APPLICATION OF ORGANOCATALYSIS TO THE SYNTHESIS OF PHARMACOLOGICAL RELEVANT SCAFFOLDS: CHIRAL β-FLUOROAMINES AND AZIRIDINES. TOTAL SYNTHESIS OF CARPANONE, POLEMANNONE B & C AND BREVISAMIDE, AND A GENERAL APPROACH FOR THE CONSTRUCTION OF AZABICYCLIC RING-CONTAINING ALKALOIDS

By

Olugbeminiyi Fadeyi

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

August, 2011

Nashville, Tennessee

Approved:

Professor Craig W. Lindsley

Professor Gary A. Sulikowski

Professor Lawrence J. Marnett

Professor Jens Meiler

To Saudat, Baby on the way,

My Dad, Mum, Professor Adamson, My brother and sisters.

ACKNOWLEGEMENTS

I would like to take a few paragraphs to acknowledge and extend my gratitude to the individuals whose encouragement and guidance provided me with the support that I needed to complete the work in this dissertation, and because of whom my graduate experience has been one that I will always cherish.

First and above all, I praise Almighty God, the author of my ability and the source of my strength for giving me the opportunity and diligence to accomplish this goal.

It is with utmost gratitude that I acknowledge my advisor, Prof. Craig Lindsley. I have been exceedingly fortunate to have an advisor who afforded me the freedom to explore and at the same time the guidance to recover when my steps faltered. Craig fulfills every meaning of an advisor, providing both support and advice in both academic and personal matters, allowing me to find my own way when necessary but making sure that I always ended in the right direction.

I would also like to thank all the members of the Lindsley Group that I have interacted with during my time at Vanderbilt. The informal support and encouragement of many friends has been indispensable, and I would like particularly to acknowledge Leslie Aldrich for her patience and kindness as a loyal friend in the lab and Nate Daniels, whose sense of humor and light-hearted spirit behooves him as a trusted companion. I also owe Kyle Emmitte, Yiu-Yin (Y-Y) Cheung, and Bruce Melancon immensely for their timely advice and solutions to problems that I encountered during the course of my research.

Special thanks to Steve Townsend for being a good friend and making my experience at Vanderbilt feel closer to home.

I am also indebted to my closest friend at Vanderbilt, Danielle Kimmel who has been like family to me. The completion of my graduate experience would not have been the same without her incomparable support, honesty and unwavering encouragement through both challenges and successes.

I am forever appreciative to my parents for their confidence in me, high esteem and encouragement throughout my life and my academic endeavors.

Finally to the love and light of my life, my wife Saudat who has given her unconditional support, understanding and motivation from the very beginning, I give my sincere appreciation and loving gratitude.

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LIST OF ABBREVIATIONS

AIBN	2,2'-azobisisobutryonitrile
Ac	acetyl
AcOH	acetic acid
9-BBN	9-borabicyclo [3.3.1]nonane
BINOL	1,1'-bi-2-napthol
$BF_3{\cdot}OEt_2$	boro trifluoride diethyl ether
Bn	benzyl
BnBr	benzyl bromide
Boc	*t*-Butyloxycarbonyl
BOM	benzyloxymethyl
BQ	1,4-benzoquinone
Bz	benzoyl
^oC	degrees Celsius
cat.	catalytic
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
conc	concentration
CSA	10-camphorsulfonic acid
Cs_2CO_3	cesium carbonate
CYP450	cytochrome P450

δ	chemical shift in ppm
d	doublet
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DIEA	*N*,*N* diisopropylethylamine
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMPK	Drug Metabolism/Pharmacokinetics
DMSO	dimethyl sulfoxide
dt	doublet of triplet
eq.	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GPCR	G-protein coupled receptor
h	hour

HCl	hydrogen chloride
hERG	human ether-a-go-go related gene
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocamphyl
K_2CO_3	potassium carbonate
KHMDS	potassium hexamethyldisilazide
L	liter(s)
LDA	lithium diisopropylamide
LIDBB	4,4'-di-tert-butyl-biphenyllithium
LiAlH4	lithium aluminum hydride
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MeI	iodomethane
MeOH	methanol
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
NaOH	sodium hydroxide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine N-oxide
Np	2-naphthyl
Ph	phenyl
Pd/C	palladium on carbon
PMB	4-methoxybenzyl
Ph	phenyl
ppm	parts per million
py	pyridine
$Rh_2(OAc)_4$	dirhodium acetate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

CHAPTER I

A NEW CATALYTIC Cu(II)/SPARTEINE OXIDANT SYSTEM FOR β-β′-PHENOLIC COUPLINGS OF STYRENYL PHENOLS: SYNTHESIS OF CARPANONE AND UNNATURAL ANALOGS

1. 1. Introduction

Natural products represent a rich source of biologically active compounds and are an example of molecular diversity, with recognized potential in drug discovery and development.[1-5] Oxygen-containing heterocycles are common motifs in natural products and pharmaceuticals, and the synthesis of these compounds remains an important challenge in total synthesis. The Benzoxanthenones class which was discovered in 1969 by Brophy and co-workers, belong to a large and constantly expanding family of lignan natural products.

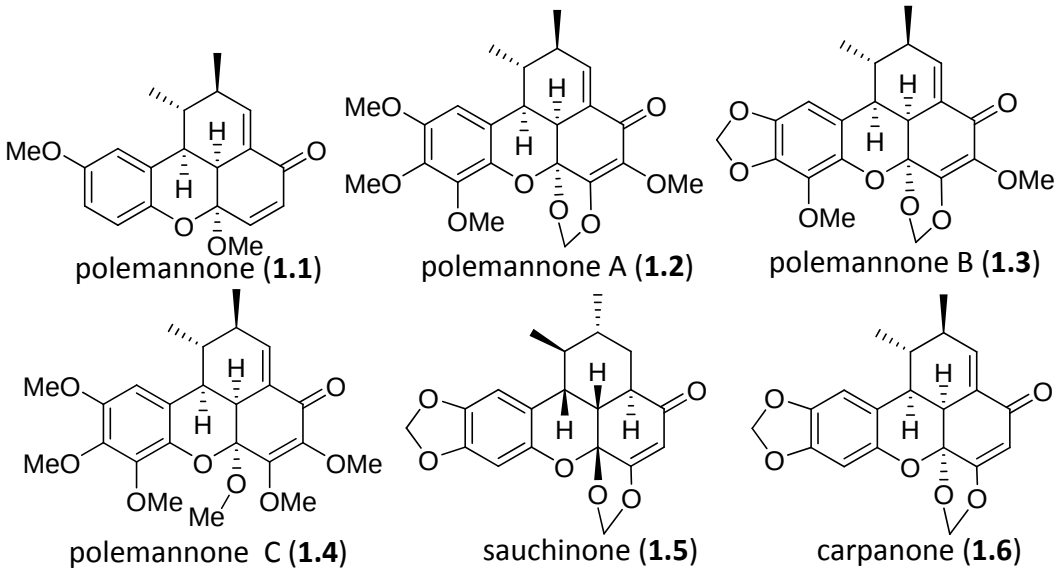


Figure 1.1. Benzoxanthone natural products.

Their highly oxygenated tetracyclic/pentacyclic carbon frameworks comprise a number of contiguous stereocenters, isolated as single diastereomers and produced in nature as racemates. Notable members include (Figure 1.1) polemannone (**1.1**), polemannone A (**1.2**), polemannone B (**1.3**), polemannone C (**1.4**),[6] sauchinone (**1.5**),[7] and carpanone (**1.6**).[8]Carpanone (**1.6**), a rigid hexacyclic core lignan with five contiguous stereocenters, was isolated in Australia from light petroleum extracts of the bark of carpano tree, a *Cinnamomium* sp. in Australia.

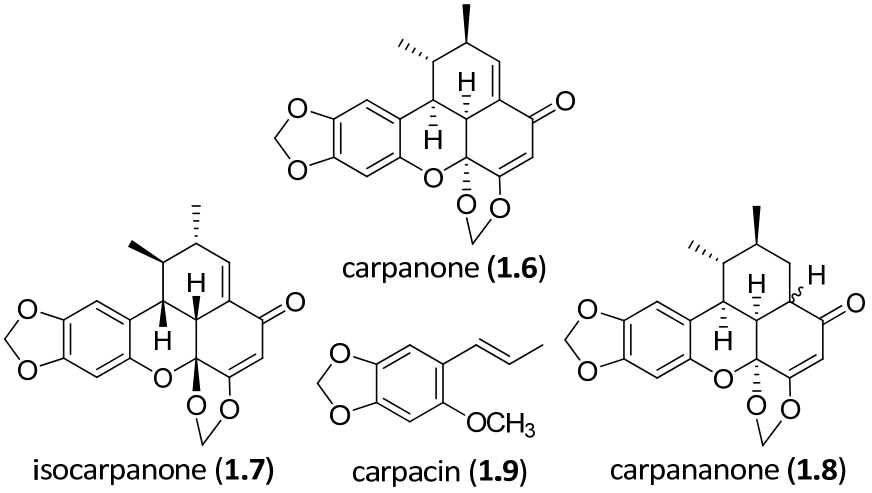
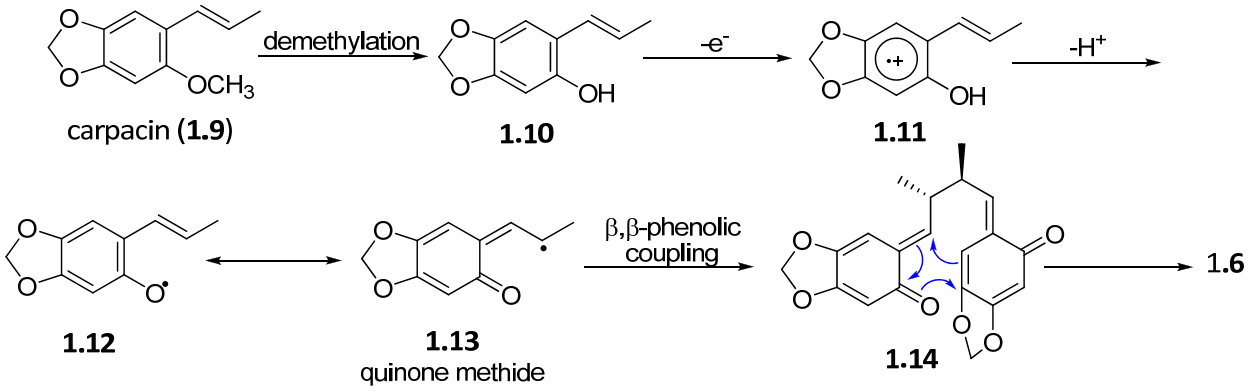


Figure 1.2. Isolation of carpanone and related natural products.

Isocarpanone (**1.7**) and carpananone (**1.8**) were also isolated in small quantity alongside carpanone (**1.6**) (Figure 1.2). carpacin (**1.9**) was also isolated in abundance from the same plant (Figure 1.2).

1. 2. Biosynthetic proposal of carpanone-like natural products

Given the occurrence of the trioxygenated propenylbenzene of carpacin (**1.9**) in the same plant, it was proposed that carpanone and isocarpanone could arise via β-β′-phenolic coupling of desmethyl carpacin (**1.10**) followed by Diels-Alder cyclization (Scheme 1.1).[8] The biosynthesis of carpanone is shown in Scheme 1.1. Demethylation of carpacin (**1.9**) generates styrenyl phenol (**1.10**), oxidation of which provides radical cation **(1.11).** After deprotonation, β-β′-phenolic coupling of *trans*-ortho-quinone methide (**1.13**) followed by endo-selective inverse electron demand Diels-Alder to afford carpanone (**1.6**) (Scheme 1.1).[8]

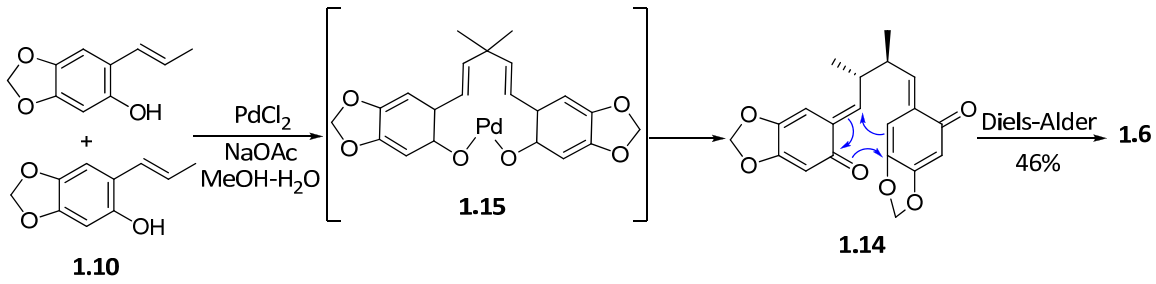


Scheme 1.1. Biosynthetic proposal of carpanone-like natural products.

1. 3. Biomimetic synthesis of carpanone

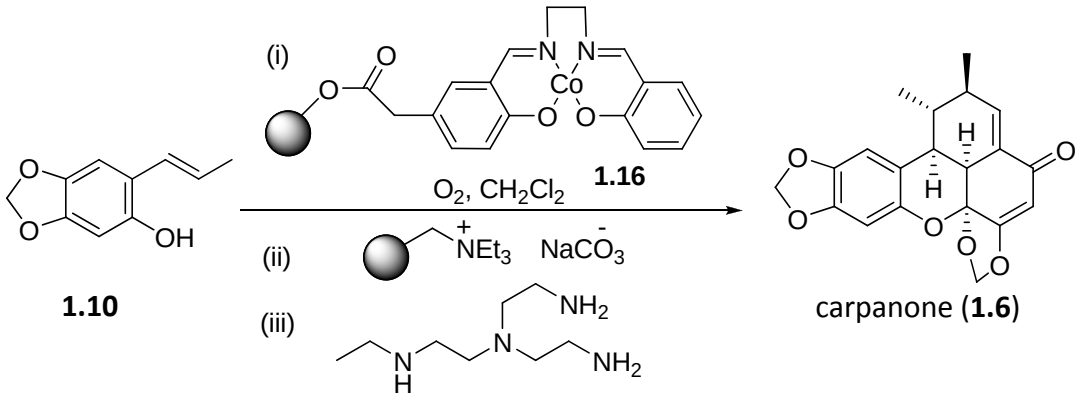
Nature assembles the complex molecular frameworks of natural products excellently and efficiently. Thus, chemists are often inspired by how nature creates these structurally diverse and complex natural products, and design biomimetic reactions to mimic the elegance of the biosynthetic pathway. Now considered a classic in total

synthesis, Chapman and coworkers in 1971 validated the biosynthetic proposal with the first total synthesis of carpanone (**1.6**) (Scheme 1.2).[9] Following the rationale in Scheme 1.1, Chapman decided that the β-β′-phenolic coupling must occur trans and that this configuration would dictate the subsequent inverse-electron demand Diels-Alder reaction. Utilizing Pd^{II} to promote the β-β′-phenolic coupling, Chapman was able to couple together the two styrenyl phenols **1.10** to deliver **1.15** *en route* to **1.14**, and then carpanone (**1.6**) via endo-selective, inverse-electron demand Diels–Alder reaction of the highly reactive bis(*ortho*quinomethane) (**1.14**). Chapman's approach afforded carpanone (**1.6**) in 46% yield as a single diastereomer, which was confirmed by single X-ray crystallography (Scheme 1.2).[9]



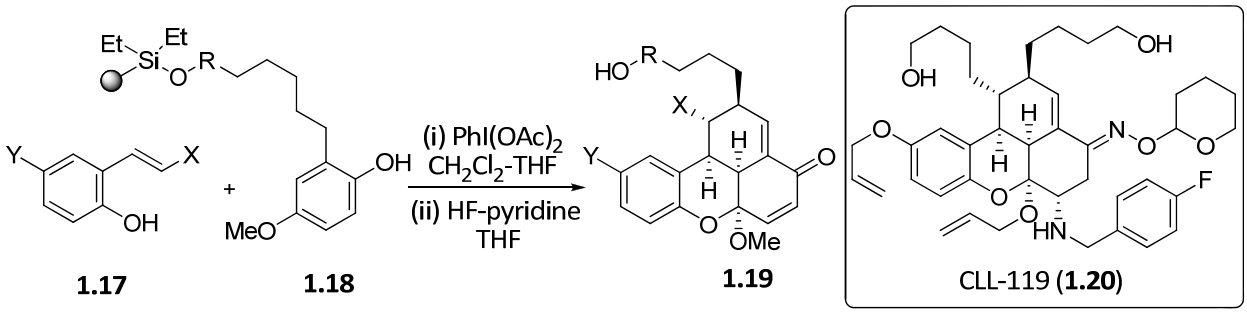
Scheme 1.2. Classical biomimetic total synthesis of carpanone (**1.6**).

After this initial report, several laboratories disclosed additional oxidative systems, stoichiometric and catalytic, to produce carpanone, including metal (II) salen/O_2 (metal = Co, Mn, Fe), O_2 (*hv*, Rose Bengal), AIBN (azobisisobutyronitrile), dibenzoyl peroxide and AgO in yields ranging from 14 to 94%.[10] In 2001, Ley and coworkers reported on the total synthesis of carpanone in 70% yield employing only solid-supported reagents and scavengers (Scheme 1.3).[12]



Scheme 1.3. Ley's synthesis of carpanone.

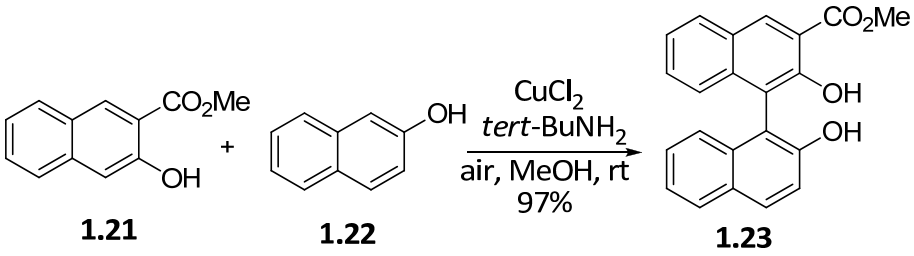
Lindsley and Shair recently developed a tandem process for use in the diversity-oriented synthesis of a library of carpanone-like molecules.[11] The reaction involved electronically differentiated phenols, with the more reactive phenol immobilized on solid support to minimize homocoupling. An oxidative dimerization with $PhI(OAc)_2$ and subsequent intramolecular inverse electron-demand Diels-Alder cycloaddition (Scheme 1.4), controlled by the differential electronic nature of the two aromatic partners, provided the carpanone-based tetracyclic derivatives in a single step. This approach was utilized to synthesis a 10,000-membered library of molecules resembling the natural product carpanone (**1.6**), where CLL-119 (**1.18**) was shown to be a potent vesicular traffic inhibitor.[11]



Scheme 1.4. Solid-phase biomimetic synthesis of carpanone-like molecules.

1. 4. Asymmetric copper mediated naphthol coupling

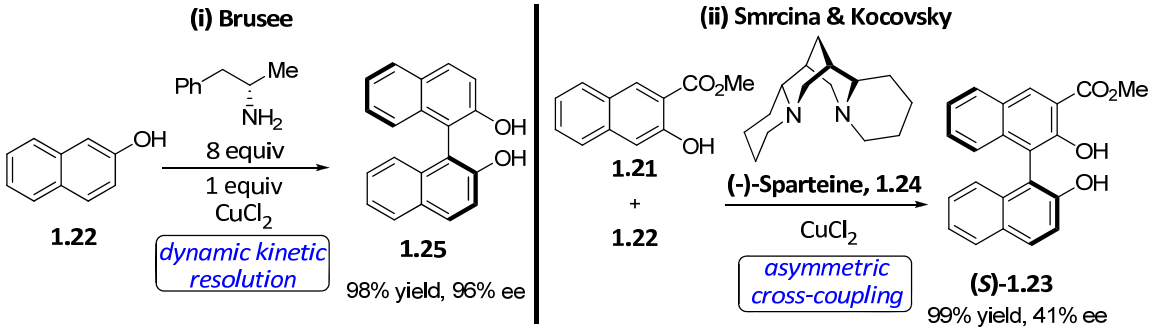
Oxidative couplings of phenols and naphthols using copper amine catalysts have been useful in the synthesis of biaryl containing natural products. Hovorka and coworkers utilized a $CuCl_2$/*tert*-butyl amine system (4.0 equiv $CuCl_2$, 16.0 equiv *tert*-butyl amine, 1.0 equiv of each naphthol) to promote a highly selective oxidative cross-couplings of substituted 2-naphthols, **1.21** and **1.22**, to afford unsymmetrical 1,1′-bi-naphthols **1.23** in 90-97% yields (Scheme 1.5).[13]



Scheme 1.5. $CuCl_2$/*t*-$BuNH_2$ oxidative coupling of 2-naphthols.

1. 4. 1. Asymmetric copper mediated naphthol coupling

Wynberg and Feringa showed that a stoichiometric amount of the chiral amine-copper salt ($Cu(NO_3)_2$/(S)-a-methylbenzylamine) complex was effective in the coupling of 2-naphthol, however it did so with very low enantioselection (3% ee).[14] Brussee and coworkers discovered that excess of (S)-amphetamine combined with $CuCl_2$ produced (S)-BINOL (**1.25**) in 98% yield and 96% ee (Scheme 1.6).[15] The high enantiopurity of this reaction resulted from a diastereoselective precipitation of the Cu(II)-(S)-amphetamine-(S)-BINOL with a concomitant atropisomerization of (R)-BINOL (dynamic kinetic resolution).

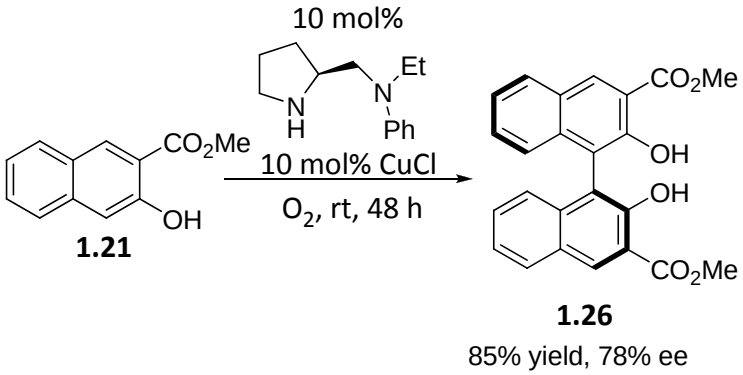


Scheme 1.6. Asymmetric copper mediated naphthol coupling.

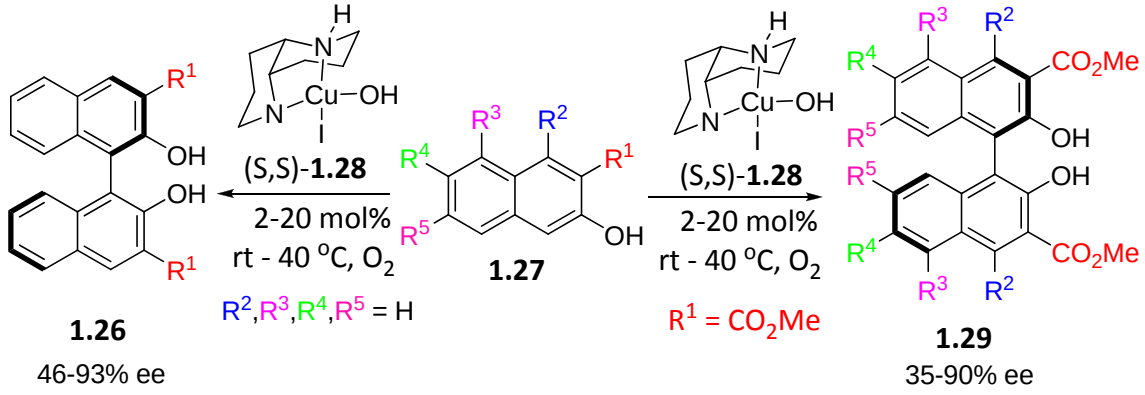
Later, Smrcina and Kocovsky reported the coupling of 2-naphthol and hydroxyl ester (**1.21**) using $CuCl_2$ and (-)-sparteine (**1.24**) in 99% yield and 41% ee, which was an important achievement even though the selectivity was modest (Scheme 1.6).[16]

Nakajima and co-workers employed chiral prolyldiamine ligands in the presence of dioxygen to obtain the coupling product in 85% yield and 78% ee (Scheme 1.7).[17]

Importantly, dioxygen was established as an effective reoxidant for this catalytic process. The use of metered amounts of pure dioxygen or air is also viable.[17]



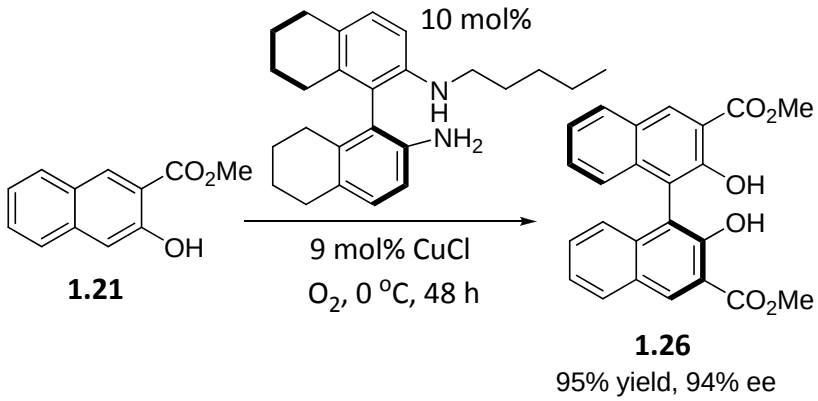
Scheme 1.7. Cu-catalyzed asymmetric homocoupling in the presence of a prolyldiamine.



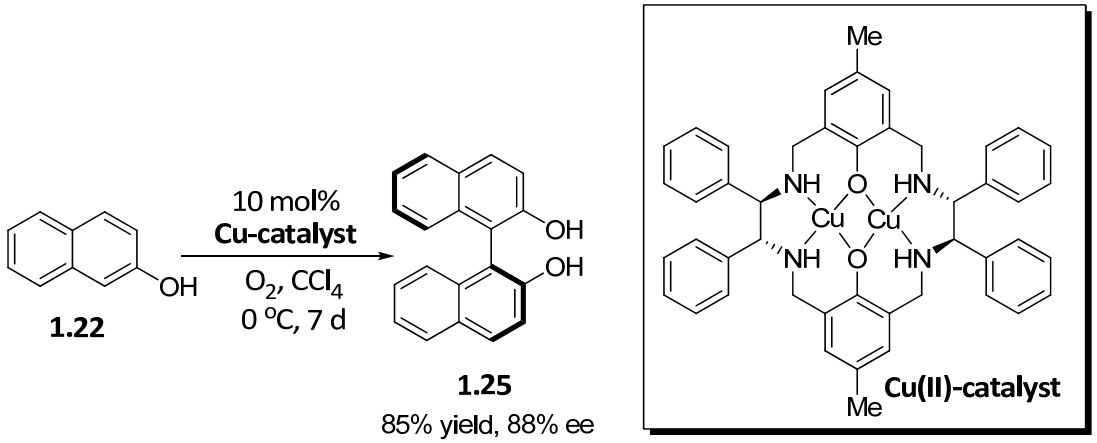
Scheme 1.8. Cu-catalyzed asymmetric coupling with 1,5-diaza-decalin ligand.

Kozlowski and coworkers, using a computer-aided procedure, identified the 1,5-diaza-cis-decalin scaffold as a new chiral diamine ligands. Using O_2 as the stoichiometric oxidant, catalyst **1.28** was found to be remarkably effective in the enantioselective oxidative couplings of a broad range of 3-substituted-2-naphthols and the generation of a number of complex binaphthols (Scheme 1.8).[18] Other copper catalysts derived from an

octahydro BINAM have been reported to give excellent selectivity (Scheme 1.9).[19] Martell and co-workers have utilized dicopper–salen complex (Scheme 1.10) to effect coupling in high yield and enantioselectivity (85%, 88% ee).[20]



Scheme 1.9. Cu-H_8-BINAM catalyzed asymmetric homocoupling.

