Epimeric L-Proline Derived Imidazolone Chiral Auxiliaries for the Stereoselective Alkylative Birch Reduction of Aromatic Esters and Benzonitriles

By

Dusty Cadwallader, B. Sc.

A thesis submitted in partial fulfilment of the requirements for the degree of
Master of Science in Chemistry
Faculty of Mathematics and Science, Brock University
St. Catharines, Ontario

© 2020

Abstract

Described in this thesis are several advancements of imidazolidinone chiral auxiliaries. Initially, attempts were made to develop a *N*-heterocyclic carbene ligand derived from the *N*-benzyl analog of the auxiliary. Attempts to design a monodentate ligand as well as a bidentate ligand bearing an alcohol side chain were both shown to be unsuccessful. Work on the *N*-phenyl variant of the auxiliary included expanding upon our recently discovered methodology; a Birch reduction alkylation sequence of an aromatic ester yielding chiral quaternary carbon centres in a stereoselective matter. In substrates that demonstrate poor stereoselectivity, modification of the auxiliary to include a larger neopentoxy directing group gives way to increased selectivity. This work also includes the same Birch reduction alkylation sequence on a series of benzonitrile substrates with up to 64:36 diastereomeric ratio from either epimer of the auxiliary. The low selectivity of the benzonitrile substrates is offset by the resulting diastereomers of the dihydrobenzonitrile products being chromatographically separable. This results in the first preparation of optically pure quaternary carbons alpha to nitrile by Birch-type reductive alkylation. Progress was also made in the manipulation of chiral auxiliaries bearing the chiral alkoxy moiety. These functional groups were transformed into hemiaminals by citric acid hydrolysis in a 3:2 ratio with imidazolone by-products formed by acid mediated elimination of alcohol.

Acknowledgements

First, I would like to thank my supervisor, Dr. Costa Metallinos, for providing me the opportunity of working in his group. The constant excitement and passion for chemistry that you demonstrate daily always puts a smile on my face. Your knowledge of synthetic chemistry and intense attention to detail have given me a perspective of science and literature I truly do not believe I would have developed anywhere else. I would also like to thank my committee members, Dr. Travis Dudding and Dr. Heather Gordon for providing guidance and support during my time at Brock.

Ngan Tran and Maria Laura Sechi, thank you for your friendship. Thank you for your advice, companionship, daily coffee runs to keep us fueled and simply for taking this journey with me. Its hard to imagine three people from places farther apart in the world than we are and I’m grateful everyday that we all ended up here together. Thank you as well to Rachel Bartkiewicz, Claire Snelgrove, Maneesha Wijesundara, and Lyzcel Talisic for being such enthusiastic undergraduate researchers and fast learners. I am also grateful to all past members of the Metallinos group for the valuable knowledge that has been passed down.

For their support and companionship, whether it was in the lab, on a weekend out or anywhere between I am thankful for the wonderful members of the Hudlicky, Yan, Atkinson, Lemaire, Dudding, Pilkington, Li, Zelisko and Nikonov groups. The incredible support staff here at Brock University deserves my gratitude as well; thank you to Razvan Simionescu and Liqun Qiu for assistance with nuclear magnetic resonance spectroscopy and mass spectrometry respectively, Irene Palumbo and Alison Moffat at science stores and all the other people who make research at Brock possible (and enjoyable).

Thank you Professor Tomáš Hudlický. Over two semesters of organic chemistry and our weekly group meetings you have taught me more about synthesis than I ever could have imagined learning. As well as Professor Georgii Nikonov for truly showing me the world of transition metal and main group chemistry and helping expand my horizon on chemistry. I owe you both my gratitude for your patients and expertise.

Table of Contents

List of Figures v

List of Schemes v

Abbreviations vii

1. Introduction 1

  1.1 Stereoselective Synthesis 2

    1.1.1 Chiral Auxiliaries 2

  1.2 Birch Reduction 20

    1.2.1 Reductive Alkylation 23

2. Objectives 33

3. Results and Discussion 36

  3.1 Towards Novel Chiral NHC Ligands Derived from *N*-benzyl Hydantoin 36

  3.2 Attempts towards controlling stereoisomerism of alkyl protected phenyl L-proline hydantoins and other improvements 37

  3.3 Effect of alkoxy protecting group on stereoselectivity of enolate alkylation 40

  3.4 Stereoselective reductive alkylation of a benzonitrile 42

  3.5 Manipulation of chiral auxiliary 47

4. Conclusion and Future Work 49

5. Experimental 51

6. References 66

7. Appendix 70

List of Figures

Figure 1 - Mechanism of the Birch reduction on benzene 20
Figure 2 - ORTEP plot of **162**. Most hydrogen atoms omitted for clarity[9] 33

List of Schemes

Scheme 1 - Chiral auxiliary utilization and removal in formal synthesis of prostaglandin 2
Scheme 2 - Alkylation of a dialkyl hydrazone with iodomethane........ 3
Scheme 3 - Synthesis of SAMP/RAMP hydrazines **13** and ent-**13**........ 3
Scheme 4 - Synthesis, alkylation and removal of SAMP coupled diethylketone 4
Scheme 5 - Synthesis of C4 acyl sidechain **24** of Zaargoic Acid A (**25**)........ 5
Scheme 6 - SAMP alkylation towards derivatives of **31**........ 6
Scheme 7 - SAMP alkylations used in the syntheses of Epithilones A (**35**) and B (**39**) 7
Scheme 8 - Aldol product from a (S)-valinol derived imide 8
Scheme 9 - Aldol product from a norephedrine derived imide 9
Scheme 10 - Alkylation of chiral oxazolidinone imides........ 9
Scheme 11 - Manipulation of oxazolidinone auxiliary 10
Scheme 12 - Stereoselective introduction of hetereoatoms directed by chiral oxazolidinones 11
Scheme 13 - Synthesis of PNO405 (**64**)........ 12
Scheme 14 - Synthesis of planar chiral amino ferrocenes 13
Scheme 15 - Synthesis of disubstituted ferrocenes and elimination products 14
Scheme 16 - Synthesis of epimeric η6-arene chromium tricarbonyl complexes 15
Scheme 17 - Lithiation of chromium carbonyl complexes and planar chiral imidazolones 16
Scheme 18: Synthesis of cyclic ferrocenyl urea **82** 17
Scheme 19 - Synthesis of chiral iridium complexes derived from ferrocenyl and phenyl auxiliaries, respectively 18
Scheme 20 - Synthesis of N-benzyl substrates and their stereoselective lithiation 19
Scheme 21 - Transmetallation studies of stananes 19
Scheme 22 - Cyclization and reductive ring opening of N-benzyl derived substrate 20
Scheme 23 - General outcome of the Birch reduction of various heterocycles 21
Scheme 24 - Birch reduction steps in the syntheses of reserpine and aphidicolin 22
Scheme 25 - Birch reduction steps from total syntheses of Herquline C (**110**)........ 23
Scheme 26 - Racemic preparation of alkylated cyclohexadienes for synthetic intermediates and expansion of methodology 24
Scheme 27 - Synthesis of tricyclic substrate for asymmetric Birch reduction........ 25
Scheme 28 - Synthesis of known compound **131** for stereoselectivity determination........ 25
Scheme 29 - Reductive alkylation of ortho-alkoxy and ortho-alkyl benzamides yielding opposite stereoselectivity........ 26
Scheme 30 - Synthesis of ortho-modified chiral benzamides for reductive alkylation 27
Scheme 31 - Reductive alkylation en route to (-)-longifolene (**139**)........ 27
Scheme 32 - Reductive alkylation in the synthesis of (+)-deoxylycorine (**63**) and (+)-lycorine (**64**)........ 28
Scheme 33 - Reductive alkylation and desilylation on route to (-)-aspidospermidine (**149**) and (-)-eburnamonine (**152**) 29
Scheme 34 - Reductive alkylation towards (+)-cepharamine (**156**)........ 30
Scheme 35 - Synthesis of cyclohexadienes from syn and anti-**77** 30

Scheme 36 - Alkylation of cyclohexadiene syn-**159** 31
Scheme 37 - Alkylation of cyclohexadiene anti-**158** 32
Scheme 38 - Experiments to determine stereochemistry of substituted dienes 32
Scheme 39 - Proposed synthesis of chiral NHC ligand precusors 34
Scheme 40 - Synthesis and Stereoselective Reductive Alkylation of Benzonitriles 35
Scheme 41 - General route to auxilliary removal 35
Scheme 42 - Attempted electrophile quench of **91** to obtain a homologated (masked) alcohol 36
Scheme 43 - Attempted oxidation of **95** 37
Scheme 44 - One-pot synthesis of syn and anti-**77** 38
Scheme 45 - Attempts towards syn hemiaminal ether derivatives like **170** 39
Scheme 46 - Proposed alternative synthesis of syn-**77** 39
Scheme 47 - Synthesis of neopentyl hemiaminal ethers as Birch reduction substrates 41
Scheme 48 - One pot reductive alkylation of anti-**172** 42
Scheme 49 - Synthesis of chiral auxiliary bound benzonitriles 42
Scheme 50 - Synthesis of achiral and novel chiral cyclohexadienes 43
Scheme 51 - Reductive alkylation of anti-**166** 44
Scheme 52 - Reductive alkylation of anti-**168** 45
Scheme 53 - Synthesis of syn-**168** 45
Scheme 54 - Reductive alkylation of syn-**168** 46
Scheme 55 - Attempts to reduce the nitrile functionality of **167a** 47
Scheme 56 - Hudlicky's acid catalyzed deprotection and adaptation to our system 48
Scheme 57 - Deprotection of reductive alkylation products 48
Scheme 58 - Planned removal of the chiral auxilliary 49
Scheme 59 - Potential cycloadditions of diene **179** 50

Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
Cp	cyclopentadienyl
DBMN	dibenzyl malononitrile
DBDMH	dibromo dimethyl hydantoin
DEAD	diethyl azodicarboxylate
D*o*M	directed *ortho* metalation
dr	diastereomeric ratio
DIBAL-H	diisobutyl aluminum hydride
E^+	electrophile
Et	ethyl
er	enantiomeric ratio
h	hours
HMDS	hexamethyldisilylazane
i-	iso
IR	infrared
LDA	lithium diisopropyl amine
Me	methyl
Min	minutes
n-	normal
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
o	ortho
p	para

PDC	pyridinium dichromate
Ph	phenyl
Pr	propyl
rt	room temperature
Sia	siamyl: 1,2-dimethylpropyl
t	tertiary
TBAF	tetrabutyl ammonium fluoride
TES	triethyl silane
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silane
TMEDA	*N*, *N*, *N*, *N*-tetramethyl ethylene diamine
Trisyl	2,4,6-triisopropylbenzenesulfonyl

1. Introduction

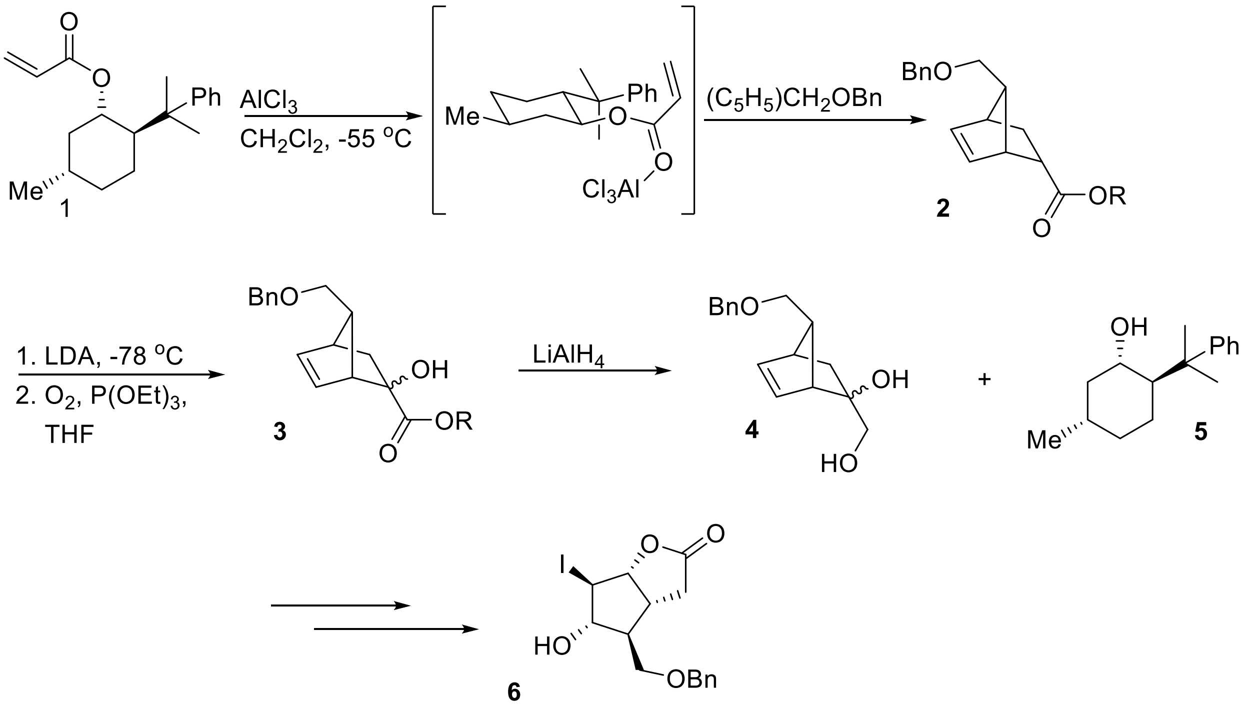
Molecules used for pharmaceutical applications often contain at least one element of chirality,[1] requiring high levels of stereochemical purity. This is achieved in nature by biosynthesis of single enantiomers by enzymes.[2] However, stereoselective synthesis has proven to be a much greater challenge to chemists seeking to design methods for obtaining molecules of interest. While many stereoselective synthetic methods exist, the topic is still a massive research area in the chemistry community.[3] Our research consists of the development of novel methods for directing a variety of chemical transformations with control of relative and absolute stereochemistry. A *N*-substituted chiral auxiliary derived from L-proline was synthesised by the Metallinos group for the preparation of planar chiral 1, 2-disubstituted amino ferrocenes after rapid deconstruction of the auxiliary.[4,5] This methodology has been expanded to develop unusual *N*-heterocyclic carbene (NHC) ligands,[6] selective substitution reactions of chromium arene complexes,[7] axially chiral allenes, as well as sp^3 benzyl and propargyl centres.[8] The most recent application will report the Birch reduction of an *ortho*-ester *N*-phenyl variant of the auxiliary, with sequential diastereoselective alkylation of the sodium or lithium enolate, yielding cyclohexadienes bearing a quaternary centre.[9]

This thesis will discuss attempts to optimize the synthesis of the lower yielding *syn* epimer of the auxiliary from the stereodivergent step to have convenient access to either stereoisomer of alkylated cyclohexadiene, as well as chiral directing group variation in hopes of improving the lower stereoselectivity of the *anti* epimer. Due to replacement of the original silyl ether moiety with an alkyl ether in some systems, a new approach to deconstruction of the auxiliary by alternate deprotection strategies will be explored.

1.1 Stereoselective Synthesis

1.1.1 Chiral Auxiliaries

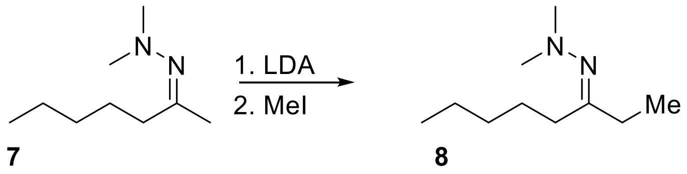
One of the earliest uses of a chiral auxiliary was in Corey's formal synthesis of prostaglandin.[10] The synthesis utilized 8-phenyl menthol acrylate **1** to direct a Diels-Alder cycloaddition of a cyclopentadiene derivative to obtain bicycle **2** as a single diastereomer, as shown in Scheme 1.


O
O
Ph
Me
1
AlCl3
CH2Cl2, -55 °C
Me
Ph
O
O
Cl3Al
(C5H5)CH2OBn
BnO
OR
O
2
1. LDA, -78 °C
2. O2, P(OEt)3,
THF
BnO
OH
OR
O
3
LiAlH4
BnO
OH
HO
4
+
OH
Ph
Me
5
I
O
O
HO
OBn
6

Scheme 1 - Chiral auxiliary utilization and removal in formal synthesis of prostaglandin

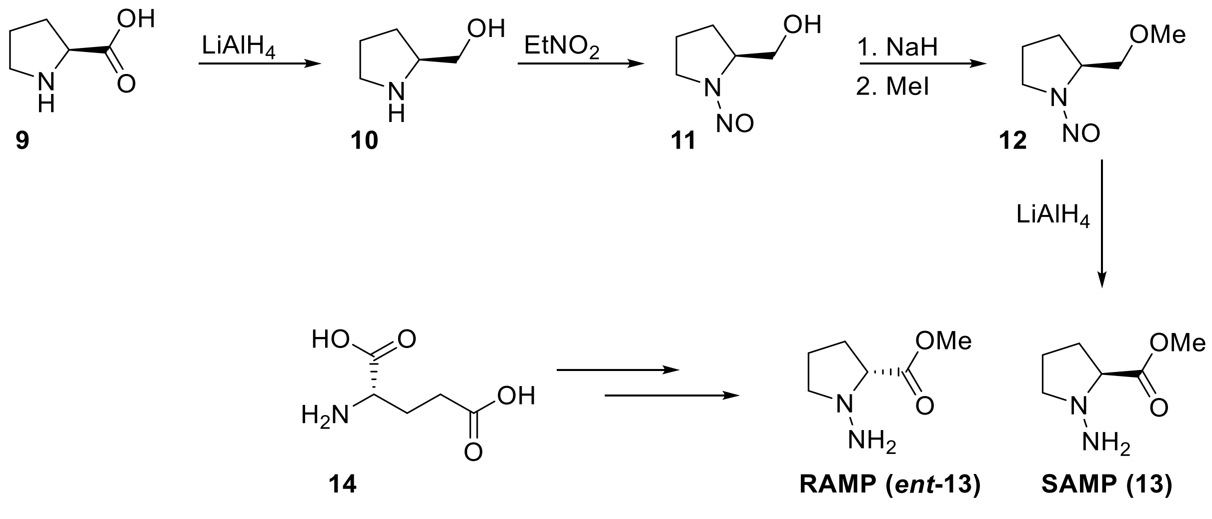
Visualizing the Lewis acid bound intermediate in the chair configuration, the stereoselectivity of the reaction can be rationalized as the diene adding to the unsaturated ester from the least hindered face. Hydroxy ester **3** was obtained by trapping the lithium enolate of **2** with oxygen and followed by reduction to diol **4** with excess $LiAlH_4$. Reduction biproduct (-)-8-phenyl menthol **5** can be isolated from the reaction in good purity, effectively making it recyclable.

Corey initially demonstrated that hydrazone compounds like **7** undergo enolate formation and possess reactivity analogous to carbonyls to yield alkylated products **8**, as shown in Scheme 2, albeit yielding achiral or racemic molecules.[11]


N
N
1. LDA
2. MeI
N
N
Me
7
8

Scheme 2 - Alkylation of a dialkyl hydrazone with iodomethane

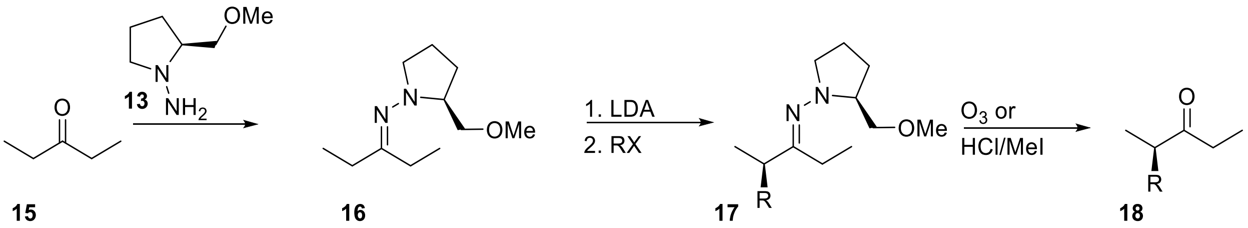
This method evolved into the use of chiral hydrazines derived from (*S*)-proline (**9**) by reduction to prolinol **10**, transformation to *N*-oxide **11,** protection as the methyl ether **12**, and finally reduction to SAMP **13** (Scheme 3). An enantiomeric series can be derived from (*R*)-glutamate (**14**) giving RAMP (***ent***-**13**) and both enantiomers have found widespread use in organic synthesis.[12]


OH
N
H
O
9
LiAlH4
OH
N
H
10
EtNO2
OH
N
NO
11
1. NaH
2. MeI
OMe
N
NO
12
LiAlH4
HO
O
H2N
OH
O
14
OMe
N
O
NH2
RAMP (ent-13)
OMe
N
O
NH2
SAMP (13)

*Scheme 3 - Synthesis of SAMP/RAMP hydrazines **13** and ent-**13***

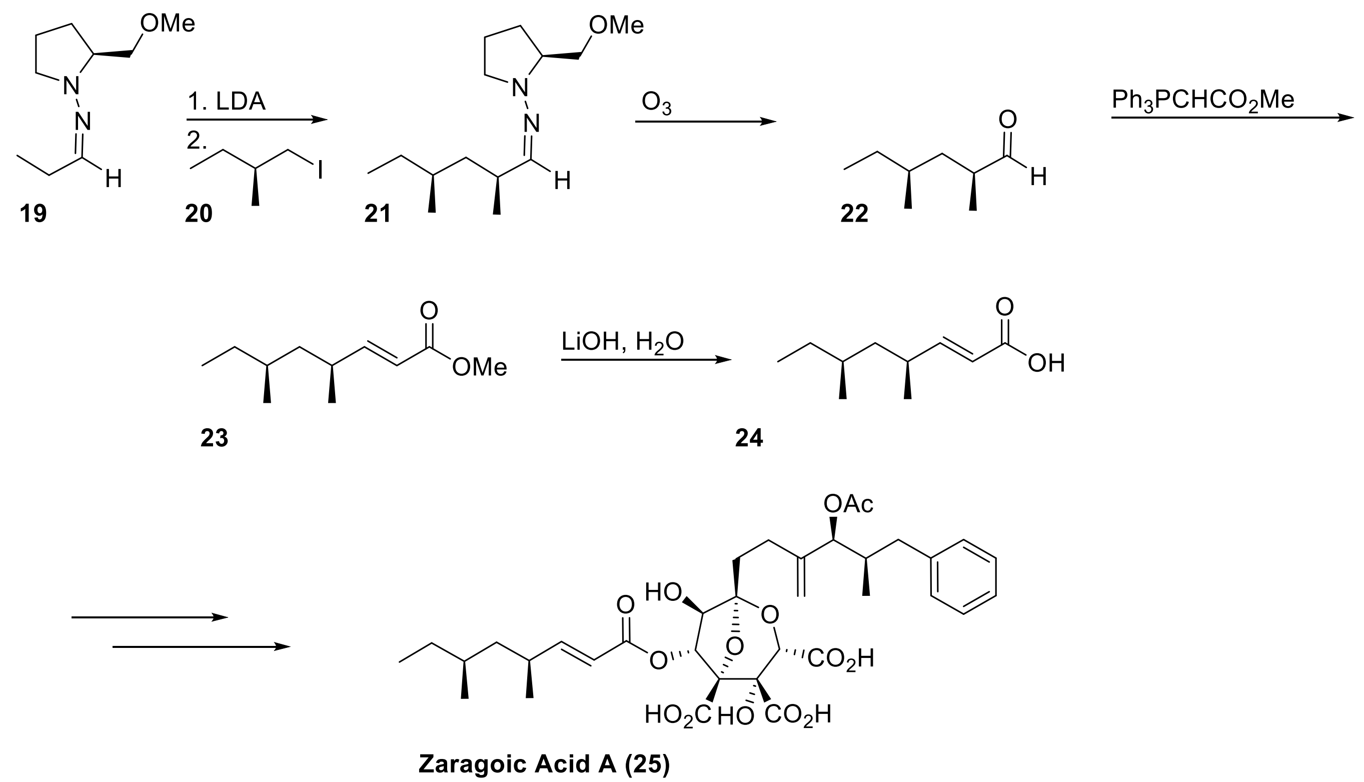
SAMP/RAMP can be incorporated into carbonyl compounds by a facile condensation in water trapping conditions and have shown good hydrazone yields in both ketones[13] and aldehydes.[14]

The subsequent alkylation of the hydrazone enolates provided moderate to good stereoselectivity and could be deprotected back to carbonyl compounds via ozonolysis or acid hydrolysis of the methyl iodide salt (Scheme 4).



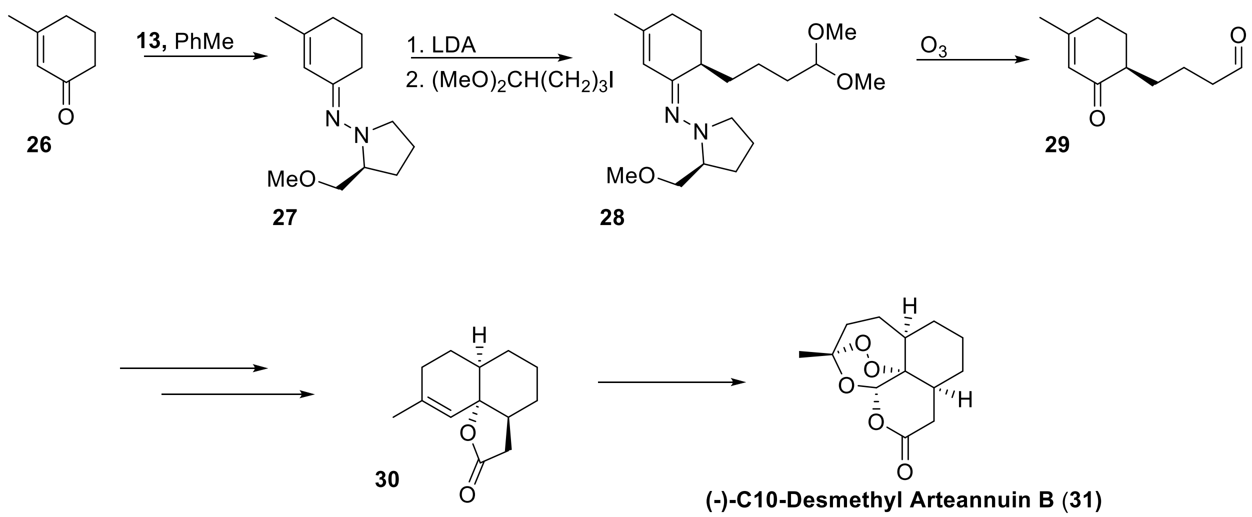
Scheme 4 - Synthesis, alkylation and removal of SAMP coupled diethylketone

As stated, RAMP/SAMP methods have found use in asymmetric synthesis, primarily in the field of total synthesis. One such example (Scheme 5) was the synthesis of a side chain of zaragoic acid A **25**,[15] in which the azaenolate of **19** was alkylated with **20**. This was found to be superior to the use of oxazolidinone, which gave a mixture of diastereomers. The diastereomerically pure (92% de) **21** was then converted to aldehyde **22** by ozonolysis, extended by Wittig olefination and finally hydrolyzed to carboxylic acid **24**. This was found to be physically and spectroscopically identical to **24** obtained from degradation of **25**.


OMe
N
N
H
1. LDA
2.
I
19
20
OMe
N
N
H
21
O3
O
H
22
Ph3PCHCO2Me
O
OMe
23
LiOH, H2O
O
OH
24
OAc
HO
O
O
O
O
CO2H
HO2C
HO
CO2H
Zaragoic Acid A (25)

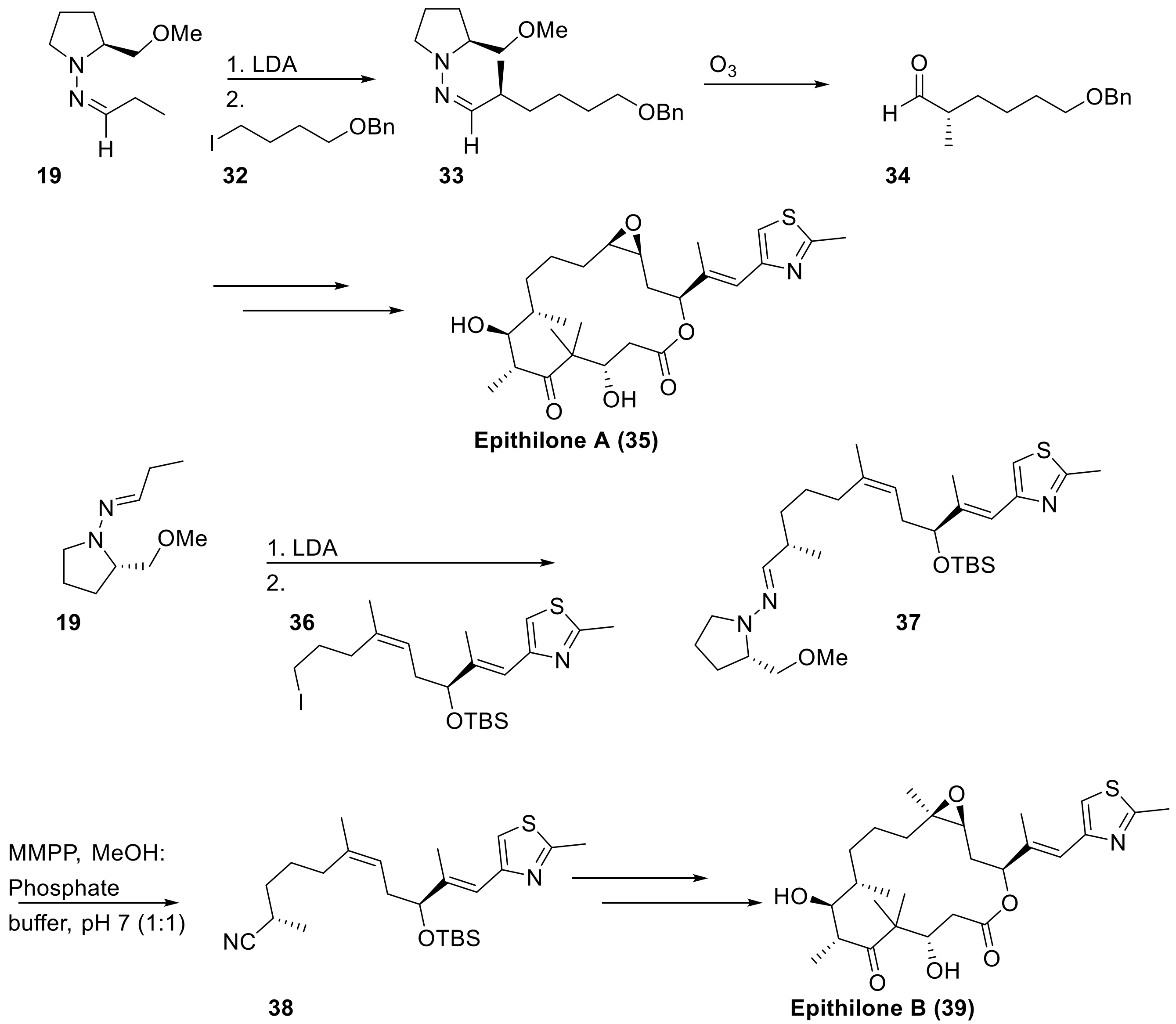
*Scheme 5 - Synthesis of C4 acyl sidechain **24** of Zaargoic Acid A (**25**)*

The formal synthesis of anti-malarial drug (-)-C10-Desmethyl Arteannuin B (**31**)[16] (Scheme 6) utilizes SAMP alkylation almost immediately from cyclohexenone **26**, to obtain dimethyl acetal **28** in 95% ee. This was then hydrolized to aldehyde **29**, which was carried forward to lactone **30**, a presumed precursor to arteannuin type molecules.


13, PhMe
1. LDA
2. (MeO)2CH(CH2)3I
O3
OMe
OMe
O
N
N
MeO
26
27
28
29
H
H
O
30
(-)-C10-Desmethyl Arteannuin B (31)

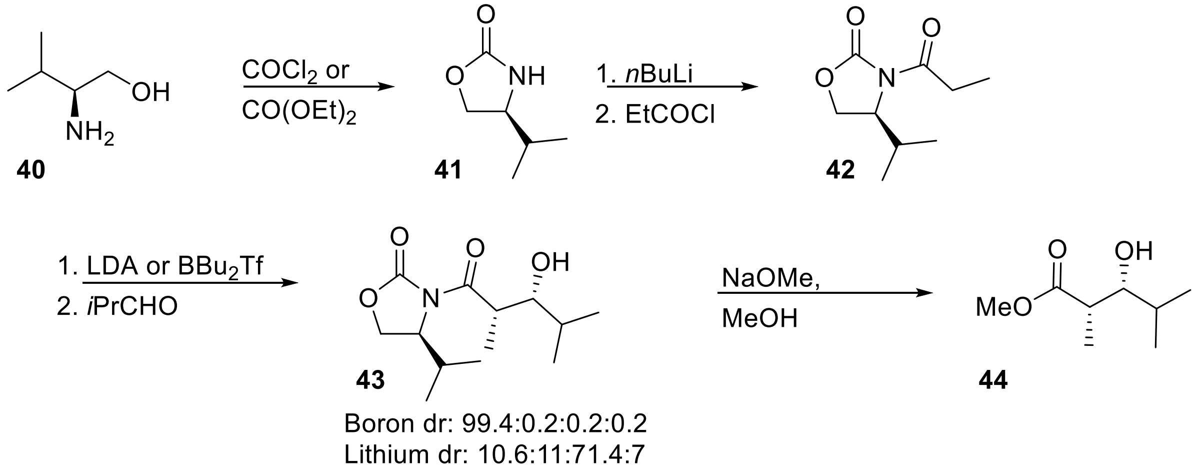
Scheme 6 - SAMP alkylation towards derivatives of ***31***

Nicolaou completed the syntheses of the macrocycles epithilones A (**35**) and B (**39**),[17] both involving early SAMP alkylations (Scheme 7). The synthesis of **35** involves the immediate alkylation of **19** with a protected butanol **32** to yield a chiral aldehyde **34** after ozonolysis of **33**. This compound is taken forward to **35**. The propanal derived hyrdrazone **19** is again alkylated in the synthesis of **39**, however with a more complex electrophile **36**. SAMP removal from thiazole **37** was achieved by conversion to nitrile **38** due to the acid sensitivity of the silyl protecting group and ozone reactive olefin moieties of the molecule. The single diastereomer of **38** was taken forward to **39**.


OMe
1. LDA
2.
OBn
19
32
33
O₃
34
Epithilone A (35)
19
1. LDA
2.
36
37
OTBS
MMPP, MeOH: Phosphate buffer, pH 7 (1:1)
38
Epithilone B (39)

*Scheme 7 - SAMP alkylations used in the syntheses of Epithilones A (**35**) and B (**39**)*

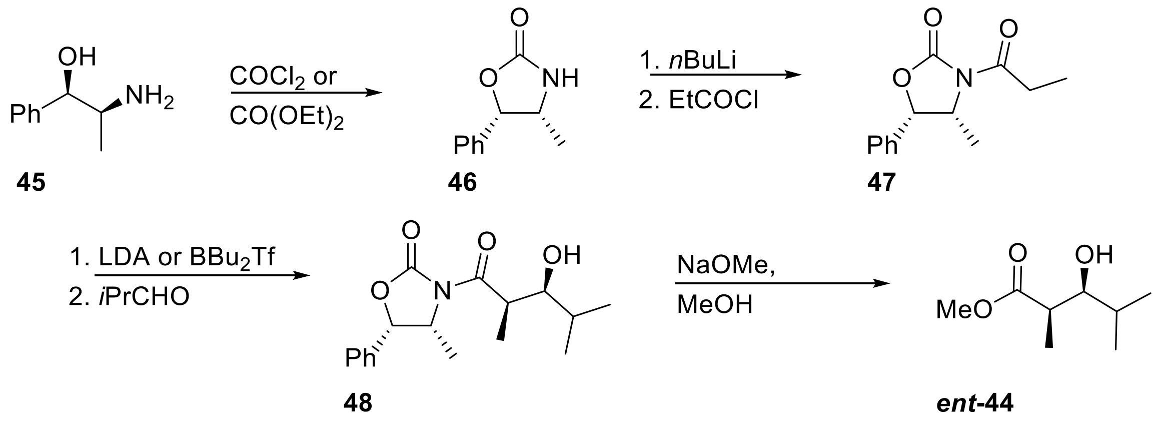
One of the most frequently used chiral auxiliaries in organic synthesis are the chiral oxazolidinones developed by Evans. The initial use of this method was in the attempt to develop a diastereoselective aldol reaction.[18] In this study, an optically pure oxazolidinone was synthesised by treatment of (*S*)-valinol (**40**) with phosgene or diethyl carbonate (Scheme 8). Lithiation of **41** and quenching of the nitrogen anion with propionyl chloride gives imide **42**. The imide enolate can be obtained by treatment with LDA or di-*n*-butylboryl trifluoromethanesulfonate and subjected to isobutyraldehyde to yield aldol product **43**. The product derived from the boron enolate was found to be almost exclusively a single diastereomer (>99%, as **43** is drawn) while the product of a lithium enolate was a various mixture of four possible diastereomers (10.6:11:71.4:7). Removal of the auxiliary, and recycling of **41**, was done by hydrolysis of the carbon substituted carbonyl of the imide to obtain hydroxy methyl ester **44**.



Boron dr: 99.4:0.2:0.2:0.2
Lithium dr: 10.6:11:71.4:7

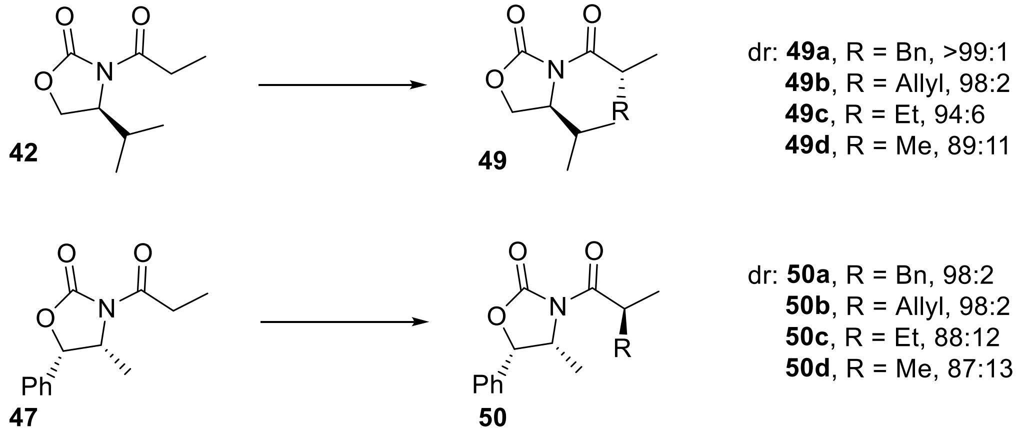
Scheme 8 - Aldol product from a (S)-valinol derived imide

A similar auxiliary was also synthesised as an enantiomeric alternative to **41**, starting from (1*S*-2*R*)-norephedrine (**45**), using an identical reaction sequence to obtain **47** (Scheme 9).[18] Results of aldol reactions of **47** again only demonstrates good selectivity from the boron enolate, with less than 1% of *threo* (new chiral substituents *anti* to each other) isomers of **48** being observed. For practicality, the selectivity of products all further products in the article were only reported as diastereomeric ratios of the two possible *erythro* (new chiral substituents *syn* to each other). Quenching boron enolate of **47** yielded **48** in a >500:1 dr. In all cases, the auxiliary could be cleaved by treatment with sodium methoxide in methanol, yielding the methyl ester of the aldol products. Carboxylic acids could also be obtained by KOH hydrolysis with no observable racemization.


45
COCl2 or
CO(OEt)2
46
1. nBuLi
2. EtCOCl
47
1. LDA or BBu2Tf
2. iPrCHO
48
NaOMe,
MeOH
ent-44

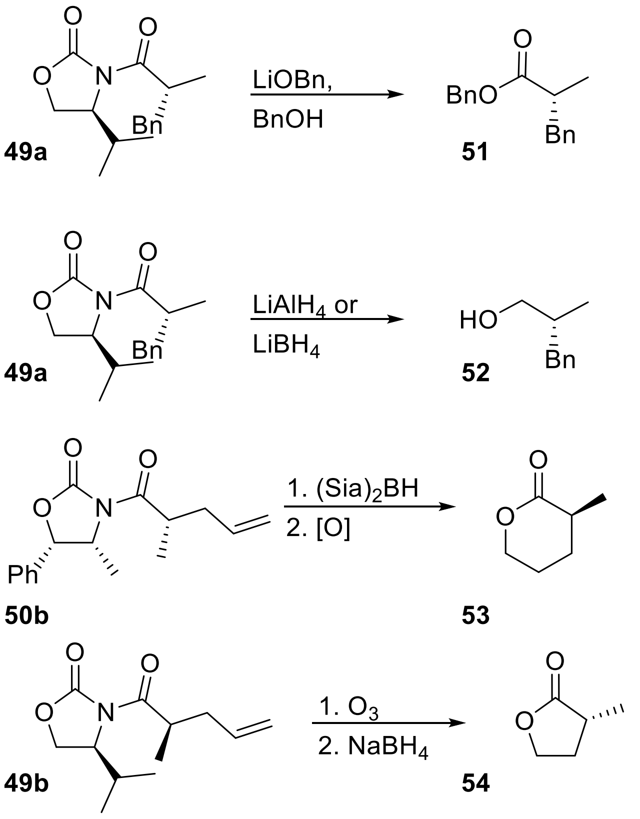
Scheme 9 - Aldol product from a norephedrine derived imide

The Evans group further developed the oxazolidinone methodology by expanding to simple alkylation of the imide enolates.[19] Reactions of the lithium (or sodium) enolates of **42** and **47** with alkyl halides demonstrate much greater stereoselectivity than their analogous aldol reactions (Scheme 10). The stereoselectivity of the reactions appear to be dependant on the size of the alkyl halide electrophile, evident by the lower selectivity observed with methylation (89:11 and 87:13 dr for **49d** and **50d** respectively) and ethylation (88:12 dr for **50c**) of the enolate as compared to alkylation with other electrophiles.


42
49
dr: 49a, R = Bn, >99:1
49b, R = Allyl, 98:2
49c, R = Et, 94:6
49d, R = Me, 89:11
47
50
dr: 50a, R = Bn, 98:2
50b, R = Allyl, 98:2
50c, R = Et, 88:12
50d, R = Me, 87:13

Scheme 10 - Alkylation of chiral oxazolidinone imides

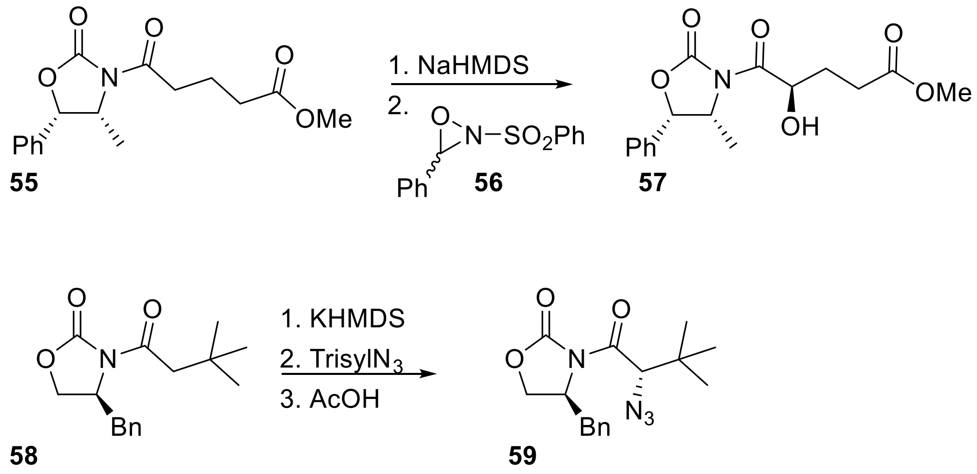
In developing these alkylation reactions several non-destructive methods for auxiliary removal were also explored and are depicted in Scheme 11.[19] Treatment of alkylated imide **49a** with lithium benzoate leads to auxiliary recovery and the benzyl ester of the alkylated product **51**. Treatment of imide **49a** with a strong reducing agents, such as lithium aluminum hydride or lithium borohydride, results in reduction to chiral primary alcohol **52**. Hydroboration and oxidation of allyl substituted substrates provide a primary alcohol that readily cleaves the auxiliary by formation of δ-lactone **53**, while ozonolysis of an allyl substrate followed by reduction of the resulting aldehyde analogously yields γ-lactone **54**.



