Two Enantiodivergent Syntheses of Balanol and the Chemoenzymatic Synthesis of Oseltamivir

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Abstract

The present thesis outlines our latest findings on the reactivity of the Burgess reagent with oxiranes. Structural, mechanistic, and computational studies are presented. Included is the development of a (–)-menthyl version of the Burgess reagent and its application to the synthesis of enantiomerically pure β-amino alcohols. This methodology has been exploited in the formal enantiodivergent synthesis of the (+)- and (–)-isomers of balanol. Also described is a second generation approach to both balanol enantiomers; each commencing with the chemoenzymatic dihydroxylation of bromobenzene. This study also describes the steric and functional limitations of the toluene dioxygenase-mediated oxidation of benzoate esters. The metabolite derived from ethyl benzoate was employed in a formal synthesis of oseltamivir. Finally, several synthetic approaches to oseltamivir and its analogs are presented, each proceeding through a different vinyl aziridine derived from bromobenzene and ethyl benzoate.

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List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstroms
Ac	acetyl
AD	Anno Domini
AIBN	azobisisobutyronitrile
AIDS	acquired immune deficiency syndrome
alloc	allyloxycarbonyl
AMP	adenosine monophosphate
Arg	arginine
Asp	aspartic acid
atm	standard atmospheres
ATP	adenosine-5'-triphosphate
BC	before Christ
BIPHEP	biphenylphosphine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
CAS	camphorsulfonic acid
CBz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CNS	central nervous system
COD	cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
DAG	1,2-diacylglycerol
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide

DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartarate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
DMT	bis-(4-methoxyphenyl)phenylmethyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EC	Enzyme Commission
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron ionization
equiv	equivalent(s)
ER	endoplasmic reticulum
FDA	Food and Drug Administration
GC	gas chromatography
Glu	glutamic acid
GPCR	G protein-coupled receptor
GS	Gilead Sciences
h	hour(s)
HA	hemagglutinin

HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
Hz	hertz
IBX	2-iodoxybenzoic acid
Ile	isoleucine
IPTG	isopropyl β-D-1-thiogalactopyranoside
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
M	molar concentration
M*	(–)-menthyl
***m*CPBA**	*meta*-chloroperoxybenzoic acid
MEM	β-methoxyethoxymethyl
MHz	megahertz
min	minute(s)
MMPP	magnesium bis(monoperoxyphthalate) hexahydrate
MOM	methoxymethyl
MOP	2-methoxy-2-propyl
Moz	*p*-methoxybenzyl carbonyl
m.p.	melting point
Ms	methanesulfonyl
MS	mass spectroscopy
MTBE	methyl *tert*-butyl ether
NA	neuraminidase
NADH	nicotinamide adenine dinucleotide
NBA	*N*-bromoacetamide

NBS	*N*-bromosuccinimide
Neu5Ac	*N*-acetylneuraminic acid
Neu5Ac2en	2-deoxy-2,3-dehydro-*N*-acylneuraminic acid
NDO	naphthalene dioxygenase
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NP	nucleocapsid proteins
PAD	potassium azodicarboxylate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
PG	prostaglandin
PIP_2	phosphoinositol-4,5-bisphosphate
Piv	pivaloyl
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	part per million
Pr	propyl
PS	phosphatidylserine
PSI	pounds per square inch
***p*-TSA**	*p*-toluenesulfonic acid
pyr	pyridine
RNA	ribonucleic acid
r.t.	room temperature
SAR	structure-activity relationship
SES	2-(trimethylsilyl)ethanesulfonyl
SM	starting material
SMEAH	sodium bis(2-methoxyethoxy)aluminum hydride

TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TDO	toluene dioxygenase
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	trimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
TPS	triphenylsilyl
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
Tr	triphenylmethyl
Trp	tryptophan
Ts	*p*-toluenesulfonyl
TSA	*p*-toluenesulfonic acid
Tyr	tyrosine
USD	United States dollars

1. Introduction

The majority of natural products and other compounds targeted by synthetic organic chemists contain at least one chiral carbon center. Early accomplishments, such as equilenin[1] and quinine,[2] have relatively few chiral atoms; two and four respectively. The most complex molecules synthesized to date, highlighted by the linear polycyclic ether marine toxins including the brevetoxins, contain more than 20 stereogenic centers. Without exception all of the chiral carbon atoms in such synthesized molecules are incorporated through use of either chiral starting materials or chiral reagents. Optically active starting materials have traditionally included amino acids, sugars and alkaloids isolated from natural sources. The stereoselectivity of chiral reagents, either organic or metal based, arises from steric and electronic effects operating during the mechanistic pathway of the reaction.

The central dogma of synthetic organic chemistry is that the discovery and application of asymmetric materials and reagents will lead to the synthesis of new target molecules, and will improve the brevity of previously accomplished syntheses. The Hudlicky group has always followed this philosophy in the pursuit of synthetically challenging alkaloids. The present study outlines our work on the synthesis of two molecules, namely balanol **(1)** and oseltamivir **(2)**. An enantiodivergent synthesis of the former will be achieved through the development of an asymmetric version of the Burgess reagent **3**, whose reaction with 1,3-cyclohexadiene oxide **(4)** provides *syn*-sulfamidates **5** (Figure 1). Balanol will also be prepared through the application of a homochiral diene diol **6** derived from the enzymatic dihydroxylation of bromobenzene.

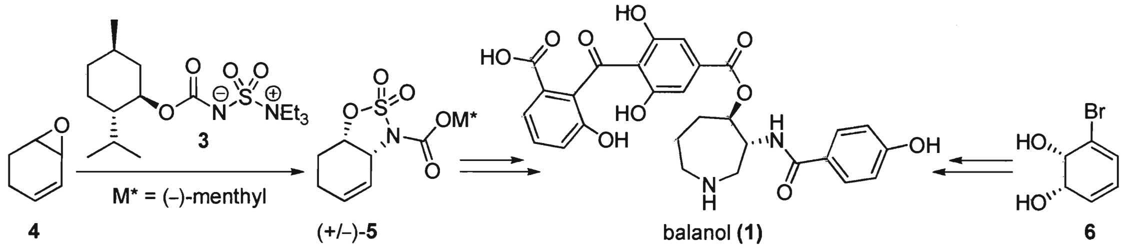


Figure 1. Two synthetic routes to balanol **(1)**

Our isolation and identification of the homochiral diol **7** from the fermentation of ethyl benzoate yields an asymmetric compound suitable for the synthesis of oseltamivir **(2)** (Figure 2).

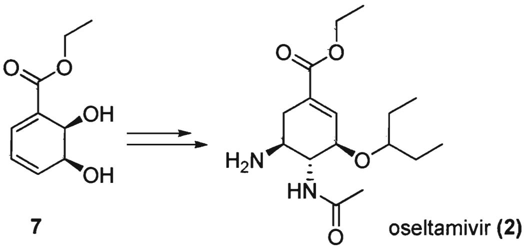


Figure 2. Synthetic route to oseltamivir **(2)**

The Burgess reagent **(8)** was originally designed and used as a mild dehydrating agent for secondary and tertiary alcohols.[4-7] The Hudlicky group's work with the Burgess reagent **(8)** began in 2003 with the discovery that oxiranes **10**, originally thought to be inert to the reagent,[3] reacted to form cyclic *syn*-sulfamidates **9** (Figure 3).[8] The present study evaluates the mechanistic options of the Burgess reagent **(8)** in its reactions with oxiranes and 1,2-diols to form 5- and 7-membered cyclic sulfamidates.

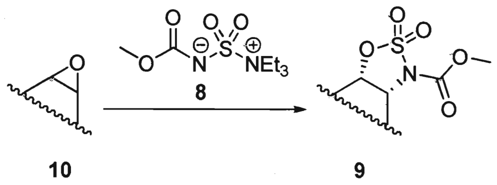


Figure 3. Reaction of the Burgess reagent **(8)** with oxiranes

It was theorized that replacement of the methoxy functionality with an asymmetric auxiliary group would lead to a pair of *syn*-sulfamidate diastereomers (+/–)-**11**. The present study outlines our development of a (–)-menthyl version of the Burgess reagent **3** and explores its reactions with epoxides **10**. The products of this reaction are separable by column chromatography and thus give access to both *cis*- and *trans*-β-amino alcohols **12a** and **12b** in enantiomerically pure forms (Figure 4). An effective application of this methodology will be presented in the enantiodivergent synthesis of the fungal metabolite (–)-balanol **(1)** with the *R*,*R* stereochemistry, and its *S*,*S* enantiomer (+)-balanol.

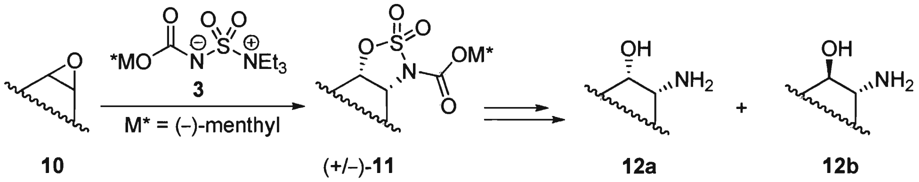


Figure 4. Synthesis of enantiomerically pure *cis*- and *trans*-β-amino alcohols **12a/b**

In the early 1990's Sphinx Pharmaceuticals, now part of Eli Lilly and Company, isolated balanol **(1)** from the *Verticillium balanoides* species of fungi.[9] Subsequent assays revealed its potent inhibitory activity against members of the protein kinase C (PKC) family of isozymes. The overactivity of PKCs have been implicated in a number of diseases including arthritis, diabetes, and some types of cancer.[10] Potent and selective inhibitors of PKC, such as balanol, have wide-ranging therapeutic potential.[11]

The first strategy discussed will take advantage of the sulfamidate diastereomers **5a/b** produced from reacting vinyl oxirane **4** with the (–)-menthyl version of the Burgess reagent **8**. The desired *trans* functionality will be achieved through inversion of the sulfamidate oxygen (Figure 5). An oxidative cleavage and reductive amination procedure will be employed in order to form the azepane functionality. Removal of the chiral auxiliary group and subsequent fictionalization will allow for the synthesis of both the naturally occurring (–)-isomer and unnatural (+)-isomer of balanol **(1)** from a single achiral starting material.

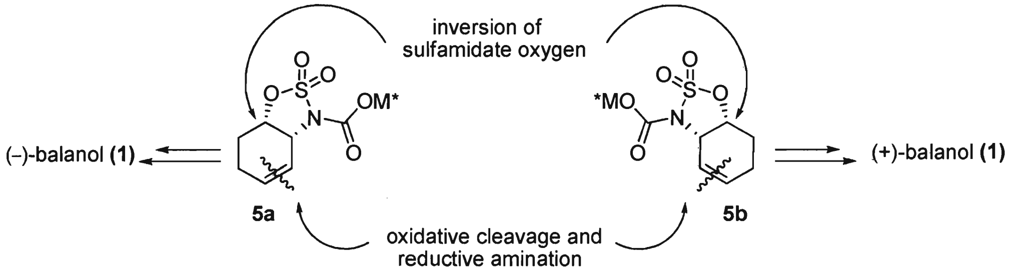

inversion of sulfamidate oxygen
OM*
*MO
(–)-balanol (1)
(+)-balanol (1)
5a
5b
oxidative cleavage and reductive amination

Figure 5. Strategy for the enantiodivergent synthesis of (–)- and (+)-balanol from vinyl sulfamidates **5a/b**

Our second generation approach will initiate from the homochiral cyclohexadiene-*cis*-1,2,-diol **6** obtained from the toluene dioxygenase (TDO) mediated dihydroxylation of bromobenzene. This reaction is performed by a recombinant *Escherichia coli* strain, developed by Dr. David Gibson, which overexpresses the TDO genes.[12-13] Many *cis*-dihydrodiol metabolites, isolated from the whole-cell fermentation of arene substrates, have been employed by the Hudlicky group and others in the enantioselective synthesis of a number of naturally occurring products.[14]

The strategy presented in this thesis relies on the preparation of diastereomeric aziridines **13** and **14** from *cis*-dihydrodiol **6**. Both vinyl aziridines are susceptible to regioselective openings with oxygen nucleophiles (Figure 6). This is followed by saturation of the vinyl bromide moiety, oxidative cleavage of the 1,2-diol and a reductive amination protocol.

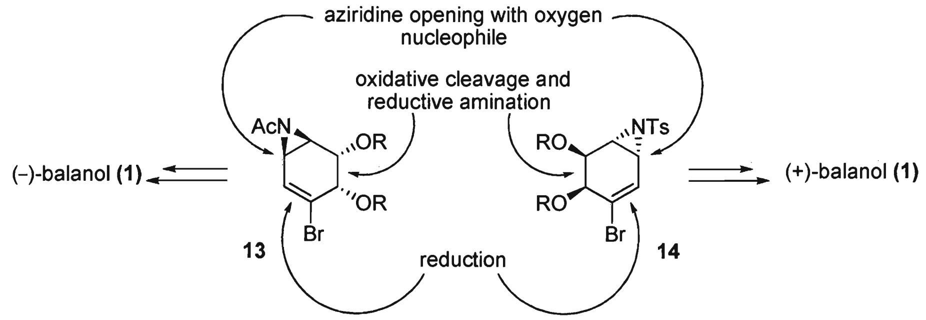

aziridine opening with oxygen nucleophile
oxidative cleavage and reductive amination
AcN
OR
OR
Br
RO
NTs
RO
Br
(-)-balanol (1)
(+)-balanol (1)
13
14
reduction

Figure 6. Strategy for the enantiodivergent synthesis of (–)- and (+)-balanol from vinyl aziridines **13** and **14**

This study will also focus on a new series of *cis*-cyclohexadiene diols **16** derived from the enzymatic dihydroxylation of various benzoate esters **15** (Figure 7).

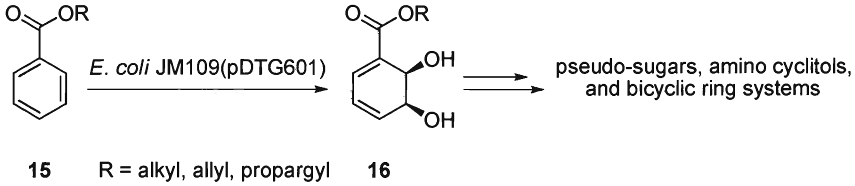
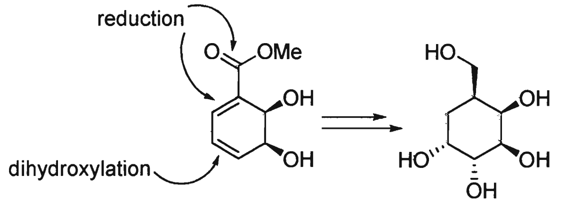

O
OR
E. coli JM109(pDTG601)
O
OR
OH
OH
pseudo-sugars, amino cyclitols, and bicyclic ring systems
15
R = alkyl, allyl, propargyl
16

Figure 7. TDO catalyzed oxidations of benzoates to *cis*-dihydrodiols

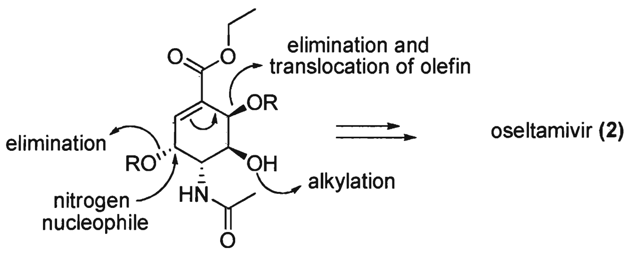
Investigations into the steric and functionality limitations of the TDO-catalyzed dihydroxylation of benzoate esters are discussed. The absolute stereochemistry of the diol metabolites **16** will be established by comparing the physical properties of their derivatives with those of known compounds. The versatility of the metabolites as intermediates in the synthesis of pseudo-sugars, amino cyclitols and bicyclic ring systems will be evaluated. Specifically, a short enantioselective synthesis of carba-α-L-galactopyranose **(17)** from the TDO-catalyzed oxidation product of methyl benzoate **18** is discussed. This pseudo-sugar will be synthesized through reduction of the acrylate and ester functionalities in addition to a stereoselective dihydroxylation reaction (Figure 8).


reduction
O
OMe
OH
OH
dihydroxylation
HO
OH
HO
OH
OH

18 carba-α-L-galactopyranose **(17)**

Figure 8. Strategy for the synthesis of carba-α-L-galactopyranose **(17)**

Highlighting the value of these metabolites will be the synthesis of oseltamivir **(2)** from the *cis*-dihydrodiol derived from ethyl benzoate **(7)**. Tamiflu (phosphate salt of oseltamivir) is an essential antiviral drug in the treatment[15] and prophylaxis[16] of the influenza viruses, especially the avian H5N1 and H9N2 strains.[17] Our approach to oseltamivir **(2)** converts *cis*-dihydrodiol **7** into derivative **19**, which possesses an amide *anti* in relation to the stereochemistry of the diol (Figure 9). Translocation of the acrylate olefin, introduction of the *trans* nitrogen functionality, and alkylation of the distal hydroxyl gives access to the target molecule.


O
O
elimination and
translocation of olefin
OR
elimination
RO
OH
alkylation
nitrogen
nucleophile
HN
O
oseltamivir (2)

19

Figure 9. Strategy for the synthesis of oseltamivir **(2)**

The final portion of this thesis will discuss our approach to the synthesis of several oseltamivir **(2)** analogs. The two examples presented aim to replace the amide functionality with a 4-toluenesulfonyl and an *N*-tert-butoxycarbonyl group.

2. Historical

The following historical chapter is divided into four sections which cover; 1. the Burgess reagent, 2. balanol, 3. enzymatic dihydroxylations of arene substrates, and 4. oseltamivir. The reactivity of the Burgess reagent and its application in synthesis are reviewed. The existing synthetic routes to balanol, a fungal metabolite with significant activity against protein kinase C, will be evaluated. The substrate specificity of the toluene dioxygenase enzyme and the known metabolites are discussed. Finally, the previous syntheses of the anti-influenza agent oseltamivir are assessed in detail.

2.1 Burgess Reagent

The Burgess reagent was originally employed in the dehydration of secondary and tertiary alcohols and the production of urethanes from primary alcohols. Subsequently, it was demonstrated to be useful in a variety of other transformations leading to numerous additional functionalities. Furthermore, the reactivity of the Burgess reagent has been exploited in the synthesis of several natural products and other complex molecules.

2.1.1 Discovery and Initial Applications

During his work on the cycloadditive reactivity of electrophilic *N*-sulfonylamines with olefins, Edward M. Burgess described the preparation of ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt **(20)** and its reaction with tetramethylallene **(21)** to form isomeric cycloadducts **22** and **23** (Figure 10).[18]

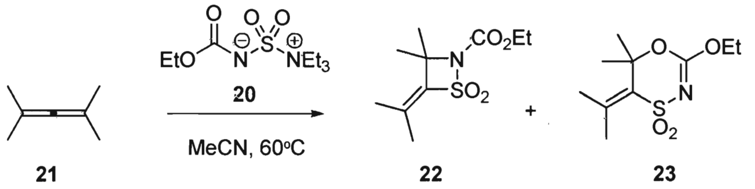


Figure 10. Cycloadditions of inner salt **20** with tetramethylallene **(21)**.[18]

Also included were the reactions with aniline **(24)**, 2-propanol **(25)**, and *N*-vinylpyrolidinone **(26)** in benzene to produce sulfamide **27**, sulfamate **28**, and vinyl pyrrilidone **29** respectively (Figure 11).

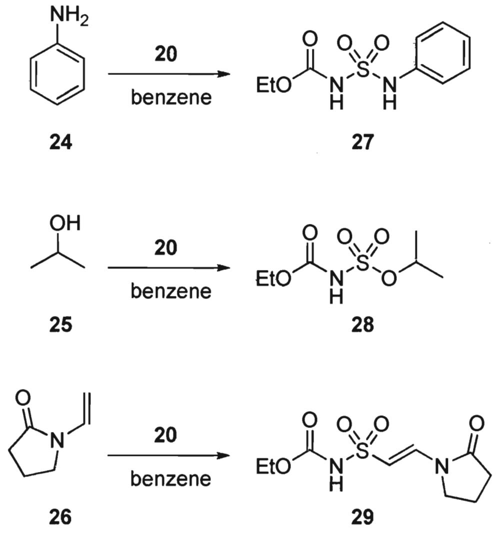


Figure 11. Reactions of ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt **(20)**.[18]

Soon after, Burgess reported the preparation of the methyl(carboxysulfamoyl) triethylammonium hydroxide inner salt **(8)**, a reagent that now bears his name. He demonstrated its use in the dehydration of secondary and tertiary alcohols.[19] Burgess described inner salt **8** as means to produce, upon reaction with alcohols, *N*-carboalkoxysulfamate anions **35**, whose intramolecular elimination produced olefins in high yields (Figure 12). As a probe of the stereochemical requirements, the dehydration of *erythro*- **(30)** and *threo*-2-deuterio-1,2-diphenyl ethanol **(31)** was examined. The former produced only *trans*-stilbene **(32)**, while the latter gave only protio-*trans*-stilbene **(33)**. These results supported a *syn*-elimination mechanism.

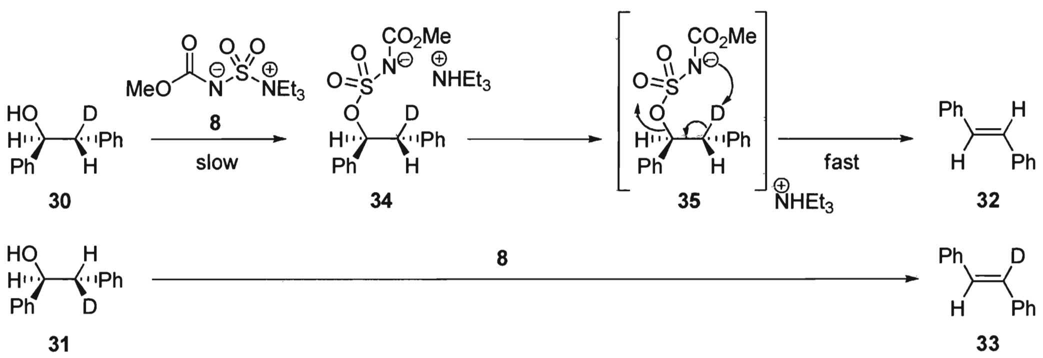


Figure 12. Kinetic and stereochemical considerations of the Burgess reagent **(8)**.[19]

It was suggested that formation of the initial ion pair **34** is rate determining, followed by a relatively fast *cis*-β-proton transfer to create the olefin. Consistent with this kinetic and stereochemical prediction was a small, but measurable, kinetic isotope effect. As expected, when tertiary alcohols are treated with the Burgess reagent **(8)**, product formation follows Zaitsev's rule in the majority of cases.

In contrast to the dehydration of secondary and tertiary alcohols, primary alcohols **36** react to form carbamates **37** (Figure 13). This is understandable considering that the S_Ni pathway is energetically favourable compared to the Ei elimination during decomposition of the triethylammonium *N*-carboalkoxysulfamate **38**.

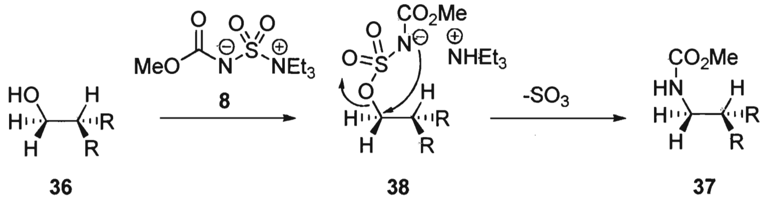


Figure 13. Burgess reagent-mediated carbamate formation from primary alcohols

Burgess also demonstrated that allylic alcohol **39** reacts with the Burgess reagent **(8)** to form intermediate **40** which can either produce diene **41** or carbamate **42** depending on the reaction conditions utilized (Figure 14). The former is produced at room temperature as a triglyme solution, while the latter results from thermal decomposition in solid form at 80°C. After his initial reports, Burgess published more comprehensives accounts on the synthesis of olefins from secondary and tertiary alcohols and urethanes from primary alcohols.[20,21]

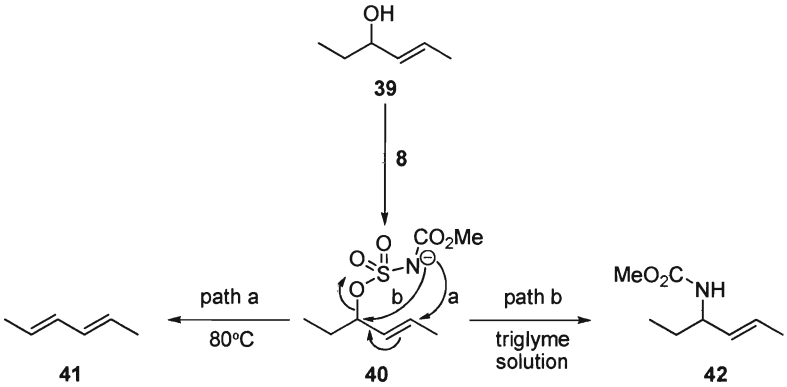


Figure 14. Reactivity of allylic alcohol **39** with the Burgess reagent **(8)**

2.1.2 Accessible Functionalities

In addition to the aforementioned transformations, the Burgess reagent **(8)** has been used in the preparation of many other functional groups.[22] The first reaction reviewed is the dehydration of primary amides **43** to the corresponding nitriles **44** first described by Claremon and Phillips (Figure 15).[23] These reactions proceed with excellent chemoselectivity, resulting from the relatively fast kinetic formation of **45**. The production of nitriles was demonstrated to be selective over epoxide openings and dehydration of secondary alcohols.

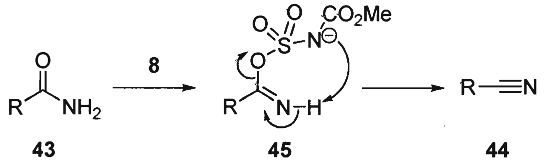


Figure 15. Conversion of primary amides to nitriles.[23]

During an investigation into the dehydration of β-trialkylsilyloxyformamides, McCarthy encountered undesired desilylations when traditional halide-based system were employed. Out of necessity, he developed a method to dehydrate formamides **46** to isocyanides **47** through application of the Burgess reagent **(8)** (Figure 16).[24]

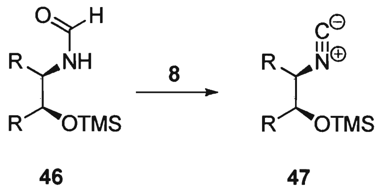


Figure 16. Synthesis of isocyanides from formamides.[24]

Nitrile oxides readily undergo 1,3-dipolar cycloadditions with alkenes to create isoxazolines. In most cases the nitrile oxide species is generated *in situ* in the presence of a dipolarophile.[25] Mioskowski published a method for the preparation of nitrile oxides **48** from primary nitroalkanes **49** (Figure 17).[26] In the presence of a terminal alkene **50**, the corresponding isoxazolines **51** were obtained in moderate yield, with some dimerization of **48** occurring.

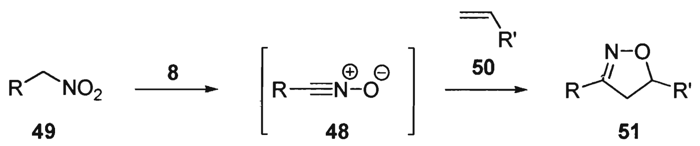
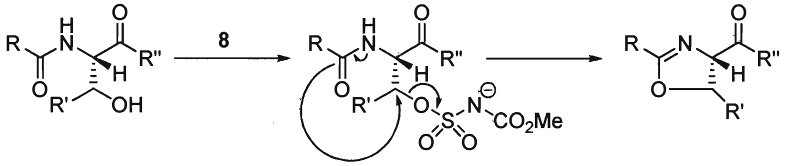


Figure 17. Isoxazoline **51** formation from nitroalkanes **49** via a nitrile oxide intermediate **48**

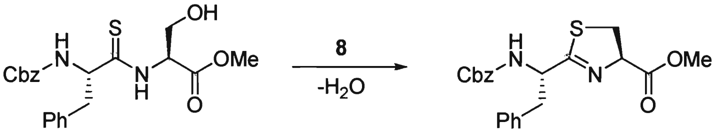
Wipf developed a cyclodehydration method to produce a variety of heterocycles through use of the Burgess reagent (**8**). First to be developed was a protocol for the synthesis of 4,5-dihydrooxazolines **52** from β-hydroxy-α-amino acids **53** via cyclodehydration of intermediate **54** (Figure 18).[27] Peptide analogs of serine and threonine were converted to dihydrooxazolines without any detectable side products, in contrast to the traditional Mitsunobu conditions attempted.[28]



53 **54** **52**

Figure 18. Synthesis of dihydrooxazolines **52** from β-hydroxy-α-amino acids **53**.[27]

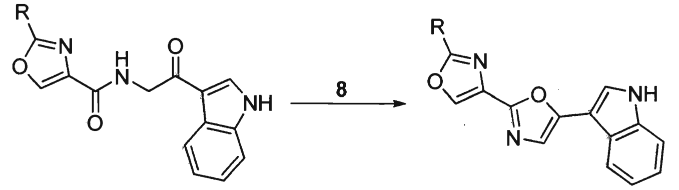
Wipf has also prepared a series of thiazoline peptide analogs using a similar methodology.[29] The Burgess reagent (**8**) was used to facilitate the rapid formation (~10 mins) of thiazoline ring **55** from β-hydroxythioamide **56** (Figure 19). The reaction proceeds without any epimerization of the C2 position. The same reaction under TsCl/NEt$_3$, SOCl$_2$ or Mitsunobu conditions suffer from low yields in addition to the undesired epimerization.[30]



56 **55**

Figure 19. Formation of thiazoline rings **55** from β-hydroxythioamides **56**.[28]

Magnus used Wipf's cyclodehydration procedure on several 2-acylamino ketones **57** while synthesizing oxazoline rings **58** (Figure 20).[31]

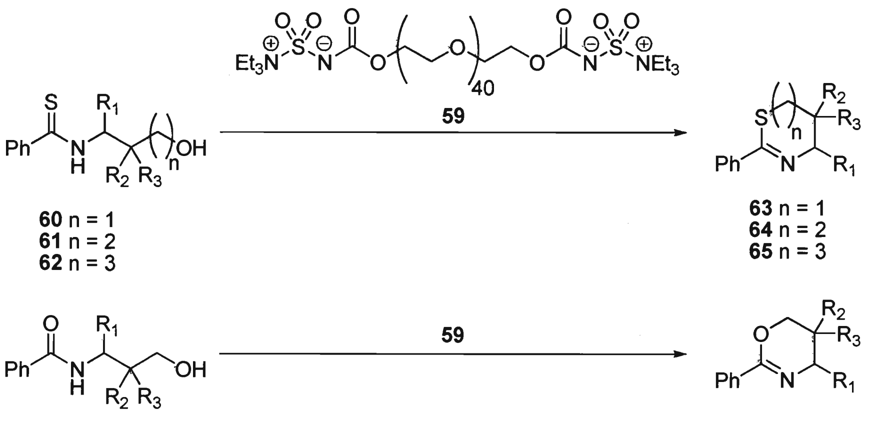


57

58

Figure 20. Synthesis of oxazolines **58** from 2-acylamino ketones **57**.[31]

In 1996, Wipf developed a poly(ethylene glycol)-linked version of the Burgess reagent **59** and employed it in the cyclodehydrations of β-hydroxyamides **53** and β-hydroxythioamides **56** to again form 4,5-dihydrooxazolines **52** and thiazolines **55**.[32] Increased yields were obtained with this PEG version of the Burgess reagent; attributed to improved solubility and stability. Soon after, the PEG-Burgess reagent **59** was used to cyclize γ- **60** and δ- **61** and ε-hydroxythioamides **62** to their corresponding 6-, 7-, and 8-membered heterocycles, **63**, **64** and **65** respectively (Figure 21).[33] Unfortunately, only the γ -hydroxyamides **66** could be successfully converted into dihydrooxazines **67**.



60 n = 1
61 n = 2
62 n = 3

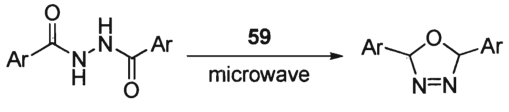
63 n = 1
64 n = 2
65 n = 3

66

67

Figure 21. Synthesis of 6-, 7- and 8-membered heterocycles.[33]

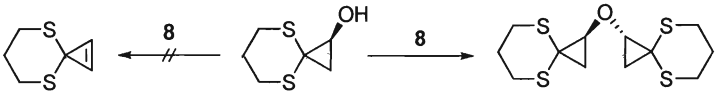
Brain extended the methodology of the PEG-Burgess reagent **59** to include the preparation of 1,3,4-oxadiazoles **68** from 1,2-diacylhydrazines **69** using a microwave reaction vessel (Figure 22).[34]



69 **68**

Figure 22. Synthesis of 1,3,4-oxadiazoles **68** from 1,2-diacylhydrazines **69**.[34]

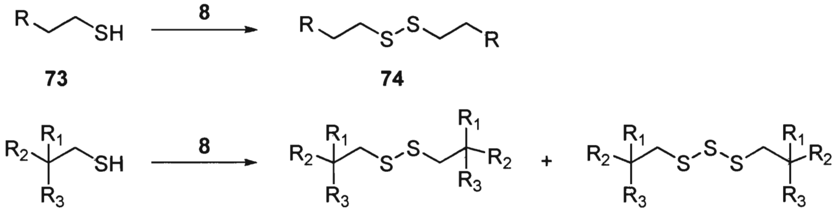
In some instances the Burgess reagent's reactivity can be quite unpredictable. While attempting to dehydrate cyclopropanol **70**, Schwarz isolated the unusual etherified product **71** instead of olefin **72** (Figure 23).[35]



72 **70** **71**

Figure 23. Unexpected etherification of cyclopropanol **70**.[35]

Similar unexpected reactivity was observed by Hudlicky while attempting to react the Burgess reagent (**8**) with primary thiols **73**.[36] Unexpectedly, disulfides **74** were produced from primary thiols, while secondary and tertiary thiols **75** also produced disulfides **77**, in addition to some trisulfides **76** (Figure 24).



R_1 = alkyl
R_2 = alkyl
R_3 = alkyl or H

Figure 24. Synthesis of disulfides **74** and **77** and trisulfides **76**.[36]

Miller has successfully employed the Burgess reagent **(8)**, and its PEG version **59**, in the synthesis of nitriles **79** from aromatic aldoximes **78**.[37]

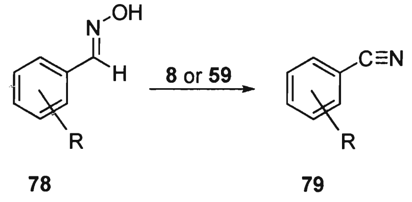

N
OH
H
8 or 59
C≡N
R
R
78
79

Figure 25. Synthesis of nitriles **79** from aldoximes **78**.[37]

Makara explored the reactivity of the Burgess reagent (**8**) against aryl carboxylic acids **80**.[38] The resulting mixed sulfocarboxy anhydrides **81** were treated with primary amines **82** to yield acyl ureas **83** and amides **84** (Figure 26). The ratio of the two products was dependent on temperature and the use of microwave conditions.

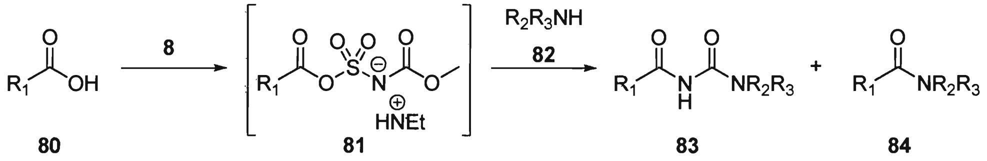
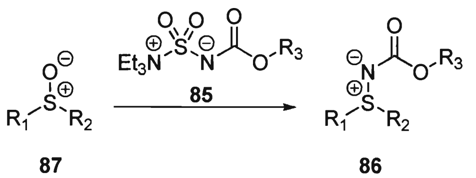

O
R1
OH
8
80
O
O
O
O
R1
O
S
N
O
HNEt
81
R2R3NH
82
O
O
R1
N
H
NR2R3
83
+
O
R1
NR2R3
84

Figure 26. Preparation of acyl ureas **83** and amides **84** from carboxylic acids **80**.[38]

Raghavan prepared several different Burgess analogs **85** and employed them in the synthesis of sulfilimines **86** from sulfoxides **87** (Figure 27).[39] The carbamate portion of the sulfilimines is can be varied by changing the carbamate portion of the Burgess reagent (R_3).


O
S
R1
R2
87
O
O
O
Et3N
S
N
O
R3
85
O
N
O
R3
S
R1
R2
86

R_3 = allyl, benzyl, Me or CH_2Cl_3

Figure 27. Preparation of sulfilimines **86** from sulfoxides **87**.[39]

Li used the cyclodehydration ability of the Burgess reagent (**8**) to create *N*-bridged-5,6-bicyclic pyridines **88**, including pyrolo-, imidazo- and triazolopyridines, from pyridines **89** (Figure 28).[40]

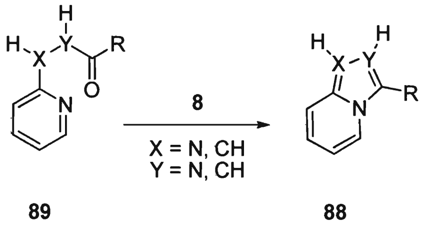


Figure 28. Preparation of pyrolo-, imidazo- and triazolopyridines **88**, from pyridines **89**.[40]

Other uses for the Burgess reagent (**8**) include the one-step production of carboxybenzyl (CBz) carbamates from primary alchols,[41] oxidation of benzoins to benzils,[42] and the conversion of Baylis-Hillman adducts into carbamates of unsaturated β-amino acids.[43]

The Nicolaou group has utilized the Burgess reagent in the synthesis of a variety of sulfonyl-containing heterocycles.[44] The first to be disclosed was the preparation of sulfamidates **90** (major) and **91** (minor) from 1,2-diols **92** (Figure 29).[45] A series of chiral 1,2-diols **92** were prepared from styrene, via Sharpless asymmetric dihydroxylation, and treated with the Burgess reagent (**8**). Production of the sulfamidates proceeded with excellent regio- and stereoselectivity except when strong electron withdrawing groups were present (R = NO_2, CF_3). Acidic hydrolysis of the sulfamidates gave clean conversion to the corresponding β-amino alcohols **93** and **94**.

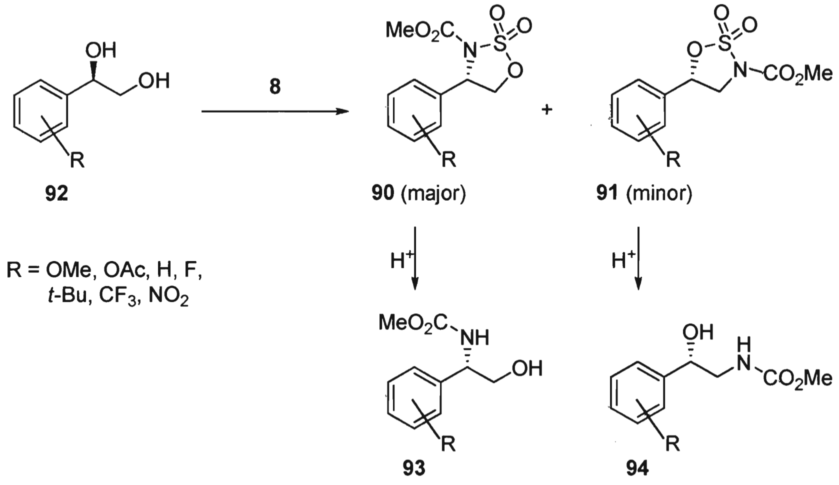


Figure 29. Two step synthesis of β-amino alcohols **93** and **94** from 1,2-diols **92**.[45]

Nicolaou subjected epoxy alcohols **95** and **96** to the Burgess reagent **(8)** and found that, upon displacement of triethylamine, the intramolecular epoxide opening could be directed by the substituent at the C3 position (methyl in **96**). The products were either 5- or 6-membered sulfamidates, **97** or **98** respectively (Figure 30).

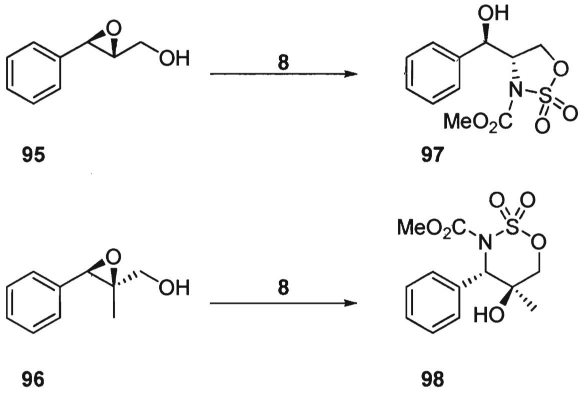
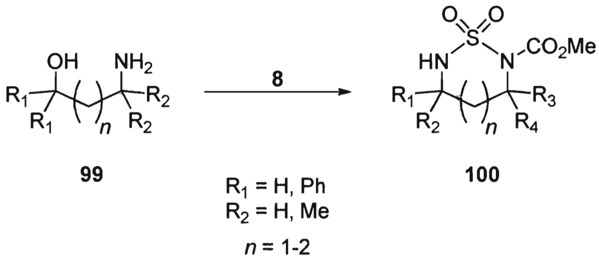


Figure 30. Synthesis of 5- and 6-membered sulfamidates from epoxy alcohols **95** and **96**.[44]

Drawing from their work with 1,2-diols, the Nicolaou group attempted the same protocol on 1,2-aminoalcohols **99** (Figure 31).[46] Unsubstituted sulfamides **100** were produced from primary amines, while mono-substituted sulfamides were also prepared from various secondary amines.



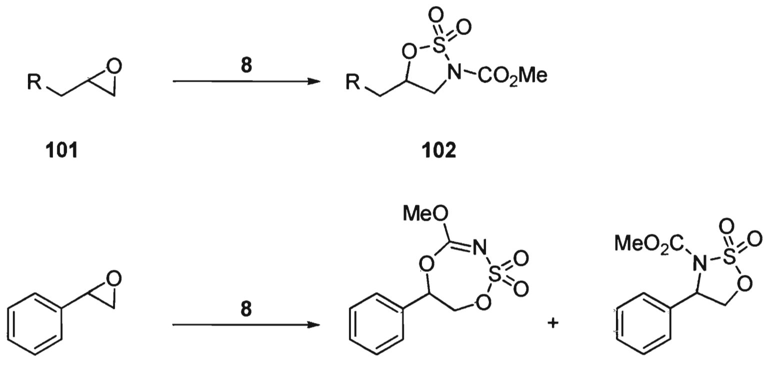
99

100

R_1 = H, Ph
R_2 = H, Me
n = 1-2

Figure 31. Synthesis of sulfamides **100** from 1,2-aminoalcohols **99**.[46]

In 2003, the Hudlicky group published preliminary work on the reactions of epoxides with the Burgess reagent **(8)**.[47] Originally thought to be inert to the Burgess reagent,[48] it was demonstrated that epoxides yielded cyclic sulfamidates. Aliphatic epoxides **101** yield 5-membered cyclic sulfamidates **102** while styrene oxide **(103)** gave mostly 7- membered sulfamidate **104** and only trace amounts of 5-membered sulfamidate **105** (Figure 32).



101

102

103

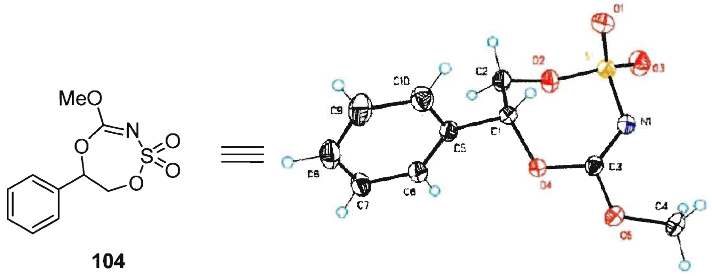
104 (major)

105 (minor)

Figure 32. Synthesis of 5- and 7-membered cyclic sulfamidates from epoxides.[47]

Initially it was though that **104** was the minor regioisomer **91** (Figure 29) obtained by Nicolaou through reaction of the Burgess reagent with styrene diol **92**. However, the

IR of **104** lacked a carbonyl signal at ~1600 cm^{-1}, indicating that another functionality was present (e.g. C=N double bond). Adding to the confusion, an authentic sample of **91** was obtained from the Nicolaou group and found to be identical to **104**. Ultimately, an x-ray crystal structure established that the structure of the minor product is the 7-membered sulfamidate **104** and not the regioisomer **91** (Figure 33).



104

Figure 33. X-ray crystal structure of sulfamidate **104**.[47]

Nicolaou and Hudlicky proposed mechanisms for the formation of *trans*-fused cyclic sulfamidates **106** from 1,2-diols **107**[45] and oxiranes **108**[47] respectively (Figure 34). In the first case, each alcohol of **107** attacks an equivalent of the Burgess reagent **(8)** displacing triethylamine and forming intermediate **109**. This is followed by S_N2 displacement at the more activated position. In the second case, epoxide **108** is opened with one equivalent of the Burgess reagent **(8)**, followed by attack of the oxyanion **110** on the sulfamidate.

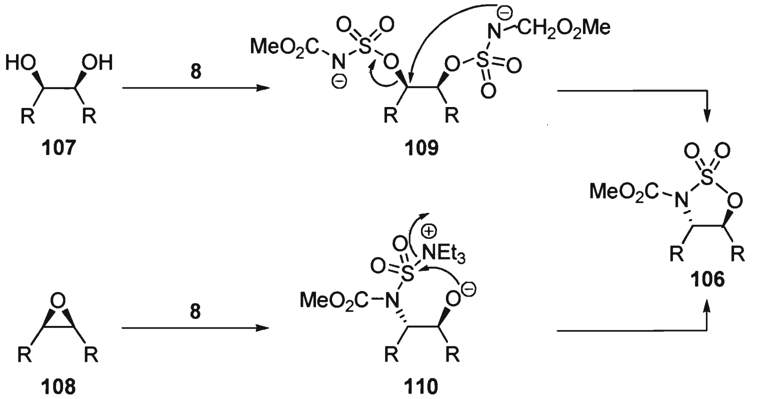


Figure 34. Proposed mechanism for formation of *trans*-sulfamidate **106** from 1,2-diol **107** and epoxide **108**.[45,47]

Hudlicky also proposed a route to the 7-membered sulfamidate **104** from either styrene diol **111** or styrene oxide (**103**).[47] The diol **111** reacts with the Burgess reagent (**8**) to form intermediate **112**, which undergoes an intramolecular deprotonation to give **113** (Figure 35). The resulting oxyanion then eliminates the sulfamidate to form styrene oxide **103**. The 7-membered sulfamidate **104** arises from opening of the epoxide with the resonance hybrid form of the Burgess reagent **8a** and subsequent elimination of triethylamine.

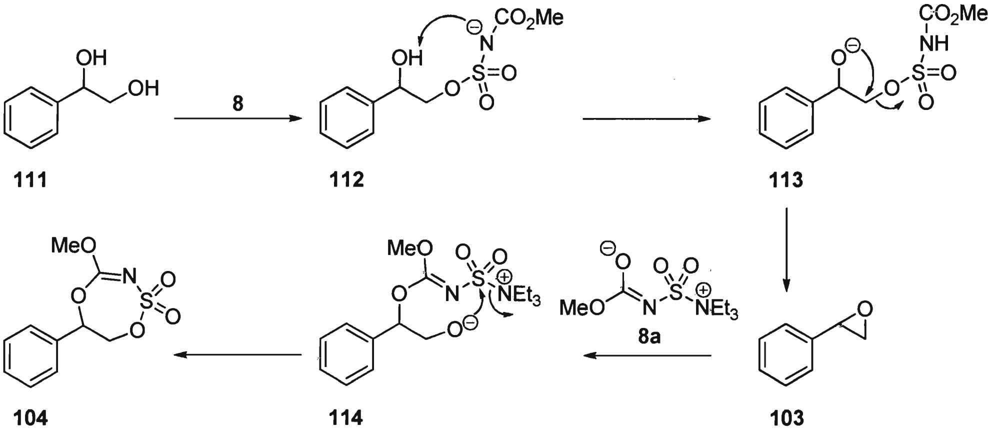


Figure 35. Proposed mechanism for the formation of 7-membered sulfamidate **104** from 1,2-diols and epoxides.[47]

2.1.3 Application of the Burgess Reagent in Synthesis

Since its discovery, the Burgess reagent **(8)** has proven to be a highly useful tool in the synthesis of complex molecules. It is soluble in most common organic solvents, even non-polar ones, despite its zwitterionic character. Many of its reactions are performed at room temperature and neutral pH. These characteristics, in addition to the wide variety of accessible functional groups, have been exploited in several syntheses.

The first application of the Burgess reagent **(8)** in synthesis was reported by Crabbé in 1970.[49] Dehydration reactions were performed on steroidal alcohols substrates, such as 3α-hydroxy-5α-androstan-17-one **(115)**, to give their corresponding olefins (Figure 36).

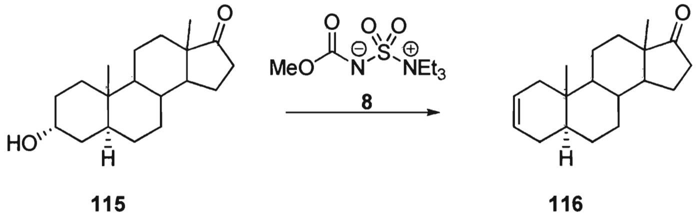
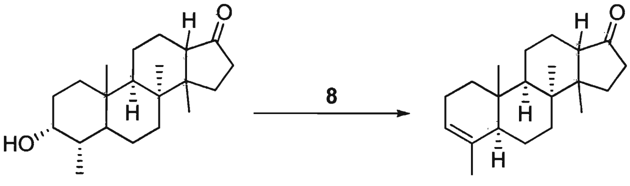


Figure 36. Dehydration of steroidal alcohols.[49]

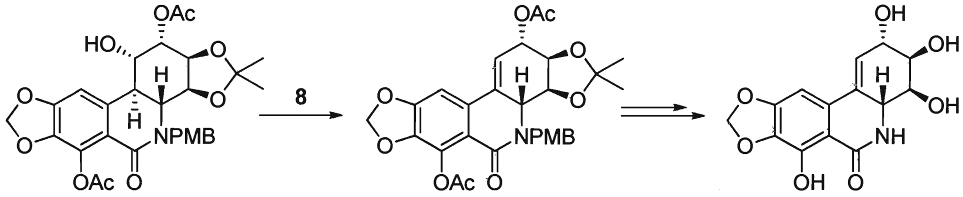
Capri also employed the Burgess reagent **(8)** in the dehydration of steroidal alcohols. One example, steroid **117**, appeared to have undergone a *trans*-dehydration to olefin **118** (Figure 37).[50] The authors acknowledge that this mechanism is doubtful, and in all likelihood a *cis*-elimination was followed by isomerisation to the more substituted olefin.



117 **118**

Figure 37. Apparent *trans*-dehydration of steroidal alcohol.[50]

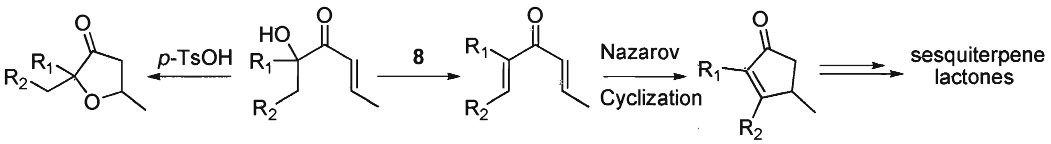
Rigby employed the Burgess reagent **(8)** in the total synthesis of (+)-narciclasine **(119)**.[51] The selective *cis*-dehydration of alcohol **120** produced allylic acetate **121**, a difficult transformation to perform under standard acidic dehydration conditions.



120 **121** **119**

Figure 38. Rigby's synthesis of (+)-narciclasine **(119)**.[51]

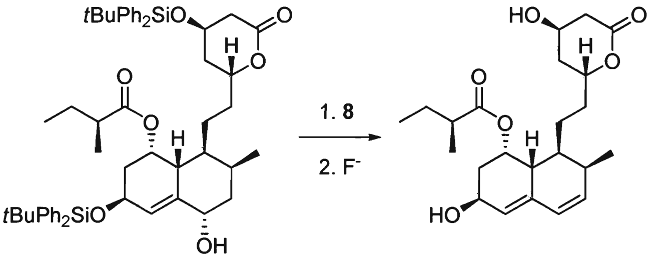
The mild dehydrations facilitated by the Burgess reagent **(8)** have been frequently used in the total synthesis of various terpene-type molecules. While investigating the synthesis of several sesquiterpene lactones, Jacobson encountered problems trying to produce the precursors for Nazarov cyclizations of **122**.[52] Treatment of alcohol **123** with *p*-toluenesulfonic acid resulted in the production of hydrofuranone **124** and not the desired diene **122** (Figure 39). This problem was circumvented through the use of the Burgess reagent **(8)**.


p-TsOH
8
Nazarov
Cyclization
sesquiterpene lactones

124 **123** **122** **125**

Figure 39. Jacobson's synthesis of sesquiterpene lactones.[52]

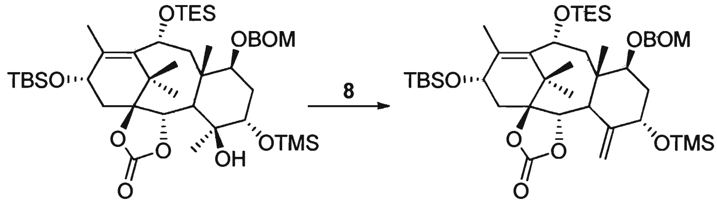
Daniewski utilized the Burgess reagent (**8**) in the penultimate step in the synthesis of pravastatin (**126**).[53] The dehydration of alcohol **127** under acidic conditions proved troublesome, however, the two-step mild dehydration with **8** and subsequent desilylation procedure successfully produced the target molecule (Figure 40).


tBuPh2SiO
tBuPh2SiO
OH
1. 8
2. F-
HO
HO

127 **126**

Figure 40. Daniewski's synthesis of pravastatin (**126**).[53]

A key step in Holton's synthesis of the C and D rings in taxol involved a selective dehydration of alcohol **128**, a compound with several acid sensitive protecting groups (Figure 41).[54] The Burgess reagent-mediated dehydration provided the terminal alkene **129** and not its more substituted isomer.


OTES
OBOM
TBSO
OTMS
OH
8
OTES
OBOM
TBSO
OTMS

128 **129**

Figure 41. Holton's synthesis of taxol.[54]

Other notable total syntheses exploiting Burgess reagent dehydrations are; Nicolaou's synthesis of efrotomycin,[55] Rigby's synthesis of cedrene,[56] and Nakamura and Kuwajima's synthesis of cortisone.[57]

As discussed previously, the Burgess reagent **(8)** has been employed in the synthesis of an assortment of oxygen, nitrogen and sulfur containing heterocycles. This methodology has been exploited in the synthesis of several heterocyclic natural products. Wipf used the Burgess reagent cyclodehydration procedure in the synthesis of cyclopeptides, including lissoclinamide 7 **(130)**.[58] The oxazoline and thiazoline rings seen in the target molecule were each installed using this method (Figure 42). Wipf also synthesized the cyclopeptide westiellamide in a similar manner.[59]

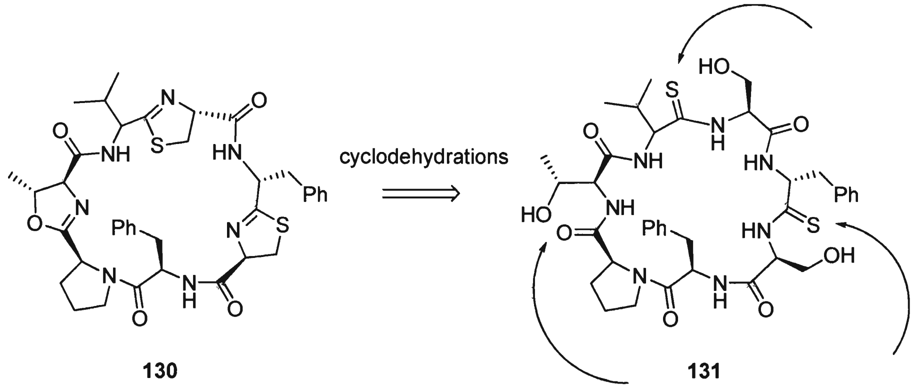
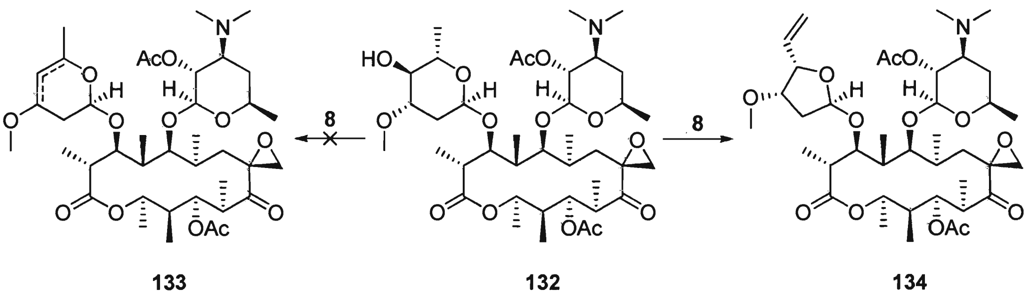


Figure 42. Wipf's synthesis of lissoclinamide 7 **(130)**.[58]

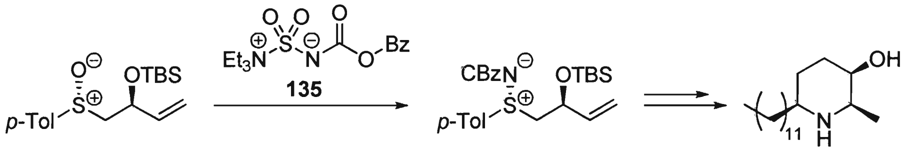
During research on the preparation of macrolide antibiotic derivatives, Nagel uncovered one of the more unusual Burgess reagent-mediated transformations.[60] The dehydration of the diacetate derivative of oleandomycin **132** was expected to yield olefin **133** resulting from elimination of one of two axial protons (Figure 43). Strangely, only the ring contraction product **134** was isolated; resulting from an oxonium shift.



133 **132** **134**

Figure 43. Unusual ring contraction of oleandomycin derivative **132.**[60]

Raghaven used a Cbz version of the Burgess reagent **135** to produce sulfilimine **136** from sulfoxides **137** during his synthesis of (–)-deoxocassine **(138)** (Figure 44).[61] Treatment of olefin **136** with *N*-bromosuccinimide (NBS) produced a bromonium ion which was stereo- and regioselectively opened with the *N*-CBz carbamate anion (not shown).



137 **136** **138**

Figure 44. Raghaven's synthesis of (–)-deoxocassine **(138).**[61]

Nicolaou has presented work on the preparation of both α- and β-glycosylamines from a single carbohydrate.[62] Synthesis of the former can be completed through reactions of the Burgess reagent **(8)** with substrates such as alcohol **139** (Figure 45). The resulting sulfamidate **140** was opened with azide to give a protected α-glycosylamine **141**. If the initial carbohydrate is protected as its benyl derivative **142** before treatment with an allyloxycarbonyl (alloc) version of the Burgess reagent **143** then β-glycosylamine **144** is formed. The alloc protecting group can be removed by hydrogenated with $Pd(OAc)_2$ and the resulting free amine can alkylated to synthesize various glycosylamine derivatives **145**.

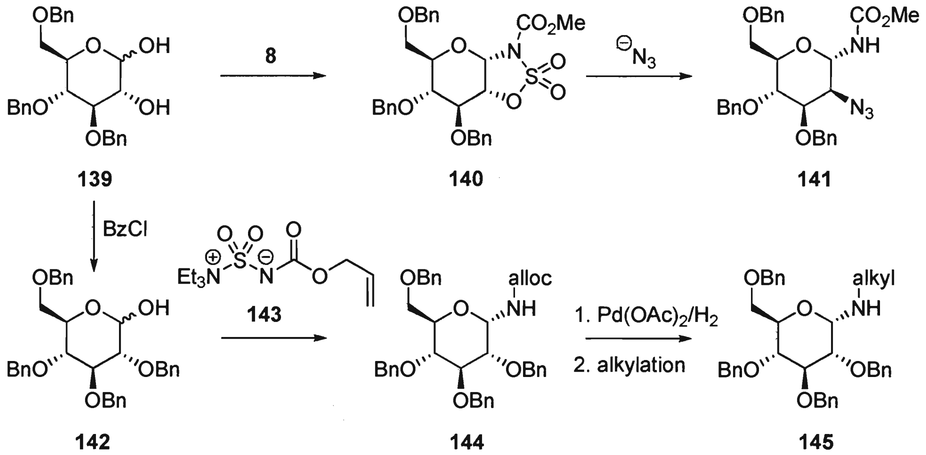

OBn
OH
BnO
OH
OBn
139
8
OBn
CO2Me
N
S
O
O
O
BnO
OBn
140
N3
OBn
CO2Me
NH
BnO
N3
OBn
141
BzCl
OBn
OH
BnO
OBn
OBn
142
Et3N
S
N
O
143
OBn
alloc
NH
BnO
OBn
OBn
144
1. Pd(OAc)2/H2
2. alkylation
OBn
alkyl
NH
BnO
OBn
OBn
145

Figure 45. Nicolaou's synthesis of α- and β-glycosylamines.[62]

2.2 Balanol

Protein kinase C (PKC) is a family of serine and threonine-specific kinases vital to the signal transduction pathways that regulate almost every cellular function. Numerous diseases have been attributed to the actions of these enzymes, making their inhibitors valuable tools for research and therapy. One example is balanol **(1)**, a structurally unusual metabolite isolated from several different fungal strains. Highlighting its importance are the more than 30 total and formal syntheses completed to date.

2.2.1 Signal Transduction Pathways and the Role of Protein Kinases

Signal transduction is the means by which a cell mediates the sensing and processing of internal and external stimuli. This system amplifies and integrates diverse external signals in order to generate the appropriate reaction. In response to stimuli, signaling molecules interact with specific membrane-associated receptors. These receptors are coupled to enzymes, or have intrinsic enzymatic activity themselves, and catalyze the release of other enzymes or small molecules (Figure 46).[63] These are referred to as 'secondary messengers' and their role is to initiate a cellular response or activate another protein/ small molecule to do so. Numerous secondary messengers are activated, amplifying the original signal causing widespread results from a minuscule stimulus. The response could be changes in gene transcription, metabolism, cell proliferation, membrane potential, apoptosis, or locomotion. The net effect is that environmental signals such as ions and large molecules, which can not passively cross lipid bilayers, can elicit intracellular events.

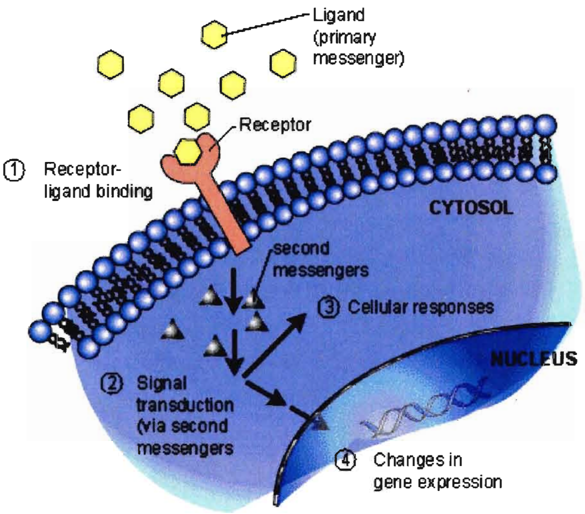

Ligand (primary messenger)
Receptor
① Receptor-ligand binding
CYTOSOL
second messengers
③ Cellular responses
NUCLEUS
② Signal transduction (via second messengers
④ Changes in gene expression

Figure 46. Basic model of the signal transduction pathway.[64]

The vast majority of cellular functions are under the control of signal transduction pathways. Therefore, it is no surprise that many diseases are a result of malfunctions in these pathways. Some examples include proliferation diseases such as cancers, atherosclerosis and psoriasis, in addition to inflammatory conditions such as sepsis, rheumatoid arthritis, multiple sclerosis, and tissue rejection.[65] Compounds which target proteins in the signal transduction pathway are crucial to research and drug development.

Commonly targeted are the protein kinases, a super family of enzymes which catalyze the addition of a phosphate (PO_4^{3-}) group from adenosine 5'-triphosphate (ATP) to other proteins. The phosphorylation or dephosphorylation of proteins is the biological equivalent of an "on" or "off" switch. In eukaryotic cells phosphorylation occurs on the hydroxyls of serine, threonine, or tyrosine residues. In prokaryotes the phosphorylation can also take place on the imine nitrogen of the imidazole ring in histidine.[66] Protein kinases require a divalent atom, typically Mg^{2+}, Mn^{2+}, or Ca^{2+}, to cooperate with acidic resides and polarize the γ-phosphate of ATP prior to is addition to the substrate (Figure 47).

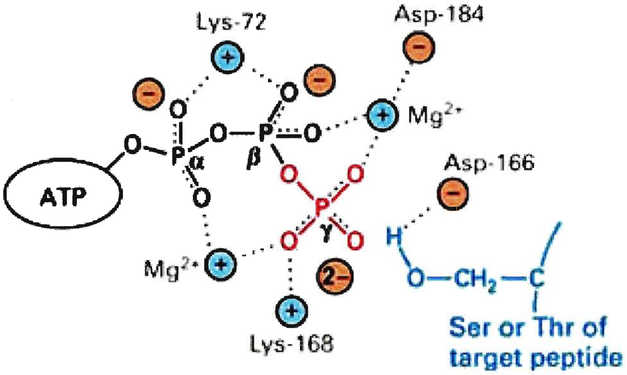


Figure 47. Initial binding of ATP and substrate with a protein kinase.[66]

2.2.2 Protein Kinase C

In the late 1970's, Nishizuka identified a new phosphorylating enzyme which he termed protein kinase C (PKC) after its dependence on calcium.[67] Subsequently it was established that PKC is actually a large enzyme family consisting of at least 11 distinct isozymes,[68] with one PKC isoform present in almost every cell type in the human body.[69] PKC isozymes differ in structure, cellular location, co-factor requirements, and substrate specificity. Every PKC is composed of a catalytic and a regulatory domain containing four conserved regions (Figure 48).[70]

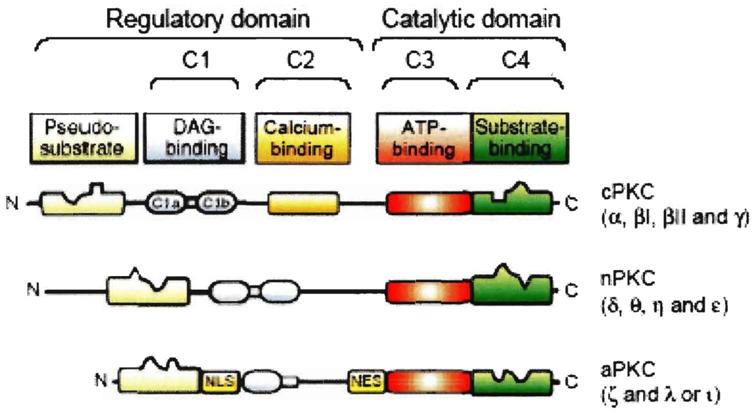

Regulatory domain
Catalytic domain
C1
C2
C3
C4
Pseudo-substrate
DAG-binding
Calcium-binding
ATP-binding
Substrate-binding
N
C1a
C1b
C
cPKC
(α, βI, βII and γ)
nPKC
(δ, θ, η and ε)
aPKC
NLS
NES
(ζ and λ or ι)

Figure 48. Schematic representation of protein kinase C isozyme structure and classification.[45]

Each catalytic domain contains an ATP and a substrate binding region, while the regulatory domains are far more varied in structure and function. The regulatory domain is where signaling molecules upstream bind to and activate PKC.[68] Domain composition of the regulatory moiety is the basis for the three subclasses which each isozyme falls under; 1. conventional, 2. novel and 3. atypical.[71] Conventional PKCs (cPKC; PKCα, PKCβI, PKCβII, and PKCγ), are calcium dependent and are activated by both phosphatidylserine (PS) and diacylglycerol (DAG).[72]

Novel PKCs (nPKCs; PKCδ, PKCε, PKCη, and PKCθ) are calcium independent and do not require DAG for activation. Atypical PKCs (aPKCs; PKCζ, PKCλ) are calcium independent and do not require DAG for activation, although PS can regulate their activities. The activation of any particular protein kinase C enzyme is tremendously complex. The activation and resulting actions of PKC is dependent on the isozyme type, tissue location, or upstream signal concentration.[72] The initiation and actions of the conventional PKC subclass is the best understood. The following life cycle description is specific for cPKC. However, many of the same events occur with the other subclasses. A more detailed description can be found in reviews by Jaken,[71] and Nishizuka.[73] cPKC enzymes are synthesized as a single polypeptide and then spliced into the two aforementioned domains and a third autoinhibitory domain. Initially cPKC is located in the cytoplasm of a cell as an inactive protein. The autoinhibitory domain is a pseudosubstrate bound to the catalytic domain preventing uninitiated phosphorylation. External stimulus, a hormone or neurotransmitter for example, binds to and initiates a G-protein-coupled receptor (GPCR) (Figure 49). This activates a stimulating G-protein, which in turn activates phospholipase C (PLC).[74] PLC cleaves a membrane bound phosphoinositol-4,5-bisphosphate (PIP_2) molecule into 1,2-diacylglycerol (DAG), which remains attached to the membrane while PIP_2 relocates to the endoplasmic reticulum (ER) where it stimulates an ion channel to release Ca^+. This prompts cPKC to translocate to the plasma membrane where it associates with DAG. It is has been demonstrated that calcium greatly increases cPKC's affinity for DAG.[75] The interactions with DAG facilitate the dissociation of the pseudosubstrate, thus activating cPKC for enzymatic activities. PKCs then function to phosphorylate and thus activate or deactivate other kinases in the cell.

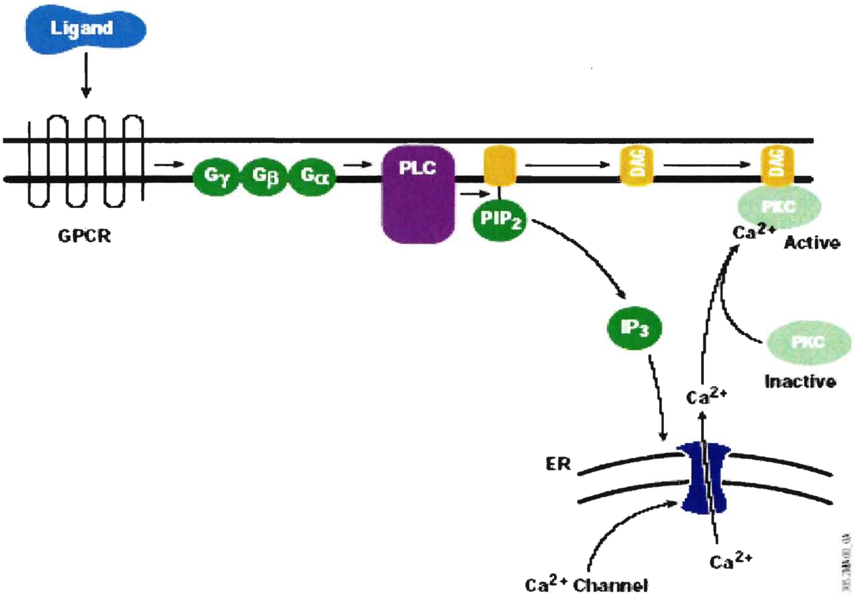
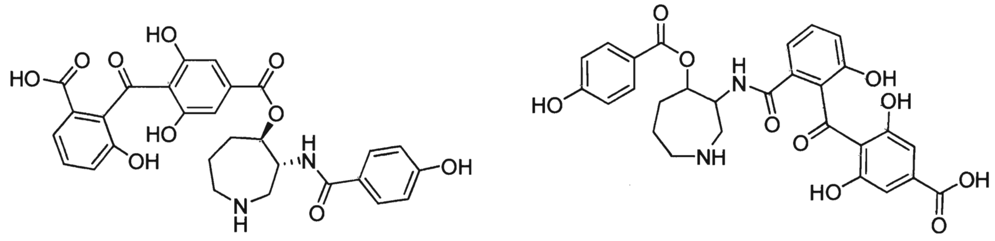


Figure 49. The activation of conventional protein kinase C.[76]

2.2.3 Isolation and Characterization of Balanol

Inhibitors that selectively target PKC isozymes have wide-ranging therapeutic potential.[47] The challenge of identifying such agents was taken on by researchers at Sphinx Pharmaceuticals, now part of Eli Lilly, in the early 1990's. Their work led to the isolation and characterization of 2-[2,6-dihydroxy-4-[(3*R*,4*R*)-3-[(4-hydroxybenzoyl)amino]azepan-4-yl]oxycarbonylbenzoyl]-3-hydroxybenzoic acid **(1)**, which they named 'balanol' after the *Verticillium balanoides* fungal species it was isolated from.[9] Balanol **(1)** recorded IC_{50} values of 4-9 nM in assays against human PKC enzymes α, βI, βII, γ, δ ,ε and η. At the same time, workers at the Nippon Roche Research Center were also perusing novel compounds with activity against PKCs. They too isolated azepane **1** from two species, *Fusarium merismoides* Corda and *Fusarium aquaeductuum* Lagh, which belong to a different genus than *Verticillium balanoides*.[77] The authors named the compound 'azepinostatin' but acknowledged that it is identical to 'balanol' isolated months earlier by Sphinx Pharmaceuticals.

Ironically neither the Roche nor the Sphinx group was actually the first to isolate metabolite **1**. In 1977, Kneifel and coworkers published the isolation and characterization of a metabolite from the *Cordyceps ophioglossoides* fungal strain.[78] They named it 'ophiocordin' and demonstrated its potent antibiotic activity against members of the Zygomycetes, Ascomycetes, and Deuteromycetes phylums of fungi. In a subsequent publication, Kneifel and coworkers proposed a structure for ophiocordin **(146)** after extensive decomposition and derivatization studies (Figure 50).[79] The Sphinx group made reference to ophiocordin **(146)** in their 1993 paper, noting that it is a structural isomer of balanol **(1)**.[9]



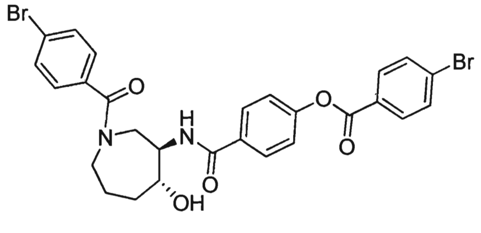
balanol **(1)**, aka azepinostatin

ophiocordin **(146)**

Figure 50. Structure of balanol (1), aka azepinostatin, compared to ophiocordin **(146)**

The Sphinx group solved the structure of **1** through detailed analysis of ^{1}H, ^{13}C, and 2D NMR (COSY, NOESY, TOCSY, HMQC, and HMBC) experiments. The absolute stereochemistry was determined by x-ray analysis of a derivative **147** synthesized from an authentic sample of **1** (Figure 51). However, in order to clarify whether or not balanol **(1)** and ophiocordin **(146)** were different compounds samples of each were collected and compared.[80] A mixed NMR experiment (600 MHz, DMSO-d_6)

confirmed that they were both the same compound, with the correct structure being that proposed by the Sphinx group.


Br
O
N
H
N
O
O
O
Br
OH

147

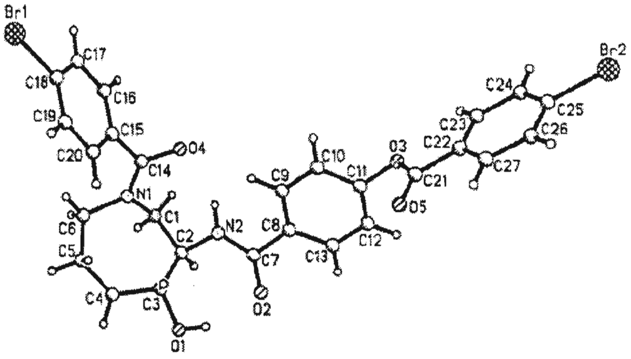

Br1
C17
C18
C16
C19
C15
C20
O4
C14
N1
C1
C6
C2
N2
C5
C4
C3
O1
C7
O2
C8
C9
C10
C11
C12
C13
O3
C21
O5
C22
C23
C24
C25
C26
C27
Br2

Figure 51. X-ray crystal structure of balanol derivative **147**.[9]

As outlined previously, protein kinases utilize a phosphate obtained from ATP to phosphorylate their protein substrates. Balanol competes with ATP for the binding pocket in the catalytic domain of PKC, in addition to some members of the cyclic-AMP-dependant protein kinases (PKA).[81] Comparisons between the crystal structures of bound balanol to that of bound ATP illustrate this fact.[82] When the two structures are superimposed it is clear that balanol adopts a similar conformation as ATP in the catalytic domain (Figure 52). Specifically, the *p*-hydroxybenzamide group (A-ring) occupies the adenine ring subsite of ATP, the hexahydroazepine ring (B-ring) occupies the ribose subsite, and the benzophenone group (C- and D-rings) mimics the triphosphate portion of ATP, although it exists in a separate portion of space. It has been calculated that balanol has a 3000 times greater affinity for the PKC catalytic domain compared to ATP.[81]

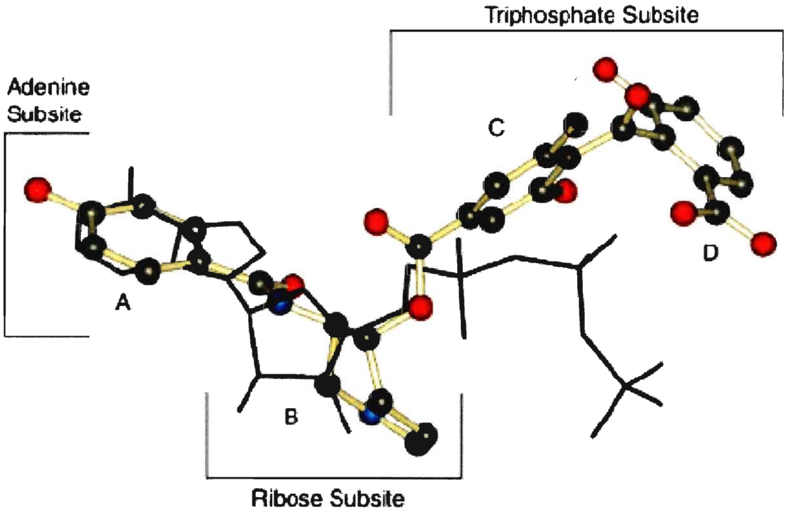

Triphosphate Subsite
Adenine Subsite
C
A
D
B
Ribose Subsite

Figure 52. Balanol (ball and stick) and ATP (atom frame) superposition.[82]

2.2.4 Balanol - Structure Activity Relationships

A significant number of balanol analogs have been synthesized in an attempt to discover a more potent and selective inhibitor.[83] Another goal is the design of a inhibitor with improved physical properties including $\mathrm{LogP}_{\mathrm{oct/wat}}$ and bioavailability. Modifications to the three major portions (Figure 53) were designed to identify the pharmacophore structure in balanol **(1)** and gain information on the structure-activity relationship (SAR).

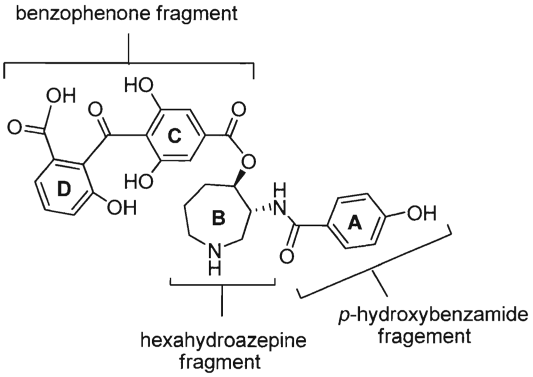

benzophenone fragment
OH
O
HO
O
O
C
D
HO
OH
O
B
H
N
A
OH
N
H
O
hexahydroazepine fragment
p-hydroxybenzamide fragement

Figure 53. Ring nomenclature of balanol **(1)**.

The first analogs produced provided variations to the carboxylic acid site on the D-ring.[84] Replacement with a hydroxyl or proton drastically reduced activity while amides, sulfonamides and tetrazoles substitutions bearing an acidic proton (pKa ≤7.6) showed improved selectivity for PKC over PKA. Crane prepared a series of benzophenone ester analogs of varying steric size and hydrolytic stability.[85] The analogs with increased activity were the small alkyl esters **148** and the pivaloyloxymethyl ester **149** (Figure 54).

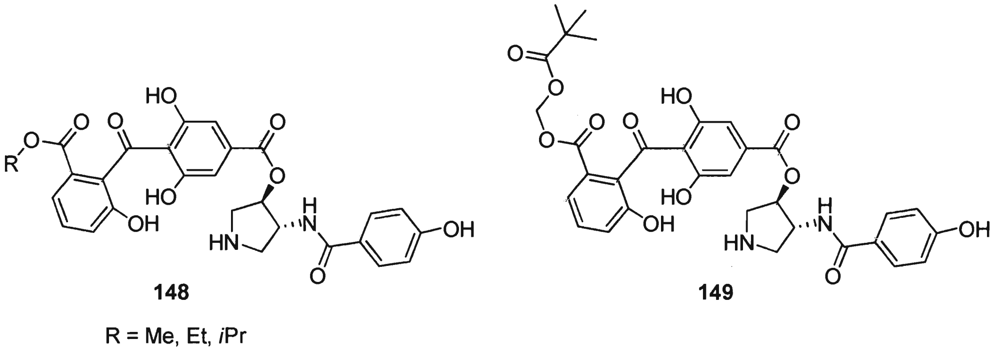


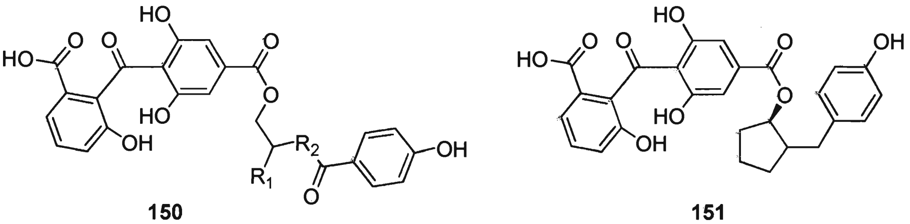
Figure 54. Balanol analogs with modified carboxylic acid groups.[85]

Lai constructed analogs in which only the hexahydroazepine ring was exchanged for a pyrrolidine or cyclopentane (with and without substituents).[86] In general, these compounds were more active than balanol itself. In a related publication, Lai replaced the nitrogen in the B-ring with other heteroatoms.[87] Although not as potent as balanol **(1)**, those analogs bearing oxygen or sulfur atoms were found to display increased selectivity among the PKC isozymes tested. It was concluded that five-membered heterocycles are more potent than the parent compound, while 4-, 6- and 8-membered rings are unfavourable. Lai also established that any heterocyclic ring that maintained the correct orientation of the ester and amide functionalities retains activity.[88]

Hu and coworkers have made extensive modifications to the *p*-hydroxybenzamide A-ring with mixed results.[89] Substitution of the 4-hydroxyphenyl group with various phenyl rings, amides, sulfamides, or esters all reduced potency. Hu did observe some improvement in PKC isozyme selectivity when an indane ring was inserted in place of the azepane ring.[90]

Jagdmann and Defauw replaced the amide linkage between the B and A rings with methylene and amine groups.[91] It was concluded that a methylene linkage in concert with a cyclopentane ring B-ring display excellent selectivity for PKC over PKA enzymes. The same researchers also replaced the ester linkage with amide, methylene and methyleneoxy groups.[92] Although these analogs suffered from a decrease in activity, they were more stable to serum esterases.

Analogs in which the perhydroazepine ring and the *p*-hydroxybenzamide moiety were combined into an acyclic linked unit were made and tested.[93] In general these compounds, such as **150**, were low-micromolar to low-nanomolar inhibitors of α, βI, βII, γ, δ ,ε and η PKC isozymes. In the same publication, a number of analogs were produced in which the amide linkage had been amended. This led to the discovery of **151**, a compound with exceptional selectivity for PKC- βI (IC$_{50}$ value of 0.003 μM) over other PKC isozymes (Figure 55).



150

151

R_1 = $NHSO_2C_6H_5$, H
R_2 = CH_2O, CH_2, CH_2CH_2

Figure 55. Acyclic linked analog **150** and cyclopentane analog **151**.[93]

Lampe and coworkers modified the benzophenone portion with the hope of reducing the overall polarity of the parent compound.[94] The results indicated that the benzophenone moiety was essential for activity against PKC but not PKA enzymes. Other essential features are a free 4-hydroxyl group in the benzamido moiety and the relative configuration of the two 'arms' in the analogs.

2.2.5 Total Syntheses of Balanol

Retrosynthetic analysis of balanol **(1)** reveals three distinct fragments arising from the most obvious disconnections at the amide and ester linkages; 1. the highly congested benzophenone derivative **152** (C- and D-rings), 2. the hexahydroazepine core **153** (B-ring), and 3. the *p*-hydroxyamide portion **154** (A ring) (Figure 56).

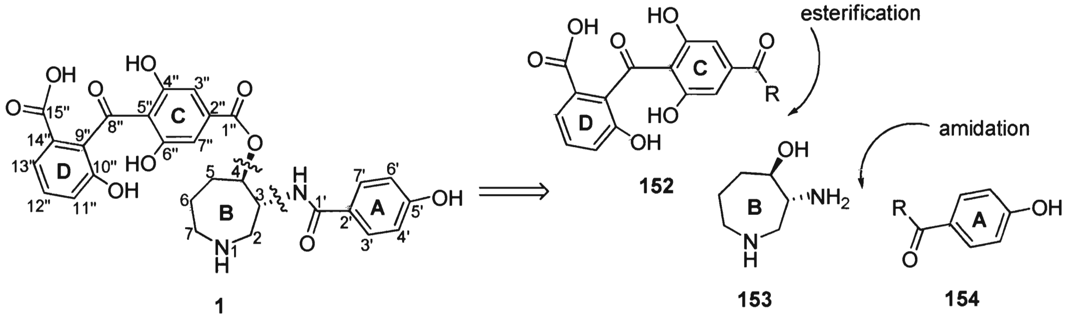


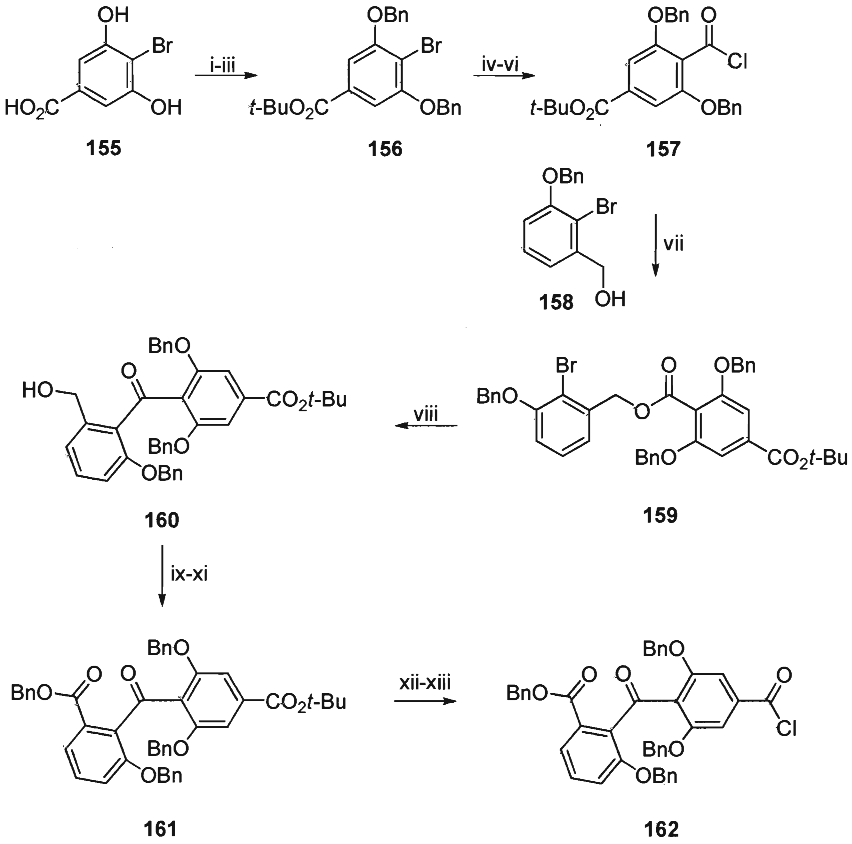
Figure 56. Nomenclature and retrosynthetic analysis of balanol **(1)**.

The majority of published balanol **(1)** syntheses focus on the construction of the hexahydroazepine core with the *anti* relationship between substituents at C3 and C4, while others have divulged methods to construct only the benzophenone portion. Every total synthesis disclosed thus far manufactures the azepane amide (A- and B-rings) fragments together prior to a coupling reaction with the benzophenone (C- and D-rings) portion. The ensuing discussion is organized into three sections; 1. total syntheses, 2. syntheses of the azepane core, and 3. syntheses of the benzophenone portion. Each section is presented chronologically, from the earliest to the latest accomplishments, and will highlight the key strategies employed.

The first total synthesis of balanol **(1)** was reported by Lampe and Hughes[95] shortly after its structural elucidation.[9] Since that time, another six total syntheses have been reported.

Lampe and Hughes (1994)[95]

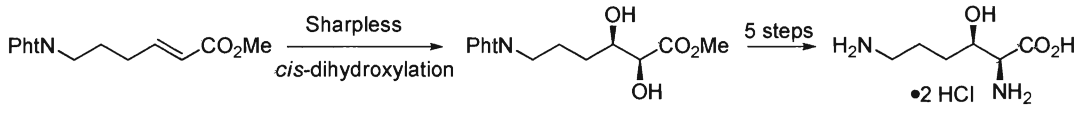
Synthesis of the benzophenone portion of balanol **(1)** began with the differential protection of benzoic acid derivative **155** in three steps (Scheme 1). Perbenzylation with benzyl bromide was followed by basic hydrolysis of the resulting benzyl ester, and reesterification with 1,1'-carbonyldiimidazole (CDI). The resulting aryl bromide **156** was treated with *n*-butyllithium at -78°C. Subsequent trapping of the aryl lithium species with carbon dioxide afforded an acid, which was treated with oxalyl chloride to produce **157**. Acylation of aryl bromide **158** with acid chloride **157** gave the highly functionalized ester **159**. Exposure of **159** to *n*-butyllithium promoted a homo-Fries rearrangement which constructed benzophenone **160**. Oxidation of alcohol **160** with pyridinium dichromate (PDC) gave an aldehyde which was further oxidized with tetrabutylammonium permanganate in pyridine. The resulting carboxylic acid was converted to its acid chloride and then protected with benzyl bromide. Thermolysis of *tert*-butyl ester **161** was followed by treatment with oxalyl chloride to give the fully protected benzophenone fragment **162**.



Reagents and conditions: (i) BnBr, K_2CO_3; (ii) NaOH; (iii) CDI, *t*-BuOH, DBU; (iv) *n*-BuLi, -78°C; (v) CO_2; (vi) $(COCl)_2$; (vii) *t*-BuOK, THF; (viii) *n*-BuLi, THF, -78°C; (ix) PDC, DMF; (x) Bu_4NMnO_4, pyr; (xi) BnBr, K_2CO_3; (xii) quinoline, 205°C; (xiii) $(COCl)_2$, DMF

Scheme 1. Lampe and Hughes' synthesis of the benzophenone fragment.[95]

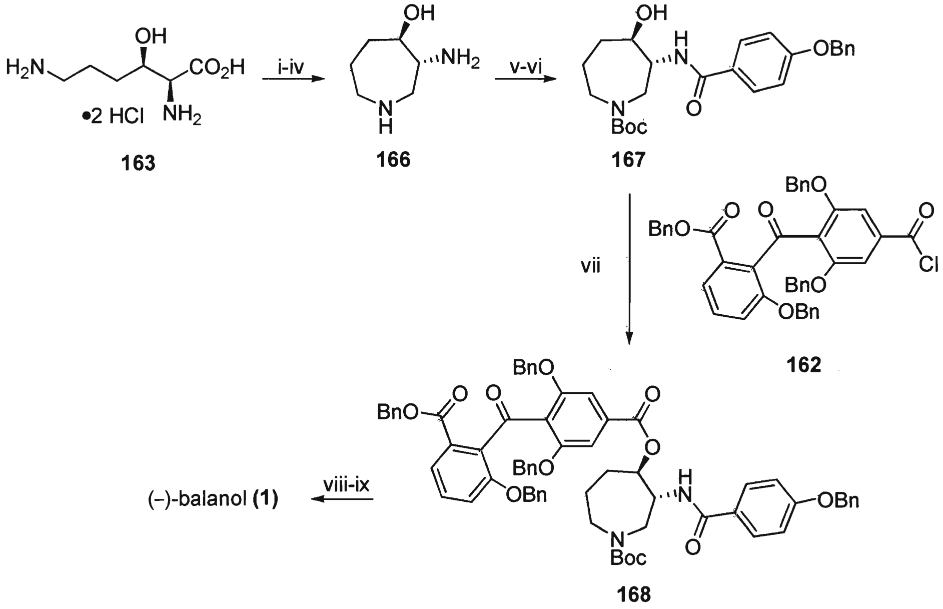
In a preceding paper, Hughes described the synthesis of (2*S*,3*R*)-3-hydroxylysine **163** and anticipated its application in the synthesis of balanol **(1)** (Figure 57).[96] The key step was a Sharpless asymmetric dihydroxylation of acrylate **164**. 1,2-Diol **165** was then converted in five steps to the aforementioned lysine derivative **163**.



164 **165** **163**

Figure 57. Hughes' synthesis of (2*S*,3*R*)-3-hydroxylysine **163**.[96]

Synthesis of the hexahydroazepine core of balanol **(1)** began with the addition of (2*S*,3*R*)-3-hydroxylysine **163** to hexamethyldisilazane (HMDS) in refluxing xylenes followed by the addition of 2-propanol (Scheme 2). This sequence produced a caprolactam which was separated from the epimeric byproduct via ion exchange chromatography and then reduced with borane to furnish azepane **166**. Selective protection of the secondary amine with di-*tert*-butyl dicarbonate (Boc_2O) and protection of the primary amine with 4-(benzyloxy)benzoyl chloride produced the fully protected A- and B-ring fragment **167**. Acylation with acid chloride **162** produced advanced intermediate **168**. Deprotection by hydrogenolysis and treatment with trifluoroacetic acid afforded (–)-balanol **(1)**.

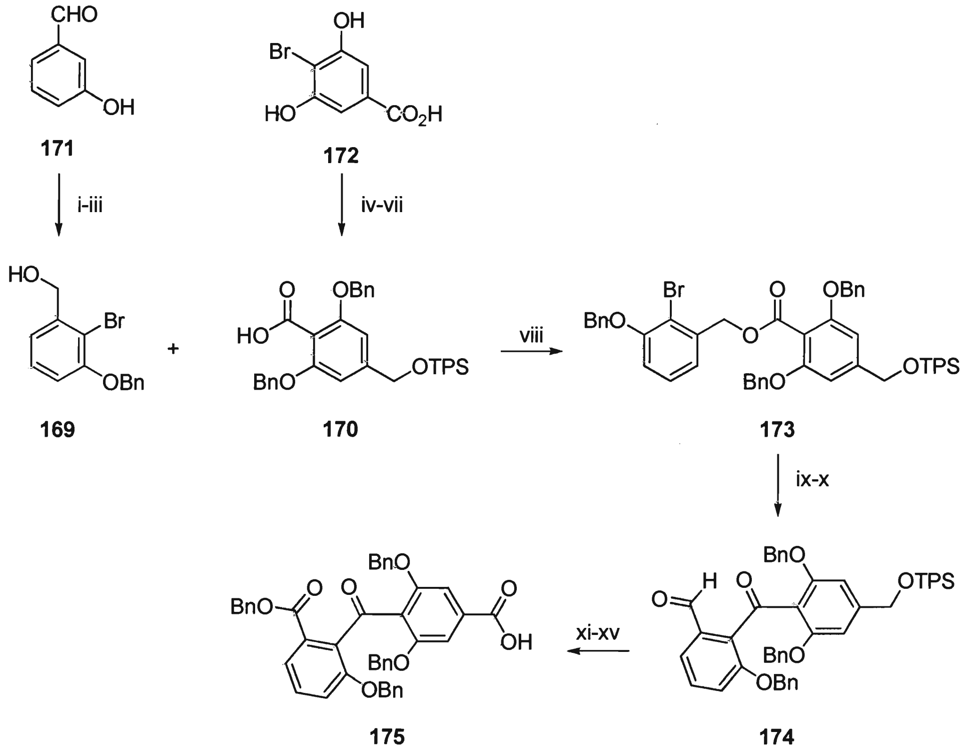


Reagents and conditions: (i) $(TMS)_2NH$, xylenes, reflux; (ii) isopropanol; (iii) ion exchange chromatography (AG-50, H^+-form, 1N HCl); (iv) BH_3, THF; (v) $(Boc)_2O$, NaOH; (vi) *p*-$BnOC_6H_4COCl$, NaOH, DCM; (vii) **162**, NEt_3, DCM; (viii) H_2, $Pd(OH)_2/C$; (ix) TFA

Scheme 2. Lampe and Hughes' synthesis of balanol **(1)**.[95]

Nicolaou (1994)[97,98]

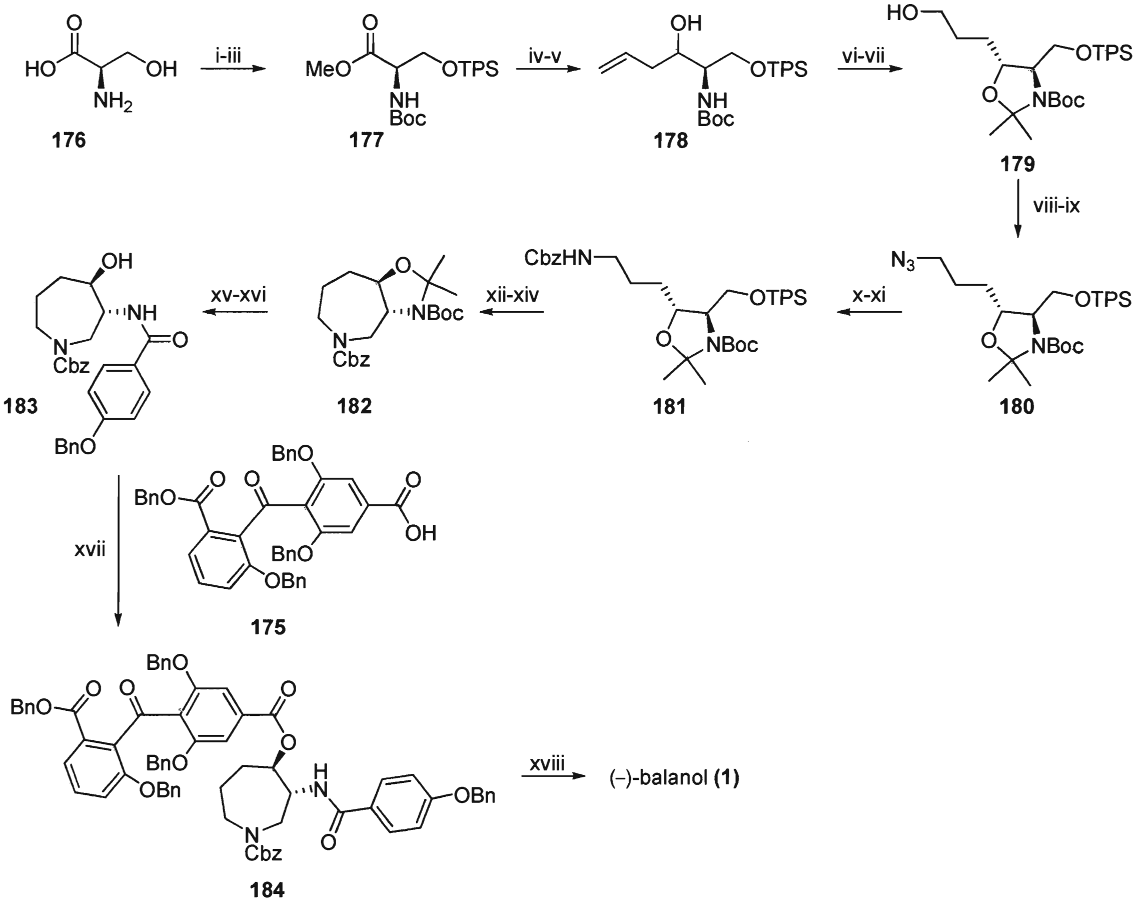
Nicolaou's synthesis of the benzophenone fragment began with the formation of benzyl alcohol **169** and carboxylic acid **170**, formed from *m*-hydroxybenzaldehyde **(171)** and aryl bromide **170** respectively (Scheme 3). A Mitsunobu coupling reaction between **169** and **170** with diethyl azodicarboxylate (DEAD) and triphenylphosphine produced ester **173**. Treatment with *n*-butyllithium provided an aryl lithium species which rearranged to a benzophenone derivative. Subsequent oxidation with tetrapropylammonium perruthenate (TPAP) yielded aldehyde **174**. Deprotection with tetrabutylammonium fluoride (TBAF) followed by sodium chlorite oxidation produced the balanol benzophenone component **175**.



Reagents and conditions: (i) BnBr, K_2CO_3, DMF; (ii) a) *n*-BuLi, $MeNHCH_2CH_2NMe_2$, PhH, 0°C; b) CF_3BrCF_3Br, THF, -78°C; c) 10% HCl; (iii) DIBALH, DCM, -78°C; (iv) BnBr, K_2CO_3, DMF; (v) DIBALH, DCM, -78°C; (vi) TPSCl, imidazole, DMF; (vii) a) *n*-BuLi, THF, -78°C; b) CO_2; c) 10% HCl; (viii) DEAD, PPh_3, THF; (ix) *n*-BuLi, THF, -78°C, NH_4Cl (aqueous); (x) NMO, TPAP, MeCN; (xi) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O; (xii) BnBr, K_2CO_3, DMF; (xiii) TBAF, THF; (xiv) NMO, TPAP, MeCN; (xv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O.

Scheme 3. Nicolaou's synthesis of benzophenone fragment **175.**[97,98]

Nicolaou's synthetic approach to the azepane core of balanol **(1)** initiated from the homochiral amino acid D-serine **(176)** (Scheme 4). Differential protection of the carboxylic acid, amine and alcohol provided **177**. Reduction with diisobutylaluminium hydride (DIBALH) afforded an amino aldehyde, which was then treated with Brown's diisopinocamphenylborane reagent (Allyl-B(^{l}Ipc)$_2$). The resulting *syn*-amino alcohol was protected as its acetonide and then subjected to a hydroboration procedure with 9-borabicyclo[3.3.1]nonane (9-BBN) with an alkaline hydroperoxide workup. The resulting alcohol **179** was converted to **180** via a mesylation and azide displacement protocol. Mild hydrogenolysis was followed by treatment with benzyl chloroformate (CbzCl) to provide **181**, a precursor to the cyclization that furnishes the azepane ring. This was achieved by desilylating **181**, mesylating the resulting alcohol, and using *tert*-butoxide to promote a 7-*exo-tet* cyclization. Acidic hydrolysis of the acetonide and *tert*-butyl carbamate protecting groups was followed by derivatization with 4-(benzyloxy)benzoyl chloride afforded azepane **183**. The two fragments, azepane **183** and benzophenone **175**, were coupled via a Mukaiyama esterification procedure[99] using 2-chloro-1-methylpyridinium iodide. Hydrogenolysis catalyzed by palladium on charcoal removed the benzyl groups in addition to the Cbz group to afford (–)-balanol **(1)**.

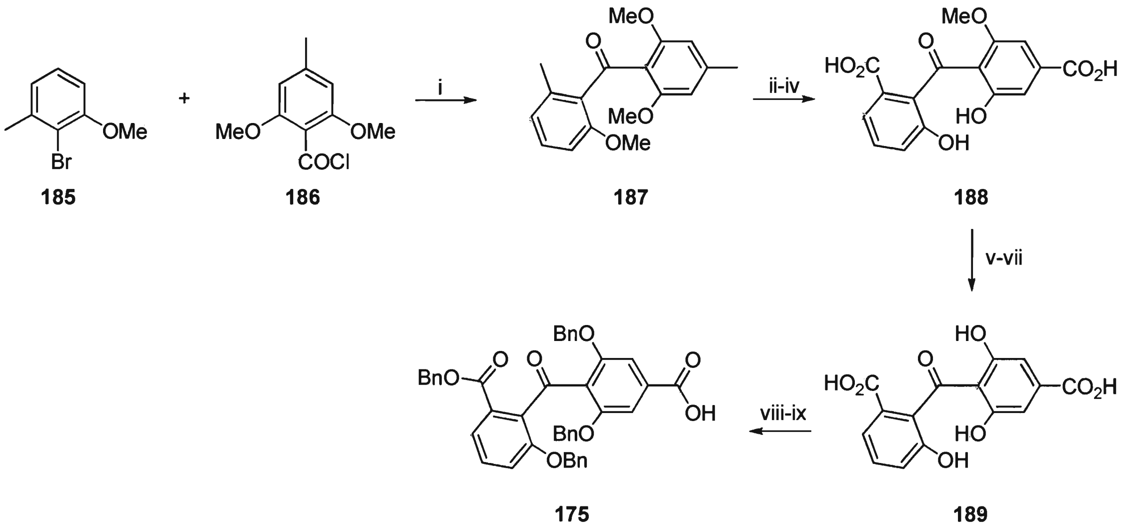


Reagents and conditions: (i) $(Boc)_2O$, NaOH, 1,4-dioxane, H_2O, 0-25 °C; (ii) K_2CO_3, MeI, DMF, 0-25°C; (iii) TPSCl, imidazole, DMF, 25°C; (iv) DIBALH, toluene, -78°C; (v) Allyl-B(^{l}Ipc)$_2$, Et_2O, -78°C, ethanolamine; (vi) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 25°C; (vii) a) 9-BBN, THF; b) NaOH, H_2O_2; (viii) MsCl, Et_3N, CH_2Cl_2, 0°C; (ix) NaN_3, DMF, 25°C; (x) H_2, Pd/C, THF; (xi) Benzyl chlorocarbonate, NaOH, 1,4-dioxane, H_2O, 0°C; (xii) TBAF, THF, 25°C; (xiii) MsCl, Et_3N, CH_2Cl_2, 0°C; (xiv) KO*t*Bu, THF, 25°C; (xv)TFA, CH_2Cl_2, 25°C; (xvi) *p*-(benzyloxy) benzoyl chloride, Et_3N, 0-25°C; (xvii) **175**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (xviii) H_2, Pd black, THF, H_2O, AcOH.

Scheme 4. Nicolaou's synthesis of balanol **(1)**.[97,98]

Vicker (1995)[100]

Vicker constructed the benzophenone portion by first reacting the Grignard reagent of **185** with 2,6-dimethoxy-4-methylbenzoyl chloride **(186)** (Scheme 5). The resulting benzophenone **187** was oxidized with potassium permanganate, but could only be partially demethylated to yield diacid **188**. The solution was a three step procedure of esterification with thionyl chloride in methanol, benzyl protection, and universal deprotection with tribromoborane to afford triphenolic diacid **189**. Two further steps provided benzophenone **175**, the coupling partner previously employed by Nicolaou.[97,98]

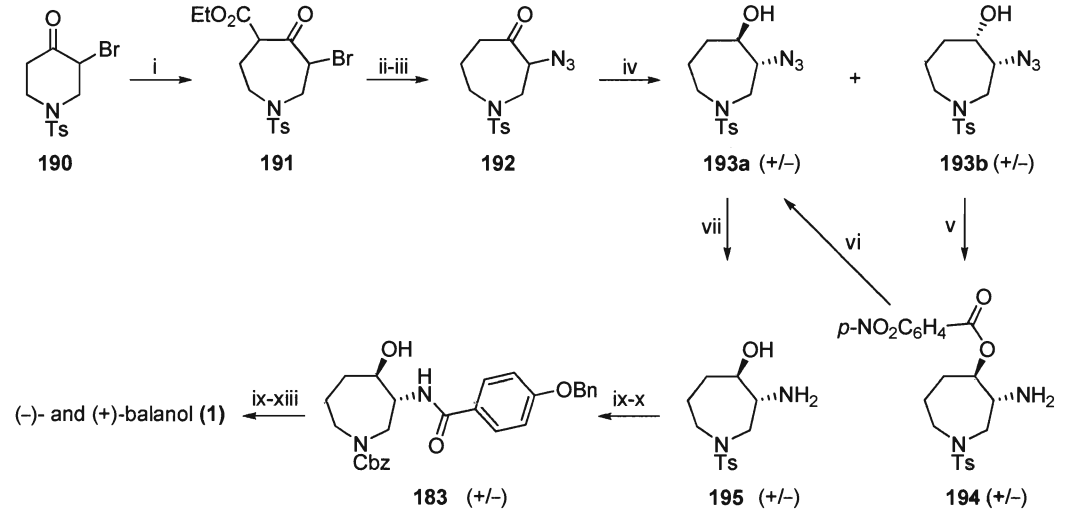


OMe
Br
185
+
MeO
OMe
COCl
186
i
MeO
O
MeO
OMe
187
ii-iv
HO2C
MeO
O
CO2H
HO
OH
188
v-vii
HO2C
HO
O
CO2H
HO
OH
189
viii-ix
BnO
O
O
BnO
O
OH
BnO
OBn
175

Reagents and conditions: (i) Mg, THF; (ii) $KMnO_4$, pyridine (aq.); (iii) $SOCl_2$, MeOH; (iv) BBr_3, DCM; (v) $SOCl_2$, MeOH; (vi) NaH, BnBr, DMF; (vii) BBr_3, DCM; (viii) NaH, BnBr, DMF; (ix) Na_2CO_3 (aq.), EtOH.

Scheme 5. Vicker's synthesis of the benzophenone fragment.[100]

Vicker's synthesis of the azepane fragment began with the ring expansion of ketone **190** to ester **191** through use of ethyl diazoacetate and boron trifluoride diethyl ($BF_3{\cdot}OEt_2$) as the Lewis acid (Scheme 6). Acidic hydrolysis and decarboxylation was followed by treatment with sodium azide to provide ketone **192**. Reduction with sodium borohydride gave a 2.4:1 mixture of the *cis* and *trans*-diastereomers **193a** and **193b**, easily separable via column chromatography. The undesired azido alcohol **193b** was recycled back to **193a** via Mitsunobu inversion with *p*-nitrobenzoate followed by hydrolysis. Azide reduction with lithium aluminum hydride (LAH) afforded amino alcohol **195** which was converted in two steps to azepane **183**. The coupling steps to join **183** with **175** were identical to those used by Nicolaou.[97,98] Subsequent hydrogenolysis and high performance liquid chromatography (HPLC) separation provided both enantiomers of balanol **(1)**.

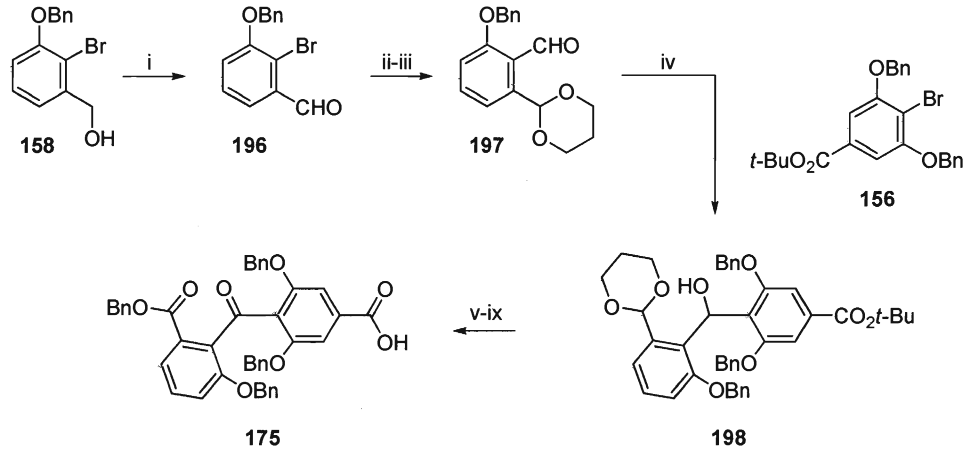


Reagents and conditions: (i) N_2CHCO_2Et, $BF_3{\cdot}OEt_2$, DCM; (ii) HCl, dioxane; (iii) NaN_3, AcOH, DMF; (iv) $NaBH_4$, EtOH; (v) PPh_3, DIAD, THF, *p*-nitrobenzoic acid; (vi) NaOH (aq.), MeOH, dioxane; (vii) $LiAlH_4$, THF; (viii) HBr (aq.); (ix) NEt_3, DCM, 18-crown-6, benzyl chloroformate; (x) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM; (xi) **175**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (xii) H_2, Pd black, EtOAc, H_2O, AcOH; (xiii) HPLC separation.

Scheme 6. Vicker's synthesis of (–)- and (+)-balanol **(1)**.[100]

Tanner (1995)[101,102]

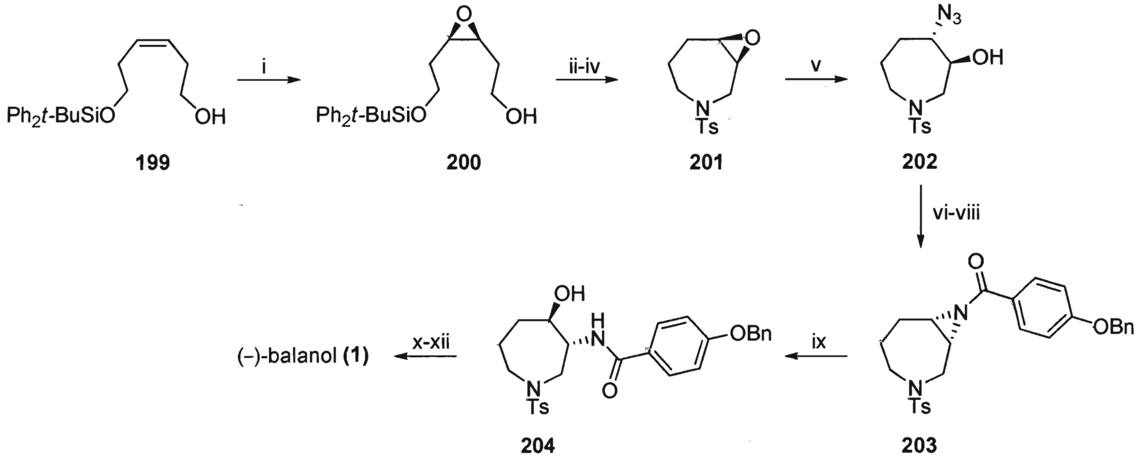
Tanner assembled the benzophenone fragment using the same building blocks (compounds **156** and **158**) as Lampe and Hughes.[95] The procedure employed is a variation of work previously reported by Hollinshead,[103] and avoids the homo-Fries rearrangement used by Lampe and Hughes. Alcohol **158** was oxidized with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), protected as its cyclic ketal, and converted to aldehyde **197** via lithiation and a dimethylformamide (DMF) quench (Scheme 7). The coupling reaction with aryl bromide **156** furnished carbinol **198**, which was oxidized with tetrapropylammonium perruthenate (TPAP) and converted to acid **175** using a previously described protocol.[95]



Reagents and conditions: (i) TEMPO, THF, NaBr, NaOCl, 0°C; (ii) $HO(CH_2)_3OH$, *p*-TSA, PhMe, reflux; (iii) *n*-BuLi, THF, -78°C, DMF; (iv) **156**, *n*-BuLi, THF, -110°C; (v) TPAP, NMO, DCM; (vi) *p*-TSA, acetone, H_2O, reflux; (vii) $NaClO_2$, H_2NSO_3H, MeCN, H_2O; (viii) BnBr, K_2CO_3, DMF; (ix) quinoline, 205°C.

Scheme 7. Tanner's synthesis of benzophenone fragment **175.**[101,102]

Tanner produced the azepane core by converting olefin **199** to epoxide **200** with a Sharpless asymmetric epoxidation procedure developed by Suzuki.[104] Desilylation followed by tosylation of both alcohols set up a cesium carbonate-catalyzed cyclization to provide azepane **201**. Opening of epoxide **201** with lithium azide in DMF proceeded with excellent regioselectivity (97:3). Reduction of azide **202** with $LiAlH_4$ provided an amino alcohol which was converted in two steps to aziridine **203**. Opening of the aziridine, exclusively at the C4 position, was accomplished with *p*-toluenesulfonic acid and water. The coupling reaction employed by Nicolaou was used to join azepane **204** with benzophenone **175.**[97,98] A sodium amalgam protocol removed the tosyl protecting group and subsequent hydrogenolysis afforded (–)-balanol **(1)**.

