Université de Montréal

Functional Group Transformations of Imidoyl & Iminium Triflates and Designing an Enantioselective Diels-Alder Catalyst.

par

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Département de chimie
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Thèse présentée à la Falculté des études supérieures
en vue de l'obtention du grade de
Philosophiæ Doctor (Ph.D.)
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Cette thèse intitluée:
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Présentée par:
Peter Chua

a été évaluée par le jury composé des personnes suivantes:

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Summary

The first part of this thesis deals with a new methodology that allows the conversion of secondary and tertiary amides to various functional groups in a two step one-pot reaction. Typically, amides are very poor electrophiles. They are the most stable of carboxylic acid derivatives and are often avoided in synthetic chemistry for this reason. Harsh and forceful conditions are usually required to make these functional groups undergo reactions with anything but the most reactive of nucleophiles. However, by taking advantage of the mild nucleophilic character of amides, they can be activated towards nucleophilic attack by using trifluoromethanesulphonic anhydride to convert secondary and tertiary amides to the corresponding imidoyl or iminium triflates. These highly electrophilic intermediates react readily with nucleophiles in a pyridine buffered acidic medium resulting the conversion of the starting amide to the new functional group. Since the generation of the triflate intermediate occurs at low temperature and treatment with the nucleophile occurs at room temperature or below, these reaction conditions are mild enough to tolerate the presence of numerous functional groups as well as to keep racemization to a minimum. This methodology allows access to esters, ortho esters, thiazolines, thioamides, ^{18}O-labelled amides, and imidates starting with secondary or tertiary amides.

The second part of this thesis deals with efforts in the design and synthesis of biarylglycines and their application as ligands for chiral Lewis acids. We have synthesized *N*-tosylated biarylglycines which possess a polarizable naphthyl group. These substituents are known to maximize induced dipole-enhanced dipole effects which can be important factors in achieving high enantioselectivities. These ligands can be used to form

oxazaborolidine catalysts for use in the Diels-Alder reaction. At low catalyst loadings, good selectivities can be observed in the cycloaddition reaction between 2-bromoacrolein and cyclopentadiene. A comparison of catalysts show that the presence of a second naphthyl group is required for the desired dipole interaction between the complexed dienophile and the polarizable naphthyl group.

Keywords:
- Amides
- Triflates
- Esters
- Thiazolines
- Lewis Acid Catalyst
- Diels Alder

Résumé

La première partie de cette thèse traite d'une nouvelle méthodologie qui permet la conversion d'amides secondaires et tertiaires en une variété de groupements fonctionnels en une seule opération. Typiquement, les amides sont des électrophiles très pauvres, à cause de la délocalisation du doublet libre de l'azote dans le système π du carbonyle. Ceci fait que la réactivité des amides ressemble plus à celle des acides carboxyliques que des esters. Par conséquent, ils sont les dérivés des acides carboxyliques les plus stables, ce qui fait qu'ils sont souvent évités en synthèse organique. Des conditions très drastiques sont habituellement nécessaires pour les faire réagir, et ce, avec des nucléophiles très agressifs. Il existe plusieurs méthodes pour rendre les amides plus réactifs. La diminution de la délocalisation du doublet libre de l'azote est efficace pour rendre l'amide plus réactif vis-à-vis les nucléophiles. Cette approche présentée ici, consiste à convertir les amides en imidoyle et iminium trifluorométhanesulfonates. La délocalisation électronique dans ces intermédiaires est réduite significativement. De plus, la nature électroattrative du groupement trifluorométhanesulfonyle rend aussi ces intermédiaires plus électrophiles. Ces propriétés électroniques rendent les imidoyle et iminium triflates très réactifs vis-à-vis les nucléophiles. Ces intermédiaires peuvent être formés en tirant avantage du léger caractère nucléophile des amides. Lorsque les amides secondaires et tertiaires sont traités avec des agents de trifluorométhylation très forts, comme l'anhydride trifluorométhanesulfonique, ils sont transformés en imidoyl ou iminium triflates correspondants. Ces intermédiaires hautement électrophiles réagissent immédiatement avec des nucléophiles, ceci dans un milieu tamponné par la pyridine. Il en résulte la conversion des amides de départ en nouveaux groupements fonctionnels. Les nombreux avantages de cette méthode sont les suivants : la génération de

l'intermédiaire triflate se produit à basse température, l'ajout des nucléophiles se fait à la température ambiante ou à des températures inférieures et la formation des imidoyle et iminium triflates peut se produire en présence de pyridine. Ces facteurs contribuent grandement à la douceur de la méthode. Les conditions de réaction douces sont responsables du fait que de nombreux groupements fonctionnels sont tolérés et que la racémisation est conservée à son niveau le plus bas.

Le traitement des imidoyle et iminium triflates avec des nucléophiles contenant un oxygène donne des imidates ou des iminium esters. Ces intermédiaires sont aussi susceptibles de subir une autre attaque nucléophile. Une attaque subséquente avec un nucléophile oxygéné donne des orthoamides qui se transforment en ions oxonium en présence d'un catalyseur doux comme l'hydrotriflate de pyridinium. L'ion oxonium peut être piégé avec un autre nucléophile oxygéné, ce qui résulte en la formation d'un orthoester. Les orthoesters acycliques sont labiles et leur traitement en milieu aqueux donne des esters. Donc, les imidoyle et iminium triflates permettent la formation d'imidates, d'orthoesters et d'esters.

Lorsque les imidoyle et iminium triflates sont traités avec des aminothiols, des thiazolines sont obtenues. Cette méthodologie s'applique bien à ce groupement fonctionnel puisque les thiazolines ne sont pas les hétérocycles les plus robustes. L'imidoyle ou l'iminium triflate réagit avec l'aminothiol à basse température et la réaction est généralement complète en une heure. Nous avons aussi démontré que les thiazolines peuvent aussi être présentes pendant la formation d'imidoyle triflates, Ainsi, nous avons été capables de synthétiser une polythiazoline via une approche séquentielle. Cette découverte est très intéressante considérant que

quelques produits naturels biologiquement actifs récemment identifiés contiennent des unités polythiazolines.

Ces dérivés électrophiles d'amides peuvent également réagir avec des nucléophiles hétéroatomiques, capables de former des doubles liaisons. Le sulfure d'hydrogène et l'eau marquée isotopiquement réagissent immédiatement avec les imidoyle et iminium triflates. Il en résulte une substitution instantanée du groupement triflate. Ceci permet de substituer l'oxygène de l'amide par un autre atome d'oxygène, de soufre ou même d'azote. Ces réactions vont à complexion très rapidement. Les imidoyle et iminium triflates permettent donc une transformation efficace des amides en thioamides et en amides marqués isotopiquement.

Même si plusieurs transformations d'amides ont été démontrées ici, l'accès à ces divers groupements fonctionnels montre que la réaction des imidoyle et iminium triflates avec des nucléophiles faibles est général. Ces dérivés d'amides électrophiles permettront sûrement d'accéder à plusieurs autres groupements fonctionnels. Nous n'avons que débuté l'exploration des nombreuses possibilités du traitement des imidoyle et iminium triflates avec des nucléophiles faibles en présence de catalyseurs acides très faibles.

La seconde partie de cette thèse traite de nos efforts dans le domaine de la catalyse asymétrique. Avec une demande grandissante pour des molécules chirales non-racémiques, les chimistes ont développé plusieurs méthodes pour leurs synthèses. La synthèse asymétrique a évolué à travers les années. Au début, les synthèses débutaient avec des molécules chirales. Ensuite, les méthodologies utilisant les auxiliaires chiraux ont pris de l'importance lorsque les chimistes ont compris comment contrôler l'induction chirale. Finalement, les méthodes catalytiques ont vu le jour

lorsque des chimistes ont réussi à utiliser moins qu'une quantité stœchiométrique de promoteur chiral. L'étape suivante semble être l'application de catalyseurs chiraux sur un support solide afin de faciliter la récupération de ceux-ci. Les catalyseurs acide de Lewis sont une des classes de catalyseurs les plus populaires. Ils sont également le sujets de nos recherches.

Le design de catalyseurs, peu importe qu'il soit pour la chimie en phase solide ou pour la chimie en solution, débute par la chimie en solution. Nous avons développé un catalyseur qui a démontré sa capacité à induire la chiralité dans la réaction de Diels-Alder entre le cyclopentadiène et la 2-bromoacroléine. Cette réaction est reconnue pour être sensible aux acides de Lewis et est souvent utilisée pour tester les catalyseurs acide de Lewis développés par les grands chimistes dans ce domaine de recherche.

Nous avons développé une synthèse asymétrique d'une biarylglycine N-tosylée qui possède un groupement naphthyle polarisable. Ces substituants sont reconnus pour maximiser les dipôles induits, car les effets de dipôles sont des facteurs importants pour l'obtention de hautes énantiosélectivités. Lorsque testé dans la réaction de Diels-Alder, le catalyseur a donné de bonnes énantiosélectivités pour la cycloaddition entre la 2-bromoacroléine et le cyclopentadiène. À la suite de ces résultats, une série de ligands ont été synthétisés afin de vérifier notre hypothèse qu'un deuxième groupement naphthyle est requis pour augmenter l'interaction désirée. Le second groupement naphthyle a eu une grande influence sur la réaction, car les sélectivités ont été complètement inversées. Le ligand sans groupement naphthyle a donné des résultats similaires à celui comportant un seul groupement naphthyle, ce qui

indique l'absence d'interaction entre le diénophile complexé et le groupement naphthyle polarisable.

Ces résultats dans la génération de catalyseurs démontre la complexité de leur design. Le catalyseur biarylglycine requiert un second naphthyle pour qu'il affecte l'issue de la réaction.

Mots-clés:
-Amides
-Triflates
-Esters
-Thiazolines
-Catalyseurs acide de Lewis
-Diels-Alder

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List of Abbreviations

$[\alpha]_D$	optical rotation (with the D line of sodium)
Å	Angstrom
Ac	acetyl
LA	Lewis acid
AIBN	azobisisobutyronitrile
anal.	elemental analysis
anh.	anhydrous
aq	aqueous
Ar	aryl
atm.	atmosphere
Bn	benzyl
b.p.	boiling point
br	large (broad)
Bz	benzoyl
c	concentration in g / 100 mL
°C	degree Celsius
CI	chemical ionization
TLC	thin layer chromatography
c-Hex	cyclohexyl
cycloprop.	cyclopropane
δ	chemical displacement
d	doublet
DCC	dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate

dq	doublet of quadruplet
dt	doublet of triplet
DIBAL-H	diisobutylaluminum hydride
diglyme	1-methoxy-2-(2-methoxyethoxy)ethane
DMAP	dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
eq	equivalent
Et	ethyl
FAB	"Fast Atom Bombardment"
g	gram
HIV	human immunodeficiency virus
h	hour
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
i-Pr	isopropyl
IR	infrared
J	coupling constant
k	rate constant
KHMDS	potassium hexamethyldisilylamide
K-selectride	potassium tri-*sec*-butylborohydride
LDA	lithium diisopropyl amide
lit.	literature

m	multiplet
M	molar
MCPBA	*m*-chloroperbenzoic aicd.
Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
min	minute
mmHg	millimetres of mercury
mmol	millimole
µL	microlitre
m.p.	melting point
Ms	methanesulfonyl
n-Bu	normal butyl
n-Pr	normal propyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxy benzyl
ppm	parts per million
p-TsOH	*p*-toluenesulfonic acid
q	quadruplet
qn	quintuplet
R_f	relative mobility
r.t.	room temperature
sat.	saturated

t	triplet
t-Bu	tertiary butyl
TBDMS	tert-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
temp.	temperature
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
T_r	retention time
Trisyl	triisopropylbenzenesulphonyl
Ts	toluenesulphonyl

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Part 1: Functional Group Transformations of Amides via Imidoyl and Iminium Triflates.

Chapter 1: Introduction: Electrophilic Activation of Amides

CHAPTER 1

Introduction: Electrophilic Activation of Amides

1.1 Amides as Electrophiles

In the carboxamide (herein, referred to as amides) functional group, the delocalization of the nitrogen lone pair into the π^* antibonding orbital of the carbonyl group results in several effects.[1] Geometrically, the principle atoms of the amide (C', C, O, N) lie in a coplanar arrangement (Figure 1). Electronically, the amide nitrogen is rendered less nucleophilic and the amide carbon is rendered less electrophilic. However, the nucleophilicity and basicity of the amide oxygen is enhanced.

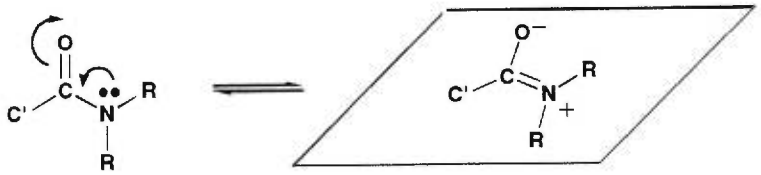


Figure 1. Delocalization of the nitrogen lone pair in amides

In fact, the reactivity of the carbonyl group of amides resembles more the parent acid than esters due to the π-electron delocalization.[2] Thus, nucleophilic additions onto amides are typically very difficult without additional polarization of the carbon-oxygen or carbon-nitrogen bond to make the amide react more like an ester.[3]

Polarization of the amide group can arise in several fashions. The first method is to distort the coplanar nature of the amide group resulting in a decrease of electron delocalization. The carbonyl group of distorted amides have been shown to react much more like esters towards

nucleophiles and the amine portion of the distorted amide has reactivity more like an amine (Figure 2).[4] Furthermore, the oxygen is no longer more nucleophilic and more basic than the nitrogen. Hence, in the typical undistorted amide **1**, the site of protonation is the oxygen,[5] but in the distorted amide **2**, the site of protonation is the nitrogen.[6]

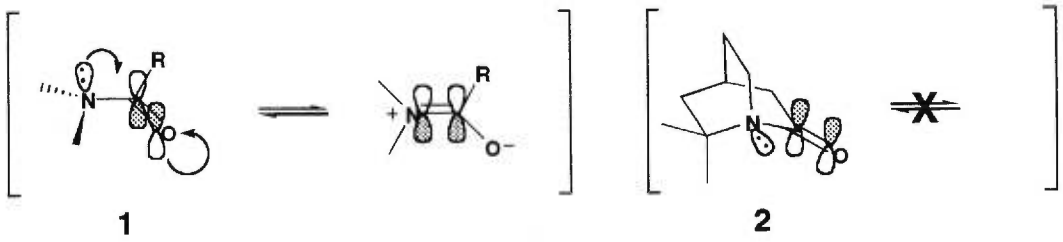
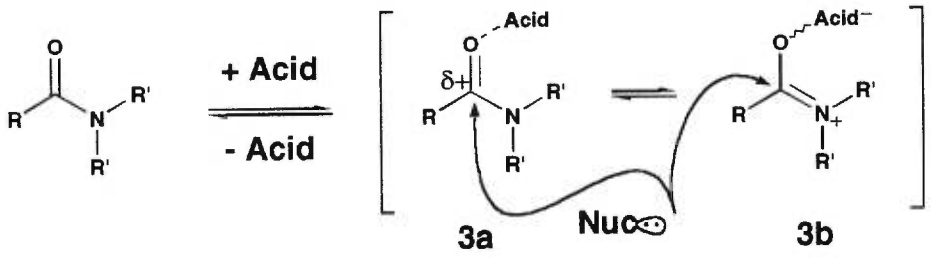


Figure 2. Loss of delocalization in distorted amides

The second method of polarizing the electronic structure of the amide is to complex it to an electrophile prior to reacting with nucleophiles. Actually to some extent, all nucleophilic additions onto amides begin with a complexation of either the amide oxygen or to a lesser extent, the nitrogen, onto an electrophilic species. In these cases where the electrophiles are Brønsted acids[7] or Lewis acids,[8,9] a non-covalently bonded complex is formed prior to the attack by the nucleophile on the amide (Scheme 1).

Scheme 1. Activation of amides by complexation with acids

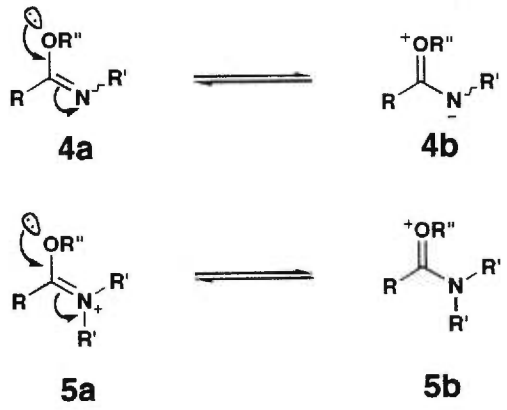


Logically, the extent of polarization depends on the strength of the electrophile. Greater polarization makes the amide-acid complex **3a** or **3b** more electrophilic, hence more reactive towards nucleophilic attack.

1.2 Covalently Bonded Electrophiles: Imidates and Alkyl Iminium Esters

Another method of activating amides is to pre-treat them with electrophiles prior to nucleophilic attack. One uses electrophiles that form covalent bonds with the amide nitrogen or amide oxygen. Treatment of amides with electrophilic alkylating groups generally results in the formation of imidates **4a** and alkyl iminium esters **5a.**[10] These intermediates are more reactive than the starting amide since the delocalization of the oxygen lone pair within the amide does not contribute to the greater stability of the molecule. Hence, the canonical form of the imidate **4b** is relatively higher in energy than the corresponding canonical forms of the amide since a positive charge resides on the oxygen which is a more electronegative atom than nitrogen (Scheme 2). The canonical form of alkyl iminium esters **5b** can lead to stabilization of the substrate, but both these species **5a** and **5b** are cationic so they are very good electrophiles.

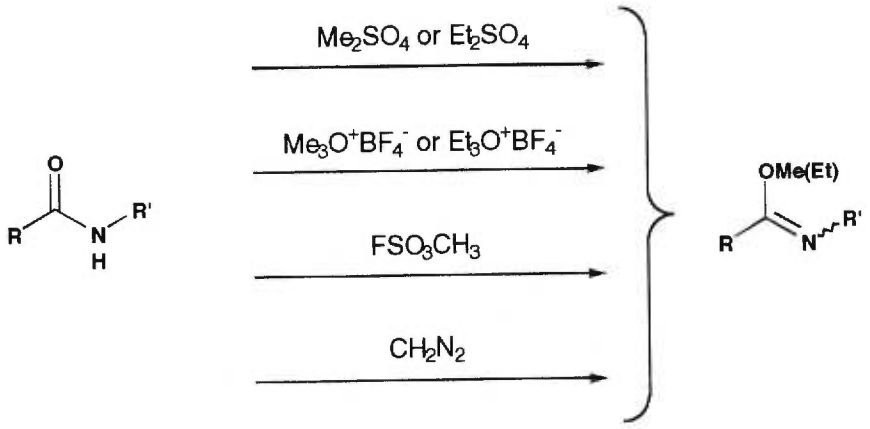
Scheme 2. Canonical forms of alkyl imidates and alkyl iminium esters



Amides are ambident nucleophiles. This creates an issue of chemoselectivity since both the oxygen or the nitrogen can act as

nucleophiles. The amide oxygen is a much better nucleophile than the nitrogen in a typical amide such that imidate and iminium ester formation is generally favored. However, some factors can cause variations in the distribution between *O*-substituted and *N*-substituted products. Hard/soft acid/base (HSAB) theory seems quite accurate at predicting product distributions, especially in the case of alkylations.[11] Lower temperatures are also associated with greater selectivity for *O*-alkylations.[12] The enhanced s-character of the amide carbonyl double bond also favors *O*-substitution as the electrons are more localized on the oxygen making it a stronger nucleophile.[13] Geometrical requirements of the resulting product are also important determinants as six and seven-membered lactams are *O*-alkylated to give products with endocyclic double bonds whereas five-membered lactams undergo *N*-alkylation to avoid the formation of a strained endocyclic double bond.[14] Ethyl chloroformate[15] and trialkyl oxonium fluoroborates (Meerwein's reagent)[16] are also useful reagents for converting secondary amides into imidates.

Scheme 3. Alkylation of amides



Selective alkylation of primary amides is more difficult to achieve. Only the harder alkylating agents such as Meerwein's reagent, alkyl fluorosuphates (i.e. Magic Methyl®),[17] dialkyl sulphates[18] and

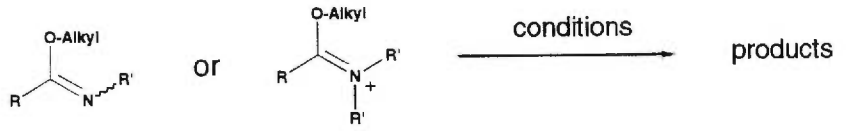
diazomethane[19] are more selective for the oxygen. Primary imidates[20] are more readily accessed by acid catalyzed (Pinner synthesis)[21] or base catalyzed[22] addition of alcohols onto nitriles.

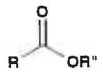
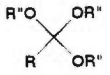
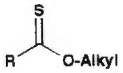
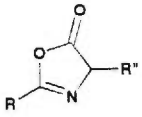
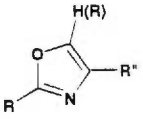
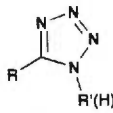
1.21 Reactions of Imidates and Alkyl Iminium Esters

Although the *O*-alkyl group of imidates and iminium esters is not considered electron withdrawing, these compounds are still more reactive than their amide counterparts because there is reduced delocalization of the electron lone pairs throughout the π-system. Alkyl imidates are much better electrophiles when protonated in acidic medium and iminium esters are positively charged, which makes them even more reactive towards nucleophiles. Various transformations of alkyl imidates and iminium esters are shown in Table 1.

Both alkyl imidates and iminium esters usually give rise to the same products when treated with the same nucleophile. Imidates and iminium esters can react with alcohols or water at medium to low pH to give esters[23,132] or ortho esters.[24] Treatment with hydrogen sulfide gives thionoesters, but often thioamides are present as side products.[25] Treatment with amines and substituted hydrazines produces amidines[26] and amidrazones,[27] respectively. Numerous heterocyclic systems can also be accessed by treating the imidate or iminium ester with various nucleophiles.[28] These nucleophiles include amino acids,[29] amino aldehydes and ketones,[30] diamines,[31] amino alcohols,[32] and azides.[33]

Table 1. Reactions of alkyl imidates and iminium esters

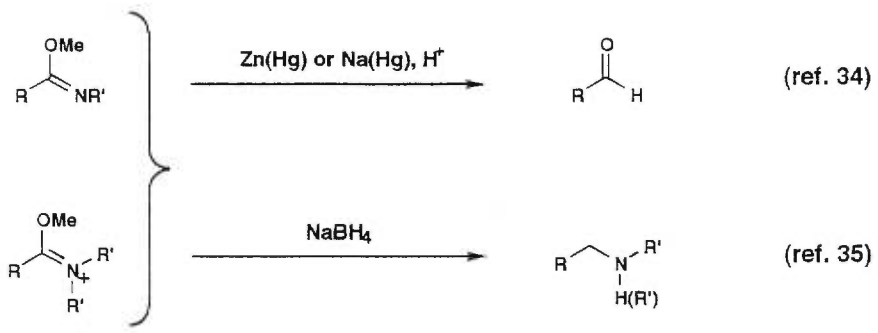


Conditions	Products	
1) R"OH, H^+ 2) H_2O, H^+		**(ref. 23)**
R"OH, H^+		**(ref. 24)**
H_2S		**(ref. 25)**
$H_2NH(R")$		**(ref. 26)**
$H_2N\text{-}NH_2(R_2")$		**(ref. 27)**
amino acids		**(ref. 29)**
amino aldehydes and ketones		**(ref. 30)**
amino alcohols		**(ref. 32)**
azides		**(ref. 33)**

Alkyl imidates and iminium esters are also much more reactive towards mild reduction than their amide counterparts (Scheme 4). Treatment with zinc or sodium amalgam in acidic solution produces

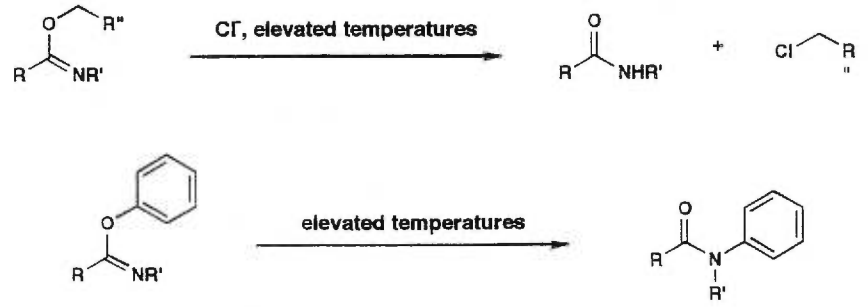
aldehydes.[34] One of the more general reactions is to reduce alkyl imidates or iminium esters to amines using sodium borohydride.[35]

Scheme 4. Reductions of imidates and iminium esters



One potential drawback of imidates is that the initial attack of a nucleophile is still relatively slow and often heating is required. Problems can arise at elevated temperatures (Scheme 5). In the presence of counter ions such as halides, imidates and iminium esters can undergo dealkylation to give amides and alkyl halides.[36] Furthermore, heating these compounds in the absence of these weak nucleophiles often results in the Chapman rearrangement (O to N migration of aryl and alkyl groups).[37]

Scheme 5. Problematic side reactions of imidates at elevated temperatures



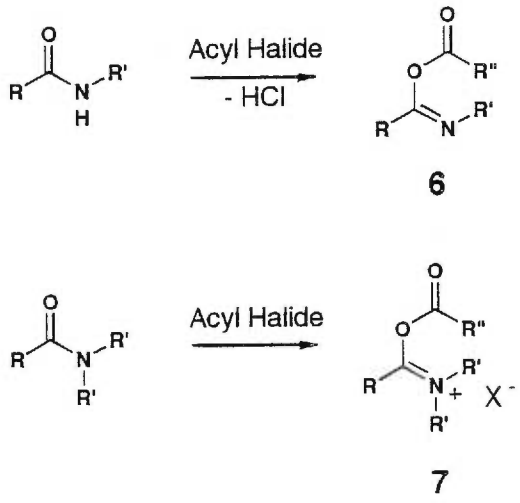
Although Meerwein's reagent is a convenient and popular method for making imidates, it is not reactive enough to *O*-alkylate tertiary amides. Typically, intramolecular alkylation is required to access *O*-alkyl iminium

esters from tertiary amides. Meerwein's reagent allows direct access to methyl or ethyl imidates. Access to other imidates requires equilibration with other alcohols.

1.3 Acyl Imidates and Iminium Salts

Another approach to making amides more reactive is to treat them with acylating reagents to give rise to acyl imidates **6** and acyl iminium salts **7**. These species are more electrophilic due to the greater electron withdrawing capacity of the acyl group compared to that of the alkyl group (Scheme 6). Hence, these electrophilic species would be able to react more readily with nucleophiles than their alkyl imidate or iminium ester counterparts. Carboxylic acid anhydrides react with amides in a similar fashion as the acid chloride, but more sluggishly. Catalysts such as hydrogen chloride, an acyl chloride or sulfuric acid are usually required.[38]

Scheme 6. *O*-acyl imidates and iminium esters from amides



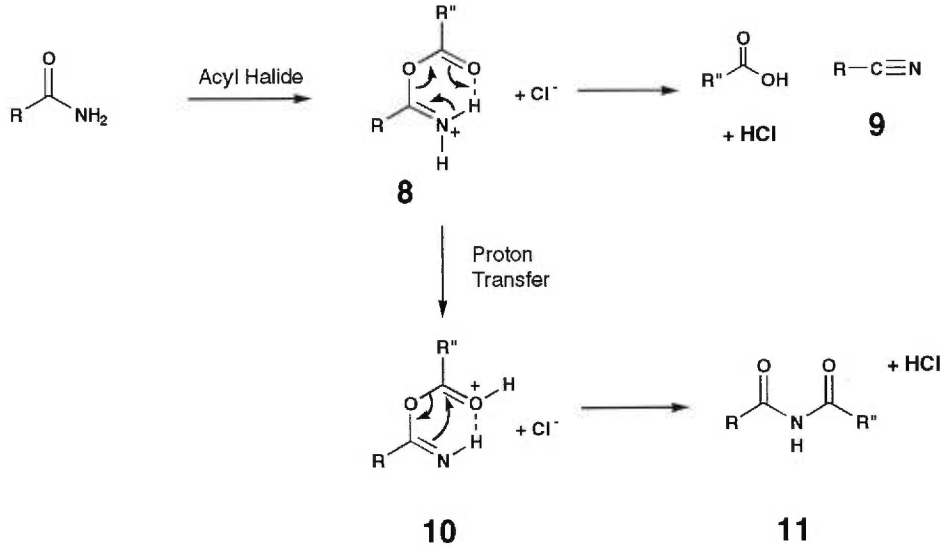
6

7

1.31 Reactions of Acyl Imidates and Iminium Salts

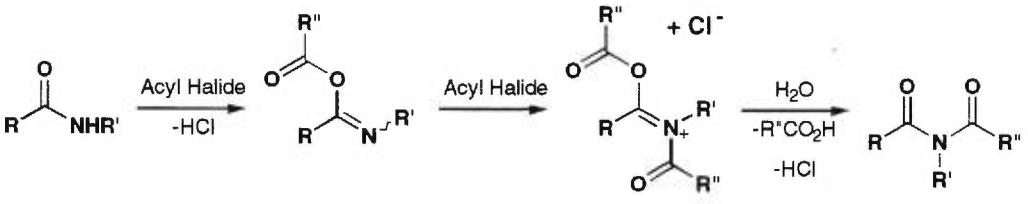
Although amides do react with carboxylic acid halides and these reactions do provide synthetically useful transformations, the products are not our desired electrophilically activated amide derivatives. Primary amides are readily dehydrated to the corresponding nitriles **9**,[39] although imidic compounds can also be formed (Scheme 7). The initial adduct between a primary amide and an acyl chloride is the *O*-acylated mixed anhydride **8**.[40] These generally dehydrate immediately, but if proton transfer is fast enough, imides **11** can be produced.[41]

Scheme 7. Nitriles from primary amides



Secondary amides also react initially to give the *O*-acylated compounds **12**.[42] These intermediates do not decarboxylate readily since this would form a nitrilium cation. A second acylation on the nitrogen gives the bis-acyl compound **13** and cleavage of the *O*-acyl bond upon aqueous work-up gives the corresponding *N*-acylated product **14** (Scheme 8). The additional electron-withdrawing group on an imide makes them about as electrophilic as an ester which is more electrophilic than the starting secondary amide.

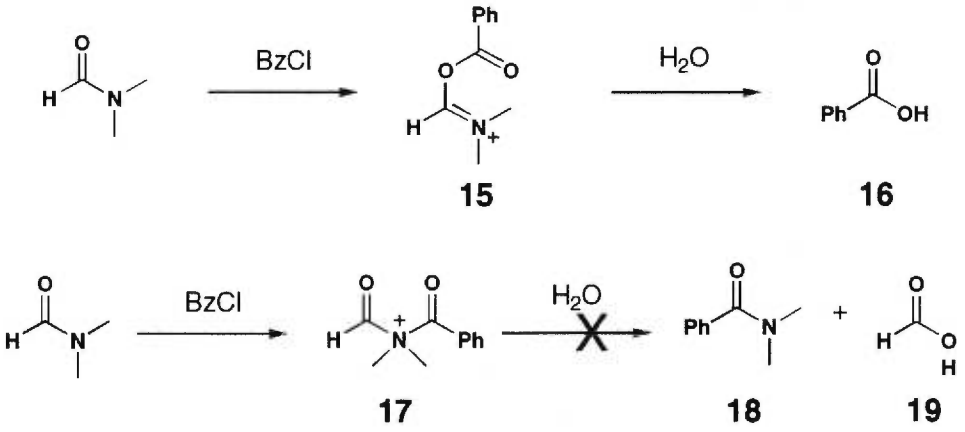
Scheme 8. O to N acyl transfer of O-acyl imidates



12 **13** **14**

Tertiary amides react with acyl halides to produce salt-like 1:1 addition complexes, which can be isolated at low temperatures. Again, these products are a result of *O*-acylation (Scheme 9).[43] The salt formed between *N,N*-dimethylformamide and benzoyl chloride is hydrolyzed to give benzoic acid **16**, but not formic acid **19**. This is consistent with the *O*-acylated intermediate **15** and not the *N*-acylated intermediate **17**.

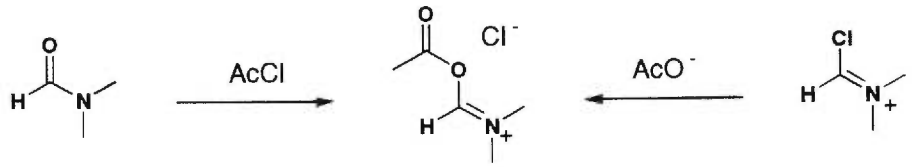
Scheme 9. Evidence of O-acylation of tertiary amides



15 **16** **17** **18** **19**

An indirect synthesis of the *O*-acyl iminium compound **20** also gives evidence towards the preferential acylation of the oxygen versus the nitrogen. Thus, adding acetate ion to the iminium chloride of *N,N*-dimethylformamide **21** gives the same product as the reaction between *N,N*-dimethylformamide and acetyl chloride (Scheme 10).[44]

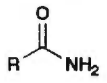
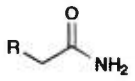
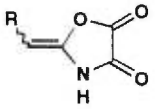
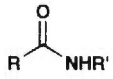
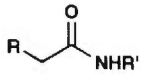
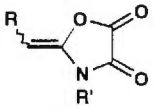
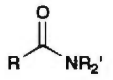
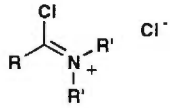
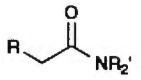
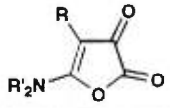
Scheme 10. Evidence of O-acylation by indirect synthesis of O-acyl complex



20 **21**

Unfortunately, treating amides with carboxylic acid halides is not a viable means for generating electrophilic species from amides. Primary and secondary amides form nitriles and imides, respectively. Tertiary amides do generate an electrophilic *O*-acyl iminium salt, but this methodology is not very general and is limited to the most reactive of tertiary amides. These reactive amides, such as *N,N*-dimethylformamide, can react further with a halide counter ion to give rise to iminium halides which is the topic of the next section. Another exception is the reaction between amides and oxalyl chloride (Table 2).[45] Various products can be produced depending on the nature of the amide.

Table 2. Reactions of amides with oxalyl chloride

Amide		Product
	(R = *t*-alkyl, Ph, H)	RCONCO
		
	(R = *t*-alkyl, Ph, H)	RCONR'COCOCl
		
	(R = *t*-alkyl, Ph, H)	
		

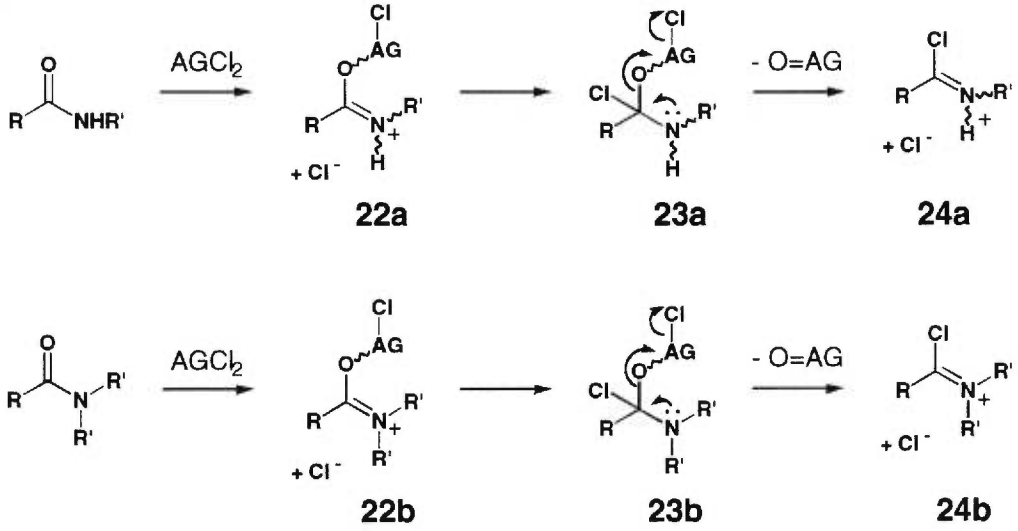
1.4 Imidoyl and Iminium Chlorides

Imidoyl[46] and iminium chlorides[47] are like their alkyl imidate or iminium ester counterparts as their structures reduce the delocalization of electrons throughout the amide functional group. Unlike their acyl equivalents, they suffer from fewer side reactions such as O to N migration of the electrophile. They induce a strong polarization of the amide functionality due to the electronegativity of the chlorine atom. These species are highly electrophilic and are very useful as intermediates for the nucleophilic additions onto amides. Problems associated with the corresponding fluorides, bromides and iodides are that they are not as reactive or are more difficult to prepare since they are unstable and readily decompose.[48]

Secondary and tertiary amides react selectively at the amide oxygen with chlorinating reagents (Scheme 11). This *O*-adduct **22** between the

amide and the inorganic acid halide strongly polarizes the amide C-O bond. Subsequent S_Ni attack of a chloride ion and elimination of a neutral fragment (CO_2, $POCl_3$, or SO_2) generates the imidoyl or iminium chlorides **24.**[49] Phosgene is the preferred reagent.[50] Other reagents[51] such as phosphorus pentachloride,[52] PCl_3/Cl_2,[53] PBr_3/Br_2,[54] $PhPCl_4$,[55] and thionyl chloride[56] can also be used, but generally, elevated temperatures are required. Primary amides invariably give nitriles under these conditions.[57]

Scheme 11. Generation of imidoyl and iminium chlorides



AG = Activating Group (PCl_3, S=O, C=O)

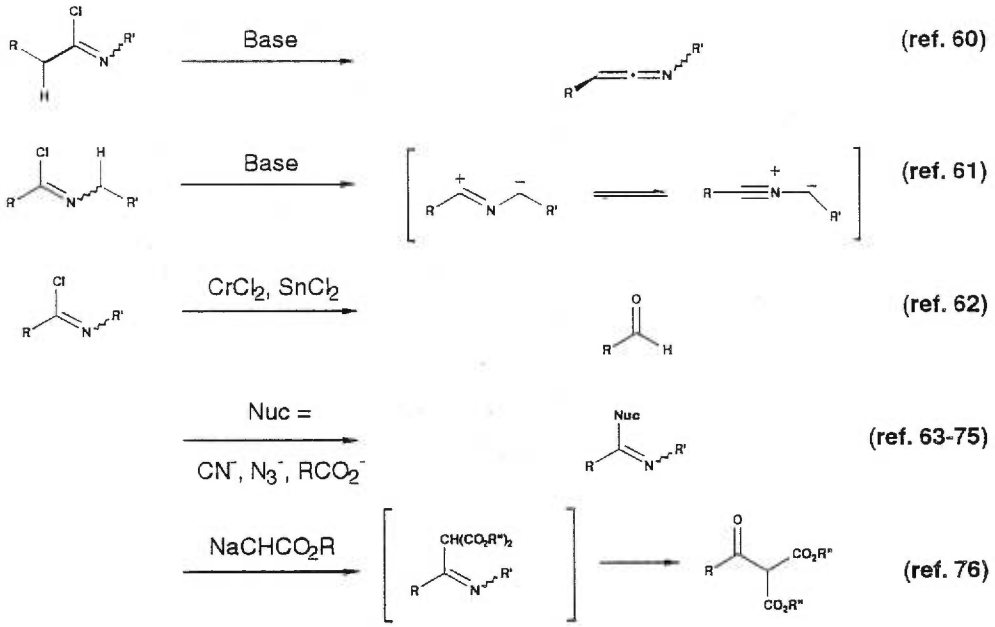
1.41 Reactions of Imidoyl and Iminium Chlorides

Relative to the alkyl imidates and alkyl iminium esters, the corresponding chlorides are much more electrophilic due to the inductive nature of the electronegative chlorine. This feature makes these intermediates very useful synthetic intermediates.[58]

Imidoyl chlorides are versatile synthetic intermediates (Scheme 12).[59] They are precursors to ketenimines[60] and 1,3-dipolar systems.[61] They can undergo reduction to give aldehydes,[62] hydrolysis,[63] and

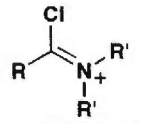
alcoholysis.[64] Amidines result after aminolysis with amines,[65] urethanes,[66] amidines,[67] hydroxylamines,[68] and hydrazines.[69] Other transformations are possible upon treatment with azides,[70] cyanides,[71] carboxylic acids,[72] thiols,[73] thioacids,[74] phosphites,[75] and activated carbanions.[76]

Scheme 12. Reactions of imidoyl chlorides

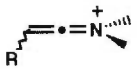
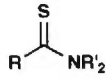
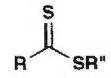
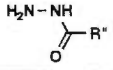
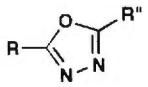
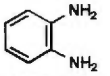
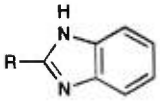
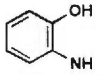
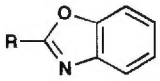


The chemistry of iminium chlorides is also diverse. They are useful for acylations and formylations in electrophilic aromatic substitutions (Vilsmeier-Haack reaction)[77] and precursors for keteniminium species.[78] They also allow for functional group transformations of amides to thioamides,[79] amidines,[80] esters,[81] thionoesters,[82] thioesters,[83] dithioesters,[84] ortho amides and ortho esters.[85] Numerous heterocyclic compounds can also be accessed such as 1,3,4-oxadiazoles,[86] imidazoles,[87] and oxazoles.[88]

Table 3. Reactions of iminium chlorides



Conditions → Products

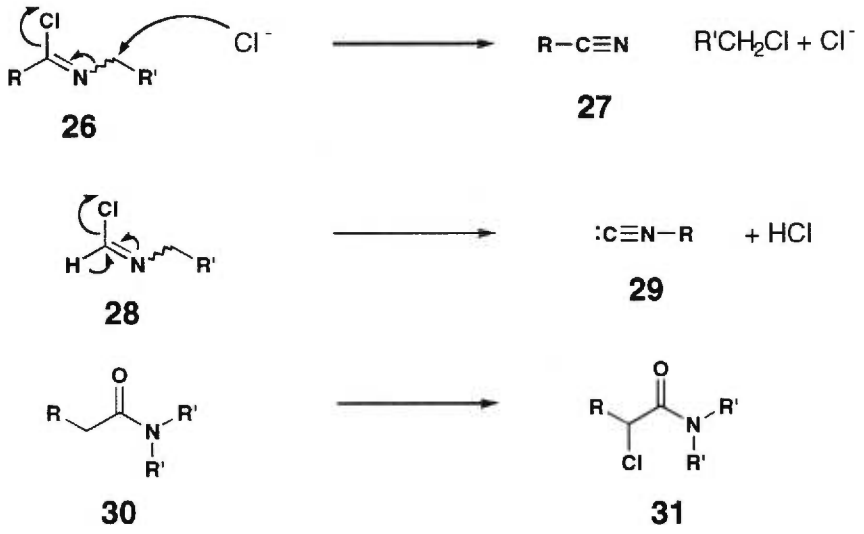
Conditions	Products	
ArH, Lewis Acid		(ref. 77)
Base		(ref. 78)
H_2S		(ref. 79)
R"SH		(ref. 84)
		(ref. 86)
		(ref. 87)
		(ref. 88)

1.42 Limitations of Imidoyl and Iminium Chlorides

Although imidoyl and iminium chlorides are useful synthetic intermediates, there are numerous limitations associated with their use. Elevated temperatures are required whenever using chlorinating agents less reactive than phosgene, which results in the possibility of side reactions such as the von Braun reaction (**26** to **27**). The ionic conditions coupled with elevated temperatures can result in N-alkyl bond fission (Scheme 13). This reaction was originally discovered by von Pechmann,[89] but subsequently, von Braun studied the reaction in depth[90] and now the reaction bears his name. This reaction is very prominent when higher

temperatures are used in conjunction with weaker chlorinating agents. In the case of secondary formamides **28**, elimination to the isonitrile **29** occurs readily.[91] Another problem associated with elevated temperatures is the formation of aliphatic α-chloro compounds **31.**[92]

Scheme 13. Side reactions at elevated temperatures



Reactions can be carried out at 0°C for secondary amides and at room temperature for tertiary amides when using an excess of highly reactive phosgene.[93] However, with a boiling point of 0°C and extreme toxicity, working with this war gas can be hazardous.[94]

Another limitation arises due to the relative low reactivity of the commonly employed chlorinating agents. An excess of the chlorinating agent is normally required for the formation of the activated amide. This requires removal of the excess reagent before treatment with various nucleophiles.[95]

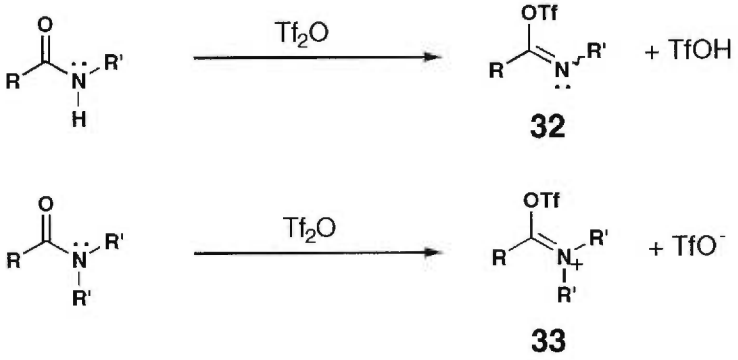
Finally, these chlorinating agents generate acid whenever they come into contact with water. So adventitious water or undistilled reagents can render the reaction quite acidic resulting in decomposition of sensitive substrates. Buffering the reaction with bases is not known to be compatible with the reaction conditions used for the conversion of amides

to imidoyl and iminium chlorides since in conjunction with elevated temperatures, the formation of ketenimine or keteniminium compounds can be competitive.

1.5 Imidoyl and Iminium Triflates

In the early 1980's, Ghosez and coworkers[96] reported the first reaction between a tertiary amide and trifluoromethanesulphonic (triflic) anhydride.[97] Due to the extremely good leaving group ability of the triflate anion,[98] triflic anhydride is so much more reactive than phosgene or any other popular chlorinating agent that the various problems associated with the generation of imidoyl and iminium chlorides can be avoided. Triflic anhydride reacts with both secondary and tertiary amides at temperatures much below 0°C (Scheme 14). These low temperatures severely reduce the possibilities of side reactions. The high reactivity of triflic anhydride also allows the reaction with amides to go to completion while using only a stoichiometric amount of the anhydride.

Scheme 14. Formation of imidoyl **32** and iminium triflates **33**



Most interesting is the compatibility of bases towards the formation of imidoyl and iminium triflates. Trialkyl amine bases can be used in these reactions at low temperatures. This eliminates the possibility of

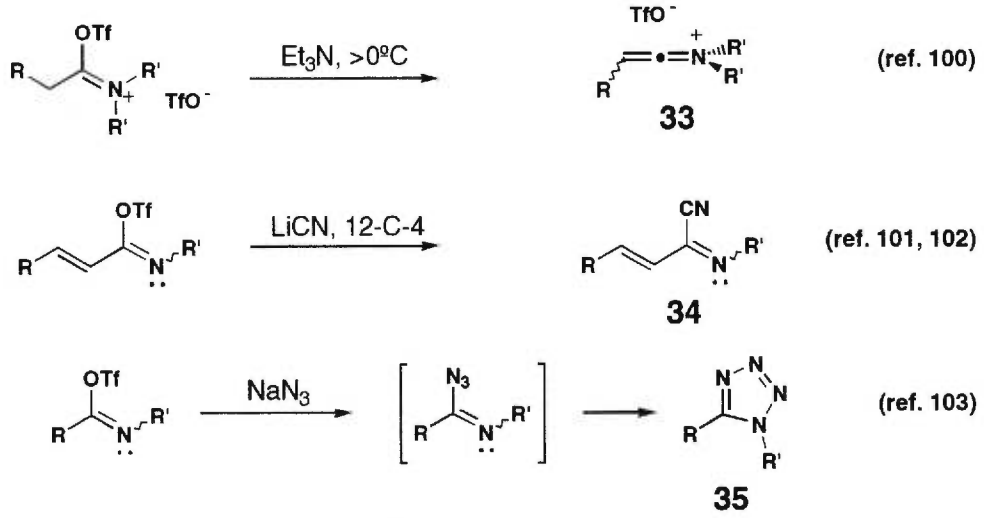
decomposition as a result of strong acids being present in the reaction media.

Like the other imidoyl and iminium derivatives, electron delocalization is reduced, but much more so in the case of in imidoyl and iminium triflates. Furthermore, since leaving group ability of the triflate anion is so much greater than that of the chloride, imidoyl and iminium triflates are even more electrophilic than the corresponding chlorides.[99]

1.51 Reactions of Imidoyl and Iminium Triflates

In his pioneering efforts, Ghosez demonstrated that iminium triflates readily eliminate triflic acid upon warming in the presence of a trialkyl amine base (Scheme 15). This is an efficient method for generating keteniminium cations **33** which readily undergo [2 + 2] cycloadditions.[100]

Scheme 15. Reactions if imidoyl and iminium triflates



Grierson and Fowler converted secondary amides to the corresponding imidoyl triflates which are electrophilic enough to react with lithium cyanide in 12-crown-4 to give rise to 2-cyano-1-aza-1,3-butadienes **34.**[101] These electron-poor dienes can be used in intramolecular Diels-Alder reactions.[102]

Imidoyl triflates also react with sodium azide.[103] This produces a highly reactive imidoyl azide which spontaneously cyclizes to give tetrazoles **35**.

1.6 Recent Advances in Imidoyl and Iminium Triflate Chemistry

In the following chapters, an account of imidoyl and iminium triflate chemistry will be given. These triflates are generated in the presence of pyridine, but unlike the predecessors in this field, we have found that the application of this mildly acidic pyridine conjugate acid acts as a very efficient catalyst in the reaction of these triflates with various weak nucleophiles. This conditions are acidic enough not only to render the amine residue of the amide a good leaving group, deprotonation of various reaction intermediates is efficient in the same media. This allows mild and efficient access to esters, ortho esters, thiazolines and thioamides starting with secondary and tertiary amides. These reactions are milder than previously available methods since the generation of the triflate is milder than the chloride and the triflate is more reactive than alkyl imidates allowing subsequent substitution by nucleophiles to occur under milder conditions. The various functional group transformations presented in the following chapters should provide evidence that all the previously available chemistry of alkyl imidates, alkyl iminium esters, imidoyl and iminium chlorides can also be extended to imidoyl and iminium triflates.

Chapter 2: Synthesis of Imidoyl and Iminium Triflates

CHAPTER 2

Synthesis of Imidoyl and Iminium Triflates

2.1 Synthesis of Imidoyl and Iminium Triflates from Secondary and Tertiary Amides

In any chemical transformation, many factors can affect the outcome of the reaction. We found that the formation of imidoyl and iminium triflates from amides is dependent on structure, temperature, and solvent. Matters can be complicated by the presence of other reagents such as pyridine. Finally, there are inherent structural aspects of primary and methylbenzyl amides which prevent the formation of triflate adducts. These factors are important and must be taken into consideration when converting amides into their corresponding triflates.

2.2 Effect of Structure on Rates of Formation

In general, the reaction between amides and triflic anhydride is fastest for primary amides, slower for secondary amides and the reaction is slowest for tertiary amides. The reasoning for this lies in the nucleophilic nature of the amide which is a function of steric and electronic factors conferred by the structure of the molecule.

2.21 Steric Factors Governed by Amide Structure

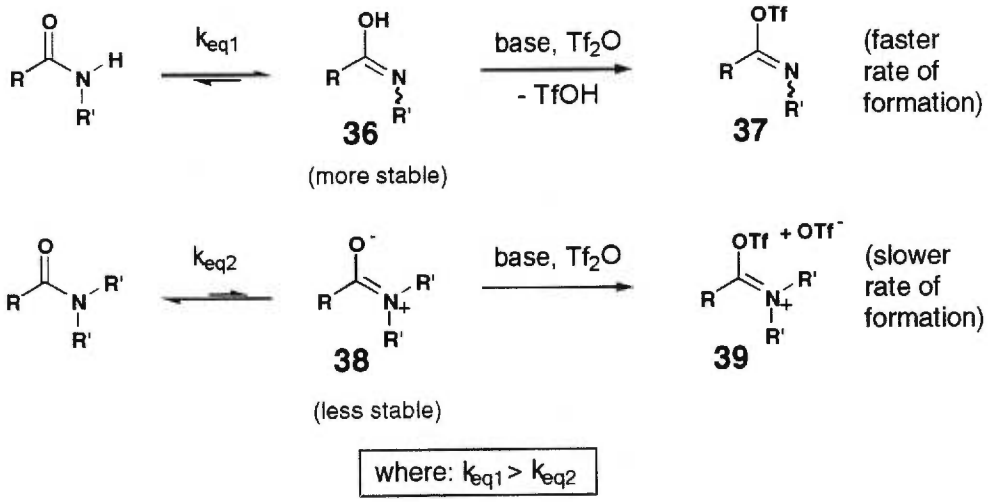
Steric hindrance reduces reactivity of both nucleophiles and electrophiles.[104] In light of this, the nucleophilic oxygen of primary amides is the least hindered relative to secondary and tertiary amides because of

its unsubstituted amine residue. Hence, primary amides react fastest with triflic anhydride. Secondary amides react with triflic anhydride at a faster rate than tertiary amides. Again, the argument for this is a steric one as the amine residue of the secondary amide is less substituted. We have observed that the relative rates of reaction between amides and triflic anhydride is: primary > secondary > tertiary (*vide infra*). Subsequent nucleophilic attack on the electrophilic intermediate is also governed by steric factors. Secondary and less hindered tertiary amides react faster than large and bulky tertiary amides.

2.22 Electronic Factors Governed by Amide Structure

The rate of formation of imidoyl and iminium triflates can also be influenced by electronic factors. If it is not the amides, but rather the iminol **36** or alkoxyl iminium species **38** which reacts with triflic anhydride, then it is the concentration of these intermediates which would determine the rates of reaction with triflic anhydride (Scheme 16).

Scheme 16. Iminols versus iminium alkoxides



The iminol of secondary amides is neutral, whereas the alkoxy iminium of tertiary amides is charged. Hence, the canonical form of

secondary amides is more stable and its greater relative abundance should result in the faster formation of imidoyl triflate **37** versus iminium triflate **39**.

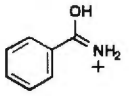
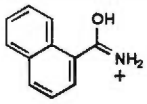
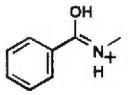
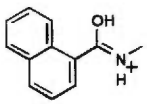
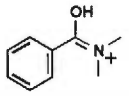
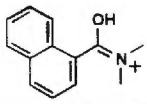
Furthermore, secondary amides have the capability of tautomerizing via a dimeric transition state (Figure 3). Although there are slightly higher entropic costs involved with this pathway which would be reflected in slightly higher activation energies, there is a significant additional stabilization of the iminol form.[105] This mode of stabilization is not possible for tertiary amides as no intramolecular hydrogen bonding can be formed.

Figure 3. Effect of dimerization on tautomerization of secondary amides

Since the formation of the S-O bond in a triflate is enthalpically favorable (~112 kcal/mol),[106] formation of the imidoyl or iminium triflate can be presumed to be irreversible. However, there are precedents for nucleophilic attack on aryl triflates resulting in alcoholysis or hydrolysis of the S-O bond.[107] In conjunction with an imidoyl or iminium-activating group, S-O bond cleavage may be enhanced. Therefore, it is arguable that the formation of imidoyl and/or iminium triflates can be reversible, thus, an equilibrium could exist between the starting amide and the triflate.

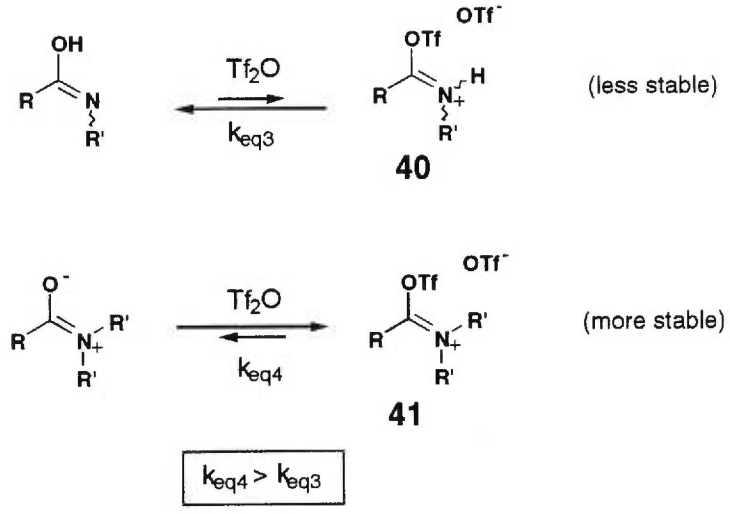
In media which is sufficiently acidic to protonate the triflate intermediates, the iminium triflate would be more stable than the protonated imidoyl triflate cation because of the extra electron donating substituents on the nitrogen, which makes tertiary amides more basic than secondary amides (Table 4).[108]

Table 4. Acidities of the conjugate acids of amides

Amide	pk_a	Amide	pk_a
	-1.54		- 1.68
	-1.5		- 1.62
	-1.2		- 1.21

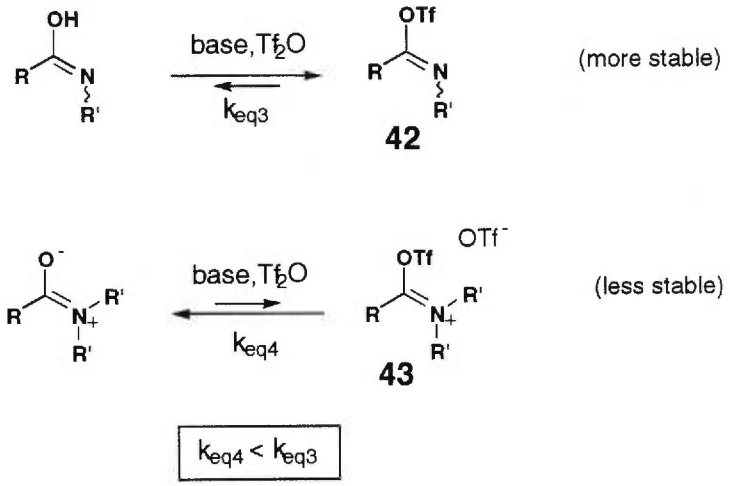
If these reactions were reversible as previously discussed, then the reaction would be under thermodynamic control with the formation of the iminium triflate **41** being favored over that of the imidoyl triflate **40** (Scheme 17). Under these conditions, the yield of iminium triflates would be greater than the yield of imidoyl triflates as the reaction would be under thermodynamic control.

Scheme 17. Stabilities in acidic medium if equilibrium were possible



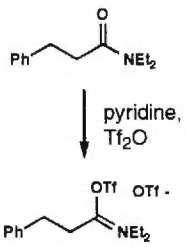
In reaction conditions which are not strongly acidic, the imidoyl triflate **42** would not be protonated and would not be charged (Scheme 18). Hence, imidoyl triflates would be more stable in a non-acidic medium. Therefore, if the formation of imidoyl and iminium triflates were under thermodynamic control in a non-acidic medium, imidoyl triflates would be formed preferentially.

Scheme 18. Iminols and iminium alkoxides in basic medium if equilibrium were possible

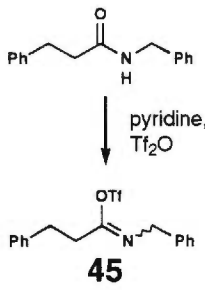


Preliminary kinetic studies at low temperatures show that the secondary amides react faster with triflic anhydride than tertiary amides (Table 5).[109] The relative rate of formation of imidoyl triflates **45** is approximately 3 times as fast as the formation of iminium triflate **44** at temperatures of -20, -10, and 0°C.

Table 5. Rates of formation of imidoyl triflate and iminium triflates



44



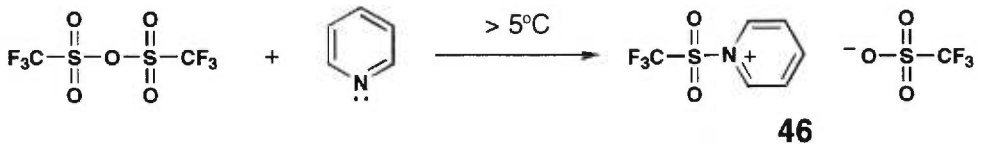
45

T (°C)	% conv. (10 min)	T (°C)	% conv. (10 min)
-50	0	-50	0.5
-40	1	-40	1.3
-30	1	-30	6
-20	3	-20	6
-10	7.5	-10	20
0	10	0	36

2.3 Effect of Temperature on Rates of Formation

Another aspect shown by Table 5 is that the absolute rates of formation are proportional to temperature. With a lower limit near –60°C where very little or no triflate is formed, the rate increases with increasing temperature. Presumably, the rate could continue increasing without limits. In practice, however, an upper temperature limit does exist. There are several reasons for this. Firstly, triflates having a α-proton begin to eliminate triflic acid near room temperature in presence of a base. This parasitic side reaction results in the formation of ketenimines and keteniminium compounds.[110] Secondly, at temperatures above 5°C, triflic anhydride begins to react with pyridine to form triflyl pyridinium triflate which severely deactivates the triflating agent and prevents the formation of the desired imidoyl or iminium triflate (Scheme 19). So in practice, the upper temperature limit for triflate formation is about 0°C when pyridine is present.

Scheme 19. Formation of triflyl pyridinium triflate **46**

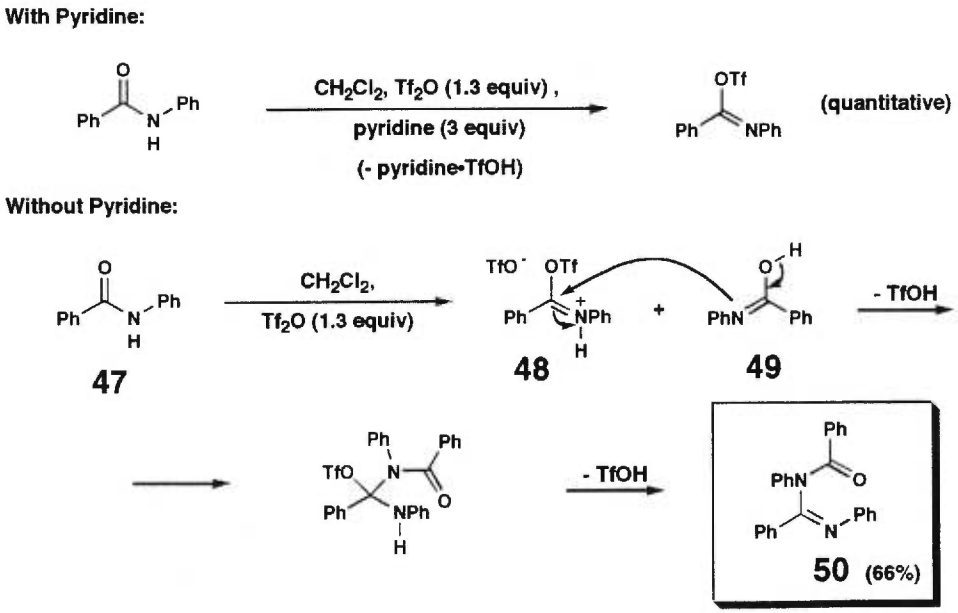


46

2.31 Beneficial Effects of Pyridine During the Generation of Imidoyl and Iminium Triflates

During the formation of imidoyl and iminium triflates, it is advantageous to have pyridine in the reaction flask before the addition of triflic anhydride. This is because pyridine buffers the reaction against any endogenous or adventitious triflic acid which could cause deleterious side reactions and decomposition due to its extremely strong Brønsted acidity.[111] One possible side reaction during the formation of imidoyl triflates is the cross coupling between the product imidoyl triflate **48** and the starting amide **49** (Scheme 20).

Scheme 20. Formation of *N*-acyl amidines **48** in acidic medium



When *N*-phenyl benzamide is converted to the imidoyl triflate **48**, there is one equivalent of triflic acid which is generated. Without base in the reaction, the imidoyl halide would be protonated and this intermediate **48** is so highly electrophilic, that it can react with a secondary amide **49** to form the *N*-acyl amidine **50** whose x-ray crystal structure is given in Figure 4.[112] When there is base in the reaction, the imidoyl triflate is not protonated and the dimerization does not occur. The formation of *N*-acyl amidines is problematic only for more acidic amides like *N*-phenyl benzamide since most other amides used in these studies usually do not undergo dimerization in the absence of a base. Nevertheless, to avoid either decomposition in highly acidic medium or dimerization, a base is necessary during the formation of imidoyl and iminium triflates.

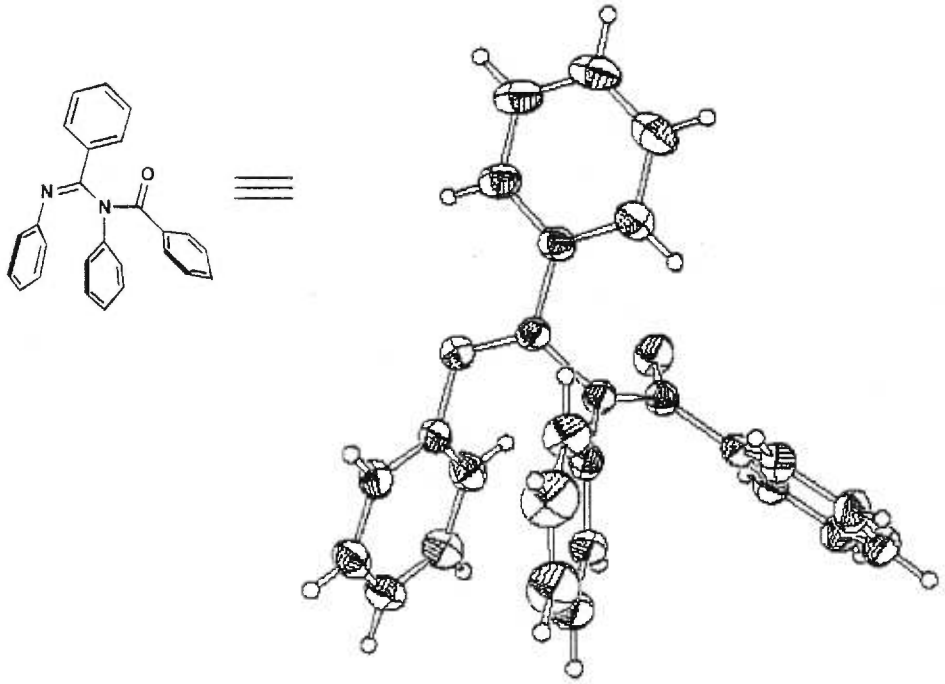


Figure 4. ORTEP representation of *N*-acyl amidine **50**

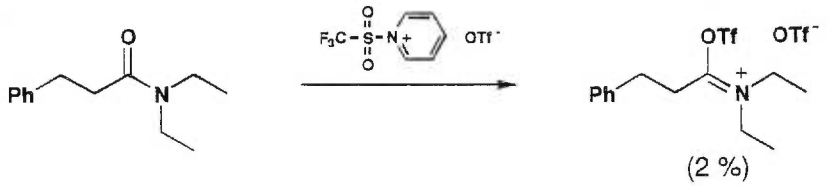
Since pyridinium hydrotriflate is usually required in subsequent stages of various transformations of these electrophiles (*vide infra*), it is logical to have the pyridine present in the reaction at this point. So

pyridine is present during the formation of triflates and the chance of forming pyridinium hydrotriflate is unavoidable in most cases. Hence, understanding this reagent is important towards developing methodology involving pyridine and triflic anhydride.

2.32 Triflyl Pyridinium Triflate

Triflyl pyridinium triflate is a salt-like adduct between pyridine and triflic anhydride.[113] It is formed when triflic anhydride is intentionally added to pyridine at temperatures above 0°C, or by accident if the addition of triflic anhydride to the reaction mixture occurs too quickly resulting in an exotherm that causes the temperature of the reaction to rise significantly. The formation of this ionic compound is disadvantageous for the formation of iminium triflates because triflyl pyridinium triflate is not electrophilic enough to react with tertiary amides (Scheme 21). In our experience, an efficient way to prevent the formation of triflyl pyridinium triflate on small scale is to add the neat triflic anhydride down the side of the cooled flask so it can cool before it mixes with the reaction. On large scale, triflic anhydride should be added as pre-cooled solution in the appropriate solvent.

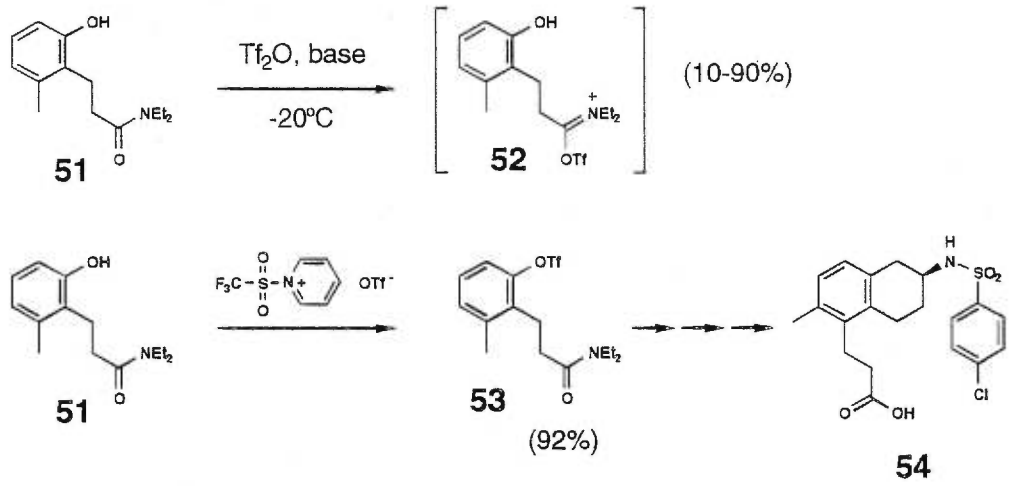
Scheme 21. Attenuated reactivity of triflyl pyridinium triflate



Triflyl pyridinium triflate can be formed by the addition of triflic anhydride to pyridine in dichloromethane at 0°C and then allowed to stir while warming up to room temperature over 15 minutes. Triflyl pyridinium triflate forms as a white precipitate in this dichloromethane solution. One useful property of this compound is that it is electrophilic

enough to react with nucleophiles such as phenols, but not electrophilic enough to react with tertiary amides. We applied this useful property to the synthesis of functionalized β-aminotetralins **54** (Scheme 22).[114] Using triflic anhydride for triflate formation gave mixtures of products **52** and **53**. Using triflyl pyridinium triflate allowed the selective transformation of phenol **51** to the aryl triflate in 92% yield.

Scheme 22. Selective aryl triflate formation by triflyl pyridinium triflate

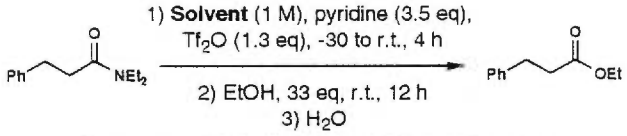


2.4 Effect of Solvent on Rates of Formation

Solvent effects[115] are an important factor in "wet chemistry" due to the importance of solvation of the nucleophile. In a preliminary survey, the formation of iminium triflates was carried out in various solvents and the triflate was treated with an excess of ethanol to assay its formation (Table 6).[116] One assumption was that the large amount of ethanol that was added would overcome any solvent effects during the second step of the conversion of the iminium triflate to the ortho ester (*vide infra*).[117] It turns out that the solubility of the reactants in various solvents at low temperatures turned out to be crucial for the triflate formation. As the formation of the iminium triflate approached 0°C, normally the solution

would become homogeneous and slightly yellowish in color. In solvents such as hexane, the amide is poorly solubilized resulting in a poor reaction. It turns out that the triflate formation was the fastest in dichloromethane; the same solvent originally used by Ghosez, Fowler, and Thomas in their studies with imidoyl and iminium triflates.[118]

Table 6. Formation of iminium triflates and conversion to esters

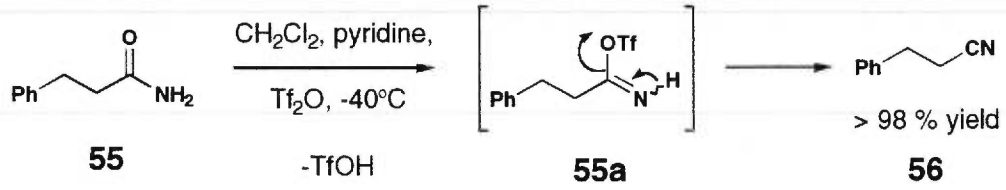


Solvent	Conversion
CH_2Cl_2	96 %
DME	97 %
Hexane	43 %
Toluene	43 %
Diethyl Ether	55%
THF	43 %

2.5 Structural Limitations of Primary and Methylbenzyl Amides

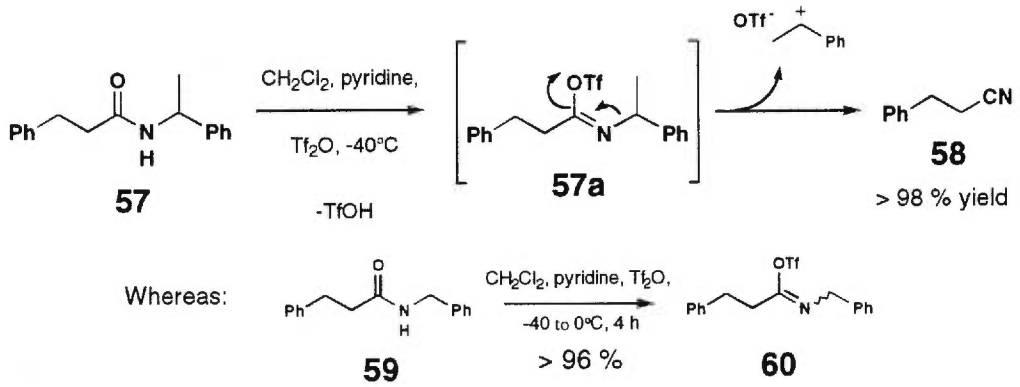
Primary amides and methylbenzyl amides do not form stable adducts with triflic anhydride as other secondary and tertiary amides do. This can be attributed to the ability of the proton (primary amides) and the α-methyl benzyl moiety to sustain a positive charge.[119] The reaction of primary amides **55** with triflic anhydride, results in the immediate formation of the *O*-triflate adduct **55a** which can be attributed to the unhindered nature of the primary amide. Compound **55a** then immediately fragments to form triflic acid and nitrile **56** (Scheme 23). The yields are excellent and the reaction can be done at low temperature. Although these conditions have never been reported,[120] this outcome could have been predicted based on existing methodologies.[121]

Scheme 23. Dehydration of primary amides by triflic anhydride



Methylbenzyl amides also form the initial *O*-triflate adduct **57a**. These compounds readily undergo a von Braun type reaction and produce the nitrile **58** (Scheme 24).[122] However, triflates are such poor nucleophiles that it is unlikely that this process occurs via an SN_2 pathway as called for in the von Braun reaction. Furthermore, because this process does not occur in the benzyl amides, this difference in reactivities is not explained well by an SN_2 mechanism. It is likely that the reaction proceeds via an SN_1 mechanism. An SN_1 mechanism can account for the poor nucleophilicity of the triflate anion as well as the reactivity of α-methyl benzylamides and lack of reactivity of benzyl amides. This reaction is more reminiscent of a "retro-Ritter" reaction or an SN_1 variant of the von Braun reaction.[123]

Scheme 24. "Retro Ritter" fragmentation of methylbenzyl imidoyl triflates



Apart from primary and α-methyl benzyl amides, other amides generally form imidoyl and iminium triflates without major side reactions.

2.6 Conclusion

Several factors affect the reaction between amides and triflic anhydride. Secondary amides react faster than tertiary amides. This can be attributed to steric as well as electronic factors. This reaction seems to be fastest in dichloromethane. Pyridine is required to protect the substrate against the damaging effects of triflic acid. However, when pyridine is present, addition of triflic anhydride to the reaction should be done at 0°C or lower to prevent the formation of triflyl pyridinium triflate. Secondary amides of α-methyl benzyl amine can be converted to the imidoyl triflate, but these compounds readily undergo a "retro-Ritter" type fragmentation to produce the nitrile. Finally, primary amides react with triflic anhydride selectively at the oxygen, but these intermediates are unstable as they immediately eliminate triflic acid to generate the nitrile.

Chapter 3: Conversion of Secondary and Tertiary Amides to Esters

CHAPTER 3

Conversion of Secondary and Tertiary Amides to Esters.[124]

3.1 Introduction

Amides are one of the most robust carboxylic acid derivatives. Their use as protecting groups in the synthesis of highly functionalized molecules is limited since removal of the amide group is usually very difficult to achieve under mild conditions.[125] Nevertheless, they are used whenever possible with robust molecules which can withstand more forceful conditions. A cursory exam of existing methods will show that mild methods are few and far in between, especially for tertiary amides. We have developed a method based on the activation of secondary and tertiary amides with triflic anhydride. Successive treatment with a primary alcohol results in the formation of the acyclic ortho ester. The ortho ester is readily hydrolyzed in an aqueous work-up to yield the ester. This method is more general than the analogous methodology using imidoyl and iminium chlorides since the formation of the corresponding triflates occurs under milder conditions. Furthermore, the novel application of a very weakly acidic pyridine buffered reaction media allows for the efficient conversion of the triflate to the ortho ester at room temperature. Racemization is minimal and numerous functional groups tolerate these conditions. This method should prove itself to be very useful in the repertoire of organic chemists.

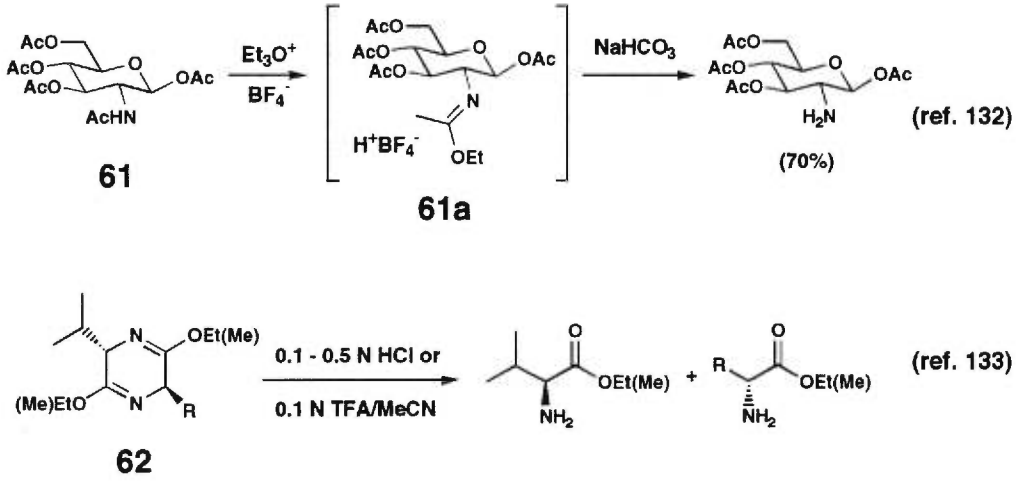
3.11 Primary Amides

Primary amides are the most readily cleaved amides.[126] Since they are dehydrated by the method being presented here, a discussion of existing methods for the cleavage of primary amides will not be presented here.

3.12 Milder Methods for Cleaving Secondary Amides

Secondary amides can be cleaved under traditional methods, but these tend to require strong acid or base coupled with elevated temperatures.[127] In peptides[128] and other bioorganic[129] systems, some interesting mild conditions exist, but are somewhat limited in scope. Milder conditions are available when hydrolyzing alkyl imidates[130] formed by the action of Meerwein's reagent on secondary amides.[131] This popular method is exemplified by Hanessian's[132] cleavage of a secondary amide on the glycoside **61** and Schöllkopf's[133] hydrolysis of bis-lactims **62** (Scheme 25).