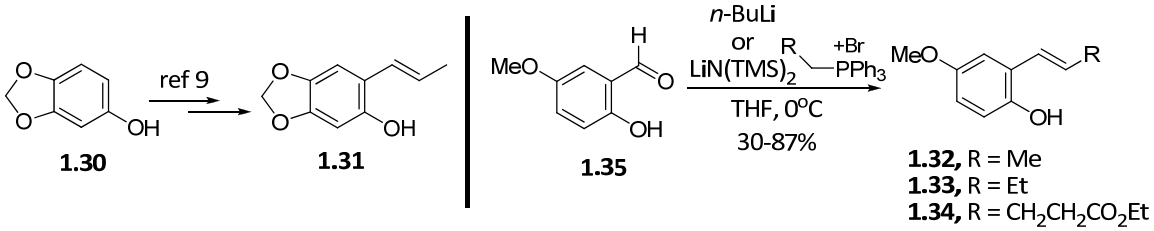


Scheme 1.10. Asymmetric homocoupling catalyzed by Cu-salen complex.

1. 5. Studies of copper mediated β-β′-phenolic coupling of styrenyl phenols

1. 5. 1. Synthesis of styrenyl phenols

The previously mentioned copper-amine complex conditions had never been applied to the β-β′-phenolic coupling of styrenyl phenols. However, in order to extend these conditions to β-β′-phenolic couplings and the synthesis of carpanone and related analogs, we first had to prepare the requisite styrenyl phenols. The synthesis of the styrenyl phenol begins from commercially available sesamol **1.30**, which is readily allylated. Following Clasien rearrangemen, isomerization gives alcohol **1.31**. Styrenyl phenols **1.32**, **1.33** and **1.34** were achieved from commercially available aldehyde **1.35**, via an *E*-selective Wittig reaction[21] in 30-87% yield (Scheme 1.11).

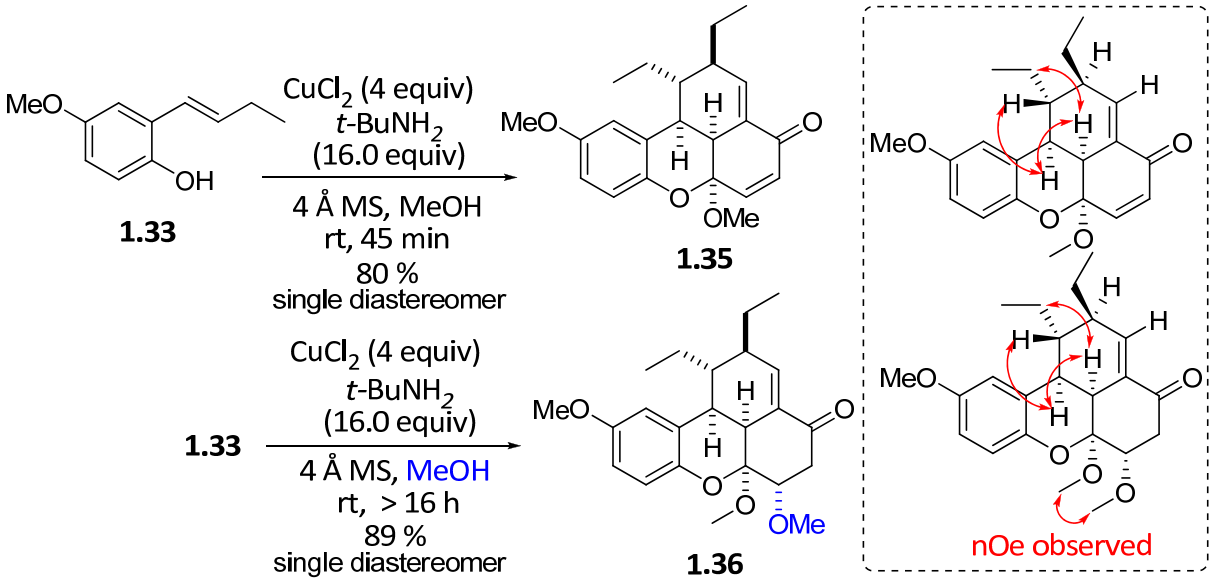


Scheme 1.11. Synthesis of styrenyl phenols **1.32-1.34**.

1. 5. 2. Cu(II)/*t*-BuNH$_2$ oxidative coupling of styrenyl phenols

Utilizing Hovorka's homocoupling method,[13] our studies began by exposing **1.33** to 4.0 equiv of $CuCl_2$ and 16.0 equiv of *tert*-butylamine in nondegassed MeOH exposed to air at room temperature for different reaction times (Scheme 1.12). When the reaction was quenched with saturated NH_4Cl after 45 min, the desired homocoupled product **1.35** was isolated in 80% yield as a single diastereomer, and the relative stereochemistry was

confirmed by NOE measurements. When reactions were quenched after 8 h, two products were isolated in ~1:1 ratio: the desired compound **1.35** along with product **1.36** consistent with the conjugate addition of MeOH to **1.35**, which afforded a single diastereomer containing six contiguous stereocenters. If the reaction was allowed to proceed in excess of 16 h, the conjugate addition product **1.36** formed exclusively with isolated yields of 89% as a single diastereomer due to selective addition to the convex face of the rigid tetracyclic scaffold.[10,22] Again, NOE measurements established the relative stereochemistry for **1.36**.[22]



Scheme 1.12. $CuCl_2$/-*t*-$BuNH_2$ oxidative β-β′-phenolic coupling of styrenyl phenol.

We were surprised by the complex molecular architecture of **1.36** that could arise in a single pot from a starting material devoid of any chiral centers by a β-β′-phenolic coupling, inverse-electron demand Diels-Alder, and subsequent conjugate addition reaction cascade. Our attention now turned to optimization of these two reactions and

evaluation of chiral amine ligands to provide enantioselectivity in the β-β′-phenolic coupling.

1.5.3. Cu(II)/chiral amine oxidative coupling of styrenyl phenols

Having developed an optimized method for the synthesis of β-β′-phenolic coupling products, we investigated the scope of this overall approach utilizing variety of chiral amines (Figure 1.3), monodentate and bidentate, under a varied temperature (-20 ^{o}C to rt), solvent systems, and copper source with both stoichiometric and catalytic manifolds in order to determine if alternative amine/copper complexes would promote the β-β′-phenolic coupling reaction and engender a degree of enantioselectivity in the product **1.35** (Figure 1.3).

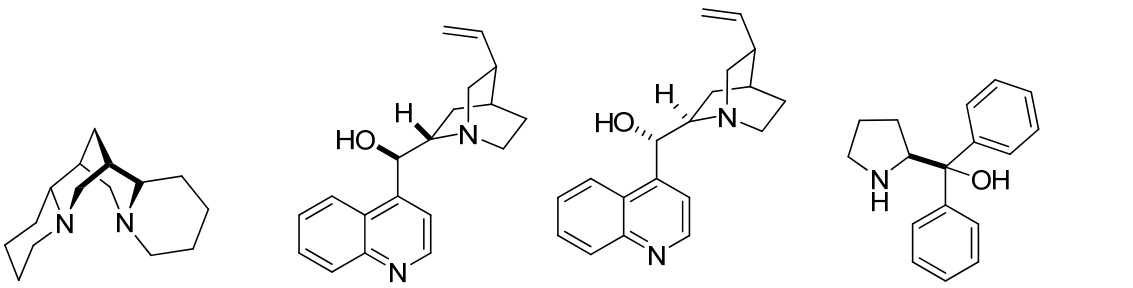
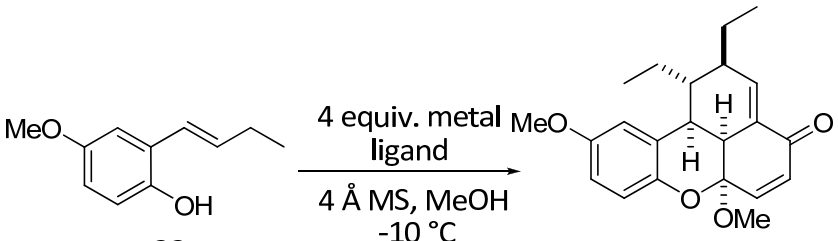


Figure 1.3. Chiral amine ligands surveyed to promote the β-β′-phenolic coupling.

Table 1.1. Copper/amine oxidative β-β′-phenolic homocoupling[a]



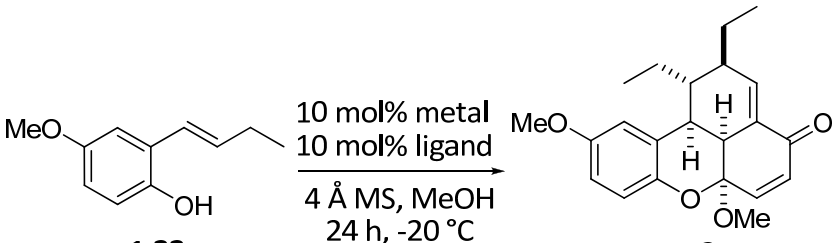
1.33 **1.35**

entry	metal source	ligand (equiv.)	time (min)	yield (%)[b]	conv.[c]
1	$CuCl_2$	**1.24**, 16	10	80	100
2	CuI	**1.24**, 16	15	73	89
3	CuI	**1.24**, 0.5	15	61	72
4	$CuCl_2$	**1.37**, 0.5	15	71	79
5	$CuCl_2$	**1.24**, 0.5	15	66	81
6	$CuCl_2$	**1.24**, 0.1	20	71	79
7	$CuCl_2$	**1.39**, 0.5	20	59	65
8	CuI	**1.37**, 0.5	20	<5	<5
9	$CuCl_2$	^{t}-$BuNH_2$,16	20	42	54
10	$CuCl_2$	**1.38**, 0.5	20	61	71

[a]All reactions were performed on a 0.05 mmol scale. [b]Isolated yields of a single diastereomer. [c]Conversion were estimated by LC/MS and ^{1}H NMR.

As shown in Table 1.1, we first examined conversion to **1.35** employing various Cu(I) and Cu(II) salts with the four chiral amines (Figure 1.3) at -10 ^{o}C in non-degassed MeOH. At this temperature, the standard conditions with *tert*-butylamine (entry 9) suffered a reduction in yield, whereas the bidentate ligand **1.24** afforded excellent conversion to **1.35** in 80% isolated yield (entry 1). Catalytic quantities of amine ligand also afforded good conversion to **1.35** with excess copper.

Table 1.2. Metal-Catalyzed β-β′-phenolic homocoupling using various chiral ligands.[a]



1.33 **1.35**

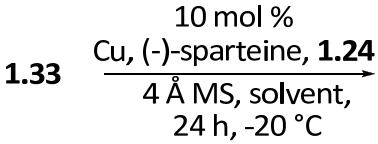
entry	metal source	ligand	yield (%)[b]	conv.[c] %
1	$CuCl_2$	**1.24**	96	100
2	CuI	**1.24**	23[d]	88
3	CuCl	**1.24**	61	72
4	$CuBr_2$	**1.24**	13[d]	75
5	$Cu(OTf)_2$	**1.24**	67	85
6	$CuCl_2$	**1.37**	89	91
7	$CuCl_2$	**1.38**	81	89
8	CuI	**1.37**	12	24
9	CuCl	**1.37**	83	92
10	CuI	**1.38**	3	10
11	$Cu(OTf)_2$	**1.37**	80	95
12	$CuBr_2$	**1.37**	0	15
13	$CuCl_2$	**1.39**	69	73
14	CuI	**1.39**	0	<5
15	$CuCl_2$	^{t}-$BuNH_2$	0	3.6

[a]All reactions were performed on a 0.05 mmol scale. [b] Isolated yields of a single diastereomer. [c]Conversion were estimated by LC/MS and ^{1}H NMR. [d]For entries 2 and 4 Michael adduct **1.36** was obtained in 24% and 35% yield respectively.

The effect of solvent on the conversion of **1.33** to **1.35** was evaluated (Table 1.3). For this study, we maintained 10 mol % copper, 10 mol % (-)-sparteine at -20 °C for 24 h and examined CH_2Cl_2, CH_3CN, and MeOH. Clearly, MeOH is the optimal solvent to facilitate the β-β′-phenolic coupling reaction as shown by Table 1.3, entries 7-11.

After an exhaustive survey, only poor enantioselectivity (<5% ee) was observed by analytical chiral LC; however, we noted that bidentate (-)-sparteine **1.24** was superior to the monodentate *tert*-butylamine facilitating the β,β-phenolic coupling reaction.

Table 1.3. Examination of solvent in the catalyzed β-β′-phenolic homocoupling[a].



entry	metal source	solvent	yield (%)[b]	conv.[c]
1	$CuCl_2$	CH_2Cl_2	53	76
2	CuI	CH_3CN	49	76
3	CuCl	CH_3CN	50	71
4	$CuBr_2$	CH_3CN	62	80
5	$CuCl_2$	CH_3CN	59	77
6	$Cu(OTf)_2$	CH_3CN	40	65
7	CuI	MeOH	85	85
8	$CuCl_2$	MeOH	96	100
9	$CuBr_2$	MeOH	23	88
10	CuCl	MeOH	61	72
11	$Cu(OTf)_2$	MeOH	67	85

[a]All reactions were performed on a 0.05 mmol scale. [b]Isolated yields of a single diastereomer. [c]Conversion were estimated by LC/MS and ^{1}H NMR.

Moreover, *tert*-butylamine failed at temperatures below 0 °C to promote the *β,β*-phenolic coupling, whereas (-)-sparteine **1.24** provided excellent results at temperatures as low as -20 °C. These data suggest that the reaction does not take place in the copper coordination sphere due to rapid dissociation of the intermediate keto-radical leading to no enantioselection. Having developed optimum catalytic conditions, these conditions were then applied to styrenyl phenols **1.32**, **1.33**, and **1.34** to provide unnatural benzoxanthenones **1.35**, **1.40** and **1.41** in 87% and 89% yield, respectively, as well as carpanone **1.6** in 91% yield (Figure 1.4).

Finally, conditions were optimized to deliver the Michael adduct product **1.36** (Table 1.4). Utilizing 8.0 equiv of **1.24** at room temperature for 4 h provided **1.36** in 91% isolated yield as a single diastereomer.

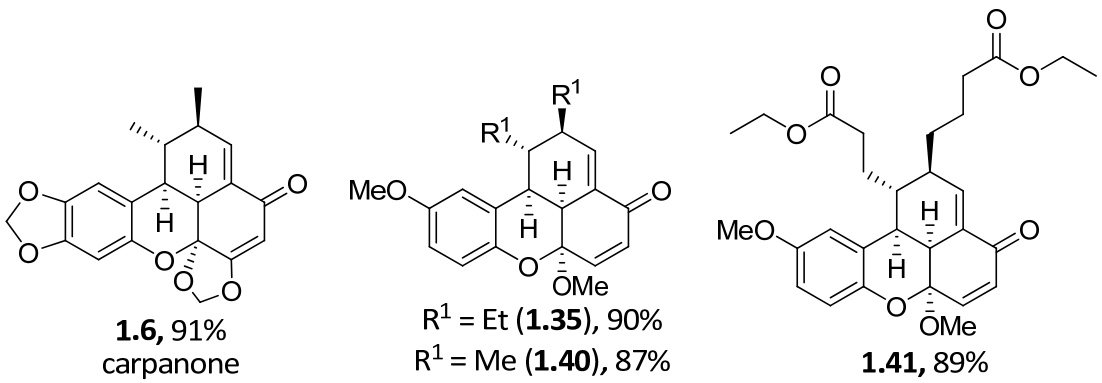
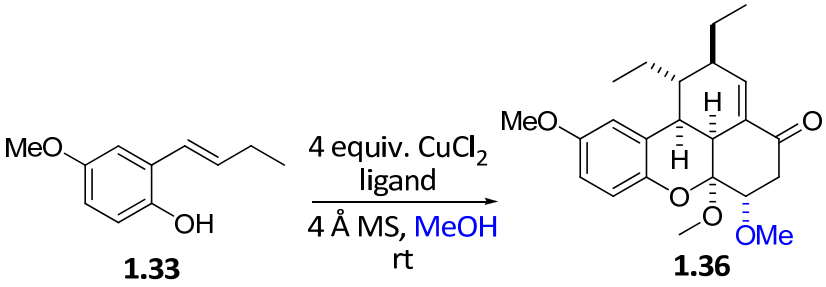


Figure 1.4. Other substrates in catalyzed β-β′-phenolic homocoupling.

Table 1.4. Diastereoselective conjugate addition.[a]



entry	ligand (equiv.)	time (h)	yield[b]
1	**1.24**, 16	4	89
2	**1.24**, 8	4	91
3	**1.24**, 4	5	81
4	^{t}-BuNH$_2$, 16	4	<5

[a]All reactions were performed on a 0.5 mmol scale. [b]Isolated yields of a single diastereomer.

If the reaction is performed in EtOH in place of MeOH, the corresponding conjugate addition product is obtained in equivalent yield.

1. 6. Biomimetic total syntheses of polemannones B and C

In 1987, Jakupovic and Eid described three new, more highly oxygenated congeners, 4,5-dimethoxy-4',5'-methylenedioxypolemannone or polemannone A (**1.2**), 4,5, 4',5'-bis-methylenedioxypolemannone or polemannone B (**1.3**), and 4,5, 4',5'-tetramethoxy-polemannone or polemannone C (**1.4**), isolated from root of *Polemannia montana* (Figure 4).[6] To date, there have been no synthetic efforts directed toward the polemannones, nor have the polemannones been subjected to biological evaluation.

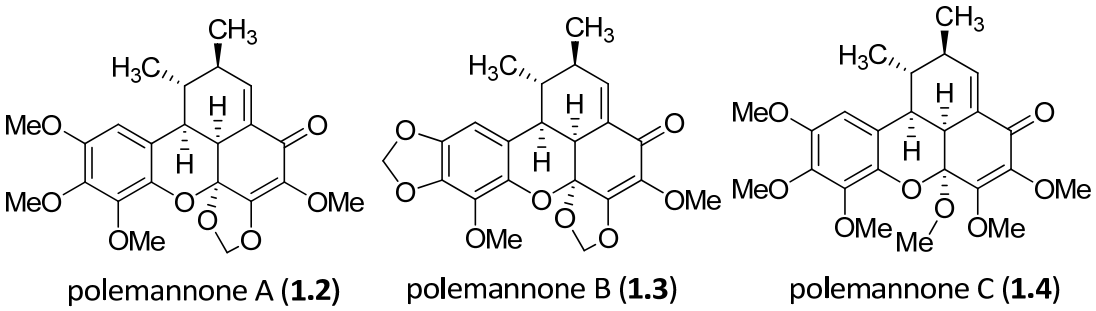


Figure 1.5. Structures of benzoxanthenone natural products (polemannones).

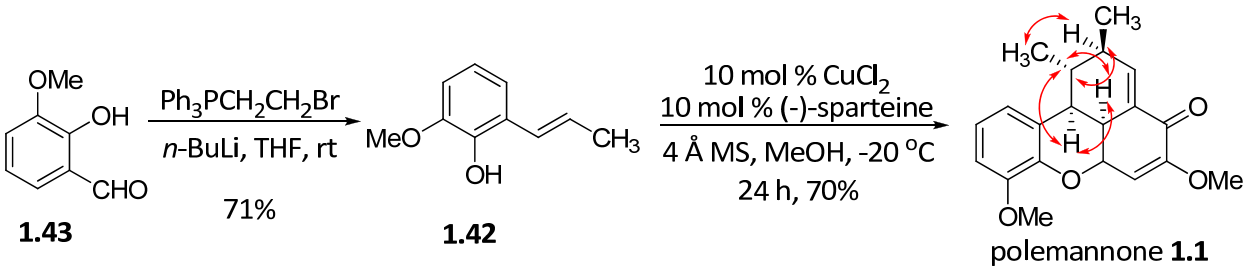
Having developed a novel, catalytic $CuCl_2$/(-)-sparteine oxidative β-β′-phenolic coupling reaction of styrenyl phenols that, after a rapid inverse-electron demand Diels-Alder reaction, affords the benzoxanthanone natural product, we now focused on the application of the methodology in the first total synthesis of polemannone, polemannones B and C. The polemannones are unique in that there is an extra electron donating ether moiety.[6]

In all previous synthetic works, only 1 or 2 electron-donating ether moieties were present, and one of these was always positioned *para* to the phenol in order to stabilize the orthoquinone methide intermediate and provide the "push" in the inverse-electron

demand Diels–Alder reaction (Scheme 1.1).[6–12] In cases where two electron-donating ether moieties were present, the second was always positioned meta to the phenol. While unprecedented, we wondered if a lone ortho-methoxy group, as in **1.42**, could equally stabilize the ortho-quinone methide intermediate and provide the "push" in the inverse-electron demand Diels–Alder reaction to provide the first total synthesis of polemannone **1.1** (Scheme 1.13).

1. 6. 1. Total synthesis of polemannone

Starting from 2-hydroxy-3-methoxybenzaldehyde **1.43**, an *E*-selective Wittig reaction[21] produced styrenyl phenol **1.42** in 71% yield. Employing our catalytic oxidant system,[22] polemannone **1.1** was obtained as a single diastereomer in 70% yield and NOE measurements confirmed the relative stereochemistry.[22] This is the first example of a β-β′-phenolic coupling and tandem inverse-electron demand Diels–Alder reaction cascade without a *para*-OMe group, and polemannone **1.1** represents a fundamentally new chemotype within the benzoxanthenone family. Importantly, this result was encouraging and suggested that our methodology may successfully allow for the first total synthesis of other members of the polemannone family of benzoxanthenones, since they all possess an electron-donating ether moiety in the ortho-position.



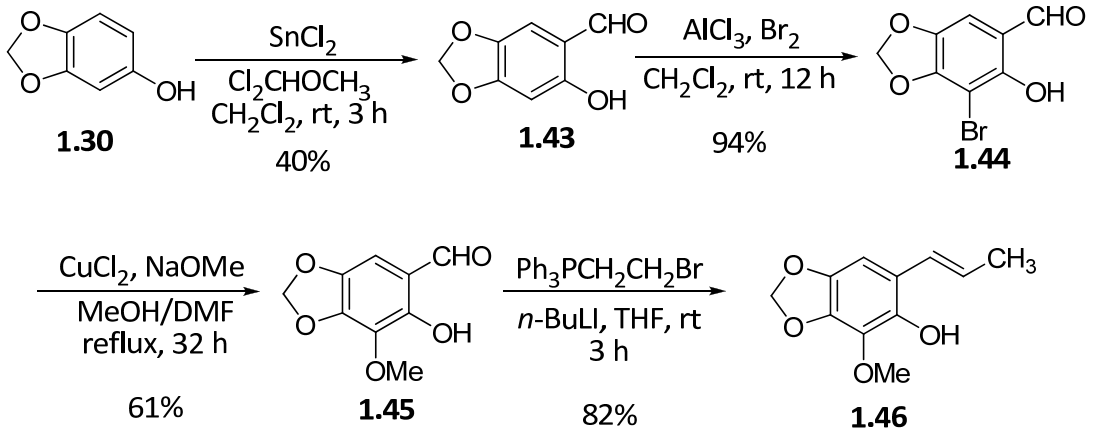
Scheme 1.13. Total synthesis of polemannone **1.1**.

1. 6. 2. Total syntheses of polemannones B and C

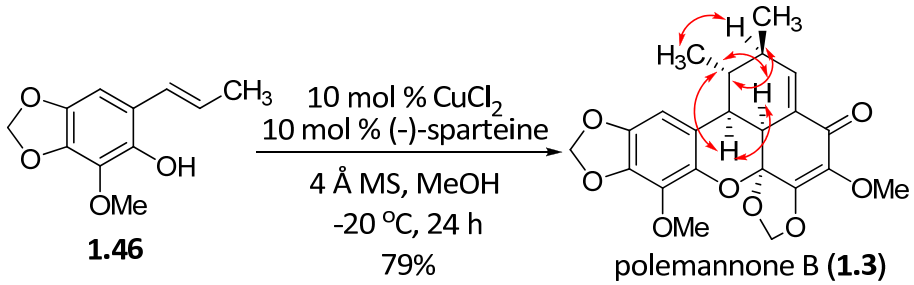
Thus, we initiated a synthetic campaign to deliver polemannones B and C both homodimers of electron-rich styrenyl phenols **1.3** and **1.4**, respectively.

The requisite styrenyl phenol for polemannone B, **1.3**, was prepared in four steps from commercial sesamol **1.30** (Scheme 1.14). Formylation provided **1.43** in 40% yield, followed by an $AlCl_3$-mediated bromination to produce **1.44** in 94% yield (Scheme 1.14). The key methoxy group was installed via a Cu(II) catalyzed etherification reaction to afford a 61% yield of **1.45**. Finally, an *E*-selective Wittig reaction[21] produced styrenyl phenol **1.46** in 82% yield, or 19% overall yield for the four steps.

Employing the catalytic Cu(II)/(-)-sparteine oxidant system,[22] polemannone B (**1.3**) was delivered as a single diastereomer in 79% yield and once again, NOE measurements confirmed the relative stereochemistry (Scheme 1.15). As with the natural product, our synthetic material was racemic. Moreover, spectral data for our synthetic polemannone B, **1.3**, were in complete accord with those reported for the natural product.[6]

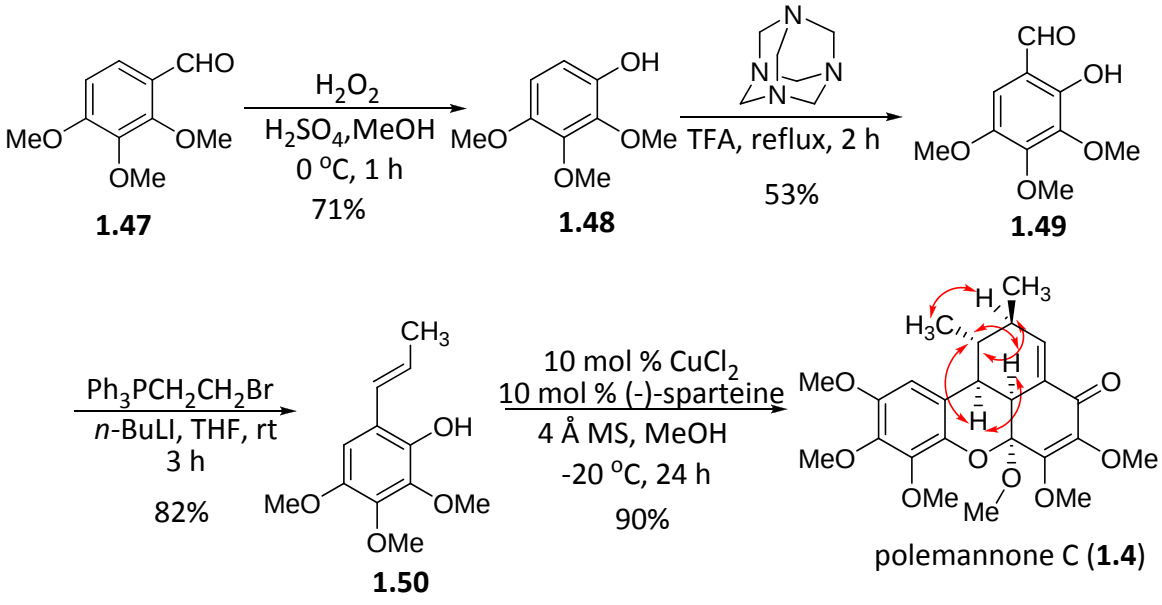


Scheme 1.14. Synthesis of styrenyl phenol **1.46**.



Scheme 1.15. Total synthesis of polemannone B (**1.3**).

The requisite styrenyl phenol for polemannone C, **1.4**, was prepared in four steps from commercial 2,3,4-trimethoxybenzaldehyde **1.47** (Scheme 1.16). Aldehyde **1.47** was smoothly converted into the corresponding phenol **1.48** by treatment with acidic hydrogen peroxide. However, the ortho-formylation step to provide **1.47** proved to be problematic.