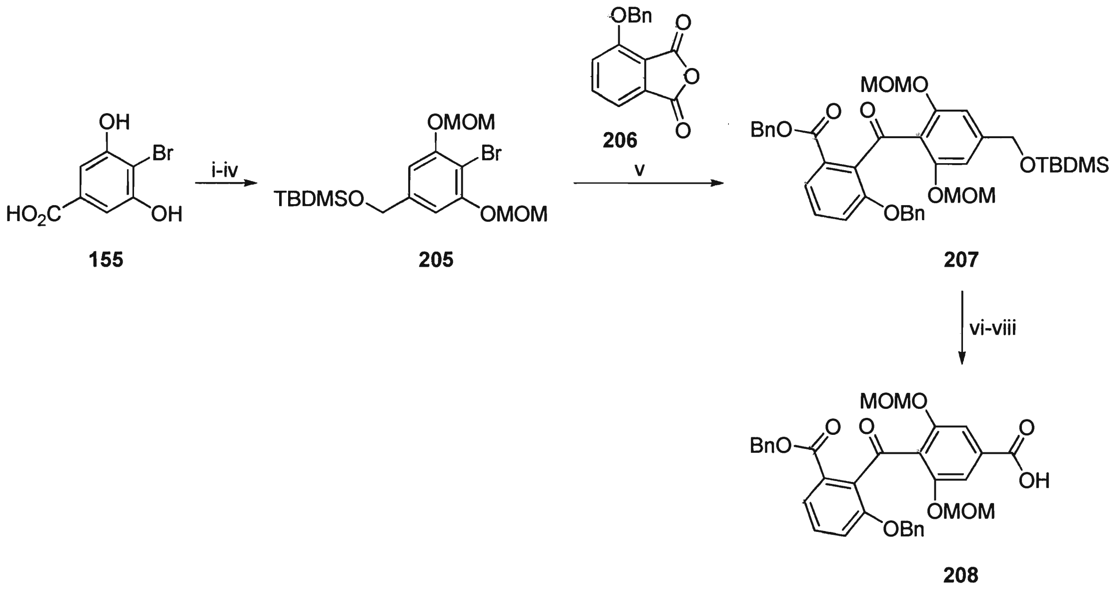


Reagents and conditions: (i) $Ti(O^iPr)_4$, (+)-DET, *t*-BuOOH, DCM; (ii) *p*-TsCl, NEt_3, DMAP, DCM; (iii) *N*-tosylimidazole, Bu_4NF, THF; (iv) *p*-$TolSO_2NH_2$, Cs_2CO_3, DMF, r.t.; (v) LiN_3, DMF, 90°C; (vi) MsCl, NEt_3, DCM; (vii) $LiAlH_4$, THF, 50°C; (viii) *p*-$MeOC_6H_4COCl$, NEt_3, DCM; (ix) *p*-TsCl, H_2O, THF; (x) **175**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (xi) Na(Hg), Na_2HPO_4, MeOH; (xii) Pd black, HCO_2H.

Scheme 8. Tanner's synthesis of (–)-balanol **(1)**.[101,102]

Barbier (1996)[105]

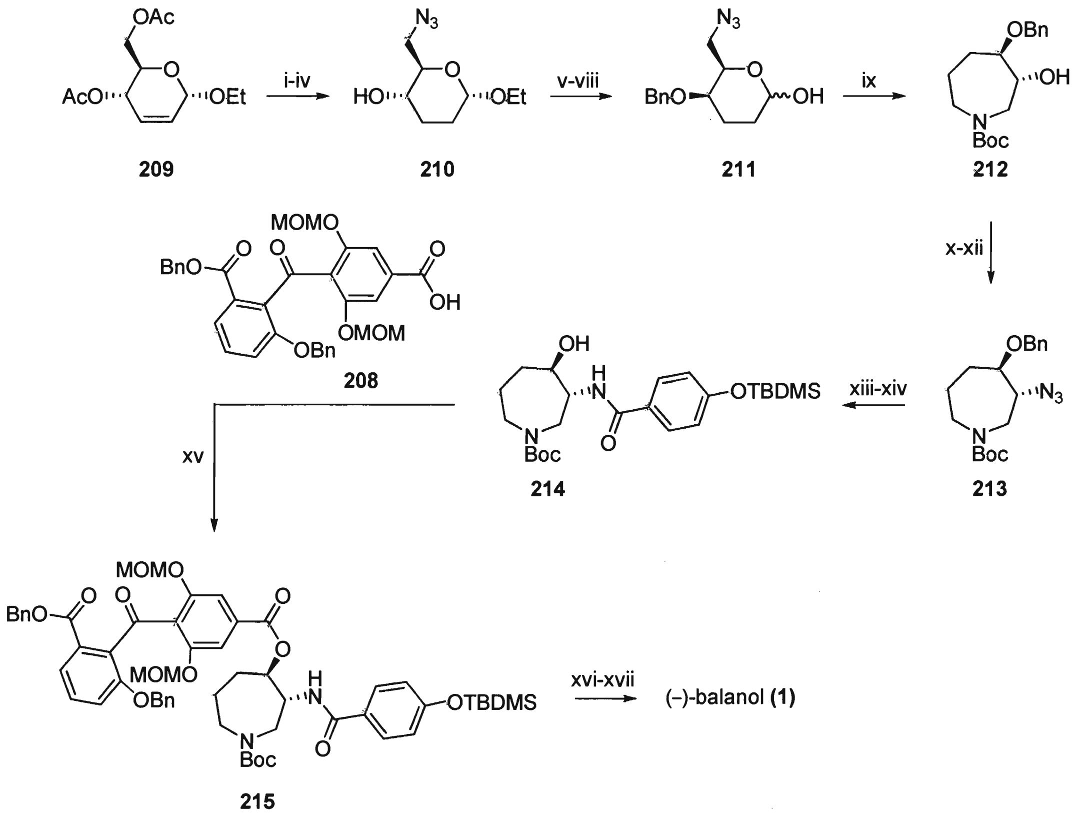
As with the Lampe and Hughes synthesis,[95] production of the benzophenone fragment begins with the differential protection of benzoic acid derivative **155**. The phenols were protected as methoxymethyl (MOM) ethers and the carboxylic acid as a *tert*-butyldimethylsilyl (TBDMS) ether (Scheme 9). Lithiation of **205** with *n*-butyllithium was followed by the addition of the benzyl derivative of 3-hydroxyphthalic anhydride **206** and benzyl bromide. The result was a separable mixture of isomers that included benzophenone **207**. Desilylation with TBAF was followed by a two step oxidation with manganese dioxide and then magnesium bis(monoperoxyphthalate) hexahydrate (MMPP) to afford benzophenone **208**.



Reagents and conditions: (i) MeOH, HCl (g); (ii) a) NaH, THF, DMF; b) MOM-Cl; (iii) $LiAlH_4$, THF; (iv) TBDMS-Cl, imidazole, DMF; (v) a) *n*-BuLi, THF; b) **206**; c) BnBr; (vi) $(Bu)_4NF$, THF; (vii) MnO_2, DCM; (viii) MMPP, DMF.

Scheme 9. Barbier's synthesis of the benzophenone fragment **208**.[105]

Barbier prepared the hexahydroazepine ring by first converting tri-*O*-acetyl-D-glucal into ether **209** through use of a procedure developed by Molina (Scheme 10).[106] Olefin reduction, ester hydrolysis and introduction of an azide functionality provided tetrahydropyran **210**. Mitsunobu inversion installed the *O*-benzyl group and was followed by acidic ester hydrolysis to furnish alcohol **211**. Hydrogenation of the azide initiated a ring-forming reaction, which was followed by treatment with di-*tert*-butyl dicarbamate to provide azepane **212**. Another Mitsunobu reaction with sodium azide installed the C3 azide, which was reduced and converted to amide **214**. Esterification with the previously synthesized benzophenone fragment **208** afforded advanced intermediate **215**. Completion of the synthesis was accomplished with benzyl hydrogenolysis, carbamate/ ether hydrolysis and desilylation with TBAF.

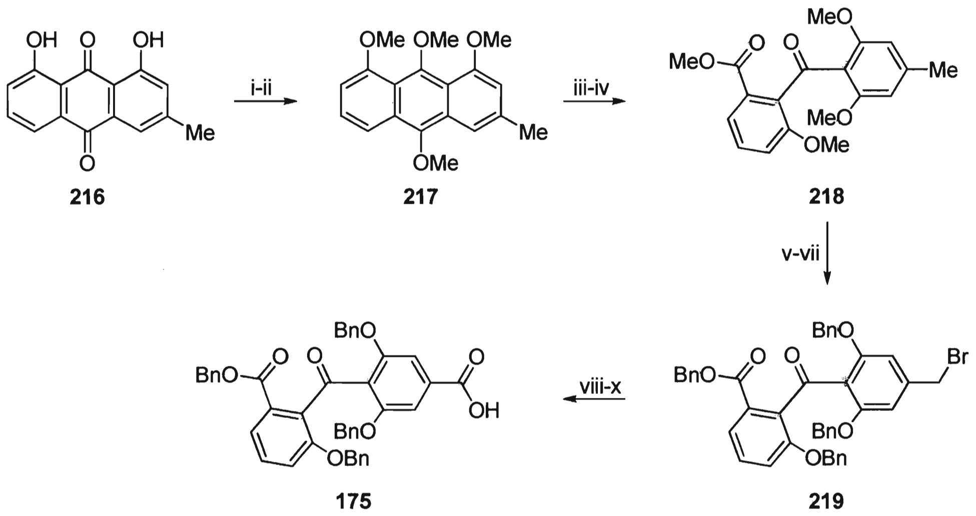


Reagents and conditions: (i) H_2, PtO_2, AcOEt; (ii) NaOEt, EtOH; (iii) *p*-TsCl, pyridine; (iv) NaN_3, TBAHS, DMF; (v) 4-O_2N-C_6H_4-CO_2H, PPh_3, DEAD, THF; (vi) KOH, EtOH; (vii) a) NaH, THF; b) BnBr, $(Bu)_4NI$, THF; (viii) 1N H_2SO_4, $(CH_3)_2CO$; (ix) a) H_2, Pd/C, THF; b) $(Boc)_2O$, dioxane; (x) 4-O_2N-C_6H_4-CO_2H, PPh_3, DEAD, THF; (xi) KOH, EtOH; (xii) HN_3, PPh_3, DEAD, THF, PhH; (xiii) a) H_2, Pd/C, THF; (xiv) *p*-TBDMSO-C_6H_4-CO_2H, EDC, DMAP, DCM; (xv) **208**, *p*-TsOH, DMAP, DCM; (xvi) TBAF, THF; (xvii) H_2, Pd/C, THF; (xviii) *i*-PrOH, DME.

Scheme 10. Barbier's synthesis of (–)-balanol **(1)**.[105]

Naito (1997)[107-109]

Naito prepared the benzophenone portion of balanol **(1)** from the naturally occurring chrysophanic acid **(216)** (Scheme 11). Methylation of the phenols followed by a reductive methylation procedure provided the corresponding anthracene **217**. Using a protocol described by Berger-Lohr,[110] irradiation of **217** in the presence of O_2 produced an oxygen adduct that, upon treatment with a catalytic amount of sulfuric acid, provided two benzophenone regioisomers that were separable after methyl esterification. The desired isomer **218** underwent radical bromination with *N*-bromosuccinimide (NBS) prior to conversion to tetrabenzyl derivative **219**. The remaining steps used the same TPAP oxidation described by Nicolaou[97] to afford carboxylic acid **175**.

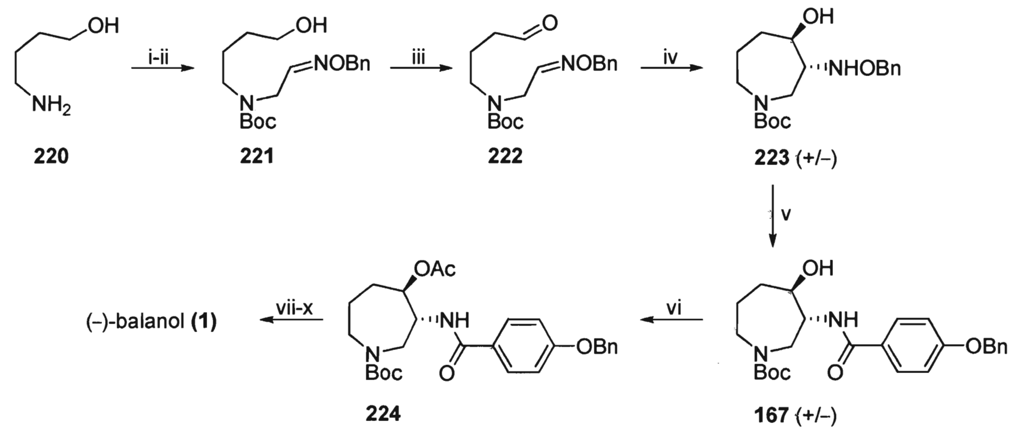


Reagents and conditions: (i) Me_2SO_4, K_2CO_3, $(CH_3)_2CO$, reflux; (ii) a) $Na_2S_2O_4$, Bu_4NBr, THF, H_2O; b) 6N KOH, Me_2SO_4, r.t.; (iii) O_2/ *hv*, Et_2O, H_2SO_4, acetone; (iv) NaH, MeI, DMF; (v) NBS, AIBN, CCl_4, reflux; (vi) BBr_3, DCM, r.t.; (vii) BnBr, K_2CO_3, DMF; (viii) $CaCO_3$, H_2O, dioxane, reflux; (ix) Pr_4NRuO_4, NMO, MeCN; (x) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O.

Scheme 11. Naito's synthesis of the benzophenone portion **175.**[108,109]

Naito prepared the azepane fragment from the commercially available 4-aminobutanol **(220)**. Alkylation with α-chloroacetaldoxime benzyl ether under Schotten-Baumann conditions was followed by *tert*-butyl carbamate formation. Alcohol **221** was oxidized with chromium(VI) oxide-pyridine to provide aldehyde **222.** Naito discovered that a samarium(II)iodide-catalyzed radical cyclization provided the best ratio of *cis*- and *trans*- isomers (1:6.6), which were separated by column chromatography. Hydrogenolysis and amide formation with *p*-(benzyloxy) benzoyl chloride afforded an intermediate **167** in the Lampe and Hughes synthesis.[95]

Resolution of the *trans*-enantiomers **167** was accomplished via an immobilized lipase protocol in the presence of vinyl acetate. Separation and hydrolysis provided the desired 3*R*,4*R* intermediate, which was converted to (–)-balanol **(1)** using previously described procedures.[97]



OH
NH2
220
i-ii
NOBn
N
Boc
221
iii
O
222
iv
NHOBn
223 (+/-)
v
OH
NH
OBn
O
167 (+/-)
vi
OAc
224
vii-x
(-)-balanol (1)

Reagents and conditions: (i) α-chloroacetaldoxime benzyl ether, Et_2O, H_2O; (ii) $(Boc)_2O$, $NaHCO_3$, $(CH_3)_2CO$; (iii) CrO_3-pyridine, DCM; (iv) SmI_2, HMPA, *t*-BuOH, -78°C; (v) a) H_2, PtO_2, MeOH; b) *p*-(benzyloxy) benzoyl chloride, $NaHCO_3$, H_2O, DCM; (vi) immobilized lipase, vinyl acetate, *t*-BuOMe, 45°C; (vii) a) TFA, DCM; b) CBz-Cl, Na_2CO_3, H_2), acetone; (viii) KOH, MeOH, r.t.; (ix) **175**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (x) H_2, Pd black, HCO_2H, r.t.

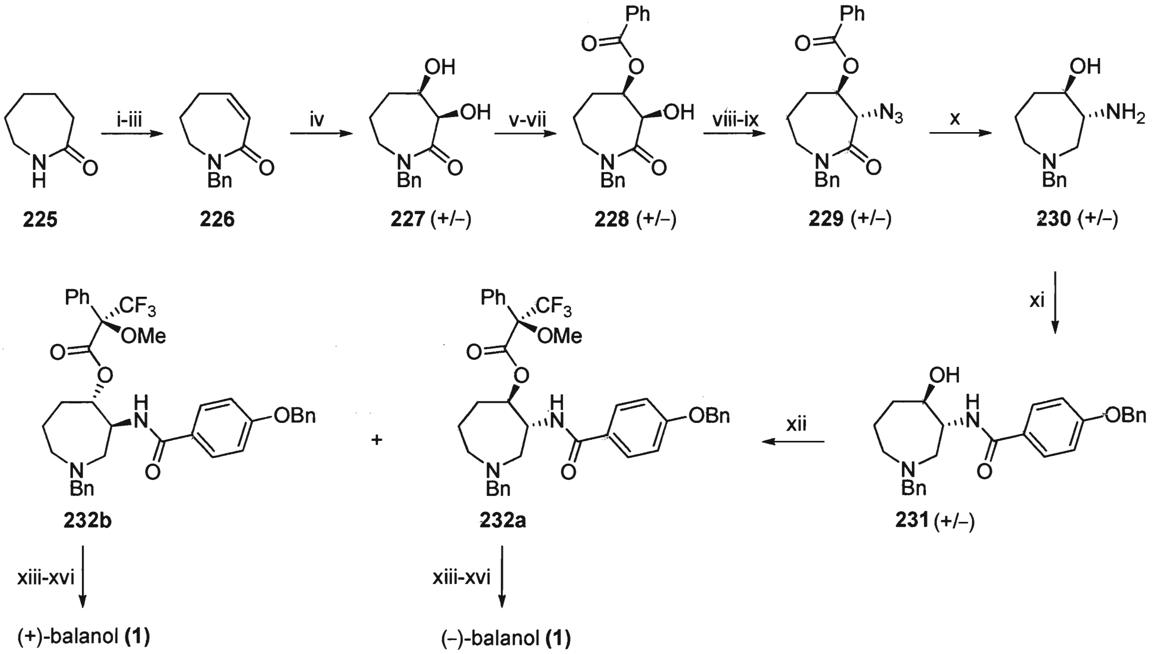
Scheme 12. Naito's synthesis of (–)-balanol **(1).**[107-109]

2.2.6 Syntheses of the Azepane Fragment of Balanol

Interest in synthesizing the azepane fragment of balanol has resulted in many formal syntheses. In each case, the formal target is one consisting of the azepane (B-ring) with a *p*-(benzyloxy)-benzamido (A-ring) already in place. The predominant formal targets are the *N*-Boc **167**,[95] *N*-Cbz **183**,[97] and *N*-Ts **204**[101] protected azepanes. The most notable syntheses thus far are discussed in chronological order.

Lampe, Hughes and Hu (1996)[111,112]

In their second approach to balanol **(1)**, Lampe and Hughes began with the benzyl protection of ε-caprolactam **(225)** followed by its conversion to olefin **226** through use of a selenation and oxidative elimination procedure (Scheme 13). This approach is an extension of work described by their colleague Hu in 1995.[112] Osmium tetroxide dihydroxylation afforded a mixture (1:1) of *cis*-enantiomers **227**. Selective protection of the β-hydroxyl with trimethyl orthobenzoate was followed by triflate formation and displacement with azide at the α-hydroxyl. Treatment of lactam **229** with $LiAlH_4$ reduced the lactam, benzoate and azide functionalities to provide azepane **230** which was then treated with *p*-(benzyloxy) benzoyl chloride. Conversion of **231** to (*S*)-Mosher's esters **232a** and **232b** facilitated the separation of the *trans*-diastereomers. Concomitant hydrolysis of the Mosher's esters permitted the synthesis of both (+)- and (–)-balanol **(1)**, after coupling reactions with benzophenone **162** and hydrogenolysis.

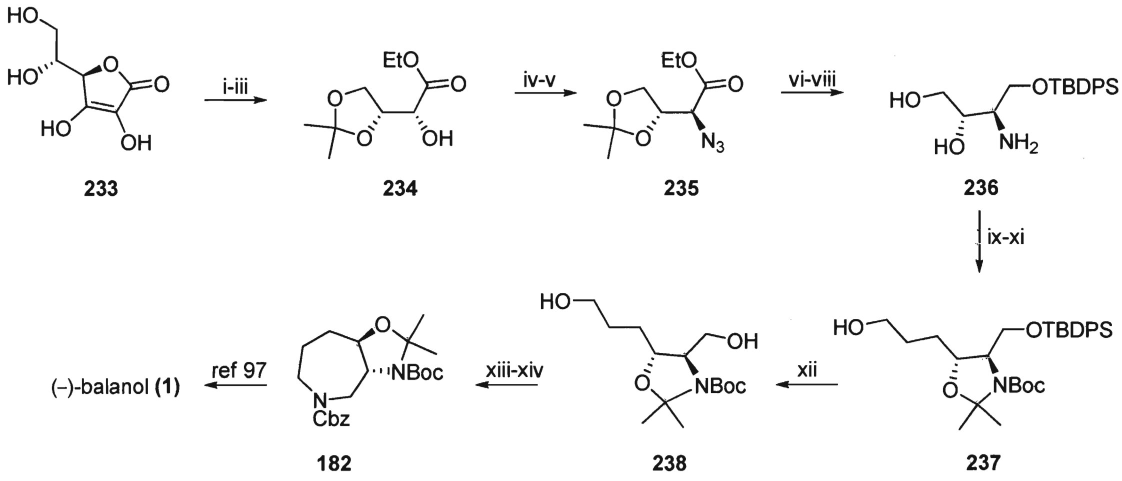


Reagents and conditions: (i) NaH, BnBr, THF; (ii) LiHMDS, PhSeCl, THF; (iii) pyridine, H_2O_2, DCM; (iv) OsO_4, NMO, $(CH_3)_2O$; (v) $PhCH(OCH_3)_3$, $BF_3•Et_2O$, DCM; (vi) H_2O; (vii) DBU, DCM; (viii) Tf_2O, 2,6-lutidine, DCM; (ix) NaN_3, *t*-BuNBr, MeOH; (x) $LiAlH_4$, THF; (xi) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM; (xii) (*S*)-Mosher's acid chloride, NEt_3, DMAP, DCM; (xiii) SiO_2 chromatography (3% NEt_3, 30% EtOAc, 66% hexanes); (xiv) KOH, MeOH; (xv) **162**, NEt_3, DCM; (xvi) H_2, $Pd(OH)_2/C$, MeOH.

Scheme 13. Lampe and Hughes synthesis of (+)- and (–)-balanol **(1)**.[111,112]

Le Merrer (1996)[113]

Le Merrer's approach to balanol **(1)** employs D-isoascorbic acid **(233)** as the starting material. In a preceding publication, the transformation of **233** into amino diol **236** via an oxidative cleavage approach was described.[114] Ketalisation of **236** followed by a Swern oxidation and *in situ* condensation with formylmethylene triphenylphosphorane provided an α,β-ethylenic aldehyde intermediate (Scheme 14). Hydrogenolysis and treatment with TBAF afforded diol **238** which cyclized upon sequential treatment with trifluoromethanesulfonic anhydride (Tf_2O) and then benzyl amine. Hydrogenolysis and reprotection of the azepane nitrogen with benzyl chloroformate yielded azepane **182**, an intermediate in Nicolaou's synthesis.[97]

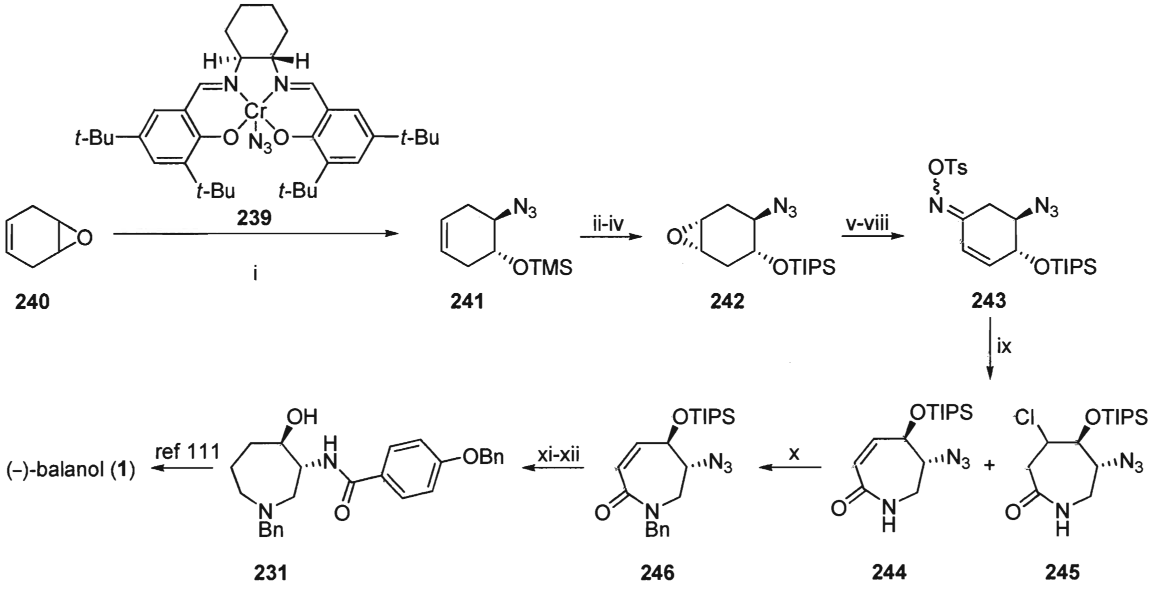


Reagents and conditions: (i) $(CH_3)_2C(OCH_3)_2$, $CuSO_4$, $(CH_3)_2CO$; (ii) K_2CO_3, H_2O_2, H_2O; (iii) C_2H_5I, CH_3CN, reflux; (iv) $(CF_3SO_2)_2O$, 2,6-lutidine, $CHCl_3$, -60°C; (v) TMGA, -60°C; (vi) $LiAlH_4$, THF reflux; (vii) TBDPSCl, Et_3N, DMAP, DCM, rt.; (viii) TFA/H_2O 1/1, -5°C; (ix) $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, TsOH, rt.; (x) a) $(COCl)_2$ DMSO, Et_3N, DCM; b) $PPh_3{=}CHCHO$; (xi) H_2, Ni, EtOH; (xii) $n$$Bu_4NF$, THF, rt; (xiii) a) $(CF_3SO_2)_2O$, CH_2Cl_2, 2,6-lutidine; b) $PhCH_2NH_2$, 20°C; (xiv) a) H_2, Pd/C, EtOH; b) $PhCH_2OCOCl$, DCM, Et_3N.

Scheme 14. Le Merrer's formal synthesis of (–)-balanol **(1)**.[113]

Jacobsen (1997)[115]

Jacobsen has developed a chromium-salen ligand **239** capable of catalyzing the enantioselective ring opening of *meso*-epoxides with trimethylsilyl azide.[116] This methodology was applied to the formal enantioselective synthesis of (–)-balanol **(1)** from 1,4-cyclohexadiene oxide **(240)**. The ring opening product **241**, obtained in 92% e.e., was deprotected prior to a molybdenum-catalyzed directed epoxidation (Scheme 15). Subsequent treatment with triisopropylsilyl chloride afforded oxirane **242**. Selective ring opening was accomplished with sodium phenyl selenate and was followed by an oxidative elimination sequence. The resulting alcohol was oxidized with TEMPO and then converted into oxime tosylate derivative **243**. A Beckmann rearrangement catalyzed by $TiCl_3(O\text{-}i\text{Pr})$ provided a mixture of amides **244** and **245**, which were treated with potassium hydride and benzyl bromide to provide lactam **246** as the sole product. Reduction of the lactam and azide functionalities, amide formation and desilylation afforded azepane **231**, an intermediate in Lampe and Hughes synthesis.[111]



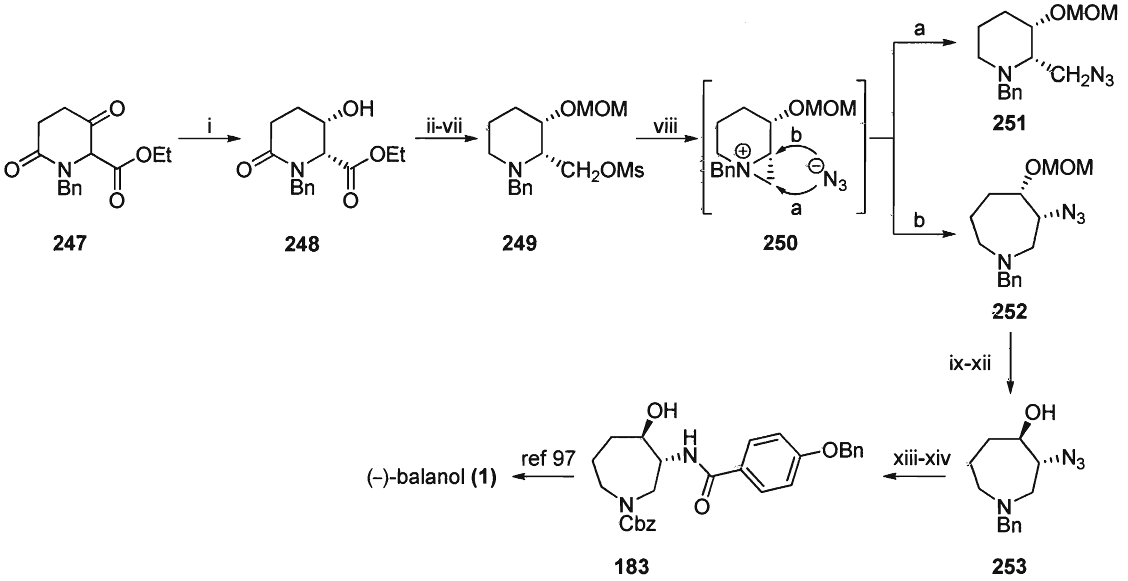
Reagents and conditions: (i) 7.5 mol% **239**, Et_2O, -10°C.; (ii) TFA, MeOH, r.t; (iii) $Mo(CO)_6$, TBPH, PhH, reflux; (iv) TIPSCl, KH, THF, 0°C; (v) PhSeSePh, $NaBH_4$, EtOH; (vi) a) H_2O, $NaHCO_3$, THF; b)$i\text{Pr}_2NH$, PhH, reflux; (vii) TEMPO, NaOCl, DCM; (viii) a) $H_2NOH{\cdot}HCl$, pyridine, DCM; b) TsCl, Et_3N, DCM; (ix) $TiCl_3(O\text{-}i\text{Pr})$, DCM, rt; (x) KH, BnBr, THF; (xi) AlH_3, THF, 0°C; (xii) a) H_2, PtO_2, EtOAc; b) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM, 0°C –r.t.; (xiii) TBAF, THF, r.t.

Scheme 15. Jacobsen's formal synthesis of (–)-balanol **(1)**.[115]

Kato (1998)[117]

Kato's formal synthesis of balanol **(1)** begins with a baker's yeast reduction of ketone **247** to alcohol **248**, a procedure first described by Momose.[118] Protection of **248** as its methoxymethyl (MOM) ether setup a series of reductions with $BH_3{\bullet}THF$

and DIBALH. Subsequent mesylation afforded piperidine **249** which was heated to reflux in the presence of sodium azide. The resulting intermediate aziridinium cation **250** is susceptible to nucleophilic attack by the azide anion at two positions. The desired path 'b' provides azepane **252**, while path 'a' gives piperidine **251**. Deprotection and a Mitsunobu inversion yielded azido alcohol **253**, which was converted to advanced intermediate **183** from Nicolaou's synthesis.[97]

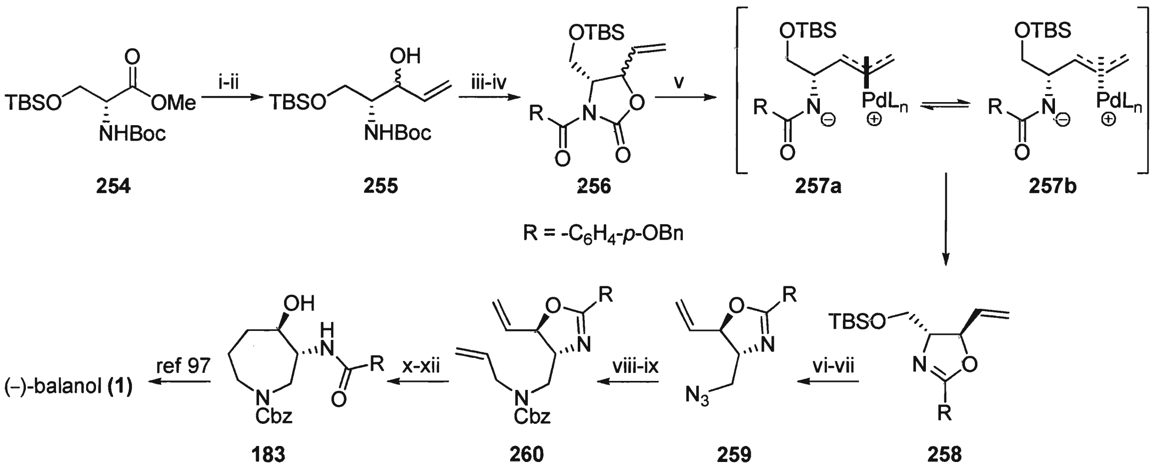


Reagents and conditions: (i) baker's yeast, tap water; (ii) MOMCl, DIPEA, $CHCl_3$, reflux; (iii) BH_3•THF, THF, r.t.; (iv) 1% aq. HCl, reflux; (v) MOMCl, DIPEA, $CHCl_3$, reflux; (vi) DIBALH, THF, 0°C; (vii) MsCl, NEt_3, DCM, 5°C; (viii) NaN_3, MeCN, reflux; (ix) CbzCl, PhMe, r.t.; (x) 10% aq. HCl, THF, reflux; (xi) DIAD, PPh_3, 4-NO_2-C_6H_4-CO_2H, THF, 0°C-r.t.; (xii) 2N aq. NaOH, MeOH-1,4-dioxane, r.t.; (xiii) PPh_3, H_2O, THF, r.t.; (xiv) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM, r.t.

Scheme 16. Kato's formal synthesis of (–)-balanol **(1)**.[117]

Cook (1999)[119]

Cook's synthesis begins with a diisobutylaluminum hydride reduction of D-serine derivative **254** followed by treatment of the crude aldehyde with vinylmagnesium bromide (Scheme 17). Alcohol **255** was converted into a cyclic carbamate intermediate which was then acylated with *p*-(benzyloxy)benzoyl chloride to afford 5-vinyloxazolidinone **256**. Subsequent palladium-catalyzed oxazoline formation/ epimerization provided **258** in a 94:6 (*trans*:*cis*) ratio. This methodology has been extensively investigated by Cook, who believes that the high selectivity is rationalized by an equilibrium between π-allyl palladium complexes **257a** and **257b**; favouring the formation of the thermodynamic product **258**.[120] Deprotection and a Mitsunobu reaction with diphenylphosphoryl azide (DPPA) furnished oxazoline **259**. Azide reduction with triphenylphosphine and water provided a free amine which was reacted with benzyl chloroformate and then allyl bromide to afford diene **260**. A Grubb's ring closing metathesis reaction formed a tetrahydroazepine ring which was reduced with potassium azodicarboxylate (PAD). Oxazoline hydrolysis under mildly acidic conditions provided Nicolaou's azepane intermediate **183**.[119]

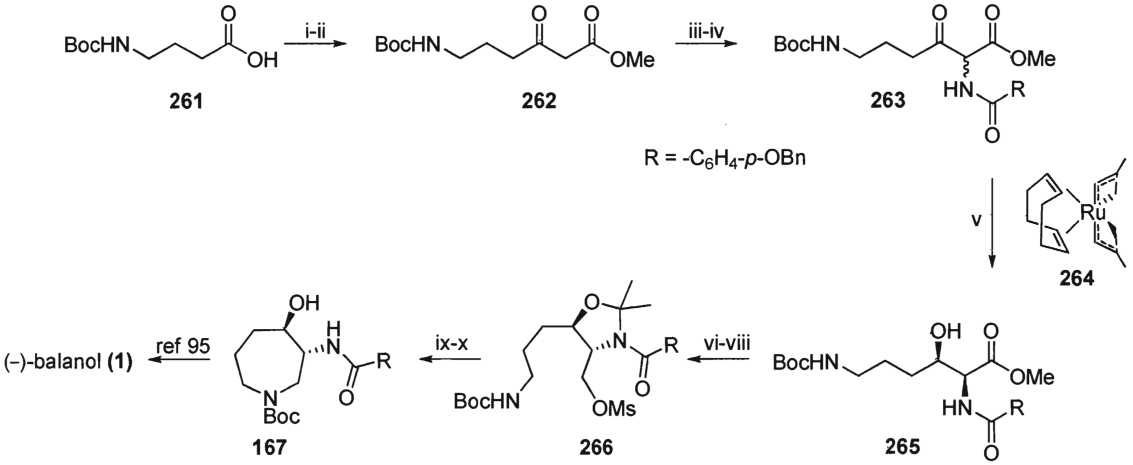


Reagents and conditions: (i) DIBALH, PhH, -78°C; (ii) vinylmagnesium bromide, THF; (iii) NaH, THF; (iv) *p*-(benzyloxy)benzoyl chloride, NaH; (v) $Pd_2(dba)_3$, $CHCl_3$, dppp, THF, 35°C (vi) TBAF, THF; (vii) DPPA, PPh_3, DEAD; (viii) a) PPh_3 THF-H_2O; b) BnOCOCl, Et_3N; (ix) NaH, allylbromide; (x) $Cl_2(PCy_3)_2Ru$=CHPh, DCM; (xi) PAD, AcOH, (xii) a) 1N HCl, EtOH; b) NEt_3, MeOH, r.t.

Scheme 17. Cook's formal synthesis of (–)-balanol **(1)**.[119]

Genêt (2000)[121]

Genêt's approach to the azepane core of (–)-balanol **(1)** relies on a dynamic kinetic resolution of a racemic α-amido β-keto ester using a ruthenium-catalyzed hydrogenation. The synthesis begins with the preparation of β-keto ester **262** from carboxylic acid **261** through use of the magnesium salt of monomethyl malonic acid (Scheme 18). Oxime formation was achieved by first reacting ester **262** with sodium nitrite and then with acetic acid and water. Acylation with *p*-(benzyloxy) benzoyl chloride provided the racemic α-amido β-keto ester **263**. Genêt has developed a method for stereoselective ruthenium-catalyzed hydrogenations[122] and applied this to the reduction of **263**. Hydrogenation with ruthenium catalyst **264** in the presence of MeO-BIPHEP provided *syn* β-hydroxy α-amino acid derivative **265** with high stereoselectivity (e.e. 94%, d.e. 93%). Amide **265** was protected as its oxazolidine derivative before reduction and mesylation reactions afforded **266**, which was cyclized through treatment of **266** with *tert*-butoxide. Subsequent acidic hydrolysis provided intermediate **183** in Lampe and Hughes' synthesis.[95]

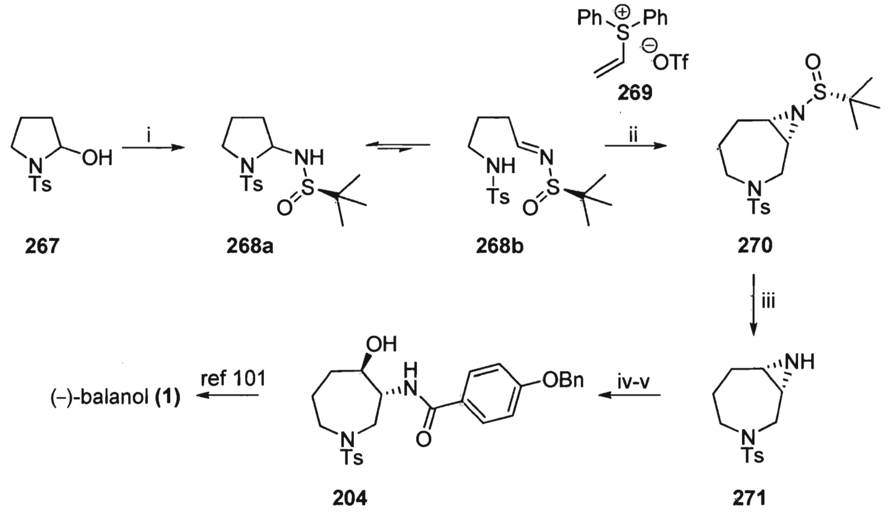

BocHN
OH
O
261
i-ii
262
OMe
iii-iv
263
HN
R
R = -C₆H₄-p-OBn
v
Ru
264
OH
OMe
265
vi-viii
266
OMs
BocHN
ix-x
167
Boc
N
H
ref 95
(-)-balanol (1)

Reagents and conditions: (i) a) Im_2CO, THF, 25°C; b) $Mg(O_2CCH_2CO_2Me)_2$, THF, 25°C; (ii) $NaNO_2$, $AcOH/H_2O$, 0°C; (iii) H_2, Pd/C, *p*-TsOH, MeOH; (iv) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM, 0°C to r.t.; (v) **264**, H_2 (130 bars), (*R*)-MeO-BIPHEP, HBr, DCM, 50°C; (vi) 2,2-DMP, DCM, *p*-TsOH, 25°C; (vii) $Ca(BH_4)_2$, EtOH/THF, -20 to 25°C; (viii) MsCl, NEt_3, DCM; (ix) *t*-BuOK, THF, 25°C; (x) *p*-TsOH, MeOH, 25°C.

Scheme 18. Genêt's formal synthesis (–)-balanol **(1)**.[121]

Aggarwal (2006)[123]

Aggarwal published one of the shortest formal synthesis of (–)-balanol **(1)** in 2006. The reaction of hemiaminal **267** with (*R*)-*tert*-butyl sulfamide provides aminal **268**, which can exist in two resonance forms, **268a** and **268b**. The sulfinimine form **268b** undergoes an aziridine annulation reaction with diphenyl vinyl sulfonium salt **269** to afford azepane **270** as a 3:1 mixture of diastereomers. Treatment with aqueous hydrochloride acid followed by ammonia provided the secondary amine **271**. Acylation with *p*-(benzyloxy) benzoyl chloride was followed by an acidic aziridine opening with water to furnish Tanner's intermediate **204**.

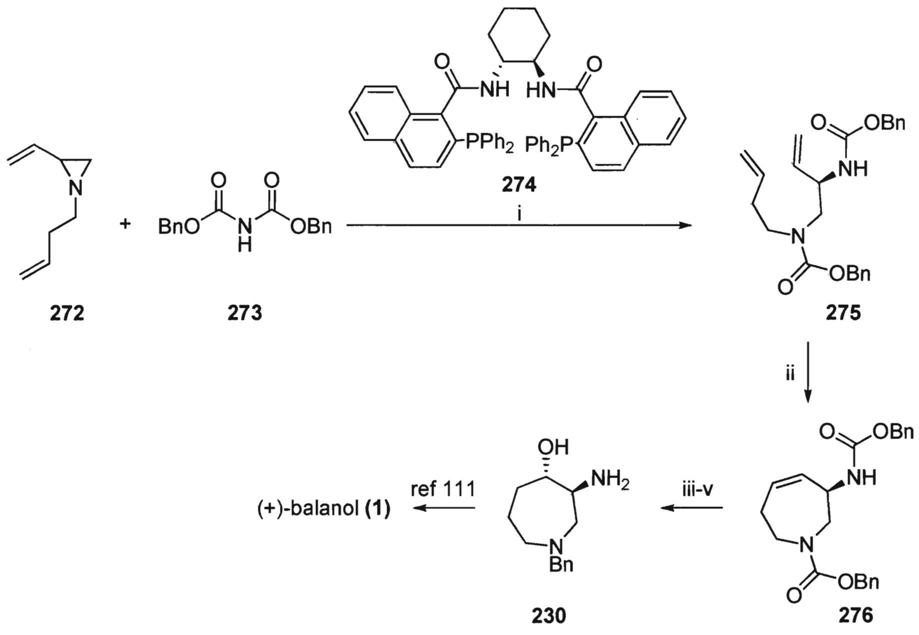


Reagents and conditions: (i) Ti(OEt)$_4$, (*R*)-*tert*-butyl sulfamides, DCM, reflux; (ii) **269**, NaH, DMF, 0°C; (iii) a) 1N HCl, dioxane; b) NH$_3$; (iv) *p*-(benzyloxy) benzoyl chloride, Et$_3$N, DCM, 0°C to r.t.; (v) *p*-TsCl, H$_2$O, THF.

Scheme 19. Aggarwal's formal synthesis of (–)-balanol **(1).**[123]

Trost (2007)[123]

Trost's strategy employs a palladium catalyzed dynamic kinetic asymmetric allylic amination and acyl migration reaction to successfully fuse vinyl aziridine **272** with imido carboxylate **273**. The stereochemistry of the resulting diene **275** arises from use a diphosphine ligand **274**. Ring closing metathesis with Grubbs' 2nd generation catalyst provides tetrahydroazepine **276**. Hydrogenation followed by a hydroboration-oxidation protocol and exchange of azepane protecting groups afforded a formal intermediate in the synthesis of (+)-balanol **(1).**[111]



Reagents and conditions: (i) 6 mol % **274**, 2 mol % $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, 10 mol % Et_3N, CH_2Cl_2, 35°C; (ii) 5 mol % Grubb's II catalyst, CH_2Cl_2, 35°C; (iii) a) $BH_3{\cdot}THF$; b) $NaBO_3{\cdot}H_2O$, 0°C; (iv) H_2, $Pd(OH)_2$, MeOH, then HCl; (v) BnCl, NEt_3, DCM.

Scheme 20. Trost's formal synthesis of (+)-balanol **(1).**[123]

Other formal syntheses

Other formal syntheses were completed by Mueller in 1994,[123] Pollini in 1996,[124-125] Herdeis in 1999,[126] Fürstner in 2000,[127] Panek in 2000,[128] Skrydstrup in 2000,[129] Yadav in 2002,[130] Raghaven in 2006,[131] Chattopadhyay in 2008,[132] and Panda in 2008.[133] Several syntheses of the benzophenone portion of balanol **(1)** have been completed as well.[134-142]

2.3 Dihydroxylations of Arene Substrates by Toluene Dioxygenase

While investigating the metabolism of aromatic substrates by *Pseudomonas putida*, David Gibson isolated a *cis*-dihydrodiol metabolite from the fermentation of *p*-chlorotoluene. Subsequent research identified toluene dioxygenase (TDO) as the enzyme responsible for this transformation. The following chapter will review the substrate specificity of TDO, and the applications of its metabolites in synthesis.

2.3.1 Historical

It is impossible to know precisely when humans observed the natural process of fermentation. The earliest evidence of mankind controlling this process dates back over 8000 years ago. Ancient pottery containing the residue of red wine suggests that Neolithic man fermented grapes in Shulaveri (part of the modern day Georgian republic).[143] Throughout history, the remarkable oxidative power of fermentation has been exploited in the production of alcoholic beverages, cheese, bread, yogurt and many other consumables.

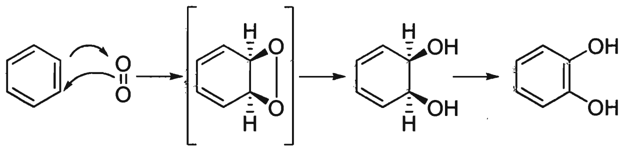
In 1857, Louis Pasteur identified yeast as the organism responsible for alcoholic fermentations.[144] Soon after, Adrian J. Brown reported the oxidation of mannitol to lævulose (fructose) by *Bacterium aceti*.[145] Pasteur believed that these transformations were effected by a vital force in the microbes called ‘ferments’, which were only active in living organisms.[146] Perhaps unknown to Pasteur, René Antoine Ferchault de Réaumur observed the digestion of meat by hawk stomach secretions (a non-living entity) in 1752.[147] In 1833, Anselme Payen and Jean-Francois Persoz precipitated a white, water soluble substance from a barley malt solution. They termed the substance 'diatase' and demonstrated its ability to digest starch into maltose.[148] Diatase is believed to be the first enzyme ever isolated, and is the source for the commonly used '–ase' suffix. In 1878, Wilhelm Kühne coined the term 'enzyme', from the Greek *to leaven*, in order to distinguish it from bacteria.[149] Shortly afterwards, Edward Buchner demonstrated that a yeast extract, termed 'zymase', was capable of performing cell-free sugar fermentations.[150] James B. Sumner was the first to identify enzymes as proteins when he crystallized jack bean urease in 1926.[151]

In 1890, Hermann Emil Fischer sought to explain why enzymes could react with some materials and not others. He proposed that both the enzyme and its substrate contain complementary geometric shapes, known as the 'lock and key' model.[152] This model explained specificity, but failed to explain how an enzyme could react with the same functional group on two compounds that are drastically different in size. Consequently, Daniel Koshland amended the theory to an 'induced fit' model in which interactions between the enzyme and the substrate induce a conformational change.[153] In 1946, Linus Pauling published a transition state theory[154] to explain enzyme catalysis based on earlier work by Erying.[155] They proposed that enzymes catalyze reactions by stabilizing the transition state, and thus lower the activation energy required.

To date, more than 4000 different enzymes have been identified.[156] Each is classified by the reaction it performs and belongs to the oxidoreductase, transferase, hydrolase, lyase, isomerase or ligase family. Enzymes are invaluable tools in the food, manufacturing and pharmaceutical industries. Of interest to this thesis is their application in the organic chemistry field. Specifically, the use of *cis*-dihydrodiols isolated from the fermentation of aromatic substrates.

2.3.2 Dihydroxylation of Arene Substrates

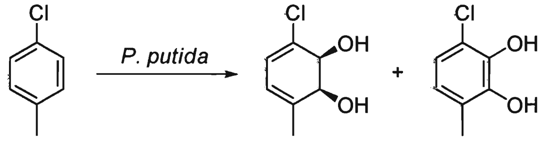
In 1908, Störmer became the first to demonstrate the microbial assimilation of aromatic hydrocarbons.[157] He isolated *Bacillus hexacarbovorum*, an organism capable of utilizing toluene and xylene for growth. Soon after, Wagner characterized *Bacterium benzoli a* and *b*, and observed their growth on hydrocarbons.[158] *Bacterium benzoli a* grew on benzene, phenol, and pyrocatechol while *Bacterium benzoli b* digested samples of crude oil, which probably contained naphthenic, aliphatic and aromatic hydrocarbons. In 1957, Haccius and Helfrich identified pyrocatechol as the major metabolite from the fermentation of benzene by *Nocardia coralline.*[159] Initially, it was proposed that pyrocatechol is produced through a phenol intermediate. Marr and Stone argued that *trans*-1,2-dihydrocyclohexa-3,5-diene, resulting from hydrolysis of an epoxide, was more likely to be the intermediate in the bacterial catabolism of benzene.[160] Their theory was based on the inability of two benzene-processing bacterial strains (*Pseudomonas aeruginosa* and *Mycobacterium rhodochrous*) to oxidize phenol, and on a similar pathway suggested by Young for naphthalene catabolism.[161] In 1968, Gibson proposed that *Pseudomonas putida* produced pyrocatechol **(280)** through a *cis*-1,2-dihydrocyclohexa-3,5-diene **(279)** intermediate; based on a considerably higher rate of oxygen consumption compared to the *trans*-isomer.[162] This observation, along with an inability to detect phenol, led to a proposed mechanism of pyrocatechol **(280)** synthesis from benzene (Figure 58).



277 **278** **279** **280**

Figure 58. Gibson's proposed mechanism of pyrocatechol **(280)** synthesis from benzene **(277)**.[162]

Gibson also discovered that *P. putida* could oxidize halobenzene substrates to their corresponding 3-halogenated catechol derivatives.[163] When *p*-chlorotoluene **(281)** was employed as a substrate, Gibson isolated two metabolites identified as (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene **(282)** and 4-chloro-2,3-dihydroxy-1-methylbenzene **(283)** (Figure 59). This result provided further evidence that the metabolic processing of benzene derivatives by *P. putida* proceeds through a *cis*-dihydrodiol intermediate.



281 **282** **283**

Figure 59. Metabolism of *p*-chlorotoluene by *P. putida.*[163]

Gibson also proposed that the *cis*-dihydrodiols were produced by an iron-mediated reaction with molecular oxygen.[164] Incubation of *P. putida* with benzene and $^{18}O_2$ provided *cis*-1,2-dihydrocyclohexa-3,5-diene, whose mass spectral analysis revealed the incorporation of two atoms of atmospheric oxygen (presumably from the same molecule).

In 1970, Gibson developed a mutant strain (*P. putida* 39/D) which accumulated (+)-*cis*-2,3-dihydroxy-1-methylcyclohexa-4,6-diene **(284)** in the culture media when grown in the presence of toluene **(285)**.[165] Gibson hoped that full analysis of this metabolite would unequivocally establish *cis*-dihydrodiols as metabolites of *P. putida* and not the *trans*-isomers. Nuclear magnetic resonance (NMR) analysis of diol **284** was inconclusive, and it was determined that a more rigid derivative would be necessary. The acetylated derivative of **284** was condensed with maleic anhydride to provide 1-methyl-2,3-diacetoxybicyclo(2,2,2)-7-hexene-5,6-dicarboxylic anhydride **(286)** (Figure 60). Hydrogenation afforded saturated derivative **287**; analysis of which established a *syn* relation between vicinal protons H_A and H_B.

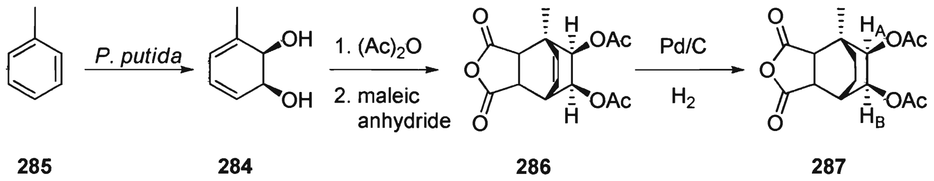

P. putida
OH
OH
1. (Ac)₂O
2. maleic anhydride
O
O
O
H
OAc
OAc
H
Pd/C
H₂
O
O
O
H_A
OAc
OAc
H_B
285
284
286
287

Figure 60. Relative stereochemical proof of *P. putida* metabolite.[165]

In a subsequent study, Gibson sought to confirm the absolute stereochemistry of *cis*-dihydrodiol **284**.[166] Hydrogenation provided *cis,trans*- and *cis,cis*-3-methylcyclohexane-1,2-diols, **288a** and **288b** respectively, which were separable as their C1 monobenzoates (Figure 61). Hydrolysis provided a pure sample of **288b** which was oxidized with Jones' reagent to provide (*R*)-(–)-methyladipic acid **(289)**, a compound whose absolute stereochemistry has been established.[167] This confirmed that the stereochemistry of diol metabolite **284** as 1*S*,2*R*.

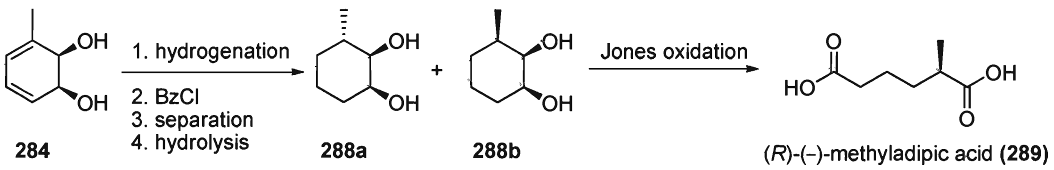

OH
OH
1. hydrogenation
2. BzCl
3. separation
4. hydrolysis
OH
OH
+
OH
OH
Jones oxidation
O
HO
OH
O
284
288a
288b
(R)-(–)-methyladipic acid (289)

Figure 61. Absolute stereochemistry proof of *P. putida* metabolite **284**.[166]

2.3.3 Toluene Dioxygenase

As the field of molecular biology progressed, it became possible to identify the genes, and the encoded proteins, responsible for the processing of benzene derivatives by *P. putida*. In 1989, Gibson was able to use sequencing information to construct clones of *Escherichia coli* JM109 that overexpressed the enzymes responsible for the oxidation of toluene to 3-methylcatechol.[168] This allowed for complete disclosure of the metabolic pathway employed in the catabolism of aromatic substrates. First, molecular oxygen is incorporated into an arene substrate (Figure 62). This reaction is performed by a multi-component enzyme system designated as toluene dioxygenase (TDO). The oxidation of nicotinamide adenine dinucleotide (NADH) supplies electrons which are initially accepted by a flavoprotein (reductase$_{\text{TOL}}$). Transfer of the electrons to a small iron-sulfur protein (ferredoxin$_{\text{TOL}}$) precedes a reduction by another iron-sulfur enzyme (ISP$_{\text{TOL}}$), which ultimately reduces molecular oxygen before substrate oxidation. 3-Methylcatechol (**290**) formation is mediated by an NAD$^+$ reducing enzyme (*cis*-(1*S*, 2*R*)-dihydroxy-3-methylcyclohexa-3,5-diene dehydrogenase) which oxidizes *cis*-dihydrodiol **284**. Another enzyme, 3-methylcatechol 2,3-dioxygenase, oxidizes **290** into an acyclic metabolite **291**, which is eventually digested into acetate.

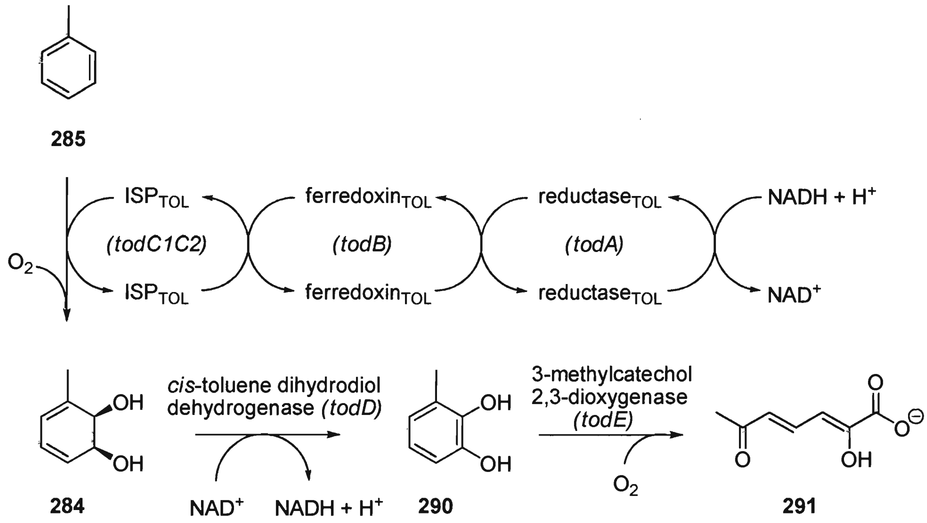

285
ISP_{TOL}
(todC1C2)
ISP_{TOL}
O_2
$ferredoxin_{TOL}$
(todB)
$ferredoxin_{TOL}$
$reductase_{TOL}$
(todA)
$reductase_{TOL}$
NADH + H$^+$
NAD$^+$
OH
OH
284
cis-toluene dihydrodiol dehydrogenase (*todD*)
NAD$^+$
NADH + H$^+$
OH
OH
290
3-methylcatechol 2,3-dioxygenase (*todE*)
O_2
O
O
OH
O$^\ominus$
291

Figure 62. Metabolic pathway for the oxidation of toluene **(285)** to 2-hydroxy-6-oxo-2,4-heptadienoate **(291)** (gene designations for individual proteins in *parentheses*).[168]

Gibson developed an *E. coli* JM109 strain which carries the recombinant pDTG601 plasmid with the genes for the toluene dioxygenase complex (todC1C2, todB and todA) under control of the *tac* promoter. This organism lacks the genes responsible for downstream processing (todD and todE) and therefore accumulates *cis*-dihydrodiols. The mutant *P. putida* strain, which also lacks todD and todE, requires chlorobenzene or toluene as an inducer. This made screening new substrates problematic; as the inducer itself is a substrate, leading to a mixture of diols. The *E. coli* JM109 (pDTG601) strain is induced by isopropyl β-D-1-thiogalactopyranoside (IPTG), thus avoiding the problem. The expression system allows for the selective growth of only those organisms which contain the plasmid; which contains intrinsic ampicillin resistance. This recombinant strain overproduces TDO and hence *cis*-dihydrodiol metabolites.

The precise mechanism of TDO dihydroxylation remains unsolved. The original 1,2-dioxetane mechanism proposed by Gibson (Figure 58) involves high energy intermediates and is therefore unlikely.[14] The absence of a TDO crystal structure has hampered mechanistic research. The x-ray structure of naphthalene dioxygenase (NDO), an enzyme which performs similar *cis*-dihydroxylations on fused aromatics, was solved and discosed in 1998.[169] TDO and NDO both utilize a Rieske [2Fe-2S] center and mononuclear iron in the active site to catalyze the addition of dioxygen to their respective substrates. In 2003, Ramaswamy used x-ray crystallography to determine the structure NDO complexes with substrate, oxygen, substrate plus oxygen and product.[170] It was concluded that the reaction sequence probably involves the three complexes depicted in Figure 63. Previous research had revealed that indole dihydroxylation by NDO proceeds through an indole C3 peroxide species,[171] although it is unclear where this structure would fit in the sequence.

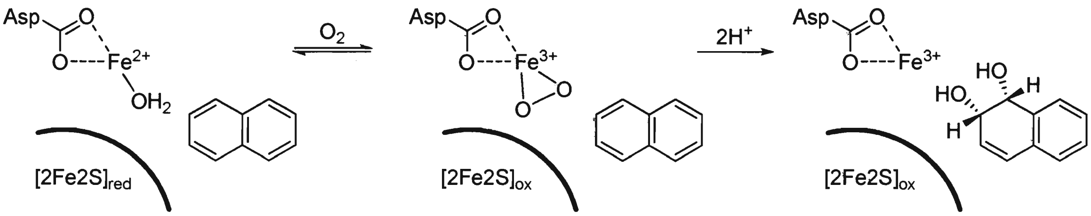


Figure 63. Proposed complexes in the dihydroxylation of naphthalene by NDO.[170]

2.3.4 Application of TDO Metabolites in Synthesis

Toluene dioxygenase is capable performing *cis*-dihydroxylations on a variety of different substrates. Since Gibson's initial findings, hundreds of metabolites have been identified. The dihydroxylations follow a similar pattern of regio-, stereo- and enantioselectivity. In 1993, Boyd screened a series of 1,4-disubstituted benzene derivatives against TDO.[172] The results aided in the development of a model which is useful for predicting the stereo- and regioselectivity of the dihydroxylations (Figure

64). In general, larger differences in relative size between R_{Large} and R_{Small} result in higher enantiomeric excess values.

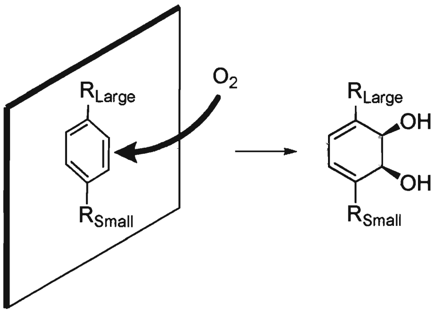


Figure 64. Boyd's model for predicting the stereo- and regioselectivity of TDO dihydroxylations.[172]

The TDO enzyme accepts substrates containing an assortment of different functionalities including; halogen, alkane, alkene, alkyne, nitrile, phenyl, carboxylic acid, and trifluoromethyl substituents.[173] Also oxidized are fused aromatics such as quinolines, indoles, anthracenes, phenylanthracenes, and phenylpyridines.[174] Despite the immense collection of *cis*-dihydrodiol metabolites available, only a few have found use in synthesis.[14] The most frequently employed are those derived from benzene, toluene, chlorobenzene, and bromobenzene.

The first recorded application of TDO metabolites was accomplished by researchers at Imperial Chemical Industries Plc in 1983.[175] The *cis*-dihydrodiol derived from benzene **279** was derivatized as a carbamate or ester and then heated to initiate the formation of polyphenylene **(293)** (Figure 65).

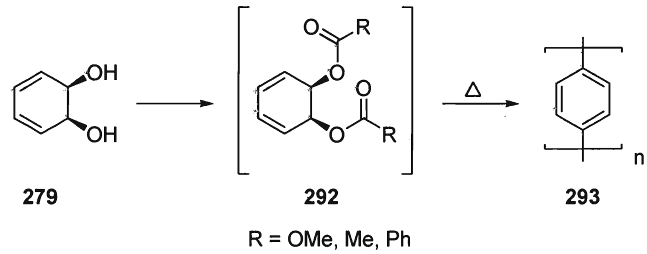
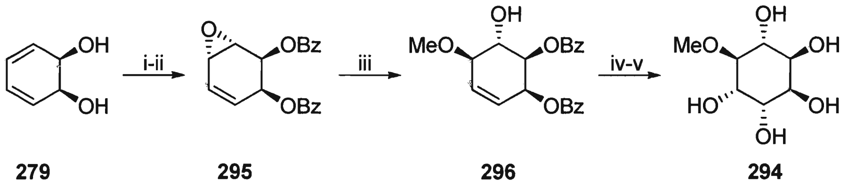


Figure 65. First application of a TDO metabolite.[175]

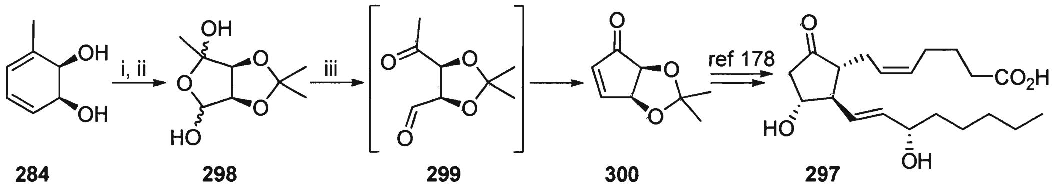
In 1987, Ley reported the synthesis of (+/–)-pinitol **(294)** from *cis*-dihydrodiol **279,** marking the first chiral application of a TDO metabolite.[176] Esterification and epoxidation of **279** provided a vinyl oxirane which was selectively opened with methanol in the presence of (+)-camphorsulfonic acid (CAS) (Scheme 21). Dihydroxylation of olefin **296** with osmium tetroxide followed by basic hydrolysis completed the synthesis.



Reagents and conditions: (i) BzCl, pyr., DMAP, 0°C; (ii) *m*-CPBA, $ClCH_2CH_2Cl$, pH 8 (phosphate buffer); (iii) MeOH, (+)-CSA; (iv) OsO_4, NMO, *t*-BuOH/THF/H_2O (10:3:1); (v) NEt_3/MeOH/H_2O (1:5:1).

Scheme 21. Ley's synthesis of (+/–)-pinitol **(294).**[176]

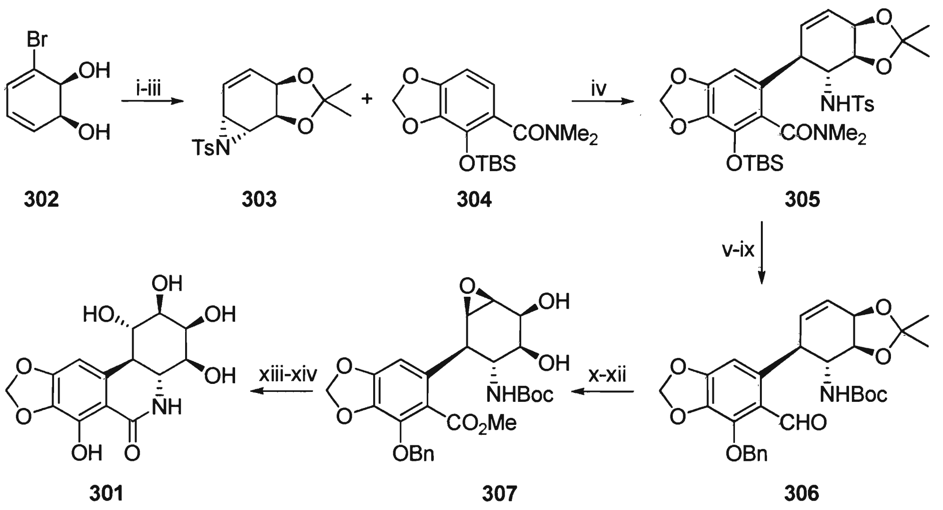
In 1988, Hudlicky reported an enantioselective synthesis of $PGE_{2\alpha}$ **(297)** from the TDO metabolite of toluene **284.**[177] Ozonolysis followed by a reductive workup with dimethyl sulfide provided tetrahydrofuran **298** (Scheme 22). Treatment with aluminum oxide effected oxidative cleavage and an aldol condensation to afford cyclic enone **300,** a compound previously converted to $PGE_{2\alpha}$ **(297).**[178] This synthesis was remarkably shorter than those reported at the time, highlighting the synthetic value of TDO metabolites.



Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, r.t.; (ii) a) O_2/O_3, EtOAc, -78°C; b) Me_2S, 0°C; (iii) Al_2O_3 (neutral), DME, reflux

Scheme 22. Hudlicky's enantioselective formal total synthesis of $PGE_{2\alpha}$ **(297)**[177]

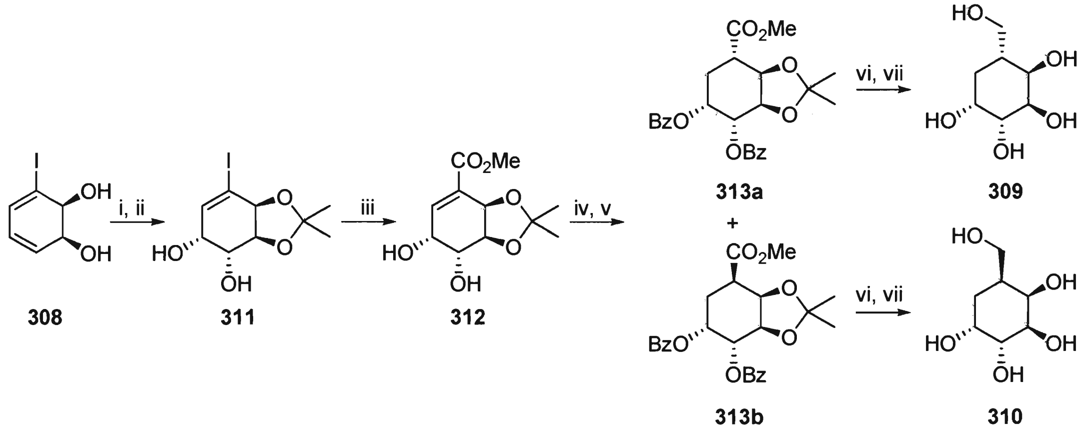
Hudlicky has employed several different TDO metabolites in the synthesis of various Amaryllidaceae alkaloids.[179] The first enantioselective synthesis of (+)-pancratistatin (**301**) was accomplished by Hudlicky in 1995 through intermediacy of the bromobenzene dihydrodiol **302** (Scheme 23).[180] The acetonide derivative of **302** was subjected to a copper(II)-catalyzed nitrene aziridination procedure followed by radical debromination to afford olefin **303**. Directed ortho metalation of amide **304**, followed by treatment with copper(I)cyanide, formed a lithium cyanocuprate species ($Ar_2Cu(CN)Li_2$) which selectively opened the tosyl aziridine. Conversion of the carbamate in **305** to an aldehyde, exchange of nitrogen protecting groups, then desilylation and benzylation of the phenolic alcohol provided olefin **306**. Conversion of the aldehyde into a methyl carbamate was achieved via a diazomethane protocol, acetonide hydrolysis and epoxidation furnished diol **307**. Treatment with aqueous sodium benzoate at 100°C resulted in the stereoselective opening of the epoxide, thermal cleavage of the Boc carbamate, and initiated δ-lactam cyclization. Palladium(II)hydroxide catalyzed hydrogenolysis removed the benzyl group and provided (+)-pancratistatin **(301)**.



Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, DCM; (ii) PhI=NTs, Cu(acac)$_2$, CH$_3$CN; (iii) *n*Bu$_3$SnH, AIBN, THF, PhMe, reflux; (iv) a) *s*-BuLi, TMEDA, THF, -90°C; b) CuCN, -90°C to -20°C; c) **303**, BF$_3$·Et$_2$O, -78°C to r.t.; (v) a) *s*-BuLi, THF; b) (Boc)$_2$O; (vi) Na/ anthracene, DME, -78°C; (vii) TBAF, THF, 0°C; (viii) SMEAH, THF, morpholine, -45°C; (ix) BnBr, K$_2$CO$_3$, DMF; (x) a) NaClO$_2$, KH$_2$PO$_4$, 2-methyl-2-butene, *t*-BuOH, H$_2$O; b) CH$_2$N$_2$, Et$_2$O; (xi) AcOH, THF, H$_2$O, 60°C; (xii) *t*-BuOOH, VO(acac)$_2$, PhH, 60°C; (xiii) H$_2$O, BzO$^-$Na$^+$ (cat), 100°C; (xiv) Pd(OH)$_2$/C, H$_2$ (1atm), EtOAc

Scheme 23. Hudlicky's synthesis of (+)-pancratistatin **(301)**.[180]

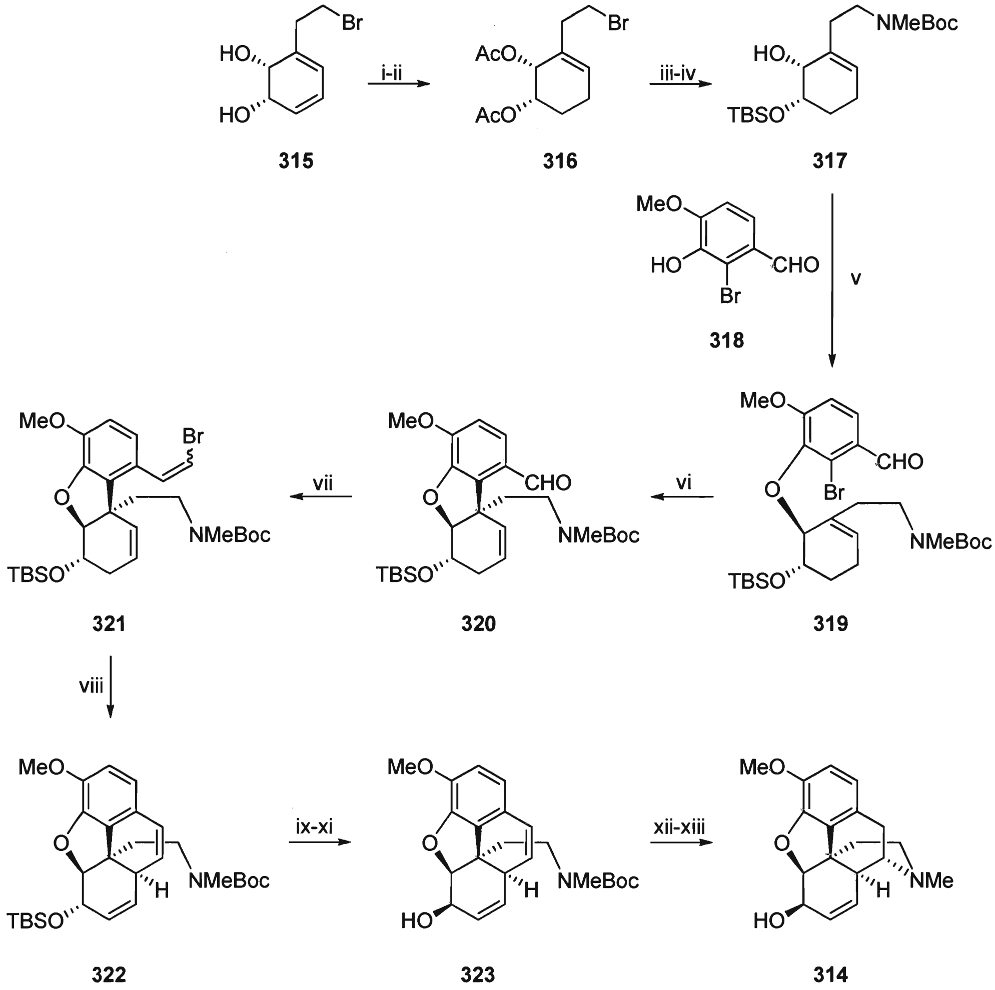
Boyd has demonstrated the versatility of *cis*-dihydrodiols in the synthesis of pseudosugars. The metabolite of iodobenzene **308** served as the starting material in the synthesis of a series of pyranose carbasugars, including carba-β-D-altropyranose (**309**) and carba-α-L-galactopyranose **(310)** (Scheme 24).[181] Dihydroxylation of the acetonide derivative of **308** with osmium tetroxide provided diol **311**. Treatment with carbon monoxide and methanol, in the presence of palladium(II)acetate, effected the synthesis of acrylate **312**. A rhodium/ alumina-catalyzed hydrogenation protocol afforded a mixture of diastereomers, which were separated as their benzoate derivatives **313a** and **313b**. Ester hydrolysis with lithium aluminum hydride and acidic acetonide hydrolysis yielded pseudosugars **309** and **310**.



Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH; (ii) OsO_4, NMO, Me_2CO, H_2O; (iii) $Pd(OAc)_2$, CO (1 atm), $NaOAc{\cdot}3H_2O$, MeOH; (iv) 5% Rh/Al_2O_3, EtOH, H_2 (55 psi); (v) BzCl, pyridine; (vi) $LiAlH_4$, THF, reflux; (vii) TFA-THF-H_2O (1:8:2), 50°C

Scheme 24. Boyd's synthesis of pyranose carbasugars **309** and **310**.[181]

Recently, Hudlicky has synthesized the unnatural (+)-isomer of codeine **(314)** from the TDO-mediated dihydroxylation product of β-bromobenzene **315**.[182] Reduction of the unsubstituted olefin with potassium azodicarboxylate (PAD) under acidic conditions was followed by exposure to acetic anhydride (Ac_2O). The resulting diacetate **316** was treated with methylamine and di-*tert*-butyl dicarbonate under basic conditions. This effected the displacement of the alkyl bromide, carbamate formation and concomitant hydrolysis of the acetates. The homoallylic alcohol of **317** was protected as its *tert*-butyldimethylsilyl ether prior to Mitsunobu coupling between the allylic alcohol and isovanillin derivative **318**. A palladium(II)acetate-catalyzed intramolecular Heck reaction formed dihydrofuran **320**. The aldehyde functionality was converted into vinyl bromide **321** through use of a Wittig reagent. A second Heck reaction effected closure of the fourth ring, and provided tetrahydrophenanthrene derivative **322**. Desilylation followed by 2-iodoxybenzoic acid (IBX) oxidation and sodium borohydride reduction effected the inversion of the allylic alcohol. Carbamate hydrolysis and then oxymercuration of the styrene olefin produced a mercurium ion which was attacked by the amino group. Reduction of the mercury-carbon bond with LiAlH completed the synthesis of (+)-codeine **(314)**.



i-ii
iii-iv
v
vi
vii
viii
ix-xi
xii-xiii
315
316
317
318
319
320
321
322
323
314

Reagents and conditions: (i) PAD, AcOH, MeOH; (ii) Ac_2O, NEt_3, DMAP, DCM, 0°C; (iii) a) $MeNH_2$, K_2CO_3, THF, -40°C to r.t.; b) $(Boc)_2O$, NEt_3, MeOH; (iv) TBS-Cl, imidazole, DCM, -78°C to r.t.; (v) *n*-Bu_3P, DIAD, THF, 0°C; (vi) $Pd(OAc)_2$, Ag_2CO_3, dppf, PhMe, 110°C; (vii) $PPh_3CH_2Br_2$, *t*-BuOK, THF, -60°C; (viii) $Pd(OAc)_2$, Ag_2CO_3, dppf, PhMe, 110°C; (ix) TBAF, THF, r.t.; (x) IBX, DMF, r.t.; (xi) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C; (xii) TFA-DCM (1:4), 0°C; (xiii) a) $Hg(OAc)_2$, NEt_3, THF; b) $LiAlH_4$, r.t.

Scheme 25. Hudlicky's synthesis of (+)-codeine **(314)**.[182]

Other *cis*-dihydrodiol products of TDO which have found applications in the synthesis of natural products include those derived from styrene **324**, 1,3-dibromobenzene **325**, and chlorobenzene **326** (Figure 66). The targets prepared, zeylena **(327)**,[183] narciclasine **(328)**,[184] and (–)-cladospolide B **(329)**[185] respectively, exemplify the synthetic value of TDO metabolites. For a more comprehensive review of products made, see excellent reviews by Hudlicky in 1993[186] and 2009.[14]

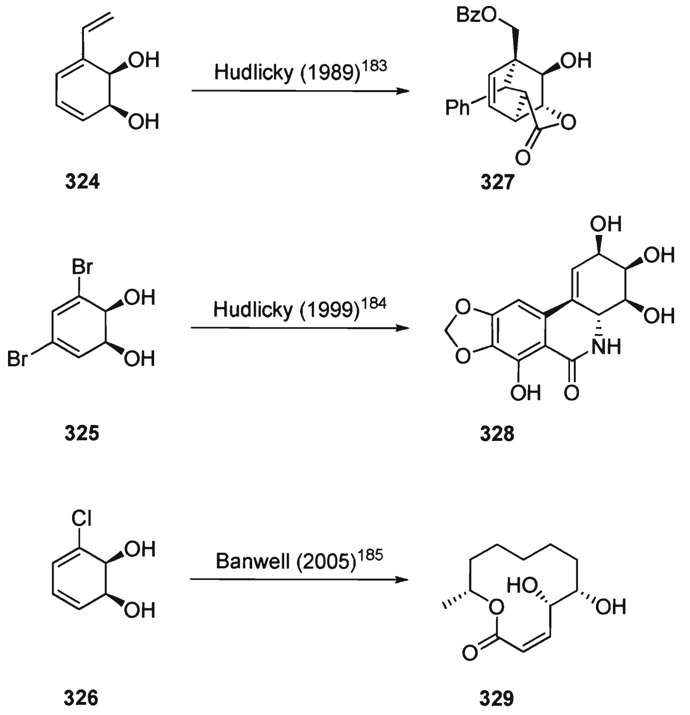

OH
OH
Hudlicky (1989)183
BzO
OH
Ph
O
O
324
327
Br
OH
Br
OH
Hudlicky (1999)184
OH
OH
OH
O
O
NH
OH
O
325
328
Cl
OH
OH
Banwell (2005)185
HO
O
OH
O
326
329

Figure 66. Natural products derived from the *cis*-dihydrodiol products of TDO.

2.4 Oseltamivir

Throughout history, infectious diseases caused by influenza viruses have haunted mankind. The Spanish flu pandemic of 1918 resulted in an estimated 40-50 million human fatalities. Recently, the avian 'bird flu' spread rapidly throughout Europe, Asia, and most of Africa, killing over half of those infected. The only pharmaceuticals that both treat and prevent infection are those which target the viral neuraminidase enzyme, essential for the release of viral progeny. The most potent member of this drug class is Tamiflu, the phosphate salt of oseltamivir. Many governments have elected to stockpile this drug in order to safeguard against another influenza pandemic. Given its vital role, oseltamivir was fast-tracked into production and promptly approved by most national drug departments. It is currently produced from (–)-shikimic acid, a scarcely available plant metabolite. Despite several excellent attempts by academic and industrial groups, no new practical synthetic route has been identified.

2.4.1 Infectious Diseases

Since the beginning of agriculture and urbanization, infectious diseases have been the major overall cause of human mortality. One early account is the death of one-quarter of the Athenian population over a four year period around 430 BC.[187] In fact, the term pandemic is derived from the Greek *pan demos*, meaning 'all people'.

Throughout history, disease pandemics have influenced war, religion, politics, economics, medicine and many other aspects of society. They have also been the leading stabilizer of human populations. In thirteenth century Europe, fatalities attributed to the Black Death have been estimated at 25-50 million, translating to 30-60% of the total population at the time.[188] Historical belief was that such pandemics had spiritual or supernatural origins. An accurate understanding of infectious disease etiology did not transpire until the late nineteenth century.

The theory that diseases were a result of factors undetected by the naked eye began in ancient Rome. In the 1st century, Marcus Terentius Varro believed that minute creatures which floated through the air could enter the body and cause serious diseases.[189] Many scholars proposed similar hypotheses, but no one could provide direct evidence for the existence of microbes. This would change with the development of the compound microscope (2 or more lenses) by Zaccharias Janssen and his father Hans in 1590. This new device caught the interest of a Dutch tradesman named Anton van Leeuwenhoek, who started to construct his own microscopes. Beginning in 1668, van Leeuwenhoek observed 'tiny animals' he termed *animalcules* (most likely bacteria and algae).[190] This discovery paved the way for Louis Pasteur and Robert Koch, whose combined work provided a rational basis for the clean water, sewage systems, food sanitation, and medicinal practices which exist today. Pasteur showed that microbes were responsible for the spoilage of food, and in turn refined the 'germ theory' of disease first proposed by Varro. Koch identified *Mycobacterium tuberculosis* and *Vibrio cholerae* as the causative bacteria responsible for tuberculosis and cholera respectively. He also developed a criterion to establish a relationship between a causative microbe and a disease, known as Koch's postulates. At the time it was understood that a porcelain filter (Chamberland filter) could exclude bacteria from a media. Consequently, it was a great surprise to Dmitry Ivanovsky that the mottling and discolouration of tobacco leaves was caused by something capable of permeating a filter.[191] Shortly afterwards, Martinus Beijerinck made a similar observation. He named this new pathogen *virus*, meaning *toxic* or *poison* in Latin. Eventually it was revealed that many infectious diseases (e.g. small pox, measles, yellow fever, poliomyelitis) were caused by viruses.

2.4.2 Viruses

Viruses are among the most numerous microorganisms on the planet. They are ubiquitously distributed throughout all eco-systems, and infect every type of cellular life.[192] All viruses are obligatory intracellular pathogens, capable of replicating independently of a cell's chromosomes but not independently of the cell itself. Outside of a host cell, a virus particle (virion) exists as little more than a macromolecular package. A complete virion consists of nucleic acid enclosed in a protein shell known as a capsid. Some viruses have an additional glycoprotein-rich lipid layer, called an envelope, derived from a membrane in the host cell from which it came.

Viruses exist in a wide variety of shapes and sizes, most being between 10 and 300 nm (~1/100th the size of a typical bacterium).[193] The most predominant morphologies are; helical, isometric, enveloped, and complex. Helical viruses (Figure 67, A) are composed of a single repetitive subunit, known as a capsomer, assembled around a central axis. The result is a hollow helical tube which is packed with the nucleic acid. Isometric viruses (Figure 67, B) are quasi-spherical hollow structures composed of a minimum of 12 capsomers, each forming a face of the structure. For example; twenty triangular faces form an icosahedron structure, while twelve pentagon faces form a dodecahedron structure. An enveloped virus (Figure 67, C) surrounds its nucleic acid-containing capsid with a membrane derived from the outer or internal bilayer (i.e. nuclear membrane or endoplasmic reticulum) of a host. The three major parts composing a complex viruses (Figure 67, D) are the; capsid head, tail sheath and tail fibers. The head is often an isometric capsule and houses the nucleic acid. These viruses use their tail fibers to recognize and dock on to a cell membrane, while the tail sheath acts as a hypodermic needle to inject the nucleic acid into the cell.

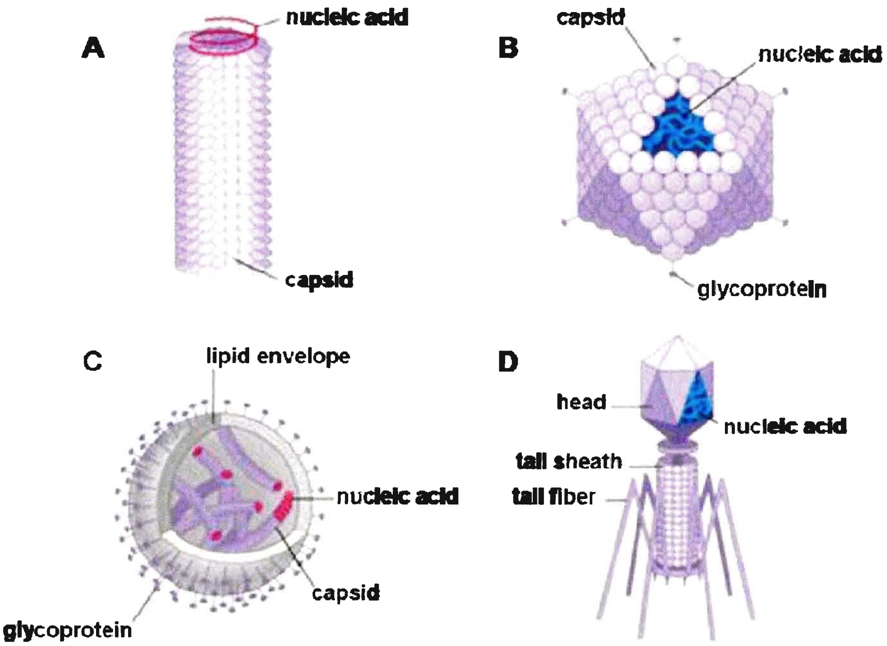

A
nucleic acid
capsid
B
capsid
nucleic acid
glycoprotein
C
lipid envelope
nucleic acid
capsid
glycoprotein
D
head
nucleic acid
tail sheath
tail fiber

Figure 67. Predominant viral morphologies: A. helical, B. isometric, C. enveloped, D. complex.[194]

The variation in composition and structure of viral genomes is unlike any other type of organism. Their genomic material can be single or double stranded DNA or RNA. The polarity of the singled-stranded nucleic acid can be either positive- or negative-sense. The obvious advantage of positive-sense RNA is that it can be translated immediately by a host. Viral genomes can be linear, circular or even segmented. The smallest genomes encode as few as four proteins, while the largest encode hundreds.[194] The proteins encoded are either structural or nonstructural in nature. The former form capsomers or are glycoproteins embedded in the envelope, while the latter have regulatory and accessory functions.

The life cycle of all viruses can be divided into five basic stages; 1. attachment, 2. penetration, 3. uncoating, 4. replication and synthesis, 5. assembly and release. Attachment is the highly specific interaction between the outermost viral proteins and receptors on the host's cell surface. Viral proteins are either capsomers or envelope glycoproteins, while the host receptors are normal surface components such as carbohydrates, glycoproteins, lipids, and lipoproteins. Viral attachment to a host cell is the most common basis for cell specificity.

In order to replicate, a virus must release its genome, and in some cases viral proteins, into the cell. For cells lacking a cell wall this can occur through endocytosis or membrane fusion. The former involves the engulfing of the virus into a section of the cell membrane, followed by release of that section into the intracellular fluid. Membrane fusion occurs when the lipid bilayers of an enveloped virus and a host cell merge into a single continuous membrane. Plants and some other eukaryotic cells (e.g. bacteria, fungi, algae) are protected by a rigid carbohydrate-based layer. Viruses can only enter these cells through disturbances in the cell wall caused by either environmental trauma or the aforementioned injection process used by the complex viruses. Some plant viruses are able to move between cells via pores (plasmodesma) in the cell wall normally used for cell-to-cell communication. Uncoating is the process of removing the protective capsid from the viral genome. Typically, this involves the unfolding and hydrolysis of the proteins by viral digestive enzymes, or comparable enzymes found in the host cell.

In order for a virus to create progeny, it must first replicate its genome and acquire the various proteins needed to construct new virions. Replication of the genome, either DNA or RNA, is accomplished by nucleic acid specific polymerase enzymes. A host cell does not typically contain a RNA-dependant RNA polymerase, consequently this enzyme is packaged into the virion. Protein biosynthesis is relatively straightforward for positive-sense RNA viruses, given that their genome serves directly as mRNA. In the case of double-stranded DNA viruses, the mRNA is produced in the same manner as it would be for the host genome. The RNA polymerase of a host cell requires double-stranded DNA in order to construct mRNA. Therefore, single-stranded DNA viruses must first rely on the production of a complementary DNA strand. Neither double-stranded RNA nor negative-sense RNA can serve as mRNA. As a result, viruses containing these types of nucleic acid necessarily package their own RNA-dependent RNA polymerases. Retroviruses are RNA viruses whose genomes exist as positive-sense RNA, but are not used in translation. These viruses replicate and produce mRNA through a double-stranded DNA intermediate. The process of copying the information in RNA into DNA is performed by a viral reverse transcriptase enzyme.

Once genomic replication and protein synthesis is complete, a virus can be assembled and released from the host cell. This process is highly variable and dependent on the type of virus. In general, a virus can exit a cell through one of three methods; 1. budding, 2. apoptosis, and 3. exocytosis. Enveloped viruses require the insertion of their own proteins into the membrane of a host cell prior to departure. The nucleic acid-containing capsids of these viruses gather themselves at the portion of the membrane containing these viral proteins. Through a process called budding, the virus is engulfed in the bilayer and released into the extracellular fluid. Each viral particle liberated takes a portion of the host's membrane with it, eventually causing the death of the cell. Viruses can also initiate programmed cell death (apoptosis) in order to escape a cell. This process involves the digestion of the cell's genome and the sequestering of that material in irregular membrane bulges called apoptotitic bodies. These bulges, which also contain viral particles, are absorbed by macrophages. This serves as an excellent way for viruses to travel throughout the body, or to infect macrophages themselves. Finally, viruses can use a cell's own transport system to breakout. Through a process known as exocytosis, viral particles can become enclosed in vacuoles and then released into the extracellular fluid. Since no cell membrane is taken, this process keeps the host cell alive longer to produce a greater quantity of viruses.

2.4.3 Influenza

Influenza, also known as the flu, is the term for any infectious disease caused by the influenza viruses. The three species, influenza virus A, B and C, all belong to the *Orthomyxoviridae* family of RNA viruses and are the only members of their respective genera.[195] Influenza virus A and C infect numerous bird and mammalian species, while influenza virus B almost exclusively infects humans. They are similar in structure and size, all being quasi-spherical enveloped viruses with a diameter of approximately 80-120 nm. All species have negative-sense RNA genomes, which are typically segmented into seven or eight fragments, each containing one or two genes. Of the three species, influenza virus A is by far the most infamous species. It is responsible for yearly epidemics and has produced dozens of deadly pandemics throughout history.

Influenza species are subdivided into different serotypes based on the antibody response to two transmembrane glycoproteins, namely hemagglutinin (H or HA) and neuraminidase (N or NA). All influenza viruses contain both proteins, but structural variations change their antigenic properties. Influenza nomenclature uses these antigens followed by number to distinguish between serotypes. For example, both the 1918 Spanish flu and the 2009 swine flu outbreaks were caused by the H1N1 serotype of influenza A. Sixteen hemagglutinin (H1-H16) and nine neuraminidase (N1-N9) subtypes have been identified thus far.[197] High rates of mutation within each serotype give rise to countless different strains. This explains how the same serotype (H1N1) can cause outbreaks 91 years apart. Many H1N1 strains are relatively harmless and are largely responsible for the 'seasonal flu' experienced during the fall and winter months. The vast majority of human illnesses are caused by influenza A (H1-3 and N1-2) and influenza B strains.

Both the influenza A and B genomes are organized into 8 separate linear segments ranging in size from 890 to 2341 nucleotides. The nine functionally important proteins encoded in these segments are depicted in Figure 68. The genomic fragments are protected by nucleocapsid proteins (NP) to form the ribonucleoprotein complex. The RNA-dependant RNA polymerase is fashioned from the PA, PB1 and PB2 proteins. This complex also has endonuclease activity, and cuts a primer from the mRNA precursors. Projecting from the lipid bilayer are the hemagglutinin (HA1/2) and neuraminidase (NA) proteins, in addition to the M2 protein. A matrix formed by M1 proteins is situated around the inside of the lipid layer.

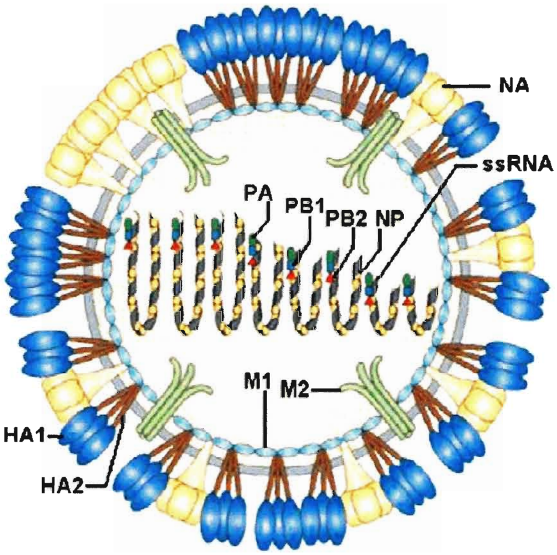


Figure 68. Diagram of the influenza A/B virus.[197]

Hemagglutinin is a transmembrane glycoprotein containing either two or three glycosylation sites. The name is derived from its ability to aggregate red blood cells, a process called hemagglutination. It functions by binding to the sialic acid (*N*-acetyl-neuraminic acid) residues protruding from glycoproteins on the surface of respiratory tract mucous membrane cells. Binding induces penetration of the virus via membrane fusion mechanism. The major portion (HA1) contains at least five antigenic sites labeled A, B (carrying the receptor binding site), C, D, and E. These are the predominant influenza virus antigens targeted by the human immune system. Neuraminidase is the other transmembrane glycoprotein found on the surface of influenza viruses, also with antigenic properties. It is the enzyme responsible for cleaving sialic acid residues from; 1. hemagglutinin, 2. other NA proteins and 3. glycoproteins and glycolipids on the host cell. Mutations of the antigenic sites on hemagglutinin and neuraminidase reduce or inhibit the binding of neutralizing antibodies. This process, termed antigenic drift, creates new strains of an influenza virus serotype. The RNA-dependant RNA polymerase responsible for replicating the viral genome lacks a proofreading mechanism. As a result, approximately one out of every 10,000 nucleotides is incorporated incorrectly. Such errors, or mutations, occur in almost every single new virus produced. The effect is the abnormally high mutation rate seen in viruses compared to other organisms. Another way in which a new strain can arise is through a process called antigenic shift. This occurs when two or more different influenza serotypes infect the same cell. During viral assembly, genome segments from different serotypes can combine. For example, infection by H1N1 and H3N2 strains could lead to the formation of new H1N2 and/ or H3N1 viruses.

The influenza replication cycle follows the same general order outlined earlier. The influenza virus binds to the sialic acid of a cell's glycoproteins and glycolipids (Figure 69). Host cell specificity is determined by the penultimate galactose residue, either α-2,3 (birds) or α-2,6 (humans).[197] After binding, the virus is taken up the cell via a clathrin-coated receptor-mediated endocytosis process. Once inside, the clathrin protein molecules are released and the vesicle containing the whole virus fuses with a membrane-bound compartment called an endosome. In response, the cell attempts to digest the endosome by acidifying its interior. The viral

M2 proteins act as ion channels and allow the influx of protons into the viral envelope. The increased acidity partially denatures hemagglutinin, inducing the fusion of the viral and vesicle membranes. Consequently, the ribonucleoproteins and RNA-dependant-RNA polymerase proteins (PA, PB1 and PB2) are released into the cytoplasm. They are then transported into the nucleus, where the viral polymerase begins transcribing positive-sense RNA nucleotides. The newly constructed viral mRNA is moved out of the nucleus where translation occurs. Some of the synthesized proteins enter the nucleus and form new ribonucleoproteins, while others (e.g. HA and NA) are processed in the endoplasmic reticulum and Golgi apparatus, where glycosylation occurs. The glycosylated proteins are relocated to the cell membrane where they insert into the cell's lipid bilayer. When the local concentrations reach a threshold, the ribonucleoproteins and M1 proteins aggregate and condense to form new viral particles. The membrane protrusions, which contain the viral components, bud off of the host cell membrane. Once again the enveloped viruses are attached to the cell via a sialic acid-hemagglutinin linkage. Neuraminidase catalyses the hydrolysis of this linkage, liberating newly formed virion.

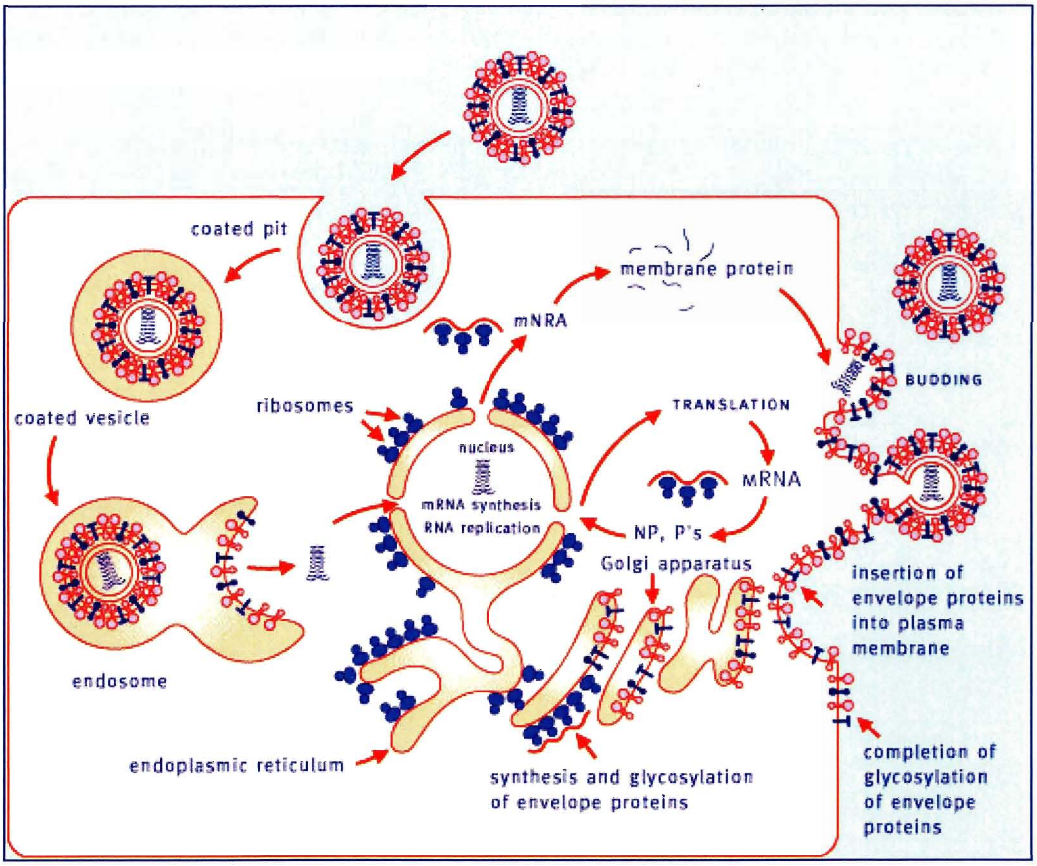

coated pit
membrane protein
mNRA
coated vesicle
ribosomes
nucleus
mRNA synthesis
RNA replication
TRANSLATION
BUDDING
mRNA
NP, P's
Golgi apparatus
insertion of envelope proteins into plasma membrane
endosome
endoplasmic reticulum
synthesis and glycosylation of envelope proteins
completion of glycosylation of envelope proteins

Figure 69. Replication cycle of the influenza virus.[198]

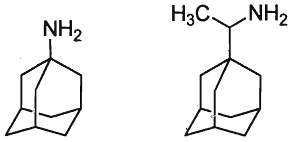
Influenza viruses are easily transmitted between people via three ways; 1. direct contact with an infected individual, 2. contact with a contaminated object, and 3. inhalation of virus containing aerosols produced by coughing or sneezing. The time between entry and the production of new viral particles is approximately six hours.[197] Symptoms include; fever, headache, fatigue to complete exhaustion, myalgia (muscle pain), chills, sore throat, rhinitis (runny nose), sneezing, and coughing. Influenza attacks the cells lining the airways and alveoli. Their replication cycle kills these cells, retarding the flow of oxygen to the blood. Additional damage results from the immune response to the infection. White blood cells, lymphocytes in particular, activate immunomodulating agents known as cytokines. This causes the alveoli to fill with fluid, further disrupting the transport of oxygen. The collective effects of the fluid and cell destruction can be fatal to many patients. Influenza mortality is typically restricted to the elderly, children, or individuals weakened by other illnesses such as AIDS, cancer, heart disease, asthma, emphysema, cystic fibrosis, chronic obstructive pulmonary disease or diabetes. Some influenza strains, including the H1N1 Spanish flu strain, actually killed more young adults than any other demographic group. These deaths resulted from an overly strong immune response to the infection.[200]

The first human influenza virus was isolated in 1933 by Christopher Andrewes, Wilson Smith, and Patrick Laidlaw.[201] Consequently, it is difficult to determine the impact influenza has had on man throughout history. Many ancient disease pandemics have been attributed to influenza, based on the symptoms recorded at the time.[203] It is certain that four major influenza pandemics have occurred in the 20th century alone; 1918 Spanish flu, 1957 Asian flu, 1968 Hong Kong flu, and 1977 Russian flu. Despite the names, all of these outbreaks likely originated in China where people are in close proximity to livestock (i.e. pigs and poultry). This increases the chance of viral infection crossing from one species to another.[204] Contemporary research estimates that the 1918 Spanish flu infected 500 million people, resulting in the death of 40-50 million.[199] Recently, an outbreak of a swine flu strain began in April 2009. It induced worldwide panic and resulted in the closure of Mexico City, a metropolis of nearly 20 million people. In 1999, the Centre for Disease Control and Prevention used a Monte Carlo mathematical model to predict the effect of a new influenza outbreak.[205] It was estimated that 89,000 to 207,000 deaths, 314,000 to

734,000 hospitalizations, 18 to 42 million outpatient visits, and 20 to 47 million additional illnesses would occur in the United States alone. The estimated economic impact was predicted to be between $71.3 to $166.5 billion USD.

Every year, a new influenza vaccine is prepared from the glycoprotein components of the influenza A H3N2, H1N1, and influenza B strains. Their production is predicated on the isolation and identification of the annual influenza mutant strains. It takes six to eight months to develop a new influenza vaccine and another one to two months to produce and distribute worldwide. This makes it impossible to stock pile vaccines in preparation of an outbreak. Furthermore, influenza vaccines are only effective when administered four weeks prior to exposure and thus have no effect on people who have already contracted the virus. Anti-influenza drugs offer a more realistic way to control the spread of influenza. Treating those already infected is far more practical than treating everyone who is not.

The two classes of anti-influenza drugs currently available are the M2 inhibitors and the neuraminidase inhibitors. The former class includes Symmetrel (amantadine, **330**) and Flumadine (rimantadine, **331**) (Figure 70). These pharmaceuticals prevent the final 'uncoating' process by which the virus releases its genome into the cell nucleus. At low concentrations (<1 μg/mL), they inhibit the viral M2 ion channel from transporting protons into the viral core. At higher concentrations (>50 μg/mL), the basic nitrogen buffers the pH of the endosomes, thus preventing the fusion of viral and cell membranes. Both drugs exclusively target influenza A, which is the only strain to contain the M2 protein. Present research as indicated that approximately 93% of all influenza A strains found today are resistant to these drugs.[202] It has also been reported that amantadine and rimantadine cause adverse central nervous system (CNS) side effects.[206] Given such issues, researchers have been searching for new influenza proteins to target. The neuraminidase enzyme has emerged as the leading target because of available structural information and its presence in all influenza strains. Exhaustive research led to the discovery and development of the anti-influenza drugs Relenza (zanamivir, **332**) and Tamiflu (oseltamivir, **2**).



330 **331**

Figure 70. M2 inhibitor anti-influenza drugs.

2.4.4 Neuraminidase

Neuraminidase (exo-α-sialidase EC 3.2.1.18) is an exoglycohydrolase that cleaves α-ketosidically linked *N*-acetylneuraminic acid (Neu5Ac, **333**) residues that cap various glycoconjugates. This releases newly formed influenza virions from host cells, thus propagating the viral infection. Neuraminidase inhibitors, such as zanamivir **(332)** and oseltamivir **(2)**, prevent this from occurring (Figure 71). Neuraminidase may also assist in the movement of the influenza virus through the upper respiratory tract. In order for the virus to reach the epithelial host cells, it must negotiate a layer of protective mucus containing sialic acid-rich glycoproteins and glycolipids. It has been proposed that hydrolysis of these residues by neuraminidase helps the virus pass through these mucosal secretions.[207]

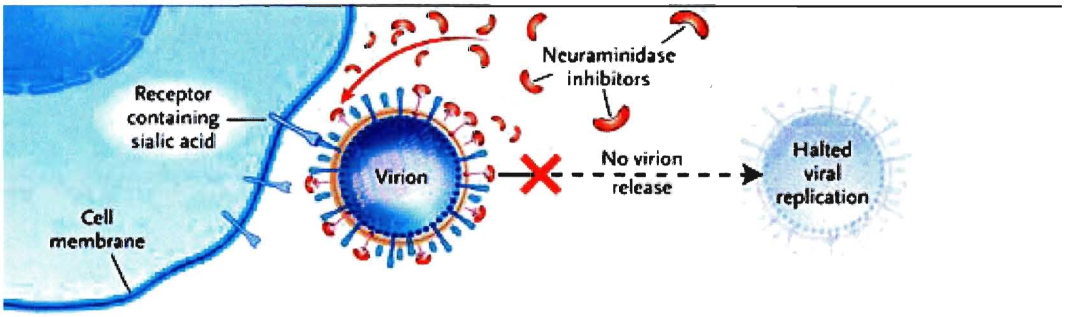
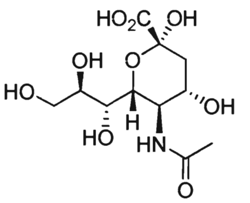

Neuraminidase inhibitors
Receptor containing sialic acid
Cell membrane
Virion
No virion release
Halted viral replication

Figure 71. Neuraminidase-mediated inhibition.[208]

The vital role of the influenza neuraminidase enzyme made it an attractive target for drug development. A screening program for neuraminidase inhibitors began as early as 1966, although without success.[209] Soon after, Meindl and Tuppy synthesized 2-deoxy-2,3-dehydro-*N*-acylneuraminic acid (Neu5Ac2en, **334**) and demonstrated its anti-neuraminidase activity (Figure 72).[210] Analogs of Neu5Ac2en, including various esters and trifluoroacetate derivatives, were prepared and tested.[211] Using electron microscopy, Palese and Compans observed the inhibitors interfering with the release of progeny virions from infected cells.[212] Unfortunately, these inhibitors performed poorly *in vivo* and were active against mammalian and bacterial sialidases.[213] Nevertheless, Neu5Ac2en **(334)** served as the starting point for all neuraminidase inhibition research.



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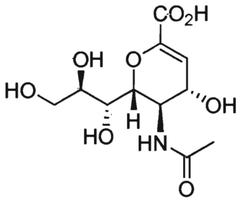


334

Figure 72. Neuraminidase substrate Neu5Ac **(333)** and inhibitor Neu5Ac2en **(334)**

Kinetic isotope studies have suggested that the neuraminidase mechanism proceeded through an endocyclic sialosyl cation transition-state intermediate (Figure 74).[214] It was proposed that the olefin functionality in Neu5Ac2en **(334)** mimicked the sialosyl cation, a likely intermediate in most glycolysis reactions.[215] The hope was that a mechanism-based transition-state inhibitor could be developed from this parent compound. The neuraminidase crystal structure available at the time had a resolution of ~3Å, and hence was of limited value in structural based drug design.[216-7] Although, it was determined that neuraminidase is a mushroom-shaped tetrameric protein, anchored to a membrane via a single hydrophobic tail, 29 amino acids in length. As a result, this enzyme can be divided and studied with no effect on antigenic or enzymatic activity. Nearly a decade later, x-ray crystallography of the neuraminidase enzyme structure in complex with Neu5Ac **(333)** and Neu5Ac2en **(334)** were successfully completed.[218] Subsequent molecular modeling studies revealed valuable details of the essential binding interactions.

The neuraminidase active site is a deep pocket located in the centre of each subunit. Although variation exists elsewhere, all residues which make direct contact with the substrate are strictly conserved among all influenza neuraminidases. These residues, 18 in total, make similar interactions with both substrate and inhibitor molecules. Specifically, the carboxylate of *N*-acetylneuraminic acid **(333)** interacts strongly with the side chains of an arginine triad (Arg 118, 292 and in particular 371) (Figure 73). In order to achieve these interactions, Neu5Ac **(333)** is distorted by the active site environment from its native chair confirmation into a pseudo-boat conformer, as depicted in both Figure 73 and 74. There are two more significant binding regions, or pockets, within the active site. First, the glycerol side chain of Neu5Ac fits into a pocket where it makes hydrogen bonding interactions with at least one glutamate residue (Glu276). The second is a hydrophobic pocket containing a tryptophan (Trp178), and an isoleucine (Ile222) residue. This pocket is vital for molecular recognition and is in close proximity to the acetamide and the hydrocarbon backbone of the glycerol side chain.

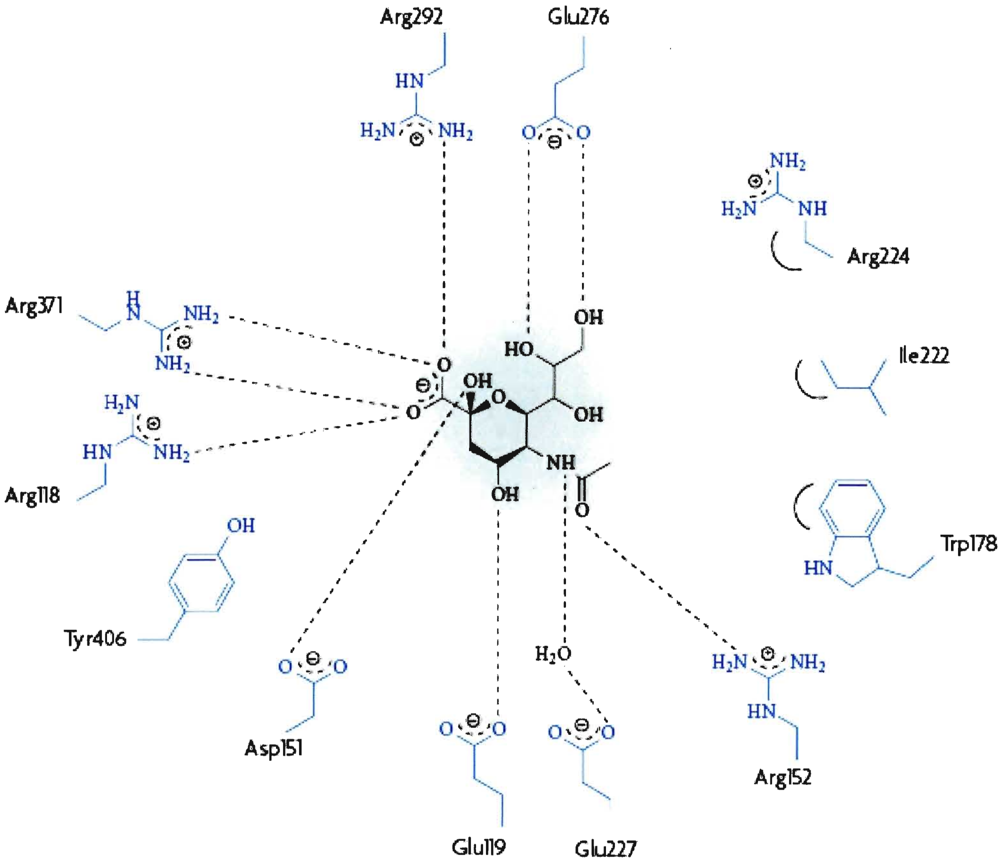

Arg292
Glu276
HN
H₂N
NH₂
O
O
NH₂
H₂N
NH
Arg224
Arg371
H
N
NH₂
NH₂
OH
HO
O
OH
O
O
OH
Ile222
H₂N
HN
NH₂
Arg118
NH
O
OH
OH
Trp178
HN
Tyr406
O
O
H₂O
H₂N
NH₂
HN
Asp151
O
O
O
O
Arg152
Glu119
Glu227

Figure 73. Interactions of *N*-acetylneuraminic acid with influenza virus neuraminidase.[219]

Based on x-ray crystallography, molecular modeling and kinetic studies, a complete mechanism of hydrolysis was proposed.[220] As previously described, binding of the substrate induces a conformation change in the pyranose ring (Figure 74). This rotates the glycosidic bond at C2 from its native equatorial position to an axial position where it hydrogen bonds to an aspartate residue (Asp151). This initiates the departure of the aglycon compound and formation of an oxocarbocation (sialosyl cation) transition-state intermediate; presumably stabilized by local negatively charged residues (i.e. Asp151, Glu119 and Glu227). It has been proposed that the cation intermediate is trapped to form a glycosyl-enzyme covalent intermediate, a common feature of glycohydrolases.[221] Reformation of the sialosyl cation would then precede stereoselective water hydrolysis to provide the α-anomer of Neu5Ac **(333)**, which mutarotates to the thermodynamically favourable β-anomer.

