Université de Montréal

Applications des interactions quadripolaires dans des réactions de macrocyclisation par métathèse de fermeture de cycle

Par

Yassir El-Azizi

Département de Chimie

Faculté des Arts et Sciences

Thèse présentée à la Faculté des études supérieures

En vue de l'obtention du grade de

Philisophiae Doctor (Ph.D.) en chimie

Octobre 2008

Université de Montréal

Faculté des études supérieures

Cette thèse s'intitule :

Applications des interactions quadripolaires dans des réactions de macrocyclisation par métathèse de fermeture de cycle

Présentée par

Yassir El-Azizi

a été évaluée par un jury composé des personnes suivantes :

Professeur	André B. Charette	Président- rapporteur
Professeur	Shawn K. Collins	Directeur de recherche
Professeur	Richard Giasson	Membre du jury
Professeur	Thierry Ollevier	Examinateur externe
Professeur		Représentant du doyen de la FES

Sommaire

Le but de ma recherche vise à développer de nouvelles stratégies pour la synthèse de paracyclophanes comportant des éléments de chiralité planaire. La préparation de ces structures est importante pour éventuellement accéder à des composés d'intérêt pharmaceutique. Bien que cette forme de chiralité se retrouve parmi plusieurs produits naturels ou des molécules utilisées en science des matériaux, les méthodes existantes en synthèse organique pour les préparer restent encore souvent sous-développées.

Pour ce faire, nous avons développé une méthodologie utilisant un nouvel élément directionnel pour rendre possible des macrocyclisations complexes via la métathèse des oléfines par fermeture de cycle. Cette méthodologie s'appuie sur des interactions quadripolaires qui sont en fait rarement observées en solution. Les interactions intramoléculaires π-π sont des interactions importantes qui peuvent contrôler les conformations réactives dans diverses réactions d'addition/cycloaddition stéréosélectives pour privilégier l'attaque sur une face en particulier. Nous avons travaillé au développement de plusieurs auxiliaires basés sur ces interactions, à la préparation de macrocycles possédant une oléfine trisubstituée et à l'usage d'un élément directionnel tel que le pentafluorophényle dans la validation de notre méthodologie dans l'approche à travers la synthèse totale de la longithorone C membre monomérique de la famille des longithorones.

Nous avons aussi testé nos principes dans un autre type de réaction de macrocyclisation. Ainsi, des paracyclophanes comportant des motifs 1,3-diènes ont été obtenus avec des rendements améliorés par la combinaison des mêmes interactions quadripolaires avec la métathèse ène-yne. L'usage d'un

nouveau auxiliaire le 2,5-bis(trifluoromethyl)phényle, nous a permis d'apprendre plus sur les interactions quadripolaires existantes dans nos substrats.

Aussi, nous avons essayé de comprendre comment les différences entre les énergies de stabilisation pouvaient influencer de façon décisive sur les distributions conformationelles de nos substrats. Des modélisations moléculaires à plusieurs niveaux de précisions ont été menées et nous ont permis de faire certaines prédictions. Ainsi, nous avons prédit qu'une jonction amide dans sa conformation *s-trans* peut contribuer encore plus à stabiliser nos conformations et nous avons trouvé effectivement que ceci contribue de façon significative à augmenter nos rendements en plus d'influer sur nos ratios *E/Z* par la même occasion.

Mots clés :

Macrocyclisation, métathèse de fermeture de cycle, interactions quadripolaires, longithorones.

Summary

The goal of the research was to develop new methods for the synthesis of paracyclophanes displaying elements of planar chirality. The preparation of these structures is of considerable importance. Although these forms of chirality are found in some natural products and in molecules exploited in materials science, methods for their formation remain often underdeveloped.

We have succeeded in developing of a new gearing element to enable difficult macrocyclizations using ring closing olefin metathesis that takes advantage of quadrupolar interactions that are rarely observed in solution. A variety of different auxiliaries for macrocyclization were developed; the use of the pentafluorophenyl-gearing element was particularly effective during studies aimed at the total synthesis of longithorone C, a monomeric member of the longithorone family of natural products.

We have also succeeded in using these auxiliaries in another type of macrocyclisation using ene-yne metathesis. Paracyclophanes formed via this reaction contain 1,3-dienes embedded in their structure. These compounds were obtained in improved yields using a 2,5-bis(trifluoromethyl)phenyl based auxiliary. Molecular modelling studies suggested that both lp:π and π:π interactions could be responsible for the successful macrocyclizations.

We have also used molecular modelling to try and understand the interplay between the conformational stability of various conformers of the substrates and the resulting yields in macrocyclization. Molecular modelling at various levels of theory allowed the prediction of which auxiliaries would be better suited for different systems. Consequently, it was predicted that amide based auxiliaries would significantly improve yields. Experimentally, improved yields and *E/Z* ratios were observed when employing the amide based auxiliaries.

Keywords :

Macrocyclisation, ring closing metathesis, quadrupolar interactions, longithorones.

Table des matières

Liste des tableaux

Liste des schémas

Arcticle 5: Yassir El-Azizi, Joseph E. Zakarian, Lisa Bouillerand, Andreea R. Schmitzer, Shawn K. Collins*. 'Exploiting Noncovalent Interactions in Synthesis: Macrocyclization Employing Amide-Based Auxiliaries', Adv. Synth. Cat. 2008, 350, 2219.

Liste des figures

Arcticle 2: Collins*, S. K.; El-Azizi, Y. 'Development of Quadrupolar Engaging Auxiliaries for Macrocyclization', *Pure App. Chem.* 2006, *78*, 783.

Liste des abréviations

Å	Angström
Ac	acétyle
br	broad (en RMN)
°C	degré Celsius
calcd	calculated
cm	centimètre
Δ	chaleur
δ	déplacement chimique
°	degré
d	doublet (en RMN)
DCM	Dichlorométhane
d	densité
dd	doublet de doublets (en RMN)
DMF	N,N- diméthyl formamide
DMSO	diméthyl sulfoxyde
dt	doublet de triplets (en RMN)
e^-	électron
eq	équivalent
ESI	electro spray ionisation
FTIR	Fourier transform infrared
Fw	formula weight

g	gramme
h	heure
HRMS	high resolution mass spectrometry
hν	sous irradiation
Hz	hertz
J	constante de couplage
lp	lone pair
M	molaire
m	masse ou multiplet (en RMN)
m/e	rapport masse / charge
mg	milligramme
MHz	mégahertz
µm	micromètre
min	minute
mL	millilitre
mm	millimètre
mM	millimolaire
mmol	millimole
mol	mole
mp	melting point
MS	mass spectrometry
nm	nanomètre
NMR	nuclear magnetic resonance

ORTEP	Oak Ridge Thermal Ellipsoid Program
Ph	phényle
π	électron π
q	quadruplet (en RMN)
quint	quintuplet (en RMN)
RMN	Résonance magnétique nucléaire
rt	room temperature
S	singulet (en RMN)
t	triplet (en RMN)
THF	tétrahydrofurane
TMS	triméthylsilyle
UV	ultraviolet
V	volume
W	Watt
wt	weight

Remerciements

Je souhaiterais tout d'abord remercier chaleureusement mon directeur de recherche, le professeur Shawn Collins, pour avoir accepté que je sois son premier étudiant gradué. Il m'a permis d'apprendre énormément sur la chimie et sur moi-même au cours de mon programme de Ph.D. De plus, il m'a toujours donné la latitude pour exprimer ma créativité et pour diriger mes projets de recherche de façon indépendante, dans la réussite comme dans l'échec. Il m'a accordé une flexibilité incroyable et a été compréhensif vis-à-vis des mes besoins et obligations familiales. Je manque réellement de mots pour lui exprimer toute ma gratitude et mon respect, je dirais tout simplement que Shawn est un énorme filon d'or que le département de chimie de l'université de Montréal vient tout juste de découvrir.

Ensuite, je voudrais remercier Joseph E. Zakarian pour avoir contribué de façon significative et décisive dans mes projets de recherche notamment en ce qui concerne les optimisations qui ont été nécessaires pour approcher le corps carbo-cyclique de la Longithorone C. Son professionnalisme et sa persévérance sont une source d'inspiration pour nous tous.

Je tiens également à remercier tous les membres de mon groupe, présents et passés : L'étudiant au doctorat Alain Grandbois, les étudiants à la maîtrise Julie Côté, Pierre- André Fournier, Jolaine Savoie, Brice Stenne, Martin Vachon, mes stagiaires Magali Martin et Lisa Bouillerand ainsi que les autres stagiaires du groupe. J'ai eu une chance appréciable de travailler avec eux. Les discussions que nous avons eues ont toujours été enrichissantes et fructueuses.

Je voudrais remercier notre collaboratrice la Professeure Andreea R. Schmitzer sans laquelle on aurait eu du mal à expliquer nos observations expérimentales. Ces modélisations moléculaires nous ont permis d'avancer avec notre chimie et d'ajouter plus de crédibilité à nos résultats.

Je remercie également tous les professeurs avec lesquels j'ai interagi soit en suivant leurs cours, en les consultant pour des questions de chimie et autres, en les sollicitant pour une lettre de référence, ou en participant avec eux à une répétition ou une démonstration : André L. Beauchamp, André Charette, Marius D'Amboise, Matthias Ernzerhof, Richard Giasson, Suzanne Giasson, Garry S. Hanan, Stephen Hanessian, Jeffrey Keillor, Joseph Hubert, Radu Ion Iftimie, Hélène Lebel, William D. Lubell, Jean-François Masson, Christian Pellerin, Joëlle Pelletier, Robert E. Prud'homme, Dominic Rochefort, Frank Schaper, William Skene, James D. Wuest, Davit Zargarian, Julian X. Zhu, et Yvan Guindon.

Un remerciement spécial est adressé toutefois au Professeur André Charette qui a été un vrai catalyseur quant à mon intégration au groupe Collins et une référence de poids dans mes demandes de bourse et autres processus importants dans ma scolarité.

Le don de réactifs, solvants et temps sur leurs propres appareils n'a pas appauvrit les groupes de recherche des professeurs André Charette, Hélène Lebel, William Lubell, Stephen Hanessian et tant d'autres, au contraire ça a agrandi leurs noms dans nos yeux et contribuer à faire de nous tous des gens riches et généreux.

Le personnel des services d'analyses régionaux de RMN : le Dr Minh Tan Phan Viet, Sylvie Bilodeau, Cédric Malveau, Véronique Desjardins, et Shawny Saint- Amant, de MS : Dr Alexandra

Furtos, Karine Venne, Dalbir Sekhon, et Marie- Christine Tang, et celui d'analyse élémentaire Huguette Dinel. En effet, mon projet leur doit plusieurs fois la vie à tous et à chacun.

Le personnel de soutien est à remercier également : Le souffleur de verre Cédric Ginart, les employés des ateliers électrique Louis Beaumont, Julien Del Tosta, Yves Teasdale et mécanique Martin Lambert, Jean-François Myre, ainsi que les responsables et techniciens des différents laboratoires : le Dr. Gaétan Caron, Stéphane Béranger, Sylvie Marceau, Amira Khoury, Hélène Laliberté, Line Pépin et Hugette Dinel.

Les gens du laboratoire de chimie combinatoire: le Dr. Pierre Lavallée, Fabrice Galaud et Benoit Jolicœur sont à remercier pour le prêt d'équipement.

Le département de chimie en son personnel administratif compétant et dévoué est à remercier du fond du cœur pour avoir facilité toutes mes affaires et transitions académiques : Barbara Bessis, Mildred Bien-Aimé, France Desfossés, Karine Poirier, Kevin Filiatrault, Jacques Laflamme, Lyne Laurin, Carol Major, Line Massé, et Line Raymond.

Les bibliothècaires de notre bibliothèque de chimie sont à remercier également : Malivanh Sananikone, et Ginette Lacoursière Gignac sans oublier le préposé Richard.

Mon portefeuille remercie beaucoup toutes les compagnies et tous les organismes subventionnaires qui ont été généreux envers moi et envers notre groupe de recherche, sans leurs appuis et sans leur générosité rien n'aurait pu être fait : L'université de Montréal, FQRNT, CRSNG, FCI, Boehringer Ingelheim Canada, Merck Frosst, et AstraZeneca.

Je tiens à remercier mon jury pour avoir accepter de lire et corriger ma thèse.

Finalement, je tiens particulièrement à remercier toute ma famille et spécialement ma mère, mon père, mes frères et sœurs, ma femme, mes deux filles, et tous mes amis pour avoir cru en moi et pour avoir été pour moi une source de force et de motivation.

J'oublie sûrement des gens, ils se reconnaîtront sans doute. Je les prie d'excuser mon oubli et d'accepter mes remerciements pour tous les services rendus.

Merci à tous

À ma mère

À mon père

À mes frères et sœurs

À ma petite famille

Notes

Pour simplifier la lecture de la présente thèse l'auteur a jugé bon d'apporter les modifications suivantes :

- La numérotation des molécules, des tableaux, schémas et figures a été maintenue dans les articles telle que dans la parution originale afin de les faire fusionner de façon adéquate dans la thèse et de garder une cohésion vis-à-vis des parties 'Supporting Informations'.

- Les références associées à chaque article sont complètements indépendantes des références qui correspondent au chapitre dans lequel l'article est rapporté.

- Toutes les informations rapportées dans les articles originaux sont préservées dans la même section. Les parties 'Supporting Informations' sont elles listées en annexes.

Veuillez notez que la liste des contributions suivantes sont des contributions personnelles de l'auteur :

- La majorité des synthèses et les caractérisations des molécules et intermédiaires rapportées des les articles ont été faites pas l'auteur.
- La majorité des procédures rapportées dans les articles ont été conçues et rédigées par l'auteur.
- Les plans de synthèse et progression de la chimie ont été élaborés en grande partie par l'auteur.

- L'auteur a contribué à la rédaction des cinq articles et a participé activement à la correction y compris les corrections à apporter à la demande des arbitres.
- L'auteur a contribué de façon significative à la rédaction des 'Supporting Information' nécessaires à la publication des résultats.

1. Introduction à la métathèse[1]

La métathèse des oléfines a émergé ces vingt dernières années comme étant une des transformations en synthèse organique les plus utiles. En effet, elle implique un processus catalytique, propre, peu coûteux, écologique et hautement efficace. Elle permet, lorsque deux oléfines sont impliquées, de faire la transposition de deux atomes de carbone des oléfines originales pour former une nouvelle oléfine. À en juger par le nombre de publications dans la presse scientifique[2] (Figure 1.1), elle est devenue une des réactions de choix pour faire des liens carbone-carbone.

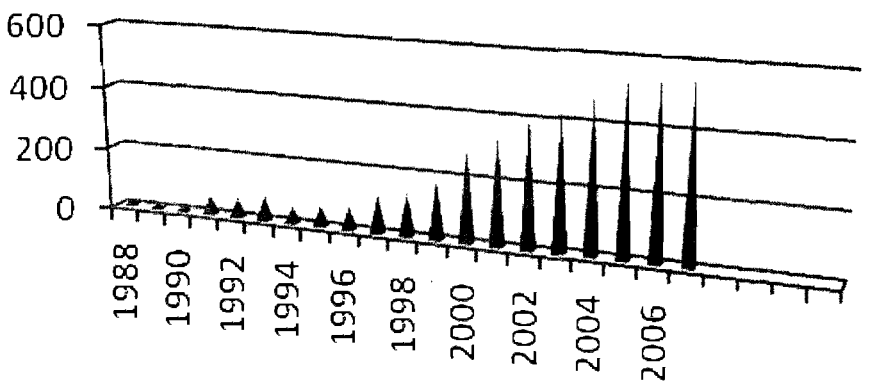


Figure 1.1: Nombre de publications portant sur la métathèse des oléfines depuis les vingt dernières années.

[1]a) *Handbook of Metathesis* Grubbs, R. H., ed.; Wiley-VCH: Weinheim, **2003**. b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. c) Grubbs; R. H. *Tetrahedron* **2004**, *60*, 7117. d) Lee, C. W.; Grubbs R. H. *J. Org. Chem.* **2001**, *66*, 7155.

[2] Recherche sur Web of Science avec 'olefin metathesis' comme mot clé, le 11 juin 2008.

Ses origines remontent à bien longtemps, tel que peut en témoigner un brevet américain[3] de 1955 qui revendique la capacité de certains complexes de Ti(II) d'induire des réactions de polymérisation du norbornène par métathèse d'ouverture de cycle (Figure 1.2). En effet, plusieurs complexes définis ou non de métaux de transition y compris ceux comportant des ligands de type carbène peuvent induire toute une panoplie de transformations impliquant des transpositions de carbènes.

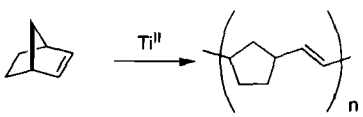


Figure 1.2 : Complexes de Ti(II) induisant une polymérisation du norbornène par métathèse d'ouverture de cycle.

D'ailleurs ce n'est pas une surprise que les inventeurs de ce type de chimie aient conduit au prix Nobel de chimie en 2005[4], soit Yves Chauvin, le premier à avoir proposé un mécanisme plausible, Robert H. Grubbs et Richard R. Schrock. Le prix a été accordé car ils ont développé, identifié des catalyseurs de métathèse et porté toute la chimie de métathèse jusqu'à la maturité qu'elle connait aujourd'hui. En effet, nous avons vu durant

[3] U.S. Patent 2,721,189

[4] "For the development of the metathesis method in organic synthesis... Considering the short time during which Grubbs' and Schrock's catalysts have been available, the breadth of applications, is truly remarkable." NOBEL LECTURES IN CHEMISTRY 2001–2005 edited by Prof. Per Ahlberg, Nobel Committee for Chemistry, *(Göteborg University, Sweden)*.

une courte période, le lancement de toute une série de précatalyseurs de métathèse (Figure 1.3) dont les réactivités vis-à-vis des oléfines sont différentes.[5]

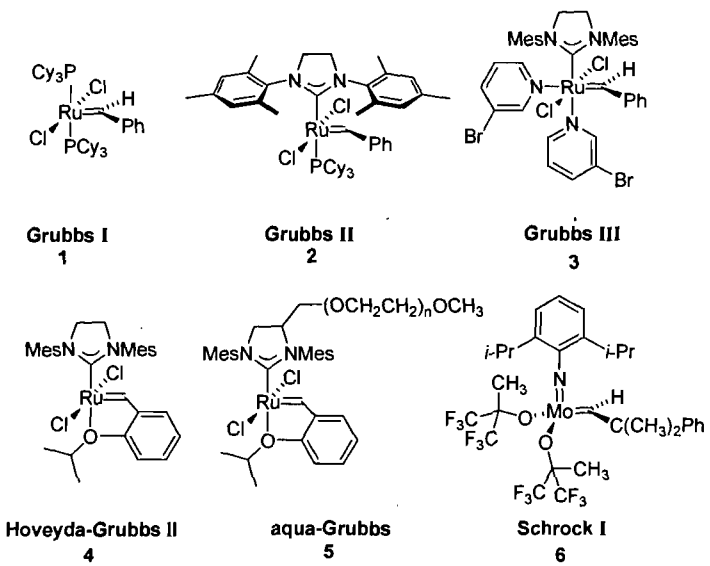


Figure 1.3 : Liste de quelques précatalyseurs de métathèse populaires qu'on retrouvera plusieurs fois dans cette thèse.[6]

De plus, la tolérance des catalyseurs de métathèse vis-à-vis des différentes fonctionnalités qu'on peut trouver en chimie organique est impressionnante, ce qui fait d'elle une transformation très versatile et utile.[7]

---

[5] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

[6] a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Reagan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int., Ed.* **1995**, *34*, 2039. c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. d) Love, J. A.; Morgan, J. P.; Tmka, T. M.; Grubbs, R. H. *Angew. Chem,. Int. Ed.* **2002**, *41*, 4035. e) Kingsbury, Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. f) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508.

La réaction de métathèse de fermeture de cycle (RCM), une des nombreuses variantes de la réaction de métathèse, est devenue un outil de poids en synthèse organique. De nombreux rapports montrent comment la synthèse totale de produits naturels et non naturels peut être grandement simplifiée en impliquant dans l'analyse rétosynthétique une ou plusieurs réactions de métathèse.[8]

Le mécanisme[9] simplifié d'une réaction de métathèse de fermeture de cycle par exemple est représenté à la Figure 1.4.

[7] a) Liu, B.; Das, S. K.; Roy, R. *Org. Lett.* **2002**, *4*, 2723. b) Demchuk, O. M.; Pietrusiewicz, K. M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217. c) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959. d) Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240. e) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. f) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

[8] a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

[9] a) Herrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161. b) Katz, T. J.; McGinnis, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 1592.

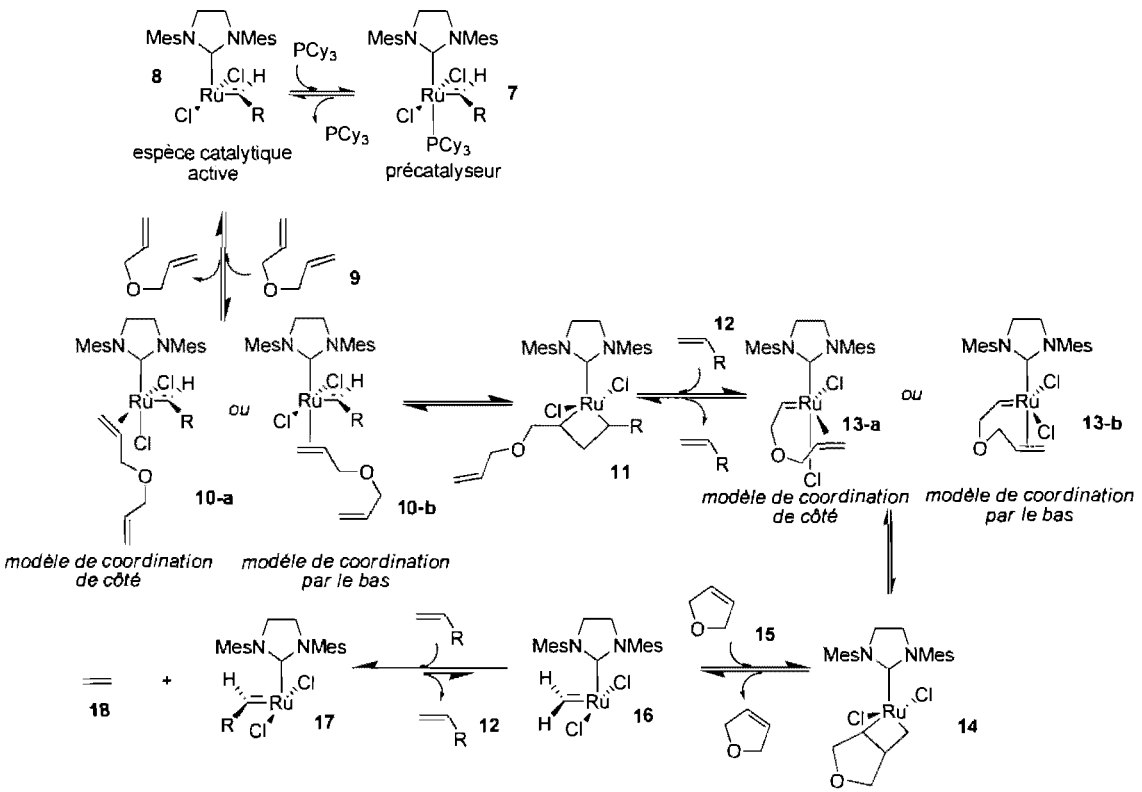


Figure 1.4 : Mécanisme proposé d'une réaction de métathèse de fermeture de cycle.

Tout d'abord, le précatalyseur **7** génère l'espèce catalytique active **8** après dissociation de la phosphine.[10] Ceci a pour effet de libérer un site de coordination sur le métal et permettre ainsi à une des oléfines d'approcher le centre métallique par le bas[11] ou de côté.[12] S'en suit une cycloaddition [2+2] pour former le ruthéna-cyclobutane puis une rétrocycloaddition pour générer l'espèce **13** sur laquelle la deuxième oléfine peut se coordonner elle aussi par le bas ou de côté. Plusieurs séquences de cycloadditions [2+2]

[10] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

[11] Tallarico, J. A.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157.

[12] Anderson, D. R.; Hickstein, D. D.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 8386.

se produisent pour former d'abord le produit de la métathèse de fermeture de cycle (RCM) et ensuite régénérer l'espèce catalytique active après libération de l'éthylène.

Il est intéressant de noter que dans certains cas le précatalyseur et l'espèce catalytique active peuvent être confondus comme dans le cas du précatalyseur **4** (Figure 1.5). En effet, dans ce cas particulier, une simple rotation du ligand benzylidène permet de libérer un site de coordination permettant de passer du précatalyseur à l'espèce catalytique active en un simple changement conformationnel. C'est pour ça que dans la suite de la thèse, l'auteur est tenté, par souci de simplification, de confondre les deux structures (i.e. précatalyseur et l'espèce catalytique active) pour ne parler que de catalyseur. Cette simplification est raisonnable étant donné qu'elle est tolérée dans la littérature. La nature du benzylidène du catalyseur **4** fait en sorte que l'étape d'initiation (i.e. libération d'un site de coordination sur le métal), qui est cinétiquement déterminante, est rendue plus rapide que la dissociation de la phosphine, faisant de ce dernier un catalyseur cinétiquement plus actif que **2**. De plus, étant un ligand bidentate, le benzylidène de **4** lui confère aussi une stabilité accrue lorsqu'il est dans sa forme latente. L'absence de phosphine contribue aussi à l'élimination de tous les processus liés à la décomposition du catalyseur suite à la décomposition de la phosphine.

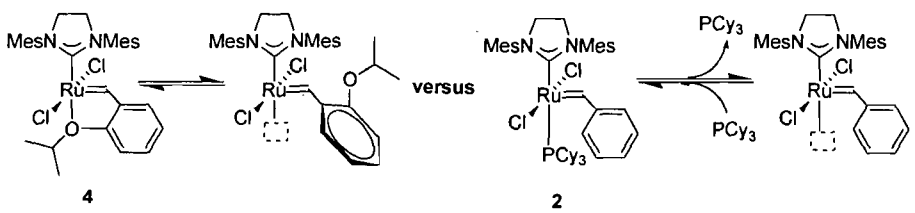
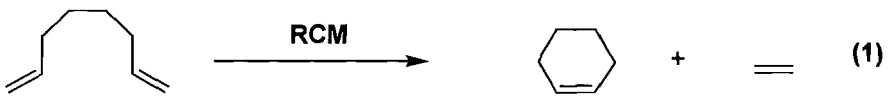


Figure 1.5: Différences structurales entres les catalyseurs **2** et **4**.

2. Métathèse de fermeture de cycle (RCM)

L'équation bilan d'une réaction de métathèse de fermeture de cycle peut s'écrire comme suit (équation 1).



Cette réaction est guidée essentiellement par des considérations entropiques car l'enthalpie de ce type de réaction est quasi nulle étant donné qu'on a brisé deux liens C=C et former le même nombre de liens C=C. Elle est donc, tout simplement, poussée par la perte d'éthylène. La formation dans le cas de l'équation (1) d'un cycle à six chainons et la proximité des deux oléfines aident aussi la réaction à aller dans le sens de formation du produit. Un exemple de l'utilisation de cette transformation dans la synthèse totale de la phomopsolide C est montré ici-bas[13] (Schéma 1.1). Un rendement de 68% est ainsi obtenu lorsque le substrat polyfonctionnalisé **19** est traité avec 5 mol% du catalyseur de Hoveyda- Grubbs II **4**, dans le dichloroéthane à 80°C.

[13] Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513.

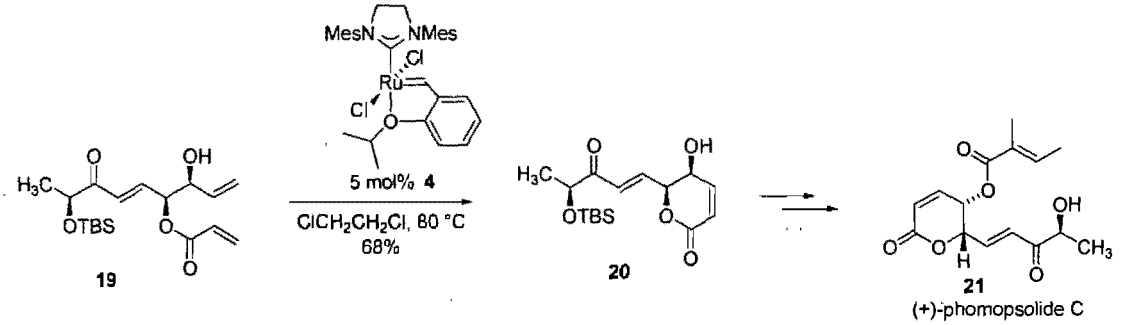


Schéma 1.1 : Formation d'un cycle à six chainons vers la synthèse totale de la (+)-phomopsolide C.

La RCM permet d'accéder à de grands cycles de différentes tailles, mais dans ces cas là des oligomères peuvent être formés si la thermodynamique est défavorable et si les deux partenaires sont loin dans l'espace l'un de l'autre. En effet, dans ces cas là, les prédispositions conformationnelles, la température de la réaction, la cinétique de la catalyse, la stabilité du catalyseur et la dilution du milieu vont avoir des influences cruciales sur l'issue de la réaction (Figure 1.6). Pour maximiser le rendement du produit monomérique, il faudrait alors forcer le substrat à adopter une conformation productive pour la métathèse. Des températures élevées et un catalyseur plus actif aiderait à maximiser la constante de vitesse $k_{métathèse}$ tandis que la haute dilution aiderait à diminuer k_{oligo}. Un catalyseur stable dans ces conditions permettrait de faire baisser la quantité du catalyseur nécessaire pour achever la réaction et éviterait que les produits de dégradation du catalyseur ne viennent perturber les schémas réactionnels en interagissant soit avec le précurseur de la métathèse ou avec le produit de la macrocyclisation.

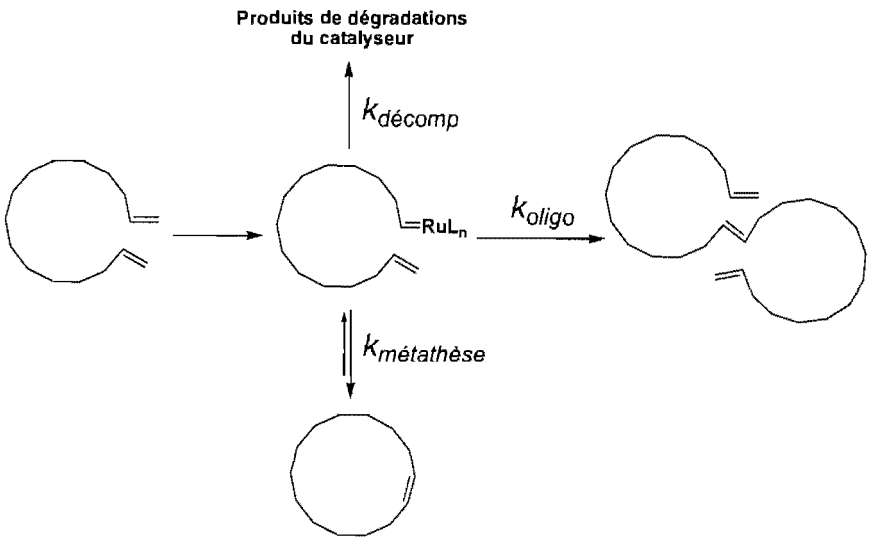


Figure 1.6 : Paramètres à maîtriser lors de la réaction de macrocyclisation par RCM.

Le premier exemple d'une macrocyclisation par RCM des oléfines paru dans la littérature fut rapporté par Langemann et Furstner[14] qui ont mis en évidence la possibilité de former de grands cycles par RCM en utilisant des catalyseurs de métathèse tel que Grubbs I. Dans leur cas, la macrocyclisation s'est produite non sans encombre, le choix de la nature du substrat à cycliser s'est avéré cruciale car l'issu de la réaction en dépend grandement tel que peuvent en témoigner les rendements obtenus (Schéma 1.2). Pour expliquer leurs observations, les auteurs ont avancé l'hypothèse que, dans le cas du substrat de droite **24,** le carbonyle pouvait se complexer au métal telque sur la structure **25** et induire de façon indirecte une prédisposition favorable à la macrocyclisation. Ainsi, des modifications intentionnelles sur le substrat peuvent parfois induire des changements conformationnels pour favoriser la macrocyclisation au détriment de l'oligomérisation.

[14] Langemann, K.; Furstner, A. *J. Org. Chem.* **1996**, *61*, 3942.

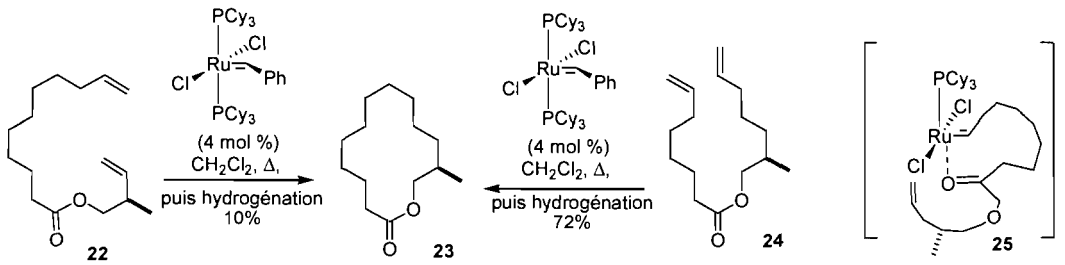


Schéma 1.2 : Premier exemple de macrocyclisation par RCM pour accéder à la phéromone **23** de l'abeille *Cryptoletes pusillus.*

Un autre exemple de l'utilisation de la macrocyclisation par RCM des oléfines en synthèse totale est rapporté par Smith et ses collaborateurs en 1999.[15] En effet, la première synthèse totale de la (-)-cylindrocyclophane F, un produit naturel membre d'une grande famille et qui possède un noyau rigide [7,7]paracyclophane à 22 chainons, a été rendue possible et ce, de façon très efficace grâce à l'utilisation de la RCM des oléfines (Schéma 1.3).

[15] Smith, A. B. III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423.

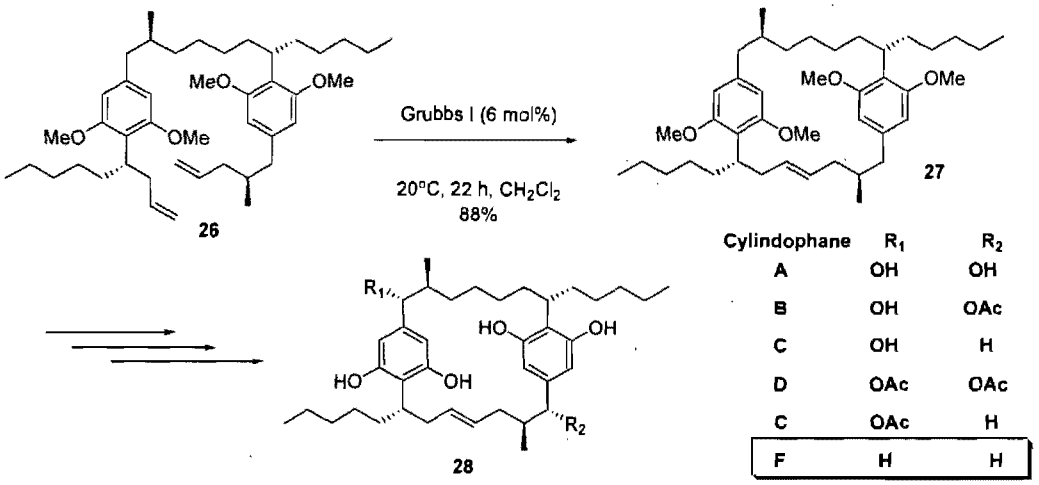


Schéma 1.3 : Accès au corps rigide de la (-)-cylindrocyclophane F par métathèse des oléfines.

Le groupe de Fürstner a rapporté quelques années plus tard[16] que la réaction de macrocyclisation par RCM des oléfines était très sensible à la nature des oléfines qui vont réagir ensemble (Schéma 1.4). En effet, le substrat **29** portant une oléfine monosubstituée et une autre disubstituée ne conduit qu'à la formation du produit de dimérisation **30** dans lequel il y a eu métathèse entre deux doubles liaisons monosubstituées et ce, dans un rendement de 79%. Ce même produit fragmente dans des conditions de métathèse légèrement différentes (i.e. utilisant un catalyseur moins sensible aux effets stériques des doubles liaisons) pour donner le produit de macrocyclisation désiré **31** dans un rendement de 60%.

[16] Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449.

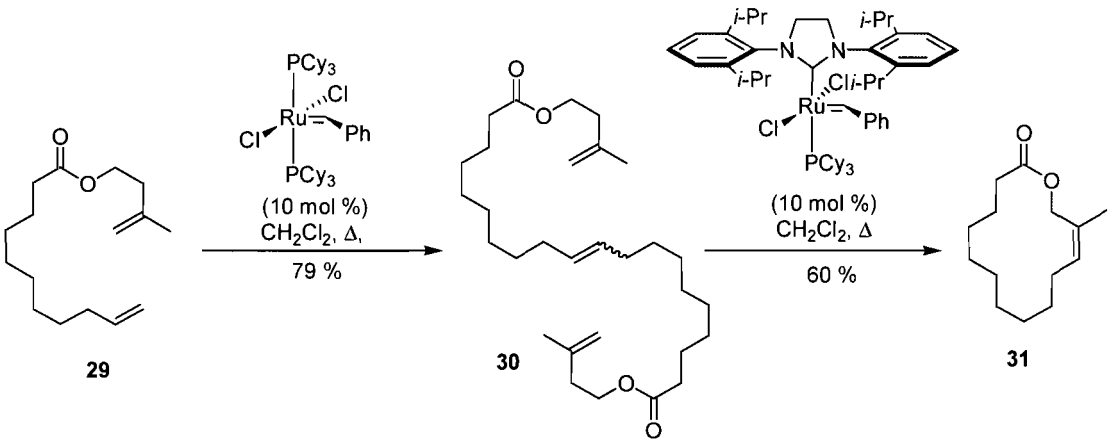


Schéma 1.4 : Formation d'un macrocycle par RCM entre une oléfine monosubstituée et une autre disubstituée.

Un autre exemple d'auteurs [17]qui ont été confrontés aux mêmes types de problèmes est représenté au Schéma 1.5. Cet exemple est intéressant d'autant plus qu'une modification structurale a été nécessaire pour faire fonctionner la réaction. En effet, comme on vient de le voir dans le cas précédent, la nature d'une oléfine (avec différentes propriétés stériques et électroniques) peut avoir une influence significative sur la réactivité de celle-ci et par conséquent sur tout le processus de macrocyclisation par RCM tel qu'à la Figure 1.6. Dans leurs efforts vers la synthèse totale de la foloresolide B **36** et la $\Delta^{6,7}$-*Z*-floresolide B **37**, les auteurs ont soumis le substrat polyfonctionnalisé **32** aux conditions de métathèse en présence du catalyseur de Grubbs I, seul le dimère **33** correspondant à la métathèse entre les deux oléfines simples a été isolé. L'utilisation d'un catalyseur plus actif tel que Grubbs II sur le substrat modifié **34** a permis l'accès aux macrocycles ***Z*-35** et ***E*-35** désirés dans un rendement combiné de 89% et un rapport *E* :*Z* de 1:3.

[17] Nicolaou, K. C.; Hao, X. *Chem. Commun.* **2006**, 600.

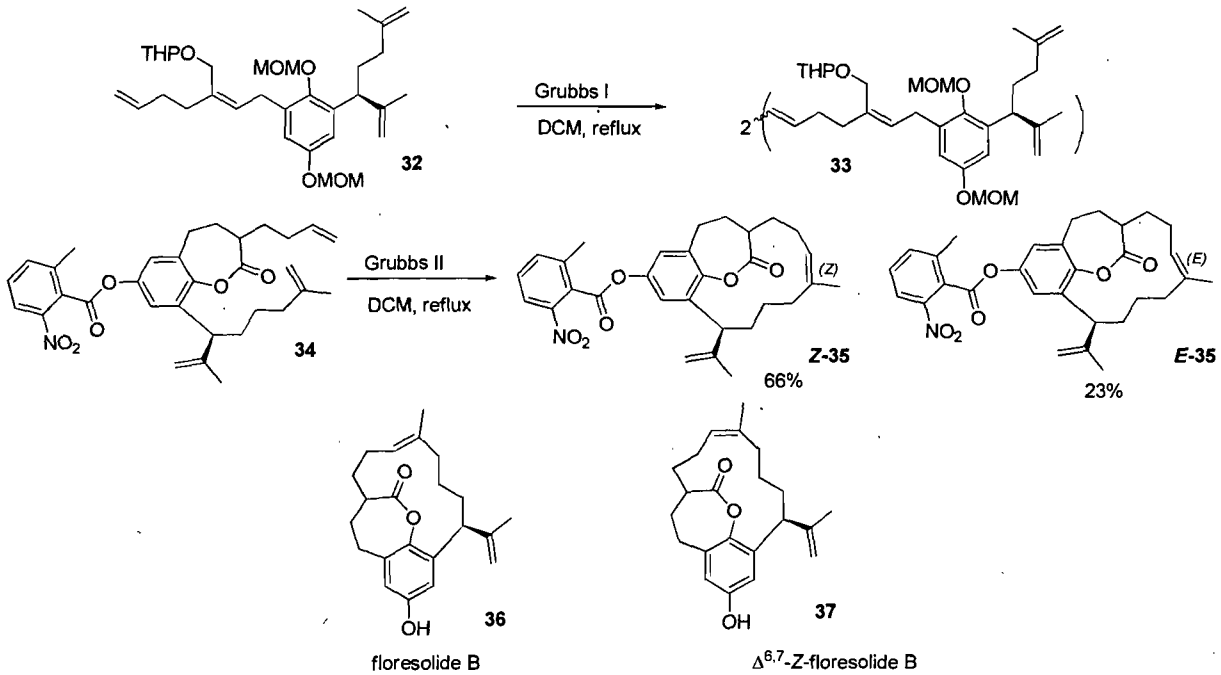


Schéma 1.5 : Formation difficile d'un macrocycle par RCM dans le cadre de la synthèse totale du produit naturel floresolide B et $\Delta^{6,7}$-*Z*-floresolide B.

Toutefois, la difficulté de faire une RCM entre une oléfine monosubstituée et une autre disubstituée peut être surmontée en utilisant une nouvelle stratégie développée dernièrement par Hoye et collaborateurs.[18] Il s'agit d'une méthode intéressante pour former des doubles liaisons tétrasubstituées telles que sur le produit **38** ou trisubstituées encombrées telles que sur la lactone à 14 membres **42**. Cette approche a été surnommée 'relay-ring closing metathesis' (RRCM) (Schéma 1.6).

[18] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004,** *126,* 10210.

En effet, il est même possible de former une liaison C=C tétrasubstituée par cette stratégie et ce, avec des catalyseurs peu actifs comme Grubbs I. Cette approche implique une modification sur une des chaines oléfiniques. Ainsi le rajout d'un pendant de type pentène, tel que sur la structure **40** et peut faire intervenir plusieurs pendants tels que sur le substrat **41**, et ce pour piéger le catalyseur et le forcer (après un premier cycle catalytique et après éjection d'un motif cyclopentène par exemple) à se complexer à une double liaison encombrée ou peu réactive avec qui il n'aurait pas réagit en premier lieu.

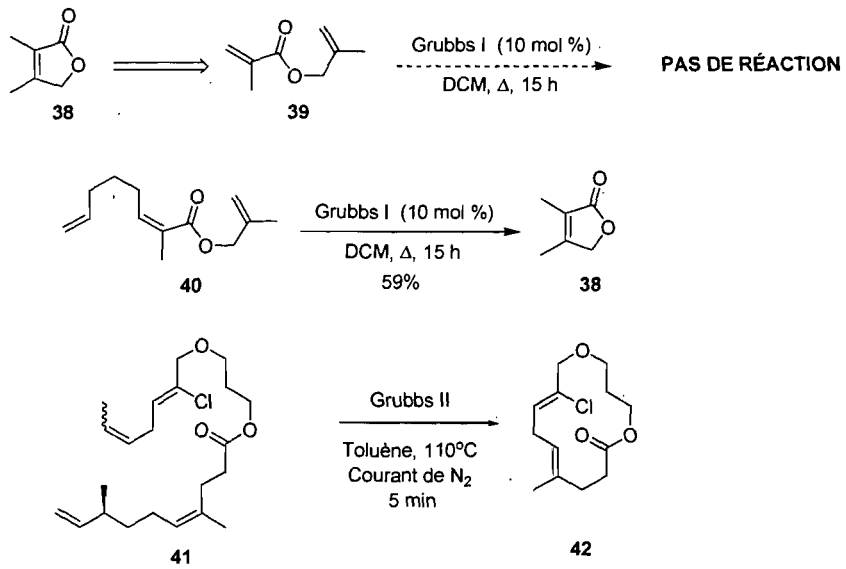


Schéma 1.6: RRCM pour former une liaison C=C tétrasubstituée **38** ou trisubstituée **42**.

Il est important de noter aussi que la stéréochimie issue de la formation du lien carbone-carbone double dans les produits de macrocyclisation par métathèse est en général difficile à contrôler car plusieurs paramètres peuvent l'influencer. Aussi, lors de la

présence de plus de deux oléfines sur le substrat, le contrôle de quelle oléfine va réagir avec quelle autre et dans quel rapport *E :Z* peut s'avérer problématique. Un excellent exemple de ce phénomène fut rapporté par Ghosh[19]. En effet, dans leur approche vers la synthèse de la amphidinolide W, ils ont rencontré plusieurs difficultés qui les ont obligées à reconsidérer le plan de synthèse pour vaincre les problèmes de sélectivité de la métathèse en présence de plus de trois oléfines sur un même substrat (Schéma 1.7) et pour contourner les problèmes de ratio *E :Z* qui en découlent. Le premier problème rencontré par les auteurs était que la réaction de macrocyclisation par RCM n'était pas chimiosélective lorsqu'elle fut appliquée au substrat **45**. En effet, lorsque **45** a été mis en présence du catalyseur de Grubbs II, il y a eu métathèse entre des mauvais partenaires pour conduire au produit secondaire **46** dans un rendement de 82%. La macrolactonisation du substrat **50** dans les conditions de Yamaguchi appliquée s'est avérée problématique et une racémisation importante au niveau du centre stéréogénique en α de l'acide a été observée.

Un autre problème,[20] qui illustre un problème de stéréosélectivité dans la réaction de métathèse a été rencontré dans le cadre de la synthèse de l'épothilone C représenté au Schéma 1.8. Lorsque le substrat très fonctionnalisé **54** a été soumis au catalyseur de Grubbs I, le produit de la macrocyclisation désiré a été obtenu dans un rendement modeste de 44% et un rapport *E :Z* de 1 :1. Il va sans dire que ceci rajoute une complication importante à l'effort synthétique d'autant plus que la séparation

[19] Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085.

[20] Karama, U.; Höfle, G. *Eur. J. Org. Chem.* **2003**, 1042.

chromatographique du produit *Z* du *E* peut s'avérer délicate étant donné la similitude structurale des deux produits.

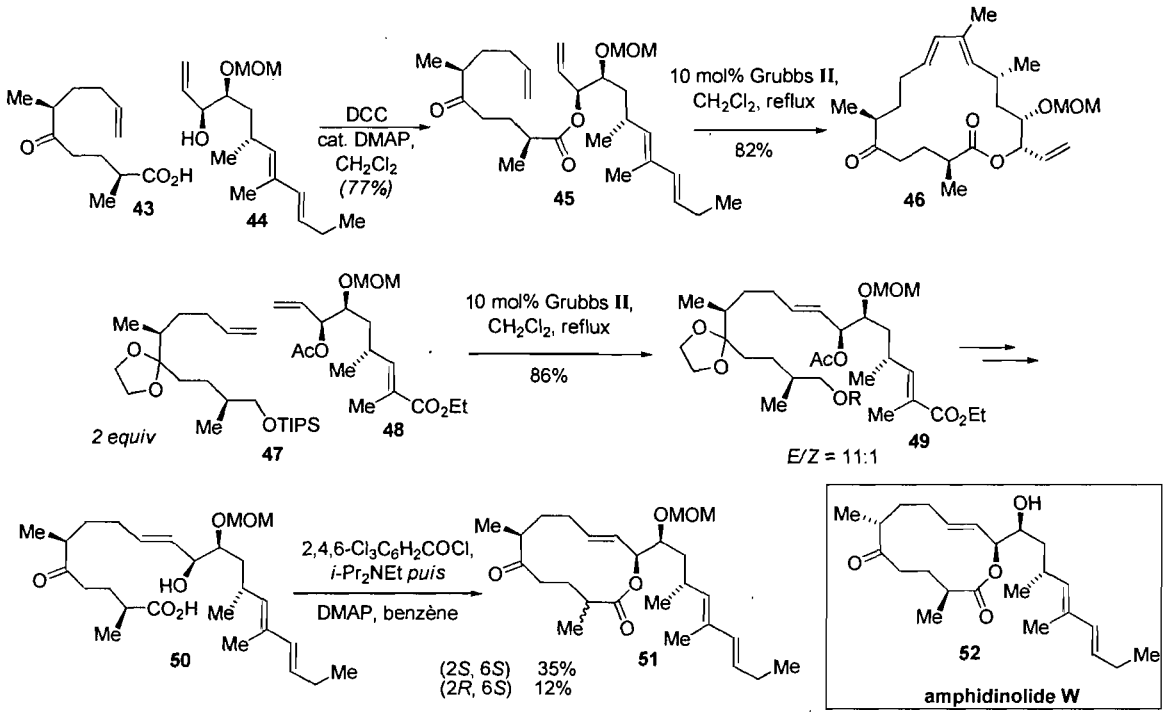


Schéma 1.7 : Diverses approches synthétiques pour la formation du cycle à 12 membres de l'amphidinolide W par RCM et par macrolactonisation de Yamaguchi.

Ceci a inspiré d'autres chimistes à développer des systèmes catalytiques de fermeture par métathèse des alcynes[21]. Cette approche a l'avantage de générer un alcyne qui peut être transformé en alcène Z par hydrogénation partielle de la triple liaison formée initialement et ainsi contrôler relativement la stéréochimie issue des réactions de métathèse. Appliquée à la synthèse totale de l'épothilone C, cette stratégie a été utilisée de façon

[21] Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem.* **1999**, *111*, 503; *Angew. Chem., Int. Ed.* **1999**, *38*, 478.

élégante par Fürstner et ses collaborateurs[22]. En effet, le précurseur de la métathèse des alcynes **56** a été transformé en épothilone C **53** en trois étapes qui incluent la métathèse des alcynes (80%), hydrogénation partielle en présence du catalyseur de Lindlar (100%). Cette approche a l'avantage de générer une sélectivité parfaite pour le produit *Z*.

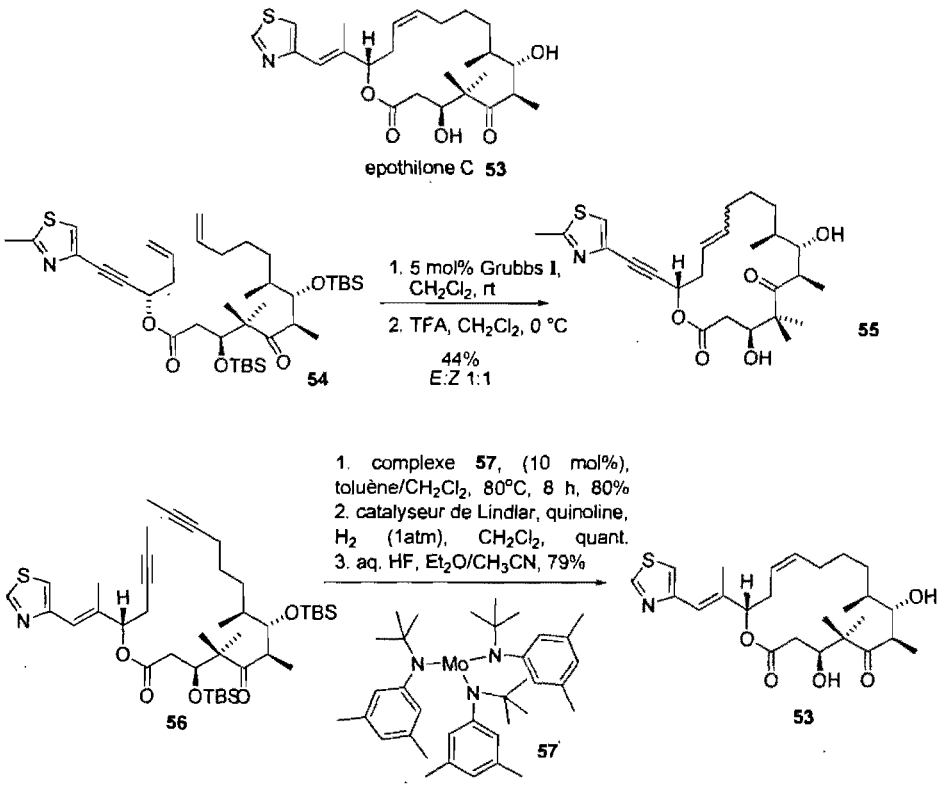


Schéma 1.8 : Application d'une macrocyclisation par RCM des oléfines et des alcynes dans la synthèse d'analogues de l'épothilone C.

[22] Furstner, A.; Mathes, M.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299.

Les problèmes et inconvénients liés à la métathèse des oléfines ne font pas de cette chimie une chimie inexploitable. Les avantages listés en introduction peuvent réellement exister tel que peut en témoigner l'exemple remarquable représenté au Schéma 1.9. En effet, le substrat multifonctionnalisé **58** cyclise de façon efficace pour donner l'amide **59** et ce, dans des conditions, rendement, et pureté exceptionnels. Notons la tolérance aux différentes fonctionnalités présentes sur le substrat et aussi la facilité de mise à l'échelle de cette chimie.

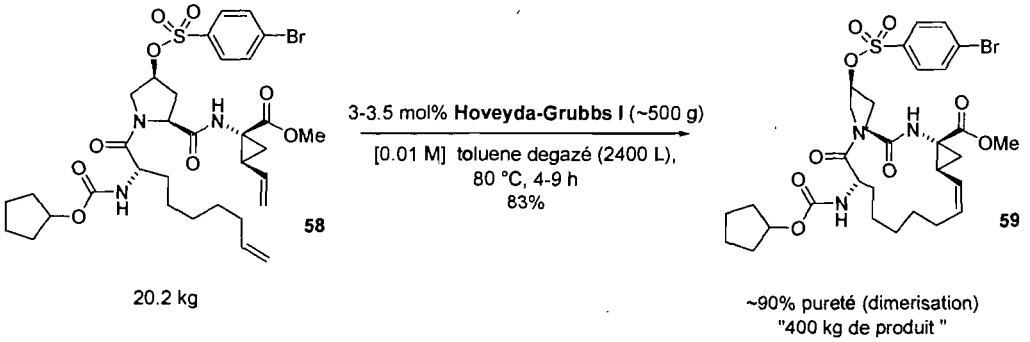
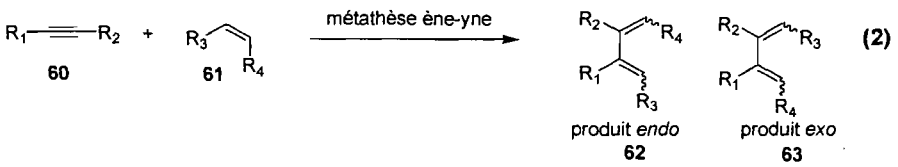


Schéma 1.9 : Application industrielle d'une macrocyclisation par RCM dans la synthèse de BILN 2061 inhibiteurs de la protéase HCV NS3[23].

[23] a) Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinas-Brunet, M. *Org. Lett.* **2004**, *6*, 2901. b) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, *P. Org. Proc. Res. Dev.* **2005**, *9*, 513.

3. La métathèse ène-yne

Initialement introduite par Katz et Sivavec,[24] la métathèse ène-yne n'est qu'une simple variante de la métathèse des oléfines. Elle fait intervenir une oléfine et une fonction alcyne (équation 2).



60 **61** **62** **63** **(2)**

Elle implique les mêmes catalyseurs que la métathèse des oléfines. Elle a toutefois des particularités qui lui sont propres dans le sens où les produits de la réaction sont des 1,3-diènes de plusieurs types dépendamment de l'ordre des transpositions dans le mécanisme de la réaction. Plusieurs produits peuvent être formés (produits dits *endo* ou *exo*). L'illustration d'un mécanisme possible pour cette transformation est représentée à la Figure 1.7. Dans un premier temps, le catalyseur réagit rapidement avec l'oléfine[25] pour lui faire abstraction par métathèse d'un carbène (par exemple celui portant le groupement R_4) et libérer le produit intermédiaire **67**. S'en suit des séquences de cycloadditions [2+2] (notons la possibilité d'avoir le métal du coté de R_1 ou de R_2 qui, dans chaque cas va

[24] Katz, T. J.; Sivavec; T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737.

[25] a) Hoye, T. R.; Donaldson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 277. b) Schramm M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. d) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762.

conduire à un régioisomère différent) pour arriver à **69** qui va faire une métathèse cette fois-ci avec **66** qui a été produit plutôt dans la séquence pour finalement libérer le produit désiré **63** et régénérer le catalyseur **64**.

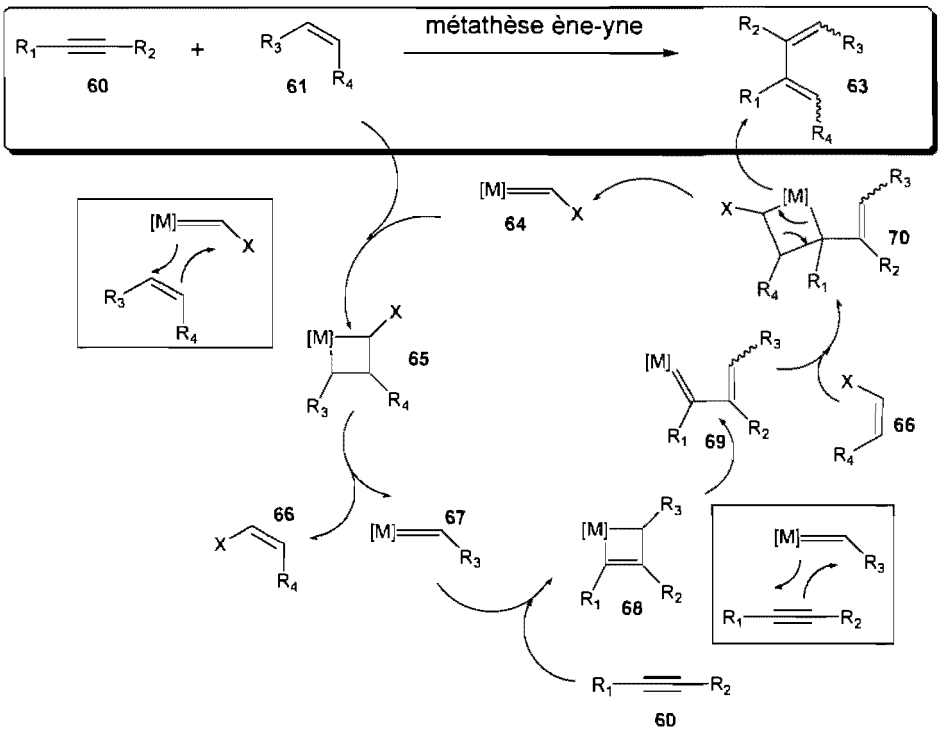


Figure 1.7 : Exemple de mécanisme simplifié d'une réaction de métathèse ène-yne intermoléculaire.[26]

[26] Toutes les flèches impliquées dans ce mécanisme devraient indiquer en équilibre, par contre elles ont été dessinées sous forme simple pour alléger la figure.

Si on rajoute à cela le fait que les liaisons C=C générées peuvent avoir des stéréochimies *Z* et *E* quelconques, il en résulte théoriquement un mélange complexe de régioisomères et stéréoisomères.

Dans la pratique, l'issue de la réaction peut être exploitable et un seul produit peut être favorisé notamment dans les cas particuliers où la réaction est intramoléculaire et/ou la taille du cycle formé joue un rôle crucial. Un exemple de l'utilisation de cette chimie comme étape clé dans la synthèse totale d'un analogue du produit naturel xanthatin **74** est représenté au Schéma 1.10. Dans ce cas particulier, la métathèse ène-yne du substrat **71** comportant une oléfine terminale et un alcyne vrai fourni le produit *exo* **72** dans lequel la configuration de la double liaison du cycle à sept chainons formé n'a le choix que d'être de configuration *Z*. Le produit *endo,* qui n'a pas été observé, il aurait impliqué la formation d'un cycle à huit membres.

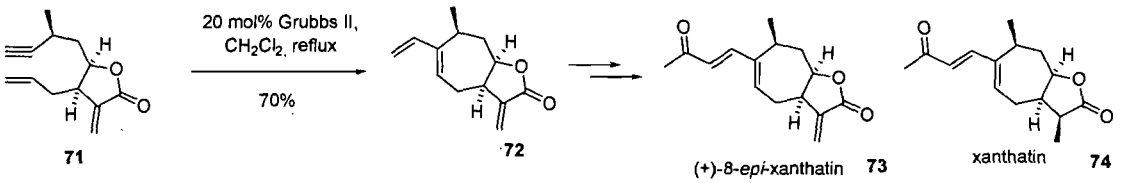


Schéma 1.10 : Métathèse ène-yne cruciale dans l'élaboration du cycle à 7 du (+)-8-*epi*-xanthatin[27].

[27] Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371.

4. Réaction de macrocyclisation par RCM ène- yne

Il va sans dire que la RCM ène-yne pour former de larges cycles est possible et envisageable. Par contre, elle rencontrera les mêmes problèmes que ceux mentionnés dans la RCM des oléfines. De plus, d'autres défis devront être relevés étant donné qu'un contrôle de la régio- et la stéréochimie devra être assuré. Quelques aspects des réactions de macrocyclisation par métathèse ène-yne seront discutés plus tard dans ce chapitre et aussi dans le chapitre 4.

5. La RCM des oléfines comme outil en synthèse organique pour atteindre des systèmes rigides[28]

La RCM est devenue maintenant une méthode standard pour la préparation de systèmes comportant des motifs carbocycliques ou hétérocycliques de différentes tailles allant de cycles à cinq chainons, jusqu'à des composés macrocycliques.[29]

De plus, les avancées récentes dans la conception de catalyseurs de métathèse ont aussi permis à leur tour aux chimistes de pousser encore plus loin le potentiel des réactions de métathèse.[30] Ainsi une balance entre la réactivité, la stabilité et la capacité d'un catalyseur à induire ou non la réaction d'ouverture (versus la RCM) peut être trouvée en procédant à un balayage du large éventail des catalyseurs connus dans la littérature.[31] Aussi, des catalyseurs chiraux [32] dont certains de notre groupe[33] ont pu être développés pour induire de la chiralité dans de telles réactions.

---

[28] Système rigide: système dans lequel certaines rotations et mouvements autour des liaisons sont interdits du fait de la présence d'encombrements stériques sur la molécule. Pour une revue sur le sujet voir : Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122.

[29] a) Paquette, L. A.; Basu, K.; Eppich, J. C.; Hofferberth, J. E. *Helv. Chim. Acta* **2002**, *10*, 3033-3051. b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *5*, 2199-2238. c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *5*, 2127.

[30] a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. b) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. c) Huang, J. K.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375. d) Jafarpour, L.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5416. e) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

[31] Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563.

[32] a) Seiders, T.J., Ward, D.W., Grubbs, R.H. *Org. Lett.* **2001**, *3*, 3225. b) Veldhuizen, J.J., Campbell, J.E., Giudici, R.E., Hoveyda, A.H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.

Malgré tous ces avantages, la préparation de certaines structures rigides est difficile, surtout celles dans lesquelles les deux oléfines dans le substrat de départ à cycliser sont éloignées l'une par rapport à l'autre et/ou dans lesquelles la tension de cycle formée après la métathèse rend le processus d'ouverture thermodynamiquement plus favorable.

Un exemple pertinent de ceci est traité dans la section qui suit et parle de la famille de produits naturels longithorones.

6. Introduction aux longithorones

En 1997, Schmitz et collaborateurs ont isolé, d'une éponge marine au nom d'*Aplidium longithorax* récoltée au large des îles Palau dans l'océan pacifique, un groupe de plusieurs quinones farnésylées.[34] Ce groupe peut être scindé en deux sous- groupes : un sous-groupe monomérique composé de membres comportant une unité quinone enveloppée en position *méta* ou *para* par une chaine farnasylée formant ainsi un para ou métacyclophane (exemple logithorone B et logithorone D respectivement, Figure 1.8). L'autre sous-groupe est lui issu d'une dimérisation entre deux membres monomériques (exemple longithorone A). Dues à la rigidité des cycles qui les forment, tous ces produits présentent des formes de chiralités planes. Les auteurs ont rapporté, par exemple, que lorsque que chauffé à reflux dans le toluène pendent 7 jours, un échantillon de la longithorone C n'a subi aucune racémisation et que seulement une dégradation mineure

[33] Fournier, P.-A.; Collins, S. K. *Organometallics* **2007**, *26*, 2945.

[34] Fu, X.; Hossain, B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810.

fut observée. Ils ont aussi rapporté que ces produits étaient très instables spécialement dans des conditions acides (dégradation en temps réel lorsque mis dans le $CDCl_3$ pour des fins d'analyse RMN). Malgré le fait que leurs activités biologiques cytotoxiques soient très modérées,[35] leurs structures ont rendu curieux deux groupes de recherche autres que le nôtre et des approches synthétiques ont été envisagées. Afin de gagner plus d'informations sur comment approcher ce type de squelette macrocyclique rigide par synthèse totale, nous avons jugé utile de regarder les solutions rapportés par les auteurs qui se sont frottés aux synthèses de ces produits naturels.

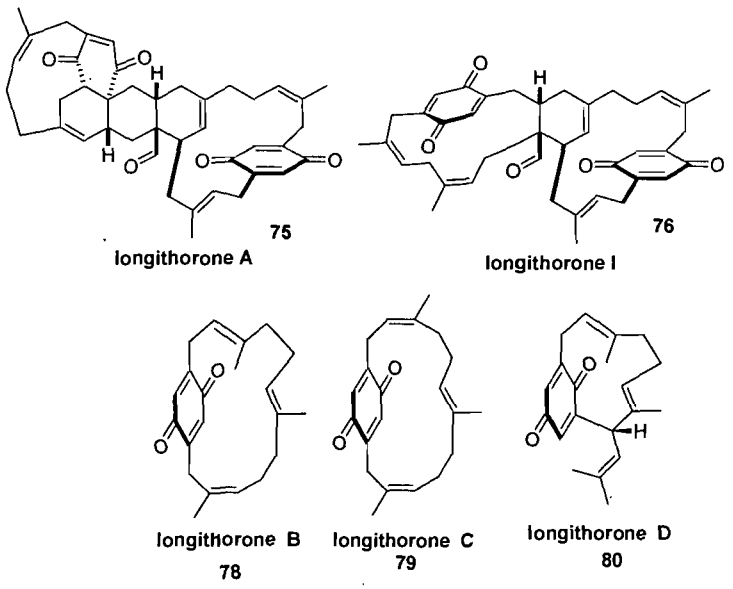


Figure 1.8 : Quelques membres de la famille des produits naturels des longithorones.

[35] a) Fu, X.; Ferreira, M. L. G.; Schmitz, F. J. *J. Nat. Prod.* **1999**, *62*, 1306. b) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. c) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113.

7. Synthèse totale de la longithorone A.

En 2002, Shair et collaborateurs[36] ont rapporté une synthèse totale de la longithorone A. Ils ont exploité d'une facon originale la proposition de biosynthèse de ce type de molécule avancée par Schmitz et collaborateurs.[37] L'analyse retrosynthétique adoptée est représentée à la Figure 1.9.

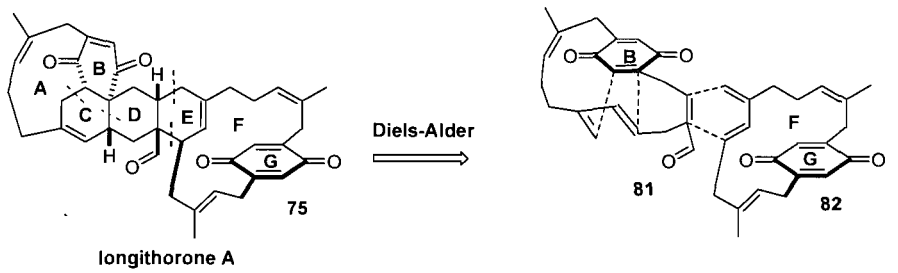


Figure 1.9 : Analyse retrosynthétique de la longithorone A impliquant des réactions de Diels-Alder intermoléculaire et transannulaire.

Les deux macrocycles **81** et **82** sont des [12]paracyclophanes dans lesquels la rotation interdite autour de la quinone induit un atropisomérisme. D'ailleurs, le groupe de Shair croit à raison que la stéréochimie générée au niveau des cycles **C**, **D** et **E** de la longithorone A est dérivée essentiellement de la chiralité plane présente dans les deux paracyclophanes rigides que sont **81** et **82**. Il était donc nécessaire de préparer les

[36] Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.

[37] Fu, X.; Hossain, M. B.; van Der Helm, D.; Schmitz, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12125.

paracyclophanes **81** et **82** de façon énantiosélective. Ces deux cyclophanes ont en commun le fait de comporter un motif 1,3-diène le long du pont *ansa*. L'accès à ce type de motif peut être facilement envisageable par métathèse ène-yne. Par conséquent, les types de substrats envisagés par les auteurs sont **83** et **84** comme représentés à la Figure 1.10.

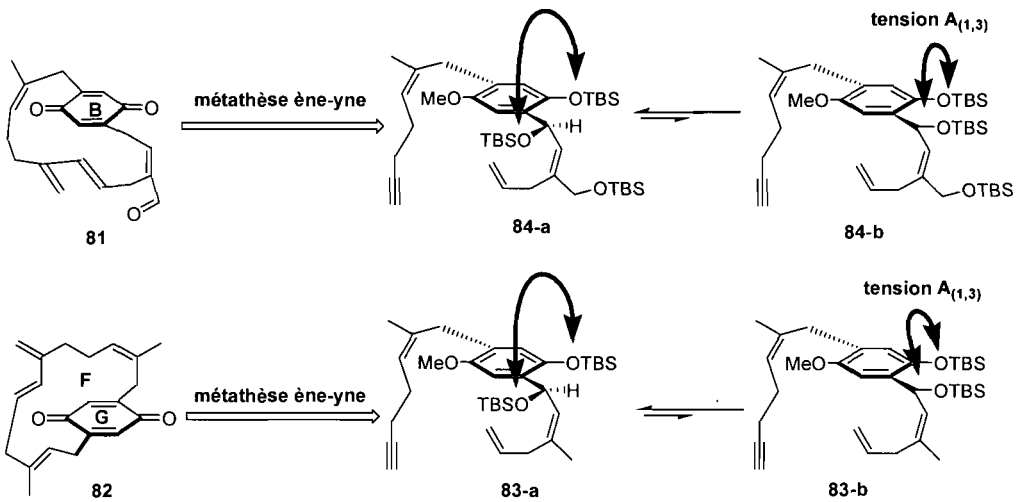


Figure 1.10: Accès aux paracyclophanes **81** et **82** via métathèse ène-yne.

Bien que la dilution, et les techniques d'addition lente puissent aider à améliorer les rendements des réactions de macrocyclisations,[38] les chimistes ont recours souvent à l'installation d'éléments de contrôle conformationel pour favoriser la cyclisation.[39].Dans le cas de la synthèse de Shair, l'exploitation de la minimisation de la tension allylique

[38] Chuchuryukin, A. V.; Dijkstra, H. P.; Suijkerbuijk, R. J. M.; van Klink, G. P. M.; Mills, A. M.; Spek, A. L.; van Koten, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 228.

[39] Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125.

$A_{1,3}$, telle que représentée sur les structures **83-a** et **84-a,** a joué un rôle crucial dans l'issue de la réaction. L'interaction entre les deux groupements OTBS sur les substrats de métathèse ène-yne défavorise considérablement les conformations **83-b** et **84-b**. L'absence de ce type de contrôle résulte tout simplement en un mélange complexe de produits d'oligomérisation indésirables. En effet, le recours à cette technique est important car sinon aucune macrocylisation ne peut être observée tel qu'en témoigne l'exemple rapporté par les mêmes auteurs et représenté au Schéma 1.11.

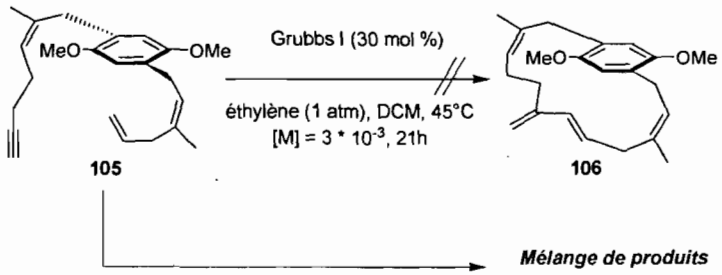


Schéma 1.11 : Résultats de la métathèse ène-yne en l'absence de l'élément de contrôle.

Jusqu'au rapport de Shair et collaborateurs, très peu d'information sur les réactions de macrocyclisation par métathèse ène-yne pouvait être trouvée dans la littérature.[40] Quelques observations générales ont déjà montré que la métathèse ène-yne intramoléculaire entre des partenaires tels que ceux illustrés au Schéma 1.12 offrait les diènes 1,2-disubstitués (**85**) et que la métathèse ène-yne intermoléculaire donnait plutôt les diènes 1,3-disubstitués (**86**).[41]

[40] Hensen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582.

[41] Mori, M.; Kitamura, T; Sato, Y. *Synthesis* **2001**, 654.

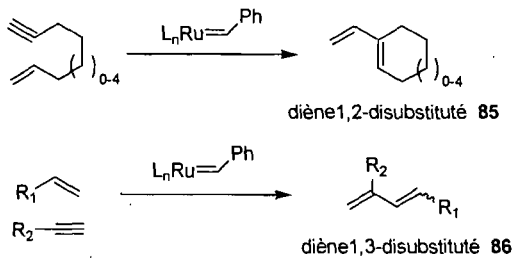
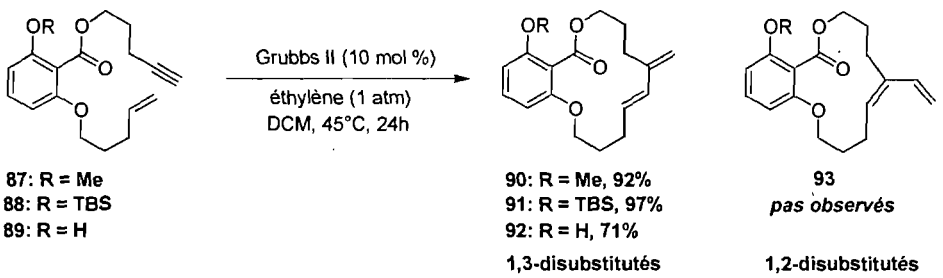


Schéma 1.12 : Métathèse ène-yne intramoléculaire versus intermoléculaire.

L'utilisation de structures modèles a permis au groupe de Shair de trouver les conditions optimales pour la réaction de macrocyclisation.[42] Ils ont trouvé que l'utilisation d'un atmosphère d'éthylène dans un premier lieu pour faire une métathèse ène-yne intermoléculaire entre ce dernier et l'alcyne terminal des substrats **87**, **88**, et **89** pouvait donner un diène-1,3 terminal linéaire qui dans un second lieu pouvait subir une macrocyclisation de type ène normale pour conduire au cycles 1,3-disubstitués **90**, **91**, et **92**. Ils ont aussi remarqué que dans ces conditions les autres produits possibles de la réaction du type 1,2-disubstitués **93** ne se formaient pas (Schéma 1.13).



Schèma 1.13: Études modèles de macrocyclisation par métathèse ène-yne.

[42] Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12036.

La synthèse énantiosélective du précurseur de la métathèse ène-yne **83** a été effectuée suivant la séquence impliquant les 9 étapes réactionnelles suivantes (Schéma 1.14).

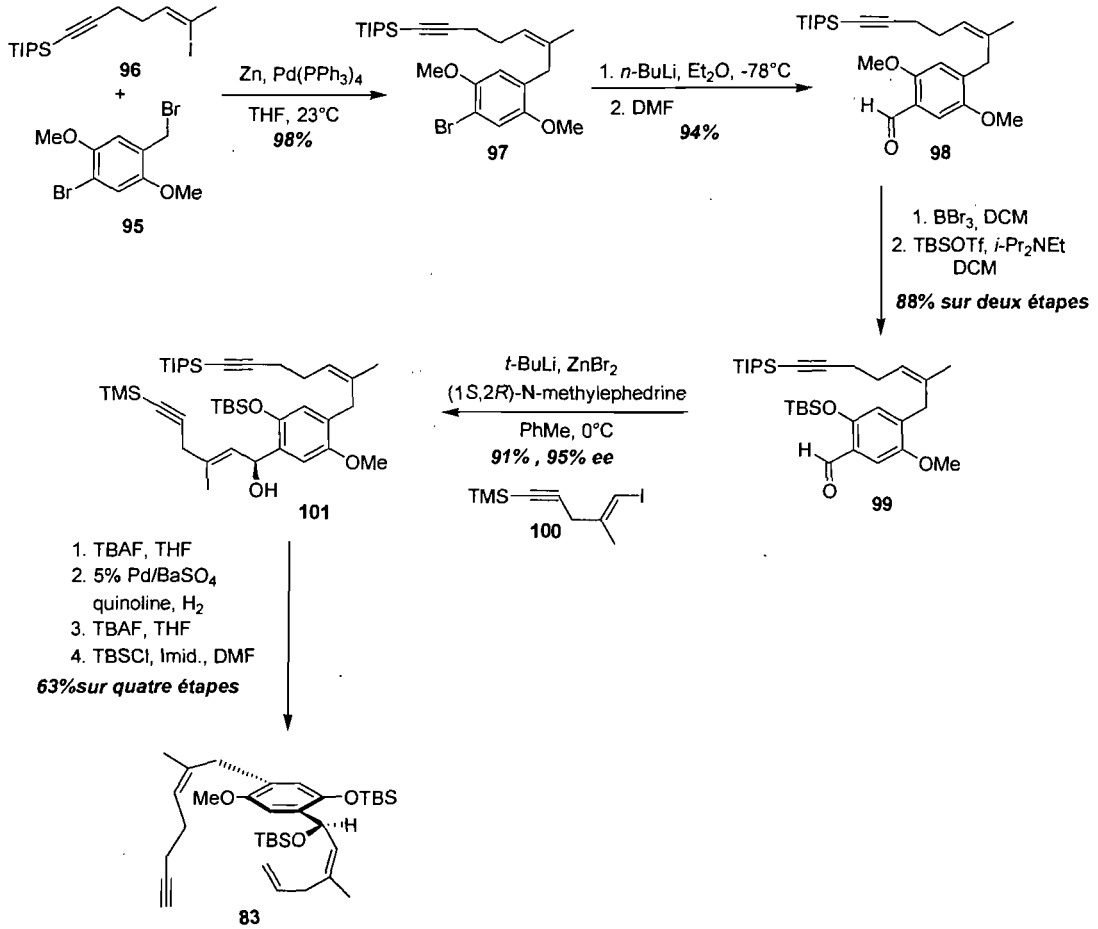


Schéma 1.14: Préparation du précurseur de métathèse ène-yne **83**.

Le couplage au palladium entre l'iodure de vinyle **96** et le zincique dérivé du bromure de benzyle **95** a permis l'obtention de **97** dans un rendement de 98%. La formylation de **97** en deux étapes (déprotonation avec *n*-BuLi et achèvement avec DMF) donne l'aldéhyde

98 dans un rendement de 94%. Une déméthylation sélective a été rendue possible par l'utilisation d'un seul équivalent de BBr_3, suivit d'une silylation avec TBSOTf; l'éther silylé **99** a été obtenu dans un rendement de 88% sur les deux étapes.

L'alkylation énantiosélective de l'éther silylé **99** en utilisant le zincique dérivé de **100** en présence de l'alkoxyde de lithium de la (1*S*,2*R*)-*N*-méthyléphédrine conduit à la formation de l'alcool benzylique **101** et ce, dans un rendement de 91% et un excès énantiomère de 95%. Il est important de noter que le contrôle de la stéréochimie de ce centre va permettre par la suite le contrôle de la chiralité plane sur le produit de la macrocyclisation par métathèse ène-yne tel qu'indiqué à la Figure 1.10.

L'alcool benzylique **101** traité avec TBAF permet la déprotection en même temps de l'alcyne-TMS et du phénol silylé. L'hydrogénolyse sélective en présence du catalyseur de Lindlar de l'alcyne terminal, suivi d'une déprotection de l'alcyne-TIPS restant par TBAF et reprotection du phénol et de l'alcool benzylique avec TBSCl donne accès à **83** dans un rendement de 63% sur quatre étapes.

Lorsque **83** et **84** sont traités en présence de catalyseur de Grubbs I sous une atmosphère d'éthylène les résultats représentés au Schéma 1.15 ont été obtenus. Comme indiqué précédemment, la haute dilution et par conséquent des temps de réactions longs ont été requis pour obtenir les produits macrocycliques. Malgré les optimisations, le macrocycle **102** issu de **84** est obtenu dans un rendement de seulement 31%, tandis que celui issu de **83** est obtenu dans un rendement de 42%. De plus, le contrôle de l'atropodiastéréosélectivité et du ratio *E/Z* dans le cas de **84** se sont avérés faibles (2.8 :1 et 3.9 :1 respectivement). Dans le cas de **83** le contrôle s'est avéré plus efficace. Aucune

explication n'a été fournie par les auteurs pour expliquer ces disparités. Toutefois, il nous paraît clair que même un changement subtil sur le précurseur de métathèse peut avoir ainsi un effet dramatique sur l'issue de la réaction.

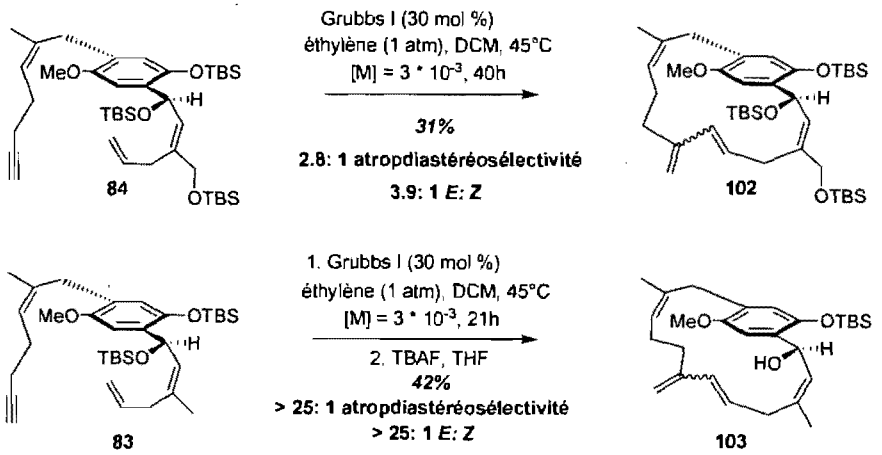
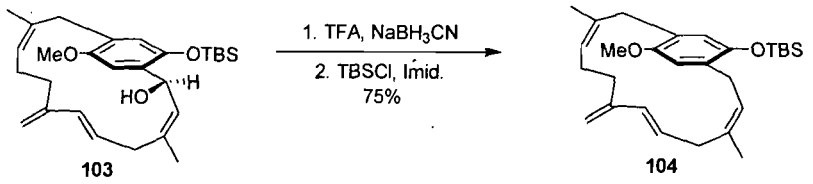


Schéma 1.15 : Résultats de la métathèse ène-yne utilisant l'élément de contrôle atropisomérique.

L'élimination de l'alcool benzylique qui faisait office d'élément de contrôle atropisomérique dans **83** par exemple a été effectuée à l'aide de TFA et $NaBH_3CN$.[43] Dans ces conditions le silyle sur le phénol est clivé et une reprotection est nécessaire pour la suite de la synthèse. Le cyclophane **25** est ainsi formé dans un rendement de 75% sur ces deux étapes (Schéma 1.16).

[43] Kursanov, D. N.; Parnes, Z. N. *Russ. Chem. Rev.* **1969**, *38*, 812.



103 104

Schéma 1.16 : Élimination de l'élément de contrôle atropisomérique.

Shair et collaborateurs ont ainsi démontré la possibilité de former des [12]paracyclophanes par métathèse ène- yne. Toutefois, ceci s'est avéré difficile à cause de la tension de cycle. L'exploitation de la tension allylique $A_{1,3}$ stéréocontrôlée grâce au stéréocentre benzylique a permis de contrôler significativement les équilibres conformationels des substrats pour les diriger vers les conformations qui sont préférentiellement productives en métathèse.

Toutefois, l'installation et l'enlèvement, non sans peine, de l'élément de contrôle sur les chaines hydrocarburess ont été nécessaires. Par rapport à la réaction de macrocyclisation clé, les quantités de catalyseurs et les impuretés générées par des processus indésirables lorsque l'éthylène est utilisé, les rendements modestes et le contrôle du rapport *E* :*Z* et de l'atropodiastéréosélectivité assez variable font en sorte que des améliorations sont encore possibles.

8. Synthèse de la longithorone B.

La longithorone B est l'un des [12]paracyclophanes les plus simples de la famille des logithorones (figure 1.11). La chaine farnésylée qui la compose comporte deux doubles liaisons *trans* et une *cis*. Le seul défi synthétique associé à la préparation de la longithorone B est étroitement lié à la difficulté d'accéder au cycle rigide et ce, de façon énantiosélective.

Le groupe de Tadahiro et colaborateurs[44] a développé une approche très intéressante visant la construction du squelette de la longithorone B racémique. En effet, ils ont fait appel à une réaction de Friedel-Crafts pour former le pont *ansa* (Figure 1.11).

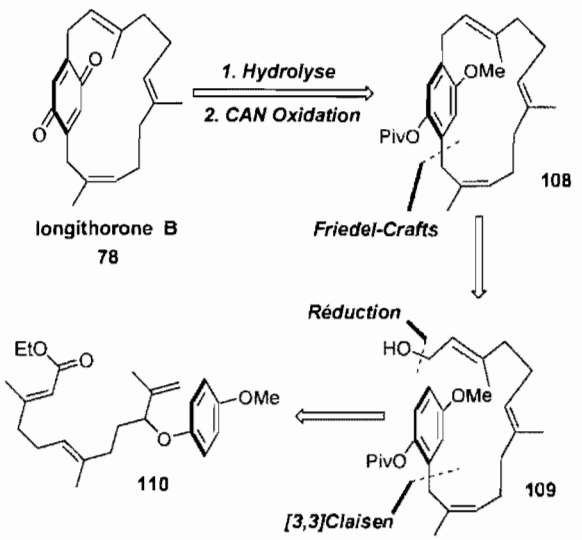


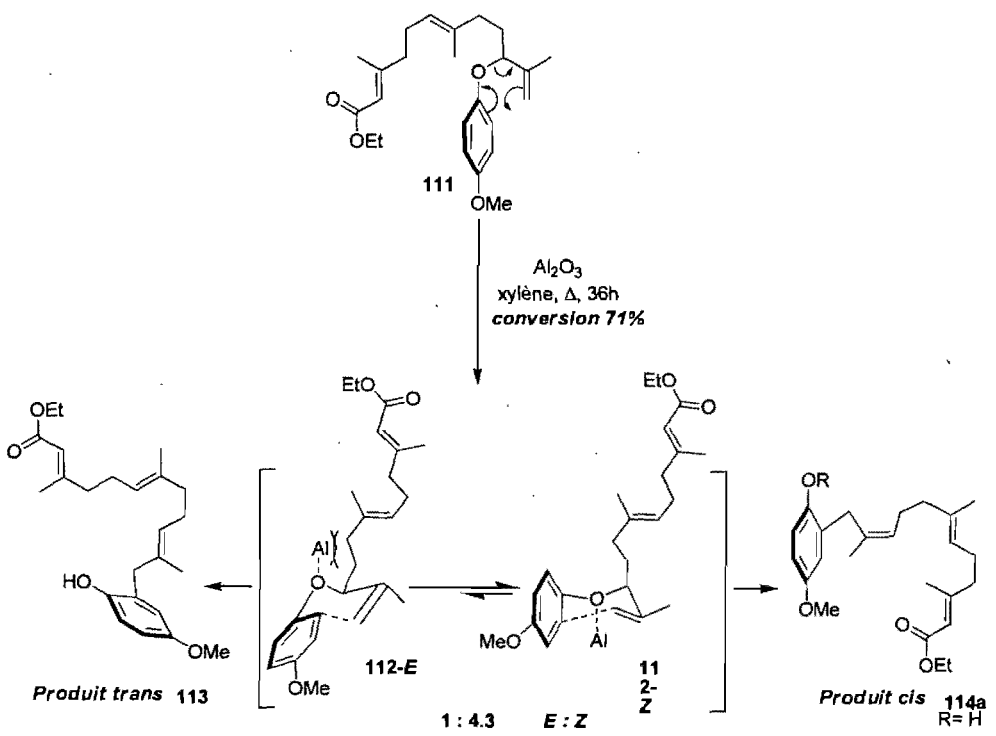
Figure 1.11 : Analyse rétrosynthétique de la longithorone B proposée par Tadahiro.

[44] Tadahiro, K.; Kentaro, N.; Masahiro, H. *Tetrahedron Lett.* **1999**, *40*, 1941.

Cette approche est doublement intéressante car elle ne fait pas appel à aucun élément de contrôle conformationnel et arrive au substrat avant la réaction de Friedel-Crafts de façon directe et efficace via un réarrangement sigmatropique [3,3] du type Claisen.

Le réarrangement sigmatropique [3,3] du type Claisen des éthers d'allyles et d'aryles est connu pour donner accès facilement à des phénols *ortho*-allylés.[45] Toutefois, dans le cas de l'approche du groupe de Tadahiro, il fallait aller plus loin et contrôler par la même occasion le ratio *E* :*Z* issu de la réaction. Ce dernier dépend énormément de la nature des additifs utilisés et des conditions de la réaction. Ils ont toutefois été capables d'obtenir un ratio de 1 :4.3 en faveur du *Z* lorsque les conditions représentées au Schéma 1.17 ont été utilisées.

[45] Krohn, K.; Bernhard, S. *Synthesis* **1996**, *6*, 699.



Schèma 1.17 : Intermédiaires formés lors des réarrangements [3,3]-sigmatropiques.

Les trois dérivés différemment protégés (**114**, **115**, et **116**) ont été ainsi soumis à l'alkylation intramoléculaire dans les conditions de Friedel-Crafts (Schéma 1.18). De toutes les conditions essayées, c'est l'acide de Lewis $Hf(OTf)_4$ jumelé avec $LiClO_4$ comme additif dans CH_2Cl_2 qui a donné les meilleurs résultats. La nature du groupement R sur le phénol s'est avérée extrêmement importante à la fois pour contrôler la régiochimie et pour augmenter le rendement du produit désiré.

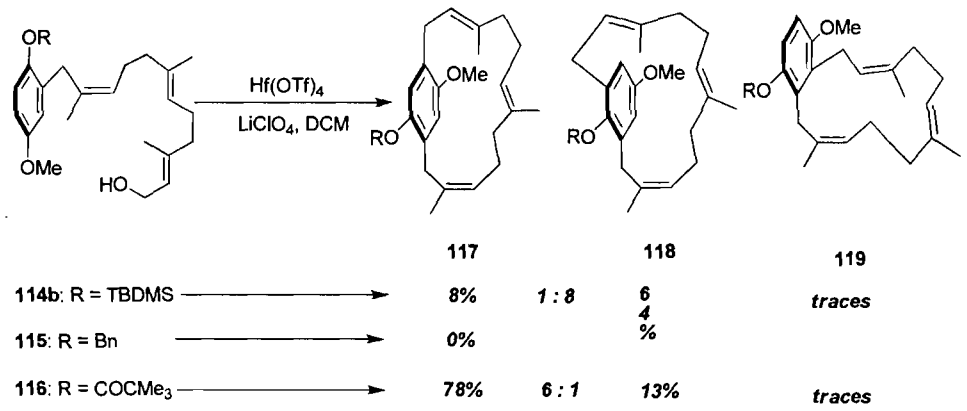


Schéma 1.18 : Préparation du [12]paracyclophane par alkylation de Friedel–Crafts.

Quand l'éther silylé **114** est traité dans les conditions précédentes un mélange de **117** et **118** est obtenu. Une purification par HPLC a permis de quantifier la quantité de **118** formée (64%). La prédominance de l'agencement à la position *méta* par rapport à l'éther methylé de **118** est probablement causée par la nature électrodonneur du groupement TBDMS. L'éther de benzyle **115** a conduit à la formation d'un mélange complexe de produits.

Quand le pivalate **116** est traité dans les mêmes conditions que précédemment, le produit désiré est isolé à la hauteur de 78%. La nature électroattracteur du groupement pivaloyle de **116** semble de contrôler la réaction, pour favoriser la substitution en *para* et conduire au macrocycle désiré **117**. Une simple hydrolyse avec KOH dans MeOH suivie d'une oxidation au CAN conduit à la formation de la longithorone B dans un rendement de 58% sur deux étapes.

L'approche du groupe Tadahiro vers de la longithorone B s'appuie sur la biosynthèse de ses produits telle qu'avancée par les auteurs de l'isolement.[37] Elle n'a recours à aucun élément de contrôle conformationnel car elle utilise la réaction d'alkylation de Friedel–Crafts. Lors de l'état de transition de cette réaction (i.e. formation d'une espèce carbocationique allylique), l'attaque intramoléculaire de l'aryle est tellement rapide que le substrat n'a pas besoin d'attendre de rencontrer un autre substrat pour se réarranger ou de faire autre chose. Toutefois, les auteurs ont rapporté le fait que les conversions n'atteignent pas les 100% en plus du fait que le produit obtenu est en fait un mélange inséparable de méta et de [12]orthocyclophane. De plus, les auteurs ne proposent aucune voie pour rendre leur approche énantiosélective.

À la lumière des deux exemples que nous venons de traiter, il est clair que des améliorations peuvent être apportées afin de développer de nouvelles méthodes pour accéder à des structures macrocycliques comportant de la chiralité plane telle que trouvée dans la famille des longithorones.

9. Buts et défis synthétiques

Comme longithorone B, la longithorone C est un des[12]paracyclophanes des plus simples de sa famille (Figure 1.12). La chaine farnésylée qui le compose comporte cette fois-ci deux doubles liaisons *cis* et une *trans*. Une analyse qualitative suggérerait alors

que le cyclophane de la longithorone B serait plus tendu que celui de la C à cause justement de la configuration de ces doubles liaisons. Le défi synthétique majeur associé à la préparation de la longithorone C est l'accès au cycle rigide et ce, de façon énantiosélective. En effet, la longithorone C a été isolée comme un seul atropisomère,[34] ses activités cytotoxiques sont modérées.[35] Toutefois, personne ne peut se prononcer sur les activités de son énantiomère. En effet, on trouve dans la littérature des exemples dans lesquels le changement dans le sens de la chiralité planaire est identique au changement dans les autres formes de chiralités conventionnelles. Un exemple de ça est le produit naturel roséophiline qui possède un énantiomère non-naturel qui a des activités anti-tumorales paradoxalement plus intéressantes que l'énantiomère naturel.[46]

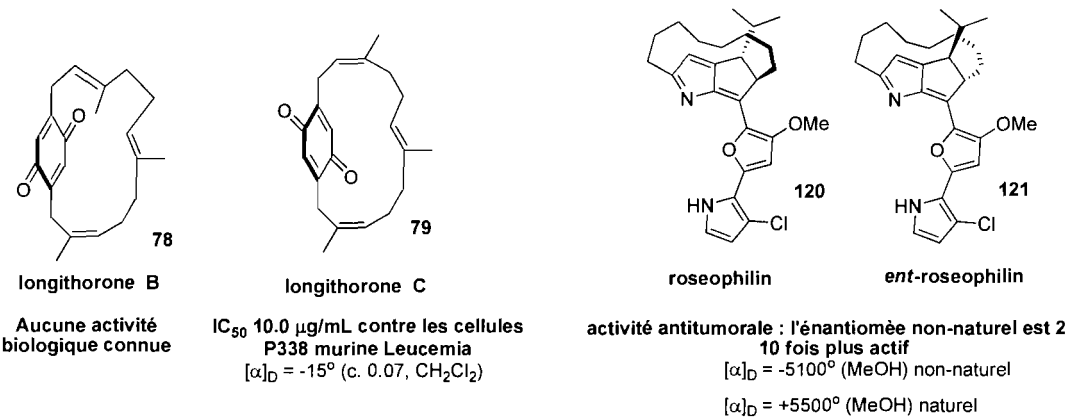


Figure 1.12: Les cyclophanes naturels longithorones B, C et roséophiline.

[46] a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. c) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.*, **2000**, *122*, 3801. d) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.

Nous avons envisagé de développer une approche synthétique efficace vers la longithorone C en utilisant la RCM comme étape clé pour former le pont *ansa* (Figure 1.13). L'objectif ultime serait d'installer la chiralité plane par une réaction de métathèse d'oléfines énantiosélective utilisant un catalyseur chiral.

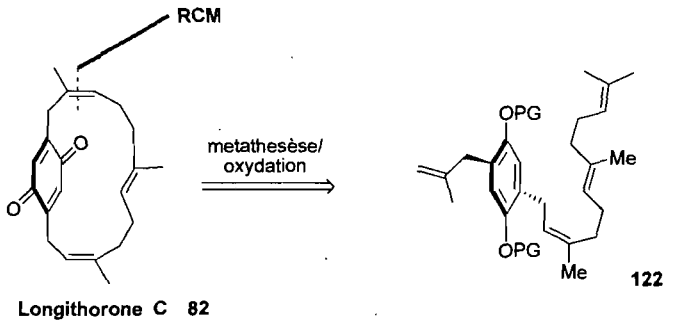


Figure 1.13: Analyse rétrosynthétique initiale de la longithorone C.

Comme on l'a vu précédemment, la formation de [12]paracyclophanes est accessible via métathèse ène-yne normale. Une macrocyclisation par RCM des oléfines pourrait en principe être utilisée pour former la structure macrocyclique de longithorone C. Les variables synthétiques à maîtriser incluent la détermination du site idéal pour la macrocyclisation (proche du noyau versus au milieu de la chaine farnésylée), la diastéréosélectivité lors de la formation de la double liaison trisubstituée (*cis* versus *trans*) et, bien sûr, la stéréosélectivité vis-à-vis de la chiralité plane du paracyclophane. L'approche synthétique que nous proposons passerait par l'énumération des défis synthétiques un par un (difficulté de la macrocyclisation, formation d'une oléfine trisbstituée, contrôle de la diastéréosélectivité de la double liaison lors de la formation du

cycle, énantiosélectivité) et s'y attaquerait chacun à la fois pour à la fin sortir avec une stratégie globale.

Chapitre 2 : La longithorone C, un composé représentatif

1. Formation des [12]paracyclophanes: Étude modèle.

Les [12]paracyclophanes sont des structures macrocycliques relativement souples. La tension et la rigidité du cycle deviennent importantes si des doubles liaisons et/ou des substitutions sur ce cycle sont nombreuses. Dans le cas où trois doubles liaisons trisubstituées sont présentes ils se les molécules possèdent de la chiralité plane. Nos études synthétiques vers la longithorone C nous ont poussé à commencer d'abord par examiner jusqu'à quel point le besoin d'un élément de contrôle conformationnel était important pour former les [12]paracyclophanes (schéma 2.1).

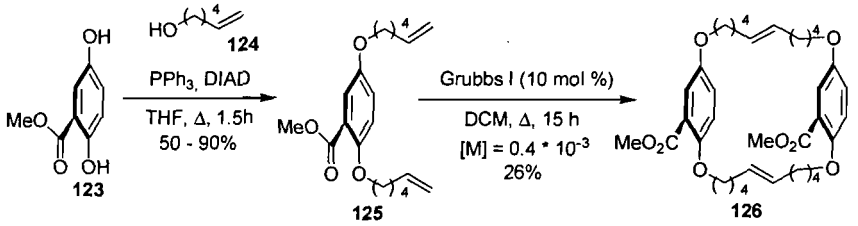
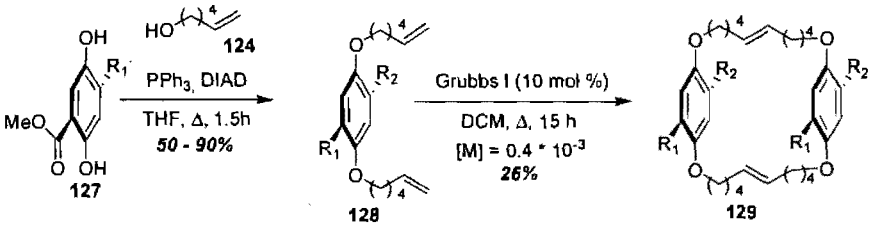


Schéma 2.1: Essais initiaux de formation de [12]paracyclophanes.

Malheureusement, les nombreuses tentatives pour cycliser divers précurseurs tel que **125** utilisant le catalyseur de Grubbs I mènent à la formation préférentielle du dimère **126** en plus d'autres oligomères supérieurs, et ce,malgré la relative haute dilution, démontrant l'importance de contrôler l'orientation des chaînes latérales (entrée 2, tableau 2.1).

Tableau 2.1 : Essais de formation de divers [12]paracyclophanes.



Entreé	R1	R2	Catalyseur	Temp (°C)	Temps (h)	Rdt (%)
1	CO_2-Pr	CO_2Me	1	21 → Δ	24	70
2	H	CO_2Me	1	21 → Δ	24	29
3	H	CH_2OTBS	1	21 → Δ	24	60
4	CO_2Me	CO_2Me	2	150 (MW)	5 min	40
5	CO_2Me	CO_2Me	1	Δ	24	20
6	CO_2Me	CO_2Me	1	150 (MW)	30 min	40
7	CO_2Me	CO_2Me	2	150 (MW)	30 min	40
8	H	CO_2CH_2Ph	1	Δ	24	26

Des variations sur le noyau aromatique central avec l'ajout d'un autre substituant ester (entrée 1 et 5) n'ont rien donné. De plus, l'utilisation d'un catalyseur réputé pour être plus cinétiquement actif (entrée 4) et l'utilisation des micro-ondes comme moyen de chauffage n'ont apporté aucune amélioration quant à la formation des produits désirés. La nature des substituants sur l'aromatique ne semble pas changer quoi que se soit à l'issue de la réaction (entrée 1, 2 et 3). Aussi, on a cru que l'usage d'un ester de benzyle (entrée 8) permettrait l'arrangement en solution du substrat de tel sorte que les deux noyaux aromatiques s'empilent l'un par-dessus l'autre. De cette façon, et tel que représenté par la structure **130-S** (schéma 2.2), les deux chaines latérales allaient être poussées à s'orienter

dans la même partie de l'espace, et ainsi adopter une conformation productive pour la RCM, mais ce ne fut pas le cas et seul le dimère a pu être isolé après chromatographie.

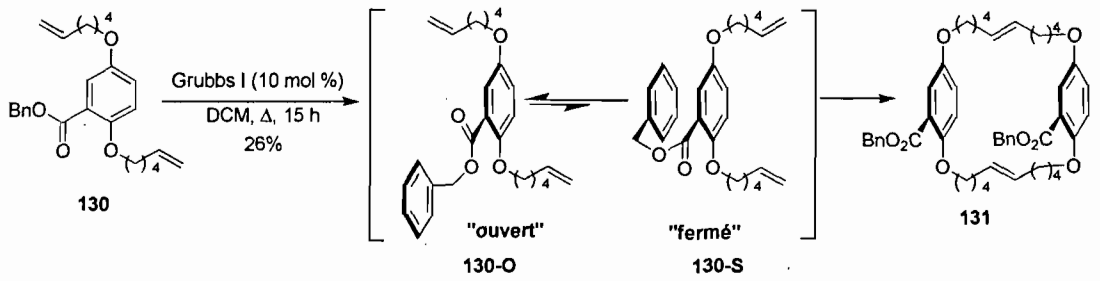


Schéma 2.2: Ester de benzyle comme élément de contrôle conformationnel.

Cependant, le passage au groupement pentafluorobenzyle a provoqué un changement spectaculaire quant à l'issue de la réaction (schéma 2.3).

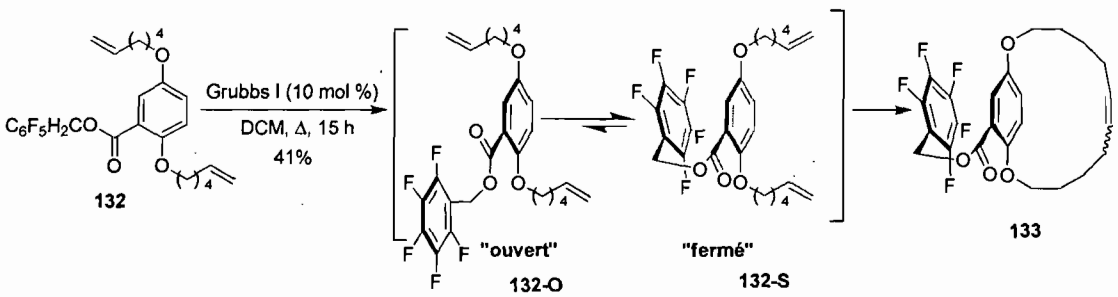


Schéma 2.3 : Ester de pentafluorobenzyle comme élément de contrôle conformationnel.

En effet, quand le substrat **132** a été traité dans les conditions similaires aux conditions précédentes, le cyclophane **133** a été isolé dans un rendement reproductible de 41%.

Nous pensons que le passage au dérivé ester de pentafluorobenzyle a favorisé énormément la structure du type **132-S** du fait de l'orthogonalité électronique[1] (figure 2.1) entre le pentafluorophenyl et l'aromatique du substrat, ce qui a pour effet de contribuer à ce que les deux aromatiques s'engagent dans des interactions non covalentes du type quadripolaires

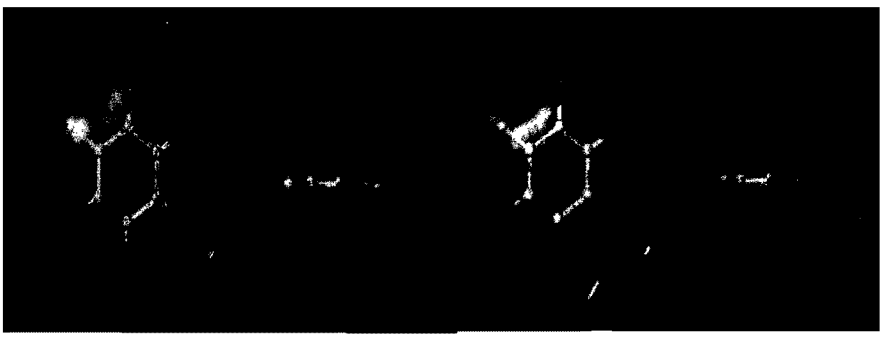


Figure 2.1 : Les densités électroniques orthogonales du perfluorobenzène et du benzène.

Ces types d'interactions sont assez connus en chimie médicinale et dans les sciences des matériaux du fait que certains arrangements intermoléculaires à l'état solide, par exemple, sont visibles.[2] En effet, lorsque mélangés dans un rapport un pour un les composés **134** et **135** forment à l'état solide un complexe bien défini qui comporte une alternance noyau riche en électrons-noyau pauvre en électrons avec un arrangement du type face à face (figure 2.2).

[1] Brown, N. M. D.; Swinton, F. L. *J. Chem. Soc., Chem. Comm.* **1974**, 770.

[2] Mann, E.; Mahia, J.; Maestro, M. A.; Herradon, B. *J. Mol. Struct.* **2002**, *641*, 101.

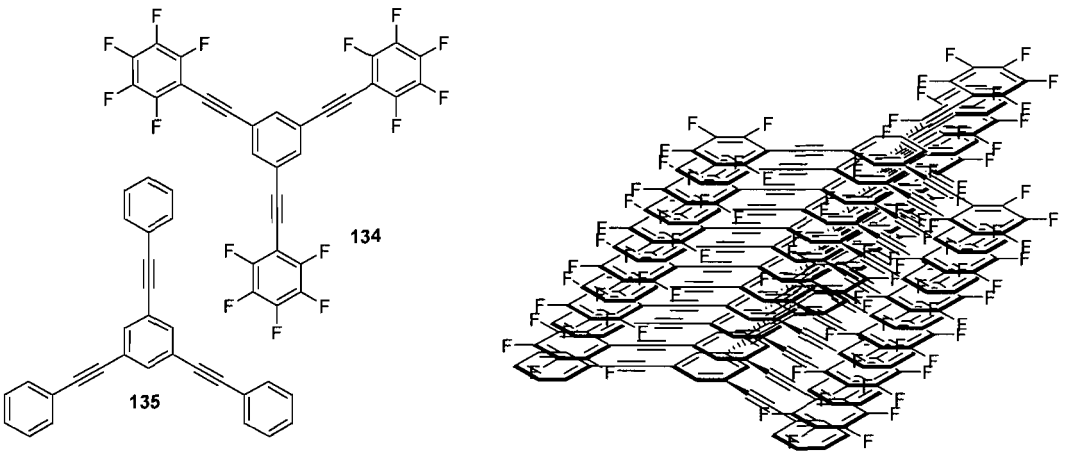


Figure 2.2 : Interactions quadripolaires intermoléculaires observées à l'état solide.[3]

Ce type d'interactions peut être observé de façon intramoléculaire. Par exemple, Cammers-Goodwin et collaborateurs[4] ont rapporté que le dérivé phénylpyridinium de benzyle **136** empile de façon intramoléculaire le phényle et le benzyle dans un arrangement canonique face à face, centre à centre (figure 2.3).

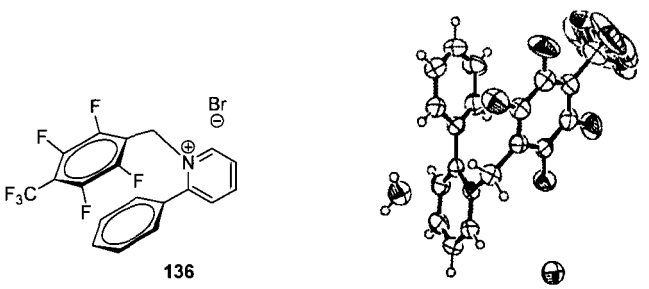


Figure 2.3 : Empilement π de type face à face, centre à centre du composé **136** à l'état solide.

[3] Ponzini, F.; Zagha, R.; Hardcastle, K.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2323.

[4] Martin, C. B.; Mulla, H. R.; Willis, P. G.; Cammers-Goodwin A. *J. Org. Chem.* **1999**, *64*, 7802.

Le traitement théorique de ces interactions ou leur modélisation moléculaire peuvent être très compliqués. Il existe toutefois dans la littérature des modèles de traitement qui peuvent être assez simples.[5] L'énergie potentielle qui varie en fonction de la distance interplanaire *r* des deux noyaux aromatiques tient compte des forces électrostatiques, de dispersion et de transfert de charge (équation 2).

$$E(r) = \underbrace{a/r^{12} + b/r^{6}}_{\text{Forces électrostatiques et de dispersion}} + \underbrace{c/e^{(-2r/L)}}_{\text{Transfert de charge}}$$

Équation (2) : Expression de l'énergie potentielle tenant compte de la somme de toutes les interactions quadripolaires entre deux aromatiques *(a,b* et *c* sont des paramètres variables, *L* est la somme du rayon de van der Waals du donneur et de l'accepteur)

Les paramètres *a, b* et *c* peuvent être ajustés jusqu'à ce qu'on s'approche des valeurs trouvées expérimentalement. Le tracé du potentiel d'énergie en fonction de la distance *r* peut ressembler à celui de la figure 2.4.

[5] Gung B. W.; Amicangelo, J. C. *J. Org. Chem.* **2006**, *71*, 9261.

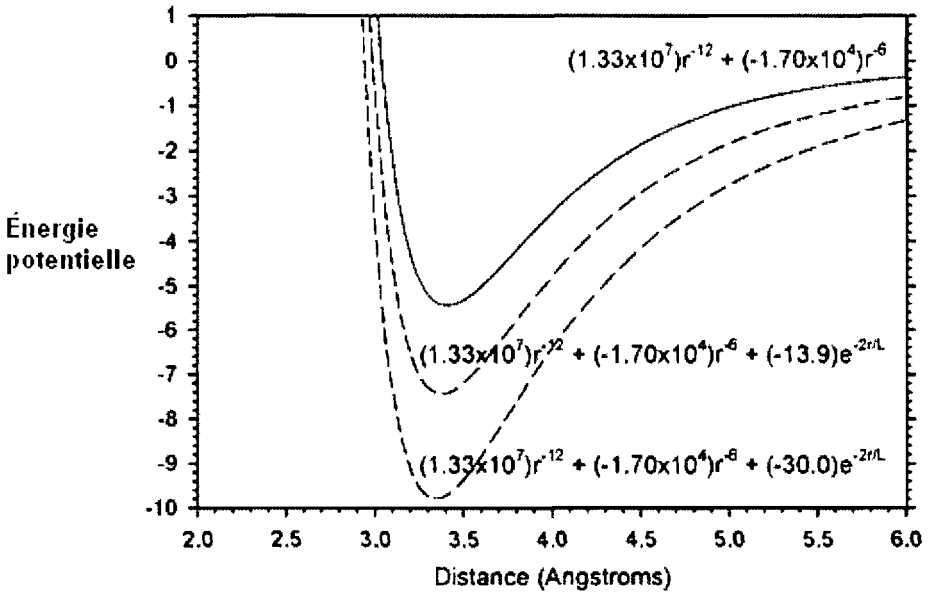


Figure 2.4: Énergie potentielle en fonction de *r* pour un potentiel du type (1) Lennard-Jones (bleu); (2) avec rajout d'un terme de transfert de charge (rouge); (3) avec un poids plus prononcé pour le terme de transfert de charge (vert).

Donc, dans le cas où on aurait deux dipôles de sens opposé en interaction l'un avec l'autre, ce graphique nous permet de faire les prédictions suivantes :

- On peut avoir des valeurs d'énergie de stabilisation jusqu'à 10 kcal/mol.
- On peut avoir une distance interplanaire aussi courte que 3.2 Å.

Ceci aurait alors pour conséquence de pousser les deux aromatiques à se rapprocher l'un de l'autre pour adopter différents arrangements spatiaux pour leur permettre d'orienter leur dipôles de façon à ce qu'ils s'opposent le moins possible contribuant ainsi à stabiliser

le système. Plusieurs arrangements peuvent se produire selon les propriétés électroniques et stériques des deux noyaux et de l'habilité de l'un et l'autre à bouger dans l'espace (figure 2.5).

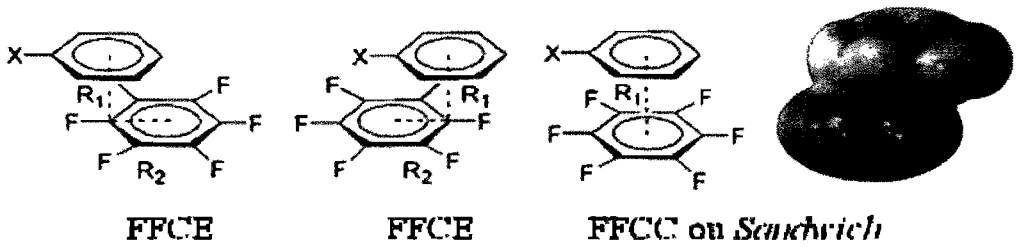


Figure 2.5: Exemples de quelques arrangements spatiaux lors d'interactions quadripolaires (FFCE : face à face centre à coté, le groupement X est vers l'extérieur ; FFCE : face à face centre à coté, le groupement X est vers l'intérieur; FFCC : face à face centre à centre ou *Sandwich*).

Il va sans dire que la valeur de l'énergie de stabilisation va chuter spectaculairement dès que le système va s'écarter de sa distance optimale (car $E(r)$ varie comme un terme en $1/r^{12}$ et $1/r^{6}$).

L'exploitation de ces interactions quadripolaires en solution en catalyse ou en synthèse organique reste assez peu répandue. Toutefois, on trouve dans la littérature un rare exemple dans lequel une réaction de macrocyclisation a été facilitée justement par ces interactions. En effet, Marsella et collaborateurs[6] ont rapporté en 2001 que leurs rendements en cyclophane acétylénique pouvaient être quasiment triplés dans le cas du substrat **139** avec X= H qui peut s'engager, selon les auteurs, dans une interaction quadripolaire intramoléculaire qui favoriserait l'espèce **139-s** et ainsi le couplage au palladium pour former le produit désiré **140** (X= H) à la hauteur des 30% au lieu de 10 % observés dans les cas contraires (figure 2.6).

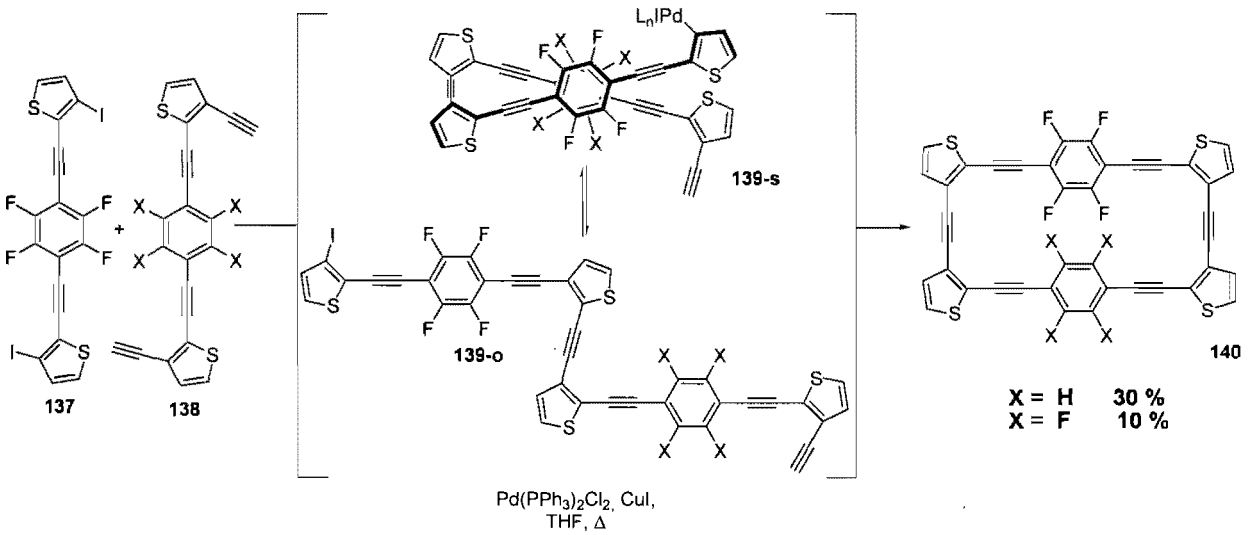


Figure 2.6 : Exemple de l'utilisation des interactions quadripolaires pour des fins de synthèse organique.

[6] Marsella, M. J.; Wang, Z.-Q.; Reid, R. J.; Yoon, K. *Org. Lett.* **2001**, *3*, 885.

Article 1

El-azizi, Y.; Schmitzer, A; Collins*, S.K.

Exploiting Perfluorophenyl-Phenyl Interactions for Achieving Difficult Macrocyclizations using Ring Closing Metathesis

Angew. Chem. Int. Ed., 2006, *45*, 968.

- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées dans cet article ont été faites par l'auteur.
- La majorité des procédures rapportées dans cet article ont été conçues et rédigées par l'auteur.
- Toutes les modélisations moléculaires rapportées dans cet article ont été faites par la Professeure Schmitzer.

Keywords

alkene metathesis • cyclophanes • macrocyclization • perfluoroarenes • quadrupolar interactions

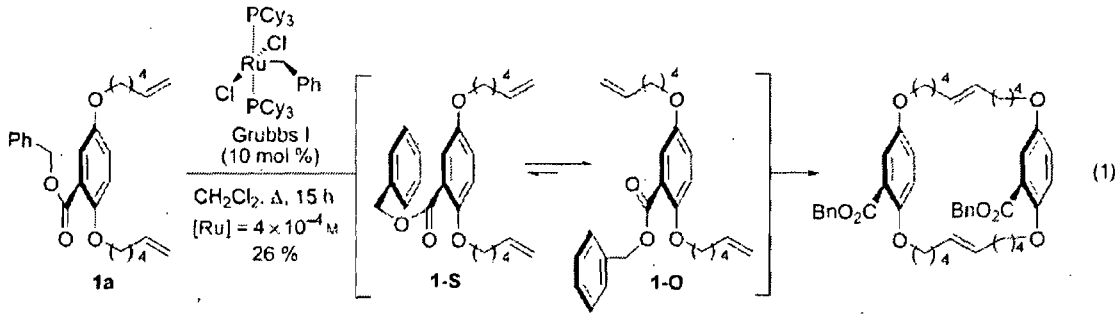
Exploitation of Perfluorophenyl–Phenyl Interactions for Achieving Difficult Macrocyclizations by Using Ring-Closing Metathesis*

Yassir El-azizi, Andreea Schmitzer, and Shawn K. Collins

Macrocycles continue to attract interest in light of their unique properties and abundance in natural products. Over the past decade, ring-closing olefin metathesis (RCM) has not only emerged as a powerful method for macrocyclization[1] but has inspired the development of ring-closing alkyne metathesis (RCAM)[2] and macrocyclic ene-yne metathesis.[3] Despite the convenience of olefin metathesis, numerous examples have been documented in which ring strain and entropic factors have spawned new and imaginative routes to coercing ring closure. Among these, templates, [4] dilution, and gearing elements [5] have been employed in directing macrocyclization processes. Our interest in the synthesis of the quinone natural product longithorone C[6] led us to investigate the preparation of 12-membered macrocyclic paracyclophanes by olefin metathesis. Numerous attempts to cyclize various substituted [12]paracyclophanes using the Grubbs first generation catalyst, such as benzyl ester **1a**, met with failure. Treatment with the Grubbs second generation catalyst also led to similarly low yields of dimeric products [Eq. (1)]. [7] Furthermore, variation in the concentration and the nature of the aromatic substituents consistently led to preferential dimer and/or oligomer formation.

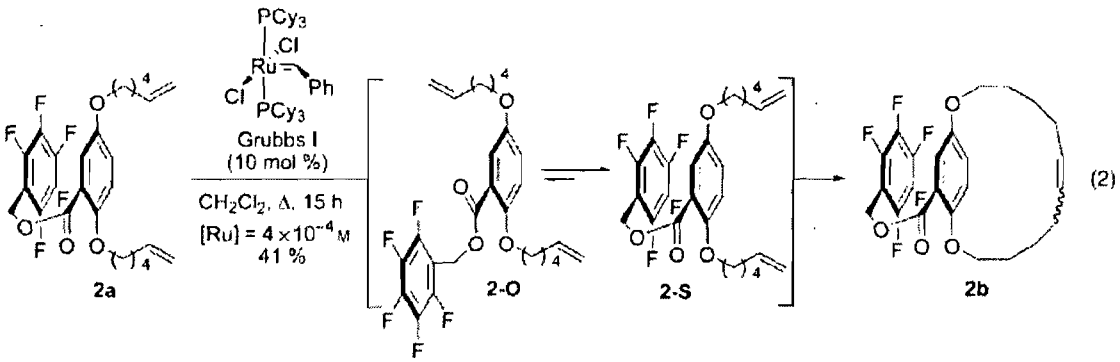
* We are grateful to the National Sciences and Engineering Research Council of Canada (NSERC), Fonds de Québec pour la Recherche en Nature et Technologie (FQRNT), the Canadian Foundation for Innovation, and the Université de Montréal for generous financial support of this research. We thank the laboratories of A. Charette and H. Lebel (University of Montréal) for sharing equipment, chemicals, and fruitful discussions.

Although **1a** likely exists in a variety of conformations in solution, we sought reaction conditions that would favor the conformation **1-S** (S=stacked) with π–π stacking interactions versus the conformation **1-O** (O = open) [Eq. (1)]. The resulting shielding of one face in **1-S** would decrease the degrees of freedom for rotation in the olefin bearing side chains and thus increase the probability of forming the desired macrocycle. Consequently, we envisioned exploiting a perfluorophenyl– phenyl interaction as a novel gearing element to favor the desired intramolecular macrocyclization. These nonbonding interactions are the result of the orthogonal electron densities of aromatic and perfluoro aromatic compounds. [8, 9] As a consequence of their predictable preference for face-to-face stacking with other aromatic compounds in the solid state,[10] these interactions have attracted considerable interest in medicinal chemistry[11] and materials science.[12] Surprisingly, relatively little use of these interactions in catalysis has been demonstrated, despite the tremendous utility of intramolecular π–π interactions in synthetically useful face-selective transformations.[13] A sole example of such quadrupolar interactions in the solution state was previously observed by Marsella *et al.*,[14] which is in contrast to π-cation–arene interactions, whose applicability in the solution state was recently demonstrated by Yamada and Morita for the face-selective addition of nucleophiles to pyridines. [15] Herein, we report the development of a strategy that exploits quadrupolar perfluorophenyl–phenyl interactions, analogous to π-cation–arene interactions, for the construction of macrocycles.



(1)

Based on precedent, [10, 11] fluorinated ester **2a** was expected to prefer the solution-state conformation **2-S** to a much greater degree than **1a** would prefer conformation **1-S** [Eq. (2)]. Consequently, fluorinated ester **2a** was treated with the Grubbs first generation catalyst, and a dramatic change in product selectivity resulted, thus solely affording the cyclised cyclophane **2b** in 41% yield.[16]



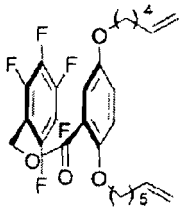
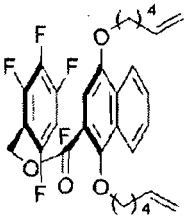
(2)

Higher yields of paracyclophane **2b** were observed using the Grubbs I versus Grubbs II catalyst; the second generation catalyst was shown to affect ring opening of **2b**, and the formation of oligomers was observed. Solvent studies revealed that the quadrupolar-interaction gearing element was effective in selectively forming the desired cyclophane in a variety of solvents. However, the rate of metathesis is significantly decreased relative to

reaction in CH_2Cl_2. [17] Ring-closing metathesis in THF afforded negligible product after 48 h despite the addition of two additional aliquots of catalyst (5 mol%). Similar reaction times and catalyst loading were necessary for macrocyclization with hexanes as the solvent at 40°C (20% yield of **2b**, 58% conversion). Interestingly, reaction in benzene at 40°C gave **2b** in 29% yield (57% conversion), and no dimer products were observed, thus suggesting that the excess benzene does not interfere with the intramolecular perfluorophenyl– phenyl interaction.

A variety of structures were cyclized by using this protocol (Table 1). [18] The site of metathesis had little effect on the yields of macrocyclization for [12]paracyclophanes. Diene **4** gave a slightly higher yield of the corresponding monomeric cyclophane (**5**: 48%) than diene **1a** (**2**: 41%; Table 1, entries 1 and 2, respectively).

Table 1: Macrocyclizations by olefin metathesis exploiting perfluorophenyl–phenyl interactions.[a]

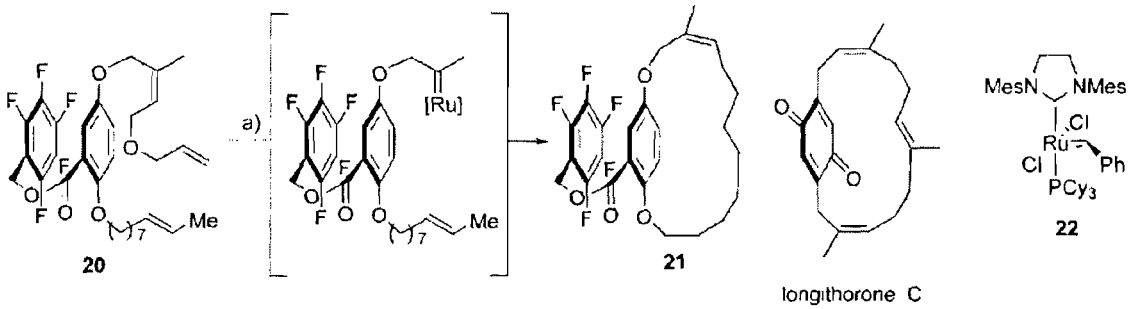
Entry	Metathesis precursor	Cyclophane	Yield [%]
1	**1a**	$n=4$, $m=4$, $R^1=H$	**2** 41
2	**4**	$n=3$, $m=5$, $R^1=H$	**5** 48
3	**6**	$n=4$, $m=4$, $R^1=CH_2OH$	**7** 41
4	**8**	$n=4$, $m=4$, $R^1=CO_2CH_2C_6F_5$	**9** 39
5	**10**		**11** 57
6	**12**	$n=5$, $m=5$	**13** 63
7	**14**	$n=8$, $m=2$	**15** 36
8	**16**		**17** 42
9	**18**	$n=8$, $R^1=H$	**19** 10

[a] Substrate was added dropwise over 2 h to a solution of Grubbs I catalyst (10 mol%) in CH_2Cl_2 at reflux for 15 h ($[Ru]=4\times10^{-4}$ M).

Further substitution of the aromatic nucleus had little impact on the yields of the cyclizations. The cyclization was found to be tolerant of a free hydroxy group (entry 3) and the addition of an additional electron-withdrawing ester substituent (entry 4). The addition of a second pentafluorobenzyl ester group had no effect on the yield of the macrocyclization, whereas the corresponding dibenzyl ester provided the dimer in only 39% yield. Larger ring sizes that produced solely dimeric products upon treatment with the olefin-metathesis catalyst gave good yields for the macrocyclic products following attachment of the pendant pentafluorobenzyl moiety. The [13]paracyclophane **11** was produced in 57% yield, whereas substitution of the pentafluorobenzyl ester for a methyl ester produced only dimeric products under identical conditions (entry 5). Although the corresponding benzyl ester of diene **12** yields the monomeric [14]paracyclophane in 51% yield, substitution for a pentafluorobenzyl ester provided an increased yield of 63% (entry 6). When the site of metathesis was moved closer to the aromatic core, the yield of macrocyclization decreased to provide **15** in 36% yield (entry 7). Interestingly, diene **16**, which possesses an additional arene moiety fused to the aromatic group, also gave the corresponding naphthylenophane **17** in 42% yield (entry 8). Examination of the ^{1}H NMR spectrum of **17** revealed diastereotopic signals for the protons of the methylene groups adjacent to the naphthenolic oxygen atoms and the ester oxygen atom, thus indicating an element of planar chirality. The trisubstituted olefins found in the cyclophane natural product longithorone C (Scheme 1) prompted us to explore their formation by using the penta- fluorophenyl–phenyl interactions to influence macrocyclization. Standard conditions all favored the formation of dimeric or oligomeric products.[19] As we were enticed by the possibility of a relay ring-closing metathesis protocol[20] in tandem with

the gearing effect of the pentafluorophenyl– phenyl interaction, diene **18** was prepared and subjected to ring closure. Unfortunately, a very low yield of cyclized product **19** was observed and a linear dimer was isolated as the major product (entry 9). [21]

Subsequently, diene **20** was synthesized to preferentially favor initial metathesis of the relay segment versus intermolecular dimerization (Scheme 1).

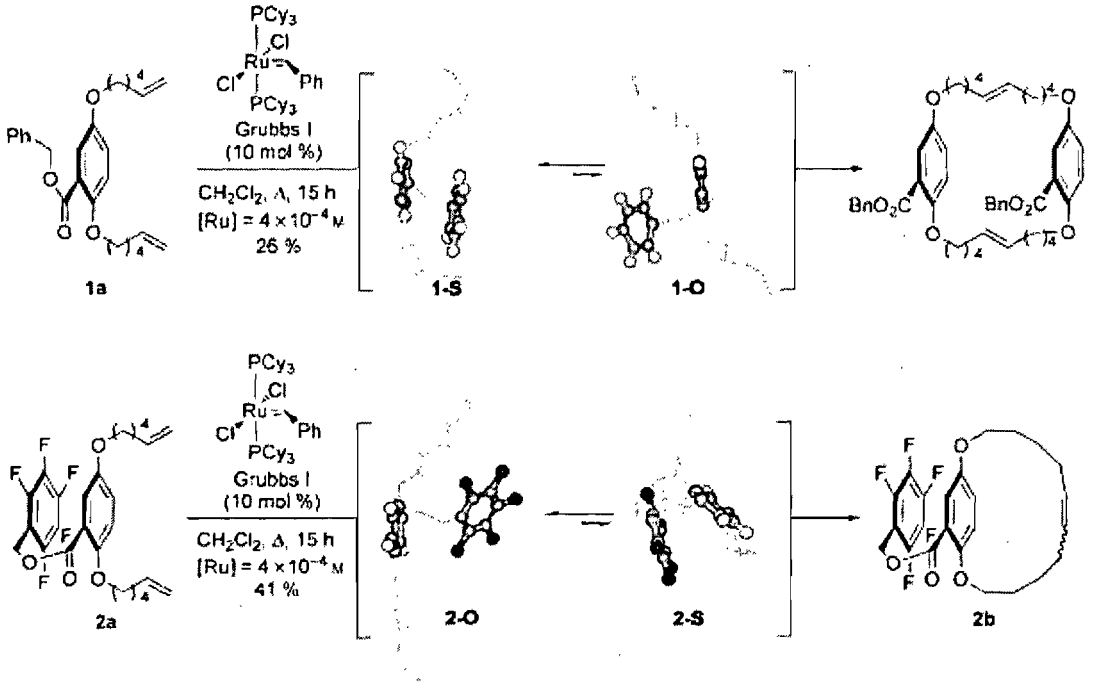


Scheme 1. Macrocyclic olefin metathesis exploiting perfluorophenyl–phenyl interactions and relay ring-closing metathesis to form tertiary olefins. Reagents and conditions: a) **22** (10 mol%), CH_2Cl_2, Δ, 15 h, (68% yield based on recovered starting material). Mes = mesityl, Cy = cyclohexyl.

Although the addition of a Me group to the terminal olefin may result in a slower rate of macrocyclization, the nonproductive intermolecular processes are slowed to a much greater extent and cyclophane **21** was isolated in 68% yield. Cyclophane **21** was isolated as a single isomer with the tertiary olefin in the *Z* configuration.

Furthermore, the methylene groups adjacent to the phenolic oxygen atoms and the ester oxygen atom all displayed diastereotopic signals in the ^1H NMR spectrum, thus revealing a possible element of planar chirality. Preliminary experiments (heating in C_6D_6) have revealed that cyclophane **21** is configurationally stable at 50°C in [D_6]benzene. The exact nature of the observed gearing effect in solution is still debatable,[22] despite the well-documented preference of perfluoroarenes and phenyl groups for face to- face stacking.

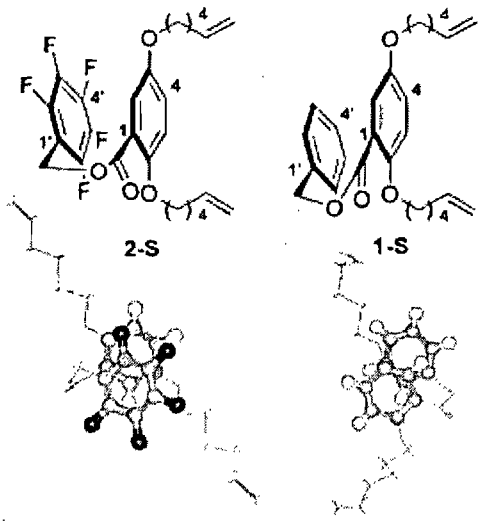
To probe the mechanism of the gearing effect further, molecular modeling studies were performed to explore whether a face–face or "slipped"[8] arrangement of both arenes were possible in the solution-state conformations. Accurate *ab initio* studies of aromatic clusters must include electron correlation to obtain good representations of dispersion and electrostatic forces that are responsible for conformation stability. High-level treatment of electron correlation or the use of large basis sets was precluded because of the large size of the molecules in question. The initial geometric optimizations for benzyl ester **1a** was performed by using semiempirical methods (AM1) [23] and afforded conformers **1-S** and **1-O** (Scheme 2). Conformer **1-O** displayed the "open" conformation, in which the benzyl ester is elongated away from the aromatic core of **1a**. A conformation was observed that resembles **1-S**, in which the arene unit of the benzyl ester moiety is orientated underneath the aromatic core in a slipped-type arrangement.



Scheme 2. Modeling studies of possible conformations that lead to productive metathesis.

The Moller–Plesset (MP2) [24] perturbation theory with a 6-31G* basis set was then used to provide more accurate energies for each conformer. Conformer **1-S** is estimated to be more stable than **1-O** by approximately -3.9 kcal mol^{-1} based on the difference of their relative heats of formation. Conformational analysis of the perfluorinated ester **2a** by using semiempirical methods (AM1) also revealed an opentype conformer **2-O**, in which the pentafluoroarene is elongated and oriented away from the aromatic core (Scheme 2). The minimum energy conformer was identified as **2-S**, in which the π-π overlap is predicted to a much greater extent than that observed for benzyl-substituted **1-S** (Scheme 3). Conformers **2- O** and **2-S** were further refined (MP2), and conformer **2-S** is estimated to be more stable than **2-O** by approximately -24.0 kcal mol^{-1}.

These calculations highlight the fact that both stacked conformers **2-S** and **1-S** are preferred relative to their respective open conformers **2-O** and **1-O**. Conformer **2-S** is preferred to **2-O** to a much greater extent than the benzyl analogues (**1-S–1-O** -4 kcal mol^{-1} vs. **2-S–2-O** -24 kcal mol^{-1}). Importantly, the nature of the π stacking in **2-S** differs considerably from **1-S** (Scheme 3). The arene units are offset in **1-S**, and minimal overlap is observed. In contrast, conformer **2-S** exhibits a face-to-face type interaction with considerable overlap of the aromatic core and pentafluoroarene. For example, the distance between C1 and C1' in conformers **1-S** and **2-S** are almost identical (3.27 and 3.22 Å, respectively). However, C4' is much closer to C4 in **2-S** than **1-S** (4.08 and 5.61 Å, respectively). It is possible that the energetic preference for conformer **2-S** in conjunction with its superior π overlap is what leads to the inclination towards macrocyclization.



Scheme 3. π–π Overlap in benzyl and pentafluorobenzyl conformers **1-S** and **2-S** respectively.

It is important not to infer that the difference in energy between conformers is due solely to the aromatic interactions. There is no quantitative comparison of the molecular-strain energy with the relative energy gained through the perfluorophenyl– phenyl interactions. Although the strain energy can be estimated by using empirical potential functions, [25] the evaluation of strain energy by semiempirical or *ab initio* calculations is tenuous. In comparing the relative differences in the MP2-optimized energies of the various conformers, the strain energy is dominant in all cases, thus the energy difference includes not only the aromatic–aromatic interactions but also a preferred conformation for the alkyl chains.

In summary, we have developed a novel gearing element to affect difficult macrocyclizations by using ring-closing olefin metathesis. Data obtained from molecular-modeling studies suggest a possible quadrupolar interaction between the pentafluorobenzyl appendage and the cyclophane core which orients the substrate in a conformation that favors macrocyclization. We have also developed a protocol for the preparation of stereodefined tertiary olefins in conjunction with a relay ring-closing-metathesis strategy. The presence of the tertiary olefin produces a configurationally stable cyclophane in select cases, thus inhibiting rotation of the macrocycle at temperatures that exceed 50°C. Currently, we are optimizing conditions for ring-closing ene-yne and alkyne metathesis and pursuing a total synthesis of longithorone C by using the methods described herein. Although π-cation–arene interactions continue to be exploited in organic synthesis, pentafluorophenyl–phenyl interactions represent a novel and complimentary π-shielding element. Considering that intramolecular π-π interactions can

be powerful conformation controlling elements in various face-selective addition/cycloaddition reactions, [13] the development of chiral auxiliaries based upon solution-phase quadrupolar interactions have significant potential for a variety of chemical reactions.

Experimental Section

General procedure: A solution of **20** (25 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise over approximately 2 h to an anhydrous solution of Grubbs II catalyst (3.5 mg, 0.004 mmol) in CH_2Cl_2 (60 mL) at reflux. The solution was cooled to room temperature after 13 h at reflux. Silica gel was added, and the reaction mixture was concentrated and purified by chromatography on silica gel (hexanes/EtOAc=7:1) to afford 16 mg of **21** (68 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35 (d, *J*=2.7 Hz, 1 H), 7.06 (dd, *J*=9.0, 3.2 Hz, 1 H), 6.92 (d, *J*=9.0 Hz, 1 H), 5.43 (dd, *J*=22.9, 8.6 Hz, 2 H), 5.07 (m, 1 H), 4.56 (d, *J*=11.4 Hz, 1 H), 4.47 (d, *J*=11.4 Hz, 2 H), 4.02 (m, 1 H), 3.95 (m, 1 H), 1.97 (m, 2 H), 1.64 (m, 2 H), 1.57 (s, 3 H), 1.40-1.13 ppm (m, 10 H); ^{13}C NMR (75 MHz, C_6D_6): δ=165.3, 152.6, 151.4, 133.5, 130.2, 124.0, 122.9, 122.5, 120.0, 78.8, 67.6, 53.4, 30.0, 29.4, 27.6, 27.4, 27.3, 25.9, 24.0, 14.0 ppm; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}O_4F_5$ ($[M+H]^+$): 485.1746; found: 485.1734 .

20 (clear oil): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.33 (d, *J*=3.6 Hz, 1 H), 7.04 (dd, *J*=9.1, 3.6 Hz, 1 H), 6.89 (d, *J*=9.1 Hz, 1 H), 5.94 (m, 1 H), 5.75 (m, 1 H), 5.44 (m, 2 H), 5.42 (s, 2 H), 5.31 (ddd, *J*=18.0, 3.2, 0.2 Hz, 1 H), 5.21 (m, 1 H), 4.40 (s, 2 H), 4.09 (d, *J*=6.6 Hz, 2 H), 4.00-3.93 (m, 4 H), 2.78-2.60 (m, 2 H), 2.11 (m, 2 H), 1.77 (s, 3 H), 1.74 (m,

2 H), 1.63 (d, *J*=6.45 Hz, 3 H) 1.34 ppm (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.9, 153.8, 152.4, 135.2, 135.1, 131.2, 125.0, 124.1, 121.4, 120.0, 117.8, 117.6, 115.4, 74.1, 71.7, 70.1, 66.6, 54.0, 29.9, 29.7, 29.62, 29.61, 27.2, 26.3, 14.5, 13.2 ppm; HRMS (ESI): *m/z* calcd for $C_{32}H_{38}O_5F_5$ ($[M+H]^+$): 597.2643; found: 597.2634.

References

[1] a)R. H. Grubbs, *Tetrahedron* 2004, **60**, 7117-7140. b) C. W. Lee, R. H. Grubbs, *J. Org. Chem.* 2001, **66**, 7155-7158.

[2] U. H. F. Bunz, L. Kloppenburg, *Angew. Chem.* 1999, **111**, 503-505; *Angew. Chem. Int. Ed.* 1999, **38**, 478-481.