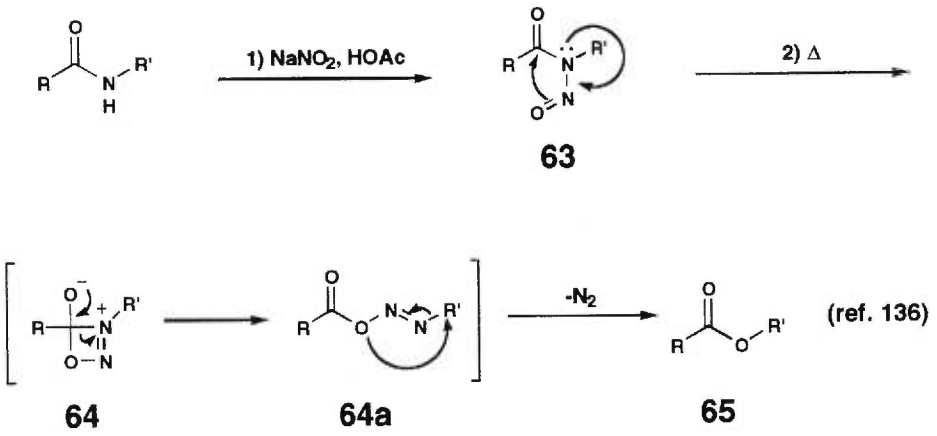
Scheme 25. Mild amide hydrolysis via imidates



Hanessian found that hydrolysis of the imidate can occur at essentially neutral pH which was novel at the time since the studies of Schmir and coworkers indicated that acidic conditions were necessary.[134] More recently, others have made the same observation with alkyl iminium esters.[135]

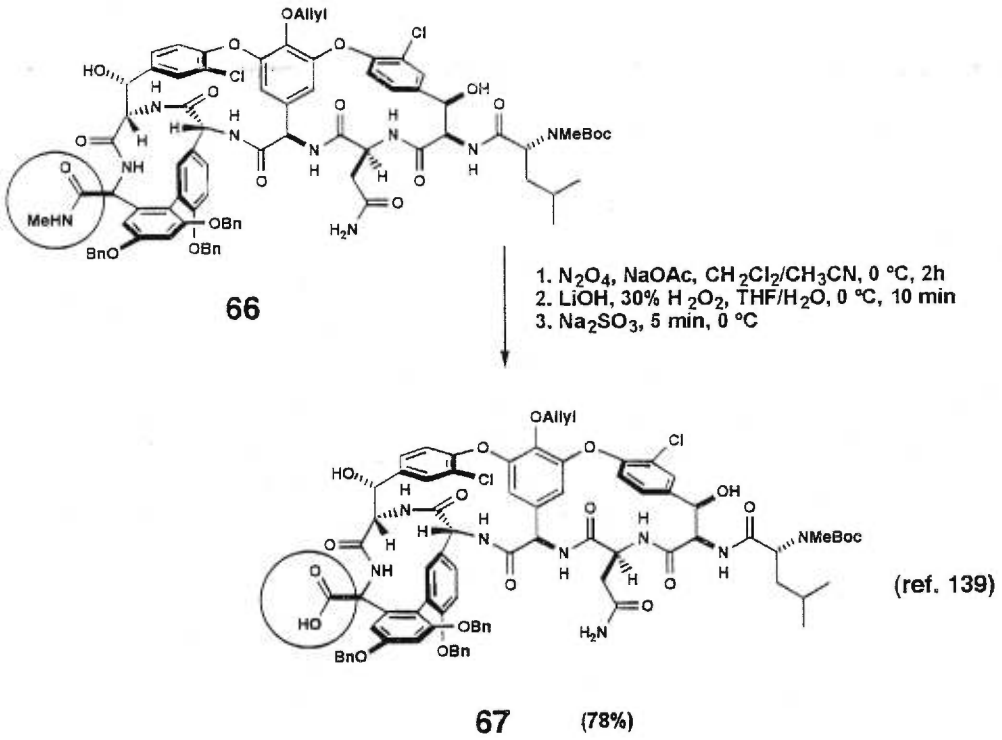
Some mild methods are also available by activation of secondary amides by *N*-nitrosylation followed by a thermal rearrangement of the *N*-nitroso amide **63** to furnish the corresponding ester **65** [136] (Scheme 26).

Scheme 26. *N*-Nitrosylation and thermal rearrangement of secondary amides



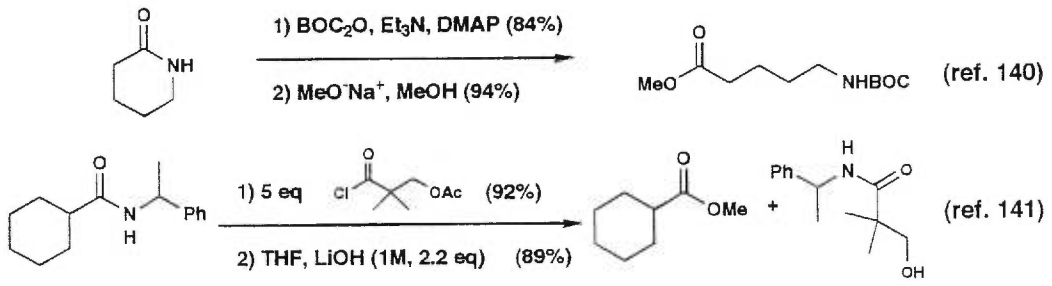
Although the thermal rearrangement of *N*-nitroso amides is somewhat harsh, *N*-nitroso amides can react under milder conditions with nucleophiles such lithium hydroperoxide to give the acids,[137] or thioesters.[138] An impressive application of this approach appears in Evan's synthesis of Vancomycin **66** where the C_1 *N*-methyl amide was selectively nitrosylated and hydrolyzed using lithium hydroperoxide to give the acid **67** (Scheme 27).[139]

Scheme 27. Mild selective cleavage of the C_1 *N*-methyl amide in Evans' synthesis of Vancomycin



Activation can also be achieved by carboxylation on the nitrogen prior to hydrolysis (Scheme 28).[140] A related approach relies on acylation with acetoxypivaloyl chloride[141] which activates the amide towards hydrolysis and provides an intramolecular hydroxyl group for neighboring group-assisted hydrolysis.[142]

Scheme 28. Activation towards hydrolysis via carboxylation/acylation

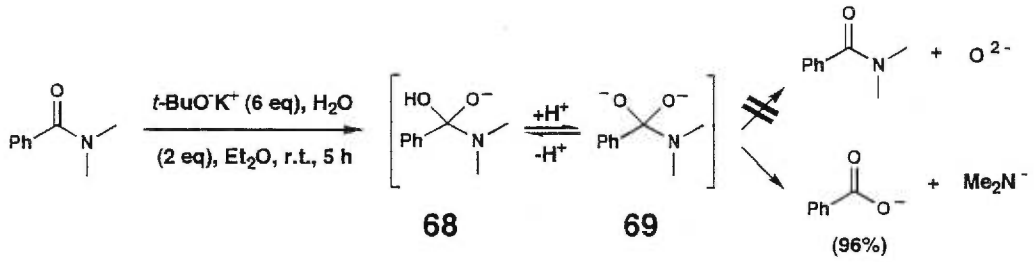


Some of these methods, however, require irreversible derivatization of the amine nitrogen which results in a transformed amine at the outcome of the reaction. These methods are more useful for obtaining the carboxylic acid portion of the molecule.

3.13 Mild Methods for Cleaving Tertiary Amides

For tertiary amides, very few mild methods exist and even fewer of these are general. Hydrolysis of tertiary amides without prior activation usually requires extremely harsh conditions. An interesting method uses the fact that the amine residue is a better leaving group than an oxygen dianion (Scheme 29).[143] In this approach, the tetrahedral intermediate **68** resulting from the nucleophilic addition of hydroxide onto the amide is deprotonated to give the highly unstable dianion **69**. This intermediate fragments to expulse the amide residue instead of an extremely unstable O^{2-} dianion, thus, cleaving the amide bond.

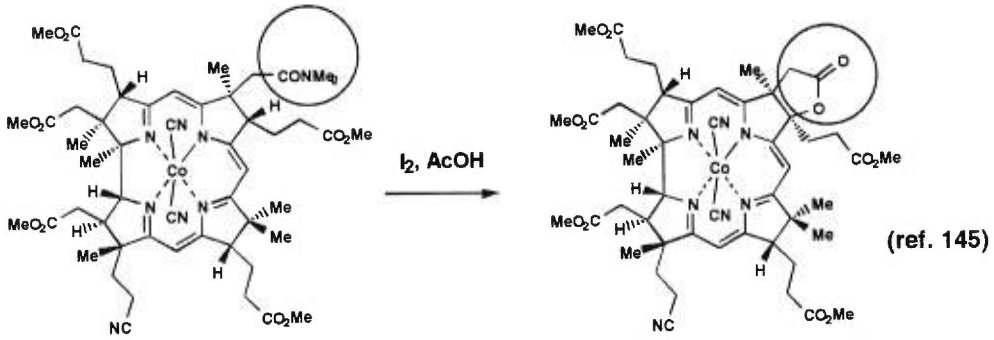
Scheme 29. Formation and fragmentation of dianion **69**



Activation of tertiary amides by acylation or chlorination is too harsh except for the most reactive tertiary amides such as dimethylformamide. Alkylation is milder, but the reagents are not reactive enough to form these intermediates quickly. Nevertheless, the application of Meerwein's reagent on oxazolines or alkylation by an intramolecular alkyl halide can form alkyl iminium esters which can be hydrolyzed under mild conditions.[144] A very elegant example of this approach was used by

Woodward in his formal synthesis of Vitamin B_{12}.[145] The B-ring *N,N*-dimethylamide is alkylated by an intramolecular iodonium cation to form the cyclic iminium ester which gives the lactone upon aqueous work-up (Scheme 30).

Scheme 30. Alkyl iminium esters formed via intramolecular alkylation in Woodward's synthesis of Cobyric acid **71** (Vitamin B_{12})



70 **71**

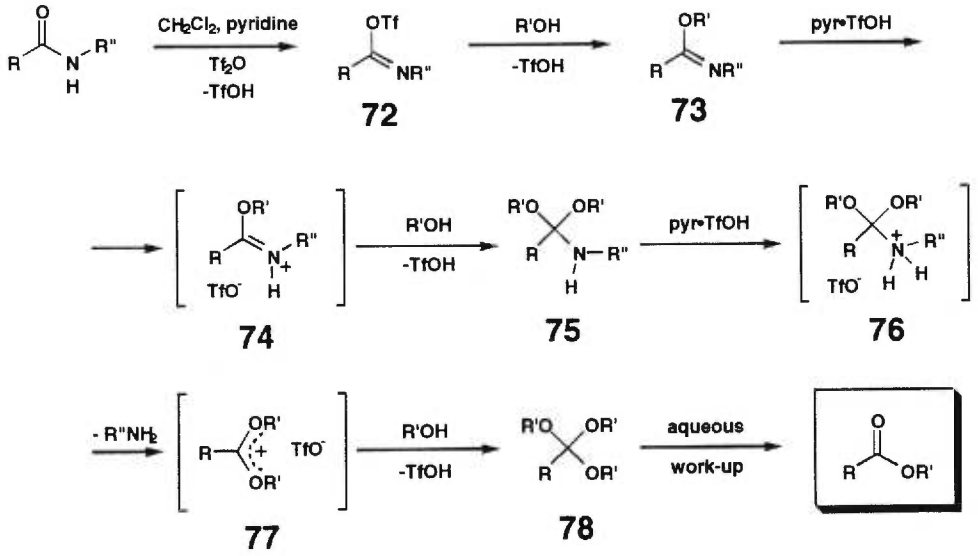
3.2 Towards a Mild Method for the Cleavage of Secondary and Tertiary Amides via Imidoyl and Iminium Triflates

The approach that will be presented in this thesis is based on the conversion of secondary and tertiary amides to the corresponding triflates. Without isolating these highly electrophilic intermediates, subsequent treatment with alcohol produces ortho esters which yield esters upon hydrolytic work-up. The formation of the imidoyl and iminium triflates occurs under mild conditions since the reaction takes place at low temperatures and in a pyridine buffered medium. Furthermore, the conversion of the triflate to the ortho ester also occurs in a pyridine buffered solution at room temperature. Hence, the low temperatures and very mildly acidic nature of both these steps make this one pot procedure very mild and simple to execute.

3.21 Mechanistic Aspects of the Conversion of Secondary and Tertiary Amides to Esters

For secondary amides, the reaction starts with the low temperature formation of the imidoyl triflate **72** in the presence of pyridine. This reaction forms one equivalent of triflic acid which is immediately neutralized to give pyridinium hydrotriflate. After about 4 hours at 0°C, the reaction is generally complete for secondary amides and the alcohol can then be added resulting in the formation of the imidate **73** and another equivalent of pyridinium hydrotriflate. The pyridinium hydrotriflate in the reaction media is a weak acid and can catalyze the addition of another alcohol onto the imidate to form the ortho amide **75**. Again, pyridinium hydrotriflate acts as a general acid catalyst to protonate the amine residue **76** and convert the ortho amide to the ortho ester **78** via the oxonium intermediate **77**. The reaction yields the acyclic ortho ester, but these types of ortho esters are very sensitive substrates and are readily converted to the simple ester by an aqueous work-up.

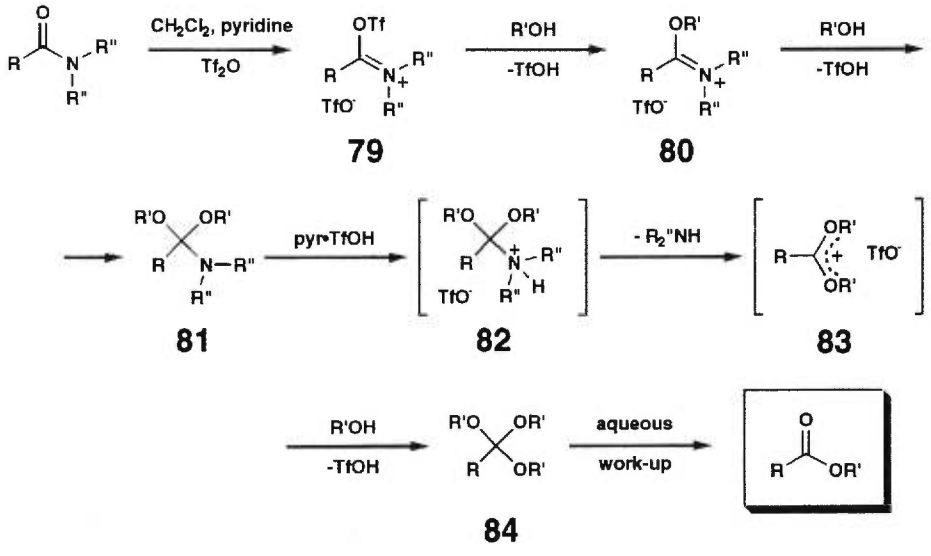
Scheme 31. Mechanism for the conversion of secondary amides to esters



The mechanism is a composite of the formation of imidoyl triflates and the conversion of imidates to ortho esters. The novel components are the conversion of imidoyl triflates to imidates and the use of pyridinium hydrotriflate as an efficient acid catalyst for this process at temperatures between 0°C and room temperature.

A similar mechanism can be invoked for tertiary amides (Scheme 32). The reaction begins with the conversion of tertiary amides to the iminium triflate **79** which generally occurs over 6 hours at 0°C. Like imidoyl triflates, the triflate intermediate is highly electrophilic and the triflate is substituted readily to give rise to the alkyl iminium ester **80**. One major difference between this mechanism and the one invoked for secondary amides is that the alkyl iminium ester is a positively charged species and nucleophiles such as alcohols should add to them without catalysis by pyridinium hydrotriflate. For secondary amides, catalysis from pyridinium hydrotriflate is required for the addition of an alcohol to an alkyl imidate.

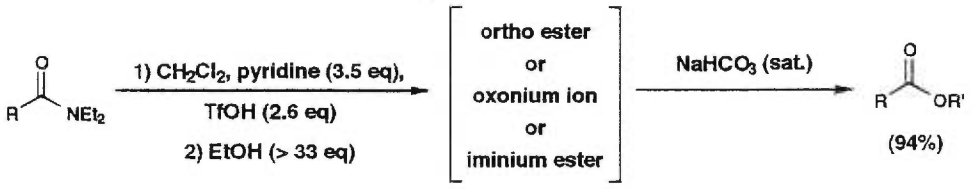
Scheme 32. Mechanism for the conversion of tertiary amides to esters



Once the ortho amide **81** is formed, the mechanisms should be similar. Pyridinium hydrotriflate protonates the amine **82** and catalyzes the formation of the ortho ester **84** via the oxonium ion intermediate **83**. Again, aqueous work-up provides the simple ester.

The formation of the ester from the ortho ester seems to be a very facile step as the normal work-up with 10% HCl readily forms the ester. Keeping the work-up neutral by only washing with saturated $NaHCO_3$ was not effective in preserving the ortho ester functionality (Scheme 33). Pyridinium hydrotriflate appears to be very efficient at hydrolyzing ortho esters and saturated $NaHCO_3$ is not effective enough to quickly neutralize this acid catalyst in a two-phase system. Perhaps prior to extraction, the reaction must be made alkaline in a very careful manner by the addition of triethylamine or saturated NaOH. It is also possible that the acyclic ortho ester is not formed and actually the oxonium ion is the final product formed prior to aqueous work up. Further studies, probably using NMR will be required.

Scheme 33. Attempts to preserve acyclic ortho esters



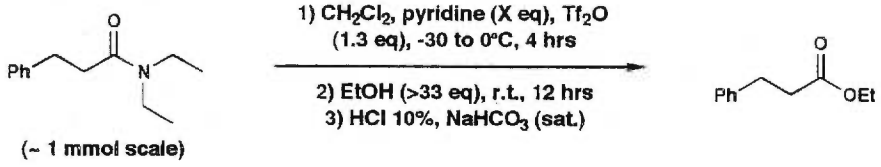
3.22 Number of Equivalents of Base and Triflic Anhydride

Quantitative formation of imidoyl triflates requires a stoichiometric amount of triflic anhydride. Amides are generally very hygroscopic due to their propensity to form hydrogen bonds. Furthermore, and adventitious water in the solvent or pyridine can also hydrolyze triflic anhydride. We found that 1.3 equivalents of triflic anhydride was effective at providing consistent and reproducible conversions of amides to imidoyl or iminium

triflates. Presumably, one equivalent is sufficient, but extreme care would be required to exclude water from the system. Therefore, triflic anhydride must be very pure and the amide, solvent, pyridine and nucleophile must be completely anhydrous or else lower conversions are likely to occur.

The amount of base required for efficient conversion of amides to esters seems to be dependent on the amount of triflic acid present which in turn depends on the amount of triflic anhydride that is used in the reaction (Table 7).

Table 7. Effect of stoichiometry of pyridine



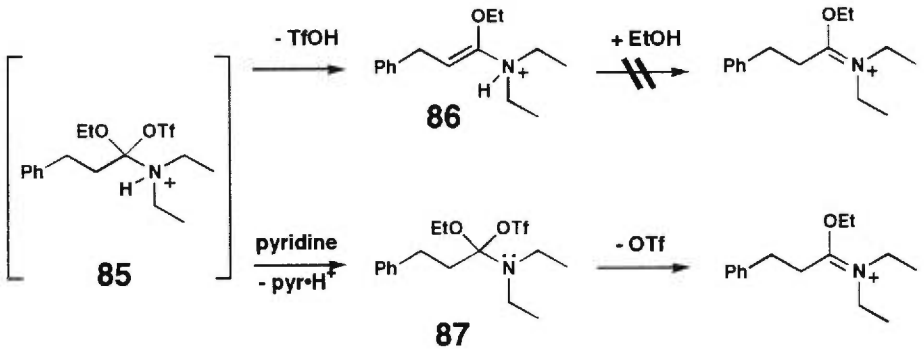
(~ 1 mmol scale)

Entry	X (eq)	Conversion (%)
1	0	2
2	0.5	3
3	1.0	9
4	1.3	10-75
5	2.0	81-96
6	3.5	95

From these results, the ratio of pyridine to triflic anhydride must be greater than 2:1 (hence, ratio of pyridine to triflic acid is greater than 1:1) or else the results are not very reproducible. When the ratio of pyridine to acid is greater than 1:1, there is an excess of weak base and a proper buffer system is created. One possible explanation is that if the system is too acidic due to an excess of triflic acid relative to pyridine, the normal breakdown of the *O*-ethyl-*O*-triflyl ortho amide **85** to alkyl iminium esters **87** may be prevented in favor of the elimination to the ketene aminal **86** (Scheme 34). Therefore, for reproducible results, the amount of base should be 2 times greater than the amount of triflic anhydride to ensure that there is an excess of base relative to triflic acid.

greater than the amount of triflic anhydride to ensure that there is an excess of base relative to triflic acid.

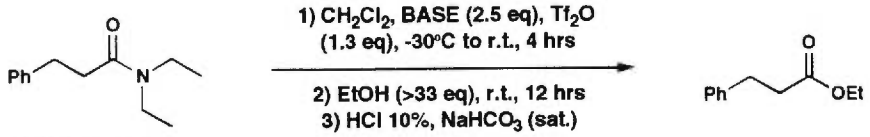
Scheme 34. Need for pyridine in triflate substitution



3.23 Nature of Base

In the previous section, it was demonstrated that enough base was needed to prevent the reaction from becoming strongly acidic. A brief survey of different types of bases showed that non-nucleophilic weak bases were required for this reaction (Table 8).[146]

Table 8. Various bases in the conversion of esters to amides

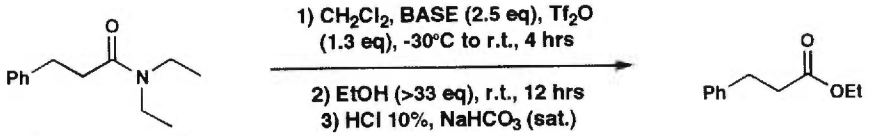


Entry	Base	Conversion (%)
1	pyridine	96
2	pyridine + 0.1 eq DMAP	85
3	DMAP	11
4	Triethylamine	4
5	2,6-lutidine	2
6	EtONa	11

One possible explanation for this is that the stronger bases such as triethylamine (Entry 3) and DMAP (Entry 4) are probably too strong and create a buffer which is too weak to protonate the alkyl amine residue of the ortho amide. Weaker bases such as pyridine form buffers that contain conjugate acids, which are strong enough as general acid catalysts to catalyze the conversion of various intermediates to the ortho ester product. Presumably, bases even weaker than pyridine, such as carboxylates or phosphines could be used when a stronger acid catalyst may be needed.

It is also possible that strongly nucleophilic bases react more readily with triflic anhydride to form products such as triflyl pyridinium triflate which deactivate the suphonylating reagent. To investigate this, the same survey of bases was carried out, but with an inverse addition of the base (Table 9). Hence, the base was added after the formation of the iminium triflate to allow ample time for triflic anhydride to react with the amide without competitive reactions from bases.

Table 9. Affect of base when added after iminium triflate formation



(~ 1 mmol scale)

Entry	Base	Conversion (%)
1	pyridine	93
2	pyridine + 0.1 eq DMAP	96
3	DMAP	20
4	Triethylamine	~0
5	2,6-lutidine	94

Inverse addition of base resulted in slight increases in conversion for the reactions which used DMAP as a base. A dramatic effect was observed for 2,6-lutidine (Table 8, Entry 5) which gave 2% conversion, but 94% conversion (Table 9, Entry 5) when it was added after the formation of the

that this aromatic heterocycle could undergo an electrophilic aromatic substitution with triflic anhydride.

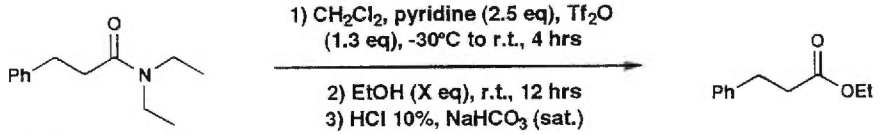
3.24 Effect of Solvent

As previously mentioned in section 2.4, the reaction was found to proceed fastest in dichloromethane. This observation is consistent with those of Ghosez, Thomas, Fowler & Grierson.[147]

3.25 Equivalents of Primary Alcohol

With ethanol and methanol, one can easily use 33 equivalents, but sometimes a large excess of alcohol is no feasible. If only 1 equivalent of alcohol was used, presumably one would obtain only the imidate in the case of secondary amides. Stoichiometry dictates that 3 equivalents are required for complete conversion of the amides to the ortho esters. Experimentally, we found that > 10 equivalents are required for reproducible and optimal yields of the esters (Table 10).

Table 10. Effect of quantity of ethanol on the conversion to ortho ester



(~ 1 mmol scale)

Entry	X (eq EtOH)	Conversion (%)
1	> 33	96
2	10	95
3	5	84
4	1.3	42
5	1.3[a]	3

[a] Basic work-up only.

This indicates that an entropic barrier must be overcome in order to form the ortho ester or that the additional alcohol serves to increase the polarity

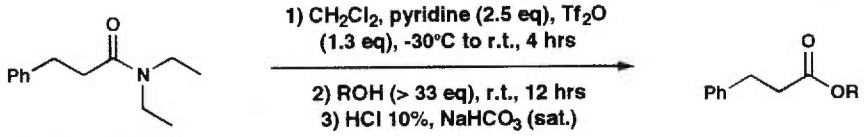
This indicates that an entropic barrier must be overcome in order to form the ortho ester or that the additional alcohol serves to increase the polarity of the solvent to make the formation of various charged intermediates more favorable.

In the case where 1.3 equivalents of ethanol were used, a conversion of 42% was achieved. This would indicate that the reaction of ethanol with the triflate is faster than with subsequent intermediates as would be expected. In this example, conversion to the ester occurred via hydrolysis of the ethyl iminium ester under acidic conditions. When using a basic work-up, only a 3% conversion to the ester was found.

3.26 Nature of Alcohol

There is a large entropic cost in forming a quaternary substituted carbon center, especially in an acyclic ortho ester. This aspect is evident in the investigation of the effect of different alcohols (Table 11). Primary alcohols such as methanol and ethanol were effective at transforming the triflate to the ester. Secondary alcohols such as iso-propanol (Table 11, Entry 3) were not effective. Presumably, secondary alcohols cannot form ortho esters due to the steric bulk of the isopropyl groups.

Table 11. Effect of the nature of the alcohol



(~ 1 mmol scale)

Entry	ROH	Conversion (%)
1	R = Me	85
2	R = Et	96
3	R = *i*-Pr	12

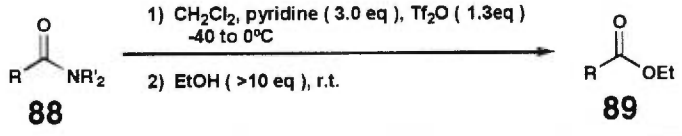
3.3 Conversion of Amides to Esters

For the remainder of this chapter, the general conditions consist of the slow careful addition of 1.3 equivalents of triflic anhydride to the secondary or tertiary amide in dichloromethane containing 3 equivalents of pyridine at temperatures at or below -40°C. The reaction was allowed to warm up slowly to 0°C where it is stirred for 10 hours, but shorter times are enough for certain substrates. Then, 33 equivalents of ethanol or methanol are added and the reaction is allowed to warm up to room temperature and stirred for another 12 hours. The reaction is then diluted with diethyl ether and washed twice with 10% HCl and once with saturated aqueous sodium bicarbonate. For almost all of the examples shown in the following sections, the conversion is nearly identical to the yield, such that any deficit in yield can be accounted for by recovered starting material.

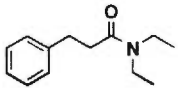
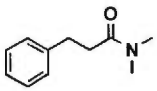
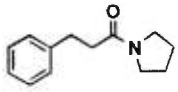
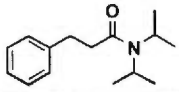
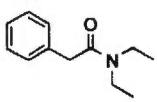
3.31 Conversion of Tertiary Amides to Esters

The results of this methodology with various α-unsubstituted tertiary amides are shown in Table 12.

Table 12. Conversion of tertiary amides to esters



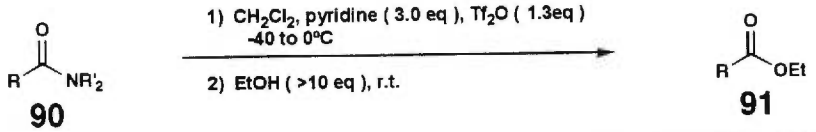
88 89

Entry	Amide	Yield of ESTER	Entry	Amide	Yield of ESTER
a		94%	d		90%
b		85%			
c		84%	e		88%

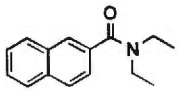
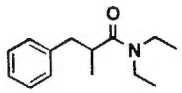
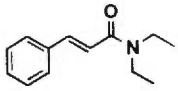
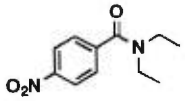
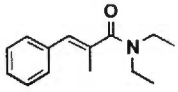
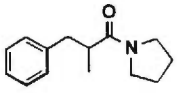
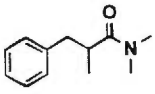
In general tertiary amides were converted to esters in good to excellent yields. *N,N*-diethyl hydrocinnamide (Entry a) and pyrolidinyl hydrocinnamide (Entry b) were converted to the ester in 94% and 85%, respectively. *N,N*-diisopropyl hydrocinnamide (Entry c) with its large isopropyl groups is quite sterically hindered about the acid carbon, but gratifyingly, it too is converted to the ester in high yield. More readily enolizable substrates such as *N,N*-diethyl phenylacetamide (Entry e) was also converted to the ester in high yield.

Table 13 shows the results with amides bearing substitution at the α-carbon. For the aromatic amide, *N,N*-diethyl-2-naphthamide (Entry a), the lower yield reflects possible steric hindrance which impedes substitution at the acid carbon or aromatic conjugation of the acid which makes intermediates less susceptible towards nucleophilic attack.

Table 13. Conversion of α-substituted, aromatic and conjugated tertiary amides to esters



90 **91**

Entry	Amide	Yield of ESTER	Entry	Amide	Yield of ESTER
a		56%	d		25%
b		68%	e		10%
c		35%	f		49%
			g		69%

N,N-diethyl cinnamide (Entry b) was also converted to the ester in slightly lower yield. Once again, this may be due to conjugation of the acid which deactivates it towards substitution. Increased steric bulk near the acid carbon in *N,N*-diethyl-α-methyl cinnamide (Entry c) and *N,N*-diethyl-α-methyl hydrocinnamide (Entry d) seems to have a large negative impact on the yield. The worse case observed is for the conversion of *N,N*-diethyl-*p*-nitrobenzamide (Entry e). In this case, the low yield may be attributed to the substituted nature of the amide, but more prominent would be the electron-poor nature of this aromatic amide which is unfavorable for the formation of positively charged intermediates such as oxonium ions.

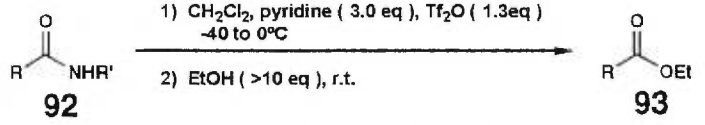
For the conversion of tertiary amides to esters, the yield is affected by substitution in the α-position, aromaticity, conjugation and electronic properties of the amide. One solution for the steric problem is to lower the steric bulk around the acid carbon by reducing the size of the substituents on the nitrogen. Thus, in going from *N,N*-diethyl-α-methyl hydrocinnamide (Entry d) to the pyrollidinyl amide (Entry f) or even smaller *N,N*-dimethyl-α-hydrocinnamide (Entry g), the yield is increased from 25% to 69%.

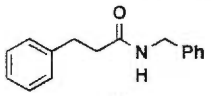
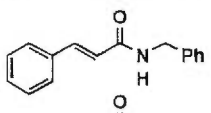
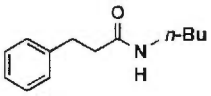
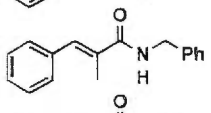
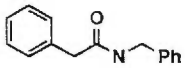
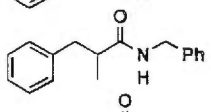
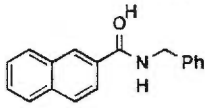
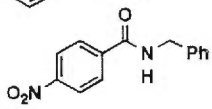
3.32 Conversion of Secondary Amides to Esters

Various secondary amides are converted to esters in Table 14. From these results, one can make the generalization that secondary amides are more readily converted to ortho esters than their tertiary counterparts. This may be primarily attributed to the fact that secondary amides are less sterically hindered around the acid carbon as the amine residue has a proton in place of a carbon substituent. This reduced steric hindrance allows nucleophilic attack at the acid carbon to occur more readily, hence, the conversion of these amides to the corresponding esters is more facile. This is quite evident when comparing **90c** or **90d** with **92f** and **92g**. The

yields have increased from 35% and 25% to 85% and 94%. The electron poor aromatic *N*-benzyl-*p*-nitrobenzamide **92g** is still converted to the ester in a low yield of 28%. This is an indication that the oxonium intermediate may be involved in these mechanisms.

Table 14. Conversion of secondary amides to esters



Entry	Amide	Yield of ESTER	Entry	Amide	Yield of ESTER
a		90%	e		94%
b		80%	f		94%
c		95%	g		89%
d		85%	h		28%

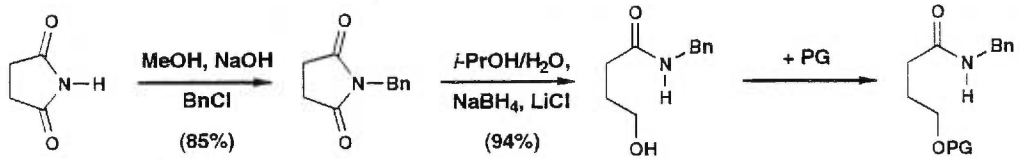
3.4 Scope and Limitations

This method can cleave amide bonds at low temperature in a near neutral media. However, it is possible that in the presence of pyridine at low temperature, the conversion of amides to triflates is a harsh enough process that more functionalized molecules would not resist to these conditions. Another longstanding problem associated with cleavage of the amide bond is racemization. The "retro-Ritter" reaction discussed in section 2.5 also prevents the methodology from cleaving secondary amides when there is a substituent on the nitrogen which can readily support a positive charge. These questions and problems will be addressed in the following sections.

3.41 Amide Cleavage in Presence of Functional Groups

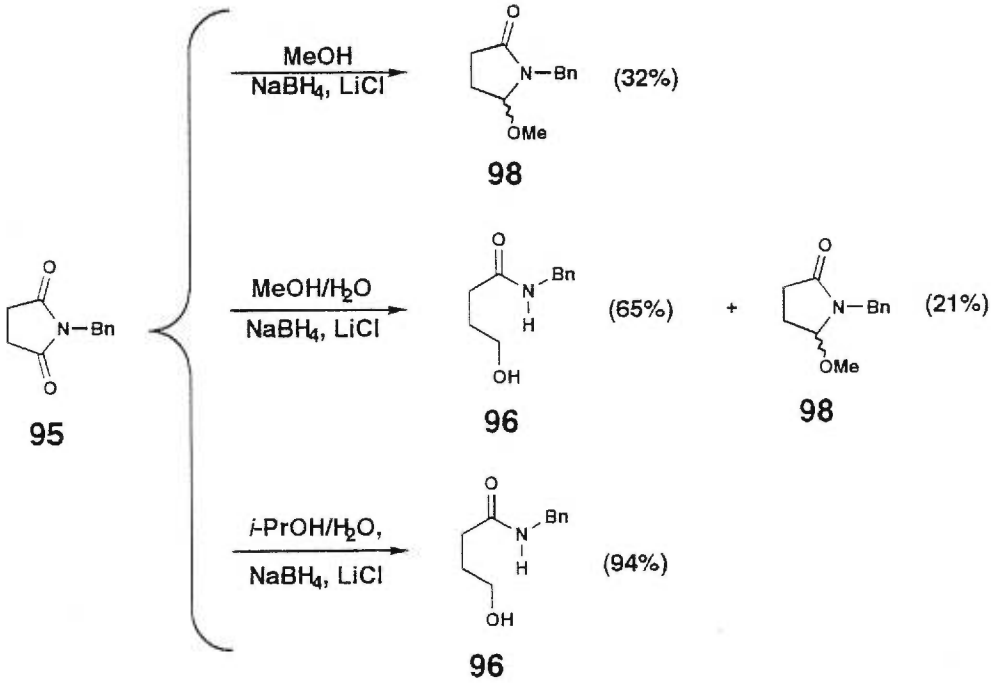
N-benzyl-4-hydroxy butanamide was synthesized from succinimide and protected with various protecting groups to generate the bi-functional compounds containing an amide (Scheme 35).

Scheme 35. Synthesis of protected *N*-benzyl-4-hydroxy butanamide **97** from succinimide



The reduction of succinimide **95** to hydroxy amide **96** required a fair amount of optimization (Scheme 36).

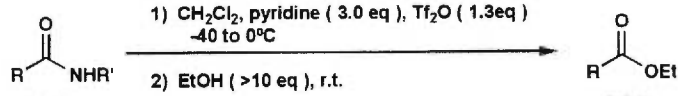
Scheme 36. *N*-acyl hemi-acetal formation in the presence of methanol



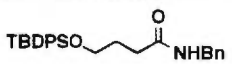
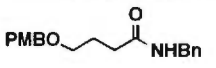
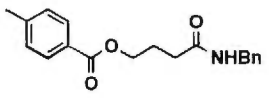
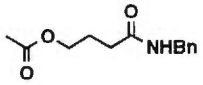
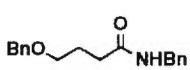
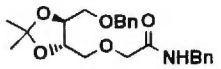
It was found that water and *iso*-propanol were required for efficient reduction of imide (**95**). The use of water as a co-solvent led to increased yields probably by increasing the solubility of LiCl and $NaBH_4$ ($LiBH_4$) in the composite solvent. Although methanol was initially used as a co-solvent to help dissolve the substrate, *O*-methyl aminal **98** was found whenever methanol was used. Replacing methanol with iso-propanol resulted in improved yields presumably by impeding the formation of the *O*-alkyl aminal through the use of a solvent which was a poor nucleophile.

These substrates were designed such that the amides were positioned nearby the protected primary hydroxyl group. This would allow the imidoyl triflate to interact with the functional group in an intramolecular fashion if the triflic anhydride did not react with the protected hydroxyl group first. These amides were then converted to the esters with the standard conditions to demonstrate the tolerability of various functional groups towards the conditions of triflate generation and subsequent alcoholysis. The results are summarized in Table 15.

Table 15. Conversion of amides to esters in presence of other functional groups



101 **102**

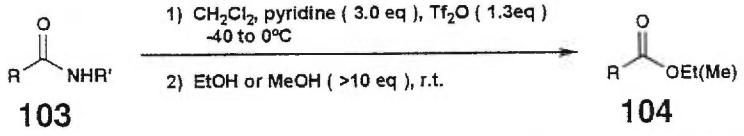
Entry	Amide	Yield of 102	Entry	Amide	Yield of 102
a		93%	d		81%
b		88%	e		77%
c		85%	f		66%

As can be seen from Table 15, various primary hydroxy-protecting groups such as silyl ethers, benzoates, benzyl ethers, electron rich benzyl ethers and primary acetates are inert under the reaction conditions. Carbonyl protecting groups such as the acetonide in **101f** are also stable towards these conditions. Having shown that various functional groups can be present in the molecule, this method should prove itself useful in latter stages of a synthesis when molecules are often highly functionalized. Being able to readily cleave an amide bond at such a point in a synthesis should allow new strategies and approaches to emerge where presently, the use of amides is often avoided.

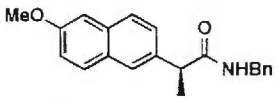
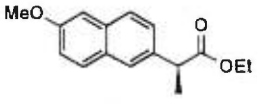
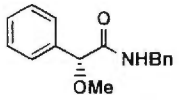
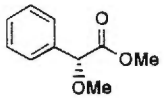
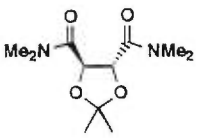
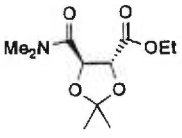
3.42 Extent of Racemization

Racemization is a problem often associated with amide cleavage due to the somewhat rigorous conditions often used to effect this transformation. To evaluate the extent of racemization in this present methodology, amides bearing chiral centres on the α-carbon were converted to the corresponding esters (Table 16).

Table 16. Extent of racemization in chiral amides



103 **104**

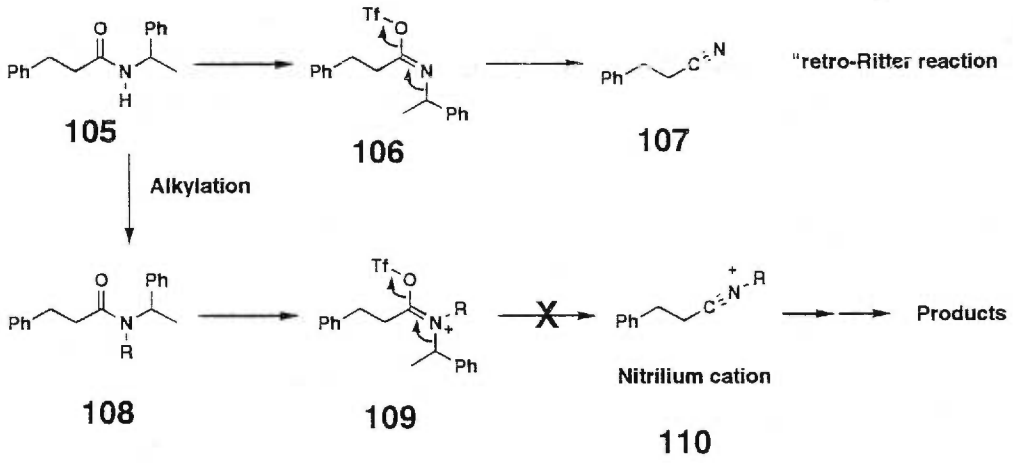
Entry	Amide	Ester	Yield	Optical Purity
a			82 % yield	92 %ee
b			28 % yield	99 %ee
c			31 % yield	99 %ee

Naproxen® ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid) is notorious for racemization.[148] Its *N*-benzyl amide **103a** was converted to the ethyl ester in 82% yield along with a small amount of racemization. *N*-benzyl *O*-methoxy phenylacetamide **103b** was converted to the ester with essentially no racemization, however the yield in this case was much lower. For *N,N,N′,N′*-tetramethyl tartaramide **103c**, this tertiary amide was converted to the corresponding mono-ethyl ester with essentially no racemization, but again in low yield. The lower yields in these two examples may be attributed to the electron withdrawing inductive effects of the alkoxyl groups in the α-position. Their presence may make the formation of the oxonium ion more difficult to achieve under these mild conditions. Stronger acid or slightly higher temperatures may be required in order to obtain greater yields with these types of substrates.

3.43 Solution to the Retro-Ritter Reaction

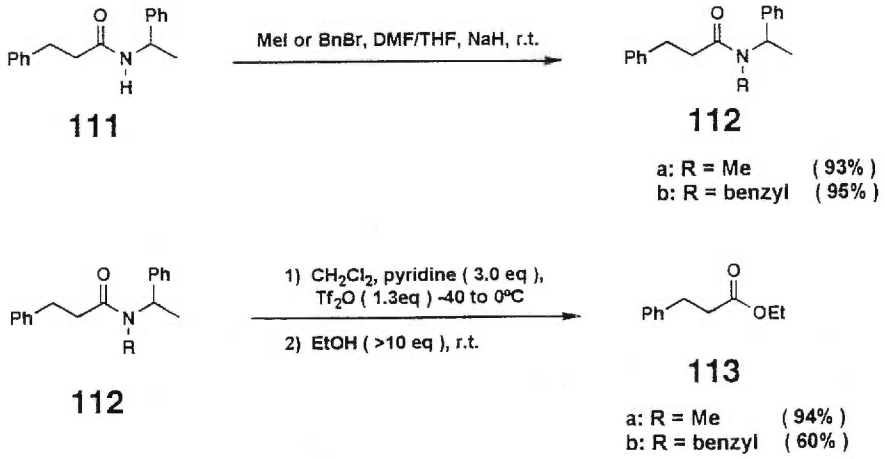
As mentioned in section 2.5, α-methyl benzyl amides undergo a "retro-Ritter" or an S_N1-like von Braun reaction. Because α-methyl benzyl amides are often used as diastereomeric derivatives for resolutions of chiral compounds, it was desirable to be able to cleave the amide bond in these types of compounds. As previously mentioned, the fragmentation of α-methyl benzamides was believed to be SN_1 in nature since the α-benzyl amides underwent this fragmentation reaction, but a normal benzyl amide did not. It was believed that the stability of the secondary benzylic carbocation was responsible for allowing this process to occur. By introducing a very high-energy step into the reaction pathway prior to the fragmentation step, it would be possible to circumvent this problem. An approach towards solving this problem is outlined in Scheme 37.

Scheme 37. An approach towards preventing the retro-Ritter reaction in α-benzyl amides



Our solution to the retro-Ritter reaction was to convert the α-methyl benzamide **105** to a tertiary amide **108** via alkylation. The tertiary amide would form a very unstable nitrilium cation **110** if the "retro-Ritter" reaction were to proceed. However, the formation of the nitrilium cation at room temperature in these near neutral reaction conditions is unlikely. The results of this approach are shown in Scheme 38.

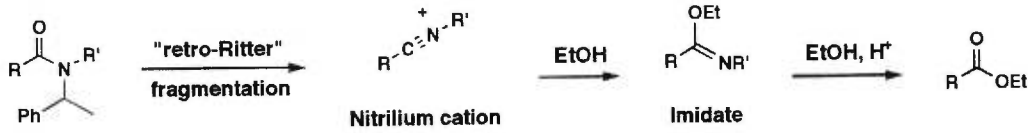
Scheme 38. Prevention of the "retro-Ritter" reaction via conversion to tertiary amides



α-Methyl benzyl hydrocinnamide **111** was alkylated with methyl iodide or benzyl bromide to give the corresponding tertiary amides **112a** and **112b** in 93% and 95%, respectively. These methylated and benzylated amides were then subjected to the amide cleavage conditions and much to our satisfaction, the substrates were converted to the esters in 94% and 60% yields, respectively. The lower yield associated with the benzyl compound maybe associated to the greater steric hindrance around the carbonyl carbon caused by the benzyl substituent.

Although we achieved our goal of cleaving this class of amides, certain mechanistic details were still unclear. It could be possible that the cleavage of amide **114** could occur via the nitrilium cation. Conversion of the amide to the nitrilium cation **115** would be followed by nucleophilic attack of ethanol to form the imidate **116**. This would then be converted to the ester **117** in the usual manner (Scheme 39).

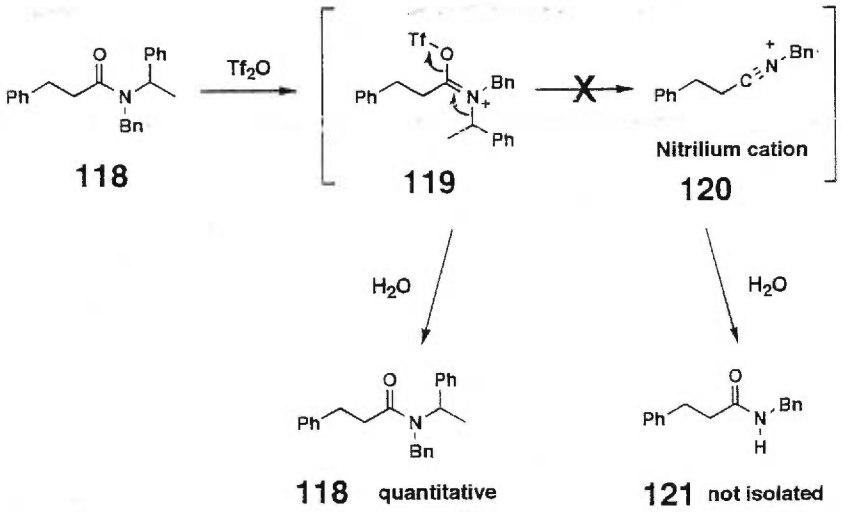
Scheme 39. Cleavage of α-methyl benzamides via nitrilium cations



114 **115** **116** **117**

However, experimental evidence indicates that at the nitrilium cation was never formed. Isolation of alkylated α-methyl benzyl amine from the acidic aqueous extractions demonstrated that the triflate had not fragmented to the nitrilium cation. Furthermore, quenching the reaction with water instead of ethanol resulted in the recovery of the starting amide **118**; not the dealkylated amide **121** which indicated that fragmentation of triflate **109** had not occurred (Scheme 40).

Scheme 40. Evidence that the nitrilium cation was not formed



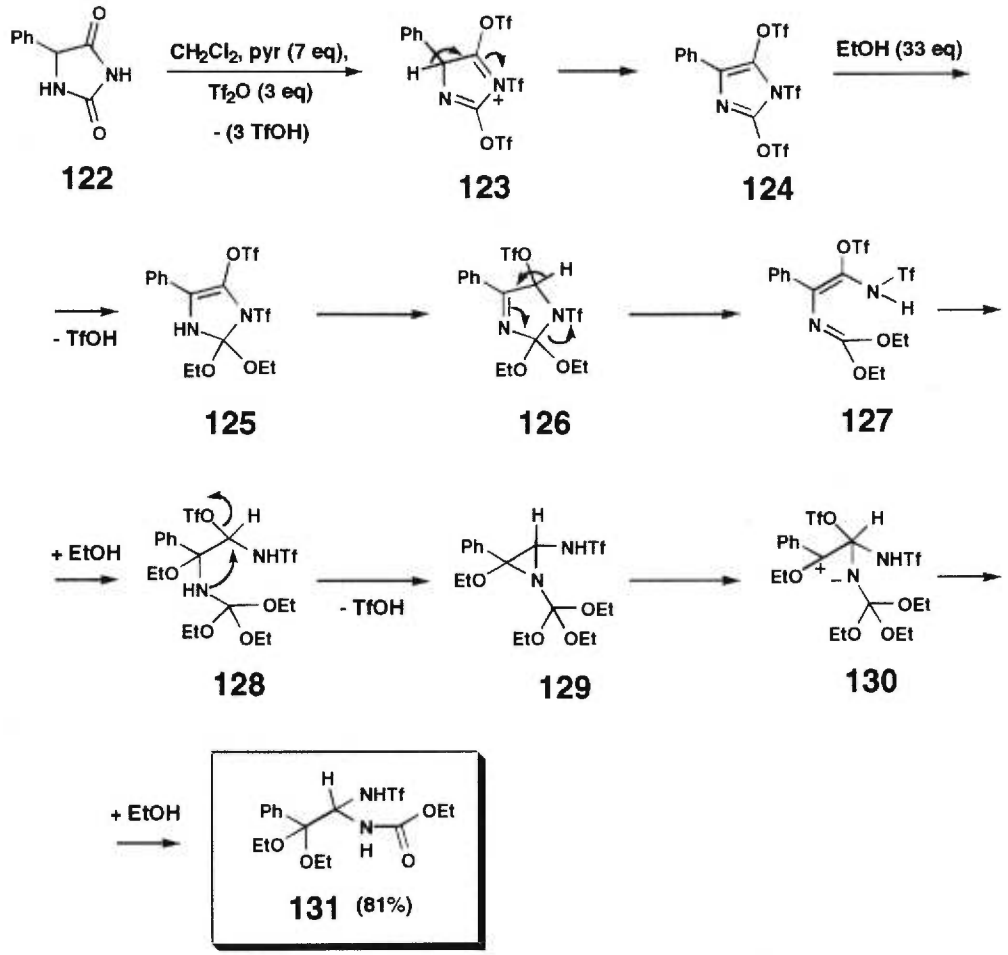
3.44 Cleavage of Amide Bonds in Hydantoins and Carbamates

Hydantoins are very useful heterocyclic compounds.[149] They are a very convenient approach to the synthesis of amino acids since the formation of natural and quaternary amino acids can be readily achieved via hydantoins. The analogous approach via the Strecker reaction is not as reliable as often carbonyl compounds may react sluggishly under these conditions.[150] The difference in these two avenues is that the hydantoin synthesizes the amino acid in a very stable 5-membered heterocyclic ring whereas the Strecker operates via an unstable cyanohydrin or α-amino nitrile. However, the drawback to the hydantoin approach comes when one must open up the 5-membered ring to liberate the amino acid.

The application of the present methodology to hydantoins would be interesting since existing methods for hydantoin hydrolysis are very harsh.[151] Unfortunately, preliminary studies indicate that this methodology is not effective at cleaving the amide bonds in 5-phenyl hydantoins to yield amino acid derivatives. However, an interesting

rearrangement took place to give rise to compounds whose structure has not been previously characterized by x-ray crystallography (Scheme 41).[152]

Scheme 41. Synthesis of **131** from 5-phenylhydantoin



In this reaction, 5-phenylhydantoin **122** reacts with 3 equivalents of triflic anhydride to give the *tris*-triflate **123**. Migration of the benzylic proton gives neutral compound **124**. Addition of an excess of ethanol results in the substitution of the most labile triflate (imidoyl triflate versus enol triflate versus triflamide) to give the ortho carbamate **125**. Ring opening of **125** between the triflamide and the ortho carbamate can now occur. Under mild acid catalysis, addition of ethanol to intermediate **127** gives triflate **128** which can undergo 3-exo-tet cyclization to form the aziridine **129**.

Under mild acid catalysis, the aziridine would open up to give the benzylic oxonium ion **130**, which is trapped again by ethanol to give the final product **131**. The x-ray crystal structure of **131** is given in Figure 5.

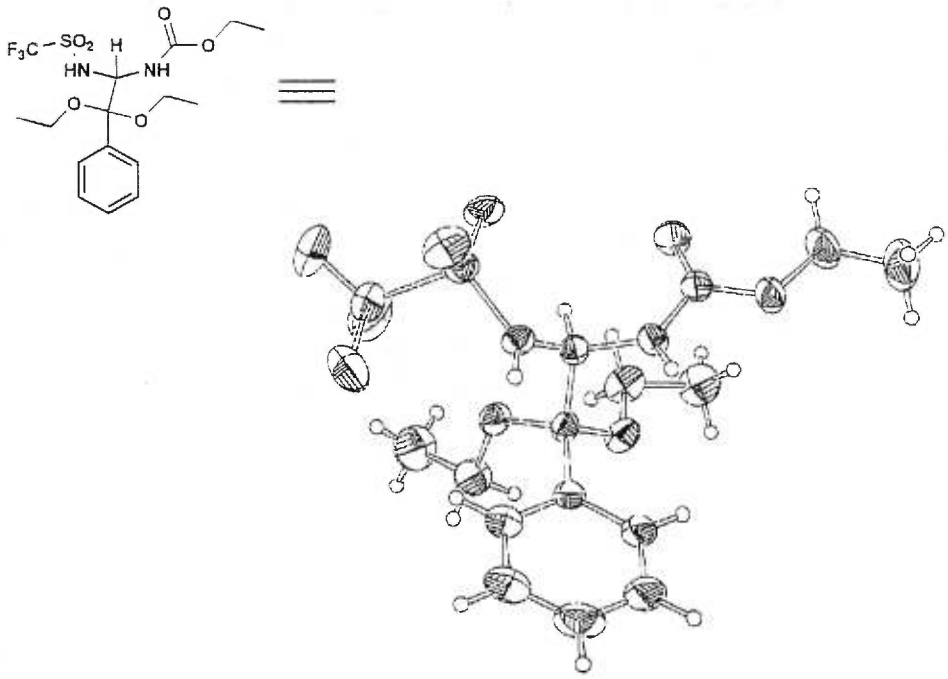


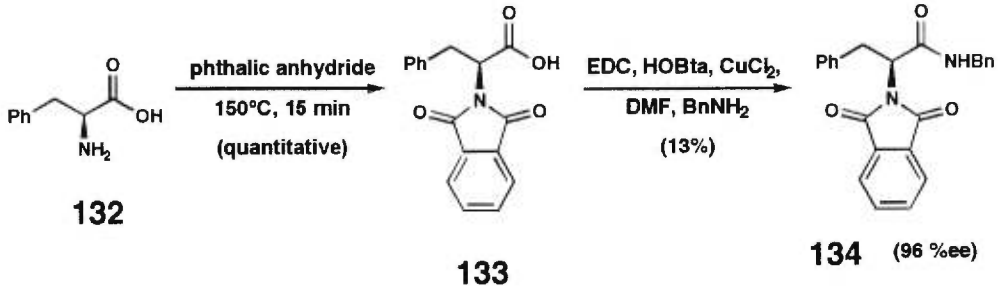
Figure 5. ORTEP representation of compound **131**

This methodology may have also proved useful for cleaving amide bonds in carbamates. However, initial attempts to cleave amide bonds in simple alkyl carbamates such as the ethoxycarbonyl group were unsuccessful.

3.45 Amine Protecting Groups

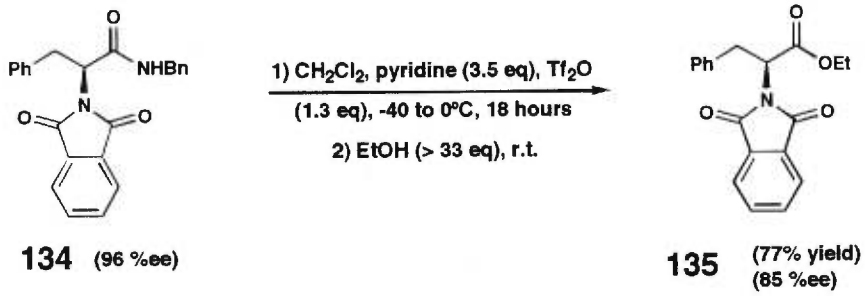
In this last section dealing with the conversion of amides to esters, we have a cursory inspection of nitrogen protecting groups which can be suitable for use in these reaction conditions. Our initial studies focussed on the possibility of using phthalimides as protecting groups for amines (Scheme 42).

Scheme 42. Synthesis of *N*-phthalimido phenylalanine



Phenylalanine **132** was heated with phthalic anhydride at 150°C for 15 minutes resulting in quantitative conversion to the phthalimide protected amino acid **133.**[153] Coupling of the acid using DCC failed to provide any of the desired *N*-benzyl amide. Using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) gave only a 13% yield of the desired amide **134**, but it was sufficient for our purposes.[154] The amino acid derivative **134** was found to be only 96% ee. This racemization can be attributed to the use of N-carboxyl protecting groups.[155] The benzamide was then converted to the ethyl ester **135** in 77 % yield using the standard conditions. Ester **135** was found to have an enantiomeric excess of 85% indicating that some racemization had occurred (Scheme 43).

Scheme 43. Amide to ester conversion in presence of a phthalimide



Racemization may be a limitation of phthalimides when applied to α-amino acids, but for non-racemizable amines, they should prove

themselves quite useful. Other potential protecting groups may be the 9-phenylfluorenyl protecting group which is known to be so large that it significantly reduces the nucleophilicity of the nitrogen.[156]

3.5 Conclusion

Secondary and tertiary amides can be readily converted to imidoyl and iminium triflates. These species can be converted to alkyl imidates and iminium esters upon treatment with alcohols. Pyridinium hydrotriflate is an efficient mild acid catalyst which can promote the conversion of alkyl imidates and iminium esters to ortho-esters which yield simple esters upon aqueous work-up. This method has proven itself mild for converting secondary and tertiary amides to esters as various functional groups can be present and racemization is minimal. Functional groups such as *tert*-butyldiphenylsilyloxy, benzoate, benzyloxy, *p*-methoxybenzyl, acetoxy, acetonide, methoxy and phthalimide groups are tolerated under these conditions. Initial attempts to cleave amide bonds in hydantoins and carbamates have been unsuccessful, but further work in this area may prove otherwise.

Chapter 4: Conversion of Secondary and Tertiary Amides to Ortho Esters

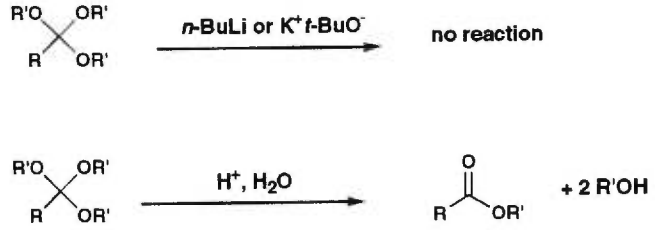
CHAPTER 4

Conversion of Secondary and Tertiary Amides to Ortho Esters.[157]

4.1 Introduction

Ortho esters are a very useful carboxylic acid derivative because they are very resistant towards strong bases and nucleophiles while they can be readily converted to an ester using very mild aqueous acid (Scheme 44).[158,159]

Scheme 44. Ortho esters as protecting groups



Acyclic ortho esters are common for smaller acids, but cyclic versions are used more often with larger molecules as they are easier to form and are more robust. The relative stabilities of representative ortho esters in acid are shown in Figure 6.[160]

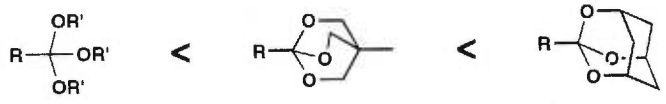
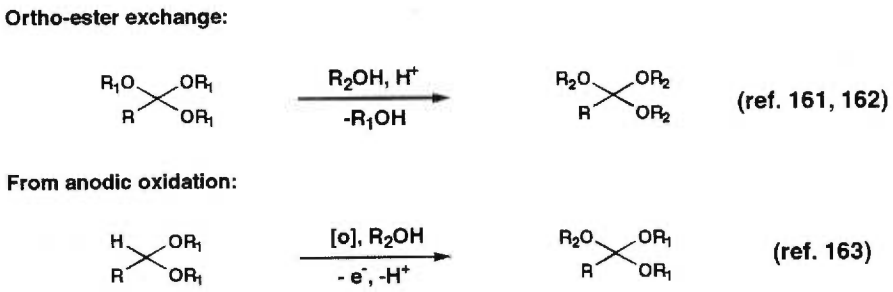


Figure 6. Relative stabilities of ortho esters

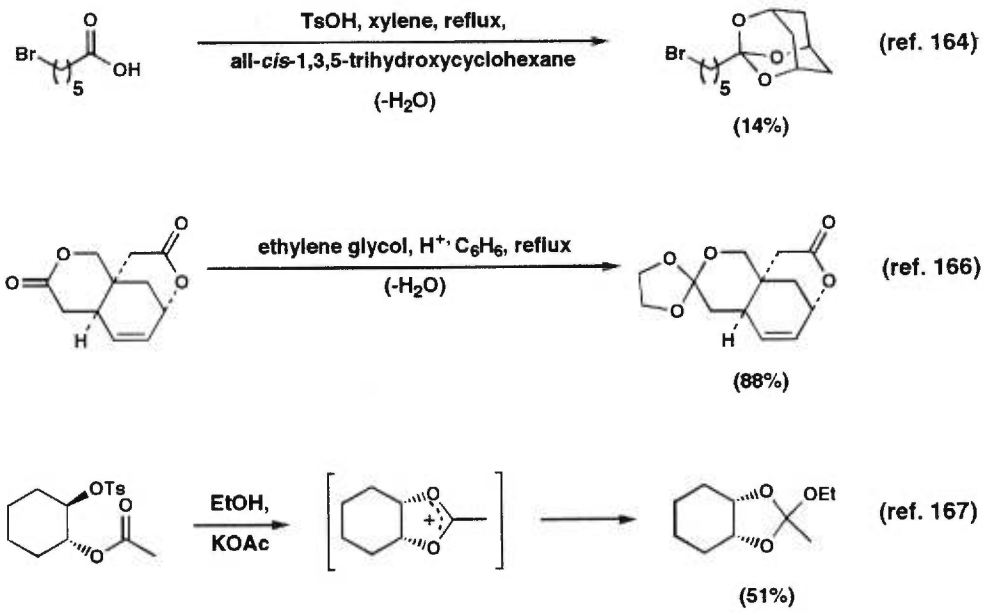
Ortho esters can be made through ortho ester exchange (i.e. alcoholysis of ortho esters), but this is an interconversion from one ortho ester to another, hence, it requires that the ortho ester is already available (Scheme 45).[161] In this exchange reaction, there is an equilibrium between alcohols in this reaction so to drive the reaction to the completion, a less volatile alcohol or a poly-hydroxy compound must be used. This allows one to favor the product side of the equilibrium by removal of the more volatile alcohol from the starting ortho ester or formation of a more stable cyclic ortho ester.[162] Another method of synthesizing ortho esters takes advantage of the fact that anodic oxidation occurs readily α to a heteroatom. When done in alcoholic solvents, ortho esters can be produced in moderate yields.[163]

Scheme 45. Synthesis of ortho esters



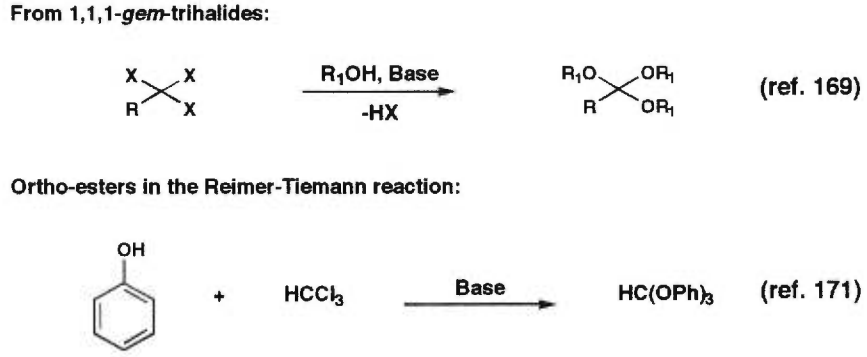
Simple esters and acids are normally not reactive enough to form ortho esters when treated with alcohols (Scheme 46).[164] However, this approach can be used with more reactive esters. There are some examples of ortho ester formed by the addition of alcohols to formates since formates are less hindered and more electrophilic .[165] The addition of diols to lactones can also produce ortho esters.[166] Intramolecular alkylation of esters to form 5 or 6-memebered dioxycarbonium cations followed by subsequent trapping with an alcohol can be an efficient approach to ortho esters.[167] Of course, these dioxycarbonium cations can also be accessed by other methods.[168]

Scheme 46. Ortho esters via the addition of alcohols to esters



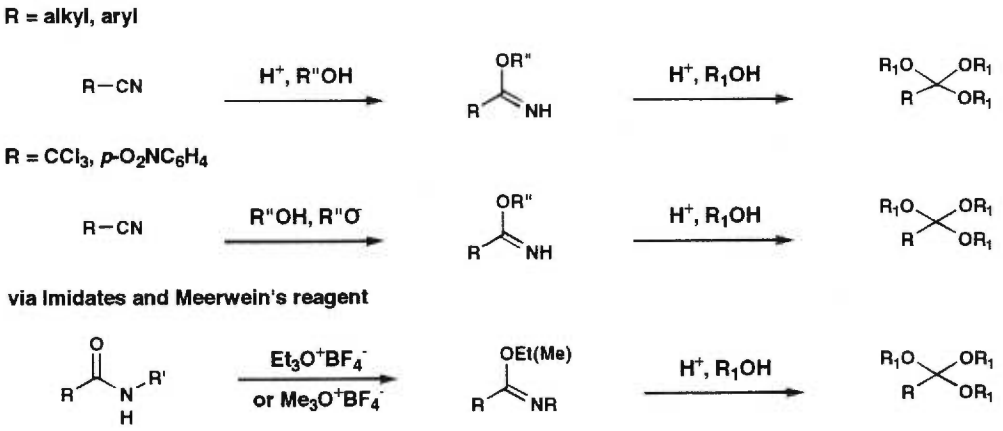
Although not a commonly used method, ortho esters can be produced by treating 1,1,1-*gem*-trihalides with alkoxides (Scheme 47).[169] This method was used to generate the first ortho ester in 1854 when Williamson made triethyl orthoformate by treating chloroform with sodium ethoxide.[170] Presumably, this reaction proceeds via the nucleophilic substitution of all three halides from the substrate by the alkoxides. Yields are generally moderate and 1,1,1- *gem*-trihalides are not widely available except for chloroform and trichloromethylbenzene. A similar situation arises whenever 1,1,1- *gem*-trihalides are used in conjunction with alcohols and a base. The formation of ortho esters can be a competitive side reaction in the Reimer-Tiemann synthesis of phenolic aldehydes.[171] Chloroform is deprotonated with a base to act as the source of carbene in this reaction. However, in cases where the phenol is electron-poor such that the attack of the carbene on the aromatic ring is hindered, attack of the phenoxide on chloroform becomes more prominent resulting in the increased formation of the ortho ester.

Scheme 47. Ortho esters via alcoholysis of 1,1,1-*gem*-trihalides



Traditional methods for making ortho esters such as the Pinner synthesis typically required treating nitriles with strong acids in presence of an alcohol. In cases of electron poor nitriles, strong bases can be used to catalyze the addition of the alkoxide. This approach converts nitriles to ortho esters with imidates being a key intermediate in this transformation (Scheme 48).[172]

Scheme 48. Synthesis of ortho esters via imidates

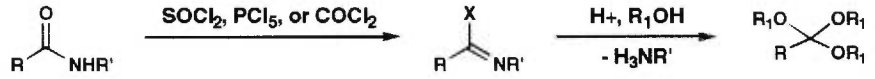


Since imidates are usually isolated and then treated with an alcohol in acidic medium, imidates made by other methods can also be used for the synthesis of ortho esters.[173] Better yields are often obtained when using larger amounts of alcohol or a bi-phasic system of alcohol and hydrocarbon.[174] Several disadvantages of this reaction are that strong

acids are usually required to catalyze the initial addition of an alcohol on a nitrile and that yields are often very sensitive towards steric hindrance.[175] A milder alternative is to make the imidate from a secondary amide using Meerwein's reagent followed by alcoholysis of the imidate.

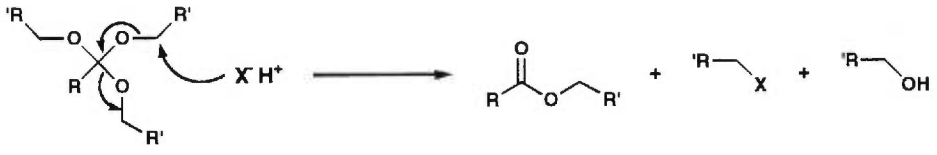
Amides can be converted to ortho esters via imidoyl halides since imidates are formed readily upon treating imidoyl halides with an alcohol (Scheme 49).[176] But as previously discussed for the synthesis of imidoyl halides in section 1.42, this method has its limitations since the formation of imidoyl triflates is often accompanied by harsh conditions and side reactions. Furthermore, an excess of the chlorinating agent is often required which necessitates purification of the imidoyl triflate prior to treatment with the alcohol.

Scheme 49. Ortho esters from imidoyl halides



Water is detrimental to these reactions, but less obvious is the effect of excess halide salts from the acid or electrophilic agents used to generate these more reactive intermediates. Yields are reduced when halide ions attack the ortho ester and cause C-O bond fission to form an ester, alcohol/alkoxide, and an alkyl halide (Scheme 50).[177]

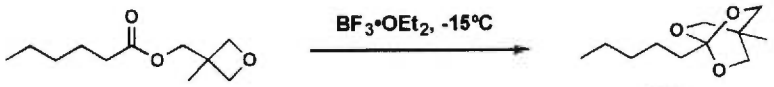
Scheme 50. Nucleophilic attack by halides causing C-O bond fission in ortho esters



More modern methods of forming cyclic ortho esters rely on the release of small ring strain to drive these kinds of reactions. Lewis acids are used to catalyze to opening of epoxides, whose carbocation is

subsequently trapped by an ester.[178] Yields are generally mediocre to moderate. One method, which has proven itself to be quite efficient, is Corey's method of using $BF_3 \bullet OEt_2$ to catalyze the opening of oxetane esters.[179] The cation is trapped in an intramolecular fashion by the ester to generate the oxonium ion. The newly generated alkoxyl group adds to the oxonium ion to complete the formation of the ortho ester (Scheme 51).

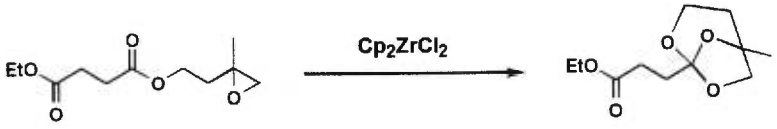
Scheme 51. Corey's rearrangement of oxetane esters



(90%)

Wipf's method is similar in the sense that a Lewis acid catalyzed ring opening is used to drive the reaction forward.[180] The epoxide is opened up with the zirconium reagent to generate the carbocation. Addition to the ester forms the oxonium ion. Attack of the newly created alkoxyl group forms the ortho ester (Scheme 52).

Scheme 52. Wipf's rearrangement of epoxide esters



(96%)

One drawback that these methods share is that the oxetane or epoxide ester is formed from an oxetane or epoxide alcohol. This prerequisite fragment may not be accessible for all kinds of substrates so not all kinds of ortho ester derivatives may be obtained via these methodologies. A more direct and convergent method would use an activated acid portion and combine it with the triol portion. Thus, the triol does not have to be pre-derivatized in the form of an epoxide or oxetane. This is the advantage of using methodologies like imidates and imidoyl

chlorides. However, the initial attack of a triol onto an imidate does not happen very readily unless catalyzed with a strong acid. Triols do react readily with imidoyl halides and subsequent intramolecular additions of alkoxide groups onto the imidate occur readily. However, the formation and purification of imidoyl halides can be problematic due to the harsh reaction conditions and the excess reagents that are often required.

4.2 Ortho Esters from Amides via Imidoyl and Iminium Triflates

The methodology being presented is based on the previously described methodology developed for the conversion of secondary and tertiary amides to esters. In the conversion of amides to esters, the intermediacy of an acyclic ortho ester is proposed. Initial attempts to isolate the acyclic ortho ester were unsuccessful, presumably do to the instability of the compounds. Using a triol in place of ethanol or methanol resulted in the efficient formation of cyclic ortho esters which are much more stable and can be handled much more readily. With some other changes to reaction conditions (*vide infra*), one can use a stoichiometric amount of triflic anhydride to activate secondary and tertiary amides and treat this with a near stoichiometric amount of a *tris*-hydroxymethylene ethane at room temperature to obtain good to excellent yields of cyclic ortho esters.

4.21 Mechanistic Aspects of Converting Secondary Amides to Cyclic Ortho Esters

Our approach to ortho esters ultimately relies on the electrophilic activation of amides via imidoyl or iminium triflates. The reaction is intimately related to the conversion of amides to esters that was presented in the previous sections. The acyclic ortho ester was proposed as an intermediate in this transformation, however, as mentioned in Section 3.21,

attempts to isolate this species were not successful. The intrinsic instability of acyclic ortho esters prompted us to focus our attention towards their more stable cyclic counterparts. We then proceeded to investigate the possibility of using the imidoyl and iminium triflates as highly reactive intermediates in the conversion of secondary and tertiary amides to cyclic carboxylic ortho esters.

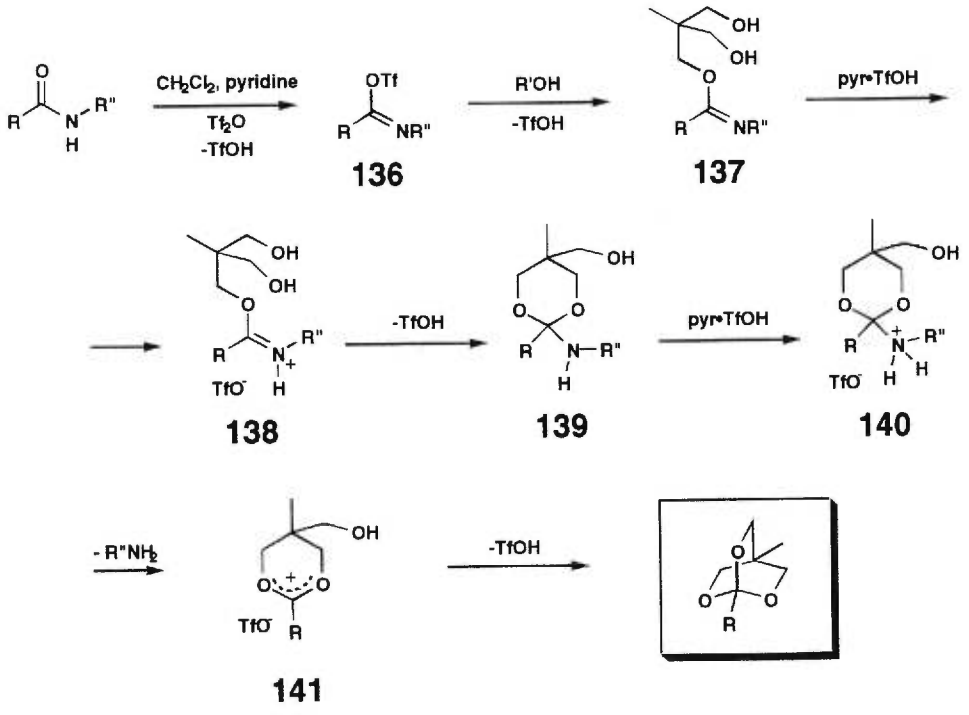
The ability to combine a triol with an amide allows for a very efficient and convergent approach to ortho esters. Furthermore, the advantage of using imidoyl and iminium triflates over other methods such as the addition of alcohols onto esters and imidates is that the initial attack of the poly-hydroxylated compound is very facile. The electrophilic nature of the triflate ensures a readily formed C-O bond which links the acid derivative to the alcohol. With the initial bond formed between the two substrates, the remaining hydroxy groups can add in an intramolecular fashion which helps to make this process much faster and easier to accomplish. With imidates, strong acids and heat are often required to have the initial transetherification of the imidate.

Imidoyl and iminium chlorides react in a similar fashion as the triflates. However, the conditions used for triflate formation are much milder than for chloride formation. Furthermore, the formation of imidoyl chlorides usually requires excess chlorinating reagents which necessitate the purification of the imidoyl chloride before treatment with the alcohol. This should result in a method which tolerates a greater number of functional groups, thus providing better yields in general.

Much like the methodology for esters, the methodology for converting secondary and tertiary amides to ortho esters is a two step-one pot process (Scheme 53). The formation of imidoyl triflates from secondary amides is readily achieved with the method described in Chapter 3. Once the triflate **136** is formed, there is no need to purify this intermediate because only a slight excess of triflic anhydride is used. The

triflate can then be immediately treated with a triol. The initial product resulting from the substitution of the triflate is the imidate **137**. Because a triol is used, the remaining hydroxyl groups are poised for intramolecular attack on the imidate. 1,1,1-*tris*-hydroxymethylene ethane was the triol used in these studies and it was chosen because it is very inexpensive and it is ideally suited for ortho ester formation.[181] The imidate that *tris*-hydroxymethylene ethane forms with an imidoyl triflate has the two remaining hydroxyl groups positioned for relatively fast cyclization to form 6-membered rings.[182] Furthermore, according to Baldwin, the intramolecular addition of the hydroxyl group to the imidate is not disfavored (6-exo-trig), neither is the cyclization of the final hydroxyl group on the oxonium ion (6-endo-trig).[183]

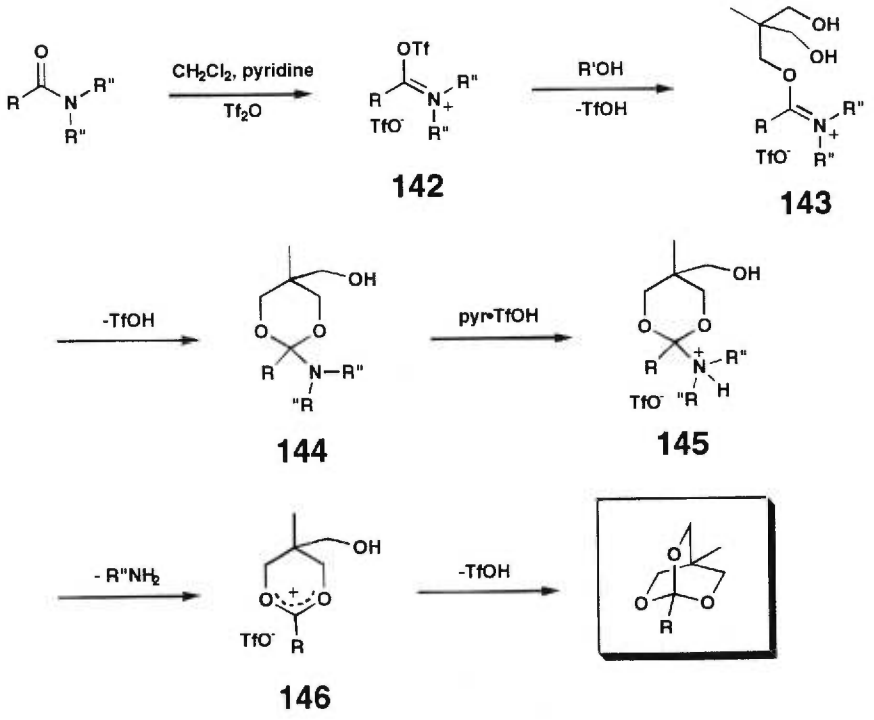
Scheme 53. Mechanism of the conversion of secondary amides to cyclic ortho esters



With this in mind, the cyclization of a hydroxyl group onto the imidate to form the ortho amide **139** occurs very readily, especially in the presence of pyridinium hydrotriflate that acts as a catalyst to protonate the nitrogen and makes the imidate **138** more electrophilic. Pyridinium hydrotriflate is also responsible for protonating the amine of the ortho amide **140** to make it a much better leaving group, thus, facilitating the formation of the oxonium ion **141**. Final ring closure forms the ortho amide.

