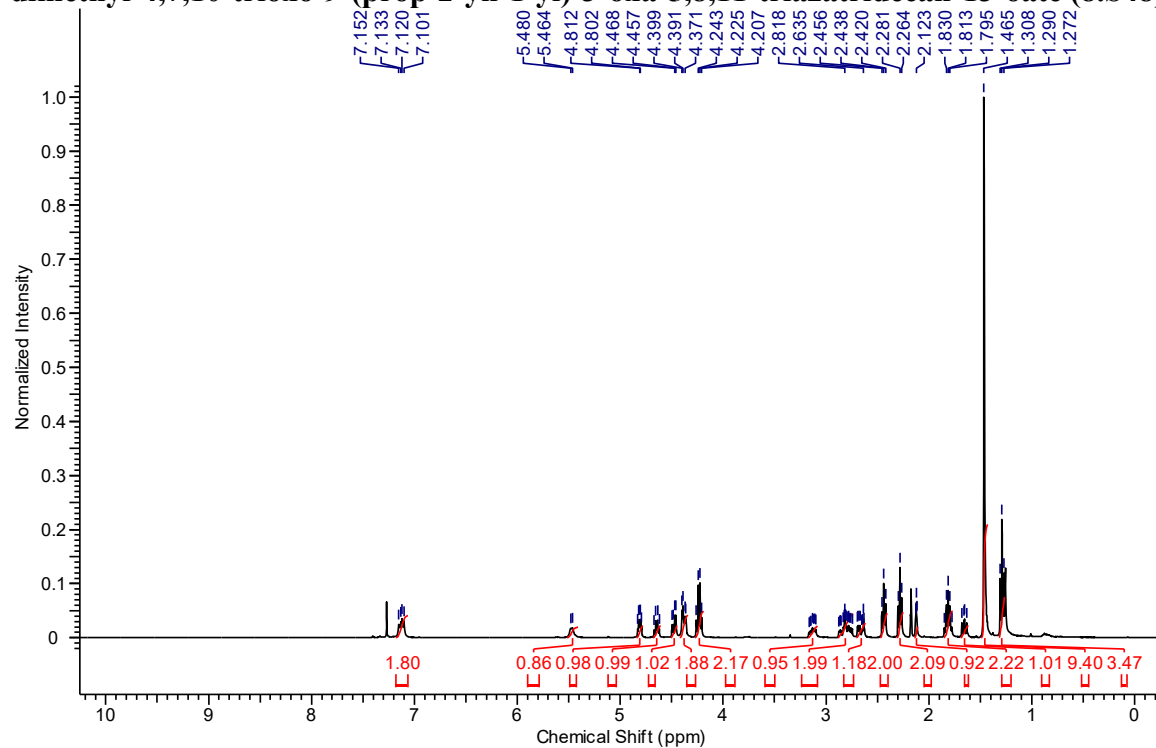
**(S)-2-((S)-2-aminopent-4-ynamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S46):**



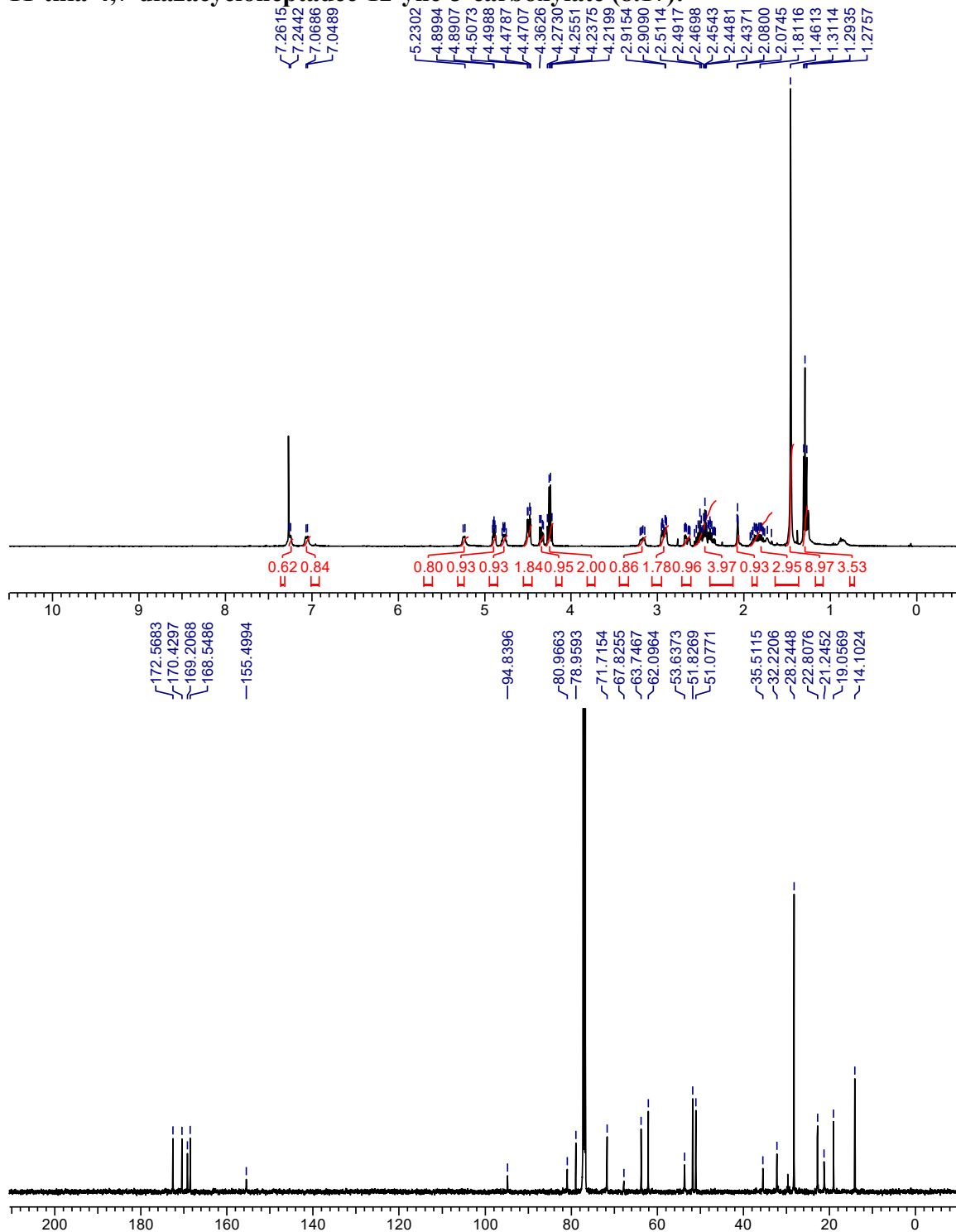
**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-2,2-dimethyl-4,7,10-trioxo-9-(prop-2-yn-1-yl)-6-((tritylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S47):**



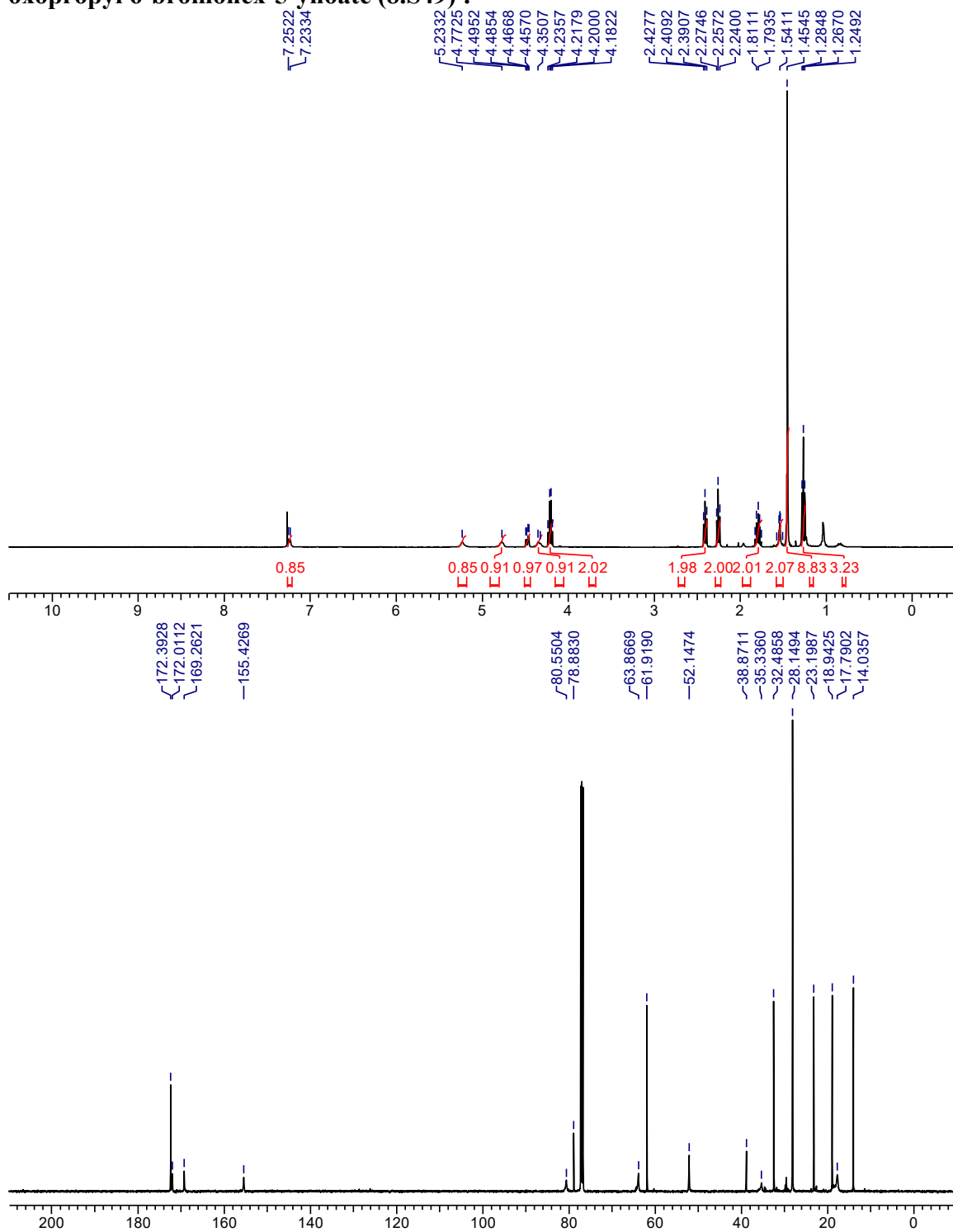
**Ethyl (6*R*,9*S*,12*S*)-12-(((6-bromohex-5-ynoyl)oxy)methyl)-6-(mercaptomethyl)-2,2-dimethyl-4,7,10-trioxo-9-(prop-2-yn-1-yl)-3-oxa-5,8,11-triazatridecan-13-oate (8.S48):**



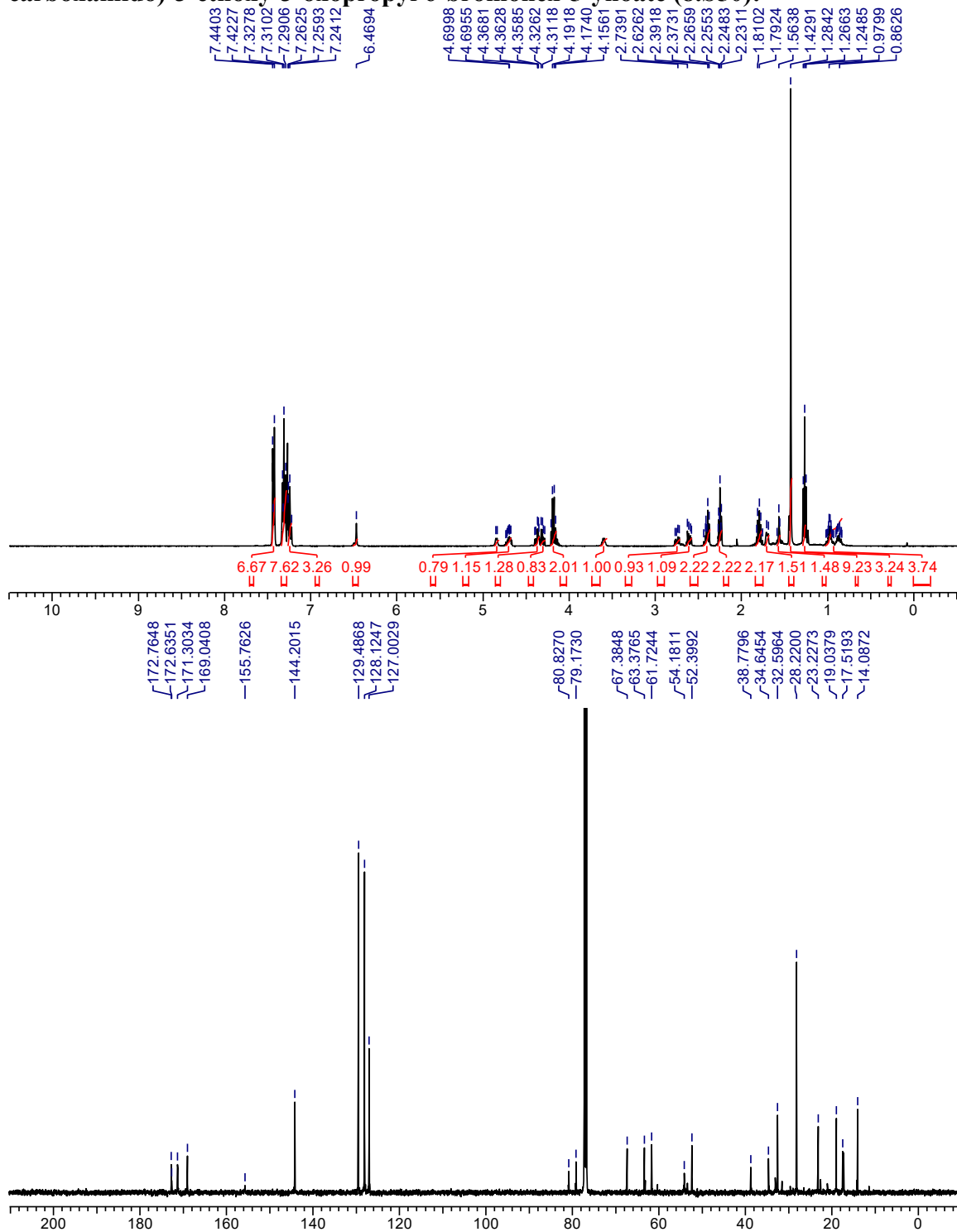
**Ethyl (3*S*,6*S*,9*R*)-9-((*tert*-butoxycarbonyl)amino)-5,8,17-trioxo-6-(prop-2-yn-1-yl)-1-oxa-11-thia-4,7-diazacycloheptadec-12-yne-3-carboxylate (8.17):**



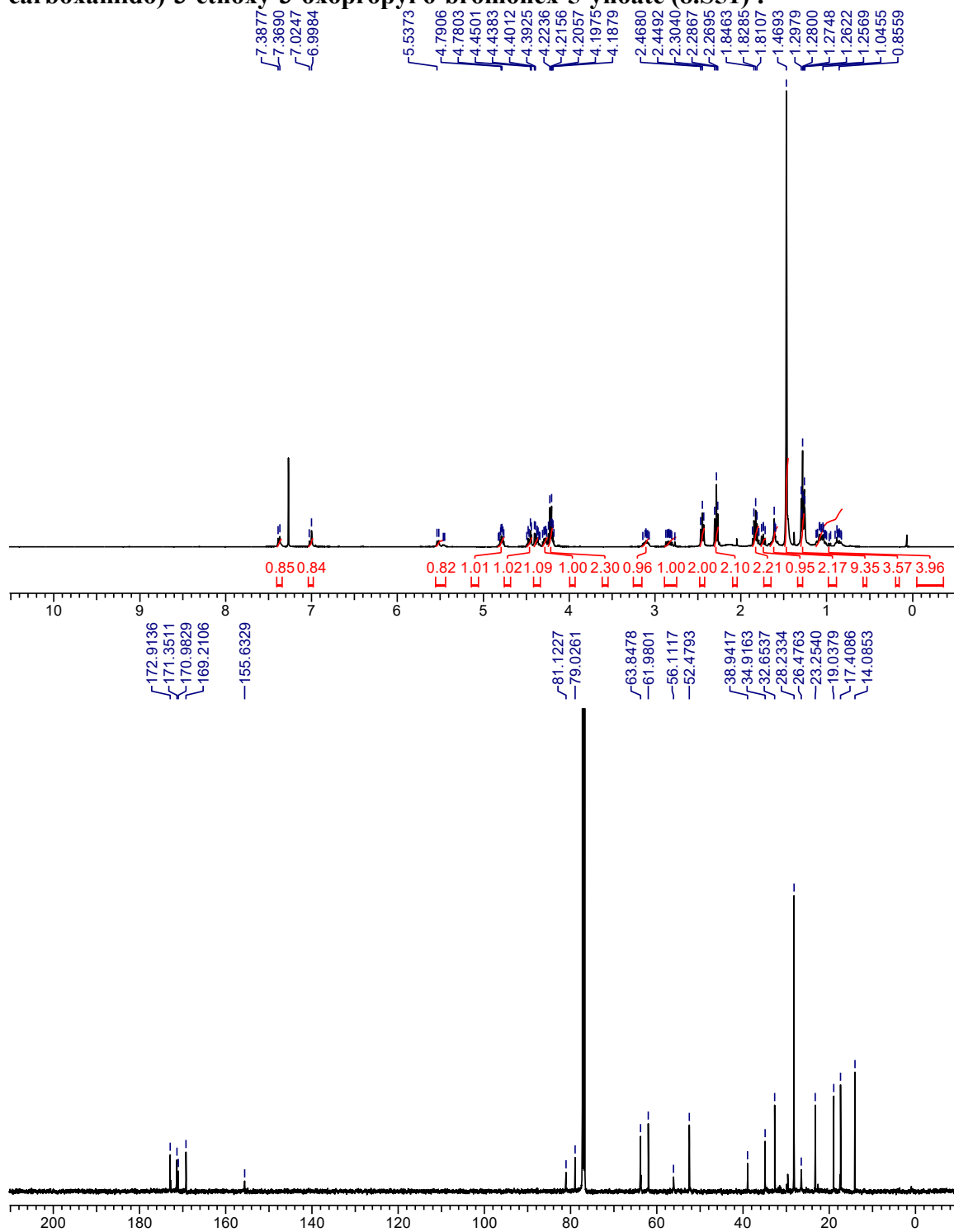
**(S)-2-(1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S49) :**



**(S)-2-(1-((R)-2-((tert-butoxycarbonyl)amino)-3-(tritylthio)propanamido)cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S50):**

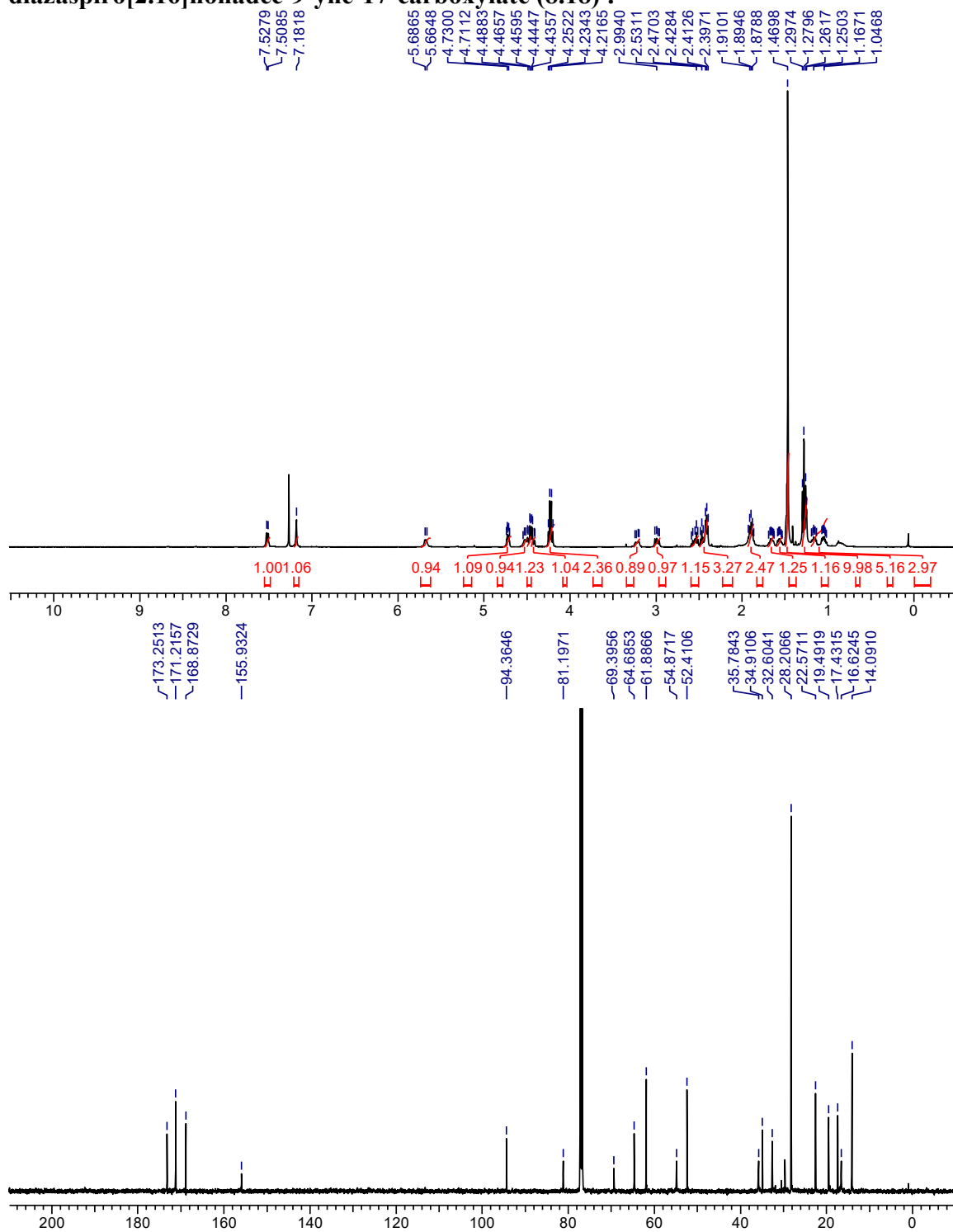


**(S)-2-(1-((R)-2-((tert-butoxycarbonyl)amino)-3-mercaptopropanamido)cyclopropane-1-carboxamido)-3-ethoxy-3-oxopropyl 6-bromohex-5-ynoate (8.S51) :**

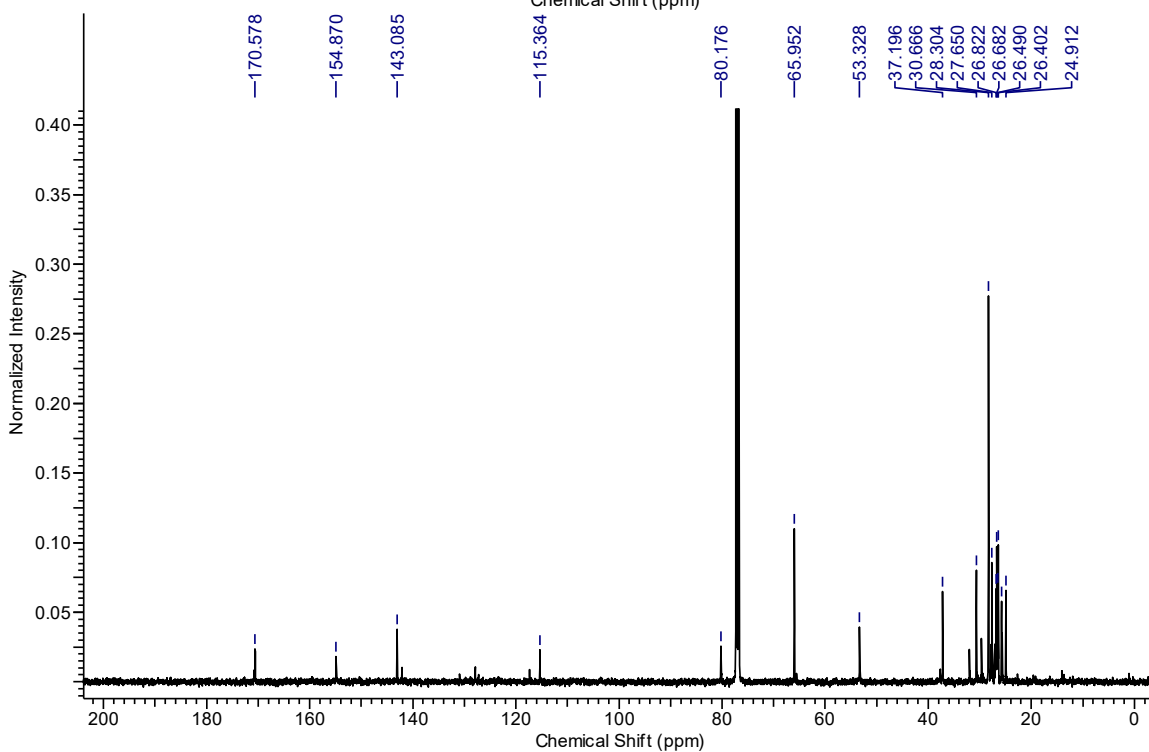
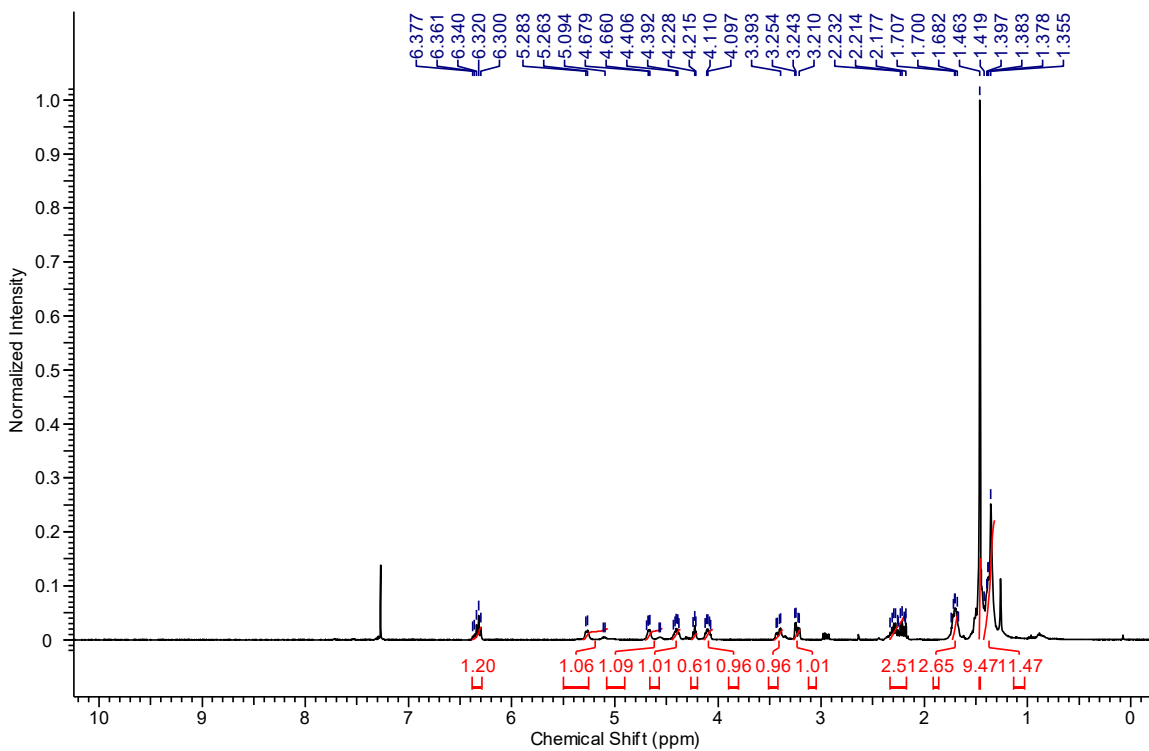




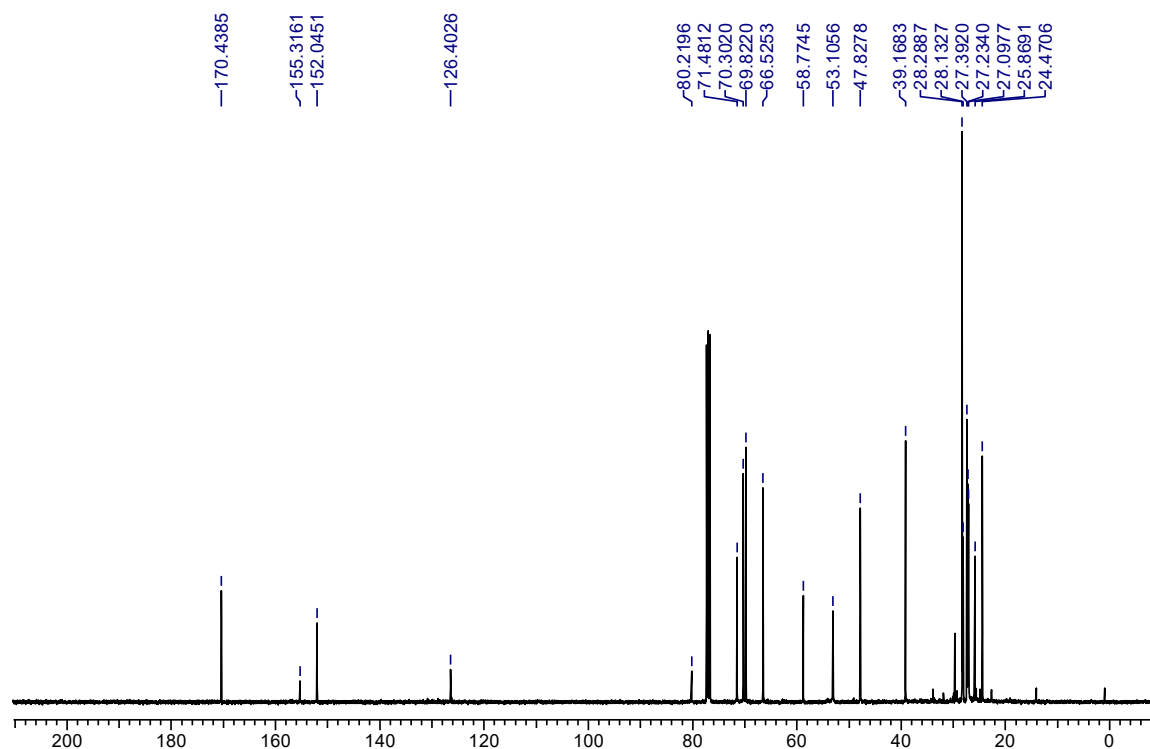
**Ethyl (6R,17S)-6-((*tert*-butoxycarbonyl)amino)-5,14,19-trioxo-15-oxa-8-thia-4,18-diazaspiro[2.16]nonadec-9-yne-17-carboxylate (8.18) :**



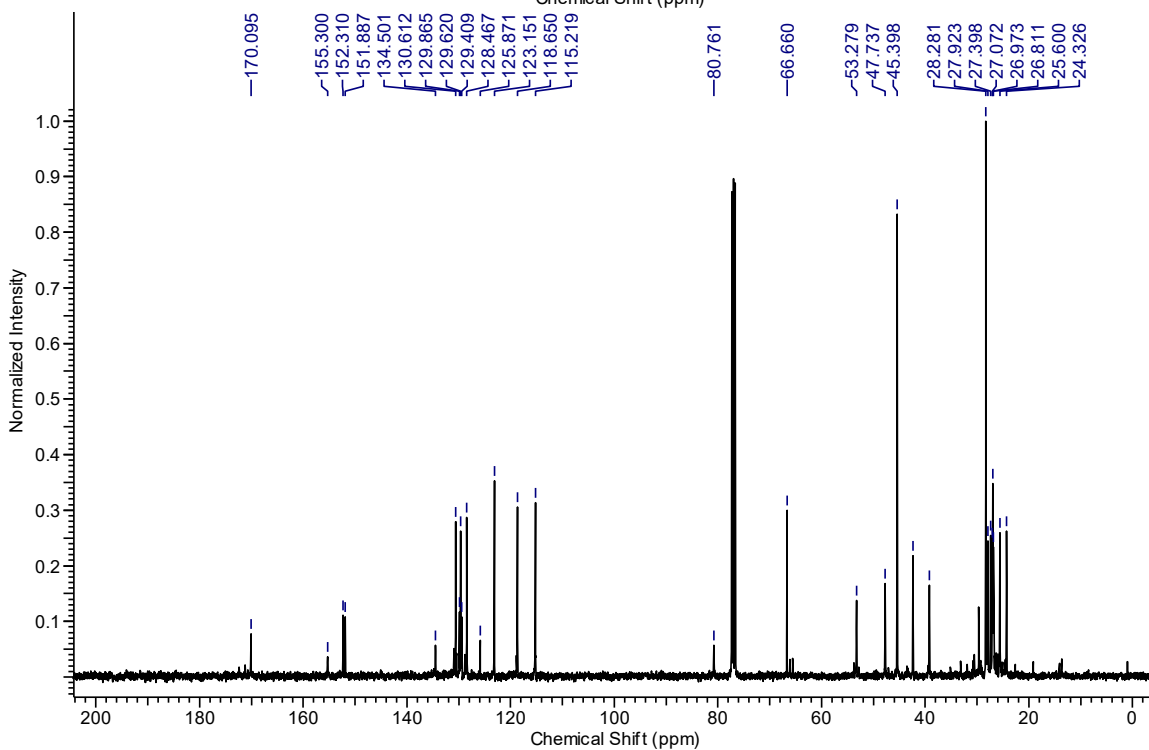
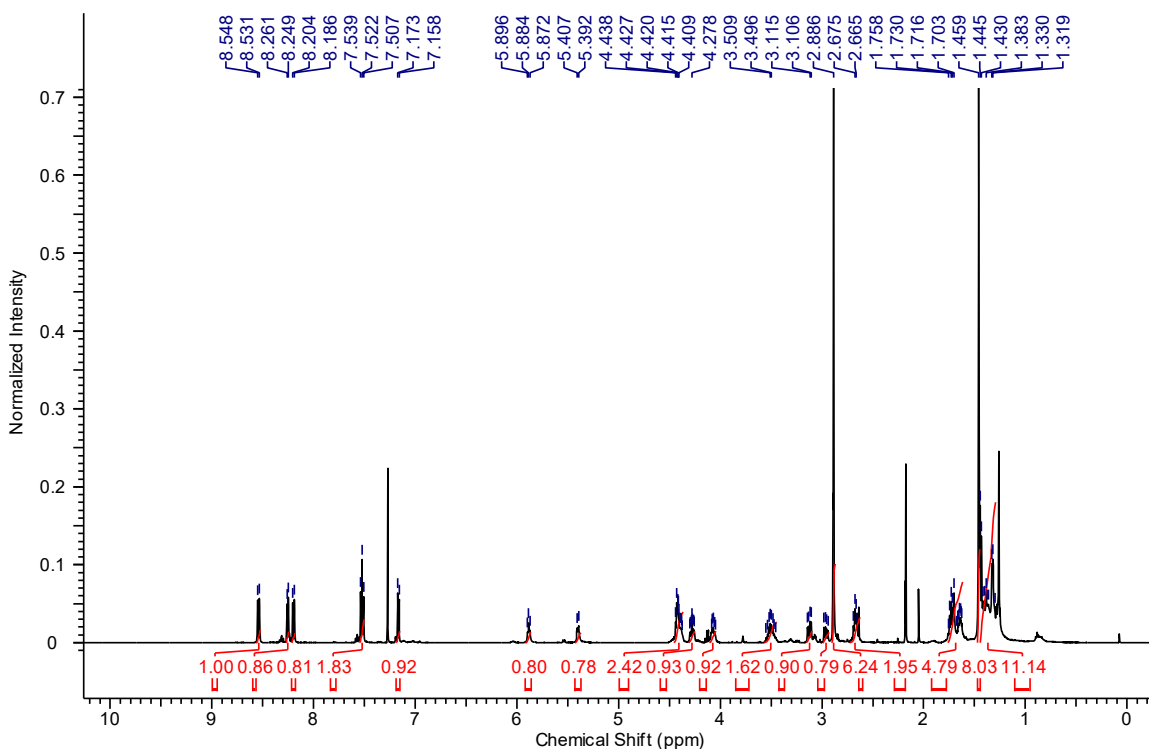
***tert*-Butyl (*R*)-(6-bromo-2-oxo-1-oxa-5-thiacyclohexadec-6-en-3-yl)carbamate (8.20):**



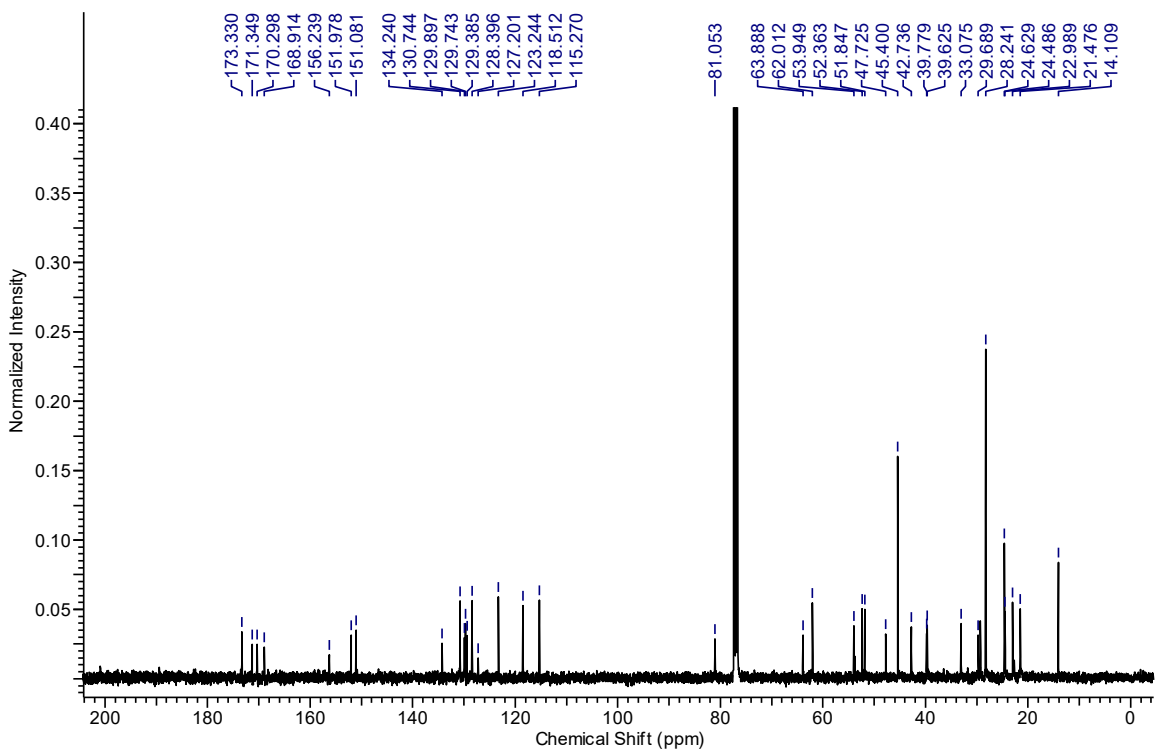
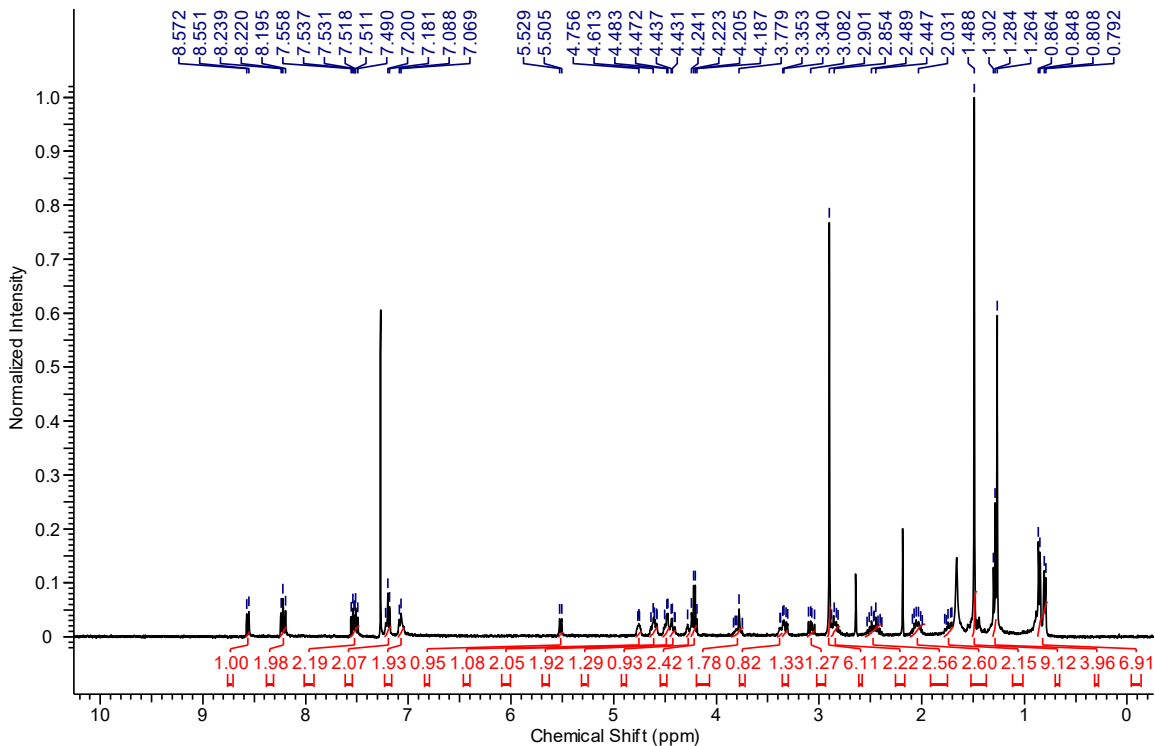
***tert*-Butyl (*R*)-(3-(2-(2-methoxyethoxy)ethyl)-7-oxo-3,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-d][[1,2,3]triazol-6-yl)carbamate (8.21):**



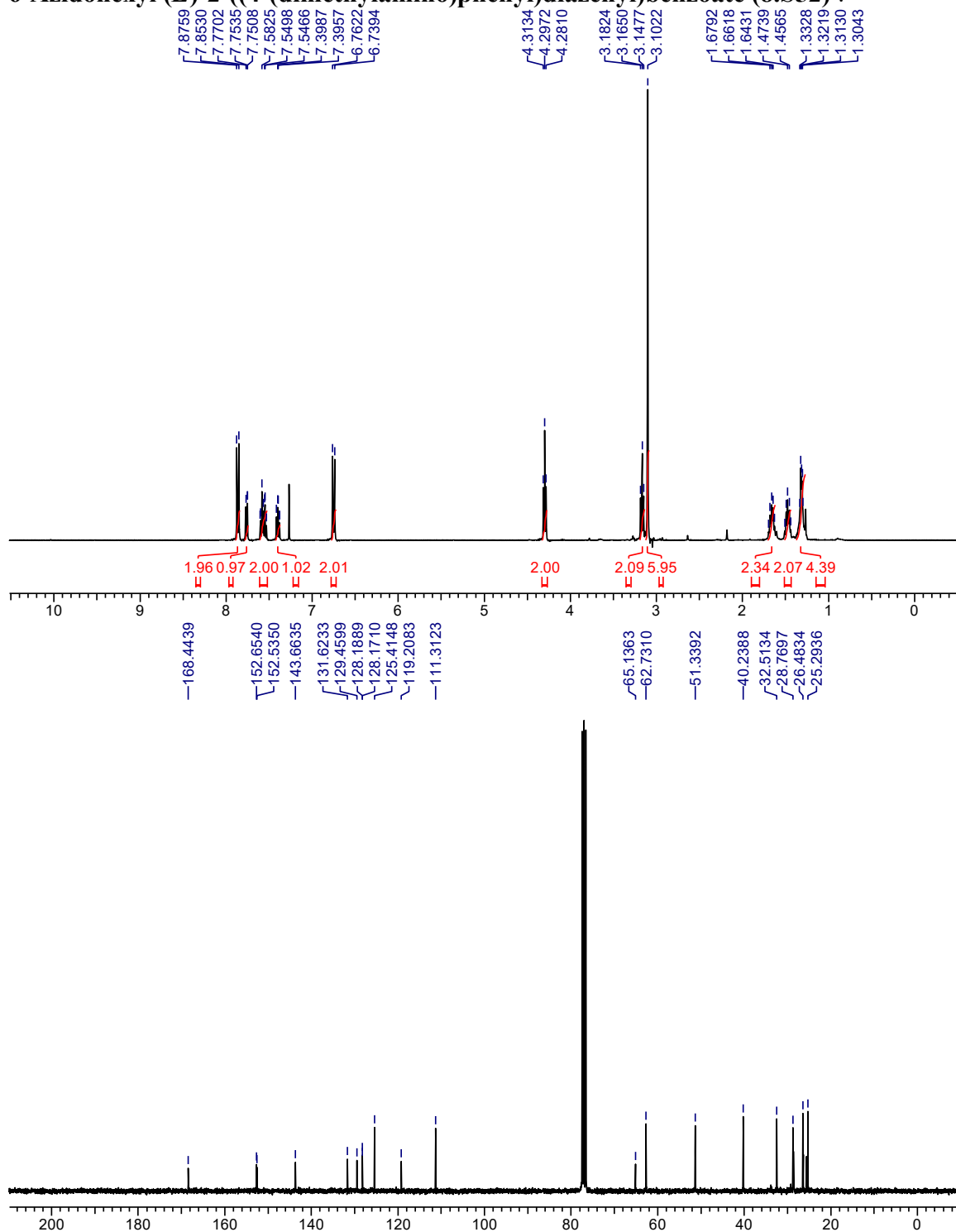
***tert*-Butyl (*R*)-(3-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethyl)-7-oxo-3,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-d][1,2,3]triazol-6-yl)carbamate (8.22):**



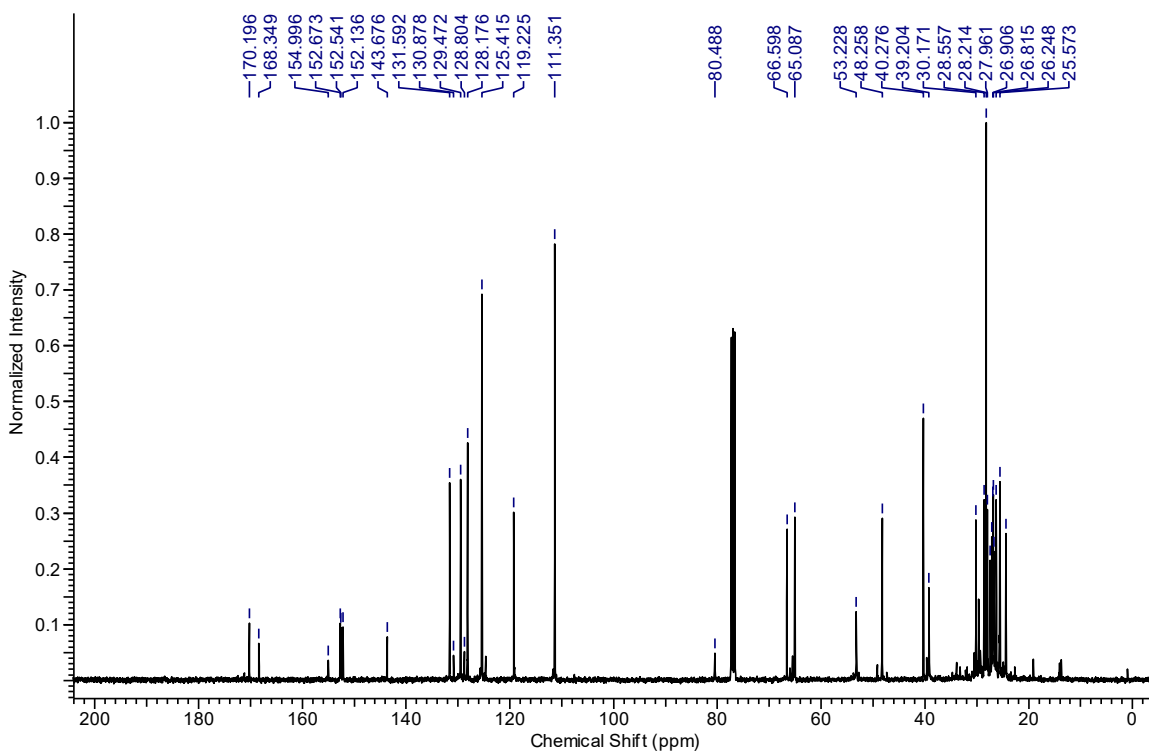
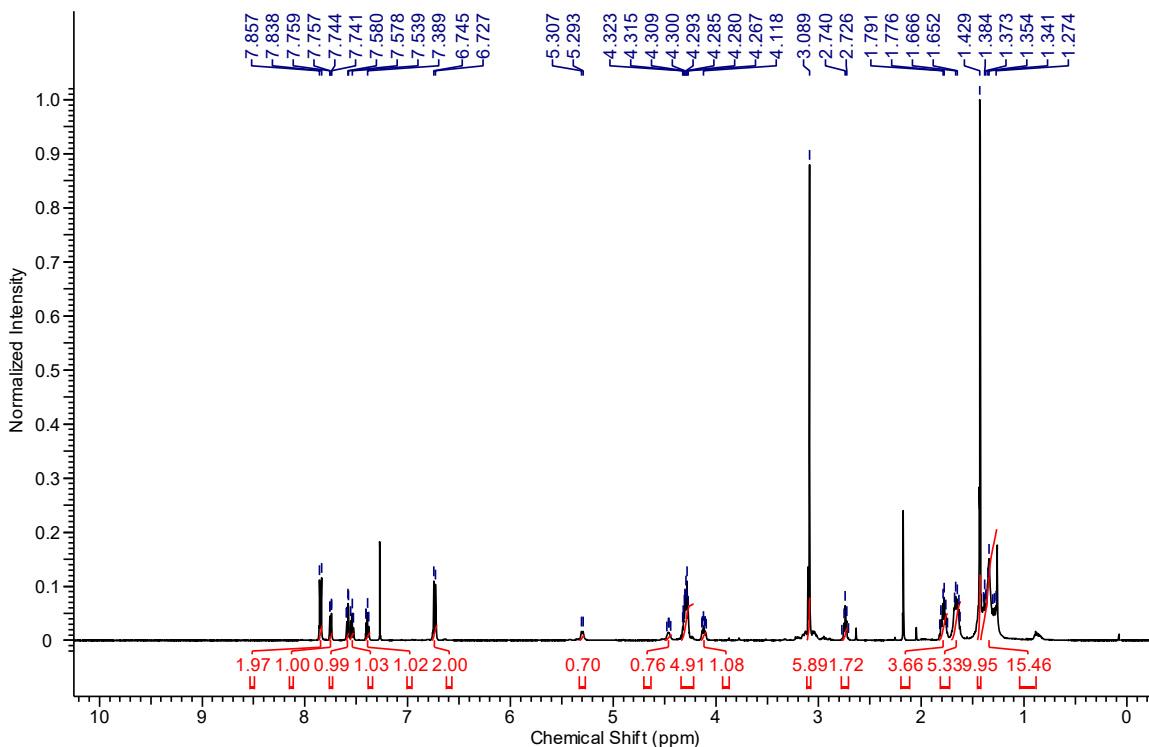
**Ethyl (6*R*,9*S*,12*S*)-6-((*tert*-butoxycarbonyl)amino)-3-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethyl)-9-isobutyl-7,10,15-trioxo-6,7,8,9,10,11,12,13,15,16,17,18-dodecahydro-3*H*,5*H*-[1,2,3]triazolo[4,5-*l*][1]oxa[11]thia[4,7]diazacycloheptadecine-12-carboxylate (8.23):**



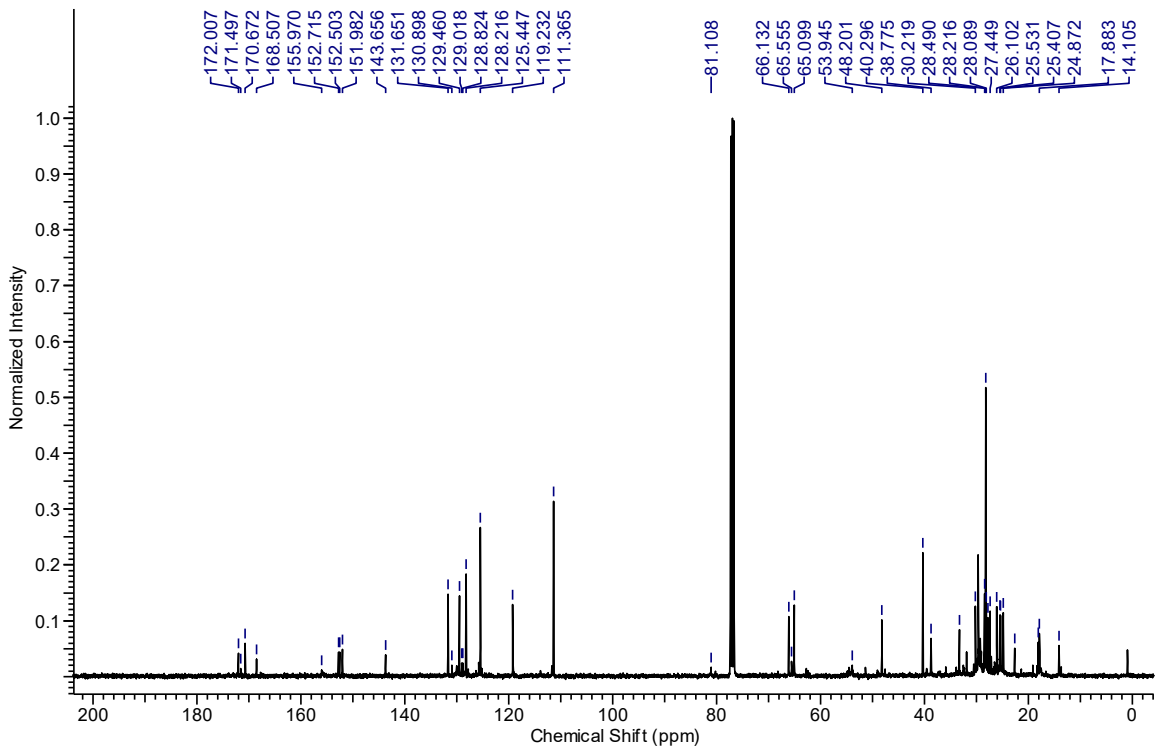
**6-Azidohexyl (*E*)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.S52) :**



**(R)-6-(6-((*tert*-Butoxycarbonyl)amino)-7-oxo-6,7,10,11,12,13,14,15,16,17-decahydro-5H-[1]oxa[5]thiacyclohexadecino[6,7-*d*][1,2,3]triazol-3(9H)-yl)hexyl (E)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.24):**



**(R)-6-(6'-((*tert*-Butoxycarbonyl)amino)-7',10'-dioxo-5',6',7',8',13',14',15',16',17',18'-decahydro-10'H-spiro[cyclopropane-1,9'-[1,2,3]triazolo[4,5-i][1]oxa[8]thia[4]azacycloheptadecin]-3'(12'H)-yl)hexyl (E)-2-((4-(dimethylamino)phenyl)diazenyl)benzoate (8.25):**





# Annexe 4. Procédures expérimentales et spectres RMN du

## Chapitre 9

### GENERAL:

Reactions carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or flame dried and cooled under a stream of argon or nitrogen.<sup>30</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company or Alfa Aesar, and were reagent quality. The following products were prepared according to their respective literature procedures: 1-ethynyl-2-nitrobenzene,<sup>31</sup> *tert*-butyl 4-ethynylisoindoline-2-carboxylate,<sup>32</sup> 1-(bromoethynyl)-4-methoxybenzene,<sup>33</sup> methyl 5-(bromoethynyl)-2-methoxybenzoate,<sup>4</sup> 1-bromo-4-(bromoethynyl)benzene,<sup>4</sup> 5-(bromoethynyl)-2-methoxypyridine,<sup>4</sup> (*S*)-1-phenylethyl mercaptan,<sup>4</sup> 4-ethynylbenzaldehyde,<sup>34</sup> prop-2-yn-1-yl 4-methoxybenzoate,<sup>35</sup> (bromoethynyl)triisopropylsilane,<sup>36</sup> hex-5-yn-1-yl acetate,<sup>37</sup> ((hex-5-yn-1-yloxy)methyl)benzene,<sup>38</sup> hex-5-yn-1-yl 4-methylbenzenesulfonate,<sup>39</sup> hept-6-yne nitrile,<sup>40</sup> 6-azidohex-1-yne<sup>41</sup>, 6-bromohex-5-yn-1-ol<sup>42</sup>, , 11-bromo-10-undecyn-1-ol<sup>43</sup>, *N*-Boc-*S*-trityl-*L*-cysteine<sup>44</sup>, *S*-Trityl-*L*-cysteine methyl ester hydrochloride<sup>45</sup>, (2-ethynylphenyl)methanol<sup>46</sup>,

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<sup>30</sup> Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

<sup>31</sup> Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fetting, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062-2065.

<sup>32</sup> Godin, É.; Bédard, A.-C.; Raymond, M.; Collins, S. K. *J. Org. Chem.* **2017**, *82*, 7576-7582.

<sup>33</sup> Santandrea, J.; Minozzi, C.; Cruché, C.; Collins, S. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 12255-12259.

<sup>34</sup> Li, Z.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 634-643.

<sup>35</sup> Wu, X.-F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, 1144-1147.

<sup>36</sup> Muriel, B.; Orcel, U.; Waser, J. *Org. Lett.* **2017**, *19*, 3548-3551.

<sup>37</sup> Jameson, V. J. A.; Cochmé, H. M.; Logan, A.; Hanton, L. R.; Smith, R. A. J.; Murphy, M. P. *Tetrahedron* **2015**, *71* 8444-8453.

<sup>38</sup> Thiel, N. O.; Kemper, S.; Teichert, J. F. *Tetrahedron* **2017**, *73*, 5023-5028.

<sup>39</sup> Qian, Y.; Schürmann, M.; Janning, P.; Hedberg, C.; Waldmann, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 7766-7771.

<sup>40</sup> Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Rainthby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *Eur. J. Org. Chem.* **2015**, 2498-2502.

<sup>41</sup> Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219-1226.

<sup>42</sup> Maleczka, R. E.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958-5965.

<sup>43</sup> Yamagishi, M.; Nishigai, K.; Ishii, A.; Hata, T.; Urabe, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 6471-6474.

<sup>44</sup> Silvia, V.; Baldisserotto, A.; Scalambra, E.; Malisardi, G.; Durini, E.; Manfredini, S. *Eur. J. Med. Chem.* **2012**, *50*, 383-392.

<sup>45</sup> Mays, J. R.; Restituyo, J. A.; Katzenberger, R. J.; Wassarman, D. A.; Rajski, S. R. *Tetrahedron Lett.* **2007**, *48*, 4579-4583.

<sup>46</sup> Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877-8888.

methyl *N*-glycyl-*S*-trityl-*L*-cysteinate<sup>47</sup>, *tert*-butyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate<sup>48</sup>, 3-(2-(2-methoxyethoxy)ethoxy)prop-1-yne<sup>49</sup>, *tert*-butyl (4-(trifluoromethyl)phenyl)carbamate<sup>50</sup>, diethyl (bromoethynyl)phosphate<sup>51</sup>. Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>52</sup> on silica gel obtained from Silicycle Chemical division (40–63 nm; 230–240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plates was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR spectroscopy. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300, AV-400 and AV-500 instruments unless otherwise noted. Signals of solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectrometry (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal on an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

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<sup>47</sup> Liu, X.; Suh, D.-Y.; Call, J.; Prestwich, G. D. *Bioconjugate Chem.* **2004**, *15*, 270-277.

<sup>48</sup> Mansfield, S. J.; Campbell, C. D.; Jones, M. W.; Anderson, E. A. *Chem. Commun.* **2015**, *51*, 3316-3319.

<sup>49</sup> Scates, B. A.; Lashbrook, B. L.; Chastain, B. C.; Tominaga, K.; Elliott, B. T.; Theising, N. J.; Baker, T. A.; Fitch, R. W. *Bioorg. Med. Chem.* **2008**, *16*, 10295-10300.

<sup>50</sup> Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Bédard, P. W.; Tam, S.; Di, L.; Clerin, V.; Sushkova, N.; Tchernychev, B.; Tsao, D. H. H.; Keith, J. C.; Shaw, G. D.; Schaub, R. G.; Wang, Q.; Kaila, N. *J. Med. Chem.* **2010**, *53*, 6003–6017.

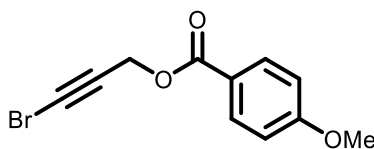
<sup>51</sup> Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem. Eur. J.* **2014**, *20*, 11101–11110.

<sup>52</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494-1514.

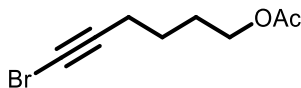
## SYNTHESIS OF PRECURSORS FOR INTERMOLECULAR COUPLINGS

**Procedure for Alkyne Bromination (A):** To a stirred solution of the aryl alkyne (1 equiv.) in acetone (0.2 M), *N*-bromosuccinimide (NBS, 1.2 equiv.) and AgNO<sub>3</sub> (20 mol%) were added at room temperature. The reaction mixture was stirred at room temperature for 15-60 minutes. Upon complete conversion of the starting material, the crude reaction mixture was filtered on a Celite<sup>®</sup> pad and the filtrate was concentrated under vacuum and was purified by column chromatography on silica-gel to afford the desired product.

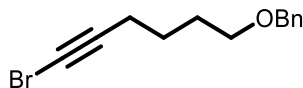
**Procedure for Steglich Esterification (B):** To a stirred solution of the alcohol (1 equiv.) and the carboxylic acid (1.1 equiv.) in dry dichloromethane (0.1 M), *N,N'*-dicyclohexylcarbodiimide (DCC, 1.1 equiv.) and 4-methylaminopyridine (DMAP, 1.1 equiv.) were added at room temperature. The reaction mixture was stirred at room temperature for 18 hours. Upon complete conversion of the starting material, the crude reaction mixture was placed in a freezer for 5 hours to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated under vacuum to provide the organic residue which was purified by column chromatography on silica-gel to afford the desired product.



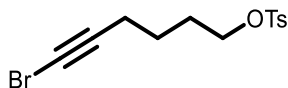
**3-Bromoprop-2-yn-1-yl 4-methoxybenzoate (9.S1):** Following Procedure A, prop-2-yn-1-yl 4-methoxybenzoate (1.78 g, 9.36 mmol, 1.0 equiv.), NBS (2.00 g, 11.2 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.318 g, 1.87 mmol, 20 mol%) were dissolved in acetone (47 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 5 % diethyl ether in hexanes), the desired product was obtained as a white solid (2.10 g, 83 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.03 (d, *J* = 9.0, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.92 (s, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 165.4, 163.7, 131.9, 121.7, 113.7, 74.4, 55.4, 53.0, 47.0; HRMS (ESI) *m/z* calculated for C<sub>11</sub>H<sub>10</sub>BrO<sub>3</sub> [M+H]<sup>+</sup> 268.9808; found 268.9806.



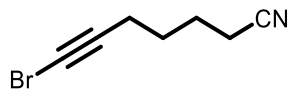
**6-Bromohex-5-yn-1-yl acetate (9.S2):** Following Procedure A, hex-5-yn-1-yl acetate (0.701 g, 5.00 mmol, 1.0 equiv.), NBS (1.07 g, 6.00 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.170 g, 1.00 mmol, 20 mol%) were dissolved in acetone (25 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 10 % diethyl ether in hexanes), the desired product was obtained as a colorless liquid (0.728 g, 66 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.08 (t, *J* = 6.4 Hz, 2H), 2.26 (t, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.78-1.71 (m, 2H), 1.63-1.56 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 171.1, 79.6, 63.8, 38.3, 27.7, 24.7, 20.9, 19.3; HRMS (APCI) *m/z* calculated for C<sub>8</sub>H<sub>12</sub>BrO<sub>2</sub> [M+H]<sup>+</sup> 219.0015; found 219.0013.



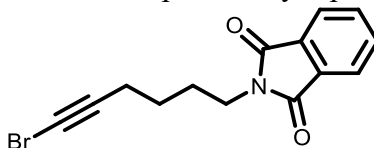
**(((6-Bromohex-5-yn-1-yl)oxy)methyl)benzene (9.S3):** Following Procedure A, ((hex-5-yn-1-yloxy)methyl)benzene (0.941 g, 5.00 mmol, 1.0 equiv.), NBS (1.07 g, 6.00 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.170 g, 1.00 mmol, 20 mol%) were dissolved in acetone (12 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 10 % diethyl ether in hexanes), the desired product was obtained as a colorless liquid (1.26 g, 94 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.38-7.28 (m, 5H), 4.51 (s, 2H), 3.50 (t, *J* = 6.2 Hz, 2H), 2.25 (t, *J* = 7.0 Hz, 2H), 1.77-1.70 (m, 2H), 1.67-1.60 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 138.5, 128.3, 127.6, 127.5, 80.1, 72.9, 69.7, 37.9, 28.8, 25.0, 19.5; HRMS (ESI) *m/z* calculated for C<sub>13</sub>H<sub>16</sub>BrO [M+H]<sup>+</sup> 267.0379; found 267.0387.



**6-Bromohex-5-yn-1-yl 4-methylbenzenesulfonate (9.S4):** Following Procedure A, hex-5-yn-1-yl 4-methylbenzenesulfonate (1.26 mL, 5.00 mmol, 1.0 equiv.), NBS (1.07 g, 6.00 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.170 g, 1.00 mmol, 20 mol%) were dissolved in acetone (12 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 20 % diethyl ether in hexanes), the desired product was obtained as a white solid (1.56 g, 94 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 2.46 (s, 3H), 2.19 (t, *J* = 6.7 Hz, 2H), 1.79-1.73 (m, 2H), 1.59-1.52 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 144.7, 132.9, 129.8, 127.7, 79.1, 69.8, 38.5, 27.7, 24.0, 21.5, 18.9; HRMS (ESI) *m/z* calculated for C<sub>13</sub>H<sub>15</sub>BrO<sub>3</sub>SNa [M+Na]<sup>+</sup> 352.9818; found 352.9821.