[3] a) E. C. Hansen, D. Lee, *J. Am. Chem. Soc.* 2004, **126**, 15074-15080. b) E. C Hansen, D. Lee, *J. Am. Chem. Soc.* 2004, **126**, 15074-15080.

[4] a) A. V. Chuchuryukin, H. P. Dijkstra, B. M. J. Suijkerbuijk, R. J. M. Klein Gebbink, G. P. M. van Klink, A. M. Mills, A. L. Spek, G. van Koten, *Angew. Chem.* 2003, **115**, 238-240; *Angew. Chem. Int. Ed.* 2003, **42**, 228-230. b) A. F. M. Kilbinger, S. J. Cantrill, A. W. Waltman, M. W. Day, R. H. Grubbs, *Angew. Chem.* 2003, **115**, 3403-3407; *Angew. Chem. Int. Ed.* 2003, **42**, 3281-3285.

[5] a) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* 2002, **124**, 773-775. b) A. G. J. Commeureuc, J. A. Murphy, M. L. Dewis, *Org. Lett.* 2003, **5**, 2785-2788.

[6] a) X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm, *J. Org. Chem.* 1997, **62**, 3810-3819. b) For a synthesis of the closely related longithorone B, see: T. Kato, K. Nagae, M. Hoshikawa, *Tetrahedron Lett.* 1999, **40**, 1941-1944.

[7] Interestingly, cyclophanes bearing unsubstituted aromatic compounds can be cyclized: J. Tae, Y.-K. Yang, *Org. Lett.* 2003, **5**, 741-744.

[8] M. R. Battaglia, A. D. Buckingham, J. H. Williams, *Chem. Phys. Lett.* 1981, **78**, 421-423.

[9] Although the exact nature of the perfluoroarene-arene interaction in the C_6H_6-C_6F_6 complex remains a controversial subject, this face-to-face stacking arrangement likely acts to minimize quadrupole-quadrupole interaction energies. The hypothesis of a charge-transfer (CT) interaction was discarded based on the absence of a characteristic CT band in the UV/Vis absorption spectrum; see T. G. Beaumont, K. M. C. Davis, *J. Chem. Soc. B* 1967, 1131-1134.

[10] a) J. S. W. Overell, G. S. Pawley, *Acta Crystallograph. B* 1982, **38**, 1966-1972. b) J. H. Williams, J. K. Cockcroft, A. N. Fitch, *Angew. Chem.* 1992, **104**, 1666-1667; *Angew. Chem. Int. Ed. Engl.* 1992, **31**, 1655-1657.

[11] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* 2003, **115**, 1244-1287; *Angew. Chem. Int. Ed.* 2003, **42**, 1210-1250.

[12] a) K. Reichenbaecher, H. I. Suess, J. Hulliger, *Chem. Soc. Rev.* 2005, **34**, 22-30. b) Grubbs and co-workers have formed polymers by using olefin metathesis that incorporates pentafluorophenyl moieties: M. Weck, A. R. Dunn, K. Matsumoto, G. W. Coates, E. B. Lobkovsky, R. H. Grubbs, *Angew. Chem.* 1999, **111**, 2909-2912; *Angew. Chem. Int. Ed.* 1999, **38**, 2741-2745. c) F. Ponzini, R. Zagha, K. Hardcastle, J. S. Siegel, *Angew. Chem.* 2000, **112**, 2413-2415; *Angew. Chem. Int. Ed.* 2000, **39**, 2323-2325.

[13] a) G. B. Jones, *Tetrahedron* 2001, **57**, 7999-8016. b) G. B. Jones, B. J. Chapman, *Synthesis* 1995, 475-497.

[14] M. J. Marsella, Z.-Q. Wang, R. J. Reid, K. Yoon, *Org. Lett.* 2001, **3**, 885-887.

[15] Y. S. Yamada, C. Morita, *J. Am. Chem. Soc.* 2002, **124**, 8184-8185.

[16] In general, the corresponding acids are pentafluorobenzylated by the Mistunobu reaction with pentafluorobenzyl alcohol or alkylated selectively using CsF on celite: a) S. Hayat, R. Atta, M. Iqbal-Choudhary, K. M. Khan, W. Schumann, E. Bayer, *Tetrahedron* 2001, **57**, 9951-9957. b) J. C. Lee, Y. Choi, *Synth. Commun.* 1998, **28**, 2021-2026; the alkyl chains were subsequently installed by sequential Mitsunobu alkylations.

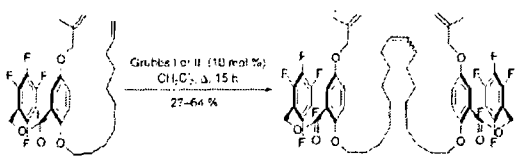
[17] M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* 2001, **123**, 6543-6554.

[18] The ^{1}H NMR signals for the alkene protons overlap and appear in the form of a complex multiplet for all compounds in Table 1; hence, the calculation of *E*/*Z* ratios was not possible.

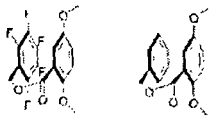
[19] For a solution that exploits catalyst reactivity, see: A. Fürstner, O. R. Thiel, L. Ackermann, *Org. Lett.* 2001, **3**, 449-451.

[20] T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc.* 2004, **126**, 10210-10211.

[21] The linear dimer below was commonly isolated in yields of up to 64 %.



[22] Attempted X-ray analysis of simple models shown below have failed as both are isolated as oils at room temperature; low-temperature crystallization techniques were not successful.



[23] Calculations performed using Hyperchem v.7.5; M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* 1985, **107**, 3902-3909.

[24] C. Moeller, M. S. Plesset, *Phys. Rev.* 1934, **46**, 618-622.

[25] N. L. Allinger, *J. Am. Chem. Soc.* 1977, **99**, 8127-8134.

Chapitre 3 : Choix du site idéal pour la RRCM

1. Détermination du site idéal pour la macrocyclisation par RCM des oléfines pour accéder au pont *ansa* de la longithorone C

Nous avons vu dans le chapitre précédent comment il nous a été possible, en exploitant la stratégie RRCM,[1] de former un [12]paracyclophane rigide comportant une double liaison trisubstituée dont la stéréochimie est identique à celle trouvée sur le pont *ansa* de la longithorone C (Schéma 3.1).

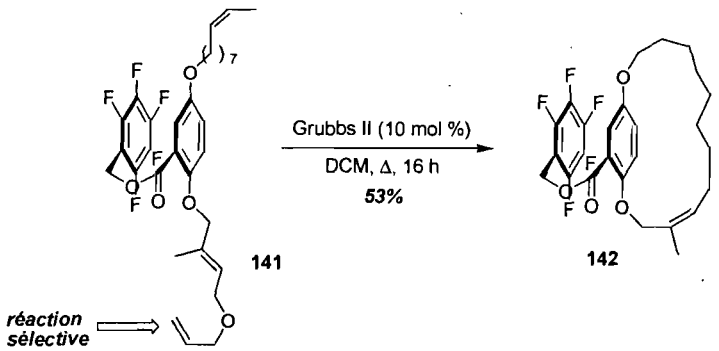


Schéma 3.1 : Étude modèle utilisant la stratégie RRCM.

Dans ce qui suit, il était question de voir si le positionnement de la coupure dans l'analyse rétrosynthétique (Figure 1.12) allait avoir une influence sur le rendement de la réaction.

[1] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

Aussi, nous avons trouvé intéressant de voir si d'autres aromatiques déficients en électrons pouvaient jouer le même rôle que le pentafluorophényle dans l'établissement d'interactions quadripolaires.

Finalement, on a investigué la possibilité pour nos substrats d'avoir une coordination intramoléculaire avec le centre métallique du catalyseur de métathèse tel que déjà observé dans la littérature[2] et tel que déjà discuté dans le chapitre 1 (Schéma 1.2).

[2] Langemann, K.; Fürstner, A. *J. Org. Chem.* **1996**, *61*, 3942.

2. Article 2

Collins*, S. K.; El-Azizi, Y.

Development of Quadrupolar Engaging Auxiliaries for Macrocyclization

Pure App. Chem. 2006, *78*, 783.

- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées des cet article ont été faites par l'auteur.
- La majorité des procédures rapportées dans cet article ont été conçues et rédigées par l'auteur.

Keywords: cyclophanes; fluoroarenes; macrocyclization; olefin metathesis; quadrupolar.

Development of quadrupolar engaging auxiliaries as novel gearing elements for macrocyclization

Shawn K. Collins and Yassir El-Azizi

Département de Chimie, Université de Montréal, Montréal H3C 3J7, Canada

Abstract: The formation of various macrocyclic cyclophanes via ring-closing olefin metathesis is possible through the use of a pendant pentafluorobenzyl ester group. A quadrupolar interaction between the cyclophane core and the auxiliary is proposed to act as a gearing element facilitating cyclization. The development of these noncovalent interactions as gearing elements as well as the investigation of the effect of the site of metathesis upon the macrocyclization process is described.

Noncovalent interactions play an integral role in many areas of chemistry, biology, and materials science. These forces are responsible for formation of the DNA double helix and the tertiary structure of proteins. Experimental and theoretical evidence implyes that these types of interactions are largely driven by electrostatic and dispersion forces, however, the interplay between the quadrupole moments arising from aromatic π-clouds is also significant. The magnitude and nature of the aromatic interaction can be altered by introduction of aromatic ring substituents that affect the quadrupole moment. A particularly striking example is the substitution of all six protons of benzene by six electronegative fluorine atoms. This results in a dramatic shift in the quadrupole moment of benzene ($Q_{C6H6} = -29.0 \times 10^{-40}$ Cm^{-2}); hexafluorobenzene possesses a quadrupole moment which is similar in magnitude but of opposite sign ($Q_{C6F6} = 31.7 \times 10^{-40}$ Cm^{-2}).[1,2] This interaction results in a crystalline complex exhibiting nearly parallel molecules, stacked alternately in infinite columns.[3] The strength of interaction in this complex has been estimated to be ~4–5 kcal mol^{-1} by *ab initio* and density functional theory (DFT) methods;[3] on the order of a moderate hydrogen-bonding interaction. Although the exact nature of the arene:perfluoroarene interaction in the C_6H_6:C_6F_6 complex remains a controversial subject,[2] the phenyl–perfluorophenyl interaction is considered general and predictable and has been exploited in a variety of applications. Perfluoroarene:arene co-crystals have been actively studied,[4] and the predictability of the packing conformations can be used to construct electro-luminescent materials for light-emitting diodes (LEDs) [5] and to stabilize liquid-crystal phases.[6] The increased hydrophobicity of perfluorinated hydrocarbons has been exploited by Kool and coworkers to investigate alternate modes of DNA base-pairing.[7] It is surprising that this

interaction has seen limited use in synthesis and catalysis, particularly since intramolecular π–π interactions such as π-cation–arene interactions,[8] are synthetically useful for face-selective transformations.[9] A sole example of such quadrupolar interactions in the *solution* state has been previously observed by Marsella *et al.*[10] The Pd-catalyzed macrocyclization of acetylenic cyclophanes gave higher yields when one arene was substituted with four fluorine atoms. It was postulated that this led to a preorganization of the linear intermediate via perfluoroarene:arene interactions, thus aiding macrocyclization. Although entropic factors are likely responsible for the inefficient ring-closing described by Marsella *et al.*, ring strain is also a recurring roadblock to efficient macrocyclization. Typically, chemists resort to templation, when possible, [11] and use high dilution conditions to favor ring-closing. Recently, the addition of gearing elements to substrates has proved an effective route to aiding macrocyclization en route to various natural products. [12] In a strict sense, the term "geared molecule" makes reference to molecules where a level of strain is present due to unavoidable steric crowding, the result of which is a rigidified structure typically incorporating bonds exhibiting restricted rotation. However, the terms "gearing effect" or "gearing element" have become increasingly used to describe functional groups that influence certain molecular conformations, regardless of the level of rigidity. The most popular of which involves a gearing element taking the form of a substituted methylene adjacent to an aromatic ring. The minimization of resulting $A_{1,3}$ strain is responsible for orienting the reactive centers in a conformation conducive to ring-closing. Consequently, we developed a new gearing element based upon perfluoroarene:arene interactions for the synthesis of [12]paracyclophanes (Fig. 1). [13]

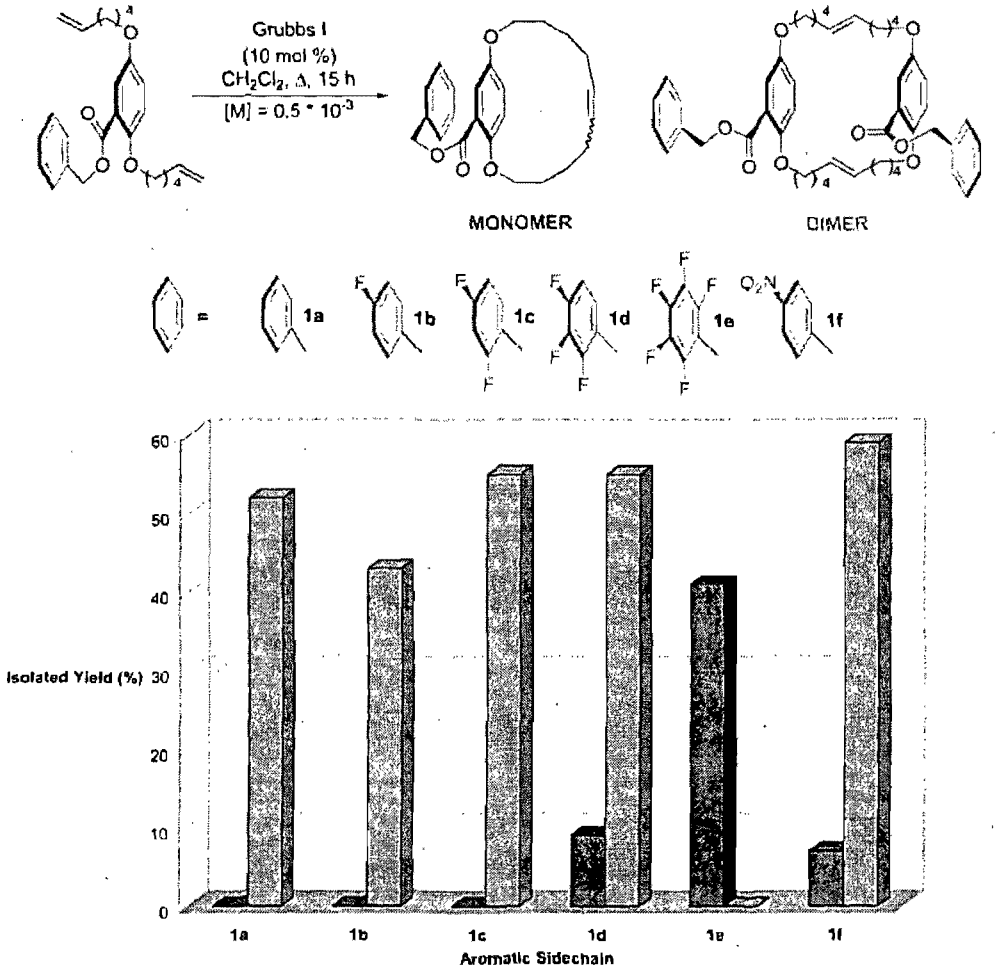


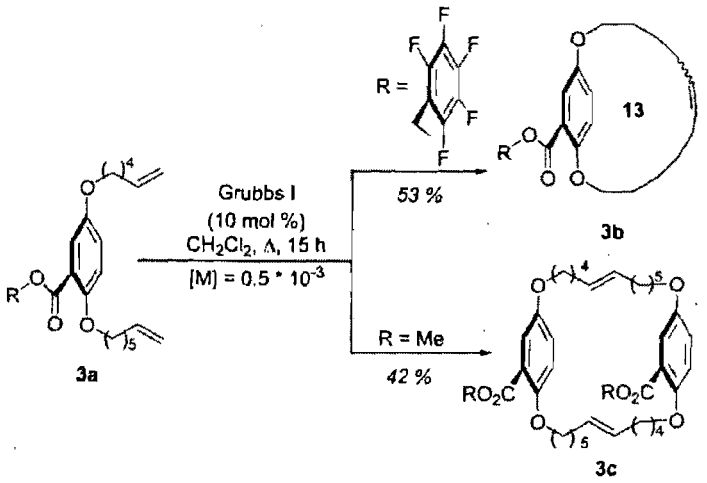
Fig. 1 Optimization of the gearing effect of pendant benzyl esters.

We have studied the mechanism of the gearing effect via molecular modeling using both AM1 and MP2 levels of theory, suggesting the gearing effect is a result of an energetically more stable π–π stacking conformer in the case of the pentafluoro substrate **1e** in comparison to the benzyl ester **1a**. In addition, the pentafluoro **1e** conformer exhibits a significantly greater degree of overlap with the aromatic core and aids in gearing the alkenyl side chains for productive metathesis. Herein, we describe our investigation of other electron-poor aromatics as gearing elements, expand the scope of

reaction to larger macrocycles, and investigate a peculiar dependence of the product yield on the site of metathesis along the *ansa*-bridge. As a model, macrocyclization via ring-closing olefin metathesis [14] to form rigid, substituted [12]paracyclophanes that resemble the carbon skeleton of the natural product Longithorone C [15] was investigated. Various methylester-substituted cyclophane precursors were synthesized and subjected to Grubbs' 1st generation catalyst, each resulting solely in the formation of a dimeric product. Treatment with Grubbs' 2nd generation catalyst also led to a similar low yield of dimeric products. [16] Varying the concentration and the nature of additional aromatic substituents did not lead to the formation of monomeric products. Subsequently, the optimization of π–π stacking interactions and their ability to induce a gearing effect was investigated. Previous tuning of electronic properties of the pendant benzyl ester, in the form of a pentafluorobenzyl ester, resulted in a π–π stacking interaction that gears the alkene-bearing side chains closer to one another for reaction. [13] However, it was unclear as to how many fluorine atoms were necessary to induce the gearing effect and whether other electron-withdrawing substituents could act in a similar manner. As a control, benzyl ester **1a** was treated with Grubbs' 1st generation catalyst and yielded a 51 % yield of the corresponding dimer. To increase the probability of π–π stacking, the quadrupole moment of pendant benzyl ester was altered via the addition of one or two fluorine atoms in the *para*- or *ortho*-positions. However, the inclusion of the fluorine atoms in precursors **1b** and **1c** had little impact on the product outcome and the dimeric products were again isolated in 43 and 55 % yield, respectively, in both cases. Upon installation of a 2,3,4-trifluorobenzyl ester **1d**, small quantities of the desired monomeric cyclophane were observed (9 % yield), however, the undesired dimer was still the major product

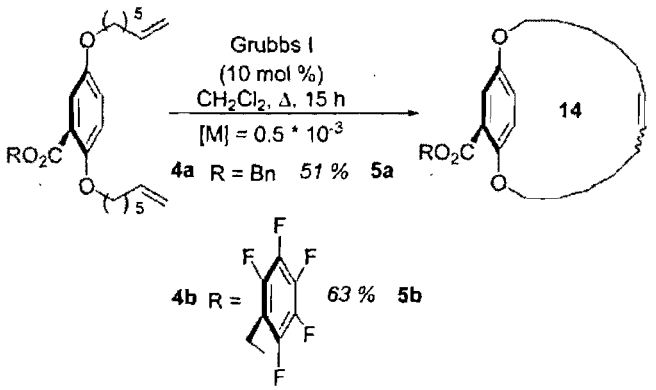
following chromatography (55 % yield). The pentafluorobenzyl ester **1e** remained the optimum auxiliary, as subjection to ring-closing conditions using Grubbs' 1st generation catalyst provided a 41 % yield of *only* the desired macrocycle following chromatography. The small size and significant electronegativity of fluorine make it an ideal substituent to modify the electronic properties of an aromatic ring. However, we also explored the usage of nitro groups to induce a dipole between the aromatic moieties. The mono-nitro benzyl ester **1f** produced a gearing effect similar to what was observed for the trifluoro-derivative **1d**. The desired cyclophane was isolated in only 7 % yield, and the dimeric product was isolated in 59 % yield.

We have expanded the reaction scope beyond the [12]paracyclophane skeleton to include both [13]- and [14]paracyclophanes. Larger ring sizes that produced solely dimeric products upon treatment with Grubbs' 1st generation catalyst gave good yields of macrocyclic products following attachment of the pendant pentafluorobenzyl moiety (Scheme 1).



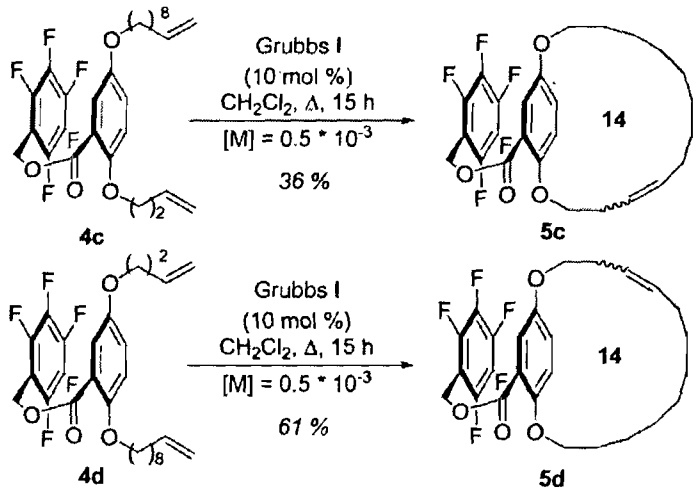
Scheme 1

The [13]paracyclophane **3b** was produced in 57 % yield, while its corresponding methyl ester produced only dimeric products under identical conditions. Although the corresponding benzyl ester **4a** yields the monomeric [14]paracyclophane in 51 % yield, substitution for a pentafluorobenzyl ester provided an increased yield of 63 % (Scheme 2).



Scheme 2

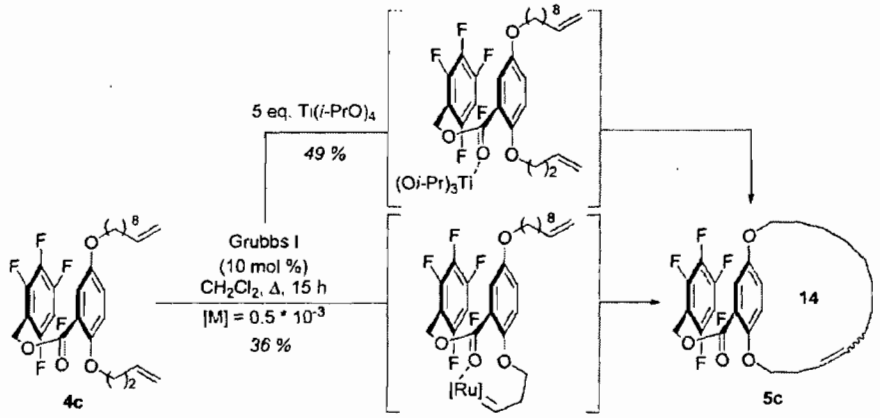
When the site of metathesis was moved closer to the aromatic core, the yield of macrocyclization decreased providing **5c** in 36 % yield (Scheme 3). However, it is also noteworthy that the site of metathesis has moved closer to the ester functionality as well. Interactions between the carbonyl of an ester group and olefin metathesis catalysts are well documented. [17] Subsequently, we performed the ring-closing closer to the aromatic core but away from the ester group. When diene **4d** was subjected o the identical reaction conditions, the macrocycle **5d** was isolated in 61 % yield. This suggests that the interaction between the catalyst and the carbonyl of the ester functionality may be inhibiting cyclization.



Scheme 3

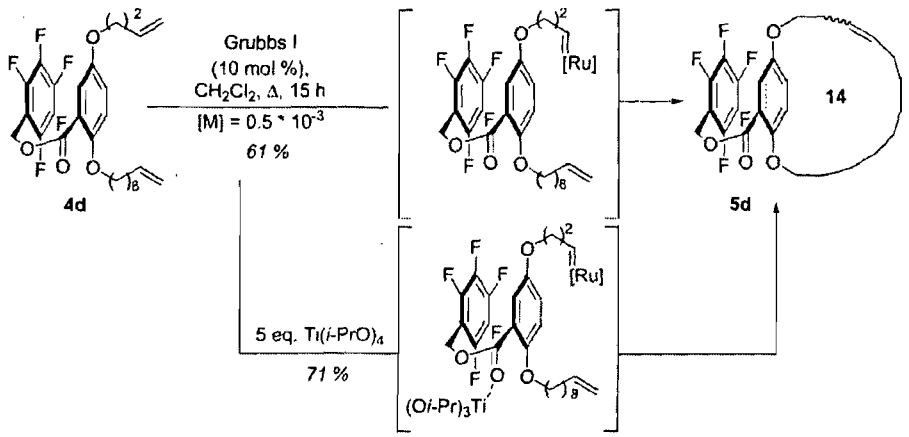
Bunz and coworkers [18] have reported that the addition of a Lewis acid such as Ti(O*i*-Pr)$_4$ to a reaction mixture prior to metathesis can prevent catalyst coordination to the ester group. Based on available precedent, the pentafluoro ester **4c** was resubjected to the ring-closing metathesis protocol as a pretreated solution with 5 equiv of Ti(O*i*-Pr)$_4$ (Scheme

4). It was believed that the coordination of the ester with the Lewis acid would result in an increase in the product yield, similar to what was obtained in the macrocyclization of substrates **4b** and **4d**. Following purification, the [14]paracyclophane **5c** was isolated in 49 % yield (compared to 36 % yield without added Lewis acid). This suggests that the coordination of the carbonyl by the catalyst may indeed be hampering the cyclization.



Scheme 4

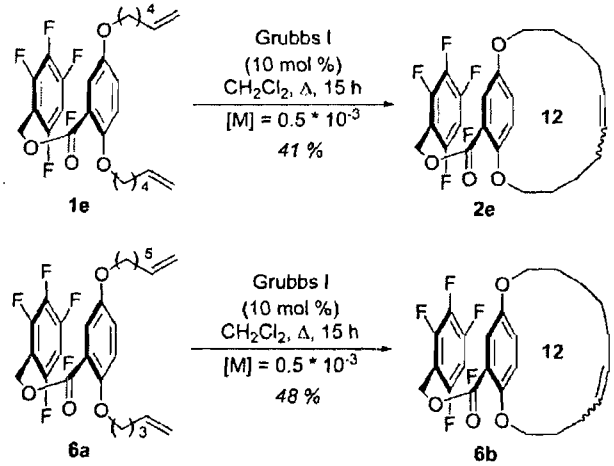
To confirm this hypothesis, diene **4d** was also resubjected to reaction conditions as a solution in the presence of 5 equiv of Ti(O*i*-Pr)$_4$ (Scheme 5). Once again, the macrocyclization pathway was favoured and an increase in the isolated yield was observed (71 % yield with added Lewis acid, Scheme 5). [19]



Scheme 5

Although it is reasonable to assume that some interaction with the carbonyl functionality may be occurring, its effect on the metathesis may still be unclear. Surprisingly, the trend is reversed with respect to [12]paracyclophanes (Scheme 6). Preliminary results show that moving the site of metathesis one methylene closer to both the aromatic ring and ester functionality results in a *slight increase* in the product yield. Further study, including trials with added Ti(*i*-PrO)$_4$, are warranted before any final conclusions can be drawn. In summary, we have developed a novel gearing element to affect difficult macrocyclizations using ring-closing olefin metathesis. Data obtained suggests that a pentafluorobenzyl auxiliary is necessary to establish efficient π–π stacking in solution and induce a favorable conformation for macrocyclization. In addition, we have established that the gearing element functions for larger ring systems and identified the importance of the site of metathesis with respect to product yield. This effect is still under study, but suggests some interaction with the ester functionality and catalyst may be responsible and that the coordination between catalyst and substrate may be controlled with a Lewis acid as an additive. To date, conditions continue to be optimized for

application towards ring-closing ene-yne and alkyne metathesis. Pentafluorophenyl–phenyl interactions represent a novel and complimentary π-shielding element to π-cation–arene interactions. Although we have demonstrated the use of pentafluorophenyl– phenyl interactions in macrocyclization, there are numerous instances of π–π interactions acting as powerful conformation controlling elements in organic synthesis. Therefore, these interactions have considerable potential and applications in various face-selective addition/cycloaddition reactions,[9] and in the development of novel chiral auxiliaries based upon solution-phase quadrupolar interactions.



Scheme 6

ACKNOWLEDGMENTS

This work was supported by the National Sciences and Engineering Research Council of Canada (NSERC), Fonds de Québec pour la Recherche en Nature et Technologie (FQRNT), the Canadian Foundation for Innovation, and the Université de Montréal. We

thank the laboratories of A. Charette and H. Lebel (University of Montréal) for the sharing of equipment, chemicals, and fruitful discussions.

References and notes

[1] M. R. Battaglia, A. D. Buckingham, J. H. Williams. *Chem. Phys. Lett.* 78, 421 (1981).

[2] Although the exact nature of the arene:perfluoroarene interaction in the C_6H_6:C_6F_6 complex remains a controversial subject, this face-to-face stacking arrangement likely acts to minimize quadrupole–quadrupole interaction energies. The hypothesis of a charge-transfer (CT) interaction was discarded based on the absence of a characteristic CT band in the UV–vis absorption spectrum. T. G. Beaumont, K. M. C. Davis. *J. Chem. Soc. B* 1131 (1967).

[3] a) J. S. W. Overell, G. S. Pawley. *Acta Crystallogr., Sect. B* 38, 1966 (1982); b) J. H. Williams,
J. K. Cockcroft, A. N. Fitch. *Angew. Chem., Int. Ed. Engl.* 31, 1655 (1992).

[4] a) A. S. Batsanov, J. C. Collings, J. A. K. Howard, T. B. Marder. *Acta Crystallogr., Sect. E* 57, 950 (2001); b) J. C. Collings, K. P. Roscoe, R. L. Thomas, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, T. B. Marder. *New J. Chem.* 25, 1410 (2001); c) J. C. Collings, K. P. Roscoe, E. G. Robins, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, S. J. Clark, T. B. Marder. *New J.Chem.* 26, 1740 (2002); d) J. C. Collings, A. S. Batsanov, J. A. K. Howard, T. B. Marder. *Cryst. Eng.* 5, 37 (2002).

[5] a) M. L. Renak, G. P. Bartholomew, S. Wang, J. P. Ricatto, R. J. Lachicotte, G. C. Bazan. *J. Am. Chem. Soc.* 121, 7787 (1999); b) B. Strehmel, A. M. Sarker, J. H. Malpert, V. Strehmel, H. Seifert, D. C. Neckers. *J. Am. Chem. Soc.* 121, 1226 (1999).

[6] M. Weck, A. R. Dunn, K. Matsumoto, G. W. Coates, E. B. Lobkovsky, R. H. Grubbs. *Angew. Chem., Int. Ed.* 38, 2741 (1999).

[7] J. S. Lai, E. T. Kool. *J. Am. Chem. Soc.* 126, 3040 (2004).

[8] Y. S. Yamada, C. Morita. *J. Am. Chem. Soc.* 124, 8184 (2002).

[9] a) G. B. Jones. *Tetrahedron* 57, 7999 (2001); b) G. B. Jones, B. J. Chapman. *Synthesis* 475 (1995).

[10] M. J. Marsella, Z.-Q. Wang, R. J. Reid, K. Yoon. *Org. Lett.* 3, 885 (2001).

[11] a) A. V. Chuchuryukin, H. P. Dijkstra, B. M. J. Suijkerbuijk, R. J. M. Klein Gebbink, G. P. M. van Klink, A. M. Mills, A. L. Spek, G. van Koten. *Angew. Chem., Int. Ed.* 42, 228 (2003); b) A. F. M. Kilbinger, S. J. Cantrill, A. W. Waltman, M. W. Day, R. H. Grubbs. *Angew. Chem., Int. Ed.* 42, 3281 (2003).

[12] a) M. E. Layton, C. A. Morales, M. D. Shair. *J. Am. Chem. Soc.* 124, 773 (2002); b) A. G. J. Commeureuc, J. A. Murphy, M. L. Dewis. *Org. Lett.* 5, 2785 (2003); c) S. H. Kim, I. Figueroa, P. L. Fuchs. *Tetrahedron Lett.* 38, 2601 (1997).

[13] S. K. Collins, Y. El-Azizi, A. Schmitzer. *Angew. Chem., Int. Ed.* 45, 968 (2006).

[14] a) R. H. Grubbs. *Tetrahedron* 60, 7117 (2004); b) C. W. Lee, R. H. Grubbs. *J. Org. Chem.* 66, 7155 (2001).

[15] a) X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm. *J. Org. Chem.* 62, 3810 (1997); b) For a synthesis of closely related longithorone B, see: T. Kato, K. Nagae, M. Hoshikawa. *Tetrahedron Lett.* 40, 1941 (1999).

[16] Interestingly, cyclophanes bearing unsubstituted aromatics can be cyclized: J. Tae, Y.-K. Yang.*Org. Lett.* 5, 741 (2003).

[17] K. Langemann, A. Fürstner. *J. Org. Chem.* 61, 3942 (1996); (b) A. Furstner, K. Langemann. *Synthesis* 792 (1997).

[18] N. G. Pschirer, U. H. F. Bunz. *Tetrahedron Lett.* 40, 2481 (1999).

[19] Reactions have been repeated twice, and the isolated yields are identical.

Chapitre 4 : Application à la RCM ène-yne

Objetcifs

Comme énoncé dans le chapitre 2 (article 1), la macrocyclisation appliquée sur nos structures modèles a été envisagée cette fois-ci par RCM ène-yne. La complexité associée à la réaction de métathèse ène-yne ne nous a pas dissuadé à mener des investigations portant sur la possibilité de former des paracyclophanes comportant des motifs 1,3-diènes.

Hensen et Lee,[1] qui sont parmi les acteurs clés dans la RCM ène-yne, nous ont beaucoup inspiré par leurs travaux dans lesquels ils ont montré qu'il était possible de contrôler la complexité relative de cette chimie étant données les observations qu'ils ont fait sur des systèmes modèles tels que **143** et **146** sur le schéma 4.1. De leurs études nous pouvons tirer les conclusions suivantes :

- Les substrats ène-yne linéaires ne se cyclisent pas, le lien tartrate est nécessaire pour que la cyclisation ait lieu.

- La sélectivité *endo/exo* et le rapport *E:Z* sont typiquement difficiles à contrôler car ils dépendent largement de la nature du substrat à cycliser.

[1] a) Hensen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582. b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074 et références incluses.

- La sélectivité *endo/exo* est fonction de la taille du cycle à former : les cycles 12 à 15 favorisent les produits *endo* tandis que les cycles 5 à 11 eux favorisent les produits *exo.*

- Le rapport *E:Z* ne peut généralement être prédit.

- Le protocole de la RCM ène-yne pouvait avoir une influence importante. La présence d'éthylène (RCM ène-yne indirecte) permet dans ce cas de favoriser les produits *endo* (car passage par le produit de la métathèse ène-yne croisée avec l'éthylène **147** qui est un 1,3-diène acyclique) et de modifier les rapports *E:Z* en faveur du *E.*

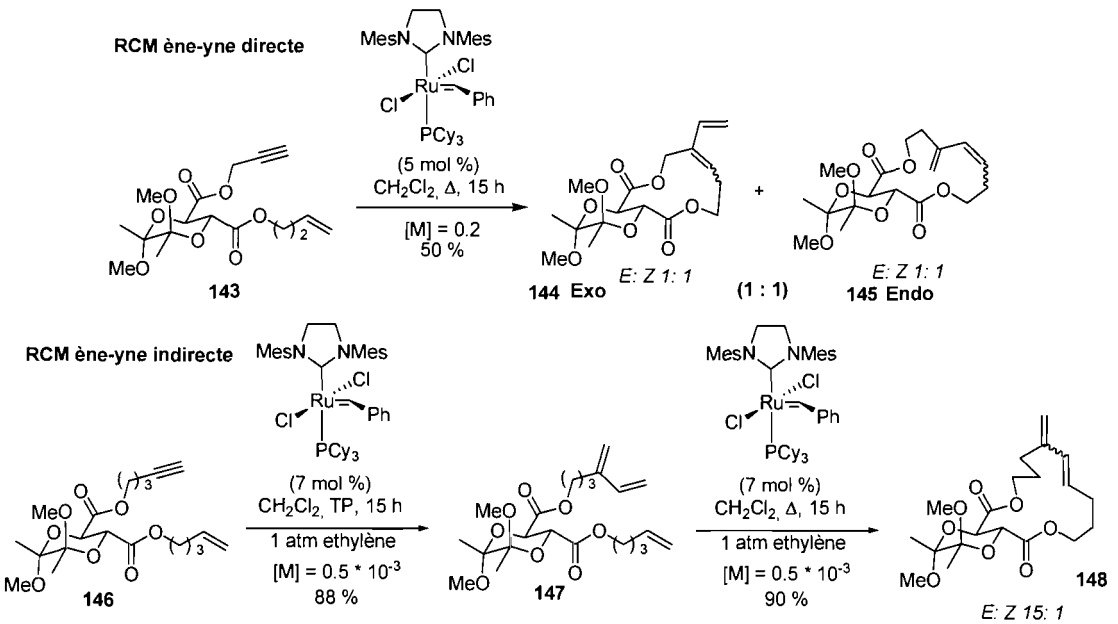


Schéma 4.1 : Études de Lee et Hansen sur la RCM ène–yne sur des substrats modèles.

Dans ce chapitre, nous nous sommes intéressés à la possibilité de contrôler la distribution des produits pouvant être issus de la réaction de macrocyclisation par RCM ène-yne.

Pour ce faire, une multitude de substrats ène-yne ont été préparés et soumis à des conditions de métathèse ène-yne en présence d'éthylène (métathèse ène-yne indirecte) et en l'absence d'éthylène (métathèse ène-yne directe). Différent catalyseurs ont été sondés et différentes conditions de réactions (solvants, températures, additifs) ont été utilisées.

Nous voulions aussi savoir si nous pouvions appliquer la stratégie du relais RCM ène-yne pour former un paracyclophane comportant un motif 1,3-diène dans lequel la double liaison intracycle est trisubstituée. Finalement pour conclure, nous avons aussi testé un nouvel auxiliaire, le 2,5-bis(trifluouorométhyl)benzyle. En effet, Tidwell et collaborateurs[2] ont déjà rapporté que ce dernier pouvait s'engager dans un empilement π de type face à face à l'état solide, lorsque par exemple, le 2,5-bis(trifluorométhyl)phényle éthanol est protégé par un groupement tosyle (figure 4.1).

[2] Allen, A. D.; Kwong-Chip, J. M.; Mistry, J.; Sawyer, J. F.; Tidwell, T. T. *J. Org. Chem.* **1987**, *52*, 4164.

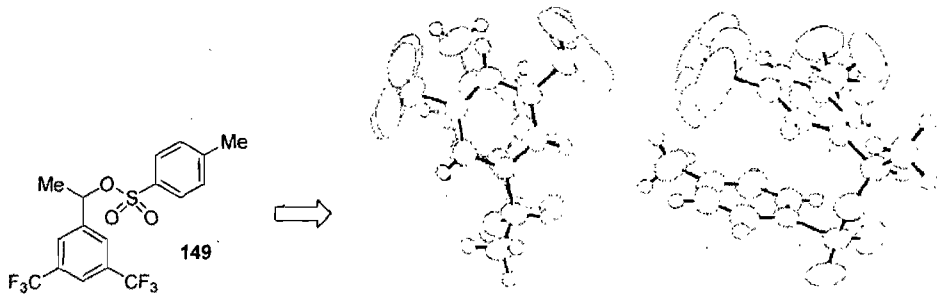


Figure 4.1 : Empilement π de type face à face centre à centre d'un dérivé du 2,5-bis(trifluorométhyl)phényle observé à l'état solide.

Article 3

Collins*, S. K.; El-azizi, Y.; Schmitzer, A. R.

Development of Perfluoroarene-Arene Interactions for Macrocyclic En-yne Metathesis and the Total Synthesis of Macrocyclic Natural Products

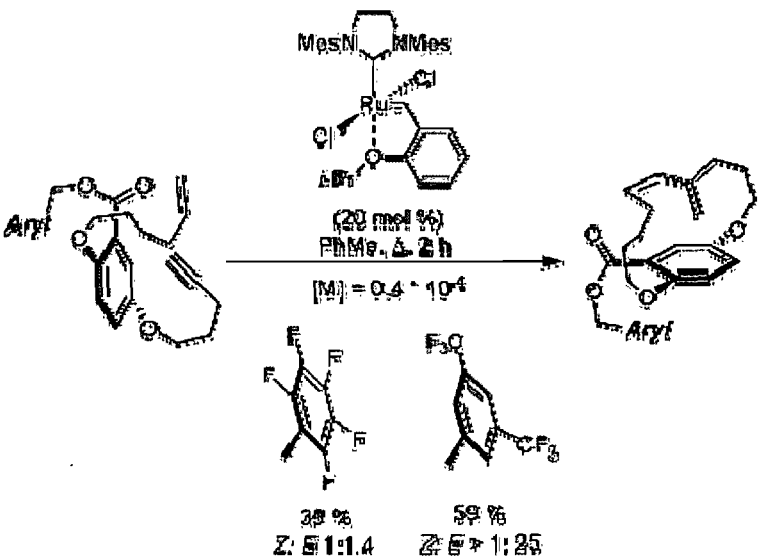
J. Org. Chem. **2007**, *72*, 6397.

- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées des cet article ont été faites par l'auteur.
- La majorité des procédures rapportées dans cet article ont été conçues et rédigées par l'auteur.
- Tous les travaux de modélisations moléculaires rapportées dans cet article ont été faits par la professeure Schmitzer.

Development of Perfluoroarene-Arene Interactions for Macrocyclic En-yne Metathesis and the Total Synthesis of Macrocyclic Natural Products

Collins*, S. K.; El-azizi, Y.; Schmitzer, A. R.

Abstract:



Efficient direct en-yne metathesis of strained macrocyclic systems is possible using highly active Grubbs-Hoveyda second-generation catalyst and when exploiting fluoroarene-arene gearing interactions. These interactions are effective even under high reaction temperatures and in the presence of a competitive π-rich solvent such as toluene. These results suggest that efficient π-π stacking or π-lp interactions between auxiliaries containing pentafluorophenyl and 3,5-bis(trifluoromethyl)phenyl groups are responsible for the good yields of macrocyclization products. The 3,5-bis(trifluoromethyl)benzyl

gearing elements provide higher yields and greater *E*-selectivity in the macrocyclic en-yne metathesis to form model paracyclophanes that could be applied toward the preparation of members of the longithorone family of natural products.

Introduction

A frequent challenge in the synthesis of complex natural products is efficient formation of macrocyclic structures.[1] Indeed, a variety of natural products that possess varying sizes of carbocyclic and heterocyclic rings systems with fascinating biological activities have been isolated.[2] Hence, macrocycles have come to play an important role in biology, medicine, and chemistry. Although the preparation of macrocyclic systems can be challenging because of entropic factors and/or ring strain, synthetic chemists have shown that many reactions can be altered to afford a macrocyclic variant. Most often in the total synthesis of macrocyclic natural products, a linear structure is constructed and fully elaborated, possessing most of its stereocenters and/or complex functionality already stereodefined. Typical retrosynthetic strategy has macrocyclization occurring near the end of the synthesis. The macrocyclization methods often employ two different functional groups that come together to form the cycle. Normally these reactions do not create stereocenters because the influence of the macrocyclic structure on their formation is difficult to predict.[3] The Yamaguchi macrolactonization is an excellent example of such a reaction that under optimized conditions favors macrocyclization to form a lactone.[4,5] While the synthetic strategy described above is both convergent and aesthetically pleasing, it can be improved. A more efficient approach would be to develop

macrocyclization reactions that would not only form the macrocycle but also, in doing so, create new important functionality present in the natural product in a stereo-, regio-, and chemoselective fashion. In addition, it would be important to develop reactions that result in the formation of carbon-carbon (C-C) bonds. This would result in an increase in convergence and a more efficient synthesis as much more complexity would be possible per synthetic operation. Macrocyclizations to form C-C bonds that result in an increase in molecular complexity have become increasingly important. The macrocyclic Ni-catalyzed coupling of aldehydes and alkynes[6] and the Ru-catalyzed cycloisomerization[7] reaction are examples of reactions that can undergo macrocyclization and produce significant levels of new functionality in the process.

Olefin metathesis has emerged as one of the "go-to" methods for macrocycle formation, especially as it forms a new C-C bond.[8,9] Despite this advantage, it is still influenced by ring strain and entropic factors that can be difficult to overcome.[10] At times, this can force a reexamination of the synthetic route and a return to a more "traditional" retrosynthetic disconnection.[11] It is also possible that the intermediate preceding macrocyclization can also adopt conformations that are unfavorable toward macrocyclization.[12] This has stimulated the development of imaginative new routes to coercing ring closure by olefin metathesis employing relay ring closing metathesis.[13] The difficulty in controlling the isomeric distribution of products has also prompted the development of macrocyclic alkyne metathesis as an alternative.[14]

Although the use of olefin metathesis in natural product synthesis is well-established, the use of en-yne metathesis is relatively poorly explored. This is surprising for a number of reasons. There has been an increased amount of study dedicated to understanding the mechanism of en-yne metathesis and how it can be exploited to afford substituted cyclic molecules. [15, 16] Most importantly, en-yne metathesis differs from olefin and alkyne metathesis in that it has the potential to form a multitude of different products using the same relatively simple functionalities of an alkene and alkyne. In macrocyclic en-yne metathesis, it is possible to afford both endo and exo products that possess different carbon connectivities.[17] The complexity of the resulting products is multiplied when considering that each cyclization mode could afford both *E*- and *Z*-isomers.[18] The exo mode of metathesis can also be rendered more complex if combined with a tandem cross-metathesis. Despite this flexibility, the ability to form a variety of products can also be problematic. Macrocyclic en-yne metathesis rarely affords a sole thermodynamic product with complete selectivity. This can lead to problems in purification of the desired product as the products often possess similar physical properties. Indeed, there is significant potential in macrocyclic en-yne metathesis; however, the challenge is to develop methods to control the products formed, via either substrate or catalyst control.[16b]

An additional level of complexity can be introduced into the macrocyclization process when strained systems are formed. In such cases, the restricted rotation of functional groups such as aromatic or heteroaromatic groups can result in the formation of an element of planar chirality. This is not uncommon as there are many classes of

biologically active natural products that possess strained macrocycles, many of which exhibit elements of planar chirality.[19] In such cases, conformational controlling elements or "gearing elements" are employed to help promote successful cyclization.[20] In a strict sense, the term "geared molecule" makes reference to molecules where a level of strain is present because of unavoidable steric crowding, the result of which is a rigidified structure typically incorporating bonds exhibiting restricted rotation. Although the term "gearing effect" or "gearing element" has become increasingly used to describe functional groups that influence certain molecular conformations, regardless of the level of rigidity of the molecule, the term "conformational control element" will be used. If en-yne metathesis is to develop into a reliable technology for total synthesis, new methods are necessary that may control one or several characteristics of the resulting products (endo vs exo mode of cyclization, *E*:*Z* selectivity, stereochemistry). One possible solution to this problem is through the development of conformational control elements or auxiliaries that may control some of these factors.

The most popular conformational control element is to position a substituted methylene group adjacent to an aromatic ring or planar heterocycle. This conformational control element was elegantly exploited by Shair and co-workers in their synthesis of longithorone A.[21] The longithorone family of natural products are farnesylated quinones, whereby the farnesyl unit is wrapped around the quinone core to produce a rigid cyclophane structure (Figure 1).[22]

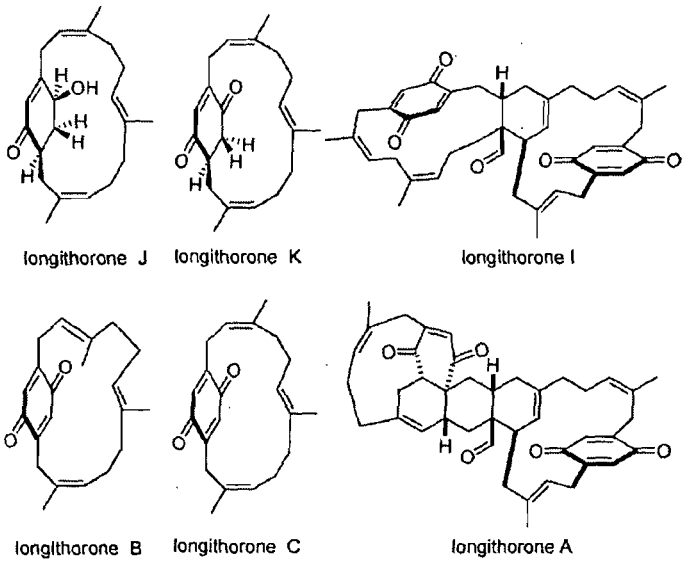
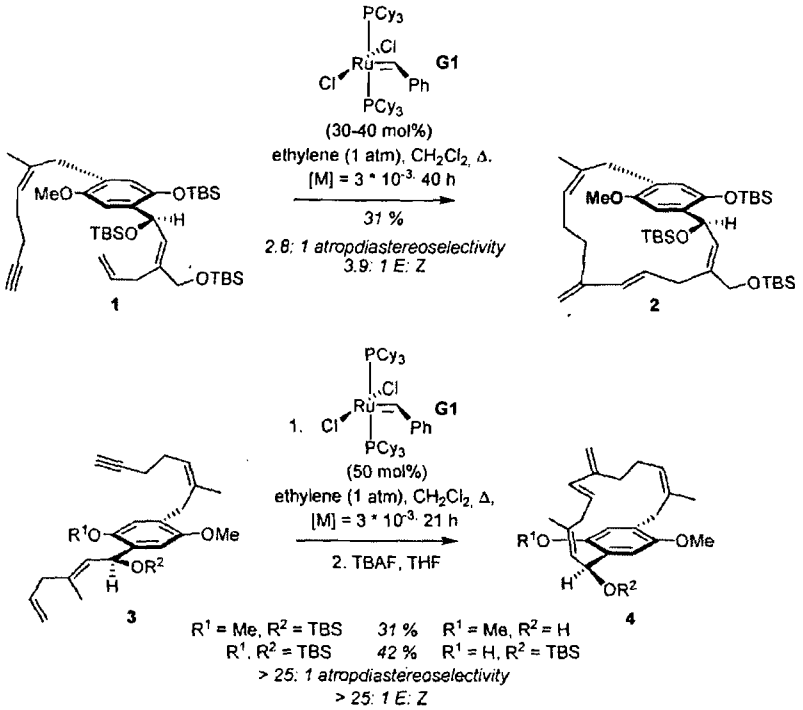


Figure 1 Members of the longithorone family of natural products.

Higher members of this family are dimers of two cyclophanes and are thought to arrive biosynthetically via intramolecular Diels-Alder reactions between two appropriately functionalized [12]paracyclophanes. Shair and co-workers used an intramolecular macrocyclic en-yne metathesis in a biomimetic strategy to form the [12]paracyclophane structures **2** and **4** (Scheme 1).



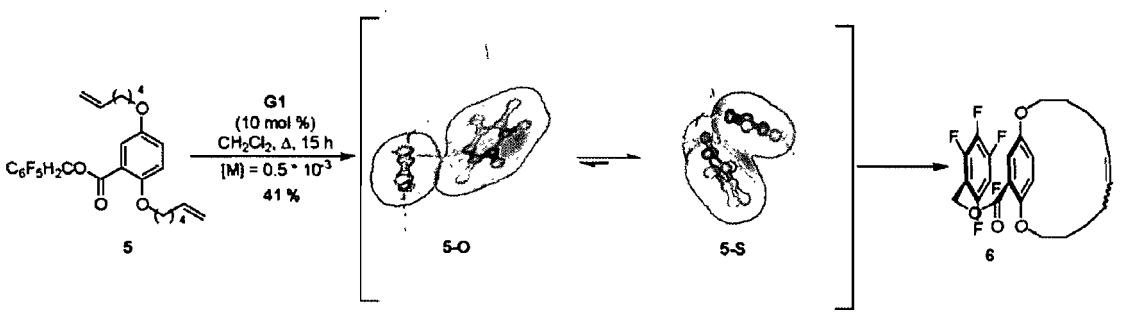
Scheme 1. Preparation of Functionalized Macrocycles by En-yne Metathesis by Shair and Co-Workers[21].

The reaction was extremely difficult, requiring large catalyst loadings, extended reaction times, and the presence of an ethylene atmosphere, and most importantly, the presence of the *t*-butyldimethylsilyl-protected alcohol adjacent to the aromatic ring was essential for any productive cyclization to occur. The control of the *E*:*Z* ratios and atroposelectivities were dependent on the nature of the product and not the removable conformational control element. Because few conformational control elements have been investigated, the development of novel gearing auxiliaries that would promote efficient macrocyclization and control the various variables in the en-yne metathesis would be of

value. Herein we report the development of fluoroarene-arene interactions and novel aromatic auxiliaries to promote intramolecular macrocyclic en-yne metathesis that influence the resulting geometry of the formed internal olefin.

Results and Discussion

As part of a research program targeted toward the total synthesis of members of the longithorone family of natural products, we focused on the development of new protocols for macrocyclization. The major synthetic challenge associated with the total synthesis of these macrocyclic quinones was likely the formation of the strained [12]paracyclophane cores. Our group has been investigating novel gearing elements that are based on noncovalent interactions. During studies directed toward the preparation of longithorone C,[23] we developed a novel conformational control element technology based upon perfluoroarene-arene interactions. We have recently reported that perfluoroarene-arene interactions in the solution state can be used to achieve difficult macrocyclizations using olefin metathesis (Scheme 2).[24]



Scheme 2. Development of a Perfluoroarene-Arene Conformational Control Element.

For example, when the pentafluorobenzyl ester **5** is treated with Grubbs first-generation catalyst (**G1**), the macrocycle **6** is obtained in 41% yield. No cyclization is observed with any other ester group. We have studied the mechanism of the gearing effect via molecular modeling using both AM1 and MP2 levels of theory, suggesting the gearing effect is a result of an energetically more stable π- π stacking conformer **5-S** that exhibits a significant degree of overlap with the aromatic core and aids in gearing the alkenyl side chains for productive metathesis. It is surprising that this interaction has seen limited use in synthesis and catalysis. A sole example of such quadrupolar interactions in the *solution* state had been previously observed by Marsella and co-workers.[25] Noncovalent interactions such as π-π interactions are known to contribute significantly to the conformational stability of biological systems.[26] Consequently, the study of the effects of the inclusion of pentafluorophenyl groups and the resulting quadrupolar interactions in peptides have attracted increased attention.[27] In addition, intramolecular π-π interactions have long been known to play important roles in stereoselective reactions. [28] Recently, π- pyridinium cation interactions[29] have emerged as synthetically useful tools for face selective transformations.[30] We chose to investigate whether we could expand the scope of the gearing elements that function via intramolecular π-π interactions to other macrocyclization protocols. Our interest in the higher members of the longithorone family of natural products (such as longithorone A and longithorone I) persuaded us to investigate macrocyclic en-yne metathesis. We immediately set forth to develop a methodology that would be synthetically useful for the preparation of functionalized macrocycles useful in natural product synthesis. We initially chose to investigate the macrocyclization to form the strained [12]paracyclophane ester **8A**, for several reasons.

We assumed that no products resulting from exo cyclization would be formed because prior investigations had demonstrated that it was not possible to form these types of [11]paracyclophanes via metathesis.[31] Second, **8A** represents a simplistic model of the [12]paracyclophanes **2** and **4** prepared by Shair and co-workers, possessing the same number of atoms in the macrocyclic ring and having the en-yne metathesis occur at exactly the same position along the ansa-bridge (Figure 2).[21]

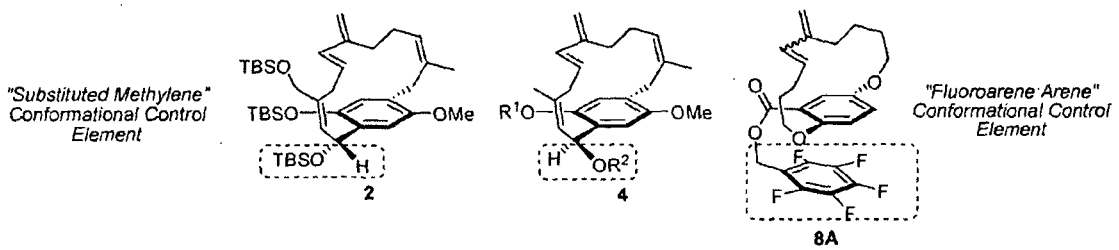
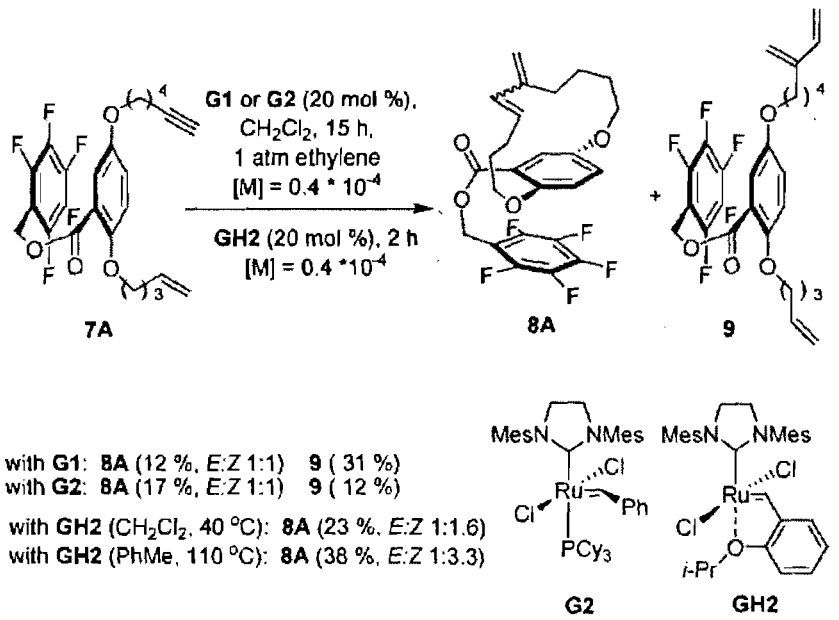


Figure 2 Target [12]paracyclophanes to be formed via en-yne metathesis.

Initial Screening/Optimization of Reaction Conditions. We decided to base our initial investigations into whether the perfluoroarene auxiliaries could be used for macrocyclic en-yne metathesis by applying the optimized conditions reported by Shair and co-workers during the synthesis of longithorone A. These reaction conditions included the use of an ethylene atmosphere. Although it is known that these conditions can lead to preferential cross-metathesis between ethylene and the alkyne moiety of the en-yne metathesis precursors, the resulting dienes have been shown to undergo subsequent olefin metathesis to yield 1,3-diene products. This strategy, termed "indirect en-yne metathesis" can result

in yields and *E*:*Z* selectivities higher than those of the "direct en-yne metathesis" that occurs between alkyne and alkene.[17, 32] Hence, the initial investigations of macrocyclization of **7A** with **G1** (10 or 20 mol %) in CH_2Cl_2 at reflux were performed under an atmosphere of ethylene (1 atm). Incomplete conversion of **7A** (56%) was observed after 15 h, and purification of the reaction mixture afforded only a 12% yield of macrocycle **8A** (Scheme 3). The macrocycle was formed with complete endo selectivity and an *E*:*Z* ratio of 1:1. The major product of the reaction was the 1,3-diene **9** isolated in 31% yield resulting from cross-metathesis of ethylene with the pendant alkyne. In an effort to improve conversion, we repeated the protocol with Grubbs' second-generation catalyst **G2** (Scheme 3).

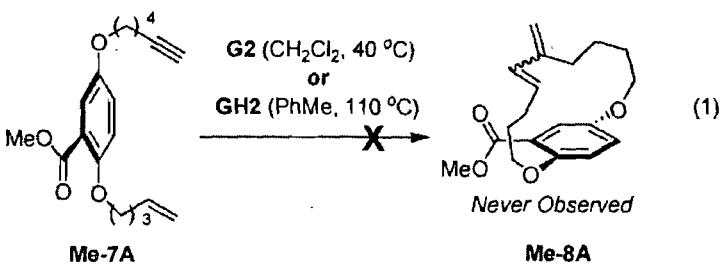


Scheme 3. Catalyst Optimization.

Although we succeeded in improving conversion (86%) and reducing the amount of **9** (isolated in 12% yield), the yield of the desired product **8A** was only marginally improved to 17% (*E*:*Z*, 1:1). The macrocycle **8A** is believed to be formed via a direct en-yne metathesis process, because subjecting **9** to similar reaction conditions does not promote ring closure and only oligomerization was observed. In an effort to evade the formation of **9**, we eliminated ethylene from the reaction conditions and investigated the use of more reactive Grubbs-Hoveyda-type catalysts (Scheme 3). Upon treatment of **7A** with Grubbs-Hoveyda second-generation catalyst (**GH2**) in CH_2Cl_2 at 40°C, **9** was completely eliminated from the reaction profile and the starting material was completely consumed. In addition, the yield of **8A** had improved to 23% (*E*:*Z*, 1:1.6). Typically, macrocyclization can be improved by using higher temperatures; however, this has been shown to afford side products that are difficult to separate from the desired product.[33] Nonetheless, other RCM reactions have been shown to benefit from higher reaction temperatures.[34] However, when the macrocyclization was performed in toluene at 110°C for 2 h, the macrocycle **8A** was obtained in an isolated yield of 38% with an *E*:*Z* ratio of 1:3.3.

These yields approach what we have observed for macrocyclizations via olefin metathesis, despite the fact that these cyclizations form macrocycles bearing 1,3-dienes that are considerably more strained than those bearing a simple olefin. This is evident from the preference for the formation of a cis olefin within the macrocycle. The ^{1}H NMR spectra also clearly show that the methylene protons of the auxiliary are diastereotopic,

indicating the formation of atropisomers due to the ansa-bridge's restricted rotation.[35] It is also important to note that only traces of the macrocycle are ever observed in the absence of the pentafluorophenyl auxiliary (eq 1). *The absence of the perfluorobenzyl conformational control element results in the formation of a linear dimer and oligomerization.* Modifying the reaction concentration, nature of the catalyst, or the method of substrate addition failed to afford any macrocyclization when using the corresponding methyl ester of **7A**. These results suggest that a combination of higher temperatures and reactive catalysts can be used to help affect macrocyclic en-yne metathesis. Perhaps what is most notable is that the auxiliary gearing element efficiently directs macrocyclization even in a solvent capable of competitive π-interactions. This may point to fluorinated aromatics as an attractive alternative for use in catalysis over pyridinium cations.[36]

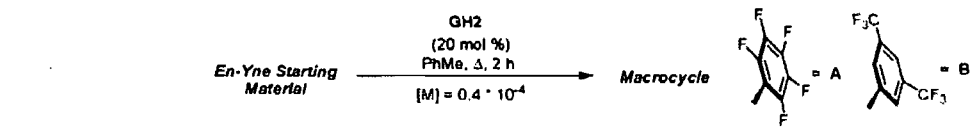


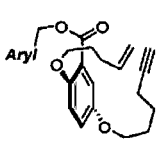
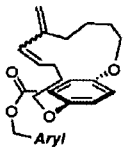
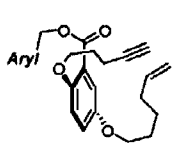
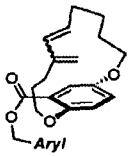
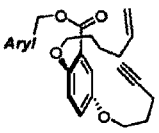
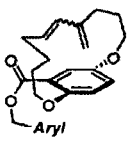
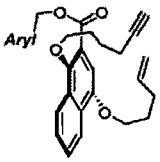
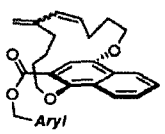
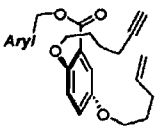
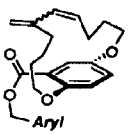
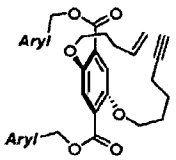
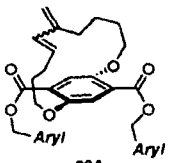
Me-7A **Me-8A** (1)

Although the yields of the macrocyclic en-yne metathesis reactions were comparable to those obtained with traditional conformational control elements, we felt further improvements were possible. We also desired a conformational control element that

might increase the preference for forming *E*-olefins in the product, as was necessary if a total synthesis of the longithorone family of natural products was to proceed.

Auxiliary Development. In an effort to develop even more efficient conformational control elements to aid in difficult macrocyclic en-yne metathesis reactions, we investigated replacing the five fluorine atoms of the pentafluorobenzyl auxiliary for other electron-withdrawing substituents. We hoped that with proper optimization, even higher, more synthetically useful macrocyclization yields could be obtained. We also wondered whether these conformational control auxiliaries could be used to control the resulting *Z*:*E* ratios of the products. In modifying the auxiliary, we decided to avoid using other pentahalogen-substituted aromatics, because we feared that an increase in the steric bulk might result in repulsion between the auxiliary and aromatic core and a less efficient control over substrate conformation in solution. We had already observed that a nitro group could be used to affect the formation of trace quantities of [12]paracyclophane products in macrocyclic olefin metathesis.[24b] However, we did not want to construct auxiliaries with multiple NO_2 groups and considered a CF_3 group, another excellent electron-withdrawing group, as an alternative.[37] In addition, Tidwell and co-workers had reported that efficient π-stacking was observed in the solid state between a tolyl group and a bis-(3,5)-trifluoromethyl group.[38] We decided to investigate the use of a (3,5)-bistrifluoromethylbenzyl ester as a gearing element (Table 1).



Entry	Precursor	Macrocycle	Aryl	Yield (%)	*Z* : *E*	Entry	Precursor	Macrocycle	Aryl	Yield (%)	*Z* : *E*
1			A	38	9.6:1	4			A	34	1: 8.3
	7A	8A					20A	21A			
	10B	11B	B	47	6: 1		22B	23B	B	54	1: 8
2			A	35	1:1.4	5			A	43	3.6:1
	12A	13A					24A	25A			
	14B	16B	B	59	> 1 25		26B	27B	B	69	2. 1
3			A	33- 36	3.3:1	6			A	51	1.8:1
	16A	17A					28A	29A			
	18B	19B	B	49	2.5 1		30B	31B	B	53	1: 10

[a] Reported yields are after isolation by silica gel flash chromatography. *Z*:*E* ratios are determined by ^{1}H NMR.

Table 1. Evaluation of Different Fluoroarene Conformational Control Elements for the Formation of Strained [12]Paracyclophanes[a]

When **8A** was formed, it was isolated in 38% yield and favored the formation of a predominately *Z*-isomer (*Z*:*E*, 9.6:1) (Table 1, entry 1). When the auxiliary was exchanged for the CF_3-bearing auxiliary, the yield increased further and **11B** was isolated in 47% while the isomeric ratio decreased to *Z*:*E*, 6:1. Although it looked as if the CF_3-bearing auxiliary was more *E*-selective, we decided to investigate moving the position of

metathesis along the ansa-bridge to confirm this hypothesis. We have previously observed that this can have a significant effect on the yield of metathesis. When the site of metathesis was moved a single carbon further along the chain, we again observed the same trend (entry 2). Cyclophane **13A** was isolated in 35% yield with a nearly equal ratio of *Z*:*E* isomers present (*Z*:*E*, 1:1.4). However, switching to the CF_3-bearing auxiliary resulted in a jump in the isolated yield and **15B** was isolated in 59%. Furthermore, the ^1H NMR spectra showed a single conformational isomer (*Z*:*E* > 1:25). This particular example demonstrates that the auxiliary is having a dramatic effect on the isomeric ratio of the products. Next, we investigated the influence of switching the relative position of the side chains with respect to **7A** (i.e., the alkynyl side chain is ortho to the ester functionality). When **16A** was submitted to the optimized metathesis conditions, the pentafluorobenzyl ester cyclophane **17A** was isolated in 33-36% yield and exhibited a *Z*:*E* ratio of 3.3:1. Switching to the CF_3-bearing auxiliary did not have a dramatic effect on the *Z*:*E* ratio, giving a slightly higher quantity of the *E*-isomer (2.5:1). However, once again the yield of the cyclophane product **19B** increased to 49%. This trend of increasing yields was also observed in the formation of cyclophanes **21A** and **23B**, as the yield of **23B** is ~20% higher than that observed for **21A**, but the isomeric ratio remains essentially the same (entry 4). The aromatic core could be modified as well while maintaining the same trends. The naphthyl en-yne **24A** (entry 5) cyclized to afford **25A** in 43% yield with a *Z*:*E* ratio of 3.6:1. However, **26B** did not provide **27B** with a significantly higher *E*-selectivity, although the product was once again observed in higher yield (69%). The addition of a second pentafluorobenzyl group (entry 6) also afforded the corresponding [12]paracyclophane product **29A** in 51% yield with an *Z*:*E* ratio of 1.8:1 (Figure 3). In

contrast, **30B** afforded the cyclophane product **31B** in a yield similar to that of **29A** (53 vs 51%). However, the *E*-selectivity was high, and a 1:10 *Z*:*E* ratio was observed. These results reinforce the belief that subtle changes in the structure of the macrocycle can alter the resulting *E*:*Z* ratios significantly. However, it is clear that, while it is not possible to completely override the thermodynamic preference of the system, the auxiliary is being shown to be capable of influencing the resultant isomeric ratio of products. To date, there has not been a catalyst-controlled method devised to influence these ratios, although Grubbs-Hoveyda-type catalysts bearing unsymmetrical NHC ligands have been shown to affect *E*:*Z* ratios in cross-metathesis reactions and may have promise in en-yne metathesis as well.[39]

Larger rings bearing less strain, such as [13]paracyclophanes, could also be formed efficiently (Table 2). The [13]paracyclophane **33A** was obtained in 31% yield, and the loss in strain was apparent as the *E*-isomer was favored (*Z*:*E*, 1:9). Once again, using the CF_3-bearing auxiliary provided the cyclophane **35B** in increased yield (45%) and with high *E*-selectivity (*Z*:*E* > 1:25). As a matter of fact, regardless of the placement of the side chains relative to the ester (entry 2) or of substitution on the aromatic core (entry 3), the yields were typically ~50% and the cyclophanes (**37B**, **39B**) were obtained in high *E*-selectivity (*Z*:*E* > 1:25).

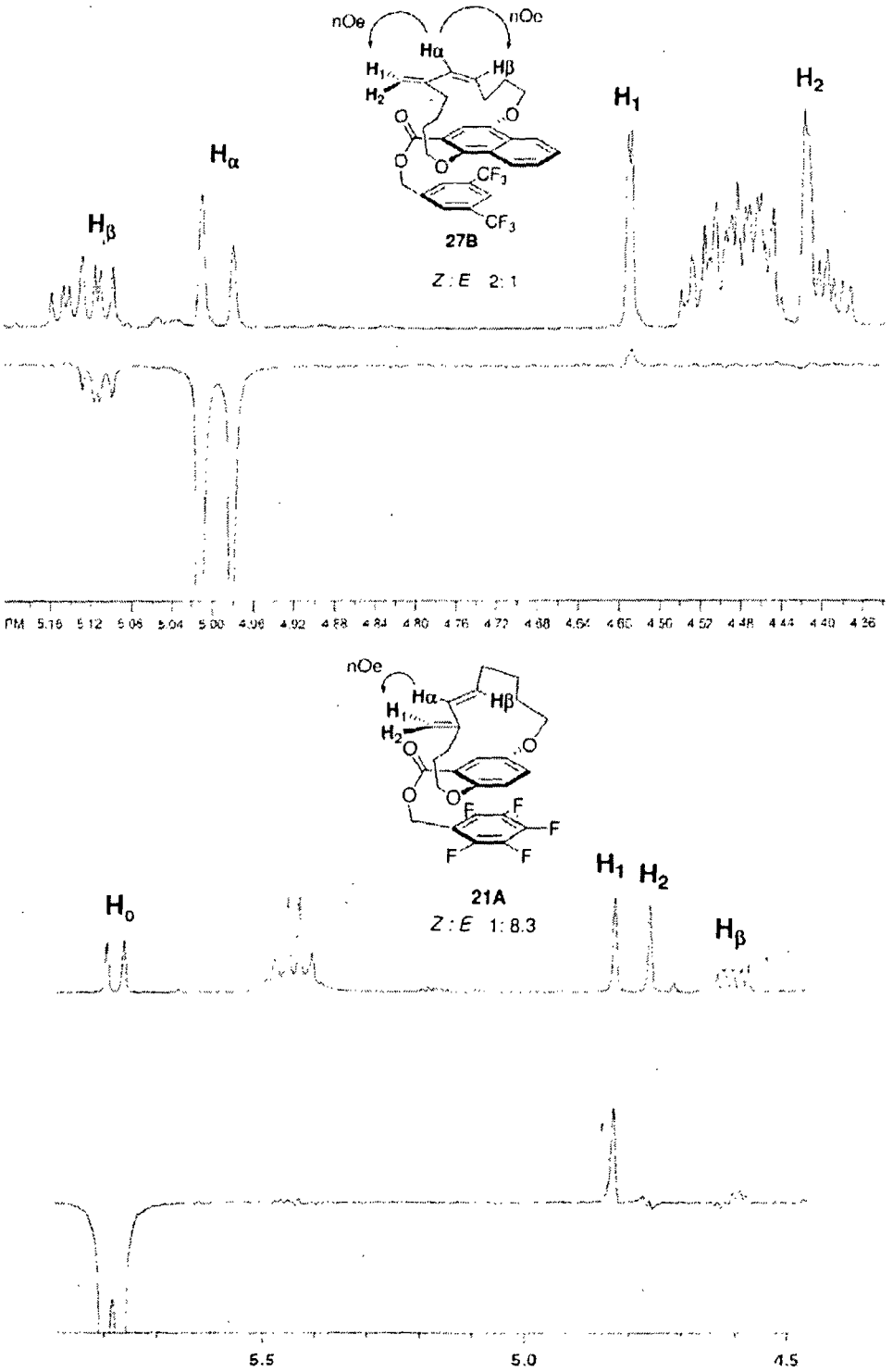
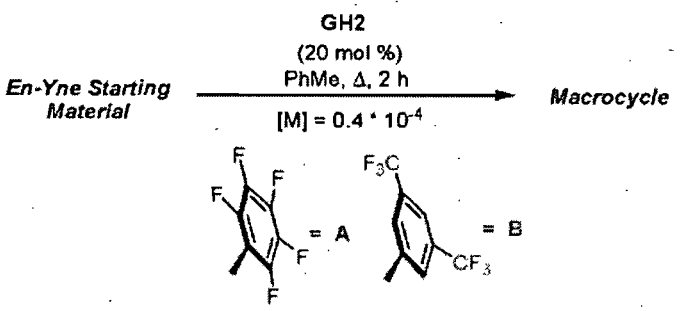
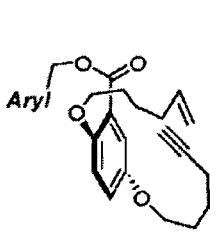
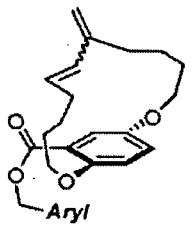
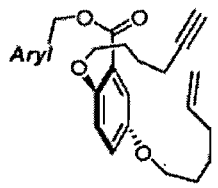
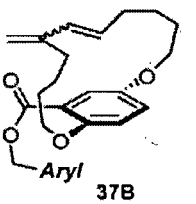
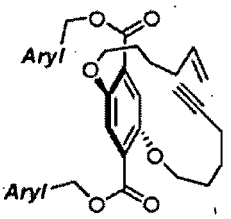
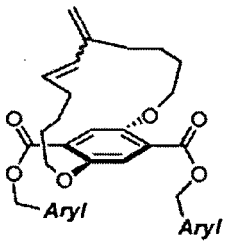


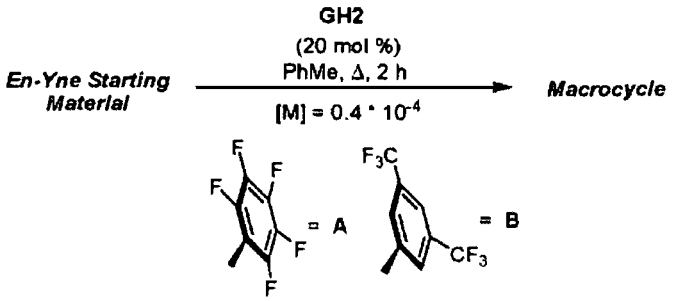
Figure 3 Determination of *Z*:*E* isomeric ratios in [12]paracyclophanes.

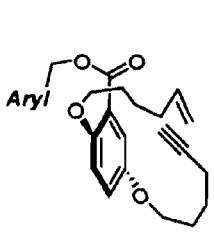
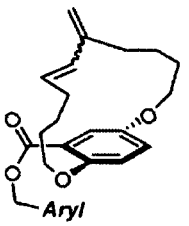
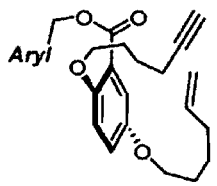
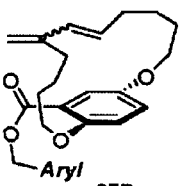
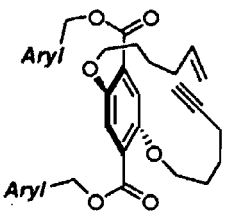
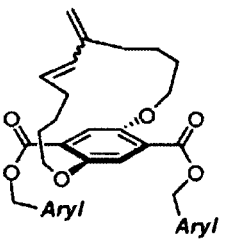


Entry	Precursor	Macrocycle	Aryl	Yield (%)	*Z* : *E*
1					
	32A	**33A**	**A**	31	1:9
	34B	**35B**	B	45	>1 :25
2					
	36B	**37B**	B	48	> 1: 25
3					
	38B	**39B**	B	51	> 1: 25

[a] Reported yields are after isolation by silica gel flash chromatography. *Z*:*E* ratios are determined by ^{1}H NMR.

Table 2. Evaluation of Different Fluoroarene Conformational Control Elements for the Formation of [13]Paracyclophanes[a]

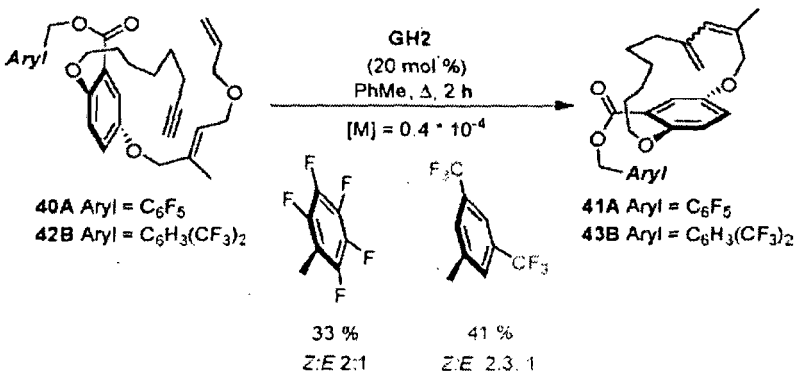


Entry	Precursor	Macrocycle	Aryl	Yield (%)	*Z* : *E*
1					
	32A	**33A**	**A**	**31**	1:9
	34B	**35B**	**B**	**45**	>1 :25
2					
	36B	**37B**	**B**	**48**	> 1: 25
3					
	38B	**39B**	**B**	**51**	> 1: 25

[a] Reported yields are after isolation by silica gel flash chromatography. *Z*:*E* ratios are determined by ^{1}H NMR.

Table 2. Evaluation of Different Fluoroarene Conformational Control Elements for the Formation of [13]Paracyclophanes[a]

We also sought to apply the fluoroarene-arene technology to the formation of more substituted 1,3-dienes (Scheme 4). We prepared the precursor **40A** bearing the appropriate extension to exploit a relay ring closing strategy.[13] When **40A** was subjected to the optimized reaction conditions, the cyclization afforded **41A** in 33% yield and an *E*:*Z* ratio of 1:2.[40] While the usage of the CF_3-bearing auxiliary did not improve the *Z*:*E* ratio of the product, we did observe higher yields of **43B** using this auxiliary (41%). To the best of our knowledge, this is the first use of the relay ring closing metathesis strategy in macrocyclic en-yne metathesis.



Scheme 4. Relay Ring Closing En-yne Metathesis.

Molecular Modeling. The success of the 3,5-(trifluoromethyl)benzyl ester group as a conformational control auxiliary prompted us to conduct a series of molecular modeling experiments to help understand why the substitution of the five fluorine atoms by two CF_3 groups provided increased yields in macrocyclization. We decided to use a model

system similar to that used in our previous studies (see **5**, Scheme 2).[41] Previous reports of the stacking interactions of perfluoroarenes and other arenes in the solid state point toward a preference for a face-to-face orientation (conformer **I**, Figure 4).[42,43] In addition, our previous molecular modeling studies using AM1 and MP2 levels of theory also suggested that π- π interactions may be responsible for the gearing effect. However, we postulated two other possible noncovalent interactions that could influence the solution-state conformation of the macrocyclization substrates (Figure 4). Doyon and Jain have previously shown that F-$H_{aromatic}$ interactions provided increased binding affinities of inhibitors of carbonic anhydrase.[44] If a similar interaction was present, we would expect a conformation resembling **II** (Figure 4) to be favored. However, previous studies have identified that all five fluorine atoms are required for efficient conformational control, suggesting that one or two F-$H_{aromatic}$ interactions are unlikely to be responsible for the macrocyclization. We also theorized that a conformer exhibiting an oxygen lone pair-arene (lp-π interaction) could be possible considering the relative electron deficiency of the gearing element and the proximity of the oxygen atoms in these model systems (conformer **III**, Figure 4). An elegant study by Gung and co-workers showed that lp-π interactions can influence solution-state conformations.[45] In addition, electron-deficient π-systems have been shown by *ab initio* calculations to engage in favorable lp-π interactions.[46] Thus, we believe a conformation resembling **III** is also plausible, where the pendant arene would interact with the phenolic oxygen that is ortho with respect to the ester group. Consequently, we conducted a new series of molecular modeling studies using a DFT[47] level geometric and energy analysis. It was hoped that the use of this

higher level of theory compared to our previous study would help to shed light on the various conformational possibilities of the arenes in these systems.

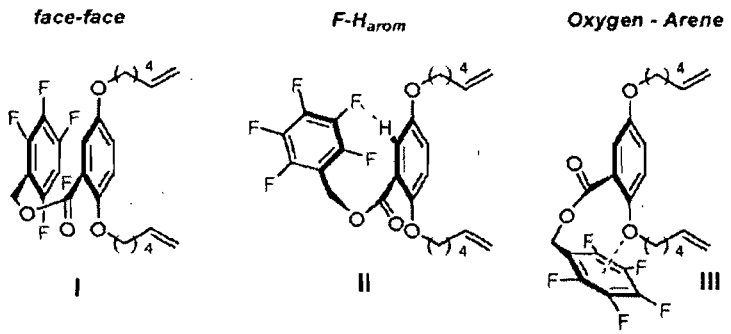


Figure 4 Potential noncovalent interactions that could influence the solution-state conformation of **5**.

To further probe the mechanism of the conformational control effect, molecular modeling studies were performed in a series of steps.[48] First, the initial geometry optimizations for **5** were performed using semiempirical methods (AM1)[49] to afford both maximum and minimum energy conformers. These conformers displayed either an "open" conformation where the benzyl ester is elongated away from the aromatic core or a "closed" conformation in which the arene of the benzyl ester is positioned underneath the aromatic core in a slipped type arrangement. MP2[50] perturbation theory with a 6-31G* basis set was then used to provide more accurate energies for each conformer. Subsequently, we resubmitted the "closed" conformer to a DFT level geometric and energy analysis. We once again observed an "open" conformer **5-O*** and a stacked or "closed" conformer **5-**

S* (Figure 5).[51] DFT calculations showed that the closed conformer was more favored by -0.20 kcal/mol than the open conformer. Importantly, the nature of the closed conformer **5-S*** differs considerably from that of **5-S** previously obtained through calculation using AM1 and MP2 levels of theory. In fact, in **5-S*** the auxiliary does not overlap efficiently with the arene core, instead opting to sit over the pendant oxygen atoms in these systems (Figure 5). This sort of lp-π interaction has been previously studied using hexafluorobenzene and a molecule of H_2O using the MP2/6-31G** level of theory. [43] We then pursued a similar analysis of the analogous 3,5-(trifluoromethyl)benzyl ester **44** to discover if similar lp-π interactions were also responsible for controlling conformer distribution and perhaps productive macrocyclization.

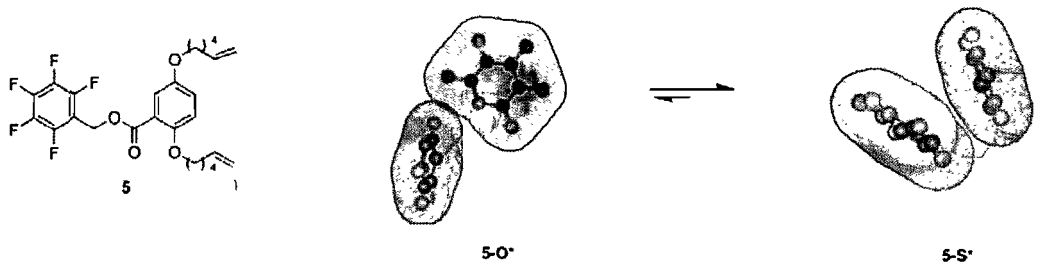


Figure 5 Conformational analysis of **5**.

The analysis of the analogous 3,5-(trifluoromethyl)benzyl ester **44** was performed in the following manner. Starting with the **5-S**, the five fluorine substituents were exchanged for

two CF_3 groups to give **44**. Subsequently, **44** was refined using the MP2 level of theory in which only the torsion angles about the ester functionality were allowed to vary. The resulting conformer was then further refined via a DFT level geometric and energy analysis. We again observed two distinct conformations, in which the stacked or "closed" conformer **44-S** was preferred over the "open" conformer **44-O** by -1.28 kcal/mol (Figure 6).

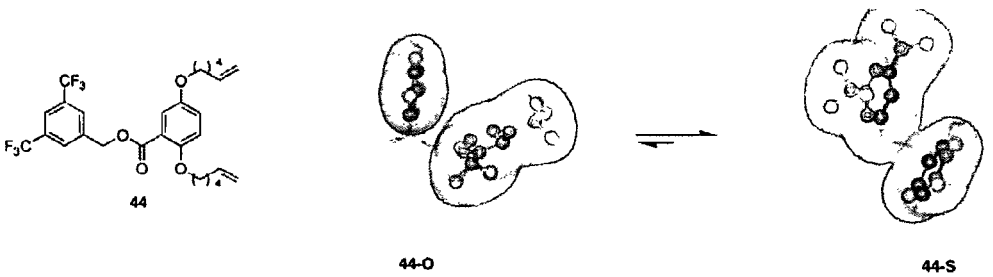


Figure 6 Conformational analysis of **44**.

These calculations suggest that both stacked conformers **5-S*** and **44-S** are preferred compared to their respective open conformers **5-O*** and **44-O**. The conformer **44-S**, however, is preferred to **44-O** to a much greater extent than the **5-S*** to **5-O***. This suggests that conformer **44-S** is highly likely to predominate in solution. It should be noted that the rates of reaction of both the "stacked" and "open" conformer, and hence the distribution of their respective macrocyclization products, depend on the relative energies of the transition states leading to those products. If the activation barrier from each

ground-state conformer were equal, the difference in energy between those ground states would be reflected in the transition-state energies and would be responsible for the observed product distribution. However, the barrier for reaction of the stacked conformers **44-S** or **5-S*** may be even lower than that of their open conformers, since the "stacked" conformations are believed to orient the alkyl side chains closer together, thereby decreasing the entropic barrier for their reaction. In the case of the open conformer, the activation barrier of the dimerization reaction is apparently lower than that of the macrocyclization.

The origin for the highly favored **44-S** may be due to the electronic nature of the CF_3 substituents. Although **5** bears five aromatic fluorine atoms, they can act simultaneously as both σ-withdrawing and π-electron-donating groups.[52] In contrast, the two CF_3 groups are σ-withdrawing, but are devoid of any π-donating capability. This may allow for the existence of a less electron-rich aromatic auxiliary, thereby increasing the possibility for stabilizing π-interactions. Gung and co-workers have demonstrated that a CF_3 group is better at inducing arene-arene interactions than a single F atom.[40]

Once again, in conformer **44-S**, the auxiliary prefers to sit over the pendant oxygen atoms of the aromatic core (Figure 7). Gung and co-workers observed similar lp-π interactions for arenes bearing a single CF_3 group even in solvents capable of forming weak CH-O hydrogen bonds.[42] Their study did not include strongly electron-deficient arenes such as

the pentafluorobenzyl and 3,5-bis(trifluoromethyl)benzyl ester groups in **5** and **44**, respectively. However, it is clear that effective macrocyclization observed with substrates bearing the CF_3 auxiliary may be explained by the superior energetic stability of the lp-π interaction of **44-S** versus **5-S***.

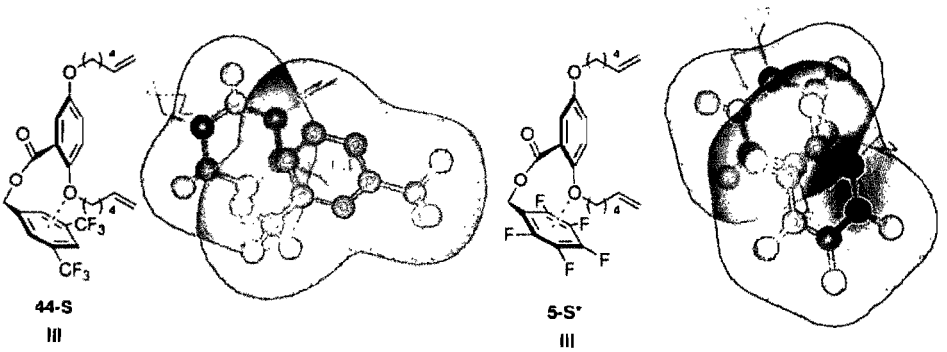


Figure 7 Conformations of **44-S** and **5-S*** exhibiting lp-π interactions.

Although these calculations provided better insight into the noncovalent interactions responsible for macrocyclization and why the CF_3 auxiliary was superior to the pentafluorobenzyl auxiliary, we were intrigued whether these conformational control elements could be used for all-carbon systems, such as those that would be explored in the context of a total synthesis of members of the longithorone natural products. Consequently, we performed an identical conformational search on **45** and **46**, in which the phenolic oxygen atoms have been replaced with methylene groups (Figure 8).

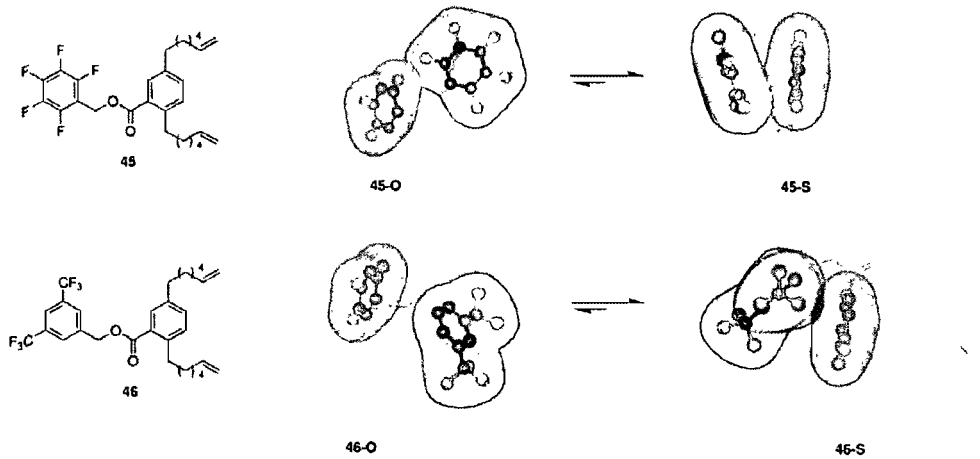


Figure 8 Conformational analysis of **45** and **46** models systems.

Once again, the DFT conformational and energetic analysis identified two major conformers corresponding to the "open" and "stacked" conformations previously observed. In the pentafluorobenzyl ester containing **45**, the "stacked" conformer **45-S** is preferred to the "open" conformer **45-O** by -0.55 kcal/mol. Satisfyingly, in this case the arenes are slightly offset and a great degree of π-overlap is observed (Figure 9). Interestingly, the "stacked" conformer **45-S**, exhibiting arene-arene interactions, is preferred energetically to a greater extent than the "stacked" conformer **5-S*** exhibiting lp-π interactions. This suggests that these auxiliaries should be equally as effective in the macrocyclization of all-carbon cyclophanes. Similarly, the "stacked" conformer **46-S** of the CF_3-bearing substrate also showed a face-to-face type arene-arene interaction with considerable overlap of the aromatic core and pendant arene. The **46-S** conformer was preferred by -0.41 kcal/mol over **46-O**, representing a decrease in energetic preference for a "stacked" conformation relative to **44-S** in which lp-π interactions were present.

This suggests that the 3,5-bis(trifluoromethyl)phenyl group is more sensitive to lp-π interactions than the pentafluorophenyl group. These results predict that the superior π overlap observed in the all-carbon series, combined with the energetic preference for the corresponding "stacked" conformations, will lead toward efficient macrocyclization.

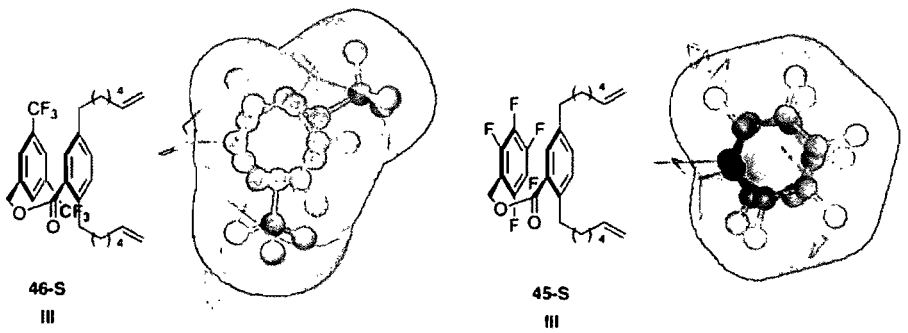


Figure 9 Conformers **46-S** and **45-S** exhibiting efficient π-overlap of the pendant auxiliary and arene core.

In summary, we have demonstrated that efficient direct en-yne metathesis of strained macrocyclic systems is possible using highly active Grubbs-Hoveyda catalysts and when exploiting fluoroarene-arene interactions. This interaction is effective even under high reaction temperatures and in the presence of a competitive π-rich solvent such as toluene. These results suggest that efficient π-π stacking displayed in a variety of solvents for both the pentafluorophenyl[24b] and 3,5-bis(trifluoromethyl)phenyl groups could prove valuable in the design of new catalysts and ligands in asymmetric catalysis. In

macrocyclization reactions, the yields of cyclophane products are comparable or better than those previously obtained via macrocyclic olefin metathesis, despite the fact that the 1,3-diene functionality resulting from en-yne metathesis creates a rigidified ansa-bridge with restricted rotation. The 3,5-bis(trifluoromethyl)benzyl conformational control elements provide higher yields and greater *E*-selectivity in the macrocyclic en-yne metathesis. Although "indirect" en-yne metathesis has been shown to afford higher yields of metathesis products with high *E*-selectivities, the 3,5-bis(trifluoromethyl)benzyl gearing elements are a rare display of an auxiliary capable of effecting "direct" en-yne metathesis macrocyclization with similarly high yields and *Z*:*E* selectivities. The efficient gearing of the macrocyclization substrates has been investigated through molecular modeling and suggests that both lp-π and π-π-interactions can be responsible for productive macrocyclization. Although study of the nature of lp-π interactions has attracted interest, the macrocyclizations described here demonstrate a practical application of these noncovalent interactions. Energetic differences of ~1 kcal between conformations believed to be responsible for macrocyclization can result in significant increases in product yields. It is expected that chiral auxiliaries based upon the pendant pentafluorobenzyl ester moiety could be devised to construct enantio-enriched paracyclophanes that could be applied toward the asymmetric preparation of members of the longithorone family of natural products. Given the importance of π-π interactions in catalysis and asymmetric synthesis, the fluoroarene-arene conformational control strategy should find application in other macrocyclization reactions and synthetic applications.

Acknowledgment

We thank the National Science and Engineering Research Council of Canada (NSERC), the FQRNT (Quebec), the Canadian Foundation for Innovation (CFI), Boehringer Ingelheim Ltd. (Canada), Merck Frosst, and the Universite de Montreal for generous financial support.

Supporting Information Available

General procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and notes

[1] For reviews on macrocyclization in synthesis, see: (a) Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, *10*, 1949-1964. (b) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4632-4653. c) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115-2134. (d) Laughrey, Z. R.; Gibb, B. C. *Top. Curr. Chem.* **2005**, *249*, 67-125.

[2] a) Shu, Y. Z. *J. Nat. Prod.* **1998**, *61*, 1053-1071. b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215-234. c) Fürstner, A. *Eur. J. Org. Chem.* **2004**, *5*, 943-958. d) Van de Weghe, P.; Eustache, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1495-1519.

[3] For some examples of macrocyclization reactions that do create stereocenters, see: a) Doyle, M. P.; Hu, W.-H. *Chin. J. Chem.* **2001**, *19*, 22-29. b) Doyle, M. P.; Hu, W.; Phillips, I. M.; Wee, A. G. *Org. Lett.* **2000**, *2*, 1777-1779. c) Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839-8847.

[4] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

[5] For other examples of procedures for macrolactonization, see: Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106-15107.

[6] a) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156-13157. b) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297-4307.

[7] a) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598-13610. b) Trost, B. M.; Matsubara, S.; Caringi, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8745-8746.

[8] a) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086-6101. b) Ghosh, S.; Ghosh, S.; Sarkar, N. *J. Chem. Sci.* **2006**, *118*, 223-235.

[9] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490-4527.

[10] Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122-5128.

[11] For an example of a switch in synthetic strategy due to macrocyclic ring strain, see: a) Leonard, M. S.; Carroll, P. J.; Joullie, M. M. *J. Org. Chem.* **2004**, *69*, 2526-2531. b) Bressy, C.; Piva, O. *Synlett* **2003**, 87-90. c) Liu, X.-X.; Pilarinou, E.; McLaughlin, J. L. *Tetrahedron Lett.* **1999**, *40*, 399-402. d) Sabitha, G.; Swapna, R.; Babu, R. S.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6145-6148.

[12] Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601-3605.

[13] a) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912-1915. b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.

[14] a) Mortreux, A.; Coutelier, O. *J. Mol. Catal. A: Chem.* **2006**, *254*, 96-104. b) Furstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307-2320. c) Mulzer, J.; Oehler, E. *Top. Organomet. Chem.* **2004**, *13*, 269-366.

[15] a) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762-5763. b) Diver, S. T. *J. Mol. Catal. A: Chem.* **2006**, *254*, 29-42. c) Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444-7457. d) Randl, S.; Lucas, N.; Connon, S. J.; Blechert, S. *Adv. Synth. Catal.* **2002**, *344*, 631-633. e) Sashuk, V.; Grela, K. *J. Mol. Catal. A: Chem.* **2006**, *257*, 59-66.

[16] a) Clark, D. A.; Kulkarni, A. A.; Kalbarczyk, K.; Schertzer, B.; Diver, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 15632-15636. b) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509-519. c) Peppers, B. P.; Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2006**, *8*, 2539-2542.

d) Maifeld, S. V.; Lee, D. *Chem.-Eur. J.* **2005**, *11*, 6118-6126. e) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382. f) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1-18.

[17] a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074-15080. b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582-9583.

[18] Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826-2830.

[19] Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582-3603.

[20] For other examples of the use of substituted methylenes as gearing elements, see: (a) Commeureuc, A. G. J.; Murphy, J. A.; Dewis, M. L. *Org. Lett.* **2003**, *5*, 2785-2788. (b) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601-2604.

[21] a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773-775. b) Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12036-12041.

[22] a) Fu, X.; Ferreira, M. L. G.; Schmitz, F. J. *J. Nat. Prod.* **1999**, *62*, 1306-1310. b) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 158-160. c) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810-3819. d) Fu, X.; Hossain, M. B.; van der Helm, D.; Schmitz, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12125-12126.

[23] Kato, T.; Nagae, K.; Hoshikawa, M. *Tetrahedron Lett.* **1999**, *40*, 1941-1944.

[24] a) El-Azizi, Y.; Schmitzer, A.; Collins, S. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 968-973. b) Collins, S. K.; El-Azizi, Y. *Pure Appl. Chem.* **2006**, *78*, 783-789.

[25] Marsella, M. J.; Wang, Z.-Q.; Reid, R. J.; Yoon, K. *Org. Lett.* **2001**, *3*, 885-887.

[26] For application of perfluoroarene-arene interactions in biological systems, see: a) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651-669. b) Waters, M. L. *Curr. Opin. Chem. Biol.* **2002**, *6*, 736-741. c) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210-1250. For a selection of other studies on perfluoroarene-arene interactions and their applications, see:

d) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003-1022. e) Bacchi, S.; Benaglia, M.; Cozzi, F.; Demartin, F.; Filippini, G.; Gavezzotti, A. *Chem.-Eur. J.* **2006**, *13*, 3538-3546. f) Vanspeybrouck, W.; Herrebout, W. A.; van der Veken, B. J.; Lundell, J.; Perutz, R. N. *J. Phys. Chem. B* **2003**, *107*, 13855-13861. g) Collings, J. C.; Roscoe, K. P.; Thomas, R. L.; Batsanov, A. S.; Stimson, L. M.; Howard, J. A. K.; Marder, T. B. *New J. Chem.* **2001**, *25*, 1410-1417. h) Kilbinger, A. F. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1563-1566. i) Adams, H.; Blanco, J. L. J.; Chessari, G.; Hunter, C. A.; Low, C. M. R.; Sanderson, J. M.; Vinter, J. G. *Chem.-Eur. J.* **2001**, *16*, 3494-3503.

[27] a) Gorske, B. C.; Blackwell, H. E. *J. Am. Chem. Soc.* **2006**, *128*, 14378-14387. b) Woll, M. G.; Hadley, E. B.; Mecozzi, S.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 15932-15933.

[28] Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

[29] Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184-8185.

[30] a) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999-8016. b) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475-497.

[31] See Supporting Information for details.

[32] Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187-190.

[33] At high temperatures or prolonged heating, migration of the alkene to form a more substituted olefin can occur. Subsequent metathesis would result in the loss of propene during the reaction. The products can be very difficult to separate; see ref 3a. For another example of the loss of propene during a macrocyclization, see: Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635-8638.

[34] Wojtkielewicz, A.; Morzycki, J. W. *Org. Lett.* **2006**, *8*, 839-842.

[35] The methylene signals of the ansa-bridge are also observed to be diastereotopic. In addition, several methylene signals can sometimes be observed resonating between 0.5-1 ppm. This shielding effect has been observed in other rigid macrocycles. See: Fürstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281-8286.

[36] Yamada, S.; Morimoto, Y. *Tetrahedron Lett.* **2006**, *47*, 5557-5560.

[37] For examples of the use of the CF_3 group in catalysis and biological chemistry, see: a) Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3839-3842. b) Yang, L.; Zhou, C.; Guo, L.; Morriello, G.; Butora, G.; Pasternak, A.; Parsons, W. H.; Mills, S. G.; MacCoss, M.; Vicario, P. P.; Zweerink, H.; Ayala, J. M.; Goyal, S.; Hanlon, W. A.; Cascieri, M. A.; Springer, M. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3735-3739. c) Vargas, A.; Hoxha, F.; Bonalumi, N.; Mallat, T.; Baiker, A. *J. Catal.* **2006**, *240*, 203-212. d) Diezi, S.; Ferri, D.; Vargas, A.; Mallat, T.; Baiker, A. *J. Am. Chem. Soc.* **2006**, *128*, 4048-4057. e) Betageri, R.; Zhang, Y.; Zindell, R. M.; Kuzmich, D.; Kirrane, T. M.; Bentzien, J.; Cardozo, M.; Capolino, A. J.; Fadra, T. N.; Nelson, R. M.; Paw, Z.; Shih, D.-T.; Shih, C.-K.; Zuvela-Jelaska, L.; Nabozny, G.; Thomson, D. S. *Bioorg. Med. Chem.*

Lett. **2005**, *15*, 4761-4769. f) Guiu, E.; Caporali, M.; Munoz, B.; Muller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, *25*, 3102-3104. g) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432-5446.

[38] Allen, A. D.; Kwong-Chip, J. M.; Mistry, J.; Sawyer, J. F.; Tidwell, T. T. *J. Org. Chem.* **1987**, *52*, 4164-4171.

[39] Vehlow, K.; Maechling, S.; Blechert, S. *Organometallics* **2006**, *25*, 25-28.

[40] We have not yet identified which is the major isomer. However, we tentatively assign the major isomer as being the *Z*-isomer, on the basis of the tendency to favor the *Z*-isomer in the formation of all other [12]paracyclophanes reported herein. Interestingly, during ^{1}H NMR studies aimed at identifying the *Z*-isomer, **41A** was heated at 110 °C in DMF-d_7 overnight and no degradation was observed with only minor coalescence of the ^{1}H NMR signals.

[41] Although the model systems in our study contain two olefinic side chains instead of an alkyne and alkene side chain, this minor structural change is unlikely to alter the solution-state conformations in a significant manner.

[42] a) Gung, B. W.; Amicangelo, J. C. *J. Org. Chem.* **2006**, *71*, 9261-9270. b) Martin, C. B.; Mulla, H. R.; Willis, P. G.; Cammers-Goodwin, A. *J. Org. Chem.* **1999**, *64*, 7802-7806.

[43] a) Watt, S. W.; Dai, C.; Scott, A. J.; Burke, J. M.; Thomas, R. L.; Collings, J. C.; Viney, C.; Clegg, W.; Marder, T. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3061-3063. b)

Collings, J. C.; Roscoe, K. P.; Robins, E. G.; Batsanov, A. S.; Stimson, L. M.; Howard, J. A. K.; Clark, S. J.; Marder, T. B. *New J. Chem.* **2002**, *26*, 1740-1746. c) Collings, J. C.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Can. J. Chem.* **2006**, *84*, 238-242. d) Collings, J. C.; Batsanov, A. S.; Howard, J. A. K.; Dickie, D. A.; Clyburne, J. A. C.; Jenkins, H. A.; Marder, T. B. *J. Fluorine Chem.* **2005**, *126*, 515-519. e) Collings, J. C.; Burke, J. M.; Smith, P. S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Org. Biomol. Chem.* **2004**, *2*, 3172-3178.

[44] Doyon, J. B.; Jain, A. *Org. Lett.* **1999**, *1*, 183-186.

[45] a) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 7232-7237. b) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 3641-3644.

[46] a) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103-105. b) Scheiner, S.; Kar, T.; Pattanayak, J. *J. Am. Chem. Soc.* **2002**, *124*, 13257-13264.

[47] a) Koch, W.; Holthausen, M. C. In *A Chemist's Guide to Density Functional Theory;* Wiley-VCH: Weinheim, 2002. b) Burke, K.; Werschnik, J.; Gross, E. K. U. *J. Chem. Phys.* **2005**, *123*, 062206.

[48] Accurate ab initio studies of aromatic clusters must include electron correlation to obtain good representations of dispersion and electrostatic forces that are responsible for conformation stability. Because of the large size of the molecules in question, high-level treatment of electron correlation or the use of large basis sets was precluded.

[49] Calculations were performed using *Hyperchem*, version 7.5; Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.

[50] Moeller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618-622.

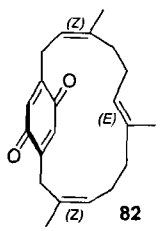
[51] We have assigned the compound numbers **5-S*** and **5-O*** to these conformers obtained from DFT analysis to distinguish them from those of an earlier study obtained from MP2 analysis that were assigned the compound numbers **5-S** and **5-O**.

[52] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

Chapitre 5 : Études synthétiques vers la longithorone

1. Application de la RRCM à la construction du corps macrocyclique de la longithorone C

Le but de ces études est de tester la viabilité de notre stratégie RRCM des oléfines en présence d'un élément de contrôle conformationnel pour la construction du corps macrocyclique de la longithorone C dans lequel les trois doubles liaisons ont une stéréochimie bien définie (figure 5.1).



82

Figure 5.1 : La longithorone C.

En effet, tel que discuté dans le chapitre précédent, la modélisation moléculaire nous a permis de prédire que lors du passage d'un substrat modèle à un substrat tout carbone les préférences qu'ont nos substrats pour les arrangements empilés pouvaient être conservées et que les deux auxiliaires 3,5-bis(trifluorométhyl)phényle et 2,3,4,5,6-pentafluorophényle avaient grossièrement les mêmes effets stabilisateurs.

Toutefois, nous ne savions pas si ces interactions allaient vaincre la tension de cycle due à la présence des trois doubles liaisons trisubstituées dans le noyau paracyclophane, et

nous ne savions pas non plus si dans les conditions de la métathèse ces doubles liaisons n'allaient pas être engagées dans des processus non productifs. Ces études font suites à des études modèles effectuées par Joseph Zakarian[1] dans lesquelles il a montré qu'il était possible de former par RRCM un [14]paracyclophane comportant une portion carbonée ressemblant à celle de la longithorone C. Le rendement obtenu dans les conditions optimisées (schéma 5.1) est de 33%. L'utilisation du catalyseur de Grubbs II sans additif ($Ti(O\textit{i}\text{-}Pr)_4$) fournissait un moins bon rendement, et l'utilisation d'un catalyseur plus actif tel que Hoveyda-Grubbs II donnait un rendement de 20% seulement. Le produit **152** dans lequel la portion relais a été consumée, a été observé comme étant le produit majoritaire de cette réaction.

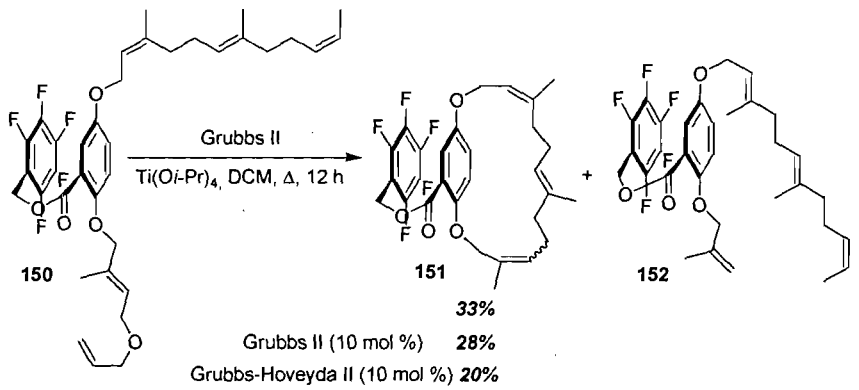


Schéma 5.1: RRCM sur un composé modèle ressemblant la longithorone C.

[1] Joseph Zakarian, mémoire de maîtrise, **2006**, Université de Montréal.

Article 4

Joseph E. Zakarian, Yassir El-Azizi and Shawn K. Collins*

Exploiting Quadrupolar Interactions in the Synthesis of the Macrocyclic Portion of Longithorone C

Org. Lett. **2008**, *10*,.2927.

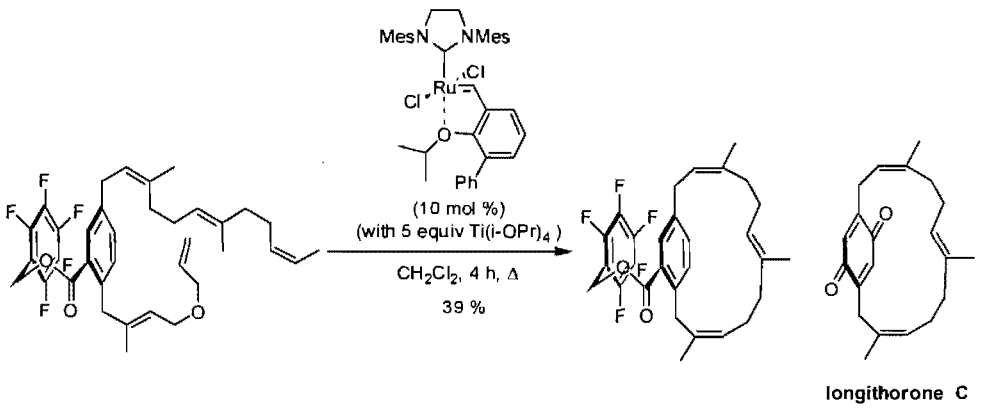
- Toutes les synthèses préliminaires et les caractérisations des molécules et intermédiaires rapportées dans le schéma 2 et dans le tableau 1 de cet article ont été effectuées pas Joseph Zakarian.
- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées dans le schéma 1, ainsi que les optimisations des conditions et rendements de la chimie représentés sur le schéma 2 et dans le tableau 1 de cet article ont été effectuées par l'auteur.
- Toutes les modélisations moléculaires rapportées dans cet article ont été effectuées par la Professeure Schmitzer.

Joseph E. Zakarian, Yassir El-Azizi and Shawn K. Collins*

Exploiting Quadrupolar Interactions in the Synthesis of the Macrocyclic Portion of Longithorone C

Department of Chemistry, Université de Montréal, C.P. 6128 Station Downtown, Montréal, Québec, CANADA H3C 3J7

[redacted]



2,3,4,5,6-Pentafluorobenzyl and 3,5-bistrifluoromethylbenzyl ester auxiliaries can enable difficult macrocyclizations to afford rigid all-carbon paracyclophanes. The effectiveness of these auxiliaries has been demonstrated in preparing the carbon skeleton of the macrocyclic natural product longithorone C.

Longithorone C, **1**, is a farnesylated quinone and a member of the longithorone family of natural products isolated in 1999 by Schmitz and co-workers from the marine tunicate *Aplodium longithorax*.[1] Longithorone C, like most members of the family, possesses a macrocyclic [12]paracyclophane skeleton (Figure 1). The macrocycle, which resembles a *cis*-farnesol unit wrapped about a quinone core, exhibits restricted rotation which imparts an element of planar chirality to the structure.[1a] Although no biological activity for longithorone C has been reported, longithorone A has been shown to display cytotoxicity against P388 murine leukemia cells (IC_{50} ~10 μg mL^{-1}) and longithorone J has displayed minimal activity in some human cells lines.[2] To demonstrate the rigidity of the skeleton of longithorone C, Schmitz and co-workers refluxed 1 in toluene for 7 days; some degradation was observed, but the optical rotation remained unchanged.[1a] Few synthetic studies directed towards the synthesis of these macrocyclic natural products have been reported, perhaps denoting the significant synthetic challenge associated with constructing the planar chiral carbon skeleton. Kato et al. have reported on the synthesis of longithorone B[3] and Shair and co-workers have prepared a dimeric member of the longithorone family, longithorone A.[4] Herein we report the first application of auxiliaries that engage in quadrupolar interactions in a total synthesis objective: the preparation of the macrocyclic portion of longithorone C.

---

(1) For the isolation of longithorone C see: (a) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810-3819. For the isolation of other family members see: (b) Fu, X.; Ferreira, M. L.; Schmitz, F. J. *J. Nat. Prod.* **1999**, *62*, 1306-1310. (c) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 158-160. (d) Fu, X.; Hossain, M. B.; van der Helm, D.; Schmitz, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12125-12126.

(2) Davis, R. A.; Carroll, A. R.; Watters, D.; Quinn, R. J. *Nat. Prod. Res., Part B* **2006**, *20*, 1277-1282.

(3) Kato, T.; Nagae, K.; Hoshikawa, M. *Tetrahedron Lett.* **1999**, *40*, 1941-1944.

(4) (a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773-775. (b) Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12036-12041.

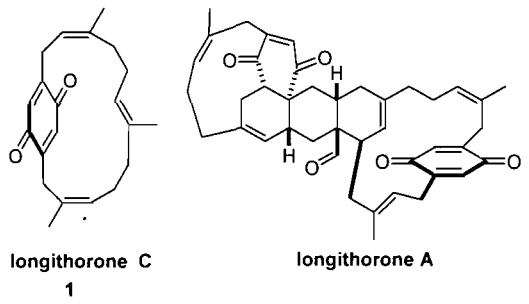


Figure 1. Representative members of the longithorone family of natural products.

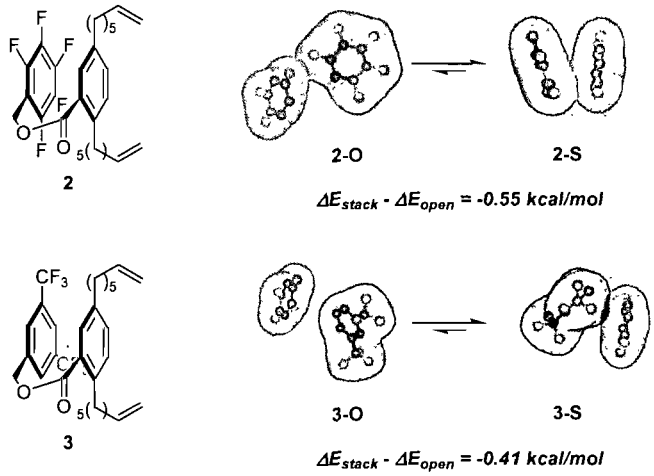


Figure 2. Comparison of Pentafluorobenzyl and 3,5-bistrifluoromethylbenzyl Ester Auxiliaries by Molecular Modelling.

The synthetic challenge of preparing extremely rigid macrocycles, such as the [12]paracyclophane core of longithorone C, in an efficient and asymmetric fashion encouraged us to develop new methods for enabling difficult macrocyclizations.[5] In 2006, we reported the use of perfluorobenzyl ester auxiliaries as conformational control elements for macrocyclizations using olefin metathesis.[6] In 2007,

(5) Some difficult macrocyclizations have been aided by the use of substituted methylenes as gearing elements. See reference 4 and: (a) Commeureuc, A. G. J.; Murphy, J. A.; Dewis, M. L. *Org. Lett.* **2003**, *5*, 2785-2788. (b) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601-2604.

(6) (a) El-azizi, Y.; Schmitzer, A.; Collins, S. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 968-973. (b) Collins, S. K.; El-Azizi, Y. *Pure Appl. Chem.* **2006**, *78*, 783-789.

we reported that 3,5-bistrifluoromethylbenzyl ester auxiliaries were also effective and demonstrated their utility in en-yne metathesis macrocyclizations.[7] The fluoroarene auxiliaries are believed to engage in non-covalent interactions with the macrocyclic precursors, coercing the substrate into a conformation conducive to ring closure.[8]

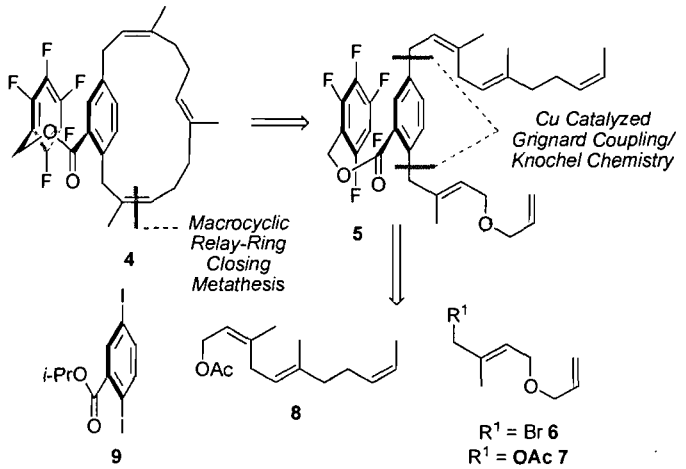


Figure 3. Retrosynthetic analysis of the carbon skeleton of longithorone C.

Our initial studies into the use of these auxiliaries were conducted using substrates that contained oxygen atoms attached to the arene core that would become part of the formed macrocycle. We had reported that molecular modelling studies suggested that the fluorinated rings of the auxiliaries engage in lp-π interactions with the lone pairs of the oxygen atoms, resulting in a preference for a "closed"

(7) Collins, S. K.; El-Azizi, Y.; Schmitzer, A. R. *J. Org. Chem.* **2007**, *72*, 6397-6408.

(8) For some recent uses of quadrupolar interactions see: (a) Marsella, M. J.; Wang, Z.-Q.; Reid, R. J.; Yoon, K. *Org. Lett.* **2001**, *3*, 885-887. (b) Gorske, B. C.; Blackwell, H. E. *J. Am. Chem. Soc.* **2006**, *128*, 14378-14387. (c) Woll, M. G.; Hadley, E. B.; Mecozzi, S.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, 15932–15933. (d) Watt, S. W.; Dai, C.; Scott, A. J.; Burke, J. M.; Thomas, R. L.; Collings, J. C.; Viney, C.; Clegg, W.; Marder, T. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3061–3063. (e) Collings, J. C.; Batsanov, A. S.; Howard, J. A. K.; Dickie, D. A.; Clyburne, J. A. C.; Jenkins, H. A.; Marder, T. B. *J. Fluorine Chem.* **2005**, *126*, 515–519. (f) Collings, J. C.; Burke, J. M.; Smith, P. S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Org. Biomol. Chem.* **2004**, *2*, 3172–3178.

conformation that is conducive to ring closure.[6,9] The molecular modelling studies also suggested that the 3,5-bistrifluoromethylbenzyl ester auxiliaries would be more effective in these model substrates. This hypothesis was also proven correct through experiment.[7] However, in the absence of oxygen containing substrates, like those found in the longithorone family of natural products, the molecular modelling studies suggested that the pentafluorobenzyl auxiliary would be more effective (Figure 2). Molecular modelling suggested that the ester **2** would prefer a conformation **2-S** in which a quadrupolar interaction would be present, over the conformation **2-O** by -0.55 kcal/mol.[10] Similarly, the ester **3** would also prefer conformation **3-S** over **3-O**, however, only by -0.41 kcal/mol.[7] To investigate whether the molecular modelling studies could be used to predict which auxiliaries would be more effective for a given substrate, we undertook the synthesis of the carbon skeleton of longithorone C to probe the efficiency of our auxiliaries and the results of the previous molecular modelling study.

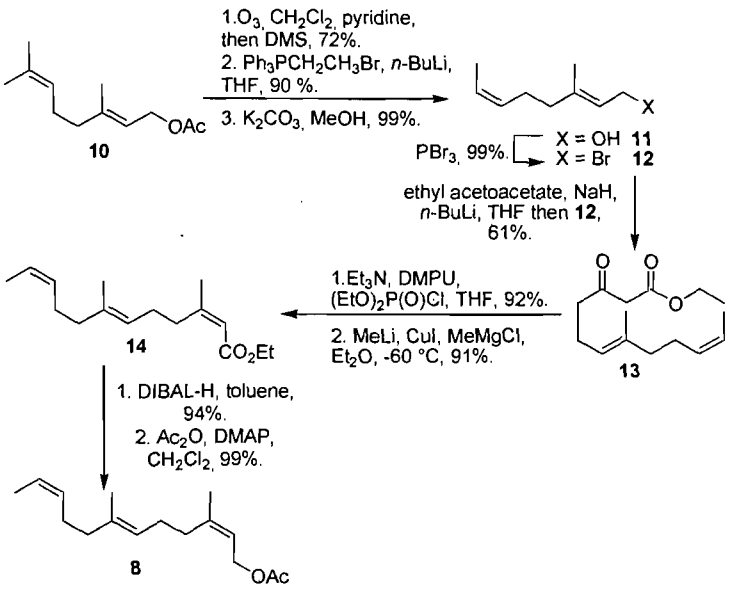
Hence, the carbon skeleton of longithorone C, represented by **4**, could arise from a macrocyclic relay ring closing metathesis (RRCM)[11] of ester **5**. The preparation of the macrocyclization precursor **5** required the installation of two carbon-arene bonds. We envisioned preparing these bonds through copper catalyzed Grignard reactions, made possible by combining recent methods for Mg-I exchanges with copper catalyzed allylic couplings. As such, the three key carbon subunits necessary are the allylic electrophiles **6, 7** and **8**, and the iso-propyl ester **9**.

---

(9) (a) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005** *70*, 7232–7237. (b) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 3641-3644.

(10) For a recent molecular modelling study on quadrupolar interactions with pentafluorobenzenes see: Gung, B. W.; Amicangelo, J. C. *J. Org. Chem.* **2006,** *71*, 9261–9270.

(11) (a) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915. (b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.



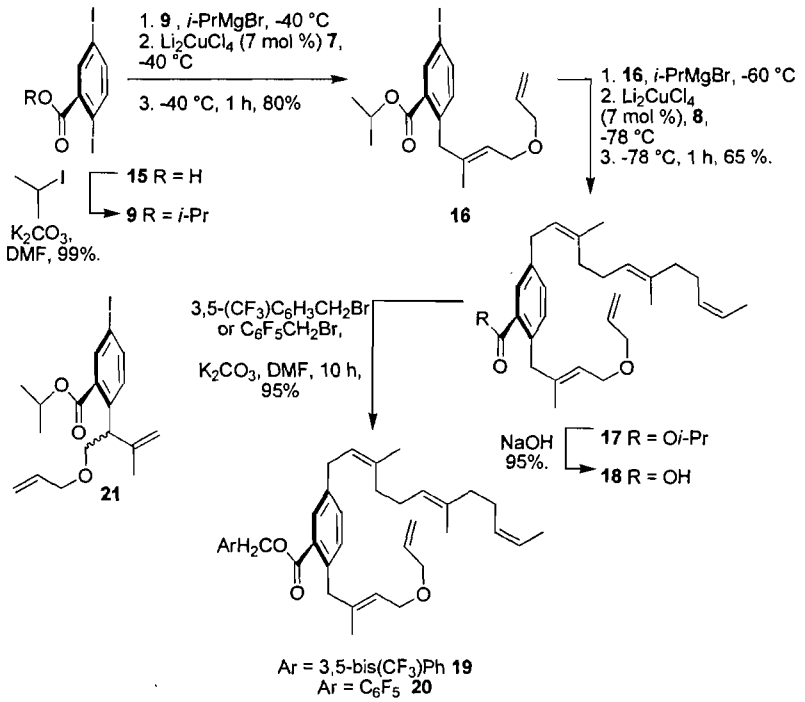
Scheme 1

The preparation of sidechains **6** and **7** have been previously reported.[12] The synthesis of sidechain **8** was adapted from a previous report on the synthesis of *cis*-farnesol.[13] Geranyl acetate **10** underwent selective ozonolysis producing the corresponding aldehyde in good yield (72 %). Wittig reaction using the ylide generated from *n*-BuLi and ethyltriphenylphosponium bromide followed by cleavage of the acetate protecting group afforded alcohol **11**. The alcohol **11** was subsequently converted to the corresponding bromide **12** in quantitative yield upon treatment with PBr_3. The bromide **12** was reacted with the Weiler dianion of ethyl acetoacetate to afford the β-ketoester **13**. The corresponding phosphonate was formed from the enolate of **13** generated from NEt_3 in the presence of DMPU in 69 % yield. Upon treatment of the phosphonate with the cuprate generated from a mixture of MeMgCl, MeLi

(12) Amslinger, S.; Kis, K.; Hecht, S.; Adam, P.; Rohdich, F.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Org. Chem.* **2002**, *67*, 4590-4594.

(13) (a) Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker T. J.; *J. Org. Chem.* **2002**, *67*, 8079-8085. (b) Gibbs, R. A.; Eummer, J. T.; Shao, Y. *Org. Lett.* **1999**, *1*, 627-630. For an alternative synthesis of *cis*-farnesol see : (c) Yu, J. S.; Kleckley, T. S.; Wiemer, D. F. *Org. Lett.* **2005**, *7*, 4803-4806.

and CuI, the ester **14** was obtained in 91 % yield and only the *cis*-isomer was observed by ^{1}H NMR. The reduction of **14** with DIBAL-H and subsequent acetylation afforded the sidechain **8**.



Scheme 2

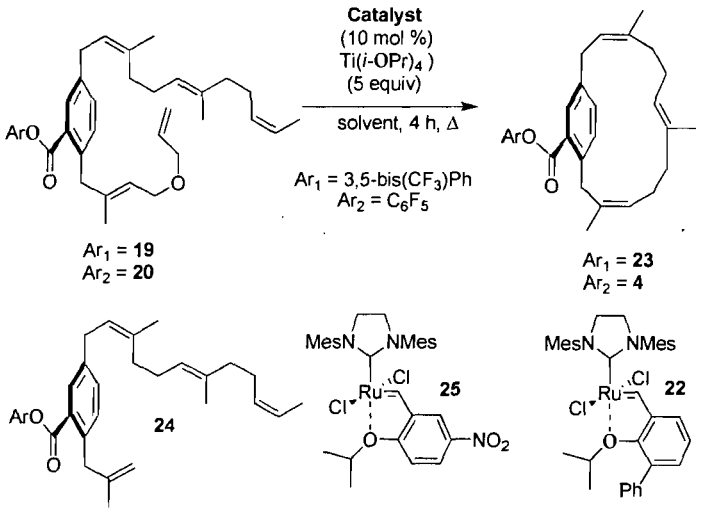
The assembly of the carbon skeleton of longithorone C, **4**, began with the esterification of 2,5-diiodobenzoic acid with 2-iodopropanol. The ester **9** was used in the subsequent copper-catalyzed Grignard reactions. The corresponding methyl esters or pentafluorobenzyl esters of **15** were incompatible in the following Mg-I exchange reaction, where the esters normally underwent competitive nucleophilic attack.[14] Treatment of ester **9** with *i*-PrMgBr at -40 °C lead to complete Mg-I

(14) For leading references on the Mg-I exchange see : (a) Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302-4320. (b) Rottlander, M.; Boymond, L.; Berillon, L.; Lepretre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Queguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767-770. (c) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565-569. (d) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun* **2006**, 583-593. (e) Krasovskiy, A.; Knochel, P.

exchange in 10 minutes. A solution of the newly formed Grignard reagent was added to a solution of acetate **7** and a catalytic amount of Li_2CuCl_4 catalyst.[15] Following work-up, the iodide **16** was isolated in 80 % yield. The configuration of the benzylic olefin in **16** was confirmed through an NOE study and was found to be identical to the configuration in acetate **7**. Other copper catalysts surveyed (CuI, CuCN·LiCl) resulted in very low yields (<20 %) of **16**. The use of an allylic bromide **6** as a coupling partner resulted in a 45 % isolated yield of the iodide **16**. All attempts to adjust the reaction conditions using bromide **6** as the coupling partner resulted in inseparable mixtures of **16** and **21**. Consequently, the acetate **8** was used in the second copper catalyzed coupling reaction.

Angew. Chem., Int. Ed. **2004**, *25*, 3333-3336. (f) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *27*, 159-162.

(15) For references on transmetallation to Cu and subsequent coupling see: (a) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Queguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767-770. (b) Bäckvall, J.E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615-6621.



substrate	cat.	solvent	yield (%) [a]
20	**25**	PhMe	32
20	**22**	CH_2Cl_2	37
19	**25**	PhMe	20
19	**25**	CH_2Cl_2	23

[a] Represents isolated yield after chromatography.

Table 1. Macrocyclization to Form the Carbon Skeleton of Longithorone C.

The Mg-I exchange in **16** was considerably more difficult. The absence of the ester functional group *ortho* to the iodide in **16** necessitated a larger quantity of *i*-PrMgBr and lower temperatures to effect a clean and quantitative Mg-I exchange. Following a similar protocol as described above, the acetate **8** was added and the product **17** was isolated in 65 % yield. It was necessary to keep the reaction mixture as concentrated as possible to maximize the yields. It should be noted that the use of *i*-PrMgCl·LiCl promoted an extremely rapid exchange, however, the yields of **17** were unexplicably low (<10 %).

To investigate the macrocyclization with both the pentafluorobenzyl ester and 3,5-bistrifluoromethylbenzyl ester auxiliaries, the esters **19** and **20** were synthesized and their

macrocyclization investigated using both the Grela catalyst **25**[16] and the Blechert catalyst **22**.[17] To construct the fluorinated esters, the iso-propyl ester **17** was first saponified using NaOH in refluxing MeOH/PhMe to yield the corresponding carboxylic acid **18** in 95 % yield. Alkylation with the corresponding benzyl bromides afforded the esters **19** and **20** in excellent overall yields following purification by chromatography. Some decomposition of **20** was observed over time and it was usually stored in frozen benzene at -18 °C.

With the two esters **19** and **20** in hand, their macrocyclization was investigated (Table 1). It should be noted that three structural features of **19** and **20** are essential for successful macrocyclization. First, the relay ring closing metathesis strategy was necessary, otherwise only dimerization of the starting material was observed. Second, esters **19** and **20** were prepared with a *cis*-olefin as the metathesis partner. If this olefin was substituted for a terminal olefin, only trace amounts of the desired macrocycle were obtained. *Last, the use of any other ester other than the fluoroarenes discussed here resulted in the formation of only dimers and oligomers.*

Treatment of the pentafluorophenyl benzyl ester **20** with catalyst **25** in PhMe afforded a 32 % isolated yield of the rigid macrocycle **4**. Changing the solvent to CH_2Cl_2 and using the more reactive Blechert catalyst **22** afforded slightly higher yields of the corresponding macrocycle (37-40%). The ester **19** containing a bis-1,3-trifluoromethylbenzyl ester auxiliary did not afford higher yields than the corresponding pentafluorobenzyl ester **20**. Treatment of **19** with catalyst **25** in either CH_2Cl_2 or PhMe afforded 20-23 % yields of the isolated macrocycle. In all cases the reactions afforded **24** as the major product, where the relay ring closing metathesis sidechain has been consumed, but no productive macrocyclization has occurred. These results are in agreement with the molecular modelling results

(16) Bieniek, M.; Michrowska, A.; Gulajski, L.; Grela, K. *Organometallics* **2007**, *26*, 1096-1099.

(17) (a) Buschmann, N.; Wakamatsu, H.; Blechert, S. *Synlett* **2004**, 667-670. (b) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733-2736.

discussed earlier. The pentafluorobenzyl ester **2** was calculated to have only a slightly higher energetic preference for its "stacked" conformer **2-S** (~0.1 kcal/mol) compared to the 3,5-bistrifluoromethylbenzyl ester. Although this represents a seemingly small energetic difference, it accounts for approximately 20 % higher yields in the formation of macrocyclization products.

In summary, we have synthesized the highly rigid macrocyclic carbon skeleton of the natural product longithorone C. The synthesis of the carbon skeleton **4** highlights the effectiveness of quadrupolar interactions as synthetically useful non-covalent interactions capable of controlling the conformation of molecules for macrocyclization. The combination of Mg-I exchange and copper-catalyzed Grignard reactions allowed the stereocontrolled installation of the olefinic chains for macrocyclization. It is likely that this strategy would be of use in the preparation of other natural products. The success of these auxiliaries opens the way to the development of chiral gearing elements to induce atropisomerism.

Acknowledgment We thank the NSERC (Canada), FQRNT (Québec), CFI (Canada), Boehringer Ingelheim (Canada) Ltd., Merck Frosst Centre for Therapeutic Research, AstraZeneca and the Université de Montréal for generous financial support. The authors thank Sylvie Bilodeau (Université de Montréal) for help in acquiring the NMR spectra of **4**.

Supporting Information Available Experimental procedures and characterisation data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Chapitre 6: Passage aux auxiliaires avec une jonction amide

Objectifs

Nos études sur la macrocyclisation ène-yne de nos substrats modèles (chapitre 3) nous ont montré que le contrôle de la sélectivité *endo/exo* des macrocycles obtenus était parfait[1]. Mais, nous étions un peu déçus de ne pas pouvoir contrôler la sélectivité *E :Z*. Les études déjà rencontrées dans la littérature[2] et nos propres observations nous ont montré comment il était difficile de prédire et de contrôler les ratios *E :Z* des produits de macrocyclisation. En effet, lorsqu'on regarde de plus près les résultats publiés dans l'article 3, on se rend compte que l'effet que peut avoir l'auxiliaire de contrôle conformationnel est assez remarquable (schéma 6.1).

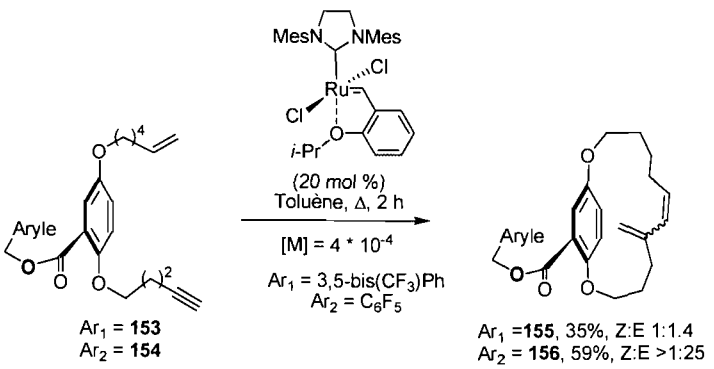


Schéma 6.1 : Résultats de RCM ène-yne avec différents auxiliaires.

[1] En effet, seuls les produits *endo* [12]paracyclophanes sont observés, les produits *exo* [11]paracyclophanes ne peuvent être formés car beaucoup plus rigides (donc thermodynamiquement moins favorisés) que les produits *endo*.

[2] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074.

Il faut dire que la seule différence entre les deux substrats **153** et **154** sur le schéma 6.1 est qu'ils portent des auxiliaires aryles différents. Le site de la RCM ène-yne est relativement loin du positionnement de cet aryle, il est donc surprenant que le ratio *Z:E* (1 :1.4 pour le cyclophane **155** et >1 :25 pour **156**) soit si dramatiquement influencé par la nature de l'auxiliaire.

Afin d'apprendre plus sur la façon que ces auxiliaires contrôlent la réaction de macrocyclisation, nous avons investigué l'influence du remplacement de la jonction ester de nos substrats modèles par une jonction amide.

Article 5

Yassir El-Azizi, Joseph E. Zakarian, Lisa Bouillerand, Andreea R. Schmitzer, Shawn K. Collins*.

Exploiting Noncovalent Interactions in Synthesis: Macrocyclization Employing Amide-Based Auxiliaries

Adv. Synth. Cat. **2008,** *350,* 2219.

- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées dans le schéma 2 de cet article ont été faites par Lisa Bouillerand sous la direction de l'auteur.
- Tous les résultats des substrats avec une fonction ester dans le schéma 4 de cet article ont été obtenus par Joseph Zakarian.
- Toutes les synthèses et les caractérisations des molécules et intermédiaires rapportées dans le schéma 3 et 5 ainsi que les résultats des substrats avec une fonction amide dans le schéma 4 de cet article ont été obtenus et faites par l'auteur.
- Toutes les modélisations moléculaires rapportées dans cet article ont été faites par la Professeure Schmitzer.
-

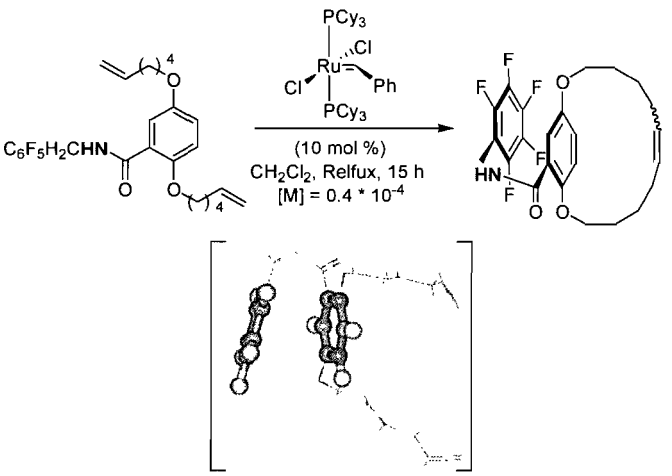
KEYWORDS cyclophane, natural product synthesis, macrocyclization, olefin metathesis, quadrupolar interactions.

Yassir El-Azizi, Joseph E. Zakarian, Lisa Bouillerand, Andreea R. Schmitzer, Shawn K. Collins*.

Exploiting Noncovalent Interactions in Synthesis: Macrocyclization Employing Amide-Based Auxiliaries.

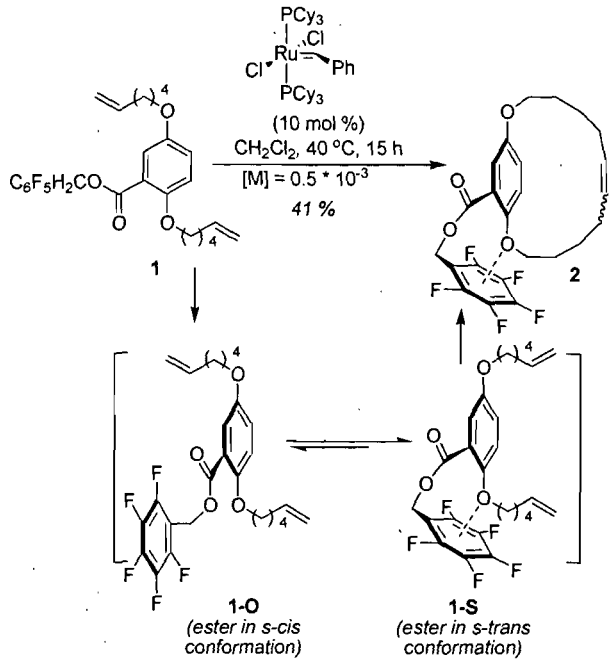
Department of Chemistry, Université de Montréal, C.P. 6128 Station Downtown, Montréal, Québec, CANADA H3C 3J7.

[redacted]



ABSTRACT Efficient macrocyclic olefin and en-yne metathesis can be conducted employing benzyl ester auxiliaries that engage in quadrupolar interactions. The use of amide linkers in place of esters results in higher overall yields. Computational studies suggest that amide auxiliaries stabilize conformers conducive to macrocyclization over 22 times more efficiently than an ester linkage. Molecular modelling studies also suggest a preference for engaging in quadrupolar interaction for the amide auxiliaries, in contrast to the lp-π interactions predicted for ester based auxiliaries.

The number of isolated biologically active macrocyclic natural products continues to expand, reinforcing the importance of developing new synthetic methods for macrocyclic compounds. Macrocyclization via olefin metathesis has evolved into one of the most efficient synthetic methods available to construct macrocycles.[1] However, in some cases the predisposition of the substrate towards macrocyclization can be difficult to overcome. This has been observed in the synthesis of macrolide natural products[2] as well as macrocyclic peptides.[3] In such cases, the availability of methodologies to enable macrocyclization becomes increasingly important. Recently our group disclosed that the formation of strained paracyclophane structures was possible using ester based auxiliaries.[4] We have demonstrated that these auxiliaries are effective in forming strained ring systems either by ring closing olefin or ring closing en-yne metathesis.[5] The auxiliaries can contain perfluorophenyl or bis-3,5-trifluoromethylphenyl groups which can engage in either lone-pair (lp):π[5] or π:π interactions[6] with the aromatic group of the substrate. These non-covalent interactions result in stabilizing conformations of the substrate that are conducive to ring closing. For example, molecular modelling investigations have suggested that the ester **1** can adopt an "open"-conformation **1-O**, whereby the auxiliary is extended and not involved in any non-covalent interactions with the central benzene ring. This conformer would exist in equilibrium favoring **1-S**, in which the perfluorophenyl ring is folded inwards and engages in a lone-pair:π interaction with oxygens connected to the central benzene ring. As a result of the lone-pair:π interaction, **1-S** is favored by –0.20 kcal/mol over **1-O**. It is remarkable that such small differences in energy can be responsible for the "gearing" of **1** towards productive macrocyclization.