Scheme 11 - Manipulation of oxazolidinone auxiliary

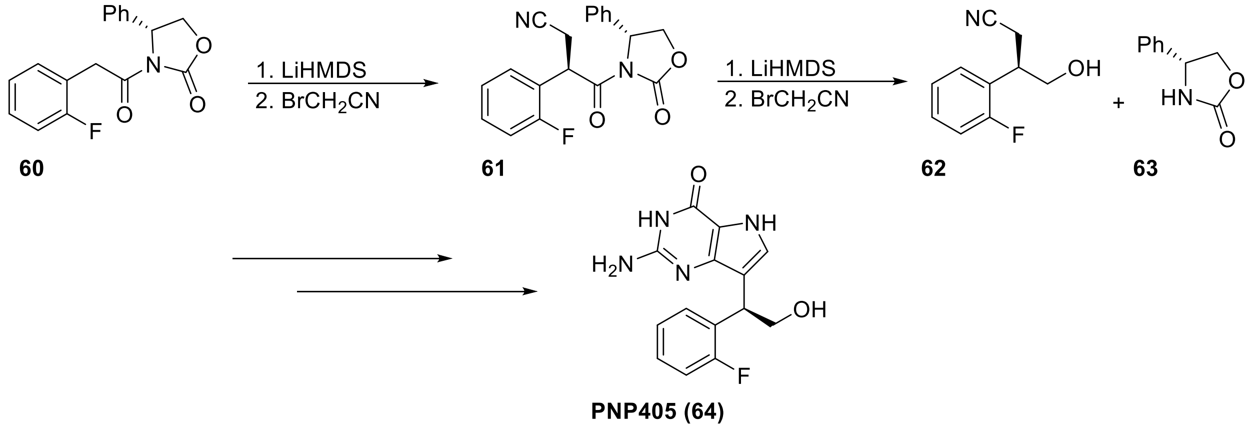
Evans' chiral oxazolidinones have also been shown to stereoselectively substitute imide enolates with a variety of heteroatom electrophiles to further demonstrate its versatility.[20] The selective hydroxylation[21] of an enolate was observed to provide **57**, however only via sodium enolate, by quenching with a sulphonyl oxiaziridine **56** (Scheme 12). Quenching of the potassium enolate of

58 with trisylazide provides a sulphonyl triazene that is degraded to azide **59** in-situ by acetic acid.[22]



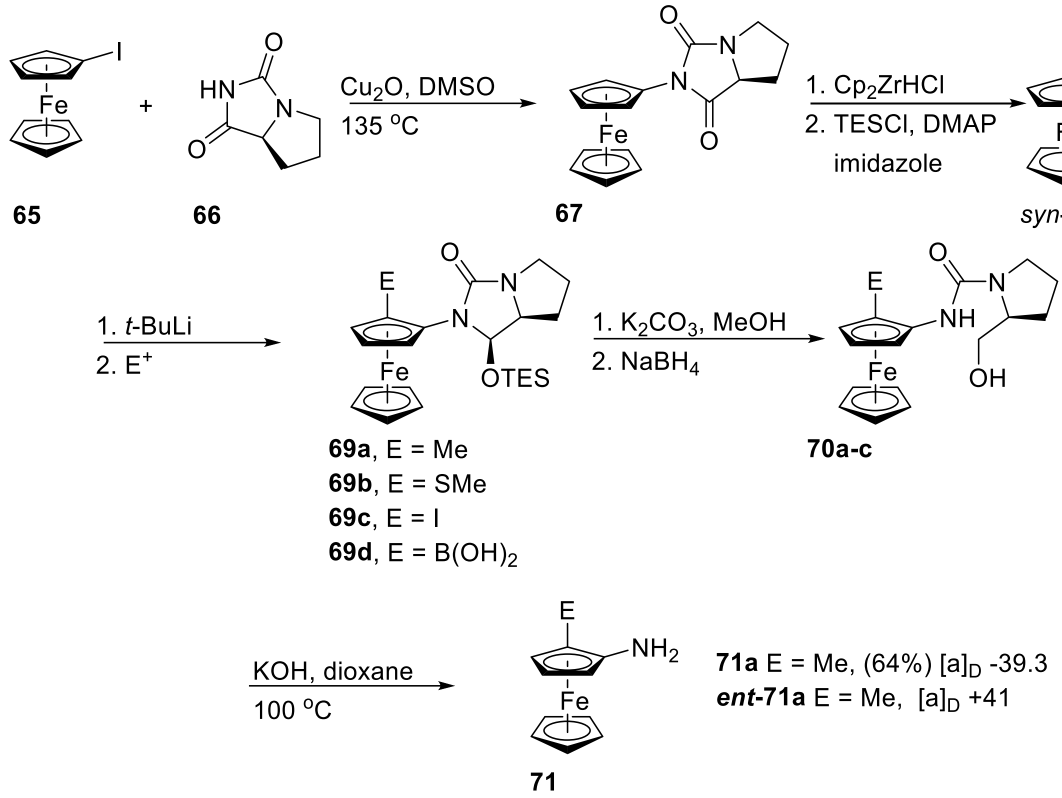
Scheme 12 - Stereoselective introduction of hetereoatoms directed by chiral oxazolidinones

Chiral oxazolidinones have also found extensive use in total synthesis since their discovery.[23] One unique application of this methodology was the synthesis of fluorinated drug PNP405 (**64**), a purine nucleoside phosphorylase inhibitor, in which the first step involved a preparation of chiral imide **60** on nearly a two mole scale.[24] This is followed by enolate formation on a similar scale which was quenched with bromoacetonitrile to give nitrile **61** followed by reductive cleavage of the oxazolidinone to yield primary alcohol **62** and oxazolidinone **63** (Scheme 13).



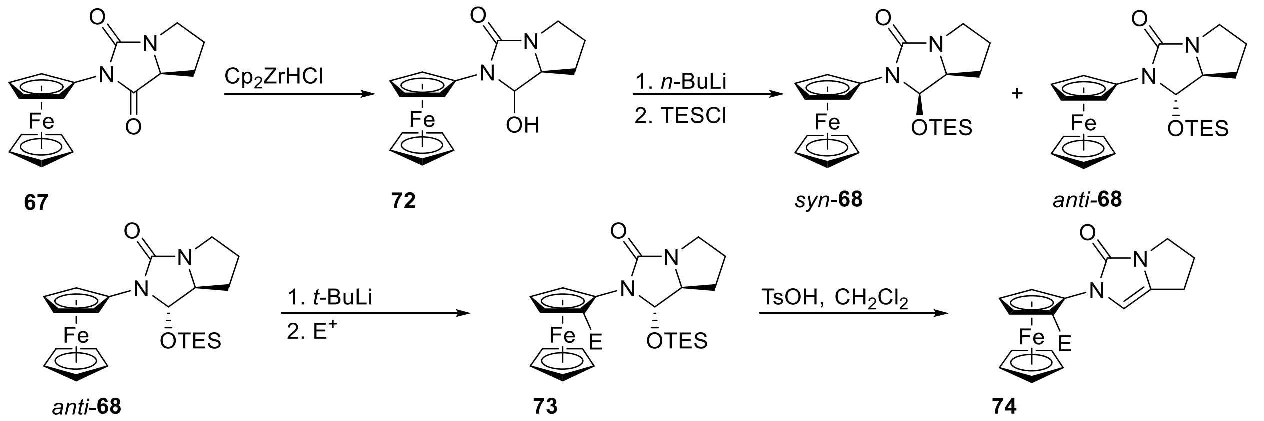
*Scheme 13 - Synthesis of PNO405 (**64**)*

Advances in the Metallinos group have lead to the discovery of a chiral auxiliary derived from L-proline, initially used for diastereoselective lithiation of planar-chiral ferrocenes.[4,5] Disubstituted ferrocenes can demonstrate planar chirality: asymmetry through a two dimensional plane. Like central chirality, two planar chiral enantiomers are non-superimposable mirror images of each other but do not require a chiral sp^3 carbon.[25] The substrate was prepared with absolute and relative stereocontrol by Ullman type coupling of iodoferrocene (**65**) and proline hydantoin **66** to give **67** (Scheme 14). After sequential hydrozirconation with Schwartz's reagent and silylation of the zirconium alkoxide, *syn*-**68** was obtained as the major isomer. Treating *syn*-**68** with *t*-BuLi followed by electrophile quench yielded a series of 1,2-disubstituted ferrocenes with >95:5 dr.[4] The versatility of the new *N* based auxiliaries was demonstrated by K_2CO_3 mediated desilyation in refluxing methanol, and reductive ring opening by $NaBH_4$ treatment gave secondary ureas **70**. Hydrolysis of **70** with aqueous base leads to the isolation of exclusively planar chiral amino ferrocenes **71**. Stereoselectivity of the lithiation was confirmed by single crystal x-ray analysis of boronic acid **68d**, as well as by comparison of the optical rotation of **71a** to its known enantiomer (*ent*-**71a**).[26]


Fe
I
HN
O
N
65
66
Cu2O, DMSO
135 °C
67
1. Cp2ZrHCl
2. TESCl, DMAP
imidazole
OTES
syn-68
1. t-BuLi
2. E+
E
69a, E = Me
69b, E = SMe
69c, E = I
69d, E = B(OH)2
1. K2CO3, MeOH
2. NaBH4
NH
OH
70a-c
KOH, dioxane
100 °C
NH2
71
71a E = Me, (64%) [a]D -39.3
ent-71a E = Me, [a]D +41

Scheme 14 - Synthesis of planar chiral amino ferrocenes

To demonstrate the opposite selectivity, configurationally unstable hemiaminal **72** was isolated after hydrozirconation of **67**, then deprotonated with *n*-BuLi and chlorotriethylsilane to give a 1:1 mixture of *syn* and *anti*-**68** that could be separated by column chromatography (Scheme 15).[5] Treatment of *anti*-**68** with *t*-BuLi again yielded disubstituted ferrocenes **73a-c** as single diastereomers. Elimination of the substituted compounds catalysed by TsOH gave a series of solely planar chiral ferrocenes **74a-c** and *ent*-**74a-c**.

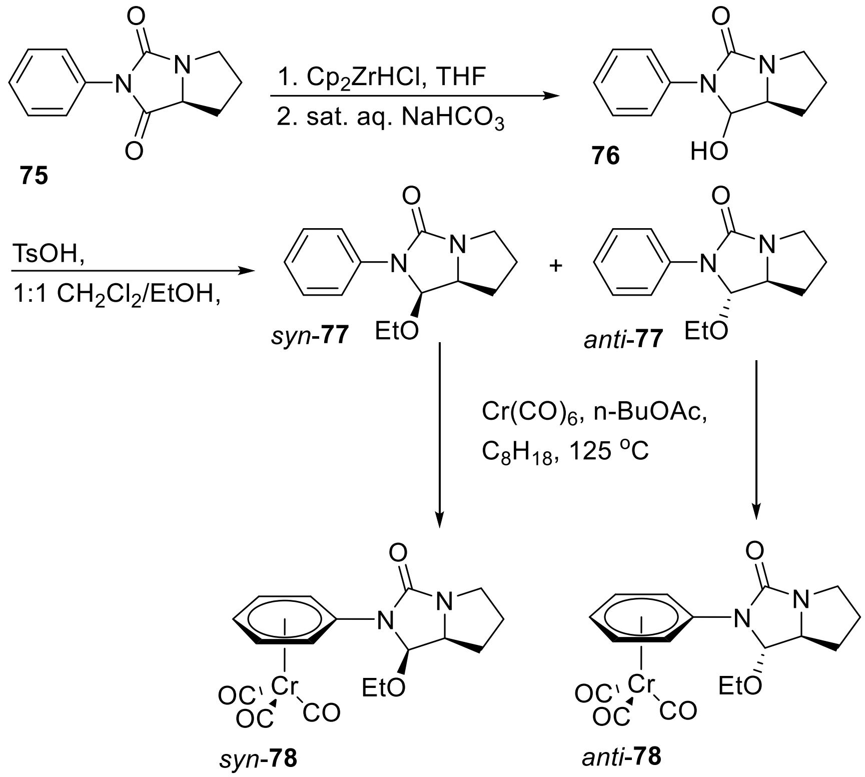


74a-c	E+	E	yld, %	[a]D **74**	[a]D *ent*-**74**
a	MeI	Me	85	-29.2	+31
b	(SMe)2	SMe	95	-129	+136
c	(ICH2)2	I	93	-38.9	+40.3

Scheme 15 - Synthesis of disubstituted ferrocenes and elimination products

Comparison of imidazolones **74a-c** with those of *ent*-**74a-c**, obtained by identical acid treatment of **69a-c**, found their optical rotations to be nearly equal but opposite (Scheme 15), implying that they are enantiomers of each other. This data, along with the x-ray crystal structure of boronic acid **69d**, can be used to as evidence that changing the relative stereochemistry of the bulky silyloxy group (*syn*-**68** to *anti*-**68**) changes the selectivity of the substitution allowing for divergent synthesis of planar chiral ferrocenes with knowledge of absolute stereochemistry. The spatial configurations of *syn* and *anti* **68** contributing to selectivity were studied by NOE NMR spectroscopy and DFT calculations, both revealing bulky silyloxy avoiding the iron centre, directing the urea oxygen to one prochiral hydrogen of the cyclopentadienyl ring.[5]

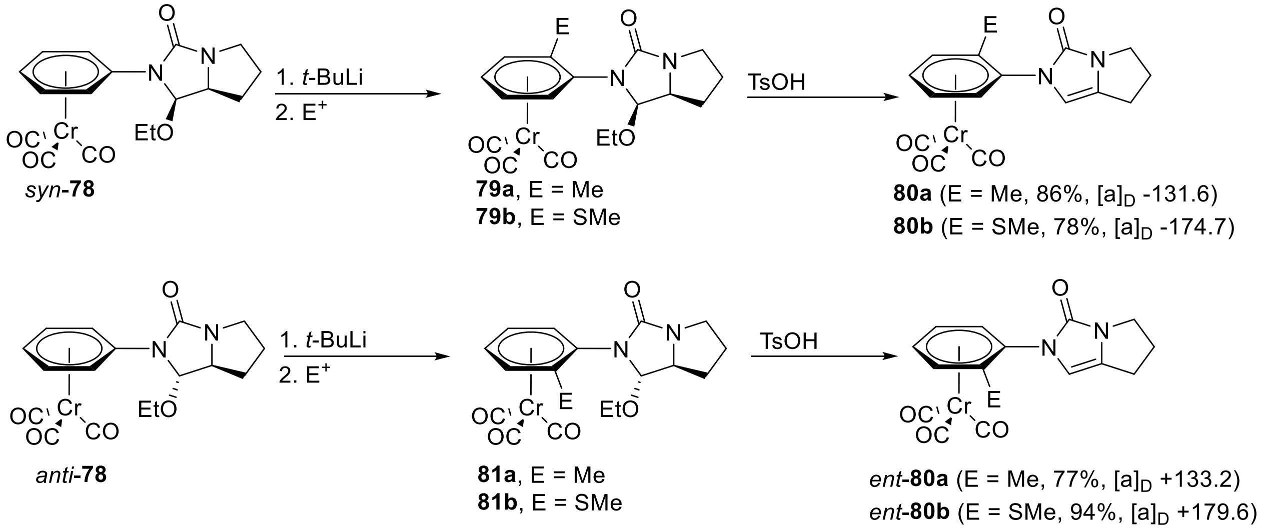
A less common example of planar chirality is observed in arene chromium tricarbonyl complexes. Expanding on the reported ferrocene methodology,[4,5] a modified *N*-phenyl version of the auxiliary was used to screen the lithiation of chromium complexes.[7] Up to 100 grams of *N*-phenyl proline hydantoin **75** was prepared by condensation of **9** with phenyl isocyanate. From hydrozirconation of **75**, hemiaminal **76** was isolated and alkylated by TsOH in the presence of excess alcohol yielding a mixture of *syn* and *anti*-**77** (Scheme 16). Both epimers were heated in the presence of hexacarbonyl chromium, forming epimeric chromium complexes *syn* and *anti*-**78**.



75
1. Cp_2ZrHCl, THF
2. sat. aq. $NaHCO_3$
76
HO
TsOH,
1:1 CH_2Cl_2/EtOH,
syn-77
EtO
+
anti-77
EtO
$Cr(CO)_6$, n-BuOAc,
C_8H_{18}, 125 °C
OC
Cr
CO
OC
EtO
syn-78
anti-78

Scheme 16 - Synthesis of epimeric η6-arene chromium tricarbonyl complexes

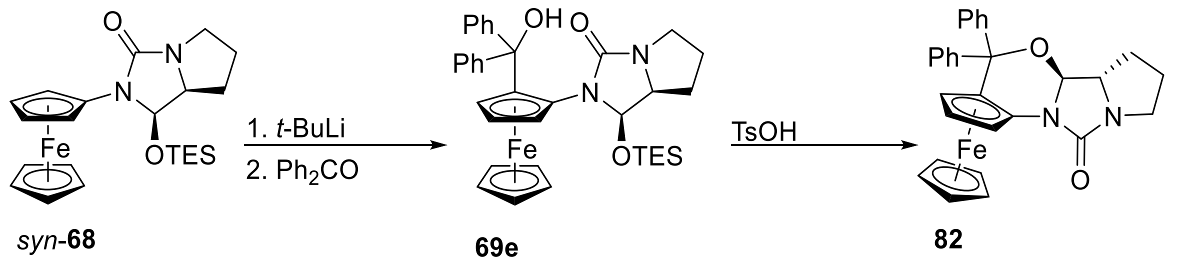
A variety of electrophiles was tested on the more abundantly synthesised *anti*-**78** after deprotonation with *t*-BuLi (Scheme 17). All substituted substrates **81** were synthesised as single diastereomers, observed by NMR spectroscopy. Lithiation of *syn*-**78** also gave disubstituted compounds **79** as single diastereomers.


syn-78
1. t-BuLi
2. E+
79a, E = Me
79b, E = SMe
TsOH
80a (E = Me, 86%, [a]D -131.6)
80b (E = SMe, 78%, [a]D -174.7)
anti-78
1. t-BuLi
2. E+
81a, E = Me
81b, E = SMe
TsOH
ent-80a (E = Me, 77%, [a]D +133.2)
ent-80b (E = SMe, 94%, [a]D +179.6)
OC
Cr
CO
EtO
E
N
O

Scheme 17 - Lithiation of chromium carbonyl complexes and planar chiral imidazolones

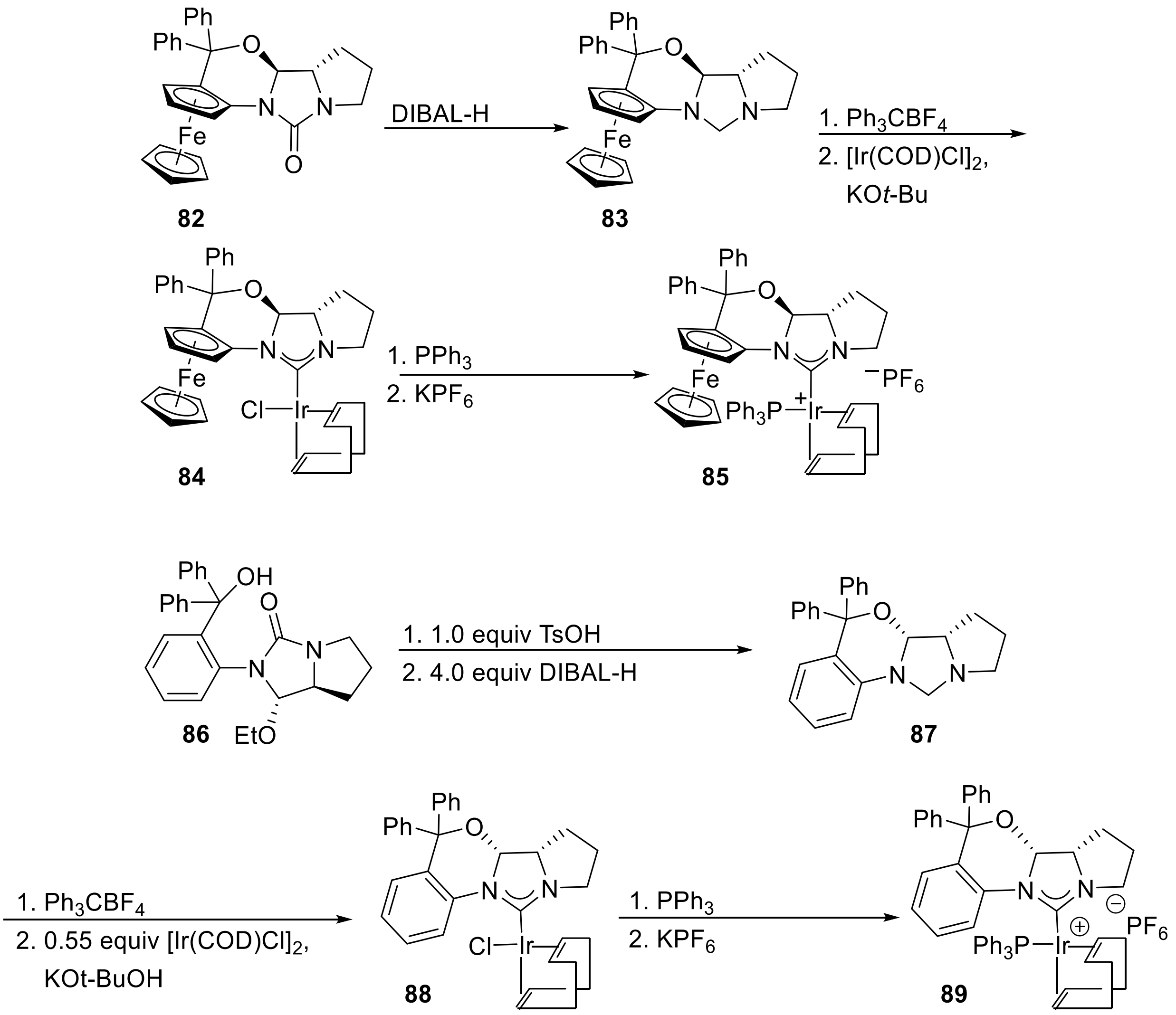
Analogous to the ferrocene series, acid mediated elimination yields exclusively planar chiral imidazolones (Scheme 17). The optical rotation of elimination products **80a-b** were observed to be nearly equal and opposite to those of *ent*-**80a-b**, indicating that opposite selectivity had been achieved. Absolute stereochemistry was confirmed by X-ray crystallography of sulfide **81b**, showing that, as for the ferrocene cases, the hemiaminal ether group orientates away from the metal centre, with the urea carbonyl directing the lithiation reaction.

During the Metallinos group's efforts to utilize chiral products derived from imidazloidinone auxiliaries, it was discovered that when subjected to acidic conditions, alcohol **69e** underwent cyclization displacing the protonated silyloxy group rather than undergoing elimination (Scheme 18).


O
N
N
Fe
OTES
syn-68
1. t-BuLi
2. Ph2CO
Ph
OH
Ph
O
N
N
Fe
OTES
69e
TsOH
Ph
Ph
O
N
N
Fe
O
82

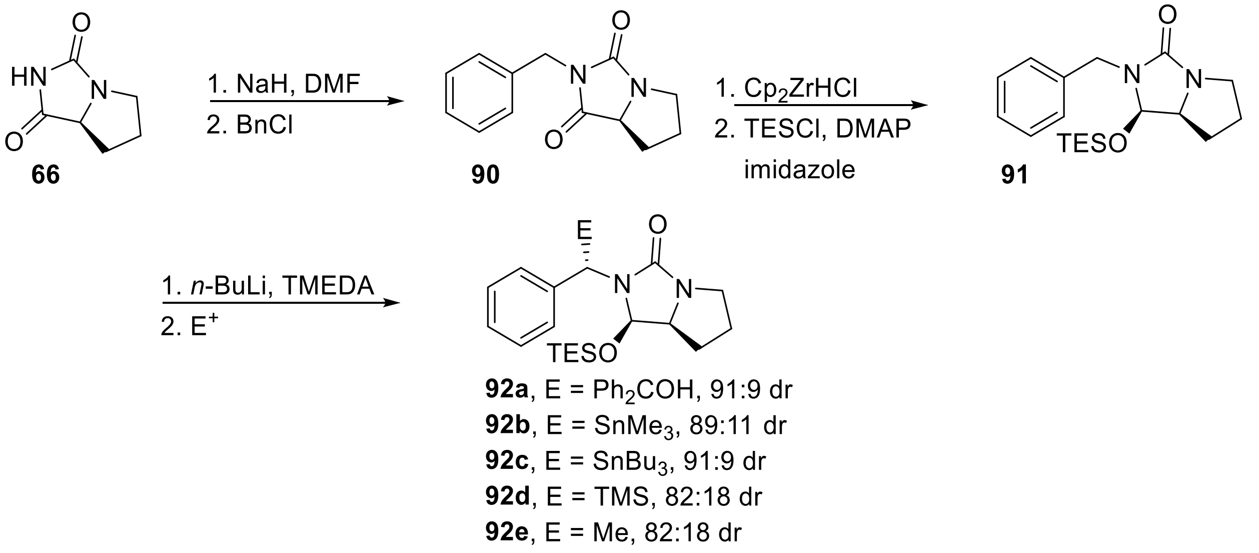
Scheme 18: Synthesis of cyclic ferrocenyl urea ***82***

Tetracyclic **82** could be reduced to aminal **83** which could be oxidized and treated with base and metal to obtain iridium NHC complex **84**.[6] This chiral complex is displaced with triphenyl phosphine to obtain the cationic **85** (Scheme 19), which was used in the asymmetric hydrogenation of quinolines with up to 90:10 er. An analogous complex was also synthesised by starting from *N*-phenyl hydantoin derived alcohol **86** (Scheme 19).


82
DIBAL-H
83
1. Ph3CBF4
2. [Ir(COD)Cl]2, KOt-Bu
84
1. PPh3
2. KPF6
85
86
1. 1.0 equiv TsOH
2. 4.0 equiv DIBAL-H
87
1. Ph3CBF4
2. 0.55 equiv [Ir(COD)Cl]2, KOt-BuOH
88
1. PPh3
2. KPF6
89

Scheme 19 - Synthesis of chiral iridium complexes derived from ferrocenyl and phenyl auxiliaries, respectively

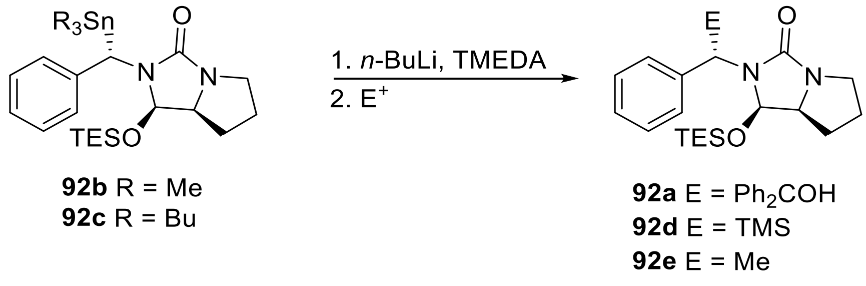
Another breakthrough in the use of pyrroloimidazolone chiral auxiliaries was incorporation of the *N*-benzyl moiety. Benzyl lithiation of said substrates gave the first example of stereoselective functionalization of an sp^3 centre using these types of auxiliaries.[8] The preparation of *N*-benzyl proline hydantoin **90** was achieved by deprotonation of **66** with NaH followed by treatment with benzyl chloride (Scheme 20). Hydrozirconation and sequential silylation of **90** yielded **91**, which was subjected to deprotonation by *n*-BuLi and electrophile quench under optimized conditions.



66
1. NaH, DMF
2. BnCl
90
1. Cp$_2$ZrHCl
2. TESCl, DMAP imidazole
91
TESO
1. n-BuLi, TMEDA
2. E$^+$
E
TESO
92a, E = Ph$_2$COH, 91:9 dr
92b, E = SnMe$_3$, 89:11 dr
92c, E = SnBu$_3$, 91:9 dr
92d, E = TMS, 82:18 dr
92e, E = Me, 82:18 dr

Scheme 20 - Synthesis of N-benzyl substrates and their stereoselective lithiation

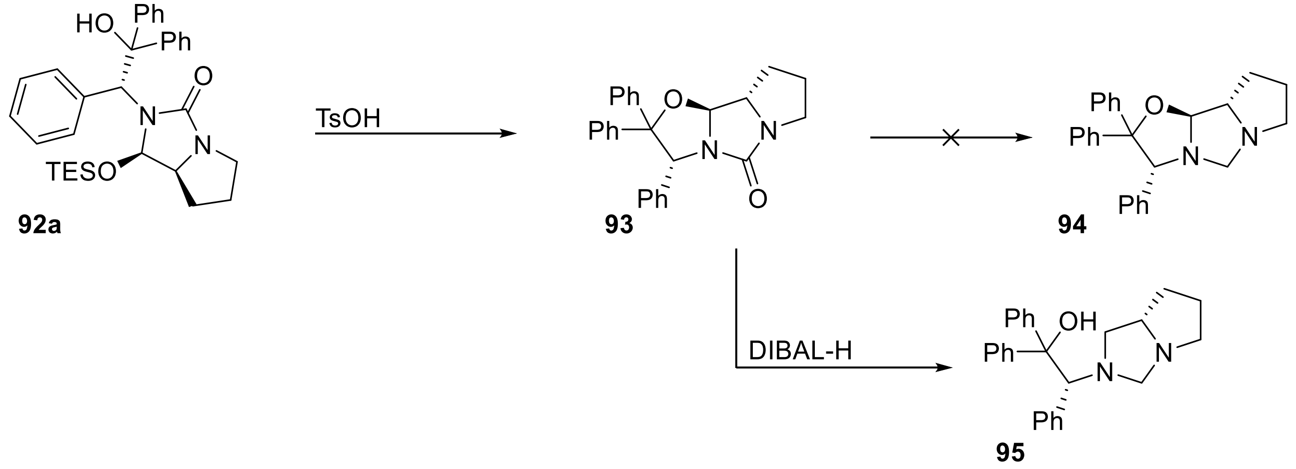
Unlike previous examples, the scope of benzyl substituted products **92** were obtained as a mixture of diastereomers up to a 91:9 dr.[4] Recrystallization of tertiary alcohol **92a** allowed for the characterization of the major diastereomer, which was determined to be of *R* configuration at the benzylic carbon, *anti* relative to the other two stereocentres, by x-ray crystallography. Treatment of stannanes **92b** and **92c** with lithiation conditions followed by electrophile quench gave products **92a**, **92d** and **92e** (Scheme 21), identical to those obtained by deprotonation of **91**. These transmetallation experiments show that stannanes **92b** and **92c** have the same relative stereochemistry as **92a**, **92d** and **92e**. Knowing the absolute stereochemistry of **84a**, coupled with these observations allows absolute stereochemical assignment of all products.



R$_3$Sn
TESO
92b R = Me
92c R = Bu
1. n-BuLi, TMEDA
2. E$^+$
E
TESO
92a E = Ph$_2$COH
92d E = TMS
92e E = Me

Scheme 21 - Transmetallation studies of stananes

Work towards an NHC ligand derived from *N*-benzyl hydantoin were reported by our group previously, showing that attempts to reduce tetracyclic urea **93** leads to the desired urea reduction but also cleaves the hemiaminal ether to give alcohol **95** rather than tricyclic **94** (Scheme 22).



Scheme 22 - Cyclization and reductive ring opening of N-benzyl derived substrate

1.2 Birch Reduction

The dissolving metal reduction of aromatic compounds was discovered by Arthur Birch in 1944. The seminal publication describes the synthesis of cyclohexadienes from benzene derivatives in the presence of lithium, sodium or potassium metal dissolved in liquid ammonia.[27] The reaction proceeds by the solvated electron of a group 1 metal adding to an aromatic ring forming a radical anion. This is then protonated to give a neutral radical, transformed to a carbanion by single electron transfer from another metal and finally protonated to obtain the reduced species.

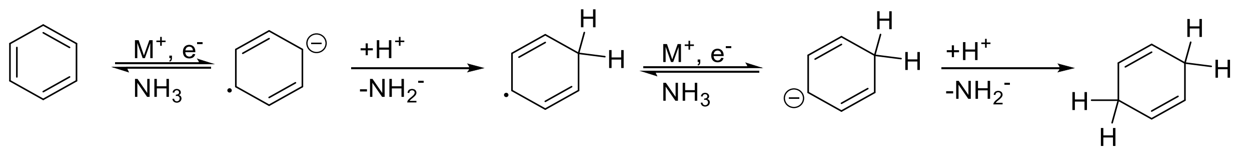
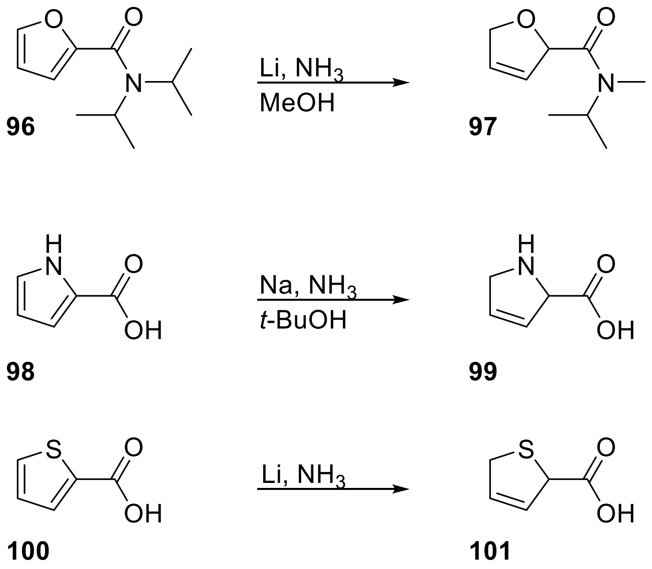


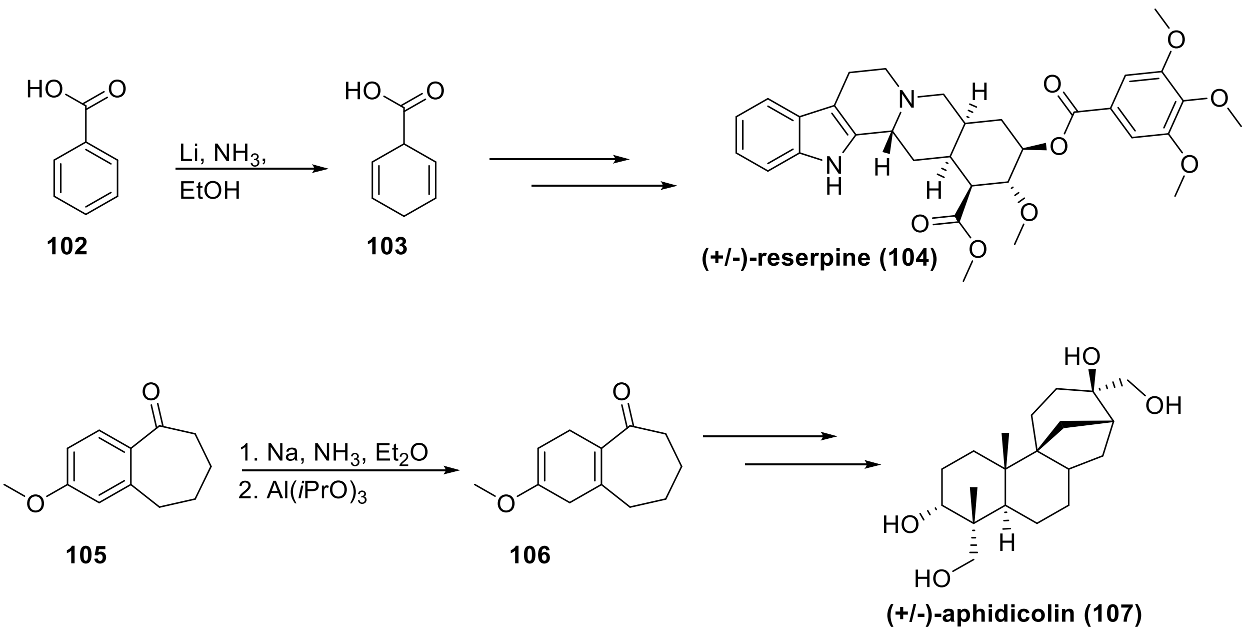
Figure 1 - Mechanism of the Birch reduction on benzene

Since its discovery, the Birch reduction has become a staple of organic synthesis[28] with an expansive methodology that continues to be explored. A key development in this field was the Birch reduction of heteroaromatic compounds. The dissolving metal reaction was shown to partially reduce heteroaromatics such as pyrroles,[29] furans[30] and thiophenes (Scheme 23).[31]



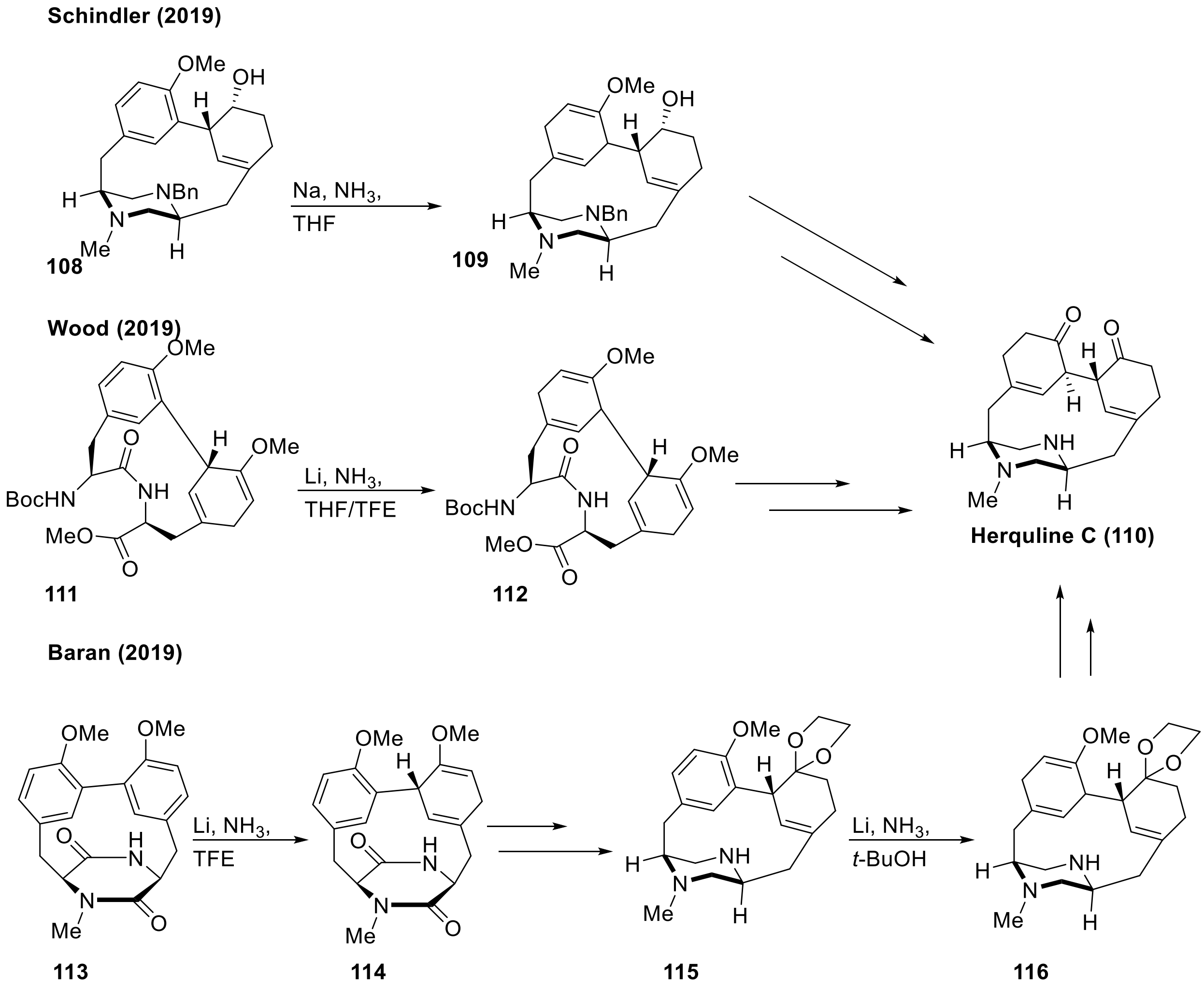
Scheme 23 - General outcome of the Birch reduction of various heterocycles

The Birch reduction has also been utilized in the synthesis of complex molecules quite extensively. The ability to reduce aromatic compounds allowed for the rapid incorporation of complexity into a six-membered ring. Starting with simple, commercially available molecules, the Birch reduction was used as the initial reaction to dearomatize benzoic acid (**102**) for the synthesis of reserpine (**104**),[32] and methoxysuberone (**105**) for the synthesis of aphidicolin (**107**)[33] (Scheme 24).



Scheme 24 - Birch reduction steps in the syntheses of reserpine and aphidicolin

Three recent syntheses of herquline C (**110**) have featured the use of at least one Birch reduction to achieve one of, or both partially saturated six-membered rings. Baran relies on two Birch reductions,[34] each on a methoxy benzene moiety and each followed by acid hydrolysis, the last of which being the final step to **110** (Scheme 25). While Baran's final reduction of **115** is quite standard, using *tert*-butanol as a proton source, the initial Birch reduction of **113** required extensive optimization and obtained the best results from using trifluoroethanol as a proton source.[34] Wood's synthesis[35] saturated the first aromatic ring by oxidative dearomatization. The second aromatic ring was reduced with similar conditions to Baron, utilizing trifluoroethanol as a source of protons to obtain **112** (Scheme 25).

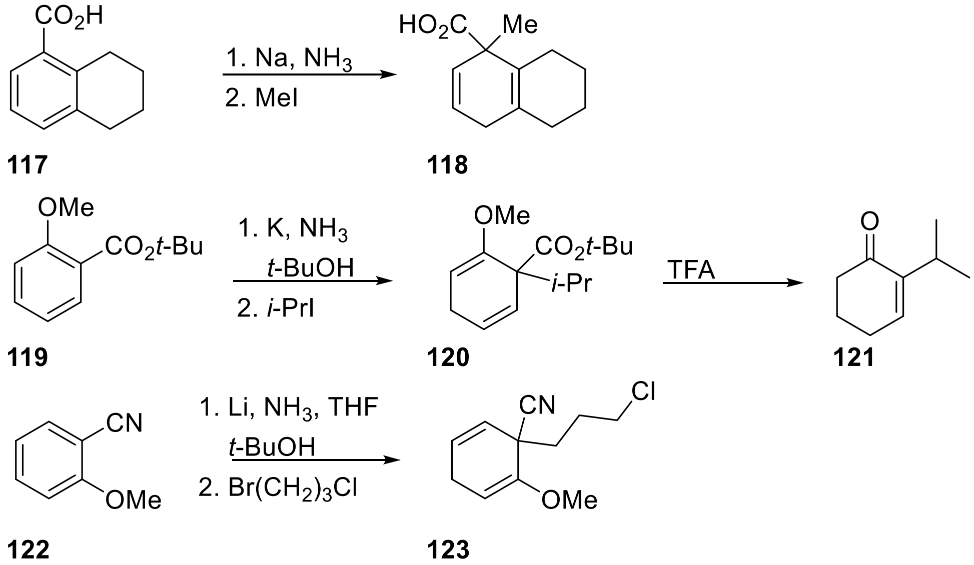

Schindler (2019)
Na, NH_3,
THF
108
109
Wood (2019)
Li, NH_3,
THF/TFE
111
112
Herquline C (110)
Baran (2019)
Li, NH_3,
TFE
Li, NH_3,
t-BuOH
113
114
115
116

*Scheme 25 - Birch reduction steps from total syntheses of Herquline C (**110**)*

The remaining synthesis was conducted by the Schindler group[36] and like Wood, relies on alternative dearomatization of one ring in early steps. Schindler's synthesis differs from the others significantly, with Birch substrate **108** bearing a free alcohol as opposed to Wood and Baron's enol ether **111** and protected ketone **115** respectively. The hydroxyl group of **108** serves as an intramolecular source of protons for the Birch reduction, increasing the rate of the reaction without the need for an external proton source and improving atom economy (Scheme 25).

1.2.1 Reductive Alkylation

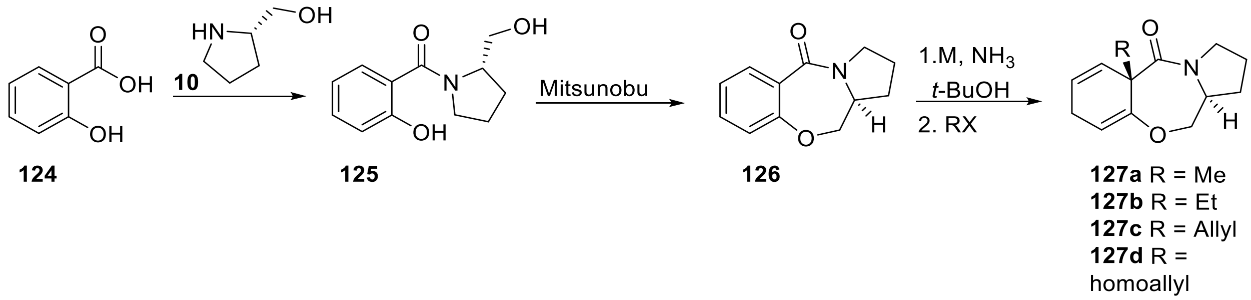
Birch established early on that treatment of a benzoic acid derivative with group one metals in liquid ammonia can be treated with an alkylating agent like methyl iodide to acquire alpha substituted dihydrobenzoic acids.[37] This methodology was expanded upon in the synthesis of cycloheptatrienes[38] and later for the racemic synthesis of gibberellic acid analogs via cyclohexadiene **118** (Scheme 26).[39]



Scheme 26 - Racemic preparation of alkylated cyclohexadienes for synthetic intermediates and expansion of methodology

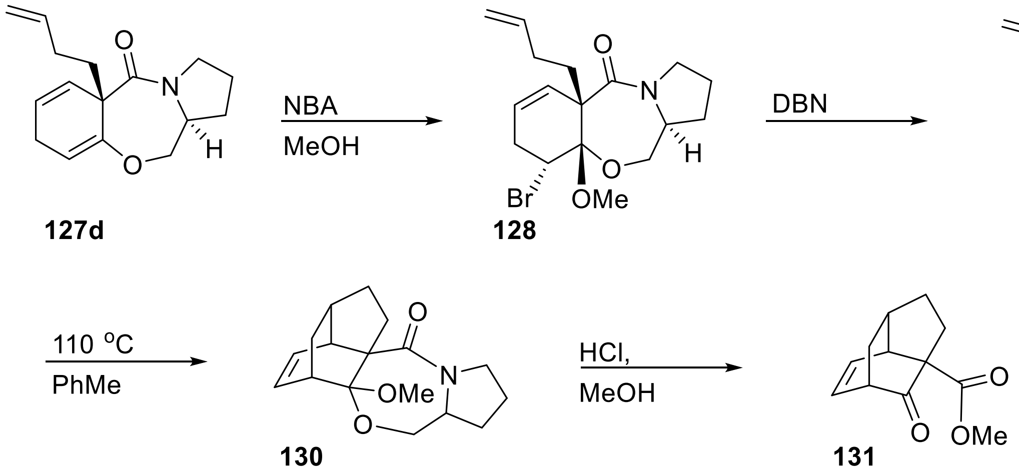
It was later established that alkylative reduction of aromatic ethers were possible in the presence of *ortho* methoxy substitution as in **119** (Scheme 26).[40] Schultz, who discovered the stereoselective alkylative Birch reduction previously, also demonstrated that alkylation could occur alpha to nitriles transforming **122** to **123** (Scheme 26).[41]

The alkylative Birch reduction was a major accomplishment in organic synthesis, but most of the methodology generates a new chiral centre in racemic fashion. This problem was solved by Shultz, who developed chiral benzamide derivatives to synthesise optically pure cyclohexadienes that could be transformed into chiral cyclohexanes and a variety of target functionalities and natural products.[42,43] Initially, 2-hydroxy benzoic acid **124** was treated with **10** to obtain the chiral benzamide **125**.[44] The benzamide was subjected to Mitsunobu conditions to reach the tricyclic substrate **126** (Scheme 27).