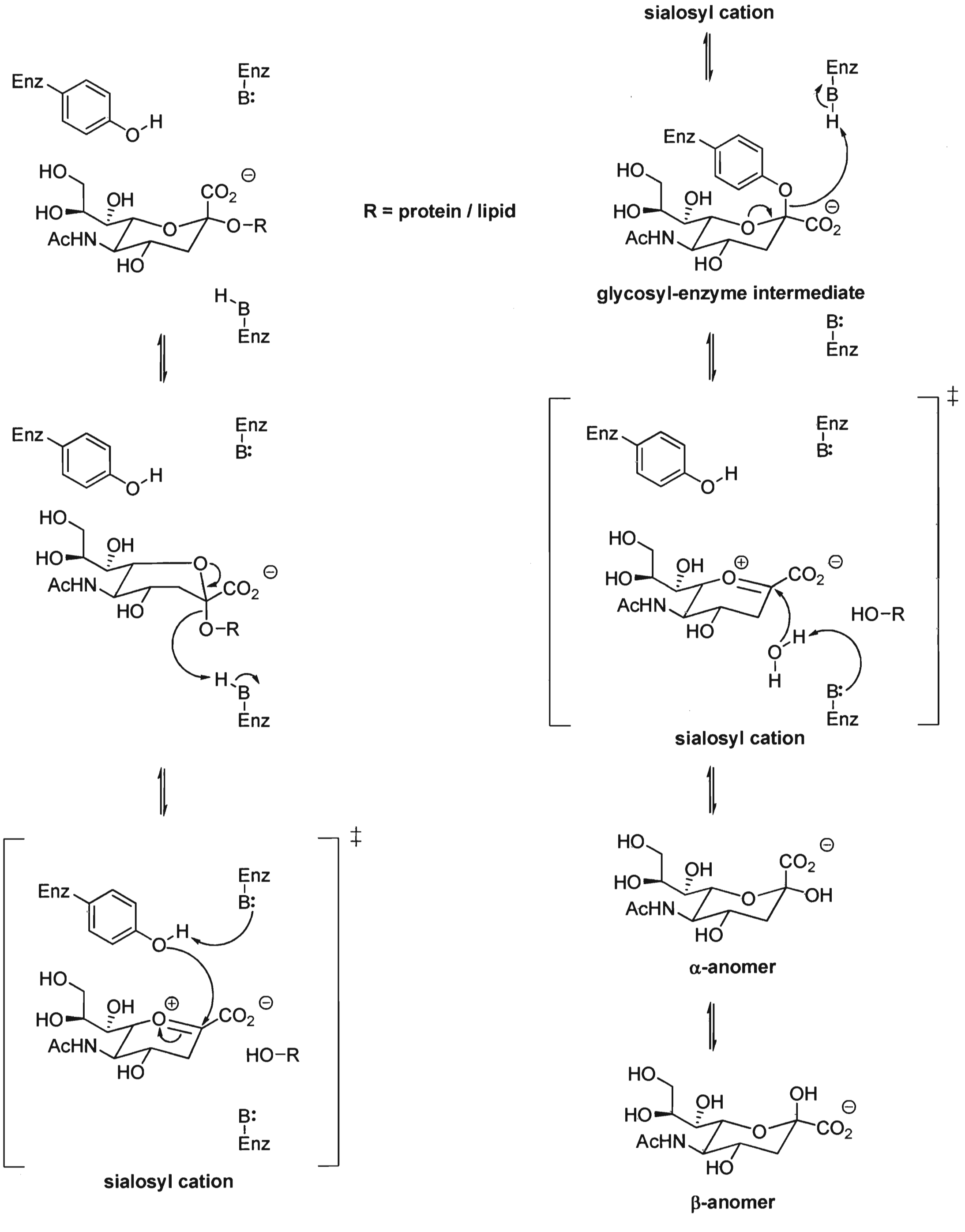
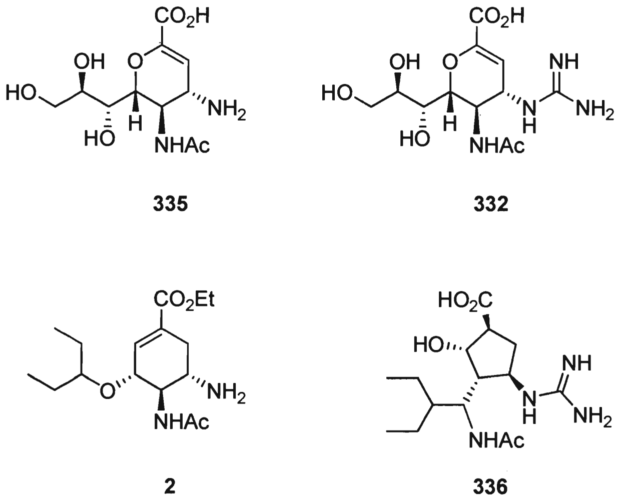

sialosyl cation
R = protein / lipid
glycosyl-enzyme intermediate
sialosyl cation
sialosyl cation
α-anomer
β-anomer
Enz
B:
HO−R
AcHN

Figure 74. Enzymatic mechanism of influenza virus neuraminidase.[219]

2.4.5 Development of Zanamivir and Oseltamivir

In the early 1990's, the newly acquired neuraminidase structural information initiated a structure-based drug design effort. Computational chemistry techniques were used to probe the active site for structural analogs of Neu5Ac2en **(334)** that could be more potent.[222-3] This technique involves the creation of a series of grid points inside of the active site using a system developed by Goodford.[224] Multi-atom probes, representing various functional groups, were inserted to measure the binding interactions. In order to determine the most favourable interactions, each probe atom was rotated to all possible orientations. The most important information obtained from this search concluded that the binding pocket into which the C4 hydroxyl of Neu5Ac **(333)** and Neu5Ac2en **(334)** inserts could interact with basic functional groups. It was predicted that such groups would form a salt-bridge with a proximal glutamate residue (Glu119), resulting in a higher affinity for the neuraminidase enzyme. The first example, 4-amino-Neu5Ac2en **(335)**, was synthesized and tested for activity. It proved to be more potent than the parent compound (*K*i (M) 4×10^{-6} vs. 4×10^{-8}) and was active *in vivo*. The molecular modeling studies also suggested that a larger basic group could fit inside this active site pocket. Insertion of a guanidinium group at C4 was predicted to form even greater hydrogen bonding interactions. The resulting compound, 4-guanidino-Neu5Ac2en (zanamivir, **332**), was even more potent (*K*i (M) 3×10^{-11}) and was also active *in vivo*. Fortunately, zanamivir was found to be inactive towards mammalian and bacterial neuraminidase enzymes. It was fast tracked by the US FDA and approved for sale in 1999 by Glaxo Wellcome (now part of GlaxoSmithKline) under the trade name Relenza.

Zanamivir is a relatively polar compound, suffering from low oral bioavailability (<3%). Therefore, the drug is administered by inhalation. Researchers felt that the carbohydrate core of zanamivir partially explained its high rate of metabolism and that cyclohexene-based compounds were the logical replacement. Based on previous computational chemistry research, three key concepts were exploited in the development of the next series of neuraminidase inhibitors. First, the olefin was shifted in order to more closely replicate the sialosyl cation transition-state. Second, the glycerol side chain was replaced by an ether group. The hope was that this increase in lipophilicity would help improve oral bioavailability. Furthermore, it was known that the glycerol hydrocarbon backbone interacted with the hydrophobic region in the active site. The belief was that the hydrocarbon portion of an ether could exploit this fact. An extensive structure-activity investigation identified the 3-pentyl ether as the most potent inhibitor.[226-7] The result was the synthesis of GS4071, the carboxylic acid analog of oseltamivir **(2)**. Finally, although a carboxylate was essential it was clearly too polar for oral administration. Instead, a prodrug approach was developed that would utilize an ester as a direct precursor to the active form. The acid functionality would be revealed upon hydrolysis by endogenous esterases. The ethyl ester of GS4071 displayed the best balance of *in vivo* activity and oral bioavailability. Developed by Gilead Sciences, oseltamivir **(2)** was approved by the Food and Drug Administration (FDA) in late 1999 and was subsequently marketed by Hoffmann-La Roche under the trade name Tamiflu.



335 **332**

2 **336**

Figure 75. Influenza neuraminidase inhibitors.

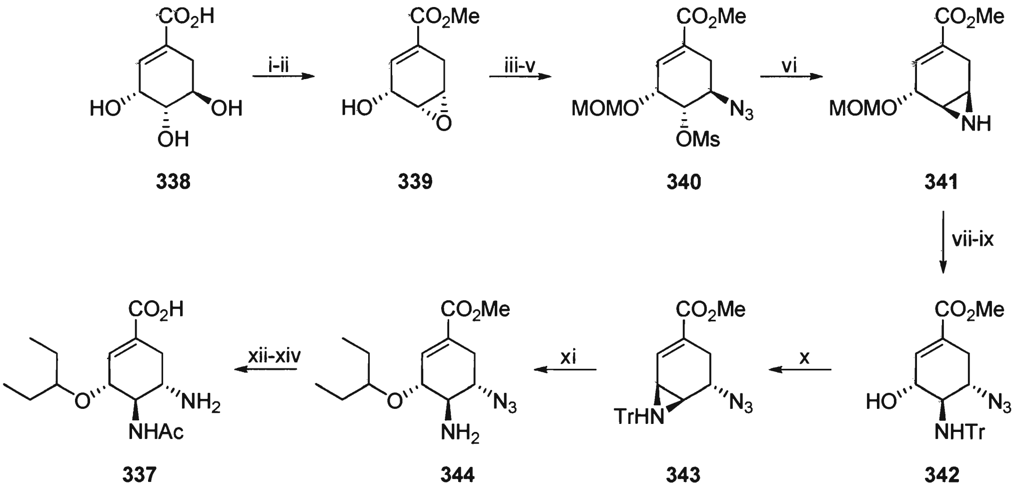
The possibility of another influenza pandemic, and the discovery of oseltamivir-resistant mutant strains,[228] has necessitated an aggressive drug-development program. The next generations of neuraminidase inhibitors are currently under development. A cyclopentane derivative, peramivir **(336)**, is currently under development by BioCryst Pharmaceuticals.

2.4.6 Oseltamivir Syntheses

During extensive structural-activity studies, researchers at Gilead Sciences identified carboxylic acid **337**, named GS4071, as a potent and selective inhibitor of influenza neuraminidase.[229] Subsequent *in vivo* studies led to the development of ethyl ester prodrug GS4104, later named oseltamivir **(2)**.[230] Since that time, many well-designed and clever syntheses have been developed by industrial and academic groups.

Gilead Sciences (1997)[229]

For their first synthesis of carboxylic acid **337**, Gilead selected the structurally similar (–)-shikimic acid **(338)** as the starting material (Scheme 26). Esterification was followed by epoxide formation using a protocol previously described by Berchtold.[231] The free alcohol of **339** was protected as its methoxymethyl ether, and then treated with sodium azide in the presence of ammonium chloride. The resulting hydroxyl was derivatized with methanesulfonyl chloride (MsCl) to provide **340**. Treatment with triphenylphosphine, and then base, reduced the azide and effected the formation of aziridine **341**. Ring opening with azide, acidic ether hydrolysis, and reaction with triphenylmethyl chloride provided azide **342**. Simultaneous treatment with MsCl and triethylamine resulted in the formation of *N*-trityl aziridine **343**. Ring opening with 3-pentanol was catalyzed by boron trifluoride etherate, this procedure also hydrolyzed the trityl protecting group. Azide reduction and basic ester hydrolysis yielded carboxylic acid **337**. Gilead Sciences have also described the synthesis of epoxide intermediate **339** and acid **337** from (–)-quinic acid **(345)**.[229]

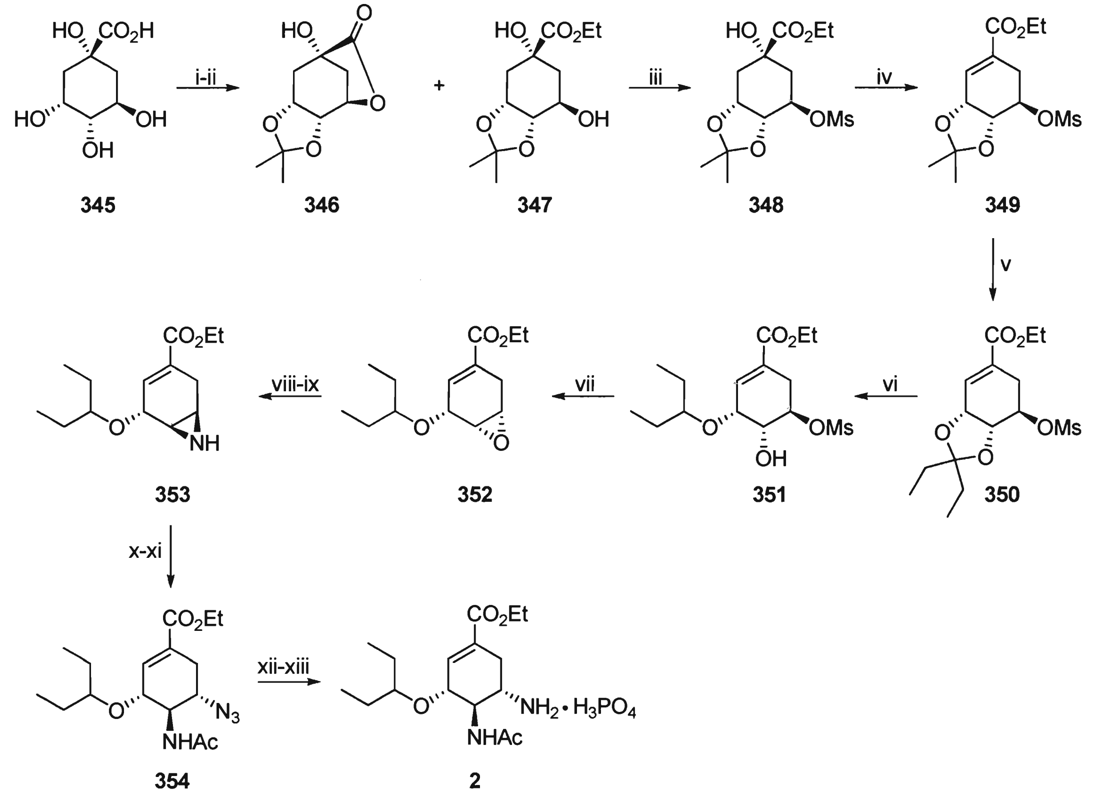


Reagents and conditions: (i) MeOH, $SOCl_2$; (ii) $EtCO_2N=NCO_2Et$, PPh_3; (iii) $MeOCH_2Cl$, DIPEA, DCM, reflux; (iv) NaN_3, NH_4Cl, $MeOH/H_2O$, reflux; (v) $MeSO_2Cl$, NEt_3, DCM, 0°C; (vi) a) PPh_3, THF, 0°C-r.t.; b) NEt_3, H_2O; (vii) NaN_3, NH_4Cl, DMF, 65-70°C; (viii) HCl, MeOH, r.t.; (ix) TrCl, NEt_3, DCM, 0°C; (x) $MeSO_2Cl$, NEt_3, DCM; (xi) $BF_3{\cdot}OEt_2$, 3-pentanol, 70-75°C; (xii) Ac_2O, DMAP, pyr., r.t.; (xiii) PPh_3, THF/H_2O, 50°C; (xiv) a) KOH, THF, r.t.; b) Dowex 50WX8

Scheme 26. Gilead Sciences' synthesis of carboxylic acid **337**.[229]

Gilead Sciences (1998)[232]

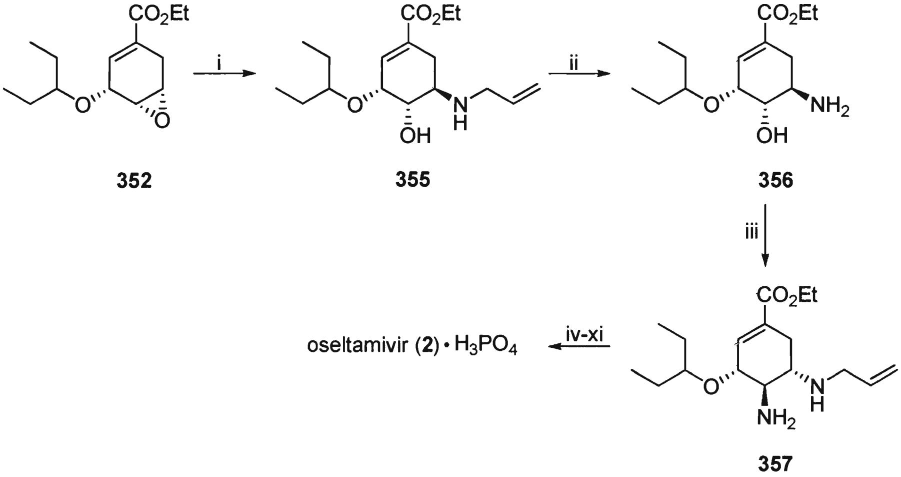
In 1998, Gilead Sciences described a large-scale procedure for preparing oseltamivir **(2)** from (–)-quinic acid **(345)**.[232] Protection of **345** as its acetonide was followed by treatment with sodium ethoxide. This resulted in the formation of lactone **346** and ester **347** in a ratio of 5:1. The mixture was reacted with methanesulfonyl chloride, a which point the undesired lactone could be removed by crystallization. Treatment with sulfuryl chloride and pyridine effected the formation of ethyl acrylate **349**. Transketalization with 3-pentanone and perchloric acid furnished ketal **350**, which was selectively opened with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and $BH_3{\cdot}Me_2S$ complex. This procedure provided a mixture of several ethers, including the desired **351**, which could be selectively extracted in hexanes. Exposure to potassium bicarbonate furnished epoxide **352**, which was opened with sodium azide. This procedure yielded a mixture of regiomeric alcohols, both of which were converted to aziridine **353** upon treatment trimethylphosphine. Ring opening with azide was followed by acylation with acetic anhydride. Azide reduction and treatment with phosphoric acid in ethanol provided Tamiflu **(2)**.



Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, reflux; (ii) NaOEt, EtOH; (iii) MsCl, NEt_3, DCM, 0°C; (iv) SO_2Cl_2, pyr., DCM, -20°C; (v) 3-pentanone, $HClO_4$, 40°C, 25 mmHg; (vi) TMSOTf, $BH_3{\cdot}Me_2S$, DCM, -10°C; (vii) $KHCO_3$, $EtOH/H_2O$, 55°C; (viii) NaN_3, NH_4Cl, $EtOH/H_2O$; (ix) Me_3P, MeCN, 38°C; (x) NaN_3, NH_4Cl, DMF, 70°C; (xi) Ac_2O, $NaHCO_3$, hexanes/DCM; (xii) Raney-Ni, H_2 (1 atm), EtOH; (xiii) H_3PO_4, EtOH, 55°C

Scheme 27. Gilead Sciences' synthesis of Tamiflu **(2)**.[232]

In 1996, F. Hoffman-La Roche signed a contract for the co-development of oseltamivir **(2)**. Shortly afterwards, they published two improved routes to the key epoxide intermediate **352** from (–)-shikimic acid and (–)-quinic acid.[233] Also published was an azide-free route to Tamiflu **(2)** (Scheme 28).[234] The process begins with the selective opening of epoxide **352** with allylamine in the presence of $MgBr_2{\cdot}OEt_2$. Deallylation of **355** was accomplished with palladium on charcoal to provide amino alcohol **356**. Amine **357** was produced in three operations via an aziridine intermediate. A second deallylation provided oseltamivir, which was then converted to Tamiflu. F. Hoffman-La Roche published another azide-free approach which used *tert*-butylamine, instead of allylamine, for the epoxide opening.[235]

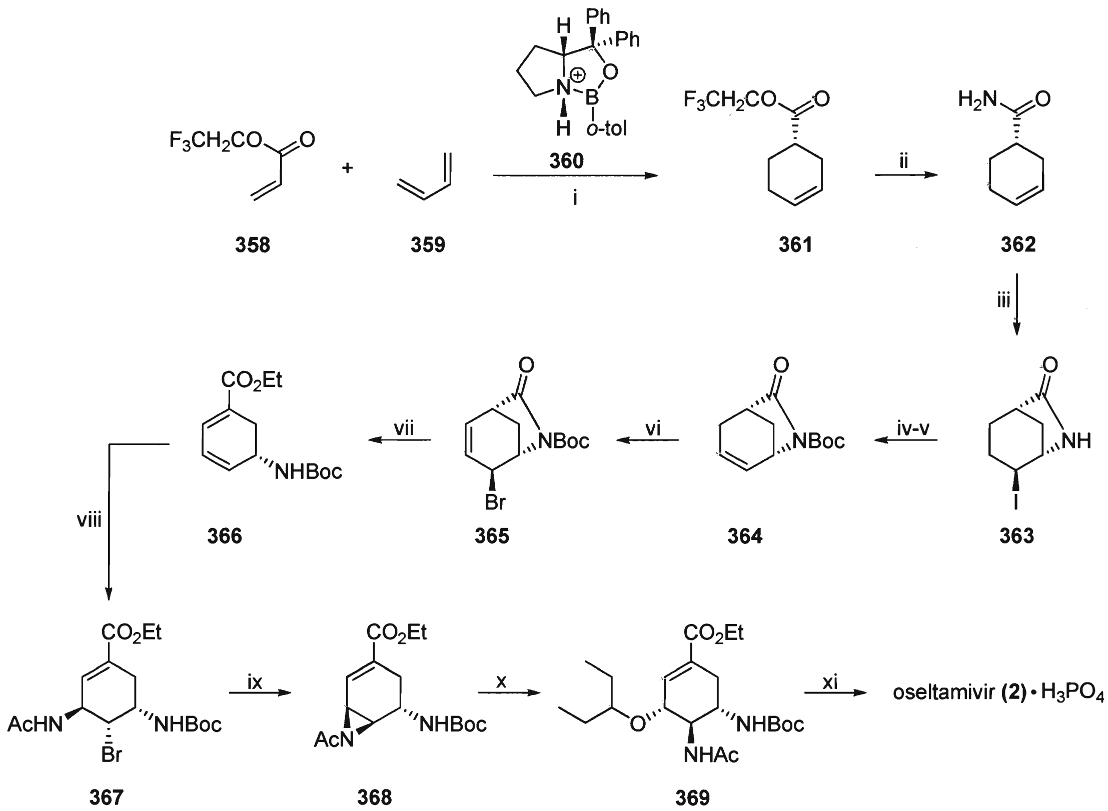


Reagents and conditions: (i) allylamine, $MgBr_2{\cdot}OEt_2$, MTBE/MeCN, 55°C; (ii) 10% Pd/C, ethanolamine, EtOH, reflux; (iii) a) PhCHO, MTBE, reflux; b) MsCl, NEt_3, 0°C; c) allylamine, 110°C , 3.5 bar; d) HCl, H_2O; (iv) Ac_2O, AcOH, $MeSO_3H$, MTBE, 0°C; (v) 10% Pd/C, ethanolamine, EtOH, reflux; (vi) H_3PO_4, EtOH, 50°C

Scheme 28. F. Hoffman-La Roche's azide-free synthesis of Tamiflu **(2)**.[234]

Corey (2006)[237]

Inspired by a Diels-Alder approach to Tamiflu published by F. Hoffman-La Roche,[236] Corey completed the first academic synthesis in 2006 (Scheme 29).[237] The synthesis begins with a stereoselective Diels-Alder reaction between 2,2,2-trifluoroethyl acrylate **(358)** and 1,3-butadiene **(359)** catalyzed by the *S*-proline derived catalyst **360**. Ammonolysis of cyclohexene adduct **361** quantitatively provided amide **362**. Iodolactamization, *tert*-butyl carbamate protection, and elimination of the halogen furnished lactam **364**. Allylic bromination with *N*-bromosuccinimide and treatment with cesium carbonate in ethanol afforded diene intermediate **366**. Formation of bromodiamide **367** was achieved via a tin(IV) bromide catalyzed reaction with *N*-bromoacetamide (NBA). This reaction presumably proceeds through a bromonium ion intermediate, which is possibly opened by acetonitrile, the solvent, in a Ritter-type reaction. Exposure to potassium bis(trimethylsilyl)amide (KHMDS) resulted in the formation of acetylaziridine **368**. Selective opening with 3-pentanol in the presence of copper(II) trifluoromethanesulfonate provided advanced intermediate **369**, which was converted to Tamiflu **(2)** in a one step procedure.

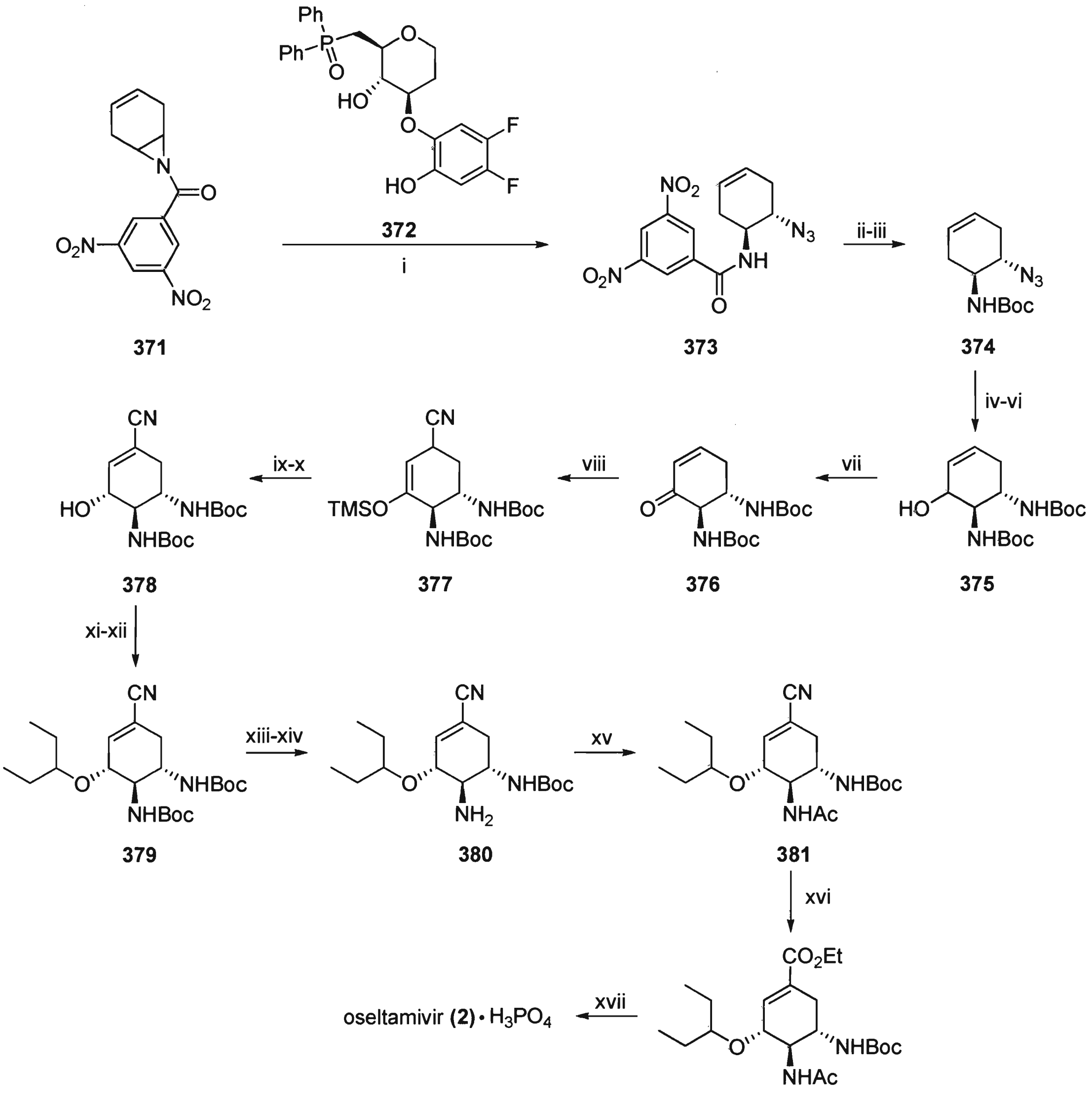


Reagents and conditions: (i) **360**, neat, 23°C; (ii) NH_3, CF_3CH_2OH, 40°C; (iii) a) TMSOTf, NEt_3, pentane; b) I_2, Et_2O/THF; (iv) $(Boc)_2O$, NEt_3, DMAP, DCM; (v) DBU, THF, reflux; (vi) NBS, AIBN, CCl_4, reflux; (vii) Cs_2CO_3, EtOH; (viii) $SnBr_2$, *N*-bromoacetamide, MeCN, -40°C; (ix) *n*-Bu_4NBr, KHMDS, DME, -20°C; (x) $Cu(OTf)_2$, 3-pentanol, 0°C; (xi) H_3PO_4, EtOH

Scheme 29. Corey's synthesis of Tamiflu **(2)**.[237]

Kanai and Shibasaki (2006)[238]

Kanai and Shibasaki of the University of Tokyo have developed several distinct strategies towards the synthesis of Tamiflu.[238-242] Their first route utilized a stereoselective ring opening of a *meso*-aziridine **371** with trimethylsilyl azide through use of chiral ligand **372**. The resulting amide was treated with di-*tert*-butyl dicarbonate and then subjected to basic hydrolysis to provide cyclohexene **374**. Azide reduction and *tert*-butyl carbamate formation was followed by a SeO_2-Dess-Martin periodinane allylic oxidation. Further oxidation with Dess-Martin periodinane preceded a Ni(COD)$_2$-catalyzed 1,4 addition of trimethylsilyl cyanide to afford TMS-enolate **377**. An *N*-bromosuccinimide bromination followed by a selective reduction with LiAlH(O*t*-Bu)$_3$ gave allylic alcohol **378**. Mitsunobu conditions yielded an aziridine, which was opened with 3-pentanol in the presence of $BF_3 \cdot OEt_2$ to furnish advanced intermediate **379**. Acidic carbamate hydrolysis and regioselective acylation provided **381**. The vinyl nitrile functionality was subjected to ethanolic-hydrogen chloride to yield Corey's intermediate **369**.[237]


371
372
i
373
ii-iii
374
iv-vi
375
vii
376
viii
377
ix-x
378
xi-xii
379
xiii-xiv
380
xv
381
xvi
369
xvii
oseltamivir (2) • H3PO4

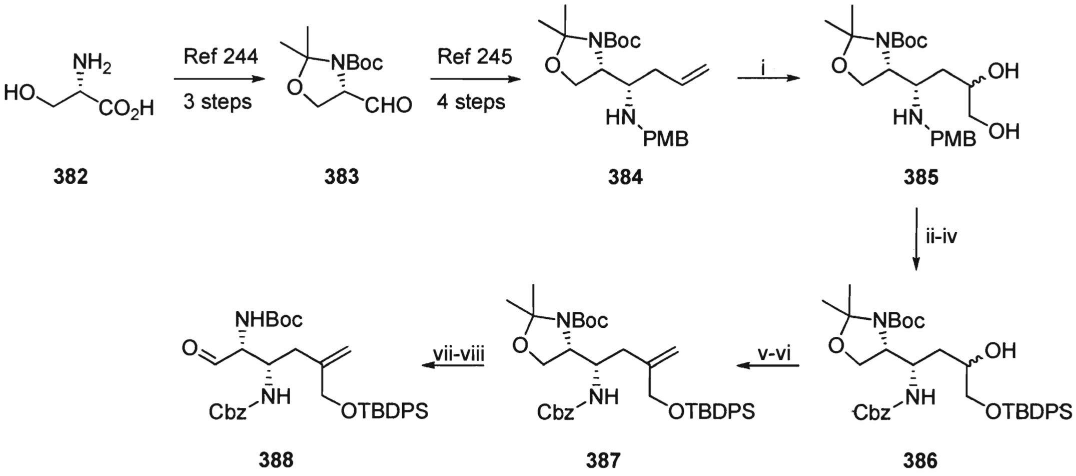
369

Reagents and conditions: (i) a) Y(O*i*-Pr)$_3$, **372**, TMS-N$_3$, CH$_3$CH$_2$CN, r.t.; b) recrystallization from IPA; (ii) Boc$_2$O, MeCN, DMAP, r.t.; (iii) 4 M NaOH, r.t.; (iv) a) PPh$_3$, MeCN, 50°C; b) H$_2$O, 40°C; (v) Boc$_2$O, NEt$_3$, DCM, r.t.; (vi) SeO$_2$, Dess-Martin periodinane, dioxane, 80°C; (vii) a) Dess-Martin periodinane, DCM; b) recrystallization from IPA/hexanes; (viii) Ni(COD)$_2$, COD, TMSCN, THF, 60°C; (ix) a) NBS, THF; b) NEt$_3$; (x) LiAlH(O*t*-Bu)$_3$, THF, 4°C; (xi) DEAD, PPh$_3$, THF; (xii) BF$_3$·OEt$_2$, 3-pentanol; (xiii) TFA, DCM, 0°C; (xiv) Boc$_2$O, NEt$_3$, DCM, r.t.; (xv) Ac$_2$O, DMAP, pyr.; (xvi) a) 4.2 M HCl·EtOH, 60°C; b) H$_2$O; (xvii) H$_3$PO$_4$, EtOH

Scheme 30. Kanai and Shibasaki's synthesis of Tamiflu **(2)**.[238]

Yao (2006)[243]

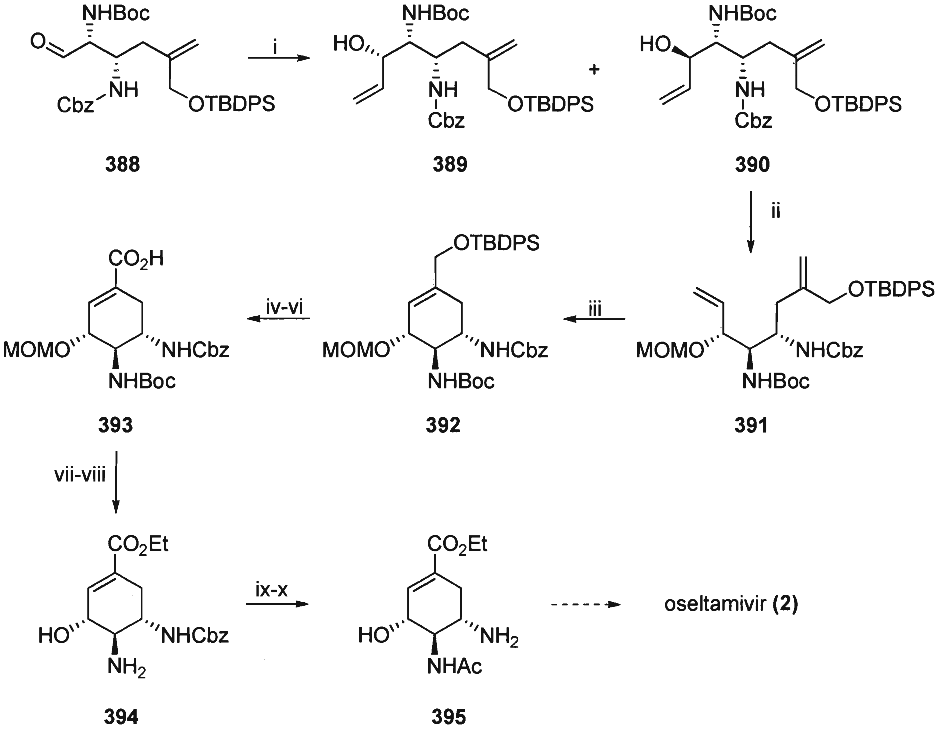
The Yao group prepared advanced Tamiflu intermediate **395** from a more readily available starting material, L-serine **(382)**, compared to many other syntheses. Using procedures developed by Lewis[244] and himself[245], Yao converted L-serine **(382)** to alkene **384** in 7 steps (Scheme 31). Osmium tetroxide-mediated dihydroxylation, benzyl formate formation and selective protection of the primary hydroxyl with *tert*-butyl(chloro)diphenylsilane afforded **386**. A Swern oxidation and subsequent Wittig olefination provided terminal alkene **387**. Hydrolysis of the *N*,*O*-acetal was achieved with bismuth bromide and was followed by another Swern oxidation to yield aldehyde **388**.


NH2
HO
CO2H
382
Ref 244
3 steps
NBoc
O
CHO
383
Ref 245
4 steps
NBoc
O
HN
PMB
384
i
NBoc
O
OH
HN
PMB
OH
385
ii-iv
NBoc
O
OH
NH
Cbz
OTBDPS
386
v-vi
NBoc
O
NH
Cbz
OTBDPS
387
vii-viii
NHBoc
O
NH
Cbz
OTBDPS
388

Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O; (ii) $Pd(OH)_2$, H_2, MeOH, 35°C; (iii) CbzCl, $NaHCO_3$, EtOAc/H_2O; (iv) TBDPSCl, imidazole, DCM; (v) $(COCl)_2$, NEt_3, DMSO, DCM, -78°C; (vi) Ph_3PCH_3Br, *n*-BuLi, THF, -78°C; (vii) $BiBr_3$, MeCN; (viii) $(COCl)_2$, NEt_3, DMSO, DCM, -78°C

Scheme 31. Yao's synthesis of Tamiflu intermediate **388.**[243]

Aldehyde **388** was reacted with vinylmagnesium bromide in the presence of zinc (II)bromide to provide a separable mixture of alcohol **390** and the undesired stereoisomer **389** (Scheme 32). Protection with chloromethyl methyl ether preceded a ring-closing metathesis with Grubbs' 2nd generation catalyst. Desilylation, then a pyridinium chlorochromate/ $NaClO_2$ two-step oxidation procedure afforded carboxylic acid **393**. Esterification and two deprotections yielded amino alcohol **394**, which was converted to **395** in two steps. Although this intermediate was not converted to oseltamivir **(2)**, it does posses most of the required functionality and stereochemistry.



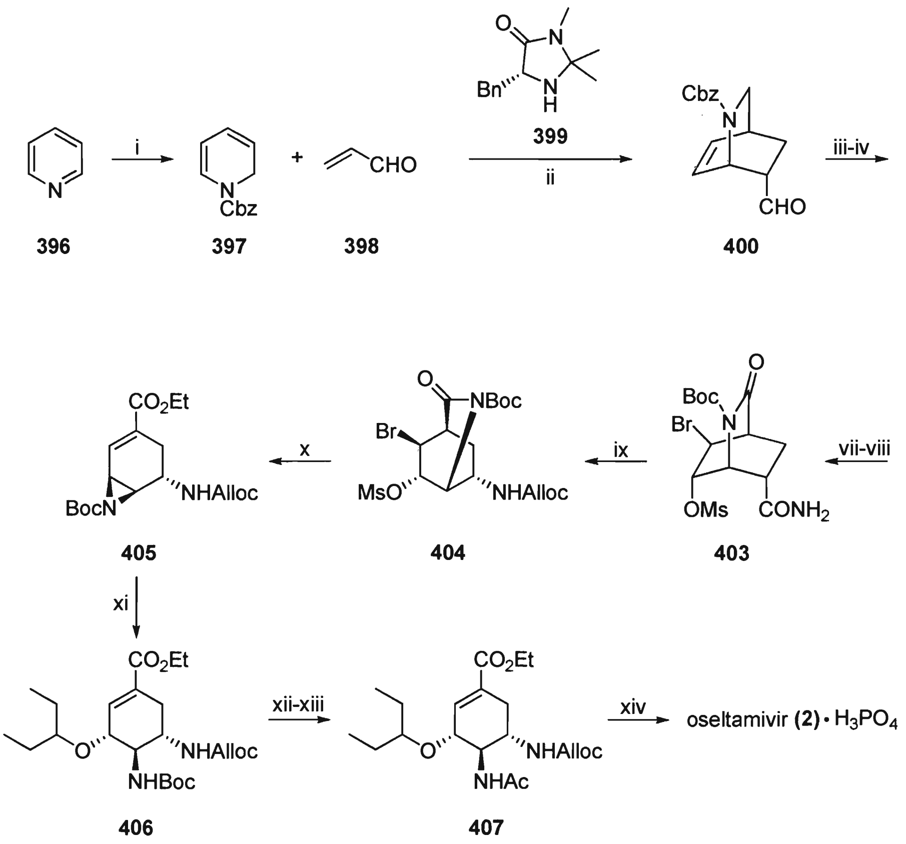
Reagents and conditions: (i) vinylMgBr, $ZnBr_2$, THF, -78°C; (ii) MOMCl, DIPEA, DCM; (iii) Grubb's II catalyst, DCM, r.t.; (iv) TBAF, THF; (v) PCC, 4Å MS, DCM; (vi) $NaClO_2$, K_2HPO_4, 2,3-dimethylbuta-1,3-diene, *t*-BuOH/THF/H_2O (4:1:1), 10°C; (vii) EtOH, HOBt, EDCl, DIPEA, DCM; (viii) 5% HCl/EtOH, 0°C; (ix) AcCl, Na_2CO_3, EtOH, 0°C; (x) $Pd(OAc)_2$, Et_3SiH, NEt_3, DCM, 0°C

Scheme 32. Yao's synthesis of Tamiflu intermediate **395**.[243]

Fukuyama (2007)[246]

Fukuyama has developed a synthetic route to Tamiflu from pyridine **(396)**, a relatively available and economic starting material.[246] The synthesis employs a Diels-

Alder reaction between the Cbz-protected dihydropyridine **397** and acrolein **(398)**. The stereochemistry was controlled through the use of catalyst **399**, previously developed by MacMillian.[247] The resulting aldehyde **400** was oxidized with sodium chlorite and then subjected to a bromolactonization procedure to provide **401**. Protecting group manipulation (Boc for Cbz) and a ruthenium(IV) oxide oxidation afforded imide **402**. Exposure to ammonia, and then methanesulfonyl chloride furnished amide **403**, which underwent a Hofmann rearrangement in the presence of allyl alcohol and iodobenzene diacetate to yield bicyclic compound **404**. Treatment with ethoxide effected the ethanolysis of the lactam, elimination of the bromide, and aziridine formation. Ring opening with 3-pentanol, carbamate hydrolysis and acylation provided alloc-oseltamivir **407**, which was deprotected and reacted with H_3PO_4 to complete the synthesis.

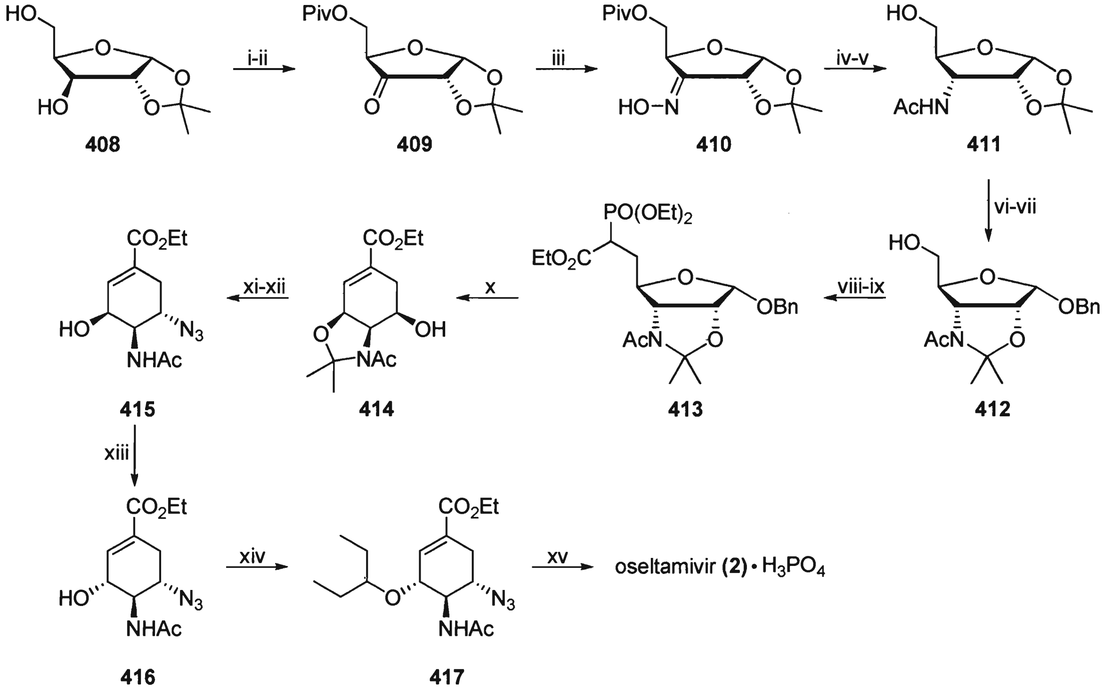


Reagents and conditions: (i) $NaBH_4$, CbzCl, MeOH, -50°C; (ii) acrolein, **399**, MeCN, H_2O; (iii) $NaClO_2$, $NaHPO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, H_2O; (iv) Br_2, $NaHCO_3$, DCM; (v) Pd/C, H_2, $(Boc)_2O$, EtOH, THF; (vi) $RuO_2{\cdot}nH_2O$, $NaIO_4$, $ClCH_2CH_2Cl$, H_2O, 80°C; (vii) NH_3, *t*-BuOH, THF, 0°C; (viii) MsCl, NEt_3, DCM; (ix) allyl alcohol, $PhI(OAc)_2$, 4 Å MS, PhMe, 60°C; (x) NaOEt, EtOH, 0°C; (xi) 3-pentanol, $BF_3{\cdot}OEt_2$, -20°C; (xii) TFA, DCM, 0°C; (xiii) Ac_2O, pyr.; (xiv) a) Pd/C, Ph_3P, 1,3-dimethylbarbituric acid, EtOH, reflux; b) H_3PO_4

Scheme 33. Fukuyama's synthesis of Tamiflu **(2)**.[246]

Fang (2007)[248]

The Fang group's synthesis of Tamiflu **(2)** commences from xylose derivative **408** (Scheme 34).[248] Reaction with pivaloyl chloride, followed by a pyridinium dichromate oxidation afforded ketone **409**. Exposure to hydroxylamine hydrochloride prepared oxime **410**. Reduction with LiAlH removed the pivaloyl ester and reduced the oxime functionality. Acylation, acidic hydrolysis in the presence of benzyl alcohol and acetonide formation yielded *N*,*O*-ketal **412**. Sequential treatment with trifluoromethanesulfonic anhydride (Tf_2O) and then triethylphosphonoacetate and sodium hydride gave phosphoryl ester **413**. A clever intramolecular Horner-Wadsworth-Emmons reaction was used to prepare ethyl acrylate **414**. Mitsunobu conditions with diphenylphosphoryl azide (DPPA) were employed to install the azide, then acidic hydrolysis provided allylic alcohol **415**. A second Mitsunobu reaction inverted the hydroxyl group, which was then reacted with *O*-pentyl trichloroacetimidate under acidic conditions to afford 3-pentyl ether **417**. Azide reduction with Lindlar's catalyst provided oseltamivir **(2)**.

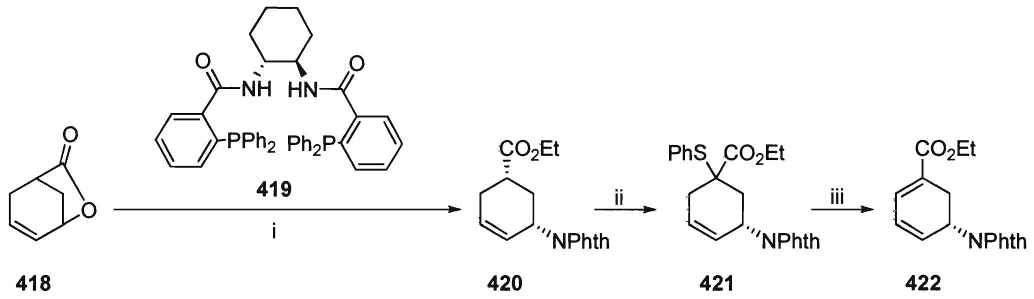


Reagents and conditions: (i) PivCl, pyr., 0°C; (ii) PDC, Ac_2O, reflux; (iii) $HONH_2 \cdot HCl$, pyr., 60°C; (iv) $LiAlH_4$, THF, 0°C – reflux; (v) Ac_2O, pyr., r.t.; (vi) BnOH, 4 M HCl in dioxane; (vii) 2,2-DMP, *p*-TsOH, PhMe, 80°C; (viii) Tf_2O, pyr., DCM, -15°C; (ix) triethylphosphonoacetate, NaH, 15-crown-5, DMF, r.t.; (x) a) H_2, Pd/C, EtOH; b) NaH, THF; (xi) DPPA, DIAD, Ph_3P, THF; (xii) HCl, EtOH, reflux; (xiii) a) Tf_2O, pyr., DCM, 15°C; b) KNO_2, 18-crown-6, DMF; (xiv) $Cl_3CC(=NH)OCHEt_2$, CF_3SO_3H, DCM; (xv) a) H_2, Lindlar's catalyst, EtOH, r.t.; b) H_3PO_4, EtOH, 40°C

Scheme 34. Fang's synthesis of Tamiflu **(2)**.[248]

Trost (2008)[249]

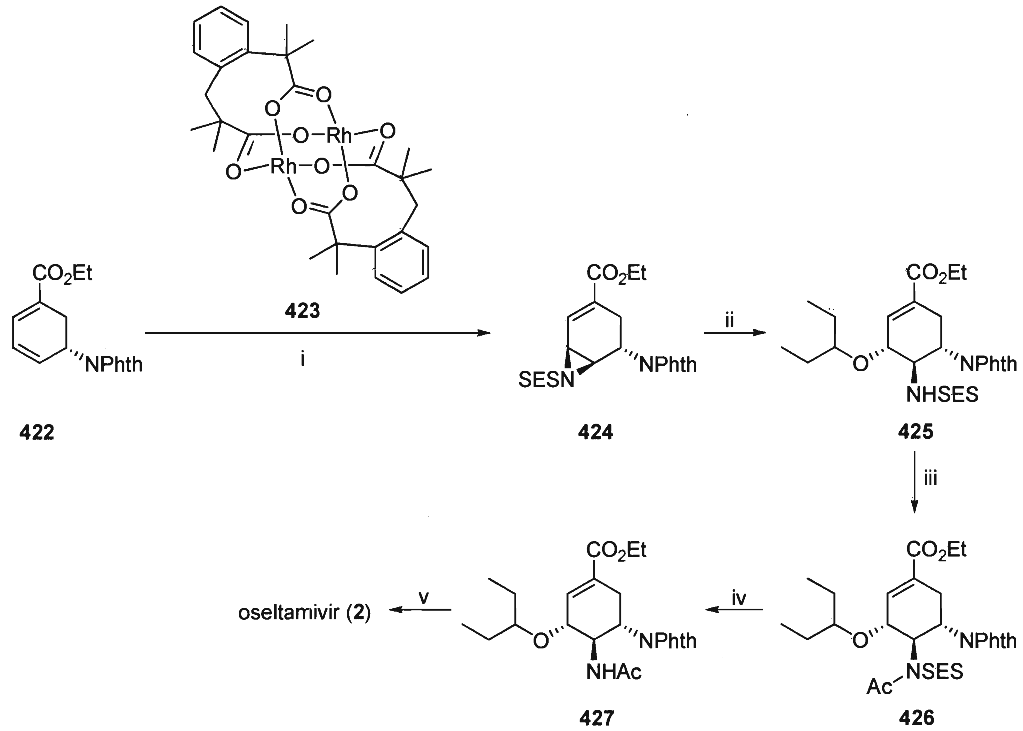
One of the shortest syntheses reported to date was accomplished by the Trost group in 2008.[249] The first step is a palladium-catalyzed asymmetric allylic alkylation of alkene **418** with trimethylsilylphthalimide in the presence of Trost's (*R*,*R*)-chiral ligand **419**. The reaction mixture was then treated with ethanol, under acidic conditions, to provide ethyl ester **420**. Sulfenylation with $PhSSO_2Ph$ afforded a diastereomeric mixture of ester **421**. Sulfur oxidation with *m*-CPBA and subsequent elimination with DBU provided diene **422**.



Reagents and conditions: (i) a) **419** $[(\eta^3\text{-}C_3H_5PdCl)_2]$, trimethylsilylphthalimide, THF, 40°C; b) *p*-TsOH·H_2O, EtOH, reflux; (ii) KHMDS, $PhSSO_2Ph$, THF, -78°C; (iii) a) *m*-CPBA, $NaHCO_3$, 0°C; b) DBU, PhMe, 60°C

Scheme 35. Trost's synthesis of oseltamivir intermediate **422**.[249]

The chiral aziridination of diene **422** was accomplished through a nitrene reagent formed *in situ* by reacting 2-(trimethylsilyl)ethanesulfonamide ($SES\text{-}NH_2$) with $PhI(O_2CCMe_3)_2$. After extensive research with copper, gold, and silver catalysts, it was found that chiral rhodium complex **423** provided the best selectivity. Opening of the SES-aziridine with 3-pentanol and acylation provided protected oseltamivir intermediate **426**. Sequential treatment with TBAF and then hydrazine completed the synthesis of oseltamivir **(2)**.

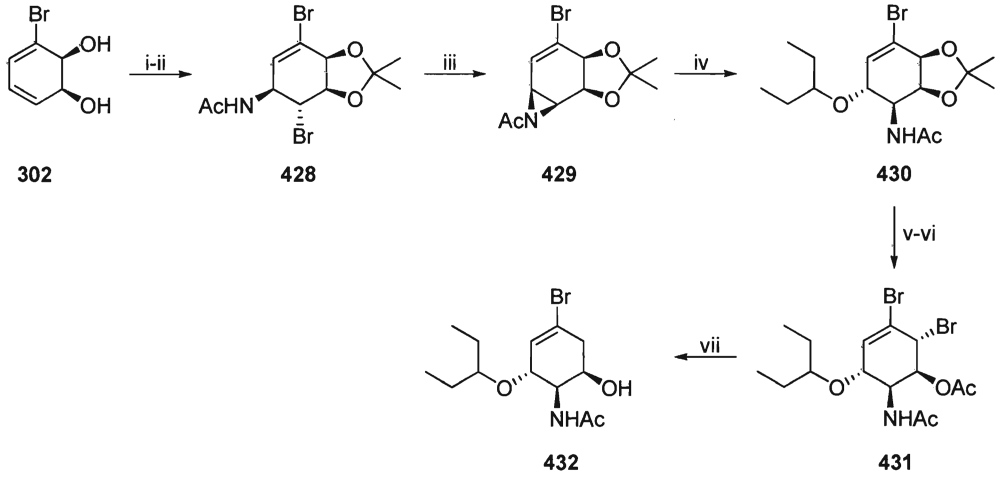


Reagents and conditions: (i) a) **423**, 2-(trimethylsilyl)ethanesulfonamide, $PhI(O_2CCMe_3)_2$, MgO, PhCl, 0°C; (ii) 3-pentanol, $BF_3{\cdot}OEt_2$, 75°C; (iii) DMAP, pyr., Ac_2O, MW, 150°C; (iv) TBAF, THF, r.t.; (v) NH_2NH_2, EtOH, 68°C

Scheme 36. Trost's synthesis of oseltamivir **(2)**.[249]

Fang (2008)[250]

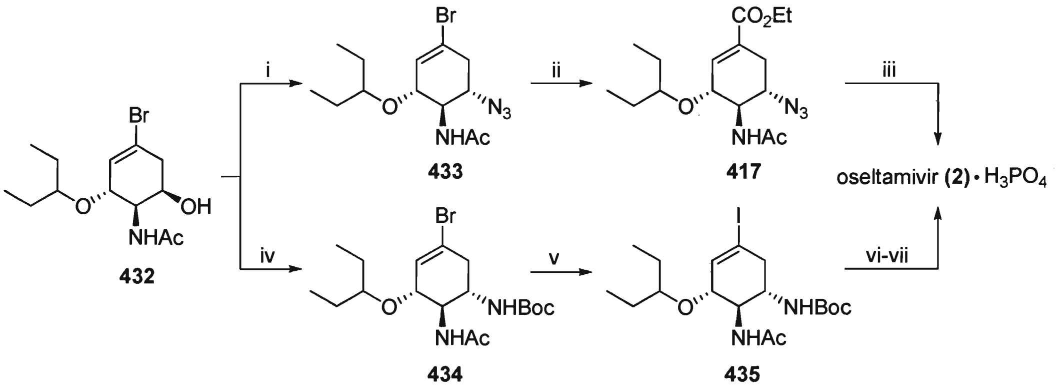
The second Tamiflu synthesis published by the Fang group employs the commercially available *cis*-dihydrodiol **302**, obtained from the TDO-dihydroxylation of bromobenzene.[250] The acetonide derivative of **302** was subjected to the bromoacetamidation-aziridination procedure used in Corey's Tamiflu synthesis (Scheme 37). Next, an aziridine opening reaction with 3-pentanol was catalyzed by boron trifluoride etherate. Acidic cleavage of the acetonide provided a free diol which was reacted with α-acetoxyisobutyryl bromide to afford dibromide **431**. The allylic bromide and the acetyl group were both reduced with lithium triethylborohydride to yield homoallylic alcohol **432**.



Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, 0°C; (ii) *N*-bromoacetamide, $SnBr_4$, $MeCN/H_2O$, 0°C; (iii) LiHMDS, THF, -10°C; (iv) 3-pentanol, $BF_3{\cdot}OEt_2$, -10°C; (v) conc. HCl, MeOH, 50°C; (vi) $AcOCMe_2COBr$, THF, 0°C; (vii) $LiBHEt_3$, THF, 0°C

Scheme 37. Fang's synthesis of Tamiflu intermediate **432**.[250]

Fang described two strategies to synthesize Tamiflu from alcohol **432**. In the first route, Mitsunobu conditions and diphenylphosphoryl azide were used to install the azide functionality. The vinyl bromide was reacted with a nickel-carbonyl-triphenylphosphine complex in ethanol to furnish ethyl ester **417**, an intermediate in Fang's first synthesis.[248] The second route described has one additional step but is azide-free. Alcohol **432** was reacted with tetrabutylammonium cyanate in the presence of triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone. The resulting isocyanate intermediate was treated with *tert*-butanol to provide Boc-protected derivative **434**. Halogen exchange provided vinyl iodide **435**, which was subjected to a palladium-catalyzed carbonylation, esterification and deprotection sequence to yield oseltamivir **(2)**.



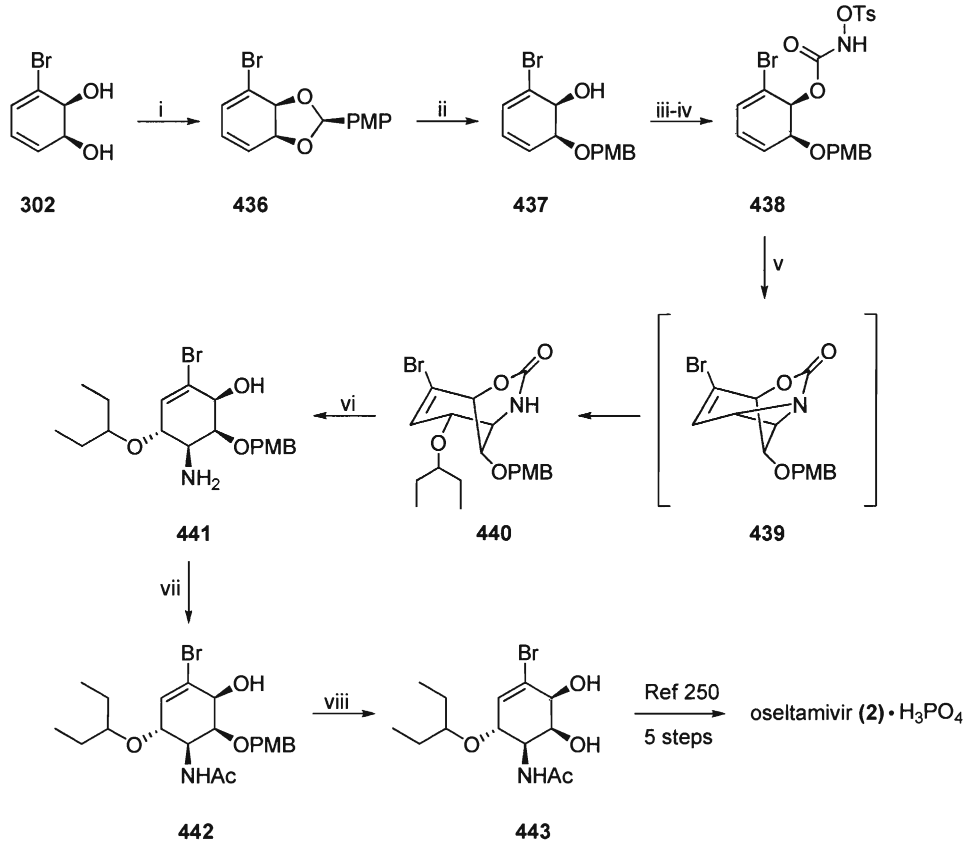
Reagents and conditions: (i) DPPA, DIAD, PPh_3, THF, 40°C; (ii) $[Ni(CO)_2(PPh_3)_2]$, DIPEA, EtOH, THF, 80°C; (iii) a) H_2, Lindlar's catalyst, EtOH; b) H_3PO_4, EtOH, 50°C; (iv) a) DDQ, PPh_3, *n*-Bu_4NOCN, MeCN, r.t.; b) *t*-BuOH, reflux; (v) CuI, KI, *N,N'*-dimethylethylenediamine, *n*-BuOH, 120°C; (vi) $Pd(OAc)_2$, CO, NaOAc, EtOH, r.t.; (vii) H_3PO_4, EtOH, 50°C

Scheme 38. Fang's two approaches to Tamiflu from **432.**[250]

Banwell (2008)[251]

As with Fang's second synthesis of Tamiflu,[250] Banwell employed the *cis*-1,2-dihydrodiol **302** derived from the whole-cell oxidation of bromobenzene (Scheme 39).[251] Treatment of **302** with 4-methoxybenzaldehyde dimethyl acetal gave ketal **436**, which was reduced with diisobutylaluminum hydride to provide a 6:1 mixture of monoprotected diol **437** and its regioisomer. The allylic alcohol was reacted with 1,1'-carbonyldiimidazole (CDI) and then hydroxylamine to form a carbamate derivative which was then *O*-tosylated. The 3-pentyl group was installed by reacting carbamate **438** with 3-pentanol in the presence of $Cu(MeCN)_4PF_6$. The authors suggested that an intramolecular aziridination between a nitrene intermediate and the unsubstituted olefin creates **439**, which is then attacked by 3-pentanol at the allylic position. The resulting cyclic carbamate **440** was then hydrolyzed with LiOH to furnish γ-amino alcohol **441**. Acylation of the primary amine and acidic hydrolysis of the *p*-

methoxybenzyl group yielded diol **443**, a formal intermediate from Fang's synthesis.[250]

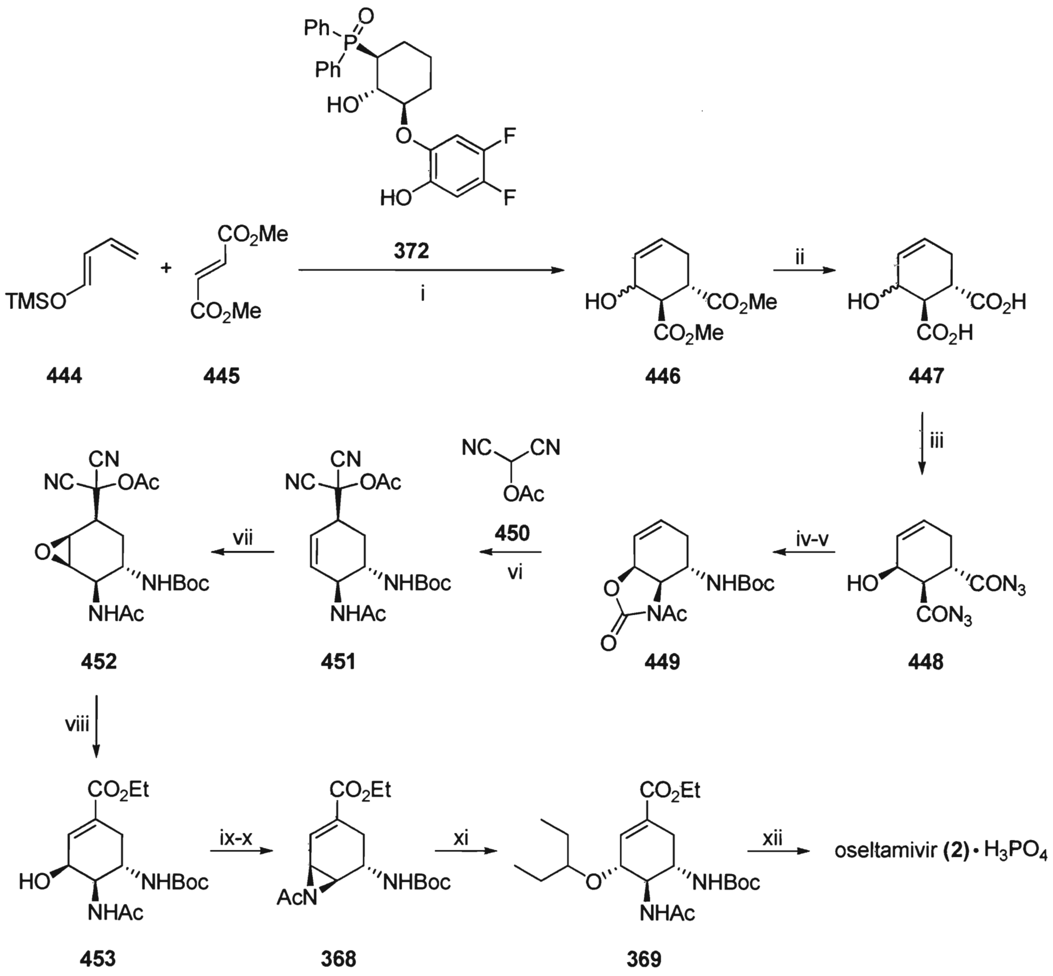

Br
OH
OH
302
i
Br
O
O
PMP
436
ii
Br
OH
OPMB
437
iii-iv
OTs
NH
O
Br
O
OPMB
438
v
Br
O
O
N
OPMB
439
Br
O
O
NH
O
OPMB
440
vi
Br
OH
O
OPMB
NH2
441
vii
Br
OH
O
OPMB
NHAc
442
viii
Br
OH
O
OH
NHAc
443
Ref 250
5 steps
oseltamivir (2) • H3PO4

Reagents and conditions: (i) 4-methoxybenzaldehyde dimethyl acetal, (+)-camphorsulfonic acid, PhMe, 0°C; (ii) DIBAL-H, NEt_3, PhMe, -78°C; (iii) a) CDI, MeCN, 0°C; b) $NH_2OH{\cdot}HCl$, imidazole, 0°C; (iv) *p*-TsCl, NEt_3, Et_2O, 0°C; (v) $Cu(MeCN)_4PF_6$, K_2CO_3, MeCN, 3-pentanol, 0°C; (vi) LiOH, 1,4-dioxane/H_2O, 100°C; (vii) AcCl, NEt_3, 0°C; (viii) HCl, MeOH, 35°C

Scheme 39. Banwell's formal synthesis of Tamiflu **(2)**.[251]

Kanai and Shibasaki (2009)[241]

Kanai and Shibasaki have recently published their 4th generation approach to Tamiflu.[241] The synthesis begins with an asymmetric barium-catalyzed Diels-Alder reaction between Danishefsky's diene **(444)** and dimethyl fumerate **(445)** using chiral ligand **372** (Scheme 40). The resulting allylic alcohol **446** was obtained in a 6:1 mixture of the α-OH/ β-OH diastereomers. Basic ester hydrolysis of the mixture was followed by exposure to DPPA. The authors report that only the α-OH diastereomer was obtained, and suggest that the β-OH decomposed (possibly via a Curtius rearrangement). Synthesis of carbamate **449** was achieved by first heating carboxylic azide **448** to 80°C in *tert*-butanol and then reacting the carbamate nitrogen with acetic anhydride. Alkene **449** was then subjected to a regioselective allylic substitution with dicyanomethyl acetate **(450)**, catalyzed by a palladium-dibenzylideneacetone-chloroform complex. Epoxidation with trifluoroperacetic acid afforded α-epoxide **452** as the lone product. Treatment with ethanolic potassium carbonate transformed the acetoxydicyanomethyl functionality into an ethyl ester and initiated an E2 epoxide opening/ elimination sequence to provide allylic alcohol **453**. Mitsunobu conditions inverted the hydroxyl group and effected the formation of aziridine **368**, an intermediate in Corey's synthesis.[237]


372
i
ii
iii
iv-v
450
vi
vii
viii
ix-x
xi
xii
oseltamivir (2) • H3PO4
444
445
446
447
448
449
451
452
453
368
369

Reagents and conditions: (i) a) Ba(*Oi*-Pr)$_2$, **372**, CsF, THF, -20°C; b)1 M HCl; (ii) 2 M NaOH, MeOH, 60°C; (iii) DPPA, NEt$_3$, THF, 0°C; (iv) *t*-BuOH, 80°C; (v) a) Ac$_2$O, NEt$_3$, DMAP, DCM; b) recrystallization from DCM/cyclopentyl methyl ether; (vi) **450**, [Pd(dba)$_3$]·CHCl$_3$, dppf, PhMe, 60°C; (vii) trifluoroperacetic acid, urea/H$_2$O, Na$_2$HPO$_4$, DCM, 4°C; (viii) K$_2$CO$_3$, EtOH, r.t.; (ix) a) DEAD, PPh$_3$, *p*-nitrobenzoic acid, THF, -20°C; b) LiOH, EtOH, 20°C; (x) DIAD, Me$_2$PPh, NEt$_3$, DCM, 4°C; (xi) 3-pentanol, BF$_3$·OEt$_2$, -20°C; (xii) a) TFA; b) H$_3$PO$_4$

Scheme 40. Kanai and Shibasaki's fourth generation approach to Tamiflu **(2)**.[241]

Other Syntheses

Several other syntheses of oseltamivir have been published since Gilead Sciences initial approach was released in 1998.[230] Briefly, Kann employed a cationic iron carbonyl complex,[252] Groaning developed a 'greener' version of the Gilead synthesis,[253] Okamura published a shorter Diels-Alder route to Corey's diene intermediate **366**,[254] a F. Hoffmann-La Roche group, led by Zutter, used an enzymatic desymmetrization strategy,[255] Fukuyama released a second generation approach,[256] Hayashi developed a high-yielding synthesis via three 'one-pot' procedures,[257] Mandai completed an azide-free synthesis from L-methionine,[258] and Shi developed two short syntheses from (–)-shikimic acid.[259-60] Comprehensive reviews on the synthesis of Tamiflu have been compiled by Kanai and Shibasaki and Magano.[261] Additionally, the Tamiflu syntheses completed before 2009 have been reviewed and subjected to environmental metric analysis by Andraos.[262]

3. Results and Discussion

The following chapter reviews the latest efforts in seven areas of research; 1. reactivity of the Burgess reagent with oxiranes, 2. development of a chiral auxiliary version of the Burgess reagent, 3. enantioselective synthesis of balanol, 4. chemoenzymatic synthesis of balanol, 5. enzymatic *cis*-dihydroxylation of benzoate esters, 6. synthesis of oseltamivir, and 7. synthesis of oseltamivir analogs. The reactivity of the Burgess reagent with oxiranes, including mechanistic considerations is presented. Additionally, the development of a chiral version of the Burgess reagent and its application to the synthesis of *cis* and *trans* enantiomerically pure β-amino alcohols is covered. The synthetic utility of this methodology will be evaluated in the enantiodivergent synthesis of (+)- and (–)-balanol. Also discussed is a second-generation approach to both balanol enantiomers, each beginning from the *cis*-dihydrodiol metabolite of bromobenzene. Next, the steric and functional limitation of the toluene dioxygenase-mediated dihydroxylation of various benzoate esters is assessed. The synthetic value of these transformations is demonstrated in the synthesis of oseltamivir from the *cis*-dihydrodiol metabolite of ethyl benzoate. Finally, recent work in the preparation of several oseltamivir analogs is outlined.

3.1 Burgess Reagent

Initially, the Burgess reagent **(8)** was used for the dehydration of secondary and tertiary alcohols and for the production of urethanes from primary alcohols. Subsequent research has discovered a wide variety of other useful transformations performed by the Burgess reagent (see Chapter 2).

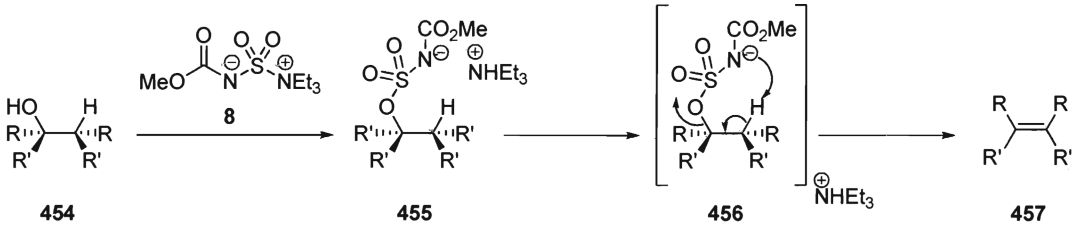


Figure 76. Dehydration of secondary and tertiary alcohols by the Burgess reagent **(8)**

3.1.1 Reactivity of the Burgess Reagent with Oxiranes

The Hudlicky group, led by Dr. Uwe Rinner, described the first reaction between an oxirane and the Burgess reagent **(8)** in 2003. Cyclic sulfamidate **459** was prepared from the corresponding oxirane **458**.[8] At the time, the relative stereochemistry of the product was assumed to be *trans* (Figure 77). The mechanism was thought to involve the nucleophilic opening of the epoxide with the nitrogen anion of the Burgess reagent to provide intermediate **463** (Figure 78). The resulting oxyanion would then attack the sulfur atom and displace triethylamine.

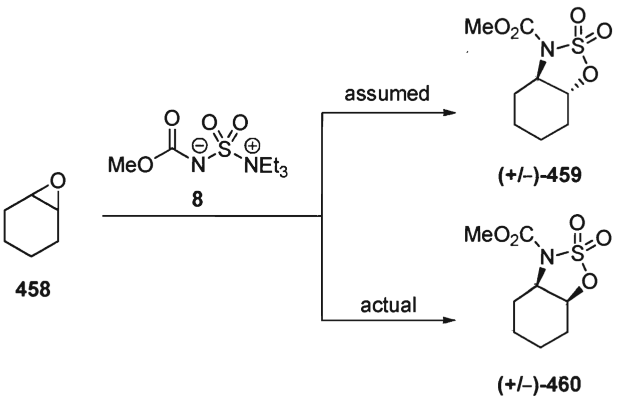


Figure 77. Assumed and actual relative stereochemistry

The Nicolaou group also reported the preparation of cyclic sulfamidates using the Burgess reagent **(8)**, in this case from 1,2-diols.[44-6] They too proposed that *trans*-fused cyclic sulfamidates were produced (Figure 78). It was believed that each hydroxyl attacked an equivalent of the Burgess reagent **(8)** displacing triethylamine. The resulting intermediate **463** would then displace a sulfite species, through an intramolecular attack, to provide the *trans*-fused sulfamidate **459**.

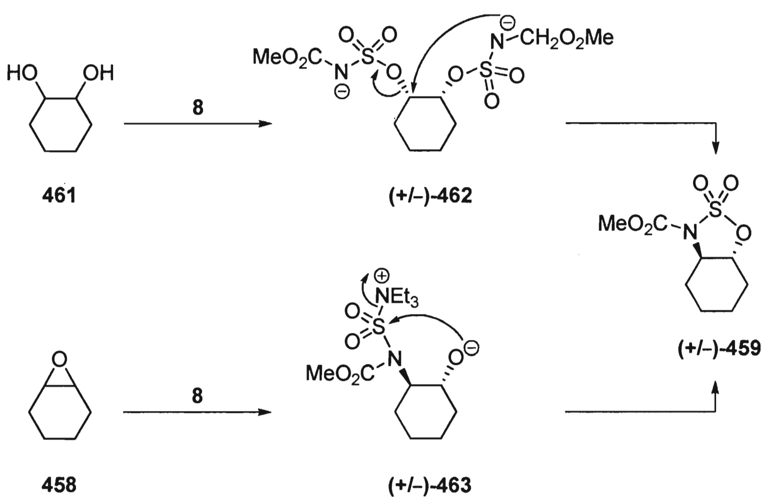
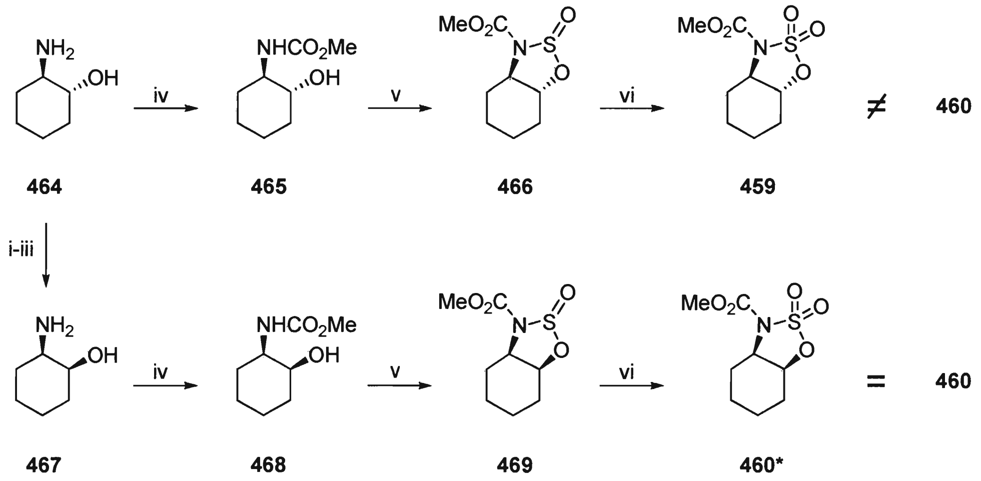


Figure 78. Initial mechanism proposed for the formation of *trans*-sulfamidate **459** from epoxide **458** and 1,2-diol **461** using the Burgess reagent **(8)**

In order to confirm the relative stereochemistry of the cyclic sulfamidates, Dr. Hannes Leisch converted the commercially available *trans*-2-aminocyclohexanol **(464)** into both the *trans*- and *cis*-cyclic sulfamidates **459** and **460*** respectively (Scheme 41). Using a method originally developed by Jacobsen,[263] the *trans*-isomer **464** was easily converted into the *cis*-isomer **467**. Treatment with methyl chloroformate afforded β-hydroxy carbamates **465** and **468**, which were reacted with thionyl chloride. The resulting sulfoxides **466** and **469** were oxidized using ruthenium(III) chloride and sodium periodate in aqueous acetonitrile. Comparative analysis of the two products revealed that the *trans*-isomer **459** did not match the product we obtained from the reaction of the Burgess reagent **(8)** with cyclohexene oxide **(458)**. Clearly the mechanism involving one equivalent of the Burgess reagent could not operate (Figure 78).



Reagents and conditions: (i) Ac_2O; (ii) $SOCl_2$; (iii) 10% HCl, 68% over 3 steps; (iv) methyl chloroformate, $NaHCO_3$, $CHCl_3$/ H_2O, 87%; (v) $SOCl_2$, MeCN, -40°C, 78%; (vi) $RuCl_3{\cdot}H_2O$, $NaIO_4$, MeCN/ H_2O, 87%

Scheme 41. Relative stereochemical proof for cyclic sulfamidate **460**

An amended mechanism, using two equivalents of the Burgess reagent **(8)**, was proposed in order to explain the formation of the *cis*-isomer **460.**[264] Not surprisingly, at least two equivalents of the Burgess reagent **(8)** were required for optimal yields. As with the first proposed mechanism, the nitrogen anion of the first equivalent opens the epoxide. However, the resulting oxyanion does not attack the sulfonyl group to displace triethylamine, but rather reacts with a second equivalent of the Burgess reagent **(8)** to form intermediate **472** (Figure 79). The resulting nitrogen anion then intramolecularly displaces the Burgess reagent to afford *cis*-cyclic sulfamidate **460**. The mechanism involving the formation of cyclic-sulfamidates from 1,2-diols remains the same, although it is now apparent that only *trans* 1,2-diols react to give *cis*-cyclic sulfamidates. The bis-sulfonated intermediate formed from a *cis*-1,2- diol would be incapable of undergoing an intramolecular S_N2 displacement.

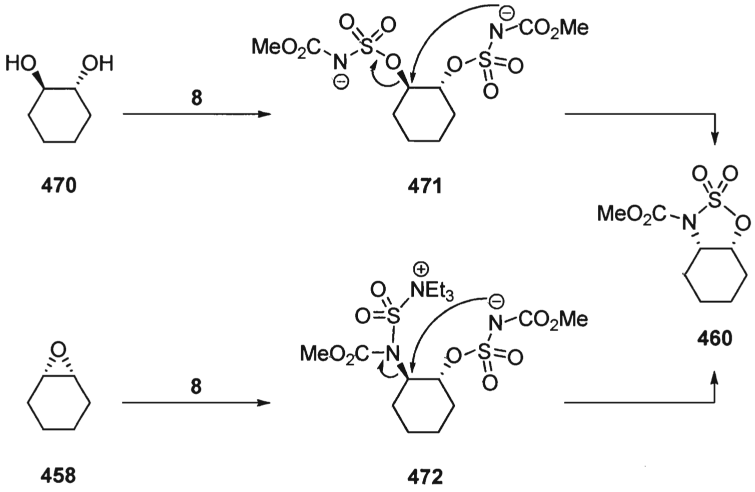


Figure 79. Mechanism for the formation of *cis*-sulfamidate **460** from epoxide **458** and 1,2-diol **470**.

3.1.2 Computational Studies

We theorized that computational studies might provide further insight into the mechanism of *cis*-cyclic sulfamidate formation. This led to a collaboration with Prof. Travis Dudding and Branden Fonovic at Brock University.[265] Their study used (GGA)-hybrid Kohn-Sham density functional theory (KS-DFT) at the B3LYP[266]-6-31G(d)[267] level in order to ascertain a possible mechanism. Briefly, this study examined two possible pathways to reach the *cis*-cyclic sulfamidate **460**. First, the previously proposed backside S_N2, attack and subsequent oxyanion sulfonation mechanism, would proceed through intermediate **474**. However, all optimized geometries scanned possessed unrealistically high activation barriers ($\Delta G^\ddagger$ >50 kcal/mol). Conversely, a front side [3+2] concerted asynchronous attack (path A) provided a significantly lower activation barrier ($\Delta G^\ddagger = 38.9$ kcal/mol).

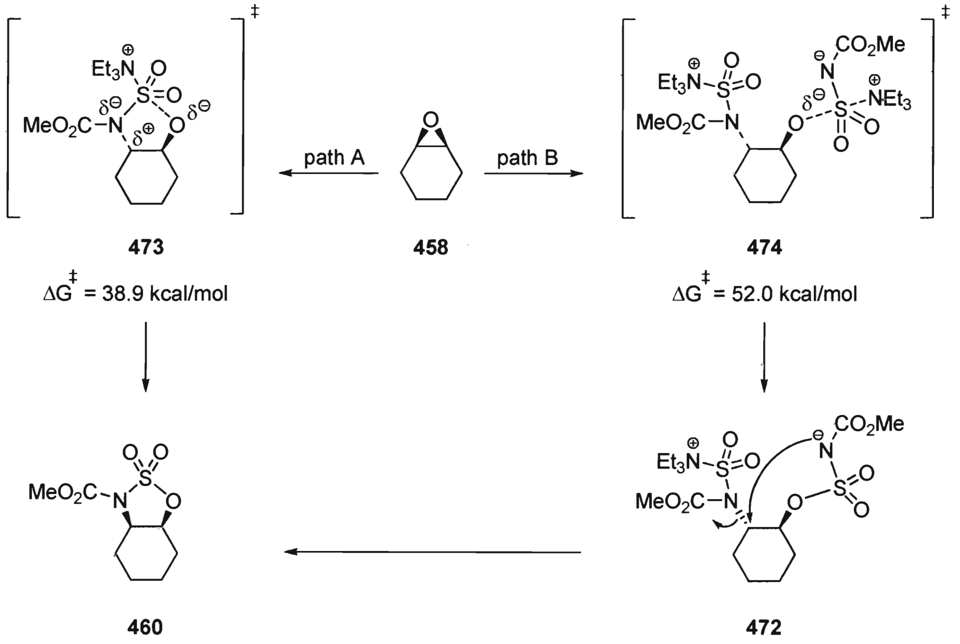

path A
path B
473
458
474
ΔG‡ = 38.9 kcal/mol
ΔG‡ = 52.0 kcal/mol
460
472

Figure 80. Possible mechanistic pathways from oxirane **458** to *cis*-sulfamidate **460**.

The computational study also revealed the possible metrics of the five-membered-TS1 (Figure 81). Multiple bond-forming and bond-breaking events occur simultaneously. Specifically, one C•••O bond of the epoxide breaks at a distance of 2.10 Å, while the C•••N and O•••S bonds form at a distance of 2.62 Å and 1.84 Å respectively.

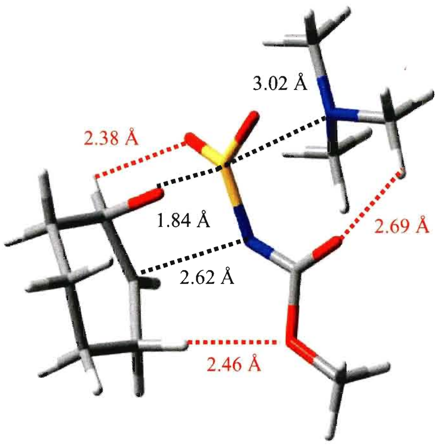


Figure 81. Five-membered-TS1 corresponding to *cis*-cyclic sulfamidate **460** formation.[265]

3.1.3 Preparation of *cis* and *trans* β-Amino Alcohols

The synthetic value of the *cis*-cyclic sulfamidates is best exemplified in the preparation of both *cis* and *trans*-β-amino alcohols (Figure 82). Acidic hydrolysis of sulfamidate **460** provides the protected *cis*-β-amino alcohol isomer **468**. Inversion of the oxygen, accomplished through a reaction with ammonium benzoate and subsequent acidic hydrolysis, provides the *trans*-β-amino alcohol isomer **475**.

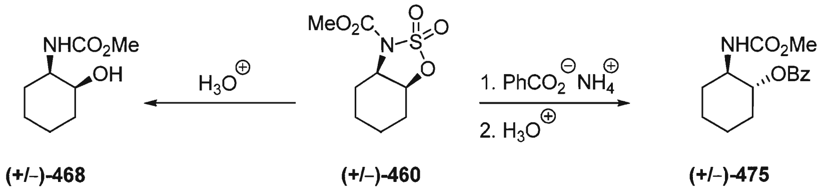


Figure 82. Synthesis of protected *cis* and *trans*-β-amino alcohols from *cis*-cyclic sulfamidates.

Practical application of this methodology is hindered by the poor yields obtained (< 40%) for the synthesis of *cis*-cyclic sulfamidates from oxiranes using the Burgess reagent (**8**). Inspired by a study on the reactions of indole derivatives with epoxides,[268] we explored SiO_2 and Al_2O_3 catalysis as a means to improve the yield (Figure 83). The results of this study (Table 1) revealed no improvements when either SiO_2 or Al_2O_3 were used, in the presence or absence of solvent. In all cases, no product could be detected (TLC monitoring) at temperatures below 70°C. The highest yields for either catalyst were obtained when THF was used as the solvent.

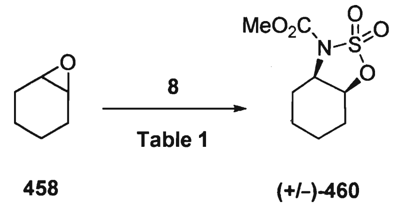


Figure 83. Attempts to improve isolated yield of *cis*-cyclic sulfamidate **460**

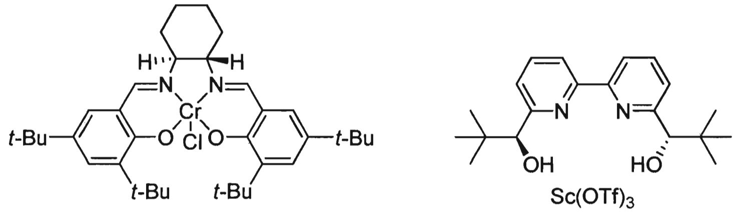
Table 1. Attempts to improve isolated yield of *cis*-cyclic sulfamidate **460**

Entry	*Catalyst*	*Solvent*	*Temp.*	*Isolated Yield*
1	**SiO_2**	**THF**	**r.t. to 70°C**	**24%**
2	Al_2O_3	THF	r.t. to 70°C	21%
3	SiO_2	DCM	r.t. to 70°C	17%
4	Al_2O_3	DCM	r.t. to 70°C	6%
5	SiO_2	MeOH	r.t. to 70°C	trace amounts[a]
6	Al_2O_3	MeOH	r.t. to 70°C	trace amounts[a]
7	SiO_2	-	r.t. to 70°C	-
8	Al_2O_3	-	r.t. to 70°C	-

[a] small traces detected in ^1H NMR

3.1.4 Development of a Chiral Version of the Burgess Reagent

We became interested in preparing enantiomerically pure β-amino alcohols from *meso*-epoxides through use of the Burgess reagent **(8)**. Our first attempts employed Jacobsen's **(476)**[269] and Bolm's **(477)**[270] catalysts; both are known to act as chiral Lewis acids in epoxide opening reactions (Figure 84). Neither catalyst, regardless of the equivalency (0.1 to 1 eq.), showed any asymmetric induction. Three possible explanations were considered. First, the Burgess reagent **(8)** itself could be acting as a pseudo acid, outcompeting the chiral catalysts. Computational studies suggested that the Burgess reagent **(8)** undergoes rapid decomposition in the presence of either chiral catalyst. The resulting excess achiral degradation species would also outcompete the chiral catalysts for coordination to the epoxide. Finally, during the asynchronous concerted five-membered-TS1 (Figure 81) the Burgess reagent **(8)** occupies the majority of the space adjacent to the oxirane, making it impossible for a Lewis acid to coordinate.



476 **477**

Figure 84. Chiral Lewis acids

Our second strategy was to prepare enantiomerically pure β-amino alcohols using a chiral auxiliary based approach to introduce stereoselectivity. Two cyclic Burgess-type reagents, **478** and **479**, were prepared from *cis*-dihydrodiol **302** by Dr. Kevin Finn (Figure 85). A third reagent **(480)** was prepared from camphor. Unfortunately, cyclic sulfamidate formation using these three reagents proved to be unreliable and they were abandoned in favour of a (–)-menthol-derived Burgess reagent **(3)**.

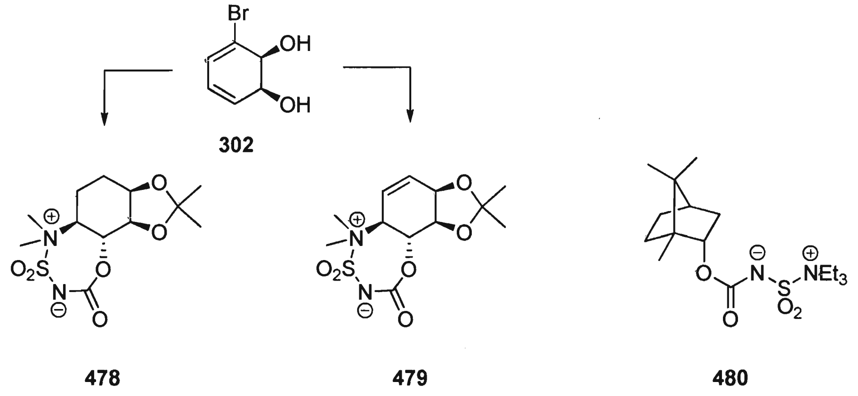
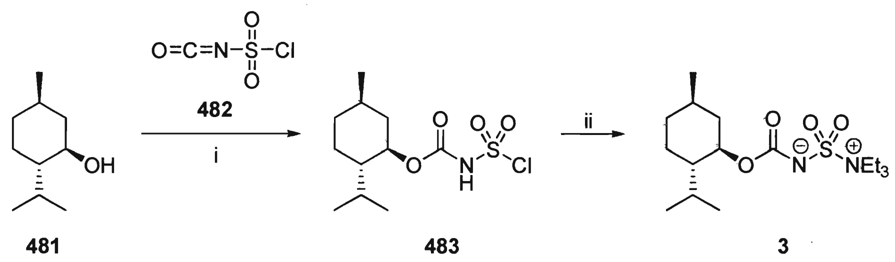


Figure 85. Chiral auxiliary versions of the Burgess reagent.

The (–)-menthyl Burgess reagent **(3)** was prepared by adding a benzene/ (–)-menthol solution to an excess of chlorosulfonyl isocyanate **(482)** (Scheme 42).[264] The resulting (–)-menthyl chlorosulfonylcarbamate **483** was added to benzene solution containing two equivalents of triethylamine. The first equivalent displaces a chloride, while the second deprotonates the nitrogen allowing for the formation of the inner salt.



Reagents and conditions: (i) benzene, 20°C, 87%; (ii) NEt_3, benzene, 10°C, 85%

Scheme 42. Preparation of (–)-menthyl Burgess reagent **(3)**

Although no chiral induction was seen, reacting the (–)-menthyl Burgess reagent **(3)** with oxiranes did provide a pair of separable diastereomers (Figure 86). The two cyclic sulfamidate diastereomers **9a** and **9b** give access to all four β-amino alcohol stereoisomers. Acidic hydrolysis provides both of the *cis*-β-amino alcohols **12a** and

12b, while inversion of the oxygen with ammonium benzoate followed by hydrolysis provides the *trans*-β-amino alcohols **485a** and **485b**.

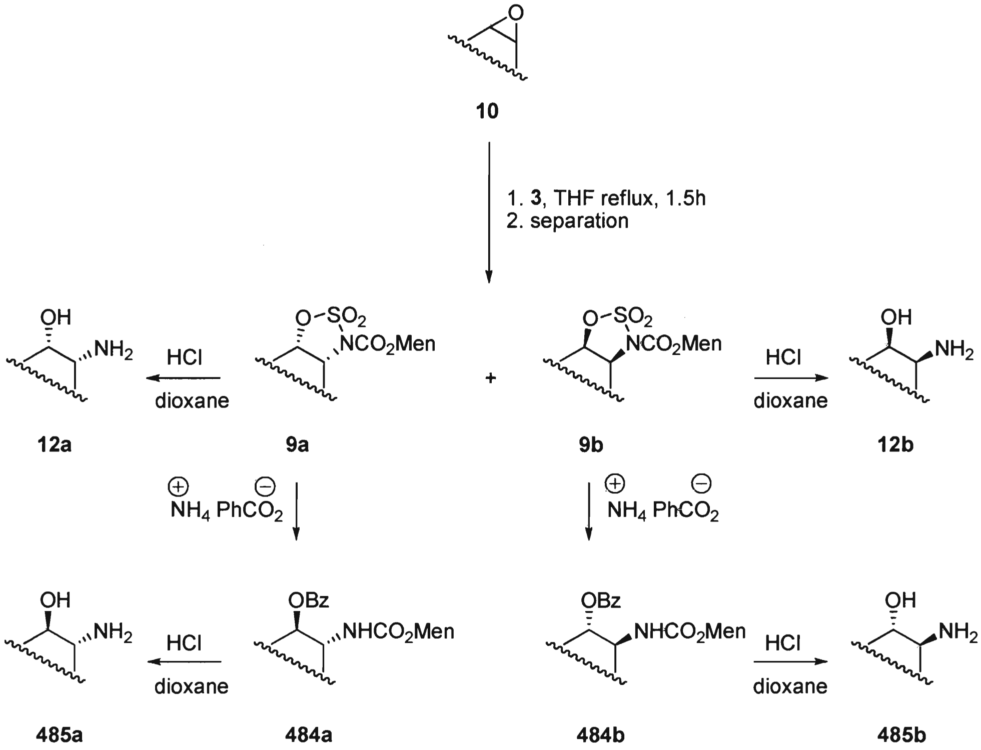
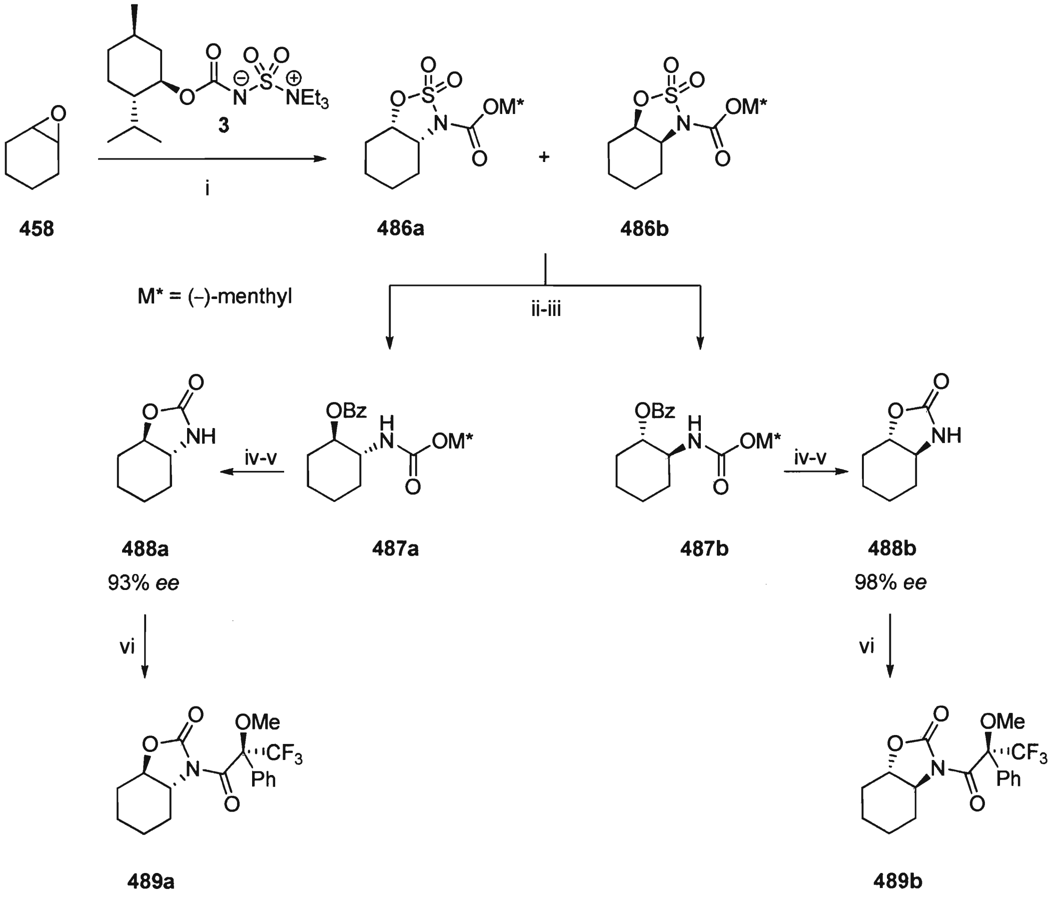


Figure 86. Access to all four β-amino alcohol stereoisomers from a single *meso*-epoxide

The next step was to determine the absolute stereochemistry of the two diastereomeric cyclic *cis*-sulfamidate products **486a** and **486b**. This was achieved by converting each diastereomer to its corresponding *trans*-cyclic carbamate, **488a** and **488b**, those specific rotations had been previously reported (Scheme 43).[270] Using the previously described ammonium benzoate sulfamidate inversion procedure, the two protected *trans*- β-amino alcohols **487a** and **487b** were prepared. Basic ester hydrolysis afforded free hydroxyls which, upon exposure to sodium hydride, underwent an intramolecular ring closure displacing (–)-menthol. The physical properties of the resulting cyclic carbamates **488a** and **488b** were in complete agreement with the literature values.[270] Conversion to (*S*)-(+)-Mosher's amide derivatives **489a** and **489b** allowed for determination of the enantiomeric excess of the products by ^{19}F NMR (**489a** = 93% e.e.; **489b** = 98% e.e.).



Reagents and conditions: (i) **3** (2 equiv.), THF, reflux, 30%; (ii) $PhCO_2^-NH_4^+$, DMF, 45°C; (iii) THF, H_2O, conc. H_2SO_4, r.t., 49% over 2 steps; (iv) 1M NaOH in MeOH; (v) NaH, THF, reflux, 70% over 2 steps; (vi) a) *n*BuLi, 0°C; b) (*S*)-(+)-Mosher's acid chloride, -78°C to r.t., 83%.

Scheme 43. Determination of absolute stereochemistry and enantiomeric excess of sulfamidates **486a** and **486b**

As with the reaction between the Burgess reagent **(8)** and oxiranes, the yields for the same reaction with the (–)-menthyl Burgess reagent **(3)** were poor (~30%). We tried using dimethoxyethane (DME) as the solvent and varied the equivalents of the reagent without success (Table 2, Entries 1 and 2). We also used dioxane and dichloromethane (DCM) as solvents, with and without the additives scandium(III) triflate and hexamethylphosphoramide (HMPA), both of which have been known to promote epoxide openings.[271-2] The only promising results employed dichloromethane or dimethoxyethane as the solvent with scandium(III) trifluoromethanesulfonate as the additive (Table 2, Entries 4 and 9).

Table 2. Attempts to improve yield of sulfamidate **486** production

Entry	*Equiv. of 3*	*Solvent*	*Additive*	*Temp.*	*Isolated Yield*
1	2.3	DME	-	r.t. to 70°C	15%
2	4.6	DME	-	r.t. to 70°C	22%
3	2.3	DME	$Sc(OTf)_3$	r.t. to 70°C	22%
4	4.6	DME	$Sc(OTf)_3$	r.t. to 70°C	26%
5	2.3	DME	HMPA	r.t. to 70°C	-
6	2.3	dioxane	-	r.t. to 70°C	11%
7	2.3	dioxane	$Sc(OTf)_3$	r.t. to 70°C	13%
8	2.3	dioxane	HMPA	r.t. to 70°C	-
9	**2.3**	**DCM**	**$Sc(OTf)_3$**	**r.t. to 70°C**	**28%**
10	2.3	DCM	HMPA	r.t. to 70°C	-
11	2.3	THF	$Sc(OTf)_3$	r.t. to 70°C	-
12	2.3	THF	HMPA	r.t. to 70°C	-

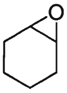
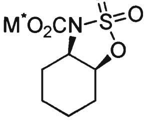
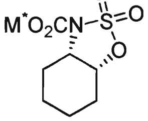
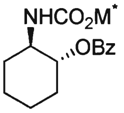
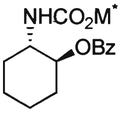
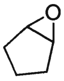
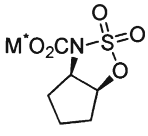
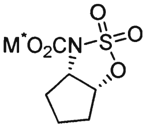
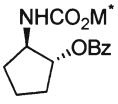
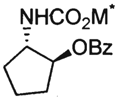
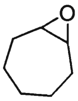
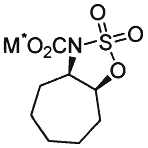
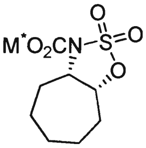
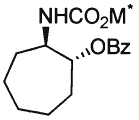
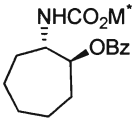
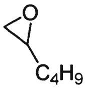
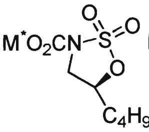
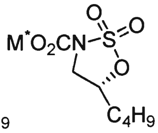
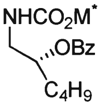
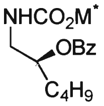
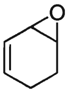
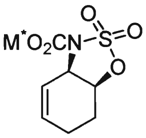
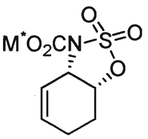
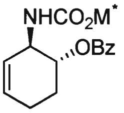
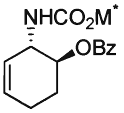
We questioned whether the order of addition contributed to the unfavourable yields. Previous results demonstrated that the (–)-menthyl Burgess reagent **(3)** did not react with oxirane **458** at room temperature. We speculated that the reagent itself degrades at elevated temperatures; subsequent studies[273] confirmed this hypothesis. Using an automated syringe pump, the order of addition and the solvent were varied (Table 3). Unfortunately, we were unable to improve upon the initial conditions reported by Hudlicky in 2003 (Table 3, Entry 3).[8] Experiments in which the oxirane was added to the reagent (Table 3, Entries 2 and 5) suffered from the lowest yields; likely resulting from the degradation of the (–)-menthyl Burgess reagent **(3)**.

Table 3. Attempts to improve yield via automated syringe pump

Entry	*Equiv. of 3*	*Solvent*	*Mode of Addition*	*Syringe Pump Time (hrs)*	*Temp.*	*Yield*
1	2.3	THF	**3** to **458**	0.5	reflux	24%
2	2.3	THF	**458** to **3**	0.5	reflux	17%
3	**2.3**	**THF**	**at once**	**-**	**reflux**	**30%**
4	2.3	DCM	**3** to **458**	0.5	reflux	14%
5	2.3	DCM	**458** to **3**	0.5	reflux	11%
6	2.3	DCM	at once	-	reflux	26%

We sought to expand the (–)-menthyl Burgess reagent **(3)** methodology to include other epoxides (Table 4).[264] Pentene and heptene oxide, **490** and **493** respectively, were both respectable substrates with modest yields for cyclic sulfamidate formation. As expected, the aliphatic 1-hexene oxide **496** and the unsaturated 1,3-cyclohexadiene oxide **(4)** substrates each produced a single regioisomer. All cyclic sulfamidates produced were converted to their corresponding benzoates and then separated via flash column chromatography, the lone exception being the aliphatic substrate.

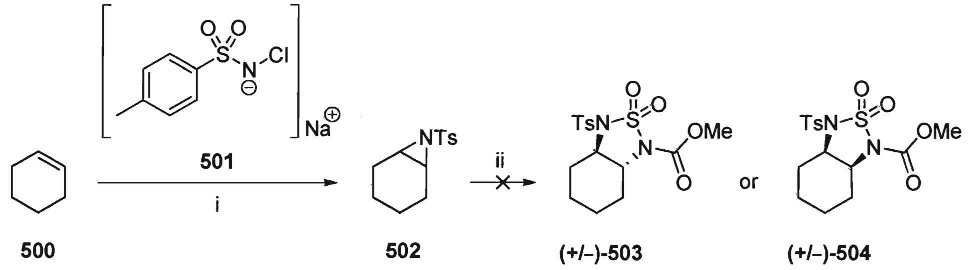
Table 4. Oxiranes reacted with the (–)-menthyl Burgess reagent **(3)**

Oxirane	Sulfamidates (%)[a]	Benzoates (%)	*ee*(%)[b] or *de*(%)[c]
 **458**	  **486a** 30% **486b**	  **487a** 49% **487b**	98 and 93[b]
 **490**	  **491a** 37% **491b**	  **492a** 52% **492b**	98 and 93[c]
 **493**	  **494a** 35% **494b**	  **495a** 75% **495b**	93 and 92[c]
 **496**	  **497a** 22% **497b**	  **498a**[d] 36% **498b**[d]	–[d]
 **4**	  **5a** 36% **5b**	  **499a** 51% **499b**	94 and 84[e]

[a] yields are isolated; [b] enantiomeric excess determined by Mosher's amide formation of cyclic carbamates, derived from the corresponding benzoates by hydrolysis and cyclization; [c] diastereomeric excess determined by GC/MS analysis of benzoates after separation by flash column chromatography; [d] not separable by flash column chromatography; [e] diastereomeric excess determined by GC/MS of separated benzoates after hydrogenation.

3.1.5 Reaction between *N*-tosyl aziridine and the Burgess Reagent

A natural progression from reacting oxiranes would be to use aziridines as substrates for this methodology. Cyclohexene **(502)** was converted into its *N*-tosyl aziridine derivative **502** using chloramine-T **(501)** (Scheme 44). Unfortunately, its reaction with the Burgess reagent **(8)** failed to produce either the *cis*- or *trans* cyclic products.



Reagents and conditions: (i) I_2, MeCN, r.t., 82%; (ii) **8** (2 equiv.), THF, reflux

Scheme 44. Reaction between the Burgess reagent **(8)** and *N*-tosyl aziridine **502**

3.2 Enantiodivergent Synthesis of Balanol

In order to illustrate the synthetic value of (–)-menthyl Burgess reagent methodology, we sought to find a natural product accessible from one of the cyclic-sulfamidates. Obviously, the added alkene functionality in the unsaturated products **5a** and **5b** offered the greatest opportunity for success. Eventually it was concluded that both the natural (–)-isomer and the unnatural (+)-isomer of balanol **(1)** could be obtained from the two sulfamidate diastereomers **5a** and **5b**. Balanol **(1)** is a potent and selective inhibitor of protein kinase C, a protein implicated in a number of disease states.[11] Inversion of the oxygen functionality in **5a** and **5b** would install the correct relative stereochemistry seen in (–)- and (+)-balanol **(1)** respectively (Figure 87). We anticipated that an oxidative cleavage/ reductive amination reaction sequence could be used to prepare the azepane ring.

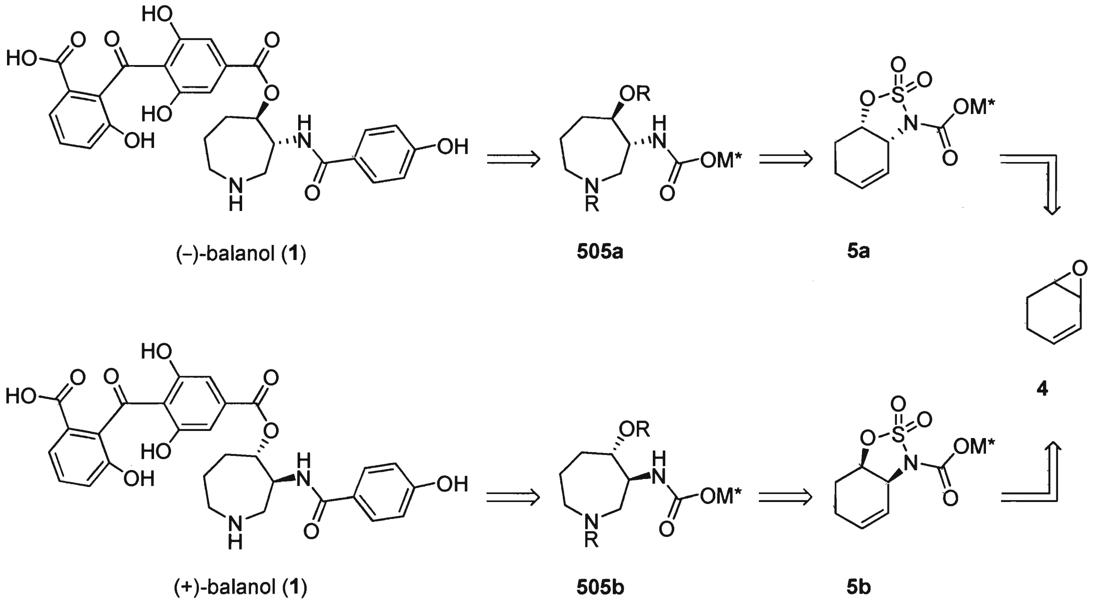
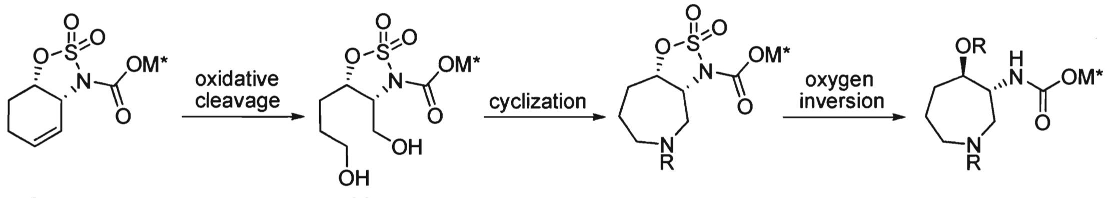


Figure 87. Retrosynthetic analysis of balanol **(1)** from 1,3-cyclohexadiene oxide **(4)**

3.2.1 Cyclization Model Study

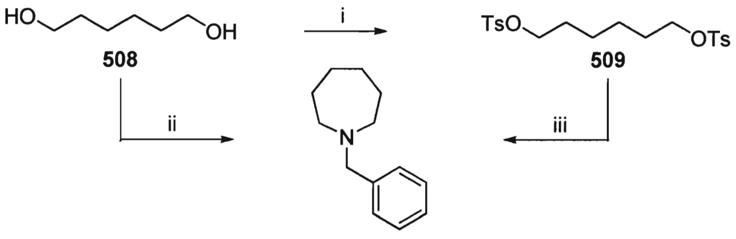
Our initial approach was to oxidatively cleave olefin **5** via an ozonolysis/ reduction protocol and to cyclize the resulting diol **506** to the azepane ring (Figure 88). Inversion of the sulfamidate oxygen would give an advanced intermediate **505** which could be converted into one of the formal intermediates of balanol (see Sections 2.2.5 and 2.2.6).



5 **506** **507** **505**

Figure 88. First strategy to synthesis balanol **(1)**

The first step was to evaluate the feasibility of generating an azepane heterocycle from an aliphatic diol. To this end, 1,6-hexanediol **(508)** was selected as a model compound. It was established that exposure of its *O*-tosyl derivative **509** to benzylamine in refluxing ethanol provided *N*-benzyl azepane **(510)**. Alternatively, diol **508** could be directly converted into azepane **510** using an iridium catalyst, $[Cp^*IrCl_2]_2$, developed by Fujita.[274]



508 **509** **510**

Reagents and conditions: (i) *p*TsOH, pyr., DMAP, DCM, 0°C, 87%; (ii) $[Cp^*IrCl_2]_2$, $NaHCO_3$, toluene, reflux, 20%; (iii) $Bn\text{-}NH_2$, EtOH, reflux, 67%

Scheme 45. Cyclization model study

Both cyclization routes require a nucleophilic nitrogen, such as benzyl amine. A review of the literature identified balanol formal intermediate **231** from the Lampe and Hughes synthesis[111-2] as a suitable target (Figure 89).

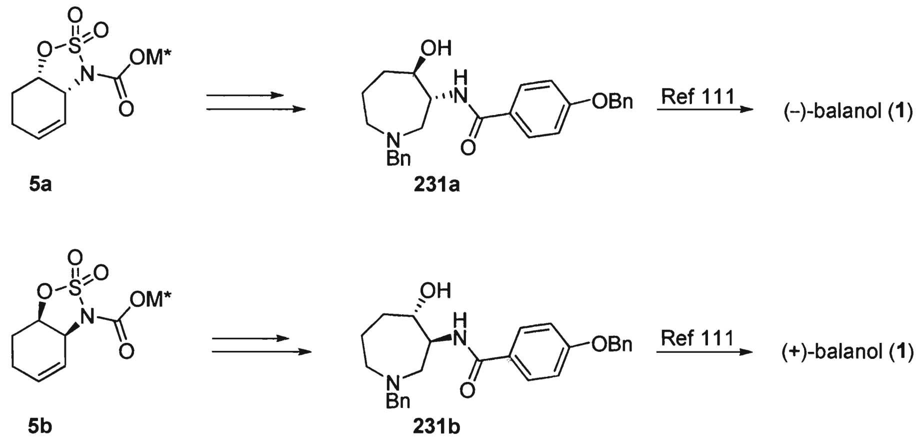


Figure 89. Balanol formal intermediates

3.2.2 Ozonolysis Strategies

The most concise approach to aliphatic diol **506** is through an ozonolysis procedure (Figure 90). Our first strategy followed standard conditions in which the ozonide species is formed by exposing olefin **5** to ozone in DCM at low temperature; followed by reductive work-up with dimethyl sulfide and hydride reduction of the intermediate dialdehyde. We attempted several procedures, which varied the temperature of each stage of the reaction sequence (Table 5). Frequent monitoring of the reaction by TLC/ 2,4-dinitrophenylhydrazine staining identified multiple (20+) aldehyde species formed. Regardless of the procedure employed, no identifiable aldehyde or hydroxyl-containing compounds could be identified.

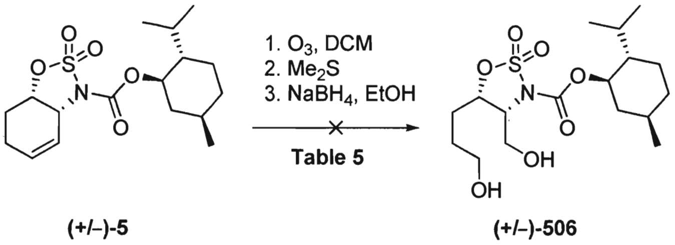


Figure 90. First ozonolysis strategy

Table 5. First ozonolysis strategy

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Temp. of $NaBH_4$*	*Result*
1	-78°C	-78°C to 0°C	-78°C to r.t.	decomposition[a]
2	-78°C	-78°C to 0°C	-40°C to r.t.	decomposition[a]
3	-78°C	-40°C	-78°C to r.t	decomposition[a]
4	-78°C	-40°C	-40°C to r.t	decomposition[a]
5	-40°C	-40°C	-40°C to r.t	decomposition[a]
6	-78°C	-78°C to 0°C	0°C to r.t.	decomposition[a]
7	-78°C	-40°C	0°C to r.t	decomposition[a]

[a] TLC evidence of multiple aldehydes

We tested whether or not the addition of a protic solvent would affect the outcome of the reaction (Figure 91). We varied the ratio of methanol and DCM but did not observe an improvement (Table 6).

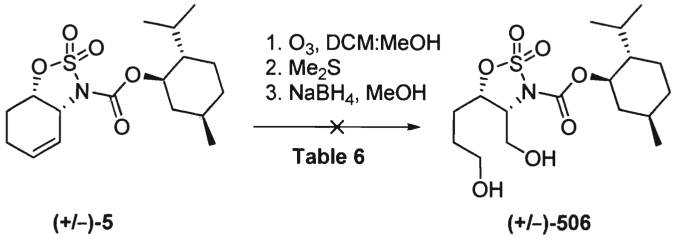


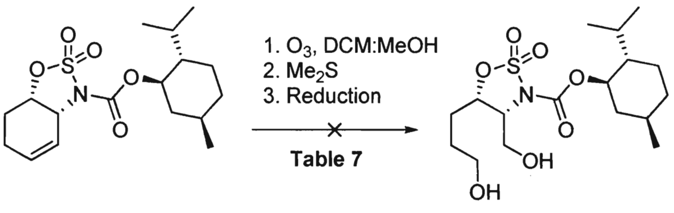
Figure 91. Second ozonolysis strategy

Table 6. Second ozonolysis strategy

Entry	*Temp. of O_3*	*DCM:MeOH Ratio*	*Temp. of Me_2S*	*Temp. of $NaBH_4$*	*Result*
1	-78°C	8:2	-78°C to 0°C	-78°C to r.t.	decomposition[a]
2	-78°C	2:8	-78°C to 0°C	-78°C to r.t.	decomposition[a]
3	-78°C	8:2	-40°C	-40°C to r.t	decomposition[a]
4	-78°C	2:8	-40°C	-40°C to r.t	decomposition[a]

[a] TLC evidence of multiple aldehydes

We questioned whether a different hydride reducing agent would produce a different result (Figure 92). Three hydride sources were tested; 1. sodium cyanoborohydride, 2. lithium aluminum hydride and 3. diisobutylaluminum hydride (Table 7). Unfortunately, this strategy had no effect on the results.



(+/-)-5 **(+/-)-506**

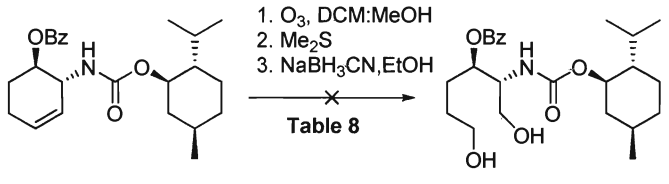
Figure 92. Third ozonolysis strategy

Table 7. Third ozonolysis strategy

Entry	*Temp. of* O_3	*Temp. of* Me_2S	*Reducing Agent*	*Temp. of Reduction*	*Result*
1	-78°C	-78 to 0°C	$NaBH_3CN$	-78°C to r.t.	decomposition[a]
2	-78°C	-78 to 0°C	LAH	-78°C to r.t.	decomposition[a]
3	-78°C	-78 to 0°C	DIBAL	-78°C to r.t.	decomposition[a]
4	-78°C	-78 to 0°C	$NaBH_3CN$	-20°C to r.t	decomposition[a]
5	-78°C	-78 to 0°C	LAH	-20°C to r.t	decomposition[a]
6	-78°C	-78 to 0°C	DIBAL	-20°C to r.t	decomposition[a]

[a] TLC evidence of multiple aldehydes.