In the case of tertiary amides, the process begins with the formation of the iminium triflate **142** (Scheme 54).

Scheme 54. Mechanism of the conversion of tertiary amides to cyclic ortho esters



The triflate is then treated with 1,1,1- *tris*-hydroxymethylene ethane in the second step of the process. Iminium triflates are charged so substitution of the triflate by the triol occurs even more readily compared

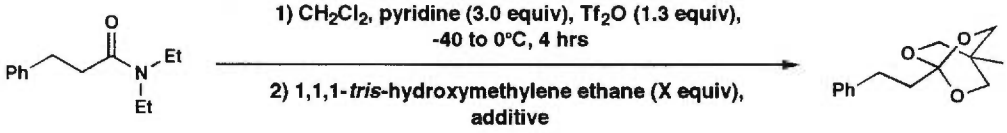
to neutral imidoyl triflates. This forms the alkyl iminium ester **143** which is also a charged species. Cyclization of one of the hydroxy groups onto the alkyl iminium ester should occur very readily due to increased electrophilicity. This results in the formation of an ortho amide **144** which when protonated by pyridinium hydrotriflate, the ammonium residue is now a much better leaving group. The ammonium compound **145** fragments to the oxonium ion **146** which gives rise to the ortho ester upon cyclization of the final hydroxyl group.

4.3 Effect of Stoichiometry and Additives

In the conversion of amides to esters, it was believed that the use of a large excess of a primary alcohol was necessary to overcome the entropic barrier present in forming the supposed acyclic ortho ester. In the case of cyclic ortho esters, the hydroxy groups add in an intramolecular fashion, so a large portion of the entropic cost is eliminated. Thus, a large excess of hydroxyl groups is presumably not required. Experimentally, however, the yield decreased when the amount of 1,1,1-*tris*-hydroxymethylene ethane was reduced to near stoichiometric amounts (Table 17).

When 7 equivalents of the triol (21 hydroxyl group equivalents) was used (Entry 1), the ortho ester was obtained in 86% yield. Using 3.5 equivalents of triol (10.5 hydroxyl group equivalents) resulted in a yield of 83% (Entry 2), which is essentially the same as using 7 equivalents of triol. When only 1.5 equivalents of triol was used (Entry 3), the isolated yield of the ortho ester dropped to 58%. This indicated that the excess 1,1,1-*tris*-hydroxymethylene ethane had an impact on the outcome of the reaction. It was likely that the excess 1,1,1-*tris*-hydroxymethylene ethane was responsible for solvent effects. The excess hydroxylic reagent could have been making the reaction medium more polar or participating in the reaction as a nucleophile.

Table 17. Effect of stoichiometry of 1,1,1-*tris*-hydroxymethylene ethane and additives[184]



Entry	X (equivalents of triol)	Additive	Yield
1	7.0	none	86%
2	3.5	none	83%
3	1.5	none	58%
4	1.5	CH_3CN	85%
5	1.5	Ethanol	88%

We wanted to find a solution which avoided using large amounts of the triol because if large amounts of this hydroxylic substrate are needed, then this methodology would not be useful for making ortho esters of triols which are not readily available. The course of action taken was to find a substitute for the excess triol. We chose to use acetonitrile as a non-nucleophilic solvent which could augment the polarity of the reaction. This approach brought yield back up to 85% (Entry 4). Another approach was to use ethanol which could increase the polarity of the medium as well as participate as a nucleophile in the reaction. When using ethanol as an additive and only 1.5 equivalents of 1,1,1-*tris*-hydroxymethylene ethane, the yield was 88% (Entry 5).

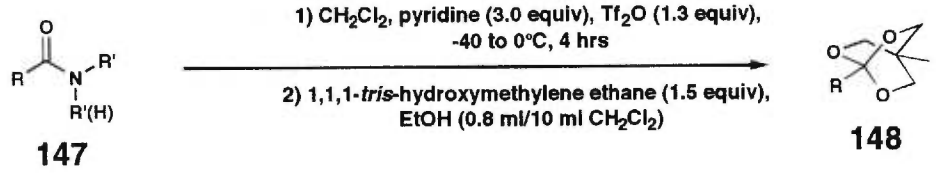
In the case of the added ethanol, more in depth studies would be necessary to sort out which factor is more important: increasing the polarity of reaction media or nucleophilic participation by the added ethanol. One preliminary observation is that reaction rates do not seem to differ much between using 7 equivalents of 1,1,1-*tris*-hydroxymethylene ethane and adding acetonitrile or ethanol. This would indicate that any

potential effect from the participation of ethanol in the mechanism is negligible in terms of overall reaction rates. It is possible that the rate-limiting step is still the formation of the oxonium ion.

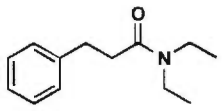
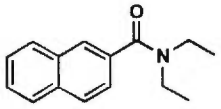
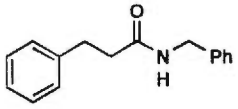
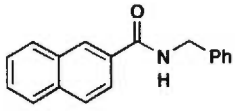
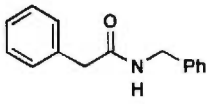
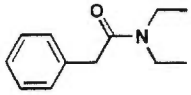
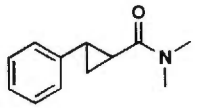
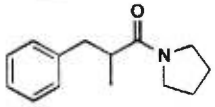
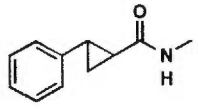
4.4 Conversion of Secondary and Tertiary Amides to Cyclic Ortho Esters

Although cyclic ortho esters are more stable than their acyclic counterparts, handling these carboxylic acid derivatives still requires more care than with other compounds as precautions should be taken to ensure the exclusion of acids and water. The results with converting various secondary and tertiary amides to cyclic ortho esters are summarized in Table 18.

Table 18. Conversion of secondary and tertiary amides to ortho esters



147 **148**

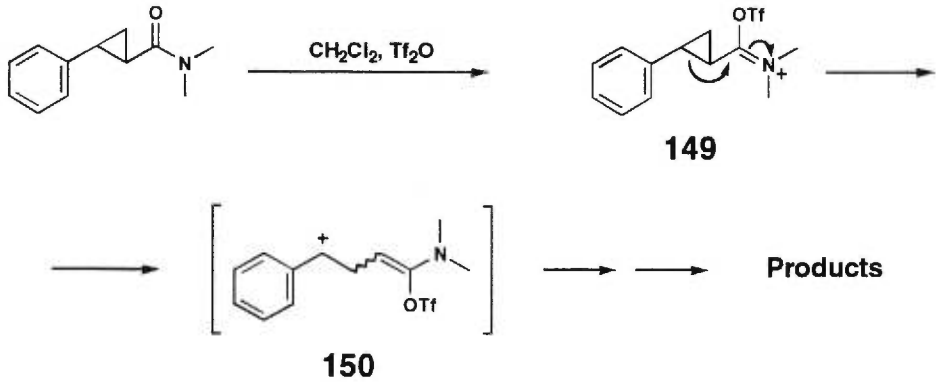
Entry	Amide	Ortho Ester	Entry	Amide	Ortho Ester
a		88%	f		69%
b		76%	g		70%
c		81%			
d		72%	h		<10%
e		59%	i		67%

Secondary and tertiary amides were converted to imidoyl or iminium triflates by slowly adding triflic anhydride to a solution of the amide in dichloromethane containing pyridine at low temperature. The reaction was allowed to warm up to 0°C while stirring and then kept at that temperature for several hours to allow for the complete formation of the triflate. 1,1,1-*tris*-Hydroxymethylene ethane was then added followed by ethanol or acetonitrile. After 6 to 12 hours at room temperature, Et_3N was added to make the solution more basic. The reaction was filtered through silica gel which was neutralized with Et_3N and then concentrated. Most of the ortho esters crystallized readily. If further purification was desired, the ortho ester could be purified by flash chromatography on Et_3N neutralized silica gel with Et_3N in the eluant.

In general, the reaction works well for secondary and tertiary amides (Entries a-d). Tertiary amides which are substituted in the α-position (Entry e) are also converted to the ortho ester quite readily demonstrating that some of the steric hindrance in these tertiary amides can be compensated by the lower entropic requirements of an intramolecular reaction.

An interesting result was found with cyclopropyl amides derived from cinnamic acid. The tertiary amide (Entry h) failed to form the ortho ester, as the product was isolated in very poor yields. Furthermore, there was very little starting material left, unlike other reactions which generally returned the starting material if the product was not formed. With this substrate, there was extensive decomposition even before the addition of 1,1,1-*tris*-hydroxymethylene ethane. One explanation for this is that 3-phenyl cyclopropane can undergo cationic ring opening to generate intermediate **150** which has a stabilized secondary benzylic carbocation. From this intermediate, numerous unidentified products could be produced (Scheme 55).

Scheme 55. Cationic ring opening of phenylcyclopropanes



When the tertiary amide is converted to the iminium triflate **149**, this intermediate is positively charged, therefore, the proposed decomposition can occur. On the other hand, the corresponding secondary amide (Entry i) forms an imidoyl triflate which is not a charged intermediate although there is a possibility of forming cationic species via protonation. Using the typical reaction conditions, the corresponding *N*-methyl amide **147i** was converted to the ortho ester with a yield of 67%.

4.5 Conclusion

Imidoyl and iminium triflates can be used as intermediates in the conversion of secondary and tertiary amides to ortho esters. Generally, most secondary and tertiary amides are converted to the ortho ester in good yields. Substrates which are very sensitive to cationic rearrangements should not be converted to the ortho esters via the tertiary amide, but rather from the secondary amide since the corresponding iminium triflate decomposes readily. The advantages of this method are that the reaction conditions are mild (low temperature and very mild acidity), only stoichiometric amounts of triol are needed, and rapid construction of the ortho ester happens in a one-pot, two step process. The use of co-solvents such as ethanol or acetonitrile were effective at substituting the excess triol required in the reaction for optimal yields. By

using these readily available solvents, the amount of triol could be reduced to a near stoichiometric amount. This should make this method more attractive when the triol is not one which is readily available.

Chapter 5: Conversion of Secondary Amides to N-Substituted Imidates

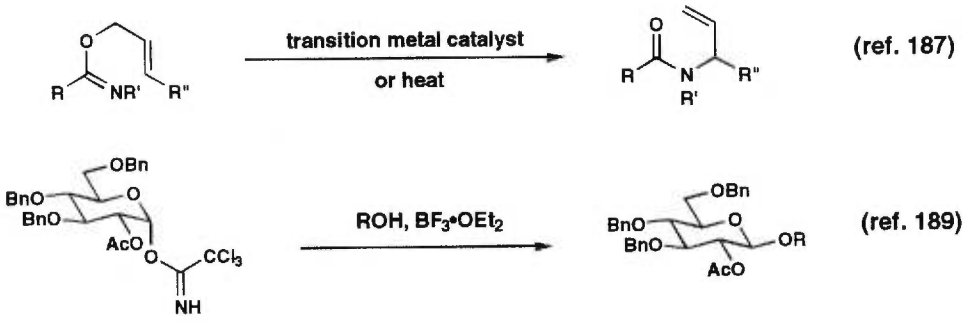
CHAPTER 5

Conversion of Secondary Amides to N-Substituted Imidates.[185]

5.1 Introduction

In the previous chapters, the addition of alcohols to imidoyl and iminium triflates proved to be efficient approaches to the synthesis of esters and ortho-esters. Another useful functional group involved in these transformations is alkyl imidates.[186] Among the previously mentioned uses for imidates, they can also be used in the formation of allylic amines via allylic rearrangement[187] or for the efficient glycosylation of carbohydrates (Scheme 56).[188]

Scheme 56. Rearrangement of allylic imidates

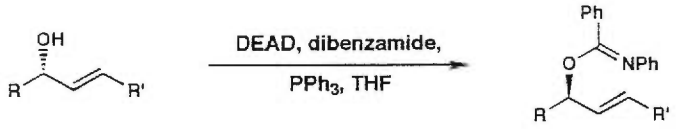


Primary imidates can be made by the acid catalyzed addition of alcohols onto nitriles.[189] For electron poor substrates, the same reaction can be achieved using base.[190]

Secondary amides can be *O*-alkylated to produce imidates using Meerwein's reagent or dialkyl sulphates.[191] However, this is limited to the

formation of *O*-methyl and *O*-ethyl imidates. Imidates can also be formed by the *O*-alkylation of amides with hindered secondary allylic alcohols using a Mitsunobu protocol (Scheme 57).[192] This procedure fails for some substrates where side products resulting from S_N2' attack and *N*-alkylation can reduce the yield of the desired compound.

Scheme 57. Synthesis of imidates from secondary allylic alcohols via Mitsunobu protocol

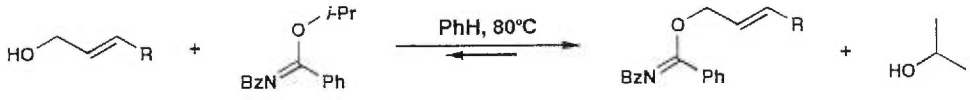


Imidates are initially formed when ortho esters are treated with amines in the presence of an acid catalyst, but they often react further to give amidines.[193] Amidine formation can be suppressed by the use of hindered amines[194] or cyclic ortho esters (Scheme 58).[195]

Scheme 58. Synthesis of imidates from ortho-esters

Treatment of activated amides can allow access to imidates. The alkoxide-catalyzed addition of alcohols to imidates can generate other imidates through the exchange of alcohols groups (Scheme 59).[196] Because this transformation is an equilibrium, higher yields can be obtained by using imidates derived from alcohols which are lower boiling or hindered to help favor the products in this exchange reaction.[197]

Scheme 59. Synthesis of imidates from other imidates

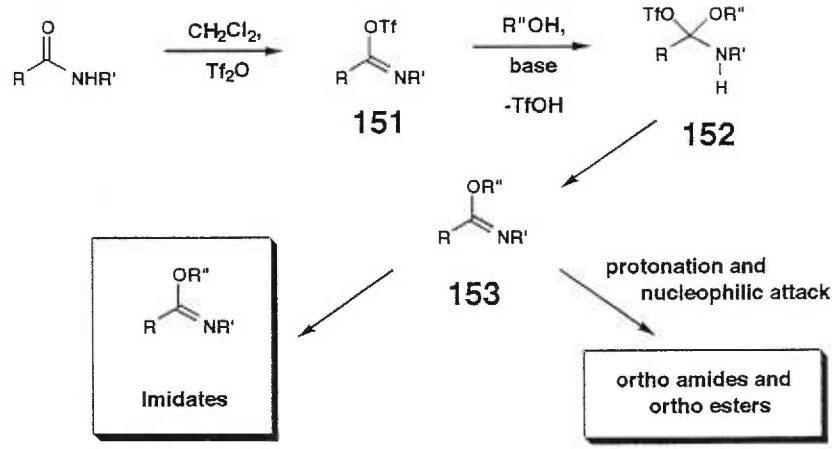


Imidoyl chlorides can be treated with alcohols to form imidates.[198] Mechanistically, this procedure is analogous to the method we wish to present here which is the formation of imidates from imidoyl triflates. The advantage of using triflates is that secondary amides can be converted to triflates under milder conditions than those used for the formation of the corresponding halides. This advantage is important when more functionalized imidates are required.

5.2 Imidates from Secondary Amides via Imidoyl Triflates

When imidoyl triflates **151** are treated with alcohol, the triflate is readily substituted to form an imidate **153** (Scheme 60).

Scheme 60. Formation of imidates from imidoyl triflates

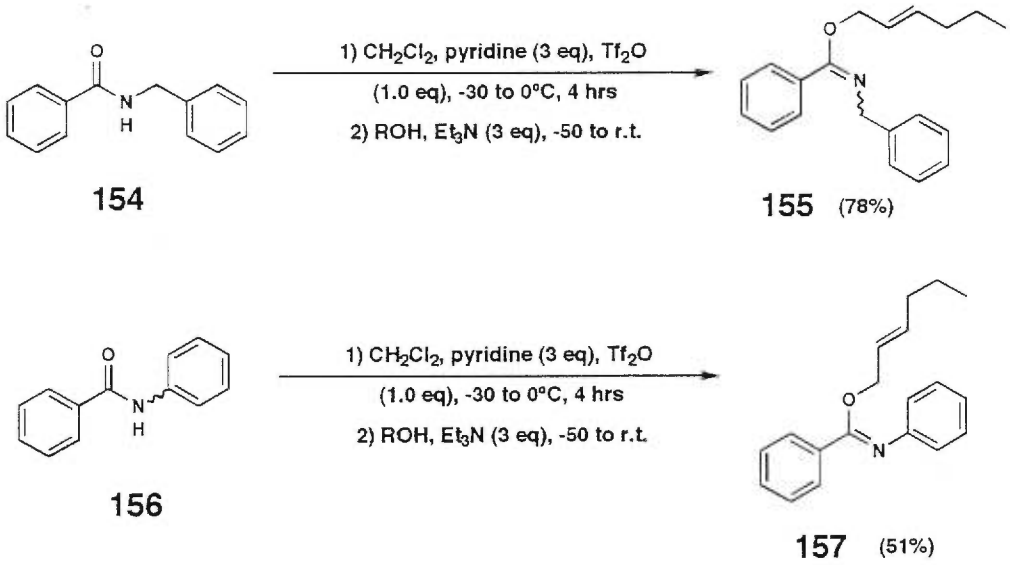


The reaction between an imidoyl triflate and an alcohol generates an imidate and one equivalent of acid. The imidate nitrogen lone pair is basic and would be protonated unless there is a stronger base in the reaction.[199] The protonated imidate is electrophilic and nucleophiles can react with these intermediates. Normally, pyridine is used and it is not strong enough to completely prevent protonation of the imidate.[200]

However, by using a stronger base that essentially prevents the protonation of the imidate, further transformation of the imidate can be

suppressed. This approach allows the isolation of imidates in modest to good yields. Thus, by treating the imidoyl triflate with a stoichiometric amount of the alcohol followed by an excess of triethylamine, imidates **155** and **157** could be isolated after a non-aqueous work-up (Scheme 61).

Scheme 61. Synthesis of imidates via imidoyl triflates



Note that pyridine is still used in the first step when the imidoyl triflate is generated. It is present to prevent the formation of *N*-acyl amidines as mentioned in section 2.31. This side reaction is problematic for *N*-phenyl benzamide, but less for other amides. It is possible to use triethylamine during the generation of imidoyl triflates in the first step. However, since triethylamine is a much stronger base than pyridine, it has a greater propensity to deprotonate imidoyl triflates resulting in the formation of ketenimines which is indicated by the reaction becoming dark red as the temperature nears 0°C.

5.3 Conclusion

Initial studies have demonstrated that imidates can be isolated from the reaction between imidoyl triflates and alcohols. Addition of a stronger

base such as triethylamine prevents the protonation of the imidate and prevents it from undergoing any further reactions. By preventing this protonation, the imidate is much less susceptible towards nucleophilic attack and hydrolysis during manipulation or work-up. Hence, higher yields of imidate can be obtained. This methodology may prove itself useful in the formation of highly functionalized imidates since the generation of imidoyl triflates occurs under much milder conditions that those used for the formation of imidoyl halides.

Chapter 6: Synthesis of Δ^2-Thiazolines via Imidoyl and Iminium Triflates

CHAPTER 6

Synthesis of Δ^2-Thiazolines via Imidoyl and Iminium Triflates.[201]

6.1 Introduction

Thiazolines[202] are a class of heterocycles which have received much attention recently due to their presence in numerous interesting biologically active natural products such as curacin A,[203] thiangazole,[204] tantazole B[205] and mirabazole B[206] (Figure 7).

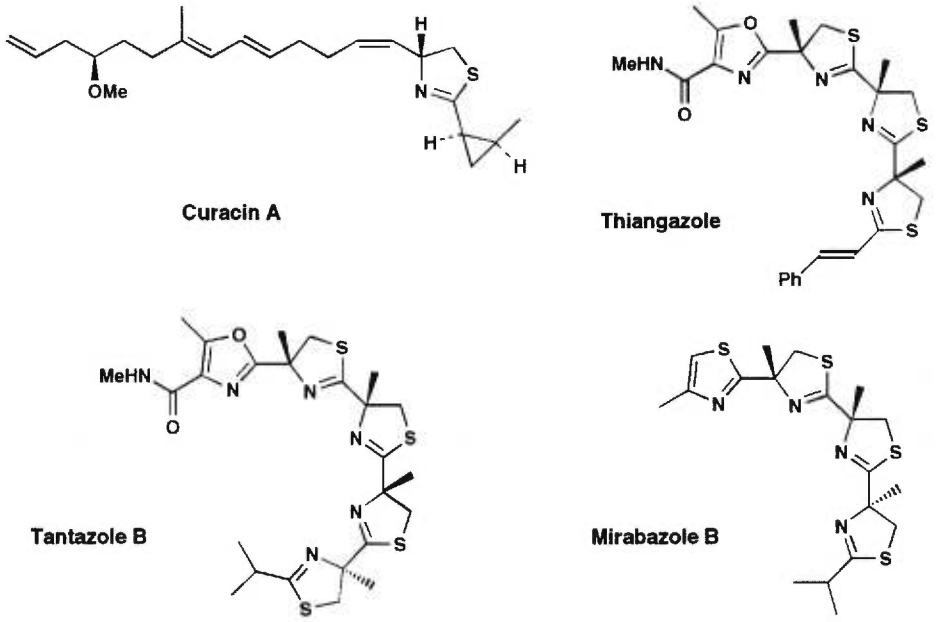
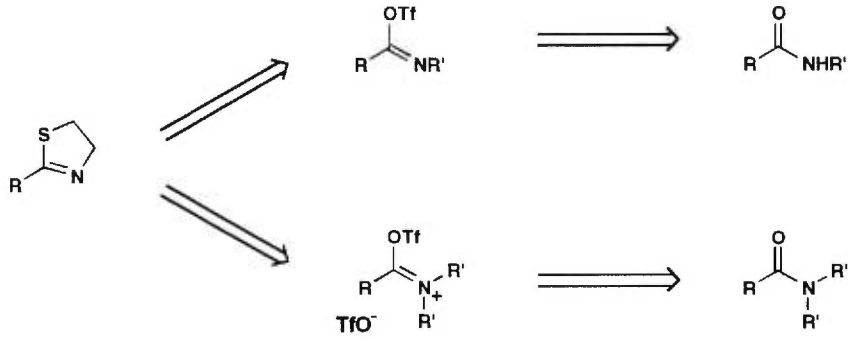


Figure 7. Thiazoline containing natural products of interest

The interest in these heterocycles also extends into our laboratories with synthetic targets which contain these interesting heterocycles.

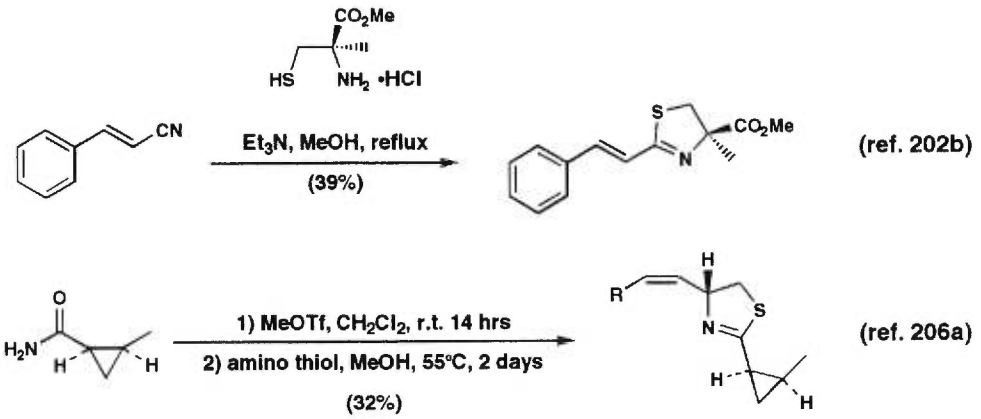
Therefore, it only seemed fitting to develop the use of imidoyl and iminium triflates as precursors to thiazolines so we could have our own methodology to use in the synthesis of these heterocycles. Furthermore, we could demonstrate the possibility of using imidoyl and iminium triflates as precursors to heterocycles in general, and not just simpler carboxylic acid derivatives (Scheme 62).

Scheme 62. Synthesis of thiazolines from secondary and tertiary amides via imidoyl and iminium triflates



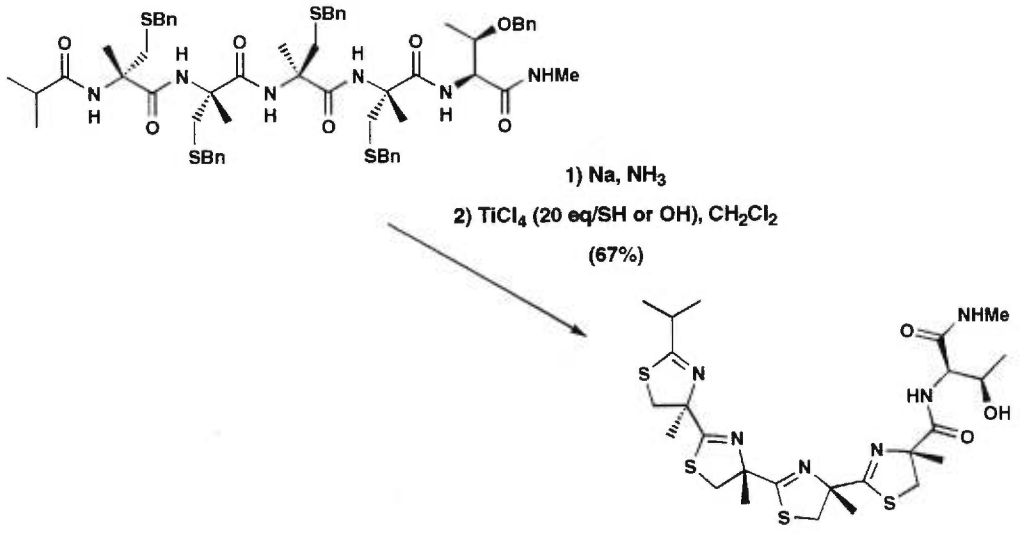
With the recent interest in these heterocycles, efforts have been made to find milder methodologies which can form thiazolines. In the context of total synthesis of natural products, a requirement of these methodologies is that it should be an efficient and mild process, suitable for use with highly functionalized and sensitive substrates. Historically, the traditional methods for the synthesis of thiazolines were quite harsh since there was no need to make these compounds in a highly complex molecule. The first thiazolines were made by Pinner type reactions using amino thiols with nitriles or imidates.[207] The advantage of this method is that the heterocycle is formed in a one step synthesis. However, one of the drawbacks of this approach is that harsh conditions are usually required since imidates and nitriles are poor electrophiles (Scheme 63).[208]

Scheme 63. Thiazolines from nitriles and imidates



More success has been found in intramolecular variants of this reaction. By using a fair excess of $TiCl_4$, Heathcock can cyclo-dehydrate amido-thiols to give thiazolines (Scheme 64).[209]

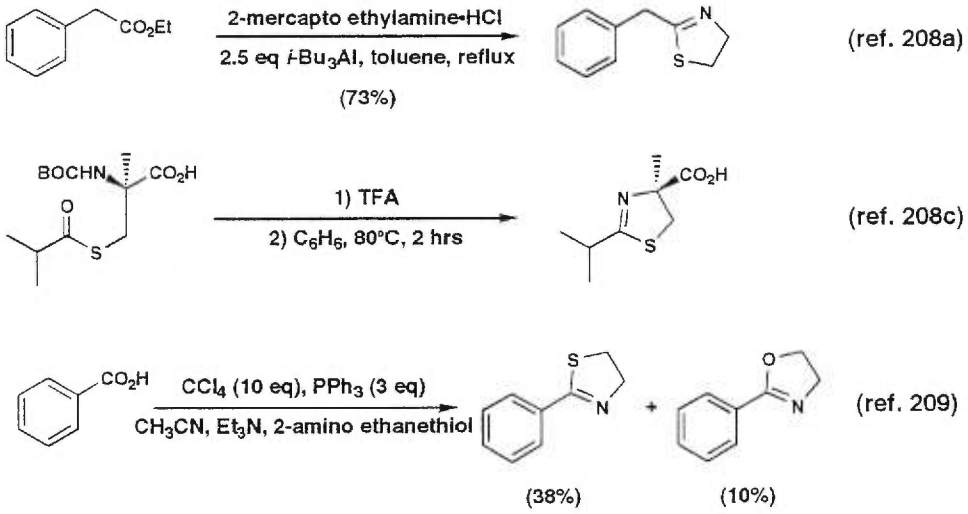
Scheme 64. Acid-mediated cyclizations of amido-thiols



In an analogous fashion, amino thiono-esters can also be cyclo-dehydrated under similar acidic conditions (Scheme 65).[210] Mitsunobu conditions can also be used to mediate this type of ring formation where the carbonyl oxygen is activated towards displacement by either sulfur or nitrogen. One can use triphenylphosphine/CCl_4 to form an amide bond

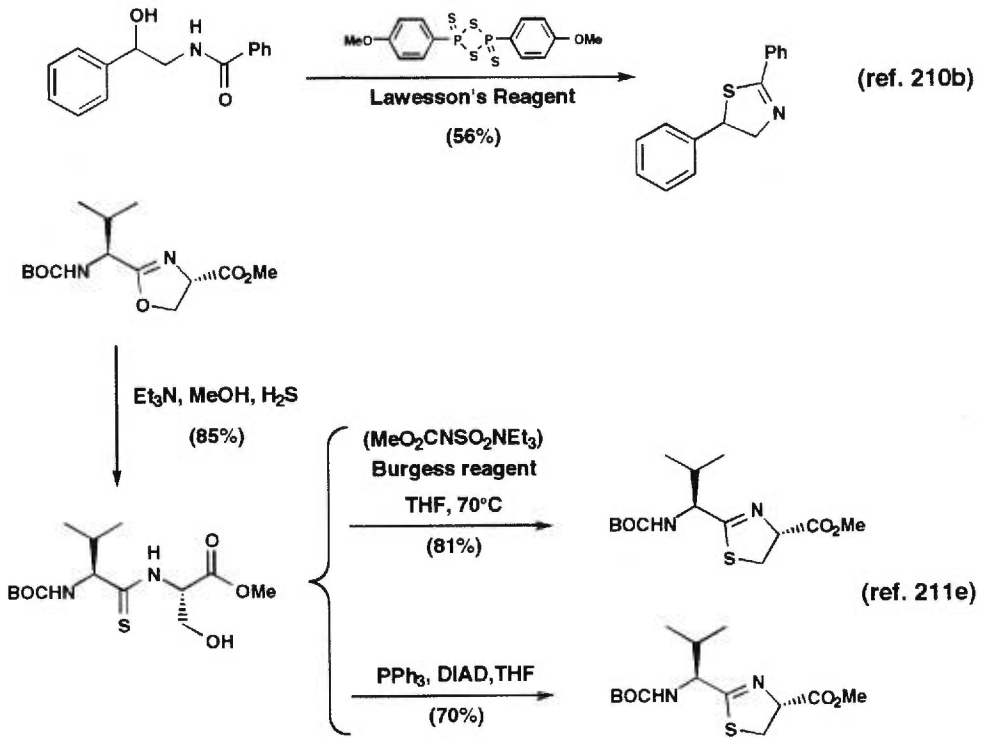
between a carboxylic acid and an amino thiol as well as subsequently activate the carbonyl oxygen of the resulting product towards cyclo-condensation.[211] This method, however, also forms some oxazoline due to a phosphonium salt's affinity for oxygen.

Scheme 65. Thiazoline ring formation via activation of the carbonyl oxygen



Mitsunobu-like conditions are more efficient at achieving ring closure through more traditional SN_2 displacements of an activated hydroxyl group (Scheme 66). Thus, a hydroxy-thioamide can be activated at the oxygen and nucleophilic displacement by the sulfur of the thioamide affects the ring closure.[212] Another very efficient example of this strategy is Wipf's conversion of oxazolines to thiazolines using H_2S to form the hydroxy-thioamide followed by the Burgess reagent to form the heterocycle.[213] Of course, hydroxy-thioamides can be made in other ways and used for the synthesis of thiazolines.[214]

Scheme 66. Thiazolines from hydroxy-thioamides via Mitsunobu-like conditions



In a similar displacement reaction, the hydroxyl group of hydroxy thioamides can be converted to a chloride for cyclization to the thiazoline.[215] This is a procedure which works well for the synthesis of oxazolines, but is not one of the preferred methods for the synthesis of thiazolines as typical conditions require refluxing with thionyl chloride.

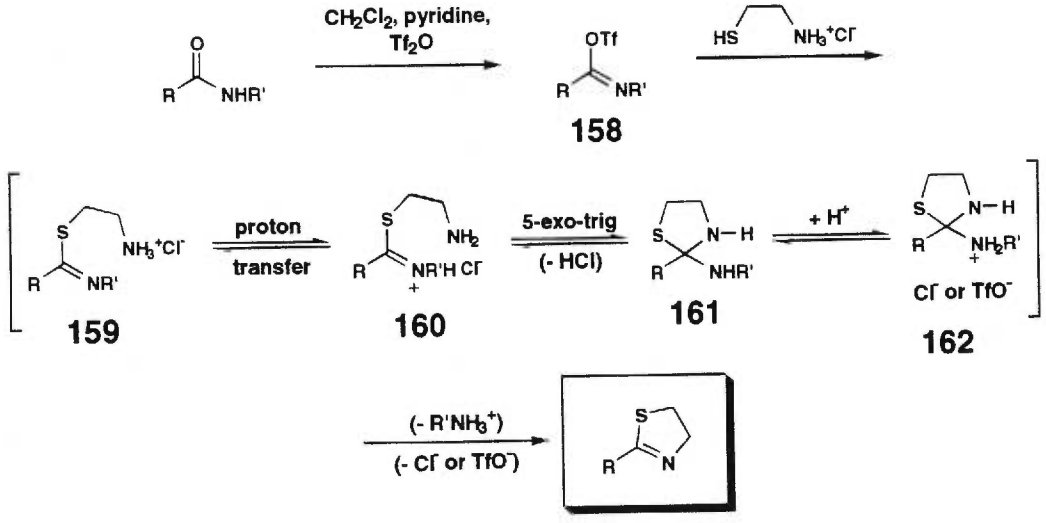
Even though numerous methodologies are available, high yields for the formation of the thiazoline is sometimes not obtained especially with acid-sensitive or racemization prone substrates.[216] Furthermore, the most efficient thiazoline syntheses from sensitive precursors usually require multi-step sequences. In the following sections, we wish to present our approach to thiazolines using imidoyl and iminium triflates. At low temperatures in a medium buffered with excess pyridine, iminium and imidoyl triflates can be generated and reacted with amino thiols to allow

access to thiazolines in a one-pot/two step process. We observed that there was essentially no racemization and the reaction is also compatible with a wide-range of protecting groups.

6.2 Mechanistic Aspects of the Synthesis of Thiazolines from Secondary and Tertiary Amides

Presumably, the use of imidoyl and iminium triflates for the synthesis of thiazolines would be analogous to the use of imidoyl or iminium halides. To the best of our knowledge, the halide electrophiles have not been used as precursors to these heterocycles. The reaction would proceed like the synthesis of thiazolines from imidates, however, the initial attack of the amino thiol on the triflate would occur in a very facile manner whereas in imidates, this reaction can be a slow and difficult process, even with strong acid catalysis. The initial addition of an amino thiol to these highly electrophilic species should result in the formation an alkyl thioimidate **159** (Scheme 67).

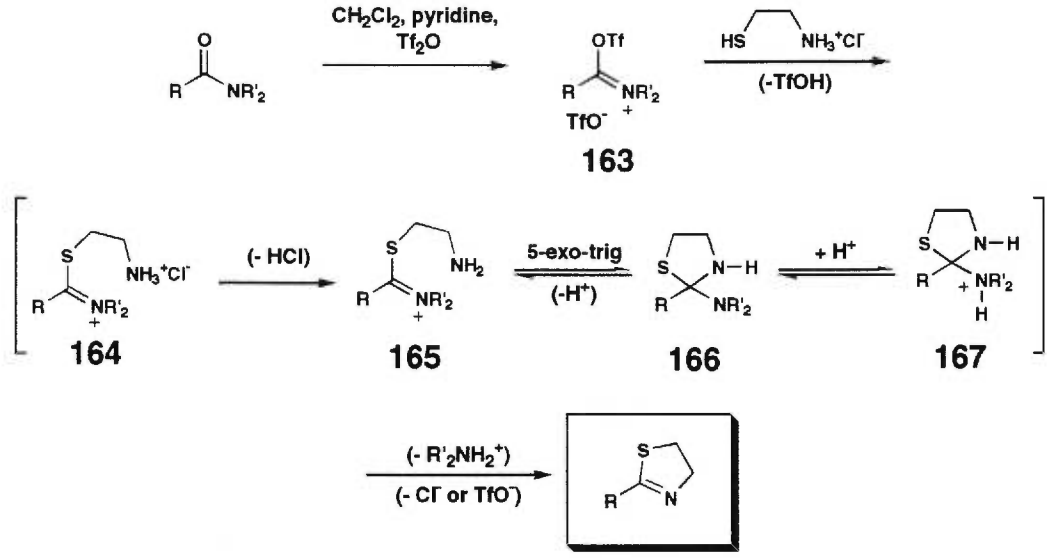
Scheme 67. Thiazolines from secondary amides via imidoyl triflates



In these reactions, there are several equivalents of acid present or generate. This requires a lot of base to ensure that an excess of base is maintained. Using pyridine as a base, the conjugate acid of pyridine is strong enough to protonate the alkyl thioimidate, presumably at the most basic site which is the primary amine **159**. The protonated thioimidate is a mono-cation which could readily transfer the proton between the amine to the imine, in an intramolecular fashion.[217] This would result in the formation of an iminium species **160** which would catalyze the cyclization of the amine group onto the itself in a highly favorable 5-exo-trig fashion. The resulting compound **161** could be protonated by the pyridine buffered medium at two sites. Protonation of the endocyclic nitrogen and elimination would give the previous intermediate as the reaction goes back-wards one step. However, protonation at the exocyclic nitrogen in compound **162** and elimination of this amine residue would lead to the irreversible formation of the thiazoline. The large gain in entropy at the last step should drive the formation of the product.

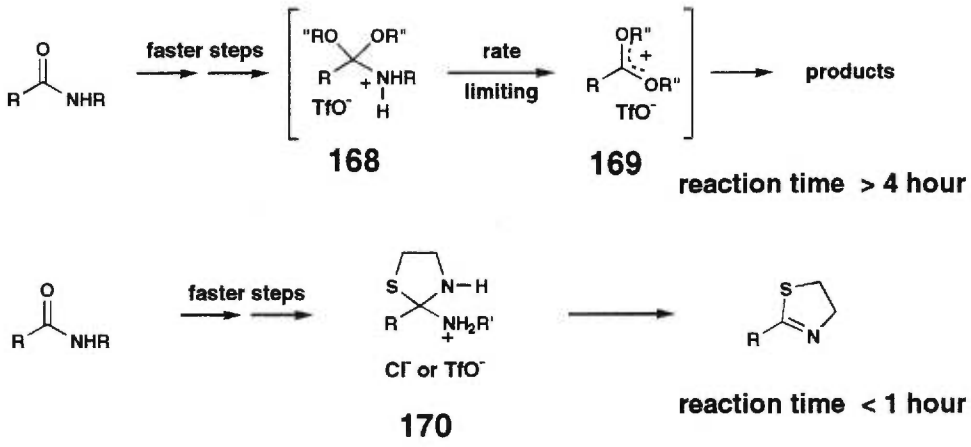
Formation of thiazolines from tertiary amides should proceed by a similar mechanism except that an iminium species predominates in the mechanism instead of an imine (Scheme 68). This should result in several differences such as acid catalysts not being required to protonate and activate the imine. After the formation of the ammonium alkyl thio-iminium ester **164**, this di-cationic species should be readily deprotonated by pyridine. The electrophilic nature of the iminium groups should allow for a very facile addition of the amine group in a 5-exo-trig fashion. Again, this cyclized intermediate **166** has two sites of protonation. One is endocyclic nitrogen which is secondary, the other site is the exocyclic nitrogen which is tertiary. The tertiary amine is slightly more basic and should be protonated more readily. Irreversible elimination of the ammonium residue from the ammonium compound **167** would immediately provide the final product.

Scheme 68. Thiazolines from tertiary amides via iminium triflates



Unlike the methodologies presented in the previous sections, the formation of thiazolines is generally complete within an hour or two (Scheme 69).

Scheme 69. Faster rates of formation due to absence of slow oxonium ion formation step



The conversion of amides to esters took at least several hours to go to completion. This indicates that the rate-limiting step in the formation of

thiazolines is faster than the rate-limiting step in the conversion of amides to esters. The formation of an oxonium ion is not present in the formation of thiazolines, but it is supposedly present in the formation of ortho esters. This difference in reaction rates may lend further evidence to the existence of the oxonium ion **169** as the rate-limiting step in the conversion of amides to esters and ortho esters.

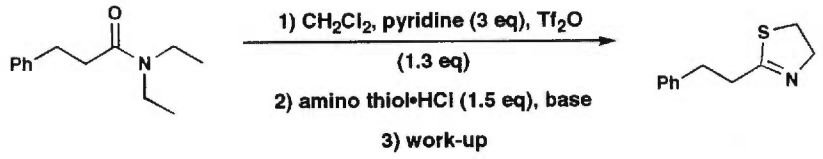
6.3 Synthesis of Thiazolines from Tertiary Amides

Tertiary amides can be converted to thiazolines in a two-step/one pot procedure. As usual, the first step requires conversion of the amide to the iminium triflate. Once formation of the triflate is complete, the amino thiol can be added. The amino thiols are often available as the hydrochloride salt which introduces additional acid to the reaction. Care must also be taken as these very hygroscopic salts can absorb a lot of moisture which could result in the hydrolysis of the imidoyl or iminium triflates. Hence, it was found that additional base was required to ensure that there was always an excess of base (Table 19). The pyridine-acid buffer system had to be maintained otherwise the pH of the reaction media would decrease drastically which resulted in lower yields and more unidentifiable secondary products. Therefore, conversion of the amide to the triflate was done using 3 equivalents of pyridine with 1.3 equivalents of triflic anhydride. After the triflate is formed, 1.5 equivalents of the amino thiol hydrochloride was added, which was followed by another 3 equivalents of pyridine.[218]

Care must be taken during the work-up of the reaction (Table 17). Aqueous acid work-ups were avoided altogether since these conditions readily hydrolyze oxazoline and thiazolines. Non-acidic aqueous work-ups seemed to give poor yields of the thiazoline also. The same work-up used for ortho esters was adopted for this methodology. By adding Et_3N at the end of the reaction and filtering the reaction through Et_3N treated silica

using an eluant containing Et_3N, good yields of the thiazolines were obtained.

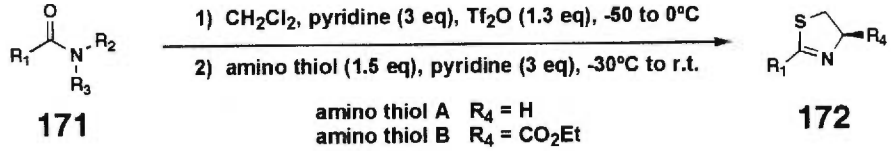
Table 19. Effects of additional base and non-aqueous work-up



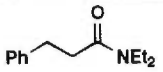
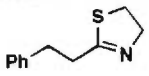
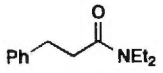
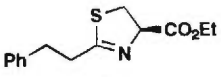
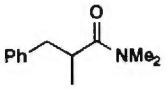
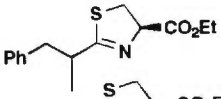
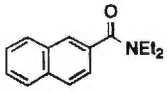
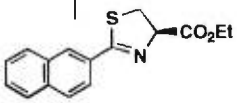
Base	Work-up	Yield
none	$NaHCO_3$ (sat), Na_2SO_3 (sat)	<10%
2 eq pyridine	$NaHCO_3$ (sat), Na_2SO_3 (sat)	20-25%
none	same work-up as for ortho esters	41%
3 eq Et_3N	same work-up as for ortho esters	91%
2 eq pyridine	same work-up as for ortho esters	87%

These general conditions were applied to various tertiary amides. The results are summarized in Table 20.

Table 20. Synthesis of Δ^2-thiazolines from tertiary amides



171 **172**

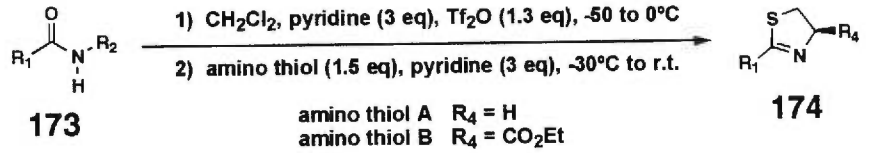
Entry	Amide	Amino-thiol	Thiazoline	Isolated Yield
a		A		91 %
b		B		90 %
c		B		55 %
d		B		65 %

Two commercially available amino thiol hydrochlorides were used; amino ethanethiol and the cysteine ethyl ester hydrochloride. Aliphatic

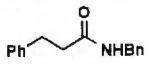
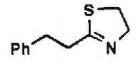
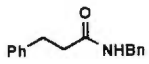
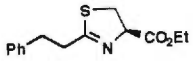
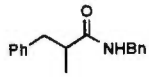
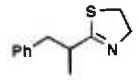
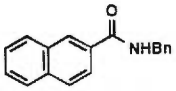
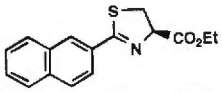
and aromatic tertiary amides are converted to thiazolines in generally good yields.

The results with secondary amides are shown in Table 21.

Table 21. Synthesis of Δ^2-thiazolines from secondary amides



173 **174**

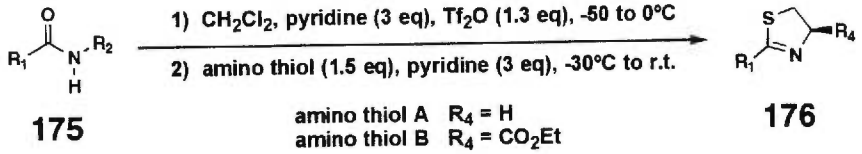
Entry	Amide	Amino-thiol	Thiazoline	Isolated Yield
a		A		72 %
b		B		91 %
c		A		71 %
d		B		58 %

Some of the variations in yield may be attributed to slight differences in pKa's between the various amino groups present in the reaction as well as the difference between iminium and imine intermediates when using tertiary or secondary amides. Cyclizations onto the iminium ion do not required acid catalysis whereas the cyclizations onto the imine do in the case of secondary amides. The reaction should be more straightforward for tertiary amides. For secondary amides, there are two basic groups involved in the reaction as shown by the imine and amine groups in alkyl thioimidate **159**. For the reaction to progress, the imine should be protonated and the amine should be free as shown by intermediate **160**. However, the amine is more basic than the imine. Nevertheless, the driving force for the reaction is the gain in entropy upon liberating the amine residue in the final step so the reaction should drive itself to completion. Furthermore, in alkyl thioimidate **159**, the ammonium

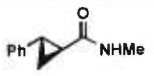
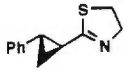
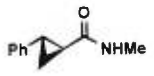
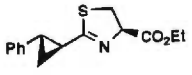
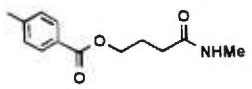
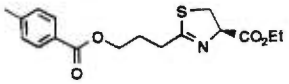
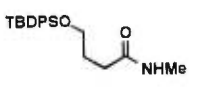
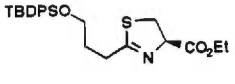
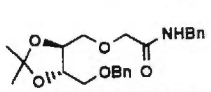
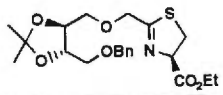
residue acts as an intramolecular acid and protonation of the imine residue and liberation of the amine residue should occur more readily than in an intermolecular case. Thiazolines should also be formed more readily from the ethyl ester of cysteine than amino ethanethiol since the carboxylic acid group would make the amine less basic through inductive effects. This would make the ammonium residue in intermediate **159** more acidic.

Table 22 shows some results with more functionalized substrates. (Entry a) is the conversion of a cyclopropyl amide to the corresponding thiazoline. This compound was found to be higher than 99 %de indicating that very little epimerization had occurred at the α-carbon. The corresponding tertiary *N,N*-dimethyl amide failed to give products as it readily decomposed during the formation of the triflate. This may be attributed to the propensity of the cinnamyl cyclopropane moiety to undergo carbocationic ring opening.

Table 22. Synthesis of more highly functionalized Δ^2-thiazolines



175 **176**

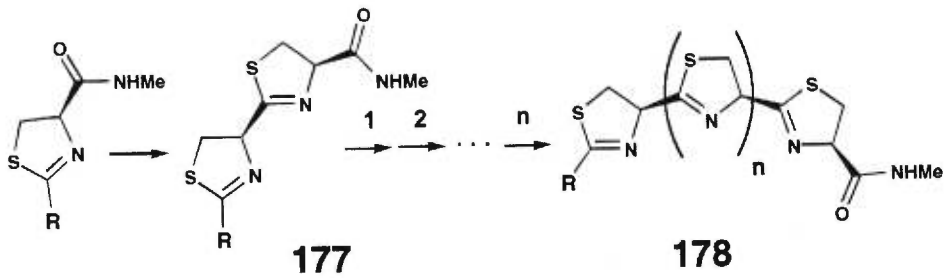
Entry	Amide	Amino-thiol	Thiazoline	Isolated Yield
a		A		72 % (99 %de)
b		B		77 % (98 %de)
c		B		76 %
d		B		73 %
e		B		80 %

Entry b shows that in the formation of the thiazoline with ethyl cysteine, the product was found to have a diastereomeric excess of 98 %. This indicates that these conditions were mild enough not to cause extensive epimerization at the α-carbon of the amino acid. The final three examples demonstrate that various functional are stable to these reaction conditions. These groups include benzoate esters (Entry c), silyl ethers (Entry d), acetonides and benzyl ethers (Entry e). The mildness of these conditions can be attributed to the low temperatures and the very weakly acidic medium required for the thiazoline formation to take place. Hence, this methodology could be useful in the synthesis of highly functionalized thiazolines.

6.4 The Imidoyl Triflate Approach to Polythiazolines

A large number of compounds containing contiguous polythiazoline units have recently caught the interest of scientists due to their promising biological activity as well as their unique structure.[219] The synthesis of these polythiazoline sub-units presented itself as an interesting challenge for this methodology. One could envision the use of imidoyl triflates as intermediates in the construction of polythiazolines where the amide of cysteine could be used to build the thiazoline in a modular fashion (Scheme 70).

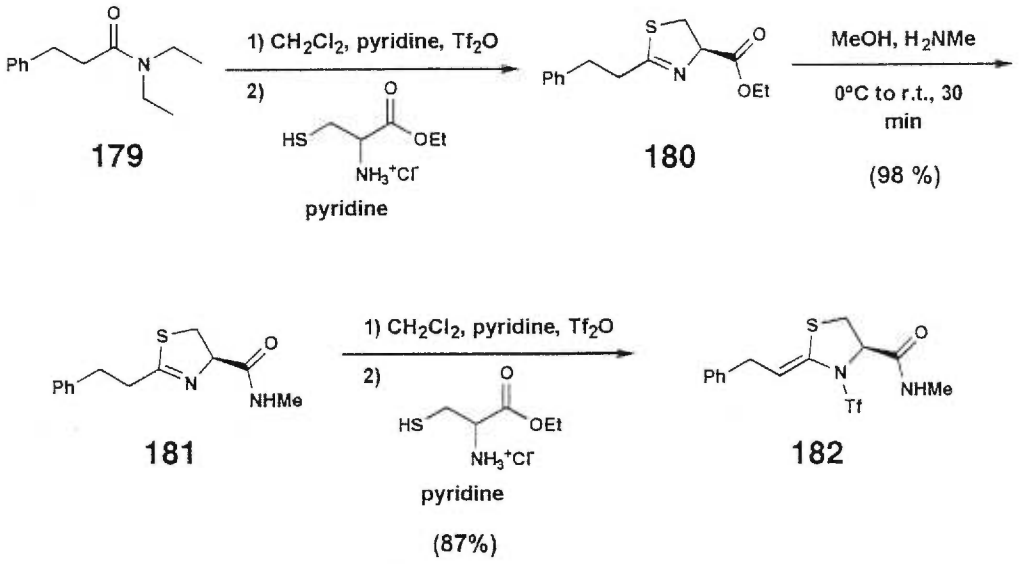
Scheme 70. Imidoyl triflate approach to sequential polythiazoline synthesis



Each newly formed thiazoline such as intermediate **177** would have an amide ready for installation of another thiazoline unit via the imidoyl triflate methodology.

Our initial attempts to form bis-thiazolines involved converting phenethyl amide **179** to the thiazoline ester **180** (Scheme 71). The ester was quantitatively aminolyzed with methylamine in methanol to provide the amide **181** in preparation for the installation of the second thiazoline group.

Scheme 71. Attempted formation of bis-thiazolines



Unfortunately, attempts to for the bis-thiazoline using standard conditions failed to give the bis-heterocyclic compound. Instead, the thiazoline was acylated at the nitrogen to give the triflamide **182** whose structure was determined by x-ray crystallography (Figure 8).[220] Thiazolines have been reported to have this type of reactivity.[221]

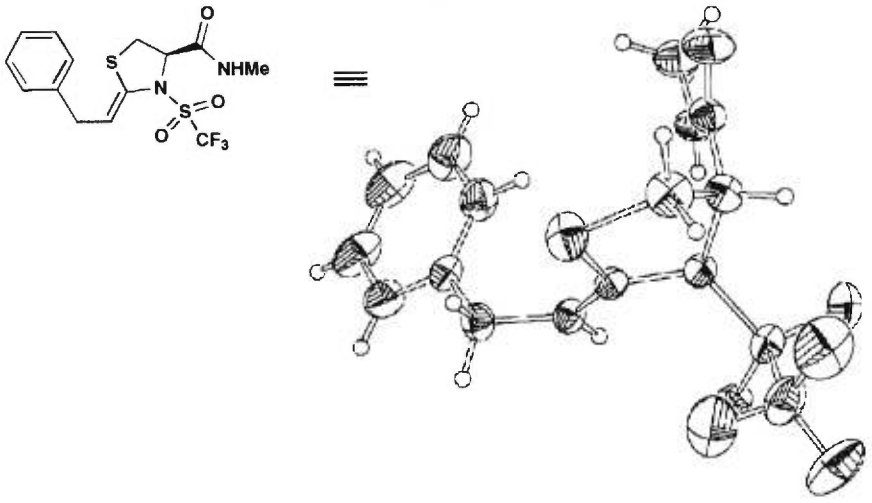
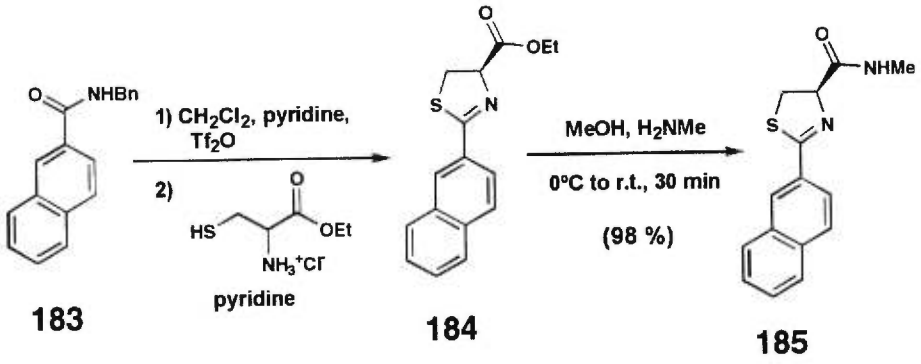


Figure 8. ORTEP representation of *N*-triflamide **182**

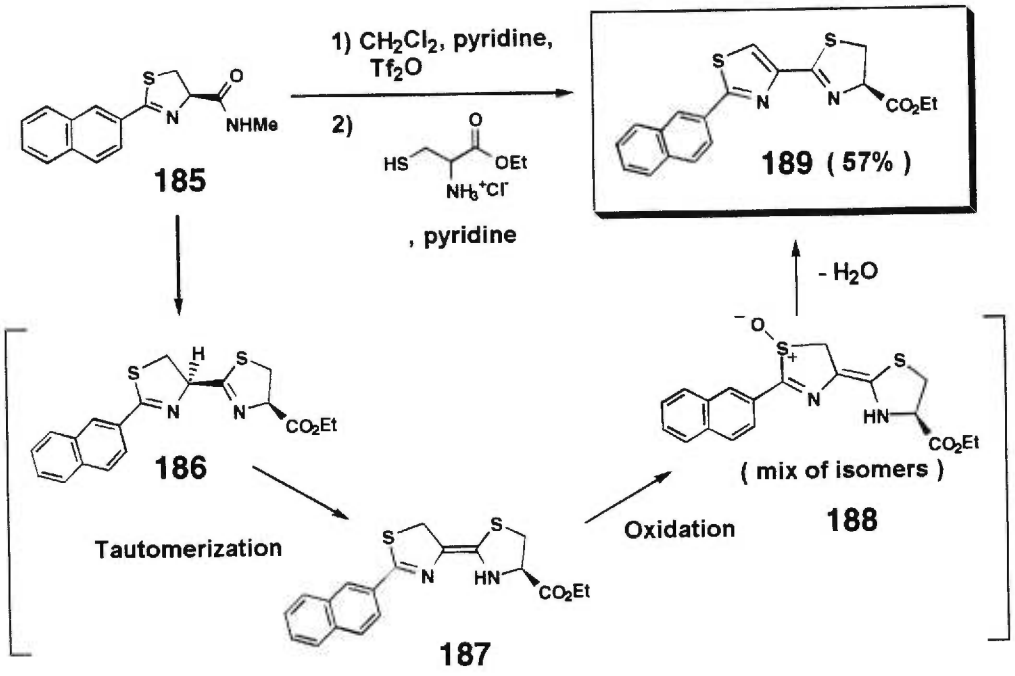
Substrates not bearing an α-proton would not undergo this type of enamine formation as the endocyclic nitrogen of the thiazoline would be less nucleophilic. Naphthylamide **183** was converted to thiazoline ester **184** (Scheme 72). Treatment with excess methylamine in methanol resulted in the quantitative conversion to *N*-methyl amide **185** in preparation for the installation of the next thiazoline ring.

Scheme 72. Synthesis of thiazoline amide **185**



Amide **185** was then submitted to the standard conditions used for thiazoline formation, but this did not produce the desired bis-thiazoline **189** as the final product (Scheme 73). Instead, two other bis-heterocyclic compounds were isolated.

Scheme 73. Synthesis of bis-heterocyclic compounds via imidoyl triflates



The first compound isolated was the bis-heterocycle **188**. This compound probably resulted from the tautomerization and subsequent oxidation of the desired bis-thiazoline **186**. The oxidation could be caused by the handling and purification of these compounds in the presence of oxygen.[222] Small quantities of this unstable ester **188** were isolated as a mixture of diastereoisomers and it eventually dehydrated to a less polar compound upon chromatography. This less polar compound turned out to be the thiazole **189** whose structure was confirmed by x-ray crystallography (Figure 9).[223] Presumably, it is the product of the aromatization of ester **188** upon the loss of a molecule of water. Although this un-optimized reaction failed to give the desired bis-thiazoline **186** as

the final product, its existence as an intermediate in this reaction could be deduced from the products which were isolated. Furthermore, the final bis-heterocyclic compound **189** could be produced in 57% yield, thus demonstrating that this methodology is capable of forming contiguous thiazolines.

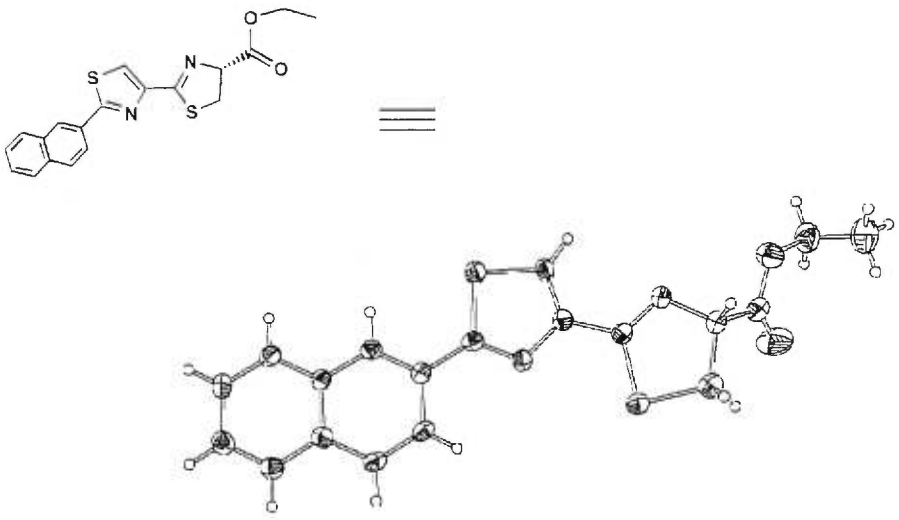
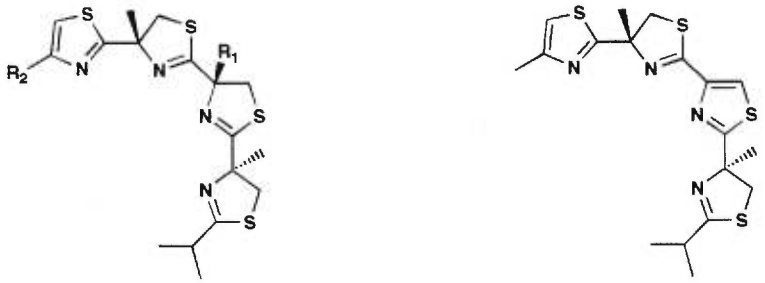


Figure 9. ORTEP representation of thiazole-thiazoline **189**

6.5 Comments on the Presence of α-Methyl Cysteine in Polythiazoline Containing Natural Products

Whereas the mono-thiazoline compounds are relatively stable, bis-thiazoline compounds made from α-amino acids with α-protons readily tautomerize to give compounds which seem to be more sensitive towards oxidation or decomposition. In comparing mirabazole and didehydromirabazole (Figure 10),[224] it seems that nature has used α-methyl cysteine to counteract this problem.



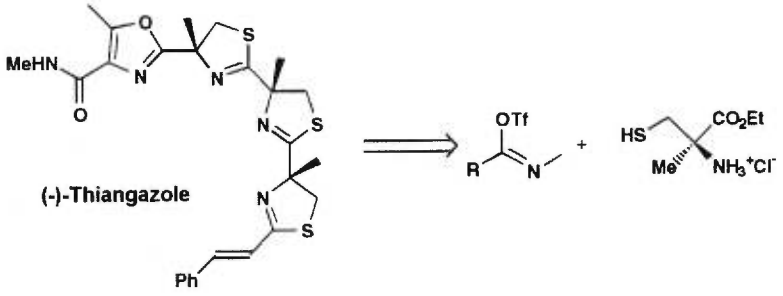
Mirabazole A, R_1 = H, R_2 = CH_3
Mirabazole B, R_1 = R_2 = CH_3
Mirabazole C, R_1 = CH_3, R_2 = H

Didehydromirabazole

Figure 10. Mirabazoles versus didehydromirabazole

The presence of the α-methyl group prevents the tautomerization and the cascade of events which ultimately result in the oxidation of the thiazoline to the thiazole. So in light of this, our methodology has potential application towards the expedient formation of contiguous poly-thiazoline heterocycles made from α-methyl cysteine as the methyl groups would ensure the preservation of the thiazoline moiety (Scheme 74). This process can be further improved by the use of the *N*-methyl amide of cysteine as the aminothiol so that the additional conversion of the ester to the amide can be avoided.

Scheme 74. Retro-synthetic analysis of thiangazole



6.6 Conclusion

In summary, it has been demonstrated that iminium and imidoyl triflates are very good electrophiles as they react readily with amino thiols in a weekly acidic medium to give rise to thiazolines. Yields are good to excellent and the reaction conditions are mild enough to tolerate various hydroxy and carbonyl protecting groups. Potential applications of this method towards the synthesis of curacin A and thiangazole should reiterate the synthetic utility of this method.

Chapter 7: Synthesis of Thioamides and ^{18}O-Labelled amides via Imidoyl and Iminium Triflates

CHAPTER 7

Synthesis of Thioamides and ^{18}O-Labelled amides via Imidoyl and Iminium Triflates.[225]

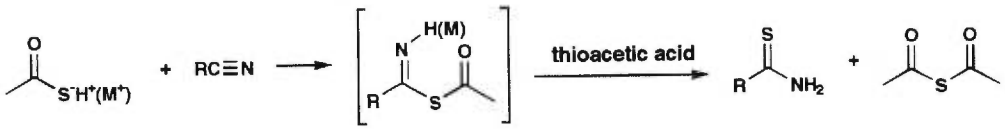
7.1 Introduction[226]

Imidoyl and iminium triflates can also be useful intermediates for the substitution of the oxygen atom in amides with other heteroatoms. These types of reactions could produce thioamides, oxygen-labeled amides and amidines. The first two types of compounds will be studies in this chapter.

7.11 De Novo Syntheses of Thioamides

Thioamides are approaching their second century of existence as Guy-Lussac obtained the first thioamide in 1815 by reacting hydrogen sulfide with cyanogen (Scheme 75).[227] This approach from nitriles has been used in many variations as the reaction can be catalyzed by acid or base.[228] In the case of acids, the source of sulfur is usually a thioacid such as thioacetic acid.[229]

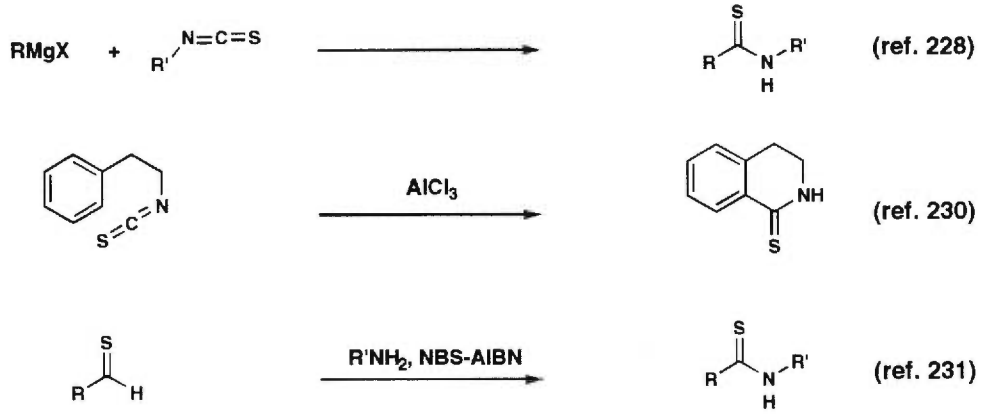
Scheme 75. Thioamides from nitriles



De novo syntheses of thioamides include reacting carbon nucleophiles with isothiocyanates (Scheme 76). Reactive nucleophiles such

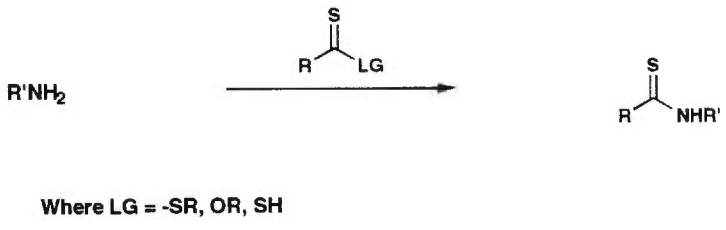
as Grignards are usually used.[230] Aromatic rings can act as nucleophiles in electrophilic aromatic substitutions with isothiocyanates,[231] but better yields are generally obtained when this reaction is done in an intramolecular fashion.[232] Amino de-hydrogenation of thioaldehydes can also be a useful route to thioamides.[233]

Scheme 76. Thioamides from isothiocyanates and thioaldehydes



Thioamides are rarely made by thioacylating amines with thioacyl halides and thioacid anhydrides since these reagents are very difficult to prepare. However, other reagents with sufficient thioacylating activity have been used (Scheme 77). These reagents include thionoesters,[234] dithiocarboxylic acids,[235] and dithiocarboxylate esters.[236]

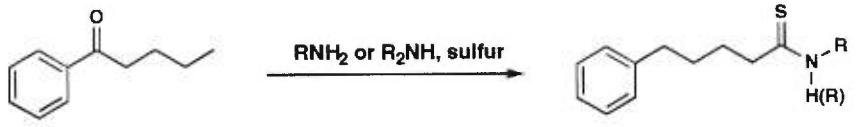
Scheme 77. Thioamides via thioacylation



Another interesting approach is represented by the Willgerodt-Kindler reaction (Scheme 78).[237] The mechanism of this reaction is still not

clear even to this day.[238] However, certain intermediates such as imines and enamines have been implicated.[239]

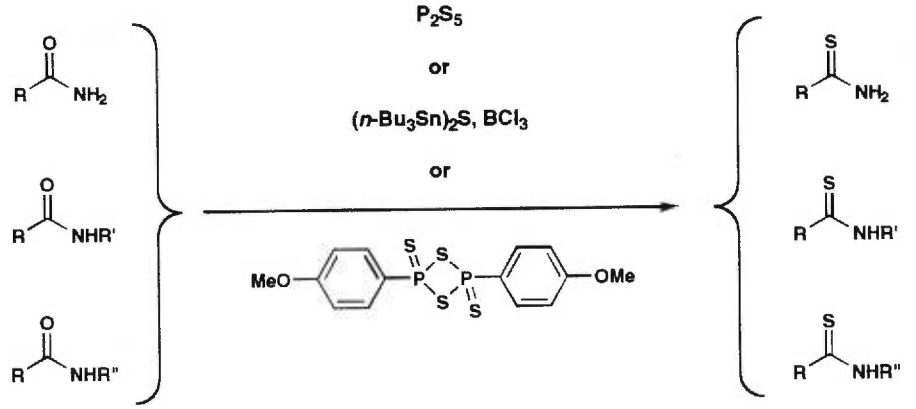
Scheme 78. Thioamides from the Willgerodt-Kindler reaction



7.12 Synthesis of Thioamides from Amide Precursors

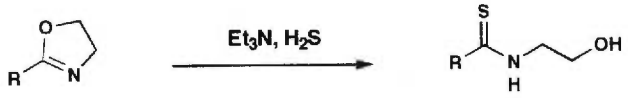
The most popular strategy for the synthesis of thioamides is probably the surfuration of the corresponding amides (Scheme 79). Traditionally, thioamides have been made by extensively heating the amide with P_2S_5.[240] Tin reagents can also used to achieve this transformation.[241] More recently, Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-1,2,3,4-dithiaphosphetane-2,4-disulfide) has become the reagent of choice for the synthesis of thioamides.[242] However, secondary and tertiary amides must be heated in toluene or benzene with Lawesson's reagent to affect this transformation. These conditions may be problematic for substrates bearing thermally labile functionality.[243]

Scheme 79. Thioamides by sulfuration of amides



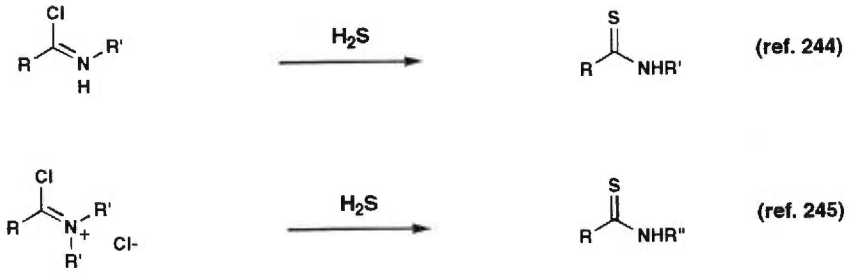
Heterocycles can also be precursors to thioamides as Wipf has recently reported that the sulfhydrolysis of Δ^2-oxazolines with basic hydrogen sulfide generates 2-hydroxyethyl (Scheme 80).[244] However, secondary and tertiary amides, which have acyclic or exocyclic C-N bonds, undergo irreversible sulfhydrolysis of the C-N bond to yield thionoesters.[245]

Scheme 80. Hydroxy thioamides from hydrogen sulfide ring opening of Δ^2-oxazolines



Activated amides have also been used as precursors to thioamides. Imidoyl chlorides[246] and iminium chlorides[247] can be treated with hydrogen sulfide to give thioamides (Scheme 81). However, the methods used to generate these intermediates are quite harsh and examples are limited to small and simple molecules which may attest to the lack of generality of these methods.

Scheme 81. Thioamides from thiolysis of imidoyl and iminium chlorides



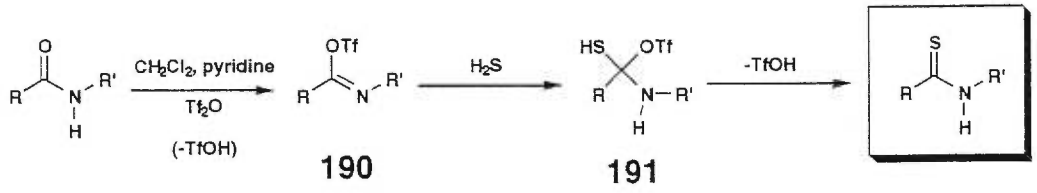
Our approach takes advantage of the leaving group ability of the triflate anion such that sulfhydrolysis of the C-N bond does not occur.[248] Another advantage is that imidoyl and iminium triflates are strong electrophiles which react instantaneously with stoichiometric amounts of hydrogen sulfide at low temperatures to immediately produce the

thioamide. This reduces the amount of toxic hydrogen sulfide needed. Furthermore, the low reaction temperatures and pyridine buffered reaction media makes this reaction milder than other methods which require heating in the presence of an acid or base. The yields range from good to excellent and this method should prove itself to be a low temperature alternative to Lawesson's reagent.

7.2 Mechanism of the Conversion of Amides to Thioamides via Imidoyl and Iminium Triflates

In the conversion of secondary amides to the corresponding thioamide, they are first converted to the imidoyl triflate **190** at low temperature using triflic anhydride in the presence of pyridine (Scheme 82).

Scheme 82. Mechanism of converting secondary amides to the corresponding thioamides

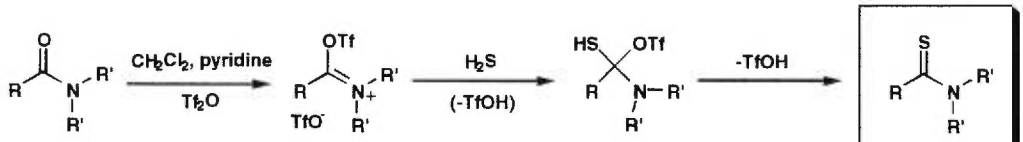


Once this electrophilic intermediate is formed, treatment with hydrogen sulfide results in substitution of the triflate to immediately give the thioamide.

For tertiary amides, the reaction is just as straightforward (Scheme 83). Treatment of the amide with triflic anhydride gives rise to the iminium triflate **192**. This species is even more electrophilic than the imidoyl triflate and reaction with hydrogen sulfide is just as instantaneous. The triflate is immediately substituted with sulfide and the resulting

iminium thiol is readily deprotonated in the pyridine buffered medium to provide the thioamide.

Scheme 83. Mechanism of converting tertiary amides to the corresponding thioamides

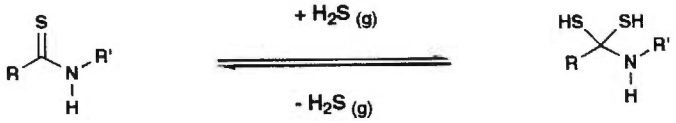


192 **193**

In theory, only one equivalent of hydrogen sulfide is required for this reaction. In practice, this turns out to be valid as the reaction between hydrogen sulfide and the triflates is instantaneous even at low temperatures. When hydrogen sulfide is added as a gas, it is often difficult to introduce just the right amount of reagent to the reaction. A predetermined solution of hydrogen sulfide in acetonitrile can be used, however, extreme care must be taken to ensure that this mixture is kept anhydrous.[249] The addition of hydrogen sulfide from a lecture bottle is quite convenient and anhydrous, however, the amount of hydrogen sulfide must be kept to a minimum.

If an excess of hydrogen sulfide is added, this can result in the formation of a meta-stable compound which is most likely the geminal bis-thiol **195** resulting from the addition of a molecule of hydrogen sulfide to the thioamide **194** (Scheme 84).[250,251] Thiocarbonyls are more reactive towards nucleophiles as the π-stabilization is reduced due to poorer orbital overlap created by the large size of the sulfur atom. The greater carbonyl reactivity and the good nucleophilicity of the sulfide anion are probably the reasons why this process can occur so readily.[252]

Scheme 84. Addition of excess hydrogen sulfide to thioamides to produce a meta-stable compound



194 **195**

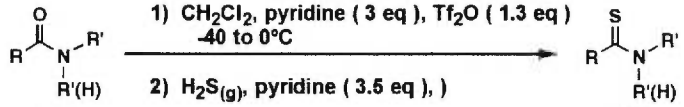
The meta-stable compound is visible on thin layer chromatography using short-wave ultra violet light just like the thioamides, but they are generally less polar. The instability of this compound has made its isolation and characterization very difficult. However, this instability also allows it to be readily converted back to the thioamide since the addition of the sulfide anion is reversible. By opening up the flask to the atmosphere in a well-ventilated fume hood and allowing the reaction to stir, one can facilitate the elimination of a molecule of hydrogen sulfide to give back to the desired thioamide. Making the reaction medium more basic by the addition of triethylamine or pyridine also seems to help this process by deprotonating the intermediate, thus further facilitating the elimination of hydrogen sulfide. Of course, the simplest way to avoid this problem is to be frugal with the addition of hydrogen sulfide.

7.3 Conversion of Secondary and Tertiary Amides to Thioamides

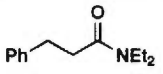
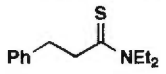
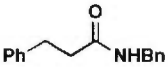
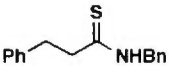
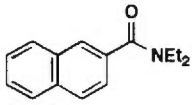
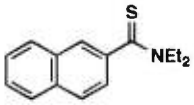
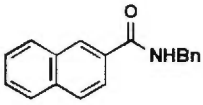
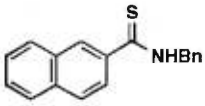
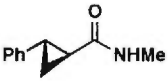
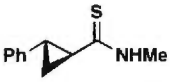
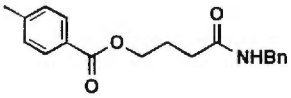
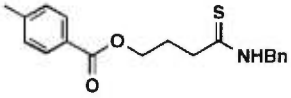
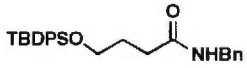
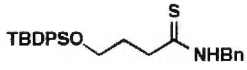
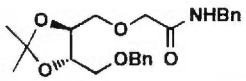
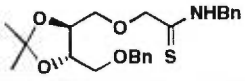
Various secondary and tertiary amides were converted to the corresponding thioamides and these results are summarized in Table 23. The imidoyl or iminium triflate is generated in the usual fashion. A minimum amount of hydrogen sulfide is then bubbled slowly into the reaction in a bolus fashion while the reaction is monitored by thin layer chromatography until judged complete. If too much hydrogen sulfide is added and some of the geminal dithiol product starts to appear, an excess of pyridine is added and the reaction is allowed to stir for at least several

hours in a well-ventilated fume hood until the thioamide is regenerated. Work-up is achieved by filtration through silica get followed by purification by flash chromatography.