10
Mitsunobu
1.M, NH3
t-BuOH
2. RX
124
125
126
127a R = Me
127b R = Et
127c R = Allyl
127d R = homoallyl

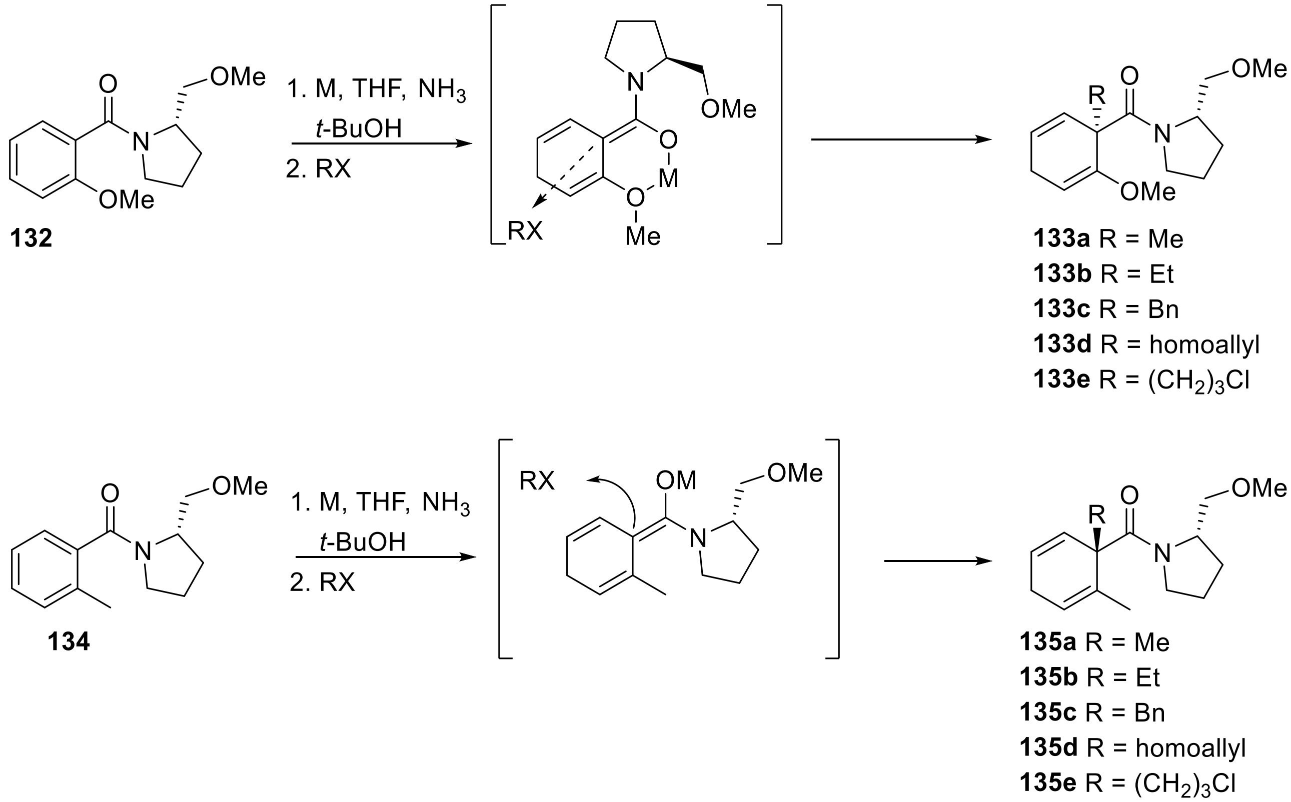
Scheme 27 - Synthesis of tricyclic substrate for asymmetric Birch reduction

Birch reduction of **126** was carried out with *t*-butanol and either lithium, sodium or potassium. The resulting metal enolate was trapped with a small range of alkyl halides generating cyclohexadienes **127a-d** (Scheme 27). Methylated product **127a** was synthesised as an 85:15 dr mixture that remained constant throughout screening of metals. **127b-d** were all formed as single diastereomers due to the increased steric bulk compared to methyl iodide, however stereoselectivity was found to be independent of the metal used in this study. The absolute configuration of alkylated products was tentatively assigned by NOE experiments as shown in depiction of **127a-d**. The stereoselectivity of **127d** was confirmed by conversion to **131** by a four-step process (Scheme 28), the last of which allows recovery of **10**, satisfying recyclability. Comparison of **131** with racemic standard by chiral shift ^{1}H NMR studies established that it was a single stereoisomer.


NBA
MeOH
DBN
110 °C
PhMe
HCl,
MeOH
127d
128
129
130
131

*Scheme 28 - Synthesis of known compound **131** for stereoselectivity determination*

A later study by Schultz examined different effects on the stereoselectivity of the reaction under modifications to substrates.[45] It was found that using a *ortho*-methoxy benzamide **132** in the Birch reduction, gave rise to an opposite stereoselectivity than the tricyclic and *ortho*-alkyl benzamides **134** (Scheme 29).

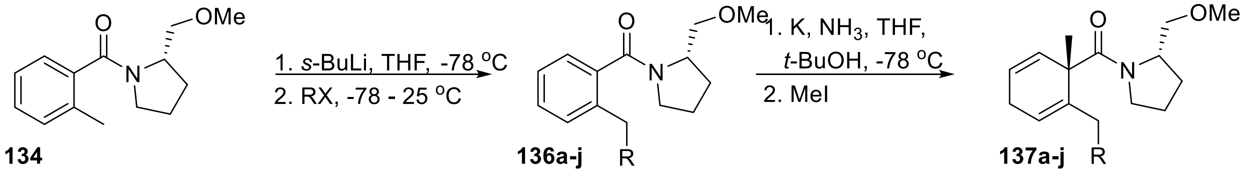


132
1. M, THF, NH3
t-BuOH
2. RX
OMe
RX
M
Me
133a R = Me
133b R = Et
133c R = Bn
133d R = homoallyl
133e R = (CH2)3Cl
134
OM
135a R = Me
135b R = Et
135c R = Bn
135d R = homoallyl
135e R = (CH2)3Cl

Scheme 29 - Reductive alkylation of ortho-alkoxy and ortho-alkyl benzamides yielding opposite stereoselectivity

This is thought to be due to a difference in enolate intermediates, likely from coordination of the metal to the extra oxygen present in the *ortho*-methoxy cases. Selectivity in all cases was independent of varying alkoxy groups bound to the pyrrolodine ring. To test the effects of different *ortho*-alkyl groups, another set of experiments by Schultz was conducted.[46] Starting with a methyl group *ortho* to the benzamide, directed benzyl metalation with *s*-BuLi and quench with electrophile gave access to a series of *ortho*-alkyl benzamides **136a-j** (Scheme 30).

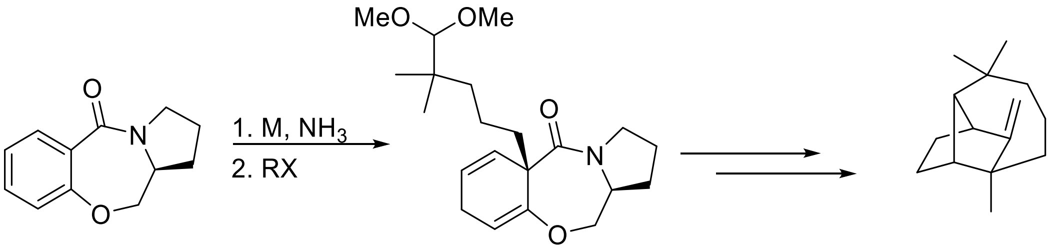
While all modified *ortho* groups did provide relatively good stereoselectivity in dihydrobenzenes **137a-j**, there are notable differences from substrate to substrate. It appears that larger alkyl groups give improved selectivity in the enolate alkylations demonstrated by **137h** giving the highest dr.



137a-j	R	Yield (%)	dr
a	Me	66	25:1
b	Et	79	19:1
c	allyl	76	29:1
d	homoallyl	69	18:1
e	Bn	62	40:1
f	CH_2Bn	77	26:1
g	$CH_2OCH_2SiMe_3$	71	33:1
h	$CH_2OCH_2SiMe_2t$-Bu	88	53:1
i	CH_2CH_2OH	79	42:1
j	Ph	69	48:1

Scheme 30 - Synthesis of ortho-modified chiral benzamides for reductive alkylation

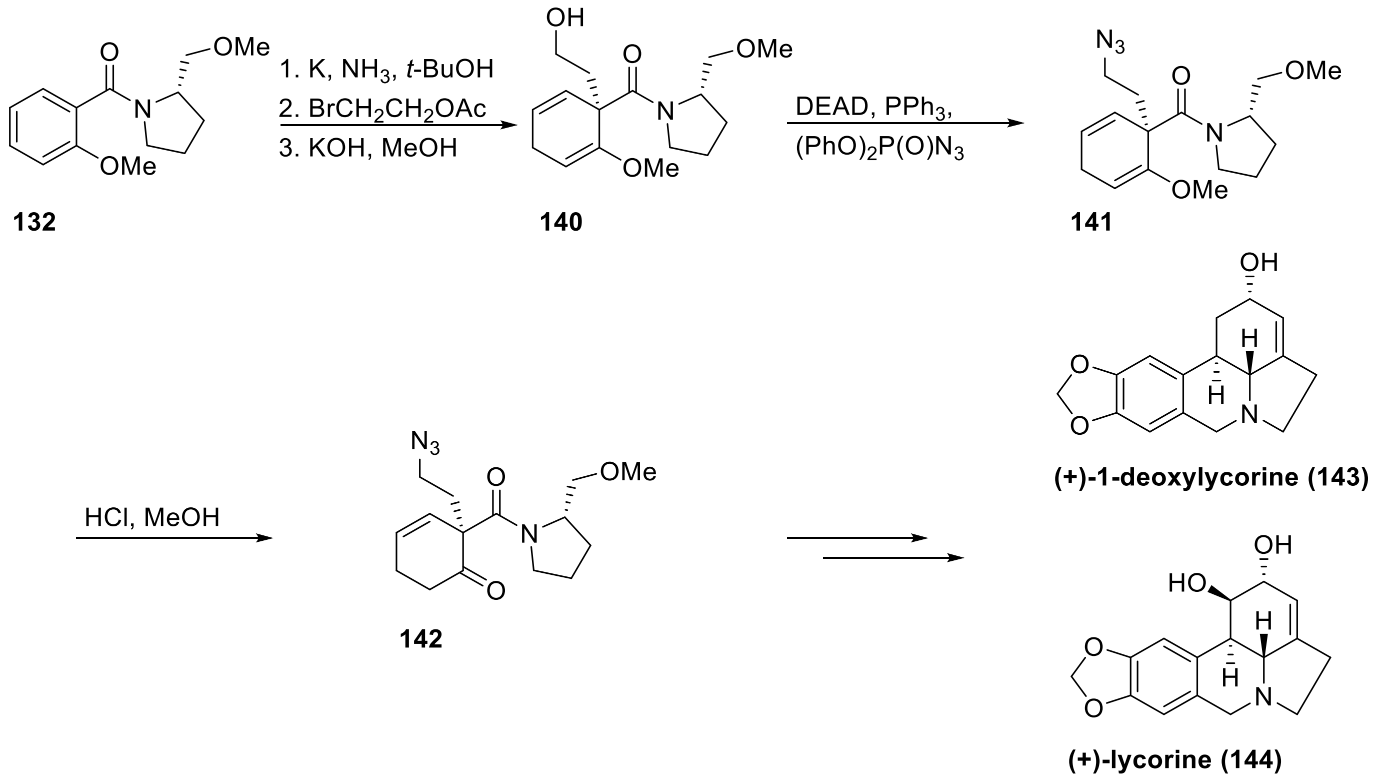
Soon after Schultz described the initial methodology of reductive alkylation, his laboratory set to applying it to the asymmetric synthesis of natural products. An early example by Schultz was the synthesis of (-)-longifolene **139**.[47] This was accomplished by reductive alkylation of cyclic benzamide **126**, quenching the enolate with a larger electrophile, bearing a dimethyl acetal, thus further improving the scope of the reaction (Scheme 31). Acid hydrolysis of the enol ether followed by several other transformations yields the optically active target molecule.



*Scheme 31 - Reductive alkylation en route to (-)-longifolene (**139**)*

Utilizing the opposite stereoselectivity induced by **132**, the first synthesis of the unnatural enantiomer, (+)-lycorine (**144**) and its derivative (+)-1-deoxylycorine (**143**) was achieved.[48,49]

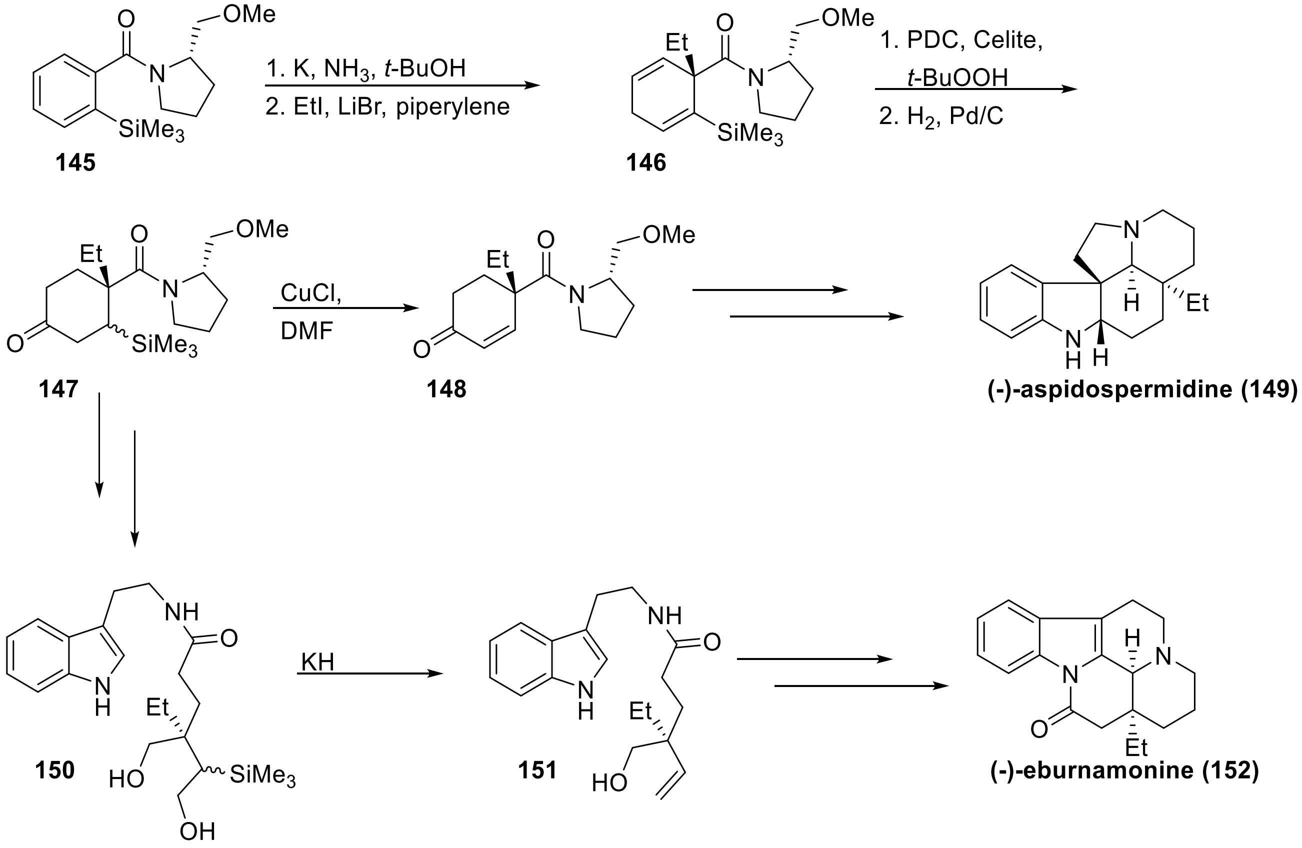
This required the reductive alkylation of **132** with 2-bromoethyl acetate and in-situ deacylation to reach alcohol **140**. This is then converted to azide **141**, again demonstrating the versatility of electrophile scope and robustness of the amino acid-derived auxiliary (Scheme 32).



1. K, NH_3, t-BuOH
2. $BrCH_2CH_2OAc$
3. KOH, MeOH
DEAD, PPh_3,
$(PhO)_2P(O)N_3$
HCl, MeOH
OMe
OH
N_3
O
N
H
HO
132
140
141
142
(+)-1-deoxylycorine (143)
(+)-lycorine (144)

*Scheme 32 - Reductive alkylation in the synthesis of (+)-deoxylycorine (**63**) and (+)-lycorine (**64**)*

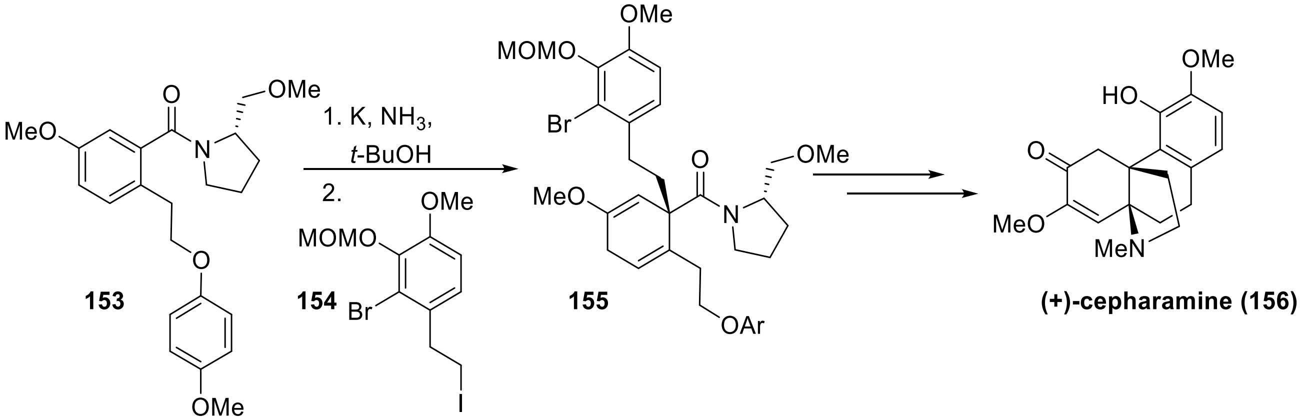
Stereoselective alkylation of a Birch enolate requires an *ortho* substituent as well as a chiral auxiliary. Early experiments by Schultz used alkyl or alkoxy substituents as they could be worked into the synthetic target or easily be manipulated. Alkylative reduction of *ortho*-trimethylsilyl benzamide **145** (Scheme 33) with ethyl iodide gives the cyclohexadiene **146** as a single stereoisomer.[50]



*Scheme 33 - Reductive alkylation and desilylation on route to (-)-aspidospermidine (**149**) and (-)-eburnamonine (**152**)*

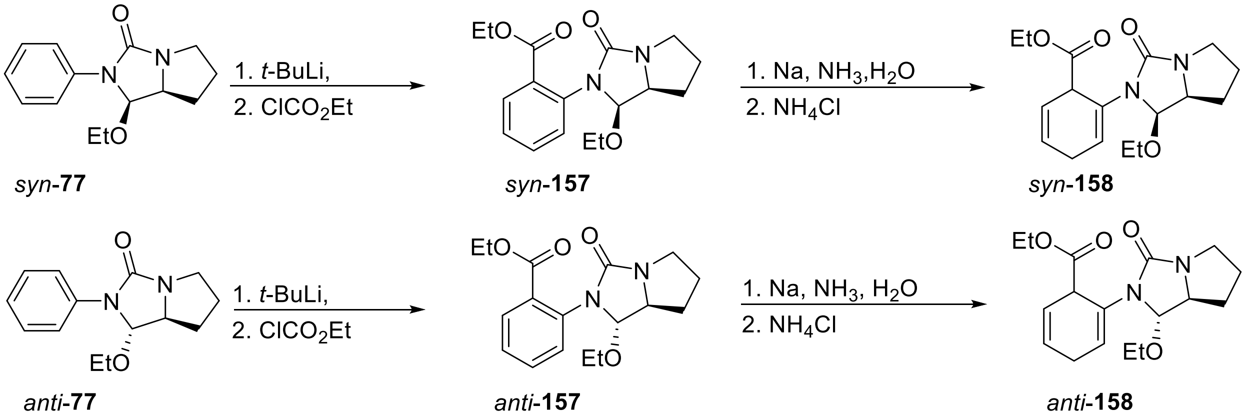
The successful reaction of such a substrate is an extremely important advancement due to the lability of a silicon-carbon bond. This presents the potential for immediate removal of silicon, mediated by a source of fluorine anions, giving access to unsubstituted alkenes that are not easily accessed from alkyl and alkoxy benzamides. This unique functionality was exploited in the synthesis of (-)-eburnamonine (**152**) and (-)-aspidospermadine (**149**). A common intermediate **147** was obtained by allylic oxidation and sequential hydrogenation of the diene moiety. Towards **149**, a copper catalyzed elimination of silyl groups beta to the ketone gave cyclohexanone **148** and towards **152**, a base induced elimination of trimethylsilanol of **150**, identical to the final phase of Peterson olefination, garnished alkene **151** (Scheme 33).

The syntheses of morphine and morphine-like alkaloids have proven to be incredibly challenging tasks to organic chemists.[51] A later synthesis by Schultz of Hasubanan alkaloid (+)-cepharamine (**156**), a tetracyclic compound structurally similar to morphine, uses his established methodology to establish stereochemistry to reach the unnatural enantiomer.[52] This involved the reduction of benzamide **153** (Scheme 34), bearing a relatively large *ortho* substituent, and alkylation with a large alkyl halide **154**.


MeO
O
OMe
N
O
OMe
153
1. K, NH3,
t-BuOH
2.
OMe
MOMO
154
Br
I
OMe
MOMO
Br
MeO
O
N
OMe
155
OAr
OMe
HO
O
MeO
MeN
(+)-cepharamine (156)

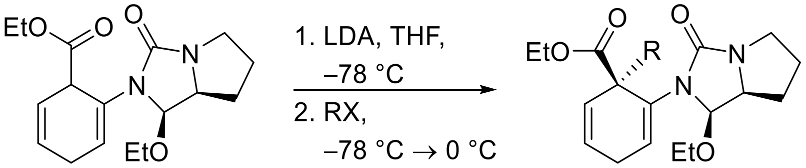
Scheme 34 - Reductive alkylation towards (+)-cepharamine (**156**)

Recent work in our laboratory has focused on incorporating the previously used imidazolone auxiliary in alkylative Birch reductions.[9] The epimeric ethoxy protected *N*-phenyl proline hydantoins, *syn* and *anti*-**77** were subjected to directed *ortho* metalation with *t*-BuLi and quenched with ethyl chloroformate to obtain aromatic esters *syn* and *anti*-**157** (Scheme 35). Birch reduction under optimized conditions, using sodium and stoichiometric water as a proton source, gives the first example of *N*-cyclohexadienes, *syn* and *anti*-**158**.


O
N
N
EtO
syn-77
1. t-BuLi,
2. ClCO2Et
EtO
O
O
N
N
EtO
syn-157
1. Na, NH3,H2O
2. NH4Cl
EtO
O
O
N
N
EtO
syn-158
anti-77
1. t-BuLi,
2. ClCO2Et
anti-157
1. Na, NH3, H2O
2. NH4Cl
anti-158

Scheme 35 - Synthesis of cyclohexadienes from syn and anti-**77**

The lithium enolate, obtained by treatment with LDA, is quenched with a number of alkyl halides to create a quaternary carbon alpha to ester, stabilizing the cyclohexadiene to aromatization. Using NMR spectroscopy, alkylated reduction products **159** were observed to be single diastereomers (Scheme 36).



syn-**158**

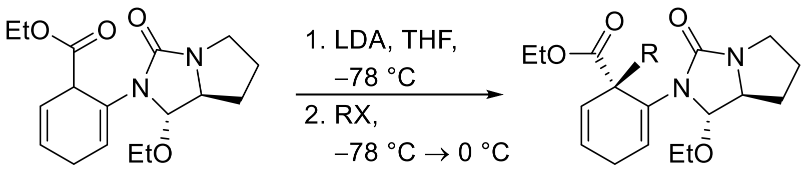
159

159a-d	RX	R	yld, %	dr
a	MeI	Me	47	>95:5
b	EtI	Et	85	>95:5
c	BnBr	Bn	74	>95:5
d	AllylBr	Allyl	93	>95:5

.

*Scheme 36 - Alkylation of cyclohexadiene syn-**159***

However alkylated products **160a-d** gave a large range of mixtures from 53:47 to 95:5 dr (Scheme 37). It is presumed that the enolate anion is configurationally unstable, meaning that the origin of stereoselectivity is likely the electrophile quench. This differs from the planar chiral cases where the selectivity originates in the deprotonation, yielding a configurationally stable anion regulated by the configuration of the silyloxy moiety.[5] The results for these substrates show that both stereocentres may play a role in directing the enolate alkylation given that alkylation of *syn*-**158** demonstrated superior diastereoselectivity. The size of the electrophile also appears to be crucial to the selectivity of synthesising **160** with the small methyl substituent showing almost no selectivity, while larger ethyl, benzyl and allyl substituents display relatively good to complete selectivity.



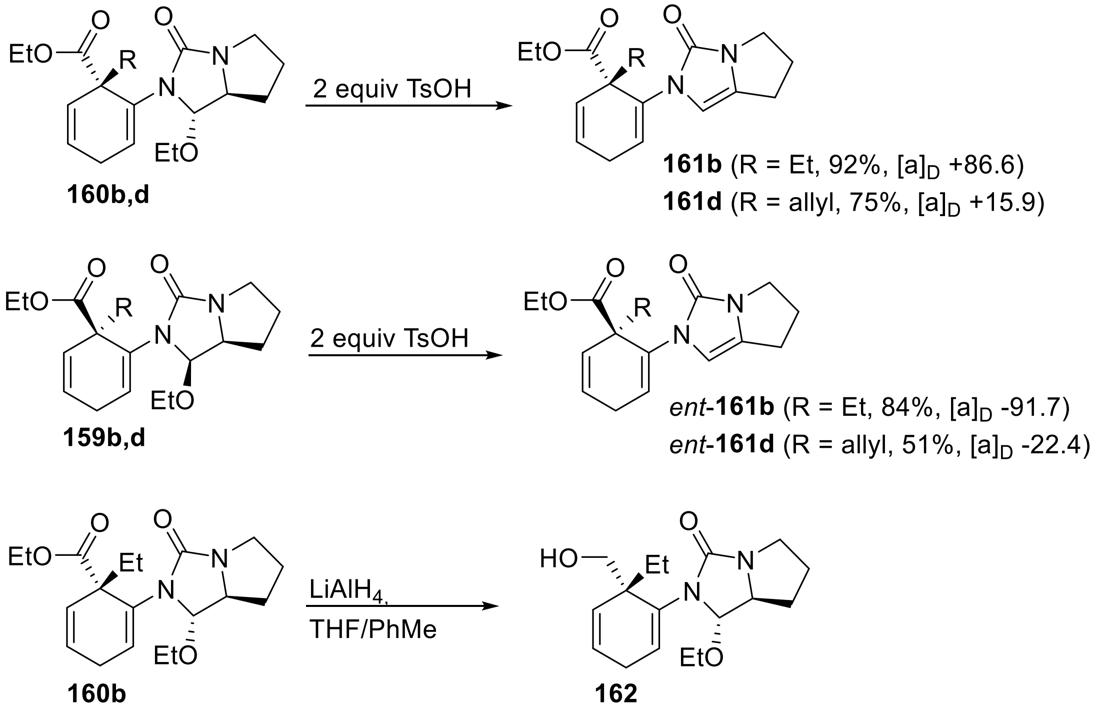
anti-**158**

160

160a-d	RX	R	yld, %	dr
a	MeI	Me	75	53:47
b	EtI	Et	72	95:5
c	$PhCH_2Br$	$PhCH_2$	78	91:9
d	AllylBr	Allyl	43	80:20

*Scheme 37 - Alkylation of cyclohexadiene anti-**158***

Similar to the ferrocene[5] and chromium complex[7] cases, acid mediated elimination of alcohol from the alkylated products gave imidazolones (Scheme 38) with a single chiral carbon **161b,d** and *ent*-**161b,d**. Determination of optical rotation of these compounds shows that alkylation of *syn*-**158** and *anti*-**158** yield opposite configuration of the quaternary carbon alpha to the ester.



160b,d

161b (R = Et, 92%, [a]$_D$ +86.6)
161d (R = allyl, 75%, [a]$_D$ +15.9)

159b,d

ent-**161b** (R = Et, 84%, [a]$_D$ -91.7)
ent-**161d** (R = allyl, 51%, [a]$_D$ -22.4)

160b

162

Scheme 38 - Experiments to determine stereochemistry of substituted dienes

With all alkylated products being isolated as colourless oils, **160b** was treated with lithium aluminum hydride to obtain alcohol **162** (Scheme 38) as a crystalline solid. Single crystal x-ray crystallography determined *R* configuration at the quaternary carbon (Figure 2). This substitution selectivity with respect to the configuration of the alkyl or silyl ether is consistent with previous observations.[4,5,7,8] Plotted X-ray structure (Figure 2) was obtained from **162** synthesised and crystalized by Ngan Tran, another member of the Metallinos group.[9]

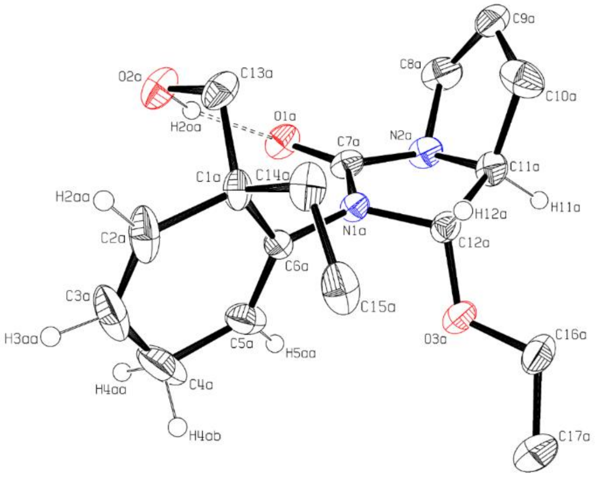
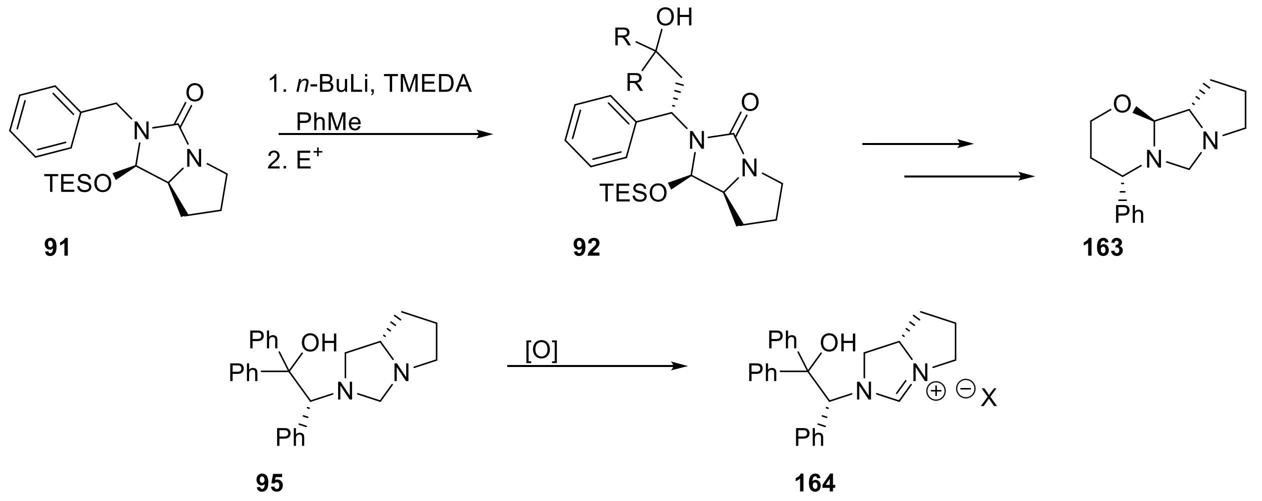


*Figure 2 - ORTEP plot of **162**. Most hydrogen atoms omitted for clarity*[9]

2. Objectives

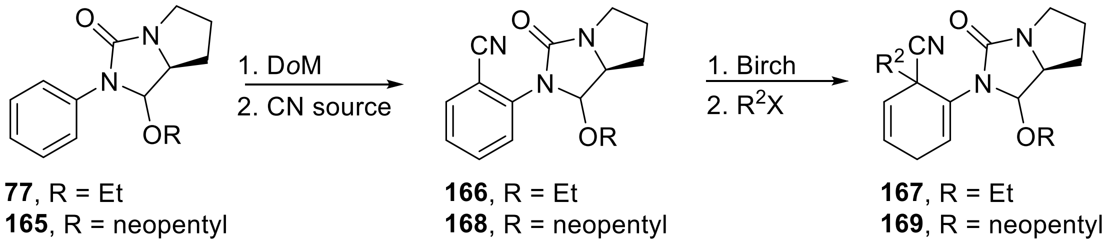
The goal of this research is to further advance the field of imidazolone chiral auxiliaries and demonstrate their utility on several different reaction conditions. With the synthesis of an NHC ligand from **92a** failing due to reductive ring opening of the strained 5-membered oxazolidine, a new approach to a *N*-benzyl ligand was devised. Quench of the anion of **91** with an electrophile bearing a homologated alcohol compared to **92a**, or a precursor that can be transformed into such. This would allow access to a substrate that may maintain structural integrity in a reduction step. Utilizing the ring-open **95** as a bidentate ligand *via* oxidation to an iminium will also be explored (Scheme 39).



Scheme 39 - Proposed synthesis of chiral NHC ligand precusors

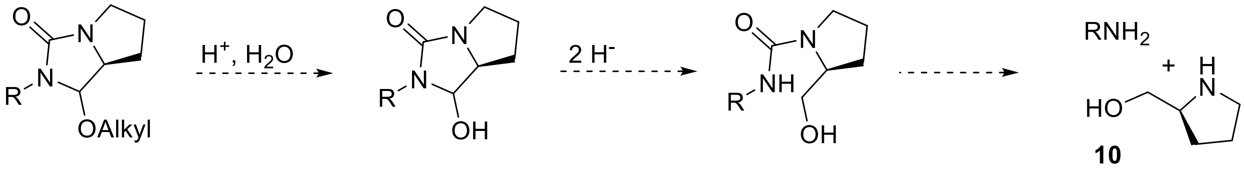
Building upon the synthesis of planar chiral arene complexes and centrally chiral benzyl systems, we have set out to apply these auxiliaries to stereoselective Birch reduction-alkylation sequences. The group has demonstrated the effectiveness of these compounds in the reductive alkylation of aryl esters but an issue regarding the synthesis of *N*-phenyl alkoxy imidazolidinones is the overwhelming selectivity bias to *anti*-**77**. Despite being the minor product of alkylation, esters derived from *syn*-**77** show much greater selectivity in alkylative reduction reactions. To approach this issue, we will explore the synthesis of exclusively *syn*-**77** from **75** or **76** for practical access to the selective reaction products by in-*situ* alkylation of the hemiaminal or *via* completely different chemical reactivity. Another approach is improving the selectivity of alkylating *anti* substrates by increasing the bulk of the chiral alkoxy group to overcome the blocking that seems to be required from the pyrrolidine chiral centre. Different alkyl groups of the hemiaminal ether moiety of either stereo conformation will be screened to observe the effects on the stereochemical outcome of the alkylation. Despite a *t*-butyl group being a large substitute for ethoxy, it would likely act as a good leaving group and result in primarily elimination product in the directed *ortho* metalation step. A neopentyl directing group would result in an increase in steric influence while retaining the stability of a primary alcohol.

One downfall of the Schultz systems is the electron withdrawing nature of the chiral benzamide. This limits the *ortho* groups to electron donating or poorly electron withdrawing groups to avoid issues in regioselectivity of the Birch reduction and enolate alkylation. This is remedied using an imidazolidinone chiral auxiliary, which acts as a surrogate for Shultz's amide with much less electron withdrawing characteristic. This gives rise to the potential of changing the electron withdrawing group on the aromatic ring. This work will attempt the first stereoselective reductive alkylation of a benzonitrile, a reaction that was not possible utilizing Shultz's benzamide[41] (Scheme 40).



Scheme 40 - Synthesis and Stereoselective Reductive Alkylation of Benzonitriles

Efforts were also made towards the manipulation and removal of the imidazolone bearing an alkyl ether rather than the much more labile silyl ether (Scheme 41). Studies for the acid catalyzed hemiaminal formation and reductive ring opening to secondary urea, similar the sequence realized in the ferrocene system.[4]

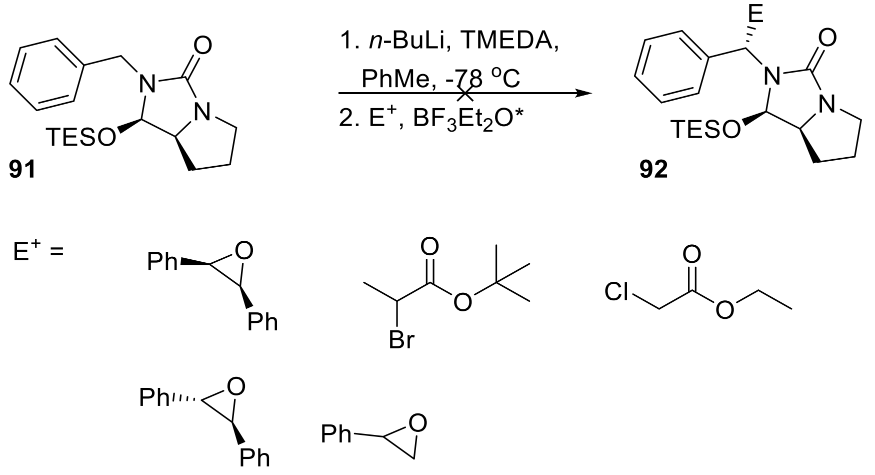


Scheme 41 - General route to auxilliary removal

3. Results and Discussion

3.1 Towards Novel Chiral NHC Ligands Derived from *N*-benzyl Hydantoin

We devised a two-pronged approach to designing a new NHC ligand; using an electrophile in the benzylic lithiation of **91** that would yield an alcohol or precursor to an alcohol with an extended benzylic carbon chain compared to **92a**, or oxidize **95** to utilize as a C, O bidentate ligand. Initial electrophiles used in the quenching the lithiation of **91** were *cis* and *trans*-stilbene oxide (Scheme 42). Another member of our group had previously demonstrated that epoxides were not reactive to the benzyl carbanion, so activation was thought to be required. Treatment of **83** with *n*-BuLi and TMEDA followed by addition of a toluene solution of *cis* or *trans* stilbene oxide and BF$_3$-EtO$_2$ resulted in a complex mixture of products that was primarily starting material. Quenching the anion of **91** with styrene oxide as the electrophile also demonstrated no reactivity.

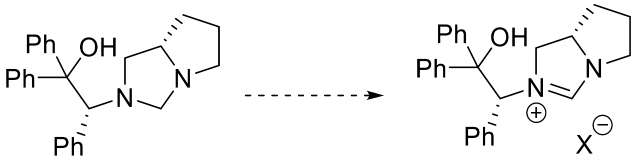


*only used with epoxide electrophiles

Scheme 42 - Attempted electrophile quench of ***91*** *to obtain a homologated (masked) alcohol*

The next approach was using alpha-halo esters for the electrophile quench with the rationale that complete reduction of the ester could yield alcohols with the desired number of carbons. Quench of the benzyl carbanion with *t*-butyl 2-chloro propionate and ethyl 2-bromo acetate gave complete recovery of starting material (Scheme 42). This was attributed to the acidity of the proton geminal to the halide in the ester quenching the carbanion faster than displacement of the halide can occur.

Another member of the group previously found that treatment of aminal **95** with triphenylcarbenium tetrafluoroborate does not lead to the formation of an iminium as with the ferrocenyl and phenyl series. Several oxidation methods were explored in attempts to achieve the NHC precursor (Scheme 43). Dehydrogenation of **95** with palladium on carbon gave no change by TLC after 24 hours in refluxing in *i*PrOH in the presence of one molar equivalent of AcOH or NH_4Cl.[53] Filtration and work up of the reaction yielded quantitative recovery of starting material. Oxidation by molecular iodine[53] in the presence of a weak base resulted in decomposition into uncharacterizable material. Treatment with NBS or DBDMH[54] gave no reaction and starting material was again recovered. It is likely that the alcohol moiety of **95** interferes with the oxidation process and oxidation of protected analogs could be explored in the future.



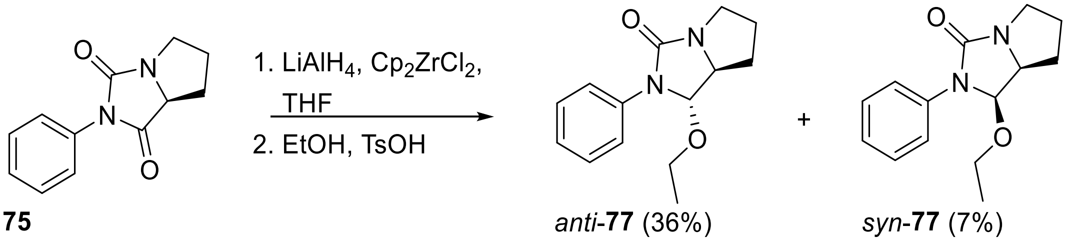
95 **164**

Oxidant	Additive	Solvent	yield, %	X^-
Pd/C	AcOH	*i*PrOH	0	OAc
Pd/C	NH_4Cl	*i*PrOH	0	Cl
I_2	$NaHCO_3$	CH_2Cl_2	0	I
NBS	n/a	THF	0	Br
DBDMH	n/a	THF	0	Br

*Scheme 43 - Attempted oxidation of **95***

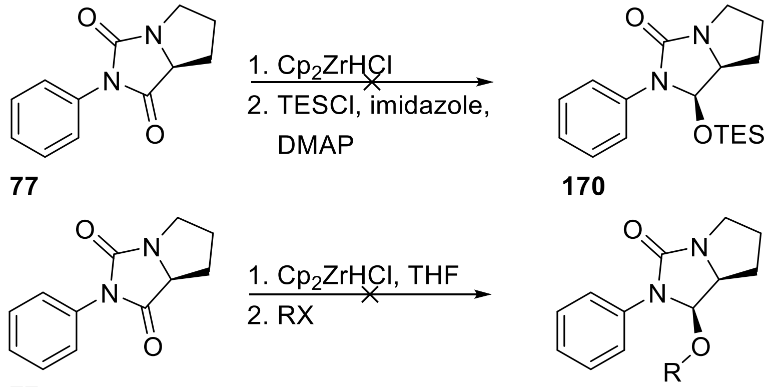
3.2 Attempts towards controlling stereoisomerism of alkyl protected phenyl L-proline hydantoins and other improvements

One potential improvement made to the overall synthesis of the chiral auxiliary was the development of a one-pot reduction-protection of the hydantoin. It was found that treating a suspension of excess $LiAlH_4$ and one molar equivalent of Cp_2ZrCl_2 in THF with hydantoin **75**, resulted in reduction to hemiaminal **76** in 30 minutes with complete conversion by TLC. This could be a vast improvement upon the use of Schwartz' reagent which is costly and arduous to obtain synthetically in moderate yield. It was theorized that quenching the reaction with a large excess of ethanol could transition into the protection, with residual lithium, aluminum or zirconium acting as Lewis base catalysts; however, addition of 3 equivalents of TsOH was required to observe any turnover. The ratio of *syn* and *anti*-**77** remains about same upon isolation (2:8); however, the messy workup of the one-pot reaction gave *syn*-**77** in only 7% yield and *anti*-**77** in 36% yield (Scheme 44), much lower than the stepwise procedure (Scheme 16).



*Scheme 44 - One-pot synthesis of syn and anti-**77***

To circumvent the observed selectivity towards *anti*-**77** in the alkylation of hemiaminal **76**, several chemical approaches are taken. Hemiaminal **76** is observed to be of relative *syn* stereochemistry by deuterium oxide spiked NMR experiments revealing the methyne proton signal to be a doublet of about 6 Hz, consistent with derivatives bearing *syn* stereochemistry. This is rationalized by exo-attack of the carbonyl from the bulky zirconium hydride. This was only observed in the unpurified reaction product and attempts to observe stereochemistry by NMR after column chromatography revealed that epimerization occurs on silica, favouring *syn*-**76**. It was theorized that like *in-situ* silyation of the hemiaminal, giving *syn*-**170** (Scheme 45) as the major diastereomer,[7] the zirconium alkoxide could also be trapped with a different electrophile. This proved to be an ineffective method of alkylation, with **76** being the only isolated product from all reactions.