We speculated that the cyclic sulfamidate functionality of **5** was reacting with one of the intermediate species formed during the ozonolysis procedure. For this reason, we chose to employ the *O*-benzyl derivative **499** in the next series of experiments (Figure 93). Once again the results were discouraging as we observed multiple aldehyde species via TLC/ 2,4-dinitrophenylhydrazine staining (Table 8).



(+/-)-499 **(+/-)-511**

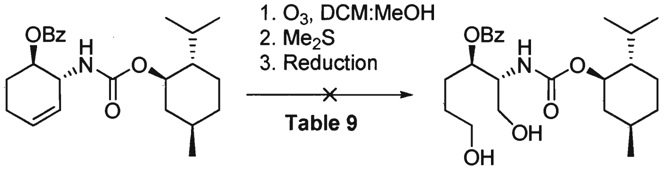
Figure 93. Fourth ozonolysis strategy

Table 8. Fourth ozonolysis strategy

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Temp. of $NaBH_3CN$*	*Result*
1	-78°C	-78°C to 0°C	-78°C to r.t.	decomposition[a]
2	-78°C	-78°C to 0°C	-40°C to r.t.	decomposition[a]
3	-78°C	-40°C	-40°C to r.t	decomposition[a]
4	-78°C	-40°C	0°C to r.t	decomposition[a]
5	-40°C	-40°C	0°C to r.t	decomposition[a]
6	-78°C	-78°C to -20°C	-20°C to r.t.	decomposition[a]

[a] TLC evidence of multiple aldehydes, 20+ compounds

As with the first substrate, we tried our ozonolysis procedure with methanol as a cosolvent and employed different reducing agents (Figure 94). Not surprisinly, we were unable to identify any compounds from these reactions (Table 9).



(+/-)-499 **(+/-)-511**

Figure 94. Fifth ozonolysis strategy

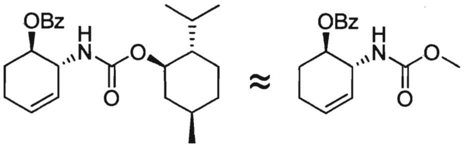
Table 9. Fifth ozonolysis strategy

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Reducing Agent*	*Temp. of Reduction*	*Result*
1	-78°C	-78 to 0°C	$NaBH_3CN$	-78°C to r.t.	decomposition[a]
2	-78°C	-78 to 0°C	LAH	-78°C to r.t.	decomposition[a]
3	-78°C	-78 to 0°C	$NaBH_4$	-78°C to r.t.	decomposition[a]
4	-78°C	-78 to 0°C	$NaBH_3CN$	-20°C to r.t	decomposition[a]
5	-78°C	-78 to 0°C	LAH	-20°C to r.t	decomposition[a]
6	-78°C	-78 to 0°C	$NaBH_4$	-20°C to r.t	decomposition[a]

[a] evidence of multiple aldehydes

3.2.3 Model Study

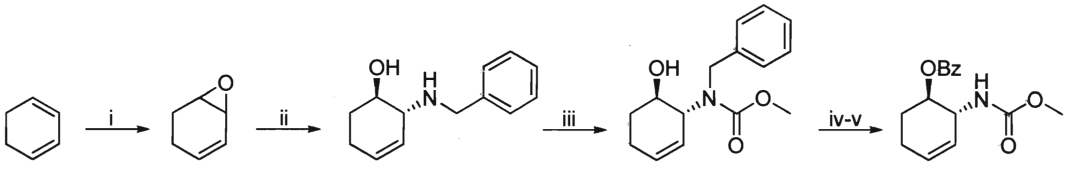
As described earlier, synthesis of carbamates **5** and benzoate **499** is hindered by the low yields of the (–)-menthyl Burgess reaction with oxirane **4**. From a logistical standpoint, it made sense to use a model compound which is easier to prepare in large quantities. We concluded that the simplest compound to use in place of the (–)-menthyl carbamate **499** is the methyl carbamate **512** (Figure 95).



(+/-)-499 **(+/-)-512**

Figure 95. (–)-Menthyl carbamate and methyl carbamates **499** and **512**

The synthesis of methyl carbamate **512** began with the epoxidation of cyclohexa-1,3-diene **(513)** with peracetic acid. Opening of the vinyl oxirane **4** with benzylamine provided amine **514**, which was then reacted with methyl chloroformate. A dissolving metal reduction removed the benzyl group and subsequent benzoyl protection completed the synthesis of carbamate **512**.

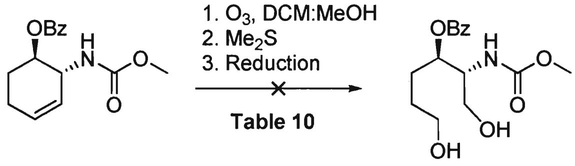


513 **(+/-)-4** **(+/-)-514** **(+/-)-515** **(+/-)-512**

Reagents and Conditions: (i) AcOOH, Na_2CO_3, DCM, 0°C, 71%; (ii) $BnNH_2$, *iso*-propanol, 80°C, 88%; (iii) methyl chloroformate, THF, pyr., r.t., 86%; (iv) Na, NH_3, -40°C; (v) BzCl, NEt_3 DMAP, DCM, 0°C, 92% over 2 steps

Scheme 46. Synthesis of methyl carbamate **512**

We wondered if any products could be identified from ozonolysis of the model compound (Figure 96). As before, the procedures used only provided complex mixtures and no identifiable compounds (Table 10).



(+/-)-512 **(+/-)-516**

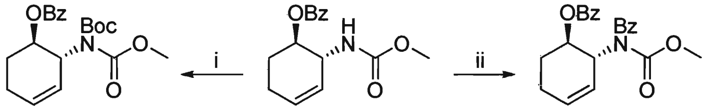
Figure 96. Ozonolysis of methyl carbamate **512**

Table 10. Ozonolysis of methyl carbamate **512**

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Reducing Agent*	*Temp. of Reduction*	*Result*
1	-78°C	-78 to 0°C	$NaBH_3CN$	-78°C to r.t.	decomposition[a]
2	-78°C	-78 to 0°C	LAH	-78°C to r.t.	decomposition[a]
3	-78°C	-78 to 0°C	$NaBH_4$	-78°C to r.t.	decomposition[a]
4	-78°C	-78 to 0°C	$NaBH_3CN$	-20°C to r.t	decomposition[a]
5	-78°C	-78 to 0°C	LAH	-20°C to r.t	decomposition[a]
6	-78°C	-78 to 0°C	$NaBH_4$	-20°C to r.t	decomposition[a]

[a] TLC evidence of multiple aldehydes, 20+ compounds

We speculated that the carbamate nitrogen could be reacting with one of the intermediate ozonide species. Therefore, we prepared *N*-Boc **517** and *N*-Bz derivatives **518** (Scheme 47).



(+/-)-517 **(+/-)-512** **(+/-)-518**

Reagents and conditions: (i) $(Boc)_2$, THF, NaH, reflux, 77%; (ii) BzCl, DCM, DMAP, pyridine, reflux, 82%

Scheme 47. *N*-Bz and *N*-Boc protection of methyl carbamate **512**

The *N*-Boc derivative **517** was treated with the same ozonolysis conditions employed previously (Figure 97). Hydride reductions performed at temperatures below 0°C gave similar results as before. However, when the reduction was carried out at 0°C (Table 11, Entries 3 and 4) we were able to isolate a compound tentatively identified as diol **519**.

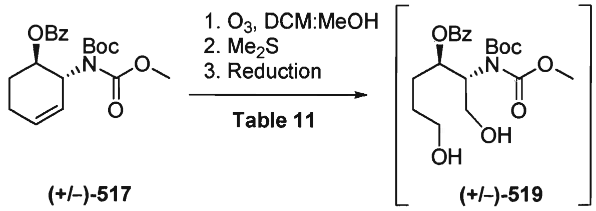

OBz
Boc
N
O
O
1. O_3, DCM:MeOH
2. Me_2S
3. Reduction
Table 11
OBz
Boc
N
O
O
OH
OH
(+/-)-517
(+/-)-519

Figure 97. Ozonolysis of *N*-Boc protected carbamate **517**

Table 11. Ozonolysis of *N*-Boc protected carbamate **517**

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Reducing Agent*	*Temp. of Reduction*	*Yield*[a]
1	-78°C	-78 to 0°C	$NaBH_3CN$	-40°C to r.t.	-
2	-78°C	-78 to 0°C	$NaBH_4$	-40°C to r.t.	-
3	-78°C	-78 to 0°C	$NaBH_3CN$	0°C to r.t.	~5%[b]
4	-78°C	-78 to 0°C	$NaBH_4$	0°C to r.t	~5%[b]
5	-78°C	-78 to 0°C	$NaBH_4$	-78°C to r.t	-

[a] yield estimated, product not pure by ^1H NMR, [b] tentative identification (^1H and ^{13}C NMR, MS)

We subjected the *N*-Bz derivative **518** to the successful ozonolysis procedures used for the *N*-Boc derivative **517** (Table 12). Once again we were able to isolate a compound tentatively assigned as diol **520**.

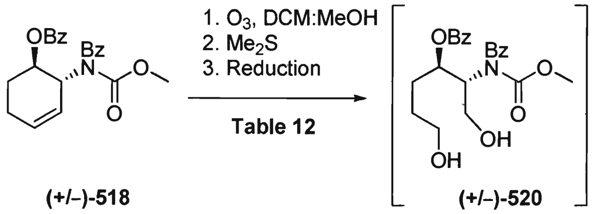

OBz
Bz
N
O
O
1. O_3, DCM:MeOH
2. Me_2S
3. Reduction
Table 12
OBz
Bz
N
O
O
OH
OH
(+/-)-518
(+/-)-520

Figure 98. Ozonolysis of of *N*-Bz protected carbamate **518**

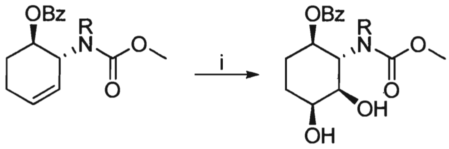
Table 12. Ozonolysis of of *N*-Bz protected carbamate **518**

Entry	*Temp. of O_3*	*Temp. of Me_2S*	*Reducing Agent*	*Temp. of Reduction*	*Yield*[a]
1	-78°C	-78 to 0°C	$NaBH_3CN$	0°C to r.t.	10%[b]
2	-78°C	-78 to 0°C	$NaBH_4$	0°C to r.t.	10%[b]

[a] yield estimated, product not pure by ^1H NMR, [b] tentative identification (^1H and ^{13}C NMR, MS)

3.2.4 Step-wise Oxidative Cleavage

As this stage of the project we decided to abandon all ozonolysis chemistry in favour of a step-wise dihydroxylation and then oxidative cleavage approach. Dihydroxylation of olefins **517** and **518** with osmium(VIII) oxide provided diols **521** and **522** respectively (Scheme 48).



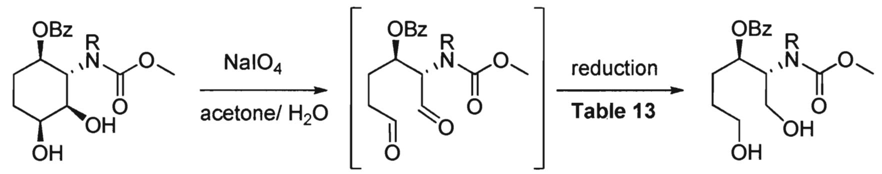
(+/-)-517 R = Boc
(+/-)-518 R = Bz

(+/-)-521 R = Boc
(+/-)-522 R = Bz

Reagents and conditions: (i) OsO_4, NMO, DCM/H_2O, 87%

Scheme 48. Dihydroxylation of olefins **517** and **518**

Oxidative cleavage of 1,2-diols **521** and **522** with sodium periodate provided dialdehyde intermediates which were subjected to a series of reduction procedures (Figure 99). This method provided aliphatic diols **519** and **520** in modest yields (Table 13). Regardless, these experiments demonstrated the validity of the step-wise approach. The best results (Table 13, Entries 1 and 2) were obtained when sodium borohydride was added to the reaction mixture at -40°C. Starting at cooler temperatures (Table 13, Entries 5 and 6) generated more side products (crude ^1H NMR identification) and lowered the isolated yields.



(+/-)-**521** R = Boc
(+/-)-**522** R = Bz

(+/-)-**523** R = Boc
(+/-)-**524** R = Bz

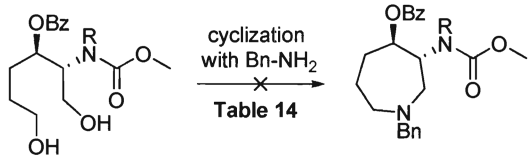
(+/-)-**519** R = Boc
(+/-)-**520** R = Bz

Figure 99. Oxidative cleavage of carbamates **521** and **522**

Table 13. Oxidative cleavage of carbamates **521** and **522**

Entry	*R =*	*Reducing Agent*	*Solvent*	*Temp.*	*Yield (% over 2 steps)*
1	Boc	$NaBH_4$	EtOH	-40°C to r.t.	51
2	**Bz**	**$NaBH_4$**	**EtOH**	**-40°C to r.t.**	**55**
3	Boc	$NaBH_3CN$	EtOH	-40°C to r.t.	25
4	Bz	$NaBH_3CN$	EtOH	-40°C to r.t.	26
5	Boc	$NaBH_4$	EtOH	-78°C to r.t.	44
6	Bz	$NaBH_4$	EtOH	-78°C to r.t.	49
7	Boc	$NaBH_3CN$	EtOH	-78°C to r.t.	33
8	Bz	$NaBH_3CN$	EtOH	-78°C to r.t.	39

We subjected aliphatic diols **519** and **520** to the cyclization protocols developed at the onset of the project (Figure 100). We first attempted direct cyclization of the diols using the iridium catalyst ([Cp*$IrCl_2$]$_2$) but isolated only starting material (Table 14). We encountered problems generating the di-tosyl derivatives of **519** and **520** and could only isolate a mixture of mono and di-tosylated compounds. Nevertheless, the mixture was submitted to the cyclization protocols with DCM and DME as the solvent. In no instance were we able to find evidence for the formation of the azepane derivatives **525** and **526**.



(+/-)-**519** R = Boc
(+/-)-**520** R = Bz

(+/-)-**525** R = Boc
(+/-)-**526** R = Bz

Figure 100. Attempted azepane cyclization

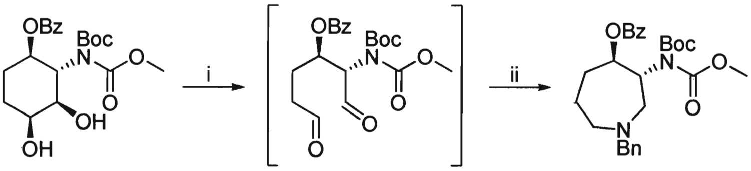
Table 14. Attempted azepane cyclization

Entry	*R =*	*Reagents*	*Solvent*	*Temp.*	*Result*
1	Boc	$[Cp^*IrCl_2]_2$, $NaHCO_3$	toluene	reflux	SM
2	Bz	$[Cp^*IrCl_2]_2$, $NaHCO_3$	toluene	reflux	SM
3	Boc	*p*-TsCl, pyridine, DMAP[a]	DCM	reflux	SM[b]
4	Bz	*p*-TsCl, pyridine, DMAP[a]	DCM	reflux	SM[b]
5	Boc	*p*-TsCl, pyridine, DMAP[a]	DME	reflux	SM[b]
6	Bz	*p*-TsCl, pyridine, DMAP[a]	DME	reflux	SM[b]
7	Boc	*p*-TsCl, pyridine, DMAP[a]	MeCN	reflux	SM[b]
8	Bz	*p*-TsCl, pyridine, DMAP[a]	MeCN	reflux	SM[b]

[a] benzylamine was added to the reaction after the complete consumption of diol; [b] referrers to the isolation of a mixture of mono and di-tosylated derivatives

3.2.5 Reductive Amination

We considered the next logical approach to be a direct reductive amination procedure of the intermediate dialdehyde species. Painter had constructed similar azepane rings using an oxidative cleavage/ reductive amination sequence.[275] We employed his procedure on the *N*-Boc carbamate **521** and were able to isolate the azepane derivative **525**, albeit in a modest yield of 16% (Scheme 49).

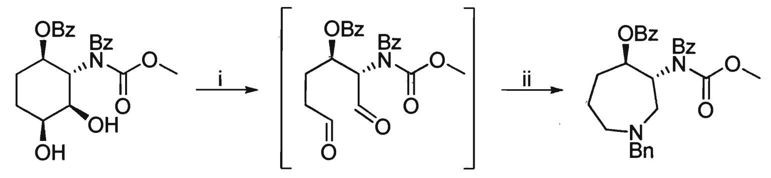


(+/–)-521 **(+/–)-523** **(+/–)-525**

Reagents and conditions: (i) $NaIO_4$, acetone/H_2O (8:2); (ii) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. Sieves, MeOH, -78°C to r.t., 15%

Scheme 49. Reductive amination of *N*-Boc protected carbamate **521**

The *N*-Bz derivative proved to be a slightly more successful substrate with an isolated yield of 23%.

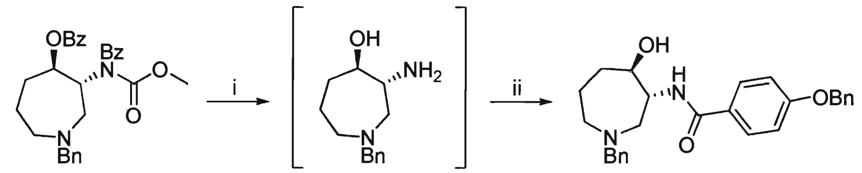


(+/–)-522 **(+/–)-524** **(+/–)-526**

Reagents and conditions: (i) $NaIO_4$, acetone/H_2O (8:2); (ii) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. Sieves, MeOH, -78°C to r.t., 23%

Scheme 50. Reductive amination of *N*-Bz protected carbamate **522**

We were able to synthesize the balanol formal intermediate **231** in racemic form through strong basic hydrolysis of azepane **526** followed by reacting the crude mixture with 4-(benzyloxy)benzoyl chloride. Subsequent chromatography identified a small amount (<5%) of the formal intermediate **231**.



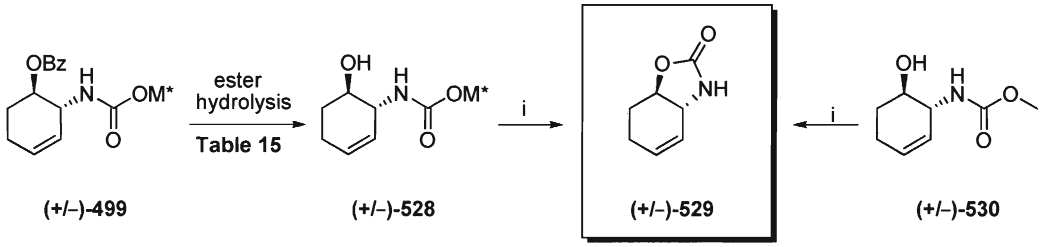
(+/–)-526 **(+/–)-527** **(+/–)-231**

Reagents and conditions: (i) 50% KOH in glycerol, 120°C; (ii) *p*-$BnOC_6H_4COCl$, 1N NaOH, Na_2CO_3, DCM, r.t., ~5% over 2 steps

Scheme 51. Racemic formal synthesis of balanol **(1)**

3.2.6 Cyclic Carbamate

The strong conditions required to hydrolyze the protecting groups of azepane **526** necessitated a different strategy. We sought to find a compound that could be accessed from either the methyl carbamate **530** model route or the (–)-menthyl carbamate **499** route. The simplest solution was to convert both into cyclic carbamate derivative **529**. Screening of various *O*-benzoyl hydrolysis procedures identified methanolic sodium hydroxide at ambient temperature as the most effective (Table 15, Entries 4). In each instance, exposure of carbamates **528** and **530** to sodium hydride led to the formation of cyclic carbamate **529** resulting from the expulsion of (–)-menthol and methanol respectively (Scheme 52).



(+/–)-499 **(+/–)-528** **(+/–)-529** **(+/–)-530**

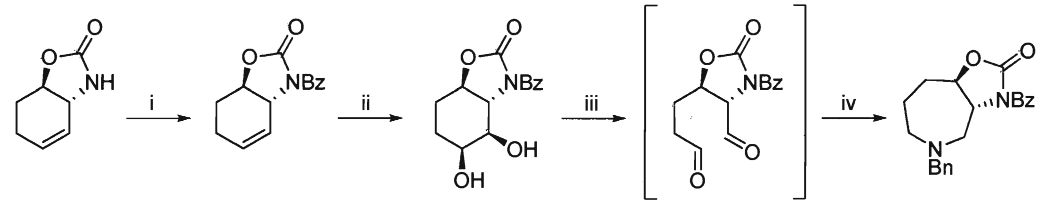
Reagents and conditions: (i) NaH, THF, reflux

Scheme 52. Synthesis of cyclic carbamate **529**

Table 15. *O*-benzoyl hydrolysis of **499**

Entry	*Reagent*	*Solvent*	*Temp.*	*Yield*
1	trifluoroacetic acid	-	r.t	14%
2	1N KOH	MeOH	r.t.	76%
3	1N KOH	MeOH	40°C	71%
4	**1N NaOH**	**MeOH**	**r.t.**	**94%**
5	1N NaOH	MeOH	40°C.	88%

Our previous studies had identified that; 1. the carbamate nitrogen should be derivatized, and 2. *N*-benzoyl protection is preferred to *N*-Boc protection. Hence, cyclic carbamate **529** was first converted into *N*-Bz carbamate **531** prior to dihydroxylation with osmium(VIII) oxide (Scheme 53). The resulting 1,2-diol **532** was then subjected to the oxidative cleavage/ reductive amination protocol to afford azepane **534**.



Reagents and conditions: (i) BzCl, NEt_3, DMAP, DCM, r.t., 77%; (ii) OsO_4, NMO, DCM/H_2O, 89%; (iii) $NaIO_4$, acetone/H_2O (8:2); (iv) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. sieves, MeOH, -78°C to r.t., 62% over 2 steps

Scheme 53. Synthesis of cyclic carbamate azepane **534**

The next step was to develop a high yielding method to hydrolyze cyclic carbamate **534** to β-amino alcohol **535** (Figure 101). Our first attempt employed potassium hydroxide in ethylene glycol (Table 16, Entry 1) and surprisingly provided a mixture of fully and partially hydrolyzed products, namely **535** and **527**. Further experiments identified a mild method (Table 16, Entry 5) to hydrolyze only the cyclic carbamate functionality. We speculated that if cyclic carbamate **534** was alternatively protected with the 4-(benzyloxy)benzoyl moiety, partial hydrolysis could give direct access to formal intermediate **231**.

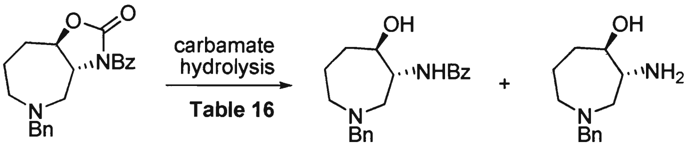


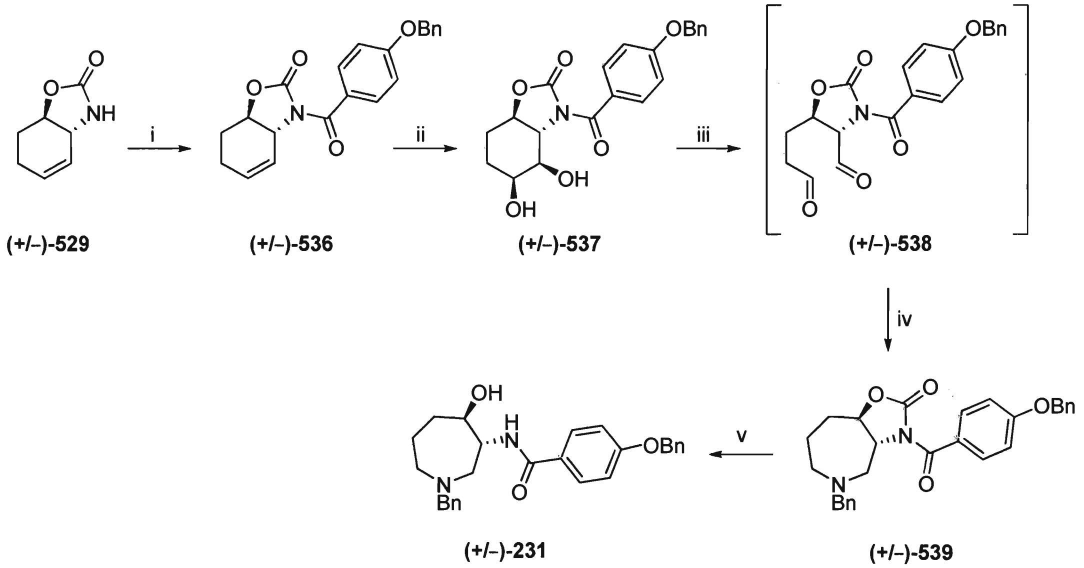
Figure 101. Hydrolysis of cyclic carbamate **534**

Table 16. Hydrolysis of cyclic carbamate **534**

Entry	*Reagent*	*Solvent*	*Temp.*	*Approx. Ratio 535:527*
1	1N KOH	ethylene glycol	40°C	15:85[a]
2	1N NaOH	ethylene glycol	r.t.	15:85[a]
3	1N NaOH	MeOH	r.t	30:70[a]
4	1N NaOH	THF	r.t	30:70[a]
5	**1N NaOH**	**THF**	**-20°C**	**>99:1**[a]

[a] ratio estimated from crude ^{1}H NMR

Derivatization of cyclic carbamate **529** with 4-(benzyloxy)benzoyl chloride afforded amide **536** (Scheme 54). Following the identical reaction sequence used to prepare azepane **534** (Scheme 53), we synthesized azepane **539**. As anticipated, our mild basic hydrolysis procedure did provide us with balanol intermediate **231** in the racemic form.

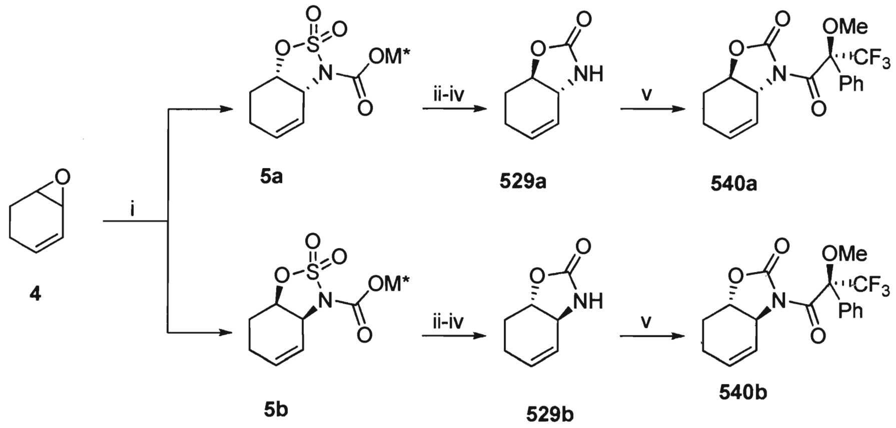


Reagents and conditions: (i) *p*-BnOC$_6$H$_4$COCl, DCM, DMAP, NEt$_3$, 0°C, 72%; (ii) OsO$_4$, NMO, DCM, r.t., 83%; (iii) NaIO$_4$, acetone/H$_2$O (8:2), r.t.; (iv) Bn-NH$_2$, AcOH, NaBH$_3$CN, 3Å mol. sieves, MeOH, -78°C to r.t., 68% over 2 steps; (v) 1N NaOH, THF, -20°C, 81%

Scheme 54. Synthesis of balanol intermediate **231**

3.2.7 Completion of an Enantiodivergent Formal Synthesis of Balanol

With an established route to balanol intermediate **231**, we sought to complete the formal syntheses of (–)- and (+)-balanol from cyclic sulfamidates **5a** and **5b** respectively. The exhausting process of separating diastereomers **499a** and **499b**, in large enough quantities, was undertaken by Jacqueline Gilmet.[276] Before proceeding, we wanted to determine the optical purity of the two diastereomers. The corresponding cyclic carbamates **529a** and **529b** were converted into their (*S*)-(+)-Mosher amide derivatives **540a** and **540b** (Scheme 55).



Reagents and conditions: (i) **3** (2.3 equiv.), THF, reflux; (ii) $PhCO_2^-NH_4^+$, DMF, 45°C; (iii) THF, H_2O, conc. H_2SO_4, r.t.; (iv) 1M NaOH in MeOH; (v) NaH, THF, reflux; (vi) (*S*)-(+)-Mosher's acid chloride, NEt_3, DMAP, DCM, 0°C to r.t.

Scheme 55. Synthesis of (*S*)-(+)-Mosher derivatives **540a** and **540b**

For the (–)-balanol **(1)** synthesis, gas chromatography/ mass spectroscopy analysis indicated a 96:4 ratio of diastereomers **540a** to **540b** (Figure 102). We suspect that incomplete separation of the **499a** and **499b** diastereomers by column chromatography accounts for this ratio, which results from enantiomeric impurities carried throughout the synthesis following removal of the (–)-menthyl group

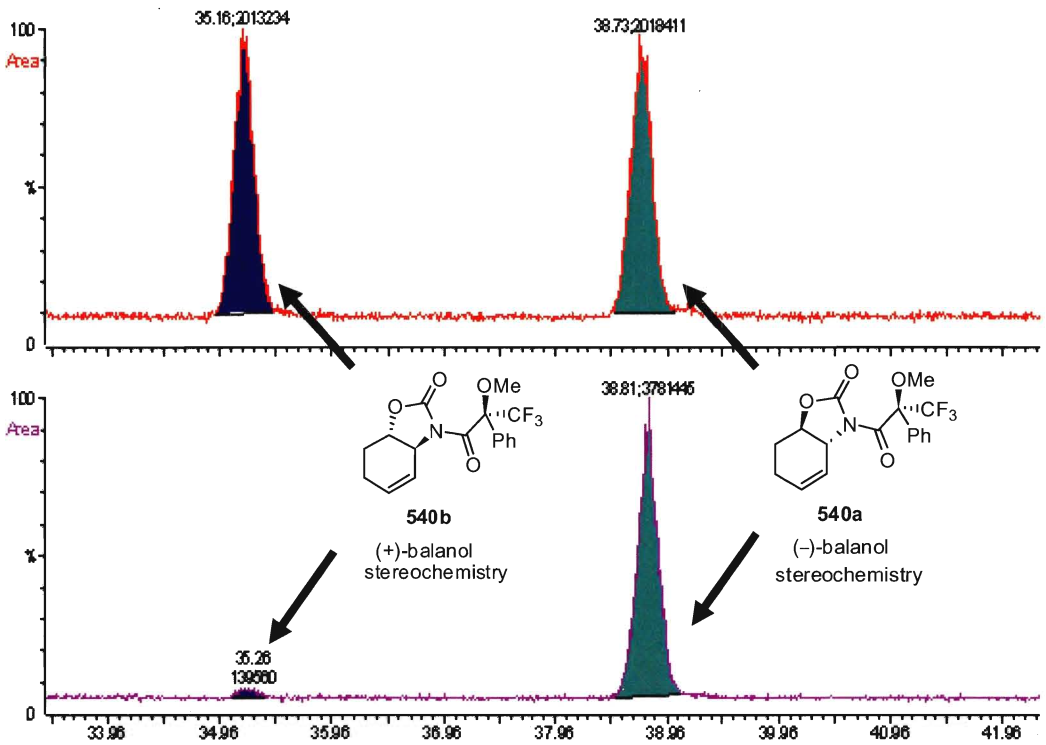
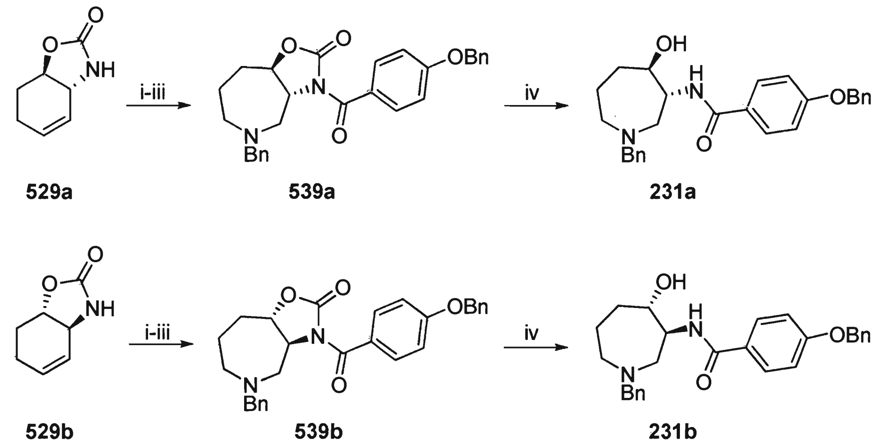


Figure 102. GC/MS analysis of (*S*)-(+)-Mosher derivatives **540a** and **540b**

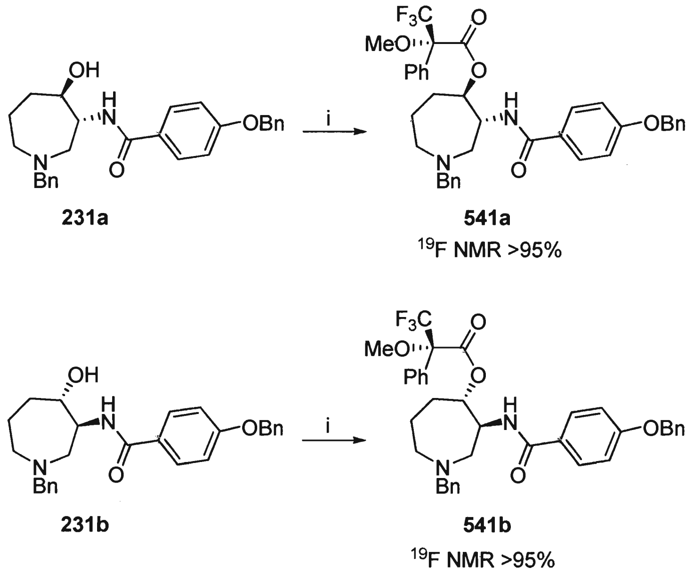
Carbamates **529a** and **529b** were each converted into their corresponding formal intermediates via the aforementioned cyclic carbamate route (Scheme 56).[277-8] This completed an enantiodivergent synthesis of (+)- and (–)-balanol from 1,3-cyclohexadiene oxide **(4)** in 8 steps.


i-iii
iv
OBn
Bn
529a
539a
231a
529b
539b
231b

Reagents and conditions: (i) *p*-BnOC$_6$H$_4$COCl, DCM, DMAP, NEt$_3$, 0°C; (ii) OsO$_4$, NMO, DCM, r.t.; (iii) a) NaIO$_4$, acetone/H$_2$O (8:2), r.t.; b) Bn-NH$_2$, AcOH, NaBH$_3$CN, 3Å mol. sieves, MeOH, -78°C to r.t.; (iv) 1N NaOH, THF, -20°C

Scheme 56. Formal enantiodivergent synthesis of (+)- and (–)-balanol.[277-8]

The optical purity of each formal intermediate was confirmed through conversion to their (*S*)-(+)-Mosher esters **541a** and **541b** (Scheme 57). In each case, ^{19}F NMR analysis established ratios greater than 95%.

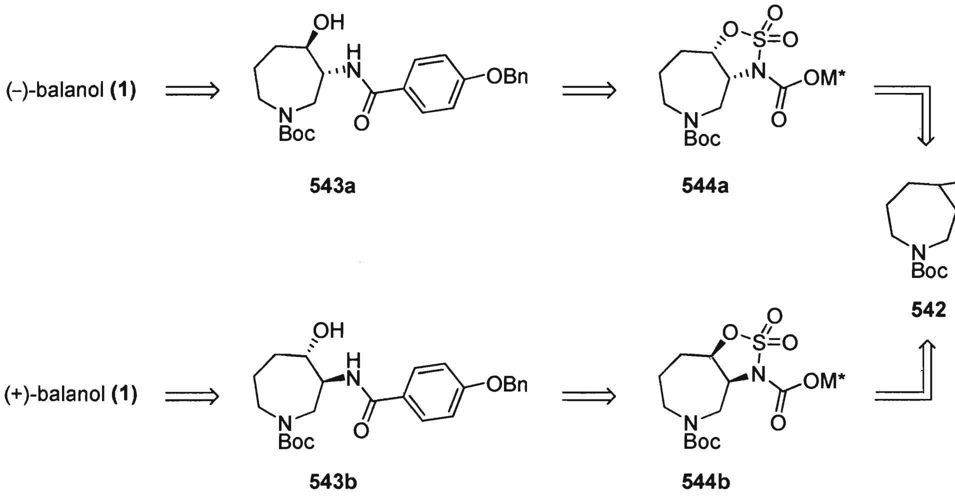

i
F3C
MeO
Ph
OBn
Bn
231a
541a
19F NMR >95%
231b
541b
19F NMR >95%

Reagents and conditions: (i) (*S*)-(+)-Mosher's acid chloride, NEt$_3$, DMAP, DCM, 40°C.

Scheme 57. Synthesis of (*S*)-(+)-Mosher ester derivatives **541a** and **541b**

3.2.8 Azepane Epoxide Route

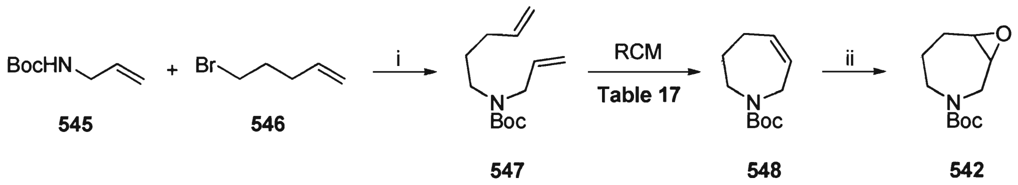
We questioned whether our (–)-menthyl Burgess reagent methodology could be extended to include azepane epoxide **542** as a substrate. This route would circumvent the oxidative cleavage/ reductive amination procedure (Figure 103).



(-)-balanol (1)
OH
H
N
OBn
N
Boc
O
543a
O
O
S=O
N
OM*
N
Boc
O
544a
O
N
Boc
542
(+)-balanol (1)
OH
H
N
OBn
N
Boc
O
543b
O
O
S=O
N
OM*
N
Boc
O
544b

Figure 103. Azepane epoxide approach balanol **(1)**

The preparation of oxirane **542** began with the displacement of alkyl bromide **546** with the *tert*-butyl carbamate derivative of allyl amine **545** (Scheme 58). The resulting diene **547** was then subjected to a series of ring closing metathesis procedures (Table 17). We obtained higher yields when Grubbs' 1st generation catalyst was used compared to the 2nd generation catalyst. Epoxidation of olefin **548** with *m*CPBA completed the synthesis of oxirane **542**.



BocHN
545
+
Br
546
i
N
Boc
547
RCM
Table 17
N
Boc
548
ii
O
N
Boc
542

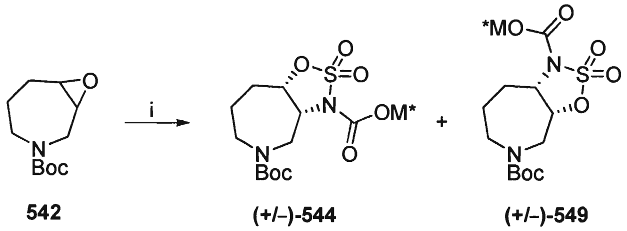
Reagents and conditions: (i) NaH, DMF, 0°C, 77%; (ii) *m*CPBA, DCM, 0°C, 86%

Scheme 58. Synthesis of azepane epoxide **542**

Table 17. Ring closing metathesis of diene **547**

Entry	*Catalyst*	*Solvent*	*Temp.*	*Yield*
1	Grubbs' 1st gen.	benzene	reflux	80%
2	**Grubbs' 1st gen.**	**DCM**	**reflux**	**86%**
3	Grubbs' 2nd gen.	benzene	reflux	64%
4	Grubbs' 2nd gen.	DCM	reflux	71%

Unfortunately, the reaction between oxirane **542** and the (–)-menthyl Burgess reagent afforded a mixture (~1:1) of the regioisomers **544** and **549**. We were unable to separate the two isomers and did not pursue this approach further.



Reagents and conditions: **3** (2.3 equiv.), THF, reflux

Scheme 59. Reaction between azepane **542** epoxide and the (–)-menthyl Burgess reagent **(3)**

3.3 Chemoenzymatic Synthesis of Balanol

We completed our first generation formal syntheses of (+)- and (–)-balanol by preparing azepanes **231a** and **231b**,[277-8] intermediates in the Lampe and Hughes synthesis.[111-2] The physical and spectral properties of our samples were in complete agreement with those previously reported. However, we were unable to locate optical rotations for either compound in the literature. This was puzzling considering several asymmetric syntheses of these intermediates have been reported.[111-2, 115, 130] Our own samples suffered from contamination of the opposite isomer, a consequence of the less than perfect separation of diastereomers **499a** and **499b**. Analysis of our **231a** and **231b** samples, via GC/ MS and ^{19}F NMR techniques, indicated >95% enantiomeric excess.

For our second generation synthesis we sought to employ a starting material which would guarantee accurate optical data for formal intermediates **231a** and **231b**. To this end, we selected *cis*-dihydrodiol **6**, which is available in large quantities[279] from the whole-cell oxidation of bromobenzene with a recombinant *E. coli* strain overexpressing the toluene dioxygenase enzyme.[13] The optical purity of this material has been well established through its use in the synthesis of several natural products.[14]

3.3.1 Vinyl Aziridine Approach to Balanol

Our enantiodivergent approach relied on the preparation of diastereomeric vinyl aziridines **550** and **551** from *cis*-dihydrodiol **6** (Figure 104). Opening of each with an appropriate oxygen nucleophile and reduction of the vinyl halide functionalities would provide 1,2-diols **552** and **553**. These would serve as substrates for the oxidative cleavage/ reductive amination procedure developed in our first generation syntheses.

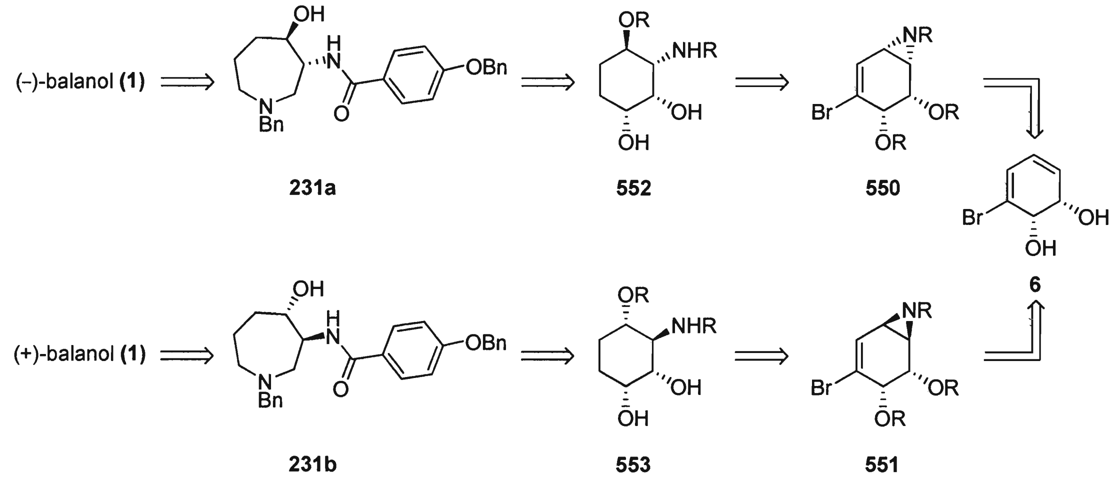
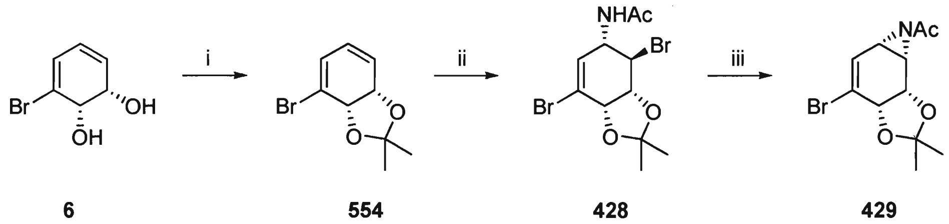


Figure 104. Retrosynthetic analysis of balanol (**1**) from *cis*-dihydrodiol **6**

3.3.2 Vinyl Aziridine Approach to (–)-Balanol

Synthesis of the (–)-balanol formal intermediate **231a** began with the preparation of vinyl aziridine **429** (Scheme 60).[280] Reaction between the acetonide derivative of *cis*-dihydrodiol **554** and *N*-bromoacetamide afforded β-bromo amide **428**. Exposure to potassium bis(trimethylsilyl)amide in the presence of tin(IV) bromide effected the formation of aziridine **429**.


Br
OH
OH
i
Br
O
O
ii
NHAc
Br
Br
O
O
iii
NAc
Br
O
O
6
554
428
429

Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, acetone, r.t.; (ii) *N*-bromoacetamide, $SnBr_4$, MeCN, -30°C, 76% over 2 steps; (iii) KHMDS, *n*-BuNBr, DME, 0°C, 67%

Scheme 60. Preparation of *N*-acetyl vinyl aziridine **429**

We began to screen oxygen nucleophiles which would open the aziridine and provide the necessary *trans* disposition seen in balanol **(1)**. Our first attempts employed benzyl alcohol and a series of Lewis acid catalysts (Figure 105). In each instance, we obtained a mixture consisting of the *trans* **555** and *cis* **556** isomers (Table 18). With the exception of ammonium chloride, each catalyst produced a similar isolated yield. The most favourable ratio was seen when copper(II) triflate was employed.

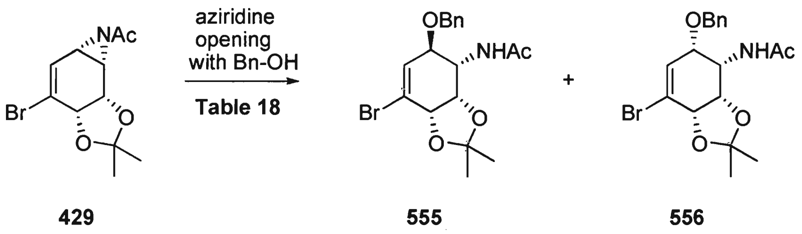

NAc
Br
O
O
aziridine
opening
with Bn-OH
Table 18
OBn
NHAc
Br
O
O
+
OBn
NHAc
Br
O
O
429
555
556

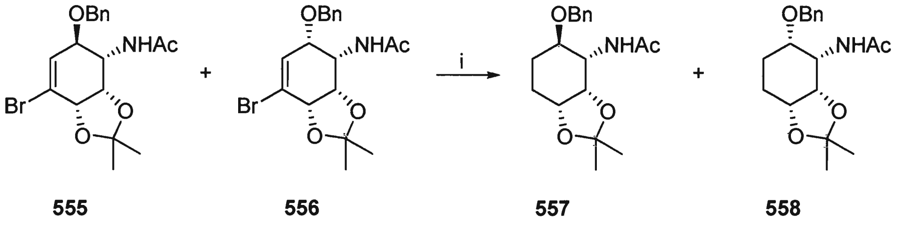
Figure 105. Opening of vinyl aziridine **429** with benzyl alcohol

Table 18. Opening of vinyl aziridine with **429** benzyl alcohol

Entry	*Catalyst*	*Solvent*	*Temp.*	*Yield*	*Ratio (555:556)*[a]
1	$BF_3{\cdot}OEt_2$	DCM	r.t.	82%	2:1
2	**$Cu(OTf)_2$**	**DCM**	**r.t.**	**72%**	**5:1**
3	NH_4Cl	DMF	r.t.	-	-
4	NH_4Cl	DMF	75°C	-	-
5	TMSOTf	DCM	r.t.	80%	3.5:1
6	TBSOTf	DCM	r.t.	81%	3.5:1

[a] approximate ratio determined by ^1H NMR

Complete separation of *O*-benzyl isomers **555** and **556** via column chromatography proved troublesome. Hence, the mixture was subjected to a hydrogenation protocol with Adams' catalyst (Scheme 61). Unfortunately, the *trans* isomer **557** could not be completely separated from the minor *cis* isomer **558** to an acceptable level (GC/ MS analysis). Therefore, this route was abandoned in favour of using another oxygen nucleophile.



Reagents and conditions: (i) H_2 (1 atm), PtO_2, MeOH, NEt_3, 88%

Scheme 61. Hydrogenation of *trans* and *cis O*-benzyl derivatives **555** and **556**

When we employed acetic acid as the oxygen nucleophile, we obtained a mixture containing the *trans* **559** and *cis* **560** isomers (Figure 106). Fortunately, these diastereomers could be separated to a satisfactory level (>99% by GC/ MS analysis). Again we screened a series of Lewis acid catalysts in an attempt to improve upon the ratio (Table 19). Unlike our studies with benzyl alcohol, copper(II) triflate produced an unfavourable ratio. Ytterbium(III) triflate afforded a higher ratio (3:1) but suffered from a lower isolated yield. When we employed silyl-based catalysts (Table 19, Entries 4 to 8) we observed a significant improvement in the ratio. We found that trimethylsilyl trifluoromethanesulfonate (TMSOTf), in either DCM or THF, provided the best results. A final experiment employing a large excess of acetic acid offered a slight improvement in yield.

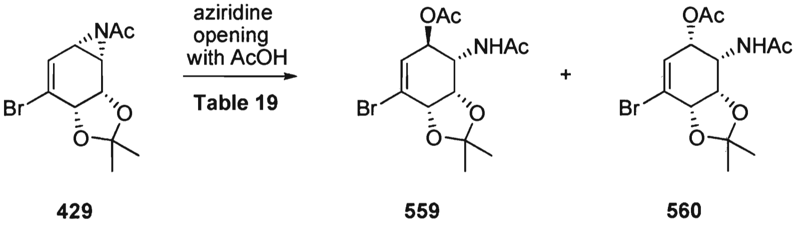


Figure 106. Opening of vinyl aziridine **429** with acetic acid

Table 19. Opening of vinyl aziridine **429** with acetic acid

Entry	*Catalyst*	*Solvent*	*Equiv. AcOH*	*Yield*	*Ratio (559:560)*[a]
1	$BF_3{\cdot}OEt_2$	DCM	5	82%	2:1
2	$Cu(OTf)_2$	DCM	5	72%	2.5:1
3	$Yb(OTf)_3$	DCM	5	66%	3:1
4	TBSOTf	DCM	5	77%	3.5:1
5	TBSOTf	THF	5	84%	3.5:1
6	TMSOTf	THF	5	85%	4:1
7	TMSOTf	DCM	5	82%	4:1
8	**TMSOTf**	**DCM**	**20**	**88%**	**4:1**

[a] approximate ratio determined by ^1H NMR

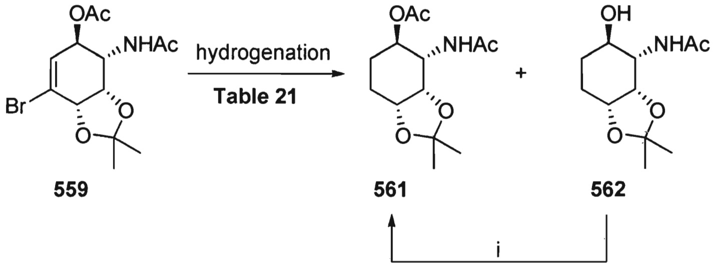
We were satisfied with the 4:1 ratio, but questioned whether or not we could find conditions that provided exclusively the *trans* isomer **559**. Lewis acid catalysis proceeds through an S_N1 mechanism in which an allylic cation is attacked from either face. We attempted to develop a S_N2 method through use of various acetate salts (Table 20). We screened various solvents and temperatures with limited success. Dimethoxyethane, with either sodium or potassium acetate, only provided minute amounts of product. The best results employed potassium acetate in *N,N*-dimethylformamide (DMF) at 80°C but were still not practical.

Table 20. Opening of vinyl aziridine **429** with acetate salts

Entry	*Nucleophile*	*Solvent*	*Concentration*	*Temp.*	*Yield*[a]
1	NaOAc	DME	1 M	35°C	5
2	KOAc	DME	1 M	35°C	5
3	$Ca(OAc)_2$	DME	1 M	35°C	-
4	KOAc	DMF	1 M	80°C	10
5	KOAc	DMF	5 M	80°C	10
6	KOAc	DMF	conc. slurry	80°C	-

[a] yield estimated from crude ^{1}H NMR

We moved on with the synthesis and attempted to hydrogenate the vinyl bromide functionality of **559** (Scheme 62). Our initial conditions produced the *O*-Ac product **561** and the hydrolysis product **562** (Table 21, Entry 1). We treated the crude mixture with acetic anhydride to obtain *O*-Ac **561** exclusively, but we wanted to develop a method that would avoid this extra operation. When isopropyl alcohol was used in place of methanol we saw a dramatic improvement in the ratio of *O*-Ac product **561**. Palladium on charcoal did not yield either **561** or **562**, only the saturated hydrogenolysis product (no OAc, not shown) could be isolated. Fortunately, we obtained only the desired product when ethyl acetate and Adams' catalyst were used.



Reagents and conditions: (i) Ac_2O, NEt_3, DCM

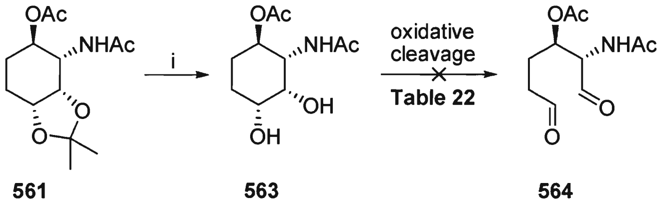
Scheme 62. Hydrogenation of vinyl bromide **559**

Table 21. Hydrogenation of vinyl bromide **559**

Entry	*Catalyst*	*Solvent*	*Yield (%)*	*Ratio **561**:**562**[a]*
1	PtO_2	MeOH	88	10:90
2	PtO_2	*i*-PrOH	71	70:30
3	5% Pd/C	MeOH	52[b]	-
4	**PtO_2**	**EtOAc**	**84**	**>99:1**

[a] approximate yield determined by ^1H NMR; [b] hydrogenolysis product

Hydrolysis of acetonide **561** afforded 1,2-diol **563**, which was subjected to the sodium periodate oxidative cleavage method developed earlier. Only starting material was isolated, necessitating the use of another method. Regardless of the solvent used, elevated temperatures resulted in the decomposition of the starting material. We also attempted oxidative cleavage protocols using lead(IV) acetate without success.



Reagents and conditions: (i) AcOH/THF/H_2O (4:1:2), reflux, 86%

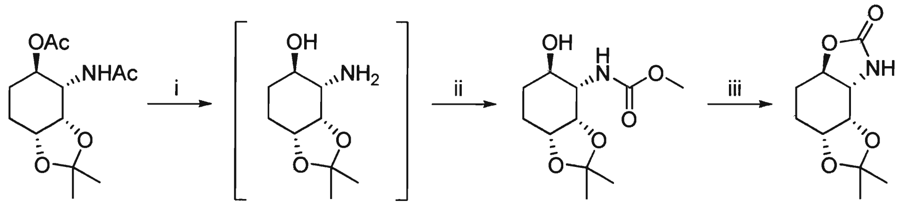
Scheme 63. Attempted oxidative cleavage of 1,2-diol **563**

Table 22. Attempted oxidative cleavage of 1,2-diol **563**

Entry	*Reagent*	*Solvent*	*Temp.*	*Result*
1	$NaIO_4$	acetone/ H_2O	r.t.	SM
2	$NaIO_4$	acetone/ H_2O	reflux	decomposition[a]
3	$NaIO_4$	H_2O	reflux	decomposition[a]
4	$NaIO_4$	0.1 M AcOH	r.t.	decomposition[a]
5	$NaIO_4$	THF	r.t.	SM
6	$Pb(OAc)_4$	acetone/ H_2O	r.t.	SM
7	$Pb(OAc)_4$	acetone/ H_2O	reflux	decomposition[a]
8	$Pb(OAc)_4$	0.1 M AcOH	r.t.	decomposition[a]

[a] complex mixture, no evidence for aldehydes (TLC/ 2,4-DNP staining and NMR)

We elected to intercept our own formal intermediate, namely azepane **539**, through cyclic carbamate **567**. Strong basic hydrolysis of **561** afforded amino alcohol **565** which was exposed to methyl chloroformate without purification. The resulting carbamate **566** underwent an intramolecular cyclization upon treatment with sodium hydride.

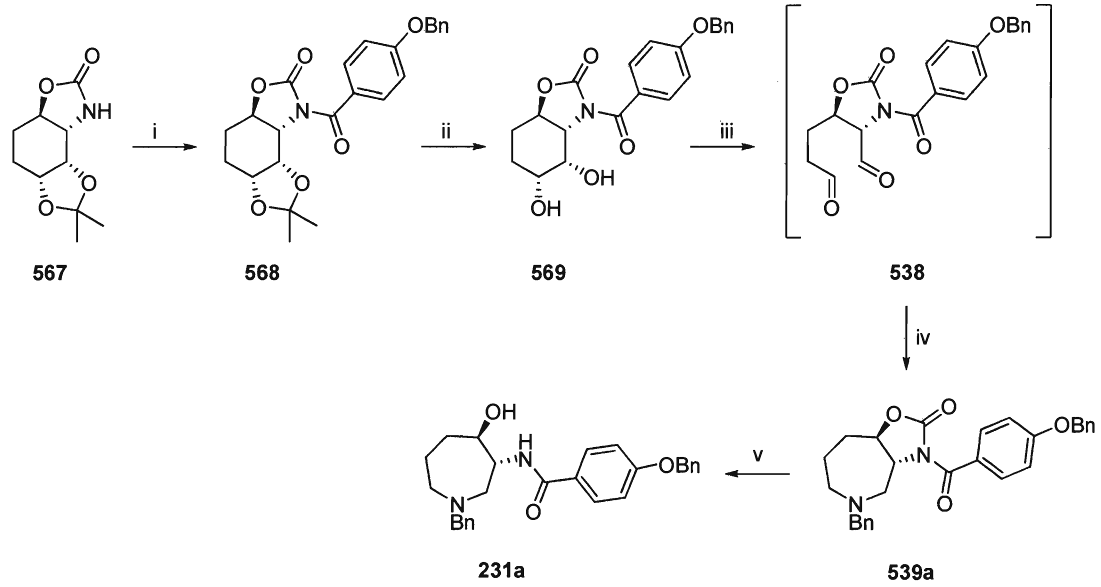


561 **565** **566** **567**

Reagents and conditions: (i) NaOMe, MeOH, reflux; (ii) methyl chloroformate, NEt_3, DCM, DMAP, r.t., 73% over 2 steps; (iii) NaH, THF, reflux, 83%

Scheme 64. Synthesis of cyclic carbamate **567**

Cyclic carbamate **567** was reacted with 4-(benzyloxy)benzoyl chloride to afford amide **568** (Scheme 65). Acetonide deprotection provided 1,2-diol **569** which proved to be an acceptable substrate for the oxidative cleavage/ reductive amination protocol. Mild hydrolysis of azepane **539** completed the formal synthesis of (–)-balanol. We established the optical purity of **231a** via ^{19}F NMR analysis of its (*S*)-(+)-Mosher ester derivative in an identical manner employed in our first synthesis (Scheme 57).

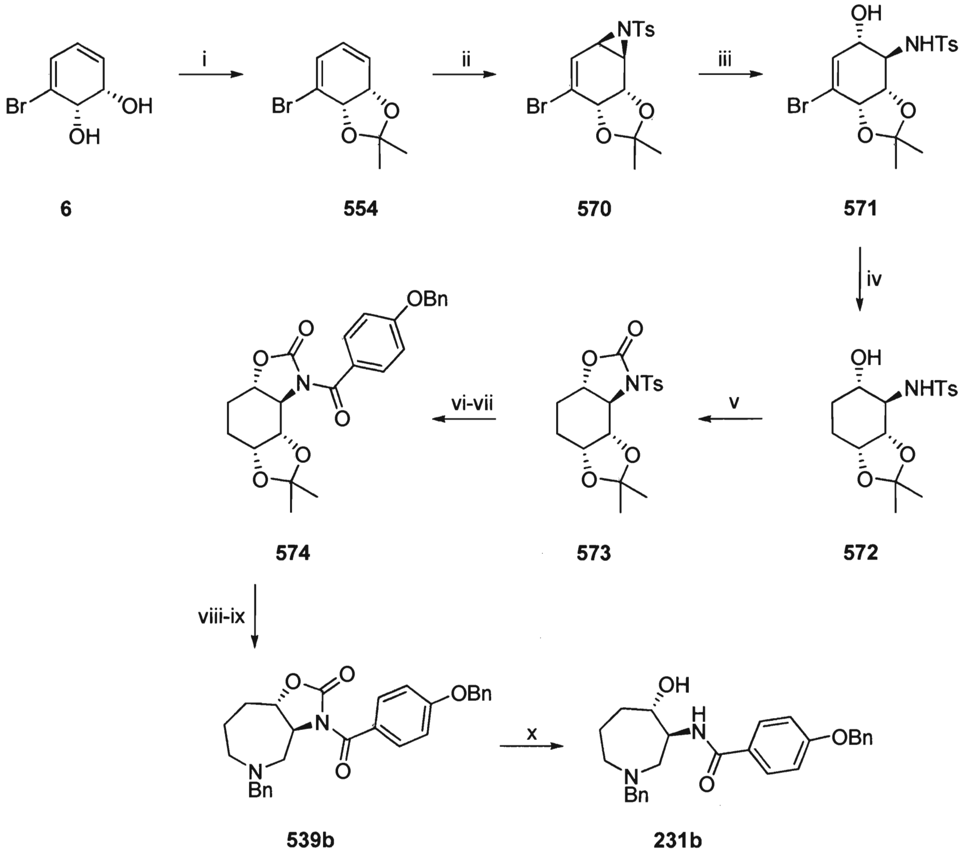


Reagents and conditions: (i) *p*-$BnOC_6H_4COCl$, DCM, DMAP, NEt_3, 0°C, 82%; (ii) $AcOH/THF/H_2O$ (9:3:1), reflux, 88%; (iii) $NaIO_4$, acetone/H_2O (8:2), r.t.; (iv) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. sieves, MeOH, -78°C to r.t., 64% over 2 steps; (v) 1N NaOH, THF, -20°C, 81%

Scheme 65. Synthesis of (–)-balanol intermediate **231a**.[278-80]

3.3.3 Vinyl Aziridine Approach to (+)-Balanol

Synthesis of the (+)-balanol intermediate **231b** from *cis*-dihydrodiol **6** was accomplished by Jacqueline Gilmet.[278, 281] This strategy employed the anti-disposed *N*-tosyl vinyl aziridine **570**, prepared via a copper(II) acetylacetonate catalyzed nitrene protocol (Scheme 66).[282-3] Opening with hydroxide provided allylic alcohol **571** which was subsequently reduced with Adams' catalyst. The resulting cyclohexanol derivative **572** was exposed to triphosgene to provide cyclic carbamate **573**. A dissolving metal reduction removed the tosyl functionality, and treatment with 4-(benzyloxy)benzoyl chloride furnished amide **574**. Acetonide hydrolysis, oxidative cleavage and reductive amination with benzyl amine yielded azepane **539b**. Mild hydrolysis of the cyclic carbamate completed the formal synthesis of (+)-balanol.


6
554
570
571
572
573
574
539b
231b
i
ii
iii
iv
v
vi-vii
viii-ix
x
Br
OH
NTs
NHTs
OBn
N
Bn

Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) PhI=NTs, Cu(acac)$_2$, MeCN, 0°C, 77% over 2 steps; (iii) DMSO, KOH, H_2O, 30°C, 94%; (iv) PtO$_2$, H_2 (1 atm), MeOH, 77%; (v) triphosgene, NEt$_3$, DCM, 0°C, 93%; (vi) Na/ naphthalene, DME, -78°C; (vii) *p*-BnOC$_6$H$_4$COCl, NaH, THF, r.t., 91% over 2 steps; (viii) AcOH/THF/H_2O (9:3:1), reflux; (ix) a) NaIO$_4$, acetone/H_2O (8:2), r.t.; b) Bn-NH$_2$, AcOH, NaBH$_3$CN, 3Å mol. sieves, MeOH, -78°C to r.t., 72% over 3 steps; (x) 1N NaOH, THF, -20°C, 56%

Scheme 66. Synthesis of (+)-balanol intermediate **231b**.[278]

3.4 Enzymatic Dihydroxylation of Benzoate Esters

Dihydroxylations catalyzed by the toluene dioxygenase (TDO) enzyme provide enantiopure *cis*-dihydrodiols from their corresponding arene substrates. The most significant research in this field has been conducted by David Gibson, who isolated the first stable metabolite in 1968.[12] Since that time, numerous new *cis*-dihydrodiol metabolites have been isolated and characterized. Many have served as building blocks in the synthesis of several naturally occurring products.[14] The most frequently employed are the diol metabolites derived from the oxidation of benzene, toluene, chlorobenzene, bromobenzene, and (2-bromoethyl)benzene. Milestones include Ley's synthesis of (+/–)-pinitol,[176] and Hudlicky's synthesis of (+)-pancratistatin[180] (see Section 2.3.4 for further details).

In addition to synthetic efforts, the Hudlicky group has long been involved in the identification of new *cis*-dihydrodiol metabolites. With that goal in mind, we became interested in the dihydroxylation of benzoate esters. We speculated that such products would provide short access to pseudo-sugars, amino cyclitols and bicyclic ring systems (Figure 107).

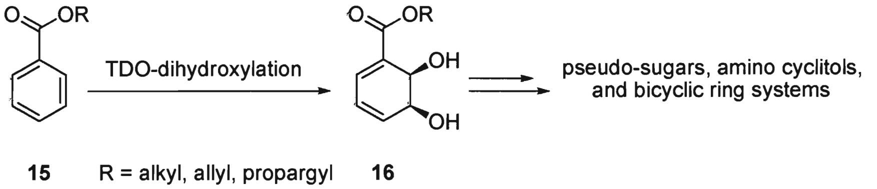
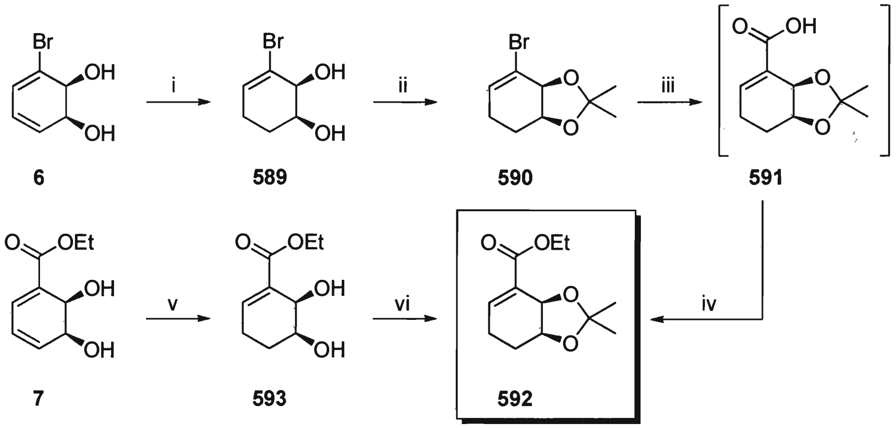

O
OR
TDO-dihydroxylation
O
OR
OH
OH
pseudo-sugars, amino cyclitols, and bicyclic ring systems
15
R = alkyl, allyl, propargyl
16

Figure 107. TDO catalyzed oxidations of benzoates **15** to *cis*-dihydrodiols **16**

3.4.1 Isolation and Stereochemical Proof

As part of our research involving a synthetic route to oseltamivir (Section 3.5), the first substrate tested was ethyl benzoate. To our delight, the corresponding *cis*-dihydrodiol **7** was obtained by Lena Rochon. Spectral analysis confirmed the regiochemistry of the dihydroxylation as being in the C5 and C6 positions. We then wished to determine the absolute stereochemistry of *cis*-dihydrodiol **7**. To this end, we wanted to convert diol **7** to acrylate **592**, a product also accessible from the *cis*-dihydrodiol **6** derived from bromobenzene.[14] Reduction of the distal olefin of **6** with potassium azodicarboxylate (PAD) and subsequent protection of the diol functionality provided vinyl bromide **590** (Scheme 67). Sequential treatment with *tert*-butyllithium, and carbon dioxide at -78°C afforded carboxylic acid **591**. Exposure of this intermediate to EDC in absolute ethanol yielded acrylate **592**. This product was also obtained via a PAD reduction/ acetonide protection sequence on *cis*-dihydrodiol **7**.



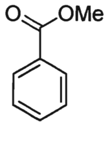
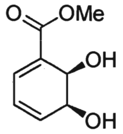
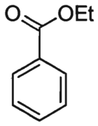
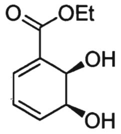
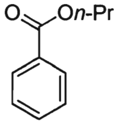
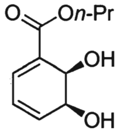
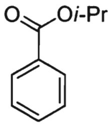
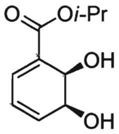
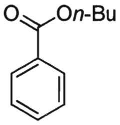
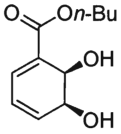
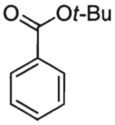
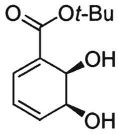
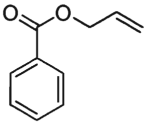
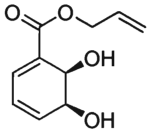
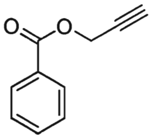
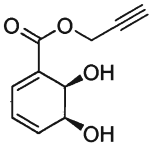
Reagents and conditions: (i) PAD, AcOH, MeOH, -15°C, 88%; (ii) 2,2-DMP, *p*-TsOH, acetone, r.t., 95%; (iii) a) *t*-BuLi, Et_2O, -78°C; b) CO_2, -78°C to r.t.; (iv) Abs. EtOH, EDC, DMAP, DCM, 0°C, 50% over 2 steps; (v) PAD, AcOH, MeOH, -15°C, 84%; (vi) 2,2-DMP, *p*-TsOH, acetone, r.t., 92%

Scheme 67. Absolute stereochemical proof of *cis*-dihydrodiol **7**.

3.4.2 Steric and Functional Limitations

Following the successful completion of the first stereochemical proof in the benzoate series, we elected to explore the steric and functional limitation of this group of substrates. In concert with Dr. Fabrizio Fabris, a visiting professor from the Università Ca' Foscari Venezia, we screened a series of benzoate esters.[284] The steric limitations were probed using alkyl esters of increasing size (methyl to *tert*-butyl), while the functional limitations were tested using two unsaturated esters (Table 23). The only substrates not accepted by the TDO were the *n*-butyl **579** and *t*-butyl **580** esters, indicating the steric limits of the enzyme. Both unsaturated esters, allylic **581** and propargyl **582**, were excellent substrates.

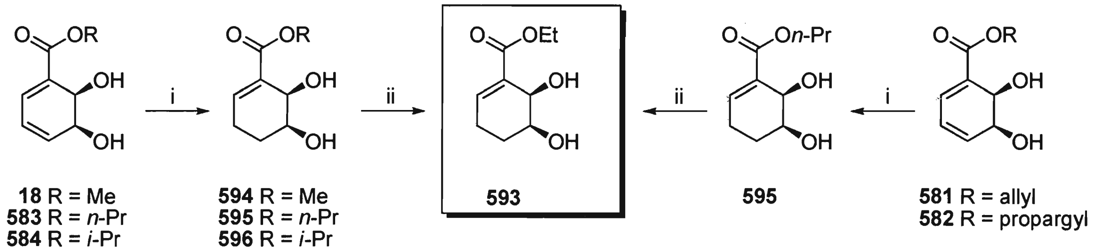
Table 23. Dihydroxylation of benzoate esters by TDO

Substrate	Product	Conversion (%)[b]	Yield (g/L)
 **575**	 **18**	95	1.30
 **576**	 **7**	56	0.80
 **577**	 **583**	78	0.07
 **578**	 **584**	41	0.05
 **579**	 **585**	–	–
 **580**	 **586**	–	–
 **581**	 **587**	89	0.60
 **582**	 **588**	91	1.00

[a] 10.0g of substrate was slowly injected into the fermentor containing 9L of broth;

[b] percent conversion is defined as: (mass substrate fed – substrate recovered)/ mass substrate fed x 100

As with the ethyl ester metabolite, the absolute configuration of the remaining *cis*-dihydrodiols was established through conversion to a fully characterized product (Scheme 68). Diimide reduction of the methyl **18**, *n*-propyl **583** and *i*-propyl **584**, followed by ethanolic transesterification provided acrylate **593**. Treatment of the allylic **581** and propargyl **582** metabolites with excess PAD reagent provided ester **595**, which was subsequently converted to ethyl ester **593**.



18 R = Me
583 R = *n*-Pr
584 R = *i*-Pr

594 R = Me
595 R = *n*-Pr
596 R = *i*-Pr

593

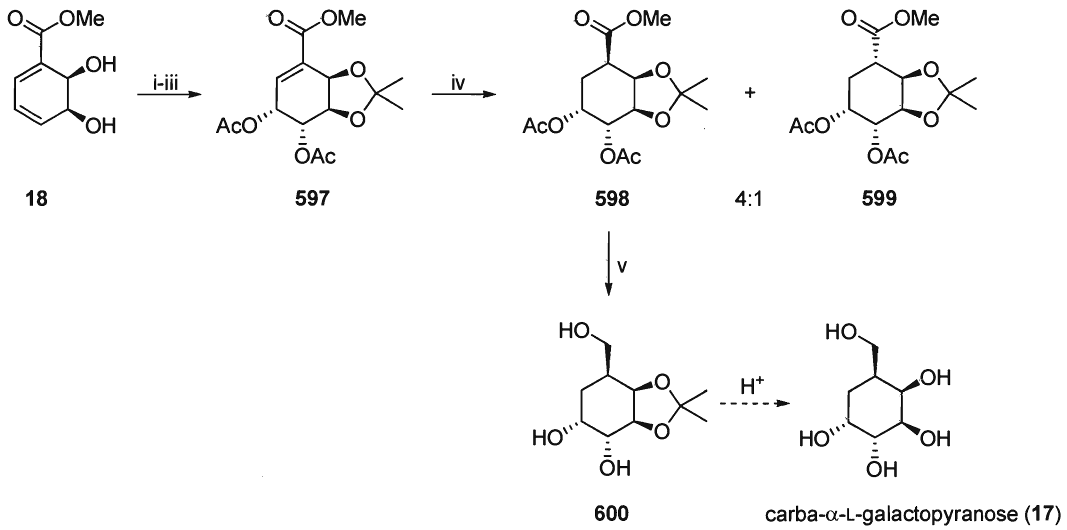
595

581 R = allyl
582 R = propargyl

Reagents and conditions: (i) PAD, AcOH, MeOH, -15°C; (ii) Abs. EtOH, H_2SO_4, r.t.

Scheme 68. Absolute configuration of benzoate ester metabolites

To demonstrate the synthetic value of the ester benzoate *cis*-dihydrodiol metabolites a short route to carba-α-L-galactopyranose **(17)** was developed by Jonathan Collins. Although other pseudo-sugars have been prepared from TDO-metabolites,[181, 285-8] they rely on the conversion of a vinyl halide moiety to a carboxylate intermediate. The *cis*-dihydrodiols derived from benzoate esters circumvent this additional step. Our route began with the treatment of the acetonide derivative of methyl ester **18** with osmium(VIII) tetroxide (Scheme 69). The resulting 1,2-diol was converted to acetylated derivative **597** prior to a rhodium on alumina-catalyzed hydrogenation protocol. This reaction furnished a 4:1 mixture of diastereomers **598** and **599**, which were separated via flash column chromatography. Reaction of the former with excess $LiAlH_4$ yielded the protected derivative **600** of pseudo-sugar carba-α-L-galactopyranose **(17)**.



Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) OsO_4, NMO, acetone/H_2O, r.t.; (iii) Ac_2O, pyr., r.t., 69% over 3 steps; (iv) 5% Rh/Al_2O_3, H_2 (60 psi), EtOH, 70%; (v) LAH, THF, reflux, 86%

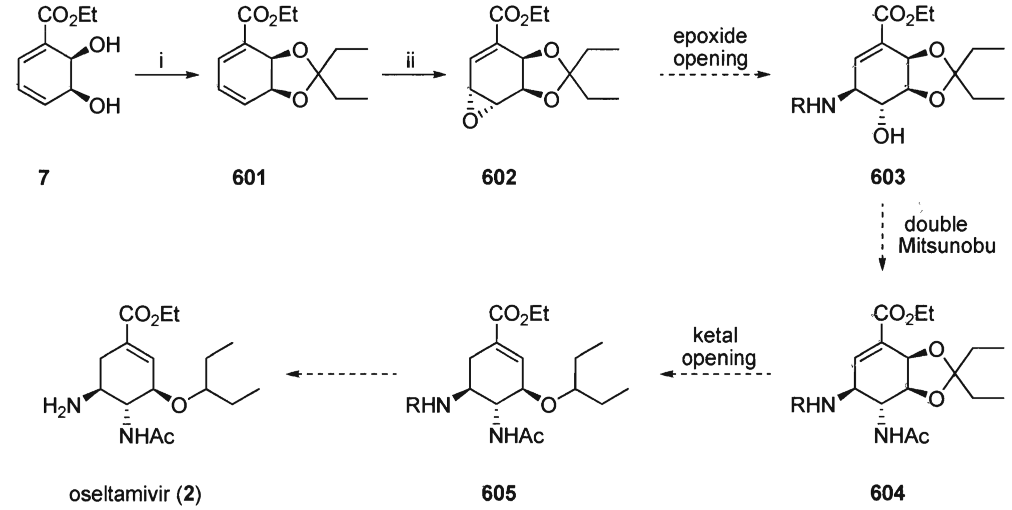
Scheme 69. Synthetic route to carba-α-L-galactopyranose **(17)**

3.5 Chemoenzymatic Synthesis of Oseltamivir

There is a distinct possibility that another world-wide influenza pandemic will occur in the near future. Oseltamivir (administered as its phosphate salt, Tamiflu) offers the best hope to control the spread of the virus. Although industrial-scale preparations of the drug exist; there is still the need for a synthesis which would allow for rapid and large-scale production (see Section 2.4.3 for further details). The following section reviews the Hudlicky group's efforts to develop a route to oseltamivir.

3.5.1 Preliminary Strategies

Our initial interest in the TDO-mediated dihydroxylation of benzoate esters stemmed from our pursuit of a synthetic route to oseltamivir **(2)**. We envisioned a synthesis employing *cis*-dihydrodiol **7**, which already contains the necessary ethyl ester functionality. Our first efforts began with the production of acetonide **601** and its subsequent epoxidation with *m*CPBA (Scheme 70). In principle, opening of epoxide **602** with a nitrogen nucleophile would provide a homo allylic alcohol which could be converted into *N*-acetyl **604** via two Mitsunobu reactions. Opening of the ketal using the reduction procedure described by Gilead Sciences[232] would give access to oseltamivir **(2)**. Although we obtained epoxide **602** in excellent yield and as a single diastereomer, we elected to abandon this approach given the proposed length of the synthesis.


CO2Et
OH
OH
7
i
601
ii
602
epoxide opening
RHN
OH
603
double Mitsunobu
604
NHAc
ketal opening
605
H2N
oseltamivir (2)

Reagents and conditions: (i) 3,3-dimethoxypentane, *p*-TsOH, 3-pentanone, r.t., 97%; (ii) *m*-CPBA, DCM, 0°C, 69%

Scheme 70. Route to oseltamivir **(2)** via vinyl epoxide **602**

Our second idea was to improve upon the route to epoxide **352**, an intermediate in the industrial synthesis employed by F. Hoffman-La Roche.[234] This approach began with the silylation of the distal hydroxyl group of *cis*-dihydrodiol **7** (Figure 108). We screened conditions using various nitrogenous bases, each employing *tert*-butyldimethylsilyl chloride (Table 24). All of our procedures utilizing pyridine or triethylamine provided mixtures of the two mono-protected regioisomers and some di-protected product. Ultimately, we found that imidazole in DMF at -15°C produced the desired silyl ether **606** as the lone product.

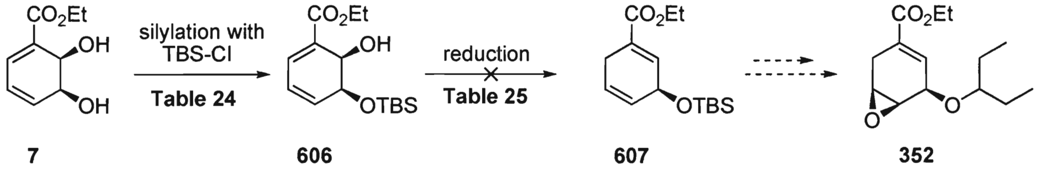


Figure 108. Proposed route to F. Hoffman-La Roche epoxide intermediate **352**

Table 24. Attempted silylation of *cis*-dihydrodiol **7** with TBS-Cl

Entry	*Base*	*Solvent*	*Catalyst*	*Temp.*	*Result*
1	pyridine	–	DMAP	-5 to r.t.	mixture[a]
2	pyridine	–	–	-5 to r.t.	mixture[a]
3	pyridine	DCM	DMAP	-5 to r.t.	mixture[a]
4	pyridine	DCM	-	-5 to r.t.	mixture[a]
5	NEt_3	DCM	DMAP	-5 to r.t.	mixture[a]
6	NEt_3	DCM	-	-5 to r.t.	mixture[a]
7	imidazole	DMF	–	0°C to r.t.	mixture[a]
8	**imidazole**	**DMF**	–	**-15°C**	**606 (52 %)**

[a] mixture of mono-protected and di-protected products

To intercept the F. Hoffman-La Roche synthesis, we needed to translocate the acrylate olefin and displace the free hydroxyl of ester **606** (Figure 108). We explored the possibility of using *o*-nitrobenzenesulfonylhydrazide (NBSH); a reagent know to effect 1,3-reductive transpositions of allylic alcohols.[289] Standard conditions (Table

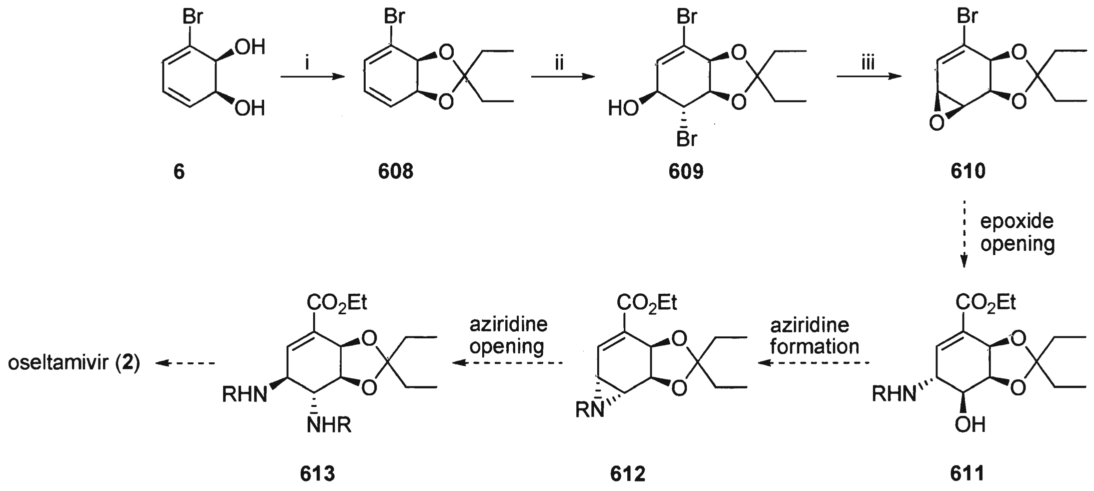
25, Entry 1) did not provide any new products, while all other methods decomposed the starting material.

Table 25. Attempted 1,3-reductive transposition of allylic alcohol **606**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	PPh_3, NMM, DIAD, NBSH	THF	r.t.	SM
2	PPh_3, NMM, DIAD, NBSH	THF	35°C	decomposition[a]
3	PPh_3, NMM, DIAD, NBSH	toluene	35°C	decomposition[a]
4	PPh_3, NMM, DIAD, NBSH	toluene	r.t.	decomposition[a]

[a] complex mixture of elimination products

Our third strategy sought to utilize the selective opening of vinyl epoxide **610** with a suitable nitrogen nucleophile (Scheme 71). For this study, *cis*-dihydrodiol **6** was exposed to 3,3-dimethoxypentane and 3-pentanone under acidic conditions. The resulting acetonide **608** was reacted with dibromodimethylhydantoin (DBDMH) in aqueous acetone. Bromocyclohexanol derivative **609** was treated with 10% NaOH in DME to effect the formation of epoxide **610**. Although this approach was not pursued further, we speculate that opening of epoxide **610**, followed an intramolecular Mitsunobu reaction, would provide an aziridine derivative **612**. Opening with a nitrogen nucleophile would install the necessary *trans*-amino moiety seen in oseltamivir **(2)**.


Br
OH
OH
6
i
608
ii
HO
Br
609
iii
610
epoxide opening
CO2Et
RHN
OH
611
aziridine formation
RN
612
aziridine opening
NHR
613
oseltamivir (2)

Reagents and conditions: (i) 3,3-dimethoxypentane, *p*-TsOH, 3-pentanone, r.t., 91%; (ii) DBDMH, acetone, H_2O, r.t., 56%; (iii) 10% NaOH, DME, r.t., 44%

Scheme 71. Route to oseltamivir **(2)** via vinyl epoxide **610**

3.5.2 Symmetry-based Design

The aforementioned preliminary approaches helped refine our strategy to construct to oseltamivir **(2)**. When the target molecule is depicted in either configuration A or B, a latent symmetry axis[290] can be drawn through the C1 and C4 positions (Figure 109). If the substituents at C3, C4 and C5 are not defined, then the two structures represent an 'enantiomeric switch' dependent on the position of the double bond. We theorized that oseltamivir **(2)** could be accessed through two vinyl aziridine approaches. Approach A would rely on an opening of *syn*-aziridine **614** with an oxygen nucleophile in order to install the ether functionality. Reduction of the C6-oxygen bond and inversion of the C5 position with a nitrogen nucleophile would install the correct substituents. In this strategy, the olefin would remain in its original position. Conversely, approach B relies on the opening of *anti*-aziridine **615** with a nitrogen nucleophile. This strategy relies on the translocation of the acrylate double bond, ideally with concomitant elimination of the C6 oxygen. The synthesis would conclude with the alkylation of the C5 oxygen.

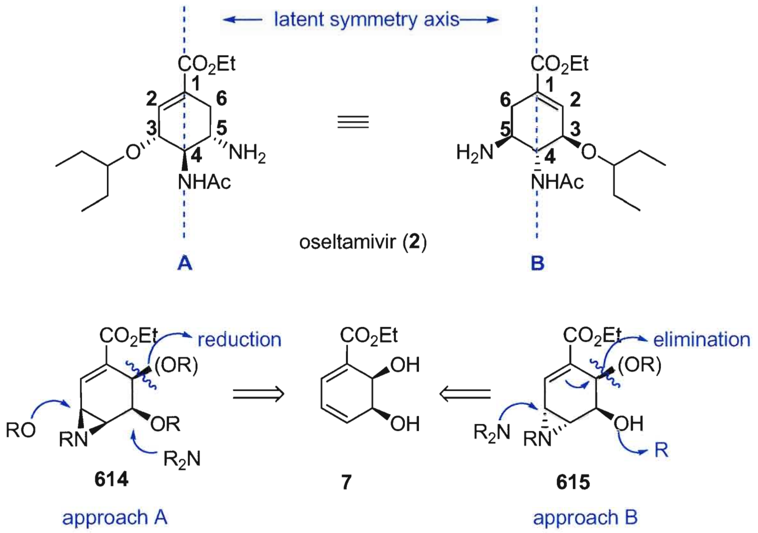

latent symmetry axis
CO2Et
1
2
6
3
5
4
NH2
O
NHAc
H2N
A
B
oseltamivir (2)
reduction
(OR)
RO
RN
OR
R2N
614
approach A
CO2Et
OH
OH
7
elimination
OH
R
615
approach B

Figure 109. Symmetry-based approach to oseltamivir **(2)**

With envisioned this approach commencing with the production of *N*-acetyl aziridine **13** from a *cis*-dihydrodiol derivative **618** (Figure 110). Opening with 3-pentanol and a palladium-catalyzed carbonylation would provide advanced intermediate **617**. Reduction of the allylic carbon-oxygen bond and inversion of the homo allylic position with an azide anion would give access to oseltamivir **(2)**. This strategy was extensively studied by Dr. Michael Moser.

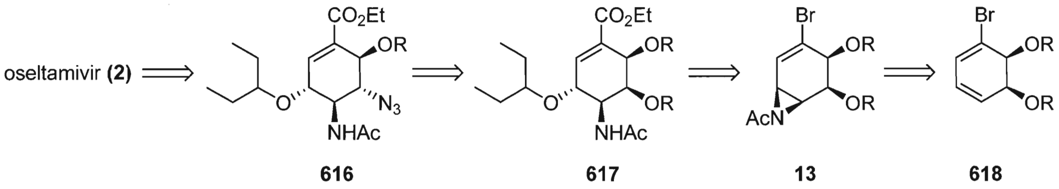
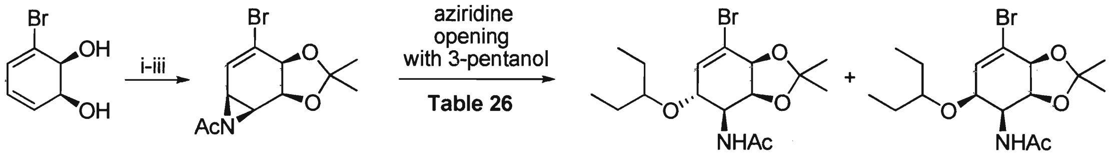

oseltamivir (2)
CO2Et
OR
O
N3
NHAc
616
CO2Et
OR
O
OR
NHAc
617
Br
OR
AcN
OR
13
Br
OR
OR
618

Figure 110. Approach to oseltamivir **(2)** via vinyl aziridine **13**

Using the procedure described in our second generation approach to balanol (Section 3.3), the acetonide derivative of *cis*-dihydrodiol **6** was reacted with *N*-bromoacetamide and then potassium bis(trimethylsilyl)amide to provide *N*-acetyl aziridine **429** (Scheme 72). We screened a series of catalysts to ascertain the most effective method of opening aziridine **429** with 3-pentanol. We found that $BF_3{\cdot}OEt_2$ and $Cu(acac)_2$ provided 5:2 and 3:1 mixtures of diastereomers **619** and **620** respectively (Table 26). More favourable ratios were obtained when $Cu(OTf)_2$ was used as the catalyst; particularly when the reaction was run at -20°C. Although tedious, we were able to separate the diastereomers via flash column chromatography.



6 **429** **619** **620**

Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, acetone, r.t.; (ii) *N*-bromoacetamide, $SnBr_4$, MeCN, -30°C; (iii) KHMDS, *n*-BuNBr, DME, 0°C, 72% over 3 steps

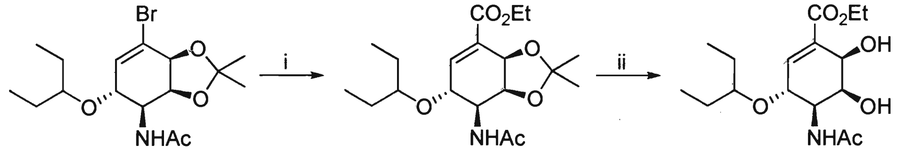
Scheme 72. Opening of a *N*-acetyl aziridine **429** with 3-pentanol

Table 26. Opening of a *N*-acetyl aziridine **429** with 3-pentanol

Entry	*Catalyst*	*Solvent*	*Temp.*	*Yield (%)*	*Ratio **619**:**620***[b]
1	$BF_3{\cdot}OEt_2$	DCM	r.t.	73	5:2
2	$Cu(acac)_2$	DCM	r.t.	75	3:1
3	$Cu(acac)_2$	-[a]	r.t.	71	3:1
4	$Cu(acac)_2$	-[a]	0°C to r.t.	79	3:1
5	$Cu(OTf)_2$	-[a]	0°C	87	4:1
6	**$Cu(OTf)_2$**	-[a]	**-20°C**	**84**	**6:1**

[a] reaction performed in 3-pentanol; [b] estimated ratio determined from ^{1}H NMR

Vinyl bromide **619** was converted into ethyl ester **621** through use of a carbonylation procedure employing two palladium catalysts, $Pd(PPh_3)_4$ and $Pd[(Cl)_2(PPh_3)_2]$ (Scheme 73). Acetonide hydrolysis with hydrochloric acid afforded 1,2-diol **622**.

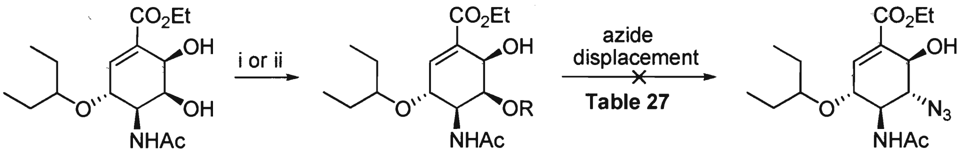


619 **621** **622**

Reagents and conditions: (i) $Pd(PPh_3)_4$, $Pd[(Cl)_2(PPh_3)_2]$, CO, NEt_3, EtOH, toluene, reflux, 68%; (ii) 6N HCl, EtOH, 71%

Scheme 73. Palladium-catalyzed carbonylation of vinyl bromide **619**

Our next goal was to invert the homoallylic hydroxyl with an azide anion. To this end, we prepared OMs derivative **624** and OTs derivative **625** by reacting **623** with one equivalent the appropriate sulfonyl chloride (Scheme 74). Using sodium azide and various solvents, we performed a temperature gradient (0 - 80°C) for each experiment (Table 27, Entries 1 to 4). In each instance, we did not observe the formation of any new compounds (TLC analysis) until the temperature exceeded 60°C, at which point 10 or more new compounds were produced. Although some evidence of azide **626** was found during ^{1}H NMR analysis of the crude mixture, no clean compound could be isolated. When we employed either trimethylsilyl azide (TMS-N_3) or diphenylphosphoryl azide (DPPA) we did not obtain any new compounds at ambient temperature, while an increase to 50°C decomposed the starting material.



622 **624** R = OMs **625** R = OTs **626**

Reagents and conditions: (i) MsCl, NEt_3, DCM, 86%; (ii) TsCl, NEt_3, DCM, 76%

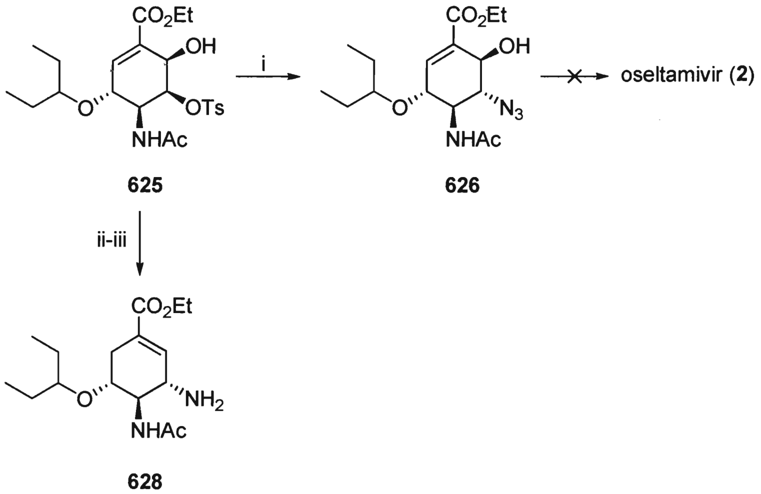
Scheme 74. Attempted inversion of sulfonyl derivatives **624** and **625** with azide

Table 27. Attempted inversion of sulfonyl derivatives **624** and **625** with azide

Entry	*Azide*	*Solvent*	*Temp.*	*Result*
1	NaN_3	DMSO	0 - 80°C	decomposition[a]
2	NaN_3	DMF	0 - 80°C	decomposition[a]
3	NaN_3	*i*-propanol	0 - 80°C	decomposition[a]
4	NaN_3	acetone	0 – 80°C	decomposition[a]
5	TMS-N_3	THF	r.t.	SM
6	TMS-N_3	THF	50°C	decomposition[a]
7	DPPA	THF	r.t.	SM
8	DPPA	THF	50°C	decomposition[a]

[a] complex mixture of sulfonyl group containing products

As stated earlier, some evidence existed that azide **626** was formed during the reaction. We reacted OTs derivative **625** with sodium azide at 80°C in DMF, and then submitted the crude mixture to a borohydride reduction protocol (Scheme 75). This method provided the undesired oseltamivir isomer **628**, with the olefin in the incorrect position resulting from a 1,3 reduction of the carbon-oxygen bond. Ultimately, we were able to synthesize azide **626** through use of tetra-*n*-butylammonium azide procedure, but we were unable to make oseltamivir via this approach.



Reagents and conditions: (i) *n*-$BuNN_3$, DME, reflux; (ii) NaN_3, DMF, 80°C; (iii) $NaBH_4$, EtOH, r.t.

Scheme 75. Synthesis of oseltamivir isomer **628**

Failing to construct oseltamivir **(2)** from vinyl aziridine **429**, we turned our attention to a cycloaddition strategy. We theorized that oxazine **631** could be prepared from *cis*-dihydrodiol **7** (Figure 111). A S_N2' reaction with a nitrogen nucleophile and reduction of the nitrogen-oxygen bond would provide advanced intermediate **630**. Subsequent translocation of the double bond, and alkylation of the free hydroxyl **629** would give access to oseltamivir **(2)**.

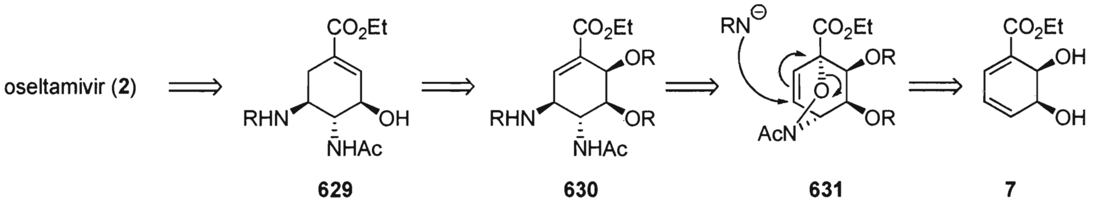
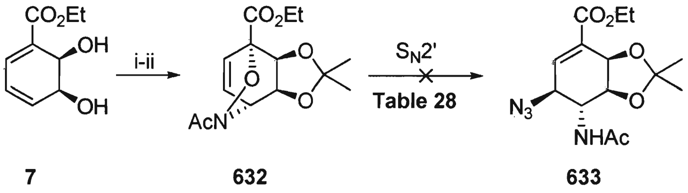


Figure 111. Cycloaddition approach to oseltamivir **(2)**

Ignacio Carrera discovered that the acetonide derivative of 1,2-diol **7** underwent an inverse electron-demand hetero-Diels-Alder reaction with a nitroso species; created *in situ* through a reaction between *N*-hydroxyacetamide and sodium periodate (Scheme 76). We then screened a series of conditions in an attempt to effect an S_N2' reaction on oxazine **632**. Our first attempts utilized NaN_3 and TMS-N_3 (Table 28, Entries 1 to 4). We were unable to obtain any new compounds, even under palladium catalyzed conditions. We were also unsuccessful when using similar conditions and protected-nitrogen nucleophiles, namely Boc-NH_2 and Bn-NH_2. Our final attempts employing a rhodium catalyst ([Rh(COD)$_2$]OTf) and did not produce any new compounds.



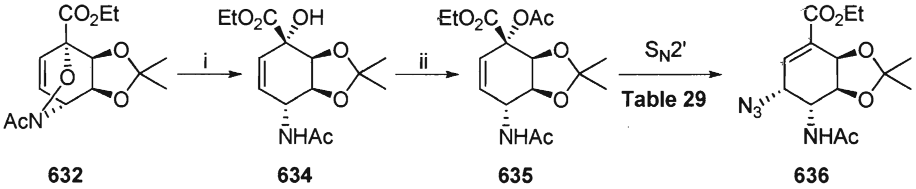
Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) MeCONHOH, $NaIO_4$, MeOH, r.t., 70% over 2 steps

Scheme 76. Attempted S_N2' reactions on oxazine **632**

Table 28. Attempted S_N2' reactions on oxazine **632**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	NaN_3	acetone	r.t. – reflux	SM
2	NaN_3, $Pd(PPh_3)_4$	acetone	r.t. – reflux	SM
3	$TMSN_3$	THF	r.t. – reflux	SM
4	$TMSN_3$, $Pd(PPh_3)_4$	THF	r.t. – reflux	SM
5	$BocNH_2$	THF	r.t. – reflux	SM
6	$BocNH_2$, $Pd(PPh_3)_4$	THF	r.t. – reflux	SM
7	$BnNH_2$	THF	r.t. – reflux	SM
8	$BnNH_2$, $Pd(PPh_3)_4$	THF	r.t. – reflux	SM
9	$BnNH_2$, $[Rh(COD)_2]OTf$	THF	r.t. – reflux	SM
10	$BnNH_2$, $[Rh(COD)_2]OTf$, dppf	THF	r.t. – reflux	SM
11	$TMSN_3$, $[Rh(COD)_2]OTf$, dppf	THF	r.t. – reflux	SM

At this stage, we abandoned using oxazine **632** for S_N2' reactions in favour of another substrate. Reduction of nitrogen-oxygen linkage with molybdenum hexacarbonyl provided allylic alcohol **634** (Scheme 77). Subsequent exposure to acetic anhydride afforded *O*-acetyl derivative **635**. We ran experiments using the same conditions employed with our first substrate. The reactions utilizing NaN_3 returned starting material, as did the reaction with TMS-N_3. However, when tetrakis(triphenylphosphine)palladium(0) was added we were able to isolate the *syn*-azide isomer **636**. We tried varying the amount of catalyst added, 0.1 to 10 equivalents, but were never able to isolate the desired *trans* isomer. All other conditions resulted in the decomposition of the starting material.


CO2Et
EtO2C OH
EtO2C OAc
CO2Et
i
ii
SN2'
Table 29
AcN
NHAc
N3
632
634
635
636

Reagents and conditions: (i) $Mo(CO)_6$, $MeCN/H_2O$ (15:1), reflux, 75%; (ii) Ac_2O, NEt_3, DMAP, 94%

Scheme 77. Attempted S_N2' reactions on allylic acetate **635**

Table 29. Attempted S_N2' reactions on allylic acetate **635**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	NaN_3	acetone	r.t. – reflux	SM
2	NaN_3, $Pd(PPh_3)_4$	acetone	r.t. – reflux	SM
3	$TMSN_3$	THF	r.t. – reflux	SM
4	**$TMSN_3$, $Pd(PPh_3)_4$**	**THF**	**r.t. – reflux**	**636 (77%)**
5	$BocNH_2$	THF	r.t. – reflux	decomposition[a]
6	$BocNH_2$, $Pd(PPh_3)_4$	THF	r.t. – reflux	decomposition[a]
7	$BnNH_2$	THF	r.t. – reflux	decomposition[a]
8	$BnNH_2$, $Pd(PPh_3)_4$	THF	r.t. – reflux	decomposition[a]
9	$BnNH_2$, $[Rh(COD)_2]OTf$	THF	r.t. – reflux	decomposition[a]
10	$BnNH_2$, $[Rh(COD)_2]OTf$, dppf	THF	r.t. – reflux	decomposition[a]
11	$TMSN_3$, $[Rh(COD)_2]OTf$, dppf	THF	r.t. – reflux	decomposition[a]

[a] complex mixture of compounds, mostly elimination products

We sought to take advantage of the undesired reactivity of **635** by employing a TMS-halide instead. The resulting *syn*-halide product **637** could be inverted with an azide anion (Figure 112).

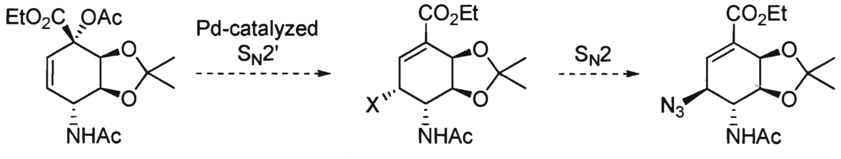

EtO2C OAc
Pd-catalyzed
SN2'
CO2Et
SN2
CO2Et
NHAc
X
NHAc
N3
NHAc
635
637
633

Figure 112. Inversion of allylic halide **637**

We reacted *O*-acetyl **635** with either TMS-Cl and TMS-I under the same conditions that yielded azide **636** (Table 30, Entries 1 and 2). The former yielded 1,3-diene derivative **638**, while the latter afforded phenol **639**. We tried the same experiments in toluene without success.

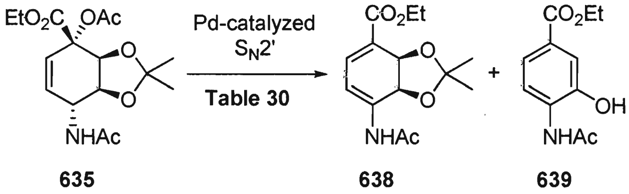


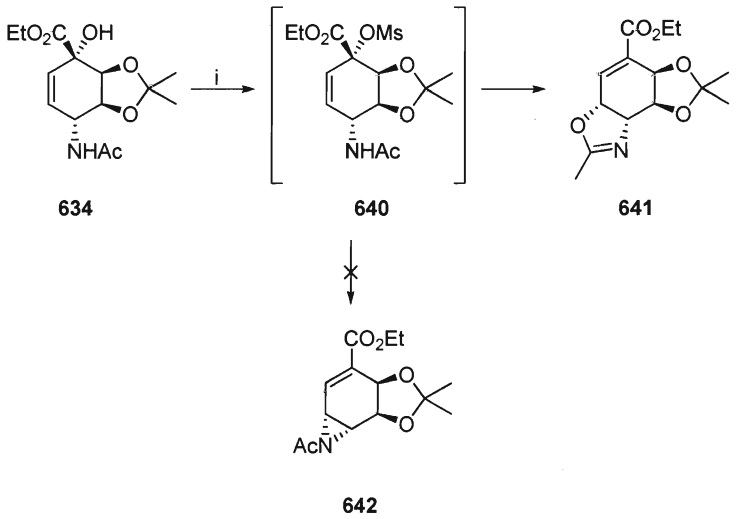
Figure 113. Attempted palladium-catalyzed S_N2' reactions on allylic acetate **635**

Table 30. Attempted palladium-catalyzed S_N2' reactions on allylic acetate **635**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	TMS-Cl, $Pd(PPh_3)_4$	THF	r.t. – reflux	**638** (83%)
2	TMS-I, $Pd(PPh_3)_4$	THF	r.t. – reflux	**639** (81%)
3	TMS-Cl, $Pd(PPh_3)_4$	DME	r.t. – reflux	**639** (54%)
4	TMS-Cl, $Pd(PPh_3)_4$	toluene	r.t. – reflux	decomposition[a]
5	TMS-I, $Pd(PPh_3)_4$	toluene	r.t. – reflux	decomposition[a]

[a] complex mixture of compounds

At this stage, we questioned whether our failures were a result of the *O*-acetyl functionality. We wondered if a better leaving group would yield the desired product. When allylic alcohol **634** was reacted with methanesulfonyl chloride, we did not obtain the OMs derivative **640**. Instead, we obtain an unknown product with an acrylate functionality. Initially we believed the compound to be *N*-acetyl aziridine **642**, which we hoped to obtain in order to test our latent symmetry approach (Scheme 78). However, careful spectral analysis identified the compound as oxazoline derivative **641**, a structural isomer.



Reagents and conditions: (i) Ms-Cl, NEt_3, DMAP, DCM, 54%

Scheme 78. Synthesis of oxazoline **641**

We hoped that the reactivity of oxazoline **641** would be similar to that of vinyl aziridine **642**. Theoretically, opening of either with an appropriate nucleophile would yield the same product.

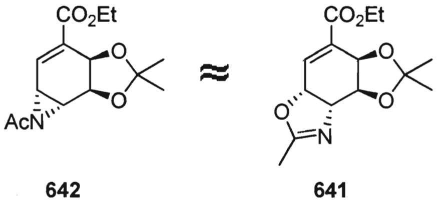


Figure 114. Structural isomers; vinyl aziridine **642** and vinyl oxirane **641**

We sought to open oxazoline **641** with an azide source in order to obtain the necessary *trans*-azide product **633** (Figure 115). We tested four sets of conditions with three separate azide sources. The first three series of trials all produced allylic alcohol **643**, presumably through a reaction between oxazoline **641** and minuscule amounts of opportunistic water in the reaction (Table 31, Entries 1 to 9). When we tested the three azide reagents in *tert*-butanol, we obtained small amounts of the desired azide **633**. However, the majority of the reaction mixture contained the allylic alcohol **643**, and complete separation proved difficult.

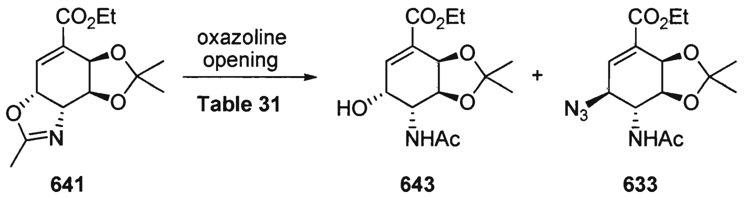


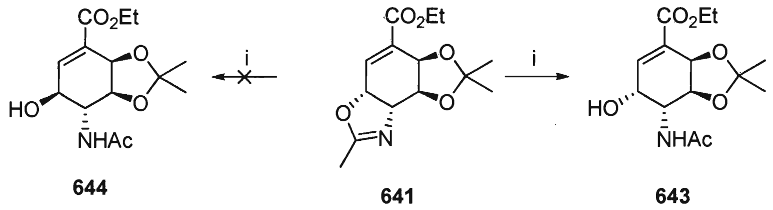
Figure 115. Opening of oxazoline **641**

Table 31. Opening of oxazoline **641**

Entry	*Azide*	*Catalyst*	*Solvent*	*Temp.*	*Result*
1	NaN_3	-	acetone	r.t.	**643** (67%)
2	DPPA	-	acetone	r.t.	**643** (71%)
3	$TMSN_3$	-	acetone	r.t	**643** (75%)
4	NaN_3	$Cu(OTf)_2$	THF	r.t.	**643** (41%)
5	DPPA	$Cu(OTf)_2$	THF	r.t	**643** (29%)
6	$TMSN_3$	$Cu(OTf)_2$	THF	r.t.	**643** (36%)
7	NaN_3	$BF_3{\cdot}OEt_2$	THF	r.t.	**643** (33%)
8	DPPA	$BF_3{\cdot}OEt_2$	THF	r.t.	**643** (56%)
9	$TMSN_3$	$BF_3{\cdot}OEt_2$	THF	r.t.	**643** (44%)
10	NaN_3	-	*t*-butanol	60°C	**643** (40%), **633** (5%)[a]
11	DPPA	-	*t*-butanol	60°C	**643** (70%), **633** (15%)[a]
12	$TMSN_3$	-	*t*-butanol	60°C	**643** (70%), **633** (5%)[a]

[a] approximate yield, estimated from crude ^{1}H NMR

We were unsure of the relative stereochemistry of oxazoline **641**, assuming it was *cis*, but not ruling out the possibility of *trans*. To this end, we hydrolyzed oxazoline **641** with calcium carbonate in ethanol/ water (Scheme 79). This reaction was originally performed using Lindlar's catalyst. Melissa Drouin discovered that the $CaCO_3$ in the catalyst was responsible for the transformation. Spectral analysis suggested we obtained the *cis* isomer **643**. However, we could not exclude the possibility that we had the *trans* isomer **644**.



Reagents and conditions: (i) $CaCO_3$, EtOH/ H_2O, reflux, 72%

Scheme 79. Hydrolysis of oxazoline **641**

We speculated that reduction of the acrylate olefin would allow for a more definitive structural analysis (Figure 116). Palladium on carbon cleanly provided 1,3-diol **646**, resulting from hydrogenolysis of the acetonide moiety. We performed several experiments with Stryker's reagent ($[(PPh_3)CuH]_6$), but did not acquire any new products. Adams' catalyst afforded two hydrogenolysis products, namely **646** and **647**, with the ratio dependant on the solvent used. We found success with a rhodium on alumina protocol, particularly when the experiment was performed at 65 psi. Fortunately, these reaction conditions provided ester **645** as the lone diastereomer.

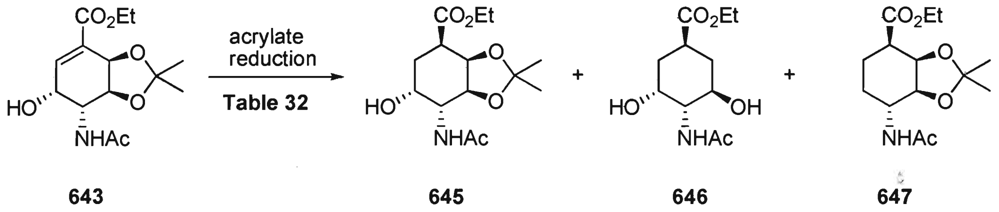


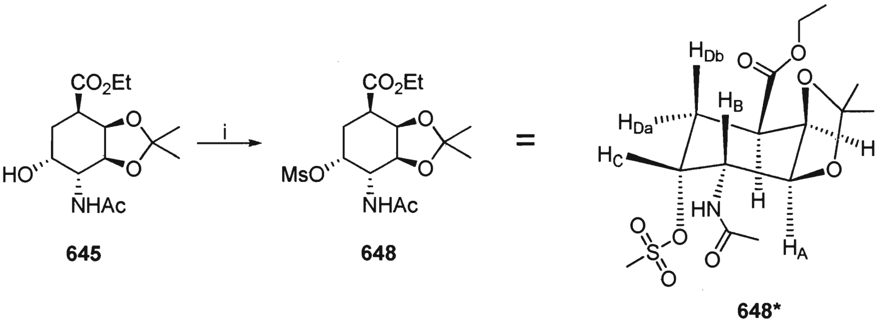
Figure 116. Reduction of acrylate **643**

Table 32. Reduction of acrylate **643**

Entry	*Catalyst*	*Solvent*	*Pressure*	*Temp.*	*Result*
1	5% Pd/C	95% EtOH	1 atm	r.t.	**646** (83%)
2	$[(PPh_3)CuH]_6$	THF	-	reflux	SM
3	$[(PPh_3)CuH]_6$	MeCN	-	reflux	SM
4	$[(PPh_3)CuH]_6$	toluene	-	reflux	SM
5	PtO_2	95% EtOH	1 atm	r.t.	**646** (30%), **647** (40%)[a]
6	PtO_2	EtOAc	1 atm	r.t.	**646** (35%), **647** (40%)[a]
7	5% Rh/Al_2O_3	95% EtOH	1 atm	r.t.	**645** (56%)
8	**5% Rh/Al_2O_3**	**95% EtOH**	**65 psi**	**r.t.**	**645 (90%)**

[a] approximate yield, estimated from crude ^1H NMR

We confirmed the absolute configuration of hydroxyl **645** through conversion to its *O*-mesyl derivative **648** (Scheme 80). Using the ^{1}H NMR coupling constants we were able to assign the correct stereochemistry. We measured the *J* coupling between H_A and H_B as 9 Hz, indicative of axial-axial coupling. Furthermore, we did not observe a large axial-axial coupling between H_C and either H_B, H_{Da} or H_{Db}. This confirmed that the *O*-mesyl group occupies the axial position; thus placing it *cis* in relation to *N*-acetyl group.



J_{AB} - 9 Hz (axial-axial)
J_{BC} - 3 Hz (axial-equitorial)
J_{CDa} - 4 Hz (equitorial-equitorial)
J_{CDb} - 5 Hz (equitorial-axial)

Reagents and conditions: (i) Ms_2O, NEt_3, DCM, 73%

Scheme 80. Spectral analysis of OMs derivative **648**

Continuing with the synthesis, we hoped to invert the allylic hydroxyl of **643** with a nitrogen nucleophile. The simplest method would be an S_N2 reaction on a sulfonylated derivative (Figure 117). Unexpectedly, reactions using pyridine exclusively provided allylic chloride **651**. Hünig's base (*N*,*N*-diisopropylethylamine, DIPEA) provided a mixture of sulfonylated products, **649** or **650**, and the allylic chloride product **651**. Ultimately, we found that triethylamine produced **649** and **650** without the chlorination product.