Table 23. Synthesis of thioamides from secondary and tertiary amides via imidoyl and iminium triflates



196 **197**

Entry	Amide	Thioamide	Yield
a			92 %
b			94 %
c			96 %
d			95%
e			91 %
f			82 %
g			86 %
h			70 %

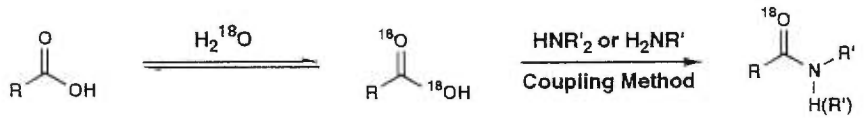
The method works well with secondary and tertiary amides of both aliphatic as well as aromatic acids (Entry a-d). *N*-Methyl-3-phenylcyclopropane carboxamide was readily converted to its thioamide (Entry e). Functional groups such as esters (Entry f), silyl ethers (Entry g),

acetonides and benzyl ethers (Entry h) are stable to these conditions as the amide can be converted to the thioamide in their presence. These reactions generally give good to excellent yields which are comparable with the best examples using Lawesson's reagent. Although Lawesson's reagent is well established as the method of choice, using triflates has the advantage that heating is not required.

7.4 ^{18}O-Labeled Amides

In an analogous fashion to the previously described method for the conversion of amides to thioamides by replacing the amide oxygen with a sulfur atom, the oxygen can also be replaced with an isotopically labeled oxygen atom. Incorporation of oxygen-17 and oxygen-18 atoms into amides is useful for analytical methods such as ^{17}O-NMR and mass spectroscopy. Existing methods for the synthesis of labeled amides require equilibrating the oxygen atoms of the parent acid with ^{18}O atoms (Scheme 85).[253]

Scheme 85. Incorporation of isotopic oxygen by equilibration with $H_2{}^{18}O$



198 **199** **200**

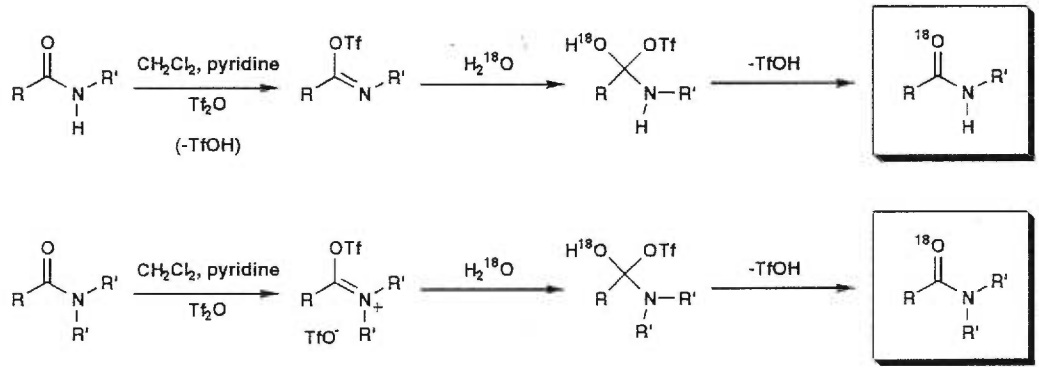
This equilibration is accomplished by dissolving the acid **198** in an excess of isotopically enriched $H_2{}^{18}O$. The labeled acid **199** is then isolated and coupled to the amine to form the ^{18}O-labeled amide **200**. Isotopic reagents such as $H_2{}^{18}O$ and $H_2{}^{17}O$ are extremely expensive and their price increases exponentially as a function of isotopic purity.[254] One inconvenience of this method is that a large excess of the water must be used to drive the equilibrium to ensure the maximum incorporation of isotopic oxygen. Furthermore, it is general practice is to recover the water

because its cost. After equilibration, however, the isotopic purity of the recovered water will have been diminished somewhat.

To the best of our knowledge, imino and iminium chlorides have not been hydrolyzed with isotopically labeled water to produce isotopically labeled amides. This may be due in part to the more rigorous conditions required to generate these compounds and that the excess chlorinating agent would have to be somehow removed or else it would also react with the water, thus increasing the amount of isotopically labeled water that is required.

Since the reactivity of H_2O is very similar to that of H_2S, we envisioned that by treating imidoyl and iminium triflates with $H_2{}^{18}O$, we could transform the amide to the ^{18}O-labeled amide (Scheme 86). Advantages of this method are that only a stoichiometric amount of water is required and that the transformation can be achieved in a single step from the unlabeled amide. These two factors allow for ready access to large quantities of these isotopically labeled compounds.

Scheme 86. Incorporation of isotopically labeled oxygen by the hydrolysis of imidoyl and iminium triflates



Mechanistically, this process is identical to the substitution of the triflate by hydrogen sulfide. Presumably, other nucleophilic heteroatoms capable of forming double bonds could also undergo these types of reactions with imidoyl and iminium triflates. One example would be the

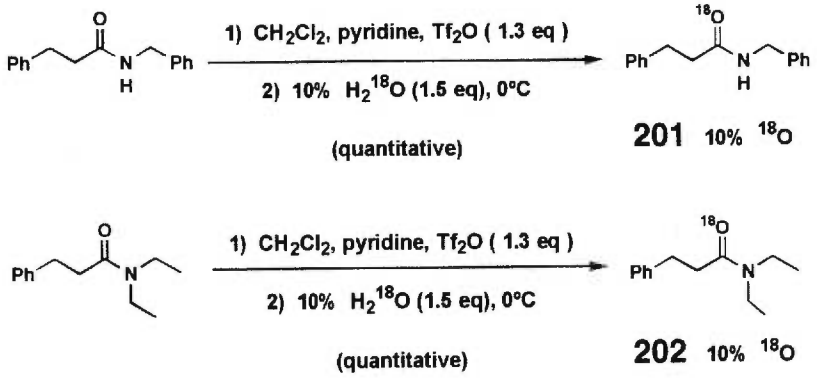
synthesis of amidines by treating imidoyl and iminium triflates with primary amines.

7.5 Synthesis of ^{18}O-labeled Amides via Imidoyl and Iminium Triflates

As expected, treatment of iminium and imidoyl triflates with near stoichiometric amounts of ^{18}O-enriched water resulted in the quantitative recovery of an amide (Scheme 87). A slight excess of $H_2{}^{18}O$ relative to triflic anhydride was used to ensure enough of the nucleophile was available. This reaction is very fast and indicates that the undesired hydrolysis of imidoyl and iminium triflates is a problem which warrants serious attention.

Using voltage regulated high resolution mass spectrometry, the isotopic purity of the amide was determined to be 10% which corresponds to the isotopic purity of the $H_2{}^{18}O$ used in the reaction. Furthermore, only a slight excess of the expensive and commercially available $H_2{}^{18}O$ was required. Therefore, in a one-pot, two step reaction, isotopic oxygen atoms can be statistically incorporated in to secondary and tertiary amides using stoichiometric amounts of $H_2{}^{18}O$.

Scheme 87. Incorporation of ^{18}O atoms into secondary and tertiary amides via imidoyl and iminium triflates



7.6 Conclusion

Imidoyl and iminium triflates react efficiently with H_2S and $H_2{}^{18}O$ to give thioamides and ^{18}O-labeled amides, respectively. Both secondary and tertiary amides undergo this reaction and various functional groups can tolerate the reaction conditions. This method provides a low temperature alternative to Lawesson's reagent for thioamide synthesis. Finally, because this method uses only stoichiometric amounts of isotopic water, this one pot synthesis of ^{18}O-labeled amides is more efficient than traditional methods. These examples with sulfur and oxygen should indicate that reactions with amines should readily give amidines and that other heteroatoms capable of forming double bonds will also react with these electrophilic intermediates in a similar fashion.

Part 2: Design of an Enantioselective Diels-Alder Catalyst.

Chapter 8: Enantioselective Synthesis of Biarylphenylglycines and Their Use as Chiral Ligands in the Lewis Acid Catalyzed Diels-Alder Reaction

CHAPTER 8

Enantioselective Synthesis of Biarylphenylglycines and Their Use as Chiral Ligands in the Lewis Acid Catalyzed Diels-Alder Reaction.[255]

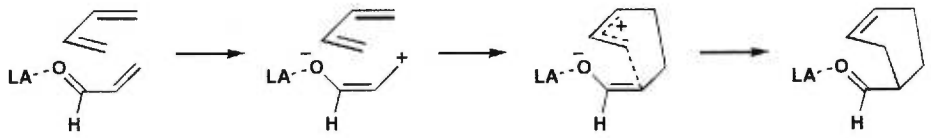
7.1 Introduction

The acceleration of some reactions by the addition of chiral Lewis acids is one of the most popular strategies used for the stereoselective synthesis of organic compounds. For example, numerous chiral Lewis acids are quite efficient at controlling the enantioselectivity of several transformations such as in the Diels-Alder, the hetero-Diels-Alder, the aldol, the ene, and conjugate addition reactions.[256] Among these, the Diels-Alder reaction has been extensively studied due to its powerful ability to form C-C bonds with very high levels of diastereoselectivity.[257] Furthermore, the Diels-Alder reaction is also one of the most popular testing grounds for chiral Lewis acids and is one of the most active fields in organic synthesis today.[258]

Traditionally, enantioselective processes with chiral catalysts are controlled through steric effects.[259] However, to improve upon selectivities, we felt additional elements, which are electronic in nature, could be added to the catalyst which would make the enantioselective reaction pathway even more favorable. According to Houk,[260] the lowest energy transition structure for the Lewis acid catalyzed Diels-Alder reactions is asynchronous (Scheme 88). In an asynchronous Diels-Alder

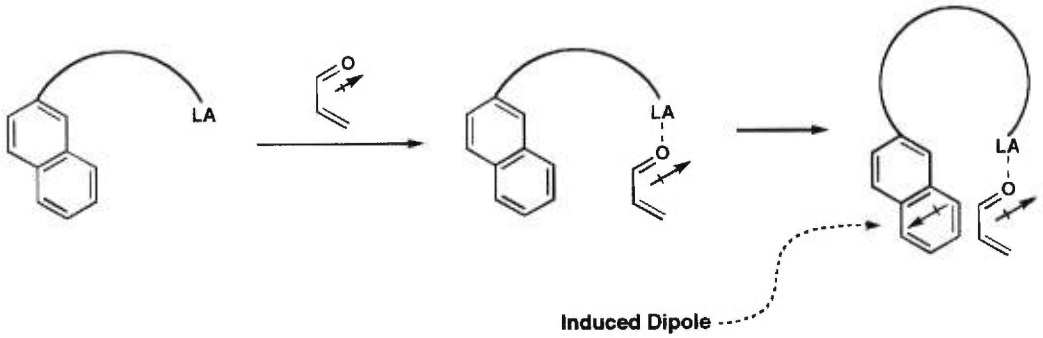
reaction, the key intermediates are the electron-deprived Lewis acid complexed dienophile and the transient, charge-separated, zwitterionic dienophile. Therefore, stabilization of these intermediates may have a catalytic effect by decreasing the energy requirements for the dienophile to be complexed to the Lewis acid.

Scheme 88. Lowest energy reaction pathway for the Diels-Alder reaction between acrolein and butadiene



Stabilization can occur via charge transfer as Corey has recently demonstrated by the design of several catalysts which operate through both charge transfer.[261] Furthermore, Hawkins[262] has recently demonstrated that the presence of polarizable groups increased enantioselectivities through a closer interaction of polarized groups between the catalyst and the dienophile (Scheme 89).

Scheme 89. Enhanced dipole-induced dipole effects



Presumably, enantioselectivities could increase due to a closer association of the steric blocking group and the reactive dienophile caused by the combined stabilization gained through charge transfer and enhanced dipole-induced dipole effects. We hoped that this could be

achieved by synthesizing ligands **203(a-d)** which incorporate a polarizable electron rich blocking group such as a naphthyl moiety (Figure 11). These ligands would then be used for the formation of catalysts **204(a-d)** which orient the naphthyl group in the vicinity of the Lewis acid-dienophile complex of an oxazaborolidine system.

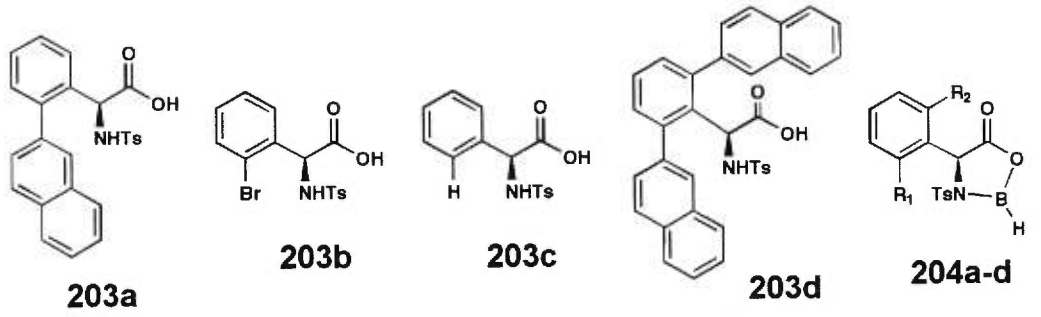
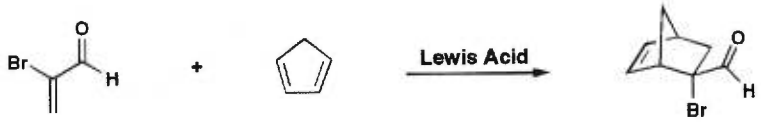


Figure 11. 2-Naphthalene as a polarizable and electron rich blocking group

Herein, we report our initial results on the design and synthesis of these chiral ligands based on the 2-arylphenylglycine framework and we disclose our preliminary results of their use as ligands for oxazaborolidine catalysts in the Diels-Alder reaction between cyclopentadiene and 2-bromoacrolein (Scheme 90).

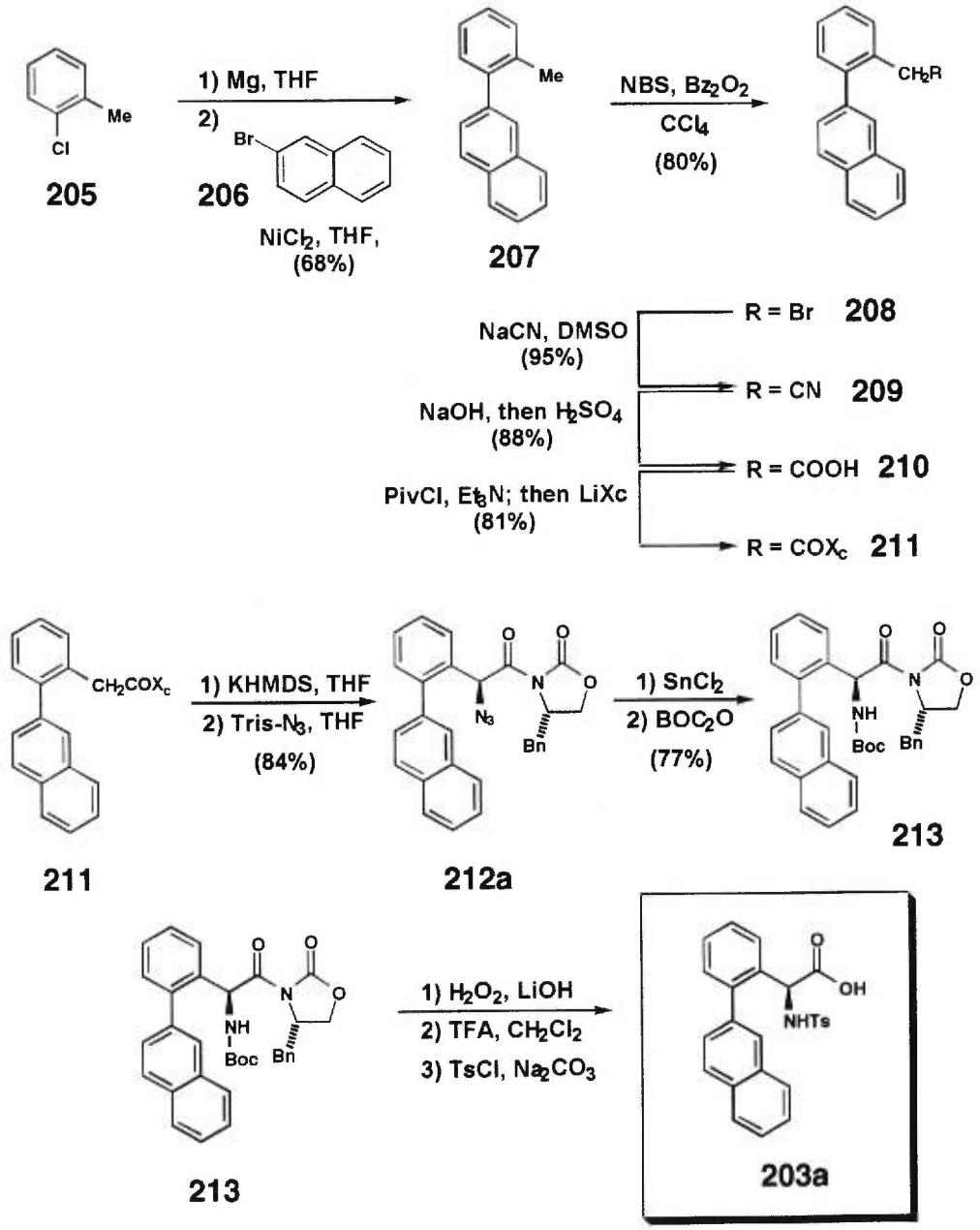
Scheme 90. Diels Alder reaction between 2-bromoacrolein and cyclopentadiene



7.2 Synthesis of Ligands

The synthesis of *N*-tosyl-2-(2-naphthyl)-phenylglycine **203a** started from a Kumada type coupling[263] between 2-chlorotoluene **205** and 2-bromonaphthalene **206**[264] (Scheme 91).

Scheme 91. Synthesis of *N*-tosyl-2-(2-naphthyl)-phenylglycine **203a**



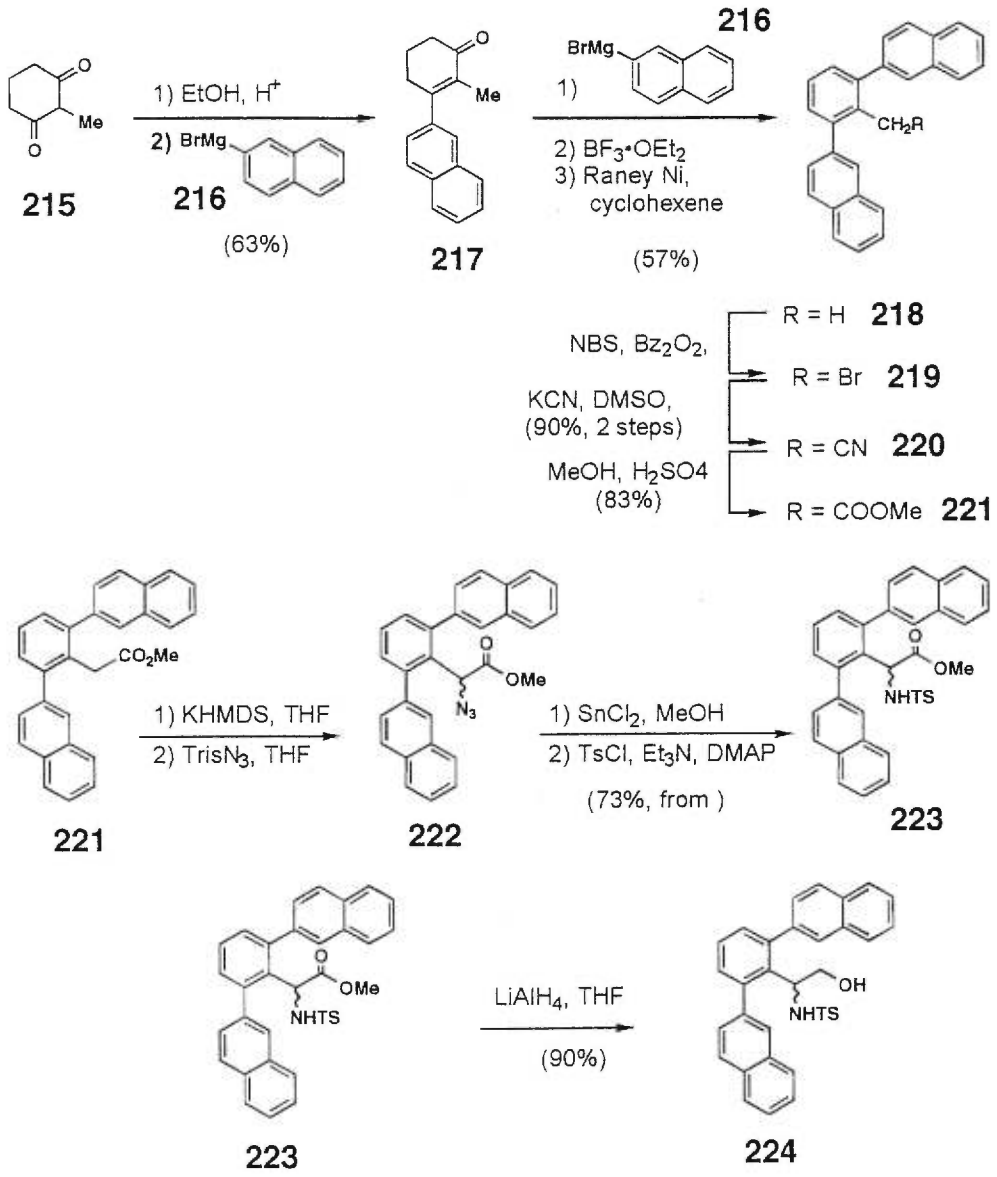
Radical bromination at the benzylic position of aromatic compound **207** gave the mono-bromide **208** along with a trace amount of di-brominated product.[265] The bromide **208** was displaced by cyanide in DMSO to produce the requisite nitrile **209**.[266] Hydrolysis of the nitrile to the acid **210** and installation of the Evan's auxiliary[267] produced the biaryl imide **211**. The subsequent electrophilic amination[268] proceeded with a diastereoselectivity of >49:1 (**212a**:**212b**) (96% ee). The diastereomeric azides were separated by flash chromatography and azide **212a** was reduced with tin (II) chloride to give the amine. Hydrolysis of the imide at this point resulted in the formation of numerous side products. Instead, the amine was protected as its BOC derivative **213** and then LiOOH[269] hydrolysis of the imide afforded the desired free acid. The BOC group was then removed with trifluoroacetic acid at room temperature and the crude amino acid was tosylated under Schotten-Baumann conditions to give the desired tosylated amino acid **203a** with an optical purity of 98% ee as determined by HPLC of the *N*-methyl benzamides (**214a** and **214b**).[270]

N-Tosyl amino acid **203b** was made in a similar manner to **203a**. Compound **203c** was prepared by the tosylation of phenylglycine under Schotten-Baumann conditions and then recrystallized from ether/hexanes.

The synthesis of non-racemic *N*-tosyl-2,6-bis(ß-naphthyl)phenylglycine **203d** could have begun with a double biaryl coupling of a 2,6-dihalo aromatic compound, but we found that such a coupling did not go to completion. To make matters worse, the incomplete reaction resulted in the contamination of the desired bis(naphthyl) derivative with mono-and unsubstituted starting materials. Since transition metal catalyzed couplings have been known to be difficult in the presence of *ortho* substituents,[271] the Woods approach was adopted to provide a clean synthesis of the triaryl moiety (Scheme 92).[272] 2-Naphthylmagnesium bromide **216**[273] was added to the monoethyl enol ether[274] **215a** of the commercially available 2-methyl-1,3-cyclohexanedione

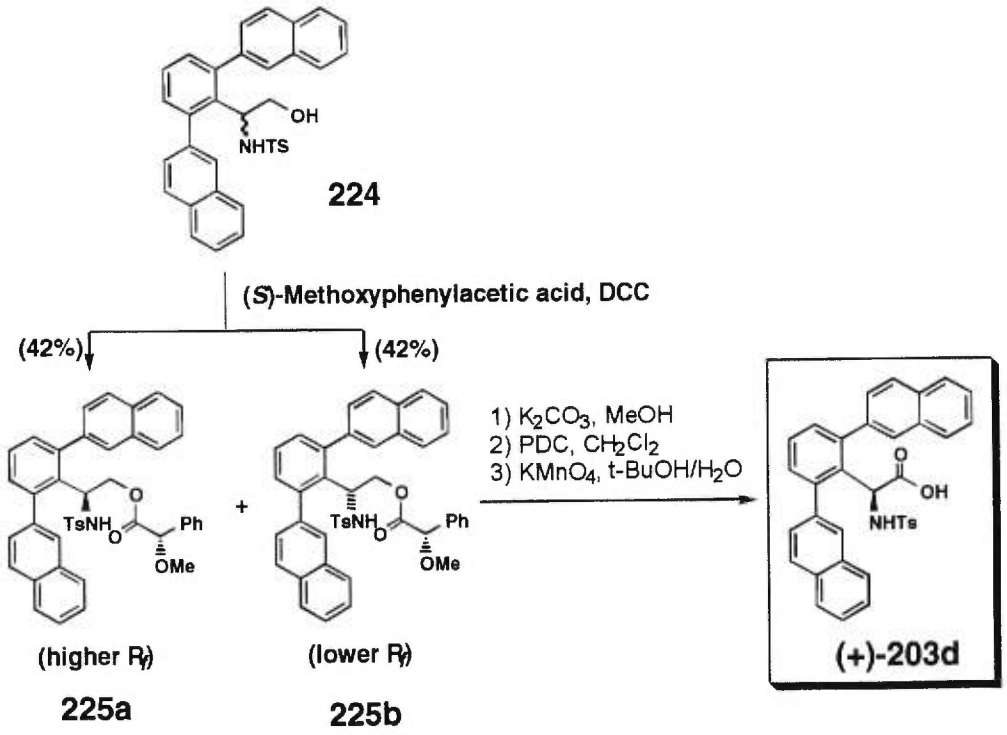
215[275] to furnish the α,β-unsaturated ketone **217**. The subsequent addition of 2-naphthylmagnesium bromide gave the tertiary alcohol which could be eliminated[276] to give the bis(naphthyl) cyclohexadiene. Transfer dehydrogenation with cyclohexene as a hydrogen acceptor gave 2,6-bis(2-naphthyl)toluene **218**. Purification by flash chromatography gave a compound which was free of any mono-naphthyl benzene products.

Scheme 92. Synthesis of *N*-tosyl-2,6-bis(ß-naphthyl)phenylglycinol

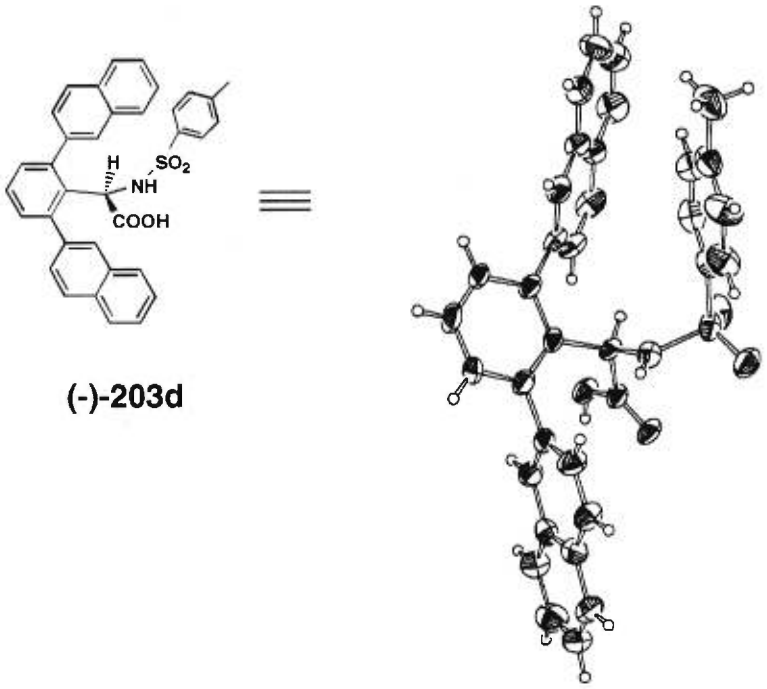


Functionalization of the hydrocarbon **218** proceeded by bromination using *N*-bromosuccinimide with benzoyl peroxide as a radical initiator. This gave the benzylic mono-bromide **219**. The bromide was converted to the nitrile **220** and then to the methyl ester **221** using methanol and sulfuric acid. Attempts to install the chiral auxiliary at this point failed presumably due to the steric constraints imposed by the pocket motif of the triaryl moiety. The synthesis was continued with racemic material by using potassium hexamethyldisilylamide to generate the enolate which was trapped with 2,4,6-triisopropylbenzenesulfonyl azide to furnish the racemic azide **222**. The azide was then reduced and tosylated to give **223**. Resolution of the racemic mixture was affected on the alcohol **224**. Reduction of the ester and coupling of the racemic alcohol **224** with *(S)*-2-methoxyphenylacetic acid gave a 1:1 mixture of diastereoisomers which were separated by flash chromatography (Scheme 93) and identified by x-ray crystallography.[277]

Scheme 93. Synthesis of *N*-tosyl-2,6-bis(ß-naphthyl)phenylglycine **203d**



The diastereomerically pure ester **225a** or **225b** was saponified and the alcohol was oxidized in a two-step procedure using PDC[278] and followed by Masamune's buffered $KMnO_4$ protocol.[279] The optical purity of **203d** was determined to be 94% ee indicating that partial racemization had occurred during the oxidation. An X-ray crystal structure of (-)-**203d** was obtained and it clearly shows the positioning of the two naphthyl groups (Figure 12).[280]



(-)-203d

Figure 12. ORTEP representation of (-)-*N*-tosyl-2,6-bis(ß-naphthyl) phenylglycine **203d**

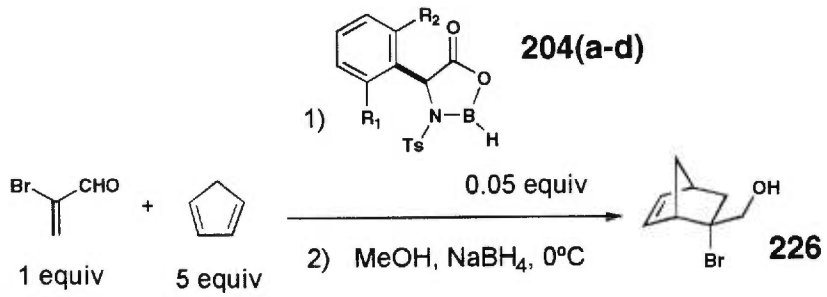
7.3 Results in the Diels Alder Reaction

The *N*-tosylated amino acids **203(a-d)** could be converted to the corresponding oxazaborolidine catalysts **204(a-d)** by treatment with BH_3•DMS in dichloromethane at room temperature for 2 hours. The

catalyst was then cooled to -78 °C and treated with 100 equivalents of freshly cracked cyclopentadiene and 20 equivalents of 2-bromoacrolein as called for in Corey's reports.[5] The Diels-Alder adduct was reduced to the alcohol **226** using sodium borohydride in methanol and analyzed by chiral GC. The results are summarized in Table 24.

Catalyst **204a** formed the Diels-Alder adduct with a selectivity of 88% ee favoring the *S* isomer. The Diels-Alder reactions catalyzed by **204b** and **204c** gave adducts with 77% ee and 83% ee and with the same sense of induction. This clearly indicated that the naphthyl group was not a necessary element for the selectivities observed with catalyst **204a**.

Table 24. Diels-Alder reaction promoted by catalysts **204(a-d)**



Catalyst	R_1 =	R_2 =	exo/endo	% ee (exo)	Absolute configuration
204a	2-naphthyl	H	98/2	88	*(S)*
204b	Br	H	98/2	77	*(S)*
204c	H	H	97/3	83	*(S)*
204d	2-naphthyl	2-naphthyl	87/13	50	*(R)*

A plausible transition state model could be derived based on those proposed by Helmchen and Yamamoto[4] and it requires the dienophile to be complexed to the Lewis acid in a s-*cis* conformation when the cycloaddition occurs (Figure 13).

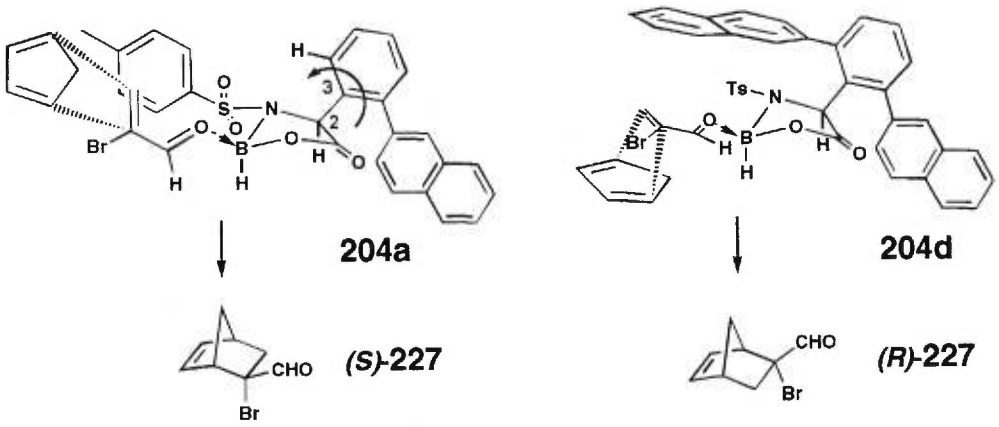


Figure 13. Proposed transition states for the Diels-Alder reaction

This prompted the design and synthesis of catalyst ligand **203d**. Catalyst **204d** has two naphthyl groups so one group will always project into the proximity of the Lewis acid/dienophile complex regardless of rotation around the C_2-C_3 bond. Catalyst **204d** promoted the formation of the Diels-Alder adduct in 50 %ee, but with the opposite sense of induction. This reversal of selectivity is a clear indication that the naphthyl group plays a large role in determining the sense of chiral induction. Although the synthesis is somewhat lengthy and the selectivities are lower that those reported with some other catalysts, these results have demonstrated that the 2,6-bis(2-naphthyl)phenyl motif projects a naphthyl group into the desired vicinity of space causing a strong effect on the transition state.

7.4 Conclusion

In conclusion, we have synthesized compounds **203(a-d)**. These compounds can be used for the formation of oxazaborolidine catalysts which can catalyze the Diels-Alder reaction. Compounds **203(a-c)** have essentially the same selectivities and the same sense of chiral induction which is an indication that the single naphthyl group of **203a** is not involved in the transition state. Catalyst **204d** has an additional naphthyl group and this catalyst produces the opposite enantiomer in the Diels-

Alder reaction. This catalyst has the naphthyl oriented within the proximity of the Lewis acid and this large aromatic moiety is involved in the transition state. Studies involving the design of second generation chiral Lewis acid catalysts possessing the 2,6-bis(2-naphthyl)benzene motif are under way and will be reported in due course.

Experimental Section

General Notes

Reaction, especially those involving triflic anhydride are very susceptible to moisture. All glassware was dried for several hours in a oven or flamed under argon and cooled under inert gas prior to use. Reagents were handled with a syringe. Generally, solvents and reagents were purified prior to use[281]. Some of the more often used are:

benzene	distilled over sodium under nitrogen
$BF_3 \bullet OEt_2$	distilled under argon
2,2-bishydroxy-methylene propanol	dried by Dean-Stark: stored over P_2O_5
dichloromethane	distilled over CaH_2 under N_2
DME	distilled over sodium under N_2
DMF	dried over molecular sieves
diethyl ether	distilled over sodium under N_2
ethanol	stored under N_2
hexane	distilled over CaH_2 under N_2
Hunig's base	dried over KOH
2,6-lutidine	dried over KOH
methanol	stored under N_2
pyridine	distilled over CaH_2: stored over KOH
tetrahydrofuran	distilled over sodium under N_2
toluene	distilled over sodium under N_2
triethylamine	distilled over CaH_2: stored over KOH
triflic anhydride	distilled over P_2O_5: refrigerated under N_2

Other reagents or solvents of reagent grade or better could be used as received, but judgement must be used as to the quality and consequences of using slightly impure chemicals. Reported yields refer to

products isolated after purification by flash chromatography, distillation or crystallization and placed under high vacuum until there is no more loss on evaporation.

Thin layer chromatography (TLC) was done with commercially available glass fluorescence indicator impregnated silica gel plates (E. Merck Science 5715 F_{254}) which were stored over Drierite© prior to use. After elution, the TLC plates were subject to revelators such as aqueous $KmnO_4$, aqueous ceric ammonium sulfate, aqueous 2,4-dintrophenyl hydrazine, phosphomolybdic acid in EtOH, *p*-anisaldehyde in EtOH, or iodine on silica gel. The relative mobility factor (R_f) is indicated. Flash chromatography was done using E. Merck Science 9385 or Silicycle 230-240 mesh (40-63 μm) silica gel[282]. Preparative thin layer chromatography was done with commercially available glass fluorescence indicator impregnated silica gel plates (E. Merck Science 13792 PSC Fertigplatten Kieselgel 60 F_{254}).

Melting points were measured on a Buchi Schmelzpunktbestimmungsapparat and are uncorrected. Infrared spectra were taken on a Perkin Elmer 781 spectrophotometer, Harmann & Braun Biomem 100 FTIR, or ATI Mattson Genesis Series FTIR between two NaCl plates for oils and in the form of a KBr pellet for solid compounds. The major absorption bands are expressed in cm^{-1}. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at the 589 nm (Sodium D line) wavelength unless otherwise specified. All measurements were taken at ambient temperature and the specific rotation (° ml/g•dm) is given followed by the concentration in g/100 ml in the specified solvent. Elemental analyses were done at the Laboratoire d'Analyse Élémentaire de l'Université de Montréal on samples which were re-purified, recrystallized or fractionally redistilled and submitted to high vacuum (< 0.2 mmHg) for at least 24 hours prior to analysis. Low and high-resolution mass spectroscopy was done at the Centre Régional de Spectrométrie de Masse

at l'Université de Montréal. Low-resolution mass spectra were taken on a Autospec Vg. The high-resolution mass spectra were determined on a MS-50 Kratos subsequently to chemical ionization (CI), electron ionization (EI), or "Fast Atom Bombardment" (FAB). Single crystal x-ray diffraction analyses were taken by the Laboratoire de Diffraction des Rayons X de l'Université de Montréal using a Enraf-Nonius CAD-3 or CAD-4 instrument. Further details are given in the appropriate appendix for the crystal in question.

The nuclear magnetic resonance spectra for ^{1}H, ^{13}C, ^{19}F, and ^{11}B were taken on a Bruker AMX-300 (300 MHz and 75 MHz) or a Bruker ARX-400 (400 MHz and 100 MHz). All the chemical shifts are expressed in parts per million (ppm) with reference to an internal standard provided by tetramethylsilane (TMS), residual non-deuterated solvent. The analysis of the NMR spectra are presented in a format specified by the chemical shift followed by parentheses enclosing the multiplicity of the system, coupling constants, integration and the assignment of the system. All the systems are analyzed to the first approximation as first order systems. As needed, the complete assignments are accomplished by COSY and HQMC experiments. All ratios evaluated by NMR methods were determined using quantitative accumulation and a standard Fourrier transform without Gaussian or Exponential enhancement.

Analyses by gas chromatography were accomplished by using a Hewlett Packard 5890 Series II capillary gas chromatograph equipped with a flame ionization detector. The injector temperatures were 250°C; the column head pressure was 25 psi and the total flow of carrier gas (helium) was adjusted to 2 ml/min. The samples were injected into the chromatograph in "split" mode. The column and temperature parameters are specified along with the retention times. High performance liquid chromatography was accomplished using a Waters Millipore 600E HPLC system using a Waters 486 UV detector at the specified wavelength.

Solvents used were HPLC grade and were filtered on a Supleco 0.45 micron membrane prior to use.

Experimental Section: Chapter 2

N-Phenyl benzamide (48).

48

According to the method of Bosnich[283], a suspension of aniline (16.3g, 175 mmol) in CH_2Cl_2 (300 ml) and pyridine (15.7 ml, 193 mmol) was cooled to -78°C. Benzoyl chloride (20.3 ml, 175 mmol) was then added slowly giving a white suspension. The reaction was stirred while warming up to room temperature slowly. EtOAc (500 ml) was added and the reaction was washed with 10% HCl (2 X 100 ml), saturated $NaHCO_3$ (100 ml), dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was crystallized from MeOH, filtered, and then placed under high vacuum until a constant mass was observed. The mother liquor was concentrated under reduced pressure and the crude product was crystallized from MeOH to give a second batch. The two batches were then combined to give 32.91 g (95.4%) of amide **48** as white crystals; R_f 0.39 (1:3 EtOAc/hexane); mp 162-164°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br, 1H, N*H*), 7.85 (m, 2H, Ph), 7.65-7.62 (m, 2H, Ph), 7.53-7.51 (m, 1H, Ph), 7.48-7.44 (m, 2H, Ph), 7.38-7.34 (m, 2H, Ph), 7.16-7.13 (m, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.9, 134.9, 131.7, 129.0, 128.7, 127.0, 124.5, 120.2; IR (KBr) ν 3340, 1660, 1600, 1580, 1530, 1450, 1440, 1320, 1260, 750, 720, 690 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{12}NO$ $[M+H]^+$: 198.09189, found: 198.09280.

N-Benzoyl-N-phenyl-N′-phenyl benzamidine (50).

48 **50**

A suspension of *N*-phenyl benzamide **48** (225 mg, 1,14 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -30°C. Triflic anhydride (192 µl, 1.14 mmol) was then slowly added and the reaction was allowed to warm up slowly to 0°C over the course of 3 hours or until which time the reaction was judged complete by TLC. The reaction was diluted with ether, washed with 10% HCl (2 X 25 ml), once with saturated $NaHCO_3$ (25 ml) and then dried over Na_2SO_4 before being concentrated under reduced pressure. The crude residue was purified by flash chromatography (1:5 EtOAc/hexanes) to give 141 mg (66%) of amidine **50** as a white solid. Crystallization of amidine **50** from ether/hexanes gave crystals which were suitable for x-ray analysis[284]; R_f 0.52 (1:3 EtOAc/hexane); mp 180-182°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (br, 2H, Ph), 7.46-7.30 (m, 6H, Ph), 7.20-6.72 (m, 12H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 140.9, 135.7, 131.3, 131.2, 131.0, 129.8, 129.7, 129.2, 128.7, 128.6, 128.1, 127.9, 127.3, 127.0, 126.7, 125.8, 125.7, 124.9, 124.3, 123.2, 120.4, 120.0; IR (KBr) ν 1650, 1620, 1590, 1580, 1450, 1310, 1140, 1080 cm^{-1}; LRMS (EI) calcd for $C_{26}H_{20}N_2O$ $[M+H]^+$: 377.16539, found: 377.1. For x-ray crystal data, see Appendix 1.

3-Phenylpropanamide (55).

55

To a solution of 3-phenyl propanoic acid (5 g, 33.3 mmol) in CH_2Cl_2 (100 ml) was added thionyl chloride (3.2 ml, 43.3 mmol) and DMF (4drops). The reaction was fitted with an exit bubbler and was refluxed until the evolution of gas ceased. The solution was allowed to cool to room temperature and then transferred to a dropping funnel. The acid chloride was slowly added to concentrated ammonium hydroxide (5 ml) at 0°C. After 15 minutes, a TLC analysis indicated that the reaction was complete. The reaction was diluted with a mixture of EtOAc/ether (150 ml), washed with water (50 ml), 10% HCl (2 X 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was crystallized from EtOAc/hexanes to give 4.91 g (98%) of amide **55** white solid; R_f 0.21 (2:1 EtOAc/hexane); mp 98-100°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H, Ph), 6.42 (br, 1H, N*H*), 5.99 (br, 1H, N*H*), 2.94 (t, *J* = 7 Hz, 2H, Ph$CH_2$$CH_2$), 2.50 (t, *J* = 7 Hz, 2H, $CH_2$$CH_2$CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 140.5, 128.3, 128.0, 126.0, 37.2, 31.1; IR (KBr) ν 3390, 3190, 1640, 1570, 1410 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{11}NO$ $[M+H]^+$: 150.09189, found: 150.09280.

3-Phenyl propanitrile (56).

55 **56**

A solution of amide **55** (128 mg, 0.86 mmol) in CH_2Cl_2 (5 ml) and pyridine (180 µl, 2.15 mmol) was cooled to -30°C. Triflic anhydride (190 µl, 1.11 mmol) was then added very slowly and the reaction was allowed to warm up to 0°C while stirring and then kept at 0°C for 4 hours. The reaction was diluted with ether (75 ml), washed with 10% HCl (2 X 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced

pressure. Purification of the crude product by flash chromatography (1:10 EtOAc/hexanes) yielded 110 mg (98%) of nitrile **56** as a colourless oil; R_f 0.24 (1:10 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 5H, Ph), 2.93 (t, *J* = 7 Hz, 2H, Ph$CH_2$$CH_2$), 2.59 (t, *J* = 7 Hz, 2H, CH_2CH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.7, 128.1, 127.0, 119.0, 31.4, 19.1; IR (neat) ν 3020, 2940, 2240, 1500, 1440, 1420, 1080 cm^{-1}; HRMS (EI) calcd for C_9H_9N $[M]^+$ 131.07350, found 131.07327.

(±)-*N*-(1-phenylethyl)-3-phenylpropanamide (57).

57

To a solution of 3-phenyl propanoic acid (3.68 g, 24.5 mmol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (2.6 ml, 29.4 mmol) and DMF (4 drops). The reaction was fitted with a exit bubbler and was refluxed until no more gas evolved. The crude reaction was concentrated under reduced pressure and then diluted in CH_2Cl_2 (100ml). The solution was cooled to –78°C and then racemic 1-phenyl ethylamine (4.1 ml, 31.9 mmol) was added slowly followed by triethylamine (5.1 ml, 36.7 mmol). The solution was allowed to warm up to room temperature over the course of several hours. The reaction was diluted with ether (200 ml) and washed with 10% HCl (2 X 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 5.96 g (96%) of amide **57** as a colourless oil; R_f 0.35 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (m, 10H, Ph), 5.85 (d, *J* = 6 Hz, 1H, N*H*), 5.08 (dt, *J* = 6 Hz, 7 Hz, 1H, NHC*H*(CH_3)Ph), 2.95, (t, *J* = 7 Hz, 2H, Ph$CH_2$$CH_2$), 2.46 (t, *J* = 7 Hz, 2H, CH_2CH_2CO), 1.39 (d, *J* = 7 Hz, 3H, CH_3CHPh); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 171.0, 143.0, 140.7, 128.4, 128.4, 128.3, 127.1, 126.1, 126.0, 48.4, 38.4, 31.6, 21.5; IR (neat) ν 3300, 3040, 1640, 1540, 1450 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.15450, found: 251.15590.

3-Phenyl propanitrile (58).

57 **58**

A solution of amide **57** (205 mg, 0.81 mmol) in CH_2Cl_2 (5 ml) and pyridine 170 µl, 2.03 mmol) was cooled to –30°C. Triflic anhydride (180 µl, 1.050 mmol) was slowly added and the reaction was allowed to stir while warming up to 0°C after which, stirring was continued for 4 hours at 0°C. The reaction was diluted with ether (75 ml), washed with 10% HCl (2 X 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 104 mg (98%) of nitrile **58** as a colourless oil; refer to nitrile **56** for characterization data.

Experimental Section: Chapter 3

N,N-Diethyl-3-phenylpropanamide (88a).

88a

To a solution of hydrocinnamic acid (2.45 g, 16 mmol) in dichloromethane (50 ml) was added thionyl chloride (1.5 ml, 21 mmol). The reaction was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane (100 ml) and cooled to -78°C in an acetone/dry ice bath. *N,N*-diethyl amine (2.2 ml, 21 mmol) was added slowly to the solution followed by pyridine or triethylamine (3.4 ml, 24.5 mmol) which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After several hours at room temperature, the reaction was diluted with diethyl ether (150 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 3.18 g (95%) of amide **88a** as a colourless oil; R_f 0.39 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H, aromatic), 3.38 (q, J = 7 Hz, 2H, NCH_2CH_3), 3.21 (q, J = 7 Hz, 2H, NCH_2CH_3), 2.96 (t, J = 8 Hz, 2H, $PhCH_2CH_2$), 2.59 (t, J = 8 Hz, 2H, CH_2CH_2CO), 1.31 (t, J = 7 Hz, 3H, NCH_2CH_3), 1.28 (t, J = 7 Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.4, 128.3, 128.2, 125.9, 41.7, 40.0, 34.9, 31.5, 14.1, 12.9; IR

(neat) ν 2970, 1640, 1450, 1430 cm^{-1}; HRMS (THIO) calcd for $C_{13}H_{20}NO$ $[M+H]^+$ 206.14670, found 206.15450.

N-Pyrrolidinyl-3-phenylpropanamide (88b).

88b

Hydrocinnamic acid (3.09 g, 22.7 mmol) was converted to *N*-pyrrolidinyl-3-phenylpropanamide **88b** following the same procedure as that used for the synthesis of *N,N*-Diethyl-3-phenylpropanamide **88a**. Purification of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 4.01 g (96%) of amide **88b** as a colourless oil ; R_f 0.28 (1:1 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 5H, aromatic), 3.46 (t, *J* = 7 Hz, 2H, NCH_2CH_2), 3.28 (t, *J* = 7 Hz, 2H, NCH_2CH_2), 2.99 (t, *J* = 8 Hz, 2H, $PhCH_2CH_2$), 2.55 (t, *J* = 8 Hz, 2H, CH_2CH_2CO), 1.92-1.76 (m, 4H, -$CH_2CH_2CH_2CH_2$-); ^{13}C NMR (100 MHz, CDC_{13}) δ 170.4, 141.3, 128.2, 128.1, 125.8, 46.3, 45.4, 36.5, 31.0, 25.8, 24.1; IR (neat) ν 3500 (br), 2970, 2880, 1640, 1440, 1340 cm^{-1}; HRMS (THIO) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.13920, found 204.13884.

N,N-Diisopropyl-3-phenylpropanamide (88c).

88c

To a solution of hydrocinnamic acid (501 mg, 2.0 mmol) in dichloromethane (20 ml) was added oxalyl chloride (190 µl, 2.2 mmol) and 2 drops of DMF. The flask was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane (20 ml) and cooled to -78°C in an acetone/dry ice bath under an argon atmosphere. *N,N*-diisopropyl amine (360 µl, 2.4 mmol) was added slowly to the solution followed by triethylamine (360 µl, 2.6 mmol) which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After several hours at room temperature, the reaction was diluted with diethyl ether (150 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 715 mg (92%) of amide **88c** as a colourless oil; R_f 0.43 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H, aromatic), 3.92 (br, 1H, NC*H*Me$_2$), 3.49 (br, 1H, NC*H*Me$_2$), 2.96 (t, *J* = 8 Hz, 2H, PHC*H*$_2$CH$_2$), 2.56 (t, *J* = 8 Hz, 2H, CH$_2$C*H*$_2$CO), 1.38 (d, *J* = 7 Hz, 3H, NCH(C*H*$_3$)$_2$), 1.12 (d, *J* = 7 Hz, 3H, NCH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 141.6, 128.4, 128.3, 125.9, 48.1, 45.5, 37.0, 31.6, 20.8, 20.6; IR (neat) ν 2980, 1640, 1440, 1370, 1320, 1210, 1130, 1040 cm^{-1}; HRMS (NBA) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 234.18579, found 234.18630.

***N,N*-Dimethyl-3-phenylpropanamide (88d).**

88d

Hydrocinnamic acid (500 mg, 2.0 mmol) was converted to *N,N*-dimethyl-3-phenylpropanamide **88d** following the same procedure as that used for the synthesis of *N,N*-diisopropyl-3-phenylpropanamide **88c**. Purification of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 570 mg (97%) of amide **88d** as a colourless oil; R_f 0.10 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H, Ph), 2.94 (t, J = 7 Hz, 2H, PhCH_2CH_2), 2.93 (s, 3H, CH_3N), 2.91 (s, 3H, CH_3N), 2.60 (t, J = 7 Hz, 2H, CH_2CH_2CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 141.4, 128.4, 128.3, 126.0, 37.0, 35.3, 35.1, 31.3; IR (neat) ν 2940, 1650, 1500, 1450, 1400, 1140, 750 cm^{-1}; HRMS (THIO) calcd for $C_{11}H_{16}NO$ $[M+H]^+$ 178.12318, found 178.12240.

***N,N*-Diethyl phenylacetamide (88e).**

88e

Phenylacetic acid (4.0 g, 29 mmol) was converted to *N,N*-diethyl-phenylacetamide **88e** following the same procedure as that used for the synthesis of *N,N*-Diethyl-3-phenylpropanamide **88a**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 5.2 g (93%) of amide **88e** as a colourless oil; R_f 0.30 (1:2

EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H, aromatic), 3.69 (s, 2H, PhCH_2CO), 3.39 (q, *J* = 7 Hz, 2H, N$CH_2$$CH_3$), 3.29 (q, *J* = 7 Hz, 2H, N$CH_2$$CH_3$), 1.12 (t, *J* = 7 Hz, 3H, NCH$_2$$CH_3$), 1.08 (t, *J* = 7 Hz, 3H, NCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 135.3, 128.4, 128.3, 126.4, 42.1, 40.7, 39.9, 14.0, 12.7; IR (neat) ν 2970, 1640, 1460, 1370, 1130 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.13884, found 192.13850.

_N,N_-Diethyl-2-naphthamide (90a).

90a

To a solution of naphthoyl chloride (2.1 g, 11 mmol) in dichloromethane (50 ml) under an argon atmosphere was slowly added triethylamine (2 ml, 14.3 mmol) and *N,N*-diethyl amine (1.37 ml, 13.2 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional hour. The reaction was diluted with diethyl ether (250 ml) washed with 10% HCl (2 x 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 2.49 g (97%) of amide **90a** as a colourless oil; R_f 0.34 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.80 (m, 4H, aromatic), 7.60-7.40 (m, 3H, aromatic), 3.60 (br, 2H, N$CH_2$$CH_3$), 3.30 (br, 2H, N$CH_2$$CH_3$), 1.25 (br, 6H, NCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 134.6, 133.3, 132.7, 128.2, 128.1, 127.7, 126.7, 126.5, 125.7, 123.9, 43.3, 39.3, 14.1, 12.9; IR (neat) ν 2980,, 1630, 1480, 1420, 1290, 1080, 810, 750 cm^{-1}; HRMS (THIO) calcd for $C_{15}H_{18}NO$ $[M+H]^+$ 228.13884, found 228.13990.

***N,N*-Diethyl cinnamide (90b).**

90b

Cinnamic acid (3.88 g, 26.2 mmol) was converted to *N,N*-diethyl-3-cinnamide **90b** following the same procedure as that used for the synthesis of *N,N*-diisopropyl-3-phenylpropanamide **88c**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 5.0 g (94%) of amide **90b** as a colourless oil; R_f 0.36 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 15 Hz, 1H, PhCHC*H*CO), 6.83 (d, *J* = 15 Hz, 1H, PhC*H*CH), 7.54-7.33 (m, 5H, aromatic), 3.49 (q, *J* = 7 Hz, 2H, NCH_2CH$_3$), 3.47 (q, *J* = 7 Hz, 2H, NCH_2CH$_3$), 1.26 (t, *J* = 7 Hz, 3H, NCH$_2$CH_3), 1.19 (t, *J* = 7 Hz, 3H, NCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 142.1, 135.3, 129.3, 129.1, 128.7, 128.6, 128.4, 127.6, 117.6, 42.1, 40.9, 14.9, 13.0; IR (neat) ν 3500, 2990, 1650, 1600, 1450, 1430, 1240, 1140 cm^{-1}; HRMS (THIO) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.13920, found 204.13884.

***N,N*-Diethyl-2-methylcinnamide (90c).**

90c

2-Methylcinnamic acid (1.78 g, 10.9 mmol) was converted *N,N*-diethyl-2-methylcinnamide **90c** following the same procedure as that used for the synthesis of *N,N*-diisopropyl-3-phenylpropanamide **88c**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 2.33 g (98%) of amide **90c** as a colourless oil; R_f 0.39 (1:2

EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H, aromatic), 6.50 (d, *J* = 1 Hz, 1H, PhC*H*CCH$_3$), 3.43 (q, *J* = 7 Hz, 4H, NC*H*$_2$CH$_3$), 2.10 (d, *J* = 1 Hz, 3H, PhCHCC*H*$_3$), 1.19 (t, *J* = 7 Hz, 3H, NCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 136.1, 133.9, 128.9, 128.2, 128.0, 127.1, 42.7, 38.7, 16.1, 12.7; IR (neat) ν 2990, 1630, 1425, 1380, 1280, 1100 cm^{-1}.

_N,N_-Diethyl-2-methyl-3-phenylpropanamide (90d).

90c **90d**

To a solution of *N,N*-Diethyl-2-methylcinnamide **90c** (78 mg, 0.33 mmol) in MeOH (4 ml) was added sodium borohydride (32 mg, 0.84 mmol) followed by $NiCl_2 \bullet H_2O$ (16 mg, 0.07 mmol) according to the method of Satoh *et al.*[285] The flask was connected to an exit bubbler and the reaction was allowed to stir at room temperature for 24 hours or until HNMR analysis of an aliquot indicated that the reaction was complete. The reaction was quenched carefully with 10% HCl (2 ml) and diluted with diethyl ether (50 ml). The organic phase was washed dried over Na_2SO_4 and filtered over celite to remove any fine black particles which were formed in the reaction. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 78 mg (99%) of amide **90d** as a colourless oil; R_f 0.29 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H, aromatic), 7.20-7.16 (m, 3H, aromatic), 3.42 (dq, *J* = 14 Hz, 7 Hz, 1H, NC*H*$_2$CH$_3$), 3.20 (dq, *J* = 14 Hz, 7 Hz, 1H, NC*H*$_2$CH$_3$), 3.12-2.99 (m, 3H, NC*H*$_2$CH$_3$ and PhC*H*$_2$CH), 2.87 (m, 1H, CH$_2$C*H*(CH$_3$)CO), 2.64 (dd, *J* = 13 Hz, 6 Hz, 1H, PhC*H*$_2$CH), 1.17 (d, *J* = 7 Hz, 3H, CHC*H*$_3$), 1.03 (t, *J* = 7 Hz, 3H, NCH$_2$C*H*$_3$), 0.98 (t, *J* = 7 Hz, 3H, NCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 140.2, 129.0, 128.1, 126.0, 41.5, 40.7, 40.3, 38.0, 18.2, 14.5,

12.9; IR (neat) ν 3450, 2960, 1640, 1450, 1370, 1250, 1210, 1130, 1070 cm^{-1}; HRMS (NBA) calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.17014, found 220.16870.

_N,N_-Diethyl-4-nitrobenzamide (90e).

90e

To a solution of 4-nitrobenzoyl chloride (1.4 g, 7.5 mmol) in dichloromethane (10 ml) under an argon atmosphere was slowly added triethylamine (1.4 ml, 9.8 mmol) and *N,N*-diethyl amine (940 µl, 13.2 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional hour. The reaction was diluted with diethyl ether (100 ml) washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 1.65 g (98%) of amide **90e** as a yellowish oil which gave a very low melting solid on standing; R_f 0.17 (1:2 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8 Hz, 2H, aromatic), 7.55 (d, *J* = 8 Hz, 2H, aromatic), 3.57 (q, *J* = 7 Hz, 2H, NCH_2CH_3), 3.21 (q, *J* = 7 Hz, 3H, NCH_2CH_3), 1.27 (t, *J* = 7 Hz, 3H, NCH_2CH_3), 1.13 (t, *J* = 7 Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 148.0, 143.3, 127.2, 123.7, 43.2, 39.4, 14.1, 12.7; IR (neat) ν 2970, 1630, 1600, 1515, 1350, 1290 cm^{-1}; HRMS (NBA) calcd for $C_{11}H_{15}N_2O_3$ $[M+H]^+$ 223.10826, found. 223.10860.

***N,N*-Dimethyl-2-methyl-3-phenylpropanamide (90f).**

90f

To a solution of 2-methyl-3-phenyl propanoic acid (1.03 g, 6.3 mmol) in dichloromethane (20 ml) was added oxalyl chloride (640 µl, 7.3 mmol) and three drops of DMF. The flask was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane (20 ml) and cooled to -78°C in an acetone/dry ice bath under an argon atmosphere. Pyrollidine (680 µl, 8.2 mmol) was added followed by pyridine (670 µl, 8.2 mmol) which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After stirring overnight at room temperature, the reaction was diluted with diethyl ether (150 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 1.21 g (89%) of amide **90f** as a colourless oil; R_f 0.16 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H, aromatic), 3.44-3.34 (m, 2H, NCH_2CH_2), 3.31-3.24 (m, 1H, NCH_2CH_2), 3.01-2.90 (m, 2H, $PhCH_2CH$ and NCH_2CH_2), 2.84-2.72 (m, 1H, $PhCH_2CH$), 2.67-2.61 (m, 1H, CH_2CHCH_3), 1.84-1.62 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.16 (d, J = 6.6 Hz, 3H, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 140.1, 128.8, 128.1, 126.0, 46.1, 45.4, 10.5, 40.3, 25.8, 24.1, 17.2; IR (neat) ν 3500, 2960, 2880, 1640, 1430, 1340, 720, 690 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}NO$ $[M]^+$ 217.14667, found. 217.14609.

***N,N*-Dimethyl-2-methyl-3-phenylpropanamide (90g).**

90g

To a solution of 2-methyl-3-phenyl propanoic acid (2.09 g, 12.7 mmol) in dichloromethane (20 ml) was added oxalyl chloride (1.33 ml, 15.3 mmol) and several drops of DMF. The flask was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane (20 ml) and cooled to -78°C in an acetone/dry ice bath under an argon atmosphere. Excess *N,N*-dimethyl amine was added which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After stirring overnight at room temperature, the reaction was diluted with diethyl ether (150 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 1.194 g (79%) of amide **90g** as a colourless oil; R_f 0.29 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H, aromatic), 2.98 (m, 2H, PhCH_2CH), 2.87 (s, 3H, CH_3N), 2.78 (s, 3H, CH_3N), 2.63 (m, 1H, CH_2CHCO), 1.13 (d, J = 6 Hz, 3H, CH_3CHCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 140.0, 128.7, 128.0, 125.9, 40.3, 37.6, 36.7, 35.3, 17.3; IR (neat) ν 2940, 2980, 1640, 1490, 1450, 1390, 1140, 1100, 1070 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.13884, found. 192.13950.

Ethyl 3-phenylpropanoate (89a).

88a **89a**

General procedure for the conversion of tertiary amides to ethyl or methyl esters. To a solution of the amide (205 mg, 1.0 mmol) in dry dichloromethane (5 ml) was added 2.5 equivalents of dry pyridine (205 µl, 2.5 mmol). The solution was cooled to -30°C using an acetone-dry ice bath and then 1.3 equivalents of neat triflic anhydride (220 µl, 1.3 mmol) was added slowly down the side of the flask (alternatively, triflic anhydride can be added via cannula as a pre-cooled solution in dichloromethane). The solution can become somewhat heterogeneous, but as the solution is stirred and allowed to warm up slowly to 0°C, the solution becomes homogeneous. The temperature is maintained at 0° for 6 to 12 hours. Absolute ethanol (2 ml, > 33 mmol) was then added to the solution at 0°C and then the reaction was stirred for and additional 4 hours at room temperature. Diethyl ether (80 ml) was then added and then the solution was washed 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. HNMR analysis of the crude product indicated >96% conversion and purification by flash chromatography (1:20 ethyl acetate/hexanes) yielded 168 mg (94%) of ethyl ester **89a** as a colourless oil; R_f 0.55 (1:20 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H, aromatic), 4.12 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 2.95 (t, *J* = 7 Hz, 2H, $PhCH_2CH_2$), 2.61 (t, *J* = 7 Hz, 2H, CH_2CH_2CO), 1.23 (t, *J* = 7 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 140.5, 128.4, 128.2, 126.1, 60.3, 35.8, 30.9, 14.1; IR (neat) ν 2950, 1740, 1500, 1450, 1370, 1150, 1030 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{15}O_2$ $[M+H]^+$ 179.10721, found 179.10690.

Ethyl 3-phenylpropanoate (89b).

88b **89b**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **88b** to ester **89b**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded (85%) of ethyl ester **89b** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl 3-phenylpropanoate (89c).

88c **89c**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **88c** to ester **89c**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded (84%) of ethyl ester **89c** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl 3-phenylpropanoate (89d).

88d **89d**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **88d** to ester **89d**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded (90%) of ethyl ester **89d** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl 3-phenylacetate (89e).

88e **89e**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **88e** (260 mg, 1.36 mmol) to ester **89e**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 196 mg (88%) of ethyl ester **89e** as a colourless oil; R_f 0.50 (1:10 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 5H, aromatic), 4.14 (q, J = 7 Hz, 2H, OCH_2CH_3), 3.60 (s, 2H, $PhCH_2CO$), 1.24 (t, J = 7 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 134.1, 129.1, 128.4, 126.9, 60.7, 41.4, 14.1; IR (neat) ν 2990, 1740, 1370, 1300, 1250, 1150, 1020 cm^{-1}; HRMS (NBA) calcd for $C_{10}H_{13}O_2$ $[M+H]^+$ 165.09155, found 165.09130.

Ethyl-2-naphthoate (91a).

90a **91a**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90a** (175 mg, 0.77 mmol) to ester **91a**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 87 mg (56%) of ethyl ester **91a** as a colourless oil; R_f 0.38 (1:20 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H, aromatic), 8.04 (d, *J* = 9 Hz, 1H, aromatic), 7.88 (d, *J* = 9 Hz, 1H, aromatic), 7.81-7.78 (m, 2H, aromatic), 7.51-7.46 (m, 2H, aromatic), 4.40 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 1.40, (t, J = 7 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 135.4, 132.4, 130.9, 129.3, 128.1, 128.0, 127.7, 126.5, 125.2, 61.0, 14.4; IR (neat) ν 2990, 2880, 1740, 1410, 1390, 1225, 1190, 1150, 1130, 1070 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{13}O_2$ $[M+H]^+$ 201.09156, found 201.09130.

Ethyl cinnamate (91b).

90b **91b**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90b** (147 mg, 0.72 mmol) to ester **91b**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 108 mg (68%) of ethyl ester **91b** as a colourless oil; R_f 0.43 (1:10 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 16 Hz, 1H, PhCHC*H*CO), 7.53-7.50 (m, 2H, aromatic), 7.39-7.36 (m, 3H, aromatic), 6.43 (d, *J* = 16 Hz, 1H, PhC*H*CH), 4.26 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 1.33 (t, *J* = 7 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.4, 134.3, 130.1, 128.7, 128.5, 128.1, 127.9, 118.2, 60.4, 14.2; IR (neat) ν 2990, 1720, 1640, 1310, 1180, 1040, 980, 760 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.09155, found 177.09210.

Ethyl 2-methylcinnamate (91c).

90c **91c**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90c** (172 mg, 0.79 mmol) to ester **91c**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 53 mg (35%) of ethyl ester **91c** as a colourless oil; R_f 0.48 (1:20 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1 Hz, 1H, PhC*H*CCH$_3$), 7.40-7.38 (m, 5H, aromatic), 4.27 (q, *J* = 7 Hz, 2H, OC*H*$_2$CH$_3$), 2.11 (d, *J* = 1 Hz, 3H, C*H*$_3$CCH), 1.35 (t, *J* = 7 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 138.5, 135.9, 129.5, 128.5, 128.2, 128.1, 60.8, 14.2, 13.9; IR (neat) ν 3000, 1720, 1250, 1110, 770 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.09938, found 190.10022.

Ethyl 2-methyl-3-phenylpropanoate (91d).

90d **91d**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90d** (126 mg, 0.54 mmol) to ester **91d**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 26 mg (25%) of ethyl ester **91d** as a colourless oil; R_f 0.30 (1:15 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H, aromatic), 4.08 (q, *J* = 7 Hz, 2H, OC*H*$_2$CH$_3$), 3.01 (dd, *J* = 13 Hz, 6 Hz, 1H, PhC*H*$_2$CH), 2.70 (ddq, *J* = 8 Hz, 7 Hz, 6 Hz, 1 H, CH$_2$C*H*(CH$_3$)CO), 2.67

(dd, J = 13 Hz, 8 Hz, 1H, PhCH_2CH), 1.18 (t, J = 7 Hz, 3H, OCH_2CH_3), 1.14 (d, 7 Hz, 3H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 139.3, 128.9, 128.2, 126.2, 60.1, 41.4, 39.7, 16.7, 14.1; IR (neat) ν 3020, 2980, 2940, 1740, 1450, 1380, 1200, 1170 cm^{-1}; HRMS (NBA) calcd for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.12285, found 193.12360.

Ethyl 4-nitrobenzoate (91e).

90e **91e**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90e** (186 mg, 0.84 mmol) to ester **91e**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 16 mg (10%) of ethyl ester **91e** as a yellowish solid; R_f 0.40 (1:10 EtOAc/hexane); mp 57-59°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 8 Hz, 2H, aromatic), 8.26 (d, J = 8 Hz, 2H, aromatic), 4.44 (q, J = 7 Hz, 2H, OCH_2CH$_3$), 1.44 (t, J = 7 Hz, 2H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.4, 135.7, 130.5, 123.4, 61.8, 14.1 IR (neat) ν 3120, 2960, 1710, 1530, 1350, 1320, 1290, 1100, 870 cm^{-1}; HRMS () calcd for $C_9H_{10}NO_4$ $[M+H]^+$ 196.06099, found 196.06210.

Ethyl 2-methyl-3-phenylpropanoate (91f).

90f **91f**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90f** (237 mg, 1.09 mmol) to ester **91f**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 103 mg (49%) of ethyl ester **91f** as a colourless oil; refer to compound **91d** for characterization data.

Ethyl 2-methyl-3-phenylpropanoate (91g).

90g **91g**

The general procedure for the conversion of tertiary amides to esters was used for the conversion of amide **90g** (237 mg, 1.24 mmol) to ester **91g**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 165 mg (69%) of ethyl ester **91g** as a colourless oil; refer to compound **91d** for characterization data.

***N*-Benzyl-3-phenylpropanamide (92a).**

92a

To a solution of hydrocinnamic acid (2.0 g, 13.3. mmol) in dichloromethane (50 ml) was added thionyl chloride (1.16 ml, mmol). The reaction was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess

thionyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane (100 ml) and slowly added via cannula to a solution of benzylamine (1.75 ml, 16.0 mmol) in dichloromethane (20 ml) at -78°C. Triethylamine (2.78 ml, 19.9 mmol) was then added which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After several hours at room temperature, the reaction was diluted with diethyl ether (250 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization in ethyl acetate/hexanes yielded 2.93 g (92%) of amide **92a** as a white solid; R_f 0.31 (1:2 EtOAc/hexane); mp 86-88°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.11 (m, *J* = 5H, aromatic), 5.70 (br, 1H, N*H*), 4.38 (d, *J* = 6 Hz, 2H, HNCH_2Ph), 2.99 (t, *J* = 7 Hz, 2H, PhCH_2CH_2), 2.51 (t, *J* = 7 Hz, 2H, CH_2CH_2CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 140.7, 138.1, 128.6, 128.5, 128.3, 127.6, 127.4, 126.2, 43.5, 38.4, 31.6; IR (KBr) ν 3300, 1640, 1540, 1450, 740 cm^{-1}; HRMS (NBA) calcd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.13884, found 240.13770.

N-Butyl-3-phenylpropanamide (92b).

92b

Hydrocinnamic acid (2.47 g, 16.4 mmol) was converted to *N*-*n*-butyl-3-phenylpropanamide **92b** following the same procedure as that used for the synthesis of *N*-benzyl-3-phenylpropanamide **92a**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 3.28 g (97%) of amide **92b** as a colourless oil; R_f 0.21 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H, aromatic), 5.53 (br, 1H, N*H*),

3.19 (dt, J = 6 Hz, 7 Hz, 2H, NHCH_2CH$_2$), 2.95 (t, J = 7 Hz, 2H, PhCH_2CH$_2$), 2.45 (t, J = 7 Hz, 2H, CH$_2$CH_2CO), 1.99-1.21 (m, 4H, NCH$_2$CH_2CH_2CH$_3$), 0.88 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.1, 140.8, 128.4, 128.2, 126.1, 39.1, 38.4, 31.7, 31.5, 19.8, 13.6; IR (neat) ν 3300, 2960, 2920, 2860, 1640, 1550, 1450 cm^{-1}; HRMS (NBA) calcd for $C_{13}H_{20}NO$ [M+H]$^+$ 206.15450, found 206.15350.

_N_-Benzyl phenylacetamide (92c).

92c

To a solution of phenylacetyl chloride (2.0 ml, 15.1 mmol) in dichloromethane (50 ml) under an argon atmosphere was slowly added benzylamine (2.1 ml, 19.7 mmol) and pyridine (1.85 ml, 22.7 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional hour. The reaction was diluted with diethyl ether (250 ml) washed with 10% HCl (2 x 50 ml), saturated NaHCO$_3$ (50 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 3.13 g (92%) of amide **92c** as a white solid; R$_f$ 0.24 (1:2 EtOAc/hexane); mp 120-122°C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35-7.13 (m, 10H, aromatic), 6.00 (br, 1H, NH), 4.36 (d, J = 6 Hz, 2H, NHCH_2Ph), 3.57 (s, 2H, PhCH_2CO); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 138.1, 134.8, 129.2, 128.8, 128.5, 127.3, 127.2, 127.1, 43.6, 43.4; IR (KBr) ν 3300, 3090, 1650, 1550, 1450, 1020 cm^{-1}; HRMS (NBA) calcd for $C_{15}H_{16}NO$ [M+H]$^+$ 226.12318, found 226.12280.

N-Benzyl-2-naphthamide (92d).

92d

To a solution of naphthoyl chloride (2.09 g, 10.9 mmol) in dichloromethane (50 ml) under an argon atmosphere was slowly added benzylamine (1.55 ml, 14.2 mmol) and pyridine (1.34 ml, 16.4 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional hour. The reaction was diluted with diethyl ether (250 ml) washed with 10% HCl (2 x 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 2.67 g (93%) of amide **92d** as a white solid; R_f 0.24 (1:2 EtOAc/hexane); mp 140-143°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H, aromatic), 7.85-7.82 (m, 4H, aromatic), 7.57-7.47 (m, 2H, aromatic), 7.37-7.24 (m, 5H, aromatic), 6.79 (br, 1H, N*H*), 4.66 (d, *J* = 6 Hz, 2H, PhCH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 138.2, 134.6, 132.5, 131.5, 128.8, 128.7, 128.3, 127.8, 127.6, 127.5, 127.4, 127.3, 126.6, 123.5, 44.1; IR (KBr) ν 3300, 1640, 1550, 1410, 1320, 710 cm^{-1}; HRMS (NBA) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 262.12320, found 262.12310.

N-Benzyl cinnamide (92e).

92e

To a solution of cinnamic acid (2.03 g, 13.7 mmol) in dichloromethane (20 ml) was added oxalyl chloride (1.46 ml, 16.4 mmol) and several drops of DMF. The flask was connected to an exit bubbler and refluxed gently until the no more gas evolved (~45 min). The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. The crude chloride could be used without purification. The chloride was dissolved in dichloromethane 100 ml) and cooled to -78°C in an acetone/dry ice bath under an argon atmosphere. Benzylamine (1.95 ml, 17.8 mmol) was then added followed by triethylamine (2.86 ml, 20.6 mmol) which resulted in a heterogeneous solution. The solution was allowed to warm up to room temperature with stirring. After stirring overnight at room temperature, the reaction was diluted with diethyl ether (250 ml), washed with 10% HCl (2 x 20 ml), saturated $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from diethyl ether/hexanes) yielded 3.08 g (95%) of amide **92e** as a white crystals; R_f 0.22 (1:2 EtOAc/hexane); mp 113-115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16 Hz, 1H, PhCHC*H*CO), 7.44-7.41 (m, 3H, aromatic), 7.31-7.25 (m, 7H, aromatic), 6.60 (br, 1H, N*H*), 6.49 (d, *J* = 16 Hz, 1H, PhC*H*CH), 4.49 (d, *J* = 6 Hz, 2H, PhCH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 141.0, 138.1, 134.6, 129.5, 129.6, 128.6, 128.5, 127.8, 127.7, 127.3, 127.2, 120.5, 43.6; IR (KBr) ν 3420, 3280, 3000, 1650, 1610, 1510, 1210, 750 cm^{-1}; HRMS (NBA) calcd for $C_{16}H_{16}NO$ $[M+H]^+$ 238.12318, found 238.12420.

N-Benzyl-2-methyl cinnamide (92f).

92f

2-Methylcinnamic acid (2.0 g, 12.3 mmol) was converted to *N*-benzyl-2-methylcinnamide **92f** following the same procedure as that used for the synthesis of *N*-benzyl-3-phenylpropanamide **92a**. Purification of the crude product by crystallization from dichloromethane/hexanes yielded 2.75 g (89%) of amide **92f** as a white crystals; R_f 0.50 (1:2 EtOAc/hexane); mp 123-125°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 11H, aromatic and PhC*H*CCH$_3$), 6.60 (br, 1H, N*H*), 4.49 (d, *J* = 6 Hz, 2H, PhC*H*$_2$NH), 2.06 (d, *J* = 1 Hz, 3H, PhCHCC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 138.3, 135.9, 133.8, 131.7, 129.1, 128.4, 128.1, 127.6, 127.2, 43.7, 14.1; IR (KBr) ν 3340, 1650, 1610, 1530, 1450, 1420, 1280, 1010 cm^{-1}; HRMS (NBA) calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 252.13884, found 252.13990.

N-Benzyl-2-methyl-3-phenylpropanamide (92g).

92f **92g**

N-benzyl cinnamide **92f** (514 mg, 2.05 mmol) was converted to *N*-benzyl-2-methyl-3-phenylpropanamide **92g** following the same procedure as that used for the synthesis of *N*-benzyl-3-phenylpropanamide **90d**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 511 mg (99%) of amide **92g** as a white solid; R_f 0.42 (1:2 EtOAc/hexane); mp 90-92°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.17 (m, 6H, aromatic), 7.15-7.11 (m, 2H, aromatic), 7.00-6.97 (m, 2H, aromatic), 6.00 (br, 1H, N*H*), 4.35 (dd, *J* = 15 Hz, 6 Hz, 1H, PhC*H*$_2$NH), 4.20 (dd, *J* = 15 Hz, 6 Hz, 1H, PhC*H*$_2$NH), 2.94 (dd, *J* = 13 Hz, 9 Hz, 1H, PhC*H*$_2$CH), 2.65 (dd, *J* = 13 Hz, 9 Hz, 1H, PhC*H*$_2$CH), 2.51(ddq, *J* = 9 Hz, 7 Hz, 6 Hz, 1H, CH$_2$C*H*(CH$_3$)CO), 1.18 (d, *J* = 7 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.7, 138.1, 128.8, 128.3, 128.2, 127.3, 127.0, 126.0, 43.5, 43.0,

40.3; IR (neat) ν 3300, 3020, 2980, 2920, 1650, 1550, 1450, 1240 cm^{-1}; HRMS (THIO) calcd for $C_{17}H_{20}NO$ $[M+H]^+$ 254.15450, found 254.15510.

N-Benzyl-4-nitrobenzamide (92h).

92h

To a solution of 4-nitrobenzoyl chloride (2.8 g, 15.1 mmol) in dichloromethane (100 ml) under an argon atmosphere was slowly added benzylamine (1.98 ml, 18.1 mmol) and triethylamine (2.73 ml, 19.6 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional hour. The reaction was diluted with diethyl ether (250 ml) washed with 10% HCl (2 x 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from ethyl acetate/hexanes yielded 3.70 g (96%) of amide **92d** as a yellowish crystals; R_f 0.44 (1:2 EtOAc/hexane); mp 142-144°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9 Hz, 2H, aromatic), 7.94, (d, *J* = 9 Hz, 2H, aromatic), 7.37-7.26 (m, 5H, aromatic), 6.58 (br, 1H, N*H*), 4.65 (d, *J* = 6 Hz, 2H, PhCH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 149.6, 139.8, 137.4, 128.9, 128.1, 127.9, 127.8, 123.8, 44.4; IR (KBr) ν 3280, 1600, 1630, 1540, 1520, 1350, 1200 cm^{-1}; Elemental analysis: calcd for $C_{14}H_{12}N_2O_3$, 65.60%C, 4.72%H, 10.93%N, found 65.53%C, 4.74%H, 10.87%N.