Scheme 1. Macrocyclization to form [12]paracyclophanes mediated by a pentafluorobenzyl ester auxiliary.

In examining the structure of conformer **1-S**, we noticed that the ester was in the *s*-trans conformation. Therefore, we reasoned that further energy stabilization of conformers such **1-S** might be achieved through replacing the ester based auxiliary with an amide-based auxiliary, in an effort to favour an *s*-trans conformation in the auxiliary. These studies would also indicate whether the use of perfluorophenyl based auxiliaries could be applied to the synthesis of cyclic peptides, where an amide linker would likely be employed. Herein, we report the investigation of amide based auxiliaries for macrocyclization using both chemical synthesis and molecular modelling in parallel.

We decided to investigate the use of amide based auxiliaries for macrocyclization through molecular modelling using a model system similar to that used in our previous studies.[5] Previous reports of the stacking interactions of perfluoroarenes and other

arenes in the solid state point towards a preference for a face-to-face orientation.[7,8] However, our previous molecular modelling studies using a DFT geometric and energy analysis[9] suggested that a conformer exhibiting an oxygen lone pair: arene (lp:π) interaction[10,11] was responsible for the gearing of the system towards macrocyclization.

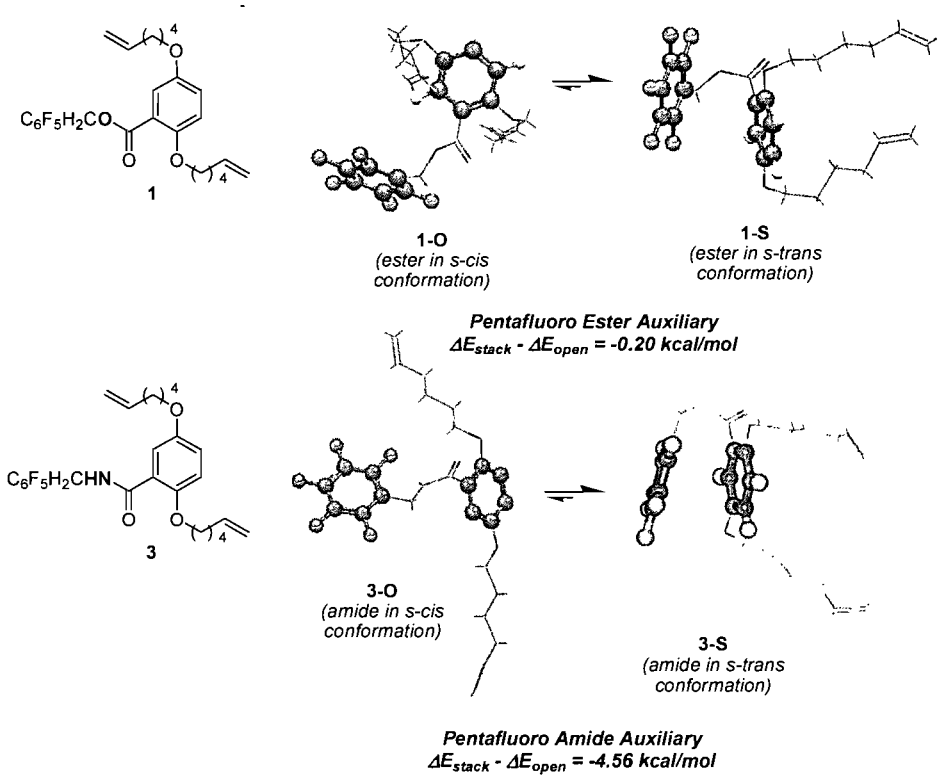


Figure 1. Molecular modelling of 1 and 3 to compare pentafluorobenzyl ester and amide auxiliaries.

DFT calculations showed that the conformer **1-S** was favored by -0.20 kcal/mol compared to the conformer **1-O**. As noted above, the auxiliary does not overlap efficiently with the arene core, instead opting to sit over the pendant oxygen atoms in these systems (Figure 1). The analysis of the analogous amide **3** was performed in the

following manner. Starting with the conformers obtained for **1-S** from AM1 calculations, the oxygen atom was exchanged for a NH group to give **3**. Subsequently, **3** was refined using AM1 level of theory in which only the torsion angles about the amide functionality were allowed to vary. The resulting conformers was then further refined via a DFT geometric and energy analysis. We again observed two distinct conformations, in which the "stacked" conformer **3-S** was preferred over the "open" conformer **3-O** by -4.56 kcal/mol (Figure 1). These calculations suggest that both stacked conformers **1-S** and **3-S** are preferred compared to their respective open conformers. The calculations suggest however, that the amide auxiliary stabilizes its respective stacked conformer (**3-S**) over 22 times more efficiently than the corresponding ester (**1-S**). This suggests that the conformer **3-S** is highly likely to predominate in solution and could result in higher yields in macrocyclization processes.

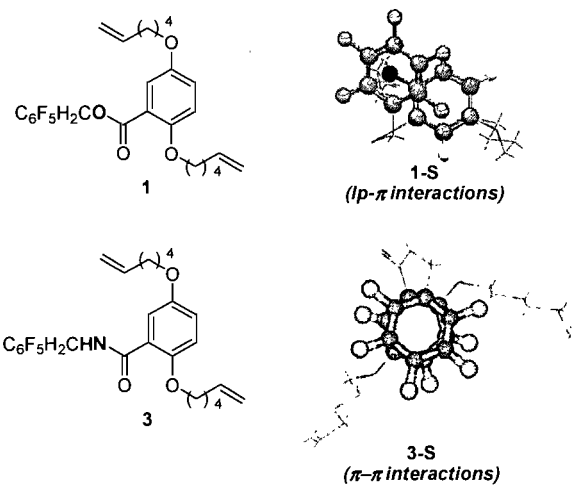
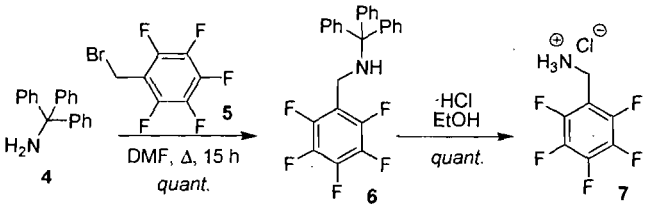


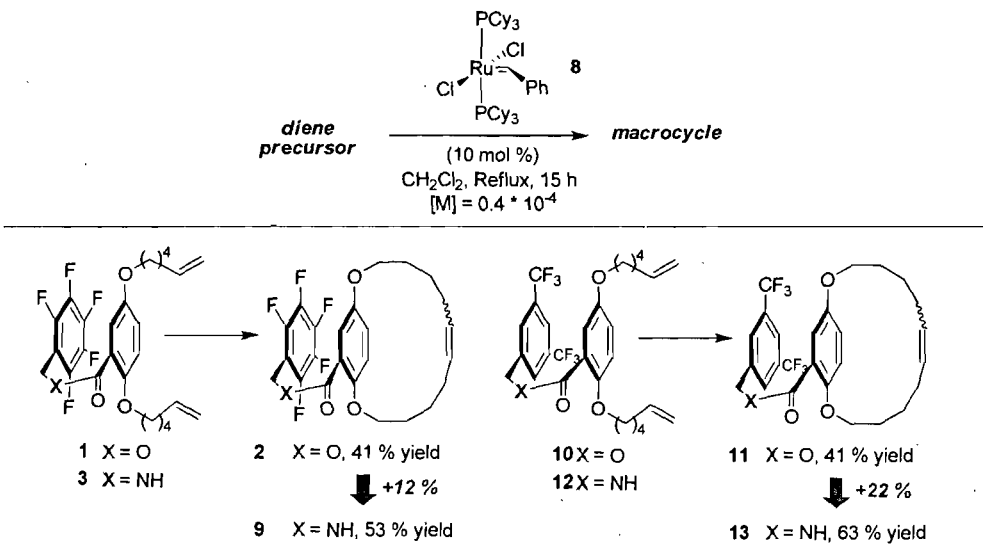
Figure 2. Calculations suggest that 1-S and 3-S are stabilized by different non-covalent interactions.

Interestingly, the molecular modelling calculations also suggest that the amide auxiliary would result in **3-S** engaging in π–π quadrupolar interactions and not lp-π interactions as was calculated for the ester conformer **1-S**. Figure 2 depicts the two different non-covalent interactions calculated for **1-S** and **3-S**. The switch in non-covalent interactions could be due to the added rigidity in **3-S** afforded by the amide auxiliary. We next decided to evaluate the amide based auxiliaries based on both 2,3,4,5,6-pentafluorobenzyl and 3,5-bis(trifluoromethyl)benzyl groups.[12] Synthesis of the respective amides (such as **3**) would most likely require access to both 1,3-bistrifluoromethylbenzyl amine, or 2,3,4,5,6-pentafluorophenylbenzyl amine. The former is commercially available,[13] and the latter has been previously prepared.[14] However, pentafluorophenylbenzyl amine has been observed to polymerize on standing and is volatile. As such, we developed a new protocol to access **7** starting from 2,3,4,5,6-pentafluorobenzyl bromide, **5** (Scheme 2). The displacement of bromide from **5** with tritylamine lead to amine **6** is quantitative yield. The trityl protecting group could be removed under acidic conditions and the corresponding HCl salt isolated via filtration. The HCl salt of **7** was observed to be bench stable for many months. The hydrochloride salt **7** was used in the synthesis of various amide precursors for their evaluation in macrocyclization.[15]



Scheme 2. Synthesis of 2,3,4,5,6-pentafluorobenzyl amine hydrochloride, 7.

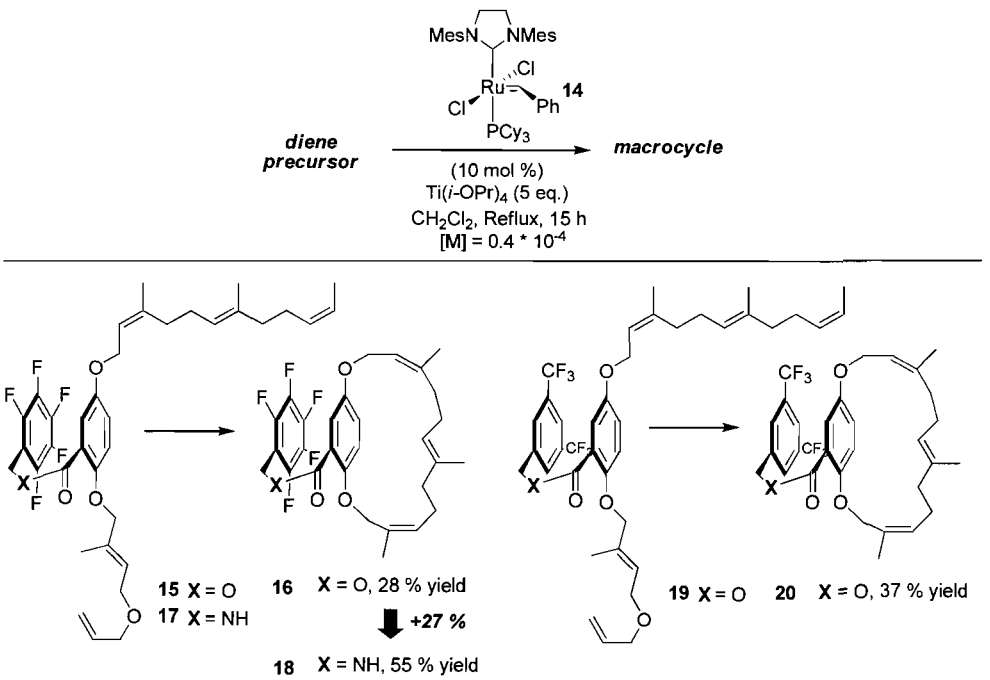
The amide based auxiliaries were first evaluated in olefin metathesis macrocyclizations; esters **1** and **10** and amides **3** and **12** were each subjected to identical macrocyclization conditions (Scheme 3). The ester **1** was found to afford the macrocycle **2** in 41% isolated yield.[4a] When the cyclization of amide **3** was performed, in which the ester linkage was replaced with an amide linkage, the corresponding macrocycle **9** was obtained in an improved yield of 53%, representing an increase of 12%. Increase in the isolated yield was also found with 3,5-bis(trifluoromethyl) benzyl auxiliaries. The 3,5-bis(trifluoromethyl) benzyl ester **10** afforded the [12]paracyclophane **11** in 41% yield upon macrocyclization. However, the corresponding amide **12** cyclized to give **13** in 63% yield - an increase of 22%!



Scheme 3. Evaluation of new amide auxiliaries in macrocyclic olefin metathesis.

The comparison of amides versus esters was also conducted with more challenging substrates, such as ester **15** (Scheme 4). Treatement of **15** with Grubbs 2nd generation

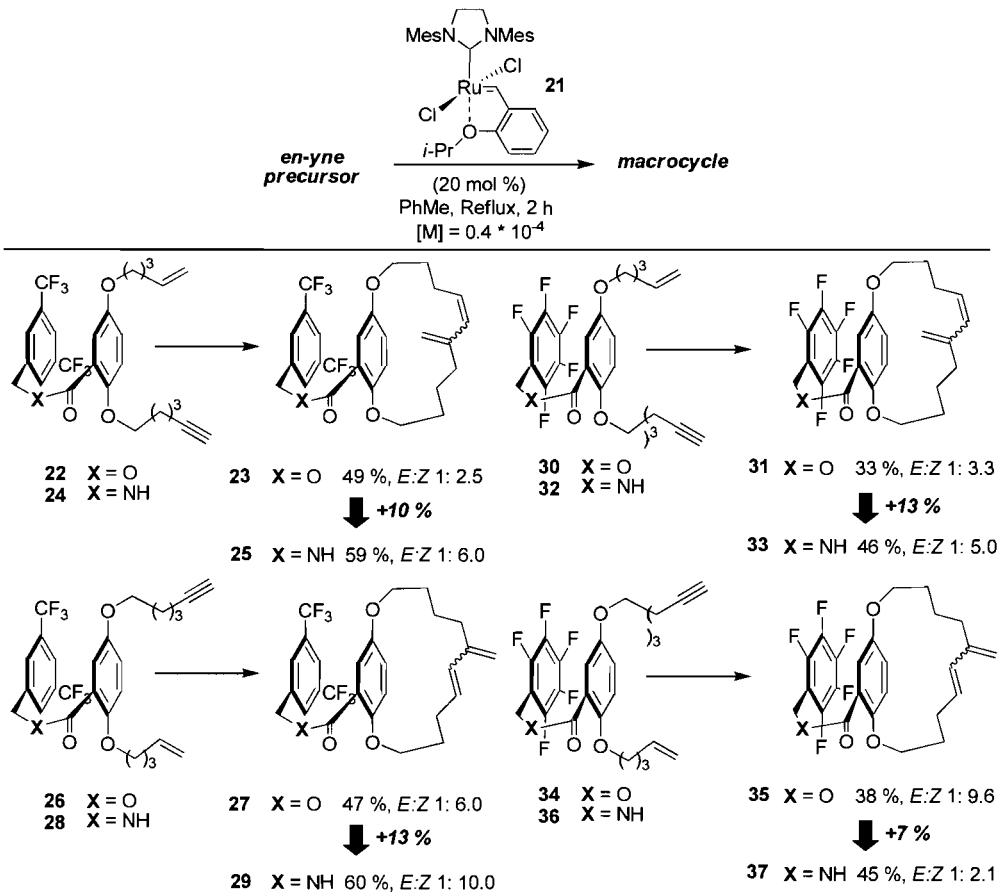
catalyst **14** forms a tri-substituted olefin and affords macrocycle **16** with a rigidified [14]paracyclophane skeleton due to the presence of three stereodefined olefins. The isolated yield of the macrocycles **16** and **20** using the ester based auxiliaries was 28% and 37% yield respectively. Gratifyingly, switching to a pentafluorobenzyl amide auxiliary nearly doubled the isolated yield of the macrocyclic product and the macrocyclization of **17** afforded the macrocyclic amide **18** in 55% yield. The synthesis of macrocycles **16**, **18** and **20** is noteworthy as the carbon skeleton of the macrocycle is identical to that observed in the longithorone family of natural products.[16]



Scheme 4. Evaluation of new amide auxiliaries in challenging macrocyclizations.

Amide based auxiliaries bearing both a 2,3,4,5,6-pentafluorobenzyl and a bis-3,5-(trifluoromethyl)benzyl group were also evaluated in macrocyclizations using en-yne metathesis substrates (Scheme 5).[17] When the amide **24** underwent macrocyclization

with Grubbs-Hoveyda catalyst **21**, the [12]paracyclophane **25** was isolated in 59% yield following purification by silica gel chromatography. The yield of **25** was approximately 10% higher than the analogous cyclization of ester **22** to give the same core macrocycle **23** (49%).[5] In addition, the *E*:*Z* ratio of the products was improved, with the *Z*-isomer still predominating (1:6.0 *E*:*Z* for **25**). The same improved yields and *E*:*Z* ratios were observed during cyclizations of ester **26** and amide **28**. While the ester **26** afforded the macrocyclic diene **27** in 47% yield (*E*:*Z* 1:6.0), the corresponding amide **28** afforded the analogous macrocyclic amide **29** in an increased yield of 60% (*E*:*Z* 1:10).



Scheme 5. Evaluation of amide-based auxiliaries in macrocyclic en-yne metathesis.

Similar results were obtained using 2,3,4,5,6-pentafluorobenzyl auxiliary series. The ester **30** afforded the cyclophane **31** in 33% yield, however treatment of the corresponding amide **32** with the same catalyst **21** afforded a 46% yield of the macrocycle **33**. Not only was the isolated yield increased by 13%, but the *E*:*Z* ratio of the amide **33** was slightly improved compared to the analogous ester **31** (1: 5.0 *vs.* 1: 3.3 *E*:*Z*). The ester **34**, in which the alkynyl and alkenyl sidechains have been reversed with respect to ester **30**, was also compared in macrocyclizations with the amide **36**. A modest 7% increase in the isolated yield of macrocyclic amide **37** versus the macrocyclic ester **35** was observed.

The improved macrocyclizations via olefin or en-yne metathesis are likely a result of the improved preference for conformers such as **3-S**, where non-covalent interactions between the auxiliary and aromatic core enable a conformation conductive to cyclization. In addition, the improved yields of products may be due to the fact that the amide auxiliaries enable quadrupolar π–π interactions over lp–π interactions. While it is difficult to make a direct comparison of the energies of these interactions, some computational investigations have studied the interactions of hexafluorobenzene with water (3.77 kcal/mol)[10a,11a] and benzene (~4-5 kcal/mol),[18] suggesting the latter may be stronger and hence more effective for gearing the conformation of molecules. In the cases of en-yne metathesis, an increase in the preference for the *Z*-isomer was observed. Although molecular modelling studies suggest a thermodynamic preference for the *Z*-isomers,[5] there is no clear cut explanation, it is clear that each auxiliary exerts an influence during the formation of macrocycle. It is reasonable to assume that the increased rigidity afforded by the amides may restrict the various degrees of freedom of

the sidechains in the macrocyclization precursors, perhaps influencing the preference for the *Z*-isomer.

In summary, the substitution of an ester linker for an amide linker results in higher overall yields and better *E*:*Z* ratios in macrocyclic olefin and en-yne metathesis. Macrocyclizations employing olefin metathesis were improved by 12-27% in terms of isolated yields, while macrocyclizations employing en-yne metathesis were improved by 7-13%. Improved macrocyclizations were observed with both the 2,3,4,5,6-pentafluorobenzyl and bis-3,5-(trifluoromethyl)benzyl series and each auxiliary type gave similar increases. Calculations suggest that conformer **3-S** is highly favoured over **3-O**, which may be responsible for the efficient macrocyclization. The molecular modelling studies also suggest that quadrupolar interactions may be responsible for the gearing the amide auxiliaries, in contrast to the lp-π interactions predicted for **1-S**. Despite the large energetic stabilisation provided the amide linkage in **3-S** compared to the ester linkage in **1-S**, further increases in yields are likely to be obtained only by exploiting stronger non-covalent interactions, such as pyridinium (cation)-π interactions. Of note is the molecular modelling calculations that suggest the selective preference for π–π interactions with the amide auxiliaries. These results bode well for further application of these auxiliaries in macrocyclization of more complex and densely functionalized substrates containing numerous heteroatoms. Of interest would be the application of these auxiliaries in the synthesis of bioactive macrocyclic peptides. Further development of these new auxiliaries through the preparation of chiral versions and investigations in atroposelective macrocyclization is also being studied in our laboratories.

ACKNOWLEDGMENT We thank NSERC (Canada), FQRNT (Québec), CFI (Canada), Boehringer Ingelheim (Canada) Ltd., Merck Frosst Centre for Therapeutic Research and the Université de Montréal for generous financial support.

SUPPORTING INFORMATION Experimental procedures and characterisation data for all new compounds. This material is available free of charge via the Internet at http://www.wiley-vch.de/

---

[1] For reviews on macrocyclization in synthesis see: a) J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, *10*, 1949–1964. (b) K.-S. Yeung, I. Paterson, *Angew. Chem.* **2002**, *114*, 4826-4847; *Angew. Chem., Int. Ed.* **2002**, *41*, 4632–4653. (c) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115–2134; d) Z. R. Laughrey, B. C. Gibb, *Top. Curr. Chem.* **2005**, *249*, 67–125.

[2] a) X. Wang, E. J. Bowman, B. J. Bowman, J. A. Porco Jr., *Angew. Chem.* **2004**, *116*, 3685-3689; *Angew. Chem., Int. Ed.* **2004**, *43*, 3601-3605; b) X. Wang, J. A. Porco Jr., *J. Am. Chem. Soc.* **2003**, *125*, 6040-6041.

[3] a) M. Toumi, F. Couty, G. Evano, *J. Org. Chem.* **2008**, *73*, 1270-1281; b) P. H. Deshmukh, C. Schulz-Fademrecht, P. A. Procopiou, D. A. Vigushin, C. R. Coombes, A. G. M. Barrett, *Adv. Synth. Cat.* **2007**, *349*, 175-183; c) M. Poirier, N. Aubry, C. Boucher, J.-M. Ferland, S. LaPlante, Y. S. Tsantrizos, *J. Org. Chem.* **2005**, *70*, 10765-10773; d) U. Kazmaier, C. Hebach, A. Watzke, S. Maier, H. Mues, V. Huch, *Org. Biomol. Chem.* **2005**, *3*, 136-145.

[4] a) Y. El-Azizi, A. R. Schmitzer, S. K. Collins, *Angew. Chem.* **2006**, *118*, 982-987; *Angew. Chem., Int. Ed.* **2006**, *45*, 968-973; b) S. K. Collins, Y. El-Azizi, *Pure Appl. Chem.* **2006**, *78*, 783-789.

[5] S. K. Collins, Y. El-Azizi, A. R. Schmitzer, *J. Org. Chem.* **2007**, *72*, 6397-6408.

[6] a) J. E. Zakarian, Y. El-Azizi, S. K. Collins, *Org Lett.* **2008**, *In Press*; b) M. J. Marsella, Z.-Q. Wang, R. J. Reid, K. Yoon, *Org. Lett.* **2001**, *3*, 885-887.

[7] a) B. W. Gung, J. C. Amicangelo, *J. Org. Chem.* **2006**, *71*, 9261–9270; b) C. B. Martin, H. R. Mulla, P. G. Willis, A. Cammers-Goodwin *J. Org. Chem.* **1999**, *64*, 7802– 7806; c) B. W. Gung, X. Xue, Y. Zou, *J. Org. Chem.* **2007**, *72*; 2469-2475; d) B. W. Gung, M. Patel, X. Xue, *J. Org. Chem.* **2005**, *70*, 10532-10537. For a discussion on the theory of aromatic-aromatic interactions see: e) S. Grimme, *Angew. Chem.* **2008**, *120*, 3478-3483; *Angew. Chem., Int. Ed.* **2008**, *47*, 3430-3434.

[8] a) S. W. Watt, C. Dai, A. J. Scott, J. M. Burke, R. L. Thomas, J. C. Collings, C. Viney, W. Clegg, T. B. Marder, *Angew. Chem.* **2004**, *116*, 3123-3125; *Angew. Chem., Int. Ed.* **2004**, *43*, 3061–3063; b) J. C. Collings, K. P. Roscoe, E. G. Robins, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, S. J. Clark, T. B. Marder, *New J. Chem.* **2002**, *26*, 1740–1746; c) J. C. Collings, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Can. J. Chem.* **2006**, *84*, 238–242; d) J. C. Collings, A. S. Batsanov, J. A. K. Howard, D. A. Dickie, J. A. C. Clyburne, H. A. Jenkins, T. B. Marder, *J. Fluorine Chem.* **2005**, *126*, 515–519; e) J. C. Collings, J. M. Burke, P. S. Smith, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Org. Biomol. Chem.* **2004**, *2*, 3172–3178.

[9] a) W. Koch, M. C. Holthausen, In *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2002; b) K. Burke, J. Werschnik, E. K. U. Gross, *J. Chem. Phys.* **2005**, *123*, 062206.

[10] a) B. W. Gung, X. Xue, H. Reich, J. *J. Org. Chem.* **2005** *70*, 7232–7237; b) B. W. Gung, X. Xue, H. Reich, J. *J. Org. Chem.* **2005**, *70*, 3641-3644; c) B. W. Gung, Y. Zou, Z. Xu, J. C. Amicangelo, D. G. Irwin, S. Ma, H.-C. Zhou, *J. Org. Chem.* **2008**, *73*, 689-693.

[11] a) J. P. Gallivan, D. A. Dougherty, *Org. Lett.* **1999**, *1*, 103–105; b) S. Scheiner, T. Kar, J. Pattanayak, *J. Am. Chem. Soc.* **2002**, *124*, 13257–13264.

[12] We also attempted to prepare tertiary amide-based auxiliaries for macrocyclization. However, the synthesis of the corresponding amides from *N*-ethyl-2,3,4,5,6-pentafluorobenzyl amine was problematic. Typical peptide couplings (EDC, DCC, HOBt) as well as various reactions involving acyl chlorides failed to afford the desired tertiary amides.

[13] 3,5-Bis(trifluoromethyl)benzyl amine, 80%, Aldrich #26330-1g, $25.60 US.

[14] a) J. B. Doyon, A. Jain, *Org. Lett.* **1999**, *1*, 183-185; b) J. M. Birchall, R. N. Haszeldine, *J. Chem. Soc.* **1961**, 3719-27.

[15] See Supporting Information for details. The preparation of all ester precursors used for en-yne metathesis macrocyclizations have been previously reported, see reference 5.

[16] For the isolation of longithorone C see: a) X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm, *J. Org. Chem.* **1997**, *62*, 3810-3819. For the isolation of other

family members see: (b) X. Fu, M. L. Ferreira, F. J. Schmitz, *J. Nat. Prod.* **1999**, *62*, 1306-1310 ; c) R. A. Davis, A. R. Carroll, R. J. Quinn, *J. Nat. Prod.* **1999**, *62*, 158-160; d) X. Fu, M. B. Hossain, D. van der Helm, F. J. Schmitz, *J. Am. Chem. Soc.* **1994**, *116*, 12125-12126.

[17] Although the model systems in our molecular modelling study contain two olefinic sidechains, we believe it is reasonable to assume that similar energetic values would be obtained for en-yne substrates. This based upon the fact that the substitution of an alkyne for a alkene is a minor structural change unlikely to alter the solution state conformations in a significant manner.

[18] a) J. S. W. Overell, G. S. Pawley. *Acta Crystallograph. B* **1982**, 1966-1972; b) J. H. Williams, J. K. Cockcroft, A. N. Fitch. *Angew. Chem.* **1992**, *104*, 1666-1669; *Angew. Chem. Int. Ed.* **1992**, *31*, 1655-1657.

1. Conclusions

L'objectif premier de nos travaux de recherche était de développer de nouvelles stratégies pour la synthèse de paracyclophanes comportant des éléments de chiralité planaire. Pour ce faire, nous avons dépensé énormément de temps et d'efforts afin d'optimiser les conditions de macrocyclisation par RCM des oléfines pour former des [12], [13] et [14]paracyclophanes modèles. Nous en sommes sortis avec une méthodologie utilisant un nouvel élément directionnel, tel que le 2,3,4,5,6-pentafluorophényle, qui a permis de rendre possible des macrocyclisations complexes via la RCM des oléfines (chapitre 2 et chapitre 3). Combiné avec la stratégie utilisant un relais RRCM, il nous a été possible de construire stéréosélectivement un paracyclophane comportant une double liaison trisubstituée ce qui lui a conféré une rigidité, et une chiralité planaire telle qu'on a pu observer pas RMN du proton (chapitre 2). Ceci nous a mis en confiance concernant l'idée de construire un [12]paracyclophane ressemblant à celui de la longithorone C, chose qui a été atteinte après plusieurs efforts synthétiques considérables, notamment ceux concernant l'attachement des chaines alkyles sur le noyau aromatique central via couplage au cuivre (chapitre 5).

La modélisation moléculaire effectuée par notre collaboratrice, la Professeur Schmitzer, nous a permis de comprendre et de rationnaliser nos observations expérimentales et faire des prédictions se basant sur les différences d'énergies entre les différents arrangements conformationnels de nos substrats et nos modèles.

Dans le chapitre 4 nous nous sommes intéressés au fait de savoir si la méthodologie développée précédemment pouvait être appliquée à la macrocyclisation ène-yne. La réponse a été positive, et la preuve de concept a été donnée dans le cadre de la macrocyclisation par RCM ène-yne. Des [12] et [13]paracyclophanes comportant un motif 1,3-diène ont été obtenus et se sont avérés chiraux sans aucune exception. Il nous a même été possible d'appliquer la stratégie RRCM ène-yne pour arriver à des [12]paracyclophanes comportant un motif 1,3-diène dans lequel la double liaison carbone-carbone intracyclique est trisubstituée, chose qui n'a jamais été rapporté auparavant. L'utilisation d'un auxiliaire 2,5-bis(trifluoromethyl)benzyles'est avérée décisive; des rendements plus élevés et des ratios *E :Z* améliorés ont été obtenus.

Dans le chapitre 6, nous avons exploré la possibilité de changer le type d'attachement de nos auxiliaires sur nos substrats modèles en optant pour une jonction amide au lieu d'une jonction ester. Pour cela, un nouveau protocole pour la préparation de l'hydrochlorure 2,3,4,5,6-pentafluorobenzylamine hydrochloride a été développé. Les résultats obtenus ont été impressionnants, les rendements obtenus ont été meilleurs et les rapports *E :Z* ont été complètement changés. Les modélisations moléculaires nous avaient prédit que la jonction amide lorsqu'elle est dans sa conformation *s-trans* allait stabiliser beaucoup plus les interactions quadripolaires qui ont lieu à l'intérieur de nos substrats.

2. Perspectives et recherches futures

2.1 Vers des macrocyclisations atroposélectives par RCM

Le développement de nouveaux auxiliaires de contrôle conformationnel chiraux est clairement une bonne voie vers laquelle toute la chimie développée précédemment devrait être poussée. Des auxiliaires chiraux substitués en position benzylique tels que l'alcool **157**[1] et l'amine **158,**[2] pourraient être envisagés pour induire de la chiralité planaire au niveau du macrocycle à former.

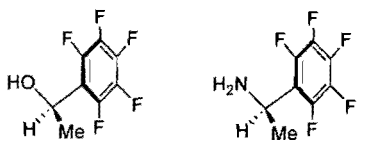


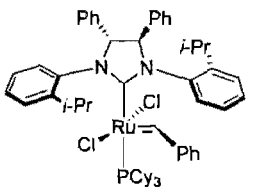
Figure 7.1: Exemples d'auxiliaires de contrôle conformationel chiraux.

Aussi, l'utilisation de catalyseurs de métathèses chiraux tels que ceux sur la figure 7.3 pourrait être envisagée. Dans ces cas-ci, il est important de noter que ces catalyseurs devraient garder une bonne réactivité et ce malgré le fait que les ligands chiraux qui les forment doivent former autour du métal une cage chirale dont l'encombrement stérique est parfois imposant, contribuant ainsi à ralentir par la même occasion tous les processus d'approche des substrats vers le centre métallique. Aussi, ces mêmes catalyseurs doivent

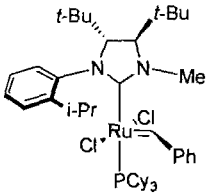
[1] Messe, C. *Liebigs Ann.* **1986**, *11*, 2004.

[2] Gorske , B. C; Blackwell, H. E. *J. Am. Chem. Soc.* **2006**, *128*, 14378.

avoir une stabilité importante car, tel que discuté dans le chapitre 1, les réactions de macrocyclisation sont très exigeantes; la haute dilution implique des temps de réaction longs et les hautes températures vont favoriser toute sorte de processus y compris ceux conduisant à la dégradation des catalyseurs.



159



160

Figure 7.2: Exemples de catalyseurs de métathèse chiraux developpés par Grubbs[3] et par Collins[4].

[3] Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett*, **2001**, *3*, 3225.
[4] Fournier, P.-A.; Collins, S. K. *Organometallics*, **2007**, *26*, 2945.

2.2 Nouvelles applications des auxiliaires de contrôle conformationnel

Nous avons montré tout au long de cette thèse qu'il était possible d'exploiter des interactions quadripolaires en solution pour favoriser des réactions de macrocyclisation par RCM et RRCM des oléfines. Nous avons montré aussi que c'était également possible de faire de même par RCM et RRCM ène-yne. Nous pensons que des succès similaires pourraient être obtenus pour d'autres réactions de macrocylisation impliquant des processus catalytiques ou non-catalytiques.

Development of Perfluoroarene:Arene Interactions for Macrocyclic En-Yne Metathesis and the Total Synthesis of Macrocyclic Natural Products.

Table of contents

SUPPORTING INFORMATION

General

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[1]. Isolated yields reflect the mass obtained following flash column silica gel chromatography using the method reported by W. C. Still[2] and using silica gel (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 coated with a fluorescence indicator (0.25 mm, F_{254}.). All the compounds were UV active, and no development of the TLCs was required. Visualization of TLC plate was performed by UV (254 nm). 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 ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$.Signals due to the solvent served as the internal standard. The acquisition parameters are shown on all spectra. The ^{1}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. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling, 2D COSY experiments. The ^{13}C NMR assignments were

[1] D. F. Shriver, M. A. Drezdon, *The Manipulation of Air-Sensitive Compounds*; 2nd Edition, ed.; Wiley: New York, 1986.
[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by two dimensional H/C correlation experiments (HSQC). High resolution mass spectroscopy (HRMS) was done using ESI mode of ionization. Charged molecular ion $[M+H]^+$ and $[M+Na]^+$ data are reported.

Preparation of ene-yne precursors

A general procedure for the preparation of precursors **7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 24A- 26B- 28A- 30B- 32A- 34B- 36B- 38- 40A- 42B** *is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that in general, we do not observe any ^{13}C NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary or for the CF_3 carbon. In select cases where a different synthetic route was necessary, these procedures are described in detail.*

Ene-Yne precursors **7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 32A- 34B- 36B- 40A- 42B** were prepared following this sequence:

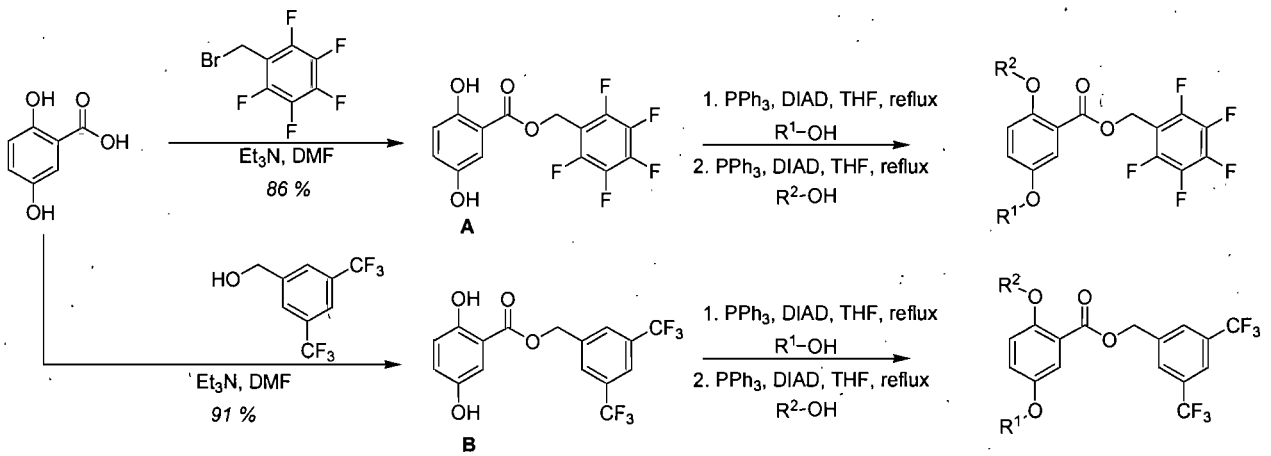
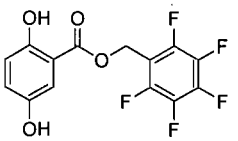


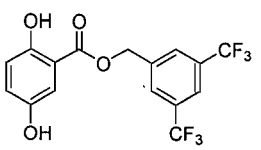
Figure SI1: Preparation of metathesis precursors **7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 32A- 34B- 36B- 40A *and* 42B.**



A

In a round bottom flask, 2, 5-dihydroxybenzoic acid (154 mg, 1.00 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop wise, the reaction is exothermic. Then, pentafluorobenzyl bromide (0.140 mL, 1.0 mmol, 1.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (287 mg, 86 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.07 (s, 1H), 7.21 (d, J = 3.1 Hz, 1H), 7.03 (dd, J = 9.0, 3.1 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 5.46 (s, 2H), 4.56 (s, 1H),; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.8, 156.1, 147.7, 124.7, 118.7, 114.6, 111.3, 54.0; **HRMS** (ES) Calculated for $C_{14}H_8F_5O_4$ $[M + H]^+$: 335.0337 found 335.0342.



B

In a round bottom flask, 2, 5-dihydroxybenzoic acid (154 mg, 1.00 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop

wise, the reaction is exothermic. Then, 3,5-di(trifluoromethyl)benzyl bromide (310 mg, 1.0 mmol, 1.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reaction could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (346 mg, 91 %).^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.17 (s, 1H), 7.89 (s, 3H), 7.30 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 9.1, 3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.45 (s, 2H), 4.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 156.1, 147.8, 137.7, 132.1 (q, CF_3), 128.4, 124.8, 122.6, 121.7, 118.8, 114.5, 111.4, 65.3; **HRMS** (ES, negative mode of ionization) Calculated for $C_{16}H_9F_6O_4$ [M - H]$^-$: 379.0405 found 379.0423.

Ene-Yne precursor **28A** was prepared following this sequence:

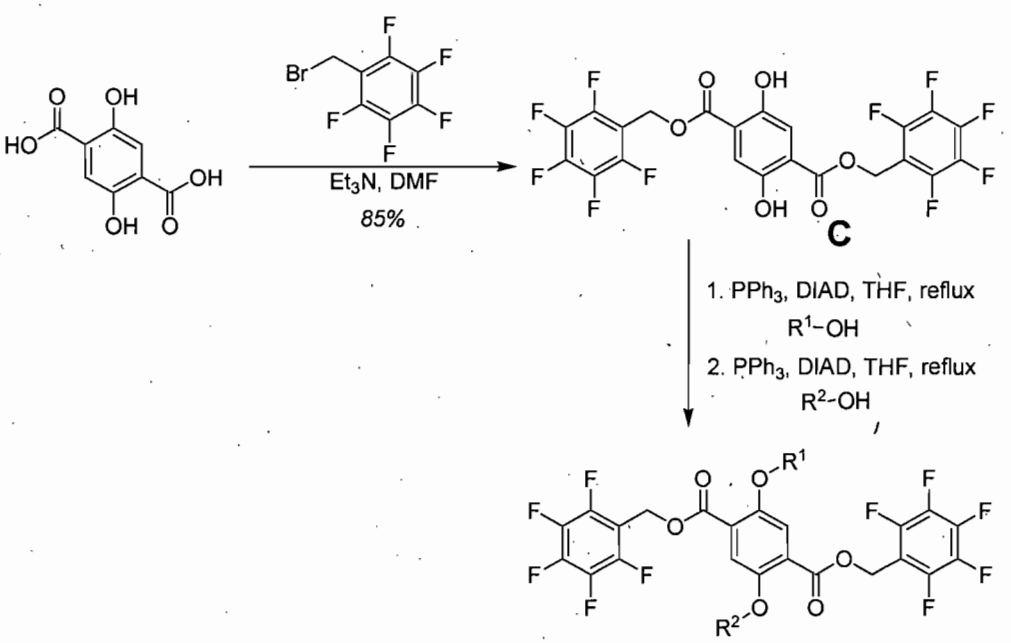
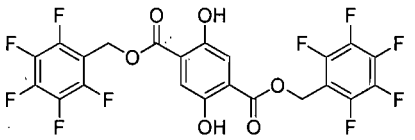


***Figure SI2: Preparation of metathesis precursor* 28A.**



C

In a round bottom flask, 2,5-dihydroxy-terephtalic acid (198 mg, 1.0 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF. Triethylamine (0.280 mL, 2.0 mmol, 2.0 equiv.) is added drop wise. The reaction is exothermic. Then, pentafluorobenzyl bromide (0.280 mL, 2.0 mmol, 2.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 4:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (475 mg, 85 %). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.79 (s, 2H), 7.41 (s, 2H), 5.48 (s, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.1, 153.0, 118.0, 117.9, 54.5; **HRMS** (ES) Calculated for $C_{22}H_9F_{10}O_6$ $[M + H]^+$: 559.0239 found 559.0226.

Ene-Yne precursor **24A** was prepared following this sequence:

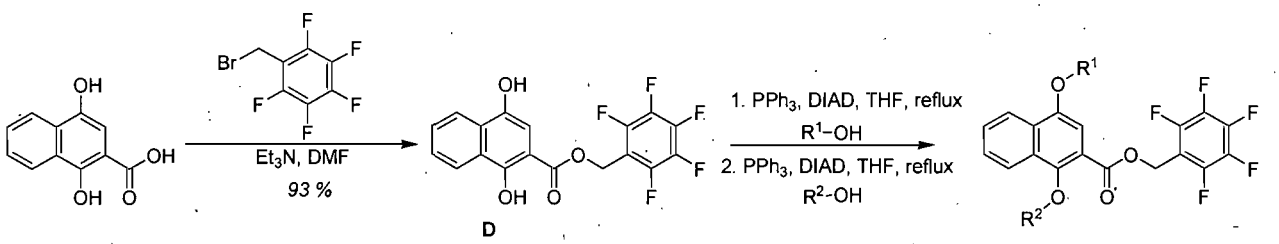
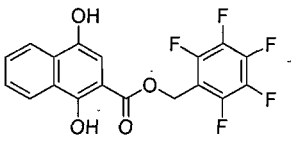


***Figure SI3: Preparation of metathesis precursor* 24A**



D

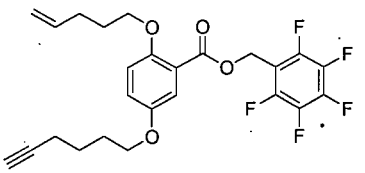
In a round bottom flask, 1, 4-dihydroxy-2-naphthanoic acid (204 mg, 1.0 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop wise, the reaction is exothermic. Then, pentafluorobenzyl bromide (0.140 mL, 1.0 mmol, 1.0 equiv.) is added to the mixture.The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colourless solid (358 mg, 93 %).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ 11.30 (s, 1H), 8.39 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.00 (s, 1H), 5.50 (s, 2H), 4.92 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.7, 156.2, 143.3, 129.4, 129.1, 126.6, 125.5, 124.1, 121.7, 104.7, 103.5, 53.9; **HRMS** (ES, negative mode of ionization) Calculated for $C_{18}H_8F_5O_4$ $[M - H]^-$: 383.0342 found 383.0351.

General procedure for alkylations via the Mitsunobu reaction.

In a round bottom flask, pentafluorobenzyl-2, 5-dihydroxybenzoate (1.0 eq.) was added to triphenylphosphine (1.2 eq.) and the alkenyl or alkynyl alcohol (0.5 to 0.6 eq.)[3]. This mixture was then dissolved in dry THF and heated to reflux. DIAD (1.2 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was

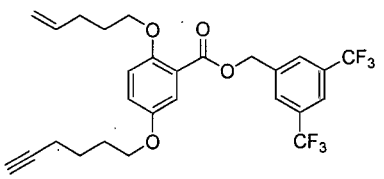
[3] This stochiometry is important to avoid the formation of dialkylated product.

complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). Isolated yields were obtained in the range of 55- 90%. The products were immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (1.0 eq.) was added to triphenylphosphine (1.6 eq.) and the alkenyl or alkynyl alcohol (1.2 eq.). This mixture was then dissolved in dry THF and heated to reflux. While under reflux, DIAD (1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). Isolated yields of approximately 60 % were typically obtained.



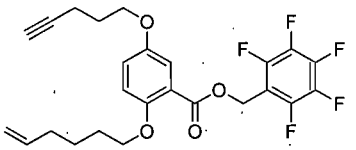
7A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 5.82 (m, 1H), 5.39 (s, 2H), 5.06- 4.97 (m, 2H), 3.97- 3.86 (m, 4H), 2.24- 2.20 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.87- 1.83 (m, 4H), 1.66- 1.63 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.0, 152.4, 146.9, 120.6, 119.6, 116.8, 115.1, 115.0, 84.0, 68.8, 68.6, 68.0, 53.6, 29.8, 28.3, 28.2, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1591. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1470.



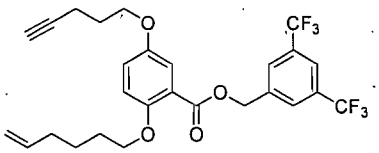
10B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.03 (dd, J = 9.1, 3.1 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.75 (m, 1H), 5.44 (s, 2H), 4.99- 4.92 (m, 2H), 4.00- 3.94 (m, 4H), 2.27- 2.24 (m, 2H), 1.17- 1.12 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.92- 1.69 (m, 4H), 1.80- 1.60 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.0, 152.4, 138.8, 137.5, 131.9 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 115.1, 115.0, 84.0, 68.8, 68.6, 67.9, 64.9, 29.8, 28.2, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1811. Calculated for $C_{27}H_{26}F_5O_4Na$ $[M + Na]^+$: 551.1627, found 551.1632.



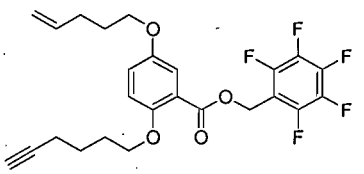
12A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.0, 3.1 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 5.85 (m, 1H), 5.39 (s, 2H), 5.02- 4.94 (m, 2H), 4.02 (t, J = 6.1 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 2.40- 2.36 (m, 2H), 2.40- 2.36 (m, 2H), 2.03- 2.10 (m, 2H), 2.00- 1.94 (m, 3H), 1.76- 1.70 (m, 2H), 1.52- 1.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.2, 152.1, 138.4, 120.6, 119.6, 116.9, 114.9, 114.6, 83.3, 69.4, 68.9, 66.7, 53.6, 33.3, 28.6, 28.1, 25.1, 15.1; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1592. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1408.



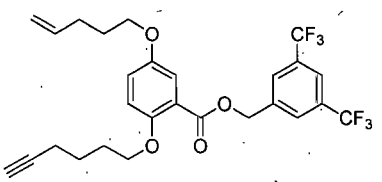
14B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.37 (d, J = 3.2 Hz, 1H), 7.05 (dd, J = 9.1, 3.2 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.75 (m, 1H), 5.44 (s, 2H), 4.98- 4.90 (m, 2H), 4.05 (t, J = 6.1 Hz, 2H), 3.99 (t, J = 6.6 Hz, 2H), 2.41- 2.37 (m, 2H), 2.04- 1.96 (m, 5H), 1.77- 1.73 (m, 2H), 1.53- 1.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.1, 152.2, 138.8, 138.4, 132.0 (q, CF_3), 128.0, 127.2, 121.8, 120.8, 119.8, 115.0, 114.7, 121.8, 120.8, 83.3, 69.4, 68.9, 66.8, 64.9, 33.2, 28.5, 28.1, 25.1, 15.1; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1803. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1627.



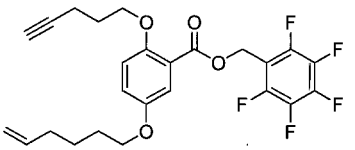
16A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 5.82 (m, 1H), 5.39 (s, 2H), 5.06- 4.97 (m, 2H), 3.97- 3.86 (m, 4H), 2.24- 2.20 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.87- 1.83 (m, 4H), 1.66- 1.63 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 152.9, 152.3, 137.6, 120.6, 119.5, 116.9, 115.1, 114.8, 83.9, 68.8, 68.5, 67.0, 53.5, 30.0, 28.3, 28.2, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1597. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1483.



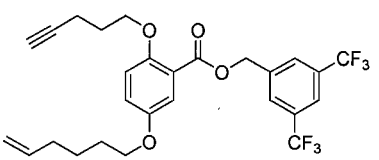
18B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 2H), 7.87 (s, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.06 (dd, J = 9.1, 3.1 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 5.85 (m, 1H), 5.46 (s, 2H), 5.09- 5.02 (m, 2H), 4.02 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 2.27- 2.20 (m, 4H), 1.98- 1.86 (m, 5H), 1.68- 1.64 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 152.9, 152.5, 138.8, 137.7, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 122.1, 121.6, 121.8, 120.8, 119.7, 116.8, 115.2, 114.9, 83.9, 68.9, 68.7, 67.8, 64.9, 30.0, 28.4, 28.1, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1804. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1623.



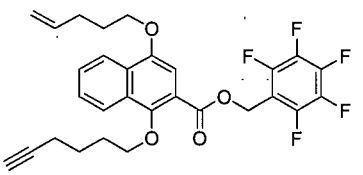
20A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 3.2 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 5.83 (m, 1H), 5.40 (s, 2H), 5.05- 4.98 (m, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.92 (t, J = 6.4 Hz, 2H), 2.33- 2.30 (m, 2H), 2.13- 2.10 (m, 2H), 1.95- 1.91 (m, 3H), 1.79- 1.75 (m, 2H); 1.59- 1.53 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 152.5, 152.2, 138.1, 120.4, 119.1, 116.6, 114.6, 114.4, 83.0, 68.4, 68.1, 67.4, 53.3, 33.0, 28.3, 27.9, 24.9, 14.7; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1572. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1449.



22B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 2H), 7.85 (s, 1H), 7.36 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 5.80 (m, 1H), 5.43 (s, 2H), 5.04- 4.96 (m, 2H), 4.07 (t, J = 6.0 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 2.34- 2.30 (m, 2H), 2.15- 2.10 (m, 2H), 1.96- 1.76 (m, 3H), 1.60- 1.53 (m, 2H), 1.71- 1.50 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.8, 152.6, 138.7, 138.4, 131.7 (q, CF_3), 128.1, 127.2, 124.5, 122.2, 122.1, 122.0, 121.8, 120.8, 119.8, 115.2, 114.8, 83.2, 68.8, 68.5, 67.8, 64.9, 33.4, 28.6, 28.0, 25.2, 14.9; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1796. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1607.



24A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (m, 1H), 8.15 (m, 1H), 7.59 (m, 2H), 7.11 (s, 1H), 5.90 (m, 1H), 5.50 (s, 2H), 5.12- 5.01 (m, 2H), 4.15 (t, J = 6.3 Hz, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.35- 2.30 (m, 4H), 2.05- 1.93 (m, 5H), 1.82- 1.75 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 151.3, 150.7, 137.7, 129.3, 129.2, 128.0, 127.1, 123.5, 122.8, 117.8, 115.3, 104.1, 83.9, 75.7, 68.6, 67.5, 53.9, 30.3, 29.3, 28.4, 25.0, 18.3; **HRMS** (ES) Calculated for $C_{29}H_{26}F_5O_4$ $[M + H]^+$: 533.1745 found 533.1768. Calculated for $C_{29}H_{25}F_5O_4Na$ $[M + Na]^+$: 555.1571, found 555.1594.

Ene-Yne precursor **26B** was prepared following this sequence:

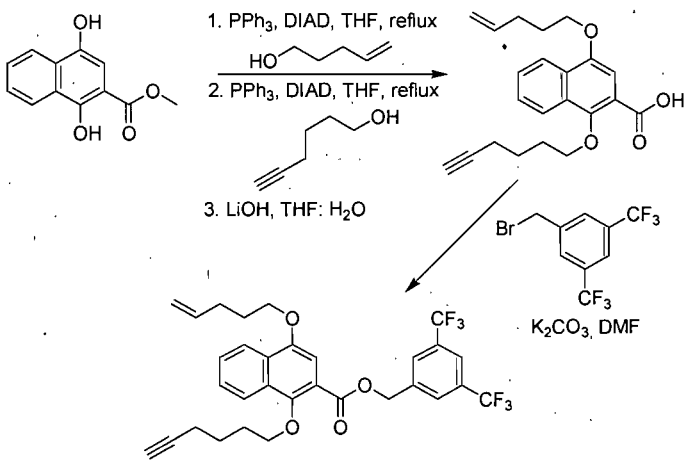
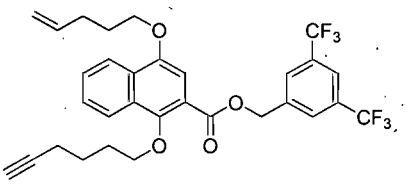


***Figure SI4: Preparation of metathesis precursor* 26B**

In a round bottom flask, methyl-1, 4-dihydroxy-2-naphthanoic acid (500mg, 2.29 mmol, 1.0 eq.) was added to triphenylphosphine (720 mg, 2.75 mmol, 1.2 eq.) and pent-4-en-1-ol (0.115 mL, 1.15 mmol, 0.5 eq.)[4] was added. This mixture was then dissolved in dry THF (12 mL) and heated to reflux. DIAD (0.56 mL, 2.75 mmol, 1.2 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (320 mg, 1.12 mmol, 1.2 eq.) was added to triphenylphosphine (470 mg, 1.8 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.145 mL, 1.34 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (10 mL) and heated to reflux. While under reflux, DIAD (0.265 mL, 1.8 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H2O (4:1, 30 mL) and LiOH (230 mg, 9.5 mmol, 10 eq.) was added. The mixture was stirred at reflux for

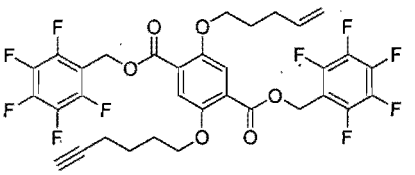
[4] This stochiometry is important to avoid the formation of dialkylated product.

18 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 30 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford a crude solid. The crude solid (316 mg, 0.90 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF. K_2CO_3 (740 mg, 5.5 mmol, 5.0 equiv.) is added. Then 3, 5-di (trifluoromethyl)benzyl bromide (330 mg, 1.1 mmol, 1.2 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reaction could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether and washed with brine (2 * 30 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



26B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (m, 1H), 8.21 (m, 1H), 8.00(s, 2H), 7.91 (s, 1H), 7.63- 7.59 (m, 2H), 7.19 (s, 1H), 5.90 (m, 1H), 5.53 (s, 2H), 5.14- 5.05 (m, 2H), 4.17 (t, J = 6.2 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H), 2.37- 2.27 (m, 4H), 2.06- 1.99 (m, 5H), 1.82- 1.70 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 151.3, 150.7, 138.7, 137.6, 131.4 (q, CF_3), 129.3, 129.1, 128.1, 127.9, 127.1, 124.5, 123.4, 122.3, 122.1, 117.9, 115.2, 103.9, 83.9, 75.6, 68.6, 67.4, 65.0, 31.5, 30.2, 29.3, 25.2, 18.2; **HRMS** (ES) Calculated for $C_{31}H_{29}F_6O_4$ $[M + H]^+$: 579.1965, found 579.1963. Calculated for $C_{31}H_{28}F_6O_4Na$ $[M + Na]^+$: 601.1784, found 601.1785.



28A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (s, 2H), 5.77 (m, 1H), 5.42 (s, 4H), 5.01- 4.97 (m, 2H), 4.00-3.94 (m, 4H), 2.24- 2.20 (m, 2H), 2.14- 2.12 (m, 2H), 1.95 (s, 1H), 1.86- 1.64 (m, 4H), 1.65- 1.61 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 165.1, 151.8, 151.7, 137.4, 123.5, 116.6, 116.5, 115.2, 83.8, 68.9, 68.7, 68.6, 54.0, 29.8, 28.1, 28.0, 24.8, 18.0; **HRMS** (ES) Calculated for $C_{33}H_{25}F_{10}O_6$ $[M + H]^+$: 707.1486 found 707.1483. Calculated for $C_{33}H_{24}F_{10}O_6Na$ $[M + Na]^+$: 729.1311, found 729.1316.

Ene-Yne precursor **30B** was prepared following this sequence:

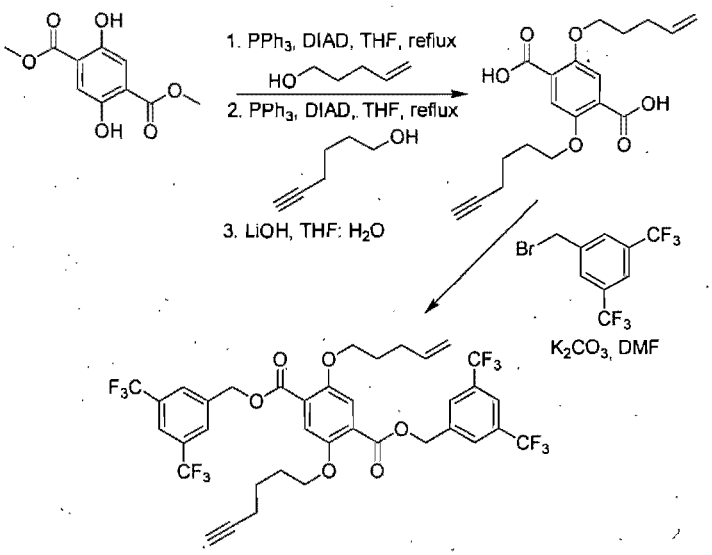
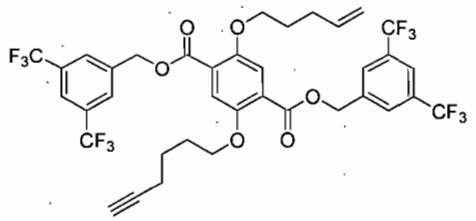


***Figure SI5: Preparation of metathesis precursor* 30B**

In a round bottom flask, methyl-2, 5-dihydroxybenzene dicarboxylate (250 mg, 1.1 mmol, 1.0 eq.) was added to triphenylphosphine (434 mg, 1.66 mmol, 1.5 eq.) and pent-4-en-1-ol (0.056 mL, 0.55 mmol, 0.50 eq.) [5] was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. DIAD (0.338 mL, 1.66 mmol, 1.5 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (177 mg, .605 mmol, 1.0 eq.) was added to triphenylphosphine (253 mg, 0.97 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.082 mL, 0.726 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. While under reflux, DIAD (0.20 mL, 0.97 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H_2O (4:1, 20 mL) and LiOH (120 mg, 5 mmol, 10 eq.) was added. The mixture was stirred at reflux for 15 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated to afford a crude solid. The crude solid (160 mg, 0.46 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and 3, 5-di(trifluoromethyl)benzyl bromide (169 mg, 0.55 mmol, 1.2 eq.) is added to the mixture. K_2CO_3 (370 mg, 2.75 mmol, 5.0 equiv.) is then added. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether

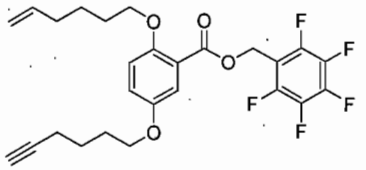
[5] This stochiometry is important to avoid the formation of dialkylated product.

and washed with brine (2 * 25 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



30B

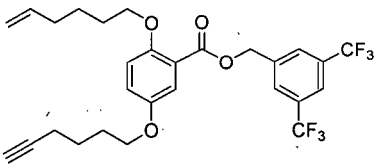
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.87 (s, 1H), 7.43 (s, 2H), 5.75 (m, 1H), 5.47 (s, 4H), 4.97- 4.92 (m, 2H), 4.07- 4.01 (m, 4H), 2.19- 2.12 (m, 4H), 1.91- 1.80 (m, 5H), 1.70- 1.55 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.4, 151.8, 151.7, 138.4, 138.3, 137.2, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 123.8, 122.3, 122.2, 121.7, 119.1, 116.6, 116.5, 115.3, 83.8, 68.9, 68.7, 68.6, 65.3, 65.2, 29.7, 28.1, 28.0, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{37}H_{31}F_{12}O_6$ $[M + H]^+$: 799.1924, found 799.1925. Calculated for $C_{37}H_{30}F_{12}O_6Na$ $[M + Na]^+$: 821.1743, found 821.1743.



32A

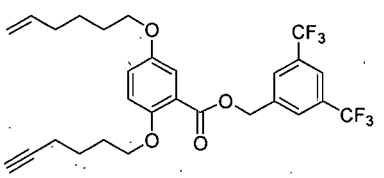
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.5, 3.1 Hz, 1H), 6.86 (d, J = 9.7 Hz, 1H), 5.78 (m, 1H), 5.39 (s, 2H), 5.03- 4.94 (m, 2H), 3.95- 3.92 (t, J = 6.1 Hz, 4H), 2.27- 2.24 (m, 2H), 2.09- 2.06 (m, 2H), 1.95 (t, J = 2.5 Hz, 1H), 1.90- 1.85 (m, 2H), 1.76- 1.67 (m, 4H), 1.52- 1.49 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.1, 152.3, 138.4, 120.6, 119.6, 116.8, 114.9,

114.6, 84.0, 69.4, 68.6, 67.9, 53.6, 33.3, 28.6, 28.2, 25.1, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_4$ $[M + H]^+$: 497.1745 found 497.1739. Calculated for $C_{26}H_{25}F_5O_4Na$ $[M + Na]^+$: 519.1571, found 519.1568.



34B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.36 (d, J = 3.0 Hz, 1H), 7.03 (dd, J = 9.1, 3.0 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.73 (m, 1H), 5.44 (s, 2H), 4.99- 4.91 (m, 2H), 4.00- 3.94 (m, 4H), 2.28- 2.21 (m, 2H), 2.10- 2.00 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.87- 1.80 (m, 2H), 1.77- 1.65 (m, 4H), 1.55- 1.45 (m 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 153.1, 152.3, 138.8, 138.4, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 114.9, 114.6, 84.0, 69.4, 68.6, 68.0, 64.9, 33.2, 28.5, 25.1, 25.0, 24.8, 18.1; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1972. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$:565.1784, found 565.1790.



36B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.88 (s, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.06 (dd, J = 9.1, 3.0 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 5.83 (m, 1H), 5.47 (s, 2H), 5.07- 4.97 (m, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 2.22- 2.10 (m, 4H), 1.94- 1.78 (m, 5H), 1.69- 1.50 (m, 4H); **^{13}C**

NMR ($CDCl_3$; 100 MHz) δ 165.8, 152.9, 152.5, 138.8, 138.4, 131.7 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 114.9, 114.7, 83.9, 68.9, 68.5, 68.4, 64.8, 33.3, 28.6, 28.1, 25.2, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1969. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1781

Ene-Yne precursor **38B** was prepared following this sequence:

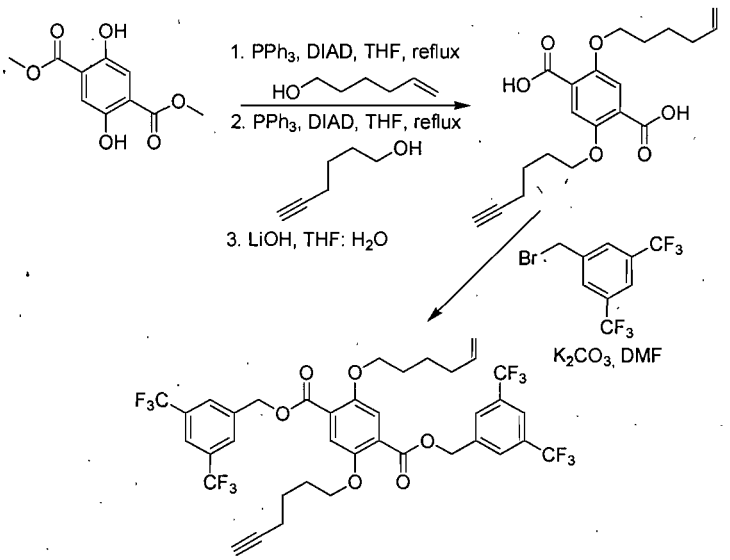
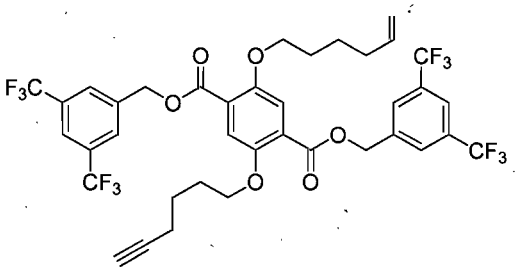


***Figure SI6: Preparation of metathesis precursor* 38B**

In a round bottom flask, methyl-2, 5-dihydroxybenzene dicarboxylate (250 mg, 1.1 mmol, 1.0 eq.) was added to triphenylphosphine (434 mg, 1.66 mmol, 1.5 eq.) and Hexen-5-en-1-ol (0.066 mL, 0.55 mmol, 0.50 eq. [6]) was added. This mixture was then dissolved in dry THF (10 mL) and heated to reflux. DIAD (0.338 mL, 1.66 mmol, 1.5 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (185 mg, .60 mmol, 1.0 eq.) was added to triphenylphosphine (253 mg, 0.97 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.080 mL, 0.72 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. While under reflux, DIAD (0.19 mL, 0.95 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the

[6] This stochiometry is important to avoid the formation of dialkylated product.

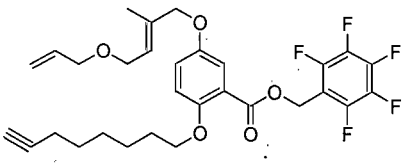
reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H_2O (4:1, 20 mL) and LiOH (120 mg, 5 mmol, 10 eq.) was added. The mixture was stirred at reflux for 15 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated to afford a crude solid. The crude solid (160 mg, 0.46 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and 3, 5-di (trifluoromethyl)benzyl bromide (170 mg, 0.55 mmol, 1.2 eq.) is added to the mixture. K_2CO_3 (370 mg, 2.75 mmol, 5.0 equiv.) is then added. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



38B

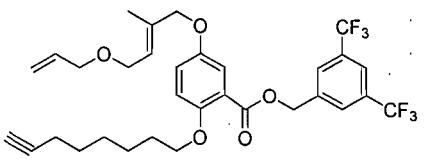
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 4H), 7.87 (s, 2H), 7.43 (s, 2H), 5.71 (m, 1H), 5.47 (s, 4H), 4.98- 4.92 (m, 2H), 4.07- 4.01 (m, 4H), 2.19- 2.16 (m, 2H), 2.10- 1.97 (m, 2H), 1.90- 1.87 (m, 3H), 1.80- 1.70 (m, 2H), 1.68- 1.60 (m, 2H), 1.57- 1.45 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.4, 151.9, 151.8, 138.5, 138.2, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 123.9, 123.8, 122.2, 121.8,

119.1, 116.6, 116.5, 114.7, 83.8, 69.5, 69.0, 68.6, 65.3, 33.1, 28.4, 28.0, 25.0, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{38}H_{33}F_{12}O_6$ $[M + H]^+$: 813.2080, found 813.2079. Calculated for $C_{38}H_{32}F_{12}O_6Na$ $[M + Na]^+$: 835.1900, found 835.1900.



40A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 9.1,3.2 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 5.90 (m, 1H), 5.72 (td, J = 6.0, 1.2 Hz, 1H), 5.39 (s, 2H,), 5.29- 5.17 (m, 2H), 4.37 (s, 2H), 4.05 (d, J = 6.4 Hz, 2H), 3.97- 3.92 (m, 4H), 2.22- 2.18 (td, J = 9.6, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.77- 1.71 (m, 5H), 1.55- 1.40 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.4, 153.3, 134.7, 134.6, 124.6, 120.9, 119.5, 117.4, 117.3, 117.2, 114.9, 84.5, 73.6, 71.2, 69.5, 68.2, 66.0, 29.0, 28.6, 28.3, 25.3, 18.3, 14.1. **HRMS** (ES) Calculated for $C_{30}H_{32}F_5O_5$ $[M + H]^+$: 567.2172 found 567.2167. Calculated for $C_{30}H_{31}F_5O_5Na$ $[M + Na]^+$: 589.1990, found 589.1983.



42B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 2H), 7.85 (s, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.1,3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.91 (m, 1H), 5.73 (td, J = 6.3, 1.2 Hz, 1H), 5.43 (s, 2H,), 5.28- 5.16 (m, 2H), 4.39 (s, 2H), 4.06 (d, J = 6.3 Hz, 2H), 4.00- 3.95 (m, 4H), 2.20- 2.15 (m, 2H),

1.92 (t, J = 2.6 Hz, 1H), 1.77- 1.72 (m, 5H), 1.53- 1.35 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.2, 152.0, 138.9, 134.7, 131.7 (m, CF_3), 127.9, 127.2, 124.5, 124.4, 122.0, 121.9, 121.8, 121.7, 121.0, 119.7, 117.3, 117.1, 114.9, 114.8, 84.4, 73.6, 71.2, 69.5, 68.2, 66.0, 53.6, 28.9, 28.6, 28.3, 25.3, 18.2, 14.0. **HRMS** (ES) Calculated for $C_{32}H_{35}F_6O_5$ $[M + H]^+$: 613.2389, found 613.2393. Calculated for $C_{32}H_{34}F_6O_5Na$ $[M + Na]^+$: 635.2208, found 635.2197.

General procedure for the direct ene-yne metathesis reaction

A general procedure for en- yne metathesis reaction is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that the determination of the configuration of the double bond (*E* or *Z)* was accomplished using ^{1}H NMR NOE and NOESY experiments. The *Z:E* ratios were determined by ^{1}H NMR through analogy with en- yne products **21A** and **27B** (see the attached spectra section).

The *Z* and *E* isomers were quantified based on the relative integrations of the ^{1}H NMR signals for protons H_a and H_b (see Figure SI7). These assignments are consistent with those observed by Lee and co-workers.[7] In all cases the two isomers produced are inseparable by flash column silica chromatography. Spectral data is reported for the major isomer in each case. The ^{1}H and ^{13}C NMR spectra of the *Z:E* mixtures are included in the *Supporting Information* as a reference. In addition, the majority of the macrocycles formed are atropisomeric. The diastereotopicity combined with the fact that the products are mixtures of *Z:E* isomers renders some spectra quite complicated. As such, many products of en –yne metathesis were fully hydrogenated[8] and the characterization data, ^{1}H and ^{13}C NMR spectra for a selection of these compounds are listed below.

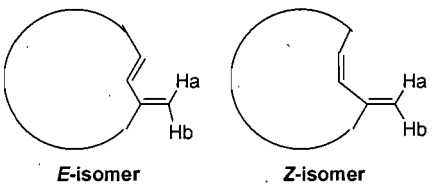
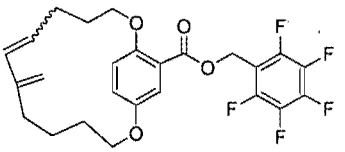


Figure SI7: Identification of Z and E isomers

[7] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**; *126,* 15074-15080 and references therein.

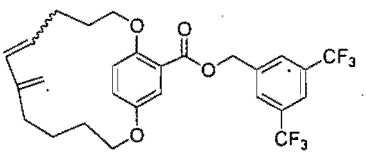
[8] Hydrogenation of 1, 3-diene paracyclophanes in solution in Ethyl Acetate: MeOH 10:1 using H_2 (1 atm) and $Pd(OH)_2/C$ (10 mol %) as a catalyst.

A flame dried 500 mL tri-neck round bottom flask, equipped with a magnetic stirrer, reflux condenser, and isobar addition funnel or a syringe pump system is charged with catalyst **G1, G2** or **GH2** (20 mol %) and anhydrous CH_2Cl_2 or toluene (volume is determined by the amount needed to afford a final concentration of [M] = $0.4x10^{-4}$ M after complete addition of the precursor). The catalyst solution is then placed at reflux (CH_2Cl_2) or 110°C (toluene). The metathesis precursor in solution (approximately 50 mL) is placed in the addition funnel or the syringe pumps system and added over 1 h. After addition, the solution was allowed to stir at reflux for 1 additional hour to ensure complete conversion (reactions performed in CH_2Cl_2 all had to be left overnight). The reaction mixture was concentrated in vacuo, dry-packed and purified by flash column silica chromatography (Hexanes-Ethyl Acetate 20:1) to afford the desired 1, 3-diene paracyclophanes.



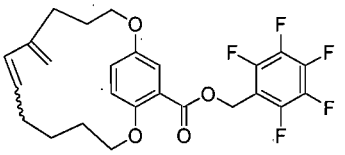
***Z*- 8A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 3.1 Hz, 1H), 7.10 (dd, J = 9.0, 3.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 5.44-5.40 (m, 2H), 5.18- 5.14 (m, 2H), 4.81 (d, J = 1.7 Hz, 1H), 4.82 (s, 1H), 4.24- 4.17 (m, 4H), 2.08- 2.04 (m, 2H), 1.84- 1.64 (m, 4H), 1.39- 1.08 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.9, 155.7, 152.7, 145.8, 131.5, 128.5, 124.6, 121.7, 121.6, 120.4, 111.0, 72.2, 70.1, 53.7, 34.6, 30.7, 28.7, 27.0, 24.8; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1601. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1411.



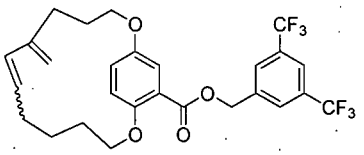
***Z*- 11B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.13 (dd, J = 9.0, 3.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 5.45 (m, 2H), 5.20 (d, J = 15.7 Hz, 1H), 5.17- 5.09 (m, 1H), 4.81 (s, 1H), 4.60 (s, 1H), 4.40- 4.10 (m, 4H), 2.05- 1.25 (m, 10H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 151.9, 150.9, 144.7, 138.9, 133.2, 132.1 (q, CF_3), 128.9, 127.7, 124.9, 123.2, 122.4, 121.9, 120.9, 119.7, 113.1, 68.5, 68.3, 64.9, 30.6, 27.5, 27.0, 24.9, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1813. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1637.



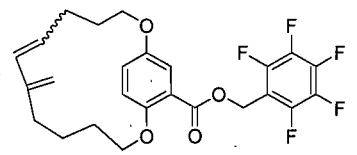
***E*- 13A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 5.77 (d, J = 15.7 Hz, 1H), 5.43 (m, 2H), 4.82 (s, 1H), 4.78 (s, 1H), 4.59- 4.53 (m, 1H), 4.47- 4.38 (m, 1H), 4.28- 4.25 (m, 3H), 1.96- 1.55 (m, 4H), 1.25-1.19 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.0, 151.8, 151.0, 144.8, 133.1, 129.1, 124.6, 123.0, 120.7, 119.9, 113.0, 72.6, 68.5, 53.8, 32.5, 30.7, 27.4, 25.2, 22.2; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1589. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1408.



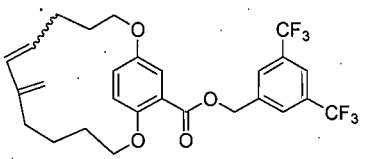
***E*- 15B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.47 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.76 (d, J = 15.8 Hz, 1H), 5.45 (m, 2H), 4.83 (s, 1H), 4.79 (s, 1H), 4.61- 4.49 (m, 1H), 4.49- 4.40 (m, 1H), 4.28- 4.25 (m, 2H), 4.23- 4.16 (m, 1H), 1.96- 1.60 (m, 6H), 1.32-1.25 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 151.9, 150.9, 144.7, 138.9, 133.2, 132.1 (q, CF_3), 128.9, 127.7, 124.9, 123.2, 122.4, 121.9, 120.9, 119.7, 113.1, 68.5, 68.3, 64.9, 30.6, 27.5, 27.0, 24.9, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1803. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1622.



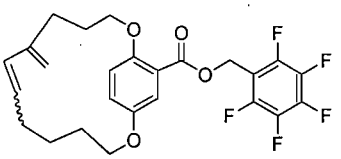
***Z*- 17A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J = 2.7 Hz, 1H), 7.06- 7.02 (m, 2H), 5.44 (d, J = 8.2 Hz, 1H), 5.38 (J = 12.1 Hz, 1H), 5.30 (d, J = 15.7 Hz, 1H), 5.17 (m, 1H), 4.82 (d, J = 1.5 Hz, 1H), 4.60 (s, 1H), 4.28 (m, 4H), 2.24- 2.05 (m, 2H), 1.79- 1.58 (m, 4H), 1.38- 1.25 (m, 2H), 0.93- 0.88 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.0, 154.9, 153.4, 145.9, 131.7, 128.7, 123.9, 122.5, 122.1, 120.6, 111.3, 71.4, 70.9, 53.9, 34.6, 29.7, 28.6, 28.2, 25.7; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ [M + H]$^+$: 483.1589 found 483.1581. Calculated for $C_{25}H_{23}F_5O_4Na$ [M + Na]$^+$: 505.1409, found 505.1407.



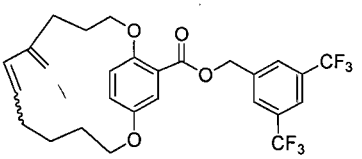
***Z*- 19B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.46 (d, J = 3.0 Hz, 1H), 7.09 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.44 (m, 2H), 5.39 (d, J = 15.6 Hz, 1H), 5.20- 5.09 (m, 1H), 4.83 (s, 1H), 4.54 (s, 1H), 4.28- 3.90 (m, 4H), 2.05- 1.57 (m, 4H), 1.42-1.19 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 152.9, 149.6, 145.4, 138.5, 135.8, 132.1 (q, CF_3), 129.3, 127.4, 123.6, 122.3, 121.6, 121.4, 120.3, 119.7, 111.0, 70.7, 70.6, 64.6, 29.3, 28.8, 27.9, 23.1, 22.3; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ [M + H]$^+$: 529.1808 found 529.1809. Calculated for $C_{27}H_{26}F_6O_4Na$ [M + Na]$^+$: 551.1627, found 505.1623.



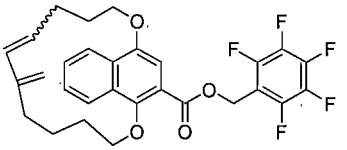
***E*- 21A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 3.0 Hz, 1H), 7.02 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 5.76 (d, *J* = 15.8 Hz, 1H), 5.43 (m, 2H), 4.81 (s, 1H), 4.74 (s, 1H), 4.63- 4.55 (m, 1H), 4.45- 4.37 (m, 1H), 4.24- 4.19 (m, 3H), 1.96- 1.80 (m, 6H), 1.72-1.40 (m, 2H), 1.37- 1.33 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 152.7, 150.1, 144.7, 133.1, 129.0, 124.0, 122.0, 121.0, 119.5, 112.9, 69.6, 67.8, 53.8, 30.8, 27.3, 26.8, 24.8, 22.8; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1593. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1408.



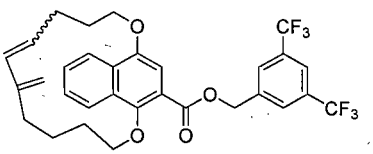
***E*- 23B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.41 (d, *J* = 3.1 Hz, 1H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 5.77 (d, *J* = 15.9 Hz, 1H), 5.48 (m, 2H), 4.80 (s, 1H), 4.73 (s, 1H), 4.63- 4.52 (m, 1H), 4.40- 4.51 (m, 1H), 4.28- 4.25 (m, 3H), 1.96- 1.79 (m, 6H), , 1.60-1.52 (m, 2H), 1.42-1.36 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 152.6, 150.2, 144.6, 138.9, 133.1, 132.7, 132.0 (q, CF_3), 129.0, 127.7, 124.2, 122.2, 122.0, 121.1, 119.3, 113.0, 69.4, 67.8, 64.9, 30.8, 27.3, 26.8, 24.8, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1808. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1607.



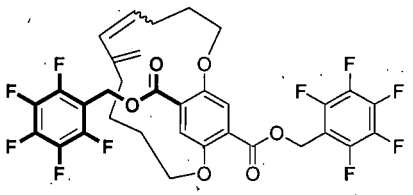
***Z*- 25A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.60- 7.54 (m, 2H), 7.20 (s, 1H), 5.48 (m, 2H), 5.09 (m, 1H), 4.92 (d, *J* = 15.9 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 1H), 4.50- 4.43 (m, 2H), 4.40 (s, 1H), 4.22- 4.06 (m, 2H), 2.17- 2.03 (m, 2H), 1.67- 1.53 (m, 2H), 1.24- 1.10 (m, 4H), 0.50 (m, 1H), 0.07 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.0, 151.5, 150.2, 145.7, 131.7, 129.8, 128.9, 128.2, 126.7, 124.4, 121.8, 116.9, 110.9, 108.6, 75.0, 70.2, 54.0, 35.0, 30.4, 28.3, 27.7, 27.5; **HRMS** (ES) Calculated for $C_{29}H_{26}F_5O_4$ $[M + H]^+$: 533.1745 found 533,1729. Calculated for $C_{29}H_{25}F_5O_5Na$ $[M + Na]^+$: 555.1571, found 555.1538.



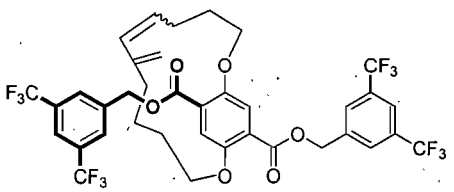
***Z*- 27B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, *J* = 8.3 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 2H), 7.90 (s, 1H), 7.65- 7.59 (m, 2H), 7.29 (m, 1H), 5.60- 5.53 (m, 2H), 5.20- 5.10 (m, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.59 (s, 1H), 4.52- 4.44 (m, 2H), 4.41 (s, 1H), 4.20- 4.00 (m, 2H), 2.28- 1.21 (m, 9H), 0.75- 0.46 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 151.5, 145.6, 138.8, 132.1, 131.2 (q, CF_3), 130.8, 129.8, 128.9, 128.2, 128.0, 126.7, 126.6, 124.5, 123.9, 122.1, 121.8, 111.5, 108.3, 103.9, 76.7, 70.0, 65.0, 34.9, 30.3, 28.3, 27.6, 24.0; **HRMS** (ES) Calculated for $C_{31}H_{29}F_6O_4$ $[M + H]^+$: 579.1965, found 579.1970. Calculated for $C_{31}H_{28}F_6O_4Na$ $[M + Na]^+$: 601.1784, found 601.1788.



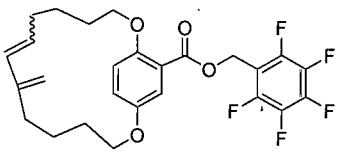
Z- 29A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (s, 1H), δ 7.39 (s, 1H), 5.43 (m, 4H), 5.30 (m, 2H), 4.77 (d, J = 1.4 Hz, 1H), 4.57 (s, 1H), 4.50- 4.00 (m, 4H), 2.21- 1.95 (m, 2H), 1.82- 1.30 (m, 4H), 0.98- 0.68 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.4, 164.2, 154.3, 152.1, 145.5, 131.7, 128.6, 126.5, 125.1, 123.8, 121.1, 113.3, 111.5, 71.9, 70.5, 53.4, 34.4, 29.6, 29.3, 28.1, 25.5; **HRMS** (ES) Calculated for $C_{33}H_{25}F_{10}O_6$ $[M + H]^+$: 707.1486 found 707.1489. Calculated for $C_{33}H_{24}F_{10}O_6Na$ $[M + Na]^+$: 729.1311, found 729.1319.



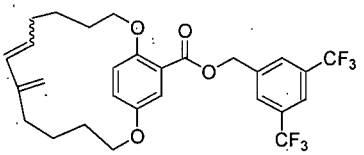
***E*- 31B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 4H), 7.87 (s, 2H), 7.51 (s, 1H), 7.48 (s, 1H), 5.70 (d, J = 15.2 Hz, 1H), 5.53- 5.37 (m, 4H), 4.93- 4.82 (m, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 4.43- 4.00 (m, 4H), 2.25- 0.88 (m, 10H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.3, 152.0, 150.7, 145.9, 143.0, 138.4, 138.4, 132.6, 132.3, 132.2, 131.8 (q, CF_3), 129.6, 128.7, 127.8, 125.8, 124.5, 122.1, 122.0, 121.8, 121.3, 120.9, 113.6, 79.0, 68.7, 65.8, 36.3.0, 31.9, 29.5, 27.9, 24.0; **HRMS** (ES) Calculated for $C_{37}H_{31}F_{12}O_6$ $[M + H]^+$: 799.1924, found 799.1924. Calculated for $C_{37}H_{30}F_{12}O_6Na$ $[M + Na]^+$: 821.1743, found 821.1742.



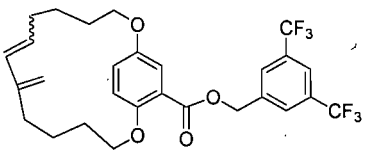
***E*- 33A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 3.1 Hz, 1H), 7.07 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 5.71 (d, J = 15.7 Hz, 1H), 5.41 (s, 2H), 4.90 (m, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.28- 4.17 (m, 4H), 1.93- 185 (m, 4H), 1.70- 1.38 (m, 4H), 1.30- 1.21 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 152.3, 151.2, 146.0, 132.6, 129.2, 123.2, 121.8, 120.3, 118.7, 113.4, 69.8, 68.6, 53.8, 32.3, 31.7, 29.9, 26.1, 25.4, 23.9; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_4$ $[M + H]^+$: 497.1745 found 497.1739. Calculated for $C_{26}H_{25}F_5O_4Na$ $[M + Na]^+$ 519.1571, found 519.1568.



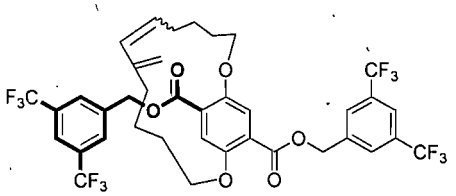
***E*- 35B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.44 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.9, 3.0 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.72 (d, J = 15.7 Hz, 1H), 5.47 (s, 2H), 4.93- 4.85 (m, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.35- 4.23 (m, 4H), 2.08- 1.86 (m, 4H), 1.80- 1.21 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 152.3, 151.1, 146.0, 138.9, 132.6, 132.0 (q, CF_3), 129.1, 127.7, 124.6, 123.4, 121.9, 121.8, 120.4, 118.6, 113.6, 69.8, 68.5, 64.9, 32.2, 31.6, 29.7, 26.0, 25.4, 23.9; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1965. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1784.



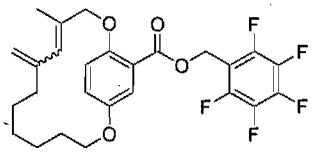
***E*- 37B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 2H), 7.85 (s, 1H), 7.40 (d, J = 2.9 Hz, 1H), 7.06 (dd, J = 8.9, 2.9 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 5.73 (d, J = 15.7 Hz, 1H), 5.45 (s, 2H), 4.99- 4.89 (m, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 4.33- 4.24 (m, 4H), 2.10- 1.91 (m, 2H), 1.85- 1.80 (m, 2H), 1.70- 1.11 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 153.0, 150.5, 145.8, 138.8, 132.6, 131.7 (q, CF_3), 129.1, 127.7, 124.5, 123.4, 122.1, 121.9, 120.3, 119.6, 113.5, 70.9, 68.0, 64.9, 32.2, 31.7, 29.7, 26.2, 25.2, 24.0; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965 found 543.1968. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1784.



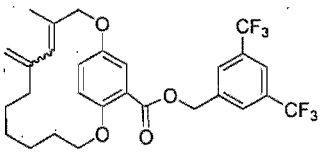
***E*- 39B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 4H), 7.87 (s, 2H), 7.52 (s, 1H), 7.47 (s, 1H), 5.70 (d, J = 15.5 Hz, 1H), 5.57- 5.38 (m, 4H), 4.91- 4.80 (m, 1H), 4.70 (s, 1H), 4.65 (s, 1H), 4.40- 3.97 (m, 4H), 2.21- 0.83 (m, 12H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 165.0, 152.0, 150.2, 145.5, 144.0, 138.5, 138.4, 132.6, 132.3, 132.2, 131.8 (q, CF_3), 129.6, 128.7, 127.8, 125.8, 124.5, 122.1, 122.0, 121.8, 120.8, 120.1, 113.5, 71.7, 68.7, 65.3, 37.0, 31.6, 29.7, 27.4, 24.6, 23.9; **HRMS** (ES) Calculated for $C_{38}H_{33}F_{12}O_6$ $[M + H]^+$: 813.2080, found 813.2074. Calculated for $C_{38}H_{32}F_{12}O_6Na$ $[M + Na]^+$: 835.1900, found 835.1894.



***Z*- 41A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, *J* = 3.0 Hz, 1H), 7.08 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.96 (s, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 5.40 (m, 2H), 4.60 (d, *J* = 1.9 Hz, 1H), 4.38 (s, 1H), 4.73- 4.47 (m, 2H), 4.25- 4.01 (m, 2H), 2.20- 1.93 (m, 2H), 1.43- 0.83 (m, 9H), 0.45- 0.35 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.9, 152.3, 151.8, 145.9, 133.6, 132.2, 128.8, 126.3, 123.2, 118.5, 112.7, 73.8, 67.6, 53.7, 36.1, 29.9, 29.7, 27.5, 23.9, 15.2; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_5$ $[M + H]^+$: 497.1746 found 497.1746. Calculated for $C_{26}H_{25}F_5O_5Na$ $[M + Na]^+$: 519.1565, found 519.1564.



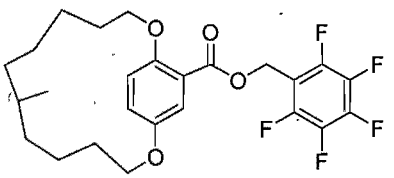
***Z*- 43B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 2H), 7.85 (s, 1H), 7.37 (d, *J* = 3.0 Hz, 1H), 7.08 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.91 (d, *J* = 9.1 Hz, 1H), 5.72 (s, 1H), 5.45- 5.40 (m, 2H), 4.75 (s, 1H), 4.40 (s, 1H), 4.39 (s, 2H), 4.20- 3.99 (m, 2H), 2.25- 0.80 (m, 13H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 152.3, 151.9, 145.9, 139.0, 135.0, 133.6, 133.5, 132.0, 131.7 (q, CF_3), 127.9, 127.2, 125.5, 118.4, 117.3, 112.7, 73.8, 67.4, 64.8, 36.0, 29.7, 27.3, 23.9, 21.3, 15.2; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_5$ $[M + H]^+$: 543.1965, found 543.1964. Calculated for $C_{28}H_{28}F_6O_5Na$ $[M + Na]^+$: 565.1784, found 565.1783.

General procedure for the hydrogenation of the ene-yne metathesis products

A general procedure for the hydrogenation of 1,3- diene paracyclophanes is detailed below. As a model, products **8A, 33A** *and* **37B** *were fully hydrogenated and the characterization data for the compounds produced are described below.*

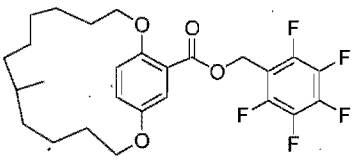
A flame dried round bottom flask, equipped with a magnetic stirrer was added the 1,3-diene product (1.0 eq.) and a mixture of ethyl acetate: MeOH (10:1). The catalyst $Pd(OH)_2/C$ (10 mol %)[9] was added the sealed flask was fitted with a baloon of $H_2(g)$. The reaction mixture was stirred at room temperature for 15 h and the balloon of $H_2(g)$ was typically refilled halfway through the reaction. The reaction mixture was concentrated in vacuo, dry-packed and purified by flash column silica chromatography (Hexanes-Ethyl Acetate 20:1) to afford the desired paracyclophanes. As a consequence of the presence of atropisomerism (due to the rigidity of the macrocycle) and the introduction of a stereogenic methyl group following hydrogenation, a mixture of inseparable diastereoisomers is present. Therefore, all ^1H and ^{13}C NMR signals are 'doubled' (see spectra for more details).



H_4- 8A

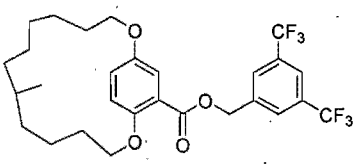
[9] Other catalysts such as Pd/C and PtO_2 were not effective for the hydrogenation.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H), 7.10 (m, 1H), 7.00 (d, J = 9.0 Hz, 1H), 5.41 (m, 2H), 4.30- 4.13 (m, 4H), 1.90- 0.82 (br, 15H), 0.70- 0.63 (d, J = 6 Hz, 3H);**^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 153.7, 153.2, 128.8, 121.8, 121.0, 120.3, 71.5, 69.6, 53.7, 35.5, 34.4, 31.8, 30.7, 28.4, 25.3, 23.9, 22.0, 19.6; **HRMS** (ES) Calculated for $C_{25}H_{28}F_5O_4$ $[M + H]^+$: 487.1902 found 487.1900. Calculated for $C_{25}H_{27}F_5O_4Na$ $[M + Na]^+$: 509.1721, found 509.1728.



H_4- 33A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, J = 2.8 Hz, 1H), 7.08 (dd, J = 8.9, 2.8 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.42 (s, 2H), 4.28- 4.14 (br, 4H), 1.85- 1.70 (br, 4H), 1.28- 0.75 (br, 13H), 0.71 (d, J = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.3, 153.0, 152.7, 123.1, 121.6, 119.3, 118.9, 69.9, 69.2, 53.7, 35.3, 34.3, 32.4, 29.7, 29.2, 27.7, 26.1, 24.2, 22.7, 20.3. **HRMS** (ES) Calculated for $C_{26}H_{30}F_5O_4$ $[M + H]^+$: 501.2059 found 501.2061. Calculated for $C_{26}H_{29}F_5O_4Na$ $[M + Na]^+$: 523.1878, found 523.1881.



H_4- 37B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.43 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.9, 3.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 5.46 (s, 2H), 4.29- 4.22 (m, 4H), 2.25- 1.89 (m, 2H), 1.60-

1.57 (m, 2H), 1.38- 1.20 (m, 9H), 1.15- 0.88 (m, 4H), 0.69 (d, J = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.2, 138.8, 132.6, 132.0 (q, CF_3), 129.7, 128.8, 126.6, 122.0, 121.5, 120.4, 118.6, 70.2, 68.8, 64.9, 35.2, 34.3, 29.2, 29.0, 27.9, 24.1, 22.4, 22.3, 20.3, 14.0; **HRMS** (ES) Calculated for $C_{28}H_{33}F_6O_4$ $[M + H]^+$: 547.2278, found 547.2279. Calculated for $C_{28}H_{32}F_6O_4Na$ $[M + Na]^+$: 569.0297, found 569.2097.

Results of MP2 energies and DFT calculations

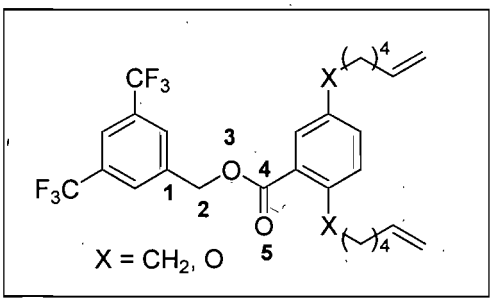
In evaluating the conformational control elements described herein, we assumed that the relative aromatic-aromatic conformational geometry in the substrates might play a crucial role in determining the product of the reaction. As such, several possible lowest energy initial geometries for each substrate were generated by a conformational search at the AM1 level.

Subsequently, we wished to further refine the geometries and energies of the open and stacked conformers and turned to the second-order Møller–Plesset (MP2) and DFT methods. Given that recent MP2 calculations for the hexafluorobenzene:benzene complex shows that dispersion forces are important for the stabilisation of the complex,[10] we first investigated MP2 level of theory in an attempt to include dispersion interactions, despite the fact that this method is very time-consuming.

However, due to the evident importance of correlation effects in the hexafluorobenzene:benzene interaction, it also seemed possible that density functional theory (DFT) could be valuable. We therefore evaluated each substrate conformer at the B3LYP/6–31G* level. Although the results obtained from the DFT are commented on in the main text, Table S1 summarizes also the results obtained from the MP2 calculations and shows that the MP2 correlation energies produced by this level of theory follow the same tendencies as the heats of formation obtained through DFT.

Table SI1: MP2 Energies and DFT Heats of Formation.

[10] (a) Hernandez-Trujillo, J.; Colmenares, F.; Cuevas, G.; Costas, M. *Chem Phys. Lett.* **1997**, *265*, 503. (b) Vanspeybrouck, W.; Herrebout, W. A.; van der Veken, B. J.; Lundell, J.; Perutz, R. N. *J. Phys. Chem. B,* **2003**, *107*, 13855.



Molecule	MP2 Energy (kcal/mol)	DFT Heat of Formation (kcal/mol)
5*	O: -899.38	O: -255.7
	S: -901.23	S: -255.9
44	O: -1283.01	O: -351.77
	S: -1288.29	S: -353.05
45	O: -1231.43	O: -207.49
	S: -1233.01	S: -208.04
46	O: -1311.27	O: -309.04
	S: -1313.08	S: -309.44

Table SI2: Dihedral Angles (as defined below)

Molecule	Dihedral angle 2 (2-3-4-5)		Dihedral angle 1 (1-2-3-4)	
5	O: 30	O: 29.38	O: 172.17	O: 173.98
	S: 165.4	S: 171.63	S: 71.38	S: 81.88
44	O: -175.12	O: -176.96	O: 89.66	O: -138.78

	S: -177.41	S: -177.43	S: 72.19	S: 88.41
45	O: 40.38	O: 77.16	O: 167.97	O: 127.89
	S: 151.93	S: 140.38	S: 63.25	S: 67.97
46	O: -176.96	O: 160.75	O: -138.78	O*: 122.27
	S: 162.18	S: -175.18	S: 83.04	S: 89.66

NMR spectra of all precursors and metathesis products

Development of Perfluoroarene:Arene Interactions for Macrocyclic En-Yne Metathesis and the Total Synthesis of Macrocyclic Natural Products.

Table of contents

SUPPORTING INFORMATION

General

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[1]. Isolated yields reflect the mass obtained following flash column silica gel chromatography using the method reported by W. C. Still[2] and using silica gel (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 coated with a fluorescence indicator (0.25 mm, F_{254}.). All the compounds were UV active, and no development of the TLCs was required. Visualization of TLC plate was performed by UV (254 nm). 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 ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$.Signals due to the solvent served as the internal standard. The acquisition parameters are shown on all spectra. The ^{1}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. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling, 2D COSY experiments. The ^{13}C NMR assignments were

[1] D. F. Shriver, M. A. Drezdon, *The Manipulation of Air-Sensitive Compounds*; 2nd Edition, ed.; Wiley: New York, 1986.
[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by two dimensional H/C correlation experiments (HSQC). High resolution mass spectroscopy (HRMS) was done using ESI mode of ionization. Charged molecular ion $[M+H]^+$ and $[M+Na]^+$ data are reported.

Preparation of ene-yne precursors

A general procedure for the preparation of precursors **7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 24A- 26B- 28A- 30B- 32A- 34B- 36B- 38- 40A- 42B** *is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that in general, we do not observe any ^{13}C NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary or for the CF_3 carbon. In select cases where a different synthetic route was necessary, these procedures are described in detail.*

Ene-Yne precursors **7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 32A- 34B- 36B- 40A- 42B** were prepared following this sequence:

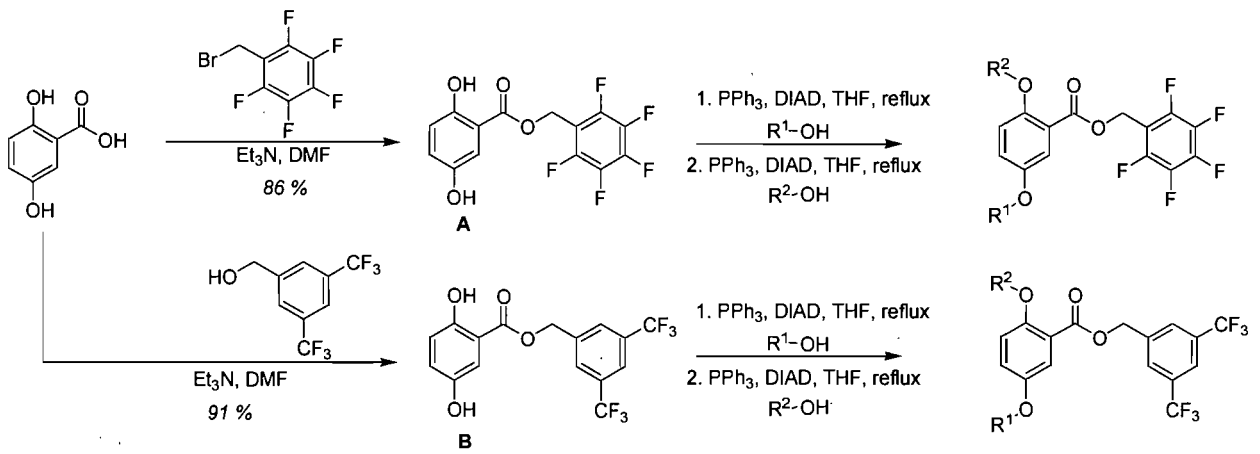
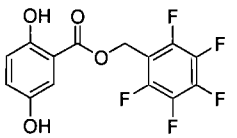


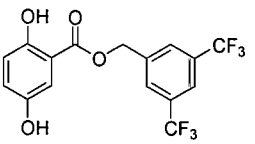
***Figure SI1: Preparation of metathesis precursors* 7A- 10B- 12A- 14B- 16A- 18B- 20A- 22B- 32A- 34B- 36B- 40A *and* 42B.**



A

In a round bottom flask, 2, 5-dihydroxybenzoic acid (154 mg, 1.00 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop wise, the reaction is exothermic. Then, pentafluorobenzyl bromide (0.140 mL, 1.0 mmol, 1.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (287 mg, 86 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.07 (s, 1H), 7.21 (d, J = 3.1 Hz, 1H), 7.03 (dd, J = 9.0, 3.1 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 5.46 (s, 2H), 4.56 (s, 1H),; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.8, 156.1, 147.7, 124.7, 118.7, 114.6, 111.3, 54.0; **HRMS** (ES) Calculated for $C_{14}H_8F_5O_4$ $[M + H]^+$: 335.0337 found 335.0342.



B

In a round bottom flask, 2, 5-dihydroxybenzoic acid (154 mg, 1.00 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop

wise, the reaction is exothermic. Then, 3,5-di(trifluoromethyl)benzyl bromide (310 mg, 1.0 mmol, 1.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reaction could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (346 mg, 91 %).^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.17 (s, 1H), 7.89 (s, 3H), 7.30 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 9.1, 3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.45 (s, 2H), 4.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 156.1, 147.8, 137.7, 132.1 (q, CF_3), 128.4, 124.8, 122.6, 121.7, 118.8, 114.5, 111.4, 65.3; **HRMS** (ES, negative mode of ionization) Calculated for $C_{16}H_9F_6O_4$ [M - H]$^-$: 379.0405 found 379.0423.

Ene-Yne precursor **28A** was prepared following this sequence:

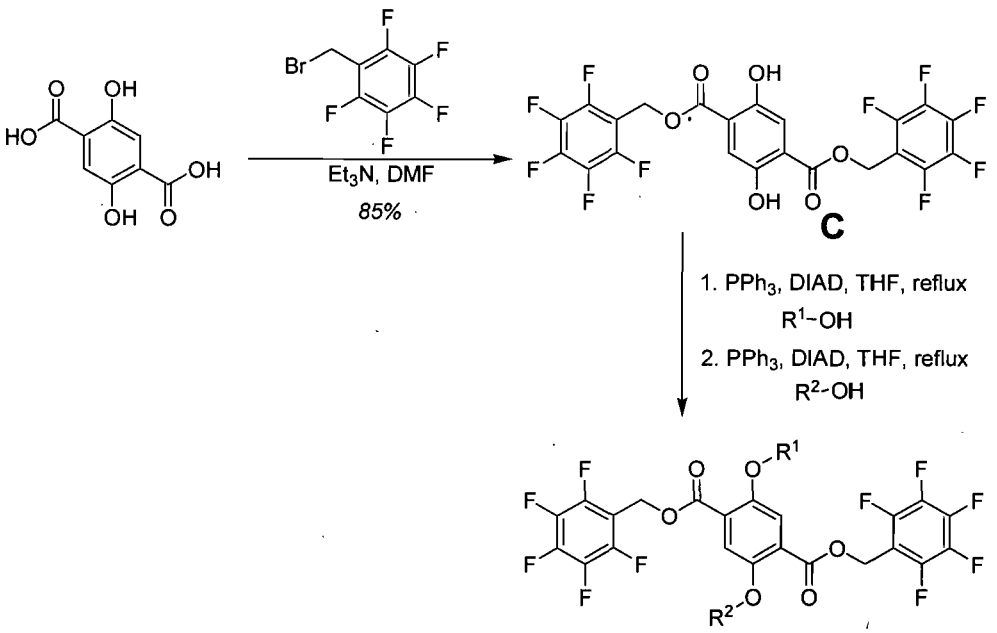
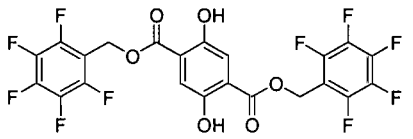


***Figure SI2: Preparation of metathesis precursor* 28A.**



C

In a round bottom flask, 2,5-dihydroxy-terephtalic acid (198 mg, 1.0 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF. Triethylamine (0.280 mL, 2.0 mmol, 2.0 equiv.) is added drop wise. The reaction is exothermic. Then, pentafluorobenzyl bromide (0.280 mL, 2.0 mmol, 2.0 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 4:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colorless solid (475 mg, 85 %). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.79 (s, 2H), 7.41 (s, 2H), 5.48 (s, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.1, 153.0, 118.0, 117.9, 54.5; **HRMS** (ES) Calculated for $C_{22}H_9F_{10}O_6$ $[M + H]^+$: 559.0239 found 559.0226.

Ene-Yne precursor **24A** was prepared following this sequence:

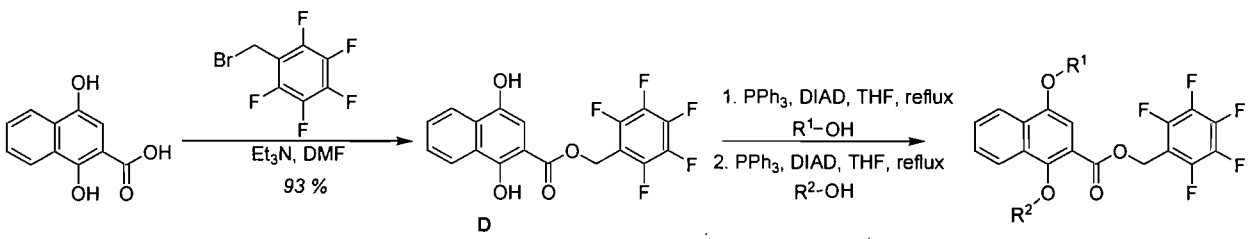
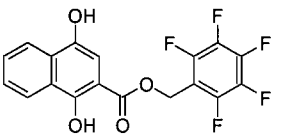


***Figure SI3: Preparation of metathesis precursor* 24A**



D

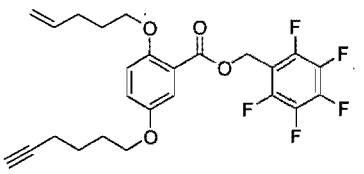
In a round bottom flask, 1, 4-dihydroxy-2-naphthanoic acid (204 mg, 1.0 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and triethylamine (0.140 mL, 1.0 mmol, 1.0 equiv.) is added drop wise, the reaction is exothermic. Then, pentafluorobenzyl bromide (0.140 mL, 1.0 mmol, 1.0 equiv.) is added to the mixture.The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 7:1) to afford the product as a colourless solid (358 mg, 93 %).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ 11.30 (s, 1H), 8.39 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 5.50 (s, 2H), 4.92 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.7, 156.2, 143.3, 129.4, 129.1, 126.6, 125.5, 124.1, 121.7, 104.7, 103.5, 53.9; **HRMS** (ES, negative mode of ionization) Calculated for $C_{18}H_8F_5O_4$ $[M - H]^-$: 383.0342 found 383.0351.

General procedure for alkylations via the Mitsunobu reaction.

In a round bottom flask, pentafluorobenzyl-2, 5-dihydroxybenzoate (1.0 eq.) was added to triphenylphosphine (1.2 eq.) and the alkenyl or alkynyl alcohol (0.5 to 0.6 eq.)[3]. This mixture was then dissolved in dry THF and heated to reflux. DIAD (1.2 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was

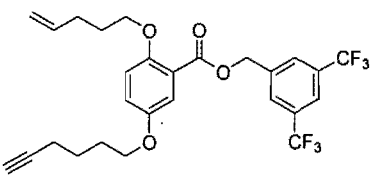
[3] This stochiometry is important to avoid the formation of dialkylated product.

complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). Isolated yields were obtained in the range of 55- 90%. The products were immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (1.0 eq.) was added to triphenylphosphine (1.6 eq.) and the alkenyl or alkynyl alcohol (1.2 eq.). This mixture was then dissolved in dry THF and heated to reflux. While under reflux, DIAD (1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). Isolated yields of approximately 60 % were typically obtained.



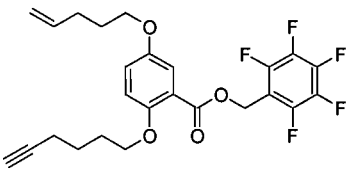
7A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 5.82 (m, 1H), 5.39 (s, 2H), 5.06- 4.97 (m, 2H), 3.97- 3.86 (m, 4H), 2.24- 2.20 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.87- 1.83 (m, 4H), 1.66- 1.63 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.0, 152.4, 146.9, 120.6, 119.6, 116.8, 115.1, 115.0, 84.0, 68.8, 68.6, 68.0, 53.6, 29.8, 28.3, 28.2, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1591. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1470.



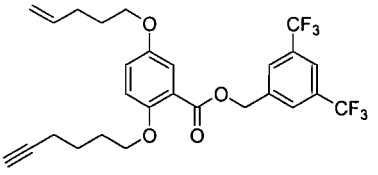
10B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.37 (d, J = 3.2 Hz, 1H), 7.05 (dd, J = 9.1, 3.2 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.75 (m, 1H), 5.44 (s, 2H), 4.98- 4.90 (m, 2H), 4.05 (t, J = 6.1 Hz, 2H), 3.99 (t, J = 6.6 Hz, 2H), 2.41- 2.37 (m, 2H), 2.04- 1.96 (m, 5H), 1.77- 1.73 (m, 2H), 1.53- 1.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.1, 152.2, 138.8, 138.4, 132.0 (q, CF_3), 128.0, 127.2, 121.8, 120.8, 119.8, 115.0, 114.7, 121.8, 120.8, 83.3, 69.4, 68.9, 66.8, 64.9, 33.2, 28.5, 28.1, 25.1, 15.1; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1803. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1627.



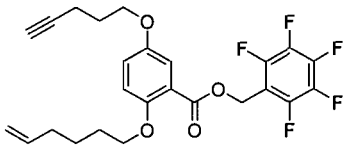
16A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 5.82 (m, 1H), 5.39 (s, 2H), 5.06- 4.97 (m, 2H), 3.97- 3.86 (m, 4H), 2.24- 2.20 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.87- 1.83 (m, 4H), 1.66- 1.63 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 152.9, 152.3, 137.6, 120.6, 119.5, 116.9, 115.1, 114.8, 83.9, 68.8, 68.5, 67.0, 53.5, 30.0, 28.3, 28.2, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1597. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1483.



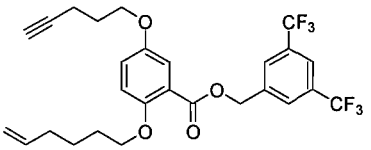
18B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.03 (dd, J = 9.1, 3.1 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.75 (m, 1H), 5.44 (s, 2H), 4.99- 4.92 (m, 2H), 4.00- 3.94 (m, 4H), 2.27- 2.24 (m, 2H), 1.17- 1.12 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.92- 1.69 (m, 4H), 1.80- 1.60 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.0, 152.4, 138.8, 137.5, 131.9 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 115.1, 115.0, 84.0, 68.8, 68.6, 67.9, 64.9, 29.8, 28.2, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1811. Calculated for $C_{27}H_{26}F_5O_4Na$ $[M + Na]^+$: 551.1627, found 551.1632.



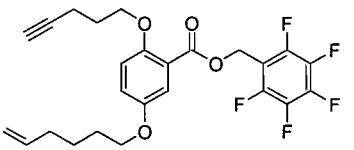
12A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.0, 3.1 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 5.85 (m, 1H), 5.39 (s, 2H), 5.02- 4.94 (m, 2H), 4.02 (t, J = 6.1 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 2.40- 2.36 (m, 2H), 2.40- 2.36 (m, 2H), 2.03- 2.10 (m, 2H), 2.00- 1.94 (m, 3H), 1.76- 1.70 (m, 2H), 1.52- 1.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.2, 152.1, 138.4, 120.6, 119.6, 116.9, 114.9, 114.6, 83.3, 69.4, 68.9, 66.7, 53.6, 33.3, 28.6, 28.1, 25.1, 15.1; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1592. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1408.



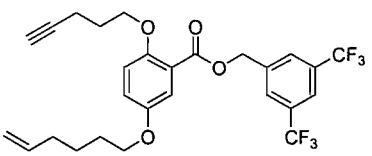
14B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 2H), 7.87 (s, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.06 (dd, J = 9.1, 3.1 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 5.85 (m, 1H), 5.46 (s, 2H), 5.09- 5.02 (m, 2H), 4.02 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 2.27- 2.20 (m, 4H), 1.98- 1.86 (m, 5H), 1.68- 1.64 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 152.9, 152.5, 138.8, 137.7, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 122.1, 121.6, 121.8, 120.8, 119.7, 116.8, 115.2, 114.9, 83.9, 68.9, 68.7, 67.8, 64.9, 30.0, 28.4, 28.1, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1804. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1623.



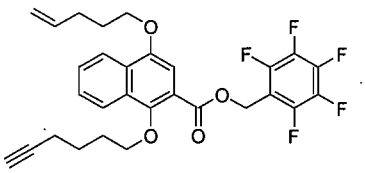
20A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 3.2 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 5.83 (m, 1H), 5.40 (s, 2H), 5.05- 4.98 (m, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.92 (t, J = 6.4 Hz, 2H), 2.33- 2.30 (m, 2H), 2.13- 2.10 (m, 2H), 1.95- 1.91 (m, 3H), 1.79- 1.75 (m, 2H); 1.59- 1.53 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 152.5, 152.2, 138.1, 120.4, 119.1, 116.6, 114.6, 114.4, 83.0, 68.4, 68.1, 67.4, 53.3, 33.0, 28.3, 27.9, 24.9, 14.7; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1572. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1449.



22B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 2H), 7.85 (s, 1H), 7.36 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 5.80 (m, 1H), 5.43 (s, 2H), 5.04- 4.96 (m, 2H), 4.07 (t, J = 6.0 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 2.34- 2.30 (m, 2H), 2.15- 2.10 (m, 2H), 1.96- 1.76 (m, 3H), 1.60- 1.53 (m, 2H), 1.71- 1.50 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.8, 152.6, 138.7, 138.4, 131.7 (q, CF_3), 128.1, 127.2, 124.5, 122.2, 122.1, 122.0, 121.8, 120.8, 119.8, 115.2, 114.8, 83.2, 68.8, 68.5, 67.8, 64.9, 33.4, 28.6, 28.0, 25.2, 14.9; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1796. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1607.



24A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (m, 1H), 8.15 (m, 1H), 7.59 (m, 2H), 7.11 (s, 1H), 5.90 (m, 1H), 5.50 (s, 2H), 5.12- 5.01 (m, 2H), 4.15 (t, J = 6.3 Hz, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.35- 2.30 (m, 4H), 2.05- 1.93 (m, 5H), 1.82- 1.75 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 151.3, 150.7, 137.7, 129.3, 129.2, 128.0, 127.1, 123.5, 122.8, 117.8, 115.3, 104.1, 83.9, 75.7, 68.6, 67.5, 53.9, 30.3, 29.3, 28.4, 25.0, 18.3; **HRMS** (ES) Calculated for $C_{29}H_{26}F_5O_4$ $[M + H]^+$: 533.1745 found 533.1768. Calculated for $C_{29}H_{25}F_5O_4Na$ $[M + Na]^+$: 555.1571, found 555.1594.

Ene-Yne precursor **26B** was prepared following this sequence:

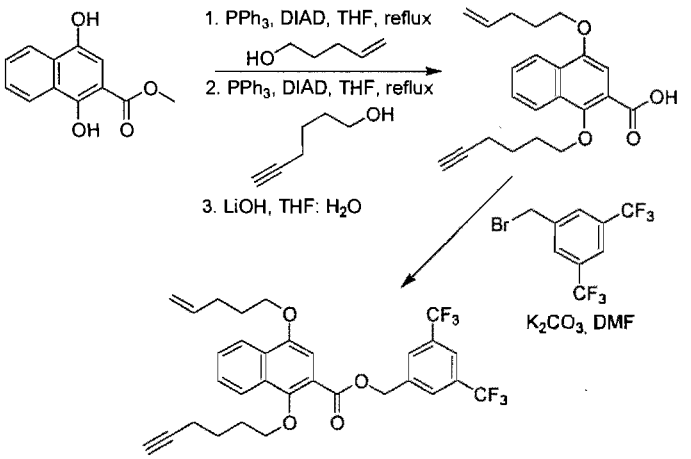
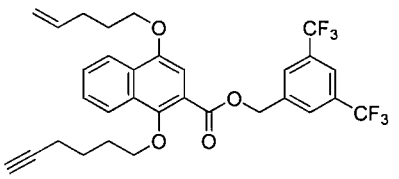


***Figure SI4: Preparation of metathesis precursor* 26B**

In a round bottom flask, methyl-1, 4-dihydroxy-2-naphthanoic acid (500mg, 2.29 mmol, 1.0 eq.) was added to triphenylphosphine (720 mg, 2.75 mmol, 1.2 eq.) and pent-4-en-1-ol (0.115 mL, 1.15 mmol, 0.5 eq.)[4] was added. This mixture was then dissolved in dry THF (12 mL) and heated to reflux. DIAD (0.56 mL, 2.75 mmol, 1.2 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (320 mg, 1.12 mmol, 1.2 eq.) was added to triphenylphosphine (470 mg, 1.8 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.145 mL, 1.34 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (10 mL) and heated to reflux. While under reflux, DIAD (0.265 mL, 1.8 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H2O (4:1, 30 mL) and LiOH (230 mg, 9.5 mmol, 10 eq.) was added. The mixture was stirred at reflux for

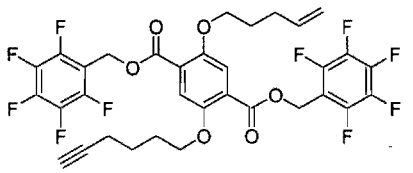
[4] This stochiometry is important to avoid the formation of dialkylated product.

18 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 30 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford a crude solid. The crude solid (316 mg, 0.90 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF. K_2CO_3 (740 mg, 5.5 mmol, 5.0 equiv.) is added. Then 3, 5-di (trifluoromethyl)benzyl bromide (330 mg, 1.1 mmol, 1.2 equiv.) is added to the mixture. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reaction could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether and washed with brine (2 * 30 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



26B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (m, 1H), 8.21 (m, 1H), 8.00(s, 2H), 7.91 (s, 1H), 7.63- 7.59 (m, 2H), 7.19 (s, 1H), 5.90 (m, 1H), 5.53 (s, 2H), 5.14- 5.05 (m, 2H), 4.17 (t, J = 6.2 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H), 2.37- 2.27 (m, 4H), 2.06- 1.99 (m, 5H), 1.82- 1.70 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 151.3, 150.7, 138.7, 137.6, 131.4 (q, CF_3), 129.3, 129.1, 128.1, 127.9, 127.1, 124.5, 123.4, 122.3, 122.1, 117.9, 115.2, 103.9, 83.9, 75.6, 68.6, 67.4, 65.0, 31.5, 30.2, 29.3, 25.2, 18.2; **HRMS** (ES) Calculated for $C_{31}H_{29}F_6O_4$ $[M + H]^+$: 579.1965, found 579.1963. Calculated for $C_{31}H_{28}F_6O_4Na$ $[M + Na]^+$: 601.1784, found 601.1785.



28A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (s, 2H), 5.77 (m, 1H), 5.42 (s, 4H), 5.01- 4.97 (m, 2H), 4.00- 3.94 (m, 4H), 2.24- 2.20 (m, 2H), 2.14- 2.12 (m, 2H), 1.95 (s, 1H), 1.86- 1.64 (m, 4H), 1.65- 1.61 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 165.1, 151.8, 151.7, 137.4, 123.5, 116.6, 116.5, 115.2, 83.8, 68.9, 68.7, 68.6, 54.0, 29.8, 28.1, 28.0, 24.8, 18.0; **HRMS** (ES) Calculated for $C_{33}H_{25}F_{10}O_6$ $[M + H]^+$: 707.1486 found 707.1483. Calculated for $C_{33}H_{24}F_{10}O_6Na$ $[M + Na]^+$: 729.1311, found 729.1316.

Ene-Yne precursor **30B** was prepared following this sequence:

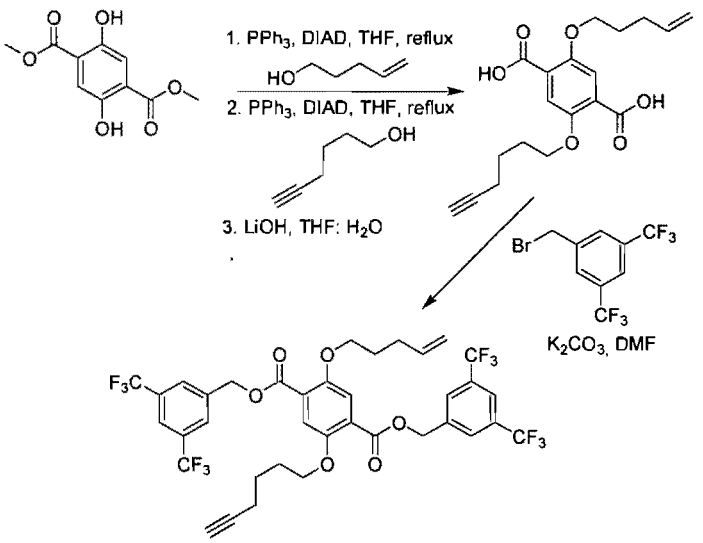
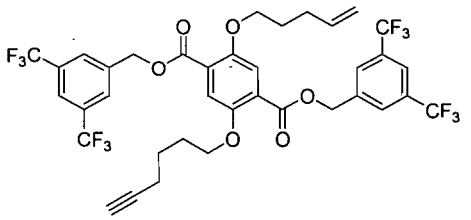


***Figure SI5: Preparation of metathesis precursor* 30B**

In a round bottom flask, methyl-2, 5-dihydroxybenzene dicarboxylate (250 mg, 1.1 mmol, 1.0 eq.) was added to triphenylphosphine (434 mg, 1.66 mmol, 1.5 eq.) and pent-4-en-1-ol (0.056 mL, 0.55 mmol, 0.50 eq.) [5] was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. DIAD (0.338 mL, 1.66 mmol, 1.5 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (177 mg, .605 mmol, 1.0 eq.) was added to triphenylphosphine (253 mg, 0.97 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.082 mL, 0.726 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. While under reflux, DIAD (0.20 mL, 0.97 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H_2O (4:1, 20 mL) and LiOH (120 mg, 5 mmol, 10 eq.) was added. The mixture was stirred at reflux for 15 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated to afford a crude solid. The crude solid (160 mg, 0.46 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and 3, 5-di(trifluoromethyl)benzyl bromide (169 mg, 0.55 mmol, 1.2 eq.) is added to the mixture. K_2CO_3 (370 mg, 2.75 mmol, 5.0 equiv.) is then added. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether

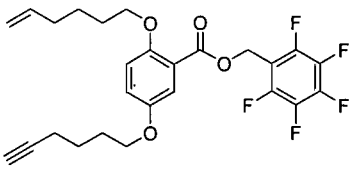
[5] This stochiometry is important to avoid the formation of dialkylated product.

and washed with brine (2 * 25 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



30B

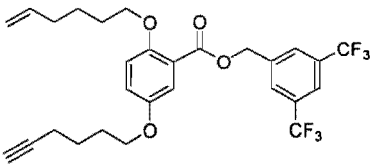
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.87 (s, 1H), 7.43 (s, 2H), 5.75 (m, 1H), 5.47 (s, 4H), 4.97- 4.92 (m, 2H), 4.07- 4.01 (m, 4H), 2.19- 2.12 (m, 4H), 1.91- 1.80 (m, 5H), 1.70- 1.55 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.4, 151.8, 151.7, 138.4, 138.3, 137.2, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 123.8, 122.3, 122.2, 121.7, 119.1, 116.6, 116.5, 115.3, 83.8, 68.9, 68.7, 68.6, 65.3, 65.2, 29.7, 28.1, 28.0, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{37}H_{31}F_{12}O_6$ $[M + H]^+$: 799.1924, found 799.1925. Calculated for $C_{37}H_{30}F_{12}O_6Na$ $[M + Na]^+$: 821.1743, found 821.1743.



32A

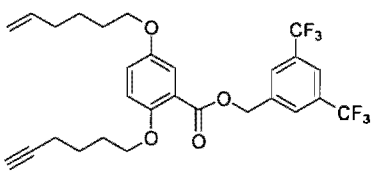
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.5, 3.1 Hz, 1H), 6.86 (d, J = 9.7 Hz, 1H), 5.78 (m, 1H), 5.39 (s, 2H), 5.03- 4.94 (m, 2H), 3.95- 3.92 (t, J = 6.1 Hz, 4H), 2.27- 2.24 (m, 2H), 2.09- 2.06 (m, 2H), 1.95 (t, J = 2.5 Hz, 1H), 1.90- 1.85 (m, 2H), 1.76- 1.67 (m, 4H), 1.52- 1.49 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 153.1, 152.3, 138.4, 120.6, 119.6, 116.8, 114.9,

114.6, 84.0, 69.4, 68.6, 67.9, 53.6, 33.3, 28.6, 28.2, 25.1, 24.9, 18.1; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_4$ $[M + H]^+$: 497.1745 found 497.1739. Calculated for $C_{26}H_{25}F_5O_4Na$ $[M + Na]^+$: 519.1571, found 519.1568.



34B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.85 (s, 1H), 7.36 (d, J = 3.0 Hz, 1H), 7.03 (dd, J = 9.1, 3.0 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.73 (m, 1H), 5.44 (s, 2H), 4.99- 4.91 (m, 2H), 4.00- 3.94 (m, 4H), 2.28- 2.21 (m, 2H), 2.10- 2.00 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.87- 1.80 (m, 2H), 1.77- 1.65 (m, 4H), 1.55- 1.45 (m 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 153.1, 152.3, 138.8, 138.4, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 114.9, 114.6, 84.0, 69.4, 68.6, 68.0, 64.9, 33.2, 28.5, 25.1, 25.0, 24.8, 18.1; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1972. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$:565.1784, found 565.1790.



36B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.88 (s, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.06 (dd, J = 9.1, 3.0 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 5.83 (m, 1H), 5.47 (s, 2H), 5.07- 4.97 (m, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 2.22- 2.10 (m, 4H), 1.94- 1.78 (m, 5H), 1.69- 1.50 (m, 4H); **^{13}C**

NMR ($CDCl_3$, 100 MHz) δ 165.8, 152.9, 152.5, 138.8, 138.4, 131.7 (q, CF_3), 128.0, 127.2, 124.5, 122.0, 121.8, 120.8, 119.7, 116.7, 114.9, 114.7, 83.9, 68.9, 68.5, 68.4, 64.8, 33.3, 28.6, 28.1, 25.2, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1969. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1781

Ene-Yne precursor **38B** was prepared following this sequence:

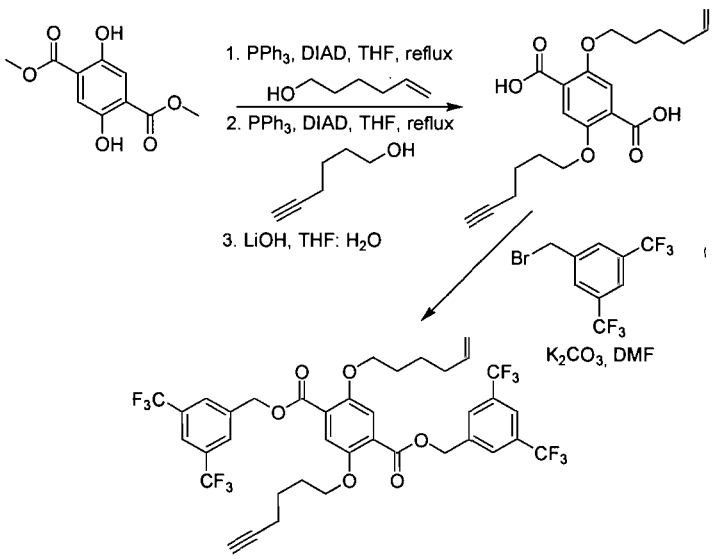
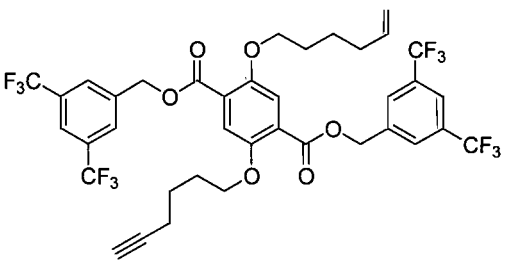


***Figure SI6: Preparation of metathesis precursor* 38B**

In a round bottom flask, methyl-2, 5-dihydroxybenzene dicarboxylate (250 mg, 1.1 mmol, 1.0 eq.) was added to triphenylphosphine (434 mg, 1.66 mmol, 1.5 eq.) and Hexen-5-en-1-ol (0.066 mL, 0.55 mmol, 0.50 eq. [6]) was added. This mixture was then dissolved in dry THF (10 mL) and heated to reflux. DIAD (0.338 mL, 1.66 mmol, 1.5 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 20:1). The product was immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (185 mg, .60 mmol, 1.0 eq.) was added to triphenylphosphine (253 mg, 0.97 mmol, 1.6 eq.) and hex-5-yn-1-ol (0.080 mL, 0.72 mmol, 1.2 eq.) was added. This mixture was then dissolved in dry THF (6 mL) and heated to reflux. While under reflux, DIAD (0.19 mL, 0.95 mmol, 1.6 eq.) was added drop wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the

[6] This stochiometry is important to avoid the formation of dialkylated product.

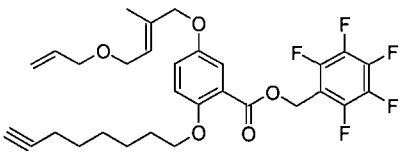
reaction mixture was concentrated, dry-packed and purified by flash chromatography using (Hexanes: Ethyl acetate 10:1). The product was subsequently dissolved in a mixture of THF: H_2O (4:1, 20 mL) and LiOH (120 mg, 5 mmol, 10 eq.) was added. The mixture was stirred at reflux for 15 hours. The reaction mixture was then quenched with HCl (10%) until acidic pH was obtained. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated to afford a crude solid. The crude solid (160 mg, 0.46 mmol, 1.0 equiv.) is dissolved at room temperature in dry DMF and 3, 5-di (trifluoromethyl)benzyl bromide (170 mg, 0.55 mmol, 1.2 eq.) is added to the mixture. K_2CO_3 (370 mg, 2.75 mmol, 5.0 equiv.) is then added. The reaction was monitored by TLC (Hexanes: Ethyl acetate 7:1) and was typically complete after 1 hour, although reactions could be left overnight at room temperature. The DMF is then evaporated under vacuum, the reaction mixture acidified with HCl (10%) until no more CO_2 was formed. The mixture was extracted many times with diethyl ether and washed with brine (2 * 25 mL). After drying over $MgSO_4$ and evaporation the residue was dry-packed and purified by flash column silica chromatography using (Hexanes: Ethyl acetate 10:1) to afford the product as a colourless oil.



38B

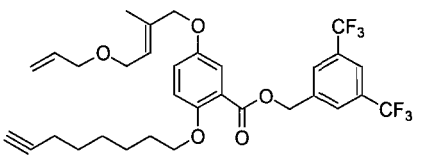
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 4H), 7.87 (s, 2H), 7.43 (s, 2H), 5.71 (m, 1H), 5.47 (s, 4H), 4.98- 4.92 (m, 2H), 4.07- 4.01 (m, 4H), 2.19- 2.16 (m, 2H), 2.10- 1.97 (m, 2H), 1.90- 1.87 (m, 3H), 1.80- 1.70 (m, 2H), 1.68- 1.60 (m, 2H), 1.57- 1.45 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.4, 151.9, 151.8, 138.5, 138.2, 131.8 (q, CF_3), 128.0, 127.2, 124.5, 123.9, 123.8, 122.2, 121.8,

119.1, 116.6, 116.5, 114.7, 83.8, 69.5, 69.0, 68.6, 65.3, 33.1, 28.4, 28.0, 25.0, 24.8, 17.9; **HRMS** (ES) Calculated for $C_{38}H_{33}F_{12}O_6$ $[M + H]^+$: 813.2080, found 813.2079. Calculated for $C_{38}H_{32}F_{12}O_6Na$ $[M + Na]^+$: 835.1900, found 835.1900.



40A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 9.1,3.2 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 5.90 (m, 1H), 5.72 (td, J = 6.0, 1.2 Hz, 1H), 5.39 (s, 2H,), 5.29- 5.17 (m, 2H), 4.37 (s, 2H), 4.05 (d, J = 6.4 Hz, 2H), 3.97- 3.92 (m, 4H), 2.22- 2.18 (td, J = 9.6, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.77- 1.71 (m, 5H), 1.55- 1.40 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.4, 153.3, 134.7, 134.6, 124.6, 120.9, 119.5, 117.4, 117.3, 117.2, 114.9, 84.5, 73.6, 71.2, 69.5, 68.2, 66.0, 29.0, 28.6, 28.3, 25.3, 18.3, 14.1. **HRMS** (ES) Calculated for $C_{30}H_{32}F_5O_5$ $[M + H]^+$: 567.2172 found 567.2167. Calculated for $C_{30}H_{31}F_5O_5Na$ $[M + Na]^+$: 589.1990, found 589.1983.



42B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 2H), 7.85 (s, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.1,3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.91 (m, 1H), 5.73 (td, J = 6.3, 1.2 Hz, 1H), 5.43 (s, 2H,), 5.28- 5.16 (m, 2H), 4.39 (s, 2H), 4.06 (d, J = 6.3 Hz, 2H), 4.00- 3.95 (m, 4H), 2.20- 2.15 (m, 2H),

1.92 (t, J = 2.6 Hz, 1H), 1.77- 1.72 (m, 5H), 1.53- 1.35 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 153.2, 152.0, 138.9, 134.7, 131.7 (m, CF_3), 127.9, 127.2, 124.5, 124.4, 122.0, 121.9, 121.8, 121.7, 121.0, 119.7, 117.3, 117.1, 114.9, 114.8, 84.4, 73.6, 71.2, 69.5, 68.2, 66.0, 53.6, 28.9, 28.6, 28.3, 25.3, 18.2, 14.0. **HRMS** (ES) Calculated for $C_{32}H_{35}F_6O_5$ $[M + H]^+$: 613.2389, found 613.2393. Calculated for $C_{32}H_{34}F_6O_5Na$ $[M + Na]^+$: 635.2208, found 635.2197.

General procedure for the direct ene-yne metathesis reaction

A general procedure for en- yne metathesis reaction is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that the determination of the configuration of the double bond (*E* or *Z)* was accomplished using ^{1}H NMR NOE and NOESY experiments. The *Z:E* ratios were determined by ^{1}H NMR through analogy with en- yne products **21A** and **27B** (see the attached spectra section).

The *Z* and *E* isomers were quantified based on the relative integrations of the ^{1}H NMR signals for protons H_a and H_b (see Figure SI7). These assignments are consistent with those observed by Lee and co-workers.[7] In all cases the two isomers produced are inseparable by flash column silica chromatography. Spectral data is reported for the major isomer in each case. The ^{1}H and ^{13}C NMR spectra of the *Z:E* mixtures are included in the *Supporting Information* as a reference. In addition, the majority of the macrocycles formed are atropisomeric. The diastereotopicity combined with the fact that the products are mixtures of *Z:E* isomers renders some spectra quite complicated. As such, many products of en –yne metathesis were fully hydrogenated[8] and the characterization data, ^{1}H and ^{13}C NMR spectra for a selection of these compounds are listed below.

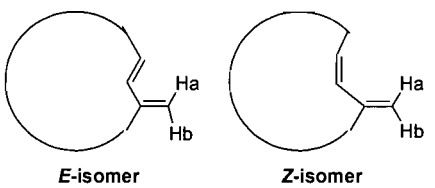
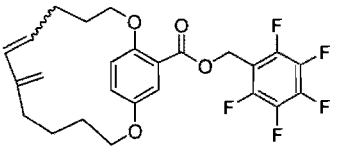


Figure SI7: Identification of Z and E isomers

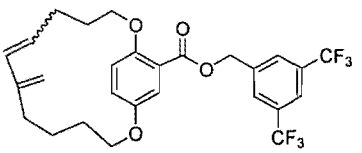
[7] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**; *126,* 15074-15080 and references therein.
[8] Hydrogenation of 1, 3-diene paracyclophanes in solution in Ethyl Acetate: MeOH 10:1 using H_2 (1 atm) and $Pd(OH)_2/C$ (10 mol %) as a catalyst.

A flame dried 500 mL tri-neck round bottom flask, equipped with a magnetic stirrer, reflux condenser, and isobar addition funnel or a syringe pump system is charged with catalyst **G1, G2** or **GH2** (20 mol %) and anhydrous CH_2Cl_2 or toluene (volume is determined by the amount needed to afford a final concentration of [M] = $0.4x10^{-4}$ M after complete addition of the precursor). The catalyst solution is then placed at reflux (CH_2Cl_2) or 110°C (toluene). The metathesis precursor in solution (approximately 50 mL) is placed in the addition funnel or the syringe pumps system and added over 1 h. After addition, the solution was allowed to stir at reflux for 1 additional hour to ensure complete conversion (reactions performed in CH_2Cl_2 all had to be left overnight). The reaction mixture was concentrated in vacuo, dry-packed and purified by flash column silica chromatography (Hexanes-Ethyl Acetate 20:1) to afford the desired 1, 3-diene paracyclophanes.



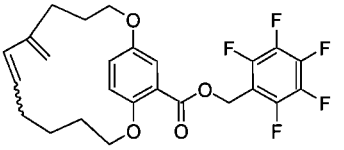
***Z*- 8A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 3.1 Hz, 1H), 7.10 (dd, J = 9.0, 3.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 5.44-5.40 (m, 2H), 5.18- 5.14 (m, 2H), 4.81 (d, J = 1.7 Hz, 1H), 4.82 (s, 1H), 4.24- 4.17 (m, 4H), 2.08- 2.04 (m, 2H), 1.84- 1.64 (m, 4H), 1.39- 1.08 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.9, 155.7, 152.7, 145.8, 131.5, 128.5, 124.6, 121.7, 121.6, 120.4, 111.0, 72.2, 70.1, 53.7, 34.6, 30.7, 28.7, 27.0, 24.8; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1601. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1411.



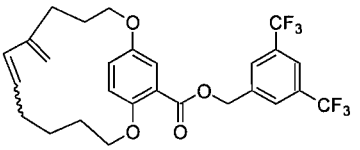
***Z*- 11B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.13 (dd, J = 9.0, 3.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 5.45 (m, 2H), 5.20 (d, J = 15.7 Hz, 1H), 5.17- 5.09 (m, 1H), 4.81 (s, 1H), 4.60 (s, 1H), 4.40- 4.10 (m, 4H), 2.05- 1.25 (m, 10H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 151.9, 150.9, 144.7, 138.9, 133.2, 132.1 (q, CF_3), 128.9, 127.7, 124.9, 123.2, 122.4, 121.9, 120.9, 119.7, 113.1, 68.5, 68.3, 64.9, 30.6, 27.5, 27.0, 24.9, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1813. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1637.



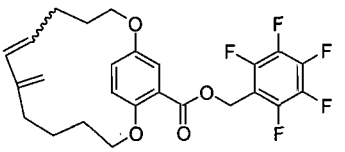
***E*- 13A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 5.77 (d, J = 15.7 Hz, 1H), 5.43 (m, 2H), 4.82 (s, 1H), 4.78 (s, 1H), 4.59- 4.53 (m, 1H), 4.47- 4.38 (m, 1H), 4.28- 4.25 (m, 3H), 1.96- 1.55 (m, 4H), 1.25-1.19 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.0, 151.8, 151.0, 144.8, 133.1, 129.1, 124.6, 123.0, 120.7, 119.9, 113.0, 72.6, 68.5, 53.8, 32.5, 30.7, 27.4, 25.2, 22.2; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ $[M + H]^+$: 483.1589 found 483.1589. Calculated for $C_{25}H_{23}F_5O_4Na$ $[M + Na]^+$: 505.1409, found 505.1408.



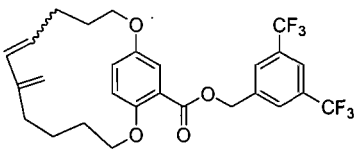
***E*- 15B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.47 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.76 (d, J = 15.8 Hz, 1H), 5.45 (m, 2H), 4.83 (s, 1H), 4.79 (s, 1H), 4.61- 4.49 (m, 1H), 4.49- 4.40 (m, 1H), 4.28- 4.25 (m, 2H), 4.23- 4.16 (m, 1H), 1.96- 1.60 (m, 6H), 1.32-1.25 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 151.9, 150.9, 144.7, 138.9, 133.2, 132.1 (q, CF_3), 128.9, 127.7, 124.9, 123.2, 122.4, 121.9, 120.9, 119.7, 113.1, 68.5, 68.3, 64.9, 30.6, 27.5, 27.0, 24.9, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ $[M + H]^+$: 529.1808 found 529.1803. Calculated for $C_{27}H_{26}F_6O_4Na$ $[M + Na]^+$: 551.1627, found 551.1622.