Scheme1.16. Total synthesis of polemannone C, **1.4**.

The ortho-formylation protocol employed for the synthesis of **1.43**, utilizing $SnCl_2$ and dichloro(methoxy)methane, surprisingly afforded meta-formylation exclusively. Ultimately, hexamethylenetetramine in refluxing TFA provided the desired ortho-formylation product **1.49** in 53% yield. Then, an *E*-selective Wittig reaction[21] produced styrenyl phenol **1.50** in 93% yield, or 35% overall yield for the three steps. Employing the catalytic Cu(II)/(-)-sparteine oxidant system polemannone C, **1.4**, was delivered as a single diastereomer in 90% yield (Scheme 1.16) and once again, NOE measurements confirmed the relative stereochemistry. Spectral data for our synthetic polemannone C were in complete accord with those reported for the natural product.[6]

1.7. Conclusion

In summary, we have developed a novel, catalytic $CuCl_2$/(-)-sparteine oxidative β-β′-phenolic coupling reaction of styrenyl phenols that, after a rapid inverse-electron demand Diels-Alder reaction, affords the benzoxanthanone natural product carpanone **1.6** and related unnatural congeners in yields exceeding 85%. With a slight variation of these reaction conditions, a simple achiral styrenyl phenol undergoes a β-β′-phenolic coupling, inverse-electron demand Diels-Alder reaction, and subsequent conjugate addition reaction to generate unnatural tetracyclic benzoxanthanones **1.36** with six contiguous asymmetric centers set diastereoselectively in a one-pot reaction. Unfortunately, <5% ee was observed when employing chiral amine ligands under a variety of reaction conditions, indicating no influence of a chiral environment for β-β′-phenolic couplings.

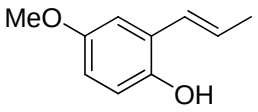
We have extended the substrate scope of β-β′-phenolic coupling/tandem inverse-electron demand Diels-Alder reaction cascade of styrenyl phenols to include ortho-

substituted ethers to afford novel, benzoxanthenones such as **1.1** by application of of a novel, catalytic $CuCl_2$/(-)-sparteine oxidation system. More importantly, this new catalytic system enabled the first total synthesis of the highly oxygenated benzoxanthenone ligans polemannones B and C from commercial starting materials in overall yields of 15% and 31.5%, respectively.

Experimental Methods

General. All ^{1}H & ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz)**,** Bruker AV-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). IR spectra were recorded as thin films and are reported in wavenumbers (cm^{-1}). Low resolution mass spectra were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra were recorded on a Waters Qtof-API-US plus Acquity system. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(ME - MT)/ MT] \times 10^6$, where ME is the experimental mass and MT is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference. Analytical thin layer chromatography was performed on 250 μM silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. Analytical HPLC was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral HPLC was performed on an Agilent 1200 Series HPLC utilizing a Chiracel OD, OJ or Chiralpak AD columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical

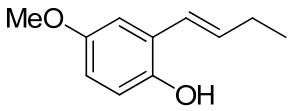
Co. and were used without purification. All polymer-supported reagents were purchased from Biotage, Inc. Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Mass spectra were obtained on a Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data.



1.32

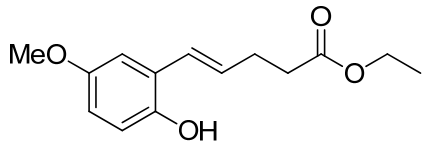
(*E*)-4-methoxy-2-(prop-1-enyl)phenol (1.32): Ethyltriphenylphosphonium bromide (7.4 g, 20 mmol) was added to a 250 mL flask which was then evacuated and filled with argon (3x). Anhydrous THF (50 mL) was added, followed by *n*-BuLi (8 mL, 20 mmol, 2.5 M in hexanes) at room temperature to form a bright-red ylide. After 45 min, 2-hydroxy-5-methoxybenzaldehyde (1.25 mL, 10 mmol) was added dropwise, and was allowed to stir at room temperature for 3 h. Upon completion, the reaction was quenched with 0.5 M HCl, extracted with EtOAc (3 x 30 mL). The organic layer was washed with water, brine and dried over magnesium sulfate. Concentration *in vacuo* gave the residue which was then purified by automated flash chromatography (1:0 to 3:1 Hex/EtOAc) to yield the product 1.44 g (88%) as a pale yellow oil: R_f = 0.72 (1:1 Hex/EtOAc); IR (neat) 3380, 2912, 1609, 1501, 1430, 1347 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 6.85 (d, *J* = 2.9 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.66 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.56 (dd, *J* = 15.8, 1.7 Hz, 1H), 6.20 (dq, *J* = 15.8, 6.6 Hz, 1H), 4.63 (brs, 1H), 3.77 (s, 3H), 1.91 (dd, *J* = 6.6, 1.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 153.7, 146.4, 128.4, 125.7,

125.3, 116.4, 113.5, 112.1, 55.7, 18.9; HRMS (TOF, ES+) $C_{10}H_{12}O_2$ $[M+H]^+$ calc'd 165.0916, found 165.0933.



1.33

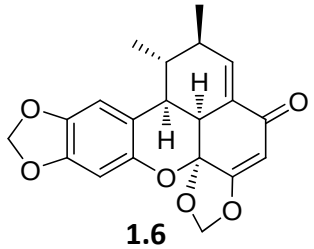
(*E*)-2-(but-1-enyl)-4-methoxyphenol (1.33): Propyltriphenylphosphonium bromide (7.7 g, 20 mmol) was added to a 250 mL flask which was then evacuated and filled with argon (3x). Anhydrous THF (50 mL) was added, followed by *n*-BuLi (8 mL, 20 mmol, 2.5 M in hexanes) at room temperature to form a bright-red ylide. After 45 min, 2-hydroxy-5-methoxybenzaldehyde (1.25 mL, 10 mmol) was added dropwise, and was allowed to stir at room temperature for 3 h. Upon completion, the reaction was quenched with 0.5 M HCl, extracted with EtOAc (3 x 30 mL). The organic layer was washed with water, brine and dried over magnesium sulfate. Concentration *in vacuo* gave the residue which was then purified by automated flash chromatography (1:0 to 3:1 Hex/EtOAc) to yield the product 1.40 g (85%) as a pale yellow oil: R_f = 0.72 (1:0 Hex/EtOAc); IR (neat) 3401, 2962, 1608, 1501, 1429, 1343 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 6.87 (d, *J* = 2.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.9, 6.4 Hz, 1H), 3.77 (s, 3H), 2.26 (dq, *J* = 6.4, 7.5 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 153.7, 146.5, 135.2, 125.7, 123.0, 116.5, 113.6, 112.0, 55.8, 26.4, 13.6; HRMS (TOF, ES+) $C_{11}H_{14}O_2$ $[M+H]^+$ calc'd 179.0919, found 179.1021.



1.34

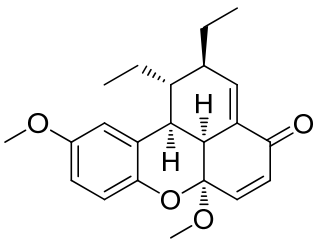
(*E*)-ethyl 4-(2-hydroxy-5-methoxyphenyl)but-3-enoate (1.34): [3-(Ethoxxycarbonyl)propyl]-triphenylphosphonium bromide 4.6 g, 10 mmol) was added to a 50 mL flask which was then evacuated and filled with argon (3x). Anhydrous THF (25 mL) was added and the solution cooled to 0 ºC. LHMDS (10 mL, 10 mmol, 1.0 M in THF) was added dropwise, the solution was allowed to warm to room temperature and stirred for 30 min. The reaction was again cooled to 0 ºC, 2-hydroxy-5-methoxybenzaldehyde (0.63 mL, 5 mmol) was added dropwise, and was allowed to warm to room temperature and stir for 3 h. Upon completion, the reaction was quenched with 0.5 M HCl, extracted with EtOAc (3 x 30 mL). The organic layer was washed with water, brine and dried over $MgSO_4$. Concentration *in vacuo* gave the residue which was then purified by automated flash chromatography (1:0 to 3:1 Hex/EtOAc) to yield the product 0.35 g (26%) as a pale yellow oil: R_f = 0.63 (1:0 Hex/EtOAc); IR (neat) 3407, 2970, 1709, 1503, 1430, 1373 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 6.85 (d, *J* = 2.9 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.64 (m, 2H), 6.16 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.40 (brs, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.53 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.4, 153.5, 146.9, 130.5, 125.5, 125.2, 116.6, 113.9, 111.9, 60.6, 55.7, 34.1, 28.6, 14.2; HRMS (TOF, ES+) $C_{14}H_{18}O_4$ $[M+Na]^+$ calc'd 273.1103, found 273.1108.

General Procedure for the β,β-Phenol Homocoupling: A solution of copper catalyst (0.1 equiv), 4Å molecular sieves and amine ligand (0.1 equiv) in appropriate anhydrous solvent (0.15 M) (see Tables in the main text for solvents) was stirred for 15-20 min until no solid copper salt was visible and then cooled to -20 ^{o}C followed by the addition of phenol (1.0 equiv). The reaction was stirred at -20 °C for 24 h. The reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with 0.5 N HCl, water and the dried over $MgSO_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (4:1 to 1:1 Hex/EtOAc).



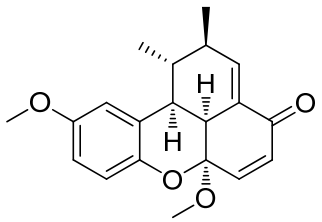
1.6

Carpanone (1.6): The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as a white solid (32.4mg, 91%): mp 184-185 ^{o}C [lit.[5] mp 185 ^{o}C]; IR (neat) 2923, 2870, 1674, 1624, 1499, 1479, 1381 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) matches literature; HRMS (TOF, ES+) $C_{20}H_{18}O_6$ $[M+Na]^+$ calc'd 377.1001, found 377.0987.



1.35

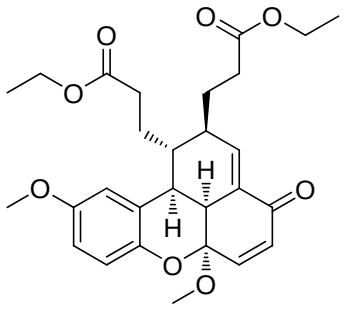
(1*R*,2*R*,3a^1*S*,6a*R*,11b*S*)-1,2-diethyl-6a,10-dimethoxy-1,2,6a,11b-tetrahydrobenzo[*kl*]xanthen-4(3a^1*H*)-one (1.35): The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as an off-white solid (32.2mg, 90%): mp 111-115 ºC; R_f = 0.68 (1:1 Hex/EtOAc); IR (neat) 2962, 2928, 1682, 1621, 1497, 1457, 1269 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J* = 10.3 Hz, 1H), 7.08 (m, 1H), 6.88 (d, *J* = 2.7 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.66 (ddd, *J* = 8.8, 2.7, 0.6 Hz, 1H), 6.31 (d, *J* = 10.3 Hz, 1H), 3.77 (s, 3H), 3.43 (d, *J* = 6.9 Hz, 1H), 3.31 (s, 3H), 3.09 (dt, *J* = 6.9, 2.6 Hz, 1H), 2.34 (t, *J* = 6.2 Hz, 1H), 2.01 (m, 1H), 1.49 (m, 1H), 1.37 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.95(m, 1H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.82 (m, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 186.8, 154.2, 144.9, 142.9, 142.5, 131.6, 128.3, 125.5, 117.9, 113.2, 112.8, 95.7, 55.7, 49.2, 42.0, 39.7, 37.4, 32.4, 28.0, 27.9, 12.9, 12.6; HRMS (TOF, ES+) $C_{22}H_{26}O_4$ $[M+H]^+$ calc'd 355.1909, found 355.1913.



1.40

(1*R*,2*R*,3a^1*S*,6a*R*,11b*S*)-6a,10-dimethoxy-1,2-dimethyl-1,2,6a,11b-tetrahydrobenzo[*kl*]xanthen-4(3a^1*H*)-one (1.40): The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as an off-white foam (28.4 mg, 87%): R_f = 0.67 (1:1 Hex/EtOAc); IR (neat) 2930, 1678, 1618, 1493, 1459, 1273 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.24 (d, *J* = 10.3

Hz, 1H), 7.02 (m, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.31 (d, *J* = 10.3 Hz, 1H), 3.76 (s, 3H), 3.32 (m, 4H), 3.14 (dt, *J* = 7.2, 2.6 Hz, 1H), 2.62 (q, *J* = 7.0 Hz, 1H), 2.21 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 186.7, 154.2, 144.9, 143.7, 142.5, 131.6, 127.9, 125.4, 117.9, 113.4, 113.1, 95.7, 55.6, 49.2, 36.9, 36.6, 35.0, 33.9, 21.6, 21.2; HRMS (TOF, ES+) $C_{20}H_{22}O_4$ $[M+H]^+$ calc'd 327.1596, found 327.1607.

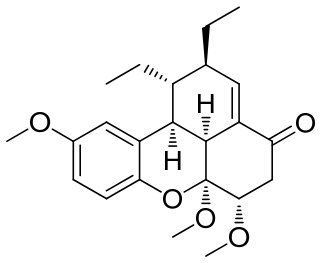


1.41

Diethyl-3,3'-((1*R*,2*R*,3a^1*S*,6a*R*,11b*S*)-6a,10-dimethoxy-4-oxo-1,2,3a^1,4,6a,11b-hexahydrobenzo[*kl*]xanthene-1,2-diyl)dipropanoate (1.41): The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as a pale yellow viscous oil (44.3 mg, 89%): R_f = 0.46 (1:1 Hex/EtOAc); IR (neat) 2926, 2851, 1729, 1681, 1494, 1458, 1420, 1376 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.22 (d, *J* = 10.3 Hz, 1H), 7.01 (m, 1H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.30 (d, *J* = 10.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.44 (d, *J* = 6.9, Hz, 1H), 3.30 (s, 3H), 3.13 (dt, *J* = 6.9, 2.5 Hz, 1H), 2.49 (t, *J* = 7.1 Hz, 1H), 2.45 (m, 2H), 2.25 (m, 2H), 2.15 (m, 1H), 1.82 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.66 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.13 (dq, *J* = 14.4 , 7.1, 1H); ^{13}C NMR

(150.9 MHz, $CDCl_3$) δ (ppm): 186.3, 173.0, 172.7, 154.6, 145.0, 142.6, 140.7, 131.6, 129.3, 124.8, 118.2, 113.7, 112.8, 95.7, 60.5, 60.3, 55.7, 49.2, 39.1, 37.8, 37.5, 32.63, 32.55, 32.51, 30.2, 30.1, 14.3, 14.2; HRMS (TOF, ES+) $C_{28}H_{34}O_8$ $[M+Na]^+$ calc'd 521.2151, found 521.2151.

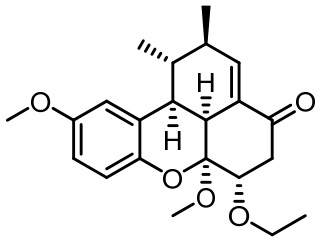
General Procedure for Conjugate Addition Products: A solution of copper catalyst (4 equiv), 4Å molecular sieves and amine ligand (8 equiv) in anhydrous MeOH (0.15 M) was stirred for 15-20 min until no solid copper salt was visible followed by the addition of phenol (1.0 equiv). The reaction was stirred at 23 °C for 4-16 h. The reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with 0.5 N HCl, water and the dried over $MgSO_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (4:1 to 1:1 Hex/EtOAc).



1.36

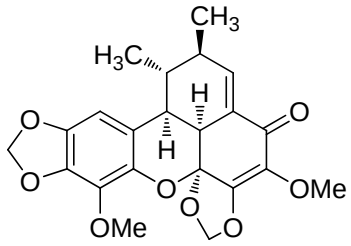
(1*R*,2*R*,3a^1*S*,6*S*,6a*S*,11b*S*)-1,2-diethyl-6,6a,10-trimethoxy-1,2,5,6,6a,11b-hexahydrobenzo[*kl*]xanthen-4(3a^1*H*)-one (1.36): The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as a yellow viscous oil (35.1 mg, 91%): R_f = 0.68 (1:1 Hex/EtOAc); IR (neat) 2927, 1691, 1622, 1493, 1462, 1258 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 6.86 (d, *J* =

2.7 Hz, 1H), 6.74 (t, *J* = 3.1 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.66 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.10 (dd, *J* = 3.9, 2.4 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.35 (dd, *J* = 6.3, 2.0 Hz, 1H), 3.26 (s, 3H), 3.17 (dt, *J* = 6.3, 2.8 Hz, 1H), 2.91 (dd, *J* = 17.8, 2.4 Hz, 1H), 2.82 (dd, *J* = 17.8, 3.9 Hz, 1H), 2.31 (t, *J* = 6.8 Hz, 1H), 1.89 (m, 1H), 1.50 (m, 1H), 1.38 (m, 1H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.97 (m, 2H), 0.90 (m, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 198.2, 153. 9, 144.4, 142.3, 130.9, 125.7, 117.8, 113.2, 112.9, 98.3, 73.9, 57.2, 55.6, 48.7, 41.8, 40.2, 38.7, 32.5, 31.9, 28.2, 28.1, 12.9, 12.4; HRMS (TOF, ES+) $C_{23}H_{30}O_5$ $[M+H]^+$ calc'd 387.2171, found 387.2172.



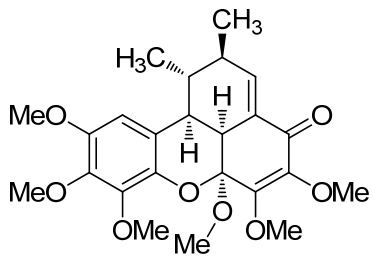
(1*R*,2*R*,3a^1*S*,6*S*,6a*S*,11b*S*)-6-ethoxy-6a,10-dimethoxy-1,2-dimethyl-1,2,5,6,6a,11b-hexahydrobenzo[*kl*]xanthen-4(3a^1*H*)-one: The product was prepared according to the general procedure except that EtOH was used as the reaction solvent. The reaction was run on a 0.1 mmol scale, to afford the product as a pale yellow viscous oil (29.3 mg, 79%): R_f = 0.73 (1:1 Hex/EtOAc); IR (neat) 2966, 2359, 2340, 1692, 1621, 1493, 1458, 1376, 1275 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 6.89 (d, *J* = 2.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.67 (m, 2H), 4.22 (m, 1H), 3.74 (m, 4H), 3.64 (q, *J* = 7.0 Hz, 1H), 3.62 (q, *J* = 7.0 Hz, 1H), 3.26 (s, 3H), 3.25 (m, 2H), 2.88 (dd, *J* = 17.6, 2.6 Hz, 1H), 2.84 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.59 (q, *J* = 7.1 Hz, 1H), 2.10 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.74 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ

(ppm): 198.6, 153.9, 144.4, 143.1, 130.8, 125.7, 117.8, 113.7, 113.0, 98.4, 72.0, 65.0, 55.6, 48.7, 41.0, 36.5, 34.2, 33.2, 32.0, 21.8, 21.6, 15.5; HRMS (TOF, ES+) $C_{23}H_{28}O_5$ $[M+H]^+$ calc'd 373.2015, found 373.2020.



Polemannone B, **1.3**

Polemannone B (**1.3**)**:** The product was prepared according to the general procedure. The reaction was run on a 0.1 mmol scale, to afford the product as a pale yellow solid (79%): Purified by column chromatography (4:1 to 1:1 Hex/EtOAc); R_f = 0.61 (1:1 Hex/EtOAc); ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.05 (dd, *J* = 4.9, 1.5 Hz, 1H), 6.51 (s, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 5.85 (d, *J* = 1.3 Hz, 1H), 5.66 (s, 1H), 5.64 (s,1H), 3.96 (s, 1H), 3.93 (s, 1H), 3.26 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.17 (dt, *J* = 7.5, 2.3 Hz, 1H), 2.48 (q, *J* = 7.2 Hz, 1H), 2.21 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H), 0.70 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 183.2, 151.4, 143.7, 143.0, 137.9, 135.7, 133.6, 131.5, 126.4, 126.4, 116.8, 101.3, 101.1, 100.6, 98.7, 60.2, 59.7, 36.3, 35.6, 35.1, 34.0, 21.4, 21.1; HRMS (TOF, ES+) $C_{22}H_{22}O_8$ [M+H]+ calcd 415.1393, found 415.1383.



Polemannone C, **1.4**

Polemannone C (**1.4**): Yellow solid, R_f = 0.58 (1:1 Hex/EtOAc); ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 6.95 (m, 1H), 6.57 (s, 1H), 4.18 (s, 3H), 3.81 (s, 6H), 3.77 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H), 3.20 (dd, *J* = 7.0, 1.8 Hz, 1H), 3.07 (m, 1H), 2.53 (q, *J* = 7.0 Hz, 1H), 2.15 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.62 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 183.2, 161.2, 147.3, 141.9, 141.2, 139.0, 138.5, 127.0, 119.1, 106.1, 97.0, 61.2, 60.9, 60.4, 56.2, 53.1, 36.3, 35.6, 35.1, 33.7, 21.3, 21.0; HRMS (TOF, ES+) $C_{24}H_{30}O_8$ [M+H]+ calcd 447.2019, found 447.2019.

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CHAPTER II

APPLICATION OF ORGANOCATALYSIS TO THE SYNTHESIS OF PHARMACOLOGICAL RELEVANT SCAFFOLDS: CHIRAL β-FLUOROAMINES AND AZIRIDINES

2. 1. General access to chiral β-fluoroamines and β,β-difluoroamines via organocatalysis

2. 1. 1. Fluorinated pharmaceuticals

In recent years, chemists have introduced one or more fluorine atoms into biologically active synthetic compounds. Fluoro-organic compounds exhibit unique properties and their potential is increasingly being exploited in various areas of life sciences, particularly in the pharmaceutical and crop-protection fields. The number of active compounds in these fields that contain fluorine-substituted moieties has increased over the past 30 years and has become an important area of medicinal chemistry.[1-3]

This relatively recent field of medicinal chemistry started its real expansion in the 1970's, and important progress has been performed in recent years, as shown by the number of fluorine-containing drugs on the market. In the US, 9 of the 31 new drugs licensed in 2002 contained fluorine, while half of the top 10 drugs sold in 2005 contained fluorine.[1-3] Thus, it can be conservatively estimated that globally about 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.[1-3] Shown in Figure 2.1; are examples of fluorinated drugs on the market, including two of the current top ten selling medicines. Pfizer's cholesterol lowering medicine, atorvastatin (*Lipitor*),[4] and the fluticasone component in GlaxoSmithKline's combination asthma treatment (*Seretide*)[5,6] (Figure 2.1).

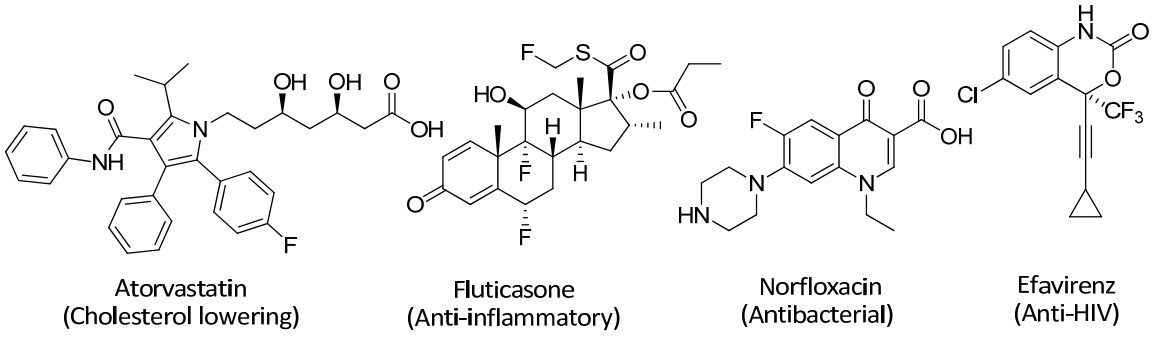


Figure 2.1. Examples of pharmaceuticals containing fluorine.

2. 1. 2. The Fluorine substituent effect

The reasons for using fluorine substitution in medicinal chemistry are based on the very specific characteristics of the fluorine atom, *i.e.* mostly its small size, high electronegativity, and subsequent effects on a molecule. The small size of the fluorine atom is a unique characteristic and its van der Waals radius is similar to that of hydrogen (Table 2.1), therefore, a fluorine atom can mimic a hydrogen atom or hydroxyl group in a bioactive compound with respect to steric requirements at receptor sites.[3]

As a consequence of its electronegativity, fluorine makes a very strong bond with carbon (Table 2.1), and it is often introduced into a target compound in order to improve the metabolic stability by blocking sensitive sites. Other effects of the electronic properties are that fluorine may modulate the physicochemical properties of a molecule, such as acidity and basicity, lipophilicity, or hydrogen bonding ability. It is also important to note that fluorine may also exert a substantial effect on the conformation of a molecule.[1,7]

Table 2.1. Physiochemical properties of the carbon-fluorine bond

Element	Electronegativity	Bond Length (CH2X, Å)	Van der Waals radius (Å)	Bond energy (kcal/mol)
H	2.1	1.09	1.20	99
F	4.0	1.39	1.35	116
O	3.5	1.43	1.40	85
Cl	3.0	1.77	1.8	81
Br	2.8	1.94	1.85	68
I	2.5	2.14	1.98	57

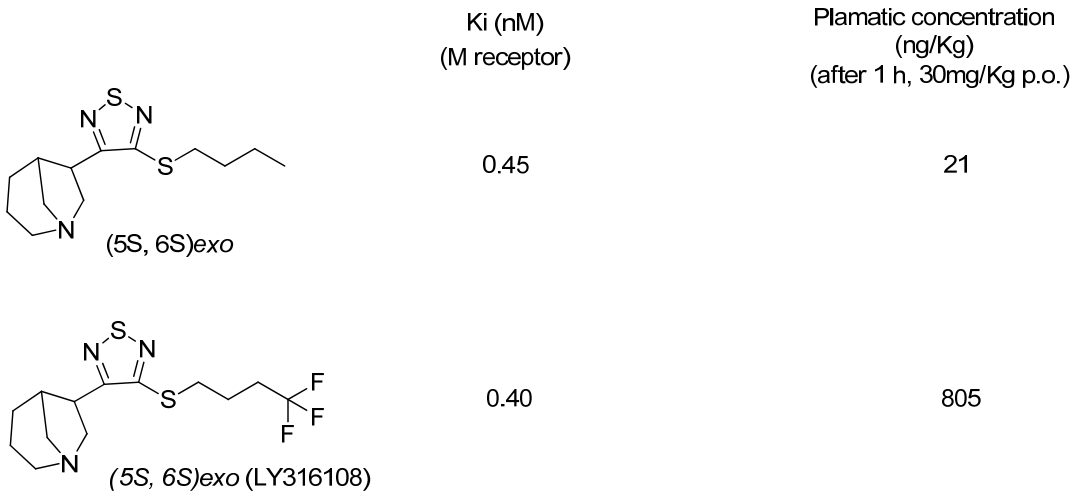


Figure 2.2: Protective effect of fluorine substitution on oxidizable site.