Ethyl-3-phenylpropanoate (93a).

92a **93a**

General procedure for the conversion of secondary amides to ethyl or methyl esters. To a solution of the amide (156 mg, 0.65 mmol) in dry dichloromethane (5 ml) was added 2.5 equivalents of dry pyridine (133 µl, 1.63 mmol). The solution was cooled to -30°C using an acetone-dry ice bath and then 1.3 equivalents of neat triflic anhydride (143 µl, 0.85 mmol) was added slowly down the side of the flask (alternatively, triflic anhydride can be added via cannula as a pre-cooled solution in dichloromethane). The solution can become somewhat heterogeneous, but as the solution is stirred and allowed to warm up slowly to 0°C, the solution becomes homogeneous. The temperature is maintained at 0° for 4 to 8 hours which is shorter in comparison to tertiary amides. Absolute ethanol (2 ml, > 33 mmol) was then added to the solution at 0°C and then the reaction was stirred for and additional 4 hours at room temperature. Diethyl ether (80 ml) was then added and then the solution was washed 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. HNMR analysis of the crude product indicated 90% conversion and purification by flash chromatography (1:20 ethyl acetate/hexanes) yielded 102 mg (88%) of ethyl ester **93a** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl-3-phenylpropanoate (93b).

92b **93b**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92b** (299 mg, 1.45 mmol) to ester **93b**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 200 mg (77%) of ethyl ester **93b** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl phenylacetate (93c).

92c **93c**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92c** (151 mg, 0.67 mmol) to ester **93c**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 105 mg (95%) of ethyl ester **93c** as a colourless oil; refer to compound **89e** for characterization data.

Ethyl-2-naphthoate (93d).

92d **93d**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92d** (147 mg, 0.56 mmol) to ester **93d**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 96 mg (85%) of ethyl ester **93d** as a colourless oil; refer to compound **91a** for characterization data.

Ethyl cinnamate (93e).

92e **93e**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92e** (136 mg, 0.57 mmol) to ester **93e**. Purification of the crude product by flash chromatography (1:15 ethyl acetate/hexanes) yielded 95 mg (94%) of ethyl ester **93e** as a colourless oil; refer to compound **91b** for characterization data.

Ethyl-2-methyl cinnamate (93f).

92f **93f**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92f** (155 mg, 0.61 mmol) to ester **93f**. Purification of the crude product by flash chromatography (1:20 ethyl acetate/hexanes) yielded 110 mg (94%) of ethyl ester **93f** as a colourless oil; refer to compound **91c** for characterization data.

Ethyl-2-methyl-3-phenylpropanoate (93g).

92g **93g**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92g** (160 mg, 0.63 mmol) to ester **93g**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 108 mg (89%) of ethyl ester **93g** as a colourless oil; refer to compound **91d** for characterization data.

Ethyl-4-nitrobenzoate (93h).

92h **93h**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **92h** (252 mg, 1.0 mmol) to ester **93h**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 53 mg (28%) of ethyl ester **93h** as a colourless oil; refer to compound **91e** for characterization data.

N-Benzyl succinimide (95).

94 **95**

To a solution of succinimide (2.04 g, 20.6 mmol) in methanol (50 ml) was added sodium hydroxide pellets (1.0 g, 24.7 mmol) and benzyl chloride (2.84 ml, 24.7 mmol). The mixture is refluxed for 12 hours or until TLC analysis indicates that the reaction is complete. The volatiles are removed under reduced pressure and the syrup is diluted with water (50 ml) and extracted with dichloromethane (3 x 75 ml). The organic phases are dried over $MgSO_4$ and concentrated under reduced pressure. The crude product can be purified by crystallization from ethyl acetate/hexanes. A second batch of product can be obtained by crystallizing the mother liquors. The fractions are combined yielded 2.793 g (81%) of imide **95** as white crystals; R_f 0.16 (1:2 EtOAc/hexane); mp 102-104°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H, aromatic), 4.66 (s, 2H, CH_2Ph), 2.70 (s, 4H, CH_2CON); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 125.7, 128.8, 128.5, 127.8, 42.3, 28.1; IR (KBr) ν 1700, 1430, 1400, 1340, 1300, 1160 cm^{-1}; HRMS (NBA) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.08681, found: 190.08730.

N-Benzyl-4-hydroxybutanamide (96).

95 **96**

To a solution of imide **95** (4.003 g, 24.3 mmol) in iso-propanol (50 ml) at 0°C is added water (20 ml), sodium borohydride (1.84 g, 48.5 mmol) and lithium chloride (1.02 g, 24.3 mmol). The mixture is allowed to warm up slowly to room temperature and stirring is continued for another 12 hours or until the reaction is judged complete by TLC analysis. The volatiles are removed under reduced pressure. Dilute aqueous sodium hydroxide (0.25 M) is added to the resulting paste and followed by extraction with ethyl acetate (3 x 75 ml). The organic phases are dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from ethyl acetate/hexanes yielded 3.949 g (97%) of hydroxy-amide **96** as white crystals; R_f 0.51 (10:1 EtOAc/MeOH); mp 76-78°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H, aromatic), 6.68 (br, 1H, N*H*), 4.34 (d, *J* = 6 Hz, 2H, C*H*$_2$Ph), 3.95 (br, 1H, O*H*), 3.60 (t, *J* = 6 Hz, 2H, C*H*$_2$OH), 2.31 (t, *J* = 6 Hz, 2H, CH$_2$C*H*$_2$CON), 1.81 (tt, *J* = 7 Hz, 6 Hz, 2H, CH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 138.0, 128.4, 127.4, 127.2, 61.6, 43.3, 33.3, 28.0; IR (KBr) ν 3300, 1640, 1550, 1450, 1420, 1010, 720 cm^{-1}; HRMS (THIO) calcd for $C_{11}H_{16}NO_2$ [M+H]$^+$: 194.11810, found: 194.11840; Elemental analysis: calcd for $C_{11}H_{15}NO_2$, 68.36%C, 7.82%H, 7.25%N, found 68.72%C, 8.09%H, 7.28%N.

N-Benzyl-4-methoxybutyrolactam (98).

95 **98**

To a solution of imide **95** (1.749 g, 10.6 mmol) in methanol (10 ml) at 0°C is added sodium borohydride (806 mg, 21.2 mmol) and lithium chloride (450 mg, 10.6 mmol). The mixture is allowed to warm up slowly to room

temperature and stirring is continued for another 12 hours. The volatiles are removed under reduced pressure. The resulting pasted is diluted with 10% HCl (25 ml) and washed with dichloromethane (3 x 50 ml). The organic phases are dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from ethyl acetate/hexanes yielded 705 mg (32%) of hydroxy-amide **96** as a colourless oil; R_f 0.27 (2:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H, aromatic), 4.94 (d, *J* = 14.7 Hz, 1H, NCH_2Ph), 4.73 (dd, *J* = 6.2 Hz, 1.6 Hz, 1H, CH_2CHOCH_3), 4.02 (d, *J* = 14.7 Hz, 1H, NCH_2Ph), 3.21 (s, 3H, OCH_3), 2.69-2.51 (m, 1H, CH_2CH_2CO), 2.41-2.31 (m, 1H, CH_2CH_2CO), 2.14-1.92 (m, 2H, $CHCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 136.3, 128.5, 128.2, 127.4, 88.8, 52.7, 43.6, 28.8, 23.5; IR (neat) ν 2920, 2820, 1700, 1440, 1410, 1360, 1280, 1240, 1160, 1070, 700 cm^{-1}; HRMS (THIO) calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.11810, found: 206.11750.

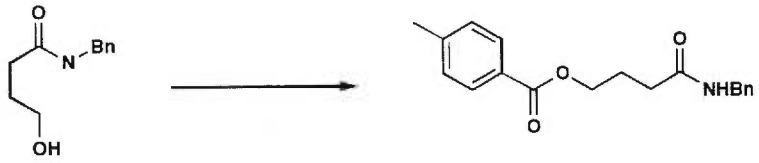
N-Benzyl-4-*t*-butyldiphenylsilyloxybutanamide (101a).

96 **101a**

To a solution of hydroxy amide **96** (501 mg, 5.2 mmol) in dichloromethane (10 ml) under argon atmosphere is added triethylamine (480 ml, 6.8 mmol), DMAP (~4 mg) and *t*-butyldiphenylsilyl chloride (800 µl, 6.3 mmol). The reaction is stirred at room temperature for 30 minutes or until the reaction is judged complete by TLC analysis. The reaction is diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:3 ethyl

acetate/hexanes) yielded 839 mg (75%) of the silyl protected alcohol **101a** as a colourless oil; R_f 0.48 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.61 (m, 4H, aromatic), 7.44-7.21 (m, 11H, aromatic), 5.87 (br, 1H, N*H*), 4.38 (d, *J* = 5.3 Hz, 2H, NHCH_2Ph), 3.71 (t, *J* = 5.9 Hz, 2H, TBDPSOCH_2CH$_2$), 2.34 (t, *J* = 7.3 Hz, 2H, CH$_2$CH_2O), 1.90 (tt, *J* = 7.3 Hz, 5.9 Hz, 2H, CH$_2$CH_2CH$_2$), 1.03 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 138.3, 135.4, 133.6, 129.6, 128.6, 127.7, 127.6, 127.3, 62.9, 43.5, 33.1, 28.3, 26.8, 19.1; IR (neat) ν 3300, 2920, 1650, 1550, 1420, 1100 cm^{-1}; HRMS (THIO) calcd for $C_{27}H_{34}NO_2Si$ [M+H]$^+$: 432.23587, found: 432.23460.

N-Benzyl-4-(4-methyl benzoyloxy)butanamide (101b).

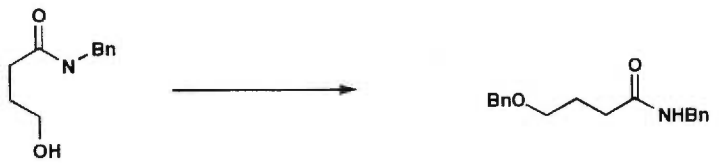


96 **101b**

To a solution of hydroxy amide **96** (650 mg, 3.37 mmol) in dichloromethane (20 ml) under argon atmosphere at 0°C is added triethylamine (610 µl, 4.38 mmol), DMAP (~4 mg) and 4-methylbenozyl chloride (534 µl, 4.04 mmol). The reaction is stirred at room temperature for 18 hours or until the reaction is judged complete by TLC analysis. The reaction is diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from ethyl acetate/hexanes yielded 866 mg (83%) of the benzoyl protected alcohol **101b** as white crystals; R_f 0.35 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.20 (d, *J* = 8.3 Hz, aromatic), 7.34-7.20 (m, 7H, aromatic), 5.96 (br, 1H, N*H*), 4.41 (d, *J* = 5.7 H, 2H, CH_2Ph), 4.34 (t, *J* = 6.2 Hz, 2H, CH$_2$CH_2O), 2.40 (s, 3H, PhCH_3), 2.35 (t, *J*

= 7.1 Hz, 2H, CH_2CH_2CO), 2.13 (tt, J = 7.1 Hz, 6.2 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 166.6, 143.6, 138.1, 129.5, 129.0, 128.6, 127.7, 127.4, 127.3, 63.9, 43.6, 33.0, 24.8, 21.6; IR (neat) ν 3460, 3380, 1720, 1640, 1540, 1260, 1160, 1100, 1090 cm^{-1}; HRMS (THIO) calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.15997, found: 312.16130.

N-Benzyl-4-benzyloxybutanamide (101c).



96 **101c**

To a suspension of sodium hydride (250 mg, 6.2 mmol) in tetrahydrofuran (10 ml) at 0°C is added hydroxy amide **96** (692 mg, 3.58 mmol) followed by DMF (2 ml). After 1 hour, benzyl bromide (454 ml, 3.9 mmol) is added slowly and the reaction is allowed to stir overnight while warming up to room temperature slowly. The reaction is diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 435 mg (43%) of the benzyl protected alcohol **101c** as a colourless oil; R_f 0.23 (1:1 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (m 10H, aromatic), 6.18 (br, 1H, N*H*), 4.43 (s, 2H, OCH_2Ph), 4.35 (d, J = 5.7 Hz, 2H, $NHCH_2Ph$), 3.49 (t, J = 6.0 Hz, 2H, CH_2CH_2OBn), 2.31 (t, J = 7.2 Hz, 2H, CH_2CH_2CO), 1.94 (tt, J = 7.2 Hz, 6.0 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 138.3, 138.1, 128.5, 128.2, 128.0, 127.8, 127.6, 127.5 (2), 127.2, 72.8, 69.3, 43.3, 33.3, 25.5; IR (neat) ν 3380, 3120, 2920, 2840, 1640, 1540, 1450, 1350, 1260, 1090, 1020, 740, 680 cm^{-1}; HRMS (NBA) calcd for $C_{18}H_{21}NO_2$ $[M+H]^+$: 284.16504, found: 284.16450.

N-Benzyl-4-(4-methoxybenzyloxy)butanamide (101d).

96 **101d**

To a suspension of sodium hydride (147 mg, 3.7 mmol) in tetrahydrofuran (10 ml) at 0°C is added hydroxy amide **96** (592 mg, 3.1 mmol) followed by DMF (2 ml). After 1 hour, 4-methoxybenzyl bromide (470 ml, 3.4 mmol) is added slowly and the reaction is allowed to stir overnight while warming up to room temperature slowly. The reaction is diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 301 mg (31%) of the benzyl protected alcohol **101d** as a colourless oil; R_f 0.45 (2:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.17 (m 7H, aromatic), 6.86-6.81 (m, 2H, aromatic), 6.16 (br, 1H, N*H*), 4.37 (s, 2H, OCH_2PhOMe), 4.36 (d, *J* = 5.0 Hz, 2H, $NHCH_2Ph$), 3.77 (s, 3H, $PhOCH_3$), 3.49 (t, *J* = 6.0 Hz, 2H, CH_2CH_2OPMB), 2.31 (t, *J* = 7.2 Hz, 2H, CH_2CH_2CO), 1.94 (tt, *J* = 7.2 Hz, 6.0 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 159.1, 138.3, 130.2, 129.2, 128.5, 127.6, 127.3, 113.7, 72.4, 69.0, 55.1, 43.4, 33.4, 25.6; IR (neat) ν 3300, 3050, 2920, 2840, 1640, 1540, 1450, 1350, 1300, 1240, 1160, 1090, 1020, 800 cm^{-1}; HRMS (THIO) calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.17563, found: 314.17730.

N-Benzyl-4-acetoxybutanamide (101e).

96 **101e**

To a solution of hydroxy amide **96** (767 mg, 3.97 mmol) in dichloromethane (10 ml) under argon atmosphere at 0°C is added pyridine (471 µl, 5.96 mmol), DMAP (~4 mg) and acetic anhydride (562 µl, 5.96 mmol). The reaction is stirred at room temperature for 24 hours or until the reaction is judged complete by TLC analysis. The reaction is diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 777 mg (83%) of the acetyl protected alcohol **101e** as a colourless oil; R_f 0.17 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5H, aromatic), 6.45 (br, 1H, N*H*), 4.36 (d, *J* = 6 Hz, 2H, PhCH_2NH), 4.04 (t, *J* = 6 Hz, 2H, AcOCH_2CH$_2$), 2.24 (t, *J* = 7 Hz, 2H, CH$_2$CH_2CO), 1.98 (s, 3H, CH_3CO), 1.96 (tt, *J* = 7 Hz, 6 Hz, 2H, CH$_2$CH_2CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.9, 138.1, 128.4, 127.5, 127.2, 63.5, 43.3, 32.5, 24.5, 20.7; IR (neat) ν cm^{-1}; HRMS (THIO) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 236.12866, found 236.12830.

(4*S*, 5*S*)-4-(2-*N*-benzyl acetamidyl)-oxymethyl-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (101f).

101f

To a solution of 4-benzyloxymethyl-5-hydroxylmethyl-2,2-dimethyl-1,3-dioxolane[286] (987 mg, 3.92 mmol) in tetrahydrofuran (20 ml) is slowly added potassium hydride (1.57 g, 13.7 mmol) followed by DMF (5 ml) and bromoacetic acid (820 mg, 5.88 mmol). The reaction is stirred while warming up to room temperature over the course of an hour. TLC analysis of the reaction at this point indicates that the reaction is complete The reaction is diluted with 10% HCl (50 ml), extracted with dichloromethane/ethyl acetate (3:1, 3 x 50 ml). The organic phases are dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (2:1 ethyl acetate/hexanes with 1% acetic acid) yielded 1.19 g (97%) of acid as colorless oil. The acid is co-evaporated with toluene to remove traces of acetic acid and diluted in dichloromethane. To a solution of this acid (1.19 g, 3.8 mmol) in dichloromethane (50 ml) at 0°C under an argon atmosphere is added trimethylacetyl chloride (pivoalyl chloride) (610 µl, 4.96 mmol) and pyridine (933 µl, 11.4 mmol). The reaction is stirred while warming to room temperature. After 1 hour at room temperature, the reaction is recooled to 0°C and then benzylamine (625 µl, 5.72 mmol) is added slowly to the mixed anhydride. The reaction is allowed to warm up to room temperature and is then stirred for 4 hours or until the reaction judged to be complete by TLC analysis. The reaction is diluted with diethyl ether (150 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification

of the crude product by flash chromatography (1:1 ethyl acetate/hexanes) yielded 1.293 g (85%, 825 overall for the 2 steps) of amide **101f** as a colourless oil; R_f 0.28 (1:1 EtOAc/hexane); $[\alpha]^{21}_D$ -12.18° (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 11H, aromatic and NH), 4.54 (s, 2H, OCH_2Ph), 4.47 (dd, *J* = 5.9 Hz, 1.6 Hz, 2H, NCH_2Ph), 4.11 (d, *J* = 15.7 Hz, 1H, CH_2OCH_2CO), 4.06 (d, *J* = 15.7 Hz, 1H, CH_2OCH_2CO), 4.00 (m, 2H, $BnOCH_2CHCHCH_2O$), 3.70 (dd, *J* = 10.6 Hz, 2.5 Hz, 1H, $OCCH_2OCH_2CH$), 3.62 (m, 2H, $OCCH_2OCH_2CH$ and $BnOCH_2$), 3.53 (dd, *J* = 10.0 Hz, 4.8 Hz, 1H, $BnOCH_2$), 1.34 (s, 3H, CCH_3), 1.27 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 137.8, 137.6, 128.6, 128.4, 127.8, 127.7, 127.4, 109.6, 77.9, 75.8, 73.5, 71.6, 70.6, 70.2, 42.8, 26.8, 26.6; IR (neat) ν 3350, 3000, 2930, 2870, 1670, 1530, 1450, 1370, 1250, 1210, 1080 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.21240, found: 400.21330.

Ethyl-4-*t*-butyldiphenylsilyloxybutanoate (102a).

101a **102a**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101a** (388 mg, 0.90 mmol) to ester **102a**. Purification of the crude product by flash chromatography (1:15 ethyl acetate/hexanes) yielded 310 mg (93%) of ethyl ester **102a** as a colourless oil; R_f 0.25 (1:15 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H, aromatic), 7.44-7.24 (m, 6H, aromatic), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.69 (t, *J* = 6.1 Hz, 2H, $TBDPSOCH_2CH_2$), 2.45 (t, *J* = 7.4 Hz, 2H, CH_2CH_2O), 1.88 (tt, *J* = 7.4 Hz, 6.1 Hz, 2H, $CH_2CH_2CH_2$), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.05 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ

174.0, 135.5, 133.7, 129.5, 127.6, 62.8, 60.2, 30.85, 27.7, 26.8, 19.1, 14.1; IR (neat) ν 2960, 2920, 1740, 1420, 1100, 1170 cm^{-1}; HRMS (NBA) calcd for $C_{22}H_{31}O_3Si$ $[M+H]^+$: 371.20425, found: 371.20300.

Ethyl-4-(4-methyl benzoyloxy)butanoaote (102b).

101b **102b**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101b** (271 mg, 0.87 mmol) to ester **102b**. Purification of the crude product by flash chromatography (1:15 ethyl acetate/hexanes) yielded 192 mg (88%) of ethyl ester **102b** as a colourless oil; R_f 0.22 (1:10 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H, aromatic), 7.22 (d, J = 8.2 Hz, 2H, aromatic), 4.34 (t, J = 6.3 Hz, 2H, OCH_2CH_2), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.48 (t, J = 7.4 Hz, 2H, CH_2CH_2CO), 2.40 (s, 3H, $PhCH_3$), 2.10 (tt, J = 7.4 Hz, 6.3 Hz, 2H, $CH_2CH_2CH_2$), 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 166.3, 143.4, 129.4, 128.9, 127.3, 63.6, 30.3, 30.8, 24.0, 21.4, 14.0; IR (neat) ν 2980, 1740, 1720, 1610, 1440, 1370, 1270, 1160, 1100, 1010, 830, 740 cm^{-1}; HRMS (NBA) calcd for $C_{14}H_{18}O_4$ $[M+H]^+$: 251.12834, found: 251.12940.

Ethyl-4-benzyloxybutanoate (102c).

101c **102c**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101c** (213 mg, 0.75 mmol) to ester **102c**. Purification of the crude product by flash chromatography (1:8 ethyl acetate/hexanes) yielded 142 mg (85%) of ethyl ester **102c** as a colourless oil; R_f 0.20 (1:5 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.31 (m, 5H, aromatic), 4.49 (s, 2H, CH_2Ph), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.50 (t, J = 6.2 Hz, 2H, CH_2CH_2OBn), 2.42 (t, J = 7.3 Hz, 2H, CH_2CH_2CO),1.94 (tt, J = 7.3 Hz, 6.2 Hz, 2H, $CH_2CH_2CH_2$)1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.4, 128.2, 127.5, 127.4, 72.8, 69.1, 60.2, 31.0, 25.0, 14.1; IR (neat) ν 2980, 2920, 2850, 1730, 1450, 1360, 1240, 1170, 1100, 1020, 730, 690 cm^{-1}; HRMS (THIO) calcd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.13342, found: 233.13290.

Ethyl-4-(4-methoxybenzyloxy)butanoate (102d).

101d **102d**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101d** (153 mg, 0.49 mmol) to ester **102d**. Purification of the crude product by flash chromatography (1:7 ethyl acetate/hexanes) yielded 99 mg (81%) of ethyl ester **102d** as a colourless oil; R_f 0.30 (1:7 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H, aromatic), 6.87 (d, J = 8.6 Hz, 2H, aromatic), 4.42 (s, 2H, $PhCH_2O$), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.79 (s, 3H, CH_3OPh), 3.47 (t, J = 6.2 Hz, 2H, CH_2CH_2O), 2.40 (t, J = 7.3 Hz, 2H, CH_2CH_2CO), 1.92 (tt, J = 7.3 Hz, 6.2 Hz, 2H, $CH_2CH_2CH_2$), 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 159.1, 130.4, 129.1, 113.7, 72.4, 68.8, 61.1, 55.2, 31.0,

25.0, 14.1; IR (neat) ν 2940, 2850, 1730, 1610, 1510, 1450, 1360, 1290, 1240, 1170, 1090, 1020, 810 cm^{-1}; HRMS (NBA) calcd for $C_{14}H_{21}O_4$ $[M+H]^+$: 253.14398, found: 253.14320.

Ethyl-4-acetoxybutanoate (102e).

101e **102e**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101e** (383 mg, 1.6 mmol) to ester **102e**. Purification of the crude product by flash chromatography (1:7 ethyl acetate/hexanes) yielded 218 mg (77%) of ethyl ester **102e** as a colourless oil; R_f 0.12 (1:10 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 4.11 (t, *J* = 6 Hz, 2H, $AcOCH_2CH_2$), 2.39 (t, *J* = 7 Hz, 2H, CH_2CH_2CO), 2.05 (s, 3H, CH_3CO), 1.97 (tt, *J* = 7 Hz, 6 Hz, 2H, $CH_2CH_2CH_2$), 1.27 (t, *J* = 6Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.8, 63.3, 60.3, 30.7, 23.9, 20.7, 14.1; IR (neat) ν 2980, 1740, 1360, 1230, 1170, 1030 cm^{-1}; HRMS (NBA) calcd for $C_8H_{15}O_4$ $[M+H]^+$ 175.19703, found 175.09650.

***(4S, 5S)*-4-(Ethyl-2-acetoxy)oxymethyl-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (102f).**

101f **102f**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **101f** (349 mg, 0.87 mmol) to ester **102f**. Purification of the crude product by flash chromatography (1:5 ethyl acetate/hexanes) yielded 195 mg (66%) of ethyl ester **102f** as a colourless oil; R_f 0.24 (1:5 EtOAc/hexane); $[\alpha]^{21}_D$ –7.13° (*c* 0.954, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H, aromatic), 4.59 (s, 2H, OCH_2Ph), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.15-4.03 (m, 4H, CH_2OCH_2CO and $BnOCH_2CHCHCH_2O$), 3.74 (dd, *J* = 10.3 Hz, 2.3 Hz, 1H, $OCCH_2OCH_2CH$), 3.71-3.59 (m, 3H, $OCCH_2OCH_2CH$ and $BnOCH_2CH$), 1.43 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 137.8, 128.3, 127.6, 127.5, 109.7, 77.4, 76.9, 73.4 (2), 71.8, 70.4, 68.7, 60.7, 26.9, 14.1; IR (neat) ν 2990, 2930, 2870, 1740, 1450, 1380, 1220, 1100, 870, 720 cm^{-1}; HRMS (THIO) calcd for $C_{18}H_{26}O_6$ $[M]^+$: 338.17294, found: 338.17250.

(2*S*)-*N*-benzyl-2-methyl-2-(6-methoxynaphthyl)acetamide (103a).

103a

To a solution of (*S*)-Naproxen® (465 mg, 2.02 mmol) and DCC (541 mg, 2.62 mmol) in dichloromethane (20 ml) under an argon atmosphere at 0°C is added benzylamine (310 µl, 2.83 mmol) and DMAP (~4 mg). The reaction is stirred while warming to room temperature slowly. After 6 hours, TLC analysis indicates that no more starting material is present. The reaction is diluted with pentane/diethyl ether (1:1, 100 ml) and filtered through celite. Purification of the crude product by flash chromatography yielded 138 mg (21%) of benzamide **103a** as a white solid. The optical purity was determined to be 99 %ee by HPLC analysis (Chiracel OD, flow

rate = 1.0 ml/min of 20:80 *i*-PrOH/hexane, T_r (major) 10.45 min, T_r (minor) 12.97 min); R_f 0.42 (1:2 EtOAc/hexane); mp 134-136°C; $[\alpha]^{21}_D$ –10.30° (*c* 0.602, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.64 (m, 3H, aromatic), 7.39-7.36 (m, 1H, aromatic), 7.25-7.09 (m, 7H, aromatic), 5.83 (br, 1H, N*H*), 4.33 (dd, *J* = 14.9 Hz, 5.8 Hz, NHCH_2Ph), 4.38 (dd, *J* = 14.9 Hz, 5.8 Hz, NHCH_2Ph), 3.88 (s, 3H, OCH_3), 3.71 (q, *J* = 7.1 Hz, C*H*CH$_3$), 1.60 (d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 157.6, 138.3, 136.3, 133.6, 129.1, 128.9, 128.4, 127.4 (2), 127.2, 126.2, 126.0, 119.0, 105.6, 55.2, 46.9, 43.4, 18.4; IR (neat) ν 3300, 2960, 2920, 1650, 1610, 1560, 1500, 1450, 1260, 1220, 1200, 1020 cm^{-1}; HRMS (THIO) calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.165054, found: 320.163700.

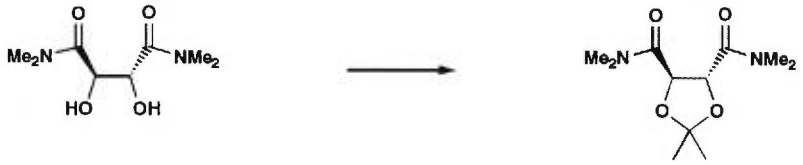
(2*S*)-*N*-Benzyl-2-methoxy phenylacetamide (103b).

103b

To a solution of (*R*)-*O*-methoxy phenylacetic acid (419 mg, 2.52 mmol), benzylamine (413 µl, 3.79 mmol) and DMAP (~4 mg) in dichloromethane (20 ml) under an argon atmosphere at 0°C is added DCC (676 mg, 3.28 mmol). The reaction is stirred while warming to room temperature slowly. After 6 hours, TLC analysis indicates that no more starting material is present. The reaction is diluted with pentane/diethyl ether (1:1, 100 ml) and filtered through celite. Purification of the crude product by flash chromatography yielded 192 mg (30%) of benzamide **103b** as a white solid. The optical purity was determined to be 99 %ee by HPLC analysis (Chiracel OD, flow rate = 1.0 ml/min of 5:95 *i*-PrOH/hexane, T_r (major, *R*) 23.8 min, T_r (minor, *S*) 26.4 min). Colourless solid; R_f 0.24 (1:2

EtOAc/hexane); mp 82-85°C; $[\alpha]^{21}_{D}$ –117.5° (*c* 0.394, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.24 (m, 10H, aromatic), 7.07 (br, 1H, NH), 4.67 (s, 1H, $CHOCH_3$), 4.49 (dd, *J* = 14.7 Hz, 5.8 Hz, 1H, $NHCH_2Ph$), 4.42 (dd, *J* = 14.7 Hz, 5.8 Hz, 1H, $NHCH_2Ph$),3.34 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 138.1, 137.0, 128.6, 128.4, 128.3, 127.6, 127.4, 126.9, 83.8, 57.1, 42.9, 25.4; IR (neat) ν 3350, 3000, 2920, 1660, 1530, 1450, 1320, 1190, 1090, 1010, 970, 740, 690 cm^{-1}; HRMS (NBA) calcd for $C_{16}H_{17}NO_2$ $[M+H]^+$: 256.13376, found: 256.13450.

***(4R,5R)-N,N,N′,N′*-tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide (103c).**



103c

To a solution of (+)-(*R,R*)-*N,N,N′,N′*-tetramethyltartramide (2.15 g, 10.5 mmol) in acetone (10 ml), prepared according to the method of Seebach,[287] was added dimethoxypropane (10 ml) and *p*-toluene sulphonic acid (20 mg). The flask is connected to an exit bubbler and stirred at room temperature for 24 hours or until TLC analysis indicates that the reaction is complete. The volatiles were removed under reduced pressure and purification of the crude product by crystallization from dichloromethane/hexanes yielded 2.42 g (94%) of acetonide **103c** as white crystals; R_f 0.48 (2:1 EtOAc/hexane); mp 87-89°C; $[\alpha]^{21}_{D}$ –1.73° (*c* 1.846, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 2H, OC*H*CO), 3.18 (s, 6H, NCH_3), 2.97 (s, 6H, NCH_3), 1.45 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 111.6, 75.1, 36.7, 35.4, 26.0; IR (KBr) ν 3000, 2940, 1750, 1380, 1260,

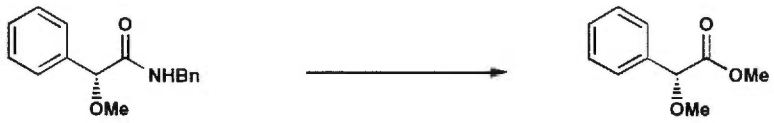
1200, 1150, 1100, 1050, 860 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{23}NO_3$ $[M+H]^+$: 245.15013, found: 245.14900.

(2*S*)-Ethyl-2-methyl-2-(6-methoxynaphthyl)acetate (104a).

103a **104a**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **103a** (128 mg, 0.40 mmol) to ester **104a**. Purification of the crude product by flash chromatography (1:15 ethyl acetate/hexanes) yielded 84 mg (82%) of ethyl ester **104a** as a colourless oil. The optical purity was determined to be 92 %ee by HPLC analysis (Chiracel OD, flow rate = 1.0 ml/min of 2:98 *i*-PrOH/hexane, T_r (minor, *R*) 8.94 min, T_r (major, *S*) 10.24 min). Colourless oil; R_f 0.48 (1:5 EtOAc/hexane); $[\alpha]^{21}_D$ +48.17° (*c* 5.834, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.66 (m, 3H, aromatic), 7.42-7.39 (m, 1H, aromatic), 7.24-7.10 (m, 2H, aromatic), 4.14 (dq, *J* = 7.1 Hz, 3.6 Hz, OCH_2CH_3), 4.11 (dq, *J* = 7.1 Hz, 3.6 Hz, OCH_2CH_3), 3.90 (s, 3H, OCH_3), 3.83 (q, *J* = 7.2 Hz, 1H, $CHCH_3$), 1.56 (d, *J* = 7.2 Hz, 3H, $CHCH_3$), 1.19 (t, *J* = 7.1 Hz, OCH_2CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 157.5, 1353.8, 133.6, 129.2, 128.9, 127.0, 126.1, 125.8, 118.8, 105.5, 60.6, 55.2, 45.4, 18.5, 14.0; IR (neat) ν 2980, 1730, 1600, 1450, 1390, 1370, 1320, 1260, 1230, 1180, 1150 ,1020, 890, 850, 810 cm^{-1}; HRMS (NBA) calcd for $C_{16}H_{18}O_3$ $[M+H]^+$: 258.12558, found: 258.12440.

(2*S*)-Ethyl-2-methoxy phenylacetamide (104b).



103b **104b**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **103b** (71 mg, 0.28 mmol) to ester **104b**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 15 mg (28%) of ethyl ester **104b** as a colourless oil. The optical purity was determined to be 99 %ee by HPLC analysis (Chiracel OJ, flow rate = 0.9 ml/min of 10:90 *i*-PrOH/hexane, T_r (*R*) 15.36 min, T_r (*S*) 17.49 min). Colourless oil; R_f 0.34 (1:7 EtOAc/hexane); $[\alpha]^{21}_D$ –124.1° (*c* 2.386, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.35 (m, 5H, aromatic), 4.78 (s, 1H, C*H*CO_2Me), 3.71 (s, 3H, COOC*H*$_3$), 3.40 (s, 3H, CHOC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 136.0, 128.6, 128.5, 127.0, 82.3, 57.1, 52.1; IR (neat) ν 3300, 2990, 1750, 1460, 1440, 1260, 1210, 1110, 1080, 1010 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{13}O_3$ $[M+H]^+$: 181.08647, found: 181.08490.

(4*R*,5*R*)-Ethyl-*N*,*N*-dimethyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide-5-carboxylate (104c).

103c **104c**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **103c** (276 mg, 1.13 mmol) to ester **104c**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 93 mg (34%) of ethyl ester **104c** as a colourless oil. R_f 0.41 (1:2 EtOAc/hexane); $[\alpha]^{21}_D$ –22.4° (*c* 1.142, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (d, *J* = 5.5 Hz, 1H, CHC*H*O), 4.90 (d, *J* = 5.5 Hz, 1H, CHC*H*O), 4.26 (q, *J* = 7.2 Hz, 1H, OCH_2CH$_3$), 4.25 (q, *J* = 7.2 Hz, 1H, OCH_2CH$_3$), 3.16 (s, *J* = 3H, NCH_3), 3.01 (s, *J* = 3H, NCH_3), 1.49 (s, *J* = 3H, CCH_3), 1.43 (s, *J* = 3H, CCH_3), 1.31 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 167.6, 112.7,.76.3, 76.2, 61.5, 36.9, 35.9, 26.2, 26.1, 14.0; IR (neat) ν 3000, 2940, 1760, 1650, 1380, 1260, 1200, 1150, 1100, 1050, 1020, 850 cm^{-1}; HRMS (THIO) calcd for $C_{11}H_{20}NO_5$ $[M+H]^+$: 246.13416, found: 246.13520.

(±)-*N*-Methyl-*N*-(1-phenylethyl)-3-phenylpropanamide (112a).

57 **112a**

To a solution of amide **57** (853 mg, 3.37 mmol) in tetrahydrofuran (10 ml) at 0°C under an argon atmosphere was added DMF (2 ml), NaH (202 mg), and methyl iodide (420 µl, 6.74 mmol). The reaction was allowed to warm to room temperature while stirring. After 1 hour at or until the reaction was judged complete by TLC analysis, water (1 ml) was carefully added to the solution. The reaction was diluted with diethyl ether (80 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude

product by flash chromatography (1:4 ethyl acetate/hexanes) yielded 836 mg (93%) of amide **112a** as a colourless oil; R_f 0.20 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.12 (m, 10H, aromatic), 6.09 (q, *J* = 7.1 Hz, 0.7H, PhC*H*CH$_3$), 5.08 (q, *J* = 7.1 Hz, 0.3H, PhC*H*CH$_3$), 3.03 (t, *J* = 7.4 Hz, 2 H, PhCH_2CH$_2$), 2.76 (t, *J* = 7.4 Hz, 0.6H, CH$_2$CH_2CO), 2.67 (s, 0.9H, CH_3N), 2.63, (t, *J* = 7.4 Hz, 1.4H, CH$_2$CH_2CO), 2.54 (s, 2.1H, CH_3N), 1.50 (d, *J* = 7.1 Hz, 0.9H, PhCHCH_3), 1.44 (d, *J* = 7.1 Hz, 2.1H, PhCHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 141.2, 140.5, 128.5, 128.3, 128.2, 127.2, 127.1, 127.0, 126.2, 125.9, 54.4, 50.0, 35.6, 35.0, 31.5, 31.3, 29.2, 27.7, 17.4, 15.4; IR (neat) ν 3020, 2980, 2940, 1640, 1490, 1450, 1400, 1310, 1110 cm^{-1}; HRMS (THIO) calcd for $C_{18}H_{22}NO$ $[M+H]^+$ 268.17014, found 268.17080.

(±)-*N*-Benzyl-*N*-(1-phenylethyl)-3-phenylpropanamide (112b).

57 **112b**

Secondary amide **57** (1.126 g, 4.45 mmol) was converted to the tertiary amide **112b** following the same procedure as that used for the synthesis of amide **112a**. Purification of the crude product by flash chromatography (1:5 ethyl acetate/hexanes) yielded 1.45 g (95%) of amide **112b** as a colourless oil; R_f 0.27 (1:5 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-6.96 (m, 5H, aromatic), 6.18, (q, *J* = 7.2 Hz, 0.7H, NC*H*CH$_3$Ph), 5.16 (q, *J* = 7.2 Hz, 0.3H, NC*H*CH$_3$Ph), 4.92 (d, *J* = 15.4 Hz, 0.3H, PhCH_2N), 4.28 (d, *J* = 18.0 Hz, 0.7H PhCH_2N), 4.07 (d, *J* = 18.0 Hz, 0.7H, PhCH_2N), 3.95 (d, *J* = 15.4 Hz, 0.3H, PhCH_2N), 3.08-2.92 (m, 1H, PhCH_2CH$_2$), 2.87-2.80 (m, 0.3H, CH$_2$CH_2CO), 2.60- 2.46 (m, 0.7H, CH$_2$CH_2CO), 1.38 (d, *J* = 7.2 Hz, 3H, PhCHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 141.0, 140.9, 138.2, 128.5, 128.4, 128.3, 128.2, 128.0, 127.3, 127.1, 126.8, 126.4, 125.9, 51.4, 46.9, 35.6,

31.5, 16.8; IR (neat) ν 3020, 1640, 1490, 1450, 1400, 1370, 1200, 1020, 740, 720 cm^{-1}; HRMS (THIO) calcd for $C_{24}H_{26}NO$ $[M+H]^+$ 344.20145, found 344.20250.

Ethyl-3-phenylpropanoate (113a).

112a **113a**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **112a** (207 mg, 0.78 mmol) to ester **113a**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 130 mg (94%) of ethyl ester **113a** as a colourless oil; refer to compound **89a** for characterization data.

Ethyl-3-phenylpropanoate (113b).

112b **113b**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **112b** (210 mg, 0.61 mmol) to ester **113b**. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 65 mg (60%) of ethyl ester **113b** as a colourless oil; refer to compound **89a** for characterization data.

(±)-5-phenylhydantoin (122).

122

Benzaldehyde (5.0 ml, 49.2 mmol), ethanol (50%, 60 ml), KCN (6.4 g, 98.4 mmol) and $(NH_4)_2CO_3$ (28 g, 295.1 mmol) were combined in a 200 ml round bottom flask. The flask was covered with a septum and wired shut. The reaction was then carefully heated to 60°C. Pressure can be periodically relieved as a hypodermic needle is inserted into the septum to vent off some HCN if the pressure begins to look excessive. After 18 hours, the yellowish solution has become brown. The volume of the reaction is reduced to half under reduced pressure and 10% HCl (50 ml) is then carefully added to acidify the reaction which results in the formation of crystals. The product was recrystallized from methanol/water which yielded 7.0 g (81%) of hydantoin **122** as beige crystals; R_f 0.10 (EtOAc); mp 180-182°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (br, 1H, N*H*), 7.53 (br, 1H, N*H*), 7.45-7.34 (m, 5H, aromatic), 5.22 (d, *J* = 1.4 Hz, 1H, C*H*NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 158.1, 136.9, 129.5, 129.2, 127.6, 62.7; IR (neat) ν 3510, 3310, 3040, 2760, 1720, 1460, 1430, 1420, 1190, 750 cm^{-1}; HRMS (FAB+) calcd for $C_9H_8N_2O_2$ $[M+H]^+$: 177.06640, found: 177.06490.

(±)-2-Phenyl-2,2-diethoxy-1-(*N'*-ethoxycarbonyl)amino-*N*-trifloromethansufonyl ethylamine (131).

122 **131**

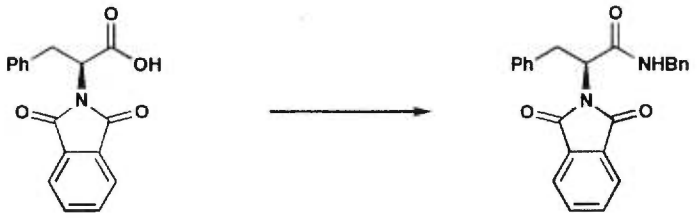
To a solution of hydantoin **122** (176 mg, 1.0 mmol) in dry dichloromethane (5 ml) was added pyridine (570 µl, 7.0 mmol). The solution was cooled to -30°C using an acetone-dry ice bath and then neat triflic anhydride (570 µl, 3.0 mmol) was added slowly down the side of the flask. The reaction is allowed to warm up 0° at which temperature it is stirred for 12 hours. Absolute ethanol (2 ml, > 33 mmol) was then added to the solution at 0°C and then the reaction was stirred for and additional 12 hours at room temperature. Diethyl ether (80 ml) was then added and then the solution was washed 10% HCl (2 x 15 ml) (which should have been avoided once the true identity of the product was discovered), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:5 ethyl acetate/hexanes) yielded 233 mg of a product which was still impure. Crystallization from diethyl ether/hexanes yielded 203 mg (47%) of compound **131** as beige crystals which were suitable for x-ray analysis[288]; R_f 0.50 (1:5 EtOAc/hexane); mp 163-166°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.26 (m, 5H, aromatic), 5.65 (br, 1H, NHC*H*NH), 5.25 (br, 1H, N*H*), 4.83 (d, *J* = 10.1 Hz, 1H, N*H*), 4.17-4.06 (m, 2H, OC*H*$_2$CH$_3$), 3.66-3.61 (m, 2H, OC*H*$_2$CH$_3$), 3.59-3.46 (m, 2H, OC*H*$_2$CH$_3$), 1.60-1.19 (m, 9H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 135.1, 129.4, 129.0, 128.7, 127.3, 124.0, 120.8, 117.6, 101.1, 65.0, 61.6, 58.2, 27.9, 14.9, 14.8, 14.3; IR (KBr) ν 3400, 3000, 2940, 1720, 1520, 1450, 1420, 1380, 1340, 1230 1190, 1140, 1050 cm^{-1}. For x-ray crystal data, see Appendix 2.

(2*S*)-2-(*N*-phthalimido)amino-3-phenylpropanoic acid (133).

132 **133**

Prepared according to Billman and Harting.[289] (*S*)-Phenylalanine **132** (1 g, 6.0 mmol) was combined with phthalic anhydride (900 mg, 6.0 mmol) in a Pyrex test tube. The mixture of solids is heated to 150°C for 15 minutes which melts the two compounds to form a homogeneous liquid. Some phthalic anhydride sublimes. The crude product is allowed to cool and is purified by crystallization from ethanol/hexanes which yields 1.60 g (90%) of acid **133** as white crystals; R_f 0.30 (EtOAc); mp 171-173°C (Lit. 174-175°C); $[\alpha]^{21}_{D}$ –204.7° (*c* 1.000, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10 (br, 1H, COOH), 7.79-7.76 (m, 2H, aromatic), 7.69-7.66 (m, 2H, aromatic), 7.26-7.13 (m, 5H, aromatic), 5.23 (t, *J* = 7.9 Hz, C*H*CH_2), 3.59 (d, *J* = 7.9 Hz, CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 167.3, 136.3, 134.1, 131.4, 128.7, 128.5, 126.9, 123.5, 53.0, 34.3; IR (neat) ν 3280, 1750, 1700, 1390, 1210, 1100, 720 cm^{-1}. The same procedure was used to make the enantiomer starting from (*R*)-phenylalanine.

(2*S*)-*N*-Benzyl-2-(*N*-phthalimido)amino-3-phenylpropanamide (134).



133 **134**

To a sample of acid **133** (552 mg, 1.87 mmol) was added benzylamine (310 µl, 2.80 mmol), hydroxybenzotriazole (HOBTa) (255 mg, 1.87 mmol), $CuCl_2$ (130 mg, 0.94 mmol), DMF (5 ml) and EDC (540 mg, 2.8 mmol) at room temperature under an argon atmosphere. After 12 hours or until TLC analysis indicates near complete consumption of the starting material, the reaction was diluted with diethyl ether (100ml), washed with 10% HCl (2 x 15 ml), filtered through celite, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 91 mg (13%) of amide **134** as a white solid. The optical purity was determined to be 96 %ee by HPLC analysis (Chiracel OJ, flow rate = 1.0 ml/min of 20:80 *i*-PrOH/hexane, T_r (major) 20.2 min, T_r (minor) 25.3 min).White solid; R_f 0.18 (1:3 EtOAc/hexane); mp 199-201°C; $[\alpha]^{21}_D$ –108.8° (*c* 0.640, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.76 (m, 2H, aromatic), 7.69-7.63 (m, 2H, aromatic), 7.33-7.07 (m, 5H, aromatic), 6.50 (br, 1H, N*H*), 5.14 (dd, *J* = 10.3 Hz, 6.5 Hz, 1H, C*H*CH_2), 4.49 (dd, *J* = 14.9 Hz, 5.7 Hz, 1H, NHC*H*$_2$Ph), 4.42 (dd, *J* = 14.9 Hz, 5.7 Hz, 1H, NHC*H*$_2$Ph), 3.60 (dd, *J* = 14.1 Hz, 6.4 Hz, 1H, CHC*H*$_2$), 3.54 (dd, *J* = 14.1 Hz, 10.3 Hz, 1H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.9, 137.6, 136.5, 134.2, 131.3, 128.8, 128.6, 128.5, 127.5, 127.4, 126.8, 123.4, 55.8, 43.7, 37.8; IR (KBr) ν 3450, 3300, 2920, 1720, 1650, 1540, 1380, 1100, 710 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{21}N_2O_3$ $[M+H]^+$: 385.15521, found: 385.15400.

(2*S*)-Ethyl-2-(*N*-phthalimido)amino-3-phenylpropanoate (135).

134 **135**

The general procedure for the conversion of secondary amides to esters was used for the conversion of amide **134** (87 mg, 0.23 mmol) to ester **135**. Purification of the crude product by flash chromatography (1:5 ethyl acetate/hexanes) yielded 56 mg (77%) of ethyl ester **104c** as a colourless oil. The optical purity was determined to be 85 %ee by HPLC analysis (Chiracel OJ, flow rate = 1.0 ml/min of 15:85 *i*-PrOH/hexane, T_r (major) 10.7 min, T_r (minor) 13.1 min). Colourless oil; R_f 0.33 (1:5 EtOAc/hexane); $[\alpha]^{21}_D$ –127.5° (*c* 2.104, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H, aromatic), 7.69-7.66 (m, 2H, aromatic), 7.49-7.14 (m, 5H, aromatic), 5.14 (dd, *J* = 11.0 Hz, 5.5 Hz, 1H, C*H*CH$_2$), 4.26 (q, *J* = 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.25 (q, *J* = 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 3.60 (dd, *J* = 14.0 Hz, 5.5 Hz, 1H, CHC*H*$_2$), 3.53 (dd, *J* = 14.0 Hz, 11.0 Hz, 1H, CHC*H*$_2$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.3, 136.7, 133.9, 131.4, 128.7, 128.4, 126.7, 123.3, 61.9, 53.3, 34.5, 14.0; IR (neat) ν 2990, 1780, 1750, 1710, 1470, 1380, 1240, 1190, 1100, 1020, 870, 710 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.12360, found: 324.12190.

Experimental Section: Chapter 4

1-(2-phenylethyl)-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148a).

147a **148a**

General procedure for the conversion of tertiary and secondary amides to cyclic ortho esters. To a solution of amide **147a** (297 mg, 1.45 mmol) in dichloromethane (10 ml) under an argon atmosphere was added pyridine (354 µl, 3.0 mmol). The solution was cooled to -40°C and neat triflic anhydride (320 µl, 1.3 mmol) was added slowly. The reaction was then allowed to slowly warm up to 0°C. Stirring was continued for another 4 to 12 hours. The septum was then removed for an instant as 1,1,1-*tris*-hydroxymethylene ethane (261 mg, 1.5 mmol) was added quickly. Then absolute ethanol (0.8 ml) or acetonitrile (2 ml) was added via syringe. The reaction was allowed to stir for 12 hours. The reaction was filtered through neutralized silica. The reaction medium was transferred using CH_2Cl_2 onto a short column of silica which was pretreated with 5% Et_3N in a 1:2 Et_2O-pentane mixture which also serves as the eluant. After filtering, the solvent was removed in under reduced pressure to provide an almost analytically pure compound which could be further purified by crystallization from diethyl ether/hexanes or by chromatography on silica using 5-15% EtOAc in hexanes with 2% Et_3N. This procedure yielded 298 mg (88%) of ortho ester **148a** as a white solid; R_f 0.37 (1:7 EtOAc/hexane with 1% Et_3N); mp 119-121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.16 (m, 5H, aromatic), 3.92 (s, 6H, OCH_2C), 2.76 (dd, J = 12.7 Hz, 4.8 Hz, 1H, CH_2CH_2Ph), 2.76 (dd, J = 9.2 Hz, 8.3 Hz, 1H, CH_2CH_2Ph), 1.98 (dd, J = 12.7

Hz, 4.8 Hz, 1H, CH_2CH_2Ph), 1.98 (dd, J = 9.2 Hz, 8.3 Hz, 1H, CH_2CH_2Ph), 0.80 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 128.3, 128.2, 125.6, 108.6, 72.5, 38.4, 30.2, 29.5, 14.4; IR (KBr) ν 2960, 2890, 1490, 1470, 1450, 1390, 1370, 1350, 1300, 1250, 1180, 1040, 980, 740, 700 cm^{-1}; HRMS (NBA) calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.13342, found: 235.13410; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.76; H, 7.76. Found: C, 71.88; H, 8.18.

1-(2-phenylethyl)-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148b).

147b **148b**

Amide **147b** (247 mg, 1.03 mmol) was converted to ortho ester **148b** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 183 mg (76%) of ortho ester **148b** as a white solid; refer to compound **148a** for characterization data.

1-phenylmethyl-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148c).

147c **148c**

Amide **147c** (231 mg, 1.03 mmol) was converted to ortho ester **148c** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 182 mg (81%) of ortho ester **148c** as a white

solid; R_f 0.35 (1:7 EtOAc/hexane with 1% Et_3N); mp 77-79°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5H, aromatic), 3.88 (s, 6H, OCH_2C), 3.00 (s, 2H, CH_2Ph), 0.77 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 130.5, 127.8, 126.4, 108.5, 72.6, 42.8, 30.4, 14.5; IR (KBr) ν 2980, 2940, 2880, 1490, 1470, 1450, 1390, 1350, 1270, 1050, 1000, 980, 840, 700 cm^{-1}; HRMS (NBA) calcd for $C_{13}H_{16}O_3$ $[M+H]^+$: 221.11777, found: 221.11710.

1-phenylmethyl-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148d).

147d **148d**

Amide **147d** (456 mg, 2.39 mmol) was converted to ortho ester **148d** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 379 mg (72%) of ortho ester **148d** as a white solid; refer to compound **148c** for characterization data.

1-(2-(1-phenylpropyl))-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148e).

147e **148e**

Amide **147e** (341 mg, 1.57 mmol) was converted to ortho ester **148e** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 230 mg (59%) of ortho ester **148e** as a white

solid; R_f 0.48 (1:10 EtOAc/hexane with 2% Et_3N); mp 86-89°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.13 (m, 5H, aromatic), 3.91 (s, 6H, OCH_2C), 3.14 (dd, *J* = 13.4 Hz, 3.2 Hz, 1H, $PhCH_2CH$), 2.25 (dd, *J* = 13.4 Hz, 11.4 Hz, 1H, $PhCH_2CH$), 2.00 (ddq, *J* = 11.4 Hz, 6.8 Hz, 3.2 Hz, 1H, $PhCH_2CHCH_3$), 0.84 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.79 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 129.2, 128.0, 125.5, 110.2, 72.6, 41.7, 36.9, 30.2, 14.4, 12.9; IR (KBr) ν 2960, 2940, 2840, 1450, 1290, 1080, 1050, 990, 950, 920, 700 cm^{-1}; HRMS (NBA) calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.14906, found: 249.15030.

1-(2-naphthyl)-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148f).

147f **148f**

Amide **147f** (247 mg, 1.09 mmol) was converted to ortho ester **148f** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 245 mg (69%) of ortho ester **148f** as a white solid; R_f 0.32 (1:7 EtOAc/hexane with 2% Et_3N); mp 110-112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H, aromatic), 7.87-7.79 (m, 3H, aromatic), 7.72-7.70 (m, 1H, aromatic), 7.47-7.23 (m, 2H, aromatic), 4.13 (s, 6H, OCH_2C), 0.87 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 133.6, 132.7, 128.6, 127.8, 127.5, 126.4, 125.9, 125.1, 123.3, 107.5, 73.3, 30.5, 14.4; IR (KBr) ν 2940, 2880, 1470, 1400, 1350, 1330, 1190, 1120, 1080, 990, 970, 900, 860, 820, 740 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{17}O_3$ $[M+H]^+$: 257.11777, found: 257.11670.

1-(2-naphthyl)-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148g).

147g **148g**

Amide **147g** (253 mg, 0.97 mmol) was converted to ortho ester **148g** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 174 mg (70%) of ortho ester **148g** as a white solid; refer to compound **148f** for characterization data.

(*1S*,2S)-*N,N*-Dimethyl-2-phenylcyclopropyl carboxamide (147h).**

147h

To a solution of *N,N*-dimethylamine (0.72 ml, 12.4 mmol) in dichloromethane (15 ml) under an argon atmosphere at 0°C was added trimethylaluminium (1.1 ml, 11.6 mmol). After 15 minutes, this solution was added slowly via cannula to a solution of methyl *trans*-2-phenyl-1-cyclopropyl carboxylate (1.477 g, 8.3 mmol) in dichloromethane (15 ml) at 0°C. After 18 hours at room temperature, water (1 ml) was carefully added to the solution. The solution was then diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 1.54 g (98%) of amide **147h** as a white solid; R_f 0.17 (2:3 EtOAc/hexane); mp 84-86°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H, aromatic), 7.20-7.16 (m, 1H,

aromatic), 7.12-7.10 (m, 2H, aromatic), 3.05 (br, 6H, NCH_3), 2.47 (ddd, J = 9.0 Hz, 6.2 Hz, 4.2 Hz, 1H, $PhCHCH_2$), 1.99 (ddd, J = 8.3 Hz, 5.3 Hz, 4.2 Hz, 1H, CH_2CHCO), 1.63 (ddd, J = 9.0 Hz, 5.3 Hz, 4.2 Hz, 1H, $CHCH_2CH$), 1.25 (ddd, J = 8.3 Hz, 6.2 Hz, 4.2 Hz, 1H, $CHCH_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.9, 128.2, 126.0, 125.9, 36.5 (br), 25.3, 22.9, 16.0; IR (film) ν 3500, 3020, 2920, 1640, 1490, 1410, 1370, 1180, 1140, 750, 690 cm^{-1}; HRMS (NBA) calcd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.12318, found: 190.12420; Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.44; H, 8.27; N, 7.48.

1-((*1S*,2S)-2-phenylcyclopropyl)-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (148h).**

147h **148h**

Amide **147h** (254 mg, 1.45 mmol) was converted to ortho ester **148h** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 240 mg (67%) of ortho ester **148h** as a white solid; R_f 0.44 (1:10 EtOAc/hexane with 1%Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.07 (m, 5H, aromatic), 3.90 (s, 6H, OCH_2C), 2.18 (ddd, J = 9.1 Hz, 5.7 Hz, 4.6 Hz, 1H, $PhCHCH_2$), 1.54 (ddd, J = 9.0 Hz, 5.7 Hz, 4.6 Hz, 1H, CH_2CHCO), 1.23 (ddd, J = 9.1 Hz, 5.7 Hz, 4.7 Hz, 1H, $CHCH_2CH$), 0.86 (ddd, J = 9.0 Hz, 5.7 Hz, 4.6 Hz, 1H, $CHCH_2CH$), 0.78 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 128.1, 126.1 (2), 125.6, 107.9, 72.7, 30.4, 26.3, 19.1, 14.4, 11.7; IR (neat) ν 2960, 2940, 2880, 1470, 1410, 1340, 1260, 1190, 1120, 1050, 1010, 980, 950, 750, 690 cm^{-1}; HRMS (NBA) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.13342, found: 247.13410.

(1*S,2*S**)-*N*-methyl-2-phenylcyclopropyl carboxamide (147i).**

147i

To a solution of *N*-methylamine (0.650 ml, 12.1 mmol) in dichloromethane (10 ml) under an argon atmosphere at 0°C was added trimethyl aluminum (1.1 ml, 11.3 mmol). After 15 minutes, this solution was added slowly via cannula to a solution of methyl *trans*-2-phenyl-1-cyclopropyl carboxylate (1.544 g, 8.6 mmol) in dichloromethane (10 ml) at 0°C. After 18 hours at room temperature, water (1 ml) was carefully added to the solution. The solution was then diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 1.30 g (86%) of amide **147i** as a white solid; R_f 0.23 (1:1 EtOAc/hexane); mp 96-98°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.00 (m, 5H, Ph), 6.31 (br, 1H, N*H*), 2.78 (d, J = 4.7 Hz, 1H, NCH_3), 2.43 (ddd, *J* = 9.1 Hz, 6.3 Hz, 4.1 Hz, 1H, PhC*H*CH_2), 1.64 (ddd, *J* = 8.2 Hz, 5.2 Hz, 4.1 Hz, 1H, CH_2C*H*CO), 1.56 (ddd, *J* = 9.1 Hz, 5.2 Hz, 4.4 Hz, 1H, CHCH_2CH), 1.18 (ddd, *J* = 8.2 Hz, 6.3 Hz, 4.4 Hz, 1H, CHCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.7, 128.2, 126.0, 125.8, 26.3, 26.2, 24.7, 15.5; IR (film) ν 3280, 3090, 1640, 1580, 1400, 1250, 1160, 1080, 930, 910, 840 cm^{-1}; HRMS (NBA) calcd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.107545, found: 176.10810; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.14; H, 7.68; N, 7.98.

1-((1*S,2*S**)-2-phenylcyclopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (148i).**

147i **148i**

Amide **147i** (456 mg, 2.39 mmol) was converted to ortho ester **148i** following the general procedure that was used for the synthesis of ortho ester **148a**. Purification of the crude product by crystallization from diethyl ether/hexanes yielded 379 mg (72%) of ortho ester **148i** as a white solid colourless oil; refer to compound **148h** for characterization data.

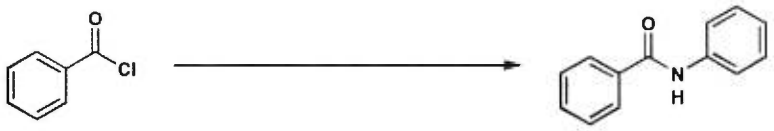
Experimental Section: Chapter 5

N-Benzyl benzamide (154).

154

To a solution of benzoyl chloride (10 ml, 86 mmol) in dichloromethane (100 ml) under an argon atmosphere was slowly added pyridine (10.5 ml, 129 mmol) and benzylamine (9.4 ml, 86 mmol) at -78°C. The heterogeneous solution was allowed to warm up to room temperature and was stirred for an additional 18 hours. The reaction was diluted with diethyl ether (250 ml) washed with 10% HCl (2 x 50 ml), saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by crystallization from ethyl acetate/hexanes yielded 14.6 g (80%) of amide **154** as white crystals; R_f 0.42 (1:2 EtOAc/hexane); mp 104-107°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H, aromatic), 7.52-7.26 (m, 8H, aromatic), 6.58 (br, 1H, N*H*), 4.62 (d, *J* = 5.7 Hz, 2H, PhCH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 138.1, 134.3, 131.4, 128.6, 128.4, 127.8, 127.4, 126.9, 44.0; IR (KBr) ν 3290, 3060, 1640, 1600, 1550, 1490, 1410, 1310, 1250, 980, 690 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{14}NO$ $[M+H]^+$: 212.10754, found: 212.10800.

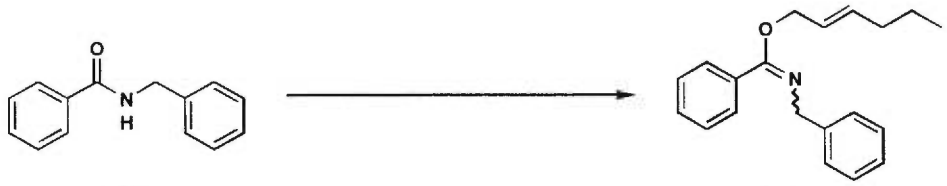
N-Phenyl benzamide (156).



156

According to the method used for the synthesis of compound **48**, a suspension of aniline (16.3g, 175 mmol) in CH_2Cl_2 (300 ml) and pyridine (15.7 ml, 193 mmol) was cooled to -78°C. Benzoyl chloride (20.3 ml, 175 mmol) was then added slowly giving a white suspension. The reaction was stirred while warming up to room temperature slowly. EtOAc (500 ml) was added and the reaction was washed with 10% HCl (2 X 100 ml), saturated $NaHCO_3$ (100 ml), dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was crystallized from MeOH, filtered, and then placed under high vacuum until a constant mass was observed. The mother liquor was concentrated under reduced pressure and the crude product was crystallized from MeOH to give a second batch. The two batches were then combined to give 32.91 g (95.4%) of amide **48** as white crystals; R_f 0.39 (1:3 EtOAc/hexane); mp 162-164°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br, 1H, N*H*), 7.85 (m, 2H, Ph), 7.65-7.62 (m, 2H, Ph), 7.53-7.51 (m, 1H, Ph), 7.48-7.44 (m, 2H, Ph), 7.38-7.34 (m, 2H, Ph), 7.16-7.13 (m, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.9, 134.9, 131.7, 129.0, 128.7, 127.0, 124.5, 120.2; IR (KBr) ν 3340, 1660, 1600, 1580, 1530, 1450, 1440, 1320, 1260, 750, 720, 690 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{12}NO$ $[M+H]^+$: 198.09189, found: 198.09280.

cis/trans-_O_-1-(_trans_-2-hexenyl)-_N_-benzyl benzimidate (155).

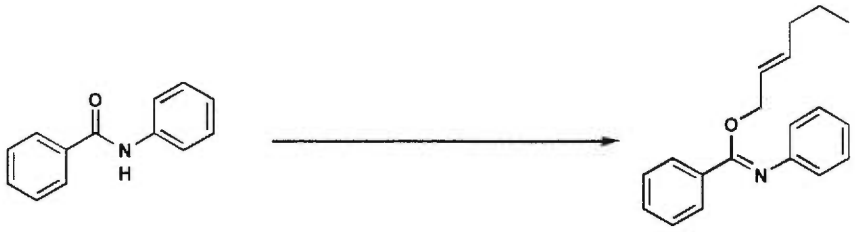


154 **155**

To a solution of amide **154** (270 mg, 1.37 mmol) in dichloromethane (10 ml) at –30°C under an argon atmosphere was added pyridine (335 µl, 4.11 mmol). Triflic anhydride (230 µl, 1.37 mmol) was then added very slowly and the reaction was allowed to stir while warming up to 0°C over the course of 2 hours. After an additional 140 minutes at 0°C, the colourless solution was cooled to -50°C and *trans*-2-hexen-1-ol (161 µl, 1.37 mmol) was added slowly followed by triethylamine (573 µl, 4.11 mmol). The solution was stirred while slowly warming up to room temperature over the course of 2 hours. The reaction was diluted with diethyl ether (50 ml) containing 2% triethylamine, filtered trough a short column of triethylamine neutralized silica gel and concentrated under reduced pressure. The crude product could be further purified by flash chromatography (1:15 ethyl acetate/hexanes with 1% triethylamine) to yield 312 mg (78%) of imidate **155** as a colourless oil; R_f 0.54 (1:15 EtOAc/hexane with 1% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H, aromatic), 7.50-7.24 (m, 8H, aromatic), 5.82 (m, 1H, CH=C*H*CH$_2$CH$_2$), 5.58 (m, 1H, CH=C*H*CH$_2$O), 4.79 (s, 2H, PHC*H*$_2$N), 4.56 (d, J = 6.5 Hz, 2H, OC*H*$_2$CH=CH), 1.52 (dt, J = 7.0 Hz, 6.2 Hz, 2H, CH=CHC*H*$_2$CH$_2$), 1.40 (dt, J = 7.3 Hz, 7.0 Hz, 2H, CH$_2$C*H*$_2$CH$_3$) ,0.89 (t, J = 7.3 Hz, 3H, CH$_2$C*H*$_3$), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 151.4, 148.1, 139.1, 137.1, 131.6, 129.5, 129.1, 128.4, 128.3, 128.0, 127.9, 127.6, 126.8, 123.3, 68.5, 49.6, 49.4, 34.2, 21.9, 13.5; IR (neat) ν 3060, 3030, 2960, 2930, 2870, 1740, 1710, 1530, 1490, 1450,

1390, 1360, 1260, 1040, 980, 920, 780, 730, 700 cm^{-1}; HRMS (THIO) calcd for $C_{20}H_{24}NO$ $[M+H]^+$: 294.18579, found: 294.18530.

O-1-(*trans*-2-hexenyl)-*N*-phenyl benzimidate (157).



156 **157**

To a solution of amide **156** (225 mg, 1.14 mmol) in dichloromethane (10 ml) at –30°C under an argon atmosphere was added pyridine (280 µl, 3.43 mmol). Triflic anhydride (192 µl, 1.14 mmol) was then added very slowly and the reaction was allowed to stir while warming up to 0°C over the course of 2 hours. After an additional 6.5 hours at 0°C, the colourless solution was cooled to -50°C and *trans*-2-hexen-1-ol (135 µl, 1.14 mmol) was added slowly followed by triethylamine (480 µl, 3.43 mmol). The solution was stirred while slowly warming up to room temperature over the course of 2 hours. The reaction was diluted with diethyl ether (50 ml) containing 2% triethylamine, filtered trough a short column of triethylamine neutralized silica gel and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:10 ethyl acetate/hexanes) yielded 160 mg (51%) of imidate **157** as a colourless oil; R_f 0.13 (3:97 Et_2O/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.13 (m, 7H, aromatic), 6.95-6.91 (m, 1H, aromatic), 6.71-6.69 (m, 2H, aromatic), 5.87 (dt, J = 15.4 Hz, 6.5 Hz, 1H, CH=C*H*CH_2), 5.78 (dt, J =15.4 Hz, 5.9 Hz, 1H, CH=C*H*CH_2O), 4.81 (d, J = 5.9 Hz, 2H, O*C*H_2CH=CH), 2.08 (dt, J = 7.8 Hz, 6.5 Hz, 2H, CH=CHCH_2CH_2), 1.44 (tq, J = 7.3 Hz, 7.3 Hz, 2H, $CH_2CH_2CH_3$), 0.93 (t, J = 7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 148.4,

135.5, 131.4, 129.7, 129.2, 128.7, 124.8, 122.4, 121.6, 67.3, 34.4, 22.1, 13.6; IR (neat) ν 2960, 2930, 2870, 1640, 1600, 1490, 1450, 1310, 1290, 1260, 1110, 1080, 1030, 980, 780, 770, 700, 6700 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{21}NO$ $[M]^+$: 279.16232, found: 279.16350.

Experimental Section: Chapter 6

2-(2-Phenylethyl)-Δ^2-thiazoline (172a).

171a **172a**

General procedure for the conversion of secondary and tertiary amides to Δ^2-thiazolines. To a solution of the amide **171** (226 mg, 1.1 mmol) in dry dichloromethane (5 ml) was added 2.5 equivalents of dry pyridine (270 µl, 3.3 mmol). The solution was cooled to -40°C using an acetone-dry ice bath and then 1.3 equivalents of neat triflic anhydride (240 µl, 1.43 mmol) was added slowly down the side of the flask. The solution was allowed to warm up to 0°C (approximately 2 hours) and was then stirred at 0°C for another 4 to 6 hours. The reaction was then cooled to -30°C. Amino ethanethiol hydrochloride (190 mg, 1.65 mmol) was quickly weighed, pulverized and then added to the reaction as a solid. This was followed by triethylamine or pyridine (270 µl, 3.3 mmol). It is essential to avoid moisture at this step since any water added to the reaction will diminish yields. The heterogeneous orange solution was allowed to stir while warming up to room temperature over 4 to 6 hours although the reaction does not seem to progress much after 1 hour. The reaction was treated with triethylamine and filtered through a short column of silica gel which was previously neutralized with triethylamine. Elution with diethyl ether/hexanes resulted in the removal of most of the coloured impurities while an optional treatment with activated charcoal would remove almost all the colouration. The volatiles were removed under reduced pressure. Purification of the crude product by flash chromatography (1:2 ethyl

acetate/hexanes) yielded 191 mg (91%) of thiazoline **172a** as a colourless oil which could become slightly yellowish upon standing. Due to the sensitive nature of these molecules, the flash chromatography can be preformed with triethylamine if the thiazoline is especially sensitive to acid; R_f 0.49 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H, aromatic), 4.22 (t, *J* = 8.4 Hz, 2H, CH_2CH_2N), 3.29 (t, *J* = 8.4 Hz, 2H, CH_2CH_2S), 2.98 (t, *J* = 7.5 Hz, $PhCH_2$), 2.81 (t, *J*= 7.5 Hz, 2H, CH_2CH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 140.5, 128.4, 128.2, 126.1, 64.3, 35.8, 33.8, 33.4; IR (neat) ν 3060, 3030, 2930, 2850, 2350, 1630, 1500, 1450, 1190, 970 cm^{-1}; HRMS (NBA) calcd for $C_{13}H_{14}NS$ $[M+H]^+$: 192.08470, found: 192.08530.

(*4R*)-4-Carboxyethyl-2-(2-phenylethyl)-Δ^2-thiazoline (172b).

171b **172b**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **171b** (265 mg, 1.29 mmol) to thiazoline **172b**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 305 mg (84%) of thiazoline **172b** as a colourless oil; R_f 0.31 (1:3 EtOAc/hexane); $[\alpha]^{21}_D$ +69.3° (*c* 0.724, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17, (m, 5H, aromatic), 5.04 (dd, *J* = 9.5, 8.8 Hz, 1H, CH_2CHN), 4.26, (q, *J* = 7.1, 2H, OCH_2CH_3), 4.25 (q, *J* = 7.1, 2H, OCH_2CH_3), 3.58 (dd, *J* = 11.2, 8.8 Hz, 1H, $CHCH_2S$), 3.50 (dd, *J* = 11.2, 9.5 Hz, 1H, $CHCH_2S$), 3.00 (m, 2H, CH_2CH_2Ph), 2.86 (m, 2H, CH_2CH_2CN), 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.6, 140.2, 128.4, 128.2, 126.2, 77.9, 76.6, 61.6, 35.9, 35.5, 33.5, 14.1; IR (neat) ν 3010, 2980, 2960, 2910, 1740, 1630, 1500, 1450, 1370, 1340, 1260, 1150, 1100, 1050

cm^{-1}; HRMS (NBA) calcd for $C_{14}H_{18}NO_2S$ $[M+H]^+$: 264.10583, found: 264.10500; Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.17. Found: C, 64.17; H, 6.87; N, 5.39; S, 12.40.

(4*R*)-4-Carboxyethyl-2-((2*R)-2-(1-phenylpropyl))-Δ^2-thiazoline (172c).**

171c **172c**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **171c** (325 mg, .1.7 mmol) to thiazoline **172c**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 260 mg (55%) of thiazoline **172c** as a colourless oil; R_f 0.41 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.17 (m, 5H, aromatic), 5.03 (dd, *J* = 9.4, 8.5 Hz, 1H, CH_2CHN), 4.24 (m, 2H, OCH_2CH_3), 3.54 (dd, *J* = 11.2, 8,5 Hz, 1H, $CHCH_2S$), 3.46 (dd, *J* = 11.2, 9.4 Hz, 1H, $CHCH_2S$), 3.06 (m, 2H, $CHCH_2Ph$), 2.71 (m, 1H, CH_2CHCH_3), 1.32 (d, *J* = 7.2 Hz, 1.5H, $CHCH_3$), 1.28 (d, *J* = 7.2 Hz, 1.5H, $CHCH_3$), 1.19, (t, *J* = 5.8 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 170.7, 139.1, 139.1, 129.0, 129.0, 128.2, 126.1, 77.6, 61.5, 41.4, 40.9, 34.9, 34.8, 18.6, 18.4, 14.0; IR (neat) ν 2980, 2940, 1740, 1640, 1450, 1370, 1330, 1270, 1230, 1180, 1030, 740 cm^{-1}; HRMS (NBA) calcd for $C_{15}H_{20}NO_2S$ $[M+H]^+$: 278.12149, found: 278.12080.

(4*R*)-4-Carboxyethyl-2-(2-naphthyl)-Δ^2-thiazoline (172d).

171d **172d**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **171d** (191 mg, 0.84 mmol) to thiazoline **172d**. Purification of the crude product by flash chromatography (1:4 ethyl acetate/hexanes) yielded 155 mg (55%) of thiazoline **172d** as a colourless oil; R_f 0.56 (1:3 EtOAc/hexane); $[\alpha]^{21}_D$ +43.1° (*c* 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H, aromatic), 8.03 (m, 1H, aromatic), 7.92-7.85 (m, 3H, aromatic), 7.56-7.52 (m, 2H, aromatic), 5.33 (dd, *J* = 9.3, 8.7 Hz, 1H, CH_2CHN), 4.32 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.77 (dd, *J* = 11.1, 8.7 Hz, 1H, $CHCH_2S$), 3.70 (dd, *J* = 11.1, 9.3 Hz, 1H, $CHCH_2S$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 134.9, 132.6, 129.9, 129.7, 126.6, 124.8, 78.3, 61.8, 35.4, 14.1; IR (neat) ν 3160, 2990, 1740, 1610, 1590, 1570, 1370, 1280, 1220, 1180, 1120, 1040, 1020, 920, 850, 820, 750 cm^{-1}; HRMS (THIO) calcd for $C_{16}H_{15}NO_2S$ $[M+H]^+$:286.09018, found: 286.09080.

2-(2-Phenylethyl)-Δ^2-thiazoline (174a).

173a **174a**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **173a** (232 mg, 1.08 mmol) to thiazoline **174a**. Purification of the crude product by flash chromatography (1:3 ethyl

acetate/hexanes) yielded 148 mg (72%) of thiazoline **174a** as a colourless oil; refer to compound **172a** for characterization data.

(4*R*)-4-Carboxyethyl-2-(2-phenylethyl)-Δ^2-thiazoline (174b).

173b **174b**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **173b** (265 mg, 1.29 mmol) to thiazoline **174b**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 292 mg (90%) of thiazoline **174b** as a yellowish oil; refer to compound **172b** for characterization data.

(±) 2-(2-(1-Phenylpropyl))-Δ^2-thiazoline (174c).

173c **174c**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **173c** (251 mg, 1.0 mmol) to thiazoline **174c**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 145 mg (71%) of thiazoline **174c** as a colourless oil; R_f 0.46 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H, aromatic), 4.19 (t, *J* = 8.3 Hz, 2H, CH_2CH_2CN), 3.25 (t, *J* = 8.3 Hz, 2H, CH_2CH_2S), 3.08 (dd, *J* = 13.2, 6.0 Hz, 1H, $CHCH_2Ph$), 3.00 (m, 1H, CH_2CHCH_3), 2.69 (dd, *J* = 13.2, 8.3 Hz, 1H, $CHCH_2Ph$), 1.17 (d, *J* = 6.8 Hz,

$CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 139.4, 124.0, 128.2, 126.1, 63.9, 41.4, 40.7, 33.1, 18.4; IR (neat) ν 2980, 2920, 1630, 1500, 1450, 1200, 980 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}NS$ $[M+H]^+$: 206.10034, found: 206.09950.

(4*R*)-4-Carboxyethyl-2-(2-naphthyl)-Δ^2-thiazoline (174d).

173d **174d**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **173d** (255 mg, 0.98 mmol) to thiazoline **174d**. Purification of the crude product by flash chromatography (1:5 ethyl acetate/hexanes) yielded 161 mg (58%) of thiazoline **174d** as a colourless oil; refer to compound **172d** for characterization data.

(1*S*,2*S*)-*N*-Methyl-2-phenylcyclopropyl carboxamide (175a and 175b).

175a, 175b

Optically pure *trans*-2-Phenylcyclopropyl methanol, a generous gift from Dr. H. Lebel,[290] was converted to the carboxylic acid using PDC[291] and KMnO4.[292] The acid was converted to the methyl ester using diazomethane. Conversion of the ester to the amide under Weinreb's[293] procedure involved adding trimethyl aluminum (1.1 ml, 11.3 mmol) to a solution of *N*-methylamine (0.650 ml, 12.1 mmol) in dichloromethane (10 ml) under an argon atmosphere at 0°. After 15 minutes, this solution was

added slowly via cannula to a solution of methyl *trans*-2-phenyl-1-cyclopropyl carboxylate (1.544 g, 8.6 mmol) in dichloromethane (10 ml) at 0°C. After 18 hours at room temperature, water (1 ml) was carefully added to the solution. The solution was then diluted with diethyl ether (100 ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography yielded 1.30 g (86%) of amide **175a,b** as a white solid; R_f 0.23 (1:1 EtOAc/hexane); mp 96-98°C; $[\alpha]^{21}_D$ +329.2° (*c* 0.390, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.00 (m, 5H, Ph), 6.31 (br, 1H, N*H*), 2.78 (d, J = 4.7 Hz, 1H, NCH_3), 2.43 (ddd, *J* = 9.1 Hz, 6.3 Hz, 4.1 Hz, 1H, PhC*H*CH_2), 1.64 (ddd, *J* = 8.2 Hz, 5.2 Hz, 4.1 Hz, 1H, CH_2C*H*CO), 1.56 (ddd, *J* = 9.1 Hz, 5.2 Hz, 4.4 Hz, 1H, CHCH_2CH), 1.18 (ddd, *J* = 8.2 Hz, 6.3 Hz, 4.4 Hz, 1H, CHCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.7, 128.2, 126.0, 125.8, 26.3, 26.2, 24.7, 15.5; IR (film) ν 3280, 3090, 1640, 1580, 1400, 1250, 1160, 1080, 930, 910, 840 cm^{-1}; HRMS (NBA) calcd for $C_{11}H_{13}NO$ $[M+H]^+$: 176.107545, found: 176.10810; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.14; H, 7.68; N, 7.98.