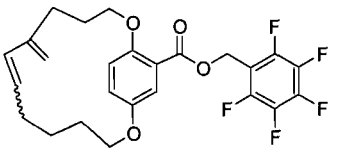
***Z*- 17A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J = 2.7 Hz, 1H), 7.06- 7.02 (m, 2H), 5.44 (d, J = 8.2 Hz, 1H), 5.38 (J = 12.1 Hz, 1H), 5.30 (d, J = 15.7 Hz, 1H), 5.17 (m, 1H), 4.82 (d, J = 1.5 Hz, 1H), 4.60 (s, 1H), 4.28 (m, 4H), 2.24- 2.05 (m, 2H), 1.79- 1.58 (m, 4H), 1.38- 1.25 (m, 2H), 0.93- 0.88 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.0, 154.9, 153.4, 145.9, 131.7, 128.7, 123.9, 122.5, 122.1, 120.6, 111.3, 71.4, 70.9, 53.9, 34.6, 29.7, 28.6, 28.2, 25.7; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ [M + H]$^+$: 483.1589 found 483.1581. Calculated for $C_{25}H_{23}F_5O_4Na$ [M + Na]$^+$: 505.1409, found 505.1407.



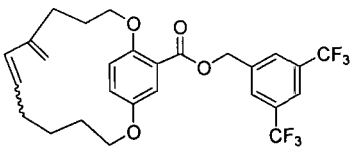
***Z*- 19B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.46 (d, J = 3.0 Hz, 1H), 7.09 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.44 (m, 2H), 5.39 (d, J = 15.6 Hz, 1H), 5.20- 5.09 (m, 1H), 4.83 (s, 1H), 4.54 (s, 1H), 4.28- 3.90 (m, 4H), 2.05- 1.57 (m, 4H), 1.42-1.19 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.2, 152.9, 149.6, 145.4, 138.5, 135.8, 132.1 (q, CF_3), 129.3, 127.4, 123.6, 122.3, 121.6, 121.4, 120.3, 119.7, 111.0, 70.7, 70.6, 64.6, 29.3, 28.8, 27.9, 23.1, 22.3; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ [M + H]$^+$: 529.1808 found 529.1809. Calculated for $C_{27}H_{26}F_6O_4Na$ [M + Na]$^+$: 551.1627, found 505.1623.



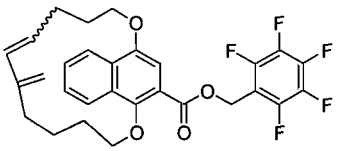
***E*- 21A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, J = 3.0 Hz, 1H), 7.02 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.76 (d, J = 15.8 Hz, 1H), 5.43 (m, 2H), 4.81 (s, 1H), 4.74 (s, 1H), 4.63- 4.55 (m, 1H), 4.45- 4.37 (m, 1H), 4.24- 4.19 (m, 3H), 1.96- 1.80 (m, 6H), 1.72-1.40 (m, 2H), 1.37- 1.33 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 152.7, 150.1, 144.7, 133.1, 129.0, 124.0, 122.0, 121.0, 119.5, 112.9, 69.6, 67.8, 53.8, 30.8, 27.3, 26.8, 24.8, 22.8; **HRMS** (ES) Calculated for $C_{25}H_{24}F_5O_4$ [M + H]$^+$: 483.1589 found 483.1593. Calculated for $C_{25}H_{23}F_5O_4Na$ [M + Na]$^+$: 505.1409, found 505.1408.



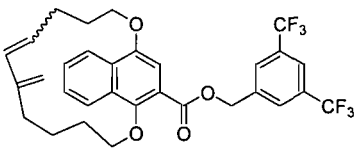
***E*- 23B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.41 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 9.0, 3.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 5.77 (d, J = 15.9 Hz, 1H), 5.48 (m, 2H), 4.80 (s, 1H), 4.73 (s, 1H), 4.63- 4.52 (m, 1H), 4.40- 4.51 (m, 1H), 4.28- 4.25 (m, 3H), 1.96- 1.79 (m, 6H), , 1.60-1.52 (m, 2H), 1.42-1.36 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 152.6, 150.2, 144.6, 138.9, 133.1, 132.7, 132.0 (q, CF_3), 129.0, 127.7, 124.2, 122.2, 122.0, 121.1, 119.3, 113.0, 69.4, 67.8, 64.9, 30.8, 27.3, 26.8, 24.8, 22.8; **HRMS** (ES) Calculated for $C_{27}H_{27}F_6O_4$ [M + H]$^+$: 529.1808 found 529.1808. Calculated for $C_{27}H_{26}F_6O_4Na$ [M + Na]$^+$: 551.1627, found 551.1607.



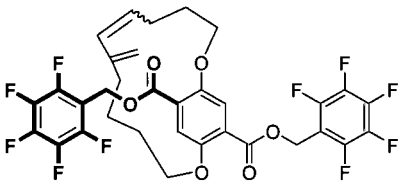
***Z*- 25A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.60- 7.54 (m, 2H), 7.20 (s, 1H), 5.48 (m, 2H), 5.09 (m, 1H), 4.92 (d, *J* = 15.9 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 1H), 4.50- 4.43 (m, 2H), 4.40 (s, 1H), 4.22- 4.06 (m, 2H), 2.17- 2.03 (m, 2H), 1.67- 1.53 (m, 2H), 1.24- 1.10 (m, 4H), 0.50 (m, 1H), 0.07 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.0, 151.5, 150.2, 145.7, 131.7, 129.8, 128.9, 128.2, 126.7, 124.4, 121.8, 116.9, 110.9, 108.6, 75.0, 70.2, 54.0, 35.0, 30.4, 28.3, 27.7, 27.5; **HRMS** (ES) Calculated for $C_{29}H_{26}F_5O_4$ $[M + H]^+$: 533.1745 found 533,1729. Calculated for $C_{29}H_{25}F_5O_5Na$ $[M + Na]^+$: 555.1571, found 555.1538.



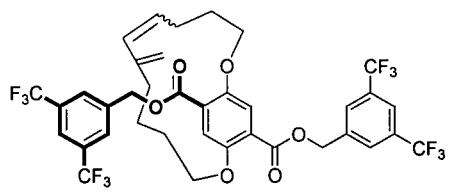
***Z*- 27B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, *J* = 8.3 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 2H), 7.90 (s, 1H), 7.65- 7.59 (m, 2H), 7.29 (m, 1H), 5.60- 5.53 (m, 2H), 5.20- 5.10 (m, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.59 (s, 1H), 4.52- 4.44 (m, 2H), 4.41 (s, 1H), 4.20- 4.00 (m, 2H), 2.28- 1.21 (m, 9H), 0.75- 0.46 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.9, 151.5, 145.6, 138.8, 132.1, 131.2 (q, CF_3), 130.8, 129.8, 128.9, 128.2, 128.0, 126.7, 126.6, 124.5, 123.9, 122.1, 121.8, 111.5, 108.3, 103.9, 76.7, 70.0, 65.0, 34.9, 30.3, 28.3, 27.6, 24.0; **HRMS** (ES) Calculated for $C_{31}H_{29}F_6O_4$ $[M + H]^+$: 579.1965, found 579.1970. Calculated for $C_{31}H_{28}F_6O_4Na$ $[M + Na]^+$: 601.1784, found 601.1788.



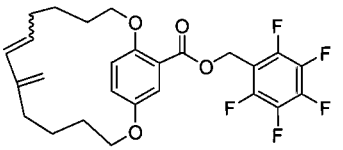
Z- 29A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (s, 1H), δ 7.39 (s, 1H), 5.43 (m, 4H), 5.30 (m, 2H), 4.77 (d, J = 1.4 Hz, 1H), 4.57 (s, 1H), 4.50- 4.00 (m, 4H), 2.21- 1.95 (m, 2H), 1.82- 1.30 (m, 4H), 0.98- 0.68 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.4, 164.2, 154.3, 152.1, 145.5, 131.7, 128.6, 126.5, 125.1, 123.8, 121.1, 113.3, 111.5, 71.9, 70.5, 53.4, 34.4, 29.6, 29.3, 28.1, 25.5; **HRMS** (ES) Calculated for $C_{33}H_{25}F_{10}O_6$ $[M + H]^+$: 707.1486 found 707.1489. Calculated for $C_{33}H_{24}F_{10}O_6Na$ $[M + Na]^+$: 729.1311, found 729.1319.



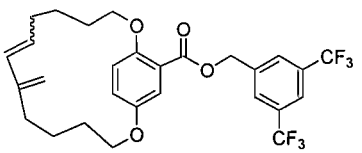
***E*- 31B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 4H), 7.87 (s, 2H), 7.51 (s, 1H), 7.48 (s, 1H), 5.70 (d, J = 15.2 Hz, 1H), 5.53- 5.37 (m, 4H), 4.93- 4.82 (m, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 4.43- 4.00 (m, 4H), 2.25- 0.88 (m, 10H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 165.3, 152.0, 150.7, 145.9, 143.0, 138.4, 138.4, 132.6, 132.3, 132.2, 131.8 (q, CF_3), 129.6, 128.7, 127.8, 125.8, 124.5, 122.1, 122.0, 121.8, 121.3, 120.9, 113.6, 79.0, 68.7, 65.8, 36.3.0, 31.9, 29.5, 27.9, 24.0; **HRMS** (ES) Calculated for $C_{37}H_{31}F_{12}O_6$ $[M + H]^+$: 799.1924, found 799.1924. Calculated for $C_{37}H_{30}F_{12}O_6Na$ $[M + Na]^+$: 821.1743, found 821.1742.



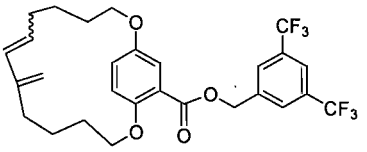
***E*- 33A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 3.1 Hz, 1H), 7.07 (dd, J = 9.0, 3.1 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 5.71 (d, J = 15.7 Hz, 1H), 5.41 (s, 2H), 4.90 (m, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.28- 4.17 (m, 4H), 1.93- 185 (m, 4H), 1.70- 1.38 (m, 4H), 1.30- 1.21 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 152.3, 151.2, 146.0, 132.6, 129.2, 123.2, 121.8, 120.3, 118.7, 113.4, 69.8, 68.6, 53.8, 32.3, 31.7, 29.9, 26.1, 25.4, 23.9; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_4$ $[M + H]^+$: 497.1745 found 497.1739. Calculated for $C_{26}H_{25}F_5O_4Na$ $[M + Na]^+$ 519.1571, found 519.1568.



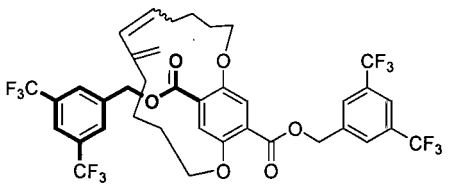
***E*- 35B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.44 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.9, 3.0 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.72 (d, J = 15.7 Hz, 1H), 5.47 (s, 2H), 4.93- 4.85 (m, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.35- 4.23 (m, 4H), 2.08- 1.86 (m, 4H), 1.80- 1.21 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.7, 152.3, 151.1, 146.0, 138.9, 132.6, 132.0 (q, CF_3), 129.1, 127.7, 124.6, 123.4, 121.9, 121.8, 120.4, 118.6, 113.6, 69.8, 68.5, 64.9, 32.2, 31.6, 29.7, 26.0, 25.4, 23.9; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965, found 543.1965. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1784.



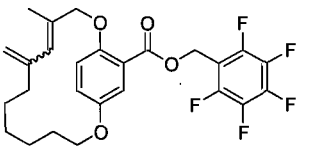
***E*- 37B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 2H), 7.85 (s, 1H), 7.40 (d, J = 2.9 Hz, 1H), 7.06 (dd, J = 8.9, 2.9 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 5.73 (d, J = 15.7 Hz, 1H), 5.45 (s, 2H), 4.99- 4.89 (m, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 4.33- 4.24 (m, 4H), 2.10- 1.91 (m, 2H), 1.85- 1.80 (m, 2H), 1.70- 1.11 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6, 153.0, 150.5, 145.8, 138.8, 132.6, 131.7 (q, CF_3), 129.1, 127.7, 124.5, 123.4, 122.1, 121.9, 120.3, 119.6, 113.5, 70.9, 68.0, 64.9, 32.2, 31.7, 29.7, 26.2, 25.2, 24.0; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_4$ $[M + H]^+$: 543.1965 found 543.1968. Calculated for $C_{28}H_{28}F_6O_4Na$ $[M + Na]^+$: 565.1784, found 565.1784.



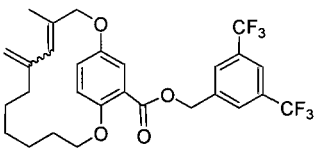
***E*- 39B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 4H), 7.87 (s, 2H), 7.52 (s, 1H), 7.47 (s, 1H), 5.70 (d, J = 15.5 Hz, 1H), 5.57- 5.38 (m, 4H), 4.91- 4.80 (m, 1H), 4.70 (s, 1H), 4.65 (s, 1H), 4.40- 3.97 (m, 4H), 2.21- 0.83 (m, 12H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 165.0, 152.0, 150.2, 145.5, 144.0, 138.5, 138.4, 132.6, 132.3, 132.2, 131.8 (q, CF_3), 129.6, 128.7, 127.8, 125.8, 124.5, 122.1, 122.0, 121.8, 120.8, 120.1, 113.5, 71.7, 68.7, 65.3, 37.0, 31.6, 29.7, 27.4, 24.6, 23.9; **HRMS** (ES) Calculated for $C_{38}H_{33}F_{12}O_6$ $[M + H]^+$: 813.2080, found 813.2074. Calculated for $C_{38}H_{32}F_{12}O_6Na$ $[M + Na]^+$: 835.1900, found 835.1894.



***Z*- 41A**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, J = 3.0 Hz, 1H), 7.08 (dd, J = 8.9, 3.0 Hz, 1H), 6.96 (s, 1H), 6.88 (d, J = 9.1 Hz, 1H), 5.40 (m, 2H), 4.60 (d, J = 1.9 Hz, 1H), 4.38 (s, 1H), 4.73- 4.47 (m, 2H), 4.25- 4.01 (m, 2H), 2.20- 1.93 (m, 2H), 1.43- 0.83 (m, 9H), 0.45- 0.35 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.9, 152.3, 151.8, 145.9, 133.6, 132.2, 128.8, 126.3, 123.2, 118.5, 112.7, 73.8, 67.6, 53.7, 36.1, 29.9, 29.7, 27.5, 23.9, 15.2; **HRMS** (ES) Calculated for $C_{26}H_{26}F_5O_5$ $[M + H]^+$: 497.1746 found 497.1746. Calculated for $C_{26}H_{25}F_5O_5Na$ $[M + Na]^+$: 519.1565, found 519.1564.



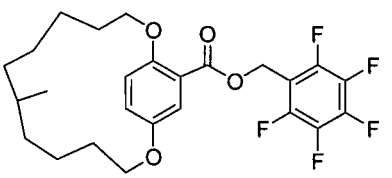
***Z*- 43B**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 2H), 7.85 (s, 1H), 7.37 (d, J = 3.0 Hz, 1H), 7.08 (dd, J = 9.1, 3.0 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.72 (s, 1H), 5.45- 5.40 (m, 2H), 4.75 (s, 1H), 4.40 (s, 1H), 4.39 (s, 2H), 4.20- 3.99 (m, 2H), 2.25- 0.80 (m, 13H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 152.3, 151.9, 145.9, 139.0, 135.0, 133.6, 133.5, 132.0, 131.7 (q, CF_3), 127.9, 127.2, 125.5, 118.4, 117.3, 112.7, 73.8, 67.4, 64.8, 36.0, 29.7, 27.3, 23.9, 21.3, 15.2; **HRMS** (ES) Calculated for $C_{28}H_{29}F_6O_5$ $[M + H]^+$: 543.1965, found 543.1964. Calculated for $C_{28}H_{28}F_6O_5Na$ $[M + Na]^+$: 565.1784, found 565.1783.

General procedure for the hydrogenation of the ene-yne metathesis products

A general procedure for the hydrogenation of 1,3- diene paracyclophanes is detailed below. As a model, products **8A, 33A** *and* **37B** *were fully hydrogenated and the characterization data for the compounds produced are described below.*

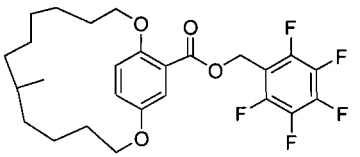
A flame dried round bottom flask, equipped with a magnetic stirrer was added the 1,3-diene product (1.0 eq.) and a mixture of ethyl acetate: MeOH (10:1). The catalyst $Pd(OH)_2/C$ (10 mol %)[9] was added the sealed flask was fitted with a baloon of $H_2(g)$. The reaction mixture was stirred at room temperature for 15 h and the balloon of $H_2(g)$ was typically refilled halfway through the reaction. The reaction mixture was concentrated in vacuo, dry-packed and purified by flash column silica chromatography (Hexanes-Ethyl Acetate 20:1) to afford the desired paracyclophanes. As a consequence of the presence of atropisomerism (due to the rigidity of the macrocycle) and the introduction of a stereogenic methyl group following hydrogenation, a mixture of inseparable diastereoisomers is present. Therefore, all ^1H and ^{13}C NMR signals are 'doubled' (see spectra for more details).



H_4- 8A

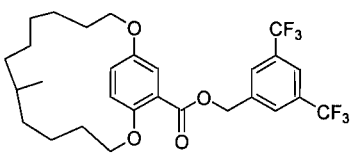
[9] Other catalysts such as Pd/C and PtO_2 were not effective for the hydrogenation.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H), 7.10 (m, 1H), 7.00 (d, J = 9.0 Hz, 1H), 5.41 (m, 2H), 4.30- 4.13 (m, 4H), 1.90- 0.82 (br, 15H), 0.70- 0.63 (d, J = 6 Hz, 3H);**^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.1, 153.7, 153.2, 128.8, 121.8, 121.0, 120.3, 71.5, 69.6, 53.7, 35.5, 34.4, 31.8, 30.7, 28.4, 25.3, 23.9, 22.0, 19.6; **HRMS** (ES) Calculated for $C_{25}H_{28}F_5O_4$ $[M + H]^+$: 487.1902 found 487.1900. Calculated for $C_{25}H_{27}F_5O_4Na$ $[M + Na]^+$: 509.1721, found 509.1728.



H_4- 33A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, J = 2.8 Hz, 1H), 7.08 (dd, J = 8.9, 2.8 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.42 (s, 2H), 4.28- 4.14 (br, 4H), 1.85- 1.70 (br, 4H), 1.28- 0.75 (br, 13H), 0.71 (d, J = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.3, 153.0, 152.7, 123.1, 121.6, 119.3, 118.9, 69.9, 69.2, 53.7, 35.3, 34.3, 32.4, 29.7, 29.2, 27.7, 26.1, 24.2, 22.7, 20.3. **HRMS** (ES) Calculated for $C_{26}H_{30}F_5O_4$ $[M + H]^+$: 501.2059 found 501.2061. Calculated for $C_{26}H_{29}F_5O_4Na$ $[M + Na]^+$: 523.1878, found 523.1881.



H_4- 37B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.85 (s, 1H), 7.43 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.9, 3.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 5.46 (s, 2H), 4.29- 4.22 (m, 4H), 2.25- 1.89 (m, 2H), 1.60-

1.57 (m, 2H), 1.38- 1.20 (m, 9H), 1.15- 0.88 (m, 4H), 0.69 (d, J = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.8, 152.2, 138.8, 132.6, 132.0 (q, CF_3), 129.7, 128.8, 126.6, 122.0, 121.5, 120.4, 118.6, 70.2, 68.8, 64.9, 35.2, 34.3, 29.2, 29.0, 27.9, 24.1, 22.4, 22.3, 20.3, 14.0; **HRMS** (ES) Calculated for $C_{28}H_{33}F_6O_4$ $[M + H]^+$: 547.2278, found 547.2279. Calculated for $C_{28}H_{32}F_6O_4Na$ $[M + Na]^+$: 569.0297, found 569.2097.

Results of MP2 energies and DFT calculations

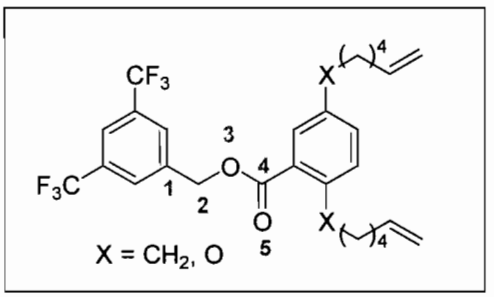
In evaluating the conformational control elements described herein, we assumed that the relative aromatic-aromatic conformational geometry in the substrates might play a crucial role in determining the product of the reaction. As such, several possible lowest energy initial geometries for each substrate were generated by a conformational search at the AM1 level.

Subsequently, we wished to further refine the geometries and energies of the open and stacked conformers and turned to the second-order Møller–Plesset (MP2) and DFT methods. Given that recent MP2 calculations for the hexafluorobenzene:benzene complex shows that dispersion forces are important for the stabilisation of the complex,[10] we first investigated MP2 level of theory in an attempt to include dispersion interactions, despite the fact that this method is very time-consuming.

However, due to the evident importance of correlation effects in the hexafluorobenzene:benzene interaction, it also seemed possible that density functional theory (DFT) could be valuable. We therefore evaluated each substrate conformer at the B3LYP/6–31G* level. Although the results obtained from the DFT are commented on in the main text, Table S1 summarizes also the results obtained from the MP2 calculations and shows that the MP2 correlation energies produced by this level of theory follow the same tendencies as the heats of formation obtained through DFT.

Table SI1: MP2 Energies and DFT Heats of Formation.

[10] (a) Hernandez-Trujillo, J.; Colmenares, F.; Cuevas, G.; Costas, M. *Chem Phys. Lett.* **1997**, *265*, 503. (b) Vanspeybrouck, W.; Herrebout, W. A.; van der Veken, B. J.; Lundell, J.; Perutz, R. N. *J. Phys. Chem. B*, **2003**, *107*, 13855.



Molecule	MP2 Energy (kcal/mol)	DFT Heat of Formation (kcal/mol)
5*	O: -899.38	O: -255.7
	S: -901.23	S: -255.9
44	O: -1283.01	O: -351.77
	S: -1288.29	S: -353.05
45	O: -1231.43	O: -207.49
	S: -1233.01	S: -208.04
46	O: -1311.27	O: -309.04
	S: -1313.08	S: -309.44

Table SI2: Dihedral Angles (as defined below)

Molecule	Dihedral angle 2 (2-3-4-5)		Dihedral angle 1 (1-2-3-4)	
5	O: 30	O: 29.38	O: 172.17	O: 173.98
	S: 165.4	S: 171.63	S: 71.38	S: 81.88
44	O: -175.12	O: -176.96	O: 89.66	O: -138.78

	S: -177.41	S: -177.43	S: 72.19	S: 88.41
45	O: 40.38	O: 77.16	O: 167.97	O: 127.89
	S: 151.93	S: 140.38	S: 63.25	S: 67.97
46	O: -176.96	O: 160.75	O: -138.78	O*: 122.27
	S: 162.18	S: -175.18	S: 83.04	S: 89.66

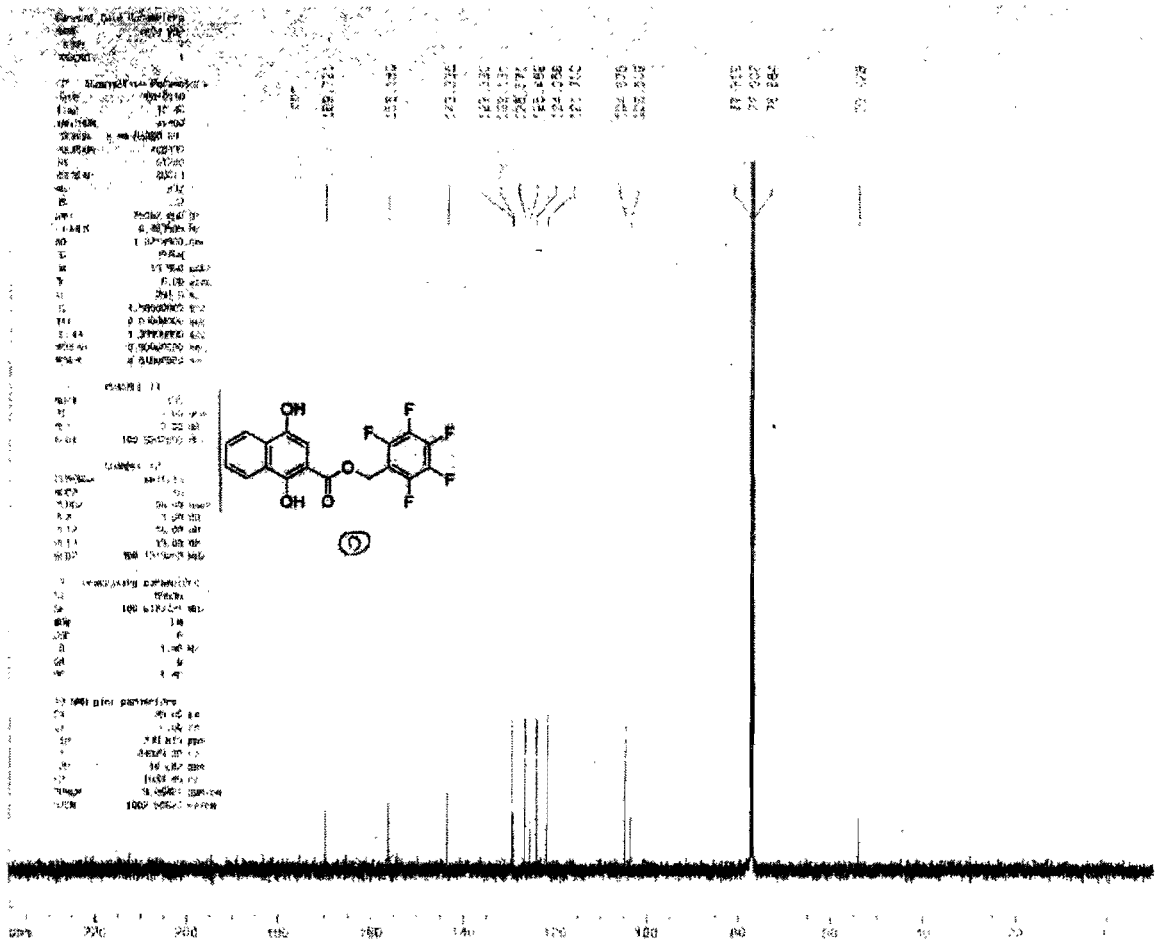
NMR spectra of all precursors and metathesis products

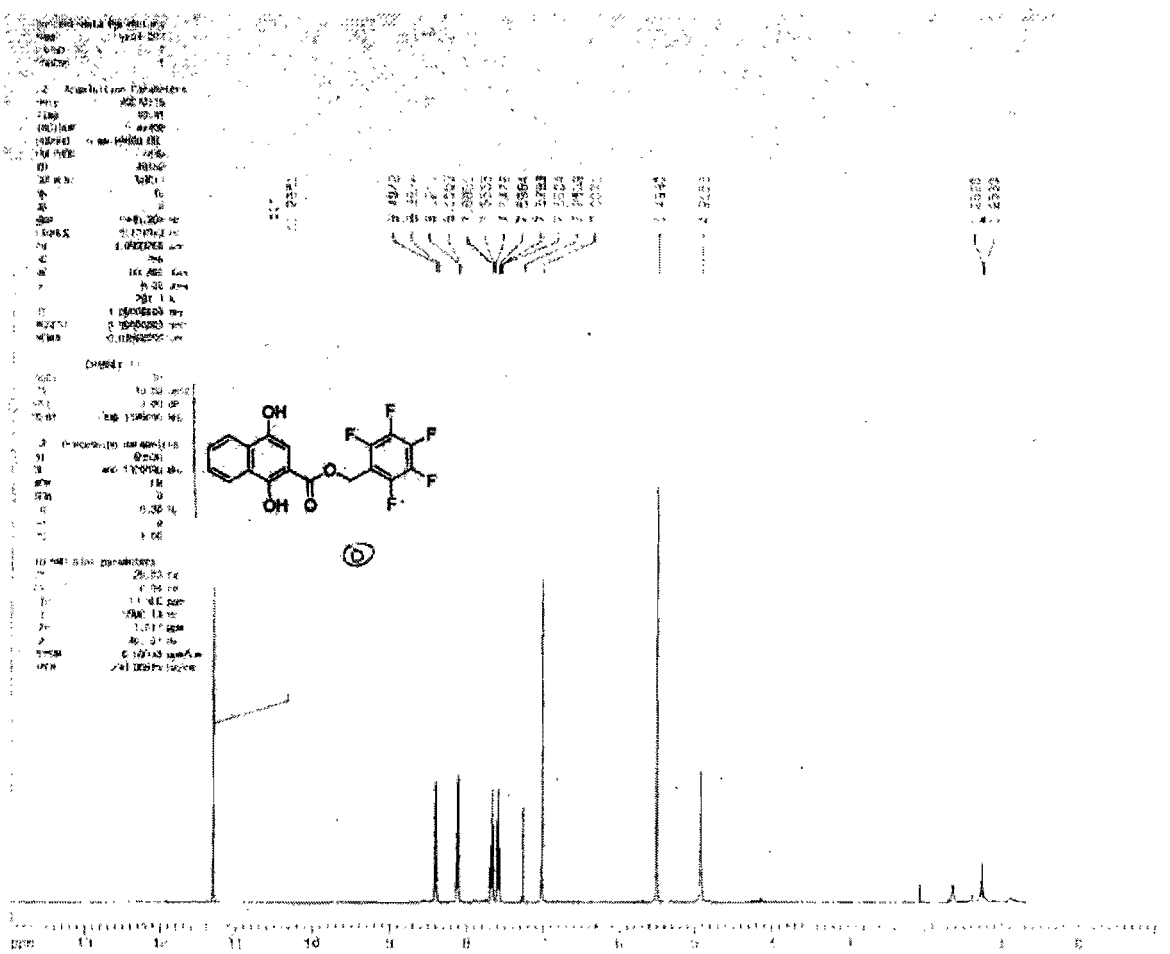
OH
OH
O
F
F
F
F
F
A

OH
OH
O
F
F
F
F
F
A

OH
CF3
OH
O
CF3
(B)

OH
CF3
OH
O
CF3
(B)



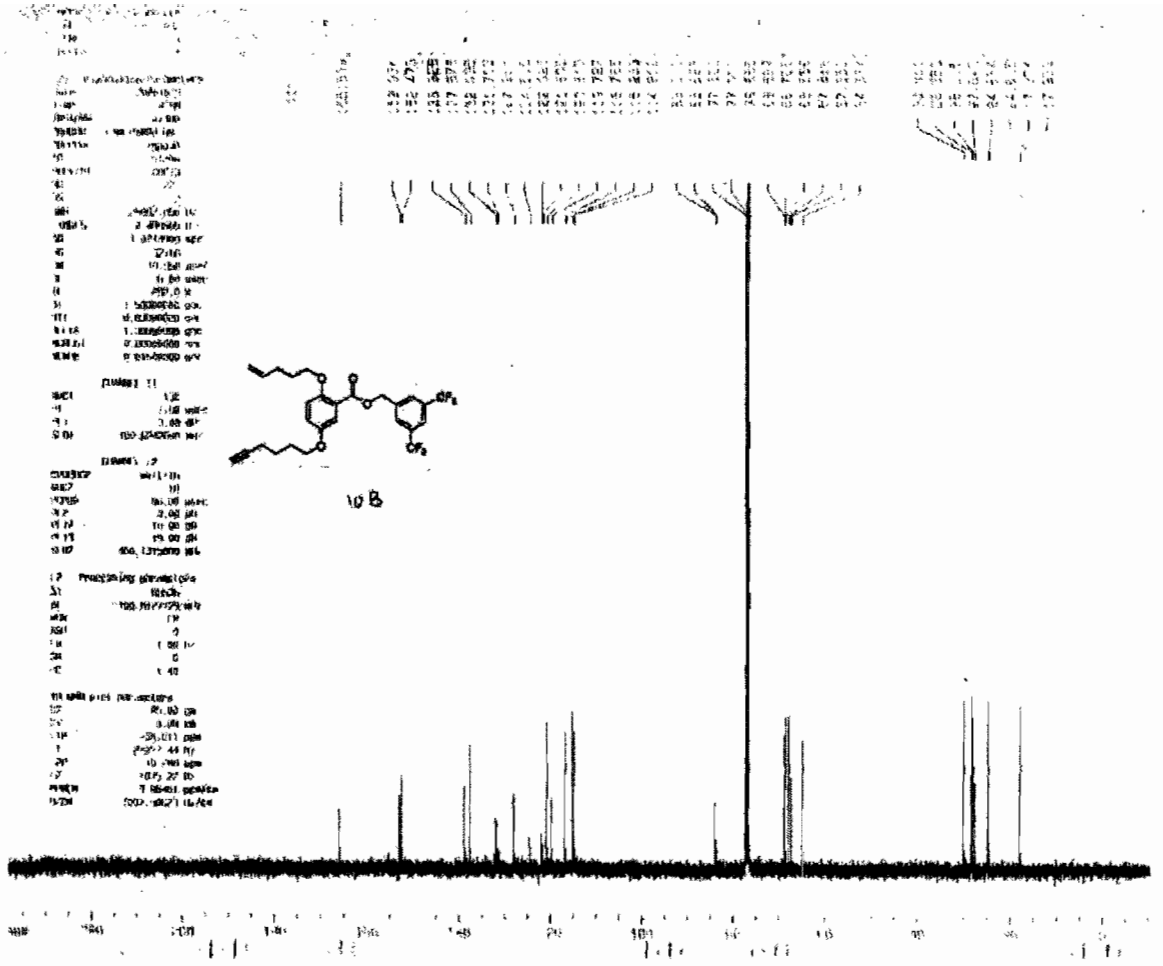


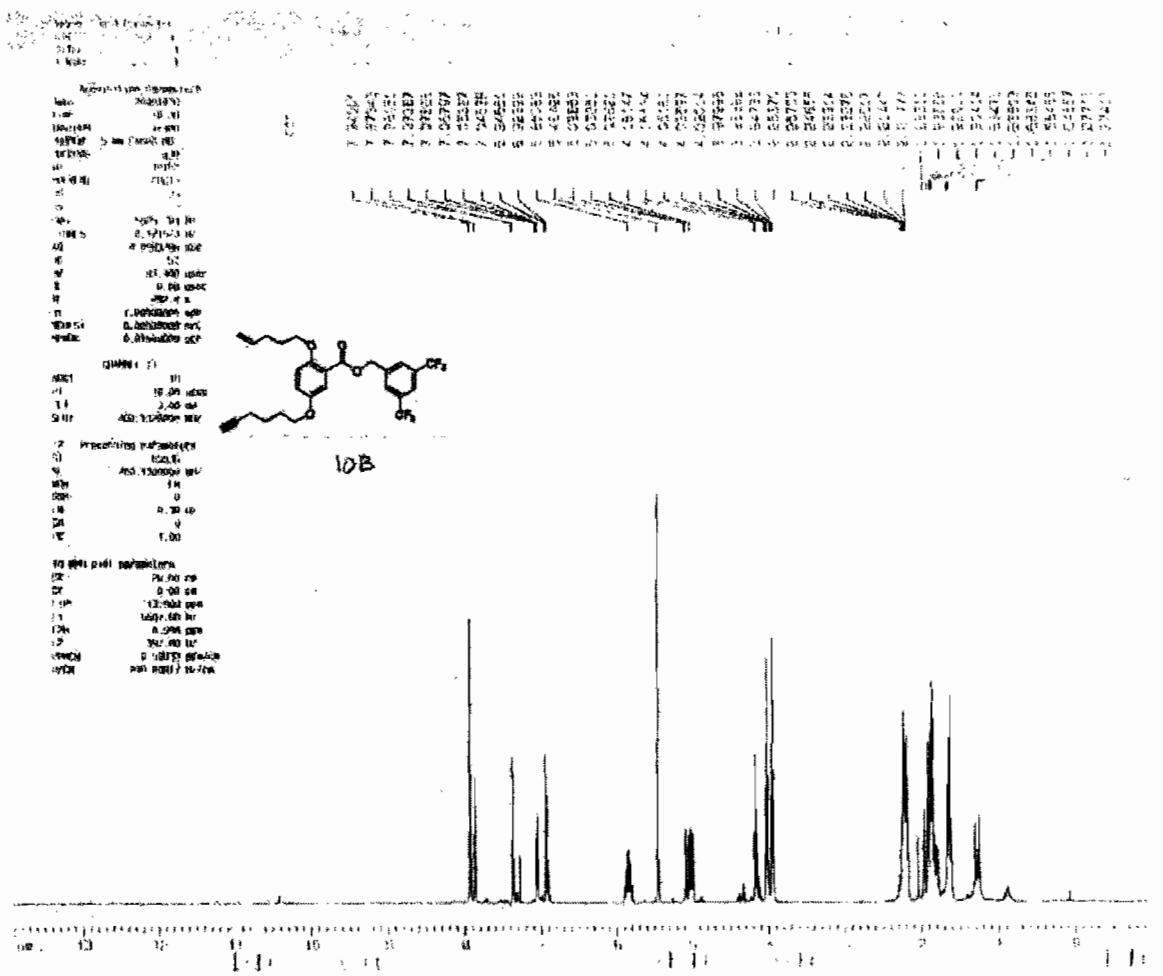
7A

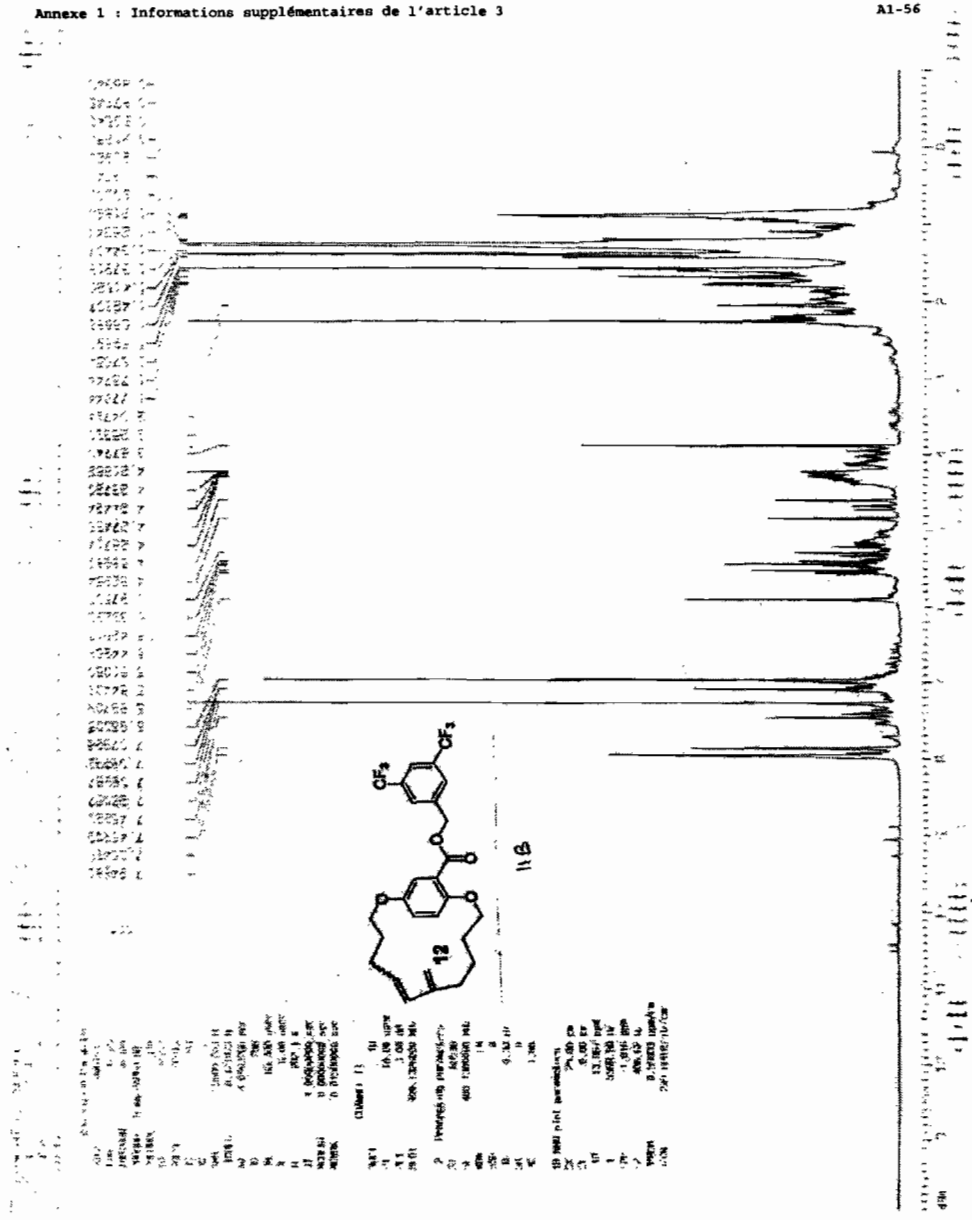
7A

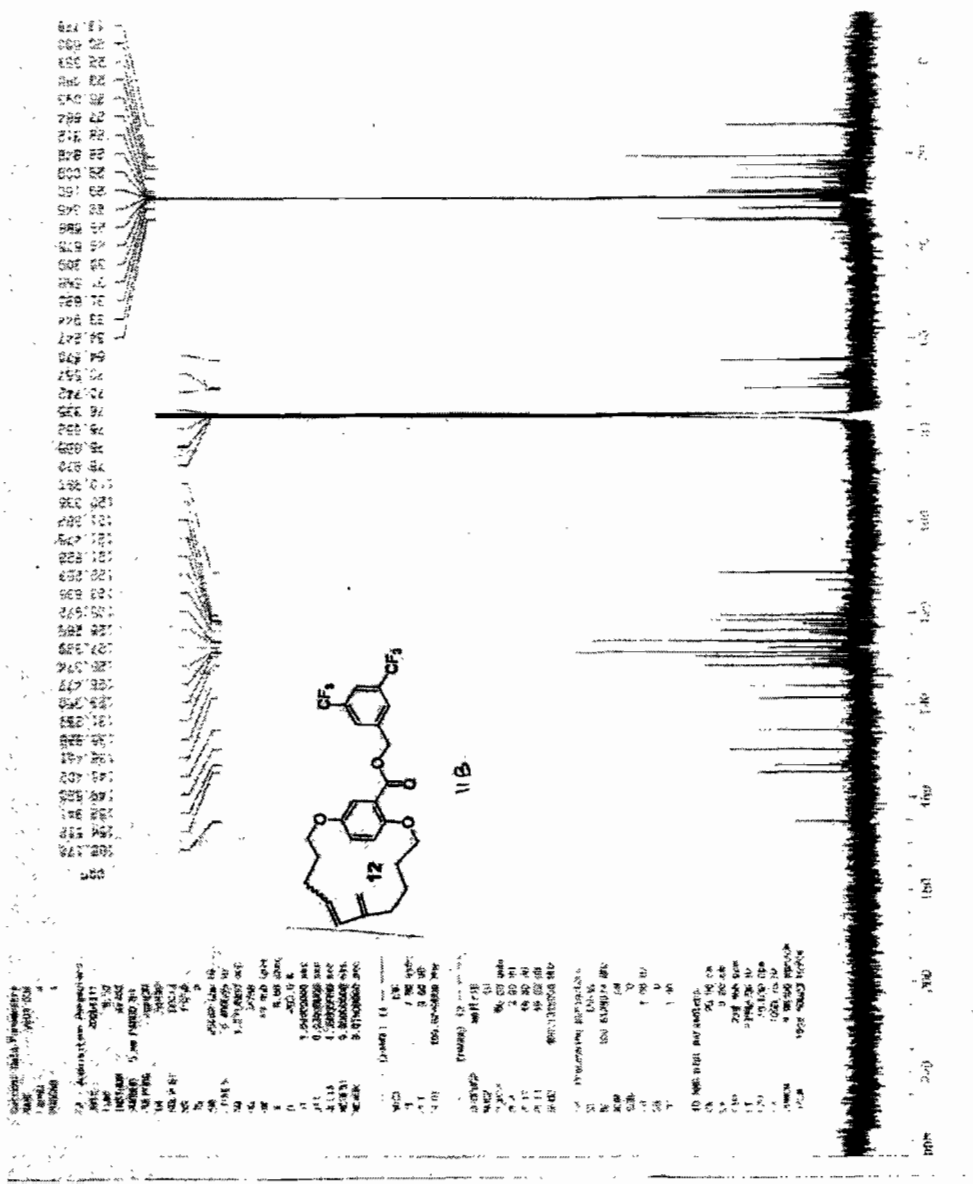
8A

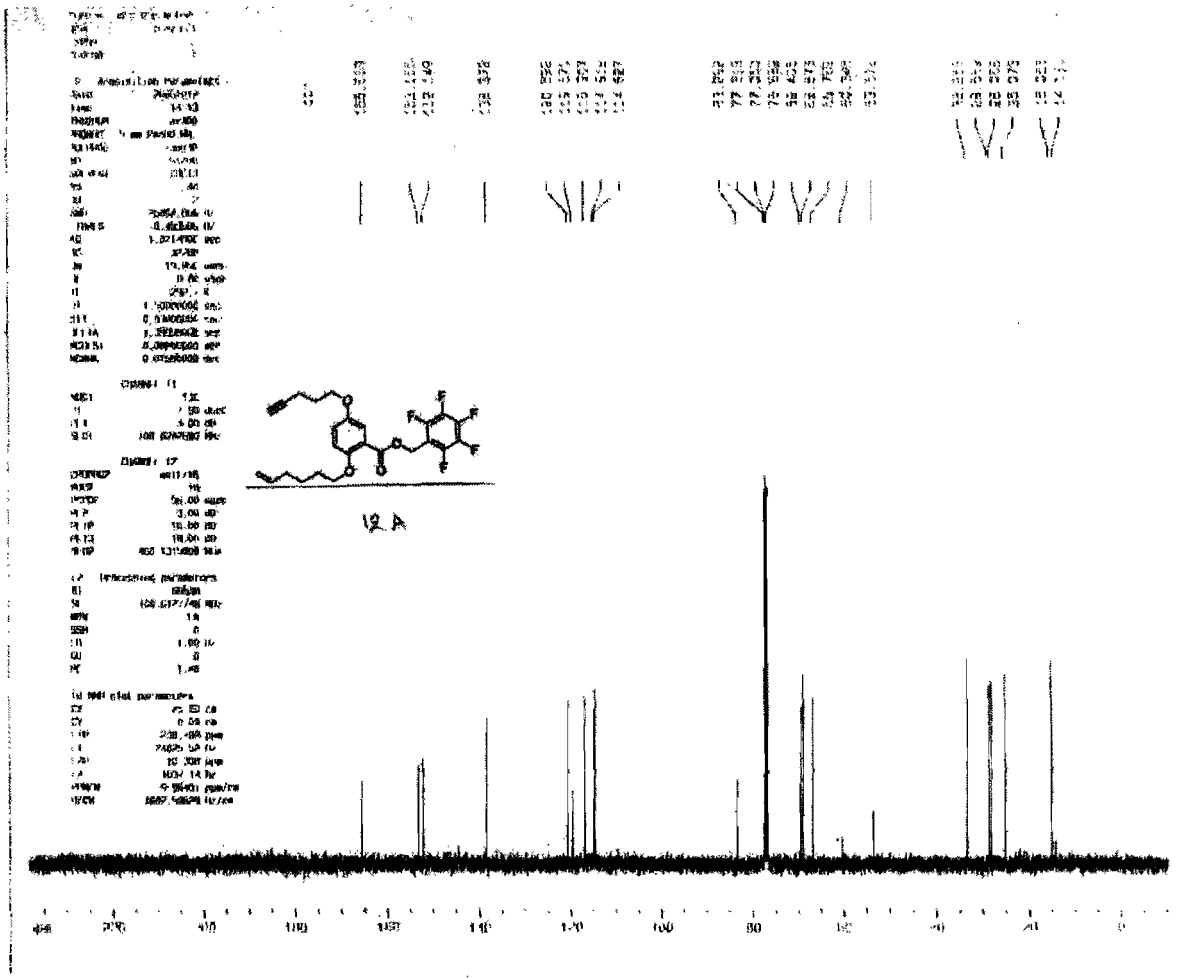
8A


10B

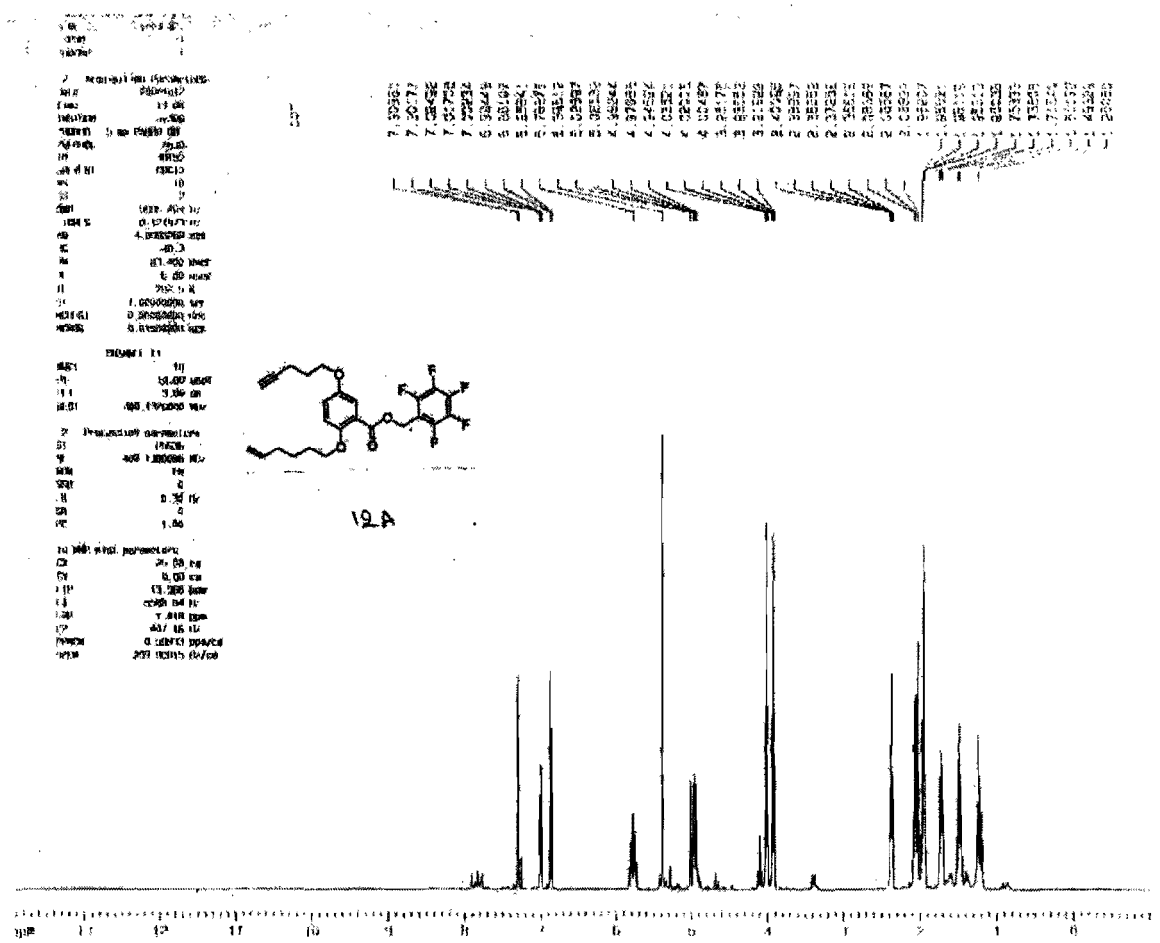

10B


CF3
CF3
O
O
O
12
11B

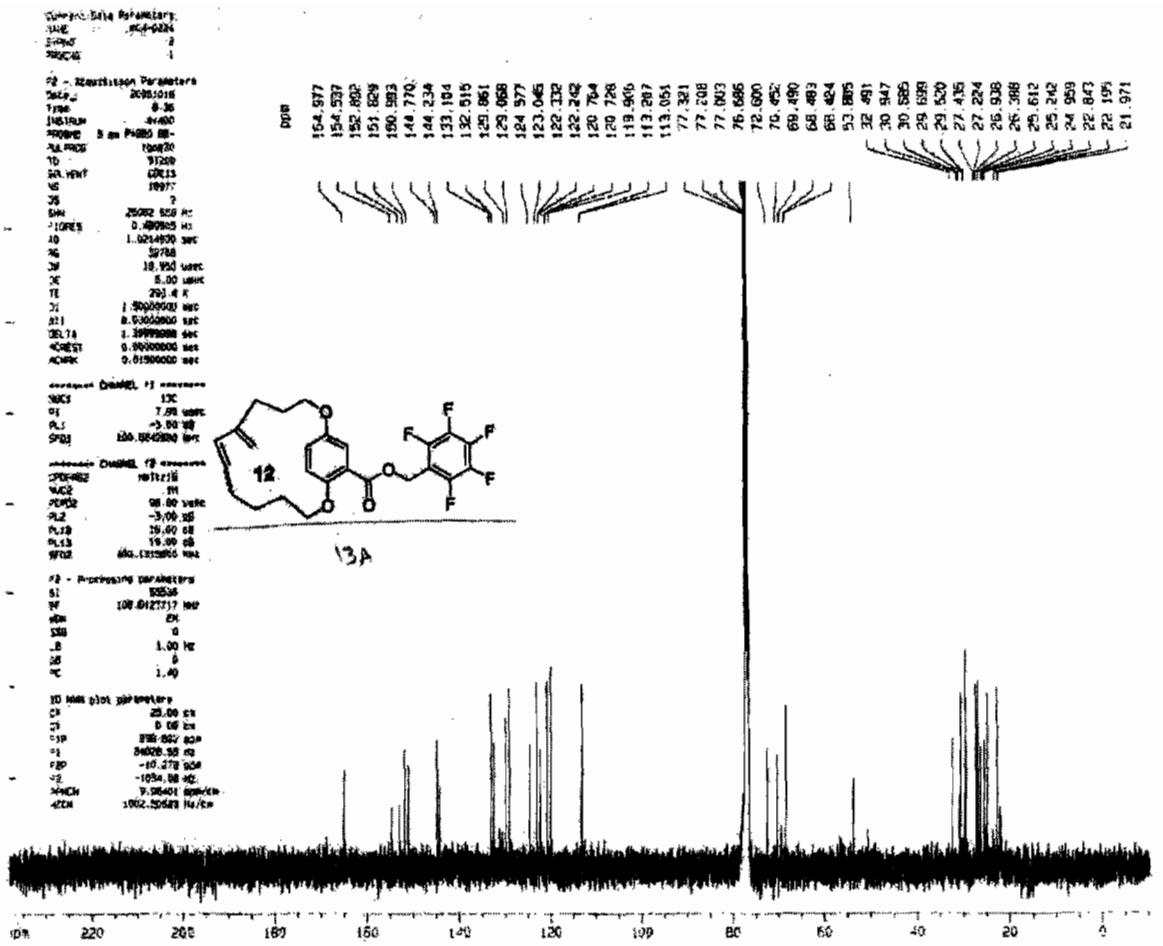

CF3
CF3
O
O
O
12
11B

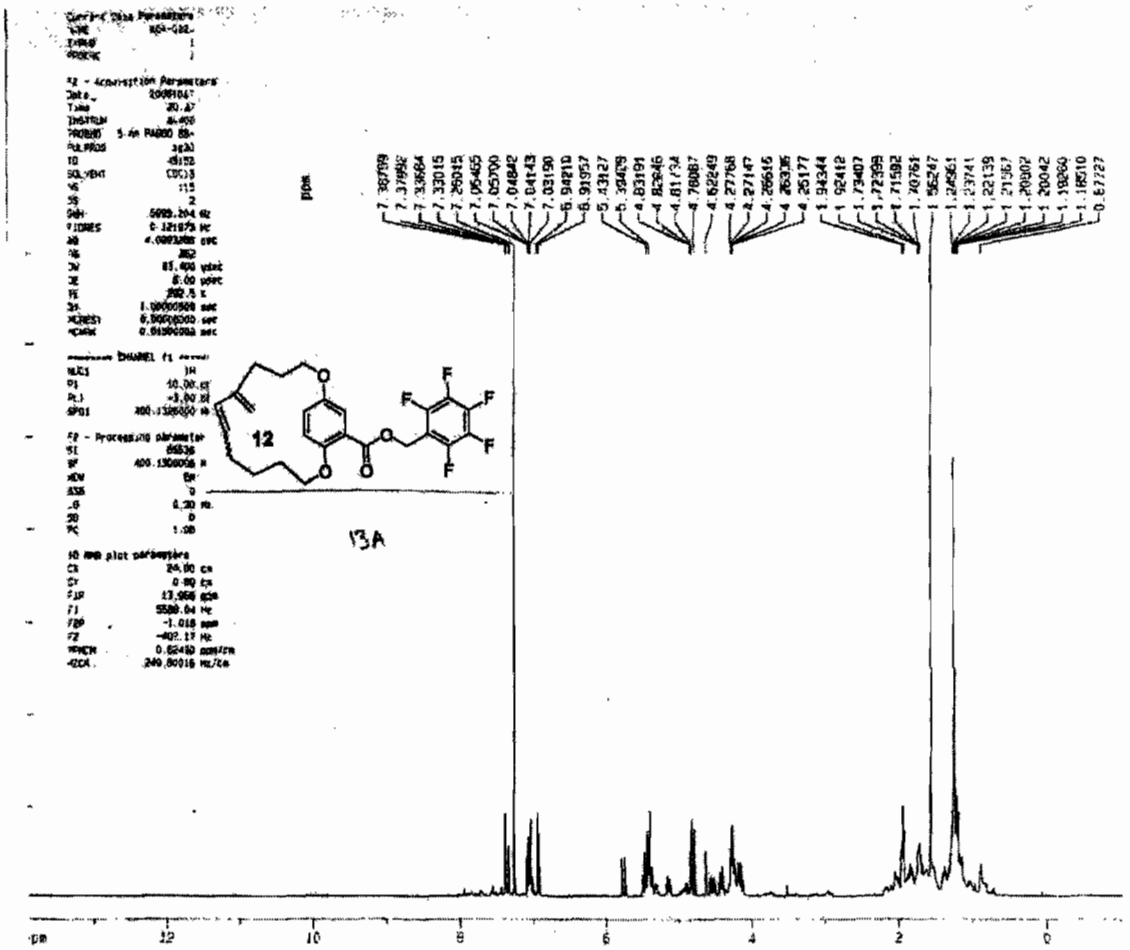


12A



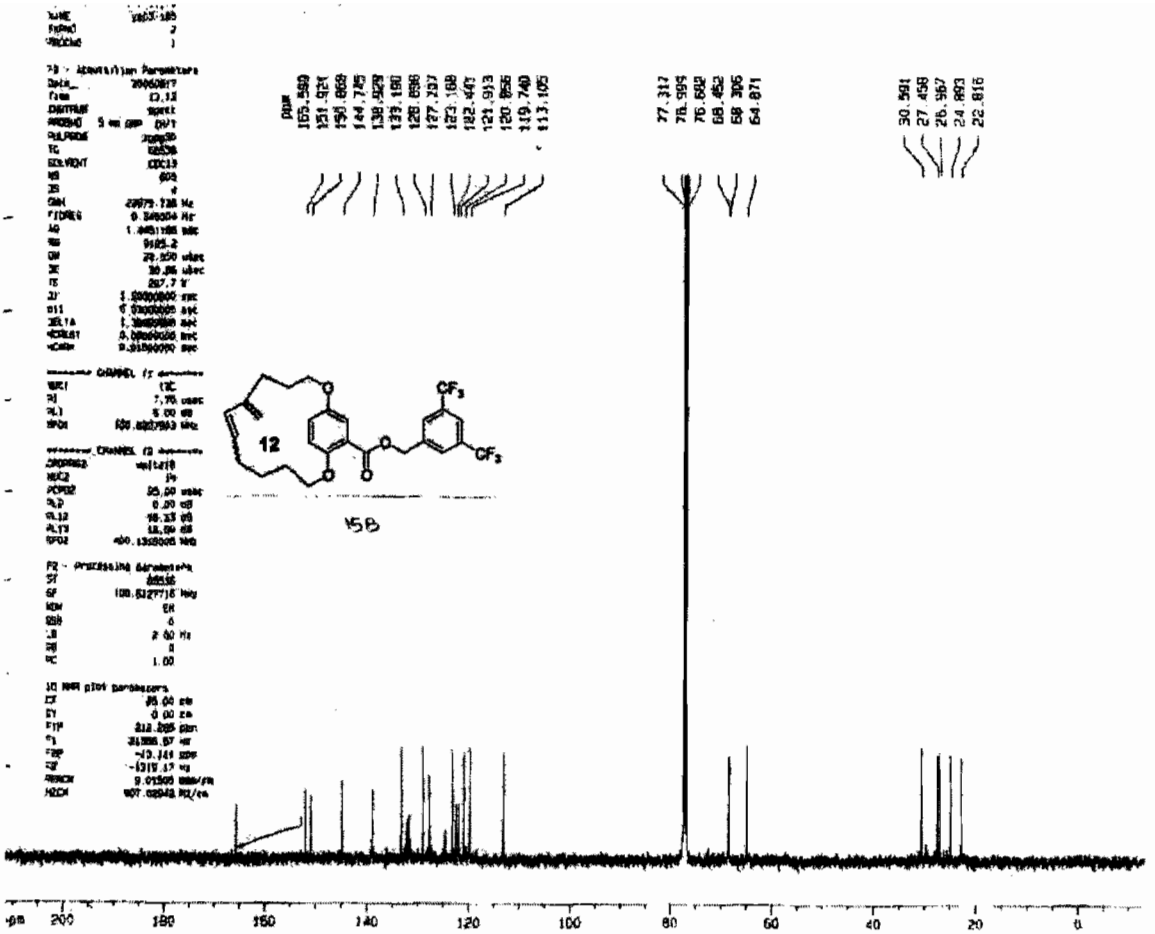
12A

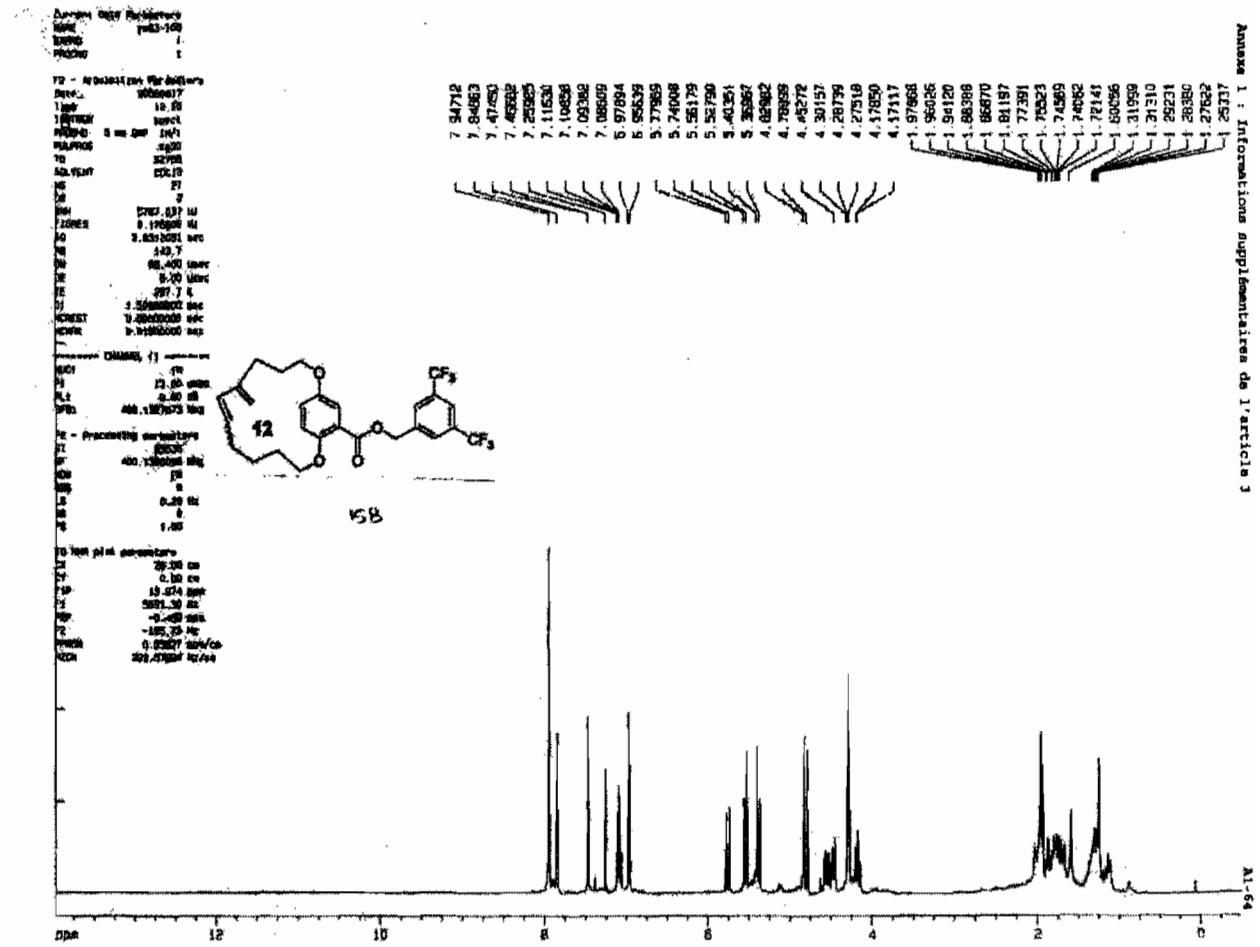

ppm
154.977
154.537
152.892
151.829
150.993
144.770
144.234
133.184
132.915
129.861
129.668
124.977
123.045
122.332
122.242
120.764
120.728
119.906
113.287
113.051
77.321
77.208
77.003
76.686
72.600
70.452
69.490
68.483
68.424
53.805
32.481
30.947
30.585
29.698
29.520
27.435
27.224
26.938
26.398
25.612
25.242
24.959
22.843
22.195
21.971
12
13A
ppm
220
200
180
160
140
120
100
80
60
40
20
0


ppm
7.38759
7.37958
7.33664
7.33015
7.26045
7.05465
7.05700
7.04842
7.04143
7.03190
6.94910
6.91957
5.43127
5.39479
4.83191
4.82646
4.81794
4.78087
4.62849
4.27768
4.27147
4.26616
4.26335
4.25177
1.94344
1.92412
1.73407
1.72399
1.71592
1.70761
1.65247
1.24961
1.23741
1.22139
1.21567
1.20902
1.20042
1.19269
1.18510
0.67727
12
13A
ppm
12
10
8
6
4
2
0