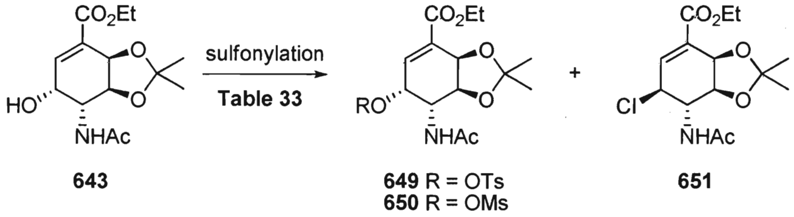


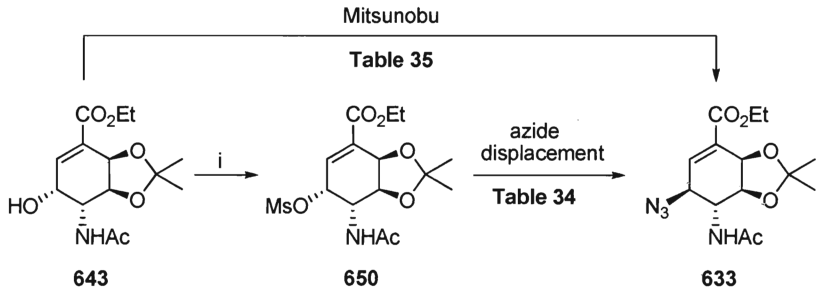
Figure 117. Sulfonylation of allylic alcohol **643**

Table 33. Sulfonylation of allylic alcohol **643**

Entry	*Reagent*	*Solvent*	*Base*	*Temp.*	*Result*
1	TsCl	DCM	pyridine	0°C - r.t.	**651** (85%)
2	MsCl	DCM	pyridine	0°C - r.t.	**651** (88%)
3	TsCl	DCM	DIPEA	0°C - r.t.	**649** (5%), **651** (25%)[a]
4	MsCl	DCM	DIPEA	0°C - r.t.	**650** (5%), **651** (20%)[a]
5	**TsCl**	**DCM**	**NEt_3**	**0°C - r.t.**	**649 (66%)**
6	**MsCl**	**DCM**	**NEt_3**	**0°C - r.t.**	**650 (90%)**

[a] approximate yield, estimated from crude ^1H NMR

We envisioned two routes which could provide us with azide **633**; 1. displacement of a sulfonyl derivative with an azide anion, and 2. Mitsunobu-type reaction performed on allylic alcohol **643** with an azide reagent. For the first method we elected to use the OMs product **650**, simply because it was available in a higher yield compared to the OTs product **649**. We employed sodium azide in acetone, DMSO and DMF. At ambient temperatures no reaction took place, while elevated temperatures decomposed the starting material (Table 34). All of our attempts using TMS-N_3 were unsuccessful, even at higher temperatures. We did observe the formation of azide **633** when DPPA was used; however, only in trace amounts. When a solution of sodium azide in acetone/ H_2O was utilized, we obtained the desired product in a nearly quantitative yield. We explored the possibility of a Mitsunobu-type reaction, which would reduce our synthesis by one step. Unfortunately, all attempts using either triphenylphosphine or *n*-tributylphosphine were unsuccessful (Table 35).



Reagents and conditions: (i) MsCl, NEt_3, DCM, 0°C - r.t., 90%

Scheme 81. Two routes to allylic azide **633**

Table 34. Displacement of allylic mesylate **650**

Entry	*Azide*	*Solvent*	*Temp.*	*Result*
1	NaN_3	acetone	r.t.	SM
2	NaN_3	acetone	50°C	decomposition[a]
3	NaN_3	DMSO	r.t.	SM
4	NaN_3	DMSO	50°C	decomposition[a]
5	NaN_3	DMF	r.t.	SM
6	NaN_3	DMF	50°C	decomposition[a]
7	TMS-N_3	THF	reflux	SM
8	TMS-N_3	MeCN	reflux	SM
9	TMS-N_3	DCM	reflux	SM
10	TMS-N_3	*t*-BuOH	80°C	SM
11	DPPA	*t*-BuOH	80°C	**633** (10%)[b]
12	**NaN_3**	**acetone/H_2O**	**r.t.**	**633 (91%)**

[a] complex mixture of sulfonylated products; [b] approximate yield, estimated from crude ^{1}H NMR

Table 35. Attempted Mitsunobu reactions on allylic alcohol **643**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	TMS-N_3, DIAD, PPh_3	THF	0°C - r.t.	SM
2	DPPA, DIAD, PPh_3	THF	0°C - r.t.	SM
3	TMS-N_3, DIAD, *n*-Bu_3P	THF	0°C - r.t.	SM
4	DPPA, DIAD, *n*-Bu_3P	THF	0°C - r.t.	SM

With the allylic azide **633** in hand, we sought to reduce and protect the functionality as its *tert*-butyl carbamate prior to the necessary acrylate reduction (Figure 118). We first explored a hydrogenation and then carbamate protection approach. Our attempts with Lindlar's catalyst, PtO_2 and Pd/C did not cleanly provide amine **652**. Regardless, the crude reaction mixture was treated with Boc_2O and NEt_3. We were unable to identify any products from these reactions. We also exposed azide **633** to triphenylphosphine, with the hope that we could derivatize the Staudinger intermediate. This approach also proved futile, no evidence for the formation of either the iminophosphorane species or the carbamate species was found.

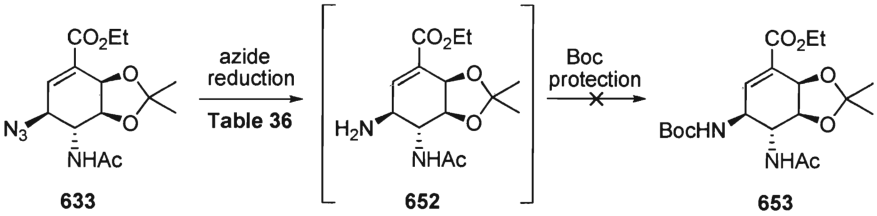


Figure 118. Reduction of allylic azide **633**

Table 36. Allylic azide reduction

Entry	*Catalyst*	*Reagents*	*Solvent*	*Pressure*	*Results*
1	Lindlar's catalyst	Boc_2O, NEt_3	EtOH	1 atm	decomposition[a]
2	PtO_2	Boc_2O, NEt_3	EtOH	1atm	decomposition[a]
3	5% Pd/C	Boc_2O, NEt_3	EtOH	1 atm	decomposition[a]
4	-	PPh_3, Boc_2O, NEt_3	THF	-	decomposition[a]
5	-	PPh_3, Boc_2O, NEt_3	THF	-	decomposition[a]

[a] complex mixture of products

As a result of our failed attempts to reduce and protect allylic azide **633**, we decided to purse its saturated derivative. Previous studies had provided us with cyclohexanol **645**, which we sought to convert to an azide derivative. Screening the same sulfonylation protocols used for allylic alcohol **643** were problematic, as we obtained a mixture of the sulfonyl product and the corresponding chloride (Table 37, Entries 1). Employing pyridine as the base provided tosylate **654** as the lone product.

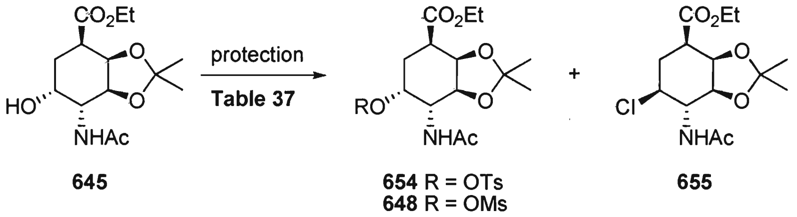

CO2Et
protection
Table 37
HO
RO
Cl
NHAc
+
645
654 R = OTs
648 R = OMs
655

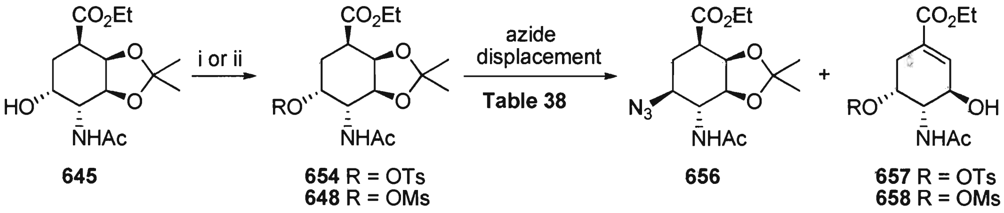
Figure 119. Sulfonylation of cyclohexanol derivative **645**

Table 37. Sulfonylation of cyclohexanol derivative **645**

Entry	*Reagent*	*Solvent*	*Base*	*Temp.*	*Result*
1	TsCl	DCM	NEt_3	0°C - r.t.	**654** (45%), **655** (15%)[a]
2	TsCl	DCM	pyridine	0°C - r.t.	**654** (55%)
3	Ms_2O	DCM	NEt_3	0°C - r.t.	**648** (73%)

[a] approximate yield, estimated from crude ^1H NMR

We attempted a series of azide displacement reactions on the OTs **654** and OMs **648** derivatives (Scheme 82). Surprisingly, sodium azide in DMSO did not provide the corresponding azide. Instead we obtain allylic alcohols **657** and **658**, a result of the base-induced collapse of the acetonide moiety. The procedures using acetone and H_2O, which had worked for allylic substrate **650**, afforded the desired azide **656** in both instances (Table 38, Entries 2 and 4).


CO2Et
i or ii
azide
displacement
Table 38
HO
RO
N3
OH
NHAc
+
645
654 R = OTs
648 R = OMs
656
657 R = OTs
658 R = OMs

Reagents and conditions: (i) TsCl, NEt_3, DCM, 0°C - r.t., 55%; (ii) Ms_2O, NEt_3, DCM, 0°C - r.t., 73%

Scheme 82. Azide displacement of mesylate **648** and tosylate **654**

Table 38. Azide displacement of mesylate **648** and tosylate **654**

Entry	*R =*	*Azide*	*Solvent*	*Temp.*	*Result*
1	Ts	NaN_3	DMSO	60°C	**657** (37%)
2	**Ts**	**NaN_3**	**acetone/H_2O**	**r.t.**	**656 (71%)**
3	Ms	NaN_3	DMSO	60°C	**658** (24%)
4	**Ms**	**NaN_3**	**acetone/H_2O**	**r.t.**	**656 (86%)**

All that remained was to collapse acetonide **656** in order to construct allylic alcohol **416**, an intermediate in Fang's synthesis[248] of oseltamivir **(2)** (Figure 120). Our first attempts employed 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in either acetone, DCM or without the addition of a solvent (Table 39, Entries 1 to 3). A significantly high isolated yield was observed when DCM was used as the solvent. Similar results were achieved using a sodium ethoxide/ ethanol procedure. We found that our sample of allylic alcohol **416** was in complete agreement with the physical data reported by the Fang group, thus completing our formal synthesis of oseltamivir **(2)**.[291]

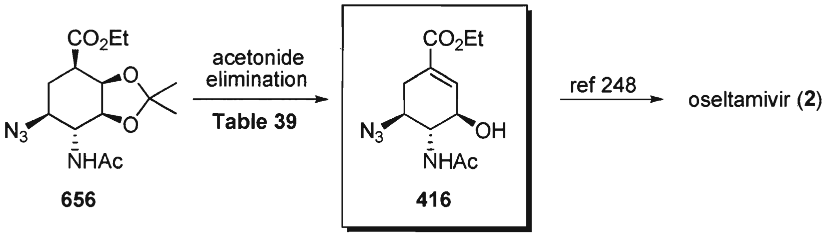


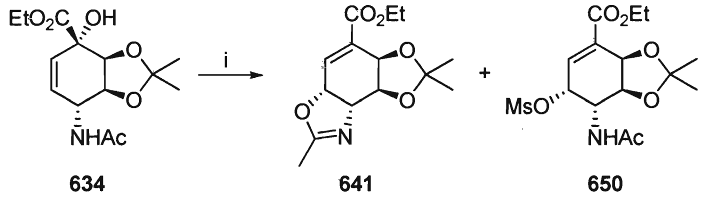
Figure 120. Elimination of acetonide **656**

Table 39. Elimination of acetonide **656**

Entry	*Base*	*Solvent*	*Temp.*	*Yield*
1	DBU	acetone	0°C - r.t.	34%
2	DBU	-[a]	0°C - r.t.	51%
3	DBU	DCM	0°C - r.t.	88%
4	**EtONa**	**EtOH**	**0°C - r.t.**	**91%**

[a] reaction performed with DBU as the solvent

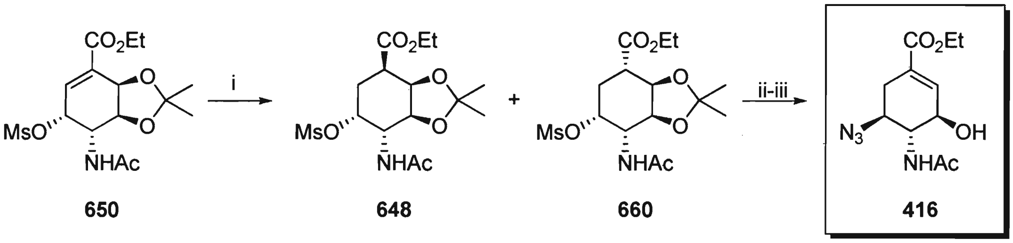
After publishing our initial formal synthesis of oseltamivir **(2)**, we discovered an alternative route which reduced the total number of steps. Careful sulfonylation of allylic alcohol **634** at -78°C allowed for the direct production of OMs derivative **650** via a [1,3]-sigmatropic rearrangement (Scheme 83). This reaction, developed by Dr. Lukáš Werner, has not been optimized and suffers from production of oxazoline **641**.


EtO2C
OH
NHAc
634
i
CO2Et
641
+
CO2Et
MsO
NHAc
650

Reagents and conditions: (i) Ms-Cl, NEt_3, DCM, -78°C

Scheme 83. Sigmatropic rearrangement of allylic alcohol **634**

Mesylate **650** was converted into Fang's intermediate **416** by first reducing the acrylate moiety with a rhodium/ alumina hydrogenation procedure to produce OMs diastereomers **648** and **660**. Exposure to sodium azide and then DBU afforded formal intermediate **416** (Scheme 84).


CO2Et
MsO
NHAc
650
i
CO2Et
MsO
NHAc
648
+
CO2Et
MsO
NHAc
660
ii-iii
CO2Et
N3
OH
NHAc
416

Reagents and conditions: (i) 5% Rh/Al_2O_3, 85% EtOH, H_2 (65 psi); (ii) NaN_3, acetone/H_2O, r.t.; (iii) DBU, DCM, 0°C to r.t.

Scheme 84. Formal synthesis of oseltamivir **(2)**

3.6 Synthetic Approaches to Oseltamivir and its Analogs

We explored several routes to oseltamivir **(2)** and its analogs initiating from *cis*-dihydrodiol **6**. We speculated that much of the same chemistry developed previously could be utilized; all beginning from an *anti*-aziridine species **663** where the *N*-substituent could be a tosyl or Boc group (Figure 121).

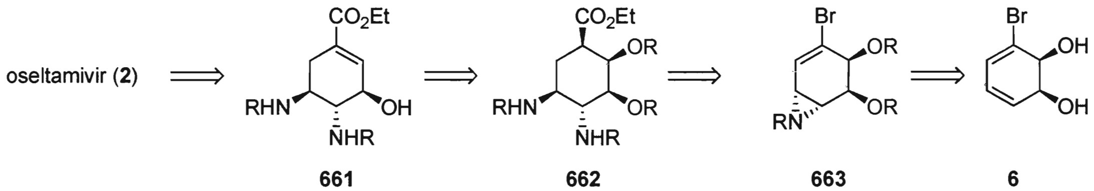
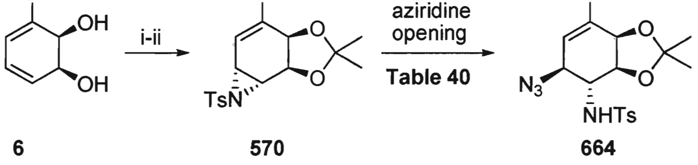


Figure 121. Retrosynthetic analysis of oseltamivir **(2)** from *cis*-dihydrodiol **6**

3.6.1 *N*-tosyl Aziridine Approach

We began by preparing *N*-tosyl aziridine **570**, an intermediate in our second generation approach to (+)-balanol (Scheme 66). We ran a series of experiments hoping to find optimal aziridine opening conditions (Scheme 85). Our initial efforts utilized $Cu(OTf)_2$ as the catalyst and various azide sources. In each case, the starting material decomposed (Table 40, Entries 1 to 3). Switching to ammonium chloride, we were able to isolate the desired azide **664**; with the best results employing sodium azide.



Reagent and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) PhI=NTs, $Cu(acac)_2$, MeCN, 0°C, 77% over two steps

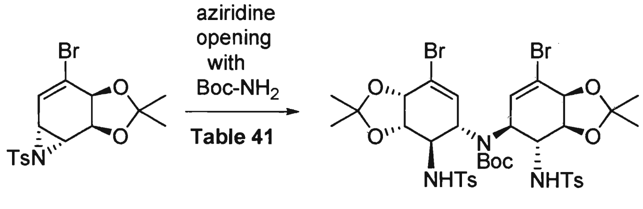
Scheme 85. Opening of *N*-tosyl aziridine **570** with azide

Table 40. Opening of *N*-tosyl aziridine **570** with azide

Entry	*Azide*	*Catalyst*	*Solvent*	*Temp.*	*Result*
1	NaN_3	$Cu(OTf)_2$	THF	r.t.	decomposition[a]
2	TMS-N_3	$Cu(OTf)_2$	THF	r.t.	decomposition[a]
3	DPPA	$Cu(OTf)_2$	THF	r.t.	decomposition[a]
4	**NaN_3**	**NH_4Cl**	**DMF**	**r.t.**	**664 (92%)**
5	TMS-N_3	NH_4Cl	DMF	r.t.	**664** (34%)
6	DPPA	NH_4Cl	DMF	r.t.	**664** (55%)

[a] complex mixture of products

We explored the possibility of opening *N*-tosyl aziridine **570** with a protected nitrogen, specifically *tert*-butyl carbamate (Figure 122). We tested NH_4Cl and TBAF as catalysts and varied the concentration of the starting material (Table 41). In each instance the dimer product **665** was obtained, resulting from the opening of two molecules of aziridine **570** with one molecule of Boc-NH_2.



570 **665**

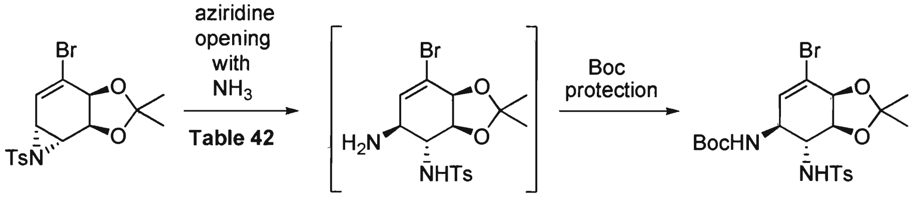
Figure 122. Opening of *N*-tosyl aziridine **570** with *tert*-butyl carbamate

Table 41. Opening of *N*-tosyl aziridine **570** with *tert*-butyl carbamate

Entry	*Catalyst*	*Conc.*[a]	*Solvent*	*Temp.*	*Yield*[b]
1	NH_4Cl	1 M	THF	r.t.	82%
2	NH_4Cl	0.1 M	THF	r.t.	75%[b]
3	**TBAF**	**1 M**	**THF**	**r.t.**	**85%[b]**
4	**TBAF**	**0.1 M**	**DMF**	**r.t.**	**85%[b]**
5	TBAF	0.05 M	DMF	r.t.	80%[b]

[a] refers to concentration of starting material; [b] approximate yield, estimated from crude ^{1}H NMR

We attempted to find an alternative route to *N*-Boc derivative **667** by first opening *N*-tosyl aziridine **570** with ammonia and then treating the amine intermediate **666** with Boc_2O (Figure 123). We performed these experiments in a sealed tube with an approximate 1:10 volumetric ratio of ammonia to solvent (Table 42). These efforts proved troublesome; only the ytterbium(III) triflate catalyzed reactions produced minuscule amounts of the desired product.



570 666 667

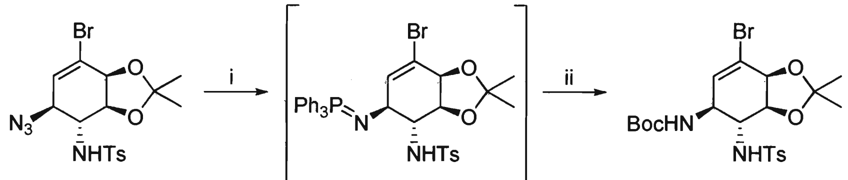
Figure 123. Opening of *N*-tosyl aziridine **570** with ammonia

Table 42. Opening of *N*-tosyl aziridine **570** with ammonia

Entry	*Catalyst*	*Reagents*	*Solvent*	*Temp.*	*Results*
1	$Cu(OTf)_2$	Boc_2O, NEt_3	DCM	-78 to 0°C	decomposition[a]
2	TBAF	Boc_2O, NEt_3	THF	-78 to 0°C	decomposition[a]
3	NH_4Cl	Boc_2O, NEt_3	DMF	-78 to 0°C	decomposition[a]
4	TMSOTf	Boc_2O, NEt_3	THF	-78 to 0°C	decomposition[a]
5	**$Yb(OTf)_3$**	**Boc_2O, NEt_3**	**THF**	**-78 to 0°C**	**667 (5%)**[b]

[a] complex mixture of products; [b] approximate yield, estimated from crude ^{1}H NMR

Unsatisfied, we sought to develop a more practical route to *N*-Boc derivative **667**. Exposure of azide **664** to triphenylphosphine provided us with a Staudinger intermediate **668**, which was easily converted to the desired product upon treatment with Boc_2O (Scheme 86).

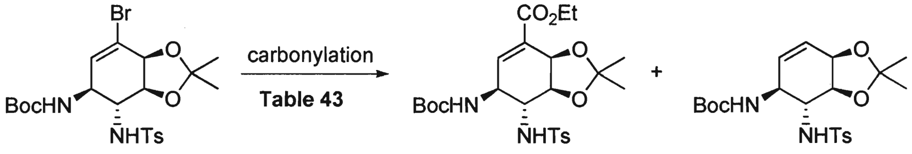


664 668 667

Reagents and conditions: (i) PPh_3, THF/H_2O (15:1); (ii) $(Boc)_2O$, DCM, NEt_3, 0°C to r.t., 77% over two steps

Scheme 86. Alternative synthesis of *N*-Boc derivative **667**

At this stage, we elected to install the acrylate functionality through use of a metal-catalyzed carbonylation protocol (Figure 124). Using a dual palladium catalyst procedure, we isolated ethyl ester **669** (Table 43, Entry 1). We also made two attempts with a nickel catalyst (Ni[$(PPh_3)_2(CO)_2$]) which did not require the addition of carbon monoxide gas. In each instance, the reduction product **670** was the lone product obtained.



667 **669** **670**

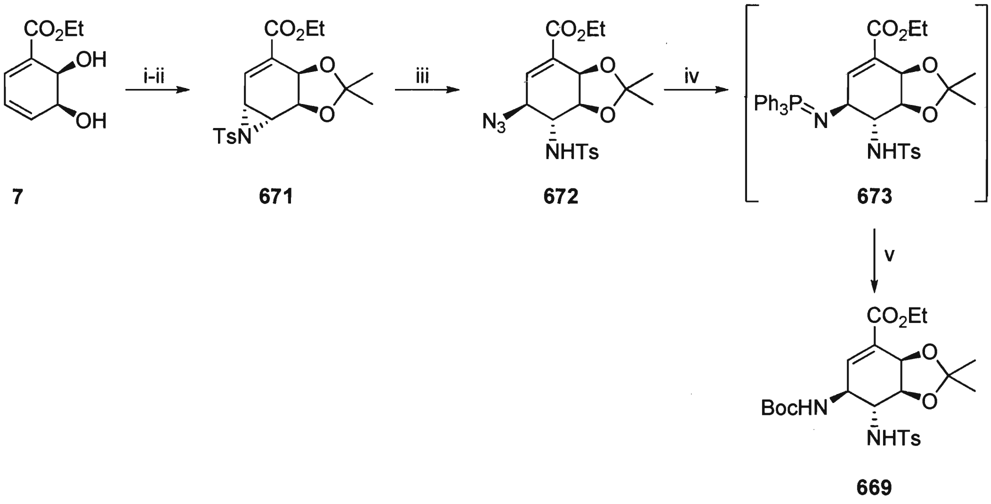
Figure 124. Carbonylation of vinyl bromide **667**

Table 43. Carbonylation of vinyl bromide **667**

Entry	*Catalyst(s)*	*Reagents*	*Solvent*	*Temp.*	*Result*
1	**$Pd(PPh_3)_4$,** **$Pd[(Cl)_2(PPh_3)_2]$,**	**NEt_3, CO**	**toluene/EtOH**	**reflux**	**669 (45%)**
2	$Ni[(PPh_3)_2(CO)_2]$	DIPEA	toluene/EtOH	reflux	**670** (50%)[a]
3	$Ni[(PPh_3)_2(CO)_2]$	DIPEA	THF/EtOH	reflux	**670** (79%)
4	$Ni[(PPh_3)_2(CO)_2]$	DIPEA	EtOH	reflux	**670** (60%)[a]

[a] approximate yield, estimated from crude ^{1}H NMR

We also attempted to prepare acrylate **669** from *cis*-dihydrodiol **7**, thus avoiding the carbonylation reaction (Scheme 87). Using the identical sequence employed with vinyl halide **6**, aziridination of olefin **7** was followed by selective opening with azide. We were able to obtain *N*-Boc derivative **669** via Staudinger intermediate **673**, albeit in a lower yield compared to our previous substrate **664**.



Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) PhI=NTs, Cu(acac)$_2$, MeCN, 0°C, 41% over 2 steps; (iii) NaN$_3$, NH$_4$Cl, DMF, r.t., 79%; (iv) PPh$_3$, THF/H$_2$O (15:1), r.t.; (v) (Boc)$_2$O, NEt$_3$, 0°C to r.t., 32% over two steps

Scheme 87. Alternative synthesis of ethyl ester **669**

We decided to examine an alternative route to *N*-Boc derivative **669** from azide **672** through use of a hydrogenation protocol (Figure 125). We tested several hydrogenation procedures without success (Table 44). Consequently, we elected to prepare ester **669** from our original route (Scheme 86) despite the additional step.

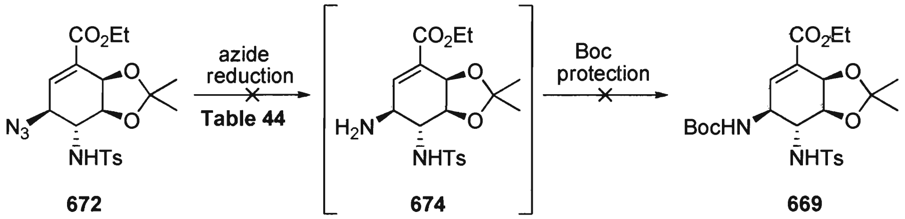


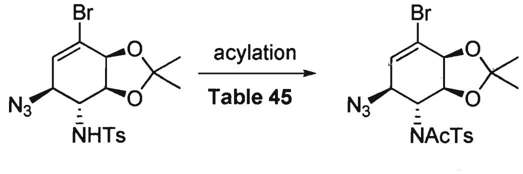
Figure 125. Attempts to synthesis ethyl ester **669** from vinyl azide **672**

Table 44. Attempts to synthesis ethyl ester **669** from vinyl azide **672**

Entry	*Catalyst*	*Reagents*	*Solvent*	*Pressure*	*Results*
1	Lindlar's catalyst	Boc$_2$O, NEt$_3$	EtOH	1 atm	decomposition[a]
2	PtO$_2$	Boc$_2$O, NEt$_3$	EtOH	1 atm	decomposition[a]
3	5% Pd/C	Boc$_2$O, NEt$_3$	EtOH	1 atm	decomposition[a]

[a] complex mixture of amines (TLC/ ninhydrin staining)

In order to access oseltamivir **(2)**, the tosyl group of **669** needed to be replaced with an acetyl group (Figure 126). To this end, we first acetylated sulfonyl amine **664**. We screened several conditions; ultimately concluding that neat acetic anhydride is the best method (Table 45).



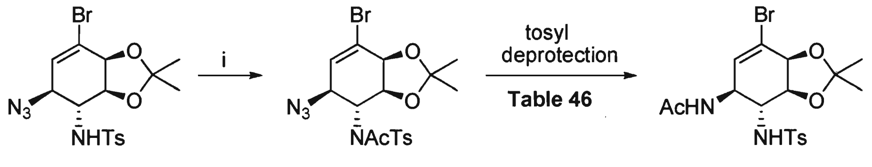
664 **675**

Figure 126. Acetylation of sulfonyl amine **664**

Table 45. Acetylation of sulfonyl amine **664**

Entry	*Reagent*	*Base*	*Solvent*	*Temp.*	*Yield (%)*
1	Ac_2O	DIPEA	DCM	0°C - r.t.	31
2	Ac_2O	pyridine	DCM	0°C - r.t.	44
3	Ac_2O	NEt_3	DCM	0°C - r.t.	77
4	Ac_2O	NEt_3	THF	0°C - r.t.	79
5	**Ac_2O**	**NEt_3**	**-**	**0°C - r.t.**	**90**

We attempted a series of detosylation procedures on the *N*-AcTs derivative **675** (Scheme 88). A sodium/ naphthalene dissolving metal reduction decomposed the starting material into several unidentified products, each with the tosyl group intact (Table 46). As was the case with the sodium amalgam and zinc dust reduction protocols we had tested. Samarium(II)iodide preferentially reduced the azide functionality to an intermediate which underwent an intramolecular acetyl-transfer reaction to afford **676**.



664 **675** **676**

Reagents and conditions: (i) Ac_2O, 0°C - r.t., 90%

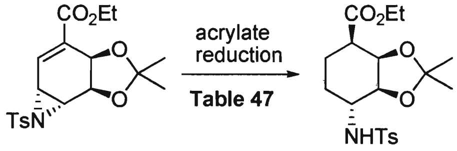
Scheme 88. Attempted detosylation of *N*-AcTs derivative **675**

Table 46. Attempted detosylation of *N*-AcTs derivative **675**

Entry	*Reagent(s)*	*Solvent*	*Temp.*	*Result*
1	Na/ naphthalene	DME	-78°C – r.t.	decomposition[a]
2	SmI_2	THF	-78°C – r.t.	**676** (93%)
3	Na/Hg	MeOH	0°C – r.t.	decomposition[a]
4	Zn	DME	0°C – r.t.	decomposition[a]

[a] complex mixture of tosylated products

As a result of the failed detosylation procedures, we elected to pursue the synthesis of an *N*-Ts oseltamivir analog. To this end, we attempted to reduce the acrylate moiety of vinyl aziridine **671** in order to simplify a subsequent azide reduction (Figure 127). Unfortunately, our hydrogenation procedures only produced the hydrogenolysis product **677**, while Stryker's reagent did not produce any new compounds (Table 47).



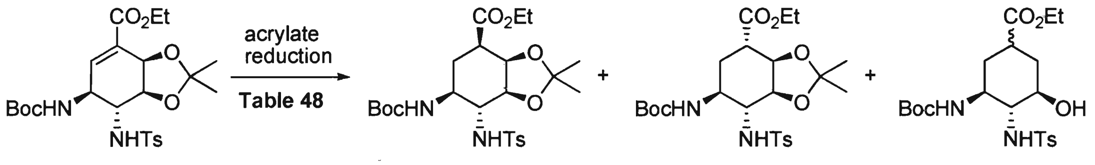
671 **677**

Figure 127. Attempted reduction of acrylate **671**

Table 47. Attempted reduction of acrylate **671**

Entry	*Catalyst*	*Solvent*	*H_2 Pressure*	*Temp.*	*Result*
1	PtO_2	95% EtOH	1 atm	r.t.	**677** (84%)
2	Stryker's reagent	THF	-	reflux	SM
3	5% Rh/Al_2O_3	95% EtOH	65 psi	r.t.	**677** (73%)

We also attempted to reduce acrylate **669** with the same reduction protocols (Figure 128). Platinum(IV) oxide yielded hydrogenolysis product **679**, while Stryker's reagent returned starting material (Table 48). The rhodium/alumina hydrogenation protocol, which we used in our formal synthesis of oseltamivir **(2)**, resulted in successful reduction of acrylate **669** to provide a 8:1 mixture of diastereomers **678a** and **678b**.



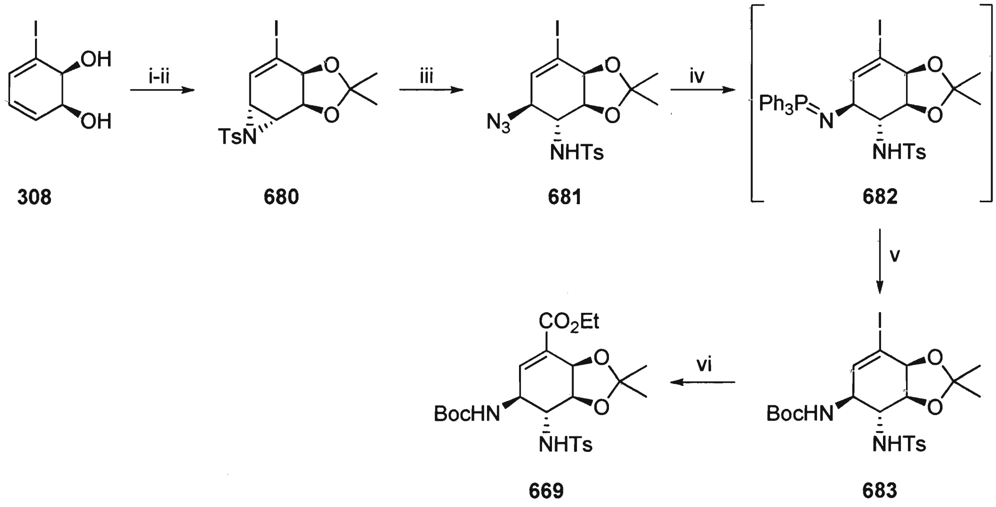
669 **678a** **678b** **679**

Figure 128. Reduction of acrylate **669**

Table 48. Reduction of acrylate **669**

Entry	*Catalyst*	*Solvent*	*H_2 Pressure*	*Temp.*	*Result*
1	PtO_2	95% EtOH	1 atm	r.t.	**679** (92%)
2	Stryker's reagent	THF	-	reflux	SM
3	**5% Rh/Al_2O_3**	**95% EtOH**	**65 psi**	**r.t.**	**678a:678b (8:1)**

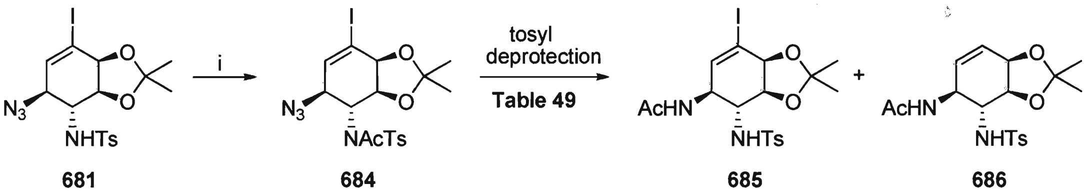
We also prepared ester **669** from the *cis*-dihydrodiol derived from iodobenzene **308** (Scheme 89). The reaction sequence employed is identical to that used for the brominated 1,2-diol **6**. Unfortunately, the yields for most transformations were slightly lower. The lone exception is the carbonylation procedure which proceeded more efficiently with the iodo derivative **683** compared to the vinylbromide **667**.


308
680
681
682
683
669
i-ii
iii
iv
v
vi
OH
OH
TsN
N3
NHTs
Ph3P=N
BocHN
CO2Et

Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) PhI=NTs, Cu(acac)$_2$, MeCN, 0°C, 55% over 2 steps; (iii) NaN$_3$, NH$_4$Cl, DMF, r.t., 90%; (iv) PPh$_3$, THF/H$_2$O (15:1), r.t.; (v) (Boc)$_2$O, NEt$_3$, 0°C to r.t., 68% over 2 steps; (vi) (PPh$_3$)$_4$, Pd[(Cl)$_2$(PPh$_3$)$_2$], CO, NEt$_3$, EtOH, toluene, reflux, 77%

Scheme 89. Synthesis of ethyl ester **669** from *cis*-dihydrodiol **308**

We submitted vinyl iodide **681** to the same acetylation/ deprotection sequence employer earlier (Scheme 90). Once again Na/naphthalene decomposed our starting material and SmI$_2$ gave us an azide reduction-acetyl transfer product **685** (Table 49). The zinc protocol cleanly reduced the halogen-carbon bond to afford olefin **686**.


681
684
685
686
i
tosyl
deprotection
Table 49
N3
NHTs
NAcTs
AcHN
+

Reagents and conditions: (i) Ac$_2$O, NEt$_3$, r.t., 87%

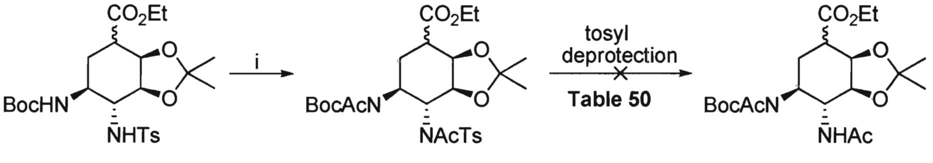
Scheme 90. Attempted detosylation of *N*-AcTs derivative **684**

Table 49. Attempted detosylation of *N*-AcTs derivative **684**

Entry	*Reagent*	*Solvent*	*Temp.*	*Result*
1	Na/ naphthalene	DME	-78°C – r.t.	decomposition[a]
2	SmI$_2$	THF	-78°C – r.t.	**685** (88%)
3	Na/Hg	MeOH	0°C – r.t.	decomposition[a]
4	Zn	DME	0°C – r.t.	**686** (66%)

[a] complex mixture of tosylated products

We treated ester **678** with access acetic anhydride and attempted to removal the tosyl group (Scheme 91). All methods employed decomposed our starting material (Table 50).


CO2Et
BocHN
NHTs
i
BocAcN
NAcTs
tosyl deprotection
Table 50
NHAc

678 **687** **688**

Reagents and conditions: (i) Ac_2O, NEt_3, DCM, r.t., 81%

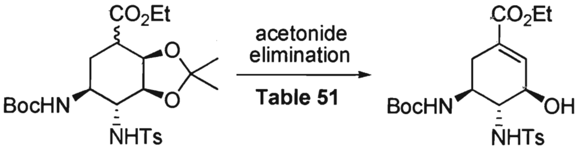
Scheme 91. Attempted detosylation of *N*-AcTs derivative **687**

Table 50. Attempted detosylation of *N*-AcTs derivative **687**

Entry	*Reagent*	*Solvent*	*Temp.*	*Result*
1	Na/ naphthalene	DME	-78°C – r.t.	decomposition[a]
2	SmI_2	THF	-78°C – r.t.	decomposition[a]
3	Na/Hg	MeOH	0°C – r.t.	decomposition[a]
4	Zn	DME	0°C – r.t.	decomposition[a]

[a] complex mixture of tosylated products

Convinced that our tosyl deprotection route was futile, we elected to collapse the acetonide of ester **678** and attempt to complete the synthesis of an *N*-tosyl oseltamivir analog (Figure 129). We tested the same conditions utilized previously; again finding sodium ethoxide was the most efficient method to furnish allylic alcohol **689**.


CO2Et
BocHN
NHTs
acetonide elimination
Table 51
OH

678 **689**

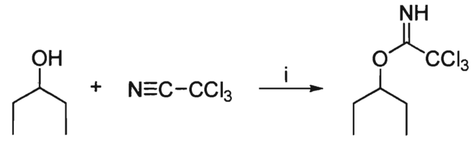
Figure 129. Elimination of acetonide **678**

Table 51. Elimination of acetonide **678**

Entry	*Base*	*Solvent*	*Temp.*	*Yield*
1	DBU	acetone	0°C - r.t.	15%
2	DBU	-[a]	0°C - r.t.	49%
3	DBU	DCM	0°C - r.t.	32%
4	**EtONa**	**EtOH**	**0°C - r.t.**	**76%**

[a] reaction performed with DBU as the solvent

In order to complete the synthesis of the *N*-Ts oseltamivir analog, the allylic alcohol **689** needed to be alkylated. Our first attempts utilized the method developed by Fang in his synthesis of oseltamivir **(2)**.[248] Trichloroacetimidate **692** was prepared by treating 3-pentanol **(690)** with 2,2,2-trichloroacetonitrile **(691)** in the presence of sodium hydride (Scheme 92).



690 **691** **692**

Reagents and conditions: (i) **690**, **691**, Et_2O, NaH, -5°C, 73%

Scheme 92. Preparation of 3-pentyl trichloroacetimidate **692**

Fang's alkylation procedure calls for the repetitive addition of trifluoromethanesulfonic acid and the alkylating agent **692**; however, this method rapidly decomposed the starting material (Table 52, Entry 1). Spectral analysis indicated the Boc-group was removed under these conditions. All other procedures attempted decomposed the starting material or did not produce any new compounds.

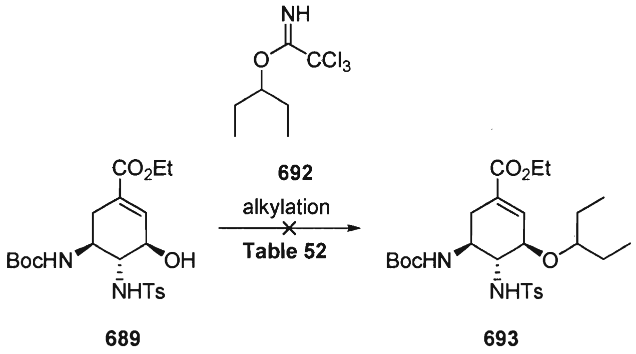


Figure 130. Alkylation of allylic alcohol **689**

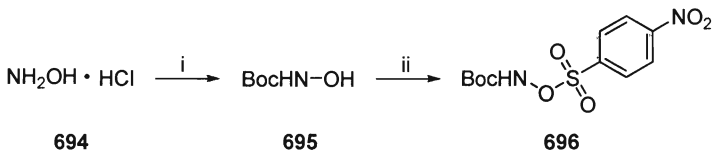
Table 52. Alkylation of allylic alcohol **689**

Entry	*Reagent(s)*	*Solvent*	*Temp.*	*Result*
1	**692**, CF_3SO_3H	DCM	r.t.	decomposition[a]
2	**692**, CF_3SO_3H	DCM	-40 – 0°C	decomposition[a]
3	**692**, AcOH	DCM	-40 – 0°C	decomposition[a]
4	**692**, AcOH	DCM	-40 – 0°C	decomposition[a]
5	**692**	-	r.t.	SM

[a] complex mixture of products

3.6.2 *N*-Boc Aziridine Approach

We explored the possibility of preparing either oseltamivir **(2)** or an analog from an *N*-Boc aziridine. For this purpose, we prepared sulfonyloxycarbamate **696** by reacting *tert*-butyl hydroxycarbamate **(695)** with 4-nitrobenzene-1-sulfonyl chloride (Scheme 93). This reagent, when treated with base, provides a nitrene intermediate capable of aziridinating olefins.



Reagents and conditions: (i) Na_2CO_3, Et_2O/ H_2O, 0°C to r.t.; (ii) *p*-NO_2-C_6H_4-SO_2Cl, NEt_3, Et_2O, 0°C to r.t., 77%

Scheme 93. Preparation of sulfonyloxycarbamate reagent **696**

We tested several biphasic (DCM/ H_2O) conditions to prepare *N*-Boc aziridine **697** from 1,3 diene **554** (Figure 131). The best result was obtained when a high excess of **696** was used (Table 53, Entry 3).

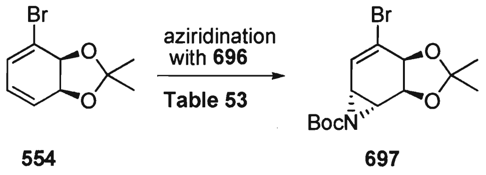

Br
554
aziridination
with 696
Table 53
Br
BocN
697

Figure 131. Preparation of *N*-Boc aziridine **697**

Table 53. Preparation of *N*-Boc aziridine **697**

Entry	*Reagents*	*Equiv.*[a]	*Solvent*	*Temp.*	*Yield (%)*
1	**696**, $NaHCO_3$, $BnNEt_3Cl$	1	DCM/ H_2O	r.t.	12
2	**696**, $NaHCO_3$, $BnNEt_3Cl$	5	DCM/ H_2O	r.t.	24
3	**696, $NaHCO_3$, $BnNEt_3Cl$**	**10**	**DCM/ H_2O**	**r.t.**	**44**

[a] equivalents of **696**

We tested a series of aziridine opening reactions with various azide sources (Figure 132). Reactions catalyzed by $Cu(OTf)_2$ decomposed the starting material, while ammonium chloride catalysis successfully provided allylic azide **698** (Table 54). Although pleased with the result, we saw this route as impractical and did not pursue it further.

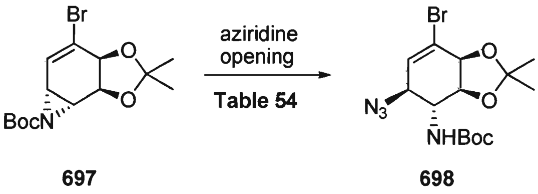

Br
BocN
697
aziridine
opening
Table 54
Br
N_3
NHBoc
698

Figure 132. Opening of *N*-Boc aziridine **697**

Table 54. Opening of *N*-Boc aziridine **697**

Entry	*Azide*	*Catalyst*	*Solvent*	*Temp.*	*Result*
1	**NaN_3**	**NH_4Cl**	**DMF**	**r.t.**	**698 (77%)**
2	TMS-N_3	$Cu(OTf)_2$	THF	r.t.	decomposition[a]
3	DPPA	$Cu(OTf)_2$	THF	r.t.	decomposition[a]

[a] complex mixture of products

We explored the possibility of removing the Boc carbamate of **697**, with the hope that it could be replaced with an acetyl group (Figure 133). However, treatment with trifluoroacetic acid resulted in the formation of cyclic carbamate **699**, while thermal deprotection returned starting material (Table 55).

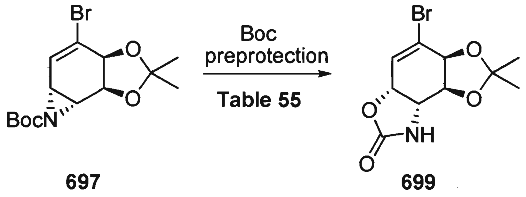


Figure 133. Attempted Boc deprotection of **697**

Table 55. Attempted Boc deprotection of **697**

Entry	*Reagent*	*Solvent*	*Temp.*	*Result*
1	**TFA**	**DCM**	**0°C - r.t.**	**699 (89%)**
2	TFA	-	0°C - r.t.	**699** (66%)
3	-	toluene	60°C	SM

4. Conclusions and Future Work

The preceding study reviewed our latest efforts in seven areas of research; 1. reactivity of the Burgess reagent with oxiranes, 2. development of a chiral auxiliary version of the Burgess reagent, 3. enantioselective synthesis of balanol, 4. chemoenzymatic synthesis of balanol, 5. enzymatic *cis*-dihydroxylation of benzoate esters, 6. synthesis of oseltamivir, and 7. synthesis of oseltamivir analogs.

We have elucidated a plausible mechanism for reactions between the Burgess reagent and oxiranes. The relative stereochemistry of the resulting cyclic sulfamidates was established as *cis*. We developed a chiral auxiliary version of the Burgess reagent and demonstrated its application in the synthesis of all four β-amino alcohol stereoisomers from a single *meso*-epoxide. This methodology was exploited in an enantiodivergent approach to both enantiomers of balanol. Formal intermediates for (+)- and (–)-balanol were each prepared in eight steps from 1,3-cyclohexadiene oxide. The same formal intermediates were prepared from a single *cis*-dihydrodiol derived from the bio-oxidation of bromobenzene by the toluene dioxygenase enzyme. The (+)-balanol intermediate was constructed in 10 steps, while the (–)-balanol was formulated in 12 steps. The β-amino alcohol moiety is common among naturally occurring products. In the future, we hope to develop a route to such a compound utilizing the (–)-menthyl Burgess reagent methodology.

We examined the steric and functional limitations of the toluene dioxygenase-mediated dihydroxylation of benzoate esters. It was concluded that methyl, ethyl, *i*-propyl, and *n*-propyl benzoate were acceptable substrates, while *n*- and *t*-butyl were not oxidized by TDO. Benzoates bearing propargyl and allyl functionalities were also accepted by the enzyme. The absolute stereochemistry of each diol metabolite was confirmed through their conversion to a single known intermediate. In the future we hope to screen benzoates with various substituents (e.g. halogen, alkyl) on the arene ring.

We employed the *cis*-dihydrodiol obtained from the enzymatic dihydroxylation of ethyl benzoate in an eight step formal synthesis of oseltamivir. We also developed several potential approaches, each employing a vinyl aziridine intermediate. In the future, we hope to conclude these strategies and prepare the *N*-tosyl and *N*-Boc analogs of oseltamivir. Furthermore, we plan to submit all of the intermediates for biologically testing against all known influenza neuraminidase enzymes.

5. Experimental Section

5.1 General experimental procedures

Viable cells of *E. coli* JM 109 (pTDG 601) were prepared as previously reported.[279] Substrate was fed in 1 g increments over the course of ~2 h with metabolites being harvested in the usual manner. All non-aqueous reactions were carried out in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride. Tetrahydrofuran and benzene were dried over sodium/benzophenone. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using 200-400 mesh silica gel. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded as thin films on NaCl plates and were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin Elmer 341 polarimeter using a sodium (589, D line) lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,°C}$ (*c* = g/100 mL, solvent). ^{1}H NMR spectra were recorded on a Bruker (300 MHz or 600 MHz) spectrometer and are reported in ppm using tetramethylsilane (0.00 ppm) or solvent ($CDCl_3$: 7.24 ppm, acetone-d_6: 2.05 ppm, DMSO-d_6: 2.50, CD_3OD: 3.31 ppm, D_2O: 2.80) as an internal standard. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz, integration. Proton-decoupled ^{13}C NMR spectra were recorded at 150 or 75 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$: 77.23 ppm, acetone-d_6: 206.68 ppm, DMSO-d_6: 39.51 ppm, CD_3OD: 49.15 ppm). Combustion analyses were performed by Atlantic Microlabs, Norcross, GA. Mass spectra were recorded on Kreatus/MsI

Concept 1S mass spectrometer at Brock University. The GC/MS data was obtained on a Perkin-Elmer Clarus 500 Gas Chromatograph and Mass Spectrometer using a Perkin Elmer Elite-5MS column, 10 m, 0.25 mmID, 2 mL/ min helium flow.

General procedure for the reaction of oxiranes with the Burgess reagent (8)

To a stirred solution of oxirane (4.0 mmol) in THF (20 mL) was added (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt **(8)** (2.38 g, 9.2 mmol) at r.t. in a single portion. The resulting reaction mixture was immediately brought to reflux by submerging it into a preheated oil bath (70 °C). The reaction mixture was stirred until complete consumption of the oxirane (TLC), then cooled to r.t. and filtered through a plug of silica to remove salts formed during the reaction. The reaction solution was then concentrated and the resulting residue was purified by flash column chromatography using an appropriate solvent gradient (hexanes: ethyl acetate) to yield the corresponding sulfamidate products.

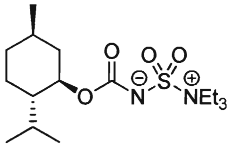
General procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent (3)

To a stirred solution of oxirane (2.0 mmol) in THF (5 mL) was added (–)-menthyl Burgess reagent **(3)** (4.60 mmol) at r.t. in a single portion. The resulting reaction mixture was immediately brought to reflux by submerging it into a preheated oil bath (70 °C). The reaction mixture was stirred until complete consumption of the oxirane (TLC), then cooled to r.t. and filtered through a plug of silica to remove salts formed during the reaction. The reaction mixture was then concentrated and the resulting residue was purified by flash column chromatography using an appropriate solvent gradient (hexanes: ethyl acetate) to afford a 1:1 mixture of sulfamidate diastereomers.

General procedure for the syntheses of benzoates from sulfamidates.

To a stirred solution of sulfamidate (1.25 mmol) in dry DMF (5 mL) was added ammonium benzoate (346 mg, 2.50 mmol). The solution was heated at 55 ˚C and stirred for 18 h before the solvent was evapourated, and the resulting residue was dissolved in THF (3 mL). Three drops of water and three drops of conc. H_2SO_4 were added, and the reaction mixture was stirred at r.t. for 12 h. The reaction mixture was diluted with water and the pH was adjusted to 9, using a sat. aqueous solution of $NaHCO_3$, before the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL), then the organic layers were combined and washed with brine (1 x 5 mL), dried over Na_2SO_4, filtered, and the solvent was evapourated. The resulting benzoate diastereomers were separated via flash column chromatography (hexanes: ethyl acetate) using an appropriate solvent system.

5.2 Detailed Experimental Procedures

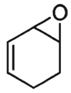


3

***N,N*-Diethyl-*N*-[[[[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl) cyclohexyl]oxy] carbonyl] amino]sulfonyl]-ethanaminium, inner salt (3)**

To a stirred solution of chlorosulfonyl isocyanate (5.21 g, 36.8 mmol) in benzene (15 mL) was added a solution of (–)-menthol **(481)** (5.00 g, 32 mmol) in benzene (15 mL) dropwise over 30 min while keeping the internal temperature between 25 - 30 °C, using an ice-water bath. The reaction mixture was then stirred at r.t. for an additional 30 min, before ice cold hexane (40 mL) was added while cooling the reaction mixture to 0-5 °C. The product was filtered and washed with ice cold hexanes (2 x 20 mL) and dried under reduced pressure to yield 8.29 g (87%) of (–)-menthol sulfamoyl chloride **(483)** as colourless crystals (87%): mp 86-88 °C (hexanes); $[\alpha]_D^{23}$ -64.5 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 - 8.55 (bs, 1H), 4.81 (td, *J* = 11.2, 4.6 Hz, 1H), 2.07 - 2.16 (m, 1H), 1.83 - 2.01 (m, 1H), 1.61 - 1.77 (m, 2H), 1.39 - 1.58 (m, 2H), 1.04 - 1.22 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 6H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm.

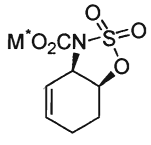
To a stirred solution of triethylamine (6.53 mL, 47.0 mmol) in benzene (20 mL) was added a solution of (–)-menthol sulfamoyl chloride **(483)** (7.00 g, 23.5 mmol) in benzene (40 mL) dropwise over 1 h, keeping the internal temperature between 10-15 °C, using an ice-water bath. The reaction mixture was stirred at r.t. for an additional 30 min and then filtered to remove the triethylamine hydrochloride salt. The filtrate was evapourated under reduced pressure, then dissolved in THF (50 mL) at 30 °C and cooled to 0-5 °C and treated with hexanes (50 mL) to precipitate out 7.24 g (85%) of the title compound **3** as a colourless solid. mp 87-89 °C (THF/hexanes); $[\alpha]_D^{23}$ -48.7 (*c* 0.48, $CHCl_3$); IR (film) ν 3426, 3020, 2958, 2872, 1682, 1457, 1389, 1369, 1340, 1285, 1253, 1216, 1105, 982, 922, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (td, *J* = 11.0, 4.6 Hz, 1H), 3.45 (q, *J* = 7.7 Hz, 6H), 3.14 - 3.26 (m, 1H), 1.93-2.08 (m, 2H), 1.65 (d, *J* = 11.9 Hz, 2H), 1.30 - 1.44 (m, 11H), 0.92 - 1.03 (m, 2H), 0.87 (t, *J* = 7.7 Hz, 6H), 0.76 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 76.4, 50.7, 47.3, 46.7, 41.3, 34.6, 31.8, 26.4, 23.7, 21.2, 16.6, 9.8, 8.8 ppm.



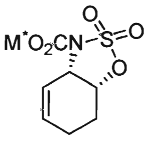
4

1,3-cyclohexadiene oxide (4)

To a mechanically stirred solution of 1,3-cyclohexadiene (33.6 g, 0.419 mol), Na_2CO_3 (177 g, 1.68 mol) in DCM (400 mL) was added peracetic acid (104.5 g, 0.440 mol) dropwise at 0 °C over 1 h. The reaction was stirred for 12 h at r.t. before removing the salts by filtration. The organic layer was distilled off at 1 atm. The product was collected by fractional distillation under reduced pressure to yield 21.2 g (56%) of the title compound as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43-2.41 (m, 4H), 3.11-3.28 (m, 1H), 3.42-3.53 (m, 1H), 4.93 (d, *J* = 4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.8, 46.9, 123.1, 132.9 ppm



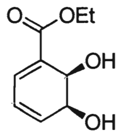
5a



5b

(3a*R*,7a*S*)-2,2-Dioxo-3a,6,7,7a-tetrahydro-2λ6-1,2,3-benzoxathiazole-3-carboxylic acid-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ester (5a) and (3a*S*,7a*R*)-2,2-Dioxo-3a,6,7,7a-tetrahydro-2λ6-1,2,3-benzoxathiazole-3-carboxylic acid-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ester (5b)

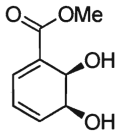
The general procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent **(3)** using 1,3-cyclohexadiene oxide **(4)** (186 mg, 2.0 mmol) as the starting material gave 257 mg (36%) of a 1:1 mixture of diastereomers **5a** and **5b** after purification by flash column chromatography (hexanes/ethyl acetate, 8:1). Colourless oil; R_f 0.68 (hexanes/ethyl acetate, 5:1); mp 115-118 °C (hexanes–ethyl acetate); R_f 0.55 (4:1 hexanes–ethyl acetate); $[\alpha]_D^{23}$ –54.5 (*c* 1.25, $CHCl_3$); IR (film) ν 3443, 3031, 2959, 2930, 2873, 1731, 1599, 1457, 1432, 1371, 1331, 1307, 1241, 1217, 1189, 1170, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (rotamers) δ 0.74-0.85 (m, 3H), 0.87-0.96 (m, 6H), 1.00-1.31 (m, 3H), 1.39-1.75 (m, 5H), 1.82-2.44 (m, 5H), 4.66-4.84 (m, 2H), 5.13-5.33 (m, 1H), 5.56-5.85 (m, 1H), 6.02-6.28 (m, 1H) ppm; ^{13}C NMR (rotamers) (75 MHz, $CDCl_3$) δ 18.7 18.7, 18.8, 18.9, 19.9, 20.3, 21.2, 22.1, 22.6, 23.7, 23.9, 24.2, 29.3, 29.3, 29.5, 32.0, 37.7, 37.9, 38.6, 44.7, 44.8, 44.9, 45.2, 51.5, 53.2, 53.2, 72.8, 72.9, 74.6, 75.1, 75.3, 75.5, 79.2, 81.6, 81.7, 117.9, 119.0, 119.0, 129.5, 135.0, 147.9 ppm; MS (FAB) *m/z* (%): 358 ($M+H^+$); (11), 220(16), 140(14), 139(90), 137(33), 97(24), 95(24), 83(100), 81(36), 80(11), 79(47), 69(43), 67(19), 57(35), 55(49), 53(12); HRMS calcd for $C_{17}H_{27}NO_5S$ 357.1610, found 357.1593.



7

6-Carboxymethyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (7)

From the fermentation of benzoate **576**, (8.06 g, 43.4%, 45.6% based on recovered starting material) Colourless crystals, mp 48 °C (ethyl acetate/hexanes); R_f 0.31 (1:2 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +54.7 (*c* 3.8, $CHCl_3$); IR (film) ν 3385, 2981, 2934, 1700, 1280, 1243, 1104, 1068, 825, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 5.3 Hz, 1H), 6.15 (dt, *J* = 1.1, *J* = 9.4 Hz, 1H), 6.03 (dq, *J* = 2.25, *J* = 9.22 Hz, 1H), 4.49-4.55 (m, 1H), 4.40-4.48 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.65-3.78 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.7, 134.1, 128.7, 122.5, 69.8, 64.5, 60.9, 14.2 ppm; MS (EI) *m/z* (%): 184(M$^+$, 9), 166(20), 138(26), 122(33), 121(52), 105(100), 77(39), 51(21), 45(20); HRMS calcd for $C_9H_{12}O_4$ 184.0736, found 184.0731; *Anal.* calcd: C 58.69, H 6.57, found C 58.77, H 6.60.

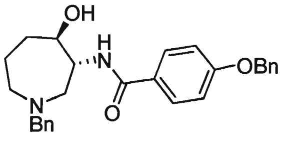


18

6-Carboxymethyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (18).

From the fermentation of benzoate **575**, (12.92 g, 19.2%, 75.8% based on recovered starting material) Pale yellow oil; R_f 0.33 (1:2 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +71.3 (*c* 1.6, $CHCl_3$); IR (film) ν 3412, 2098, 1690, 1639, 1291, 820, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 5.3 Hz, 1H), 6.17 (dd, *J* = 0.6, *J* = 10.3 Hz, 1H), 6.05 (qd,

$J = 2.2$, $J = 5.1$ Hz, 1H), 4.50-4.56 (m, 1H), 4.41-4.50 (m, 1H), 3.77 (s, 3H), 3.52-3.67 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 138.6, 134.3, 128.4, 122.6, 69.5, 64.8, 52.1 ppm; MS (EI) *m/z* (%): 170(M^+, 33), 152(61), 139(22), 138(96), 136(71), 121(100), 110(95), 109(66), 105 (23), 93(42), 92(22) 82(57), 81(56), 65(59), 53(49), 51(22); HRMS calcd for $C_8H_{10}O_4$ 170.0579, found 170.0580.



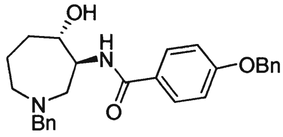
231a

_N_-[(3_R_,4_R_)-1-benzyl-4-hydroxyazepan-3-yl]-4-(benzyloxy)benzamide (231a)

To a stirred solution of **539a** (12 mg, 0.0263 mmol) in freshly distilled THF (0.2 mL) was added 1 N NaOH (1 mL) at -20 °C. The reaction was warmed to r.t. slowly over 12 h before concentrating under reduced pressure. The reaction was concentrated, extracted into ethyl ether (5 x 1 mL), washed with brine and then dried over Na_2SO_4. The crude product was subjected to flash column chromatography (3:1 hexanes-ethyl acetate) to yield 9 mg (81%) of the title compound as yellow oil. R_f 0.19 (1:3 ethyl acetate-hexanes); $[\alpha]_D^{23}$ –4.7 (*c* 0.02, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.55–1.99 (m, 4H), 2.50 (m, 1H), 2.73 (dd, $J = 1.9$, 14.3 Hz, 1H), 2.93 (dd, $J = 2.0$, 14.2 Hz, 1H), 3.00 (m, 1H), 3.42 (d, $J = 13.2$ Hz, 1H), 3.74–3.78 (m, 2H), 3.88 (m, 1H), 5.15 (s, 2H), 6.54 (d, $J = 8.7$ Hz, 1H), 6.99 (d, $J = 6.8$ Hz, 2H), 7.22–7.50 (m, 12H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 29.7, 31.5, 54.4, 58.0, 59.9, 64.2, 70.1, 77.5, 114.5, 126.4, 127.4, 127.5 (2x C), 128.2, 128.7 (2x C), 128.9 (2x C), 129.0, 129.5 (2x C), 136.4, 161.4, 167.8 ppm;

MS (FAB) *m/z* (%) 431 (M + H$^+$); 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.

Alternative method: To a stirred solution of **539a** (21 mg, 0.0460 mmol) in THF (0.3 mL) was added 1 N NaOH (1.5 mL) at -20 °C. The reaction was warmed allowed to warm to r.t. slowly over 12 h before concentrating under reduced pressure. The resulting residue was diluted with H_2O (1 mL) and extracted into EtOAc (5 x 1 mL), washed with brine (1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes-ethyl acetate) yield **231a** (17 mg, 86 %) as a pale yellow oil; $[\alpha]_D^{23}$ -5.6 (*c* 0.2, $CHCl_3$)

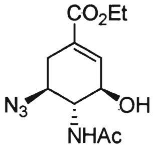


231b

N-[(3S,4S)-hexahydro-4-hydroxy-1-(phenylmethyl)-1H-azepin-3-yl]-4-(phenylmethoxy)benzamido (231b)

To a stirred solution of azepane **539b** (12 mg, 0.026 mmol) in tetrahydrofuran (0.3 mL) was added 1 N NaOH (1.5 mL) at –20 °C. The reaction mixture was allowed to warm to r.t. slowly over 12 h before concentrating under reduced pressure. The resulting residue was diluted with H_2O (1 mL) and extracted into ethyl acetate (5 x 1 mL), then the combined organic layers were washed with brine (1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes-ethyl acetate) yield **231b** (6.5 mg, 56 %) as a pale yellow oil: R_f 0.31 (3:2 hexane-ethyl acetate); $[\alpha]_D^{23}$ + 5.77 (*c* 0.75, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ

7.22–7.50 (m, 12H), 6.99 (d, J = 6.8 Hz, 2H), 6.54 (d, J = 8.7 Hz, 1NH), 5.11 (s, 2H), 3.88 (m, 1H), 3.69–3.78 (m, 1H), 3.63 (d, J = 13.2 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.00 (m, 1H), 2.93 (dd, J = 2.0, 14.2 Hz, 1H), 2.73 (dd, J = 1.9, 14.3 Hz, 1H), 2.50 (m, 1H), 1.85-1.95(m, 2H), 1.60-1.85 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.4, 136.4(2xC), 129.5(2xC), 129.0, 128.9(2xC), 128.7(2xC), 128.2(2xC), 127.5(2xC), 127.4(2xC), 126.4, 114.5(2xC), 77.5, 70.1, 64.2, 59.9, 58.0, 54.4, 31.5, 29.7 ppm; MS (FAB) *m/z* (%): 431 ($M+H^+$), 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.

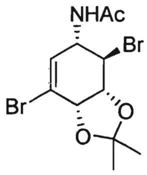


416

Ethyl(3*R*,4*R*,5*S*)-4-(acetylamino)-5-azido-3-hydroxycyclohex-1-ene-1-carboxylate (416)

To a stirred solution of **648** (25 mg, 0.066 mmol) in acetone:H_2O/ 10:1 (0.5 mL) was added sodium azide (43 mg, 0.66 mmol). The resulting solution was stirred at r.t. for 12 h and then concentrated under reduced pressure to provide **ethyl (3a*R*,4*R*,6*S*,7*R*,7a*S*)-7-(acetylamino)-6-azido-2,2-dimethylhexahydro-1,3-benzodioxole-4-carboxylate (656)** which was used without further purification; data for **656**: R_f 0.41 (1: 10 hexanes-ethyl acetate); IR (film) 3583, 3284, 2987, 2108, 1720, 1655, 1540, 1372, 1248, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, J = 7.5 Hz, 1NH), 4.58 (dd, J = 4.0, 4.8 Hz, 1H), 4.43 (dd, J = 4.8, 8.6 Hz, 1H), 4.13-4.29 (m, 2H), 3.91 (dt, J = 3.4, 11.7 Hz, 1H), 3.20 (dd, J = 8.1, 11.1 Hz, 1H), 2.85 (dt, J =

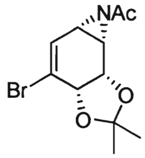
3.9, 13.2 Hz, 1H), 2.17 (dt, $J = 3.9, 13.2$ Hz, 1H), 2.02 (s, 3H), 1.91 (q, $J = 13.1$ Hz, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H) ppm; MS (FAB) *m/z* (%): 327 (M+ H^+), 43(23), 257(100), 299 (33); HRMS calcd for $C_{14}H_{23}N_4O_5$ 327.1668, found 327.1670. To a stirred solution of crude azide in methylene chloride (150 μL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (14.8 μL, 0.099 mmol) at 0 °C. The resulting solution was stirred until complete consumption of starting material (TLC analysis, ~12 h). The reaction was diluted with methylene chloride (500 μL), washed with 1 N HCl (3 x 250 μL), and brine (1 x 500 μL) and then dried over Na_2SO_4. The crude material was purified by flash column chromatography with a solvent system of 1:7 (hexanes-ethyl acetate) to yield **(416)** (15 mg, 86% over 2 steps) as a yellow oil: R_f 0.22 (1:10 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +44.3 (*c* 0.65, $CHCl_3$); IR (film) ν 3509, 2103, 1701, 1690, 1510, 1214 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (t, $J = 2.4$ Hz, 1H), 5.96 (br s, 1NH), 5.28 (br s, 1OH), 4.39 (d, $J = 2.8$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 3.59-3.66 (m, 2H), 2.98 (dd, $J = 4.3, 15.9$ Hz, 1H), 2.42-2.49 (m, 1H), 2.10 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 165.6, 138.1, 127.6, 71.2, 61.4, 57.9, 57.6, 29.5, 23.2, 14.1 ppm; MS (FAB) *m/z* (%): 269 (M+ H^+), 41(44), 43(100), 56(54), 57(46), 84(22), 227 (55); HRMS calcd for $C_{11}H_{17}N_4O_4$ 269.1250, found 269.1248.



428

N-[(3aR,4R,5S,7aS)-4,7-dibromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl]acetamide (428)

To a solution of N-bromoacetamide (309 mg, 2.25 mmol) in acetonitrile (40 mL) was added 0.28 mL $SnBr_4$ (0.4 M in CH_2Cl_2, 0.11 mmol) at -40 °C in the dark. Diene **554** (432 mg; 1.87 mmol) in acetonitrile (20 mL) was added slowly to the reaction mixture by syringe pump at the same temperature over 4 h. The resulting reaction mixture was stirred for 1 h, before saturated aqueous $NaHCO_3$ (10 mL) and Na_2SO_3 (10 mL) were carefully added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on neutral alumina (CH_2Cl_2) to afford bromo amide **2** (526 mg, 76%) as colourless crystals: R_f 0.71 (CH_2Cl_2/MeOH 96:4); mp 181 °C; $[\alpha]_D^{23}$ +188.2 (*c* 0.50, $CHCl_3$); IR (film) ν 3684, 3019, 2400, 1676, 1498, 1425, 1216, 1064, 929, 757, 669, 497, 478, 472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, J = 9.0 Hz, 1H), 4.93 (m, 1H), 4.68 (d, J = 5.1 Hz, 1H), 4.60 (t, J = 4.5 Hz, 1H), 4.21 (t, J = 3.6 Hz, 2H), 1.97 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 128.0, 124.7, 112.0, 77.8, 75.8, 50.3, 44.4, 27.8, 26.5, 23.3 ppm; MS (EI) *m/z* (%): 366 (M), 354(6), 313(6), 294(6), 255(6), 253(12), 251(7), 232(33), 230(34), 190(11), 189(6), 188(12), 187(5), 174(6), 173(10), 172(8), 171(9), 165(8), 163(8), 151(6), 109(22), 108(9), 93(7), 81(8), 80(10), 65(8), 59(11), 55(8), 43(100), 42(11), 41(6); HRMS (EI) calcd for $C_{11}H_{15}O_3NBr_2$ 366.9419, found 366.9418. *Anal.* calcd: C 35.80, H 4.10, found C 35.77, H 4.11.

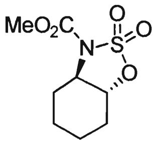


429

(3a*S*,4*S*,5*S*,7a*S*)-8-acetyl-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole (429)

To a solution of amide **428** (17.61 g, 47.72 mmol) in dimethoxyethane (400 mL) was added *n*-Bu_4NBr (16.33 g, 52.49 mmol) at 0 ˚C under argon. At this temperature potassium bis(trimethylsilyl)amide (100 mL, 0.5 M in toluene, 52.49 mmol) was added dropwise. The reaction mixture was stirred for 3 h at 0 ˚C and then quenched by the addition of potassium phosphate monobasic sodium hydroxide (350 mL, set to pH 7). The two-phase mixture was extracted with ethyl acetate (3 x 150 mL) and then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a solvent gradient of 2:1 then 1:1 (hexanes-ethyl acetate) to afford **429** (9.21 g, 67%) as colourless crystals: R_f 0.44 (1:1, hexanes-ethyl acetate); mp 128 ˚C; $[\alpha]_D^{23}$ -57.6 (*c* 0.75, $CHCl_3$); IR (film) ν 3017, 2938, 1704, 1423, 1383, 1372, 1289, 1267, 1216, 1161, 1063, 994, 967, 894, 868, 819, 756, 668, 619, 554, 510, 485, 468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, $J = 4.8$ Hz, 1H), 4.72 (dd, $J = 0.9$, 6.9 Hz, 1H), 4.46 (dd, $J = 4.2$, 6.9 Hz, 1H), 3.19 (dd, $J = 5.1$, 6.0 Hz, 1H), 3.11 (ddd, $J = 0.9$, 6.0, 6.1 Hz, 1H), 2.17 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$)

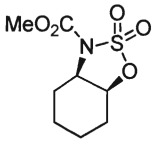
δ 181.7, 129.9, 122.8, 108.5, 76.6, 71.9, 39.6, 36.7, 27.0, 24.9, 23.2 ppm; MS (EI) *m/z* (%) 272 (M^+-CH_3), 232(9), 230(9), 208(5), 190(9), 189(8), 188(9), 187(7), 172(6), 170(5), 160(13), 158(13), 150(18), 109(18), 108(45), 100(23), 85(10), 84(5), 81(9), 80(17), 79(7), 78(7), 59(9), 53(7), 52(6), 51(10), 43(100), 42(6), 41(6); HRMS (EI) calcd for $C_{11}H_{14}O_3NBr$ 287.0157, found 287.0161. *Anal.* calcd: C 45.85, H 4.90, found C 45.84, H 4.95.



459

trans-2,2-Dioxide-hexahydro-3H-1,2,3-benzoxathiazole-3-carboxylic acid, methyl ester (459)

To a solution of oxathiazolidine **466** (140 mg, 0.64 mmol) in CH_3CN (3 mL) was added sequentially ruthenium(III)chloride hydrate (catalytic amount), sodium periodate (205 mg, 0.96 mmol), and H_2O (3 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. was stirred for 3 h. The reaction mixture was extracted three times with Et_2O. The organic layers were combined and washed with H_2O and brine, then dried over anhydrous $MgSO_4$. Filtration, evaporation of the solvent and purification by flash column chromatography (hexanes/ethyl aceate) afforded **459** (130 mg, 87 % as a colourless oil. R_f 0.55 (2:1, hexanes/ethyl aceate); IR (film) *ν* 3367, 2958, 2870, 2255, 1746, 1444, 1384, 1329, 1299, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (dt, J = 11 Hz, 4 Hz, 1H), 3.88 (s, 3H), 3.73–3.84 (m, 1H), 2.59–2.73 (m, 1H), 2.19–2.31 (m, 1H), 1.81–2.05 (m, 2H), 2.05 (dq, J = 12 Hz, 4 Hz, 1H), 1.30–1.58 (m, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 151.6, 84.6, 64.7, 54.9, 29.0, 28.3, 23.7, 23.5 ppm; MS (EI) *m/z* (%): 235, 155 (37), 150 (100), 140 (12), 124 (13), 114 (19), 101 (52), 98 (26), 95 (22), 81 (44)69 (24), 59 (53); HRMS (EI) calcd for $C_8H_{13}NO_5S$: 235.0514, found, 235.0519; *Anal.* calcd: C 40.84, H 5.57, found C 41.18, H 5.84.



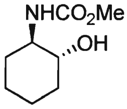
460

cis-Hexahydro-2,2-dioxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid methyl ester (460)

The general procedure for the reaction of oxiranes with the Burgess reagent **(8)** using cyclohexene oxide **(458)** provided **460** in 64% yield (604 mg) as colourless crystals: mp 97-98 °C (ethyl acetate/hexanes); R_f 0.49 (hexanes : ethyl acetate, 1:1); IR (film) ν 2943, 1743, 1385, 1183 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.00 (bs, 1H), 4.22 (bs, 1H), 3.90 (bs, 3H), 2.33 (bs, 2H), 1.45 - 1.85 (m, 4H), 1.16 - 1.33 (m, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.4, 80.0, 58.3, 54.7, 27.4, 27.2, 22.0, 19.1 ppm; HRMS (FAB) (M + H$^+$) calcd for $C_8H_{14}O_5NS$: 236.0593, found 236.0608; *Anal.* calcd for $C_8H_{13}O_5NS$: C 40.84% H 5.70%, found C 40.98% H 5.70%.

Alternatively, compound 460 was prepared by following procedure:

To a solution of oxathiazolidine **469** (300 mg, 1.37 mmol) in CH_3CN (5 mL) was added sequentially, ruthenium(III)chloride hydrate (catalytic amount), sodium periodate (439 mg, 2.05 mmol) and water (5 mL) at 0 °C. The reaction mixture was warmed to r.t. and was stirred for an additional 3 h. The reaction mixture was extracted with Et_2O (3 x 2 mL). The organic layers were combined, washed with water, then brine, and dried over anhydrous Mg_2SO_4. Filtration, evapouration of the solvent, and purification by flash column chromatography (hexanes: ethyl acetate, 4:1) afforded 287 mg (82%) of compound **460*** as white solid after recrystallization from hexanes/ethyl acetate. The analytical data obtained for compound **460*** is identical to data of compound **460**.

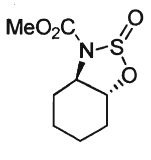


465

***trans*-(2-Hydroxycyclohexyl)carbamic acid, methyl ester (465)**

Methyl chloroformate (0.3 mL, 3.94 mmol) was added dropwise to a vigorously stirred solution of *trans* 2-aminocyclohexanol hydrochloride (**464**) (0.5 g, 3.3 mmol) and $NaHCO_3$ (0.83 g, 9.9 mmol) in a 1:1 mixture of $CHCl_3$ and H_2O (30 mL). The mixture was allowed to stir at r.t. for 1 h, before the reaction mixture was neutralized with 1 M aq HCl. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporation of the solvent and recrystallization from hexanes/ethyl acetate furnished **465** as colourless solid (498 mg, 87%): mp 109–111 °C (hexanes/ethyl acetate); IR (film) *v* 3436, 3156, 2942, 2863, 2253, 1708, 1517, 1452, 1517, 1452, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75–5.15 (bs, 1H), 3.66 (s, 3H), 3.21–3.46 (m, 1H), 2.98–3.18 (bs, 1H), 1.91–2.12 (m, 2H), 1.60-1.79 (m, 2H), 1.05-1.41 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 75.6, 57.5, 52.9, 34.6, 32.2, 25.1, 24.5 ppm; MS

(EI) *m/z* (%): 173, 141 (18), 114 (75), 112 (22), 102 (12), 98 (100), 88 (42), 69 (26), 56 (51), 51 (66); HRMS (EI) calcd for $C_8H_{15}NO_3$: 173.1052, found, 173.1053; *Anal.* calcd: C 55.47, H 8.73; found C 55.16, H 8.73.

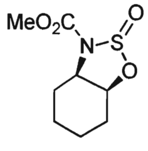


466

(3a*R*,7a*R*)-Hexahydro-2-oxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid, methyl ester (466)

To a solution of thionyl chloride (0.84 mL, 11.6 mmol) in CH_3CN (60 mL) was added a solution of methyl ester **465** (0.8 g, 4.62 mmol) in CH_3CN (20 mL) dropwise at –35 °C over 10 min. The reaction mixture was stirred at the same temperature for 5 min before pyridine (1.8 mL, 23.11 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t. over 3 h. The solvent was evaporated, and the residue was triturated with Et_2O. After filtration, the mixture was concentrated under reduced pressure. Flash column chromatography (hexanes/ethyl acetate, 5:1) of the residue afforded **466** as colourless solid (0.79 g, 78%): mp 51-54 °C; R_f 0.5 (hexanes/ethyl acetate, 2:1); IR (film) *v* 3368, 2954, 2254, 1733, 1572, 1444, 1384, 1328, 1300 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (dt, *J* = 11 Hz, 4 Hz, 1H), 3.83 (s, 3H), 3.13 (dt, *J* = 13 Hz, 3 Hz, 1H), 2.61–2.74 (m, 1H), 2.20–2.34 (m, 1H), 1.79–2.02 (m, 2H), 1.69 (dq, *J* = 12 Hz, 4 Hz, 1H), 1.19–1.54 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 86.8, 63.2, 54.0, 29.8, 29.5, 24.3, 23.9 ppm; MS (EI) *m/z* (%): 219 (5), 140

(10), 114 (100), 81 (12), 59 (24), 44(17); HRMS (EI) calcd for $C_8H_{13}NO_4S$: 219.0565, found, 219.0565; *Anal.* calcd: C 43.82, H 5.98, found: C 44.12, H, 6.05.

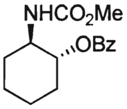


469

cis-Hexahydro-2-oxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid, methyl ester (469)

To a solution of thionyl chloride (0.83 mL, 11.41 mmol) in CH_3CN (60 mL) was added a solution of methyl carbamate **468** (0.79 g, 4.56 mmol) in CH_3CN (20 mL) dropwise at –35 °C over 10 min. The reaction mixture was stirred at –35 °C for 5 min, before pyridine (1.84 mL, 22.82 mmol) was added dropwise. The reaction mixture was warmed to r.t. over 3 h. The solvent was evaporated, and the residue was triturated with Et_2O. The suspension was filtered, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexanes/ethyl acetate, 5:1) afforded 0.63 g (63%) of **469** as colourless oil. R_f 0.75 (hexanes/ethyl acetate, 1:1); IR (film) ν 2943, 2867, 1730, 1442, 1359, 1328, 1288, 1187, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 5.24–5.31 (bs, 0.66H), 4.66 (q, J = 4.0 Hz, 0.33H), 3.94–4.12 (m, 1H), 3.84 (s, 1H), 3.82 (s, 2H), 2.09–2.34 (m, 2H), 1.54–2.45 (m, 4H), 1.33–1.52 (m, 1H), 1.08–1.31 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) (two rotamers) δ 152.9, 85.0, 80.0, 55.6, 54.1, 53.7, 53.6, 28.8, 28.4, 27.9, 26.8, 22.6, 22.2, 19.6, 19.5 ppm; MS (EI) *m/z* (%): 219 (12), 171 (16), 155 (29), 154 (26), 140 (65), 127 (44), 126 (13), 124 (16), 77 (100), 75 (16), 64

(33); HRMS (EI) calcd for $C_8H_{13}NO_4S$: 219.0565, found 219.0561; *Anal.* calcd: C 43.82, H 5.98, found C 43.90, H 6.01.

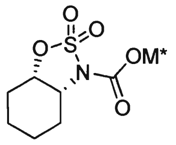


475

trans-2-Methylcarbonylamino-benzoic acid, cyclohexyl ester (475)

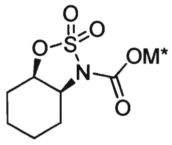
To a solution of benzoxathiazole **460** (550 mg, 2.34 mmol) in dry DMF (10 mL) was added ammonium benzoate (651 mg, 4.68 mmol). The solution was heated to 55 °C until TLC analysis indicated full conversion of the starting material (18 h). The solvent was evapourated, and the residue was dissolved in THF (6 mL), three drops of water and three drops of conc. H_2SO_4 were added. The reaction mixture was stirred at r.t. for 3 h, before the pH was adjusted to 8 with sat. aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The organic layers were combined and washed with H_2O and brine. After the solvent was evaporated under reduced pressure, the residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1) affording 265 mg of colourless oil (41%). R_f 0.55 (hexanes/ethyl acetate, 2:1); IR (film) ν 3339, 3064, 2940, 2861, 1714, 1538, 1452, 1320, 1279, 1235, 1115, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 7.5$ Hz, 2H), 7.55 (m, 1H), 7.43 (t, $J = 7.5$ Hz, 2H), 4.83 (m, 2H), 3.71–3.88 (m, 1H), 3.53 (s, 3H), 2.02–2.24 (m, 2H), 1.69–2.02 (m, 2H), 1.49–1.68 (m, 1H), 1.18–1.48 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 156.8, 133.2, 130.3, 129.9, 128.5, 75.9, 54.5, 52.2, 32.6, 31.3, 24.6, 24.2 ppm; HRMS

(FAB) calcd for $C_{15}H_{20}NO_4$: 278.1392, found, 278.1382; *Anal.* calcd: C 64.97, H 6.91, found C 65.03, H 6.94.



486a

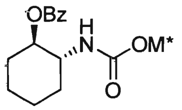
+



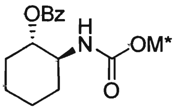
486b

(3a*R*,7a*S*)-*rel*-2,2-Dioxide-hexahydro-3H-1,2,3-benzoxathiazole-3-carboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester (486a and 486b)

The general procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent **(3)** using cyclohexene oxide **(458)** (196 mg, 2.00 mmol) as starting material gave 215 mg (30%) of a 1:1 mixture of diastereomers **486a** and **486b** after purification by flash column chromatography (hexanes/ethyl acetate, 15:1 to 3:1) as colourless oil. R_f 0.65 (hexanes/ethyl acetate, 3:1); $[\alpha]_D^{23}$ –52.2 (*c* 1.00, $CHCl_3$); IR (film) *v* 3401, 2958, 2873, 2254, 1728, 1457, 1383, 1314, 908, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.98–5.04 (bs, 1H), 4.73 (dt, *J* = 10.7, 4.5 Hz, 1H), 4.15–4.27 (m, 1H), 2.28–2.40 (m, 2H), 1.97–2.17 (m, 2H), 1.43–1.89 (m, 9H), 1.02–1.37 (m, 4H), 0.94 (d, *J* = 3.1 Hz, 3H), 0.92 (d, *J* = 3.1 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 79.7, 79.3, 58.2, 58.1, 47.2, 47.1, 41.0, 40.9, 34.3, 31.8, 27.6, 27.5, 27.4, 26.1, 23.5, 23.4, 22.30, 22.25, 21.3, 21.2, 19.3, 16.4, 16.3 ppm; HRMS (EI) calcd for $C_{17}H_{29}NO_5S$: 359.1766, found 359,1761; *Anal.* calcd: C 56.80, H 8.12, found C 57.12, H 8.30.



487a



487b

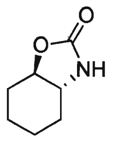
[(1*R*,2*R*)-2-(Benzoyloxy)cyclohexyl]carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (487a) and [(1*S*,2*S*)-2-benzoyloxy)cyclohexyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (487b)

The general procedure for the syntheses of benzoates using a mixture of **486a** and **486b** (449 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers 246 mg (49%), which were separated by flash column chromatography (CH_2Cl_2/MeOH, 200:1).

487a: mp 111–113 °C (ethyl acetate/hexanes); R_f 0.50 (CH_2Cl_2/methanol, 100:1); $[\alpha]_D^{20}$ –77.8 (*c* 1.05, $CHCl_3$); IR (film) *ν* 3434, 3368, 3019, 2954, 2868, 1711, 1603, 1585, 1513, 1452, 1370, 1318, 1279, 1216, 1115, 1038, 1028, 757, 712, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.83 (dt, *J* = 10.6, 4.5 Hz, 1H), 4.59 (d, *J* = 9.3 Hz, 1H), 4.34–4.46 (m, 1H), 3.76–3.90 (m, 1H), 2.07–2.19 (m, 2H), 1.73–1.93 (m, 3H), 1.13–1.69 (m, 10H), 0.91–1.06 (m, 1H), 0.86 (d, *J* = 10.0 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.46–0.68 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 156.5, 133.4, 130.6, 130.2, 128.7, 76.6, 74.7, 54.3, 47.5, 41.2, 34.6, 32.8, 31.5, 26.6, 25.0, 24.5, 23.8, 22.2, 21.1, 16.8 ppm; HRMS (EI) calcd for $C_{24}H_{35}NO_4$: 401.2566, found 401.2579; $C_{24}H_{35}NO_4$(401): calcd. C 71.79, H 8.79, found C 71.82, H 8.80.

487b: mp 138–141 °C (ethyl acetate/hexanes); R_f 0.45 (CH_2Cl_2/MeOH, 100:1); $[\alpha]_D^{20}$ –15.8 (*c* 1.05, $CHCl_3$); IR (film) *ν* 3685, 3435, 3020, 2956, 2869, 1711, 1515, 1452, 1318, 1279, 1216, 1115, 1039, 929, 759, 714, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 8.05 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.86 (dt, *J* = 10.6, 4.5 Hz, 1H), 4.69 (d, *J* = 9.3 Hz, 1H), 4.35–4.49 (m, 1H), 3.73–3.90 (m, 1H), 2.12 (d, *J* = 12.5 Hz, 2H), 1.98 (d, *J* = 11.9 Hz, 1H), 1.73–1.88 (m, 2H), 1.08–1.68 (m, 10H), 0.79–0.97 (m, 5H), 0.55 (d, *J* = 6.4 Hz, 3H), 0.30 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 156.3, 133.3, 130.4, 130.1, 128.7, 76.0, 74.6, 54.4, 47.6, 41.8, 34.6, 33.2, 31.7, 31.6, 26.5, 24.9, 24.5, 23.9, 22.4, 20.7, 16.3 ppm; HRMS (EI) calcd for $C_{24}H_{35}NO_4$: 401.2566, found 401.2575; $C_{24}H_{35}NO_4$(401): calcd. C 71.79, H 8.79, found C 71.84, H 8.76.



488a

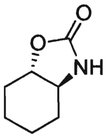
(3a*R*,7a*R*)-3H-Hexahydrobenzoxazolidin-2-one (488a)

Benzoic acid 2-menthylcarbonylaminocyclohexyl ester **487a** (260 mg, 0.65 mmol) was dissolved in 1 M NaOH in MeOH (30 mL), and the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with water (30 mL) and extracted three times with dichloromethane. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Flash column chromatography (hexanes/ethyl acetate, 4:1) of the residue afforded **[(1*R*,2*R*)-2-hydroxycyclohexyl]-carbamic acid menthol ester** as colourless solid (152 mg, 79%): mp 130–132 ˚C (hexanes/ethyl acetate); R_f 0.15 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{20}$ –53.7 (*c* 1.35, $CHCl_3$); IR (film) *v* 3685, 3620, 3020, 2870, 2401, 1693, 1510, 1477, 1451, 1423, 1215, 1046, 1024, 929 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60–4.79 (bs, 1H), 4.53 (dt, *J* = 11.2, 4.0 Hz, 1H), 3.21–

3.44 (m, 2H), 3.00–3.21 (bs, 1H), 1.79–2.09 (m, 4H), 1.54–1.75 (m, 2H), 1.38–1.53 (m, 2H), 0.66–1-38 (m, 17H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 75.8, 75.4, 57.2, 47.7, 41.7, 34.6, 34.5, 32.2, 31.7, 26.6, 25.0, 24.4, 23.8, 22.4, 21.2, 16.8 ppm; MS (EI) *m/z* (%): 297 (1), 158 (10), 139 (27), 138 (17), 115 (19), 114 (28), 98 (100), 97 (21), 96 (19), 95 (23), 83 (90), 82 (14), 81 (43), 71 (21), 70 (10), 69 (46), 67 (13); HRMS (EI) calcd for $C_{17}H_{31}NO_3$: 279.2304, found 297.2298; *Anal.* calcd: C 68.65, H 10.51, found C 68.65, H 10.81.

[(1*R*,2*R*)-2-Hydroxycyclohexyl]- carbamic acid menthyl ester (140 mg, 0.47 mmol) was dissolved in THF (5 mL) and sodium hydride (42 mg, 1.04 mmol) was added in one portion. The reaction mixture was heated at reflux for 12 h until TLC indicated complete conversion of starting material. The reaction mixture was quenched by the addition of an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. Flash column chromatography (hexanes/ethyl acetate, 2:1 to 1:1) of the residue afforded **488a** as colourless solid (55 mg, 83%): mp 133–134 °C (hexanes/ethyl acetate); $[\alpha]_D^{22}$ +7.5 (*c* 1.0, EtOH); R_f 0.45 (hexanes/ethyl acetate, 1:1); IR (film) *v* 3684, 3622, 3020, 1757, 1521, 1476, 1423, 1215, 1034, 929 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96–6.19 (bs, 1H), 3.81 (dt, *J* = 11.1, 4.3 Hz, 1H), 3.16–3.33 (m, 1H), 2.05–2.20 (m, 1H), 1.93–2.05 (m, 1H), 1.67–1.90 (m, 2H), 1.49–1.65 (m, 1H), 1.14–1.47 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 84.2, 61.3, 29.5, 28.9, 24.1, 23.9 ppm; MS (EI) *m/z* (%): 141 (32), 140 (11), 99 (6), 96 (5), 69

(42), 57 (15), 56 (100), 54 (8), 43 (40); HRMS (EI) calcd for $C_7H_{11}NO_2$: 141.0790, found 141.0788.

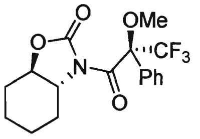


488b

(3a*S*,7a*S*)-3H-Hexahydrobenzoxazolidin-2-one (488b)

Benzoic acid 2-menthylcarbonylamino-cyclohexyl ester **487b** (270 mg, 0.67 mmol) was dissolved in 1 M NaOH in MeOH (30 mL), and the reaction mixture was stirred at r.t. for 10 h, then diluted with water (30 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography (hexanes/ethyl acetate, 4:1) of the residue afforded **488b** as colourless solid (179 mg, 89%): mp 151–153 °C (hexanes/ethylacetate); R_f 0.15 (hexanes/ethyl acetate, 1:1); $[\alpha]_D{}^{20}$ –58.2 (*c* 1.2, $CHCl_3$); IR (film) *ν* 3684, 3621, 3437, 3020, 2939, 2869, 2400, 1693, 1510, 1477, 1451, 1424, 1389, 1215, 1046, 1023, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62–4.85 (bs, 1H), 4.55 (dt, *J* = 11.1, 4.2 Hz, 1H), 3.21–3.42 (m, 2H), 2.98–3.21 (bs, 1H), 1.81–2.14 (m, 4H), 1.56–1.80 (m, 2H), 1.39–1.55 (m, 2H), 0.60–1.39 (m, 17H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 75.8, 75.5, 57.3, 47.9, 41.8, 34.6, 34.5, 32.1, 31.8, 26.6, 25.0, 24.4, 23.8, 22.4, 21.2, 16.8 ppm; MS (EI) *m/z* (%): 297 (1), 160 (8), 159 (8), 158 (9), 139 (24), 138 (17), 115 (19), 114 (28), 98 (100), 97 (22), 96 (23), 95 (30), 83 (96), 82 (18), 81 (49), 71 (29), 70 (13), 69 (54), 67 (17); HRMS (EI) calcd for $C_{17}H_{31}NO_3$: 279.2304, found 297.2303; $C_{17}H_{31}NO_3$(279): calcd. C 68.65, H 10.51, found C 68.82, H 10.79.

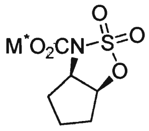
Following the same procedure as for the preparation of compound **488a** using [(*1S,2S*)-2-hydroxycyclohexyl]-carbamic acid menthol ester (160 mg, 0.54 mmol) and sodium hydride (32 mg, 1.33 mmol) as starting materials, gave 62 mg (82%) of compound **488b** as colourless crystals: mp 131–133 °C (hexanes/ethyl acetate); $[\alpha]_D^{22}$ –7.4 (*c* 1.1, EtOH); HRMS (EI) calcd for $C_7H_{11}NO_2$: 141.0790, found 141.0785.



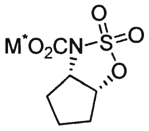
489a

(3a*R*,7a*R*)-3-((*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl)-hexahydrobenzo[d]oxazol-2(3H)-one (489a)

To a solution of cyclic carbamate **488a** (20 mg, 0.14 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (2 M in THF, 78 μL, 0.16 mmol). The reaction mixture was stirred at the same temperature for 1 h then cooled to –78 °C. (*S*)-(+)-Mosher's chloride (43 mg, 0.17 mmol) was added, and the reaction mixture was warmed to r.t. over 14 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 x 2 mL). The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. The organic layer was filtered and the solvent was evaporated. The crude residue was analyzed by ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.61 (not detected), –69.30 (1F). Compound **489b** as well as a racemic standard were prepared in the same manner, using **488b** and a racemate of **488** as starting materials. Compound **489a**: ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.61 (1F), –69.31 (0.035F), Compound **489**: –72.61 (1F), –69.30 (1F). The results were confirmed by GC/MS analysis.



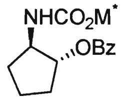
491a



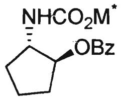
491b

(3a*R*,6a*S*)-*rel*-2,2-Dioxide-tetrahydro-3(3aH)-cyclopent-1,2,3-oxathiazolecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester (491a and 491b)

The general procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent **(3)** using cyclopentene oxide (**490**) (168 mg, 2.00 mmol) as starting material gave 305 mg (37%) of a 1:1 mixture of diastereomers **491a** and **491b** after purification by flash column chromatography (hexanes/ethyl acetate, 15:1 to 3:1). Colourless oil; R_f 0.81 (hexanes/ethyl acetate, 2:1); $[\alpha]_D^{23}$ –79.2 (*c* 1.02, $CHCl_3$); IR (film) *v* 3400, 3019, 2962, 2400, 1731, 1522, 1423, 1383, 1307, 1030, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (t, *J* = 5.3 Hz, 1H), 4.74 (dt, *J* = 10.9, 4.4 Hz, 1H), 4.55 –4.63 (m, 1H), 2.08–2.15 (m, 5H), 1.81–1.89 (m, 2H), 1.66–1.74 (m, 2H), 1.42–1.50 (m, 2H), 1.10–1.18 (m, 2H), 0.88–0.95 (m, 7H), 0.76–0.85 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 83.8, 79.1, 78.3, 71.2, 61.4, 61.3, 46.7, 40.6, 40.5, 33.9, 32.75, 32.7, 32.3, 31.4, 31.4, 26.2, 26.0, 25.6, 23.3, 23.2, 22.9, 22.6, 21.9, 20.8, 20.8 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{16}H_{27}NO_5S$: 346.1688, found 346.1659.



492a



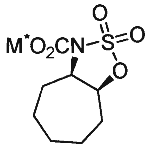
492b

trans-2-(Benzoyloxy)cyclopentyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (492a and 492b)

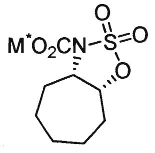
The general procedure for the syntheses of benzoates using a mixture of **491a** and **491b** (433 mg, 1.25 mmol) as the starting material gave a mixture of diastereomers **492a** and **492b** (252 mg, 52%), which were separated by flash column chromatography (CH_2Cl_2/MeOH, 200:1).

492a: mp 85–86 °C (ethyl acetate/hexanes); R_f 0.73 (CH_2Cl_2/MeOH; 400:1); $[\alpha]_D^{23}$ –99.6 (*c* 1.00, $CHCl_3$); IR (film) *v* 3684, 3019, 2961, 2400, 1711, 1512, 1424, 1031, 929, 669, 627 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.42–7.52 (m, 3H), 5.16 (q, *J* = 5.8 Hz, 1H), 4.91 (bs, 1H), 4.40–4.48 (m, 1H), 4.03–4.12 (m, 1H), 2.19–2.23 (m, 2H), 1.73–1.85 (m, 5H), 1.51–1.58 (m, 7H), 1.20–1.25 (m, 2H), 0.67–0.85 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 132.9, 130.2, 129.7, 128.3, 80.4, 75.0, 47.3, 41.3, 34.2, 31.3, 26.2, 22.0, 20.8 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{23}H_{33}NO_4$: 388.2488, found 388.2474.

492b: mp 86–89 °C (ethyl acetate/hexanes); R_f 0.70 (CH_2Cl_2/MeOH, 400:1); $[\alpha]_D^{23}$ –5.59 (*c* 1.05, $CHCl_3$); IR (film) *v* 3436, 3019, 2960, 2400, 1711, 1512, 1037, 929, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 6.9 Hz, 2H), 7.50–7.57 (m, 3H) 5.11–5.19 (m, 1H), 4.78–4.82 (m, 1H), 4.52–4.57 (m, 1H), 4.11–4.14 (m, 1H), 2.11–2.21 (m, 2H), 1.80–1.83 (m, 1H), 1.72–1.79 (m, 4H), 1.46–1.58 (m, 6H), 1.38–1.45 (m, 4H), 0.80–1.25 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 132.9, 130.2, 129.7, 128.3, 80.1, 74.7, 47.3, 41.4, 34.2, 31.3, 29.7, 26.2, 23.5, 22.0, 20.7, 16.3 ppm; HRMS (FAB) (M+H$^+$) calcd for $C_{23}H_{33}NO_4$: 388.2488, found 388.2481.



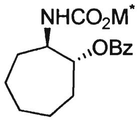
494a

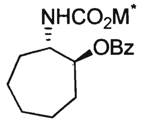


494b

(3a*R*,8a*S*)-*rel*-2,2-dioxide-hexahydro-cyclohept-1,2,3-oxathiazole-3(3aH)-carboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester (494a and 494b)

The general procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent **(3)** cyclohepteneoxide **(493)** (224 mg, 2.00 mmol) as starting material gave 211 mg (35%) of a 1:1 mixture of diastereomers **494a** and **494b** after purification by flash column chromatography (hexanes/ethyl acetate, 15:1 to 4:1). colourless oil; R_f 0.57 (hexanes/ethyl acetate, 4:1); $[\alpha]_D^{23}$ –60.5 (*c* 0.75, $CHCl_3$); IR (film) *v* 2958, 2931, 1729, 1457, 1381, 1332, 1307, 1190 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00–5.17 (m, 1H), 4.72 (dt, *J* = 11.0, 4.5 Hz, 1H), 4.21–4.36 (m, 1H), 2.20–2.37 (m, 1H), 1.63–2.18 (m, 10H), 1.35–1.58 (m, 4H), 1.03–1.33 (m, 3H), 0.85–1.00 (m, 8H), 0.71–0.84 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 149.8, 81.6, 81.6, 79.1, 79.0, 63.1, 63.0, 46.8, 46.7, 40.6, 40.5, 33.9, 31.5, 31.4, 30.2, 30.2, 29.2, 28.6, 28.5, 26.0, 25.9, 25.6, 23.3, 22.9, 22.6, 21.9, 21.6, 20.9, 20.8, 15.8 ppm; MS (FAB) *m/z* (%) 374 (M+H$^+$): 139 (52), 137 (22), 97 (19), 95 (44), 83 (100), 81 (37), 79 (11), 77 (12), 69 (46), 67 (21), 57 (36), 55 (62), 53 (14); HRMS (FAB) (M+H$^+$) Calcd for $C_{18}H_{33}NO_5S$: 374.2001, found 374.2018.


495a

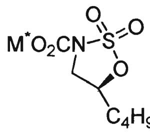

495b

trans-2-(Benzoyloxy)cycloheptyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (495a and 495b)

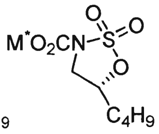
The general procedure for the syntheses of benzoates with a mixture of **494a** and **494b** (468 mg, 1.25 mmol) as starting material gave a mixture of two diastereomers **495a** and **495b** 389 mg (75%), which were separated by flash column chromatography (CH_2Cl_2/MeOH, 200:1).

495a: mp 89–91 °C (ethyl acetate/hexanes); R_f 0.55 (CH_2Cl_2/MeOH, 100:1); $[\alpha]_D^{23}$ –105.1 (*c* 0.8, $CHCl_3$); IR (film) *v* 3363, 2930, 2867, 1714, 1602, 1585, 1526, 1452, 1370, 1316, 1279, 1239,1179, 1117, 1070, 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 4.91 (dt, *J* = 9.0, 3.4 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.28–4.36 (m, 1H), 3.83–3.93 (m, 1H), 1.85–1.94 (m, 2H), 1.74–1.93 (m, 2H), 1.47–1.71 (m, 10H), 1.36–1.44 (m, 1H), 1.16–1.27 (m, 1H), 0.89–1.02 (m, 1H), 0.81–0.88 (m, 2H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H), 0.56–0.61 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 155.9, 132.9, 130.3, 129.8, 128.3, 127.8, 78.4, 74.4, 56.2, 47.2, 40.9, 34.2, 32.0, 31.2, 26.2, 25.9, 23.9, 23.5, 22.4, 21.9, 20.7, 16.5 ppm; MS (EI) *m/z* (%): 415 (1), 137 (13), 123 (11), 111 (20), 105 (100), 97 (11), 95 (27), 83 (44), 82 (11), 81 (20), 77 (23), 71 (25), 69 (26), 67 (10), 57 (29), 56 (26), 55 (30); HRMS (EI) calcd for $C_{25}H_{37}NO_4$: 415.2723, found 415.2715.

495b: mp 121–124 °C (ethyl acetate/hexanes); R_f 0.50 (CH_2Cl_2/MeOH, 100:1); $[\alpha]_D^{23}$ –37.6 (*c* 0.75, $CHCl_3$); IR (film) *v* 3369, 2928, 2866, 1714, 1524, 1452, 1369, 1315, 1279, 1180, 1116, 1070, 1028 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.96 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 4.93 (dt, J = 8.7, 3.7 Hz, 1H), 4.69–4.77 (m, 1H), 4.29–4.40 (m, 1H), 3.85–3.94 (m, 1H), 1.77–1.93 (m, 4H), 1.64–1.74 (m, 2H), 1.43–1.62 (m, 8H), 1.31–1.41 (m, 1H), 1.04–1.11 (m, 1H), 0.76–0.88 (m, 5H), 0.66–0.73 (m, 1H), 0.49 (d, J = 5.3 Hz, 3H), 0.27 (d, J = 0.48 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ 166.6, 155.8, 132.9, 130.3, 129.7, 128.3, 127.8, 78.2, 74.3, 56.5, 47.3, 41.5, 34.3, 32.2, 31.3, 27.5, 26.2, 24.0, 23.6, 22.4, 22.0, 20.4, 16.1 ppm; MS (EI) *m/z* (%): 415 (1), 155 (10), 138 (18), 137 (14), 123 (16), 111 (20), 105 (100), 97 (11), 96 (12), 95 (43), 94 (10), 83 (47), 82 (16), 81 (31), 77 (23), 71 (28), 69 (34), 67 (14), 57 (32), 56 (25), 55 (37); HRMS (EI) calcd for C$_{25}$H$_{37}$NO$_4$: 415.2723, found 415.2720.



497a

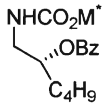


497b

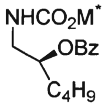
5-Butyl-2,2-dioxide-1,2,3-oxathiazolidine-3-carboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester (497a and 497b)

The general procedure for the reaction of oxiranes with the (–)-menthyl Burgess reagent **(3)** using 2-butyloxirane **(496)** (200 mg, 2.00 mmol) as starting material gave 159 mg (22%) of a 1:1 mixture of diastereomers **497a** and **497b** after purification by flash column chromatography (hexanes/ethyl acetate, 20:1 to 5:1). Colourless oil; R$_f$ 0.68 (hexanes/ethyl acetate, 5:1); [α]$_D^{23}$ –51.7 (*c* 2.3, CHCl$_3$); IR (film) ν 3019, 2961, 2400, 1730, 1384, 1316, 1215, 1046, 928, 724, 669 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.71–4.84 (m, 1H), 4.58–4.71 (m, 1H), 3.90–4.09 (m, 1H), 3.57–3.71 (m, 1H), 2.10

(m, 3H), 1.52–1.77 (m, 4H), 1.25–1.53 (m, 6H), 1.16–1.23 (s, 3H), 0.92–1.12 (m, 2H), 0.85–0.91 (m, 6H), 0.70–0.74 (m, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 149.8, 79.9, 79.2, 50.6, 46.7, 40.5, 33.9, 32.1, 31.4, 29.7, 26.6, 25.8, 23.1, 22.1, 21.9, 20.8, 16.0, 13.7 ppm; MS (EI) *m/z* (%) 361 (1), 176 (44), 83 (88), 42 (60), 43 (39), 54 (31), 55 (61); HRMS (EI) calcd for $C_{17}H_{31}NO_5S$: 361.1923, found 361.1920.



498a

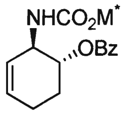


498b

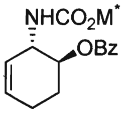
[2-(Benzoyloxy)hexyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2- (1-methylethyl)cyclohexyl ester (498a and 498b)

The general procedure for the syntheses of benzoates with a mixture of **497a** and **497b** (451 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers **498a** and **498b** (181 mg, 36%), which were inseparable by flash column chromatography: mp 121–124 °C (ethyl acetate/hexanes); R$_f$ 0.50 (CH$_2$Cl$_2$/MeOH, 100:1); $[\alpha]_D^{23}$ –37.6 (*c* 0.75, CHCl$_3$); IR (film) *v* 3684, 3401, 3019, 2961, 2400, 1713, 1517, 1423, 1215, 1046, 929, 641, 669, 627 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.97 (d, *J* = 7.3, 2H), 7.46–7.54 (m, 1H), 7.33–7.43 (m, 2H), 5.03–5.20 (m, 1H), 4.70–4.86 (m, 1H), 4.35–4.54 (m, 1H), 3.33–3.49 (m, 2H), 1.88–2.01 (m, 1H), 1.72–1.88 (m, 2H), 1.46–1.73 (m, 6H), 1.23–1.44 (m, 6H), 1.08–1.22 (m, 2H), 0.90–1.06 (m, 2H), 0.77–0.88 (m, 3H), 0.64–0.75 (m, 4H), 0.58 (d, *J* = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.9, 154.0, 130.6, 127.2, 125.9, 72.2, 71.7, 44.9, 41.9, 38.9, 31.8, 29.0, 28.9, 28.8, 24.9, 23.8, 21.1, 20.1, 19.6, 18.3, 13.9, 13.9, 11.5 ppm; MS (EI) *m/z*

(%) 403 (1), 221 (15), 176 (13), 55 (61), 54 (31), 43 (37); HRMS (EI) calcd for $C_{24}H_{37}NO_4$: 403.2723, found 403.2720.



499a



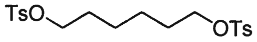
499b

[(1*S*,6*R*)-2-(Benzoyloxy)cyclohex-2-enyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (499a) and [(1*R*,6*S*)-2-(benzoyloxy)cyclohex-2-enyl]-carbamic acid, (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (499b)

The general procedure for the syntheses of benzoates using a mixture of **5a** and **5b** (446 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers **499a** and **499b** (254 mg, 51%), which were separated by flash column chromatography (CH_2Cl_2/MeOH, 400:1).

499a: mp 103–105 °C (ethyl acetate/hexanes); R_f 0.67 (CH_2Cl_2/MeOH, 400:1); $[\alpha]_D^{23}$ –100.8 (*c* 0.25, $CHCl_3$); IR (film) *v* 3436, 3019, 2962, 1713, 1602, 1511, 1424, 1277, 1117, 1048, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.85 (d, *J* = 10.2 Hz, 1H), 5.69 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.04–5.11 (m, 1H), 4.66 (d, *J* = 9.2 Hz, 1H), 4.52–4.62 (m, 1H), 4.46 (dt, *J* = 10.7, 3.9 Hz, 1H), 2.25–2.28 (m, 2H), 2.08–2.11 (m, 1H), 1.96–2.00 (m, 1H), 1.88–1.93 (m, 1H), 1.59–1.72 (m, 4H), 1.26–1.42 (m, 2H), 1.21–1.25 (m, 1H), 0.98–1.04 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 5.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 156.2, 133.0, 130.2, 129.8, 129.5, 128.4, 128.3, 126.8, 77.2, 74.8, 73.9, 51.7, 47.2, 41.0, 34.2, 31.2, 26.4, 26.3, 24.0, 23.5, 21.9, 20.8, 16.5 ppm; HRMS (EI) calcd for $C_{24}H_{33}NO_4$: 399.2410, found 399.2403; *Anal.* calcd: C 72.15, H 8.33, found C 72.42, H 8.44.

499b: mp 107–109 °C (ethyl acetate/hexanes); R_f 0.62 (CH_2Cl_2/MeOH, 400:1); $[\alpha]_D^{23}$ +16.2 (*c* 0.4, $CHCl_3$); IR (film) *v* 3369, 3033, 2954, 2928, 2869, 1714, 1523, 1277, 1241, 1116, 1027 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.84 (d, *J* = 8.6 Hz, 1H), 5.59 (dq, *J* = 9.8, 2.2 Hz, 1H), 5.04–5.12 (m, 1H), 4.70 (d, *J* = 9.5 Hz, 1H), 4.55–4.61 (m, 1H), 4.49 (td, *J* = 10.8, 3.7 Hz, 1H), 2.23–2.29 (m, 2H), 2.06–2.13 (m, 1H), 1.91–2.03 (m, 2H), 1.54–1.71 (m, 3H), 1.41–1.49 (m, 1H), 1.21 (t, *J* = 11.5 Hz, 1H), 0.85–0.97 (m, 6H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.42 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 156.0, 132.9, 130.1, 129.8, 129.3, 128.3, 127.0, 74.5, 73.7, 51.7, 47.3, 41.4, 34.2, 31.3, 26.6, 26.2, 24.0, 23.5, 22.0, 20.5, 16.1 ppm; HRMS (EI) calcd for $C_{24}H_{33}NO_4$: 399.2410, found 399.2410.

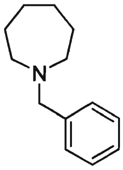


509

1,6-bis(4-methylbenzenesulfonate) 1,6-Hexanediol (509)

To a stirred solution of 1,6-hexanediol **(508)** (1 g, 8.47 mmol), pyridine (1.36 mL, 16.9 mmol), and DMAP (catalytic amount) in DCM (5 mL) was added *p*TsOH (2.91 g, 16.9 mmol) in 3 equal portions over 30 min at 0 °C. The reacton was allowed to stir for 12 h before diluting with DCM (5 mL) and washed with 1 N HCl (2 x 2 mL), brine (1 x 3 mL) and dried over Na_2SO_4. The crude material was recrystallized from ethyl acetate-hexanes to yield **509** (3.14 g, 87%). IR (film) v 3436, 2095, 1644, 1352,

1172, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.28 (m, 4H), 1.52-1.59 (m, 4H), 2.43 (s, 6 H), 3.96 (t, *J* = 6.4 Hz, 4H), 7.32 (d, *J* = 8.3 Hz, 4H), 7.75 (d, *J* = 8.3 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 24.8, 28.6, 70.2, 127.9, 129.9, 133.4, 133.1, 144.8 ppm; MS (EI) *m/z* (%): 426 (M); 41(14), 54(11), 55(24), 67(10), 82(12), 83(100), 91(49), 155(19), 172(11.5), 173(17.1); HRMS calcd for $C_{20}H_{26}O_6S_2$ 426.1170, found 426.1171

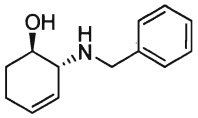


510

N-benzylazepane (510)

Method 1: To a round-bottomed flask charged with abs. EtOH (10 mL), **509** (1.0 g, 2.34 mmol) and benzylamine (0.75 g, 7.0 mmol). The resulting solution was brought to reflux (78 ˚C) and stirred for 48 h before cooling then diluting in 15 mL DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and then filtered through a sintered glass funnel. The resulting crude mixture was subjected to flash column chromatography with a solvent gradient of 5:1, 3:1, 2:1 and 1:1(hexanes-ethyl acetate) to yield **510** (88 mg, 20%) as a clear oil.

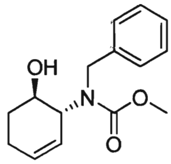
Method 2: To a round-bottomed flask charged with toluene (4 mL), $[Cp^*IrCl_2]_2$ (33 mg, 0.42 mmol), and $NaHCO_3$ (7 mg, 0.085 mmol) was added benzylamine (1.83 g, 17.09 mmol) in a was added dropwise over a period of 1 min before the addition of 1,6-hexane diol **(508)** (2.0 g, 16.9 mmol). The resulting solution was brought to reflux (110 ˚C) and stirred for 48 h before cooling, and concentrating under reduced pressure. The crude mixture was subjected to flash column chromatography with a solvent gradient of 3:1, 1:2, and 1:8 (hexanes-ethyl acetate) to yield **510** (53 mg, 67%) as a clear oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.52-1.67 (m, 8H), 2.53-2.61 (m, 4H), 3.61 (s, 2H), 7.16-7.33 (m, 5H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 27.1, 28.3, 55.5, 62.8, 126.5, 127.9, 128.5, 139.9 ppm; HRMS calcd for $C_{13}H_{19}N$ 189.1517, found 189.1518.



514

2-Benzylamino-cyclohex-3-enol (514)

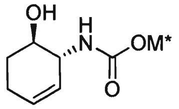
A sealed tube was charged with *iso*-propanol (80 mL), oxirane **4** (10.0 g, 104 mmol), and benzylamine (11.1 g, 104 mmol) and then stirred at 80 ˚C for 6 h before the solvent was removed under reduced pressure. Recrystallization of the crude material from ethyl ether-hexanes yielded **514** (18.9 g, 88%) as a white solid. mp 54-57 ˚C (ethyl ether-hexanes); R_f 0.42 (1:1 hexanes-ethyl acetate); IR (film) ν 3305, 3062, 3026, 2924, 2838, 1454, 1066, 699 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.55-1.78 (m, 1H), 1.84-1.97 (m, 1H), 2.03-2.17 (m, 2H), 3.53-3.85 (m, 4H), 4.33 (d, J = 16.0, 1H), 4.51 (d, J = 17.3, 1H), 4.61-4.83 (m, 1H), 5.33 (d, J = 9.6, 1H), 5.61-5.88 (m, 1H), 7.10-7.45 (m, 5H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.5, 128.5, 128.4, 128.3, 127.1, 126.8, 71.0, 61.1, 50.6, 29.0, 24.8; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1307; *Anal.* calcd: C 76.81, H 8.43, found C 76.88, H 8.44.



515

Benzyl-(6-hydroxy-cyclohex-2-enyl)-carbamic acid methyl ester (515)

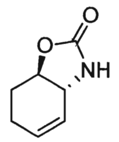
To a stirred solution of **514** (9.25 g, 45.5 mmol) and Na_2CO_3 (9.65 g, 91.0 mmol) in THF (75 mL) was added methyl chloroformate (4.30 g, 45.5 mmol) in 2 equal portions over 30 min. The reaction was stirred at r.t. for 14 h, concentrated and then extracted into DCM (5 x 40 mL). The combined organic layers were washed with 1 N HCl (3 x 10 mL), then dried over Na_2SO_4. The crude material was subjected to flash column chromatography with a solvent gradient of 3:1, 1:1 hexanes-ethyl acetate to yield **515** (10.2 g, 86%) as a clear oil; R_f 0.52 (2:1 hexanes-ethyl acetate); IR (film) ν 3426, 3063, 3029, 2933, 1682, 1469, 1452, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-1.78 (m, 1H), 1.84-1.97 (m, 1H), 2.03-2.17 (m, 2H), 3.53-3.85 (m, 4H), 4.33 (d, *J* = 16.0, 1H), 4.51 (d, *J* = 17.3, 1H), 4.61-4.83 (m, 1H), 5.33 (d, J = 9.6, 1H), 5.61-5.88 (m, 1H), 7.10-7.45 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO) δ 24.7, 30.6, 47.7, 53.0, 61.8, 70.1, 126.6, 127.0, 128.6, 131.1, 139.4 ppm; MS (EI) *m/z* (%):261 (M), 91(100), 217(39); HRMS calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1366; *Anal.* calcd: C 68.94, H 7.33, found C 68.87, H 7.22.