77

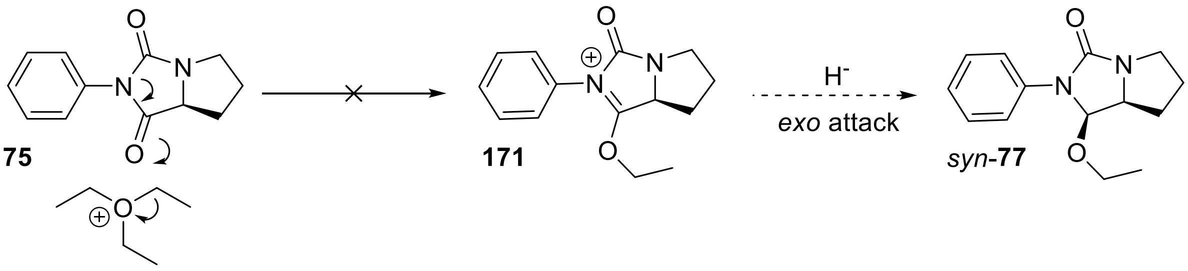
170

77

RX	R	yld, %
MeI	Me	0
Me_2SO_4	Me	0
EtI	Et	0
Et_3OBF_4	Et	0
AllylBr	Allyl	0

*Scheme 45 - Attempts towards syn hemiaminal ether derivatives like **170***

Next, we envisioned direct *O*-alkylation of the hydantoin **75** by treatment with Meerwein's salt (triethyloxonium tetrafluoroborate), an extremely electrophilic ethyl source. Typical conditions involve the treatment of an amide with Meerwein's salt and a non-nucleophilic tertiary amine in dichloromethane to obtain an imidate salt of tetrafluoroborate, or imidate free base can be obtained in the cases of primary and secondary amides. It was speculated that the treatment of a phenyl hydantoin imidate-type salt **171** with a source of hydride would reduce from the exo-face, giving *syn*-**77** as the major product (Scheme 46).



75

171

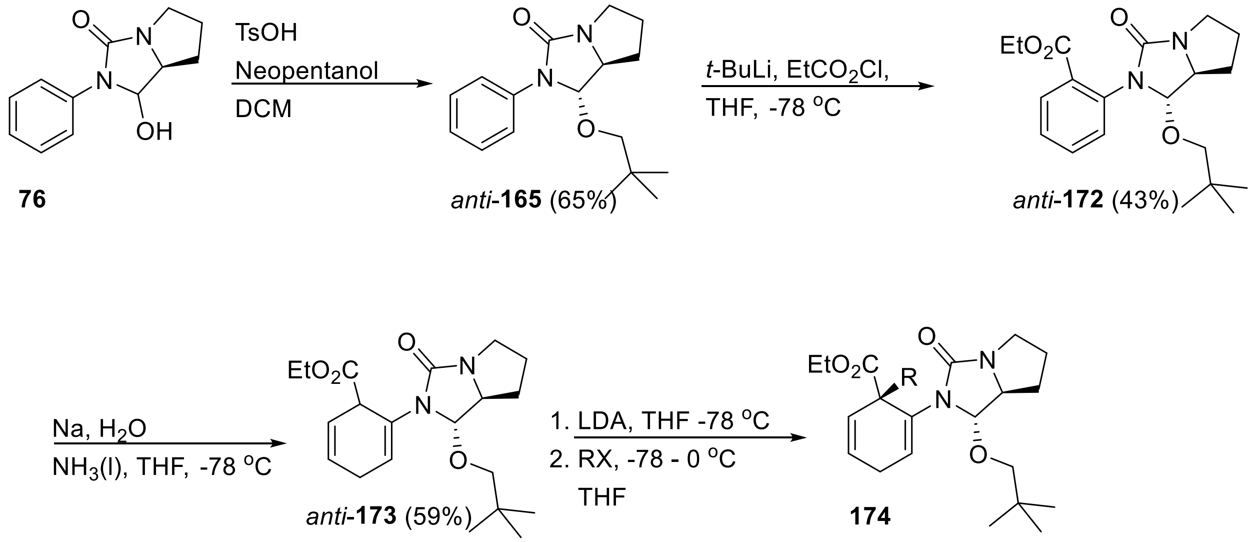
syn-**77**

*Scheme 46 - Proposed alternative synthesis of syn-**77***

The Somfai group discovered, during the total synthesis of dehaloperophoramidine,[55] that an older bottle of Meerwein's salt gave them better *O*-selectivity than a newer bottle when they were obtaining undesired *N*-alkylation by-products. This was attributed to hydrolysis over time leading to the presence of acid and optimization showed TFA as the most efficient additive.[56] Unfortunately after screening several conditions for *O*-alkylation of **75**, only recovery of starting material was observed. It is possible that unlike amides, the nitrogen lone pair of hydantoin **75** is highly distributed by resonance through the two carbonyls and phenyl ring, leading to no single oxygen atom with enough electron density to act as an active nucleophile.

3.3 Effect of alkoxy protecting group on stereoselectivity of enolate alkylation

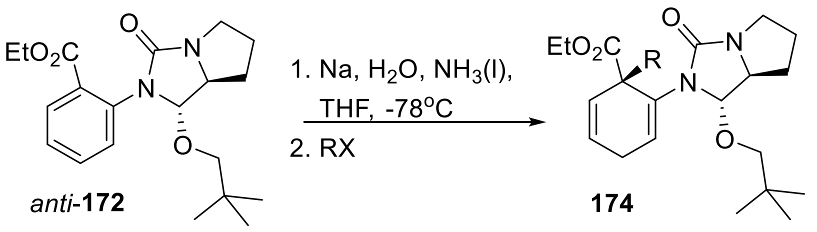
To approach the issue of low selectivity on alkylation of *anti*-**158**, the use of different alkyl groups of the hemiaminal ether were investigated. Studies with isopropyl substituted hemiaminal were conducted within the group with limited results,[9] and tertiary alkyl groups are highly prone to elimination of alcohol. The approach taken was that of a neopentyl protecting group. Under typical conditions, hemiaminal **76** was treated with acid and excess neopentyl alcohol dissolved in dichloromethane to give *anti* and *syn*-**165** as colourless solids. Directed *ortho* lithiation yield aromatic ester *anti*-**172**, which was converted into diene *anti*-**173** by Birch reduction. The key alkylation step was carried out under the same conditions as the ethyl substituted case, giving various selectivity (Scheme 47).


76
TsOH
Neopentanol
DCM
anti-**165** (65%)
t-BuLi, EtCO2Cl,
THF, -78 °C
EtO2C
anti-**172** (43%)
Na, H2O
NH3(l), THF, -78 °C
anti-**173** (59%)
1. LDA, THF -78 °C
2. RX, -78 - 0 °C
THF
R
174

174a-b	RX	R	yld, %	dr	dr (Ethoxy)
a	MeI	Me	74	71:29	>53:47
b	EtI	Et	43	89:11	>95:5

Scheme 47 - Synthesis of neopentyl hemiaminal ethers as Birch reduction substrates

The most promising case was quenching the enolate of *anti*-**173** with iodomethane to obtain **174a** in 71:29 dr, as opposed to nearly no selectivity in the ethyl protected analog **160a**. However, a decrease in selectivity of the ethylation from 95:5 in **160b** to 89:11 in **174b** was also observed. For synthetic convenience the reductive alkylation of *anti*-**165** was carried out in one pot. The methylation of *anti*-**172** proceeded with superior yield to the stepwise sequence but sacrifices the selectivity down to 68:32 dr. Quenching with iodoethane however, showed a 98:2 dr by NMR (Scheme 47).

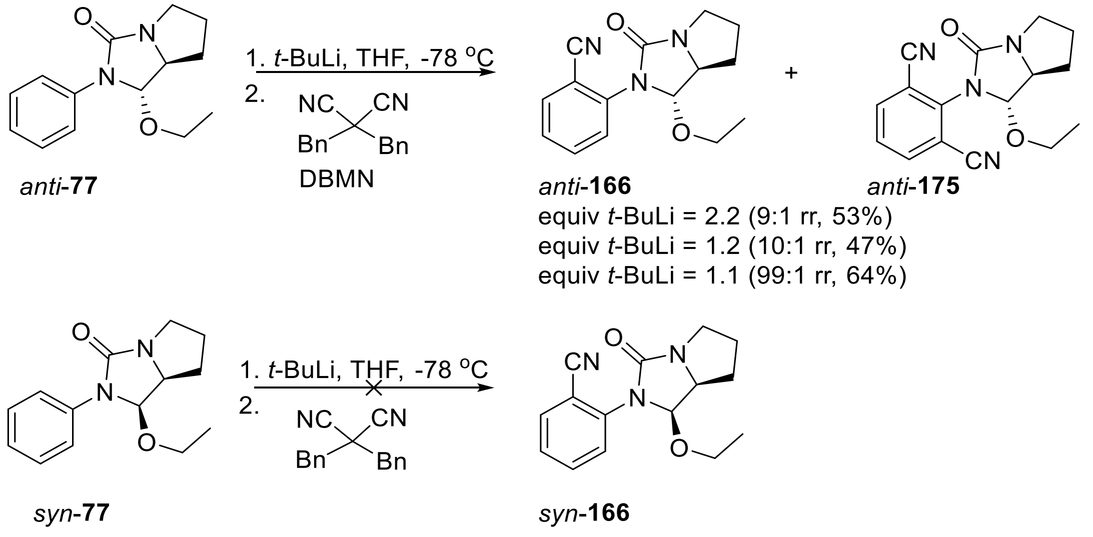

anti-172
1. Na, H2O, NH3(l), THF, -78°C
2. RX
174
EtO2C
R

174a-b	RX	R	yld, %	dr	dr (Ethoxy)
a	MeI	Me	87	68:32	53:47
b	EtI	Et	62	98:2	>95:5

Scheme 48 - One pot reductive alkylation of anti-**172**

3.4 Stereoselective reductive alkylation of a benzonitrile

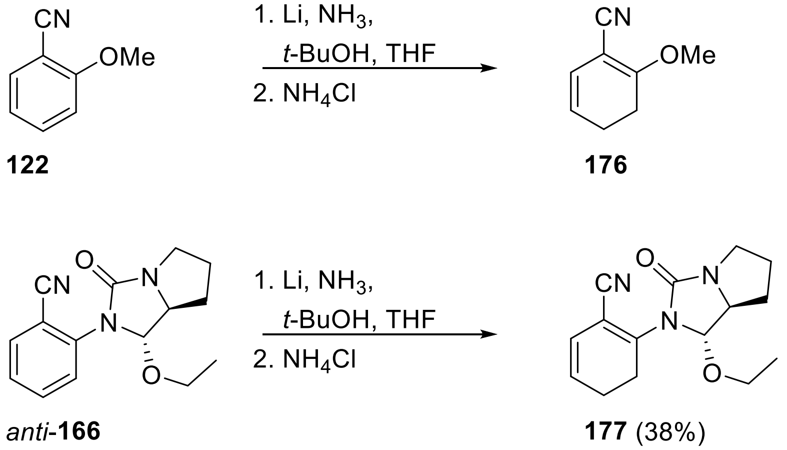
As previously described, Schultz[41] (Section 1.2.1) developed the reductive alkylation of benzonitrile and 2-methoxy benzonitrile. This methodology was limited to achiral or racemic products as the asymmetric alkylation reliant on enolate formation of a chiral benzamide. Incorporating a nitrile *ortho* to our *N*-based auxiliary on a phenyl ring allowed for chiral direction that was not part of the electron withdrawing group, while the nitrile could give an enolate-like intermediate that could be quenched with alkyl halides. The *ortho* nitrile was installed by directed metalation of *anti*-**77**, using DBMN in the electrophilic quench[57] (Scheme 49).


anti-77
1. t-BuLi, THF, -78 °C
2. NC CN Bn Bn
DBMN
anti-166
+
anti-175
equiv t-BuLi = 2.2 (9:1 rr, 53%)
equiv t-BuLi = 1.2 (10:1 rr, 47%)
equiv t-BuLi = 1.1 (99:1 rr, 64%)
syn-77
1. t-BuLi, THF, -78 °C
2. NC CN Bn Bn
syn-166

Scheme 49 - Synthesis of chiral auxiliary bound benzonitriles

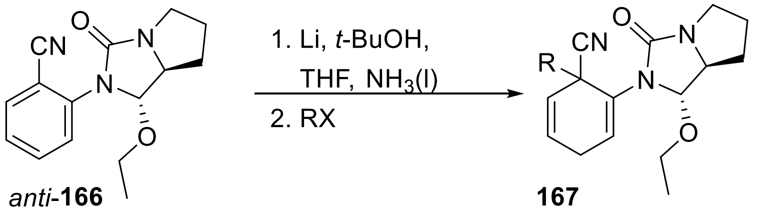
A moderate yield of *anti*-**166** was obtained but contained an impurity that was inseparable by column chromatography. The impurity is speculated to be a dinitrile substituted in both *ortho* positions of the aromatic ring relative to the auxiliary (*anti*-**175**). Evidence of this compound is observed in the ^{1}H NMR spectrum as a 0.4 Hz doublet at 5.6, characteristic of the oxygen and nitrogen bound methyne and the aromatic doublet at 8.2 ppm and a triplet at 7.8 ppm integrating half the area as the doublet, which is characteristic of a 1,2,3-trisubstituted aromatic ring. Reducing the molar equivalents of *t*-BuLi and DBMN from 2.2 to 1.1 resulted in an increase of yield from 53% to 64%, higher proportion (9:1 to 99:1) of monosubstituted product and could be purified by a single recrystallization. Attempts to synthesise a *syn*-**166** resulted in a very low yield of a yellow oil that is very impure by NMR after column chromatography.

In Shultz's initial reduction of benzonitriles it was discovered that quenching the Birch reduction of benzonitrile **122** and quenching with ammonium chloride lead to isolation of an achiral 1,3-cyclohexadiene **176** (Scheme 50) in a procedure nearly identical to our isolation of **159** and **173**, 1,4-cyclohexadienes. Following this procedure on our benzonitrile *anti*-**166** gives 1,3-diene **177**, analogous to Schultz' compound (Scheme 50). With potential isomerization being induced by acidic ammonium chloride, the reaction was worked up using only water. This results in isolation of **177** again, albeit in lower yield. Attempts to use these new dienes in Diels-Alder cycloadditions are currently underway in our lab.



Scheme 50 - Synthesis of achiral and novel chiral cyclohexadienes

With 1,4-diene isolation being problematic, a one-pot approach in the alkylative reduction was taken following the procedure of Schultz and others.[58,59] Reduction and alkylation of *anti*-**166** with iodoethane gave complete consumption of starting material but **167a** was found to be a mixture of diastereomers of 63:37 dr (Scheme 51). However, the diastereomers formed from the reaction were chromatographically separable, allowing for access of single compounds. Alkylation with benzyl bromide proceeded in moderate yield (64%) and similar selectivity (59:41 dr). Enolate quench with allyl bromide gives **167c** in moderate yield and 58:42 dr. Synthesis of methyl derivative, **167d**, proceeds in good yield (87%) and surprisingly similar dr to the other substrates. This compound proves to be the most difficult to separate, with the minor product trailing into the major during column chromatography. This resulted in the minor diastereomer of **167d** being obtained as an analytically pure sample, while the major product was always contaminated with the minor.



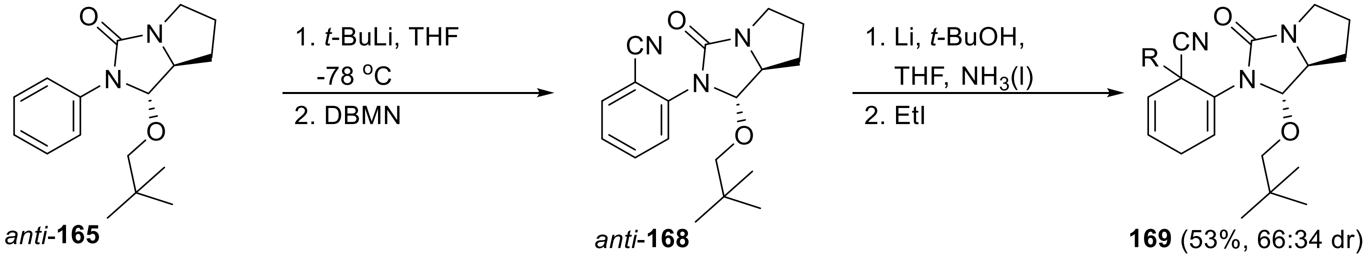
anti-**166**

167

167a-b	RX	R	yld, %	dr
a	EtI	Et	>95	63:37
b	BnBr	Bn	64	59:41
c	AllylBr	Allyl	70	58:42
d	MeI	Me	87	58:42

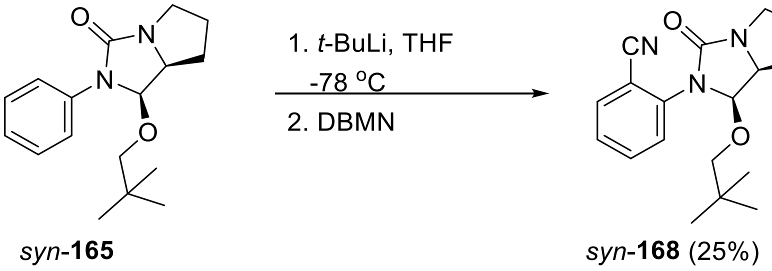
*Scheme 51 - Reductive alkylation of anti-**166***

To improve the stereoselectivity of the alkylation, neopentyl protected *anti*-**165** was subjected to cyannation conditions, using 1.1 equivalent of DBMN, yielded benzonitrile *anti*-**168**, with less than 5% bis nitrile impurity, as a yellow oil. Addition of less than one equivalent of DBMN gives *anti*-**168** as a single compound by NMR. After a scale-up of the reaction, several hundred milligrams of *anit*-**168** stored on the benchtop began to solidify. Recrystallization of the yellow amorphous solid lead to colourless, crystalline analytically pure solid. Subjecting *anti*-**168** to reductive alkylation conditions with lithium and quenching with iodoethane yielded **169** in 66:34 dr (Scheme 52). Replacing lithium with sodium resulted in an identical outcome regarding both yield and stereoselectivity.



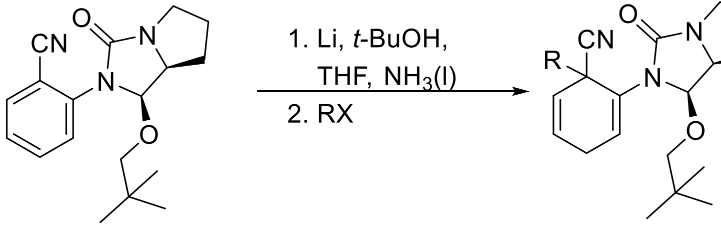
*Scheme 52 - Reductive alkylation of anti-**168***

With a larger directing alkoxy group demonstrating selectivity within experimental error to the reductive alkylation of *anti*-**166**, attempts to obtain dienes from a *syn* neopentyl made a viable alternative to obtaining *syn*-**166**. Lithiation and DBMN quench of *syn*-**165** does lead to benzonitrile *syn*-**168**, although in a 1:1 ratio with the bis-nitrile by-product. Decreased stoichiometry to 0.9 equivalents of *t*-BuLi and DBMN yielded an improved ratio of 3:1 in favour of the mono-nitrile. The impurity can be partially be removed by crystallizing the solid; however, the impurity is quite persistent, still appearing as about 4% of the sample after three recrystallizations. Using 0.8 equivalents of base and DBMN gives *syn*-**168** in 25% yield with 4% dinitrile after chromatography and can be completely removed by a single crystallization. Despite low yield, starting material *syn*-**168** could recovered by chromatography in 69% yield.



*Scheme 53 - Synthesis of syn-**168***

Birch reduction-alkylation sequence of *syn*-**168** with iodomethane gives **178a** (Scheme 54) as chromatographically isolable diastereomers in equimolar yields (1:1 dr). Quench with iodoethane gives **178b** in 48% yield and 69:31dr. These results greatly differ from the reductive alkylation of ester *syn*-**158**, which proceeded with excellent selectivity (Scheme 36).

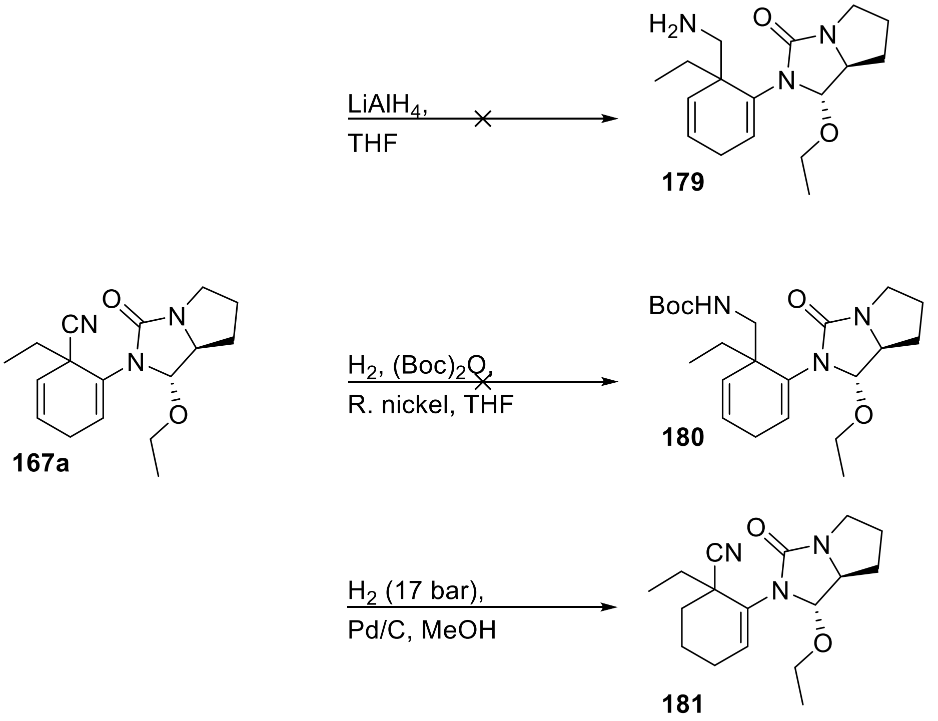


syn-**168** **178**

178a-b	RX	R	Yield (%)	dr
a	MeI	Me	66	1:1
b	EtI	Et	48	69:31

*Scheme 54 - Reductive alkylation of syn-**168***

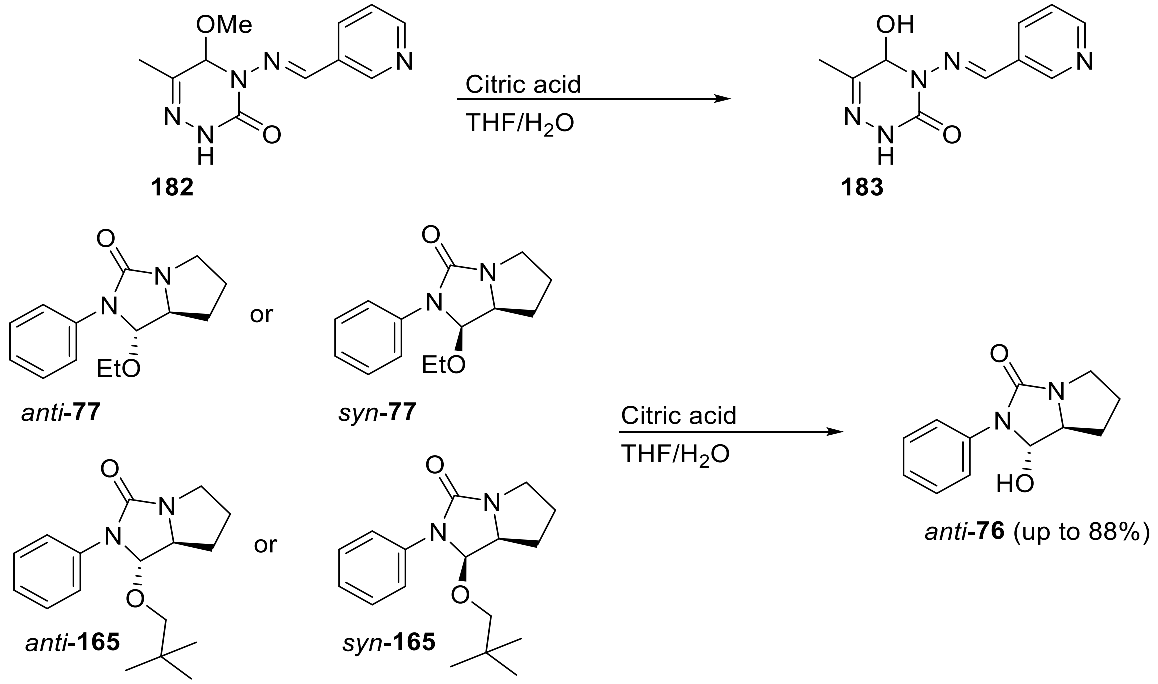
To determine the absolute stereochemistry of the alkylated compounds, it was envisioned that a solid compound could be obtained by reduction of the nitrile moiety. This was observed in the ester system, with reduction to the crystalline alcohol **162** showing hydrogen bonding to the urea carbonyl oxygen in the X-ray crystal structure. This could potentially be mimicked in the nitrile case by reduction to a primary amine in the same position. The first attempt to reduce **167a** with $LiAlH_4$ in THF at room temperature resulted only in recollection of starting material. Hydrogenation with Raney nickel in the presence of di-tert-butyl decarbonate[60] gave a complex mixture of products that could not be characterized. The nitrile of functionality of **167a** proved to be extremely persistent; hydrogenation in the presence of palladium on carbon at 17 bar resulted in only reduction of the disubstituted alkene to obtain acyl enamine **181**.



Scheme 55 - Attempts to reduce the nitrile functionality of ***167a***

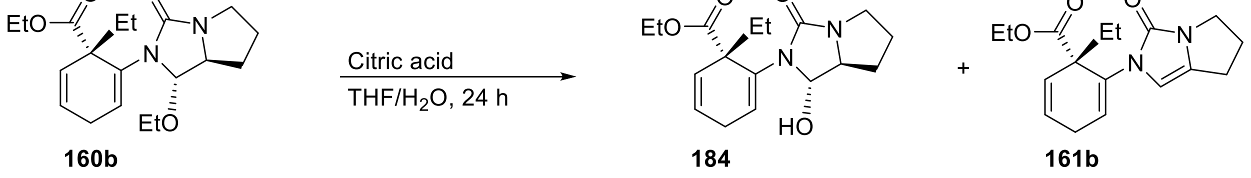
3.5 Manipulation of chiral auxiliary

To demonstrate the utility of the *N*-based auxiliary developed by the Metallinos group, we have investigated chemical manipulability of the alkyl hemiaminal ether moiety. While desilylation of *syn*-**68** was done in a facile manner (Scheme 14), removal of the alkyl group proved to be more challenging. Citric acid catalyzed removal, demonstrated by Hudlicky in the synthesis of azathymine derivative **183**[61] involving the protonation of the ether, ejection of alkoxy group promoted by iminium formation and attack by water was screened. The main issue of acid catalyzed deprotection is that a source of protons also creates a path to an imidazolone by elimination of alcohol.


182
Citric acid
THF/H2O
183
anti-77
or
syn-77
anti-165
or
syn-165
Citric acid
THF/H2O
anti-76 (up to 88%)

Scheme 56 - Hudlicky's acid catalyzed deprotection and adaptation to our system

Initial studies on aromatic compounds *syn* and *anti*-**77** showed great potential, with no elimination product observed and hemiaminal **76** in exclusively *anti* configuration. Identical results were observed in deprotection of *syn* and *anti*-**165** (Scheme 56). This was determined by the *J* coupling values of the methyne alpha to oxygen and nitrogen after deuterium exchange. Deprotection of the alkylated diene **160b** was more troublesome with elimination product **161b** being observed. It was found dissolving the reactant in minimal THF (1.0 M), and diluting to 0.2 M, with respect to water in a 1% by weight citric acid solution gave a majority of hemiaminal **184** over elimination product (3:2). The hemiaminal was isolated entirely in *anti* configuration, analogous to the aromatic model study product (Scheme 57).

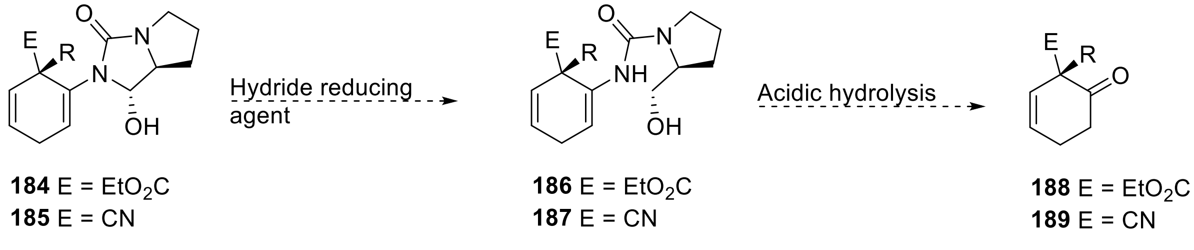

160b
Citric acid
THF/H2O, 24 h
184
+
161b

Scheme 57 - Deprotection of reductive alkylation products

4. Conclusion and Future Work

Attempts to synthesize NHC precursor **164** by oxidation of aminal **95** by several methods were shown to be unfruitful. It is likely that the free hydroxyl group interferes with the oxidation process as no aminal oxidations to iminium have been reported in the presence of intramolecular alcohol groups. Protection of the alcohol as a silyl ether may allow for oxidation to proceed as in the cases of aminals **83** and **87**. Attempts to synthesize an analog of **92** that could annulated as a morpholine rather than a highly strained oxazolidine, or a five membered cyclic system that is stable to reduction, also proved difficult.

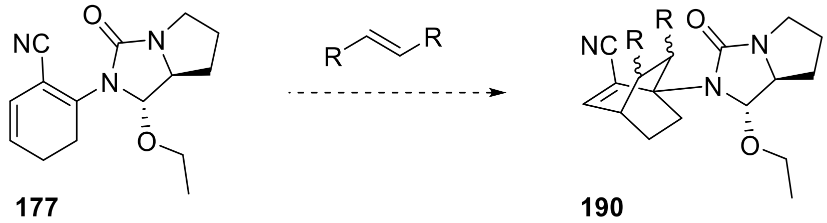
Neopentyl protected hemiaminal ethers *syn* and *anti*-**165** were synthesized to improve the selectivity of alkylative Birch reductions of esters derived from *anti*-**77**. Initial experiments found that the neopentyl protecting group generally increases the diastereoselectivity observed in cyclohexadiene products bearing *anti* configuration of the protected hemiaminal. Acidic hydrolysis was demonstrated to be efficient at deprotecting the ether moiety of aromatic compounds of either configuration to obtain *anti*-**76**. This method was also shown to deprotect the cyclohexadiene hemiaminal ethers **160**, although imidazolone **161** was observed as a major by-product by elimination of ethanol or water. Future work regarding these auxiliaries will focus on full removal and partial recyclability by reductive ring opening and hydrolysis of the secondary urea (Scheme 58).



Scheme 58 - Planned removal of the chiral auxilliary

A new benzonitrile class of the imidazolidinone chiral auxiliaries was also synthesized by directed ortho metalation. Reductive alkylation of the compounds in *anti* configuration, i.e. *anti*-

166, proceeded in low to moderate selectivity of dihydrobenzonitriles but resulted in chromatographically separable diastereomers. Preparation of *syn*-**166** proved to be impractical but neopentyl derivative *syn*-**168** was obtained with minor optimization of reagent stoichiometry but in low yield. The diastereomers of the *syn* reduction products **178** were obtained in nearly equal yields. Despite disappointing diasteromeric ratios, this method represents the first preparation of optically pure alpha quaternary nitriles *via* a Birch reduction pathway. The 1,3-diene **177** can also be reached by acidic quench of the Birch reduction in the absence of an organohalide and can be a potential reactant in Diels-Alder cycloadditions (Scheme 59). Manipulation of the auxiliary of nitrile compounds will also be explored in our lab (Scheme 58).

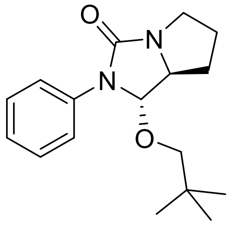


Scheme 59 - Potential cycloadditions of diene ***179***

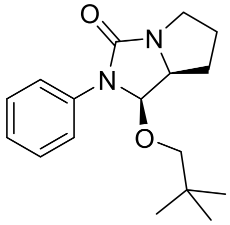
5. Experimental

General. All reagents were purchased from Aldrich, Fisher Scientific, Acros, Strem or Oakwood chemicals and used as received unless otherwise indicated. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone ketyl under an atmosphere of nitrogen. Toluene was distilled from sodium under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. All alkyllithiums were titrated against N-benzylbenzamide to a blue endpoint.[62] All reactions were performed under nitrogen or argon in flame- or oven-dried glassware using syringe-septum cap techniques unless otherwise indicated. All reactions were run in round-bottom flasks with magnetic stir bars unless otherwise noted. The size/volume of the glassware used in all reactions was dictated by the amount of solvent required, such that each reaction vessel was no more than half-full. TLC was performed on silica gel. Column chromatography was performed on silica gel 60 (70-230 mesh). Schwartz's reagent was prepared according to a literature procedure.[63] Triethyloxonium tetrafluoroborate was prepared according to literature procedures.[64] NMR spectra were obtained at room temperature, unless otherwise stated, on a Bruker Avance 300, 400 or 600 MHz instrument and are 94 referenced to the residual proton signal of the deuterated solvent for 1H spectra, and to the carbon multiplet of the deuterated solvent for 13C spectra according to published values. FT-IR spectra were obtained on Bruker ALPHA platinum ATR spectrometer as neat materials. Specific rotations of diastereomerically and enantiomerically pure materials were measured on a Rudolph Research Autopol III automatic polarimeter. Mass spectra were obtained on a Micromass GCT spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

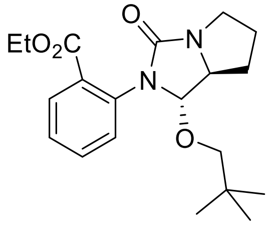
165: To a stirred solution of hemiaminal **76** (0.305 g, 1.40 mmol) in neopentyl alcohol (5 mL) and CH_2Cl_2 (5 mL) was added *p*-toluenesulfonic acid monohydrate (0.266 g, 1.40 mmol). After stirring for 30 minutes at room temperature, the reaction mixture was treated with sat. aq. $NaHCO_3$ solution (10 mL) and extracted with EtOAc (10 mL). The organic extract was washed twice with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes/EtOAc) gave, sequentially, *anti*-**165** (R_f = 0.45) and *syn*-**165** (R_f = 0.29)



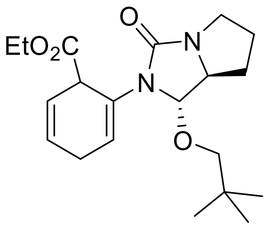
anti-**165**: Colourless crystals (0.262 g, 0.91 mmol, 65%); mp 99 – 100 ^{o}C; [α] 8.1 (c 1.0, acetone); IR (ATR, solid) ν_{max} 2954, 1697, 1601, 1400, 1084 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.70 (dd, 2H, *J* = 8.84, 1.08 Hz), 7.32 (m, 2H), 7.07 (tt, 1H, *J* = 7.36, 1.04 Hz), 5.57 (s, 1H), 3.68 – 3.61 (m, 2H), 3.20 (d, 1H, *J* = 8.4 Hz), 3.14 (d, 1H, *J* = 8.4 Hz), 3.09 (m, 1H), 2.12 (m, 1H), 2.0 – 1.85 (m, 2H), 1.44 (m, 1H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 162.4, 141.0, 130.1, 124.9, 121.5, 89.4, 75.4, 63.8, 47.0, 32.9, 30.1, 27.8, 26.1; EI-MS [m/z (%)] 288 (M+ 100), 218 (15), 217 (25); HRMS (EI) calcd. for $C_{17}H_{24}O_2N_2$ 288.1838; found: 288.1829.



syn-**165**: Colourless crystals (0.064 g, 0.22mmol, 16%); mp 117 – 118 ^{o}C; [α] -105.5 (c 1.05, acetone); IR (ATR, solid) ν_{max} 2950, 2866, 1693, 1598, 1403, 1097 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.57 (dd, 2H, *J* = 8, 1.08 Hz), 7.30 (tt, 2H, *J* = 7.44, 2.08,Hz), 7.06 (tt, 1H, *J* = 6.36, 1.08), 5.47 (d, 1H, *J* = 6.6 Hz), 4.11 (m, 1H), 3.52 (m, 1H), 3.25 (dd, 2H, *J* = 18.72, 1.76 Hz), 3.08 (m, 1H), 1.98 (m, 4H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 159.8, 141.4, 130.0, 125.0, 122.2, 88.7, 80.2, 61.8, 46.7, 33.5, 27.9, 27.7, 26.3; ; EI-MS [m/z (%)] 288 (M$^+$ 76), 217 (32), 200 (100), 171 (71); HRMS (EI) calcd. For $C_{17}H_{24}O_2N_2$ 288.1838; found: 288.1836.

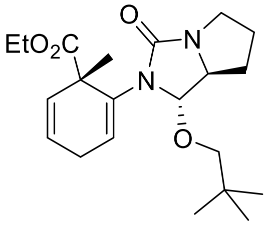


anti-**172:** A -78 ^{o}C solution of *anti*-**165** (0.449 g, 1.56 mmol) in THF was treated dropwise with *t*-BuLi (2.74 mL, 1.14 M, 3.11 mmol) giving a yellow solution. After 1 h the solution was treated with ethylchloroformate (0.3 mL, 3.11 mmol) causing the reaction mixture to turn dark brown/green. After another 1 h of stirring, the reaction was allowed to reach room temperature over 30 min upon which it was quenched with 3 mL of water. The mixture was extracted with EtOAc (10 mL), washed with brine, dried over Na_2SO_4 and the organic extract was concentrated under reduced pressure. Flash column chromatography (7:3 hexanes/EtOAc, $R_f = 0.29$) gave ester *anti*-**172** (0.241 g, 43%) as a colourless oil; [α] -7.0 (c 0.95, acetone); IR (ATR, solid) ν_{max} 2954, 1713, 1601, 1492, 1252, 1080 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.82 (dd, 1H, *J* = 7.92, 1.52 Hz), 7.57 (td, 1H, *J* = 7.44, 1.6 Hz), 7.49 (dd, 1H, *J* = 7.92, 1.16 Hz), 7.36 (td, 1H, *J* = 7.44, 1.32 Hz), 5.39 (d, 1H, *J* = 0.84 Hz), 4.26 (m, 2H), 3.69 (ddd, 1H, *J* = 9.66, 6.56, 0.84 Hz), 3.56 (m, 1H), 3.27 (d, 1H, *J* = 8.64 Hz), 3.13 (d, 1H, *J* = 8.68 Hz), 3.05 (m, 1H), 2.09 (1H, m), 2.00 (m, 1H), 1.88 (m, 1H), 1.73 (m, 1H,), 1.33 (t, 3H, *J* = 7.12 Hz), 0.86 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.7, 161.8, 138.18, 132.5, 130.9, 129.8, 128.4, 126.8, 91.54, 76.4, 64.1, 61.2, 45.9, 32.1, 31.2, 26.7, 25.4, 14.3; EI-MS [m/z (%)] 360 (M+ 5), 289 (73), 272 (100), 243 (67), 227 (68), 200 (74); HRMS (EI) calcd. for $C_{20}H_{28}O_4N_2$ 360.2049; found: 360.2050.

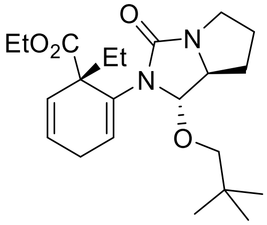


anti-**173**: Ester *anti*-**172** (0.24 g, 0.67 mmol) and water (0.02 ml, 1 mmol) were dissolved in THF (5 mL) and sequentially treated with liquid ammonia at -78 °C. To the ammonia solution was added sodium metal (0.038 g, 1.67 mmol) in small portions to give a deep blue reaction mixture. After stirring for 5 h, the reaction was quenched with sat. aq. NH_4Cl and the cold bath was removed. After evaporation of liquid ammonia, the reaction was extracted with EtOAc (10 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (8:2 hexanes/EtOAc, $R_f = 0.3$) gave diene *anti*-**173** as a colourless oil (0.144 g, 0.40 mmol, 59%): [α] -61.1 (c 5.9, acetone); IR (ATR, solid) ν_{max} 2954, 2901, 2868, 1731, 1708, 1398, 1073 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 5.89 (t, 1H, *J* = 3.70 Hz), 5.83 (m, 1H), 5.75 (m, 1H), 5.03 (s, 1H), 4.81 (broad m, 1H), 4.07 (m, 2H), 3.49 (m, 2H), 3.17 (s, 2H), 2.96 (m, 1H), 2.83 (broad m, 2H), 2.02 (m, 1H), 1.83 (m, 2H), 1.35 (m, 1H), 1.21 (t, 3H, *J* = 7.12 Hz), 0.95 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.6, 162.8, 133.7, 126.9, 124.0, 116.2, 91.9, 75.1, 64.8, 61.9, 47.9, 44.8, 32.9, 31.3, 29.7, 27.9, 27.6, 25.9, 15.2; ESIMS [m/z (%)] 401

(M+K, 22), 385 (M+Na, 100), 363 (M+H$^+$, 25); EI-MS [m/z (%)] 362 (M+ <1), 273 (62), 227 (100), 201 (16); HRMS (EI) calcd. for $C_{20}H_{30}O_4N_2$ 362.2206; found: 362.2202.

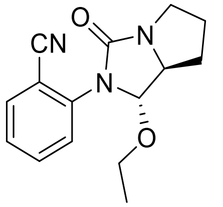


174a: LDA (0.14 mL, 1.19 M, 0.17 mmol) was added dropwise to a colourless solution of *anti*-**173** (0.03 g, 0.08 mmol) in THF at -78 ^oC turning the reaction orange. After 1 h of stirring the reaction mixture was treated with iodomethane (0.01 mL, 0.17 mmol) and allowed to slowly warm to 0 ^oC at which point it was quenched with water (2 mL). The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes/EtOAc, R_f = 0.15) gave colourless oil **174a** as a 71:29 ratio of inseparable diastereomers (0.023 g, 74%); IR (ATR, solid) ν_{max} 2954, 2902, 2868, 1715, 1682, 1399, 1218, 1074 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) (major isomer) δ 5.93 (m, 1H) 5.79 (m, 1H5.), 5.53 (m, 1H), 4.98 (s, 1H), 4.03 (m, 2H), 3.52 (m, 2H), 3.19 (m, 2H), 2.97 (m, 1H), 2.85 (m, 1H), 2.81 (m, 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.35 (s, 3H), 1.16 (t, 3H, J = 7.1 Hz), 0.93 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.2, 162.5, 135.8, 131.9, 124.1, 121.4, 91.0, 75.1, 64.2, 61.1, 48.6, 46.5, 32.2, 27.6, 27.1, 25.3, 24.1, 23.8, 14.4; EI-MS [m/z (%)] 376 (M+ 5), 331 (9), 303 (100), 288 (24), 243 (23), 215 (87); HRMS (EI) calcd. for $C_{21}H_{32}O_4N_2$ 376.2362; found: 376.2350.

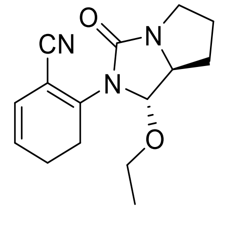


174b: LDA (0.21 mL, 1.19 M, 0.25 mmol) was added dropwise to a colourless solution of *anti*-**173** (0.045 g, 0.08 mmol) in THF at -78 ^oC turning the reaction orange. After 1 h of stirring the reaction mixture was treated with iodoethane (0.02 mL, 0.25 mmol) and allowed to slowly warm to 0 ^oC at which point it was quenched with water (2 mL). The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (8:2 hexanes/EtOAc, R_f = 0.1) gave **174b** as a 89:11 ratio of diastereomers (21 mg, 43%). IR (ATR, solid) ν_{max} 2974, 2936, 1721, 1657, 1366, 1070 cm^{-1}; ^1H

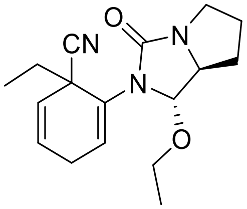
NMR (400 MHz, acetone-d_6) δ 6.03 (td, 1H, *J* = 3.7, 1.3 Hz), 5.88 (dtd, 1H, *J* = 10.0, 3.3, 1.3 Hz), 5.40 (dt, 1H, *J* = 9.9, 2.0 Hz), 5.00 (s, 1H), 4.02 (m, 2H), 3.51 (m, 2H), 3.20 (d, 1H, *J* = 8.7 Hz), 3.14 (d, 1H, *J* = 8.7 Hz), 2.97 (m, 1H), 2.82 (m, 2H), 1.97 (m, 2H), 1.86 (m, 2H), 1.73 (m, 1H), 1.33 (m, 1H), 1.16 (t, 3H, *J* = 7.4 Hz), 0.93 (s, 9H), 0.75 (t, 3H, *J* = 7.6); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.0, 162.5, 133.1, 129.6, 125.4, 123.3, 90.4, 74.8, 63.9, 61.0, 53.2, 46.6, 32.2, 28.9, 28.5, 27.7, 27.2, 25.3, 14.4, 9.1; EI-MS [m/z (%)] 390 (M+ 15), 345 (10), 317 (100), 302 (34), 229 (86); HRMS (EI) calcd. for $C_{22}H_{34}O_4N_2$ 390.2519; found: 390.2513.