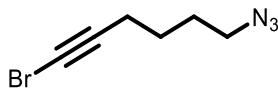
**7-Bromohept-6-ynenitrile (9.S5):** Following Procedure A, hept-6-ynenitrile (0.165 g, 1.54 mmol, 1.0 equiv.), NBS (0.329 g, 1.85 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.052 g, 0.308 mmol, 20 mol%) were dissolved in acetone (8 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 15 % diethyl ether in hexanes), the desired product was obtained as a white solid (0.238 g, 83 % yield). NMR data was in accordance with what was previously reported.<sup>53</sup>



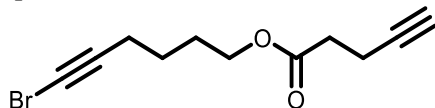
**2-(6-Bromohex-5-yn-1-yl)isoindoline-1,3-dione (9.S6):** Following Procedure A, *N*-(5-hexynyl)phthalimide (1.14 g, 5.00 mmol, 1.0 equiv.), NBS (1.07 g, 6.00 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.170 g, 1.00 mmol, 20 mol%) were dissolved in acetone (25 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 20 % diethyl ether in hexanes), the desired product was obtained as a white

<sup>53</sup> Wang, Y.; Chen, C.; Zhang, S.; Lou, Z.; Su, X.; Wen, L.; Li, M. *Org. Lett.* **2013**, *15*, 4794-4797.

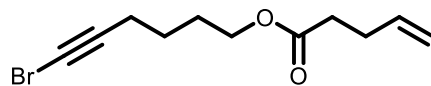
solid (1.42 g, 93 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 3.72 (t,  $J$  = 7.0 Hz, 2H), 2.28 (t,  $J$  = 7.0 Hz, 2H), 1.84-1.76 (m, 2H), 1.61-1.54 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 168.3, 133.9, 132.0, 123.2, 79.5, 38.3, 37.3, 27.6, 25.4, 19.2; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{13}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  306.0124; found 306.0126.



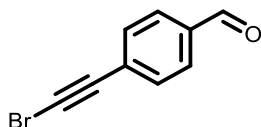
**6-Azido-1-bromohex-1-yne (9.S7):** Following Procedure A, 6-azidohex-1-yne (0.100 g, 0.812 mmol, 1.0 equiv.), NBS (0.173 g, 0.974 mmol, 1.2 equiv.) and  $\text{AgNO}_3$  (0.028 g, 0.162 mmol, 20 mol%) were dissolved in acetone (4 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes), the desired product was obtained as a colorless oil (0.118 g, 72 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.32 (t,  $J$  = 6.6 Hz, 2H), 2.27 (t,  $J$  = 6.9 Hz, 2H), 1.76-1.69 (m, 2H), 1.65-1.58 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 79.4, 50.9, 38.5, 27.9, 25.3, 19.2; HRMS (ESI)  $m/z$  calculated for  $\text{C}_6\text{H}_9\text{BrN}_3$   $[\text{M}+\text{H}]^+$  201.9974; found 201.9972.



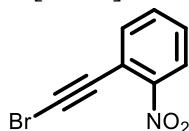
**6-Bromohex-5-yn-1-yl pent-4-ynoate (9.S8):** Following Procedure B, 6-bromohex-5-yn-1-ol (0.310 g, 1.75 mmol, 1.0 equiv.), pent-4-ynoic acid (0.189 g, 1.93 mmol, 1.1 equiv.), DCC (0.398 g, 1.93 mmol, 1.1 equiv.) and DMAP (0.236 g, 1.93 mmol, 1.1 equiv.) were dissolved in anhydrous dichloromethane (18 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  5 % diethyl ether in hexanes), the desired product was obtained as a colorless oil (0.407 g, 90 % yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.14 (t,  $J$  = 6.3 Hz, 2H), 2.60-2.48 (m, 4H), 2.26 (t,  $J$  = 7.0 Hz, 2H), 1.98 (t,  $J$  = 2.6 Hz, 1H), 1.81-1.71 (m, 2H), 1.65-1.55 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.7, 82.4, 79.6, 69.0, 64.1, 38.3, 33.3, 27.7, 24.7, 19.3, 14.4; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{11}\text{H}_{14}\text{BrO}_2$   $[\text{M}+\text{H}]^+$  257.0172; found 257.0182.



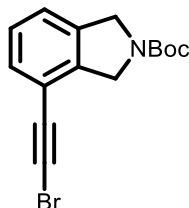
**6-Bromohex-5-yn-1-yl pent-4-enoate (9.S9):** Following Procedure B, 6-bromohex-5-yn-1-ol (0.245 g, 1.38 mmol, 1.0 equiv.), pent-4-enoic acid (0.16 mL, 1.52 mmol, 1.1 equiv.), DCC (0.314 g, 1.52 mmol, 1.1 equiv.) and DMAP (0.186 g, 1.52 mmol, 1.1 equiv.) were dissolved in anhydrous dichloromethane (14 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  5 % diethyl ether in hexanes), the desired product was obtained as a colorless oil (0.327 g, 91 % yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.90-5.77 (m, 1H), 5.10-4.99 (m, 2H), 4.10 (t,  $J$  = 6.3 Hz, 2H), 2.45-2.34 (m, 4H), 2.26 (t,  $J$  = 7.0 Hz, 2H), 1.79-1.70 (m, 2H), 1.64-1.54 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.0, 136.7, 115.5, 79.6, 63.8, 38.3, 33.5, 28.9, 27.7, 24.8, 19.3; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{11}\text{H}_{16}\text{BrO}_2$   $[\text{M}+\text{H}]^+$  259.0328; found 259.0337.



**4-(Bromoethynyl)benzaldehyde (9.S10):** Following Procedure A, 4-ethynylbenzaldehyde (0.564 g, 4.33 mmol, 1.0 equiv.), NBS (0.925 g, 5.20 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.147 g, 0.866 mmol, 20 mol%) were dissolved in acetone (22 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 5 % diethyl ether in hexanes), the desired product was obtained as a white solid (0.890 g, 98 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 10.02 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 191.3, 135.8, 132.6, 129.5, 128.9, 79.3, 54.7; HRMS (ESI) *m/z* calculated for C<sub>9</sub>H<sub>6</sub>BrO [M+H]<sup>+</sup> 208.9597; found 208.9587.



**1-(Bromoethynyl)-2-nitrobenzene (9.S11):** Following Procedure A, 1-ethynyl-2-nitrobenzene (0.50 g, 3.40 mmol, 1.0 equiv.), NBS (0.726 g, 4.08 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.116 g, 0.68 mmol, 20 mol%) were dissolved in acetone (17 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 2.5 % diethyl ether in hexanes), the desired product was obtained as a yellow solid (0.548 g, 71 % yield). NMR data was in accordance with what was previously reported.<sup>54</sup>

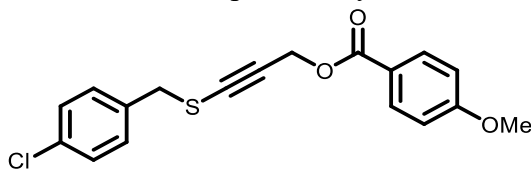


**tert-Butyl 4-(bromoethynyl)isoindoline-2-carboxylate (9.S12):** Following Procedure A, *tert*-butyl 4-ethynylisoindoline-2-carboxylate (0.243 g, 1.00 mmol, 1.0 equiv.), NBS (0.214 g, 1.20 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.034 g, 0.200 mmol, 20 mol%) were dissolved in acetone (10 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes → 10 % diethyl ether in hexanes), the desired product was obtained as a white solid (46 mg, 88 % yield). *Note that rotamers are formed and can result in complex splitting patterns in the <sup>1</sup>H NMR, or can cause doubling/broadening of some peaks in the <sup>13</sup>C NMR spectrum. For clarity, all peaks are reported.* <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33-7.31 (m, 1H), 7.23-7.21 (m, 2H), 4.74-4.67 (m, 4H), 1.54-1.52 (m, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 154.4, 154.3, 140.31, 140.27, 137.5, 137.2, 130.8, 130.4, 127.5, 123.1, 122.8, 117.8, 117.5, 79.9, 79.8, 54.0, 53.7, 52.6, 52.4, 52.0, 28.52, 28.47; HRMS (ESI) *m/z* calculated for C<sub>10</sub>H<sub>8</sub>BrN [M-Boc+H]<sup>+</sup> 223.9893; found 223.9884.

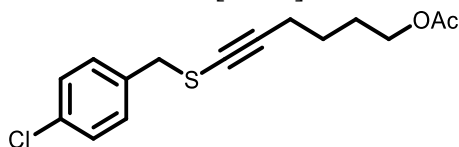
<sup>54</sup> Moodapelly, S. K.; Sharma, G. V. M.; Doddi, V. R. *Adv. Synth. Catal.* **2017**, *359*, 1535-1540.

## SYNTHESIS OF ALKYNYL SULFIDES

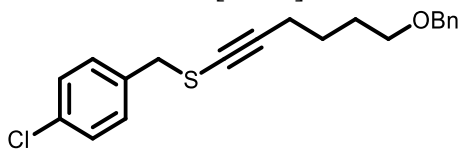
**Representative Procedure for the Cu-Catalyzed C(sp)-S Coupling (C):** A 118.5 mM solution of  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  (0.088 g, 0.237 mmol) in acetonitrile (2 mL) was prepared under nitrogen. The solution was then sonicated under nitrogen until complete homogeneity was obtained. The bromoalkyne (0.237 mmol, 1.0 equiv.), the thiol (0.261 mmol, 1.1 equiv.), dtbbpy (0.013 g, 0.0474 mmol, 20 mol%) and 2,6-lutidine (0.055 mL, 0.474 mmol, 2.0 equiv.) were added to an 8 mL screw cap vial equipped with a stir bar. A septum was used to seal the vial and it was secured with parafilm. The vial was then purged with nitrogen for 2 minutes under vacuum. Afterwards, degassed acetonitrile (4.6 mL) was added to the vial under nitrogen. Once the vial was positioned onto a stir plate, the  $\text{Cu}(\text{MeCN})_4\text{PF}_6$  solution (0.2 mL, 0.0237 mol, 10 mol%) was added to the vial in one portion. The reaction mixture was stirred for 10 minutes. Upon completion of the reaction (TLC), it was concentrated under vacuum to provide a crude reaction mixture which was purified by column chromatography on silica-gel.



**3-((4-Chlorobenzyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.1):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (74 mg, 90 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.02 (d,  $J$  = 9.0 Hz, 2H), 7.30-7.26 (m, 4H), 6.95 (d,  $J$  = 9.0 Hz, 2H), 4.97 (s, 2H), 3.89 (s, 2H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 165.6, 163.6, 135.0, 133.7, 131.8, 130.4, 128.7, 121.9, 113.7, 90.7, 77.2, 55.4, 53.1, 39.2; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{18}\text{H}_{16}\text{ClO}_3\text{S}$   $[\text{M}+\text{H}]^+$  347.0503; found 347.0512.

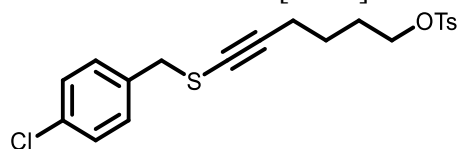


**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl acetate (9.2):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (49 mg, 70 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32-7.25 (m, 4H), 4.05 (t,  $J$  = 6.5 Hz, 2H), 3.84 (s, 2H), 2.31 (t,  $J$  = 6.9 Hz, 2H), 2.07 (s, 3H), 1.69-1.61 (m, 2H), 1.56-1.49 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.1, 135.5, 133.4, 130.3, 128.6, 95.5, 68.2, 63.8; 39.2, 27.6, 25.0, 21.0, 19.7; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{18}\text{ClO}_2\text{S}$   $[\text{M}+\text{H}]^+$  297.0711; found 297.0700.

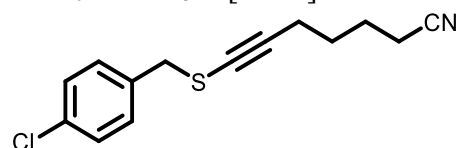


**(6-(Benzyloxy)hex-1-yn-1-yl)(4-chlorobenzyl)sulfane (9.3):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (56 mg, 68 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.39-7.25 (m, 9H), 4.52 (s, 2H), 3.83 (s, 2H), 3.48 (t,  $J$  = 6.0 Hz, 2H), 2.31 (t,  $J$  = 7.0 Hz, 2H), 1.70-1.54 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  =

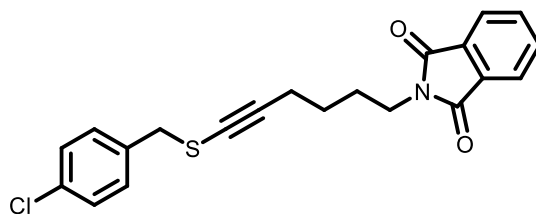
138.5, 135.6, 133.4, 130.3, 128.6, 128.3, 127.6, 127.5, 96.1, 72.9, 69.7, 67.8, 39.2, 28.8, 25.4, 19.9; HRMS (ESI)  $m/z$  calculated for  $C_{20}H_{22}ClOS$   $[M+H]^+$  345.1074; found 345.1077.



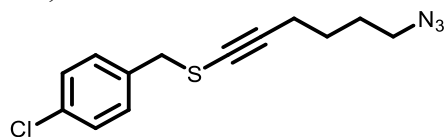
**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl 4-methylbenzenesulfonate (9.4):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  20 % diethyl ether in hexanes) to afford the desired product as a colorless oil (70 mg, 72 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.79 (d,  $J$  = 8.3 Hz, 2H), 7.35 (d,  $J$  = 8.2 Hz, 2H), 7.29-7.22 (m, 4H), 4.01 (t,  $J$  = 6.2 Hz, 2H), 3.81 (s, 2H), 2.45 (s, 3H), 2.24 (t,  $J$  = 6.9 Hz, 2H), 1.69-1.61 (m, 2H), 1.52-1.43 (m, 2H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 144.7, 135.5, 133.4, 133.0, 130.3, 129.8, 128.6, 127.8, 95.1, 69.9, 68.5, 39.1, 27.7, 24.4, 21.6, 19.3; HRMS (ESI)  $m/z$  calculated for  $C_{20}H_{22}ClO_3S_2$   $[M+H]^+$  409.0693; found 409.0703.



**7-((4-Chlorobenzyl)thio)hept-6-ynenitrile (9.5):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  20 % diethyl ether in hexanes) to afford the desired product as a colorless oil (50 mg, 79 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.33-7.25 (m, 4H), 3.84 (s, 2H), 2.34-2.31 (m, 4H), 1.69-1.56 (m, 4H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 135.4, 133.4, 130.3, 128.6, 119.3, 94.6, 68.9, 39.1, 27.2, 24.2, 19.3, 16.7; HRMS (ESI)  $m/z$  calculated for  $C_{14}H_{15}ClNS$   $[M+H]^+$  264.0608; found 264.0605.



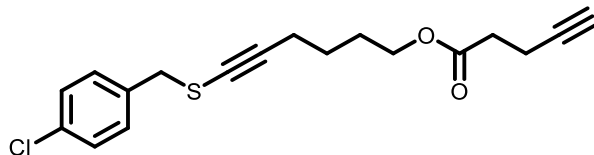
**2-(6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl)isoindoline-1,3-dione (9.6):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  20 % diethyl ether in hexanes) to afford the desired product as a colorless oil (50 mg, 55 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.86-7.82 (m, 2H), 7.73-7.70 (m, 2H), 7.29-7.23 (m, 2H), 3.82 (s, 2H), 3.70-3.66 (m, 2H), 2.32 (t,  $J$  = 7.0 Hz, 2H), 1.76-1.69 (m, 2H), 1.54-1.47 (m, 2H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 168.3, 135.9, 133.9, 133.3, 132.0, 130.3, 128.6, 123.1, 95.4, 68.3, 39.2, 37.3, 27.6, 25.8, 19.6; HRMS (ESI)  $m/z$  calculated for  $C_{21}H_{19}ClNO_2S$   $[M+H]^+$  384.0820; found 384.0818.



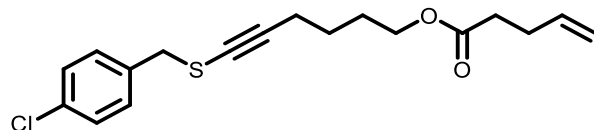
**(6-Azidohex-1-yn-1-yl)(4-chlorobenzyl)sulfane (9.7):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  2.5 % diethyl ether in hexanes) to afford the desired product as a colorless oil (40 mg, 62 % yield).



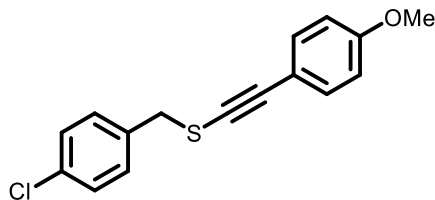
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32-7.25 (m, 4H), 3.84 (s, 2H), 3.26 (t,  $J$  = 6.4 Hz, 2H), 2.31 (t,  $J$  = 6.8 Hz, 2H), 1.65-1.50 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 135.5, 133.4, 130.3, 128.6, 95.3, 68.4, 50.9, 39.2, 27.8, 25.7, 19.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{13}\text{H}_{15}\text{ClN}_3\text{S}$   $[\text{M}+\text{H}]^+$  280.0670; found 280.0681.



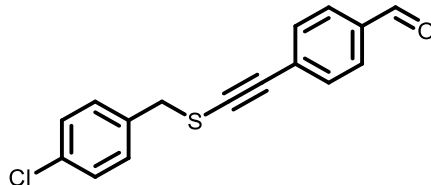
**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl pent-4-ynoate (9.8):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (52 mg, 66 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32-7.25 (m, 4H), 4.10 (t,  $J$  = 6.4 Hz, 2H), 3.84 (s, 2H), 2.59-2.49 (m, 4H), 2.31 (t,  $J$  = 7.0 Hz, 2H), 1.99 (t,  $J$  = 2.4 Hz, 1H), 1.70-1.62 (m, 2H), 1.57-1.50 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.7, 135.5, 133.4, 130.3, 128.6, 95.5, 82.4, 69.0, 68.2, 64.1, 39.2, 33.3, 27.6, 25.0, 19.7, 14.3; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{18}\text{H}_{20}\text{ClO}_2\text{S}$   $[\text{M}+\text{H}]^+$  335.0867; found 335.0875.



**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl pent-4-enoate (9.9):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (50 mg, 62 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32-7.25 (m, 4H), 5.88-5.78 (m, 1H), 5.09-5.00 (m, 2H), 4.07 (t,  $J$  = 6.4 Hz, 2H), 3.84 (s, 2H), 2.45-2.37 (m, 4H), 2.31 (t,  $J$  = 7.0 Hz, 2H), 1.69-1.62 (m, 2H), 1.56-1.49 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.0, 136.6, 135.5, 133.4, 130.3, 128.6, 115.5, 95.5, 68.2, 63.8, 39.2, 33.5, 28.8, 27.7, 25.0, 19.7; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{18}\text{H}_{22}\text{ClO}_2\text{S}$   $[\text{M}+\text{H}]^+$  337.1024; found 337.1025.

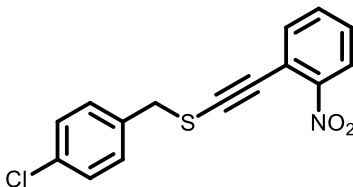


**(4-Chlorobenzyl)((4-methoxyphenyl)ethynyl)sulfane (9.10):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  2.5 % diethyl ether in hexanes) to afford the desired product as a white solid (72 mg, 96 % yield). NMR data was in accordance with what was previously reported.<sup>4</sup>

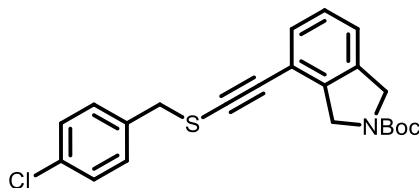


**4-(((4-Chlorobenzyl)thio)ethynyl)benzaldehyde (9.11):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a white solid (53 mg, 78 % yield).

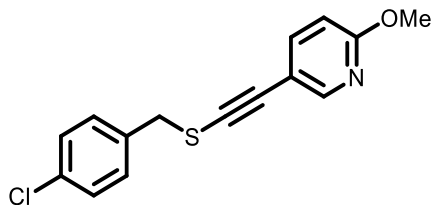
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.98 (s, 1H), 7.80 (d,  $J$  = 8.1 Hz, 2H), 7.43 (d,  $J$  = 8.2 Hz, 2H), 7.36-7.31 (m, 4H), 4.01 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 191.1, 135.0, 134.8, 133.8, 131.2, 130.4, 129.5, 129.3, 128.8, 94.6, 84.2, 39.5; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{16}\text{H}_{12}\text{ClOS}$   $[\text{M}+\text{H}]^+$  287.0292; found 287.0301.



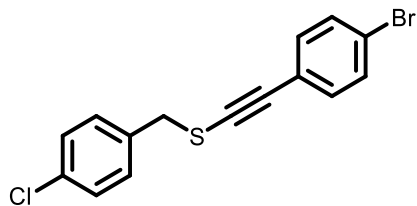
**(4-Chlorobenzyl)((2-nitrophenyl)ethynyl)sulfane (9.12):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  5 % diethyl ether in hexanes) to afford the desired product as an orange oil (71 mg, 98 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.07 (d,  $J$  = 8.3 Hz, 1H), 7.55-7.51 (m, 1H), 7.45-7.32 (m, 6H), 4.06 (s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 148.1, 135.0, 133.8, 133.4, 132.9, 130.4, 128.8, 127.6, 124.7, 119.0, 91.9, 89.7, 39.8; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{11}\text{ClNO}_2\text{S}$   $[\text{M}+\text{H}]^+$  304.0194; found 304.0203.



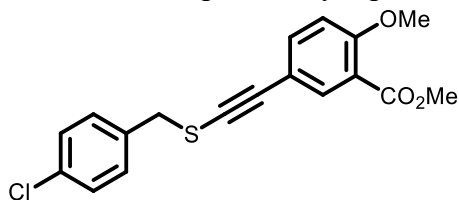
**tert-Butyl 4-(((4-chlorobenzyl)thio)ethynyl)isindoline-2-carboxylate (9.13):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a white solid (93 mg, 98 % yield). *Note that rotamers are formed and can result in complex splitting patterns in the  $^1\text{H}$  NMR, or can cause doubling of some peaks in the  $^{13}\text{C}$  NMR spectrum. For clarity, all peaks are reported.*  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.36-7.30 (m, 4H), 7.22-7.11 (m, 3H), 4.69-4.58 (m, 4H), 3.96 (s, 2H), 1.56-1.54 (m, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 154.34, 154.27, 139.3, 139.1, 137.3, 137.0, 135.0, 134.9, 133.7, 130.3, 130.3, 130.0, 129.5, 128.8, 128.7, 127.43, 127.40, 122.5, 122.1, 118.2, 118.0, 92.1, 91.8, 83.2, 82.7, 79.8, 79.7, 52.6, 52.4, 52.2, 52.1, 39.7, 39.6, 28.5, 28.4; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{22}\text{ClNO}_2\text{SNa}$   $[\text{M}+\text{Na}]^+$  422.0952; found 422.0950.



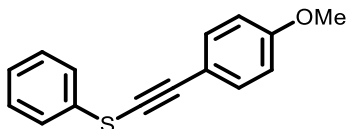
**5-(((4-Chlorobenzyl)thio)ethynyl)-2-methoxypyridine (9.14):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (4 % diethyl ether in hexanes) to afford the desired product as a white solid (69 mg, 99 % yield). NMR data was in accordance with what was previously reported.<sup>4</sup>



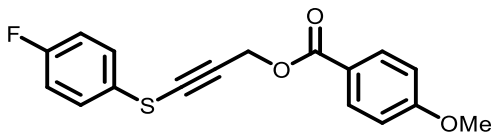
**((4-Bromophenyl)ethynyl)(4-chlorobenzyl)sulfane (9.15):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 2.5 % diethyl ether in hexanes) to afford the desired product as a white solid (80 mg, 98 % yield). NMR data was in accordance with what was previously reported.<sup>4</sup>



**Methyl 5-(((4-chlorobenzyl)thio)ethynyl)-2-methoxybenzoate (9.16):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 25 % diethyl ether in hexanes) to afford the desired product as a white solid (77 mg, 94 % yield). NMR data was in accordance with what was previously reported.<sup>4</sup>

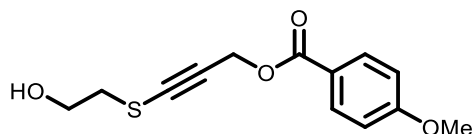


**((4-Methoxyphenyl)ethynyl)(phenyl)sulfane (9.18):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 2 % diethyl ether in hexanes) to afford the desired product as an amber oil (40 mg, 71 % yield). NMR data was in accordance with what was previously reported.<sup>55</sup>

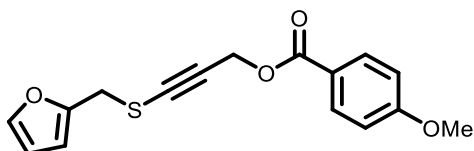


**3-((4-Fluorophenyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.19):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (61 mg, 81 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.04 (d, *J* = 8.6 Hz, 2H), 7.43 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.07 (dd, *J* = 8.5, 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.12 (s, 2H), 3.87 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 165.5, 163.6, 162.0 (d, *J* = 246.8 Hz), 131.8, 128.7 (d, *J* = 8.2 Hz), 126.9 (d, *J* = 3.3 Hz), 121.8, 116.5 (d, *J* = 22.4 Hz), 113.7, 93.4, 74.8, 74.6, 55.4, 53.1, 52.1; HRMS (ESI) *m/z* calculated for C<sub>17</sub>H<sub>13</sub>FO<sub>3</sub>SNa [M+Na]<sup>+</sup> 339.0462; found 339.0468.

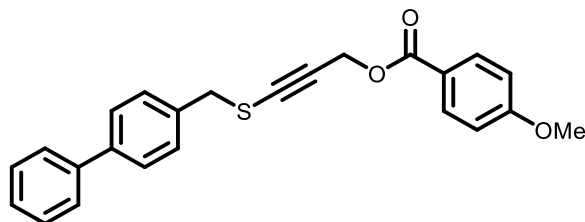
<sup>55</sup> Reddy, R. J.; Ball-Jones, M. P.; Davies, P. W. *Angew. Chem., Int. Ed.* **2017**, *56*, 13310-13313.



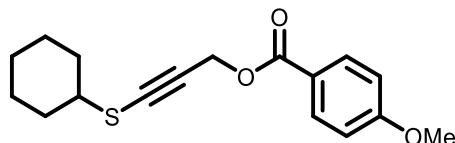
**3-((2-Hydroxyethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.20):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 50 % diethyl ether in hexanes) to afford the desired product as a colorless oil (54 mg, 85 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.01 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.98 (s, 2H), 3.93 (t, *J* = 5.6 Hz, 2H), 3.86 (s, 3H), 3.89 (t, *J* = 5.8 Hz, 2H), 2.41 (br s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 165.7, 163.6, 131.8, 121.8, 113.6, 88.6, 76.8, 60.4, 55.4, 53.2, 37.9; HRMS (ESI) *m/z* calculated for C<sub>13</sub>H<sub>14</sub>O<sub>4</sub>SNa [M+Na]<sup>+</sup> 289.0505; found 289.0504.



**3-((Furan-2-ylmethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.21):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (5 % → 10 % diethyl ether in hexanes) to afford the desired product as a brown solid (56 mg, 78 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.03 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 6.36-6.32 (m, 1H), 6.32-6.28 (m, 1H), 5.00 (s, 2H), 3.99 (s, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 165.6, 163.6, 149.2, 142.8, 131.8, 122.0, 113.6, 110.6, 109.1, 90.8, 77.2, 55.4, 53.2, 32.6; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>SNa [M+Na]<sup>+</sup> 325.0505; found 325.0492.

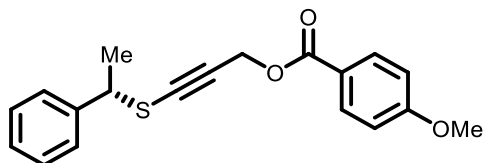


**3-((1,1'-Biphenyl-4-ylmethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.22):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (10 % diethyl ether in hexanes) to afford the desired product as a white solid (89 mg, 97 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.02 (d, *J* = 9.0 Hz, 2H), 7.58-7.52 (m, 4H), 7.48-7.40 (m, 4H), 7.39-7.33 (m, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.00 (s, 2H), 4.00 (s, 2H), 3.85 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 165.6, 163.5, 141.1, 131.8, 128.5, 127.8, 127.2, 122.0, 113.6, 91.1, 77.4, 55.4, 53.3, 48.1, 21.1; HRMS (ESI) *m/z* calculated for C<sub>24</sub>H<sub>21</sub>O<sub>3</sub>S [M+H]<sup>+</sup> 389.1206; found 389.1215.

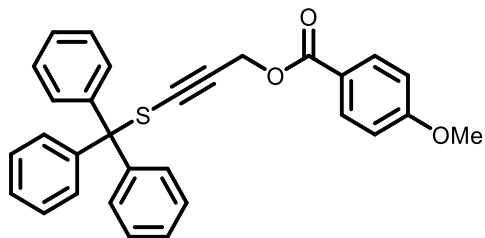


**3-(Cyclohexylthio)prop-2-yn-1-yl 4-methoxybenzoate (9.23):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (59 mg, 82 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.02 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.03

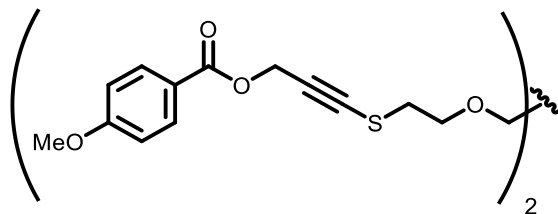
(s, 2H), 3.86 (s, 3H), 2.97-2.90 (m, 1H), 2.07-2.03 (m, 2H), 1.82-1.78 (m, 2H), 1.64-1.60 (m, 1H), 1.54-1.26 (m, 5H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 165.6, 163.6, 131.8, 122.1, 113.7, 113.6, 89.8, 77.2, 55.4, 53.5, 47.3, 32.9, 26.0, 25.4; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{21}\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  305.1206; found 305.1219.



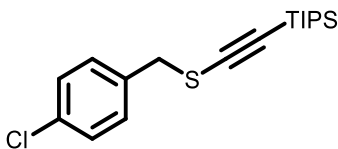
**(S)-3-((1-Phenylethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.24):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (10 % diethyl ether in hexanes) to afford the desired product as a colorless oil (68 mg, 88 % yield).  $[\alpha]_{\text{D}}^{25} = -44.8$  ( $c = 0.00906$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.03 (d,  $J = 9.0$  Hz, 2H), 7.40-7.30 (m, 4H), 7.29-7.24 (m, 1H), 6.94 (d,  $J = 8.9$  Hz, 2H), 5.00 (s, 2H), 4.30 (q,  $J = 7.0$  Hz, 1H), 3.88 (s, 3H), 1.78 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 165.6, 163.5, 141.1, 131.8, 128.5, 127.8, 127.2, 122.0, 113.6, 91.1, 77.4, 55.4, 53.3, 48.1, 21.1; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{19}\text{H}_{18}\text{O}_3\text{SNa}$   $[\text{M}+\text{Na}]^+$  349.0869; found 349.0880.



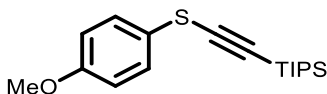
**3-(Tritylthio)prop-2-yn-1-yl 4-methoxybenzoate (9.25):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired product as a white solid (89 mg, 80 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.96 (d,  $J = 8.8$  Hz, 2H), 7.35-7.25 (m, 15H), 6.95 (d,  $J = 8.8$  Hz, 2H), 4.77 (s, 2H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 165.4, 163.5, 143.7, 131.8, 129.8, 127.9, 127.3, 122.0, 113.6, 93.5, 79.3, 71.6, 55.4, 53.2; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{30}\text{H}_{25}\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  465.1519; found 465.1513.



**7,10-Dioxa-4,13-dithiahexadeca-2,14-diyne-1,16-diyl bis(4-methoxybenzoate) (9.26):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (40 % ethyl acetate in hexanes) to afford the desired product as a white solid (75 mg, 59 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.02 (d,  $J = 9.0$  Hz, 2H), 6.93 (d,  $J = 8.9$  Hz, 2H), 5.00 (s, 2H), 3.87 (s, 3H), 3.79 (t,  $J = 6.5$  Hz, 2H), 3.66 (s, 2H), 2.92 (t,  $J = 6.5$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 165.6, 163.6, 131.8, 122.0, 113.7, 88.7, 77.5, 70.5, 69.2, 55.4, 53.3, 34.7; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{30}\text{O}_8\text{S}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  581.12743; found 581.12793.



**(((4-Chlorobenzyl)thio)ethynyl)triisopropylsilane (9.27):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes) to afford the desired product as a colorless oil (74 mg, 95 % yield). NMR data was in accordance with what was previously reported.<sup>56</sup>



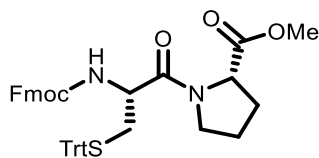
**Triisopropyl(((4-methoxyphenyl)thio)ethynyl)silane (9.28):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 2 % diethyl ether in hexanes) to afford the desired product as a colorless oil (224 mg, 91 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.38 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 1.11 (s, 21 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 158.8, 128.3, 123.0, 115.0, 101.5, 92.6, 55.4, 18.6, 11.4; HRMS (ESI) *m/z* calculated for C<sub>18</sub>H<sub>29</sub>OSSi [M+H]<sup>+</sup> 321.1707; found 321.1703.

## DIPEPTIDE LABELLING VIA Cu-CATALYZED CROSS-COUPLING

**Procedure for EDC-Mediated Esterification/Amidation (D):** To a stirred solution of the carboxylic acid (1 equiv.) and the hydrochloride amine salt (1.3 equiv.) in dry dichloromethane (0.1 M), 1-hydroxybenzotriazole hydrate (HOBt-H<sub>2</sub>O) (1.5 equiv.), *N,N*-diisopropylethylamine (DIPEA) (1.5 equiv.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) (1.5 equiv.) were added at room temperature. The reaction mixture was stirred at room temperature for 18 hours. Upon complete conversion of the starting material, HCl 1 M and dichloromethane were added to the reaction mixture and the phases were separated. The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The crude reaction mixture was concentrated under vacuum and was then purified by column chromatography on silica-gel to afford the desired product.

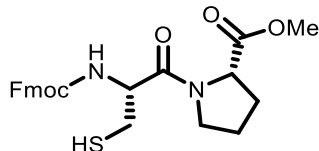
**Procedure for Tritel Deprotection (E):** To a stirred solution of the trityl-protected thiol (1 equiv.) in dry dichloromethane (0.1 M) under nitrogen atmosphere, triisopropylsilane (TIPS-H) (5 equiv.) and trifluoroacetic acid (TFA) (5 equiv.) were added at room temperature. The reaction mixture was stirred at room temperature for 4 hours. Upon complete conversion of the starting material, the crude reaction mixture was concentrated under vacuum and was then purified by column chromatography on silica-gel to afford the desired product.

<sup>56</sup> Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620-9623.



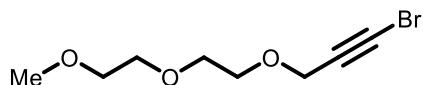
**Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*S*-trityl-*L*-cysteinyl-*L*-prolinate (9.S13):**

Following Procedure D, to a stirred solution of *N*-Fmoc-*S*-Trityl-*L*-cysteine (500 mg, 0.854 mmol, 1 equiv.) and *L*-proline methyl ester hydrochloride (184 mg, 1.11 mmol, 1.3 equiv.) in dry dichloromethane (8.5 mL) was added HOBt-H<sub>2</sub>O (173 mg, 1.28 mmol, 1.5 equiv.), DIPEA (0.22 mL, 1.28 mmol, 1.5 equiv.) and EDC-HCl (245 mg, 1.28 mmol, 1.5 equiv.) at room temperature. After purification by column chromatography on silica-gel (40 % ethyl acetate in hexanes), the desired product was obtained as a white solid (529 mg, 89 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.78 (d, *J* = 7.4 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.52-7.45 (m, 5H), 7.45-7.37 (m, 3H), 7.36-7.32 (m, 8H), 7.27-7.22 (m, 3H), 5.58 (d, *J* = 9.0 Hz, 15 % of 1H), 5.50 (d, *J* = 8.9 Hz, 85 % of 1H), 4.55-4.28 (m, 4H), 4.25 (t, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.57-3.41 (m, 1H), 3.20-3.09 (m, 1H), 2.73-2.54 (m, 2H), 2.22-2.04 (m, 1H), 2.01-1.84 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 171.8, 169.1, 155.7, 144.4, 143.7, 143.6, 141.1, 129.6, 127.9, 127.5, 126.9, 126.7, 125.1, 119.8, 67.1, 67.0, 58.8, 52.0, 51.9, 46.9, 46.5, 34.0, 28.7, 24.6; HRMS (ESI) *m/z* calculated for C<sub>43</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup> 719.2550; found 719.2558.

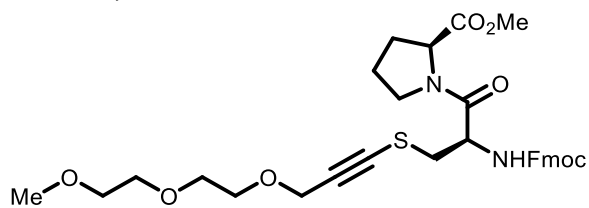


**Methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-cysteinyl-*L*-prolinate (9.S14):**

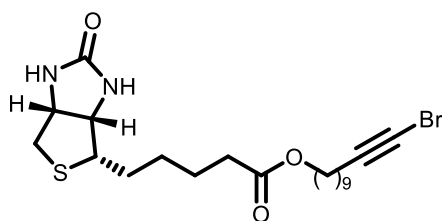
Following Procedure E, To a stirred solution of the trityl-protected thiol **9.S13** (300 mg, 0.431 mmol, 1 equiv.) in dry dichloromethane (4.3 mL) under nitrogen atmosphere was added TIPS-H (0.44 mL, 2.15 mmol, 5 equiv.) and TFA (0.17 mL, 2.15 mmol, 5 equiv.) at room temperature. After purification by column chromatography on silica-gel (30 % → 50 % ethyl acetate in hexanes), the desired product was obtained as a white solid (186 mg, 95 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.75 (d, *J* = 7.3 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.39 (dd, *J* = 7.3, 7.2 Hz, 2H), 7.30 (dd, *J* = 7.1, 6.9 Hz, 2H), 5.92 (d, *J* = 8.3 Hz, 1H), 4.79-4.71 (m, 1H), 4.58-4.51 (m, 1H), 4.43, 4.31 (m, 2H), 4.21 (dd, *J* = 6.9, 6.7 Hz, 1H), 3.89-3.81 (m, 1H), 3.75 (s, 3H), 3.76-3.68 (m, 1H), 2.98-2.89 (m, 1H), 2.89-2.79 (m, 1H), 2.27-2.18 (m, 1H), 2.09-1.90 (m, 3H), 1.93 (t, *J* = 8.8 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 172.1, 168.9, 155.6, 143.64, 143.58, 141.1, 127.6, 126.9, 125.04, 124.99, 119.9, 67.0, 58.9, 53.8, 52.3, 47.3, 47.0, 28.9, 27.0, 24.8; HRMS (ESI) *m/z* calculated for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>SNa [M+Na]<sup>+</sup> 477.1455; found 477.1461.



**1-Bromo-3-(2-(2-methoxyethoxy)ethoxy)prop-1-yne (9.S15):** Following Procedure A, 3-(2-(2-methoxyethoxy)ethoxy)prop-1-yne (200 mg, 1.26 mmol, 1.0 equiv.), NBS (270 mg, 1.52 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (43 mg, 0.253 mmol, 20 mol%) were dissolved in acetone (13 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (20 % ethyl acetate in hexanes), the desired product was obtained as a light yellow oil (286 mg, 95 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.24 (s, 2H), 3.73-3.68 (m, 4H), 3.68-3.64 (m, 2H), 3.58-3.55 (m, 2H), 3.39 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 76.2, 71.9, 70.6, 70.4, 69.3, 59.4, 59.0, 46.0; HRMS (ESI) m/z calculated for C<sub>8</sub>H<sub>14</sub>BrO<sub>3</sub> [M+H]<sup>+</sup> 237.0127; found 237.0121.



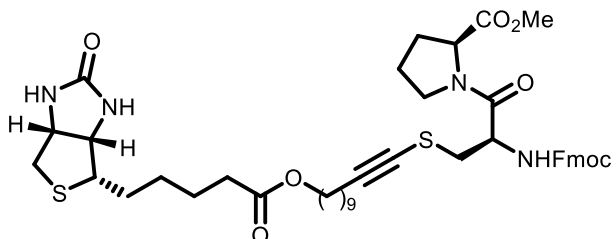
**Methyl ((R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2,5,8-trioxa-12-thiapentadec-10-yn-15-oyl-L-prolinate (9.29):** Following Procedure C (0.1 mmol), the crude reaction mixture was purified by column chromatography on silica-gel (60 % → 75 % ethyl acetate in hexanes) to afford the desired product as a light yellow oil (53 mg, 87 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.79-7.74 (m, 2H), 7.61-7.57 (m, 2H), 7.43-7.38 (m, 2H), 7.34-7.28 (m, 2H), 5.76-5.63 (m, 1H), 4.94-4.87 (m, 1H), 4.57-4.52 (m, 1H), 4.40-4.29 (m, 4H), 4.25-4.18 (m, 1H), 3.83-3.77 (m, 2H), 3.76-3.71 (m, 4H), 3.69-3.63 (m, 4H), 3.57-3.51 (m, 2H), 3.37 (s, 3H), 3.22-3.13 (m, 1H), 3.02-2.89 (m, 1H), 2.25-2.19 (m, 1H), 2.10-1.96 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 171.9, 168.9, 155.8, 143.7, 141.2, 127.7, 127.0, 125.1, 119.9, 91.0, 76.3, 71.8, 70.5, 70.4, 68.9, 67.2, 59.4, 59.0 (2C), 52.3, 51.7, 47.1, 47.01, 46.96, 29.0, 24.8; HRMS (ESI) m/z calculated for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>8</sub>S [M+Na]<sup>+</sup> 633.2241; found 633.2244.



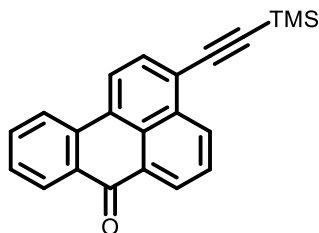
**11-Bromoundec-10-yn-1-yl 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoate (9.S16):** To a stirred solution of the *D*-biotin (66 mg, 0.270 mmol, 1 equiv.) and 11-bromo-10-undecyn-1-ol (100 mg, 0.405 mmol, 1.5 equiv.) dissolved in DMF/Et<sub>3</sub>N (3:1) (0.1 M), were added HOBT-H<sub>2</sub>O (44 mg, 0.324 mmol, 1.2 equiv.) and EDC-HCl (62 mg, 0.324 mmol, 1.2 equiv.) at room temperature. The diluted solution was washed with a saturated aqueous solution NH<sub>4</sub>Cl and dichloromethane. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. After purification by column chromatography on silica-gel (100 % dichloromethane → 5 % methanol in dichloromethane), the desired product was obtained as a white solid (120 mg, 94 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 5.94 (s, 1H), 5.56 (s, 1H), 4.50 (dd, *J* = 7.6, 5.4 Hz, 1H), 4.30



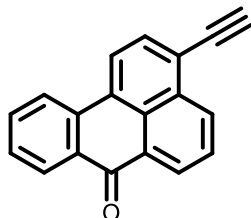
(dd,  $J = 7.6, 5.8$  Hz, 1H), 4.05 (t,  $J = 6.8$  Hz, 2H), 3.19-3.12 (m, 1H), 2.93 (dd,  $J = 12.8, 5.0$  Hz, 1H), 2.74 (d,  $J = 12.8$  Hz, 1H), 2.32 (t,  $J = 7.5$  Hz, 2H), 2.19 (t,  $J = 7.0$  Hz, 2H), 1.76-1.57 (m, 6H), 1.54-1.42 (m, 4H), 1.40-1.25 (m, 10H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 173.8, 163.7, 80.4, 64.5, 61.9, 60.1, 55.4, 40.5, 37.4, 33.9, 29.3, 29.1, 28.9, 28.7, 28.6, 28.3, 28.21, 28.19, 25.8, 24.8, 19.6$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{21}\text{H}_{34}\text{BrN}_2\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  473.1488; found 473.1468.



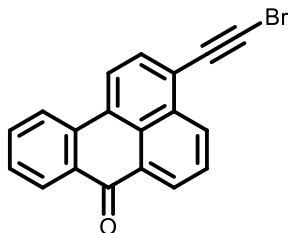
**Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*S*-((11-((5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoyl)oxy)undec-1-yn-1-yl)-*L*-cysteinyl)-*L*-prolinate (9.30):** Following Procedure C (0.1 mmol), the crude reaction mixture was purified by column chromatography on silica-gel (2 %  $\rightarrow$  5 % methanol in dichloromethane) to afford the desired product as a yellow oil (71 mg, 84 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.76$  (d,  $J = 7.4$  Hz, 2H), 7.64-7.59 (m, 2H), 7.40 (dd,  $J = 7.4, 7.3$  Hz, 2H), 7.31 (dd,  $J = 7.7, 7.3$  Hz, 2H), 6.04 (d,  $J = 9.7$  Hz, 1H), 5.51-5.40 (m, 1H), 5.26-5.17 (m, 1H), 5.02-4.86 (m, 1H), 4.58-4.47 (m, 2H), 4.39-4.33 (m, 2H), 4.33-4.28 (m, 1H), 4.27-4.22 (m, 1H), 4.05 (t,  $J = 6.7$  Hz, 2H), 3.85-3.68 (m, 2H), 3.74 (s, 3H), 3.20-3.09 (m, 2H), 2.94-2.86 (m, 2H), 2.77-2.71 (m, 1H), 2.40-2.21 (m, 6H), 2.08-2.00 (m, 2H), 1.72-1.60 (m, 6H), 1.54-1.43 (m, 4H), 1.39-1.27 (m, 10H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 173.7, 172.6, 169.4, 163.3, 156.0, 143.80, 143.76, 141.22, 127.7, 127.1, 125.2, 120.0, 95.3, 67.3, 64.5, 61.9, 60.1, 59.0, 55.3, 52.3, 51.9, 47.1, 40.5, 37.8, 33.9, 29.3, 29.2, 29.0, 28.8, 28.64, 28.59, 28.57, 28.3, 28.2, 25.6, 24.8, 20.1$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{45}\text{H}_{59}\text{N}_4\text{O}_8\text{S}_2$   $[\text{M}+\text{H}]^+$  847.3780; found 847.3769.



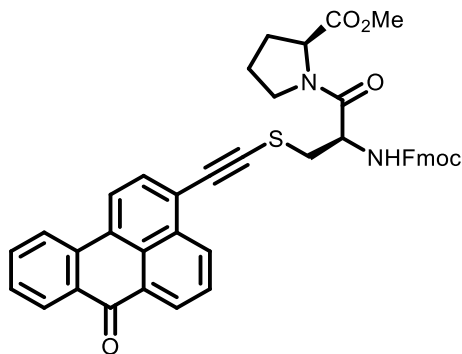
**3-((Trimethylsilyl)ethynyl)-7H-benzo[de]anthracen-7-one (9.S17):** In a dried sealable tube, 3-bromobenzanthrone (1.0 g, 3.07 mmol, 1 equiv) was dissolved in Et<sub>3</sub>N (5 mL) and 1,4-dioxane (5 mL). The aperture of the tube was covered with a rubber septum and the solution was bubbled with nitrogen for 5 minutes. Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (66 mg, 0.092 mmol, 3 mol%) and CuI (18 mg, 0.092 mmol, 3 mol%) were added and the solution was bubbled a second time with nitrogen for 5 minutes. Ethynyltrimethylsilane (2.13 mL, 15.4 mmol, 5 equiv) was added and the septum was then replaced by a Teflon-coated screw cap. The sealed-tube was placed in a pre-heated oil bath at 100 °C and the reaction mixture was stirred for 24 hours at 100 °C. Upon completion, the mixture was passed through a pad of Celite® and concentrated under vacuum. Purification by silica gel chromatography (2 % → 5 % ethyl acetate in hexanes) afforded the desired product as a yellow solid (770 mg, 73 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.66 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.60 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.39 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.76 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.63 (ddd, *J* = 8.3, 8.3, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.7, 7.7 Hz, 1H), 0.40 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 183.3, 135.4, 133.2, 132.7, 131.0, 130.7, 130.0, 128.5, 128.4, 128.0, 127.4, 127.0, 123.1, 122.9, 102.5, 102.3, 0.0; HRMS (APPI) *m/z* calculated for C<sub>22</sub>H<sub>18</sub>OSi [M]<sup>-</sup> 326.1132; found 326.1127.



**3-Ethynyl-7H-benzo[de]anthracen-7-one (9.S18):** 3-((Trimethylsilyl)ethynyl)-7H-benzo[de]anthracen-7-one (770 mg, 2.25 mmol, 1.0 equiv.) was solubilized in anhydrous diethyl ether (11 mL) in a round bottom flask equipped with a stir bar, and the solution was cooled to 0 °C. A tetrabutylammonium fluoride (TBAF) solution (1 M in THF) (4.5 mL, 4.5 mmol, 2.0 equiv.) was then added dropwise under nitrogen. The reaction mixture was stirred at 0 °C for 2 hours. After purification by column chromatography on silica-gel (5 % → 15 % ethyl acetate in hexanes), the desired product was obtained as an orange solid (215 mg, 35 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.78 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.74 (d, *J* = 8.1 Hz, 1H), 8.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 7.4, 7.4, 0.8 Hz, 1H), 7.75 (ddd, *J* = 7.2, 7.2, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.0, 8.0, 0.9 Hz, 1H), 3.65 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 183.6, 135.5, 133.5, 133.2, 133.1, 131.6, 131.0, 130.2, 128.8, 128.7, 128.2, 127.71, 127.69, 127.4, 123.3, 123.2, 122.0, 84.5, 81.2; HRMS (APPI) *m/z* calculated for C<sub>19</sub>H<sub>10</sub>O [M]<sup>-</sup> 254.0737; found 254.0731.

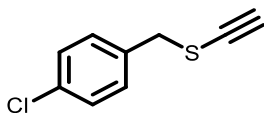


**3-(Bromoethynyl)-7H-benzo[de]anthracen-7-one (9.S19):** Following Procedure A, 3-ethynyl-7H-benzo[de]anthracen-7-one (100 mg, 0.37 mmol, 1.0 equiv.), NBS (79 mg, 0.44 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (12.6 mg, 0.074 mmol, 20 mol%) were dissolved in acetone (3.7 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (5 % ethyl acetate in hexanes), the desired product was obtained as a yellow solid (60 mg, 46 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.80 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.70 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.87 (ddd, *J* = 7.4, 7.4, 0.8 Hz, 1H), 7.77 (ddd, *J* = 7.2, 7.2, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 183.6, 135.6, 133.5, 133.22, 133.16, 131.5, 131.0, 130.3, 128.8, 128.2, 127.8, 127.6, 127.4, 123.32, 123.27, 122.7, 78.0, 57.3; HRMS (APPI) *m/z* calculated for C<sub>19</sub>H<sub>10</sub>BrO [M+H]<sup>+</sup> 332.9910; found 332.9919.

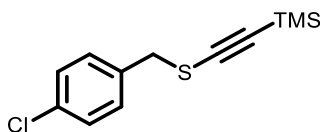


**Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-((7-oxo-7H-benzo[de]anthracen-3-yl)ethynyl)-L-cysteinyl-L-prolinate (9.31):** Following Procedure C (0.1 mmol), the crude reaction mixture was purified by column chromatography on silica-gel (30 % → 50 % ethyl acetate in hexanes) to afford the desired product as a yellow solid (31 mg, 44 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.80-8.70 (m, 2H), 8.50 (d, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 13.5, 7.4 Hz, 2H), 7.88-7.78 (m, 2H), 7.77-7.65 (m, 3H), 7.62-7.53 (m, 2H), 7.52-7.45 (m, 1H), 7.38-7.30 (m, 2H), 7.27-7.20 (m, 2H), 5.84-5.71 (m, 1H), 5.15-4.88 (m, 1H), 4.62-4.53 (m, 1H), 4.42-4.29 (m, 2H), 4.15-4.08 (m, 1H), 3.88-3.72 (m, 1H), 3.77 (s, 3H), 3.45-3.36 (m, 1H), 3.24-3.14 (m, 1H), 2.32-2.19 (m, 2H), 2.08-1.91 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 183.6, 172.0, 168.7, 155.8, 143.7, 143.5, 141.2, 135.6, 133.5, 133.4, 132.7, 130.9, 130.5, 130.2, 128.7, 128.6, 128.2, 127.70, 127.67, 127.3, 127.0, 125.04, 124.98, 123.4, 123.2, 123.1, 119.9, 91.4, 87.1, 67.3, 59.0, 52.4, 52.1, 47.0, 38.6, 29.2, 29.0, 24.8, ; HRMS (ESI) *m/z* calculated for C<sub>43</sub>H<sub>35</sub>N<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup> 707.2221; found 707.2226.

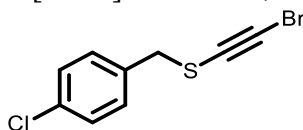
## SYNTHESIS OF BIS-HETEROATOM-SUBSTITUTED ALKYNES



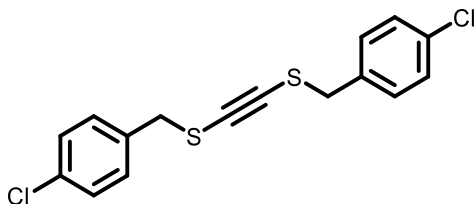
**(4-Chlorobenzyl)ethynylsulfane (9.S20):** (((4-Chlorobenzyl)thio)ethynyl)triisopropylsilane (0.076 g, 0.203 mmol, 1.0 equiv.) was solubilized in anhydrous tetrahydrofuran (2 mL) in a round bottom flask equipped with a stir bar, and the solution was cooled to 0 °C. A tetrabutylammonium fluoride (TBAF) solution (0.20 mL, 0.203 mmol, 1.0 equiv.) was then added dropwise under nitrogen. The reaction mixture was stirred at 0 °C for five minutes. After purification by column chromatography on silica-gel (100 % hexanes), the desired product was obtained as a white solid (54 mg, 92 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.34-7.27 (m, 4H), 3.91 (s, 2H), 2.83 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 135.0, 133.7, 130.3, 128.8, 83.8, 73.7, 38.9; HRMS (ESI) m/z calculated for C<sub>9</sub>H<sub>8</sub>ClS [M+H]<sup>+</sup> 183.0030; found 183.0033.



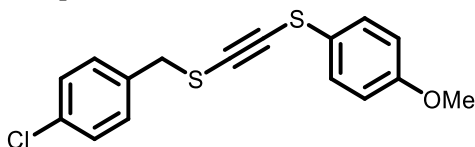
**(((4-Chlorobenzyl)thio)ethynyl)trimethylsilane (9.43):** Silver nitrate (2.3 mg, 0.0137 mmol, 5 mol%) was suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL). (4-Chlorobenzyl)ethynylsulfane (50 mg, 0.274 mmol, 1.0 equiv.) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.43 mL, 0.287 mmol, 1.05 equiv.) were added to the suspension. The reaction mixture was heated to 40 °C and freshly distilled trimethylsilyl chloride (0.49 mL, 0.383 mmol, 1.4 equiv.) was added dropwise. The solution was stirred for 24 h at 40 °C, cooled to room temperature, and concentrated under reduced pressure. After purification by column chromatography on silica-gel (100 % hexanes), the desired product was obtained as a yellow oil (63 mg, 90 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 2H), 0.15 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 135.0, 133.6, 130.4, 128.6, 102.8, 93.6, 39.4, -0.16; HRMS (ESI) m/z calculated for C<sub>12</sub>H<sub>16</sub>ClSSi [M+H]<sup>+</sup> 255.0425; found 255.04221.



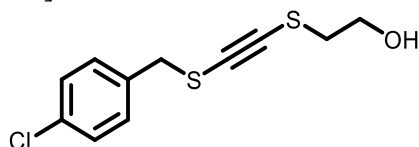
**(Bromoethynyl)(4-chlorobenzyl)sulfane (9.44):** Following Procedure A, (4-chlorobenzyl)ethynylsulfane (0.043 mL, 0.236 mmol, 1.0 equiv.), NBS (0.051 g, 0.284 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (0.008 g, 0.047 mmol, 20 mol%) were dissolved in acetone (1.2 mL) in a round bottom flask equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes), the desired product was obtained as a white solid (0.038 g, 61 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.35-7.24 (m, 4H), 3.91 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 134.9, 133.8, 130.3, 128.8, 68.3, 52.4, 38.8; HRMS (ESI) m/z calculated for C<sub>9</sub>H<sub>7</sub>BrClS [M+H]<sup>+</sup> 260.9135; found 260.9128.



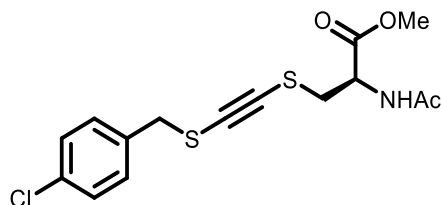
**1,2-Bis((4-chlorobenzyl)thio)ethyne (9.32):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 1 % diethyl ether in hexanes) to afford the desired product as a white solid (33 mg, 92 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.30 (d, *J* = 8.4 Hz, 4H), 7.17 (d, *J* = 8.4 Hz, 4H), 3.78 (s, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 135.0, 130.6, 130.4, 128.7, 87.9, 40.5; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>13</sub>Cl<sub>2</sub>S<sub>2</sub> [M+H]<sup>+</sup> 338.9830; found 338.9818.



**(4-Chlorobenzyl)((4-methoxyphenyl)thio)ethynyl)sulfane (9.33):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 2.5 % diethyl ether in hexanes) to afford the desired product as an amber oil (51 mg, 67 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33-7.28 (m, 4H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 2H), 3.81 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 159.0, 135.1, 133.6, 130.5, 128.8, 128.2, 123.6, 114.9, 89.7, 86.1, 55.4, 40.6; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>14</sub>ClOS<sub>2</sub> [M+H]<sup>+</sup> 321.0174; found 321.0169.

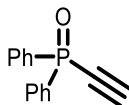


**2-(((4-Chlorobenzyl)thio)ethynyl)thio)ethan-1-ol (9.34):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (20 % ethyl acetate in hexanes) to afford the desired product as an amber oil (28 mg, 51 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 2H), 3.79 (t, *J* = 5.7 Hz, 2H), 2.77 (t, *J* = 5.8 Hz, 2H), 1.96 (bs, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 135.0, 133.6, 130.4, 128.7, 87.1, 85.5, 60.3, 40.4, 39.0; HRMS (ESI) *m/z* calculated for C<sub>11</sub>H<sub>12</sub>ClOS<sub>2</sub> [M+H]<sup>+</sup> 259.0015; found 259.0013.

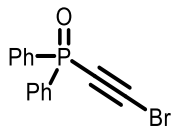


**Methyl *N*-acetyl-*S*-(((4-chlorobenzyl)thio)ethynyl)-*L*-cysteinate (9.35):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (30 % → 50 % ethyl acetate in hexanes) to afford the desired product as an amber oil (68 mg, 81 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.33 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 7.0 Hz, 1H), 4.90 (dt, *J* = 7.5, 4.6 Hz, 1H), 3.89 (d, *J* = 12.7 Hz, 1H), 3.82 (d, *J* = 12.7 Hz, 1H), 3.76 (s, 3H), 3.15 (dd, *J* = 13.8, 4.5 Hz, 1H), 3.08 (dd, *J* = 13.8, 4.7 Hz, 1H),

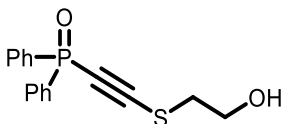
1.99 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.2, 169.8, 134.9, 133.7, 130.4, 128.8, 87.1, 86.1, 52.8, 51.9, 40.4, 37.7, 23.0; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{17}\text{ClNO}_3\text{S}_2$   $[\text{M}+\text{H}]^+$  358.0333; found 358.0341.



**Ethynyldiphenylphosphine oxide (9.S21):** In a flame-dried round-bottom flask filled with dry THF (27 mL) at  $-78\text{ }^\circ\text{C}$  under nitrogen atmosphere, a solution of ethynylmagnesium bromide (0.5 M in THF) (16.4 mL, 8.18 mmol, 1 equiv.) was added. Diphenylphosphinic acid (1.72 mL, 9.00 mmol, 1.1 equiv) was added dropwise and the solution was stirred at  $-78\text{ }^\circ\text{C}$  for 30 min. The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum. The residue was purified by column chromatography on silica-gel (50% ethyl acetate in hexanes) to afford the desired product as a colorless oil (1.85 g, 99 % yield). NMR data was in accordance with what was previously reported.<sup>57</sup>



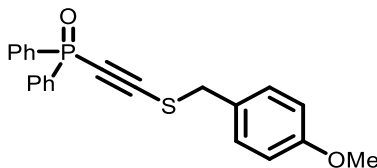
**(Bromoethynyl)diphenylphosphine oxide (9.S22):** Following Procedure A (0.44 mmol), the crude reaction mixture was concentrated under vacuum. The residue was dissolved in EtOAc and washed with NaOH 6M in order to remove the residual succinimide which co-eluted with final product. The organic layer was dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum. The residue was purified by column chromatography on silica-gel (50 % ethyl acetate in hexanes) to afford the desired product as a white solid (122 mg, 90 % yield). NMR data was in accordance with what was previously reported.<sup>58</sup>



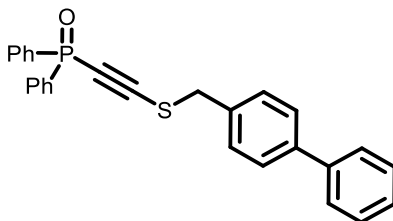
**(((2-Hydroxyethyl)thio)ethynyl)diphenylphosphine oxide (9.36):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (20 %  $\rightarrow$  40 % acetone in hexanes) to afford the desired product as a light brown oil (42 mg, 82 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.86-7.75 (m, 4H), 7.57-7.50 (m, 2H), 7.50-7.41 (m, 4H), 3.90 (t,  $J$  = 6.0 Hz, 2H), 3.02 (t,  $J$  = 6.0 Hz, 2H), 2.17 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 132.6 (d,  $J$  = 122.8 Hz), 132.3 (d,  $J$  = 2.6 Hz), 130.9 (d,  $J$  = 11.3 Hz), 128.7 (d,  $J$  = 13.7 Hz), 100.5 (d,  $J$  = 28.1 Hz), 88.0 (d,  $J$  = 167.2 Hz), 60.3, 38.3; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{16}\text{H}_{16}\text{O}_2\text{PS}$   $[\text{M}+\text{H}]^+$  303.06031; found 303.06158.

<sup>57</sup> Pellizzaro, L.; Tatibouët, A.; Fabris, F.; Rollin, P.; De Lucchi, O. *Tetrahedron Lett.* **2009**, *50*, 101–103.

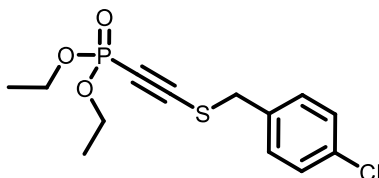
<sup>58</sup> Padovan, P.; Tartaggia, S.; Lorenzon, S.; Rosso, E.; Zonta, C.; De Lucchi, O.; Fabris, F. *Tetrahedron Lett.* **2009**, *50*, 1973–1976.



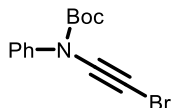
**(3-(4-Methoxyphenyl)prop-1-yn-1-yl)diphenylphosphine oxide (9.37):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (40 % → 60 % ethyl acetate in hexanes) to afford the desired product as a colorless oil (67 mg, 75 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.74 (dd,  $J$  = 13.8, 7.1 Hz, 4H), 7.53 (ddd,  $J$  = 7.2, 7.2, 1.3 Hz, 2H), 7.44 (ddd,  $J$  = 7.6, 7.6, 3.1 Hz, 4H), 7.20 (d,  $J$  = 8.5 Hz, 2H), 6.78 (d,  $J$  = 8.6 Hz, 2H), 4.03 (s, 2H), 3.78 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 159.5, 132.9 (d,  $J$  = 122.4 Hz), 132.1 (d,  $J$  = 2.6 Hz), 130.9 (d,  $J$  = 11.3 Hz), 130.4, 128.5 (d,  $J$  = 13.4 Hz), 127.3, 114.1, 110.3 (d,  $J$  = 28.1 Hz), 90.0 (d,  $J$  = 167.5 Hz), 55.2, 39.7; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{20}\text{O}_2\text{PS}$   $[\text{M}+\text{H}]^+$  379.09161; found 379.09168.



**((([1,1'-Biphenyl]-4-ylmethyl)thio)ethynyl)diphenylphosphine oxide (9.38):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (40 % → 50 % ethyl acetate in hexanes) to afford the desired product as a white solid (130 mg, 99 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.73 (ddd, *J* = 13.8, 8.3, 1.3 Hz, 4H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.52-7.36 (m, 11H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.09 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 140.9, 140.2, 134.3, 132.8 (d, *J* = 122.4 Hz), 132.1 (d, *J* = 2.6 Hz), 130.9 (d, *J* = 11.3 Hz), 129.5, 128.7, (d, *J* = 13.4 Hz), 127.5, 127.4, 127.0, 99.8 (d, *J* = 27.8 Hz), 90.3 (d, *J* = 166.5 Hz), 39.7; HRMS (ESI) *m/z* calculated for C<sub>27</sub>H<sub>22</sub>OPS [M+H]<sup>+</sup> 425.1124; found 425.1117.



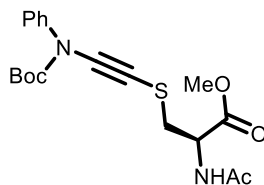
**Diethyl (((4-chlorobenzyl)thio)ethynyl)phosphonate (9.39):** Following Procedure C (0.124 mmol scale), the crude reaction mixture was purified by column chromatography on silica-gel (30 % → 40 % ethyl acetate in hexanes) to afford the desired product as a yellow oil (40 mg, 99 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.34 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 4.11-4.01 (m, 4H), 4.00 (s, 2H), 1.32 (t, *J* = 7.0 Hz, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 134.2, 133.8, 130.5, 129.0, 93.2 (d, *J* = 51.3 Hz), 86.0 (d, *J* = 295.8 Hz), 63.2 (d, *J* = 5.5 Hz), 39.0 (d, *J* = 1.9 Hz), 16.0 (d, *J* = 7.2 Hz); HRMS (ESI) *m/z* calculated for C<sub>13</sub>H<sub>17</sub>ClO<sub>3</sub>PS [M+H]<sup>+</sup> 319.0319; found 319.0309.