528a

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl [(1*R*,6*R*)-6-hydroxycyclohex-2-en-1-yl]carbamate (528a)

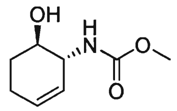
A round-bottomed flask was charged with benzoate **499a** (122 mg, 0.305 mmol) and 1 N NaOH (12 mL) in methanol. The resulting solution was stirred at r.t. for 1 h, and then concentrated before the residue was dissolved in 5 mL of water, and the aqueous layer was extracted with CH_2Cl_2 (3 x 7 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evapourated to give the crude product. Recrystallization of the crude material from ethyl ether-hexanes afforded 85 mg (94%) of **528a** as a white solid: mp 115-116 ˚C (ethyl ether-hexanes); R_f 0.44 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –72.9 (*c* 0.775, $CHCl_3$); IR (film) ν 3435, 2955, 2869, 1645, 1529, 1455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 2.2 Hz, 3H), 0.86 (d, *J* = 2.2 Hz, 3H), 0.89-1.07 (m, 2H), 1.21-1.32 (m, 1H), 1.36-1.48 (m, 1H), 1.54-1.63 (m, 2H), 1.63-1.69 (m, 1H), 1.82-1.96 (m, 2H), 1.96-2.02 (m, 1H), 2.03-2.13 (m, 2H), 3.01-3.18 (br s, 1H), 3.60 (dq, *J* = 10.7 Hz, 3.6, 1H), 3.96-4.16 (m, 1H), 4.51 (td, *J* = 9.9, 1.6 Hz, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 5.36 (d, *J* = 9.8 Hz, 1H), 5.77 (d, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.4, 20.8, 22.0, 23.4, 23.9, 26.2, 28.9, 31.3, 34.2, 41.3, 47.3, 55.3, 73.2, 75.4, 125.4, 130.9, 157.8 ppm; MS (EI) *m/z* (%): 295; 41(58), 43(43), 54(29), 55(56), 56(21), 57(34), 67(67), 68(23), 69(70), 71(68), 81(61), 82(32), 83(66), 95(100), 96(31), 113(75), 123(28), 138(29); HRMS calcd for $C_{17}H_{29}NO_3$ 295.2147, found 295.2147; *Anal.* calcd: C 69.12, H 9.89, found C 68.86, H 9.89.



529a

(3a*R*,7a*R*)-3a,6,7,7a-tetrahydro-1,3-benzoxazol-2(3*H*)-one (529a)

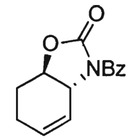
To a suspension of NaH (60% in mineral oil, 33 mg, 1.35 mmol, prewashed with hexanes (5 mL x 3) in THF (15 mL) at 0 °C was added dropwise to a solution of alcohol **528a** (200 mg, 6.77 mmol) in freshly distilled THF (7 mL), then the reaction mixture was brought to reflux. After stirring for 12 h, the mixture was cooled to r.t. and the reaction was quenched by the addition of saturated NH_4Cl and then concentrated before extracting the aqueous layer with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evapourated to give the crude product. Recrystallization of the crude material from ethyl ether-hexanes to afforded 81 mg (86%) of the title compound as a white solid: mp 114-115 °C (ethyl ether-hexanes); R_f 0.36 (1:1 hexane-ethyl acetate); $[\alpha]_D^{23}$ -37.7 (*c* 1.37, $CHCl_3$); IR (film) ν 3854, 3435, 3020, 1751, 1644, 1216, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (td, *J* = 9.8, 0.94 Hz, 1H), 2.21-2.28 (m, 1H), 2.29-2.50 (m, 2H), 4.07 (t, *J* = 11.4 Hz, 1H), 4.14 (td, *J* = 12.3, 1.1 Hz, 1H), 5.50-5.65 (m, 1H), 5.85 (dd, *J* = 9.1, 0.77 Hz, 1H), 5.88-6.15 (br s, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.5, 25.3, 58.1, 81.3, 123.9, 128.4, 161.6 ppm; MS (EI) *m/z* (%): 139; 41(22), 54(100), 55(11), 67(55), 68(17), 95(13), 111(26); HRMS calcd for $C_7H_9NO_2$ 139.0633, found 139.0632; *Anal.* calcd: C 60.42, H 6.52, found C 60.55, H 6.62.



530

(6-Hydroxy-cyclohex-2-enyl)-carbamic acid methyl ester (530)

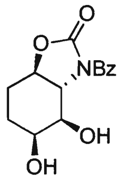
A round-bottomed flask was fitted with a cold finger gas trap, cooled to -45 °C, charged with NH$_3$ gas until ~120 mL had condensed and then charged with freshly cut Na (1.43 mg, 0.016 mol). The resulting suspension was stirred for 5 min before the addition of **515** (8.15 g, 0.031 mol) dropwise as a THF (20 mL) solution. The resulting mixture was stirred for 2 h before the slow addition of NaHCO$_3$ (10 mL). All volatile components were removed under reduced pressure, before the aqueous layer was extracted with DCM (5 x 30 mL) and dried over Na$_2$SO$_4$. Recrystallization from ethyl ether-hexanes yielded **530** as a white solid (4.92 g, 92%); mp 81-82 °C (ethyl ether-hexanes); R$_f$ 0.33 (1:2 hexanes-ethyl acetate); IR (film) ν 3429, 2951, 2105, 1648, 1536, 754 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.65-1.78 (m, 1H), 1.94-2.04 (m, 1H), 2.12-2.23 3.65-3.71 (m, 1H), 3.74 (s, 3H), 4.10- 4.26 (m, 1H), 4.98 (d, *J*= 6.3 Hz, 1H), 5.46 (d, *J* = 9.5 Hz, 1H), (m, 2H), 5.86 (d, *J* = 9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-D$_6$) δ 24.0, 29.0, 52.5, 55.4, 72.7, 125.5, 130.8, 158.2 ppm; MS (EI) *m/z* (%):171, 41(14), 59(14), 67(12), 68(35), 127(100), 128(10); HRMS calcd for C$_8$H$_{13}$NO$_3$ 171.0895, found 171.0897; *Anal.* calcd: C 56.13, H 7.65, found C 56.31, H 7.69.



531

trans-3-benzoyl-3a,6,7,7a-tetrahydro-1,3-benzoxazol-2(3*H*)-one (531)

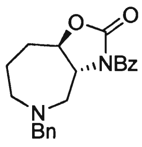
To a stirred solution of cyclic carbamate **529** (55 mg, 0.395 mmol), triethylamine (48 mg, 0.474 mmol), and DMAP (10 mg, 0.079 mmol) in DCM (1 mL) was added benzoyl chloride (66 mg, 0.474 mmol). The reaction was stirred at room temperature for 1.5 h before diluting with DCM (5 mL). The organic layer was washed with cold 1 N HCl (3 x 1 mL), sat. $NaHCO_3$ (1 x 1 mL) and then extracted into DCM (5 x 5 mL). The crude material was subjected to flash column chromatography with a solvent gradient of 12:1, then 5:1 hexane-ethyl acetate to yield **531** (74mg, 77%) as a white solid. mp 159-161 ˚C R_f 0.45 (1:2 hexanes-ethyl acetate); IR (film) ν 3019, 2400, 1793, 1423, 1215, 767, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87-2.19 (m, 1H), 2.27-2.60 (m, 3H), 4.30-4.46 (m, 1H), 4.55 (d, *J* = 10.7 Hz, 1H), 5.62-5.83 (m, 1H), 6.22 (dd, *J* = 9.8 Hz, 1.5 Hz, 1H), 7.55-7.68 (m, 2H), 7.80 (d, *J* = 7.3 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4. 25.3, 60.3, 78.6, 122.9, 128.1, 128.9, 129.8, 132.8, 133.1, 155.0, 171.0 ppm; MS (EI) *m/z* (%):243 (M), 77(36), 105(100), 106(11); HRMS calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0895; *Anal.* calcd: C 69.12, H 5.39, found C 69.14, H 5.44.



532

3-benzoyl-4,5-dihydroxyhexahydro-1,3-benzoxazol-2(3*H*)-one (532)

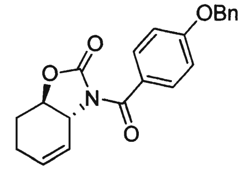
To a stirred solution of olefin **531** (100 mg, 0.286 mmol), 4-methylmorpholine *N*-oxide (25 mg, 0.216 mmol), in DCM (3 mL) with H_2O (3 drops) was added Osmium(VIII)tetroxide (1 crystal). The reaction was stirred at r.t. for 6 h before filtering through celite and concentrating. The crude material was subjected to flash column chromatography with a solvent gradient of 1:1, then 1:3 hexanes-ethyl acetate to yield **532** (97 mg, 89%) as a white solid; mp 184-186 °C (ethyl ether-hexanes); R_f 0.57 (1:4 hexanes-ethyl acetate); IR (film) 3380, 3019, 1799, 1688, 1354, 1330, 1215, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57-1.80 (m, 3H), 2.00-2.13 (m, 1H), 2.46-2.48 (m, 1H), 3.57-3.73 (m, 1H), 3.93 (dd, *J* = 10.9 Hz, 0.61 Hz), 4.46 (s, 1H), 4.52-4.66 (m, 1H), 4.78 (d, *J* = 5.9 Hz, 2H), 5.22 (d, *J* = 3.9 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H) 7.70 (d, *J* = 7.9 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO) δ 24.9, 26.9, 64.1, 66.9, 69.3, 74.9, 128.5, 129.8, 133.3, 133.6, 155.1, 170.8 ppm; MS (EI) *m/z* (%):277 (M), 77(26), 105(100); HRMS calcd for $C_{14}H_{15}NO_5$ 277.0950, found 277.0950.



534

***trans*-5-Benzyl-3-benzoyl-octahydro-1-oxa-3,5-diaza-azulen-2-one (534)**

To a stirred solution of **532** (170 mg, 0.614 mmol) in acetone (10 mL) was added a suspension of $NaIO_4$ (525 mg, 2.45 mmol) in distilled water. The reaction was stirred at room temperature for 4 h, then the solvent was removed. The crude residue was triturated with ethyl acetate (3 x 10 mL), then washed with brine (2 x 10 mL). The resulting solution was filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4*S*,5*R*)-3-benzoyl-2-oxo-5-(3-oxopropyl)-1,3-oxazolidine-4-carbaldehyde (533)** which was used without further purification. Dialdehyde **533** was dissolved in dry MeOH (9 mL) and cooled to −78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (300 mg), followed by $NaCNBH_3$ (42 mg, 0.676 mmol) then AcOH (70 μL, 1.23 mmol) and finally benzylamine (80 μL, 0.737 mmol). The reaction was warmed to r.t. slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 x 10 mL) and washed with $NaHCO_3$ (1 x 5 mL). The organic layer was washed with brine (5 mL), then dried with Na_2SO_4 before concentrating. The crude material was purified via column chromatogrpahy to yield 133 mg (62%) of the title compound as a pale yellow oil: R_f 0.62 (1:2 hexanes-ethyl acetate); IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69-1.78 (m, 3H), 2.33-2.45 (m, 1H), 2.50-2.73 (m, 1H), 3.40-3.47 (m, 1H), 3.68 (q, *J* = 18.6 Hz, 2H), 4.39 (q, *J* = 8.7 Hz, 2H), 4.90 (t, *J* = 8.5 Hz, 1H), 5.11 (s, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.28-7.44 (m, 10H), 7.74 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 31.2, 51.4, 55.3, 61.8, 63.0, 70.1, 78.0, 114.1, 125.2, 127.2, 127.5, 128.2, 128.4, 128.7, 132.3, 136.1, 138.9, 154.1, 162.8, 169.7 ppm; MS (EI) *m/z* (%): 412 (M–CO_2); 44(20), 91(100), 160(76), 161(10); HRMS (M–CO_2) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151.

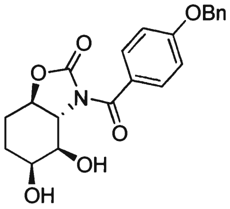


536a

(3a*R*,7a*R*)-3-[4-(benzyloxy)benzoyl]-3a,6,7,7a-tetrahydro-1,3-benzoxazol-2(3*H*)-one (536a)

To a stirred solution of **529a** (57 mg, 0.409 mmol) in freshly distilled CH_2Cl_2 (7 mL) was added triethylamine (0.11 mL, 0.819 mmol), and DMAP (17 mg, 0.122 mmol). The reaction was cooled to 0 ˚C, then 4-benzyloxybenzoyl chloride (101 mg, 0.409 mmol) was added portionwise over a period of 30 min. The reaction was stirred for 12 h before diluting with CH_2Cl_2 (5 mL). The organic layer was washed with cold 1 N HCl (3 x 3 mL), and then with saturated $NaHCO_3$ (1 x 3 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 then evaporated. The crude product was subjected to flash column chromatography (6:1 hexanes-ethyl acetate) then recrystallized from ethyl ether-hexanes to afford 102 mg (72%) of **536a** as a white solid: mp 167-169 ˚C (ethyl ether-hexanes); R_f 0.47 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –104.6 (*c* 0.5, $CHCl_3$); IR (film) ν 2922, 1790, 1674, 1604, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97-2.07 (m, 1H), 2.27-2.45 (m, 2H), 2.45-2.55 (m, 1H), 4.24-4.38 (m, 1H), 4.50 (d, *J* = 8.6 Hz, 1H), 5.10 (s, 2H), 5.68 (dd,

$J = 6.6, 3.2$ Hz, 1H), 6.13 (dd, $J = 9.6, 1.3$ Hz, 1H), 6.98 (d, $J = 8.6$ Hz, 2H), 7.31-7.45 (m, 5H), 7.77 (d, $J = 8.6$ Hz, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.4, 25.3, 60.4, 70.2, 78.5, 114.3, 123.1, 125.1, 127.6, 128.3, 128.7, 128.8, 132.3, 136.2, 155.2, 162.9, 169.9 ppm; MS (EI) *m/z* (%): 349; 43(11), 83(10), 91(100), 113(10), 167(56), 168(16), 183(18), 184(15), 211(12), 226(27), 349(18); HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314, found 349.1314; *Anal.* calcd: C 72.19, H 5.48, found C 72.22, H 5.55.

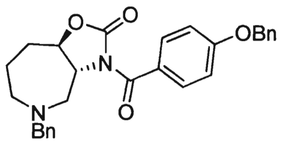


537a

(3a*R*,4*R*,5*S*,7a*R*)-3-[4-(benzyloxy)benzoyl]-4,5-dihydroxyhexahydro-1,3-benzoxazol-2(3*H*)-one (537a)

To a stirred solution of **536** (93 mg, 0.266 mmol) in freshly distilled CH_2Cl_2 (5 mL) was added *N*-methylmorpoline-*N*-oxide (47 mg, 3.99 mmol), one drop of distilled water, and a catalytic amount of OsO_4. The reaction was stirred at room temperature for 36 h before filtering through a plug of celite and silica gel. The crude material was recrystallized from ethyl ether-hexanes and then dried over P_2O_5 to yield 84 mg (83%) of **537a** as a white solid: mp 178-180 °C (ethyl ether-hexanes); R_f 0.35 (1:3 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –67.2 (*c* 0.8, $CHCl_3$); IR (film) ν 2922, 1790, 1674, 1604, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65-1.75 (m, 2H), 2.02-2.07 (m, 1H), 2.22-2.28 (m, 1H), 3.75 (dd, $J = 11.1, 0.93$ Hz, 1H), 3.81-3.91 (m, 1H), 4.60-4.68 (m, 1H), 4.75-4.80 (m, 1H), 5.10 (s, 2H), 6.98 (d, $J = 7.9$ Hz, 2H), 7.31-

7.34 (m, 1H), 7.36-7.42 (m, 4H), 7.76 (d, $J = 8.2$ Hz, 2H) ppm; ^{13}C NMR (300 MHz, CDC13) δ 24.4, 25.3, 60.4, 70.2, 78.5, 114.3, 123.1, 125.1, 127.6, 128.3, 128.7, 128.8, 132.3, 136.2, 155.2, 162.9, 169.9 ppm; MS (EI) *m/z* (%): 349; 43(11), 83(10), 91(100), 113(10), 167(56), 168(16), 183(18), 184(15), 211(12), 226(27), 349(18); HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314, found 349.1314.

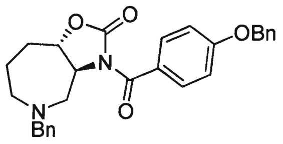


539a

(3a*R*,8a*R*)-5-benzyl-3-[4-(benzyloxy)benzoyl]octahydro-2*H*-[1,3]oxazolo[4,5-*c*]azepin-2-one (539a)

To a stirred solution of **537a** (58 mg, 0.151 mmol) in acetone (3 mL) was added a suspension of $NaIO_4$ (322 mg, 1.51 mmol) in distilled water. The reaction was stirred at room temperature for 6 h, then the solvent was removed. The crude residue was triturated with ethyl acetate (3 x 5 mL), then washed with brine (2 x 5 mL). The resulting solution was filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4*S*,5*R*)-3-[4-(benzyloxy)benzoyl]-2-oxo-5-(3-oxopropyl)-1,3-oxazolidine-4-carbaldehyde (538)** which was used without further purification. Dialdehyde **538** was dissolved in dry MeOH (3 mL) and cooled to −78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (150 mg), followed by $NaCNBH_3$ (10 mg, 0.166 mmol) then AcOH (17.3 μL, 0.302 mmol) and finally benzylamine (18.2 μL, 0.166 mmol). The reaction was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 x 5 mL) and washed with $NaHCO_3$ (1 x 3 mL). The organic layer was washed with brine (3 mL), then dried with Na_2SO_4 before concentrating. The crude material was recrystallized from ethyl ether-hexanes to yield 47 mg (68%) of the title compound as a pale yellow solid: mp 126-128 °C (ethyl ether-hexanes); R_f 0.68 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –17.9 (*c* 0.07, $CHCl_3$; IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.37-7.43 (m, 4H), 7.32-7.37 (m, 2H), 7.29-7.32 (m, 4H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.11 (s, 2H), 4.90 (td, *J* = 3.2, 10.5 Hz, 1H), 4.39 (td, *J* = 7.1, 9.6 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.44 (dd, *J* = 6.6, 11.1 Hz, 1H), 2.65-2.70 (m, 1H), 2.60-2.65 (m, 1H), 2.55-2.60 (m, 1H), 2.35-2.39 (m, 1H), 1.73-1.77 (m, 1H), 1.70-1.73 (m, 1H), 1.66-1.70 (m, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 162.8, 154.1, 138.9, 136.1, 132.3, 128.7, 128.4, 128.2, 127.5, 125.2, 114.1, 78.0, 70.1, 63.0, 61.8, 55.3, 51.4, 31.2, 26.4 ppm; MS (EI) *m/z* (%): 412 ($M–CO_2$); 44(20), 91(100), 160(76), 161(10); HRMS ($M–CO_2$) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151; *Anal.* calcd: C 73.66, H 6.18, found C 73.55, H 6.20.

Alternative method: To a stirred solution of **569** (30 mg, 0.078 mmol) in 10:1 acetone-H_2O (1 mL) was added $NaIO_4$ (167 mg, 0.78 mmol). The resulting suspension was stirred at room temperature for 6 h, then the solvent was removed and the crude residue was triturated with ethyl acetate (3 × 5 mL), then washed with brine (2 × 5 mL). The resulting solution was filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4*S*,5*R*)-3-[4-(benzyloxy)benzoyl]-2-oxo-5-(3-oxopropyl)-1,3-oxazolidine-4-carbaldehyde (538)**, which was used without further purification. The crude dialdehyde **538** was dissolved in dry MeOH (2 mL) and cooled to –78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (75 mg), followed by $NaCNBH_3$ (6 mg, 0.086 mmol), then AcOH (8.9 μL, 0.156 mmol), and finally benzylamine (9.4 μL, 0.086 mmol). The reaction was warmed to r.t. slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 × 2 mL) and washed with $NaHCO_3$ (1 × 1 mL). The organic layer was washed with brine (1 mL), then dried over Na_2SO_4. The crude material was recrystallized from ethyl ether-hexanes to yield **539a** as a pale yellow solid (23 mg, 64%); $[\alpha]_D^{23}$ –31.9 (*c* 0.8, $CHCl_3$).



539b

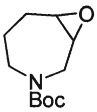
(3a*S*,7a*S*)-5-Benzyl-3-(4-benzyloxy-benzoyl)-octahydro-1-oxa-3,5-diaza-azulen-2-one (539b)

A stirred solution of amide **574** (20 mg, 0.047 mmol) in 1 mL of 9:3:1 (AcOH:tetrahydrofuran:H_2O) was brought to reflux for 16 h then cooled to r.t. and concentrated under reduced pressure. The resulting residue was triturated with benzene (2 x 1 mL) and $CHCl_3$ (2 x 1 mL), filtered through a plug of SiO_2 then recrystallized from $CHCl_3$ to yield **(3aS,4S,5R,7aS)-3-(4-Benzyloxy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one** (15 mg, 83%) as a white solid: mp 166-167 °C (hexanes-ethyl acetate); R_f 0.31 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +80.2 (*c*

0.47, $CHCl_3$); IR (film) ν 3684, 3091, 1794, 1604, 1511, 1422, 1303, 1215, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 2H), 7.29-7.44 (m, 5H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.93 (br s, 1OH), 5.11 (s, 2H), 4.34 (dd, *J* = 9.7, 11.1 Hz, 1H), 4.07 (dd, *J* = 2.6, 5.5 Hz, 1H), 3.95-4.05 (m, 1H), 3.87 (dd, *J* = 3.1, 9.6 Hz, 1H), 3.10 (br s, 1OH), 2.26 (ddd, *J* = 0.1, 3.1, 14.7 Hz, 1H), 2.01-2.10 (m, 2H), 1.54-1.59 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 163.1, 153.6, 136.0, 132.1(2xC), 128.7, 128.3(2xC), 127.6(2xC), 124.6, 114.2(2xC), 77.6, 72.7, 70.2, 68.6, 64.6, 26.7, 22.2 ppm; MS (EI) *m/z* (%): 383 (M), 43(12), 83(20), 84(10), 85(13), 91(100), 211(15); HRMS calcd for $C_{21}H_{21}NO_6$ 383.1369, found 383.1369.

To a stirred solution of **(3aS,4S,5R,7aS)-3-(4-Benzyloxy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one** (58 mg, 0.151 mmol) in 10:1 acetone-H_2O (2 mL) was added $NaIO_4$ (600 mg, 3.00 mmol). The resulting suspension was stirred at r.t. for 6 h, before the solvent was removed under reduced pressure. The crude residue was triturated with ethyl acetate (3 × 5 mL), then washed with brine (2 × 5 mL). The resulting organic layers were filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4R,5S)-3-(4-Benzyloxy-benzoyl)-2-oxo-5-(3-oxo-propyl)-oxazolidine-4-carbaldehyde**, which was used without further purification. The dialdehyde species was dissolved in dry MeOH (2 mL) and cooled to –78 ˚C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (100 mg), followed by $NaCNBH_3$ (10 mg, 0.166 mmol), then AcOH (17 μL, 0.302 mmol), and finally benzylamine (18 μL, 0.166 mmol). The reaction was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 × 2 mL) and washed with

$NaHCO_3$ (1 × 2 mL). The organic layer was washed with brine (1 mL), then dried over Na_2SO_4. The crude material was recrystallized from ethyl ether-hexanes to yield **539b** (38 mg, 60% over 2 steps) as a pale yellow solid: mp 126-128 °C (ethyl ether-hexanes): R_f 0.68 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +31.1 (*c* 0.9, $CHCl_3$); IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.6 Hz, 2H), 7.28-7.44 (m, 10H), 6.98 (d, *J* = 8.6 Hz, 2H), 5.11 (s, 2H), 4.90 (t, *J* = 8.5 Hz, 1H), 4.39 (q, *J* = 8.7 Hz, 1H), 3.68 (q, *J* = 18.6 Hz, 2H), 3.40-3.47 (m, 1H), 2.50-2.73 (m, 3H), 2.33-2.45 (m, 1H), 1.69-1.78 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 162.8, 154.1, 138.9, 136.1, 132.5, 132.3(2xC), 128.8, 128.7, 128.4(2xC), 128.2, 127.5(2xC), 127.2, 125.2, 114.2(2xC), 114.1, 78.0, 70.1, 63.0, 61.8, 55.3, 51.4, 31.2, 26.3 ppm; MS (EI) *m/z* (%): 412 (M–CO_2), 44(20), 91(100), 160(76), 161(10); HRMS (M–CO_2) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151.

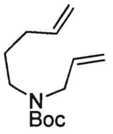


542

***tert*-butyl 8-oxa-3-azabicyclo[5.1.0]octane-3-carboxylate (542)**

A round-bottom flask was flame-dried and purged with argon. To this was added 6 mL of freshly distilled DCM, olefin **548** (413mg, 2.09 mmol) and *m*-CPBA titrated to 77% (1.41g, 6.28 mmol). The resulting solution was stirred at r.t. overnight. The reaction was quenched with 5ml of sat. Na_2CO_3, then diluted with 7ml of DCM. The organic layer was washed with 10ml of $NaHCO_3$, then 10 ml of H_2O. The organic layer was then washed with brine then dried over $MgSO_4$ to yield **542** (410 mg, 92%); IR (film) ν 3442, 2976, 1693, 1478, 1459, 1366, 1276, 1141, 943, 889, 757 cm^{-1}; ^1H

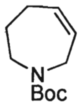
NMR (300 MHz, $CDCl_3$) δ 3.97-3.64 (m, 1H), 3.54-3.39 (m, 2H), 3.12-2.99 (m, 2H), 2.95-2.73 (m, 1H), 2.16-1.99 (m, 1H), 1.98-1.82 (m, 1H), 1.73-1.56 (m, 2H), 1.41 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 79.6, 54.7, 54.5, 49.3, 48.9, 46.2, 45.5, 28.4, 27.6, 23.8, 23.4 ppm; MS (EI) *m/z* (%): 213(M), 41(29), 42(17), 43(17), 56(22), 57(100), 158(12); HRMS calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1361



547

tert-butyl allyl(pent-4-en-1-yl)carbamate (547)

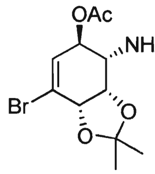
A flame-dried round bottom flask was charged with argon, 10 mL of distilled DMF, *t*-butyl-*N*-allyl carbamate **(545)** (1g, 6.36 mmol) and 5-bromo-1-pentene **(546)** (632mg, 4.24 mmol). The resulting solution was cooled to 0 °C prior to the addition of NaH (102mg, 4.24 mmol). The reaction was stirred at 0 °C for 45 min, and then stirred for an additional 30 min at r.t. before the addition of H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was washed EtOAc (3 x 10 mL). Then the combined organic layers were washed H_2O then brine. The organic layer was then dried over $MgSO_4$ to yield **547** as an colourless oil (735mg, 77%); IR (film) ν 3429, 2977, 1695, 1642, 1409, 1365, 1246, 1172, 912, 771, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85-5.66 (m, 2H), 5.13-4.88 (m, 4H), 3.77 (s, 2H), 3.15 (s, 2H), 2.00 (q, J = 7.5 Hz, 2H), 1.57 (m, J = 7.6 Hz, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 137.8, 134.3, 114.7, 79.1, 46.1, 30.9, 28.3 ppm; MS (EI) *m/z* (%): 225(M), 41(39), 57(100), 70(40), 114(23); HRMS calcd for $C_{13}H_{23}NO_2$ 225.1729, found 225.1737; *Anal.* calcd: C 69.29, H 10.29, found C 69.35, H 10.39.



548

tert-butyl 2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (548)

A round bottom flask was flame-dried and purged with argon. Added was 2 mL of freshly distilled DCM, diene **547** (200 mg, 0.887 mmol) and benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (22 mg, 0.0266 mmol). The resulting suspension was placed in a pre-heated oil bath at 52 °C and stirred for 1 h. The reaction was then concentrated and purified by flash column chromatography with 12 g of SiO_2, and a solvent system of 1:1 (DCM-hexanes) to yield **548** as a yellow oil (150 mg, 86%); IR (film) ν 3510, 3022, 2975, 2932, 1695, 1458, 1414, 1245, 1169, 1113, 865, 770, 665 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 2H), 3.86 (d, J = 22.8 Hz, 2H), 3.56-3.40 (m, 2H), 2.21-2.11 (m, 2H), 1.84-1.68 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 131.9, 131.0, 79.2, 47.9, 47.6, 45.6, 28.4, 26.9, 26.7, 26.5 ppm; MS (EI) *m/z* (%): 197(M), 41(31), 57(100), 68(11), 82(22), 96(10), 124(13), 126(11), 140(21), 141(46); HRMS calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1405; *Anal.* calcd: C 66.97, H 9.71, found C 66.97, H 9.71.



559

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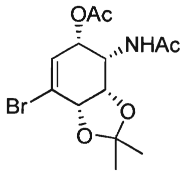


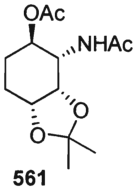
560

(3a*S*,4*S*,5*R*,7a*S*)-4-(acetylamino)-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (559) and (3a*S*,4*S*,5*S*,7a*S*)-4-(acetylamino)-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (560)

To a stirred solution of aziridine **429** (50 mg, 0.174 mmol), acetic acid (0.19 mL, 3.47 mmol) in DCM (0.5 mL) was added trimethylsilyl trifluoromethanesulfonate (3.1 μL, 0.0174 mmol). The reaction was allowed to stir at room temperature for 12 h and then filtered through a plug of SiO_2 and Na_2SO_4 before concentrating under reduced pressure. The crude material was subjected to flash column chromatography with a solvent gradient of 3:1, 1:1 hexanes-ethyl acetate to yield **559** (43 mg, 70%) and **560** (11 mg, 18%) as white solids.

559: R_f 0.35 (1:3 hexanes-ethyl acetate); mp 168-169 °C (ethyl acetate-hexanes); $[\alpha]_D^{23}$ -111.4 (*c* 1.00, $CHCl_3$); IR (film) ν 3583, 3272, 1743, 1655, 1371, 1226, 1043 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.03 (d, *J* = 9.85 Hz, 1H), 6.02 (d, *J* = 2.0 Hz, 1H), 5.45 (dt, *J* = 2.1, 9.3 Hz, 1H), 4.62 (dd, *J* = 1.98, 5.04 Hz, 1H), 4.41 (td, *J* = 2.3, 9.5 Hz, 1H), 4.39 (t, *J* = 3.3 Hz, 1H), 2.05 (s, 3H), 1.97 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 170.1, 129.4, 124.7, 110.7, 77.3, 76.0, 69.4, 50.8, 27.4, 26.4, 23.3, 20.1 ppm; MS (EI) *m/z* (%): 347 (M), 43(100), 84(45), 142(79); HRMS calcd for $C_{13}H_{18}BrNO_5$ 347.0368, found 347.0384; *Anal.* calcd: C 44.84, H 5.21, found C 44.90, H 5.26.

560: R_f 0.21 (1:3 hexane-ethyl acetate); mp 95-97 °C (ethyl acetate-hexanes); $[\alpha]_D^{23}$ +102.6 (*c* 1.28, $CHCl_3$); IR (film) ν 3391, 2947, 2835, 1731, 1653, 1375, 1250, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, *J* = 5.7 Hz, 1H), 6.14 (d, *J* = 9.0 Hz, 1H), 5.17 (t, *J* = 5.1 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.54-4.61 (m, 1H), 4.41-4.45 (m, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.9, 129.6, 127.2, 111.3, 76.9, 75.0, 67.3, 45.8, 27.3, 26.3, 23.2, 20.9 ppm; MS (EI) *m/z* (%): 347 (M), 43(100), 56(45), 57(52); HRMS calcd for $C_{13}H_{18}BrNO_5$ 347.0368, found 347.0368.

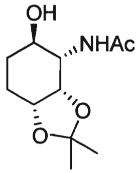


561

(3a*S*,4*S*,5*R*,7a*R*)-4-(acetylamino)-2,2-dimethylhexahydro-1,3-benzodioxol-5-yl acetate (561)

To a stirred solution of aziridine **559** (753 mg, 2.16 mmol), NEt_3 (2.1 mL, 15.1 mmol) in ethyl acetate (3 mL) was added platinum(IV)oxide (12 mg, 0.433 mmol) before evacuating the reaction flask with H_2. The reaction was stirred at r.t. with 1 atm of H_2 for 36 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 1:2 then 1:5 (hexanes-ethyl acetate) to yield **561** (493 mg, 84%) as a clear oil: R_f 0.3 (1:5 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -49.2 (*c* 1.24, $CHCl_3$); IR (film) ν 3286, 2939, 2988, 1735, 1657, 1547, 1374, 1243, 1041, 868, 755 cm^{-1}; ^1H NMR (600 MHz, DMSO-D_6) δ 7.99 (d, *J* = 8.7 Hz, 1H), 4.79 (dt, *J* = 5.8, 11.1 Hz, 1H), 4.29 (dd, *J* = 5.7, 11.0 Hz, 1H) 4.23

(dd, *J* = 3.2, 5.9 Hz, 1H), 4.13 (td, *J* = 2.4, 9.4 Hz, 1H), 1.96 (m, 1H), 1.94 (s, 3H), 1.82 (s, 3H), 1.73 (td, *J* = 4.4, 9.3 Hz, 1H), 1.47 (td, *J* = 4.4, 9.1 Hz, 1H), 1.42 (s, 3H), 1.33-1.39 (m, 1H), 1.24 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.0, 108.7, 75.7, 73.3, 70.0, 50.7, 27.3, 25.2, 25.1(2xC), 23.3, 21.1 ppm; MS (EI) *m/z* (%): 256 ($M\text{-}CH_3^+$), 43(100), 60(32), 84(43), 94(45), 111(48), 112(36), 153(57), 213(31); HRMS calcd for $C_{12}H_{18}NO_5^{\bullet}$ 256.1180, found 256.1187; *Anal.* calcd: C 57.55, H 7.80, found C 57.67, H 7.90.

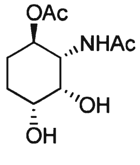


562

N-[(3a*S*,4*S*,5*R*,7a*R*)-5-hydroxy-2,2-dimethylhexahydro-1,3-benzodioxol-4-yl]acetamide (562)

To a stirred solution of **559** (60 mg, 0.173 mmol), NEt_3 (0.17 mL, 1.206 mmol) in methanol (0.7 mL) was added platinum(IV)oxide (9 mg, 0.0344 mmol) before evacuating the reaction flask with H_2. The reaction was stirred at r.t. with 1 atm of H_2 for 36 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 1:2, and then 1:5 (hexanes-ethyl acetate) to yield **562**; R_f 0.2 (hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.9 (s, 1H), 6.32 (d, *J* = 5.6 Hz, 1H), 4.18-4.30 (m, 2H), 3.98-4.06 (m, 1H), 3.71-3.83 (m, 1H), 2.09 (s, 3H), 1.94-2.02 (m, 1H), 1.79-1.87 (m, 1H), 1.47-1.63 (m, 2H), 1.46 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 108.9, 75.6, 73.9, 69.7, 54.4, 46.2, 28.2, 27.6, 25.9, 25.5, 23.3, 8.63 ppm; MS

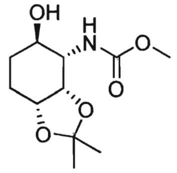
(EI) *m/z* (%): 214 ($M-CH_3^+$), 43(100), 60(32), 84(43), 94(45), 111(48), 112(36), 153(57), 213(31); HRMS calcd for $C_{10}H_{16}NO_4^{\bullet}$ 214.1079, found 214.1079.



563

(1*R*,2*R*,3*S*,4*R*)-2-(acetylamino)-3,4-dihydroxycyclohexyl acetate (563)

A solution of acetonide **561** (338 mg, 1.25 mmol), acetic acid (2 mL), H_2O (0.5 mL) and THF (2 mL) was stirred at 80 °C for 12 h and then triturated (benzene then Et_2O), dried over Na_2SO_4 and concentrated. Recrystallization from MeOH-hexanes yielded **563** (0.248 mg, 86%) as a white solid: mp 170-171 °C (MeOH-hexanes); R_f 0.21 (10:1 $CHCl_3$-MeOH); IR (film) ν 3434, 2524, 1641, 1559, 1262, 1057 cm^{-1}; ^1H NMR (600 MHz, DMSO-D_6) δ 7.67 (d, *J* = 8.7 Hz, 1H), 4.84 (d, *J* = 3.8 Hz, 1H), 4.76 (td, *J* = 4.4, 10.8 Hz, 1H) 4.63 (d, *J* = 5.3 Hz, 1H), 3.77 (td, *J* = 1.9, 9.6 Hz, 1H), 3.68 (br s, 1H), 3.50 (t, *J* = 5.3 Hz, 1H), 1.91 (s, 3H), 1.81-1.84 (m, 1H), 1.80 (s, 3H), 1.64 (qd, *J* = 3.2, 12.5 Hz, 1H), 1.46-1.52 (m, 1H), 1.27 (qd, *J* = 3.3, 12.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO) δ 170.6, 169.3, 72.2, 71.0, 70.0, 53.4, 27.2, 26.4, 23.1, 21.4 ppm; MS (FAB) *m/z* (%): 232 ($M+H^+$), 41(58), 43(100), 55(76), 57(66), 69(56), 149(43), 232(84); HRMS calcd for $C_{10}H_{18}NO_5$ 232.1185, found 232.1185.



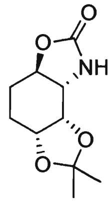
566

Methyl [(3a*S*,4*S*,5*R*,7a*R*)-5-hydroxy-2,2-dimethylhexahydro-1,3-benzodioxol-4-yl]carbamate (566)

To a stirred solution of acetate **561** (300 mg, 1.11 mmol) in methanol (5 mL) was added Na (254 mg, 11.1 mmol) portionwise until completely dissolved (30 min). The reaction mixture was brought to reflux and stirred for 18 h then cooled to r.t. and quenched by the addition of H_2O (5 mL). The reaction mixture was concentrated under reduced pressure and then extracted into $CHCl_3$ (5 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield **(3a*S*,4*S*,5*R*,7a*R*)-4-amino-2,2-dimethylhexahydro-1,3-benzodioxol-5-ol (565)** as a pale yellow oil which was used without further purification: ^{1}H NMR (300 MHz, CD_3OD) δ 4.33-4.39 (m, 1H), 4.22 (dt, *J* = 5.6, 8.5 Hz, 1H), 3.54 (td, *J* = 4.6, 9.5 Hz, 1H), 2.64 (dd, *J* = 3.6, 9.6 Hz, 1H), 1.80-1.95 (m, 2H), 1.54-1.66 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.30-1.33 (m, 1H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 108.4, 77.0, 74.2, 70.6, 55.6, 28.6, 27.0, 26.7, 24.5 ppm.

β-amino alcohol **565** (178 mg, 0.951 mmol), NEt_3 (0.26 mL, 1.90 mmol), and DMAP (catalytic amount) in DCM (1 mL) was added methyl chloroformate (80.5 μL, 1.05 mmol) at 0 °C. The reaction was allowed to warm to r.t. over 12 h then diluted with DCM (1 mL), washed with sat. $NaHCO_3$ (1 x 1 mL) and brine (1 mL) then dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 60:1 ($CHCl_3$-MeOH) to yield **566** (197 mg, 73% over 2 steps) as a

yellow oil: R$_f$ 0.43 (10:1 $CHCl_3$-MeOH); $[\alpha]_D^{23}$ -24.7 (*c* 0.7, MeOH); IR (film) ν 3433, 2988, 2940, 1695, 1645, 1241, 1219, 1035, 1077 cm^{-1}; ^{1}H NMR (600 MHz, $CO(CD_3)_2$) δ 5.98 (br d, *J* = 4.9 Hz, NH), 4.36 (dd, *J* = 3.6, 5.5 Hz, 1H), 4.29 (dd, *J* = 2.8, 5.6, 1H), 3.89 (br s, OH), 3.67-3.77 (m, 2H), 3.63 (s, 3H), 1.93-1.99 (m, 1H), 1.79-1.86 (m, 1H), 1.53-1.61 (m, 1H), 1.44 (s, 3H), 1.37-1.42 (m, 1H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CO(CD_3)_2$) δ 158.8, 107.9, 76.1, 73.8, 67.8, 55.9, 51.1, 28.6, 27.2, 26.1, 24.8 ppm; MS (EI) *m/z* (%): 230 ($M-CH_3^+$), 43(34), 59(43), 76(38), 95(31), 99(34), 130(100), 143(33); HRMS calcd for $C_{10}H_{16}NO_5$ 230.1028, found 230.1028; *Anal.* calcd: C 53.87, H 7.81, found C 53.77, H 7.80.

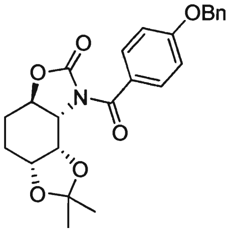


567

(3a*R*,5a*R*,8a*S*,8b*S*)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*e*][1,3]benzoxazol-7(4*H*)-one (567)

To a stirred suspension of NaH (128 mg, 5.34 mmol) in THF (4 mL) was added a solution of carbamate **566** (131 mg, 0.534 mmol) in THF (2.5 mL). The reaction mixture was brought to reflux and stirred for 24 h then cooled to r.t. and quenched by the addition of sat. NH_4Cl (5 mL). The reaction mixture was extracted into EtOAc (5 x 2 mL), washed with brine (2 mL) and dried over Na_2SO_4 and concentrated. Recrystallization from acetone yielded **567** (95 mg, 83%) as white needles: R$_f$ 0.21 (1:3 hexanes-ethyl acetate); mp 179-181 °C (acetone); $[\alpha]_D^{23}$ -19.7 (*c* 0.75, $CHCl_3$); IR (film) ν 3459, 2983, 2925, 1733, 1639, 1136 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ

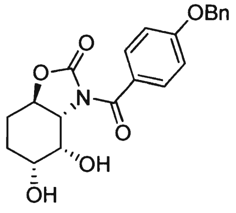
5.49 (br s, 1 NH), 4.61 (m, 1H), 4.43-4.51 (m, 2H), 3.49 (dd, J = 1.9, 12.1 Hz, 1H), 2.22-2.37 (m, 1H), 1.99-2.17 (m, 1H), 1.76-1.94 (m, 2H), 1.53 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 109.5, 73.8, 73.5, 70.9, 58.3, 58.2, 26.1, 23.8, 22.2, 21.9 ppm; MS (EI) *m/z* (%): 213 (M), 43(92), 59(41), 67(45), 94(42), 99(100), 198(64); HRMS calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.0998.



568

(3a*R*,5a*R*,8a*S*,8b*S*)-8-[4-(benzyloxy)benzoyl]-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*e*][1,3]benzoxazol-7(4*H*)-one (568)

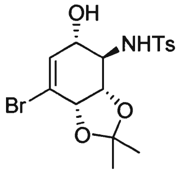
To a stirred solution of cyclic carbamate **567** (40 mg, 0.188 mmol), NEt_3 (104 μL, 0.750 mmol), and DMAP (catalytic) in DCM (0.25 mL) was added 4-benzyloxybenzoyl chloride (51 mg, 0.206 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. slowly over 16 h then diluted with DCM (0.5 mL), washed with cold 1 N NaOH (1 x 0.5 mL), brine (1 x 0.5 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 6:1 then 4:1 (hexanes-ethyl acetate) to yield **568** (65 mg, 82%) as a white solid: R_f 0.38 (2:1 hexanes-ethyl acetate); mp 153-154 °C (MeOH); $[\alpha]_D^{23}$ -163.8 (*c* 0.425, $CHCl_3$); IR (film) ν 3433, 1638, 1259, 1027 cm^{-1}; ^{1}H NMR (600 MHz, $CO(CD_3)_2$) δ 7.79 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 5.26 (s, 2H), 4.94 (dd, J = 3.4, 7.2 Hz, 1H), 4.77 (ddd, *J* = 7.7, 10.2, 12.1 Hz, 1H), 4.66 (dt, *J* = 3.2, 7.2 Hz, 1H), 4.11 (dd, *J* = 3.4, 12.1 Hz, 1H), 2.27-2.36 (m, 1H), 2.14-2.20 (m, 2H), 1.89-1.98 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, CO(CD$_3$)$_2$) δ 169.2, 162.6, 154.2, 136.9, 132.0, 128.5, 128.0, 127.7, 125.8, 114.0, 108.9, 73.9, 71.3, 70.1, 69.8, 60.2, 25.4, 23.2, 21.6, 20.9 ppm; MS (EI) *m/z* (%): 423 (M), 43(24), 83(23), 91(100), 211(26), 423(21); HRMS calcd for $C_{24}H_{25}NO_6$ 423.1682, found 423.1662; *Anal.* calcd: C 68.07, H 5.95, found C 68.15, H 5.99.



569

(3a*R*,4*S*,5*R*,7a*R*)-3-[4-(benzyloxy)benzoyl]-4,5-dihydroxyhexahydro-1,3-benzoxazol-2(3*H*)-one (569)

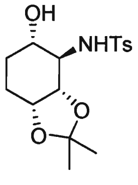
A stirred solution of **568** (65 mg, 0.153 mmol) in 1 mL of 9:3:1 (AcOH:THF:H$_2$O) was brought to reflux for 16 h then cooled to r.t. and concentrated under reduced pressure. The resulting residue was triturated with benzene (2 x 1 mL) and CHCl$_3$ (2 x 1 mL), filtered through a plug of SiO$_2$ then recrystallized from CHCl$_3$ to yield **569** (52 mg, 88%) as a white solid: R$_f$ 0.33 (1:3 hexanes-ethyl aceate); mp 174-175 °C (CHCl$_3$); $[\alpha]_D^{23}$ -68.4 (*c* 0.05, MeOH); IR (film) ν 3435, 2918, 1786, 1660, 1604, 1220, 1036 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.38-7.44 (m, 4H), 7.34 (t, *J* = 7.1 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 5.12 (s, 2H), 4.79-4.82 (m, 1H), 4.66 (td, *J* = 3.5 Hz, 11.6, 1H), 3.86-3.91 (m, 1H), 3.78 (dd, *J* = 1.5, 11.5 Hz, 1H), 2.24-2.29 (m, 1H), 2.02-2.09 (m, 1H) 1.65-1.80 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 162.9, 154.7, 136.1, 132.4, 128.7, 128.3, 127.6, 127.5, 124.9, 114.3, 73.6, 70.2, 69.6, 67.3, 64.3, 27.4, 25.4 ppm; MS (EI) *m/z* (%): 383 (M), 43(15), 65(10), 91(100), 92(25), 121(13), 211(19); HRMS calcd for $C_{21}H_{21}NO_6$ 383.1369, found 383.1372.



571

N-((3aS,4R,5S,7aS)-7-Bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (571)

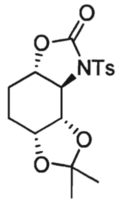
To a stirred solution of *N*-tosyl aziridine **(570)** (200 mg, 0.499 mmol), in dimethyl sulfoxide (1.5 mL) was added 10% KOH (1.5 mL). The reaction was heated to 40 °C and then stirred for 2 h. The reaction mixture was then neutralized with sat. NH_4Cl and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was recrystallized from hexane-ethyl acetate to yield (196 mg, 94%) as white crystals: mp 155-156 °C (hexanes-ethyl acetate); R_f 0.43 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –22.7 (*c* 0.7, $CHCl_3$); IR (film) ν 3445, 2993, 2087, 1646, 1216, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.24 (d, *J* = 3.1 Hz, 1H), 5.48 (br s, 1NH), 4.58(d, *J* = 5.6 Hz, 1H), 4.17 (t, *J* = 6.7 Hz, 1H), 3.99 (br s, 1OH), 3.79 (d, *J* = 4.7 Hz, 1H), 3.33 (t, *J* = 6.8, 1H), 2.41 (s, 3H), 1.28 (s, 3H), 1.06 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 135.9, 134.1, 129.9, 127.6, 120.6, 111.4, 76.3, 75.9, 70.0, 56.7, 27.2, 25.9, 21.6 ppm; MS (EI) *m/z* (%): 402(M-CH_3^+), 43(40), 59(32), 65(30), 91(85), 92(16), 97(15), 98(48), 99(68), 139(30), 155(26), 254(100), 255(15); HRMS calcd for $C_{15}H_{17}BrNO_5S$ 402.0011, found 402.0004; *Anal.* calcd: C 45.94, H 4.82, found C 45.88, H 4.80.



572

N-((3aS,4R,5S,7aR)-5-Hydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (572)

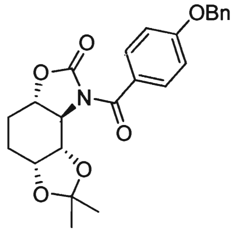
To a stirred solution of allylic alcohol **571** (196 mg, 0.468 mmol), in MeOH (2 mL) was added K_2CO_3 (10 mg), and platinum(IV)oxide (catalytic amount) before purging the reaction flask with H_2. The reaction mixture was stirred at r.t. and 1 atm of H_2 for 36h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 then 1:2 (hexanes-ethyl acetate) to yield **572** (123 mg, 77%) as a white solid: mp 155-156 °C (hexanes-ethyl acetate); R_f 0.30 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ −105.2 (*c* 1.32, $CHCl_3$); IR (film) ν 3381, 3255, 2985, 2934, 2893, 2765, 1597, 1155, 1088, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.48 (d, *J* = 6.9 Hz, 1H), 4.17-4.10 (m, 1H), 3.72 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.51 (d, *J* = 3.0 Hz, 1H), 3.50-3.35 (m, 1H), 2.97, (q, *J*= 17.4, 8.3 Hz, 1H), 2.39 (s, 3H), 2.11-2.03 (m, 1H), 1.88-1.80 (m, 1H), 1.72-1.57 (m, 2H), 1.18 (s, 3H), 0.937 (s, 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.1, 129.7, 129.4, 127.8, 127.4, 108.9, 78.7, 73.6, 70.7, 63.0, 27.5, 27.4, 26.1, 23.2, 21.5 ppm; MS (EI) *m/z* (%): 341(M), 43(21), 59(34), 65(29), 82(35), 83(20), 91(100), 100(28), 128(65), 155(34), HRMS calcd for $C_{16}H_{23}NO_5S$ 341.1297 found 341.1297; *Anal.* calcd: C 56.29, H 6.79, found C 56.21, H 6.70.



573

(3aR,5aS,8aR,8bS)-2,2-dimethyl-8-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one (573)

To a stirred solution of sulfonamide **572** (600 mg, 1.76 mmol), in methylene chloride (5 mL) was added pyridine (1.42 mL, 17.6 mmol) then triphosgene (625 mg, 2.11 mmol). The reaction was stirred at 0 °C for 30 min before being quenched by the addition of water (10 mL) and extracted into methylene chloride (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography with a solvent gradient of 2:1, 1:1 then 1:2 (hexanes-ethyl acetate) to yield **573** (567 mg, 93%) as a white solid: mp 197-198 °C (hexanes-ethyl acetate); R_f 0.58 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –2.56 (*c* 0.56, $CHCl_3$); IR (film) ν 3557, 3027, 2987, 2890, 1797, 1597, 1495, 1438, 1379, 1180, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.59 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.38-4.32 (m, 1H), 3.90 (td, *J* = 11.7, 3.5 Hz, 1H), 3.38 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.42 (s, 3H), 2.32-2.22 (m, 1H), 2.06-1.97 (m, 1H), 1.90-1.74 (m, 1H), 1.73-1.65 (m, 1H) 1.46 (s, 3H), 1.40 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 145.6, 133.8, 130.1, 129.7, 128.8, 128.6, 108.9, 76.4, 76.1, 73.2, 68.4, 28.5, 25.9, 24.7, 22.4, 21.7 ppm; MS (EI) *m/z* (%): 367 (M), 41(23), 43(52), 65(29), 83(69), 85(45), 91(100), 155(47), 352(48) HRMS calcd for $C_{17}H_{21}NO_6S$ 367.1089, found 367.1089; *Anal.* calcd: C 55.57, H 5.76, found C 55.67, H 5.60.



574

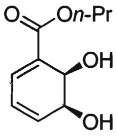
(3aR,5aS,8aR,8bS)-8-(4-Benzyloxy-benzoyl)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one (574)

To a stirred solution of *N*-tosyl cyclic carbamate **573** (560 mg, 1.52 mmol), in tetrahydrofuran (2 mL) was added sodium naphthalide (0.5 M.) at –78 °C until a green colour persisted. The reaction mixture was stirred at –78 °C for 30 min before being quenched by the addition of sat. NH_4Cl (5 mL) and extracted into diethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified via flash column chromatography with a solvent gradient of 2:1, 1:1 then 1:2 (hexanes-ethyl acetate) to yield **(3aR,5aS,8aR,8bS)-2,2-dimethyl-hexahydro[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one** (300 mg, 92%) as a white solid: mp 134-136 °C (hexanes-ethyl acetate); R_f 0.31 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –89.2 (*c* 2.9, $CHCl_3$); IR (film) ν 3450, 3305, 2987, 2938, 2894, 1860, 1855, 1647, 1547, 1466, 1383, 1239, 1061 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, br, 1H), 4.30-4.25 (m, 1H), 4.07 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.81 (td, *J* = 11.5, 3.6 Hz, 1H), 3.48 (dd, *J* = 11.5, 9.1 Hz, 1H), 2.42-2.27 (m, 1H), 2.10-2.03 (m, 1H), 1.89-1.79 (m, 1H), 1.57 (s, br, 1H), 1.47 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 109.4, 77.9, 77.7, 73.3, 62.9, 28.4, 25.9, 24.7, 24.0 ppm; MS (EI) *m/z* (%): 213 (M), 41(31), 43(100), 55(28), 59(34), 67(48), 82(35), 83(21), 85(22), 98(23), 99(80), 127(22), 198(87), HRMS calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.1001; *anal.* calcd C 56.33, H 7.09, found C 56.23, H 7.02.

To a stirred solution of NaH (18.5 mg, 0.774 mmol) in THF (1 mL) was added **(3aR,5aS,8aR,8bS)-2,2-Dimethyl-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one** (110 mg, 0.516 mmol), in tetrahydrofuran (1 mL) dropwise at 0 °C. The reaction was allowed to warm slowly to r.t. and stirred for 1 h before the addition of 4-benzyloxy benzoyl chloride (127 mg, 0.516 mmol) in four portions over 2 h. The reaction mixture was stirred for 12 h before being quenched by the addition of sat. NH_4Cl (2 mL). The tetrahydrofuran was removed under reduced pressure and the aqueous layer was extracted into ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified via flash column chromatography with a solvent gradient of 4:1, 2:1 then 1:1 (hexanes-ethyl acetate) to yield **574** (220 mg, 91%) as a white solid: mp 149-150 °C (hexanes-ethyl acetate); R_f 0.62 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ + 0.72 (*c* 2.1, $CHCl_3$); IR (film) ν 3682, 3531, 3379, 3066, 3019, 2989, 2937, 2889, 2587, 1952, 1786, 1697, 1603, 1382, 1256, 1216 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.31-7.42 (m, 5H), 6.97 (d, *J* = 8.3 Hz, 2H), 5.10 (s, 2H), 4.29 (dd, *J* =

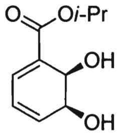
4.2, 7.9 Hz, 1H), 4.20-4.27 (m, 2H), 3.94 (dd, *J* = 3.8, 11.3 Hz, 1H), 2.31-2.36 (m, 1H), 2.15-2.20 (m, 1H), 1.93-1.97 (m, 1H), 1.88-1.93 (m, 1H), 1.68 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 163.3, 155.1, 136.1, 132.6(2xC), 128.7, 128.3(2xC), 127.6(2xC), 125.4, 114.3(2xC), 109.6, 78.2, 75.4, 73.7, 70.2, 63.8, 27.9, 25.9, 24.7, 23.5 ppm; MS (EI) *m/z* (%): 423 (M), 43(67), 65(20), 83(24), 85(68), 91(100), 92(25), HRMS calcd for $C_{24}H_{25}NO_6$ 423.1682, found 423.1682; *anal.* calcd C 68.07, H 5.95, found C 68.14, H 5.96.



583

6-Carboxypropyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (583)

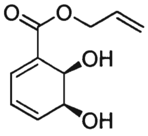
From the fermentation of benzoate **583**, (711 mg, 5.8%, 65.0% based on recovered starting material) waxy solid; R_f 0.15 (1:1 ethyl acetate/hexanes); $[\alpha]_D^{22}$ +58.8 (*c* 1.1, $CHCl_3$); IR (film) ν 3398, 2968, 1700, 1280, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 5.4 Hz, 1H), 6.20 (dd, *J* = 9.5, *J* = 2.5 Hz, 1H), 6.09 (ddd, *J* = 9.5, *J* = 5.4, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 6.3 Hz, 1H), 4.48 (ddd, *J* = 6.3, *J* = 2.5, *J* = 2.2 Hz, 1H), 4.16 (t, *J*= 6.7 Hz, 2H), 3.40 (bs, 2H), 1.72 (qt, *J*= 7.4, *J* = 6.7 Hz, 2H), 0.98 (t, *J*= 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.4, 133.9, 128.7, 122.6, 69.4, 66.6, 64.8, 22.0, 10.4 ppm; MS (EI) *m/z* (%): 198(M$^+$, 18), 180(22), 138(100), 121(81), 110 (54), 105 (77); HRMS calcd for $C_9H_{12}O_4$ 198.0892, found 198.0892.



584

6-Carboxyisopropyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (584)

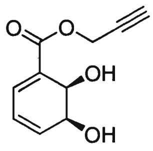
From the fermentation of benzoate **578**, (488 mg, 4.1%, 34.0% based on recovered starting material); colourless crystals; mp 83-85 °C (ethyl acetate/hexane); R_f 0.31 (6:4 ethyl acetate/hexane); $[\alpha]_D^{22}$ +64.70 (*c* 1.1, $CHCl_3$); IR (KBr) ν 3274, 2981, 1698, 1263, 1241 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (ddd, *J* = 5.5, 1.0, 0.5 Hz, 1H), 6.20 (ddt, *J* = 9.6, 2,7, 0.9 Hz, 1H), 6.08 (ddd, *J* = 9.6, *J* = 5.5, *J* = 2.2 Hz, 1H), 5.12 (hept, *J* = 6.3 Hz, 1H), 4.58 (dd, *J* = 6.4, *J* = 0.5 Hz, 1H), 4.48 (br m, 1H), 3.60-3.25 (br s, 2H), 1.30 (d, *J* = 6.3 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 138.2, 133.6, 128.9, 122.63, 99.4 69.2, 68.5, 64.9, 21.8 ppm; MS (EI) *m/z* (%): 198(M^+, 19), 180(16), 156(14), 138(100); HRMS (EI) calcd for $C_{10}H_{14}O_4$: 198.08921, found: 198.08896. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.68; H, 7.19.



587

6-Carboxyallyl-(1*S*,2*S*)-1,2-dihydroxycyclohexa-3,5-diene (587)

From the fermentation of benzoate **581**, (5.79 g, 52.0%, 73.6% based on recovered starting material), colourless crystals; mp 48-50 °C (ethyl acetate/hexane). R_f 0.23 (1:1 ethyl acetate/hexane); $[\alpha]_D^{22}$ +72.54 (*c* 1.6, $CHCl_3$); IR (KBr) ν 3394, 1704, 1273, 1238 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 5.5 Hz, 1H), 6.23 (ddt, *J* = 9.6, *J* = 2,7, *J* = 1.0 Hz, 1H), 6.11 (ddd, *J* = 9.5, *J* = 5.5, *J* = 2.2 Hz, 1H), 5.98 (ddt, *J* = 17.2, *J* = 10,4 *J* = 5.7 Hz, 1H), 5.37 (dt, *J* = 17.2, *J* = 1.5 Hz, 1H), 5.28 (dt, *J* = 10.4, *J* = 1.3 Hz, 1H), 4.72 (ddd, *J* = 5.7, *J* = 1.5, *J* = 1.3 Hz, 1H), 4.61 (br s, 1H), 4.50 (br s, 1H), 3.25 (d, *J* = 3.8 Hz, 1H), 3.18 (bd, *J* = 7.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.8, 134.4, 131.9, 128.4, 122.4, 118.3, 69.6, 65.5, 64.5 ppm; MS (EI) *m/z* (%): 196(M^{+}, 20), 178(18), 138(80), 121(95), 41(100). HRMS (EI) calcd for $C_{10}H_{12}O_4$: *m/z* 196.07356, found: 196.07364. *Anal.* Calcd. for $C_{10}H_{12}O_4$ + 1/8 H_2O: C, 60.52; H, 6.22. Found: C, 60.52; H, 6.26.

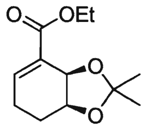


588

6-Carboxyisopropyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (588)

From the fermentation of benzoate **582**, (9.20g, 69.1%, 75.8% based on recovered starting material); colourless crystals; mp 70-72 °C (ethyl acetate/hexane). R$_f$ 0.31 (6:4 ethyl acetate/hexane); $[\alpha]_D^{22}$ +88.20 (*c* 1.6, $CHCl_3$); IR (KBr) ν 3385, 3291, 1707, 1270, 1234 cm^{-1}; ^{1}H NMR (300 MHz, acetone-*d*$_6$) δ 7.01 (dd, *J* = 5.3, *J* = 1.1 Hz, 1H), 6.16 (dq, *J* = 9.5, *J* = 1.4 Hz, 1H), 6.09 (ddd, *J* = 9.5, *J* = 5.3, *J* = 2.2 Hz, 1H), 4.86 (dd, *J* = 15.8, *J* = 2.5 Hz, 1H), 4.80 (dd, *J* = 15.8, *J* = 2.5 Hz, 1H), 4.50-4.23 (m, 2H), 4.10 (d, *J* = 7.4 Hz, 1H), 3.96 (d, *J* = 5.0 Hz, 1H), 3.06 (t, *J* = 2.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d$_6$) δ 167.2, 142.5, 136.3, 131.1, 123.5, 80.0, 77.3, 72.5, 65.5, 53.4 ppm; MS (EI) *m/z* (%): 194(M^{+}, 7%), 176(28), 138(47), 121(100);

HRMS (EI) calcd for $C_{10}H_{10}O_4$: *m/z* 194.0579, found: 194.0581. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.08; H, 5.18.



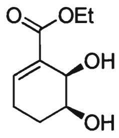
592

Ethyl (5S, 6R)-5,6-dihydroxycyclohex-1-ene-1-carboxylate (592)

Method A - To a stirring solution of 1,2-diol **593** (155 mg, 0.832 mmol) and 2,2 dimethoxypropane (0.71 mL, 5.83 mmol) in acetone (1 mL) was added a catalytic amount of *p*-TsOH. The reaction was allowed to stir at room temperature for 2 h, and then diluted with ethyl acetate (5 mL) and washed with saturated $NaHCO_3$ (3 x 2 mL). The combined organic layers were washed with brine (1 x 3 mL) then dried with Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 2:1 hexanes-ethyl acetate to yield **592** (173 mg, 92%) as a pale yellow oil.

Method B – To a stirring solution of vinyl bromide **590** (500 mg, 2.14 mmol) in Et_2O (4 mL) was added *t*BuLi (4.4 mL, 0.82 M) dropwise at -78 °C and then stirred for 45 min prior to the addition of solid CO_2 (2 g, 45.4 mmol). The reaction was allowed to warm to r.t. slowly over 12 h and then diluted with Et_2O (7 mL) and washed with saturated $NaHCO_3$ (3 x 10 mL). The organic layer was diluted with H_2O (3 mL) before adjusting the pH to 3.5 (10% citric acid) and extracting with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield carboxylic acid **591** which as used without further purification. To a stirring solution of **591** (244 mg, 1.23 mmol) in DCM (2 mL) was added 1-ethyl-3-(3'dimethylaminopropyl) carbodiimide·HCl (260 mg, 1.35 mmol), DMAP (15 mg, 0.123 mmol), and finally absolute EtOH (0.22 mL, 3.69 mmol) at 0 °C. The reaction was allowed to stir for 12 h, then diluted with DCM (2 mL) and washed with saturated NH_4Cl (1 x 3 mL), saturated $NaHCO_3$ (1 x 3 mL) and then H_2O (1 x 3 mL). The combined organic layers were washed with brine (1 x 5 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 2:1 hexanes-ethyl acetate to yield **592** (243 mg, 50% over 2 steps) as a pale yellow oil.

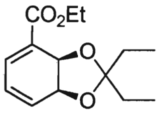
R_f 0.56 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +74.6 (*c* 4.02, $CHCl_3$); IR (film): ν 3018, 2987, 2936, 1712, 1651, 1425, 1380, 1259, 1155, 1031, 917, 856, 697, 667, 512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 5.3, 3.1 Hz, 1H), 4.84 (d, *J* = 5.7 Hz, 1H), 4.28-4.41 (m, 1H), 4.07-4.26 (m, 2H), 2.21-2.45 (m, 1H), 1.99-2.16 (m, 1H), 1.86-1.99 (m, 1H), 1.58-1.72 (m, 1H), 1.33 (d, *J* = 10.2 Hz, 6H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 142.3, 130.0, 108.5, 72.6, 70.4, 60.5, 27.8, 26.2, 25.1, 20.9, 14.2 ppm; MS (EI) *m/z* (%) 226 (M^+-CH_3^+), 41(14), 43(82), 55(11), 59(10), 67(14), 79(76), 83(11), 95(13), 105(17), 123(100), 169(17), 181(15), 211(77); HRMS (M^+-CH_3^+) calcd for $C_{12}H_{18}O_4$ 211.0970, found 211.0969; *Anal.* calcd: C 63.70, H 8.02, found C 63.72, H 8.05.



593

6-Carboxyethyl-(1*S*,2*S*)-1,2-dihydroxycyclohex-3-ene (593)

To a stirring solution of **5** (445 mg, 2.42 mmol) and potassium azodicarboxylate (1.41 g, 7.25 mmol) in MeOH (4 mL) was added glacial acetic acid (0.97 mL, 16.9 mmol) dropwise at -15 °C. The reaction was allowed to warm to r.t. slowly over 14 h, then quenched by the addition of Na_2CO_3 (7 mL) and concentrated under reduced pressure and extracted with ethyl acetate (5 x 5 mL). The combined organic layers were washed with brine (1 x 7 mL) and dried over Na_2SO_4. Recrystallization of the crude material from ethyl acetate-hexanes yielded **6** (378 mg, 84%) as a white solid. mp 91-92 °C (ethyl acetate-hexanes); R_f 0.29 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -53.3 (*c* 1.6, $CHCl_3$); IR (film) ν 3400, 2981, 2937, 2909, 1731, 1647, 1372, 1251, 1105, 1073, 993, 921, 878, 761, 670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (t, *J* = 4.1 Hz, 1H), 4.50 (d, *J* = 3.8 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.81-3.93 (m, 1H), 3.51 (s, OH), 2.69 (s, OH), 2.37-2.50 (m, 1H), 1.79-1.94 (m, 1H), 1.66-1.75 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 143.1, 130.1, 67.7, 65.7, 60.9, 25.0, 23.9, 14.2 ppm; MS (EI) *m/z* (%) 186(M), 41(12), 67(10), 68(38), 96(100), 97(16), 105(12), 142(90), 143(12); HRMS calcd for $C_9H_{14}O_4$ 186.0892, found 186.0892; *Anal.* calcd: C 58.05, H 7.58, found C 57.97, H 7.51.

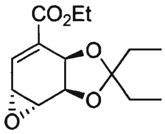


601

ethyl (3a*R*,7a*S*)-2,2-diethyl-3a,7a-dihydro-1,3-benzodioxole-4-carboxylate (601)

To a stirred solution of *cis*-dihydrodiol **7** (1.15 g, 6.24 mmol) in 3,3 dimethoxypentane (4.5 mL) was added 3-pentanone (2 mL). The resulting solution was cooled to 0 °C prior to the addition of a catalytic amount of *p*-TsOH. The reaction was allowed to warm to r.t. overnight. The reaction was diluted with EtOAc (10 mL), washed with 1 N NaOH (3 x 3 mL), brine (1 x 5 mL) and then dried over $MgSO_4$.

The crude material was purified via flash column chromatography with a solvent system of 2:1 (hexanes-ethyl acetate) to yield **601** (1.52 g, 97%) as a clear and colourless oil: R_f 0.41 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +9.31 (*c* 3.7, $CHCl_3$); IR (film) ν 3408, 2975, 2939, 1713, 1589, 1463, 1295, 1224, 1171, 1083, 1025, 931, 759, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 6.0, 0.7 Hz, 1H), 6.06-5.97 (m, 2H), 4.87 (d, *J* = 8.3 Hz, 1H), 4.81 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.70-1.60 (m, 2H), 1.56 (q, *J* = 7.4 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.75 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 133.8, 133.5, 126.5, 121.1, 109.2, 72.6, 68.2, 60.8, 29.2, 29.1, 14.2, 8.5, 7.9 ppm; MS (EI) *m/z* (%): 252 (M), 57(100), 65(10), 77(15), 95(49), 105(13), 121(32), 123(13), 139(23), 167(24), 223(33); HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1366.

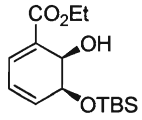


602

Ethyl(3a*R*,5a*R*,6a*R*,6b*R*)-2,2-diethyl-3a,5a,6a,6b-tetrahydrooxireno[*e*][1,3]benzodioxole-4-carboxylate (602)

To a stirred solution of 1,3-diene **601** (300 mg, 1.189 mmol) in methylene chloride (5 mL) was added *m*-CPBA (264 mg, 1.189 of 77.6%) at 0 ˚C. Upon complete consumption of starting material, the reaction was quenched by the addition of sat. NH_4Cl (5 mL). The reaction mixture was extracted with Et_2O (5x 15 mL), before the combined organic layers were washed with brine (1 x 5 mL) and dried over $MgSO_4$. The crude mixture was purified via flash column chromatography with 10%

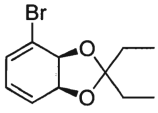
deactivated SiO_2 and a solvent gradient of 100:0, 25:1, 15:1, 8:1 (hexanes-ethyl acetate) to yield **602** (209 mg, 69%) as a clear and colourless oil: R_f 0.55 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +33.31 (*c* 3.2, $CHCl_3$); IR (film) ν 3408, 2975, 2939, 1713, 1589, 1463, 1295, 1224, 1171, 1083, 1025, 931, 759, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.8 Hz, 1H), 4.79 (q, *J* = 8.0 Hz, 2H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.57 (dd, *J* = 3.4 Hz, 1.1, 1H), 3.44 (t, *J* = 3.7 Hz, 1H), 1.73 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 133.7, 133.6, 114.7, 71.14, 68.6, 61.1, 50.9, 46.3, 29.9, 29.5, 14.2, 8.3, 7.8 ppm; MS (EI) *m/z* (%): 268 (M), 57(100), 65(10), 77(15), 95(49), 105(13), 121(32), 123(13), 139(23), 167(24), 223(33); HRMS calcd for $C_{14}H_{20}O_5$ 268.1311, found 268.1371.



606

Ethyl (5*S*,6*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-6-hydroxycyclohexa-1,3-diene-1-carboxylate (606)

To a stirred solution of *cis*-dihydrodiol **7** (770 mg, 4.18 mmol) in DMF (5 mL) was added imidazole (369 mg, 5.43 mmol) and *tert*-butyldimethylsilyl chloride (693 mg, 4.59 mmol) at 0 °C. The reaction was left to stir for 20 min before being capped and placed in a -15 °C freezer overnight. The reaction was then diluted with Et_2O (50 mL) and then washed with H_2O (20 x 2 mL), 5% citric acid (3 x 20 mL), and brine (1 x 5 mL) before the organic layer was dried over $MgSO_4$. The resulting crude mixture was purified via column chromatogprahy with a solvent system of 8:1 (hexanes-ethyl acetate) to yield **606** (306 mg, 52%) as a clear and colourless oil: R$_f$ 0.44 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +59.66 (*c* 1.2, $CHCl_3$); IR (film) ν 3408, 3502, 2954, 2930, 1710, 1471, 1373, 1230, 1080, 997, 898, 838, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 4.9 Hz, 1H), 6.03-5.88 (m, 2H), 4.49 (d, *J* = 5.7 Hz, 1H), 4.33 (d, *J* = 5.8 Hz, 1H), 4.24-4.11 (m, 2H), 2.62 (s, OH), 1.23 (t, *J* = 7.16 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.8, 134.4, 128.6, 122.4, 71.9, 64.4, 60.8, 41.5, 25.8, 18.2, 14.3, -4.7, -4.8 ppm; MS (EI) *m/z* (%): 298(M), 45(12), 57(11), 73(34), 75(100), 77(14), 105(11), 120(12), 121(15), 151(20), 167(19), 195(48), 223(11); HRMS calcd for $C_{15}H_{26}O_4Si$ 298.1600, found 298.1603.

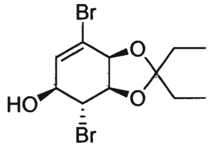


608

(3a*S*,7a*S*)-4-bromo-2,2-diethyl-3a,7a-dihydro-1,3-benzodioxole (608)

To a stirred solution of *cis*-dihydrodiol **6** (3.00 g, 15.7 mmol) in 3,3 dimethoxypentane (12 mL) was added 3-pentanone (5 mL). The resulting solution was cooled to 0 °C prior to the addition of a catalytic amount of *p*-TsOH. The reaction was allowed to warm to r.t. overnight. The reaction was diluted with EtOAc (15 mL), washed with 1 N NaOH (3 x 5 mL), brine (1 x 7 mL) and then dried over $MgSO_4$. The crude material was purified via flash column chromatography with a solvent system of 2:1 (hexanes-ethyl acetate) to yield **608** (3.68 g, 91%) as a clear and colourless oil: R$_f$ 0.42 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +109.0 (*c* 1.25, $CHCl_3$); IR (film) ν 3248, 3050, 2973, 2939, 2881, 1724, 1584, 1463, 1202, 1170, 1071, 1055, 924, 728, 636 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, *J* = 6.1 Hz, 1H), 5.96 (dd,

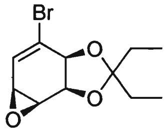
$J = 9.5, 3.1$ Hz, 1H), 5.84 (q, $J = 5.3$ Hz, 1H), 4.78-4.65 (m, 2H), 1.71-1.61 (m, 4H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4, 125.0, 124.3, 123.9, 110.2, 76.0, 72.6, 29.4, 28.9, 8.4, 7.8 ppm; MS (EI) *m/z* (%): 258 (M), 57(100), 65(12), 77(13), 94(16), 173(25), 175(24), 229(14), 231(14); HRMS calcd for $C_{11}H_{15}BrO_2$ 258.0255, found 258.0242; *Anal.* calcd: C 50.98, H 5.83, found C 50.87, H 5.70.



609

(3a*R*,4*R*,5*S*,7a*S*)-4,7-dibromo-2,2-diethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-ol (609)

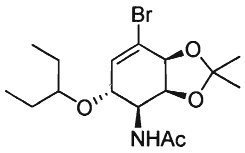
To a stirred solution of 1,3-diene **608** (5.75 g, 22.2 mmol) in acetone (70 mL) and H_2O (30 mL) was added 1,3-dibromo-5,5- dimethylhydantoin (5.07 g, 17.8 mmol) in 5 portions over a total of 30 mins. After 3 h the reaction was quenched by the addition of 10% NaS_2O_3 (50 mL). The acetone was removed on a rotary evaporator prior to extracting the aqueous layer with methylene chloride (4 x 30 mL). The combined organic layers were washed with 1 N NaOH (3 x 5 mL) and dried over Mg_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 2:1 (hexanes-ethyl acetate) to yield **609** (4.41 g, 56%) as a clear and colourless oil: R_f 0.23 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +10.72 (*c* 0.6, $CHCl_3$); IR (film) ν 3435, 2973, 2940, 1724, 1644, 1463, 1383, 1353, 1244, 1204, 1172, 1055, 921, 636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, $J = 4.6$ Hz, 1H), 4.70 (d, $J = 5.3$ Hz, 1H), 4.63 (t, $J = 5.5$ Hz, 1H), 4.37-4.27 (m, 2H), 3.03 (d, $J = 9.0$ Hz, OH), 1.80-1.65 (m, 4H), 0.98 (t, J = 6.0 Hz, 3H), 0.93 (t, J = 6.1, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.4, 124.6, 116.2, 78.1, 76.6, 76.0, 70.46, 47.9, 30.3, 29.5, 8.4, 8.2 ppm; MS (EI) *m/z* (%): 353(M), 57(100), 172(14), 174(13), 253(13), 325(19), 327(36), 329(18); HRMS calcd for $C_{11}H_{16}Br_2O_3$ 353.9466, found 353.9376



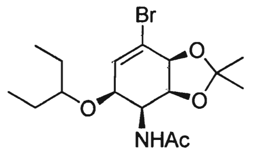
610

(3a*S*,5a*S*,6a*S*,6b*S*)-4-bromo-2,2-diethyl-3a,5a,6a,6b-tetrahydrooxireno[*e*][1,3]benzodioxole (610)

To a stirred solution of β-bromo hydroxyl **609** (3.41g, 9.58 mmol) in dimethoxymethane (20 mL) was added 10% NaOH (4.02 mL, 10.0 mmol) dropwise. Upon complete consumption of starting material (TLC) the reaction was diluted with H_2O (10 mL), extracted with Et_2O (5 x 15 mL), washed with brine (1 x 5 mL) and dried with $MgSO_4$. The crude mixture was purified via flash column chromatography with 10% deactivated SiO_2 and a solvent system of 6:1 (hexanes-ethyl acetate) to afford **610** as a clear and colourless oil (1.16 g, 44%): R_f 0.55 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -2.46 (*c* 4.98, $CHCl_3$); IR (film) ν 3400, 2973, 2940, 2881, 1643, 1462, 1356, 1171, 1079, 993, 922, 880, 800, 580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, J = 4.1 Hz, 1H), 4.65 (dd, J = 6.9, 0.8 Hz, 1H), 4.47 (dd, J = 6.9, 2.9 Hz, 1H), 3.63-3.55 (m, 1H), 3.35 (t, J = 4.1 Hz, 1H), 1.72 (q, J = 7.5 Hz, 2H), 1.60 (q, J = 7.5 Hz, 2H), 0.94-0.83 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.3, 126.1, 110.6, 76.8, 73.7, 54.6, 49.9, 29.5, 28.3, 8.5, 8.1 ppm; MS (EI) *m/z* (%): 274(M), 57(100), 109(21), 245(22), 247(22); HRMS calcd for $C_{11}H_{15}BrO_3$ 274.0205, found 274.0414.



619



620

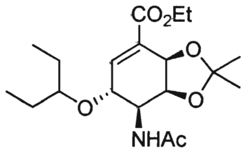
***N*-[(3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-5-(1-ethylpropoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]acetamide (619)**

***N*-[(3a*S*,4*S*,5*S*,7a*S*)-7-Bromo-5-(1-ethylpropoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]acetamide (620)**

To a solution of aziridine **429** (7.78 g, 27.0 mmol) in 3-pentanol (30 mL) was added copper(II) trifluoromethanesulfonate (976 mg, 2.70 mmol) at 0 ˚C. The reaction mixture was stirred for 16 h before concentrating under reduced pressure. The crude residue was dissolved in methylene chloride (20 mL), washed with sat. $NaHCO_3$ (3 x 5 mL), and brine (1 x 10 mL) and then dried over Na_2SO_4. The residue was purified by flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-diethyl ether) to afford **619** (7.64 g, 76%) and **620** (1.09 g, 11%) as clear oils.

619: R_f 0.40 (diethyl ether); $[\alpha]_D^{23}$ -100.0 (*c* 1.0, $CHCl_3$); IR (film) ν 3439, 3019, 2971, 2936, 2879, 1675, 1514, 1463, 1384, 1373, 1342, 1514, 1463, 1384, 1373, 1342, 1216, 1163, 1095, 1046, 965, 931, 888, 865, 758, 669, 502 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.14 (d, *J* = 1.5 Hz, 1H), 5.83 (d, *J* = 9.0 Hz, 1H), 4.57 (dd, *J* = 1.5, 5.3 Hz, 1H), 4.40 (dd, *J* = 2.4, 5.1 Hz, 1H), 4.30 (dt, *J* = 2.4, 8.9 Hz, 1H), 3.89 (dd, *J* = 1.5, 8.9 Hz, 1H), 3.24 (quin., *J* = 5.6 Hz, 1H), 2.00 (s, 3H), 1.43-1.49 (m, 4H), 1.38 (s, 3H), 1.34 (s, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 132.5, 122.7, 110.2, 82.4, 77.3, 76.0, 73.6, 51.2, 27.4, 26.3, 26.1, 25.6, 23.5, 9.6, 9.2 ppm; MS (EI) *m*/*z* (%) 375 (M), 232(8), 231(7), 230(9), 229(5), 190(21), 189(16), 188(22), 187(13), 166(6), 164(6), 143(22), 142(100), 137(9), 136(8), 126(6), 125(6), 110(5), 109(32), 108(7), 100(30), 85(6), 84(61), 83(9), 80(9), 71(8), 70(9), 60(9), 59(12), 43(73), 41(7); HRMS (EI) calcd for $C_{16}H_{26}BrNO_4$ 375.1045, found 375.1045; *Anal.* calcd: C 51.07, H 6.96, found C 51.07, H 6.98.

620: R$_f$ 0.45 (diethyl ether); $[\alpha]_D^{23}$ +41.5 (*c* 1.0, $CHCl_3$); IR (film) ν 3439, 3019, 2971, 2936, 2879, 1675, 1514, 1463, 1384, 1373, 1342, 1514, 1463, 1384, 1373, 1342, 1216, 1163, 1095, 1046, 965, 931, 888, 865, 758, 669, 502 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.35 (d, *J* = 8.7 Hz, 1NH), 6.31 (d, *J* = 5.3 Hz, 1H), 4.57 (d, *J* = 5.3 Hz, 1H), 4.40-4.44 (m, 2H), 3.90 (t, *J* = 5.3 Hz, 1H), 3.19 (quin., *J* = 5.8 Hz, 1H), 2.03 (s, 3H), 1.41-1.55 (m, 4H), 1.46 (s, 3H), 1.36 (s, 3H), 0.88 (t, *J* = 7.6 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 129.0, 127.5, 111.1, 81.6, 76.7, 75.3, 70.6, 46.6, 27.5, 26.6, 26.4, 25.9, 23.3, 9.8, 9.6 ppm; MS (EI) *m*/*z* (%) 375 (M), 232(8), 231(7), 230(9), 229(5), 190(21), 189(16), 188(22), 187(13), 166(6), 164(6), 143(22), 142(100), 137(9), 136(8), 126(6), 125(6), 110(5), 109(32), 108(7), 100(30), 85(6), 84(61), 83(9), 80(9), 71(8), 70(9), 60(9), 59(12), 43(73), 41(7); HRMS (EI) calcd for $C_{16}H_{26}BrNO_4$ 375.1045, found 375.1045.

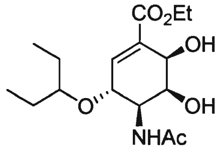


621

Ethyl (3a*R*,6*R*,7*S*,7a*S*)-7-(acetylamino)-6-(1-ethylpropoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (621)

To a solution of vinyl bromide **619** (6.50g, 17.27 mmol) in toluene (300 mL) and ethanol (82 mL) was passed CO gas (1 atm). After 10 min triethylamine (84.19 mL, 604.6 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (998 mg, 0.864 mmol) at r.t.. The resulting solution was heated to 60 °C while a continuous flow of CO gas (1 atm) was passed through the reaction mixture. After 2 h dichlorobis(triphenylphosphine)palladium(II) (1.212 g, 1.727 mmol) was added in two portions over 15 min. The reaction mixture was brought to reflux for 4 h, cooled to r.t., and filtered through a plug of celite. The crude material was purified by flash column chromatography with a solvent gradient of 2:1 then 1:1 (hexanes-ethyl acetate) to yield **621** (4.34 g, 68%) as a colourless solid: R_f 0.22 (96:4, methylene chloride/methanol); mp 112-115 °C;$[\alpha]_D^{23}$ -122.7 (*c* 1.0, $CHCl_3$); IR (film) ν 3383, 3022, 2975, 2879, 1711, 1663, 1576, 1464, 1374, 1254, 1218, 1094, 1068, 929, 776, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.9 Hz, 1H), 5.82 (d, *J* = 8.7 Hz, 1NH), 5.03 (dd, *J* = 0.76, 5.7 Hz, 1H), 4.49 (dd, *J* = 2.6, 5.7 Hz, 1H), 4.22-4.31 (m, 3H), 4.04 (d, *J* = 9.0 Hz, 1H), 3.34 (quin, *J* = 5.6 Hz, 1H), 2.03 (s, 3H), 1.48-1.56 (m, 4H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 165.5, 141.1, 129.9, 109.5, 82.6, 74.7, 72.0, 71.6, 61.1, 51.9, 27.3, 26.1, 25.9, 25.5, 23.6, 14.2, 9.6, 9.3

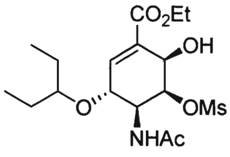
ppm; MS (EI) *m/z* (%) 369(M^+-CH_3), 228(10), 182(12), 181(11), 154(6), 153(8), 143(8), 142(88), 136(10), 112(8), 110(7), 109(7), 100(17), 88(6), 87(13), 86(32), 85(8), 84(100), 83(9), 80(6), 71(12), 70(11), 69(5), 60(8), 59(13), 58(5), 57(11), 55(11), 49(10), 47(11), 43(87), 42(6), 41(13); HRMS (EI) calcd for $C_{18}H_{28}NO_6$ 354.1917, found 354.1919; *Anal.* calcd: C 61.77, H 8.46, found C 61.74, H 8.40.



622

Ethyl (3*R*,4*R*,5*S*,6*R*)-4-(acetylamino)-3-(1-ethylpropoxy)-5,6-dihydroxycyclohex-1-ene-1-carboxylate (622)

To a solution of ethyl ester **621** (1.13 g, 3.06 mmol) in ethanol (20 mL) was added 6 M HCL (500 μL) at room temperature. The resulting solution was stirred for 5 h at 60 °C before the addition of H_2O (500 μL). The reaction was stirred for an additional 1 h at 60 °C before cooling to room temperature and concentrating under reduced pressure. The crude material was purified by flash column chromatography with a solvent system of 24:1 (methylene chloride/methanol) to yield **622** (715 mg, 71%) as white solid: R_f 0.71 (9:1, methylene chloride/methanol); $[\alpha]_D^{23}$ -44.1 (*c* 0.47, $CHCl_3$); mp 154 °C; IR (film) ν 3380, 3020, 2970, 2937, 2879, 1715, 1661, 1576, 1464, 1374, 1244, 1217, 1094, 1060, 929, 756, 667 cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.36 (d, *J* = 6.4 Hz, 1NH), 6.78 (d, *J* = 3.8 Hz, 1H), 4.86 (d, *J* = 4.2 Hz, 1OH), 4.64 (t, *J* = 3.9 Hz, 1H), 4.21-4.25 (m, 1H) 4.21 (dq, *J* = 1.1, 7.2 Hz, 2H), 4.01-4.15 (m, 2H), 3.96 (dd, *J* = 4.3, 6.6 Hz, 1H), 3.56 (quin, *J* = 5.8 Hz, 1H), 1.87 (s, 3H), 1.44-1.58 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ 169.2, 165.9, 137.7, 132.6, 81.4, 73.4, 67.0, 65.7, 60.4, 53.1, 26.1, 26.0, 22.4, 13.6, 9.2, 8.8 ppm; MS (FAB) *m*/*z* (%) 330 (M^+), 260(21), 242(25), 224(13), 182(23), 178(14), 152(11), 136(13), 112(11), 110(21), 109(16), 81(13), 71(13), 69(17), 67(10), 60(19), 57(19), 55(31), 43(100), 41(34), 39(16), 29(45); HRMS calcd for $C_{16}H_{28}NO_6^+$ 330.1917, found 330.1919.

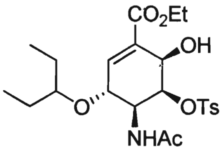


624

Ethyl (3*R*,4*S*,5*S*,6*R*)-4-(acetylamino)-3-(1-ethylpropoxy)-6-hydroxy-5-[(methylsulfonyl)oxy]cyclohex-1-ene-1-carboxylate (624)

To a stirred solution of 1,2-diol **622** (20 mg, 0.061 mmol) in pyridine (0.5 mL) was added mesyl chloride (5 µL, 0.061 mmol) at 0 °C. The resulting solution was stirred for 24h before diluting with Et_2O (1 mL) and H_2O (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 x 0.2 mL). The combined organic layers were washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 1:20 then 1:10 (hexane-ethyl acetate) to yield **624** (21 mg, 86%) as a white solid: R_f 0.47 (1:15 hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 4.1 Hz, 1H), 6.83 (d, *J* = 6.8 Hz, 1NH), 5.09 (t, *J* = 3.6 Hz, 1H), 4.95 (d, *J* = 4.2 Hz, 1H), 4.42 (dt, *J* = 3.7, 7.3 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14 (t, *J* = 4.2 Hz, 1H), 3.69 (br s, 1OH), 3.53 (qn, *J* = 5.7 Hz, 1H), 3.13)s, 3H), 1.98 (s, 3H), 1.48-1.60 (m, 4H), 1.33 (t, *J* =

7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H) ppm; MS (EI) *m/z* (%): 362 ($M-C_2H_5O^+$), 43(100), 112(66), 136(39), 149(25), 158(32), 181(29), 182(21), 228(44); HRMS calcd for $C_{15}H_{24}NO_7S$ 362.1270, found 362.1278; *Anal.* calcd: C 50.11, H 7.17, found C 50.16, H 7.31.

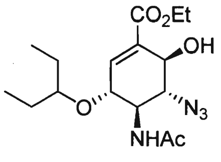


625

Ethyl (3*R*,4*S*,5*S*,6*R*)-4-(acetylamino)-3-(1-ethylpropoxy)-6-hydroxy-5-{[(4-methylphenyl)sulfonyl]oxy}cyclohex-1-ene-1-carboxylate (625)

To a solution of 1,2-diol **622** (2.32 g, 7.04 mmol) in dry pyridine (15 mL) was added 4-toluenesulfonyl chloride (1.48 g, 7.74 mmol) portion wise over 5 min. The reaction mixture was stirred at room temperature for 48 h and then diluted with methylene chloride (10 mL). The organic layer was washed with cold 1 N HCl (3 x 5 mL), brine (1 x 10 mL) and dried over Na_2SO_4. The crude mixture was purified by flash column chromatography with a solvent system gradient of 99:1 then 96:4 (methylene chloride/methanol) to yield **625** (1.76 g, 76%, based on 0.587 g recovered starting material) as clear oil; R_f 0.71 (96:4, methylene chloride/ methanol); $[\alpha]_D^{23}$ -36.6 (*c* 2.5, $CHCl_3$); IR (film) ν 3375, 2971, 2937, 2879, 2733, 2458, 2252, 1920, 1716, 1660, 1598, 1527, 1463, 1444, 1372, 1248, 1218, 1190, 1178, 1121, 1096, 1059, 1002, 970, 915, 848, 815, 769, 704, 666, 556, 486 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 6.8 Hz, 1NH), 6.87 (d, J = 4.9 Hz, 1H), 4.95 (t, J = 3.5 Hz, 1H), 4.76 (t, J = 3.8 Hz, 1H), 4.26 (q,

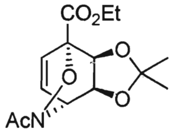
$J = 7.2$ Hz, 2H), 4.15 (dt, $J = 3.2$, 6.8 Hz, 1H), 4.08 (dd, $J = 2.6$, 4.9 Hz, 1H), 3.45 (quin, $J = 5.8$ Hz, 1H), 3.25 (d, $J = 3.4$ Hz, 1OH), 2.45 (s, 3H), 1.92 (s, 3H), 1.45-1.51 (m, 2H), 1.34-1.40 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.24-1.26 (m, 1H), 0.84 (t, $J = 7.4$, 3H), 0.70 (t, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 165.3, 145.4, 137.4, 132.9, 131.2, 130.1 (2 x C), 128.0 (2 x C), 82.2, 74.6, 72.6, 64.6, 61.6, 50.9, 26.3, 25.9, 23.4, 21.7, 14.2, 9.8, 8.9 ppm; MS (FAB) *m/z* (%) 484(M^+), 29(13), 39(10), 41(13), 43(27), 55(12), 57(8), 69(6), 77(5), 91(8), 136(8), 178(5), 224(7), 396(5); HRMS (FAB) calcd for $C_{23}H_{34}NO_8S$ 484.2005, found 484.1998.



626

Ethyl (3*R*,4*R*,5*R*,6*R*)-4-(acetylamino)-5-azido-3-(1-ethylpropoxy)-6-hydroxycyclohex-1-ene-1-carboxylate (626)

To a stirred solution of *O*-tosylate **625** (24 mg, 0.049 mmol) in dimethoxyethane (2 mL) was added tetrabutylammonium azide (141 mg, 0.49 mmol). The resulting suspension was heat to reflux for 16 h, cooled and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a solvent system of 2:1 (hexanes-ethyl acetate) to yield **626** (12 mg, 69%) as a pale yellow oil: R_f 0.27 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -39.71 (*c* 1.00, $CHCl_3$); mp 112-115 ˚C (hexanes-ethyl acetate); IR (film) ν 3684, 3019, 2400, 1676, 1498, 1425, 1216, 1064, 929, 757, 669, 497, 478, 472 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, $J = 0.94$, 2.8 Hz, 1H), 6.10 (d, $J = 7.9$ Hz, 1NH), 4.71 (ddd, $J = 0.94$, 1.1, 6.4 Hz, 1H), 4.48 (dd, $J = 6.4, 9.4$ Hz, 1H), 4.43 (ddd, $J = 2.1, 2.7, 6.8$ Hz, 1H), 4.28 (dq, $J = 2.7, 7.1$ Hz, 2H), 3.82 (ddd, $J = 6.7, 7.9, 9.4$ Hz, 1H), 3.47 (quin, $J = 5.8$ Hz, 1H), 2.01 (s, 3H), 1.48-1.56 (m, 4H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J = 7.5$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 166.0, 139.4, 130.3, 82.5, 73.0, 71.3, 61.5, 58.9, 55.9, 26.1, 25.8, 23.5, 14.2, 9.6, 9.4 ppm; MS (EI) *m/z* (%): 366 (M), 354(6), 313(6), 294(6), 255(6), 253(12), 251(7), 232(33), 230(34), 190(11), 189(6), 188(12), 187(5), 174(6), 173(10), 172(8), 171(9), 165(8), 163(8), 151(6), 109(22), 108(9), 93(7), 81(8), 80(10), 65(8), 59(11), 55(8), 43(100), 42(11), 41(6); HRMS (EI) calcd for $C_{16}H_{26}N_4O_5$ 354.1903, found 354.1900.



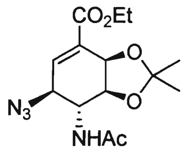
632

Ethyl (3a*S*,4*S*,7*R*,7a*S*)-8-acetyl-2,2-dimethyl-7,7a-dihydro-4,7-(epoxyimino)-1,3-benzodioxole-4(3a*H*)-carboxylate (632)

To a stirred solution of *cis*-dihydrodiol **7** (5 g, 27.1 mmol) in 2,2-dimethoxypropane (80 mL) was added *p*-toluenesulfonic acid (catalytic amount) at r.t.. After complete consumption of starting material (TLC analysis), the solution was cooled 0 °C before the addition of H_2O (10 mL). On a preparative scale the intermediate acetonide was not isolated (analytical samples were purified via flash column chromatography with a solvent system of 3:1 (hexanes-ethyl acetate)). Data for the intermediate **ethyl (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole-4-carboxylate**: R_f 0.56 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +74.6 (*c* 4.02, $CHCl_3$); IR (film): ν 3018, 2987, 2936, 1712, 1651, 1425, 1380, 1259, 1155, 1031, 917, 856, 697, 667, 512 cm^{-1}; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 5.3, *J* = 3.1 Hz, 1H), 4.84 (d, *J* = 5.7 Hz, 1H), 4.28-4.41 (m, 1H), 4.07-4.26 (m, 2H), 2.21-2.45 (m, 1H), 1.99-2.16 (m, 1H), 1.86-1.99 (m, 1H), 1.58-1.72 (m, 1H), 1.33 (d, *J* = 10.2 Hz, 6H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 142.3, 130.0, 108.5, 72.6, 70.4, 60.5, 27.8, 26.2, 25.1, 20.9, 14.2 ppm; MS (EI) *m/z* (%): 226 (M^+-CH_3), 211(77), 181(15), 169(17), 123(100), 105(17), 95(13), 83(11), 79(76), 67(14), 59(10), 55(11), 43(82), 41(14); HRMS (M^+-CH_3) calcd for $C_{12}H_{16}O_4$ 211.0970, found 211.0969; *Anal.* calcd: C 64.27; H 7.19. Found C 64.52; H 7.08.

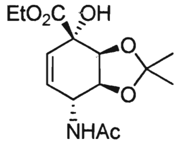
$NaIO_4$ (5.80 g, 27.1 mmol) was added to the reaction vessel prior to the addition of a solution of acetohydroxamic acid (2.03 g, 27.1 mmol) in MeOH (25 mL) dropwise over 5 min. The resulting solution was stirred at room temperature for 16 h, quenched by the slow addition of sat. $NaHSO_3$ (10 mL) and extracted into Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 30 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 2:8 (hexanes-ethyl acetate) to yield **632** (5.65 g, 70% over 2 steps) as a white solid: R_f 0.33 (3:7 hexanes- ethyl acetate); mp 89-90 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ -18.0 (*c* 0.54, $CHCl_3$); IR (film) ν 3466, 2938, 2987, 1747, 1684, 1620, 1372, 1275, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.57-6.65 (m, 2H), 5.47-5.52 (m, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.56 (dd, *J* = 4.7, 6.6 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.01 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 166.6, 132.4, 128.4, 111.7, 79.2, 76.1, 72.8, 62.7, 50.0, 25.6, 25.4, 21.7, 14.1 ppm; MS (EI) *m/z* (%): 297 (M), 43(100), 96(30), 100(32), 105(35), 124(52); HRMS calcd for $C_{14}H_{19}NO_6$ 297.1212, found 297.1215; *Anal.* calcd: C 56.56, H 6.44, found C 56.67, H 6.45.



633

Ethyl (3a*R*,6*S*,7*R*,7a*S*)-7-(acetylamino)-6-azido-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (633)

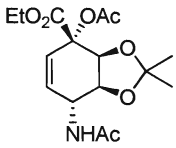
To a stirred solution of *O*-mesylate **650** (40 mg, 0.11 mmol) in 3:1 - acetone:H_2O (1 mL) was added sodium azide (69 mg, 1.1 mmol) at r.t.. The resulting solution was stirred for 24 h, and then extracted with ethyl acetate (5 x 1 mL). The combined organic layers were washed with brine (1 x 1 mL) and then dried over Na_2SO_4. The crude material was recrystallized from hexanes-ethyl acetate to yield **633** (30 mg, 87%) as a pale yellow solid: R_f 0.24 (1:5 hexanes-ethyl acetate); mp 90 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ +65.5 (*c* 1.15, $CHCl_3$); IR (film) ν 3298, 2983, 2103, 1722, 1658, 1372, 1251 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (d, *J* = 2.0 Hz, 1H), 6.14 (d, *J* = 8.2 Hz, 1NH), 4.93 (d, *J* = 5.6 Hz, 1H), 4.54 (dd, *J* = 2.0, 10.1 Hz, 1H), 4.46 (ddd, *J* = 1.7, 5.6, 10.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.68 (dt, *J* = 8.2, 9.6 Hz, 1H), 2.05 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 164.5, 140.4, 129.3, 110.9, 74.1, 70.7, 61.5, 58.9, 54.3, 28.2, 26.1, 23.7, 14.1 ppm; MS (EI) *m/z* (%): 309 ($M-CH_3^+$), 41(44), 43(100), 56(54), 57(46), 84(22); HRMS calcd for $C_{13}H_{17}N_4O_5$ 309.1199, found 309.1200.



634

Ethyl (3a*S*,4*S*,7*R*,7a*S*)-7-(acetylamino)-4-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (634)

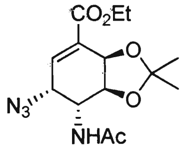
To a stirred solution of oxazine **632** (955 mg, 3.21 mmol) in 15:1/ CH_3CN:H_2O (10 mL) was added molybdenum hexacarbonyl (848 mg, 3.21 mmol) at r.t.. The reaction was brought to reflux for 3 h, and then cooled before the addition of activated charcoal (spatula tip). The resulting suspension was stirred for 30 min and then filtered through a plug of celite. The crude material was purified via flash column chromatography with a solvent system of 1:9 (hexanes-ethyl acetate) to yield **634** (720 mg, 75%) as a white solid: R_f 0.20 (ethyl acetate); mp 97-99 ˚C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ -94.3 (*c* 0.79, $CHCl_3$); IR (film) ν 3433, 2094, 1644, 1271, 1217, 1060 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.25 (d, *J* = 8.7 Hz, 1NH), 5.98 (dd, *J* = 3.8, 9.8 Hz, 1H), 5.94 (dd, *J* = 0.9, 9.9 Hz, 1H), 4.77-4.81 (m, 1H), 4.37 (t, *J* = 8.3 Hz, 1H), 4.34 (dd, *J* = 4.3, 7.7 Hz, 1H), 4.22-4.29 (m, 2H), 4.12 (s, 1OH), 1.99 (s, 3H), 1.35 (s, 3H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 170.0, 132.9, 129.6, 109.3, 81.0, 76.3, 74.5, 62.8, 48.8, 26.2, 24.2, 23.5, 14.0 ppm; MS (EI) *m/z* (%): 284 ($M-CH_3^+$), 43(90), 83(47), 84(100), 86(61), 96(37), 125(36), 153(38), 199(99); HRMS calcd for $C_{13}H_{18}NO_6$ 284.1130, found 284.1137; *Anal.* calcd: C 56.18, H 7.07, found C 56.27, H 7.11.



635

Ethyl (3a*S*,4*S*,7*R*,7a*S*)-7-(acetylamino)-4-(acetyloxy)-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (635)

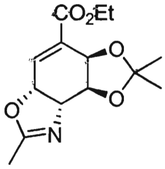
To a stirred solution of allylic alcohol **634** (527 mg, 1.76 mmol) in acetic anhydride (3 mL) was added DMAP (catalytic amount) at r.t.. The resulting solution was stirred for 1 h before diluting with EtOAc (2 mL) and H_2O (2 mL). The reaction was quenched by the slow addition of $NaHCO_3$, and then extracted into EtOAc (3 x 2 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over $NaSO_4$ and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of 1:9 (hexanes-ethyl acetate) to yield **635** (565 mg, 94%) as a white solid: R_f 0.26 (2:8 hexanes-ethyl acetate); mp 189-190 ˚C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ +69.4 (*c* 0.27, $CHCl_3$); IR (film) ν 3429, 3264, 2916, 1758, 1630, 1374, 1226, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.59 (d, *J* = 10.2 Hz, 1H), 6.14 (dd, *J* = 5.9, 10.0 Hz, 1H), 5.52 (d, *J* = 8.7 Hz, 1NH), 4.79 (ddd, *J* = 2.7, 5.8, 8.8 Hz, 1H), 4.64 (dd, *J* = 0.76, 6.8 Hz, 1H), 4.51 (dd, *J* = 2.6, 6.8 Hz, 1H), 4.21-4.31 (m, 2H), 2.10 (s, 3H), 1.99 (s, 3H), 1.34 (s, 3H), 1.27-1.30 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 168.5, 167.8, 131.9, 128.5, 109.5, 78.0, 77.1, 75.7, 62.0, 46.9, 26.1, 24.5, 23.6, 21.0, 14.0 ppm; MS (EI) *m/z* (%): 326 ($M-CH_3^+$), 43(100), 136(12), 153(13), 199(17), 282(10); HRMS calcd for $C_{15}H_{20}NO_7$ 326.1240, found 326.1235; *Anal.* calcd: C 56.30, H 6.79, found C 56.40, H 6.80.



636

Ethyl (3a*R*,6*R*,7*R*,7a*S*)-7-(acetylamino)-6-azido-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (636)

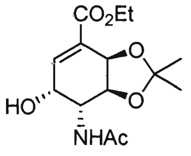
A solution of allylic acetate **635** (102 mg, 0.299 mmol) and trimethylsilyl azide (138 mg, 1.20 mmol) in THF (1 mL) was brought to reflux prior to the addition of freshly prepared tetrakis(triphenylphosphine)palladium (17 mg, 0.0149 mmol) in one portion. The reaction was allowed to reflux for 1 h, then cooled to r.t. and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of 7:3 (hexanes-ethyl acetate) to yield **636** (75 mg, 77%) as a pale yellow solid: R_f 0.51 (8:2 hexanes-ethyl acetate); mp 156-157 °C ($CHCl_3$); $[\alpha]_D^{23}$ -183.6 (*c* 0.34, $CHCl_3$); IR (film) ν 3583, 3284, 2987, 2108, 1720, 1655, 1540, 1372, 1248, 1072 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.97 (d, *J* = 4.5 Hz, 1H), 5.64 (br s, 1NH), 4.96 (d, *J* = 5.7 Hz, 1H), 4.54 (t, *J* = 4.3 Hz, 1H), 4.44 (td, *J* = 4.4, 7.9 Hz, 1H), 4.25-4.32 (m, 3H), 2.04 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 164.7, 136.2, 132.0, 110.4, 73.1, 70.1, 61.6, 56.7, 50.2, 27.7, 25.9, 23.3, 14.2 ppm; MS (EI) *m/z* (%): 309 ($M-CH_3^+$), 43(100), 84(37), 167(15), 224(10), 309(18); HRMS calcd for $C_{13}H_{17}N_4O_5$ 309.1200, found 309.1197.



641

Ethyl (3a*R*,5a*R*,8a*R*,8b*S*)-2,2,7-trimethyl-3a,5a,8a,8b-tetrahydro[1,3]dioxolo[4,5-*e*][1,3]benzoxazole-4-carboxylate (641)

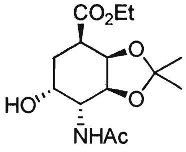
To a stirred solution of allylic alcohol **634** (400 mg, 1.33 mmol) in methylene chloride (5 mL) was added NEt_3 (0.74 mL, 4.0 mmol), DMAP (catalytic amount) and methanesulfonyl chloride (0.16 mL, 1.4 mmol) at r.t.. The resulting solution was stirred for 4 h before being quenched by the slow addition of sat. $NaHCO_3$ (5 mL), and then extracted into ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over $NaSO_4$ and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of 1:2 (hexanes-ethyl acetate) to yield **641** (204 mg, 54%) as a white yellow solid: R_f 0.40 (1:4 hexanes-ethyl acetate); mp 54-55 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ +150.4 (*c* 1.25, $CHCl_3$); IR (film) ν 3543, 2986, 1722, 1667, 1372, 1218 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 5.14 (dd, *J* = 2.9, 8.5 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.86 (dd, *J* = 2.7, 5.1, Hz, 1H), 4.58 (d, *J* = 8.4 Hz, 1H), 4.27-4.34 (m, 2H), 1.97 (d, *J* = 1.3 Hz, 3H), 1.42 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 165.6, 133.3, 130.5, 109.1, 73.6, 73.2, 68.9, 64.3, 61.2, 27.8, 26.3, 14.2, 14.1 ppm; MS (EI) *m/z* (%): 266 ($M-CH_3^+$), 43(52), 136(19), 266(100); HRMS calcd for $C_{13}H_{16}NO_5$ 266.1028, found 266.1032.



643

Ethyl (3a*R*,6*R*,7*R*,7a*S*)-7-(acetylamino)-6-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (643)

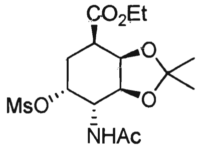
To a stirred solution of oxazoline **641** (800 mg, 2.86 mmol) in 1:1/ ethanol:water (8 mL) was added calcium carbonate (570 mg, 5.69 mmol) at r.t.. The reaction mixture was brought to reflux for 48 h before concentrating. The crude residue was dissolved in ethyl acetate and then filtered through a plug of celite. The crude material was purified via flash column chromatography with a solvent system of 1:4 (hexanes-ethyl acetate) to yield **643** (616 mg, 72%) as a white solid: R_f 0.23 (96:4 methylene chloride-methanol); mp 115-118 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ -54.33 (*c* 1,7, $CHCl_3$); IR (film) ν 3307, 2624, 2247, 1718, 1655, 1541, 1247, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 3.1 Hz, 1NH), 5.76 (br s, 1NH), 5.01 (d, *J* = 5.6 Hz, 1H), 4.73 (t, *J* = 3.4 Hz, 1H), 4.53 (q, *J* = 5.9 Hz, 1H), 4.47 (t, *J* = 5.8 Hz, 1H), 4.26-4.31 (m, 2H), 3.07 (bs, 1OH), 2.04 (s, 3H), 1.42 (s, 6H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 165.4, 141.0, 130.3, 109.9, 73.8, 69.8, 68.8, 61.3, 52.3, 27.48, 25.7, 23.4, 14.2 ppm; MS (FAB) *m/z* (%): 299 (M^+), 29(34), 43(71), 136(29), 182(23), 242(100); MS (EI) *m/z* (%): 284 ($M-CH_3^+$), 43(100), 84(25), 142(23), 284(17); HRMS calcd for $C_{13}H_{18}NO_6$ 284.1134, found 284.1132; *Anal.* calcd: C 56.18, H 7.07, found C 56.22, H 7.17.



645

Ethyl (3a*R*,4*R*,6*R*,7*R*,7a*S*)-7-(acetylamino)-6-hydroxy-2,2-dimethyl hexahydro-1,3-benzodioxole-4-carboxylate (645)

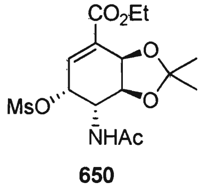
A hydrogenation vial was charged with ethyl acrylate **643** (150 mg, 0.501 mmol), 5% Rh/Al_2O_3 (60 mg) and 85% ethanol (2 mL) before evacuating with H_2. The reaction was stirred at r.t. and 60 psi for 144h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 (hexanes-ethyl acetate) then methanol to yield **645** (143 mg, 95%) as a white solid: R_f 0.66 (90:10 $CHCl_3$-methanol); mp 156-158 ˚C ($CHCl_3$); $[\alpha]_D^{23}$ -90.15 (*c* 1.1, $CHCl_3$); IR (film) ν 3305, 2986, 1722, 1666, 1553, 1374, 1219, 1066, 771 cm^{-1}; ^1H NMR (600 MHz, ($CO(CD_3)_2$) δ 7.17 (d, *J* = 7.7 Hz, 1NH), 4.59 (t, *J* = 4.1 Hz, 1H), 4.38 (br s, 1OH), 4.21 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.14 (dd, *J* = 4.6, 9.0 Hz, 1H), 4.11 (dq, *J* = 3.3, 7.0 Hz, 1H), 4.00-4.03 (m, 1H), 3.85 (td, *J* = 2.2, 4.5 Hz, 1H), 3.24 (dt, *J* = 4.3, 12.6 Hz, 1H), 1.92 (s, 3H), 1.88-2.00 (m, 2H), 1.42 (s, 3H), 1.28 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; MS (EI) *m/z* (%): 301 (M), 43(38), 47(29), 49(24), 47(100), 86(80), 91(20); HRMS calcd for $C_{14}H_{23}NO_6$ 301.1525, found 301.1524.



648

Ethyl (3a*R*,4*R*,6*R*,7*S*,7a*S*)-7-(acetylamino)-2,2-dimethyl-6-[(methylsulfonyl)oxy]hexahydro-1,3-benzodioxole-4-carboxylate (648)

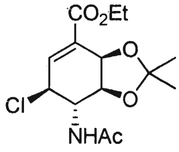
To a stirred solution of alcohol **645** (50 mg, 0.17 mmol) and triethylamine (93 µL, 0.66 mmol) in methylene chloride (100 µL) was added methanesulfonic anhydride (58 mg, 0.33 mmol) at 0 °C. The reaction was slowly raised to r.t. over 24 h before it was diluted with methylene chloride (500 µL), and then washed with 1 N HCl (2 x 500 µL), sat. $NaHCO_3$ (2 x 500 µL) and brine (1 x 1 mL). The crude material was purified via flash column chromatography with a solvent gradient of 1:2 then 1:5 (hexanes-ethyl acetate) to yield **648** (46 mg, 73%) as a white solid: R_f 0.47 (1:10 hexanes-ethyl acetate); mp 101-102 °C ($CHCl_3$); $[\alpha]_D^{23}$ -49.91 (*c* 1.21, $CHCl_3$); IR (film) ν 3307, 2628, 1719, 1651, 1361 cm cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.15-5.17 (m, 1H), 4.74 (d, *J* = 8.9 Hz, 1NH), 4.62 (t, *J* = 4.1 Hz, 1H), 4.22-4.28 (m, 1H), 4.15-4.19 (m, 1H), 4.03 (dd, *J* = 4.6, 8.6 Hz, 1H), 3.58 (dt, *J* = 2.7, 8.8 Hz, 1H), 3.12 (s, 3H), 2.92 (dt, *J* = 4.2, 13.3 Hz, 1H), 2.25 (dt, *J* = 4.2, 14.9 Hz, 1H), 2.09-2.13 (m, 1H), 2.08 (s, 3H), 1.55 (s, 3H), 1.37 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.7, 109.9, 77.7, 73.8, 73.3, 61.1, 56.4, 42.6, 37.6, 28.1, 26.2, 25.2, 21.0, 14.1 ppm; MS (FAB) *m/z* (%): 380 (M+ H^+), 43(23), 257(100); HRMS calcd for $C_{15}H_{26}NO_8S^+$ 380.1379, found 380.1366.



650

Ethyl (3a*R*,6*R*,7*S*,7a*S*)-7-(acetylamino)-2,2-dimethyl-6- [(methylsulfonyl)oxy]-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (650)

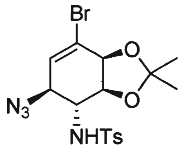
To a stirred solution of allylic alcohol **643** (40 mg, 0.13 mmol) and triethylamine (37 μL, 0.27 mmol) in methylene chloride (100 μL) was added methanesulfonyl chloride (13 μL, 0.16 mmol) at 0 °C. The reaction was slowly raised to room temperature over 12 h before extracting into EtOAc (5 x 1 mL). The combined organic layers were washed with sat. NH_4Cl (2 x 1 mL), brine (1 x 1 mL), and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 then 1:3 (hexane-ethyl acetate) to yield **650** (45 mg, 90%) as a white solid: R_f 0.22 (1:5 hexanes-ethyl acetate); mp 163-165 °C (hexanes-ethyl acetate); $[\alpha]_D^{23}$ -109.6 (*c* 1.25, $CHCl_3$); IR (film) ν 3307, 2628, 1719, 1651, 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 4.3 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1NH), 5.46 (t, *J* = 4.1 Hz, 1H), 5.01 (d, *J* = 5.3 Hz, 1H), 4.58 (td, *J* = 4.0, 4.1 Hz, 1H), 4.34 (dd, *J* = 5.5, 8.1 Hz, 1H), 4.24-4.32 (m, 2H), 3.07 (s, 3H), 2.05 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 164.5, 134.7, 133.5, 110.7, 73.5, 73.0, 69.9, 61.7, 49.8, 38.7, 27.6, 25.9, 23.3, 14.1 ppm; MS (FAB) *m/z* (%): 378 ($M+H^+$), 29(17), 43(39), 102(100), 136(24), 182(19), 224(18), 320(53), 378(41); HRMS calcd for $C_{15}H_{24}NO_8S^+$ 378.1223, found 378.1195; *Anal.* calcd: C 47.74, H 6.14, found C 47.80, H 6.04.



651

Ethyl (3a*R*,6*S*,7*S*,7a*S*)-7-(acetylamino)-6-chloro-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (651)

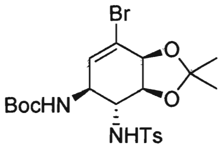
To a stirred solution of allylic alcohol **643** (40 mg, 0.13 mmol) and pyridine (22 μL, 0.13 mmol) in methylene chloride (100 μL) was added methanesulfonyl chloride (13 μL, 0.16 mmol) at 0 °C. The reaction was slowly raised to room temperature over 12 h before extracting into EtOAc (5 x 1 mL). The combined organic layers were washed with sat. NH_4Cl (2 x 1 mL), brine (1 x 1 mL), and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 then 1:3 (hexane-ethyl acetate) to yield **651** (36 mg, 88%) as a clear oil. R_f 0.27 (96:4 methylene chloride – methanol); ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 2.0 Hz, 1H), 5.79 (d, *J* = 7.7 Hz, 1NH), 5.15 (dt, *J* = 1.1, 9.8 Hz, 1H), 4.98 (d, *J* = 5.6 Hz, 1H), 4.61 (dd, *J* = 5.6, 9.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.68 (q, *J* = 9.2 Hz, 1H), 2.06 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H) ppm; MS (EI) *m/z* (%): 302 ($M-CH_3^+$), 43(100),106 (14), 266 (16); HRMS calcd for $C_{13}H_{17}ClNO_5$ 302.0795, found 302.0800.



664

N-[(3a*S*,4*R*,5*S*,7a*S*)-5-azido-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (664)

To a stirred solution of *N*-tosyl aziridine **570** (200 mg, 0.499 mmol) in DMF (2 mL) was added NH_4Cl (400mg) and NaN_3 (324 mg, 4.99 mmol) at 0 °C. The reaction mixture was stirred for 12 h, extracted into Et_2O (5 x 1 mL), washed with H_2O (20 x 0.5 mL), washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was recrystallized from $CHCl_3$-hexanes to yield **664** (203 mg, 92%) as a white solid: R_f 0.53 (2:1 hexanes-ethyl acetate); mp 119-120 °C ($CHCl_3$-hexanes); $[\alpha]_D^{23}$ +82.36 (*c* 3.5, $CHCl_3$); IR (film) ν 3435, 2108, 1645, 1599, 1219, 1159 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.14 (d, *J* = 3.4 Hz, 1H), 5.61 (d, *J* = 8.3 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 1H), 4.19 (dd, *J* = 5.8, 6.9 Hz, 1H), 3.73 (dd, *J* = 3.0, 6.4 Hz, 1H), 3.56 (q, *J* = 7.5 Hz, 1H), 2.45 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 137.5, 129.7, 129.0, 127.3, 127.2, 127.1, 127.0, 124.0, 111.3, 75.9, 75.6, 60.5, 55.2, 27.5, 25.9, 21.5 ppm; MS (EI) *m/z* (%): 442 (M), 43(47), 91(100), 155(35); HRMS calcd for $C_{15}H_{16}N_4O_4BrS^{\cdot}$ 442.0076, found 442.0072.