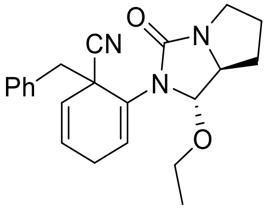
anti-**166**: A -78 °C solution of *anti*-**165** (1.16g, 4.70 mmol) in THF was treated dropwise with *t*-BuLi (3.86 mL, 1.34 M, 5.17 mmol) giving a yellow-orange solution. After one hour stirring the, a THF solution of DBMN (1.273 g, 5.17 mmol) was added to the reaction mixture causing a gradual change in colour to dark red and was let to stir for another hour. At this time the reaction was allowed to warm to room temperature for one final hour. The reaction mixture was quenched with water and extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (65:35 hexanes/EtOAc, R_f = 0.15) gave *anti*-**166** as a pale yellow oil that crystalized upon standing. (0.82 g, 3.02 mmol, 64%); 101 – 104 °C (EtOH/Hexanes); [α] -8.9 (c 1.2, acetone); IR (ATR, solid) ν_{max} 2974, 2230, 1713, 1594, 1396, 1076 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.83 (d, 1H, *J* = 5.6 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 7.50 (t, 1H, *J* = 7.6 Hz), 5.6 (s, 1H), 3.7 (dd, 1H, *J* = 9.6, 6.2 Hz), 3.59 (m, 2H), 3.48 (m, 1H), 3.09 (m, 1H), 2.15 (m, 1H), 2.03 – 1.87 (m, 2H), 1.62 (m, 1H), 1.08 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.3, 141.6, 134.5, 134.3, 129.3, 128.2, 117.4, 112.6, 90.4, 64.8, 62.7, 46.2, 29.0, 25.4, 15.5; EI-MS [m/z (%)] 271 (M+ 47), 242 (18), 226; HRMS (EI) calcd. For $C_{15}H_{17}O_2N_3$ 271.1321 found: 271.1315.



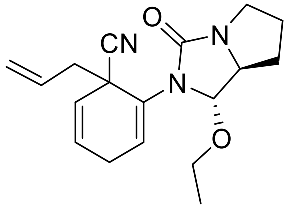
177: To a -78 ^{o}C solution of nitrile *anti*-**166** (40 mg, 0.15 mmol) and *t*-BuOH (11 mg, 0.15 mmol) in THF and liquid NH_3 was added lithium metal (3 mg, 0.37 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was quenched with 1 mL of saturated aqueous NH_4Cl solution then warmed to room temperature to allow evaporation of NH_3. The residue was extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes/EtOAc R_f = 0.16) gave **177** as a clear and colourless oil (15 mg, 0.05 mmol, 37%); [α] -301.3 (c 0.54, acetone) IR (ATR, solid) ν_{max} 2974, 2213, 1714, 1384, 1070 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.93 (m, 2H), 5.65 (s, 1H), 3.65 (m, 3H), 3.55 (m, 1H), 3.07 (m, 1H), 2.90 (m, 1H), 2.32 (m, 3H), 2.13 (m, 1H), 1.99 (m, 1H), 1.90 (m, 1H), 1.46 (m, 1H), 1.17 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 159.5, 149.0, 126.7, 122.7, 117.7, 101.2, 88.4, 64.4, 62.3, 45.9, 29.2, 26.5, 25.3, 22.6, 15.6; EI-MS [m/z (%)] 273 (M+ 17), 244 (7), 228(12), 84 (100); HRMS (EI) calcd. For $C_{15}H_{19}O_2N_3$ 273.1477 found: 273.1467.



167a: To a -78 ^{o}C solution of nitrile *anti*-**166** (54 mg, 0.20 mmol) and *t*-BuOH (15 mg, 0.20 mmol) in THF and liquid NH_3 was added lithium metal (4 mg, 0.5 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with iodoethane (0.04 mL, 0.40 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes:EtOAc) gave **18a** as separable diastereomers, both as a clear and colourless oil. **Major** (39 mg, 0.13 mmol, 65%); (R_f = 0.10); [α] -3.0 (c = 1.3, acetone): IR (ATR, solid) ν_{max} 2973, 2233, 1713, 1396, 1076 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 6.05 (dtd, 1H, *J* = 9.6, 3.4, 1.6 Hz), 5.98 (td, 1H, *J* = 3.9, 1.3 Hz), 5.69 (dt, 1H, *J* = 9.6, 2.3 Hz), 5.10 (s, 1H), 3.57 (m, 5H), 3.02 (m, 1H), 2.14 (m, 2H), 1.91 (m, 3H), 1.42 (m, 2H), 1.18 (t, 3H, *J* = 6.9 Hz), 0.91 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 162.9, 129.3, 129.1, 127.4, 126.3, 121.5, 90.2, 63.8, 61.3, 46.4, 42.6, 32.8, 29.0, 27.9, 25.3, 15.4, 8.2; EI-MS [m/z (%)] 301 (M+ 43), 272 (45), 256 (29), 229 (17), 124 (100); HRMS (EI) calcd. For $C_{17}H_{23}O_2N_3$ 301.1790 found: 301.1788; **Minor**: (23 mg, 0.08 mmol, 35%); (R_f = 0.05); [α] -62.4 (c = 0.26, acetone): IR (ATR, solid) ν_{max} 2930, 2229, 1712, 1406, 1085 1H NMR (400 MHz, acetone-d$_6$) 6.06 (dtd, 1H, *J* = 9.8, 3.5, 1.4 Hz), 6.02 (td, 1H, *J* = 3.6, 1.4 Hz), 5.30 (s, 1H), 3.64 (q, 2H, *J* = 7.1 Hz), 3.6 (m, 2H), 3.02 (m, 1H), 2.9 (m, 2H, behind water), 2.09 (m, 1H), 1.98 – 1.79 (m, 4H), 1.41 (m, 1H), 1.16 (t, 3H, *J* = 7.0 Hz), 0.93 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 163.3, 131.7, 128.2, 127.7, 125.4, 122.5, 89.1, 64.7, 63.3, 46.5, 41.6, 32.5, 28.8, 27.9, 25.5, 15.6, 8.4; EI-MS [m/z (%)] 301 (M+ 17), 272 (23), 256 (15), 142 (100); HRMS (EI) calcd. for $C_{17}H_{23}O_2N_3$ 301.1790 found: 301.1785.

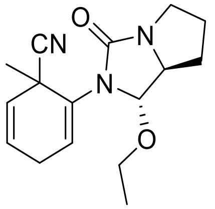


167b: To a -78 °C solution of nitrile *anti*-**166** (65 mg, 0.24 mmol) and *t*-BuOH (18 mg, 0.24 mmol) in THF and liquid NH_3 was added lithium metal (5 mg, 0.60 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with benzyl bromide (0.06 mL, 0.48 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes:EtOAc) gave separable diastereomers, both as a clear and colourless oil. **Major:** (33 mg, 0.09 mmol, 38%), (R_f = 0.12), [α] 24.3 (c = 1.38, acetone); IR (ATR, solid) ν_{max} 2973, 2231, 1710, 1397, 1073 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.39 (m, 2H), 7.30 (m, 3H), 6.05 (m, 1H), 5.90 (m, 1H), 5.51 (dt,1H, *J* = 9.9, 1.66 Hz), 5.33 (s, 1H), 3.64 (m, 4H), 3.27 (d, 1H, *J* = 12.8 Hz), 3.17 (d, 1H, *J* = 12.8 Hz), 3.06 (m, 1H), 2.82 (m, 2H), 2.60 (m, 1H), 2.11 (m, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.54 (m, 1H), 1.17 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 163.6, 135.8, 132.0, 131.4, 129.7, 128.7, 127.9, 127.3, 125.6, 121.7, 89.8, 65.0, 63.4, 46.5, 45.7, 42.9, 28.9, 27.8, 25.6, 15.6; EI-MS [m/z (%)] 363 (M+ 11), 318 (11), 290 (100), 284 (8); HRMS (EI) calcd. for $C_{22}H_{25}O_2N_3$ 363.1947 found: 363.1944; **Minor:** (23 mg, 0.06 mmol, 26%), (R_f = 0.09), [α]   -160.1 (c = 1.05, acetone): IR (ATR, solid) ν_{max} 2975, 2237, 1712, 1395, 1074 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.36 (m, 2H), 7.28 (m, 3H), 5.95 (m, 1H), 5.89 (m, 1H), 5.36 (s, 1H), 3.67 (m, 4H), 3.44 (d, 1H, *J* = 12.9 Hz), 3.18 (d, 1H, *J* = 12.9 Hz), 3.05 (m, 1H), 2.73 (m, 1H), 2.31 (m, 1H), 2.11 (m, 1H), 1.96 (m, 1H), 1.88 (m, 1H), 1.55 (m, 1H), 1.27 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.9, 135.6, 132.2, 130.2, 128.6, 128.5, 127.9, 127.5, 126.2, 121.0, 90.3, 63.8, 61.3, 46.4, 45.5, 43.5, 29.0, 27.6, 25.3, 15.5; EI-MS [m/z (%)] 363 (M+ 24), 318 (17), 290 (10), 226 (100); HRMS (EI) calcd. for $C_{22}H_{25}O_2N_3$ 363.1947 found: 363.1942;



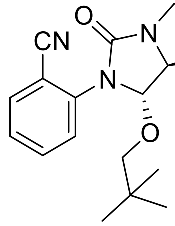
167c: To a -78 °C solution of nitrile *anti*-**166** (75 mg, 0.28 mmol) and *t*-BuOH (20 mg, 0.28 mmol) in THF and liquid NH_3 was added lithium metal (5 mg, 0.69 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with allyl bromide (0.05 mL, 0.55 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography gave separable diastereomers, both as a clear and colourless oil. **Major**: (35 mg, 0.11 mmol, 40%); (R_f = 0.12); [α] -51.7 (c = 1.3, acetone): IR (ATR, solid) ν_{max} 2975, 2933, 2898, 2228, 1711, 1398, 1076 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.01 (m, 2H), 5.91 (m, 1H), 5.68 (dt, 1H, *J* = 9.7, 1.9 Hz), 5.30 (s, 1H), 5.14 (m, 2H), 3.66 (q, 2H, *J* = 7.0 Hz), 3.58 (m, 2H), 3.02 (m, 1H), 2.89 (m, 2H), 2.60 (d, 2H, *J* = 7.2 Hz), 2.09 (m, 1H), 1.91 (m, 1H), 1.44 (m, 1H), 1.16 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.3, 132.9, 131.8, 128.6, 127.2, 125.5, 121.8, 120.1, 89.3, 64.9, 63.5, 46.4, 43.9, 41.2, 28.8, 27.9, 25.5, 15.6; EI-MS [m/z (%)] 313 (M+ 16), 284 (6), 266 (70), 85 (100); HRMS (EI) calcd. for $C_{18}H_{23}O_2N_3$ 313.1790 found: 313.1783; **Minor**: (25 mg, 0.08

mmol, 29%); ($R_f = 0.05$), [α] -12.5 (c = 1.0, acetone); IR (ATR, solid) ν_{max} 2975, 2931, 2899, 2228, 1711, 1398, 1076 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 6.00 (m, 2H), 5.82 (m, 1H), 5.72 (dt, 1H, *J* = 9.6, 2.0 Hz), 5.16 (m, 2H), 5.12 (s, 1H), 3.59 (m, 4H), 3.02 (m, 1H), 2.86 (m, 2H), 2.75 (m, 2H), 2.06 (m, 1H, behind acetone), 1.89 (m, 2H), 1.44 (m, 1H), 1.18 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 163.0, 132.6, 129.8, 129.2, 127.0, 126.4, 120.9, 120.2, 90.5, 64.0, 61.5, 46.4, 43.5, 41.9, 29.0, 27.9, 25.3, 15.4; EI-MS [m/z (%)] 313 (M+ 4), 266 (19), 71 (100); HRMS (EI) calcd. for $C_{18}H_{23}O_2N_3$ 313.1790 found: 313.1783.

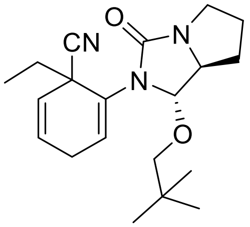


167d: To a -78 °C solution of nitrile *anti*-**166** (75 mg, 0.28 mmol) and *t*-BuOH (20 mg, 0.28 mmol) in THF and liquid NH_3 was added lithium metal (5 mg, 0.69 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with iodomethane (0.04 mL, 0.55 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography gave separable diastereomers, both as a clear and colourless oil. **Major**: (43 mg, 0.15 mmol, 53%); ($R_f = 0.09$); [α] -116.5 (c = 0.5, acetone); IR (ATR, solid) ν_{max} 2976, 2933, 2899, 2234, 1710, 1401, 1075 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.95 (m, 2H), 5.77 (dt, 1H, *J* = 10.0, 2.0 Hz), 5.28 (s, 1H), 3.66 (q, 2H, *J* = 6.9 Hz), 3.58 (m, 2H), 3.02 (m, 1H), 2.93 (m, 2H), 2.10 (m, 1H), 1.91 (m, 2H), 1.52 (s, 3H), 1.43 (m, 1H), 1.17 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 163.3, 130.6, 130.0, 127.6, 126.1, 122.8, 89.3, 64.9, 63.4, 46.5, 37.1, 29.0, 27.8, 27.2, 25.5, 15.6; EI-MS [m/z (%)]287 (M+ 50), 272 (26), 258 (14), 241 (100), 215 (21); HRMS (EI) calcd. for $C_{16}H_{21}O_2N_3$ 287.1634 found: 287.1624; **Minor**: (26 mg, 0.09 mmol, 33%); ($R_f = 0.06$); IR (ATR, solid) ν_{max} 2975, 2932, 2899, 2235, 1713, 1398, 1076 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.94 (m, 2H), 5.79 (dt, 1H, *J* = 9.6, 2.0 Hz), 5.09 (s, 1H), 3.60 (m, 4H), 3.01 (m, 1H), 2.90 (m, 2H), 2.06 (m, 1H, behind acetone), 1.90 (m, 2H), 1.62 (s, 3H), 1.44 (m, 1H), 1.18 (t, 3H, *J* =

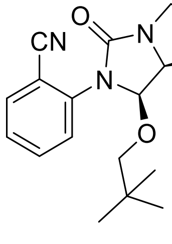
6.9 Hz); NMR (100 MHz, acetone-d_6) δ 162.9, 131.9, 128.8, 128.0, 125.8, 121.8, 90.9, 64.2, 61.9, 46.4, 37.9, 29.0, 27.7, 27.4, 25.3, 15.5; EI-MS [m/z (%)] 287 (M+ 41), 258 (12), 241 (87), 215 (16), 70 (100); HRMS (EI) calcd. for $C_{16}H_{21}O_2N_3$ 287.1634 found: 287.1628.



anti-**168**: A -78 °C solution of *anti*-**165** (1.18 g, 4.08 mmol) in THF (20 mL) was treated dropwise with *t*-BuLi (3.36 mL, 1.34 M, 4.49 mmol) giving a yellow-red solution. After one hour of stirring , a THF solution of DBMN (1.11 g 0.9 M, 4.49 mmol) was added to the reaction mixture causing a gradual change in colour to dark red and was let to stir for another hour after which the reaction was warmed to room temperature and stirred for more hour. The reaction mixture was quenched with water (10 ml) and extracted with EtOAc (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (85:15 to 7:3 hexanes/EtOAc, $R_f = 0.18$) gave *anti*-**181** as a yellow oil that crystalized upon standing. (0.563 g, 1.77 mmol, 43%) 99-101 °C (acetone/hexanes); [α] -5.2 (c 1.0, acetone); IR (ATR, solid) ν_{max} 2953, 2228, 1398, 1079 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.82 (dd, 1H, *J* = 7.8, 1.4 Hz), 7.75 (1H, td, *J* = 7.9, 1.4 Hz), 7.61 (dd, 1H, *J* = 8.0, 0.75 Hz), 7.49 (td, 1H, *J* = 7.6, 1.1 Hz), 5.58 (d, 1H, *J* = 0.32 Hz), 3.75 (dd, 1H, *J* = 9.9, 6.26 Hz), 3.62 (m, 1H), 3.26 (d, 1H, *J* = 8.7 Hz), 3.10 (m, 1H), 3.09 (d, 1H, *J* = 8.7 Hz), 2.16 (m, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.63 (m, 1H), 0.81 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.2, 141.5, 134.4, 134.2, 129.4, 128.1, 117.4, 112.6, 90.8, 77.1, 64.3, 46.1, 32.3, 29.0, 26.7, 25.4; EI-MS [m/z (%)] 313 (M+ 17), 242 (7), 226(100), 225 (35); HRMS (EI) calcd. For $C_{18}H_{23}O_2N_3$ 313.1790 found: 313.1784.

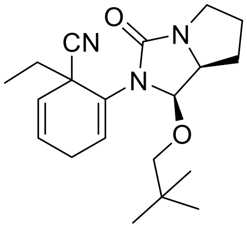


169: To a -78 °C solution of nitrile *anti*-**168** (85 mg, 0.27 mmol) and *t*-BuOH (20 mg, 0.27 mmol) in THF and liquid NH_3 was added lithium metal (5 mg, 0.67 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with iodoethane (0.04 mL, 0.53 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography gave **182** as separable diastereomers; the major as a white solid and the minor as a clear and colourless oil. **Major**: (R_f = 0.26), [α] -10.8 (c = 0.37, acetone); mp 138-139 °C (Et_2O/Hexanes); IR (ATR, solid) ν_{max} 2954, 2232, 1717, 1397, 1075 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 6.05 (m, 2H), 5.71 (dt, 1H, *J* = 9.8, 2.1 Hz), 5.14 (s, 1H), 3.60 (m, 2H), 3.25 (d, 1H, *J* = 8.4 Hz), 3.21 (d, 1H, *J* = 8.4 Hz), 3.03 (m, 1H) 2.90 (td, 1H, *J* = 4.0, 1.7 Hz), 2.87 (q, 1H, *J* = 3.1 Hz), 2.12 (m, 1H), 1.99 – 1.79 (m, 4H), 1.46 (m, 1H), 0.92 (t, 3H, *J* = 7.2 Hz), 0.92 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.9, 129.7, 128.8, 127.5, 126.4, 121.6, 89.8, 75.5, 63.6, 46.6, 42.9, 33.1, 32.3, 29.0, 27.9, 27.1, 25.3, 8.3; EI-MS [m/z (%)] 343 (M+ 38), 270 (52), 256 (94), 70 (100); HRMS (EI) calcd. for $C_{20}H_{29}O_2N_3$ 343.2260 found: 343.2252; **Minor**: (R_f = 0.17), [α] -98.7 (c = 0.85, acetone); IR (ATR, solid) ν_{max} 2954, 2231, 1716, 1398, 1079 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 6.05 (m, 2H), 5.68 (dt, 1H, *J* = 10.1, 2.0 Hz), 5.30 (s, 1H), 3.58 (m, 2H), 3.28 (s, 2H), 3.03 (m, 1H), 2.91 (m, 2H), 2.09 (m, 1H), 1.98 – 1.80 (m, 4H), 1.41 (m, 1H), 0.94 (t, 3H, *J* = 7.4 Hz), 0.91 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.3, 132.1, 128.2, 127.7, 125.5, 122.5, 89.5, 78.0, 64.4, 46.5, 41.6, 32.6, 32.5, 28.8, 27.9, 27.0, 25.5, 8.5; EI-MS [m/z (%)] 343 (M+ 47), 314 (22), 256 (100), HRMS (EI) calcd. for $C_{20}H_{29}O_2N_3$ 343.2260 found: 343.2259.



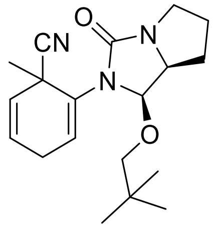
syn-**168**: A -78 °C solution of *syn*-**165** (338 mg, 1.17 mmol) in THF (6 mL) was treated dropwise with *t*-BuLi (0.79 mL, 1.34 M, 1.06 mmol) giving a yellow-red solution. After one hour of stirring, a THF (3 mL) solution of DBMN (260 mg, 1.06 mmol) was added to the reaction mixture causing a gradual change in colour to dark red and was let to stir for another hour after which the reaction was warmed to room temperature and stirred for more hour. The reaction mixture was quenched with water (5 ml) and extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (7:3 hexanes/EtOAc, R_f = 0.10) gave *syn*-**181** (103 mg, 0.33 mmol, 28%) as a yellow oil that crystalized upon standing (142-144 °C EtOH/hexanes). [α]

-85.4 (c = 0.4, acetone): IR (ATR, solid) ν_{max} 2955, 2868, 2230, 1695, 1408, 1091; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.81 (ddd, 1H, *J* = 7.8, 1.6, 0.4 Hz), 7.74 (td, 1H, *J* = 7.9, 1.6 Hz), 7.65 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.5 (td, 1H, *J* = 7.7, 1.3 Hz), 5.51 (d, 1H, *J* = 6.5 Hz), 3.75 (dd, 1H, *J* = 10.0, 6.4 Hz), 3.62 (m, 1H), 3.26 (d, 1H, *J* = 8.6 Hz), 3.10 (m, 1H), 3.09 (d, 1H, *J* = 8.6 Hz), 2.16 (m, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.62 (m, 1H), 0.81 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 159.4, 141.7, 134.2, 134.0, 130.6, 128.4, 117.4, 113.8, 89.7, 80.9, 62.3, 46.4, 32.7, 27.0, 26.7, 25.4; EI-MS [m/z (%)] 313 (M+ 17), 242 (10), 226(100), 225 (95); HRMS (EI) calcd. For $C_{18}H_{23}O_2N_3$ 313.1790 found: 313.1786.



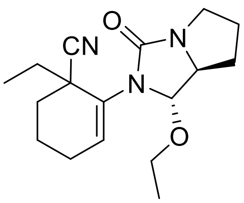
178b: To a -78 °C solution of nitrile *syn*-**168** (31 mg, 0.10 mmol) and *t*-BuOH (7 mg, 0.10 mmol) in THF and liquid NH_3 was added lithium metal (2 mg, 0.24 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with iodoethane (0.02 mL, 0.20 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography gave separable diastereomers, both as a clear and colourless oil. **Major**: 11 mg, 0.03 mmol, 33%. (R_f = 0.17), [α] -3.2 (c = 0.3, acetone): IR (ATR, solid) ν_{max} 2954, 2869, 2230, 1711, 1400, 1078 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.05 (m, 2H), 5.68 (dt, 1H, *J* = 9.6, 2.0 Hz), 5.32 (d, 1H, *J* = 6.1 Hz), 4.11 (q, 1H, *J* = 6.7 Hz), 3.43 (m, 1H), 3.35 (d, 1H, *J* = 8.7 Hz), 3.27 (d, 1H, *J* = 8.7 Hz), 3.0 (m, 1H), 2.91 (m, 2H), 2.03-1.78 (m, 6H), 0.93 (t, 3H, *J* = 7.3 Hz), 0.91 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.2, 133.8, 128.0, 127.7, 125.4, 122.6, 89.1, 81.3, 61.9, 46.2, 42.1, 33.1, 32.1, 28.0, 27.4, 26.9, 25.5; EI-MS [m/z (%)] 343 (M+ 87), 316 (14), 256 (100); HRMS (EI) calcd. for $C_{20}H_{29}O_2N_3$ 343.2260; found: 343.2254. **Minor**: 5 mg, 0.02 mmol, 15%. (R_f = 0.12), [α] -12.0 (c = 0.15, acetone); IR (ATR, solid) ν_{max} 2955, 2925, 2871, 2232, 1702, 1408, 1086 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.04 (m, 2H), 5.69 (dt, 1H, *J* = 9.8, 2.0 Hz), 5.05

(d, 1H, *J* = 6.2 Hz), 4.11 (q, 1H, *J* = 6.0 Hz), 3.41 (m, 1H), 3.26 (d, 1H, *J* = 8.4 Hz), 3.22 (d, 1H, *J* = 8.4 Hz), 2.99 (m, 1H), 2.91 (m, 1H), 2.00 – 1.85 (m, 6H), 0.94 (t, 3H, *J* = 7.4 Hz), 0.92 (s, 9H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 160.6, 132.7, 129.3, 127.3, 126.1, 121.3, 90.1, 80.3, 62.1, 45.9, 43.4, 32.9, 32.4, 28.0, 27.3, 27.1, 25.5, 8.5; EI-MS [m/z (%)] 343 (M+ 33), 272 (19), 256 (83), 229 (31), 71 (73), 70 (100); HRMS (EI) calcd. for $C_{20}H_{29}O_2N_3$ 343.2260; found: 343.2253.

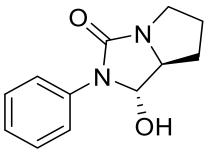


178a: To a -78 ^{o}C solution of nitrile *syn*-**168** (38 mg, 0.12 mmol) and *t*-BuOH (9 mg, 0.12 mmol) in THF and liquid NH_3 was added lithium metal (2 mg, 0.3 mmol) in small pieces causing a colour change to deep blue. After 2.5 hours of stirring at this temperature the reaction was treated with iodomethane (0.02 mL, 0.24 mmol) and stirred for another hour. The reaction was quenched with solid NH_4Cl and then warmed to room temperature to allow evaporation of NH_3. The residue was treated with brine then extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography gave separable diastereomers, both as a clear and colourless oil. **Major**: 13 mg, 0.04 mmol, 33%. (R_f = 0.10); [α] -11.7 (c = 0.6, acetone); IR (ATR, solid) ν_{max} 2954, 2901, 2870, 2233, 1710, 1402, 1094 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.94 (m, 2H), 5.77 (dt, 1H, *J* = 9.6, 2.0 Hz), 5.31 (d, 1H, *J* = 6.3 Hz), 4.14 (q, 1H, *J* = 6.5 Hz), 3.44 (m, 1H), 3.34 (d, 1H, *J* = 8.4 Hz), 3.27 (d, 1H, *J* = 8.4 Hz), 3.00 (m, 1H), 2.92 (m, 2H), 2.02 – 1.85 (m, 4H), 1.51 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 161.2, 132.3, 129.8, 127.5, 126.1, 122.8, 88.9, 81.3, 62.1, 46.2, 37.7, 33.1, 27.8, 27.3, 27.0, 26.8, 25.6; EI-MS [m/z (%)]) 329 (M+ 47), 302 (6), 242 (86), 215 (22), 71 (38), 70 (100); HRMS (EI) calcd. for $C_{19}H_{27}O_2N_3$ 329.2103; found: 329.2099. **Minor**: 13 mg, 0.04 mmol, 33%. (R_f = 0.05); [α] -39.9 (c = 0.36, acetone); IR (ATR, solid) ν_{max} 2953, 2870, 2234, 1703, 1405, 1086 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.94 (m, 2H), 5.77 (dt, 1H, *J* = 9.7, 2.0 Hz), 5.13 (d, 1H, *J* = 6.4 Hz), 4.11 (q, 1H, *J* = 6.6 Hz), 3.44 (m, 1H), 3.31 (d, 1H, *J* = 8.5 Hz), 3.22 (d, 1H, *J* = 8.5 Hz), 2.99 (m, 1H), 2.92 (m, 1H), 2.87 (m, 1H), 2.02 – 1.83 (m, 4H), 1.64 (s, 3H), 0.91 (s, 9H); EI-MS [m/z

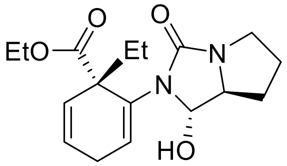
(%)]) 329 (M+ 50), 242 (100), 215 (29); HRMS (EI) calcd. for $C_{19}H_{27}O_2N_3$ 329.2103; found: 329.2098



181: A glass vial charged with ethylated diene **167a** (major, 30 mg, 0.1 mmol) and palladium on carbon (3 mg, 10% by mass) was capped with a rubber septum and purged with three balloons of hydrogen. Using a balloon, the reaction was maintained with 1 atmosphere of hydrogen and stirred for 24 hours. Once the reaction was observed to be complete by TLC analysis it was exposed to air, filtered through a pad of celite and washed with methanol. The methanol solution was concentrated under reduced pressure and purified by column chromatography (6:4 hexanes/EtOAc, $R_f = 0.1$) and isolated as a clear and colourless oil (23 mg, 0.76 mmol, 76%). [α] -43.8 (c = 0.9, acetone); IR (ATR, solid) ν_{max} 2969, 2937, 2880, 2229, 1715, 1397, 1079 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 5.86 (t, 1H, *J* = 4.1 Hz), 4.84 (s, 1H), 3.56 (m, 5H), 2.98 (m, 1H), 2.22 (m, 2H), 2.14 (m, 2H), 1.90 (m, 1H), 1.83 (m, 3H), 1.67 (m, 2H), 1.37 (m, 1H), 1.19 (t, 3H, *J* = 7.4 Hz), 1.00 (t, 3H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 163.1, 134.2, 133.2, 122.7, 92.1, 64.5, 62.1, 46.2, 42.2, 33.6, 29.2, 29.1, 25.4, 25.3, 19.1, 15.4, 8.9; δ EI-MS [m/z (%)] 303 (M+ 33), 274 (58), 258 (44), 257 (100); HRMS (EI) calcd. for $C_{17}H_{25}O_2N_3$ 303.1947; found: 303.1946.



anti-**76:** A solution of hemiaminal ether (0.2 mmol) in THF (0.5 mL) was treated with 0.5 mL of a 1% citric acid solution in water. The resulting suspension was stirred at room temperature for 24 h. If ether starting material was oil (*anti*-**77**) solid could simply be collected by filtration and washing with hexanes. If starting material was solid, the reaction was extracted 3 times with EtOAc (5 mL), concentrated under reduced pressure and purified by column chromatography (1:1 hexanes/EtOAc, $R_f = 0.3$) to give *anti*-**76** a white solid. (0.039 g, 0.18 mmol, 88%), mp 171 – 172 °C (acetone/hexanes); [α] -8.2 (c 1.0, acetone); IR (ATR, solid) ν_{max} 3266, 2961, 2433, 1658, 1416, 1056 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) 7.71 (m, 2H), 7.30 (m, 2H), 7.05 (m, 1H), 5.66 (d, 1H, *J* = 7.88 Hz), 5.53 (d, 1H, *J* = 8.20 Hz), 3.64 (m, 1H), 3.56 (dd, 1H, *J* = 10.10, 6.21 Hz), 3.05 (m, 1H), 2.11 (m, 1H), 2.00 – 1.81 (m, 2H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 162.0, 141.0, 130.0, 124.7, 121.8, 83.9, 67.7, 46.9, 29.9, 26.1; EI-MS [m/z (%)] 218 (M+ 8), 200 (83), 171 (100), 77 (51); HRMS (EI) calcd. for $C_{12}H_{14}O_2N_2$ 218.1055; found: 218.1056.



184 A solution of diene **160b** (0.039 g, 0.11 mmol) in THF (1 M) was treated with 0.6 mL of a 1% citric acid solution in water. The mixture was stirred for 24 h at room temperature then extracted with 5 mL of EtOAC, washed with brine and dried over Na_2SO_4. The organic extract was concentrated under reduced pressure. Flash column chromatography (1:1 hexanes/EtOAc, R_f = 0.12) gave **189** as a colourless oil (0.021 g, 60%): [α] 22.8 (c = 0.25, acetone); IR (ATR, solid) ν_{max} 3330, 2929, 1676, 1410, 1222, 1028 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 6.04 (td, 1H, *J* = 3.80, 1.24 Hz), 5.87 (dtd, 1H, *J* = 9.82, 3.27, 1.28 Hz), 5.41 (dt, 1H, *J* = 9.92, 1.93 Hz), 5.17 (d, 1H, *J* = 8.22 Hz), 5.07 (d, 1H, *J* = 8.14), 4.02 (qd, 2H, *J* = 7.19, 1.17 Hz), 3.53 (m, 1H), 3.39 (dd, 1H, *J* = 10.01, 6.21 Hz), 2.92 (m, 1H), 2.80 (m, 1H), 2.04 – 1.65 (m, 6H), 1.32 (pd, 1H, *J* = 9.61, 2.49 Hz), 1.16 (t, 3H, *J* = 7.10 Hz), 0.77 (t, 3H, *J* = 7.55 Hz); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 174.1, 163.3, 133.8, 130.5, 126.3, 126.2, 85.9, 68.6, 61.9, 54.3, 47.2, 31.4, 29.6, 29.1, 28.6, 26.1, 15.1, 9.8; EI-MS [m/z (%)] 320 (M+ <1), 302 (88), 272 (84), 229 (100), 228 (81); HRMS (EI) calcd. for $C_{17}H_{24}O_4N_2$ 320.1736; found: 320.1733.

6. References

(1) Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, *2*, 85.

(2) Turner, N. J. *Curr. Opin. Biotechnol.* **2003**, *14* (4), 401.

(3) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106* (7), 2734–2793.

(4) Metallinos, C.; John, J.; Zaifman, J.; Emberson, K. *Adv. Synth. Catal.* **2012**, *354* (4), 602–606.

(5) Metallinos, C.; John, J.; Nelson, J.; Dudding, T.; Belding, L. *Adv. Synth. Catal.* **2013**, *355* (6), 1211–1219.

(6) John, J.; Wilson-Konderka, C.; Metallinos, C. *Adv. Synth. Catal.* **2015**, *357* (9), 2071–2081.

(7) Wilson-Konderka, C.; Doxtator, K.; Metallinos, C. *Adv. Synth. Catal.* **2016**, *358* (16), 2599–2603.

(8) Emberson, K.; Tran, N.; Metallinos, C. *Synlett* **2017**, *28* (20), 2901–2905.

(9) Tran, N. Synthesis and Determination of Relative and Abolute Stereochemistry of Chiral Cyclohexadiene Esters. *Unpubl. Work* **2019**.

(10) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97* (23), 6908–6909.

(11) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3.

(12) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

(13) Enders, D.; Eichenauer, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 549.

(14) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, *18*, 191.

(15) Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem. - Eur. J.* **1995**, *1* (7), 467–494.

(16) Schwaebe, M.; Little, R. D. *J. Org. Chem.* **1996**, *61* (10), 3240–3244.

(17) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119* (34), 7974–7991.

(18) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103* (8), 2127–2129.

(19) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104* (6), 1737–1739.

(20) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96* (2), 835–876.

(21) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107* (14), 4346–4348.

(22) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112* (10), 4011–4030.

(23) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. *RSC Adv.* **2016**, *6* (36), 30498–30551.

(24) Prashad, M.; Har, D.; Chen, L.; Kim, H.-Y.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2002**, *67* (19), 6612–6617.

(25) Lemiere, G. L.; Alderweireldt, F. C. *J. Org. Chem.* **1980**, *45* (21), 4175–4179.

(26) Bertogg, A.; Camponovo, F.; Togni, A. *Eur. J. Inorg. Chem.* **2005**, *2005* (2), 347–356.

(27) Birch, A. J. *J. Chem. Soc* **1944**, 430–436.

(28) Birch, A. J. *Pure Appl. Chem.* **1996**, *68* (3), 553–556.

(29) Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61* (22), 7664–7665.

(30) Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33* (4), 1313.

(31) Blenderman, W. G.; Joullie, M. M. *Tetrahedron Lett.* **1979**, *20* (52), 4985.

(32) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101* (21), 6404–6408.

(33) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103* (9), 2446–2448.

(34) He, C.; Stratton, T. P.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141* (1), 29–32.

(35) Cox, J. B.; Kimishima, A.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141* (1), 25–28.

(36) Zhu, X.; McAtee, C. C.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141* (8), 3409–3413.

(37) Birch, A. J. *J. Chem. Soc.* **1950**, 1551.

(38) Nelson, N. A.; Fassnacht, J. H.; Piper, J. U. *J. Am. Chem. Soc.* **1961**, *83* (1), 206–213.

(39) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34* (1), 126–135.

(40) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* *23* (10), 1095.

(41) Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51* (25), 4983–4987.

(42) Schultz, A. G. *Chem. Commun.* **1999**, No. 14, 1263–1271.

(43) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23* (7), 207–213.

(44) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25* (41), 4591.

(45) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, Martha. *J. Am. Chem. Soc.* **1988**, *110* (23), 7828–7841.

(46) Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113* (13), 4931–4936.

(47) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50* (6), 915–916.

(48) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115* (17), 7904–7905.

(49) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118* (26), 6210–6219.

(50) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62* (20), 6855–6861.

(51) Reed, J. W.; Hudlicky, T. *Acc. Chem. Res.* **2015**, *48* (3), 674–687.

(52) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120* (32), 8259–8260.

(53) Pytkowicz, J.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2001**, *631*, 157.

(54) Caterina, M. C.; Figueroa, M. A.; Perilla, I. A.; Salerno, A. *Heterocycles* **2006**, *68*, 701.

(55) Popov, K.; Hoang, A.; Somfai, P. *Angew. Chem. Int. Ed.* **2016**, *55* (5), 1801–1804.

(56) Popov, K.; Somfai, P. *J. Org. Chem.* **2016**, *81* (8), 3470–3472.

(57) Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. *J. Am. Chem. Soc.* **2015**, *137* (29), 9481–9488.

(58) Orecchia, P.; Yuan, W.; Oestreich, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3579.

(59) Bhunia, A.; Bergander, K.; Studer, A. *J. Am. Chem. Soc.* **2018**, *140* (47), 16353–16359.

(60) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137* (33), 10480–10483.

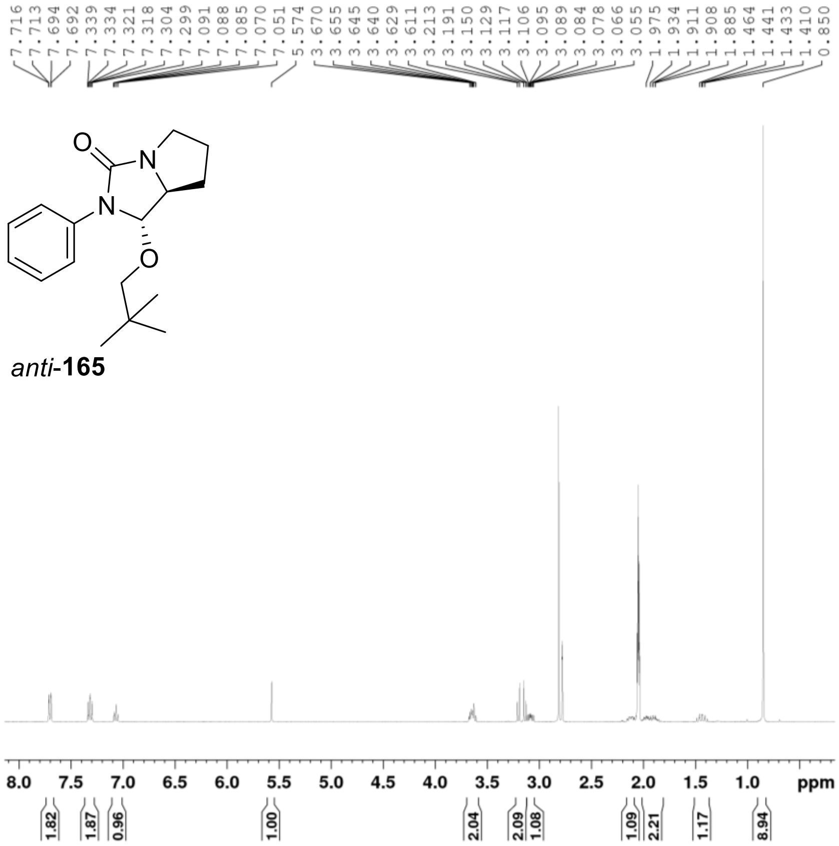
(61) Butora, G.; Reed, J. W.; Hudlicky, T.; Brammer, L. E.; Higgs, P. I.; Simmons, D. P.; Heard, N. E. *J. Am. Chem. Soc.* **1997**, *119* (33), 7694–7701.

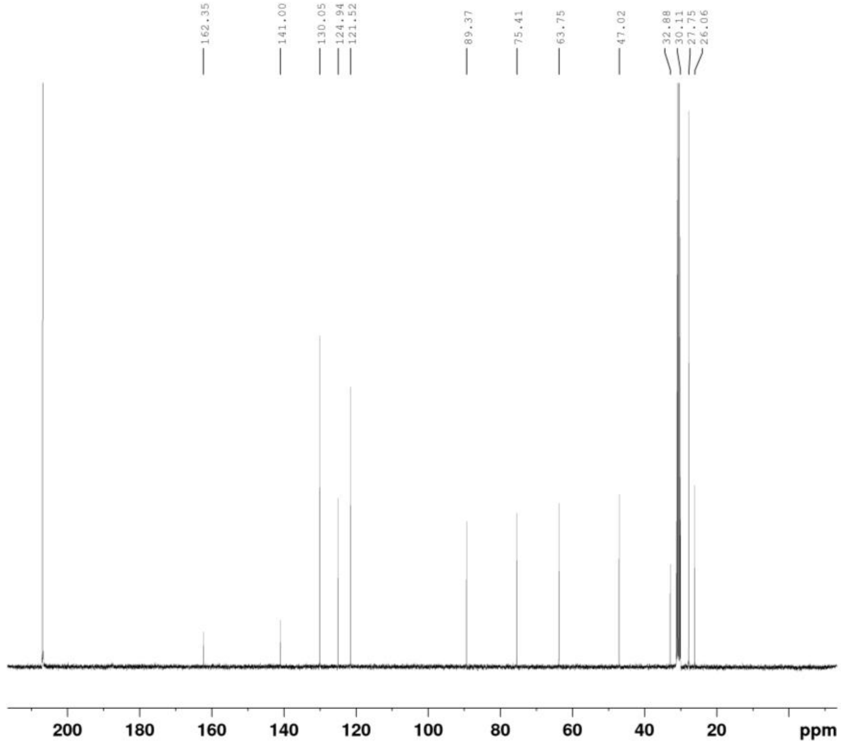
(62) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281.

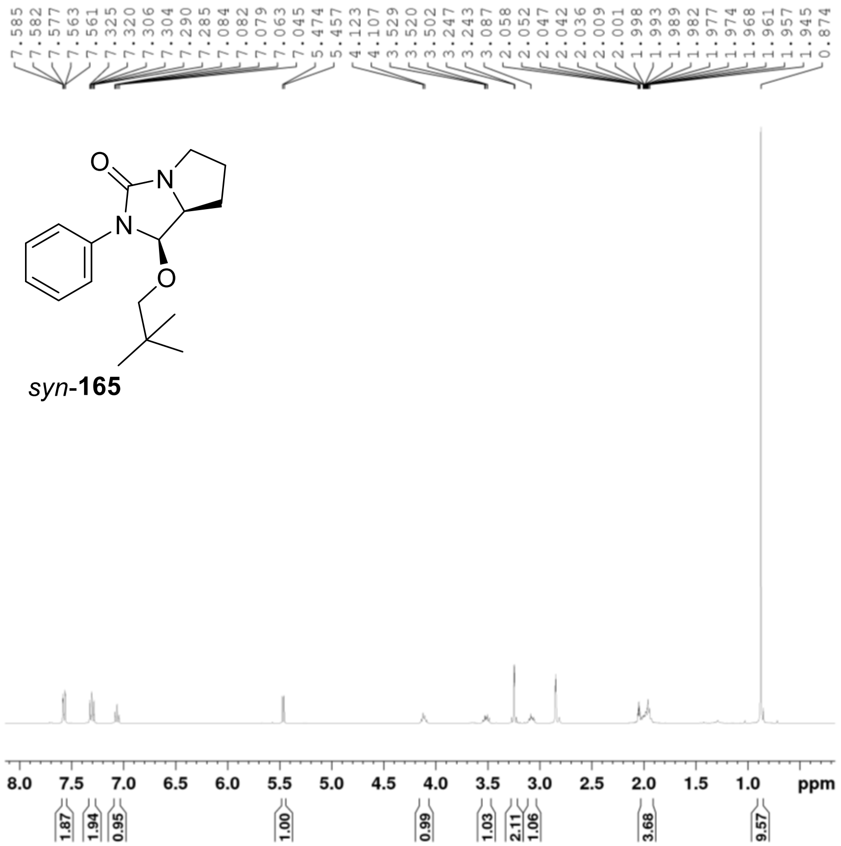
(63) Buchwald, S. L.; Lamaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

(64) Curphey, T. J. *Org. Synth.* **1971**, *51*, 142.