14B

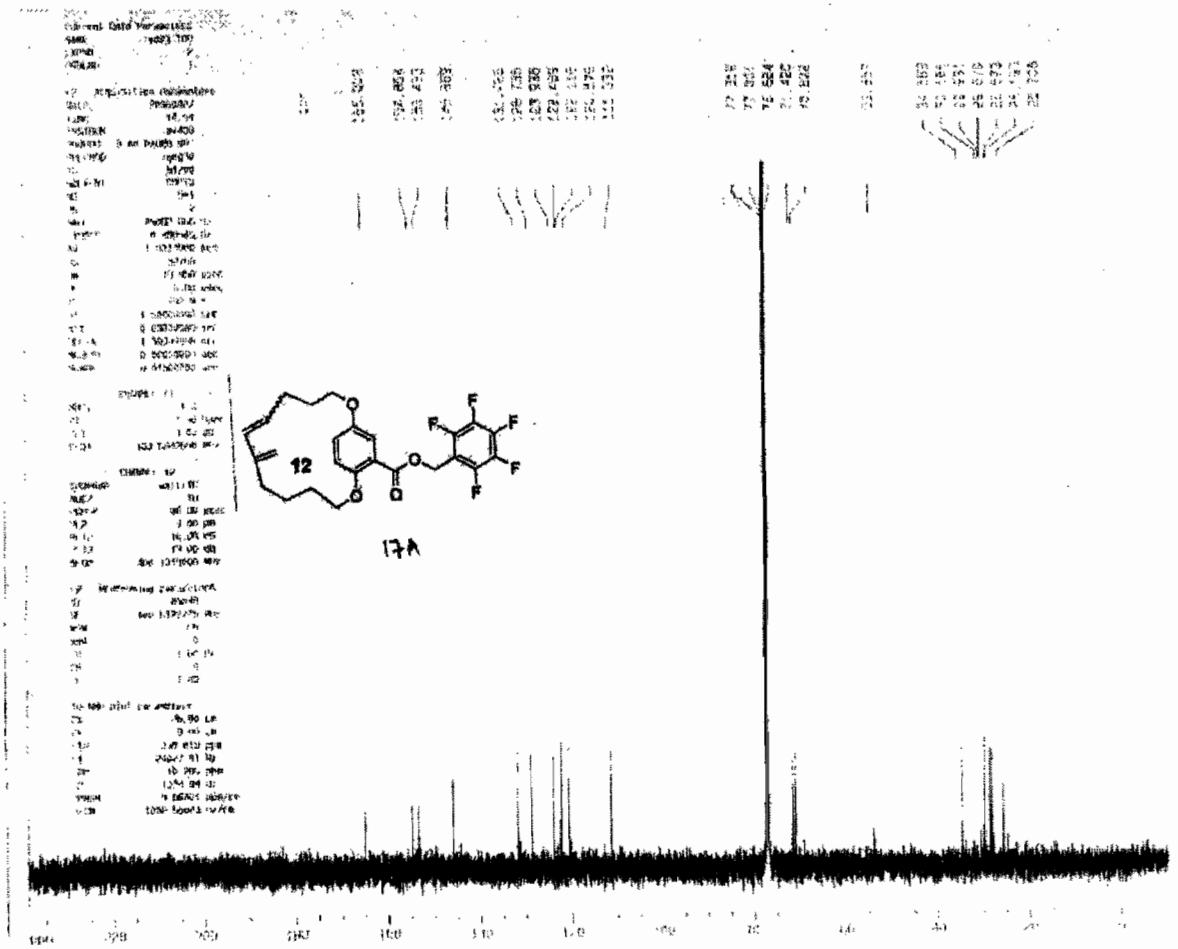
14B

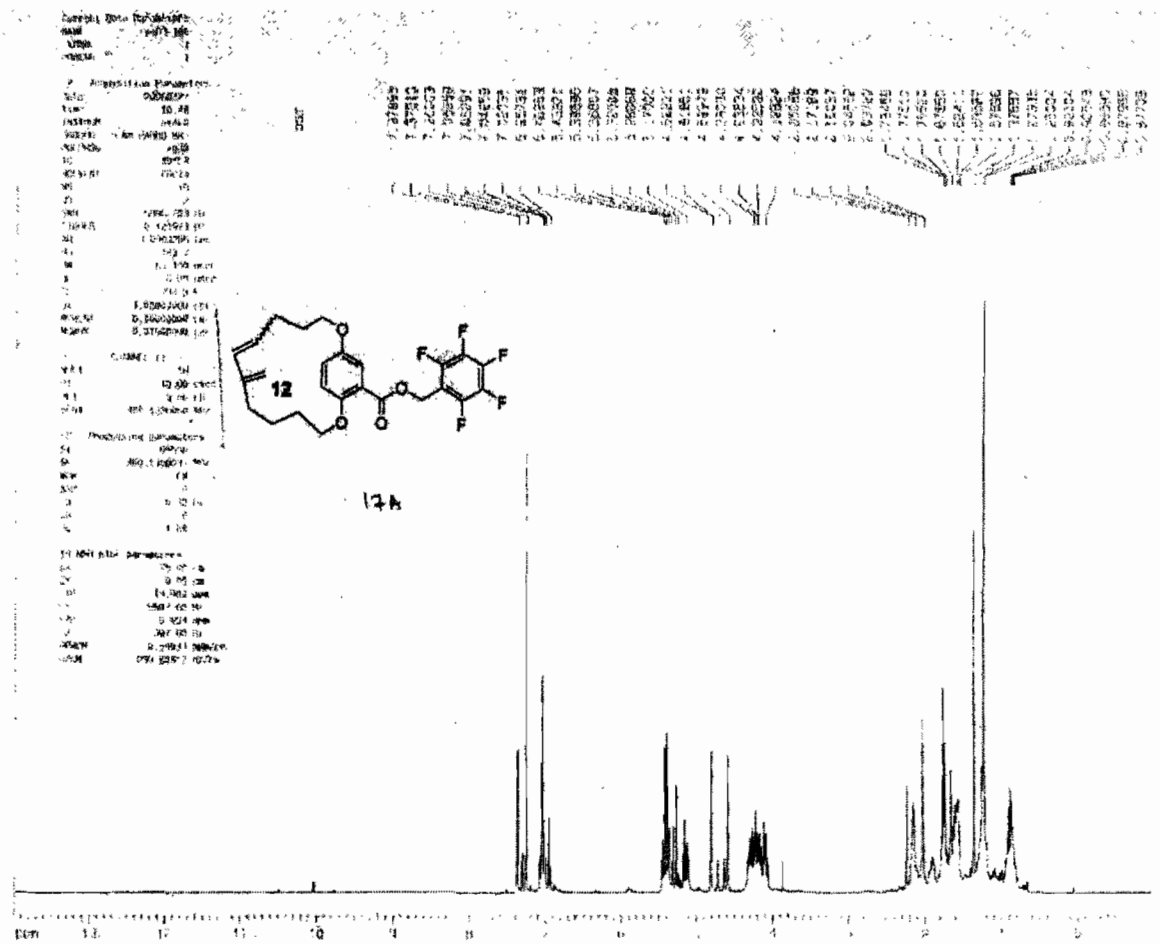

12
CF3
CF3
15B

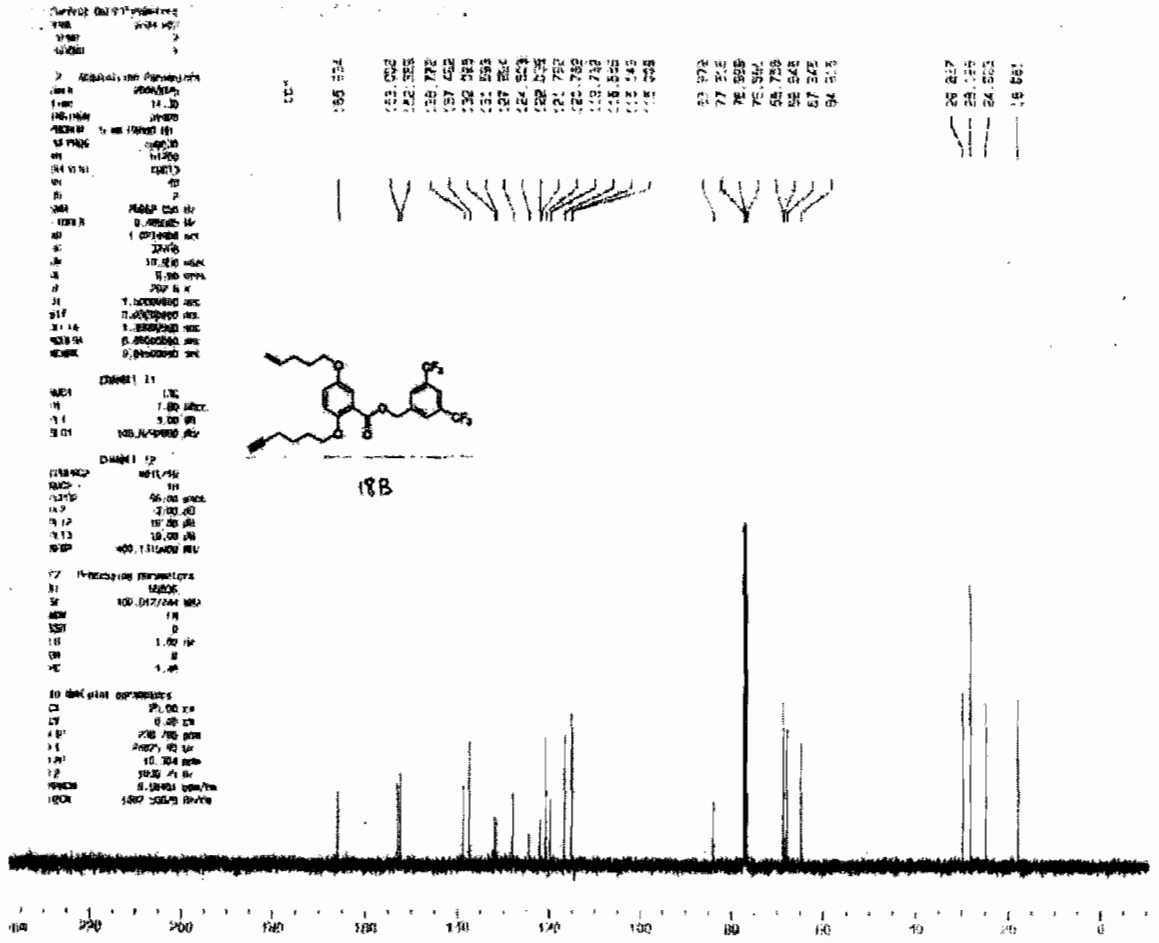

12
CF3
CF3
15B

16A

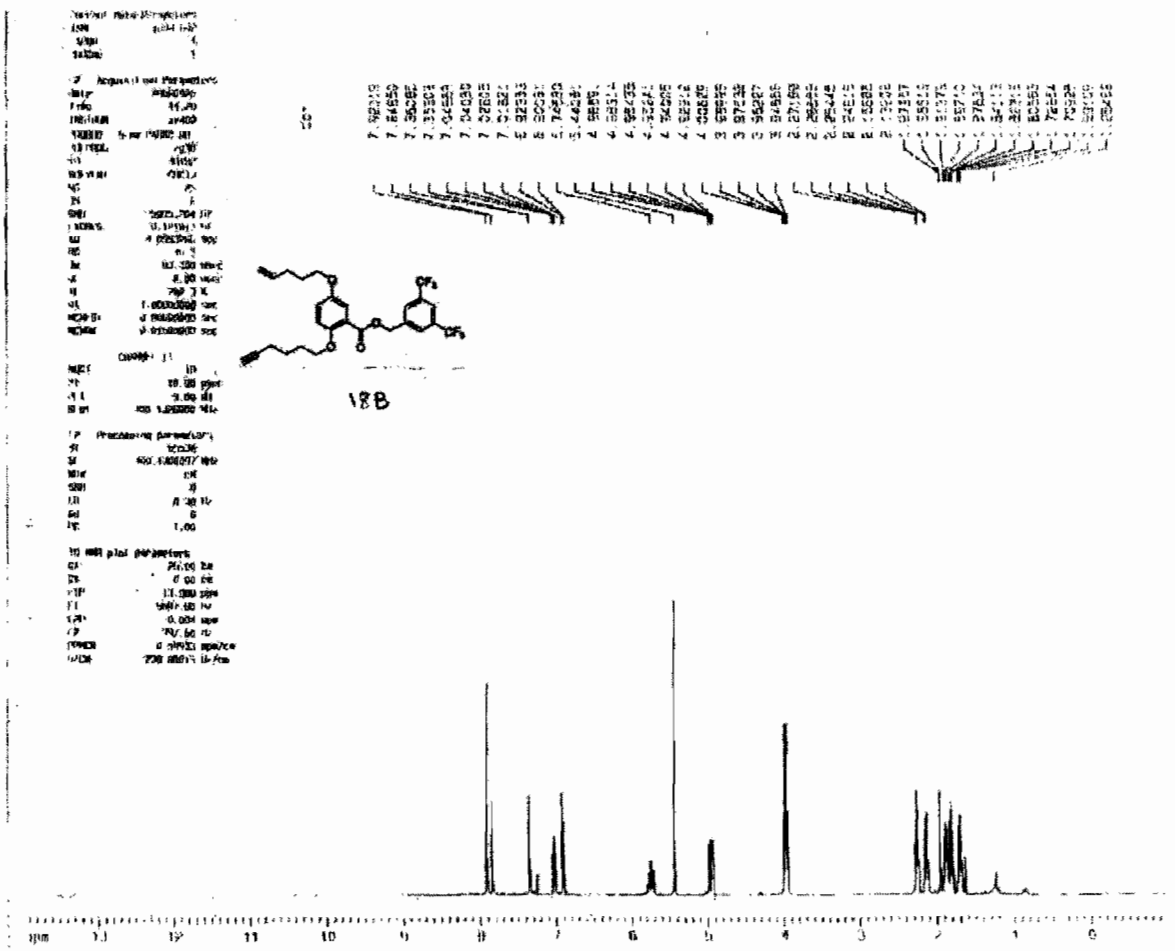
16A


12
17A

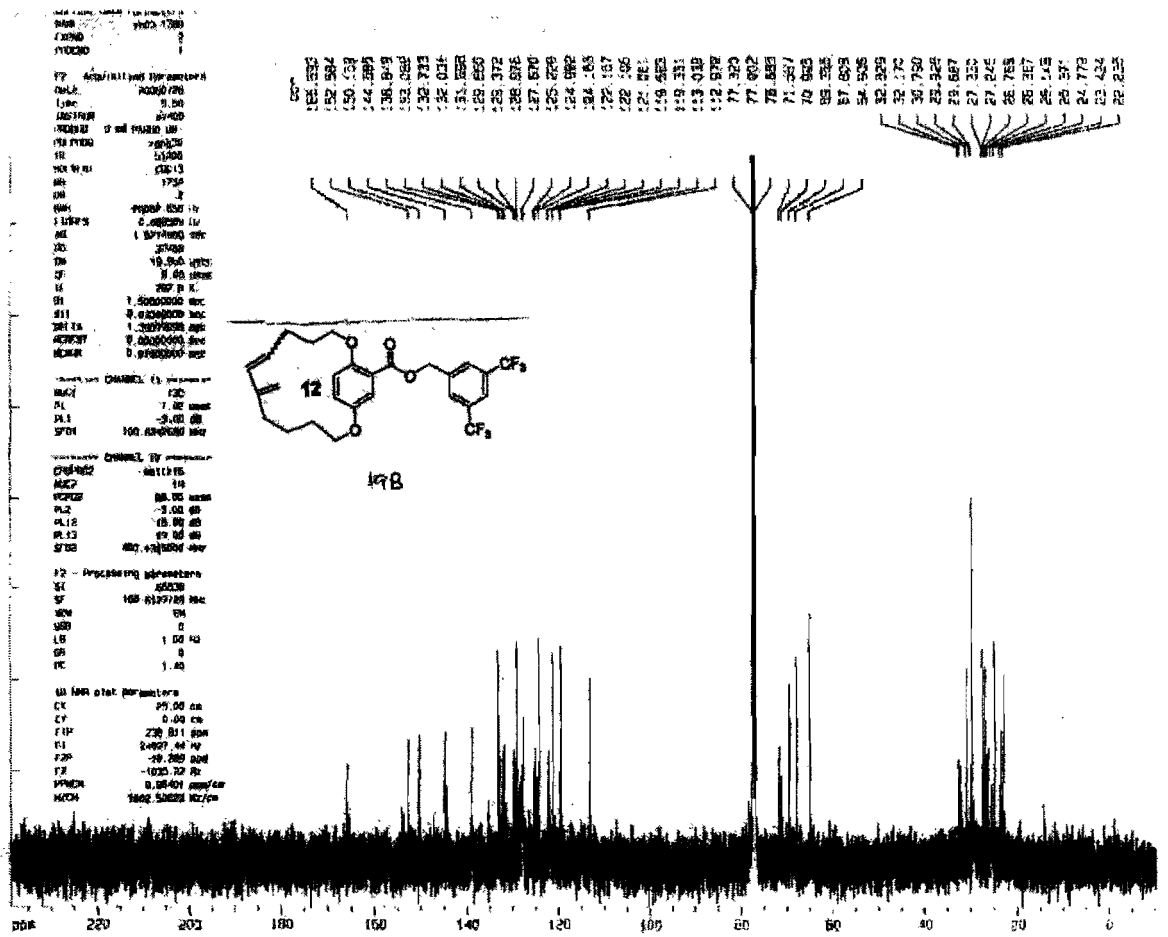

12
17A

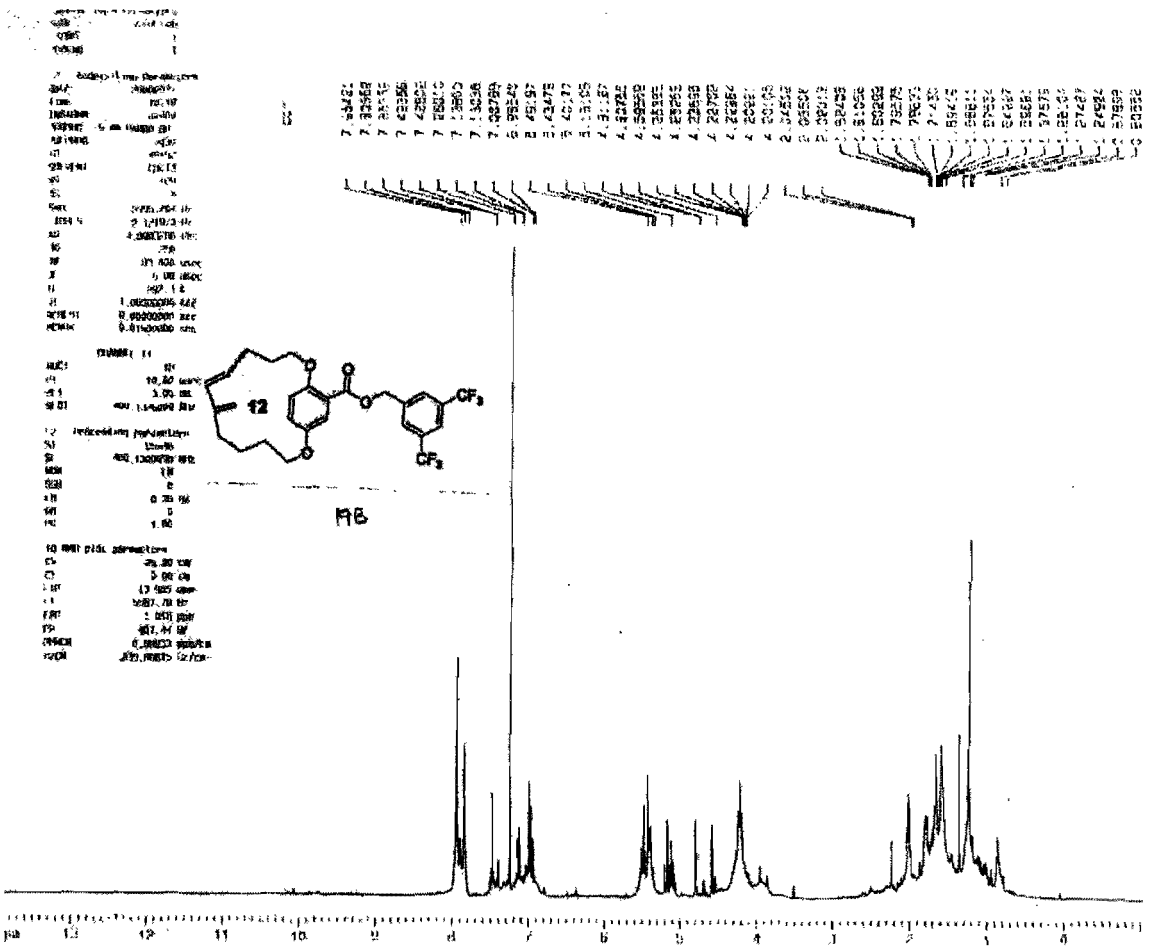


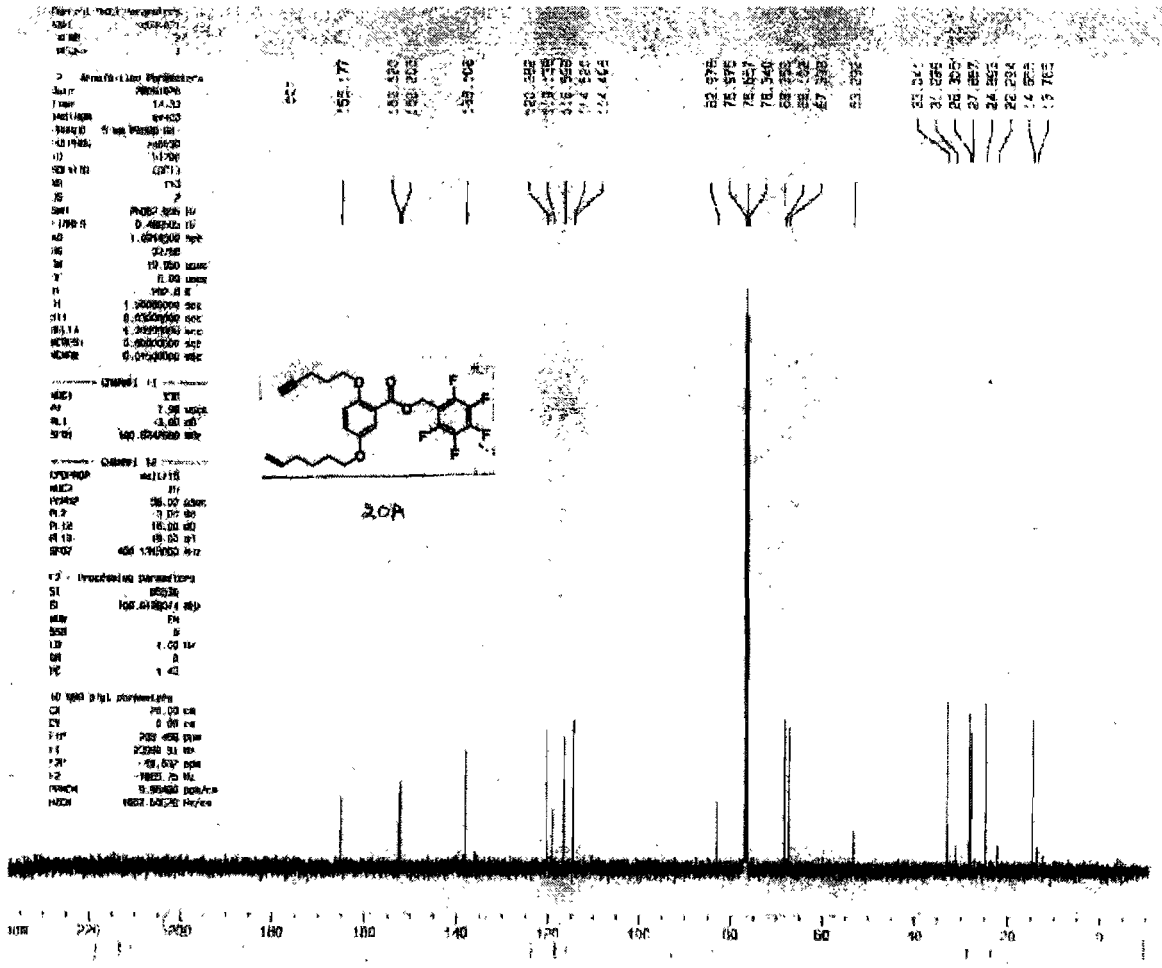
18B

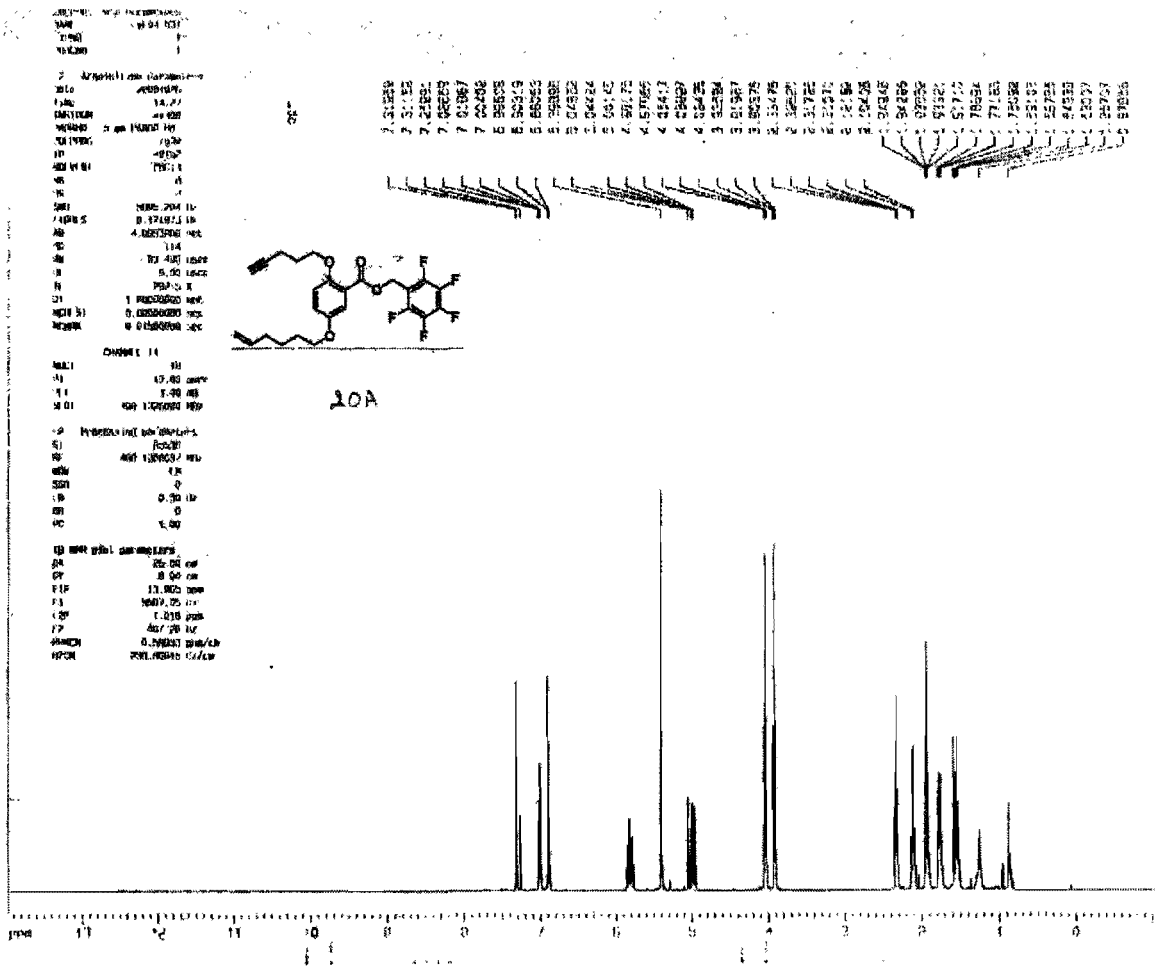


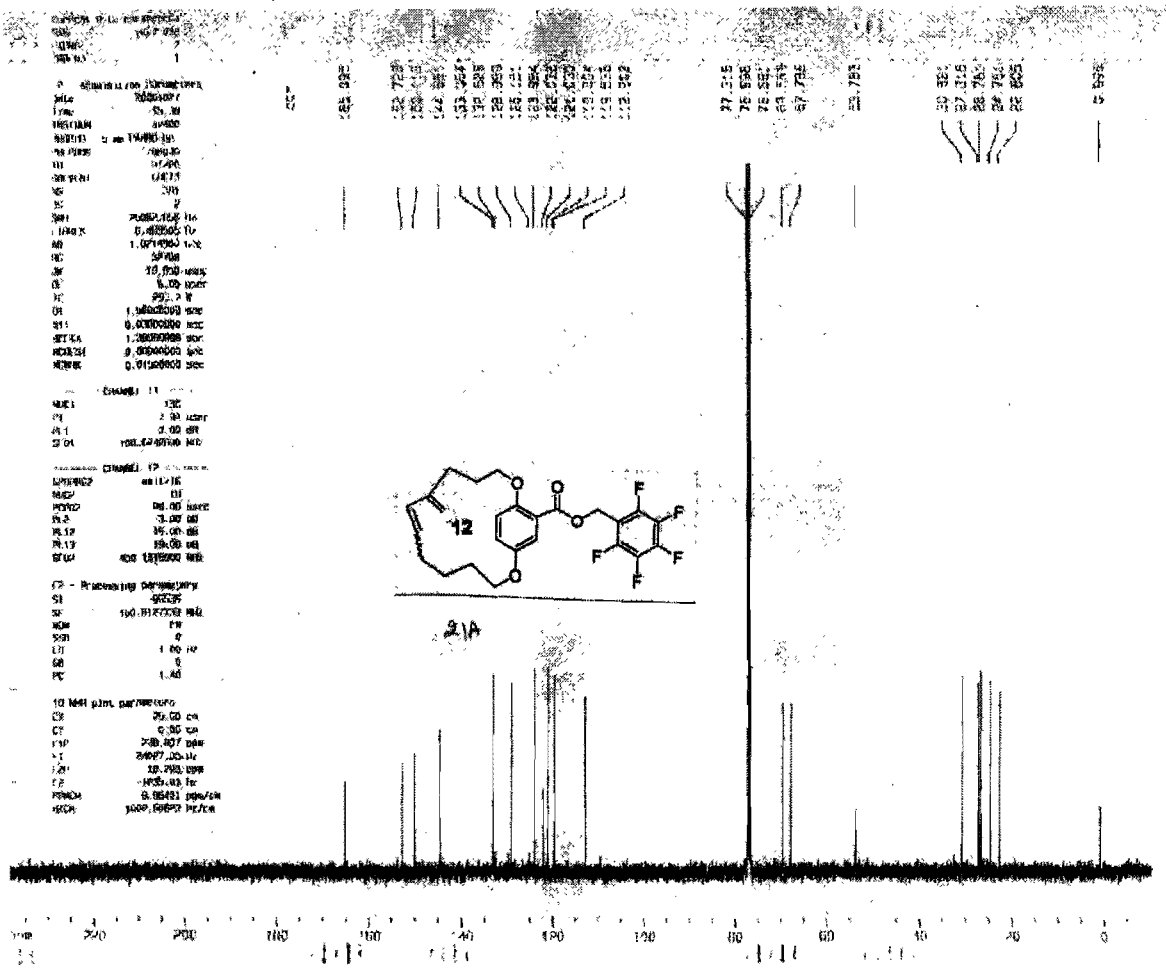
18B

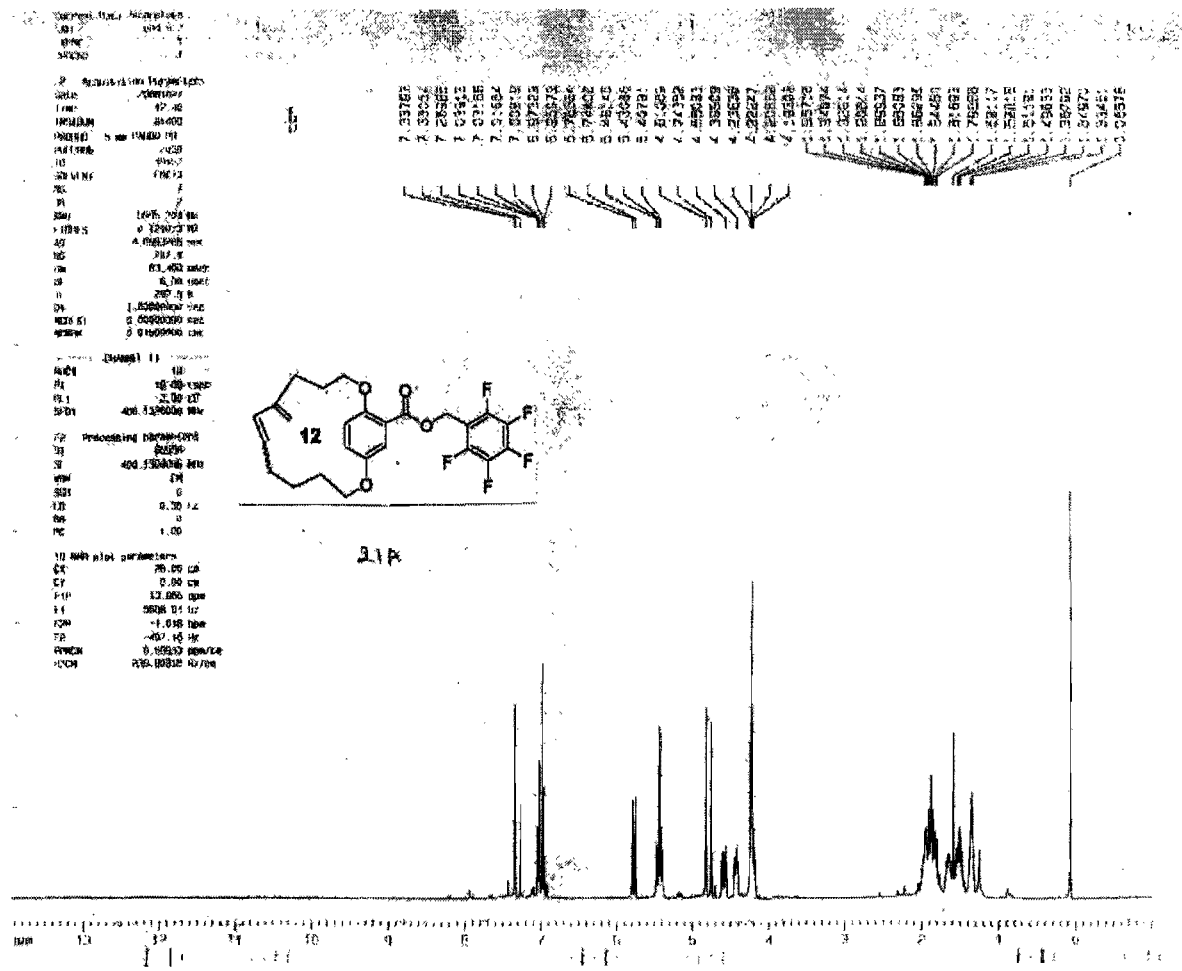

12
CF3
CF3
198

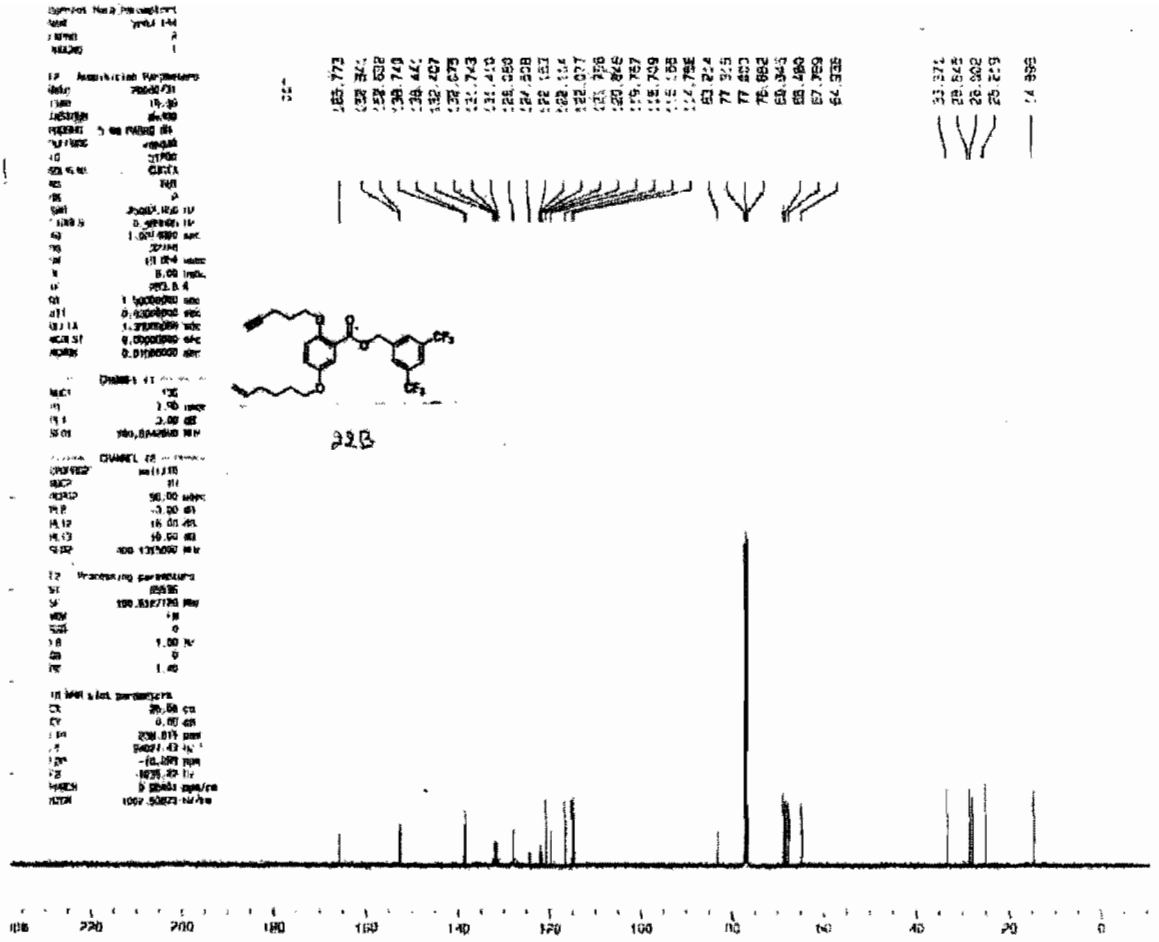

12
CF3
CF3
196

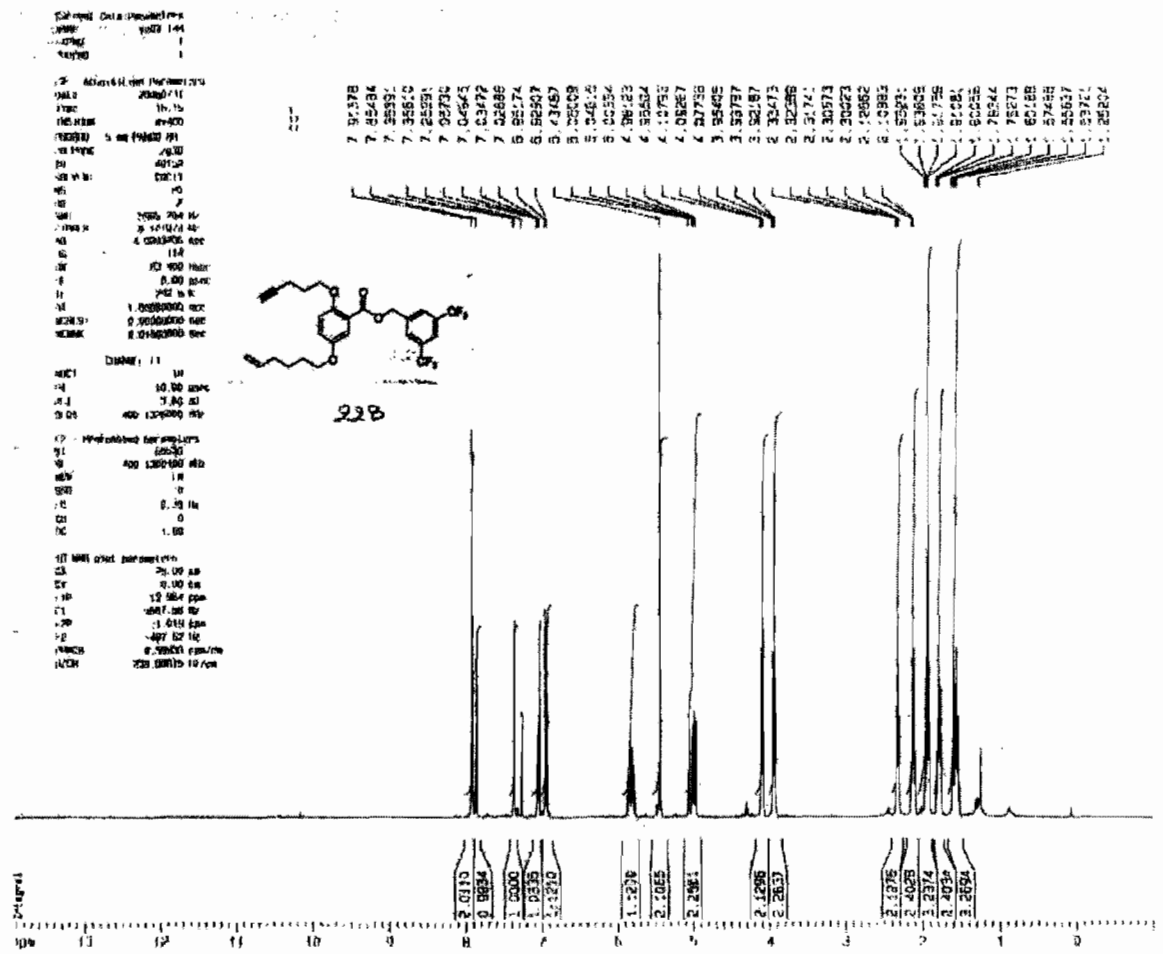

20A

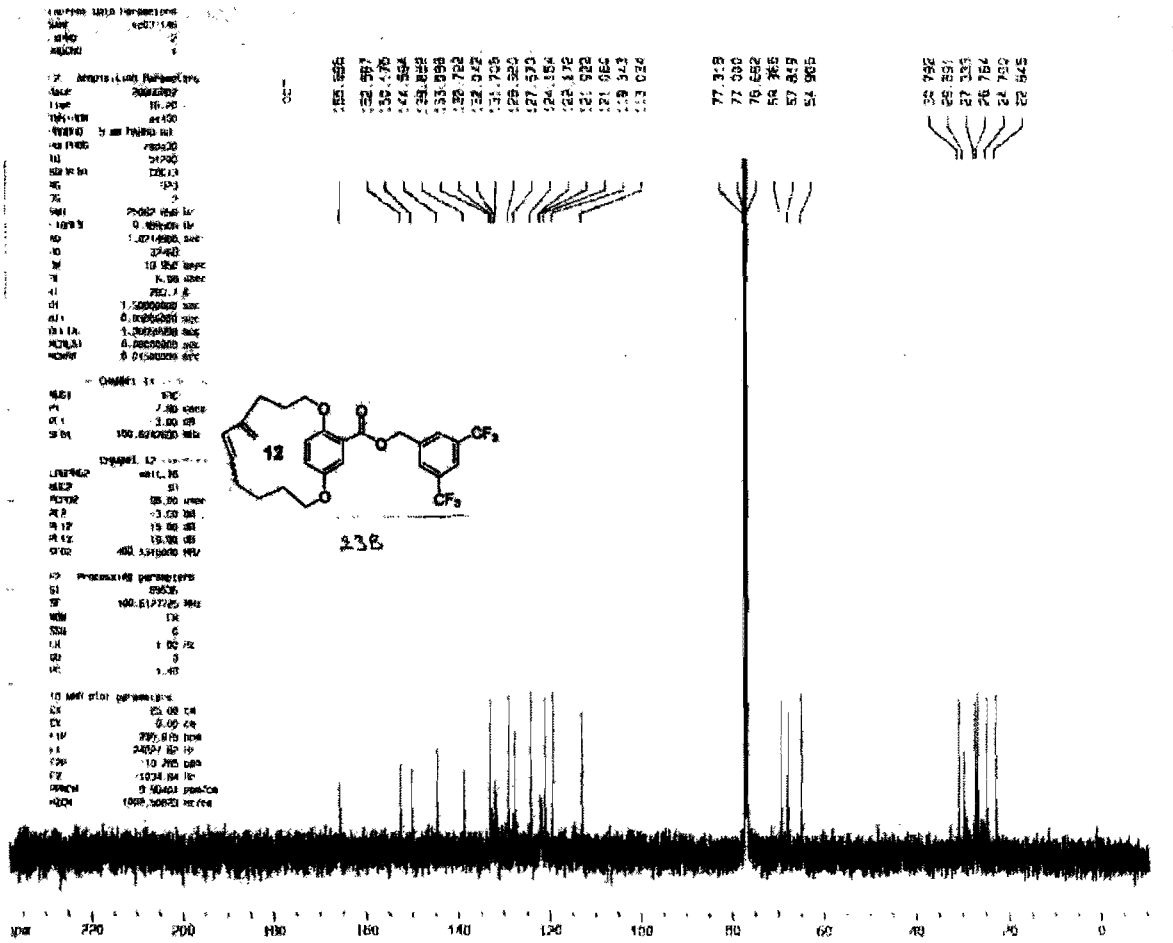

20A

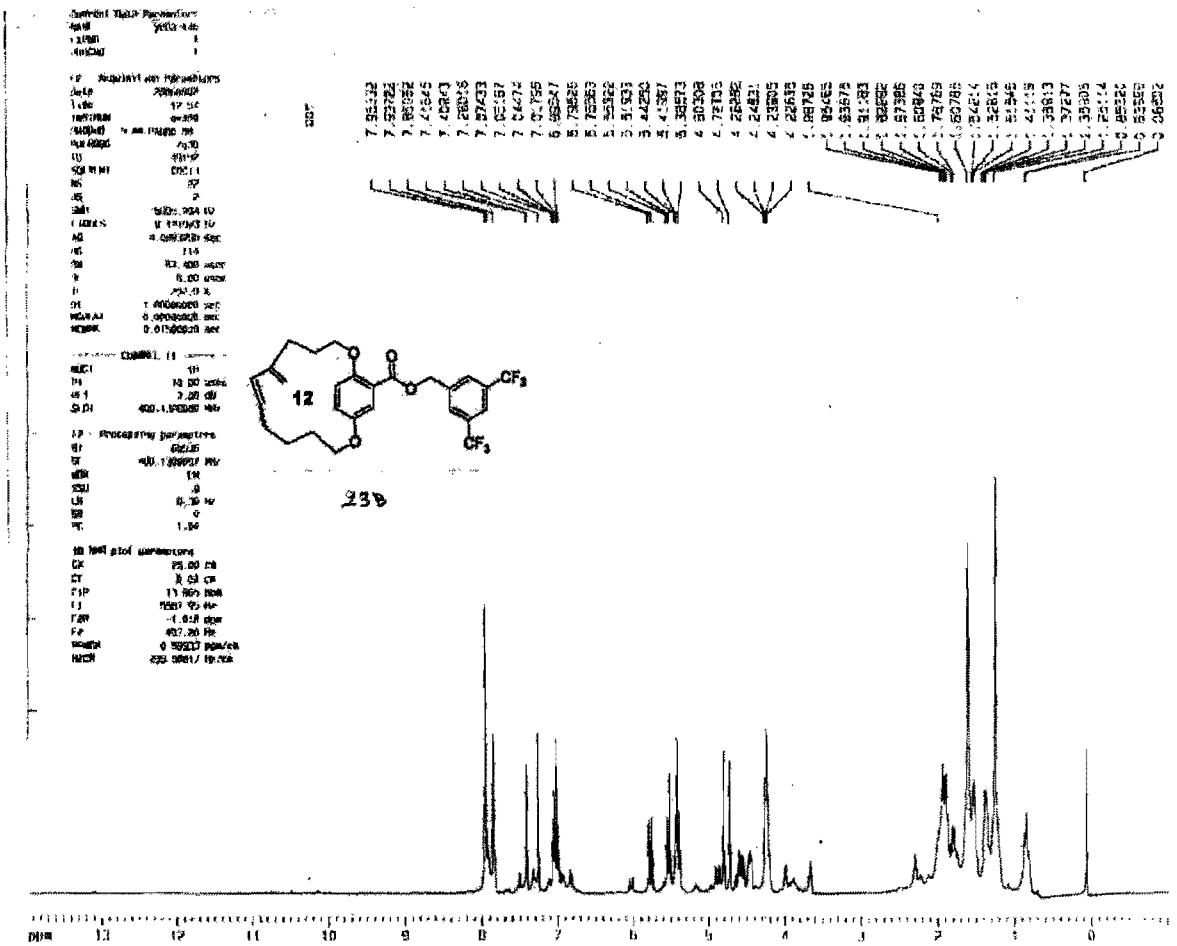

12
F
F
F
F
F
O
O
O
O
2.1A

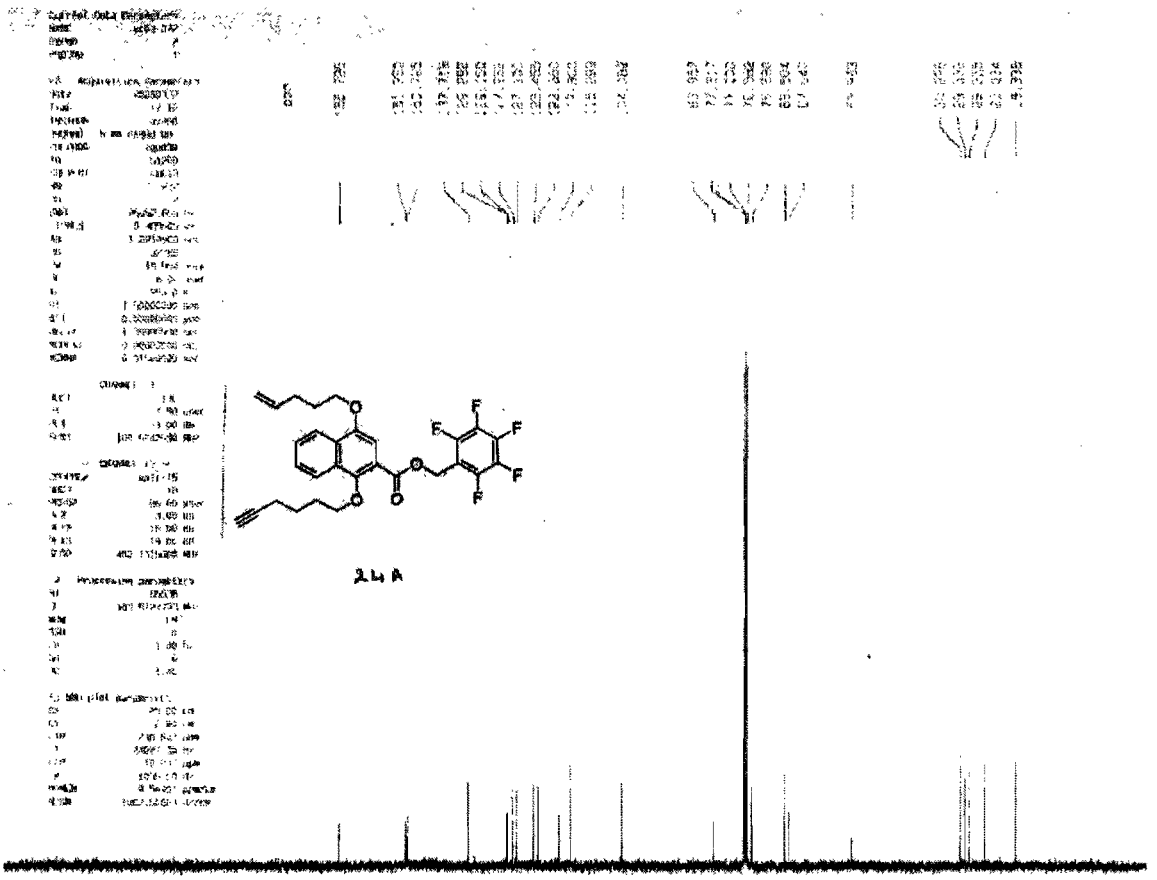

12
F
F
F
F
F
O
O
O
O
2.1A


22B

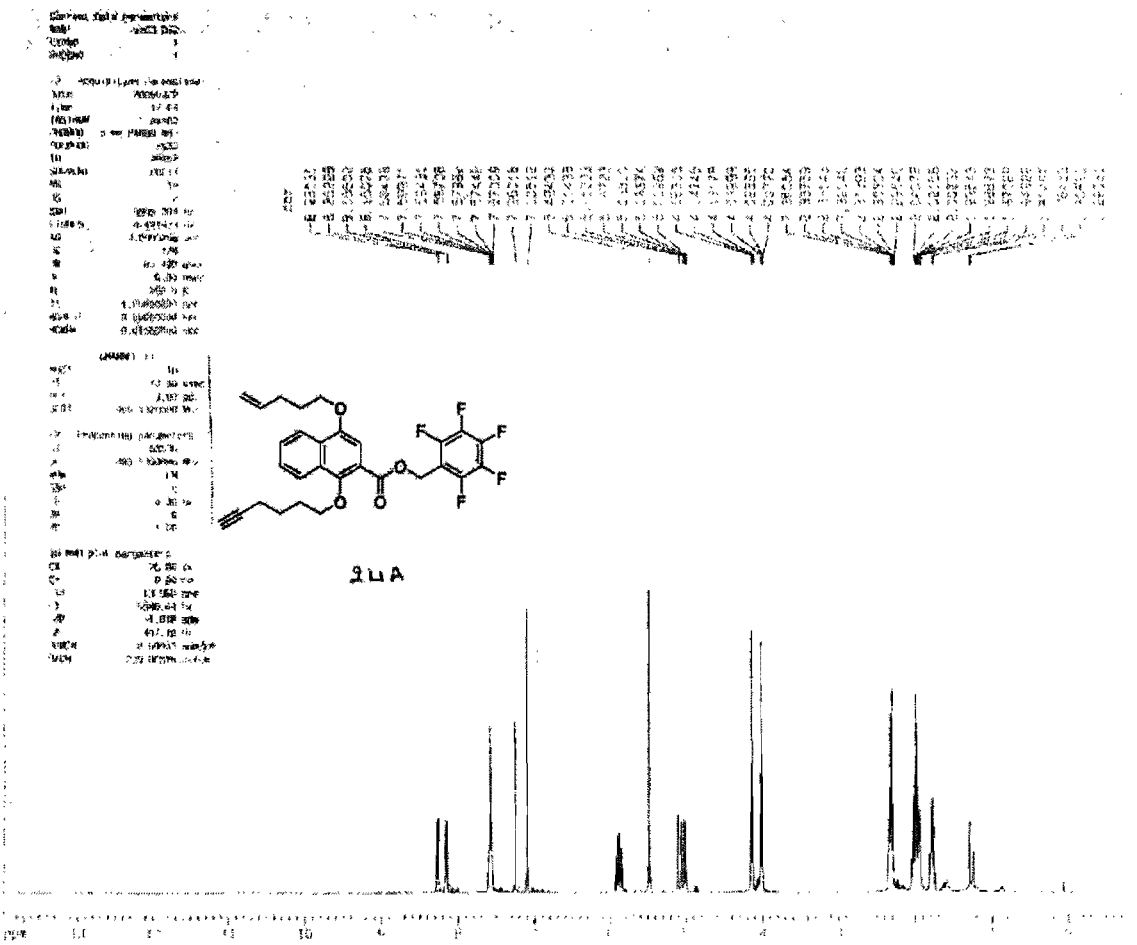

22B


12
CF3
CF3
238
ppm


12
CF3
CF3
239
ppm



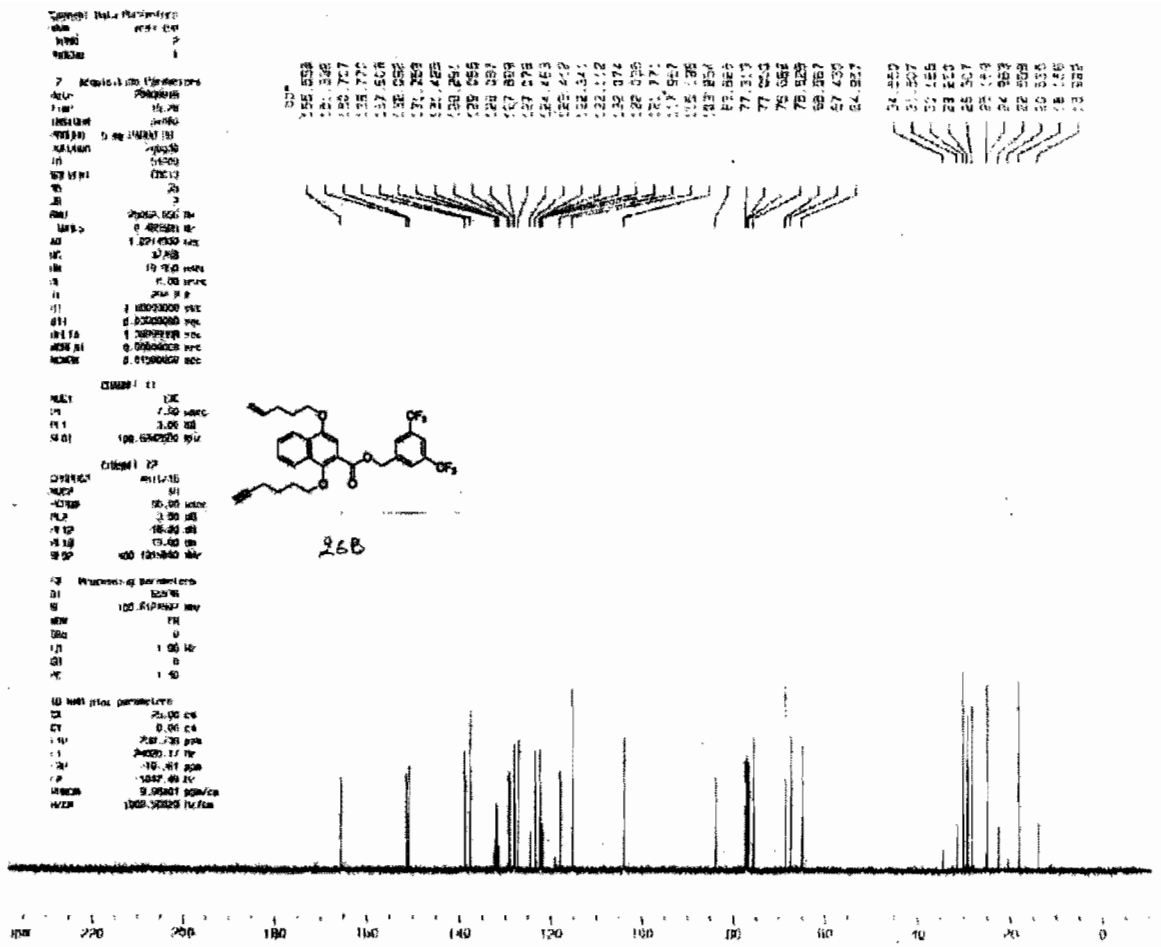
2L4A



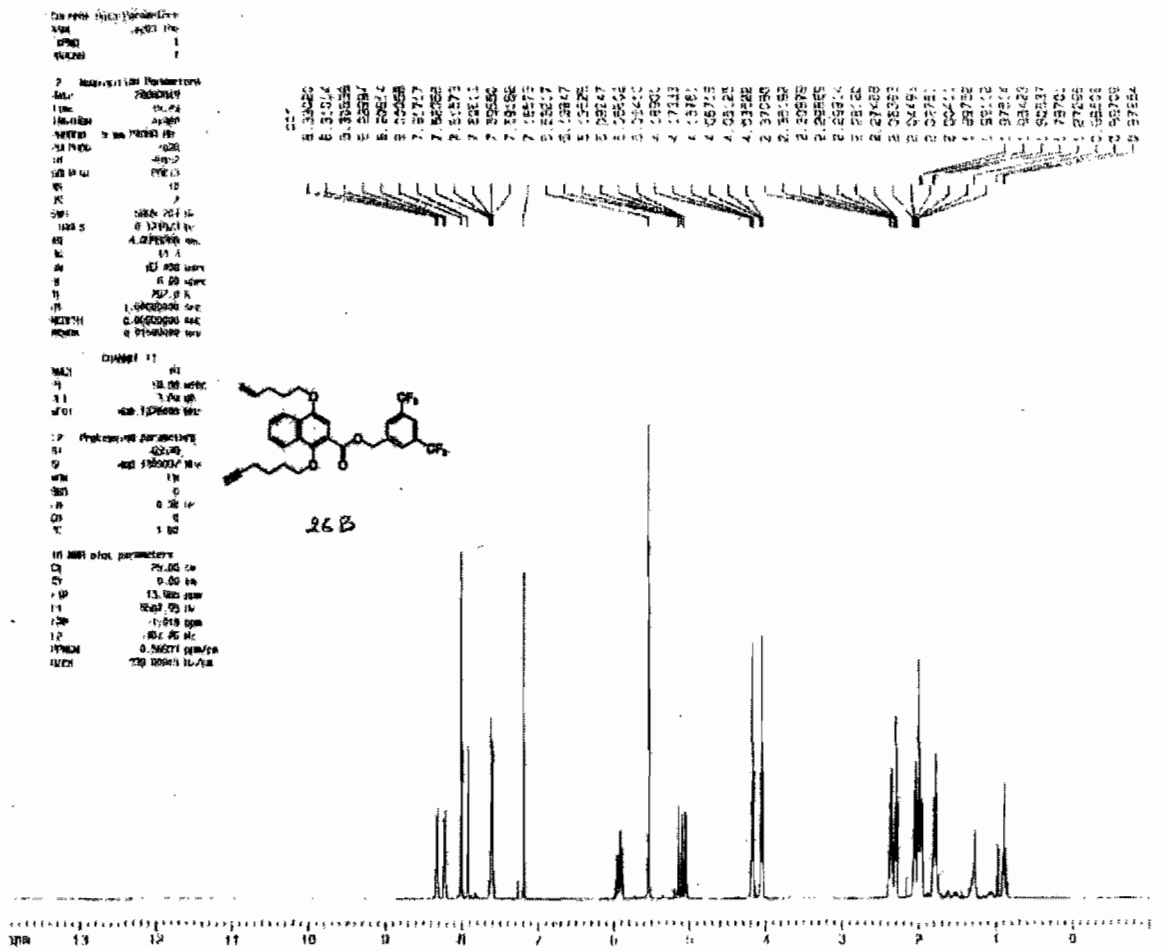
2L4A

25A

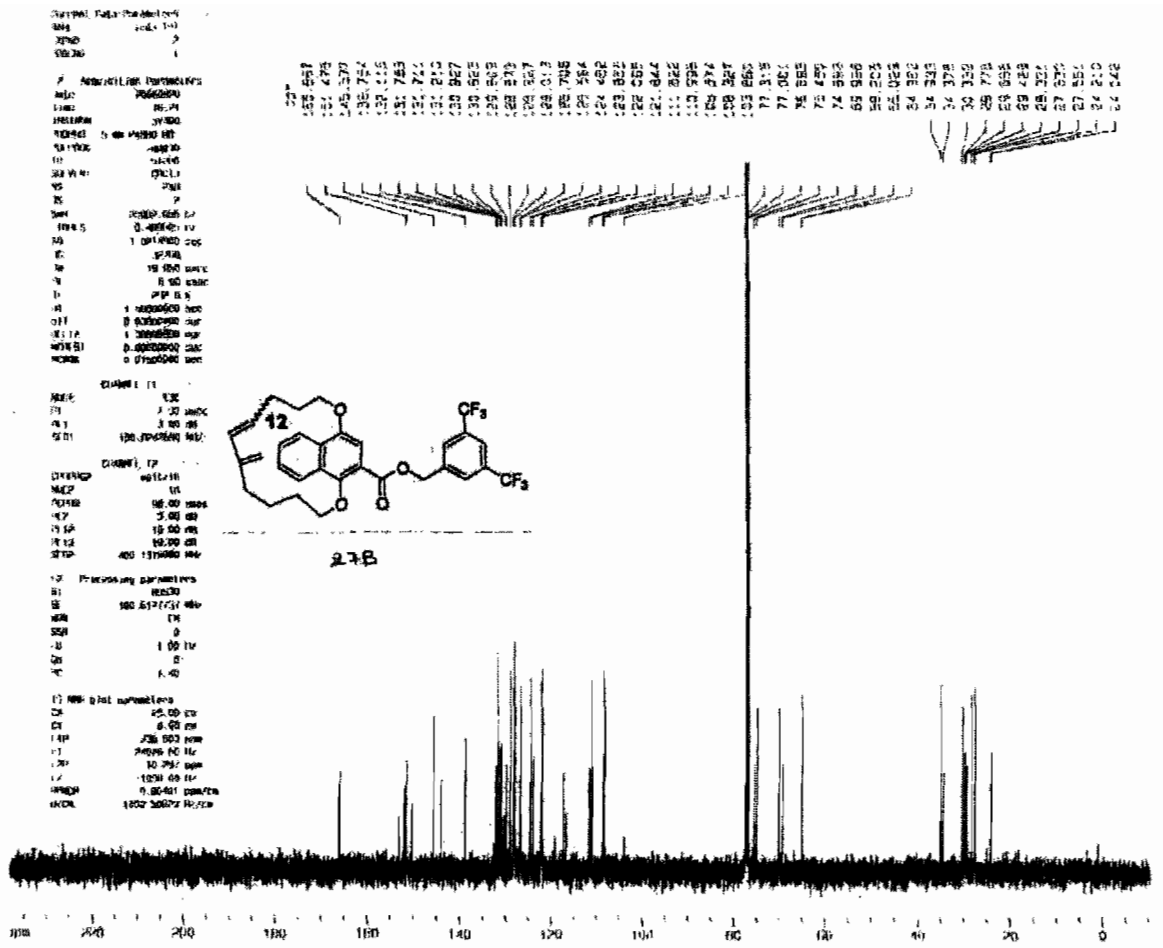
25A

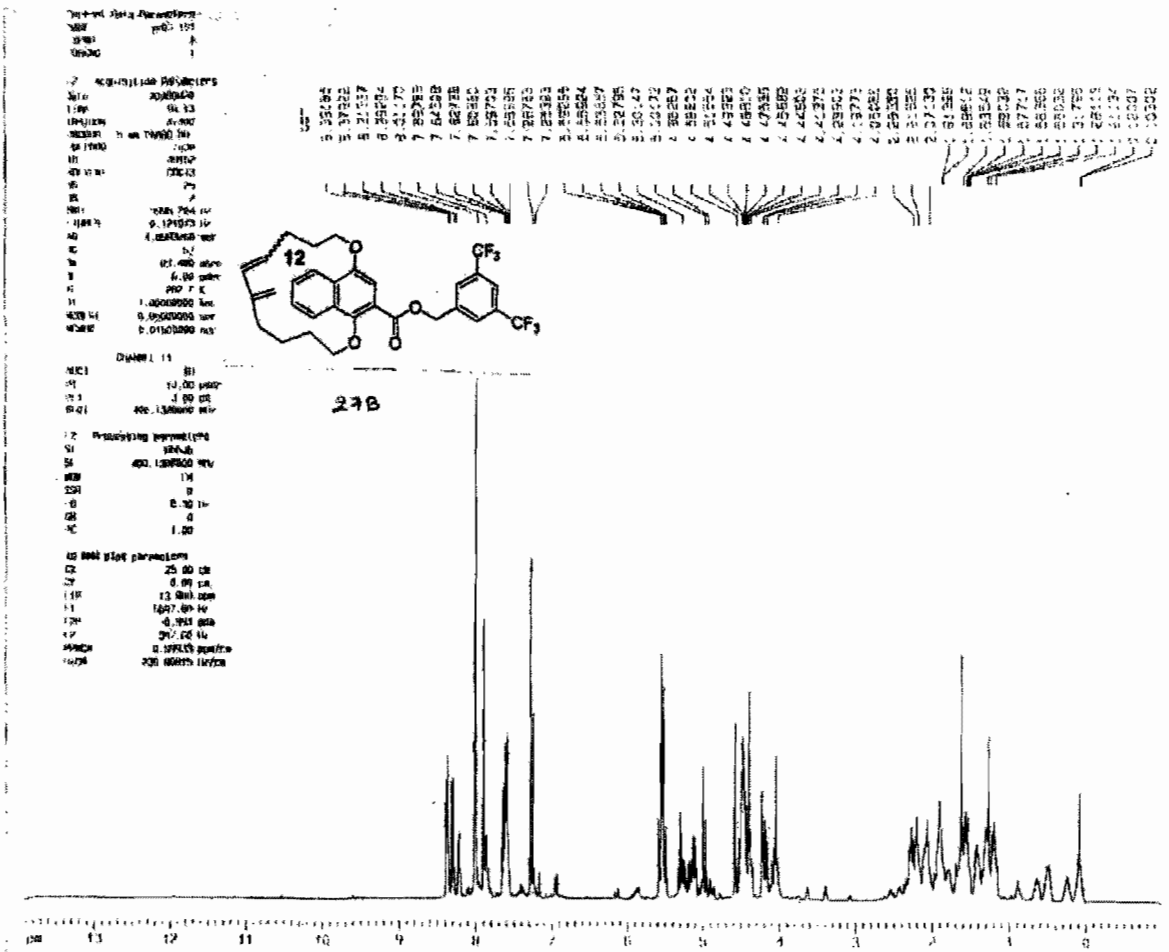


26B



26B


12
CF3
CF3
O
O
O
O
27B


12
CF3
CF3
O
O
O
O
27B

28A

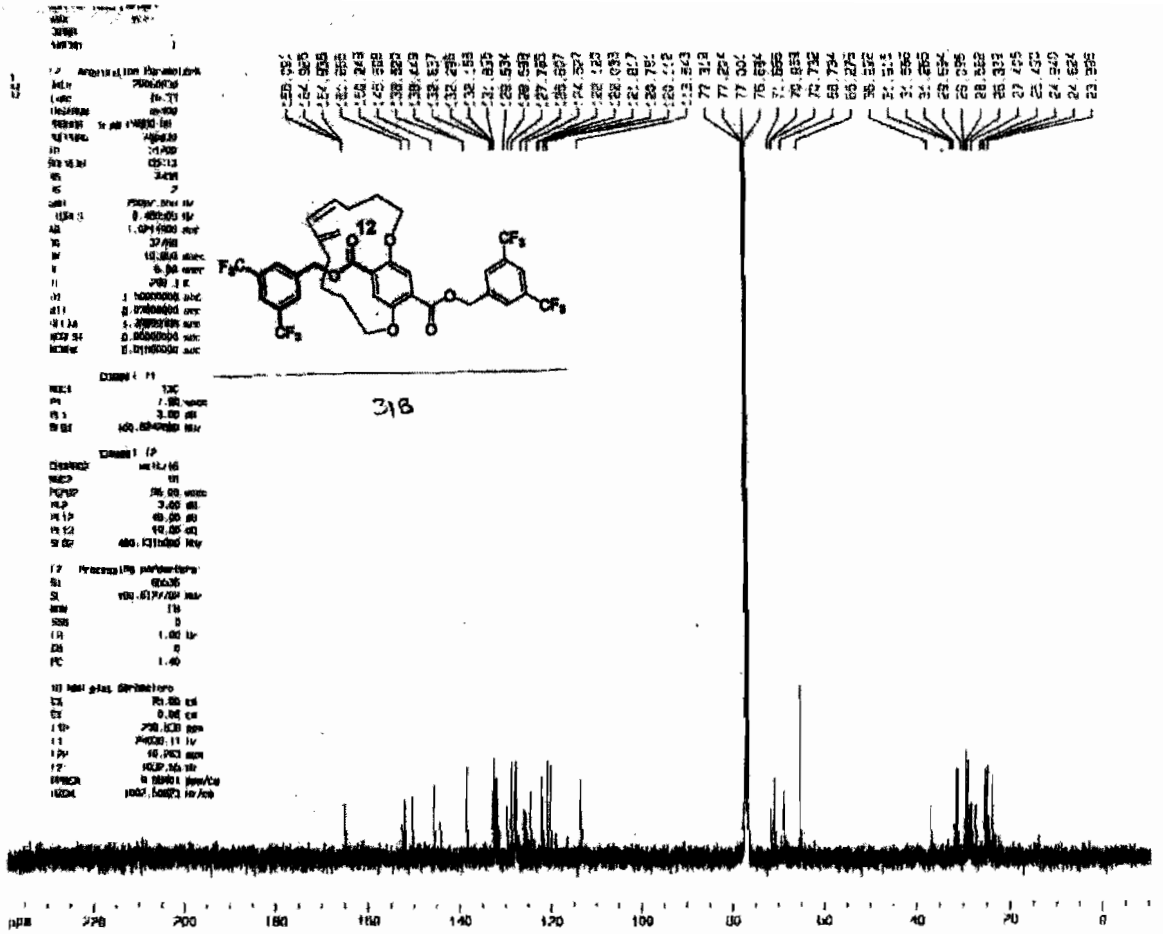
28A

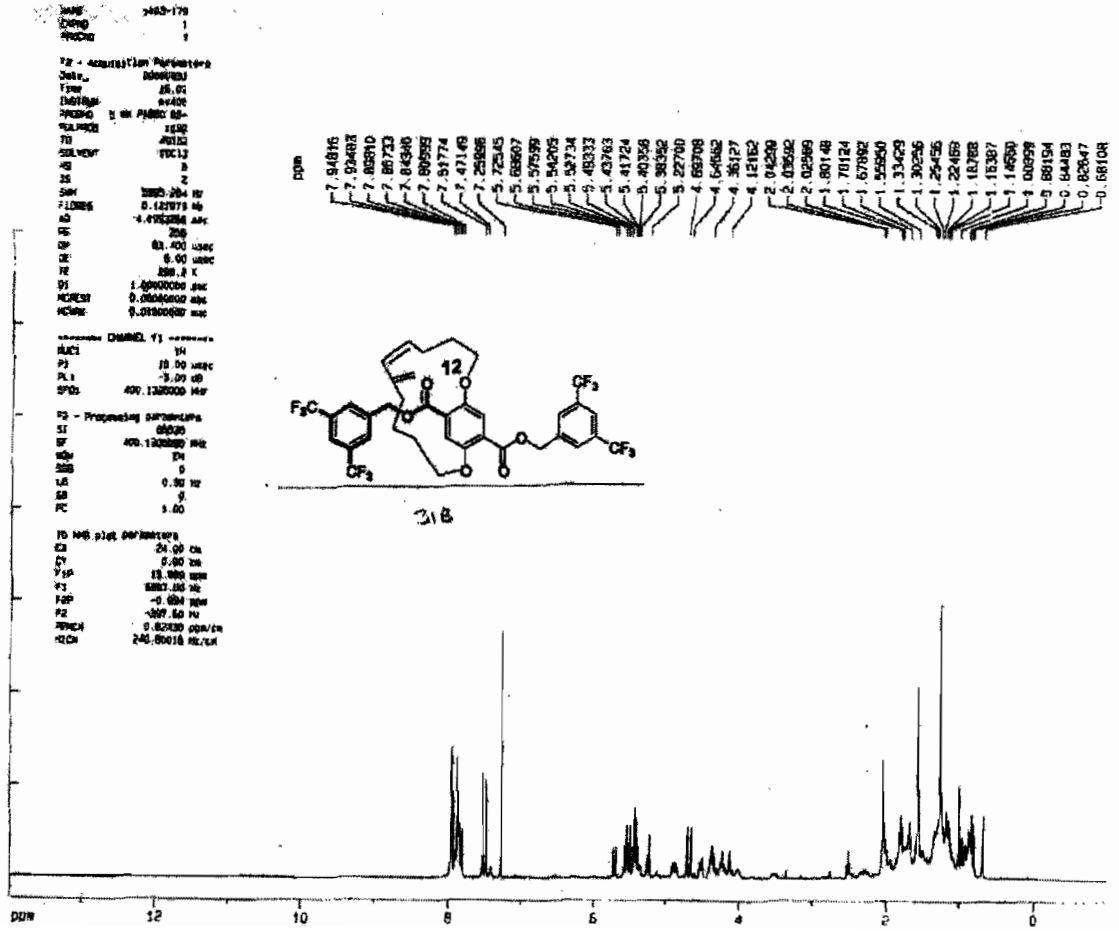
29A

39A

30B

30B


318

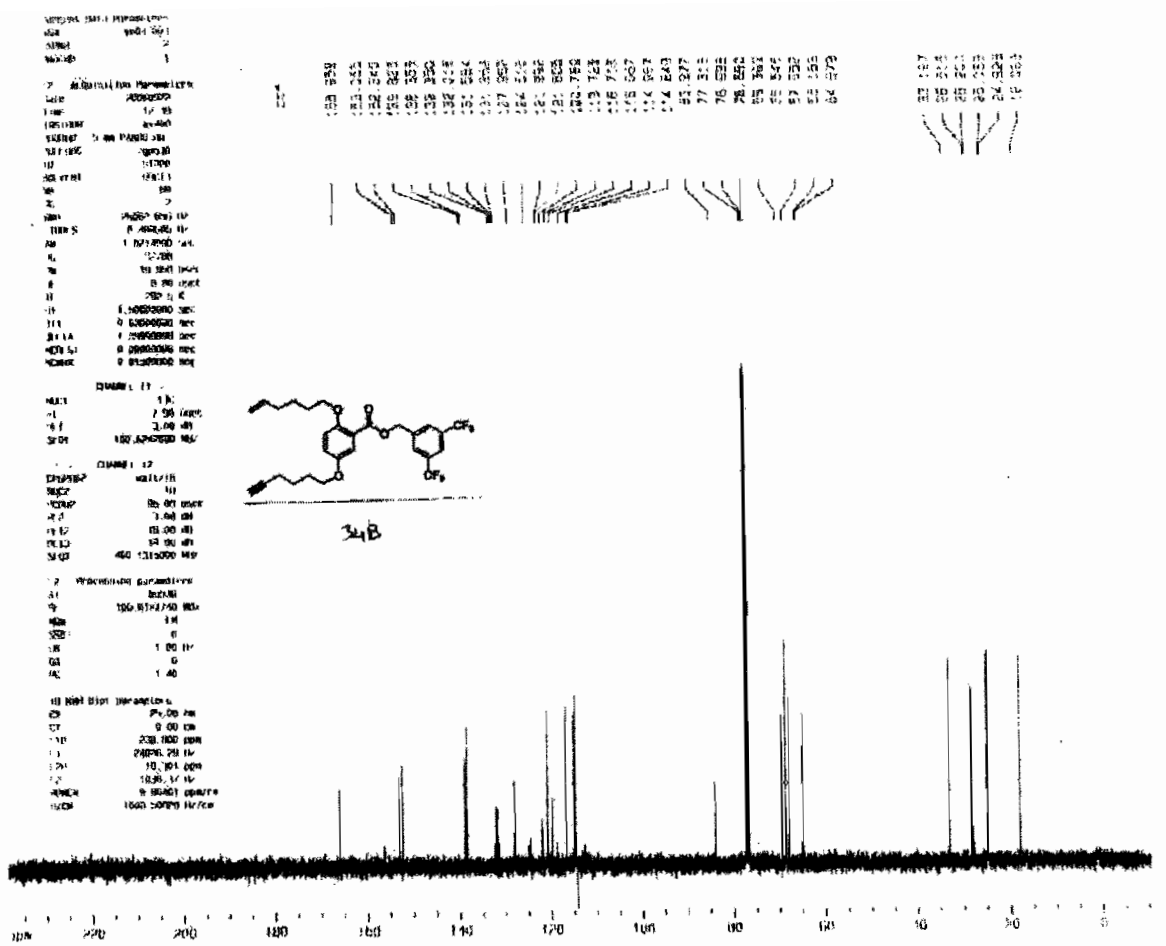

318

32 A

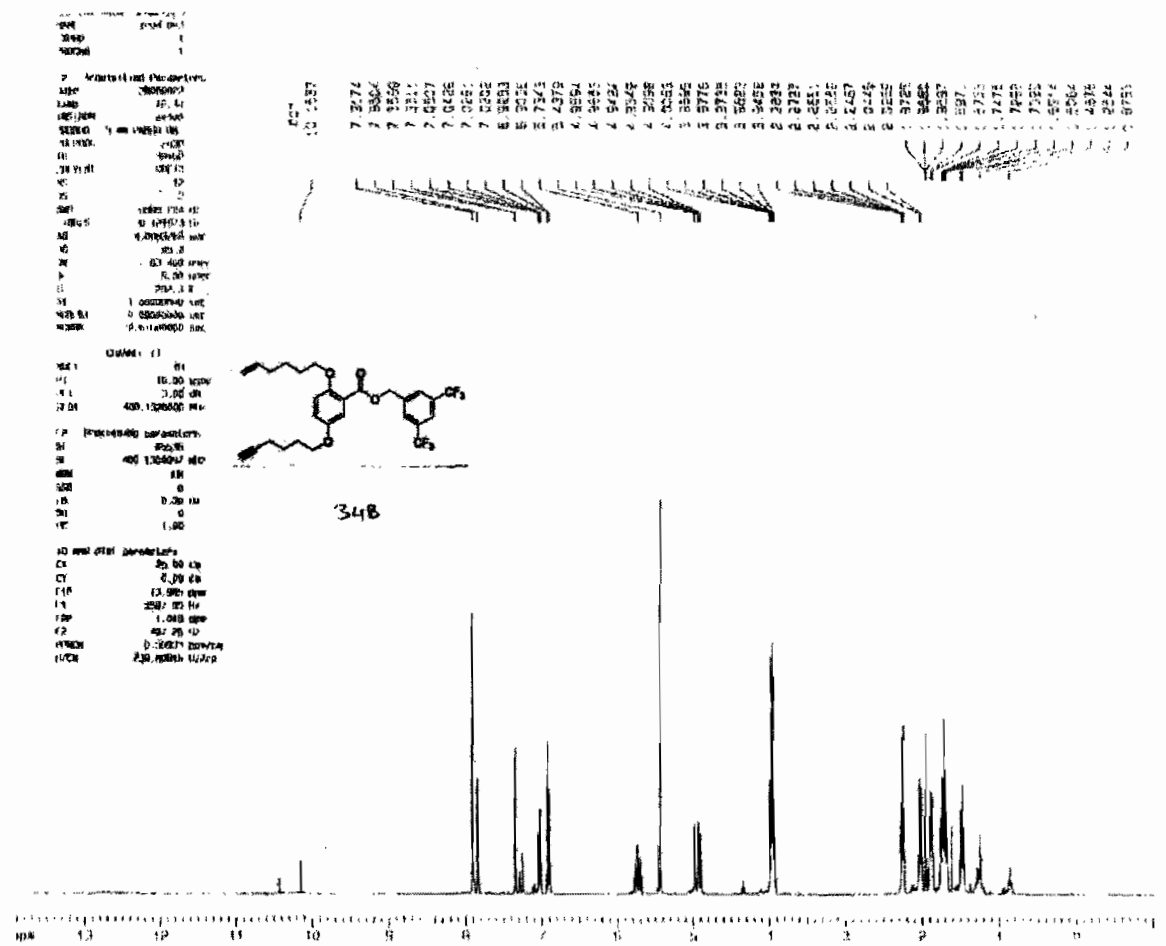
32 A

A1-101

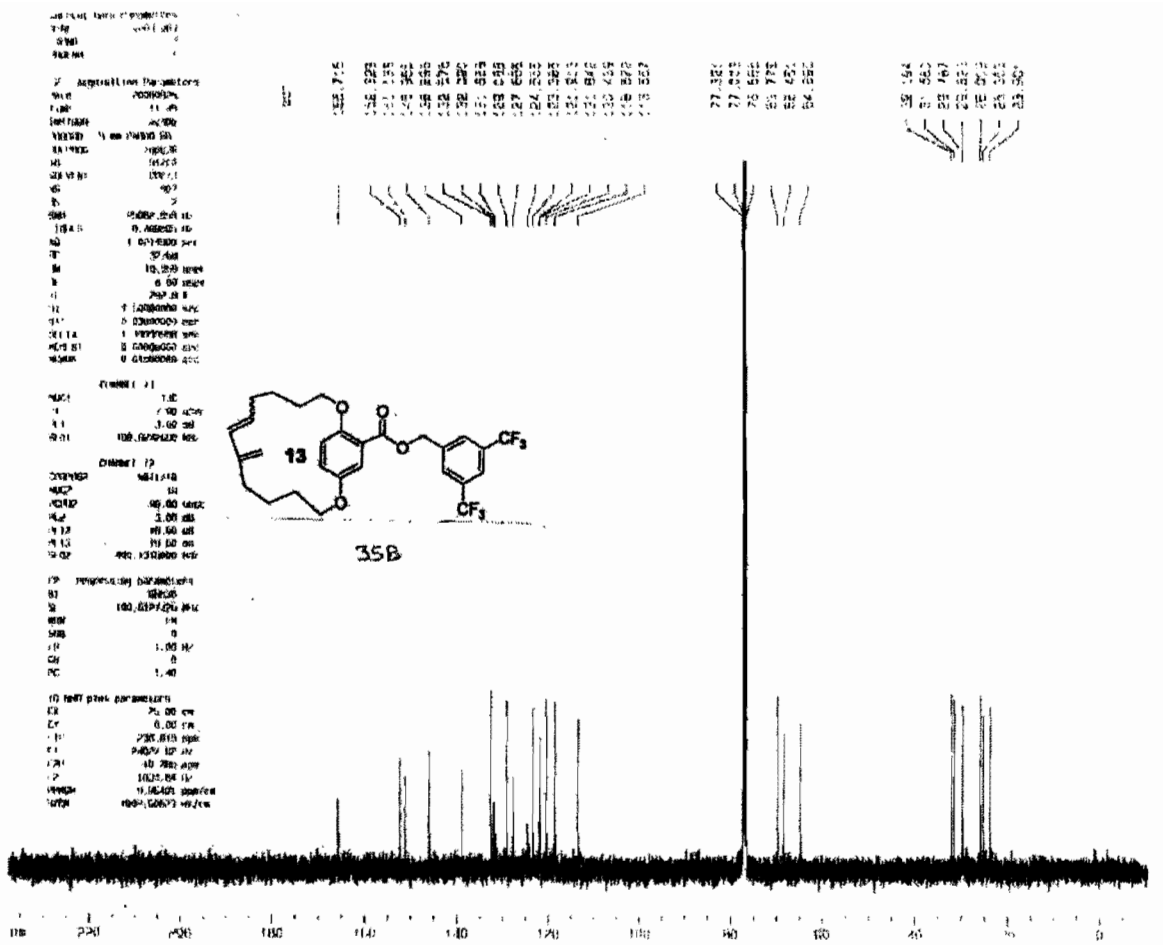
A1-100

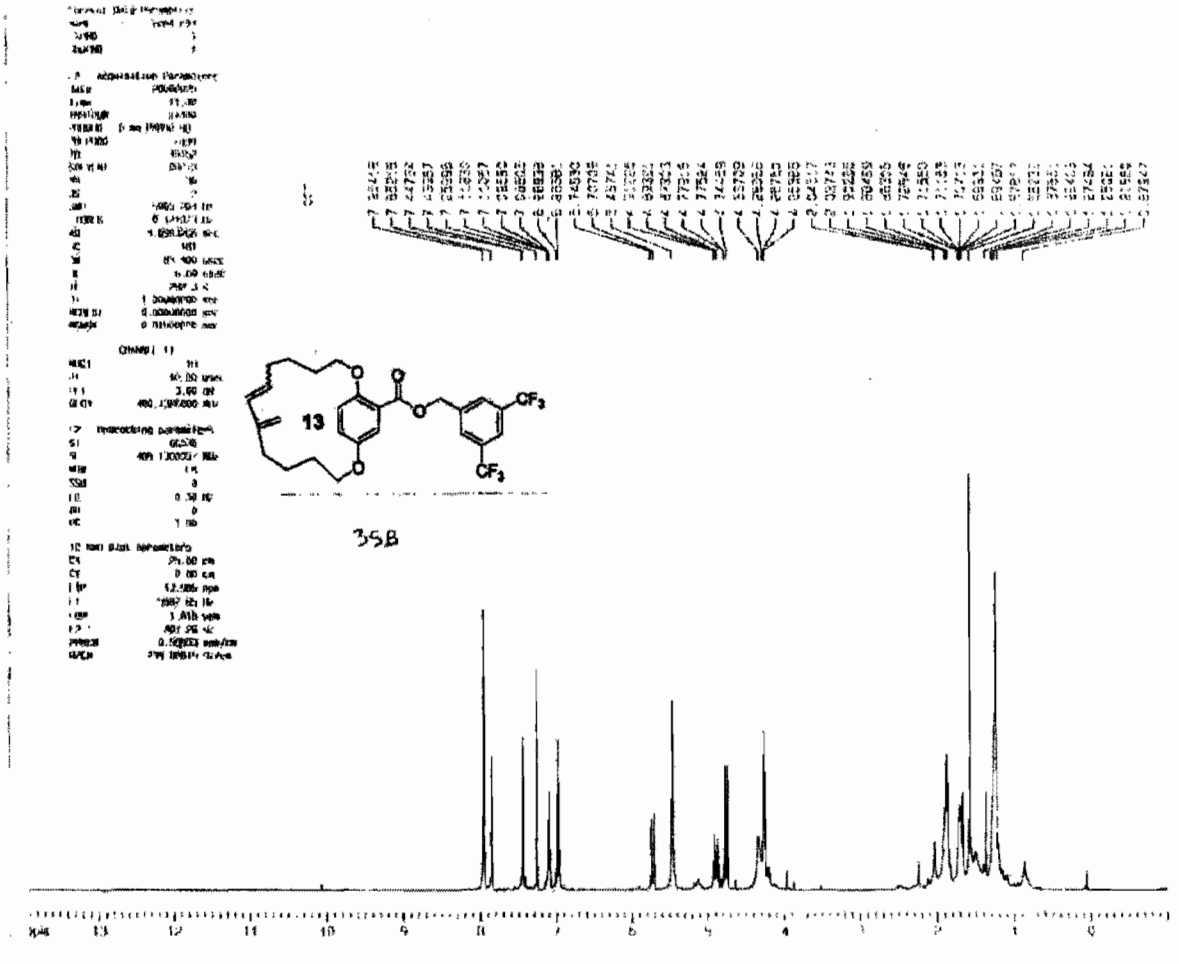


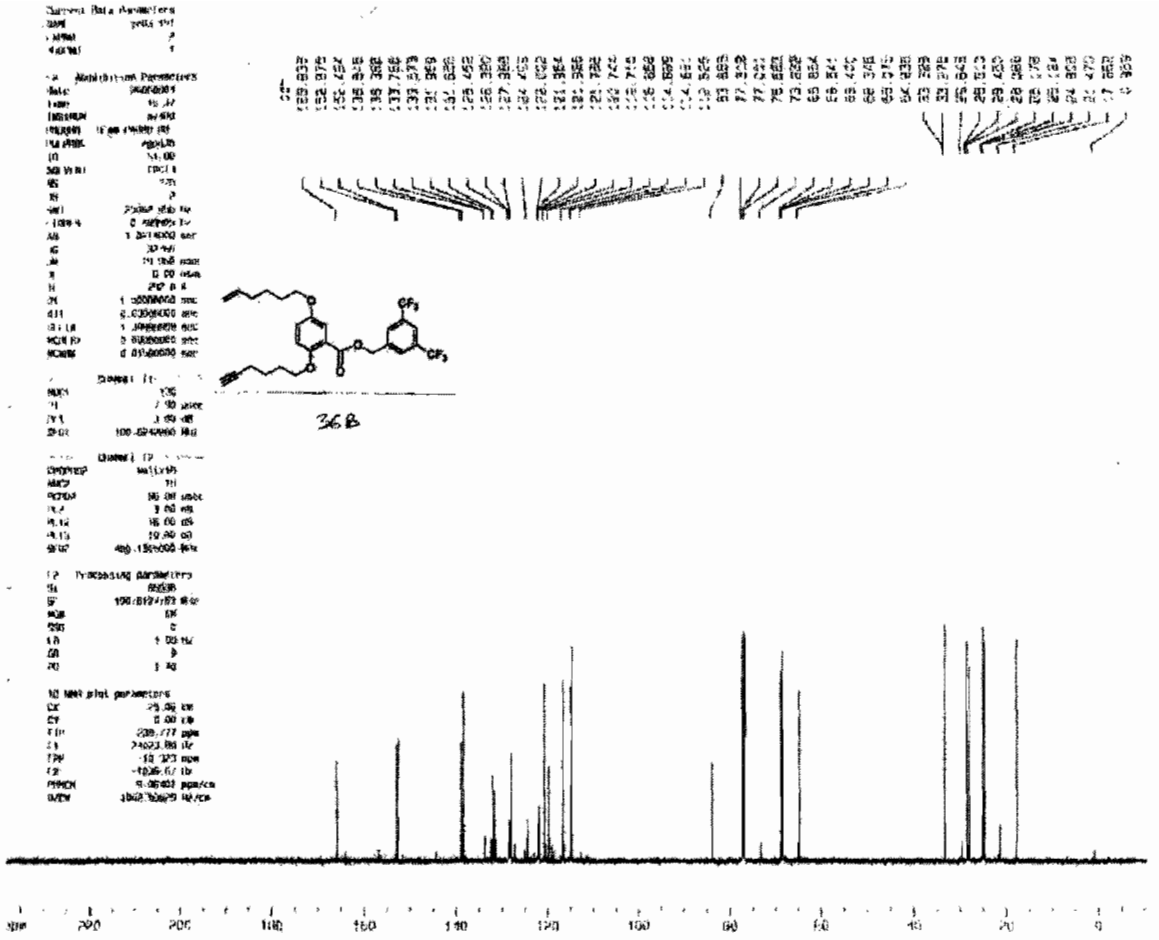
34B



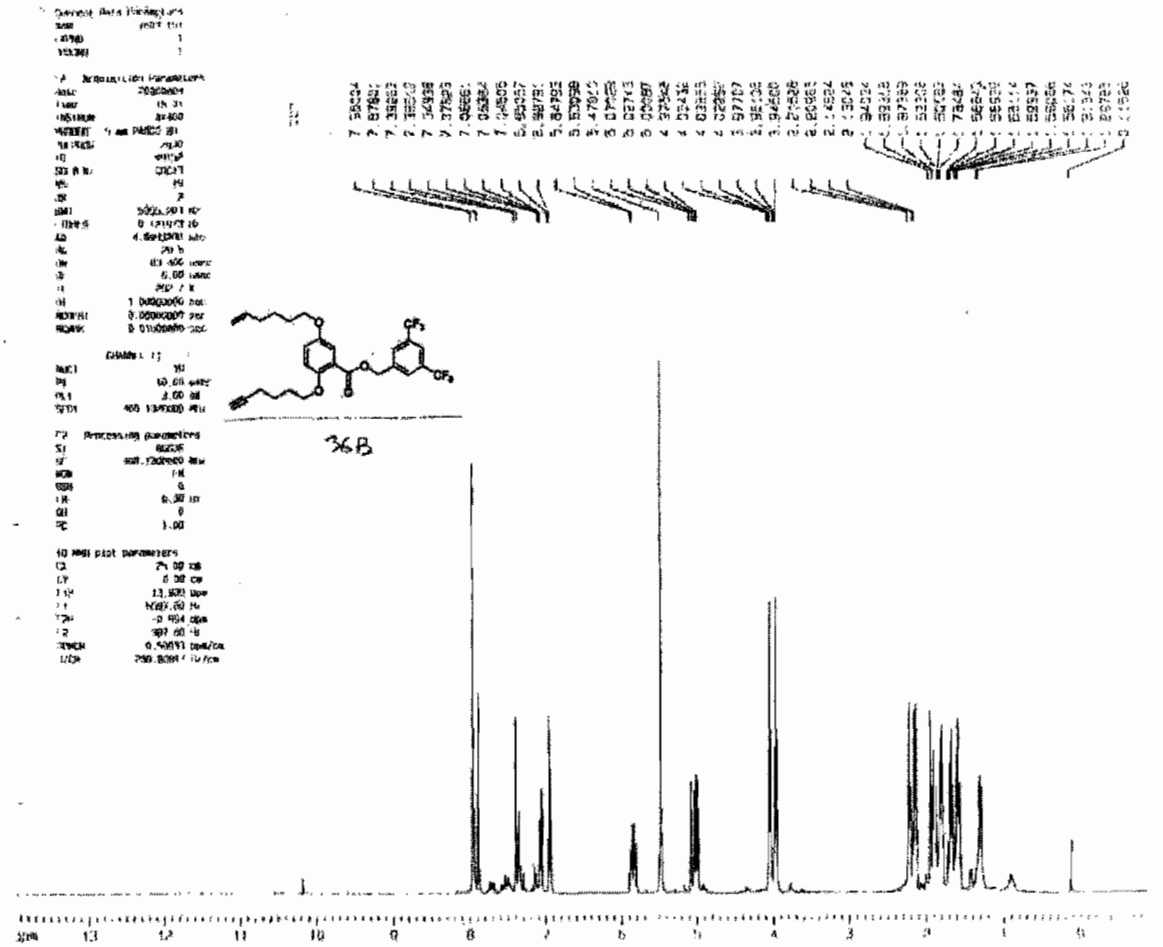
34B


13
CF3
CF3
35B

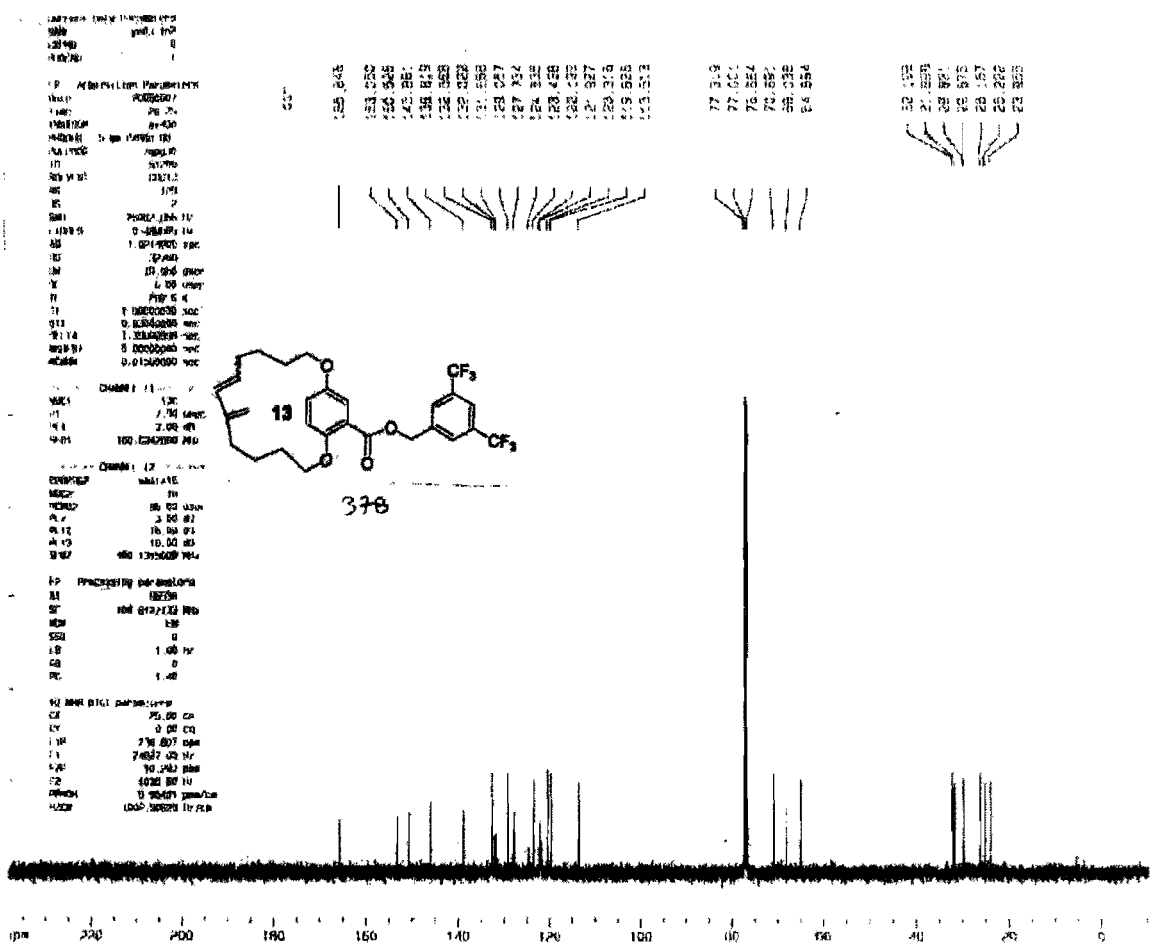

13
CF3
CF3
35B

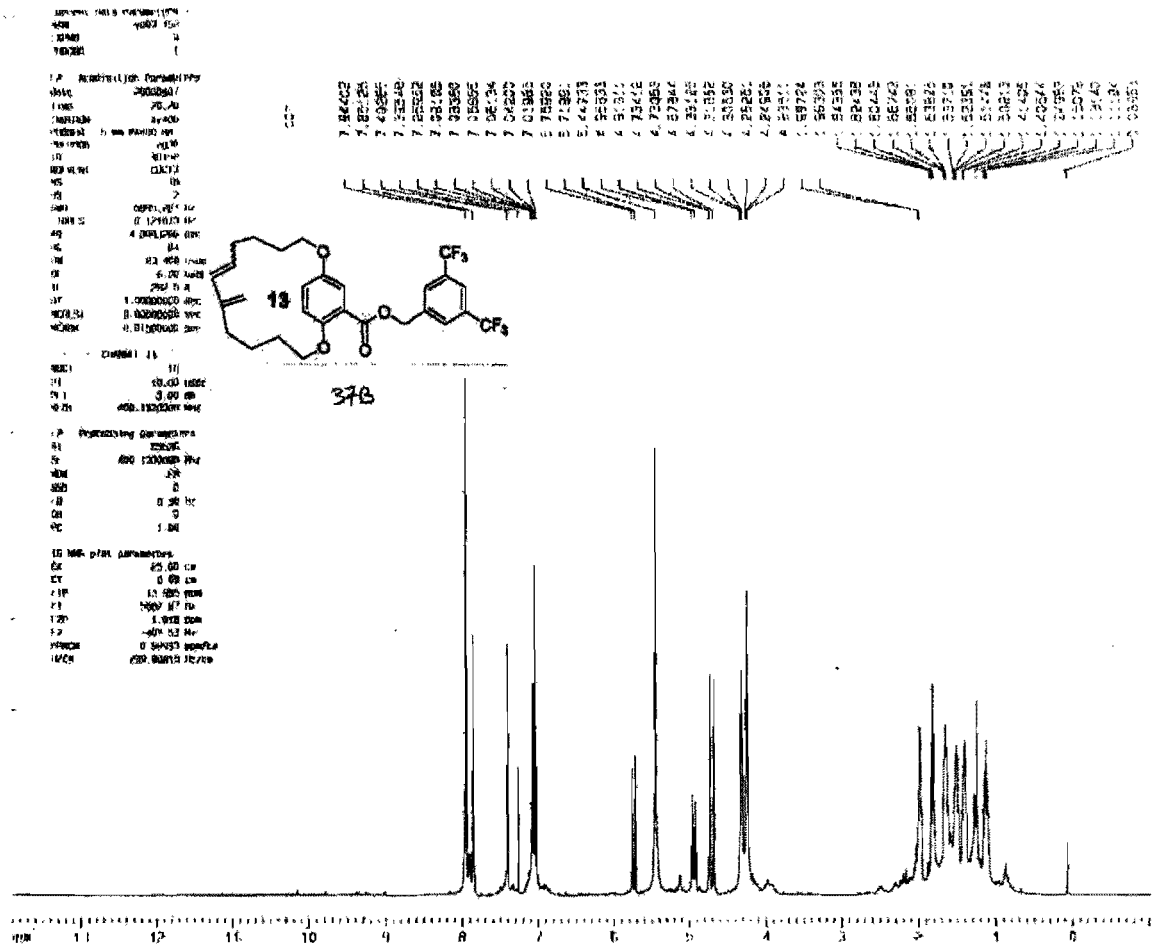


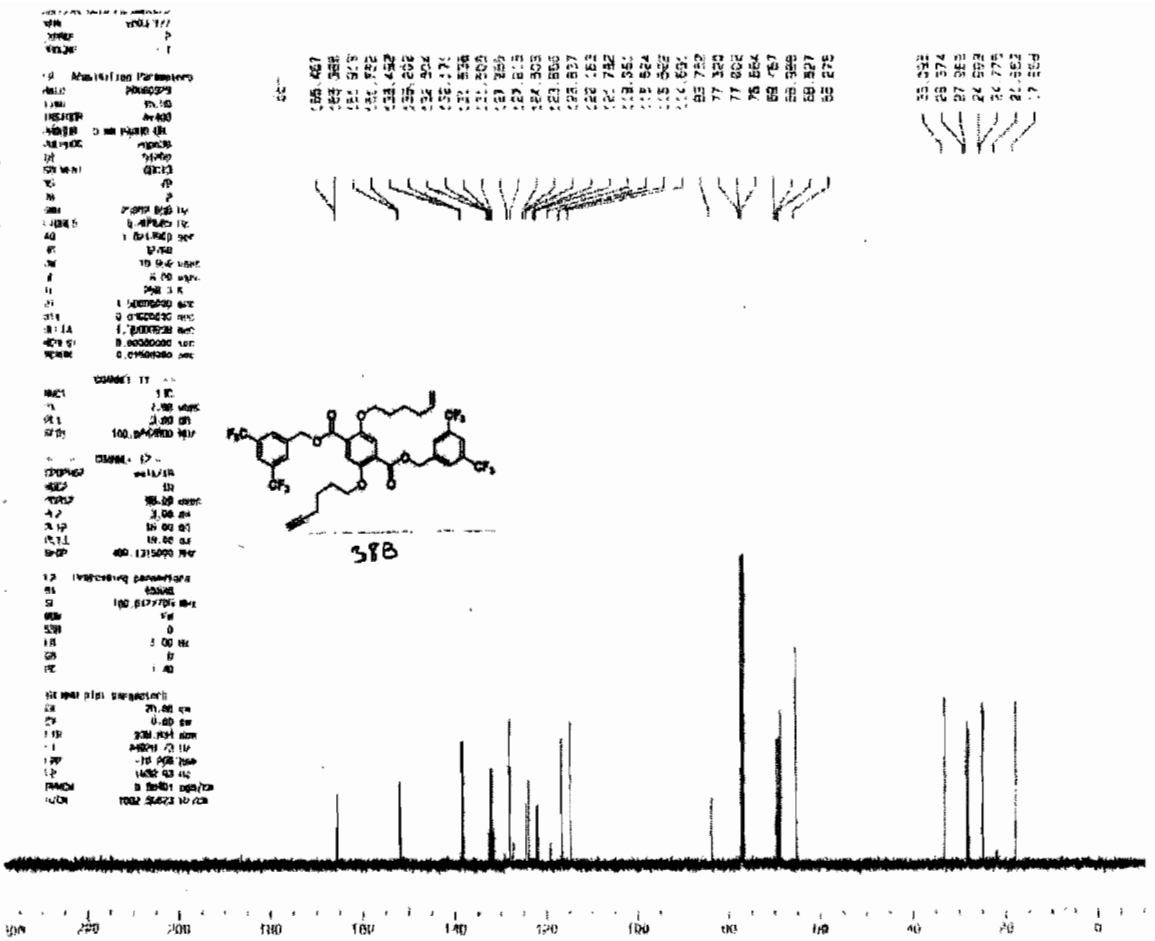
36B

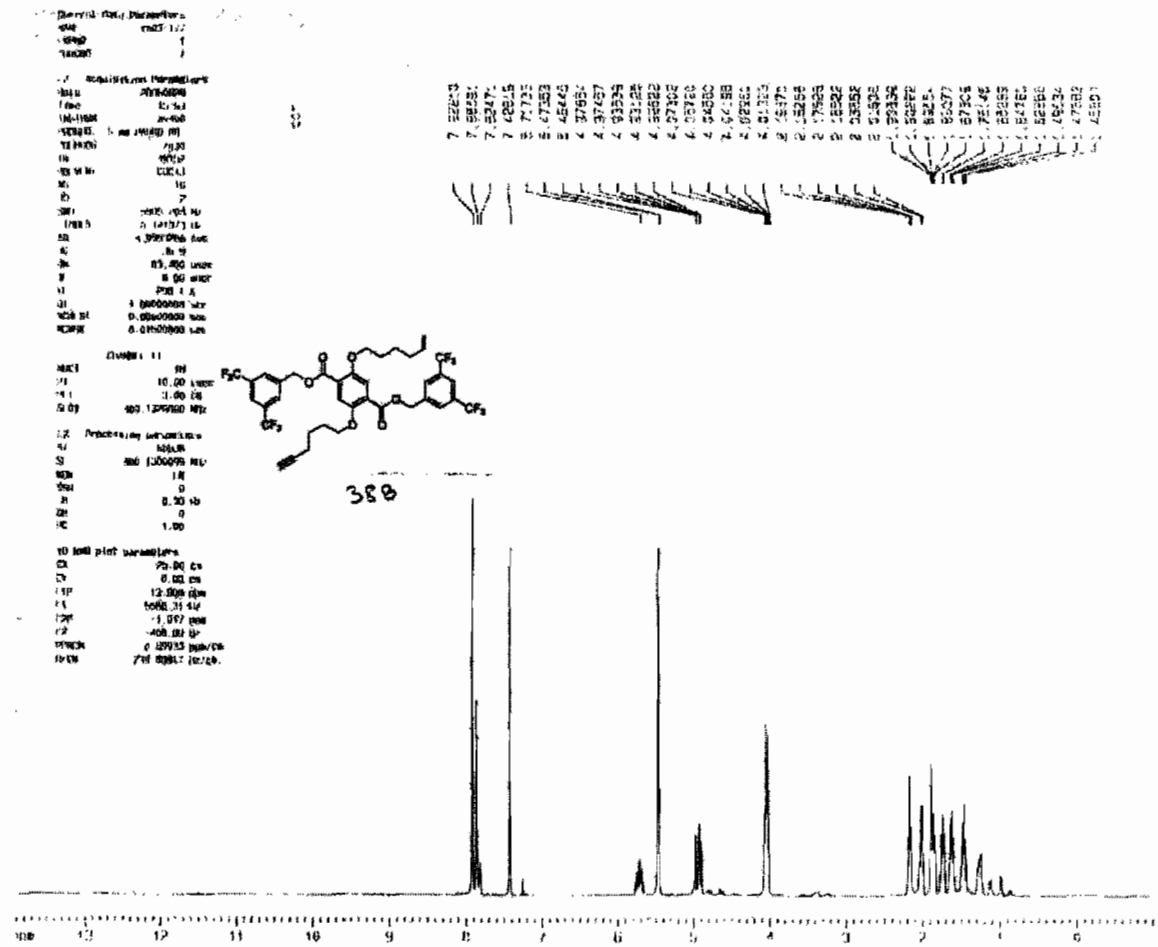


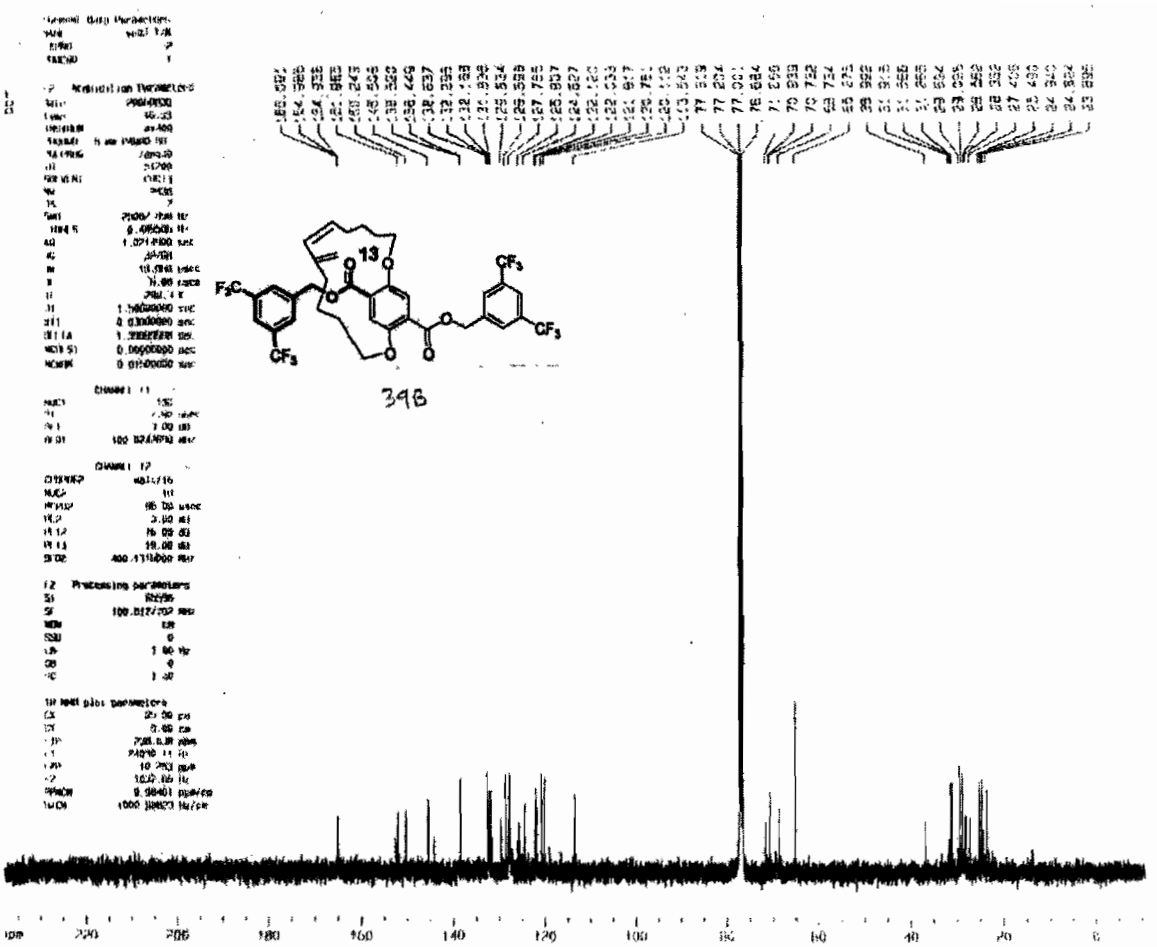
36B

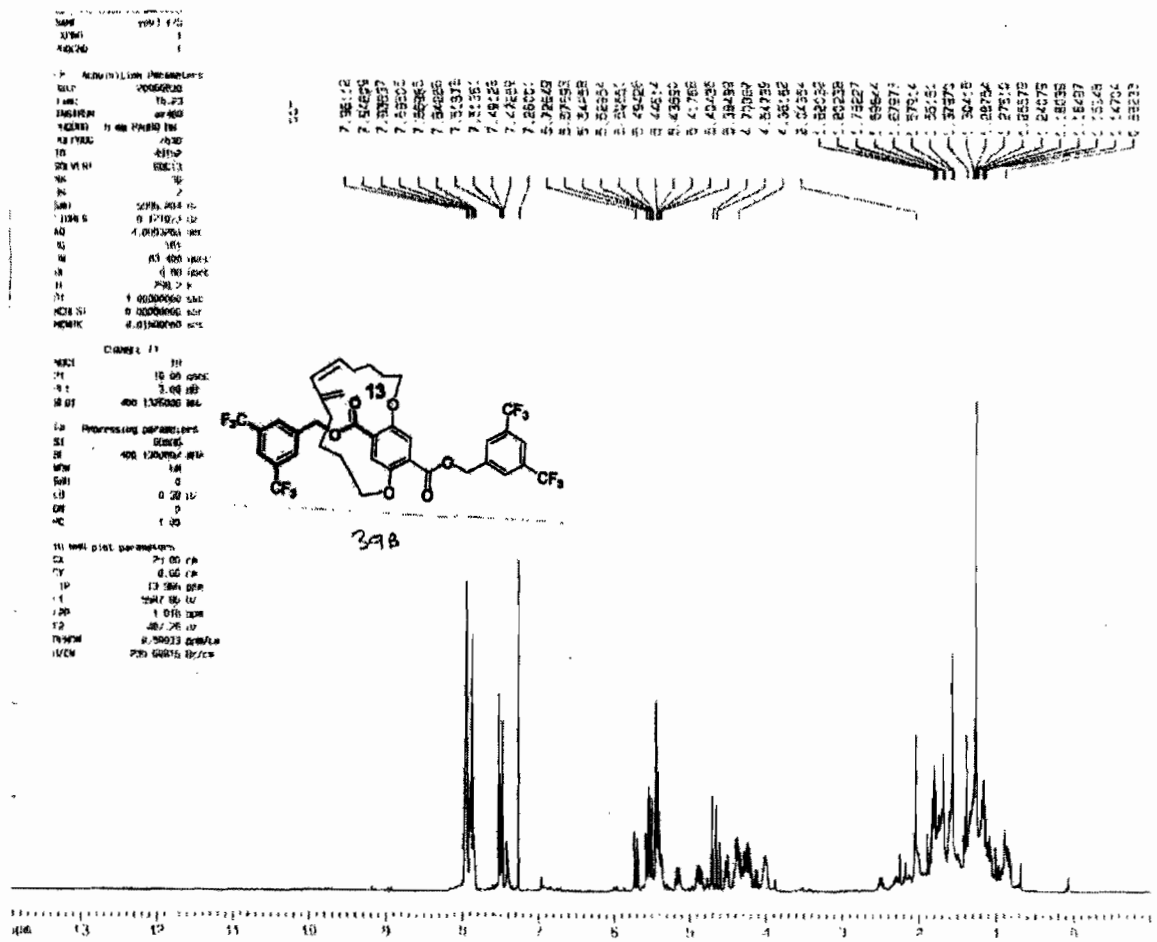

13
CF3
CF3
378

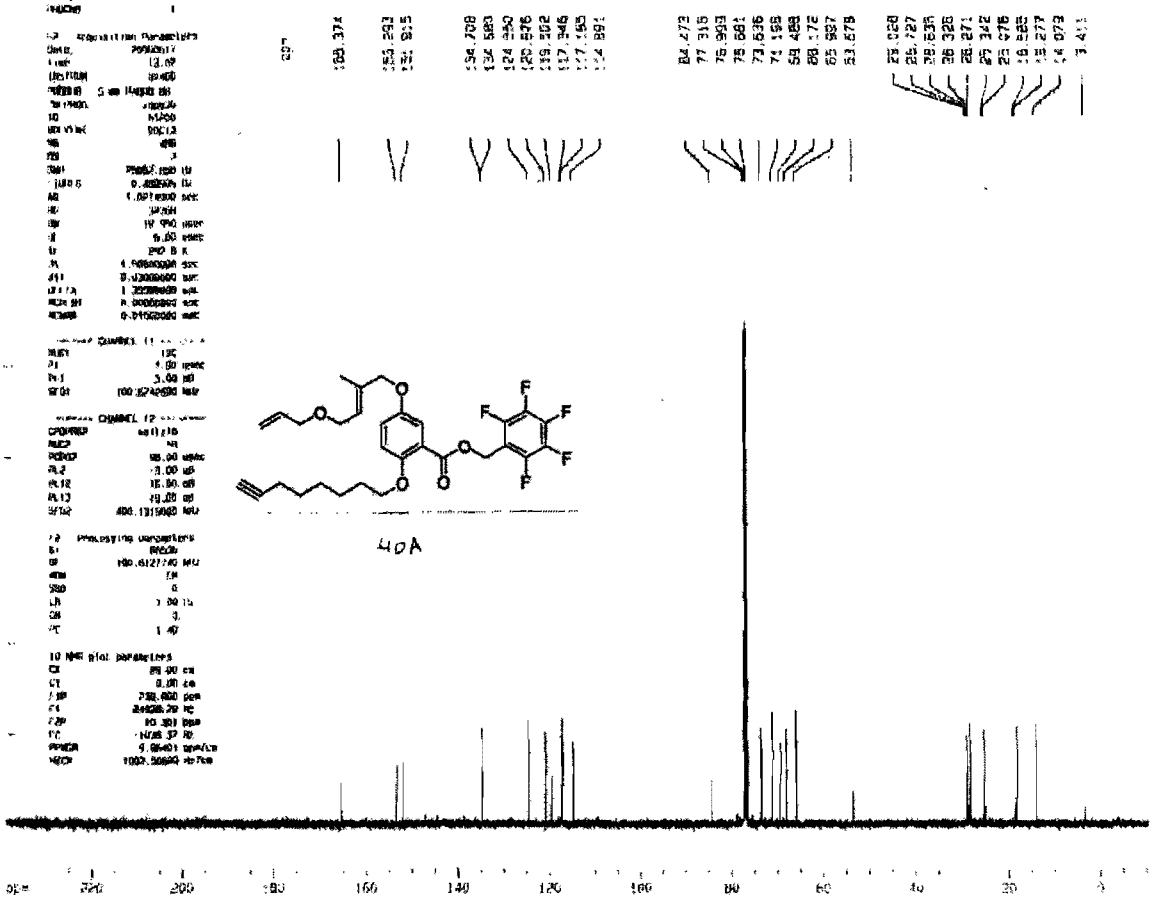

13
CF3
CF3
378

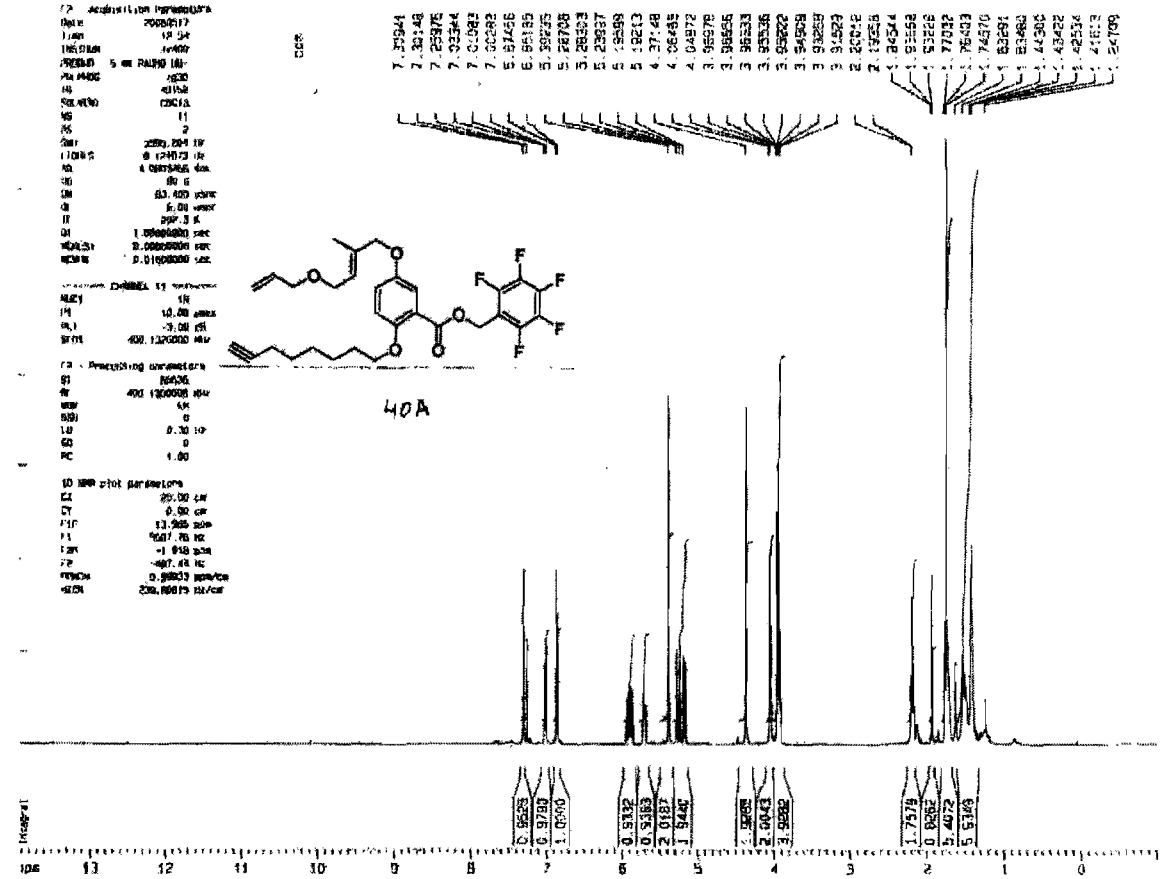

3SB

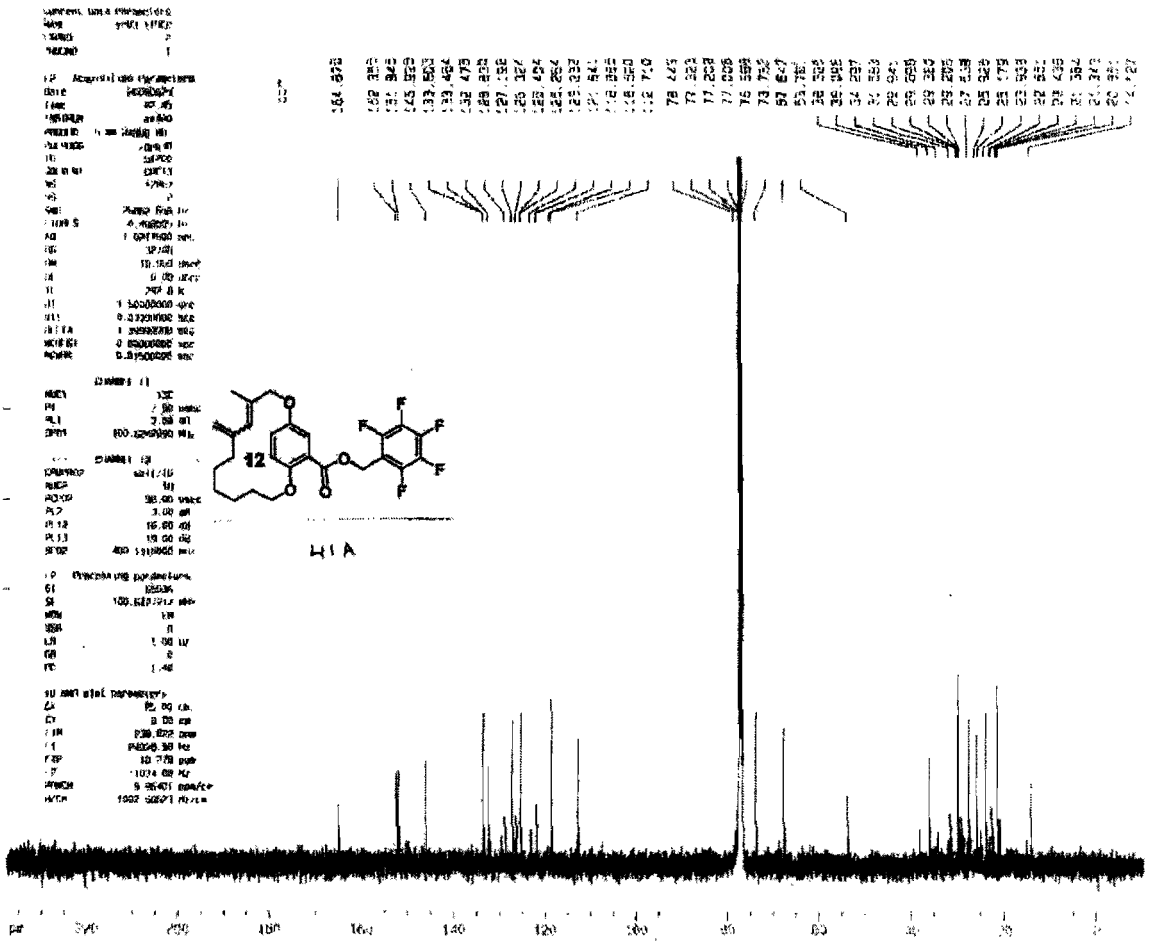

3SB


13
CF3
F3C
CF3
CF3
398

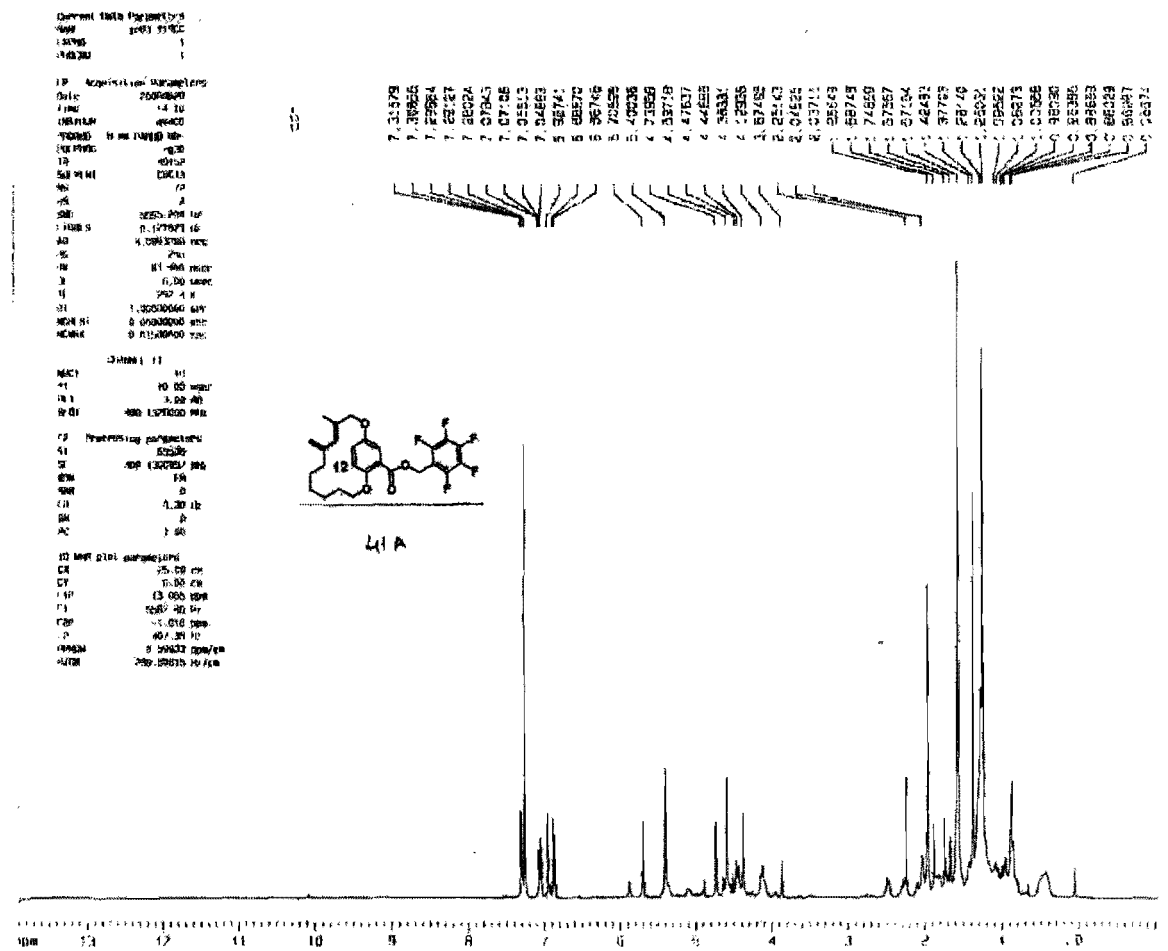

13
CF3
F3C
CF3
CF3
398


40A

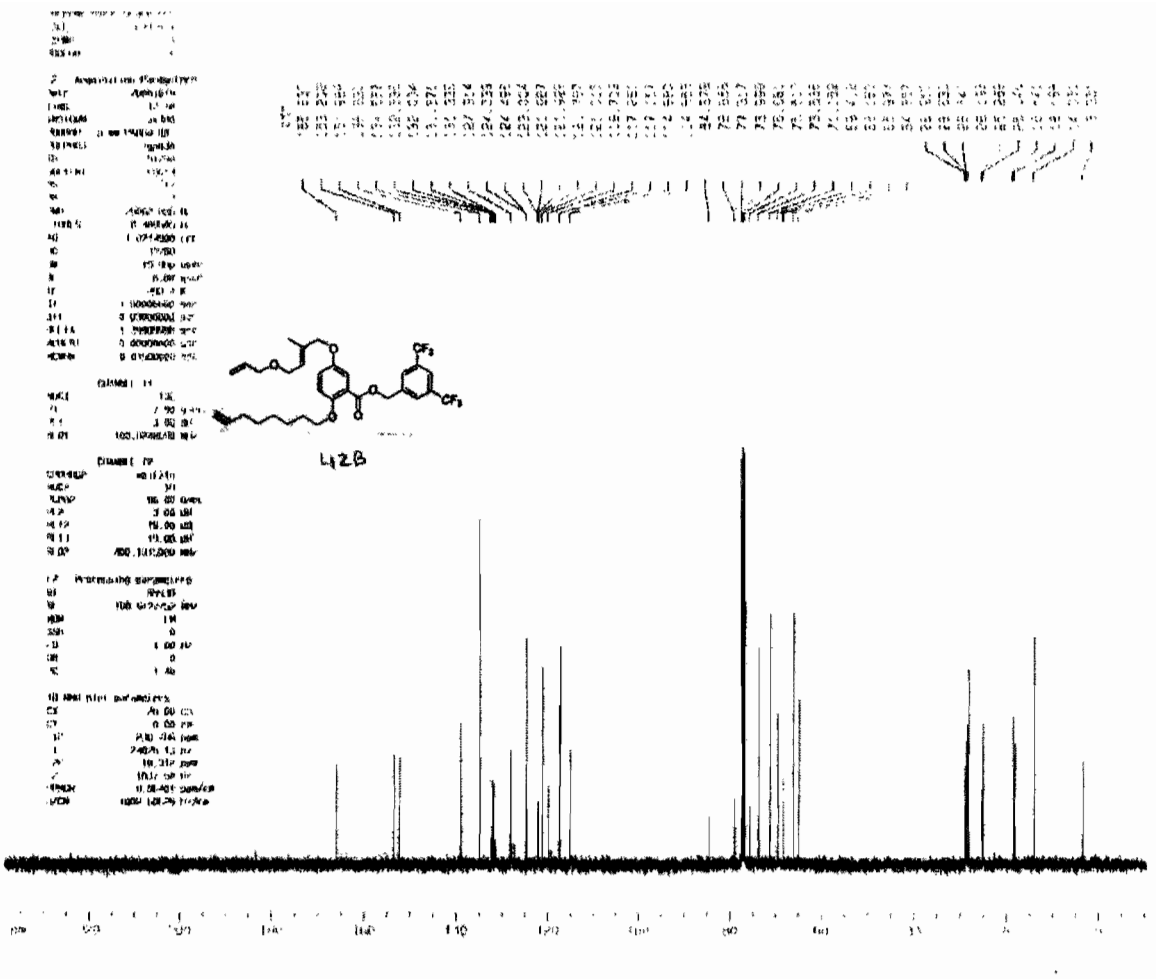

40A



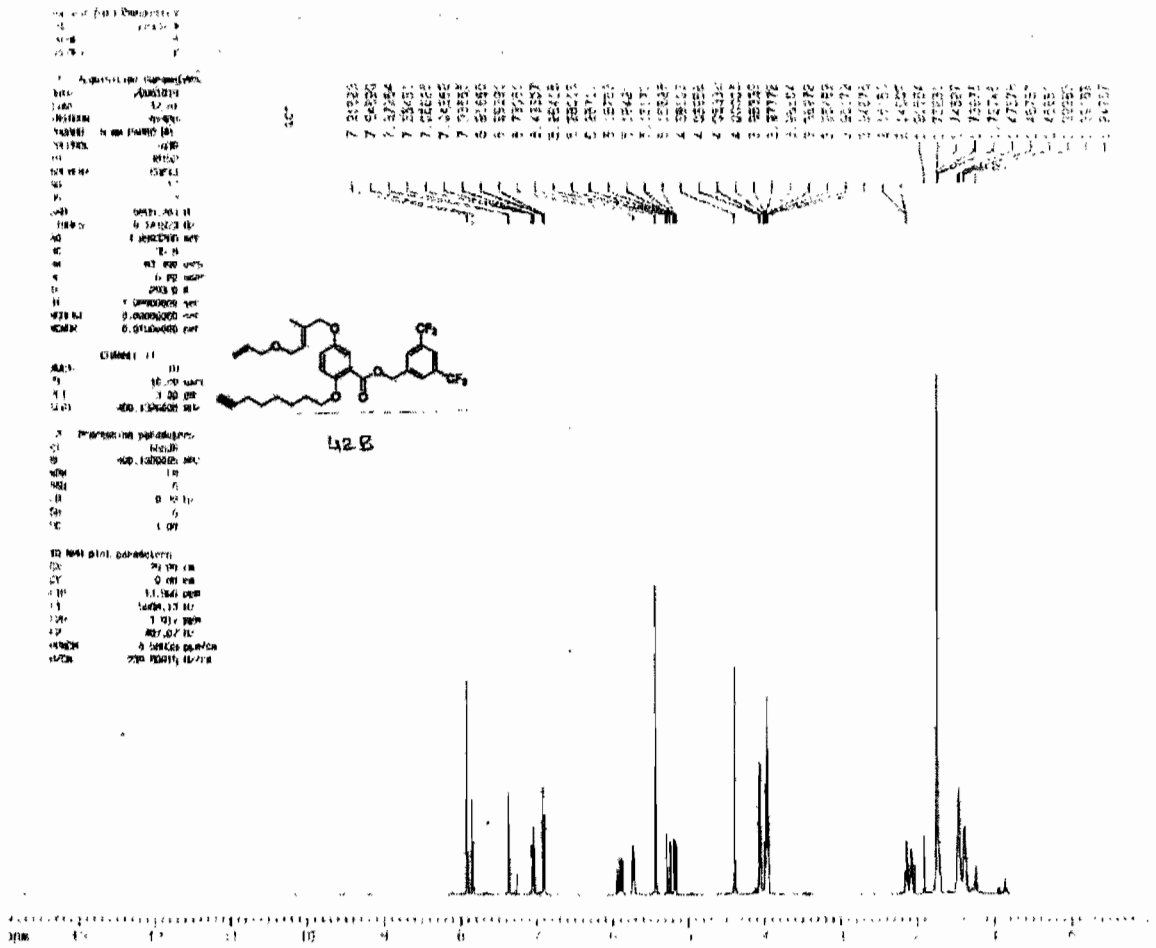
41A

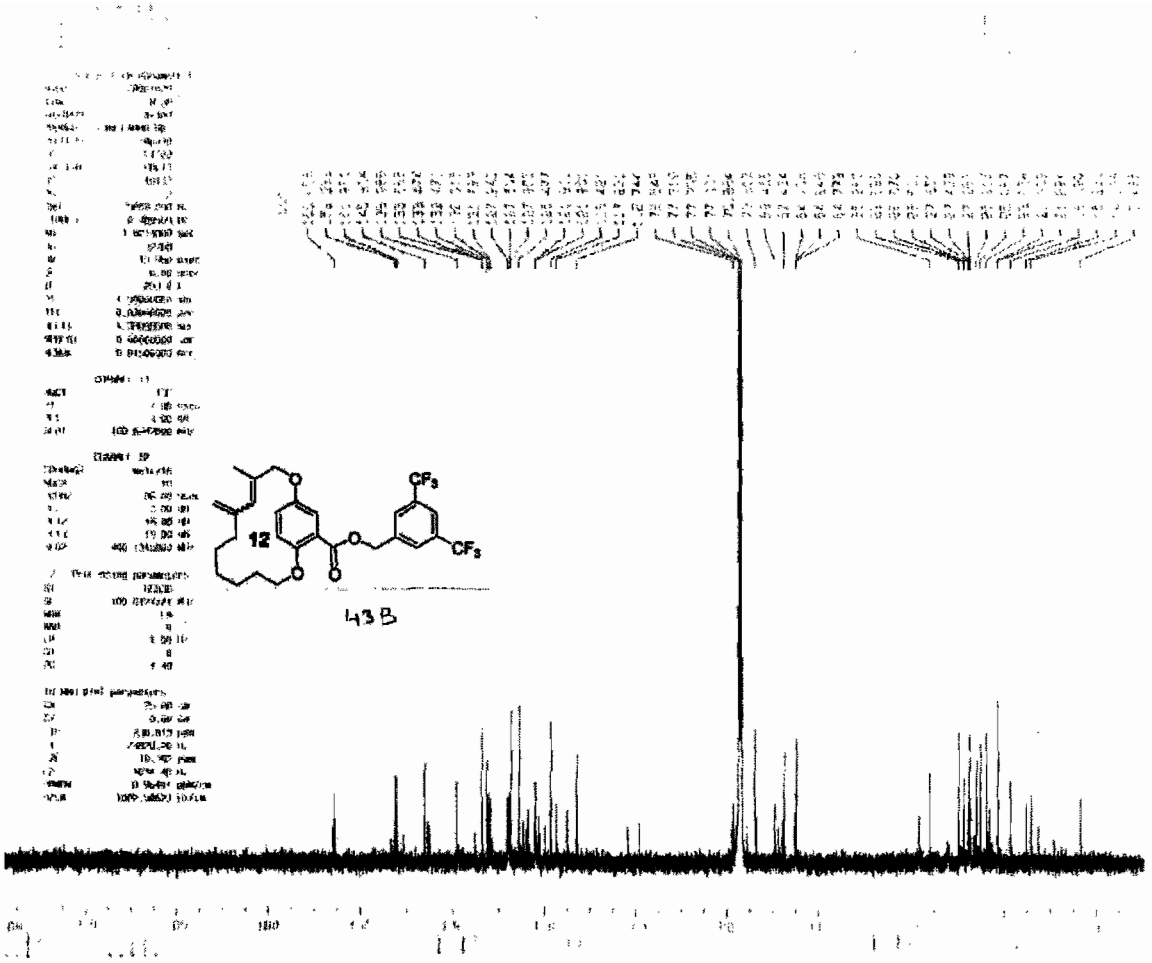


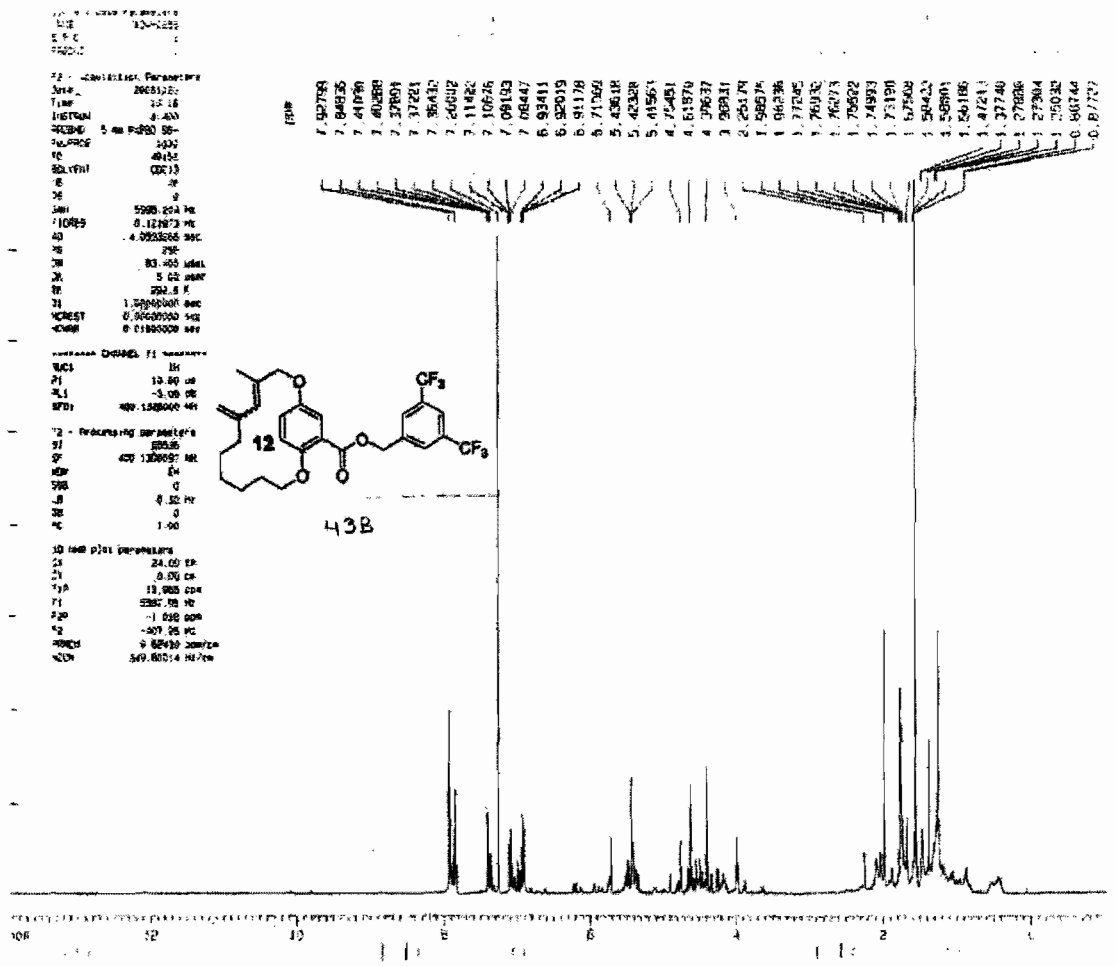
41A

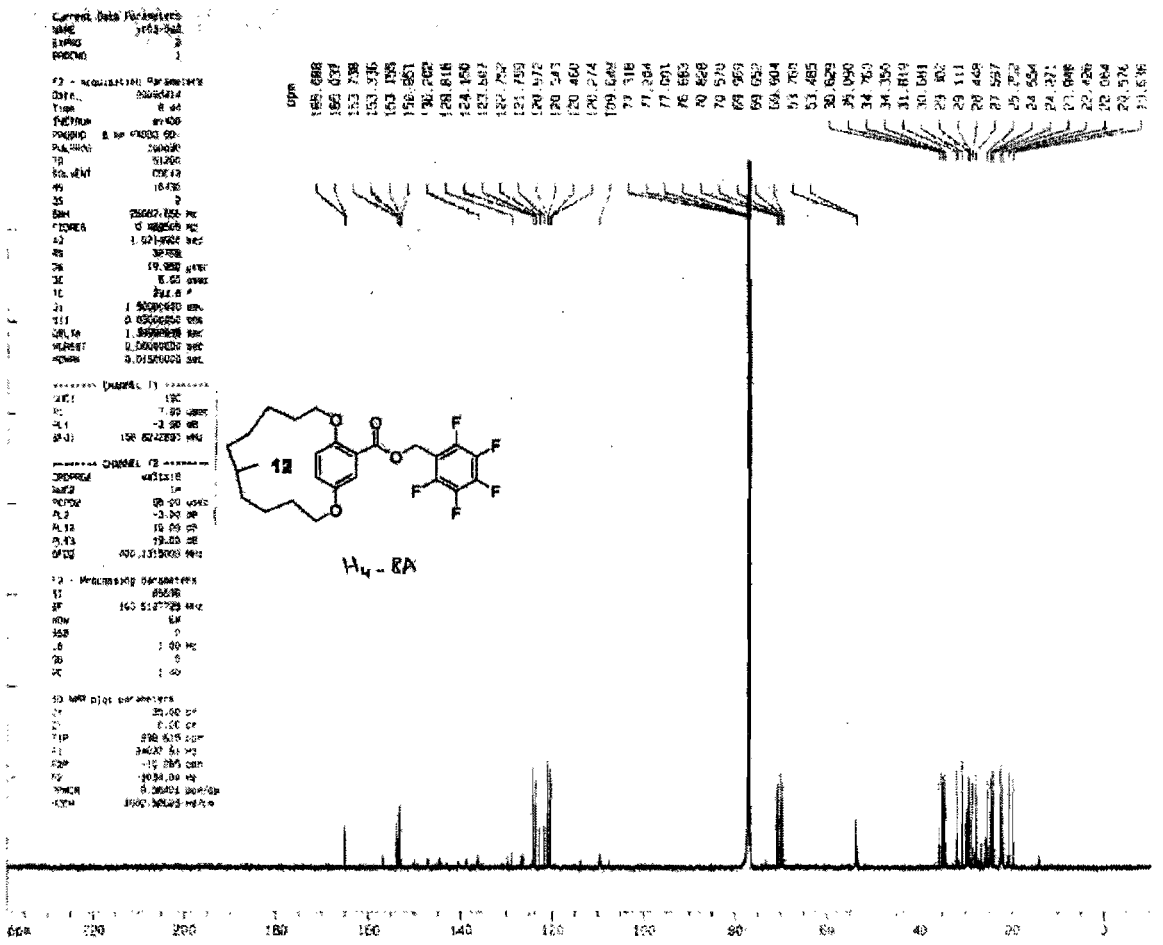


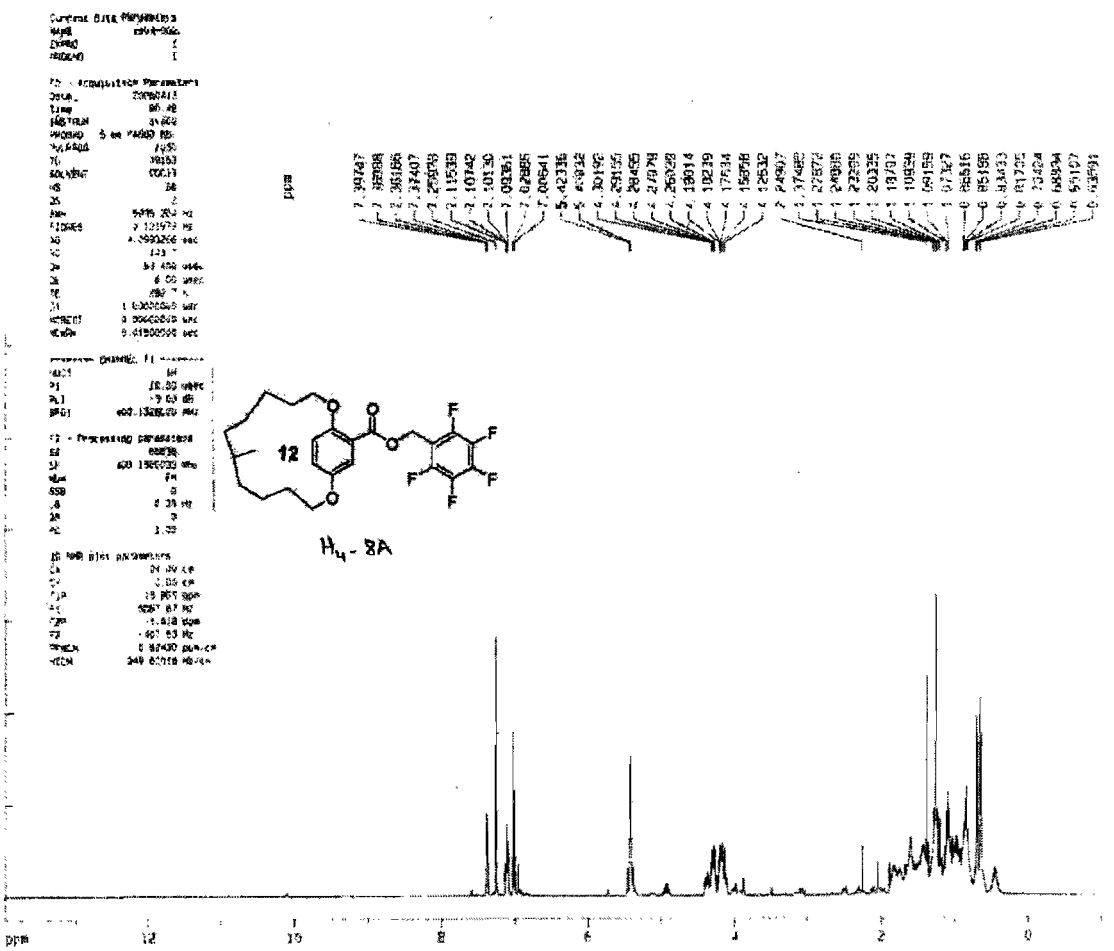
Annexe 1 : Informations supplémentaires de l'article 3




12
CF3
CF3
43B

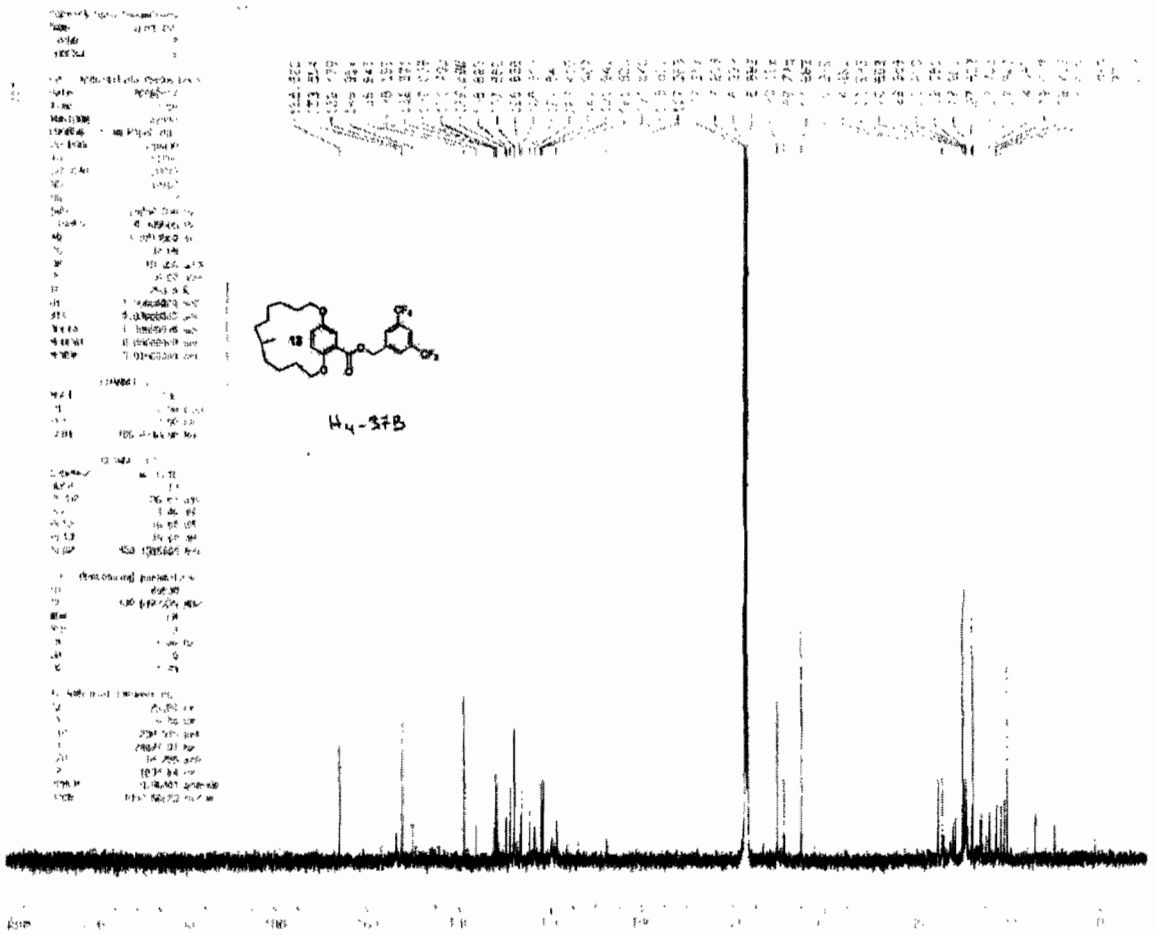

12
CF3
CF3
43B

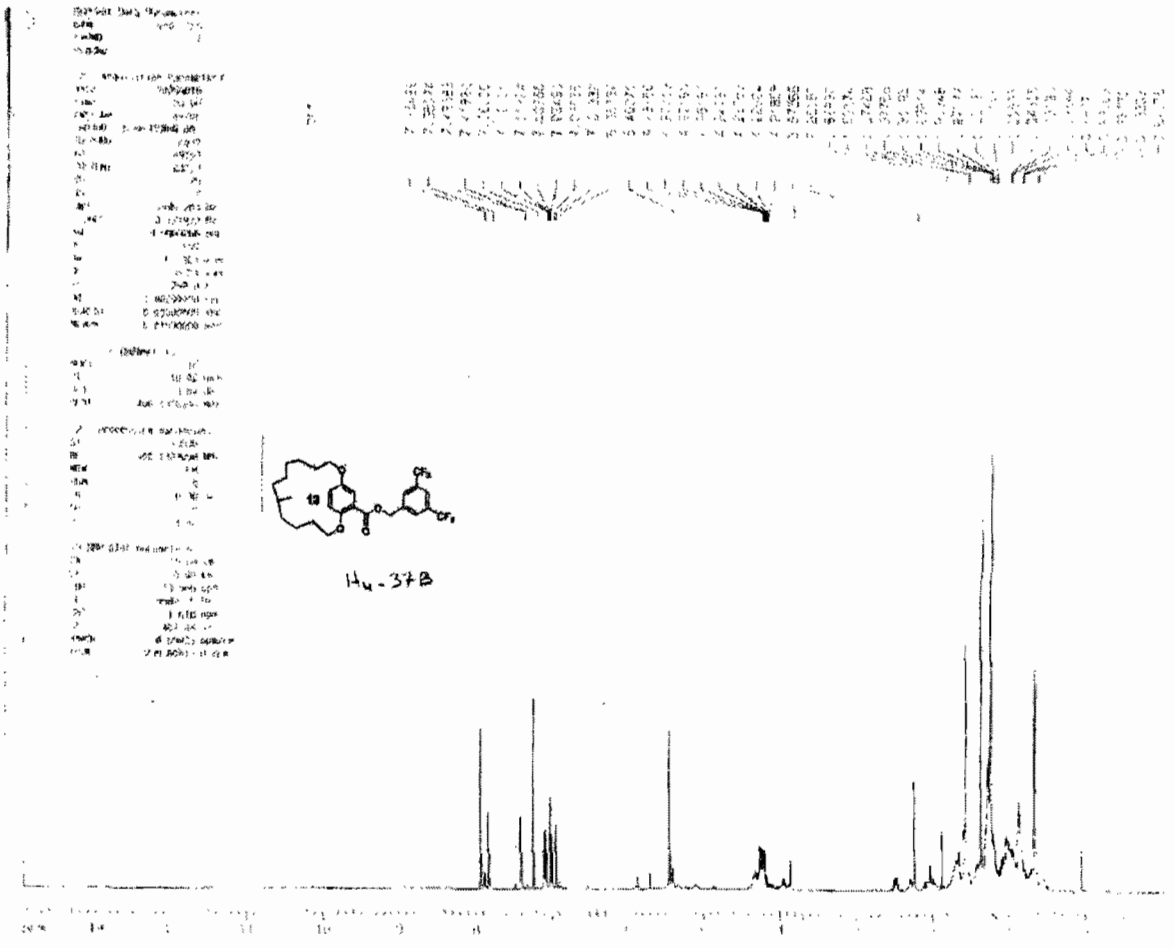

12
F
F
F
F
F
H_4 - 8A
ppm


12
F
F
F
F
F
H_4 - 8A
ppm

13
H4-33A

12
H4-33A


H4-37B


H4-37B

Exploiting Quadrupolar Interactions in the Synthesis of the Macrocyclic Portion of Longithorone C.

*Joseph E. Zakarian, Yassir El-Azizi and Shawn K. Collins**

Département de chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7. [redacted]

SUPPORTING INFORMATION

Table of contents

General

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.[1] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. These products were used without further purification. Catalysts **22**[2] and **23**[3] were prepared according to known procedures. Technical solvents were obtained from VWR International Co. Anhydrous solvents (DCM, Diethyl Ether, THF, Toluene, DMF 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[4] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}). Visualization of TLC plate was performed by UV (254 nm), ninhydrin or $KMnO_4$ 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 ^1H NMR. NMR spectra were taken in $CDCl_3$ or C_6D_6 using Bruker AV300, AV-400 or Bruker UltraShield Plus 700 MHz instruments (300, 400 or 700MHz, ^1H NMR, respectively, and 75, 100 or 175 MHz, ^{13}C NMR, respectively). Signals due to the solvent served as the internal standard (chloroform δ7.26 ppm ^1H, δ77.0 ppm ^{13}C; benzene δ7.16 ppm ^1H, δ 128.4 ppm ^{13}C). The acquisition parameters are shown on all spectra. The ^1H NMR chemical shifts and coupling constants

[1] D. F. Shriver, M. A. Drezdon in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
[2] Bieniek, M.; Michrowska, A.; Gulajski, L.; Grela, K. *Organometallics* **2007**, *26*, 1096-1099.
[3] a) Buschmann, N.; Wakamatsu, H.; Blechert, S. *Synlett* **2004**, *4*, 667-670. b) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733- 2736.
[4] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

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. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling, 2D COSY experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by two dimensional correlation experiments (HSQC). Chemical shifts are reported in parts per million (ppm). High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization.

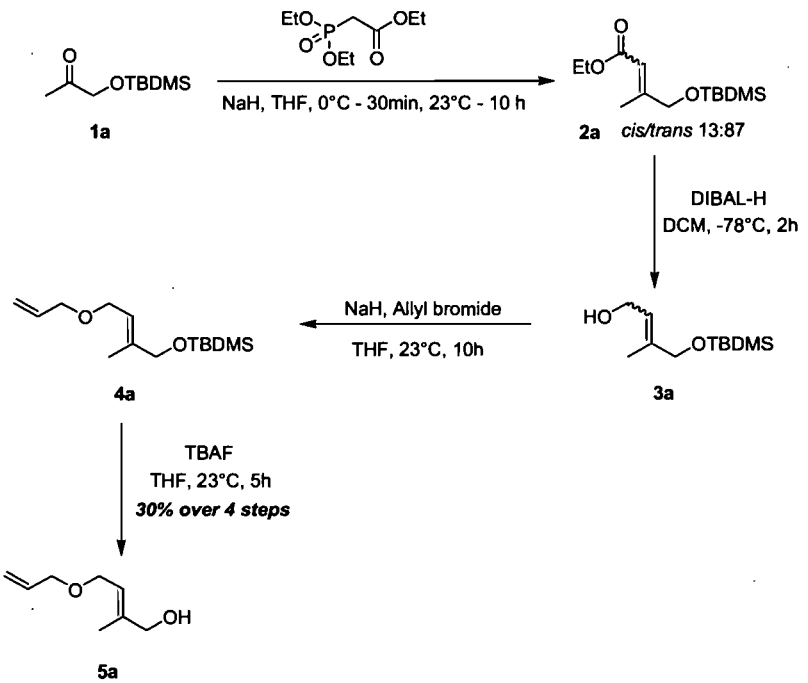
Procedures for the preparation of compounds **7-20** *and* **25** *are detailed below. Following this description, the spectral data is indicated for each individual compound and intermediate. Note that in general, we do not observe any ^{13}C NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary or for the two CF_3 of the 3,5-bis(trifluoromethyl)benzyl auxiliary .*

Preparation of dilithium tetrachlorocuprate

LiCl and $CuCl_2$ were independently dried for 10 h at 100°C under reduced pressure. Both reagents were transferred to a glove box under a nitrogen atmosphere. To a round bottom flask containing $CuCl_2$ (0.670 g, 5 mmol, 1.0 equiv.) and LiCl (0.420 g, 10 mmol, 2.0 equiv.) anhydrous THF (10 mL) was added. The solution was allowed to stir at room temperature for 10 min affording a homogeneous dark red colored solution. The concentration of Li_2CuCl_4 prepared in this manner was 0.5 M and was used immediately. This solution was never stored for more than a couple of hours.

Preparation of Sidechains (7) and (8)

(*E*)-4-(Allyloxy)-2-methylbut-2-en-1-ol (5a)



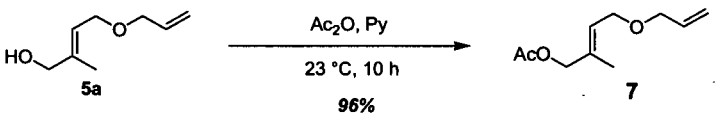
In a round bottom flask, under nitrogen, NaH (15.2 g, 0.38 mol, 1.08 equiv.) was washed with anhydrous hexane (3 x 100 mL), taken up in anhydrous THF (500 mL), cooled to 0°C, and treated dropwise with *tris*(triethyl)phosphonoacetate (70.0 mL, 0.35 mol, 1.0 equiv.) monitoring closely the release of hydrogen gas. The solution was allowed to stir at 0°C for 1 h. The solution gradually changed appearance, becoming transparent. Acetol silyl ether **1a** (55.0 g, 0.29 mol, 0.83 equiv.) was added dropwise at 0°C to the reaction mixture that was stirred for 0.5 h and allowed to warm to room temperature, with stirring for 10 h. The reaction was monitored by TLC (Hexanes/Ethyl acetate 7/1). The solution was quenched with water (100 mL) at 0°C. The mixture was extracted with Diethyl ether (3 x 100 mL). The combined organic extracts

were washed with brine (1 x 100 mL), and dried over Na_2SO_4. The volatiles were evaporated to a residue as *cis* :*trans* isomers (13:87, determined by LCMS: Gimini C-18, 5 μ, 50 x 4.6 mm Column, 0.5 mL/min, 70% ACN/H_2O). The pale yellow oil was immediately carried over to the next reaction. Spectral data for **2a** matched that reported in the literature.[5] In a round bottom flask, a solution of ester **2a** (75.0 g, 0.29 mol, 1.0 euiv.) in anhydrous DCM (500 mL) was cooled to -78°C, treated dropwise over 2 h with DIBAL-H (697 mL, 0.69 mol, 2.4 equiv.), stirred at -78°C for 2 h, and monitored by TLC (Hexanes/Ethyl acetate 7/1). The reaction was quenched at -78°C with a saturated solution of Rochelle's salt, and stirred at room temperature until a successful partition between the two phases had been achieved. At times, the separation was achieved by adding more Rochelle's salt. The mixture was extracted with Diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (1 x 100 mL), and dried over Na_2SO_4, and evaporated to give crude **3a** as a pale-yellow oil used without further purification. Spectral data for **3a** matched that reported in the literature. In a round bottom under nitrogen, NaH (15.2 g, 0.38 mol, 1.3 equiv.) was washed with anhydrous Hexane (3 x 100 mL), suspended in anhydrous DMF (500 mL), cooled to 0°C, and treated dropwise with alcohol **3a** (63.0 g, 0.29 mol, 1.0 equiv.) monitoring closely the release of hydrogen gas. After stirring for 1 h at 0°C, the mixture was treated dropwise with allyl bromide (27.0 mL, 0.32 mol, previously passed through a short plug of basic alumina, 1.1 equiv.), stirred for 0.5 h, warmed to room temperature, stirred for 10 h, monitored by TLC (Hexanes/Ethyl acetate 10/1), cooled to 0°C, and quenched with water (100 mL). The mixture was extracted with Diethyl ether (3 x 100 mL), dried over Na_2SO_4, and evaporated to give crude **4a** as a pale-yellow oil, that was used without further purification. In a round bottom flask, silyl ether **4a** (36.7 g, 0.14 mol, 1.0 equiv.) was dissolved in anhydrous THF (500 mL), cooled to 0°C, treated dropwise with TBAF (430 mL, 0.43 mol, 3.0 equiv.), and allowed to warm to room temperature. The reaction was monitored by TLC (Hexanes/Ethyl Acetate

[5] Baldwin, I. R.; Whitby, R. J. *Chem. Comm.* **2003**, *22*, 2786-2787.

5/1). After stirring for 12 h, the reaction was quenched with $NaHCO_3$ (500 mL), and extracted with Diethyl ether (3 x 250 mL). The combined organic extracts were washed with brine (1 x 250 mL), dried over Na_2SO_4, and evaporated to give a residue that was purified by silica gel flash chromatography (Hexanes/Ethyl Acetate 5/1) to afford alcohol **5a** as a pale-yellow oil (8.10 g, 30% over four steps). ^1H NMR (400 MHz, $CDCl_3$ δ 5.83 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H), 5.51 (t, J = 6.7 Hz, 1H), 5.19 (dd, J = 17.1, 3.3 Hz, 1H), 5.10 (dd, J = 10.5, 3.3 Hz 1H), 3.95 (d, J = 6.7 Hz, 2H), 3.89 (m, 4H), 3.29 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$δ 139.2, 134.4, 120.5, 116.9, 70.9, 67.2, 65.9, 13.5; HRMS (ESI) calculated for $C_8H_{15}O_2$ $[M + H]^+$, 143.1067, found 143.1064.

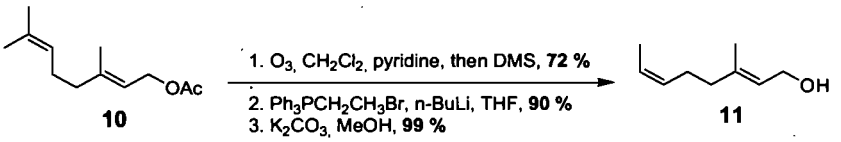
(*E*)-4-(Allyloxy)-2-methylbut-2-enyl acetate (7)



In a round bottom flask were added alcohol **5a** (5.50 g, 38.7 mmol, 1.0 equiv.) and Ac_2O (4.40 mL, 46.4 mmol, 1.2 equiv.), followed by distilled pyridine (3.8 mL, 46.4 mmol, 1.2 equiv.) at 0°C. The reaction was stirred for 10 h at room temperature and was monitored by TLC (Hexanes/Ethyl acetate 4/1). The reaction mixture was purified as is by silica gel flash chromatography (Hexanes/Ethyl acetate 4/1) to give acetate **7** as a pale-yellow oil (6.83 g, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H), 5.60 (t, J = 6.6 Hz, 1H), 5.24 (dd, J = 17.1, 3.0 Hz, 1H), 5.15 (dd, J = 10.5, 3.0 Hz, 1H), 4.45 (s, 2H), 4.00 (d, J = 6.6 Hz, 2H), 3.94 (dt, J = 5.7, 1.2 Hz, 2H), 2.04 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz,

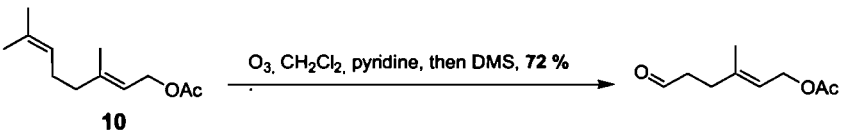
$CDCl_3$) δ 170.6, 134.6, 133.8, 124.5, 117.1, 71.2, 68.8, 65.9, 20.8, 14.1; HRMS (ESI) calculated for $C_{10}H_{16}O_3Na$ $[M + Na]^+$, 207.0992, found 207.0996.

(2*E*,6*Z*)-3-methylocta-2,6-dien-1-ol (11)



10 **11**

(*E*)-3-methyl-6-oxohex-2-enyl acetate

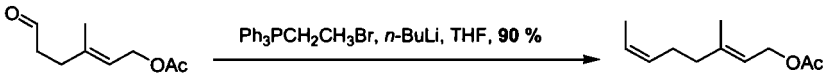


10

Ozone was bubbled through a solution of geranyl acetate **10** (2.944g, 15 mmol, 1.0 equiv.), pyridine (4.0 mL) and DCM (100 mL) that had been cooled to -78°C. The reaction was closely monitored via TLC (Hexanes/Ethyl Acetate, 10/1) until complete consumption of starting material was observed. At that time, the excess ozone was removed by bubbling nitrogen through the solution and dimethylsulfide (3.2 mL, 44 mmol, 3.0 equiv.) was added and the reaction was warmed slowly to room temperature overnight under a gentle steam of air to evaporate the solvent and the excess dimethylsulfide. The resulting crude mixture was diluted in water and extracted many times with Ethyl Acetate. The organic phases were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by silica gel flash chromatography (Hexanes/Ethyl Acetate 7/1) to yield pure product (*E*)-3-methyl-6-oxohex-2-

enyl acetate (1.828 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 5.24 (t, J = 7.0 Hz, 1H), 4.44 (d, J = 7.0 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 1.91 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 170.6, 139.7, 119.0, 60.7, 41.4, 31.1, 20.6, 16.2. HRMS (ESI) calculated for $C_9H_{14}O_3Na$ $[M + Na]^+$ 193.0835 found 193.0831.

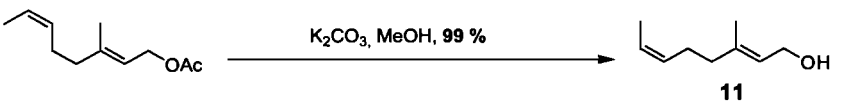
(2*E*,6*Z*)-3-methylocta-2,6-dienyl acetate



Ethyltriphenylphosponium bromide (30.0 g, 80.1 mmol, 1.1 equiv.) in a suspension of anhydrous THF (200 mL) was treated at -78°C with a solution of *n*-BuLi (35.0 mL, 80.1 mmol, 2.5 M in Hexanes, 1.1 equiv.). After stirring for 2 hours at -78°C, the mixture was warmed to room temperature for 20 minutes then cooled to -78°C. A solution of (*E*)-3-methyl-6-oxohex-2-enyl acetate (12.39 g, 72.81 mmol, 1.0 equiv.) in THF (100 mL) was then slowly cannulated into the flask containing the ylide at -78°C and the reaction mixture was allowed to warm to room temperature over night. The mixture was then concentrated *in vacuo* to remove THF and the resulting crude slurry was filtered through a Büchner funnel. The filter cake was washed many times with Ethyl Acetate. The filtrate was concentrated *in vacuo* to give brown viscous oil that was purified by silica gel flash chromatography (Hexanes/Ethyl Acetate, 10/1) to yield (2*E*,6*Z*)-3-methylocta-2,6-dienyl acetate (11.194 g, 90 %) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45-5.39 (m, 2H), 5.30 (t, J = 6.1 Hz, 1H), 4.54 (d, J = 7.0 Hz, 2H), 2.18-2.03 (m, 4H), 2.00 (s, 3H), 1.67 (s, 3H), 1.58 (d, J = 6.5 Hz,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 141.7, 129.5, 124.1, 118.3, 61.2,

39.0, 24.9, 20.9, 16.3, 12.6; HRMS (ESI) calculated for $C_{11}H18O_2Na$ $[M + Na]^+$, 205.1199, found 205.1195.

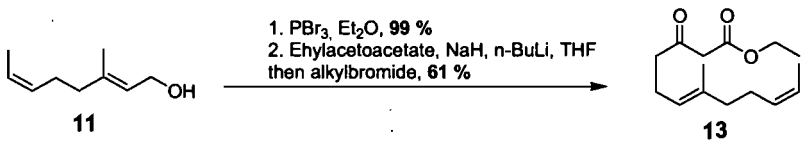
(2*E*,6*Z*)-3-methylocta-2,6-dien-1-ol (11)



11

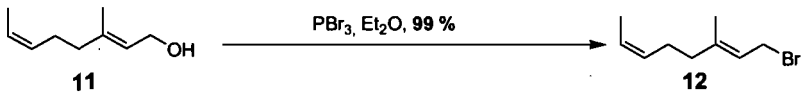
(2*E*,6*Z*)-3-methylocta-2,6-dienyl acetate (7.97 g, 43.74 mmol, 1.0 equiv.) was dissolved in MeOH (60 mL). Potassium carbonate (7.250 g, 52.48 mmol, 1.2 equiv.) was then added at room temperature and the reaction was monitored by TLC (Hexanes/Ethyl Acetate, 7/1). After consumption of all the starting material (typically 1 hour) the reaction was diluted with water (100 mL) and acidified with 1N HCl. After extraction many times with Diethyl Ether/Hexanes (1/1) the organic phases were dried aver $MgSO_4$, filtered and concentrated *in vacuo* to give (2*E*,6*Z*)-3-methylocta-2,6-dien-1-ol **(11)** as a colorless oil (6.070 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39-5.32 (m, 3H), 4.08 (d, J = 6.8 Hz, 2H), 2.86 (br, 1H), 2.13-1.97 (m, 4H), 1.62 (s, 3H), 1.56 (d, J = 6.5 Hz,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 129.7, 123.9, 123.5, 58.9, 39.0, 24.9, 15.9, 12.5.; HRMS (ESI) calculated for $C_9H_{17}O$ $[M + H]^+$, 141.1273, found 141.1269.

(6*E*,10*Z*)-ethyl 7-methyl-3-oxododeca-6,10-dienoate (13)



11 **13**

(2*E*,6*Z*)-1-bromo-3-methylocta-2,6-diene (12)

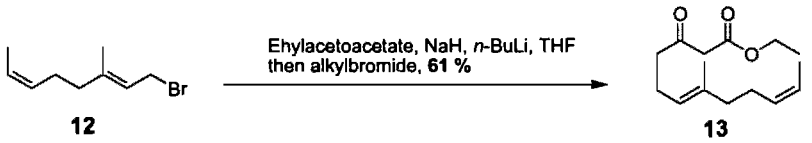


11 **12**

To a solution of (2*E*,6*Z*)-3-methylocta-2,6-dien-1-ol **(11)** (2.90 g, 20.98 mmol, 1.00eq.) in dry diethyl ether (20.0 mL) was slowly added phosphorus tribromide (970 µL, 10.34 mmol, 0.50 eq.) at 0 °C. The reaction mixture was protected from light and was monitored by TLC (Hexanes/ Ethyl Acetate, 10/1). After being stirred at 0 °C for 1 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted many times using Diethyl Ether/Hexanes (1/1). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude (2*E*,6*Z*)-1-bromo-3-methylocta-2,6-diene (4.22 g, 20.77 mmol, 99%). The bromide **12** was unstable and was typically used immediately in the following reaction.[6]

(6*E*,10*Z*)-ethyl 7-methyl-3-oxododeca-6,10-dienoate (13)

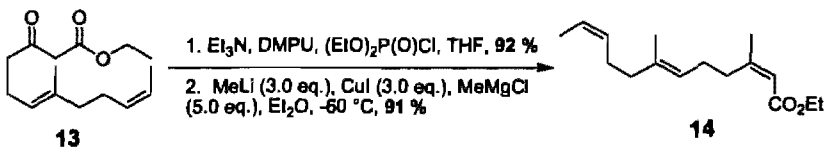
[6]a) Xie, H.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. *J. Org. Chem.* **2000**, *65*, 8552-8563.
b) Brown,R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker T. J.; *J. Org. Chem.* **2002**, *67*, 8079-8085.



12 **13**

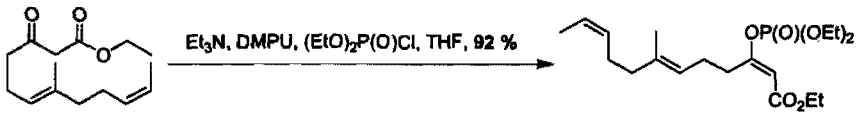
To an ice-cooled suspension of sodium hydride (2.18 g of a 60% dispersion in mineral oil, 54.8 mmol, 1.0 equiv.) in dry THF (30 mL) was added dropwise ethyl acetoacetate (7.40 mL, 54.81 mmol, 1.0 equiv.). After 10 min, *n*-BuLi (22.0 mL of a 2.5 M solution in Hexanes, 54.81 mmol, 1.0 equiv.) was added and the mixture was stirred for a further 20 min. A solution of (2*E*,6*Z*)-1-bromo-3-methylocta-2,6-diene (11.13 g, 54.81 mmol, 1.0 equi.) in dry THF (50 mL) was added to the reaction and the mixture was allowed to warm to room temperature. After 2 hours a solution of 6 N HCl (50 mL) and diethyl ether (100 mL) was added. The organic layer was separated, and the aqueous phase re-extracted with diethyl ether. The organic layers were combined, washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange oil. Purification by silica gel flash chromatography (Hexanes/Ethyl Acetate, 20/1) gave the (6*E*,10*Z*)-ethyl 7-methyl-3-oxododeca-6,10-dienoate **(13)** as a yellow oil (8.451 g, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38- 5.29 (m, 2H), 5.06- 4.80 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.39 (s, 2H), 2.54 (t, J = 7.2 Hz, 2H), 2.15-2.10 (m, 2H), 2.08- 1.95 (m, 4H), 1.63 (s, 3H), 1.59 (d, J = 8.0 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 167.1, 136.3, 130.0, 123.8, 122.2, 61.2, 49.3, 42.9, 39.2, 25.2, 22.0, 15.8, 14.1, 12.6. HRMS (ESI) calculated for $C_{15}H_{25}O_3$ $[M + H]^+$, 253.1798, found 253.1795, calculated for $C_{15}H_{24}O_3Na$ $[M + Na]^+$, 275.1618, found 275.1616.

(2*Z*,6*E*,10*Z*)-ethyl 3,7-dimethyldodeca-2,6,10-trienoate (14)



13 14

Ethyl (2*E*,6*E*,10*Z*)-3-[(Diethoxyphosphoryl)oxy]-7-methyl-2,6,10-dodecatrienoate

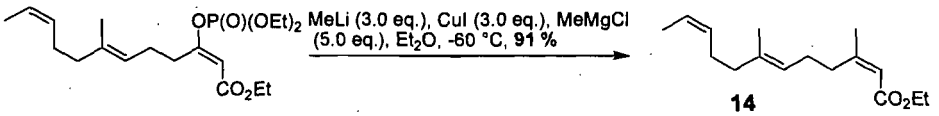


13

To a solution of DMAP (300 mg, 2.47 mmol, 11 mol %) and Et_3N (6.2 mL, 45.0 mmol, 2.0 equiv.) in DMPU (60 mL) at 0 °C was added a solution of **13** (5.67 g, 22.47 mmol, 1.0 equiv.) in DMPU (40 mL). After 1 hour the mixture was cooled to -30 °C and $(EtO)_2P(O)Cl$ (6.5 mL, 36.0 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred over night. The mixture was diluted with diethyl ether and acidified with 1N HCl. The aqueous layer was extracted with Ethyl Acetate and the organic layers combined, dried aver $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting orange oil was purified by silica gel flash chromatography (Hexanes/Ethyl Acetate, 4/1) to give Ethyl (2*E*,6*E*,10*Z*)-3-[(Diethoxyphosphoryl)oxy]-7-methyl-2,6,10-dodecatrienoate as a pale yellow oil (8.04 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.35- 5.20 (m, 2H), 5.06 (t, J = 6.4 Hz, 1H), 4.13- 4.00 (q, 6H), 2.74 (t, J = 7.2 Hz, 2H), 2.18 (q, J = 6.1 Hz, 2H), 2.03-1.88 (4H, m), 1.53 (s, 3H), 1.48 (d, J = 6.0 Hz 3H), 1.27 (t, J = 7.2 Hz, 6H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 136.0, 129.9, 123.5, 122.3, 105.3, 105.2, 64.5, 64.4, 59.8, 39.1, 31.5, 31.4, 25.1, 25.0, 15.8, 15.6, 13.9, 12.4; HRMS (ESI) Calculated for C19H23O6PNa [M + Na]+ 4.11.1907, found 411.1897.

389.2087, found 389.2078. Calculated for $C_{19}H_{23}O_6PNa$ $[M + Na]^+$ 4.11.1907, found 411.1897.

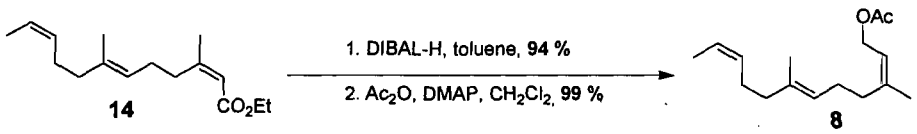
Ethyl (2*E*,6*E*,10*Z*)-3,7-drimethyl-2,6,10-dodecatrienoate (14)



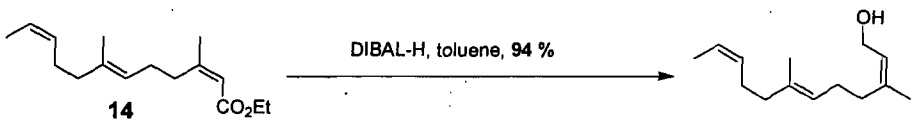
To a suspension of CuI (9.31 g, 49.0 mmol, 3.0 equiv.) in THF (150 mL) at 0 °C was added dropwise MeLi (30.6 mL of a 1.6M solution in diethyl ether, 49.0 mmol, 3.0 equiv.). The orange mixture was stirred at 0 °C for 15 min, before being cooled to -30 °C. MeMgCl (27.2 mL of a 3 M solution in THF, 82.0 mmol, 5.0 equiv.) was added dropwise as to maintain a reaction temperature of -30 °C. After 30 min, the resulting light brown suspension was treated with a solution of Ethyl (2*E*,6*E*,10*Z*)-3-[(Diethoxyphosphoryl)oxy]-7-methyl-2,6,10-dodecatrienoate (6.16 g, 16.43 mmol, 1.0 equiv.) in THF (50 mL), and the mixture was stirred at -30 °C for 3 h, then quenched by pouring onto ice-cold saturated $NH_4Cl_{(aq)}$. The organic layer was diluted with Ethyl Acetate and washed with saturated $NH_4Cl_{(aq)}$ until the organic phase was no longer blue. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an orange oil. Purification by silica gel flash chromatography (Hexanes/Ethyl Acetate, 20/1) afforded **14** as a pale yellow oil (3.73 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (s, 1H), 5.45- 5.30 (m, 2H), 5.15 (t, J = 6.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.19- 1.97 (m, 6H), 1.87 (s, 3H), 1.61- 1.57 (m, 6H), 1.24 (t, J = 7.6 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) 166.3, 160.0, 135.4, 130.2, 123. 8, 123. 6, 116.2, 59.3, 39.3, 33.3, 26.6, 25.4, 25.3, 15.9, 14.3,

12.7; HRMS (ESI) calculated for $C_{16}H_{27}O_2$ $[M + H]^+$, 251.2006, found 251.2010, calculated for $C_{16}H_{26}O_2Na$ $[M + Na]^+$, 273.1825, found 273.1827.

(2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl acetate (8)



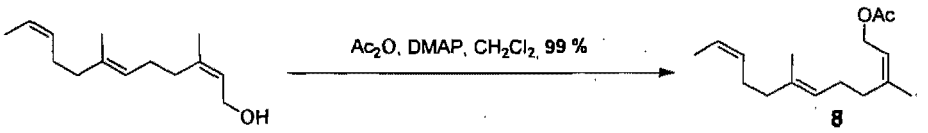
(2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trien-1-ol



To a solution of the ester **14** (2.04 g, 9.58 mmol, 1.0 equiv.) in anhydrous diethyl ether (100 ml) was added a 1.0 M solution of DIBAL-H in Toluene (48.0 mL, 48.0 mmol, 5.0 equiv.) at 0 °C and the solution stirred at this temperature for 1 hour. An aqueous solution of sodium hydroxide (10 %) and diethyl ether were added. The aqueous phase was extracted with diethyl ether. The combined organic phases were washed successively with aqueous NaOH (10%), water and brine, and then dried over anhydrous $MgSO_4$ and filtered. Purification by silica gel flash chromatography (Hexanes/Ethyl Acetate, 7/1) gave the alcohol (2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trien-1-ol (1.878 g, 94%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40-5.29 (m, 3H), 5.12 (t, J = 4.7 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 2.19-2.08 (m, 8H), 1.75 (s, 3H), 1.61 (s, 3H), 1.59 (s, 1H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 135.7, 130.1, 124.3,

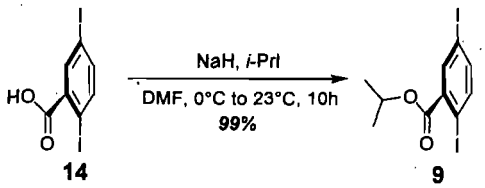
123.9, 123.7, 59.0, 39.3, 31.9, 26.5, 25.4, 23.4, 15.9, 12.8; HRMS (ESI) calculated for $C_{14}H_{25}O$ $[M + H]^+$, 209.1899, found 209.1900.

(2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl acetate (8)



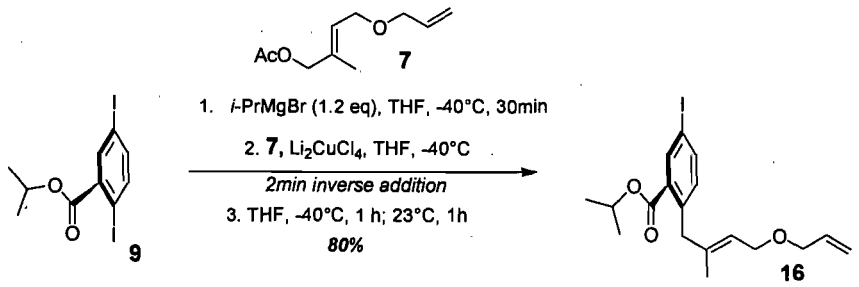
To a solution of (2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trien-1-ol (1.878 g, 9.01 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) was added Ac_2O (2.0 mL, 18.0 mmol, 2.0 equiv.) and DMAP (10 mg, 0.99 mmol, 1 mol %). The reaction was stirred for 3 h at room temperature and was monitored by TLC (Hexanes/Ethyl Acetate, 7/1). The reaction mixture was then diluted with MeOH (10 mL). After waiting for 15 min, water was added (50 mL) and the mixture was extracted with Ethyl Acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. Purification by silica gel flash chromatography (Hexanes/Ethyl Acetate, 10/1) gave the ester (2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl acetate **(8)** (2.255 g, 99%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50-5.39 (m, 3H), 5.12 (t, J = 6.1 Hz, 1H), 4.56 (d, J = 7.3 Hz, 2H), 2.18-2.07 (m, 8H), 2.05 (s, 3H), 1.77 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 142.7, 135.6, 130.2, 123.8, 123.5, 119.1, 61.1, 39.4, 32.1, 26.5, 25.4, 23.5, 21.1, 15.9, 12.8; HRMS (ESI) calculated for $C_{16}H_{26}O_2Na$ $[M + Na]^+$, 273.1825, found 273.1827.

Iso-propyl 2,5-diiodobenzoate (9)



To a DMF solution (20 mL) of acid **14** (5.18 g, 13.85 mmol. 1.0 equiv.) was added potassium carbonate (9.30 g, 70.0 mmol, 5 equiv.) and 2-iodopropane (2.07 mL, 20.7 mmol, 1.5 equiv) at room temperature. The mixture was stirred for 10 h and monitored by TLC (Hexanes/Ethyl Acetate, 7/1). After completion of the reaction, 1 N HCl was added. The reaction mixture was extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$, evaporated *in vacuo* and purified by silica gel flash chromatography (Hexanes/Ethyl Acetate, 10/1) to afford ester **9** as a pale-yellow solid (5.70 g, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 8.3, 2.2 Hz, 1H), 5.25 (sept., J = 6.3 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 142.5, 141.1, 139.1, 137.5, 93.2, 93.1, 70.0, 21.8; HRMS (ESI) calculated for $C_{10}H_{10}I_2O_2Na$ $[M + Na]^+$, 438.8662, found 438.8650.

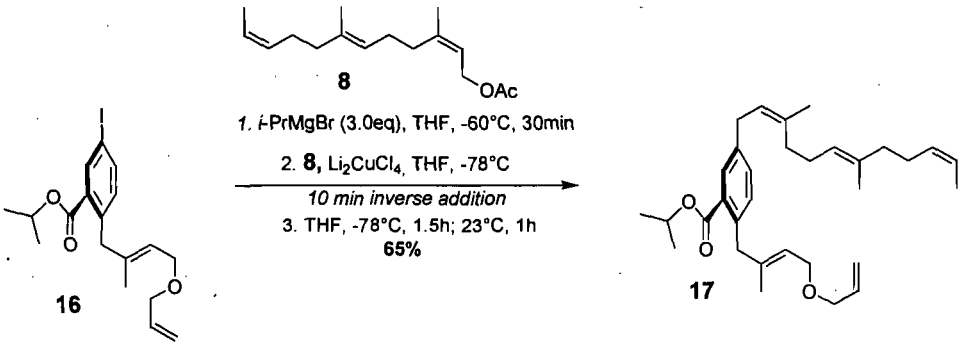
Iso-propyl 2-((*E*)-4-(allyloxy)-2-methylbut-2-enyl)-5-iodobenzoate (16)



In a round bottom flask *iso*-propyl ester **9** (6.87 g, 16.5 mmol, 1.0 equiv.) was dissolved in anhydrous THF (55 mL). The solution was cooled to -40°C and treated dropwise with a freshly made solution of *i*-PrMgBr (7.60 mL, 2.6 M in THF, 19.8 mmol, 1.2 equiv.) affording a color change from clear to yellow. The solution was stirred for 0.5 h and the Mg-I exchange was monitored by GC analysis (exchange intermediate R_t = 12.85 min) or by TLC (benzene). This solution was transferred over 2 minutes via cannula to a second round bottom flask containing Li_2CuCl_4 (2.2 mL, 1.10 mmol, 7 mol %) and acetate **7** (2.00 g, 11.0 mmol, 0.66 equiv.) in anhydrous THF (55 mL) at -40°C affording a color change from dark red to clear and then to orange. The reaction was stirred for 1 h at -40°C, warmed to room temperature, and stirred for 1 h. The reaction was monitored by TLC (Hexanes/Ethyl Acetate, 10/1). The reaction was quenched with saturated NH_4Cl solution (1 x 55 mL), diluted with water (1 x 55 mL), and extracted with diethyl ether (3 x 55 mL). The combined organic extracts were washed with NH_4OH (1 x 55 mL) and brine (1 x 55 mL), dried over Na_2SO_4, and evaporated to a residue that was purified by silica gel flash chromatography (Hexanes/Ethyl Acetate, 20/1). Ester **16** was obtained as a yellow oil (3.60 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 1.8 Hz, 1H), 7.69 (dd, J = 8.1, 1.8 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 5.88 (ddt, J = 17.3, 10.5, 5.7 Hz, 1H), 5.28-5.23 (m, 2H), 5.21-5.16 (m, 2H), 3.97 (d, J = 6.5 Hz, 2H), 3.91 (d, J = 5.7 Hz, 2H), 3.64 (s, 2H), 1.63 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 165.7, 140.2, 139.9, 138.9, 138.7, 134.8, 133.1, 133.0, 122.9, 117.0, 90.8, 71.0, 68.8, 66.4, 42.3, 21.8, 21.8, 16.9; HRMS (ESI) calculated for $C_{18}H_{23}IO_3Na$ $[M + Na]^+$, 437.0582, found 437.0584.

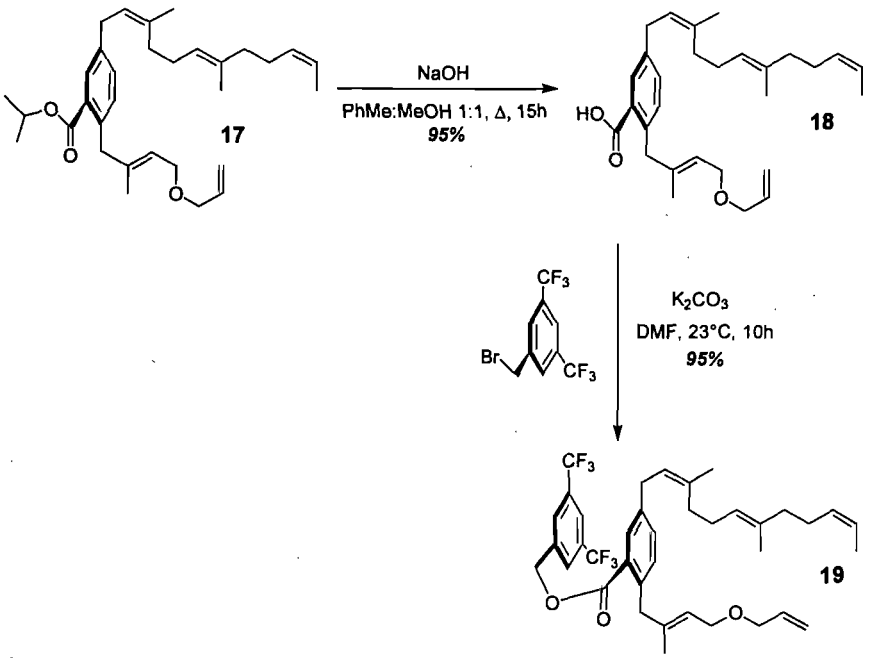
Iso-propyl2-((*E*)-4-(allyloxy)-2-methylbut-2-enyl)-5-((2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl)benzoate (17)



In a round bottom flask a concentrated solution of *iso*-propyl ester 15 (2.455 g, 5.93 mmol, 1.0 equiv.) dissolved in anhydrous THF (4 mL) was prepared. The solution was cooled to -60 °C. A solution of freshly made i-PrMgBr (18.0 mL, 1M in THF, 18.0 mmol, 3.0 equiv.) was added dropwise and stirred for 1 h at -60 °C affording a color change from clear to yellow. This solution was transferred over 10 minutes via cannula to a second round bottom flask containing Li_2CuCl_4 (0.83 mL, 0.42 mmol, 7 mol %) and acetate **8** (0.824 g, 3.30 mmol, 0.55 equiv.) in anhydrous THF (2.0 mL) at -78 °C. The reaction was stirred for an additional 1.5 h at -78°C, warmed to room temperature, and stirred for 1 h. The reaction was monitored by TLC (benzene). The reaction was quenched with saturated NH_4Cl solution (1 x 50 mL), diluted with water (1 x 50 mL), and extracted with Hexanes (3 x 50 mL). The combined organic extracts were washed with NH_4OH (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, and evaporated to a

residue that was purified by silica gel flash chromatography (benzene) to afford **17** as a pale yellow oil (1.03 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.90 (ddt, J = 17.3, 10.5, 5.7 Hz, 1H), 5.48-5.30 (m, 8H), 3.99 (d, J = 6.7 Hz, 2H), 3.93 (d, J = 5.7 Hz, 2H), 3.67 (s, 2H), 3.35 (d, J = 7.2 Hz, 2H), 2.13 (m, 6H), 2.01 (m, 2H), 1.76 (s, 3H), 1.65 (s, 3H), 1.62 (s, 6H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 139.8 (2C), 137.4, 136.7, 135.2 (2C), 131.3 (2C), 130.3 (2C), 123.8, 123.5, 123.3, 122.3 (2C), 117.0, 70.9, 68.2, 66.5, 42.5, 39.4, 33.5, 32.0, 26.5, 25.4, 23.5, 21.9 (2C), 16.9, 16.0, 12.8; HRMS (ESI) calculated for $C_{32}H_{47}O_3$ $[M+H]^+$, 479.3520, found 479.3522.

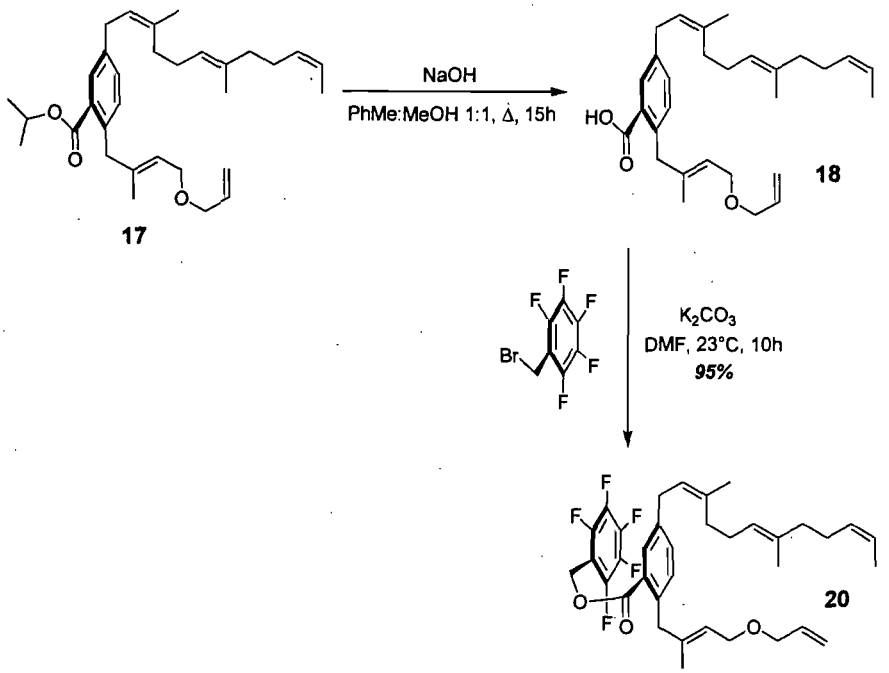
3,5-Bis(trifluoromethyl)benzyl 2-((*E*)-4-(allyloxy)-2-methylbut-2-enyl)-5-((2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl)benzoate (19)



In a round bottom flask equipped with a reflux condenser, ester **17** (465 mg, 0.972 mmol, 1.0 equiv.) was dissolved in a 1: 1 mixture of toluene:methanol (20 mL), heated to a reflux, treated with NaOH pellets (505 mg, 12.63 mmol, 13.0 equiv.) and stirred for 24 h. The reaction was monitored by TLC (Hexanes/Ethyl Acetate, 10/1). The solvent was removed by evaporation under reduced pressure, dissolved in diethyl ether, quenched with 1 N HCl (6.50 mL), extracted with diethyl ether (3 x 20 mL), washed with brine, dried over $MgSO_4$, and evaporated to afford acid **18** (400 mg, 95%). Acid **18** degrades rapidly and is immediately esterified. Acid **18** (0.10 g, 0.23 mmol) was treated with potassium carbonate (60 mg, 0.46 mmol) and 3,5-bis(trifluoromethhyl)benzyl bromide (50 µL, 0.25 mmol, which prior to

addition was passed through a short plug of basic alumina) in DMF (4 mL) at room temperature, stirred for 10 h, filtered, evaporated *in vacuo* to give a residue that was purified by silica gel flash chromatography (Hexanes Ethyl Acetate, 10/1) to afford ester **19** as a pale-yellow oil (143 mg, 95%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.88 (d, J = 1.5 Hz, 1H), 7.63 (s, 1H), 7.46 (s, 2H), 7.11 (dd, J = 7.8, 1.5 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 5.81 (ddt, J = 17.1, 10.6, 5.3 Hz, 1H), 5.54-5.45 (m, 2H), 5.38 (t, J = 7.2 Hz, 1H), 5.30 (t, J = 6.8 Hz, 1H), 5.25-5.20 (m, 2H), 5.00 (ddd, J = 10.4, 3.3, 1.4 Hz, 1H), 4.81 (s, 2H), 3.87 (d, J = 6.6 Hz, 2H), 3.80-3.78 (m, 4H), 3.25 (d, J = 7.3 Hz, 2H), 2.21-2.10 (m, 8H), 1.67 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 167.1, 140.4, 139.3, 139.0, 138.9, 137.0, 135.8, 135.2, 132.6, 132.1, 132.1, 131.6, 130.7, 130.5, 130.1, 124.5, 124.0, 123.6, 123.5, 121.9, 116.0, 71.0, 66.8, 64.8, 42.9, 39.8, 33.8, 32.2, 26.8, 25.8, 23.5, 16.9, 16.0, 12.9; HRMS (ESI) calculated for $C_{38}H_{45}F_6O_3$ $[M + H]^+$, 663.3267, found 663.3295.

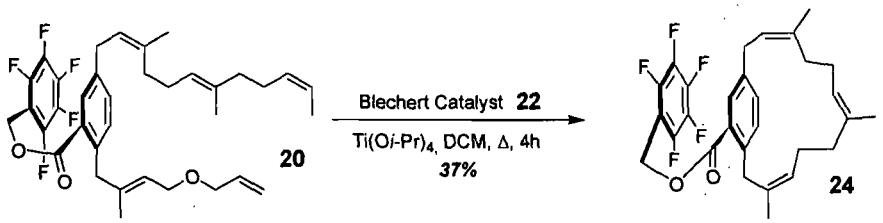
Pentafluorobenzyl 2-((*E*)-4-(allyloxy)-2-methylbut-2-enyl)-5-((2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyl)benzoate (20)



Follow experimental procedure for **3,5-Bis(trifluoromethyl)benzyl 5-((2*Z*,6*Z*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyloxy)-2-((*E*)-4-(allyloxy)-2-methylbut-2-enyloxy)benzoate (19)** for the preparation of **18**. Acid **18** (100 mg, 0.23 mmol) was treated with potassium carbonate (60 mg, 0.46 mmol) and 2,3,4,5,6-pentafluorobenzylbromide (50 µL, 0.25 mmol, which prior to addition was passed through a short plug of basic alumina) in DMF (4 mL) at room temperature, stirred for 10 h, filtered, evaporated *in vacuo* to give a residue that was purified by silica gel flash chromatography (Hexanes/Ethyl acetate 10/1) to afford ester **20** as a pale-yellow oil (131 mg, 95%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.90 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 7.9, 1.6 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.85 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H), 5.55-5.48 (m, 2H),

5.38 (t, J = 6.6 Hz, 1H), 5.31-5.23 (m, 3H), 5.06-5.03 (m, 3H), 3.90 (d, J = 6.6, 2H), 3.83-3.80 (m, 4H), 3.23 (d, J = 7.3 Hz, 2H), 2.21-2.15 (m, 2H), 2.15-2.10 (m, 6H), 1.65 (s, 3H), 1.58 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 166.8, 140.3, 139.1, 138.9, 137.0, 135.8, 135.2, 132.6, 132.1, 130.9, 130.5, 129.9, 124.5, 124.0, 123.7, 123.6, 116.0, 71.0, 66.8, 53.4, 42.9, 39.8, 33.7, 32.2, 26.8, 25.8, 23.5, 16.9, 15.9, 15.8, 12.9; HRMS (ESI) calculated for $C_{36}H_{42}F_5O_3$ $[M + H]^+$, 617.3049, found 617.3069.

Cyclophane (24)



To a flame dried three neck round bottom flask equipped with a reflux condenser under nitrogen, Blechert catalyst **22** (10 mg, 0.014 mmol, 10 mol %) and anhydrous DCM (300 mL) were added. The solution was heated to reflux and treated dropwise with a solution of ester **20** (87 mg, 0.141 mmol) and Ti(O*i*-Pr)$_4$ (0.97 mL, 0.71 mmol, 5.0 equiv.), dissolved in DCM (50 mL) over 3h using a syringe pump. The reaction was allowed to stir at reflux for an additional 1h and was monitored by TLC (Hexanes/Ethyl Acetate, 10/1). The reaction was quenched with ethyl vinyl ether (5 mL) and the solvent was evaporated down to about 1 mL to give a residue that was further purified by silica gel flash chromatography (Hexanes/ Toluene 1/1) to afford cyclophane **24** as a pale-yellow oil (26 mg, 37%). ^{1}H NMR was carried out in C_6D_6 since running the sample in $CDCl_3$ caused decomposition. In addition, running the sample in C_6D_6 prevents overlapping of the three alkenyl proton signals. ^{1}H NMR (700 MHz, C_6D_6) δ 8.07 (d, *J* = 1.6 Hz, 1H), 7.13 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 5.56 (t, *J* = 7.0 Hz, 1H), 5.03 (dd, *J* = 14.0, 5.3 Hz, 2H), 4.59 (t, *J* = 5.8 Hz, 1H), 4.53-4.48 (m, 2H), 3.23 (dd, *J* = 16.0, 7.8 Hz, 1H), 3.03 (d, *J* = 15.8 Hz, 1H), 2.010-1.91 (m, 2H), 1.90 (t, *J* = 5.6 Hz, 2H), 1.80-1.68 (m, 4H), 1.73 (s, 3H), 1.58 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (175 MHz, C_6D_6) δ; 166.9, 141.6, 140.9, 140.8, 136.9, 133.6, 133.4, 133.3, 131.7, 129.8, 127.1, 124.3, 122.0, 53.5, 42.5, 39.1, 33.7, 32.2, 25.9, 24.0, 22.9, 16.8, 15.4. HRMS (ESI) calculated for $C_{29}H_{30}F_5O_2$ $[M + H]^+$, 505.2160, found 505.2167.