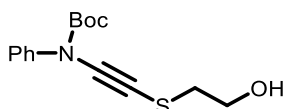
***tert*-Butyl (bromoethynyl)(phenyl)carbamate (9.S23):** To an oven-dried nitrogen-flushed round bottom flask, *tert*-butyl (*E*)-(1,2-dichlorovinyl)(phenyl)carbamate (199 mg, 0.69 mmol, 1.0 equiv.) and anhydrous THF (3 mL), were added and cooled to −78 °C. A solution of *n*-butyllithium (2.07 M solution in hexanes) (0.40 mL, 0.83 mmol, 1.2 equiv.) was then added dropwise over 10 minutes, such that the reaction does not exceed −70 °C. The resulting mixture was then stirred at −78 °C for 5 minutes, followed by warming to −41 °C for 30 minutes. Upon re-cooling to −78 °C, another portion of *n*-butyllithium (2.07 M solution in hexanes) (0.33 mL, 0.69 mmol, 1.0 equiv.) was added dropwise over 10 minutes, and stirred for a further 10 minutes. Next, NBS (147 mg, 0.83 mmol, 1.2 equiv.) was added and the reaction mixture was allowed to warm to room temperature. Upon reaction completion (TLC, ~1 h), the reaction mixture was quenched with water, followed by extraction with Et<sub>2</sub>O (×2). The organic layers were combined and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (1 % diethyl ether in hexanes) to afford yellow solid (107 mg, 52



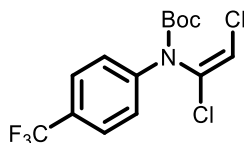
% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.46-7.41 (m, 2H), 7.41-7.36 (m, 2H), 7.29-7.24 (m, 1H), 1.54 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.0, 139.0, 128.9, 126.9, 124.8, 83.8, 72.9, 31.8, 28.0; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{13}\text{H}_{15}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  318.0095; found 318.0100.



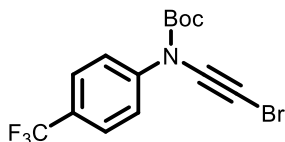
**Methyl *N*-acetyl-*S*-(((*tert*-butoxycarbonyl)(phenyl)amino)ethynyl)-*L*-cysteinate (9.40):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (30 %  $\rightarrow$  60 % ethyl acetate in hexanes) to afford the desired product as a yellow oil (79 mg, 85 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.40-7.33 (m, 4H), 7.27-7.22 (m, 1H), 6.57 (d,  $J$  = 7.2 Hz, 1H), 2.18 (dt,  $J$  = 7.5, 4.5 Hz, 1H), 3.71 (s, 3H), 3.17 (d,  $J$  = 4.4 Hz, 2H), 1.97 (s, 3H), 1.53 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.3, 169.8, 153.2, 139.7, 128.8, 126.9, 124.7, 87.8, 84.0, 61.3, 52.5, 52.3, 37.8, 27.9, 22.8; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$  415.1309; found 415.1298.



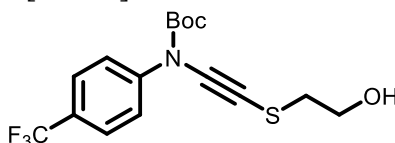
***tert*-Butyl (((2-hydroxyethyl)thio)ethynyl)(phenyl)carbamate (9.41):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (20 % ethyl acetate in hexanes) to afford the desired product as a colorless oil (35.1 mg, 50 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.43-7.35 (m, 4H), 7.29-7.23 (m, 1H), 4.00-3.89 (m, 2H), 2.83 (t,  $J$  = 5.8 Hz, 2H), 2.18 (bs, 1H), 1.54 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.4, 139.8, 128.8, 126.8, 124.7, 87.6, 83.9, 60.8, 38.9, 29.7, 27.9; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$  294.1158; found 294.1160.



***tert*-Butyl (*E*-(1,2-dichlorovinyl)(4-(trifluoromethyl)phenyl)carbamate (9.S24):** To a stirring mixture of *tert*-butyl (4-(trifluoromethyl)phenyl)carbamate (1.14 g, 4.35 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (TBAHS) (295 mg, 0.869 mmol, 0.2 equiv.), toluene (12.5 mL) and  $\text{CH}_2\text{Cl}_2$  (8.5 mL), at room temperature under nitrogen, was added 6 M aqueous NaOH (13.5 mL, 81 mmol, 18.6 equiv.). The solution was then stirred vigorously for 15 minutes, followed by the dropwise addition of trichloroethylene (1.17 mL, 13 mmol, 3.0 equiv.) over 10 minutes. The reaction was then stirred 18 h at room temperature. The aqueous layer was then extracted with  $\text{Et}_2\text{O}$  ( $\times 3$ ), organic extracts combined, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude reaction mixture was purified by column chromatography on silica-gel (2 %  $\rightarrow$  4 % ethyl acetate in hexanes) to afford a colorless oil (1.15 g, 74 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.64 (d,  $J$  = 8.6 Hz, 2H), 7.51 (d,  $J$  = 8.5 Hz, 2H), 6.39 (s, 1H), 1.55 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 150.7, 141.5, 131.3, 128.5 (q,  $J$  = 32.9 Hz), 126.1 (q,  $J$  = 3.7 Hz), 123.9 (q,  $J$  = 272.0 Hz), 124.8, 117.1, 83.6, 28.0; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{F}_3\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  378.0246; found 378.0264.



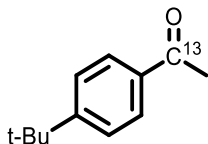
***tert*-Butyl (bromoethynyl)(4-(trifluoromethyl)phenyl)carbamate (9.S25):** To an oven-dried nitrogen-flushed round bottom flask, *tert*-butyl (*E*-(1,2-dichlorovinyl)(4-(trifluoromethyl)phenyl)carbamate (400 mg, 1.12 mmol, 1.0 equiv.) and anhydrous THF (4.5 mL), were added and cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of *n*-butyllithium (1.84 M solution in hexanes) (0.732 mL, 1.35 mmol, 1.2 equiv.) was then added dropwise over 10 minutes, such that the reaction does not exceed  $-70\text{ }^{\circ}\text{C}$ . The resulting mixture was then stirred at  $-78\text{ }^{\circ}\text{C}$  for 5 minutes, followed by warming to  $-41\text{ }^{\circ}\text{C}$  for 30 minutes. Upon re-cooling to  $-78\text{ }^{\circ}\text{C}$ , another portion of *n*-butyllithium (1.84 M solution in hexanes) (0.610 mL, 1.12 mmol, 1.0 equiv.) was added dropwise over 10 minutes, and stirred for a further 10 minutes. Next, NBS (300 mg, 1.68 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to warm to room temperature for 2 h. Upon completion, the reaction mixture was quenched with water, followed by extraction with  $\text{Et}_2\text{O}$  ( $\times 2$ ). The organic layers were combined and dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (0.5 % diethyl ether in hexanes) to afford yellow solid (140 mg, 34 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.67\text{--}7.59$  (m, 4H), 1.56 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 152.3, 142.0, 128.5$  (q,  $J = 32.6$  Hz), 125.9 (q,  $J = 3.6$  Hz), 124.2, 123.8 (q,  $J = 272.1$  Hz), 84.6, 71.8, 33.3, 27.9; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{13}\text{BrF}_3\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  385.9974; found 385.9969.



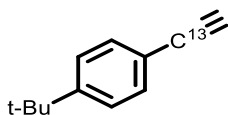
***tert*-Butyl (((2-hydroxyethyl)thio)ethynyl)(4-(trifluoromethyl)phenyl)carbamate (9.42):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (20 % ethyl acetate in hexanes) to afford the desired product as a colorless oil (38 mg, 44 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.64$  (d,  $J = 8.8$  Hz, 2H), 7.59 (d,  $J = 8.8$  Hz, 2H), 3.99-3.93 (m, 2H), 2.85 (t,  $J = 5.6$  Hz, 2H), 2.13 (bs, 1H), 1.56 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta = 152.7, 142.9, 128.5$  (q,  $J = 32.9$  Hz), 125.9 (q,  $J = 3.8$  Hz), 124.3, 123.8 (q,  $J = 272.1$  Hz), 86.4, 84.6, 62.4, 60.9, 38.9, 27.9; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{16}\text{H}_{18}\text{F}_3\text{NO}_3\text{SNa}$   $[\text{M}+\text{Na}]^+$  384.0852; found 384.0865.

## MECHANISTIC INVESTIGATIONS:

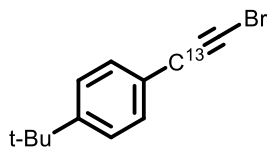
### SYNTHESIS OF <sup>13</sup>C-LABELLED COMPOUNDS



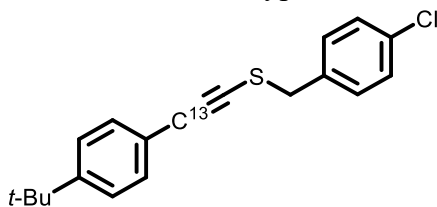
**1-(4-(*tert*-Butyl)phenyl)ethan-1-one-1-<sup>13</sup>C (9.S26):** In a flame-dried round-bottom flask equipped with a magnetic bar, *tert*-butylbenzene (385 mg, 2.87 mmol, 1 equiv) and acetyl-1-<sup>13</sup>C chloride (221  $\mu$ L, 3.15 mmol, 1.1 equiv) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The mixture was cooled to 0 °C then AlCl<sub>3</sub> (459 mg, 3.44 mmol, 1.2 equiv) was added portion wise. The reaction mixture was stirred at room temperature for 2 h then poured into 20 mL ice/water. The aqueous phase was extracted three times using dichloromethane (3 $\times$ 10 mL). The collected organic layers were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5 %  $\rightarrow$  5 % ethyl acetate in hexanes) to afford the desired product as a colorless oil (374 mg, 74% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.94-7.88 (m, 2H), 7.49 (d,  $J$  = 8.3 Hz, 2H), 2.61 (d,  $J$  = 5.9 Hz, 3H), 1.36 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 197.8 (<sup>13</sup>C-enriched), 156.8 (d,  $J$  = 0.9 Hz), 134.5 (d,  $J$  = 53.6 Hz), 128.3 (d,  $J$  = 3.0 Hz), 125.5 (d,  $J$  = 4.0 Hz), 35.1, 31.1, 26.6 (d,  $J$  = 42.5 Hz); HRMS (ESI)  $m/z$  calculated for C<sub>11</sub>[<sup>13</sup>C]H<sub>17</sub>O [M+H]<sup>+</sup> 178.1308; found 178.1306.



**1-(*tert*-Butyl)-4-(ethynyl-1-<sup>13</sup>C)benzene (9.S27):** To a third of a solution (1/3) of lithium diisopropylamide (LDA, prepared at 0 °C from diisopropylamine (0.53 mL, 3.75 mmol, 3.5 equiv) and *n*-BuLi (1.9 M in hexane) (1.98 mL, 3.75 mmol, 3.5 equiv)) in dry THF (9 mL) was added 1-(4-(*tert*-butyl)phenyl)ethan-1-one-1-<sup>13</sup>C (189 mg, 1.07 mmol, 1 equiv) in dry THF (2 mL) dropwise at -78 °C. After stirring for 1 h, diethyl chlorophosphate (178  $\mu$ L, 1.23 mmol, 1.15 equiv) was added. The resulting mixture was gradually warmed to room temperature. After stirring for 1 h, the reaction mixture was added dropwise to the other 2/3 of the solution of LDA at -78 °C. The reaction mixture was warmed to room temperature over 3 h then the solution was cooled to 0 °C, quenched with saturated aq. NH<sub>4</sub>Cl (10 mL), and extracted with diethyl ether (3x). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100 % hexanes) to afford the desired product as a colorless oil (88 mg, 52% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.47-7.42 (m, 2H), 7.36 (d,  $J$  = 8.1 Hz, 2H), 3.03 (d,  $J$  = 49.5 Hz, 1H), 1.33 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 152.1 (d,  $J$  = 1.4 Hz), 131.8 (d,  $J$  = 1.7 Hz), 125.3 (d,  $J$  = 5.5 Hz), 119.0 (d,  $J$  = 89.5 Hz), 83.8 (<sup>13</sup>C-enriched), 74.3 (d,  $J$  = 172.0 Hz), 34.8, 31.1; Note that compound **S27** did not ionize under ESI or APCI-type conditions.

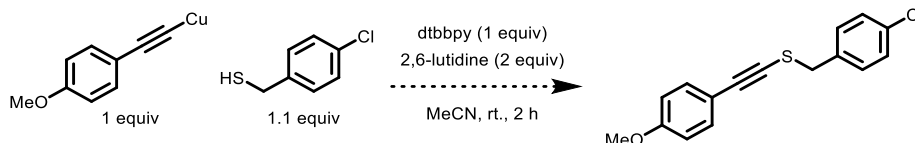


**1-(Bromoethynyl-1-<sup>13</sup>C)-4-(tert-butyl)benzene (9.S28):** Following Procedure A, 1-(tert-butyl)-4-(ethynyl-1-<sup>13</sup>C)benzene (88 mg, 0.56 mmol, 1.0 equiv.), NBS (109 mg, 0.61 mmol, 1.2 equiv.) and AgNO<sub>3</sub> (19 mg, 0.11 mmol, 20 mol%) were dissolved in acetone (47 mL) in a vial equipped with a stir bar. After purification by column chromatography on silica-gel (100 % hexanes), the desired product was obtained as a colorless semi-solid (131 mg, 99 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.41-7.37 (m, 2H), 7.34 (d, *J* = 8.0, 2H), 1.32 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 152.0 (d, *J* = 1.4 Hz), 131.7 (d, *J* = 1.9 Hz), 125.3 (d, *J* = 5.8 Hz), 119.7 (d, *J* = 92.6 Hz), 80.1 (<sup>13</sup>C-enriched), 48.6 (d, *J* = 202.7 Hz), 34.8, 31.1; Note that compound **S28** did not ionize under ESI or APCI-type conditions.



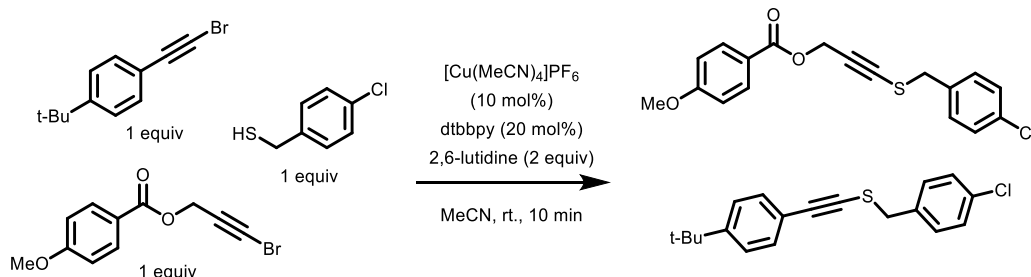
**((4-tert-Butyl)phenyl)ethynyl-2-<sup>13</sup>C(4-chlorobenzyl)sulfane (9.17):** Following Procedure C, the crude reaction mixture was purified by column chromatography on silica-gel (100 % hexanes → 2.5 % diethyl ether in hexanes) to afford the desired product as a white solid (60 mg, 80 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.36-7.29 (m, 8H), 3.96 (s, 2H), 1.32 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 151.6 (d, *J* = 1.4 Hz), 135.3, 133.6, 131.3 (d, *J* = 1.7 Hz), 130.4, 128.7, 125.3 (d, *J* = 5.5 Hz), 120.1 (d, *J* = 96.5 Hz), 95.1 (<sup>13</sup>C-enriched), 77.5 (d, *J* = 185.0 Hz), 39.7 (d, *J* = 2.6 Hz), 34.8, 31.1; HRMS (ESI) *m/z* calculated for C<sub>18</sub>[<sup>13</sup>C]H<sub>20</sub>ClS [M+H]<sup>+</sup> 316.1002; found 316.0998.

## REACTION BETWEEN COPPER-ACETYLIDE AND THIOL



The copper acetylide (46 mg, 0.237 mmol, 1.0 equiv.) (prepared following Evano's procedure : *Org. Lett.* **2013**, *15*,4592 – 4595) was added to a solution of the 4-chlorophenylmethanethiol (35.2  $\mu$ L, 0.261 mmol, 1.1 equiv.), dtbbpy (65 mg, 0.237 mmol, 1 equiv), 2,6-lutidine (55.3  $\mu$ L, 0.474 mmol, 2.0 equiv.) and degassed MeCN (4.6 mL) under nitrogen atmosphere in a 8 mL screw cap vial equipped with a stir bar. The reaction mixture was stirred for 2 h. After 2 h, a TLC analysis showed no formation of the desired alkynyl sulfide.

## ALKYL/ARYL BROMOALKYNE COMPETITION REACTION



Following Procedure C, both bromoalkynes (1 equiv.) and thiol (1 equiv.) were mixed with the ligand (20 mol%), base (2 equiv.) in degassed MeCN (0.05 M) under nitrogen atmosphere. Upon addition of the copper solution (20 mol%), the reaction mixture was stirred for 10 min. The crude reaction mixture was purified by column chromatography on silica-gel (2.5 %  $\rightarrow$  10 % diethyl ether in hexanes) to afford the desired alkyl alkynyl sulfide (38 % yield) and aryl alkynyl sulfide (32 % yield).

## COMPUTATIONAL DETAILS

The calculations were performed using DFT<sup>59,60</sup> with the M06<sup>61</sup> functional implemented in the Gaussian16<sup>62</sup> software. We used the default temperature and pressure given by the software,

<sup>59</sup> Kohn, W.; Sham, L. J., Self-Consistent Equations Including Exchange and Correlation Effects. *Physical Review* **1965**, *140* (4A), A1133-A1138.

<sup>60</sup> The Definition of the Model. In *A Chemist's Guide to Density Functional Theory*, pp 1-1.

<sup>61</sup> Zhao, Y.; Truhlar, D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theoretical Chemistry Accounts* **2008**, *120* (1), 215-241.

<sup>62</sup> Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.;

which are 298.15 K and 1 atm. All the structures geometry were first optimized using the 6-31+G(d,p) basis set<sup>63</sup> for the C H N S atoms and LANL2DZ<sup>64</sup> as a pseudopotential and basis set for the Cu and Br. Afterward, single point calculation was done on the optimized geometries using the def2tzvpp<sup>65,66</sup> basis set on every atom. To simulate the acetonitrile solvent environment, we used the solute molecule density (SMD)<sup>67</sup> universal solvation model and added D3 Grimme's<sup>68</sup> empirical dispersion interaction to the single point calculations. Since the gas phase standard state is different from the liquid phase standard state (1 mol of gas at 1 atm vs 1 mol/L), a correction of 1.89 kcal/mol ( $\text{corr}_{\text{gas/liq}}$ )<sup>67</sup> was added to the total Gibbs free energy ( $G_{\text{tot}}$ ) **Eq. (1)**. The minima were confirmed by doing frequency calculations on each optimized structure using the same method. The transition states were confirmed by getting the proper negative frequency associated with the reaction coordinate and by doing IRC calculation on each of them.<sup>69,70</sup>

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Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16 Rev. C.01*, Wallingford, CT, 2016.

<sup>63</sup> Hariharan, P. C.; Pople, J. A., The influence of polarization functions on molecular orbital hydrogenation energies. *Theoretica chimica acta* **1973**, *28* (3), 213-222.

<sup>64</sup> Hay, P. J.; Wadt, W. R., Ab initio effective core potentials for molecular calculations. Potentials for the transition metal atoms Sc to Hg. *The Journal of Chemical Physics* **1985**, *82* (1), 270-283.

<sup>65</sup> Weigend, F.; Ahlrichs, R., Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Physical Chemistry Chemical Physics* **2005**, *7* (18), 3297-3305.

<sup>66</sup> Weigend, F., Accurate Coulomb-fitting basis sets for H to Rn. *Physical Chemistry Chemical Physics* **2006**, *8* (9), 1057-1065.

<sup>67</sup> Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *The Journal of Physical Chemistry B* **2009**, *113* (18), 6378-6396.

<sup>68</sup> Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *The Journal of Chemical Physics* **2010**, *132* (15), 154104.

<sup>69</sup> Fukui, K., The path of chemical reactions - the IRC approach. *Accounts of Chemical Research* **1981**, *14* (12), 363-368.

<sup>70</sup> Hratchian, H. P.; Schlegel, H. B., Chapter 10 - Finding minima, transition states, and following reaction pathways on ab initio potential energy surfaces. In *Theory and Applications of Computational Chemistry*, Dykstra, C. E.; Frenking, G.; Kim, K. S.; Scuseria, G. E., Eds. Elsevier: Amsterdam, 2005; pp 195-249.

$$(1) \quad G_{tot} = G_{gas} + G_{SMD,MeCN} + G_{D3} + Corr_{gas/liq}$$

**CARTESIAN COODINATES AND ELECTRONIC ENERGIES (au) OF OPTIMIZED STRUCTURES**

**BrCCPh**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -2881.733964

0 1

C	1.26438500	-0.00007700	-0.00000300
C	0.05264400	-0.00007800	-0.00000100
Br	3.09681100	0.00001400	-0.00000500
C	-1.37442000	-0.00006300	0.00000200
C	-2.08315900	1.21067300	-0.00001900
C	-2.08323000	-1.21074700	0.00002500
C	-3.47266700	1.20633900	-0.00001500
H	-1.53094900	2.14756600	-0.00003700
C	-3.47275700	-1.20621900	0.00002800
H	-1.53109000	-2.14768300	0.00004000
C	-4.17074900	0.00010700	0.00000800
H	-4.01399600	2.14955300	-0.00003200
H	-4.01441800	-2.14924100	0.00004500
H	-5.25822000	-0.00029200	0.00001100

**BnSH**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -669.638237

0 1

C	-0.02729600	-0.00001100	0.48089500
C	0.64350600	1.19789500	0.26111600
C	1.96374400	1.19920200	-0.15731200
C	2.62686500	0.00001200	-0.36741000
C	1.96376000	-1.19918800	-0.15732800
C	0.64352100	-1.19790400	0.26110000
H	0.12174100	2.13477500	0.42590900
H	2.47727000	2.13907700	-0.31900100
H	2.47729800	-2.13905500	-0.31903000
H	0.12176800	-2.13479300	0.42588000
C	-1.45890900	-0.00002200	0.90200600
H	-1.69754300	0.88801700	1.48573700
H	-1.69754000	-0.88808400	1.48570300
S	-2.49396500	0.00000500	-0.61461300
H	-3.69042600	0.00005700	0.00319600
H	3.65972200	0.00002100	-0.69299900

**Lutidine**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -326.801352

0 1

C	1.15394000	0.26660800	0.00000000
C	1.19706200	-1.12961800	-0.00001000
C	0.00000000	-1.83392500	-0.00001600
C	-1.19706100	-1.12961800	-0.00001200
C	-1.15393900	0.26660800	-0.00000100
N	0.00000000	0.94387200	0.00000300
H	0.00000000	-2.92180000	-0.00002600
H	2.15405900	-1.64635800	-0.00001500
H	-2.15405900	-1.64635800	-0.00001800
C	2.40488800	1.08900900	0.00001100
H	3.30469900	0.46594200	-0.00003500
H	2.42885100	1.74181600	-0.87972600
H	2.42888800	1.74173400	0.87980900
C	-2.40488900	1.08900800	0.00001500
H	-2.42882500	1.74186000	-0.87968900
H	-3.30469900	0.46594100	-0.00008700
H	-2.42891500	1.74168700	0.87984600

**Lutidinium**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -327.264370

1 1

C	1.20758400	0.22560200	-0.00001200
C	1.20925700	-1.15827900	-0.00001800
C	0.00000000	-1.84775900	-0.00001100
C	-1.20925700	-1.15828000	0.00000000
C	-1.20758400	0.22560200	0.00000300
N	0.00000000	0.84843600	-0.00000300
H	0.00000000	-2.93455800	-0.00001500
H	2.15826200	-1.68479200	-0.00002800
H	-2.15826100	-1.68479300	0.00000400
C	2.42377900	1.07934000	0.00001700
H	3.32526900	0.46422600	-0.00027400
H	2.45385800	1.72421800	-0.88623500
H	2.45412000	1.72374700	0.88660400
C	-2.42377900	1.07934000	0.00000900
H	-2.45399300	1.72398400	-0.88641000
H	-3.32527000	0.46422600	0.00001200
H	-2.45398500	1.72398100	0.88642900
H	0.00000000	1.86730800	-0.00000100

**Lutidinium-Br**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -2901.507864

0 1



C	1.23979400	-1.19243300	0.00223500
C	2.62901600	-1.20710400	-0.00329700
C	3.32103200	-0.00002300	-0.00601700
C	2.62904100	1.20707400	-0.00326400
C	1.23982000	1.19243100	0.00225800
N	0.61367400	0.00000600	0.00507600
H	4.40844200	-0.00003500	-0.01044500
H	3.15187800	-2.15916600	-0.00560000
H	3.15192400	2.15912300	-0.00553900
C	0.38178500	-2.40720200	0.00592400
H	0.99297300	-3.31297700	-0.00599500
H	-0.27132000	-2.41536800	0.88655500
H	-0.29325100	-2.40563500	-0.85806600
C	0.38183600	2.40721800	0.00590900
H	-0.27159400	2.41521600	0.88630100
H	0.99304700	3.31298200	-0.00562300
H	-0.29288000	2.40584500	-0.85833100
H	-0.48019900	0.00001700	0.00582500
Br	-2.46624800	0.00000600	-0.00248800

### Lutidinium-PF<sub>6</sub>

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -1268.148511

0 1

C	-2.12462600	-1.19896100	-0.19733500
C	-3.42431300	-1.21840900	0.28751600
C	-4.07875800	-0.01423900	0.52678100
C	-3.43869800	1.19912600	0.29511900
C	-2.13945200	1.19781900	-0.19118100
N	-1.56402900	0.00356900	-0.43777100
H	-5.09601000	-0.02143400	0.91011100
H	-3.90357700	-2.17214100	0.48472700
H	-3.92911300	2.14590600	0.49834600
C	-1.27904900	-2.39367100	-0.44815000
H	-1.83024400	-3.31290300	-0.24003400
H	-0.92676500	-2.41521400	-1.48584700
H	-0.38007100	-2.35520100	0.18187400
C	-1.31028200	2.40406400	-0.44295600
H	-1.00958500	2.45881500	-1.49568000
H	-1.85561100	3.31341600	-0.18251700
H	-0.38169600	2.35406100	0.14177200
H	-0.57274800	0.01177500	-0.75311900
P	2.04072300	0.00073100	0.10776500
F	0.68680100	-0.08845900	1.05541300
F	2.98392100	-0.05827800	1.39845700
F	2.00926200	-1.61733500	-0.01919800
F	0.98840200	0.06271900	-1.22862300

F	1.93722000	1.62032900	0.18392900
F	3.28259900	0.09242300	-0.90003000

**bpy**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -495.203038

0 1

C	-0.00195700	0.74330200	-0.00453600
C	-0.39729700	2.68301700	-1.14908800
C	-0.03404000	3.47781500	-0.06370700
C	0.36759500	2.84163400	1.10431500
C	0.38358300	1.45316100	1.13790700
C	0.00195700	-0.74330200	-0.00453600
C	0.39729700	-2.68301700	-1.14908800
C	0.03404000	-3.47781500	-0.06370700
C	-0.36759500	-2.84163400	1.10431500
C	-0.38358300	-1.45316100	1.13790700
H	-0.71877700	3.14562500	-2.08282900
H	-0.06322900	4.56137600	-0.13919400
H	0.67291300	3.41691500	1.97529900
H	0.71723400	0.92355200	2.02730100
H	0.71877700	-3.14562500	-2.08282900
H	0.06322900	-4.56137600	-0.13919400
H	-0.67291300	-3.41691500	1.97529900
H	-0.71723400	-0.92355200	2.02730100
N	-0.38358300	1.35290500	-1.13284600
N	0.38358300	-1.35290500	-1.13284600

**[bpy<sub>2</sub>Cu]<sup>+</sup>**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -2630.864231

1 1

Cu	0.00000000	0.00000200	-0.00000200
C	-2.80496900	-0.64276000	-0.37073000
C	-3.97183400	-1.35057000	-0.66011800
C	-3.88318000	-2.54929400	-1.35708800
C	-2.63309100	-3.01716800	-1.74649900
C	-1.51709800	-2.25883500	-1.41495900
C	-2.80497000	0.64276100	0.37072200
C	-3.97183600	1.35057000	0.66010900
C	-3.88318400	2.54929400	1.35708000
C	-2.63309600	3.01716900	1.74649200
C	-1.51710200	2.25883700	1.41495300
H	-4.94112600	-0.98454000	-0.33538300
H	-4.78267200	-3.11348700	-1.58867400
H	-2.52014600	-3.94825500	-2.29332900
H	-0.51454700	-2.58128800	-1.69394300
H	-4.94112800	0.98453900	0.33537300

H	-4.78267700	3.11348600	1.58866500
H	-2.52015300	3.94825700	2.29332200
H	-0.51455200	2.58129100	1.69393800
N	-1.59747600	1.10348100	0.74933600
N	-1.59747400	-1.10347800	-0.74934200
C	2.80497000	0.64276000	-0.37072200
C	3.97183700	1.35056700	-0.66010800
C	3.88318600	2.54929100	-1.35707900
C	2.63310000	3.01716600	-1.74649300
C	1.51710500	2.25883500	-1.41495500
C	2.80496800	-0.64276200	0.37073100
C	3.97183200	-1.35057100	0.66012100
C	3.88317700	-2.54929500	1.35709200
C	2.63308800	-3.01716800	1.74650100
C	1.51709600	-2.25883500	1.41495900
H	4.94112800	0.98453700	-0.33537000
H	4.78268000	3.11348300	-1.58866300
H	2.52015700	3.94825400	-2.29332300
H	0.51455500	2.58128900	-1.69394200
H	4.94112600	-0.98454200	0.33538700
H	4.78266900	-3.11348800	1.58867900
H	2.52014200	-3.94825600	2.29333100
H	0.51454400	-2.58128800	1.69394200
N	1.59747800	1.10347900	-0.74933800
N	1.59747300	-1.10347900	0.74934200

**[bpy<sub>2</sub>Cu<sup>I</sup>]PF<sub>6</sub>**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -3571.748413

0 1

Cu	1.28263900	-0.77646800	0.23029200
C	3.87259700	0.50953600	-0.08620100
C	5.24456600	0.69323000	-0.27313900
C	6.08775600	-0.40924600	-0.27400800
C	5.54568100	-1.67700700	-0.08859100
C	4.17248400	-1.78072200	0.08901200
C	2.90460100	1.63420800	-0.06331300
C	3.27103700	2.97026900	-0.21591000
C	2.27816200	3.94638300	-0.17823200
C	0.95700800	3.56969700	0.02291400
C	0.67111000	2.21507900	0.17728100
H	5.65356000	1.68867400	-0.41786500
H	7.15733500	-0.27872100	-0.41816500
H	6.16766800	-2.56705200	-0.08076500
H	3.69774500	-2.74928400	0.23739500
H	4.30785900	3.25814500	-0.36545200
H	2.54211600	4.99354900	-0.30509200

H	0.14675200	4.29180000	0.05280900
H	-0.34436500	1.86334200	0.34462900
N	1.62212200	1.28139300	0.12372300
N	3.35508700	-0.72334900	0.09234900
C	-1.29067500	-1.77511300	1.04594400
C	-2.45836600	-1.96121800	1.78527600
C	-2.48221100	-1.58409400	3.11921300
C	-1.34157100	-1.03123700	3.68987200
C	-0.21550100	-0.88813700	2.89140500
C	-1.20147800	-2.08230700	-0.40212600
C	-2.26896000	-2.61176300	-1.12674400
C	-2.13070700	-2.80509300	-2.49269400
C	-0.92740900	-2.47794000	-3.10746800
C	0.09259000	-1.96914900	-2.31599900
H	-3.35669100	-2.34805800	1.31744900
H	-3.39300800	-1.69975600	3.70069500
H	-1.32427200	-0.70360100	4.72503200
H	0.70244800	-0.45465000	3.28661200
H	-3.21463800	-2.82999600	-0.64349300
H	-2.96330500	-3.19227700	-3.07404900
H	-0.78293000	-2.59840200	-4.17693200
H	1.05274000	-1.69036900	-2.74819700
N	-0.18368800	-1.26015300	1.61023200
N	-0.03559300	-1.78099400	-1.00142500
P	-3.07772900	1.31366900	-0.39952100
F	-3.87660000	1.58421500	-1.77695800
F	-4.28355400	1.95104900	0.46738300
F	-3.75912200	-0.17211300	-0.27493900
F	-1.83231800	0.65120900	-1.24468700
F	-2.35334100	2.77528300	-0.50281600
F	-2.23611100	1.02132000	0.99053200

**[bpy<sub>2</sub>Cu<sup>I</sup>BrCCPH]<sup>+</sup> (A)**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -5512.612446

1 1

Cu	0.27684400	0.17288200	-0.05994200
C	3.21649900	0.18211600	0.88055900
C	2.16021600	-1.27631600	2.31409600
C	4.46203200	-0.37679300	1.17540400
C	3.05936300	1.27751200	-0.10679600
C	3.35622800	-1.88853400	2.67244900
H	1.21301900	-1.61531500	2.73791900
C	4.52876000	-1.42523100	2.08490100
H	5.36201400	-0.02413200	0.67902600
C	4.10253300	2.14895800	-0.42182400
H	3.36379600	-2.70867700	3.38413700

H	5.48543800	-1.88306400	2.32272600
C	1.64871100	2.36620100	-1.58229900
C	3.89051400	3.15103400	-1.36033300
H	5.06190900	2.06258900	0.08049100
C	2.64038600	3.26362000	-1.95776900
H	0.64496100	2.41731600	-2.00302500
H	4.69062300	3.84165800	-1.61368500
H	2.43026900	4.03336300	-2.69402900
C	0.42100400	-1.73727900	-0.76065700
C	-0.69590600	-1.77533300	-0.22751500
Br	1.96032900	-2.40150900	-1.55084100
N	2.08610800	-0.26544900	1.44785500
N	1.84995400	1.39632800	-0.68527500
C	-2.04291800	-1.88441100	0.24095600
C	-3.05147000	-2.28330500	-0.65021100
C	-2.37535800	-1.59370500	1.57349600
C	-4.36844400	-2.37297100	-0.21583800
C	-3.69348100	-1.68447900	1.99906200
C	-4.69335300	-2.06874200	1.10495200
C	-2.49969400	1.35360600	-0.66723100
C	-1.69782500	0.72212900	-2.73110200
C	-2.97608700	0.66495200	-3.27829300
C	-4.05467900	0.96033900	-2.45137200
C	-3.81793400	1.30208800	-1.12543400
C	-2.16532000	1.69966500	0.73636900
C	-0.60879900	1.57107200	2.44481600
C	-1.43907600	2.24479000	3.33136300
C	-2.68283500	2.66774600	2.87389400
C	-3.04753400	2.39978700	1.56089900
H	-0.82025900	0.48057200	-3.33429700
H	-3.11781200	0.39095800	-4.31967300
H	-5.07245400	0.91243200	-2.83026900
H	-4.65007600	1.49592100	-0.45382100
H	0.38090700	1.22261500	2.74144900
H	-1.11221000	2.43745800	4.34868600
H	-3.35877200	3.21097400	3.52928000
H	-4.00177700	2.74842000	1.17662500
N	-1.46023600	1.06465800	-1.46502800
N	-0.96159800	1.29955300	1.18464500
H	-1.59182000	-1.28916200	2.26498900
H	-3.94310700	-1.45967700	3.03333400
H	-5.72440600	-2.14246100	1.44197700
H	-2.78886700	-2.52266400	-1.67850900
H	-5.14419100	-2.68660400	-0.91018900

**bpyCu<sup>I</sup>BnS (B)**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -2804.831024

0 1

Cu	-0.85225100	-0.54578200	-1.24768900
C	1.48134400	1.15786100	-0.48460500
C	-0.17312300	2.59929000	-1.19097500
C	2.15788200	2.19086100	0.16709800
C	1.93764200	-0.25388100	-0.44432700
C	0.44306500	3.69104700	-0.58580100
H	-1.12315600	2.69731400	-1.71729400
C	1.63169500	3.47555100	0.10433600
H	3.06160100	1.99778100	0.73932100
C	3.21197200	-0.62388200	-0.01184200
H	-0.00514700	4.67871200	-0.64710600
H	2.13734500	4.29742500	0.60564800
C	1.36843200	-2.47108500	-0.78875200
C	3.55027200	-1.96984800	0.03248100
H	3.93728100	0.13117800	0.27743700
C	2.61222800	-2.91821300	-0.36107500
H	0.59223300	-3.16829300	-1.10122500
H	4.53877500	-2.27401200	0.36782600
H	2.83310700	-3.98112900	-0.33895100
S	-3.05079000	-0.45588600	-1.22791100
N	0.34218100	1.37300100	-1.15388200
N	1.03946900	-1.17740100	-0.83256800
C	-3.28173500	-0.76186000	0.58762100
H	-4.12232600	-0.13577500	0.91257600
H	-3.56817300	-1.80966700	0.74102300
C	-2.06151000	-0.44592400	1.39417600
C	-1.73312200	0.87809300	1.71426400
C	-1.19666200	-1.46191500	1.81639000
C	-0.56785500	1.17737200	2.41173400
H	-2.39733600	1.67631500	1.38123700
C	-0.02625800	-1.16720400	2.51357000
H	-1.44264300	-2.49626500	1.57180500
C	0.29582800	0.15527700	2.81080900
H	-0.33013500	2.21366500	2.64840400
H	0.63543900	-1.97375300	2.82741400
H	1.20892900	0.38990300	3.35597900

C‡

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -8317.446960

1 1

Cu	-3.06318514	-1.90705232	1.32396137
C	-5.51170115	-0.40671812	0.54585700
C	-5.24739758	-0.46698459	2.84190158
C	-6.54930921	0.51931313	0.66618367

C	-5.05691785	-0.92683846	-0.76985935
C	-6.27933153	0.44096074	3.04583931
H	-4.69958108	-0.90476462	3.67557409
C	-6.93378069	0.94920186	1.93030180
H	-7.04817734	0.91428670	-0.21387408
C	-5.76146323	-0.69520618	-1.95506088
H	-6.55104915	0.74428917	4.05237269
H	-7.73681188	1.67359789	2.03988112
C	-3.45483532	-2.13818103	-1.90762591
C	-5.27492864	-1.22229816	-3.14455579
H	-6.68692289	-0.12702668	-1.95538819
C	-4.09077362	-1.95264772	-3.13043682
H	-2.52109114	-2.70051058	-1.83811990
H	-5.81428902	-1.05972773	-4.07429697
H	-3.66985733	-2.37067327	-4.04019939
C	-1.18651237	-1.20536602	1.04914793
C	-1.33166461	-0.02993579	1.46045874
Br	0.06434870	-2.28160053	0.14437417
N	-4.86580025	-0.87405330	1.62956348
N	-3.92989846	-1.65474611	-0.75990758
C	-1.96024406	1.11182803	2.04656482
C	-2.95152674	1.80001015	1.33240978
C	-1.60283972	1.55401909	3.33029365
C	-3.58869323	2.89425011	1.90286973
H	-3.19570720	1.47978596	0.32003720
C	-2.25072156	2.64279401	3.89792269
H	-0.79072654	1.05061617	3.85375825
C	-3.24989856	3.31207390	3.18855935
H	-4.34782808	3.42756438	1.33302219
H	-1.96356590	2.98740093	4.88861806
H	-3.74699317	4.17171045	3.63198060
C	4.77847129	-1.76405300	0.41855325
C	6.01808871	-2.14736746	-0.09299264
C	6.51561433	-1.48904372	-1.21163480
C	5.76996613	-0.46533105	-1.78480253
H	6.12587211	0.07586371	-2.65626611
C	4.54857606	-0.13748951	-1.20535594
H	3.93049814	0.66609229	-1.60435013
N	4.06313567	-0.77249725	-0.13817761
C	4.16455845	-2.40171902	1.60890203
N	3.11518594	-1.75263022	2.14516007
C	2.48606301	-2.28019847	3.19831541
C	2.88480842	-3.47349574	3.78731620
C	3.97586430	-4.14568488	3.24726098
C	4.62030357	-3.60874343	2.14071567
H	5.45597202	-4.13434251	1.68799517

Cu	2.41682121	-0.11708633	1.09744154
S	1.01619118	1.54650924	0.89168062
C	-0.52997425	2.00779402	-1.37382760
C	-1.01656655	3.30213823	-1.15659589
C	-2.30405658	3.65563939	-1.54633095
H	-2.66129535	4.66897719	-1.37360438
C	-3.13454217	2.71618668	-2.15890828
H	-4.13875087	2.99315751	-2.47579178
C	-2.66089898	1.42443081	-2.37679919
H	-3.29374569	0.68748143	-2.86903583
C	-1.37092096	1.07397006	-1.98343479
H	-1.00215819	0.06178252	-2.15839400
H	-0.37259894	4.03272209	-0.66730482
C	0.85892993	1.63376950	-0.95770773
H	1.13232723	0.66825400	-1.40147438
H	1.57566420	2.38710921	-1.31055408
H	7.48155136	-1.76801024	-1.62457866
H	6.60159400	-2.93112097	0.38167978
H	1.62799398	-1.71969099	3.57419090
H	2.35088204	-3.86451144	4.64886337
H	4.31757297	-5.08417022	3.67621619
C	-1.94852355	-3.57514589	3.68900690
C	-2.14880031	-1.51875900	4.68611674
C	-1.07956918	-1.75948837	5.54524522
C	-0.42527475	-2.98111609	5.44700197
C	-0.85959339	-3.90262645	4.50061856
C	-2.45573775	-4.52451572	2.66836096
C	-3.48801864	-4.81830247	0.62560351
C	-3.43413885	-6.20270273	0.72917774
C	-2.86543462	-6.75463952	1.87114256
C	-2.37208619	-5.90568001	2.85341865
H	-2.67947777	-0.56584647	4.72946485
H	-0.77726156	-1.00818682	6.26987190
H	0.41286429	-3.21311776	6.10147000
H	-0.34881141	-4.85526138	4.37989934
H	-3.93559210	-4.33864199	-0.24430636
H	-3.83750747	-6.82607542	-0.06311469
H	-2.81740520	-7.83259303	2.00236702
H	-1.95370897	-6.30991850	3.77131809
N	-2.58015293	-2.39471455	3.77930457
N	-3.01409290	-3.99572964	1.56553800

## D

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -8317.472034

1 1

Cu	-2.99192681	-1.84723170	1.20539359
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C	-5.68431963	-0.91028921	0.24399272
C	-5.61913513	-1.08524674	2.54645408
C	-6.99300290	-0.42604766	0.28801438
C	-4.95448131	-1.10638241	-1.03179274
C	-6.91763614	-0.60560039	2.67592175
H	-5.02060066	-1.36731252	3.41294468
C	-7.61515341	-0.26991123	1.52079660
H	-7.52929310	-0.20201295	-0.63026068
C	-5.27040320	-0.38406978	-2.18526785
H	-7.36656663	-0.50306433	3.65944522
H	-8.63650279	0.09833598	1.57592505
C	-3.24960698	-2.20518573	-2.11844452
C	-4.53106331	-0.60516375	-3.34135472
H	-6.06416999	0.35921574	-2.17401007
C	-3.49886701	-1.53702347	-3.31385660
H	-2.44149850	-2.93474796	-2.04508285
H	-4.75240214	-0.04836748	-4.24901743
H	-2.89753758	-1.74295495	-4.19485513
C	-1.29549146	-0.95370904	0.86099785
C	-0.77513563	0.25685675	1.14323677
Br	-0.05655669	-2.22910175	-0.21315432
N	-5.01452147	-1.23164851	1.36517281
N	-3.95253543	-1.99994174	-1.00396039
C	-1.62169508	1.21893977	1.89997738
C	-2.97092530	1.39100019	1.57033401
C	-1.09940560	1.96201474	2.96700066
C	-3.78215505	2.25350522	2.30050048
H	-3.37396557	0.85086536	0.71725606
C	-1.90745158	2.82916217	3.69616162
H	-0.04791305	1.85436153	3.23155567
C	-3.25585081	2.97497145	3.37028203
H	-4.82651643	2.37423770	2.01460902
H	-1.48198890	3.39637614	4.52143115
H	-3.88521954	3.65787385	3.93617006
C	4.77322617	-2.12555943	0.26018614
C	6.06359148	-2.43142880	-0.17308505
C	6.51062654	-1.92887912	-1.38856500
C	5.66119709	-1.13176719	-2.14673791
H	5.96934253	-0.72098258	-3.10316821
C	4.39376466	-0.86443646	-1.64513838
H	3.69120985	-0.24258504	-2.19807958
N	3.95976888	-1.34413065	-0.47677946
C	4.21079612	-2.63795666	1.53684759
N	2.98274812	-2.19620335	1.85468637
C	2.38713917	-2.62946071	2.96609447
C	2.99885826	-3.52148922	3.83922307

C	4.27424512	-3.97853801	3.52611539
C	4.88873136	-3.53751497	2.36058537
H	5.87788592	-3.90215606	2.10114493
Cu	2.14452880	-0.91636853	0.41506285
S	0.84842693	0.92721094	0.68668658
C	-0.72990201	2.29698458	-1.16794658
C	-0.71980086	3.60972101	-0.68625485
C	-1.86377880	4.39570674	-0.75301560
H	-1.84482034	5.41424090	-0.37281282
C	-3.03397097	3.87790180	-1.30796982
H	-3.92875834	4.49360983	-1.36322331
C	-3.05232877	2.57232521	-1.78927997
H	-3.96366817	2.16046172	-2.21996854
C	-1.90706628	1.78218192	-1.71481874
H	-1.92746650	0.75174390	-2.07605318
H	0.19251361	4.00937872	-0.24290542
C	0.48897009	1.44087149	-1.06842197
H	0.39010525	0.52768051	-1.66579086
H	1.39939559	1.97314577	-1.37227354
H	7.51381664	-2.15846716	-1.73786425
H	6.72143403	-3.05074777	0.42873957
H	1.38259601	-2.24384056	3.15294066
H	2.48744583	-3.84962974	4.73967530
H	4.78767486	-4.67828127	4.18044432
C	-1.99942159	-3.19224248	3.79447223
C	-2.25816267	-0.99110356	4.41009762
C	-1.20114210	-1.05618742	5.31454844
C	-0.53294171	-2.26705756	5.45450026
C	-0.93234698	-3.35299644	4.68114239
C	-2.45081299	-4.29319835	2.90861811
C	-3.40002776	-4.87191185	0.88594912
C	-3.30705396	-6.23078998	1.16559864
C	-2.76453989	-6.61572079	2.38683371
C	-2.32925226	-5.63587028	3.27076199
H	-2.80799250	-0.05811011	4.26745278
H	-0.91952337	-0.17850797	5.89028362
H	0.29503776	-2.36333216	6.15417918
H	-0.41044802	-4.30536304	4.74793031
H	-3.82304509	-4.50928932	-0.05176610
H	-3.65932931	-6.96367181	0.44573070
H	-2.68924609	-7.66703905	2.65319265
H	-1.92721185	-5.90874563	4.24323454
N	-2.65249951	-2.02645463	3.66951535
N	-2.98802314	-3.92685258	1.73292853

E‡

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -8317.455429

l 1

Cu	-2.79544738	-1.95714817	0.73419526
C	-5.48729465	-0.71978342	0.24301594
C	-5.15432401	-1.08040007	2.50329129
C	-6.62970598	0.03907338	0.51022822
C	-5.01603781	-0.99881353	-1.13777177
C	-6.28756298	-0.35383339	2.84887267
H	-4.52426217	-1.55630585	3.25356347
C	-7.02874056	0.22847040	1.82728115
H	-7.21202850	0.47618123	-0.29514466
C	-5.67873195	-0.51103919	-2.26678908
H	-6.57292465	-0.24697734	3.89128378
H	-7.91636810	0.81568192	2.04891111
C	-3.44750236	-2.05573509	-2.46148490
C	-5.18677751	-0.81989804	-3.52905097
H	-6.56844313	0.10500695	-2.17394380
C	-4.05004807	-1.61131671	-3.63445912
H	-2.53785188	-2.65596883	-2.48939854
H	-5.68874393	-0.44517305	-4.41744531
H	-3.62929627	-1.87895366	-4.59903579
C	-1.36286410	-0.75865734	0.83836230
C	-0.70298125	0.36315620	1.05846924
Br	-0.07736235	-2.51227592	-1.38208708
N	-4.75669106	-1.24804454	1.24049277
N	-3.91345068	-1.76020928	-1.24549104
C	-1.28997639	1.25249513	2.09591950
C	-2.66805021	1.49861700	2.13141719
C	-0.46803259	1.81502827	3.08129256
C	-3.21449400	2.27572158	3.14940640
H	-3.30292624	1.10264709	1.33995827
C	-1.01823476	2.59540350	4.09157387
H	0.60862417	1.65188731	3.04264965
C	-2.39489737	2.82039958	4.13458002
H	-4.28534382	2.46940350	3.15824341
H	-0.37016196	3.03830205	4.84447744
H	-2.82181519	3.43569612	4.92287359
C	4.37108636	-2.23231649	0.73244729
C	5.65306554	-2.77592874	0.64723358
C	6.11689466	-3.21122699	-0.58899392
C	5.29020242	-3.10260288	-1.70161035
H	5.61413454	-3.43639034	-2.68277471
C	4.02073397	-2.56100439	-1.52876741
H	3.32150368	-2.46925946	-2.35951882
N	3.57876336	-2.13037889	-0.34717755
C	3.78431535	-1.75100752	2.00716246

N	2.44953785	-1.57521805	2.01389671
C	1.85572238	-1.13434470	3.12502037
C	2.55533628	-0.83688846	4.28828611
C	3.93547635	-1.00924298	4.28789850
C	4.55756885	-1.47489957	3.13611884
H	5.63706341	-1.59271185	3.10968778
Cu	1.56111763	-1.59921177	0.11067614
S	0.80117603	0.81899371	0.20040700
C	-1.13096761	2.14855904	-1.31622385
C	-1.01229448	3.49185384	-0.94583266
C	-2.14303871	4.28416129	-0.78390154
H	-2.03690710	5.32823123	-0.49927781
C	-3.41112237	3.74076914	-0.98862671
H	-4.29571280	4.36138546	-0.86534965
C	-3.53862629	2.40442937	-1.35739578
H	-4.52578299	1.97422313	-1.52410764
C	-2.40462339	1.61025350	-1.51826295
H	-2.50234822	0.55923404	-1.79519581
H	-0.02137035	3.91286610	-0.77507108
C	0.07593634	1.28009767	-1.44938419
H	-0.13883628	0.33908597	-1.97093155
H	0.90691605	1.78944559	-1.95200596
H	7.11137070	-3.64080522	-0.67822506
H	6.27551850	-2.88212708	1.53129936
H	0.77153389	-1.01575883	3.07155852
H	2.02501291	-0.47259678	5.16479213
H	4.52501908	-0.77617445	5.17092639
C	-1.66717192	-3.61232513	3.21576477
C	-1.96389334	-1.58204006	4.25300778
C	-0.94280131	-1.82539813	5.16681261
C	-0.25115170	-3.02803309	5.06663783
C	-0.60463601	-3.92868353	4.06940671
C	-2.11251379	-4.55640053	2.15914699
C	-3.10389382	-4.86676758	0.09833577
C	-2.96287248	-6.24688819	0.16812028
C	-2.37363428	-6.78892288	1.30320166
C	-1.94534490	-5.93432477	2.31063575
H	-2.51417487	-0.63719085	4.28034145
H	-0.70015749	-1.08582133	5.92625101
H	0.56634445	-3.25837025	5.74643471
H	-0.05060170	-4.85528284	3.94477660
H	-3.56392331	-4.39394876	-0.76848164
H	-3.31175550	-6.87357737	-0.64690140
H	-2.25550173	-7.86426547	1.40908756
H	-1.50905402	-6.33613960	3.22089501
N	-2.33078176	-2.45193624	3.31213084

N -2.69610936 -4.03881187 1.06336845

**F**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -8317.492820

1 1

C	-4.64635867	0.17198739	0.34985816
C	-5.96701112	0.55884130	0.12344138
H	-6.38716396	0.53826553	-0.87747559
C	-6.75563182	0.95445296	1.19637083
C	-6.20780286	0.94878521	2.47155703
C	-4.88592026	0.54734507	2.61543344
N	-4.12454474	0.16463097	1.58926798
C	-3.75162842	-0.24692027	-0.75808271
N	-2.62074507	-0.87460642	-0.40415163
C	-1.77056660	-1.26454243	-1.35266769
C	-1.99716474	-1.06773595	-2.71061084
C	-3.16768051	-0.41488296	-3.08453194
C	-4.05316780	0.00812246	-2.10092522
H	-4.95524355	0.54568780	-2.37838986
C	0.79565212	-0.81712925	1.26814066
C	-0.21336197	0.02515538	1.42015876
Br	-2.65722583	3.29949260	1.87033870
Cu	-2.09250778	-0.22451312	1.89716089
C	1.38427482	3.63812303	0.46585646
C	2.54426483	4.41207970	0.55559273
C	3.22454718	4.47329820	1.76559432
C	2.73814091	3.76320932	2.85889765
H	3.24009388	3.78895795	3.82159098
C	1.58155019	3.01176067	2.68416397
H	1.15481398	2.42590219	3.50098068
N	0.93059310	2.95074428	1.52435199
C	0.58036608	3.52160856	-0.77799079
N	-0.46832253	2.68680128	-0.72409382
C	-1.26549850	2.55976049	-1.78153014
C	-1.04456257	3.23559188	-2.97565545
C	0.04668071	4.09356502	-3.04872518
C	0.86629568	4.24565897	-1.93684817
H	1.70668082	4.93224480	-1.97577546
Cu	-0.88479434	1.79468366	1.17885719
S	1.66136675	-0.31450727	-0.22363203
C	4.06324802	-0.57316428	1.22250258
C	4.84054932	-1.52586403	0.55716432
C	5.59256555	-2.44851061	1.27506933
H	6.19959601	-3.18087164	0.74801139
C	5.57164033	-2.43237546	2.66970512
H	6.15975821	-3.15414927	3.23144016

C	4.80260670	-1.48538047	3.34017986
H	4.78330726	-1.46820934	4.42768393
C	4.05553187	-0.55861550	2.61798441
H	3.44957370	0.18323940	3.14081255
H	4.84912105	-1.54314045	-0.53301859
C	3.22797476	0.39894845	0.45808478
H	2.94671515	1.26408621	1.06967152
H	3.73877144	0.76733696	-0.44134874
H	-4.40372663	0.54526139	3.59134155
H	-6.78158899	1.25777271	3.33960681
H	-7.78569092	1.26089649	1.03433018
H	-0.86067241	-1.76149932	-1.00571496
H	-1.27637367	-1.41206281	-3.44644380
H	-3.38688065	-0.22741648	-4.13306608
H	4.12753827	5.07198061	1.85307092
H	2.91896473	4.96173240	-0.30273912
H	-2.12066778	1.89436724	-1.65645316
H	-1.71858395	3.09923280	-3.81663737
H	0.25390836	4.65097034	-3.95854274
C	1.12664942	-2.02148092	2.04189539
C	1.54747555	-3.19524295	1.41024438
C	0.99326935	-2.00115327	3.43539130
C	1.79972062	-4.33985559	2.15932064
H	1.68099369	-3.20226751	0.32915074
C	1.24538334	-3.14643337	4.18077424
H	0.70984905	-1.06943694	3.92814791
C	1.64348984	-4.32107494	3.54427491
H	2.12693783	-5.24908367	1.66051529
H	1.14501442	-3.11832072	5.26466280
H	1.84939021	-5.21541495	4.12767932
C	-1.95919676	-1.11823834	4.83656881
C	-1.76453149	1.18616763	4.81407603
C	-1.42365315	1.22297091	6.16341706
C	-1.34782030	0.02076850	6.85838575
C	-1.61930300	-1.16795091	6.19045925
C	-2.21371772	-2.34229887	4.03713653
C	-2.30788707	-3.27553633	1.92461607
C	-2.51107619	-4.55233298	2.43405997
C	-2.60066492	-4.70172186	3.81317389
C	-2.45456240	-3.58467127	4.62528780
H	-1.85102324	2.09689356	4.21331831
H	-1.22685303	2.17334115	6.65107081
H	-1.07621141	0.00512571	7.91102433
H	-1.54232790	-2.11717671	6.71372537
H	-2.60800481	-5.40016351	1.76280345
H	-2.78330214	-5.67830674	4.25417536

H	-2.53462668	-3.68056096	5.70428772
N	-2.02240484	0.04461312	4.17158371
N	-2.16489400	-2.20176233	2.70193917
H	-2.25871534	-3.09187925	0.85161156

**G‡**

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -3607.561163

1 1

C	3.32833100	0.71061500	0.41802500
C	2.01710200	1.35793400	2.20779700
C	3.12677800	1.72034500	2.96271100
C	4.38722500	1.57245300	2.39368900
C	4.49107700	1.06504000	1.10458100
C	3.35272100	0.15798500	-0.95790400
C	2.13456400	-0.28098500	-2.86696900
C	3.22591600	-0.86402900	-3.50248800
C	4.42984300	-0.92713900	-2.80873600
C	4.49737500	-0.41057700	-1.52027100
H	1.00075300	1.46901500	2.58773300
H	3.00058300	2.11778500	3.96549600
H	5.28083800	1.85935900	2.94229500
H	5.46478700	0.96942000	0.63194200
H	1.16853100	-0.20616400	-3.36747900
H	3.13041300	-1.25648100	-4.51056800
H	5.30765000	-1.37987800	-3.26299900
H	5.42349100	-0.47343700	-0.95469800
Cu	0.43567600	0.46404700	-0.23850400
C	-0.81562600	-0.94702000	-0.75993300
C	-2.06338900	-1.20200800	-0.76965700
S	-0.45100700	-2.48802100	-1.75382500
C	0.01866100	-3.62420500	-0.38650600
H	-0.89988500	-3.91750900	0.13627000
H	0.39404200	-4.50815200	-0.91907800
C	1.03437400	-3.07659400	0.56305000
C	0.64349300	-2.63906900	1.83114500
C	2.38545600	-3.01323800	0.21207000
C	1.58419700	-2.16414500	2.74076800
H	-0.41013300	-2.68789800	2.10881800
C	3.32781100	-2.54539400	1.12212900
H	2.69919000	-3.34446800	-0.77899500
C	2.93057700	-2.12344000	2.38989300
H	1.26839900	-1.83606800	3.72954700
H	4.38082500	-2.52215900	0.84639800
H	3.67073800	-1.76586800	3.10282200
N	2.19340300	0.22024400	-1.63267200
N	2.11306700	0.86255700	0.97217900

C	-3.46041100	-1.38981200	-0.68399100
C	-4.31344500	-0.75455500	-1.60625600
C	-4.00472800	-2.18670000	0.34147400
C	-5.68708300	-0.90604500	-1.49256300
H	-3.87775700	-0.14489900	-2.39463600
C	-5.37872700	-2.34381200	0.43884600
H	-3.33408000	-2.66667600	1.05186500
C	-6.21666300	-1.70028800	-0.47384900
H	-6.34968600	-0.41481100	-2.20008800
H	-5.80272600	-2.96428900	1.22396100
H	-7.29410400	-1.82357800	-0.39336000
C	-1.38543000	2.93915300	-0.11129400
C	0.40742300	3.23900200	-1.53147900
C	-0.01889800	4.51123400	-1.89595500
C	-1.18913500	5.00087300	-1.32689700
C	-1.88244900	4.20585400	-0.42222700
C	-2.07061100	2.05097000	0.85952400
C	-1.85337100	0.42606100	2.46664400
C	-3.22945100	0.35003100	2.66475700
C	-4.04803400	1.17184300	1.89720800
C	-3.46303100	2.03865100	0.98168800
H	1.31758500	2.80603600	-1.94827500
H	0.55719600	5.10005000	-2.60355900
H	-1.55277500	5.99483100	-1.57482300
H	-2.78263800	4.57494000	0.06274500
H	-1.17259800	-0.20799300	3.03933400
H	-3.64489000	-0.33714500	3.39721800
H	-5.12979900	1.13278100	2.00286100
H	-4.07893100	2.67524900	0.35061400
N	-0.25512300	2.46838200	-0.66543500
N	-1.28108400	1.24810700	1.58768700

### BnSCCPh (H)

EE SMD(MeCN)-[M06-D3/def2tzvpp] = -976.721231

0 1

S	0.85255900	-1.10059800	0.06561100
C	-0.77895700	-0.67127700	0.04047200
C	-1.96824500	-0.40491100	0.02597700
C	1.62460500	0.58450800	-0.04908900
H	1.26996400	1.04487600	-0.97698100
H	1.26309900	1.16843300	0.80358200
C	3.11010000	0.42770000	-0.03235300
C	3.81711700	0.25053700	-1.22399700
C	3.80654400	0.41227800	1.17846000
C	5.19718400	0.07569000	-1.20744500
H	3.27585400	0.25002100	-2.16970100



C	5.18653200	0.23763900	1.19773000
H	3.25684100	0.53790200	2.11086300
C	5.88448500	0.07057600	0.00397900
H	5.73750700	-0.05619800	-2.14185200
H	5.71852200	0.23245000	2.14609400
H	6.96335900	-0.06445200	0.01785700
C	-3.35852300	-0.10036700	0.00807800
C	-4.31107500	-1.13146000	0.03375100
C	-3.79829000	1.23214100	-0.03564800
C	-5.66726700	-0.83225900	0.01604200
H	-3.97234300	-2.16420500	0.06747100
C	-5.15667400	1.52113600	-0.05406100
H	-3.06250500	2.03269200	-0.05502300
C	-6.09638800	0.49269100	-0.02819500
H	-6.39500700	-1.64012600	0.03647300
H	-5.48425700	2.55761100	-0.08837200
H	-7.15887400	0.72283600	-0.04239100

### bpyCu<sup>I</sup>Br

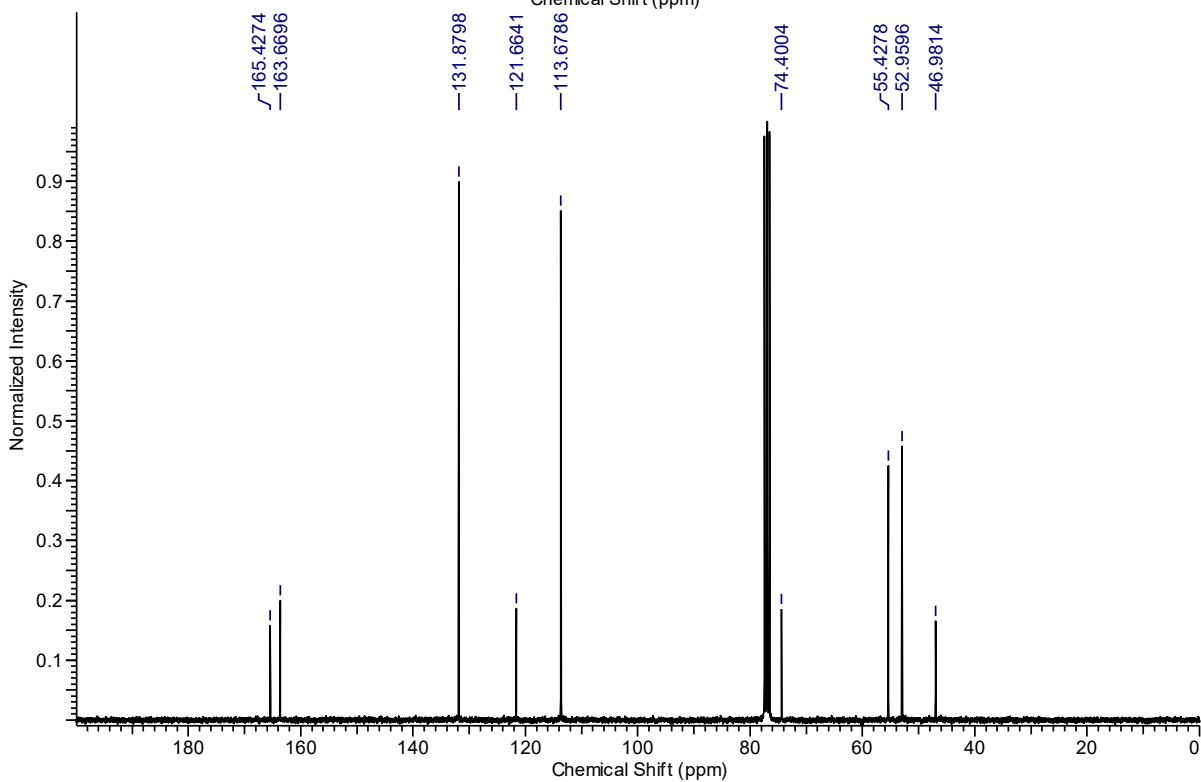
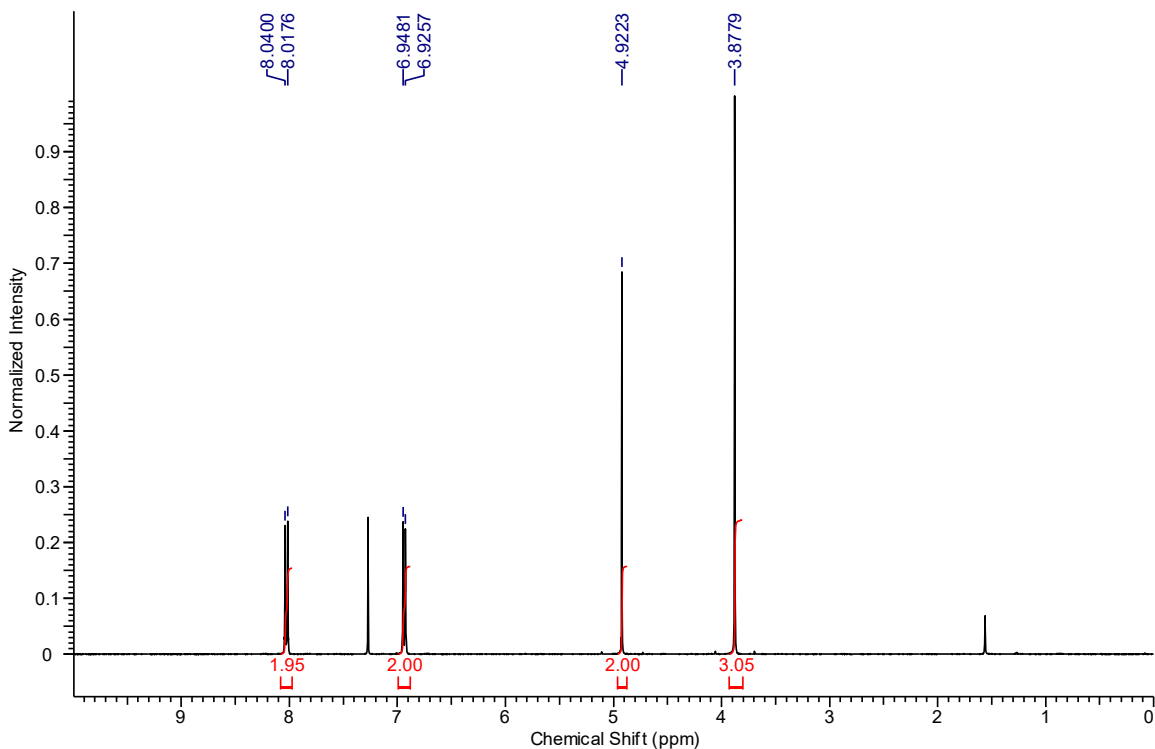
EE SMD(MeCN)-[M06-D3/def2tzvpp] = -4709.882646