2. 1. 2. 1. Metabolic stability

Metabolic stability is one of the key factors in limiting the bioavailability of a compound. Rapid oxidative metabolism by liver enzymes (CYP 450 cytochrome enzymes) and/or the acidic stomach medium may decompose the drug early. It has been shown, however, that introducing fluorine atoms to a molecule makes the molecule to be

resistant to these phenomena. For instance, the replacement of hydrogen atoms on an oxidizable site by fluorine atoms of Eli Lilly's muscarinic analgesic *LY316108* protects the site from hydroxylation processes mediated by CYP450 cytochrome enzymes.[7b]

2. 1. 2. 2. Acidity and basicity

As electronegative substituents, fluorine and fluoroalkyl groups have strong effects on the acidity (and basicity) of neighboring functions.[1-3] For instance, the inductive effects of a β-fluorine atom are pronounced, lowering the p*K*a of a linear aliphatic amine (pKa ~10.7) to pKa ~9.0 with single β-fluorine and to pKa ~7.3 with β,β-difluoro substitution. These effects are general and additive, with a β-CF_3 moiety lowering the pKa to ~5.7 (Figure 2.2).[1-3]

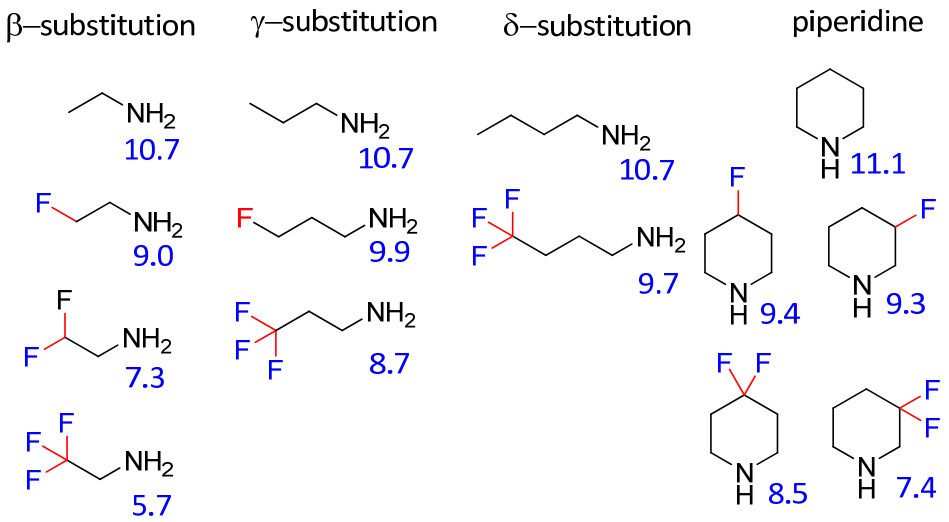


Figure 2.3. The effect of fluorine substitution on p*K*a.

These changes could have important consequences on transportation and absorption (pharmacokinetic properties) of the drug in the organism. Quite often, a change in the pKa has a strong effect on the transportation and absorption of a drug.

An example of this is the incorporation of fluorine into selective indole 5HT receptor ligand compounds. The incorporation of fluorine was found to significantly reduce the pKa of these compounds, leading to better bioavailabilty of the molecules (Figure 2.4).[8]

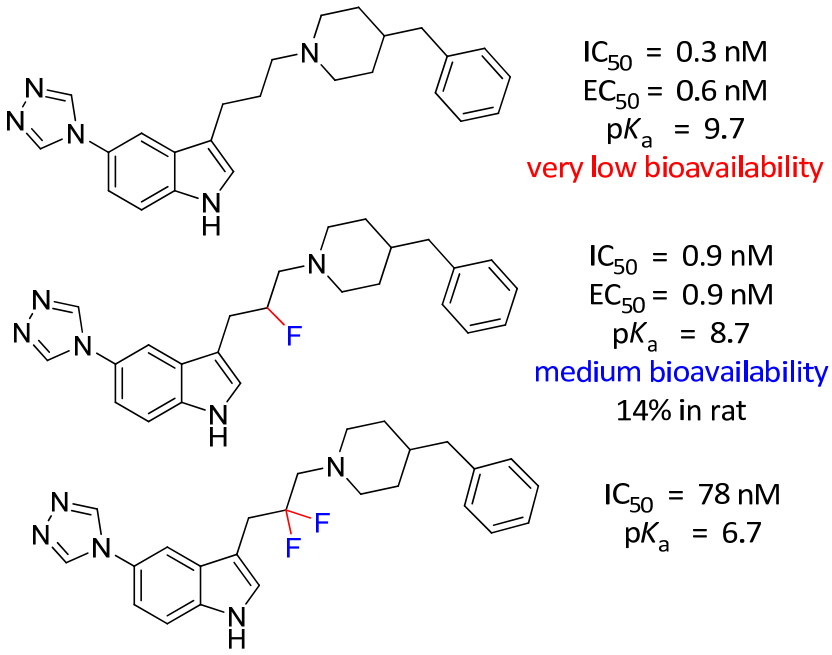


Figure 2.4. Effects of pKa values on the bioavailability and receptor binding agonist.

2. 1. 2. 3. Prenominal fluorine substitution effects

Prenominal effects of fluorine substituents are a change in the preferred molecular conformation of molecules, significant effects on the binding affinity in protein-ligand complexes and the lipophilicity of drug molecules.[1-3]

2. 1. 3. General access to chiral β-fluoroamines and β,β-difluoroamines via organocatalysis

Fluorinated analogs, in particular fluorinated analogs of nitrogen-containing compounds [9] of biologically active compounds, are regarded as tools of high interest for pharmaceutical research.[10] The incorporation of β-fluoroamines into drug candidates has increased dramatically in the past 5 years, with >150 fluorinated drug candidates in phase II and phase III clinical trials.[3] The role of the β-fluorine atom is diverse and has been shown to enhance binding interactions, improve metabolic stability, increase CNS penetration, and eliminate ancillary ion channel activity by attenuating amine basicity (p*K*a).[1-3]

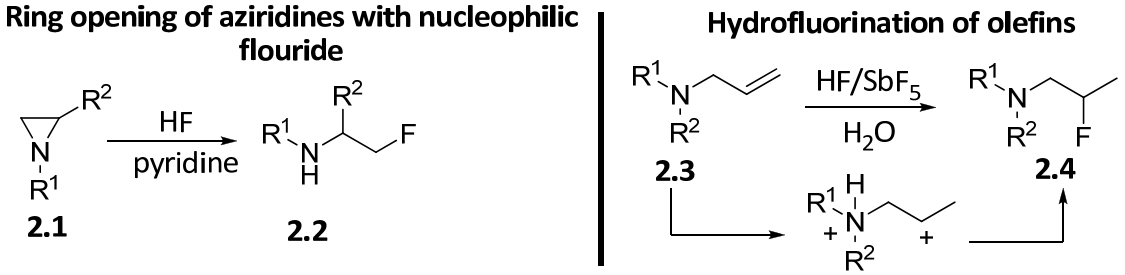
The substitution of fluorine in β-fluoroamines affects the pKa and the biological properties of the amine molecules. Some examples have been shown to prove this trend. For example, the incorporation of fluorine lead to a change in affinity and activity of propranolols for cytochrome oxidase enzymes,[11,12] change in the affinity of fluoroisoquinolines for the α_2-adrenoceptor,[13] metabolic and tissue distribution change of amphetamines,[14] increased activity of lung *N*-methyltransferase for fluoro-alkylarylamines,[15] and better oral absorption of fluoro-piperidine and fluoro-piperazine indoles.[16] The introduction of fluorine, especially γ- or β-fluorine substitution, not only strongly reduces amine basicity, it affect the degree of protonation at physiological pH,[17] membrane permeability,[18] and interference with the hERG (human ether a-go-go–related gene) K^+ channel associated with cardiovascular toxicity.[19]

The human ether a-go-go–related gene (hERG) contributes to the electrical activity of the heart that coordinates the heart's beating and is a major cause of toxicity in

many drug molecules. Several therapeutic drug molecules have failed to progress due to interference with hERG ion channel. About 25-40% of all lead compounds have been estimated to bind hERG ion channel. Drug interference with hERG channels cause prolongated electrocardiographic QT interval which result to long QT syndrome and thus increased risk of cardiac arrhythmia.[20] Due to toxicity from drug-hERG interefence, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) regulators now require a compusory screening of new drugs on hERG function.[21]

2. 1. 3. 1. Synthesis of β-fluoroamines.

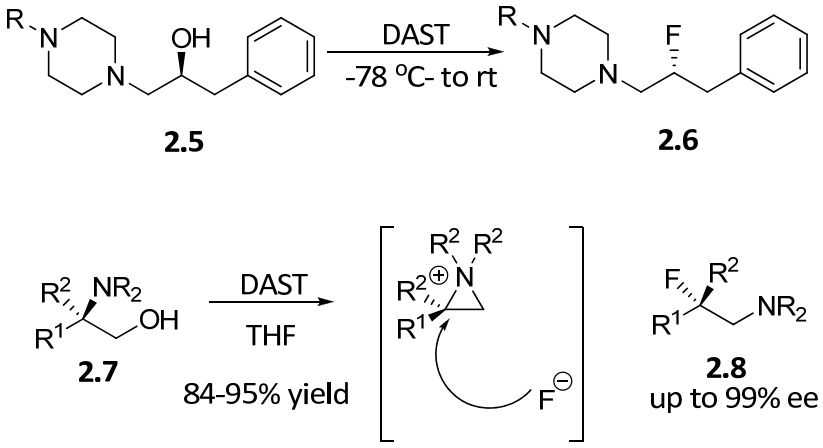
Despite the importance of the β-fluoroamine moiety, there are few synthetic methods in the literature for their preparation.[1-3,9] Two common methods, the ring opening of aziridines with nucleophilic flouride sources[10] and the hydrofluorination of olefins,[22] deliver β-fluoroamines but lack generality/substrate scope, require starting materials that are not readily available, or in the latter case, do not provide access to enantiopure β-fluoroamines (Scheme 2.1).



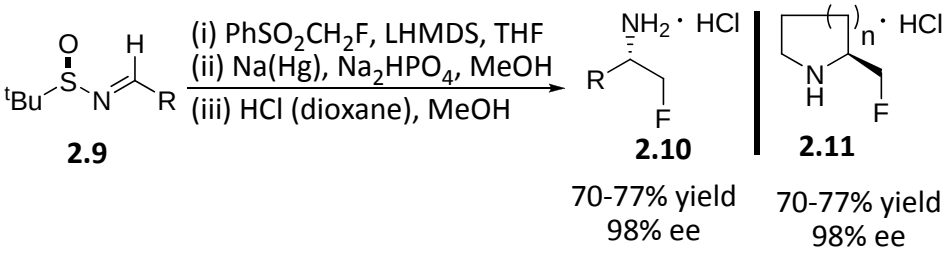
Scheme 2.1. Known approach to β-fluoroamine.

The route most utilized involves the treatment of ketones or secondary alcohols with DAST, (diethylamino)sulfur trifluoride, to provide β,β-difluoroamines and β-

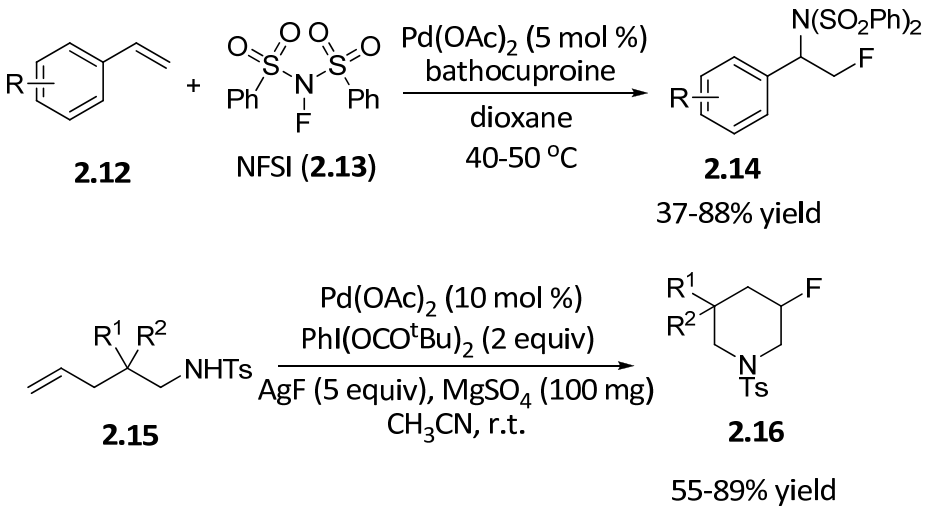
fluoroamines (with inversion of stereochemistry), respectively.[1-3,9-10,22-24] However, this methodology requires the synthesis of enantiopure secondary alcohols and then suffers from the formation of rearranged and dehydrated products, which in many published cases greatly diminished yields of the desired β-fluoroamines.[24] Cossy and co-workers utilized DAST to effect an enantiospecifically and regioselectively rearrangement of *N*,*N*-dialkyl-β-amino alcohols **2.7** to give optically active β-fluoroamines **2.8** (Scheme 2.2).[25]



Scheme 2.2. Synthesis of β-fluoroamine using DAST.

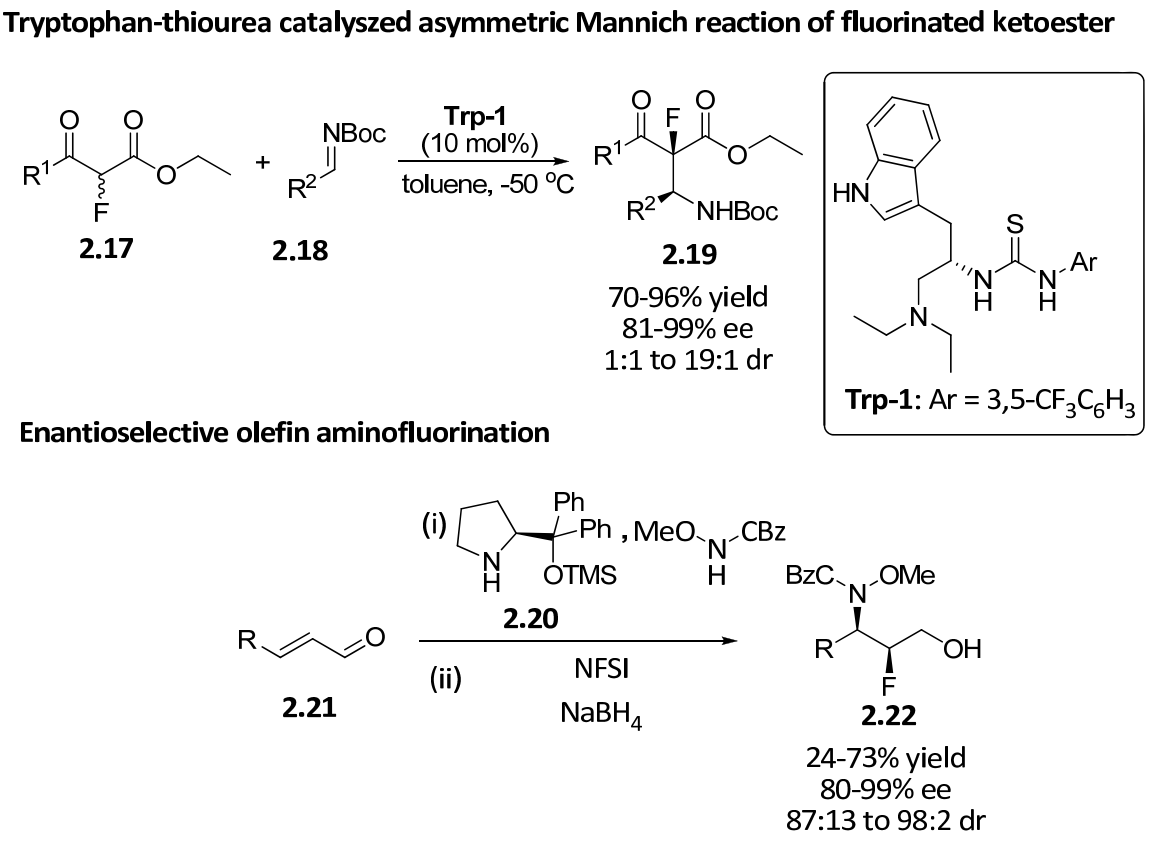


Scheme 2.3. Hu's stereoselective nucleophilic monofluoromethylation of chiral imines.



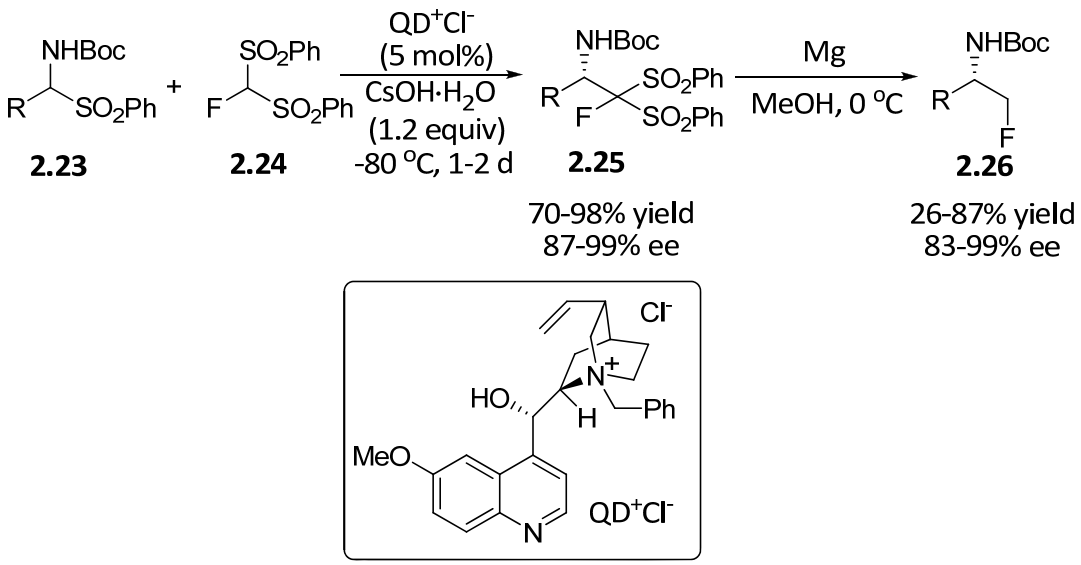
Scheme 2.4. Palladium-catalyzed oxidative aminofluorination

Hu and co-workers reported a highly stereoselective nucleophilic monofluoromethylation of chiral imines with fluoromethyl phenyl sulfone to afford α-monofluoromethylamines and α-monofluoromethyled cyclic amines (Scheme 2.3).[26] In 2009, Liu and co-workers developed a novel palladium-catalyzed intermolecular and intramolecular oxidative aminofluorination of unactivated alkenes to yield acyclic and cyclic β-fluoroamines (Scheme 2.4).[27] Asymmetric catalysis using chiral organocatalysis has been utilized in the synthesis of enantiopure β-fluoroamines.



Scheme 2.5. Organocatalyzed synthesis of enantiopure β-fluoroamines

Lu and co-workers developed a novel tryptophan-based bifunctional thiourea catalyst that was remarkably effective in promoting the asymmetric Mannich reaction of α-fluoro-β-ketoester **2.17** with *N*-Boc imine **2.18** to afford α-fluoro-β-amino acids **2.19** in good to excellent yield, diastereoselectivity and enantioselectivity (Scheme 2.5).[28] Brenner-Moyer and co-workers reported an organocatalytic asymmetric olefin aminofluorination reaction. Enantiopure α-fluoro-β-amino alcohols (generated after reduction of corresponding aldehydes) were generated in a single flask from achiral α,β-unsaturated aldehydes **2.21** in low to moderate yields and excellent enantioselectivity (Scheme 2.5).[29]



Scheme 2.6. Cinchona alkaloid-catalyzed enantioselective monofluoromethylation

The first catalytic enantioselective fluorobisphenylsulfonylmethylation was developed by Toru and co-workers. In situ generation of imines from α-amido sulfones **2.23** underwent Mannich-type reaction with 1-fluorobis(phenylsulfonyl)methane **2.24** to give α-fluorobisphenylsulfonyl **2.25** in excellent yield and enantioselectivity. Further reductive desulfonylation of **2.25** under Mg/MeOH conditions gave monofluoromethylated amines **2.26** in high yields and retained enantiopurity (Scheme 2.6).[30]

Organofluorine compounds are generally formed using prepared or commercially available nucleophilic, electrophilic, and radical fluorine reagents. Some common examples of nucleophilic fluorine reagents are DAST, DFI and Deoxofluor (Figure 2.5).

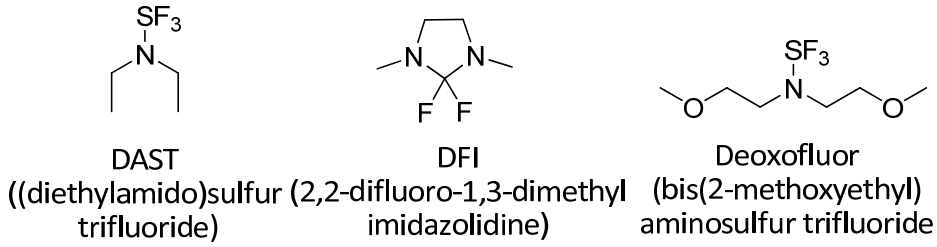


Figure 2.5. Common nucleophilic fluorine reagents.

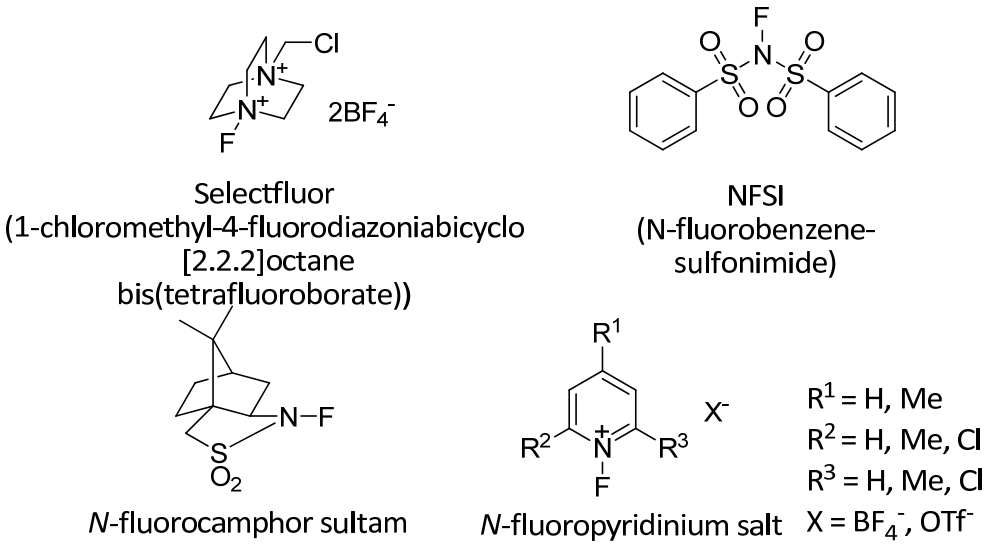
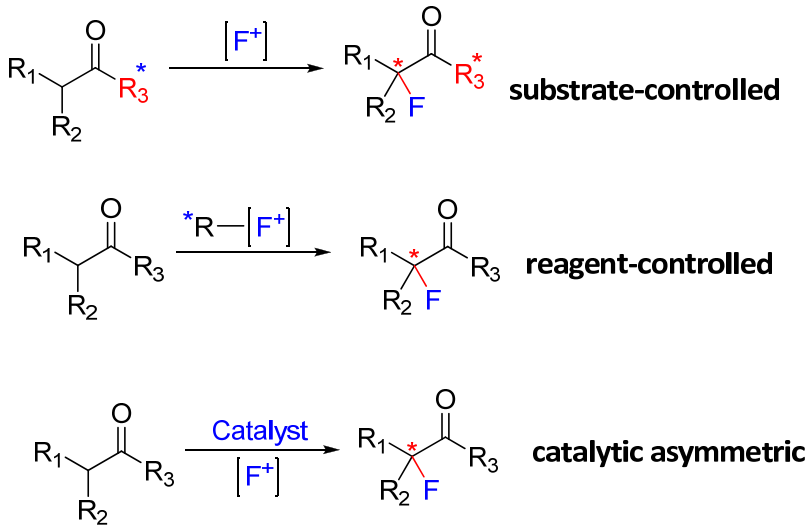


Figure 2.6. Common electrophilic fluorine reagents.

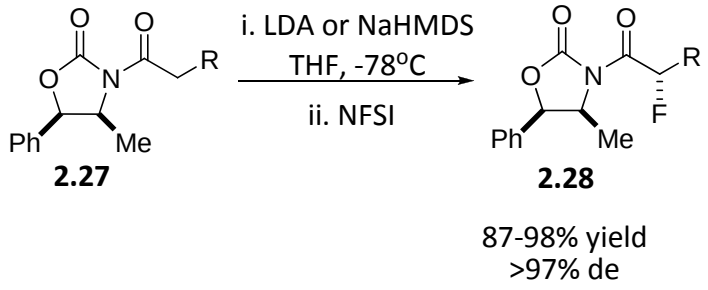
2. 1. 3. 2. Enantioselective fluorination

Common examples of electrophilic fluorine reagents are Selectfluor, NFSI, *N*-fluorocamphor sultam and *N*-fluoropyridinium salt (Figure 2.6). Many methods for the synthesis of enantioenriched organofluoro compounds have been reported. The enantioselective fluorination is usually accomplished through substrate-controlled, reagent-controlled and catalytic asymmetric fluorinations (Scheme 2.7).