NMR spectra of compounds and intermediates

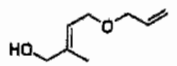
Current Data Parameters
NAME JZ3-163
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070918
Time 11.26
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312034 sec
RG 35.8
DW 86.400 usec
DE 6.00 usec
TE 297.5 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

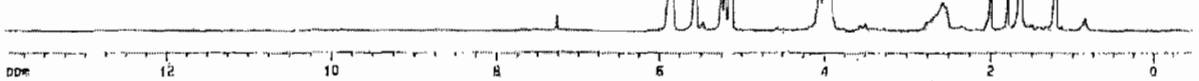
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SF01 400.1327073 MHz

F2 - Processing parameters
SI 65536
SF 400.1300084 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.974 ppm
F1 5591.39 Hz
F2P -0.489 ppm
F2 -195.65 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm



5.881 5.878 5.863 5.849 5.837 5.570 5.252 5.209 5.193 5.127 4.077 4.059 4.002 3.986 3.944 3.929
1.993 1.769 1.637 1.226 1.209



Annexe 2 : Informations supplémentaires de l'article 4

JZ3-26

Current Data Parameters
NAME JZ3-163
EXPNO 2
PROCNO 1

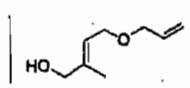
F2 - Acquisition Parameters
Date_ 20070918
Time 11.30
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 32
DS 4
SWH 22675.736 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 9195.2
DW 22.050 usec
DE 30.86 usec
TE 297.9 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.60 dB
SF01 100.6227903 MHz

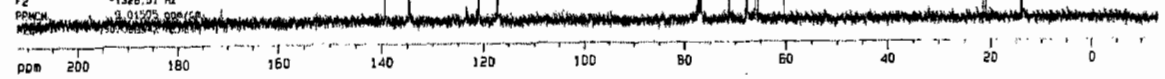
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 16.50 dB
SF02 400.1318065 MHz

F2 - Processing parameters
SI 65536
SF 100.6127809 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.172 ppm
F1 21347.23 Hz
F2P -13.204 ppm
F2 -1328.51 Hz
PPMCM 9.01975 ppm/cm

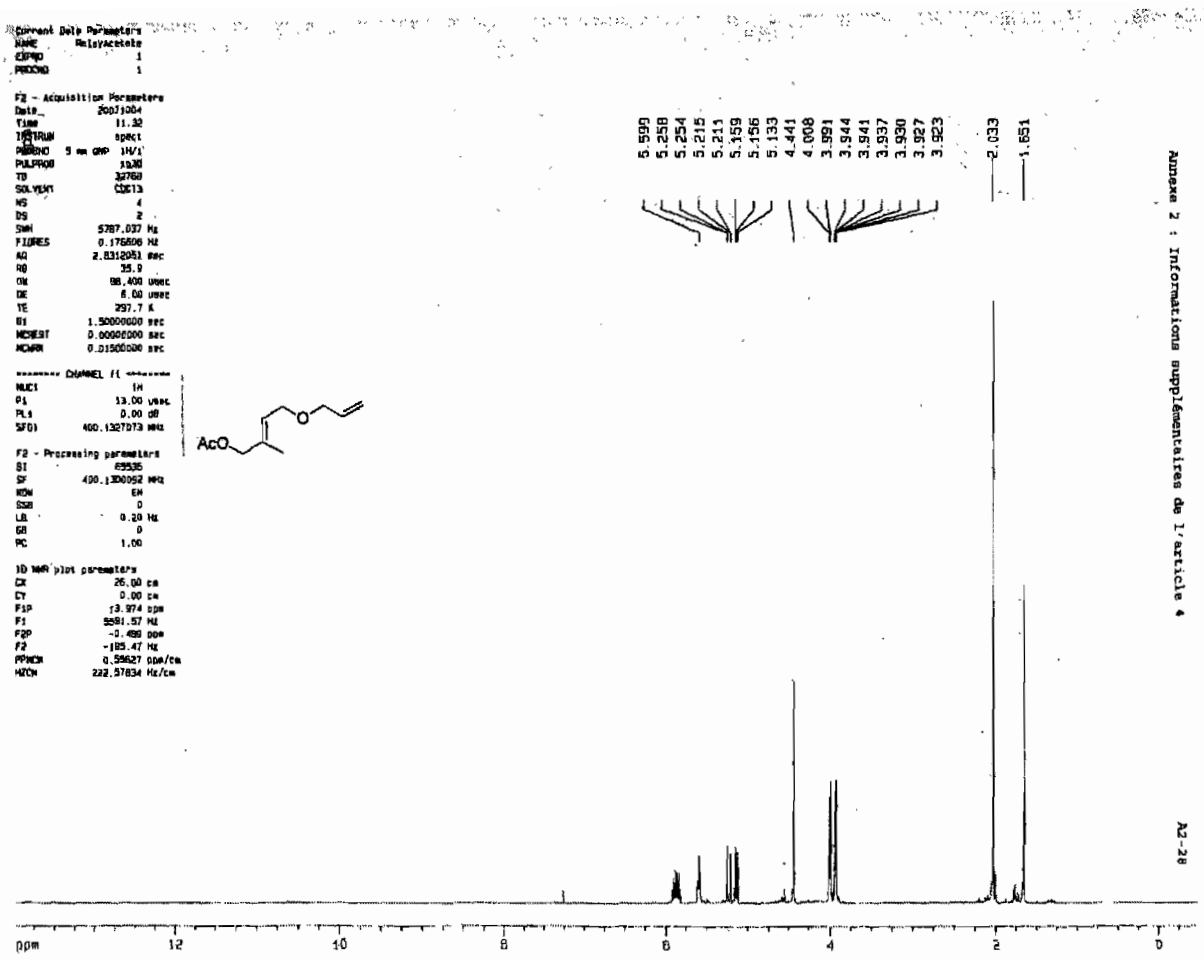


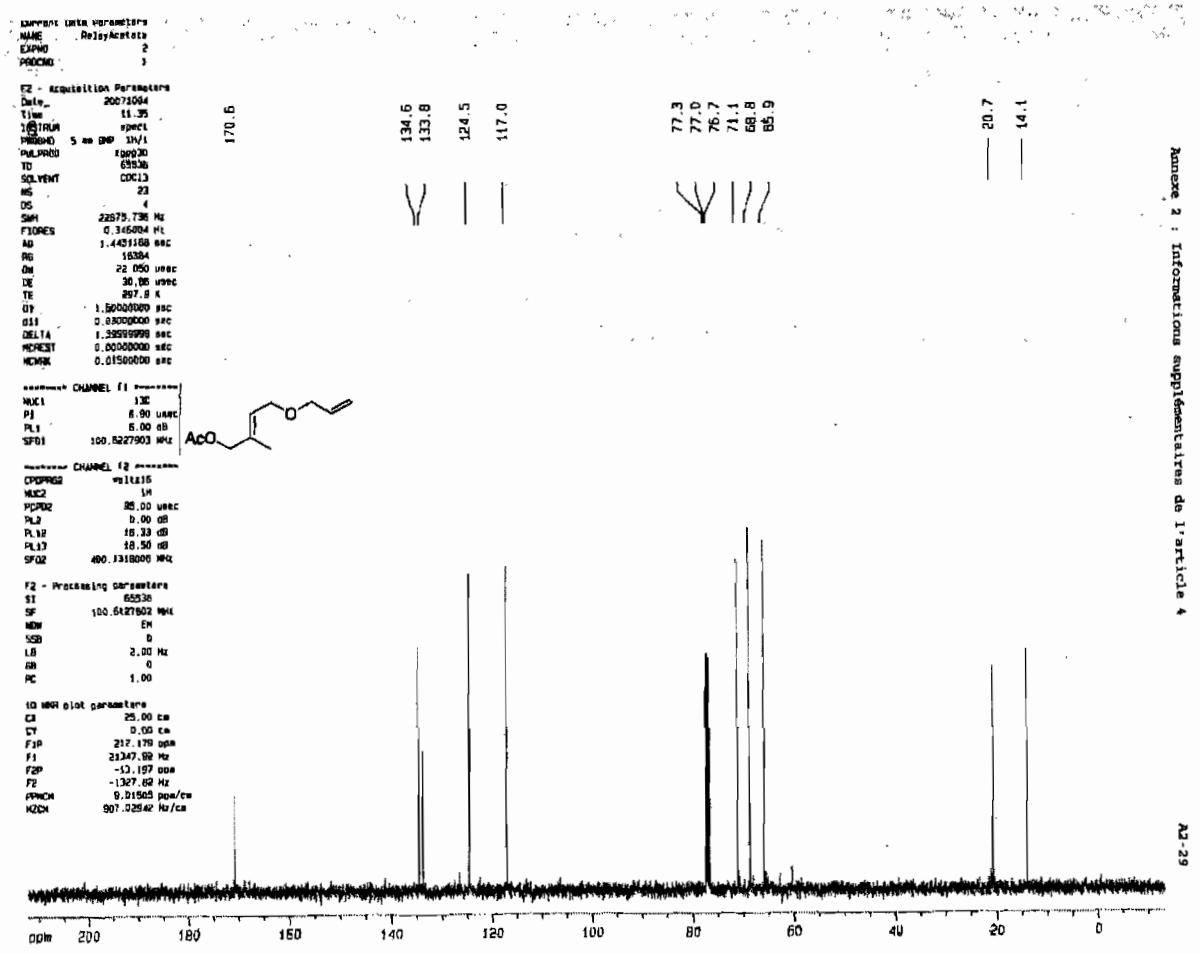
139.2 134.6 120.9 117.0 77.3 77.0 76.7 71.0 67.6 66.0 13.7



Annexe 2 : Informations supplémentaires de l'article 4

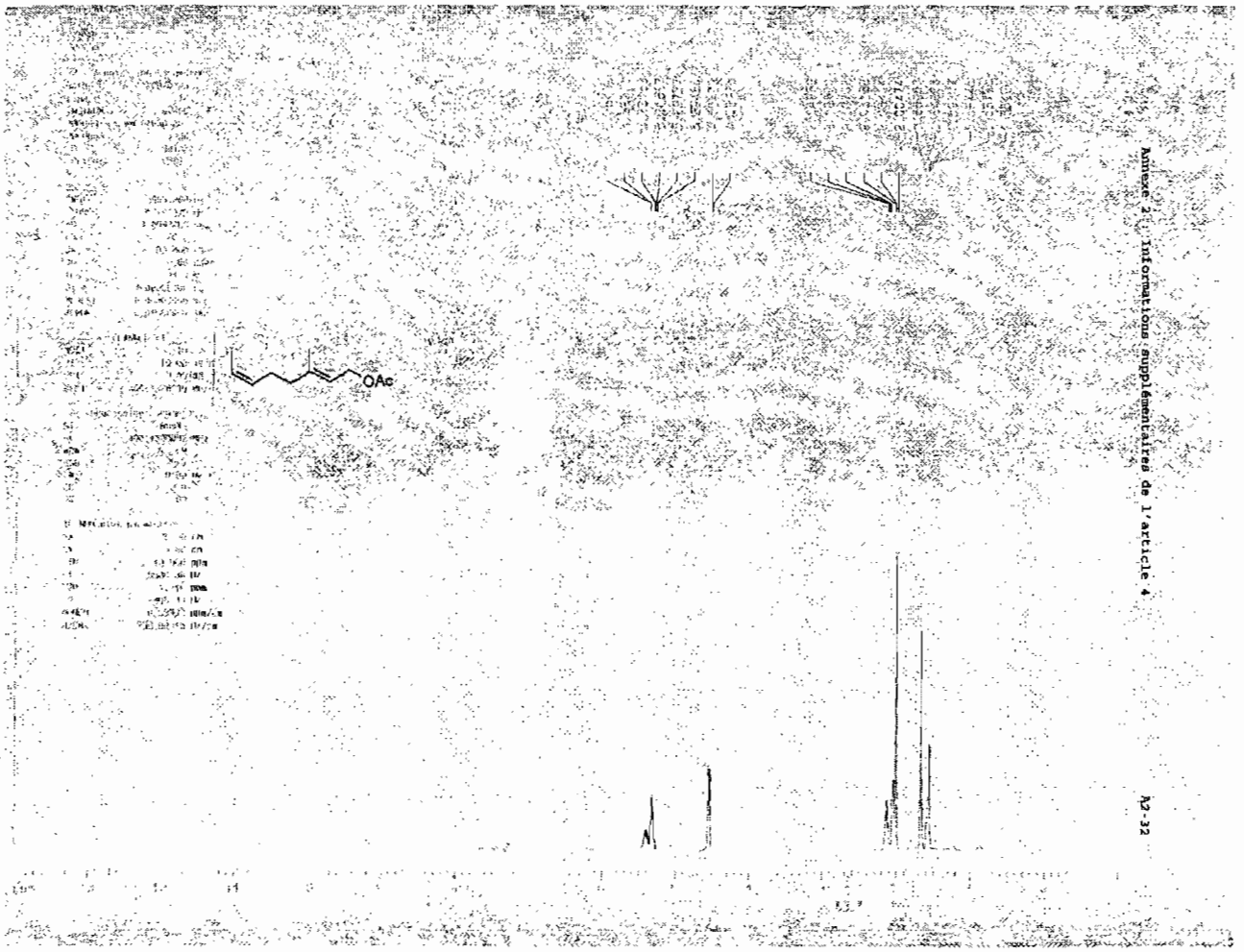
JZ3-27

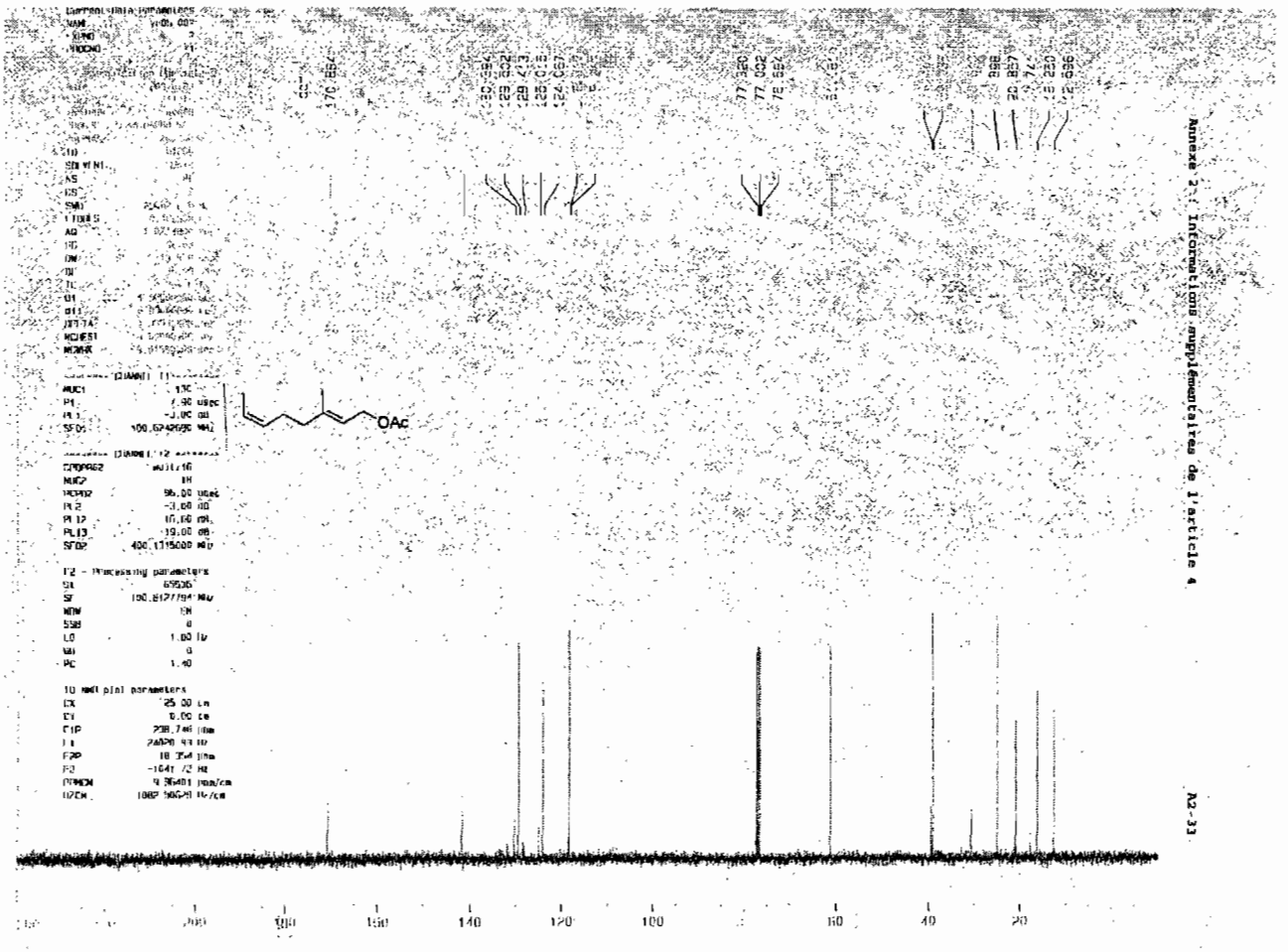

Current Data Parameters
NAME RelayAcetate
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071004
Time 11.32
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 35.9
DW 86.400 usec
DE 6.00 usec
TE 297.7 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300052 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.974 ppm
F1 5591.57 Hz
F2P -0.499 ppm
F2 -185.47 Hz
PPMCM 0.59627 ppm/cm
HZCM 222.57834 Hz/cm
AcO
5.599
5.258
5.254
5.215
5.211
5.159
5.156
5.133
4.441
4.008
3.991
3.944
3.941
3.937
3.930
3.927
3.923
2.033
1.651
ppm
12
10
8
6
4
2
0


Current Data Parameters
NAME RelayAcetate
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071004
Time 11.35
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 23
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4491168 sec
RG 16384
DW 22.050 usec
DE 30.06 usec
TE 297.8 K
D1 1.60000000 sec
D11 0.03000000 sec
DELTA 1.39599998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 6.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 85.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127802 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 217.179 ppm
F1 21847.98 Hz
F2P -13.197 ppm
F2 -1327.62 Hz
PPMCM 9.91505 ppm/cm
HZCM 997.02542 Hz/cm
AcO
170.6
134.6
133.8
124.5
117.0
77.3
77.0
76.7
71.1
68.8
65.9
20.7
14.1
ppm
200
180
160
140
120
100
80
60
40
20
0

A2-10

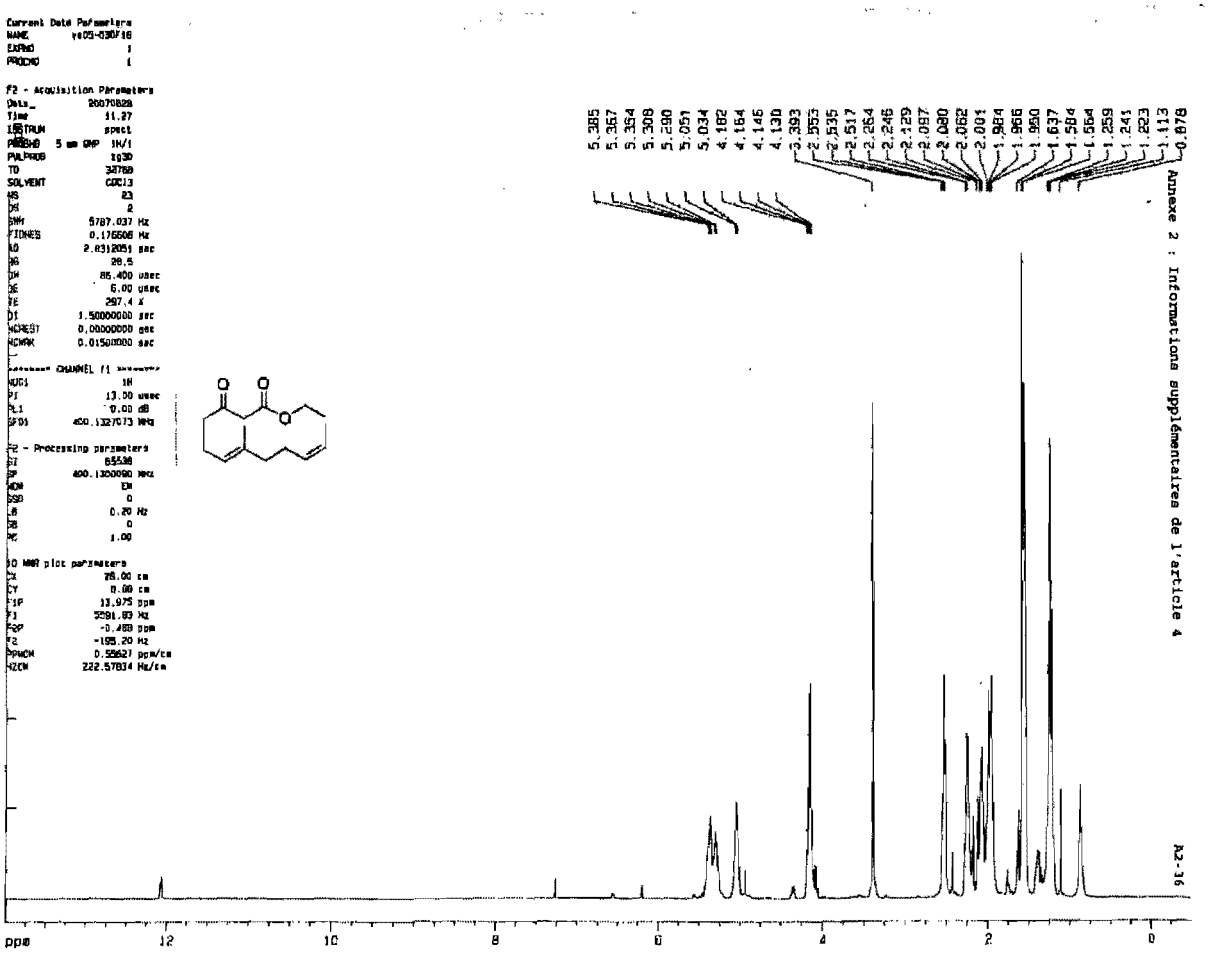
A2-11

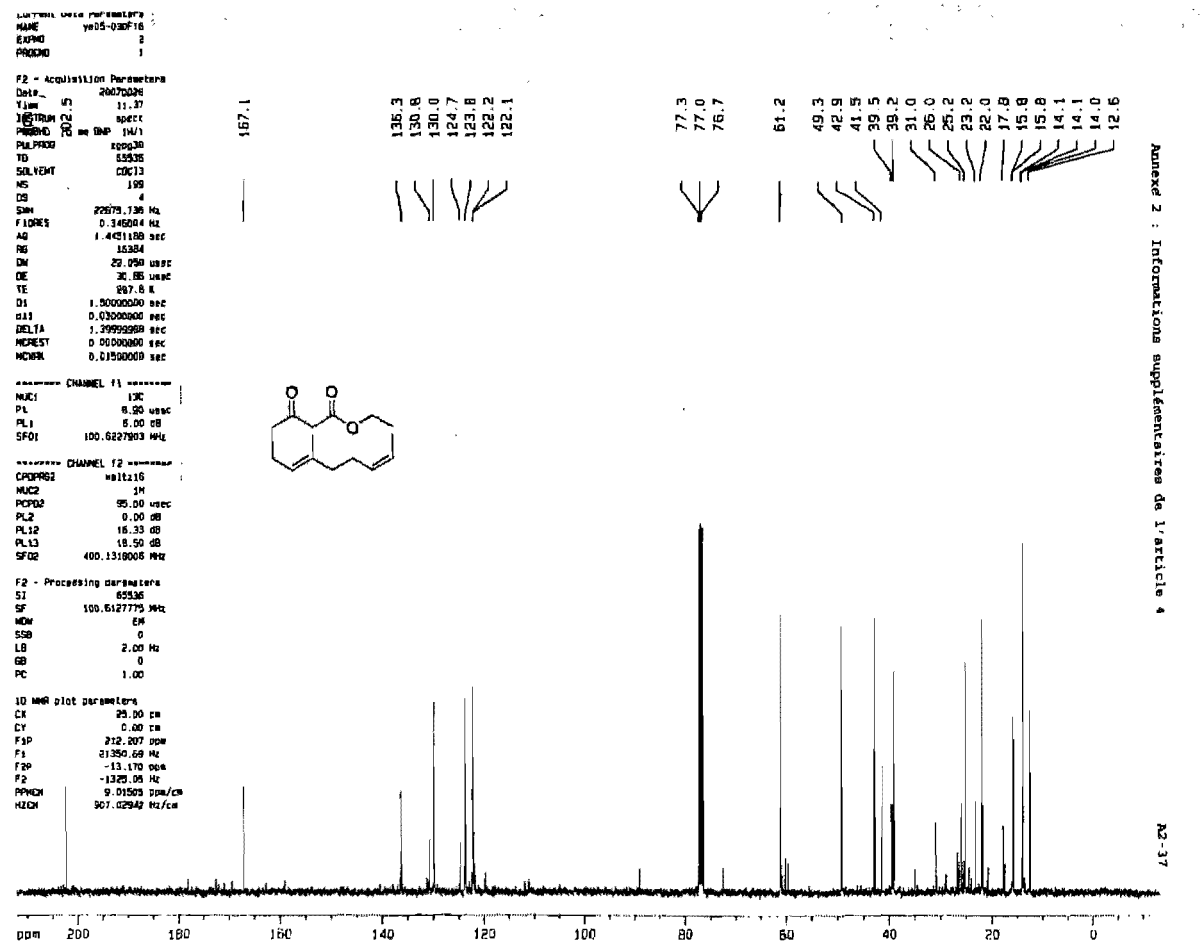

OAc

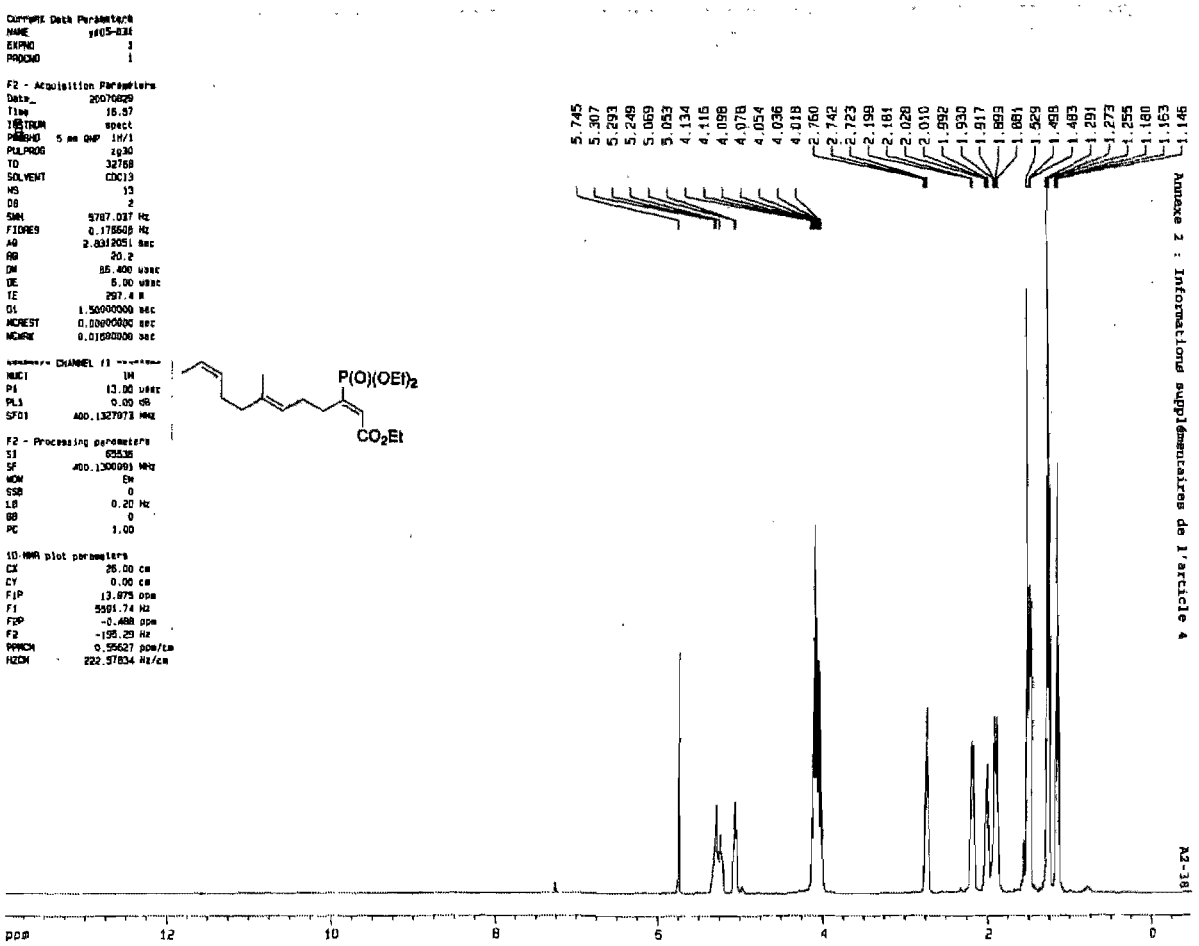

OAc

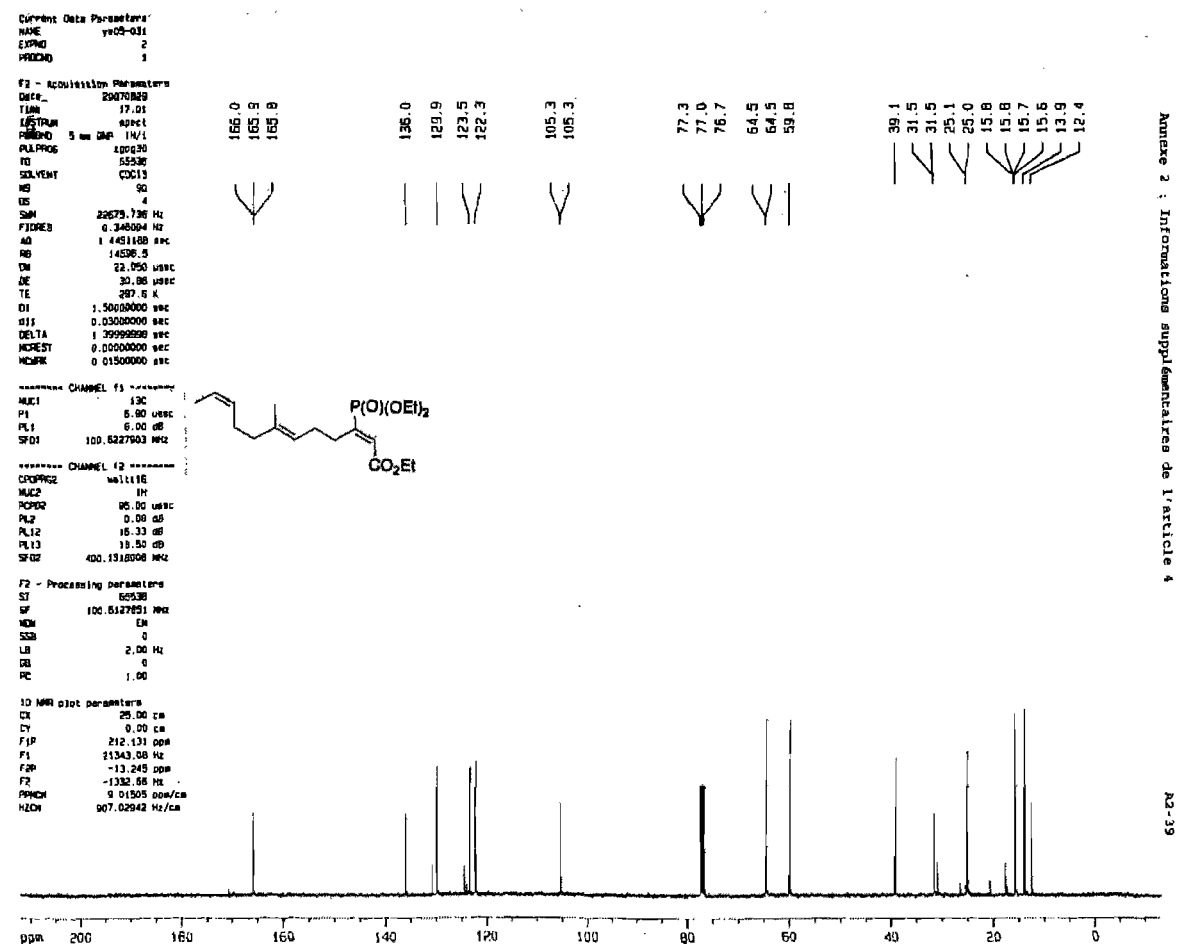
OH

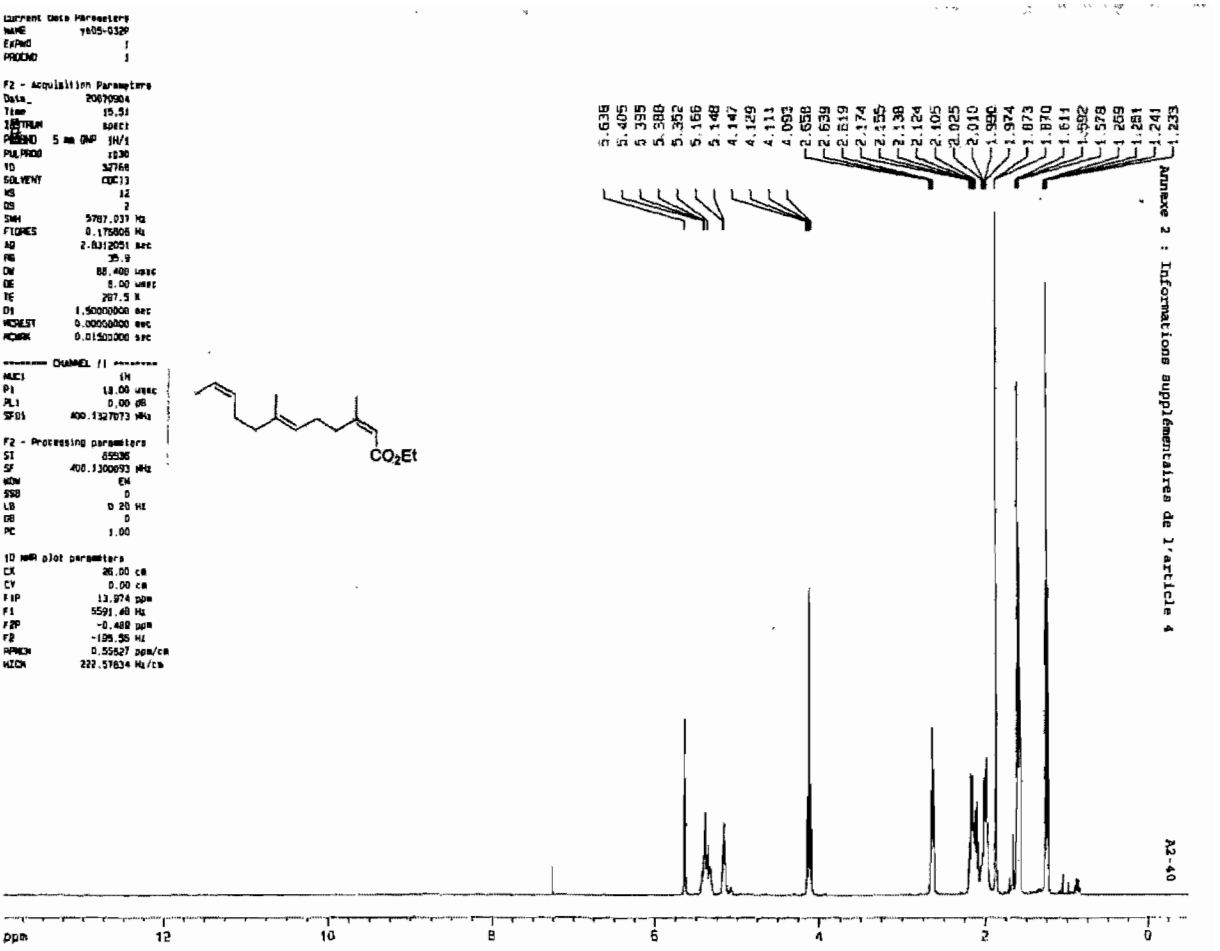
OH


Current Data Parameters
NAME ye05-030F16
EXPNO 1
PROCNO 1
f2 - Acquisition Parameters
Date_ 20070828
Time 11.27
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 23
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 28.5
DW 86.400 usec
DE 6.00 usec
TE 297.4 K
D1 1.50000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D13 0.00000400 sec
D16 0.00020000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 13.975 ppm
F1 5591.89 Hz
F2P -0.469 ppm
F2 -185.20 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
5.385
5.367
5.334
5.308
5.290
5.051
5.034
4.182
4.164
4.146
4.130
3.393
2.553
2.535
2.517
2.264
2.246
2.129
2.087
2.080
2.062
2.001
1.984
1.966
1.950
1.637
1.584
1.564
1.259
1.241
1.223
1.113
0.878
Annexe 2 : Informations supplémentaires de l'article 4
A2-16
ppm
12
10
8
6
4
2
0


MNAME ye05-030F16
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070829
Time 11.37
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 199
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4451188 sec
RG 16384
DW 29.050 usec
DE 30.65 usec
TE 297.6 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999988 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.20 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1319005 MHz
F2 - Processing parameters
SI 65536
SF 100.6127775 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 212.207 ppm
F1 21350.69 Hz
F2P -13.170 ppm
F2 -1325.05 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02942 Hz/cm
167.1
136.3
130.8
130.0
124.7
123.8
122.2
122.1
77.3
77.0
76.7
61.2
49.3
42.9
41.5
39.5
39.2
31.0
26.0
25.2
23.2
22.0
17.8
15.8
15.8
14.1
14.1
14.0
12.6
Annexe 2 : Informations supplémentaires de l'article 4
A2-17
ppm
200
180
160
140
120
100
80
60
40
20
0

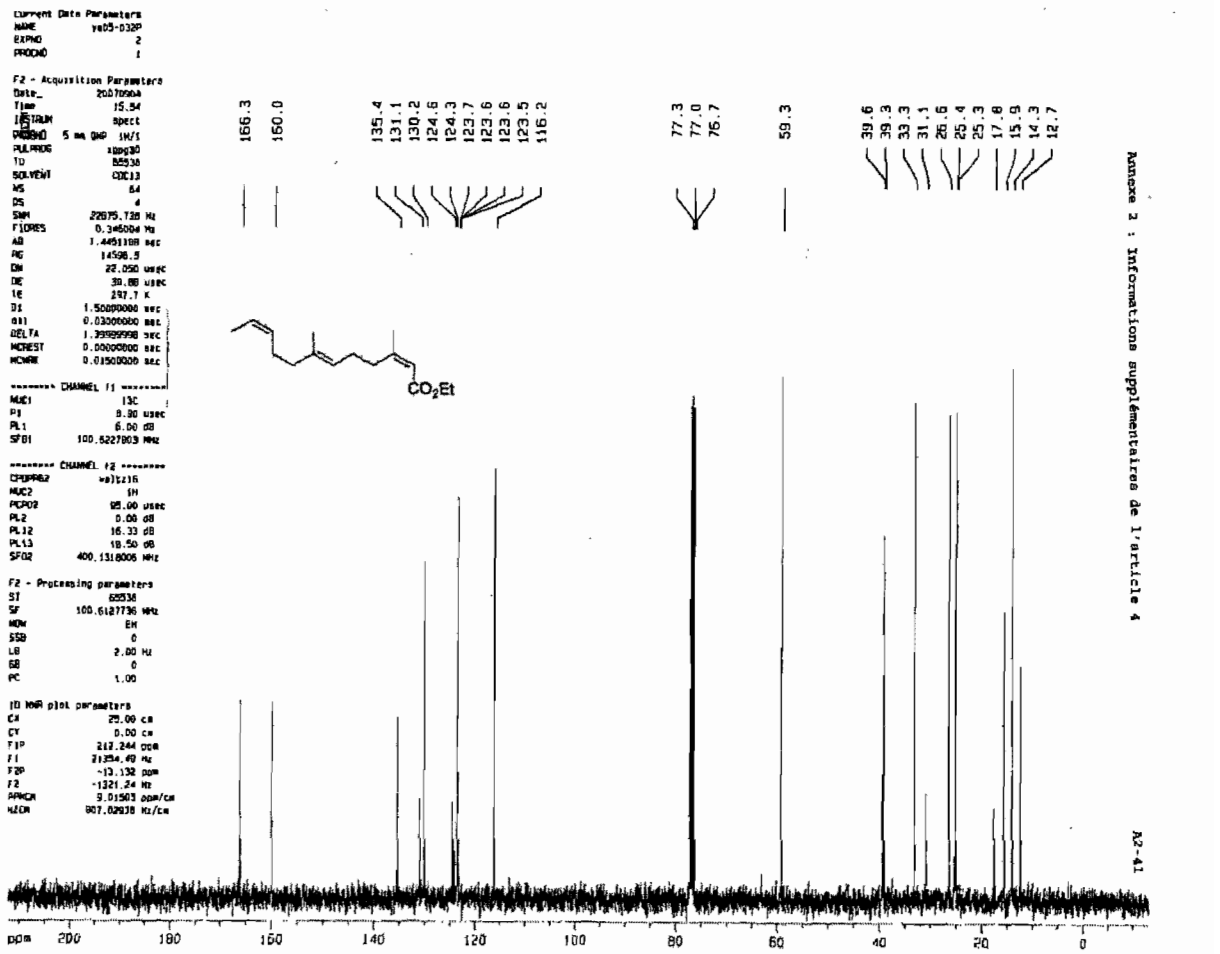

Current Data Parameters
NAME ye05-036
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070829
Time 16.57
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 13
DS 2
SWH 9787.037 Hz
FIDRES 0.178508 Hz
AQ 2.8312051 sec
RG 20.2
DW 85.400 usec
DE 6.00 usec
TE 297.4 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327973 MHz
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.875 ppm
F1 5551.74 Hz
F2P -0.488 ppm
F2 -195.29 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
P(O)(OEt)2
CO2Et
5.745
5.307
5.293
5.249
5.069
5.053
4.134
4.115
4.098
4.078
4.054
4.036
4.018
2.760
2.742
2.723
2.199
2.181
2.028
2.010
1.992
1.930
1.917
1.889
1.881
1.529
1.498
1.483
1.291
1.273
1.255
1.180
1.163
1.146
Annexe 2 : Informations supplémentaires de l'article 4
A2-38
ppm
12
10
8
6
4
2
0


Current Data Parameters
NAME ye05-031
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070829
Time 17.01
INSTRUM spect
PROBHD 5 mm BNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4451168 sec
RG 14336.5
DW 22.050 usec
DE 30.86 usec
TE 297.6 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 19.50 dB
SFO2 400.1318008 MHz
F2 - Processing parameters
SI 65536
SF 100.6127851 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 212.131 ppm
F1 21343.08 Hz
F2P -13.245 ppm
F2 -1332.66 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02942 Hz/cm
P(O)(OEt)2
CO2Et
166.0
165.9
165.8
136.0
129.9
123.5
122.3
105.3
105.3
77.3
77.0
76.7
64.5
64.5
59.8
39.1
31.5
31.5
25.1
25.0
15.8
15.8
15.7
15.6
13.9
12.4
Annexe 2 : Informations supplémentaires de l'article 4
A2-39
ppm
200
160
160
140
120
100
80
60
40
20
0



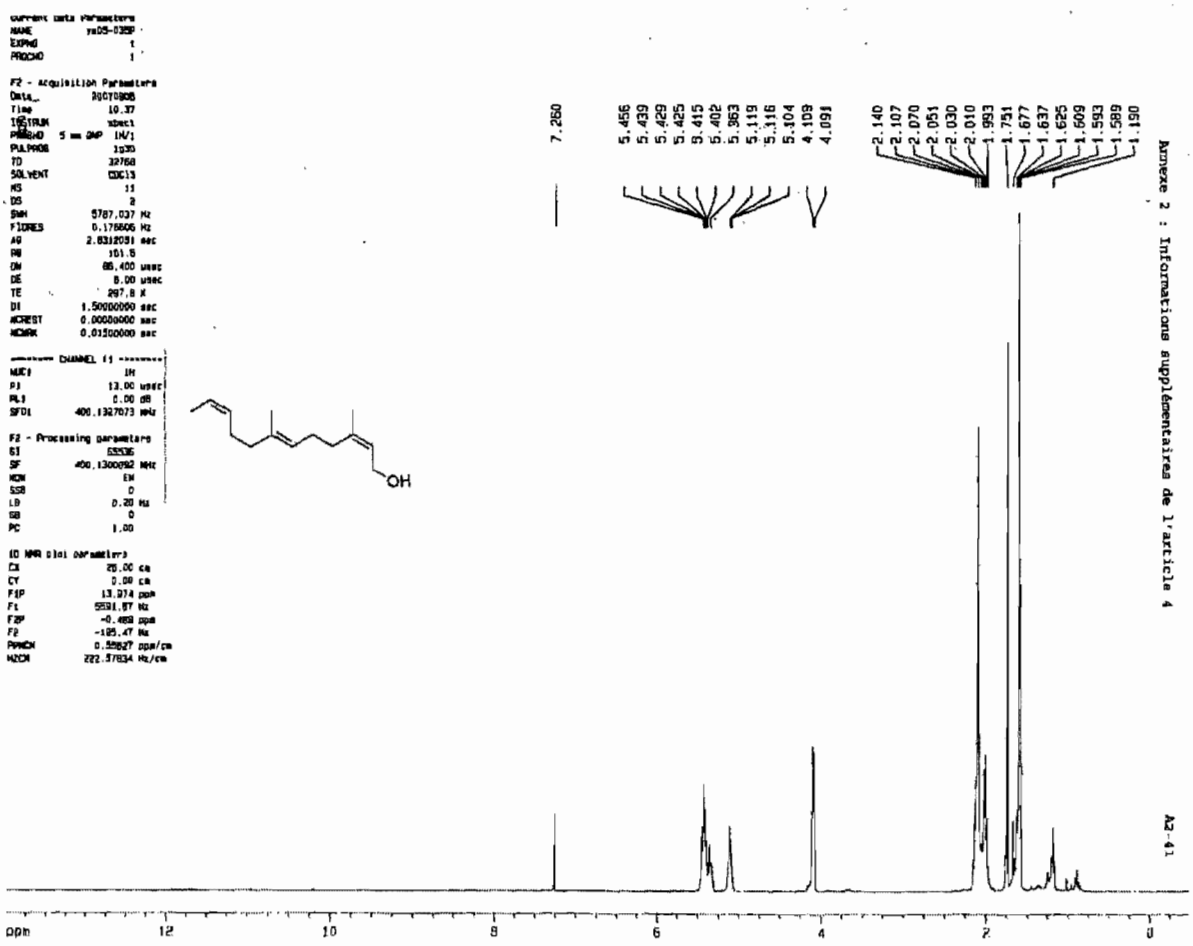
Annexe 2 : Informations supplémentaires de l'article 4

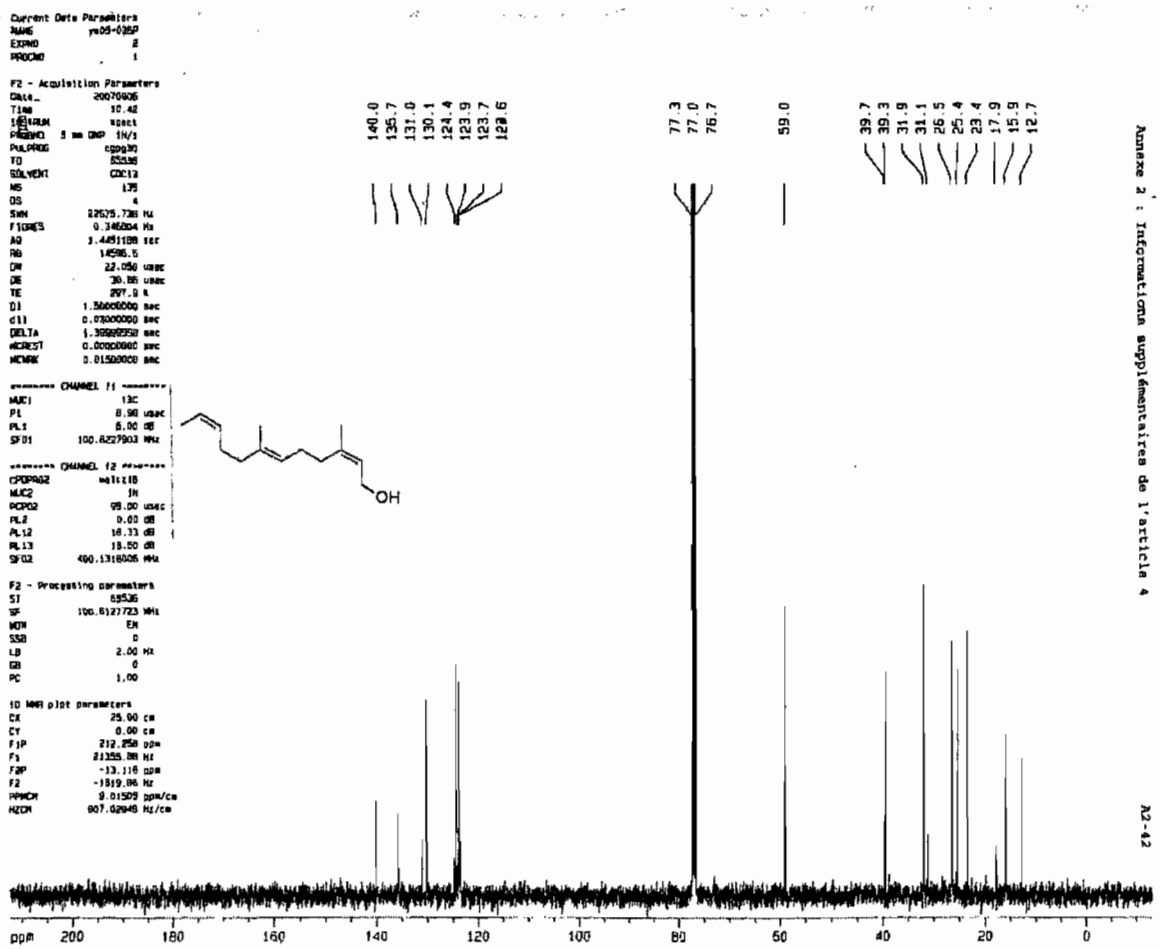
A2-40

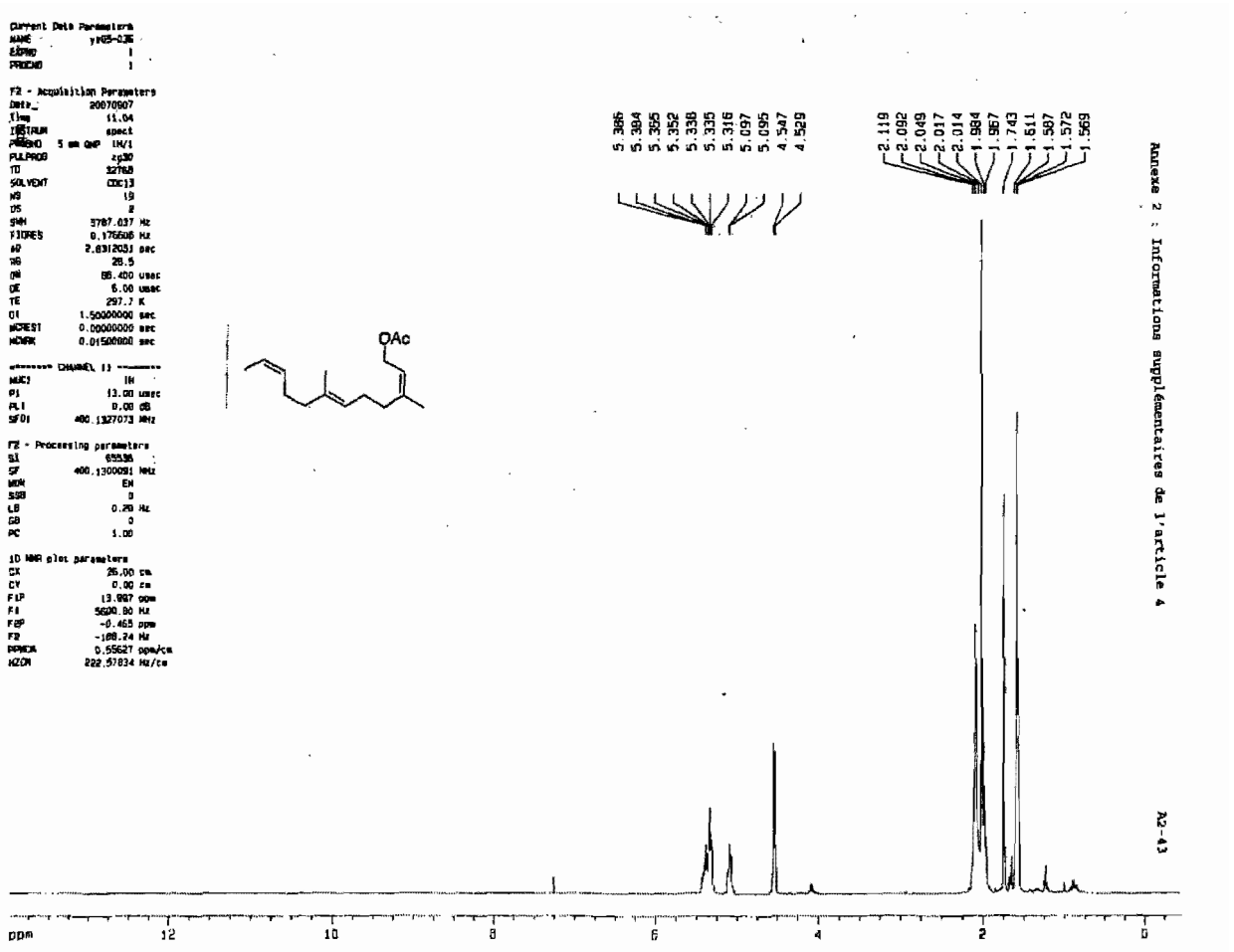


Annexe 2 : Informations supplémentaires de l'article 4

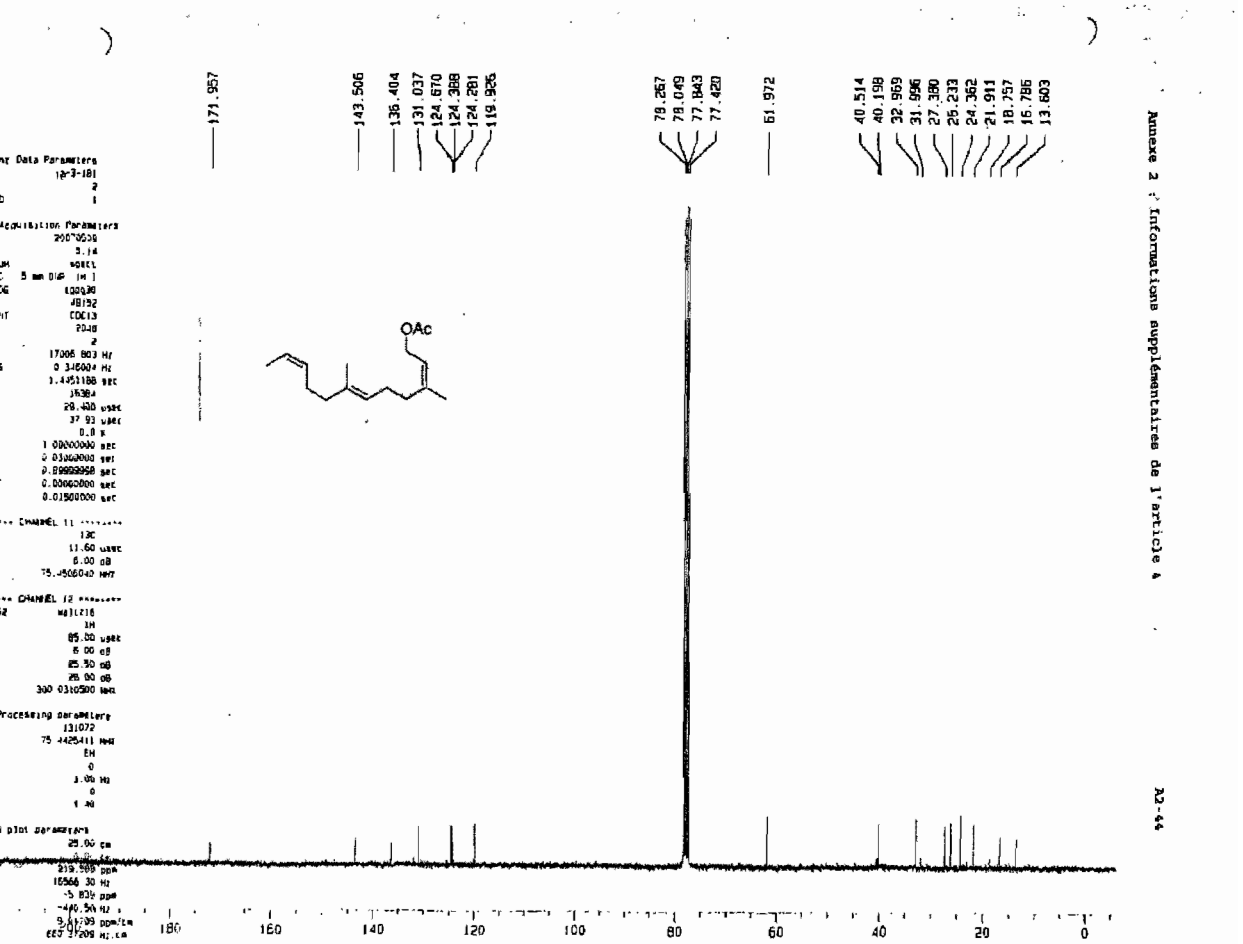
A2-41


Annexe 2 : Informations supplémentaires de l'article 4
A2-41
OH
7.260
5.456
5.439
5.429
5.425
5.415
5.402
5.363
5.119
5.116
5.104
4.109
4.091
2.140
2.107
2.070
2.051
2.030
2.010
1.993
1.731
1.677
1.637
1.625
1.609
1.593
1.589
1.190
ppm

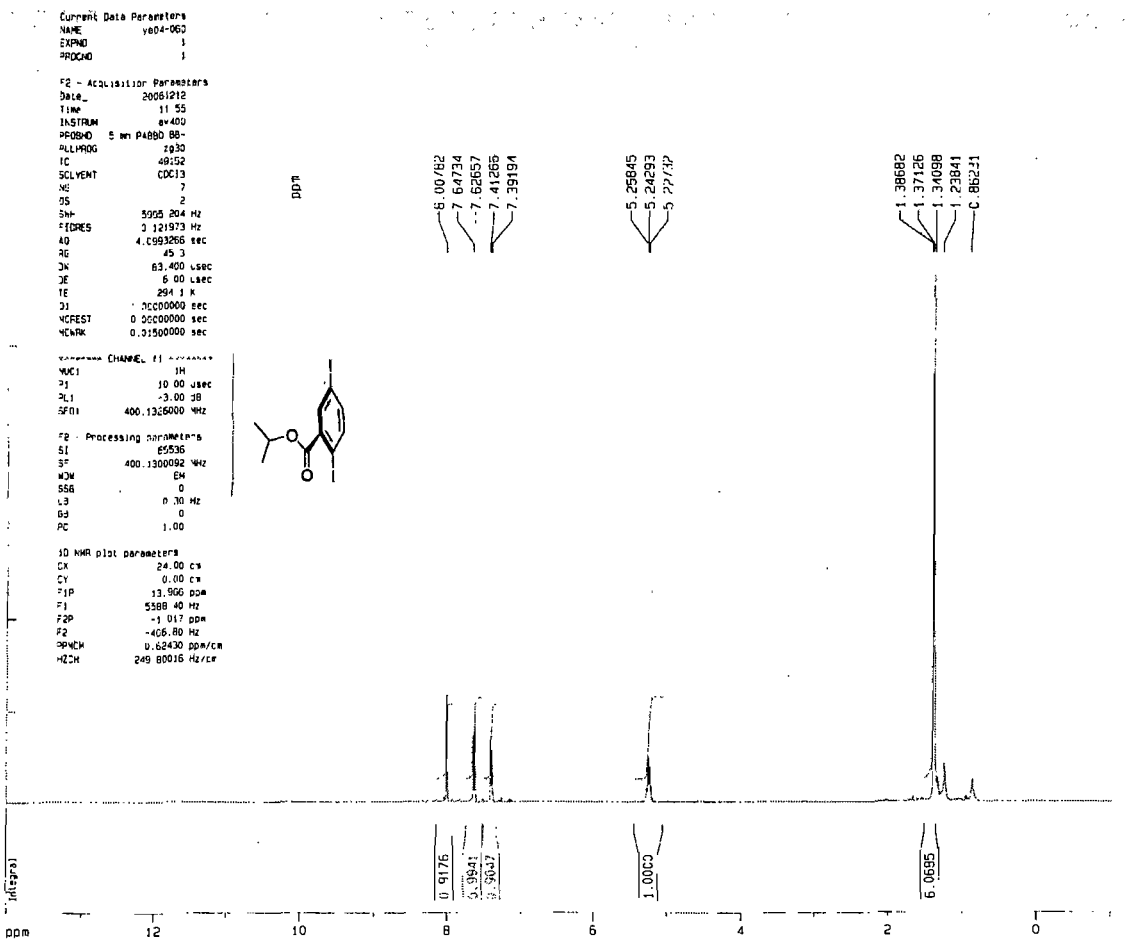

Annexe 2 : Informations supplémentaires de l'article 4
A2-42
OH
140.0
135.7
131.0
130.1
124.4
123.9
123.7
123.6
77.3
77.0
76.7
59.0
39.7
39.3
31.9
31.1
26.5
25.4
23.4
17.9
15.9
12.7
ppm

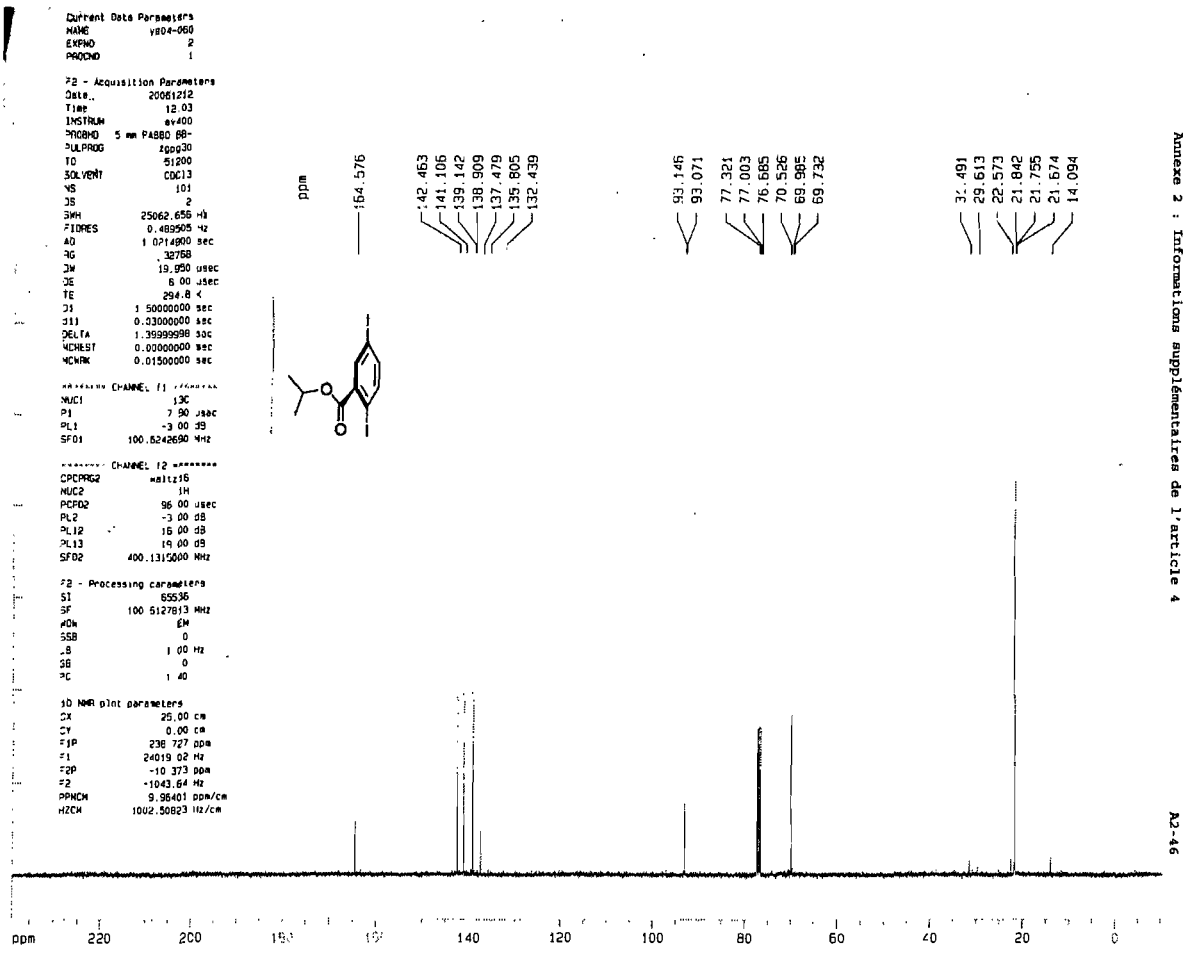

5.386
5.384
5.365
5.352
5.338
5.335
5.316
5.097
5.095
4.547
4.529
2.119
2.092
2.049
2.017
2.014
1.984
1.967
1.743
1.611
1.587
1.572
1.569
OAc
ppm
12
10
8
6
4
2
0

A2-43


171.957
143.506
136.404
131.037
124.670
124.388
124.281
119.926
78.267
78.049
77.843
77.420
61.972
40.514
40.198
32.969
31.996
27.380
25.233
24.362
21.911
18.757
16.786
13.603
OAc
180
160
140
120
100
80
60
40
20
0

A2-44


Current Data Parameters
NAME ya04-060
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061212
Time 11 55
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 7
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0993266 sec
RG 45.3
DW 83.400 usec
DE 6.00 usec
TE 294.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300092 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 13.966 ppm
F1 5588.40 Hz
F2P -1.017 ppm
F2 -406.80 Hz
PPMCM 0.62430 ppm/cm
HZCM 249.80016 Hz/cm
ppm
7.00782
7.64734
7.62657
7.41265
7.39194
5.25845
5.24293
1.38682
1.37126
1.34098
1.23841
0.86241
Integral
0.9176
0.9941
0.9047
1.0000
6.0695
ppm 12 10 8 6 4 2 0


Current Data Parameters
NAME ya04-060
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061212
Time 12.03
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 101
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214900 sec
RG 32768
DW 19.950 usec
DE 6.00 usec
TE 294.8 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6242690 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 96.00 usec
PL2 -3.00 dB
PL12 16.00 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.5127813 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.727 ppm
F1 24019.02 Hz
F2P -10.373 ppm
F2 -1043.64 Hz
PPMCM 9.96401 ppm/cm
HZCM 1002.50823 Hz/cm
ppm
164.576
142.463
141.106
139.142
138.909
137.479
135.805
132.439
93.146
93.071
77.321
77.003
76.685
70.526
69.985
69.732
31.491
29.613
22.573
21.842
21.755
21.674
14.094
ppm 220 200 180 160 140 120 100 80 60 40 20 0

```
Current Data Parameters
NAME                  ye05-049
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20071004
Time                   11.38
INSTRUM                spect
PROBHD     5 mm QNP  1H/1
PULPROG                zg30
TD                    32768
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                9787.037 Hz
FIDRES             0.176506 Hz
AQ                 2.8312051 sec
RG                       256
DW                  86.400 usec
DE                      6.00 usec
TE                     297.7 K
D1                 1.50000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                     13.00 usec
PL1                     0.00 dB
SFO1             400.1327073 MHz

F2 - Processing parameters
SI                        65536
SF               400.1300093 MHz
WDW                       EM
SSB                        0
LB                      0.20 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     25.00 cm
CY                      0.00 cm
F1P                   13.974 ppm
F1                  5591.48 Hz
F2P                  -0.489 ppm
F2                  -195.56 Hz
PPMCM                0.55627 ppm/cm
HZCM               222.57834 Hz/cm
```

8.105 8.101 7.720 7.715 7.700 7.695 7.260 6.986 6.966 5.270 5.266 5.227 5.223 5.203 5.188 5.179 5.172 5.156 5.153 5.150 3.988 3.971 3.939 3.936 3.924 3.921 3.651 1.645 1.604 1.372 1.367 1.348 1.332

A2-47

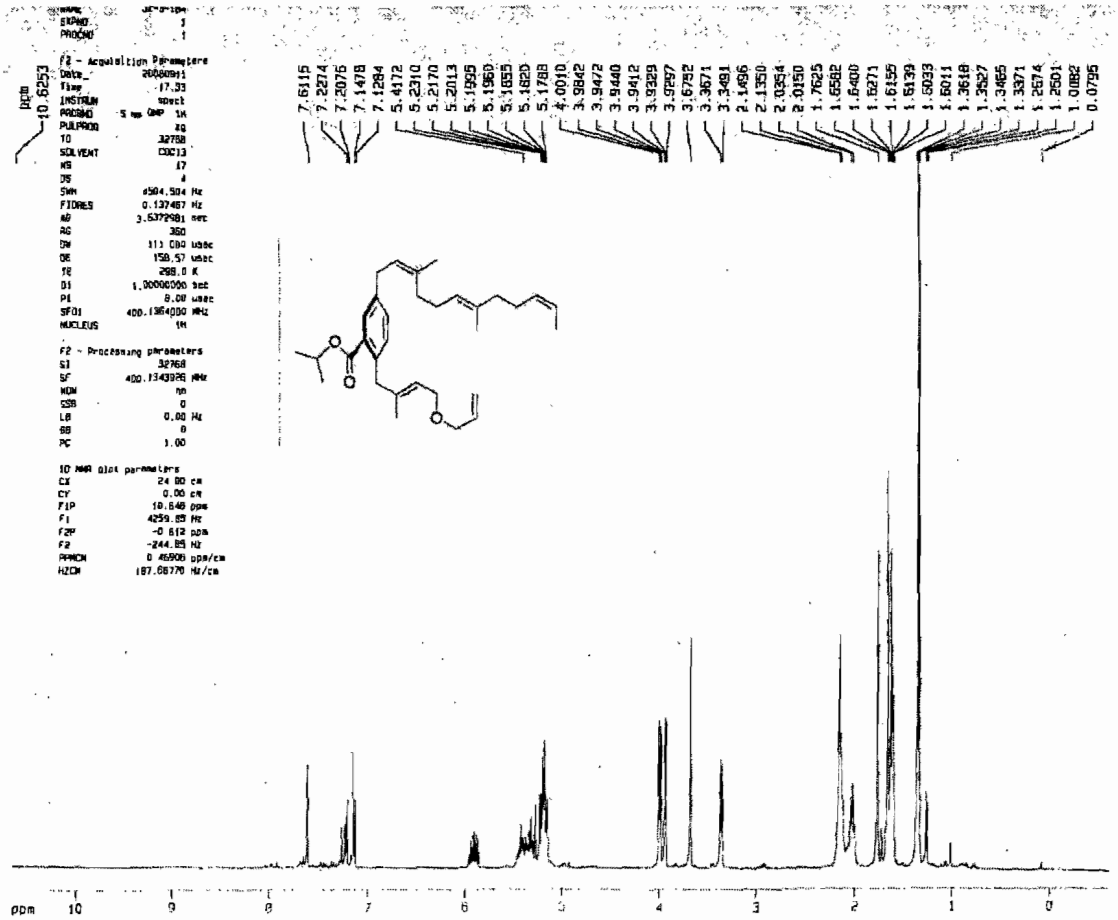
ppm 12 10 8 6 4 2 0

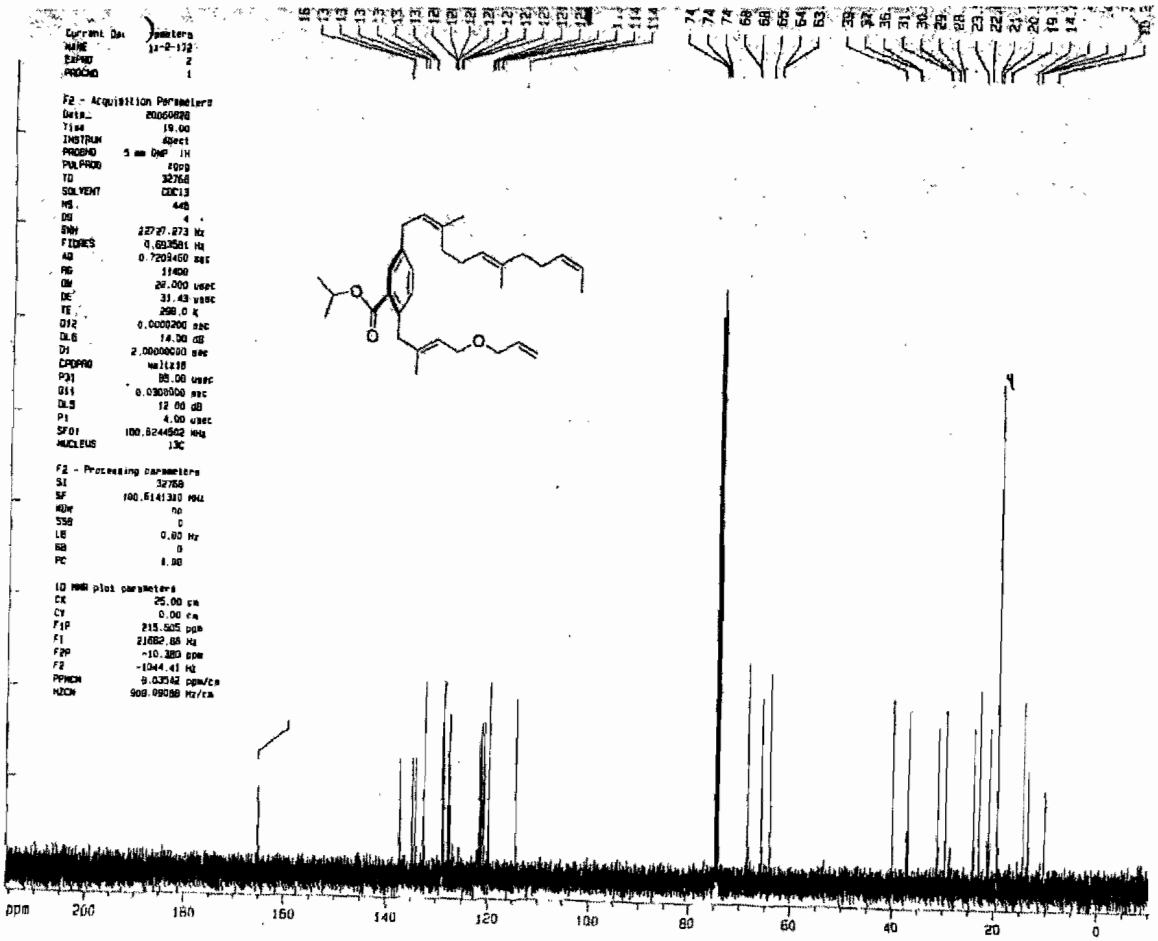

```
Current Data Parameters
NAME                  Ye05-049
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20071004
Time                   11.42
INSTRUM                spect
PROBHD     5 mm QNP  1H/1
PULPROG                zgpg30
TD                    65536
SOLVENT                CDCl3
NS                       222
DS                         4
SWH                22675.736 Hz
FIDRES             0.345004 Hz
AQ                 1.4451168 sec
RG                     16384
DW                  22.050 usec
DE                      6.00 usec
TE                     297.9 K
D1                 1.50000000 sec
D11                0.03000000 sec
DELTA              1.39999998 sec
MCREST             0.00000000 sec
MCWRK              0.01300000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                      8.80 usec
PL1                     0.00 dB
SFO1             100.6227903 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  95.00 usec
PL2                     0.00 dB
PL12                   16.33 dB
PL13                   18.50 dB
SFO2             400.1318006 MHz

F2 - Processing parameters
SI                        65536
SF               100.6127719 MHz
WDW                       EM
SSB                        0
LB                      2.00 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     25.00 cm
CY                      0.00 cm
F1P                  212.262 ppm
F1                 21356.22 Hz
F2P                 -131.115 ppm
F2                 -1319.81 Hz
PPMCM                9.01505 ppm/cm
HZCM               907.02938 Hz/cm
```

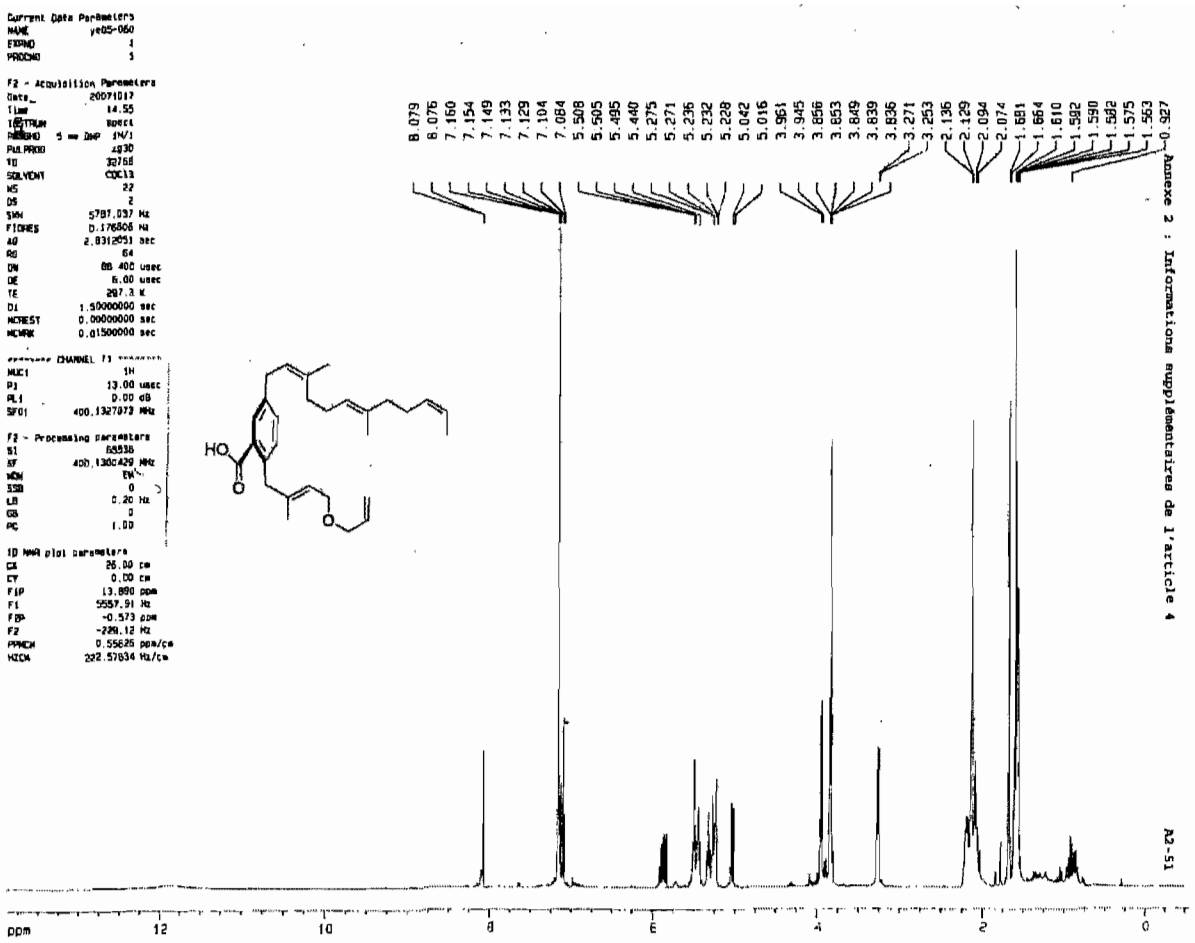
165.8 140.3 139.9 139.0 138.8 134.9 133.2 133.1 122.9 117.0 90.8 77.3 77.0 76.7 71.0 68.8 66.5 42.3 21.8 16.9

A2-48

ppm 200 180 160 140 120 100 80 60 40 20 0

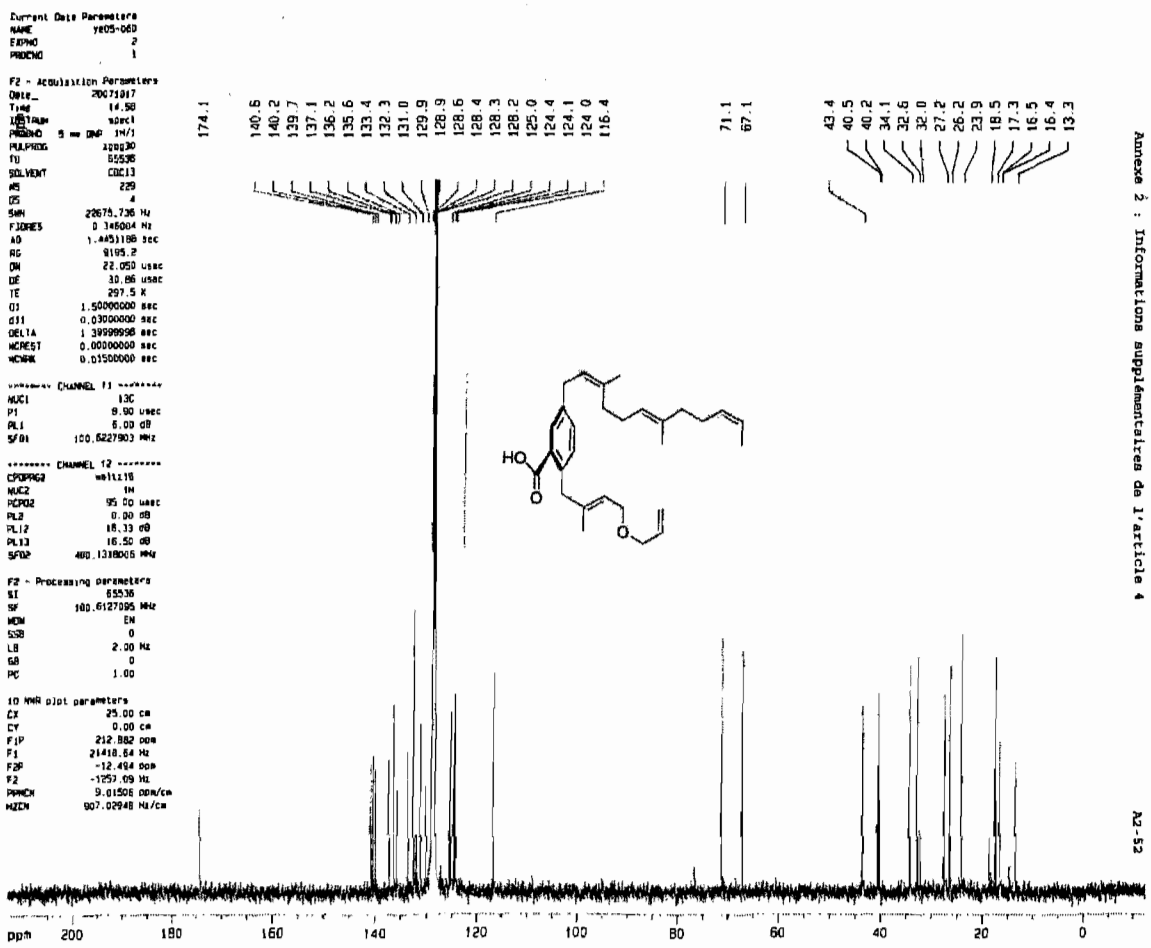

EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060911
Time 17.33
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 17
DS 4
SWH 4504.504 Hz
FIDRES 0.137467 Hz
AQ 3.6372981 sec
RG 360
DW 111.000 usec
DE 158.57 usec
TE 298.0 K
D1 1.00000000 sec
P1 8.00 usec
SFO1 400.1364000 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 32768
SF 400.1343926 MHz
WDW nn
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 10.648 ppm
F1 4259.85 Hz
F2P -0.612 ppm
F2 -244.85 Hz
PPMCM 0.46906 ppm/cm
HZCM 187.68770 Hz/cm
7.6115
7.2274
7.2076
7.1478
7.1284
5.4172
5.2310
5.2170
5.2013
5.1995
5.1960
5.1855
5.1825
5.1788
4.0010
3.9842
3.9472
3.9440
3.9412
3.9329
3.9297
3.6782
3.6671
3.3491
2.1496
2.1350
2.0354
2.0150
1.7625
1.6582
1.6400
1.6271
1.6155
1.6139
1.6033
1.6011
1.3618
1.3527
1.3465
1.3371
1.2674
1.2501
1.0082
0.0795
ppm
10
9
8
7
6
5
4
3
2
1
0


Current Data Parameters
NAME 11-2-172
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060828
Time 19.00
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 448
DS 4
SWH 22727.273 Hz
FIDRES 0.693581 Hz
AQ 0.7209450 sec
RG 11400
DW 22.000 usec
DE 31.43 usec
TE 298.0 K
D12 0.0000200 sec
DL6 14.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 85.00 usec
D11 0.0300000 sec
DL5 12.00 dB
P1 4.00 usec
SFO1 100.6244502 MHz
NUCLEUS 13C
F2 - Processing parameters
SI 32768
SF 100.6141310 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 215.505 ppm
F1 21682.66 Hz
F2P -10.380 ppm
F2 -1044.41 Hz
PPMCM 9.03542 ppm/cm
HZCM 909.09088 Hz/cm
ppm
200
180
160
140
120
100
80
60
40
20
0



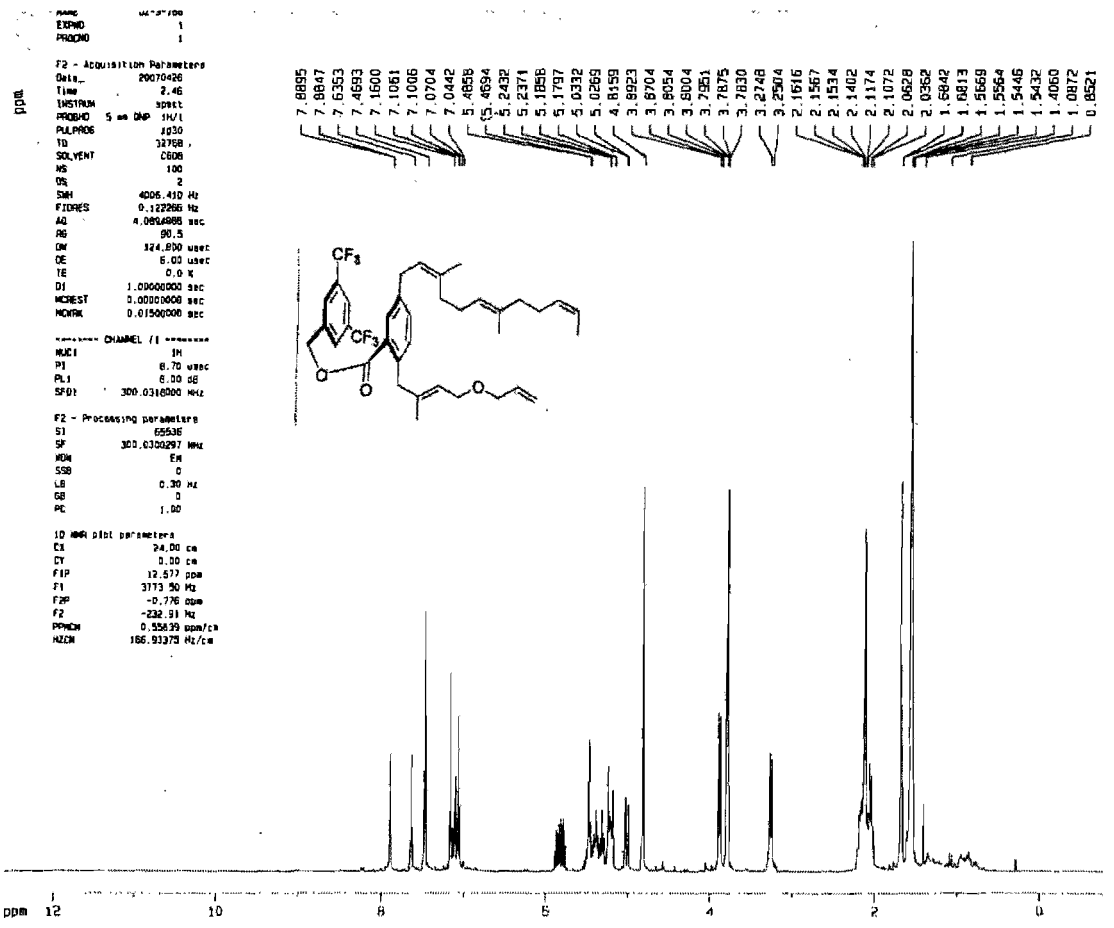
Annexe 2 : Informations supplémentaires de l'article 4

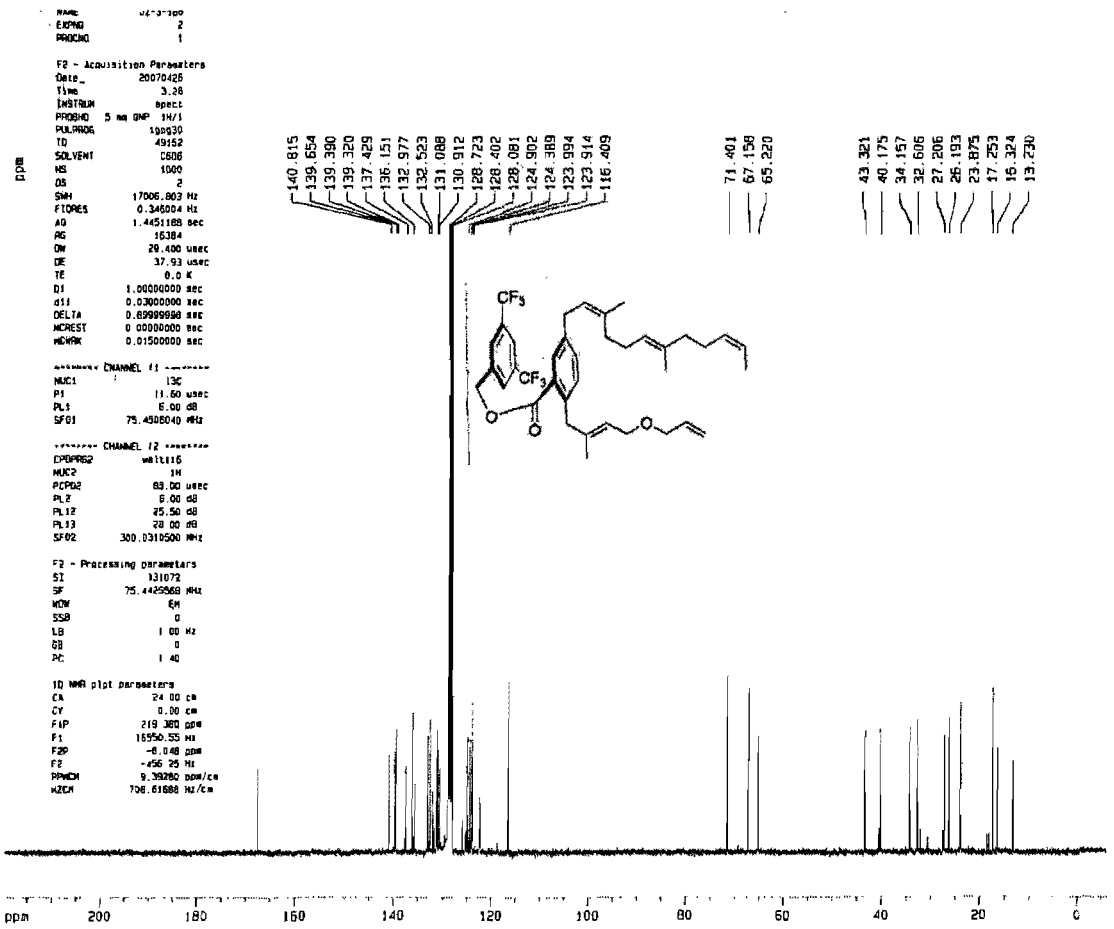
A2-51

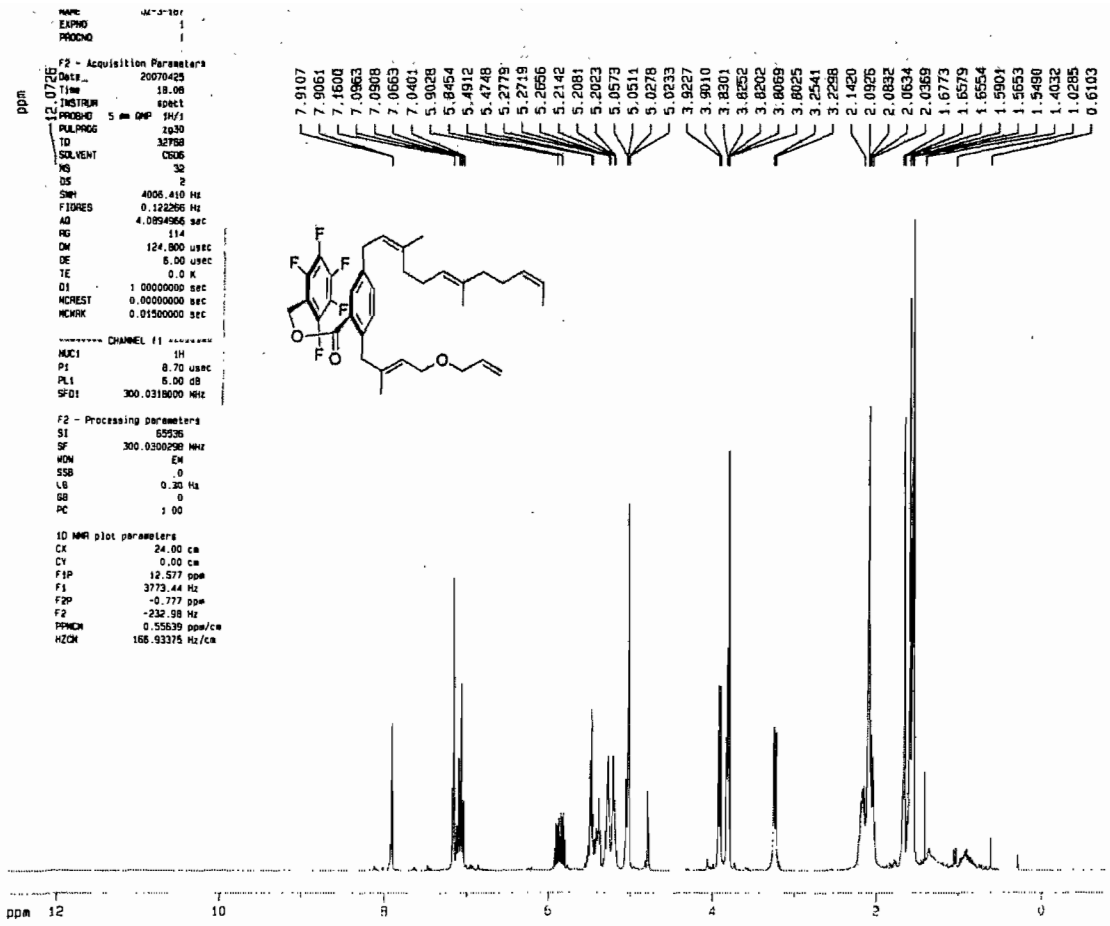


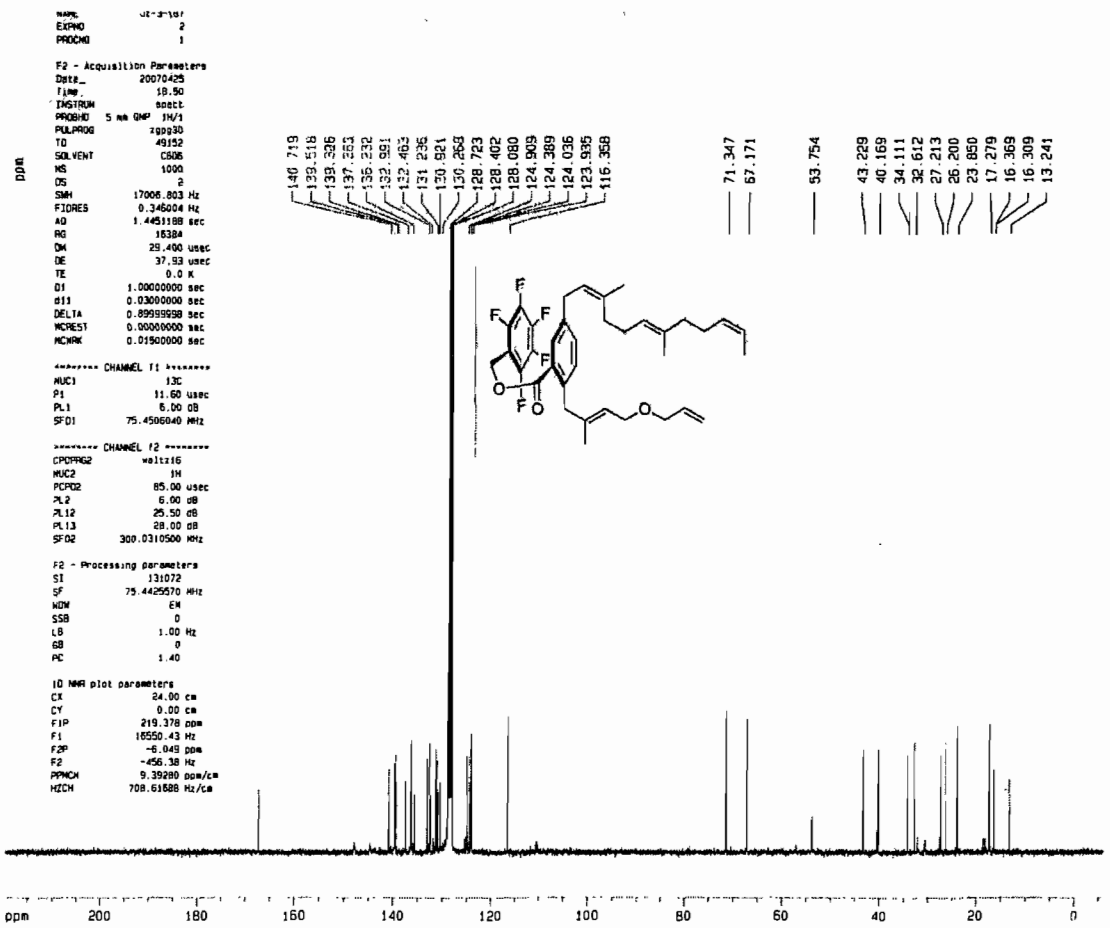
Annexe 2 : Informations supplémentaires de l'article 4

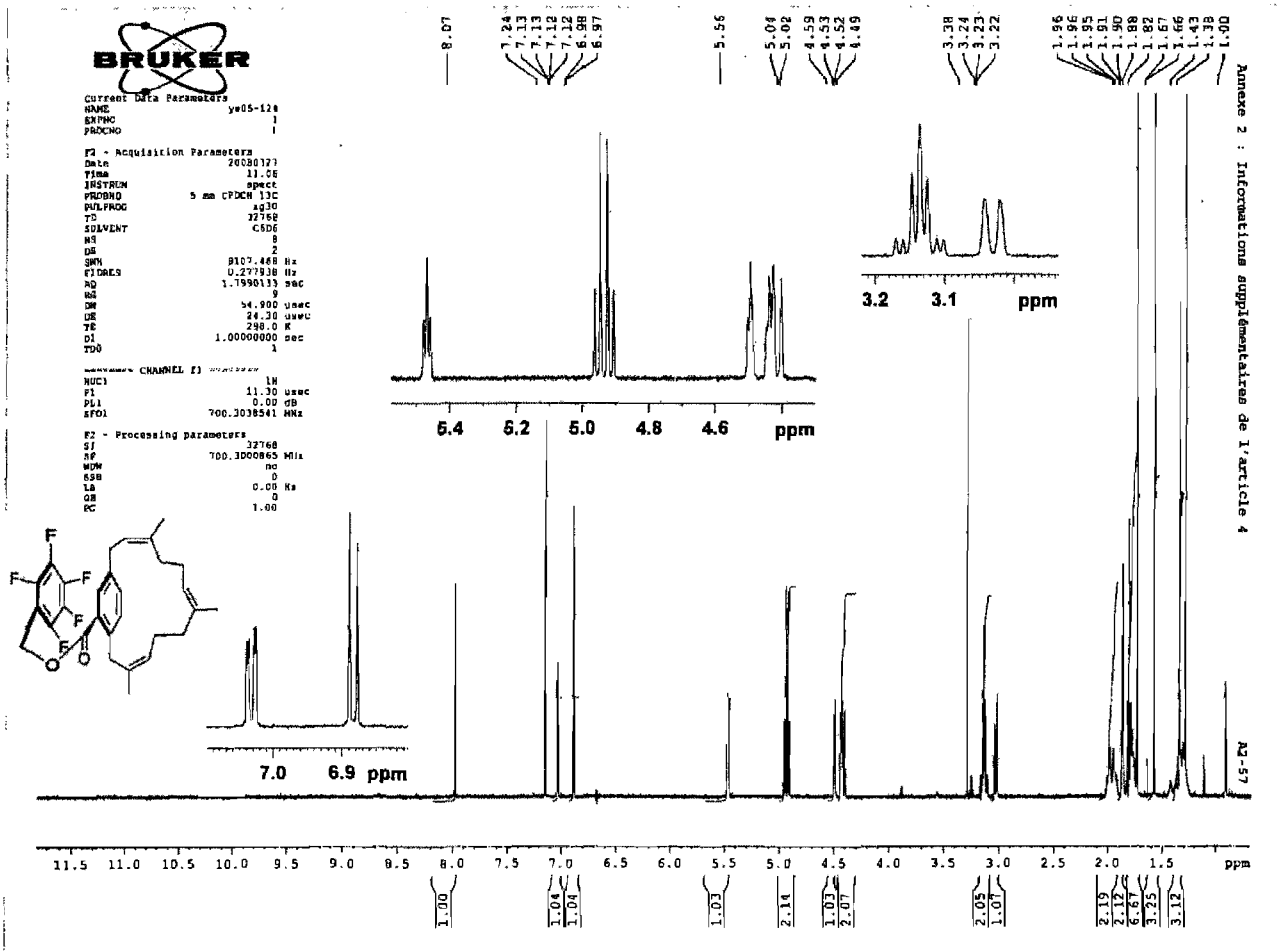
A2-52

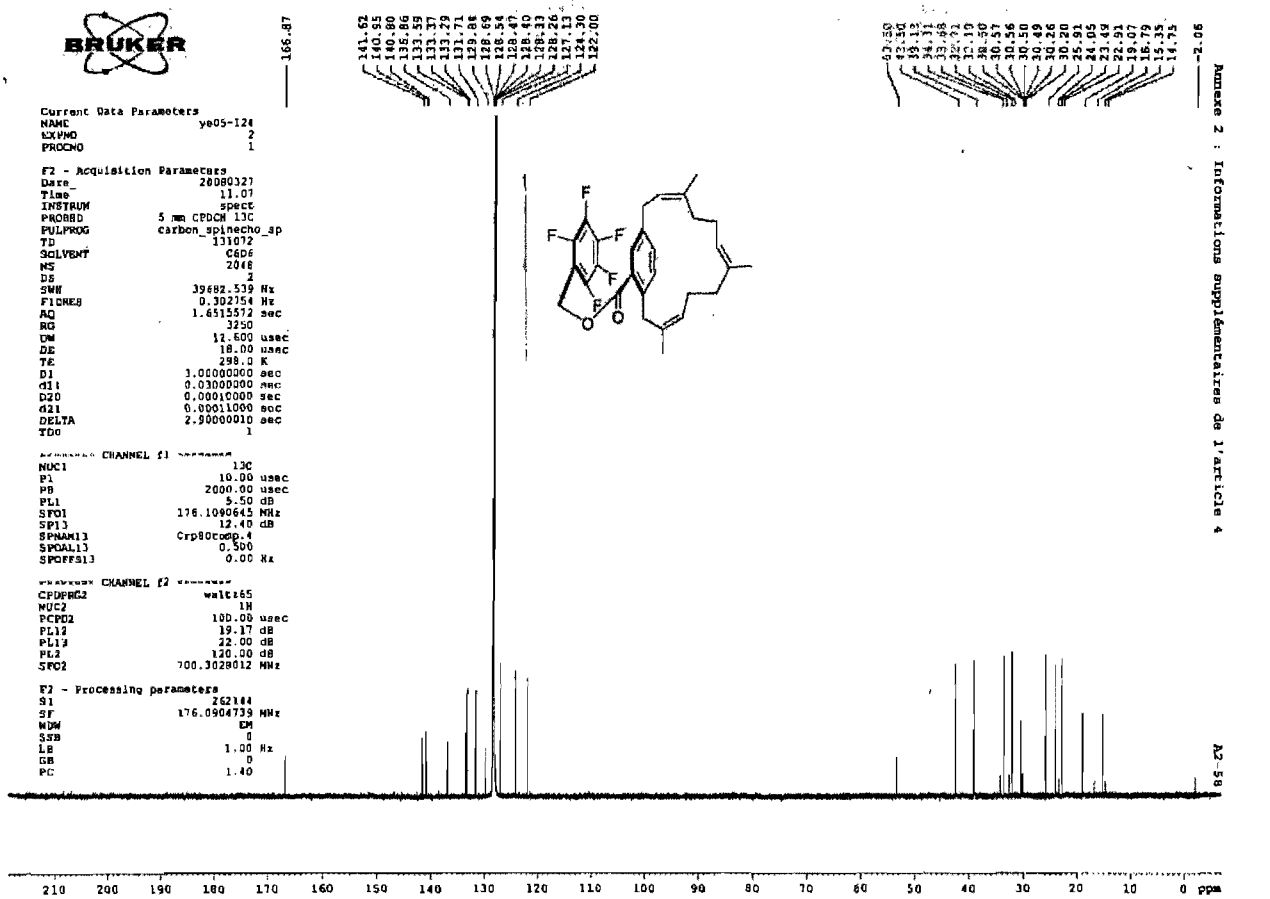

EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070426
Time 2.46
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 100
DS 2
SWH 4006.410 Hz
FIDRES 0.122266 Hz
AQ 4.0894886 sec
RG 90.5
DW 124.800 usec
DE 6.00 usec
TE 0.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 8.70 usec
PL1 0.00 dB
SFO1 300.0318000 MHz
F2 - Processing parameters
SI 65536
SF 300.0300297 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 12.577 ppm
F1 3773.50 Hz
F2P -0.776 ppm
F2 -232.91 Hz
PPMCM 0.55839 ppm/cm
HZCM 166.93373 Hz/cm
7.8895
7.8847
7.6353
7.4693
7.1600
7.1061
7.1006
7.0704
7.0442
5.4859
5.4694
5.2432
5.2371
5.1856
5.1797
5.0332
5.0269
4.8159
3.8923
3.8704
3.8054
3.8004
3.7951
3.7875
3.7830
3.2748
3.2504
2.1616
2.1567
2.1534
2.1402
2.1174
2.1072
2.0628
2.0362
1.6842
1.6813
1.5669
1.5564
1.5446
1.5432
1.4060
1.0872
0.8521
CF3
CF3
O
O
O
ppm
12
10
8
6
4
2
0


EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070426
Time 3.28
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zgpg30
TD 49152
SOLVENT CDCl3
NS 1000
DS 2
SWH 17006.803 Hz
FIDRES 0.345804 Hz
AQ 1.4451188 sec
RG 16384
DW 29.400 usec
DE 37.93 usec
TE 0.0 K
D1 1.00000000 sec
d11 0.03000000 sec
DELTA 0.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 11.60 usec
PL1 6.00 dB
SFO1 75.4508040 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 68.00 usec
PL2 6.00 dB
PL12 25.50 dB
PL13 28.00 dB
SFO2 300.0310500 MHz
F2 - Processing parameters
SI 131072
SF 75.4425568 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 219.380 ppm
F1 16550.55 Hz
F2P -8.048 ppm
F2 -456.25 Hz
PPMCM 9.39280 ppm/cm
HZCM 708.61688 Hz/cm
140.815
139.654
139.390
139.320
137.429
136.151
132.977
132.523
131.088
130.912
128.723
128.402
128.081
124.902
124.389
123.994
123.914
116.409
71.401
67.156
65.220
43.321
40.175
34.157
32.606
27.206
26.193
23.873
17.253
15.324
13.730
CF3
CF3
O
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0

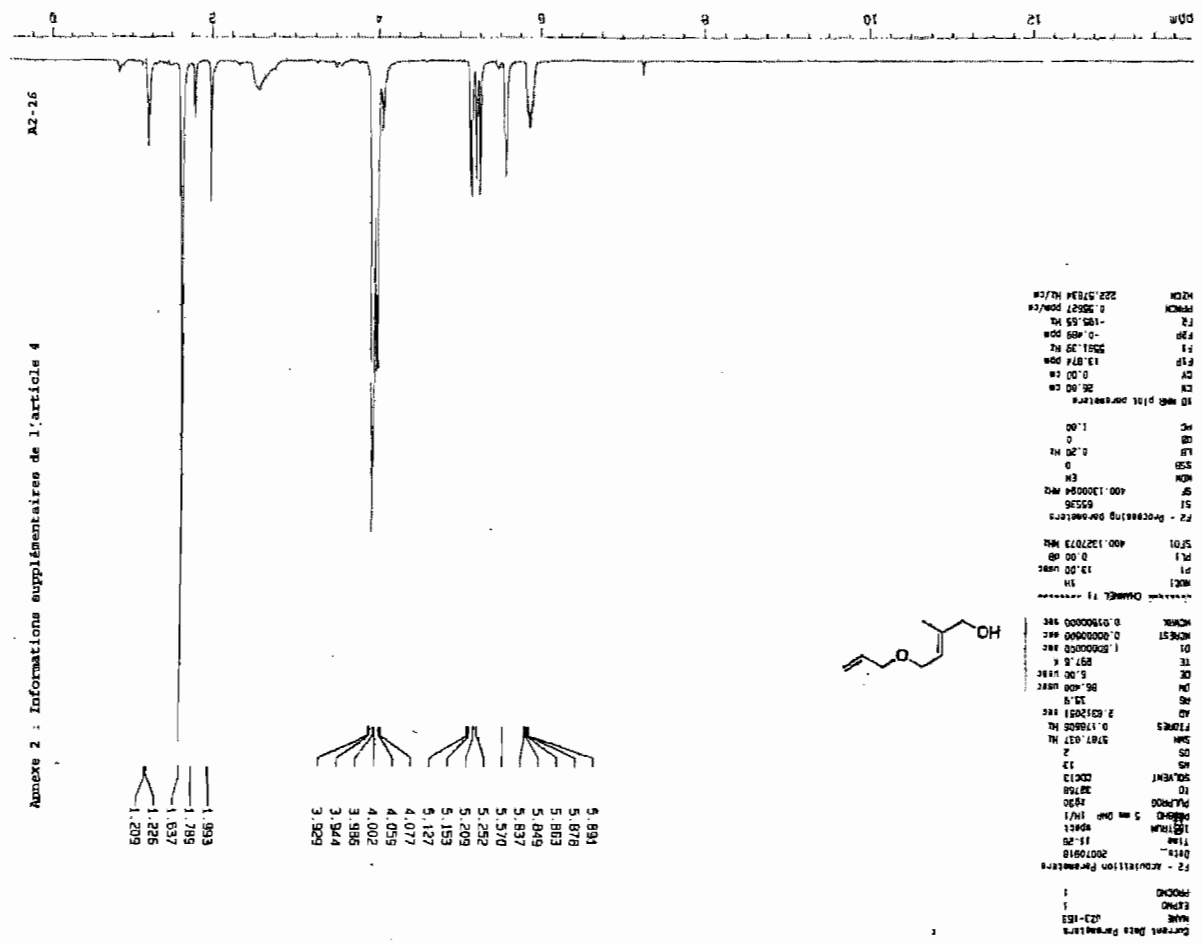

NAME
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070425
Time 18.08
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 4006.410 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 114
DW 124.800 usec
DE 6.00 usec
TE 0.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 8.70 usec
PL1 0.00 dB
SFO1 300.0318000 MHz
F2 - Processing parameters
SI 65536
SF 300.0300298 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 12.577 ppm
F1 3773.44 Hz
F2P -0.777 ppm
F2 -232.98 Hz
PPMCM 0.55639 ppm/cm
HZCM 166.93375 Hz/cm
12.0726
7.9107
7.9061
7.1600
7.0963
7.0908
7.0663
7.0401
5.9028
5.8454
5.4912
5.4748
5.2779
5.2719
5.2656
5.2142
5.2081
5.2023
5.0573
5.0511
5.0278
5.0233
3.9227
3.9010
3.8301
3.8252
3.8202
3.8069
3.8025
3.2541
3.2298
2.1420
2.0926
2.0832
2.0634
2.0369
1.6773
1.6579
1.6554
1.5901
1.5653
1.5490
1.4032
1.0285
0.6103
ppm
12
10
8
6
4
2
0

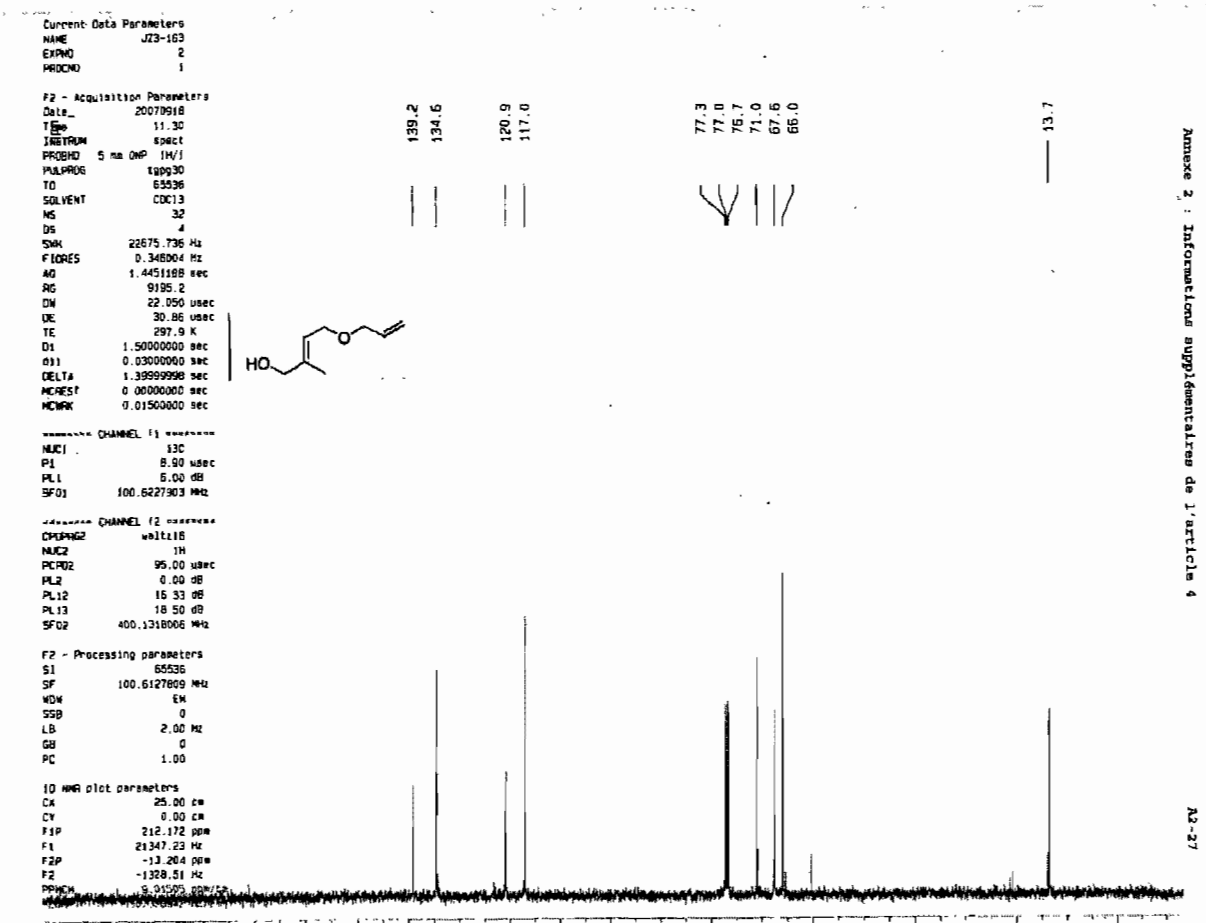

NAME
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070425
Time 18.50
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 49152
SOLVENT CDCl3
NS 1000
DS 2
SWH 17006.803 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 16384
DW 29.400 usec
DE 37.93 usec
TE 0.0 K
D1 1.00000000 sec
d11 0.03000000 sec
DELTA 0.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 11.60 usec
PL1 6.00 dB
SFO1 75.4506040 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 85.00 usec
PL2 6.00 dB
PL12 25.50 dB
PL13 28.00 dB
SFO2 300.0310500 MHz
F2 - Processing parameters
SI 131072
SF 75.4425570 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 219.378 ppm
F1 16550.43 Hz
F2P -6.049 ppm
F2 -456.38 Hz
PPMCM 9.39280 ppm/cm
HZCM 708.61688 Hz/cm
146.719
139.518
139.336
137.253
136.232
132.991
132.463
131.236
130.921
130.269
128.723
128.402
128.080
124.909
124.389
124.036
123.935
116.358
71.347
67.171
53.754
43.229
40.169
34.111
32.612
27.213
26.200
23.850
17.279
16.369
16.309
13.241
ppm
200
180
160
140
120
100
80
60
40
20
0


Current Data Parameters
NAME ye05-12a
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080327
Time 11.06
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 8
DS 2
SWH 8107.468 Hz
FIDRES 0.247938 Hz
AQ 1.7990133 sec
RG 9
DW 54.900 usec
DE 24.30 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.30 usec
PL1 0.00 dB
SFO1 700.3038541 MHz
F2 - Processing parameters
SI 32768
SF 700.3000065 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.07
7.24
7.13
7.13
7.12
6.98
6.97
5.56
5.04
5.02
4.59
4.53
4.52
4.49
3.38
3.24
3.23
3.22
1.96
1.96
1.95
1.91
1.90
1.88
1.82
1.67
1.66
1.43
1.38
1.00
5.4 5.2 5.0 4.8 4.6 ppm
3.2 3.1 ppm
7.0 6.9 ppm
Annexe 2 : Informations supplémentaires de l'article 4
A2-57
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00
1.04
1.04
1.03
2.14
1.03
2.07
2.05
1.07
2.19
2.12
6.67
3.25
3.12


166.87
141.62
140.95
140.80
136.86
133.55
133.35
133.29
131.71
129.86
128.69
128.54
128.47
128.40
128.33
128.26
127.13
124.30
122.00
63.50
63.50
33.13
34.31
33.68
32.71
32.19
30.80
30.57
30.56
30.50
30.49
30.26
30.20
25.91
24.65
22.54
22.31
19.07
18.79
15.35
14.75
2.06
Current Data Parameters
NAME ye05-12a
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080327
Time 11.07
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG carbon_spinecho_dp
TD 131072
SOLVENT C6D6
NS 2048
DS 2
SWH 39682.539 Hz
FIDRES 0.302754 Hz
AQ 1.6515572 sec
RG 3250
DW 12.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
d11 0.03000000 sec
D20 0.00010000 sec
d21 0.00011000 sec
DELTA 2.90000010 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 10.00 usec
PB 2000.00 usec
PL1 5.50 dB
SFO1 176.1090645 MHz
SPL3 12.40 dB
SPNAM13 Crp80comp.4
SPOAL13 0.500
SPOFFS13 0.00 Hz
CHANNEL f2
CPDPRG2 waltz65
NUC2 1H
PCPD2 100.00 usec
PL12 19.17 dB
PL13 22.00 dB
PL2 120.00 dB
SFO2 700.3028012 MHz
F2 - Processing parameters
SI 262144
SF 176.0904739 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Annexe 2 : Informations supplémentaires de l'article 4
A2-58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

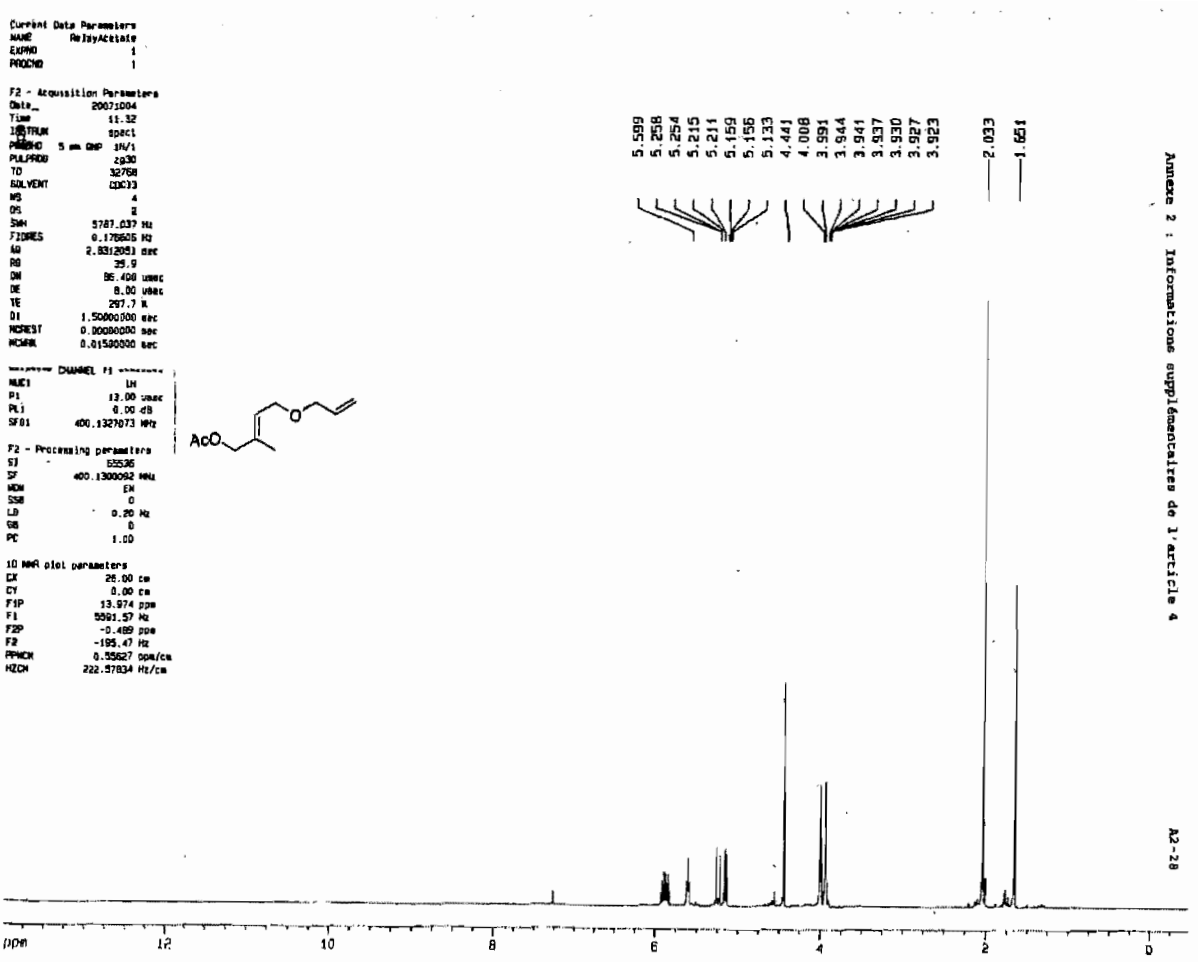
Annexe 2 : Informations supplémentaires de l'article 4

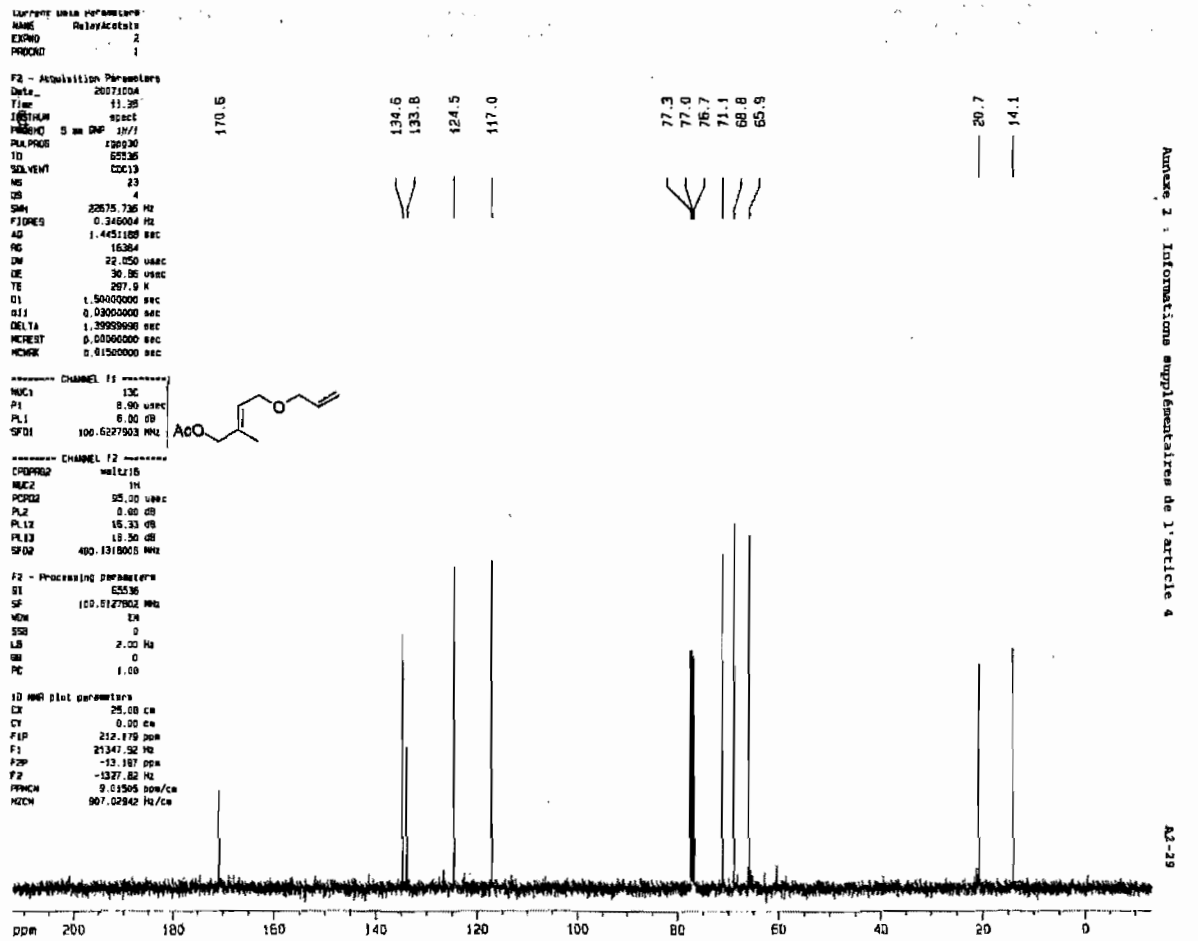




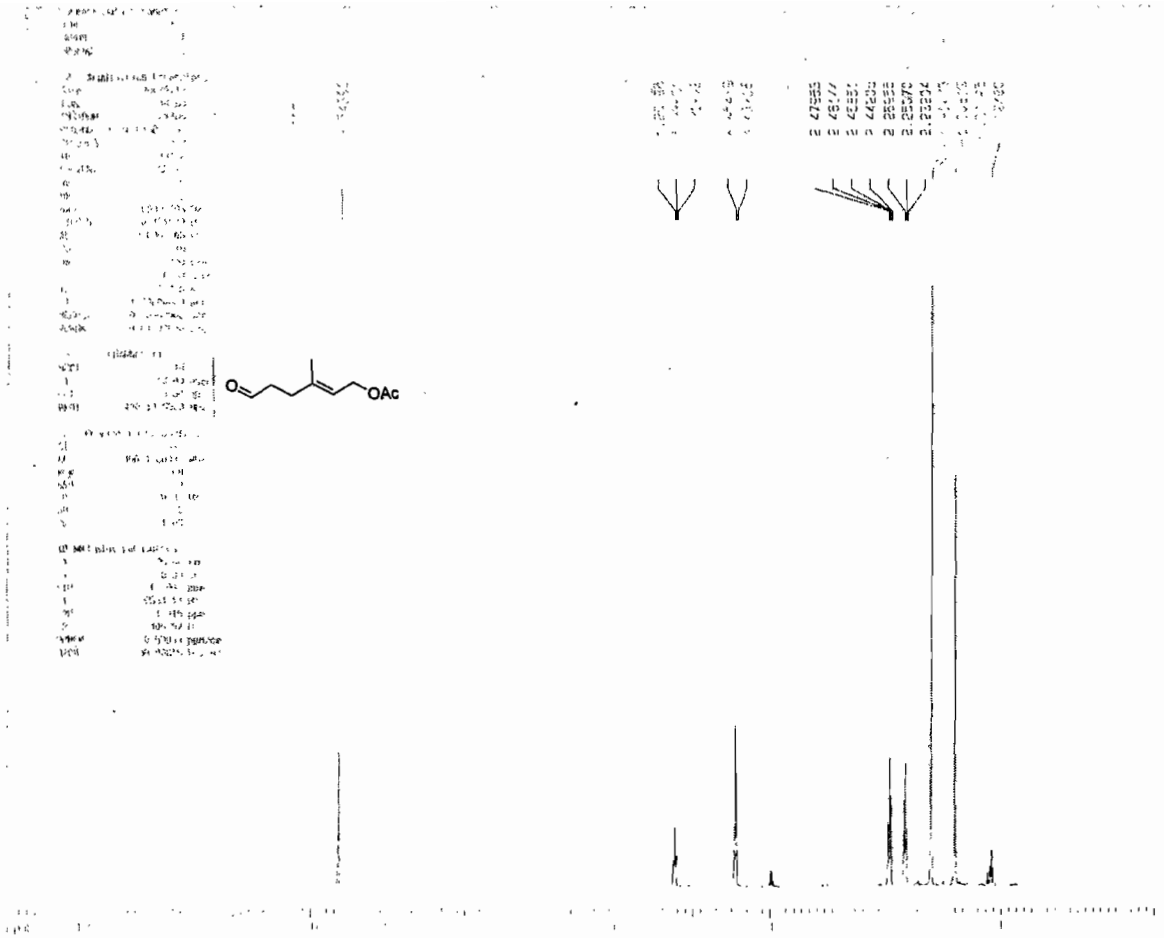
Annexe 2 : Informations supplémentaires de l'article 4

A2-27

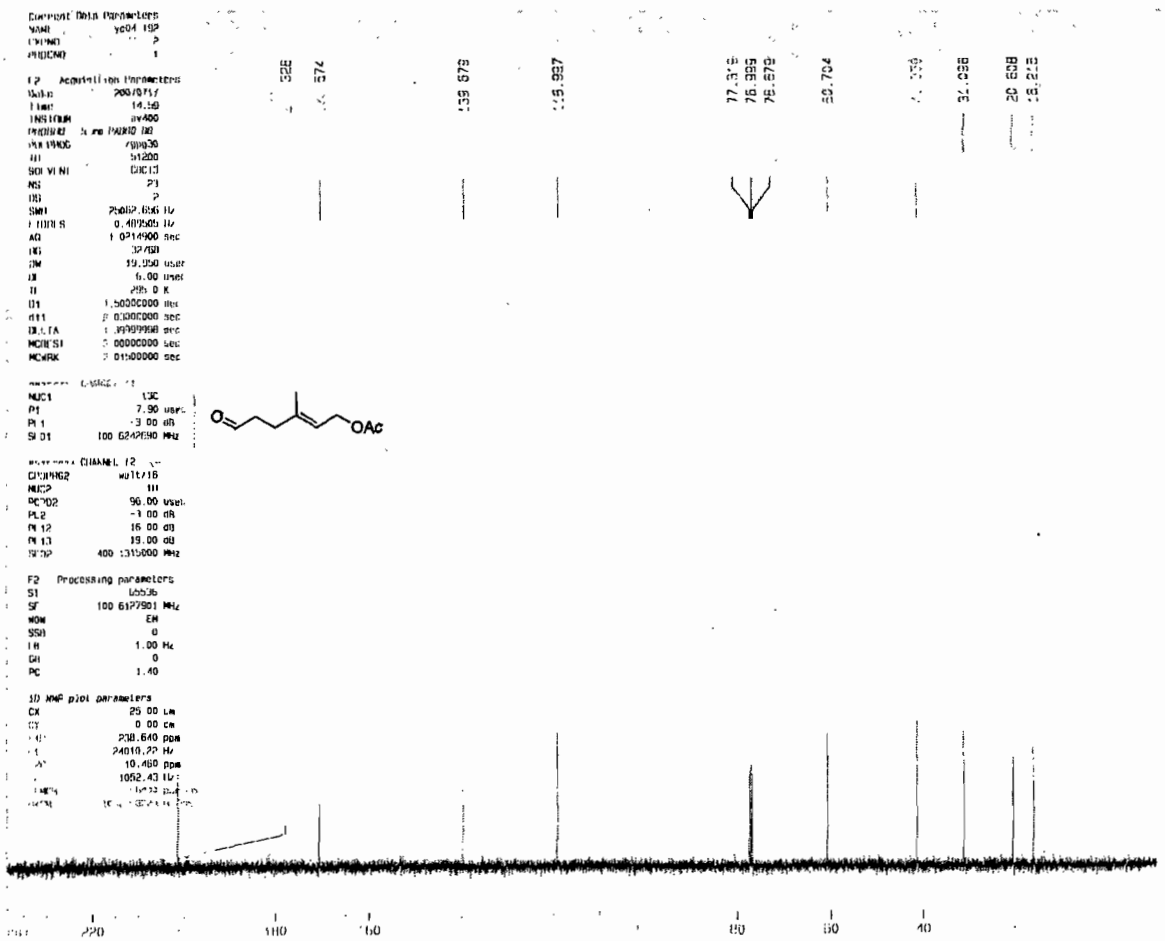




Annexe 2 : Informations supplémentaires de l'article 4



A2-30



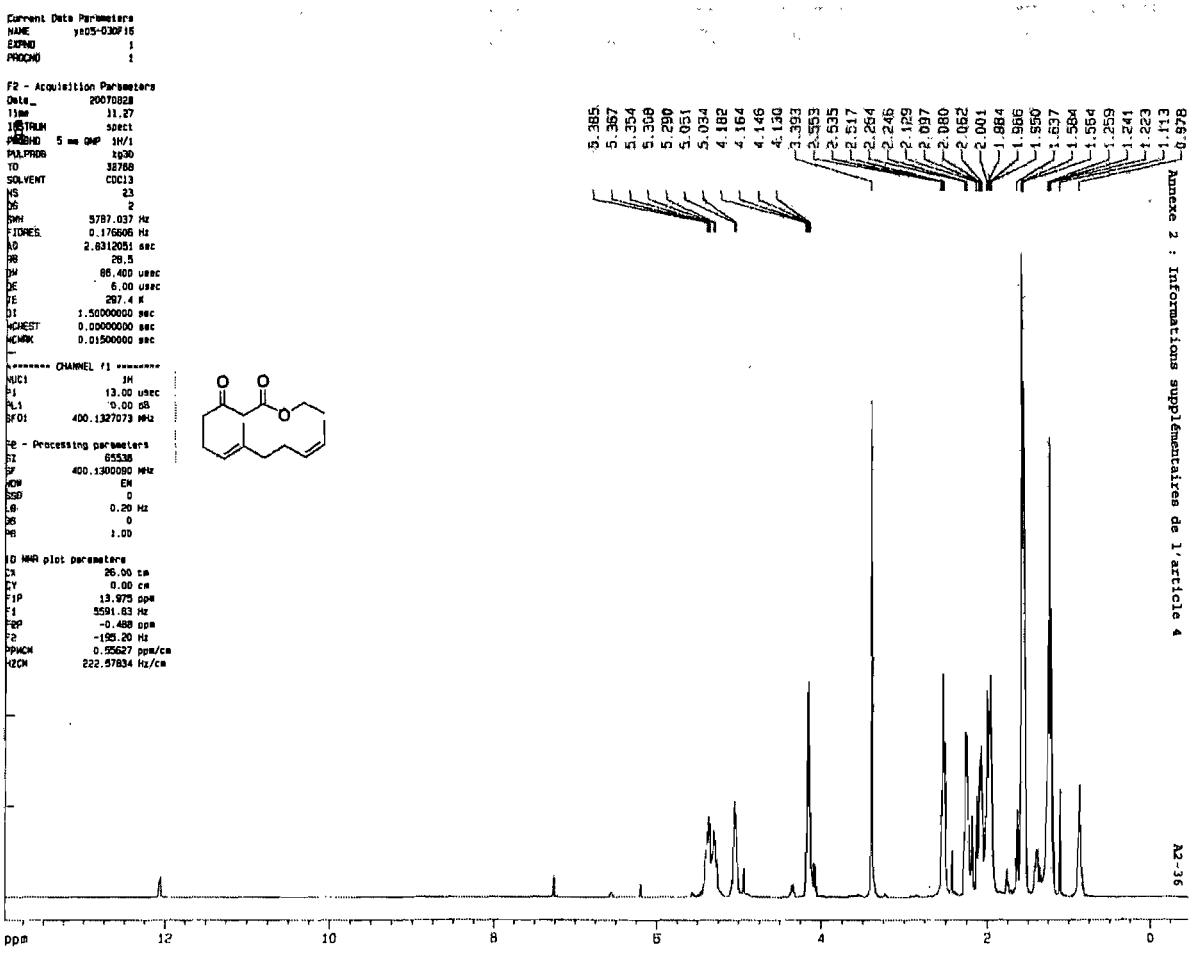
A2-31

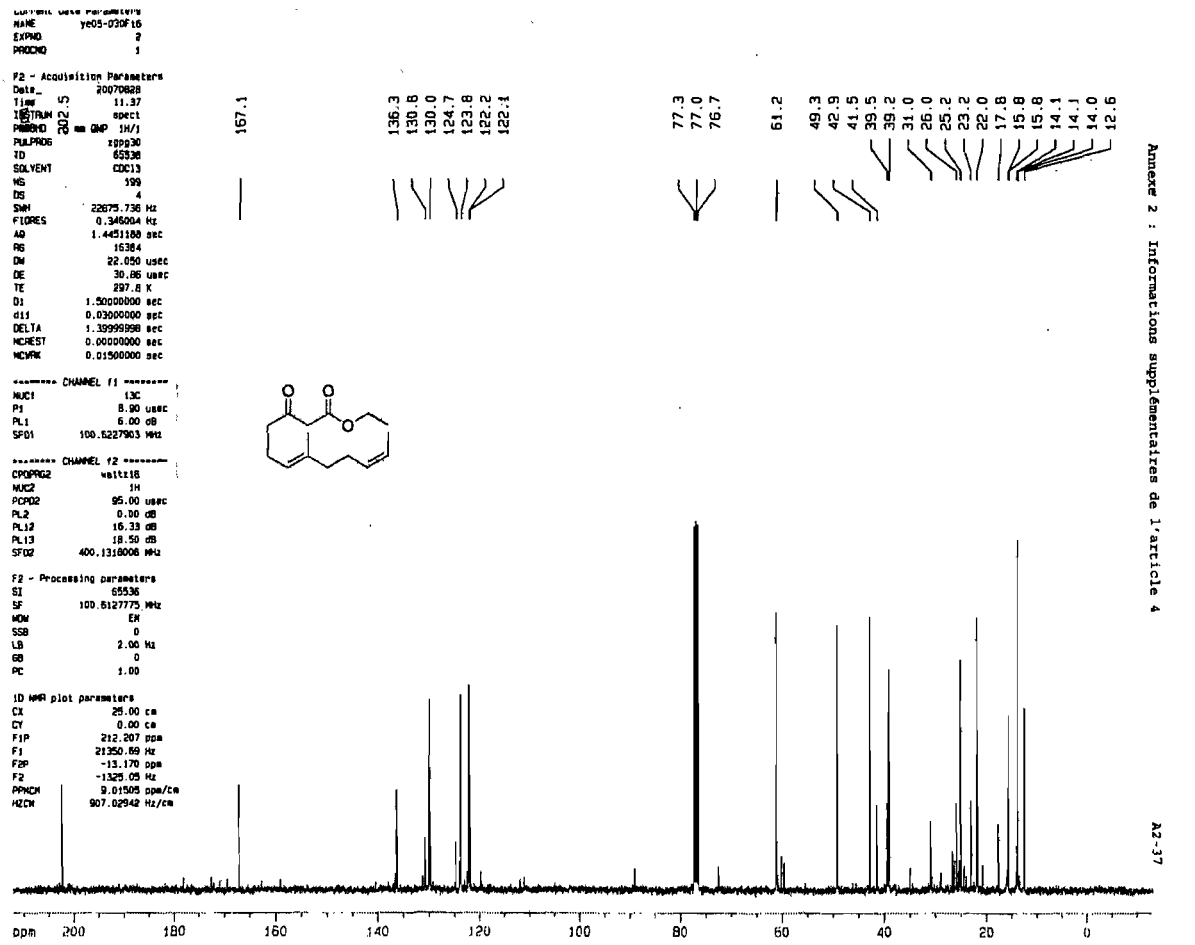
Annexe 2 : Informations supplémentaires de l'article 4

A2-32

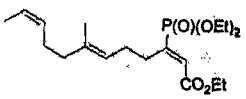
Annexe 2 : Informations supplémentaires de l'article 4

A2-33

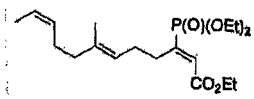

Current Data Parameters
NAME ye05-030F16
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070828
Time 11.27
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 23
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 28.5
DW 86.400 usec
DE 6.00 usec
TE 297.4 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300090 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.975 ppm
F1 5591.63 Hz
F2P -0.488 ppm
F2 -195.20 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
5.385
5.367
5.354
5.308
5.290
5.051
5.034
4.182
4.164
4.146
4.130
3.393
2.553
2.535
2.517
2.254
2.246
2.129
2.097
2.080
2.062
2.001
1.984
1.966
1.950
1.637
1.584
1.564
1.259
1.241
1.223
1.113
0.878
Annexe 2 : Informations supplémentaires de l'article 4
A2-36
ppm
12
10
8
6
4
2
0


Current Data Parameters
NAME ye05-030F16
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070828
Time 11.37
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 199
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4451188 sec
RG 16384
DW 22.050 usec
DE 30.86 usec
TE 297.8 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318008 MHz
F2 - Processing parameters
SI 65536
SF 100.6127775 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.207 ppm
F1 21350.69 Hz
F2P -13.170 ppm
F2 -1325.05 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02942 Hz/cm
167.1
136.3
130.8
130.0
124.7
123.8
122.2
122.1
77.3
77.0
76.7
61.2
49.3
42.9
41.5
39.5
39.2
31.0
26.0
25.2
23.2
22.0
17.8
15.8
15.8
14.1
14.1
14.0
12.6
Annexe 2 : Informations supplémentaires de l'article 4
A2-37
ppm
200
180
160
140
120
100
80
60
40
20
0

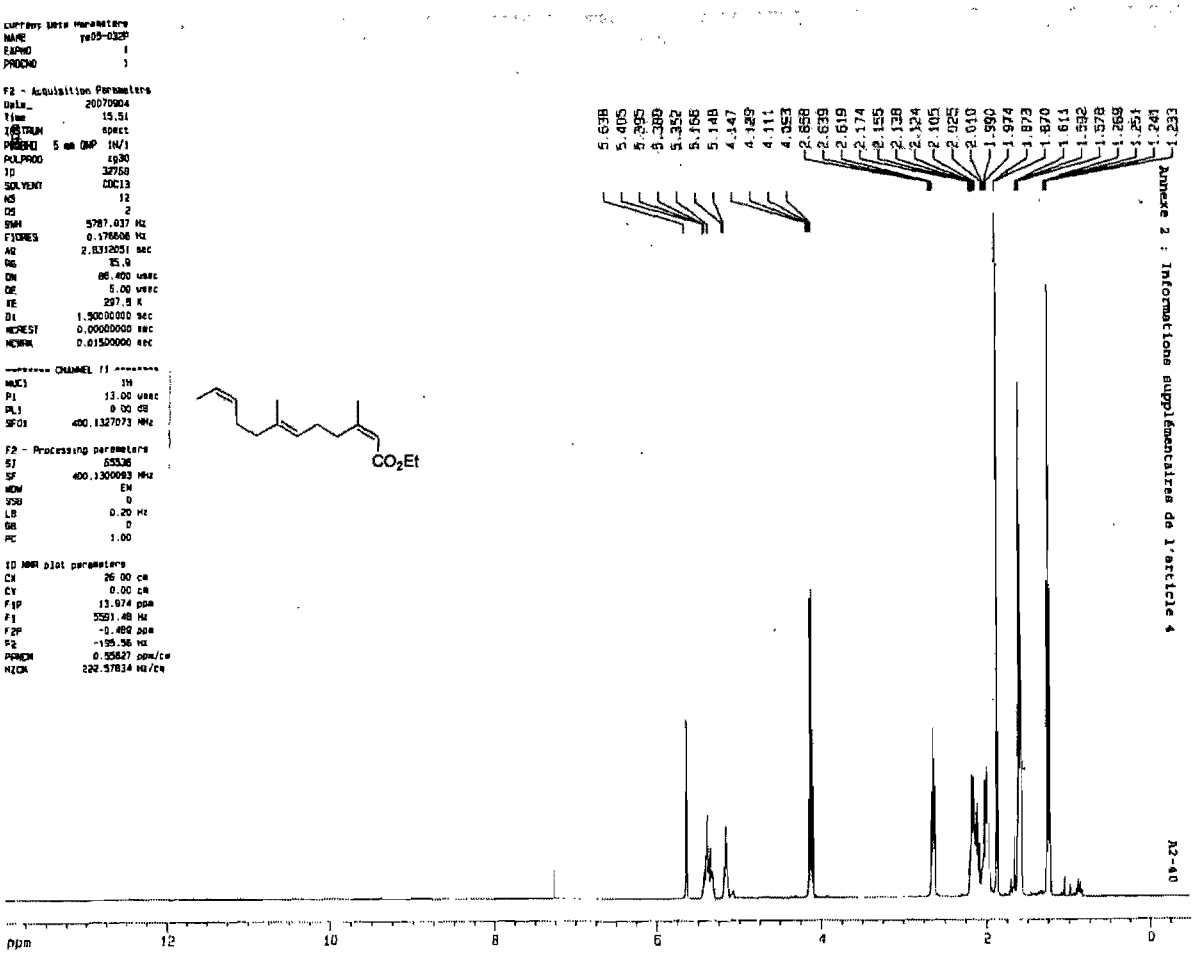
```
Current Data Parameters
NAME            ya05-031
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20070829
Time              16.57
INSTRUM           spect
PROBHD  5 mm QNP  1H/1
PULPROG           zg30
TD               32768
SOLVENT           CDCl3
NS                  13
DS                   2
SWH           5787.037 Hz
FIDRES        0.176606 Hz
AQ            2.8312051 sec
RG                20.2
DW               86.400 usec
DE                6.00 usec
TE              297.4 K
D1            1.50000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                13.00 usec
PL1                0.00 dB
SFO1        400.1327073 MHz

F2 - Processing parameters
SI                 65536
SF          400.1300091 MHz
WDW                   EM
SSB                    0
LB                0.20 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                26.00 cm
CY                 0.00 cm
F1P              13.975 ppm
F1              5591.74 Hz
F2P              -0.488 ppm
F2              -195.29 Hz
PPMCM            0.55827 ppm/cm
HZCM          222.57834 Hz/cm
```

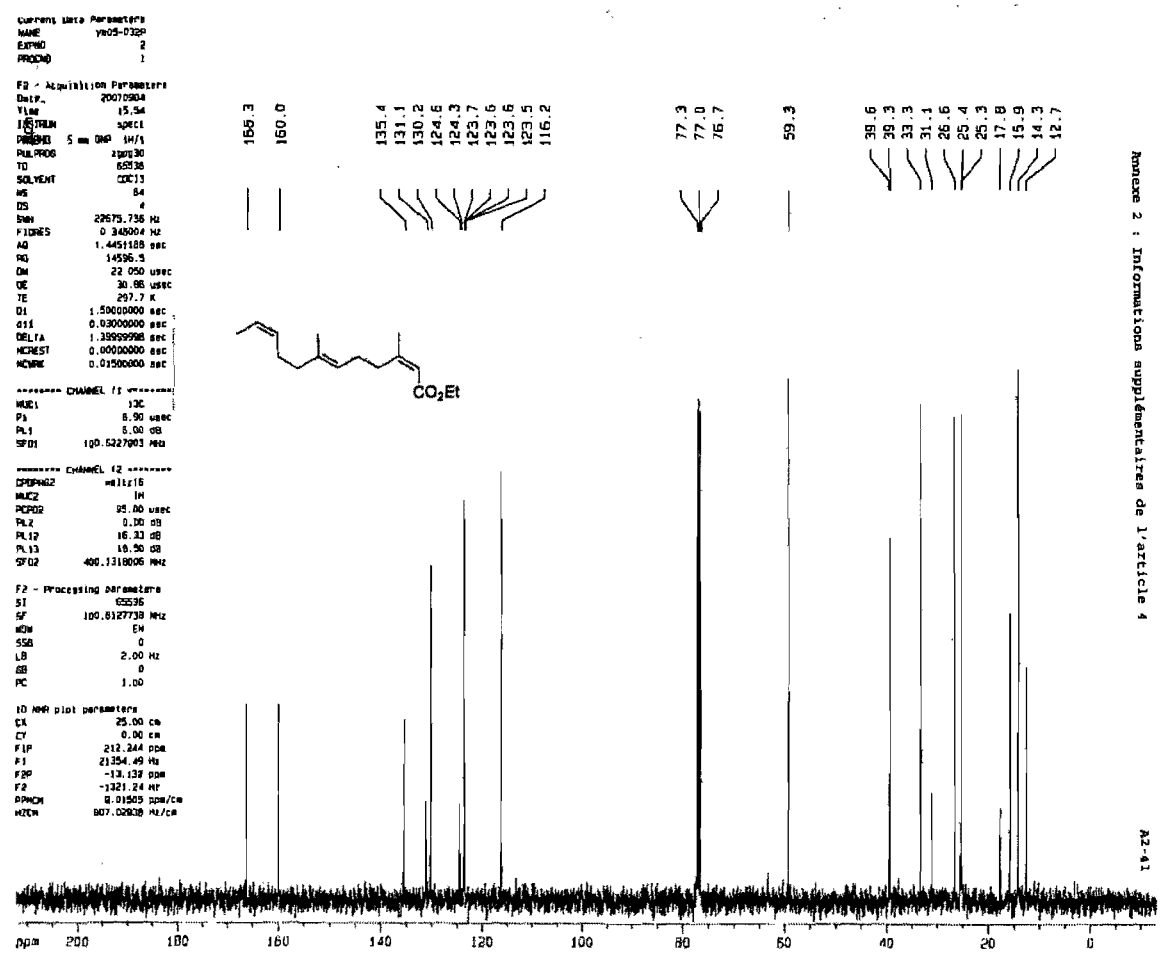


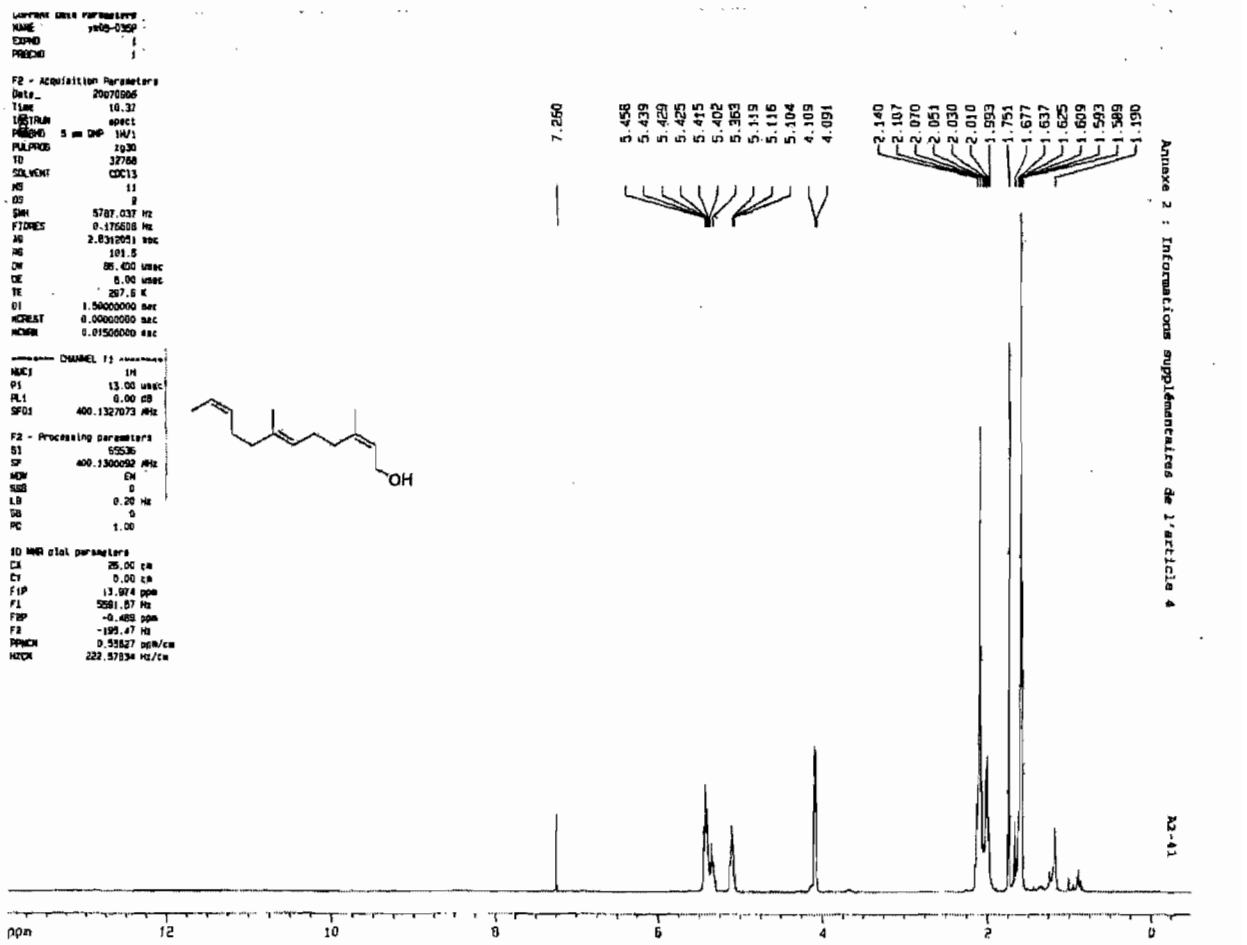

```
Current Data Parameters
NAME            ya05-031
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20070829
Time              17.01
INSTRUM           spect
PROBHD  5 mm QNP  1H/1
PULPROG           zgpg30
TD               65536
SOLVENT           CDCl3
NS                   90
DS                    4
SWH           22675.736 Hz
FIDRES        0.346004 Hz
AQ            1.4451186 sec
RG               14596.5
DW               22.050 usec
DE                30.86 usec
TE              297.6 K
D1            1.50000000 sec
d11           0.03000000 sec
DELTA         1.39999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                8.90 usec
PL1                6.00 dB
SFO1        100.6227903 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             95.00 usec
PL2                0.00 dB
PL12              16.33 dB
PL13              18.50 dB
SFO2        400.1319006 MHz

F2 - Processing parameters
SI                 65536
SF          100.6127851 MHz
WDW                   EM
SSB                    0
LB                2.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                25.00 cm
CY                 0.00 cm
F1P             212.131 ppm
F1              21343.08 Hz
F2P             -13.245 ppm
F2              -1332.66 Hz
PPMCM            9.01505 ppm/cm
HZCM          907.02942 Hz/cm
```