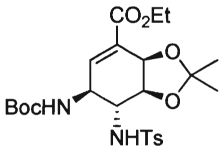


667

***tert*-butyl((3a*S*,4*R*,5*S*,7a*S*)-7-bromo-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl)carbamate (667)**

To a stirred solution of azide **664** (41 mg, 0.092 mmol) in 12:1 THF:H_2O (1 mL) was added triphenylphosphine (48 mg, 0.18 mmol). The reaction mixture was stirred for 12 h, extracted into diethyl ether (5 x 0.5 mL), washed with brine (1 x 1 mL) and dried over Na_2SO_4 to provide ***N*-{(3a*S*,4*R*,5*S*,7a*S*)-7-bromo-2,2-dimethyl-5-[(triphenylphosphoranylidene)amino]-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl}-4-methylbenzenesulfonamide (668)**. To a stirred solution of the crude Staudinger intermediate **668** (0.092 mmol) in DCM (1 mL) and triethylamine (50 μL) was added $(Boc)_2O$ (29 mg, 0.14 mmol) at 0 °C. The reaction mixture was stirred for 12 h, extracted into $CHCl_3$ (5 x 0.5 mL), washed with sat. NH_4Cl (2 x 1 mL), washed with brine (1 x 1 mL) and then dried over Na_2SO_4. The crude material was purified by flash column chromatography with a solvent gradient of 10:1, 6:1 then 3:1 (hexane-ethyl acetate) to yield **667** (36 mg, 77%): R_f 0.31 (2:1 hexanes-ethyl acetate); mp 153-154 °C (EtOAc-hexanes); $[\alpha]_D^{23}$ +15.467 (*c* 2.1, $CHCl_3$); IR (film) ν 3408, 2090, 1642, 1161 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.17 (d, *J* = 3.4 Hz, 1H), 5.32 (d, *J* = 8.9 Hz, 1H), 5.26 (d, *J* = 8.2 Hz, 1H), 4.60 (d, *J* = 5.6 Hz, 1H), 4.23 (dd, *J* = 6.2, 6.9 Hz, 1H), 4.08-4.13 (m, 1H), 3.46 (q, *J* = 7.4 Hz, 1H), 2.40 (s, 3H), 1.43 (s, 9H), 1.29 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C

NMR (150 MHz, $CDCl_3$) δ 155.6, 143.5, 137.5, 132.7, 129.6, 127.32, 121.4, 110.9, 80.3, 76.4, 76.3, 55.0, 51.2, 28.3, 27.3, 25.9, 21.5 ppm; MS (EI) *m/z* (%): 516 (M), 57(46), 91(81), 98(62), 99(97), 139(48), 254(100); HRMS calcd for $C_{21}H_{29}N_2O_6SBr$ 516.0930, found 516.0930.0940; *Anal.* calcd: C 48.75, H 5.65, found C 48.81, H 5.69.

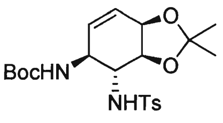


669

Ethyl (3a*R*,6*S*,7*R*,7a*S*)-6-[(*tert*-butoxycarbonyl)amino]-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino}-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (669)

A solution of vinyl bromide **667** (2 g, 3.86 mmol), ethanol (15 mL) and triethylamine (15 mL) in toluene (70 mL) was purged with CO (g) for 10 min. The solution was charged with CO(g), $Pd(PPh_3)_4$ (223 mg, 0.193 mmol) and then heated to 60 °C for 1 h before the addition of $Pd[(PPh_3)_2(Cl)_2]$ (271 mg, 0.386 mmol). The reaction was then heated to reflux for 6 h, cooled to r.t. and filtered through a plug of SiO_2. The crude material was purified by flash column chromatography to yield **669** (888 mg, 45%) as a yellow oil: R_f 0.46 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -11.77 (*c* 0.72, $CHCl_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 2.2 Hz, 1H), 5.36 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 8.3 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.10 (dd, *J* = 6.0, 8.9 Hz, 1H), 3.38 (q, *J* = 8.7 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.05 (s, 3H) ppm; ^{13}C NMR (75 MHz,

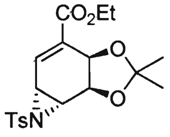
$CDCl_3$) δ 171.1, 143.5, 136.7, 129.6, 127.6, 109.5, 78.3, 74.0, 60.7, 42.9, 28.7, 27.4, 26.0, 21.5, 20.5, 14.1 ppm; MS (EI) *m/z* (%): 510 (M), 43(100), 57(52), 84(54); HRMS calcd for $C_{24}H_{34}N_2O_8S$ 510.2036, found 510.2038; *Anal.* calcd: C 56.45, H 6.71, found C 56.39, H 6.80.



670

***tert*-Butyl ((3a*S*,4*R*,5*S*,7a*R*)-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl)carbamate (670)**

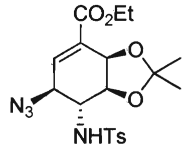
To a stirred solution of vinyl bromide **667** (730 mg, 1.41 mmol), N(*i*Pr)$_2$Et (1.93 mL, 21.6 mmol), abs. ethanol (6 mL) in THF (30 mL) was added Ni[(PPh$_3$)$_2$(CO)$_2$] (1.35g, 2.12 mmol). The reaction mixture was heated to 60 °C and stirred for 24 h, cooled to r.t. and charged with activated charcoal (1 g). The resulting mixture was stirred for 1 h and then filtered through a plug of celite and SiO_2. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **(16)** (488 mg, 79%) as a clear oil: R_f 0.52 (1:1 hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 5.80-5.82 (m, 1H), 5.22 (d, J = 9.1 Hz, 1H), 4.88 (d, J = 7.5 Hz, 1H), 4.55 (dd, J = 2.4, 6 Hz, 1H), 3.99-4.10 (m, 1H), 3.31 (q, J = 8.8 Hz, 1H), 2.38 (s, 3H), 1.44 (s, 9H, 1.22 (s, 3H), 1.08 (s, 3H) ppm; MS (EI) *m/z* (%): 438 (M), 41(91), 85(100), 91(70), 99(51), 139(41); HRMS calcd for $C_{21}H_{30}N_2O_6S$ 438.1825, found 438.1829.



671

Ethyl (3a*S*,4*R*,5*R*,7a*R*)-2,2-dimethyl-8-[(4-methylphenyl)sulfonyl] -3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole-7-carboxylate (671)

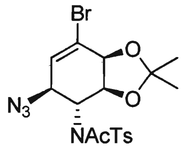
To a stirred solution of **ethyl (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole-4-carboxylate** (500 mg, 2.23 mmol) and Cu(acac)$_2$ (58 mg, 0.223 mmol) in MeCN (1 mL) was added PhI=NTs (832 mg, 2.23 mmol) at 0 ˚C. The resulting solution was stirred for 5 h before filtering through SiO$_2$ and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 10:1, 6:1 then 3:1 (hexane-ethyl acetate) to yield **671** (359 mg, 41%) as colourless crystals: R$_f$ 0.46 (2:1 hexanes-ethyl acetate); mp 106-107 ˚C (MeOH-hexanes); $[\alpha]_D^{23}$ -52.526 (*c* 0.62, CHCl$_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^{1}H NMR (600 MHz, (CO(CD$_3$)$_2$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 4.5 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.62 (dd, *J* = 0.9, 6.9 Hz, 1H), 4.14-4.21 (m, 2H), 3.56 (dd, *J* = 4.5, 6.2 Hz, 1H), 3.34 (dd, *J* = 1.1, 6.4 Hz, 1H), 2.45 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.6, 145.2, 134.7, 134.1, 131.2, 130.0 (2x C), 127.9 (2x C), 110.3, 70.0, 68.6, 60.7, 37.5, 35.3, 27.0, 24.9, 20.8, 13.6 ppm; MS (EI) *m/z* (%): 393 (M), 43(38), 47(29), 49(24), 47(100), 86(80), 91(20); HRMS calcd for $C_{19}H_{23}NO_6S$ 393.1246, found 393.1239; *Anal.* calcd: C 58.00, H 5.89, found C 58.02, H 5.90.



672

Ethyl(3a*R*,6*S*,7*R*,7a*S*)-6-azido-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino}-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (672)

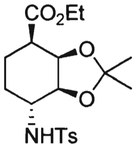
To a stirred solution of *N*-tosyl aziridine **671** (25 mg, 0.0636 mmol) and NH_4Cl (51 mg, 0.953 mmol) in DMF (0.5 mL) was added NaN_3 (8 mg, 0.127 mmol) at 0 °C. The resulting suspension was stirred for 3 h before diluting with Et_2O (1 mL) and H_2O (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 x 0.2 mL). The combined organic layers were washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 4:1 then 2:1 (hexanes-ethyl acetate) to yield **672** (22 mg, 79%) as a white solid: R_f 0.43 (1:1 hexanes-ethyl acetate); mp 116-118 °C (hexanes-ethyl acetate); IR (film) v 3432, 2102, 1655, 1598, 1219, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 2.6 Hz, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 4.91 (d, *J* = 5.5 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.10 (dd, *J* = 5.7, 9.1 Hz, 1H), 3.93 (dd, *J* = 2.6, 9.0 Hz, 1H), 3.45-3.54 (m, 1H), 2.42 (s, 3H), 1.32-1.37 (m, 4H), 1.28-1.32 (m, 5H) ppm; MS (FAB) *m/z* (%): 437 (M+ H$^+$), 43(18), 91(100), 136(20), 139(39), 152(23), 155(72), 167(24), 168(22), 181(27), 196(38), 437(27); HRMS calcd for $C_{19}H_{25}N_4O_6S$ 437.1495, found 437.1494



675

N-[(3a*S*,4*R*,5*S*,7a*S*)-5-azido-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-*N*-[(4-methylphenyl)sulfonyl]acetamide (675)

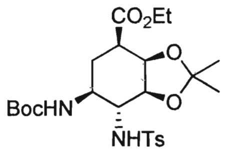
As solution of azide **664** (65 mg, 0.146 mmol) in triethylamine (0.5 mL) and Ac_2O (0.5 mL) was stirred at r.t. for 12 h, diluted with EtOAc (2 mL) and washed with H_2O (3 x 1 mL), washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **675** (73 mg, 90%) as a clear oil: R_f 0.62 (2:1 hexanes-ethyl acetate); IR (film) ν 3427, 2109, 1666, 1599, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.30-6.34 (m, 1H), 5.00-5.11 (m, 1H), 4.75-4.84 (m, 2H), 4.53-4.66 (m, 1H), 2.45 (s, 3H), 2.21 (s, 3H), 1.60 (s, 3H), 1.43 (s, 3H) ppm; MS (EI) *m/z* (%): 558 (M), 43(100), 65(44), 91(92), 155(86), 214(60); HRMS calcd for $C_{23}H_{31}BrN_2O_7S$ 558.1035, found 558.1034



677

Ethyl(3a*R*,4*R*,7*R*,7a*S*)-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino} hexahydro-1,3-benzodioxole-4-carboxylate (677)

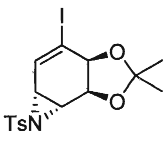
A round-bottomed flask was charged with *N*-tosyl aziridine **671** (25 mg, 0.0636 mmol), and platinum(IV)oxide (catalytic amount) and methanol (0.5 mL) before evacuating with H_2. The reaction was stirred at room temperature with 1 atm of H_2 for 12 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **677** (21 mg, 84%) as a white solid: R_f 0.34 (1:1 hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.64 (d, *J* = 4.8 Hz, 1NH), 4.50 (t, *J* = 4.2 Hz, 1H), 4.08-4.25 (m, 2H), 3.70 (dd, *J* = 4.6, 8.6 Hz, 1H), 2.90-3.02 (m, 1H), 2.60-2.70 (m, 1H), 2.41 (s, 3H), 2.12-2.23 (m, 1H), 1.68-1.83 (m, 2H), 1.20-1.25 (m, 6H), 1.07-1.20 (m, 1H), 0.96 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 143.5, 136.7, 129.6, 127.6, 109.5, 78.3, 74.0, 60.7, 42.9, 28.7, 27.4, 26.0, 21.5, 20.5, 14.1 ppm; MS (EI) *m/z* (%): 382 ($M-CH_3^+$), 43(52), 47(39), 69(31), 83(99), 84(100), 85(64), 86(60), 91(94), 138(49), 155(53), 184(88), 196(75); HRMS calcd for $C_{18}H_{24}NO_6S$ 382.1320, found 382.1326



678a

Ethyl (3a*R*,4*R*,6*S*,7*R*,7a*S*)-6-[(*tert*-butoxycarbonyl)amino]-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino}hexahydro-1,3-benzodioxole-4-carboxylate (678a)

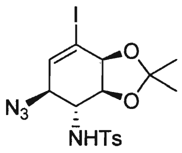
A hydrogenation vial was charged with ethyl acrylate **669** (240 mg, 0.470 mmol), and 5 % Rh/Al_2O_3 (60 mg) and 85% ethanol (1.5 mL) before evacuating with H_2. The reaction was stirred at r.t. and 55 psi for 144 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **678a** (228 mg, 95%) as a white solid: R_f 0.49 (1:1 hexanes-ethyl acetate); mp 246-247 ˚C ($CHCl_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.30 (d, *J* = 8.6 Hz, 1H), 5.12 (d, *J* = 8.3 Hz, 1H), 4.46 (t, *J* = 4.3 Hz, 1H), 4.18-4.25 (m, 1H), 4.09-4.15 (m, 1H), 3.86 (dd, *J* = 5.1, 8.8 Hz, 1H), 3.40 (dq, *J* = 1.3, 10.2 Hz, 1H), 3.21 (q, *J* = 9.3 Hz, 1H), 2.81 (dt, *J* = 3.8, 12.6 Hz, 1H), 2.42 (s, 3H), 2.13 (dt, *J* = 3.7, 13.5 Hz, 1H), 1.80 (q, *J* = 12.8 Hz, 1H), 1.45 (s, 9H), 1.22 (t, *J* = 6.9 Hz, 3H), 1.18 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 156.4, 142.8, 138.6, 129.1, 127.4, 109.4, 80.1, 79.2, 73.8, 60.9, 60.2, 50.4, 41.2, 28.5, 28.4, 27.7, 26.0, 21.4, 14.1 ppm; MS (EI) *m/z* (%): 497 (M-CH_3), 41(52), 43(44), 57(100), 91(99), 100(35), 155(44), 182(46), 240(47), 257(79); HRMS calcd for $C_{23}H_{33}N_2O_8S$ 497.1958, found 497.1962.



680

(3a*S*,4*R*,5*R*,7a*S*)-7-Iodo-2,2-dimethyl-8-[(4-methylphenyl)sulfonyl]-3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole (680)

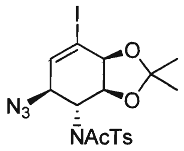
To a stirred solution of **(3a*S*,7a*S*)-4-iodo-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole** (5.16 g, 18.6 mmol) and Cu(acac)$_2$ (484 mg, 1.85 mmol) in MeCN (15 mL) was added PhI=NTs (4.8 g, 12.9 mmol) at 0 °C in 3 portions over 2 min. The resulting mixture was stirred for 30 min before the solid material was collected by filtration, dissolved in EtOAc and washed with 1 N HCl (2 x 5 mL) and sat. NaHCO$_3$ (2 x 5 mL). The crude material was recrystallized from ethyl acetate-hexanes to yield **680** (4.56g, 55%) as a white solid: R_f 0.64 (2:1 hexanes-ethyl acetate); mp 193-194 °C (EtOAc-hexanes); $[\alpha]_D^{23}$ +23.629 (*c* 1.175, CHCl$_3$); IR (film) ν 3435, 2890, 1651, 1644, 1159 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 6.65 (dd, *J* = 1.5, 4.8 Hz, 1H), 4.61 (dd, *J* = 1.4, 6.3 Hz, 1H), 4.27 (dd, *J* = 1.1, 6.5 Hz, 1H), 3.45 (dd, *J* = 1.8, 6.6 Hz, 1H), 3.13 (dd, *J* = 5.1, 6.5 Hz, 1H), 2.48 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ 145.1, 134.2, 131.4, 129.9, 128.0, 111.3, 108.5, 75.5, 70.7, 37.7, 36.2, 27.5, 26.3, 21.7 ppm; MS (EI) *m/z* (%): 447(M), 43(69), 79(52), 91(100), 155(34), 165(56), 206(40), 262(62); HRMS calcd for $C_{16}H_{18}INO_4S$ 447.0001, found 447.0004; *Anal.* calcd: C 42.96, H 4.06, found C 42.96, H 4.06.



681

N-[(3a*S*,4*R*,5*S*,7a*S*)-5-azido-7-iodo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (681)

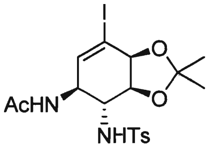
To a stirred solution of *N*-tosyl aziridine **680** (2 g, 4.47 mmol) in DMF (15 mL) was added NH_4Cl (4 g) and NaN_3 (377 mg, 5.8 mmol) at 0°C. The reaction mixture was stirred for 12 h, extracted into Et_2O (5 x 5 mL), washed with H_2O (20 x 1 mL), washed with brine (1 x 5 mL) and dried over Na_2SO_4. The crude material was recrystallized from EtOAc-hexanes to yield **681** (1.97 g, 90%) as a white solid: R_f 0.39 (2:1 hexanes-ethyl acetate); mp 151 °C (EtOAc-hexanes); IR (film) ν 3435, 2108, 1645, 1599, 1219, 1159 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.48 (d, *J* = 8.3 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 1H), 4.15 (dd, *J* = 5.7, 7.2 Hz, 1H), 3.69 (ddd, *J* = 0.9, 3.2, 6.5 Hz, 1H), 3.56 (q, *J* = 7.5 Hz, 1H), 2.42 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8, 137.5, 136.5, 129.7, 127.2, 110.8, 99.9, 78.1, 75.2, 61.4, 55.0, 27.5, 25.9, 21.5 ppm; MS (EI) *m/z* (%): 490(M), 43(55), 79(53), 91(100), 165(50), 206(33), 262(62); HRMS calcd for $C_{16}H_{19}IN_4O_4S$ 490.0172, found 490.0171.



684

N-[(3aS,4R,5S,7aS)-5-Azido-7-iodo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-N-[(4-methylphenyl)sulfonyl]acetamide (684)

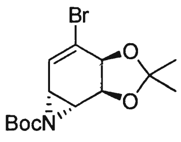
As solution of azide **681** (300 mg, 0.612 mmol) in triethylamine (0.7 mL) and Ac_2O (0.7 mL) was stirred at r.t. for 12 h, diluted with EtOAc (3 mL) and washed with H_2O (3 x 1 mL), washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **684** (283 mg, 87% as a clear oil: R_f 0.61 (2:1 hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 6.55 (d, J = 1.5 Hz, 1H), 4.91-5.07 (m, 1H), 4.69-4.82 (m, 2H), 4.50-4.61 (m, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.58 (s, 3H), 1.40 (s, 3H) ppm; MS (EI) m/z (%): 517 ($M-CH_3^+$), 43(100), 91(58), 155(86), 214(60); HRMS calcd for $C_{17}H_{18}IN_4O_5S$ 517.0043, found 517.0033.



685

***N*-((3a*S*,4*R*,5*S*,7a*S*)-7-Iodo-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl)acetamide (685)**

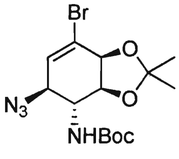
To a stirred solution of azide **684** (30 mg, 0.056 mmol) in THF (0.5 mL) was added SmI_2 (0.2 M in THF) dropwise until the reaction maintained a blue colour for 5 min. The reaction was quenched by the addition of 10% $Na_2S_2O_3$ until the reaction mixture became clear. The organics were extracted into EtOAc (5 x 1 mL), washed with brine (1 x 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes-ethyl acetate) to yield **685** (25 mg, 88% as a clear oil: R_f 0.73 (1:1 hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 5.79 (d, *J* = 7.6 Hz, 1H), 4.64 (d, *J* = 5.6 Hz, 1H), 4.41 (dd, *J* = 6.8, 8.3 Hz, 1H), 4.17 (dd, *J* = 6.0, 7.9 Hz, 1H), 3.38 (q, *J* = 8.1 Hz, 1H), 2.40(s, 3H), 2.01 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 143.5, 141.1, 137.6, 129.5, 127.3, 110.0, 95.1, 79.0, 76.8, 75.8, 54.9, 51.5, 27.1, 25.7, 23.2, 21.5 ppm; MS (EI) *m/z* (%): 506 (M), 43(74), 91(47), 99(54), 253(48), 254(72), 277(100), 278(42); HRMS calcd for $C_{18}H_{23}IN_2O_5S$ 506.0372, found 506.0376.



697

tert-Butyl (3a*S*,4*R*,5*R*,7a*S*)-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole-8-carboxylate (697)

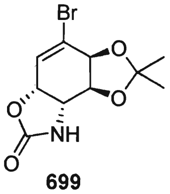
To a stirred solution of 1,3-diene **554** (1.45 g, 6.27 mmol), *tert*-butyl 4-nitrophenylsulfonyloxycarbamate **(696)** (19.9 g, 62.7 mmol) and benzyltriethylammonium chloride (715 mg, 3.14 mmol) in methylene chloride (19 mL) was added a solution of $NaHCO_3$ (6.32 g, 73.7 mmol) in H_2O (19 mL). The reaction was stirred at r.t. for 12 h before the layers were separated and the aqueous layer was extracted with methylene chloride (3 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL) and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent gradient of 10:1 then 5:1 (hexane-ethyl acetate) to yield **697** (955 mg, 44%) as a white crystal solid: R_f 0.45 (4:1 hexanes-ethyl acetate); mp 93-95 °C ($CHCl_3$); $[\alpha]_D^{23}$ -88.91 (*c* 1.1, $CHCl_3$); IR (film) ν 2983, 1723, 1281, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 1.1, 4.9 Hz, 1H), 4.86 (dd, *J* = 0.7, 6.4 Hz, 1H), 4.35 (d, *J* = 6.4 Hz, 1H), 3.08 (dd, *J* = 1.7, 5.4 Hz, 1H), 2.86 (t, *J* = 5.2 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 3H), 1.39 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 128.0, 126.2, 111.2, 82.3, 73.9, 72.2, 35.2, 34.8, 27.8, 27.5, 26.1 ppm; MS (EI) *m/z* (%): 345 (M), 41(62), 43(75), 58(31), 59(35), 108(43), 135(36); HRMS calcd for $C_{14}H_{20}BrNO_4$ 345.0576, found 345.0575.



698

tert-Butyl [(3a*S*,4*R*,5*S*,7a*S*)-5-azido-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]carbamate (698)

To a stirred solution of *N*-Boc aziridine **697** (100 mg, 0.289 mmol) in *N,N*-dimethylformamide (1 mL) was added NH_4Cl (150 mg), and then NaN_3 (75 mg, 1.16 mmol) at 0 °C. The reaction was slowly raised to room temperature over 12 h before extracting into diethyl ether (5 x 1 mL). The combined organic layers were washed with H_2O (20 x 0.5 mL), brine (1 x 2 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 8:1 then 4:1 (hexane-ethyl acetate) to yield **698** (87 mg, 77%) as a white solid; R_f 0.33 (4:1 hexanes-ethyl acetate); mp 88-89 °C (ethyl acetate-hexanes); $[\alpha]_D^{23}$ +104.7 (*c*1.4, $CHCl_3$); IR (film) ν 3432, 2102, 1655, 1598, 1219, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 6.19 (d, *J* = 2.6 Hz, 1H), 4.73 (d, *J* = 7.9 Hz, 1H), 4.63 (dt, *J* = 0.6, 5.4 Hz, 1H), 4.38-4.45 (m, 1H), 4.18-4.27 (m, 1H), 3.52 (q, *J* = 8.5 Hz, 1H), 1.55 (s, 3H), 1.48 (s, 9H), 1.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 131.4, 110.9, 80.5, 74.7, 59.9, 54.5, 28.3, 28.0, 26.0 ppm; MS (FAB) *m/z* (%): 389 (M+ H^+), 41(30), 57(100), 333(31), 335(29); HRMS calcd for $C_{12}H_{22}N_4BrO_4^+$ 389.0824, found 389.0905.

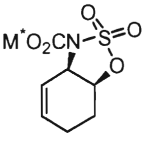


699

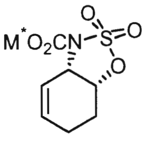
(3a*S*,5a*R*,8a*R*,8b*S*)-4-bromo-2,2-dimethyl-3a,8,8a,8b-tetrahydro[1,3]dioxolo[4,5-*e*][1,3]benzoxazol-7(5a*H*)-one (699)

To a stirred solution of aziridine *N*-Boc aziridine **697** (20 mg, 0.058 mmol) in methylene chloride (100 μL) was added trifluoroacetic acid (400 μL) at 0 °C. The reaction was slowly raised to r.t. over 12 h before being poured into sat. $NaHCO_3$ (1.5 mL) and extracted into chloroform (3 x 1 mL). The combined organic layers were washed with brine (1 x 1 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexane-ethyl acetate) to yield **699** (15 mg, 89%) as a clear oil: R_f 0.42 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -27.71 (*c* 0.9, $CHCl_3$); IR (film) ν 3444, 2099, 1717, 1647, 1260, 1101 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.20 (d, *J* = 3.2 Hz, 1H), 5.80 (br s, 1NH), 5.07 (dd, *J* = 3.0, 7.2 Hz, 1H), 4.63 (d, *J* = 4.7 Hz, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 4.51 (d, *J* = 2.8, 4.7 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 128.5, 124.9, 110.7, 73.9, 73.3, 72.3, 51.2, 27.5, 26.4 ppm; MS (EI) *m/z* (%): 273 (M – $CH_3^{\bullet}$), 43(45), 83(50), 84(100), 85(37), 86(82); HRMS calcd for $C_9H_9BrNO_4^{\bullet}$ 273.9715, found 273.9710; *Anal.* calcd: C 41.40, H 4.17, found C 41.44, H 4.15.

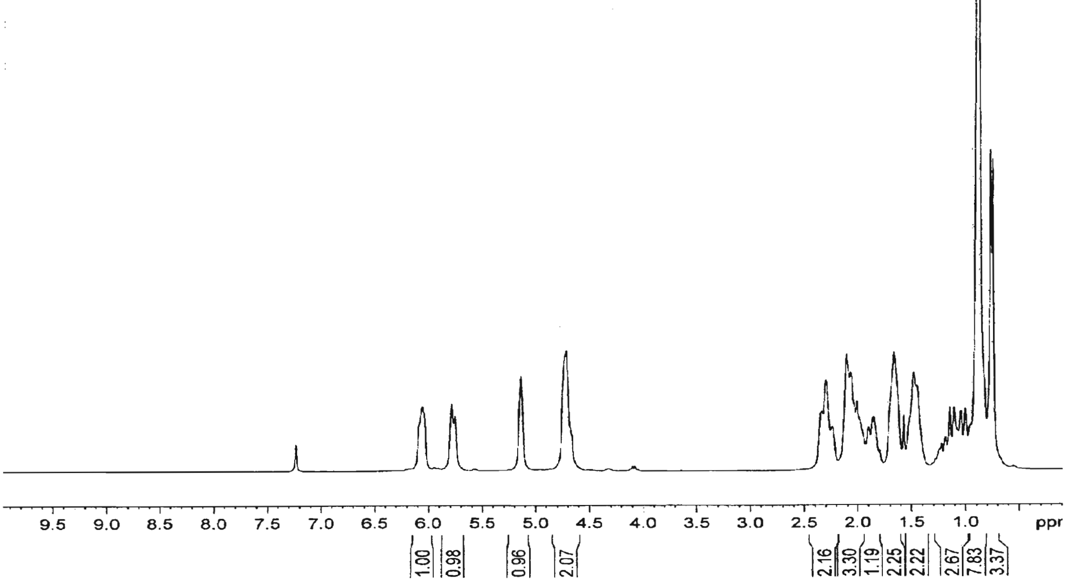
6. Select Spectra



5a



5b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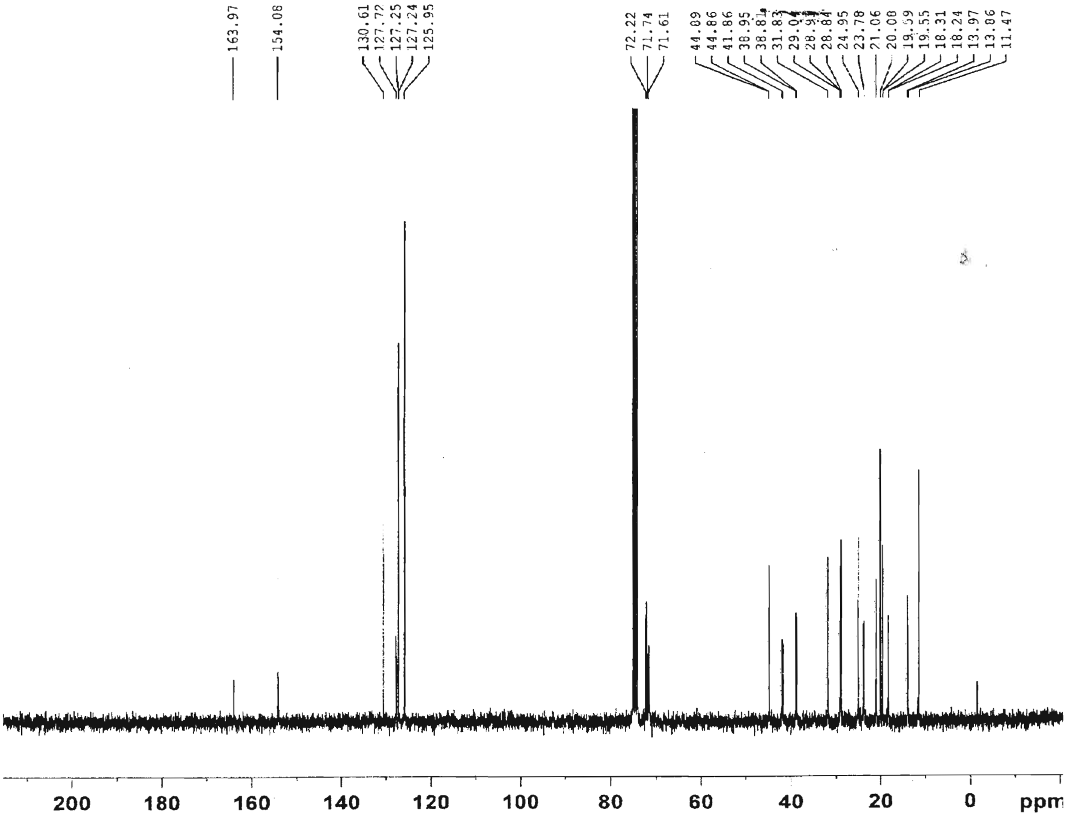
2.111
2.072
2.011
1.859
1.667
1.576
1.484
0.902
0.883
0.771
0.749
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.98
0.96
2.07
2.16
3.30
1.19
2.25
2.22
2.67
7.83
3.37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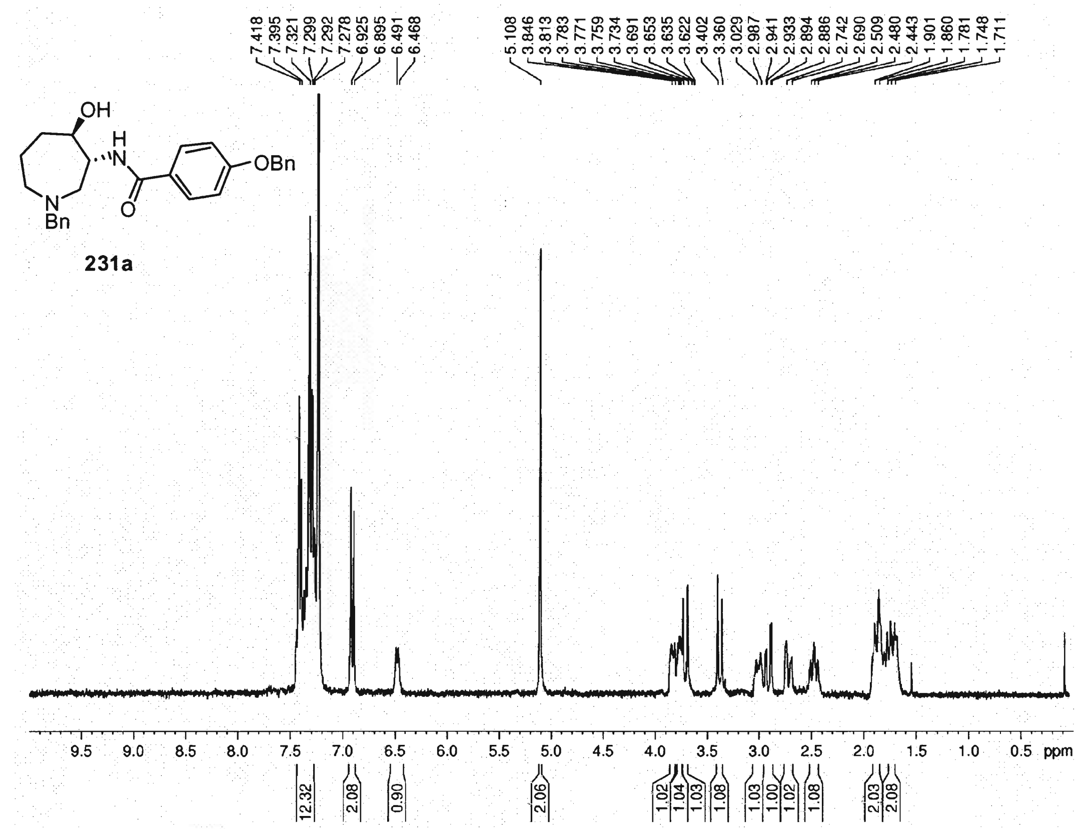
154.08
130.61
127.72
127.25
127.24
125.95
72.22
71.74
71.61
44.09
44.86
41.86
38.95
38.81
31.83
29.04
28.91
28.84
24.95
23.78
21.06
20.08
19.59
19.55
18.31
18.24
13.97
13.86
11.47
200 180 160 140 120 100 80 60 40 20 0 ppm



231a

OH
H
N
OBn
N
Bn
O
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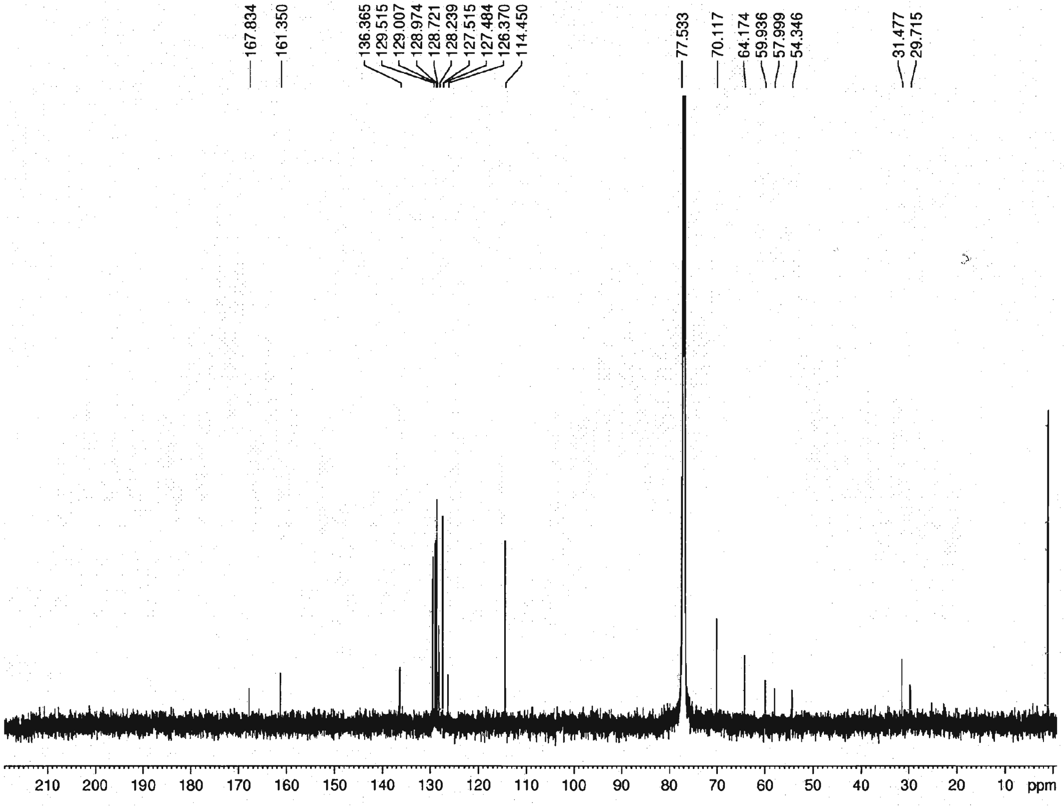
7.395
7.321
7.299
7.292
7.278
6.925
6.895
6.491
6.468
5.108
3.846
3.813
3.783
3.771
3.759
3.734
3.691
3.653
3.635
3.622
3.402
3.360
3.029
2.987
2.941
2.933
2.894
2.886
2.742
2.690
2.509
2.480
2.443
1.901
1.860
1.781
1.748
1.711
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
12.32
2.08
0.90
2.06
1.02
1.04
1.03
1.08
1.03
1.00
1.02
1.08
2.03
2.08



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161.350
136.365
129.515
129.007
128.974
128.721
128.239
127.515
127.484
126.370
114.450
77.533
70.117
64.174
59.936
57.999
54.346
31.477
29.715
210
200
190
180
170
160
150
140
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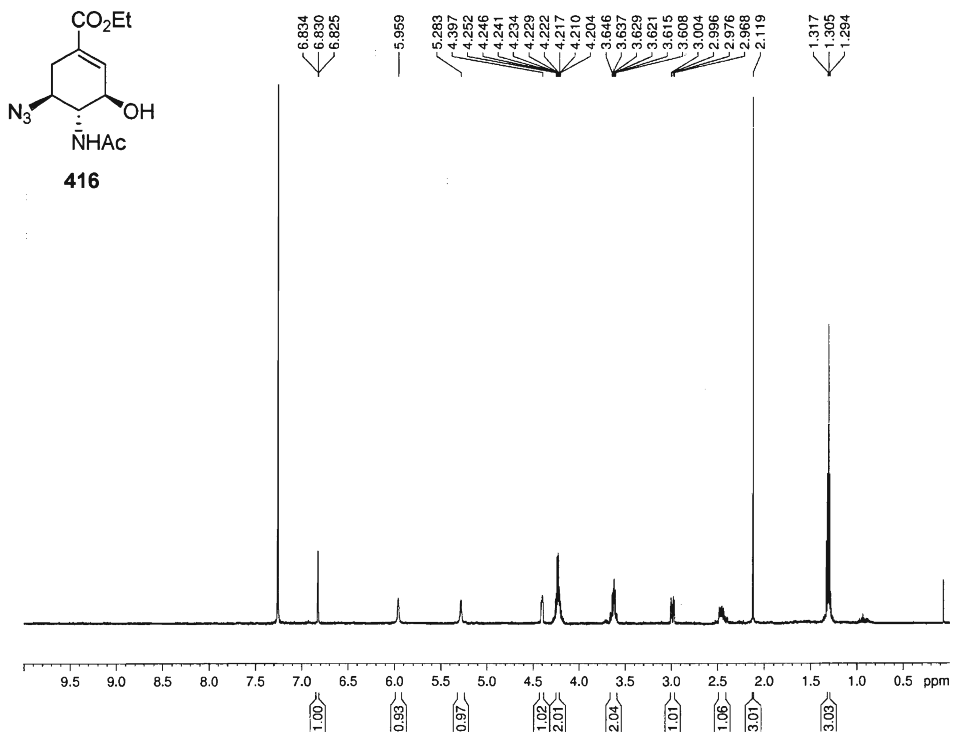
50
40
30
20
10
ppm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N3
OH
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5.959
5.283
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4.252
4.246
4.241
4.234
4.229
4.222
4.217
4.210
4.204
3.646
3.637
3.629
3.621
3.615
3.608
3.004
2.996
2.976
2.968
2.119
1.317
1.305
1.294
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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0.93
0.97
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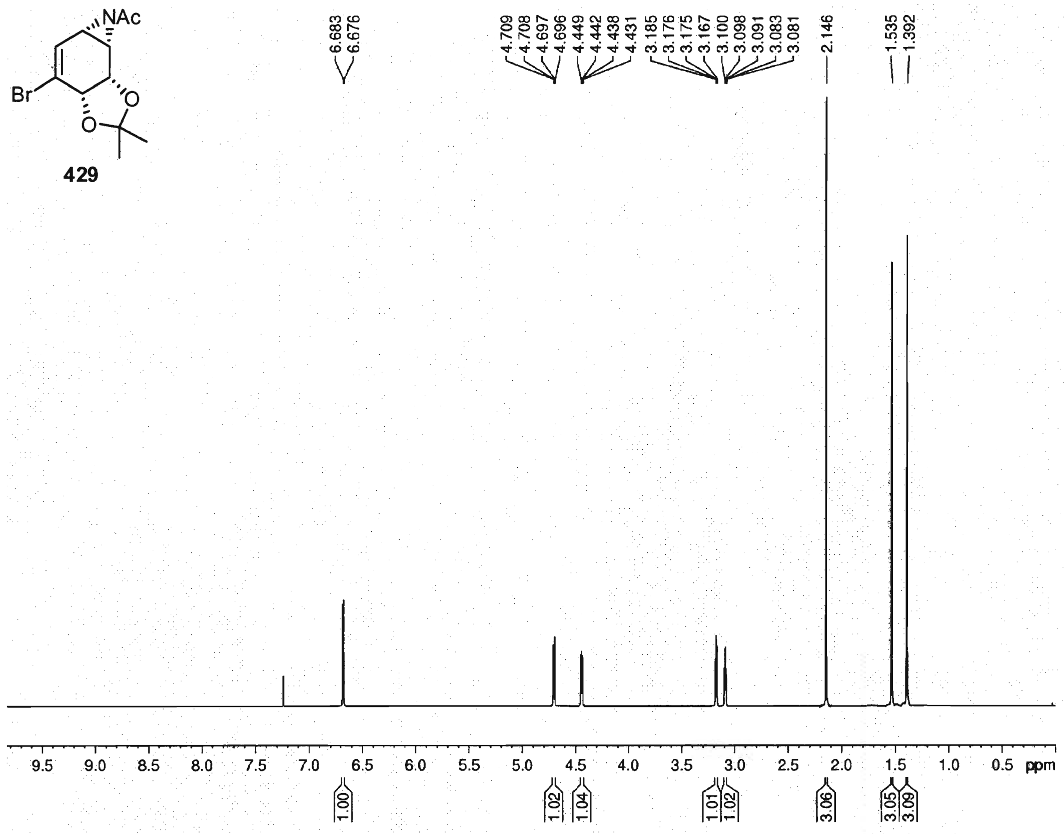
2.01
2.04
1.01
1.06
3.01
3.03

416


429

Br
O
O
NAc
6.683
6.676
4.709
4.708
4.697
4.696
4.449
4.442
4.438
4.431
3.185
3.176
3.175
3.167
3.100
3.098
3.091
3.083
3.081
2.146
1.535
1.392
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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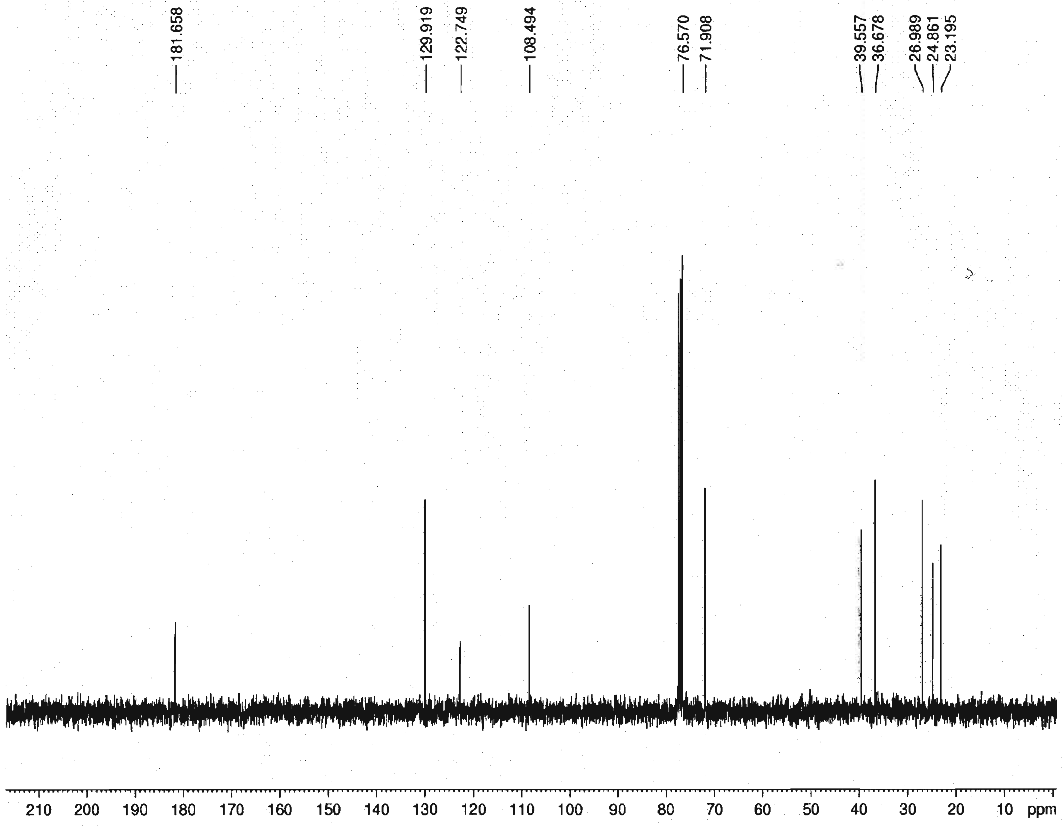
1.02
1.04
1.01
1.02
3.06
3.05
3.09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122.749
108.494
76.570
71.908
39.557
36.678
26.989
24.861
23.195
210
200
190
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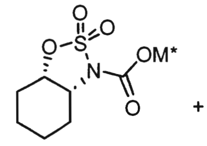
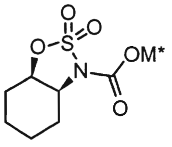
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

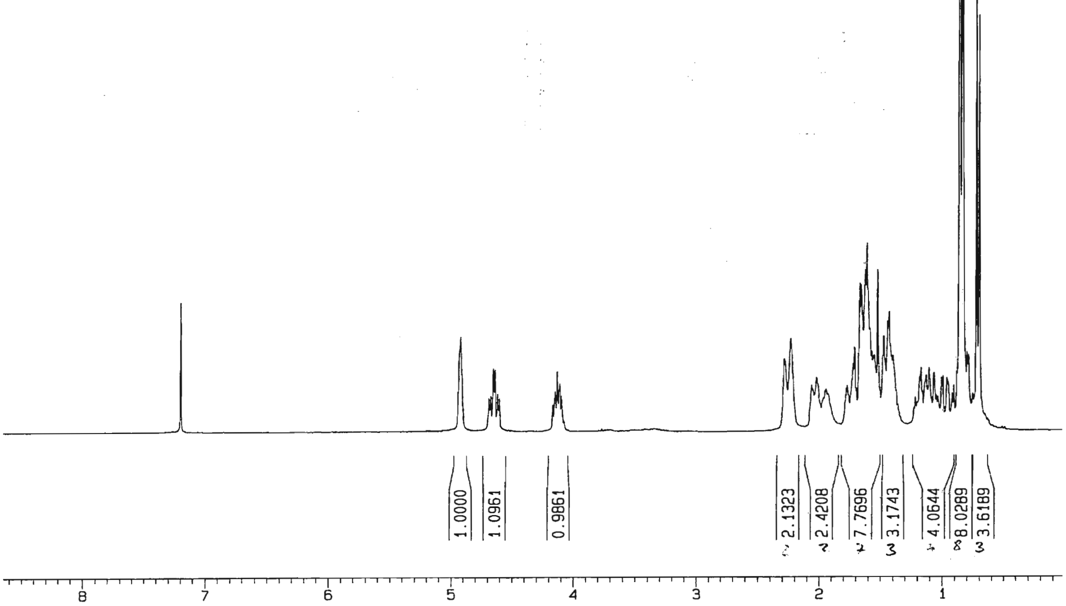


486a

+



486b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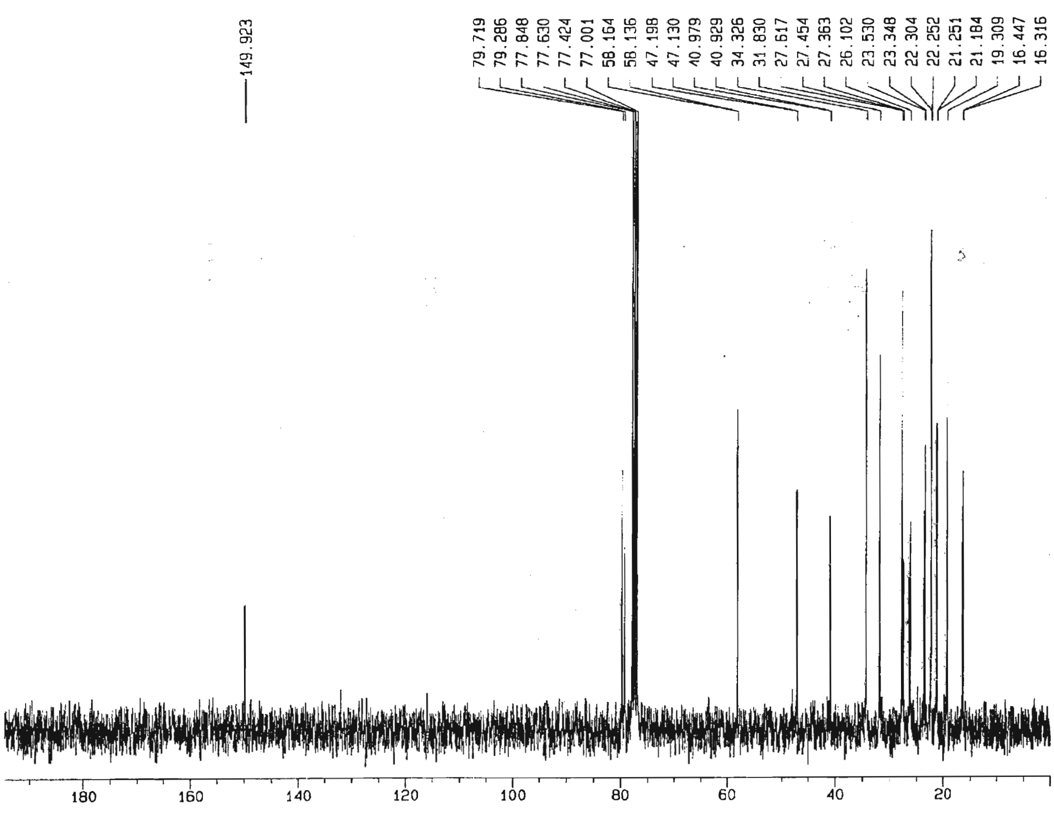
7.7696
3.1743
4.0644
8.0289
3.6189
2
2
4
3
4
8
3
8
7
6
5
4
3
2
1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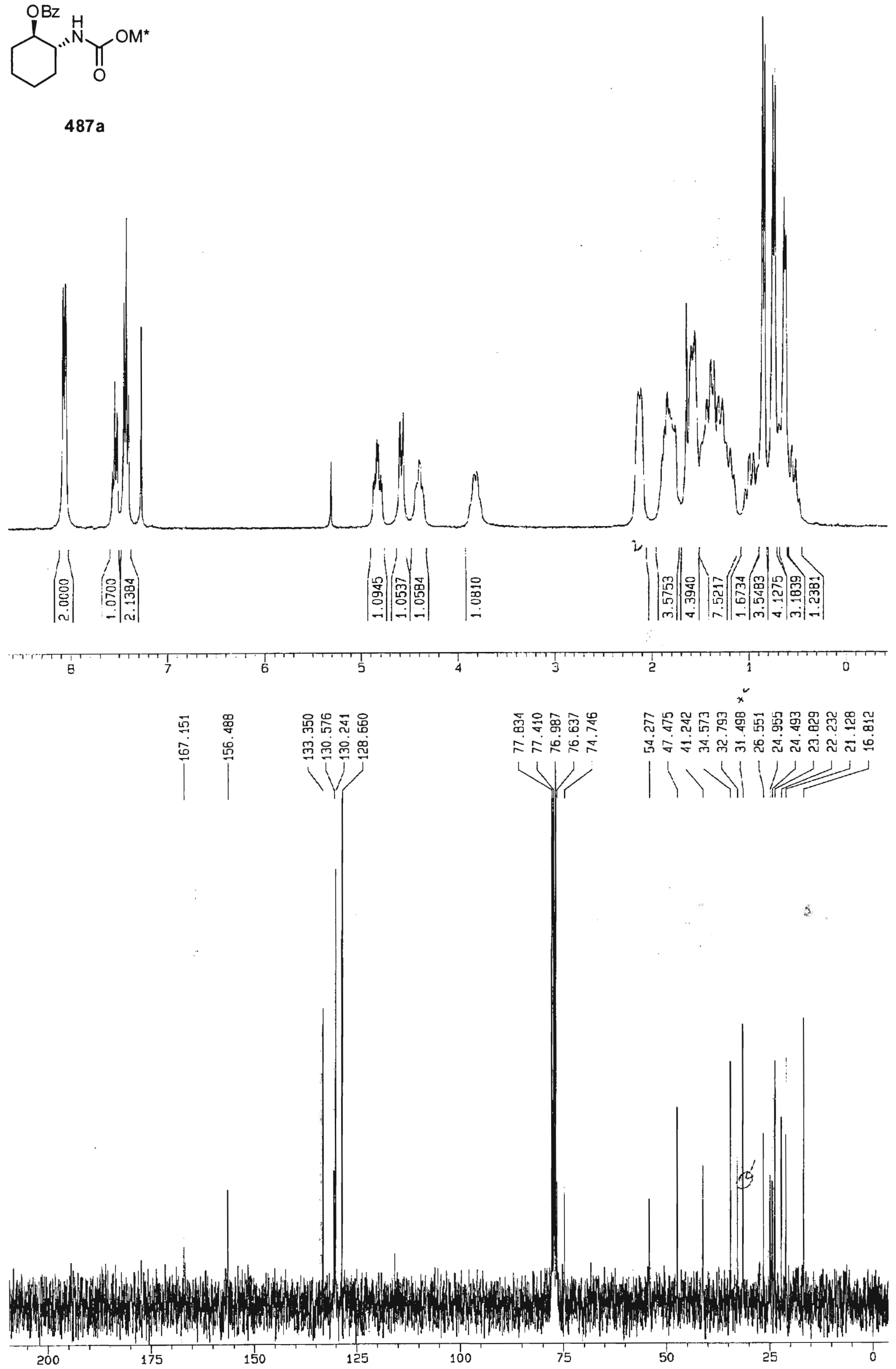
77.848
77.630
77.424
77.001
58.164
58.136
47.198
47.130
40.979
40.929
34.326
31.830
27.617
27.454
27.363
26.102
23.530
23.348
22.304
22.252
21.251
21.184
19.309
16.447
16.316
180
160
140
120
100
80
60
40
20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H
N
OM*
O
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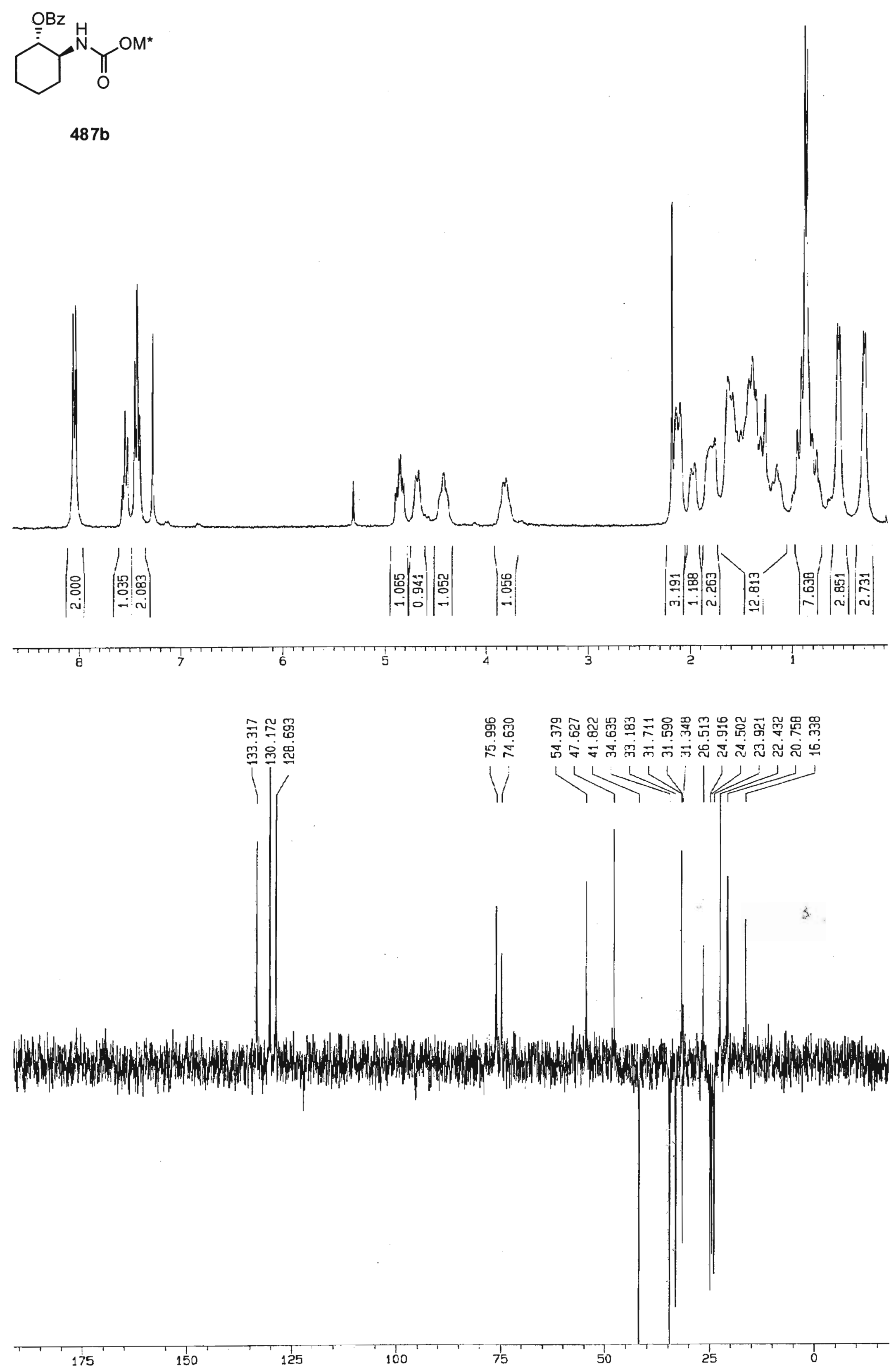
1.0700
2.1384
1.0945
1.0537
1.0584
1.0810
3.5753
4.3940
7.5217
1.6734
3.5483
4.1275
3.1839
1.2381
8
7
6
5
4
3
2
1
0
167.151
156.488
133.350
130.576
130.241
128.660
77.834
77.410
76.987
76.637
74.746
54.277
47.475
41.242
34.573
32.793
31.498
26.551
24.955
24.493
23.829
22.232
21.128
16.812
200
175
150
125
100
75
50
25
0

487a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H
N
OM*
O
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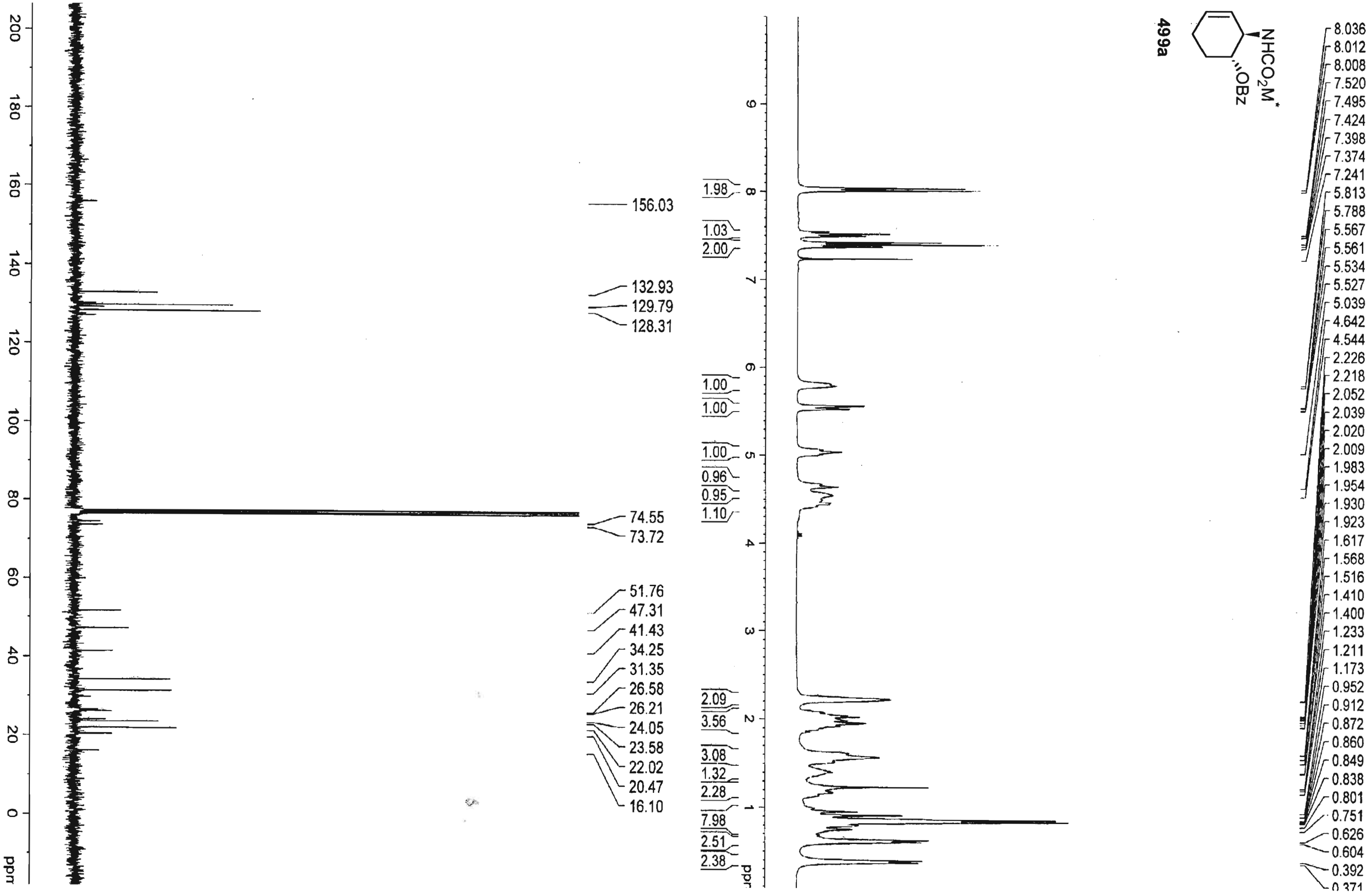
2.083
1.065
0.941
1.052
1.056
3.191
1.188
2.263
12.813
7.638
2.851
2.731
8
7
6
5
4
3
2
1
133.317
130.172
128.693
75.996
74.630
54.379
47.627
41.822
34.635
33.183
31.711
31.590
31.348
26.513
24.916
24.502
23.921
22.432
20.758
16.338
175
150
125
100
75
50
25
0

487b


NHCO2M*
OBz
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180
160
140
120
100
80
60
40
20
0
ppm
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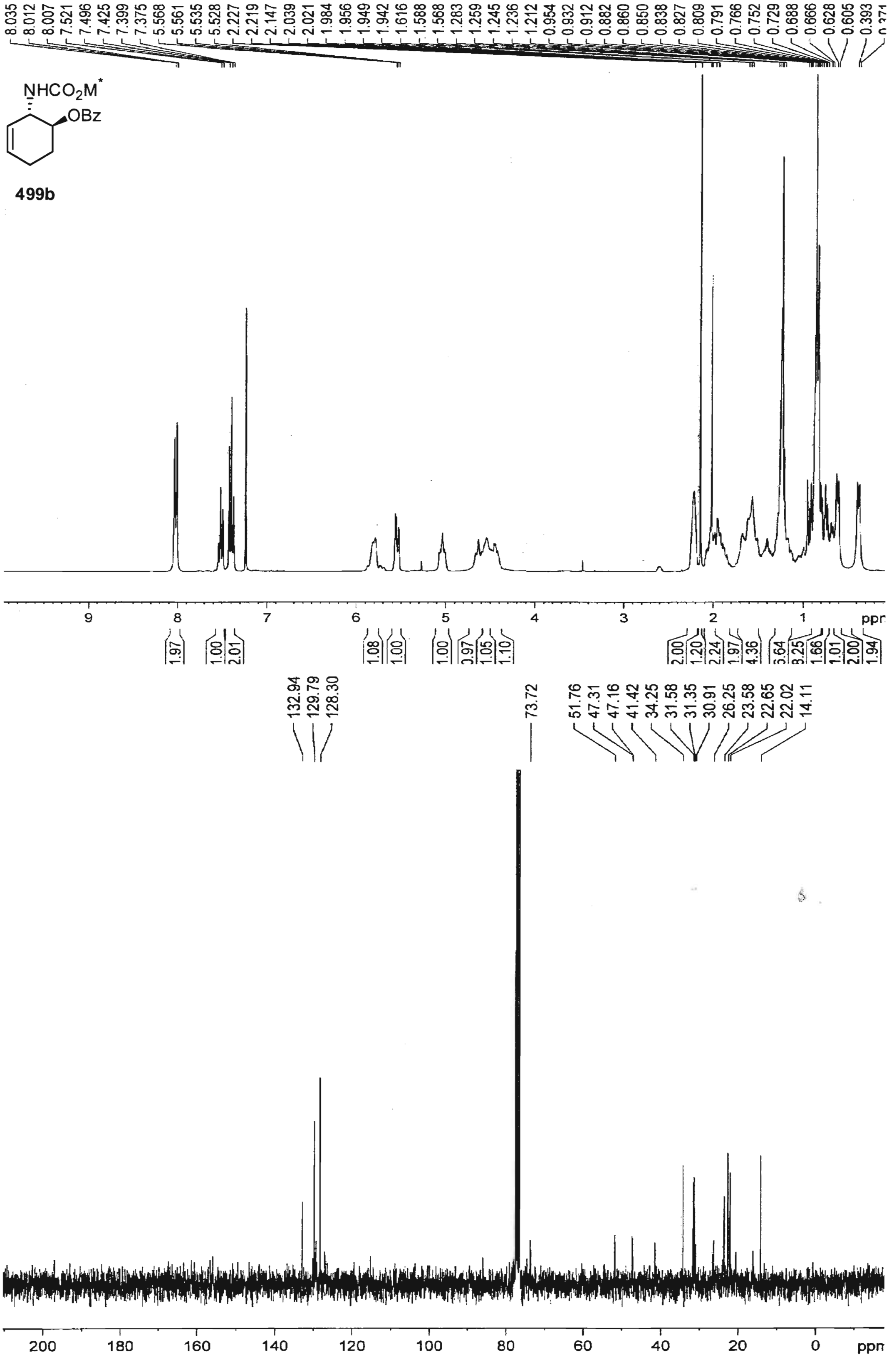
132.93
129.79
128.31
74.55
73.72
51.76
47.31
41.43
34.25
31.35
26.58
26.21
24.05
23.58
22.02
20.47
16.10
9
8
7
6
5
4
3
2
1
ppm
1.98
1.03
2.00
1.00
1.00
1.00
0.96
0.95
1.10
2.09
3.56
3.08
1.32
2.28
7.98
2.51
2.38
8.036
8.012
8.008
7.520
7.495
7.424
7.398
7.374
7.241
5.813
5.788
5.567
5.561
5.534
5.527
5.039
4.642
4.544
2.226
2.218
2.052
2.039
2.020
2.009
1.983
1.954
1.930
1.923
1.617
1.568
1.516
1.410
1.400
1.233
1.211
1.173
0.952
0.912
0.872
0.860
0.849
0.838
0.801
0.751
0.626
0.604
0.392
0.371

499a


499b

NHCO$_2$M*
OBz
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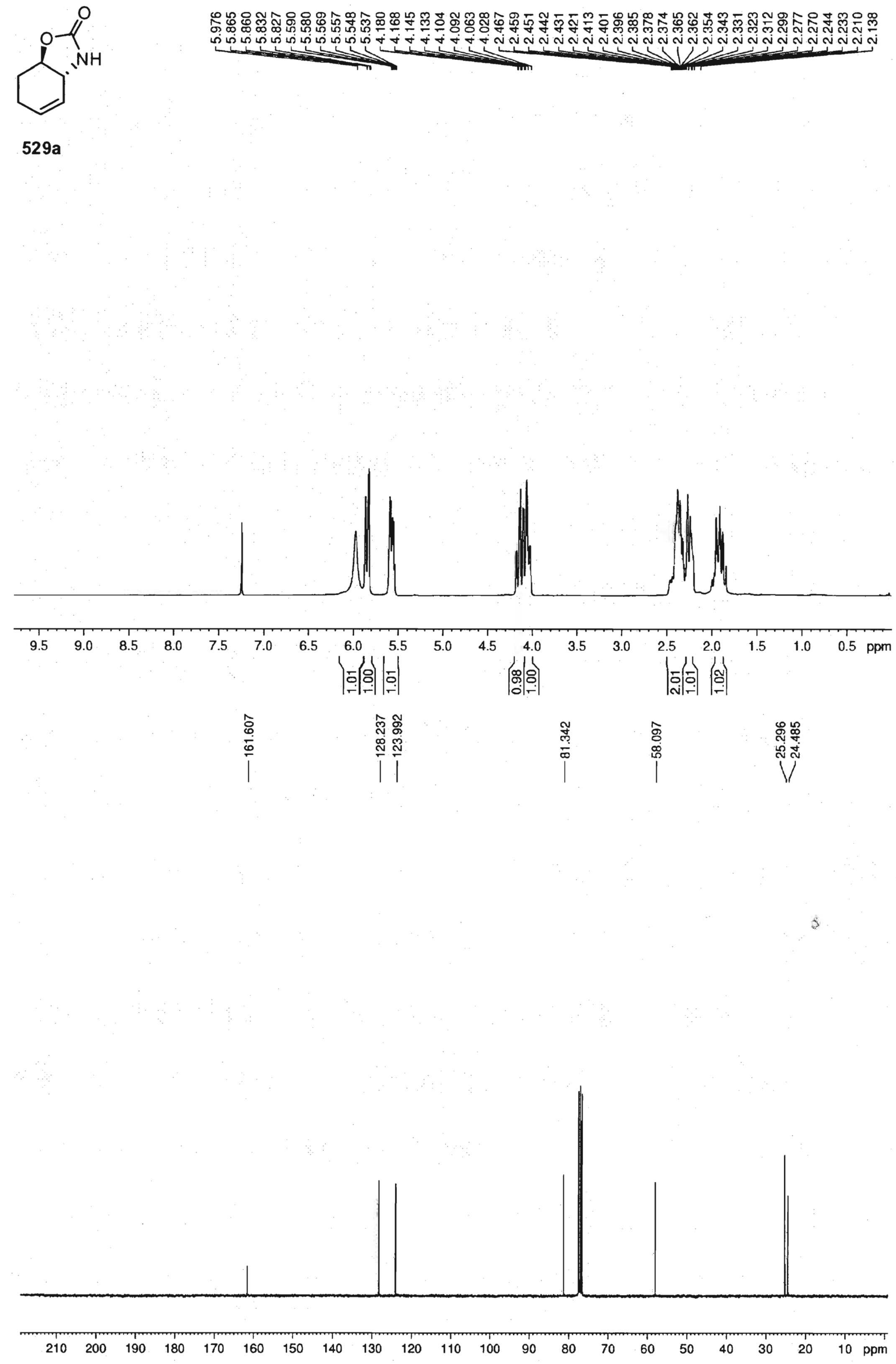
8.012
8.007
7.521
7.496
7.425
7.399
7.375
5.568
5.561
5.535
5.528
2.227
2.219
2.147
2.039
2.021
1.984
1.956
1.949
1.942
1.616
1.588
1.568
1.283
1.259
1.245
1.236
1.212
0.954
0.932
0.912
0.882
0.860
0.850
0.838
0.827
0.809
0.791
0.766
0.752
0.729
0.688
0.666
0.628
0.605
0.393
9
8
7
6
5
4
3
2
1
ppm
1.97
1.00
2.01
1.08
1.00
1.00
0.97
1.05
1.10
2.00
1.20
2.24
1.97
4.36
5.64
8.25
1.66
1.01
2.00
1.94
132.94
129.79
128.30
73.72
51.76
47.31
47.16
41.42
34.25
31.58
31.35
30.91
26.25
23.58
22.65
22.02
14.11
200
180
160
140
120
100
80
60
40
20
0
ppm


529a
NH
O
O
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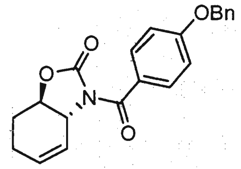
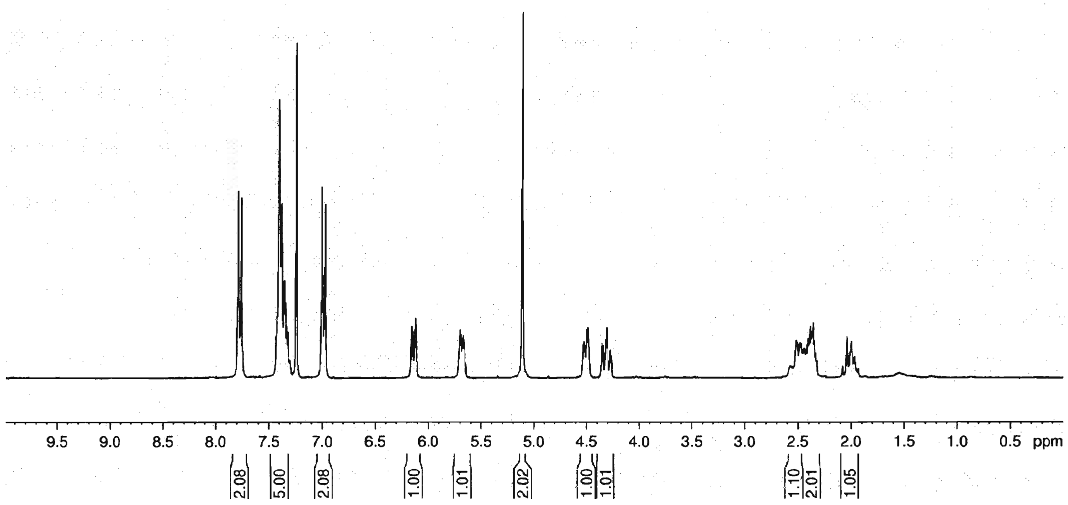
5.860
5.832
5.827
5.590
5.580
5.569
5.557
5.548
5.537
4.180
4.168
4.145
4.133
4.104
4.092
4.063
4.028
2.467
2.459
2.451
2.442
2.431
2.421
2.413
2.401
2.396
2.385
2.378
2.374
2.365
2.362
2.354
2.343
2.331
2.323
2.312
2.299
2.277
2.270
2.244
2.233
2.210
2.138
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.01
1.00
1.01
0.98
1.00
2.01
1.01
1.02
161.607
128.237
123.992
81.342
58.097
25.296
24.485
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OBn
O
O
N
O

536a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7.358
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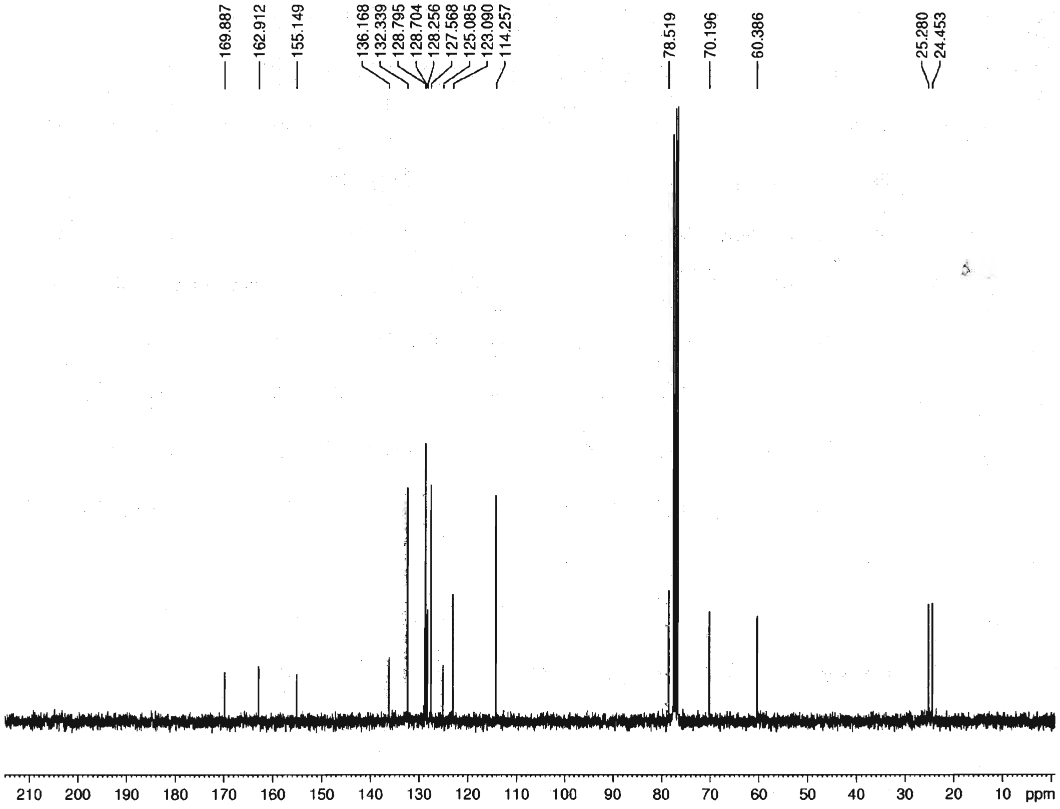
7.321
7.240
7.002
6.996
6.979
6.973
6.154
6.149
6.121
6.116
5.701
5.692
5.680
5.668
5.659
5.105
4.522
4.493
4.487
4.354
4.342
4.317
4.310
4.300
4.275
2.515
2.479
2.471
2.444
2.436
2.424
2.413
2.405
2.394
2.382
2.369
2.358
2.347
2.332
2.038
1.998
1.545
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.08
5.00
2.08
1.00
1.01
2.02
1.00
1.01
1.10
2.01
1.05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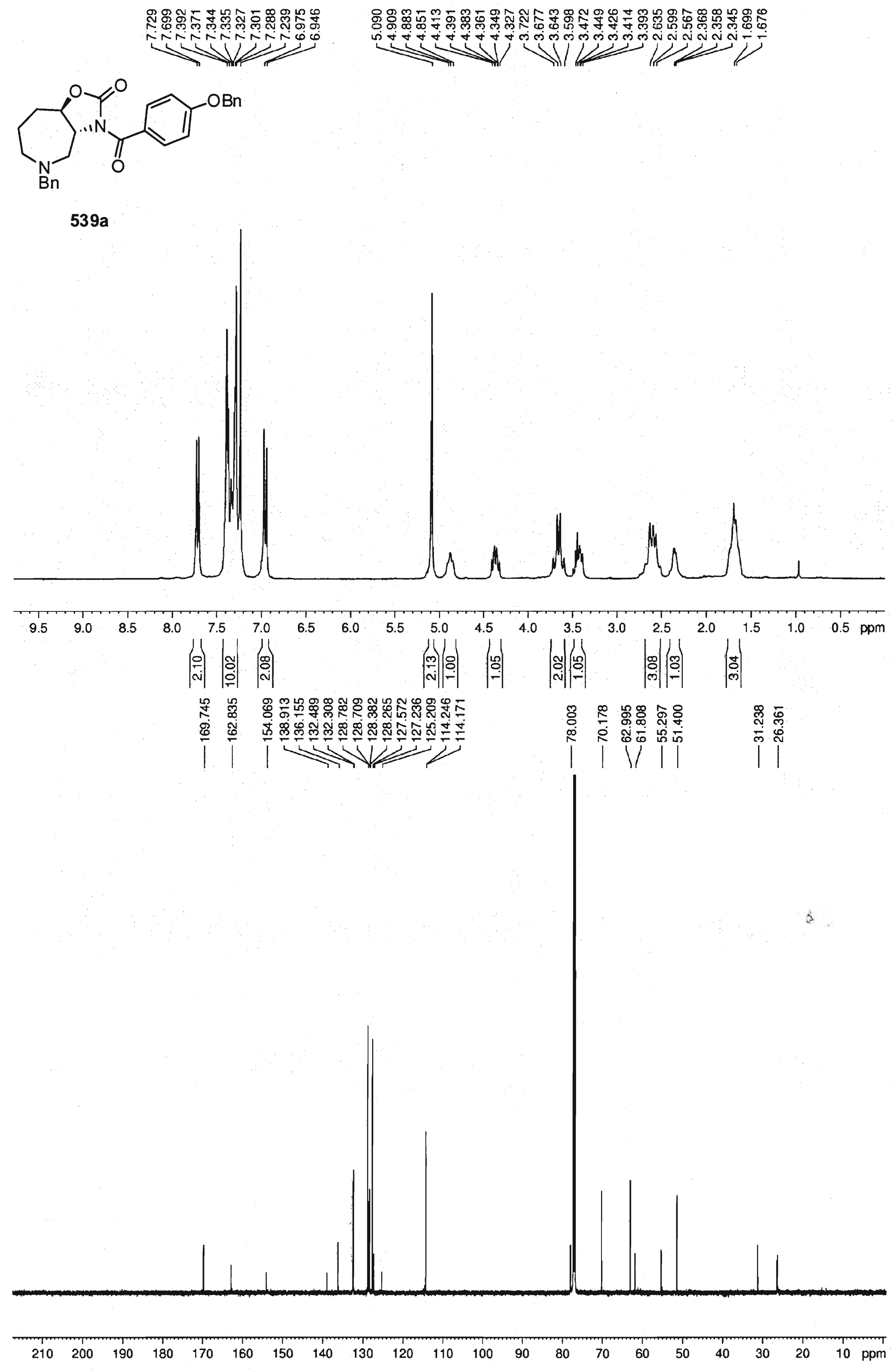
136.168
132.339
128.795
128.704
128.256
127.568
125.085
123.090
114.257
78.519
70.196
60.386
25.280
24.453
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



539a

OBn
N
Bn
O
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7.344
7.335
7.327
7.301
7.288
7.239
6.975
6.946
5.090
4.909
4.883
4.851
4.413
4.391
4.383
4.361
4.349
4.327
3.722
3.677
3.643
3.598
3.472
3.449
3.426
3.414
3.393
2.635
2.599
2.567
2.368
2.358
2.345
1.699
1.676
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.10
10.02
2.08
2.13
1.00
1.05
2.02
1.05
3.08
1.03
3.04
169.745
162.835
154.069
138.913
136.155
132.489
132.308
128.782
128.709
128.382
128.265
127.572
127.236
125.209
114.246
114.171
78.003
70.178
62.995
61.808
55.297
51.400
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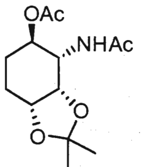
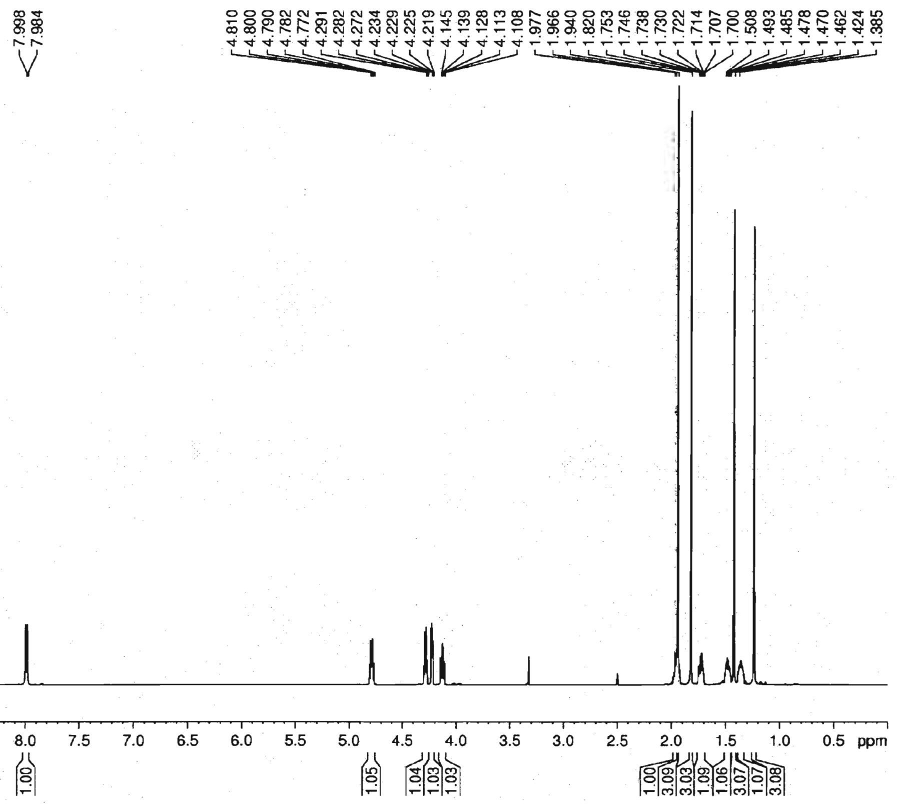
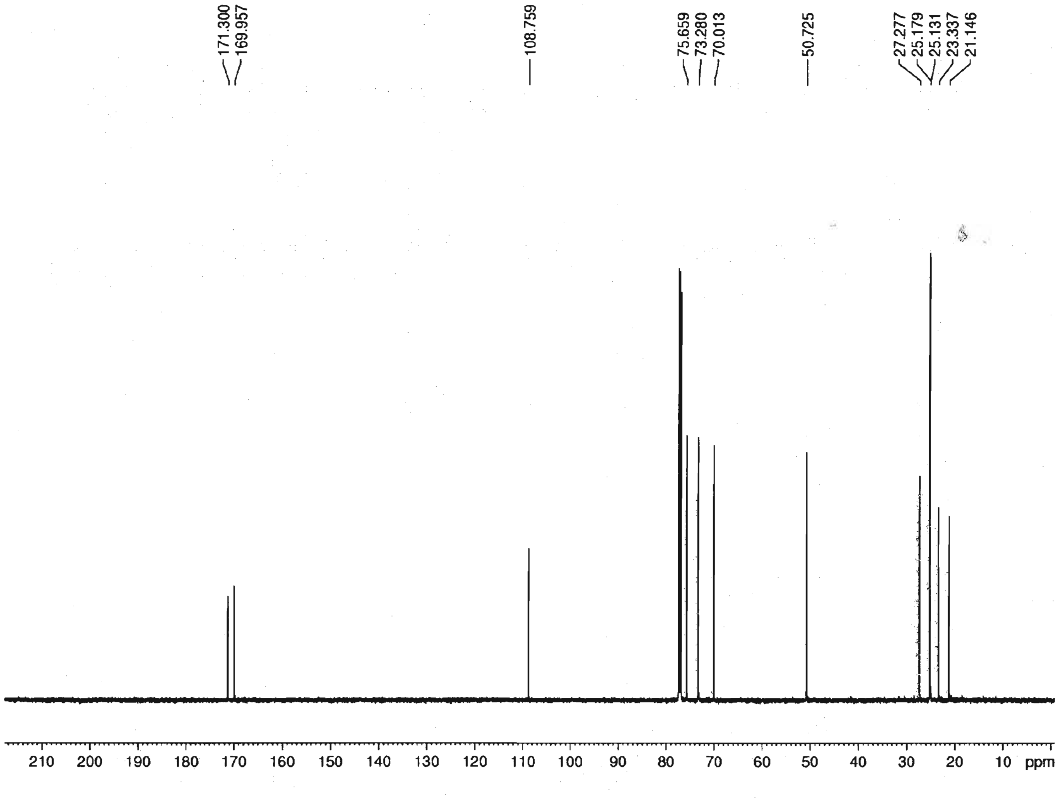
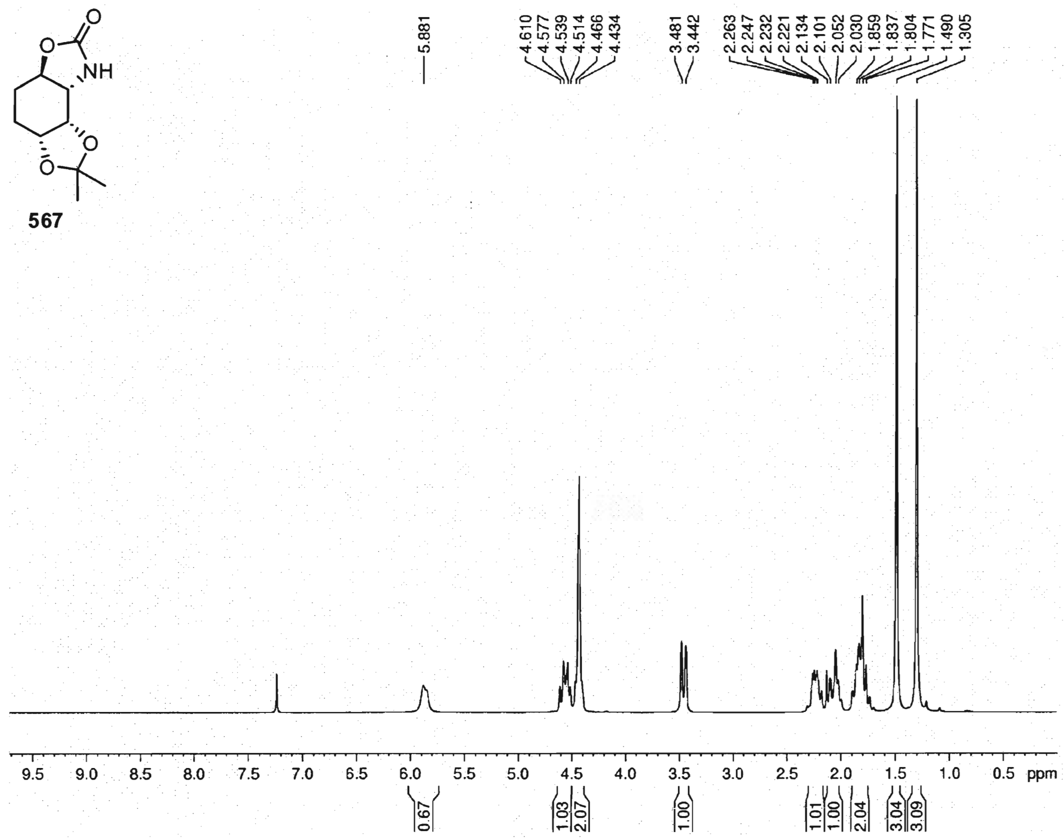
26.361
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



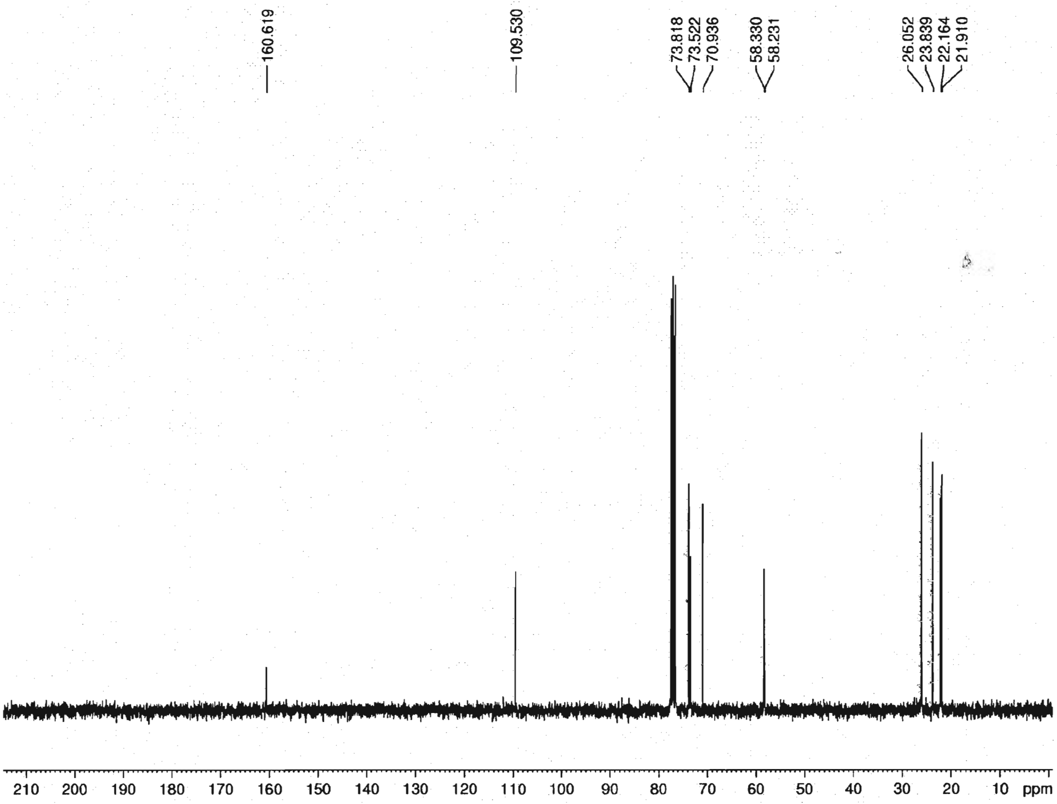
561

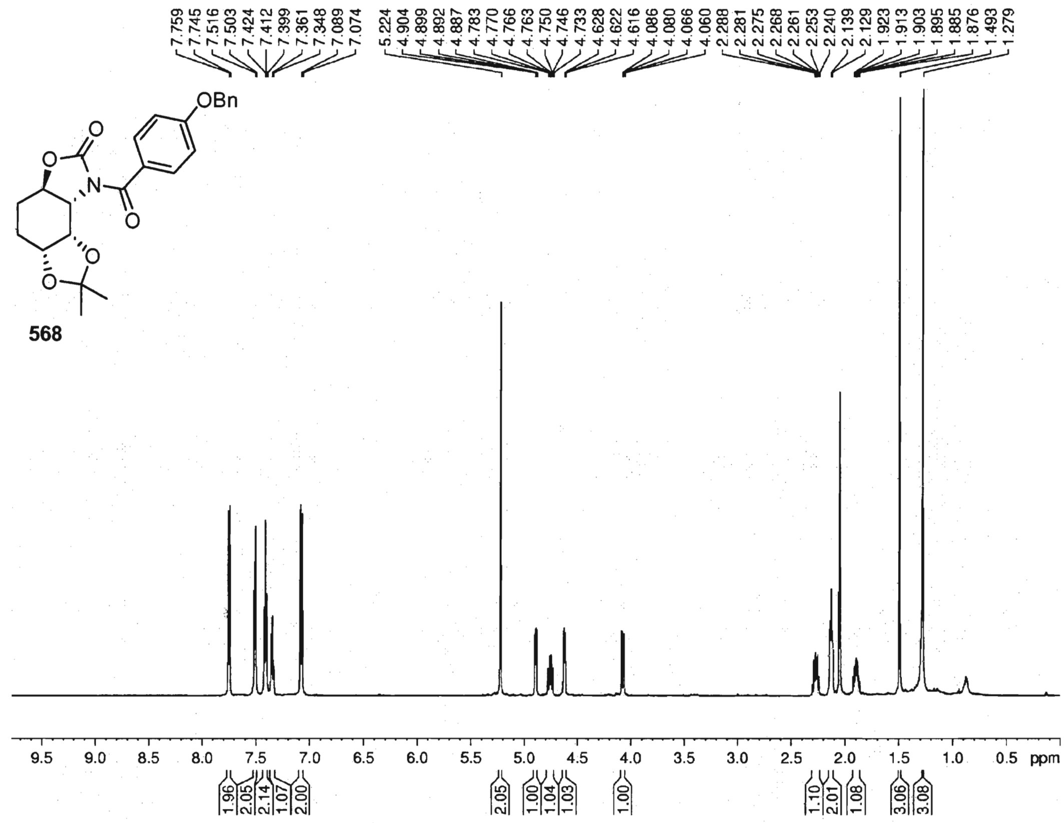

7.998
7.984
4.810
4.800
4.790
4.782
4.772
4.291
4.282
4.272
4.234
4.229
4.225
4.219
4.145
4.139
4.128
4.113
4.108
1.977
1.966
1.940
1.820
1.753
1.746
1.738
1.730
1.722
1.714
1.707
1.700
1.508
1.493
1.485
1.478
1.470
1.462
1.424
1.385
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.05
1.04
1.03
1.03
1.00
3.09
3.03
1.09
1.06
3.07
1.07
3.08


171.300
169.957
108.759
75.659
73.280
70.013
50.725
27.277
25.179
25.131
23.337
21.146
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

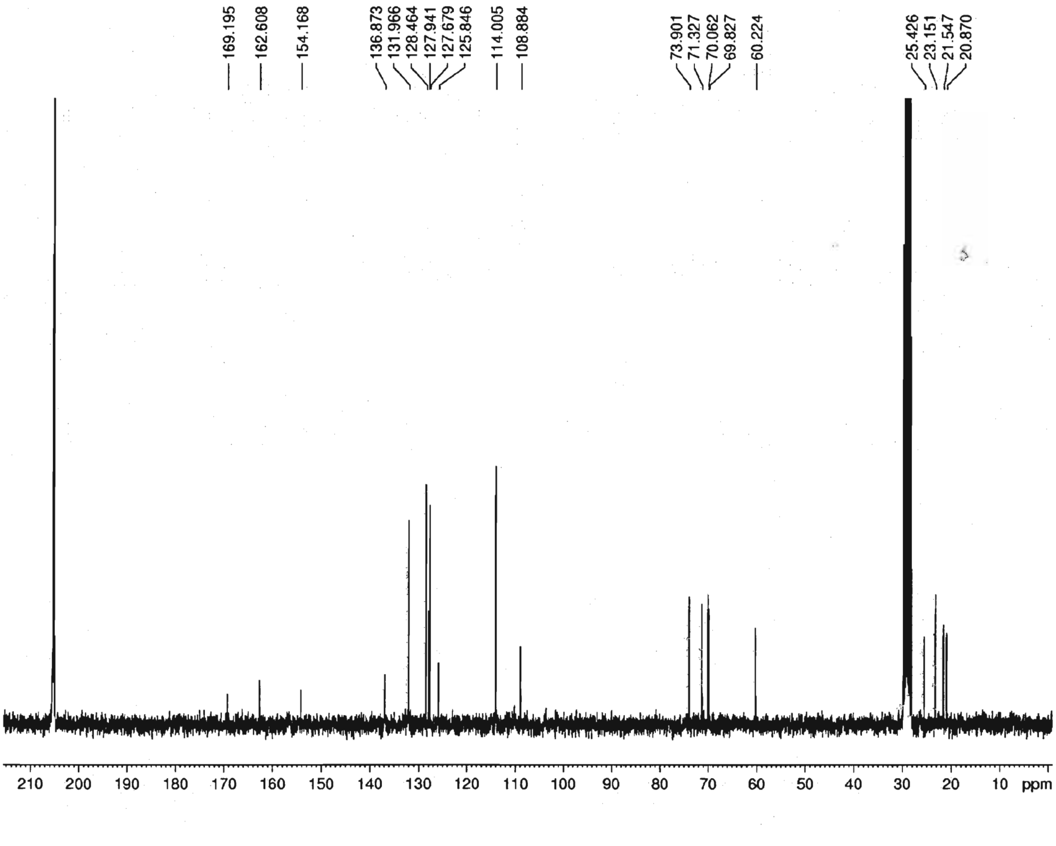

5.881
4.610
4.577
4.539
4.514
4.466
4.434
3.481
3.442
2.263
2.247
2.232
2.221
2.134
2.101
2.052
2.030
1.859
1.837
1.804
1.771
1.490
1.305
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.67
1.03
2.07
1.00
1.01
1.00
2.04
3.04
3.09
O
O
NH
O
O

567

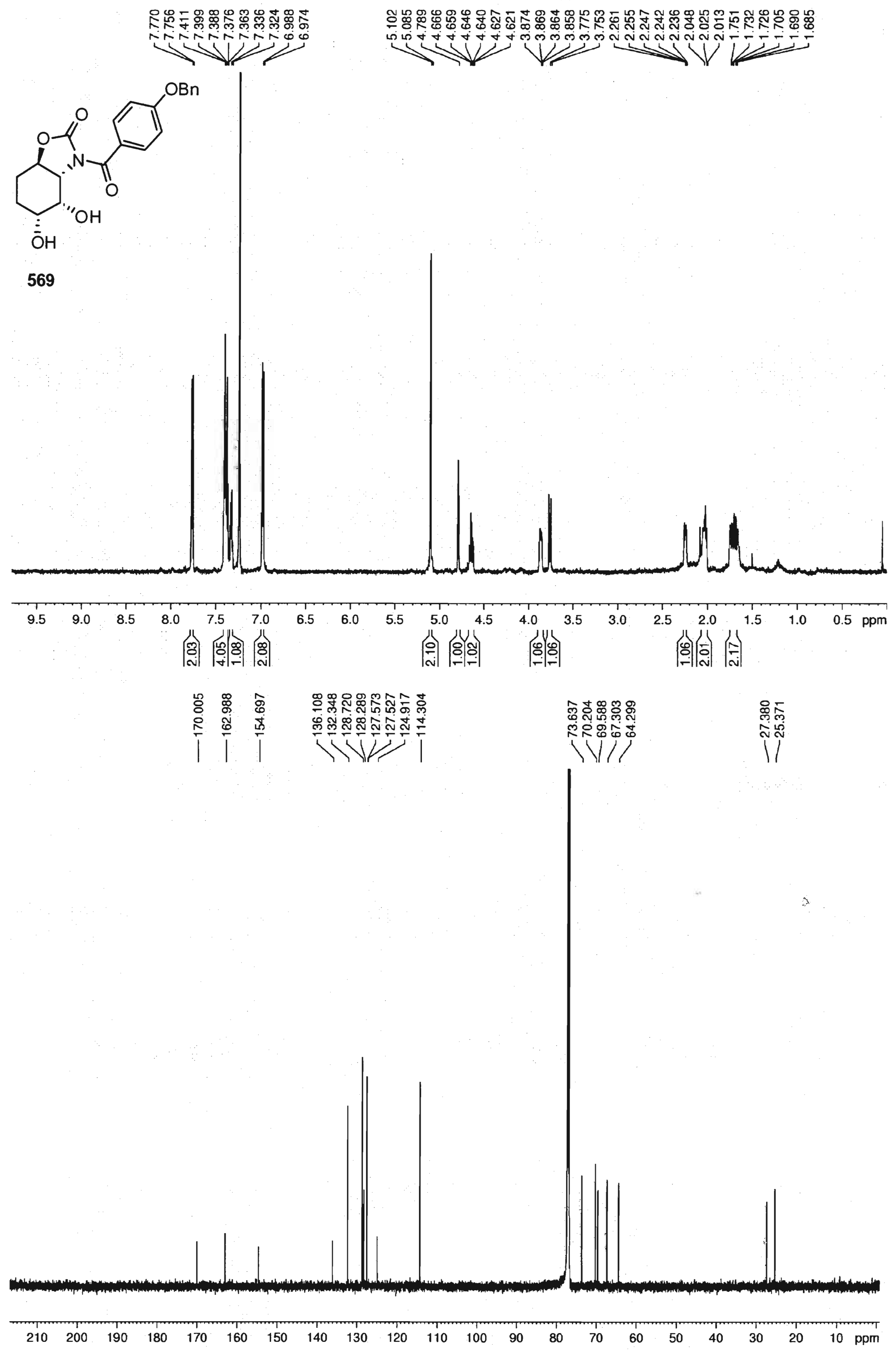

160.619
109.530
73.818
73.522
70.936
58.330
58.231
26.052
23.839
22.164
21.910
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


568

OBn
O
N
7.759
7.745
7.516
7.503
7.424
7.412
7.399
7.361
7.348
7.089
7.074
5.224
4.904
4.899
4.892
4.887
4.783
4.770
4.766
4.763
4.750
4.746
4.733
4.628
4.622
4.616
4.086
4.080
4.066
4.060
2.288
2.281
2.275
2.268
2.261
2.253
2.240
2.139
2.129
1.923
1.913
1.903
1.895
1.885
1.876
1.493
1.279
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.96
2.05
2.14
1.07
2.00
2.05
1.00
1.04
1.03
1.00
1.10
2.01
1.08
3.06
3.08

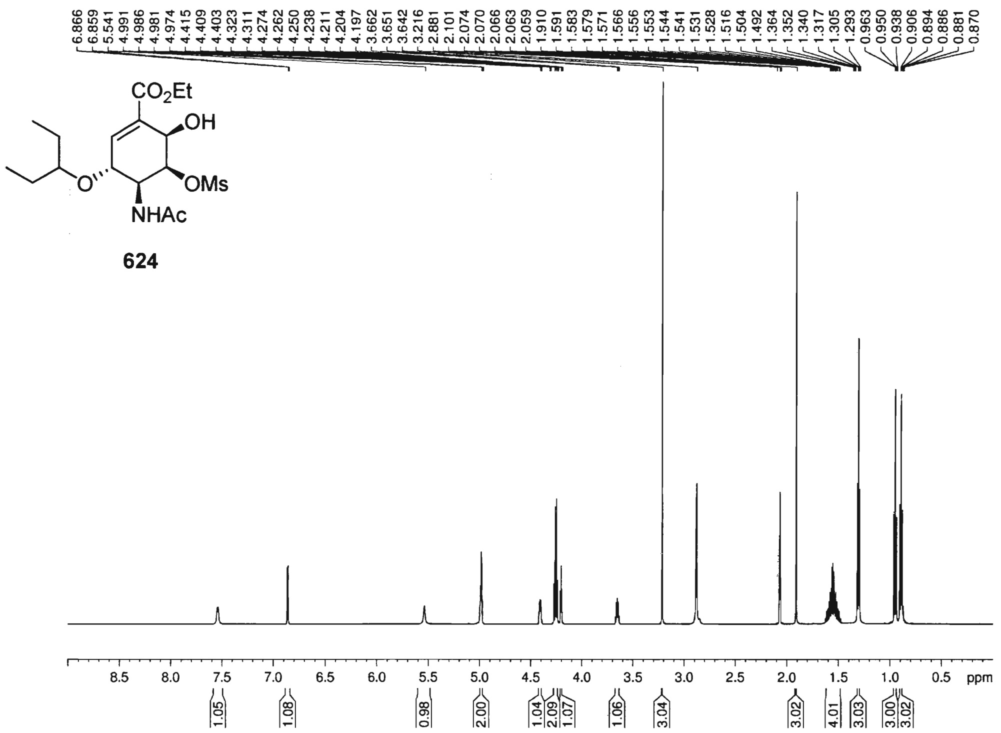


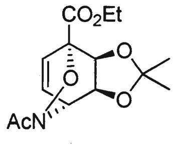
169.195
162.608
154.168
136.873
131.966
128.464
127.941
127.679
125.846
114.005
108.884
73.901
71.327
70.062
69.827
60.224
25.426
23.151
21.547
20.870
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



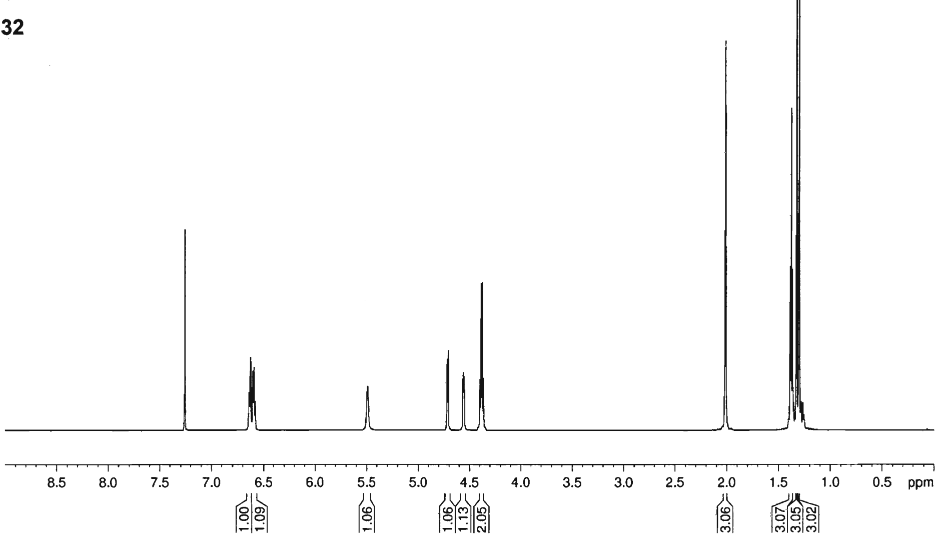
569

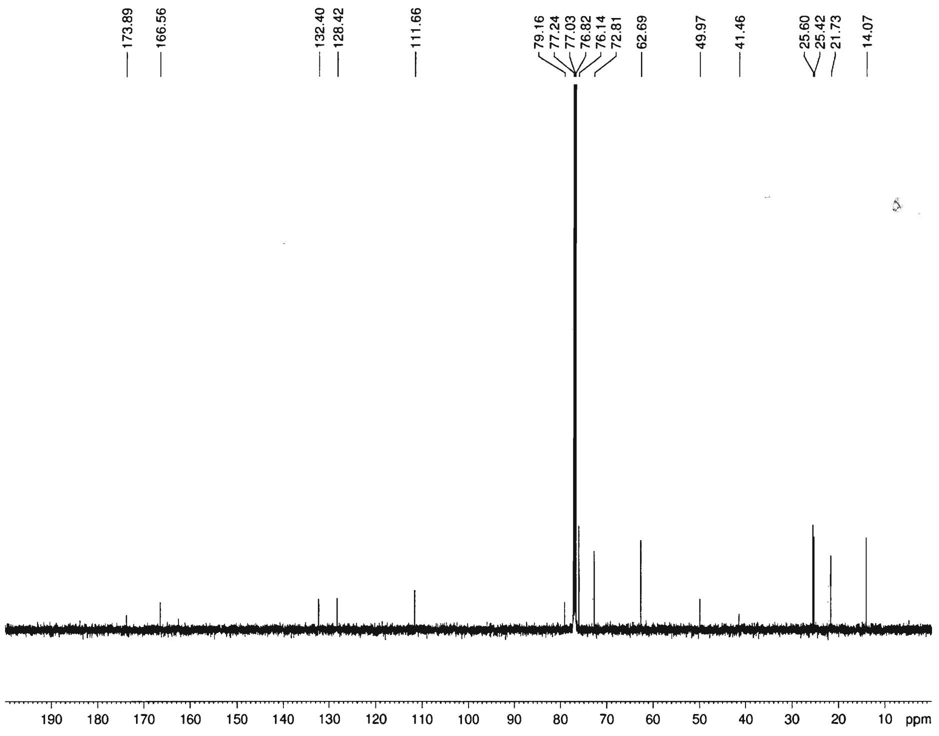
OBn
O
N
OH
7.770
7.756
7.411
7.399
7.388
7.376
7.363
7.336
7.324
6.988
6.974
5.102
5.085
4.789
4.666
4.659
4.646
4.640
4.627
4.621
3.874
3.869
3.864
3.858
3.775
3.753
2.261
2.255
2.247
2.242
2.236
2.048
2.025
2.013
1.751
1.732
1.726
1.705
1.690
1.685
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.03
4.05
1.08
2.08
2.10
1.00
1.02
1.06
1.06
1.06
2.01
2.17
170.005
162.988
154.697
136.108
132.348
128.720
128.289
127.573
127.527
124.917
114.304
73.637
70.204
69.588
67.303
64.299
27.380
25.371
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


6.866
6.859
5.541
4.991
4.986
4.981
4.974
4.415
4.409
4.403
4.323
4.311
4.274
4.262
4.250
4.238
4.211
4.204
4.197
3.662
3.651
3.642
3.216
2.881
2.101
2.074
2.070
2.066
2.063
2.059
1.910
1.591
1.583
1.579
1.571
1.566
1.556
1.553
1.544
1.541
1.531
1.528
1.516
1.504
1.492
1.364
1.352
1.340
1.317
1.305
1.293
0.963
0.950
0.938
0.906
0.894
0.886
0.881
0.870
CO2Et
OH
OMs
NHAc
O
624
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.05
1.08
0.98
2.00
1.04
2.09
1.07
1.06
3.04
3.02
4.01
3.03
3.00
3.02


CO2Et
O
O
O
AcN

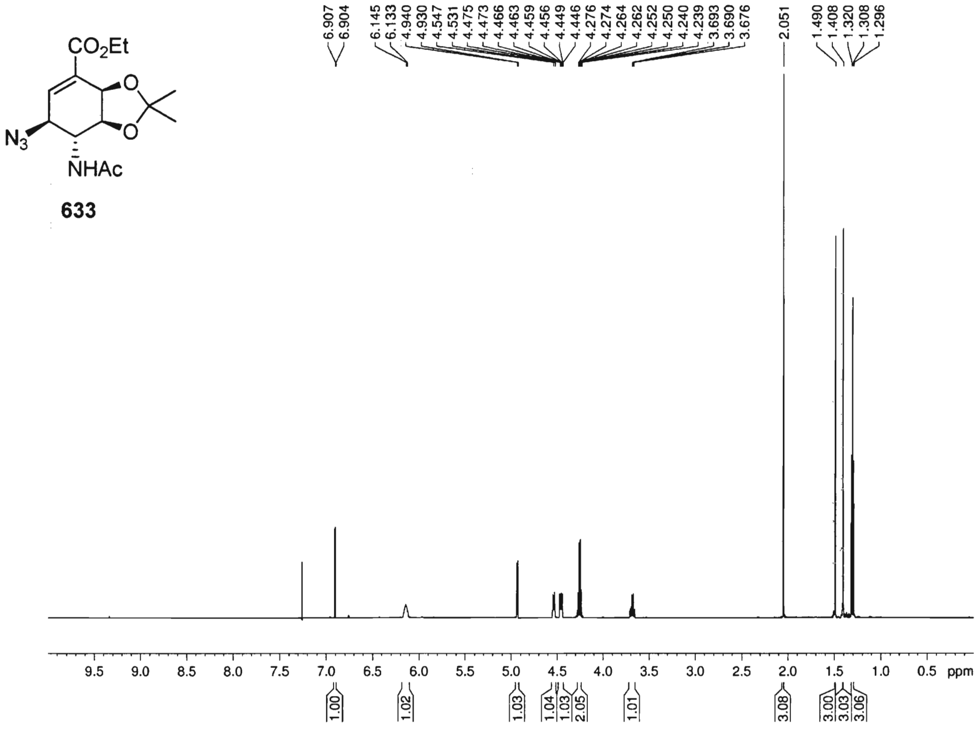
632

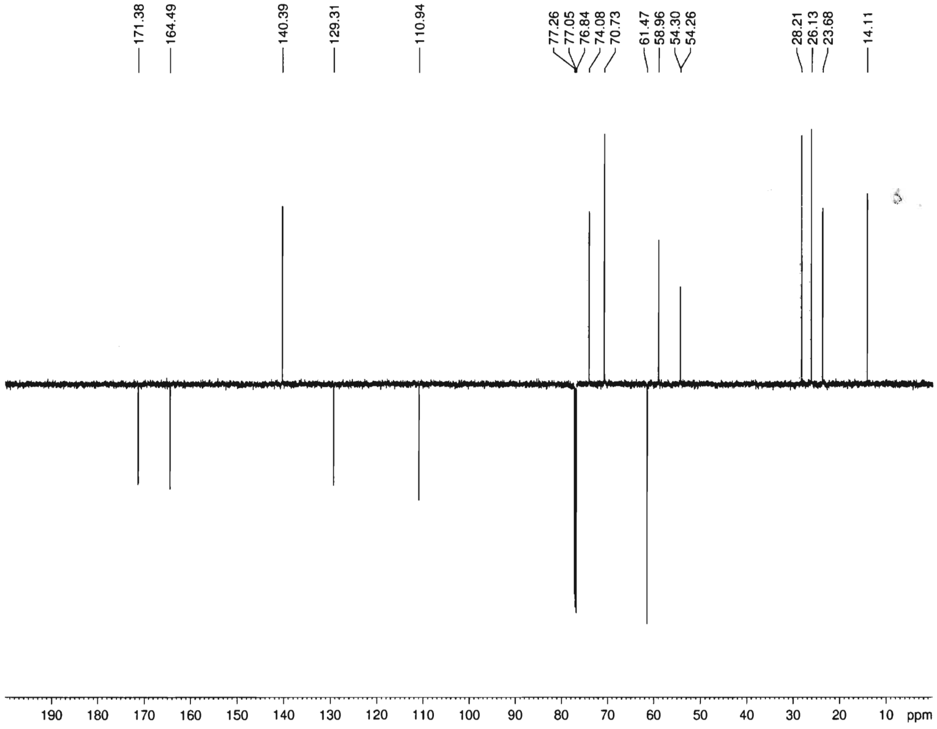

7.260
6.640
6.626
6.605
6.595
5.495
4.720
4.709
4.566
4.559
4.548
4.400
4.388
4.376
4.364
2.011
1.376
1.324
1.302
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.09
1.06
1.06
1.13
2.05
3.06
3.07
3.05
3.02