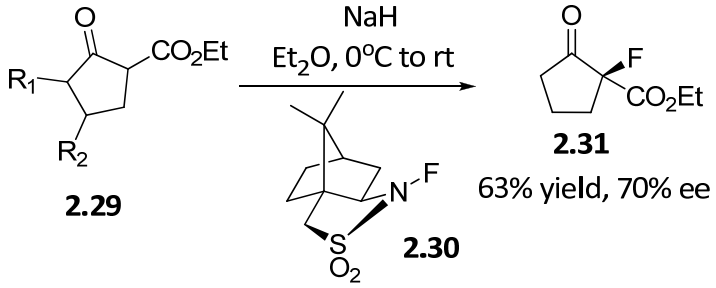


Scheme 2.7. General approach to enantioselective fluorination

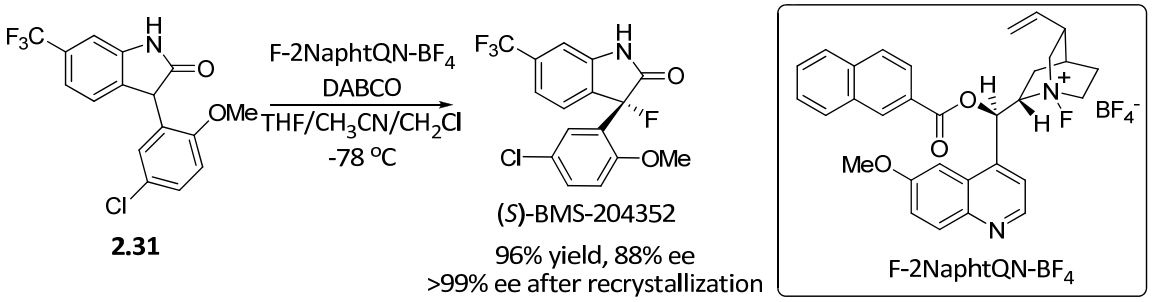
Early methods for the synthesis of enantiopure organofluorine compounds relied on substrate-controlled diastereoselective fluorinations. This approach was commonly accomplished by enolate trapping of chiral auxiliaries such as Evan's oxazolidinones with an electrophilic fluorinating reagent to afford chiral α-fluorocarbonyl compounds (Scheme 2.8).[31] Alternatively, enantioselective fluorinations can be achieved using reagent-controlled, which utilize stochiometric amounts of electrophilic fluorinating reagents. Chiral *N*-fluorinating reagents such as *N*-fluorosultams, *N*-fluorosulfonamides and *N*-fluoroammonium salts of cinchona alkaloids have been used for the enantioselective fluorination of various enolizable substrates.[32]



Scheme 2.8. Substrate-controlled enantioselective fluorination



Scheme 2.9. Enantioselective fluorination using *N*-Fluorocamphorsultams



Scheme 2.10. Enantioselective synthesis of BMS-204352

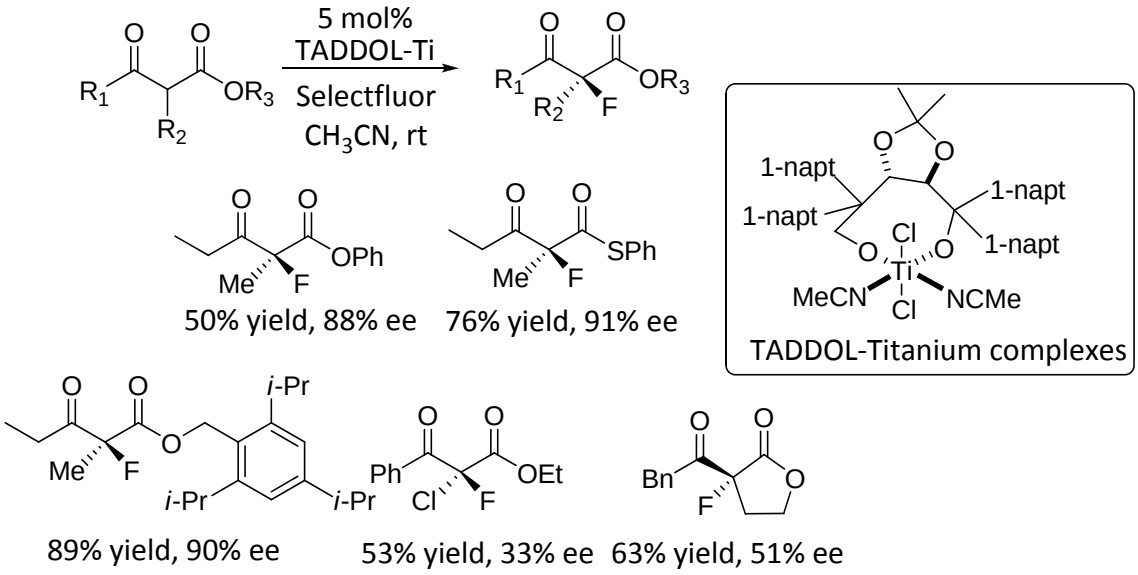
In 1988 Differding and Lang developed *N*-Fluorocamphorsultams **2.30** and its derivatives as the first enantioselective fluorinating reagent. Subjecting various achiral metal enolates generated from keto-ester **2.29** led to fluorinated keto-esters **2.31** in low to

moderate enantioselectivities (Scheme 2.9), these results demonstrated the possibility of reagent controlled asymmetric fluorination by using chiral electrophilic fluorine atom.[33] One of the most remarkable demonstrations of the effectiveness of $[N\text{-}F]^+$ reagents was reported by Cahard and co-workers. A new N-fluoroammonium salt F-2NaphtQN-BF4 was developed and applied to the enantioselective synthesis of BMS-204352 (MaxiPost), a potent opener of maxi-K channels, which is evaluated in a worldwide phase III clinical trial for treatment of acute ischemic stroke. Cahard and co-workers reacted oxindole **2.31** with the N-fluoroammonium salt F-2NaphtQN-BF_4 in the presence of a base (DABCO), to yield the target product (*S*)-BMS-204352 in excellent yield and high enantioselectivity (Scheme 2.10).[34]

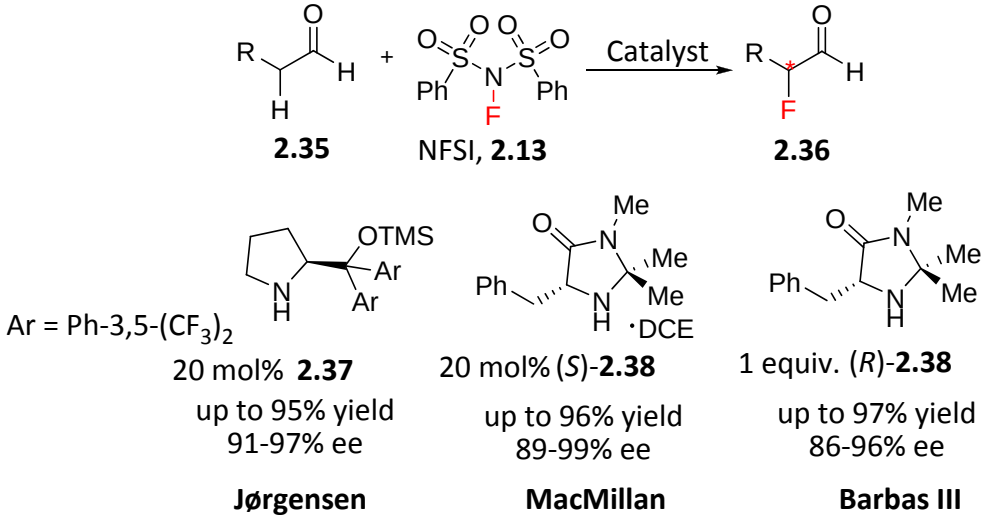
2. 1. 3. 3. Catalytic enantioselective fluorination

Togni and co-workers reported the first catalytic enantioselective fluorination reaction in 2000. In this reaction, β-keto esters **2.32** were subjected to catalytic transition-metal complex $TiCl_2$(*R*,*R*)-TADDOLato **2.33** (complex acted as a Lewis acid to activate the β-keto) in the presence of Selectfluor to give α-fluoro-β-keto esters **2.34** in good yields and moderate enantioselectivty. (Scheme 2.11).[35] Recently, an important breakthrough in the field of asymmetric fluorination, namely chiral secondary amine-catalyzed fluorination of aldehydes was achieved. Jørgensen, [36] Barbas[37] and MacMillan[38] simultaneously reported their findings on the use of various cyclic secondary amines as catalysts for the direct α-fluorination of aldehydes with excellent asymmetric induction. Their approaches to direct enantioselective α-fluorination of

aldehydes used N-fluorobenzenesulfonimide (NFSI) as the fluorination reagent (Scheme 2.12).



Scheme 2.11. TADDOL-titanium catalyzed asymmetric fluorination

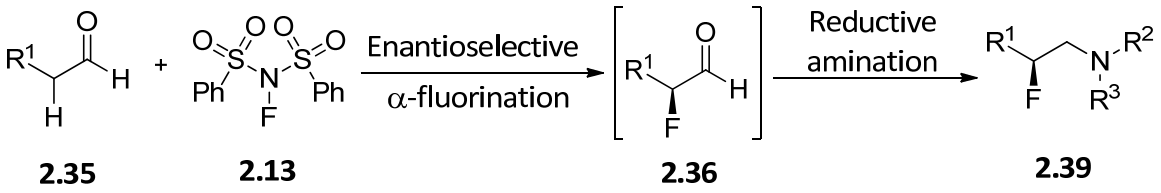


Scheme 2.12. Organocatalytic enantioselective α-fluorination of aldehydes.

2. 1. 3. 4. Studies of Organocatalyzed Synthesis of β-fluoroamine

` One major issue to be addressed upon enantioselective fluorination of aldehydes is the need to avoid racemization of the enantioenriched fluorinated compound. Owing to the instability of the aldehydes, products were isolated more often as the corresponding α-fluoroalcohols after their reduction with hydride sources. Given the developments of this chemistry, it should be noted that such methodology has yet to be applied to more complex targets or analogues of important structural components of various drug candidates.

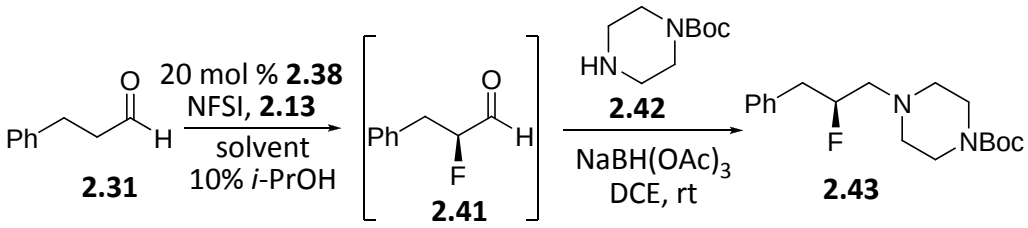
If these chiral α-fluoroaldehydes **2.13** were subjected to a reductive amination protocol, we surmised that chiral β-fluroamines would result, and depending on the chirality of the imidazolidinone ligand, either the (*S*)- or (*R*)-β-fluoroamine would be delivered. Moreover, there are thousands of commercially available amines and aldehydes to employ as reactants, providing improved generality in terms of substrate scope. Surprisingly, this powerful extension of the MacMillan enantioselective α-fluorination of aldehydes has never been described; thus the enantioselective synthesis of highly important β-fluoroamines was embarked on (Scheme 2.13).



2.35 **2.13** **2.36** **2.39**

Scheme 2.13. Synthesis of enantioenriched β-fluoroamines.

Table 2.2. Effect of Reagent, Solvent and Temperature survey on α-Fluorination.[a]



entry[a]	2.13 (equiv.)	solvent	temp (°C)	time (h)	conv (%)[d]	ee (%)[b]
1[c]	5.0	THF	-20	24	99	>98
2[c]	3.0	THF	-20	24	98	>98
3[c]	2.0	THF	-20	24	99	>99
4	1.5	THF	24	3	97	<98
5	1.5	acetone	24	3	91	>96
6	1.5	CH_2Cl_2	24	3	37	>84
7	1.5	EtOAc	24	3	89	>95
8[c]	1.5	THF	4	12	98	>98
9	1.2	THF	-20	24	99	>99
10	1.0	THF	-20	24	96	>99

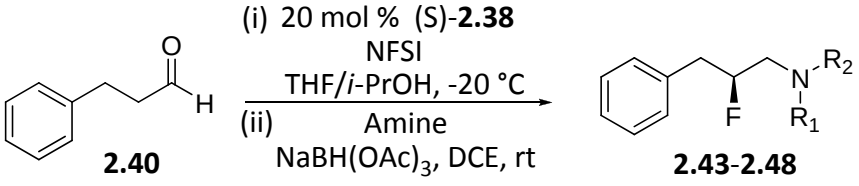
[a]All reactions were performed on a 0.05 mmol scale. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]α,α-difluoro product was observed. [d]Conversion determined by LC/MS and ^{1}H NMR.

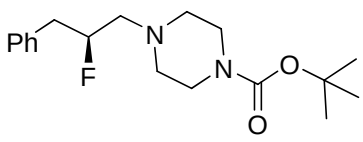
To determine suitable reaction conditions, we examined the reaction under varied temperature, solvent systems and the effect of fluorinating reagent loading on reaction efficiency, utilizing MacMillan's catalyst **2.38**.[38] In the presence of catalyst **2.38**, phenylpropanal **2.40** reacted with *N*-fluorobenzenesulfonimide (NFSI) **2.13** to give α-fluoroaldehyde **2.41**, which was immediately subjected to reductive amination conditions with Boc-piperazine **2.42** and sodium triacetoxyborohydride ($NaBH(OAc)_3$) to give the desired β-fluoroamine **2.43**.

Our initial attempt (entry 1) employed the conditions prescribed by MacMillan[38] for the α-fluorination, with a quick aqueous workup prior to the reductive amination step. Conversion and enantioselectivity to the desired β-fluoroamine were excellent, but about 20% of the undesired β,β-difluoroamine was also observed. To avoid this side product,

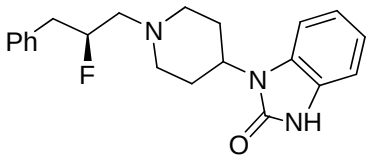
we decreased the equivalents for NFSI from 5.0 (Table 2.2, entry 1) to 3.0 (Table 2.2, entry 2), to 2.0 (Table 2.2, entry 3), and finally to 1.5 (Table 2.2, entry 4). Only in the latter case was the β,β-difluoroamine side product eliminated; moreover, the success of the α-fluorination was not hindered by decreasing the equivalents of costly NFSI, and workup was greatly improved. Other solvent systems were also evaluated, with acetone (Table 2.2, entry 6) proving to be generally useful, while CH_2Cl_2 (Table 2.2, entry 6) suffered diminished yields (37%) and low ee (84%).

Table 2.3. Scope of catalytic enantioselective synthesis of β-fluoroamines.*

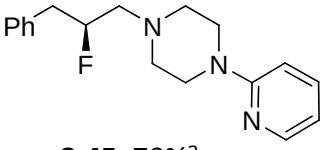




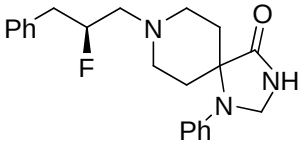
2.43, 80%[a]
>99% ee (S)[b]



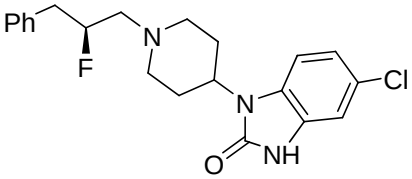
2.44, 70%[a]
>98% ee (*S*)[b]



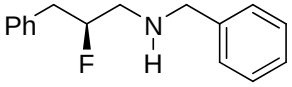
2.45, 70%[a]
>98% ee (*S*)[b]



2.46, 70%[a]
>98% ee (*S*)[b]



2.47, 70%[a]
>98% ee (*S*)[b]

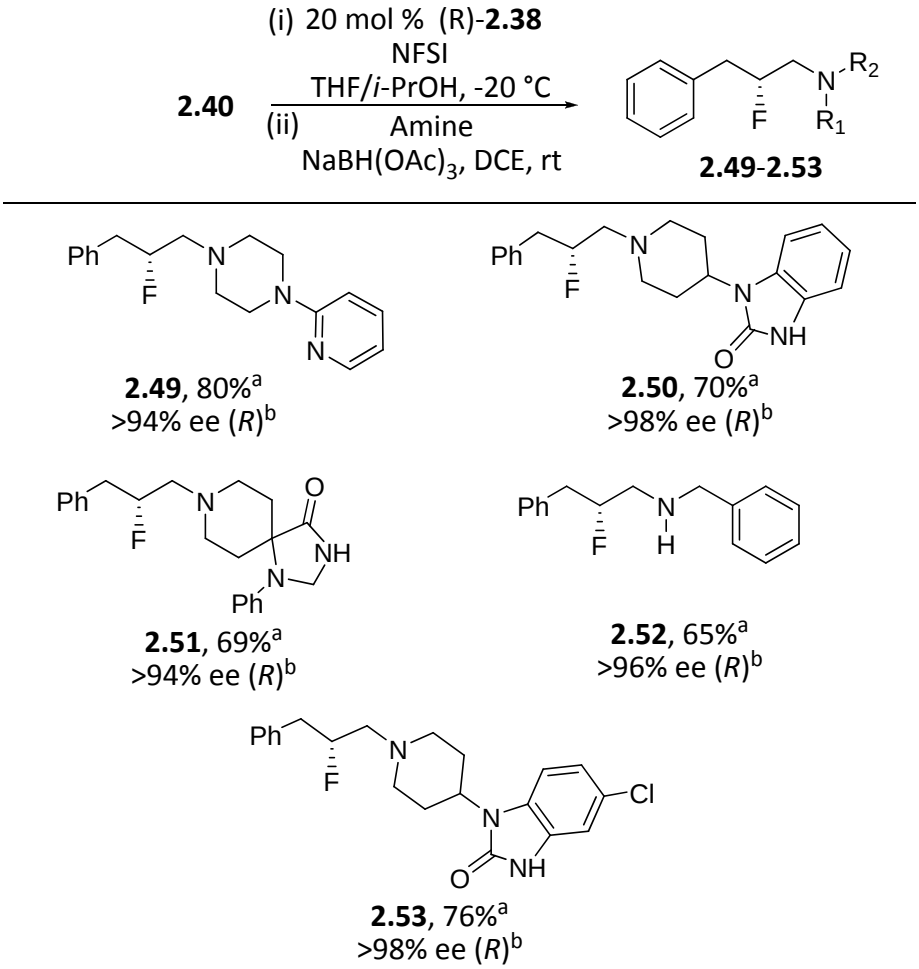


2.48, 70%[a]
>98% ee (*S*)[b]

*All reactions were performed on a 0.5 mmol scale and proceeded to complete conversion. [a]Yield after chromatography. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. See Supplementary Material for complete details.

Ultimately, optimal conditions for the two-step sequence (Table 2.2, entry 9) employed 1.2 equiv of NFSI in THF at -20 °C for 24 h, followed by a quick aqueous workup, suspension of the resulting α-fluoroaldehyde **2.41** in DCE with Boc-piperazine **2.42** and $NaB(OAc)_3H$ at ambient temperature to provide enantiopure (>99% ee) **2.43** with 96% conversion and 80% isolated yield.

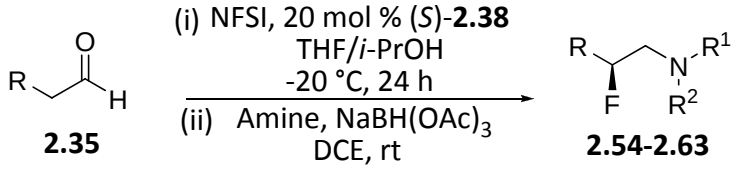
Table 2.4. Catalytic enantioselective synthesis of (*R*)-β-fluoroamines.[a]



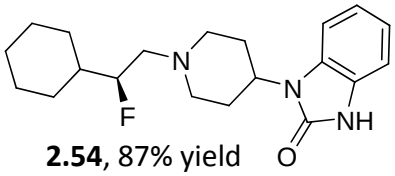
*All reactions were performed on a 0.5 mmol scale and proceeded to complete conversion. [a]Yield after chromatography. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. See Supplementary Material for complete details.

Encouraged by these results, we next examined the general application of the catalytic enantioselective synthesis of various β-fluoroamines. As shown in Tables 2.3 and 2.4, this two-pot protocol is general with respect to the amine component, providing yields from 65-82% employing both primary and secondary amines, which include therapeutically relevant G protein-coupled receptors (GPCR) privileged structures.[39]

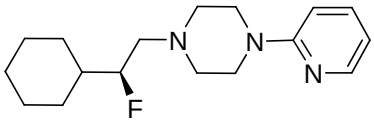
Table 2.5. Enantioselective β-fluoroamines substrate scope.[a]



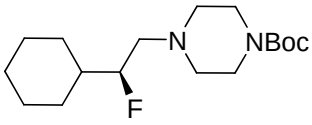
2.35 **2.54-2.63**



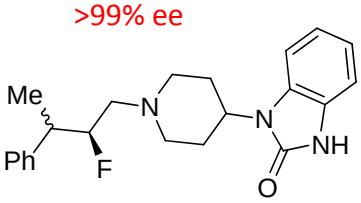
2.54, 87% yield
>99% ee



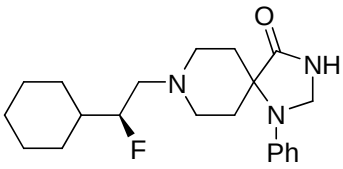
2.55, 88% yield
>99% ee



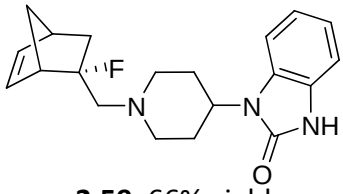
2.56, 92% yield
>98% ee



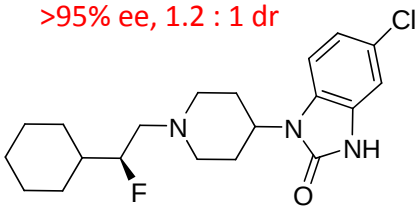
2.57, 75% yield
>95% ee, 1.2 : 1 dr



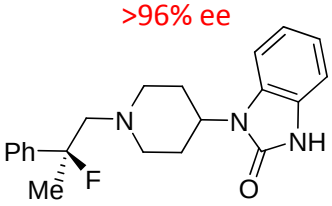
2.58, 90% yield
>96% ee



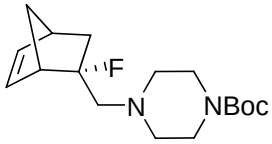
2.59, 66% yield
12% ee 14 : 1 (endo:exo)



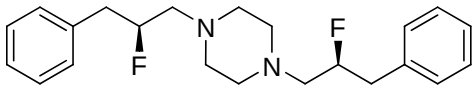
2.60, 84% yield
>97% ee



2.61, 74% yield
17% ee



2.62, 70% yield
15% ee
14 : 1 (endo:exo)



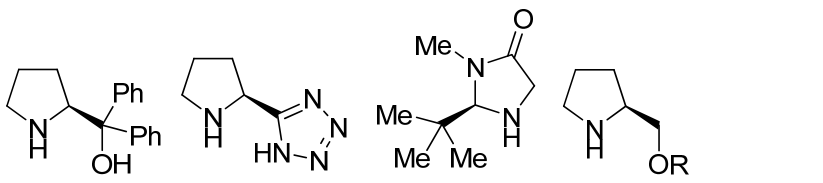
2.63, 58% yield

[a]All reactions were performed on a 0.05 mmol scale. [b]Yield after chromatography. [c]Enantiomer ratios were measured using chiral stationary phase HPLC. [d]Diastereomer ratios were measured by ^{19}F NMR. [e]Reaction were performed at room temperature for 24 h. See Supplementary Material for complete details.

Importantly, the (*S*)-imidazolidinone catalyst **2.38** provides the corresponding (*S*)-β-fluoroamines **2.43-2.48** in 95-99% ee (Table 2.3), whereas the (*R*)-imidazolidinone catalyst **2.38** provides the corresponding (*R*)-β-fluoroamines **2.49-2.53** in 87->95% ee (Table 2.4).

The optimized reaction condition appears general with respect to both aldehyde and amine component, furnishing chiral β-fluoroamines products (**2.54**-**2.63**) in good to excellent isolated yields (84-92%) and with high enantioselectivities (up to 99% ee) (Table 2.5). If the aldehyde bears a β-stereogenic center, as in **2.57**, the β-fluoroine is still installed with high ee (>95%) but with a 1.2:1 dr. However, formation of quaternary stereocenters using branched aldehydes under standard conditions with (*S*)-**2.38** provide moderate chemical yields (66-74%) for installation of the tertiary β-fluoroamine (Table 2.5) but suffer low enantioselectivities (12-17% ee).[28a] Compounds **2.59**, **2.61** and **2.62** represent transformations of tertiary β-fluoroamines that cannot be produced by standard β-fluoroamines methodology .

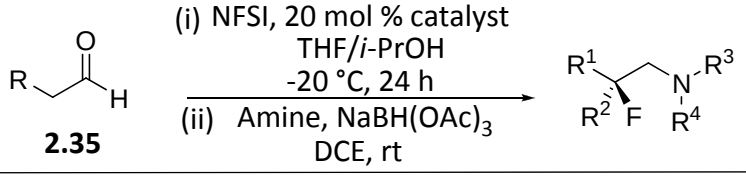
To optimize the fluorination reaction with branched aldehydes, a variety of proline catalysts (Figure 2.6) were examined. It was thought that using a less-sterically demanding catalyst such as **2.65**-**2.67** might be required for sterically encumbered substrates. The use of prolinol **2.67** afforded the desired product with poor conversion and selectivity. No improvement in the conversion was observed when a sterically demanding silylated prolinol derivative **2.68** was used (Table 2.6). Interestingly, tetrazole catalyst **2.65** installed the tertiary β-fluoroamine **2.59** in good chemical yields (94 %), but the maximum ee observed was 31%. A similar trend was observed in the synthesis of tertiary β-fluoroamine **2.61**. Our standard methodolgy with (*S*)-**2.38** provided good conversion but only 17% ee. Switching to the tetrazole catalyst **2.65** provided the desired tertiary β-fluoroamine **2.61** in comparable yield but with improved ee (40%). Thus, our new methodology allows access to tertiary β-fluoroamines with modest % ee, as opposed to existing methods that are unable to install tertiary β-fluoroamines (Table 2.6).

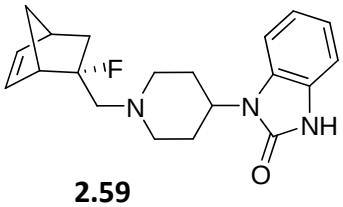


2.64 **2.65** **2.66** **2.67**, R = H; **2.68**, R = TBDPS

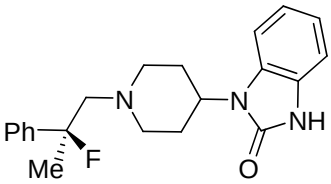
Figure 2.7. Catalysts screened for branched aldehydes.

Table 2.6. Screening of catalyst for tertiary β-fluoroamines.[a]





2.59



2.61

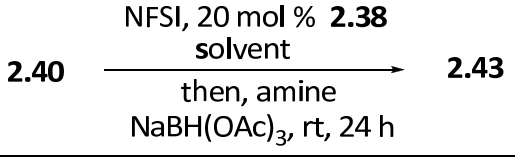
catalyst	yield (%)[c]	ee (%)[b]	catalyst	yield (%)[c]	ee (%)[b]
2.38	93	15	**2.38**	74	17
2.67	25	13	**2.65**	75	40
2.68	<10	nd[d]			
2.65	94	31			
2.66	83	16			
2.64	16	12			

[a]All reactions were performed on a 0.05 mmol scale. [b]Yield after chromatography. [c]Enantiomer ratios were measured using chiral stationary phase HPLC. See Supplementary Material for complete details.

Our attention now turned to developing a one-pot organocatalytic approach to β-fluoroamines to avoid the aqueous workup step. For this study, we utilized standard reductive amination solvents. The α-fluorination step only proceed smoothly at room temperature in THF or CH_3CN to give moderate yields of the desired product (Table 2.7, entries 1-2), with no loss in selectivity (>95% ee). CH_2Cl_2 and DCE both failed under all

conditions (entries 3-4). Interestingly, using THF and 10% *i*-PrOH was suitable for the reductive amination step to afforded the desired product in 65% yield and >96% ee (entry 5). It should be noted that these reactions are operationally convenient and can be performed without exclusion of air and moisture. This one-pot tandem procedure allows the enantioselective synthesis of β-fluoroamine derivatives from an aldehyde and does not require the isolation of a preformed α-fluoro aldehyde.

Table 2.7. Enantioselective synthesis of β-fluoroamine in one-pot.[a]

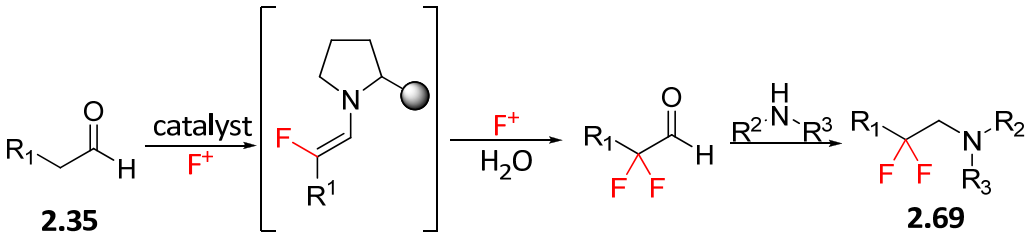


entry[a]	solvent	temp (°C)	time (h)	yield (%)[c]	ee (%)[b]
1	THF	24	3	45	>95
2	CH_3CN	24	3	36	>95
3	CH_2Cl_2	24	24	12	nd[d]
4	DCE	24	24	0	nd[d]
5	THF/*i*-PrOH	-20	3	65	>96

[a]All reactions were performed on a 0.05 mmol scale. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Yield after chromatography. [d]Not determined.

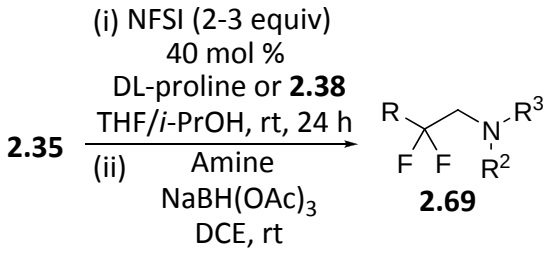
There are many examples in the literature where a β,β-difluoroamineis required to address a specific liability of a candidate molecule.[1-3] On the basis of an earlier observation of β,β-difluoroamine formation (Table 2.2) when excess NFSI was employed, we attempted to access this valuable moiety (Scheme 2.14). In the presence of 40 mol % of D,L-proline as the catalyst, aldehyde **2.35** reacted with 2-3 equiv of NFSI **2.13** at room-temperature to give α,α-difluoroaldehyde, which was subsequently

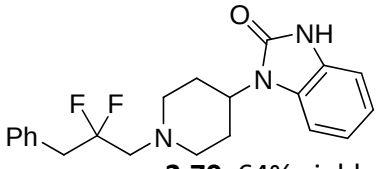
subjected to standard reductive amination conditions, to give the desired β,β-difluoroamines in good yields ranging from 64% to 77% (Table 2.8).