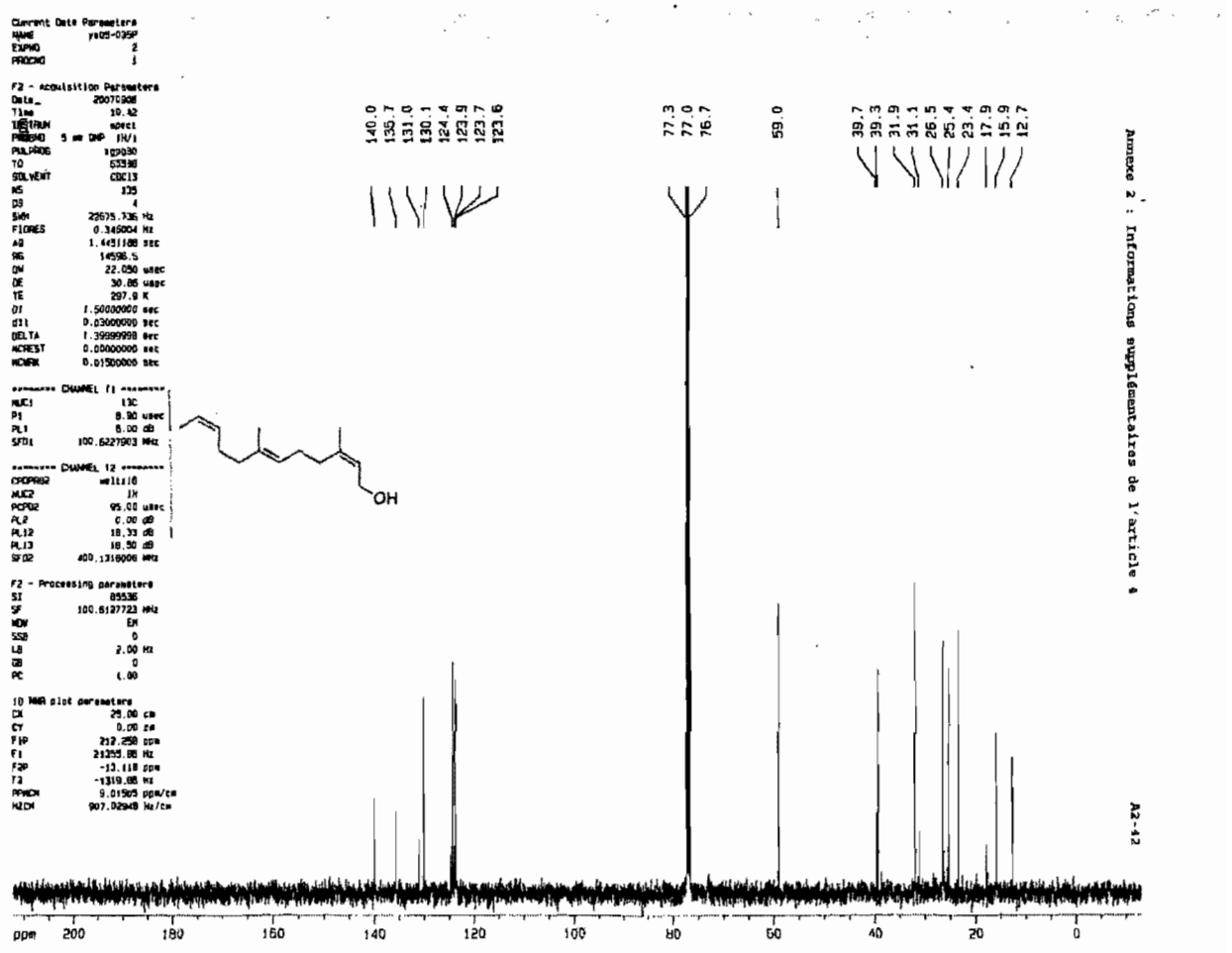


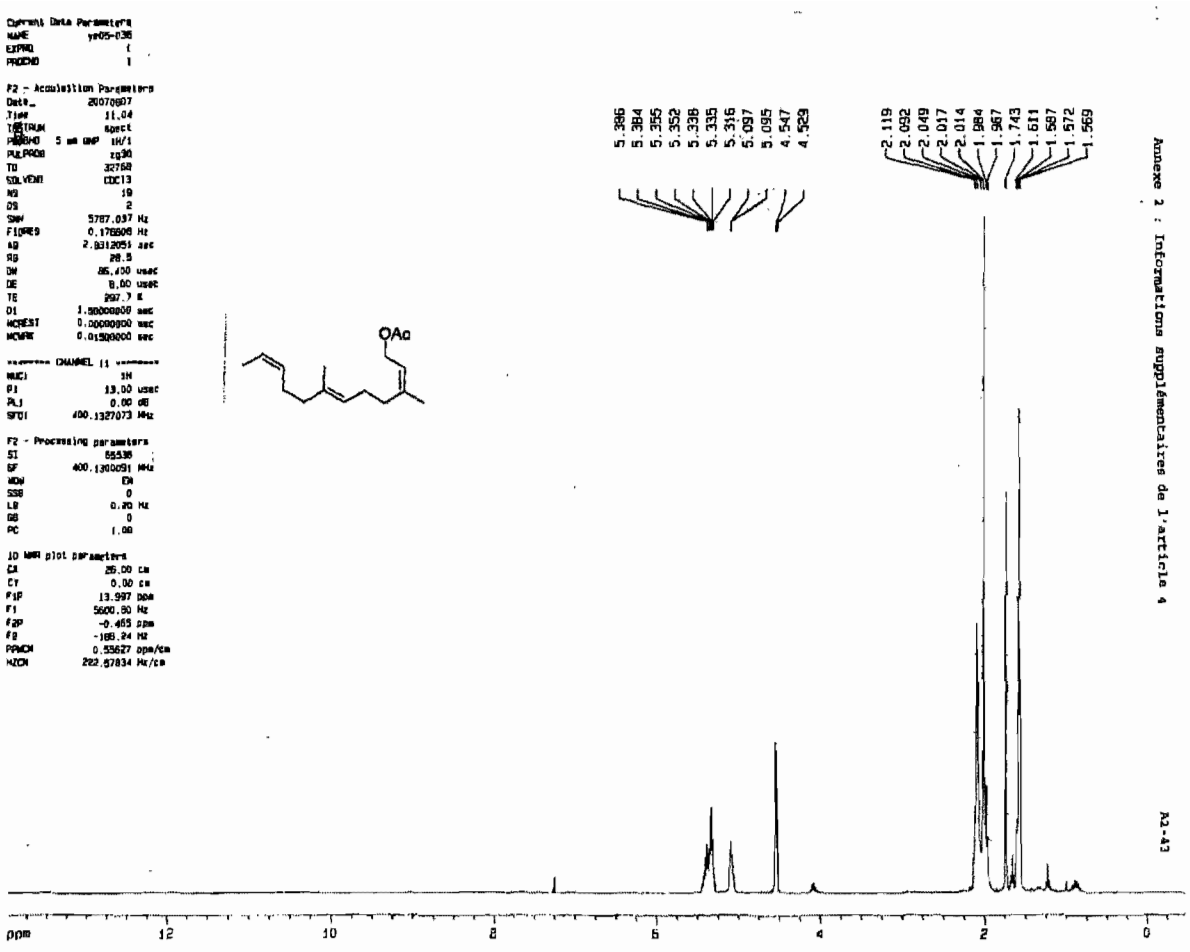
Annexe 2 : Informations supplémentaires de l'article 4

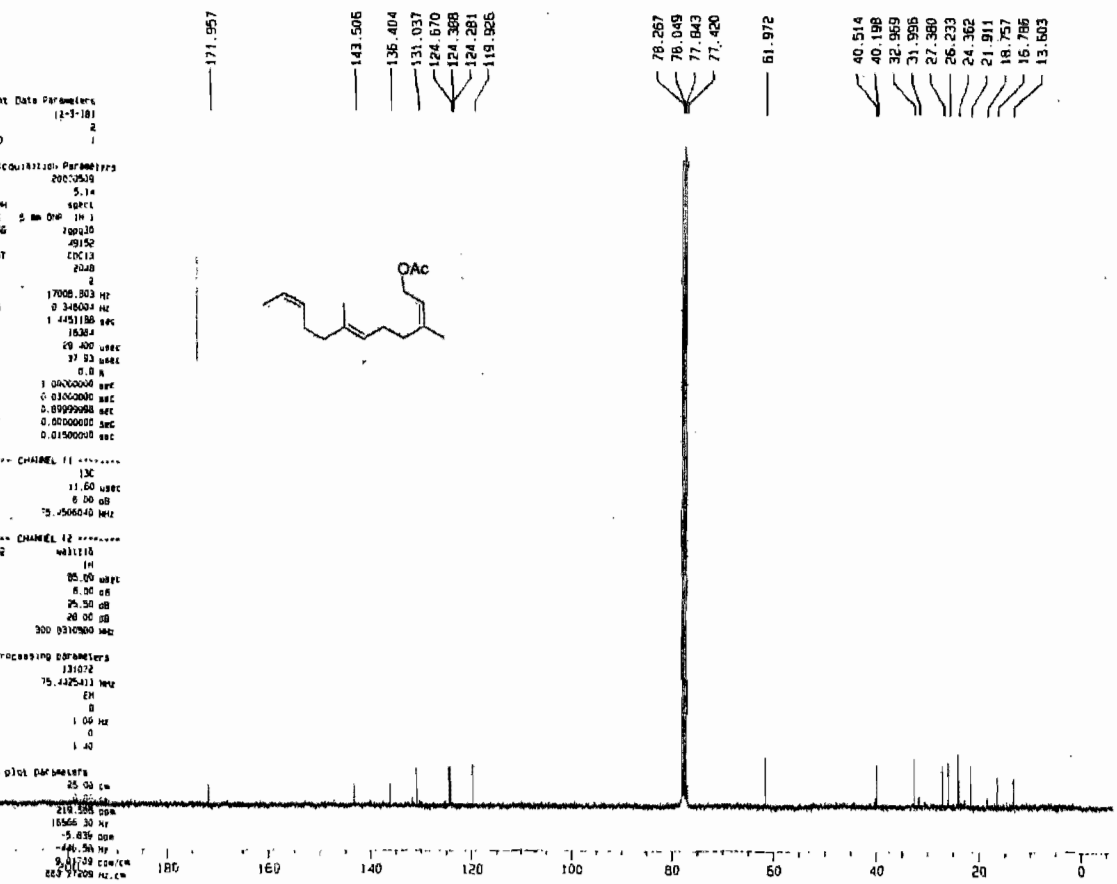

Annexe 2 : Informations supplémentaires de l'article 4
A2-40
ppm

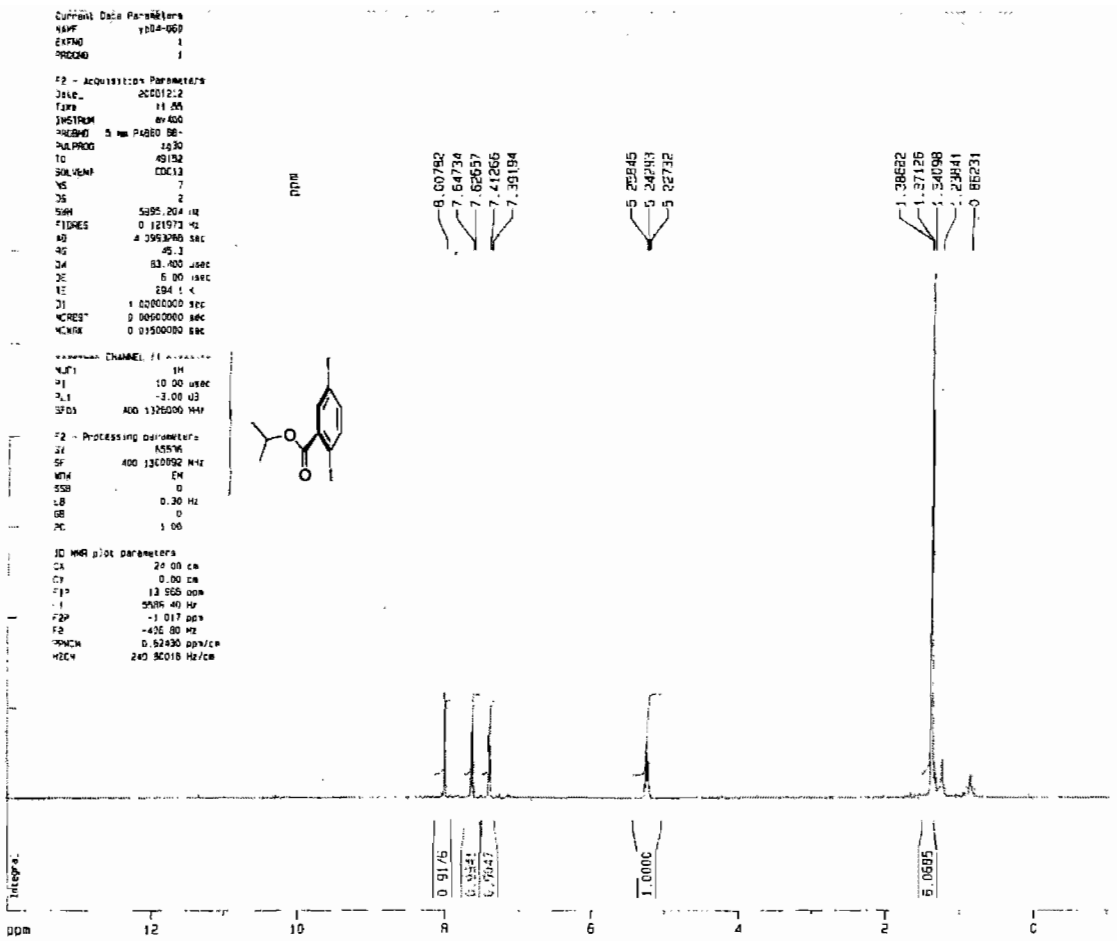

Annexe 2 : Informations supplémentaires de l'article 4
A2-41
ppm

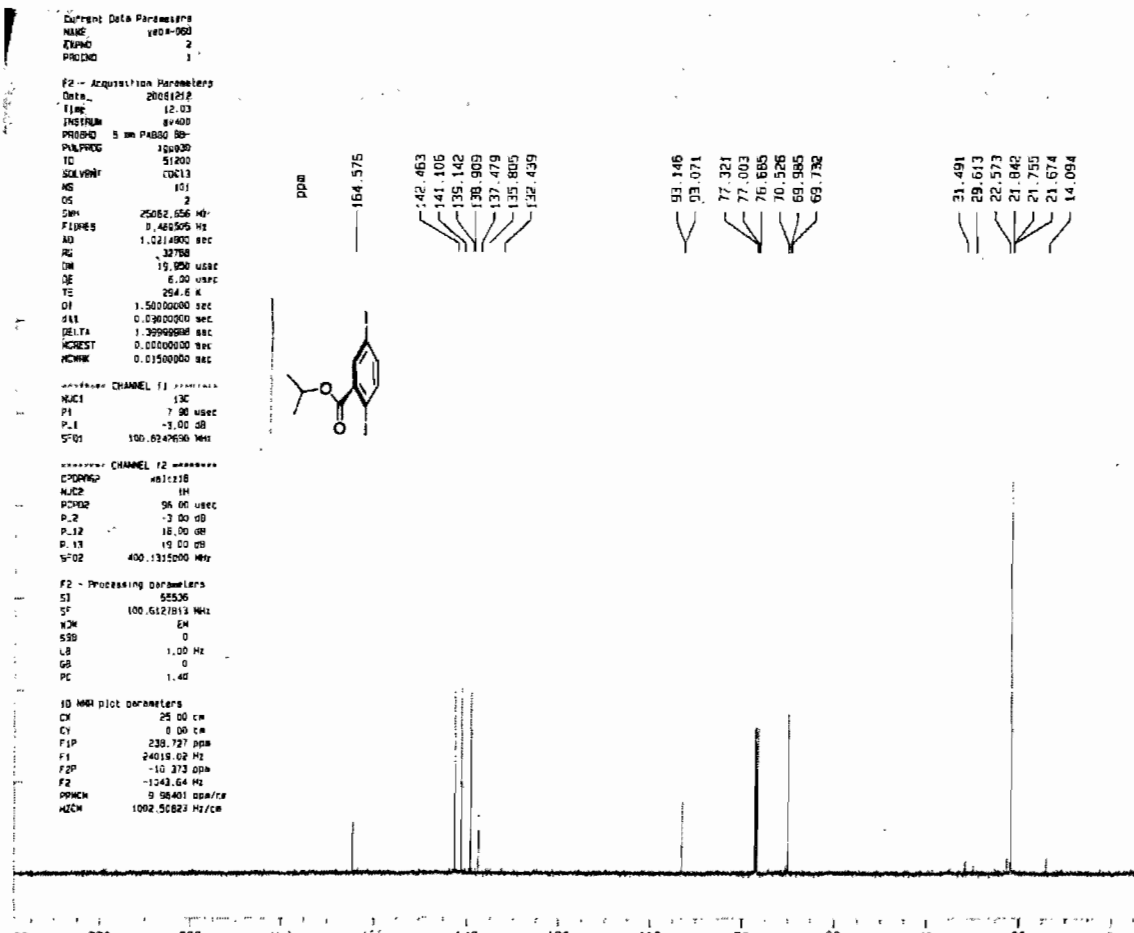

Current Data Parameters
NAME ya05-035P
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070906
Time 10.37
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 11
DS 2
SWH 5787.037 Hz
FIDRES 0.176608 Hz
AQ 2.8312051 sec
RG 101.5
DW 86.400 usec
DE 6.00 usec
TE 297.6 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300092 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.974 ppm
F1 5591.87 Hz
F2P -0.488 ppm
F2 -195.47 Hz
PPMCM 0.55827 ppm/cm
HZCM 222.57834 Hz/cm
7.250
5.458
5.439
5.429
5.425
5.415
5.402
5.363
5.119
5.116
5.104
4.109
4.091
2.140
2.107
2.070
2.051
2.030
2.010
1.993
1.751
1.677
1.637
1.625
1.609
1.593
1.589
1.510
OH
Annexe 2 : Informations supplémentaires de l'article 4
A2-41
ppm
12
10
8
6
4
2
0

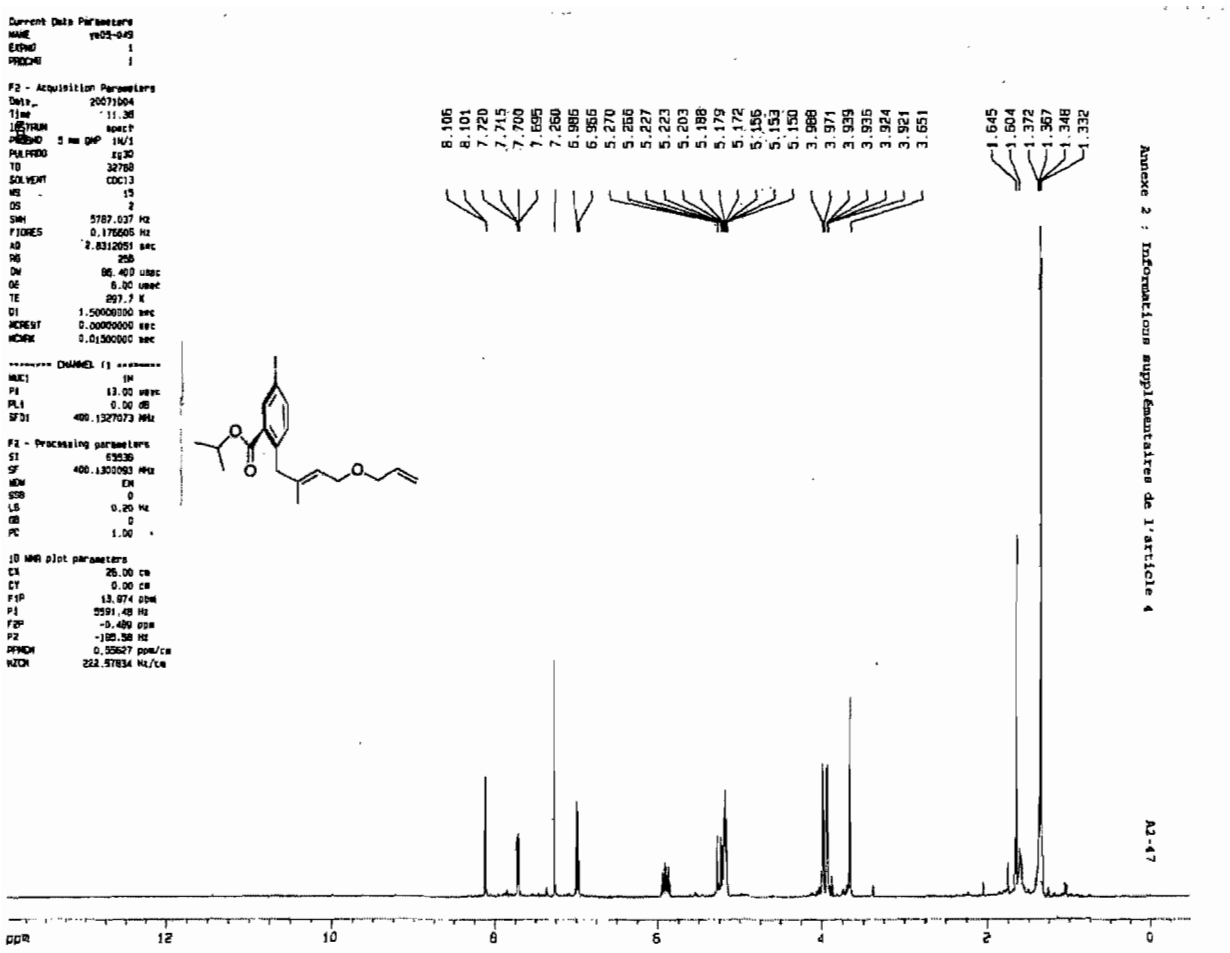

Current Data Parameters
NAME ya05-035P
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070908
Time 10.42
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 105
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4451188 sec
RG 14596.5
DW 22.050 usec
DE 30.86 usec
TE 297.0 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 18.33 dB
PL13 18.50 dB
SFO2 400.1318008 MHz
F2 - Processing parameters
SI 65536
SF 100.6127723 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.258 ppm
F1 21355.88 Hz
F2P -13.118 ppm
F2 -1319.88 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02948 Hz/cm
140.0
135.7
131.0
130.1
124.4
123.9
123.7
123.6
77.3
77.0
76.7
59.0
39.7
39.3
31.9
31.1
26.5
25.4
23.4
17.9
15.9
12.7
OH
Annexe 2 : Informations supplémentaires de l'article 4
A2-42
ppm
200
180
160
140
120
100
80
60
40
20
0

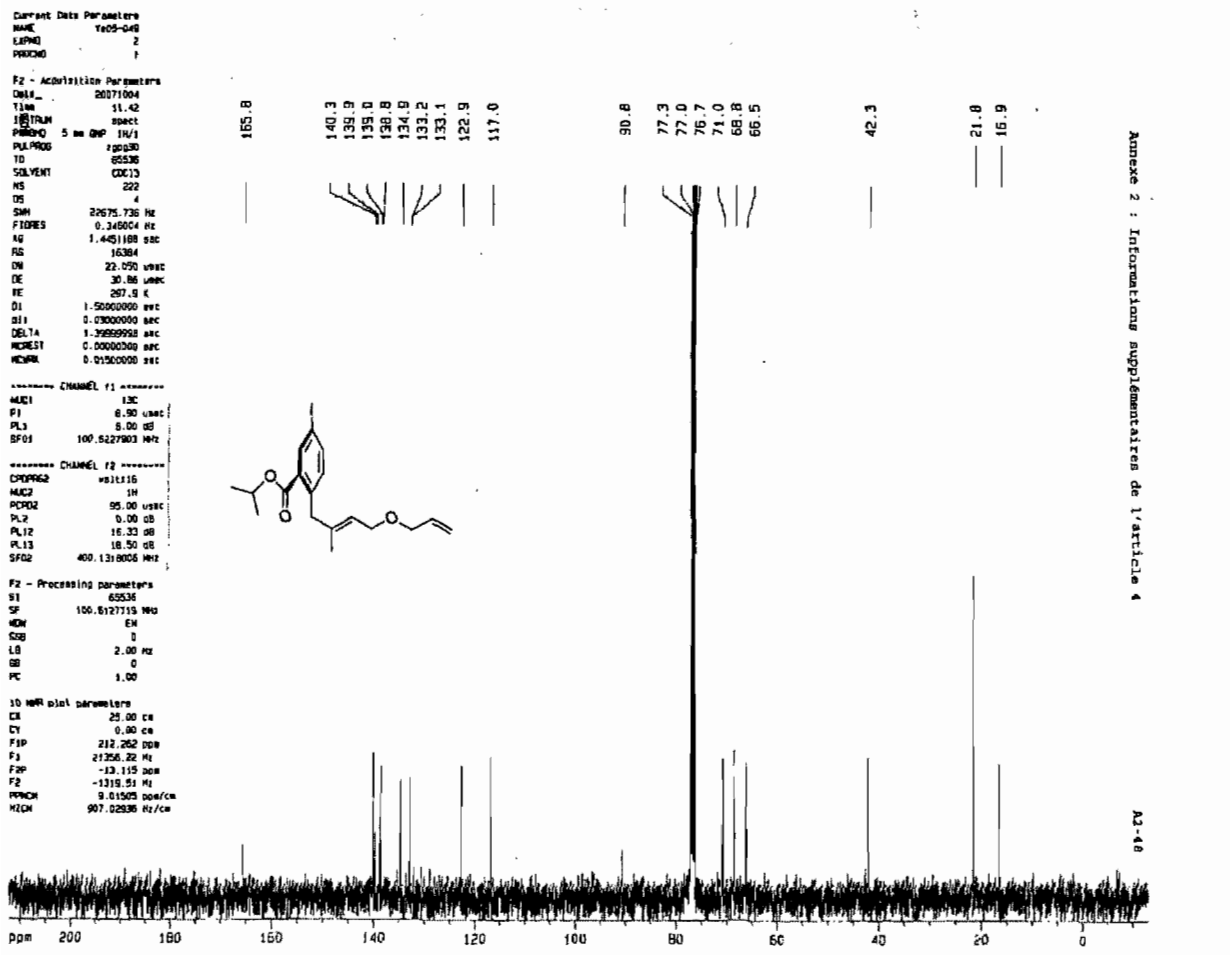

5.386
5.384
5.355
5.352
5.338
5.335
5.316
5.097
5.095
4.547
4.529
2.119
2.092
2.049
2.017
2.014
1.984
1.967
1.743
1.611
1.587
1.572
1.569
OAc
ppm
12
10
8
6
4
2
0

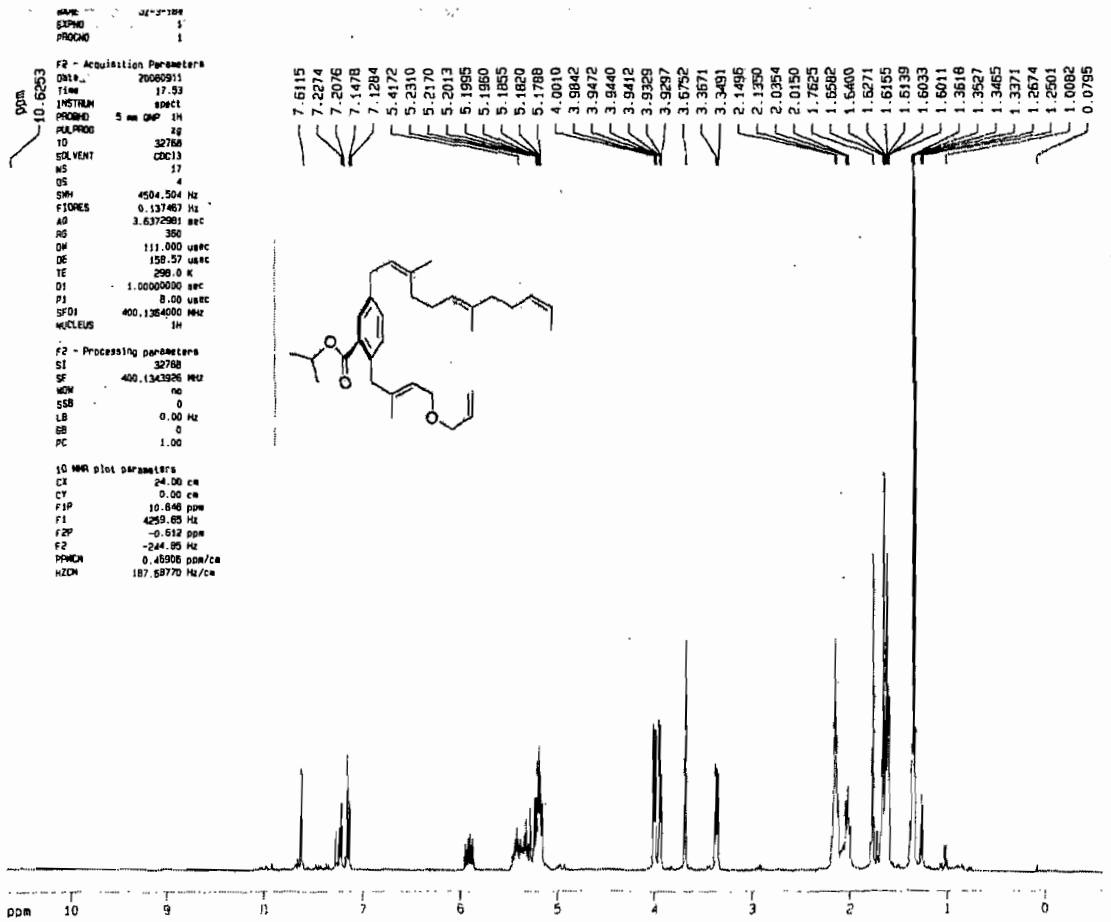

ppm
171.957
143.506
136.404
131.037
124.670
124.388
124.281
119.926
78.267
78.049
77.843
77.420
61.972
40.514
40.198
32.969
31.996
27.380
26.233
24.362
21.911
18.757
15.786
13.603
OAc
180
160
140
120
100
80
60
40
20
0

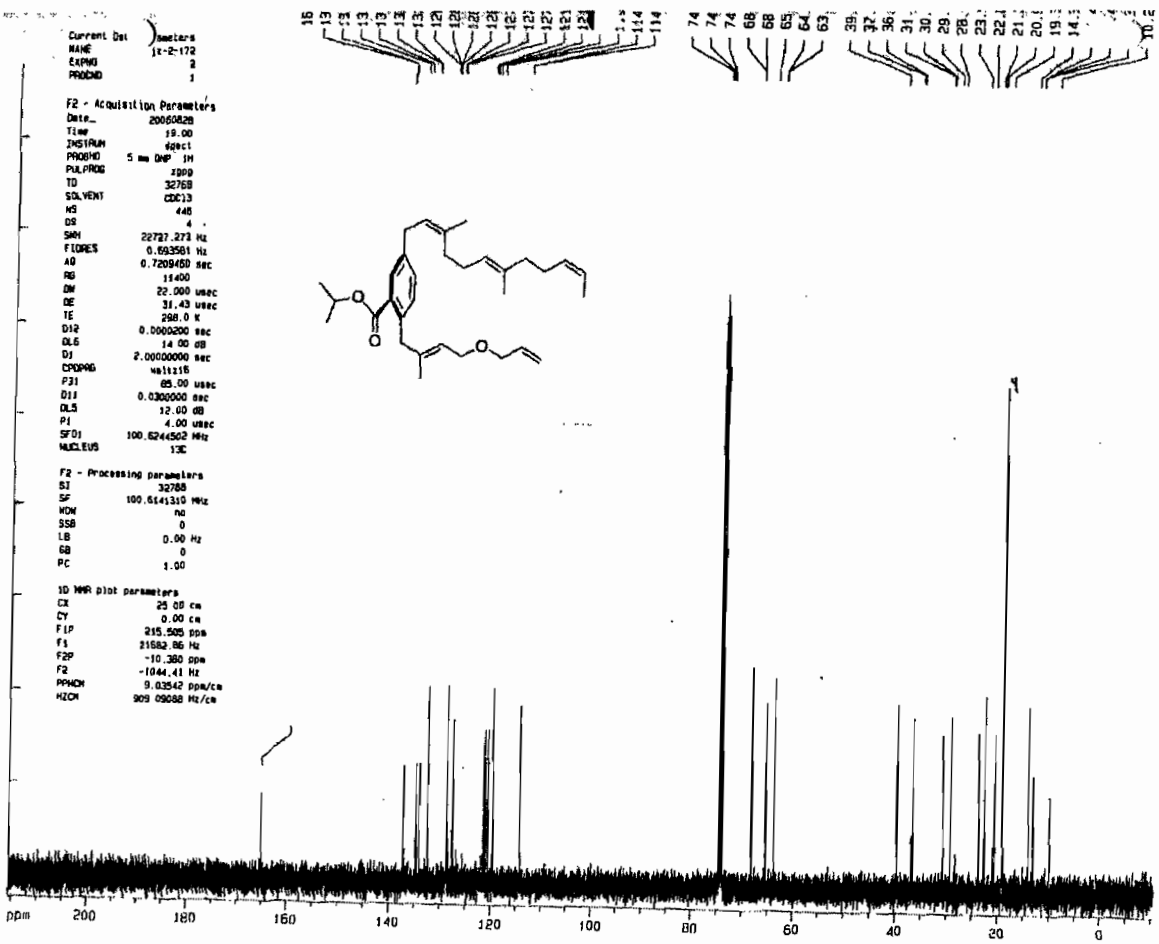

Current Data Parameters
NAME yp84-060
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081212
Time 11.55
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 7
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0963968 sec
RG 45.3
DW 83.400 usec
DE 6.00 usec
TE 294.1 K
D1 1.00000000 sec
MCREST 0.00600000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300092 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 13.965 ppm
F1 5585.40 Hz
F2P -1.017 ppm
F2 -406.80 Hz
PPMCM 0.62490 ppm/cm
HZCM 249.90018 Hz/cm
ppm
8.00782
7.64734
7.62657
7.41266
7.39194
5.25845
5.24243
5.22732
1.38622
1.37126
1.34098
1.23841
0.86231
Integra.
0.9176
1.0000
5.0695
ppm 12 10 8 6 4 2 0

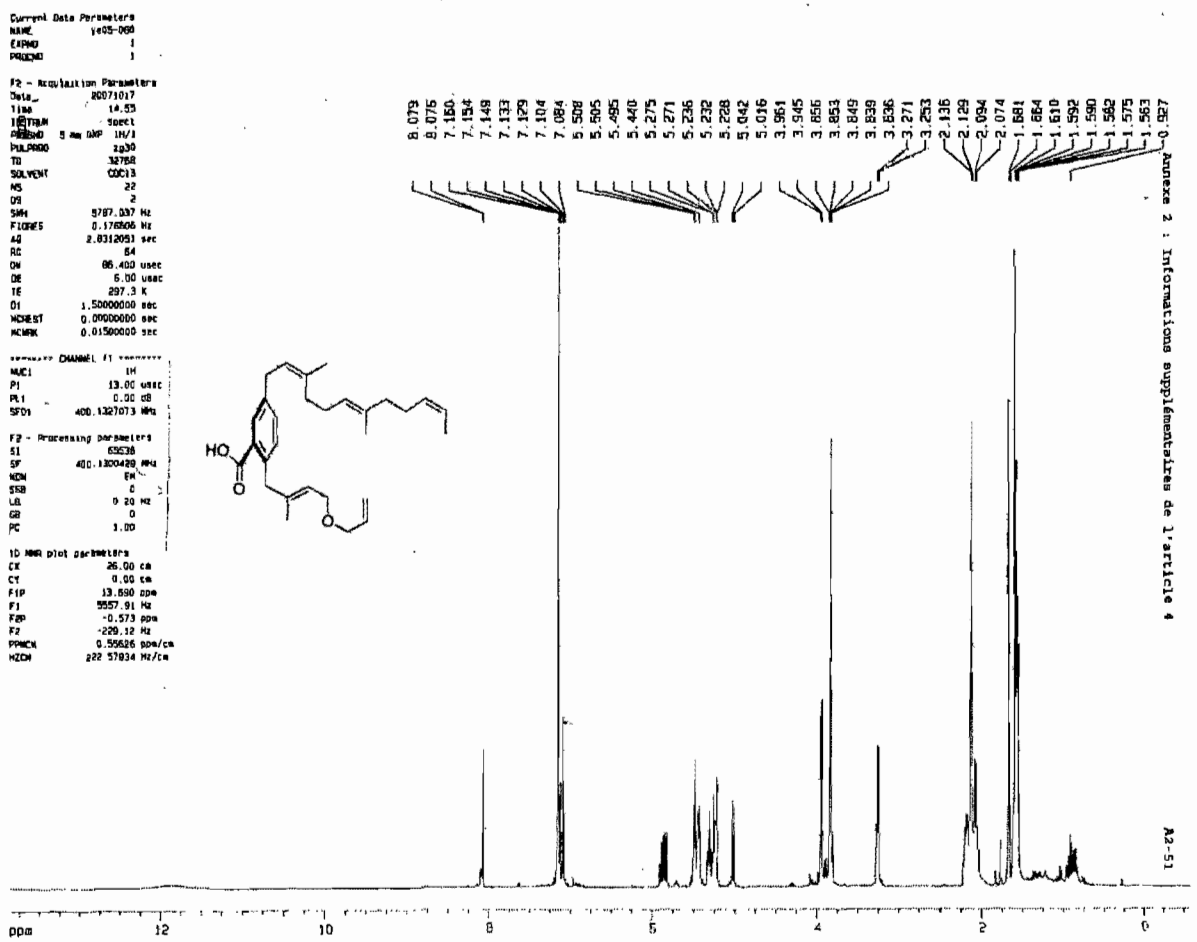

Current Data Parameters
NAME yp84-060
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081212
Time 12.03
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 101
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214902 sec
RG 32768
DW 19.950 usec
DE 6.00 usec
TE 294.6 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999988 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6249690 MHz
CHANNEL f2
DPRGNP waltz16
NUC2 1H
PCPD2 96.00 usec
PL2 -3.00 dB
PL12 18.00 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127813 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.727 ppm
F1 24019.02 Hz
F2P -10.373 ppm
F2 -1043.64 Hz
PPMCM 9.56401 ppm/cm
HZCM 1092.50823 Hz/cm
ppm
164.575
142.463
141.106
135.142
130.909
127.479
125.805
122.439
93.146
93.071
77.321
77.003
76.685
70.526
69.985
69.732
31.491
29.613
22.573
21.842
21.755
21.674
14.094
ppm 220 200 180 160 140 120 100 80 60 40 20 0

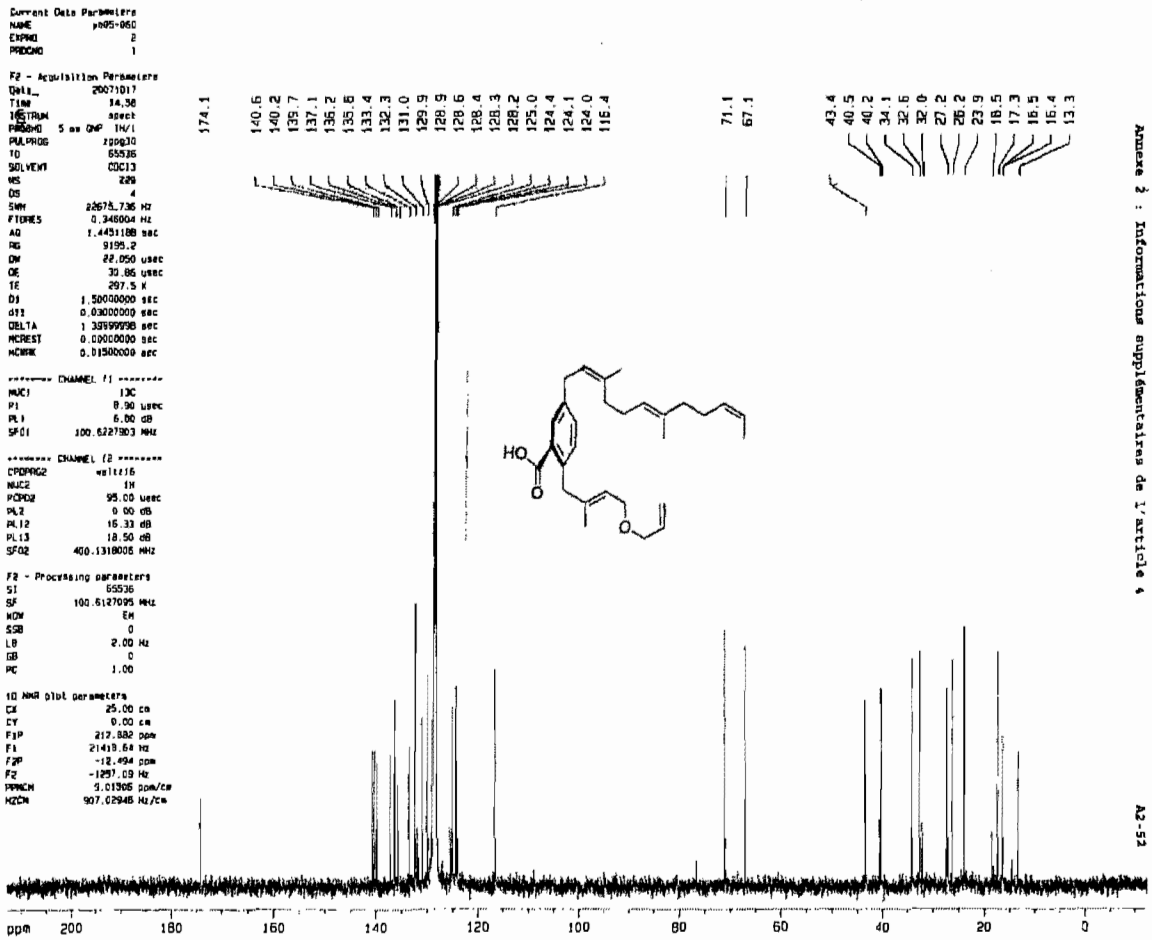

Current Data Parameters
NAME ye05-049
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071004
Time 11.38
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5787.037 Hz
FIDRES 0.176605 Hz
AQ 2.8312051 sec
RG 258
DW 86.400 usec
DE 6.00 usec
TE 297.7 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300093 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.874 ppm
F1 5551.48 Hz
F2P -0.489 ppm
F2 -195.58 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
8.106
8.101
7.720
7.715
7.700
7.695
7.260
6.986
6.965
5.270
5.256
5.227
5.223
5.203
5.188
5.179
5.172
5.156
5.153
5.150
3.988
3.971
3.939
3.935
3.924
3.921
3.651
1.645
1.604
1.372
1.367
1.348
1.332
A2-47
ppm
12
10
8
6
4
2
0
Annexe 2 : Informations supplémentaires de l'article 4


Current Data Parameters
NAME Ye05-049
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071004
Time 11.42
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 222
DS 4
SWH 22675.736 Hz
FIDRES 0.345804 Hz
AQ 1.4451188 sec
RG 16384
DW 22.050 usec
DE 30.86 usec
TE 297.9 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.95599968 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127715 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.262 ppm
F1 21356.22 Hz
F2P -13.115 ppm
F2 -1319.51 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02936 Hz/cm
165.8
140.3
139.9
139.0
138.8
134.9
133.2
133.1
122.9
117.0
80.8
77.3
77.0
76.7
71.0
68.8
66.5
42.3
21.8
16.9
A2-48
ppm
200
180
160
140
120
100
80
60
40
20
0
Annexe 2 : Informations supplémentaires de l'article 4

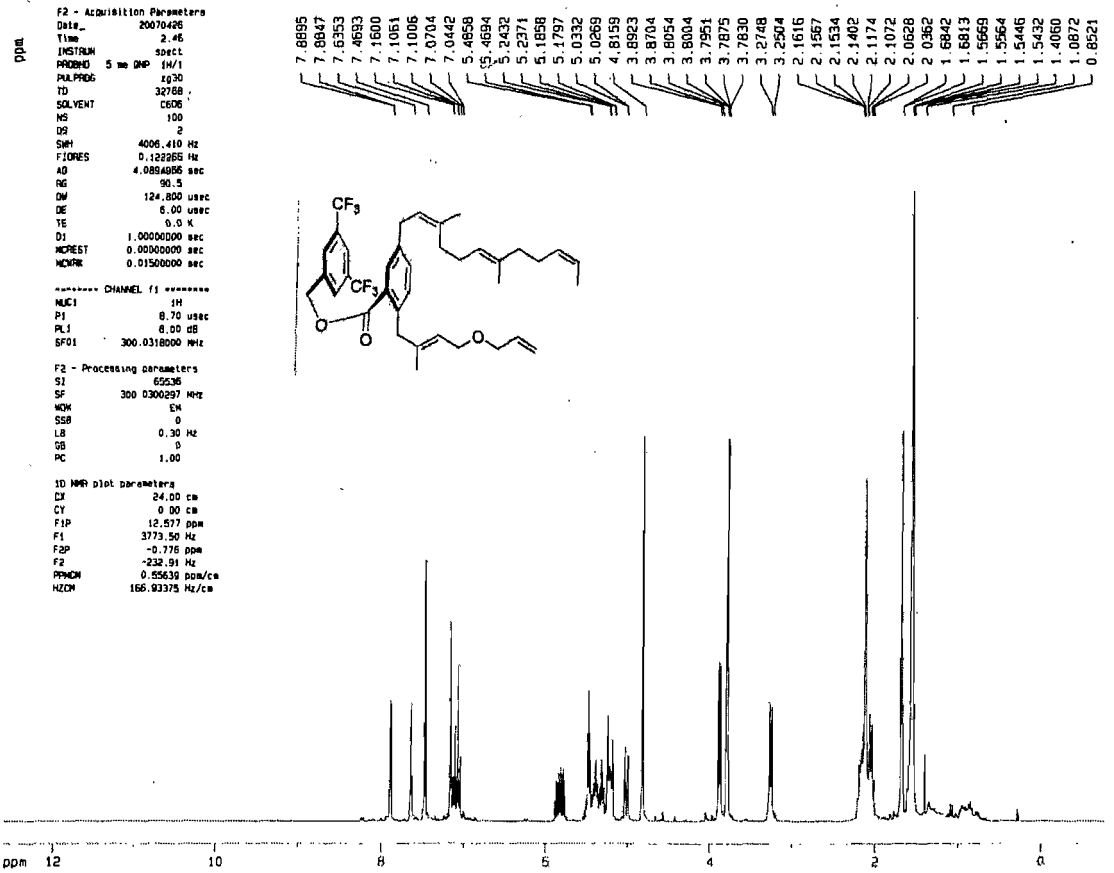

EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060911
Time 17.53
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 17
DS 4
SWH 4504.504 Hz
FIDRES 0.137467 Hz
AQ 3.6372981 sec
RG 350
DW 111.000 usec
DE 158.57 usec
TE 298.0 K
D1 1.00000000 sec
P1 8.00 usec
SFO1 400.1354000 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 32768
SF 400.1343926 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 10.646 ppm
F1 4259.65 Hz
F2P -0.612 ppm
F2 -244.95 Hz
PPMCM 0.46906 ppm/cm
HZCM 187.69770 Hz/cm
ppm 10.6253
7.6115 7.2274 7.2076 7.1478 7.1284 5.4172 5.2310 5.2170 5.2013 5.1985 5.1950 5.1855 5.1820 5.1788 4.0010 3.9842 3.9472 3.9440 3.9412 3.9329 3.9297 3.6752 3.3671 3.3491 2.1495 2.1350 2.0354 2.0150 1.7625 1.6582 1.6400 1.6271 1.6155 1.6139 1.6033 1.6011 1.3618 1.3527 1.3465 1.3371 1.2674 1.2501 1.0082 0.0795
ppm 10 9 8 7 6 5 4 3 2 1 0


NAME jz-2-172
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060828
Time 19.00
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 448
DS 4
SWH 22727.273 Hz
FIDRES 0.693581 Hz
AQ 0.7209450 sec
RG 11400
DW 22.000 usec
DE 31.43 usec
TE 298.0 K
D12 0.0000200 sec
DL6 14.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 85.00 usec
D11 0.0300000 sec
DL5 12.00 dB
P1 4.00 usec
SFO1 100.6244502 MHz
NUCLEUS 13C
F2 - Processing parameters
SI 32768
SF 100.6141310 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 215.505 ppm
F1 21682.86 Hz
F2P -10.380 ppm
F2 -1044.41 Hz
PPMCM 9.03542 ppm/cm
HZCM 909.09088 Hz/cm
ppm 200 180 160 140 120 100 80 60 40 20 0

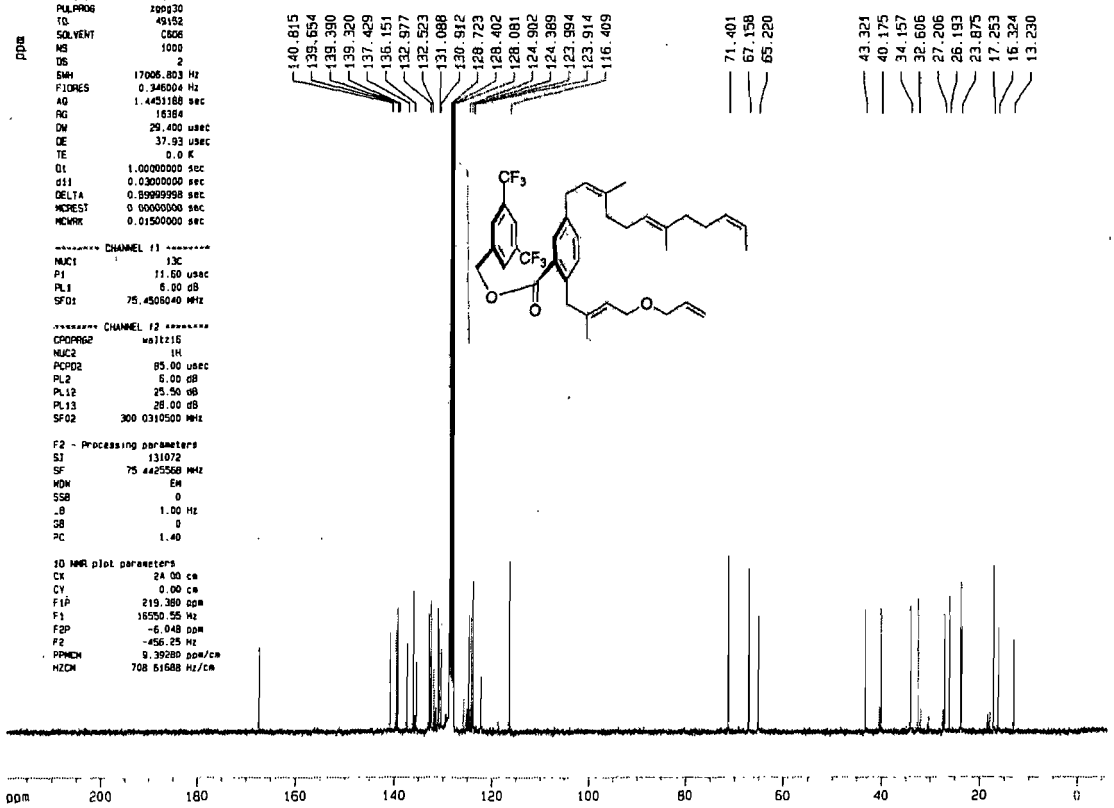

Current Data Parameters
NAME ye05-060
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071017
Time 14.55
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 22
DS 2
SWH 9787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 64
DW 86.400 usec
DE 6.00 usec
TE 297.3 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SF01 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300420 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.690 ppm
F1 5557.91 Hz
F2P -0.573 ppm
F2 -229.12 Hz
PPMCM 0.55626 ppm/cm
HZCM 222.57034 Hz/cm
8.079
8.076
7.160
7.154
7.149
7.133
7.129
7.104
7.084
5.508
5.505
5.495
5.440
5.275
5.271
5.236
5.232
5.228
5.042
5.016
3.961
3.945
3.856
3.853
3.849
3.839
3.836
3.271
3.253
2.136
2.129
2.094
2.074
1.681
1.664
1.610
1.592
1.582
1.575
1.563
0.927
HO
O
O
ppm
12
10
8
6
4
2
0
A2-51
Annexe 2 : Informations supplémentaires de l'article 4

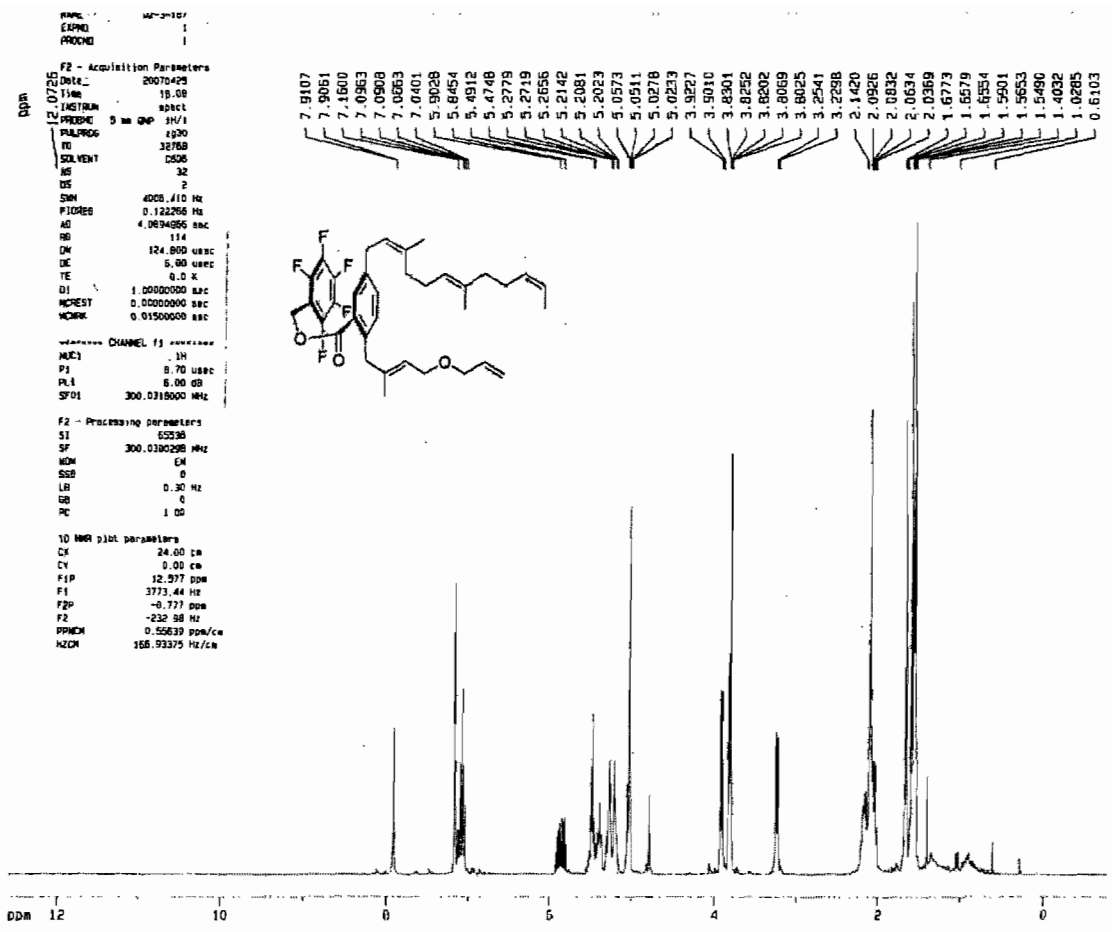

Current Data Parameters
NAME ye05-060
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071017
Time 14.38
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 229
DS 4
SWH 22675.736 Hz
FIDRES 0.346004 Hz
AQ 1.4451888 sec
RG 9195.2
DW 22.050 usec
DE 30.86 usec
TE 297.5 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.38999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SF01 100.6227803 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SF02 400.1318008 MHz
F2 - Processing parameters
SI 65536
SF 100.6127095 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 217.882 ppm
F1 21918.64 Hz
F2P -12.494 ppm
F2 -1257.09 Hz
PPMCM 9.01305 ppm/cm
HZCM 907.02948 Hz/cm
174.1
140.6
140.2
135.7
137.1
136.2
135.8
133.4
132.3
131.0
129.9
128.9
128.6
128.4
128.3
128.2
125.0
124.4
124.1
124.0
116.4
71.1
67.1
43.4
40.5
40.2
34.1
32.6
32.0
27.2
26.2
23.9
18.5
17.3
16.5
16.4
13.3
HO
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0
A2-52
Annexe 2 : Informations supplémentaires de l'article 4

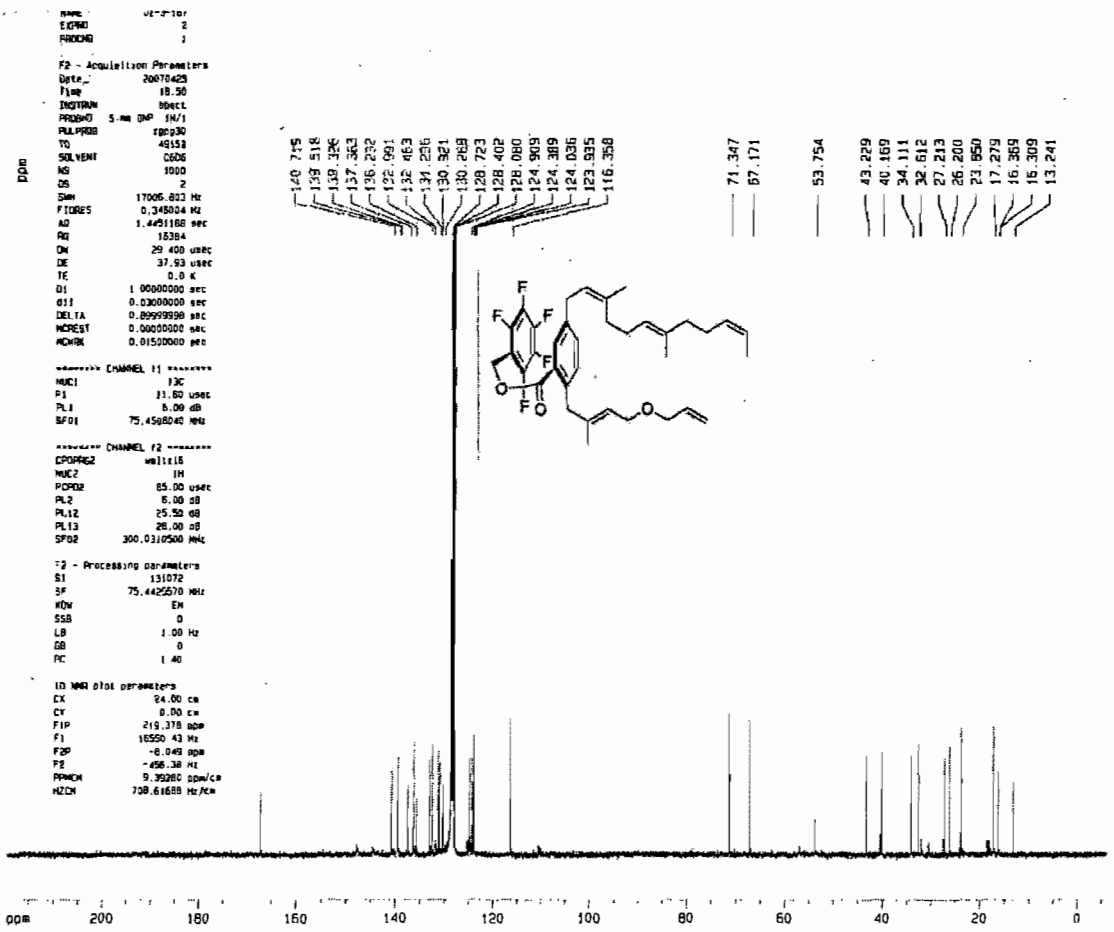
```
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_              20070426
Time                  2.46
INSTRUM              spect
PROBHD     5 mm QNP  1H/1
PULPROG              zg30
TD                  32768
SOLVENT              CDCl3
NS                     100
DS                       2
SWH               4006.410 Hz
FIDRES            0.122265 Hz
AQ                4.0894955 sec
RG                    90.5
DW                  124.800 usec
DE                    6.00 usec
TE                     0.0 K
D1                1.00000000 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.70 usec
PL1                  0.00 dB
SFO1          300.0318000 MHz

F2 - Processing parameters
SI                    65536
SF          300.0300297 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   24.00 cm
CY                    0.00 cm
F1P                  12.577 ppm
F1                 3773.50 Hz
F2P                 -0.776 ppm
F2                 -232.91 Hz
PPMCM                0.55639 ppm/cm
HZCM               166.93375 Hz/cm
```

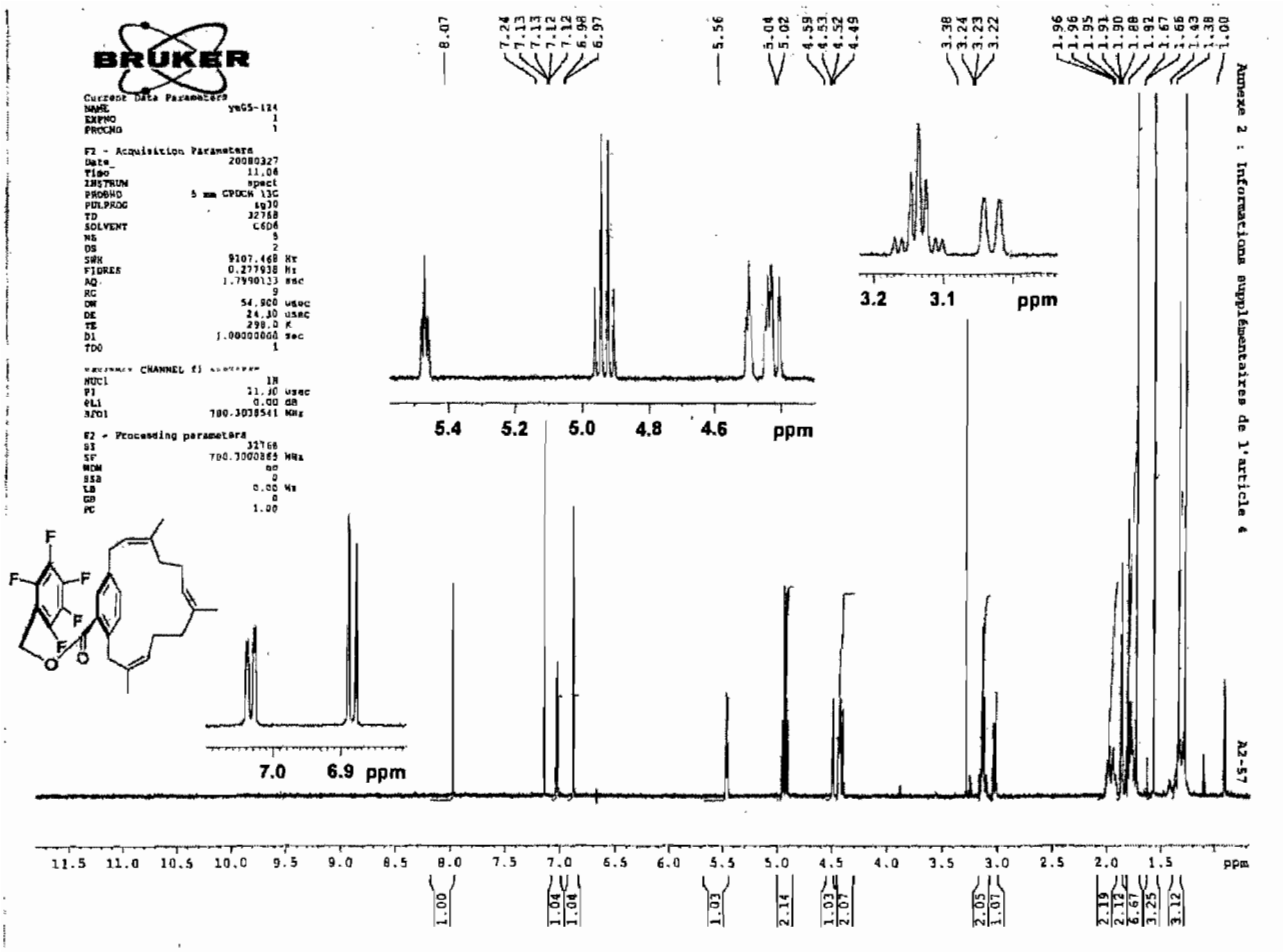


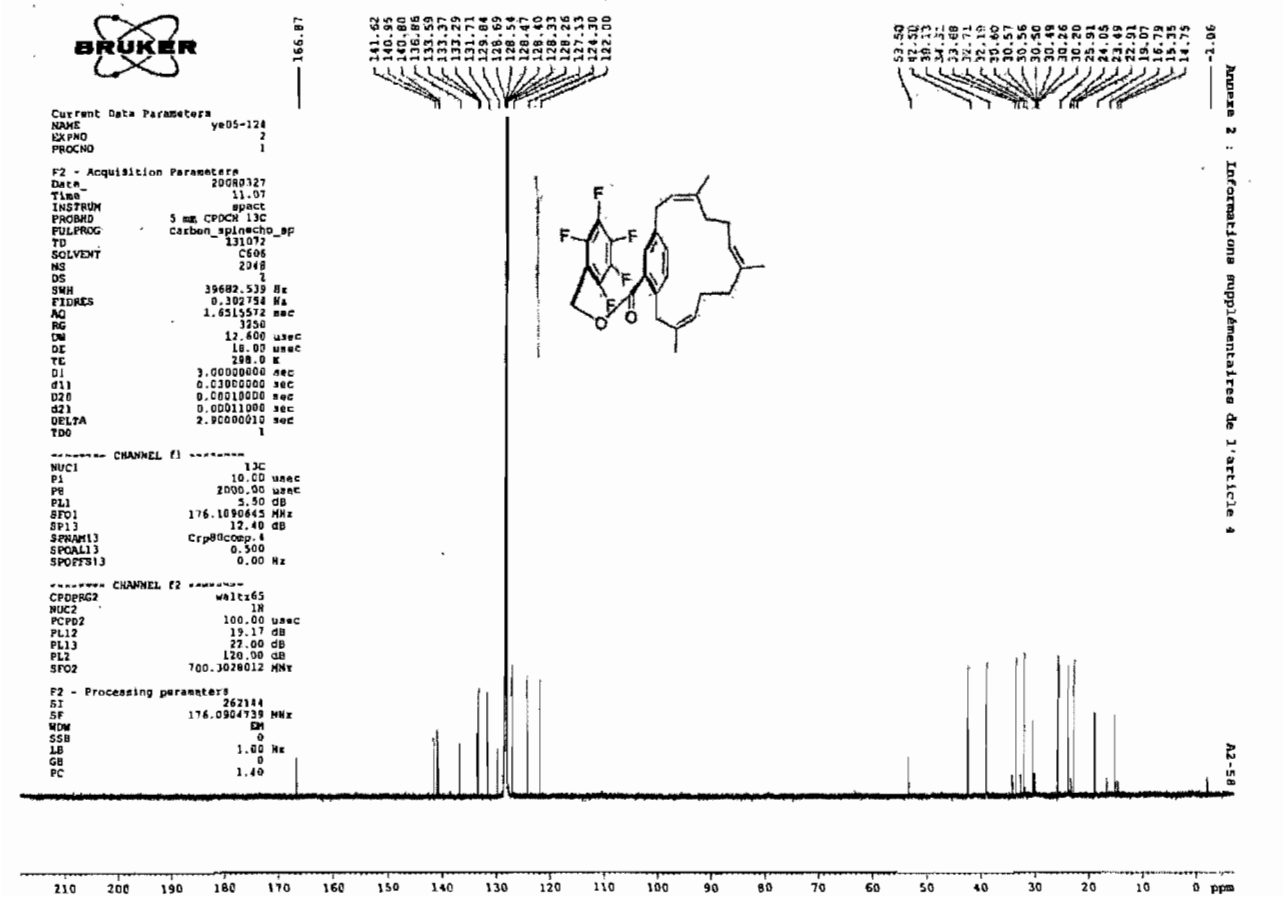

```
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_              20070426
Time                  3.28
INSTRUM              spect
PROBHD     5 mm QNP  1H/1
PULPROG          zgpg30
TD                  49152
SOLVENT              CDCl3
NS                    1000
DS                       2
SWH              17006.803 Hz
FIDRES            0.346004 Hz
AQ                1.4451188 sec
RG                   16384
DW                  29.400 usec
DE                  37.93 usec
TE                     0.0 K
D1                1.00000000 sec
d11               0.03000000 sec
DELTA             0.89999998 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                   11.60 usec
PL1                   6.00 dB
SFO1          75.4508040 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                   1H
PCPD2                85.00 usec
PL2                   6.00 dB
PL12                 25.50 dB
PL13                 28.00 dB
SFO2          300.0310500 MHz

F2 - Processing parameters
SI                   131072
SF          75.4425568 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   24.00 cm
CY                    0.00 cm
F1P                 219.380 ppm
F1                 16550.55 Hz
F2P                 -6.048 ppm
F2                 -456.25 Hz
PPMCM                9.39280 ppm/cm
HZCM               708.61688 Hz/cm
```




EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070429
Time 18.09
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 4006.410 Hz
FIDRES 0.122266 Hz
AQ 4.0894066 sec
RG 114
DW 124.800 usec
DE 6.00 usec
TE 0.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 8.70 usec
PL1 6.00 dB
SF01 300.0318000 MHz
F2 - Processing parameters
SI 65536
SF 300.0300298 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 12.577 ppm
F1 3773.44 Hz
F2P -0.777 ppm
F2 -232.98 Hz
PPMCM 0.55639 ppm/cm
HZCM 166.93375 Hz/cm
7.9107
7.9061
7.1600
7.0963
7.0908
7.0883
7.0401
5.9028
5.8454
5.4912
5.4748
5.2779
5.2719
5.2656
5.2142
5.2081
5.2023
5.0573
5.0511
5.0278
5.0233
3.9227
3.9010
3.8301
3.8252
3.8202
3.8069
3.8025
3.2541
3.2298
2.1420
2.0926
2.0832
2.0634
2.0369
1.6773
1.6579
1.6554
1.5901
1.5653
1.5490
1.4032
1.0285
0.6103
ppm
12
10
8
5
4
2
0


EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070429
Time 18.50
INSTRUM spect
PROBHD 5 mm DNP 1H/1
PULPROG zgpg30
TD 49152
SOLVENT CDCl3
NS 1000
DS 2
SWH 17006.803 Hz
FIDRES 0.345004 Hz
AQ 1.4451168 sec
RG 16384
DW 29.400 usec
DE 37.93 usec
TE 0.0 K
D1 1.00000000 sec
d11 0.03000000 sec
DELTA 0.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 11.60 usec
PL1 6.00 dB
SF01 75.4598040 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 85.00 usec
PL2 6.00 dB
PL12 25.52 dB
PL13 26.00 dB
SF02 300.0310500 MHz
F2 - Processing parameters
SI 131072
SF 75.4425570 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 24.00 cm
CY 0.00 cm
F1P 219.378 ppm
F1 16550.43 Hz
F2P -8.049 ppm
F2 -456.38 Hz
PPMCM 9.39280 ppm/cm
HZCM 708.61688 Hz/cm
140.715
139.518
138.326
137.363
136.232
132.991
132.463
131.226
130.321
130.269
128.723
128.402
128.080
124.909
124.389
124.036
123.935
116.358
71.347
67.171
53.754
43.229
40.169
34.111
32.612
27.213
26.200
23.650
17.279
16.369
16.309
13.241
ppm
200
180
160
140
120
100
80
60
40
20
0


BRUKER
Current Data Parameters
NAME ye05-124
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080327
Time 11.06
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 8
DS 2
SWH 9107.468 Hz
FIDRES 0.277938 Hz
AQ 1.7990133 sec
RG 8
DW 54.900 usec
DE 24.30 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
NUC1 1H
P1 11.30 usec
PL1 0.00 dB
SFO1 700.3038541 MHz
F2 - Processing parameters
SI 32768
SF 700.3000865 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.07
7.24
7.13
7.13
7.12
7.12
6.98
6.97
5.56
5.04
5.02
4.59
4.53
4.52
4.49
3.38
3.24
3.23
3.22
1.96
1.96
1.95
1.91
1.90
1.88
1.92
1.67
1.66
1.43
1.38
1.00
5.4 5.2 5.0 4.8 4.6 ppm
3.2 3.1 ppm
7.0 6.9 ppm
Annexe 2 : Informations supplémentaires de l'article 4
A2-57
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00
1.04
1.04
1.03
2.14
1.03
2.07
2.05
1.01
2.19
2.12
6.67
3.25
3.12


BRUKER
166.87
141.62
140.95
140.80
136.86
133.59
133.37
132.29
131.71
129.84
128.69
128.54
128.47
128.40
128.33
128.26
127.13
124.30
122.00
53.50
42.50
39.13
34.32
33.68
32.71
32.19
30.60
30.57
30.56
30.50
30.48
30.26
30.20
25.91
24.05
23.49
23.01
19.07
16.79
15.35
14.79
-2.06
Current Data Parameters
NAME ye05-124
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080327
Time 11.07
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG carbon_spinecho_gp
TD 131072
SOLVENT C6D6
NS 2048
DS 1
SWH 39682.539 Hz
FIDRES 0.302758 Hz
AQ 1.6515572 sec
RG 3250
DW 12.600 usec
DE 18.00 usec
TE 298.0 K
D1 3.00000000 sec
d11 0.03000000 sec
D20 0.00010000 sec
d21 0.00011000 sec
DELTA 2.90000010 sec
TD0 1
NUC1 13C
P1 10.00 usec
P8 2000.00 usec
PL1 5.50 dB
SFO1 176.1090445 MHz
SP13 12.40 dB
SPNAM13 Crp80comp.4
SPOAL13 0.500
SPOFFS13 0.00 Hz
CPDPRG2 waltz65
NUC2 1H
PCPD2 100.00 usec
PL12 19.17 dB
PL13 27.00 dB
PL2 120.00 dB
SFO2 700.3028012 MHz
F2 - Processing parameters
SI 262144
SF 176.0904739 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Annexe 2 : Informations supplémentaires de l'article 4
A2-58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Efficient Macrocyclizations via Metathesis Employing Amide-Based Auxiliaries

Yassir El-Azizi, Joseph E. Zakarian, Lisa Bouillerand, Andreea R. Schmitzer, Shawn K. Collins*

Département de chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7. [redacted]

SUPPORTING INFORMATION

TABLE OF CONTENTS

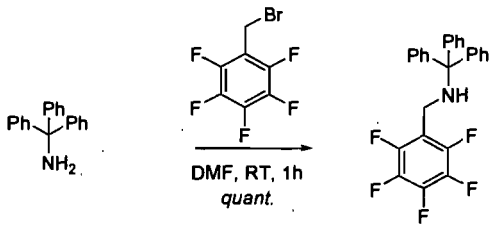
General

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[1]. All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. These products were used without further purification. Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, Toluene, DMF and hexanes) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography using the method reported by W. C. Still[2] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). All the compounds were UV active, and no development of the TLCs was required. Visualization of TLC plate was performed by UV (254 nm). 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 ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300, AV-400 or AV-500 instruments. Signals due to the solvent served as the internal standard. The acquisition parameters are shown on all spectra. The ^{1}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. The ^{1}H NMR assignments were made based on chemical shift and

[1] D. F. Shriver, M. A. Drezdon, *The Manipulation of Air-Sensitive Compounds*; 2e Édition, ed.; Wiley: New York, **1986**.
[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

multiplicity and were confirmed, where necessary, by homonuclear decoupling, 2D COSY experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by two dimensional H/C correlation experiments (HSQC). High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization. Charged molecular ion $[M+H]^+$, $[M+Na]^+$ and/ or $[M+Ag]^+$ data are reported.

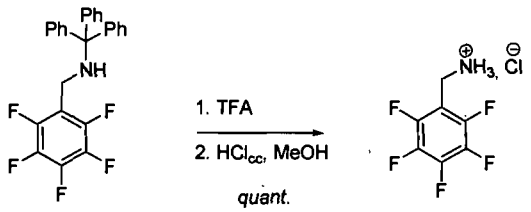
Preparation of 2,3,4,5,6-pentafluorobenzyl amine hydrochloride (7)



***N*-trityl-2,3,4,5,6-pentafluorobenzyl amine (6)**. 2,3,4,5,6-Pentafluorobenzyl amine was prepared using a protocol reported by Theodorou with slight modifications.[3] To a solution of tritylamine (520 mg, 2.0 mmol) in DMF (5 mL) was added 2,3,4,5,6-pentafluorobenzylbromide (260 mg, 1.0 mmol) and the resulting solution was stirred at room temperature for 1 h and monitored by TLC (hexanes/ ethyl acetate, 7/ 1). The salt $TrNH_2 \cdot HBr$ had precipitated from solution was removed by filtration. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel flash column chromatography (hexanes/ ethyl acetate, 7/ 1) to give **6** (438 mg, 99 %). ^1H NMR ($CDCl_3$, 400

[3] Theodorou, V.; Ragoussis, V.; Strongilos, A.; Zelepos, E.; Eleftheriou, A.; Dimitriou, M. *Tetrahedron Lett.* **2005**, *6*, 1357.

MHz) δ 7.54 (d, J = 8.0 Hz, 6H), 7.33 (t, J = 8.08 Hz, 6H), 7.24 (q, J = 8.0 Hz, 3H), 3.40 (s, 2H), 2.08 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 128.5, 128.0, 126.6, 71.3, 36.1; HRMS (ESI) Calculated for C26H19F5NAg $[M + Ag]^+$: 546.04044 found 546.04044. *Note that in general, we do not observe any ^{13}C NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary or for the CF_3 carbon.*

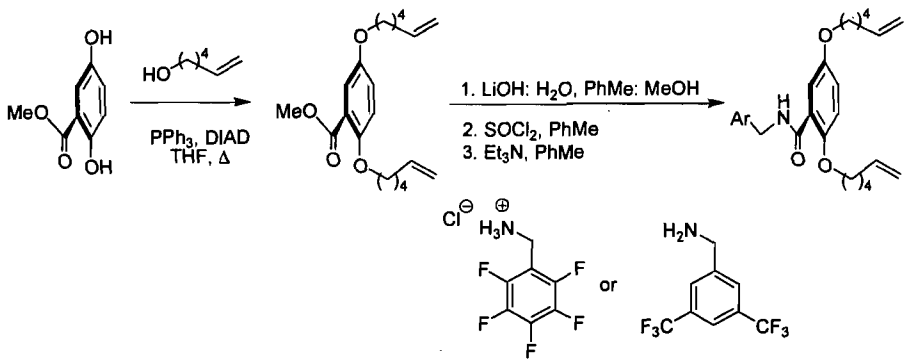


2,3,4,5,6-Pentafluorobenzyl amine hydrochloride (7). *N*-Trityl-2,3,4,5,6-pentafuorobenzylamine (438 mg, 1.0 mmol) in a solution of 60% TFA in CH_2Cl_2 (v/ v) (5 mL) was stirred for 10 min at room temperature, then CH_3OH (2 mL) was added. The solution was stirred for 1 h and the solvent was evaporated in vacuo. A solution of concentrated HCl in CH_3OH (1:1) (10 mL) was added and **XX** precipitated. The slurry was filtered and the solid washed with dry ether to afford 7 as a white solid (232 mg, 99 %). ^{1}H NMR (d_6-DMSO, 400 MHz) δ 4.87 (s, 2H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 30.5; HRMS (ESI) Calculated for $C_7H_6F_5N$ $[M + H]^+$: 198.03367 found 198.03392. *Note that in general, we do not observe any ^{13}C NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary or for the CF_3 carbon.*

Preparation of metathesis precursors

GENERAL PROCEDURE FOR THE PREPARATION OF METATHESIS PRECURSORS VIA THE MITSUNOBU REACTION.

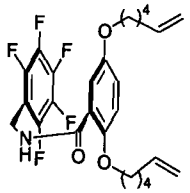
A general procedure for the preparation of precursors **3** *and* **12** *is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that in general, we do not observe any* ^{13}C *NMR signals for the five fluorine-bearing carbon atoms of the pentafluorobenzyl auxiliary. In select cases where a different synthetic route was necessary, these procedures are described in detail.*



Experimental Procedure: In a round bottom flask, methyl-2, 5-dihydroxybenzoate (1.0 eq.) was added to triphenylphosphine (1.2 eq.) and the alkenyl or alkynyl alcohol (0.5 to 0.6 eq.). This mixture was then dissolved in dry THF and heated to reflux. DIAD (1.2 eq.) was then added drop wise and the reaction was left under reflux and monitored by TLC. Typically after 10-15 hours the reaction was complete and no starting material was observed by TLC. The reaction mixture was then concentrated, dry-packed and purified by flash column silica chromatography using (hexanes/ ethyl acetate 20:1). Isolated yields were obtained in the range of 55- 90%. The products were immediately carried onto the second alkylation. In a round bottom flask, the mono-alkylated product (1.0 eq.) was added to triphenylphosphine (1.6 eq.) and the alkenyl or alkynyl alcohol (1.2 eq.). This mixture was then dissolved in dry THF and heated to reflux. While under reflux, DIAD (1.6 eq.) was added drop

wise and the reaction was left under reflux and monitored by TLC. After 15 hours, the reaction mixture was concentrated, dry-packed and purified by flash chromatography using (hexanes/ ethyl acetate 7/1). Isolated yields of approximately 60 % were typically obtained. The methyl benzoate ester obtained was dissolved in a 1:1 mixture of toluene: methanol, heated to a reflux, treated with either LiOH: H_2O or NaOH pellets, and stirred for 3 to 4 h. The reaction was monitored by TLC (hexanes/ ethylacetate 10/ 1). The solvent was removed by evaporation under reduced pressure, dissolved in diethyl ether, quenched with 1 N HCl, extracted with Et_2O, washed with brine, dried over Na_2SO_4, and evaporated to afford the corresponding carboxylic acid.

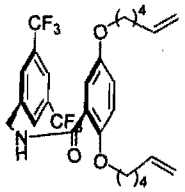
The carboxylic acid was then converted to the corresponding acyl chloride by dissolving it in toluene and adding an excess of thionyl chloride (4.0 equiv.) and letting it stir for 2 hours. After that, the reaction mixture was concentrated *in vacuo* and a solution of 2,3,4,5,6-Pentafluorobenzyl amine hydrochloride or 3,5-bis(trifuoromethyl)benzyl amine in Toluene: Et_3N (1:1) was added. The reaction was monitored by TLC (hexanes/ hthylacetate 7/ 1). After completion of the reaction the mixture was dry- packed and purifief by flash chromatography (hexanes/ ethylacetate 10 1) to give the desired compounds in high yields.



3

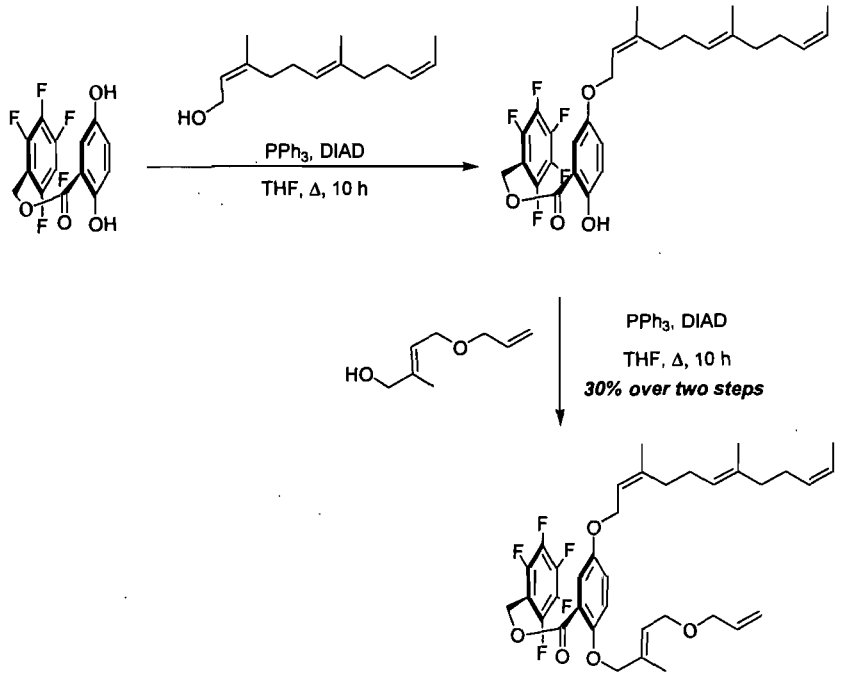
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 6.94 (dd, J = 9.0, 3.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 5.80- 5.75 (m, 2H), 5.04- 4.96 (m, 4H), 4.69 (d, J = 5.9 Hz, 2H), 4.05 (t, J = 6.1 Hz, 2H), 3.93 (t, J = 6.5 Hz, 2H), 2.12- 2.05 (m, 4H), 1.84- 1.80 (m, 2H), 1.77-

1.70 (m, 2H), 1.54- 1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 153.2, 151.1, 138.4, 137.8, 127.8, 127.7, 127.0, 120.8, 120.5, 115.8, 115.0, 114.6, 113.7, 69.3, 68.2, 33.3, 33.1, 31.2, 28.5, 28.4, 28.2, 25.1; HRMS (ESI) Calculated for $C_{26}H_{29}F_5NO_3$ $[M + H]^+$: 498.2062 found 498.2122. Calculated for $C_{25}H_{28}F_5NO_3Na$ $[M + Na]^+$: 520.1882, found 520.1904.



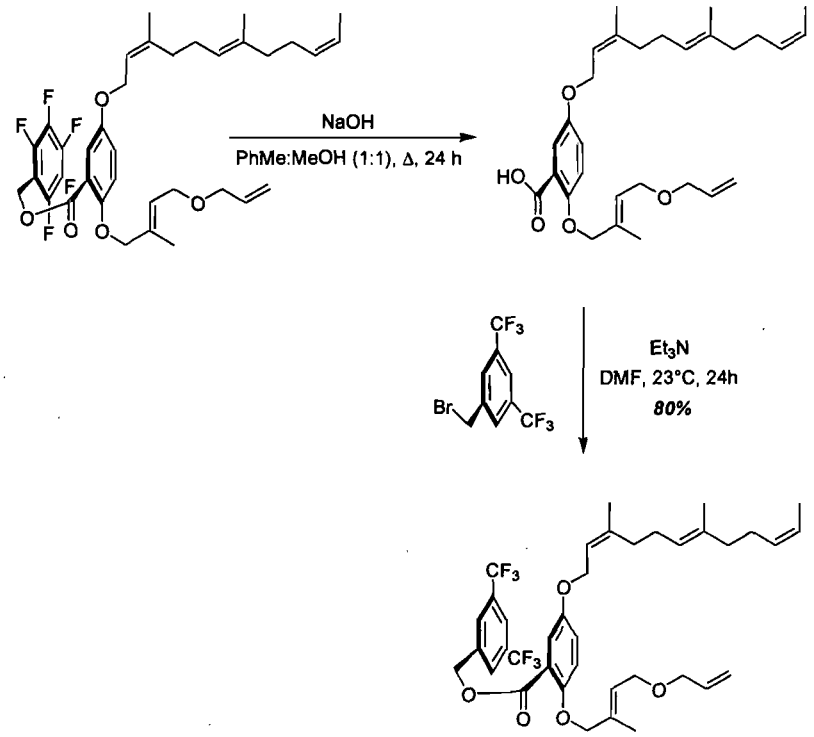
12

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.60 (t, J = 5.7 Hz, 1H), 7.81 (s, 2H), 7.80 (s, 1H), 7.76 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.0, 3.2 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 5.87- 5.75 (m, 1H), 5.72- 5.60 (m, 1H), 5.04- 4.90 (m, 4H), 4.77 (d, J = 5.9 Hz, 2H), 4.07 (t, J = 6.1 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 2.13- 2.06 (m, 2H), 2.03- 1.92 (m, 2H), 1.80- 1.72 (m, 4H), 1.70- 1.55 (m, 2H), 1.47- 1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ165.5, 153.4, 151.1, 141.5, 138.5, 137.7, 132.1 (q, J = 33.3 Hz, CF_3); 127.7, 124.6, 121.9, 121.3, 121.2, 121.2, 120.4, 116.2, 115.1, 114.7, 113.9, 69.4, 68.4, 42.9, 33.4, 33.0, 28.7, 28.5, 25.2; HRMS (ESI) Calculated for $C_{28}H_{32}F_6NO_3$ $[M + H]^+$: 544.22809 found 544.23074.



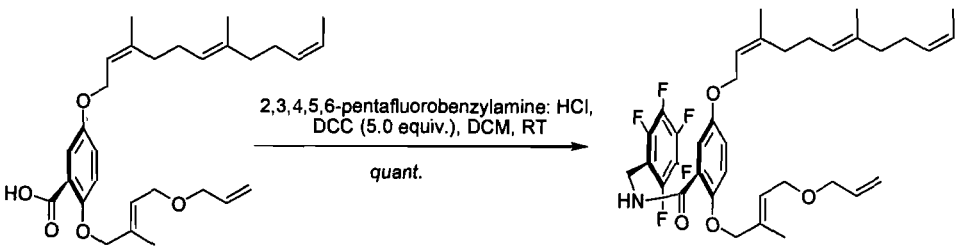
Pentafluorobenzyl 5-((2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienoxy)-2-((*E*)-4-(allyloxy)-2-methylbut-2-enoxy)benzoate (15): In a round bottom flask, 2',3',4',5',6'-pentafluorobenzyl-2,5-dihydroxybenzoate (0.17 g, 0.51 mmol), (2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trien-1-ol (0.06 g, 0.25 mmol), and PPh_3 (0.11 g, 0.41 mmol) were dissolved in anhydrous THF (50 mL), heated to a reflux using an oil bath, treated dropwise with DIAD (0.08 mL, 0.41 mmol) such that the yellow color disappeared before the next drop, and stirred for 4 h. The reaction was monitored by TLC (13% ethyl acetate/hexanes). The solution was allowed to cool to room temperature, treated with PPh_3 (0.05 g, 0.21 mmol) until the yellow color disappeared, and evaporated to give a residue that was further purified by silica gel flash chromatography ((hexanes/ ethylacetate 20/ 1)). Evaporation of the collected fractions gave the monoalkylated phenol as a pale-yellow oil (0.08 g, 55%), contaminated with traces of dialkylated byproduct as indicated by both ^{1}H-NMR and ^{13}C-NMR spectroscopy. Without any further purification, the obtained phenol was treated with (*E*)-4-(allyloxy)-2-methylbut-2-en-1-ol (0.03 g, 0.23 mmol), and PPh_3 (0.10 g, 0.36 mmol), dissolved in

anhydrous THF (50 mL), heated to a reflux using an oil bath and treated dropwise with DIAD (0.07 mL, 0.36 mmol) such that the yellow color disappeared before the next drop. The solution was stirred for 4 h, and monitored by TLC (hexanes/ ethyl acetate 10/ 1). The reaction was allowed to cool to room temperature, treated with PPh_3 (0.05 g, 0.18 mmol) until the yellow color disappeared, and evaporated to a residue that was purified by silica gel flash chromatography (hexanes/ ethyl acetate 20/ 1). The desired product was obtained as a pale-yellow oil (0.05 g, 30% over two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) □ 7.33 (d, J = 3.1 Hz, 1H), 7.01 (dd, J = 9.1, 3.1 Hz, 1H), 6.87 (d, J = 9.1 Hz, 1H), 5.92 (ddt, J = 17.1, 10.7, 5.7 Hz, 1H), 5.73 (t, J = 6.1 Hz, 1H), 5.47 (t, J = 6.2 Hz, 1H), 5.42-5.37 (m, 3H), 5.27 (dd, J = 17.1, 3.3 Hz, 1H), 5.19 (dd, J = 10.7, 3.3 Hz, 1H), 5.16-5.10 (m, 1H), 4.45 (d, J = 6.6 Hz, 2H), 4.42 (s, 2H), 4.05 (d, J = 6.5 Hz, 2H), 3.97 (dt, J = 5.7, 1.2 Hz, 2H), 2.16-2.11 (m, 6H), 2.04-1.99 (m, 2H), 1.79 (s, 3H), 1.72 (s, 3H), 1.64-1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) □ 165.2, 152.7, 152.3, 141.1, 135.6, 134.8, 130.2, 124.5, 123.8, 123.7, 123.5, 120.7, 120.0, 119.7, 117.1 (3C), 115.4, 74.6, 71.2, 66.0, 65.1, 53.6, 39.3, 32.4, 26.5, 25.4, 23.5, 15.9, 13.9, 12.7; HRMS (ESI) Calculated for $C_{36}H_{42}F_5O_5$ $[M + H]^+$, 649.2947, found 649.2935.



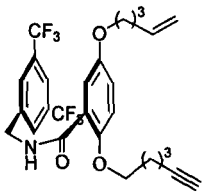
3,5-Bis(trifluoromethyl)benzyl 5-((2*Z*,6*Z*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyloxy)-2-((*E*)-4-(allyloxy)-2-methylbut-2-enyloxy)benzoate (19): In a round bottom flask equipped with a reflux condenser, pentafluorobenzyl 5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoxy)-2-((*E*)-4-(allyloxy)-2-methylbut-2-enoxy)benzoate (0.05 g, 0.10 mmol), was dissolved in a 1:1 mixture of toluene:methanol (10 mL), heated to a reflux, treated with NaOH pellets (0.05 g, 1.32 mmol), and stirred for 24 h. The reaction was monitored by TLC ((hexanes/ ethylacetate 10 1)). The solvent was removed by evaporation under reduced pressure, dissolved in ethyl acetate, quenched with 1 N HCl (6.50 mL, 6.50 mmol), extracted with Et_2O (3 x 20 mL), washed with brine, dried over Na_2SO_4, and evaporated to afford the corresponding carboxylic acid (0.11 g, 0.22 mmol) that was dissolved in anhydrous DMF (22 mL), cooled to 0°C, treated dropwise with Et_3N (0.04 mL, 0.25 mmol), stirred for 0.5 h, treated with 3,5-bis(trifluoromethyl)benzylbromide (0.04 mL, 0.22 mmol, which prior to addition was passed through a short plug of basic alumina), and stirred for 10 h at room temperature. The reaction was monitored by TLC (hexanes/ethyl acetate 1/1). The solvent was removed by

evaporation, and the residue was taken up in Et_2O (20 mL). The solution was quenched with 1N HCl (5 mL), extracted with Et_2O (3 x 20 mL), washed with a 10% aqueous $CuSO_4$ solution (3 x 20 mL), brine (1 x 20 mL), dried over Na_2SO_4, and evaporated to a residue that was purified by silica gel flash chromatography (hexanes/ethyl acetate 10/1) to afford the corresponding ester as a pale-yellow solid (0.13 g, 80%). ^1H NMR ($CDCl_3$, 300 MHz), δ 7.92 (s, 2H), 7.84 (s, 1H), 7.38 (d, J = 3.1 Hz, 1H), 7.03 (dd, J = 9.1, 3.1 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.89 (ddt, J = 17.1, 10.4, 5.7 Hz, 1H), 5.74 (t, J = 5.9 Hz, 1H), 5.49 (t, J = 5.6 Hz, 1H), 5.45 (s, 2H), 5.36 (m, 2H), 5.25 (dd, J = 17.3, 3.3 Hz, 1H), 5.17 (dd, J = 10.4, 3.3 Hz, 1H), 5.11-5.01 (m, 1H), 4.48-4.45 (m, 4H), 4.03 (d, J = 6.4 Hz, 2H), 3.94 (dt, J = 5.7, 1.3 Hz, 2H), 2.14-2.12 (m, 6H), 2.01-2.00 (m, 2H), 1.79 (s, 3H), 1.69 (s, 3H), 1.63-1.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 165.8, 152.6, 152.4, 142.1, 138.8, 135.6, 134.7, 134.5, 131.0, 128.0, 125.3, 125.1, 124.9 (2C), 124.7, 124.6, 123.8, 123.4, 121.9, 120.2, 117.1, 116.9, 115.4, 74.3, 71.2, 66.0, 65.1, 64.9, 39.3, 32.3, 26.5, 25.4, 23.5, 15.9, 13.8, 12.7; HRMS (ESI) Calculated for $C_{38}H_{45}F_6O_5$ $[M + H]^+$, 695.3166, found 695.3161.



2,3,4,5,6-pentafluorobenzyl-5-((2*Z*,6*Z*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyloxy)-2-((*E*)-4-(allyloxy)-2-methylbut-2-enyloxy)benzylamide (17) : 2-((*E*)-4-(allyloxy)-2-methylbut-2-enyloxy)-5-((2*Z*,6*E*,10*Z*)-3,7-dimethyldodeca-2,6,10-trienyloxy)benzoic acid (69 mg, 0.15 mmol) was dissolved in DCM (2 mL) at room temperature, then DCC (151 mg, 5.0 equiv., 0.735 mmol) and 2,3,4,5,6-pentafluorobenzylamine•HCl (41 mg, 1.2 equiv., 0.18 mmol) were added. The reaction

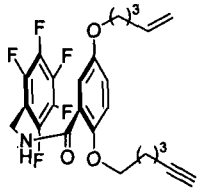
mixture was stirred for 2 h at room temperature and the reaction was monitored by TLC (hexanes/ethyl acetate, 7/1). The solvent was removed by evaporation, and the residue dry packed for purification by silica gel flash chromatography (hexanes/ ethyl acetate, 10/ 1). The amide **XX** was obtained as a yellow oil (95 mg, 99 %): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (t, J = 5.6 Hz, 1H), 7.74 (d, J = 3.1 Hz, 1H), 6.96 (dd, J = 9.1, 3.1 Hz, 1H), 6.87 (d, J = 9.1 Hz, 1H), 5.92- 5.80 (m, 1H), 5.74 (t, J = 6.1 Hz, 1H), 5.50-5.37 (m, 3H), 5.30-5.20 (m, 2H), 5.11 (t, J = 6.0 Hz, 1H), 4.70 (d, J = 5.8 Hz, 2H), 4.50- 4.47 (m, 4H), 4.06 (d, J = 6.6 Hz, 2H), 3.99 (d, J = 6.6 Hz, 2H), 2.20-1.95 (m, 8H), 1.78 (s, 3H), 1.71 (s, 3H), 1.65- 1.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 153.3, 151.0, 142.0, 135.5, 134.5, 133.5, 130.3, 126.6, 123.8, 123.6, 123.5, 121.2, 120.9, 120.0, 117.4, 115.7, 114.5, 71.5, 65.9, 65.0, 39.6, 39.3, 32.3, 31.5, 26.6, 25.4, 23.5, 16.0, 15.9, 14.1, 12.7; HRMS (ESI) Calculated for $C_{36}H_{43}F_5NO_4$ $[M + H]^+$, 648.3168, found 648.30956, calculated for $C_{36}H_{42}F_5NO_4Na$ $[M + Na]^+$, 470.29262, found 470.29236.



24

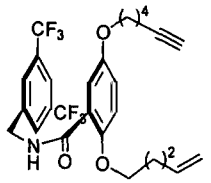
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (t, J = 5.6 Hz, 1H), 7.82 (s, 2H), 7.79 (s, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.1, 3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.95- 5.77 (m, 1H), 5.07- 4.90 (m, 2H), 4.77 (d, J = 5.9 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 4.00 (t, J = 6.4 Hz, 2H), 2.30- 2.10 (m, 4H), 1.98- 1.82 (m, 5H), 1.68- 1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 153.4, 151.0, 141.5, 137.7, 132.0, 131.7, 127.7, 124.6, 121.3, 120.5, 116.4, 115.2, 113.9, 83.3, 69.0, 67.8, 43.0, 30.0,

28.4, 28.1, 24.9, 17.9; HRMS (ESI) Calculated for $C_{27}H_{28}F_6NO_3$ [M + H]+: 528.1968 found 528.1967.



32

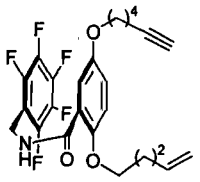
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (t, J = 5.6 Hz, 1H), 7.72 (d, J = 3.0 Hz, 1H), 6.96 (dd, J = 9.1, 3.1 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 5.90- 5.75 (m, 1H), 5.05- 4.95 (m, 2H), 4.71 (d, J = 5.8 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 3.95 (t, J = 6.2 Hz, 2H), 2.33- 2.25 (m, 2H), 2.21- 2.16 (m, 2H), 1.99- 1.94 (m, 3H), 1.87- 1.80 (m, 2H), 1.69- 1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 153.3, 151.0, 144.0, 137.7, 120.9, 120.6, 116.0, 115.1, 113.7, 83.3, 69.9, 69.0, 67.7, 31.4, 30.0, 28.3, 28.2, 25.0, 18.0; HRMS (ESI) Calculated for $C_{25}H_{25}F_5NO_3$ [M + H]$^+$: 482.17491 found 482.17531. Calculated for $C_{25}H_{24}F_5NO_3Na$ [M + Na]$^+$: 504.15686 found 504.15712.



28

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (t, J = 5.6 Hz, 1H), 7.81 (s, 2H), 7.79 (s, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 9.1, 3.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 5.75- 5.63 (m, 1H), 4.98- 4.90 (m, 2H), 4.77 (d, J = 5.9 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 4.00 (t, J = 6.4 Hz, 2H), 2.30- 2.20 (m, 2H),

2.11- 2.06 (m, 2H), 1.96 (t, J = 2.4 Hz, 1H), 1.89- 1.80 (m, 4H), 1.75- 1.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 153.3, 151.1, 141.4, 136.6, 131.7 (q, J = 33.3 Hz, CF_3), 127.7, 121.3, 122.5, 121.5, 120.4, 116.3, 115.7, 114.0, 84.0, 68.9, 68.6, 67.9, 43.0, 30.0, 28.2, 24.9, 18.1; HRMS (ESI) Calculated for $C_{27}H_{28}F_6NO_3$ $[M + H]^+$: 528.1968 found 528.1959. Calculated for $C_{27}H_{27}F_6NO_3Na$ $[M + Na]^+$: 550.1787, found 550.1778.



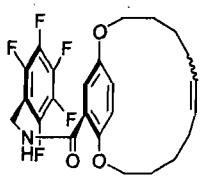
36

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (t, J = 5.6 Hz, 1H), 7.70 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 9.1, 3.1 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 5.90- 5.75 (m, 1H), 5.07- 5.01 (m, 2H), 4.70 (d, J = 5.8 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.2 Hz, 2H), 2.27- 2.15 (m, 4H), 1.95- 1.84 (m, 5H), 1.70- 1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 153.2, 151.2, 136.8, 120.9, 120.6, 115.9, 115.7, 113.8, 84.0, 68.9, 68.6, 67.8, 31.3, 30.0, 28.2, 28.1, 24.9, 18.1; HRMS (ESI) Calculated for $C_{25}H_{25}F_5NO_3$ $[M + H]^+$: 482.1749 found 482.1755. Calculated for $C_{25}H_{24}F_5NO_3Na$ $[M + H]^+$: 504.1569 found 504.1571.

GENERAL PROCEDURES FOR OLEFINE METATHESIS MACROCYCLIZATION: PREPARATION OF CYCLOPHANES 9 AND 13

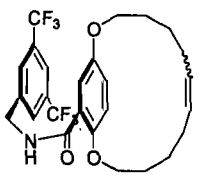
To a flame dried three neck round bottom flask equipped with a reflux condenser under nitrogen, the appropriate metathesis catalyst (10 mol %) and anhydrous CH_2Cl_2 (volume is determined by the

amount needed to afford a final concentration of [M] = $0.4x10^{-4}$ M after complete addition of the precursor solution) were added. The solution was heated to a reflux and treated dropwise with a solution of the precursor dissolved in CH_2Cl_2 (50 mL) over 1 h using a syringe pump or an addition funnel. The reaction was allowed to stir at reflux for 10 h and was monitored by TLC (hexanes / ethyl acetate, 10/ 1). The reaction was quenched with ethyl vinyl ether (5 mL), evaporated down to about 1 mL, and purified by silica gel flash chromatography (hexanes/ ethyl acetate, 20/ 1) to afford the desired macrocycles in the indicated yields.



9

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (t, J = 5.7 Hz, 1H), 7.80 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 9.0, 3.1 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 4.98- 4.70 (m, 3H), 4.62 (dd, J = 15.7, 6.8 Hz, 1H), 4.50- 4.42 (m, 1H), 4.38- 4.30 (m, 1H), 4.28- 4.18 (m, 1H), 4.15- 4.05 (m, 1H), 1.89- 1.45 (m, 8H), 1.35- 1.10 (m, 3H), 0.95- 0.8 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 153.0, 150.8, 130.7, 129.6, 124.4, 124.2, 120.3, 119.0, 70.6, 69.0, 31.5, 30.7, 30.6, 26.9, 26.8, 24.4, 24.3. HRMS (ESI) Calculated for $C_{24}H_{25}F_5NO_3$ $[M + H]^+$: 470.1749 found 470.1740. Calculated for $C_{24}H_{24}F_5NO_3Na$ $[M + Na]^+$: 492.1569 found 492.1552.

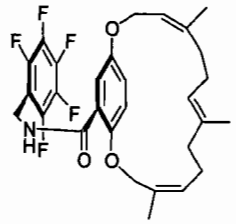


13

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (t, J = 5.7 Hz, 1H), 7.85 (d, J = 3.1 Hz, 1H), 7.82 (s, 2H), 7.80 (s, 1H), 7.10 (dd, J = 9.0, 3.2 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 4.98 (dd, J = 15.7, 6.8 Hz, 1H), 4.92- 4.79 (m, 2H), 4.60 (dd, J = 15.7, 6.8 Hz, 1H), 4.52- 4.42 (m, 1H), 4.40- 4.35 (m, 1H), 4.25- 4.15 (m, 1H), 4.17- 4.10 (m, 1H), 1.85- 1.35 (m, 8H), 1.33- 1.10 (m, 3H), 1.05- 0.9 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 153.1, 151.0, 141.7, 132.0 (q, J = 33.3 Hz, CF_3), 130.8, 129.6, 127.6, 124.6, 124.4, 124.3, 121.2, 120.5, 119.0, 70.6, 69.1, 42.8, 30.7, 30.5, 27.0, 26.9, 24.5, 24.4. HRMS (ES) Calculated for $C_{26}H_{28}F_6NO_3$ $[M + H]^+$: 516.1968 found 516.1981. Calculated for $C_{26}H_{27}F_6NO_3Na$ $[M + Na]^+$: 538.1787 found 538.1793.

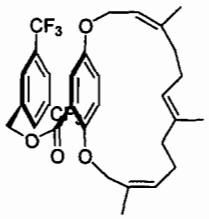
REPRESENTATIVE PROCEDURE FOR OLEFINE METATHESIS MACROCYCLIZATION: PREPARATION OF CYCLOPHANES 18 AND 20

A flame dried 500 mL tri-neck round bottom flask, equipped with a magnetic stirrer, reflux condenser, and isobar addition funnel or a syringe pump system is charged with 2nd Generation Grubbs Catalyst (10 mol %) and anhydrous CH_2Cl_2 (volume is determined by the amount needed to afford a final concentration of [M] = 0.4x10^{-4} M after complete addition of the precursor solution). The catalyst solution is then placed at reflux (CH_2Cl_2). The metathesis precursor in DCM solution (approximately 50 mL) along with 5.0 equiv. of and Ti(O*i*-Pr)$_4$ is placed in the addition funnel or the syringe pump system and added over 1 to 3h. After addition, the solution was allowed to stir at reflux overnight. The reaction was quenched with ethyl vinyl ether (5 mL), evaporated down to about 1 mL, dry-packed and purified by flash column silica chromatography (hexanes/ethylacetate 20/ 1) to afford the desired paracyclophanes in the indicated yields.



18

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.63 (t, *J* = 5.6 Hz, 1H), 7.78 (d, *J* = 3.0 Hz, 1H), 7.00 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 6.36 (d, *J* =15.6 Hz, 1H), 5.50 (t, *J* = 7.0 Hz, 1H), 5.18 (t, *J* = 7.0 Hz, 1H), 5.06 (d, *J* = 13.4 Hz, 1H), 4.73 (s, 2H), 4.54 -4.49 (m, 3H), 2.32-2.20 (m, 2H), 2.15-2.07 (m, 6H), 1.83 (s, 3H), 1.77 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 158.1, 147.2, 145.1, 136.8, 134.8, 133.0, 130.6, 126.4, 125.3, 122.8, 120.2, 117.7, 116.6, 112.7, 111.6, 73.9, 65.9, 42.3, 35.8, 35.2, 35.1, 30.5, 27.8, 24.0, 21.0; HRMS (ESI) calculated for $C_{29}H_{30}F_5O_3N$ $[M + H]^+$, 536.22186, found 536.22184. Calculated for $C_{29}H_{30}F_5NO_3Na$ $[M + Na]^+$: 558.20381 found 558.20362.



20

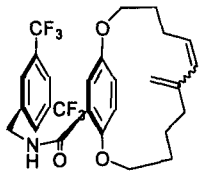
^{1}H NMR ($CDCl_3$,400 MHz) δ 7.91 (d, *J* = 3.0 Hz, 1H), 7.71 (s, 1H), 7.58 (s, 2H), 7.02 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.67 (d, *J* = 9.1 Hz, 1H), 5.47 (t, *J* = 8.1 Hz, 1H), 5.25 (t, *J* = 7.0 Hz, 1H), 4.88 (s, 2H), 4.67 (t, *J* = 6.3 Hz, 1H), 4.54-4.49 (m, 4H), 2.09-2.05 (m, 2H), 2.05-1.97 (m, 2H), 1.91-1.88 (m, 2H), 1.61 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H), 1.52-1.49 (m, 2H); ^{13}C NMR (CDCl3, 101 MHz) δ

165.7, 152.8, 151.6, 144.5, 139.0, 132.2, 132.0, 131.7, 130.4, 128.0, 127.6, 126.0, 124.1, 123.4, 121.8, 119.8, 119.4, 115.8, 73.6, 68.1, 64.7, 39.0, 31.7, 27.1, 25.0, 23.6, 15.4, 13.2; HRMS (ESI) calculated for $C_{31}H_{33}F_6O_4$ $[M + H]^+$, 583.2278, found 583.2289.

GENERAL PROCEDURES FOR EN-YNE METATHESIS MACROCYCLIZATION: PREPARATION OF CYCLOPHANES 25, 29, 33 AND 37

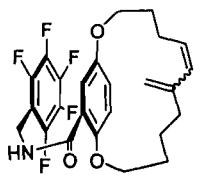
A general procedure for en-yne metathesis reaction is detailed below. Following this description, the spectral data is indicated for each individual compound. Note that the determination of the configuration of the double bond (E or Z) was accomplished using ^1H NMR NOE and NOESY experiments. The Z:E ratios were determined using the method previously described. [4] A flame dried 500 mL tri-neck round bottom flask, equipped with a magnetic stirrer, reflux condenser, and isobar addition funnel or a syringe pump system is charged with Grubbs-Hoveyda II Catalyst (20 mol %) and anhydrous toluene (volume is determined by the amount needed to afford a final concentration of $[M] = 0.4x10^{-4}$ M after complete addition of the precursor solution). The catalyst solution is then placed at reflux 110°C (toluene). The metathesis precursor in solution (approximately 50 mL) is placed in the addition funnel or the syringe pump system and added over 1 h. After addition, the solution was allowed to stir at reflux for 1 additional hour to ensure complete conversion. The reaction mixture was concentrated in vacuo, dry-packed and purified by flash column silica chromatography (hexanes/ ethyl acetate, 20/ 1) to afford the desired 1,3-diene paracyclophanes.

[4] Collins, S. K.; El-Azizi, Y.; Schmitzer, A. R. *J. Org. Chem.* **2007**, *72*, 6397- 6408.



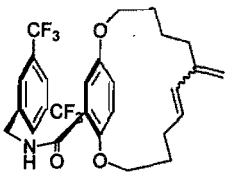
***Z*-25**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (t, J = 5.4 Hz, 1H), 7.84 (s, 1H), 7.81 (s, 2H), 7.80 (s, 1H), 7.02 (s, 2H), 5.25 (d, J = 15.7 Hz, 1H), 5.15 (m, 1H), 4.95 (dd, J = 15.7, 6.8 Hz, 1H), 4.83 (s, 1H), 4.62 (dd, J = 15.7, 6.8 Hz, 1H), 4.57 (s, 1H), 4.45- 4.22 (m, 3H), 2.30- 1.45 (m, 9H), 1.02-0.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 155.6, 151.2, 145.5, 141.6, 132.0 (q, J = 33.0 Hz, CF_3), 131.3, 129.0, 127.5, 124.2, 123.0, 120.7, 120.2, 111.4, 71.3, 70.7, 60.4, 42.8, 34.5, 29.3, 28.6, 28.2, 25.2, 14.2; HRMS (ESI) Calculated for $C_{27}H_{27}F_6NO_3$ $[M + H]^+$: 528.1968 found 528.1968.



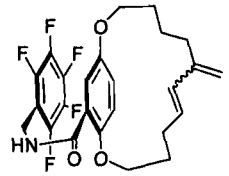
***Z*-33**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (t, J = 5.6 Hz, 1H), 7.79 (s, 1H), 7.00 (d, J = 1.1 Hz, 2H), 5.90-5.27 (d, J = 15.7 Hz, 1H), 5.15- 5.06 (m, 1H), 4.80 (dd, J = 15.7, 6.8 Hz, 1H), 4.79 (s, 1H), 4.61 (dd, J = 15.7, 6.8 Hz, 1H), 4.55 (s, 1H), 4.45- 4.38 (m, 1H), 4.35- 4.25 (m, 2H), 4.18- 4.00 (m, 1H), 2.20-1.45 (m, 8H), 1.30- 1.20 (m, 1H), 0.97- 0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 155.4, 151.2, 145.6, 143.7, 131.3, 129.1, 124.1, 123.0, 120.2, 120.0, 111.4, 71.4, 70.6, 60.4, 36.0, 31.5, 29.3, 28.5, 28.1, 25.3; HRMS (ESI) Calculated for $C_{25}H_{25}F_5NO_3$ $[M + H]^+$: 482.17491 found 482.17656. Calculated for $C_{25}H_{24}F_5NO_3Na$ $[M + Na]^+$: 504.1569 found 504.1574.



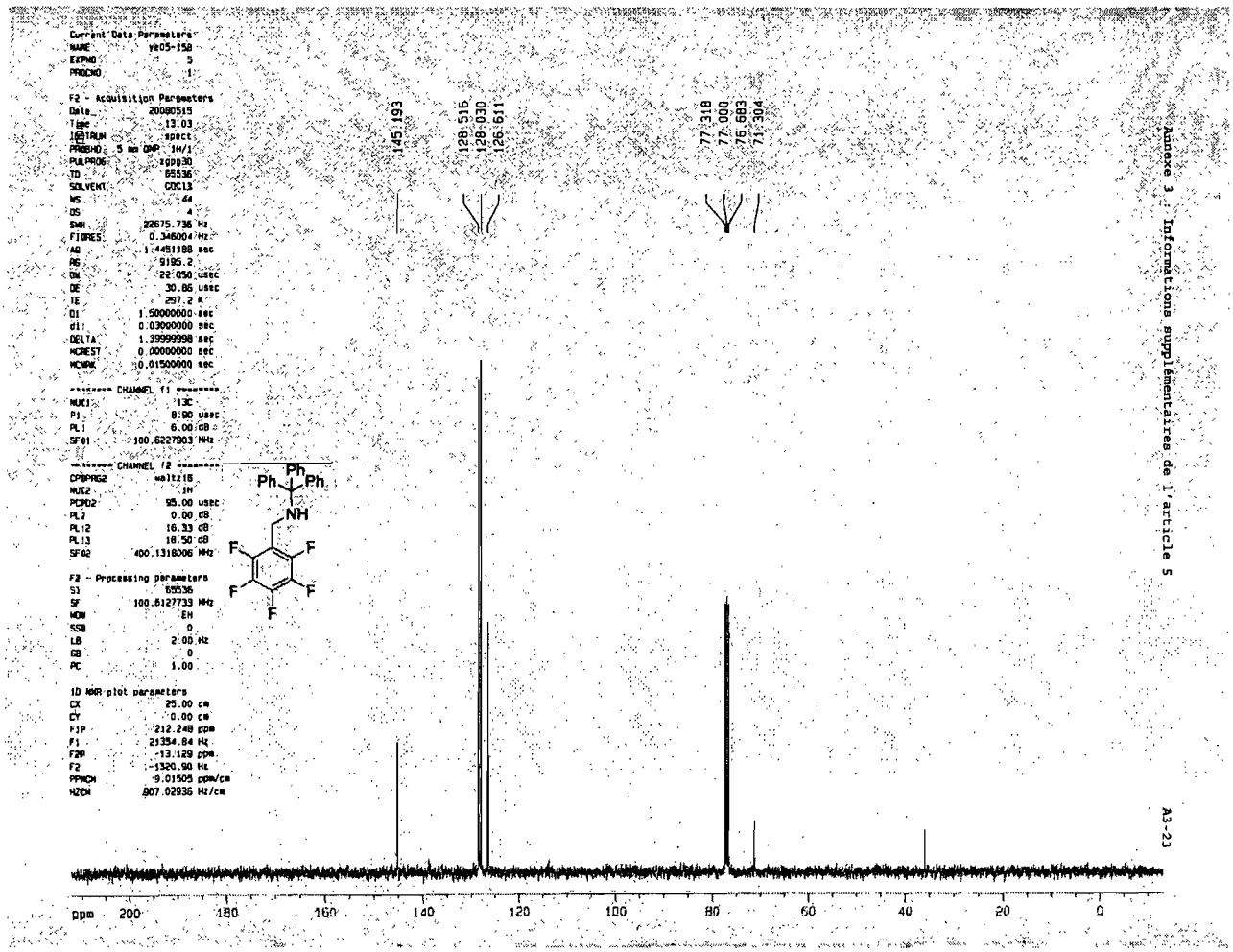
***Z*- 29**

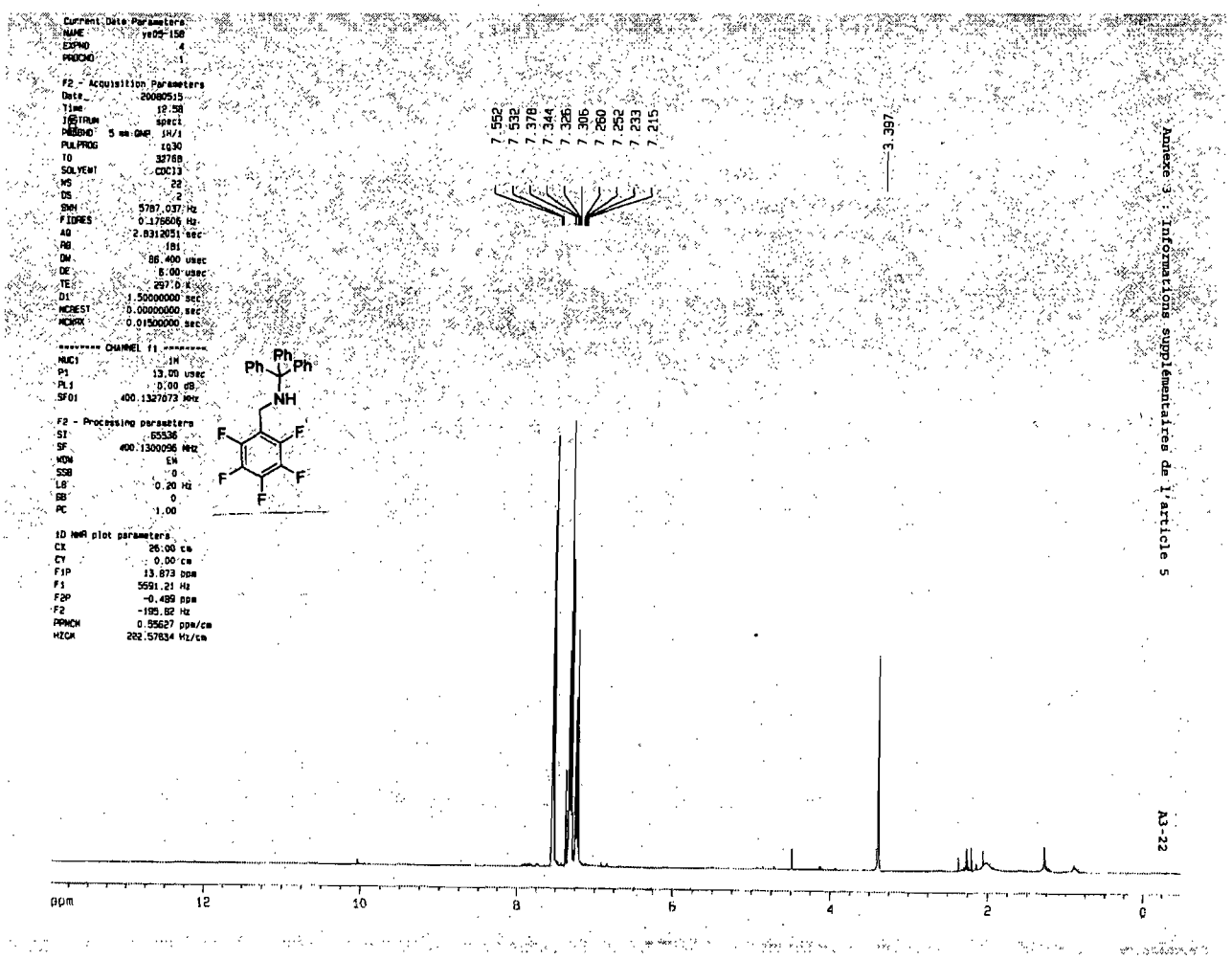
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (t, J = 5.6 Hz, 1H), 7.86 (d, J = 3.0 Hz, 1H), 7.83 (s, 2H), 7.80 (s, 1H), 7.09 (dd, J = 9.0, 3.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.17 (d, J = 15.7 Hz, 1H), 5.09- 5.00 (m, 1H), 4.95 (dd, J = 15.7, 6.8 Hz, 1H), 4.83 (s, 1H), 4.62 (dd, J = 15.7, 6.8 Hz, 1H), 4.61 (s, 1H), 4.41- 4.37 (m, 1H), 4.30- 4.23 (m, 3H), 2.18- 1.80 (m, 2H), 1.75- 1.50 (m, 6H), 1.45-1.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 153.8, 153.2, 145.7, 141.5, 132.1 (q, CF_3), 132.0, 131.7, 127.4, 127.8, 123.9, 123.1, 121.6, 119.4, 111.5, 72.7, 69.5, 53.4, 42.8, 34.4, 29.4, 28.8, 28.1, 24.4; HRMS (ES) Calculated for $C_{27}H_{28}F_6NO_3$ $[M + H]^+$: 528.1968 found 528.1978. Calculated for $C_{27}H_{27}F_6NO_3Na$ $[M + Na]^+$: 550.1787, found 550.1797.

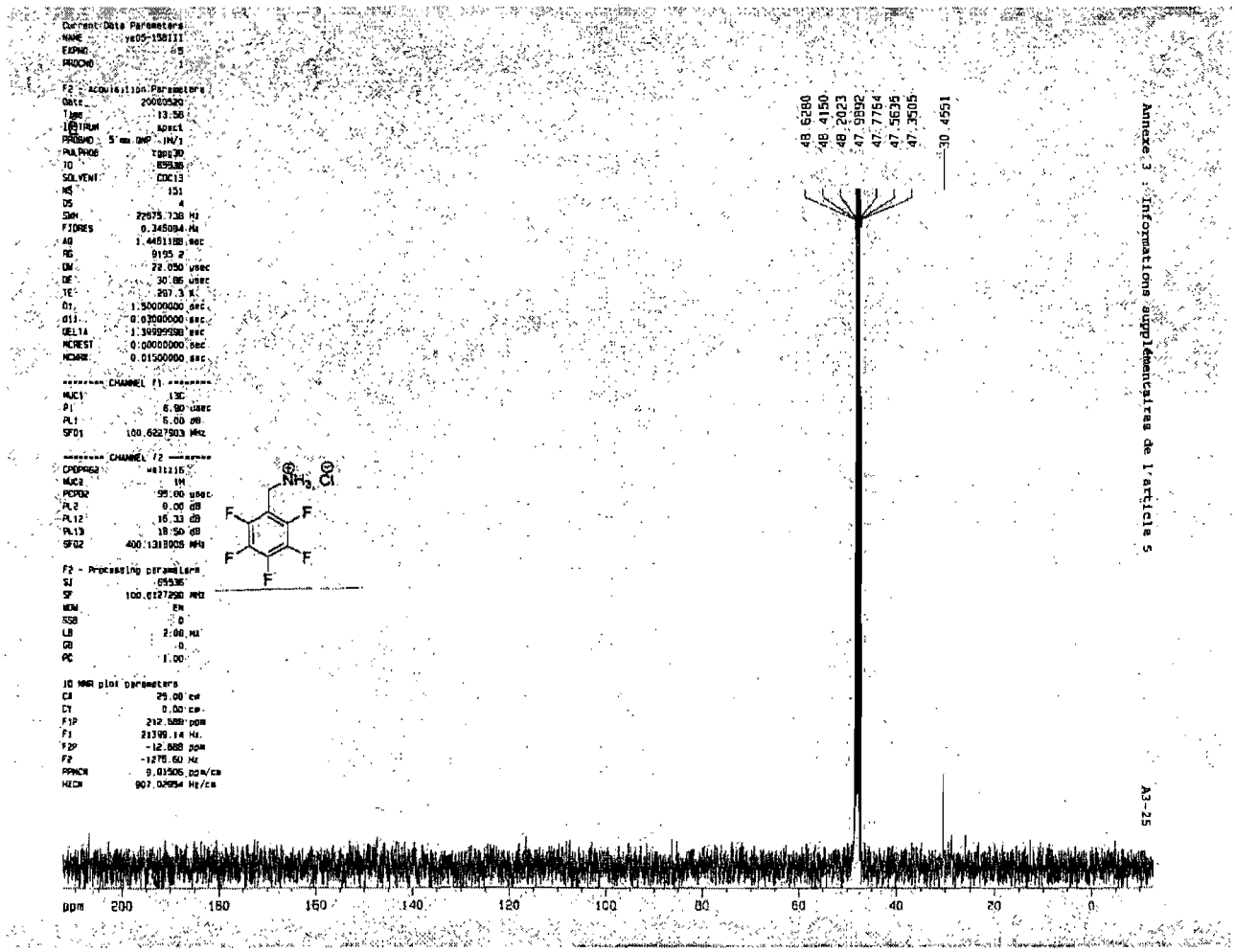


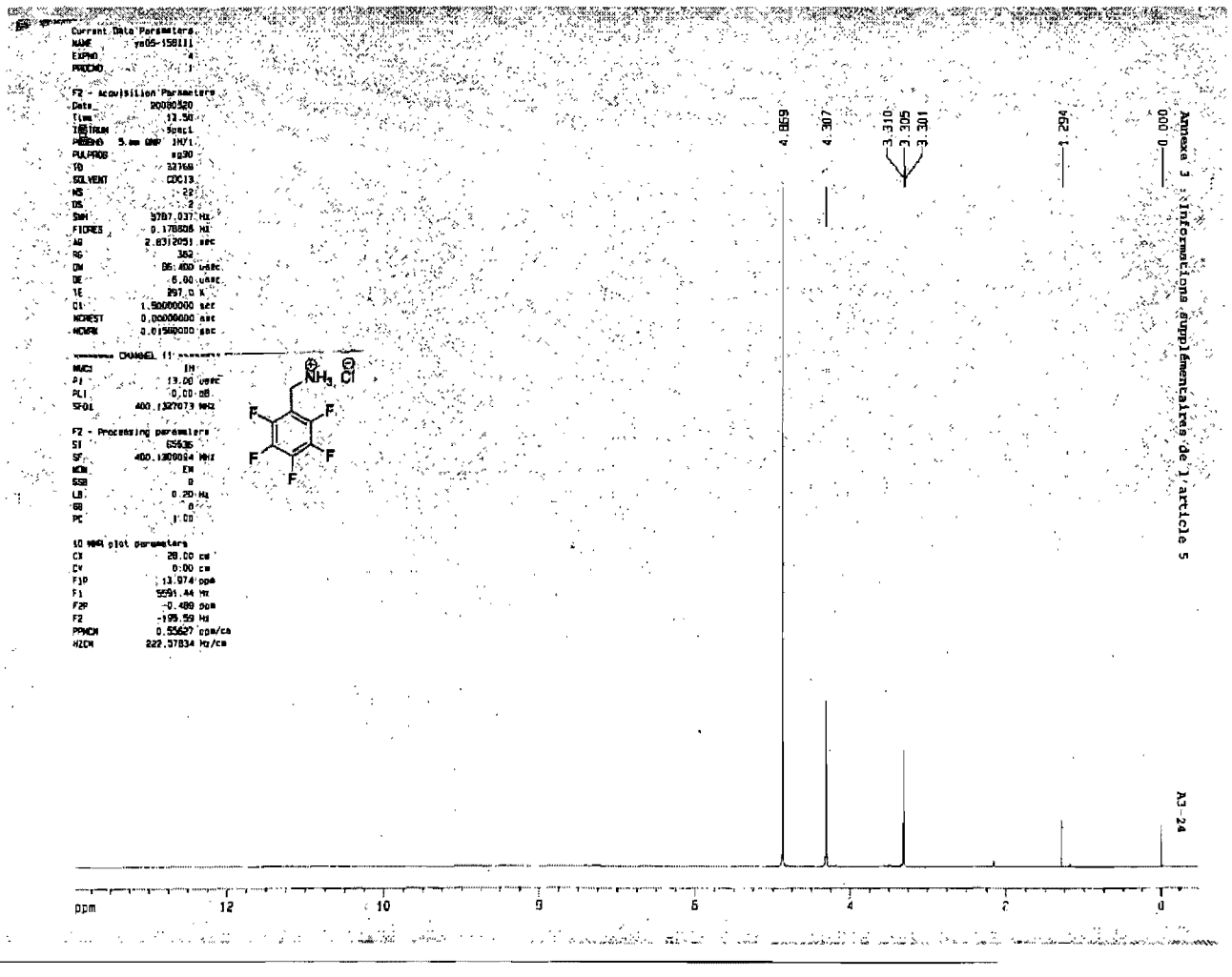
***Z*–37**

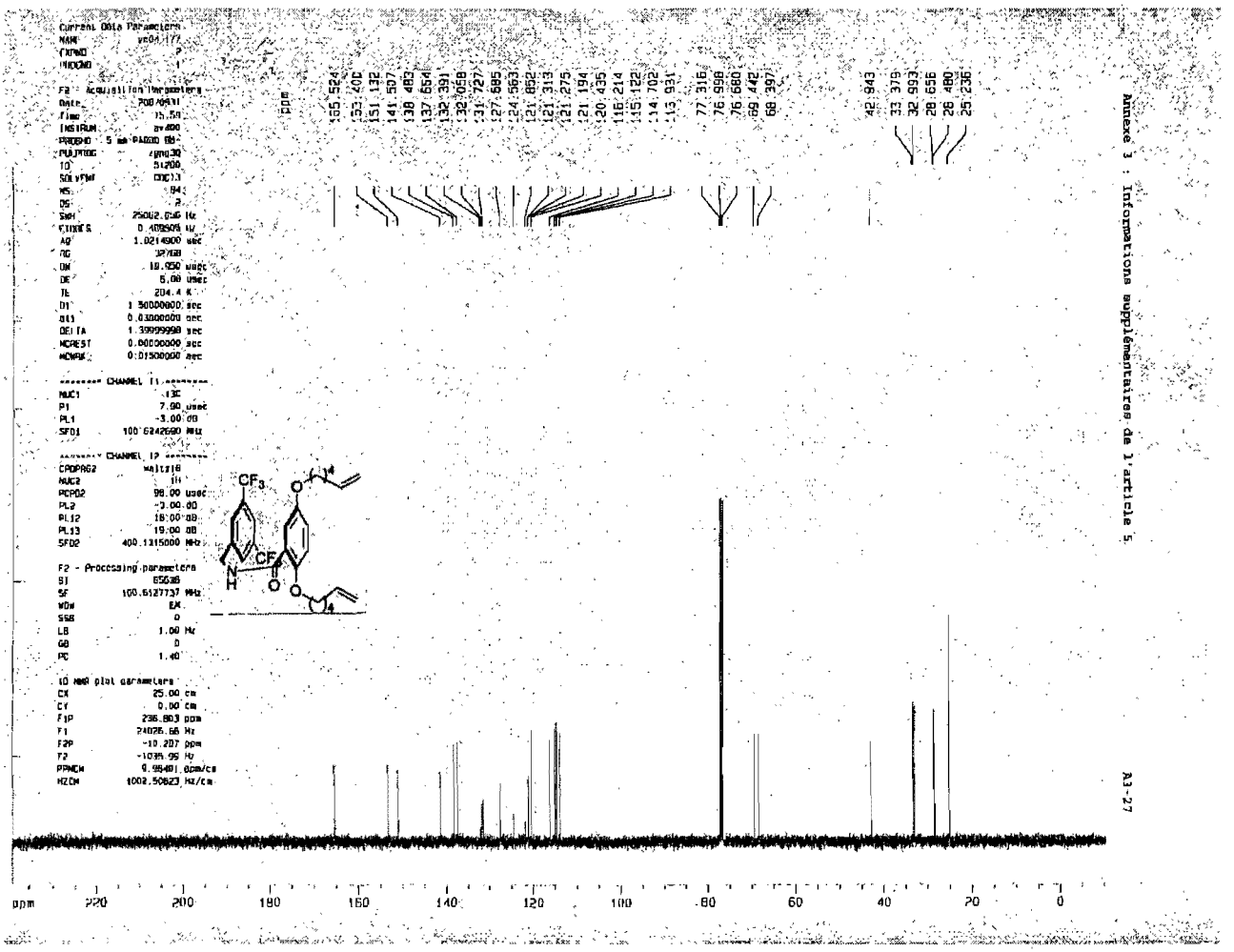
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (t, J = 5.6 Hz, 1H), 7.82 (d, J = 3.1 Hz, 1H), 7.07 (dd, J = 9.1, 3.1 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 5.40 (d, J = 15.7 Hz, 1H), 5.20- 5.00 (m, 2H), 4.85 (dd, J = 15.7, 6.8 Hz, 1H), 4.80 (d, J = 2.0 Hz, 1H), 4.68- 4.55 (m, 1H), 4.46- 4.36 (m, 2H), 4.28- 4.20 (m, 2H), 2.15- 1.50 (m, 8H), 1.30- 1.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 153.7, 145.8, 132.0, 127.5, 123.2, 121.6, 119.1, 111.3, 77.2, 72.7, 70.6, 69.6, 34.4, 31.4, 29.5, 28.8, 28.1, 24.9; HRMS (ESI) Calculated for $C_{25}H_{25}F_5NO_3$ $[M + H]^+$: 482.1749 found 482.1754. Calculated for $C_{25}H_{24}F_5NO_3Na$ $[M + H]^+$: 504.1569 found 504.1569.