0 1

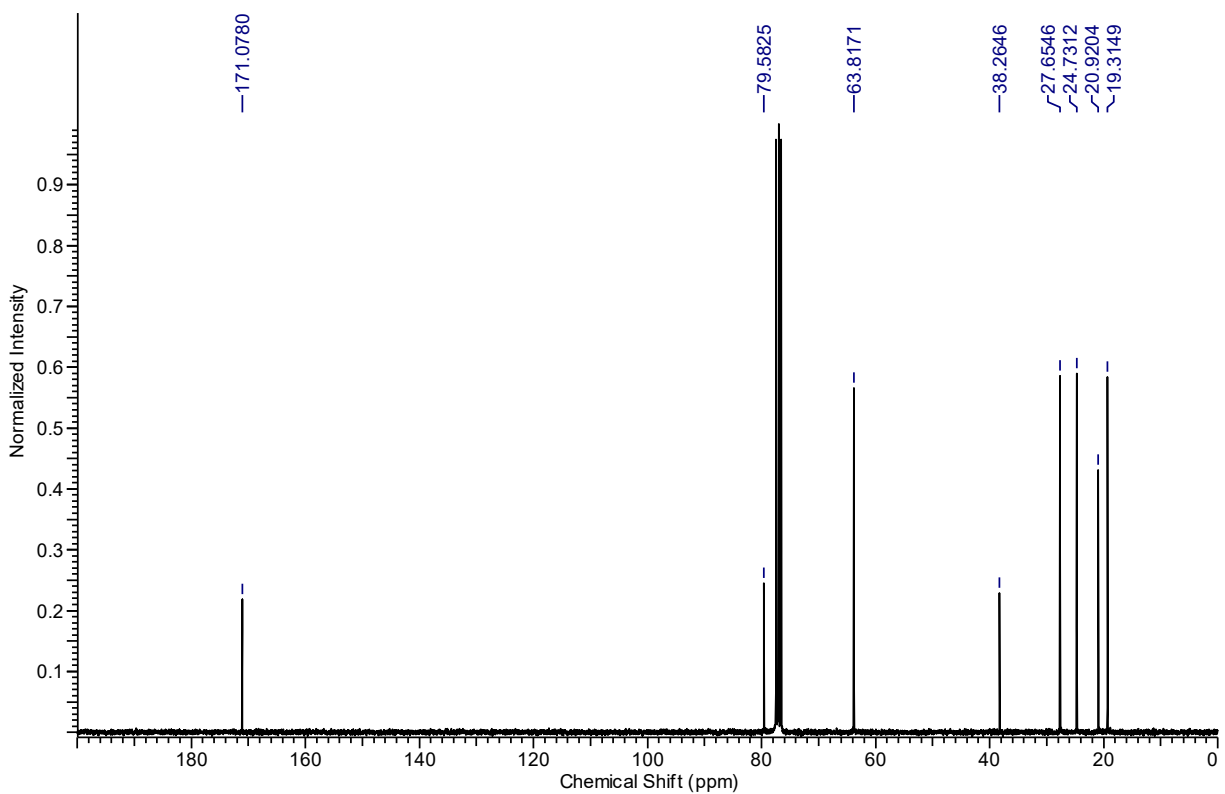
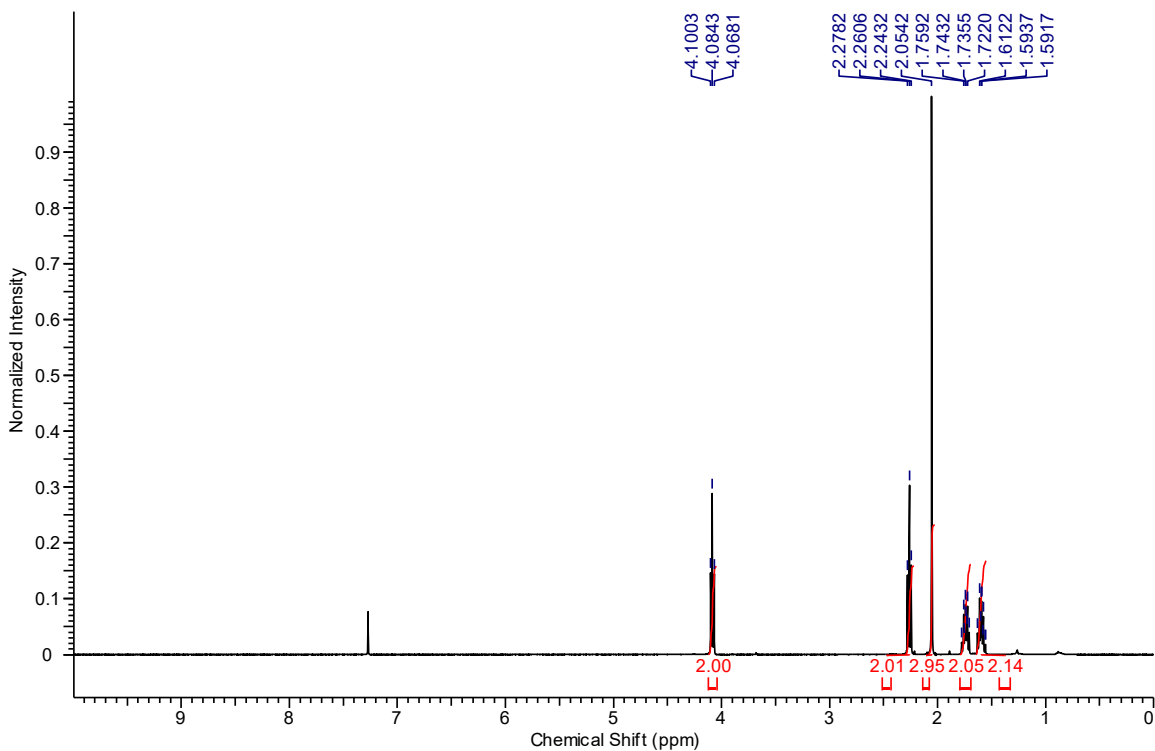
Br	3.25137200	-0.26418400	-0.00078400
Cu	0.95673500	-0.47794800	-0.00002700
C	-1.62099000	1.02367200	0.00032900
C	0.08857500	2.58064500	0.00693200
C	-0.80834000	3.64569000	0.00122100
C	-2.16833000	3.35712600	-0.00564900
C	-2.58730200	2.03088200	-0.00630700
C	-1.94844500	-0.42661600	0.00032800
C	-1.12176800	-2.59177900	-0.00288700
C	-2.39776100	-3.14125900	-0.00024200
C	-3.48503900	-2.27538600	0.00317900
C	-3.25885500	-0.90495300	0.00353300
H	1.16846200	2.73287400	0.01186800
H	-0.44683000	4.66979400	0.00183600
H	-2.90310200	4.15852700	-0.01080300
H	-3.64856400	1.79917300	-0.01262000
H	-0.23487700	-3.22246800	-0.00543900
H	-2.52756900	-4.21916500	-0.00067000
H	-4.50146100	-2.66088400	0.00577600
H	-4.09961400	-0.21789300	0.00694800
N	-0.31426700	1.31351300	0.00666100
N	-0.90005500	-1.27367600	-0.00256300

# NMR DATA FOR ALL NEW COMPOUNDS

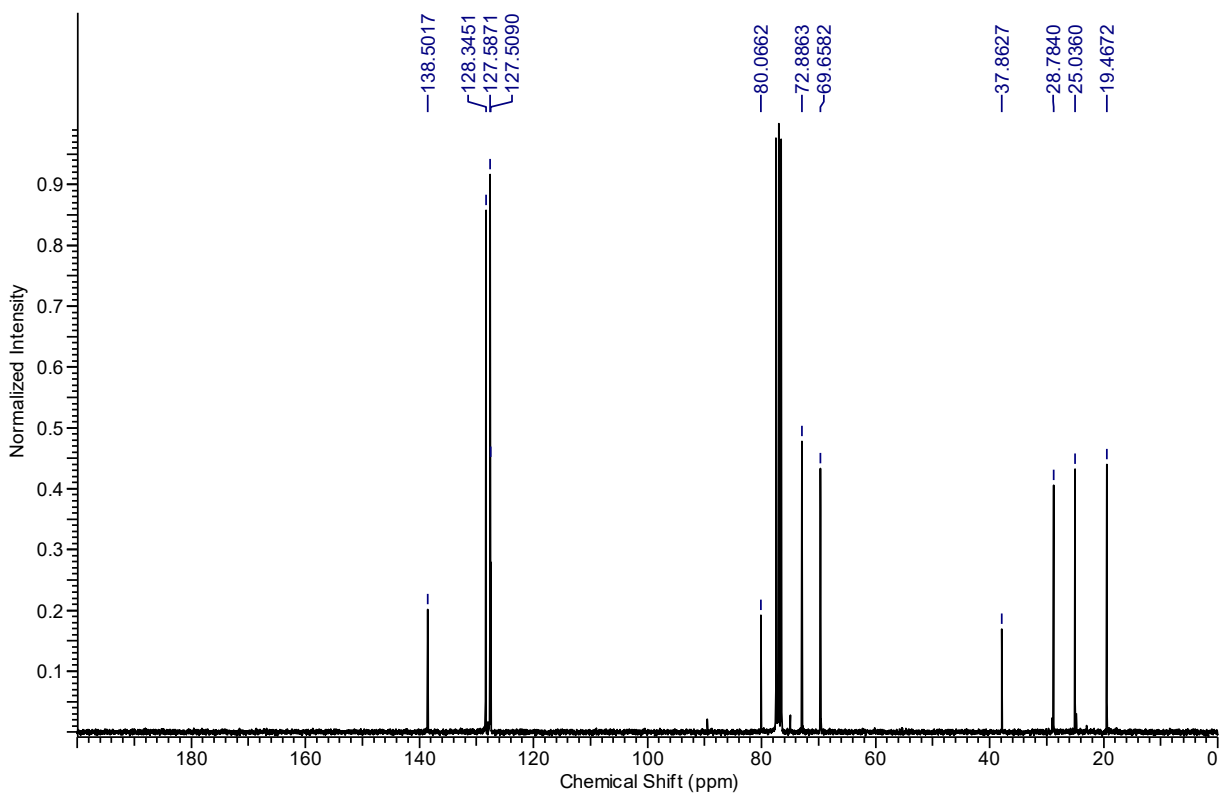
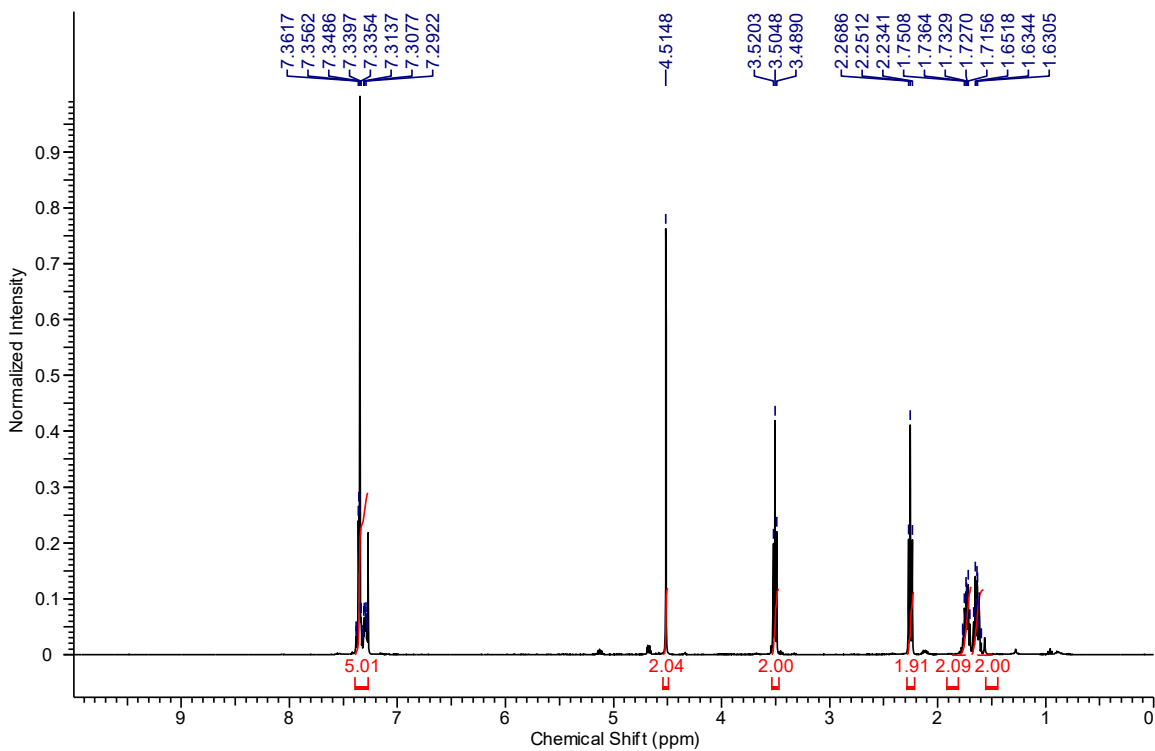
## 3-Bromoprop-2-yn-1-yl 4-methoxybenzoate (9.S1):



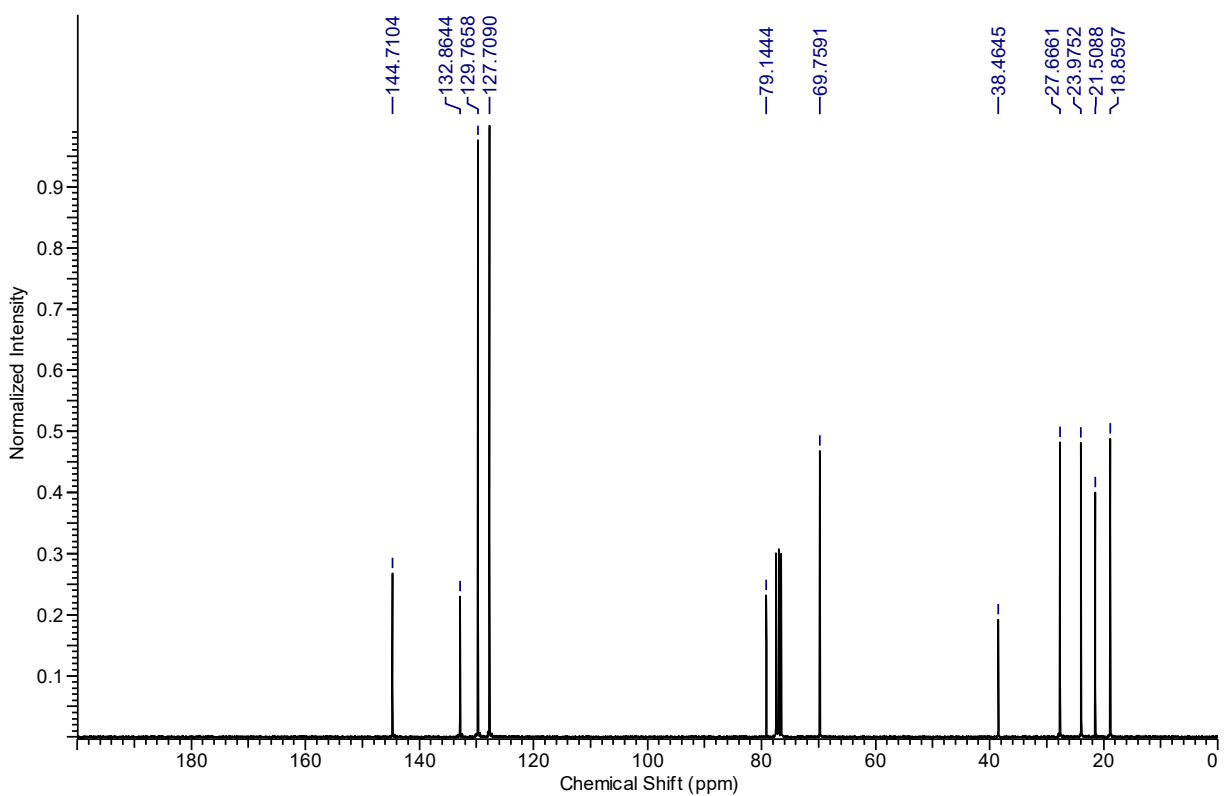
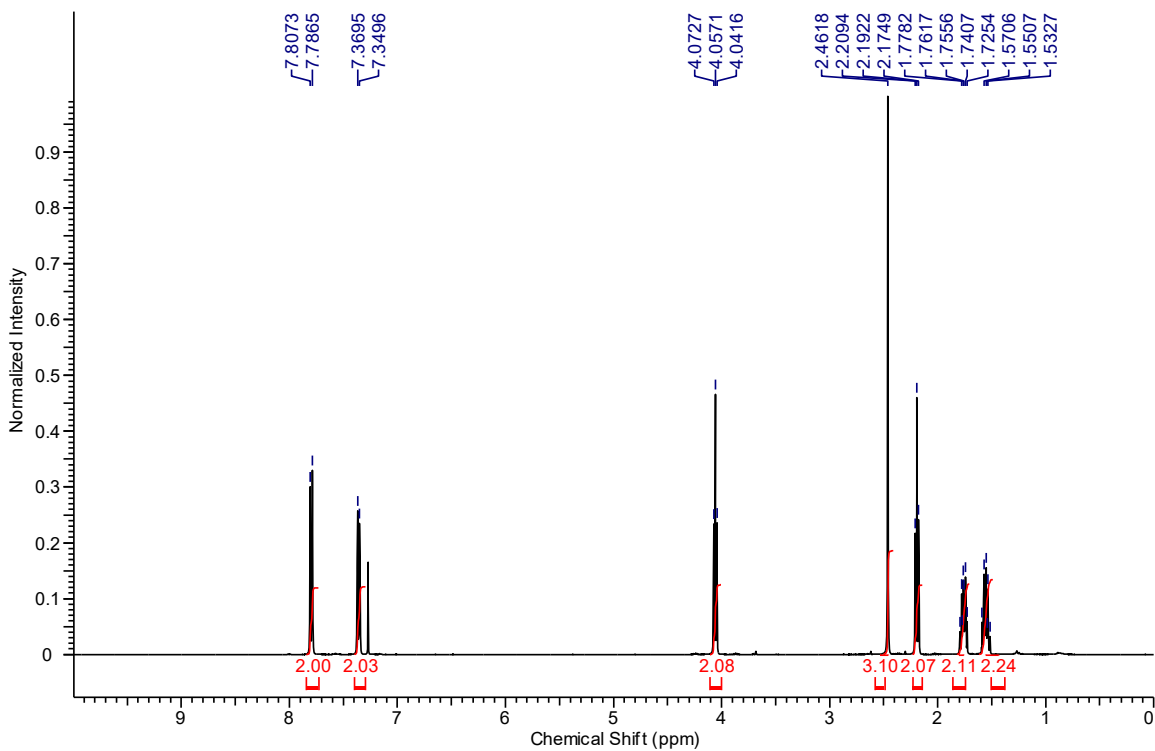
**6-Bromohex-5-yn-1-yl acetate (9.S2):**



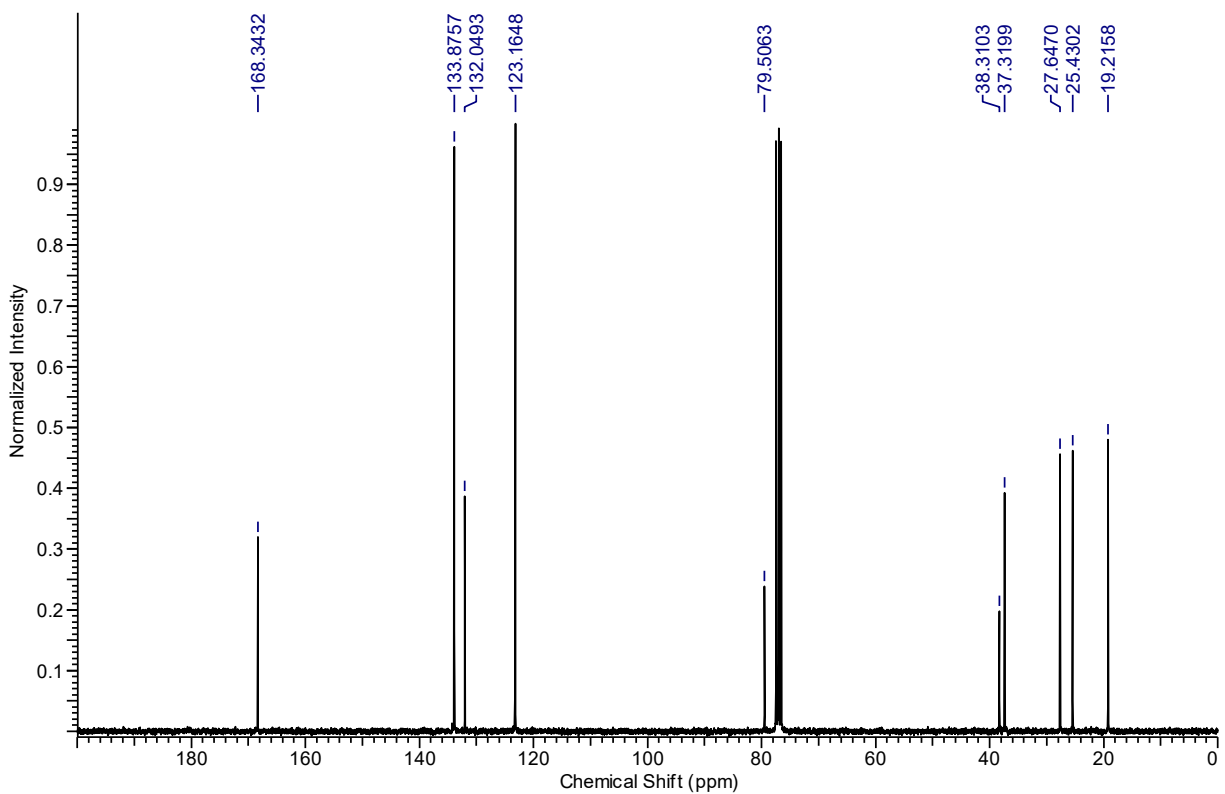
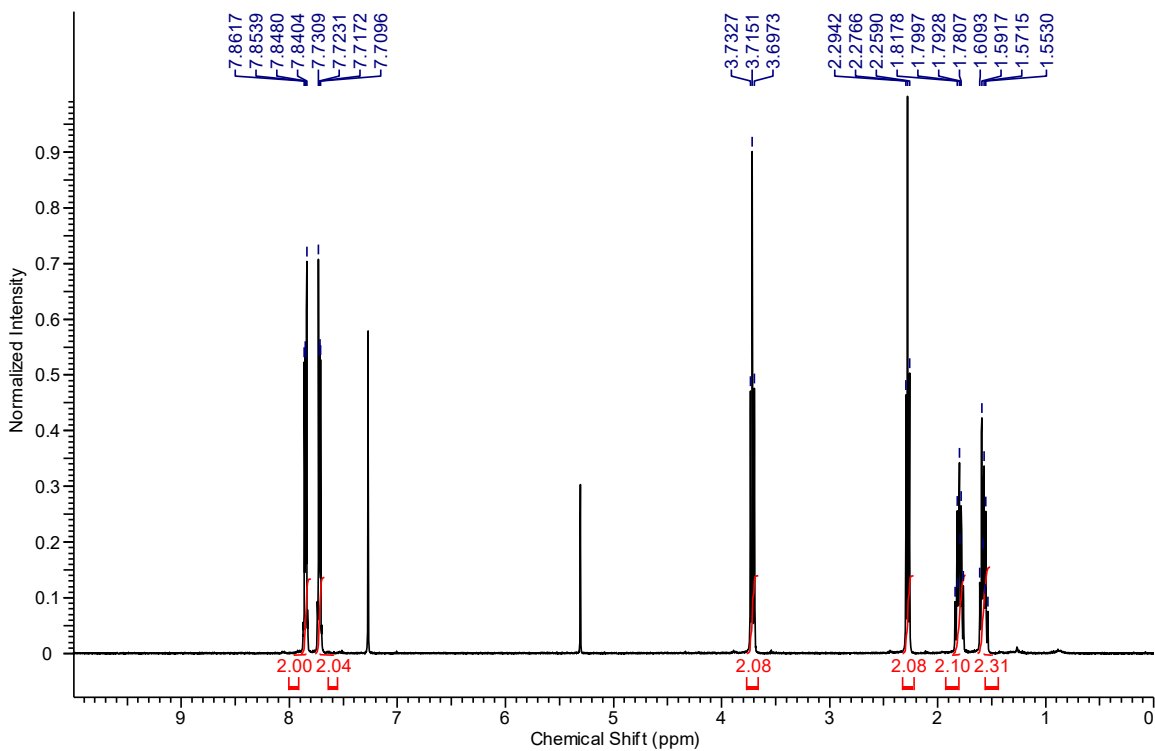
**(((6-Bromohex-5-yn-1-yl)oxy)methyl)benzene (9.S3):**



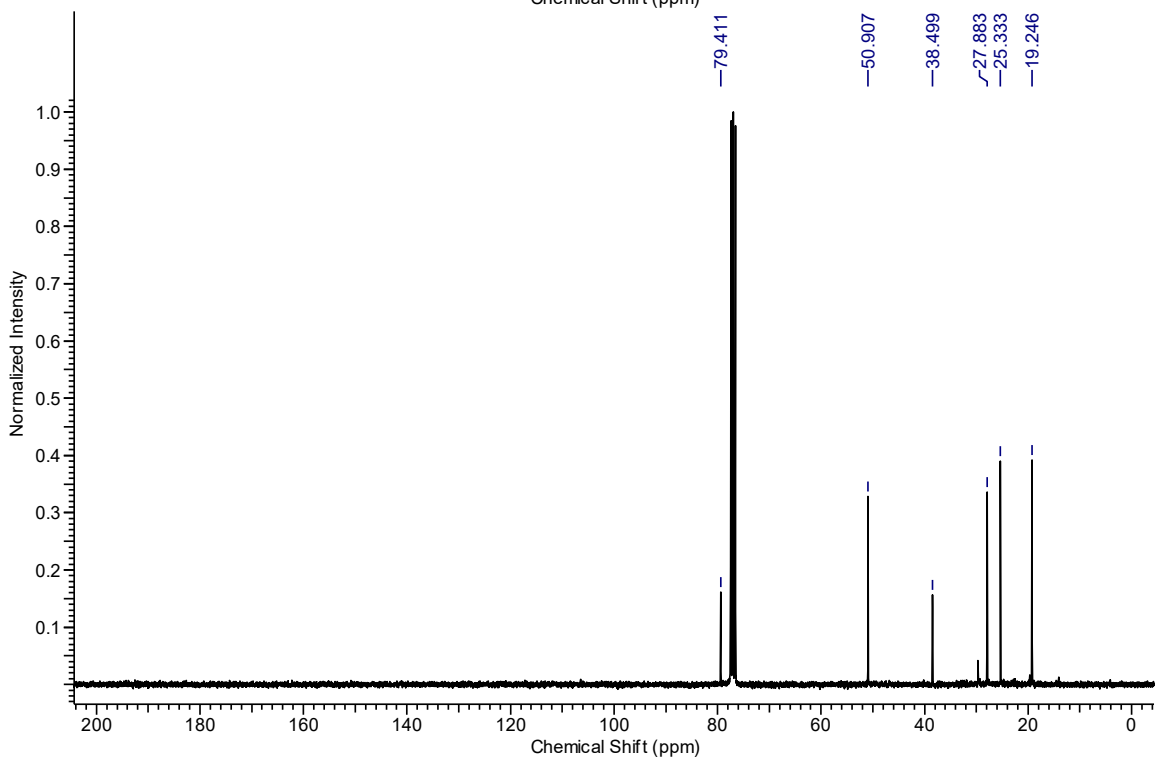
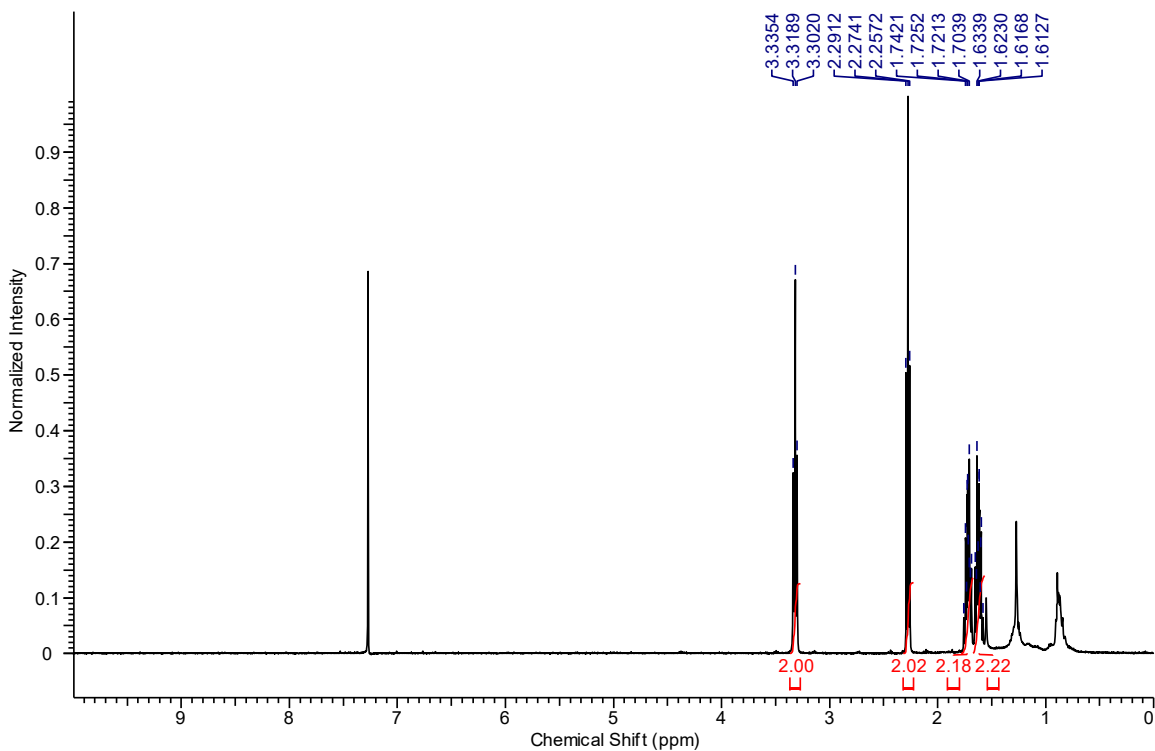
**6-Bromohex-5-yn-1-yl 4-methylbenzenesulfonate (9.S4):**



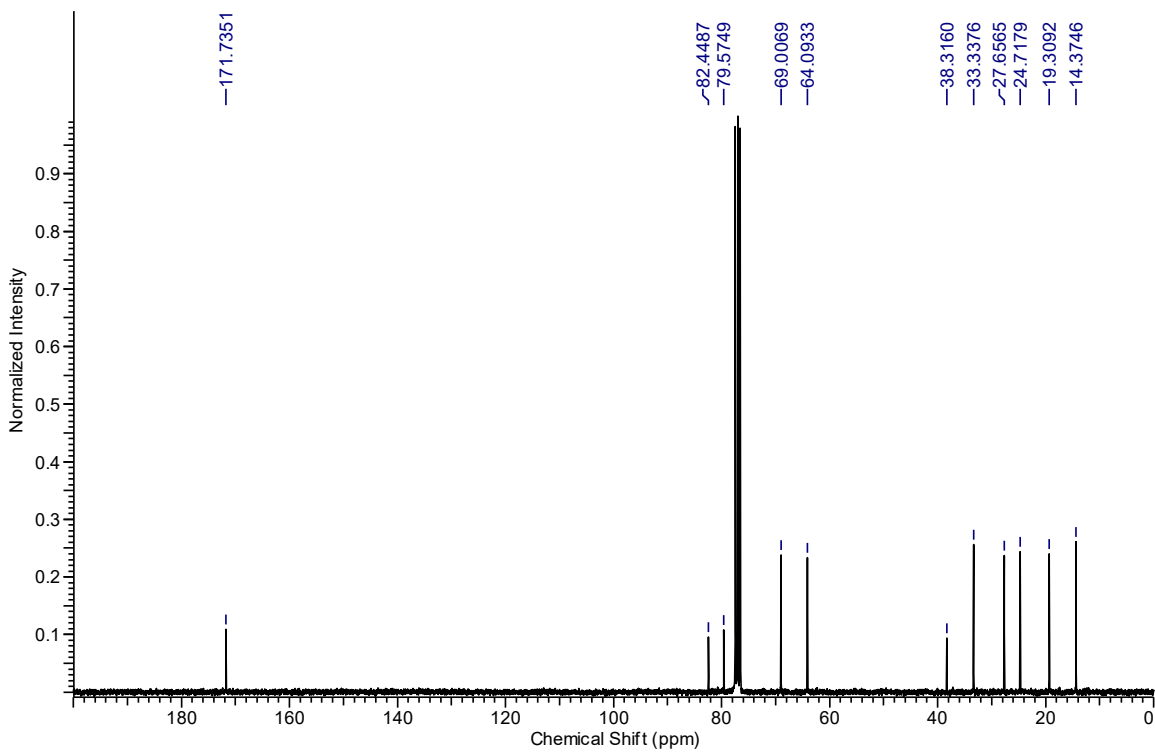
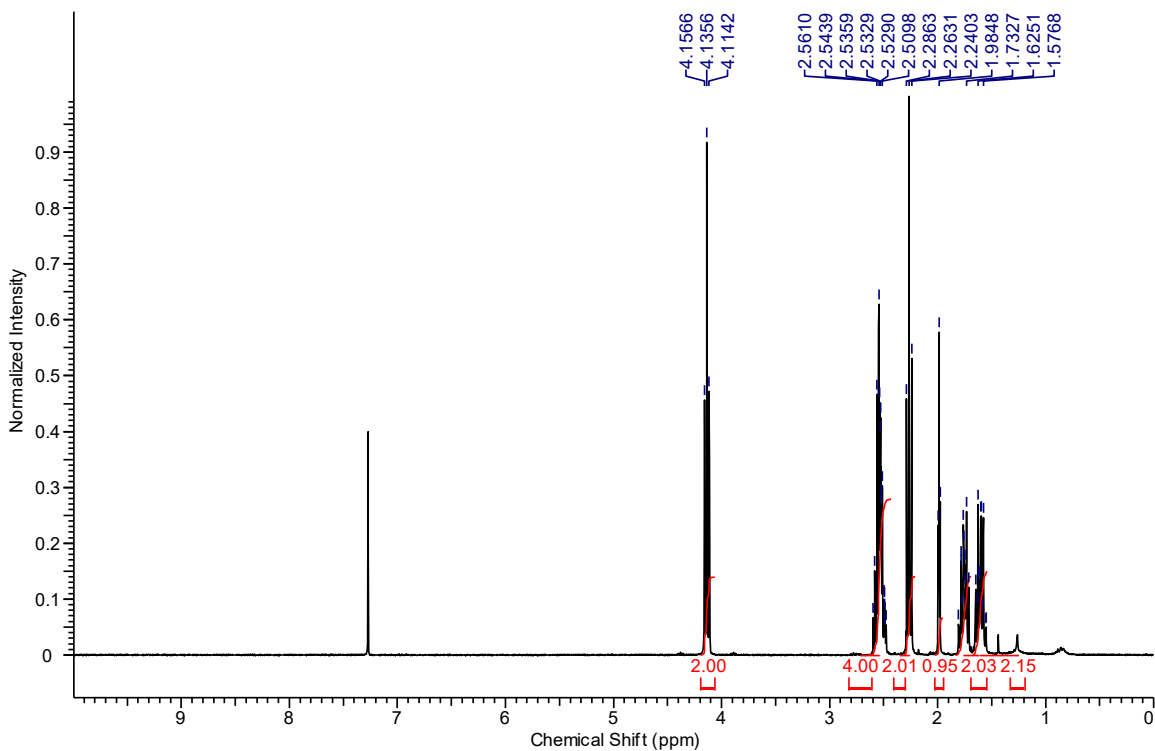
**2-(6-Bromohex-5-yn-1-yl)isoindoline-1,3-dione (9.S6):**



**6-Azido-1-bromohex-1-yne (9.S7):**

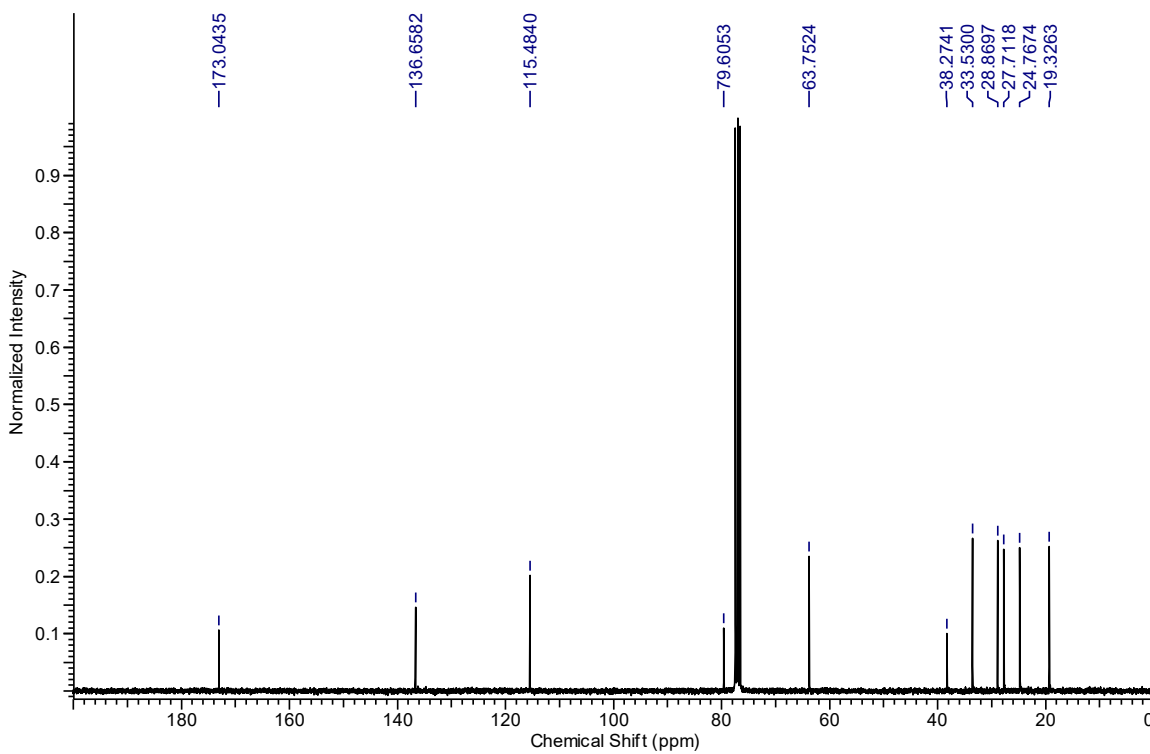
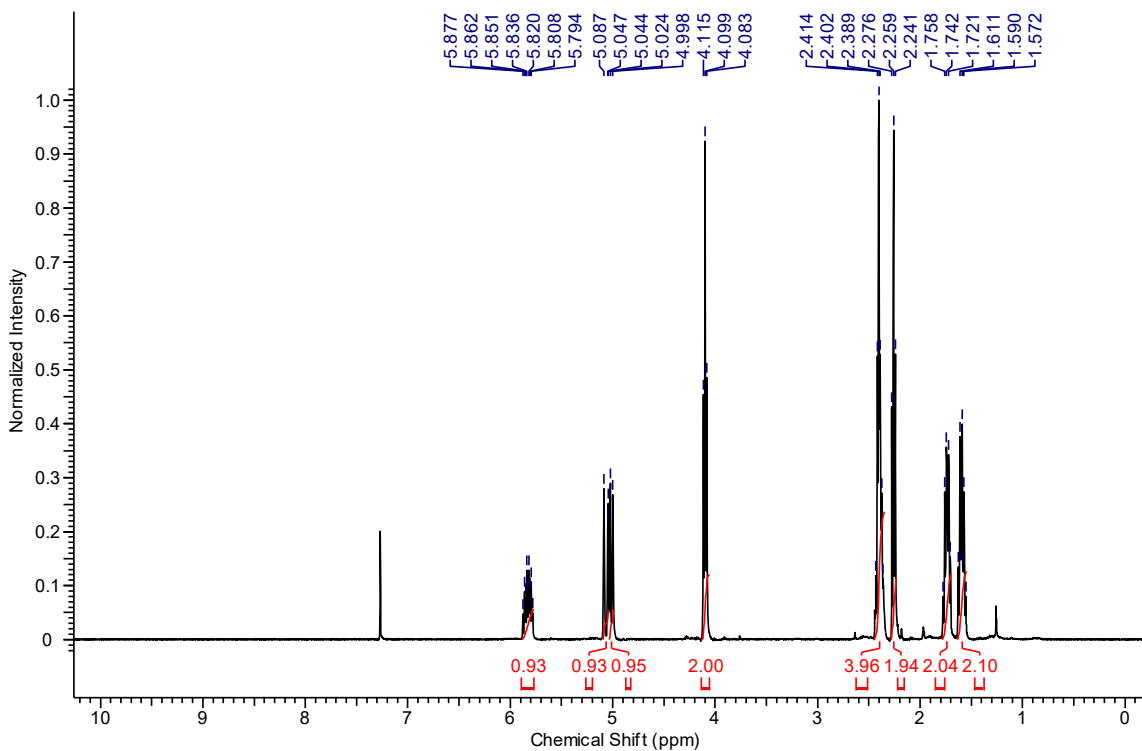


**6-Bromohex-5-yn-1-yl pent-4-ynoate (9.S8):**

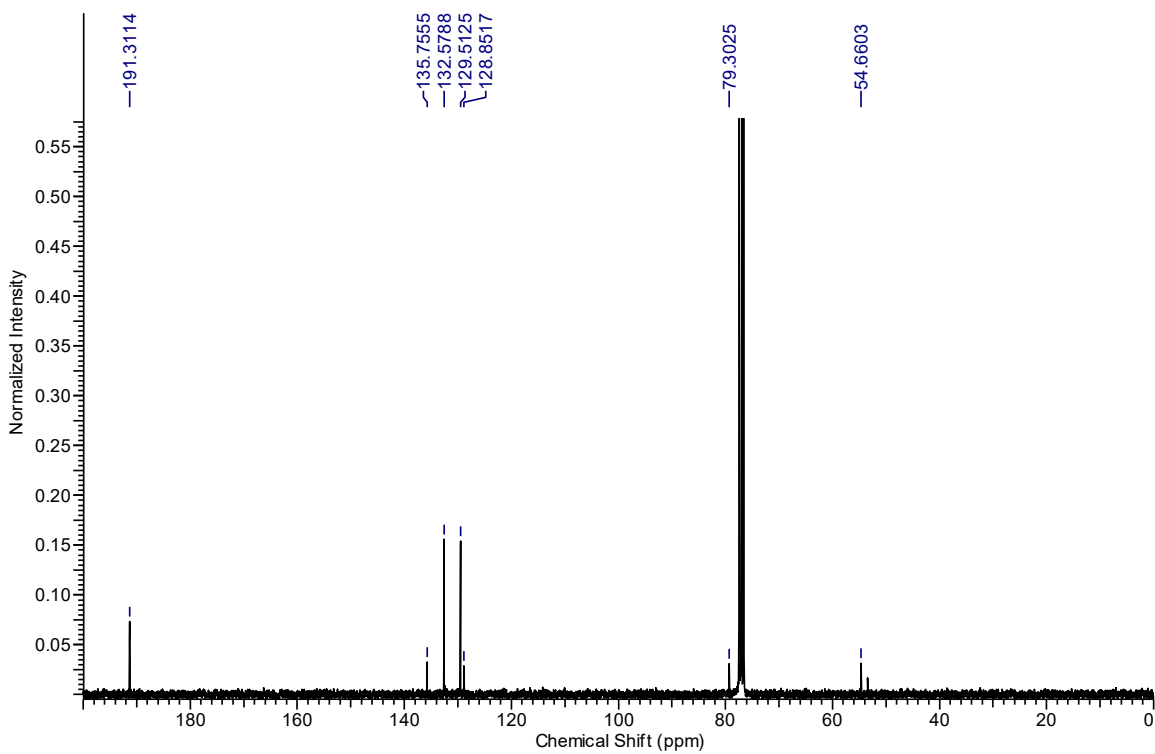
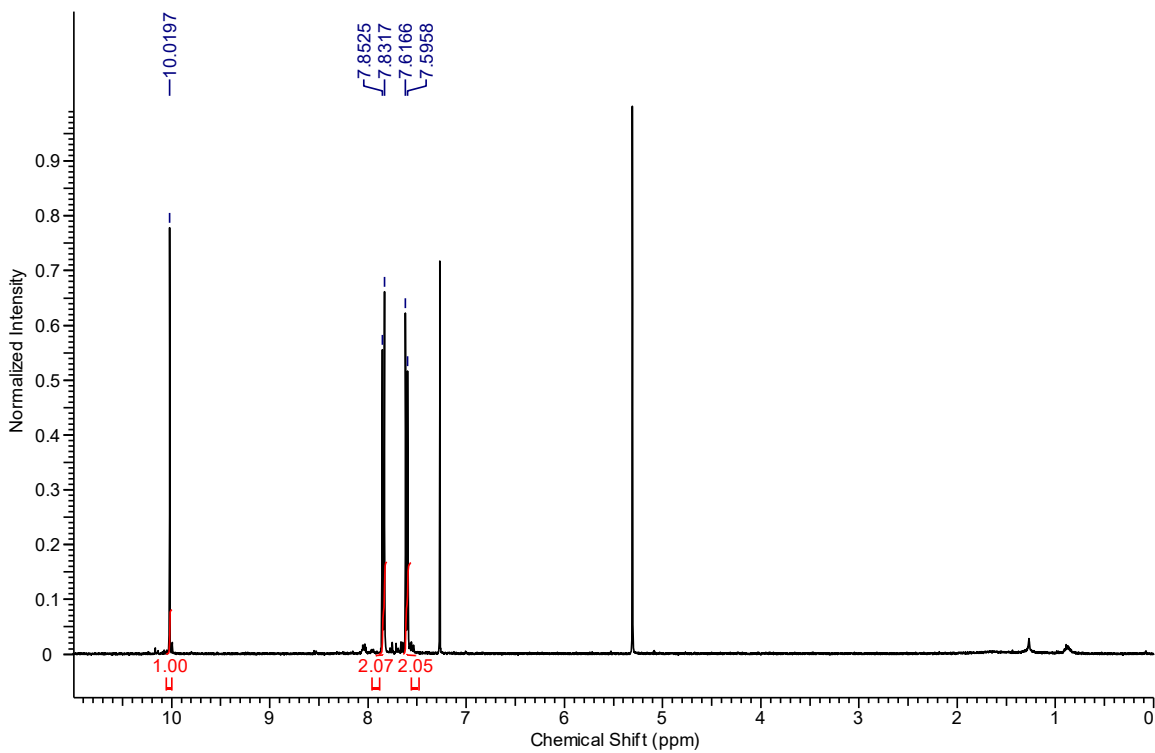




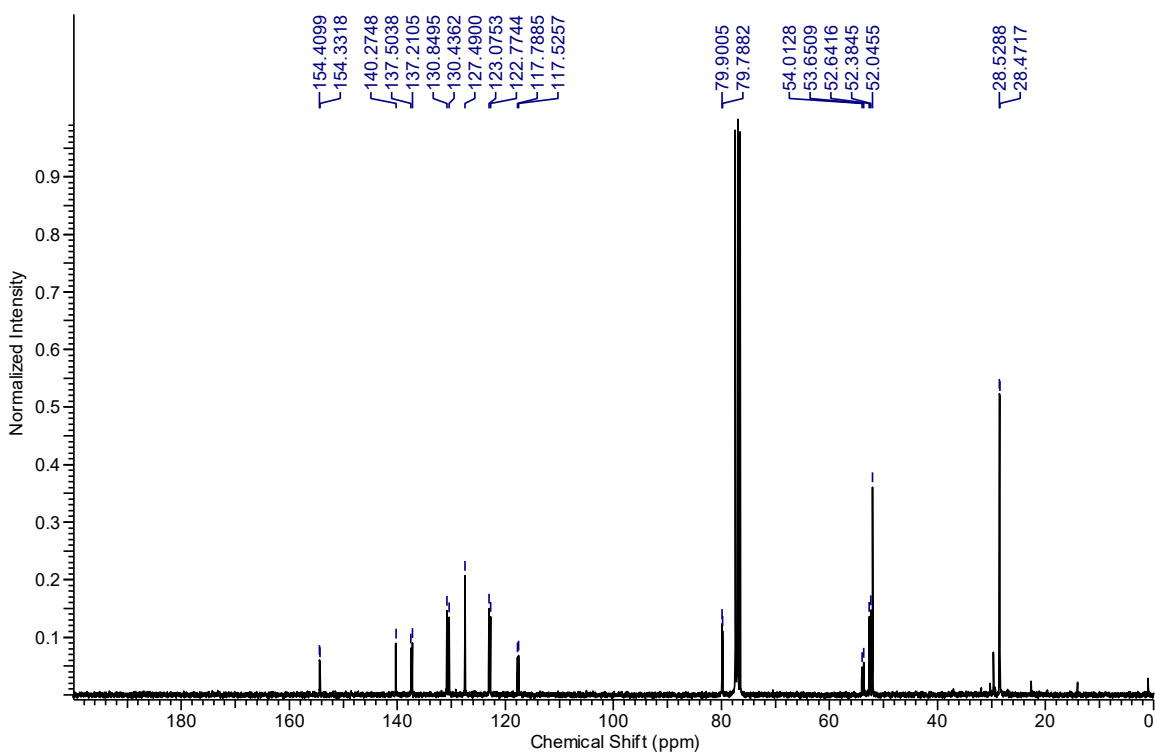
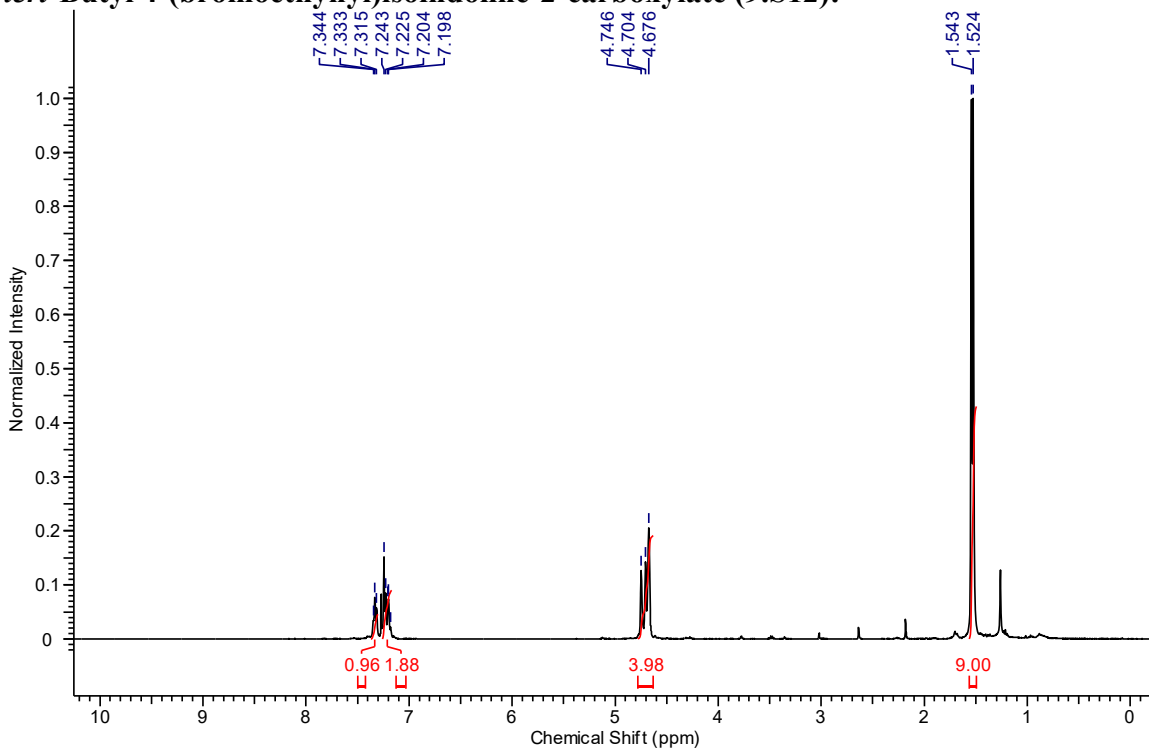
**6-Bromohex-5-yn-1-yl pent-4-enoate (9.S9):**



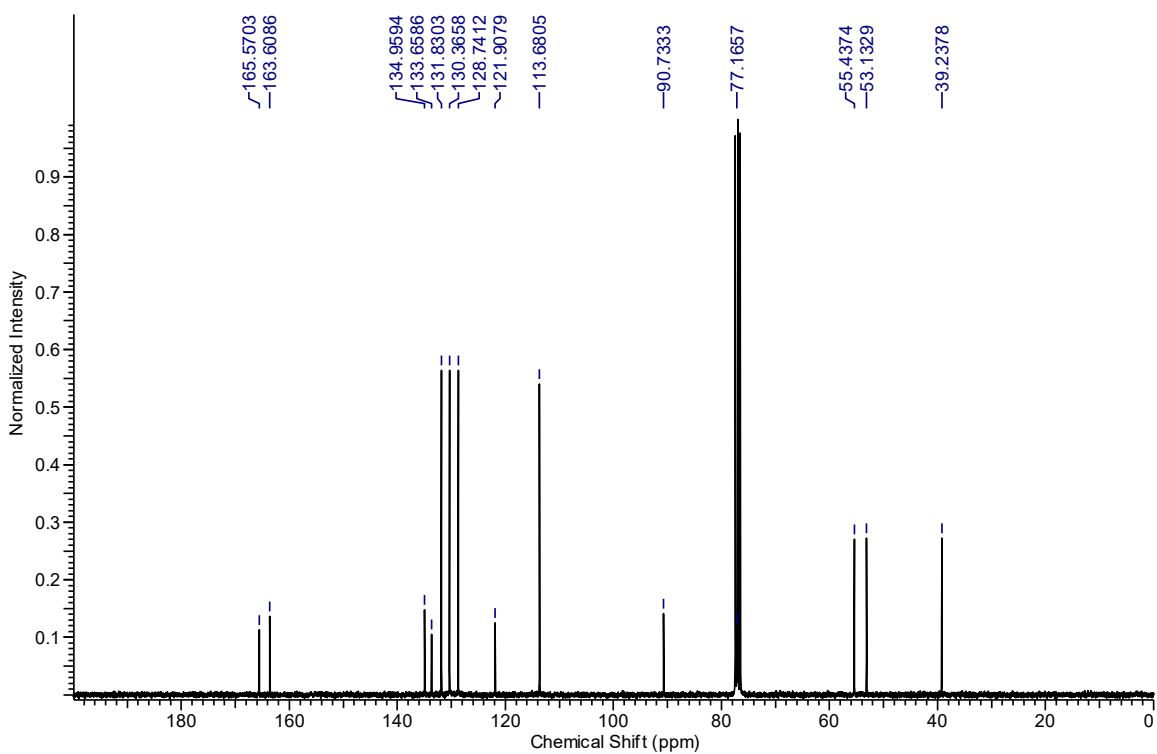
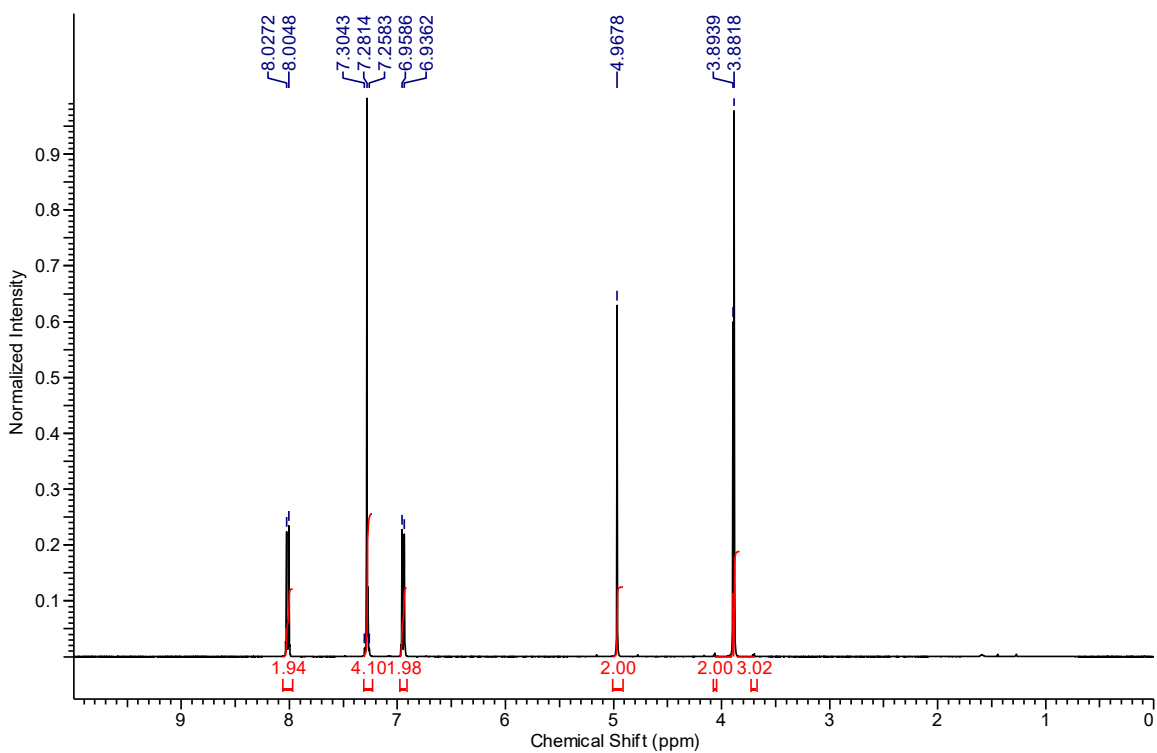
**4-(Bromoethynyl)benzaldehyde (9.S10):**



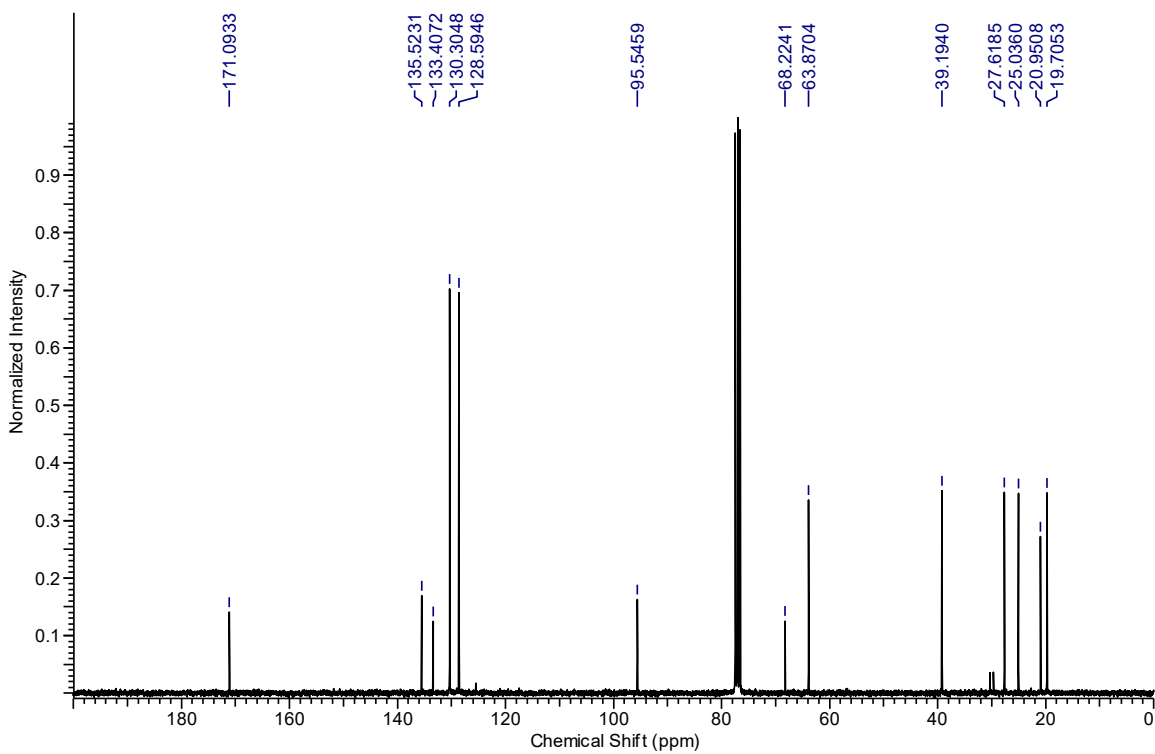
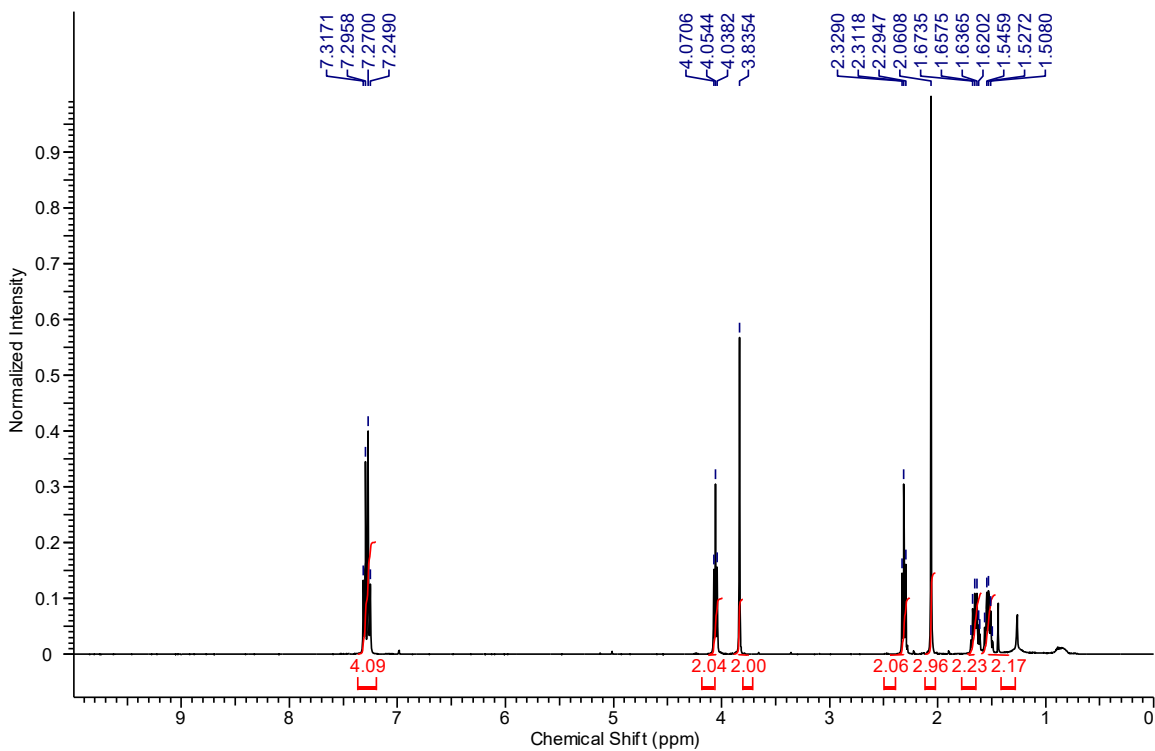
***tert*-Butyl 4-(bromoethynyl)isoindoline-2-carboxylate (9.S12):**



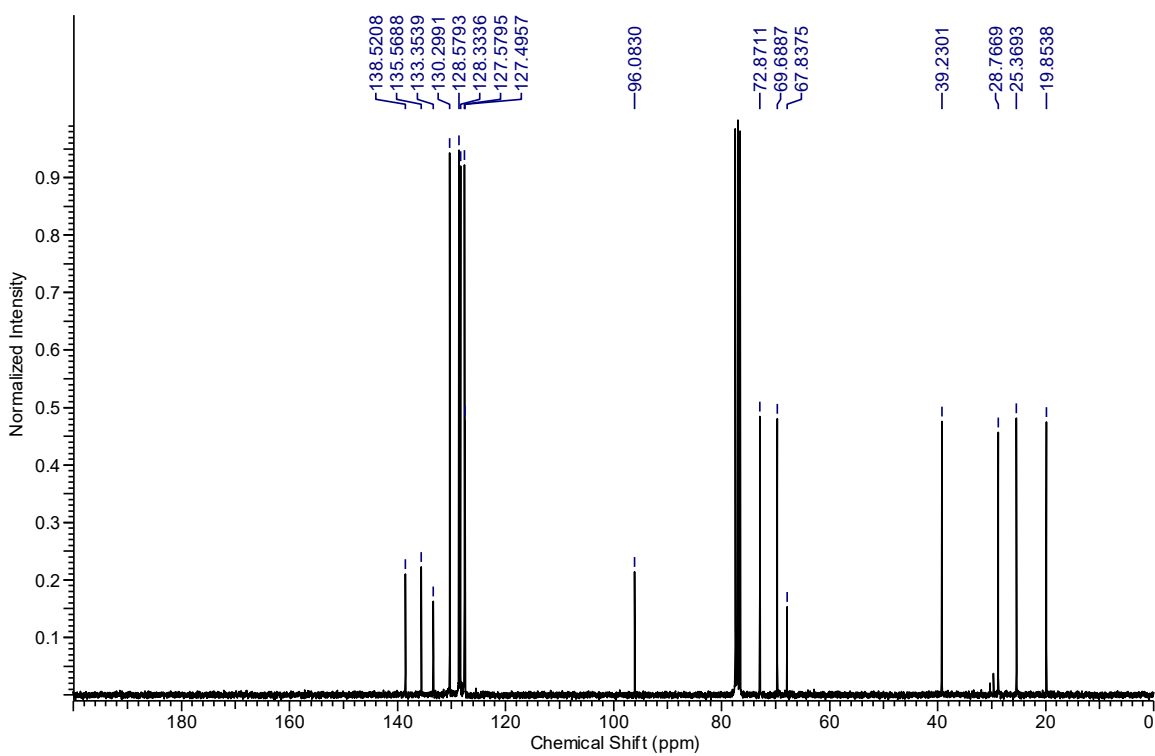
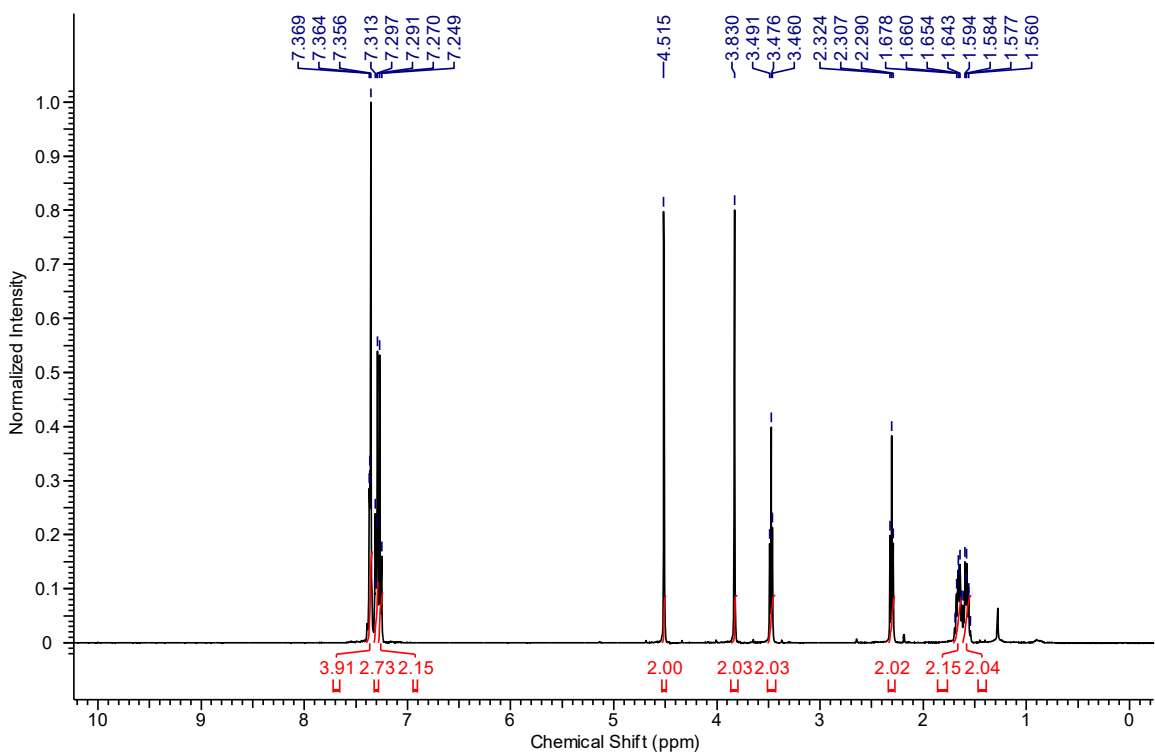
**3-((4-Chlorobenzyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.1):**