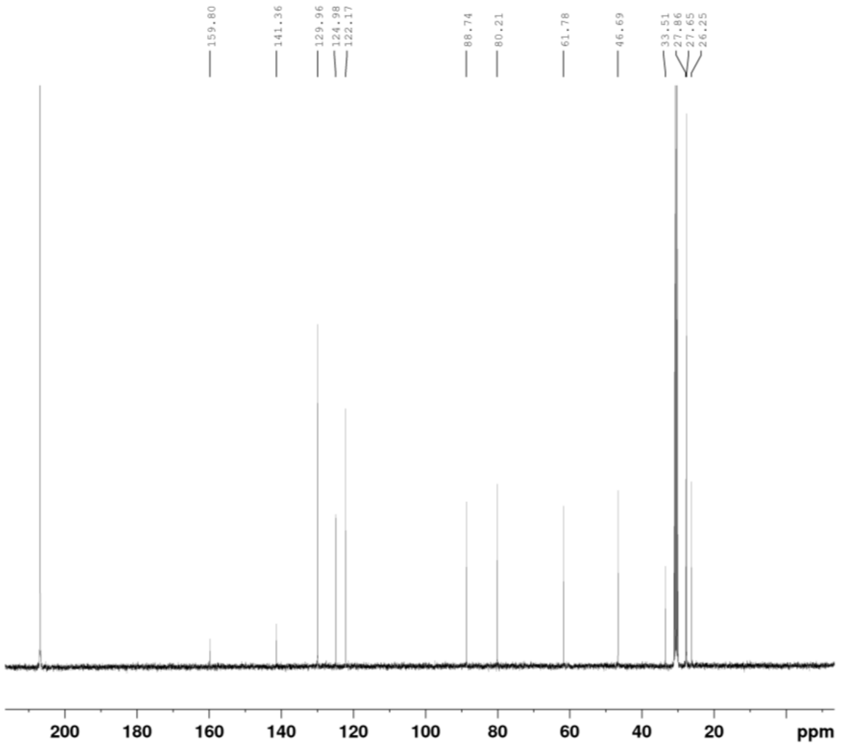
7. Appendix

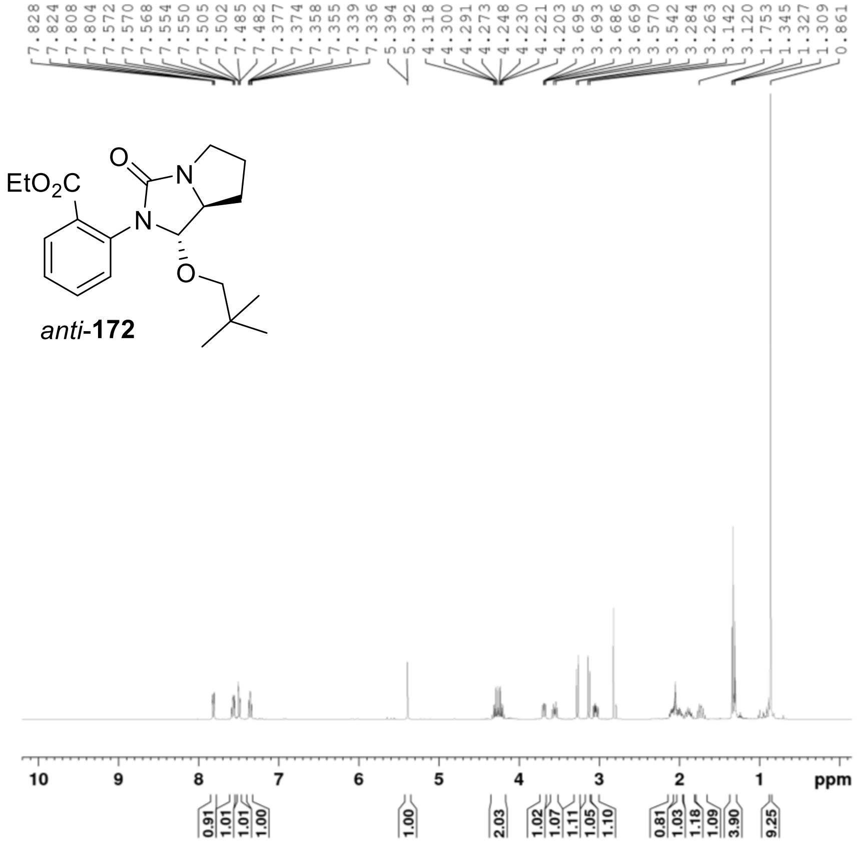

anti-**165**



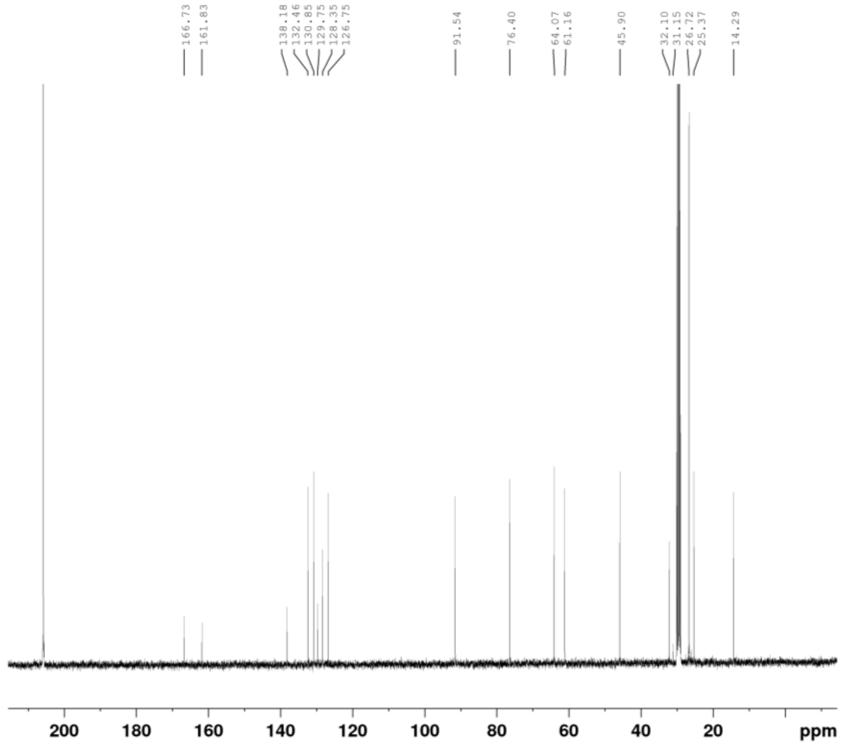

syn-**165**

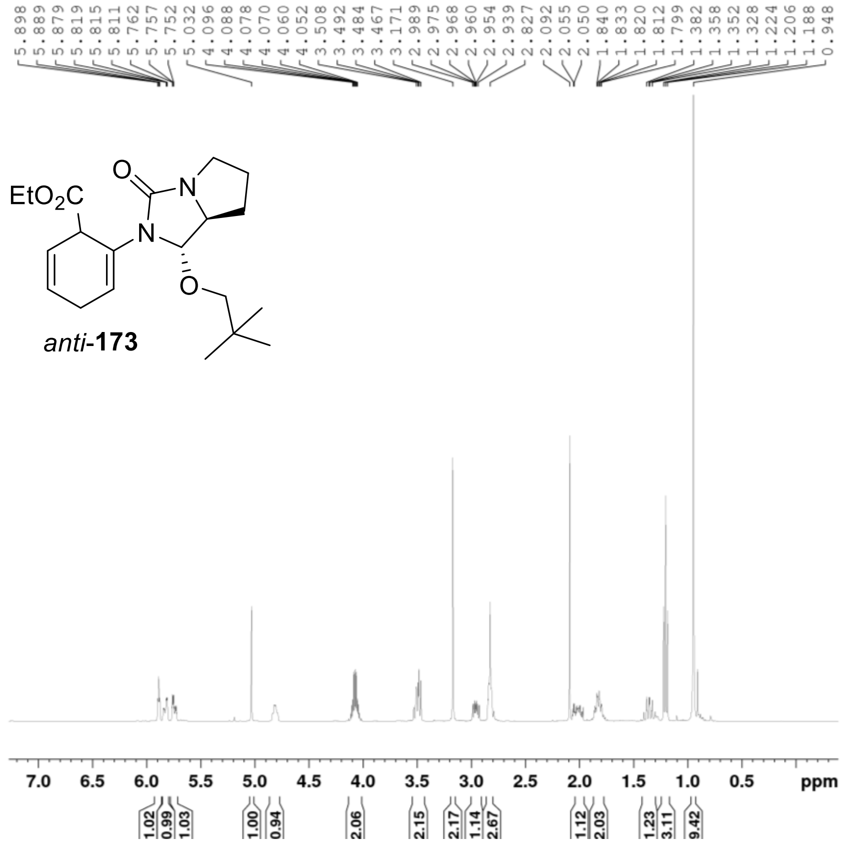
7.585
7.582
7.577
7.563
7.561
7.325
7.320
7.306
7.304
7.290
7.285
7.084
7.082
7.079
7.063
7.045
5.474
5.457
4.123
4.107
3.529
3.520
3.502
3.247
3.243
3.087
2.058
2.052
2.047
2.042
2.036
2.009
2.001
1.998
1.993
1.989
1.982
1.977
1.974
1.968
1.961
1.957
1.945
0.874
O
N
N
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.87
1.94
0.95
1.00
0.99
1.03
2.11
1.06
3.68
9.57


159.80
141.36
129.96
124.98
122.17
88.74
80.21
61.78
46.69
33.51
27.86
27.65
26.25
200
180
160
140
120
100
80
60
40
20
ppm

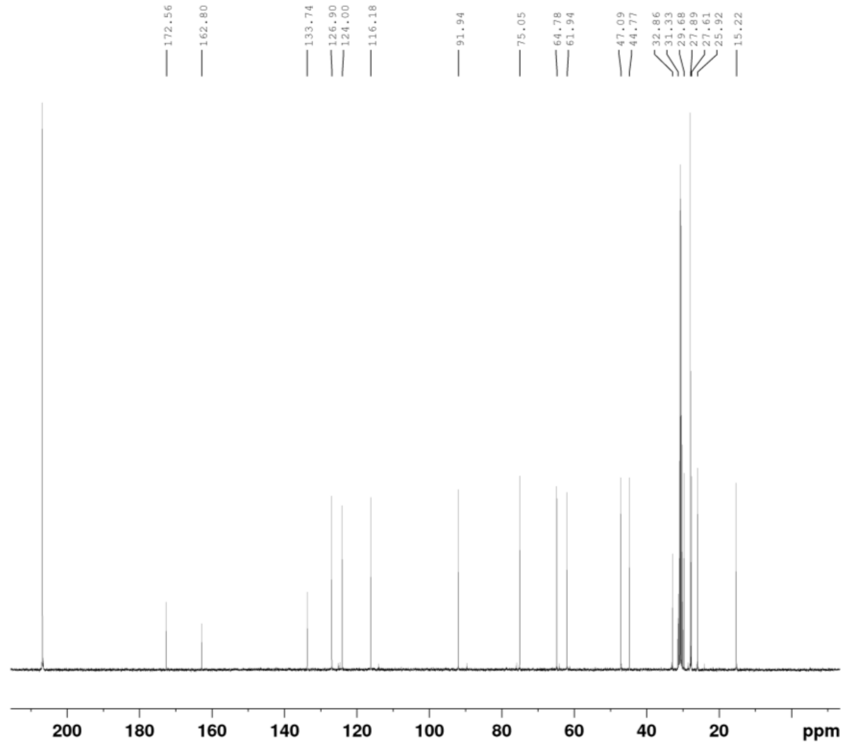

7.828
7.824
7.808
7.804
7.572
7.570
7.568
7.554
7.550
7.505
7.502
7.485
7.482
7.377
7.374
7.358
7.355
7.339
7.336
5.394
5.392
4.318
4.300
4.291
4.273
4.248
4.230
4.221
4.203
3.695
3.693
3.686
3.669
3.570
3.542
3.284
3.263
3.142
3.120
1.753
1.345
1.327
1.309
0.861
EtO$_2$C
O
N
N
O
10
9
8
7
6
5
4
3
2
1
ppm
0.91
1.01
1.01
1.00
1.00
2.03
1.02
1.07
1.11
1.05
1.10
0.81
1.03
1.18
1.09
3.90
9.25

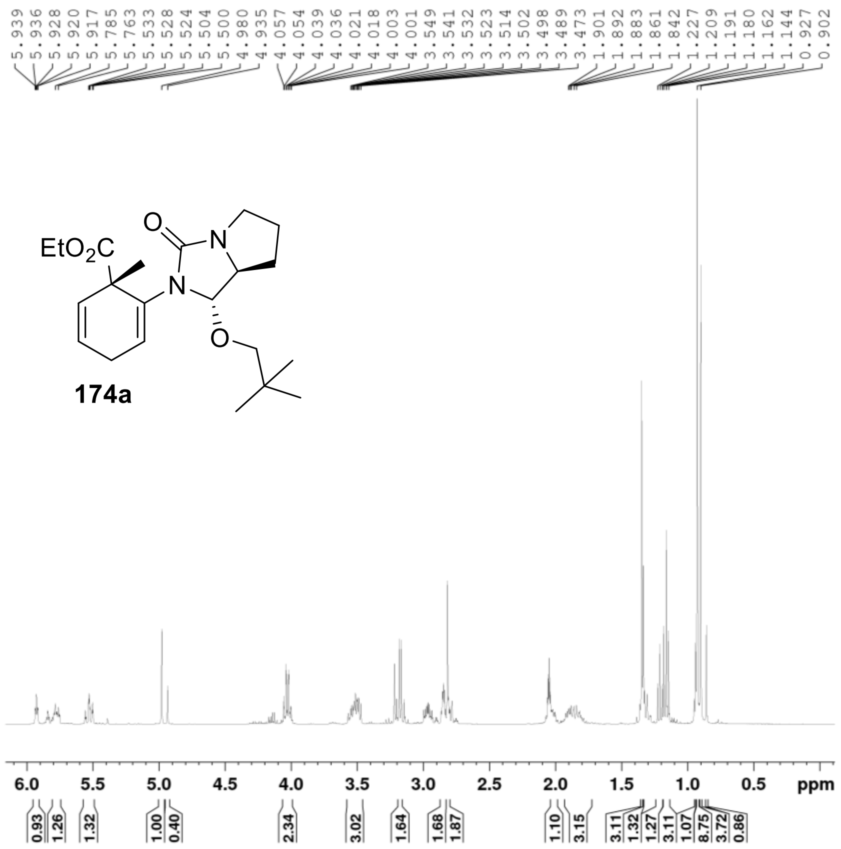
anti-**172**

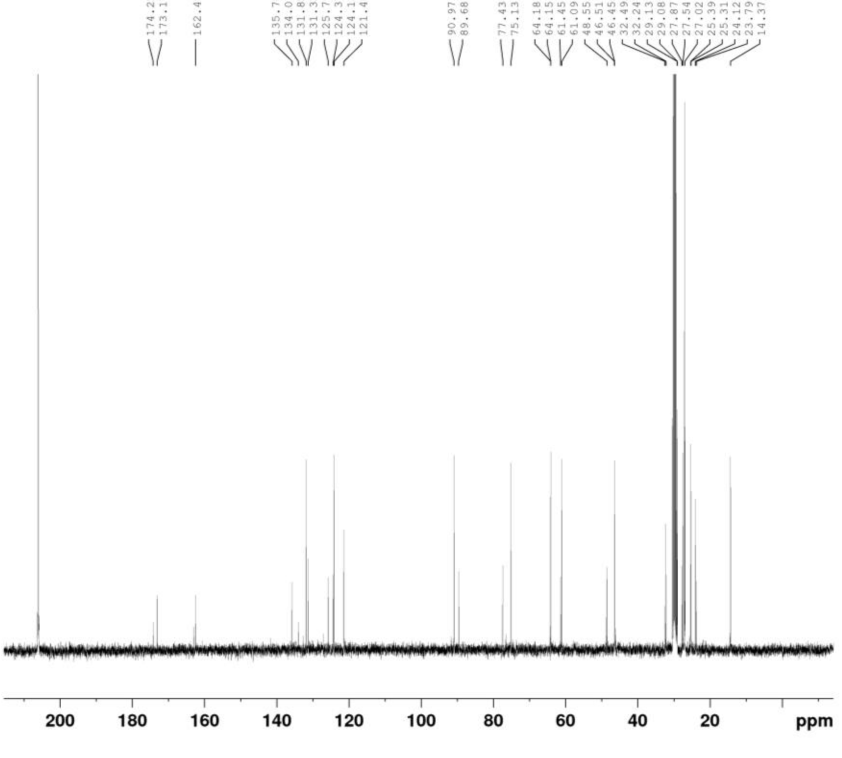

166.73
161.83
138.18
132.46
130.85
129.75
128.35
126.75
91.54
76.40
64.07
61.16
45.90
32.10
31.15
26.72
25.37
14.29
200
180
160
140
120
100
80
60
40
20
ppm

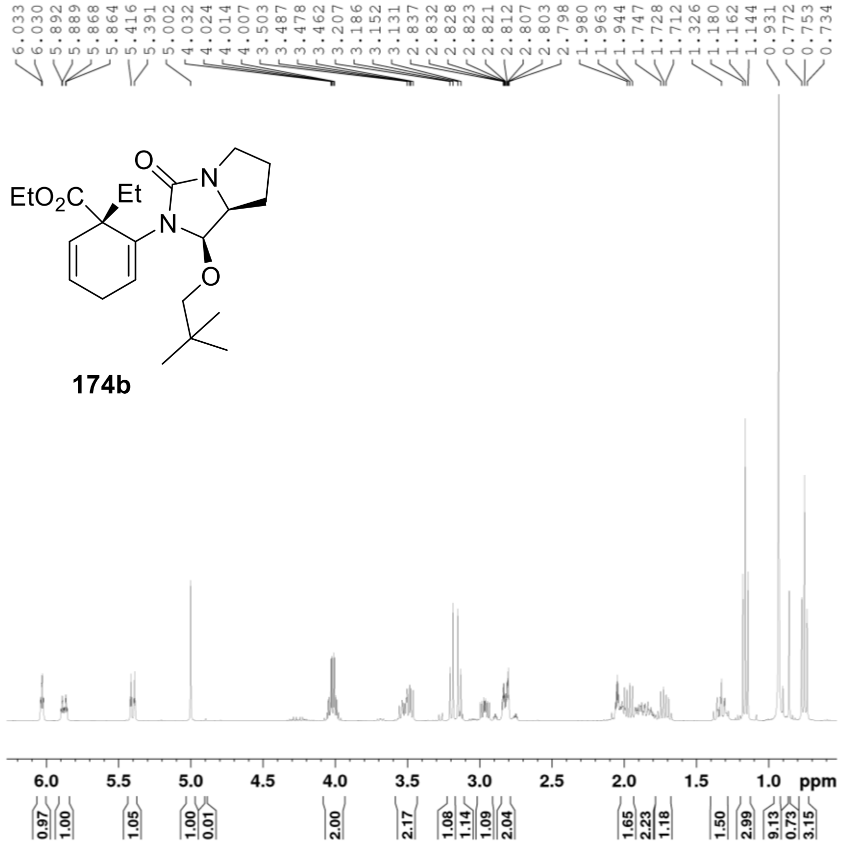

EtO$_2$C
O
N
N
O
5.898
5.889
5.879
5.819
5.815
5.811
5.762
5.757
5.752
5.032
4.096
4.088
4.078
4.070
4.060
4.052
3.508
3.492
3.484
3.467
3.171
2.989
2.975
2.968
2.960
2.954
2.939
2.827
2.092
2.055
2.050
1.840
1.833
1.820
1.812
1.799
1.382
1.358
1.352
1.328
1.224
1.206
1.188
0.948
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.02
0.99
1.03
1.00
0.94
2.06
2.15
2.17
1.14
2.67
1.12
2.03
1.23
3.11
9.42

anti-**173**

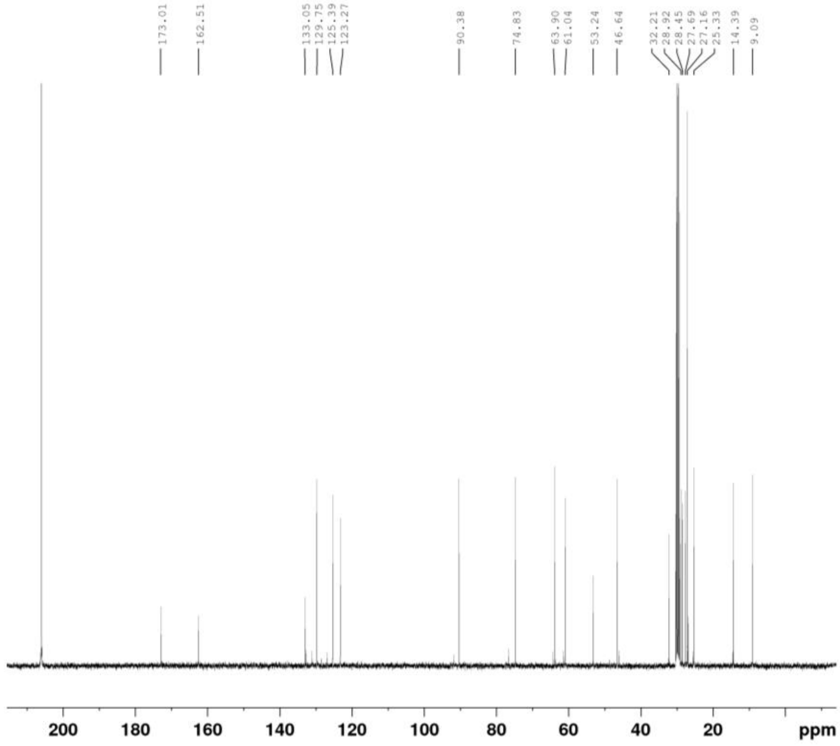

172.56
162.80
133.74
126.90
124.00
116.18
91.94
75.05
64.78
61.94
47.09
44.77
32.86
31.33
29.68
27.89
27.61
25.92
15.22
200
180
160
140
120
100
80
60
40
20
ppm

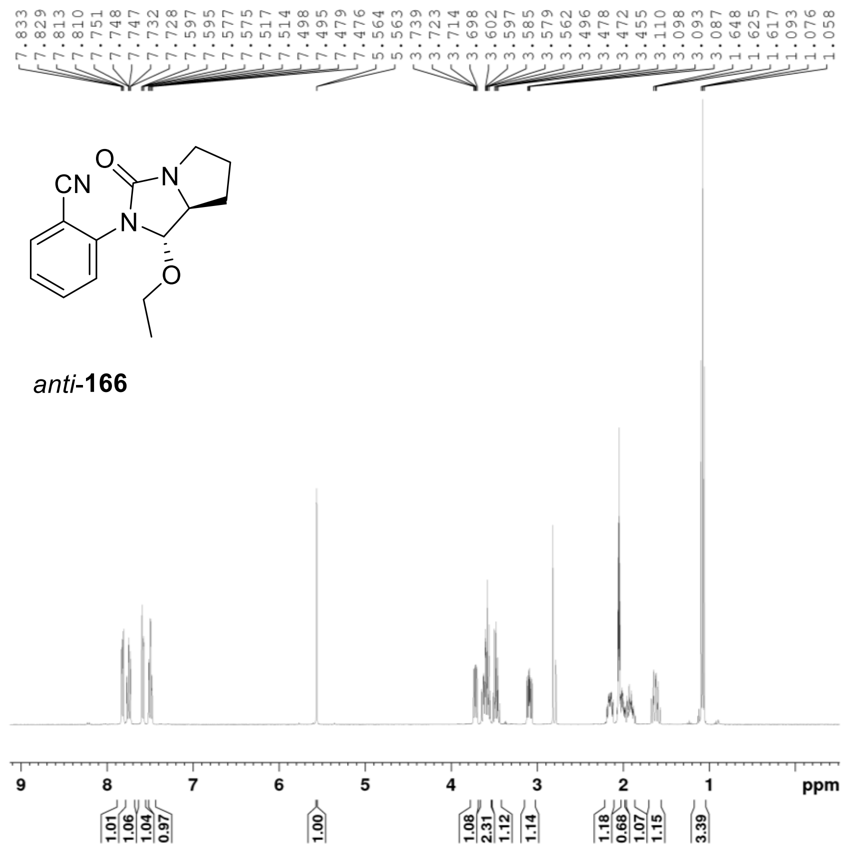

5.939
5.936
5.928
5.920
5.917
5.785
5.763
5.533
5.528
5.524
5.504
5.500
4.980
4.935
4.057
4.054
4.039
4.036
4.021
4.018
4.003
4.001
3.549
3.541
3.532
3.523
3.514
3.502
3.498
3.489
3.473
1.901
1.892
1.883
1.861
1.842
1.227
1.209
1.191
1.180
1.162
1.144
0.927
0.902
EtO2C
O
N
N
O
174a
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.93
1.26
1.32
1.00
0.40
2.34
3.02
1.64
1.68
1.87
1.10
3.15
3.11
1.32
1.27
3.11
1.07
8.75
3.72
0.86


174.25
173.17
162.49
135.78
134.07
131.85
131.33
125.79
124.37
124.13
121.40
90.97
89.68
77.43
75.13
64.18
64.15
61.45
61.09
48.55
46.51
46.45
32.49
32.24
29.13
29.08
27.87
27.54
27.02
25.39
25.31
24.12
23.79
14.37
200
180
160
140
120
100
80
60
40
20
ppm

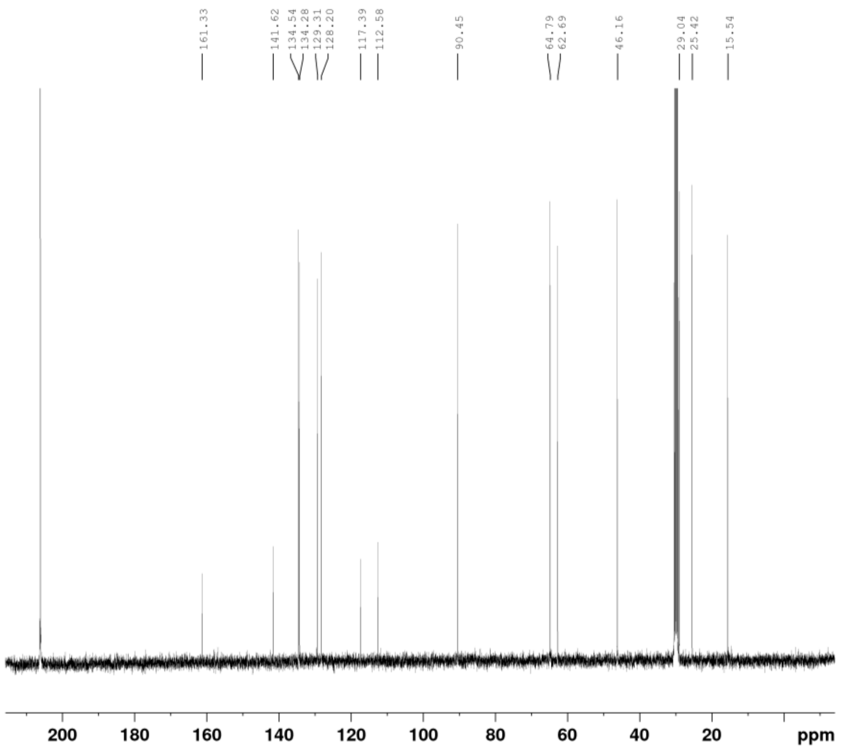

EtO2C
Et
O
N
N
O
6.033
6.030
5.892
5.889
5.868
5.864
5.416
5.391
5.002
4.032
4.024
4.014
4.007
3.503
3.487
3.478
3.462
3.207
3.186
3.152
3.131
2.837
2.832
2.828
2.823
2.821
2.812
2.807
2.803
2.798
1.980
1.963
1.944
1.747
1.728
1.712
1.326
1.180
1.162
1.144
0.931
0.772
0.753
0.734
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.97
1.00
1.05
1.00
0.01
2.00
2.17
1.08
1.14
1.09
2.04
1.65
2.23
1.18
1.50
2.99
9.13
0.73
3.15

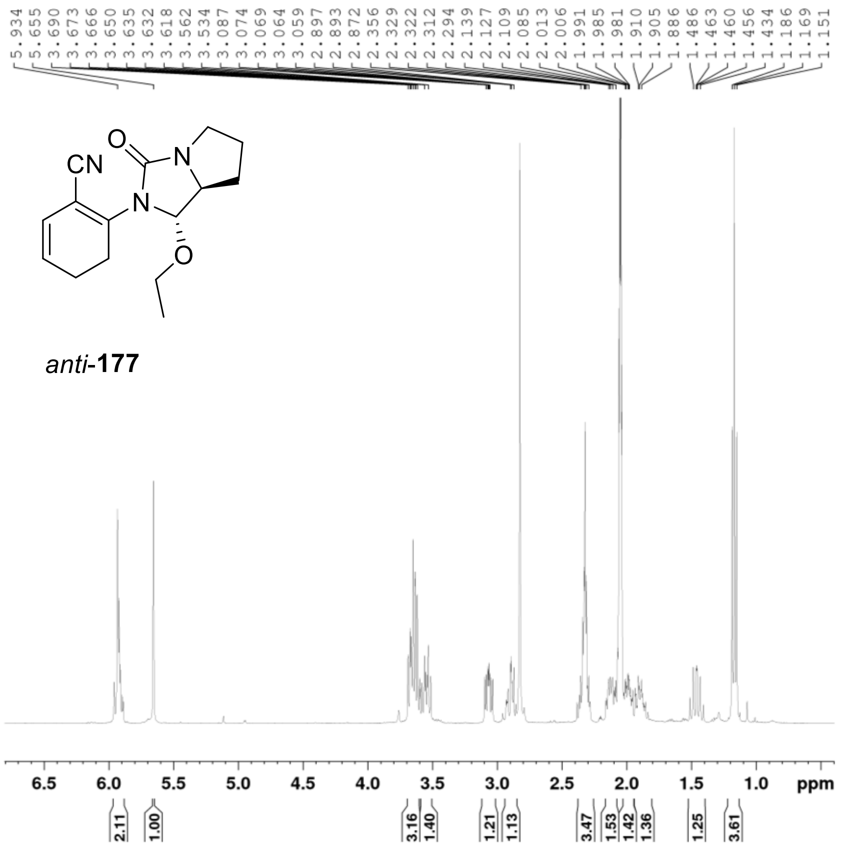
174b


173.01
162.51
133.05
129.75
125.39
123.27
90.38
74.83
63.90
61.04
53.24
46.64
32.21
28.92
28.45
27.69
27.16
25.33
14.39
9.09
200
180
160
140
120
100
80
60
40
20
ppm


7.833
7.829
7.813
7.810
7.751
7.748
7.747
7.732
7.728
7.597
7.595
7.577
7.575
7.517
7.514
7.498
7.495
7.479
7.476
5.564
5.563
3.739
3.723
3.714
3.698
3.602
3.597
3.585
3.579
3.562
3.496
3.478
3.472
3.455
3.110
3.098
3.093
3.087
1.648
1.625
1.617
1.093
1.076
1.058
CN
O
N
N
O
9
8
7
6
5
4
3
2
1
ppm
1.01
1.06
1.04
0.97
1.00
1.08
2.31
1.12
1.14
1.18
0.68
1.07
1.15
3.39

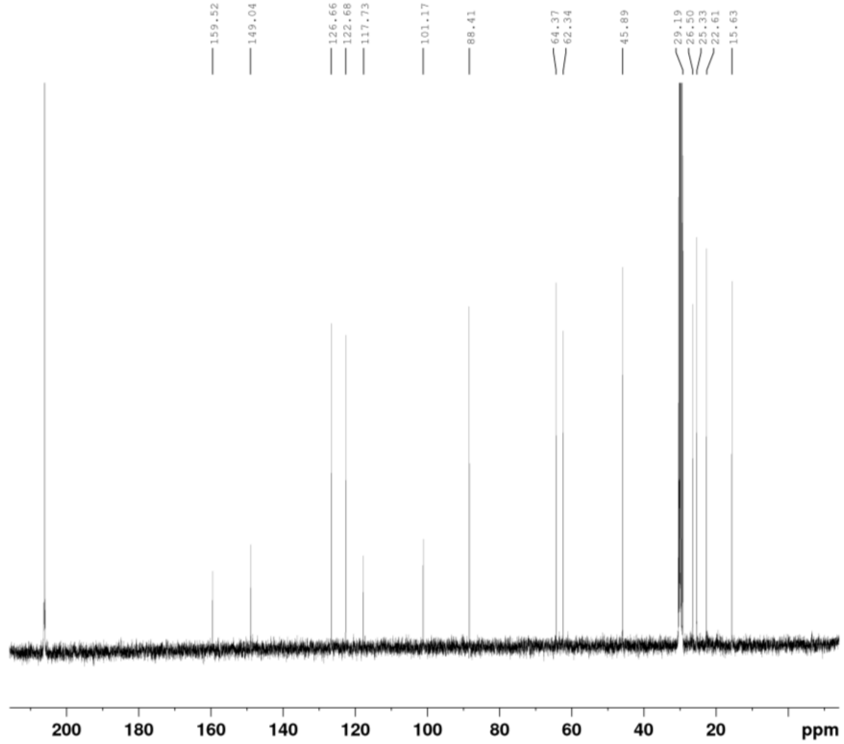
anti-**166**


161.33
141.62
134.54
134.28
129.31
128.20
117.39
112.58
90.45
64.79
62.69
46.16
29.04
25.42
15.54
200
180
160
140
120
100
80
60
40
20
ppm



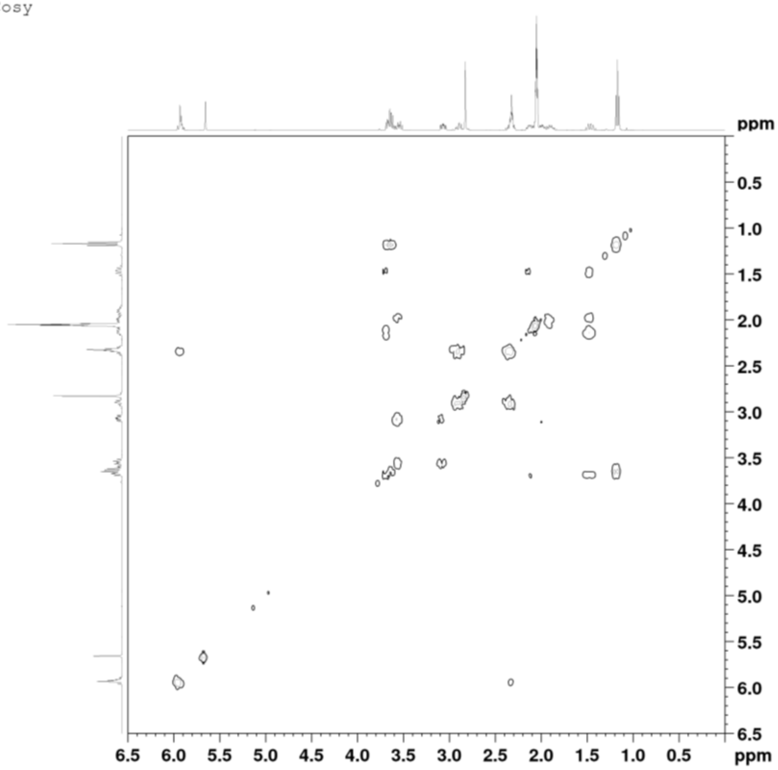
anti-**177**

CN
O
N
N
O
5.934
5.655
3.690
3.673
3.666
3.650
3.635
3.632
3.618
3.562
3.534
3.087
3.074
3.069
3.064
3.059
2.897
2.893
2.872
2.356
2.329
2.322
2.312
2.294
2.139
2.127
2.109
2.085
2.013
2.006
1.991
1.985
1.981
1.910
1.905
1.886
1.486
1.463
1.460
1.456
1.434
1.186
1.169
1.151
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
2.11
1.00
3.16
1.40
1.21
1.13
3.47
1.53
1.42
1.36
1.25
3.61

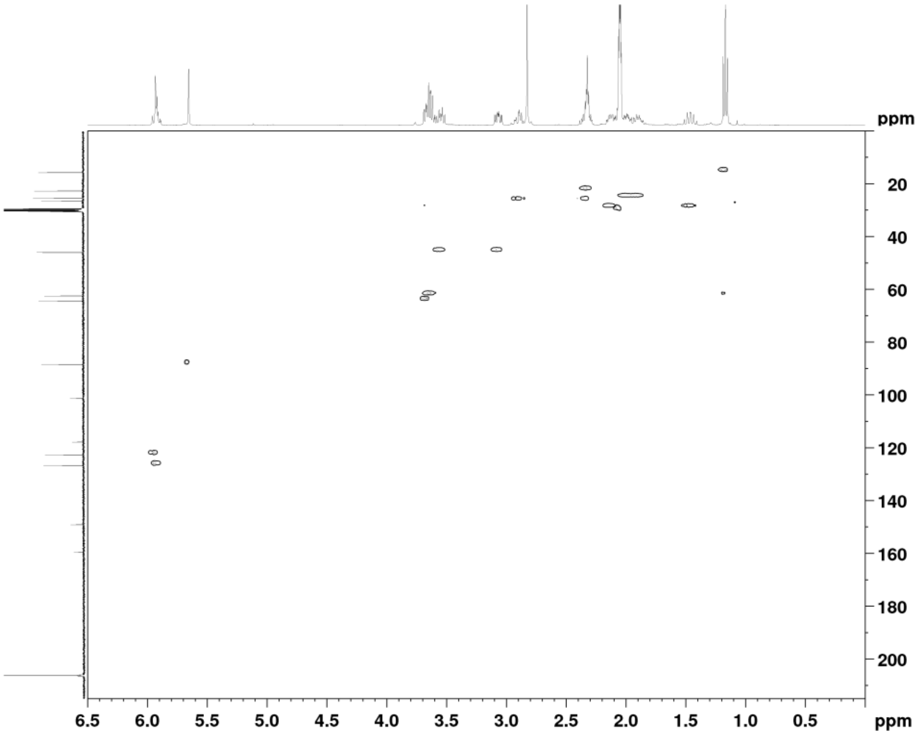


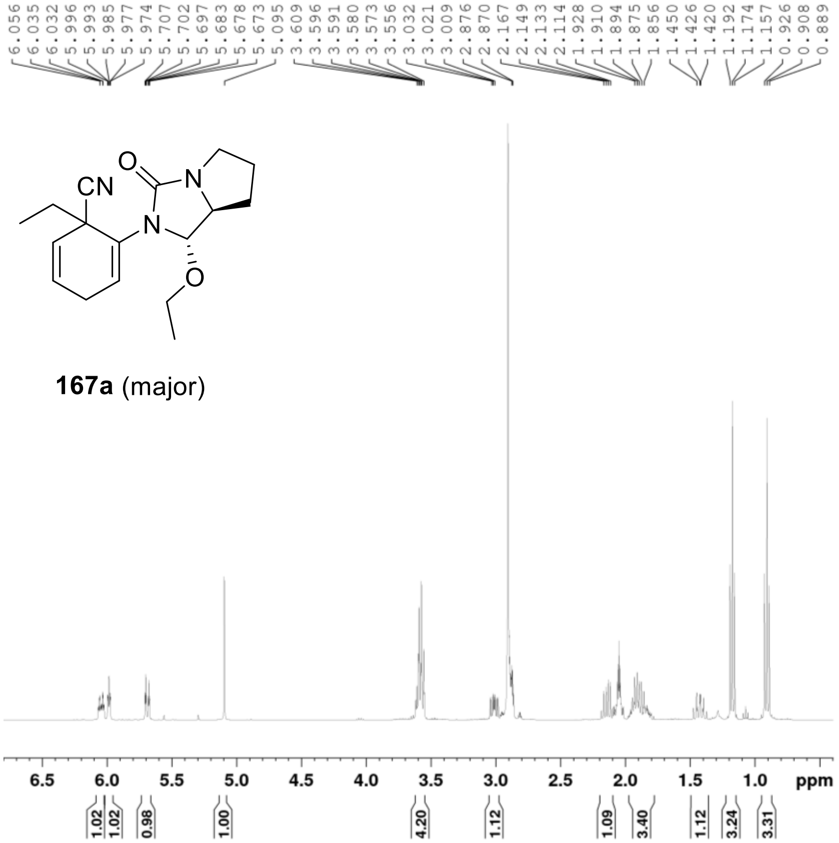
159.52
149.04
126.66
122.68
117.73
101.17
88.41
64.37
62.34
45.89
29.19
26.50
25.33
22.61
15.63
200
180
160
140
120
100
80
60
40
20
ppm

1H Cosy

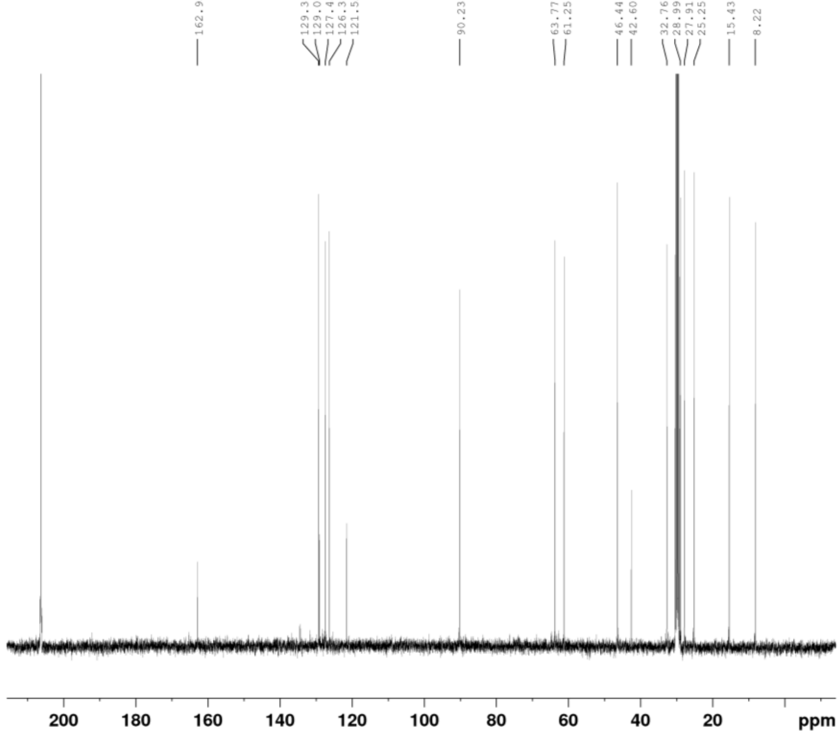


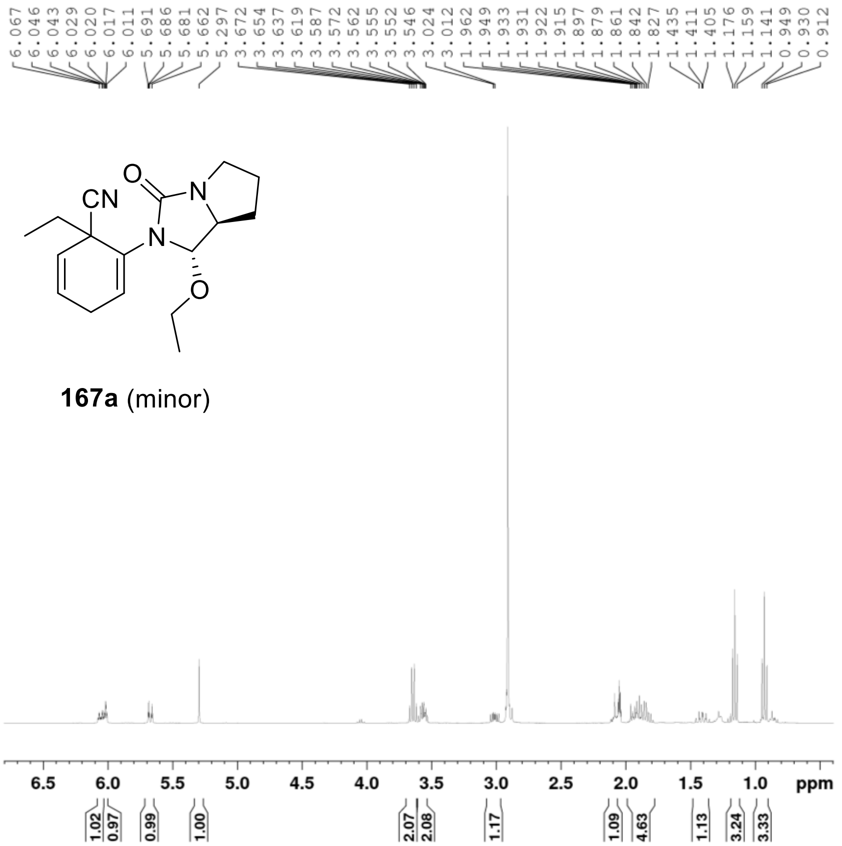
1H-13C HSQC



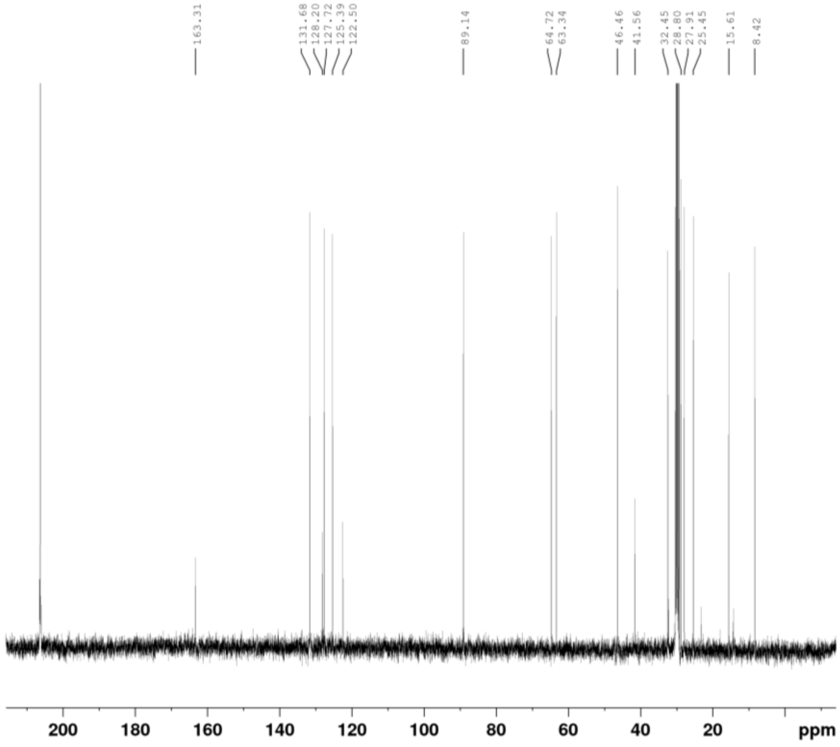

6.056
6.035
6.032
5.996
5.993
5.985
5.977
5.974
5.707
5.702
5.697
5.683
5.678
5.673
5.095
3.609
3.596
3.591
3.580
3.573
3.556
3.032
3.021
3.009
2.876
2.870
2.167
2.149
2.133
2.114
1.928
1.910
1.894
1.875
1.856
1.450
1.426
1.420
1.192
1.174
1.157
0.926
0.908
0.889
CN
O
N
N
O
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.02
1.02
0.98
1.00
4.20
1.12
1.09
3.40
1.12
3.24
3.31

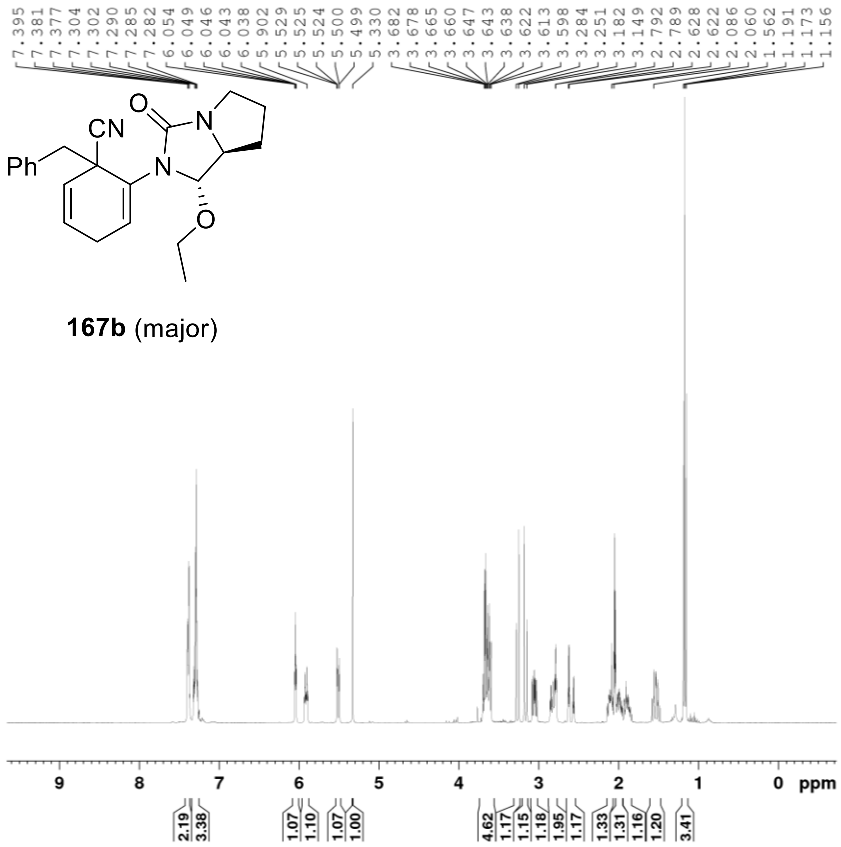
167a (major)