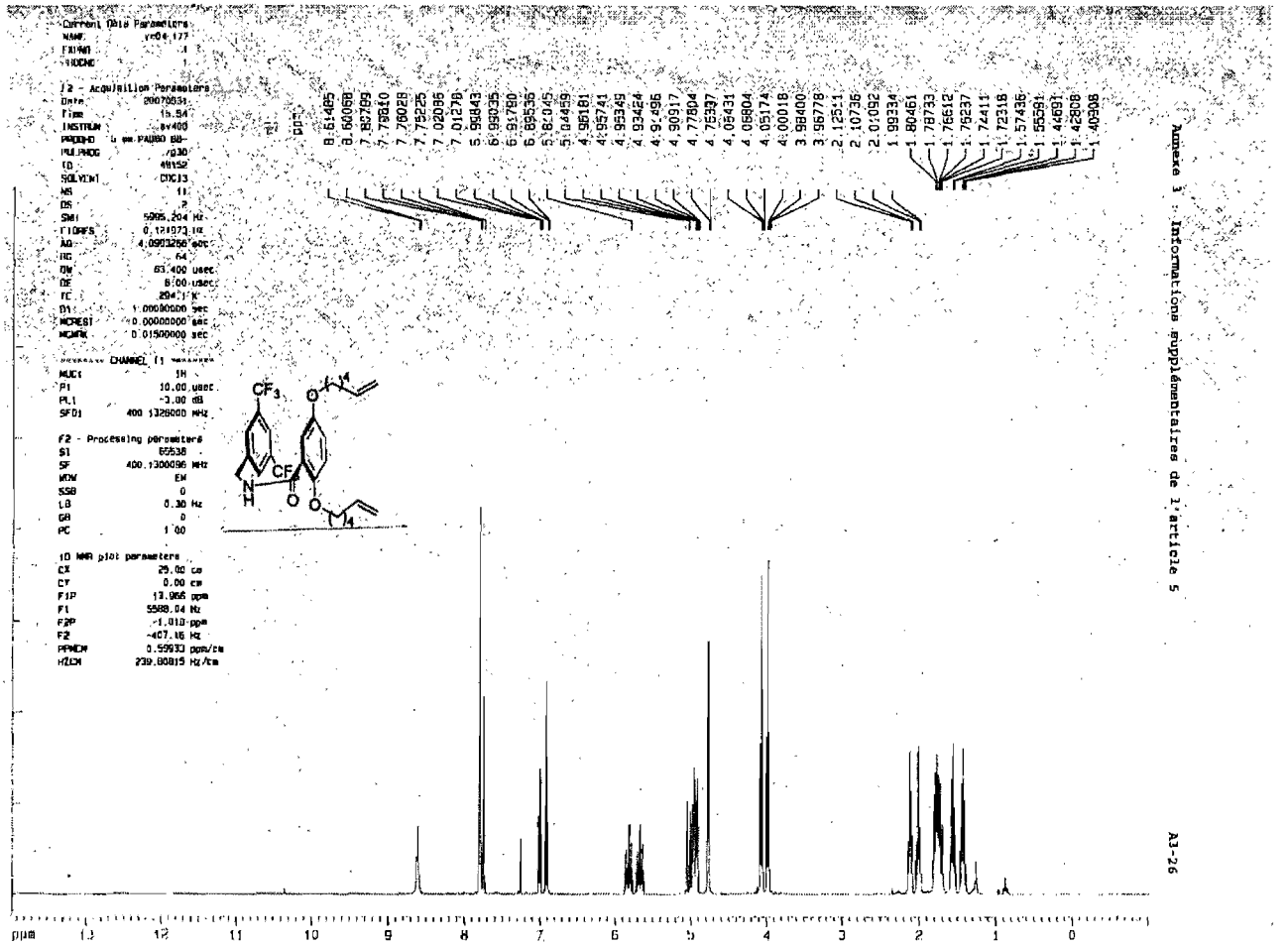

Current Data Parameters
NAME ye05-158
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080515
Time 13.03
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 44
DS 4
SWH 22675.736 Hz
FIDRES 0.346004 Hz
AQ 1.4451888 sec
RG 9195.2
DW 22.050 usec
DE 30.86 usec
TE 297.2 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127733 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.248 ppm
F1 21354.84 Hz
F2P -13.129 ppm
F2 -1320.90 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02936 Hz/cm
145.193
128.516
128.030
126.611
77.318
77.000
76.683
71.304
Ph
Ph
Ph
NH
F
F
F
F
F
ppm
200
180
160
140
120
100
80
60
40
20
0
A3-23

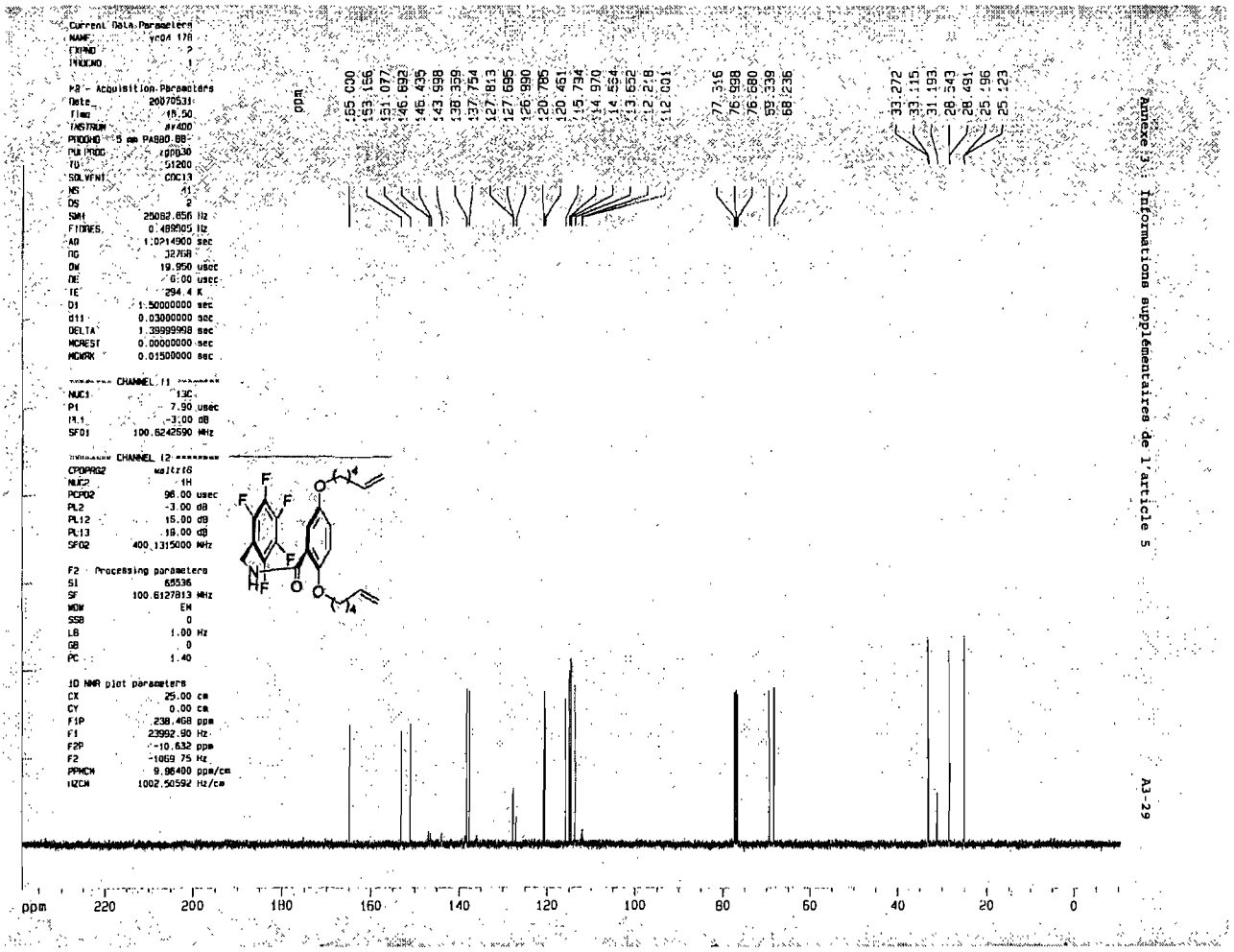

Current Data Parameters
NAME ye05-158
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080515
Time 12.58
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 22
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 181
DW 86.400 usec
DE 6.00 usec
TE 297.0 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300096 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.873 ppm
F1 5551.21 Hz
F2P -0.489 ppm
F2 -195.82 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
7.552
7.532
7.378
7.344
7.326
7.306
7.260
7.252
7.233
7.215
3.397
Ph
Ph
Ph
NH
F
F
F
F
F
ppm
12
10
8
6
4
2
0
A3-22

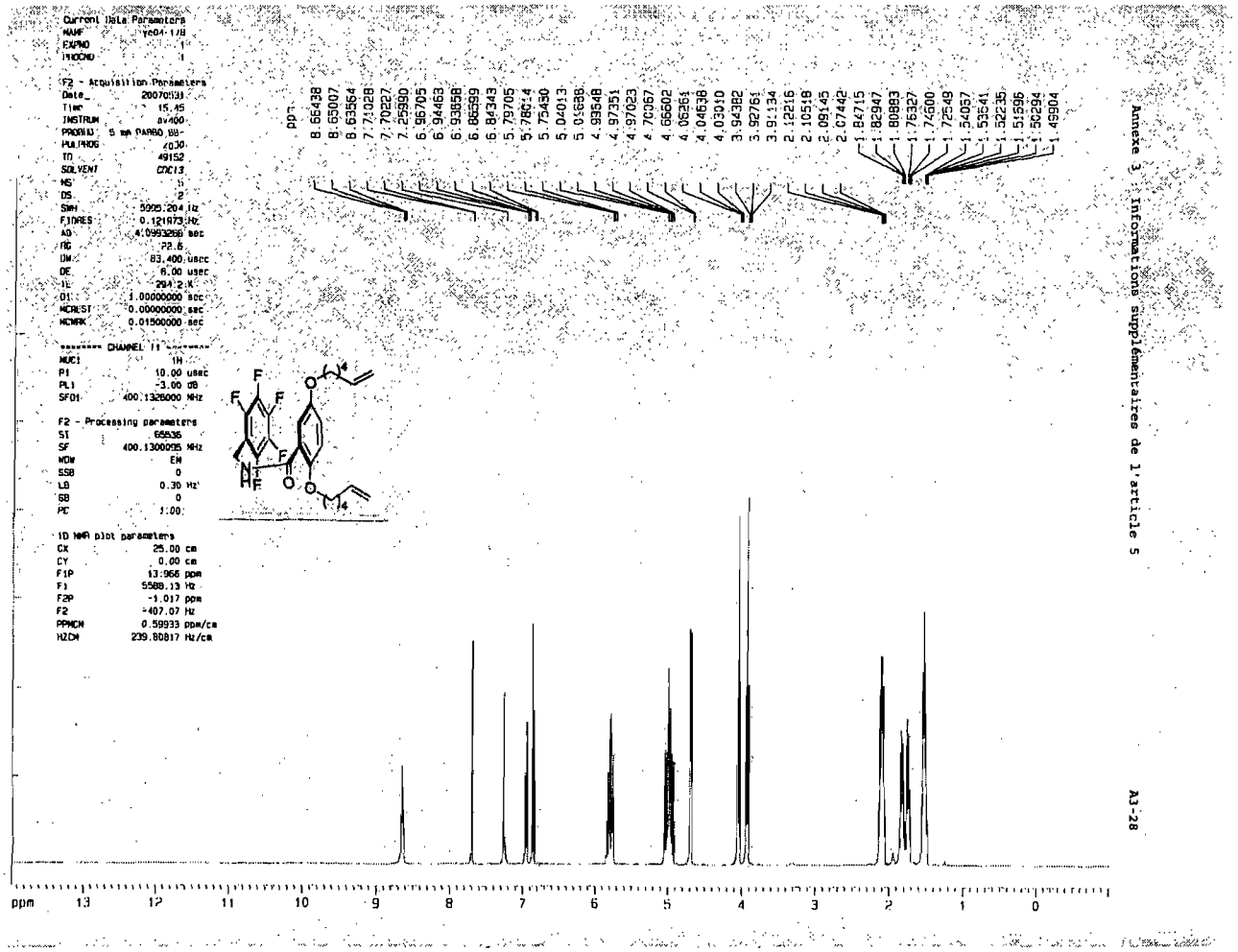

Current Data Parameters
NAME ye05-158III
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080520
Time 13.56
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 151
DS 4
SWH 27675.738 Hz
FIDRES 0.345084 Hz
AQ 1.4451888 sec
RG 9195.2
DW 22.050 usec
DE 30.86 usec
TE 297.3 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 6.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318005 MHz
F2 - Processing parameters
SI 65536
SF 100.6127950 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.888 ppm
F1 21399.14 Hz
F2P -12.888 ppm
F2 -1276.60 Hz
PPMCM 8.01505 ppm/cm
HZCM 907.02954 Hz/cm
48.6280
48.4150
48.2023
47.9892
47.7764
47.5635
47.3505
30.4551
A3-25
ppm 200 180 160 140 120 100 80 60 40 20 0

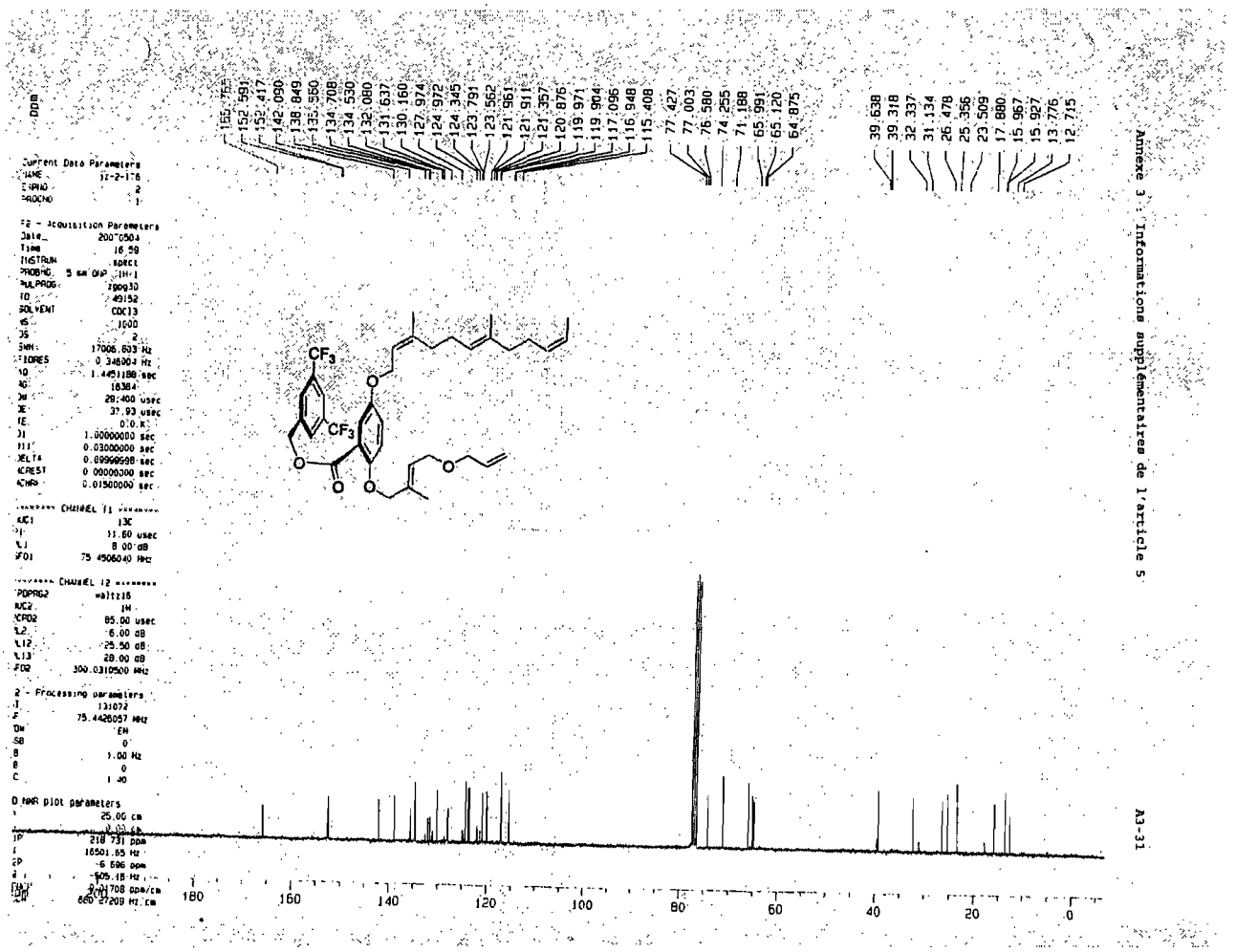

Current Data Parameters
NAME ye05-158III
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080520
Time 13.50
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 22
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 362
DW 86.400 usec
DE 6.00 usec
TE 297.0 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300014 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 28.00 cm
CY 0.00 cm
F1P 13.974 ppm
F1 5591.44 Hz
F2P -0.489 ppm
F2 -195.59 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
4.869
4.307
3.310
3.305
3.301
1.942
1.000
A3-24
ppm 12 10 8 6 4 2 0

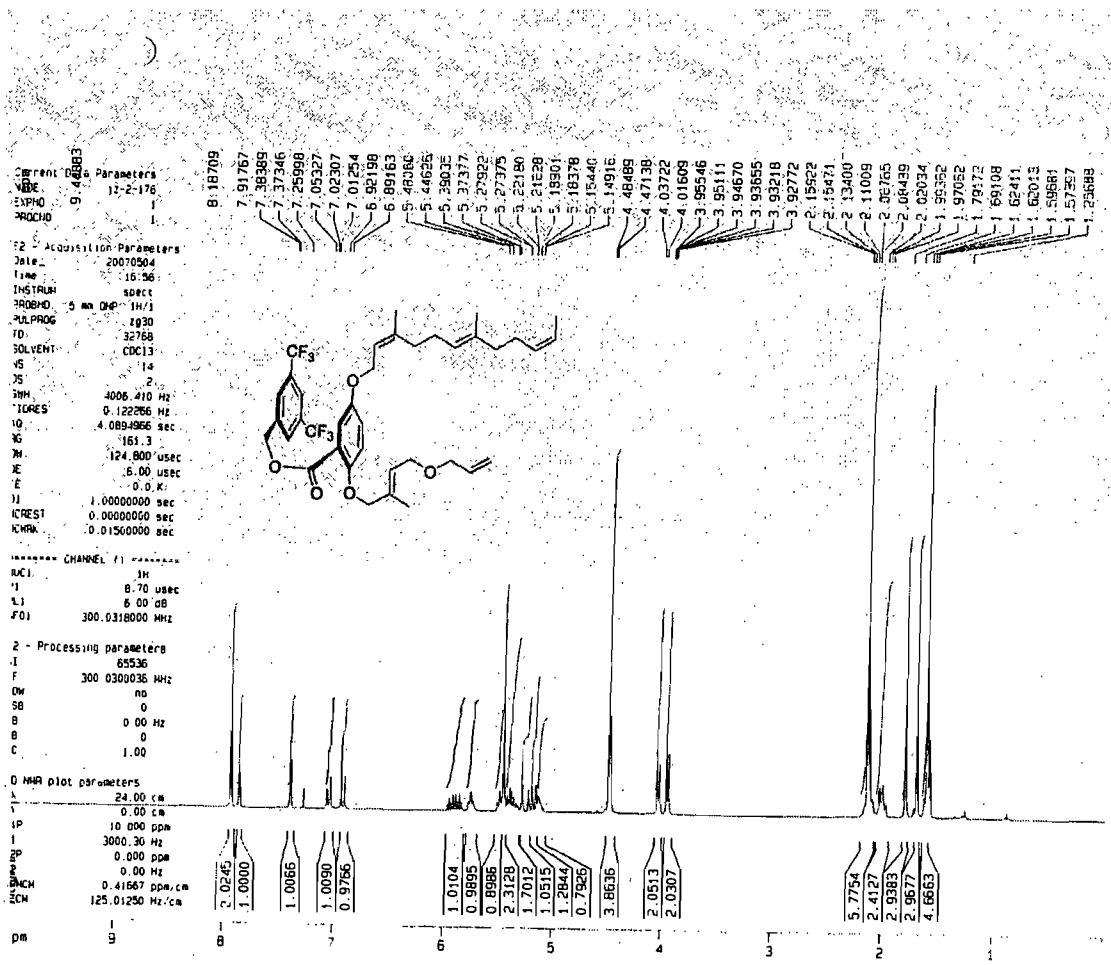

A3-27
ppm

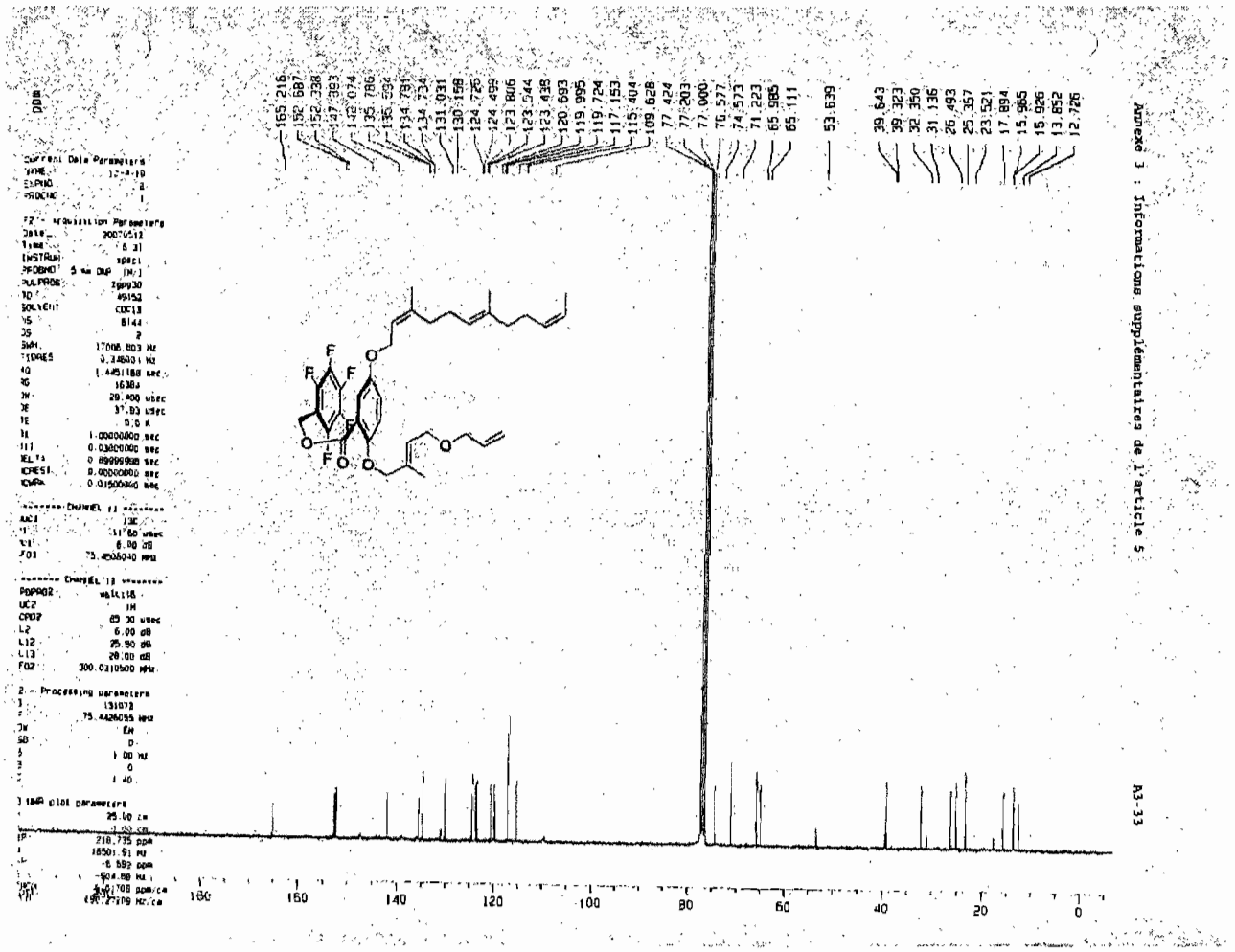

A3-26
ppm


Current Data Parameters
NAME yc04 17B
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070531
Time 19.50
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 41
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214900 sec
RG 3276.8
DW 19.950 usec
DE 6.00 usec
TE 294.4 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6242590 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 96.00 usec
PL2 -3.00 dB
PL12 15.00 dB
PL13 18.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127813 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.468 ppm
F1 23992.90 Hz
F2P -10.632 ppm
F2 -1069.75 Hz
PPMCM 9.86400 ppm/cm
HZCM 1002.50592 Hz/cm
ppm
155.030
153.156
151.077
146.692
146.435
143.998
138.359
137.754
127.813
127.695
126.990
120.795
120.461
115.734
114.970
114.554
113.652
112.218
112.001
77.316
76.998
76.680
59.339
68.236
33.272
33.115
31.193
28.543
28.491
25.196
25.123
ppm 220 200 180 160 140 120 100 80 60 40 20 0

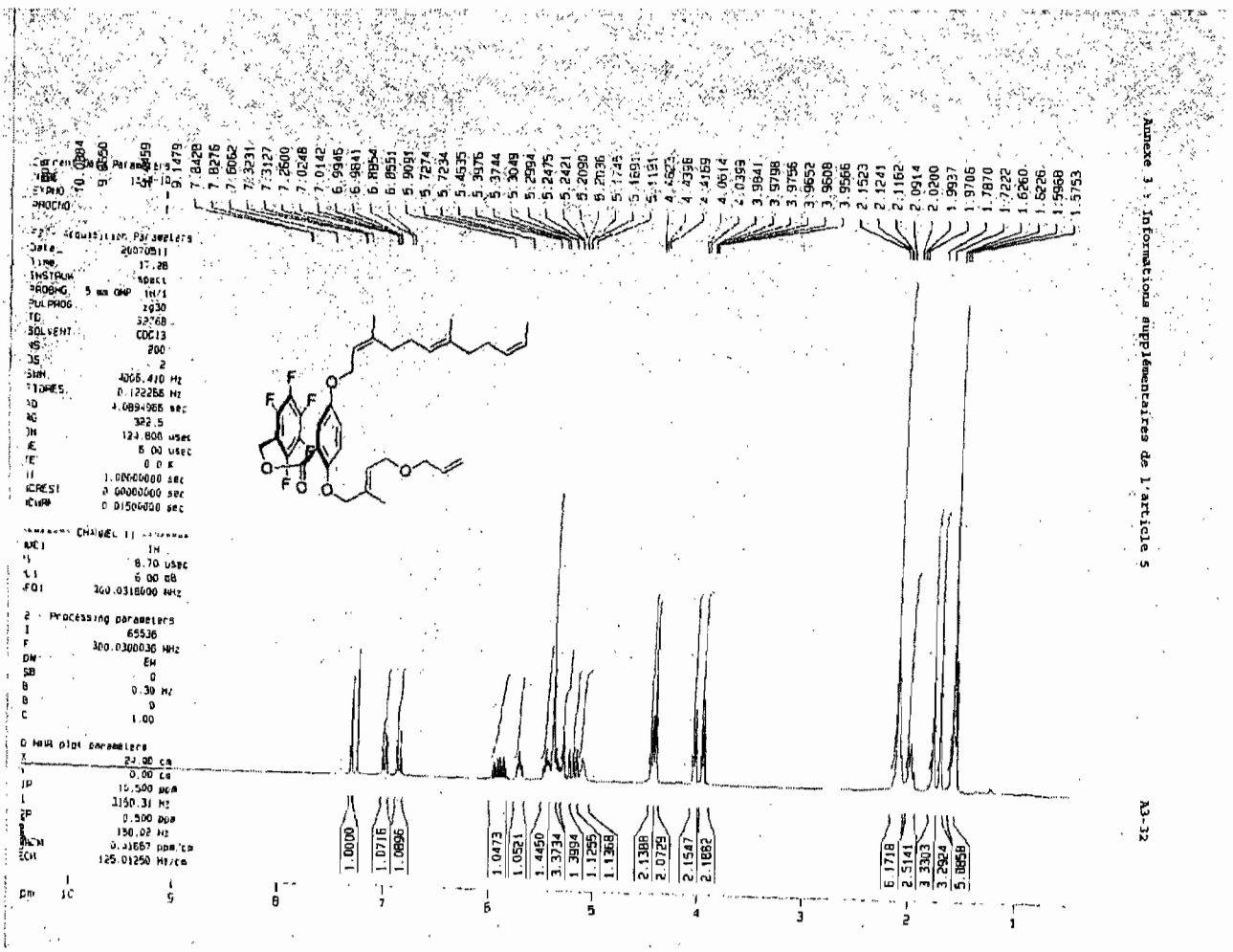

Current Data Parameters
NAME yc04-17B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070531
Time 15.45
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 5
DS 2
SWH 5995.204 Hz
FIDRES 0.121873 Hz
AQ 4.0993986 sec
RG 22.6
DW 83.400 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300095 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.966 ppm
F1 5588.13 Hz
F2P -1.017 ppm
F2 -407.07 Hz
PPMCM 0.59933 ppm/cm
HZCM 239.80817 Hz/cm
ppm
8.66438
8.65007
8.63564
7.71028
7.70227
7.25980
6.96705
6.94463
6.93858
6.86599
6.84343
5.79705
5.78614
5.75430
5.04013
5.01636
4.99548
4.97351
4.97023
4.70367
4.66602
4.06261
4.04638
4.03010
3.94382
3.92761
3.91134
2.12216
2.10518
2.09145
2.07442
1.84715
1.82947
1.80883
1.76327
1.74600
1.72548
1.54057
1.53541
1.52235
1.51596
1.50294
1.49904
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0



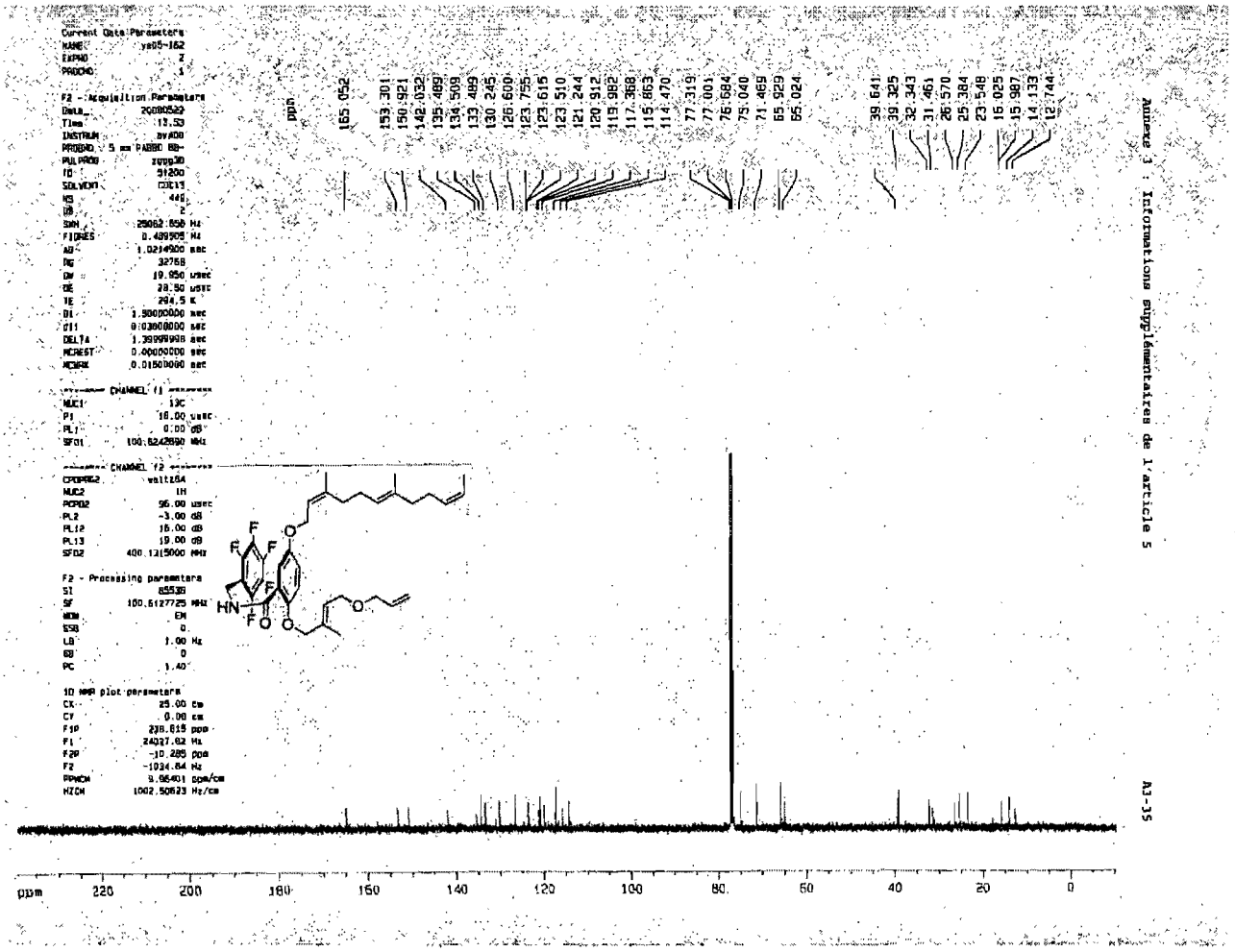


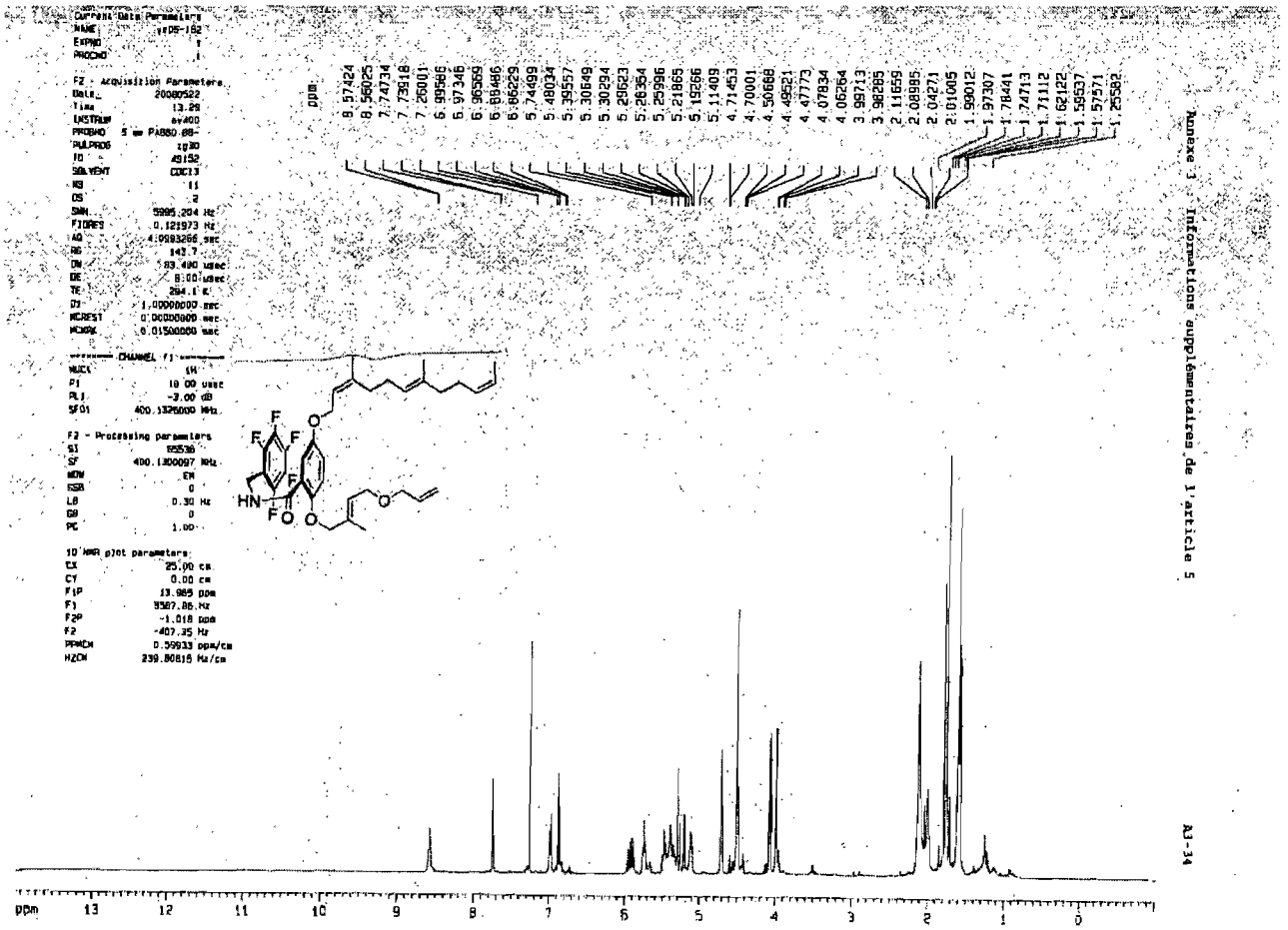


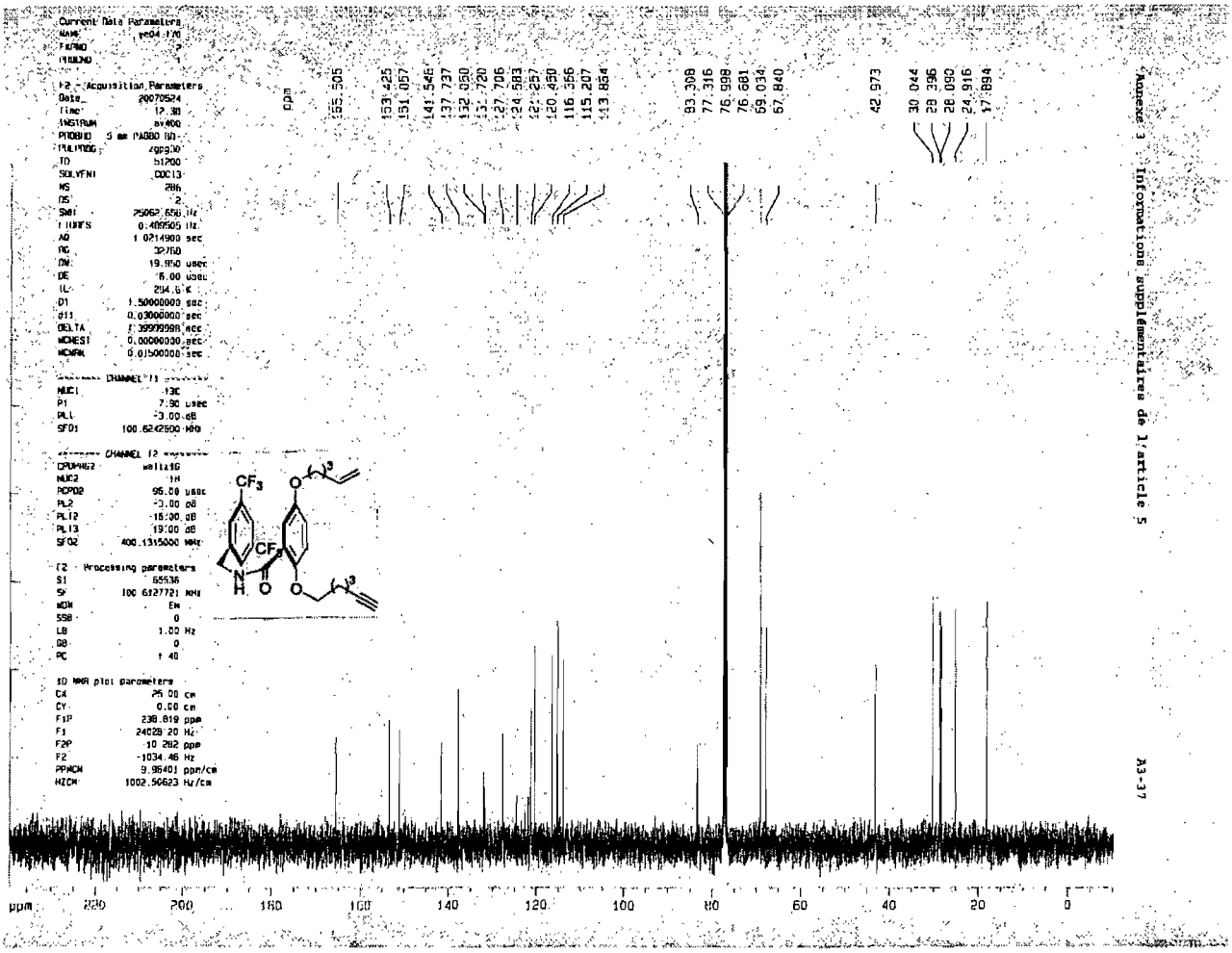
A3-33

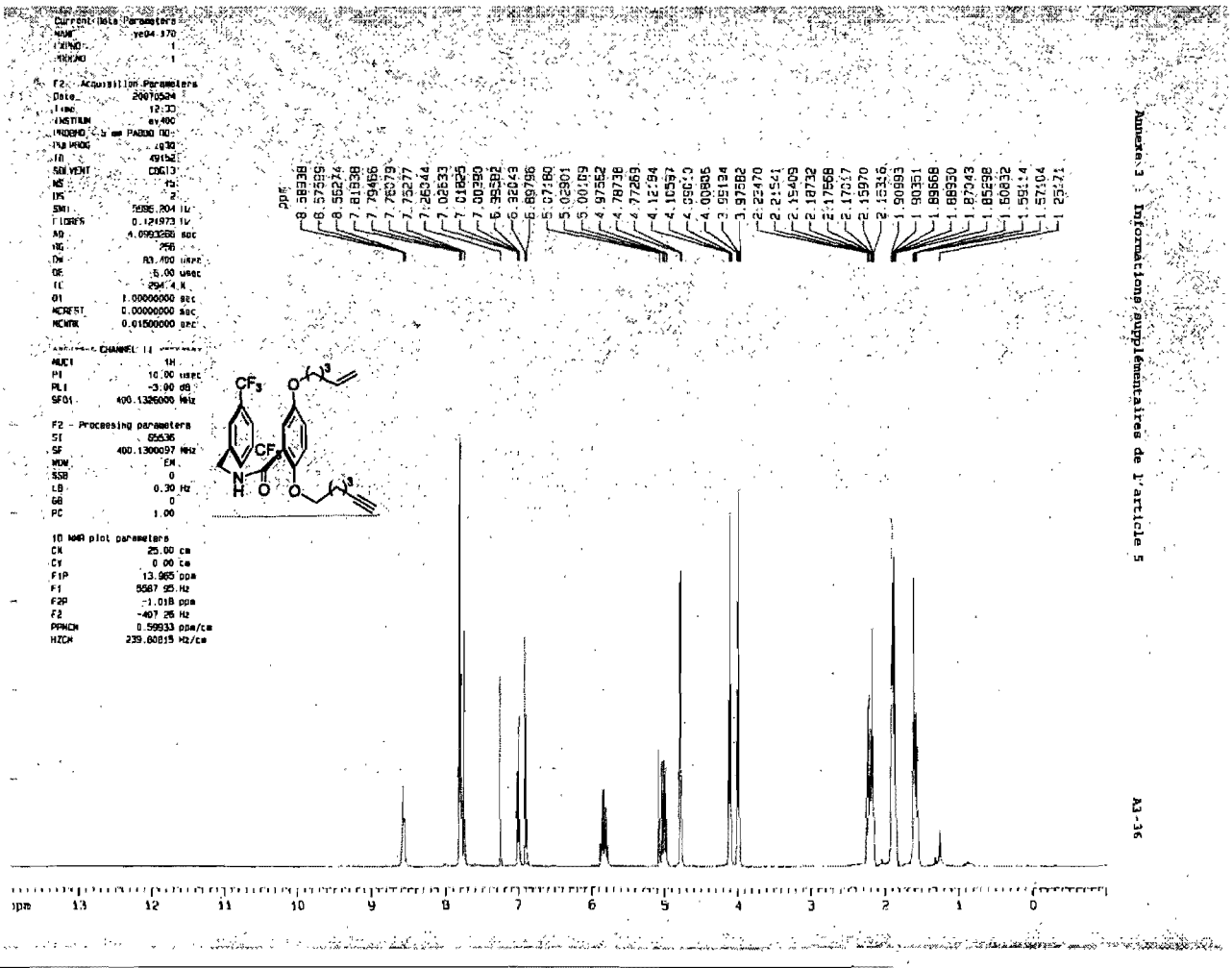


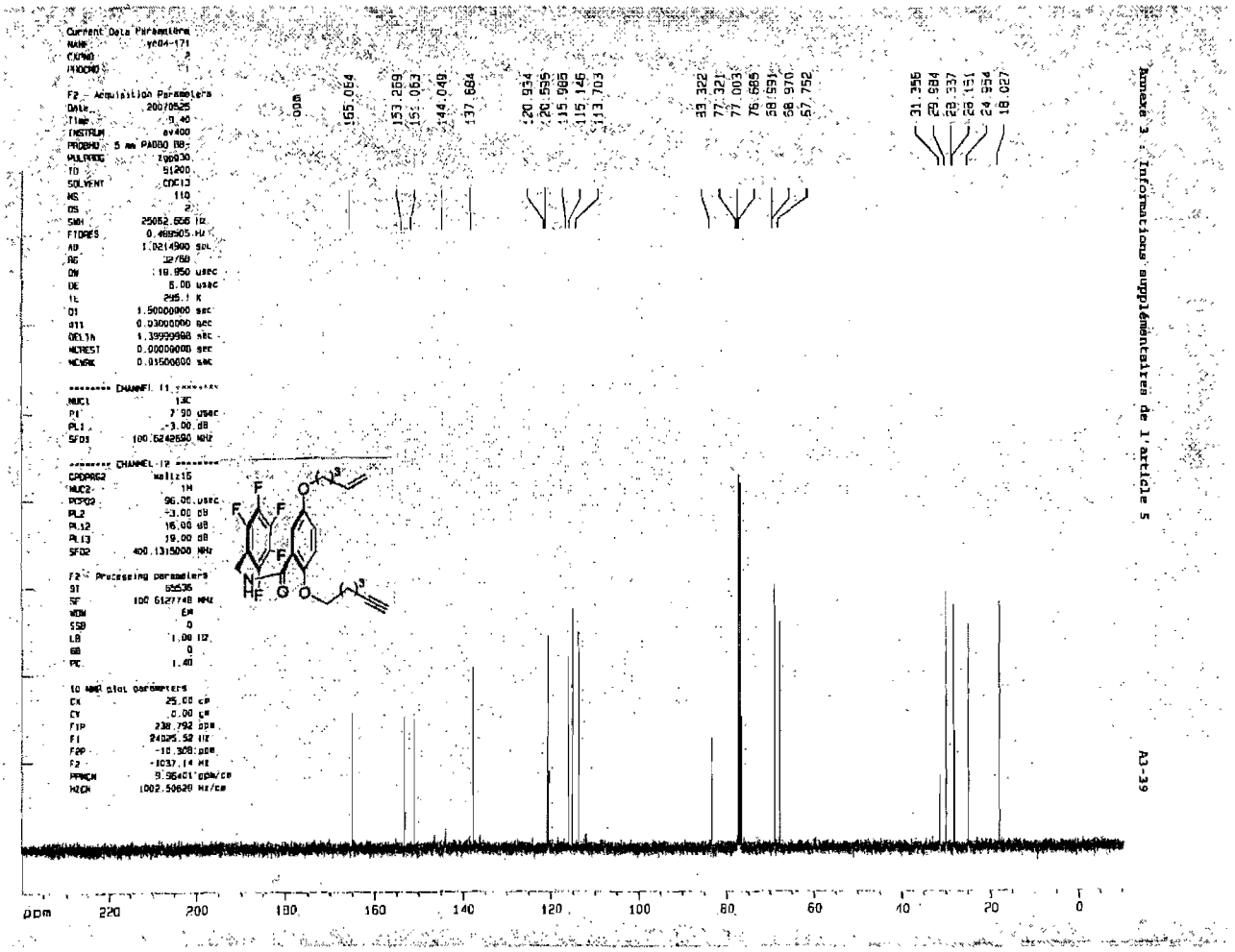
A3-32

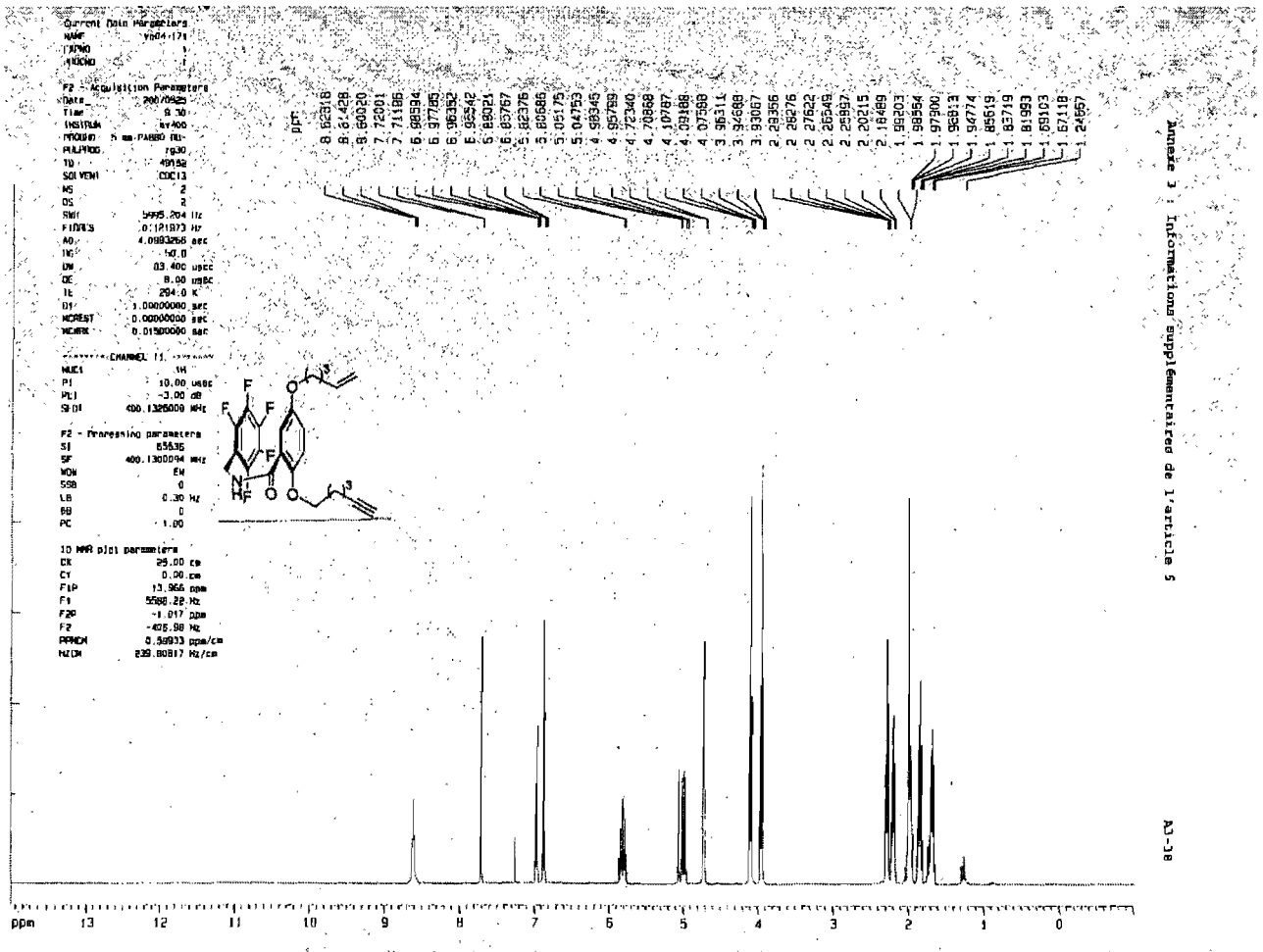

Current Data Parameters
NAME ysd5-162
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080522
Time 13.53
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 91200
SOLVENT CDCl3
NS 448
DS 2
SWH 25062.656 Hz
FIDRES 0.489905 Hz
AQ 1.8214400 sec
RG 32768
DW 19.950 usec
DE 28.50 usec
TE 294.5 K
D1 1.30000000 sec
D11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 16.00 usec
PL1 0.00 dB
SFO1 100.6242690 MHz
CHANNEL f2
CPDPRG2 waltz64
NUC2 1H
PCPD2 96.00 usec
PL2 -3.00 dB
PL12 16.00 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127725 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.815 ppm
F1 24027.62 Hz
F2P -10.285 ppm
F2 -1034.64 Hz
PPMCM 9.56401 ppm/cm
HZCM 1002.50623 Hz/cm
ppm
165.052
153.301
150.921
142.032
135.489
134.509
133.499
130.245
126.600
123.755
123.615
123.510
121.244
120.912
119.982
117.368
115.863
114.470
77.319
77.001
76.684
75.040
71.469
65.929
65.024
39.641
39.325
32.343
31.461
26.570
25.384
23.548
16.025
15.987
14.133
13.744
HN
F
O
ppm
220
200
180
160
140
120
100
80
60
40
20
0

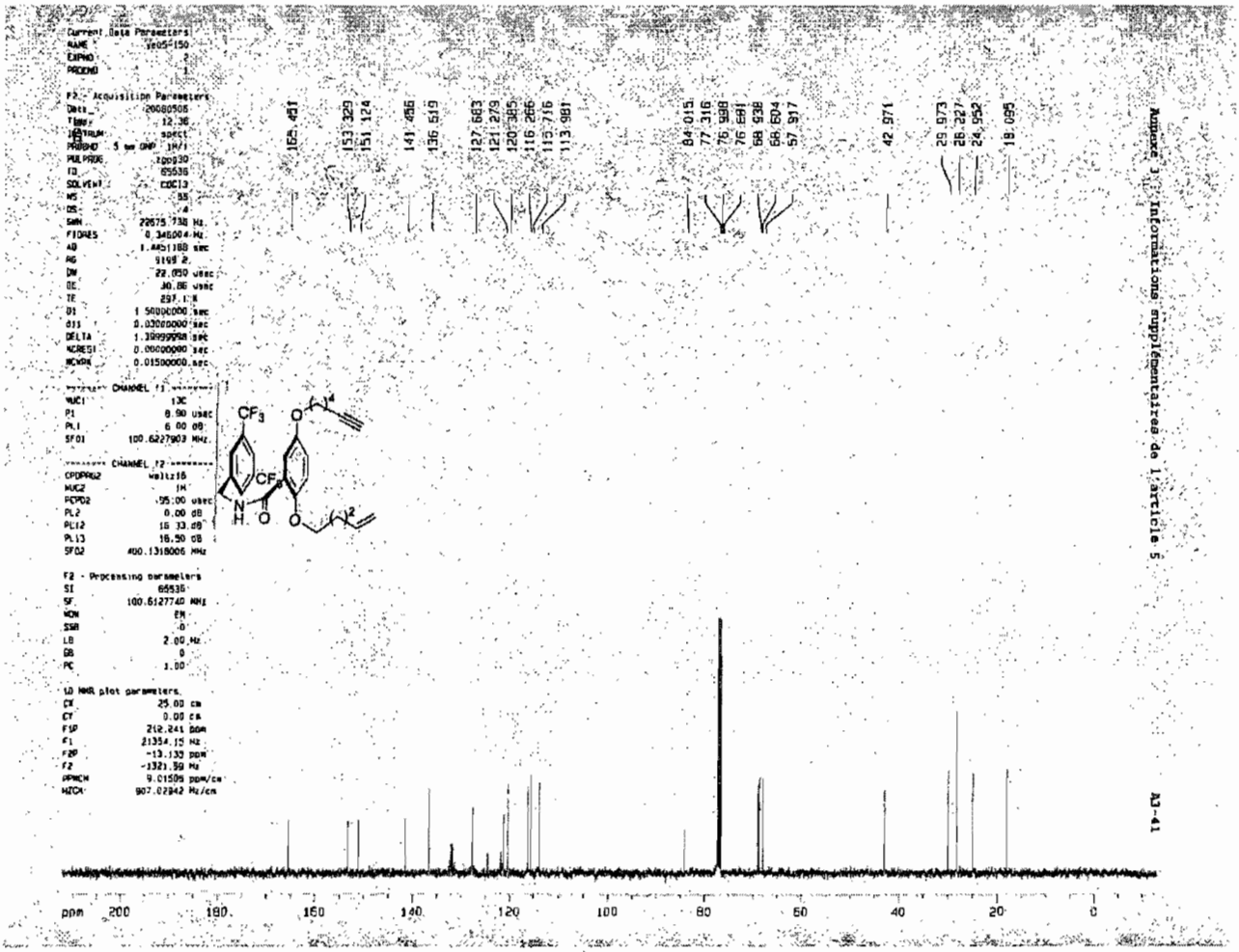

Current Data Parameters
NAME ysd5-162
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080522
Time 13.28
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0983296 sec
RG 142.7
DW 83.400 usec
DE 6.00 usec
TE 294.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -2.00 dB
SFO1 400.1325000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.985 ppm
F1 5597.86 Hz
F2P -1.016 ppm
F2 -407.35 Hz
PPMCM 0.55933 ppm/cm
HZCM 239.80816 Hz/cm
ppm
8.57424
8.56025
7.74734
7.73918
7.26001
6.99586
6.97346
6.96959
6.88486
6.86229
5.74499
5.48034
5.39557
5.30649
5.30294
5.29623
5.26354
5.25996
5.21865
5.19266
5.11409
4.71453
4.70001
4.50668
4.49521
4.47773
4.07834
4.06264
3.99713
3.98265
2.11659
2.08985
2.04271
2.01005
1.99012
1.97307
1.78441
1.74713
1.71112
1.62122
1.58537
1.57571
1.25582
HN
F
O
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0

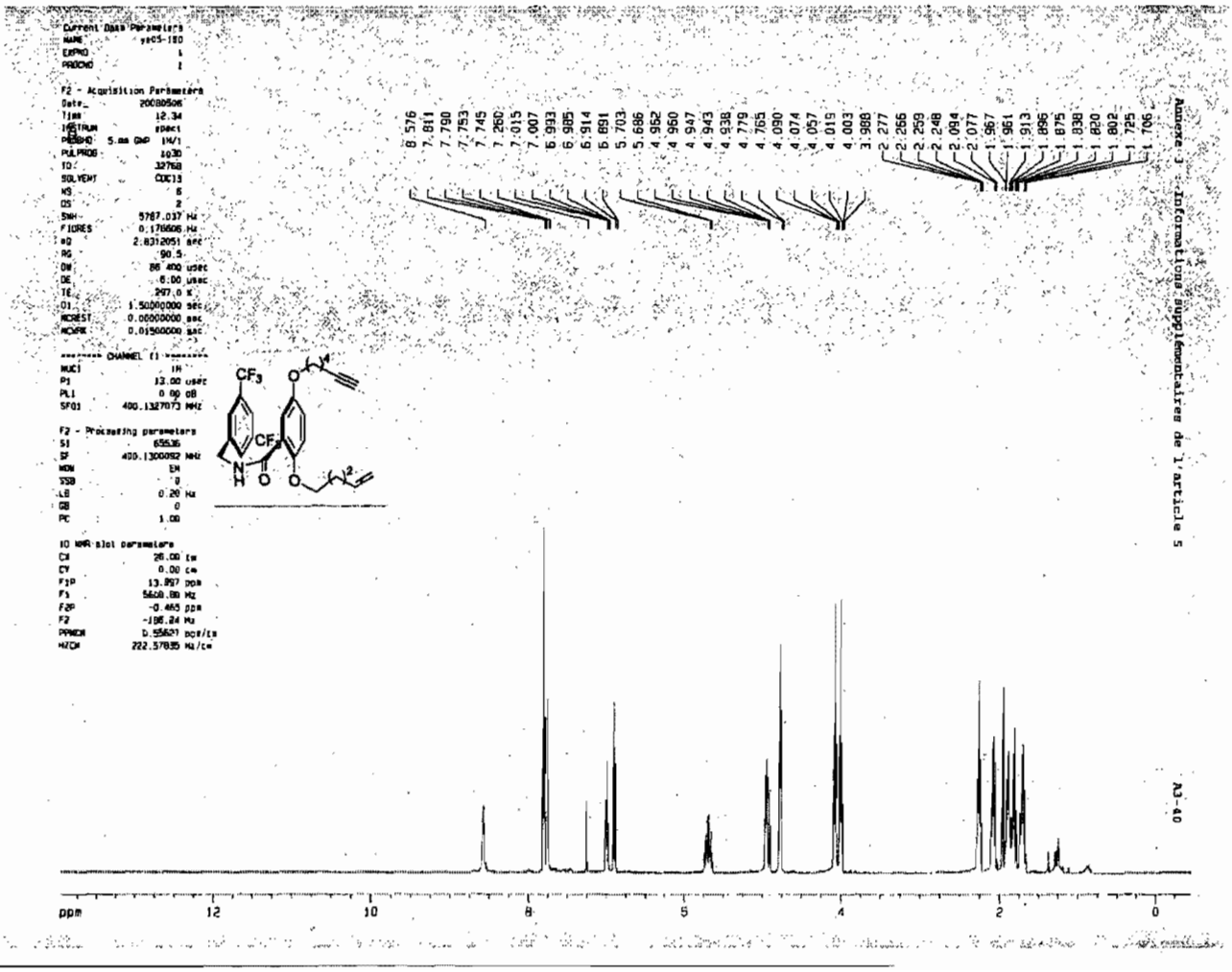

Annexe 3 : Informations supplémentaires de l'article 5
A3-37
Current Data Parameters
NAME ye04-170
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070524
Time 12.30
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 256
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214900 sec
RG 32768
DW 19.950 usec
DE 6.00 usec
TE 294.6 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000030 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6242600 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 -3.00 dB
PL12 -15.00 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127721 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.819 ppm
F1 24028.20 Hz
F2P 10.282 ppm
F2 -1034.46 Hz
PPMCM 9.95401 ppm/cm
HZCM 1002.50623 Hz/cm
ppm
155.505
153.425
151.057
141.546
137.737
132.050
131.720
127.706
124.583
121.257
120.450
116.366
115.207
113.854
83.308
77.316
76.998
76.681
69.034
67.840
42.973
30.044
29.396
28.050
24.916
17.894
CF3
CF2
N
H
O
O
ppm
220
200
180
160
140
120
100
80
60
40
20
0

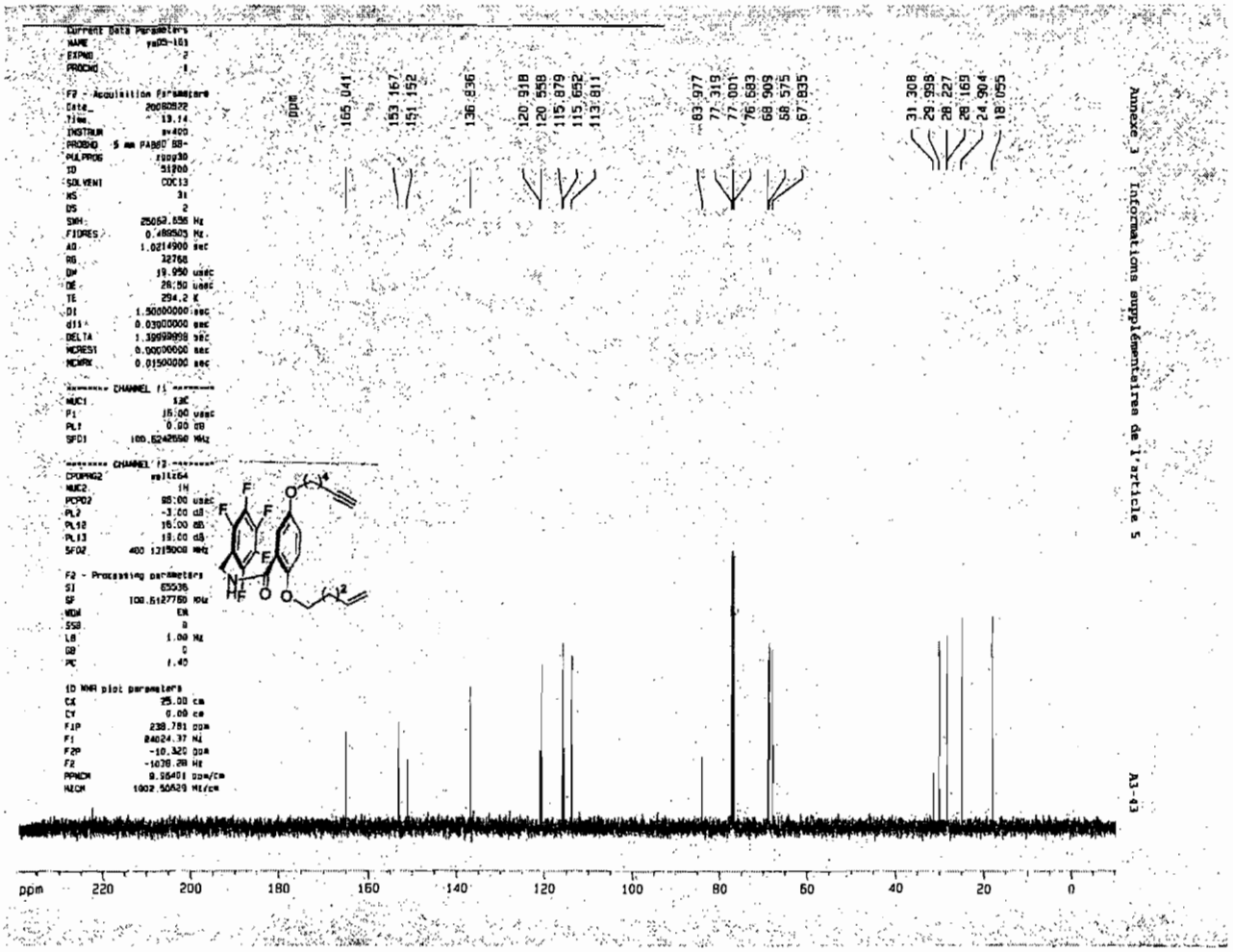

Annexe 3 : Informations supplémentaires de l'article 5
A3-36
Current Data Parameters
NAME ye04-170
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070524
Time 12.30
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 16
DS 2
SWH 7986.204 Hz
FIDRES 0.121973 Hz
AQ 4.0993266 sec
RG 256
DW 62.400 usec
DE 6.00 usec
TE 294.4 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.965 ppm
F1 5587.95 Hz
F2P -1.018 ppm
F2 -407.25 Hz
PPMCM 0.59933 ppm/cm
HZCM 239.80815 Hz/cm
ppm
8.58338
8.57599
8.56274
7.81938
7.79486
7.76579
7.75277
7.26544
7.02633
7.01825
7.00390
6.95582
6.92643
6.89796
5.07180
5.02901
5.00169
4.97552
4.78738
4.77269
4.12794
4.10597
4.09510
4.00885
3.99134
3.97582
2.22470
2.21541
2.15409
2.10732
2.17568
2.17017
2.15970
2.15346
1.90993
1.90351
1.89868
1.88950
1.87243
1.85298
1.60832
1.59114
1.57104
1.25271
CF3
CF2
N
H
O
O
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0


A3-39
ppm

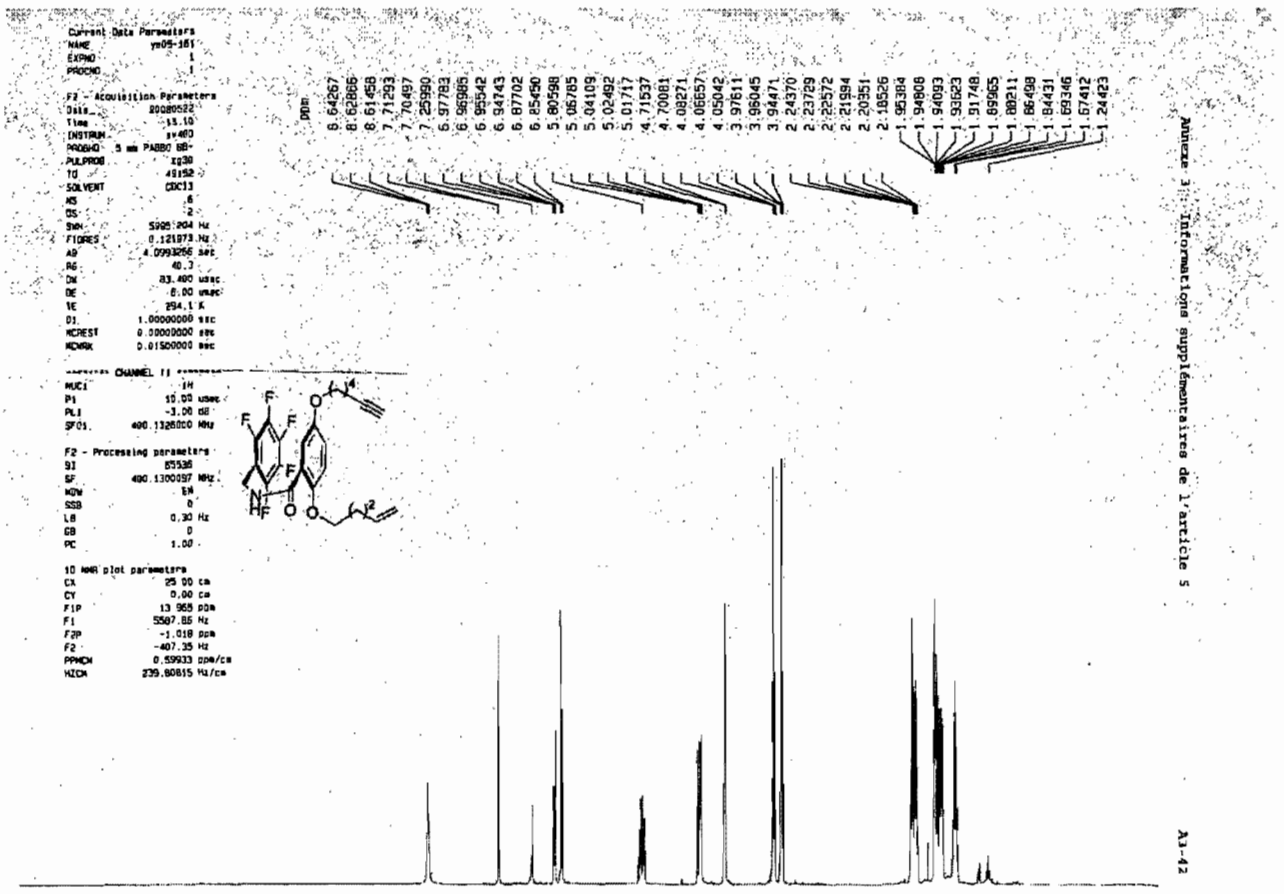

A3-38
ppm


Current Data Parameters
NAME ye05-150
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080505
Time 12.36
INSTRUM spect
PROBHD 5 mm QNP 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 55
DS 4
SWH 29575.738 Hz
FIDRES 0.346004 Hz
AQ 1.1451188 sec
RG 9198.2
DW 22.050 usec
DE 30.86 usec
TE 297.1 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 55.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 16.50 dB
SFO2 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127740 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.241 ppm
F1 21354.15 Hz
F2P -13.133 ppm
F2 -1321.39 Hz
PPMCM 9.01505 ppm/cm
HZCM 907.02942 Hz/cm
165.451
153.329
151.124
141.456
136.619
127.683
121.279
120.385
116.266
113.716
113.981
84.015
77.316
76.998
76.681
68.938
66.604
57.917
42.971
29.973
26.227
24.952
19.095
A3-41
ppm 200 180 160 140 120 100 80 60 40 20 0

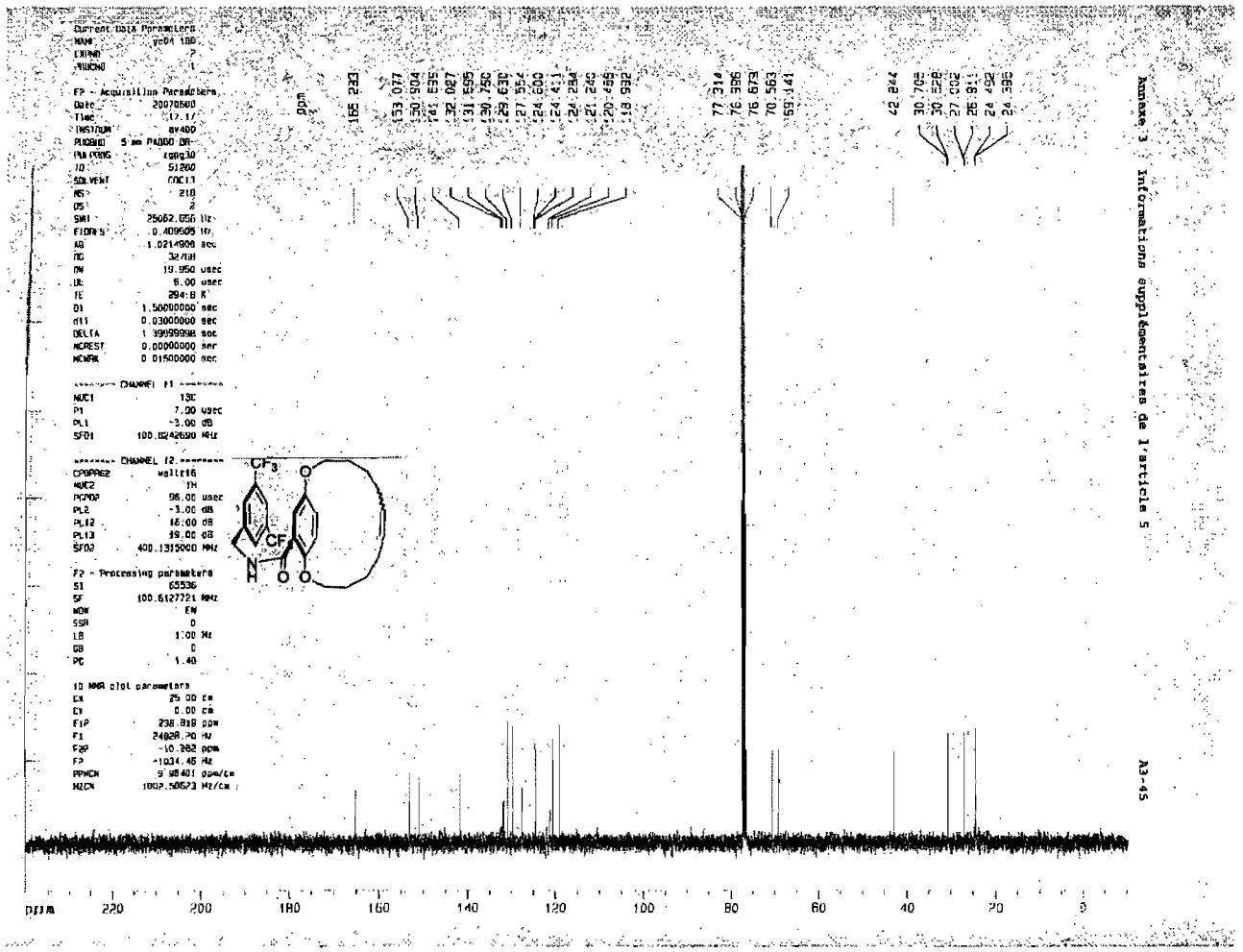

Current Data Parameters
NAME ye05-180
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080506
Time 12.34
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 90.5
DW 86.400 usec
DE 6.00 usec
TE 297.0 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300092 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.957 ppm
F1 5608.80 Hz
F2P -0.465 ppm
F2 -186.24 Hz
PPMCM 0.55621 ppm/cm
HZCM 222.57835 Hz/cm
8.576
7.811
7.790
7.753
7.745
7.260
7.015
7.007
6.933
6.985
6.914
6.891
5.703
5.686
4.982
4.960
4.947
4.943
4.938
4.779
4.765
4.090
4.074
4.057
4.019
4.003
3.988
2.277
2.266
2.259
2.248
2.094
2.077
1.967
1.961
1.913
1.896
1.875
1.838
1.820
1.802
1.725
1.706
A3-40
ppm 12 10 8 5 4 2 0

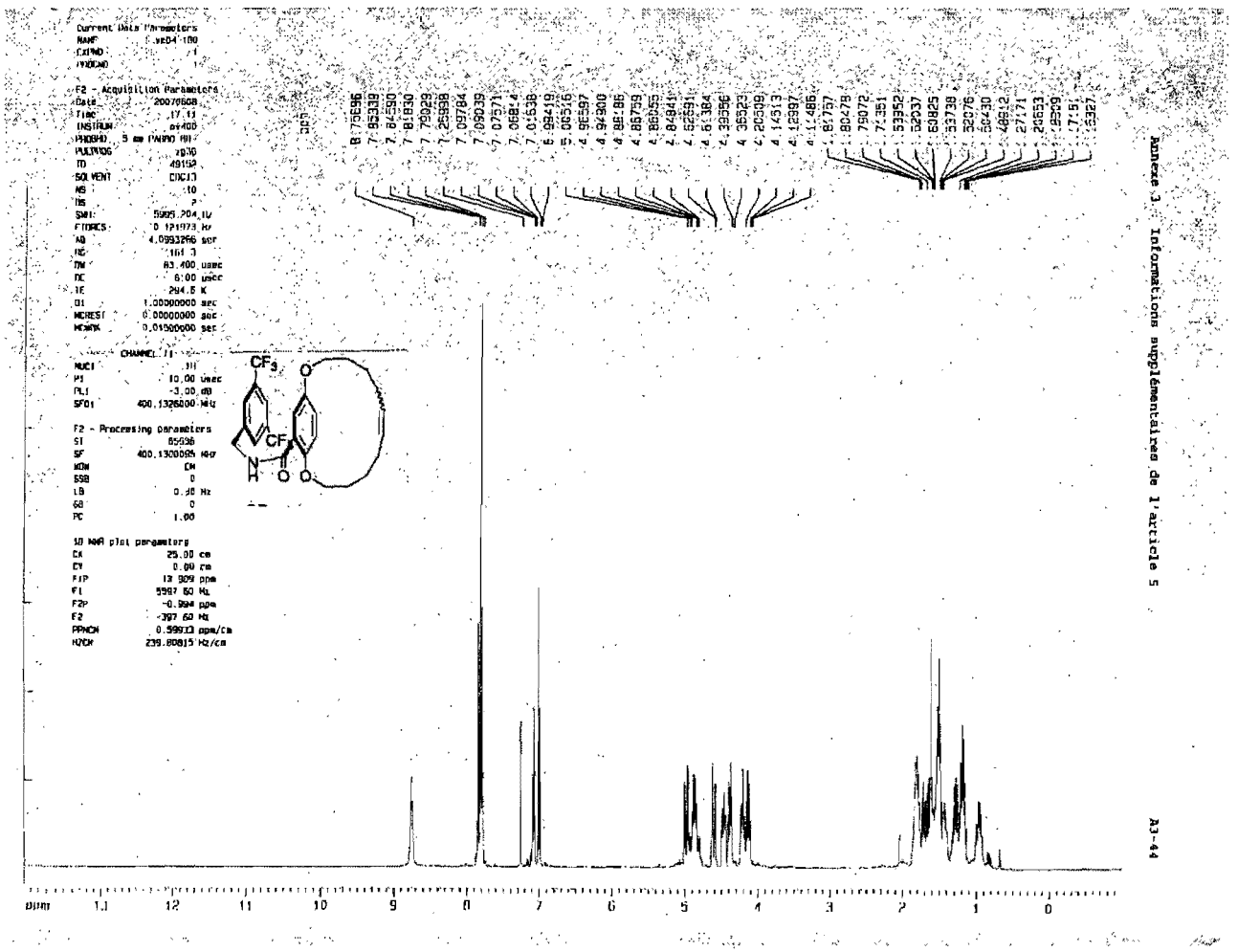

Current Data Parameters
NAME ya05-163
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080822
Time 19.14
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 31
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214900 sec
RG 32768
DW 19.950 usec
DE 26.50 usec
TE 294.2 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 15.00 usec
PL1 0.00 dB
SFO1 100.6240590 MHz
CHANNEL f2
CPDPRG2 waltz64
NUC2 1H
PCPD2 85.00 usec
PL2 -3.00 dB
PL12 16.00 dB
PL13 18.00 dB
SFO2 400.1215008 MHz
F2 - Processing parameters
SI 65536
SF 100.6127780 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.781 ppm
F1 24024.37 Hz
F2P -10.320 ppm
F2 -1038.28 Hz
PPMCM 9.55401 ppm/cm
HZCM 1902.50429 Hz/cm
ppm
165.041
153.167
151.152
136.836
120.918
120.558
115.879
115.652
113.811
83.977
77.319
77.001
76.683
68.909
68.575
67.835
31.308
29.998
28.227
28.169
24.904
18.055
ppm 220 200 180 160 140 120 100 80 60 40 20 0

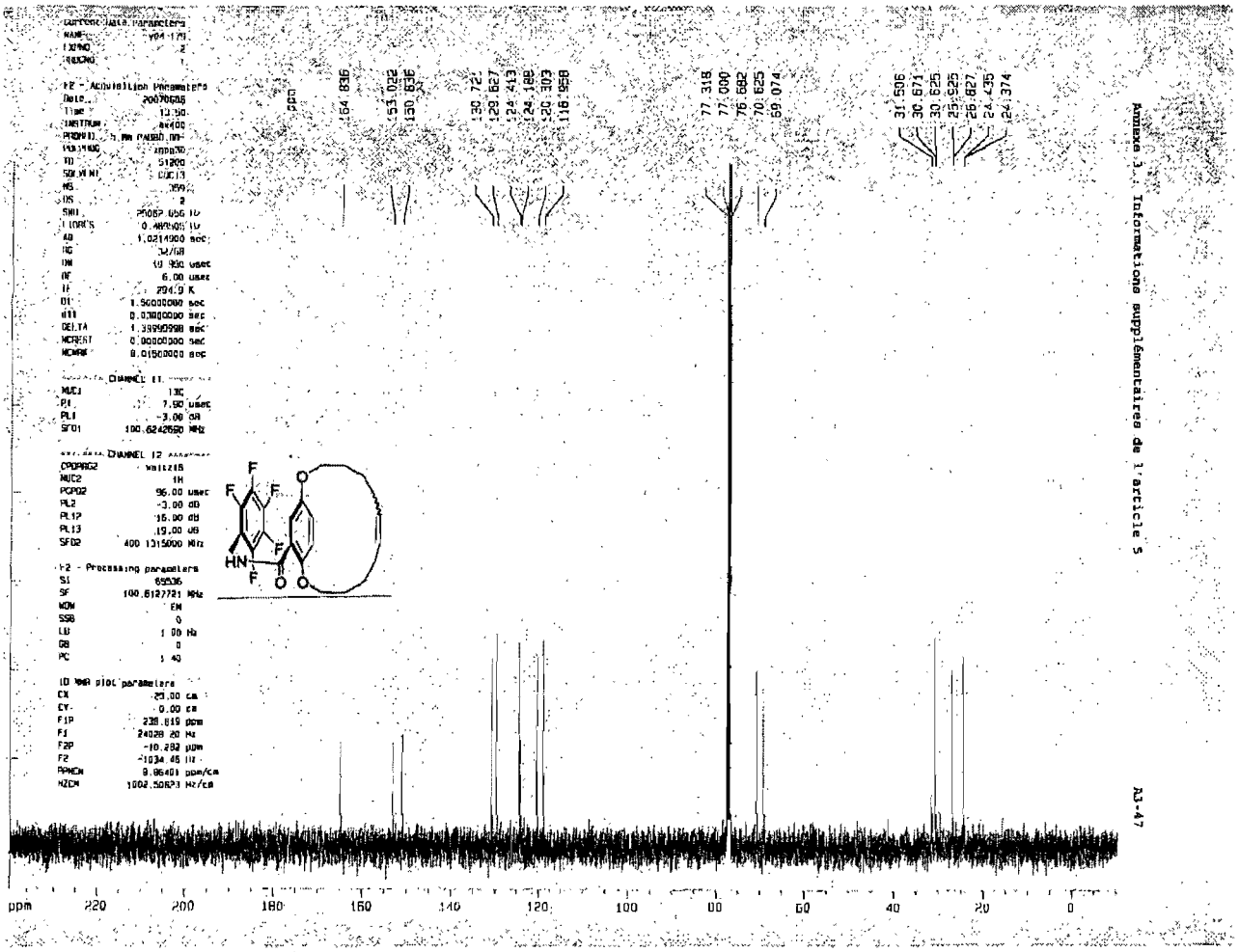
A3-43

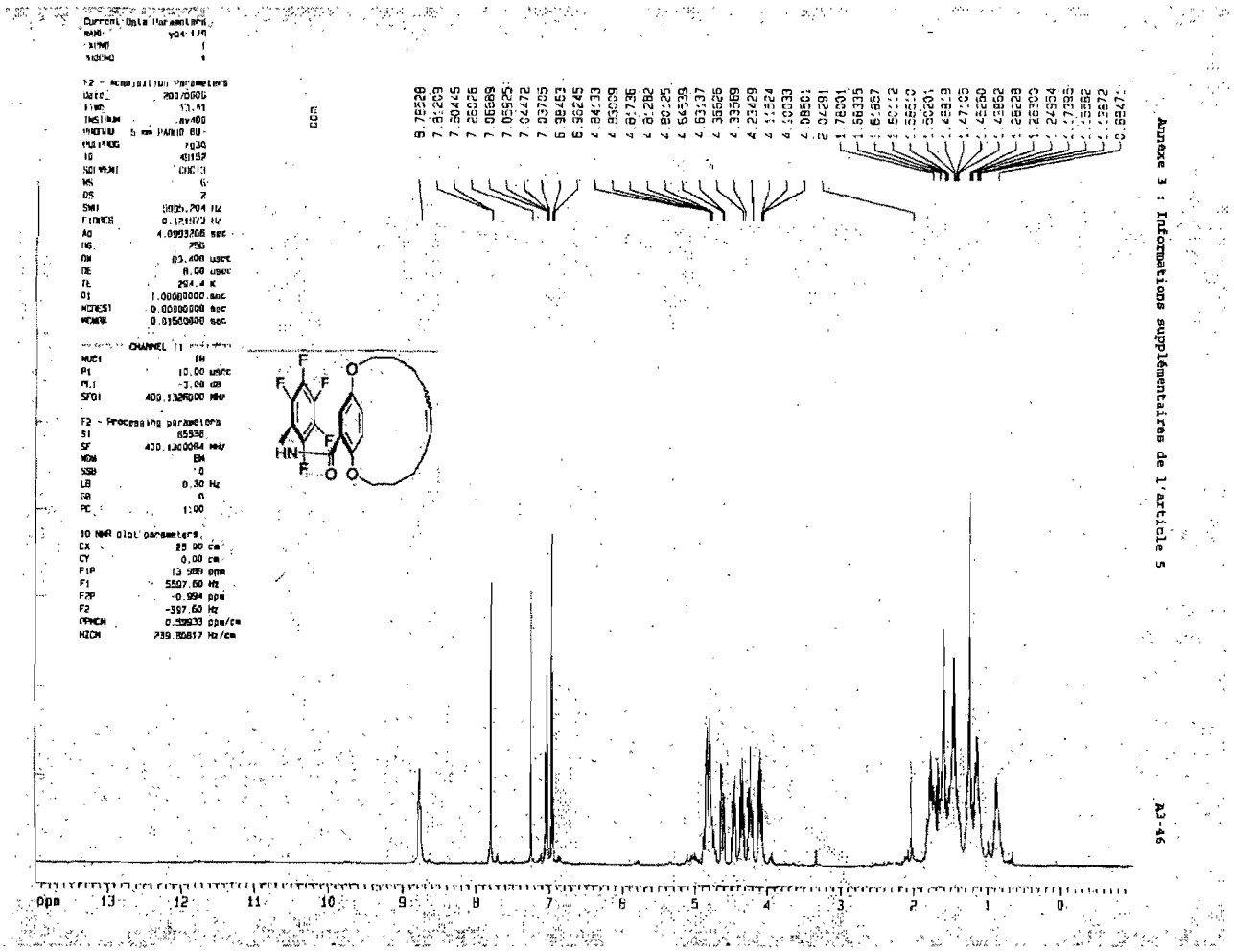

Current Data Parameters
NAME ya05-161
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080522
Time 15.10
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 6
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0993256 sec
RG 40.3
DW 83.400 usec
DE 6.00 usec
TE 294.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 15.00 usec
PL1 -3.00 dB
SFO1 400.1328000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.965 ppm
F1 5587.85 Hz
F2P -1.018 ppm
F2 -407.35 Hz
PPMCM 0.59933 ppm/cm
HZCM 239.80815 Hz/cm
ppm
8.64267
8.62866
8.61458
7.71293
7.70497
7.25990
6.97783
6.96986
6.95542
6.94743
6.87702
6.85490
5.80598
5.06785
5.04109
5.02492
5.01717
4.71537
4.70081
4.08271
4.06657
4.05042
3.97611
3.96045
3.94471
2.24370
2.23729
2.22572
2.21984
2.20351
2.18526
1.95384
1.94808
1.94093
1.93623
1.91748
1.89965
1.88211
1.86498
1.84431
1.69346
1.67412
1.24423
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0

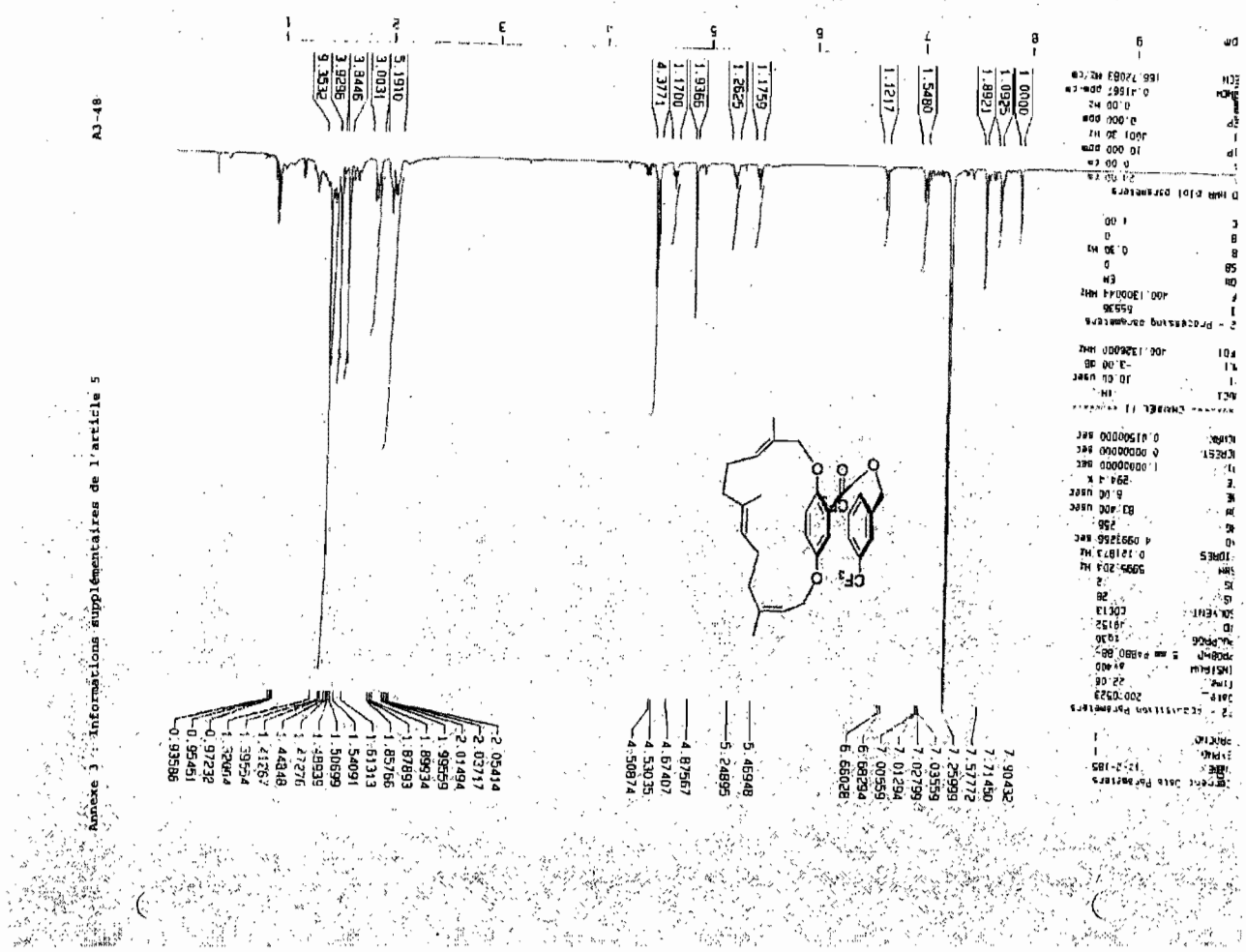
A3-42

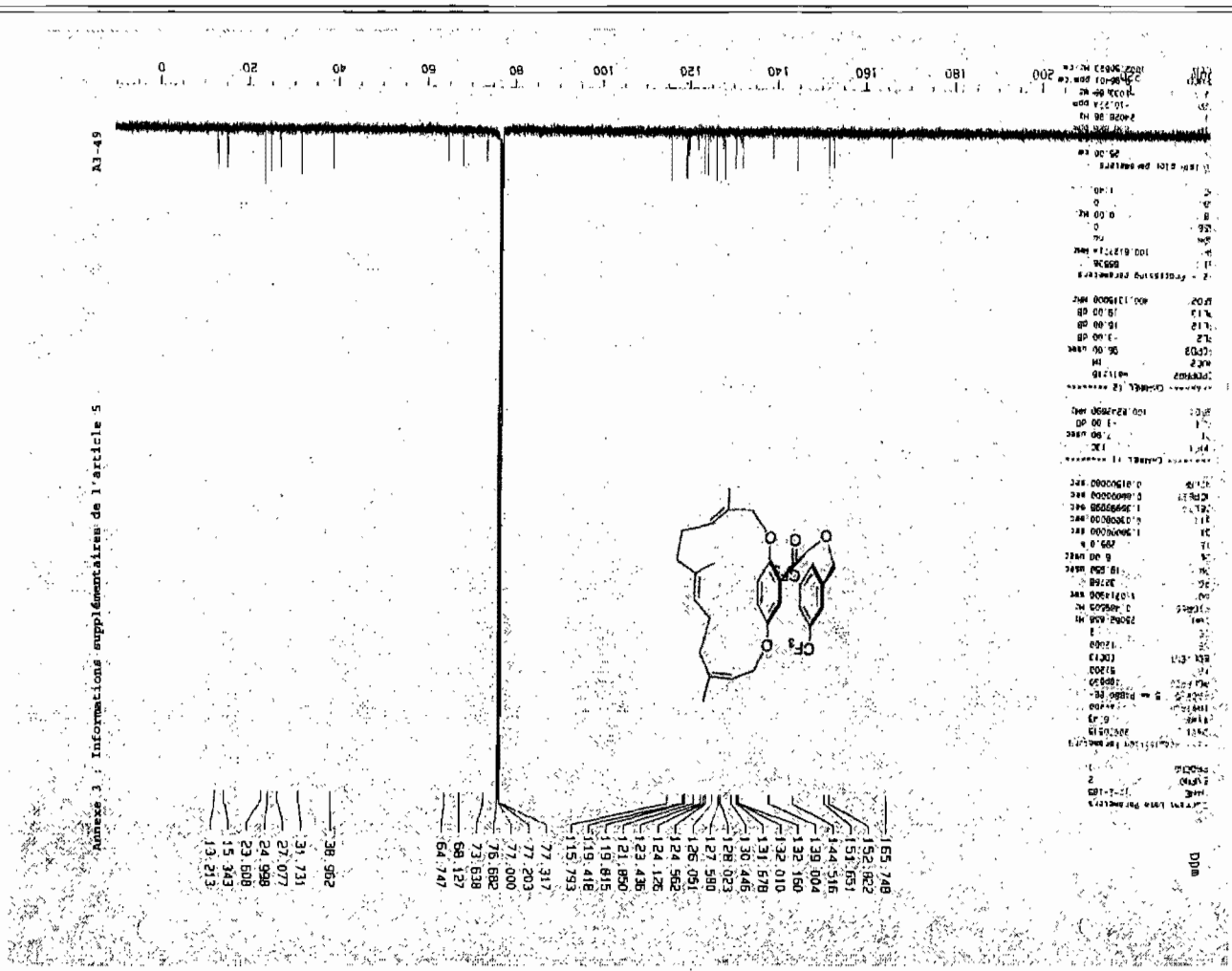

Annexe 3 : Informations supplémentaires de l'article 5
A3-45
ppm

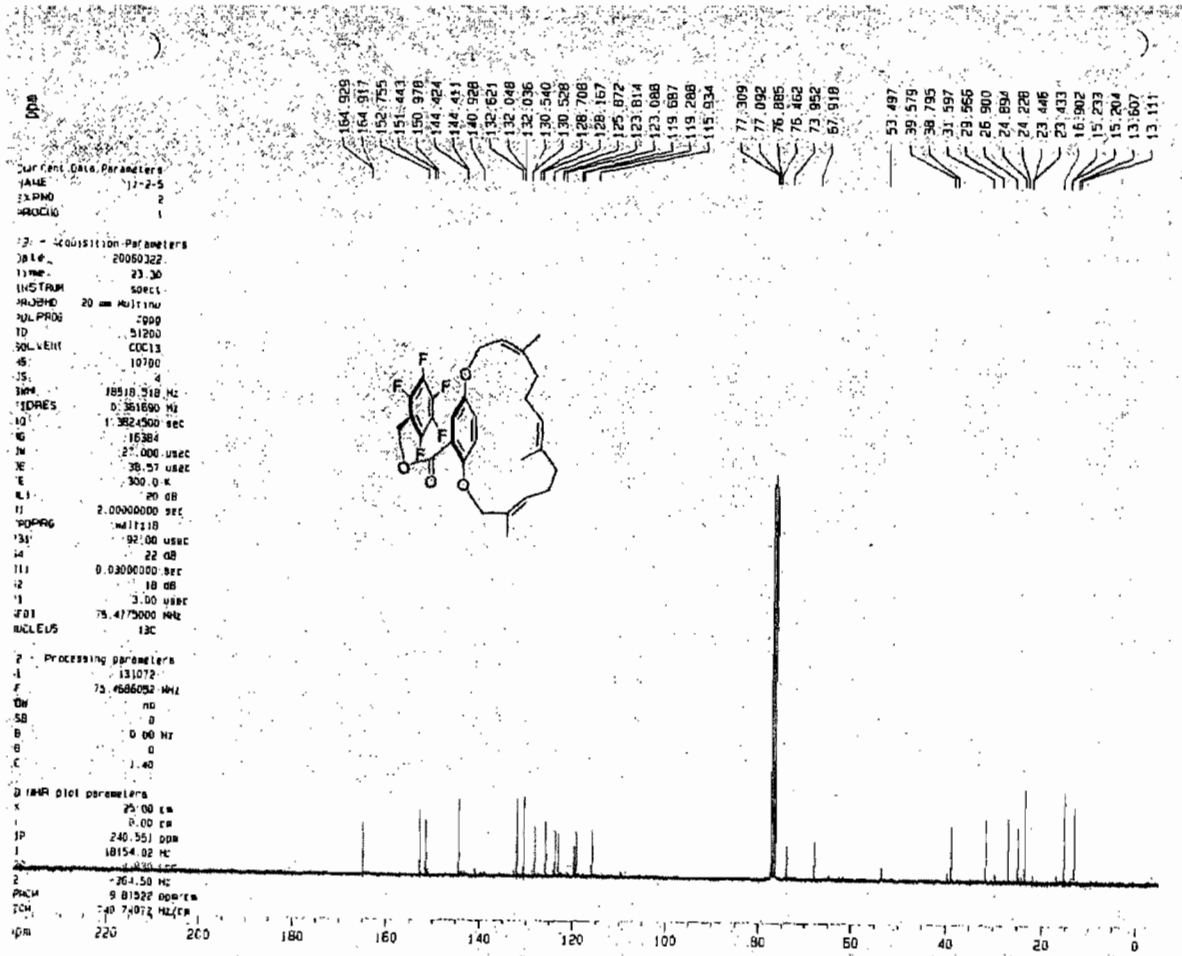

Annexe 3 : Informations supplémentaires de l'article 5
A3-44
ppm


Annexes 1 : Informations supplémentaires de l'article 5
AJ-47
ppm

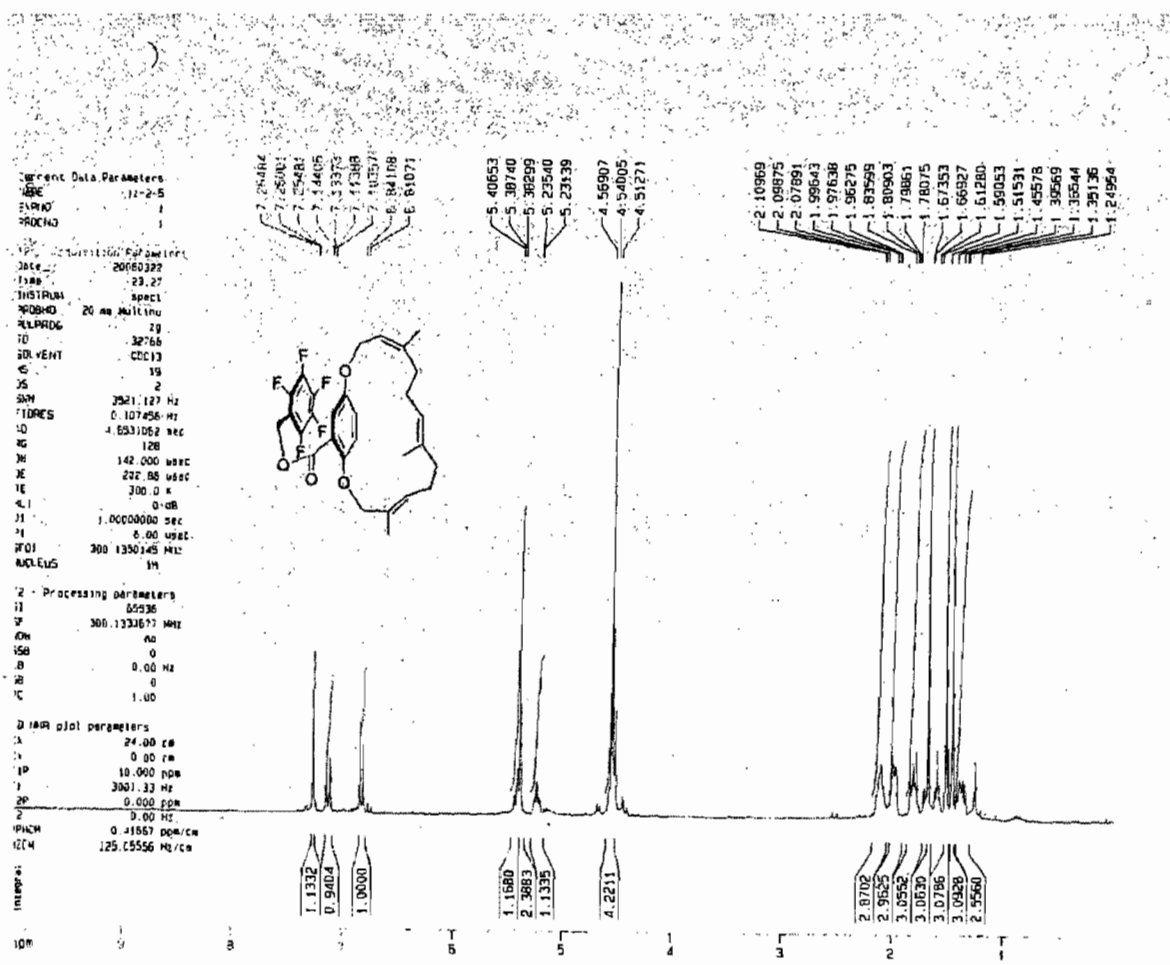

Annexes 1 : Informations supplémentaires de l'article 5
AJ-46
ppm


A3-48
Annexe 3 : Informations supplémentaires de l'article 5
CF3

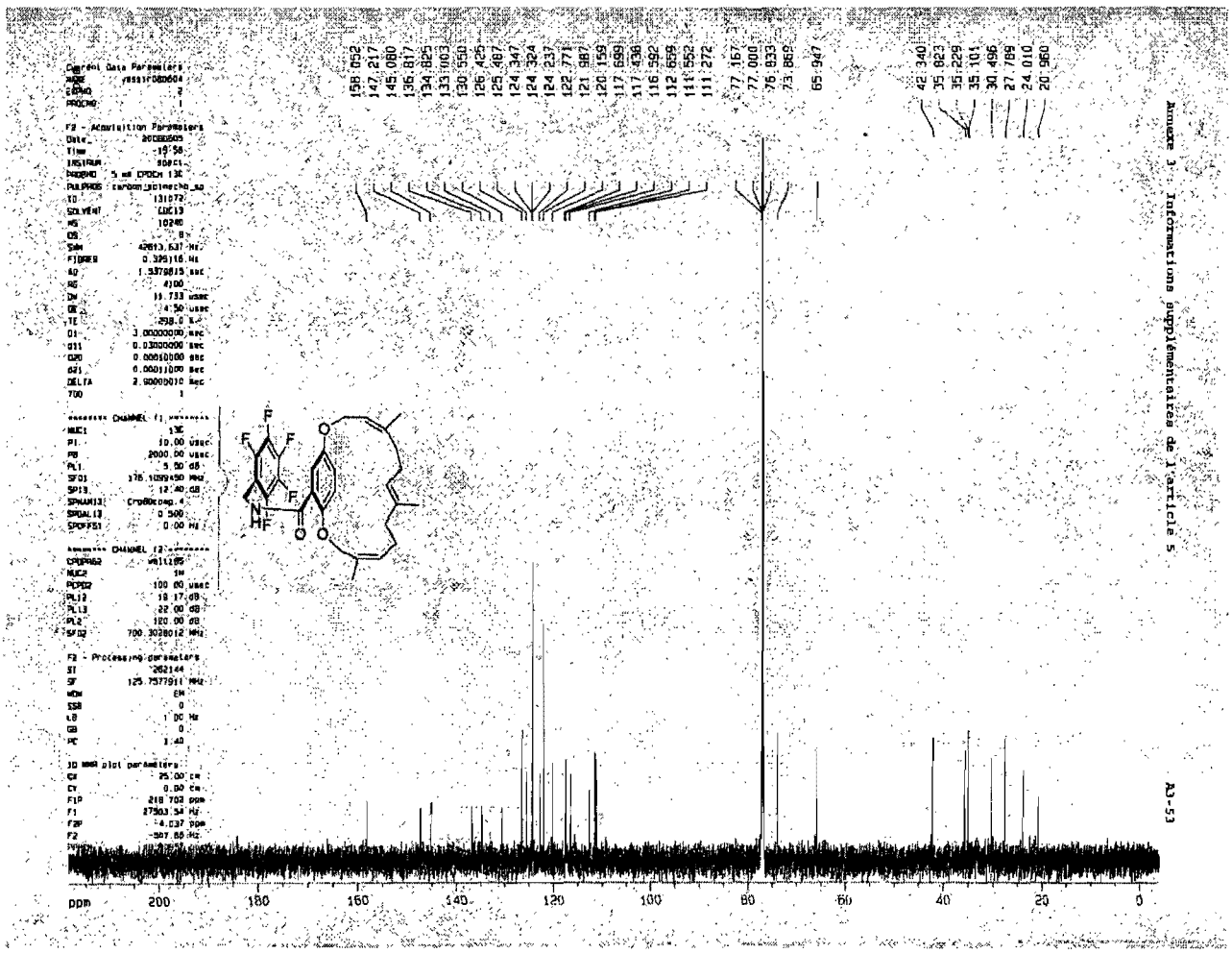

A3-49
Annexe 3 : Informations supplémentaires de l'article 5
CF3


164.929
164.917
152.755
151.443
150.978
144.424
134.451
140.928
132.621
132.048
132.036
130.540
130.528
128.708
128.167
125.872
123.814
123.088
119.687
119.288
115.934
77.309
77.092
76.885
76.462
73.952
67.918
53.497
39.579
38.795
31.597
29.566
26.900
24.894
24.228
23.446
23.433
16.902
15.233
15.204
13.607
13.111
F
O
200
180
160
140
120
100
80
60
40
20
0

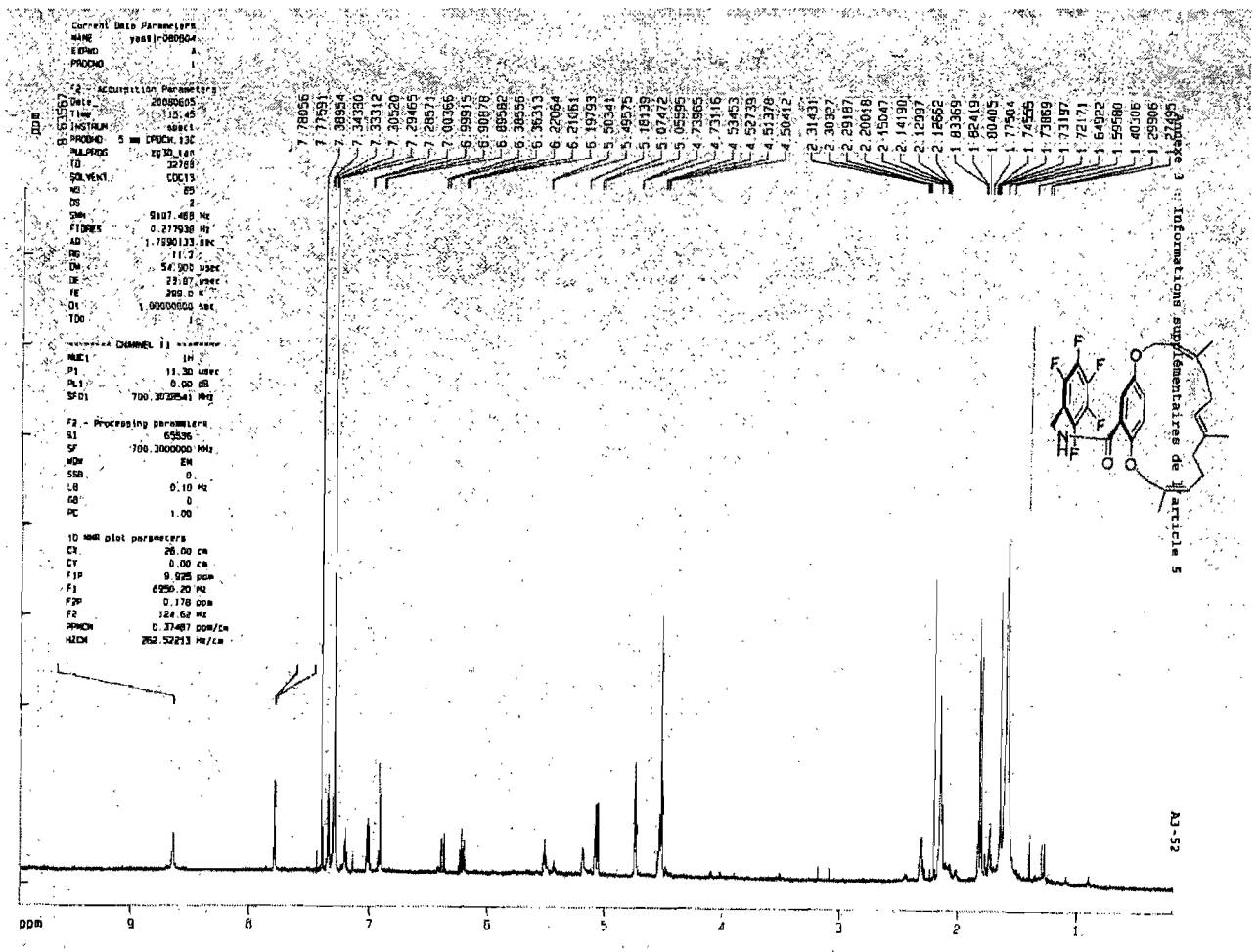
A3-51


2.10969
2.09875
2.07891
1.99643
1.97638
1.96275
1.83599
1.80903
1.79861
1.78075
1.67353
1.66927
1.61280
1.59053
1.51531
1.45578
1.39569
1.38544
1.35136
1.24954
5.40653
5.38740
5.38299
5.23540
5.23139
4.56907
4.54005
4.51271
F
O
1.1332
0.9404
1.0000
1.1680
2.3883
1.1335
4.2211
2.8702
2.9625
3.0552
3.0639
3.0796
3.0928
2.5560
10
9
8
7
6
5
4
3
2
1

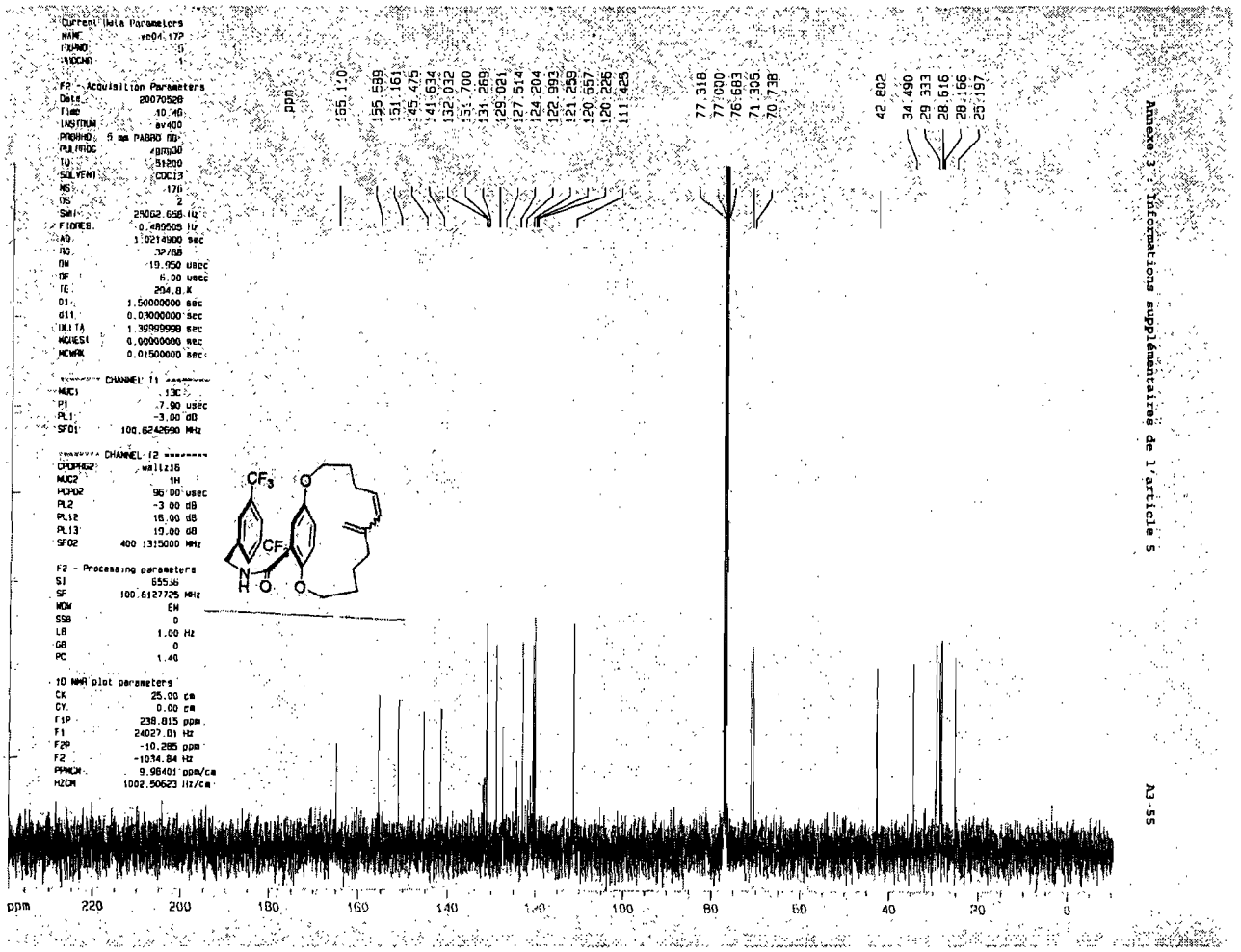
A3-50



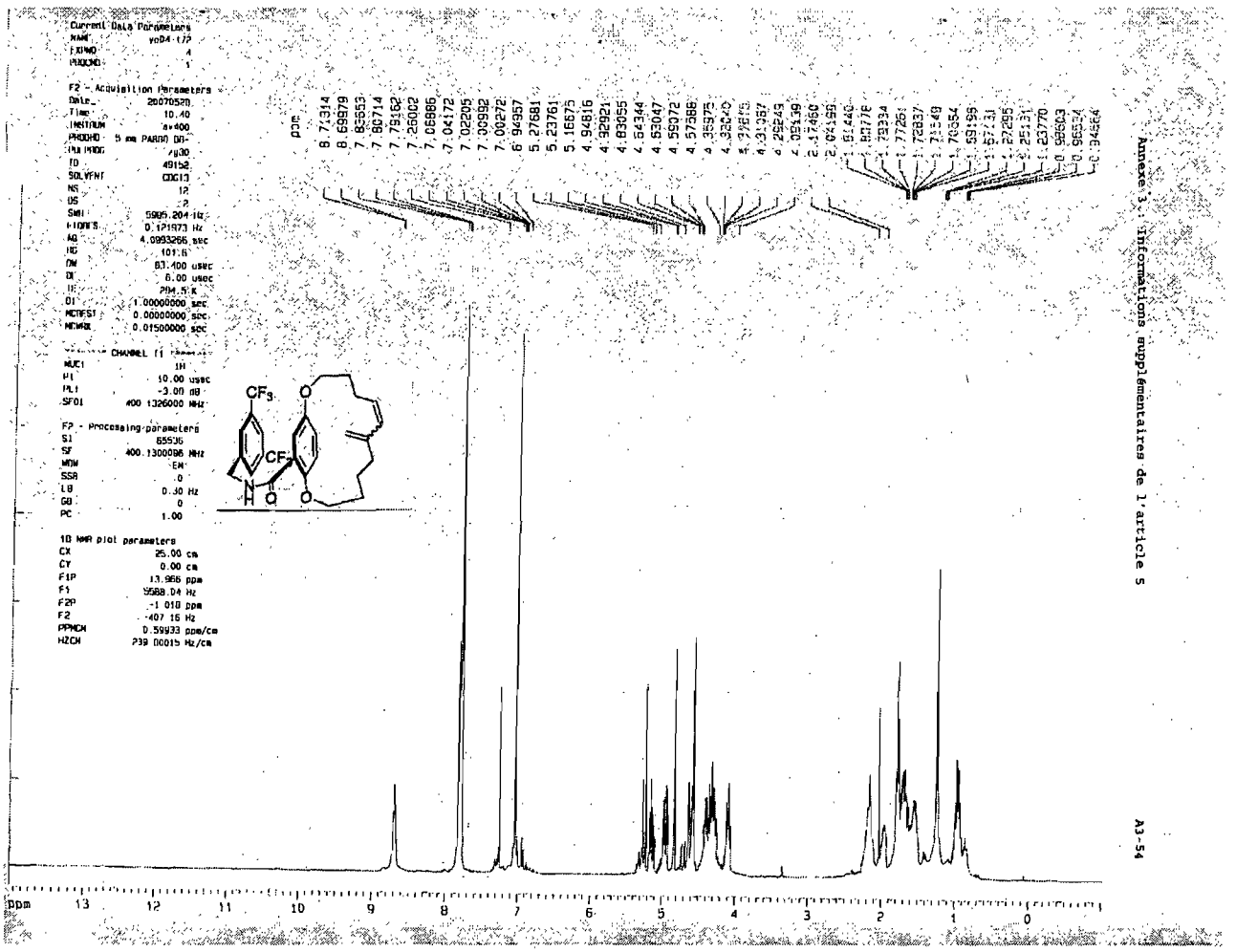
Annexe 3 : Informations supplémentaires de l'article 5



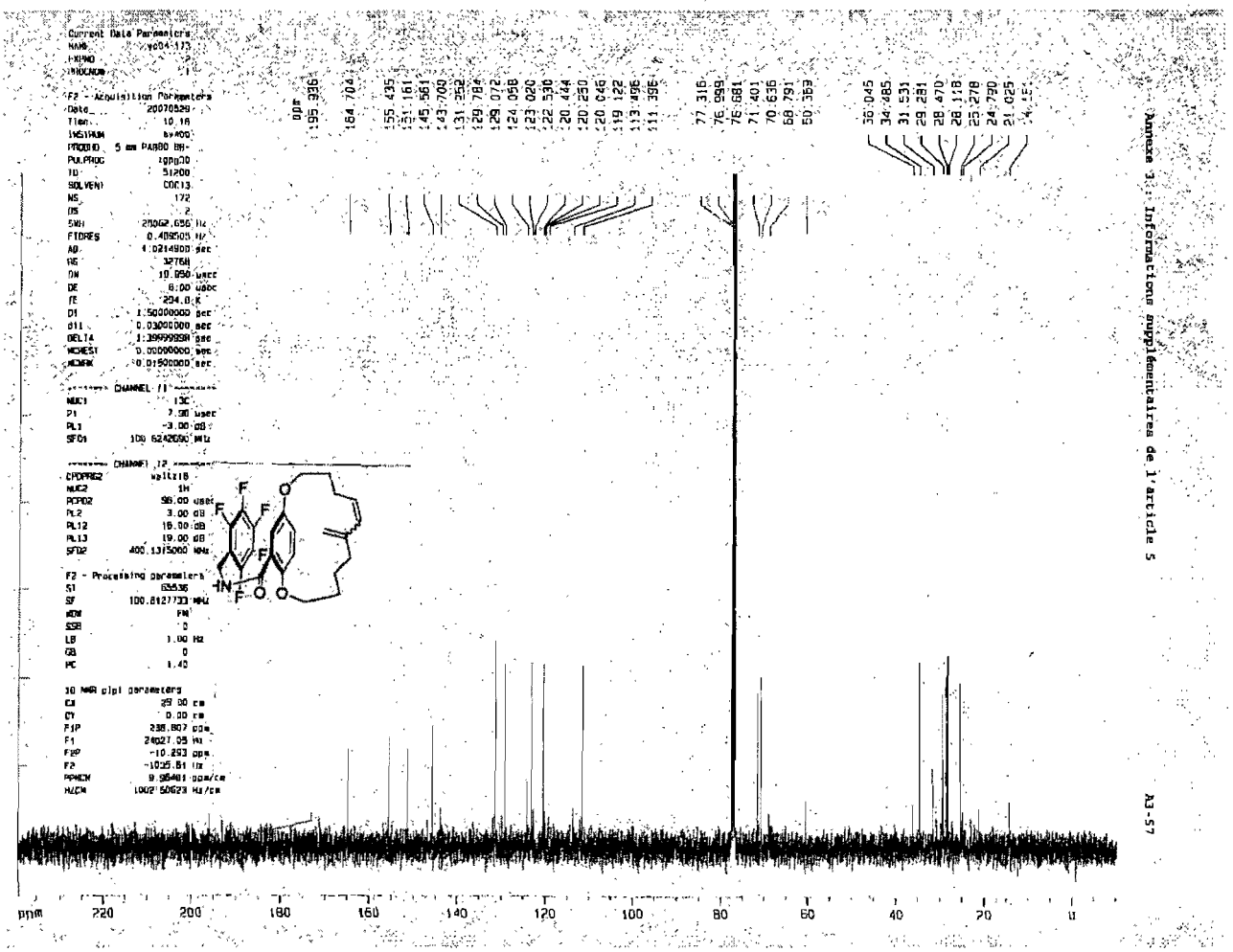
Annexe 3 : Informations supplémentaires de l'article 5

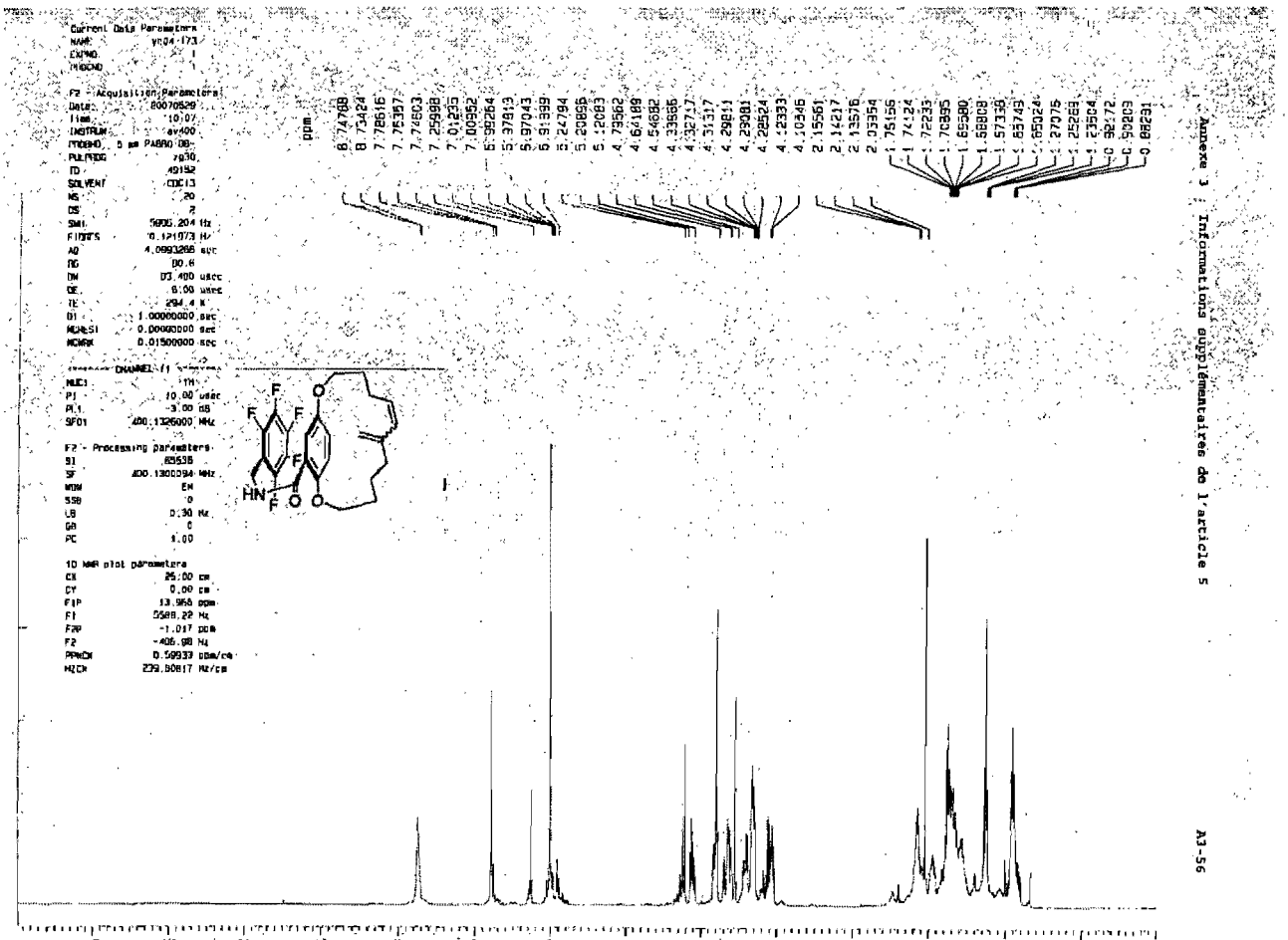

Current Data Parameters
NAME yp04-172
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date 20070528
Time 10.46
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 170
DS 2
SWH 25062.656 Hz
FIDRES 0.489505 Hz
AQ 1.0214900 sec
RG 32768
DW 19.950 usec
DE 6.00 usec
TE 294.8 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6242690 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 96.00 usec
PL2 -3.00 dB
PL12 16.00 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127725 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 238.815 ppm
F1 24027.81 Hz
F2P -10.285 ppm
F2 -1034.84 Hz
PPMCM 9.96401 ppm/cm
HZCM 1002.50623 Hz/cm
166.110
155.589
151.161
145.475
141.634
132.032
131.700
131.269
129.021
127.514
124.204
122.993
121.259
120.657
120.226
111.425
77.318
77.000
76.683
71.306
70.738
42.602
34.490
29.333
28.616
28.166
25.197
CF3
CF2
N
H
O
ppm
220
200
180
160
140
120
100
80
60
40
20
0

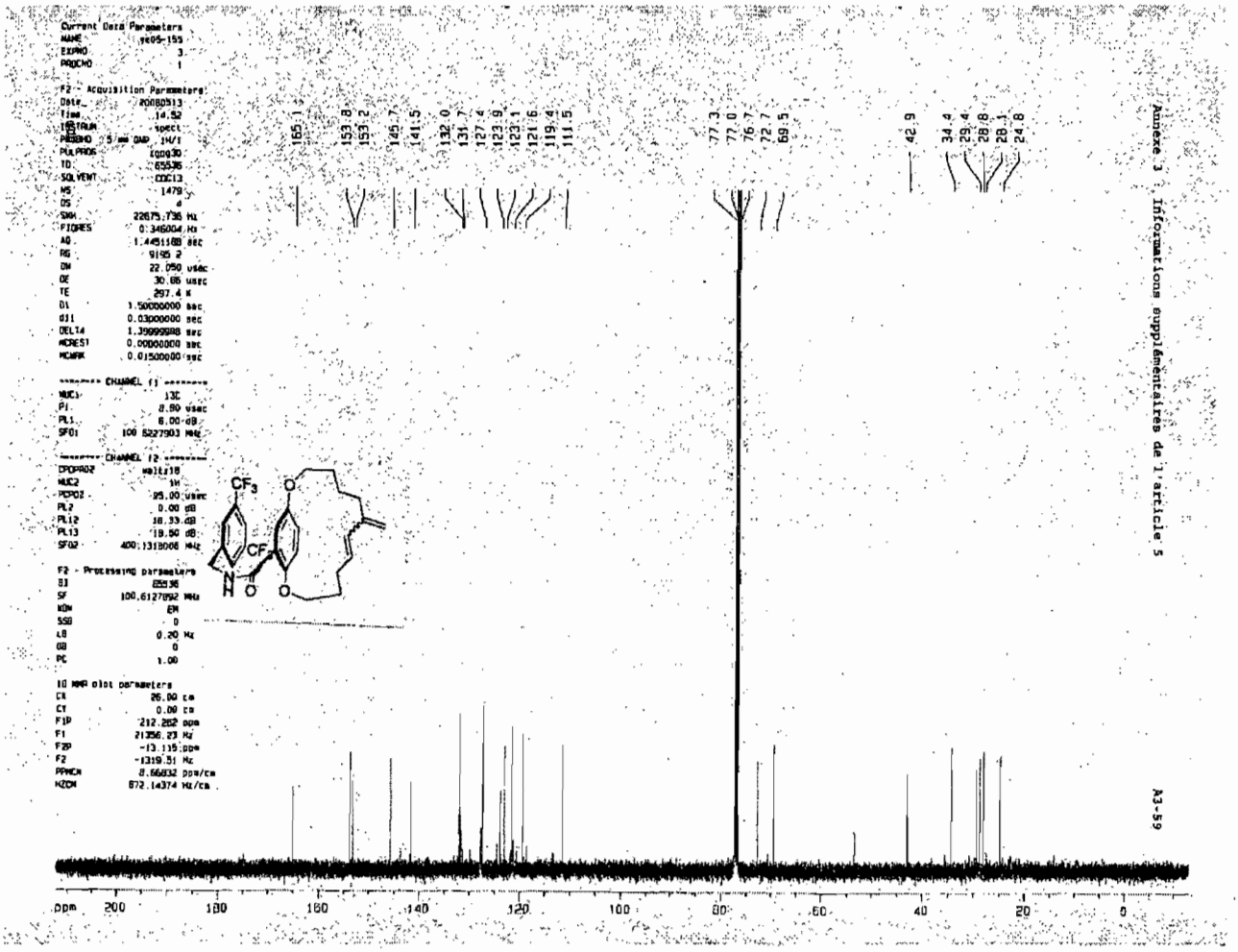
A3-55

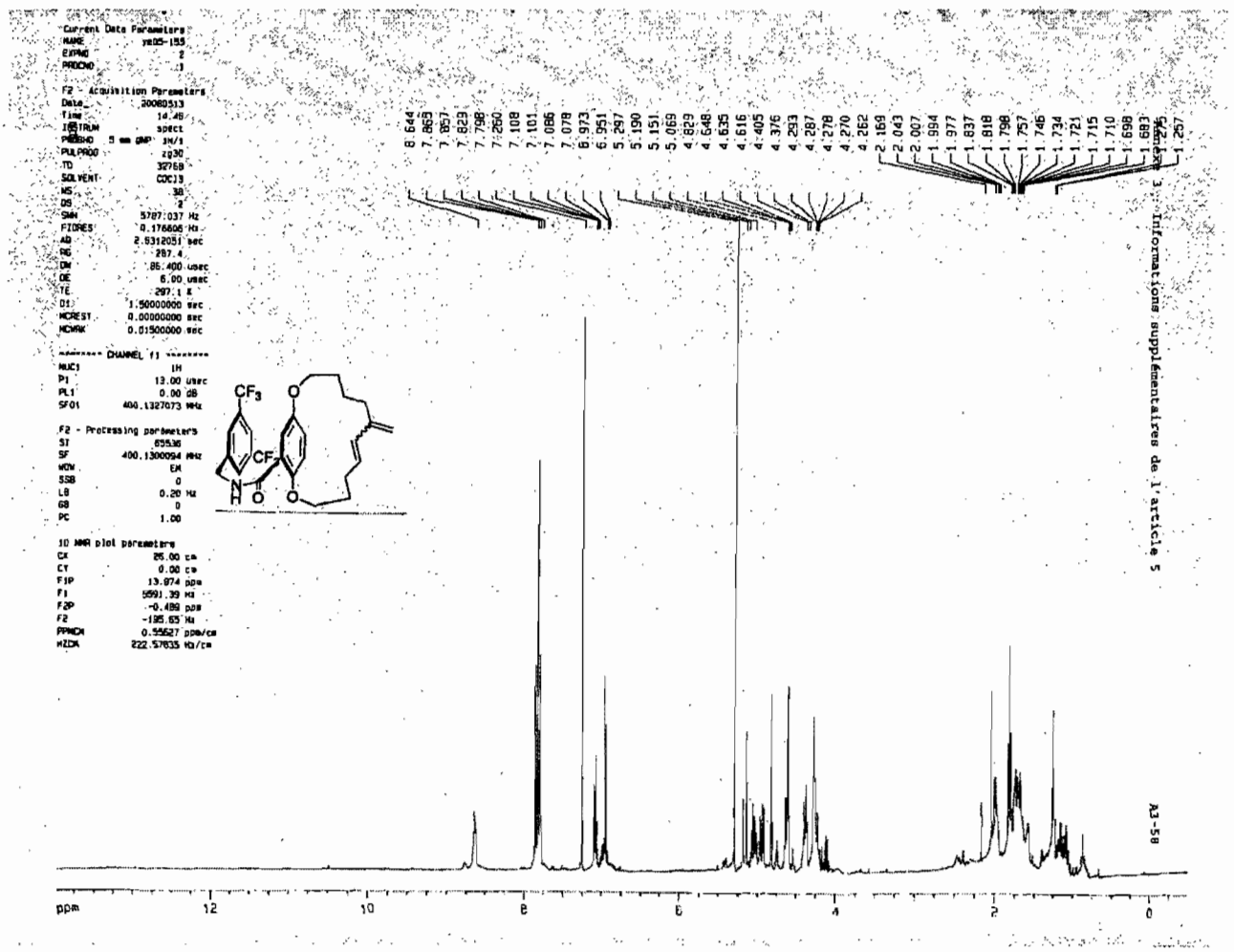

Current Data Parameters
NAME yp04-172
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070528
Time 10.40
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 12
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0993266 sec
RG 101.6
DW 83.400 usec
DE 6.00 usec
TE 294.5 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300096 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.966 ppm
F1 5588.04 Hz
F2P -1.010 ppm
F2 -407.16 Hz
PPMCM 0.59933 ppm/cm
HZCM 239.80015 Hz/cm
8.71314
8.69879
7.83653
7.80714
7.79162
7.26002
7.06886
7.04172
7.02205
7.00992
7.00272
6.94957
5.27681
5.23761
5.16675
4.94816
4.92921
4.83055
4.64344
4.63047
4.59072
4.57388
4.35975
4.33820
4.31967
4.29249
4.05139
2.17460
2.07195
1.81778
1.79334
1.77261
1.72837
1.71549
1.70354
1.59199
1.57131
1.27295
1.25131
1.23770
0.98563
0.96574
0.94264
CF3
CF2
N
H
O
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0

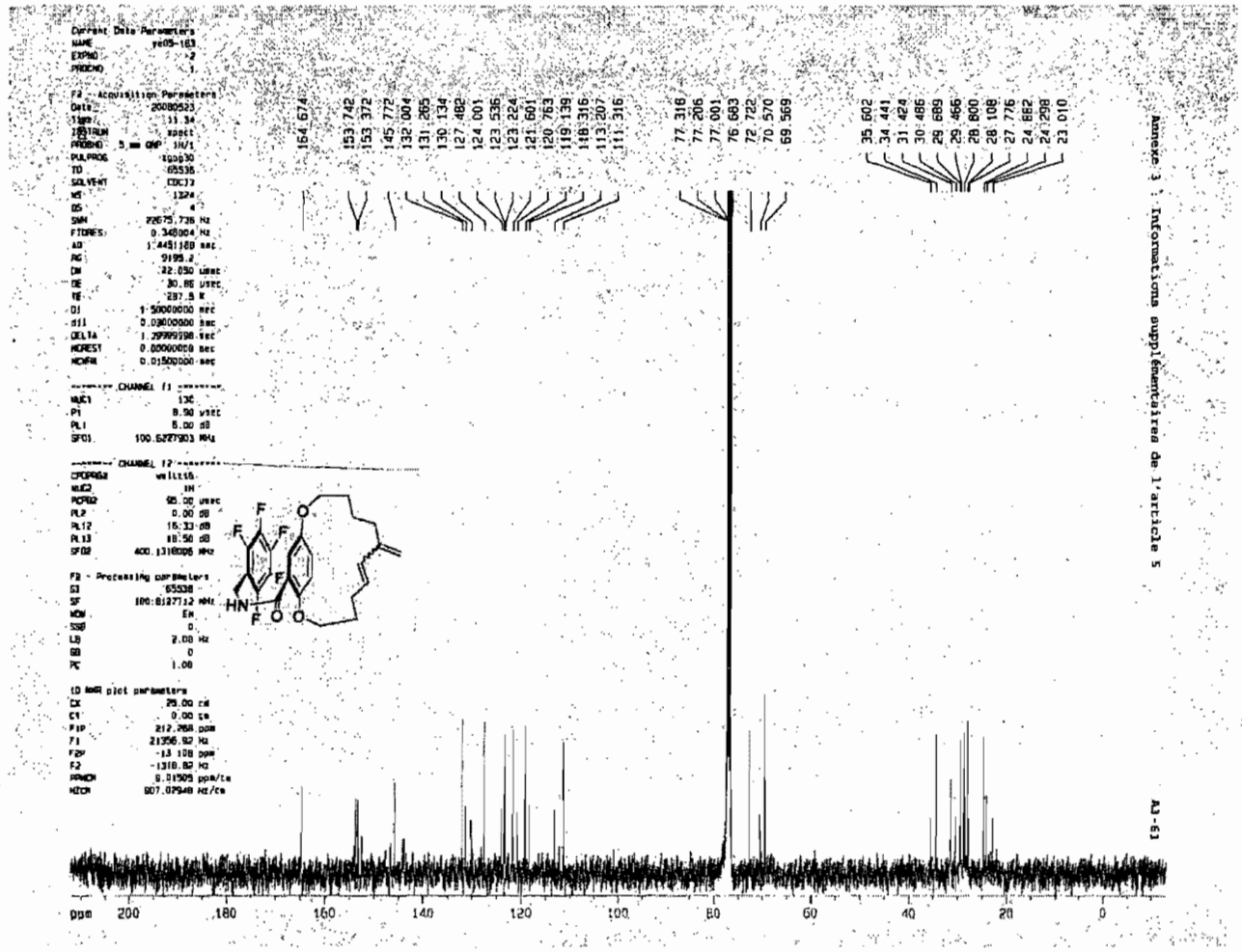
A3-54

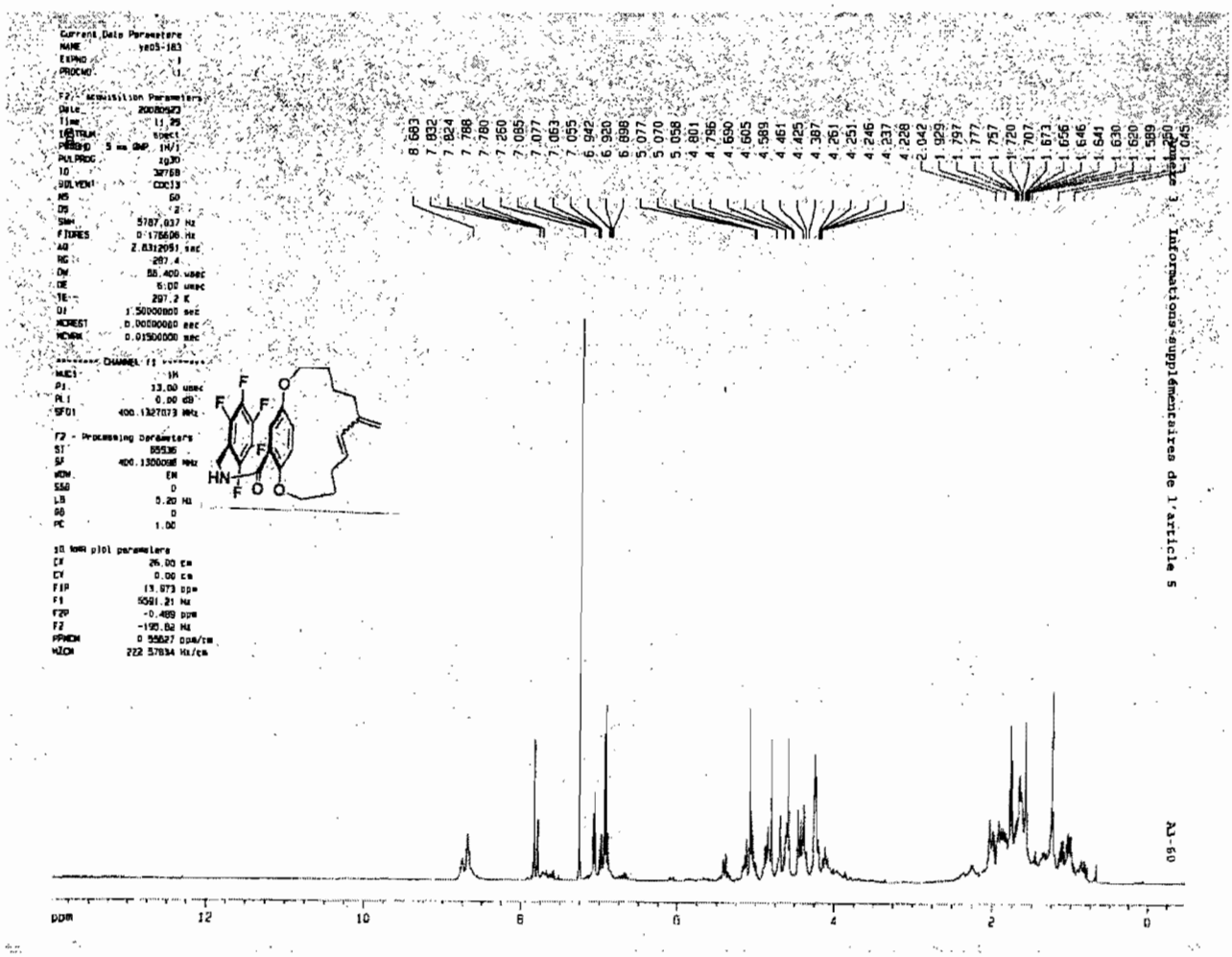

Current Data Parameters
NAME vp04-173
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070529
Time 10.16
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 51200
SOLVENT CDCl3
NS 172
DS 2
SWH 28062.656 Hz
FIDRES 0.409505 Hz
AQ 1.0214900 sec
RG 3276
DW 19.950 usec
DE 6.00 usec
TE 294.0 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.39999998 sec
MCWEST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 7.90 usec
PL1 -3.00 dB
SFO1 100.6242690 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 98.00 usec
PL2 3.00 dB
PL12 16.50 dB
PL13 19.00 dB
SFO2 400.1315000 MHz
F2 - Processing parameters
SI 65536
SF 100.6127703 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 39.00 cm
CY 0.00 cm
F1P 238.807 ppm
F1 24021.05 Hz
F2P -10.293 ppm
F2 -1035.81 Hz
PPMCM 9.95481 ppm/cm
HZCM 1002.50623 Hz/cm
ppm
195.336
164.704
155.435
151.161
145.561
143.709
131.252
129.784
129.072
124.058
123.020
122.530
120.444
120.230
120.046
119.122
113.496
111.396
77.316
76.999
76.681
71.401
70.635
68.791
50.369
36.045
34.485
31.531
29.281
28.470
28.118
25.278
24.790
21.025
14.151
ppm 220 200 180 160 140 120 100 80 60 40 20 0


Current Data Parameters
NAME vp04-173
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070529
Time 10.07
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 49152
SOLVENT CDCl3
NS 20
DS 2
SWH 5995.204 Hz
FIDRES 0.121973 Hz
AQ 4.0992266 sec
RG 90.6
DW 83.400 usec
DE 6.00 usec
TE 294.4 K
D1 1.00000000 sec
MCWEST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.00 usec
PL1 -3.00 dB
SFO1 400.1326000 MHz
F2 - Processing parameters
SI 65536
SF 400.1300094 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 13.958 ppm
F1 5588.22 Hz
F2P -1.017 ppm
F2 -406.98 Hz
PPMCM 0.58933 ppm/cm
HZCM 235.80817 Hz/cm
ppm
8.74768
8.73424
7.78616
7.75357
7.74603
7.25998
7.01235
7.00552
5.98264
5.97813
5.97043
5.91399
5.24794
5.20865
5.12083
4.73562
4.64199
4.54692
4.33686
4.32717
4.31317
4.29811
4.29081
4.28524
4.12333
4.10345
2.15561
2.14217
2.13576
2.03354
1.75156
1.74124
1.72233
1.70895
1.65580
1.58808
1.57338
1.55745
1.55024
1.27075
1.25269
1.23564
0.92172
0.90809
0.88231
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0


Current Data Parameters
NAME ye05-155
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080513
Time 14.52
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1479
DS 4
SWH 22675.736 Hz
FIDRES 0.346004 Hz
AQ 1.4451168 sec
RG 9185.2
DW 22.050 usec
DE 30.68 usec
TE 297.4 K
D1 1.50000000 sec
D11 0.03000000 sec
DELTA 1.39999988 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SF01 100.5227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 25.00 usec
PL2 0.00 dB
PL12 18.33 dB
PL13 18.50 dB
SF02 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127692 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 212.282 ppm
F1 21356.23 Hz
F2P -13.115 ppm
F2 -1319.51 Hz
PPMCM 8.66832 ppm/cm
HZCM 872.14374 Hz/cm
165.1
153.8
153.2
145.7
141.5
132.0
131.7
127.4
123.9
123.1
121.6
119.4
111.5
77.3
77.0
76.7
72.7
69.5
42.9
34.4
29.4
28.8
28.1
24.8
A3-59
ppm 200 180 160 140 120 100 80 60 40 20 0


Current Data Parameters
NAME ye05-155
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080513
Time 14.48
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312051 sec
RG 287.4
DW 86.400 usec
DE 6.00 usec
TE 297.1 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SF01 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300094 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.974 ppm
F1 5591.39 Hz
F2P -0.489 ppm
F2 -195.65 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57635 Hz/cm
8.644
7.863
7.857
7.829
7.798
7.260
7.108
7.101
7.086
7.078
6.973
6.951
5.297
5.190
5.151
5.069
4.829
4.648
4.635
4.616
4.405
4.376
4.293
4.287
4.278
4.270
4.262
2.169
2.043
2.007
1.994
1.977
1.837
1.818
1.798
1.757
1.746
1.734
1.721
1.715
1.710
1.698
1.683
1.267
A3-58
ppm 12 10 8 6 4 2 0


Current Data Parameters
NAME ye05-183
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080523
Time 11.34
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 22675.736 Hz
FIDRES 0.346004 Hz
AQ 1.4451180 sec
RG 9195.2
DW 22.050 usec
DE 30.86 usec
TE 297.5 K
D1 1.50000000 sec
d11 0.03000000 sec
DELTA 1.29999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 8.90 usec
PL1 6.00 dB
SFO1 100.6227903 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 0.00 dB
PL12 16.33 dB
PL13 18.50 dB
SFO2 400.1318006 MHz
F2 - Processing parameters
SI 65536
SF 100.6127712 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 25.00 cm
CY 0.00 cm
F1P 212.268 ppm
F1 21356.52 Hz
F2P -13.108 ppm
F2 -1318.82 Hz
PPMCM 8.21505 ppm/cm
HZCM 807.07948 Hz/cm
164.674
153.742
153.372
145.772
132.004
131.265
130.134
127.482
124.001
123.536
123.224
121.661
120.763
119.139
118.316
113.207
111.316
77.316
77.206
77.001
76.683
72.722
70.570
69.569
35.602
34.441
31.424
30.486
29.689
29.466
28.800
28.108
27.776
24.682
24.298
23.010
ppm 200 180 160 140 120 100 80 60 40 20 0
Annexe 3 : Informations supplémentaires de l'article 5
AJ-61


Current Data Parameters
NAME ye05-183
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080523
Time 11.29
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 5787.037 Hz
FIDRES 0.176606 Hz
AQ 2.8312091 sec
RG 287.4
DW 86.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.50000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1327073 MHz
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 26.00 cm
CY 0.00 cm
F1P 13.973 ppm
F1 5591.21 Hz
F2P -0.489 ppm
F2 -195.62 Hz
PPMCM 0.55627 ppm/cm
HZCM 222.57834 Hz/cm
8.663
7.832
7.824
7.788
7.780
7.260
7.085
7.077
7.063
7.055
6.942
6.930
6.898
5.077
5.070
5.058
4.801
4.796
4.690
4.605
4.589
4.461
4.425
4.387
4.261
4.251
4.246
4.237
4.228
2.042
1.929
1.797
1.777
1.757
1.720
1.707
1.673
1.656
1.646
1.641
1.630
1.620
1.589
1.560
1.545
ppm 12 10 8 6 4 2 0
Annexe 3 : Informations supplémentaires de l'article 5
AJ-60