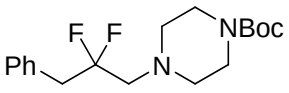
Scheme 2.14. Synthesis of β,β-difluoroamine.

Table 2.8. Scope of catalytic α,α-difluorination.[a]

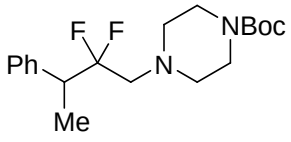




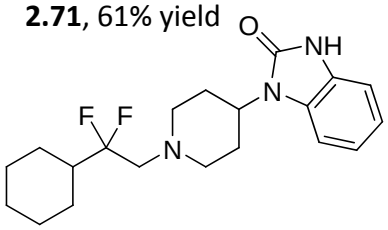
2.70, 64% yield



2.71, 61% yield



2.72, 68% yield



2.73, 77% yield

[a]All reactions were performed on a 0.05 mmol scale. [b]Yield after chromatography

To show the application of the synthesized β-fluoroamines, we made new fluorinated analogues of five known amine based medicinal agents (Figure 2.7) having likely affinity for human ether-a-go-go-related gene (hERG) potassium channel. The non-fluotinated and fluorinated compounds are currently being screened for hERG activity (Figure 2.8).

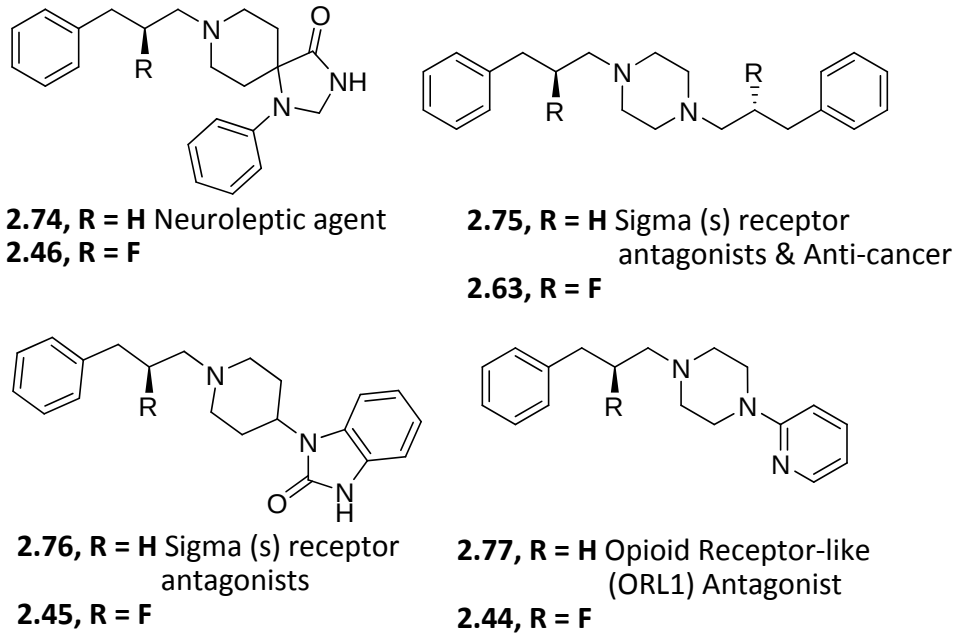


Figure 2.8. Medicinal Agents and its fluorinated analogs.

2. 2. General access to chiral *N*-alkyl terminal aziridines via organocatalysis

2. 2. 1. Importance and synthetic utility of aziridines

Aziridines represent an important class of nitrogen heterocycles with a wide range of synthetic utility and prevalence in natural products.[40] The inherent reactivity of aziridines is mainly due to the high strain energy of about 27 kcal/mol of the 3-membered

heterocycle ring.[41] This high strain energy renders them susceptible to a variety of transformations involving ring opening. These features make them an important intermediate in synthetic chemistry. Aziridines are present as structural motifs in various biologically active natural products such as mitomycins C and azinomycin A (potent antitumor and antibiotic agents (Figure 2.9)).[42]

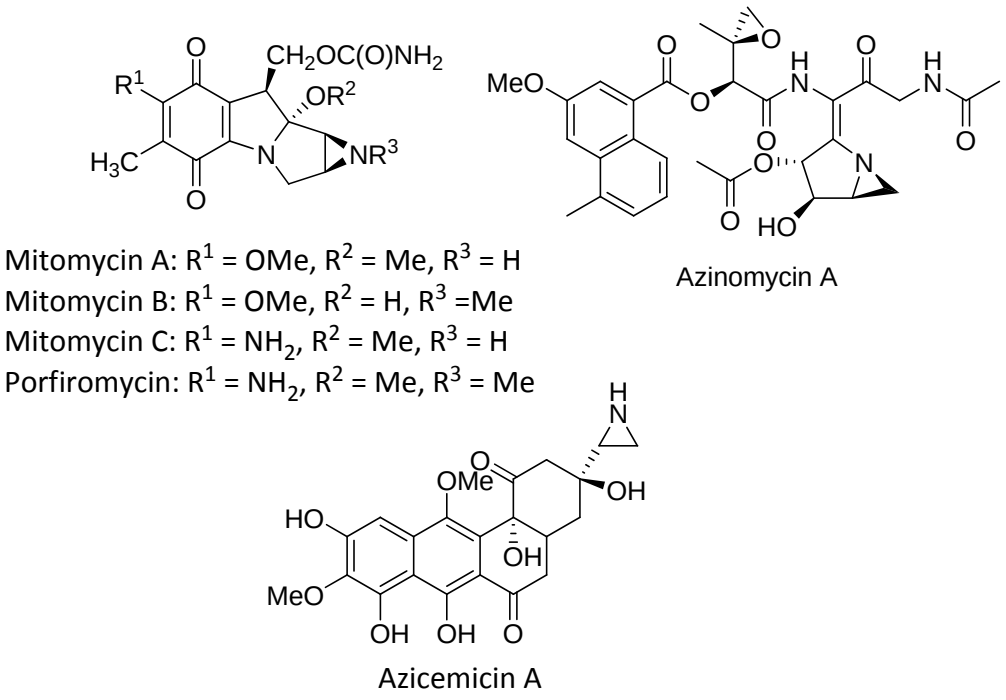


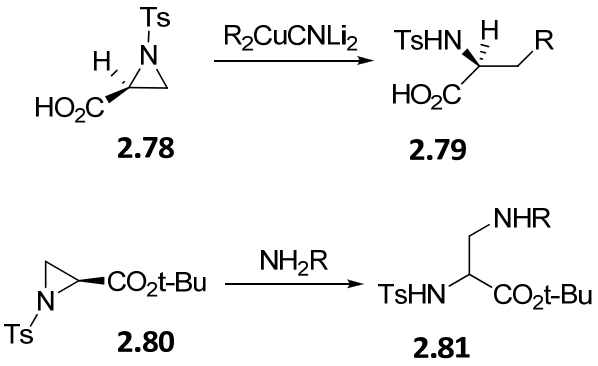
Figure 2.9. Aziridine containing biologically active natural products.

There are two classes of aziridines namely, the activated and non-activated aziridines. Activated aziridines have N-electron-withdrawing groups and non-activated aziridines are N-alkyl substituted. The presence of the N-withdrawing group in activated aziridines renders the ring susceptible to opening through nucleophilic attack. Unactivated aziridine requires activation by quaternization, protonation or Lewis acid

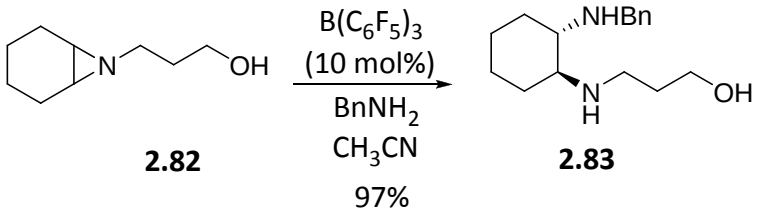
chelation to affect the ring opening. Several methods have been reported for the regioselective ring opening of aziridines.

2. 2. 2. Nucleophilic ring-opening reactions

The nucleophilic ring opening is the most popular transformation of aziridines. For example, *N*-tosyl aziridine **2.78** can be efficiently opened by carbon-nucleophiles such as higher-order cuprates to give protected amino acid **2.79**[43] and with primary amines to afford tosyl-protected diamino acids **2.81**.[44]

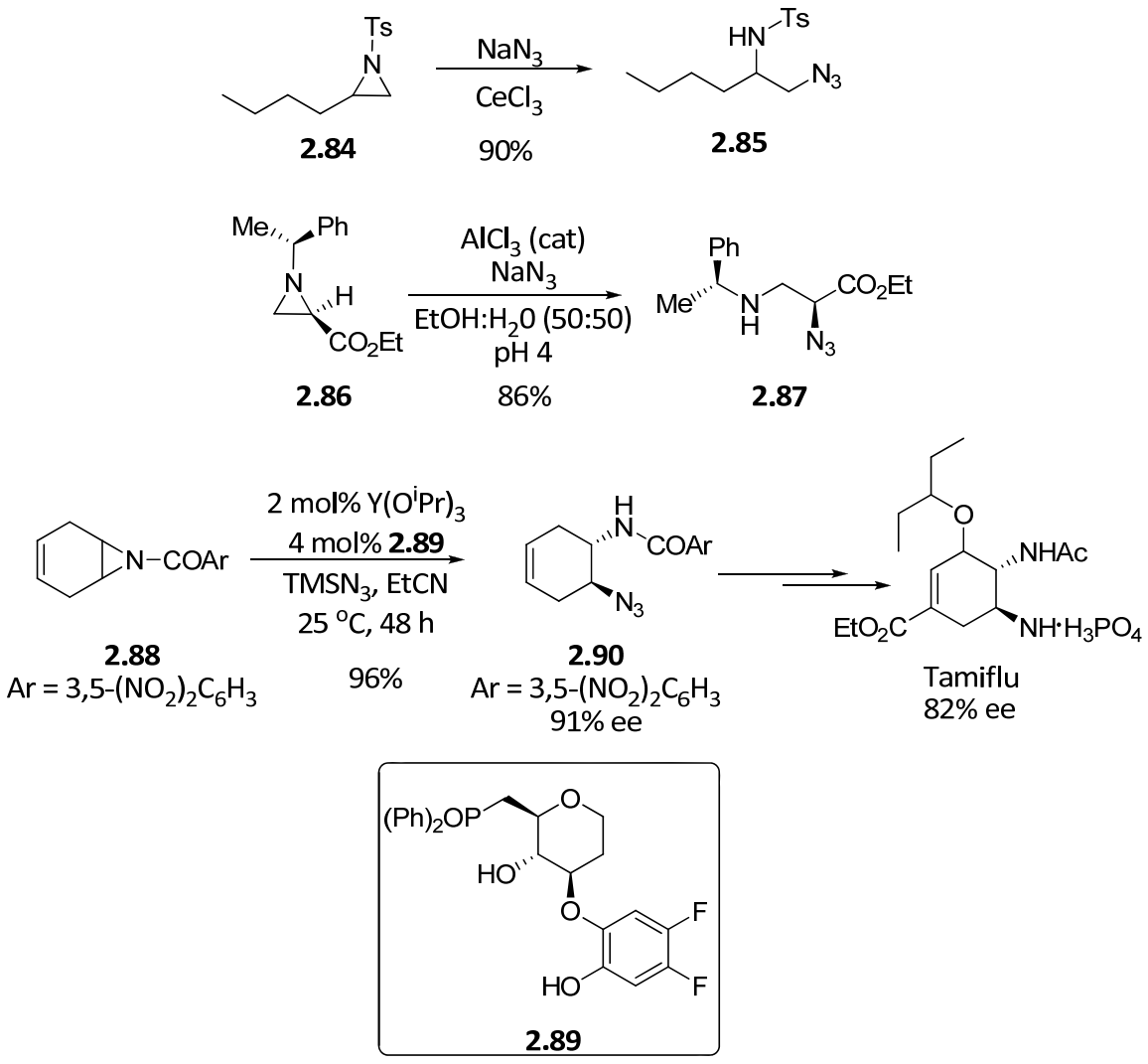


Scheme 2.15. Ring-opening of activated aziridine by cuprate and amine.



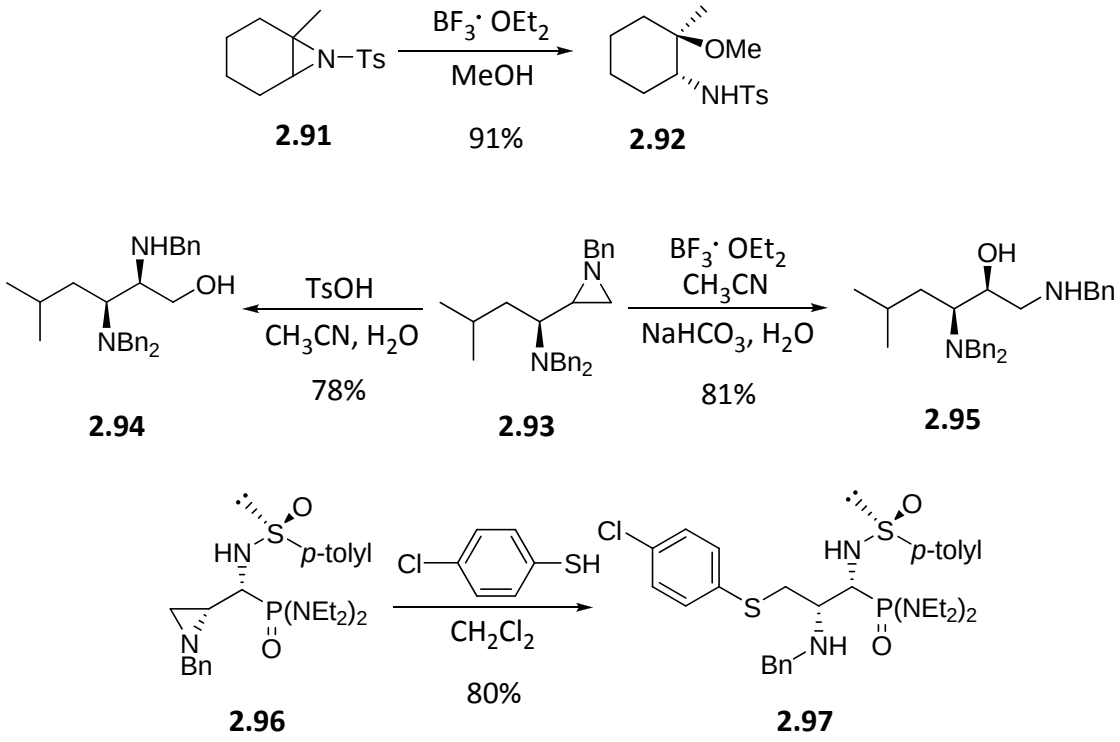
Scheme 2.16. Ring-opening of unactivated aziridine with amine nucleophile.

The azide anion is often used as a nitrogen-nucleophile in aziridine ring opening. For example, tosyl aziridine **2.84** is readily transformed to azido amine **2.85**, upon treatment with NaN_3 and $CeCl_3$.[45] Unactivated aziridine **2.86** can also undergo similar azide opening in the presence of Lewis acids, such as $AlCl_3$[46] (Scheme 2.17). Shibaski and co-workers reported the desymmetrization of meso-aziridine **2.88** with chiral Lewis acid **2.89** and silyl azide to afford azide **2.90**[47] (Scheme 2.17). Oxygen/sulfur-nucleophiles are other common nucleophiles for the opening of aziridine ring systems (Scheme 2.18).[48-50]

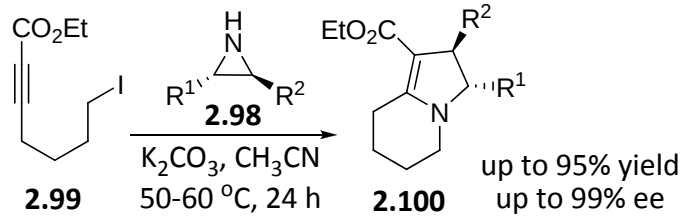


Scheme 2.17. Ring-opening reaction by azide anion.

Zhu and co-workers reported a formal S_N2/[3+2] cycloaddition reaction for the synthesis of substituted indolizidines. N-alkylation of the N-unsubstituted aziridine **2.98** with iodide **2.99** followed by Michael addition/rearrangement cascade to afford various indolizidine derivatives **2.100** in excellent yields and enantioselectivity (Scheme 2.19).[51]



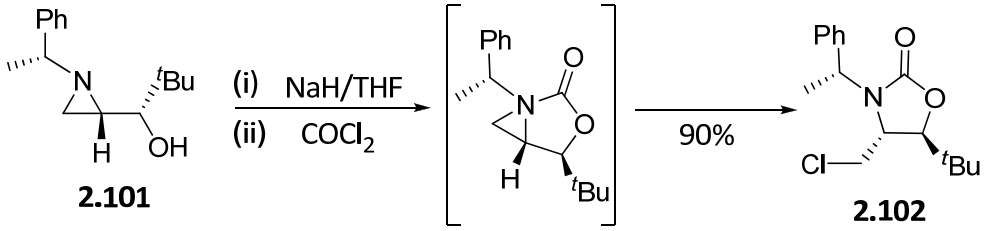
Scheme 2.18. Ring-opening reaction by oxygen/sulfur nucleophiles.



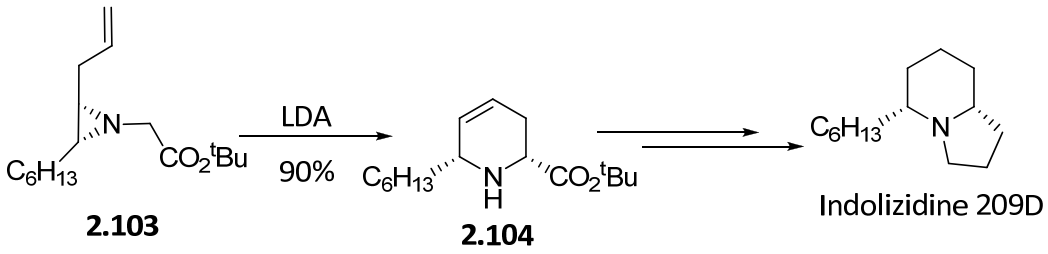
Scheme 2.19. S_N2/[3+2] cycloaddition reaction for the synthesis indolizidines.

2. 2. 3. Rearrangement Chemistry

Ha and co-workers disclosed the synthesis of substituted oxazolidinone **2.101** from aziridine **2.102** (Scheme 2.20).[52] Somafai and co-workers reported the total synthesis of indolizidine 209D via aza-[2,3]-Wittig rearrangement of vinyl aziridine **2.103** (Scheme 2.21).[53] Other known rearrangements of aziridines include [3+3] annulation reactions, ring expansion (with heterocumulenes, isocyanates, nitriles and carbonylative ring expansion) and radical reactions.[54]



Scheme 2.20. Synthesis substituted oxazolidinone via aziridine rearrangement.



Scheme 2.21. Indolizidine 209D via aza-[2,3]-Wittig rearrangement of vinyl aziridine.

2. 2. 4. Synthesis of Aziridines

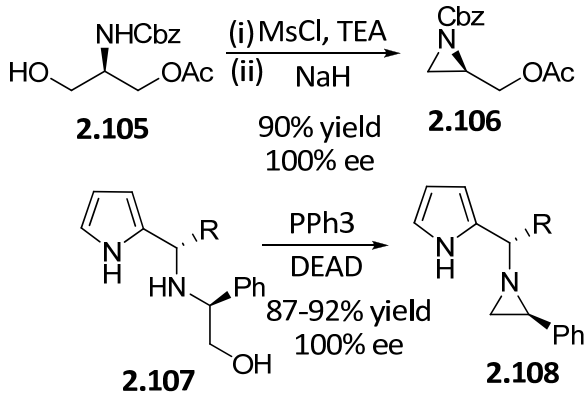
Gabriel in 1888 was the first to report the synthesis of an aziridine via nucleophilic ring closure of *vic*-amino alcohols.[55] This approach was further developed later by Wenker in 1935.[55] Since the classic work of Gabriel, the synthetic scope of

aziridines has broadened tremendously. The main methods for the synthesis of aziridines include the addition to olefins (nitrene transfer to alkene and addition/elimination sequences), addition to imines (carbene methodology, azaDarzens approaches and ylide-mediated strategies) and intramolecular nucleophilic substitution.

2. 2. 4. 1. Aziridination via intramolecular substitution

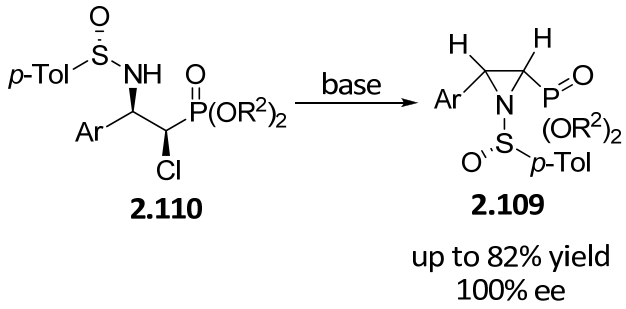
Since reported by Gabriel in 1888, the nucleophilic ring closure of *vic*-amino alcohols is one of the most utilized routes to aziridines. Nucleophilic ring closure utilizes a leaving group vicinal to the amine. To form enantiopure azirdines, non-racemic starting materials is required. The intramolecular displacement can then be achieved using 1,2-amino alcohols, 1,2-azido alcohols, 1,2-amino halides, 1,2-amino sulfides, 1,2-amino selenides or epoxides.[40]

Borch and Choi have reported the synthesis of enantiopure *N*-protected aziridine **2.106** in excellent yield and selectivity via nucleophilic ring closure of mesylate alcohol generated from monoacetate **2.105** (Scheme 2.22).[56] Similarly, the synthesis of enantiopure pyrrole-aziridines was reported by Savoia and co-workers. The treatment of enantiopure β-hydroxyamines 2.107 derived from (*S*)-phenylglycinol bearing a pyrrole moiety, with triphenylphosphine and DEAD led to enantiopure pyrrole-aziridines 2.108 in excellent yields (Scheme 2.22).[57]



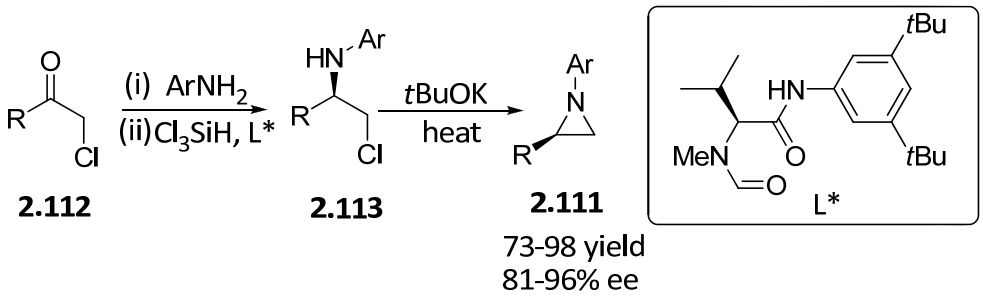
Scheme 2.22. Synthesis of aziridines from 1,2-amino alcohols.

Davis and co-workers have reported the synthesis of *N*-sulfinylaziridine 2-phosphonates **2.109** in high yields and enantioselectivities, via a base induced cyclization of by β -amino α-chlorophosphonates **2.110** (Scheme 2.23).[58]



Scheme 2.23. Syntheses of *N*-sulfinylaziridine 2-phosphonates.

One recent example was reported by Kocovsky and co-workers for the synthesis of terminal diarylaziridines by organocatalytic enantioselective reductive amination of α-chloroketones followed by base-induced intramolecular substitution of the corresponding α-chloroamines (Scheme 2.24).[59]

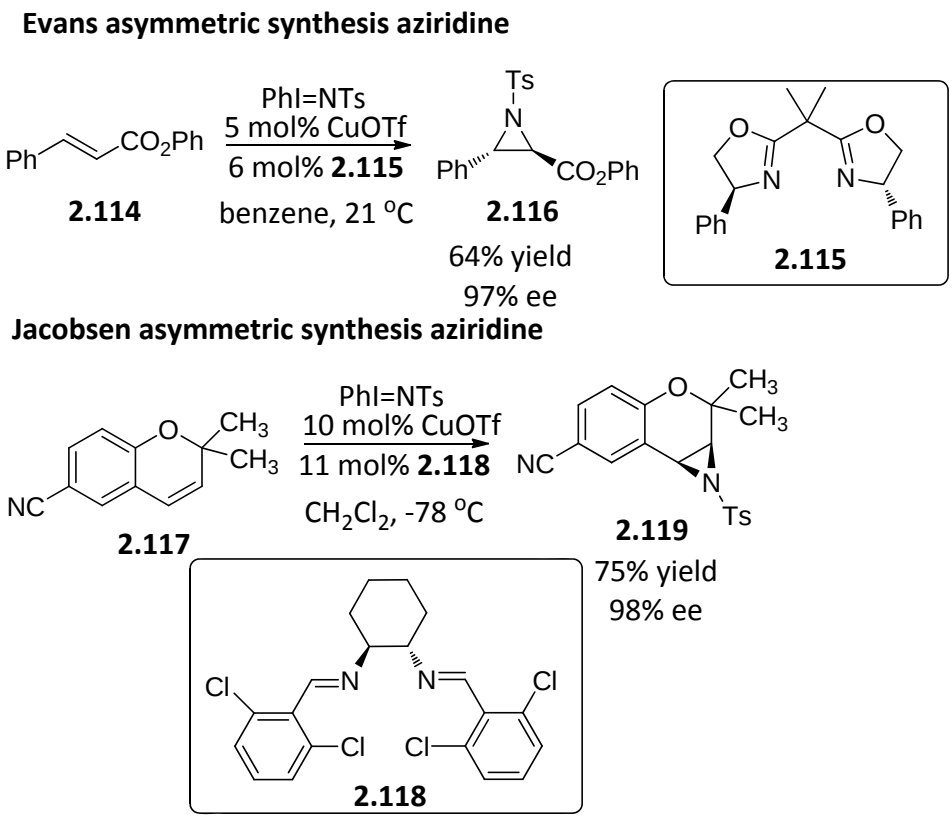


Scheme 2.24. Synthesis of 1,2-diaryl aziridines.

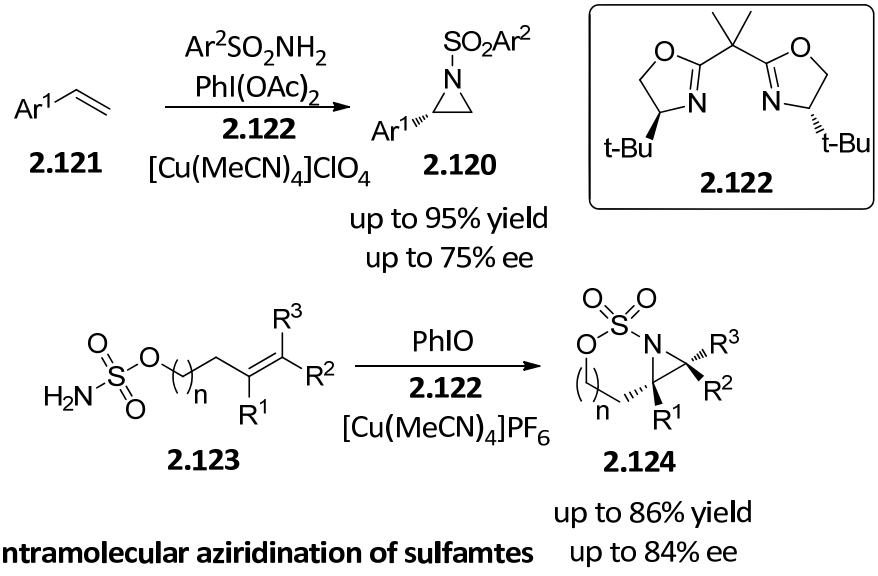
2. 2. 4. 2. Aziridine Formation via Nitrene Addition to Olefins

Nitrene addition to olefins, which is usually accomplished using a nitrene-transfer reagent, is one of the most common approaches to aziridination of olefins. Several metal-based reagents (Copper, Manganese, Rhodium) have been developed to generate the nitrene source which, in the presence of chiral ligands and [*N*-(p-toluenesulfonyl)imino]aryliodinanes, provides a route for catalytic asymmetric aziridination. In 1993, Evans[60] and Jacobsen[61] were the first to report a catalytic asymmetric synthesis of aziridine utilizing copper-(I)-complexes generated from chiral bisoxazoline or diammine ligands (Scheme 2.25). Another known approach to generate nitrene is by the oxidation of primary amines.