2-((*1S*,2S)-2-Phenylcyclopropyl)-Δ^2-thiazoline (176a).**

175a **176a**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **175a** (222 mg, 1.27 mmol) to thiazoline **176a**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 185 mg (72%) of thiazoline **176a** as a colourless oil; R_f 0.31 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.09 (m,

5H, aromatic), 4.21 (t, J = 8.3 Hz, 1H, CH_2CH_2N), 4.20 (t, J = 8.3 Hz, 1H, CH_2CH_2N), 3.29 (t, J = 8.3 Hz, 2H, CH_2CH_2S), 2.51 (ddd, J = 9.2, 6.2, 4.2 Hz, 1H, CH_2CHPh), 2.14 (ddd, J = 8.2, 5.3, 4.2 Hz, 1H, CH_2CHCN), 1.63 (ddd, J = 9.2, 5.3, 4.4 Hz, 1H, $CHCH_2CH$), 1.40 (ddd, J = 8.2, 6.2, 4.4 Hz, 1H, $CHCH_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 140.6, 128.3, 126.2, 126.0, 64.2, 33.7, 26.9, 25.8, 18.0; IR (neat) ν 3010, 2940, 2860, 1620, 1500, 1450, 1140, 1400, 1340, 1200, 1180, 1100, 1000, 990 cm^{-1}; HRMS (NBA) calcd for $C_{12}H_{13}NS$ $[M+H]^+$: 204.08470, found: 204.08520.

(4*R*)-4-Carboxyethyl-2-((1*S*,2*S*)-2-phenylcyclopropyl)-Δ^2-thiazoline (176b).

175b **176b**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **175b** (265 mg, 1.51 mmol) to thiazoline **176a**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 320 mg (77%) of thiazoline **176a** as a colourless oil; R_f 0.50 (1:2 EtOAc/hexane); $[\alpha]^{21}_D$ +362.8° (*c* 0.392, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.09 (m, 5H, aromatic), 5.06 (dd, J = 9.3, 8.3 Hz, 1H, CH_2CHN), 4.27 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.58 (dd, J = 11.2, 8.3 Hz, $CHCH_2S$), 3.51 (dd, J = 11.2, 9.3 Hz, $CHCH_2S$), 2.54 (ddd, J = 9.2, 6.4, 4.3 Hz, 1H, CH_2CHPh), 2.22 (ddd, J = 8.6, 5.4, 4.3 Hz, 1H, CH_2CHCN), 1.69 (ddd, J = 9.2, 5.4, 5.1 Hz, 1H, $CHCH_2CH$), 1.42 (ddd, J = 8.6, 6.4, 5.1 Hz, 1H, $CHCH_2CH$), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 140.2, 128.3, 126.3, 126.0, 77.6, 61.6, 35.4, 27.4, 25.9, 18.3, 14.1; IR (neat) ν 3250, 2990, 1740, 1610, 1500, 1460, 1440, 1380, 1370, 1330, 1230, 1180, 1150, 1100, 1040, 950 cm^{-1}; HRMS (NBA) calcd for $C_{15}H_{18}NO_2S$

$[M+H]^+$: 276.10583, found: 276.10530 The (4*S*)-diastereoisomer has distinguishing ^1H NMR signals at δ 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 3.57 (dd, *J* = 11.1, 8.8 Hz, $CHCH_2S$), and 3.50 (dd, *J* = 11.1, 9.4 Hz, $CHCH_2S$).

(4*R*)-4-carboxyethyl-2-(3-(4-methylbenzoyloxy)propyl)-Δ^2-thiazoline (176c).

175c **176c**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **175c** (312 mg, 1.0 mmol) to thiazoline **176c**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 255 mg (76%) of thiazoline **176c** as a colourless oil; R_f 0.29 (1:2 EtOAc/hexane); $[\alpha]^{21}_D$ +45.7° (*c* 1.452, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 2H, aromatic), 7.24 (m, 2H, aromatic), 5.07 (dd, *J* = 9.6, 8.6 Hz, 1H, CH_2CHN), 4.37 (t, *J* = 6.3 Hz, 2H, CH_2CH_2O), 4.27 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.60 (dd, *J* = 11.2, 8.6 Hz, 1H, $CHCH_2S$), 3.52 (dd, *J* = 11.2, 9.6 Hz, 1H, $CHCH_2S$), 2.74 (m, 2H, CH_2CH_2CN), 2.41 (s, 3H, $PhCH_3$), 2.17 (m, 2H, $CH_2CH_2CH_2$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 170.7, 166.4, 143.5, 129.5, 129.0, 127.3, 77.9, 63.5, 61.7, 35.6, 30.9, 26.6, 21.6, 14.1; IR (neat) ν 2960, 1730, 1620, 1270, 1200, 1120, 1030, 740 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{22}NO_4S$ $[M+H]^+$: 336.12695, found: 336.12630.

(4*R*)-4-carboxyethyl-2-(3-(tert-butyldiphenylsiloxy)propyl)-Δ^2-thiazoline (176d).

175d **176d**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **175d** (317 mg, 0.74 mmol) to thiazoline **176d**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 244 mg (73%) of thiazoline **176d** as a colourless oil; R_f 0.47 (1:3 EtOAc/hexane); $[\alpha]^{21}_D$ +30.5° (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.26 (m, 10H, aromatic), 5.02 (dd, *J* = 9.2, 9.1 Hz, 1H, CH_2CHN), 4.26 (q, *J* = 7.2 Hz, 1H, OCH_2CH_3), 4.23 (q, *J* = 7.2 Hz, 1H, OCH_2CH_3), 3.70 (t, *J* = 6.1 Hz, 2H, CH_2CH_2O), 3.56 (dd, *J* = 11.2, 8.8 Hz, 1H, $CHCH_2S$), 3.48 (dd, *J* = 11.2, 9.5 Hz, 1H, $CHCH_2S$), 2.70 (t, *J* = 7.7 Hz, 2H, CH_2CH_2CN), 1.93 (m, 2H, $CH_2CH_2CH_2$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.05 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 170.8, 135.5, 133.6, 129.5, 127.6, 77.9, 62.7, 61.6, 35.4, 30.9, 30.4, 26.7, 19.1, 14.1; IR (neat) ν 3070, 2940, 2880, 1740, 1620, 1450, 1370, 1200, 1100, 720 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{33}NO_3SSi$ $[M+H]^+$: 456.20288, found: 456.20510.

(4*S*,5*S*)-5-benzyloxymethyl-2,2-dimethyl-4-(2-((4*R*)-4-carboxyethyl-2-methyloxy-Δ^2-thiazoline))methyloxymethyl-1,3-dioxolane (176e).

175e **176e**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **175e** (328 mg, 0.82 mmol) to thiazoline

176e. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 278 mg (80%) of thiazoline **176e** as a colourless oil; R_f 0.36 (1:1 EtOAc/hexane); $[\alpha]^{21}_D$ +31.6° (*c* 2.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H, aromatic), 5.07 (dd, *J* = 9.6, 9.2 Hz, 1H, CH_2CHN), 4.62 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.58 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.48 (dd, *J* = 14.4, 1.8 Hz, 1H, OCH_2CN), 4.41 (dd, *J* = 14.4, 1.8 Hz, 1H, OCH_2CN), 4.26 (m, 2H, OCH_2CH_3), 4.09 (dt, *J* = 8.3, 4.8 Hz, 1H, $CHCHCH_2O$), 4.02 (ddd, *J* = 8.3, 5.2, 4.0 Hz, 1H, $BnOCH_2CHCH$), 3.70 (dd, *J* = 10.2, 4.0 Hz, 1H, $BnOCH_2CH$), 3.65 (dd, *J* = 10.2, 5.2 Hz, 1H, $BnOCH_2CH$), 3.63 (d, *J* = 4.8 Hz, 2H, $CHCH_2OCH_2CN$), 3.53 (dd, *J* = 11.3, 9.2 Hz, 1H, $CHCH_2S$), 3.46 (dd, *J* = 11.3, 9.6 Hz, 1H, $CHCH_2S$), 1.43 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.4, 137.8, 128.3, 127.6, 127.5, 109.7, 77.9, 77.2, 76.9, 73.4, 71.5, 70.7, 70.4, 61.8, 34.1, 26.9, 26.0, 14.1; IR (neat) ν 2980, 2930, 2900, 2870, 1740, 1610, 1530, 1450, 1370, 1210, 1160, 1080, 850 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{30}NO_6S$ $[M+H]^+$: 424.17938, found: 424.17830.

(4*R*)-4-*N*-Methylcarboxamido-2-(2-phenylethyl)-Δ^2-thiazoline (181).

180 **181**

To a solution of ester **180** (1.021 mg, 3.88 mmol) in methanol (50 ml) was added *N*-methylamine (5 ml, 174 mmol) at 0°C. The solution is allowed to warm up slowly with stirring. The reaction is stirred at room temperature for 20 minutes or until TLC analysis indicates that the reaction is complete. All the volatiles are removed under reduced pressure. Purification of the crude product by flash chromatography yielded 948 mg (98%) of amide **181** as a colorless oil; R_f 0.21 (1:1 EtOAc/hexane); $[\alpha]^{21}_D$ –6.67° (*c* 0.420,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H, aromatic), 6.23 (br, 1H, N*H*), 4.95 (dd, *J* = 10.0 Hz, 8.4 Hz, 1H, NC*H*CH_2), 3.61 (dd, *J* = 11.3 Hz, 10.0 Hz, 1H, SC*H*$_2$CH), 3.53 (dd, *J* = 11.3 Hz, 8.4 Hz, 1H, SC*H*$_2$CH), 3.09-2.94 (m, 2H, N=CC*H*$_2$CH$_2$), 2.90-2.86 (m, 2H, PhC*H*$_2$CH$_2$), 2.70 (d, *J*= 5.0 Hz, 3H, NC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.7, 139.9, 128.4, 128.2, 126.2, 78.4, 36.0, 35.4, 32.9, 26.0; IR (neat) ν 3390, 3030, 2940, 1660, 1620, 1530, 1500, 1450, 1410, 1190, 1050, 750, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{17}N_2OS$ $[M+H]^+$: 249.10616, found: 249.10480.

_E/Z_-(_4R_)-4-_N_-Methylcarboxamido-2-(2-phenylethylene)-_N_-trifluoromethanesuphonamidoyl-thiazolane (182).

181 **182**

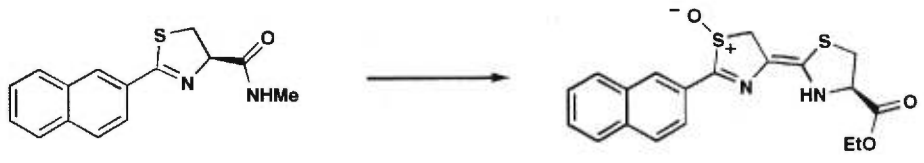
The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **181** (216 mg, 0.87 mmol) to *N*-triflyl amide **182**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 264 mg of a product which was still crude. Crystallization from ethyl acetate/hexanes yielded 194 mg (69%) of thiazoline **182** as slightly yellowish low melting crystals which were suitable for x-ray analysis[294]; R_f 0.34 (1:2 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H, aromatic), 6.31 (br, 1H, NH), 6.19 (t, *J* = 7.0 Hz, 1H, CH_2CH=C), 5.07 (m, 1H, SCH_2CHN), 3.85 (d, *J* = 10.0 Hz, 1H, SC*H*$_2$CH), 3.41 (d, *J* = 7.0 Hz, 2H, PhC*H*$_2$CH), 3.37 (d, *J* = 9.1 Hz, 1H, SC*H*$_2$CH), 2.90 (d, *J* = 5.0 Hz, 3H, NC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 138.6, 132.4, 128.5, 128.1, 126.5, 124.6, 121.4, 118.1, 115.1, 66.1, 36.8, 31.4, 26.9; IR (neat) ν 3440, 3330, 3050, 1670, 1540, 1410, 1210, 1140, 1060, 900, 720 cm^{-1}; See Appendix 3 for X-ray crystal data.

(*4R*)-4-*N*-Methylcarboxamido-2-(2-naphthyl)-Δ^2-thiazoline (185).

184 **185**

To a solution of ester **184** (902 mg, 3.16 mmol) in methanol (20 ml) was added *N*-methylamine (5 ml, 174 mmol) at 0°C. The solution is allowed to warm up slowly with stirring. The reaction is stirred at room temperature for 20 minutes or until TLC analysis indicates that the reaction is complete. All the volatiles are removed under reduced pressure. Purification of the crude product by flash chromatography yielded 835 mg (98%) of amide **185** as a colorless White solid; R_f 0.24 (1:1 EtOAc/hexane); mp 131-133°C; $[\alpha]^{21}_D$ -0.842° (*c* 0.594, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H, aromatic), 8.02-8.00 (m, 1H, aromatic), 7.93-7.86 (m, 3H, aromatic), 7.59-7.26 (m, 2H, aromatic), 6.93 (br, 1H, N*H*), 5.24 (dd, *J* = 9.7, 9.5 Hz, 1H, CH_2CHN), 3.80 (dd, *J* = 11.3, 9.7 Hz, 1H, $CHCH_2S$), 3.70 (dd, *J* = 11.3, 9.5 Hz, 1H, $CHCH_2S$), 2.90 (d, *J* = 5.0 Hz, 3H, $HNCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.1, 134.8, 132.6, 129.9, 129.6, 128.8, 128.2, 127.8, 127.7, 1265.8, 124.3, 79.2, 35.6, 26.1; IR (KBr) ν 3340, 3050, 2930, 1660, 1600, 1530, 1410, 1270, 920, 810 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{22}NO_4S$ $[M+H]^+$: 271.09052, found: 271.08920.

(*4R*)-4-Carboxyethyl-2-(4-(2-naphthyl-*S*-oxido-thiazolyl)-Δ^2-thiazoline (188).



185 **188**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **185** (395 mg, 01.46 mmol) to thiazoline **188**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 135 mg (25%) of bis-thiazoline **188** as a yellowish oil. This compound is somewhat unstable and dehydrates to give bis-thiazoline **189** upon standing; R_f 0.18 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 1H, aromatic), 8.06-8.02 (m, 1H, aromatic), 7.95-7.84 (m, 3H, aromatic), 7.61-7.52 (m, 2H, aromatic), 5.19 (dd, *J* = 18.8, 9.8 Hz, 1H, CH_2CHN), 4.70 (br, 1H, N*H*), 4.27 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3), 4.26 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3), 4.08 (d, *J* = 12.2 Hz, 0.5H, SCH_2C=C), 4.02 (d, *J* = 12.2 Hz, 0.5H, SCH_2C=C), 3.77 (d, *J* = 12.2 Hz, 0.5H, SCH_2C=C), 3.76 (d, *J* = 12.2 Hz, 0.5H, SCH_2C=C), 3.66 (m, 2H, SCH_2CH), 1.34 (t, *J* = 7.1 Hz, 1.5H, OCH_2CH_3), 1.33 (t, *J* = 7.1 Hz, 1.5H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 177.4, 170.1, 135.2, 135.1, 132.5, 132.4, 130.0, 129.9, 129.1, 129.0, 128.3, 128.0, 127.9, 127.7, 126.7, 124.8, 106.1, 77.4, 61.9, 42.7, 42.6, 36.5, 36.1, 14.1, 14.0; IR (neat) ν 3260, 3060, 2980, 1730, 1660, 1600, 1370, 1270, 1190, 1120, 1040, 930, 860, 820, 740 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}N_2O_3S_2$ $[M+H]^+$: 387.08371, found: 387.08460.

(4*R*)-4-carboxyethyl-2-(4-(2-naphthylthiazolyl)-Δ^2-thiazoline (189).

185 **189**

The general procedure for the conversion of amides to thiazolines was used for the conversion of amide **185** (395 mg, 01.46 mmol) to thiazoline **189**. Purification of the crude product by flash chromatography (1:2 ethyl acetate/hexanes) yielded 172 mg (32%) of thiazoline **189** as a white solid. Compound **188** is dehydrated to give bis-thiazoline **189** upon standing

resulting in a total yield of 57% for bis-thiazoline **189**. The bis-thiazoline could be crystallized from ethyl acetate/hexanes to give crystals which were suitable for x-ray analysis[295]; R_f 0.50 (1:2 EtOAc/hexane); $[\alpha]^{21}_D$ +60.9° (*c* 0.412, $CHCl_3$); mp 146-148°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (m, 1H, aromatic), 8.11 (m, 1H, aromatic), 8.09-8.07 (m, 1H, aromatic), 7.97-7.84 (m, 3H, aromatic), 7.56-7.51 (m, 2H, aromatic), 5.33 (t, *J* = 9.1 Hz, 1H, CH_2CHN), 4.32 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.71 (m, 2H, SCH_2CH), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 1668.4, 148.7, 134.3, 133.1, 130.0, 128.8, 128.6, 127.8, 127.3, 126.9, 126.4, 123.9, 122.4, 77.8, 77.2, 62.0, 34.9, 31.4, 22.6, 14.1; IR (KBr) ν 3060, 2980, 2930, 1740, 1600, 1180, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{17}N_2O_2S_2$ $[M+H]^+$; Anal. Calcd for $C_{19}H_{16}N_2O_2S_2$: C, 61.93; H, 7.48; N, 7.99; S, 17.40. Found: C, 61.95; H, 4.41; N, 7.65; S, 17.32. For x-ray crystal data, see Appendix 4.

Experimental Section: Chapter 7

N,N-Diethyl-3-phenylpropane thioamide (197a).

196a **197a**

General procedure for the conversion of tertiary and secondary amides to cyclic thioamides. To a solution of amide **196a** (242 mg, 1.18 mmol) in dichloromethane (10 ml) under an argon atmosphere was added pyridine (290 µl, 3.54 mmol). The solution was cooled to -40°C and neat triflic anhydride (260 µl, 1.53 mmol) was added slowly. The reaction was then allowed to slowly warm up to 0°C. Stirring was continued for another 4 to 12 hours. H_2S (g) was then bubbled very slowly into the reaction and stopped after 10 seconds. Pyridine (290 µl, 3.54 mmol) is again added to neutralize the reaction. Alternatively, an anhydrous solution of NaSH in acetonitrile or acetone could be used in place of gaseous H_2S. Only a stoichiometric amount is required so the reaction is monitored carefully by TLC analysis to determine if enough H_2S has been used. If too much H_2S has been added, the meta-stable geminal *bis*-thiol can be formed. In this case, the septum is removed and the solution is stirred in the fume hood until the thioamide is regenerated. The reaction was filtered through neutralized silica using diethyl ether as an eluant. After filtering, the solvent was removed in under reduced pressure. Further purification of the crude product by flash chromatography (1:8 ethyl acetate/hexanes) yielded 240 mg (92%) of the thioamide **197a** as a yellowish oil; R_f 0.48 (1:7 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.21 (m, 5H, aromatic), 3.99 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 3.38 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 3.15

(m, 2H, CH_2CH_2Ph), 3.02 (m, 2H, CH_2CH_2CS), 1.67 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 1.57 (t, J = 7.1 Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 140.6, 128.4 (2), 126.3, 48.0, 45.7, 44.1, 36.3, 13.4, 11.0; IR (neat) ν 2980, 2940, 1500, 1470, 1450, 1420, 1300, 1270, 1230, 1090, 1060, 720 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{20}NS$ $[M+H]^+$: 222.13165, found: 22.13120.

N-Benzyl-3-phenylpropane thioamide (197b).

196b **197b**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196b** (266 mg, 1.24 mmol) to thioamide **197b**. Purification of the crude product by flash chromatography (1:7 ethyl acetate/hexanes) yielded 268 mg (94%) of thioamide **197b** as a yellowish solid; R_f 0.21 (1:7 EtOAc/hexane); mp 78-80°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.01 (m, 11H, aromatic and N*H*), 4.67 (d, J = 5.1 Hz, 2H, $PhCH_2NH$), 3.11 (t, J = 7.3 Hz, 2H, $PhCH_2CH_2$), 2.92 (t, J = 7.3 Hz, 2H, CH_2CH_2CS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 140.0, 135.8, 128.7, 128.5, 128.4, 128.0, 127.9, 126.3, 50.1, 48.7, 35.3; IR (KBr) ν 3220, 3060, 1540, 1450, 1430, 1400, 1350, 1130, 950, 720, 690 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{17}NS$ $[M+H]^+$: 256.11600, found: 256.11640; Anal. Calcd for $C_{16}H_{17}NS$: C, 75.24; H, 6.72; N, 5.48; S, 12.55. Found: C, 75.40; H, 6.83; N, 5.48; S, 12.49.

N,N-Diethyl-2-naphthyl thioamide (197c).

196c **197c**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196c** (240 mg, 1.06 mmol) to thioamide **197c**. Purification of the crude product by flash chromatography (1:7 ethyl acetate/hexanes) yielded 247 mg (96%) of thioamide **197c** as a yellowish solid; R_f 0.36 (1:7 EtOAc/hexane); mp 102-104°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.81 (m, 3H, aromatic), 7.70 (s, 1H, aromatic), 7.52-7.49 (m, 2H, aromatic), 7.40-7.37 (m, 1H, aromatic), 3.15 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 2.63 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 1.10 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 0.89 (t, J = 7.1 Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 140.9, 132.5 (2), 128.0 (2), 127.5, 126.4, 123.3, 47.7, 45.9, 13.7, 11.1; IR (KBr) ν 3450, 3060, 2980, 2940, 1500, 1450, 1430, 1380, 1360, 1310, 1270, 1250, 1230, 1140, 1120, 1060, 990, 920, 850, 810, 740 cm^{-1}; HRMS (THIO) calcd for $C_{15}H_{18}NS$ $[M+H]^+$: 244.11600, found: 244.11670; Anal. Calcd for $C_{15}H_{17}NS$: C, 74.02; H, 7.05; N, 5.75; S, 13.17. Found: C, 73.82; H, 7.09; N, 5.75; S, 13.44.

***N*-Benzyl-2-naphthyl thioamide (197d).**

196d **197d**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196d** (273 mg, 1.05 mmol) to thioamide **197d**. Purification of the crude product by flash chromatography (1:6 ethyl acetate/hexanes) yielded 275 mg (95%) of thioamide **197d** as a yellowish solid; R_f 0.29 (1:5 EtOAc/hexane); mp 139-140°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H, aromatic), 7.92 (br, 1H, N*H*), 7.86-7.74 (m, 4H, aromatic), 7.53-7.45 (m, 2H, aromatic), 7.41-7.31 (m, 5H, aromatic), 5.01 (d, J = 5.2 Hz, 2H, $PhCH_2NH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 136.1, 134.4, 132.3, 128.9, 128.8, 128.3, 128.2, 127.6, 126.8, 125.9, 124.3, 50.9; IR (neat) ν

3310, 2930, 1520, 1390, 1300, 820, 740, 700 cm^{-1}; HRMS (NBA) calcd for $C_{18}H_{16}NS$ $[M+H]^+$: 278.10034, found: 278.09910; Anal. Calcd for $C_{18}H_{15}NS$: C, 77.93; H, 5.46; N, 5.05; S, 11.56. Found: C, 77.84; H, 5.26; N, 5.00; S, 11.58..

(*1S*,2S)-*N*-methyl-2-phenylcyclopropyl carboxythioamide (197e).**

196e **197e**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196e** (185 mg, 1.06 mmol) to thioamide **197e**. Purification of the crude product by flash chromatography (1:3 ethyl acetate/hexanes) yielded 184 mg (91%) of thioamide **197e** as a yellowish solid; R_f 0.32 (1:3 EtOAc/hexane); mp 113-115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (br, 1H, N*H*), 7.29-7.18 (m, 3H, aromatic), 7.10-7.07 (m, 2H, aromatic), 3.17 (d, J = 4.8 Hz, 3H, NHCH_3), 2.72 (ddd, J = 8.5 Hz, 6.6 Hz, 4.6 Hz, 1H, PhC*H*CH$_2$), 1.97 (m, 2H, C$H_{cycloprop.}$), 1.41 (m, 2H, C$H_{cycloprop.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 140.4, 128.4, 126.4, 126.1, 36.0, 33.0, 29.8, 19.7; IR (KBr) ν 3360, 3250, 3060, 1650, 1540 ,1460, 1360, 1220, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}NS$ $[M+H]^+$: 192.08470, found: 192.08490.

***N*-Benzyl-4-(4-methyl benzoyloxy)butane thioamide (197f).**

196f **197f**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196f** (315 mg, 1.01 mmol) to thioamide

197f. Purification of the crude product by flash chromatography (1:4 ethyl acetate/hexanes) yielded 272 mg (82%) of thioamide **197f** as a yellowish oil; R_f 0.18 (1:5 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.3 Hz, 1.8 Hz, 2H, aromatic), 7.71 (br, 1H, N*H*), 7.37-7.30 (m, 5H, aromatic), 7.22-7.20 (m, 2H, aromatic), 4.82 (d, *J* = 5.1 Hz, 2H, PhCH_2NH), 4.35 (t, *J* = 6.1 Hz, 2H, CH_2CH_2O), 2.78 (t, *J* = 7.2 Hz, 2H, CH_2CH_2CS), 2.40 (s, 3H, PhCH_3), 2.31 (tt, *J* = 7.2 Hz, 6.1 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 166.8, 143.8, 136.0, 129.5, 129.0, 128.8, 128.3, 128.0, 127.1, 63.4, 50.3, 43.0, 28.6, 21.6; IR (neat) ν 3310, 3030, 2960, 1710, 1610, 1530, 1450, 1410, 1270, 1180, 1100, 1010, 960, 750 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{22}NO_2S$ $[M+H]^+$: 328.13712, found: 328.13640.

N-Benzyl-4-*t*-butyldiphenylsilyloxybutane thioamide (197g).

196g **197g**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196g** (452 mg, 1.05 mmol) to thioamide **197g**. Purification of the crude product by flash chromatography (1:8 ethyl acetate/hexanes) yielded 403 mg (86%) of thioamide **197g** as a yellowish oil; R_f 0.43 (1:7 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.69 (m, 1H, aromatic), 7.60-7.57 (m, 4H, aromatic), 7.43-7.23 (m, 10H, aromatic), 5.52 (br, 1H, N*H*), 4.77 (d, *J* = 5.2 Hz, 2H, PhCH_2NH), 3.70 (t, *J* = 5.9 Hz, 2H, PhCH_2CH_2), 2.84 (t, *J* = 7.2 Hz, 2H, CH_2CH_2CS), 1.98 (tt, *J* = 7.2 Hz, 5.9 Hz, 2H, $CH_2CH_2CH_2$), 1.00 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 136.0, 135.3, 134.7, 133.3, 129.7, 129.5, 128.9, 128.8, 128.5, 128.2, 128.0, 127.8, 127.6 (2), 62.3, 50.2, 43.1, 31.4, 26.8, 19.1; IR (neat) ν 3360, 3070, 2960, 2930,

2850 ,1520, 1420, 1370, 1230, 1190, 1140, 1100, 810, 740, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{27}H_{34}NOSSi$ $[M+H]^+$: 448.21304, found: 448.21400.

(4*S*, 5*S*)-4-(2-*N*-benzyl thioacetamidyl)oxymethyl-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (197h).

196h **197h**

The general procedure for the conversion of amides to thioamides was used for the conversion of amide **196h** (295 mg, 0.74 mmol) to thioamide **197h**. Purification of the crude product by flash chromatography (1:6 ethyl acetate/hexanes) yielded 214 mg (70%) of thioamide **197h** as a yellowish oil; R_f 0.39 (1:5 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.95 (br, 1H, NH), 7.37-7.25 (m, 10H, aromatic), 4.91 (dd, *J* = 15.0 Hz, 5.4 Hz, 1H, PhCH_2NH), 4.84 (dd, *J* = 15.0 Hz, 5.4 Hz, 1H, PhCH_2NH), 4.52 (s, 2H, PhCH_2O), 4.49 (d, *J* = 16.9 Hz, 2H, OCH_2CS), 3.97 (m, 2H, CHCH_2O), 3.68 (dd, *J* = 3.6 Hz, 2.3 Hz, 1H, CHCH_2O), 3.62-3.57 (m, 2H, $CH_2CHCHCH_2$), 3.50 (dd, *J* = 4.9 Hz, 3.6 Hz, 1H, CHCH_2O), 1.27 (s, 3H, CCH_3), 1.17 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 137.4, 135.7, 128.7, 128.3, 128.2, 127.7, 127.5, 109.5, 77.7, 76.6, 75.5, 73.4, 71.0, 70.0, 48.6, 26.6, 26.4; IR (neat) ν 3290, 3030, 2990, 2910, 1530, 1500, 1450, 1410, 1380, 1370, 1310, 1250, 1220, 1170, 1090 , 740, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}NO_4S$ $[M+H]^+$: 416.18954, found: 416.19010.

^{18}O-*N*-Benzyl-3-phenylpropanamide (201).

92a **201**

General procedure for the conversion of tertiary and secondary amides to ^{18}O-labelled amides. To a solution of amide **92a** (246 mg, 1.03 mmol) in dichloromethane (10 ml) under an argon atmosphere was added pyridine (252 µl, 3.09 mmol). The solution was cooled to -40°C and neat triflic anhydride (255 µl, 1.34 mmol) was added slowly. The reaction was then allowed to slowly warm up to 0°C. Stirring was continued for another 4 to 12 hours. $H_2{}^{18}O$ (<1 drop ~ 40 mg, 1.5 mmol) was then added to the reaction and stirring was continued for another 5 minutes. The reaction was diluted with diethyl ether (100ml), washed with 10% HCl (2 x 15 ml), saturated $NaHCO_3$ (15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by filtering through a short column of silica (diethyl ether as an eluant) yielded a quantitative amount of ^{18}O-labelled amide **201** as a white solid; R_f 0.31 (1:2 EtOAc/hexane); mp 86-88°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.11 (m, *J* = 5H, aromatic), 5.70 (br, 1H, N*H*), 4.38 (d, *J* = 6 Hz, 2H, HNCH_2Ph), 2.99 (t, *J* = 7 Hz, 2H, PhCH_2CH_2), 2.51 (t, *J* = 7 Hz, 2H, CH_2CH_2CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 140.7, 138.1, 128.6, 128.5, 128.3, 127.6, 127.4, 126.2, 43.5, 38.4, 31.6; IR (KBr) ν 3300, 1640, 1540, 1450, 740 cm^{-1}; Voltage regulated HRMS (FAB+) calcd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.13884, found 240.13790 (100% relative intensity); calcd for $C_{16}H_{18}N^{18}O$ $[M+H]^+$ 242.37438 found 242.3835 (12.20% relative intensity, uncorrected for other isotopes).

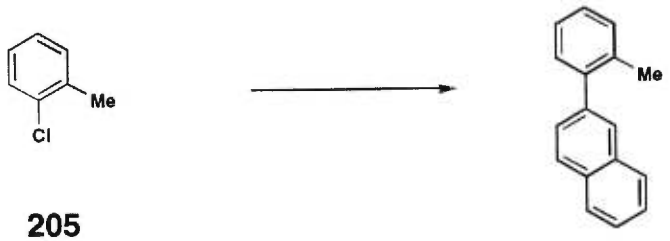
^{18}O-*N,N*-Diethyl-3-phenylpropanamide (202).

88a **202**

The general procedure for the conversion of amides to ^{18}O-labelled amides was used for the conversion of amide **88a** (277 mg, 1.35 mmol) to thioamide **202**. Purification of the crude product by filtering through a short column of silica gel (diethyl ether as an eluant) yielded a quantitative amount of ^{18}O-labelled amide **202** as a colourless oil; R_f 0.39 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H, aromatic), 3.38 (q, *J* = 7 Hz, 2H, NCH_2CH_3), 3.21 (q, *J* = 7 Hz, 2H, NCH_2CH_3), 2.96 (t, *J* = 8 Hz, 2H, $PhCH_2CH_2$), 2.59 (t, *J* = 8 Hz, 2H, CH_2CH_2CO), 1.31 (t, *J* = 7 Hz, 3H, NCH_2CH_3), 1.28 (t, *J* = 7 Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.4, 128.3, 128.2, 125.9, 41.7, 40.0, 34.9, 31.5, 14.1, 12.9; IR (neat) ν 2970, 1640, 1450, 1430 cm^{-1}; Voltage regulated HRMS (FAB+) calcd for $C_{13}H_{20}NO$ $[M+H]^+$ 206.154489, found 206.155500 (100% relative intensity); calcd for $C_{13}H_{20}N^{18}O$ $[M+H]^+$ 208.158734, found 157.800 (11.78% relative intensity, uncorrected for other isotopes).

Experimental Section: Chapter 8

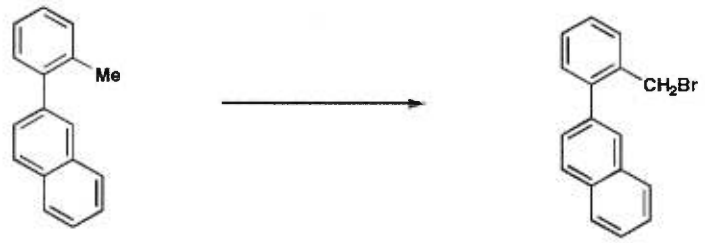
2-(2-naphthyl)-toluene (207).



205 **207**

Magnesium turnings (845 mg, 34.8 mmol) were dried with a flame under vacuum. The flask was then charged with dry THF (15 ml) followed by 2-chlorotoluene (2.26 ml, 19.3 mmol) under an argon atmosphere. The solution was refluxed for 18 h and then allowed to cool to ambient temperature. The Grignard was then added via cannula to a slurry containing 2-bromonaphthalene (2.00 g, 9.7 mmol) and $NiCl_2$ (69.5 mg, 0.09 mmol) in dry THF (5 ml). The resulting black solution was heated to 50-55°C for 3 h or until TLC analysis showed that the reaction was complete. The reaction was quenched by the careful addition of several drops of water. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (100% hexane) to produce the hydrocarbon (1.43 g, 68%) as a colorless oil; R_f 0.35 (100% hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.84 (m, 3H, aromatic), 7.77 (s, 1H, aromatic), 7.51-7.45 (m, 3H, aromatic), 7.32-7.23 (m, 4H, aromatic), 2.31 (s, 3H, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 139.5, 135.5, 133.3, 132.2, 130.3, 129.9, 127.9, 127.7, 127.6 (2), 127.4, 127.3, 126.1, 125.8, 20.5; IR (neat) ν 3150, 1610, 1490, 1450, 1470, 850, 810, 750, 710 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}$ $[M+H]^+$: 219.11737, found: 219.11700.

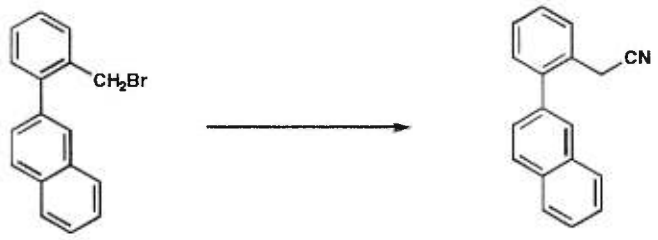
2-(2-naphthyl)-benzyl bromide (208).



207 **208**

To a solution of the methylaryl compound (224 mg, 1.026 mmol) in CCl_4 (5 ml) was added *N*-bromosuccinimide (219 mg, 1.21 mmol) and benzoyl peroxide (15 mg, 0.6 mmol). The yellowish solution was connected to an exit bubbler and brought to reflux for 3 h. After cooling the near colorless solution to ambient temperature, the solution was diluted with ether (50 ml) and then washed with 10% HCl (15 ml) and saturated aqueous $NaHCO_3$ (2 X 15 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (starting with 100% hexane and finishing with 1:50 Et_2O/hexane) to yield the bromide (242 mg, 80%) as a colorless oil; R_f 0.22 (100% hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.89 (m, 4H, aromatic), 7.59-7.51 (m, 4H, aromatic), 7.41-7.25 (m, 3H, aromatic), 4.50 (s, 2H, CH_2Br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 137.6, 135.4, 133.1, 132.5, 131.0, 130.6, 128.5, 128.1, 128.0, 127.8, 127.7, 127.2, 126.4, 126.1, 32.2; IR (neat) ν 3200, 1590, 1480, 1440, 1210, 850, 810, 750 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{13}{}^{79}$Br $[M+H]^+$: 296.02005, found: 296.02082.

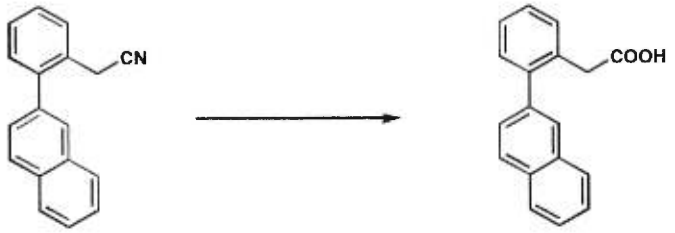
2´-(2-naphthyl)-phenyl acetonitrile (209).



208 **209**

To a solution of the bromide (110 mg, 0.37 mmol) in DMSO (2 ml) was added NaCN (22 mg, 0.45 mmol). The mixture was connected to an exit bubbler in a well-ventilated hood and heated to 70°C for 1 h or until TLC showed the reaction was complete. The solution was diluted with ether (50 ml) and washed with $NaHCO_3$ (2 X 15 ml). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc/hexane) to yield the nitrile (86 mg, 95%) as a colorless oil; R_f 0.26 (1:20 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.86 (m, 3H, aromatic), 7.76 (s, 1H, aromatic), 7.61-7.53 (m, 3H, aromatic), 7.47-7.25 (m, 4H, aromatic), 3.67 (s, 2H, CH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 137.2, 133.1, 132.5, 130.6, 128.9, 128.3, 128.2 (2), 128.0, 127.9, 127.8, 127.7, 126.8, 126.6, 126.4, 22.0; IR (neat) ν 3300, 2200, 1600, 1490, 1410, 1120, 850, 810, 750 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{13}N$ $[M]^+$: 243.10480, found: 243.10398.

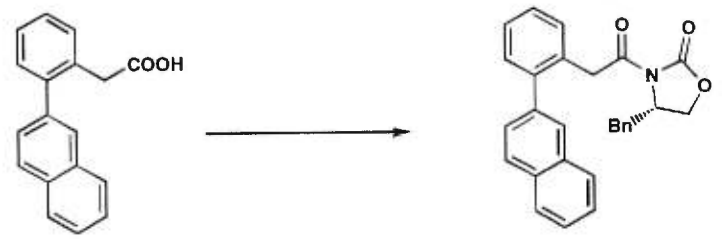
2′-(2-naphthyl)phenyl acetic acid (210).



209 **210**

To a solution of the nitrile (24.6 g, 101 mmol) in EtOH (5 ml) was added a solution of NaOH (40.49 g, 1012 mmol) in H_2O (40 ml). The mixture was refluxed for 5 h or until TLC analysis showed that the reaction was complete. After cooling to ambient temperature, the solution was acidified by the careful addition of aqueous H_2SO_4 (20%, 270 ml) while cooling in an ice bath. The solution was extracted with Et_2O/EtOAc (1:1, 3 X 200 ml) and the organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized using Et_2O/hexane to give the acid as a white solid (14.89 g, 56%) and a mother liquor which could be further purified by flash chromatography (1:1 EtOAc/hexane with 2% acetic acid) to yield another crop of acid (8.50 g, 32%); R_f 0.31 (1:1 EtOAc/hexane with 2% acetic acid); mp 130-132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (br, 1H, COO*H*), 7.88-7.80 (m, 3H, aromatic), 7.78 (s, 1H, aromatic), 7.51-7.22 (m, 7H, aromatic), 3.65 (s, 2H, PhC*H*$_2$COOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 142.5, 138.3, 133.1, 132.4, 131.2, 130.4 (2), 128.0, 127.8, 127.6, 127.4, 126.3, 126.0, 38.5; IR (neat) ν 3050, 1710, 1600, 1490, 1410, 1290, 1230, 1190, 1160, 940, 900, 580, 810, 750 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{14}O_2$ [M]$^+$: 262.09937, found: 262.09932.

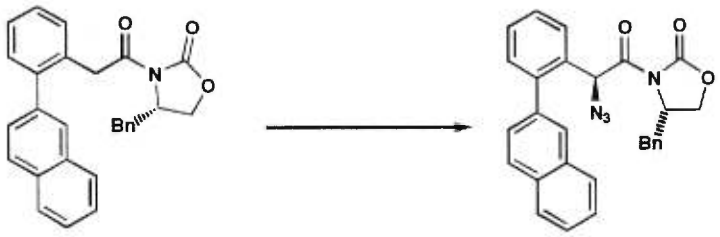
(2*S*)-3-(2′-(2-naphthyl)phenyl-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (211).



To a solution of the acid (598 mg, 2.28 mmol) in dry Et_2O (13 ml) at ambient temperature was added triethylamine (335 µl, 2.39 mmol). The solution was cooled to -78°C and trimethylacetyl chloride (300 µl, 2.44 mmol) was then added slowly. The resulting slurry was warmed to 0°C for 1 h and then recooled to -78°C. In a separate flask, dry THF (5 ml) was added to (4*S*)-4-(phenylmethyl)-2-oxazolidinone (445 mg, 2.51 mmol). This solution was cooled to -78°C and *n*-butyllithium (1.05 ml, 2.5 M in hexanes) was added slowly. After stirring for 15 min, the cold solution of the lithium anion was transferred via cannula into the mixed anhydride. After 15 min at -78°C, the solution was allowed to warm up to 0°C and stirred for an additional 1 h. The solution was poured onto saturated aqueous NH_4Cl (15 ml) and extracted with CH_2Cl_2 (3 X 30 ml). The organic extracts were combined and washed with 10% HCl (2 X 15 ml), saturated aqueous $NaHCO_3$ (15 ml) and then dried over Na_2SO_4 before being concentrated under reduced pressure. The residue was then purified by flash chromatography (1:5 EtOAc/hexane) to yield the acyl oxazolidinone (795 mg, 81%) as a colorless viscous oil; R_f 0.20 (1:5 EtOAc/hexane); $[\alpha]^{21}_D$ +75.8° (*c* 0.178, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.78 (m, 4H, aromatic), 7.50-7.18 (m, 10H, aromatic), 7.03-6.99 (m, 2H, aromatic), 4.38 (d, *J* = 17.9 Hz, 1H, ArC*H*$_2$CO), 4.35 (m, 1H, BnC*H*N), 4.30 (d, *J* = 17.9 Hz, 1H, ArC*H*$_2$CO), 3.92 (dd, *J* = 9.1, 2.7 Hz, 1H, CHC*H*$_2$O), 3.74 (dd, *J* = 8.8, 8.1 Hz,

1H, $CHCH_2O$), 3.02 (dd, J = 13.4, 3.2 Hz, 1H, $PhCH_2CH$), 2.39 (dd, J = 13.4, 9.6 Hz, 1H, $PhCH_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 153.0, 142.3, 138.7, 135.0, 133.0, 132.2, 132.0, 130.7, 130.2, 129.1, 128.7, 127.9, 127.6, 127.5 (2), 127.4, 127.3, 127.0, 126.2, 125.9, 65.7, 54.9, 40.2, 37.3; IR (neat) ν 3010, 1780, 1700, 1600, 1490, 1450, 1380, 1360, 1240, 1210, 1190, 1100, 980, 900, 850, 810, 750, 720, 690 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{23}NO_3$ $[M+H]^+$: 421.16779, found: 421.16581.

(2*S*)-3-((2*S*)-azido-2-(2′-(2-naphthyl)phenyl)-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (212a).

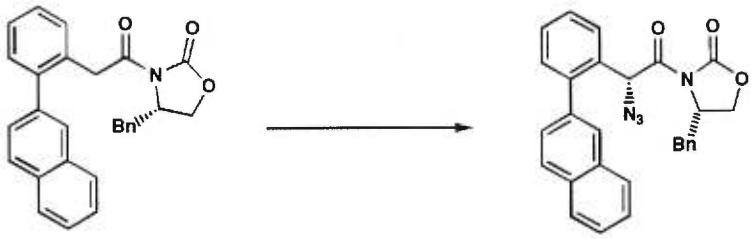


211 **212a**

To a solution of potassium hexamethyldisilylamide (3.91 ml, 0.5 M in toluene) in dry THF (6 ml) was added via cannula, the acyl oxazolidinone (744 mg, 1.77 mmol) in dry THF (10 ml) at -78°C. After stirring the yellow solution for 30 min, it was added to a solution of tri-*iso*-propylbenzenesulfonyl azide (675 mg, 2.17 mmol) in dry THF (6 ml) at -78°C. After 3 min, glacial acetic acid (505 µl, 0.88 mmol) and potassium acetate (867 mg, 0.88 mmol) were added to the solution which was then allowed to stir for 12 h while warming up to ambient temperature slowly. Brine (30 ml) was added and the solution was extracted with CH_2Cl_2 (3 X 30 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 X 15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The diastereoselectivity was determined to be 98:2 by

^{1}H NMR analysis of the crude residue as well as by HPLC (Novapak 6 μm silica gel, 8 mm X 100 mm, flow rate = 1.5 ml/min of 10:90 EtOAc/hexane, T_r (minor) 10.47 min, T_r (major) 13.35 min). The residue was purified by flash chromatography (1:4 EtOAc/hexanes) to yield the diastereomerically pure azide (743 mg, 84%) as a colorless viscous oil; R_f 0.48 (1:3 EtOAc/hexane); $[\alpha]^{21}_D$ +126.8° (*c* 0.164, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.86 (m, 4H, aromatic), 7.59-7.13 (m, 12H, aromatic), 6.05 (s, 1H, Ar*CH*N_3), 4.44 (dddd, *J* = 9.8,, 7.9, 3.3, 2.4 Hz, 1H, Bn*CH*N), 3.98 (dd, *J* = 8.9, 2.4 Hz, 1H, O*CH*$_2$CH), 3.70 (dd, *J* = 8.9, 7.9, 1H, O*CH*$_2$CH), 3.27 (dd, *J* = 13.5, 3.3 Hz, 1H, PhC*H*$_2$CH), 2.66 (dd, *J* = 13.5, 9.8 Hz, 1H, PhC*H*$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 151.8, 143.0, 137.3, 134.7, 132.8, 132.5, 131.4, 131.1, 129.2, 129.1, 128.9, 128.3, 128.2, 127.7, 127.6, 127.3, 136.2 (2), 66.1, 62.0, 55.5, 37.5; IR (neat) ν 3020, 2100, 1710, 1600, 1490, 1450, 1380, 1200, 1100, 1050, 990, 850, 810, 750, 720, 690, 660 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{22}N_2O_3$ $[M-N_2]^+$: 434.16306, found: 434.16361.

(2*S*)-3-((2*R*)-azido-2-(2′-(2-naphthyl)phenyl)-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (212b).



211 **212b**

The minor diastereoisomer generated in the above reaction was contaminated with traces of the major diastereoisomer. Further purification by semi-preparative HPLC (Novapak 6 μm silica gel, 25 X 100 mm, flow rate = 15.0 ml/min of 10:90 EtOAc/hexane, T_r 10.47 min)

produced the diastereomerically pure minor isomer (10 mg, 1%) as a colorless oil; R_f 0.50 (1:3 EtOAc/hexane); $[\alpha]^{21}_{D}$ -74.3° (*c* 0.334, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-7.85 (m, 4H, aromatic), 7.62-7.11 (m, 12H, aromatic), 5.90 (s, 1H, Ar*CH*N_3), 4.66 (m, 1H, Bn*CH*N), 4.02 (m, 2H, O*CH*$_2$CH), 3.36 (dd, *J* = 13.3, 3.4 Hz, 1H, Ph*CH*$_2$CH), 2.46 (dd, *J* = 13.3, 10.2 Hz, 1H, , Ph*CH*$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 151.9, 143.8, 137.4, 134.7, 132.9, 132.6, 131.8, 130.5, 129.3, 129.0, 128.4, 128.3, 127.8, 127.7, 127.6 (2), 127.4, 126.5, 126.2, 126.1, 66.4, 61.9, 55.2, 37.3; IR (neat) ν 3050, 2090, 1790, 1700, 1490, 1390, 1370, 1210, 1100, 900, 820, 750, 720 cm^{-1}; HRMS (FAB+) calcd for $C_{28}H_{22}N_4O_3$ $[M]^+$: 463.17700, found: 463.17450.

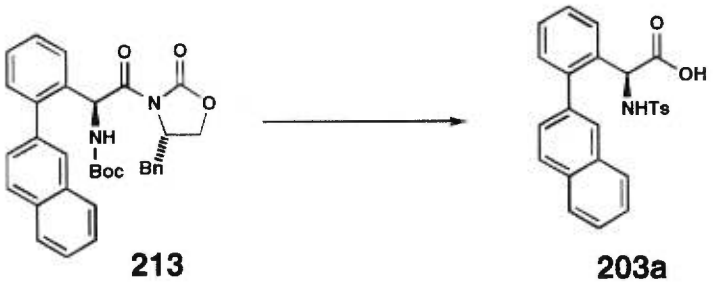
(2*S*)-3-((2*S*)-*N*-*tert*-butoxycarbamido-2-(2´-(2-naphthyl)phenyl)-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (213).

212a **213**

To a solution of water (4 ml) at ambient temperature under argon was added $SnCl_2$ (826 mg, 4.36 mmol) followed by a solution of the azide (671 mg, 1.45 mmol) in dioxane (12 ml). After 24 h, $NaHCO_3$ (610 mg, 7.26 mmol) and BOC_2O (1.5g, 7.26 mmol) were added and the solution was stirred for another 24 h. Dimethyl aminopropylamine (2 ml) was added the solution was stirred for another 2 h. The solution was diluted with ether (100 ml), filtered through celite, washed with 10% HCl (2 X 25 ml) and saturated aqueous $NaHCO_3$ (25 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash

chromatography (1:3.5 EtOAc/hexane) gave the BOC derivative as a colorless viscous oil; Rf 0.45 (1:2 EtOAc/hexane); $[\alpha]^{21}_{D}$ +169.6° (*c* 0.316, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.82 (m, 4H, aromatic), 7.62-7.59 (m, 1H, aromatic), 7.49-7.15 (m, 11H, aromatic), 6.44 (d, *J* = 8.5 Hz, 1H, N*H*), 5.14 (m, 0.8H, ArC*H*NHBOC), 4.82 (m, 0.2H, ArC*H*NHBOC), 4.52 (m, 1H, BnC*H*CH_2O), 4.00 (dd, *J* = 9.0, 1.2 Hz, 1H, CHCH_2O), 3.95 (m, 1H, CHCH_2O), 3.29 (dd, *J* = 13.5, 3.2 Hz, 1H, CHCH_2Ph), 2.69 (m, 1H, CHCH_2Ph), 1.35 (m, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 1554.3, 121.8, 143.5, 137.6, 135.2, 133.3, 133.0, 132.5, 131.5, 129.4, 128.9, 128.6, 128.1, 127.6, 127.2, 126.2, 126.0, 125.9, 79.9, 66.1, 55.8, 55.6, 37.6, 28.1; IR (neat) ν 3400, 2990, 1790, 1700, 1490, 1390, 1360, 1250, 1210, 1160, 1100, 1050, 900, 820, 750, 720 cm^{-1}; HRMS (FAB+) calcd for $C_{33}H_{33}N_2O_5$ $[M+H]^+$: 537.23895, found: 537.23500.

(2*S*)-*N*-tosyl-2-amino-2´-(2-naphthyl)phenyl acetic acid (203a).

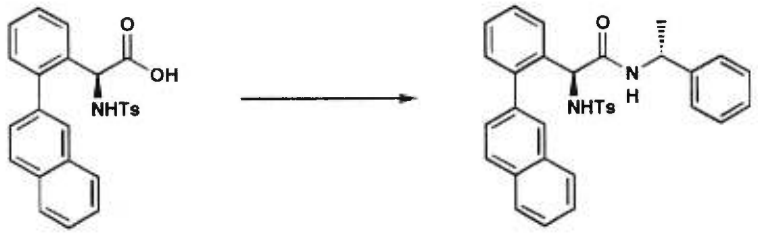


213 **203a**

To a solution of the imide (3.10 g, 5.78 mmol) in THF (60 ml) and H_2O (20 ml) at 0°C was added aqueous H_2O_2 (2.62 ml, 30%) and then LiOH•H_2O (485 mg, 11.6 mmol). After 30 min, TLC analysis showed that the reaction was complete. 10% HCl (20 ml) was carefully added and the mixture was extracted with CH_2Cl_2 (3 X 40 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography, first eluting with 1:1 EtOAc containing 5% Et_3N to give the recovered *(4S)*-4-(phenylmethyl)-2-oxazolidinone and

then with 1:1 EtOAc/hexanes containing 5% acetic acid to give the BOC derivative. After concentration under reduced pressure, the BOC derivative was diluted in CH_2Cl_2 (10 ml) and treated carefully with trifluoroacetic acid (10 ml). After 1h, TLC analysis showed that the reaction was complete and the volatiles were removed under reduced pressure at ambient temperature. The residue was taken up in THF (25 ml) and treated with saturated aqueous Na_2CO_3 (10 ml) and *p*-toluenesulfonyl chloride (2.20 g, 11.6 mmol) at ambient temperature for 12 h. The volatiles were removed under reduced pressure and the residue was diluted 10% HCl (30 ml) and extracted with EtOAc/CH_2Cl_2 (1:3, 3 X 50 ml)). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (2:1 EtOAc/hexane with 1% acetic acid) gave the *N*-tosyl free acid as a viscous oil which produced a foam under reduced pressure. The enantiomeric purity was determined to be 98:2 by the formation of the diastereomeric amides with phenethyl amine and subsequent analysis by HPLC (*vide infra*). The compound was diluted in benzene and lyophilized to give the desired compound as an amorphous white solid (1.87 g, 75%); R_f 0.33 (2:1 EtOAc/hexane with 1% HOAc); mp 180°C (decomp.); $[\alpha]^{21}_D$ +210.8° (*c* 0.120, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.94-7.91 (m, 4H, aromatic), 7.60-7.57 (m, 4H, aromatic), 7.38-7.30 (m, 5H, aromatic), 7.10 (d, *J* = 6.5 Hz, 1H, N*H*), 6.94 (d, *J* = 8.0 Hz, 2H, aromatic), 5.27 (m, 1H, HNC*H*CO_2H), 2.25 (s, 3H, PhCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.1, 143.6, 142.7, 138.6, 135.7, 134.2, 133.5, 131.3, 130.0, 129.5, 129.1, 129.0, 128.8, 128.6 (2), 128.3, 127.6, 127.2, 127.1, 56.3, 21.3; IR (neat) ν 3250, 1730, 1600, 1330, 1150, 1080, 8550, 800, 750, 650 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{22}NO_4S$ $[M+H]^+$: 432.12695, found: 432.12870.

N-((1R)-phenylethyl)-(2S)-N-tosyl-2-amino-2´-(2-naphthyl)phenyl acetamide (214a).

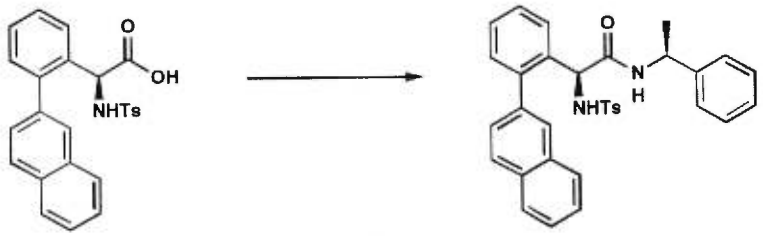


203a **214a**

To a solution of the acid (39.5 mg, 0.092 mmol) in dry DMF (2 ml) at 0°C under argon was added $CuCl_2$ (12 mg, 0.92 mmol), hydroxybenzotriazole (25 mg, 0.183 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (33 mg, 0.11 mmol). After 15 min, *(R)*-phenethylamine (18 µl, 0.14 mmol) was added to the orange solution which turns black immediately. After 30 min, the ice bath is removed and the solution is allowed to warm up to ambient temperature and is stirred for 12 h. The solution is diluted with Et_2O (50 ml), washed with H_2O (3 X 15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by flash chromatography (1:3 EtOAc/hexane) to give the amide (48 mg, 97%) as a colorless oil; R_f 0.40 (1:2 EtOAc/hexane); T_r 18.45 min (Novapak 4 µm silica gel, 8 X 200 mm, 25:75 EtOAc/hexane, 1.0 ml/min); $[\alpha]^{21}_D$ +122.3° (*c* 0.318, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.77 (m, 4H, aromatic), 7.59-7.50 (m, 3H, aromatic), 7.40-7.27 (m, 6H, aromatic), 7.25-7.14 (m, 3H, aromatic), 6.93-9.89 (m, 2H, aromatic), 6.83 (d, *J* = 8.0 Hz, 2H, aromatic), 5.77 (m, 2H, N*H* and N*H*-tosyl), 5.13, (d, *J* = 4.9 Hz, 1H, ArC*H*CO_2H), 4.84 (dq, *J* = 7.5, 6.9 Hz, 1H, HNC*H*CH_3), 2.23 (s, 3H, PhCH_3), 1.27 (d, *J* = 6.9 Hz, 3H, CH_3CHNH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 143.3, 142.2, 140.9, 137.2, 135.8, 134.8, 133.2, 132.5, 130.6, 129.3, 128.5 (3), 128.4, 120.0, 127.7, 127.4, 127.2, 126.9, 126.7, 126.5, 125.7, 56.5, 49.3, 21.5, 21.3; IR (neat) ν 3400, 3280, 3160, 2980, 1670, 1600, 1510, 1490, 1440, 1330, 1160, 1090, 900, 850, 800, 720,

690, 650 cm^{-1}; HRMS (FAB+) calcd for $C_{33}H_{31}N_2O_3S$ $[M+H]^+$: 535.20557, found: 535.20410.

N-((1S)-phenylethyl)-(2S)-N-tosyl-2-amino-2´-(2-naphthyl)phenyl acetamide (214b).



203a **214b**

The amide was produced using the method mentioned above. Flash chromatography gave the desired amide (48 mg, 98%) as a colorless oil; R_f 0.38 (1:2 EtOAc/hexane); T_r 20.23 min (Novapak 4 μm silica gel, 8 X 200 mm, 25:75 EtOAc/hexane, 1.0 ml/min); $[\alpha]^{21}_D$ +132.7° (*c* 0.404, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.20 (m, 16H, aromatic), 6.96 (m, 2H, aromatic), 6.90-6.85 (m, 2H, aromatic), 5.95 (d, *J* = 5.4 Hz, 1H, TsN*H*), 5.57 (d, *J* = 7.7 Hz, 1H, MeCHN*H*), 5.15 (d, *J* = 5.4 Hz, 1H, ArC*H*CO_2H), 4.77 (dq, *J* = 7.7, 6.9 Hz, 1H, HNC*H*CH_3), 2.26 (s, 3H, PhCH_3), 1.17 (d, *J* = 6.9 Hz, 3H, NHCHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 143.3, 142.1, 140.6, 137.3, 136.3, 134.9, 133.2, 132.5, 130.6, 129.3, 128.5, 128.4, 128.3, 128.0, 127.7, 127.3, 127.1, 127.0, 126.7, 126.5, 125.5, 56.1, 49.2, 21.5, 21.4; IR (neat) ν 3400, 3360, 3040, 2940, 1670, 1600, 1510, 1490, 1450, 1340, 1160, 1090, 900, 850, 800, 750, 690, 650 cm^{-1}; HRMS (FAB+) calcd for $C_{33}H_{31}N_2O_3S$ $[M+H]^+$: 535.20557, found: 535.20290.

2-methyl-3-ethoxy-2-cyclohexenone (215a).

215 **215a**

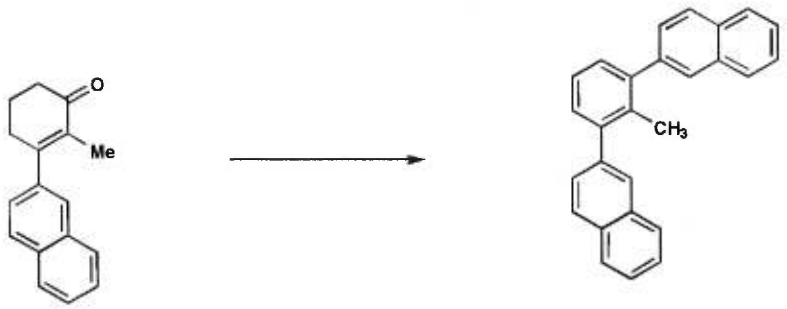
To a solution of 2-methyl-1,3-cyclohexanedione (1.30 g, 10 mmol) in benzene (20 ml) is added *p*-toluenesulfonic acid hydrate (49 mg, 0.25 mmol) and absolute ethanol (6 ml). The mixture is heated to reflux and the ethanol/benzene/water azeotrope is continually removed by a Dean-Stark trap and dry ethanol/benzene (1:3) added every half hour. After 4 h TLC analysis showed that the reaction was complete. The volatiles are removed under reduced pressure and the residue is purified by flash chromatography (1:1 EtOAc/hexane) to yield the mono-ketone (1.54 g, 97%) as a colorless oil; R_f 0.35 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 2.57 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2C{=}C$), 2.33 (t, *J* = 6.2 Hz, 2H, CH_2CH_2CO), 1.98 (tt, *J* = 7.6, 6.2 Hz, 2H, $CH_2CH_2CH_2$), 1.69 (s, 3H, $C{=}CCH_3$), 1.35 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 171.3, 114.5, 63.2, 36.0, 25.0, 20.7, 15.0, 7.0; IR (neat) ν 2940, 1640, 1620, 1380, 1350, 1310, 1240, 1200, 1120, 930, 910, 810 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}O_2$ $[M+H]^+$: 155.10723, found: 155.10483.

2-methyl-3-(2-naphthyl)-2-cyclohexenone (217).

215a **217**

A three neck flask is charged with magnesium turnings (320 mg, 13.2 mmol) and a stir bar. The flask is then equipped with a dropping funnel, condenser and a stopper. The turnings are dried by flaming the flask under aspirator vacuum with efficient stirring and allowed to cool under argon. The flask is then charged with dry THF (7 ml) while the dropping funnel is charged with 2-bromonaphthalene (1.80 g, 8.8 mmol) and dry THF (20 ml). The bromide is added to the magnesium at ambient temperature and the mixture is then refluxed for 1 h and then allowed to cool to ambient temperature. The Grignard is then added slowly via cannula to the ketone (922 mg, 5.98 mmol) in dry THF (20 ml) at -78°C under argon. The dry ice bath is removed and the reaction is allowed to stir while warming up to ambient temperature slowly. After 1 h, EtOAc (2 ml) is carefully added followed by Et_2O (150 ml). The organic phase is washed with $NaHCO_3$ (3 X 20 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by flash chromatography (1:8 EtOAc/hexane) to give the desired ketone as a slightly yellow oil; R_f 0.45 (1:5 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.23 (m, 7H, aromatic), 2.68 (t, J = 5.1 Hz, 2H, CH_2CH_2C=C), 2.55 (t, J = 7.1 Hz, 2H, CH_2CH_2CO), 2.10 (tt, J = 7.1, 5.1 Hz, 2H, $CH_2CH_2CH_2$), 1.78 (s, 3H, C=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 156.5, 154.4, 138.5, 134.6, 132.8, 132.5, 132.0, 129.4, 128.4, 127.9, 127.5, 126.3 (2), 126.2, 126.0 (2), 125.1, 122.9, 118.1, 109.3, 37.6, 32.8, 22.7, 12.9; IR (neat) ν 3300, 3040, 2940, 2860, 1660, 1370, 1350, 1320, 1300, 1210, 1190, 1100, 1030, 850, 810, 740 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}O$ $[M+H]^+$: 236.12012, found: 236.11954 .

2,6-bis(2-naphthyl)-toluene (218).

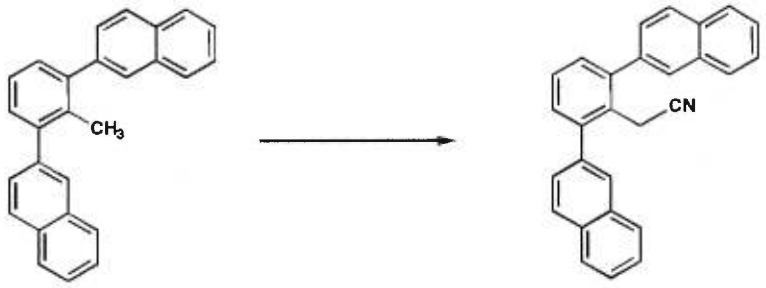


217 **218**

A three neck flask is charged with magnesium turnings (2.61 g, 107.5 mmol) and a stir bar. The flask is then equipped with a dropping funnel, condenser and a stopper. The turnings are dried by flaming the flask under aspirator vacuum with efficient stirring and allowed to cool under argon. The flask is then charged with dry THF (27 ml) while the dropping funnel is charged with 2-bromonaphthalene (13.1 g, 63.0 mmol) and dry THF (100 ml). The bromide is added to the magnesium at ambient temperature and the mixture is then refluxed for 1 h and then allowed to cool to ambient temperature. The Grignard is then added slowly via cannula to the ketone (8.054 g, 34.1 mmol) in dry THF (50 ml) at -78°C under argon. The dry ice bath is removed and the reaction is allowed to stir while warming up to ambient temperature slowly. After 1 h, EtOAc (10 ml) is carefully added followed by Et_2O (350 ml). The organic phase is washed with $NaHCO_3$ (3 X 40 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude alcohol is dissolved in CH_2Cl_2 (200 ml) and $BF_3 \bullet Et_2O$ (5.05 ml, 40.9 mmol) in CH_2Cl_2 (50 ml) is added slowly resulting in a black solution which discharges it color slowly. After 3 h, the reaction was found to be complete by TLC analysis. Saturated aqueous $NaHCO_3$ (30 ml) is carefully added and the mixture is washed with saturated aqueous $NaHCO_3$ (2 X 50ml). The organic phase is dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified

through a small silica gel column using Et_2O as an eluant to give the diene as a crude yellow solid (12.1 g). To a solution of the diene in EtOAc (300 ml) is added 5% palladium on carbon (1.20 g) followed by cyclohexene (10 ml). The mixture is refluxed and the progress of the reaction is monitored by ^1H NMR of aliquots which are removed, filtered and evaporated to dryness under reduced pressure prior to analysis. After 5 days, cyclohexene (10 ml) is again added and after another 5 days, the reaction is complete and the solution is cooled to room temperature, filtered through celite and concentrated under reduced pressure. The residue is purified by flash chromatography (1:40 Et_2O/hexane) to give the desired hydrocarbon (6.692 g, 57%) as a low melting white solid; R_f 0.45 (1:20 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.84 (m, 8H, aromatic), 7.55-7.47 (m, 6H, aromatic), 7.37-7.35 (m, 3H, aromatic), 2.19 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 139.9, 133.3 (2), 132.2, 129.3, 127.9 (3), 127.6, 127.5, 126.1, 125.8, 125.4, 18.8; IR (neat) ν 3020, 1600, 1500, 1440, 1260, 1120, 1010, 940, 880, 850, 810, 780, 730, 710 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{20}$ $[M]^+$: 344.15649, found: 344.15851.

2,6-bis(2-naphthyl)-phenylacetonitrile (220).



218 **220**

To a solution of the methyl aryl hydrocarbon (1.20 g, 3.5 mmol) in CCl_4 (40 ml) was added *N*-bromosuccinimide (745 mg, 4.2 mmol) and benzoyl

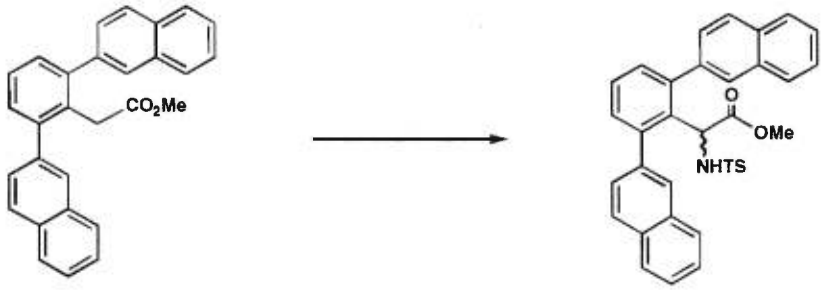
peroxide (170 mg, 0.7 mmol). The yellowish solution was connected to an exit bubbler and brought to reflux for 2 h. After cooling the near colorless solution to ambient temperature, the solution was diluted with Et_2O/EtOAc (1:1, 100 ml) and then washed with 10% HCl (2 X 25 ml) and saturated aqueous $NaHCO_3$ (15 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was combined with EtOH (8 ml), H_2O (1 ml), $CHCl_3$ (9 ml) and KCN (340 mg, 5.2 mmol). The mixture was warmed to 60°C for 2.5 h or until TLC analysis showed that the reaction was complete. After cooling to ambient temperature, the mixture was diluted with Et_2O (150 ml) and washed with 10% HCl (2 X 25 ml), saturated aqueous $NaHCO_3$ (25 ml) and dried over Na_2SO_4. The residue was purified by flash chromatography (1:15 EtOAc/hexane) to give the nitrile (1.155 g, 90%) as a colorless oil; R_f 0.11 (1:10 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.94 (m, 8H, aromatic), 7.65-7.46 (m, 9H, aromatic), 3.48 (s, 2H, ArCH_2CN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 137.7, 133.1, 132.6, 130.0, 128.3, 128.1, 128.0, 127.7, 127.0, 126.6, 126.5, 126.4, 118.9, 20.5; IR (neat) ν 3030, 2220, 1600, 1580, 1500, 1410, 1260, 1190, 1120, 900, 850, 810, 790, 720 cm^{-1}; HRMS (THIO) calcd for $C_{28}H_{19}N$ $[M+H]^+$: 370.15958, found: 370.16100.

Methyl 2,6-bis(2-naphthyl)-phenylacetate (221).

220 **221**

To a solution of the nitrile (2.64g, 7.15 mmol) in EtOH (60 ml) was added NaOH (1.4 g, 35 mmol) in H_2O (1.4 ml). The mixture was refluxed for 24 h or until TLC analysis showed that the reaction was complete. The volatiles were then removed under reduced pressure and the residue was diluted with Et_2O (150 ml), washed with 10% HCl (2 X 25 ml), and saturated aqueous $NaHCO_3$ (25 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in dry MeOH (80 ml) and concentrated H_2SO_4 (4.0 ml) was added carefully. The mixture was then refluxed for 72 h or until TLC analysis showed that the reaction was complete. The volatiles were removed under reduced pressure and saturated aqueous $NaHCO_3$ (50 ml) was carefully added to the residues. The mixture was then extracted with Et_2O/EtOAc (1:1, 3 X 50 ml). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc/hexane) to give the methyl ester (2.38 g, 83%) as a yellowish oil; R_f 0.35 (1:10 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.83 (m, 8H, aromatic), 7.52-7.39 (m, 9H, aromatic), 3.57 (s, 2H, ArCH_2CO_2Me), 3.33 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 143.4, 139.0, 133.1, 132.4, 130.4, 129.5, 127.9 (2), 127.7, 127.6, 127.4, 127.0, 126.8, 126.2, 126.0, 51.4, 36.9; IR (neat) ν 3020, 2940, 1740, 1600, 1580, 1500, 1430, 1340, 1200, 1150, 1000, 900, 850, 810, 790, 740, 720 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{23}O_2$ $[M+H]^+$: 403.16980, found: 403.17110.

(±) Methyl-2-*N*-tosylamino-2′,6′-bis(2-naphthyl)-phenylacetate (223).

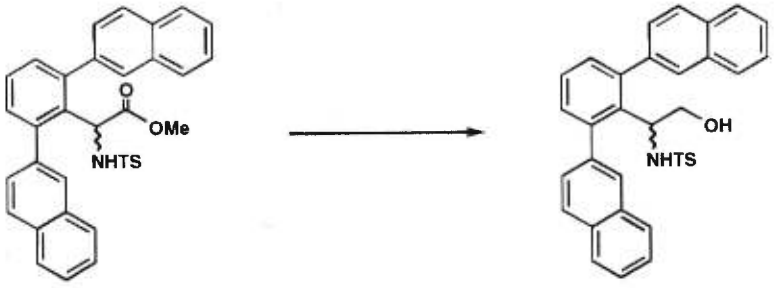


221 **223**

To a solution of potassium hexamethyldisilylamide (9.6 ml, 0.5 M in toluene) in dry THF (20 ml) was added via cannula, the methyl ester (1.393 mg, 4.38 mmol) in dry THF (20 ml) at -78°C. After stirring the yellow solution for 30 min, the anion was added to a solution of tri-*iso*-propylbenzenesulphonyl azide (1.62 g, 5.25 mmol) in dry THF (10 ml) at -78°C. After 3 min, acetic acid (1.31 ml, 21.9 mmol) and potassium acetate (2.15 g, 21.9 mmol) was added to the solution which was then allowed to stir for 12 h while warming up to ambient temperature slowly. The reaction was diluted with Et_2O (150 ml) washed with 10% HCl (2 X 15 ml) and saturated aqueous $NaHCO_3$ (2 X 15 ml). The aqueous washings were extracted with Et_2O/EtOAc (100 ml) and washed with 10% HCl (2 X 15 ml) and saturated aqueous $NaHCO_3$ (2 X 15 ml). The organic phases were combined and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then dissolved in dry MeOH (20 ml) and $SnCl_2$ (1.25g, 6.57 mmol) was added and the resulting slurry was stirred at ambient temperature for 24 h at which time more $SnCl_2$ (1.25g, 6.57 mmol) was added. After another 24 h, TLC analysis showed the reaction was complete. The volatiles were removed under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (100 ml) and aqueous NaOH (50 ml, 2.5 M) was added. The resulting slurry was filtered through celite and separated. The aqueous phase was extracted with CH_2Cl_2/EtOAc (3 X 30

ml) and resulting organic phases were dried with Na_2SO_4 and concentrated under reduced pressure to give a crude gum. The gum was then immediately dissolved in CH_2CH_2 (10 ml) and Et_3N (1.34 ml, 9.60 mmol), DMAP (10 mg) and *p*-toluenesulfonyl chloride (1.66 g, 8.76 mmol) were added at room temperature. After 12h, TLC analysis showed that the reaction was complete. The mixture was diluted with Et_2O (100 ml), washed with 10% HCl (2 X 25 ml) and saturated aqueous $NaHCO_3$ (25 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (1:3 EtOAc/hexane) to give the desired ester (1.64 g, 73%) as a colorless gum; R_f 0.43 (1:3 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.77 (m, 8H, aromatic), 7.54-7.32 (m, 9H, aromatic), 6.80 (d, *J* = 7.9 Hz, 2H, aromatic), 6.53 (d, *J* = 7.9 Hz, 2H, aromatic), 5.20 (br, 1H, N*H*), 4.95 (d, *J* = 5.5 Hz, 1H, ArC*H*NH), 3.51 (s, 3H, OCH_3), 2.11 (s, 3H, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 142.9, 142.8, 138.1, 135.2, 133.4, 132.8, 132.5, 132.3, 130.4, 129.3, 129.0, 128.8, 128.2, 128.0, 127.8, 127.7 (2), 127.1, 126.9, 126.5, 126.3, 55.3, 53.1, 21.3; IR (neat) ν 3410, 3010, 1750, 1350, 1220, 1160, 1090, 750, 660 cm^{-1}; HRMS (FAB+) calcd for $C_{36}H_{30}NO_4S$ $[M+H]^+$: 572.18958, found: 572.18680.

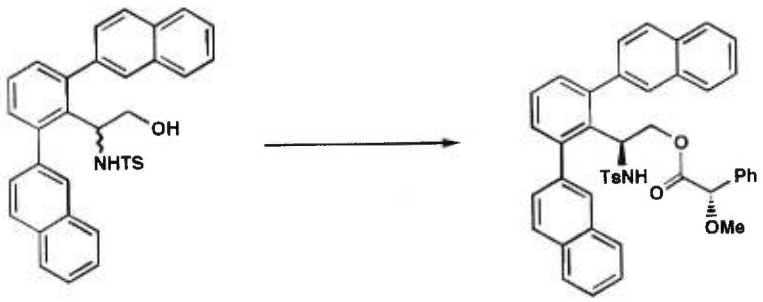
(±) 2-*N*-tosylamino-2´,6´-bis(2-naphthyl)-phenyl ethyl alcohol (224).



223 **224**

To a solution of the ester (1.653 g, 2.89 mmol) in Et_2O (30 ml) at 0°C under argon was added $LiAlH_4$ (200 mg, 5.21 mmol). The mixture was stirred for 4 h or until TLC analysis showed that the reaction was complete. H_2O (10 drops) was added dropwise at 0°C until the mixture became white and no more gas evolved. Na_2SO_4 was added and the mixture was filtered through celite. The volatiles were then removed under reduced pressure. The residue was purified by flash chromatography (1:3 EtOAc/hexane) to give the alcohol (1.52 g, 90%) as a colorless oil; R_f 0.34 (1:3 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.91-7.85 (m, 6H, aromatic), 7.75 (s, 2H, aromatic), 7.57-7.52 (m, 4H, aromatic), 7.46-7.44 (m, 2H, aromatic), 7.37-7.33 (m, 1H, aromatic), 7.25-7.23 (m, 2H, aromatic), 7.19-7.17 (m, 2H, aromatic), 6.82-6.81 (m, 2H, aromatic), 4.63 (br, 1H, N*H*), 4.43 (br, 1H, ArC*H*NH), 3.61 (dd, *J* = 11.5, 4.7 Hz, 1H, CHCH_2OH), 3.53 (dd, *J* = 11.5, 9.3 Hz, 1H, CHCH_2OH), 2.23 (s, 3H, PhCH_3), 1.46 (br, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.2, 138.6, 136.4, 133.5, 132.8, 132.4, 130.9, 0129.1, 128.5, 128.0, 127.8, 127.7, 126.9, 126.8, 126.6, 126.3, 66.3, 57.2, 21.3; IR (neat) ν 3520, 3440, 3050, 2930, 1600, 1310, 1160, 1060, 950, 910, 860, 810, 750, 670 cm^{-1}; HRMS (THIO) calcd for $C_{35}H_{30}NO_3S$ $[M+H]^+$: 544.19464, found: 544.19310.

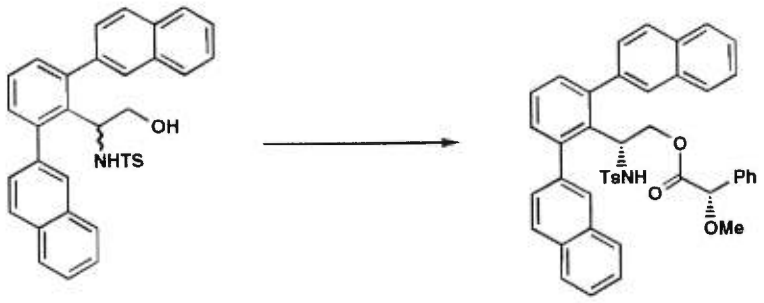
((2*S*)-2-*N*-tosylamino-2′,6′-bis(2-naphthyl)-phenethyl)-(2*S*)-O-methoxymandelate (225a).



224 **225a**

To a solution of the alcohol (798 mg, 1.47 mmol) in CH_2Cl_2 (5.0 ml) at ambient temperature under nitrogen was added *(R)*-O-methoxymandelic acid (293 mg, 1.76 mmol), dicyclohexylcarbodiimide (363 mg, 1.76 mmol) and DMAP (10 mg). After 2 h, TLC analysis showed that the reaction was complete. The reaction was diluted with Et_2O/hexane (1:1, 50 ml) and filtered through celite. The residue was purified by a flash chromatography (1:3 EtOAc/hexane) to remove contaminants (mainly dicyclohexylurea) from the product. A second flash chromatography (1:2 Et_2O/hexane) was used to separate the diastereoisomers which produced the more chromatographically mobile ester (423 mg, 42%) in pure form. Its absolute stereochemistry was determined by x-ray[296] crystallography; R_f 0.23 (1:3 EtOAc/hexane); T_r 24.06 min (Novapak 6 μm silica gel, 8 X 100 mm, 10/90 EtOAc/hexane, 1.0 ml/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.04 (m, 24H, aromatic), 6.77 (d, *J* = 8.0 Hz, 2H, aromatic), 4.88 (br, 1H, N*H*), 4.44 (m, 1H, OC*H*$_2$CH), 4.34 (m, 1H, NHC*H*CH$_2$), 4.21 (s, 1H, PhC*H*OCH$_3$), 3.64 (dd, *J* = 11.4, 9.1 Hz, 1H, OC*H*$_2$CH), 3.08 (s, 3H, OC*H*$_3$), 2.22 (s, 3H, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 142.8, 135.6, 132.4, 129.0, 128.7, 128.5, 128.2, 128.0, 127.8, 127.7, 127.1, 127.0, 126.6 (2), 126.3, 82.1, 66.4, 57.0, 53.7, 21.3; IR (neat) ν 3380, 3060, 2910 ,1750, 1600, 1490, 1450, 1330, 1150, 1090, 1010, 950, 850, 770, 740, 650 cm^{-1}; HRMS (THIO) calcd for $C_{44}H_{38}NO_5S$ $[M+H]^+$: 692.24707, found: 692.24930. For x-ray crystal data, see Appendix 5.