162.93
129.31
129.04
127.43
126.34
121.52
90.23
63.77
61.25
46.44
42.60
32.76
28.99
27.91
25.25
15.43
8.22
200
180
160
140
120
100
80
60
40
20
ppm

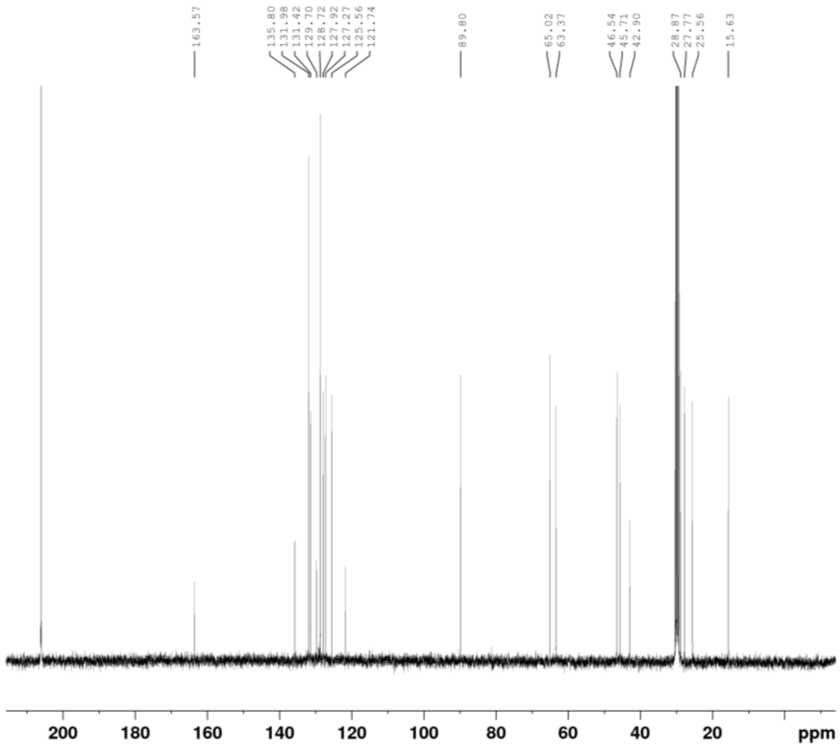

CN
O
N
N
O
6.067
6.046
6.043
6.029
6.020
6.017
6.011
5.691
5.686
5.681
5.662
5.297
3.672
3.654
3.637
3.619
3.587
3.572
3.562
3.555
3.552
3.546
3.024
3.012
1.962
1.949
1.933
1.931
1.922
1.915
1.897
1.879
1.861
1.842
1.827
1.435
1.411
1.405
1.176
1.159
1.141
0.949
0.930
0.912
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.02
0.97
0.99
1.00
2.07
2.08
1.17
1.09
4.63
1.13
3.24
3.33

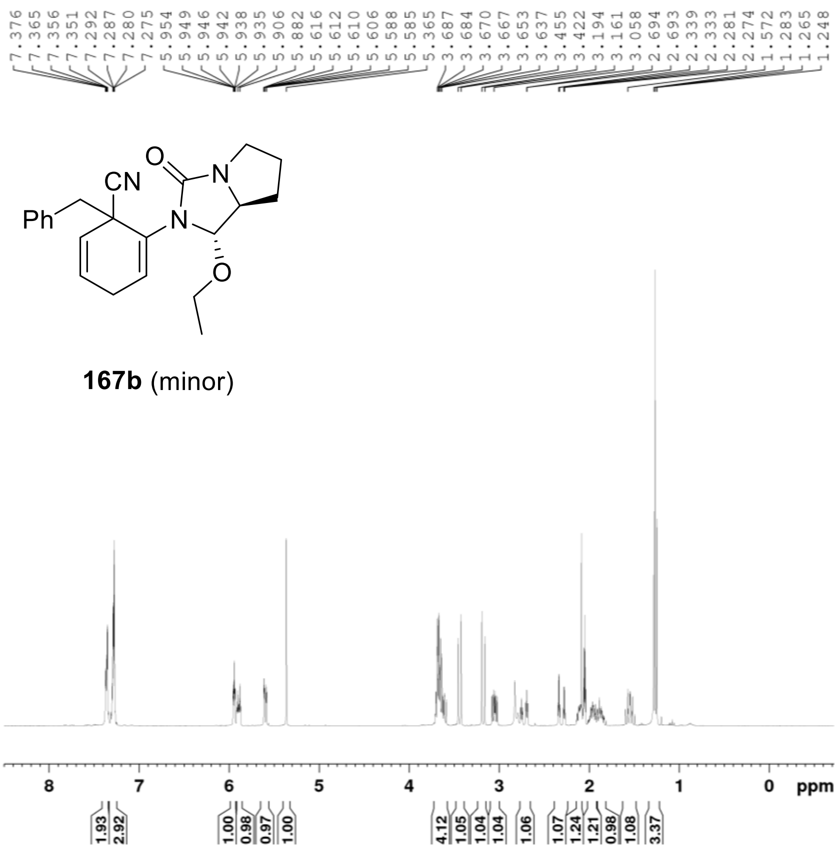
167a (minor)


163.31
131.68
128.20
127.72
125.39
122.50
89.14
64.72
63.34
46.46
41.56
32.45
28.80
27.91
25.45
15.61
8.42
200
180
160
140
120
100
80
60
40
20
ppm

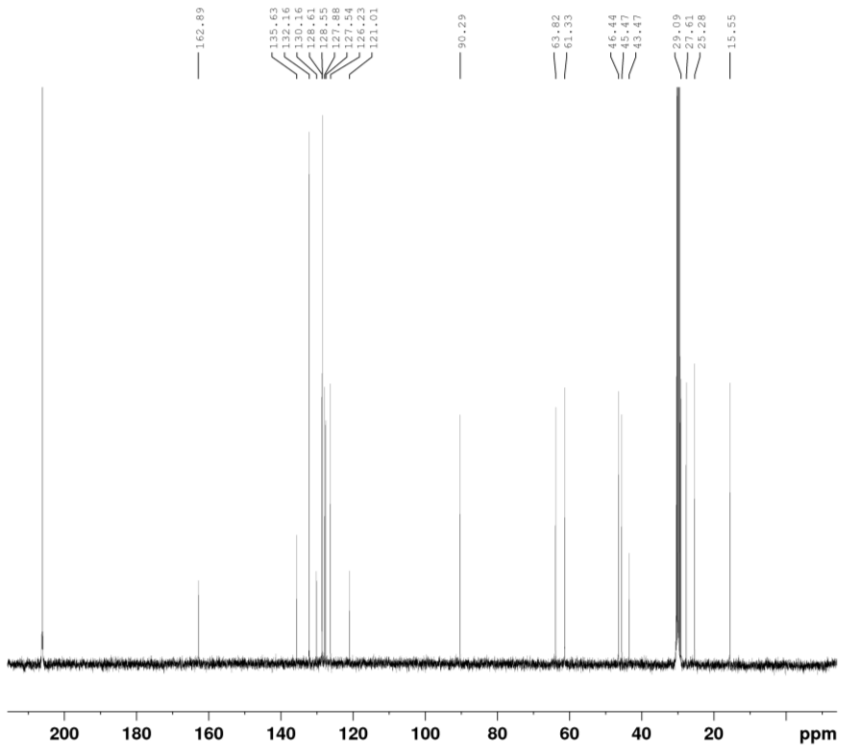

7.395
7.381
7.377
7.304
7.302
7.290
7.285
7.282
6.054
6.049
6.046
6.043
6.038
5.902
5.529
5.525
5.524
5.500
5.499
5.330
3.682
3.678
3.665
3.660
3.647
3.643
3.638
3.622
3.613
3.598
3.284
3.251
3.182
3.149
2.792
2.789
2.628
2.622
2.086
2.060
1.562
1.191
1.173
1.156
CN
O
N
Ph
N
O
9
8
7
6
5
4
3
2
1
0
ppm
2.19
3.38
1.07
1.10
1.07
1.00
4.62
1.17
1.15
1.18
1.95
1.17
1.33
1.31
1.16
1.20
3.41

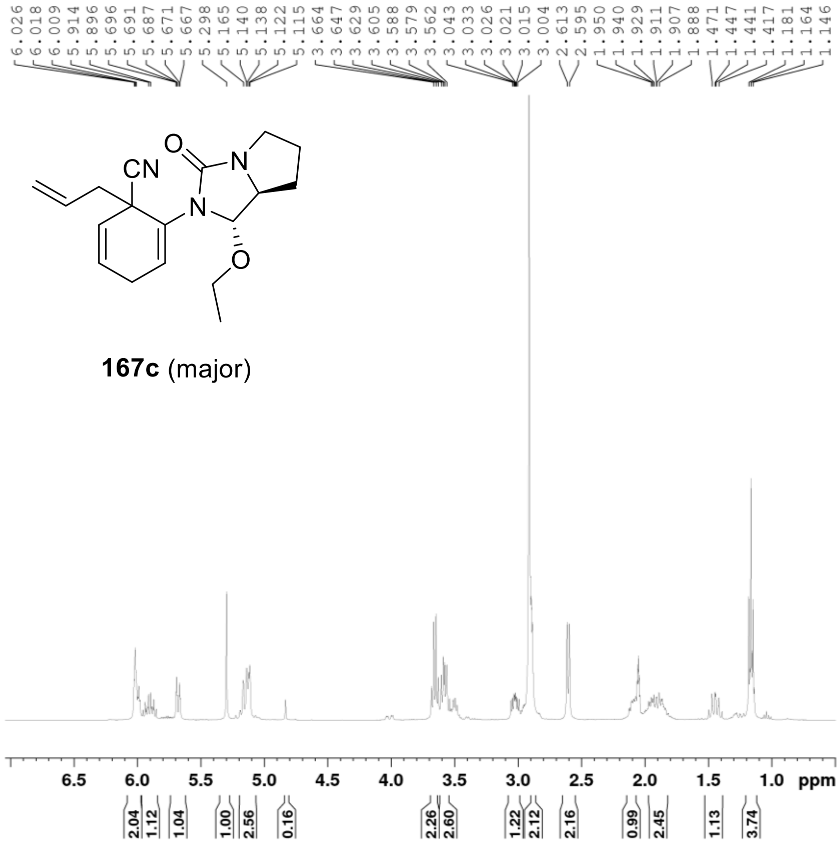
167b (major)


163.57
135.80
131.98
131.42
129.70
128.72
127.92
127.27
125.56
121.74
89.80
65.02
63.37
46.54
45.71
42.90
28.87
27.77
25.56
15.63
200
180
160
140
120
100
80
60
40
20
ppm


7.376
7.365
7.356
7.351
7.292
7.287
7.280
7.275
5.954
5.949
5.946
5.942
5.938
5.935
5.906
5.882
5.616
5.612
5.610
5.606
5.588
5.585
5.365
3.687
3.684
3.670
3.667
3.653
3.637
3.455
3.422
3.194
3.161
3.058
2.694
2.693
2.339
2.333
2.281
2.274
1.572
1.283
1.265
1.248
O
N
CN
Ph
N
O
8
7
6
5
4
3
2
1
0
ppm
1.93
2.92
1.00
0.98
0.97
1.00
4.12
1.05
1.04
1.04
1.06
1.07
1.24
1.21
0.98
1.08
3.37

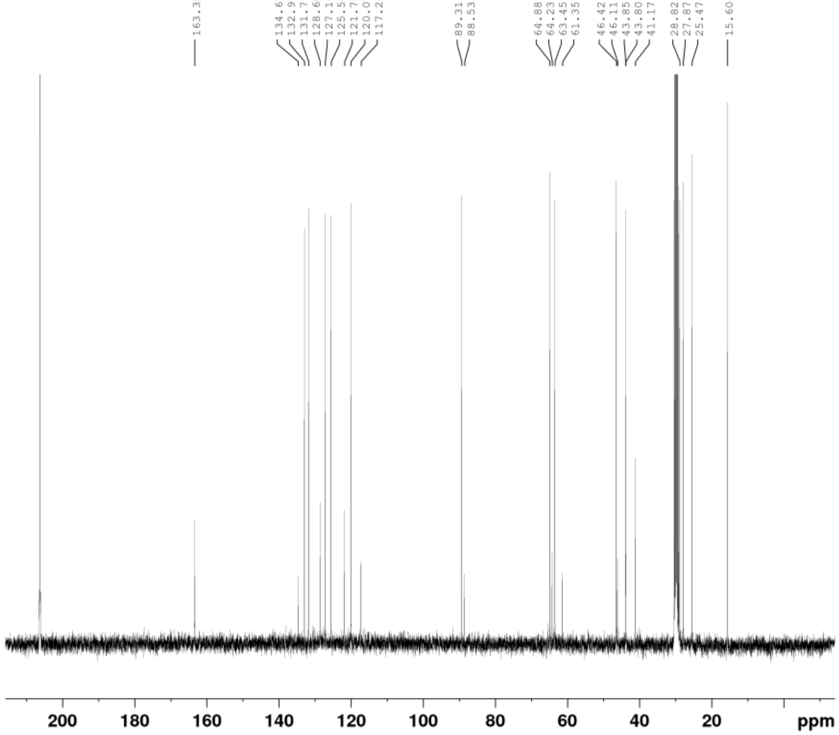
167b (minor)


162.89
135.63
132.16
130.16
128.61
128.55
127.88
127.54
126.23
121.01
90.29
63.82
61.33
46.44
45.47
43.47
29.09
27.61
25.28
15.55
200
180
160
140
120
100
80
60
40
20
ppm

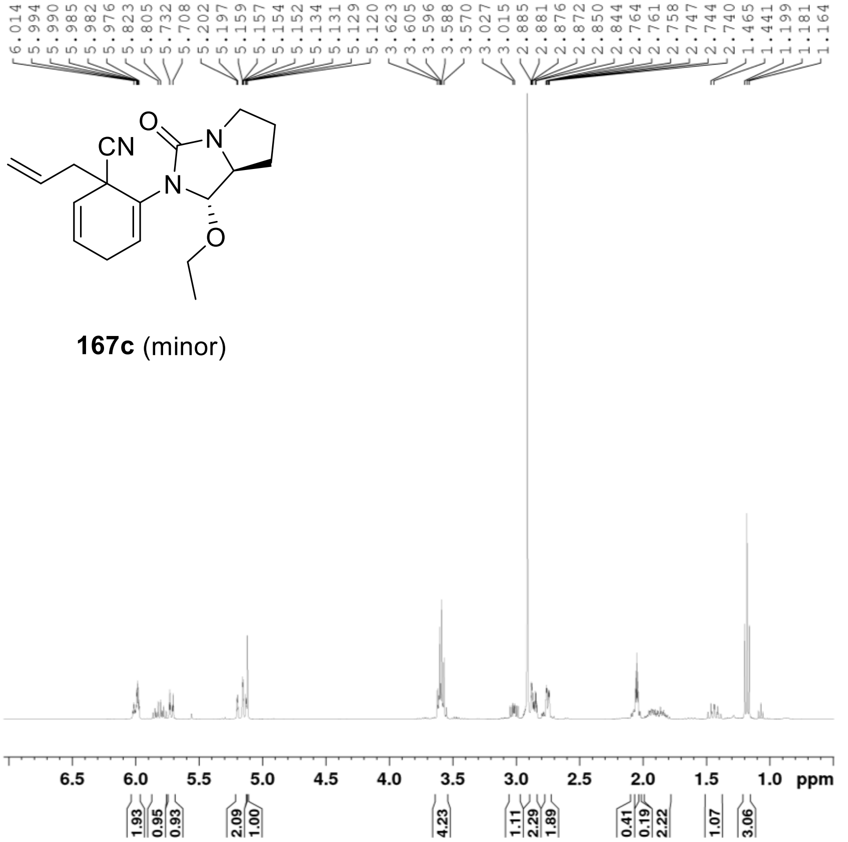


167c (major)

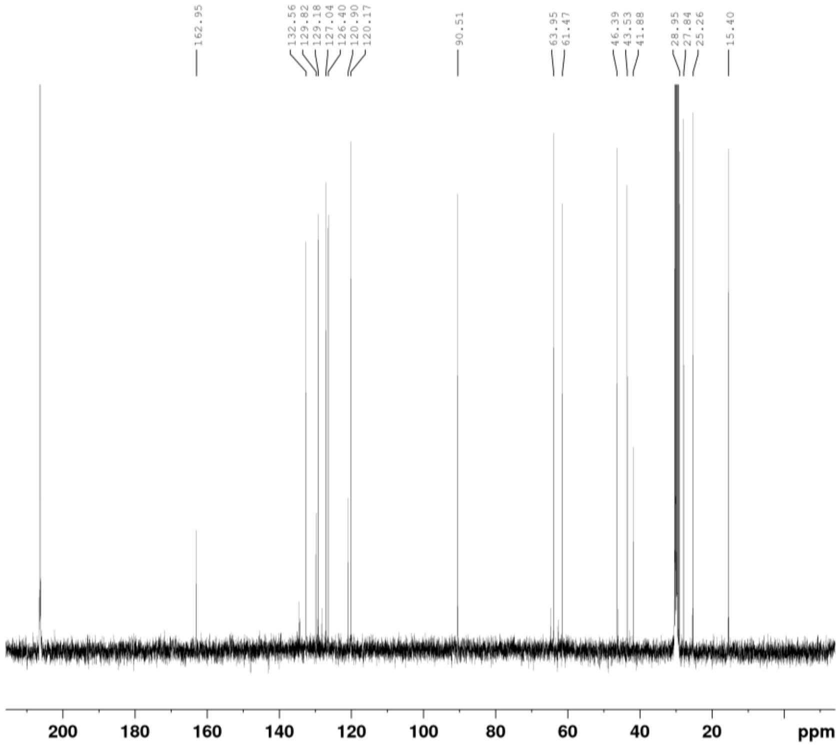
6.026
6.018
6.009
5.914
5.896
5.696
5.691
5.687
5.671
5.667
5.298
5.165
5.140
5.138
5.122
5.115
3.664
3.647
3.629
3.605
3.588
3.579
3.562
3.043
3.033
3.026
3.021
3.015
3.004
2.613
2.595
1.950
1.940
1.929
1.911
1.907
1.888
1.471
1.447
1.441
1.417
1.181
1.164
1.146
O
N
CN
N
O
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.04
1.12
1.04
1.00
2.56
0.16
2.26
2.60
1.22
2.12
2.16
0.99
2.45
1.13
3.74

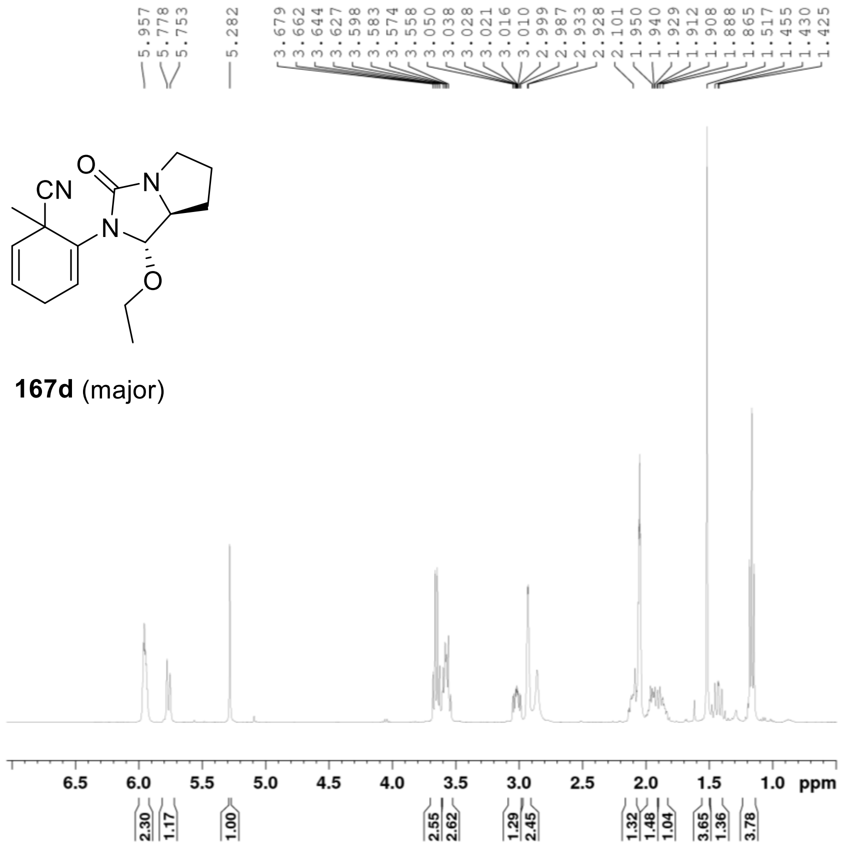


163.35
134.67
132.91
131.79
128.60
127.16
125.54
121.78
120.07
117.24
89.31
88.53
64.88
64.23
63.45
61.35
46.42
46.11
43.85
43.80
41.17
28.82
27.87
25.47
15.60
200
180
160
140
120
100
80
60
40
20
ppm

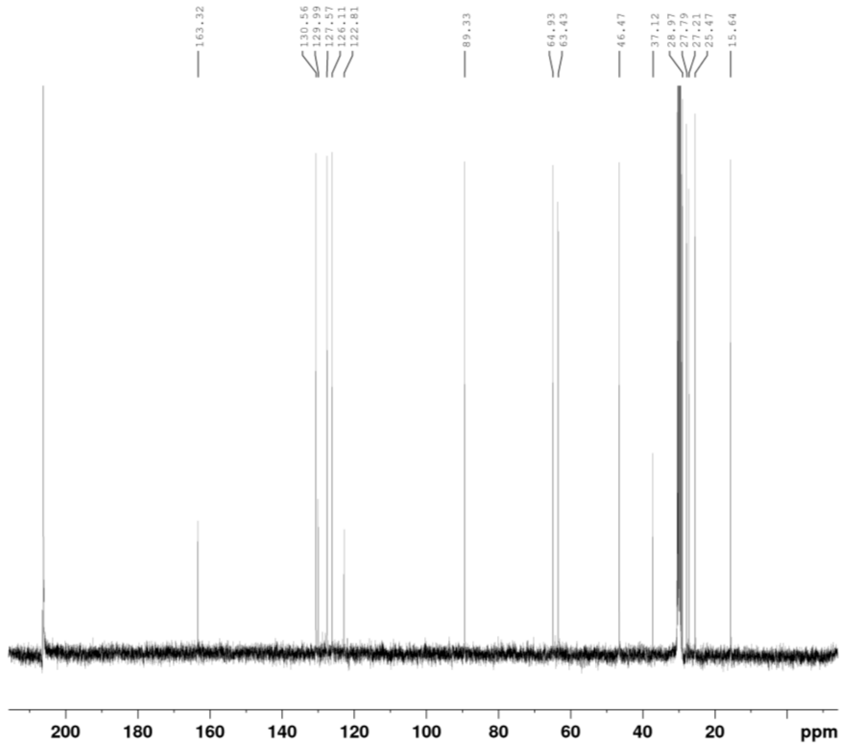

6.014
5.994
5.990
5.985
5.982
5.976
5.823
5.805
5.732
5.708
5.202
5.197
5.159
5.157
5.154
5.152
5.134
5.131
5.129
5.120
3.623
3.605
3.596
3.588
3.570
3.027
3.015
2.885
2.881
2.876
2.872
2.850
2.844
2.764
2.761
2.758
2.747
2.744
2.740
1.465
1.441
1.199
1.181
1.164
CN
O
N
N
O
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.93
0.95
0.93
2.09
1.00
4.23
1.11
2.29
1.89
0.41
0.19
2.22
1.07
3.06

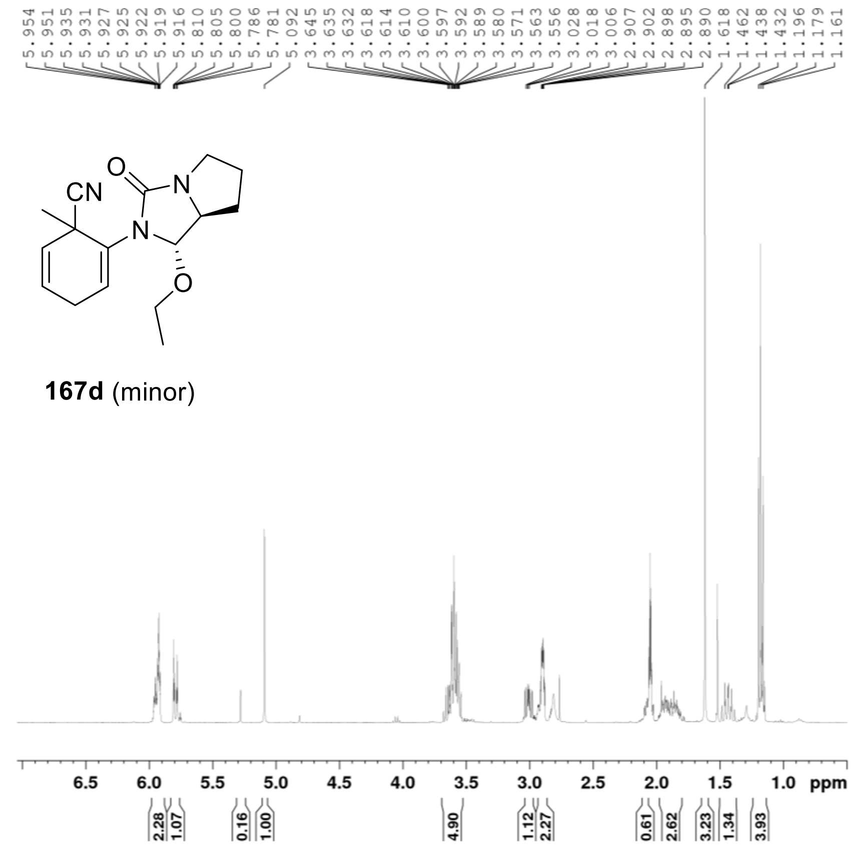
167c (minor)


162.95
132.56
129.82
129.18
127.04
126.40
120.90
120.17
90.51
63.95
61.47
46.39
43.53
41.88
28.95
27.84
25.26
15.40
200
180
160
140
120
100
80
60
40
20
ppm

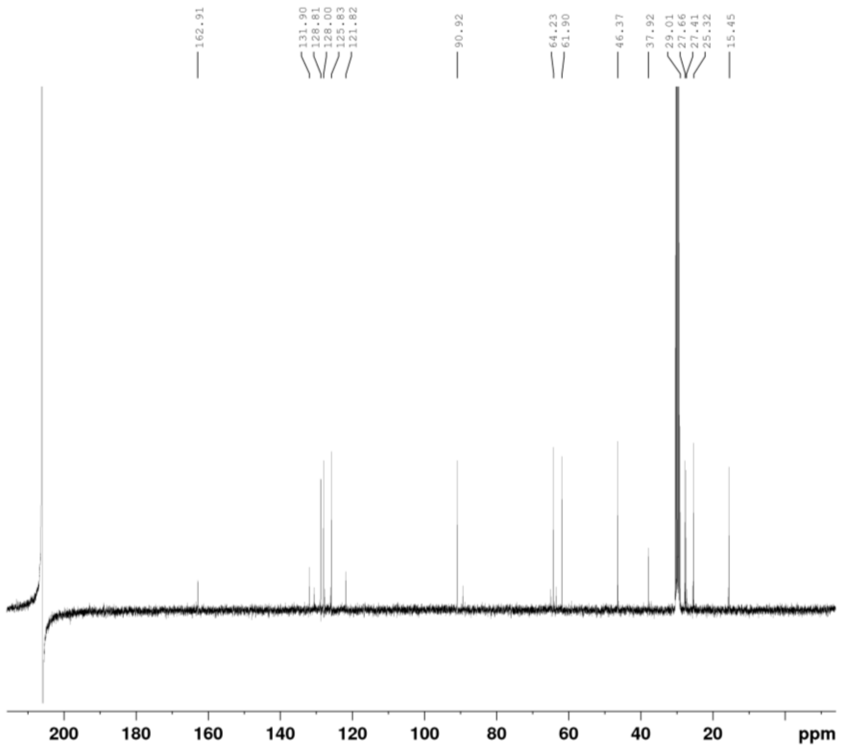

167d (major)

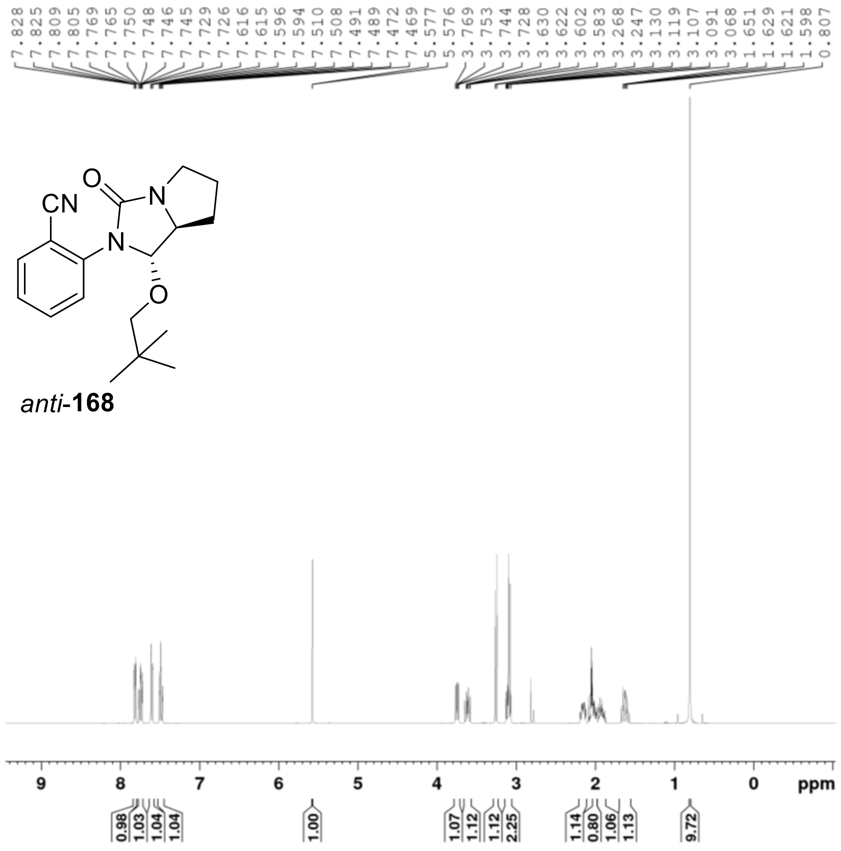
CN
O
N
N
O
5.957
5.778
5.753
5.282
3.679
3.662
3.644
3.627
3.598
3.583
3.574
3.558
3.050
3.038
3.021
3.016
3.010
2.999
2.987
2.933
2.928
2.101
1.950
1.940
1.929
1.912
1.908
1.888
1.865
1.517
1.455
1.430
1.425
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.30
1.17
1.00
2.55
2.62
1.29
2.45
1.32
1.48
1.04
3.65
1.36
3.78


163.32
130.56
129.99
127.57
126.11
122.81
89.33
64.93
63.43
46.47
37.12
28.97
27.79
27.21
25.47
15.64
200
180
160
140
120
100
80
60
40
20
ppm

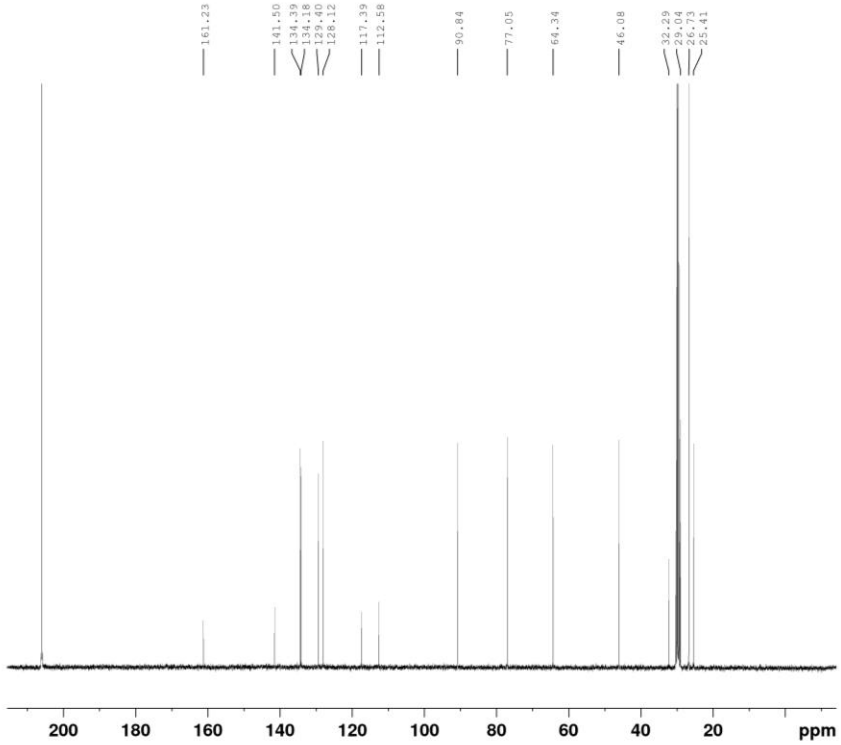

5.954
5.951
5.935
5.931
5.927
5.925
5.922
5.919
5.916
5.810
5.805
5.800
5.786
5.781
5.092
3.645
3.635
3.632
3.618
3.614
3.610
3.600
3.597
3.592
3.589
3.580
3.571
3.563
3.556
3.028
3.018
3.006
2.907
2.902
2.898
2.895
2.890
1.618
1.462
1.438
1.432
1.196
1.179
1.161
CN
O
N
N
O
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.28
1.07
0.16
1.00
4.90
1.12
2.27
0.61
2.62
3.23
1.34
3.93

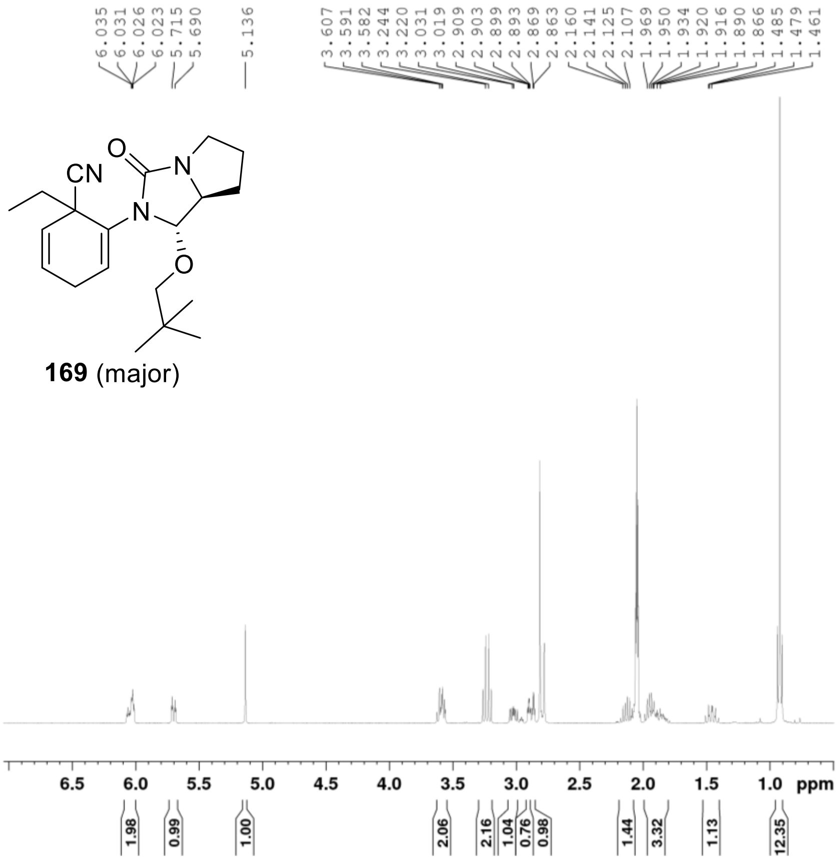
167d (minor)


162.91
131.90
128.81
128.00
125.83
121.82
90.92
64.23
61.90
46.37
37.92
29.01
27.66
27.41
25.32
15.45
200
180
160
140
120
100
80
60
40
20
ppm


7.828
7.825
7.809
7.805
7.769
7.765
7.750
7.748
7.746
7.745
7.729
7.726
7.616
7.615
7.596
7.594
7.510
7.508
7.491
7.489
7.472
7.469
5.577
5.576
3.769
3.753
3.744
3.728
3.630
3.622
3.602
3.583
3.268
3.247
3.130
3.119
3.107
3.091
3.068
1.651
1.629
1.621
1.598
0.807
CN
O
N
N
O
9
8
7
6
5
4
3
2
1
0
ppm
0.98
1.03
1.04
1.04
1.00
1.07
1.12
1.12
2.25
1.14
0.80
1.06
1.13
9.72

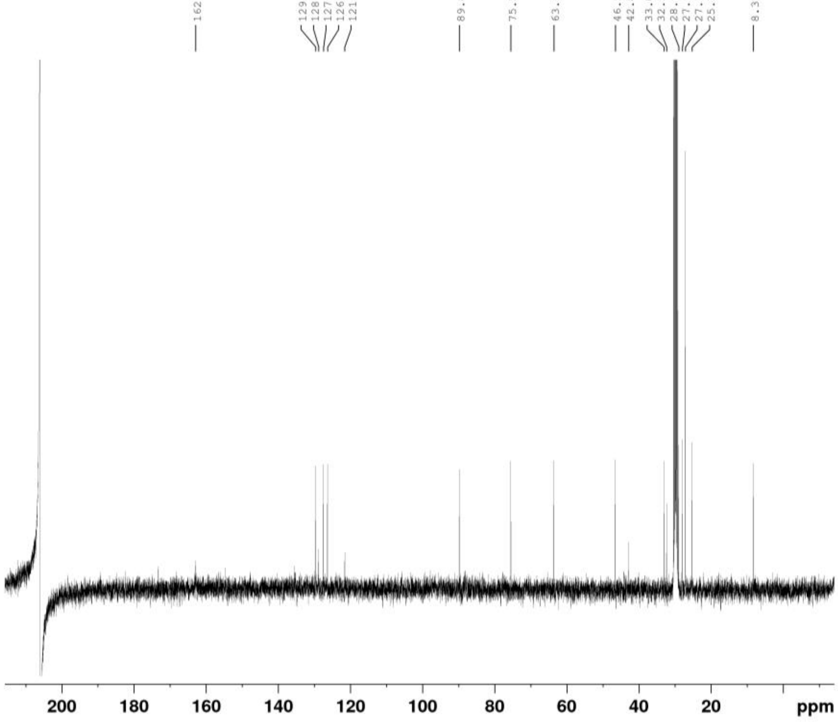
anti-**168**


161.23
141.50
134.39
134.18
129.40
128.12
117.39
112.58
90.84
77.05
64.34
46.08
32.29
29.04
26.73
25.41
200
180
160
140
120
100
80
60
40
20
ppm

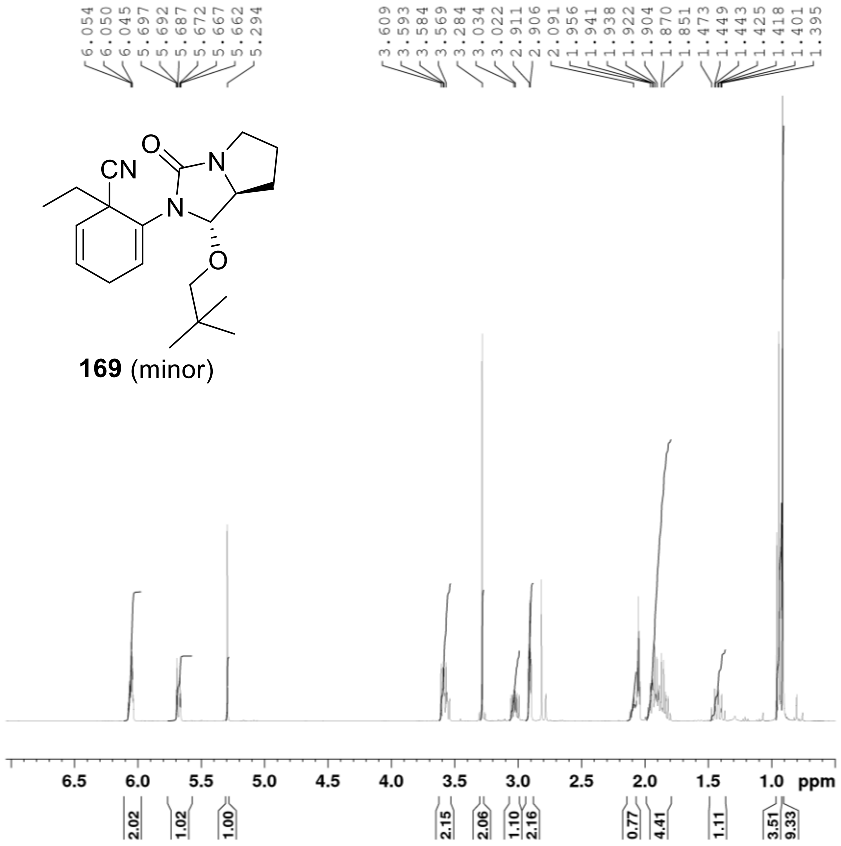


169 (major)

CN
O
N
N
O
6.035
6.031
6.026
6.023
5.715
5.690
5.136
3.607
3.591
3.582
3.244
3.220
3.031
3.019
2.909
2.903
2.899
2.893
2.869
2.863
2.160
2.141
2.125
2.107
1.969
1.950
1.934
1.920
1.916
1.890
1.866
1.485
1.479
1.461
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
1.98
0.99
1.00
2.06
2.16
1.04
0.76
0.98
1.44
3.32
1.13
12.35

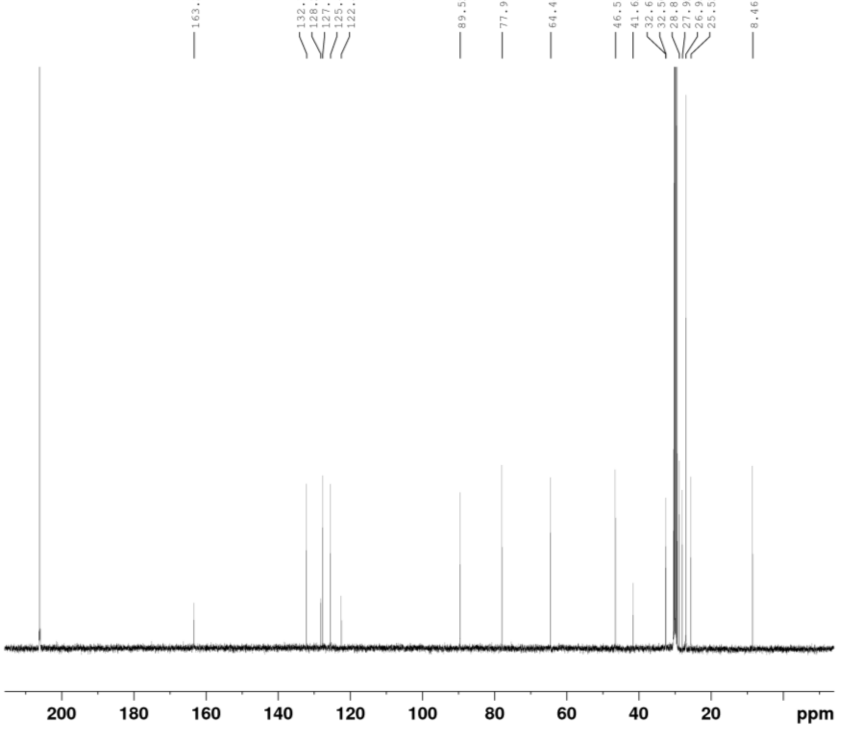


162.91
129.66
128.84
127.49
126.37
121.57
89.83
75.53
63.61
46.55
42.85
33.07
32.33
28.97
27.93
27.12
25.30
8.31
200
180
160
140
120
100
80
60
40
20
ppm