Che and co-workers reported the asymmetric synthesis of an aziridine via a copper-bisoxazoline complex and nitrene precursor generated from $PhI(OAc)_2$ and sulfonamides (Scheme 2.26).[62] Dauban and co-workers later reported an intramolecular copper-catalyzed aziridination using bisoxazoline chiral ligand **2.122** as well. The sulfamates **2.123** were subjected to Iodosylbenzene and [Cu(MeCN)4]PF6, to give the corresponding aziridines **2.124** in good yields and enantioselectivities (Scheme 2.26).[63]

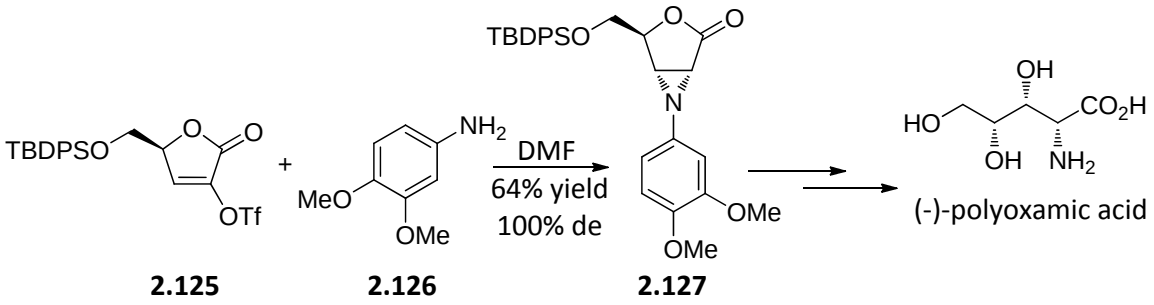


Scheme 2.25. Asymmetric aziridination via copper-catalyzed nitrene.



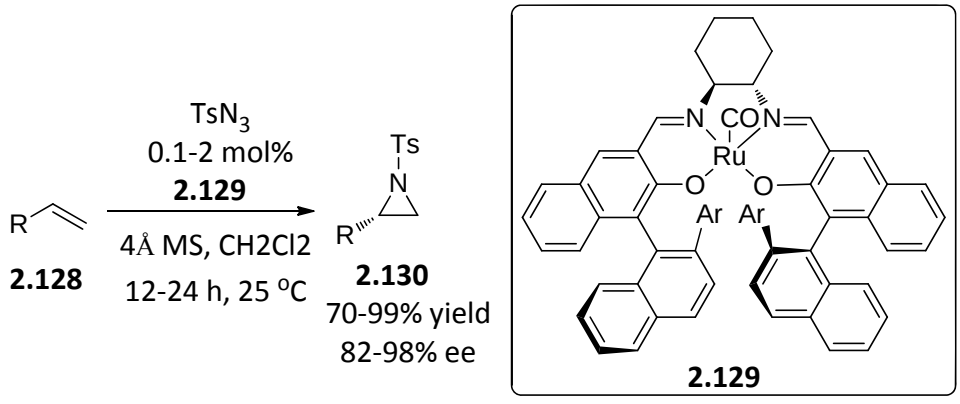
Scheme 2.26. Aziridination of alkenes mediated by bisoxazoline ligand.

An aziridination method utilizing the approach of addition to olefins is aziridination through an addition–elimination sequence. Dodd and co-workers utilize a Michael-type addition-elimination sequence in the total synthesis of the non-natural enantiomer of polyoxamic acid (Scheme 2.27).[64]



Scheme 2.27. Synthesis of (-)-polyoxamic acid via addition/elimination sequence.

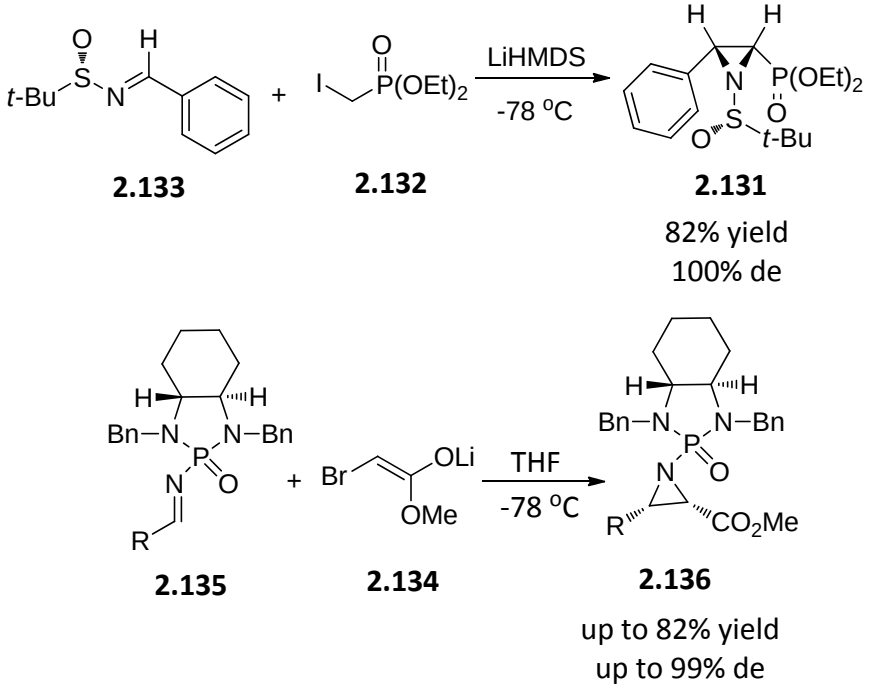
Decomposition of organyl azides is an additional method in the aziridination of olefins. Using a ruthenium salen complex Katsuki and coworkers reported an improvement in the scope of olefins. The nitrenes addition occurred in moderate to excellent yield with enantiomeric excess up to 98% (Scheme 2.28).[65]



Scheme 2.28. Aziridination via organyl azides using ruthenium salen complex.

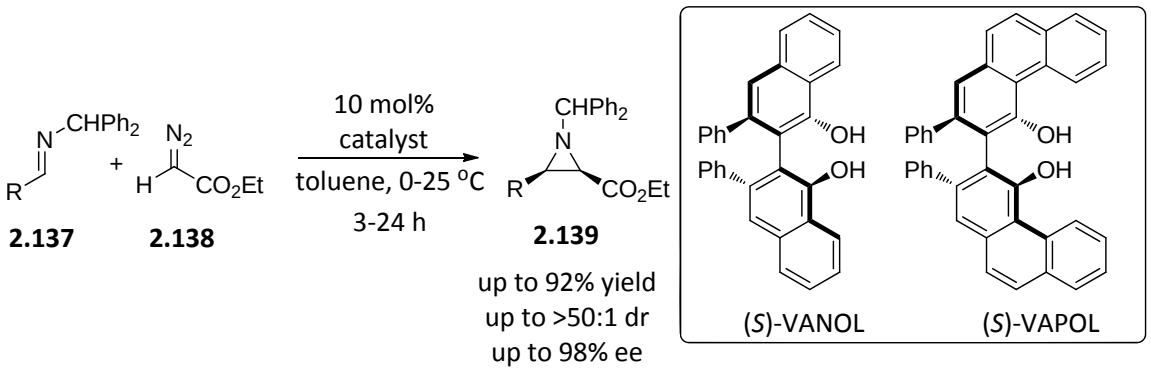
2. 2. 4. 3. Aziridine via Addition to Imines

There are three major ways aziridination can be achieved by addition to imines, this includes the addition of a carbene, α-haloenolates (aza-Darzens) and ylides. The use of chiral imines or nucleophiles allows diasterocontrol of the aziridine formed. The aza-Darzen is a common, efficient approach in the synthesis of azaridines. It involves the use of chiral imines or in some cases the use of chiral enolates. The enolate is often generated using lithium base, with the reaction proceeding through a Zimmerman-Traxler transition state. Davis and co-workers reported the asymmetric synthesis of cis-*N*-sulfinylaziridine-2-phosphonate **2.131** as a single diastereomer in good yields. The asymmetric aza-Darzens reaction involves the addition of iodophosphonate anion **2.132** to chiral sulfinimine **2.133** (Scheme 2.29).[66]

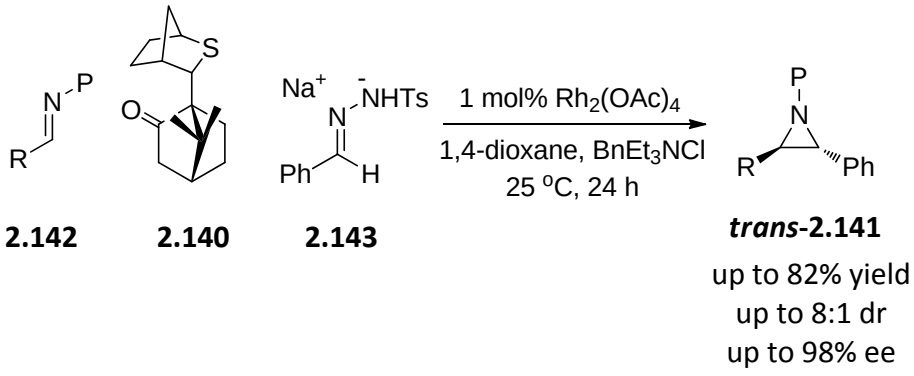


Scheme 2.29. Aza-Darzens reactions of chiral imines.

Li and Kattuboina developed an asymmetric aza-Darzens reaction employing the lithium enolate of methyl 2-bromoacetate **2.134** and chiral *N*-phosphonyl imines **2.135** to afford cis-aziridines **2.136** in moderate yields with diastereoselectivity up to 99 % (Scheme 2.29).[67]



Scheme 2.30. Boron-catalysed aziridination mediated by VANOL and VAPOL ligands.

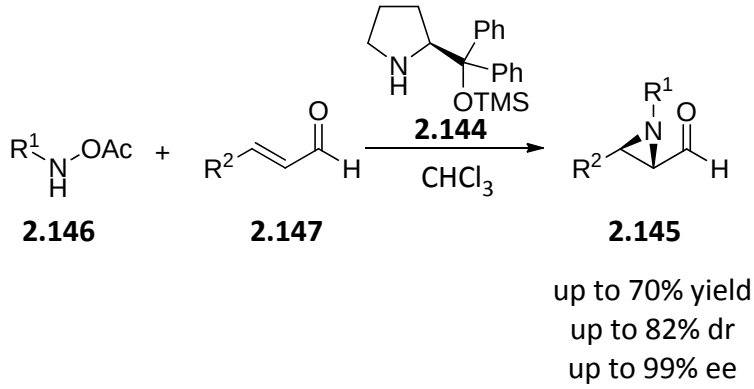


Scheme 2.31. Catalytic asymmetric ylide-mediated aziridination.

Aziridination by transfer of carbenes to imines is well established. Wulff and co-workers have reported an asymmetric catalytic aziridination of *N*-dianisylmethylimines **2.137** with ethyl diazoacetate **2.138** in the presence of boron chiral ligands binaphthol

(VANOL) and biphenanthrol (VAPOL) to give aziridine **2.139**. This reaction is highly efficient largely due to the reduced formation of enamine by-products previously reported and the aziridines are produced in moderate to excellent yields with high enantio- and diastereoselectivity (Scheme 2.30).[68] Aggarwal and coworkers recently utilized an *in situ* formation of chiral sulfur ylides **2.140** from metallocarbenes for a catalytic asymmetric ylide-mediated aziridination to give *trans*-aziridines **2.141** (Scheme 2.31).[69]

In 2007, Cordova and co-workers disclosed an organocatalytic aziridination of α,β-unsaturated aldehydes with acylated hydroxycarbamates. Utilizing a chiral silyl-protected pyrrolidine alcohol **2.144**, 2-formylaziridines **2.145** were achieved in moderate yields with moderate to high diastereoselectivities and enantioselectivities (Scheme 2.31).[70]

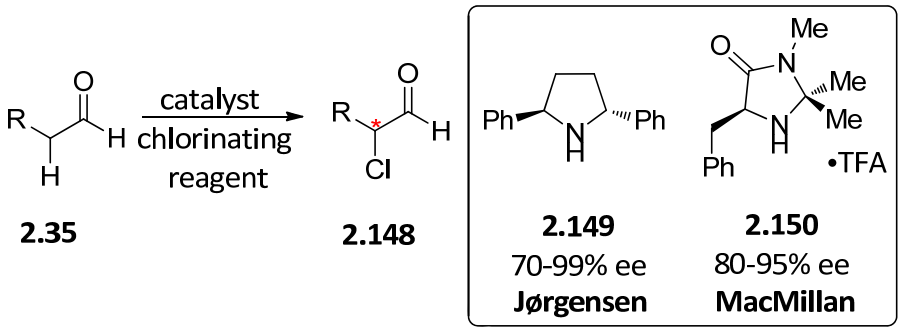


Scheme 2.32. Organocatalysed aziridination aziridination of α,β-unsaturated aldehydes.

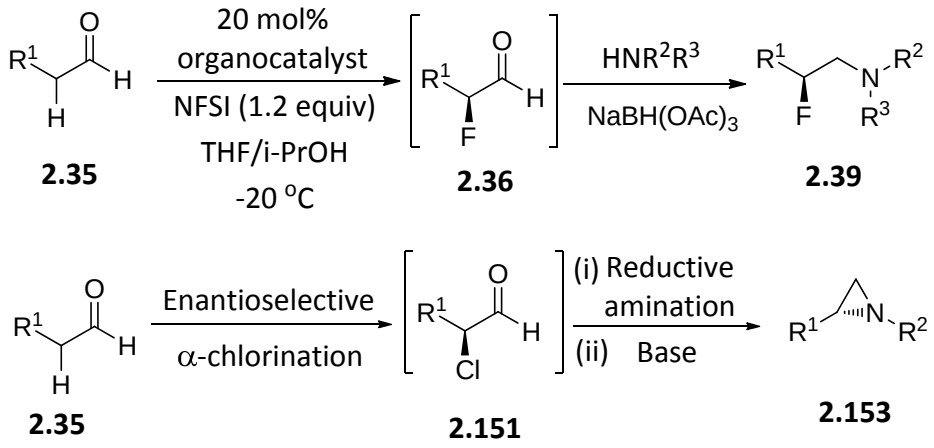
Despite their value, synthetic routes to aziridines are limited in terms of generality and diversity of the *N*-substituent. Many of the classical methods for the synthesis of terminal aziridines, typically incorporate a *p*-toluenesulfonyl moiety or other electron-withdrawing group as the the *N*-substituent.[40] The synthesis of chiral terminal aziridines with diversity at the *N*-substituent is extremely rare. One recent example was reported for

the synthesis of terminal diarylaziridines by the enantioselective reductive amination of α-chloroamines (Scheme 2.24).[59]

However, this approach lacks generality and substrate scope, as only *N*-arylaziridines can be achieved using this method. Since there are few synthetic methods in the literature for the preparation of enantiopure *N*-alkylziridines, and due to some interesting biologically properties these molecules possess,[71] we embarked on developing a synthetic methodology towards the enantioselective synthesis of *N*-alkyl terminal aziridines. Previously, both MacMillan[72] and Jørgensen[73] disclosed the enantioselective α-chlorination of aldehydes via organocatalysis (Scheme 2.33). Based on this precedent and our chiral β-fluoroamine work (Scheme 2.33), we envisioned a three-step, one-pot protocol involving enantioselective α-chlorination of aldehydes, subsequent reductive amination with a primary amine, and S_N2 displacement to afford previously unattainable chiral terminal aziridines with a wide range of *N*-substituents (Scheme 2.34). Overall, this new approach represents the effective addition of a primary amine across an olefin to form aziridines.



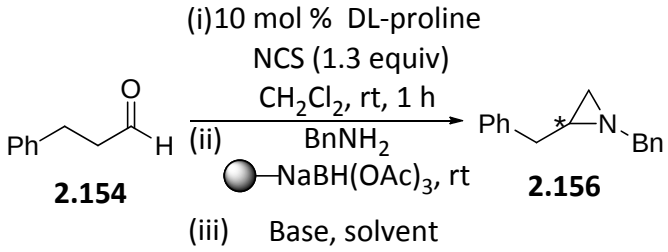
Scheme 2.33. Organocatalytic enantioselective α-chlorination of aldehydes.



Scheme 2.34. Organocatalytic approach to chiral β-fluoroamines and envisioned route to chiral *N*-alkyl terminal aziridines.

For a one-pot protocol involving a reductive amination step, we could not use the MacMillan α-chlorination chemistry, as that route employed a chloroquinone as the chlorinating agent and acetone as a solvent.[73] The Jørgensen route was attractive, as NCS was the chlorinating agent, and the optimized solvent was DCE.[74]First, we set out to determine if this proposal would allow access to racemic *N*-alkyl terminal aziridines. Thus, DL-proline-catalyzed α-chlorination of **2.154** with NCS, followed by reductive amination with benzylamine and subsequent base-induced S_N2 cyclization with KOH in THF/H_2O at 65 °C, did provide racemic aziridine **2.155** in 70% yield (Scheme 2.35) for the three step, one-pot protocol (average of 90% per step). Importantly, KOH was critical for the production of **2.155**, as a screen of organic (i.e, Et_3N, pyridine, DBU, KO-*t*-Bu) and inorganic bases (ie., NaH, K_2CO_3) provided less than 60% conversion to **2.155** (Table 2.9).

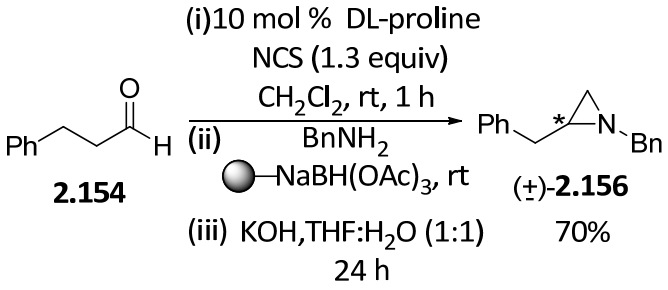
Table 2.9. Screening of base for S_N2 cyclization.



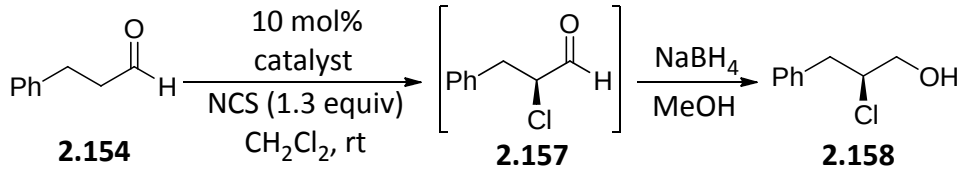
entry[a]	Base	Solvent	time	temp (°C)	conv (%)[b]
1	Et_3N	CH_2Cl_2	2 days	25	<30
2	Pyridine	CH_2Cl_2	2 days	25	<30
3	DBU	CH_2Cl_2	24 h	25	>40
4	NaH	THF	16 h	25	decomposed
5	*t*-BuOK	THF	16 h	25	>60
6	K_2CO_3	THF/DMF/Acetone	24 h	85	<50
7	KOH	THF:H_2O (1:1)	24 h	65	100
8	Et_3N	CH_2Cl_2	24 h	45	<60
9	Pyridine	CH_2Cl_2	24 h	45	<50
10	DBU	CH_2Cl_2	24 h	45	<60

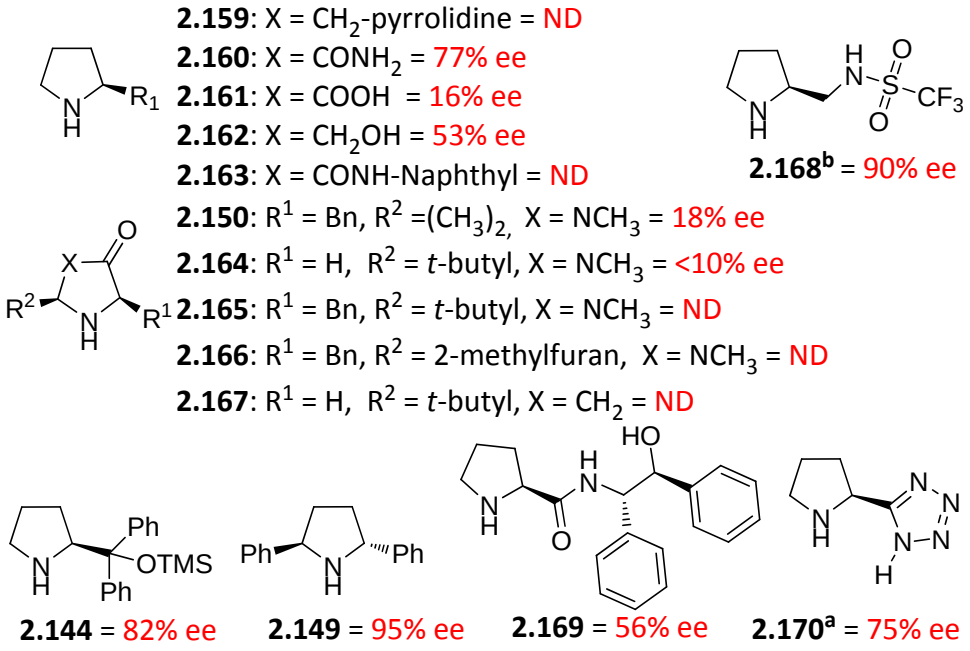
[a]All reactions were performed on a 0.05 mmol scale. [b]Conversion determined by LC/MS and ^{1}H NMR.

Efforts now focused on developing an enantioselective one-pot protocol. To ensure we had optimal conditions for the enantioselective α-chlorination of **2.154**, we elected to survey a set of thirteen organocatalysts (Scheme 2.36) employing NCS as the chlorinating agent and DCM as the solvent. This study demonstrated that the Jørgensen[74] catalyst **2.149** was indeed optimal, affording **2.157** in >97% conversion.



Scheme 2.35. One-pot protocol for racemic *N*-alkyl terminal aziridines.





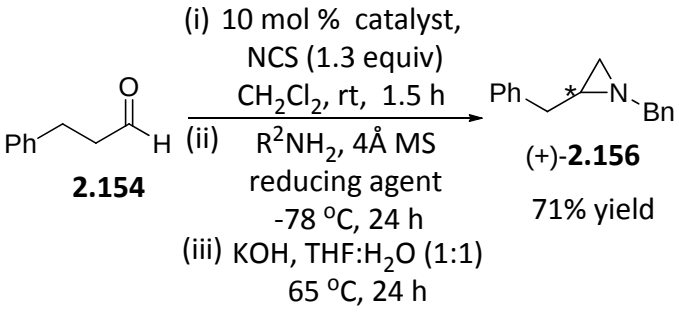
All reactions were 0.05 mmol scale. Enantiomer ratios were measured using chiral stationary phase HPLC. [a]5 mol % catalyst loading. [b]Reaction conducted at -20 °C for 16 h.

Scheme 2.36. Enantioselective α-chlorination of hydrocinnamaldehyde.

In order to determine the degree of enantioselectivity by chiral HPLC, **2.157** was reduced to the corresponding α-chloroalcohol **2.158**, and found to possess 95% ee

(Scheme 2.36). The other novel organocatalysts **2.144**, **2.168**, **2.169** and **2.170** for this transformation afforded comparable conversion (>95%), but lower enantioselectivity (56-90% ee).

Table 2.10. Examination of temperature for reductive amination step.



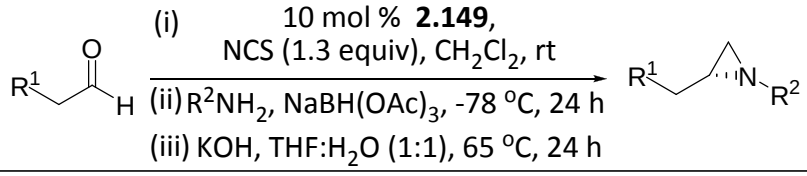
entry[a]	Reducing agent	temp (°C)	ee (%)[b]
1[c]	PS-NaBH(OAc)$_3$	25	45
2	NaBH(OAc)$_3$	25	68
3	NaBH(OAc)$_3$	-10	70
4	NaBH(OAc)$_3$	-20	85
5	NaBH(OAc)$_3$	-30	85
6[c]	PS-NaBH(OAc)$_3$	-78	60
7	NaBH(OAc)$_3$	-78	94

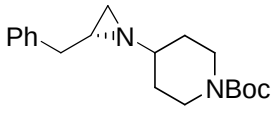
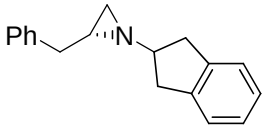
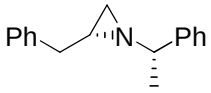
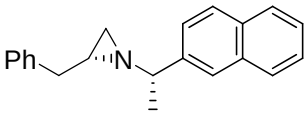
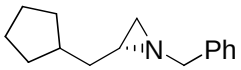
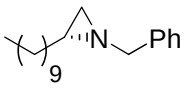
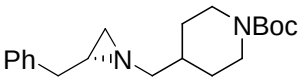
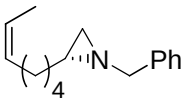
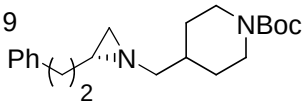
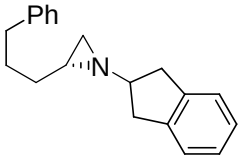
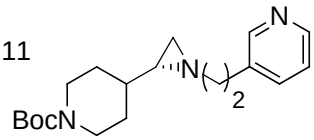
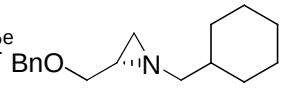
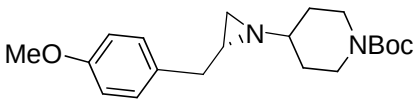
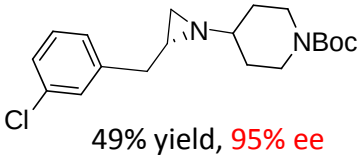
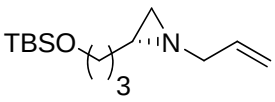
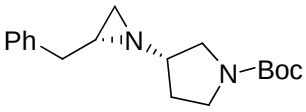
[a]All reactions were performed on a 0.05 mmol scale.
[b]Enantiomer ratios were measured using chiral stationary phase HPLC.
[c]Polymer-bound sodium triacetoxy-borohydride

With optimal α-chlorination conditions in hand, we attempted the three step, one-pot protocol to deliver **2.156** enantioselectively. Utilizing the protocol in Scheme 2.35, but replacing DL-proline with catalyst **2.149**, we were disappointed to find that this approach afforded **2.156** in comparable yield, but in less than 40% ee. Thus, we investigated the most probable source of epimerization in the system: the room temperature reductive amination step. Molecular sieves proved essential, and we found a direct correlation between enantioselectivity and temperature (Table 2.10). As shown in

Table 2.10, reducing the temperature for the reductive amination step to -78 ^{o}C resulted in the enantioselective synthesis of aziridine **2.156** in 71% yield for the three steps (~90% per step) and 94% ee. As shown in Table 2.11, the reaction scope was also found to be general with respect to both aldehyde and amine, providing chiral *N*-alkyl-1,2-aziridines in overall yields of 40-65% (50-88% per step) and, in most cases, >90% ee for the three step, one-pot protocol. Determining the enantioselectivity was an arduous task, and required classical reverse phase chiral HPLC, SFC or NMR chiral shift reagents.