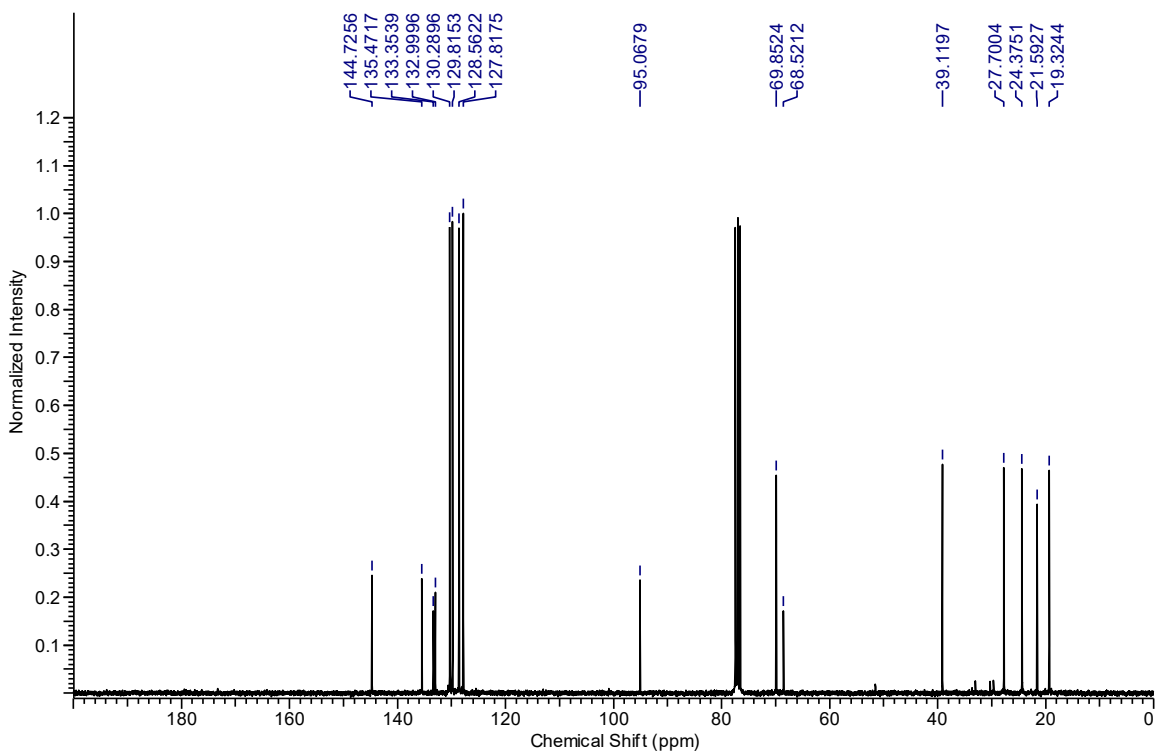
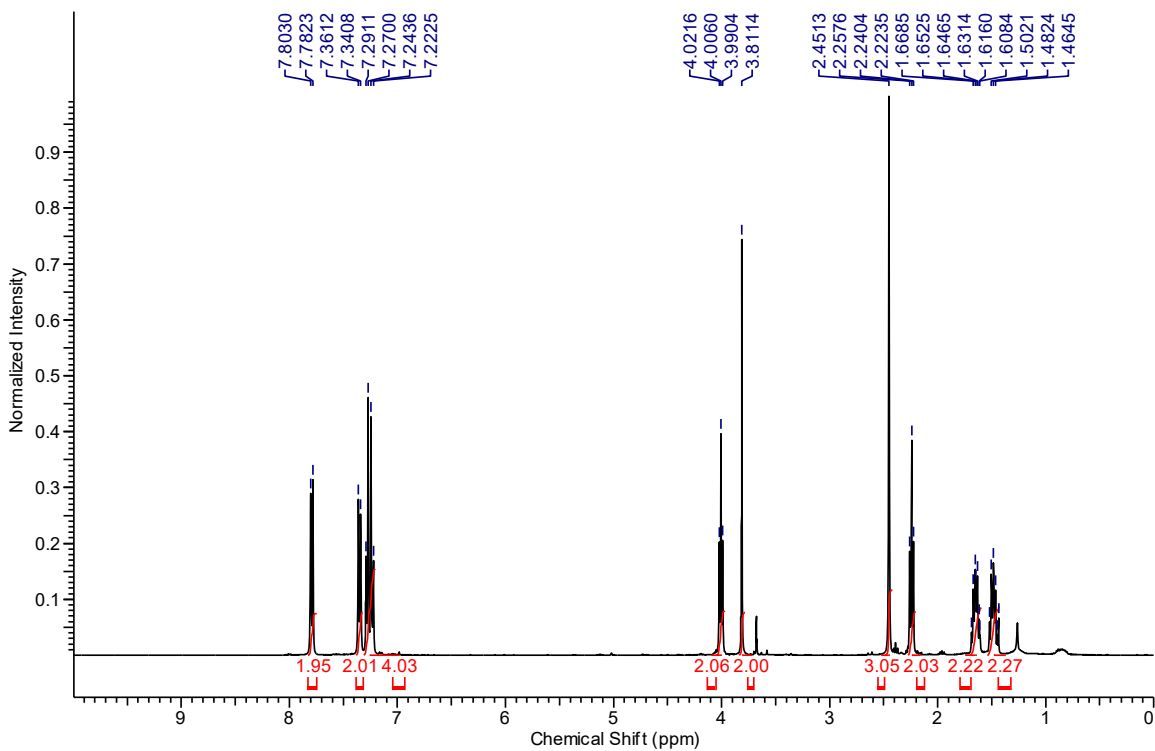
**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl acetate (9.2):**



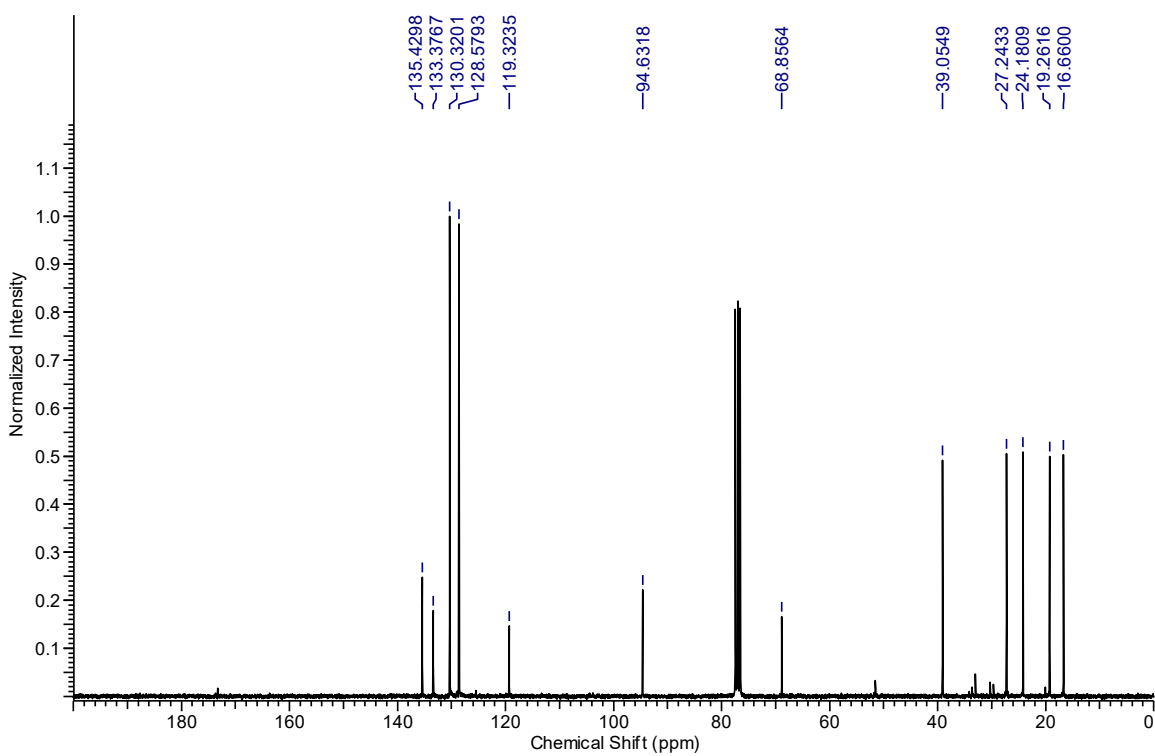
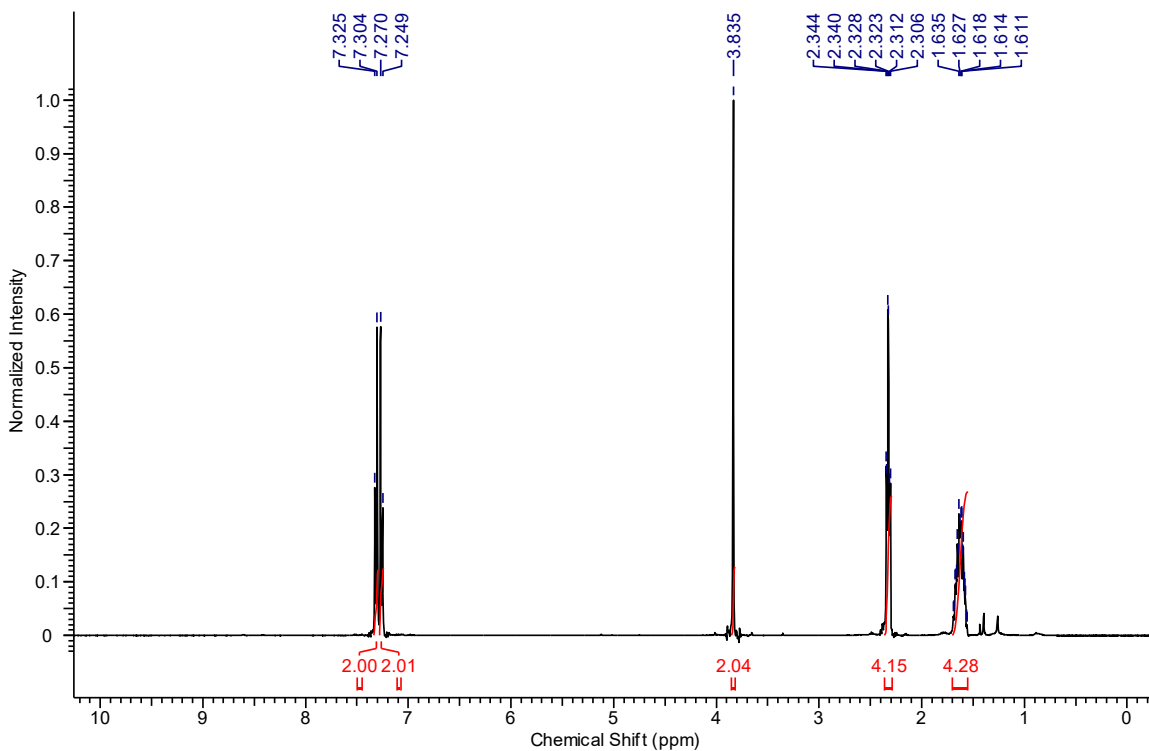
**(6-(Benzyloxy)hex-1-yn-1-yl)(4-chlorobenzyl)sulfane (9.3):**



**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl 4-methylbenzenesulfonate (9.4):**

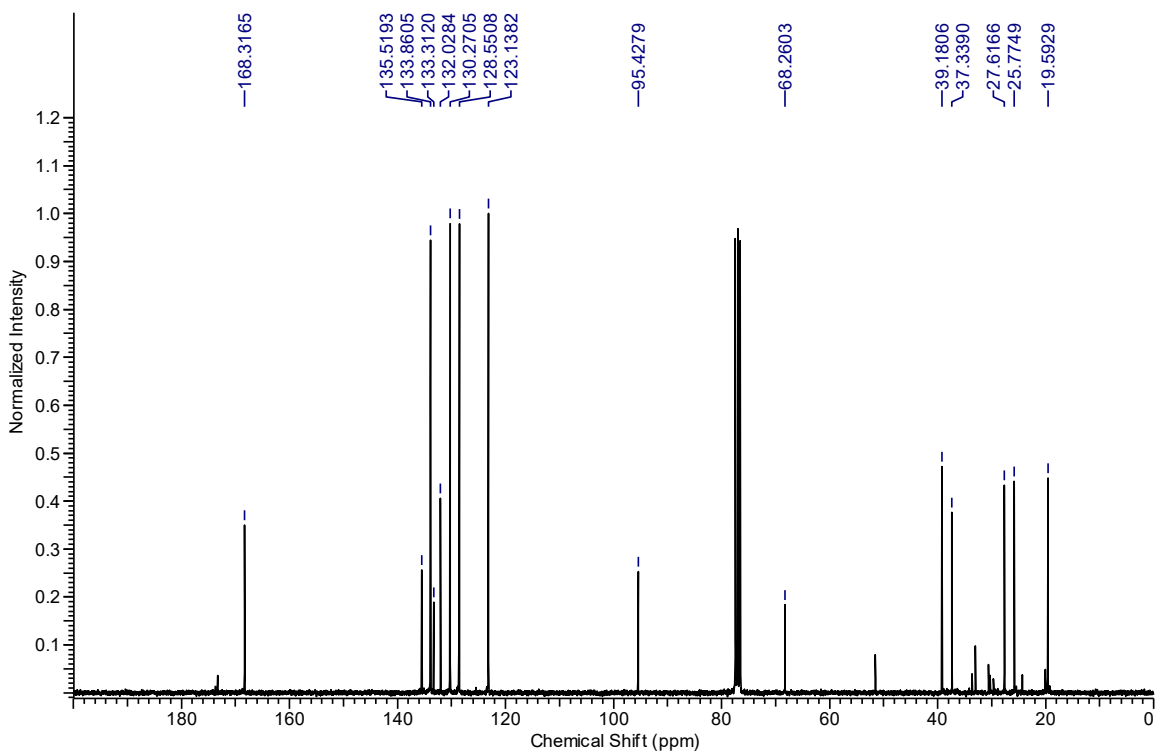
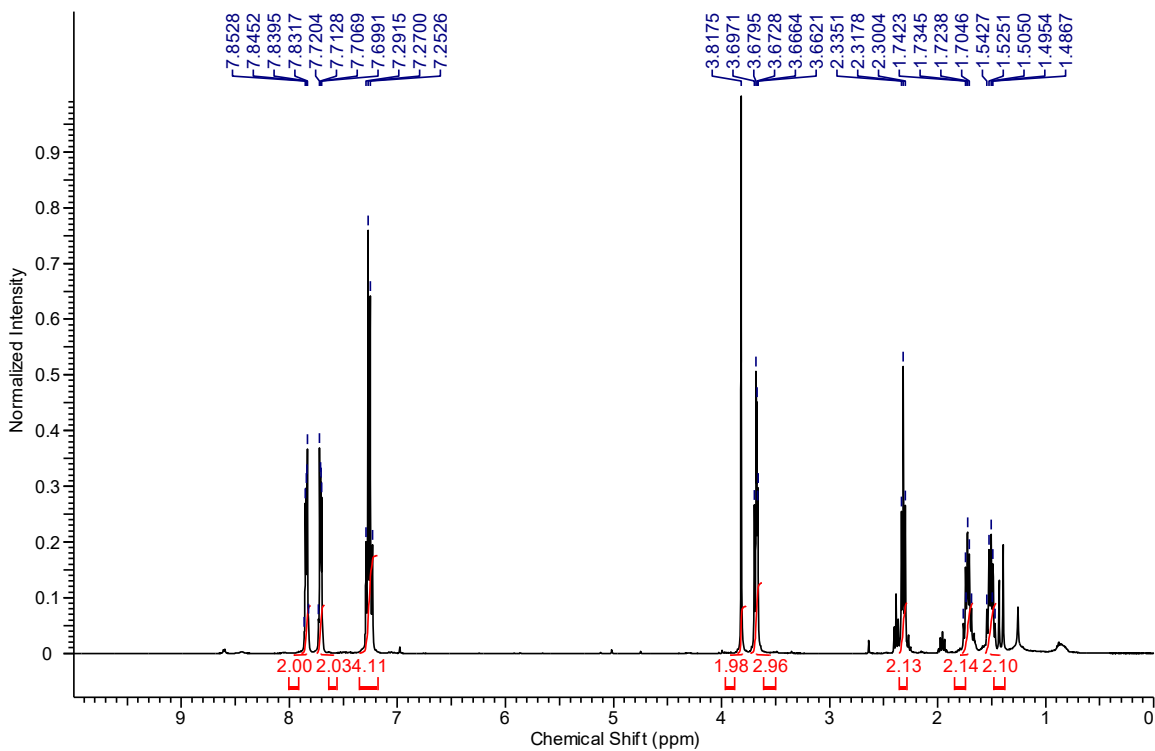


7-((4-Chlorobenzyl)thio)hept-6-yne nitrile (9.5):

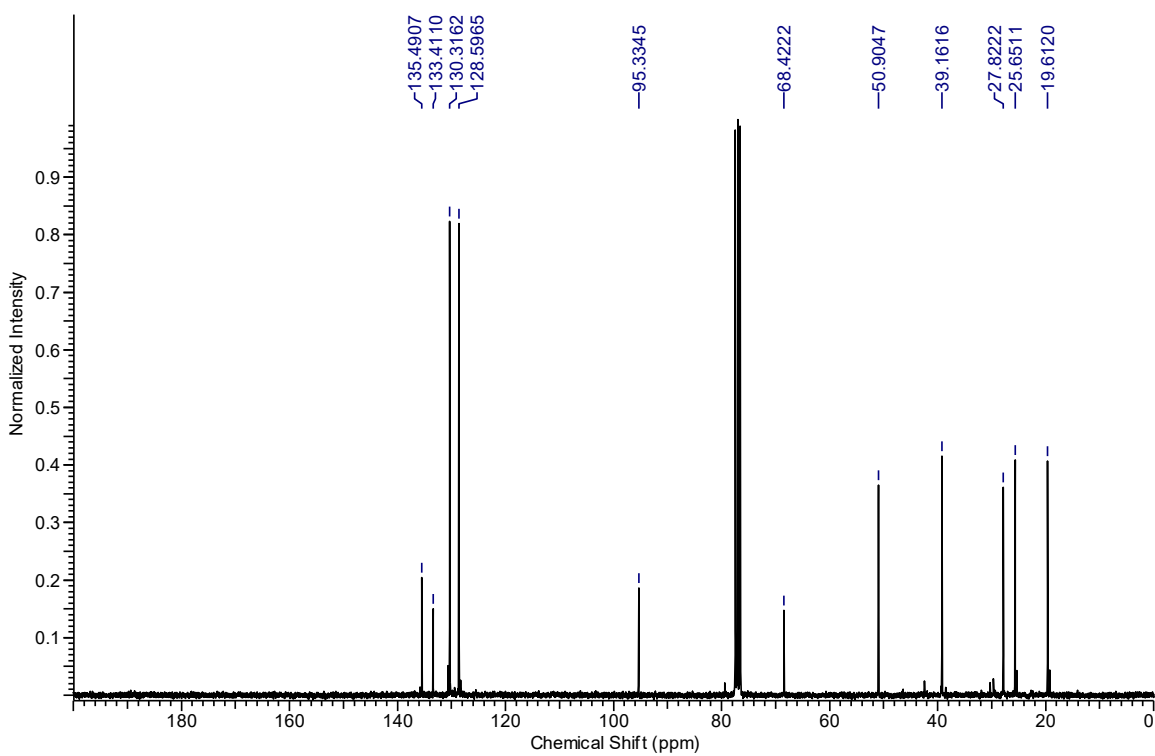
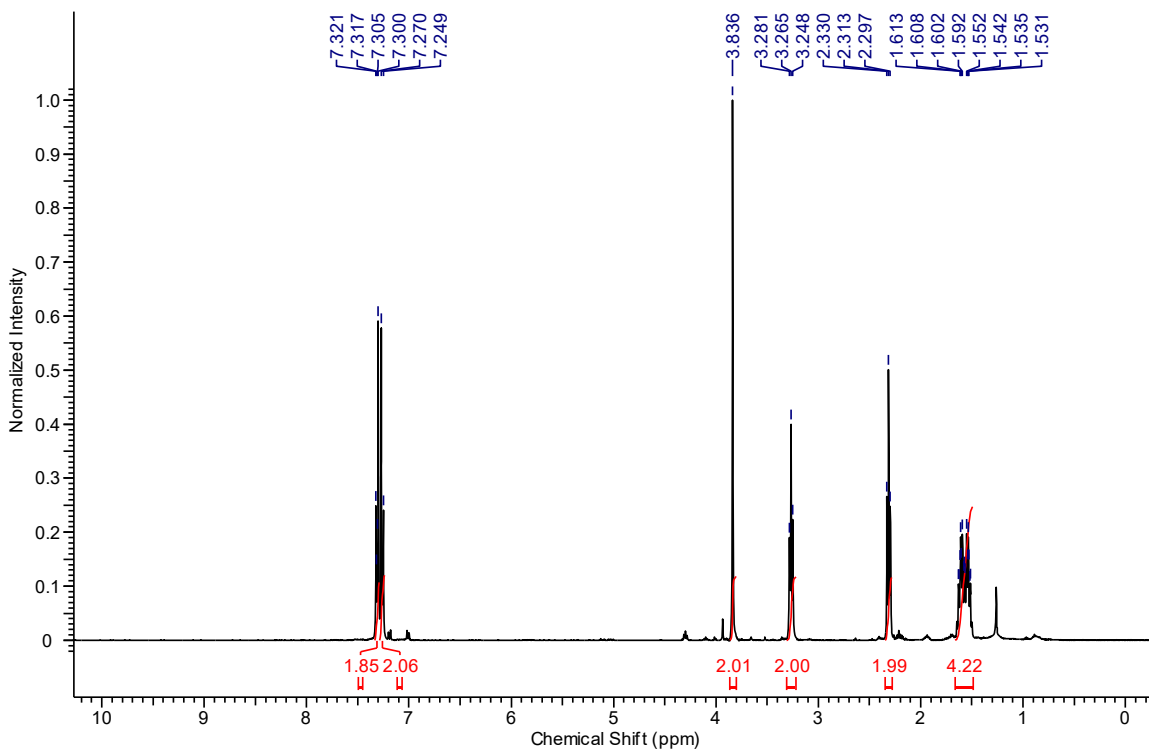




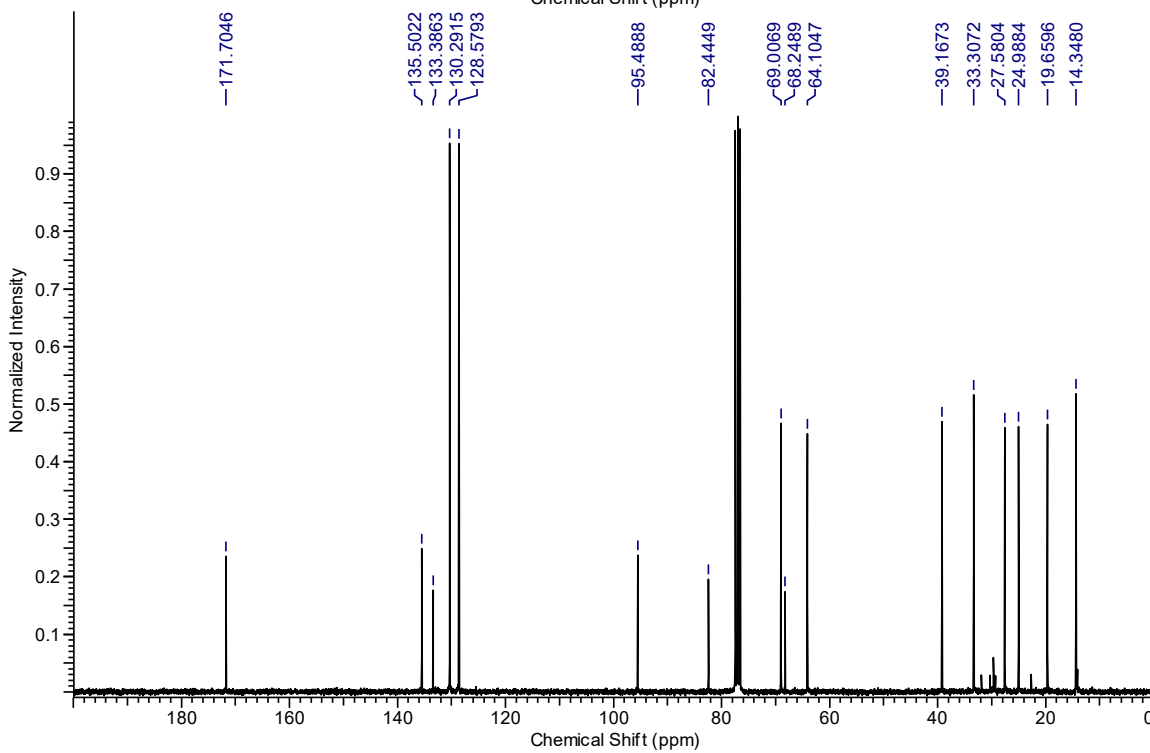
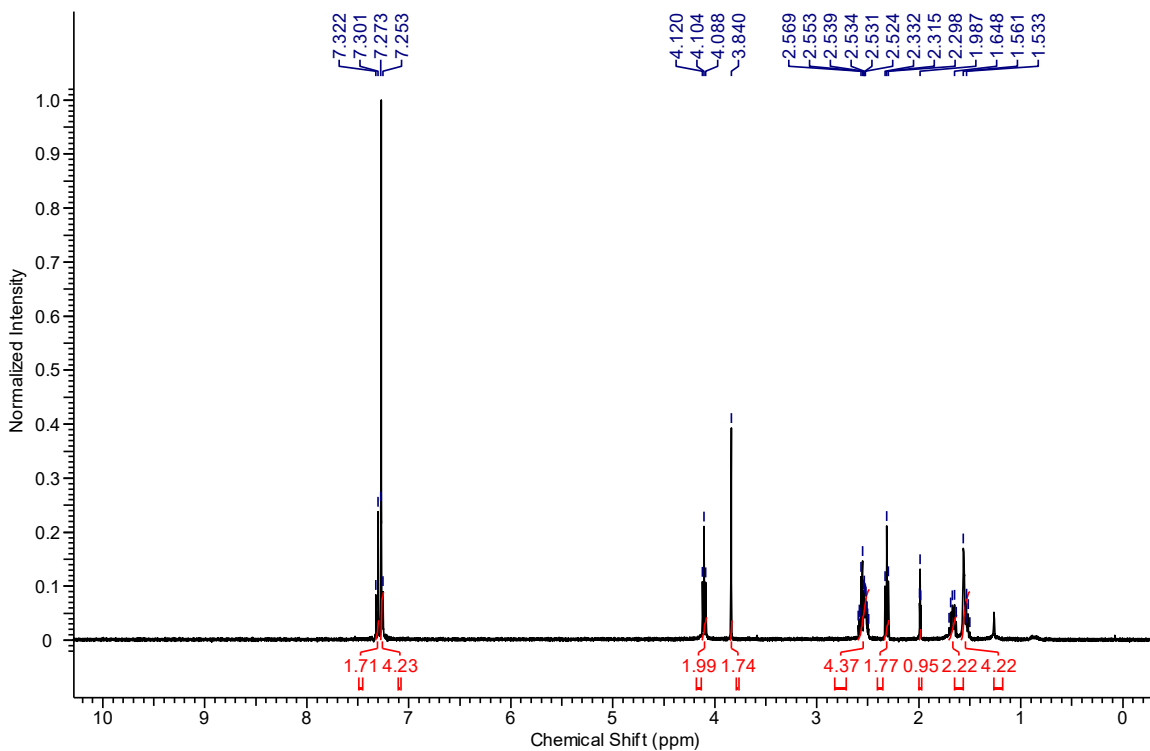
**2-((4-Chlorobenzyl)thio)hex-5-yn-1-yl)isoindoline-1,3-dione (9.6):**



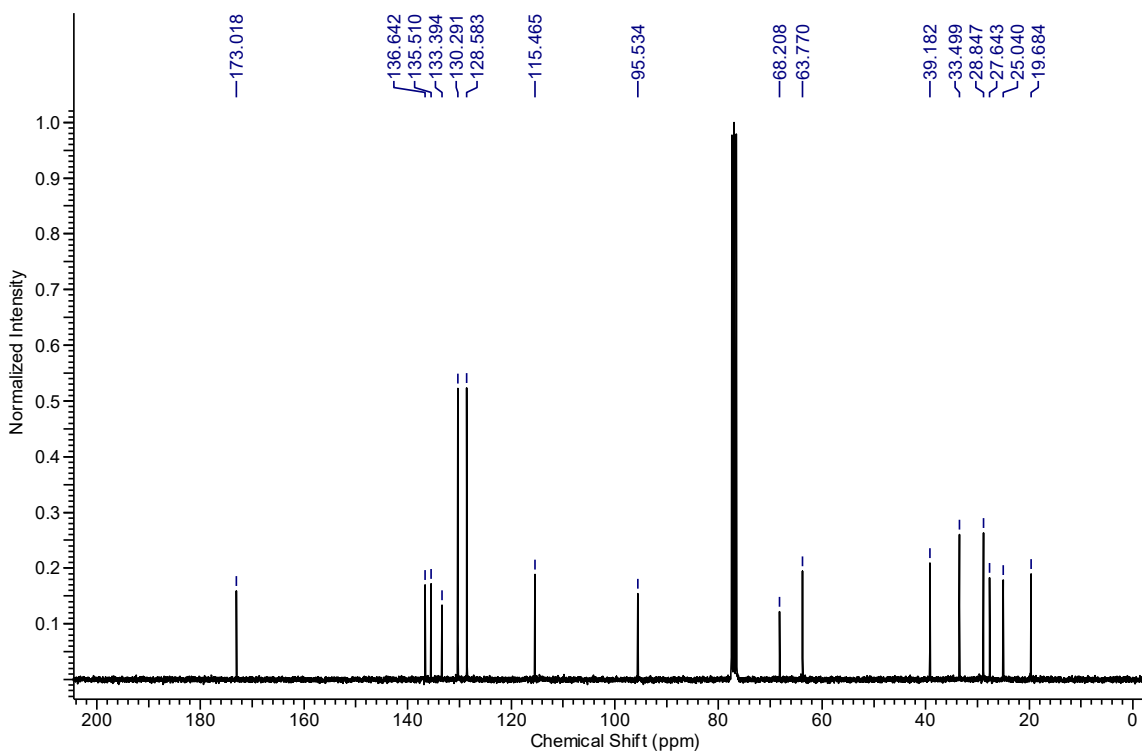
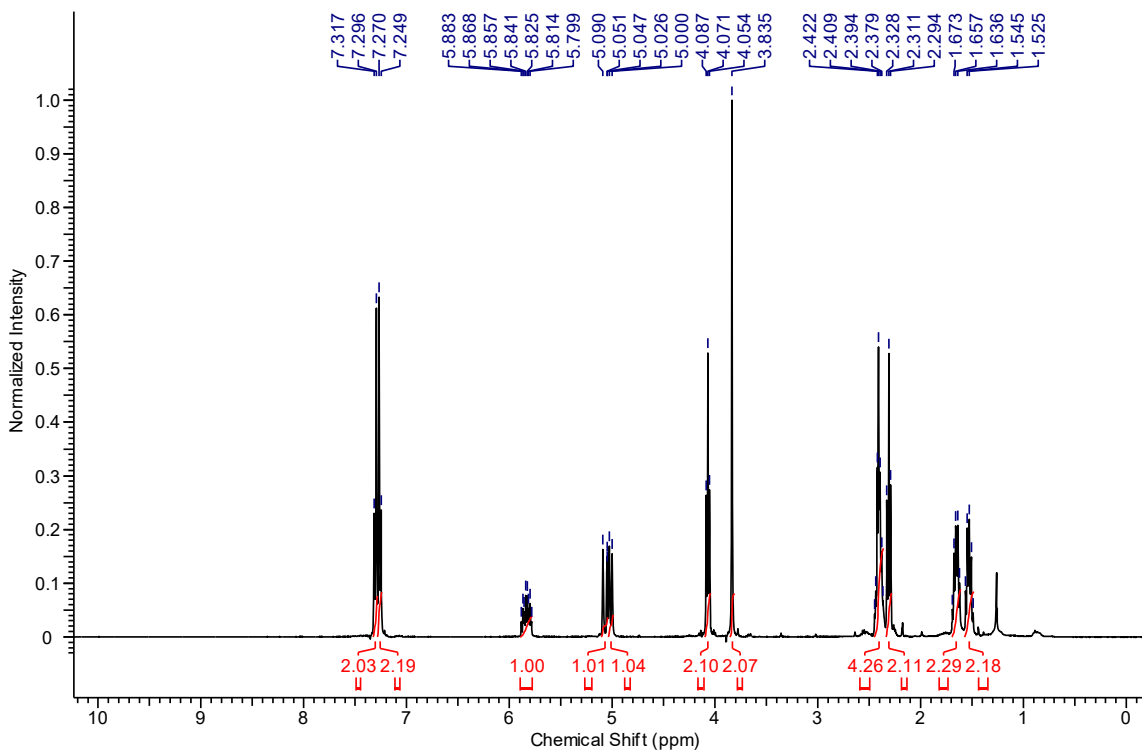
**(6-Azidohex-1-yn-1-yl)(4-chlorobenzyl)sulfane (9.7):**



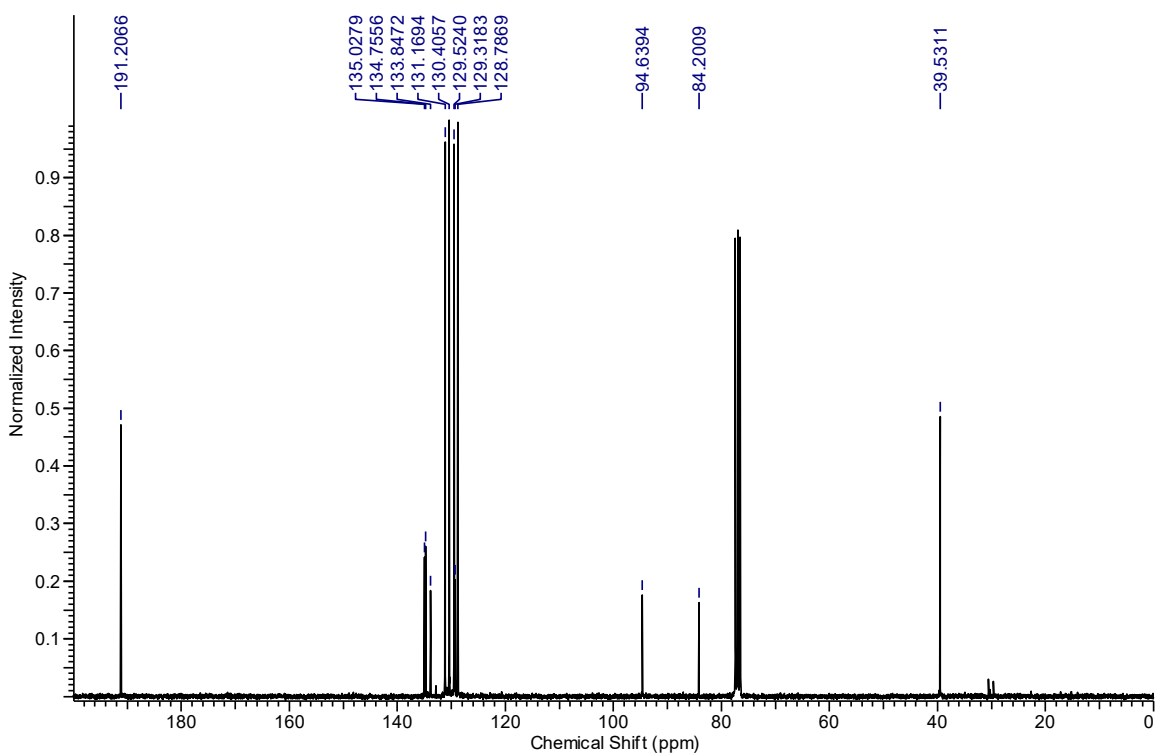
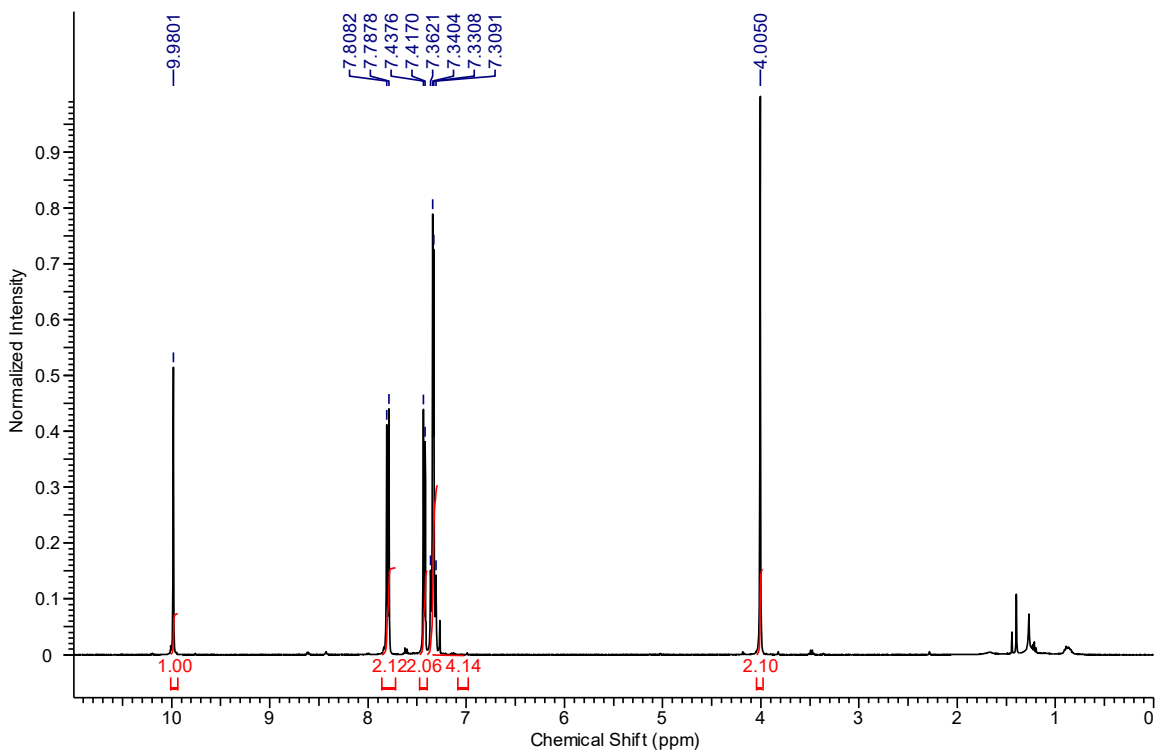
**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl pent-4-ynoate (9.8):**



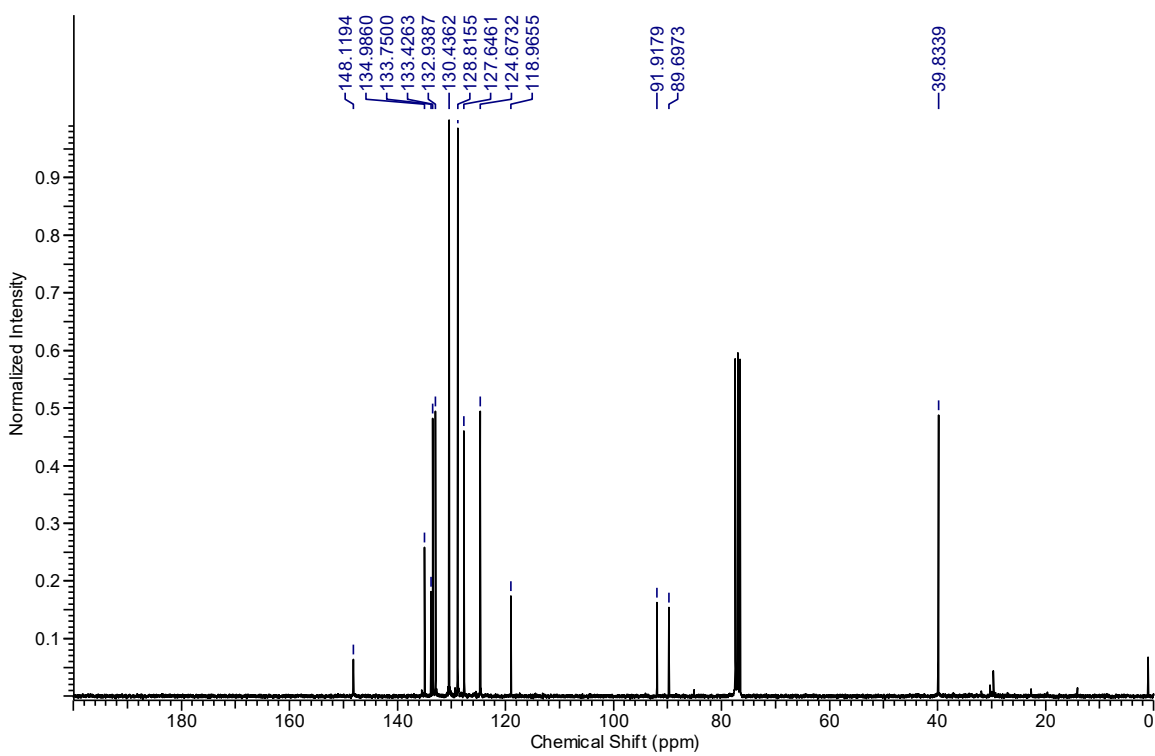
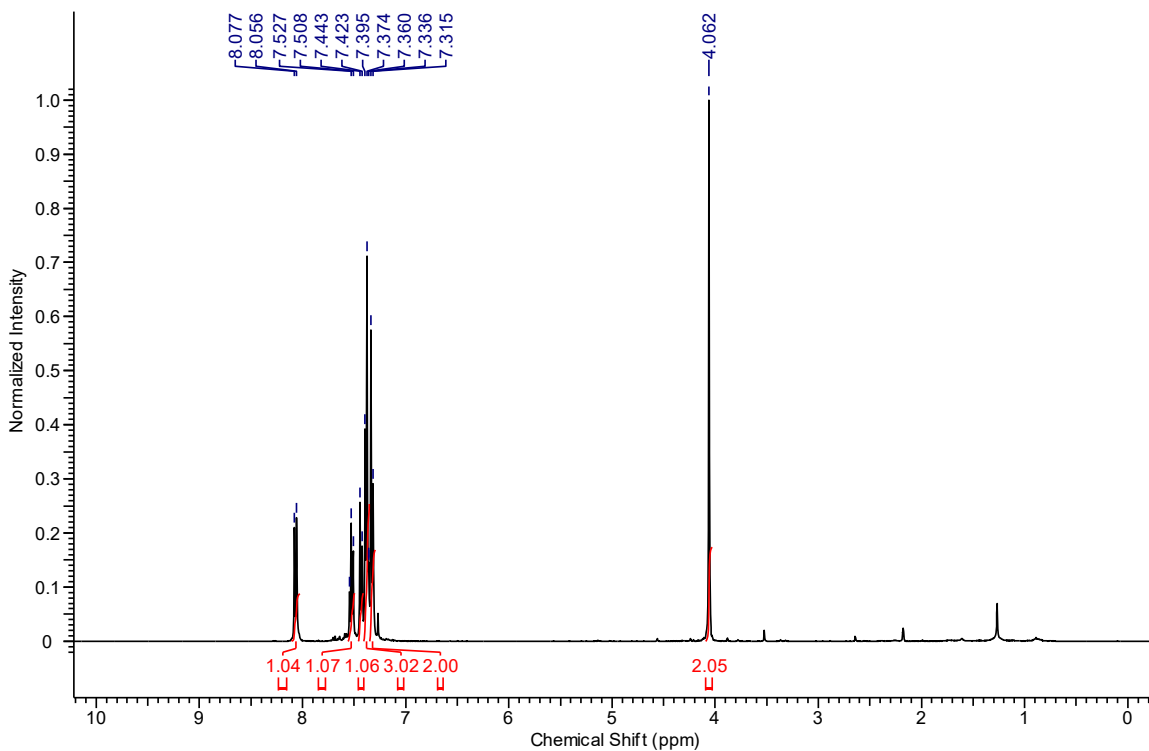
**6-((4-Chlorobenzyl)thio)hex-5-yn-1-yl pent-4-enoate (9.9):**



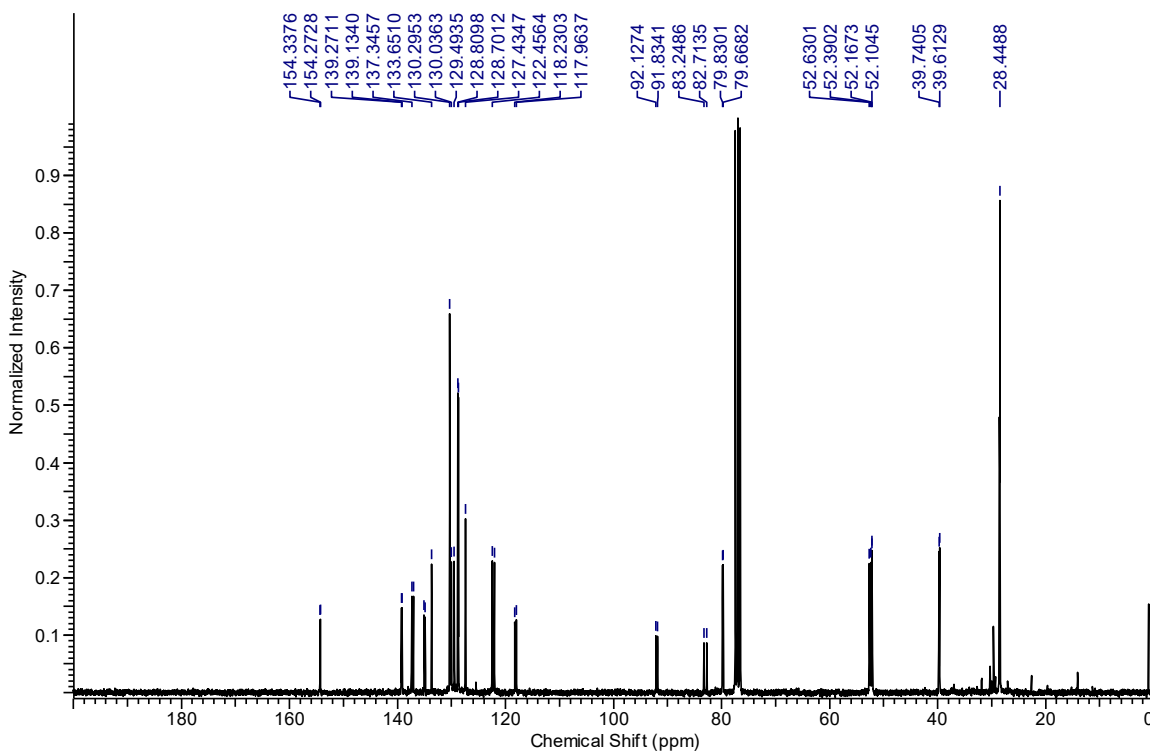
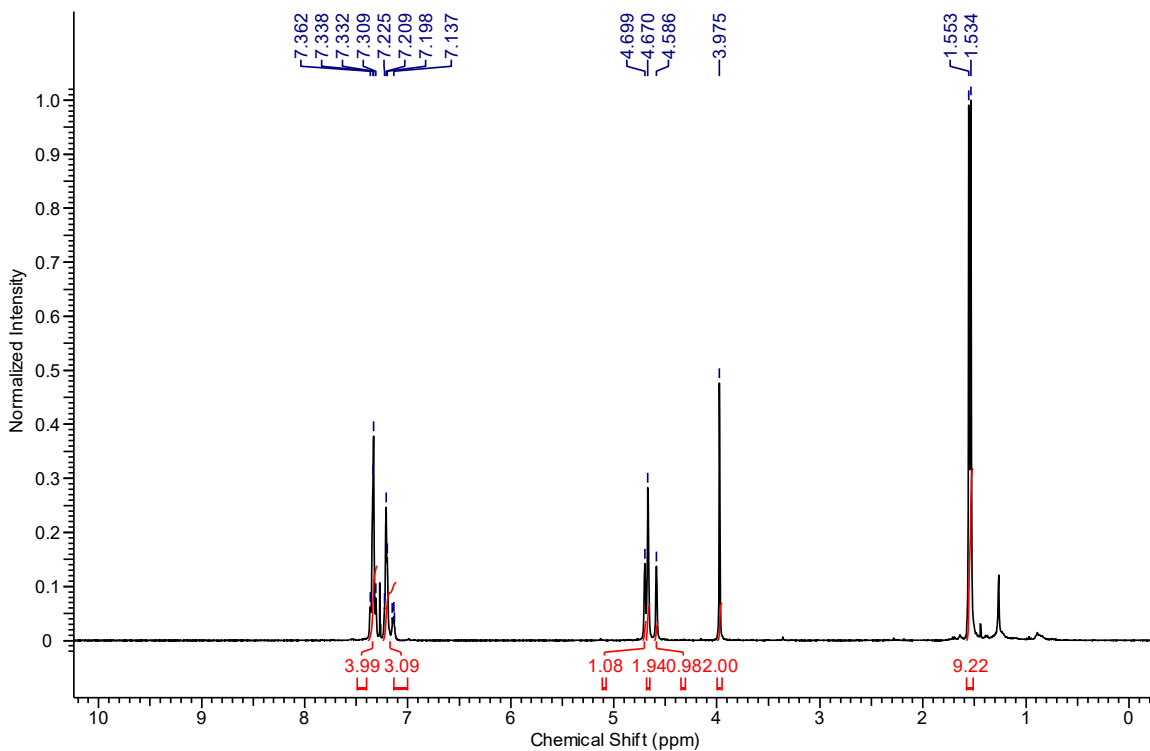
**4-(((4-Chlorobenzyl)thio)ethynyl)benzaldehyde (9.11):**



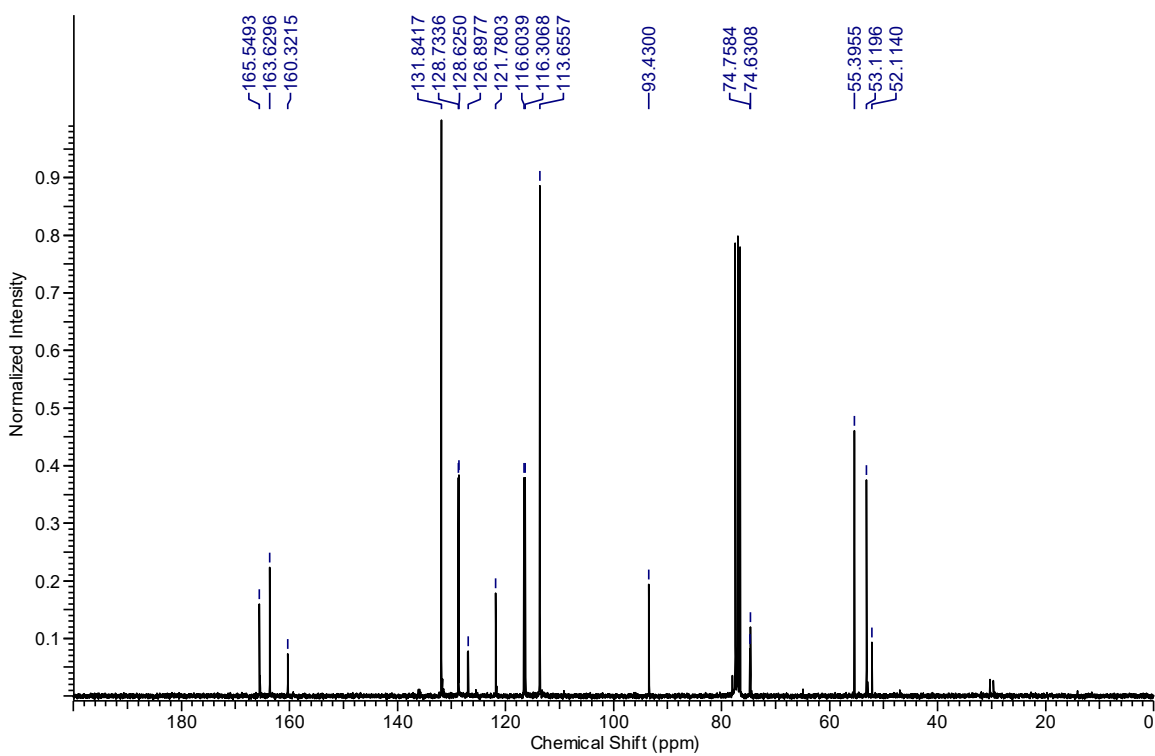
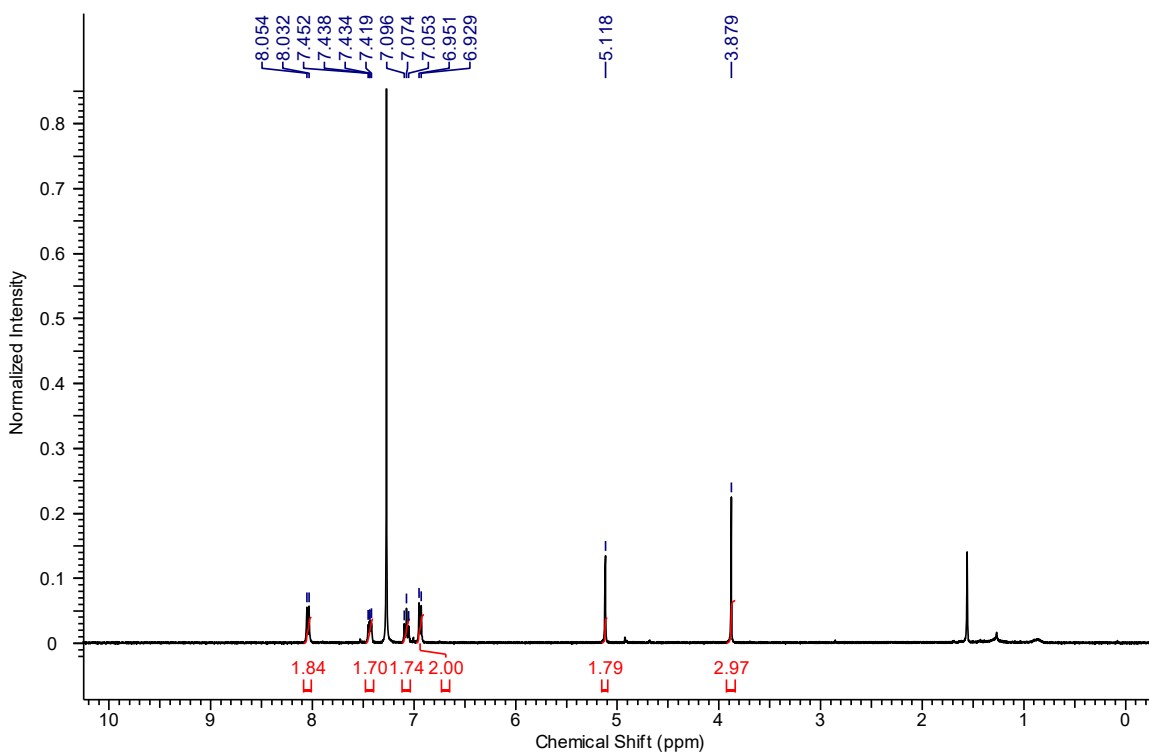
**(4-Chlorobenzyl)((2-nitrophenyl)ethynyl)sulfane (9.12):**



***tert*-Butyl 4-(((4-chlorobenzyl)thio)ethynyl)isoindoline-2-carboxylate (9.13):**

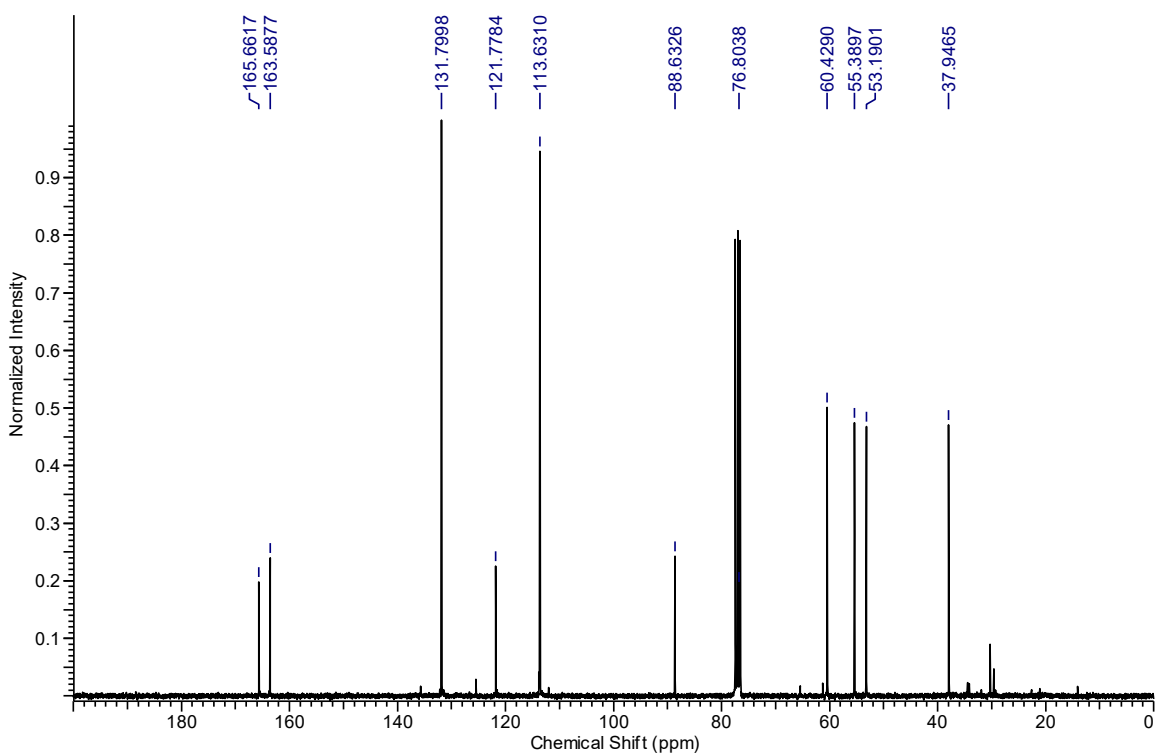
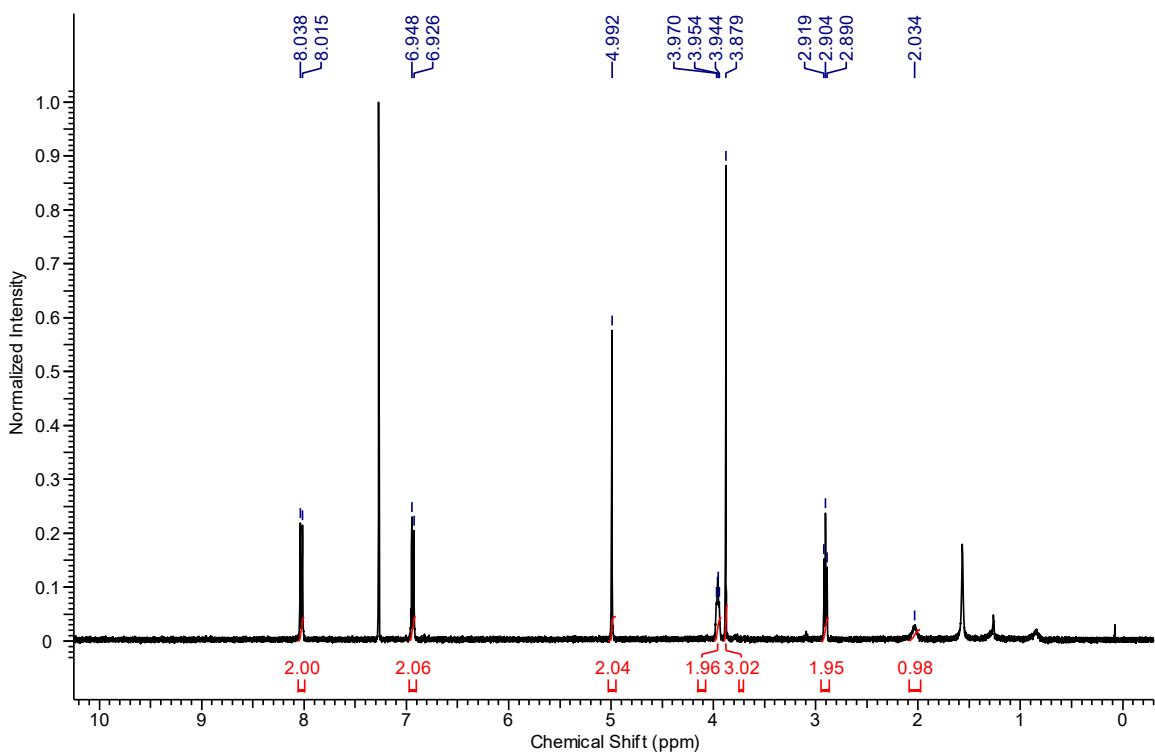