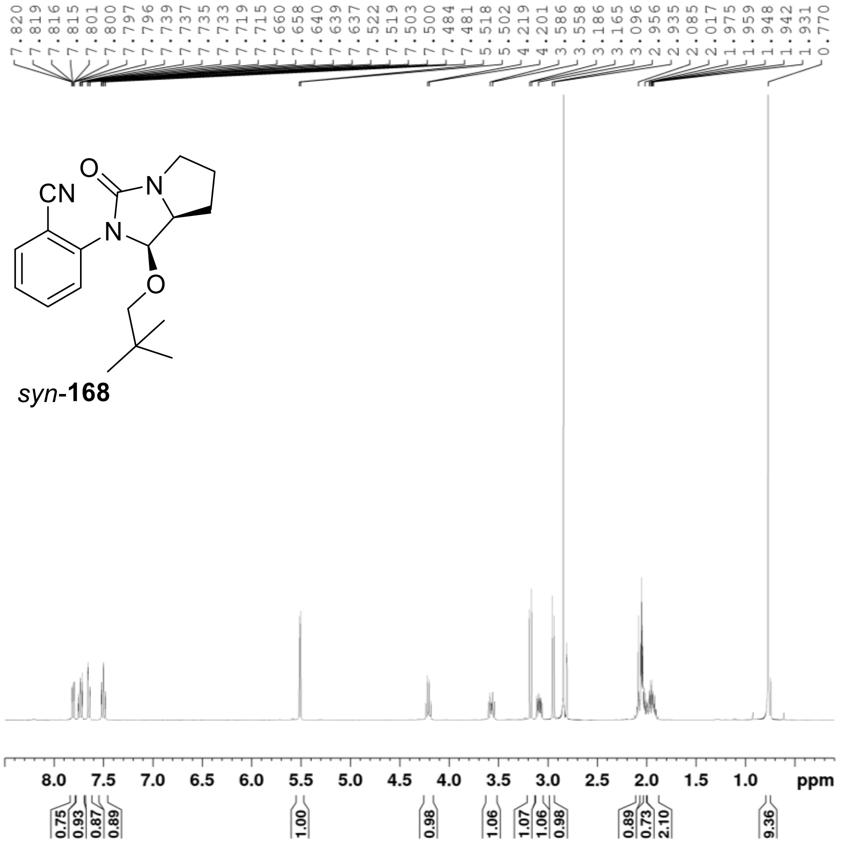


169 (minor)

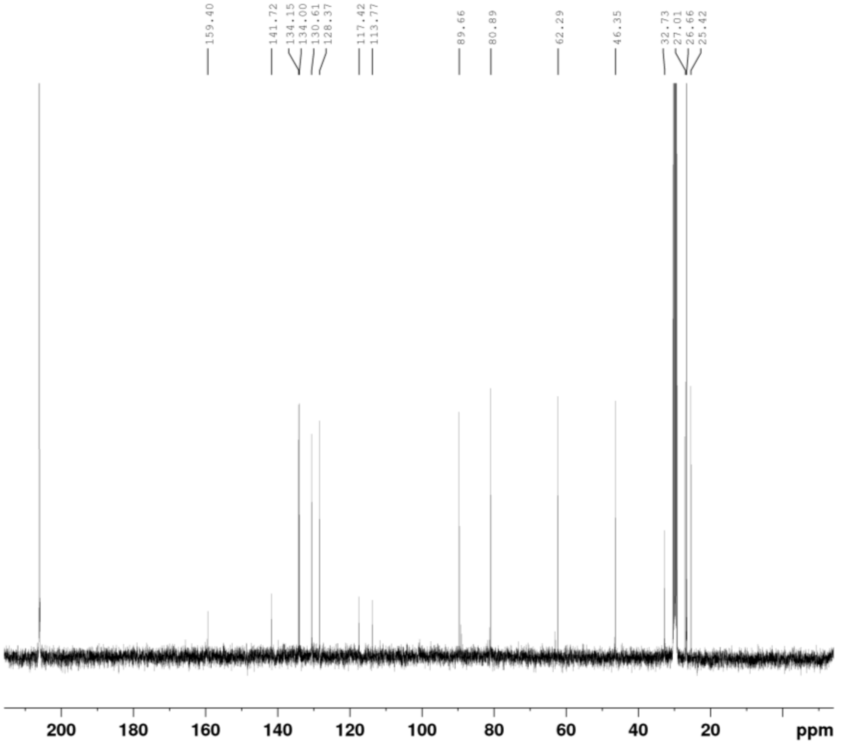
O
N
CN
N
O
6.054
6.050
6.045
5.697
5.692
5.687
5.672
5.667
5.662
5.294
3.609
3.593
3.584
3.569
3.284
3.034
3.022
2.911
2.906
2.091
1.956
1.941
1.938
1.922
1.904
1.870
1.851
1.473
1.449
1.443
1.425
1.418
1.401
1.395
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.02
1.02
1.00
2.15
2.06
1.10
2.16
0.77
4.41
1.11
3.51
9.33

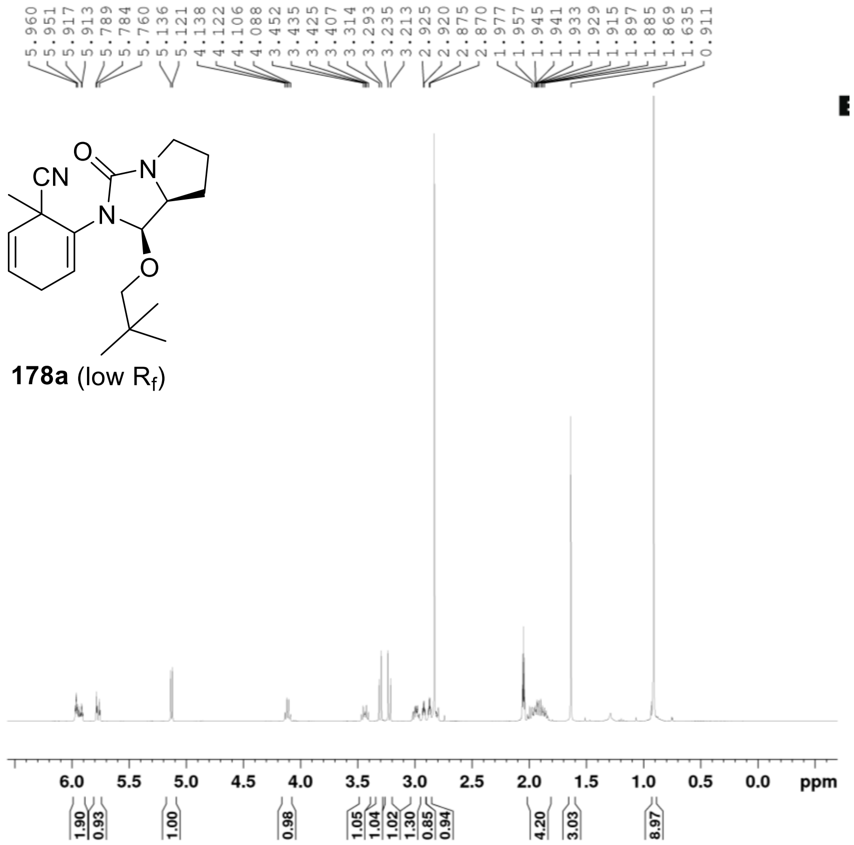


163.31
132.10
128.22
127.68
125.48
122.50
89.52
77.96
64.44
46.51
41.62
32.61
32.50
28.81
27.92
26.95
25.52
8.46
200
180
160
140
120
100
80
60
40
20
ppm

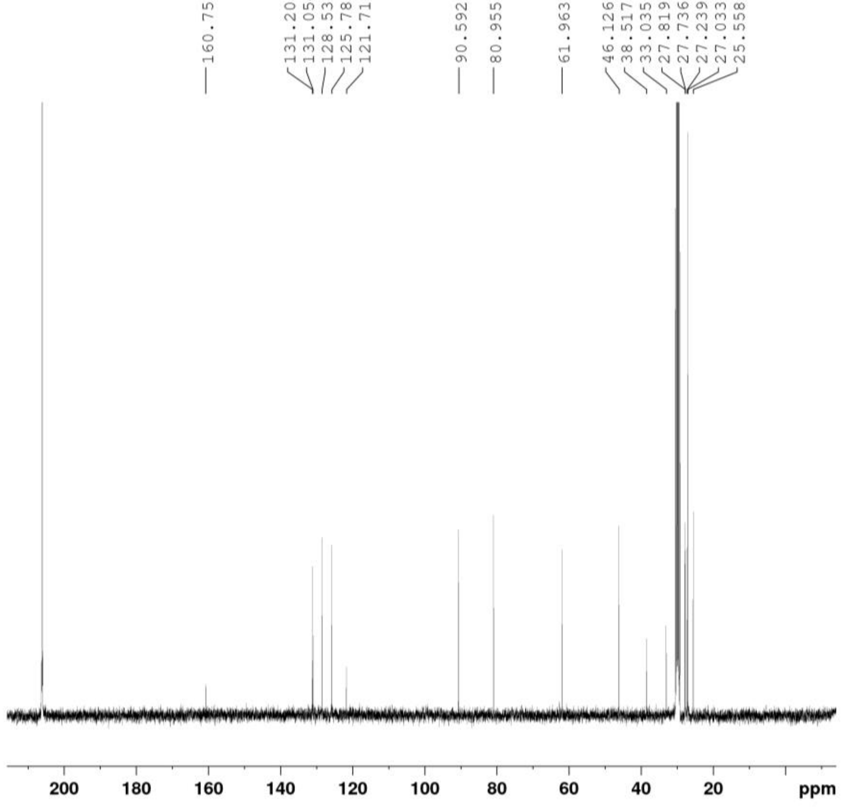

CN
O
N
N
O
7.820
7.819
7.816
7.815
7.801
7.800
7.797
7.796
7.739
7.737
7.735
7.733
7.719
7.715
7.660
7.658
7.640
7.639
7.637
7.522
7.519
7.503
7.500
7.484
7.481
5.518
5.502
4.219
4.201
3.586
3.558
3.186
3.165
3.096
2.956
2.935
2.085
2.017
1.975
1.959
1.948
1.942
1.931
0.770
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.75
0.93
0.87
0.89
1.00
0.98
1.06
1.07
1.06
0.98
0.89
0.73
2.10
9.36

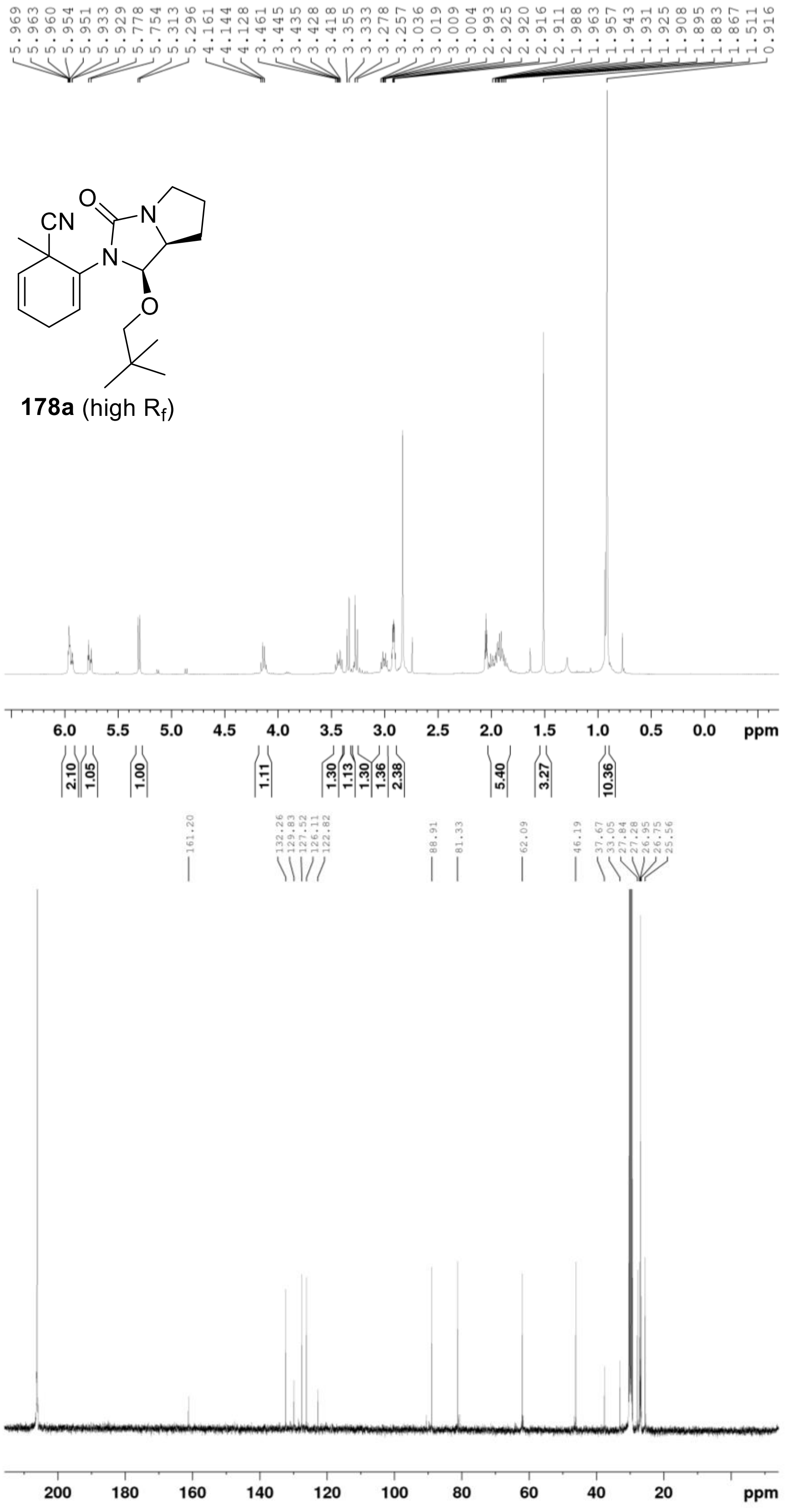
syn-**168**


159.40
141.72
134.15
134.00
130.61
128.37
117.42
113.77
89.66
80.89
62.29
46.35
32.73
27.01
26.66
25.42
200
180
160
140
120
100
80
60
40
20
ppm

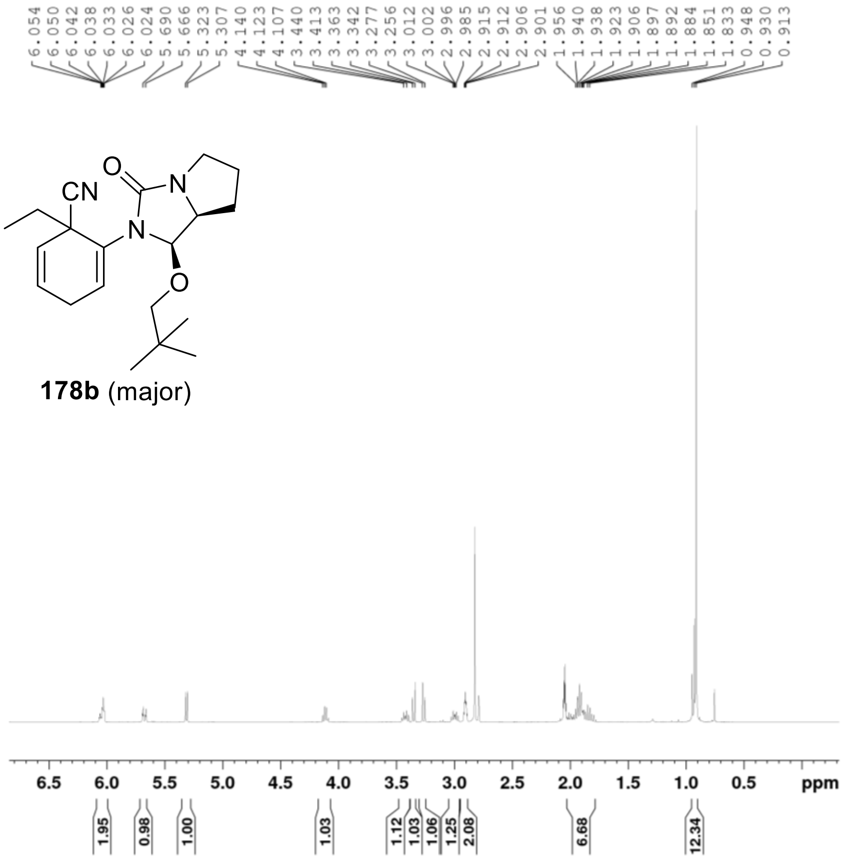

5.960
5.951
5.917
5.913
5.789
5.784
5.760
5.136
5.121
4.138
4.122
4.106
4.088
3.452
3.435
3.425
3.407
3.314
3.293
3.235
3.213
2.925
2.920
2.875
2.870
1.977
1.957
1.945
1.941
1.933
1.929
1.915
1.897
1.885
1.869
1.635
0.911
CN
O
N
N
O
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.90
0.93
1.00
0.98
1.05
1.04
1.02
1.30
0.85
0.94
4.20
3.03
8.97

178a (low R_f)

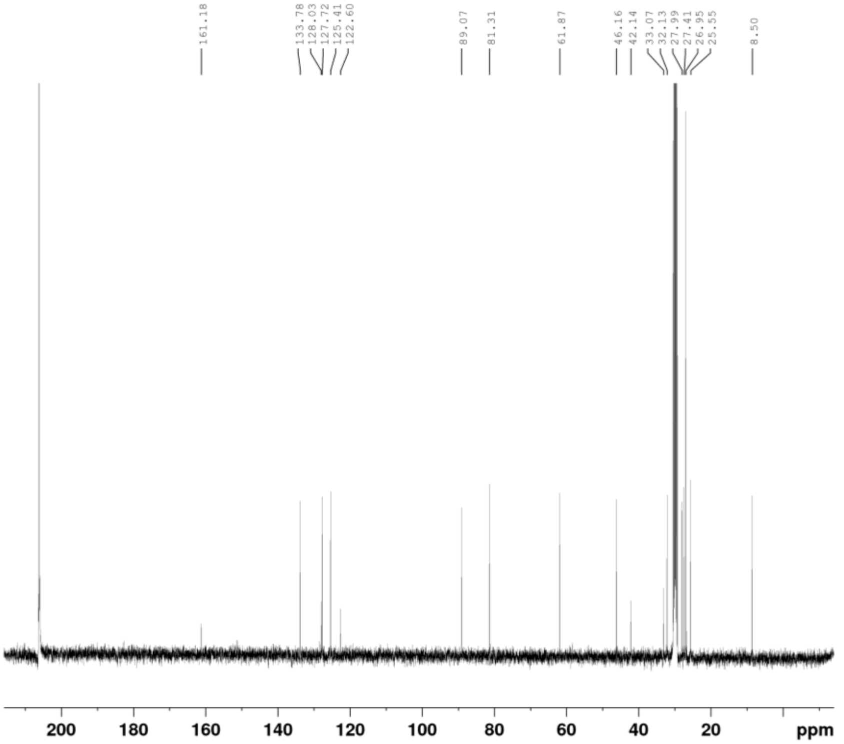

160.759
131.205
131.054
128.531
125.786
121.719
90.592
80.955
61.963
46.126
38.517
33.035
27.819
27.736
27.239
27.033
25.558
200
180
160
140
120
100
80
60
40
20
ppm

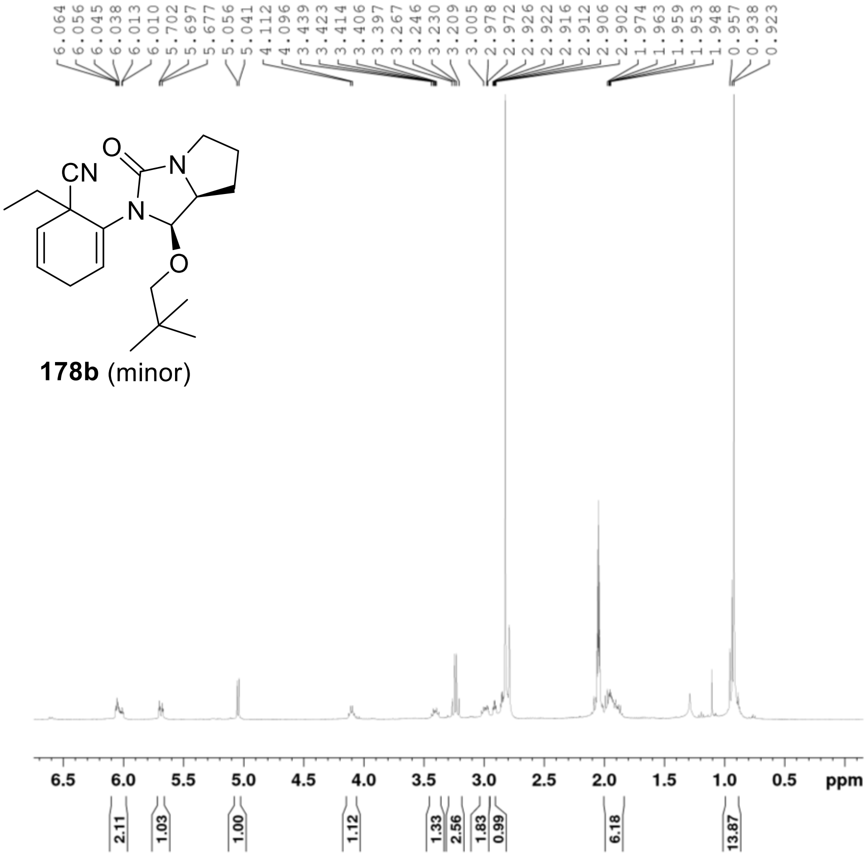

CN
O
N
N
O
5.969
5.963
5.960
5.954
5.951
5.933
5.929
5.778
5.754
5.313
5.296
4.161
4.144
4.128
3.461
3.445
3.435
3.428
3.418
3.355
3.333
3.278
3.257
3.036
3.019
3.009
3.004
2.993
2.925
2.920
2.916
2.911
1.988
1.963
1.957
1.943
1.931
1.925
1.908
1.895
1.883
1.867
1.511
0.916
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.10
1.05
1.00
1.11
1.30
1.13
1.30
1.36
2.38
5.40
3.27
10.36
161.20
132.26
129.83
127.52
126.11
122.82
88.91
81.33
62.09
46.19
37.67
33.05
27.84
27.28
26.95
26.75
25.56
200
180
160
140
120
100
80
60
40
20
ppm

178a (high R_f)

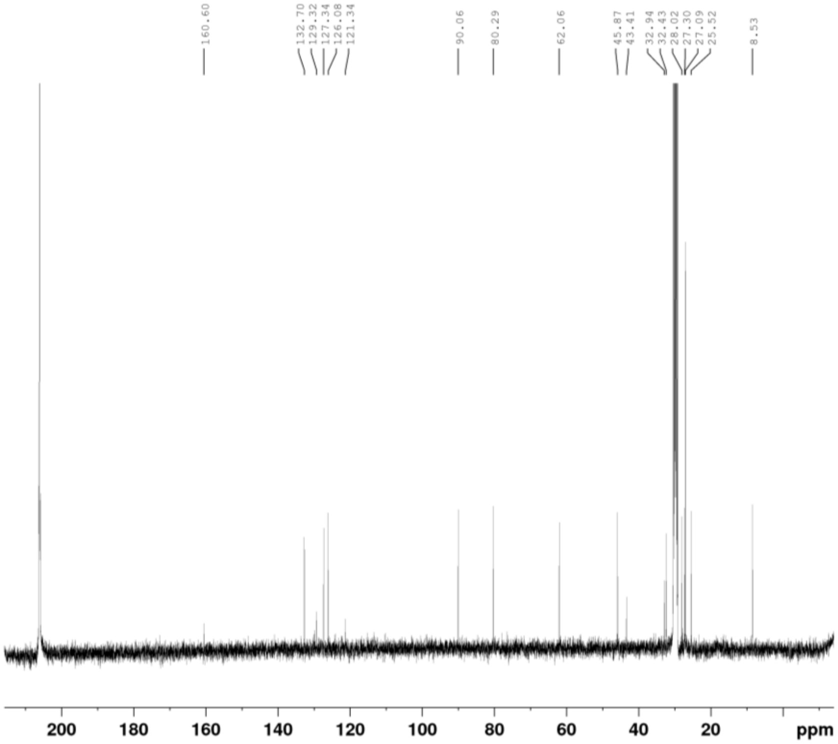

CN
O
N
N
O
6.054
6.050
6.042
6.038
6.033
6.026
6.024
5.690
5.666
5.323
5.307
4.140
4.123
4.107
3.440
3.413
3.363
3.342
3.277
3.256
3.012
3.002
2.996
2.985
2.915
2.912
2.906
2.901
1.956
1.940
1.938
1.923
1.906
1.897
1.892
1.884
1.851
1.833
0.948
0.930
0.913
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.95
0.98
1.00
1.03
1.12
1.03
1.06
1.25
2.08
6.68
12.34

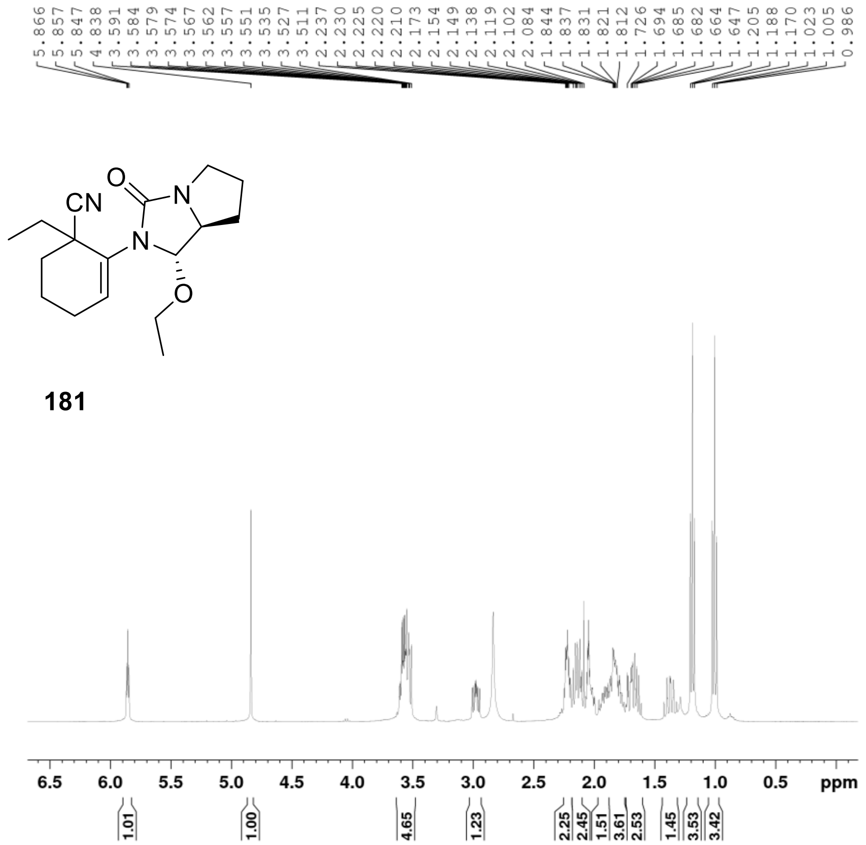
178b (major)

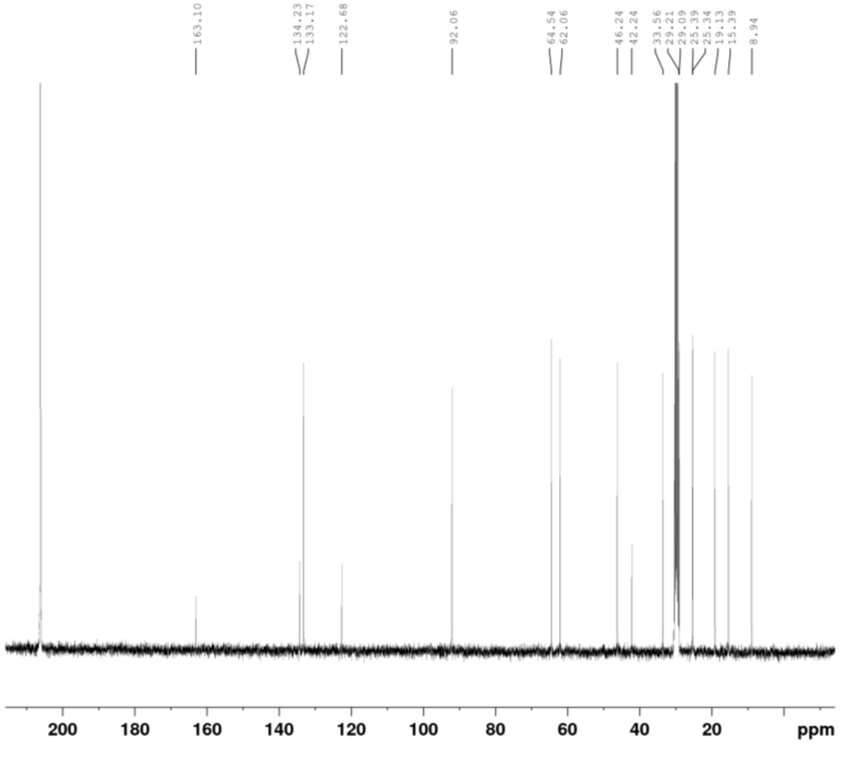

161.18
133.78
128.03
127.72
125.41
122.60
89.07
81.31
61.87
46.16
42.14
33.07
32.13
27.99
27.41
26.95
25.55
8.50
200
180
160
140
120
100
80
60
40
20
ppm

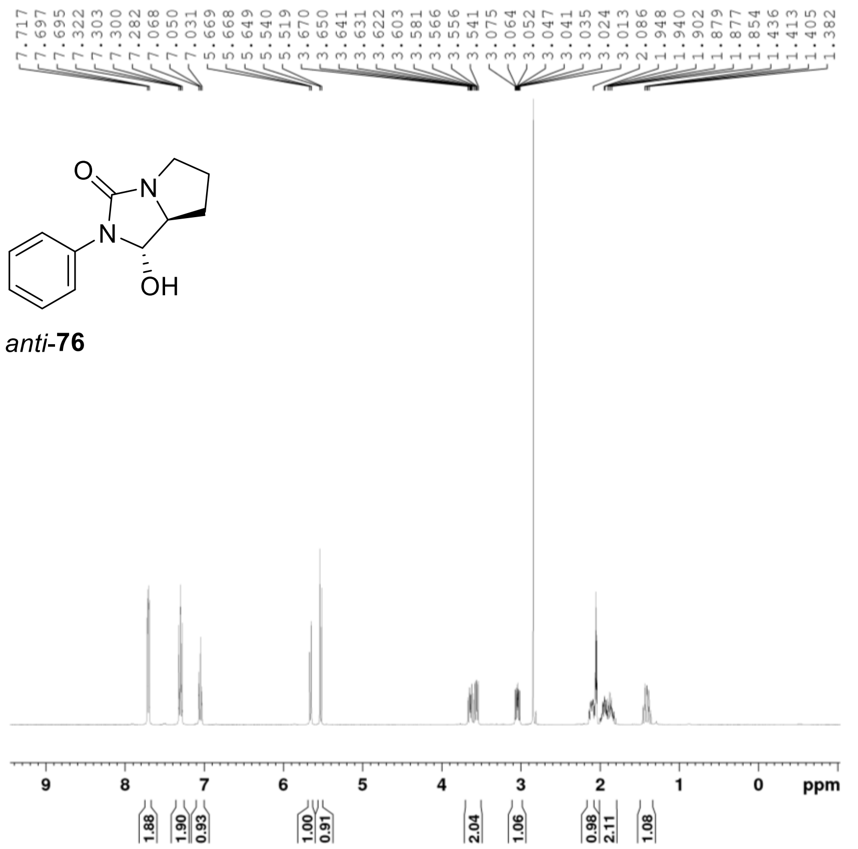

CN
O
N
N
O
6.064
6.056
6.045
6.038
6.013
6.010
5.702
5.697
5.677
5.056
5.041
4.112
4.096
3.439
3.423
3.414
3.406
3.397
3.267
3.246
3.230
3.209
3.005
2.978
2.972
2.926
2.922
2.916
2.912
2.906
2.902
1.974
1.963
1.959
1.953
1.948
0.957
0.938
0.923
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.11
1.03
1.00
1.12
1.33
2.56
1.83
0.99
6.18
13.87

178b (minor)

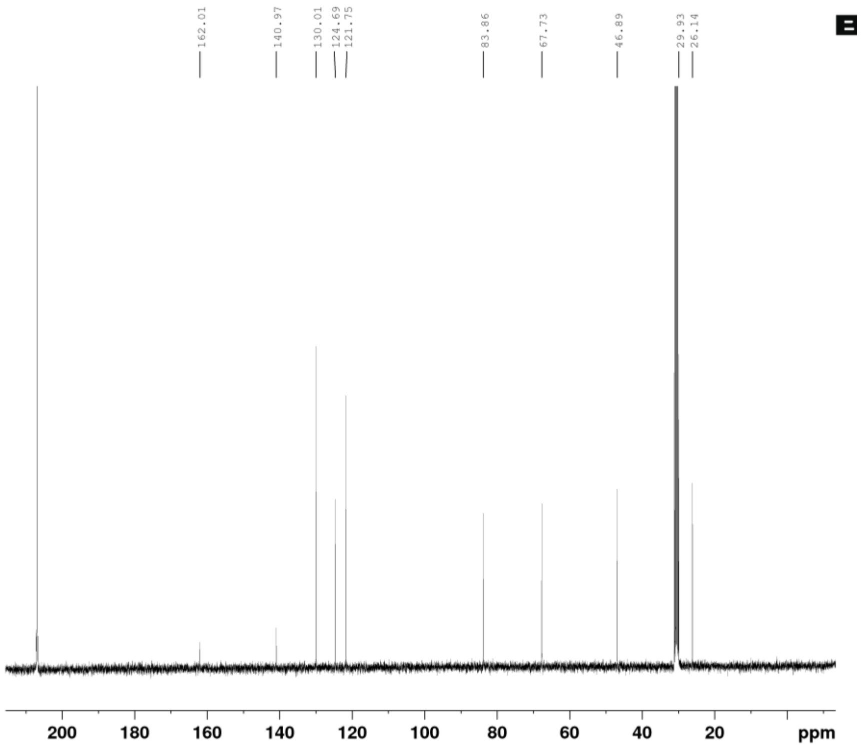

160.60
132.70
129.32
127.34
126.08
121.34
90.06
80.29
62.06
45.87
43.41
32.94
32.43
28.02
27.30
27.09
25.52
8.53
200
180
160
140
120
100
80
60
40
20
ppm

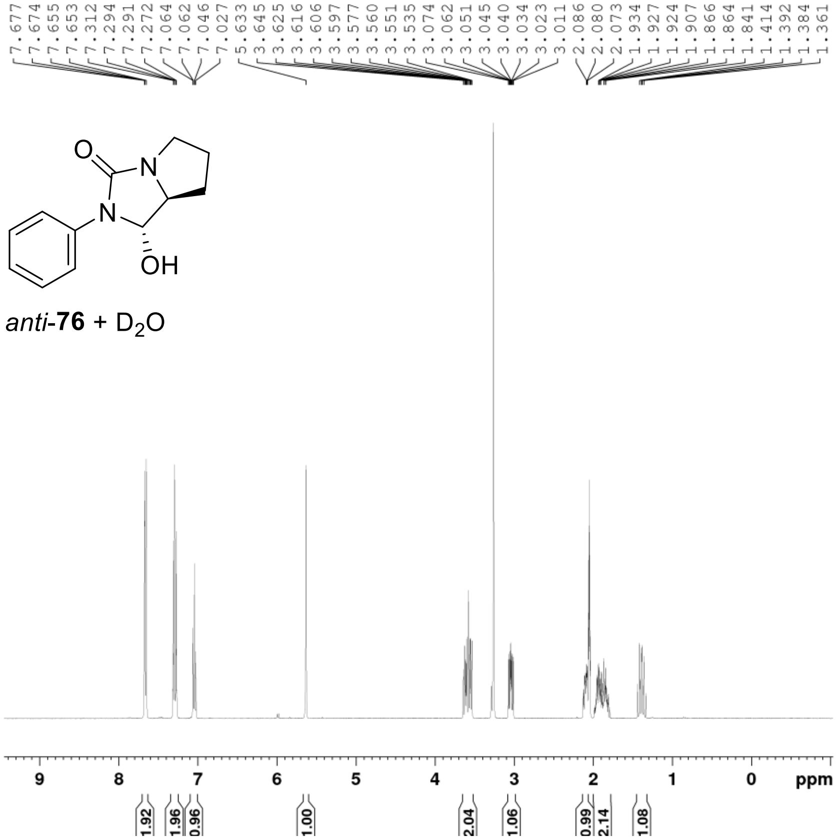

5.866
5.857
5.847
4.838
3.591
3.584
3.579
3.574
3.567
3.562
3.557
3.551
3.535
3.527
3.511
2.237
2.230
2.225
2.220
2.210
2.173
2.154
2.149
2.138
2.119
2.102
2.084
1.844
1.837
1.831
1.821
1.812
1.726
1.694
1.685
1.682
1.664
1.647
1.205
1.188
1.170
1.023
1.005
0.986
CN
O
N
N
O
181
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.01
1.00
4.65
1.23
2.25
2.45
1.51
3.61
2.53
1.45
3.53
3.42


163.10
134.23
133.17
122.68
92.06
64.54
62.06
46.24
42.24
33.56
29.21
29.09
25.39
25.34
19.13
15.39
8.94
200
180
160
140
120
100
80
60
40
20
ppm


7.717
7.697
7.695
7.322
7.303
7.300
7.282
7.068
7.050
7.031
5.669
5.668
5.649
5.540
5.519
3.670
3.650
3.641
3.631
3.622
3.603
3.581
3.566
3.556
3.541
3.075
3.064
3.052
3.047
3.041
3.035
3.024
3.013
2.086
1.948
1.940
1.902
1.879
1.877
1.854
1.436
1.413
1.405
1.382
O
N
N
OH
9
8
7
6
5
4
3
2
1
0
ppm
1.88
1.90
0.93
1.00
0.91
2.04
1.06
0.98
2.11
1.08

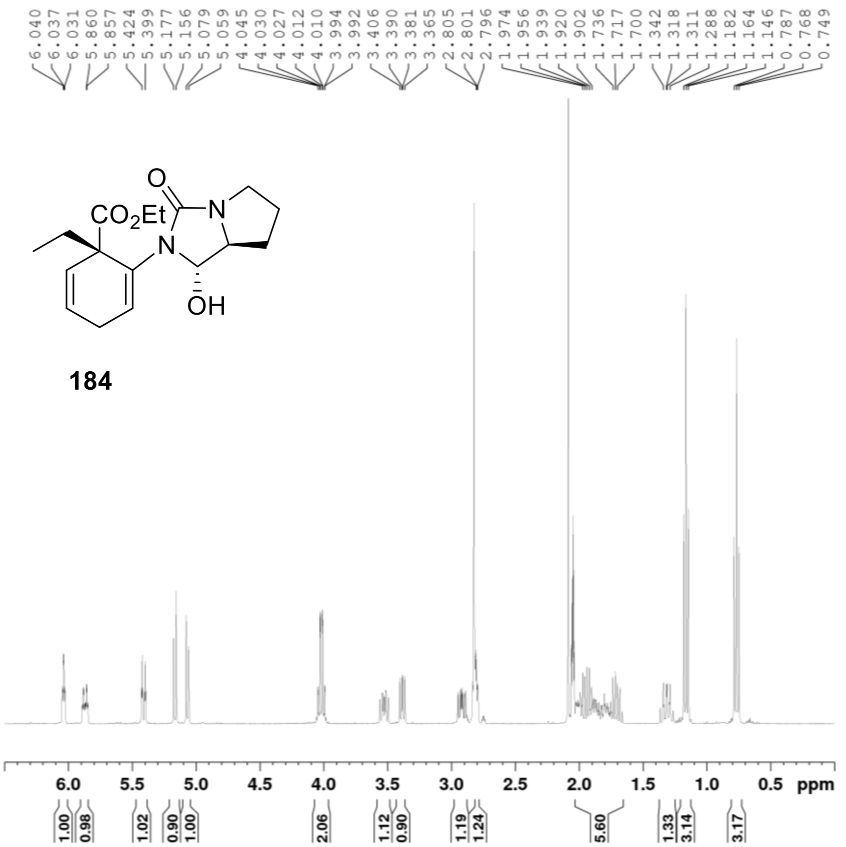
anti-**76**


162.01
140.97
130.01
124.69
121.75
83.86
67.73
46.89
29.93
26.14
200
180
160
140
120
100
80
60
40
20
ppm

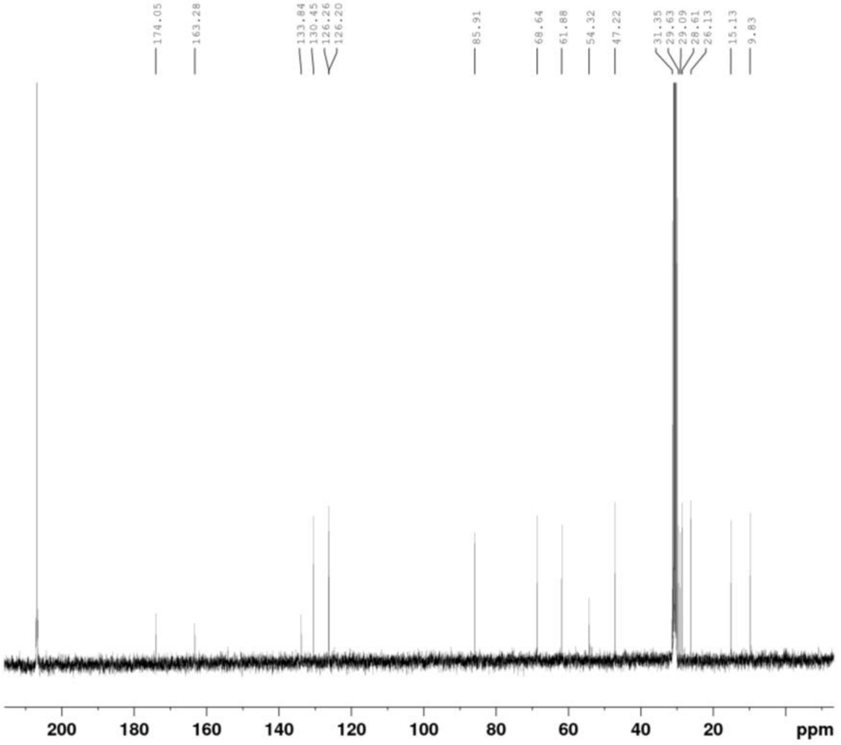


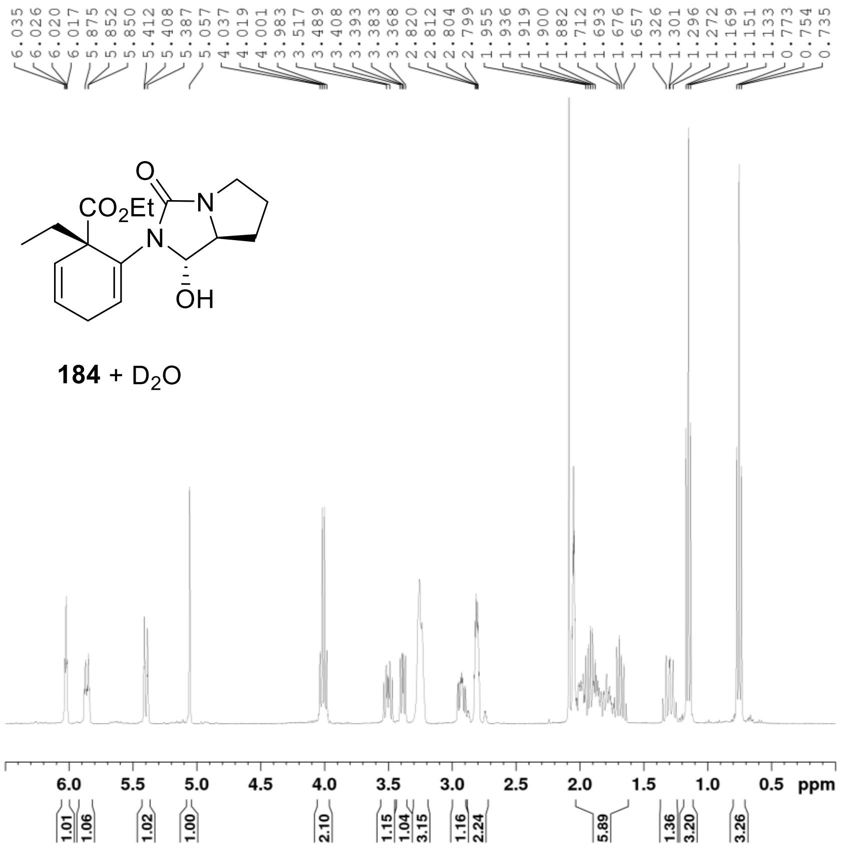
anti-**76** + D_2O

7.677
7.674
7.655
7.653
7.312
7.294
7.291
7.272
7.064
7.062
7.046
7.027
5.633
3.645
3.625
3.616
3.606
3.597
3.577
3.560
3.551
3.535
3.074
3.062
3.051
3.045
3.040
3.034
3.023
3.011
2.086
2.080
2.073
1.934
1.927
1.924
1.907
1.866
1.864
1.841
1.414
1.392
1.384
1.361
O
N
N
OH
9
8
7
6
5
4
3
2
1
0
ppm
1.92
1.96
0.96
1.00
2.04
1.06
0.99
2.14
1.08


6.040
6.037
6.031
5.860
5.857
5.424
5.399
5.177
5.156
5.079
5.059
4.045
4.030
4.027
4.012
4.010
3.994
3.992
3.406
3.390
3.381
3.365
2.805
2.801
2.796
1.974
1.956
1.939
1.920
1.902
1.736
1.717
1.700
1.342
1.318
1.311
1.288
1.182
1.164
1.146
0.787
0.768
0.749
O
CO2Et
N
N
OH
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
0.98
1.02
0.90
1.00
2.06
1.12
0.90
1.19
1.24
5.60
1.33
3.14
3.17

184


174.05
163.28
133.84
130.45
126.26
126.20
85.91
68.64
61.88
54.32
47.22
31.35
29.63
29.09
28.61
26.13
15.13
9.83
200
180
160
140
120
100
80
60
40
20
ppm



184 + D$_2$O

6.035
6.026
6.020
6.017
5.875
5.852
5.850
5.412
5.408
5.387
5.057
4.037
4.019
4.001
3.983
3.517
3.489
3.408
3.393
3.383
3.368
2.820
2.812
2.804
2.799
1.955
1.936
1.919
1.900
1.882
1.712
1.693
1.676
1.657
1.326
1.301
1.296
1.272
1.169
1.151
1.133
0.773
0.754
0.735
CO2Et
O
N
N
OH
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
1.06
1.02
1.00
2.10
1.15
1.04
3.15
1.16
2.24
5.89
1.36
3.20
3.26