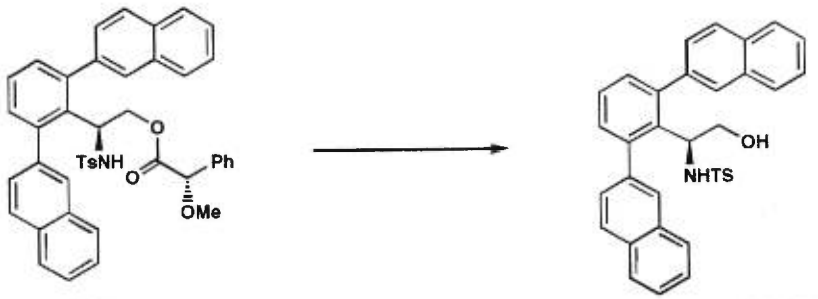
((2*R*)-2-*N*-tosylamino-2´,6´-bis(2-naphthyl)-phenethyl)-(2*S*)-O-methoxymandelate (225b).



224 **225b**

This ester (402 mg, 40%) was produced in the above reaction and is the less chromatographically mobile of the two. It was found to be only 87.5 %de by HPLC analysis. Repurification provided an analytically pure sample; R_f 0.20 (1:3 EtOAc/hexane); T_r 28.51 min (Novapak 6 μm silica gel, 8 X 100 mm, 10/90 EtOAc/hexane, 1.0 ml/min); $[\alpha]^{21}_{D}$ +37.9° (*c* 0.552, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-6.99 (m, 24H, aromatic), 6.81-6.79 (m, 2H, aromatic), 4.88 (br, 1H, N*H*), 4.34 (br, 1H, HNC*H*CH_2), 4.27 (s, 1H, PhC*H*OCH_3), 3.99 (m, 2H, OCH_2CH), 3.18 (s, 3H, OCH_3), 2.24 (s, 3H, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 142.8, 142.3, 138.4, 136.8, 135.6, 133.1, 132.4, 131.1, 129.0, 128.5, 128.4, 128.1, 127.8, 127.7, 127.0, 126.9, 126.6 (2), 126.3, 81.7, 66.7, 57.1, 53.2, 30.8, 21.3; IR (neat) ν 3380, 3300, 3060, 1750, 1600, 1580, 1500, 1450, 1430, 1330, 1150, 1110, 1090, 900, 850, 810, 720, 650 cm^{-1}; HRMS (THIO) calcd for $C_{44}H_{38}NO_5S$ $[M+H]^+$: 692.24707, found: 692.24930.

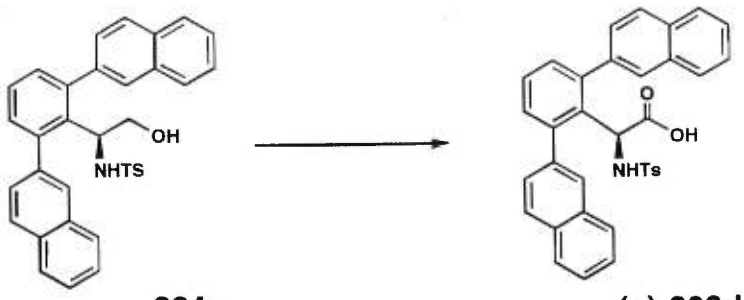
(2*S*)-2-*N*-tosylamino-2′,6′-bis(2-naphthyl)-phenyl ethyl alcohol (224a).



225a **224a**

To a solution of the ester (563 mg, 0.8 mmol) in MeOH (5 ml) at room temperature was added K_2CO_3 (800 mg, 5.7 mmol). The solution was stirred for 30 min or until TLC analysis showed that the reaction was complete. The volatiles were removed under reduced pressure. The residue was taken up in Et_2O (50 ml) and washed with 10% HCl (2 X 15 ml) and saturated aqueous $NaHCO_3$ (15 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1:3 EtOAc/hexane) to give the alcohol (434 mg, 98%) as a colorless oil; R_f 0.34 (1:3 EtOAc/hexane); $[\alpha]^{21}_D$ +108.8° (*c* 1.134, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.85 (m, 6H, aromatic), 7.75 (s, 2H, aromatic), 7.57-7.52 (m, 4H, aromatic), 7.46-7.44 (m, 2H, aromatic), 7.37-7.33 (m, 1H, aromatic), 7.25-7.23 (m, 2H, aromatic), 7.19-7.17 (m, 2H, aromatic), 6.82-6.81 (m, 2H, aromatic), 4.63 (br, 1H, N*H*), 4.43 (br, 1H, ArC*H*NH), 3.61 (dd, *J* = 11.5, 4.7 Hz, 1H, CHCH_2OH), 3.53 (dd, *J* = 11.5, 9.3 Hz, 1H, CHCH_2OH), 2.23 (s, 3H, PhCH_3), 1.46 (br, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.2, 138.6, 136.4, 133.5, 132.8, 132.4, 130.9, 0129.1, 128.5, 128.0, 127.8, 127.7, 126.9, 126.8, 126.6, 126.3, 66.3, 57.2, 21.3; IR (neat) ν 3520, 3440, 3050, 2930, 1600, 1310, 1160, 1060, 950, 910, 860, 810, 750, 670 cm^{-1}; HRMS (THIO) calcd for $C_{35}H_{30}NO_3S$ $[M+H]^+$: 544.19464, found: 544.19310.

(2*S*)-2-*N*-tosylamino-2´,6´-bis(2-naphthyl)-phenyl acetic acid ((+)-203d).



224a **(+)-203d**

To a solution of the alcohol (337 mg, 0.62 mmol) in CH_2Cl_2 (20 ml) at 0°C was added molecular sieves (4 Å, 350 mg) and pyridinium dichromate (350 mg, 0.93 mmol). The solution was stirred at 0°C for 10 min and then the ice bath was removed and the solution stirred for another 2 h at which time TLC analysis showed that the reaction was complete. The reaction was diluted with Et_2O (50 ml) and filtered through silica. The volatiles were then removed under reduced pressure. The residue was immediately taken up in *t*-BuOH (4 ml). To this mixture at 0°C was added an aqueous solution of 5% NaH_2PO_4 (3 ml) and an aqueous solution of $KMnO_4$ (4 ml). The reaction was monitored carefully by TLC and after 3 minutes the reaction was complete. Saturated aqueous Na_2SO_3 (3 ml) was added followed by 10% HCl (5 ml) which discharged the color of the solution. The mixture was then extracted with Et_2O/EtOAc (3 X 20 ml). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The enantiomeric purity of the crude acid was determined to be 94 %ee by chiral HPLC analysis (Chiracel OJ, 10:90 2-propanol/hexane, 1.0 ml/min, T_r *(S)* 17.15 min, T_r *(R)* 20.87 min) of the corresponding methyl ester (Et_2O, diazomethane). The residue was purified by flash chromatography to give a colorless gum which was dissolved in benzene (10 ml) and lyophilized to give the acid (251 mg, 73%) as a white amorphous powder; R_f 0.23 (1:2 EtOAc/hexane with 1% acetic acid); $[\alpha]^{21}_D$ +194.2° (*c* 0.278, $CHCl_3$); ^1H

NMR (300 MHz, acetone-d_6) δ 8.02-7.90 (m, 8H, aromatic), 7.62-7.51 (m, 7H, aromatic), 7.39-7.37 (m, 2H, aromatic), 6.87 (d, *J* = 7.8 Hz, 2H, aromatic), 6.66 (d, *J* = 7.8 Hz, 2H, aromatic), 5.16 (br, 1H, N*H*), 5.07 (d, *J* = 5.1 Hz, 1H, ArC*H*NH), 2.15 (s, 3H, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 143.9, 143.8, 139.3, 136.7, 134.7, 133.9, 133.6, 131.2, 129.8, 129.2, 129.0, 128.6, 128.4, 127.8, 127.2, 127.1, 56.0, 21.2; IR (neat) ν 3350, 3060, 1730, 1600, 1400, 1340, 1160, 1090, 910, 890, 860, 820, b800, 750, 650 cm^{-1}; HRMS (FAB+) calcd for $C_{35}H_{28}NO_4S$ $[M+H]^+$: 558.17371 , found: 558.17096. For x-ray crystal data on **(-)-203d**, see Appendix 6.

(*R*)-1-bromo-1-hydroxymethyl [2.2.1] bicyclohept-4-ene (226).

226

To a solution of acid (24.7 mg, 0.046 mmol) in dry CH_2Cl_2 (5 ml) at ambient temperature under argon was added BH_3•DMS (46 µl, 0.046 mmol, 1.0 M in THF). The solution was stirred for 3 h. The catalyst solution was then cooled to -78°C. Freshly cracked cyclopentadiene (380 µl, 4.56 mmol) was added followed by the slow dropwise addition of 2-bromoacrolein (75 µl, 0.91 mmol). The solution was kept at -24°C for 12 h and then treated with MeOH (5 ml)and $NaBH_4$ (38 mg, 1.0 mmol) at 0°C for 1 h. The mixture was then diluted with Et_2O (100 ml) and washed with 10% HCl (2 X 20 ml) and saturated aqueous $NaHCO_3$ (20 ml). The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure. The Diels-Alder adduct was determined to be 50 %ee *(R)* by chiral gas chromatography analysis (30 m Cyclodex-B, 115°C isothermal, 25 psi column head pressure, T_r *(R)*: 14.79 min, T_r *(S)*: 15.01 min) of the trifluoroacetate derivative (CH_2Cl_2, pyridine, trifluoroacetic anhydride). The residue was purified by flash chromatography to give the alcohol as a colorless oil; R_f 0.40 (1:4

EtOAc/hexane); $[\alpha]^{21}_{D}$ +23.15° (*c* 0.378, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (m, 1H, CH=C*H*CHCBr), 6.15 (m, 1H, CH=C*H*CH), 3.85 (d, *J* = 12.5 Hz, 1H, BrCCH_2OH), 3.72 (d, *J* = 12.5 Hz, 1H, BrCCH_2OH), 3.23 (m, 1H, HCC*H*CBr), 2.91 (m, 1H, HCC*H*CH_2), 2.33 (br, 1H, O*H*), 1.92 (dd, *J* = 13.5, 2.4 Hz, 1H, HCCH_2CBr), 1.72 (dd, *J* = 13.5, 2.0 Hz, 1H, HCCH_2CBr), 1.50 (m, 2H, HCCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 136.8, 79.3, 72.4, 50.6, 46.5, 42.1, 40.4; IR (neat) ν 3320, 2980, 1440, 1360, 1330, 1270, 1250, 1230, 1190, 1080, 1040, 1010, 700 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{12}O^{79}Br$ $[M+H]^+$: 203.00716 , found: 203.00790.

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Appendix 1

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CHAR40

ANDRÉ CHARETTE, PETER CHUA AND FRANCINE BÉLANGER-GARIÉPY

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Abstract

resume

Comment

comment

Experimental

Synthesis was carried out by reaction of ...

Crystal data

$C_{26}H_{20}N_2O$
$M_r = 376.440$
Monoclinic
$P2_1/c$
$a = 10.918(6)$ Å
$b = 20.303(8)$ Å
$c = 9.311(4)$ Å
$\beta = 97.57(4)°$
$V = 2046.0(16)$ Å^3
$Z = 4$
$D_x = 1.2221$ Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
$\lambda = 1.54056$ Å

Cell parameters from 25 reflections
$\theta = 23.00$–$25.00°$
$\mu = 0.587$ mm^{-1}
$T = 293(2)$ K
Block
0.65 × 0.47 × 0.31 mm
Colourless
Crystal source: synthesized by the authors, see text

Data collection

Nonius CAD-4 diffractometer
$\omega/2\theta$ scan
Absorption correction:
by integration ABSORP in *NRC-VAX* (Gabe *et al.* 1989)
$T_{min} = 0.7081$, $T_{max} = 0.8689$
29340 measured reflections
3879 independent reflections
3181 reflections with $>2\sigma(I)$
$R_{int} = 0.024$

$\theta_{max} = 69.80°$
$h = -13 \rightarrow 13$
$k = -24 \rightarrow 24$
$l = -11 \rightarrow 11$
5 standard reflections
frequency: 60 min
intensity decay: no decay, variation 2.5%

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.0345$

$wR(F^2) = 0.0990$

$S = 1.173$

3879 reflections

263 parameters

H-atom parameters constrained

$w=1/[\sigma^2(F_o^2) + (0.0554P)^2 + 0.0452P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.001$

$\Delta\rho_{max} = 0.137$ e Å^{-3}

$\Delta\rho_{min} = -0.128$ e Å^{-3}

Extinction correction: *SHELXL96* (Sheldrick, 1996)

Extinction coefficient: 0.0065 (4)

Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
C1	0.32090 (11)	0.05426 (5)	0.77443 (11)	0.0418 (3)
N1	0.43476 (9)	0.06511 (5)	0.81169 (11)	0.0487 (3)
C2	0.47501 (10)	0.12056 (6)	0.89805 (12)	0.0452 (3)
C3	0.45263 (12)	0.18406 (7)	0.84650 (13)	0.0538 (3)
C4	0.49752 (13)	0.23732 (7)	0.93047 (15)	0.0597 (3)
C5	0.56448 (13)	0.22735 (7)	1.06467 (14)	0.0585 (3)
C6	0.58675 (13)	0.16417 (7)	1.11554 (14)	0.0574 (3)
C7	0.54334 (11)	0.11083 (7)	1.03246 (14)	0.0514 (3)
N8	0.22503 (8)	0.09126 (5)	0.83217 (9)	0.0403 (2)
C8	0.15193 (11)	0.13111 (6)	0.73652 (12)	0.0425 (3)
O8	0.17921 (9)	0.14014 (5)	0.61481 (9)	0.0598 (3)
C9	0.03912 (10)	0.16127 (6)	0.78329 (12)	0.0424 (3)
C10	−0.03560 (11)	0.12899 (7)	0.86982 (13)	0.0517 (3)
C11	−0.14133 (13)	0.15910 (8)	0.90375 (16)	0.0639 (4)
C12	−0.17141 (13)	0.22155 (8)	0.85471 (16)	0.0687 (4)
C13	−0.09886 (15)	0.25348 (7)	0.76819 (17)	0.0677 (4)
C14	0.00552 (12)	0.22338 (6)	0.73023 (14)	0.0538 (3)
C15	0.22701 (10)	0.09043 (6)	0.98711 (12)	0.0436 (3)
C16	0.22996 (14)	0.03014 (8)	1.05564 (14)	0.0634 (4)
C17	0.23598 (19)	0.02736 (11)	1.20438 (18)	0.0897 (6)
C18	0.23778 (18)	0.08386 (12)	1.28458 (16)	0.0934 (6)
C19	0.23540 (15)	0.14379 (9)	1.21645 (16)	0.0753 (5)
C20	0.23143 (12)	0.14807 (7)	1.06673 (13)	0.0545 (3)
C21	0.28107 (11)	−0.00133 (6)	0.67621 (11)	0.0456 (3)
C22	0.36810 (14)	−0.03189 (6)	0.60208 (13)	0.0543 (3)
C23	0.33498 (17)	−0.08460 (7)	0.51179 (14)	0.0666 (4)
C24	0.21613 (18)	−0.10774 (7)	0.49482 (15)	0.0718 (5)

C25	0.12917 (16)	−0.07820 (8)	0.56678 (17)	0.0720 (4)
C26	0.16114 (13)	−0.02476 (7)	0.65765 (15)	0.0596 (3)

Table 2. *Selected geometric parameters (Å, °)*

C1—N1	1.2651 (16)	C10—C11	1.3791 (19)
C1—N8	1.4482 (15)	C11—C12	1.373 (2)
C1—C21	1.4814 (16)	C12—C13	1.366 (2)
N1—C2	1.4192 (16)	C13—C14	1.380 (2)
C2—C7	1.3841 (18)	C15—C16	1.3787 (18)
C2—C3	1.3862 (18)	C15—C20	1.3828 (17)
C3—C4	1.3857 (18)	C16—C17	1.379 (2)
C4—C5	1.377 (2)	C17—C18	1.367 (3)
C5—C6	1.378 (2)	C18—C19	1.371 (3)
C6—C7	1.3781 (18)	C19—C20	1.392 (2)
N8—C8	1.3774 (15)	C21—C26	1.3824 (19)
N8—C15	1.4400 (14)	C21—C22	1.3918 (18)
C8—O8	1.2229 (14)	C22—C23	1.3794 (19)
C8—C9	1.4911 (17)	C23—C24	1.370 (2)
C9—C10	1.3846 (17)	C24—C25	1.370 (2)
C9—C14	1.3860 (18)	C25—C26	1.392 (2)

N1—C1—N8	122.69 (11)	C11—C10—C9	119.91 (13)
N1—C1—C21	119.99 (11)	C12—C11—C10	120.26 (14)
N8—C1—C21	117.17 (10)	C13—C12—C11	120.19 (13)
C1—N1—C2	120.88 (10)	C12—C13—C14	120.25 (14)
C7—C2—C3	119.69 (12)	C13—C14—C9	120.03 (13)
C7—C2—N1	119.27 (12)	C16—C15—C20	120.41 (12)
C3—C2—N1	120.95 (11)	C16—C15—N8	118.06 (11)
C4—C3—C2	119.83 (12)	C20—C15—N8	121.47 (11)
C5—C4—C3	120.22 (13)	C15—C16—C17	119.75 (15)
C4—C5—C6	119.83 (12)	C18—C17—C16	120.63 (17)
C5—C6—C7	120.43 (13)	C17—C18—C19	119.59 (14)
C6—C7—C2	120.00 (13)	C18—C19—C20	121.01 (15)
C8—N8—C15	125.85 (9)	C15—C20—C19	118.58 (14)
C8—N8—C1	116.75 (9)	C26—C21—C22	118.81 (12)
C15—N8—C1	116.72 (9)	C26—C21—C1	122.38 (11)
O8—C8—N8	119.75 (11)	C22—C21—C1	118.80 (12)
O8—C8—C9	121.37 (11)	C23—C22—C21	120.46 (14)
N8—C8—C9	118.87 (10)	C24—C23—C22	120.32 (15)
C10—C9—C14	119.30 (12)	C23—C24—C25	120.03 (14)
C10—C9—C8	123.25 (11)	C24—C25—C26	120.27 (15)
C14—C9—C8	117.36 (11)	C21—C26—C25	120.12 (14)

N8—C1—N1—C2	−8.73 (17)	C11—C12—C13—C14	−0.4 (2)
C21—C1—N1—C2	175.90 (10)	C12—C13—C14—C9	−1.9 (2)
C1—N1—C2—C7	119.20 (13)	C10—C9—C14—C13	2.46 (19)
C1—N1—C2—C3	−64.31 (16)	C8—C9—C14—C13	179.18 (12)
C7—C2—C3—C4	−0.74 (18)	C8—N8—C15—C16	136.79 (13)
N1—C2—C3—C4	−177.22 (11)	C1—N8—C15—C16	−53.02 (15)
C2—C3—C4—C5	0.2 (2)	C8—N8—C15—C20	−46.06 (17)
C3—C4—C5—C6	0.0 (2)	C1—N8—C15—C20	124.13 (12)
C4—C5—C6—C7	0.5 (2)	C20—C15—C16—C17	0.7 (2)
C5—C6—C7—C2	−1.1 (2)	N8—C15—C16—C17	177.90 (13)
C3—C2—C7—C6	1.23 (18)	C15—C16—C17—C18	0.7 (3)
N1—C2—C7—C6	177.77 (11)	C16—C17—C18—C19	−1.0 (3)
N1—C1—N8—C8	113.25 (13)	C17—C18—C19—C20	−0.1 (3)
C21—C1—N8—C8	−71.26 (13)	C16—C15—C20—C19	−1.8 (2)
N1—C1—N8—C15	−57.85 (15)	N8—C15—C20—C19	−178.85 (12)
C21—C1—N8—C15	117.64 (11)	C18—C19—C20—C15	1.5 (2)
C15—N8—C8—O8	161.19 (11)	N1—C1—C21—C26	165.08 (12)
C1—N8—C8—O8	−8.99 (16)	N8—C1—C21—C26	−10.54 (16)
C15—N8—C8—C9	−20.09 (16)	N1—C1—C21—C22	−13.64 (17)
C1—N8—C8—C9	169.73 (10)	N8—C1—C21—C22	170.74 (10)
O8—C8—C9—C10	141.50 (13)	C26—C21—C22—C23	0.00 (19)
N8—C8—C9—C10	−37.20 (16)	C1—C21—C22—C23	178.77 (11)
O8—C8—C9—C14	−35.08 (17)	C21—C22—C23—C24	−0.4 (2)
N8—C8—C9—C14	146.23 (11)	C22—C23—C24—C25	0.5 (2)
C14—C9—C10—C11	−0.82 (19)	C23—C24—C25—C26	−0.2 (2)
C8—C9—C10—C11	−177.34 (11)	C22—C21—C26—C25	0.3 (2)
C9—C10—C11—C12	−1.4 (2)	C1—C21—C26—C25	−178.40 (12)
C10—C11—C12—C13	2.1 (2)	C24—C25—C26—C21	−0.2 (2)

Data collection: CAD-4 software (Enraf–Nonius, 1989). Cell refinement: CAD-4 software (Enraf–Nonius, 1989). Data reduction: NRC-2, NRC-2A (Ahmed *et al.* 1973). Program(s) used to solve structure: *SHELXS*96 (Sheldrick, 1990). Program(s) used to refine structure: *NRCVAX* (Gabe *et al.* 1989) and *SHELXL*96 (Sheldrick, 1996). Molecular graphics: *ORTEP*II (Johnson (1976) in *NRCVAX* (Gabe *et al.*(1989)). Software used to prepare material for publication: *NRCVAX* (Gabe *et al.*(1989) and *SHELXL*96 (Sheldrick (1996)).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: PRINTCIF). Services for accessing these data are described at the back of the journal.

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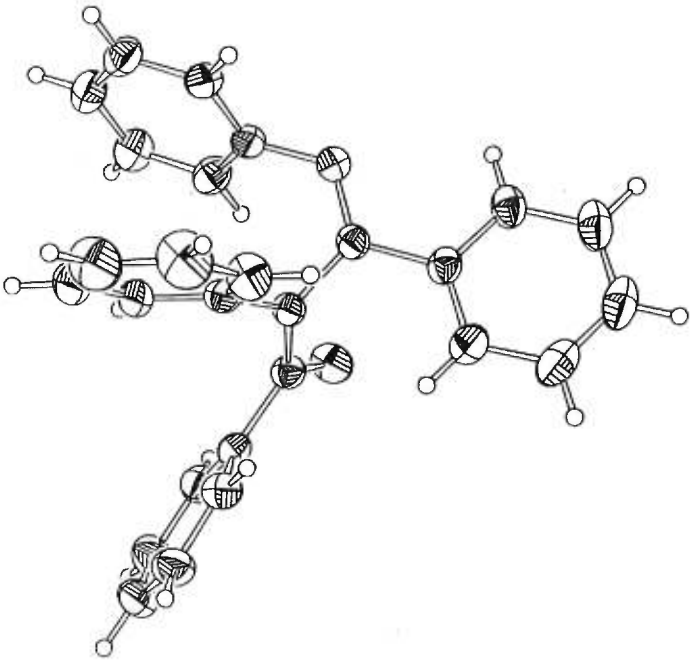
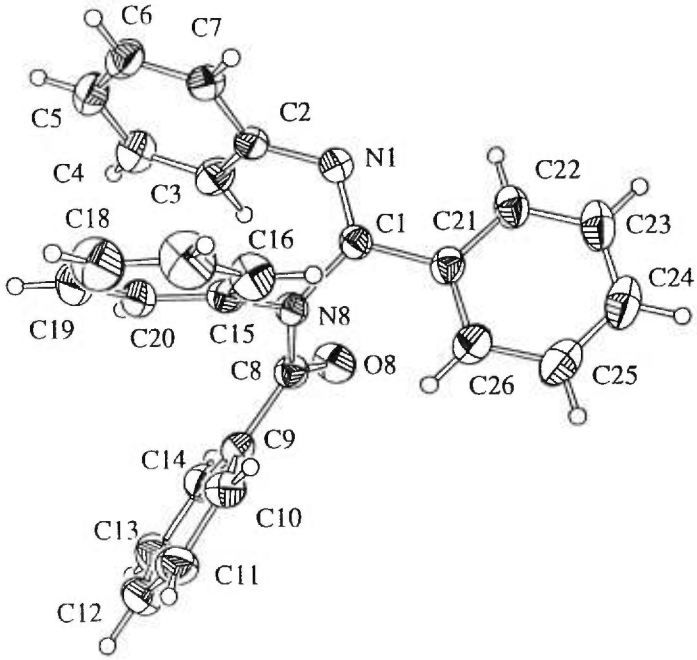
Fig. 1 *ORTEP* (Johnson, 1976) drawing of the molecule. Ellipsoids correspond to 40% probability.

Space group confirmed by *PLATON* program (Spek, 1995). Data reduction performed using a locally modified version of the NRC-2 program (Ahmed *et al.* 1973). The structure was solved by direct method using *SHELXS*96 (Sheldrick, 1990) and difmap synthesis using *NRCVAX* (Gabe *et al.*(1989) and *SHELXL*96 (Sheldrick, 1996). All non-H atoms anisotropic. H atoms isotropic. H atoms constrained to the parent site using a riding model: *SHELXL*96 defaults. C—H 0.93 Å. The isotropic factors, U_{iso} , were adjusted to 20% higher value of the parent site. A final verification of possible voids was performed using the VOID routine of the *PLATON* program (Spek, 1995).

Data collection: CAD-4 software (Enraf–Nonius, 1989). Cell refinement: CAD-4 software (Enraf–Nonius, 1989). Data reduction: NRC-2, NRC-2A (Ahmed *et al.* 1973). Program(s) used to solve structure: *SHELXS*96 (Sheldrick, 1990). Program(s) used to refine structure: *NRCVAX* (Gabe *et al.* 1989) and *SHELXL*96 (Sheldrick, 1996). Molecular graphics: *ORTEP*II (Johnson (1976) in *NRCVAX* (Gabe *et al.*(1989)). Software used to prepare material for publication: *NRCVAX* (Gabe *et al.*(1989) and *SHELXL*96 (Sheldrick (1996)).




C6
C7
C5
C2
N1
C4
C3
C22
C18
C16
C1
C21
C23
C24
C19
C20
C15
N8
C8
O8
C26
C25
C9
C14
C10
C13
C11
C12

IAXXX

Appendix 2

29 Nov 1996

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titre, habituellement le nom du compose

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Abstract

The crystal stucture of the title compound, recrystallized from &&&&&&, contains one molecule in the asymmetric unit and is stabilized by intermolecular hydrogen bonds.

Comment

comment

Experimental

The title compound was prepared according to the method described by &&&... and recrystallized in &&&&&&&&.

Crystal data

$C_{16}H_{23}F_3N_2O_6S$
$M_r = 428.42$
Monoclinic
$P2_1/n$
$a = 12.801\,(3)$ Å
$b = 9.534\,(2)$ Å
$c = 17.246\,(5)$ Å
$\beta = 102.90\,(2)°$
$V = 2051.7\,(9)$ Å^3
$Z = 4$
$D_x = 1.387$ Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
$\lambda = 1.54056$ Å

Cell parameters from 25 reflections
$\theta = 20.00$–$22.00°$
$\mu = 1.93$ mm^{-1}
$T = 293\,(2)$ K
Block
0.53 × 0.11 × 0.08 mm
Transparent
Crystal source: synthesized by the authors, see text

Data collection

Nonius CAD-4 diffractometer
Theta/2θ scans
Absorption correction:
by integration
$T_{min} = 0.5620$, $T_{max} = 0.8765$
14772 measured reflections
3892 independent reflections
2404 observed reflections
$[I > 2\sigma(I)]$

$R_{int} = 0.024$
$\theta_{max} = 69.85°$
$h = -15 \rightarrow 15$
$k = -11 \rightarrow 11$
$l = -21 \rightarrow 20$
5 standard reflections
frequency: 60 min
intensity decay: 3.3%

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.0394$

$wR(F^2) = 0.0926$

$S = 0.841$

3892 reflections

257 parameters

riding (*SHELXL* defaults, C—H 0.93 to 0.98, N—H 0.86 Å)

$w=1/[\sigma^2(F_o^2) + (0.0368P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.198$ e Å^{-3}

$\Delta\rho_{min} = -0.246$ e Å^{-3}

Extinction correction: *SHELXL*93 (Sheldrick,1993)

Extinction coefficient: 0.00067 (7)

Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S	0.25233 (5)	0.05838 (6)	0.59794 (3)	0.0477 (2)
C1	0.3676 (2)	0.0235 (2)	0.74718 (12)	0.0397 (5)
C2	0.4887 (2)	−0.0136 (2)	0.77285 (12)	0.0425 (5)
C3	0.5079 (2)	−0.1714 (2)	0.77017 (14)	0.0456 (6)
C4	0.5104 (2)	−0.2537 (3)	0.8363 (2)	0.0614 (7)
C5	0.5210 (2)	−0.3983 (3)	0.8323 (2)	0.0822 (10)
C6	0.5297 (3)	−0.4595 (3)	0.7625 (2)	0.0916 (10)
C7	0.5293 (2)	−0.3789 (3)	0.6964 (2)	0.0831 (10)
C8	0.5176 (2)	−0.2350 (3)	0.7001 (2)	0.0620 (7)
O9	0.52950 (12)	0.0283 (2)	0.85168 (9)	0.0529 (4)
C10	0.5308 (2)	0.1763 (3)	0.8690 (2)	0.0643 (8)
C11	0.5347 (2)	0.1931 (3)	0.95547 (15)	0.0807 (9)
O12	0.53369 (12)	0.0625 (2)	0.71836 (9)	0.0508 (4)
C13	0.6481 (2)	0.0556 (3)	0.7290 (2)	0.0701 (8)
C14	0.6810 (2)	0.1758 (3)	0.6851 (2)	0.0915 (10)
N15	0.31043 (14)	−0.0206 (2)	0.80608 (10)	0.0449 (5)
C16	0.2684 (2)	0.0741 (2)	0.84790 (14)	0.0474 (6)
O17	0.26065 (15)	0.1984 (2)	0.83231 (10)	0.0653 (5)
O18	0.23805 (14)	0.0149 (2)	0.90917 (9)	0.0616 (5)
C19	0.2054 (3)	0.1096 (3)	0.9652 (2)	0.0781 (9)
C20	0.1753 (3)	0.0261 (4)	1.0271 (2)	0.1151 (14)
N21	0.31841 (13)	−0.0329 (2)	0.66867 (10)	0.0420 (4)
O22	0.23425 (14)	0.1953 (2)	0.62456 (10)	0.0632 (5)
O23	0.16903 (14)	−0.0232 (2)	0.55184 (10)	0.0727 (6)
C24	0.3435 (3)	0.0849 (4)	0.5320 (2)	0.0750 (9)
F25	0.4216 (2)	0.1707 (2)	0.56138 (11)	0.1127 (7)
F26	0.2907 (2)	0.1374 (2)	0.46354 (9)	0.1121 (7)

F27	0.3862 (2)	−0.0363 (2)	0.51748 (11)	0.1248 (8)

Table 2. *Selected geometric parameters (Å, °)*

S—O23	1.412 (2)	C6—C7	1.374 (4)
S—O22	1.420 (2)	C7—C8	1.383 (3)
S—N21	1.581 (2)	O9—C10	1.442 (3)
S—C24	1.821 (3)	C10—C11	1.490 (3)
C1—N15	1.441 (2)	O12—C13	1.437 (3)
C1—N21	1.462 (2)	C13—C14	1.484 (3)
C1—C2	1.555 (3)	N15—C16	1.341 (3)
C2—O9	1.401 (2)	C16—O17	1.214 (3)
C2—O12	1.408 (2)	C16—O18	1.330 (3)
C2—C3	1.527 (3)	O18—C19	1.451 (3)
C3—C4	1.379 (3)	C19—C20	1.450 (4)
C3—C8	1.383 (3)	C24—F25	1.303 (3)
C4—C5	1.388 (3)	C24—F26	1.321 (3)
C5—C6	1.365 (4)	C24—F27	1.325 (3)

O23—S—O22	122.08 (11)	C5—C6—C7	120.4 (3)
O23—S—N21	109.74 (10)	C6—C7—C8	119.8 (3)
O22—S—N21	110.76 (10)	C7—C8—C3	120.5 (3)
O23—S—C24	103.50 (14)	C2—O9—C10	117.7 (2)
O22—S—C24	104.36 (14)	O9—C10—C11	108.0 (2)
N21—S—C24	104.55 (12)	C2—O12—C13	116.7 (2)
N15—C1—N21	111.3 (2)	O12—C13—C14	107.3 (2)
N15—C1—C2	111.3 (2)	C16—N15—C1	120.7 (2)
N21—C1—C2	112.1 (2)	O17—C16—O18	124.5 (2)
O9—C2—O12	112.4 (2)	O17—C16—N15	124.1 (2)
O9—C2—C3	106.4 (2)	O18—C16—N15	111.4 (2)
O12—C2—C3	113.3 (2)	C16—O18—C19	116.4 (2)
O9—C2—C1	110.1 (2)	C20—C19—O18	108.2 (2)
O12—C2—C1	102.9 (2)	C1—N21—S	123.87 (14)
C3—C2—C1	111.9 (2)	F25—C24—F26	107.8 (3)
C4—C3—C8	118.9 (2)	F25—C24—F27	108.0 (3)
C4—C3—C2	120.7 (2)	F26—C24—F27	108.2 (3)
C8—C3—C2	120.3 (2)	F25—C24—S	112.7 (2)
C3—C4—C5	120.5 (3)	F26—C24—S	109.8 (2)
C6—C5—C4	119.8 (3)	F27—C24—S	110.2 (2)

N15—C1—C2—O9	−47.8 (2)	C3—C2—O12—C13	−62.0 (3)
N21—C1—C2—O9	−173.2 (2)	C1—C2—O12—C13	177.0 (2)
N15—C1—C2—O12	−167.8 (2)	C2—O12—C13—C14	−161.5 (2)
N21—C1—C2—O12	66.8 (2)	N21—C1—N15—C16	−121.5 (2)
N15—C1—C2—C3	70.3 (2)	C2—C1—N15—C16	112.7 (2)
N21—C1—C2—C3	−55.2 (2)	C1—N15—C16—O17	11.3 (4)
O9—C2—C3—C4	29.3 (3)	C1—N15—C16—O18	−167.6 (2)
O12—C2—C3—C4	153.3 (2)	O17—C16—O18—C19	−7.4 (4)
C1—C2—C3—C4	−90.9 (3)	N15—C16—O18—C19	171.6 (2)
O9—C2—C3—C8	−154.0 (2)	C16—O18—C19—C20	179.9 (3)
O12—C2—C3—C8	−30.0 (3)	N15—C1—N21—S	107.6 (2)
C1—C2—C3—C8	85.8 (3)	C2—C1—N21—S	−127.0 (2)
C8—C3—C4—C5	−0.9 (4)	O23—S—N21—C1	−146.3 (2)
C2—C3—C4—C5	175.9 (2)	O22—S—N21—C1	−8.6 (2)
C3—C4—C5—C6	0.5 (5)	C24—S—N21—C1	103.2 (2)
C4—C5—C6—C7	0.7 (5)	O23—S—C24—F25	173.6 (2)
C5—C6—C7—C8	−1.4 (5)	O22—S—C24—F25	44.9 (3)
C6—C7—C8—C3	1.0 (5)	N21—S—C24—F25	−71.5 (2)
C4—C3—C8—C7	0.2 (4)	O23—S—C24—F26	53.4 (3)
C2—C3—C8—C7	−176.6 (2)	O22—S—C24—F26	−75.3 (3)
O12—C2—O9—C10	49.6 (3)	N21—S—C24—F26	168.3 (2)
C3—C2—O9—C10	174.1 (2)	O23—S—C24—F27	−65.7 (3)
C1—C2—O9—C10	−64.5 (2)	O22—S—C24—F27	165.6 (2)
C2—O9—C10—C11	157.9 (2)	N21—S—C24—F27	49.2 (3)
O9—C2—O12—C13	58.6 (3)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N15—H15···O22^{i}	0.86	2.248 (2)	3.066 (2)	158.82 (6)
N21—H21···O17^{i}	0.86	2.067 (2)	2.753 (2)	136.29 (7)

Symmetry codes: (i) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{3}{2}-z$.

Data collection: CAD-4 software (Enraf–Nonius, 1989). Cell refinement: CAD-4 software (Enraf–Nonius, 1989). Data reduction: NRC-2, NRC-2A (Ahmed *et al.* 1973). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson (1976) in *NRCVAX*94 (Gabe *et al.*(1989)). Software used to prepare material for publication: *SHELXL*93 (Sheldrick, 1993).

The financial support from the Natural Sciences and Engineering Research Council of Canada and from the Fonds FCAR du Ministère de l'Éducation du Québec is gratefully acknowledged.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PRINTCIF). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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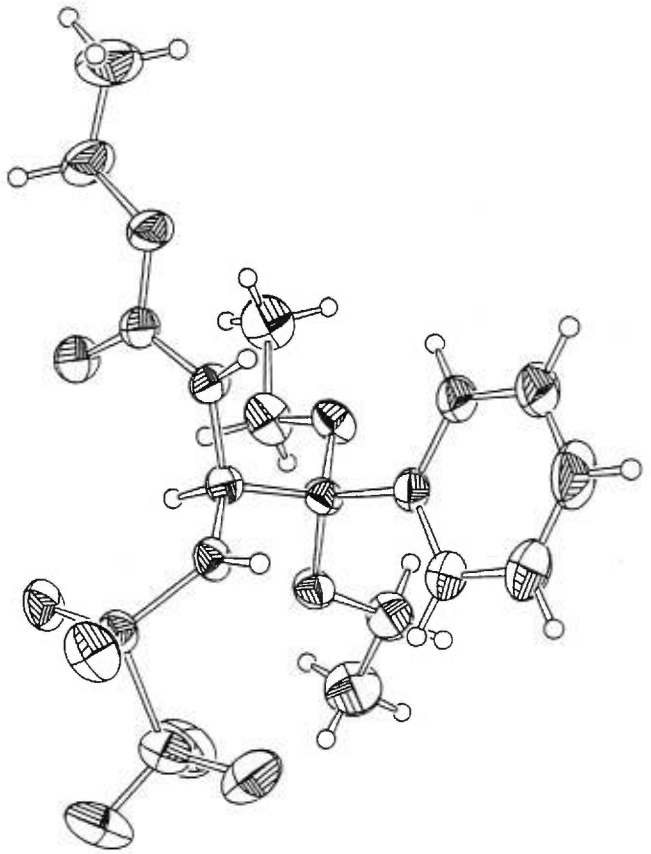
Fig. 1 *ORTEP* (Johnson, 1976) drawing of the molecule. Ellipsoids correspond to 40% probability.

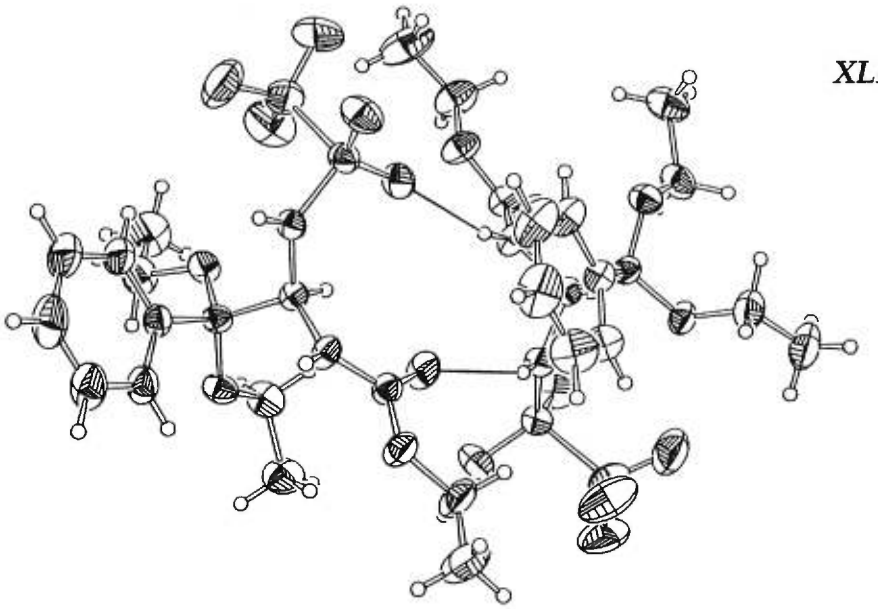
Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j a_i \cdot a_j$

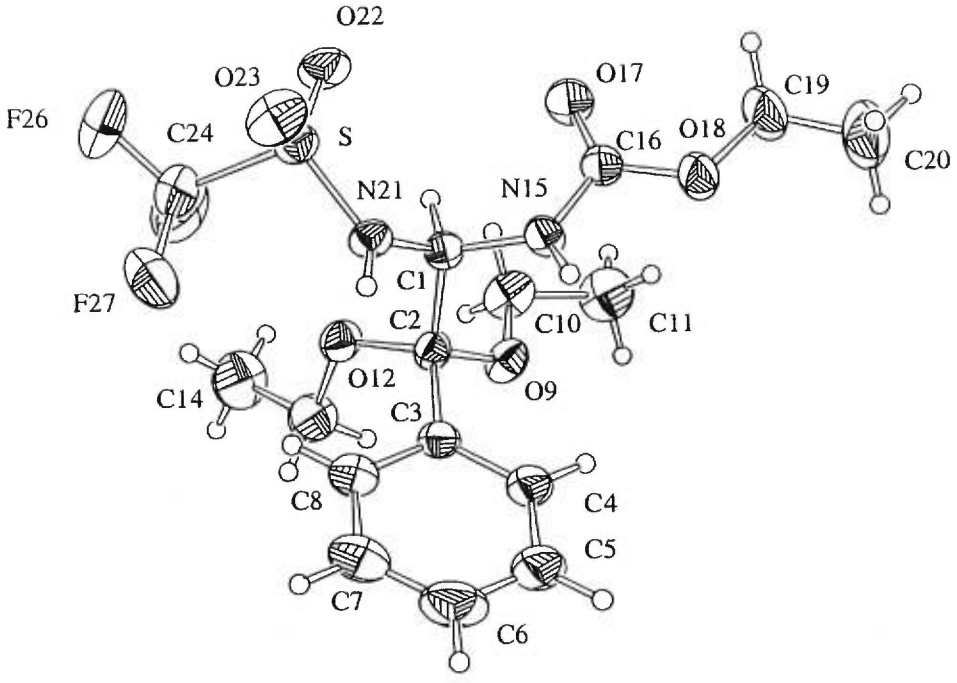
Table 2. Selected geometric parameters (Å, °)

Table 3. Bond distances and angles related to the hydrogen bonding



XLIII

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O23
F26
C24
S
O17
C19
C16
O18
C20
N21
N15
F27
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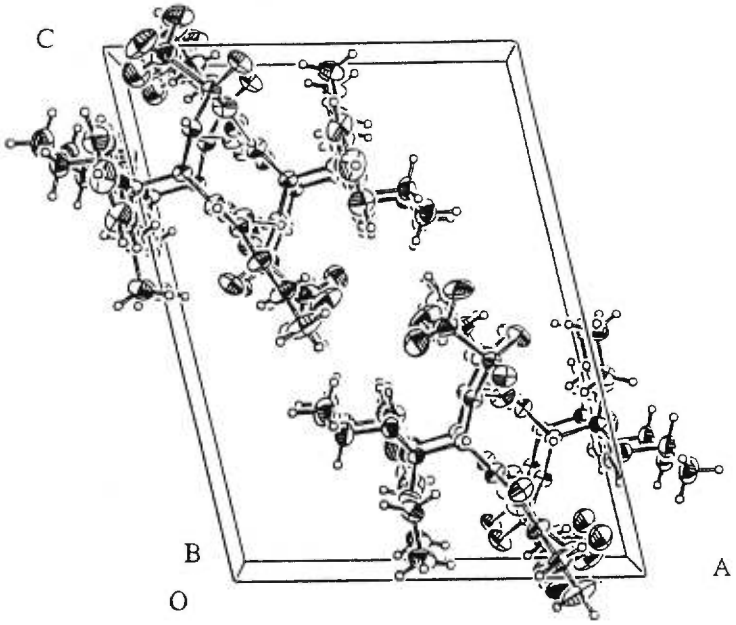
C2
C10
C11
O12
O9
C14
C3
C8
C4
C5
C7
C6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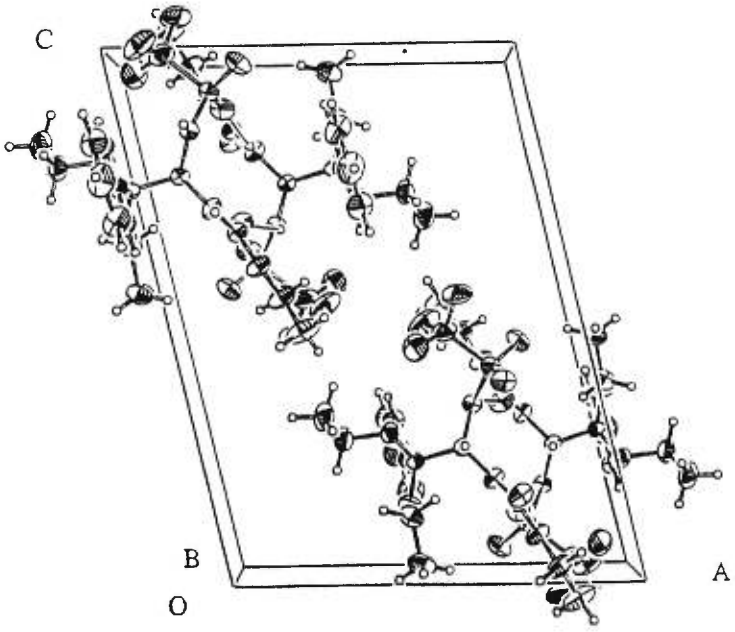
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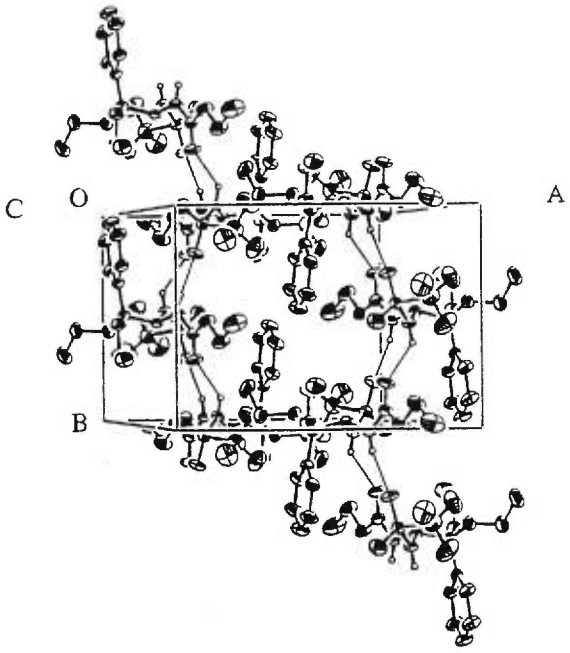
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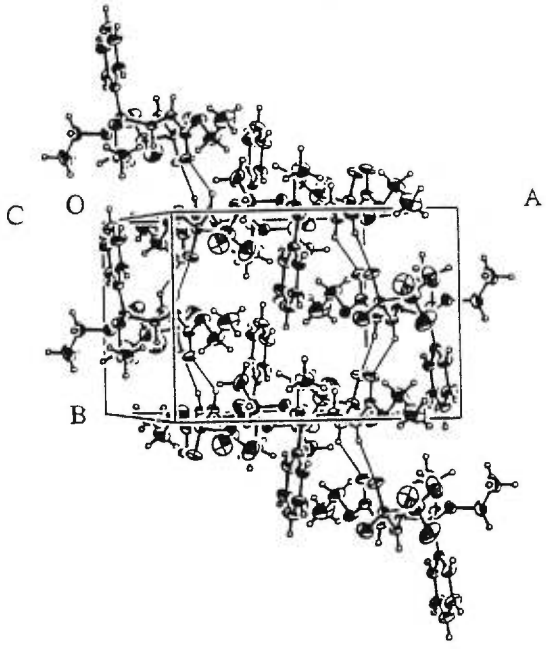
C
O
A
B

Appendix 3

CRYSTAL AND MOLECULAR STRUCTURE OF

C14 H15 F3 N2 O3 S2 COMPOUND (char35)

Equipe CHARETTE (Peter Chua)

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Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Francine Bélanger-Gariépy, septembre 1997.

Table 1. Crystal data and structure refinement for C14 H15 F3 N2 O3 S2.

Identification code	CHAR35
Empirical formula	C14 H15 F3 N2 O3 S2
Formula weight	380.40
Temperature	293(2)K
Wavelength	1.54056Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 9.914(4)Å α = 90° b = 18.075(8)Å β = 108.42(3)° c = 10.115(4)Å γ = 90°
Volume	1719.7(12)Å^3
Z	4
Density (calculated)	1.469 Mg/m^3
Absorption coefficient	3.247 mm^{-1}
F(000)	784
Crystal size	0.62 x 0.11 x 0.05 mm
Theta range for data collection	4.70 to 69.82°
Index ranges	-12<=h<=12, -22<=k<=22, -12<=l<=12
Reflections collected	12585
Independent reflections	3260 [R(int) = 0.025]
Absorption correction	Integration
Max. and min. transmission	0.8450 and 0.4958
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3260 / 0 / 219
Goodness-of-fit on F^2	0.844
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.0807
R indices (all data)	R1 = 0.0595, wR2 = 0.0874
Extinction coefficient	0.00172(17)
Largest diff. peak and hole	0.231 and -0.208 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C14 H15 F3 N2 O3 S2.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	7081(1)	537(1)	809(1)	68(1)
S(2)	9427(1)	1862(1)	-750(1)	49(1)
O(1)	6022(2)	2491(1)	1703(2)	73(1)
O(2)	9707(2)	2623(1)	-466(2)	69(1)
O(3)	9303(2)	1553(1)	-2069(2)	63(1)
N(1)	5722(2)	2532(1)	-589(2)	50(1)
N(2)	8042(2)	1646(1)	-313(2)	40(1)
C(1)	6437(3)	2347(1)	707(2)	49(1)
C(2)	7859(2)	1948(1)	982(2)	48(1)
C(3)	7952(3)	1285(1)	1931(2)	62(1)
C(4)	7277(2)	958(1)	-687(2)	40(1)
C(5)	6693(2)	731(1)	-1979(2)	44(1)
C(6)	5774(2)	57(1)	-2380(2)	50(1)
C(7)	4271(2)	249(1)	-3246(2)	47(1)
C(8)	3620(3)	874(2)	-2940(3)	66(1)
C(9)	2234(3)	1045(2)	-3707(4)	86(1)
C(10)	1500(3)	607(2)	-4778(4)	90(1)
C(11)	2115(3)	-14(2)	-5095(3)	91(1)
C(12)	3507(3)	-192(2)	-4321(3)	69(1)
C(13)	4340(3)	2887(2)	-957(3)	69(1)
C(14)	10942(3)	1377(2)	469(3)	73(1)
F(1)	11176(2)	1644(1)	1751(2)	108(1)
F(2)	12096(2)	1484(1)	127(2)	115(1)
F(3)	10693(2)	678(1)	505(2)	109(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C14 H15 F3 N2 O3 S2.

	x	y	z	U(eq)
H(1)	6087	2438	-1237	75
H(2)	8637	2292	1419	57
H(3A)	7478	1388	2616	74
H(3B)	8937	1161	2416	74
H(5)	6861	1006	-2687	53
H(6A)	5757	-199	-1544	60
H(6B)	6181	-275	-2906	60
H(8)	4118	1181	-2211	80
H(9)	1803	1464	-3487	103
H(10)	573	730	-5299	108
H(11)	1607	-318	-5825	109
H(12)	3923	-616	-4539	82
H(13A)	4357	3270	-293	104
H(13B)	3630	2528	-951	104
H(13C)	4120	3100	-1870	104

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C14 H15 F3 N2 O3 S2.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
S(1)	93(1)	66(1)	47(1)	11(1)	28(1)	-13(1)
S(2)	42(1)	57(1)	46(1)	3(1)	12(1)	-6(1)
O(1)	88(1)	101(2)	38(1)	-9(1)	32(1)	10(1)
O(2)	74(1)	54(1)	77(1)	2(1)	22(1)	-19(1)
O(3)	59(1)	90(1)	49(1)	-9(1)	27(1)	-10(1)
N(1)	55(1)	61(1)	34(1)	2(1)	16(1)	9(1)
N(2)	40(1)	51(1)	29(1)	-2(1)	9(1)	-4(1)
C(1)	61(2)	52(2)	36(1)	-5(1)	19(1)	-3(1)
C(2)	55(1)	60(2)	25(1)	-4(1)	8(1)	-3(1)
C(3)	75(2)	76(2)	29(1)	10(1)	10(1)	3(1)
C(4)	39(1)	45(1)	37(1)	3(1)	13(1)	0(1)
C(5)	42(1)	50(1)	40(1)	0(1)	10(1)	-4(1)
C(6)	48(1)	48(1)	51(1)	-3(1)	10(1)	-4(1)
C(7)	42(1)	56(2)	43(1)	3(1)	14(1)	-7(1)
C(8)	53(2)	62(2)	77(2)	3(2)	10(1)	0(1)
C(9)	58(2)	83(2)	111(3)	24(2)	18(2)	11(2)
C(10)	46(2)	142(3)	74(2)	30(2)	7(2)	2(2)
C(11)	56(2)	160(4)	53(2)	-17(2)	11(2)	-26(2)
C(12)	53(2)	94(2)	58(2)	-20(2)	16(1)	-12(2)
C(13)	62(2)	79(2)	67(2)	4(2)	20(1)	16(2)
C(14)	42(2)	85(2)	82(2)	6(2)	5(2)	-4(2)
F(1)	76(1)	152(2)	69(1)	7(1)	-17(1)	3(1)
F(2)	43(1)	156(2)	142(2)	28(2)	25(1)	3(1)
F(3)	74(1)	75(1)	156(2)	28(1)	7(1)	13(1)

Table 5. Bond lengths [Å] and angles [°] for C14 H15 F3 N2 O3 S2

S(1)-C(4)	1.758(2)	S(1)-C(3)	1.799(3)
S(2)-O(2)	1.4150(18)	S(2)-O(3)	1.4157(17)
S(2)-N(2)	1.6176(19)	S(2)-C(14)	1.836(3)
O(1)-C(1)	1.230(3)	N(1)-C(1)	1.321(3)
N(1)-C(13)	1.451(3)	N(2)-C(4)	1.444(3)
N(2)-C(2)	1.483(3)	C(1)-C(2)	1.528(3)
C(2)-C(3)	1.521(3)	C(4)-C(5)	1.316(3)
C(5)-C(6)	1.498(3)	C(6)-C(7)	1.511(3)
C(7)-C(12)	1.367(3)	C(7)-C(8)	1.384(3)
C(8)-C(9)	1.383(4)	C(9)-C(10)	1.354(4)
C(10)-C(11)	1.362(5)	C(11)-C(12)	1.392(4)
C(14)-F(3)	1.290(3)	C(14)-F(2)	1.310(3)
C(14)-F(1)	1.333(3)		

C(4)-S(1)-C(3)	93.28(11)	O(2)-S(2)-O(3)	121.87(11)
O(2)-S(2)-N(2)	107.95(11)	O(3)-S(2)-N(2)	109.48(10)
O(2)-S(2)-C(14)	105.19(14)	O(3)-S(2)-C(14)	104.68(14)
N(2)-S(2)-C(14)	106.63(12)	C(1)-N(1)-C(13)	122.3(2)
C(4)-N(2)-C(2)	110.39(17)	C(4)-N(2)-S(2)	123.85(15)
C(2)-N(2)-S(2)	120.26(15)	O(1)-C(1)-N(1)	123.0(2)
O(1)-C(1)-C(2)	118.6(2)	N(1)-C(1)-C(2)	118.4(2)
N(2)-C(2)-C(3)	105.47(19)	N(2)-C(2)-C(1)	112.08(17)
C(3)-C(2)-C(1)	110.8(2)	C(2)-C(3)-S(1)	105.83(15)
C(5)-C(4)-N(2)	124.0(2)	C(5)-C(4)-S(1)	125.89(18)
N(2)-C(4)-S(1)	109.77(15)	C(4)-C(5)-C(6)	124.2(2)
C(5)-C(6)-C(7)	112.0(2)	C(12)-C(7)-C(8)	118.2(2)
C(12)-C(7)-C(6)	121.7(2)	C(8)-C(7)-C(6)	120.1(2)
C(9)-C(8)-C(7)	120.6(3)	C(10)-C(9)-C(8)	120.4(3)
C(9)-C(10)-C(11)	120.2(3)	C(10)-C(11)-C(12)	119.7(3)
C(7)-C(12)-C(11)	121.0(3)	F(3)-C(14)-F(2)	110.1(3)
F(3)-C(14)-F(1)	107.7(3)	F(2)-C(14)-F(1)	107.7(3)
F(3)-C(14)-S(2)	111.3(2)	F(2)-C(14)-S(2)	110.4(2)
F(1)-C(14)-S(2)	109.5(2)		

Table 6. Torsion angles [°] for C14 H15 F3 N2 O3 S2.

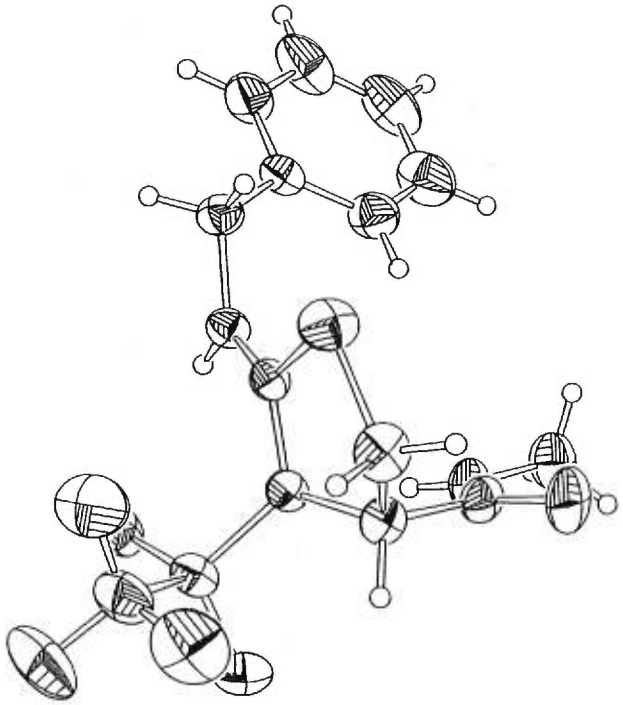
O(2)-S(2)-N(2)-C(4)	167.89(16)
O(3)-S(2)-N(2)-C(4)	33.20(19)
C(14)-S(2)-N(2)-C(4)	-79.5(2)
O(2)-S(2)-N(2)-C(2)	-40.82(19)
O(3)-S(2)-N(2)-C(2)	-175.51(16)
C(14)-S(2)-N(2)-C(2)	71.8(2)
C(13)-N(1)-C(1)-O(1)	-3.4(4)
C(13)-N(1)-C(1)-C(2)	177.8(2)
C(4)-N(2)-C(2)-C(3)	40.7(2)
S(2)-N(2)-C(2)-C(3)	-114.13(19)
C(4)-N(2)-C(2)-C(1)	-80.0(2)
S(2)-N(2)-C(2)-C(1)	125.17(18)
O(1)-C(1)-C(2)-N(2)	165.5(2)
N(1)-C(1)-C(2)-N(2)	-15.7(3)
O(1)-C(1)-C(2)-C(3)	48.0(3)
N(1)-C(1)-C(2)-C(3)	-133.2(2)
N(2)-C(2)-C(3)-S(1)	-37.2(2)
C(1)-C(2)-C(3)-S(1)	84.3(2)
C(4)-S(1)-C(3)-C(2)	20.72(18)
C(2)-N(2)-C(4)-C(5)	147.9(2)
S(2)-N(2)-C(4)-C(5)	-58.3(3)
C(2)-N(2)-C(4)-S(1)	-25.4(2)
S(2)-N(2)-C(4)-S(1)	128.35(14)
C(3)-S(1)-C(4)-C(5)	-171.2(2)
C(3)-S(1)-C(4)-N(2)	1.96(17)
N(2)-C(4)-C(5)-C(6)	-173.48(19)
S(1)-C(4)-C(5)-C(6)	-1.3(3)
C(4)-C(5)-C(6)-C(7)	116.1(3)
C(5)-C(6)-C(7)-C(12)	142.8(2)
C(5)-C(6)-C(7)-C(8)	-38.7(3)
C(12)-C(7)-C(8)-C(9)	-0.2(4)
C(6)-C(7)-C(8)-C(9)	-178.6(3)
C(7)-C(8)-C(9)-C(10)	-0.6(5)
C(8)-C(9)-C(10)-C(11)	1.0(5)
C(9)-C(10)-C(11)-C(12)	-0.7(5)
C(8)-C(7)-C(12)-C(11)	0.5(4)
C(6)-C(7)-C(12)-C(11)	178.9(3)
C(10)-C(11)-C(12)-C(7)	-0.1(5)
O(2)-S(2)-C(14)-F(3)	167.7(2)
O(3)-S(2)-C(14)-F(3)	-62.7(3)
N(2)-S(2)-C(14)-F(3)	53.2(3)
O(2)-S(2)-C(14)-F(2)	-69.7(3)
O(3)-S(2)-C(14)-F(2)	59.8(3)
N(2)-S(2)-C(14)-F(2)	175.8(2)
O(2)-S(2)-C(14)-F(1)	48.8(2)
O(3)-S(2)-C(14)-F(1)	178.3(2)
N(2)-S(2)-C(14)-F(1)	-65.7(2)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C14 H15 F3 N2 O3 S2.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
N(1)-H(1)	0.86	2.07	150.3	2.848(3)	O(1)#1

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1/2,z-1/2



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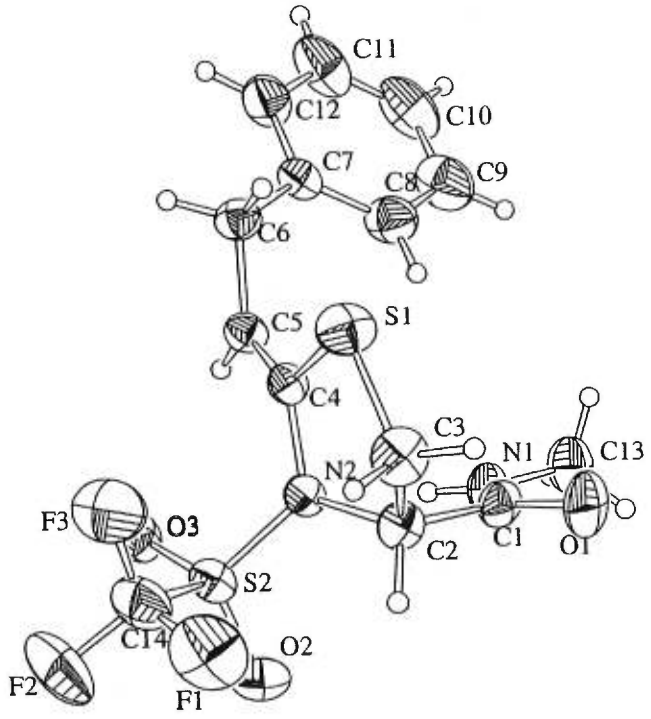

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Appendix 4

CRYSTAL AND MOLECULAR STRUCTURE OF

C19 H16 N2 O2 S2 COMPOUND (CHAR37)

Equipe CHARETTE

Département de chimie, Université de Montréal,

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Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Francine Bélanger-Gariépy (October 29, 1997).

Table 1. Crystal data and structure refinement for C19 H16 N2 O2 S2.

Identification code	CHAR37
Empirical formula	C19 H16 N2 O2 S2
Formula weight	368.458
Temperature	220(2)K
Wavelength	1.54056Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 10.268(5)Å α = 90° b = 5.917(3)Å β = 102.06(3)° c = 14.656(6)Å γ = 90°
Volume	870.8(7)Å^3
Z	2
Density (calculated)	1.4053 Mg/m^3
Absorption coefficient	2.897 mm^{-1}
F(000)	384.0
Crystal size	0.35 x 0.17 x 0.03 mm
Theta range for data collection	3.08 to 69.87°
Index ranges	-12<=h<=12, -7<=k<=7, -17<=l<=17
Reflections collected	6473
Independent reflections	3295 [R(int) = 0.062]
Absorption correction	Integration
Max. and min. transmission	0.9253 and 0.5770
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3295 / 1 / 228
Goodness-of-fit on F^2	0.880
Final R indices [I>2sigma(I)]	R1 = 0.0481, wR2 = 0.0865
R indices (all data)	R1 = 0.0705, wR2 = 0.0954
Absolute structure parameter	0.01(2)
Extinction coefficient	0.0004(2)
Largest diff. peak and hole	0.212 and -0.230 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C19 H16 N2 O2 S2.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	3936(1)	6530(2)	2721(1)	47(1)
S(2)	7062(1)	326(2)	1900(1)	52(1)
O(1)	1448(3)	3377(7)	4127(3)	90(1)
O(2)	2981(3)	1703(6)	5193(2)	63(1)
N(1)	4576(3)	3177(6)	3910(2)	47(1)
N(2)	5830(3)	4098(6)	1801(2)	37(1)
C(1)	2568(4)	3239(8)	4529(3)	46(1)
C(2)	3721(4)	4626(7)	4350(3)	45(1)
C(3)	3228(4)	6704(9)	3738(3)	58(1)
C(4)	4738(4)	4006(7)	3143(3)	36(1)
C(5)	5584(4)	2955(7)	2565(3)	36(1)
C(6)	6170(4)	898(6)	2731(3)	41(1)
C(7)	6602(4)	2923(7)	1376(3)	36(1)
C(8)	7070(4)	3662(7)	547(3)	36(1)
C(9)	7962(4)	2446(7)	172(3)	36(1)
C(10)	8426(4)	3185(7)	-613(3)	34(1)
C(11)	9352(4)	1954(7)	-994(3)	40(1)
C(12)	9785(4)	2709(8)	-1758(3)	46(1)
C(13)	9322(4)	4801(8)	-2169(3)	48(1)
C(14)	8436(4)	6042(7)	-1808(3)	43(1)
C(15)	7962(3)	5301(7)	-1022(3)	37(1)
C(16)	7030(4)	6528(8)	-639(3)	41(1)
C(17)	6590(4)	5767(7)	120(3)	41(1)
C(18)	1961(4)	142(9)	5421(3)	70(2)
C(19)	1480(4)	1047(10)	6205(3)	82(2)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C19 H16 N2 O2 S2.

	x	y	z	U(eq)
H(2)	4245	5162	4956	54
H(3A)	3513	8100	4081	69
H(3B)	2254	6701	3559	69
H(6)	6096	-64	3228	49
H(9)	8277	1064	450	44
H(11)	9682	579	-717	48
H(12)	10390	1841	-2012	55
H(13)	9627	5333	-2691	56
H(14)	8132	7426	-2089	51
H(16)	6703	7907	-914	49
H(17)	5971	6622	364	49
H(18A)	1222	-14	4881	83
H(18B)	2353	-1356	5577	83
H(19A)	2216	1187	6738	123
H(19B)	814	37	6360	123
H(19C)	1087	2522	6044	123

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C19 H16 N2 O2 S2.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
S(1)	53(1)	37(1)	54(1)	5(1)	15(1)	6(1)
S(2)	62(1)	38(1)	63(1)	8(1)	31(1)	11(1)
O(1)	44(2)	100(3)	114(3)	26(3)	-8(2)	-1(2)
O(2)	45(2)	73(2)	69(2)	18(2)	9(2)	-8(2)
N(1)	51(2)	51(2)	42(2)	5(2)	19(2)	14(2)
N(2)	38(2)	37(2)	37(2)	-1(2)	12(2)	-2(2)
C(1)	39(2)	48(3)	50(3)	-6(2)	7(2)	5(2)
C(2)	42(2)	49(3)	48(3)	0(2)	16(2)	8(2)
C(3)	70(3)	49(3)	59(3)	3(3)	25(3)	15(3)
C(4)	28(2)	39(3)	40(2)	-2(2)	5(2)	1(2)
C(5)	32(2)	37(3)	40(2)	1(2)	7(2)	-3(2)
C(6)	48(2)	36(3)	44(2)	3(2)	22(2)	0(2)
C(7)	33(2)	32(2)	41(2)	2(2)	5(2)	-1(2)
C(8)	32(2)	36(2)	38(2)	-3(2)	6(2)	-3(2)
C(9)	38(2)	29(2)	42(2)	2(2)	8(2)	1(2)
C(10)	33(2)	33(2)	38(2)	-3(2)	8(2)	0(2)
C(11)	36(2)	38(3)	46(2)	1(2)	8(2)	2(2)
C(12)	41(2)	55(3)	44(3)	-5(2)	16(2)	-1(2)
C(13)	41(2)	55(3)	49(3)	6(2)	11(2)	-5(2)
C(14)	43(2)	37(3)	47(3)	2(2)	6(2)	-3(2)
C(15)	35(2)	38(2)	37(2)	1(2)	3(2)	-4(2)
C(16)	43(2)	34(2)	44(2)	0(2)	5(2)	9(2)
C(17)	39(2)	38(3)	46(3)	-4(2)	7(2)	11(2)
C(18)	53(3)	85(4)	74(4)	0(4)	21(3)	-3(3)
C(19)	66(3)	96(6)	89(4)	-16(4)	28(3)	-17(3)

Table 5. Bond lengths [Å] and angles [°] for C19 H16 N2 O2 S2

S(1)-C(4)	1.755(4)	S(1)-C(3)	1.791(4)
S(2)-C(6)	1.704(4)	S(2)-C(7)	1.738(4)
O(1)-C(1)	1.180(5)	O(2)-C(1)	1.334(5)
O(2)-C(18)	1.486(5)	N(1)-C(4)	1.268(5)
N(1)-C(2)	1.470(5)	N(2)-C(7)	1.307(5)
N(2)-C(5)	1.376(4)	C(1)-C(2)	1.508(5)
C(2)-C(3)	1.544(6)	C(4)-C(5)	1.472(5)
C(5)-C(6)	1.357(5)	C(7)-C(8)	1.463(5)
C(8)-C(9)	1.368(5)	C(8)-C(17)	1.434(5)
C(9)-C(10)	1.403(5)	C(10)-C(11)	1.404(5)
C(10)-C(15)	1.426(5)	C(11)-C(12)	1.363(5)
C(12)-C(13)	1.415(6)	C(13)-C(14)	1.359(5)
C(14)-C(15)	1.411(5)	C(15)-C(16)	1.409(5)
C(16)-C(17)	1.362(5)	C(18)-C(19)	1.446(6)
C(4)-S(1)-C(3)	89.9(2)	C(6)-S(2)-C(7)	90.2(2)
C(1)-O(2)-C(18)	117.1(3)	C(4)-N(1)-C(2)	111.4(4)
C(7)-N(2)-C(5)	111.0(3)	O(1)-C(1)-O(2)	122.6(4)
O(1)-C(1)-C(2)	126.4(5)	O(2)-C(1)-C(2)	110.9(4)
N(1)-C(2)-C(1)	108.8(3)	N(1)-C(2)-C(3)	111.3(3)
C(1)-C(2)-C(3)	111.2(4)	C(2)-C(3)-S(1)	107.3(3)
N(1)-C(4)-C(5)	123.3(4)	N(1)-C(4)-S(1)	120.2(3)
C(5)-C(4)-S(1)	116.5(3)	C(6)-C(5)-N(2)	115.9(4)
C(6)-C(5)-C(4)	124.6(4)	N(2)-C(5)-C(4)	119.4(4)
C(5)-C(6)-S(2)	109.5(3)	N(2)-C(7)-C(8)	125.0(4)
N(2)-C(7)-S(2)	113.3(3)	C(8)-C(7)-S(2)	121.6(3)
C(9)-C(8)-C(17)	118.6(4)	C(9)-C(8)-C(7)	122.7(4)
C(17)-C(8)-C(7)	118.6(4)	C(8)-C(9)-C(10)	122.4(4)
C(9)-C(10)-C(11)	122.6(4)	C(9)-C(10)-C(15)	118.5(3)
C(11)-C(10)-C(15)	118.9(4)	C(12)-C(11)-C(10)	121.4(4)
C(11)-C(12)-C(13)	119.8(4)	C(14)-C(13)-C(12)	120.0(4)
C(13)-C(14)-C(15)	121.5(4)	C(16)-C(15)-C(14)	123.0(4)
C(16)-C(15)-C(10)	118.7(4)	C(14)-C(15)-C(10)	118.3(4)
C(17)-C(16)-C(15)	121.6(4)	C(16)-C(17)-C(8)	120.1(4)
C(19)-C(18)-O(2)	108.8(4)		

Table 6. Torsion angles [°] for C19 H16 N2 O2 S2.

C(18)-O(2)-C(1)-O(1)	-0.4(7)
C(18)-O(2)-C(1)-C(2)	-177.6(4)
C(4)-N(1)-C(2)-C(1)	124.6(4)
C(4)-N(1)-C(2)-C(3)	1.8(5)
O(1)-C(1)-C(2)-N(1)	-108.3(6)
O(2)-C(1)-C(2)-N(1)	68.8(5)
O(1)-C(1)-C(2)-C(3)	14.5(7)
O(2)-C(1)-C(2)-C(3)	-168.4(4)
N(1)-C(2)-C(3)-S(1)	-0.9(5)
C(1)-C(2)-C(3)-S(1)	-122.3(3)
C(4)-S(1)-C(3)-C(2)	-0.1(3)
C(2)-N(1)-C(4)-C(5)	177.9(3)
C(2)-N(1)-C(4)-S(1)	-2.0(5)
C(3)-S(1)-C(4)-N(1)	1.2(4)
C(3)-S(1)-C(4)-C(5)	-178.7(3)
C(7)-N(2)-C(5)-C(6)	0.2(5)
C(7)-N(2)-C(5)-C(4)	179.6(4)
N(1)-C(4)-C(5)-C(6)	7.0(6)
S(1)-C(4)-C(5)-C(6)	-173.1(3)
N(1)-C(4)-C(5)-N(2)	-172.3(4)
S(1)-C(4)-C(5)-N(2)	7.6(5)
N(2)-C(5)-C(6)-S(2)	-0.5(4)
C(4)-C(5)-C(6)-S(2)	-179.8(3)
C(7)-S(2)-C(6)-C(5)	0.5(3)
C(5)-N(2)-C(7)-C(8)	-179.2(4)
C(5)-N(2)-C(7)-S(2)	0.2(4)
C(6)-S(2)-C(7)-N(2)	-0.4(3)
C(6)-S(2)-C(7)-C(8)	179.0(3)
N(2)-C(7)-C(8)-C(9)	174.6(4)
S(2)-C(7)-C(8)-C(9)	-4.6(5)
N(2)-C(7)-C(8)-C(17)	-4.2(6)
S(2)-C(7)-C(8)-C(17)	176.5(3)
C(17)-C(8)-C(9)-C(10)	0.1(6)
C(7)-C(8)-C(9)-C(10)	-178.8(4)
C(8)-C(9)-C(10)-C(11)	179.3(4)
C(8)-C(9)-C(10)-C(15)	1.0(6)
C(9)-C(10)-C(11)-C(12)	179.9(4)
C(15)-C(10)-C(11)-C(12)	-1.8(6)
C(10)-C(11)-C(12)-C(13)	1.5(6)
C(11)-C(12)-C(13)-C(14)	-0.8(6)
C(12)-C(13)-C(14)-C(15)	0.3(6)
C(13)-C(14)-C(15)-C(16)	-179.1(4)
C(13)-C(14)-C(15)-C(10)	-0.6(6)
C(9)-C(10)-C(15)-C(16)	-1.8(5)
C(11)-C(10)-C(15)-C(16)	179.9(4)
C(9)-C(10)-C(15)-C(14)	179.7(3)
C(11)-C(10)-C(15)-C(14)	1.4(5)
C(14)-C(15)-C(16)-C(17)	179.9(4)
C(10)-C(15)-C(16)-C(17)	1.5(6)
C(15)-C(16)-C(17)-C(8)	-0.3(6)
C(9)-C(8)-C(17)-C(16)	-0.5(6)
C(7)-C(8)-C(17)-C(16)	178.4(4)
C(1)-O(2)-C(18)-C(19)	-94.9(5)

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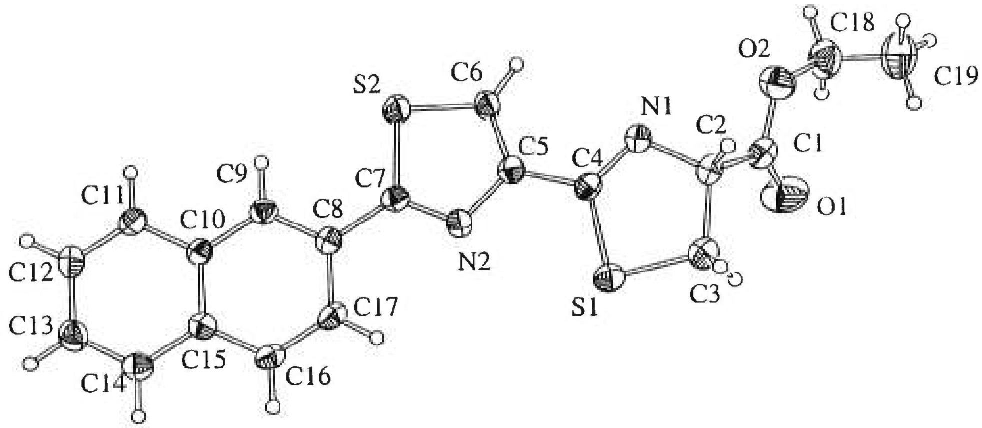

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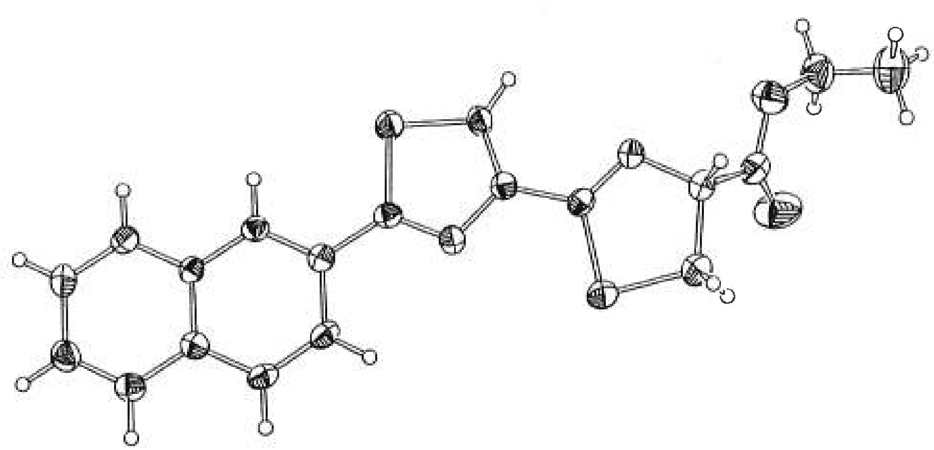

Appendix 5

CRYSTAL AND MOLECULAR STRUCTURE OF

$[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$ COMPOUND (char24)

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Structure résolue au Laboratoire de Diffraction des Rayons X de l'Université de Montréal par Francine Bélanger-Gariépy, septembre 1996.