**3-((4-Fluorophenyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.19):**

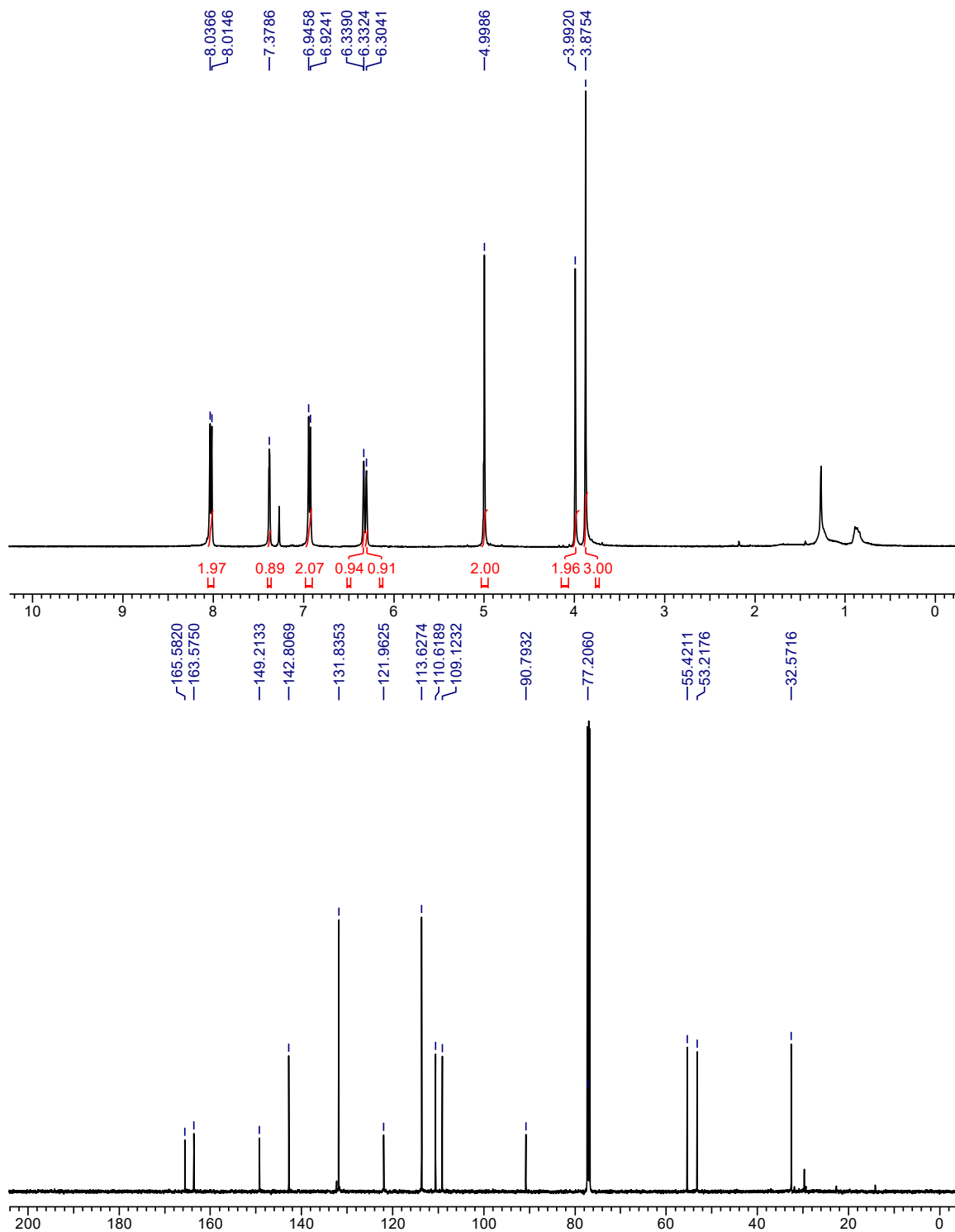




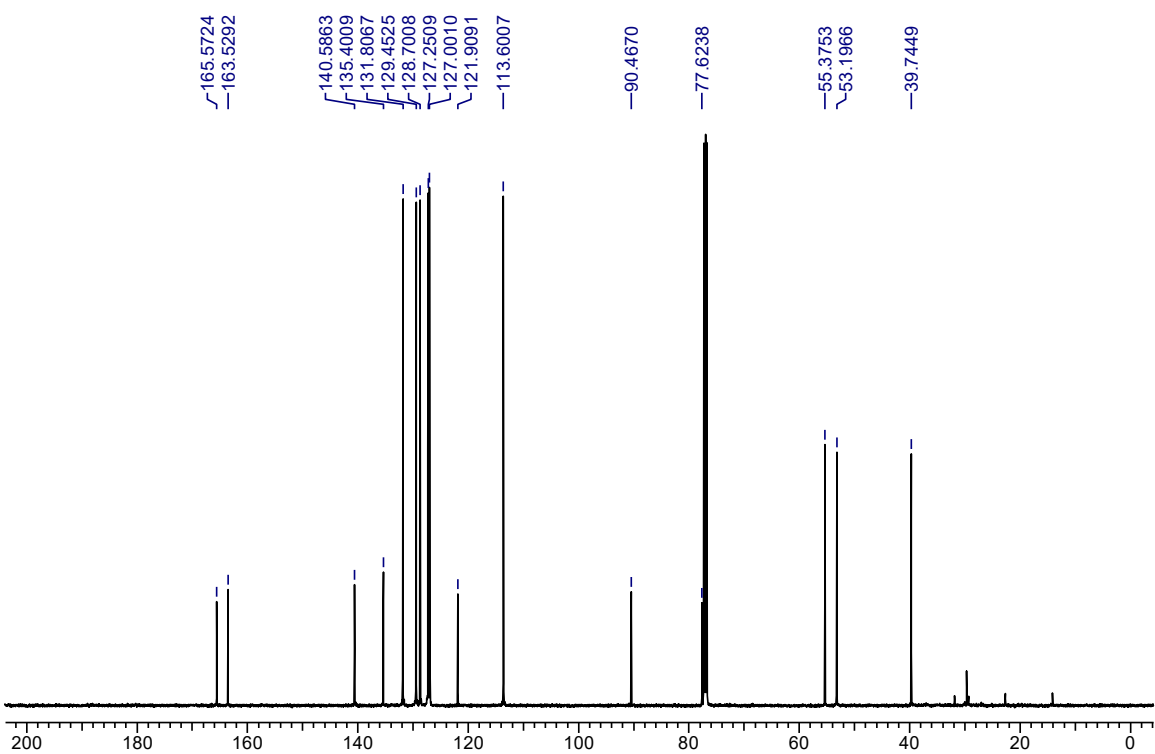
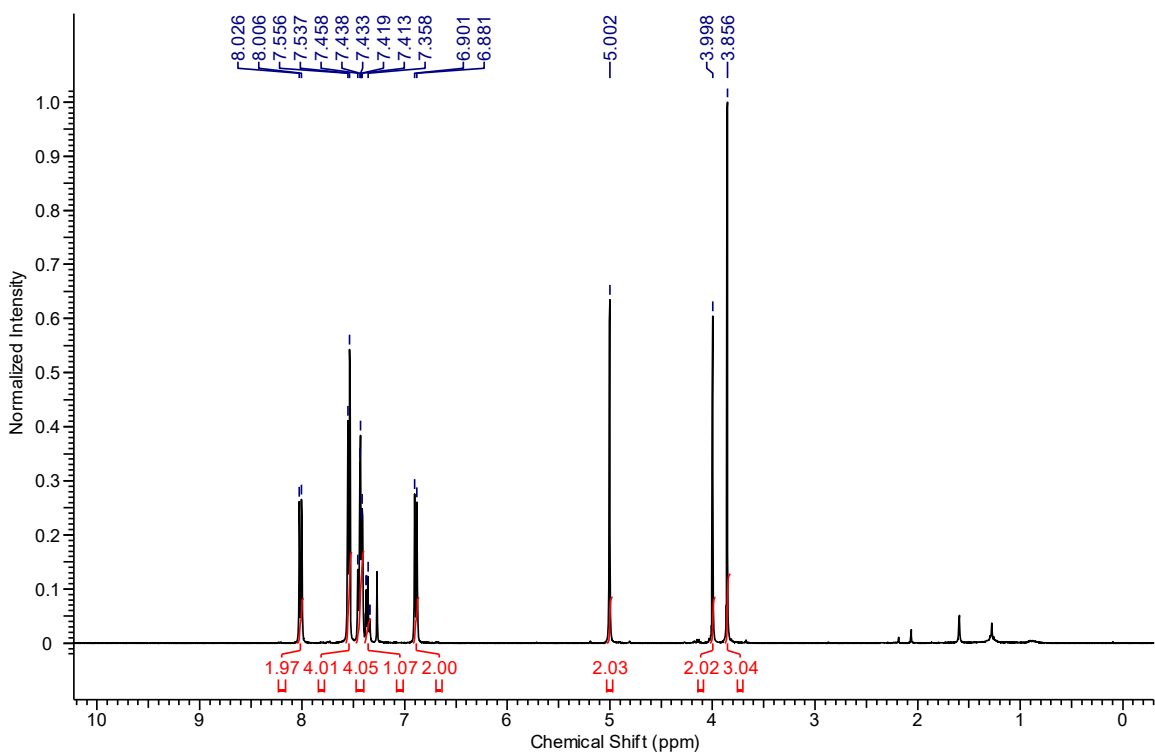
**3-((2-Hydroxyethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.20):**



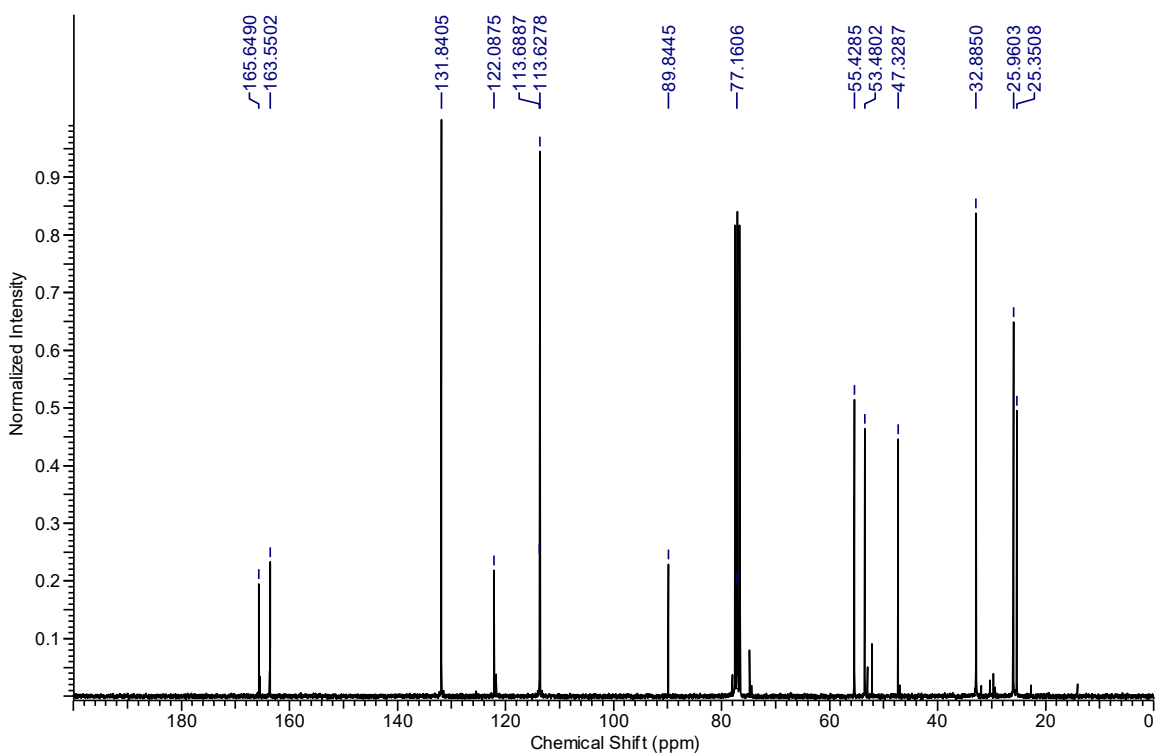
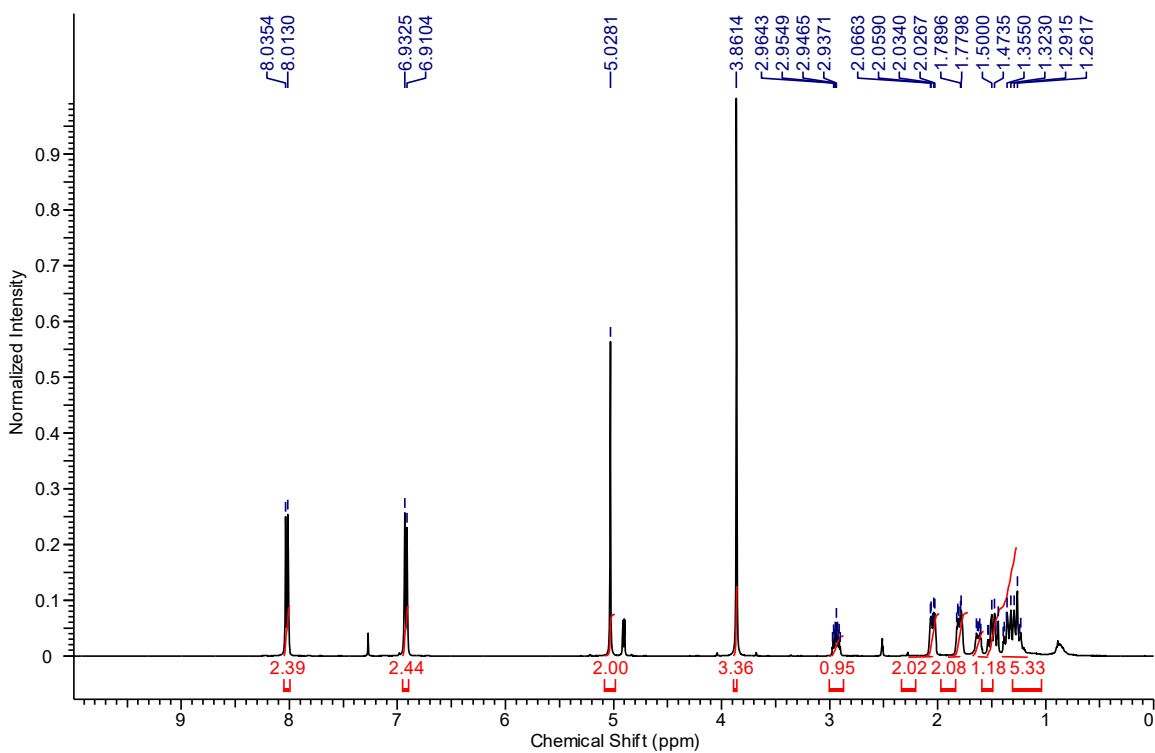
**3-((Furan-2-ylmethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.21):**



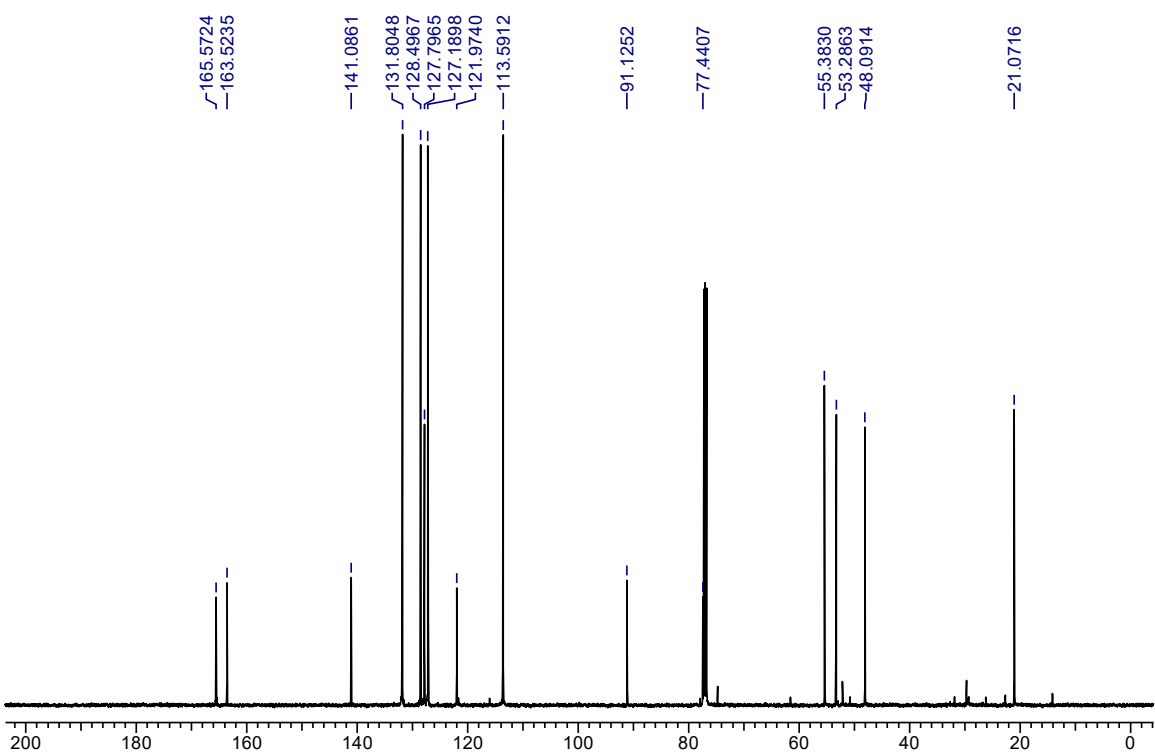
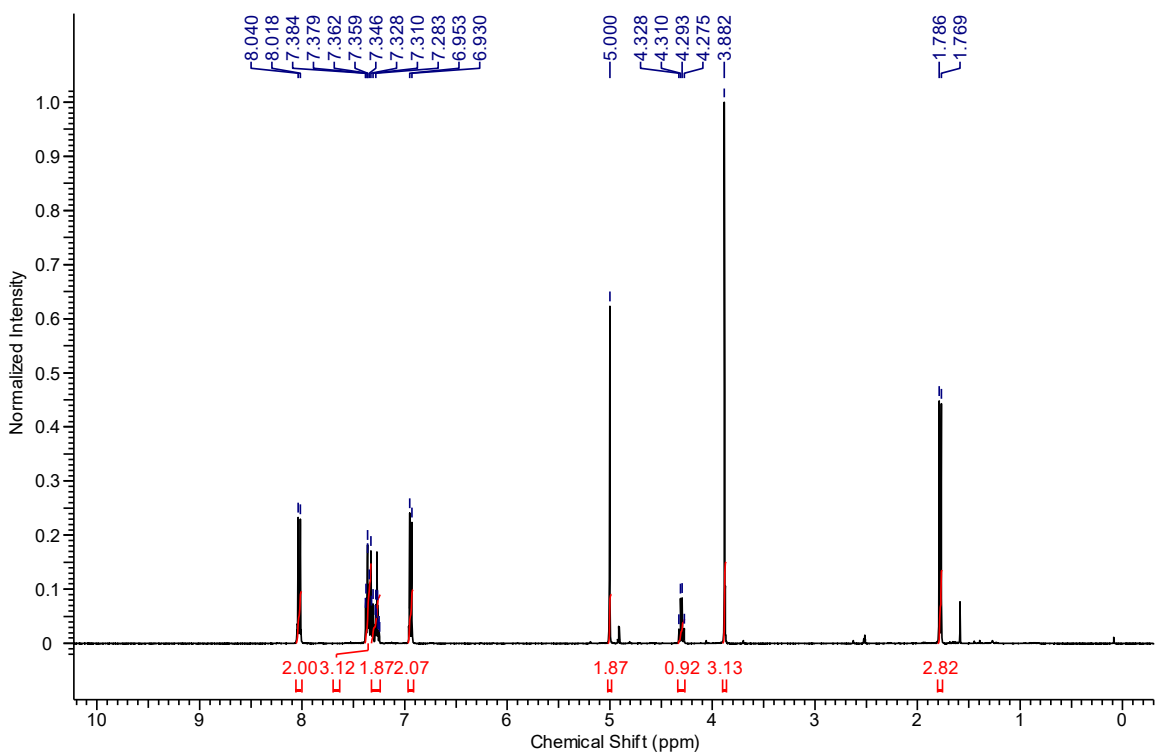
3-(((1,1'-Biphenyl)-4-ylmethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.22):



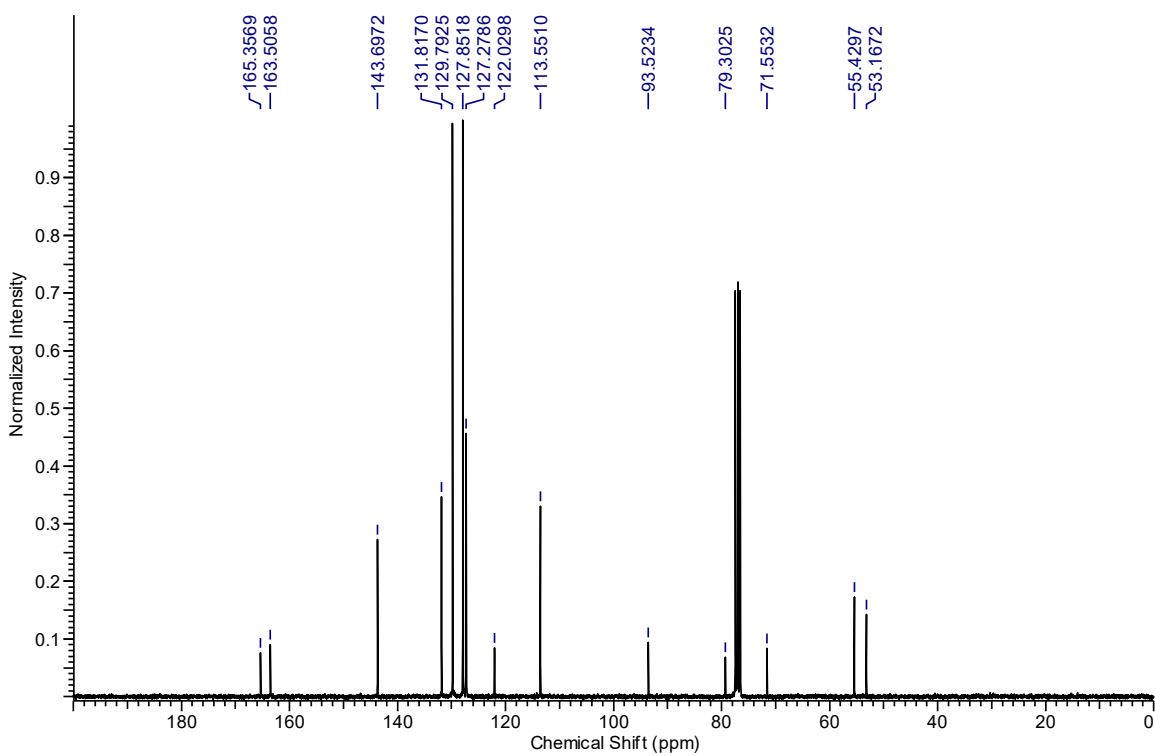
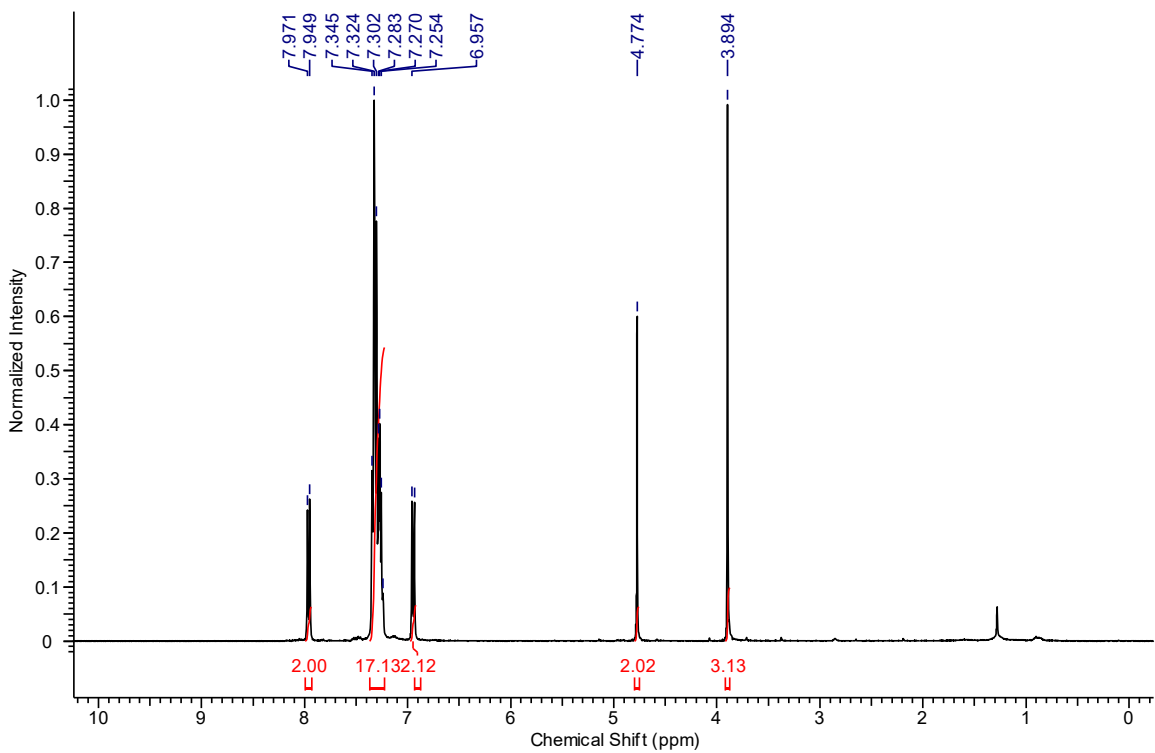
**3-(Cyclohexylthio)prop-2-yn-1-yl 4-methoxybenzoate (9.23):**



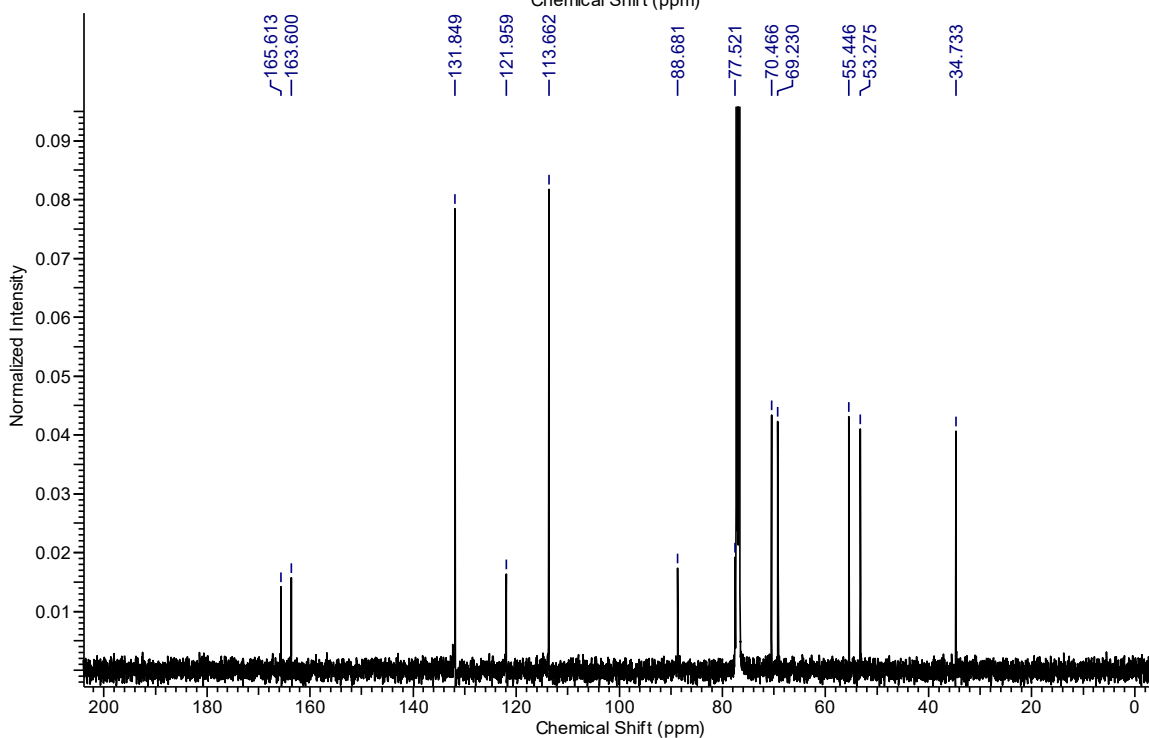
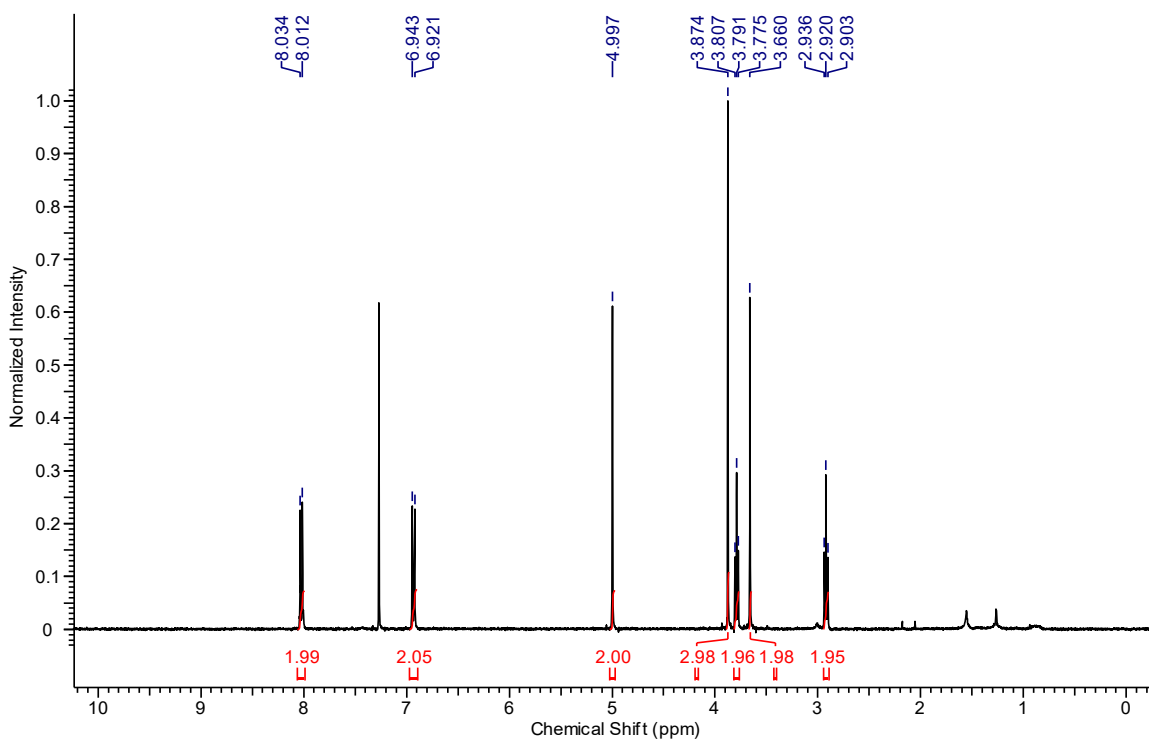
**(S)-3-((1-Phenylethyl)thio)prop-2-yn-1-yl 4-methoxybenzoate (9.24):**



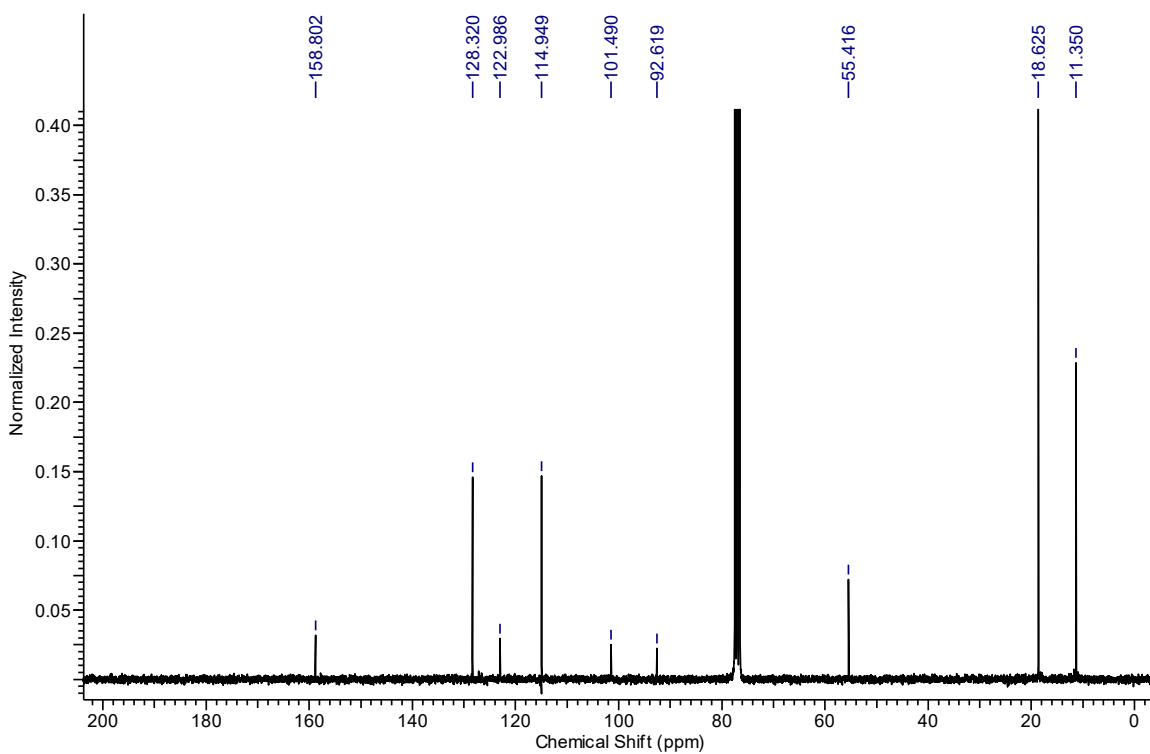
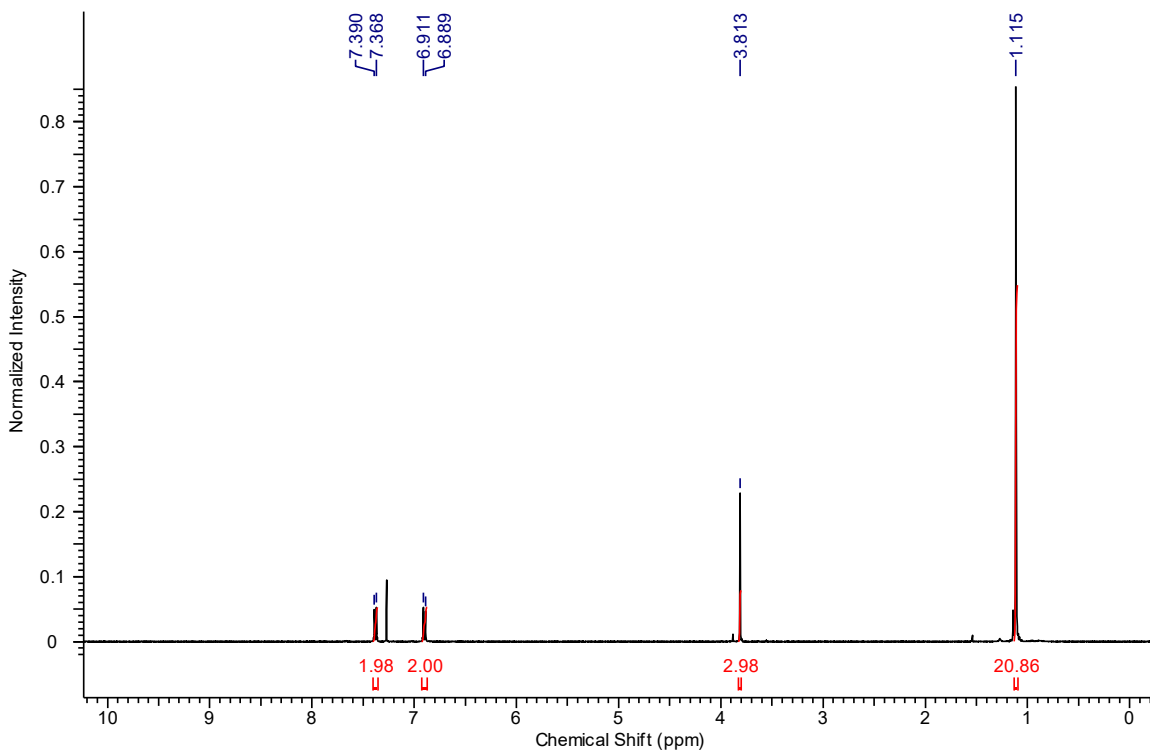
**3-(Tritylthio)prop-2-yn-1-yl 4-methoxybenzoate (9.25):**



**7,10-dioxa-4,13-dithiahexadeca-2,14-diyne-1,16-diyl bis(4-methoxybenzoate) (9.26):**

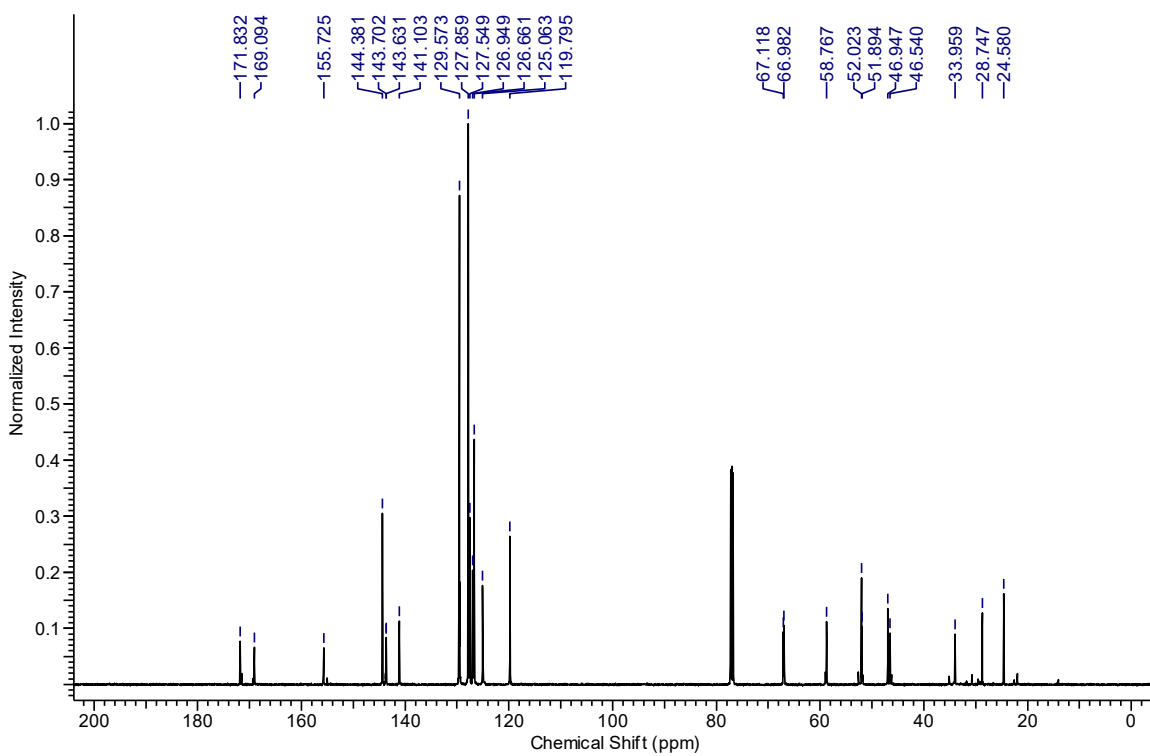
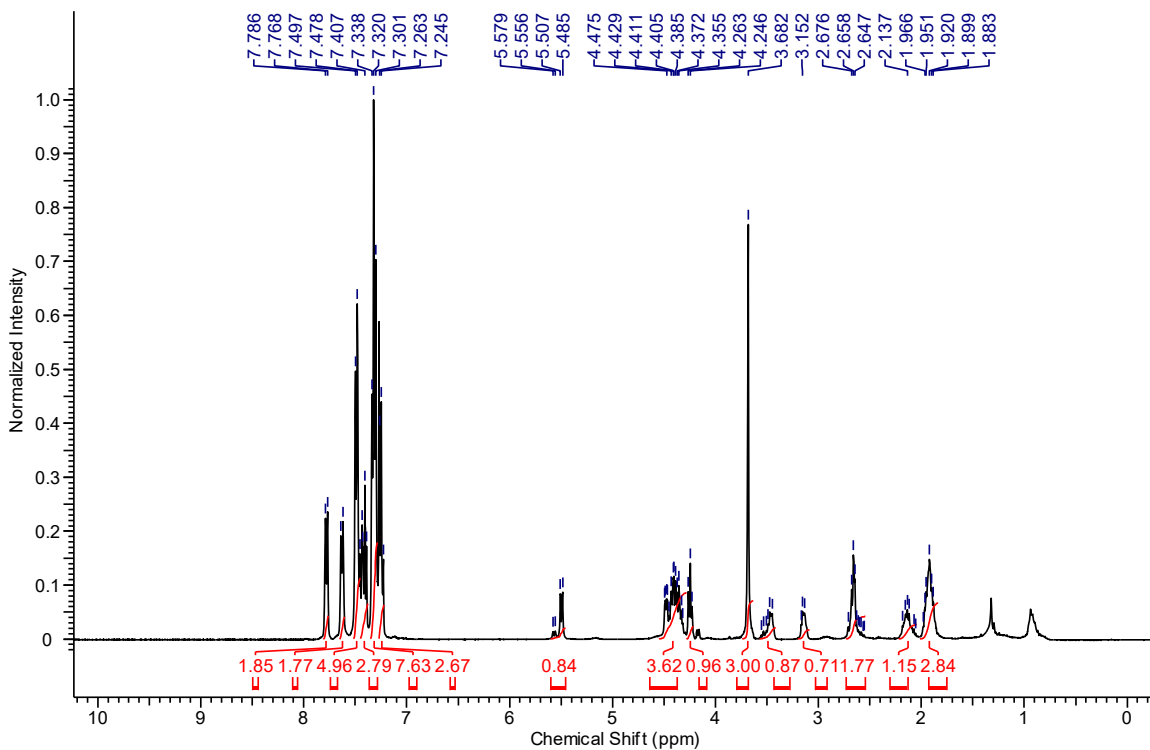


**Triisopropyl(((4-methoxyphenyl)thio)ethynyl)silane (9.28):**

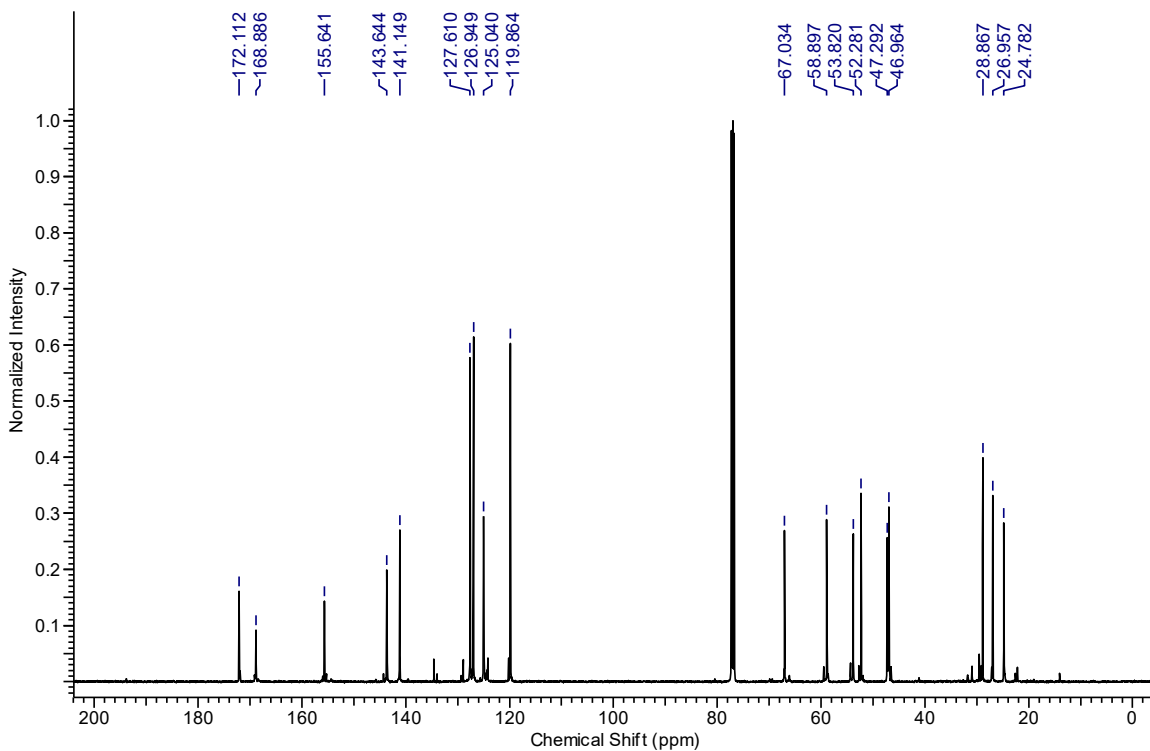
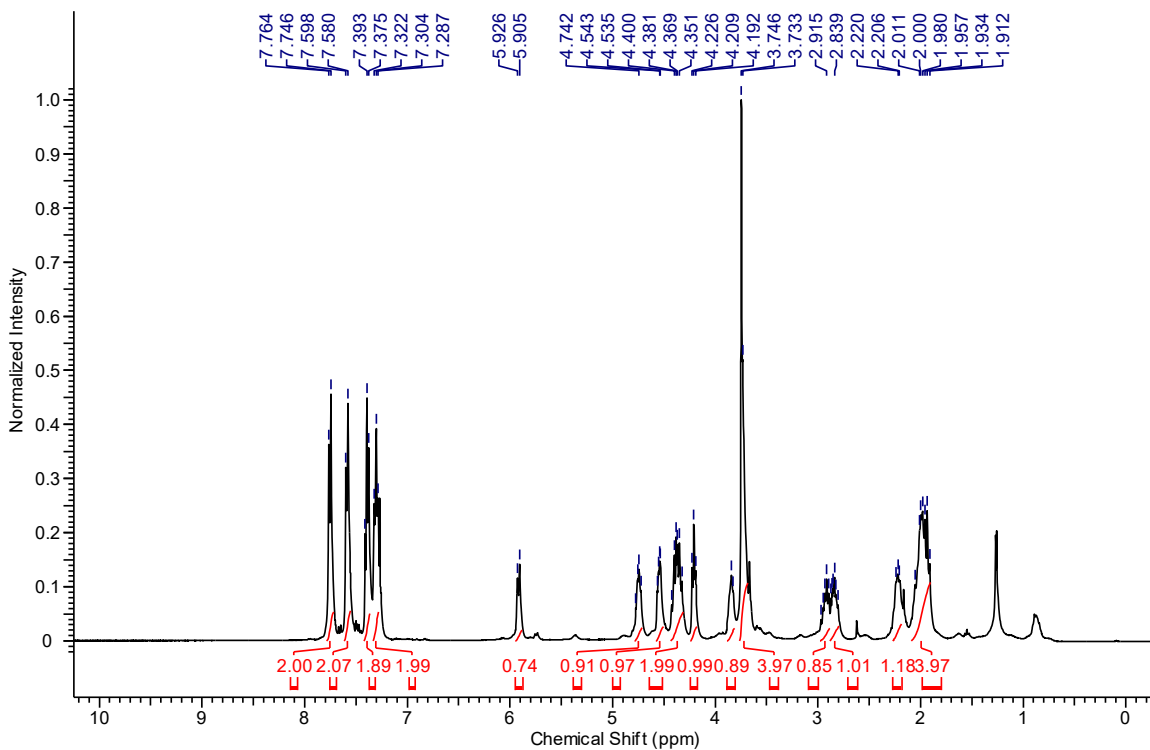




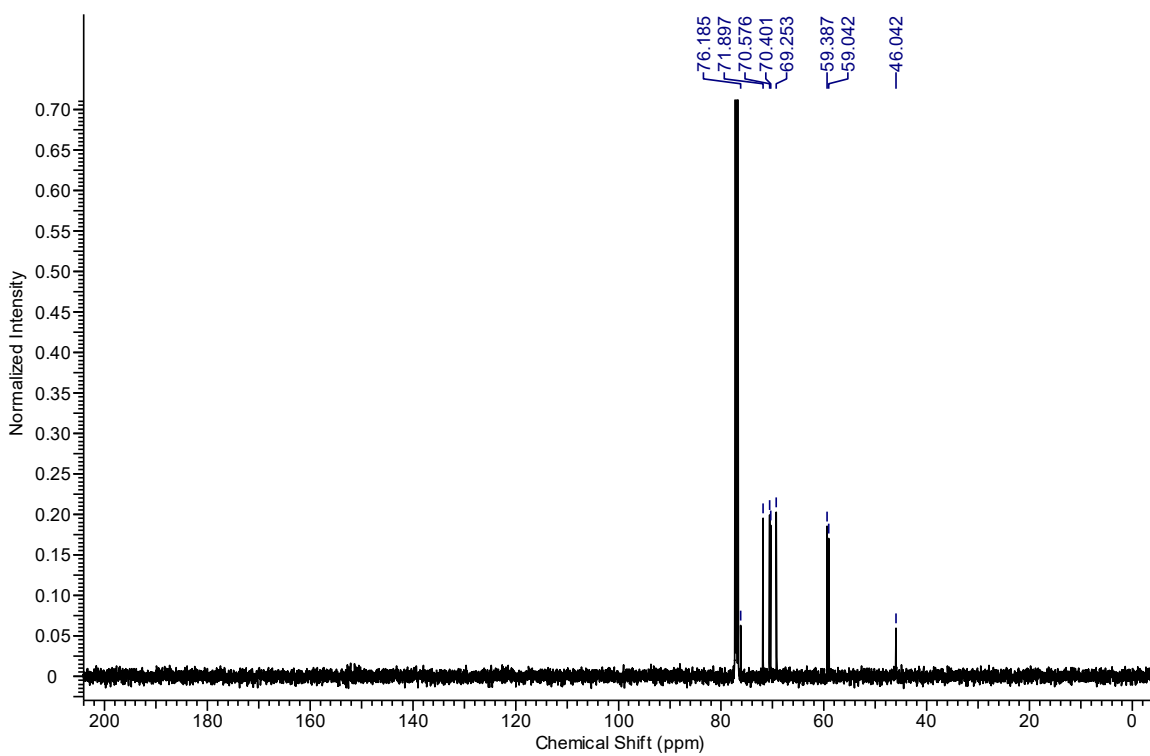
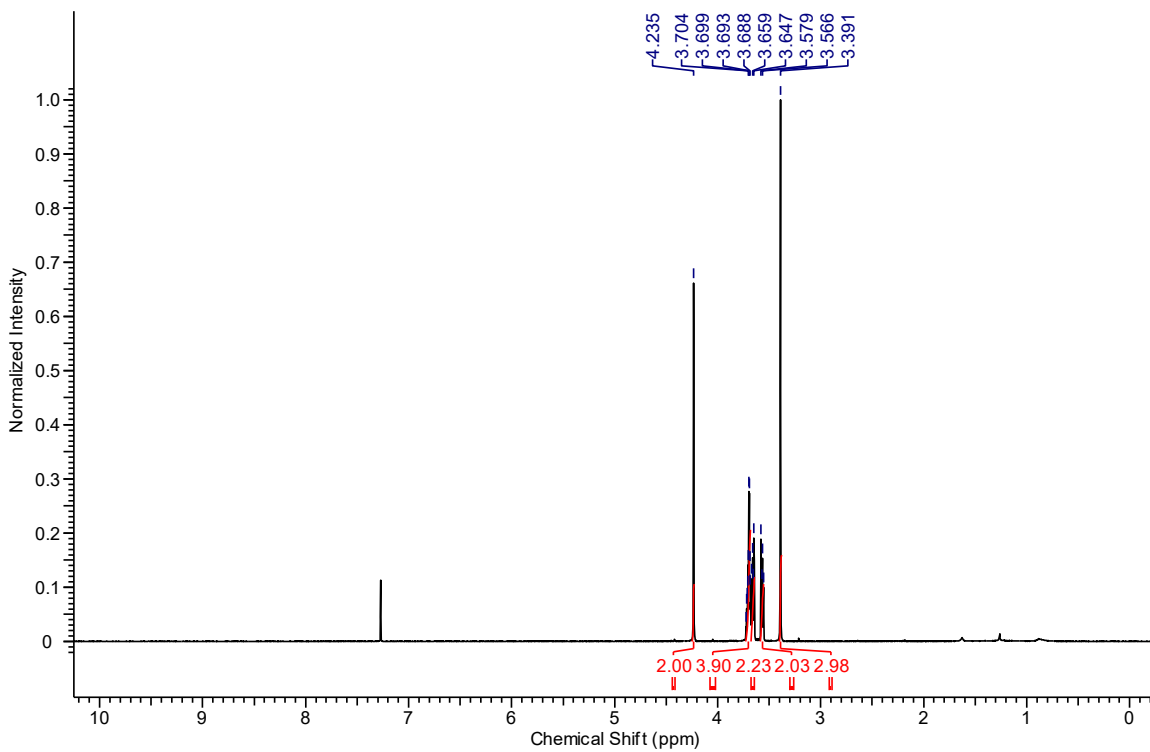
**Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*S*-trityl-*L*-cysteinyl-*L*-prolinate (9.S13):**



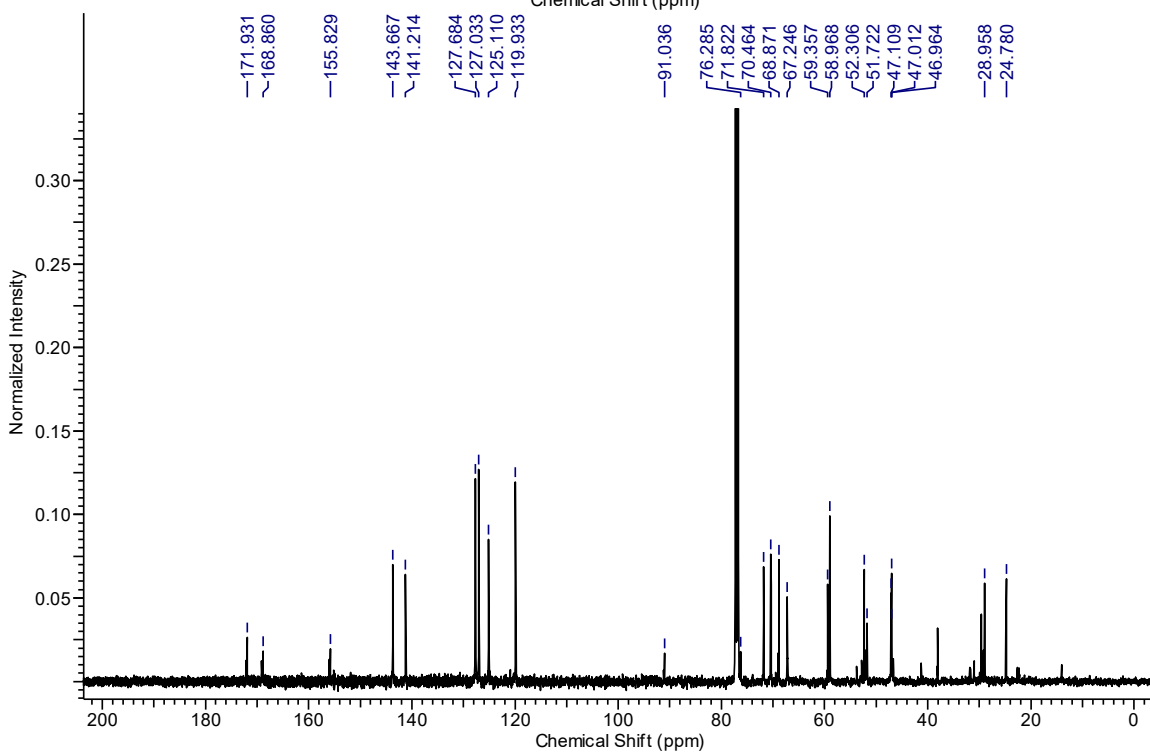
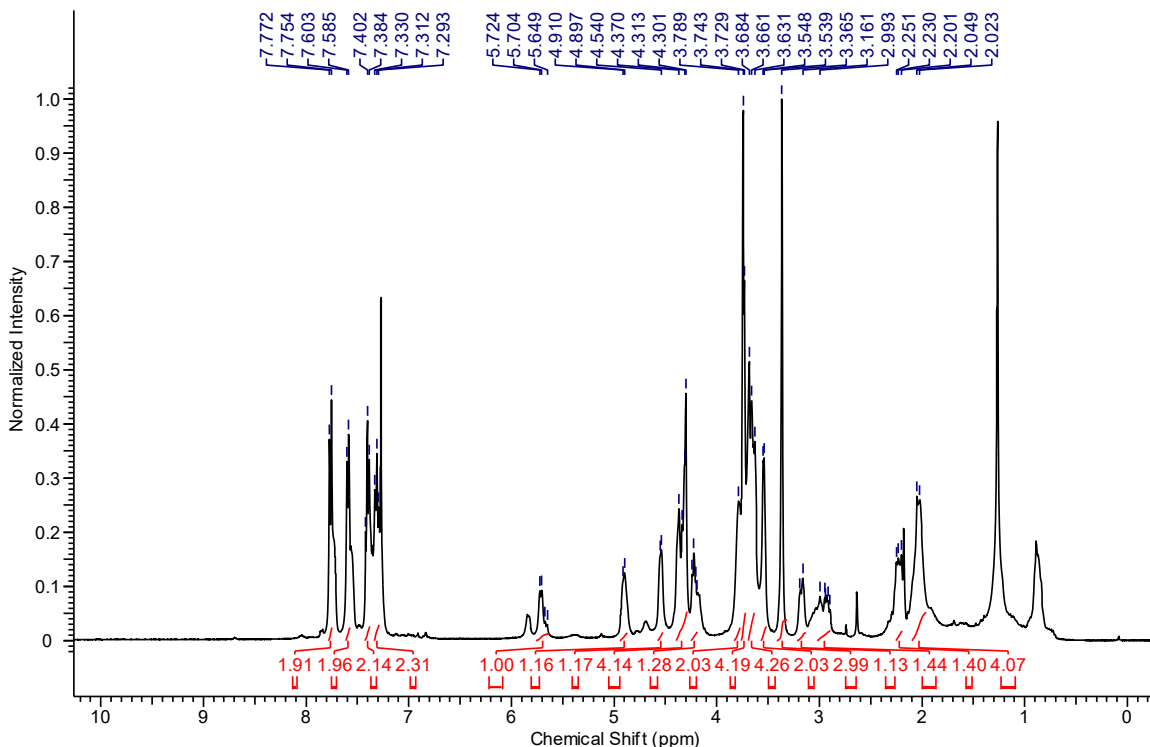
**Methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-cysteinyl-*L*-prolinate (9.S14):**



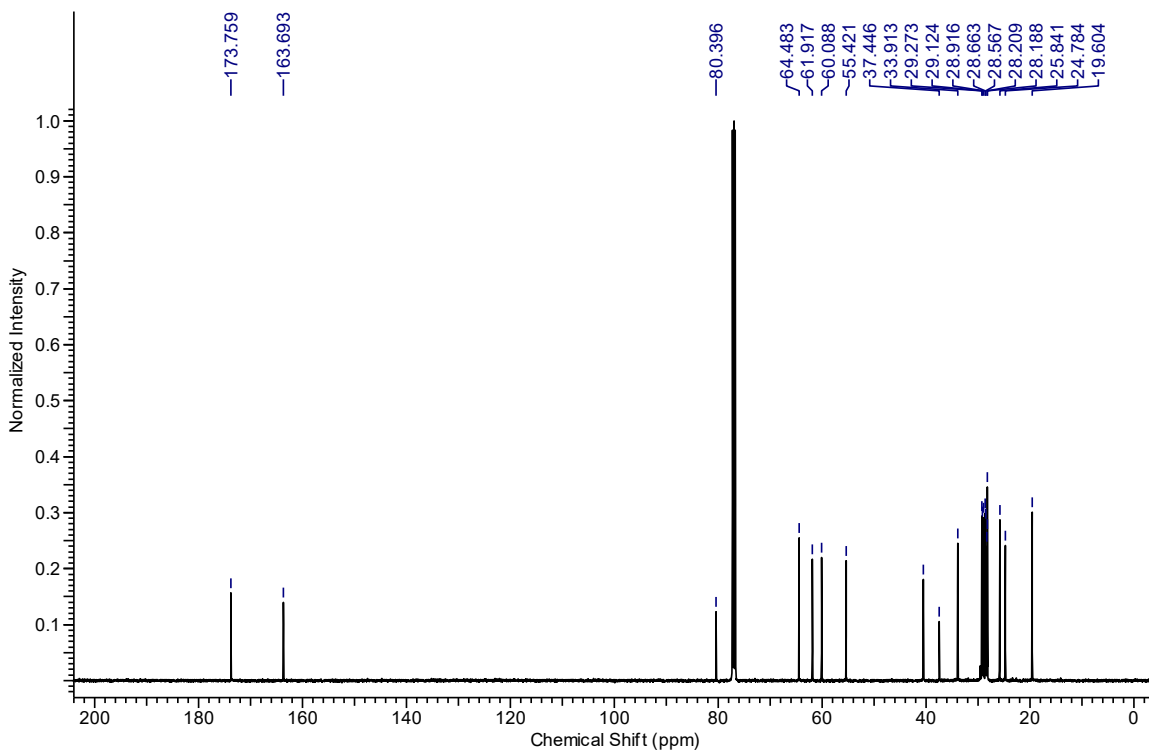
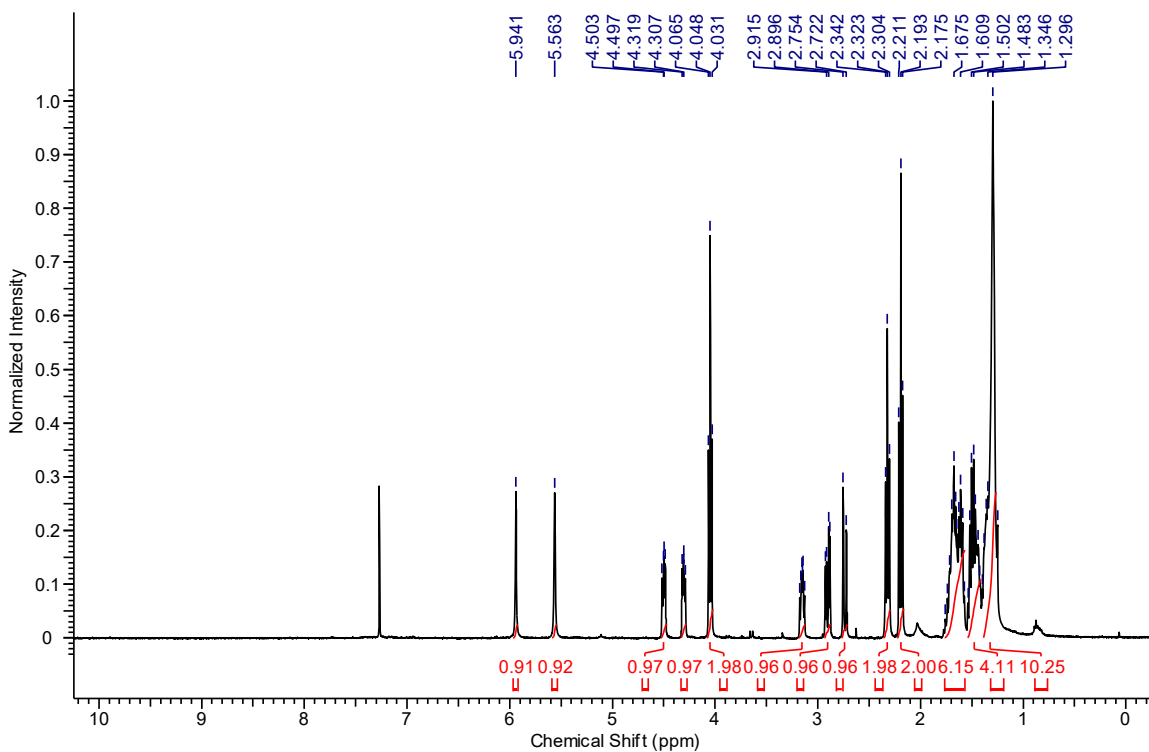
**1-Bromo-3-(2-(2-methoxyethoxy)ethoxy)prop-1-yne (9.S15):**



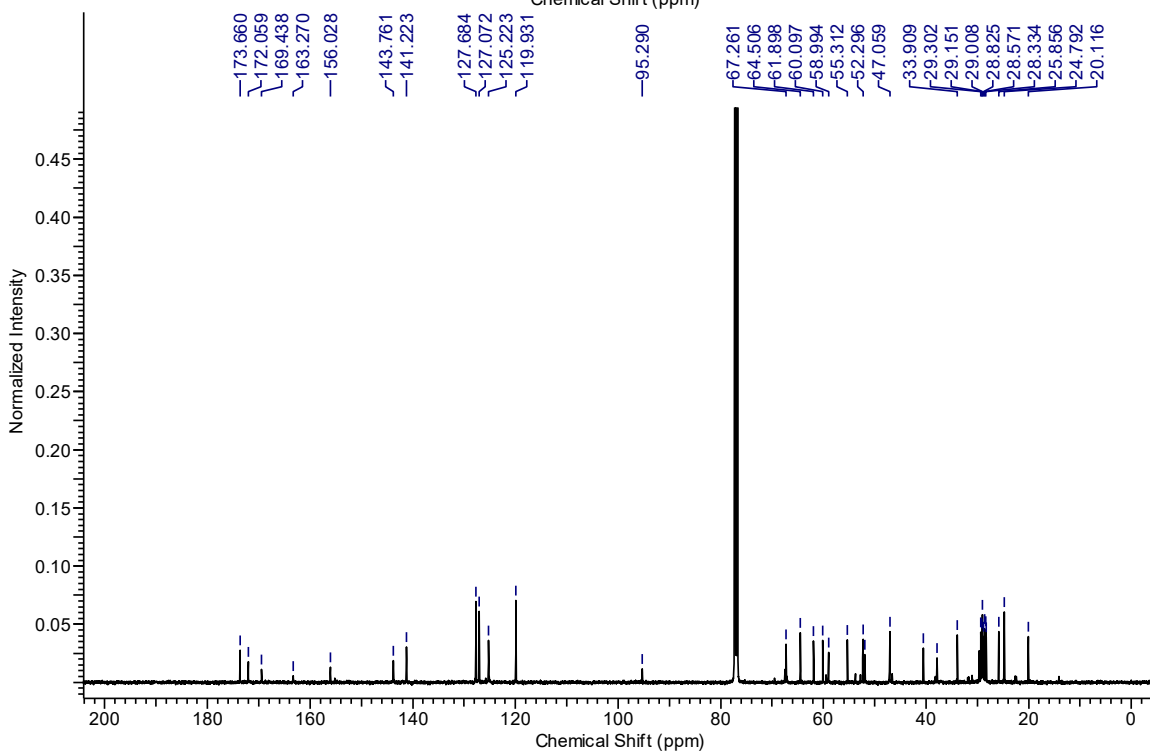
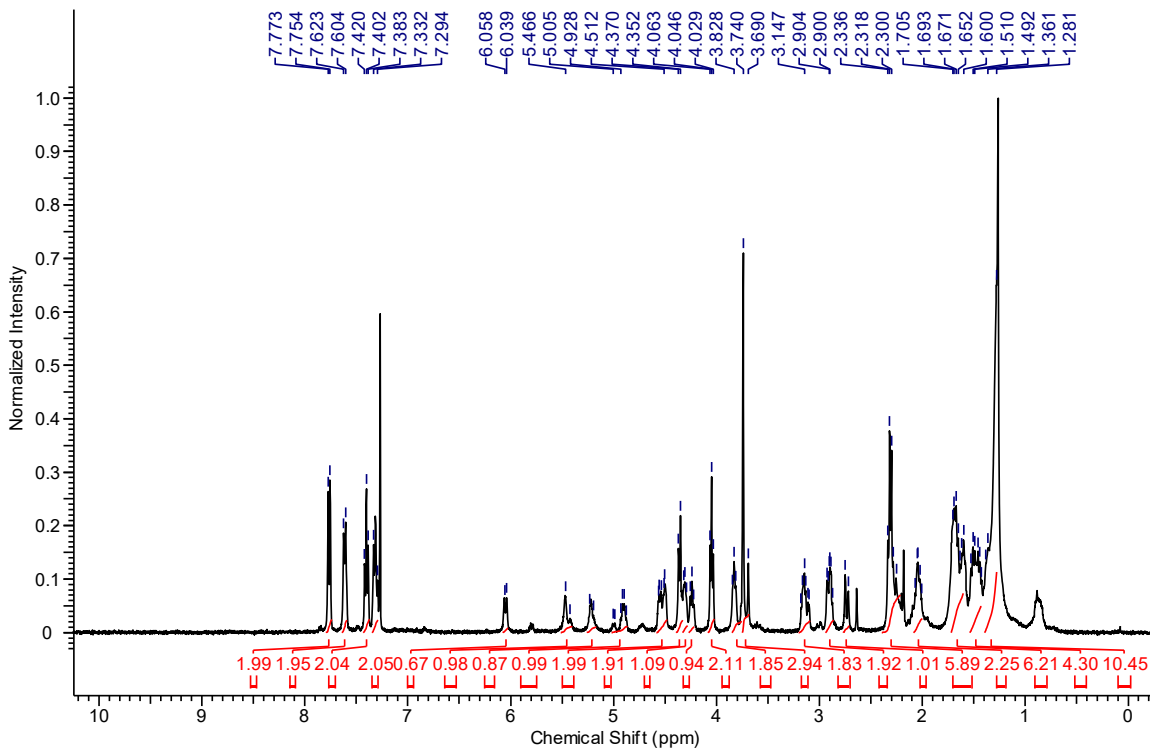
**Methyl ((R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2,5,8-trioxa-12-thiapentadec-10-yn-15-oyl)-L-prolinate (9.29):**