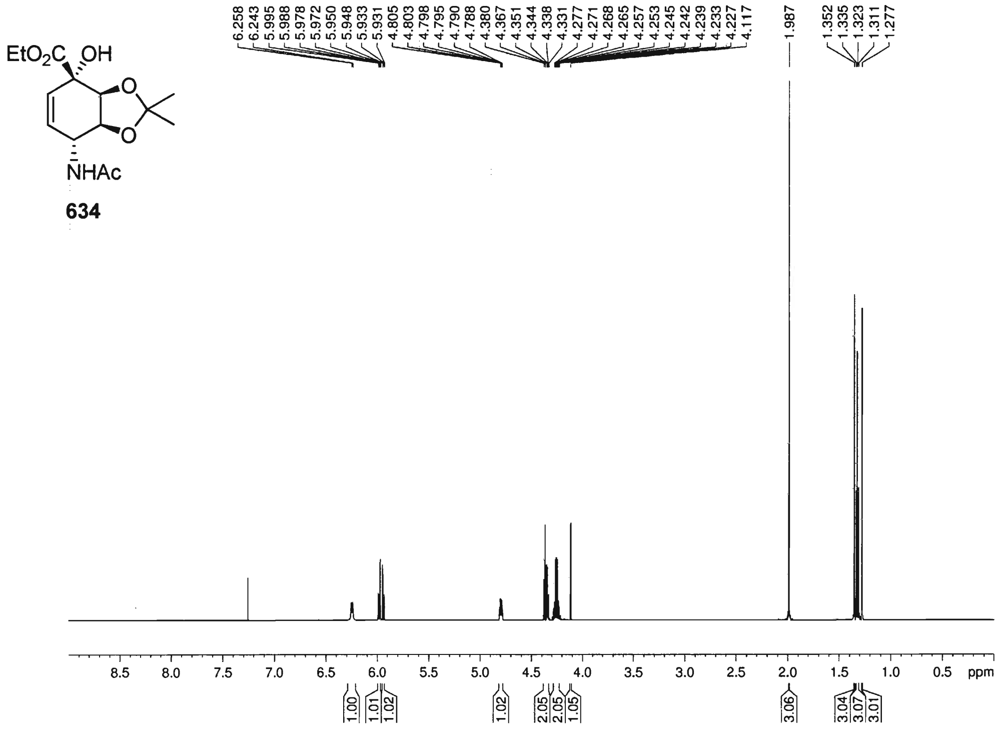

173.89
166.56
132.40
128.42
111.66
79.16
77.24
77.03
76.82
76.14
72.81
62.69
49.97
41.46
25.60
25.42
21.73
14.07
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

CO2Et
O
O
N3
NHAc

633


6.907
6.904
6.145
6.133
4.940
4.930
4.547
4.531
4.475
4.473
4.466
4.463
4.459
4.456
4.449
4.446
4.276
4.274
4.264
4.262
4.252
4.250
4.240
4.239
3.693
3.690
3.676
2.051
1.490
1.408
1.320
1.308
1.296
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.02
1.03
1.04
1.03
2.05
1.01
3.08
3.00
3.03
3.06


171.38
164.49
140.39
129.31
110.94
77.26
77.05
76.84
74.08
70.73
61.47
58.96
54.30
54.26
28.21
26.13
23.68
14.11
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


EtO$_2$C
OH
O
O
NHAc

634

6.258
6.243
5.995
5.988
5.978
5.972
5.950
5.948
5.933
5.931
4.805
4.803
4.798
4.795
4.790
4.788
4.380
4.367
4.351
4.344
4.338
4.331
4.277
4.271
4.268
4.265
4.257
4.253
4.245
4.242
4.239
4.233
4.227
4.117
1.987
1.352
1.335
1.323
1.311
1.277
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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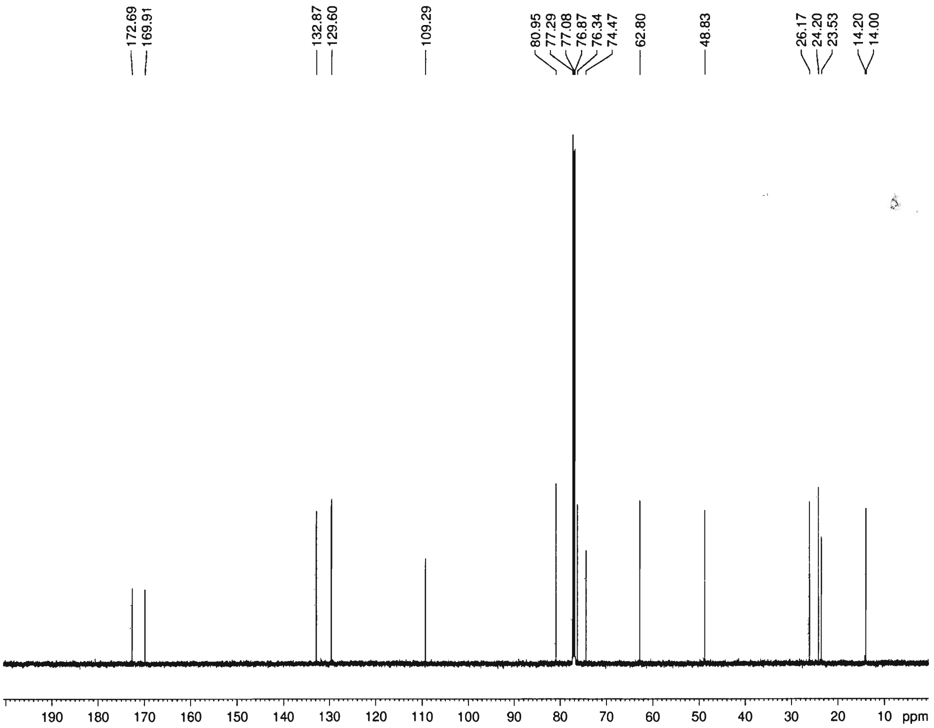
1.01
1.02
1.02
2.05
2.05
1.05
3.06
3.04
3.07
3.01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132.87
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80.95
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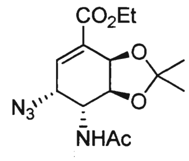
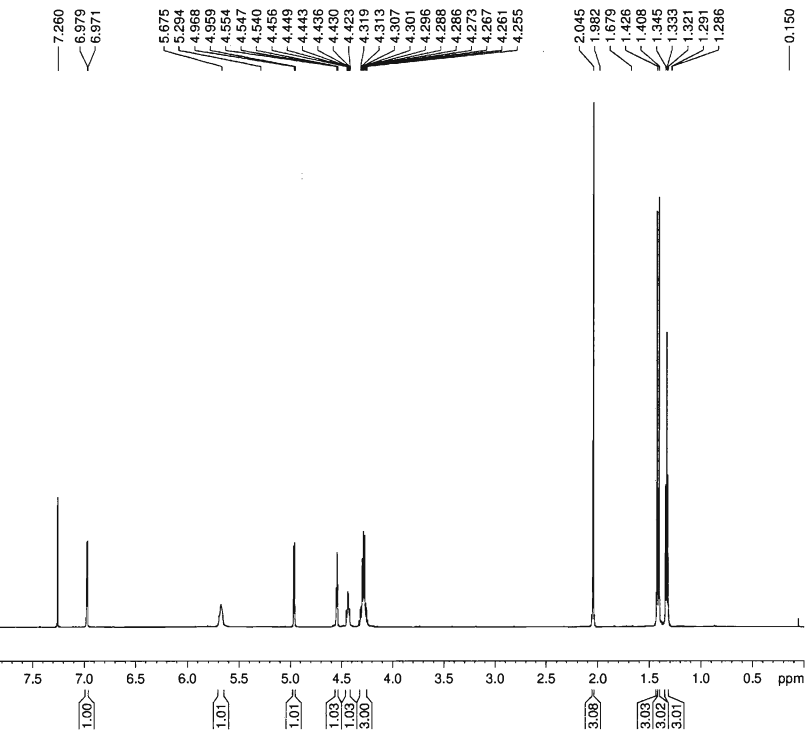
77.08
76.87
76.34
74.47
62.80
48.83
26.17
24.20
23.53
14.20
14.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



636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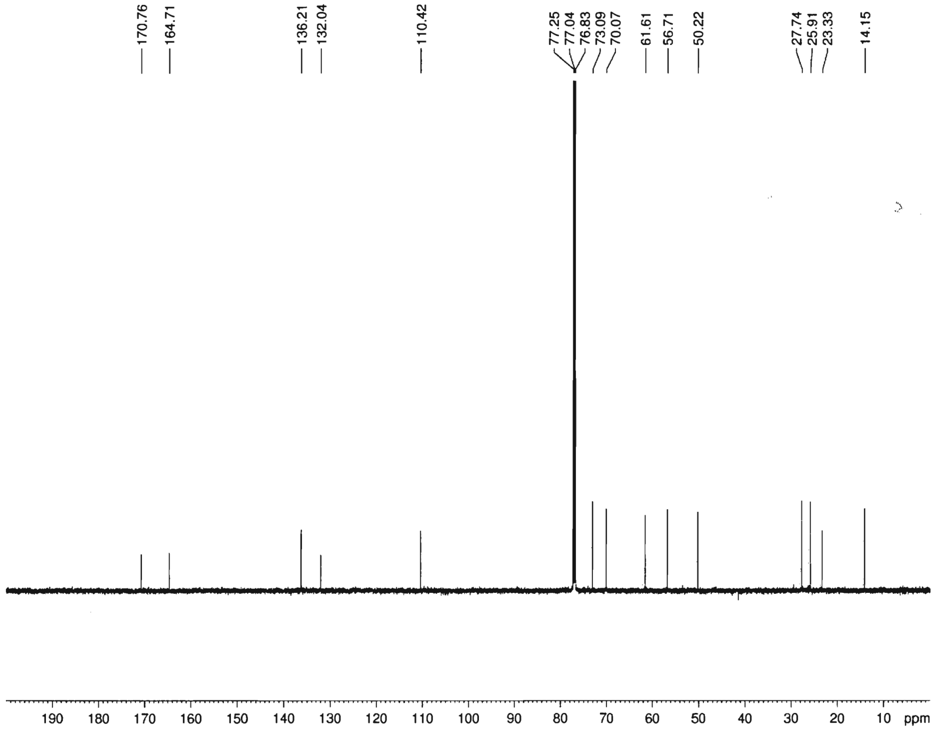
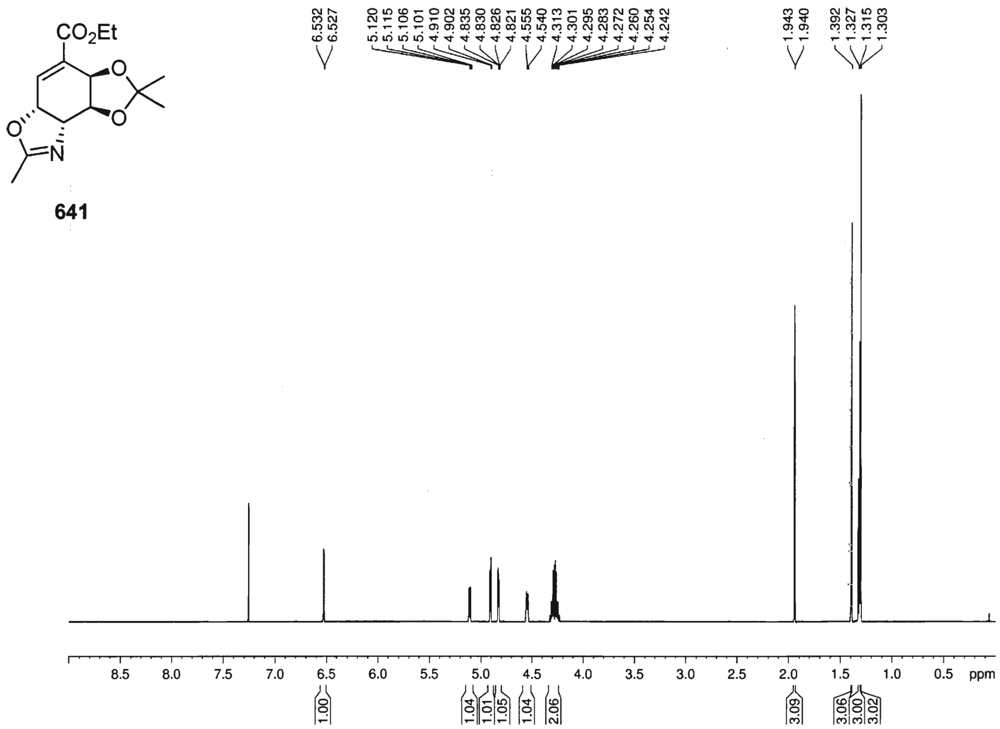
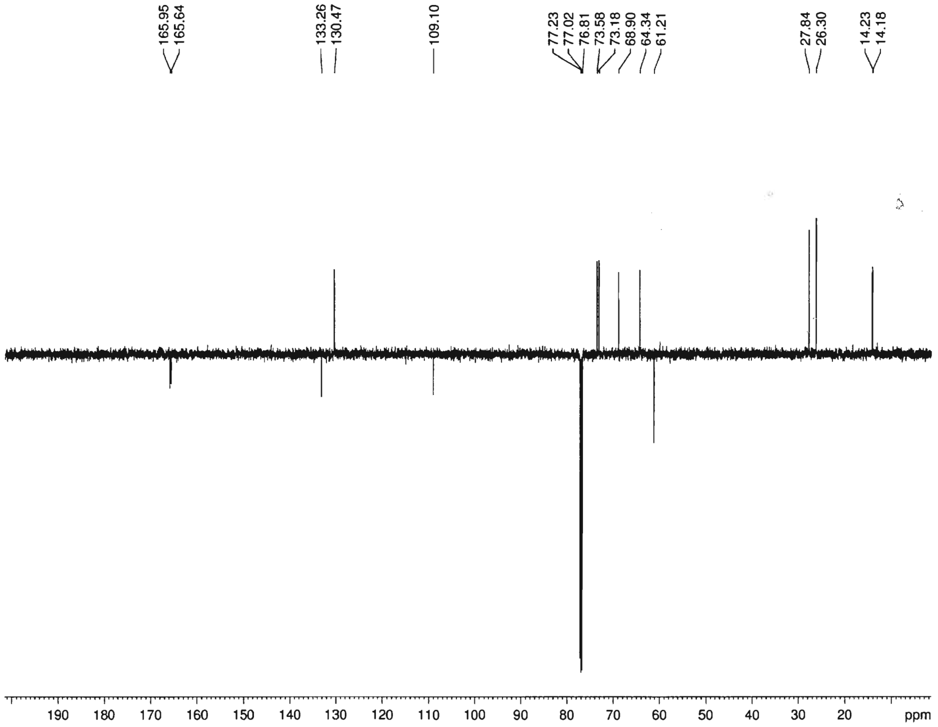
4.554
4.547
4.540
4.456
4.449
4.443
4.436
4.430
4.423
4.319
4.313
4.307
4.301
4.296
4.288
4.286
4.273
4.267
4.261
4.255
2.045
1.982
1.679
1.426
1.408
1.345
1.333
1.321
1.291
1.286
0.150
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.01
1.01
1.03
1.03
3.00
3.08
3.03
3.02
3.01

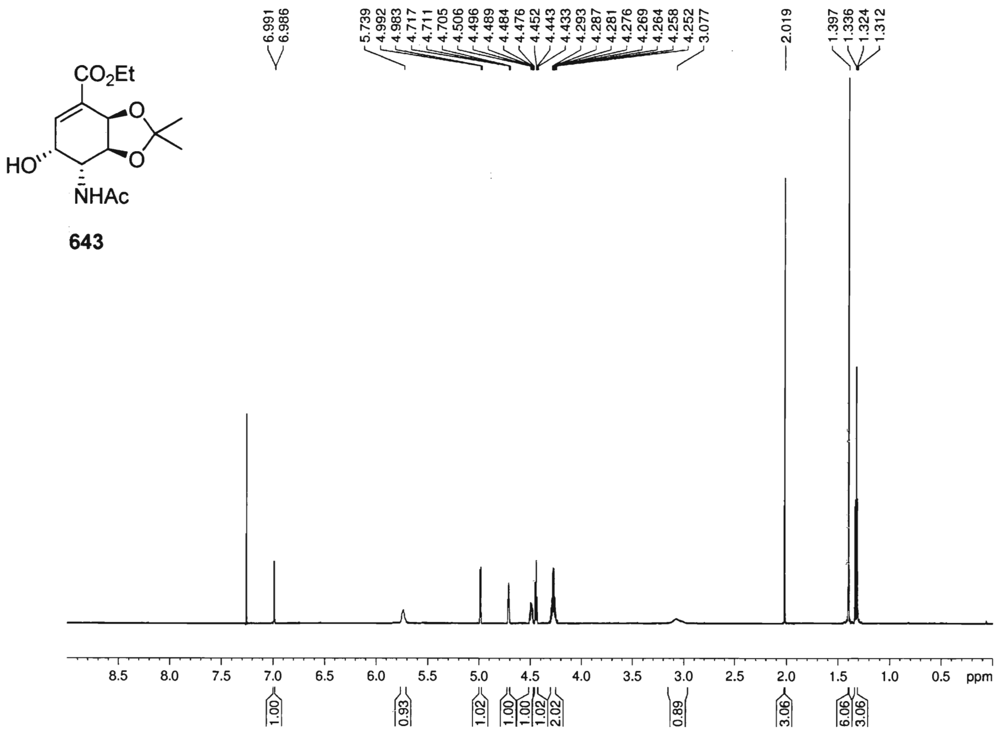

170.76
164.71
136.21
132.04
110.42
77.25
77.04
76.83
73.09
70.07
61.61
56.71
50.22
27.74
25.91
23.33
14.15
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



641

6.532
6.527
5.120
5.115
5.106
5.101
4.910
4.902
4.835
4.830
4.826
4.821
4.555
4.540
4.313
4.301
4.295
4.283
4.272
4.260
4.254
4.242
1.943
1.940
1.392
1.327
1.315
1.303
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.04
1.01
1.05
1.04
2.06
3.09
3.06
3.00
3.02


165.95
165.64
133.26
130.47
109.10
77.23
77.02
76.81
73.58
73.18
68.90
64.34
61.21
27.84
26.30
14.23
14.18
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


CO2Et
O
O
HO
NHAc

643

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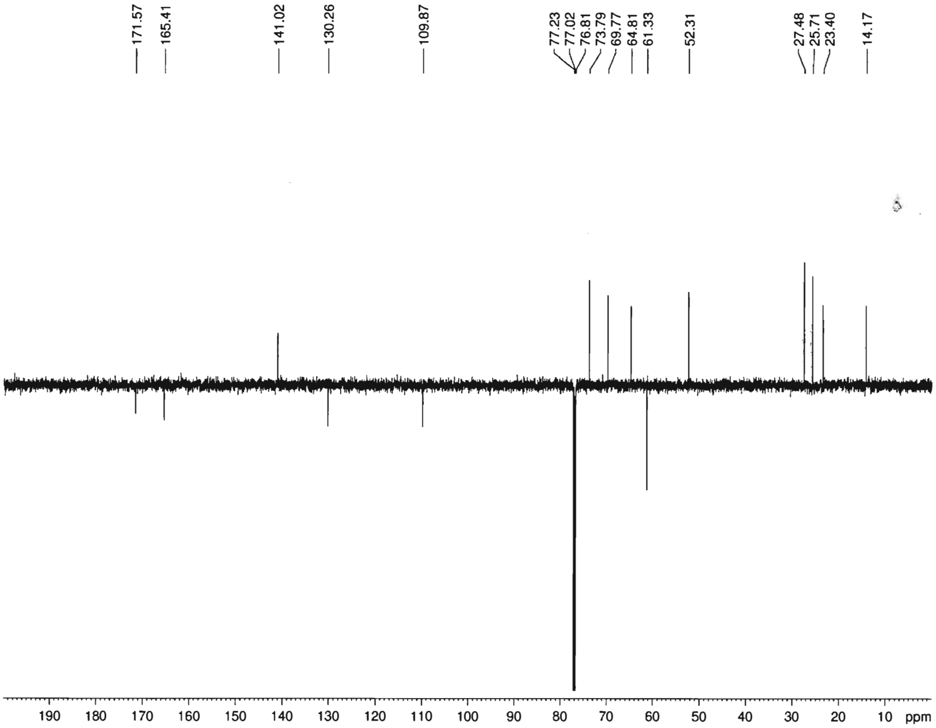
4.992
4.983
4.717
4.711
4.705
4.506
4.496
4.489
4.484
4.476
4.452
4.443
4.433
4.293
4.287
4.281
4.276
4.269
4.264
4.258
4.252
3.077
2.019
1.397
1.336
1.324
1.312
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.93
1.02
1.00
1.00
1.02
2.02
0.89
3.06
6.06
3.06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77.23
77.02
76.81
73.79
69.77
64.81
61.33
52.31
27.48
25.71
23.40
14.17
190
180
170
160
150
140
130
120
110
100
90
80
70
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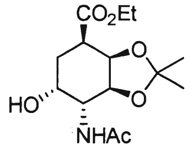
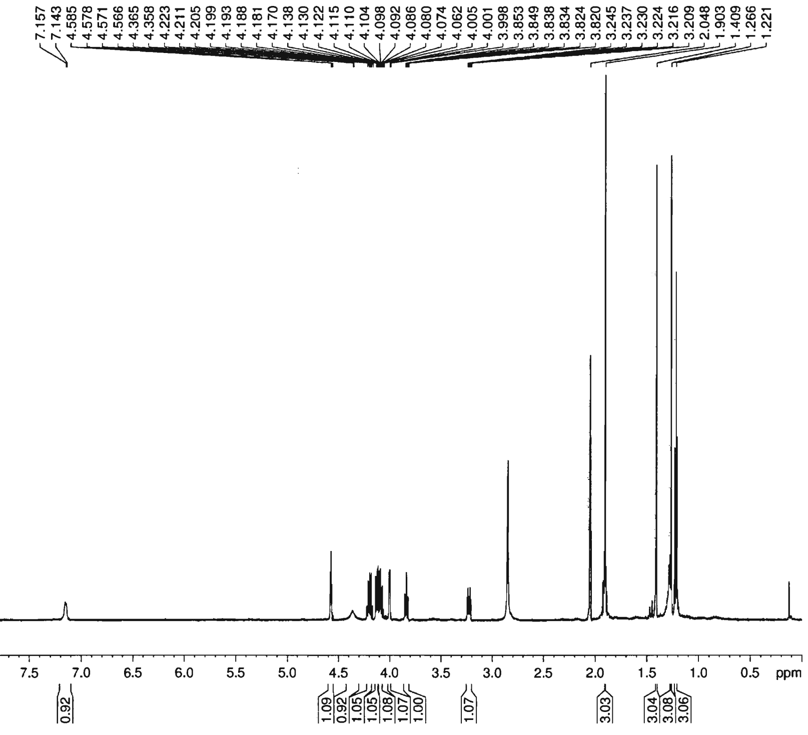
50
40
30
20
10
ppm


CO2Et
O
O
HO
NHAc

645


7.157
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4.585
4.578
4.571
4.566
4.365
4.358
4.223
4.211
4.205
4.199
4.193
4.188
4.181
4.170
4.138
4.130
4.122
4.115
4.110
4.104
4.098
4.092
4.086
4.080
4.074
4.062
4.005
4.001
3.998
3.853
3.849
3.838
3.834
3.824
3.820
3.245
3.237
3.230
3.224
3.216
3.209
2.048
1.903
1.409
1.266
1.221
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.92
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1.05
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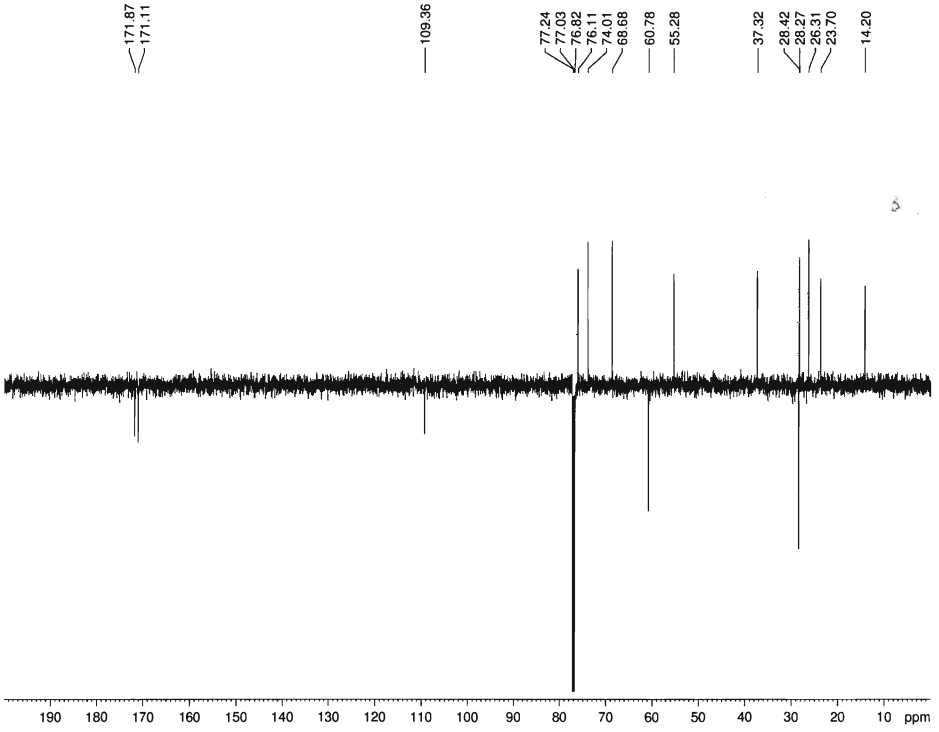
1.07
1.00
1.07
3.03
3.04
3.08
3.06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77.24
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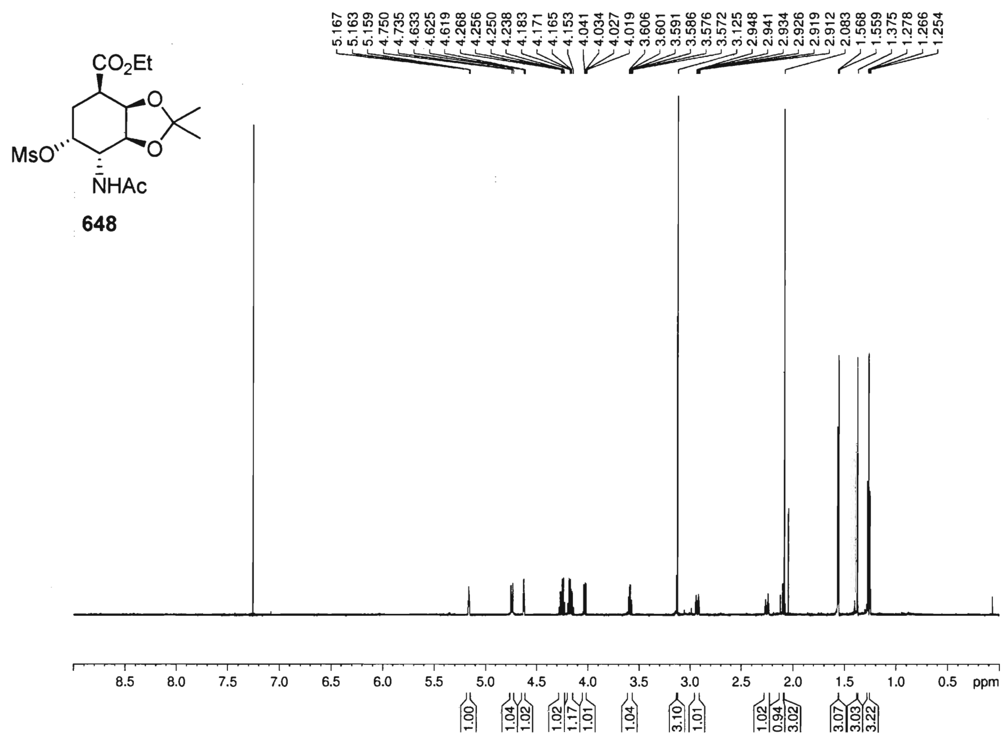
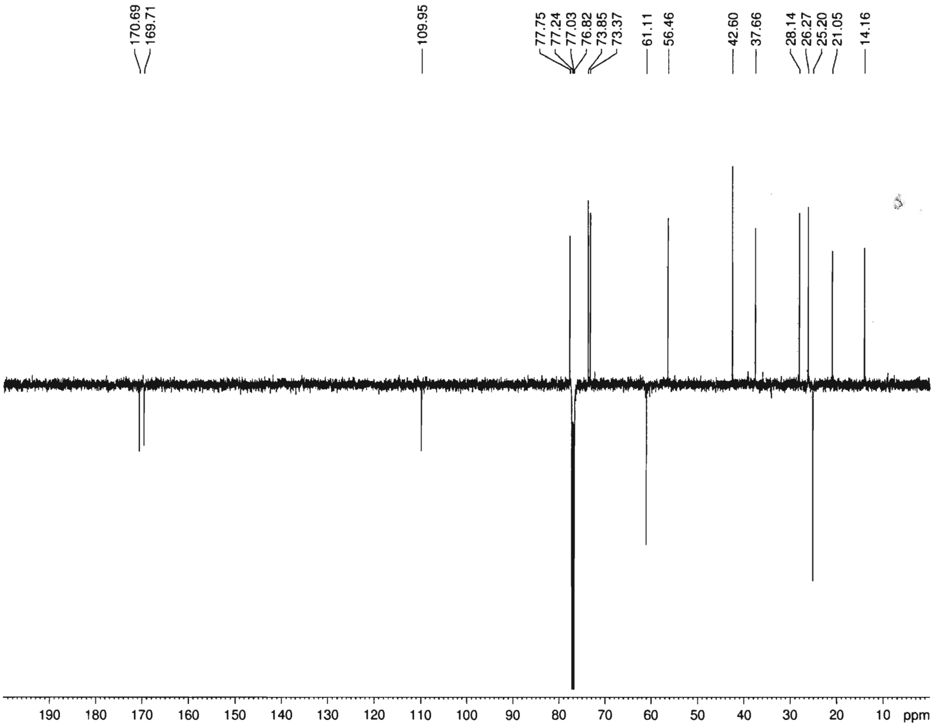
76.82
76.11
74.01
68.68
60.78
55.28
37.32
28.42
28.27
26.31
23.70
14.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Et
MsO
NHAc
O
O

648

5.167
5.163
5.159
4.750
4.735
4.633
4.625
4.619
4.268
4.256
4.250
4.238
4.183
4.171
4.165
4.153
4.041
4.034
4.027
4.019
3.606
3.601
3.591
3.586
3.576
3.572
3.125
2.948
2.941
2.934
2.926
2.919
2.912
2.083
1.568
1.559
1.375
1.278
1.266
1.254
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.04
1.02
1.02
1.17
1.01
1.04
3.10
1.01
1.02
0.94
3.02
3.07
3.03
3.22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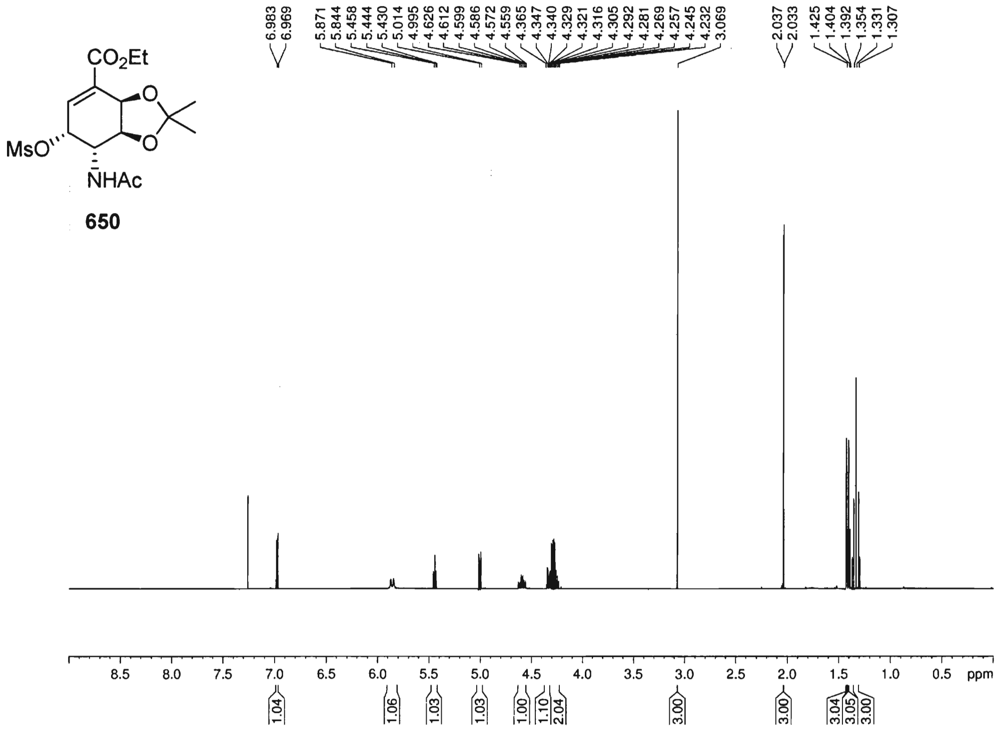
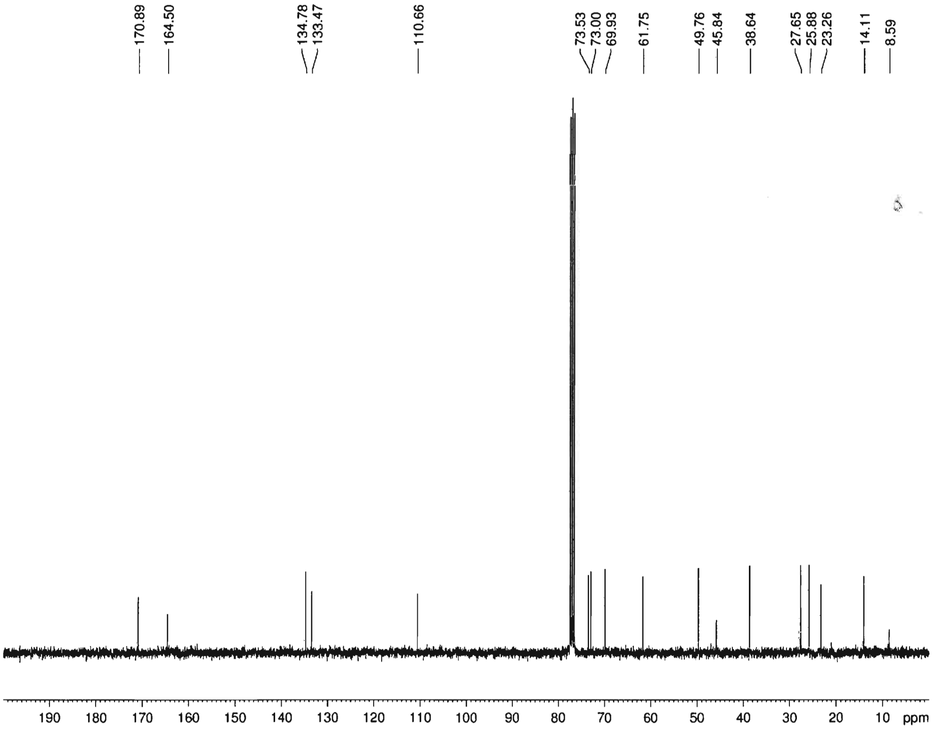
169.71
109.95
77.75
77.24
77.03
76.82
73.85
73.37
61.11
56.46
42.60
37.66
28.14
26.27
25.20
21.05
14.16
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

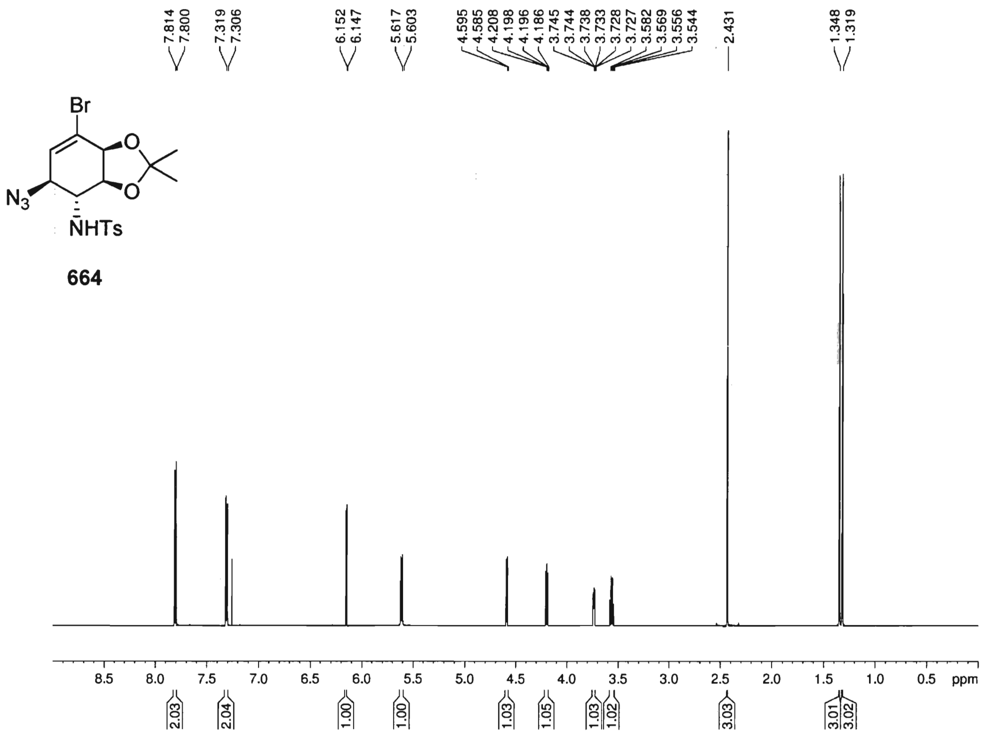


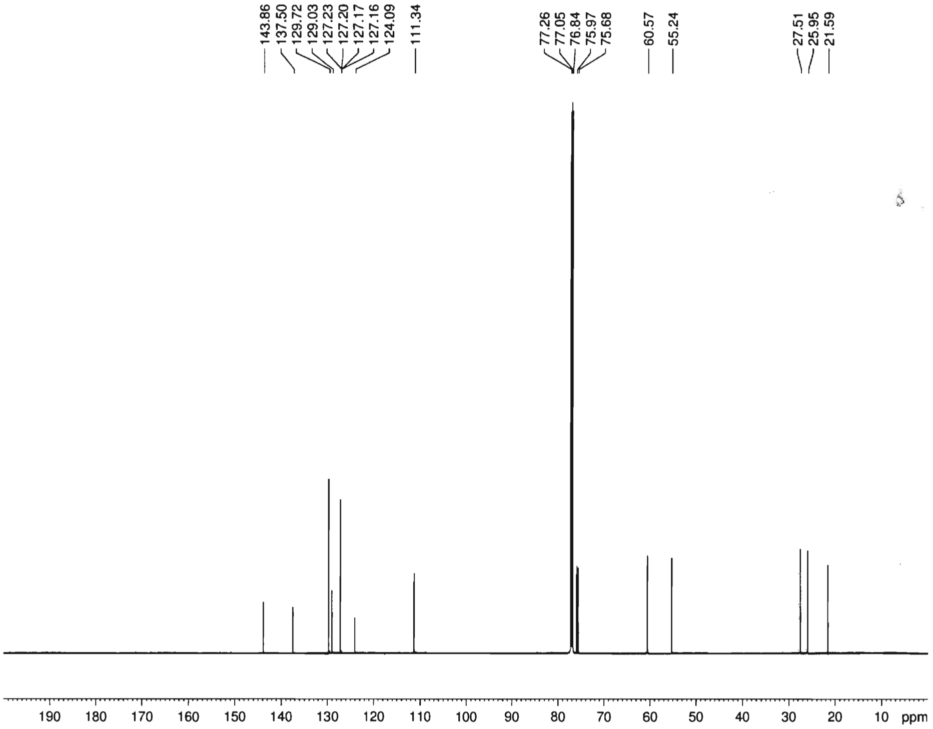
650
6.983
6.969
5.871
5.844
5.458
5.444
5.430
5.014
4.995
4.626
4.612
4.599
4.586
4.572
4.559
4.365
4.347
4.340
4.329
4.321
4.316
4.305
4.292
4.281
4.269
4.257
4.245
4.232
3.069
2.037
2.033
1.425
1.404
1.392
1.354
1.331
1.307
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.04
1.06
1.03
1.03
1.00
1.10
2.04
3.00
3.00
3.04
3.05
3.00

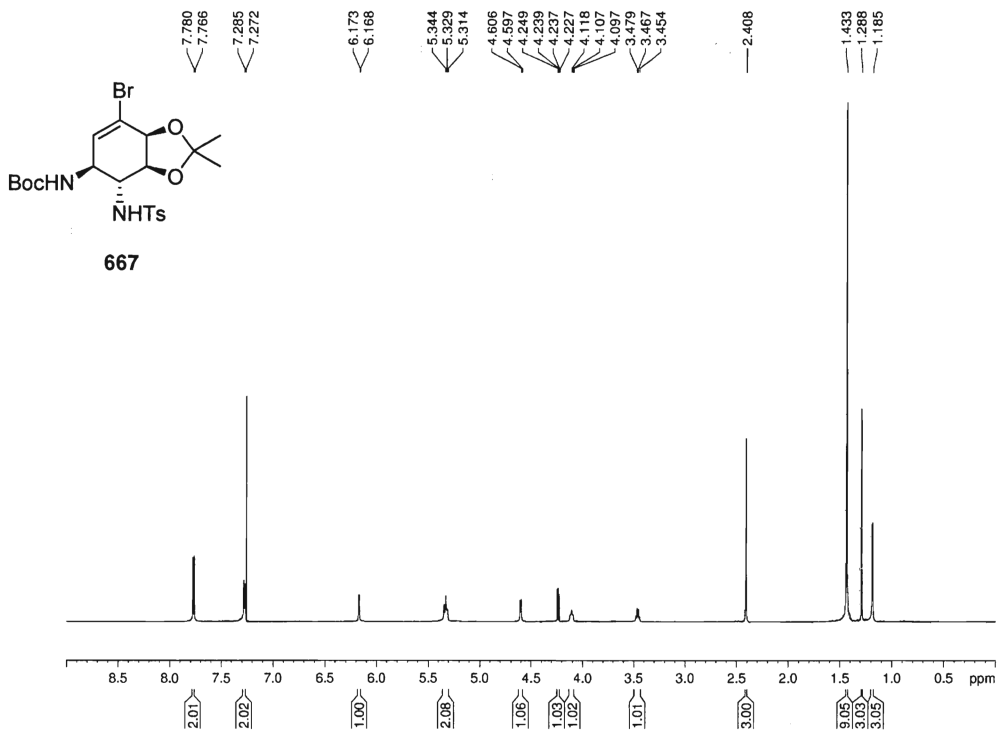

170.89
164.50
134.78
133.47
110.66
73.53
73.00
69.93
61.75
49.76
45.84
38.64
27.65
25.88
23.26
14.11
8.59
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Br
O
O
N3
NHTs

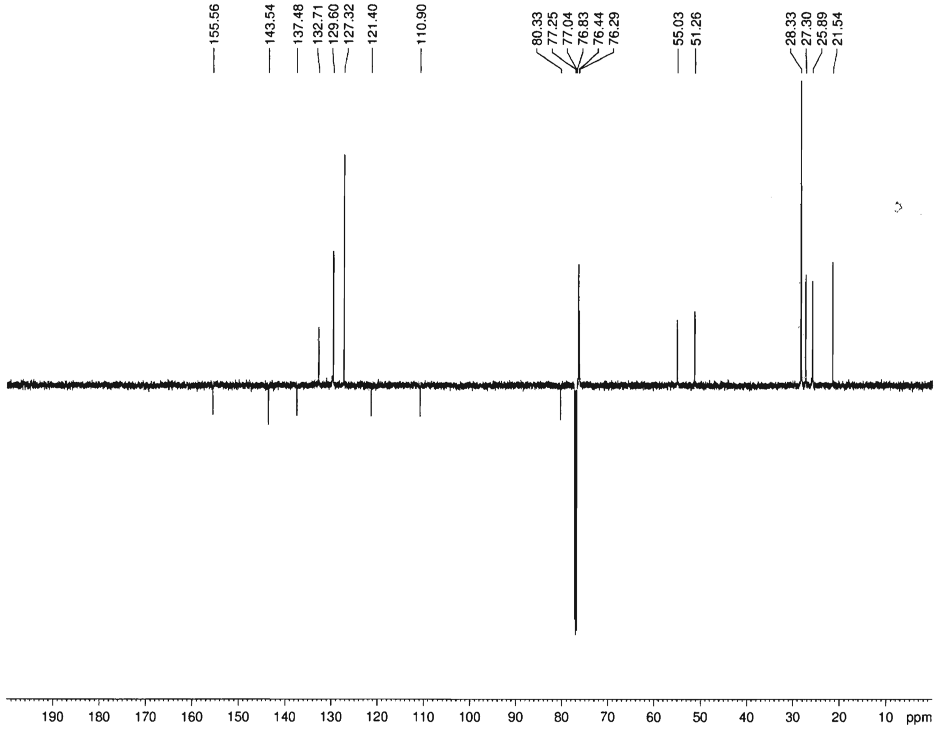
664

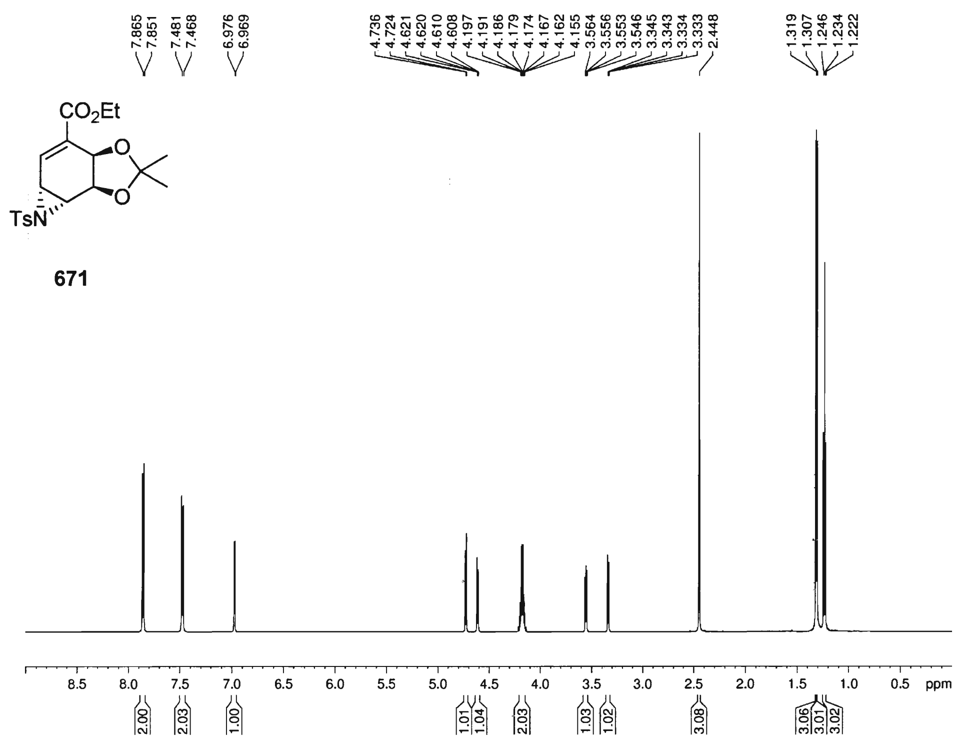

7.814
7.800
7.319
7.306
6.152
6.147
5.617
5.603
4.595
4.585
4.208
4.198
4.196
4.186
3.745
3.744
3.738
3.733
3.728
3.727
3.582
3.569
3.556
3.544
2.431
1.348
1.319
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
2.04
1.00
1.00
1.03
1.05
1.03
1.02
3.03
3.01
3.02


143.86
137.50
129.72
129.03
127.23
127.20
127.17
127.16
124.09
111.34
77.26
77.05
76.84
75.97
75.68
60.57
55.24
27.51
25.95
21.59
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Br
BocHN
O
O
NHTs
7.780
7.766
7.285
7.272
6.173
6.168
5.344
5.329
5.314
4.606
4.597
4.249
4.239
4.237
4.227
4.118
4.107
4.097
3.479
3.467
3.454
2.408
1.433
1.288
1.185
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.01
2.02
1.00
2.08
1.06
1.03
1.02
1.01
3.00
9.05
3.03
3.05

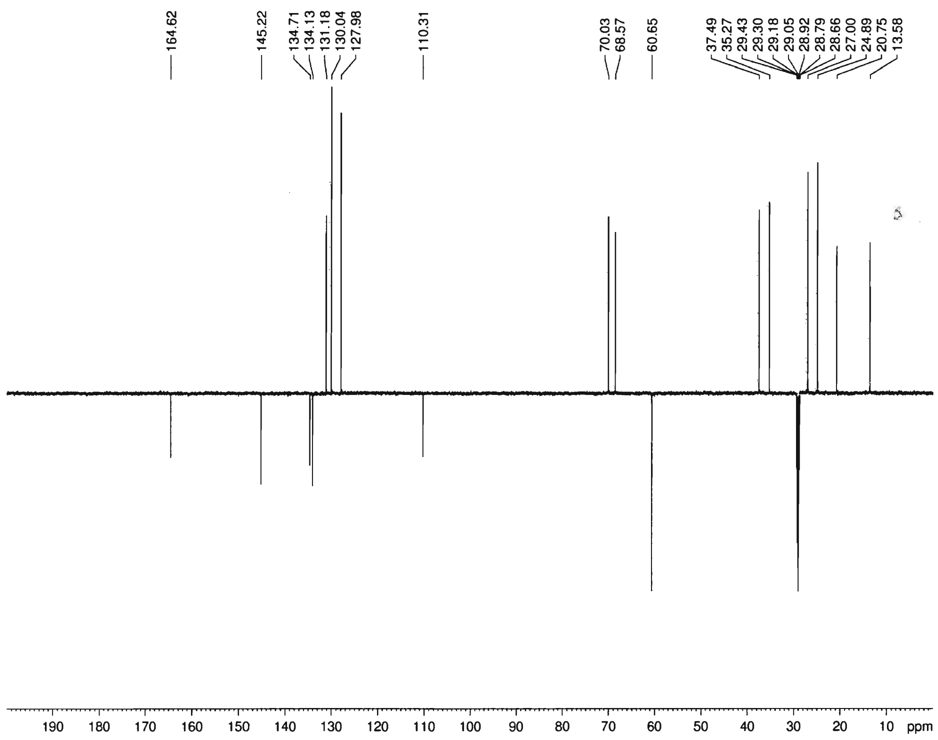
667


155.56
143.54
137.48
132.71
129.60
127.32
121.40
110.90
80.33
77.25
77.04
76.83
76.44
76.29
55.03
51.26
28.33
27.30
25.89
21.54
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

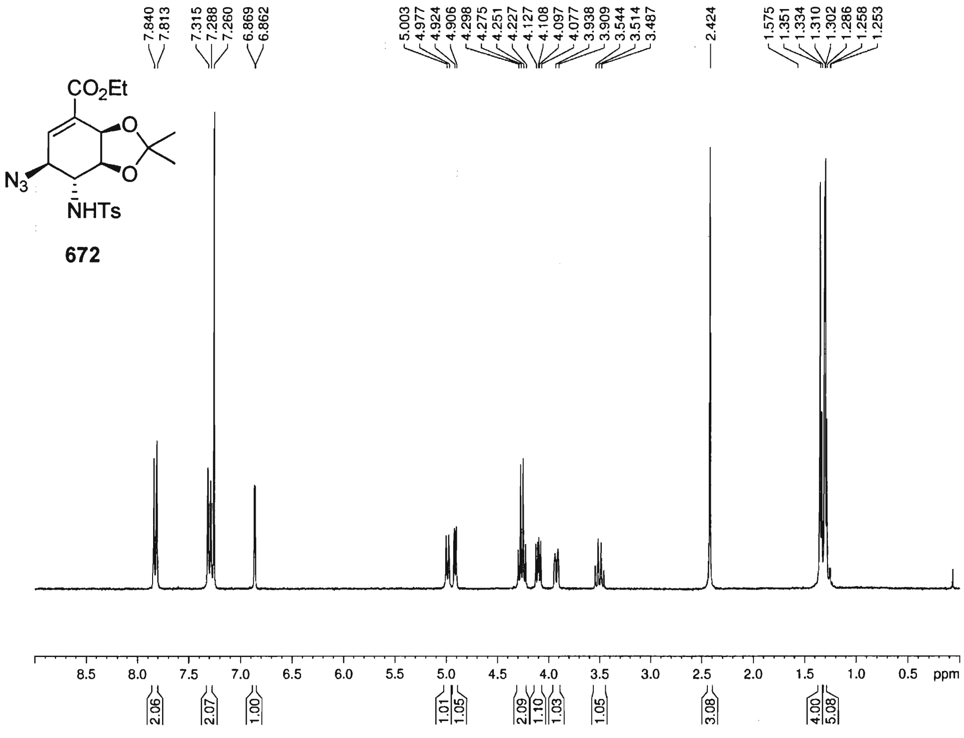


671

CO2Et
TsN
O
O
7.865
7.851
7.481
7.468
6.976
6.969
4.736
4.724
4.621
4.620
4.610
4.608
4.197
4.191
4.186
4.179
4.174
4.167
4.162
4.155
3.564
3.556
3.553
3.546
3.345
3.343
3.334
3.333
2.448
1.319
1.307
1.246
1.234
1.222
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.03
1.00
1.01
1.04
2.03
1.03
1.02
3.08
3.06
3.01
3.02



164.62
145.22
134.71
134.13
131.18
130.04
127.98
110.31
70.03
68.57
60.65
37.49
35.27
29.43
29.30
29.18
29.05
28.92
28.79
28.66
27.00
24.89
20.75
13.58
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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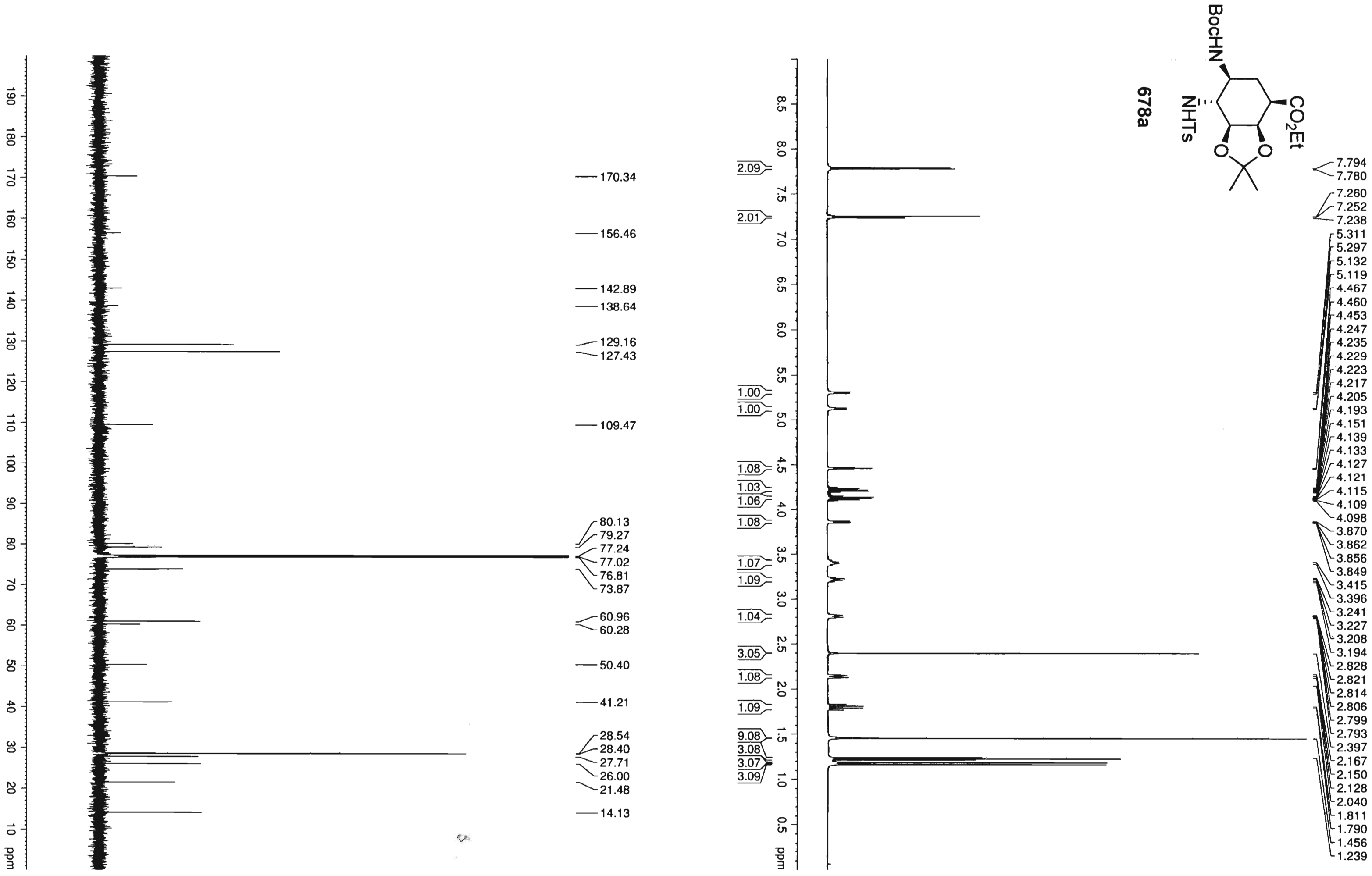
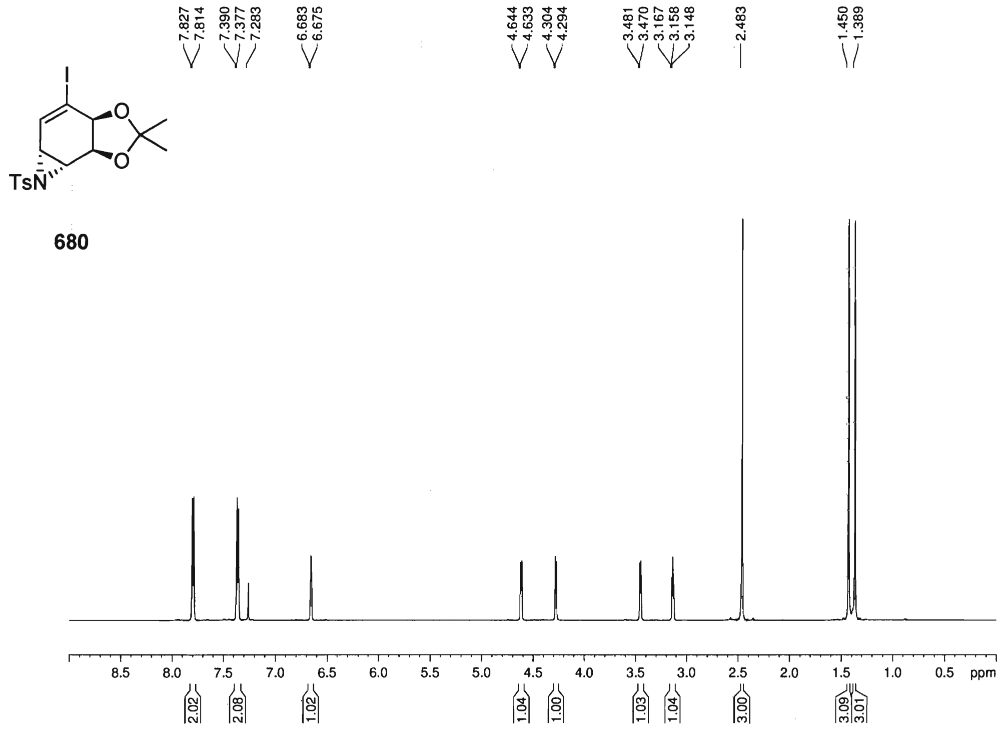
7.813
7.315
7.288
7.260
6.869
6.862
5.003
4.977
4.924
4.906
4.298
4.275
4.251
4.227
4.127
4.108
4.097
4.077
3.938
3.909
3.544
3.514
3.487
2.424
1.575
1.351
1.334
1.310
1.302
1.286
1.258
1.253
CO2Et
O
O
N3
NHTs
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.06
2.07
1.00
1.01
1.05
2.09
1.10
1.03
1.05
3.08
4.00
5.08

672

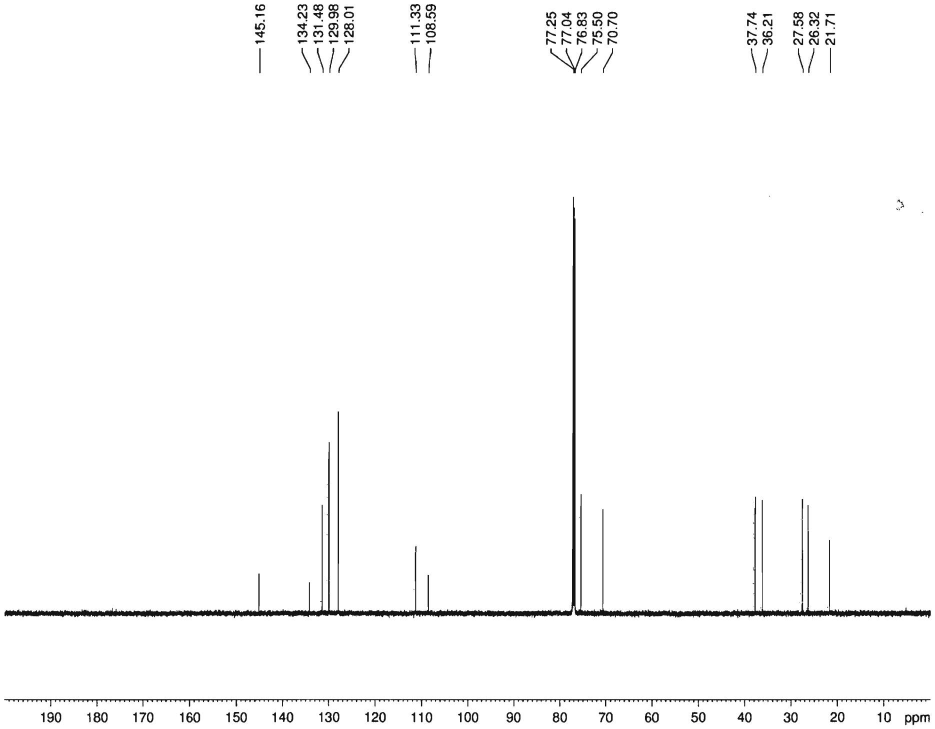

BocHN
CO2Et
NHTs
O
O
7.794
7.780
7.260
7.252
7.238
5.311
5.297
5.132
5.119
4.467
4.460
4.453
4.247
4.235
4.229
4.223
4.217
4.205
4.193
4.151
4.139
4.133
4.127
4.121
4.115
4.109
4.098
3.870
3.862
3.856
3.849
3.415
3.396
3.241
3.227
3.208
3.194
2.828
2.821
2.814
2.806
2.799
2.793
2.397
2.167
2.150
2.128
2.040
1.811
1.790
1.456
1.239
2.09
2.01
1.00
1.00
1.08
1.03
1.06
1.08
1.07
1.09
1.04
3.05
1.08
1.09
9.08
3.08
3.07
3.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
170.34
156.46
142.89
138.64
129.16
127.43
109.47
80.13
79.27
77.24
77.02
76.81
73.87
60.96
60.28
50.40
41.21
28.54
28.40
27.71
26.00
21.48
14.13
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

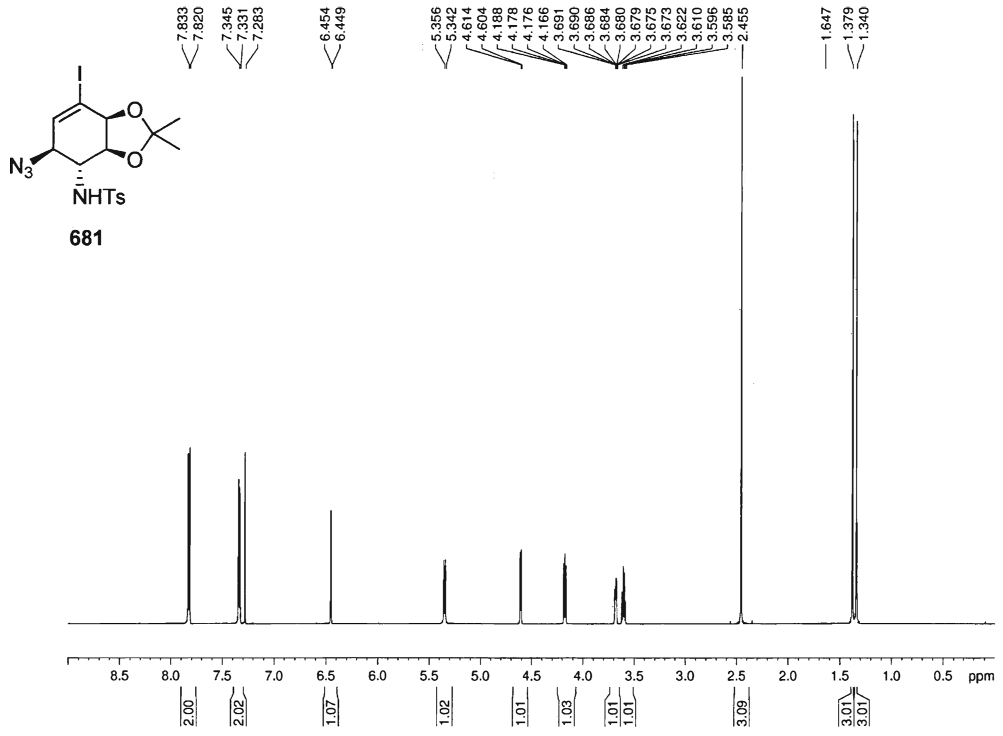
678a


I
O
O
TsN

680

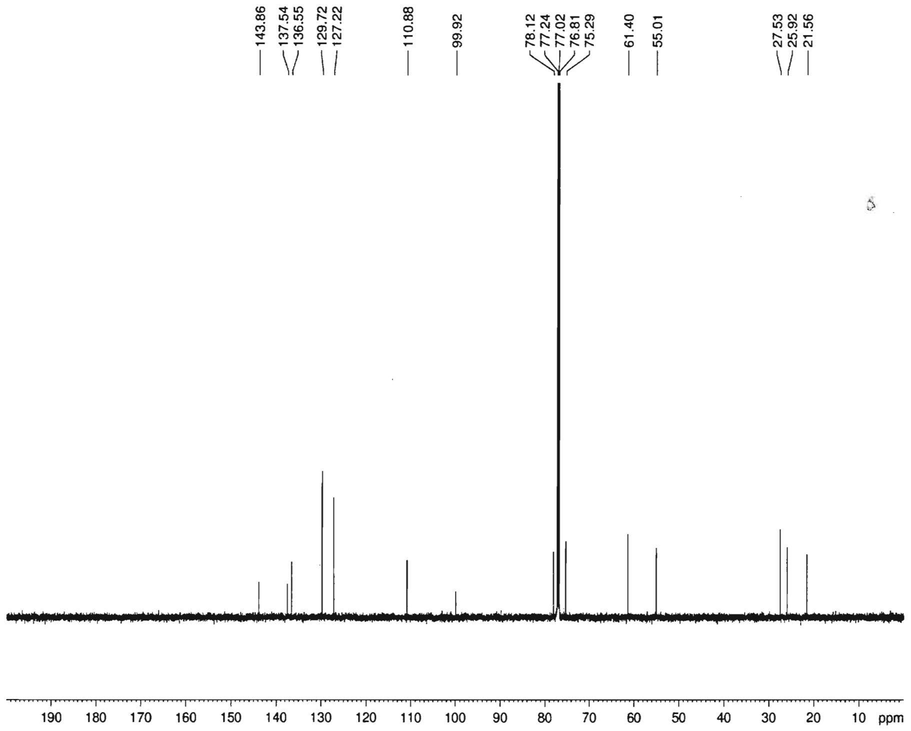
7.827
7.814
7.390
7.377
7.283
6.683
6.675
4.644
4.633
4.304
4.294
3.481
3.470
3.167
3.158
3.148
2.483
1.450
1.389
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.02
2.08
1.02
1.04
1.00
1.03
1.04
3.00
3.09
3.01

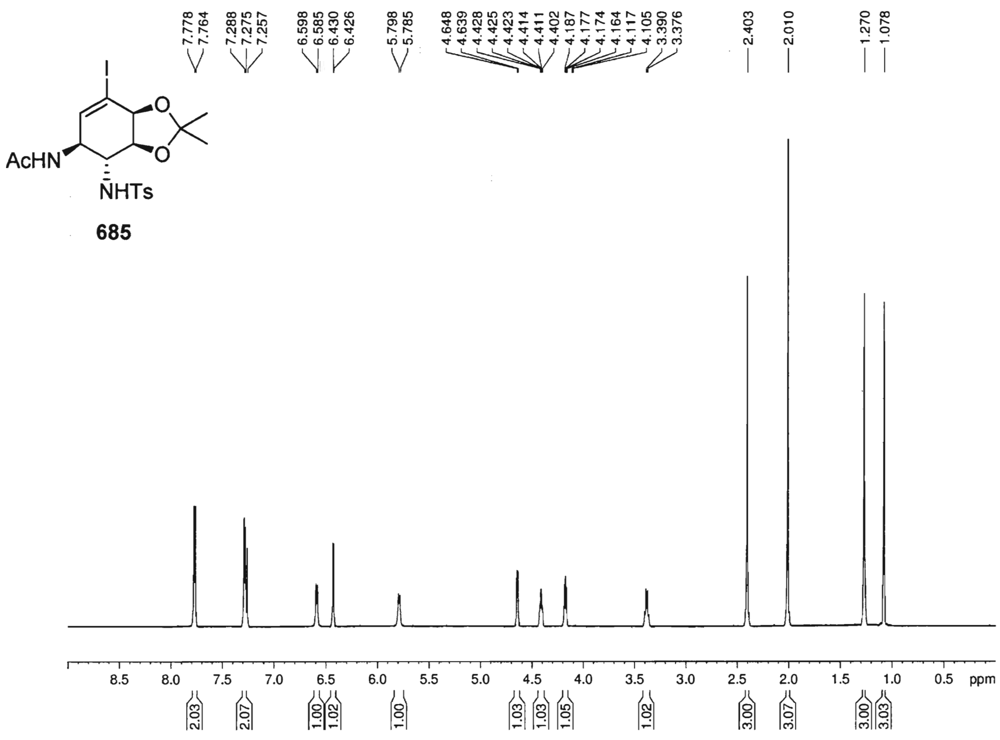

145.16
134.23
131.48
129.98
128.01
111.33
108.59
77.25
77.04
76.83
75.50
70.70
37.74
36.21
27.58
26.32
21.71
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


I
O
O
N3
NHTs

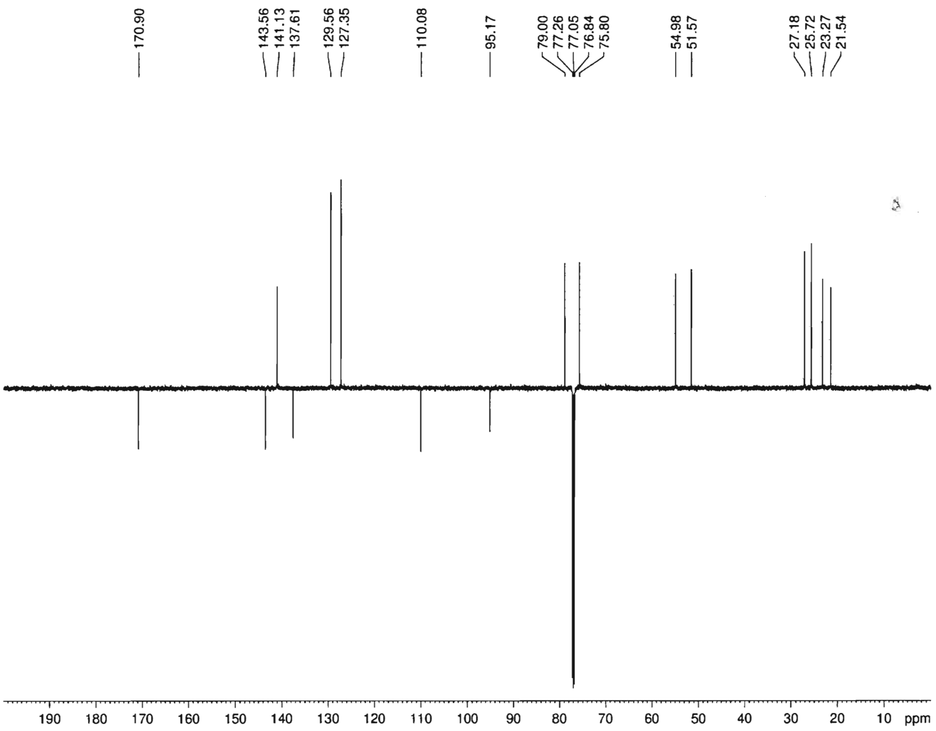
681

7.833
7.820
7.345
7.331
7.283
6.454
6.449
5.356
5.342
4.614
4.604
4.188
4.178
4.176
4.166
3.691
3.690
3.686
3.684
3.680
3.679
3.675
3.673
3.622
3.610
3.596
3.585
2.455
1.647
1.379
1.340
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.02
1.07
1.02
1.01
1.03
1.01
1.01
3.09
3.01
3.01


143.86
137.54
136.55
129.72
127.22
110.88
99.92
78.12
77.24
77.02
76.81
75.29
61.40
55.01
27.53
25.92
21.56
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


I
O
O
AcHN
NHTs
7.778
7.764
7.288
7.275
7.257
6.598
6.585
6.430
6.426
5.798
5.785
4.648
4.639
4.428
4.425
4.423
4.414
4.411
4.402
4.187
4.177
4.174
4.164
4.117
4.105
3.390
3.376
2.403
2.010
1.270
1.078
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
2.07
1.00
1.02
1.00
1.03
1.03
1.05
1.02
3.00
3.07
3.00
3.03

685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141.13
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129.56
127.35
110.08
95.17
79.00
77.26
77.05
76.84
75.80
54.98
51.57
27.18
25.72
23.27
21.54
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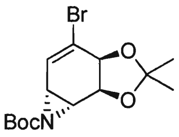
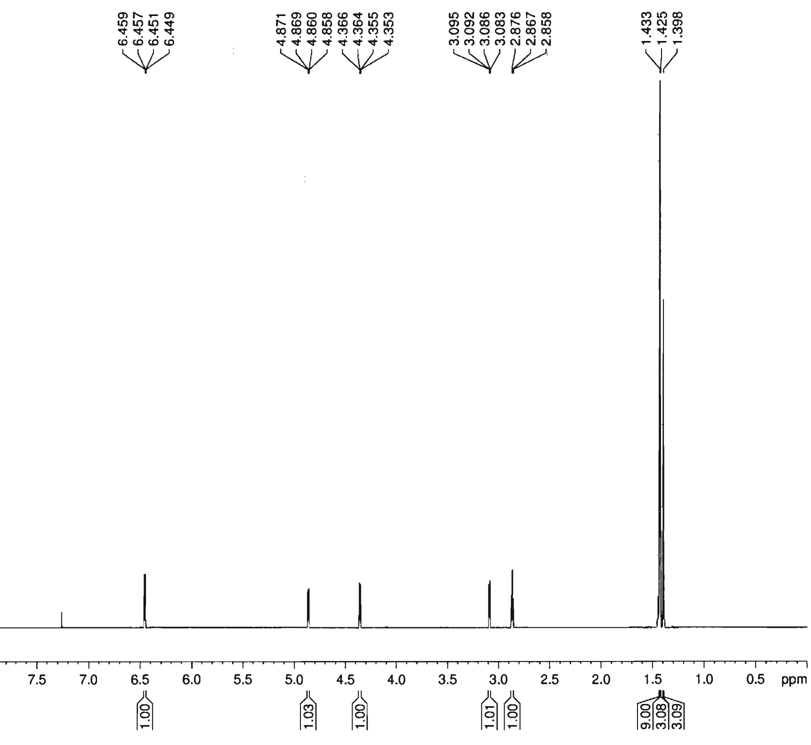
50
40
30
20
10
ppm


Br
O
O
BocN

697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6.451
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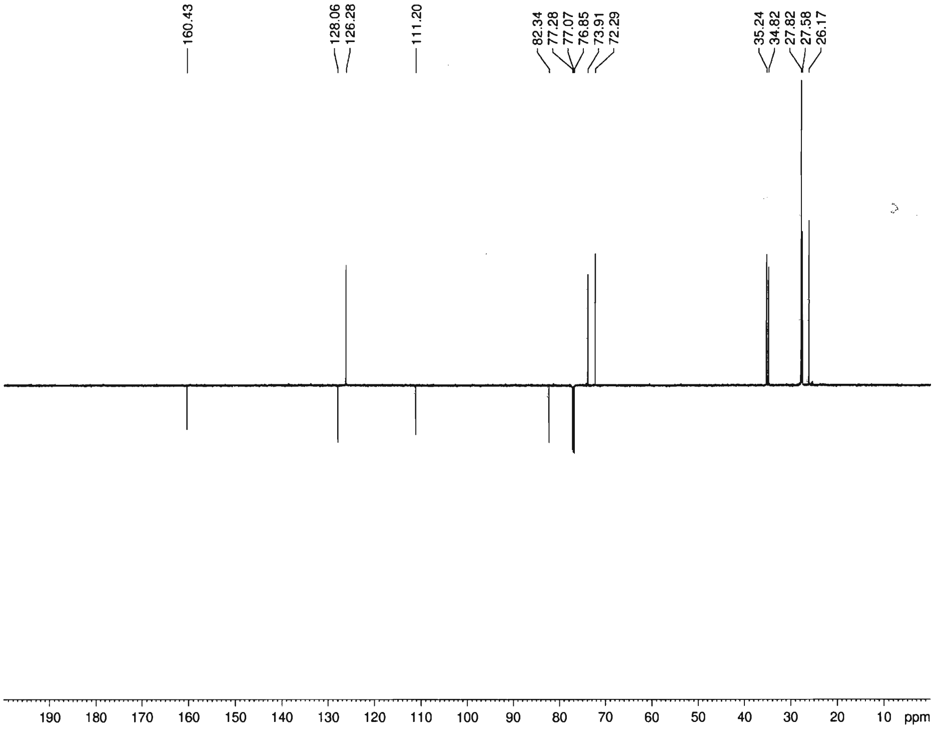
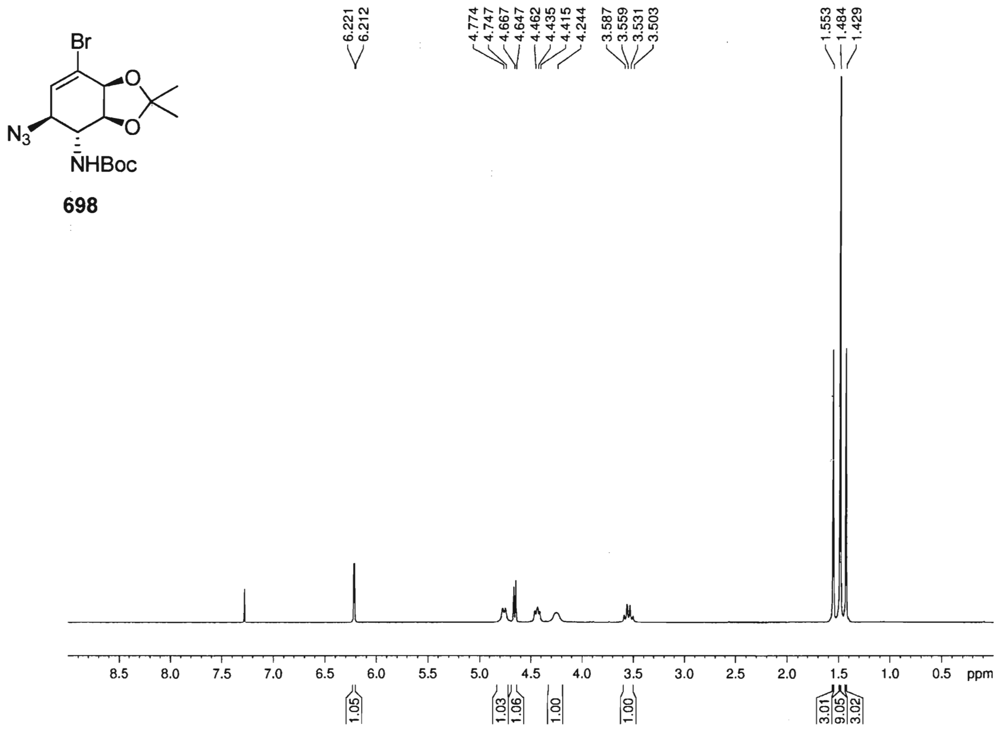
4.871
4.869
4.860
4.858
4.366
4.364
4.355
4.353
3.095
3.092
3.086
3.083
2.876
2.867
2.858
1.433
1.425
1.398
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
1.00
1.01
1.00
9.00
3.08
3.09


160.43
128.06
126.28
111.20
82.34
77.28
77.07
76.85
73.91
72.29
35.24
34.82
27.82
27.58
26.17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Br
O
O
N3
NHBoc

698

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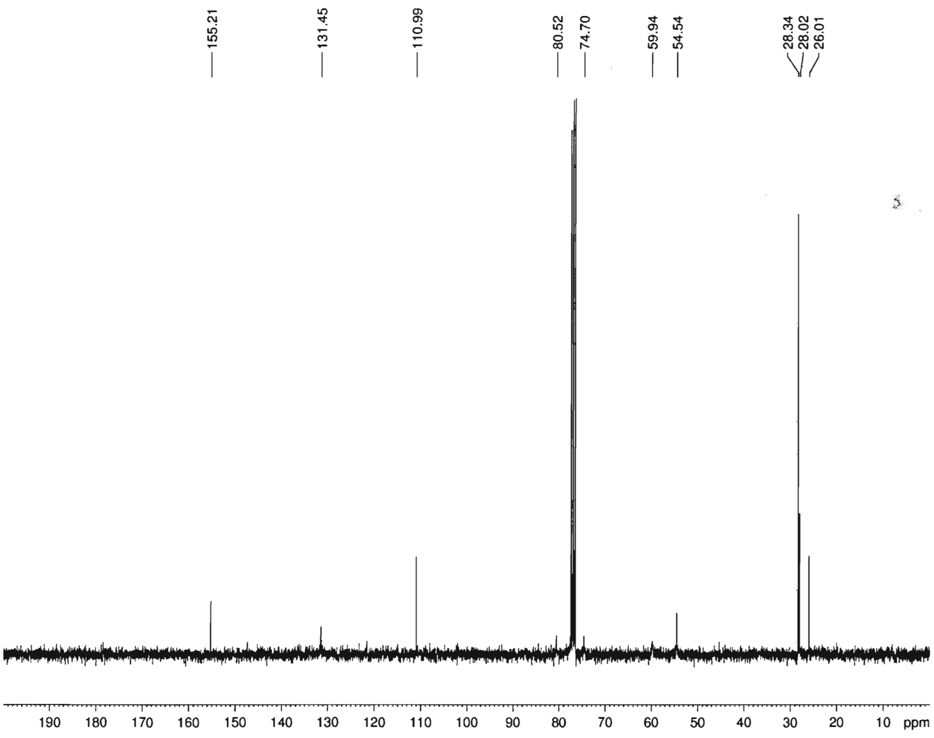
4.774
4.747
4.667
4.647
4.462
4.435
4.415
4.244
3.587
3.559
3.531
3.503
1.553
1.484
1.429
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.05
1.03
1.06
1.00
1.00
3.01
9.05
3.02


155.21
131.45
110.99
80.52
74.70
59.94
54.54
28.34
28.02
26.01
190
180
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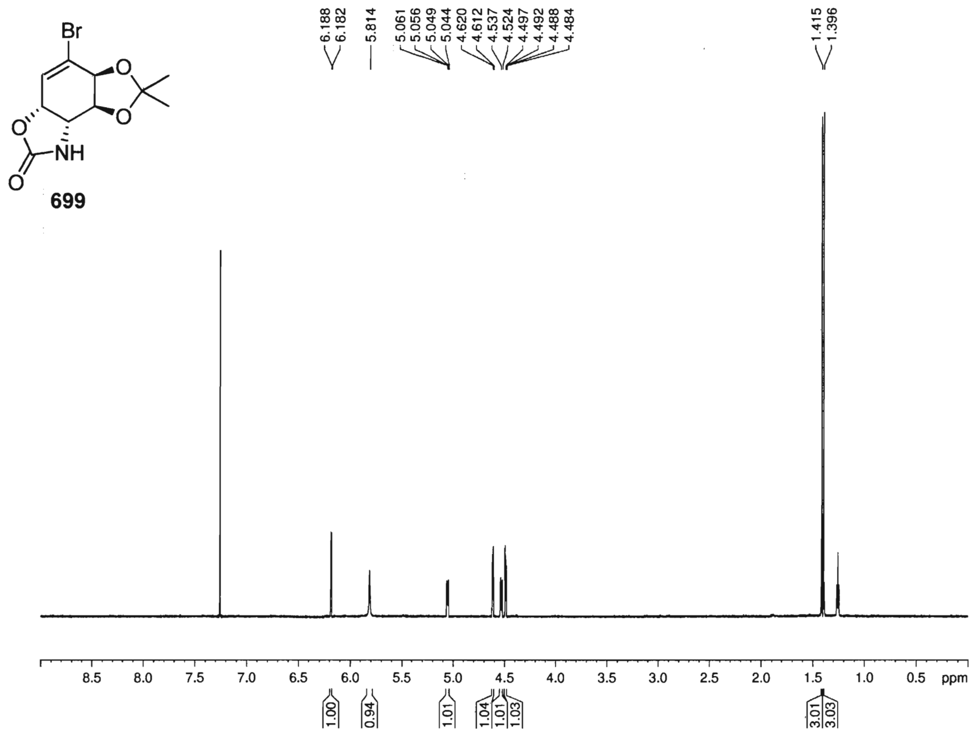
50
40
30
20
10
ppm


Br
O
O
O
NH
O
699
6.188
6.182
5.814
5.061
5.056
5.049
5.044
4.620
4.612
4.537
4.524
4.497
4.492
4.488
4.484
1.415
1.396
8.5
8.0
7.5
7.0
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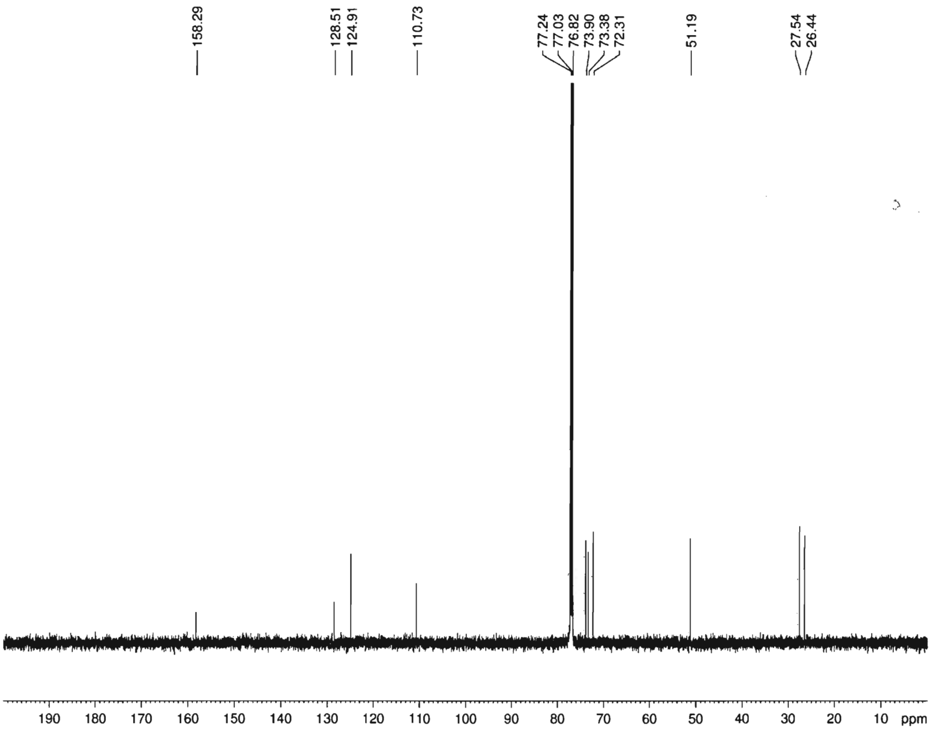
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7. References

1. Bachman, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 974.
2. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849.
3. Lamberth, C. J. *J. Prakt. Chem.* **2000**, *342*, 518.
4. Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.
5. Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224.
6. Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 6135.
7. Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
8. Rinner, U.; Adams, D. R.; dos Santos, M. L.; Abboud, K. A.; Hudlicky, T. *Synlett* **2003**, 1247.
9. Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452.
10. Hidaka, H.; Kobayashi, R. *Annu. Rev. Pharmacol. Toxicol.* **1992**, *32*, 377.
11. Bradshaw, D.; Hill, C. H.; Nixon, J. S.; Wilkinson, S. E. *Agents Actions* **1993**, *38*, 135.
12. Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E. *Biochemistry* **1968**, *7*, 3795.
13. Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.
14. Reed, J. W.; Hudlicky, T. *Synlett* **2009**, 685.
15. Hayden, F. G.; Atmar, R. L.; Schilling, M.; Johnson, C.; Portez, D.; Paar, D.; Huson, L.; Ward, P.; Mills, R. G. *NEJM* **1998**, *341*, 1336.
16. Ward, P.; Small, I.; Smith, J.; Suter, P.; Dutkowski, R. *J. Antimicrobial Chemotherapy* **2005**, *55*, i5.
17. Leneva, I. A.; Roberts, N.; Govorkova, E. A.; Goloubeva, O. G.; Webster, R. G. *Antiviral. Res.* **2000**, *48*, 101.
18. Atkins Jr., G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.
19. Burgess, E. M.; Penton Jr., H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224.

20. Burgess, E. M.; Penton Jr., H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
21. Burgess, E. M.; Penton Jr., H. R.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1977**, *56*, 40.
22. For reviews on uses of the Burgess reagent see: a) Lamberth, C. *J. Prakt. Chem.* **2000**, *342*, 518.; b) Burckhardt, S. *Synlett* **2000**, *4*, 559.; c) Khapli, S.; Dey, S.; Mal, D. *J. Indian Inst. Sci.* **2001**, *81*, 461.; d) Santra, S. *Synlett* **2009**, *2*, 328.
23. Claremon, D. A.; Phillips, B. T. *Tetrahedron Lett.* **1988**, *29*, 2155.
24. Creedon, S. M.; Crowley, H. K.; McCarthy, D. G. *J. Chem. Soc. Perkin Trans. I* **1998**, 1015.
25. Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719.
26. Maugein, N.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 1547.
27. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.
28. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.
29. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.
30. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
31. Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831.
32. Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.
33. Wipf, P.; Hayes, G. B. *Tetrahedron Lett.* **1998**, *54*, 6987.
34. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275.
35. Schwarz, H.; Dreessen, S.; Tersakian, A.; Schaumann, E. *Liebigs Ann. Chem.* **1997**, 1447.
36. Banfield, S. C.; Omori, A. T.; Leisch, H.; Hudlicky, T. *J. Org. Chem.* **2007**, *72*, 4989.
37. Miller, C. P.; Kaufman, D. H. *Synlett* **2000**, *8*, 1169.
38. Wodka, D.; Robbins, M.; Lan, P.; Martinez, R. L.; Athanasopoulos, J.; Makara, G. M. *Tetrahedron Lett.* **2006**, *47*, 1825.
39. Raghavan, S.; Mustafa, S.; Rathore, K. *Tetrahedron Lett.* **2008**, *49*, 4256.

40. Li, J. J.; Li, J. J.; Li, J.; Trehan, A. K.; Wong, H. S.; Krishnananthan, S.; Kennedy, L. J.; Gao, Q.; Ng, A.; Robl, J, A.; Balasubramanian, B.; Chen, B. C. *Org. Lett.* **2008**, *10*, 2897.
41. Wood, M. R.; Kim, J. Y.; Books, K. M. *Tetrahedron Lett.* **2002**, *43*, 3887.
42. Jose, B.; Unni, M. V. V.; Prathapan, S.; Vadakkan, J. J. *Syn. Comm.* **2002**, *32*, 2495.
43. Mamaghani, M.; Badrian, A. *Tetrahedron Lett.* **2004**, *45*, 1547.
44. Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004**, *10*, 5581.
45. Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem. Int. Ed.* **2002**, *41*, 834.
46. Nicolaou, K. C.; Longbottom, D. A.; Nalbanadian, A. Z.; Huang, X. *Angew. Chem. Int. Ed.* **2002**, *41,* 3866.
47. Rinner, U.; Adams, D. R.; dos Santos, M. L.; Abboud, K. A.; Hudlicky, T. *Synlett* **2003**, *9*, 1247.
48. The following statement appeared in a review by Lamberth (ref 22b) published in 2000: "The compatability of the Burgess reagent with many functionalities, e.g. halogens, epoxides, alkenes, alkynes, aldehydes, ketones, acetals, esters, secondary amines, makes it an attractive technique for the introduction of C-C double bonds into highly functionalized molecules."
49. Crabbé, P.; León, C. *J. Org. Chem.* **1970**, *35*, 2594.
50. O'Grodnick, J. S.; Ebersole, R. C.; Wittstruck, T.; Caspi, E. *J. Org. Chem.* **1974**, *39*, 2124.
51. Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655.
52. Jacobson, R. M.; Lahm, G. P. *J. Org. Chem.* **1979**, *44*, 462.
53. Daniewski, A. R.; Wokulicj, P. M.; Uskokvic, M. R. *J. Org. Chem.* **1992**, *57*, 7133.
54. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

55. Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.
56. Rigby, J. H.; Kirova-Snover, M. *Tetrahedron Lett.* **1997**, *38*, 8153.
57. Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257.
58. Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358.
59. Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975.
60. Nagel, A. A.; DiBrino, J.; Vincent, L. A.; Retsema, J. A. *J. Med. Chem.* **1982**, *25*, 881.
61. Raghaven, S.; Mustafa, S. *Tetrahedron* **2008**, *64*, 10055.
62. Nicolaou, K. C.; Snyder, S. A.; Nalbandian, A. Z.; Longbottom, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 6234.
63. Krauss, G. *Biochemistry of Signal Transduction and Regulation*; Wiley-VCH: Weinheim, **2007**, 111.
64. Secko, D. *The Science Creative Quarterly* **2003**, *2*, 1.
65. Levitzki, A. *Curr. Opin. Cell Biol.* **1996**, *8*, 239.
66. Lodish, H. *Molecular cell biology;* W.H. Freeman and Company: New York, **2004**, 157.
67. Inoue, M.; Kishimoto, A.; Takai, Y.; Nishizuka, Y. *J. Biol. Chem.* **1977**, *252*, 7610.
68. Jaken, S. *Curr. Opin. Cell Biol.* **1996**, *8*, 168.
69. Yoshida, Y.; Huang, F. L.; Nakabayashi, H.; Huang, K. P. *J. Biol. Chem.* **1988**, *263*, 9868.
70. Newton, A. C. *J. Biol. Chem.* **1995**, *270*, 28495.
71. Jaken, S.; Parker, P. J. *Bioessays* **2000**, *22*, 245.
72. Newton, A. C. *Chem. Rev.* **2001**, *101*, 2353.
73. Kikkawa, U.; Nishizuka, Y. *Ann. Rev. Cell Biol.* **1986**, *2*, 149.
74. Nishizuka, Y. *Science* **1992**, *258*, 607.
75. Grandy, S.; Czernik, A. J.; Greengard, P. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 6218.
76. Wilkinson, S. E.; Nixon, J. S. *Cell. Mol. Life Sci.* **1998**, *54*, 1122.

77. Ohshima, S.; Yanagisawa, M.; Katoh, A.; Fujii, T.; Sano, T.; Matsukuma, S.; Furumai, T.; Fujiu, M.; Watanabe, K.; Yokose, K.; Arisawa, M.; Okuda, T. *J. Antibiot.* **1994**, *47*, 639.
78. Kneifel, H.; König, W. A.; Loeffler, W.; Müller, R. *Arch. Microbiol.* **1977**, *113*, 121.
79. König, W. A.; Sinnwell, V.; Witt, S.; Kneifel, H. *Chem. Ber.* **1980**, *113*, 2221.
80. Boros, C.; Hamilton, S. M.; Katz, B.; Kulanthaivel, P. *J. Antibiot (Tokyo)* **1994**, *47*, 1010.
81. Koide, K.; Bunnage, M. E.; Gomez Paloma, L.; Kanter, J. R.; Taylor, S. S.; Brunton, L. L.; Nicolaou, K. C. *Chem Biol.* **1995**, *2*, 601.
82. Akamine, P.; Madhusudan, Brunton, L. L.; Horng, D. O.; Canaves, J. M.; Xuong, N.; Taylor, S. S. *Biochemistry* **2004**, *43*, 85.
83. Pande, V.; Ramos, M. J.; Gago, F. *Anticancer Agents Med. Chem.* **2008**, *8*, 638.
84. Heerding, J. M.; Lampe, J. W.; Darges, J. W.; Stamper, M. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1839.
85. Crane, H. M.; Menaldino, D. S.; Jagdmann, G. E.; Darges, J. W.; Buben, J. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2133.
86. Lai, Y-. S.; Menaldino, D. S.; Nichols, J. B.; Jagdmann, G. E.; Mylott, F.; Gillespie, J.; Hall, S. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2151.
87. Lai, Y-. S.; Stamper, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2147.
88. Lai, Y-. S.; Mendoza, J. S.; Jagdmann, G. E.; Menaldino, D. S.; Biggers, C. K.; Heerding, J. M.; Wilson, J. W.; Hall, S. E.; Jiang, J. B.; Janzen, W. P.; Ballas, L. M.; *J. Med. Chem.* **1997**, *40*, 226.
89. Hu, H.; Mendoza, J. S.; Lowden, C. T.; Ballas, L. M.; Janzen, W. P. *Bioorg. Med. Chem.* **1997**, *5*, 1873.
90. Hu, H.; Hollinshead, S. P.; Hall, S. E.; Kalter, K.; Ballas, L. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973.
91. Jagdmann, G. E.; Defauw, J. M.; Lampe, J. W.; Darges, J. W.; Kalter, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1759.

92. Jagdmann, G. E.; Defauw, J. M.; Lai, Y-. S.; Crane, H.; Hall, S. E.; Buben, J. A.; Hu, H.; Gosnell, P. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2015.

93. Defauw, J. M.; Murphy, M. M.; Jagdmann, G. E.; Hu, H.; Lampe, J. W.; Hollinshead, S. P.; Mitchell, T. J.; Crane, H.; Heerding, J. M.; Mendoza, J. S.; Davis, J. E.; Darges, J. W.; Hubbard, F. R.; Hall, S. E. *J. Med. Chem.* **1996**, *39*, 5215.

94. Lampe, J. W.; Biggers, C. K.; Defauw, J. M.; Foglesong, R. J.; Hall, S. E.; Heerding, J. M.; Hollinshead, S. P.; Hu, H.; Hughes, P. F.; Jagdmann, G. E.; Johnson, M. G.; Lai, Y-. S.; Lowden, C. T.; Lynch, M. P.; Mendoza, J. S.; Murphy, M. M.; Wilson, J. W.; Ballas, L. M.; Carter, K.; Darges, J. W.; Davis, J. E.; Hubbard, F. R.; Stamper, M. L. *J. Med. Chem.* **1996**, *45*, 2624.

95. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147.

96. Hughes, P. F.; Smith, S. H.; Olsen, J. T. *J. Org. Chem.* **1994**, *59*, 5799.

97. Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.

98. Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur.* **1995**, *1*, 454.

99. Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707.

100. Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc. Perkin. Trans. 1* **1995**, 2355.

101. Tanner, D.; Almario, A.; Högberg, H. *Tetrahedron* **1995**, *51*, 6061.

102. Tanner, D.; Tedenborg, L.; Almario, A.; Pettersson, I.; Csöregh, I.; Kelly, N. M.; Andersson, P. G.; Högberg, T. *Tetrahedron* **1997**, *53*, 4857.

103. Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703.

104. Suzuki, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505.

105. Barbier, P.; Stadlwieser, J. *Chimia* **1996**, *50*, 530.

106. Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197.

107. Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624.

108. Miyabe, H.; Torieda, M.; Kiguchi, T.; Naito, T. *Synlett* **1997**, 580.

109. Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397.

110. Franck, B.; Berger-Lohr, B. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 818.

111. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572.

112. Hu, H.; Jadgmann, G. E.; Hughes, P. F.; Nichols, J. B. *Tetrahedron Lett.* **1995**, *36*, 3659.

113. Tuch, A.; Saniere, M.; Le Merrer Y.; Deezay, J. *Tetrahedron Asymmetry* **1996,** *7,* 2901.

114. Tuch, A.; Saniere, M.; Le Merrer Y.; Deezay, J. *Tetrahedron Asymmetry* **1996,** *7,* 897.

115. Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693.

116. Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

117. Morie, T.; Kato, S. *Heterocycles* **1998**, *48*, 427.

118. Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715.

119. Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999,** *1,* 615.

120. Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405.

121. Phannarath, P.; Dupart de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J. -P. *Eur. J. Org. Chem.* **2000**, 3903.

122. Genêt, J. -P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron Aymmmetry* **1991**, *2*, 555.

123. Mueller, A.; Takyar, D. K.; Witt, S.; Koeing, W. A. *Liebigs Annalen der Chemie* **1993**, *6*, 651.

124. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Synlett* **1996**, 29.

125. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1997**, *55*, 17177.

126. Herdeis, C.; Mohareb, R. M.; Neder, R. B.; Schwabenländer, F.; Telser, J. *Tetrahedron Asymmetry* **1999**, *10*, 4521.

127. Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738.

128. Masse, C. E.; Morgan, A. J.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2571.

129. Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382.

130. Yadav, J. S.; Srinivas, Ch. *Tetrahedron Lett.* **2002**, *43*, 3837.

131. Raghaven, S.; Kumar, C. N. *Tetrahedron Lett.* **2006**, *47*, 1585.

132. Roy, S. P.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2008**, *49*, 5498.

133. Srivastava, A. K.; Panda, G. *Chem. Eur. J.* **2008**, *14*, 4675.

134. Hollinshead, S. P; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703.

135. Nilsson, J. P.; Andersson, C-. M. *Tetrahedron Lett.* **1997**, *38*, 4635.

136. Denieul, M-. P.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 4901.

137. Storm, J. P.; Andersson, C-. M. *Org. Lett.* **1999**, *1*, 1451.

138. Denieul, M-. P.; Laursen, B.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 6052.

139. Storm, J. P.; Andersson, C-. M. *J. Org. Chem.* **2000**, *65*, 5264.

140. Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001.

141. Patil, M. L.; Deshpande, V. H.; Ramlingam, S.; Borate, H. B. *Tetrahedron* **2004**, *60*, 1869.

142. Laursen, B.; Denieul, M-. P.; Skrydstrup, T. *Tetrahedron* **2002**, *58*, 2231.

143. McGovern, P. E.; Glusker, D. L.; Exner, L. J.; Voight, M. M. *Nature* **1996**, *381*, 480.

144. Pasteur, L. *C. R. Acad. Sci.* **1857**, *45*, 913.

145. Brown, A. *J. Chem. Soc. Trans.* **1886**, *49*, 172.

146. Pasteur, L. *Annales de Chimie Ser.* **1858**, *52*, 404.

147. de Réaumer, R. A. F. *Histoire de l'academie royale des sciences* **1752**, *266*, 461.

148. Payen, A.; Persoz, J. F. *Annales de chimie et de physique* **1833**, 53, 73.

149. Kühne, W. *Untersuch.Physiol. Inst. Heidelberg* **1878**, *1* , 291.

150. Buchner, E. *Ber. Dt. Chem. Ges.* **1897**, 30, 117.

151. Somner, J. *J. Biol. Chem.* **1926**, *69*, 435.

152. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2611.

153. Koshland, D. E. *Proc. Natl. Acad. Sci.* **1958**, *44*, 98.

154. Pauling, L. *Chem. Eng. News.* **1946**, *24*, 1375.
155. Erying, H. *J. Chem. Phys.* **1935**, *3*, 107.
156. Bairoch, A. *Nucelic Acids. Res.* **2000**, *28*, 304.
157. Störmer, K. *Zentralbl. Bakteriol. Parisitenk. Infek.* **1908**, *20*, 282.
158. Wagner, R. *Z. Gärungsphysiol.* **1914**, *4*, 289.
159. Haccius, B.; Helfrich, O. *Arch. Mikrobiol.* **1957**, *28*, 394.
160. Marr, E. K.; Stone, R. W. *J. Bacteriol.* **1961**, *81*, 425.
161. Young, L. *Biochem. J.* **1947**, *41*, 417.
162. Gibson, D. T.; Koch, J. R.; Kalliol, R. E. *Biochemistry* **1968**, *7*, 2653.
163. Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kalliol, R. E. *Biochemistry* **1968**, *7*, 3795.
164. Gibson, D. T.; Cardini, G. E.; Maseles, F. C.; Kallio, R. E. *Biochemistry* **1970**, 9, 1631.
165. Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, 9, 1626.
166. Ziffer, H.; Jerina, D. M.; Gibson, D. T.; Kobal, V. M. *J. Am. Chem. Soc.* **1973**, *95*, 4048.
167. Wong, C. F.; Auee, E.; LaLonde, R. T. *J. Org. Chem.* **1970**, *35*, 517.
168. Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.
169. Kauppi, B.; Lee, K.; Carredano, E.; Parales, R. E.; Gibson, D. T.; Eklund, H.; Ramaswamy, S. *Structure* **1998**, *6*, 571.
170. Karlsson, A.; Parales, J. V.; Parales, R. E.; Gibson, D. T.; Eklund, H.; Ramaswamy, S. *Science* **2003**, *299*, 1039.
171. Carredano, E.; Karlsson, A.; Kauppi, B.; Choudhury, D.; Parales, R.; Parales, J. V.; Lee, K.; Gibson, D. T.; Eklund, H.; Ramaswamy, S. *J. Mol. Biol.* **2000**, *296*, 701.
172. Boyd, D. R.; Sharma, N. D.; Hand, M. V.; Groocock, M. R.; Kerley, N. A.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Comm.* **1993**, *11*, 974.
173. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35.

174. Johnson, R. A. *Organic Reactions*, Vol. 63, John Wiley and Sons Inc.: New York, **2004**, 117.
175. Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *J. Chem. Soc., Chem. Comm.* **1983**, *17*, 954.
176. Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225.
177. Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.
178. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655.
179. Hudlicky, T. *J. Heterocyclo. Chem.* **2000**, *37*, 535.
180. Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.
181. Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; Malone, J. F.; O'Dowd, C. R.; Allen, C. C. R. *Org. Biomol. Chem.* **2005**, *3*, 1953.
182. Omori, T. A.; Finn, K. J.; Leisch, H.; Carroll, R. J.; Hudlicky, T. *Synlett*, **2007**, 2859.
183. Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239.
184. Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077.
185. Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, *3*, 1081.
186. Brown, S. M.; Hudlicky, T. *Organic Synthesis: Theory and Applications*, Vol. 2, JAI Press: London, **1993**, 113.
187. Kelman, A.; Sequeira, L.; Nester, F. W. *Science* **2000**, *289*, 1689.
188. Barry, S.; Gualde, N. *L'Histoire* **2006**, *310*, 45.
189. Hooper, W. D. *Marcus Porcius Cato on Agriculture Marcus Terentius Varro on Agriculture*, Harvard University Press: Cambridge, **1960**, 792.
190. Dobell, C. *Anthony van Leeuwenhoek and His "Little Animals"* New York: Dover Publications, **1962**, 388.
191. Lecoq, H. *Comptes Rendus de L'Académie des Sciences – Series III – Sciences de la Vie* **2001**, *324*, 929.
192. Karp, G. *Cell and Molecular Biology*, 3rd Ed., John Wiley & Sons Inc, New York: **2002**.

193. Madigan, M. T.; Martinko, J. M.; Parker, J. *Brock Biology of Microorganisms*, 10th Ed., Prentice Hall: Upper Saddle River, NJ: **2003**.

194. Campbell, N.; Reece, J.; Taylor, M.; Simon, E.; Dickey, J. *Biology: Concepts and Connections*: International Edition. Pearson Educational: Toronto, **2008**.

195. Kuszewski, L.; Brydak, L. *Biomed. & Pharmacother.* **2000**, *54*, 188.

196. Bouvier, N. M.; Palese, P. *Vaccine* **2008**, *26*, Suppl 4:D49.

197. Nicholson, K. G.; Webster, R. G.; Hay, A. J. *Textbook of Influenza*. Blackwell Science: Oxford, **1998**.

198. Murphy, B.R.; Webster, R.G. *Orthomyxoviruses.* In: Fields Virology (Ed. Fields, B. N.), Lippincott-Raven: Philadelphia, **1996**, 1353-1445.

199. Oxford, J. S. *Rev. Med. Virol.* **2000**, *10*, 119.

200. Mackeller, L. *Population Development Rev.* **2007**, *33*, 429.

201. Smith, W.; Andrewes, C. H.; Laidlaw, P. P. *Lancet* **1933**, *2*, 66.

202. Bright, R. A.; Shay, D. K.; Shu, B.; Cox, N. J.; Klimov, A. I. *JAMA* **2006**, *295*, 891.

203. Potter, C. W. *J. Appl. Microbiol.* **2001**, *91*, 572.

204. Patrick, G. L. *An Introduction to Medicinal Chemistry*, 3rd Ed. Oxford University Press: Oxford, **2005**, 471.

205. Meltzer, M. I.; Cox, N. J.; Fukuda, K. *Emerg. Infect. Dis.* **1999**, *5*, 659.

206. Keyser, L. A.; Karl, M.; Nafziger, A. N.; Bertino, J. S. *Arch. Intern. Med.* **2000**, *160*, 1485.

207. Liu, C.; Eichelberger, M. C.; Compans, R. W.; Air, G. M. *J. Virol.* **1995**, *69*, 1099.

208. GlaxoSmithKline http://www.relenza.com/hcp/relenza-action-mechanism.html, **2009**, Aug 1st.

209. Edmond, J. D.; Johnston, R. G.; Kidd, D.; Rylance, H. J.; Sommerville, R. G. *Br. J. Pharmacol. Chemother.* **1966**, *2*, 415.

210. Meindl, P.; Tuppy, H. *Monatsh. Chem.* **1969**, *100*, 1295.

211. Meindl, P.; Bodo, G.; Palese, P.; Schulman, J.; Tuppy, H. *Virology* **1974**, *58*, 457.

212. Palese, P.; Compans, R. W. *J. Gen. Virol.* **1976**, *33*, 159.

213. Palese, P.; Schulman, J. L. *Inhibitors of viral neuraminidase as potential antiviral drugs.* In: Chemoprophylaxis and virus infections of the upper respiratory tract. Part I (Ed. Oxford, J. S.), CRC Press: Cleveland, **1977**, 189.

214. Chong, A. K. J.; Pegg, M. S.; Taylor, N. R.; von Itzstein, M. *Eur. J. Biochem.* **1992**, *207*, 335.

215. Flashner, M.; Kessler, J.; Tanenbaum, S. W. *Arch. Biochem. Biophys.* **1983**, *221*, 188.

216. Varghese, J. N.; Laver, W. G.; Colman, P. M. *Nature* **1983**, *303*, 35.

217. Colman, P. M.; Varghese, J. N.; Laver, W. G. *Nature* **1983**, *303*, 41.

218. Varghese, J. N.; McKimm-Breschkin, J. L.; Caldwell, J. B.; Kortt, A. A.; Colman, P. M. *Proteins Struct. Funct. Genet.* **1992**, *14*, 327.

219. von Itzstein, M. *Nature Rev.* **2007**, *6*, 967.

220. Taylor, N. R.; von Itzstein, M. *J. Med. Chem.* **1994**, *37*, 616.

221. Zechel, D. L.; Withers, S. G. *Curr. Opin. Chem. Biol.* **2001**, *5*, 643.

222. von Itzstein, M.; Wu, W-.Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Van Phan, T.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.

223. von Itzstein, M.; Dyason, J. C.; Oliver, S. W.; White, H. F.; Wu, W-.Y.; Kok, G. B.; Pegg, M. S. *J. Med. Chem.* **1996**, *39*, 388.

224. Goodford, P. J. *J. Med. Chem.* **1985**, *28*, 849.

225. Cass, L. M.; Efthymiopoulos, C.; Bye, A. *Clin. Pharmacokinet.* **1999**, *36 Suppl 1*, 1.

226. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

227. Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451.

228. Moscona, A. *Lancet* **2004**, *364*, 733.

229. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

230. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Lavern W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451.

231. McGowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381.

232. Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545.

233. Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.

234. Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044.

235. Harrington, P. J.; Brown, J. D.; Foderano, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.

236. Abrecht, S.; Karpf, M.; Trussardi, R.; Wirz, B. *Chem. Abstr.* **2001**, *135*, 195452.

237. Yeung, Y-. Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

238. Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

239. Fukuta, Y.; Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259.

240. Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403.

241. Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070.

242. Yamatsugu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2009**, *65*, 6017.

243. Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365.

244. Mckillop, A.; Taylor, R. J. K.; Waston, R. J.; Lewis, N. *Synthesis* **1994**, 31.

245. Cong, X.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2004**, *69*, 5314.

246. Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734.

247. Ahrendt, K. A.; Borths, C. J.; MacMillian, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

248. Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892.

249. Zhang, T.; Trost, B. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759.

250. Shie, J.-J.; Fang, J. -M.; Wong, C. -H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5788.

251. Matveenko, M.; Willis, A. C.; Banwell, M. G. *Tetrahedron* **2008**, *49*, 7018.

252. Bromfield, K. M.; Gradén, Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Comm.* **2007**, 3183.

253. Carr, R.; Ciccone, F.; Gabel, R.; Guinn, M.; Johnston, D.; Mastriona, J.; Vandermeer, T.; Groaning, M. *Green Chemistry* **2008**, *10*, 743.

254. Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815.

255. Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895.

256. Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239.

257. Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304.

258. Oshitari, T.; Mandai, T. *Synlett* **2009**, *5*, 787.

259. Nie, L. -D.; Shi, X. -X.; Ko, K. H.; Lu, W. -D. *J. Org. Chem.* **2009**, *74*, 3970.

260. Nie, L. -D.; Shi, X. -X. *Tetrahedron: Asymmetry* **2009**, *20*, 124.

261. a) Kanai, M.; Shibasaki, M. *Eur. J. Org. Chem.* **2008**, 1839; b) Magano, J. *Chem. Rev.* **2009**, *109*, 4398.

262. Andraos, J. *Org. Process. Res. Dev.* **2009**, *13*, 161.

263. Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

264. Leisch, H.; Saxon, R.; Sullivan, B.; Hudlicky, T. *Synlett* **2006**, *3*, 445.

265. Leisch, H.; Sullivan, B.; Fonovic, B.; Dudding, T.; Hudlicky, T. *Eur. J. Org. Chem.* **2009**, *17*, 2806.

266. a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

267. a) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654; b) Rassolov, V. A.; Pople, J. A.; Ratner, M. A.; Windus, T. L. *J. Chem. Phys.* **1998**, *109*, 1223.

268. Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem*. **2005**, *70*, 3490.

269. Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1995**, *117*, 5897.

270. Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber*. **1992**, *125*, 1169.

271. Placzek, A. T.; Donelson, J. L.; Trivedi, R.; Gibbs, R. A.; De, S. K. Tetrahedron Lett. **2005**, *46*, 9029.

272. Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 14818.

273. Metcalf, T.; Hudlicky, T. *Unpublished results*, **2009**.

274. Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525.

275. Painter, G. F.; Eldridge, P. J.; Falshaw, A. *Bioorg. Med. Chem.* **2004**, *12*, 225.

276. Gilmet, J. *BSc. Thesis*, Brock University, **2006**.

277. Sullivan, B.; Gilmet, J.; Leisch, H.; Hudlicky, T. *J. Nat. Prod.* **2008**, *71*, 346.

278. Gilmet, J.; Sullivan, B.; Hudlicky, T. *Tetrahedron* **2009**, *65*, 212.

279. Endoma, M. A.; Bui, V. P.; Hansen, J.; Hudlicky, T. *Org. Process Res. Dev.* **2002**, *6*, 525.

280. Sullivan, B.; Hudlicky, T. *Tetrahedron Lett.* **2008**, *49*, 5211.

281. Gilmet, J. *MSc. Thesis*, Brock University, **2009**.

282. Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

283. Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744.

284. Fabris, F.; Collins, J.; Sullivan, B.; Leisch, H and Hudlicky, T. *Org. Biomol. Chem.* **2009**, *21*, 2619.

285. Entwistle, D. A.; Hudlicky, T. *Tetrahedron Lett.* **1995**, *36*, 2591.

286. Hudlicky, T.; Abboud, K. A.; Entwistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synthesis* **1996**, 897.

287. Boyd, D. R.; Sharma, N. D.; Coen, G. P.; Gray, P. J.; Malone, J. F.; Gawronski, J. *Chem. Eur. J.* **2007**, *13*, 5804.

288. Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; Coen, G. P.; McGeehin, P. K. M.; Allen, C. C. R. *Org. Biomol. Chem.* **2007**, *5*, 514.

289. Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

290. For definitions and discussions on the concept of latent symmetry see: a) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Price, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 9439; b) Hudlicky, T. *Pure Appl. Chem.* **1992**, *64*, 1109; c) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3; d) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley–VCH: Weinheim, 2007, 146-154.

291. Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem Int. Ed.*, **2009**, *48*, 4229.

8. Vita

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