Table 1. Crystal data and structure refinement for $[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$

Identification code	char24
Empirical formula	C46 H42 N O5.50 S
Formula weight	728.87
Temperature	293(2)K
Wavelength	1.54056Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 11.622(3)Å α = 74.28(2) b = 13.716(3)Å β = 72.61(2) c = 14.293(4)Å γ = 67.00(2)
Volume	1970.4(9)Å^3
Z	2
Density (calculated)	1.229 Mg/m^3
Absorption coefficient	1.08 mm^{-1}
F(000)	770
Crystal size	0.42 x 0.11 x 0.09 mm
Theta range for data collection	3.29 to 69.96
Index ranges	-14<=h<=14, -14<=k<=16, -16<=l<=17
Reflections collected	14706
Independent reflections	7481 [R(int) = 0.050]
Absorption correction	Integration
Max. and min. transmission	0.9168 and 0.7652
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7481 / 838 / 701
Goodness-of-fit on F^2	0.788
Final R indices [I>2sigma(I)]	R1 = 0.0671, wR2 = 0.1339
R indices (all data)	R1 = 0.2024, wR2 = 0.1787
Extinction coefficient	0.0016(2)
Largest diff. peak and hole	0.197 and -0.315 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for $[C_{44}H_{37}NO_2S]\cdot[C_4H_{10}O]_{0.5}$.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

c is the occupancy factor.

	x	y	z	U(eq)	c
S	4473(1)	8829(1)	3257(1)	73(1)	1.00
O(1)	5016(3)	9384(2)	3625(2)	94(1)	1.00
O(2)	5200(3)	7782(2)	3017(2)	90(1)	1.00
O(3)	298(3)	8342(2)	4061(2)	76(1)	1.00
O(4)	-1468(3)	9431(3)	4917(3)	99(1)	1.00
O(5)	-923(3)	7523(3)	3481(3)	95(1)	1.00
N	3214(3)	8760(2)	4074(2)	62(1)	1.00
C(1)	1040(4)	8883(3)	4241(3)	70(1)	1.00
C(2)	2450(4)	8187(3)	3942(3)	63(1)	1.00
C(3)	2746(4)	7028(4)	4507(4)	61(1)	1.00
C(4)	3186(4)	6179(4)	3983(4)	68(1)	1.00
C(5)	3504(5)	5119(4)	4494(5)	89(2)	1.00
C(6)	3378(5)	4906(5)	5504(5)	97(2)	1.00
C(7)	2937(5)	5727(5)	6022(4)	94(2)	1.00
C(8)	2635(4)	6789(4)	5535(4)	75(1)	1.00
C(9)	1942(10)	7510(11)	6280(9)	67(4)	0.50
C(10)	2671(11)	8002(10)	6446(9)	67(4)	0.50
C(11)	2185(13)	8722(10)	7117(9)	64(4)	0.50
C(12)	2930(11)	9247(10)	7294(10)	80(4)	0.50
C(13)	2444(17)	9858(23)	7988(21)	106(6)	0.50
C(14)	1176(22)	10086(28)	8502(26)	108(7)	0.50
C(15)	408(14)	9662(16)	8329(16)	104(5)	0.50
C(16)	888(16)	8927(17)	7658(14)	81(6)	0.50
C(17)	167(10)	8428(8)	7446(8)	83(3)	0.50
C(18)	675(10)	7739(8)	6786(8)	75(3)	0.50
C(19)	3412(12)	6322(9)	2892(6)	71(3)	0.75
C(20)	2410(11)	6754(12)	2415(8)	85(4)	0.75
C(21)	2661(10)	6826(9)	1366(8)	86(3)	0.75
C(22)	1656(8)	7275(7)	844(8)	132(3)	0.75
C(23)	1910(11)	7333(8)	-156(8)	155(4)	0.75
C(24)	3154(14)	6978(12)	-710(8)	154(5)	0.75
C(25)	4141(12)	6535(11)	-253(9)	138(5)	0.75
C(26)	3926(11)	6460(9)	811(7)	100(4)	0.75
C(27)	4926(10)	5994(10)	1329(9)	113(4)	0.75
C(28)	4664(12)	5947(13)	2315(9)	108(4)	0.75
C(29)	3980(4)	9665(4)	2165(4)	70(1)	1.00
C(30)	3655(5)	10751(4)	2050(4)	89(2)	1.00
C(31)	3253(5)	11407(4)	1210(5)	100(2)	1.00
C(32)	3128(5)	10992(5)	487(5)	92(2)	1.00
C(33)	3462(5)	9885(6)	609(4)	95(2)	1.00
C(34)	3878(4)	9220(4)	1451(4)	82(2)	1.00
C(35)	2667(5)	11728(5)	-433(4)	133(2)	1.00
C(49)	2459(11)	7676(10)	6119(10)	54(4)	0.50
C(50)	1312(11)	8106(9)	6759(8)	75(3)	0.50
C(51)	1132(14)	8816(14)	7377(12)	60(4)	0.50
C(52)	-45(12)	9263(11)	8031(9)	86(4)	0.50
C(53)	-189(14)	9935(17)	8601(16)	114(6)	0.50
C(54)	801(21)	10270(29)	8566(27)	117(8)	0.50
C(55)	1956(15)	9878(22)	7962(21)	93(6)	0.50
C(56)	2178(13)	9122(11)	7365(10)	67(4)	0.50
C(57)	3347(10)	8700(8)	6700(8)	83(3)	0.50
C(58)	3491(9)	7990(8)	6131(8)	64(3)	0.50

Table 2. (continued)

C(59)	3149(32)	6418(33)	2899(13)	105(13)	0.25
C(60)	4317(27)	6115(31)	2231(17)	81(9)	0.25
C(61)	4444(19)	6288(24)	1204(15)	87(9)	0.25
C(62)	5625(16)	5997(16)	492(16)	89(7)	0.25
C(63)	5691(20)	6145(17)	-475(16)	115(9)	0.25
C(64)	4606(27)	6683(29)	-870(15)	138(11)	0.25
C(65)	3453(25)	6934(35)	-232(16)	112(10)	0.25
C(66)	3310(20)	6815(34)	814(15)	90(9)	0.25
C(67)	2131(21)	7105(32)	1500(18)	95(10)	0.25
C(68)	2052(27)	6973(36)	2488(20)	69(8)	0.25
C(1')	-955(5)	8700(4)	4471(4)	74(2)	0.75
C(2')	-1664(4)	8044(4)	4313(5)	79(2)	0.75
C(3')	-1994(9)	7339(7)	5271(7)	77(2)	0.75
C(4')	-3154(10)	7632(8)	5904(9)	91(3)	0.75
C(5')	-3421(10)	6977(10)	6788(9)	103(3)	0.75
C(6')	-2506(12)	6029(10)	7072(10)	125(4)	0.75
C(7')	-1340(10)	5751(12)	6434(11)	138(5)	0.75
C(8')	-1063(8)	6369(10)	5548(10)	109(3)	0.75
C(9')	-1632(5)	7099(4)	3137(4)	117(2)	1.00
C(11')	-955(5)	8700(4)	4471(4)	74(2)	0.25
C(12')	-1664(4)	8044(4)	4313(5)	79(2)	0.25
C(13')	-1762(26)	7242(18)	5256(15)	77(2)	0.25
C(14')	-2890(27)	7296(28)	5913(25)	91(3)	0.25
C(15')	-2939(32)	6630(35)	6813(28)	103(3)	0.25
C(16')	-1869(36)	5758(35)	7005(27)	125(4)	0.25
C(17')	-771(28)	5672(33)	6296(32)	138(5)	0.25
C(18')	-652(25)	6407(31)	5467(28)	109(3)	0.25
C(71)	-29(89)	5491(77)	-950(37)	356(39)	0.25
C(72)	707(56)	4678(39)	-172(31)	279(23)	0.25
O(73)	496(43)	5246(33)	619(35)	305(17)	0.25
C(74)	-478(71)	4906(69)	1394(33)	249(22)	0.25
C(75)	-1041(50)	4380(41)	896(39)	244(22)	0.25
C(81)	-1184(33)	4992(54)	1214(40)	233(22)	0.25
C(82)	192(36)	4235(52)	1261(49)	271(22)	0.25
O(83)	1043(33)	4664(36)	424(33)	305(16)	0.25
C(84)	167(52)	5479(36)	-167(38)	269(21)	0.25
C(85)	726(85)	5302(96)	-1252(36)	370(44)	0.25

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for $[C_{44}H_{32}NC_6S] \cdot [C_6H_{10}O]_{0.25}$.

c is the occupancy factor.

	x	y	z	U(iso)	c
H(N)	2981(3)	9056(2)	4589(2)	92	1.00
H(1A)	819(4)	8944(3)	4938(3)	84	1.00
H(1B)	879(4)	9599(3)	3843(3)	84	1.00
H(2)	2638(4)	8165(3)	3231(3)	76	1.00
H(5)	3803(5)	4554(4)	4145(5)	106	1.00
H(6)	3594(5)	4198(5)	5838(5)	116	1.00
H(7)	2837(5)	5574(5)	6711(4)	112	1.00
H(10)	3520(11)	7852(10)	6101(9)	80	0.50
H(12)	3760(11)	9158(10)	6920(10)	96	0.50
H(13)	2964(17)	10141(23)	8136(21)	127	0.50
H(14)	853(22)	10538(28)	8970(26)	130	0.50
H(15)	-451(14)	9853(16)	8656(16)	125	0.50
H(17)	-690(10)	8576(8)	7769(8)	100	0.50
H(18)	168(10)	7417(8)	6674(8)	91	0.50
H(20)	1573(11)	6997(12)	2777(8)	101	0.75
H(22)	813(8)	7533(7)	1191(8)	159	0.75
H(23)	1232(11)	7618(8)	-480(8)	186	0.75
H(24)	3302(14)	7048(12)	-1397(8)	185	0.75
H(25)	4970(12)	6274(11)	-623(9)	166	0.75
H(27)	5768(10)	5718(10)	986(9)	135	0.75
H(28)	5344(12)	5651(13)	2636(9)	130	0.75
H(30)	3706(5)	11051(4)	2542(4)	106	1.00
H(31)	3061(5)	12145(4)	1130(5)	120	1.00
H(33)	3406(5)	9585(6)	120(4)	114	1.00
H(34)	4088(4)	8479(4)	1533(4)	99	1.00
H(35A)	3078(30)	12262(20)	-675(18)	199	1.00
H(35B)	1756(7)	12076(25)	-264(8)	199	1.00
H(35C)	2876(35)	11312(7)	-940(11)	199	1.00
H(50)	619(11)	7914(9)	6782(8)	89	0.50
H(52)	-744(12)	9075(11)	8060(9)	103	0.50
H(53)	-973(14)	10187(17)	9035(16)	137	0.50
H(54)	676(21)	10763(29)	8955(27)	140	0.50
H(55)	2619(15)	10109(22)	7938(21)	112	0.50
H(57)	4035(10)	8911(8)	6650(8)	100	0.50
H(58)	4292(9)	7698(8)	5734(8)	77	0.50
H(60)	5056(27)	5779(31)	2483(17)	97	0.25
H(62)	6383(16)	5688(16)	718(16)	107	0.25
H(63)	6481(20)	5883(17)	-898(16)	139	0.25
H(64)	4671(27)	6866(29)	-1555(15)	166	0.25
H(65)	2719(25)	7196(35)	-488(16)	135	0.25
H(67)	1379(21)	7400(32)	1267(18)	114	0.25
H(68)	1262(27)	7251(36)	2904(20)	83	0.25
H(2')	-2469(4)	8552(4)	4138(5)	95	0.75
H(4')	-3775(10)	8286(8)	5735(9)	109	0.75
H(5')	-4232(10)	7176(10)	7201(9)	124	0.75
H(6')	-2675(12)	5590(10)	7680(10)	149	0.75
H(7')	-711(10)	5110(12)	6618(11)	166	0.75
H(8')	-261(8)	6151(10)	5127(10)	131	0.75
H(9'A)	-1913(30)	6580(22)	3662(10)	175	1.00
H(9'B)	-1098(12)	6759(27)	2577(18)	175	1.00
H(9'C)	-2364(20)	7673(6)	2939(26)	175	1.00

Table 3. (continued)

H(12')	-2517(26)	8509(18)	4202(15)	95	0.25
H(14')	-3645(27)	7797(28)	5747(25)	109	0.25
H(15')	-3693(32)	6760(35)	7300(28)	124	0.25
H(16')	-1900(36)	5256(35)	7591(27)	149	0.25
H(17')	-57(28)	5066(33)	6390(32)	166	0.25
H(18')	144(25)	6361(31)	5045(28)	131	0.25
H(71A)	86(89)	5145(77)	-1489(37)	534	0.25
H(71B)	290(89)	6082(77)	-1202(37)	534	0.25
H(71C)	-924(89)	5753(77)	-646(37)	534	0.25
H(72A)	394(56)	4076(39)	89(31)	335	0.25
H(72B)	1614(56)	4406(39)	-469(31)	335	0.25
H(74A)	-1141(71)	5518(69)	1664(33)	299	0.25
H(74B)	-103(71)	4393(69)	1930(33)	299	0.25
H(75A)	-1694(50)	4140(41)	1381(39)	365	0.25
H(75B)	-374(50)	3777(41)	632(39)	365	0.25
H(75C)	-1406(50)	4897(41)	366(39)	365	0.25
H(81A)	-1777(33)	4736(54)	1756(40)	350	0.25
H(81B)	-1360(33)	5010(54)	594(40)	350	0.25
H(81C)	-1272(33)	5704(54)	1262(40)	350	0.25
H(82A)	384(36)	4210(52)	1884(49)	326	0.25
H(82B)	295(36)	3513(52)	1213(49)	326	0.25
H(84A)	92(52)	6193(36)	-114(38)	323	0.25
H(84B)	-675(52)	5409(36)	64(38)	323	0.25
H(85A)	172(85)	5827(96)	-1668(36)	555	0.25
H(85B)	795(85)	4594(96)	-1295(36)	555	0.25
H(85C)	1559(85)	5374(96)	-1471(36)	555	0.25

Table 4. Anisotropic parameters (Å² x 10^3) for $[C_{24}H_{29}NO_5S]\cdot[C_6H_{10}O]_{0.5}$.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
S	57(1)	67(1)	103(1)	-15(1)	-31(1)	-18(1)
O(1)	73(2)	90(2)	146(3)	-27(2)	-51(2)	-34(2)
O(2)	67(2)	75(2)	124(3)	-29(2)	-39(2)	0(2)
O(3)	57(2)	70(2)	115(3)	-29(2)	-36(2)	-15(2)
O(4)	70(2)	81(2)	164(4)	-57(3)	-42(2)	-8(2)
O(5)	71(2)	91(2)	146(3)	-46(2)	-50(2)	-16(2)
N	59(2)	72(2)	68(3)	-11(2)	-25(2)	-30(2)
C(1)	62(3)	52(3)	110(4)	-14(3)	-40(3)	-18(2)
C(2)	62(3)	50(3)	84(4)	-14(3)	-28(3)	-17(2)
C(3)	53(3)	65(3)	71(4)	-8(3)	-25(3)	-20(2)
C(4)	70(3)	65(3)	85(4)	-12(3)	-34(3)	-25(3)
C(5)	101(4)	54(3)	124(5)	-7(3)	-54(4)	-24(3)
C(6)	109(5)	70(4)	121(6)	17(4)	-65(4)	-33(4)
C(7)	97(4)	89(4)	89(4)	0(4)	-42(4)	-20(4)
C(8)	64(3)	67(4)	84(4)	-7(3)	-31(3)	-6(3)
C(9)	44(9)	90(9)	60(9)	17(7)	-10(7)	-38(7)
C(10)	28(6)	85(9)	71(9)	-2(7)	-1(7)	-17(6)
C(11)	70(8)	73(9)	31(7)	-16(6)	16(6)	-21(7)
C(12)	56(8)	87(9)	99(10)	-14(7)	-18(8)	-26(7)
C(13)	97(13)	118(11)	98(11)	-48(9)	-25(12)	-7(12)
C(14)	101(16)	111(13)	121(14)	-65(11)	-14(13)	-23(14)
C(15)	78(12)	110(13)	117(13)	-45(9)	-17(10)	-10(10)
C(16)	80(11)	83(10)	65(12)	-21(8)	-7(9)	-14(9)
C(17)	62(7)	98(8)	86(8)	-20(7)	-13(6)	-24(6)
C(18)	65(7)	81(8)	87(8)	6(6)	-22(7)	-41(6)
C(19)	93(7)	42(5)	97(8)	-11(5)	-43(6)	-27(5)
C(20)	105(9)	59(7)	92(7)	-22(5)	-35(7)	-14(7)
C(21)	110(9)	60(6)	99(8)	-21(6)	-55(7)	-12(7)
C(22)	127(8)	120(7)	124(9)	-11(7)	-57(7)	-1(6)
C(23)	199(12)	158(9)	77(7)	-1(7)	-64(8)	-16(8)
C(24)	205(13)	116(8)	103(9)	-5(8)	-38(10)	-21(9)
C(25)	175(13)	108(10)	102(9)	-10(8)	-39(9)	-16(8)
C(26)	135(11)	69(8)	86(8)	-26(6)	-19(7)	-21(7)
C(27)	101(9)	111(9)	128(9)	-26(8)	-47(8)	-19(7)
C(28)	97(8)	129(9)	97(7)	-46(7)	-42(6)	-3(6)
C(29)	71(3)	60(3)	83(4)	-7(3)	-21(3)	-27(3)
C(30)	94(4)	76(4)	110(5)	-11(4)	-42(4)	-32(3)
C(31)	105(5)	76(4)	121(5)	-7(4)	-42(4)	-26(3)
C(32)	63(4)	99(5)	104(5)	-10(4)	-24(3)	-20(3)
C(33)	85(4)	118(5)	84(5)	-27(4)	-17(3)	-30(4)
C(34)	77(4)	73(4)	95(4)	-23(3)	-22(3)	-15(3)
C(35)	116(5)	145(5)	103(5)	17(4)	-49(4)	-15(4)
C(49)	30(8)	53(7)	71(9)	-3(6)	-5(6)	-17(5)
C(50)	67(8)	91(9)	57(8)	7(7)	-15(7)	-30(7)
C(51)	63(9)	75(9)	32(8)	-2(6)	4(7)	-26(8)
C(52)	81(9)	110(10)	68(9)	-26(7)	-4(7)	-37(8)
C(53)	72(11)	132(14)	119(13)	-44(9)	-4(10)	-10(11)
C(54)	77(13)	116(15)	141(14)	-44(11)	-15(12)	-9(12)
C(55)	80(13)	105(11)	108(12)	-36(10)	-32(11)	-26(11)
C(56)	61(8)	82(10)	60(9)	-22(7)	-10(7)	-23(7)
C(57)	88(9)	66(7)	81(9)	-14(6)	-21(7)	-8(6)
C(58)	52(6)	61(6)	72(8)	-25(5)	-11(6)	-3(6)
C(59)	105(19)	87(17)	92(18)	-27(15)	-49(15)	27(15)

Table 4. (continued)

C(60)	91(18)	83(16)	83(17)	-9(14)	-56(14)	-21(15)
C(61)	84(17)	83(16)	87(17)	-18(14)	-44(14)	-1(15)
C(62)	76(14)	114(15)	64(14)	-15(14)	25(12)	-49(12)
C(63)	94(16)	67(15)	99(17)	-16(14)	34(15)	-3(13)
C(64)	176(22)	104(18)	87(18)	-13(18)	-2(19)	-22(18)
C(65)	160(20)	89(17)	81(17)	1(16)	-50(16)	-27(16)
C(66)	117(20)	72(17)	83(17)	-16(15)	-41(15)	-17(15)
C(67)	92(18)	74(17)	91(17)	-21(14)	-24(15)	11(14)
C(68)	75(13)	62(16)	87(16)	-4(13)	-62(12)	-15(12)
C(1')	77(4)	63(3)	91(4)	-5(3)	-39(3)	-24(3)
C(2')	55(3)	59(3)	136(5)	-29(4)	-42(3)	-8(3)
C(3')	72(5)	52(4)	122(5)	-11(4)	-48(4)	-19(4)
C(4')	90(6)	61(7)	122(6)	-21(5)	-36(5)	-14(5)
C(5')	108(9)	75(9)	125(7)	-18(6)	-32(7)	-26(6)
C(6')	166(12)	71(9)	152(9)	-2(6)	-93(10)	-26(8)
C(7')	114(11)	89(6)	193(13)	4(7)	-76(10)	-2(9)
C(8')	84(7)	75(5)	161(7)	10(4)	-59(7)	-17(6)
C(9')	95(4)	108(4)	184(6)	-57(4)	-68(4)	-25(3)
C(11')	77(4)	63(3)	91(4)	-5(3)	-39(3)	-24(3)
C(12')	55(3)	59(3)	136(5)	-28(4)	-42(3)	-8(3)
C(13')	72(5)	52(4)	122(5)	-11(4)	-48(4)	-19(4)
C(14')	90(6)	61(7)	122(6)	-21(5)	-36(5)	-14(5)
C(15')	108(9)	75(9)	125(7)	-18(6)	-32(7)	-26(6)
C(16')	166(12)	71(9)	152(9)	-2(6)	-93(10)	-26(8)
C(17')	114(11)	89(6)	193(13)	4(7)	-76(10)	-2(9)
C(18')	84(7)	75(5)	161(7)	10(4)	-59(7)	-17(6)

Table 5. Bond lengths [Å] and angles [ ] for $[C_{46}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$.

S-O(2)	1.428(3)	S-O(1)	1.430(3)
S-N	1.594(3)	S-C(29)	1.770(5)
O(3)-C(11')	1.338(5)	O(3)-C(1')	1.338(5)
O(3)-C(1)	1.447(4)	O(4)-C(11')	1.191(5)
O(4)-C(1')	1.191(5)	O(5)-C(9')	1.425(4)
O(5)-C(12')	1.426(5)	O(5)-C(2')	1.426(5)
N-C(2)	1.471(4)	C(1)-C(2)	1.537(5)
C(2)-C(3)	1.530(5)	C(3)-C(8)	1.394(6)
C(3)-C(4)	1.398(5)	C(4)-C(5)	1.397(6)
C(4)-C(19)	1.473(8)	C(4)-C(59)	1.51(2)
C(5)-C(6)	1.367(6)	C(6)-C(7)	1.361(6)
C(7)-C(8)	1.389(6)	C(8)-C(9)	1.482(12)
C(8)-C(49)	1.572(11)	C(9)-C(10)	1.372(13)
C(9)-C(18)	1.383(13)	C(10)-C(11)	1.402(14)
C(11)-C(16)	1.428(14)	C(11)-C(12)	1.432(14)
C(12)-C(13)	1.32(2)	C(13)-C(14)	1.39(2)
C(14)-C(15)	1.35(2)	C(15)-C(16)	1.42(2)
C(16)-C(17)	1.40(2)	C(17)-C(18)	1.359(13)
C(19)-C(20)	1.374(11)	C(19)-C(28)	1.411(11)
C(20)-C(21)	1.423(11)	C(21)-C(26)	1.408(12)
C(21)-C(22)	1.419(11)	C(22)-C(23)	1.357(10)
C(23)-C(24)	1.388(12)	C(24)-C(25)	1.342(13)
C(25)-C(26)	1.447(12)	C(26)-C(27)	1.410(12)
C(27)-C(28)	1.339(12)	C(29)-C(30)	1.362(6)
C(29)-C(34)	1.375(5)	C(30)-C(31)	1.376(6)
C(31)-C(32)	1.373(6)	C(32)-C(33)	1.387(6)
C(32)-C(35)	1.522(7)	C(33)-C(34)	1.388(6)
C(49)-C(50)	1.383(13)	C(49)-C(58)	1.429(12)
C(50)-C(51)	1.40(2)	C(51)-C(52)	1.42(2)
C(51)-C(56)	1.427(14)	C(52)-C(53)	1.32(2)
C(53)-C(54)	1.38(2)	C(54)-C(55)	1.35(2)
C(55)-C(56)	1.42(2)	C(56)-C(57)	1.413(14)
C(57)-C(58)	1.363(12)	C(59)-C(60)	1.39(2)
C(59)-C(68)	1.41(2)	C(60)-C(61)	1.39(2)
C(61)-C(62)	1.43(2)	C(61)-C(66)	1.43(2)
C(62)-C(63)	1.33(2)	C(63)-C(64)	1.39(2)
C(64)-C(65)	1.35(2)	C(65)-C(66)	1.42(2)
C(66)-C(67)	1.41(2)	C(67)-C(68)	1.35(2)
C(1')-C(2')	1.530(6)	C(2')-C(3')	1.488(8)
C(3')-C(4')	1.358(9)	C(3')-C(8')	1.395(9)
C(4')-C(5')	1.367(9)	C(5')-C(6')	1.370(10)
C(6')-C(7')	1.364(11)	C(7')-C(8')	1.346(11)
C(11')-C(12')	1.530(6)	C(12')-C(13')	1.50(2)
C(13')-C(14')	1.35(2)	C(13')-C(18')	1.40(2)
C(14')-C(15')	1.36(2)	C(15')-C(16')	1.38(2)
C(16')-C(17')	1.36(2)	C(17')-C(18')	1.34(2)
C(71)-C(72)	1.538(9)	C(72)-O(73)	1.451(9)
O(73)-C(74)	1.453(9)	C(74)-C(75)	1.541(9)
C(81)-C(82)	1.539(9)	C(82)-O(83)	1.457(9)
O(83)-C(84)	1.454(9)	C(84)-C(85)	1.538(9)
O(2)-S-O(1)	121.0(2)	O(2)-S-N	108.2(2)
O(1)-S-N	105.9(2)	O(2)-S-C(29)	106.8(2)
O(1)-S-C(29)	107.0(2)	N-S-C(29)	107.3(2)
C(11')-O(3)-C(1)	114.6(3)	C(1')-O(3)-C(1)	114.6(3)
C(9')-O(5)-C(2')	112.4(4)	C(2)-N-S	119.8(3)
O(3)-C(1)-C(2)	106.0(3)	N-C(2)-C(3)	113.9(3)
N-C(2)-C(1)	106.3(3)	C(3)-C(2)-C(1)	113.0(4)
C(8)-C(3)-C(4)	118.7(5)	C(8)-C(3)-C(2)	121.5(4)
C(4)-C(3)-C(2)	119.8(4)	C(5)-C(4)-C(3)	119.8(5)
C(5)-C(4)-C(19)	116.2(6)	C(3)-C(4)-C(19)	123.9(6)

Table 5. (continued)

C(5)-C(4)-C(59)	120(2)	C(3)-C(4)-C(59)	119(2)
C(6)-C(5)-C(4)	120.4(5)	C(7)-C(6)-C(5)	120.3(5)
C(6)-C(7)-C(8)	120.8(5)	C(7)-C(8)-C(3)	120.0(5)
C(7)-C(8)-C(9)	109.2(7)	C(3)-C(8)-C(9)	129.1(7)
C(7)-C(8)-C(49)	118.3(7)	C(3)-C(8)-C(49)	120.4(7)
C(10)-C(9)-C(18)	118.9(11)	C(10)-C(9)-C(8)	113.8(9)
C(18)-C(9)-C(8)	127.2(10)	C(9)-C(10)-C(11)	122.5(11)
C(10)-C(11)-C(16)	118.1(10)	C(10)-C(11)-C(12)	123.2(11)
C(16)-C(11)-C(12)	118.6(11)	C(13)-C(12)-C(11)	120.2(12)
C(12)-C(13)-C(14)	121.6(14)	C(15)-C(14)-C(13)	120.7(13)
C(14)-C(15)-C(16)	121.0(14)	C(17)-C(16)-C(15)	125.0(13)
C(17)-C(16)-C(11)	117.4(12)	C(15)-C(16)-C(11)	117.5(12)
C(18)-C(17)-C(16)	122.5(11)	C(17)-C(18)-C(9)	120.5(10)
C(20)-C(19)-C(28)	118.1(8)	C(20)-C(19)-C(4)	121.2(10)
C(28)-C(19)-C(4)	120.6(9)	C(19)-C(20)-C(21)	119.6(9)
C(26)-C(21)-C(22)	117.8(9)	C(26)-C(21)-C(20)	120.7(9)
C(22)-C(21)-C(20)	121.5(10)	C(23)-C(22)-C(21)	120.8(9)
C(22)-C(23)-C(24)	121.8(10)	C(25)-C(24)-C(23)	120.0(11)
C(24)-C(25)-C(26)	120.5(11)	C(21)-C(26)-C(27)	118.0(9)
C(21)-C(26)-C(25)	119.1(10)	C(27)-C(26)-C(25)	122.8(11)
C(28)-C(27)-C(26)	120.0(10)	C(27)-C(28)-C(19)	123.5(10)
C(30)-C(29)-C(34)	120.2(5)	C(30)-C(29)-S	119.9(4)
C(34)-C(29)-S	119.9(4)	C(29)-C(30)-C(31)	120.2(5)
C(32)-C(31)-C(30)	121.3(6)	C(31)-C(32)-C(33)	118.2(6)
C(31)-C(32)-C(35)	120.7(6)	C(33)-C(32)-C(35)	121.1(6)
C(32)-C(33)-C(34)	120.7(5)	C(29)-C(34)-C(33)	119.5(5)
C(50)-C(49)-C(58)	115.4(9)	C(50)-C(49)-C(8)	121.0(9)
C(58)-C(49)-C(8)	123.1(8)	C(49)-C(50)-C(51)	123.8(11)
C(50)-C(51)-C(52)	123.9(12)	C(50)-C(51)-C(56)	119.5(11)
C(52)-C(51)-C(56)	116.6(12)	C(53)-C(52)-C(51)	122.7(13)
C(52)-C(53)-C(54)	121.2(13)	C(55)-C(54)-C(53)	119.6(14)
C(54)-C(55)-C(56)	121(2)	C(57)-C(56)-C(55)	124.5(13)
C(57)-C(56)-C(51)	117.0(11)	C(55)-C(56)-C(51)	118.4(11)
C(58)-C(57)-C(56)	121.7(11)	C(57)-C(58)-C(49)	122.6(9)
C(60)-C(59)-C(68)	116.7(14)	C(60)-C(59)-C(4)	117(2)
C(68)-C(59)-C(4)	126(2)	C(59)-C(60)-C(61)	124(2)
C(60)-C(61)-C(62)	125(2)	C(60)-C(61)-C(66)	118(2)
C(62)-C(61)-C(66)	116.2(14)	C(63)-C(62)-C(61)	123(2)
C(62)-C(63)-C(64)	121(2)	C(65)-C(64)-C(63)	118(2)
C(64)-C(65)-C(66)	123(2)	C(67)-C(66)-C(65)	125(2)
C(67)-C(66)-C(61)	117.4(14)	C(65)-C(66)-C(61)	117.5(14)
C(68)-C(67)-C(66)	122(2)	C(67)-C(68)-C(59)	121(2)
O(4)-C(1')-O(3)	124.9(5)	O(4)-C(1')-C(2')	123.3(5)
O(3)-C(1')-C(2')	111.8(5)	O(5)-C(2')-C(3')	116.6(5)
O(5)-C(2')-C(1')	108.7(4)	C(3')-C(2')-C(1')	108.9(5)
C(4')-C(3')-C(8')	118.8(8)	C(4')-C(3')-C(2')	122.1(7)
C(8')-C(3')-C(2')	119.0(8)	C(3')-C(4')-C(5')	120.8(8)
C(4')-C(5')-C(6')	120.7(9)	C(7')-C(6')-C(5')	117.9(11)
C(8')-C(7')-C(6')	122.6(11)	C(7')-C(8')-C(3')	119.1(9)
O(4)-C(11')-O(3)	124.9(5)	O(4)-C(11')-C(12')	123.3(5)
O(3)-C(11')-C(12')	111.8(5)	O(5)-C(12')-C(13')	111.2(10)
O(5)-C(12')-C(11')	108.7(4)	C(13')-C(12')-C(11')	104.9(10)
C(14')-C(13')-C(18')	119(2)	C(14')-C(13')-C(12')	122(2)
C(18')-C(13')-C(12')	119(2)	C(13')-C(14')-C(15')	121(2)
C(14')-C(15')-C(16')	120(2)	C(17')-C(16')-C(15')	117(2)
C(18')-C(17')-C(16')	124(2)	C(17')-C(18')-C(13')	118(2)
O(73)-C(72)-C(71)	106.8(12)	C(72)-O(73)-C(74)	103.5(12)
O(73)-C(74)-C(75)	106.2(12)	O(83)-C(82)-C(81)	106.9(12)
C(84)-O(83)-C(82)	103.0(12)	O(83)-C(84)-C(85)	106.9(12)

Table 6. Torsion angles [ ] for $[C_{44}H_{37}NOS]\cdot[C_4H_8O]_{0.5}$.

O(2)-S-N-C(2)	-46.3(3)	O(1)-S-N-C(2)	-177.3(3)
C(29)-S-N-C(2)	68.6(3)	C(11')-O(3)-C(1)-C(2)	166.5(6)
C(1')-O(3)-C(1)-C(2)	166.5(4)	S-N-C(2)-C(3)	87.1(6)
S-N-C(2)-C(1)	-137.8(3)	O(3)-C(1)-C(2)-N	177.2(3)
O(3)-C(1)-C(2)-C(3)	-57.1(5)	N-C(2)-C(3)-C(8)	57.2(5)
C(1)-C(2)-C(3)-C(8)	-64.3(5)	N-C(2)-C(3)-C(4)	-120.3(4)
C(1)-C(2)-C(3)-C(4)	116.3(4)	C(8)-C(3)-C(4)-C(5)	0.0(6)
C(2)-C(3)-C(4)-C(5)	177.5(4)	C(8)-C(3)-C(4)-C(19)	-176.5(7)
C(2)-C(3)-C(4)-C(19)	1.0(8)	C(8)-C(3)-C(4)-C(59)	172.(2)
C(2)-C(3)-C(4)-C(59)	-10.(2)	C(3)-C(4)-C(5)-C(6)	0.5(7)
C(19)-C(4)-C(5)-C(6)	177.3(6)	C(59)-C(4)-C(5)-C(6)	-172.(2)
C(4)-C(5)-C(6)-C(7)	0.2(8)	C(5)-C(6)-C(7)-C(8)	-1.4(8)
C(6)-C(7)-C(8)-C(3)	1.9(8)	C(6)-C(7)-C(8)-C(9)	168.6(6)
C(6)-C(7)-C(8)-C(49)	-165.2(7)	C(4)-C(3)-C(8)-C(7)	-1.2(7)
C(2)-C(3)-C(8)-C(7)	-178.7(4)	C(4)-C(3)-C(8)-C(9)	-164.9(7)
C(2)-C(3)-C(8)-C(9)	17.6(9)	C(4)-C(3)-C(8)-C(49)	165.7(6)
C(2)-C(3)-C(8)-C(49)	-11.8(8)	C(7)-C(8)-C(9)-C(10)	104.9(10)
C(3)-C(8)-C(9)-C(10)	-90.0(12)	C(49)-C(8)-C(9)-C(10)	-11.(2)
C(7)-C(8)-C(9)-C(18)	-76.5(13)	C(3)-C(8)-C(9)-C(18)	88.7(13)
C(49)-C(8)-C(9)-C(18)	168.(3)	C(18)-C(9)-C(10)-C(11)	1.(2)
C(8)-C(9)-C(10)-C(11)	179.4(10)	C(9)-C(10)-C(11)-C(16)	1.(2)
C(9)-C(10)-C(11)-C(12)	-179.6(14)	C(10)-C(11)-C(12)-C(13)	-175.(2)
C(16)-C(11)-C(12)-C(13)	4.(3)	C(11)-C(12)-C(13)-C(14)	-6.(4)
C(12)-C(13)-C(14)-C(15)	2.(5)	C(13)-C(14)-C(15)-C(16)	3.(5)
C(14)-C(15)-C(16)-C(17)	179.(2)	C(14)-C(15)-C(16)-C(11)	-5.(4)
C(10)-C(11)-C(16)-C(17)	-3.(2)	C(12)-C(11)-C(16)-C(17)	178.(2)
C(10)-C(11)-C(16)-C(15)	-180.(2)	C(12)-C(11)-C(16)-C(15)	1.(3)
C(15)-C(16)-C(17)-C(18)	179.(2)	C(11)-C(16)-C(17)-C(18)	3.(3)
C(16)-C(17)-C(18)-C(9)	-1.(2)	C(10)-C(9)-C(18)-C(17)	-1.(2)
C(8)-C(9)-C(18)-C(17)	-179.4(11)	C(5)-C(4)-C(19)-C(20)	111.7(10)
C(3)-C(4)-C(19)-C(20)	-71.7(11)	C(59)-C(4)-C(19)-C(20)	-2.(10)
C(5)-C(4)-C(19)-C(28)	-63.6(10)	C(3)-C(4)-C(19)-C(28)	113.0(9)
C(59)-C(4)-C(19)-C(28)	-178.(11)	C(28)-C(19)-C(20)-C(21)	-1.(2)
C(4)-C(19)-C(20)-C(21)	-176.6(10)	C(19)-C(20)-C(21)-C(26)	0.(2)
C(19)-C(20)-C(21)-C(22)	-179.4(12)	C(26)-C(21)-C(22)-C(23)	1.(2)
C(20)-C(21)-C(22)-C(23)	-179.6(10)	C(21)-C(22)-C(23)-C(24)	-1.(2)
C(22)-C(23)-C(24)-C(25)	2.(2)	C(23)-C(24)-C(25)-C(26)	-2.(2)
C(22)-C(21)-C(26)-C(27)	-178.8(11)	C(20)-C(21)-C(26)-C(27)	2.(2)
C(22)-C(21)-C(26)-C(25)	-1.(2)	C(20)-C(21)-C(26)-C(25)	179.3(11)
C(24)-C(25)-C(26)-C(21)	2.(2)	C(24)-C(25)-C(26)-C(27)	179.(2)
C(21)-C(26)-C(27)-C(28)	-3.(2)	C(25)-C(26)-C(27)-C(28)	-179.9(12)
C(26)-C(27)-C(28)-C(19)	2.(2)	C(20)-C(19)-C(28)-C(27)	0.(2)
C(4)-C(19)-C(28)-C(27)	175.9(12)	O(2)-S-C(29)-C(30)	-158.0(4)
O(1)-S-C(29)-C(30)	-27.1(5)	N-S-C(29)-C(30)	86.2(4)
O(2)-S-C(29)-C(34)	24.5(4)	O(1)-S-C(29)-C(34)	155.4(4)
N-S-C(29)-C(34)	-91.3(4)	C(34)-C(29)-C(30)-C(31)	-1.5(8)
S-C(29)-C(30)-C(31)	-179.0(4)	C(29)-C(30)-C(31)-C(32)	2.2(8)
C(30)-C(31)-C(32)-C(33)	-2.2(8)	C(30)-C(31)-C(32)-C(35)	179.3(5)
C(31)-C(32)-C(33)-C(34)	1.7(8)	C(35)-C(32)-C(33)-C(34)	-179.9(5)
C(30)-C(29)-C(34)-C(33)	1.0(7)	S-C(29)-C(34)-C(33)	178.5(4)
C(32)-C(33)-C(34)-C(29)	-1.1(8)	C(7)-C(8)-C(49)-C(50)	-82.6(12)
C(3)-C(8)-C(49)-C(50)	110.3(11)	C(9)-C(8)-C(49)-C(50)	-8.(2)
C(7)-C(8)-C(49)-C(58)	89.2(12)	C(3)-C(8)-C(49)-C(58)	-77.9(13)
C(9)-C(8)-C(49)-C(58)	164.(3)	C(58)-C(49)-C(50)-C(51)	1.(2)
C(8)-C(49)-C(50)-C(51)	173.3(12)	C(49)-C(50)-C(51)-C(52)	180.(2)
C(49)-C(50)-C(51)-C(56)	0.(2)	C(50)-C(51)-C(52)-C(53)	-180.(2)
C(56)-C(51)-C(52)-C(53)	0.(3)	C(51)-C(52)-C(53)-C(54)	2.(3)
C(52)-C(53)-C(54)-C(55)	-2.(5)	C(53)-C(54)-C(55)-C(56)	0.(5)
C(54)-C(55)-C(56)-C(57)	178.(3)	C(54)-C(55)-C(56)-C(51)	3.(4)
C(50)-C(51)-C(56)-C(57)	1.(2)	C(52)-C(51)-C(56)-C(57)	-176.7(13)
C(50)-C(51)-C(56)-C(55)	177.(2)	C(52)-C(51)-C(56)-C(55)	-3.(3)

Table 6. (continued)

C(55)-C(56)-C(57)-C(58)	-179.(2)	C(51)-C(56)-C(57)-C(58)	-3.(2)
C(56)-C(57)-C(58)-C(49)	4.(2)	C(50)-C(49)-C(58)-C(57)	-3.(2)
C(8)-C(49)-C(58)-C(57)	-174.9(10)	C(5)-C(4)-C(59)-C(60)	-71.(3)
C(3)-C(4)-C(59)-C(60)	117.(2)	C(19)-C(4)-C(59)-C(60)	1.(9)
C(5)-C(4)-C(59)-C(68)	113.(2)	C(3)-C(4)-C(59)-C(68)	-59.(4)
C(19)-C(4)-C(59)-C(68)	-176.(14)	C(68)-C(59)-C(60)-C(61)	-3.(2)
C(4)-C(59)-C(60)-C(61)	-179.(3)	C(59)-C(60)-C(61)-C(62)	180.(3)
C(59)-C(60)-C(61)-C(66)	1.(3)	C(60)-C(61)-C(62)-C(63)	178.(2)
C(66)-C(61)-C(62)-C(63)	-3.(4)	C(61)-C(62)-C(63)-C(64)	6.(4)
C(62)-C(63)-C(64)-C(65)	-8.(5)	C(63)-C(64)-C(65)-C(66)	10.(4)
C(64)-C(65)-C(66)-C(67)	177.(4)	C(64)-C(65)-C(66)-C(61)	-8.(7)
C(60)-C(61)-C(66)-C(67)	-1.(5)	C(62)-C(61)-C(66)-C(67)	180.(4)
C(60)-C(61)-C(66)-C(65)	-177.(3)	C(62)-C(61)-C(66)-C(65)	4.(5)
C(65)-C(66)-C(67)-C(68)	180.(4)	C(61)-C(66)-C(67)-C(68)	5.(7)
C(66)-C(67)-C(68)-C(59)	-7.(6)	C(60)-C(59)-C(68)-C(67)	6.(5)
C(4)-C(59)-C(68)-C(67)	-176.(4)	C(1)-O(3)-C(1')-O(4)	3.(17)
C(1)-O(3)-C(1')-C(2')	-176.1(4)	C(9')-O(5)-C(2')-C(3')	70.(16)
C(9')-O(5)-C(2')-C(1')	-166.4(4)	O(4)-C(1')-C(2')-O(5)	159.(15)
O(3)-C(1')-C(2')-O(5)	-21.7(5)	O(4)-C(1')-C(2')-C(3')	-73.(17)
O(3)-C(1')-C(2')-C(3')	106.2(6)	O(5)-C(2')-C(3')-C(4')	-142.3(9)
C(1')-C(2')-C(2')-C(4')	95.4(9)	O(5)-C(2')-C(3')-C(8')	4.(11)
C(1')-C(2')-C(3')-C(8')	-81.7(10)	C(8')-C(3')-C(4')-C(5')	-2.(2)
C(2')-C(3')-C(4')-C(5')	-178.7(12)	C(3')-C(4')-C(5')-C(6')	3.(2)
C(4')-C(5')-C(6')-C(7')	-2.(2)	C(5')-C(6')-C(7')-C(8')	0.(2)
C(6')-C(7')-C(8')-C(3')	1.(2)	C(4')-C(3')-C(8')-C(7')	0.(2)
C(2')-C(3')-C(8')-C(7')	177.1(12)	C(1)-O(3)-C(11')-O(4)	3.(17)
C(1)-O(3)-C(11')-C(12')	-176.1(4)	C(9')-O(5)-C(12')-C(13')	78.6(12)
C(9')-O(5)-C(12')-C(11')	-166.4(4)	O(4)-C(11')-C(12')-O(5)	159.(15)
O(3)-C(11')-C(12')-O(5)	-21.7(5)	O(4)-C(11')-C(12')-C(13')	-62.9(12)
O(3)-C(11')-C(12')-C(13')	97.2(11)	O(5)-C(12')-C(13')-C(14')	-155.(3)
C(11')-C(12')-C(13')-C(14')	110.(3)	O(5)-C(12')-C(13')-C(18')	47.(3)
C(11')-C(12')-C(13')-C(18')	-70.(3)	C(18')-C(13')-C(14')-C(15')	2.(5)
C(12')-C(13')-C(14')-C(15')	-173.(4)	C(13')-C(14')-C(15')-C(16')	-12.(8)
C(14')-C(15')-C(16')-C(17')	6.(9)	C(15')-C(16')-C(17')-C(18')	4.(10)
C(16')-C(17')-C(18')-C(13')	-8.(9)	C(12')-C(13')-C(18')-C(17')	3.(6)
C(12')-C(13')-C(18')-C(17')	-177.(4)	C(72)-O(73)-C(74)-C(75)	102.(5)
C(72)-O(73)-C(74)-C(75)	-15.(8)	C(81)-C(82)-O(83)-C(84)	-11.(8)
C(82)-O(83)-C(84)-C(85)	-132.(8)		

Table 7. Bond distances (Å) and angles ( ) related to the hydrogen bonding for $[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$.

(A-H···B)	A-B	A-H	H-B	A-H-B
N-H(N)···O(4)[a]	2.935(5)	0.86	2.257(5)	135.67(12)

Symmetry transformations used to generate equivalent atoms:

a: -x,2-y,1-z

Structure determination and refinement procedure for $[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$.

A single crystal was mounted in air on an Enraf-Nonius CAD-4 diffractometer at room temperature. 24 reflections found on a polaroid photograph were used by the indexing procedure to obtain a preliminary cell. The cell parameters reported in table 1 were obtained by least-squares refinement on the setting of the 25 reflections (2θ between 40.0 to 50.0). A set of reflection sphere limited by $2\theta \leq 140$ was collected. The orientation was checked every 400 measurements and intensity was checked every hour using five standard reflections. Variation of 10.2% attributed to decomposition was observed during the collection of full data set.

Corrections were introduced for the Lorentz, polarization effects. The structure was solved by direct method using SHELXS86 (Sheldrick, 1985) and difmap synthesis using SHELXL93 (Sheldrick, 1993).

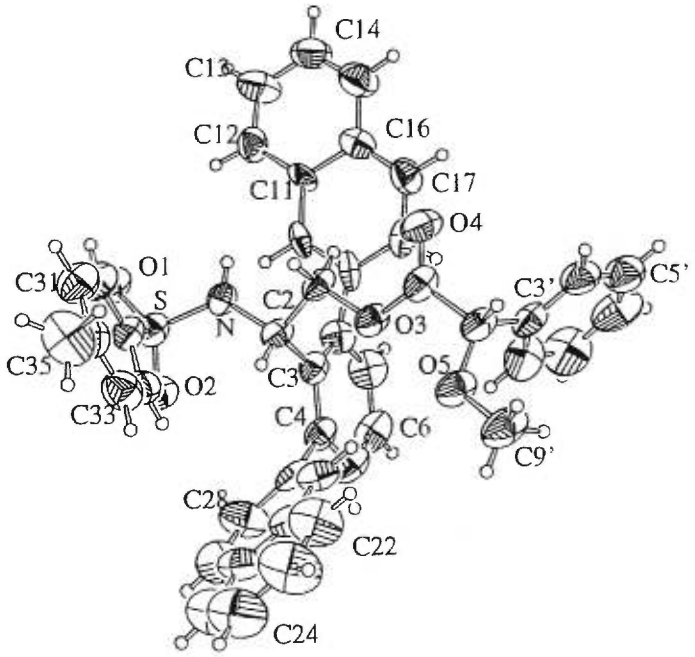
Two models were used for describe naphtalene group bond at C8. The first model (C9 to C18) refined to occupancy factor of 0.503(6) and was fixed in last cycle to 0.5. The occupancy factor of second model (C49 to C58) fixed also to 0.5. In other way, the other naphtalene group bonded to C4 showed disorder. Two models described this group. The occupancy factor of the first model (C19 to C28) refined to 0.744(7) and was fixed in last cycles to 0.75. The occupancy factor of the second model (C59 to C68) fixed to 0.25. Note that for the refinement of the occupancy factors, constraints were applied to keep them normalized to unity. These molecules were refined anisotropically use SIMU restraint while geometric restraint FLAT and SAME were applied.

One phenyl group is also disordered. The occupancy factor of the first model (C1' to C8') refined to 0.73(4) and was fixed in last cycles to 0.75. The occupancy factor of the second model fixed (C11' to C18') to 0.25. Note that for the refinement of the occupancy factors, constraints were applied to keep them normalized to unity. These atoms were refined anisotropically using EADP constraints and the geometric restraint FLAT used for two models. The atoms C1' and C11' as C2' and C12' converged to the same coordinates. The constraints EXYZ and EADP were applied for these atoms in the last cycles.

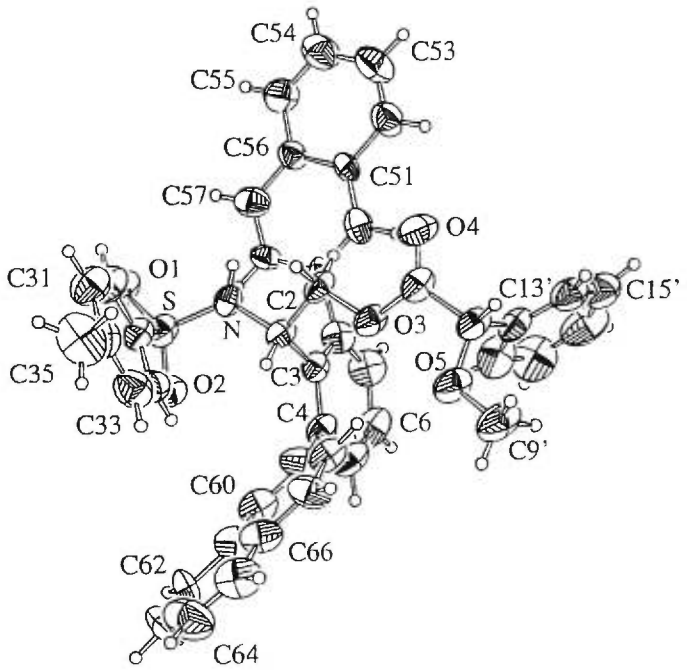
Diethylether solvent located in the vicinity of an inversion center imposing a disorder distribution over 2 positions. Solvent refined isotropically using geometric constraints. Identity of the solvent was confirmed by using the SQUEEZE technique from the PLATON (Spek, A. L. 1995) program. Vs = 196.4Å^3/cell and 52.4 electrons/cell (one site). The expected volume for diethylether are 173.06Å^3. Final refinement used the disordered description of the solvent and no SQUEEZE correction for the solvent contribution.

The crystal structure is stabilized by intermolecular hydrogen bonds of the N-H...O type.

The structure was refined on F_o^2 by full-matrix least-squares procedure. Individual weights based on counting statistics applied in the last cycles gave the refinement indicators presented. Hydrogen atoms were calculated at idealized positions using a riding model with different C-H distances for type of hydrogen. The isotropic displacement factors, U_{iso}, were adjusted to 50% higher value of the bonded carbon atom (methyl, amine) and 20% higher (others). The final ΔF map was essentially featurless. A general background below 20e/Å^3 was observed.



ORTEP view of the $[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$, molecule 1a with the numbering scheme adopted. Ellipsoids drawn at 40% probality level. Hydrogens represented by sphere of arbitrary size.



ORTEP view of the $[C_{44}H_{37}NO_5S]\cdot[C_4H_{10}O]_{0.5}$, molecule 1b with the numbering scheme adopted. Ellipsoids drawn at 40% probality level. Hydrogens represented by sphere of arbitrary size.

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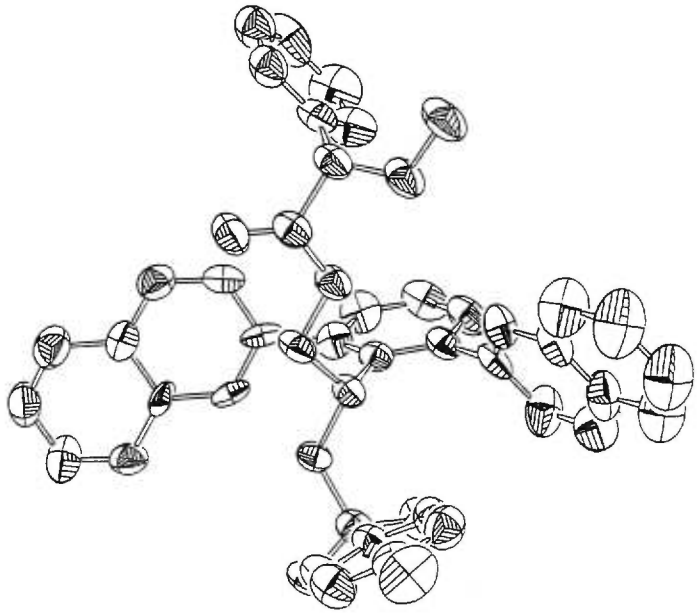

Appendix 6

CRYSTAL AND MOLECULAR STRUCTURE OF

$C_{35}H_{27}NO_4S$ COMPOUND (char25)

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Structure résolue au Laboratoire de Diffraction des Rayons X de l'Université de Montréal par Francine Bélanger-Gariépy, octobre 1996.

Table 1. Crystal data and structure refinement for $C_{35}H_{27}NO_4S$.

Identification code	char25
Empirical formula	C35 H27 N O4 S
Formula weight	557.64
Temperature	293(2)K
Wavelength	1.54056Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.841(2)Å α = 84.60(3)° b = 10.967(3)Å β = 87.28(3)° c = 15.291(7)Å γ = 71.39(2)°
Volume	1398.6(8)Å^3
Z	2
Density (calculated)	1.324 Mg/m^3
Absorption coefficient	1.32 mm^{-1}
F(000)	584
Crystal size	0.37 x 0.15 x 0.09 mm
Theta range for data collection	2.90 to 69.80°
Index ranges	0<=h<=10, -12<=k<=13, -18<=l<=18
Reflections collected	10410
Independent reflections	5295 [R(int) = 0.040]
Absorption correction	Integration
Max. and min. transmission	0.8895 and 0.7178
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5295 / 0 / 373
Goodness-of-fit on F^2	1.088
Final R indices [I>2sigma(I)]	R1 = 0.1179, wR2 = 0.3527
R indices (all data)	R1 = 0.1734, wR2 = 0.3715
Extinction coefficient	0.0030(7)
Largest diff. peak and hole	0.526 and -0.350 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $C_{35}H_{27}NO_4S$.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S	2349(3)	6874(2)	7734(2)	58(1)
O(1)	1670(8)	8158(6)	7355(5)	74(2)
O(2)	1396(8)	6023(7)	7895(5)	77(2)
O(3)	2012(7)	10039(6)	9559(5)	60(2)
O(4)	660(6)	8646(6)	9520(4)	60(2)
N	3070(8)	6924(7)	8687(5)	51(2)
C(1)	1840(9)	8946(9)	9373(6)	49(2)
C(2)	3328(9)	8108(8)	8915(6)	46(2)
C(3)	4884(9)	7822(8)	9409(6)	46(2)
C(4)	5042(10)	7249(9)	10269(6)	54(2)
C(5)	6537(11)	6816(11)	10644(7)	65(3)
C(6)	7843(11)	6975(11)	10202(8)	73(3)
C(7)	7717(9)	7579(10)	9375(6)	56(2)
C(8)	6238(9)	8026(8)	8953(6)	49(2)
C(9)	6194(9)	8723(8)	8067(7)	52(2)
C(10)	7327(10)	8201(9)	7438(7)	60(3)
C(11)	7418(10)	8860(9)	6628(7)	56(2)
C(12)	8647(12)	8329(12)	5987(8)	77(3)
C(13)	8752(16)	8985(14)	5198(8)	91(4)
C(14)	7602(17)	10197(15)	4993(9)	103(4)
C(15)	6397(16)	10742(12)	5582(9)	89(4)
C(16)	6317(11)	10050(10)	6415(7)	62(3)
C(17)	5136(12)	10594(10)	7056(8)	76(3)
C(18)	5068(10)	9948(9)	7851(8)	62(3)
C(19)	3650(10)	7055(9)	10798(6)	51(2)
C(20)	3330(12)	5869(10)	10862(7)	69(3)
C(21)	2125(11)	5675(9)	11380(7)	64(3)
C(22)	1219(11)	6636(9)	11904(7)	60(2)
C(23)	-59(11)	6462(11)	12480(7)	69(3)
C(24)	-914(13)	7390(13)	12959(7)	77(3)
C(25)	-673(14)	8578(13)	12881(8)	87(4)
C(26)	526(12)	8821(10)	12360(7)	67(3)
C(27)	1475(11)	7818(9)	11882(6)	53(2)
C(28)	2778(10)	8011(9)	11298(6)	54(2)
C(29)	3963(11)	6123(9)	7066(6)	56(2)
C(30)	4766(14)	6852(11)	6548(8)	78(3)
C(31)	6007(15)	6210(14)	6001(9)	89(4)
C(32)	6465(13)	4922(14)	5935(8)	81(4)
C(33)	5664(16)	4226(12)	6447(8)	90(4)
C(34)	4441(16)	4803(11)	6999(8)	84(4)
C(35)	7817(15)	4289(16)	5289(8)	117(6)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for $C_{35}H_{27}NO_4S$.

	x	y	z	U(iso)
H(3)	1295(78)	10394(53)	9900(58)	90
HN	3300(8)	6252(7)	9056(5)	77
H(2)	3451(9)	8592(8)	8359(6)	55
H(5)	6650(11)	6408(11)	11210(7)	78
H(6)	8834(11)	6667(11)	10467(8)	87
H(7)	8617(9)	7696(10)	9087(6)	67
H(10)	8053(10)	7382(9)	7561(7)	72
H(12)	9385(12)	7517(12)	6117(8)	93
H(13)	9571(16)	8639(14)	4800(8)	110
H(14)	7656(17)	10639(15)	4449(9)	123
H(15)	5650(16)	11545(12)	5439(9)	106
H(17)	4399(12)	11406(10)	6928(8)	92
H(18)	4273(10)	10313(9)	8257(8)	75
H(20)	3961(12)	5204(10)	10542(7)	83
H(21)	1901(11)	4902(9)	11386(7)	77
H(23)	-280(11)	5684(11)	12512(7)	83
H(24)	-1685(13)	7243(13)	13351(7)	92
H(25)	-1344(14)	9237(13)	13193(8)	104
H(26)	698(12)	9618(10)	12327(7)	81
H(28)	3002(10)	8786(9)	11272(6)	65
H(30)	4476(14)	7742(11)	6570(8)	94
H(31)	6552(15)	6692(14)	5664(9)	106
H(33)	5962(16)	3337(12)	6418(8)	108
H(34)	3919(16)	4303(11)	7335(8)	101
H(35A)	7366(15)	4153(102)	4763(32)	176
H(35B)	8471(81)	3475(51)	5556(30)	176
H(35C)	8457(82)	4845(50)	5148(57)	176

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for $C_{35}H_{27}NO_4S$.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
S	44(1)	55(1)	74(2)	-19(1)	-12(1)	-9(1)
O(1)	65(4)	53(4)	92(5)	-6(4)	-31(4)	4(3)
O(2)	63(4)	86(5)	97(6)	-26(4)	6(4)	-40(4)
O(3)	42(3)	57(4)	83(5)	-29(3)	16(3)	-17(3)
O(4)	31(3)	70(4)	84(5)	-26(4)	9(3)	-17(3)
N	47(4)	43(4)	62(5)	-15(3)	-1(4)	-8(3)
C(1)	33(4)	56(5)	59(6)	-19(4)	1(4)	-13(4)
C(2)	29(4)	47(5)	60(6)	-11(4)	7(4)	-11(3)
C(3)	27(4)	55(5)	54(5)	-19(4)	-4(4)	-5(4)
C(4)	40(5)	64(6)	62(6)	-18(5)	2(4)	-20(4)
C(5)	43(5)	100(8)	53(6)	-8(5)	-12(4)	-22(5)
C(6)	37(5)	104(9)	79(8)	-23(7)	-13(5)	-19(5)
C(7)	28(4)	80(7)	62(6)	-19(5)	1(4)	-17(4)
C(8)	30(4)	56(5)	62(6)	-13(4)	3(4)	-13(4)
C(9)	33(4)	52(5)	76(7)	-7(5)	2(4)	-21(4)
C(10)	43(5)	58(6)	76(7)	-14(5)	-3(5)	-10(4)
C(11)	43(5)	58(6)	64(6)	3(5)	2(4)	-15(4)
C(12)	50(6)	94(8)	77(8)	-15(7)	-1(5)	-6(6)
C(13)	86(9)	117(11)	56(7)	2(7)	10(6)	-15(8)
C(14)	96(10)	129(13)	78(9)	1(9)	2(8)	-30(9)
C(15)	90(9)	77(8)	90(9)	15(7)	-7(7)	-19(7)
C(16)	53(6)	70(7)	64(6)	-12(5)	4(5)	-21(5)
C(17)	52(6)	54(6)	111(10)	10(6)	-2(6)	-8(5)
C(18)	38(5)	54(6)	93(8)	-8(6)	11(5)	-14(4)
C(19)	37(4)	64(6)	53(6)	-12(5)	-2(4)	-15(4)
C(20)	57(6)	74(7)	77(7)	-18(6)	15(5)	-21(5)
C(21)	57(6)	53(6)	86(8)	-15(5)	7(5)	-21(5)
C(22)	55(6)	57(6)	60(6)	-2(5)	-1(5)	-9(5)
C(23)	52(6)	78(7)	79(8)	1(6)	5(5)	-27(5)
C(24)	65(7)	100(9)	65(7)	-3(7)	11(6)	-29(7)
C(25)	64(7)	100(10)	76(8)	-5(7)	10(6)	1(7)
C(26)	70(7)	55(6)	75(7)	-3(5)	5(6)	-18(5)
C(27)	58(6)	47(5)	50(5)	-8(4)	-8(4)	-8(4)
C(28)	49(5)	58(6)	59(6)	-9(5)	1(4)	-19(4)
C(29)	64(6)	59(6)	42(5)	-4(4)	-14(4)	-15(5)
C(30)	89(8)	70(7)	78(8)	-8(6)	-24(7)	-24(6)
C(31)	77(8)	103(10)	89(9)	-12(8)	9(7)	-33(7)
C(32)	52(6)	110(10)	67(8)	-28(7)	-10(5)	4(6)
C(33)	111(10)	64(7)	72(8)	-12(6)	16(7)	3(7)
C(34)	116(10)	61(7)	74(8)	-20(6)	4(7)	-24(7)
C(35)	80(9)	167(14)	80(9)	-45(9)	-6(7)	6(9)

Table 5. Bond lengths [Å] and angles [°] for $C_{35}H_{27}NO_4S$

S-O(1)	1.420(7)	S-O(2)	1.443(7)
S-N	1.631(7)	S-C(29)	1.740(10)
O(3)-C(1)	1.314(10)	O(4)-C(1)	1.196(10)
N-C(2)	1.463(10)	C(1)-C(2)	1.525(10)
C(2)-C(3)	1.530(11)	C(3)-C(4)	1.396(12)
C(3)-C(8)	1.425(11)	C(4)-C(5)	1.386(12)
C(4)-C(19)	1.502(12)	C(5)-C(6)	1.362(14)
C(6)-C(7)	1.363(14)	C(7)-C(8)	1.407(11)
C(8)-C(9)	1.487(13)	C(9)-C(10)	1.379(12)
C(9)-C(18)	1.414(12)	C(10)-C(11)	1.387(13)
C(11)-C(16)	1.377(13)	C(11)-C(12)	1.443(13)
C(12)-C(13)	1.36(2)	C(13)-C(14)	1.41(2)
C(14)-C(15)	1.38(2)	C(15)-C(16)	1.43(2)
C(16)-C(17)	1.422(14)	C(17)-C(18)	1.357(14)
C(19)-C(28)	1.363(12)	C(19)-C(20)	1.410(13)
C(20)-C(21)	1.357(13)	C(21)-C(22)	1.397(13)
C(22)-C(27)	1.382(13)	C(22)-C(23)	1.449(13)
C(23)-C(24)	1.319(14)	C(24)-C(25)	1.38(2)
C(25)-C(26)	1.38(2)	C(26)-C(27)	1.398(13)
C(27)-C(28)	1.480(13)	C(29)-C(34)	1.385(13)
C(29)-C(30)	1.40(2)	C(30)-C(31)	1.39(2)
C(31)-C(32)	1.35(2)	C(32)-C(33)	1.37(2)
C(32)-C(35)	1.54(2)	C(33)-C(34)	1.36(2)
O(1)-S-O(2)	120.9(4)	O(1)-S-N	106.7(4)
O(2)-S-N	105.0(4)	O(1)-S-C(29)	107.1(5)
O(2)-S-C(29)	107.7(5)	N-S-C(29)	106.7(4)
C(2)-N-S	120.2(6)	O(4)-C(1)-O(3)	124.9(8)
O(4)-C(1)-C(2)	123.6(8)	O(3)-C(1)-C(2)	111.5(7)
N-C(2)-C(1)	110.0(6)	N-C(2)-C(3)	111.8(7)
C(1)-C(2)-C(3)	115.2(7)	C(4)-C(3)-C(8)	119.5(7)
C(4)-C(3)-C(2)	121.0(8)	C(8)-C(3)-C(2)	119.2(8)
C(5)-C(4)-C(3)	119.2(8)	C(5)-C(4)-C(19)	118.5(9)
C(3)-C(4)-C(19)	122.2(8)	C(6)-C(5)-C(4)	121.3(10)
C(5)-C(6)-C(7)	120.8(9)	C(6)-C(7)-C(8)	120.6(9)
C(7)-C(8)-C(3)	118.3(9)	C(7)-C(8)-C(9)	117.0(8)
C(3)-C(8)-C(9)	124.6(7)	C(10)-C(9)-C(18)	117.9(9)
C(10)-C(9)-C(8)	119.8(8)	C(18)-C(9)-C(8)	122.3(8)
C(9)-C(10)-C(11)	122.0(9)	C(16)-C(11)-C(10)	120.2(9)
C(16)-C(11)-C(12)	118.2(10)	C(10)-C(11)-C(12)	121.6(9)
C(13)-C(12)-C(11)	121.6(11)	C(12)-C(13)-C(14)	119.1(12)
C(15)-C(14)-C(13)	121.5(13)	C(14)-C(15)-C(16)	118.9(12)
C(11)-C(16)-C(17)	118.3(10)	C(11)-C(16)-C(15)	120.8(10)
C(17)-C(16)-C(15)	120.9(10)	C(18)-C(17)-C(16)	121.1(10)
C(17)-C(18)-C(9)	120.5(9)	C(28)-C(19)-C(20)	119.4(9)
C(28)-C(19)-C(4)	118.5(8)	C(20)-C(19)-C(4)	121.8(8)
C(21)-C(20)-C(19)	121.6(9)	C(20)-C(21)-C(22)	120.1(10)
C(27)-C(22)-C(21)	121.4(9)	C(27)-C(22)-C(23)	116.5(9)
C(21)-C(22)-C(23)	122.0(10)	C(24)-C(23)-C(22)	120.9(11)
C(23)-C(24)-C(25)	120.5(11)	C(26)-C(25)-C(24)	122.2(11)
C(25)-C(26)-C(27)	117.0(10)	C(22)-C(27)-C(26)	122.5(9)
C(22)-C(27)-C(28)	117.2(8)	C(26)-C(27)-C(28)	120.2(9)
C(19)-C(28)-C(27)	120.2(8)	C(34)-C(29)-C(30)	118.2(10)
C(34)-C(29)-S	121.2(9)	C(30)-C(29)-S	120.5(8)
C(31)-C(30)-C(29)	118.2(11)	C(32)-C(31)-C(30)	123.4(13)
C(31)-C(32)-C(33)	117.5(11)	C(31)-C(32)-C(35)	120.3(14)
C(33)-C(32)-C(35)	122.3(13)	C(34)-C(33)-C(32)	121.7(12)
C(33)-C(34)-C(29)	121.0(12)		

Table 6. Torsion angles [°] for $C_{35}H_{27}NO_4S$.

O(1)-S-N-C(2)	-15.9(7)	O(2)-S-N-C(2)	-146.5(6)
C(29)-S-N-C(2)	99.3(7)	S-N-C(2)-C(1)	90.8(8)
S-N-C(2)-C(3)	-140.0(6)	O(4)-C(1)-C(2)-N	0.6(13)
O(3)-C(1)-C(2)-N	-177.7(7)	O(4)-C(1)-C(2)-C(3)	-126.8(10)
O(3)-C(1)-C(2)-C(3)	54.9(11)	N-C(2)-C(3)-C(4)	-70.5(10)
C(1)-C(2)-C(3)-C(4)	56.0(11)	N-C(2)-C(3)-C(8)	103.3(9)
C(1)-C(2)-C(3)-C(8)	-130.3(8)	C(8)-C(3)-C(4)-C(5)	-4.0(13)
C(2)-C(3)-C(4)-C(5)	169.7(8)	C(8)-C(3)-C(4)-C(19)	177.5(8)
C(2)-C(3)-C(4)-C(19)	-8.8(13)	C(3)-C(4)-C(5)-C(6)	2(2)
C(19)-C(4)-C(5)-C(6)	-179.3(9)	C(4)-C(5)-C(6)-C(7)	1(2)
C(5)-C(6)-C(7)-C(8)	-1(2)	C(6)-C(7)-C(8)-C(3)	-0.5(14)
C(6)-C(7)-C(8)-C(9)	177.5(9)	C(4)-C(3)-C(8)-C(7)	3.2(12)
C(2)-C(3)-C(8)-C(7)	-170.6(8)	C(4)-C(3)-C(8)-C(9)	-174.6(8)
C(2)-C(3)-C(8)-C(9)	11.6(12)	C(7)-C(8)-C(9)-C(10)	48.5(12)
C(3)-C(8)-C(9)-C(10)	-133.6(9)	C(7)-C(8)-C(9)-C(18)	-128.4(9)
C(3)-C(8)-C(9)-C(18)	49.5(13)	C(18)-C(9)-C(10)-C(11)	2.4(14)
C(8)-C(9)-C(10)-C(11)	-174.7(8)	C(9)-C(10)-C(11)-C(16)	-3(2)
C(9)-C(10)-C(11)-C(12)	177.5(9)	C(16)-C(11)-C(12)-C(13)	1(2)
C(10)-C(11)-C(12)-C(13)	-178.8(11)	C(11)-C(12)-C(13)-C(14)	-2(2)
C(12)-C(13)-C(14)-C(15)	2(2)	C(13)-C(14)-C(15)-C(16)	0(2)
C(10)-C(11)-C(16)-C(17)	2(2)	C(12)-C(11)-C(16)-C(17)	-178.0(9)
C(10)-C(11)-C(16)-C(15)	179.9(10)	C(12)-C(11)-C(16)-C(15)	0(2)
C(14)-C(15)-C(16)-C(11)	0(2)	C(14)-C(15)-C(16)-C(17)	177.5(12)
C(11)-C(16)-C(17)-C(18)	-2(2)	C(15)-C(16)-C(17)-C(18)	-179.2(11)
C(16)-C(17)-C(18)-C(9)	1(2)	C(10)-C(9)-C(18)-C(17)	-1.6(14)
C(8)-C(9)-C(18)-C(17)	175.3(9)	C(5)-C(4)-C(19)-C(28)	91.6(11)
C(3)-C(4)-C(19)-C(28)	-90.0(11)	C(5)-C(4)-C(19)-C(20)	-81.7(12)
C(3)-C(4)-C(19)-C(20)	96.8(12)	C(28)-C(19)-C(20)-C(21)	3(2)
C(4)-C(19)-C(20)-C(21)	176.3(10)	C(19)-C(20)-C(21)-C(22)	-4(2)
C(20)-C(21)-C(22)-C(27)	3(2)	C(20)-C(21)-C(22)-C(23)	-178.8(10)
C(27)-C(22)-C(23)-C(24)	-1(2)	C(21)-C(22)-C(23)-C(24)	-179.0(10)
C(22)-C(23)-C(24)-C(25)	4(2)	C(23)-C(24)-C(25)-C(26)	-5(2)
C(24)-C(25)-C(26)-C(27)	2(2)	C(21)-C(22)-C(27)-C(26)	176.1(9)
C(23)-C(22)-C(27)-C(26)	-2.3(14)	C(21)-C(22)-C(27)-C(28)	-1.6(14)
C(23)-C(22)-C(27)-C(28)	179.9(8)	C(25)-C(26)-C(27)-C(22)	2(2)
C(25)-C(26)-C(27)-C(28)	179.3(9)	C(20)-C(19)-C(28)-C(27)	-1.9(14)
C(4)-C(19)-C(28)-C(27)	-175.3(8)	C(22)-C(27)-C(28)-C(19)	1.2(13)
C(26)-C(27)-C(28)-C(19)	-176.6(9)	O(1)-S-C(29)-C(34)	-151.2(8)
O(2)-S-C(29)-C(34)	-19.8(10)	N-S-C(29)-C(34)	92.5(9)
O(1)-S-C(29)-C(30)	25.7(9)	O(2)-S-C(29)-C(30)	157.1(8)
N-S-C(29)-C(30)	-90.6(8)	C(34)-C(29)-C(30)-C(31)	-1(2)
S-C(29)-C(30)-C(31)	-177.6(8)	C(29)-C(30)-C(31)-C(32)	1(2)
C(30)-C(31)-C(32)-C(33)	-1(2)	C(30)-C(31)-C(32)-C(35)	177.9(11)
C(31)-C(32)-C(33)-C(34)	1(2)	C(35)-C(32)-C(33)-C(34)	-178.2(11)
C(32)-C(33)-C(34)-C(29)	0(2)	C(30)-C(29)-C(34)-C(33)	0(2)
S-C(29)-C(34)-C(33)	177.3(9)		

Table 7. Bond distances (Å) and angles (°) related to the hydrogen bonding for $C_{35}H_{27}NO_4S$.

(A-H···B)	A-B	A-H	H-B	A-H-B
O(3)-H(3)···O(4)[a]	2.744(8)	0.82	1.937(25)	168(11)

Symmetry transformations used to generate equivalent atoms:

a: -x,2-y,2-z

Short Intramolecular contact

N···O2	2.441(10)
N···O4	2.713(9)
HN···O2	2.586(10)
HN···O4	3.022(9)

Structure determination and refinement procedure for $C_{35}H_{27}NO_4S$

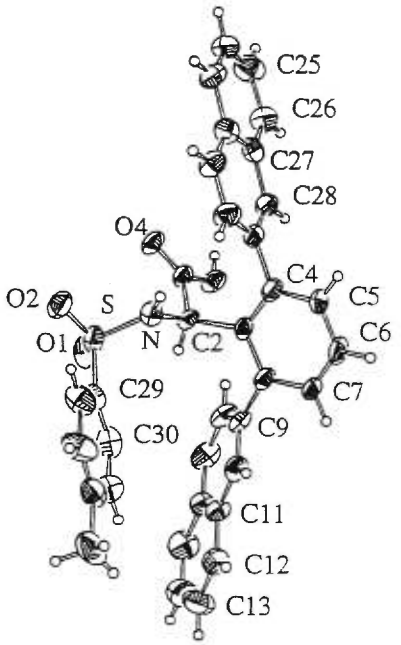
A single crystal was mounted in air on an Enraf-Nonius CAD-4 diffractometer at room temperature. 14 reflections found on a polaroid photograph were used by the indexing procedure to obtain a preliminary cell. The cell parameters reported in table 1 were obtained by least-squares refinement on the setting of the 25 reflections (2θ between 40.0 to 50.0°). A set of reflection sphere limited by $2\theta \leq 140°$ was collected. The orientation was checked every 400 measurements and intensity was checked every hour using five standard reflections. Variation of ±3.9% was observed during the collection of full data set.

Corrections were introduced for the Lorentz, polarization and absorption effects. The structure was solved by direct method using SHELXS86 (Sheldrick, 1985) and difmap synthesis using SHELXL93 (Sheldrick, 1993). All non-hydrogens atoms anisotropic, solvent excepted, hydrogen atoms isotropic.

The structure was refined on F_o^2 by full-matrix least-squares procedure. Individual weights based on counting statistics applied in the last cycles gave the refinement indicators presented. Hydrogen atoms were calculated at idealized positions using a riding model with different C-H distances for type of hydrogen. The isotropic displacement factors, U_{iso}, were adjusted to 50% higher value of the bonded carbon atom (methyl, amine) and 20% higher (others). The final ΔF map was essentially featurless. A general background below ±53e/Å^3 was observed.

The crystal structure is stabilized by intermolecular hydrogen bonds of the O-H...O type.

Examination of the structure with PLATON program (Spek, A. L. 1995) showed that there were no solvent accessible voids in the crystal lattice.



ORTEP view of the $C_{35}H_{27}NO_4S$ compound with the numbering scheme adopted. Ellipsoids drawn at 40% probality level. Hydrogens represented by sphere of arbitrary si

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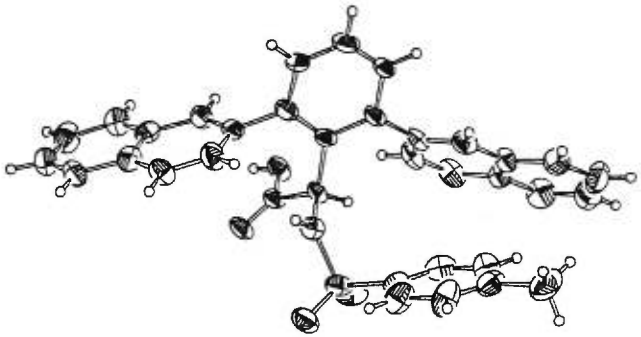

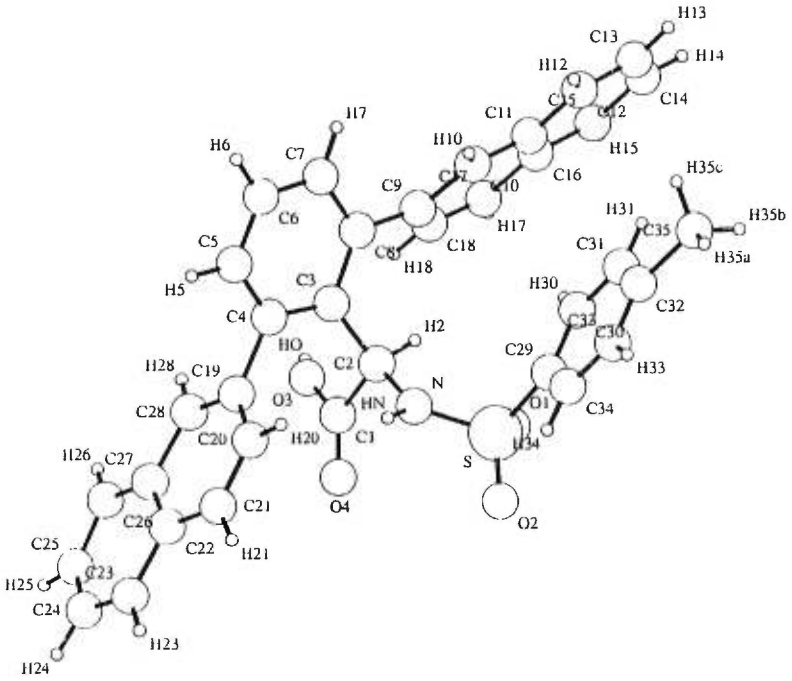
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C12
C14
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H6
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C10
H35c
H31
H35b
C6
H17
C35
C5
C18
C31
H35a
C8
H18
H5
C3
H30
C4
C32
HO
H2
C33
C30
C29
H28
C19
C2
H33
N
O3
HN
C28
D1
C34
C20
H20
C1
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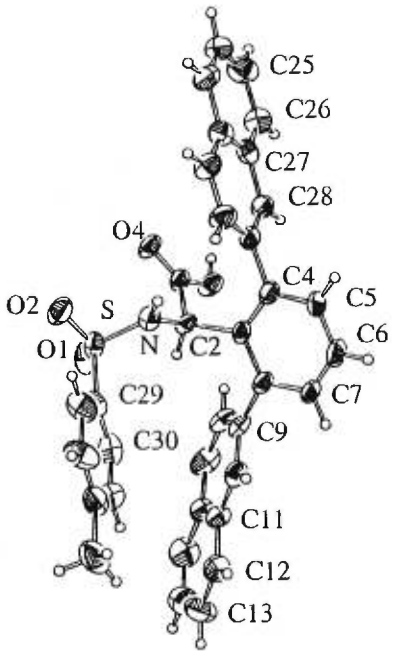
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C12
C13