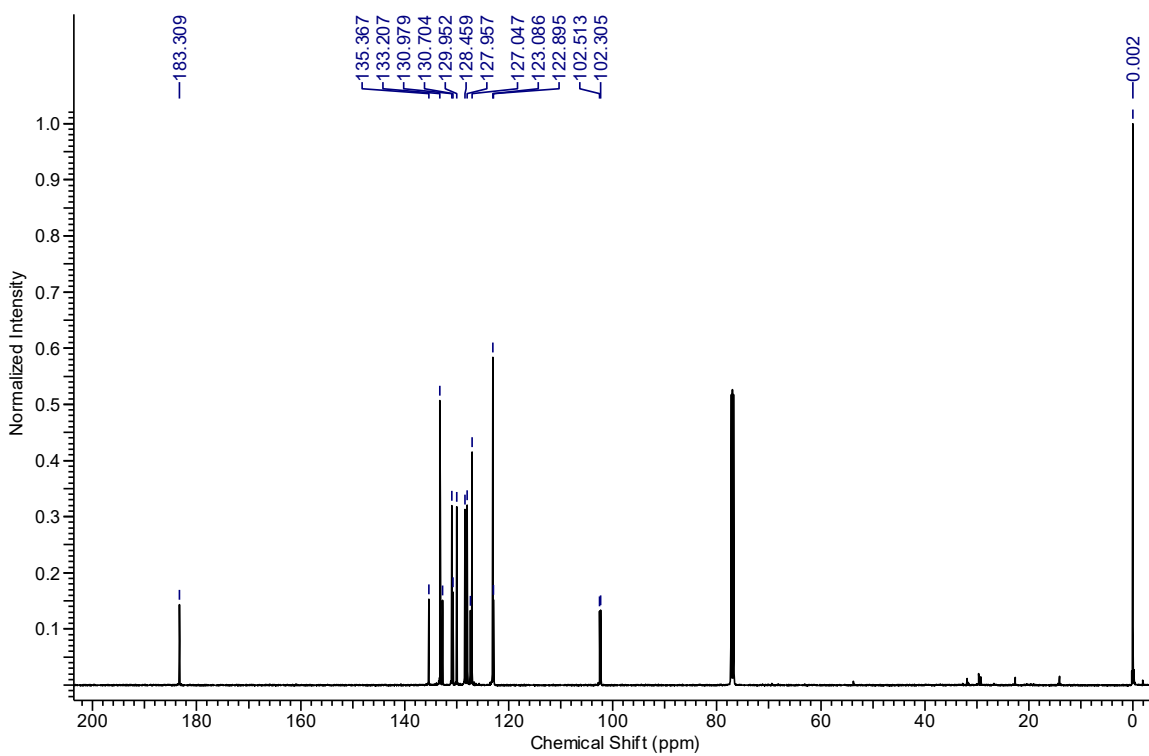
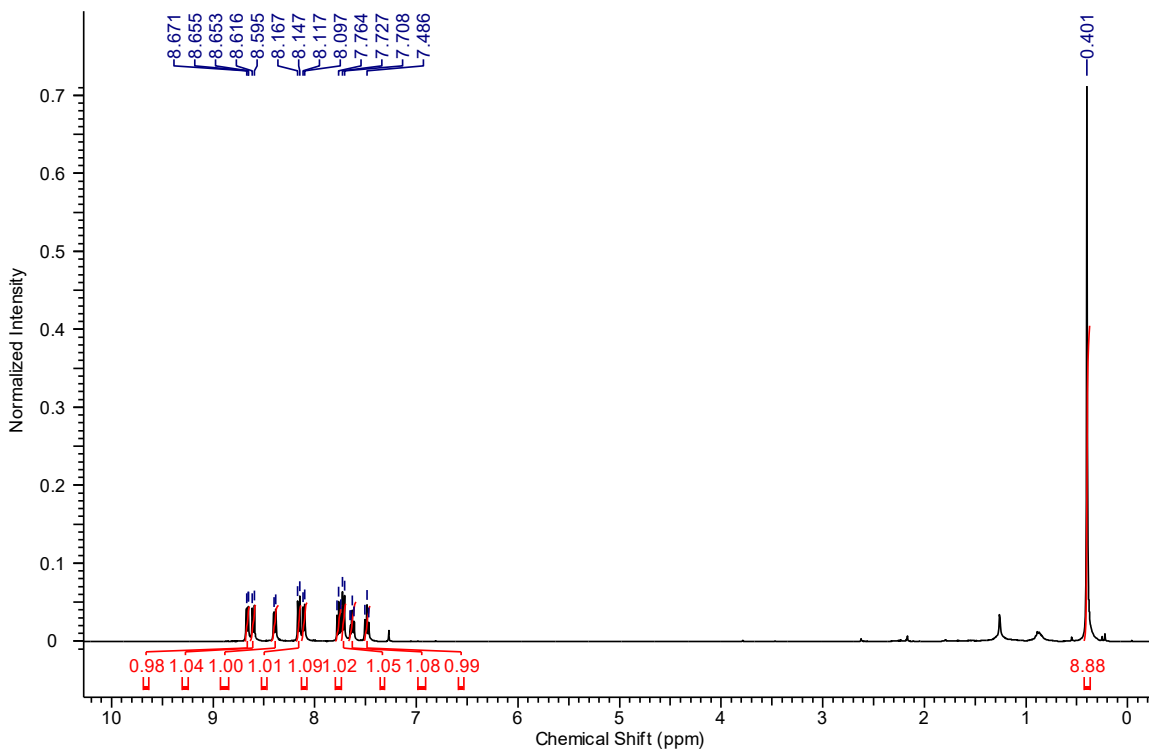
**11-Bromoundec-10-yn-1-yl 5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoate (9.S16):**



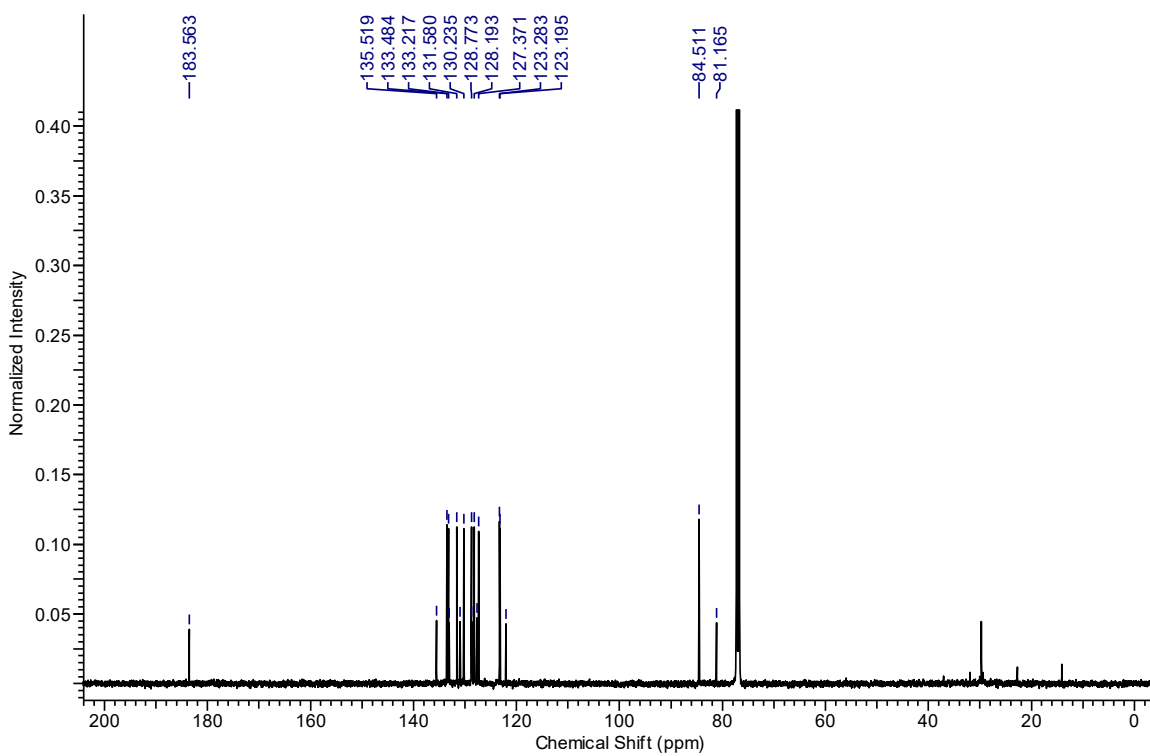
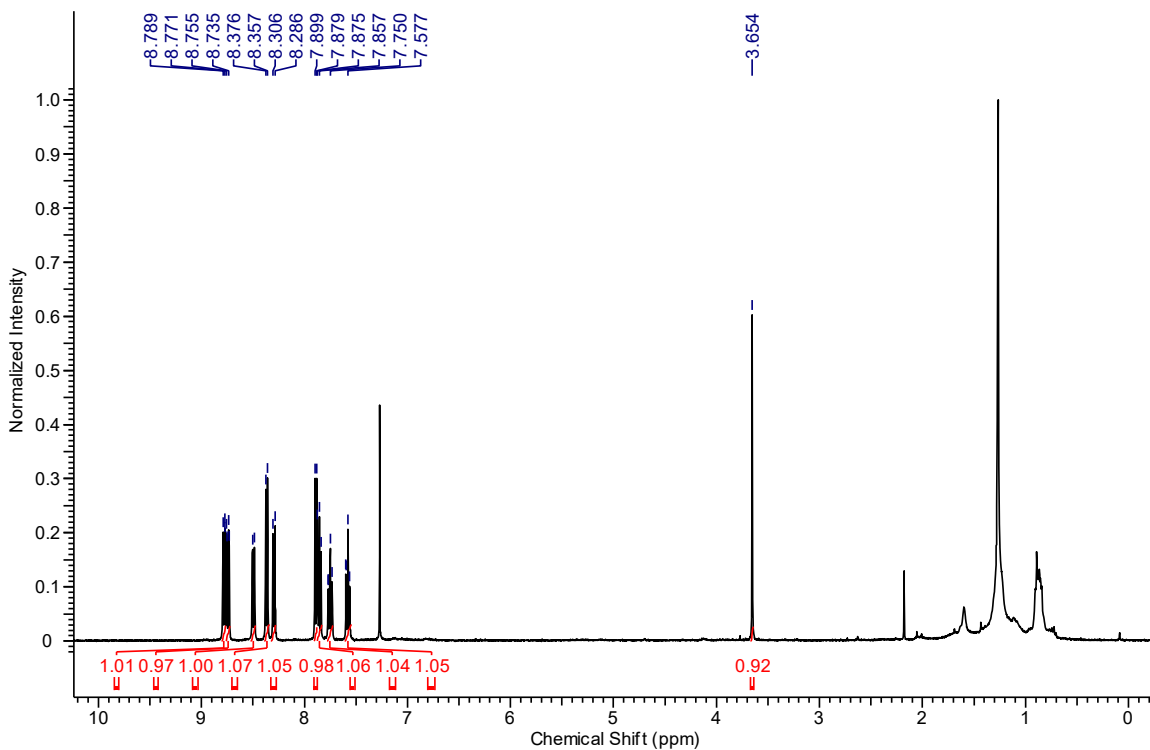
**Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(11-((5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)oxy)undec-1-yn-1-yl)-L-cysteinyl-L-prolinate (9.30):**



**3-((Trimethylsilyl)ethynyl)-7H-benzo[de]anthracen-7-one (9.S17):**

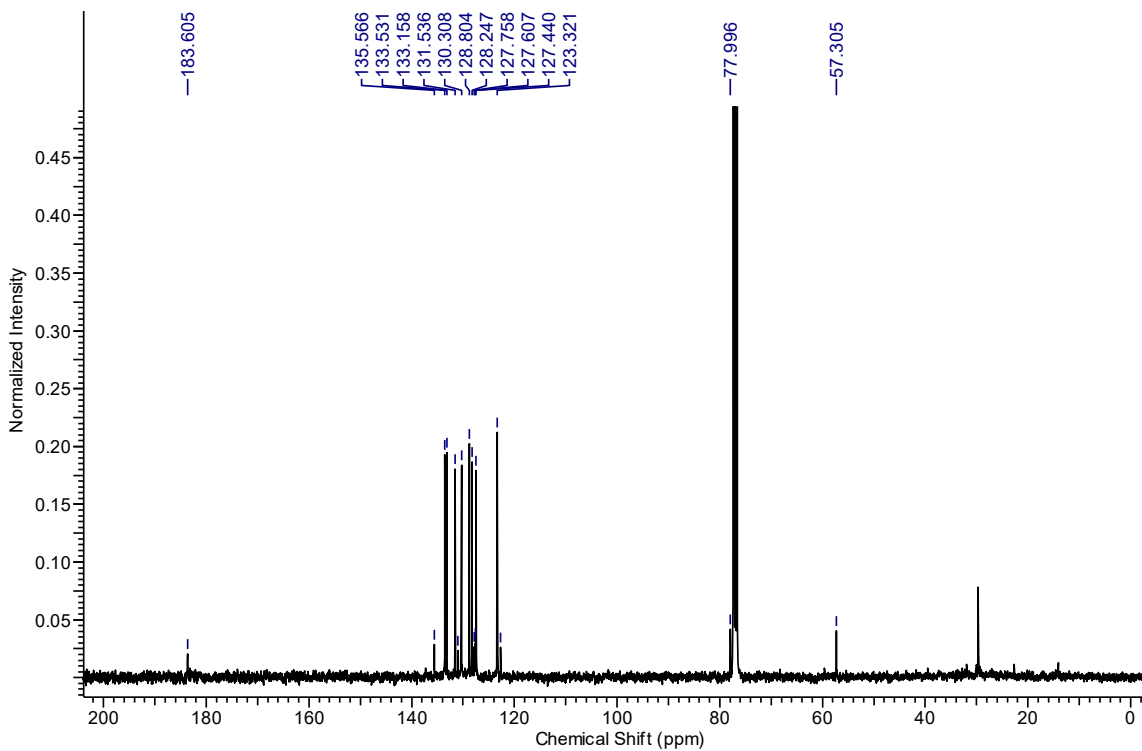
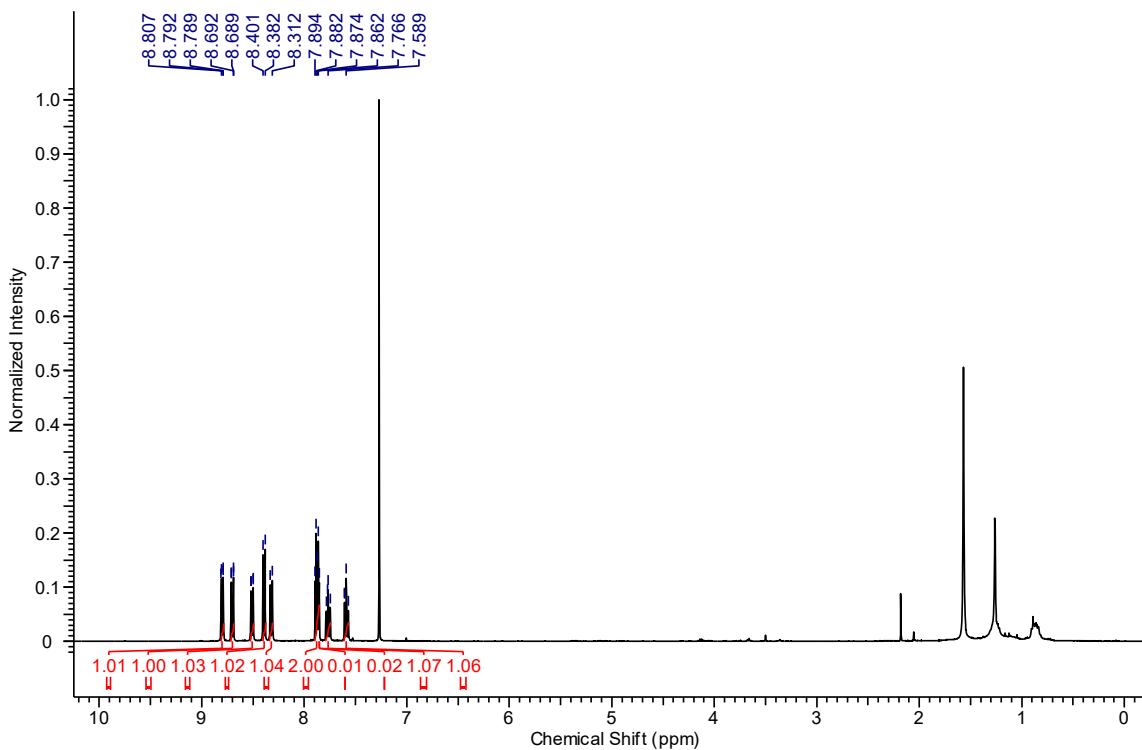


### 3-Ethynyl-7H-benzo[de]anthracen-7-one (9.S18):

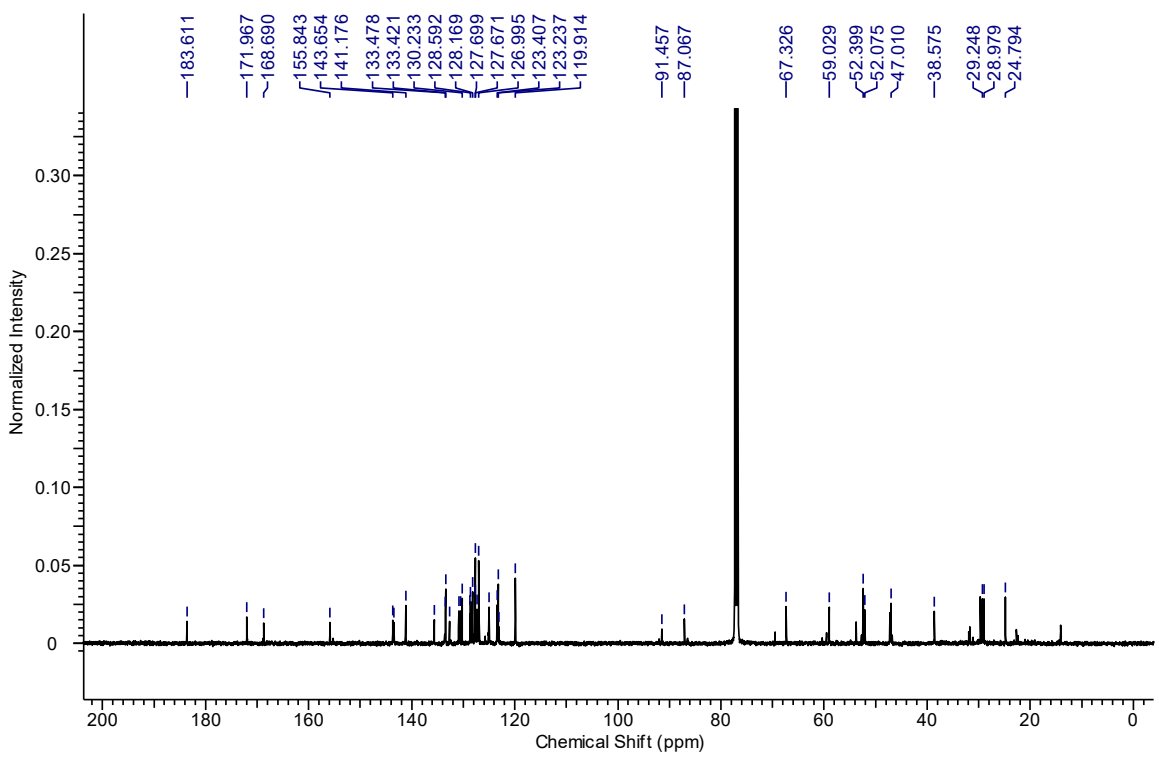
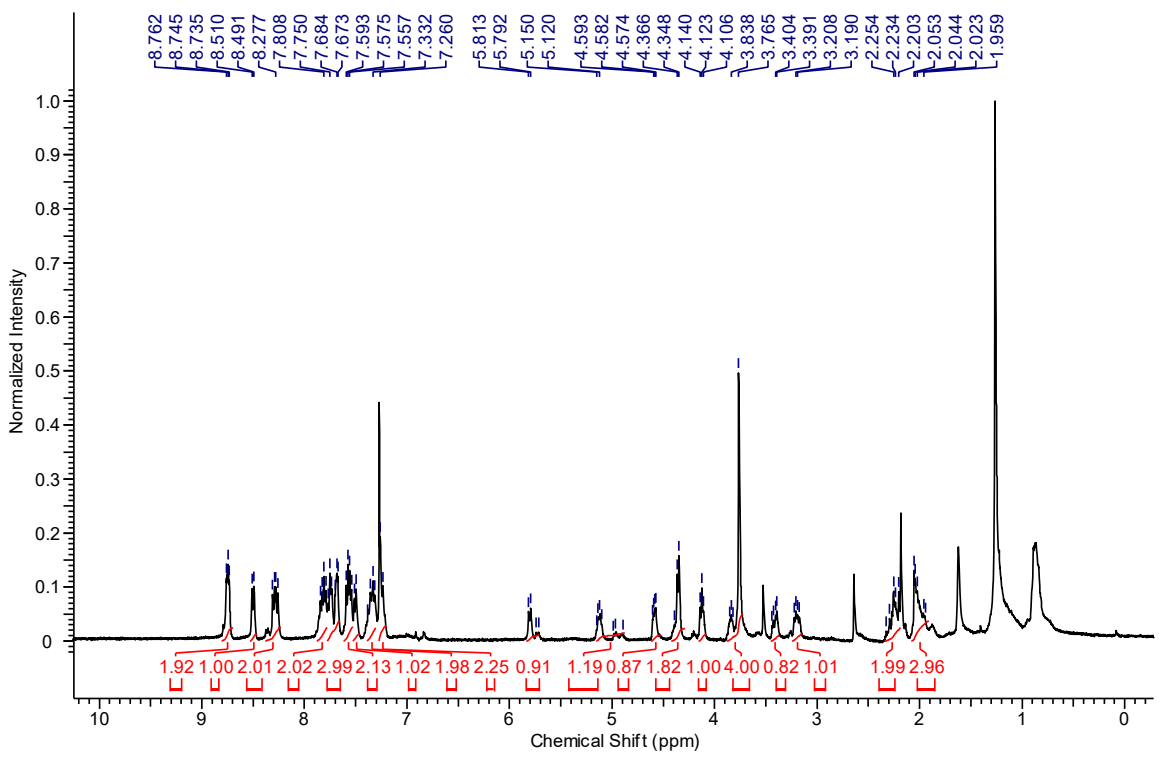




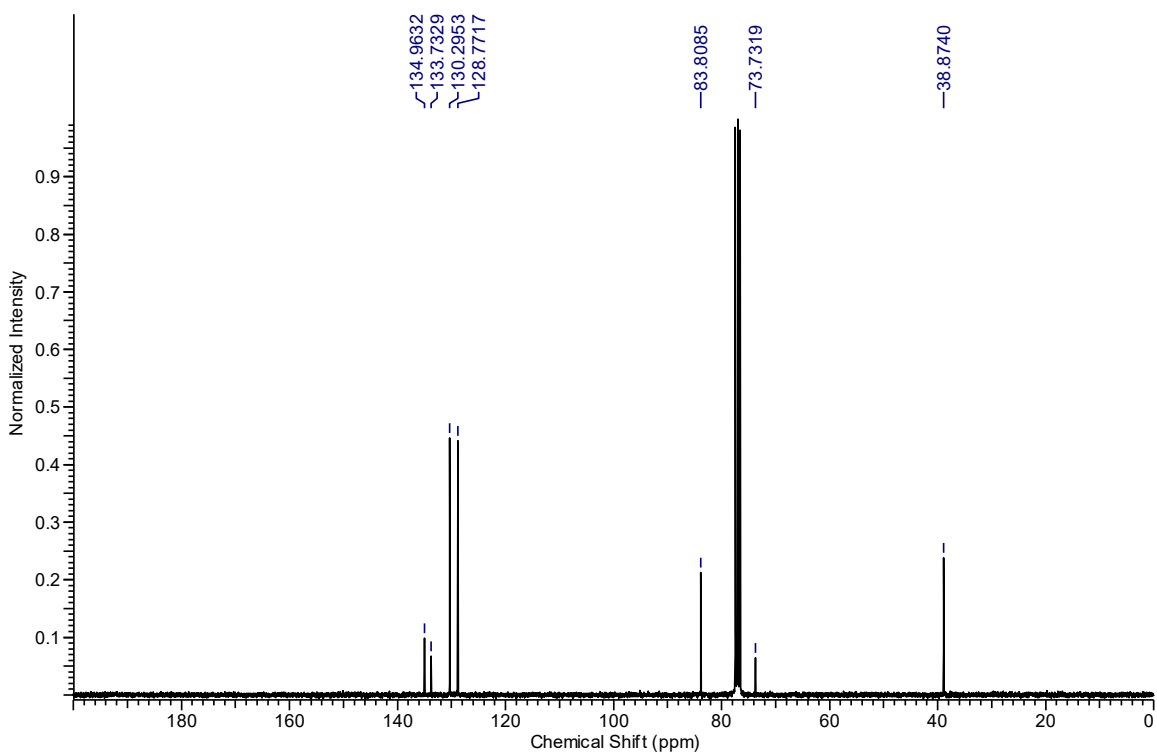
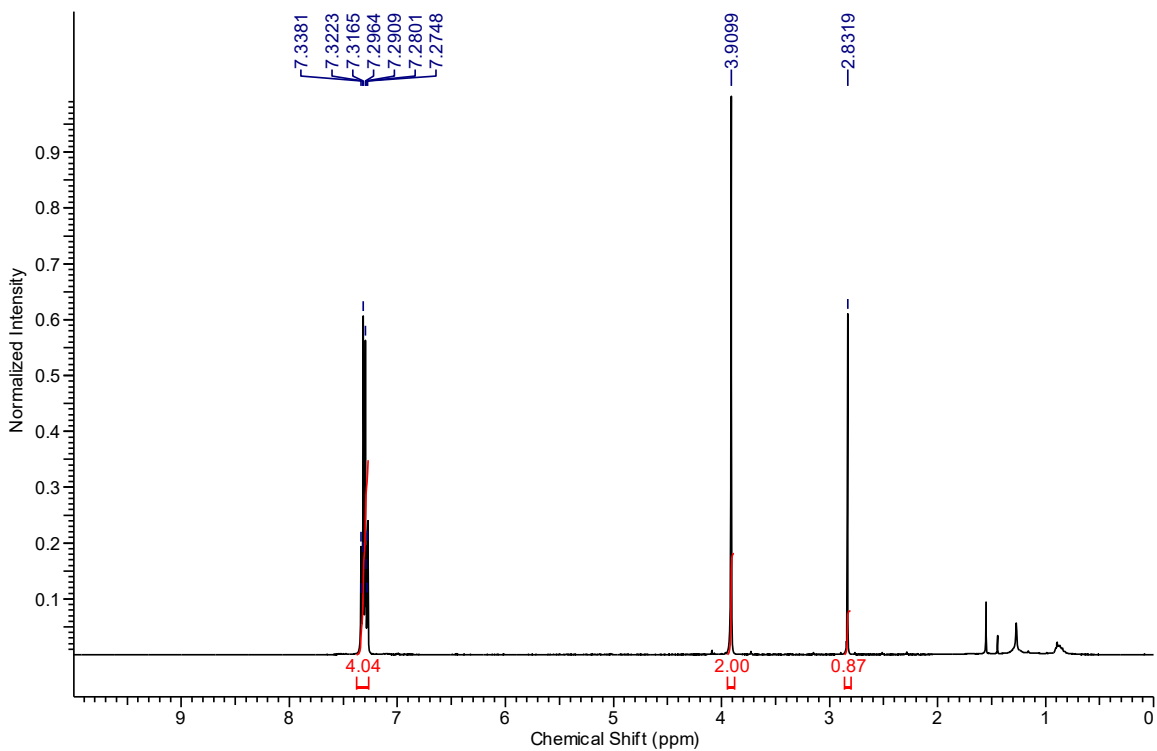
**3-(Bromoethynyl)-7H-benzo[de]anthracen-7-one (9.S19):**



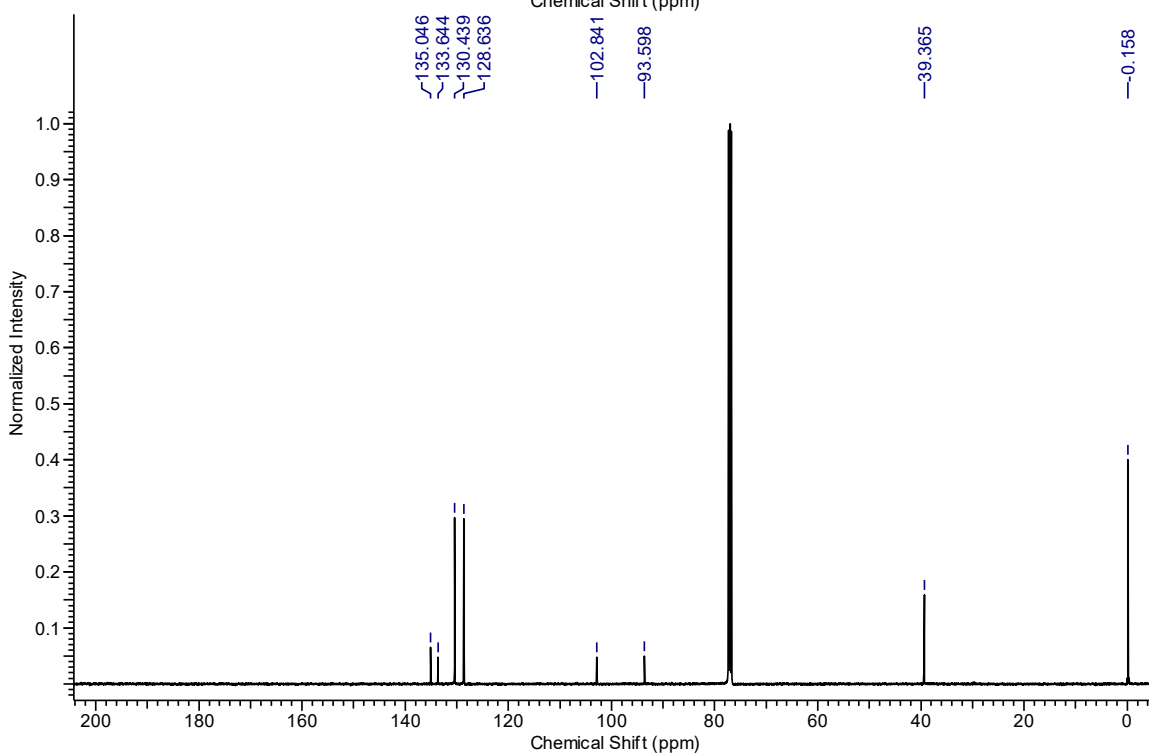
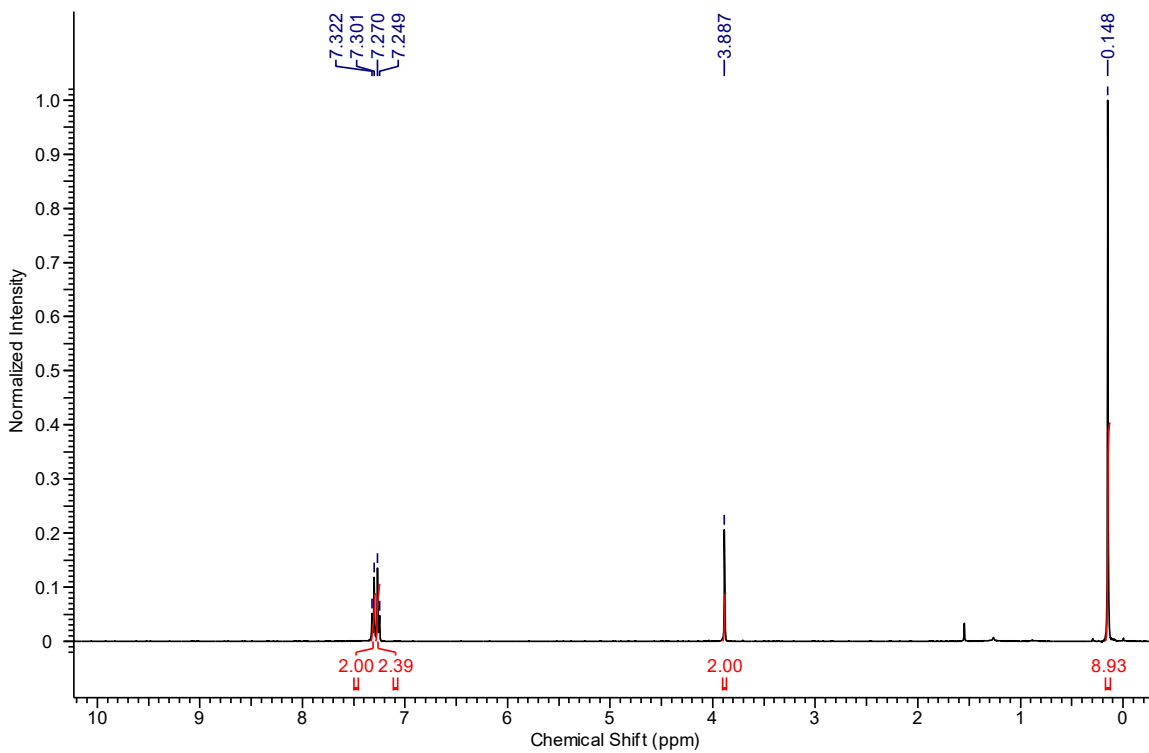
**Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*S*-((7-oxo-7*H*-benzo[*de*]anthracen-3-yl)ethynyl)-*L*-cysteinyl-*L*-prolinate (9.31):**



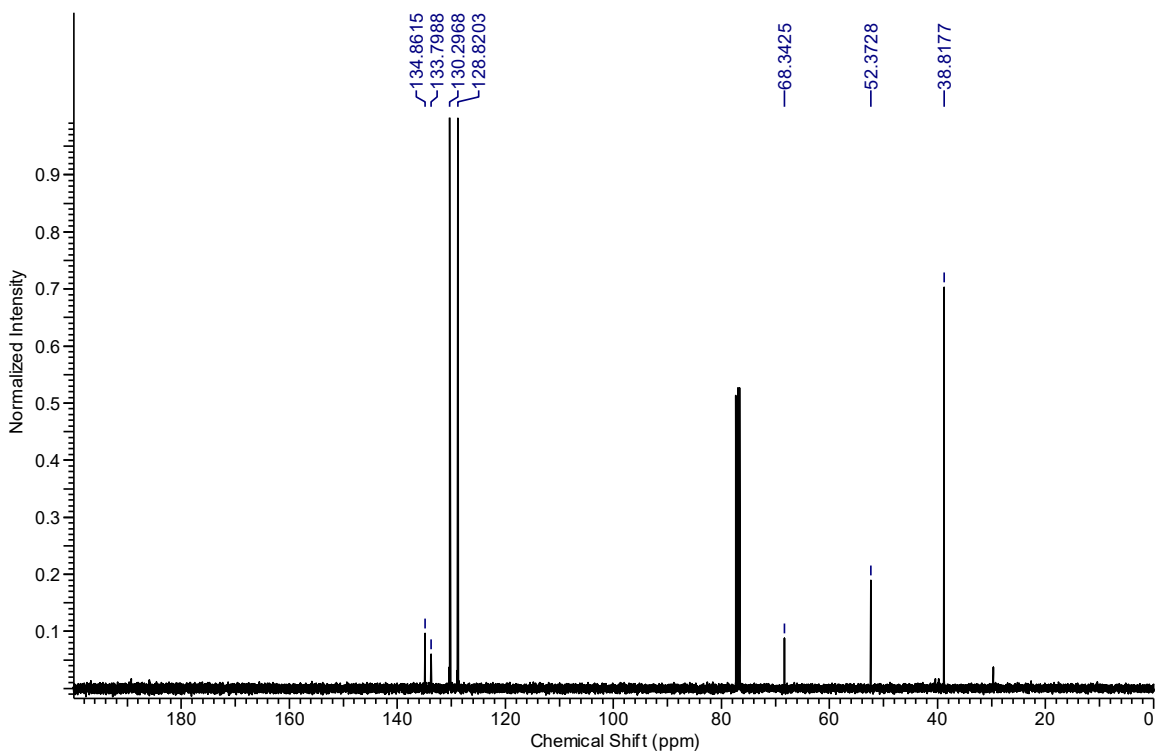
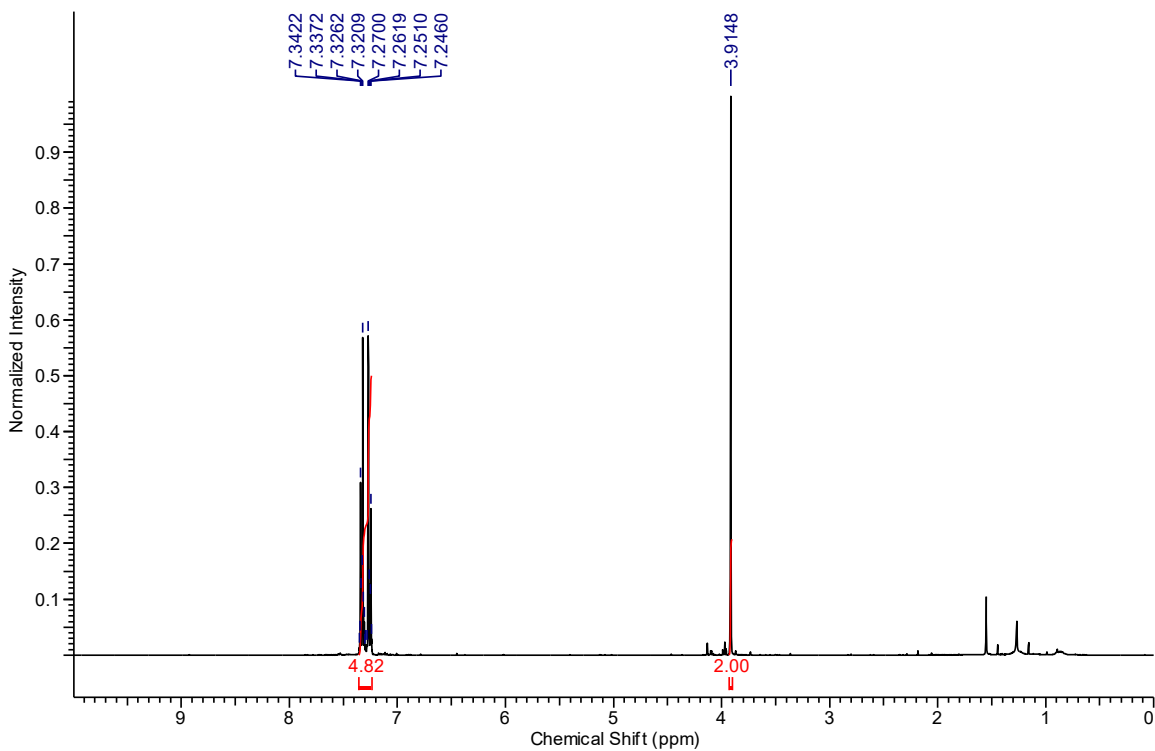
**(4-Chlorobenzyl)(ethynyl)sulfane (9.S20):**



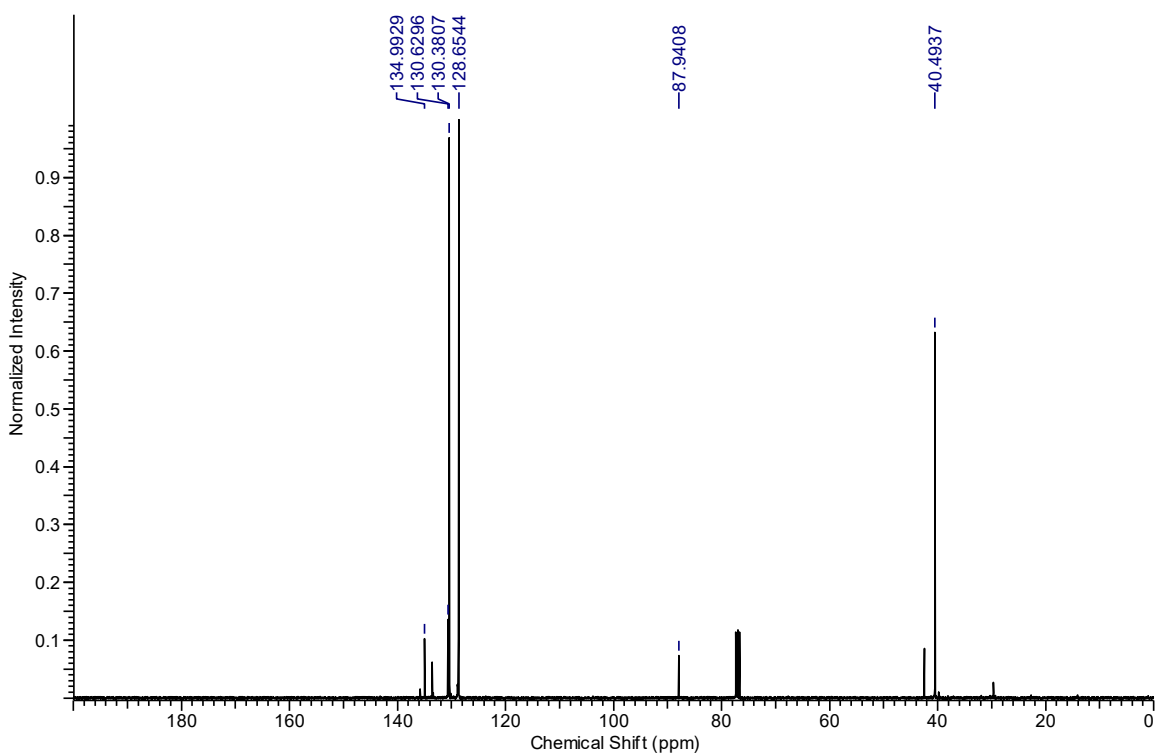
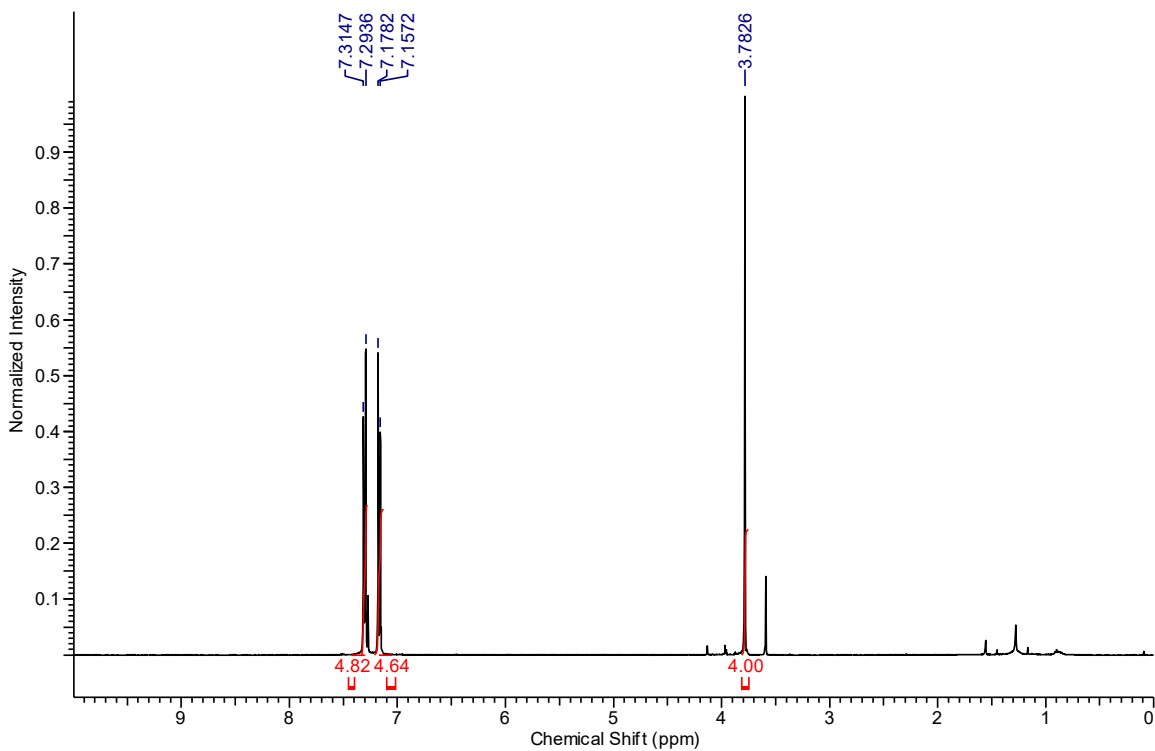
**(((4-Chlorobenzyl)thio)ethynyl)trimethylsilane (9.43):**



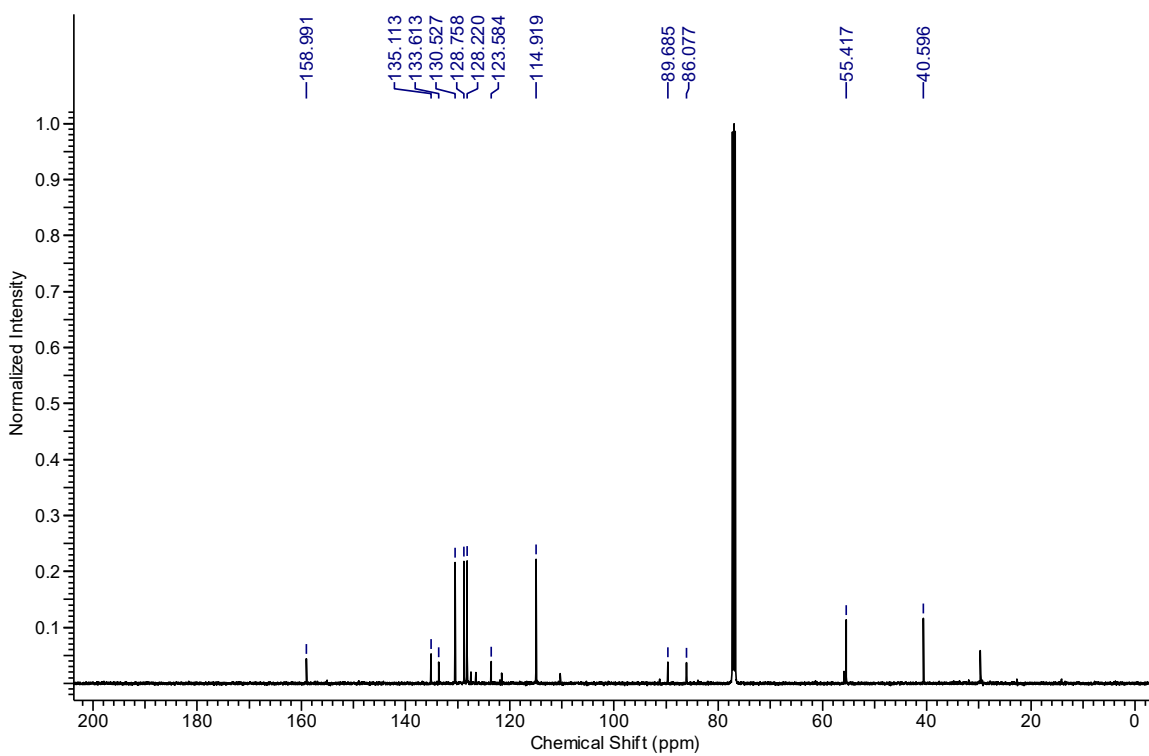
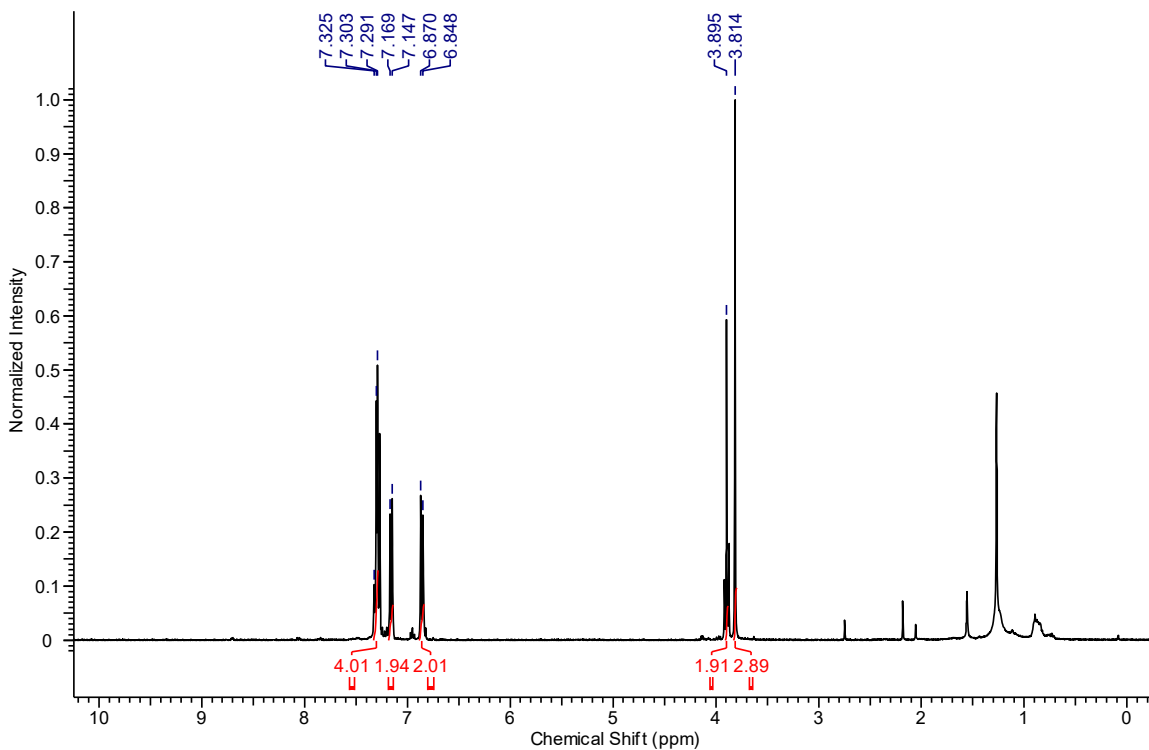
**(Bromoethynyl)(4-chlorobenzyl)sulfane (9.44):**



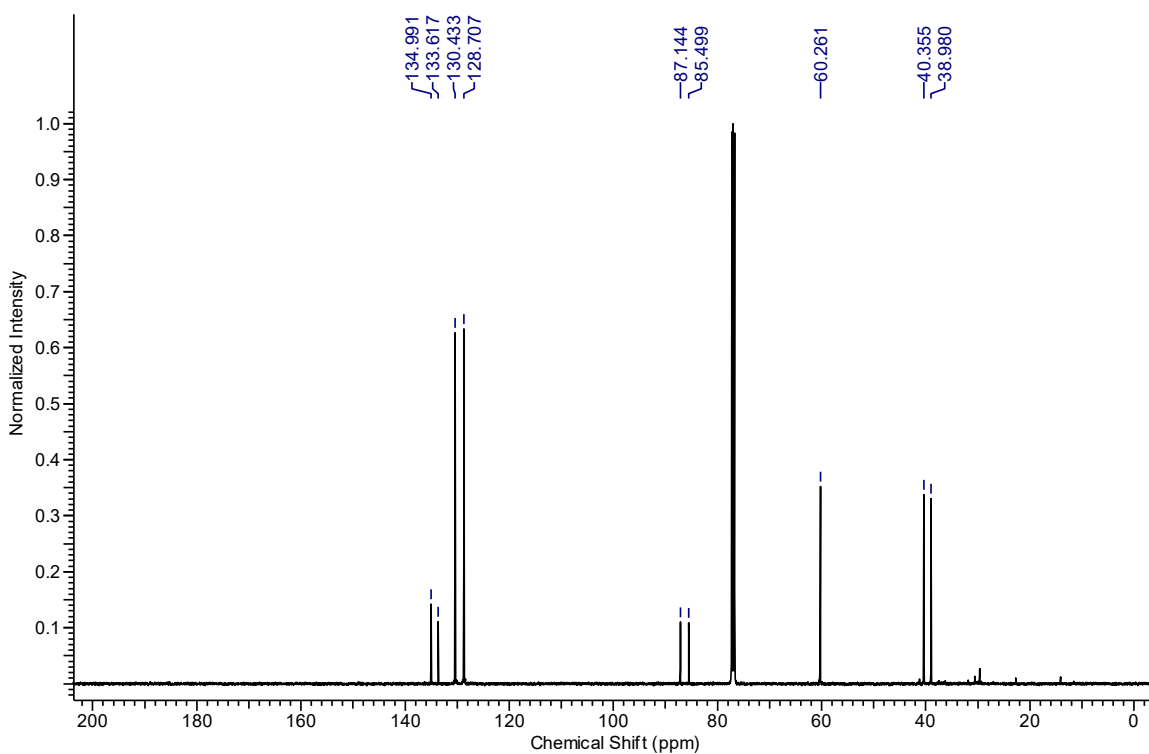
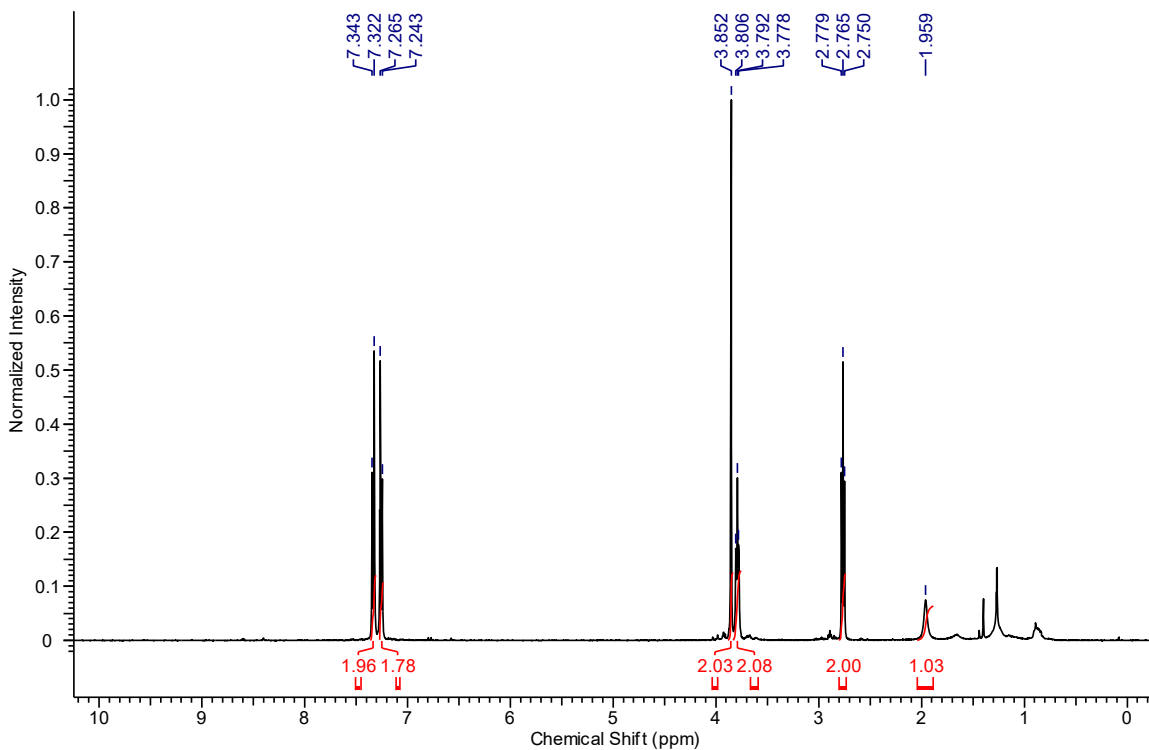
**1,2-Bis((4-chlorobenzyl)thio)ethyne (9.32):**



**(4-Chlorobenzyl)((4-methoxyphenyl)thio)ethynyl)sulfane (9.33):**

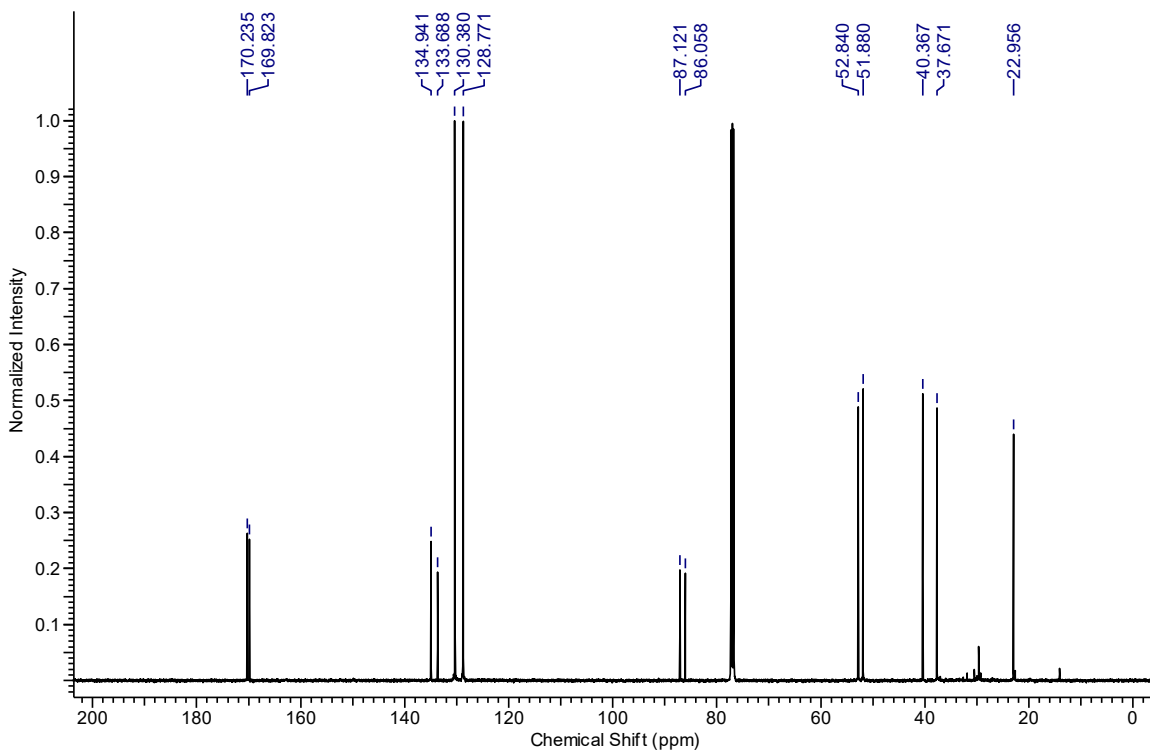
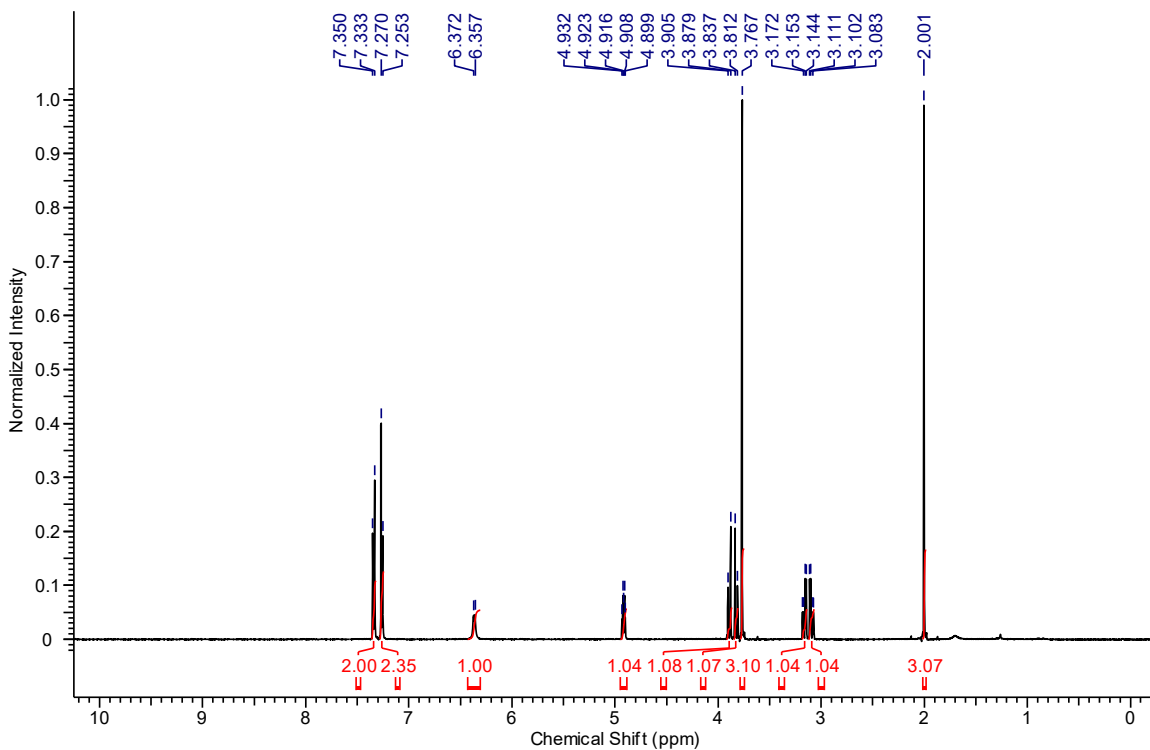


**2-(((4-Chlorobenzyl)thio)ethynyl)thio)ethan-1-ol (9.34):**





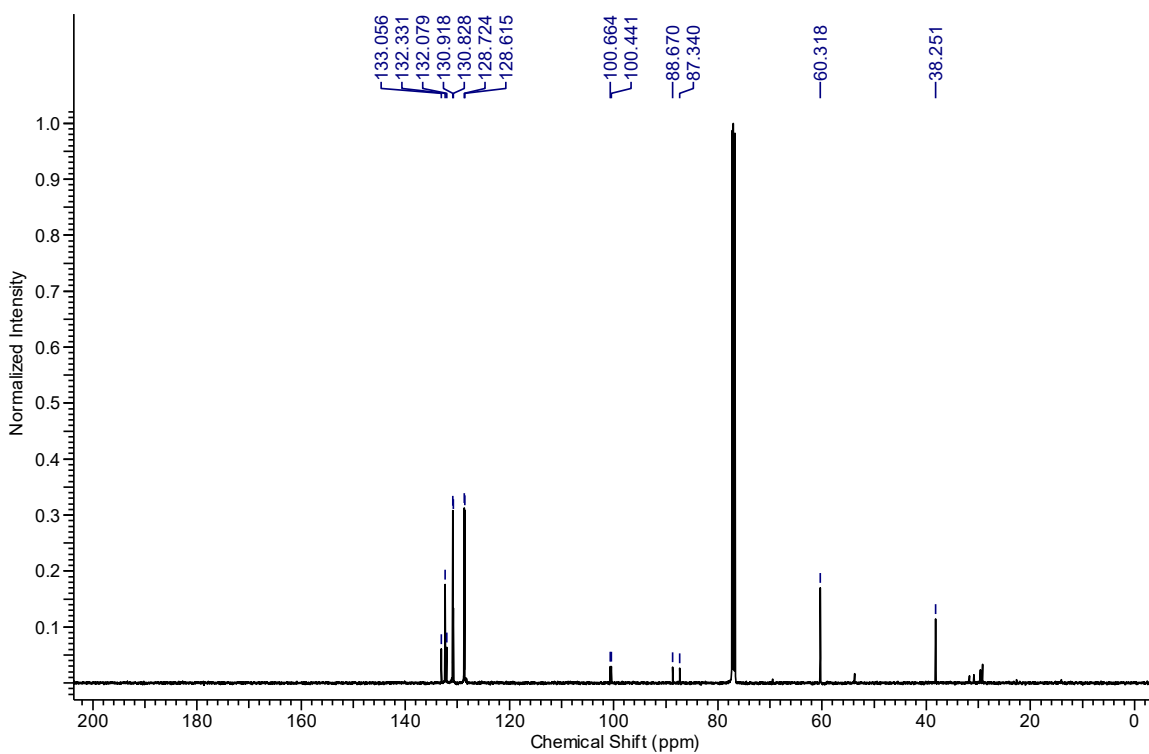
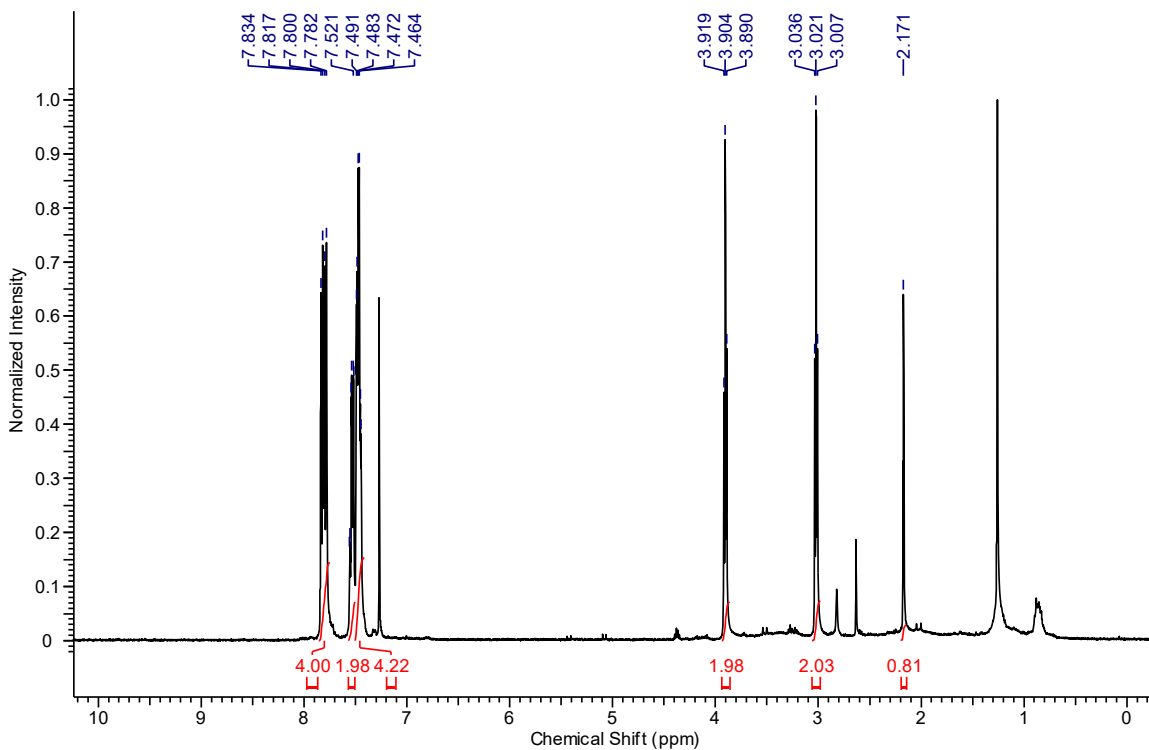
**Methyl *N*-acetyl-*S*-(((4-chlorobenzyl)thio)ethynyl)-*L*-cysteinate (9.35):**



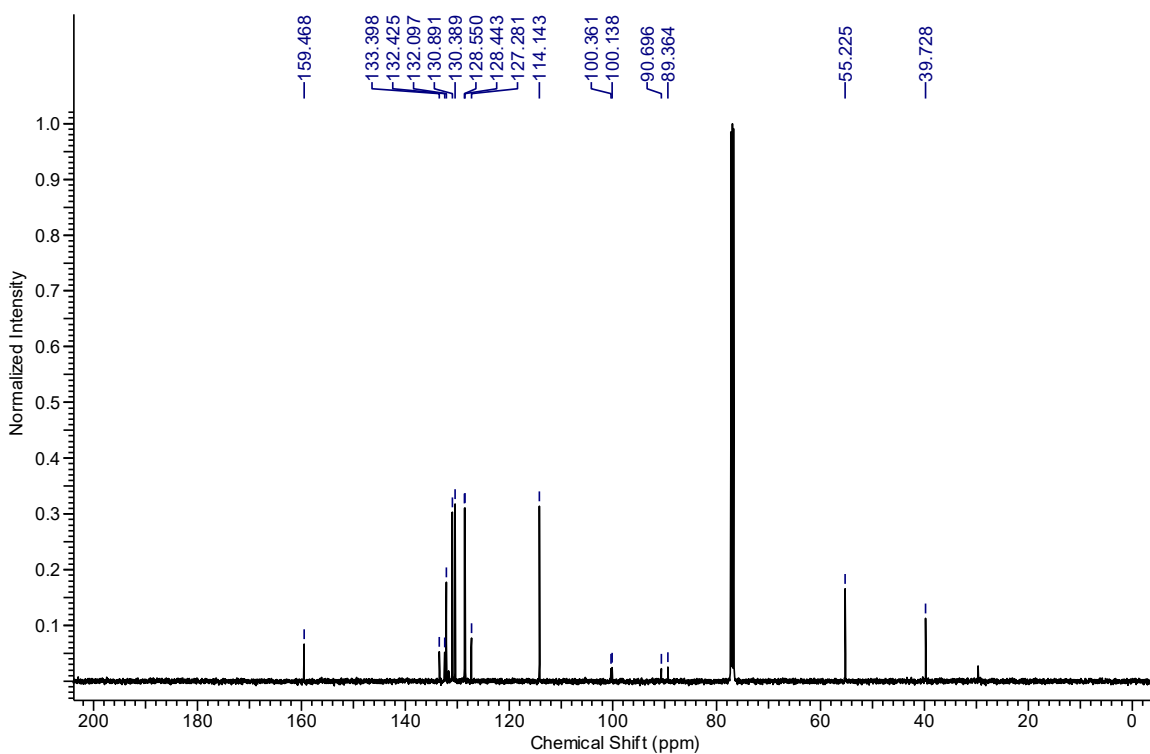
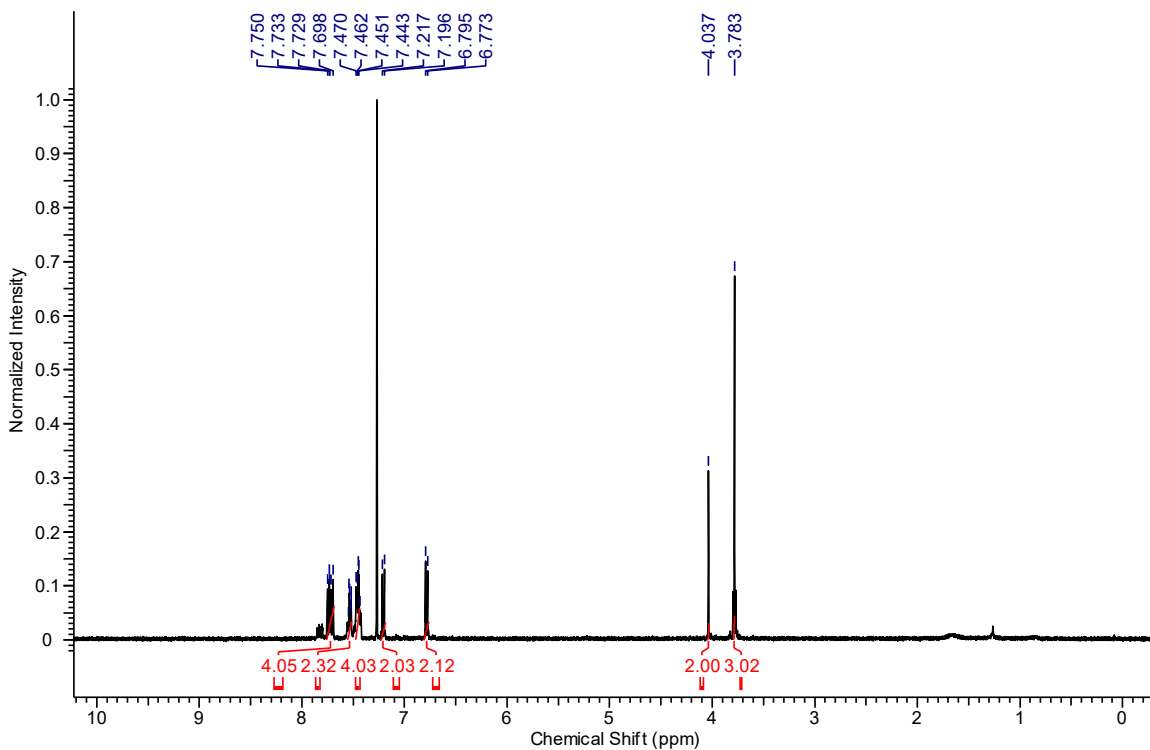
**(((2-Hydroxyethyl)thio)ethynyl)diphenylphosphine**

**oxide**

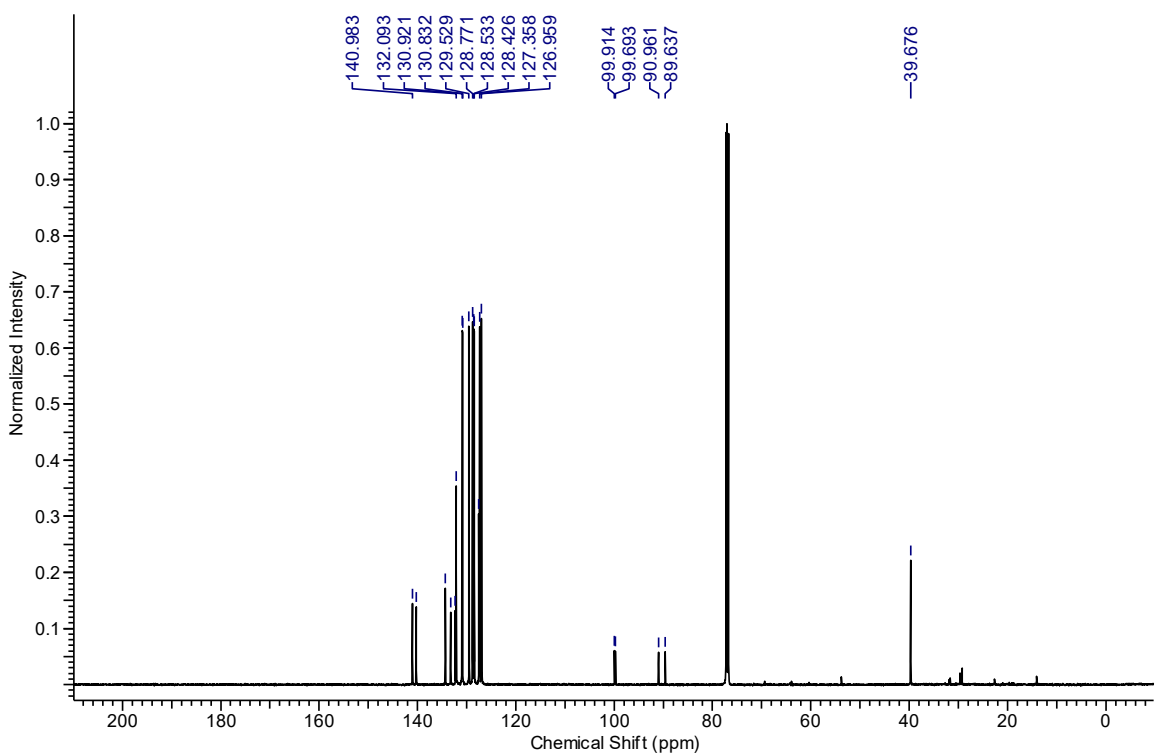
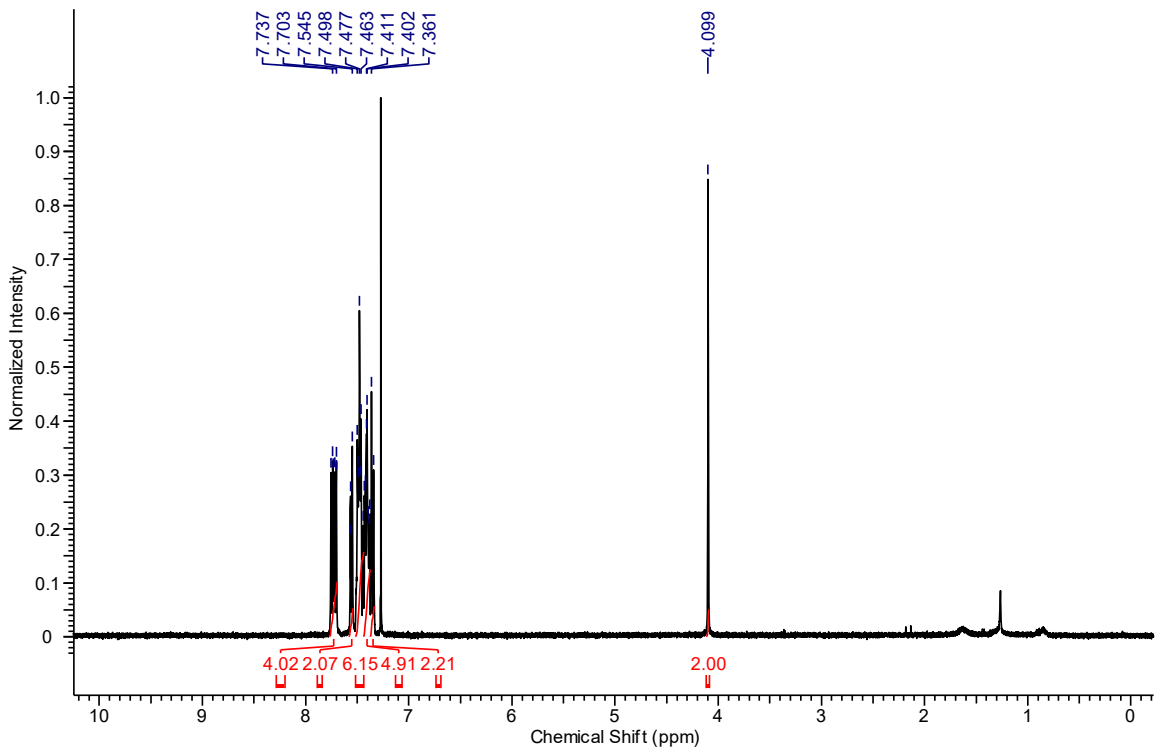
**(9.S36):**



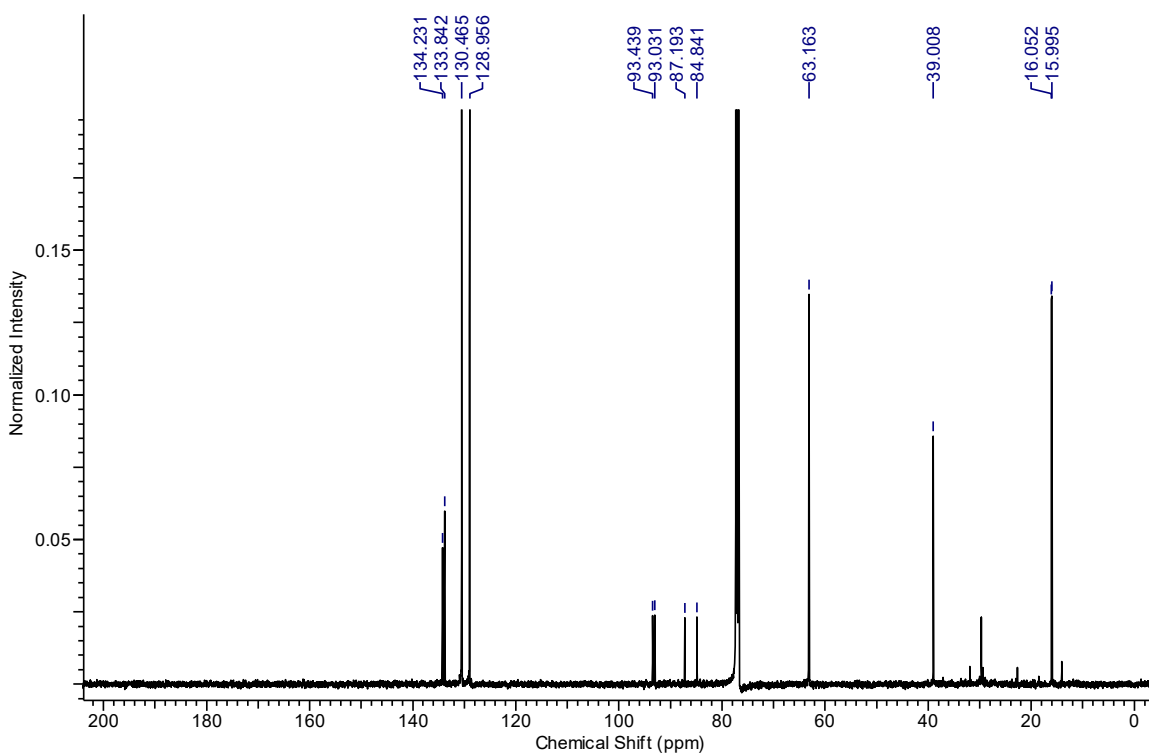
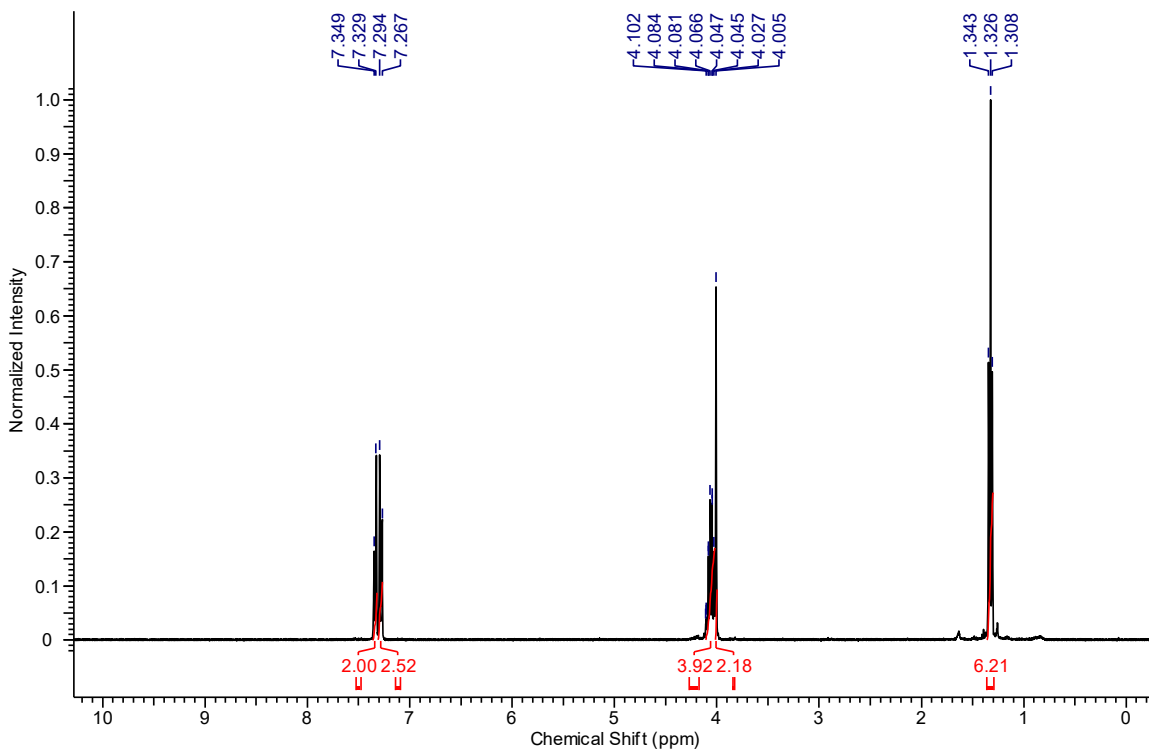
**(3-(4-Methoxyphenyl)prop-1-yn-1-yl)diphenylphosphine oxide (9.37):**



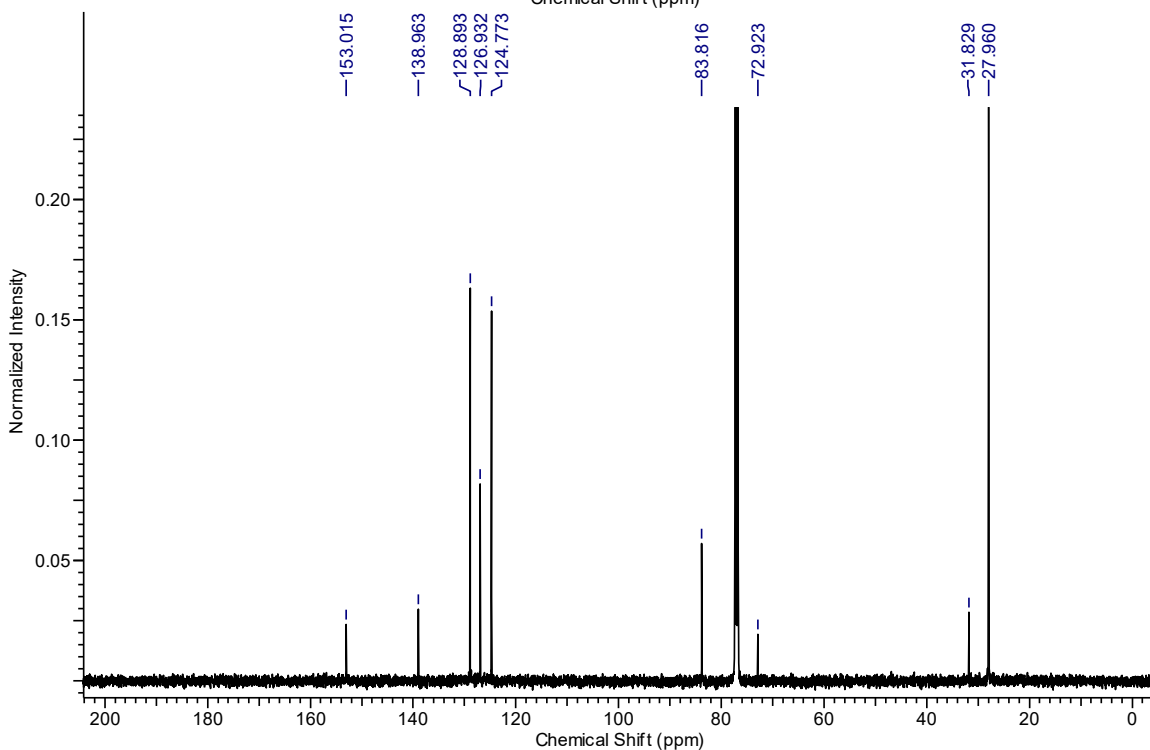
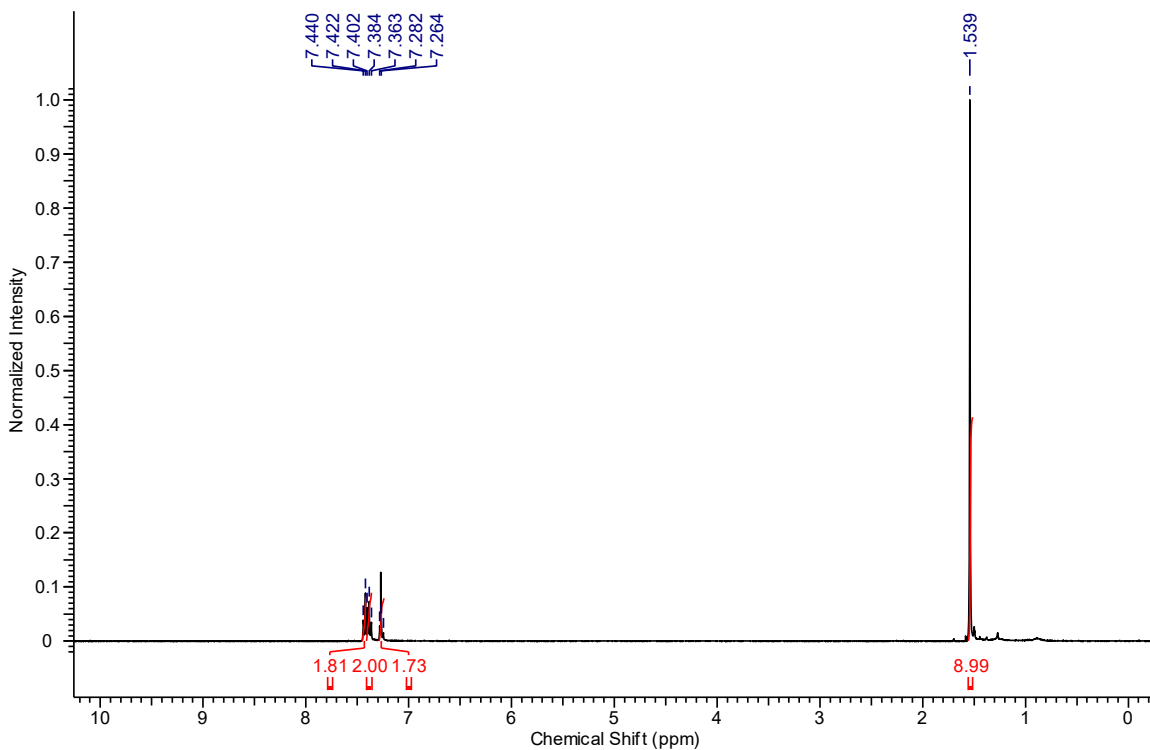
**(((1,1'-Biphenyl)-4-ylmethyl)thio)ethynyl)diphenylphosphine oxide (9.38):**



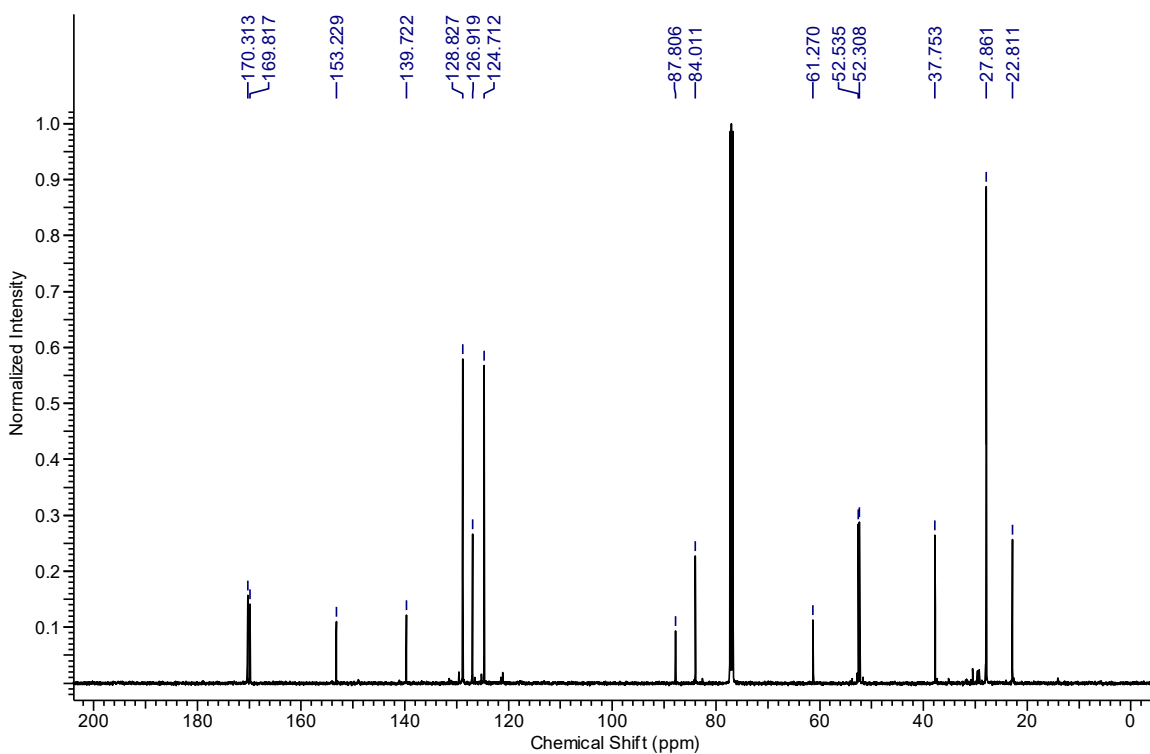
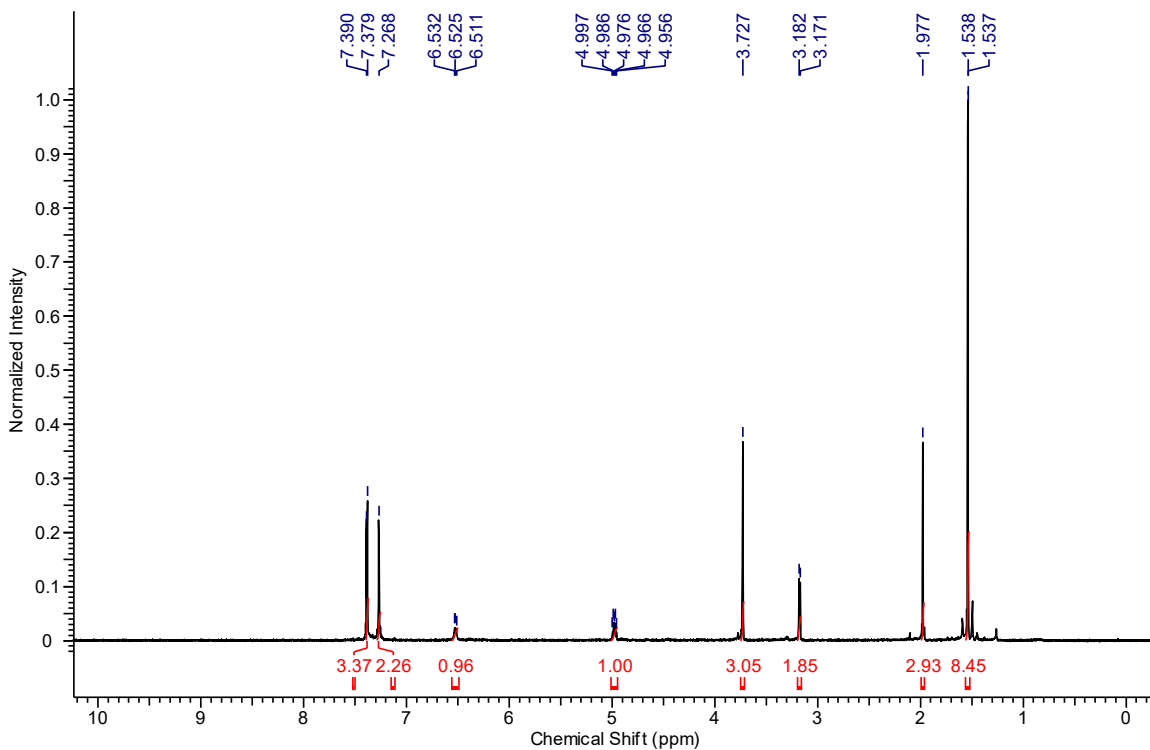
**Diethyl (((4-chlorobenzyl)thio)ethynyl)phosphonate (9.39):**



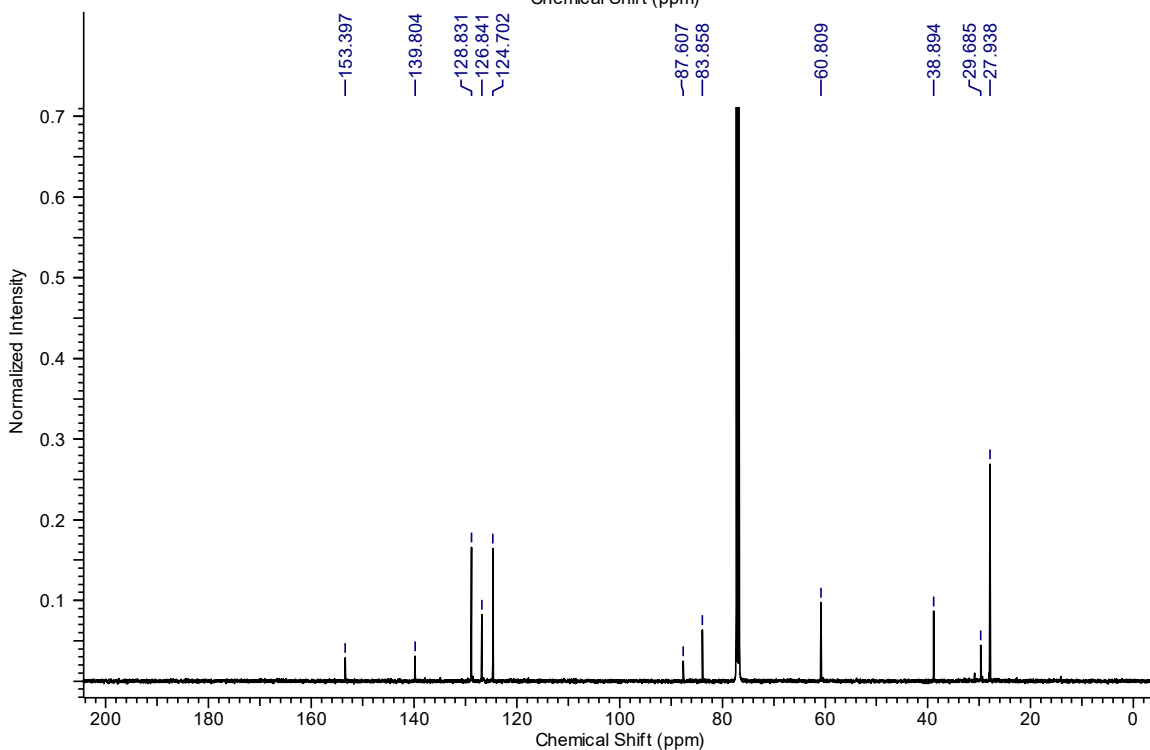
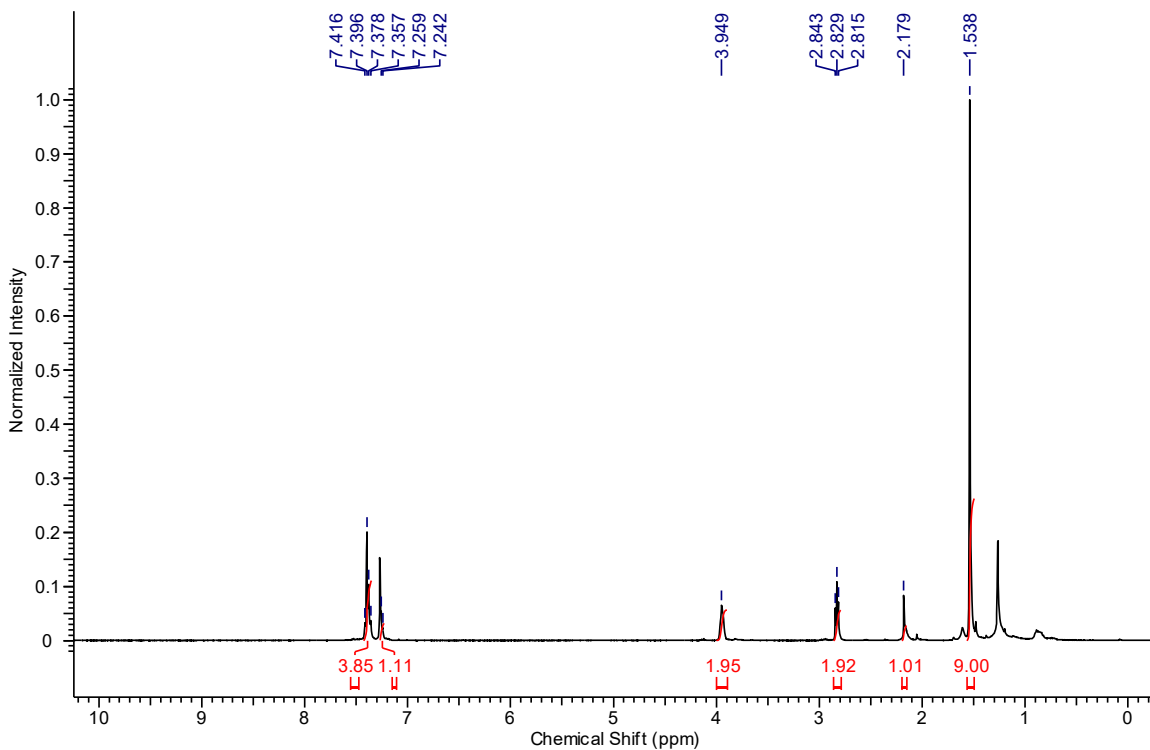
***tert*-Butyl (bromoethynyl)(phenyl)carbamate (9.S23):**



**Methyl *N*-acetyl-*S*-(((*tert*-butoxycarbonyl)(phenyl)amino)ethynyl)-*L*-cysteinate (9.40):**

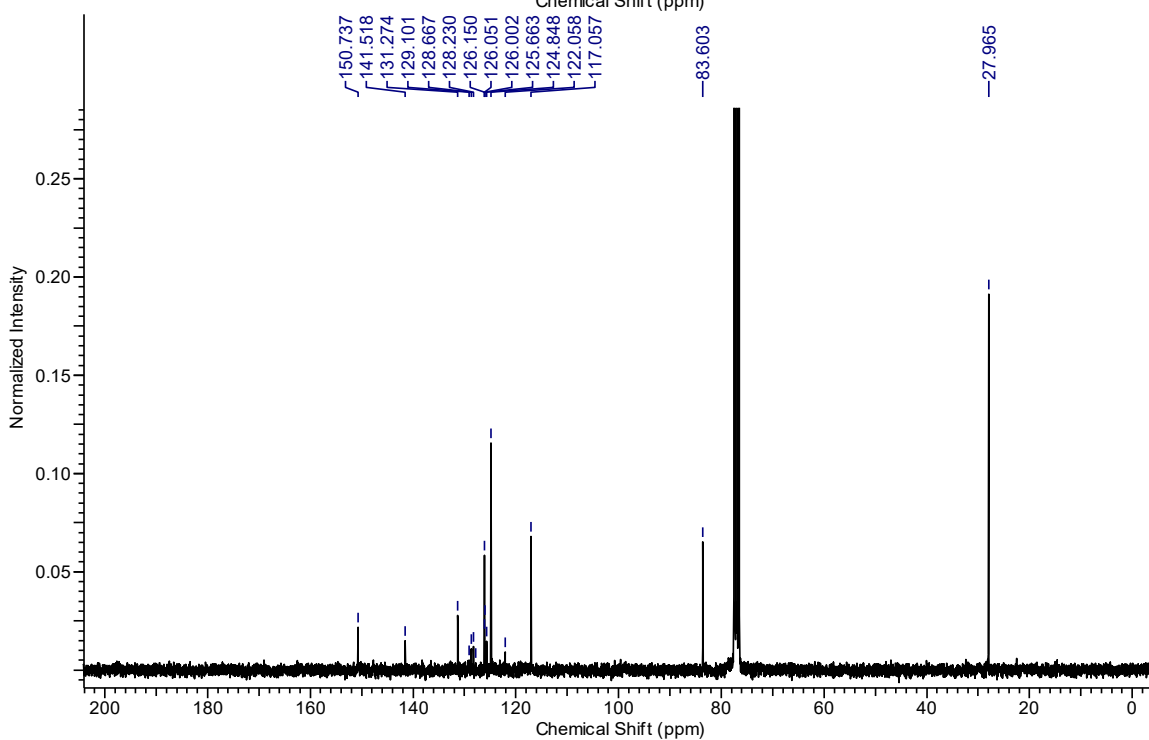
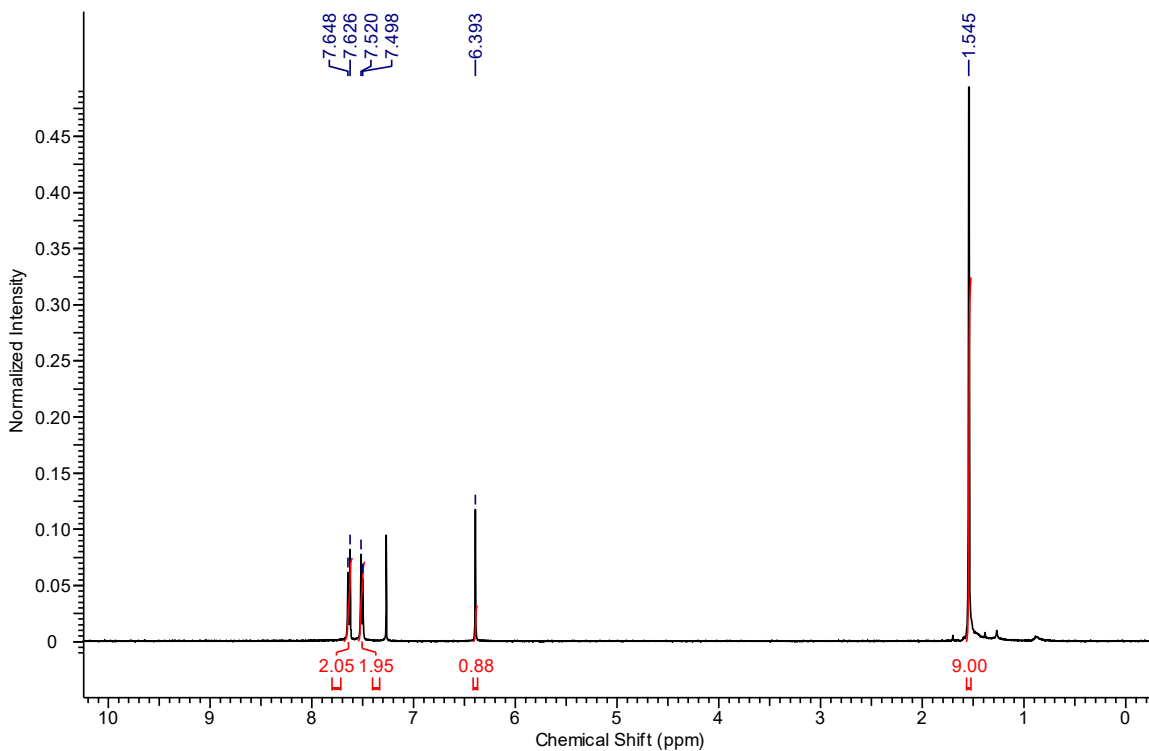


***tert*-Butyl (((2-hydroxyethyl)thio)ethynyl)(phenyl)carbamate (9.41):**

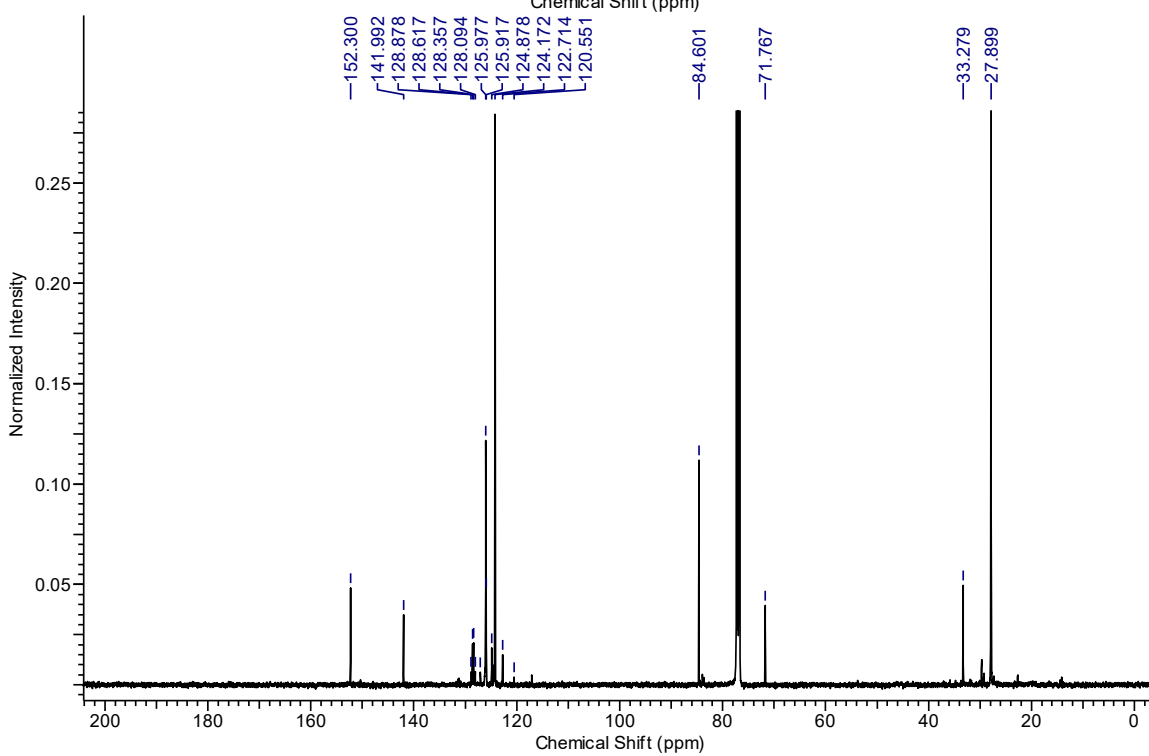
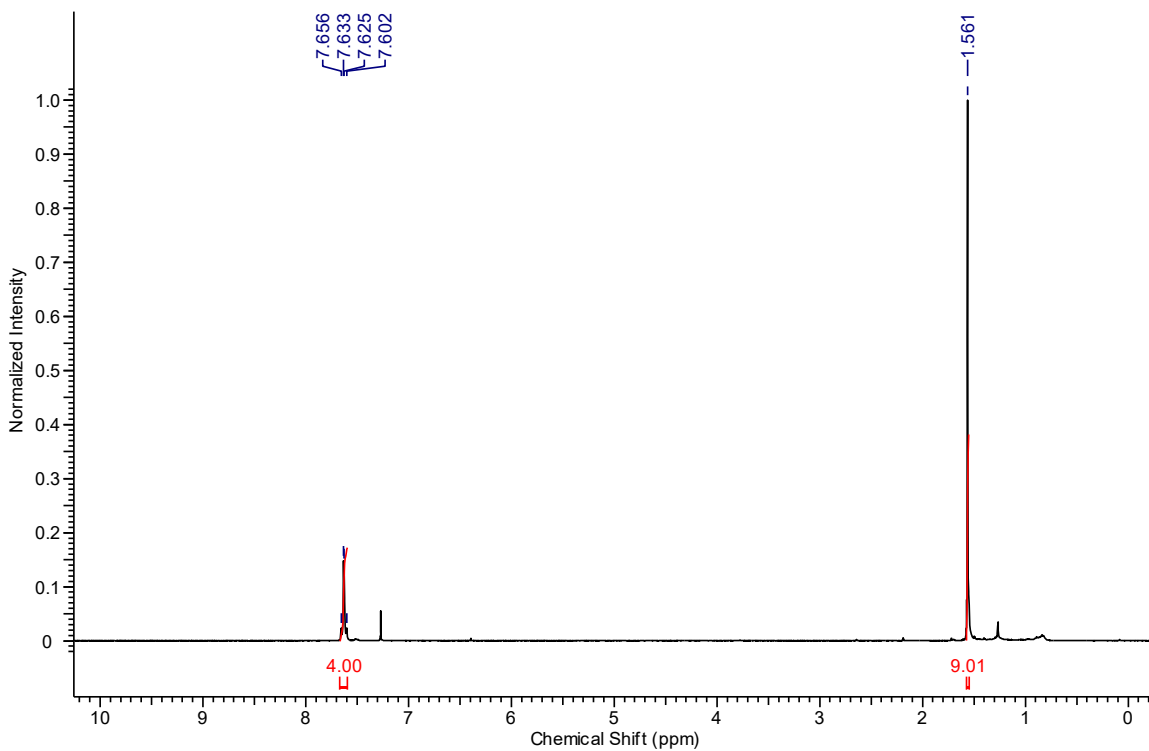




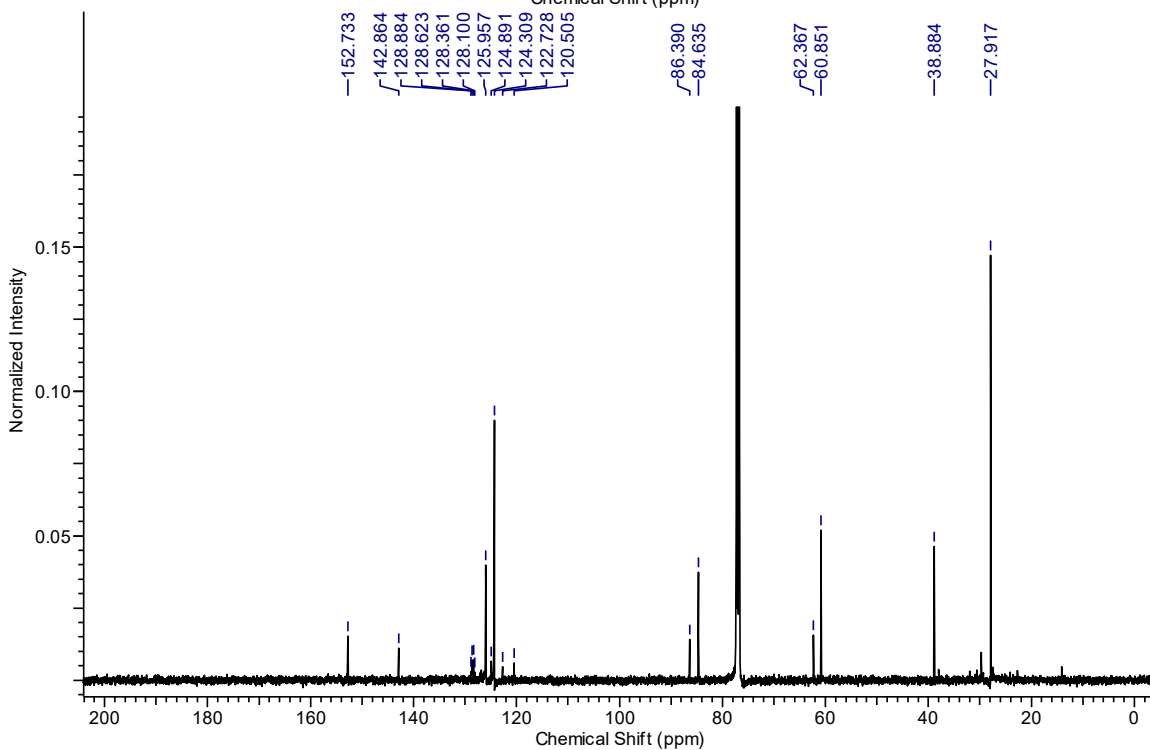
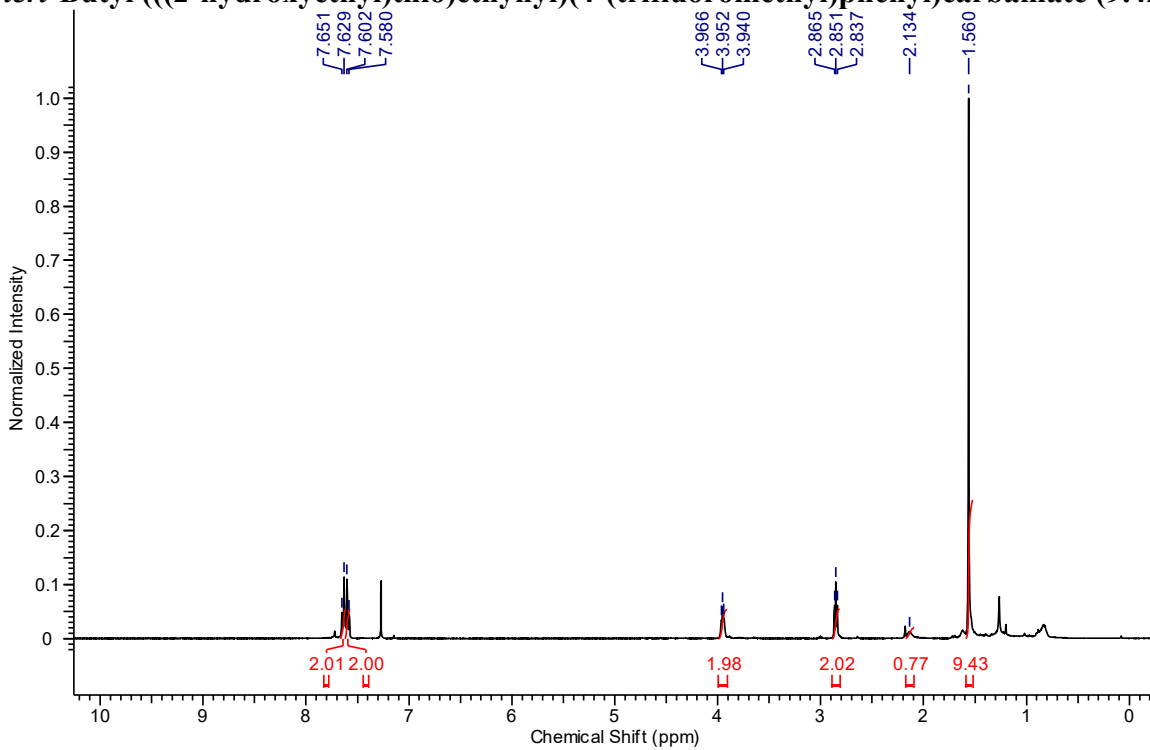
***tert*-Butyl (*E*-(1,2-dichlorovinyl)(4-(trifluoromethyl)phenyl)carbamate (9.S24)**



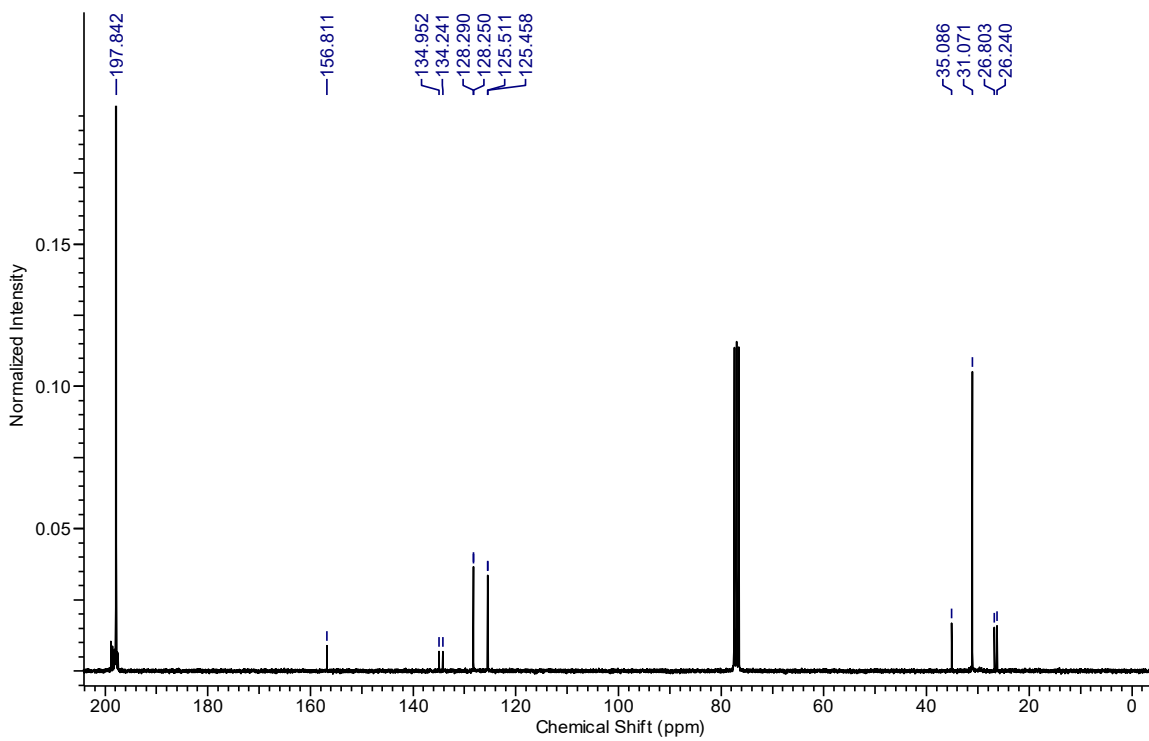
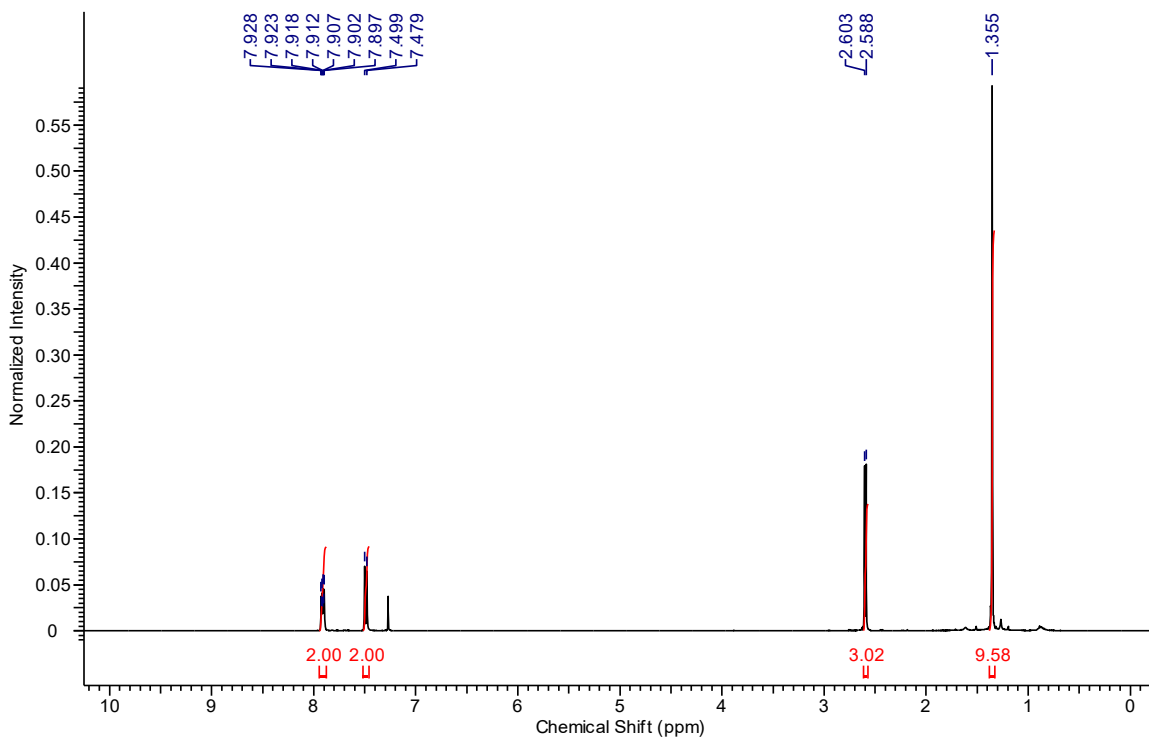
***tert*-Butyl (bromoethynyl)(4-(trifluoromethyl)phenyl)carbamate (9.S25)**



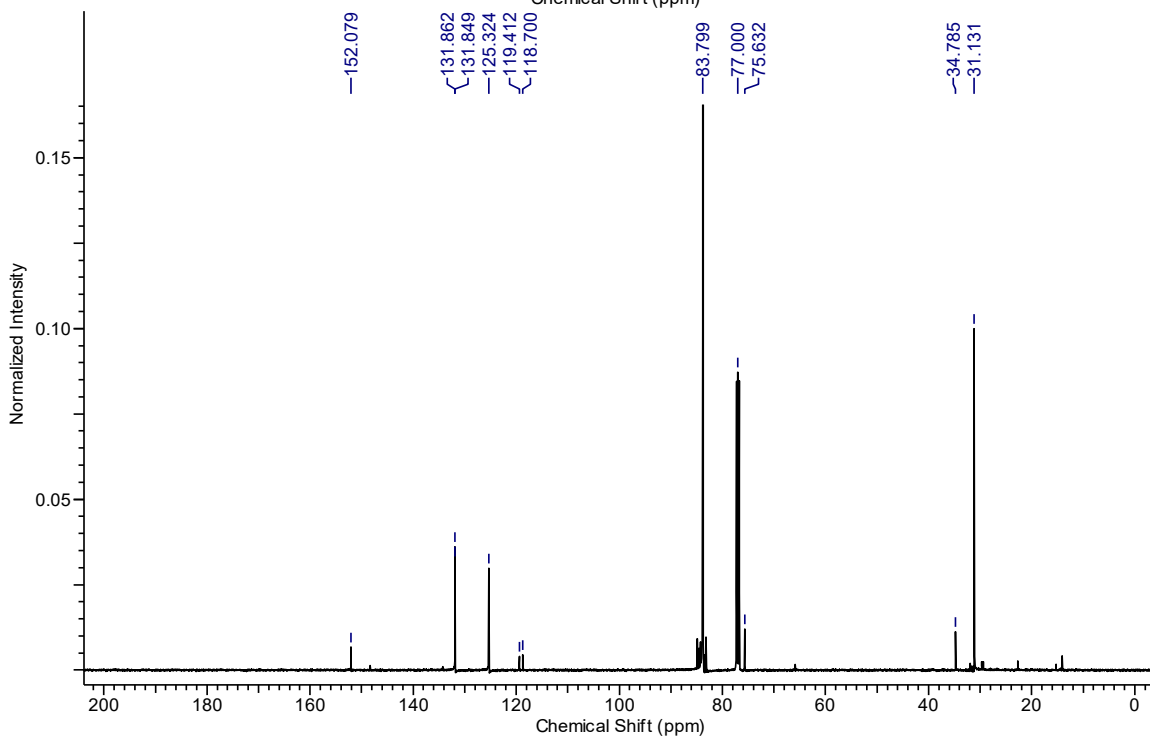
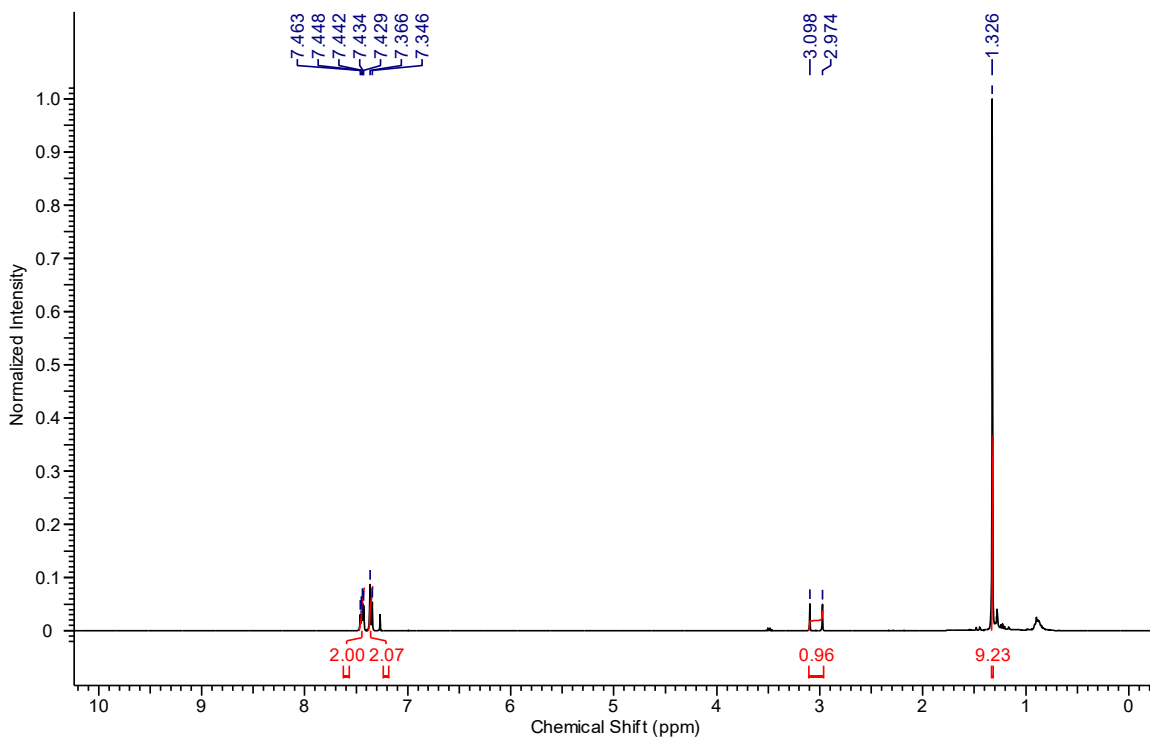
***tert*-Butyl (((2-hydroxyethyl)thio)ethynyl)(4-(trifluoromethyl)phenyl)carbamate (9.42):**



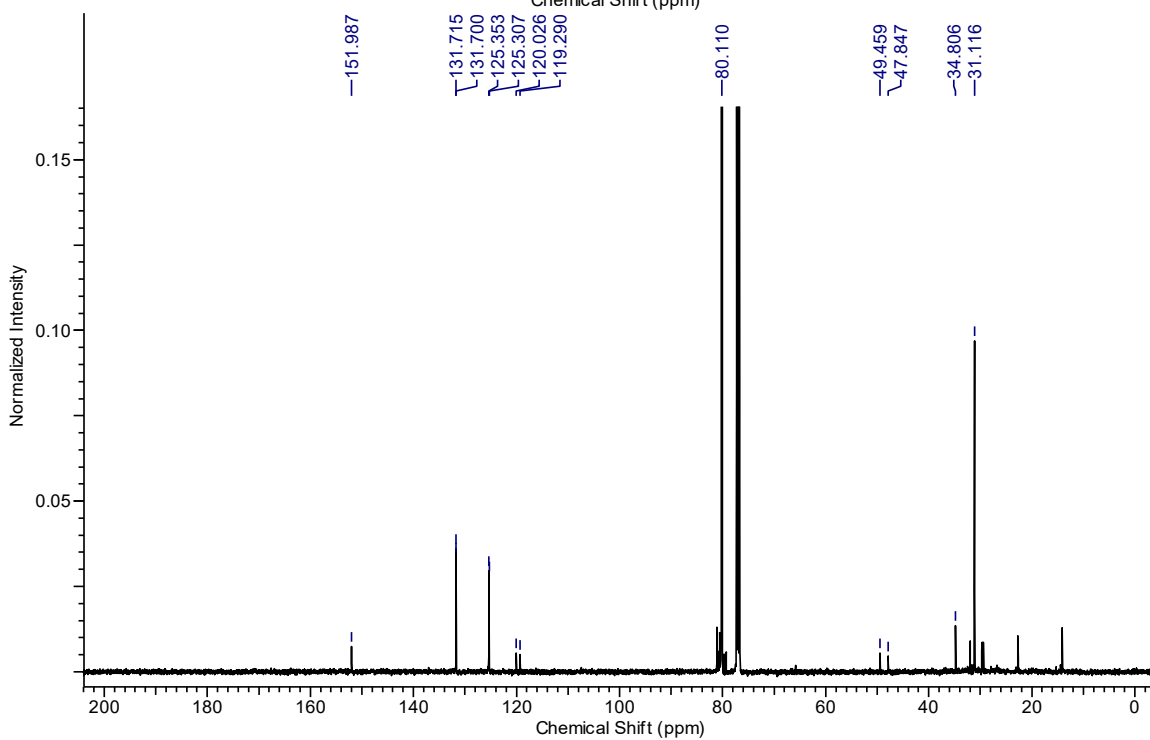
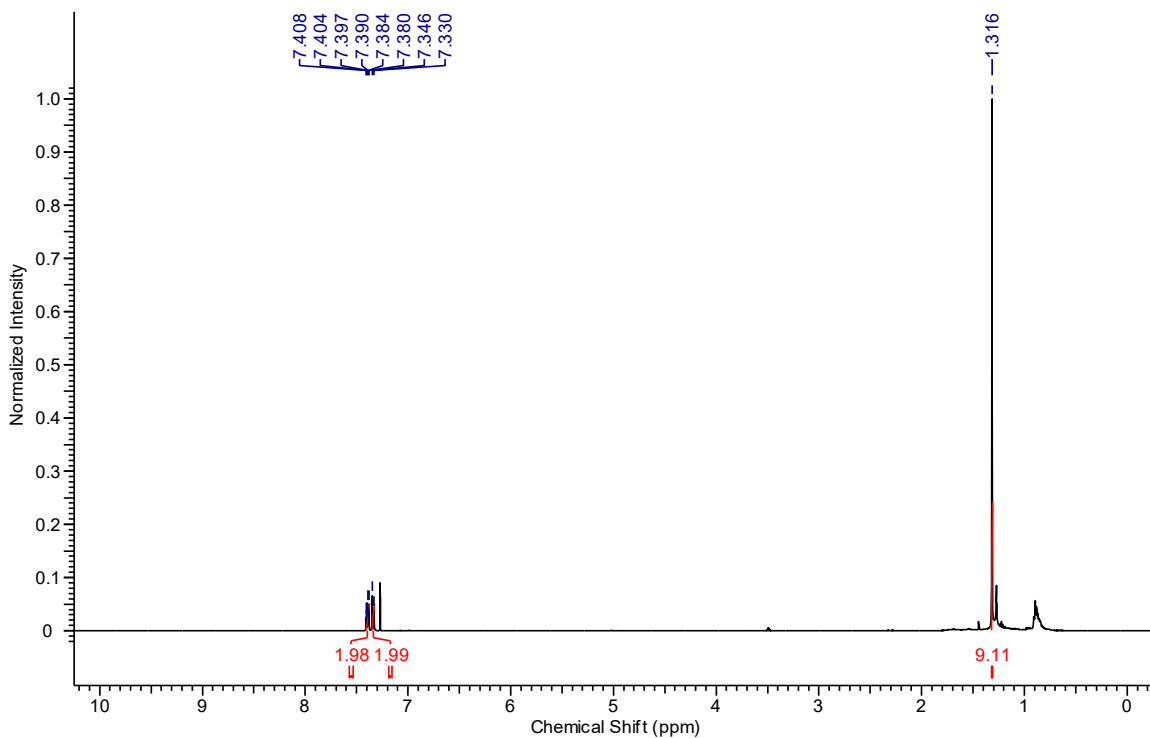
1-(4-(*tert*-Butyl)phenyl)ethan-1-one-1-<sup>13</sup>C (9.S26):



**1-(*tert*-Butyl)-4-(ethynyl-1-<sup>13</sup>C)benzene (9.S27):**



**1-(Bromoethynyl-1-<sup>13</sup>C)-4-(*tert*-butyl)benzene (9.S28):**



**((4-*tert*-Butyl)phenyl)ethynyl-2-<sup>13</sup>C(4-chlorobenzyl)sulfane (9.17):**