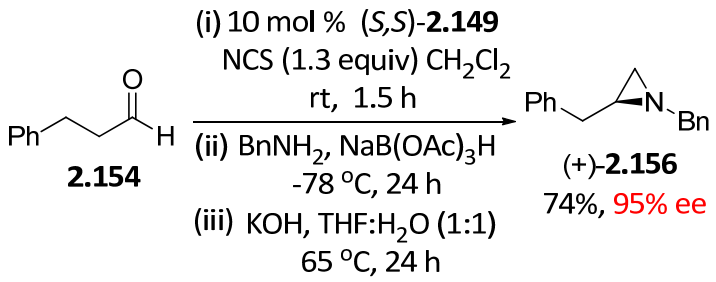
Table 2.11. Substrate scope of enantioselective *N*-alkyl-1,2-disubstituted aziridines.*



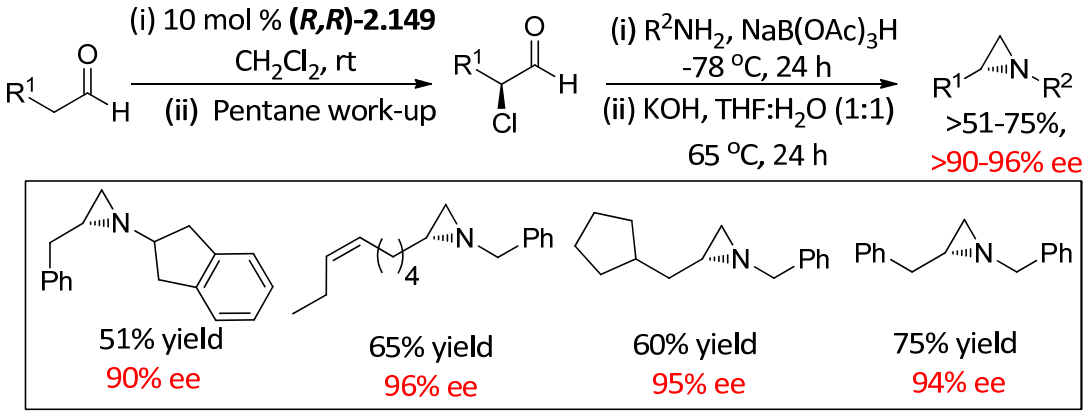
entry	product[a]	% yield[b]	ee[c]
1		46% yield, 91% ee	
2		41% yield, 90% ee	
3[d]		64% yield, >10:1 dr	
4[d]		46% yield, >10:1 dr	
5		54% yield, 95% ee	
6		65% yield, 94% ee	
7		52% yield, 86%ee	
8		60% yield, 96% ee	
9		52% yield, 90% ee	
10		56% yield, 92%ee	
11		53% yield, 77% ee	
12[e]		40% yield, 56% ee	
13		52% yield, 92%ee	
14		49% yield, 95% ee	
15		57% yield, ND	
16		32% yield, >10:1 dr	

*All reactions were 0.50 M in substrate and proceeded to complete conversion.[a]Yield after chromatography. [b]Enantiomeric excess detreminedby chiral HPLC or SFC analysis.[c]Diastereomeric ratio determined via NMR experiments using chiral solvating agents (Pirkle alcohol).[174] [d]Because homoaldol product formation occurred at -20 °C with use of **2.149**, catalyst **2.170** was used.

To further expand on the utility of this new methodology (Scheme 2.37), the (*S,S*)-**2.149** catalyst afforded, as anticipated, the opposite enantiomer of **2.156** in good yield (74%) and excellent enantioselectivity (95% ee).



Scheme 2.37. One-pot protocol for chiral *N*-alkly-1,2-aziridines



Scheme 2.38. Two-pot protocol for chiral *N*-alkly-1,2-aziridines

Finally, modest improvements in yield and enantioselectivty were observed if we performed a work-up after the α-chlorination step. The addition of pentane to the crude reaction mixture precipitated both the succinimide and organocatalyst **2.149**. Removal of the pentane, concentration, resupsension in CH_2Cl_2 and proceeding with the reductive

amination and base-induced cyclization now provided *N*-alkyl-1,2-disubstituted aziridines in 51-75% yield and >90% ee (Scheme 2.38).

2.1.4. Conclusion

Prior to this study the synthesis of pharmaceutically relevant β-fluoroamine, β,β-difluoroamines and *N*-alkyl aziridines was limited. Previous approaches to these useful moieties required long-step syntheses, lack of generality and substrate scope, and required starting materials that were not readily available. This study, has led to the development of a powerful extension of the organocatalyzed enantioselective synthesis of fluoroaldehydes and chloroaldehydes for the *general* enantioselective synthesis of β-fluoroamines and unattainable *N*-alkyl terminal aziridines in yields and % ee.

The new methodology allows for the first synthesis of tertiary β-fluoroamines with enantioselectivities up to 40%. Furthermore, slight modification of our protocol provides rapid, high-yielding access to β,β-difluoroamines. Overall, these novel three step or two step one-pot protocols for the synthesis of β-fluoroamines, β,β-difluoroamines and *N*-alkyl terminal aziridines from readily available precursors, represents a significant improvement in the art to access these therapeutically relevant moieties.

This new methodology provides access to these useful pharmalogically relevant scaffolds that were previously difficult to prepare, utilizing aldehydes and amines for which thousands are commercially available.

Experimental Methods

General. All ^{1}H & ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz)**,** Bruker AV-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). IR spectra were recorded as thin films and are reported in wave-numbers (cm^{-1}). Low resolution mass spectra were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra were recorded on a Waters Qtof-API-US plus Acquity system. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(ME - MT)/ MT] \times 10^6$, where ME is the experimental mass and MT is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference. Analytical thin layer chromatography was performed on 250 μM silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. Analytical HPLC was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral HPLC was performed on an Agilent 1200 Series HPLC utilizing a Chiracel OD, OJ or Chiralpak AD columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical

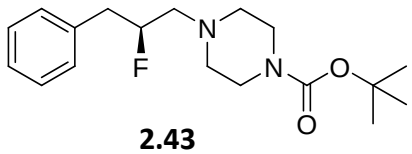
Co. and were used without purification. All polymer-supported reagents were purchased from Biotage, Inc. Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Mass spectra were obtained on a Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data.

Experimental Section for β-Fluoroamines and β, β-Difluoroamines

General Procedure for β-Fluoroamines Synthesis: A solution of **2.38** (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.2 equiv) and *N*-fluorobenzenesulfonimide (1.2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature then cooled to -20 °C and treated with aldehyde substrate **2.35** (1 equiv). The reaction mixture was stirred at -20 °C for 24 h, and then cooled to -78 °C, diluted with 10 mL Et_2O and filtered through a pad of Davisil® Silica Gel, eluting with Et_2O. Me_2S (5.0 mL) was added, washed with Sat. $NaHCO_3$ (3x) and brine (1x) and then dried over $MgSO_4$. Filtration and concentration afforded the crude oil which was dissolved in DCE, followed by the addition of amine (1.0 equiv), and $NaBH(OAc)_3$ (1.5 equiv). The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. $NaHCO_3$ and extracted thrice with EtOAc and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds. The enantioselectivity was determined either by chiral HPLC analysis.

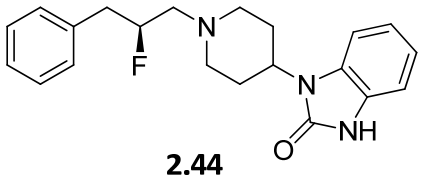
One-Pot Procedure for β-Fluoroamines Synthesis: A solution of **2.38** (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.2 equiv) and *N*-

fluorobenzenesulfonimide (1.2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature then cooled to -20 °C and treated with aldehyde substrate **2.35** (1 equiv). The reaction mixture was stirred at -20 °C for 24 h, followed by the addition of amine (1.0 equiv), and $NaBH(OAc)_3$ (2.2 equiv). The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. $NaHCO_3$ and extracted thrice with EtOAc and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds. The enantioselectivity was determined either by chiral HPLC analysis.



2.43

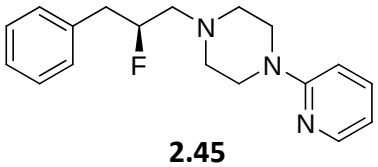
(S)-*tert*-butyl 4-(2-fluoro-3-phenylpropyl)piperazine-1-carboxylate (2.43): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% $MeOH/CH_2Cl_2$) to afford the product as a off white solid (128.8 mg, 80%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel® OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 8.9 min, t_R (minor) = 10.9 min). R_f = 0.75 (10% $MeOH/CH_2Cl_2$); IR (neat) 2927, 1692, 1420, 1365, 1275, 1260 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.30 (d, *J* = 7.28 Hz, 2H), 7.25 (m, 3H), 4.94-4.82 (dm, *J* = 48.0 Hz, 1H), 3.43 (t, *J* = 4.9 Hz, 4H), 2.98 (m, 2H), 2.56 (m, 2H), 2.45 (t, *J* = 4.7 Hz, 4H), 1.45 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.65, 136.7 (d, *J* = 5.0 Hz), 129.3, 128.4, 126.6, 92.6 (d, *J* = 173.0 Hz), 79.5, 61.2 (d, *J* = 21.1 Hz), 53.4, 39.6 (d, *J* = 22.1 Hz) 28.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –176.4; HRMS (TOF, ES+) $C_{18}H_{27}FN_2O_2$ $[M+H]^+$ calc'd 323.2135, found 323.2125.



2.44

(S)-1-(1-(2-fluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.44):

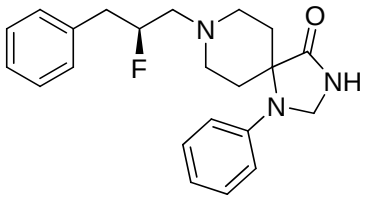
The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a white solid (123.5 mg, 70%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel® OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 14.6 min, t_R (minor) = 17.0 min). R_f = 0.63 (50% EtOAc/hexanes); IR (neat) 3004, 2924, 1694, 1484, 1376 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 10.56 (s, 1H) 7.35 (m, 2H), 7.27 (m, 4H), 7.15(m, 1H), 7.05(m, 2H), 4.93 (dm, *J* = 47.6 Hz, 1H), 4.41-4.34 (m, 1H), 3.14 (br m, 2H), 3.00 (m, 2H), 2.68 (m, 2H), 2.52 (m, 2H), 2.34-2.27 (m, 2H), 1.81 (br d, *J* = 11.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.3, 136.8 (d, *J* = 4.0 Hz), 129.3, 128.9, 128.4, 128.1, 126.6, 121.0 (d, *J* = 23.1 Hz), 109.7, (d, *J* = 11.0 Hz), 92.7 (d, *J* = 173.0 Hz), 61.2 (d, *J* = 21.1 Hz), 53.7 (d, *J* = 8.0 Hz), 50.5, 39.8 (d, *J* = 21.1 Hz) 29.1 (d, *J* = 2.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –176.5; HRMS (TOF, ES+) $C_{21}H_{24}FN_3O$ $[M+H]^+$ calc'd 354.1982, found 354.1990.



2.45

(S)-1-(2-fluoro-3-phenylpropyl)-4-(pyridin-2-yl)piperazine (2.45): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50%

EtOAc/hexanes) to afford the product as a off white solid (113.6 mg, 76%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel® OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 9.4 min, t_R (minor) = 12.3 min). R_f = 0.74 (50% EtOAc/hexanes); IR (neat) 2924, 1625, 1455, 1372 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 8.2 (dd, *J* = 4.5 Hz, 1.0 Hz, 1H), 7.48 (dt, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.26-7.33,(m, 5H), 6.63 (m, 2H), 4.89-5.00 (dm, *J* = 49.2 Hz, 1H), 3.57 (m, 4H), 3.02 (m, 2H), 2.64 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 159.4, 147.8, 137.3, 136.7 (d, *J* = 4.0 Hz), 129.3, 128.4, 126.6, 113.2, 107.0, 92.7 (d, *J* = 173.0 Hz), 61.3 (d, *J* = 21.1 Hz), 53.4, 45.1, 39.7 (d, *J* = 21.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –176.4; HRMS (TOF, ES+) $C_{18}H_{22}N_3F$ $[M+H]^+$ calc'd 300.1876, found 300.1876.

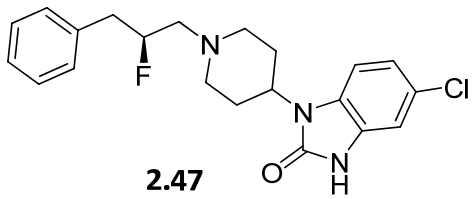


2.46

(S)-8-(2-fluoro-3-phenylpropyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (2.46):

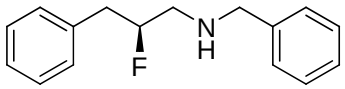
The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a white solid (119.2 mg, 65%), which was determined to be >96% ee by chiral HPLC analysis. (Chiralcel® OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 12.1 min, t_R (minor) = 13.4 min). R_f = 0.65 (10% MeOH/CH_2Cl_2); IR (neat) 3005, 2924, 1705, 1557, 1463, 1376 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.25-7.32 (m, 7H), 7.15 (s, 1H), 6.91 (d, *J* = 16.0 Hz, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 4.88 (dm, *J* = 48.0 Hz, 1H), 4.72 (s, 2H), 2.81-3.02 (m, 6H), 2.54-2.74 (m, 4H), 1.7 (d, *J* = 14.0 Hz 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ

(ppm): 178.0, 143.0, 137.0 (d, J = 5.0 Hz), 129.2 (d, J = 16.0 Hz), 128.3, 126.5, 119.0, 115.5, 92.8 (d, J = 173.0 Hz), 61.2 (d, J = 21.1 Hz), 59.1 (d, J = 19.1 Hz), 50.2 (d, J = 12.0 Hz) 39.8 (d, J = 21.1 Hz), 29.3 (d, J = 51.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.9; HRMS (TOF, ES+) $C_{22}H_{26}N_3OF$ $[M+H]^+$ calc'd 368.2138, found 368.2126.



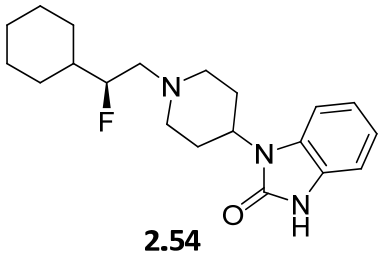
2.47

(S)-5-chloro-1-(1-(2-fluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.47): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a off white solid (133.5 mg, 69%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel® OD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 10.6 min, t_R (minor) = 14.0 min). R_f = 0.59 (10% MeOH/CH_2Cl_2); IR (neat) 3011, 2925, 1698, 1487, 1375 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 10.58 (s, 1H) 7.33 (m, 2H), 7.25 (m, 3H), 7.17 (d, J = 6.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 6.4, 2.0 Hz, 1H), 4.93 (dm, J = 49.2 Hz, 1H), 4.29-4.37 (m, 1H), 3.11 (br m, 2H), 3.00 (m, 2H), 2.69 (m, 2H), 2.45 (m, 2H), 2.31 (m, 2H), 1.80 (br d, J = 10.8 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.3, 136.7 (d, J = 4.0 Hz), 129.3, 129.0, 128.4, 127.5, 126.8, 126.6,120.9, 110.2 (d, J = 22.1 Hz), 92.6 (d, J = 173.0 Hz), 61.1 (d, J = 21.1 Hz), 53.6 (d, J = 5.0 Hz), 50.6, 39.8 (d, J = 21.1 Hz), 29.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –176.4; HRMS (TOF, ES+) $C_{21}H_{23}FN_3OCl$ $[M+H]^+$ calc'd 388.1592, found 388.1584.



2.48

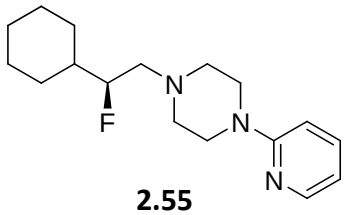
(S)-*N*-benzyl-2-fluoro-3-phenylpropan-1-amine (2.48): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a yellow oil (99.6 mg, 82%), which was determined to be >95% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 4.5 min, t_R (minor) = 4.9 min). R_f = 0.47 (50% EtOAc/hexanes); IR (neat) 3095, 2929, 1609, 1037 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.28 (m, 10H) 4.85 (dm, *J* = 52.0 Hz, 1H), 3.81 (m, 2H), 2.75-3.07 (m, 4H), 1.7 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.8, 136.7 (d, *J* = 6.0 Hz), 129.2, 128.4, 128.3, 128.3, 128.0, 126.9, 126.5, 93.9 (d, *J* = 172.0 Hz), 53.7, 52.2 (d, *J* = 21.1 Hz), 39.3 (d, *J* = 21.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –181.9; HRMS (TOF, ES+) $C_{16}H_{18}FN$ $[M+H]^+$ calc'd 244.1502, found 244.1501.



2.54

(S)-1-(1-(2-cyclohexyl-2-fluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.54): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a white solid (15.0 mg, 87%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 5% *i*-PrOH/Hexanes, t_R (major) = 7.8 min, t_R (minor) = 9.4 min). R_f = 0.61 (10%

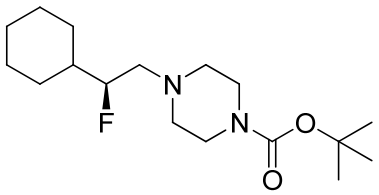
MeOH/CH_2Cl_2); IR (neat) 3006, 2924, 1691, 1462, 1377, 1275, 1260 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 9.93 (s, 1H) 7.29 (m, 1H), 7.11 (m, 1H), 7.04 (m, 2H), 4.43-4.51 (dm, *J* = 52.5 Hz, 1H), 4.38 (br m, 1H), 3.13 (m, 2H), 2.70 (m, 1H), 2.54 (m, 2H), 2.28 (m, 2H), 1.77-1.83 (m, 5H), 1.68 (m, 2H) 1.58 (m, 1H), 1.07-1.31 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.0, 129.0, 127.9, 121.0 (d, *J* = 13.3 Hz), 109.7, (d, *J* = 18.0 Hz), 95.9 (d, *J* = 171.7 Hz), 60.2 (d, *J* = 21.4 Hz), 53.9, 53.6, 50.5, 41.0 (d, *J* = 19.4 Hz) 29.6, 29.1, 28.7 (d, *J* = 4.2 Hz), 27.1 (d, *J* = 6.1 Hz), 26.2, 25.9, 25.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.9; HRMS (TOF, ES+) $C_{20}H_{28}FN_3O$ $[M+H]^+$ calc'd 346.2295, found 346.2279.



2.55

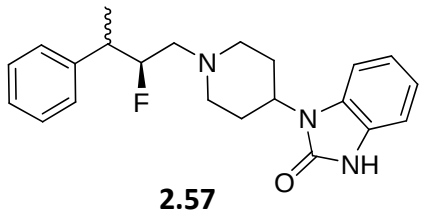
(S)-1-(2-cyclohexyl-2-fluoroethyl)-4-(pyridin-2-yl)piperazine (2.55): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a white solid (12.8 mg, 88%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 5% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 3.9 min, t_R (minor) = 7.5 min). R_f = 0.81 (50% EtOAc/hexanes); IR (neat) 2924, 1608, 1593, 1459, 1272 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 8.18 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.46 (dt, *J* = 8.2 Hz, 2.0 Hz, 1H), 6.62 (m, 2H), 4.41-4.54 (dm, *J* = 49.6 Hz, 1H), 3.56 (m, 4H), 2.63 (m, 5H), 1.78 (m, 3H), 1.69 (m, 2H), 1.57 (m, 1H) 1.19 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 159.4, 147.8, 137.3, 113.1, 106.9, 95.9 (d, *J* = 172.0 Hz), 60.4 (d, *J* = 22.1 Hz), 53.5, 45.0, 41.0

(d, J = 19.1 Hz), 28.6 (d, J = 4.0 Hz), 27.2 (d, J = 6.0 Hz), 26.1, 25.8 (d, J =18.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.7; HRMS (TOF, ES+) $C_{17}H_{26}N_3F$ $[M+H]^+$ calc'd 292.2189, found 292.2193.



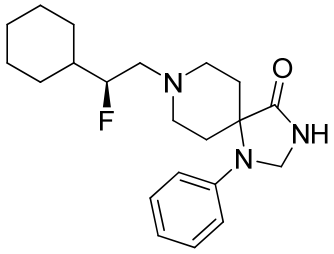
2.56

(S)-tert-butyl 4-(2-cyclohexyl-2-fluoroethyl)piperazine-1-carboxylate (2.56): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a off white solid (14.4 mg, 92%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 6.7 min, t_R (minor) = 8.1 min). R_f = 0.73 (10% MeOH/CH_2Cl_2); IR (neat) 2926, 1701, 1681, 1458, 1365, 1275, 1172 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 4.37-4.48 (dm, J = 49.2 Hz, 1H), 3.44 (brs, 4H), 2.59-2.66 (m, 1H), 2.46 (brs, 4H), 1.74-1.82 (brs, 3H), 1.66-1.68 (m, 2H), 1.59-1.60(m, 1H), 1.4 (s, 9H), 1.14-1.28 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.6, 95.8 (d, J = 172.0 Hz), 79.5, 60.3 (d, J = 21.1 Hz), 53.4, 40.9 (d, J = 19.1 Hz) 28.6 (d J = 4.0 Hz) 28.3, 27.1 (d, J = 6.0 Hz), 26.1, 25.8, 25.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.7; HRMS (TOF, ES+) $C_{17}H_{31}FN_2O_2$ $[M+H]^+$ calc'd 315.2448, found 315.2437.



2.57

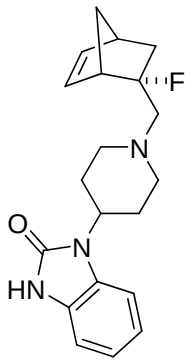
1-(1-((2S)-2-fluoro-3-phenylbutyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.57): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a off white solid (13.8 mg, 75%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel® OJ, Isocratic 40% EtOH/60% Hexanes, (t_R (major) = 4.3 min, t_R (minor) = 4.9 min; (t_R (major) = 5.5 min. t_R (minor) = 6.7 min). R_f = 0.61 (50% EtOAc/hexanes); IR (neat) 3005, 2920, 1694, 1487, 1376 cm^{-1}; (^1H NMR spectra of the mixture of two diastereomers); ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 10.7 (s, 1H), 7.27-7.36 (m, 6H), 7.15 (m, 1H), 7.06 (m, 2H), 4.76-4.91 (m, 1H), 4.37 (m, 1H), 3.07 (m, 3H), 2.54 (m, 4H), 2.24 (m, 2H), 1.81 (dt, *J* = 12.9, 1.8 Hz, 2H), 1.43 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.3, 143.0 (d, *J* = 6.0 Hz), 141.6 (d, *J* = 2.0 Hz), 128.9, 128.5, 128.3, 128.2, 127.6, 126.6 (d, *J* = 6.0 Hz), 120.9 (d, *J* = 26.1 Hz), 109.7, (d, *J* = 12.0 Hz), 96.0 (d, *J* = 176.0 Hz), 95.3 (d, *J* = 175.0 Hz), 60.3, 60.1 (d, *J* = 1.0 Hz), 53.7 (d, *J* = 5.0 Hz), 53.5, 50.5 (d, *J* = 2.0 Hz), 43.0 (d, *J* = 21.1 Hz), 42.9 (d, *J* = 20.1 Hz), 29.6, 29.2, 29.1, 17.6 (d, *J* = 6.0 Hz), 16.8 (d, *J* = 6.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –182.3, -184.3; HRMS (TOF, ES+) $C_{22}H_{26}FN_3O$ $[M+Na]^+$ calc'd 390.1958, found 390.1943.



2.58

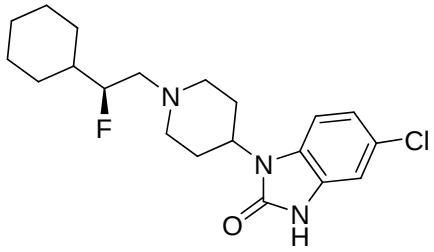
(S)-8-(2-cyclohexyl-2-fluoroethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (2.58):

The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a off white solid (16.1 mg, 90%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 3% *i*-PrOH/Hexanes, t_R (major) = 10.0 min, t_R (minor) = 13.6 min). R_f = 0.60 (10% MeOH/CH_2Cl_2); IR (neat) 3013, 2940, 1704, 1598, 1463, 1367, 1302 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.52 (s, 1H), 7.29 (m, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 4.47 (dm, *J* = 49.8 Hz, 1H), 4.76 (s, 2H), 2.92 (m, 4H), 2.71 (m, 4H), 1.78 (m, 6H), 1.60 (m, 1H), 1.25 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 178.2, 143.1, 129.1, 119.0, 115.6, 96.0 (d, *J* = 172.0 Hz), 60.2 (d, *J* = 22.1 Hz), 59.2 (d, *J* = 14.0 Hz), 50.2 (d, *J* = 55.3 Hz) 41.1 (d, *J* = 19.1 Hz), 29.1, 28.7 (d, *J* = 5.0 Hz), 27.2 (d, *J* = 5.0 Hz), 26.1 (d, *J* = 5.0 Hz), 25.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.9; HRMS (TOF, ES+) $C_{21}H_{30}N_3OF$ $[M+Na]^+$ calc'd 382.2271, found 382.2267.



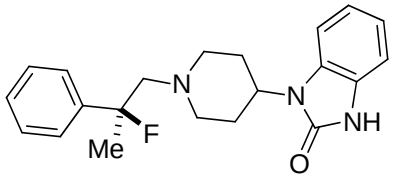
2.59

1-(1-(((1S,2S,4S)-2-fluorobicyclo[2.2.1]hept-5-en-2-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.59): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a off white solid (11.2 mg, 66%), which was determined to be >12% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 2% *i*-PrOH/Hexanes, t_R (major) = 14.5 min, t_R (minor) = 15.6 min). R_f = 0.71 (50% EtOAc/hexanes); IR (neat) 3009, 2926, 1674, 1484, 1386, 1164 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 9.70 (s, 1H), 7.28 (m, 1H), 7.13 (m, 1H), 7.07 (m, 2H), 6.24 (m, 1H), 6.06 (m, 1H), 4.35 (m, 1H), 3.23 (d, *J* = 11.4 Hz, 1H), 3.09(s, 1H), 3.06 (d, *J* = 11.4 Hz, 1H) 2.92 (s, 1H), 2.59 (m, 1H), 2.49 (m, 3H), 2.35 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 2.30 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.79 (m, 2H), 1.68 (d, *J* = 8.4, 1H), 1.47 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.9, 140.1 (d, *J* = 4.0 Hz), 133.3 (d, *J* = 9.1 Hz), 129.1, 127.9, 120.9 (d, *J* = 8.0 Hz), 109.6 (d, *J* = 13.1 Hz), 108 (d, *J* = 186.1 Hz), 63.7 (d, *J* = 22.1 Hz), 54.7, 54.1 (d, *J* = 3.0 Hz), 50.7, 50.4 (d, *J* = 23.1 Hz), 47.6, 40.9, 39.3 (d, *J* = 21.1 Hz), 29.3 (d, *J* = 21.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –139.4 (major), -143.4 (minor); HRMS (TOF, ES+) $C_{20}H_{24}N_3OF$ $[M+H]^+$ calc'd 342.1982, found 342.197



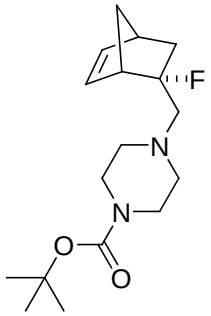
2.60

(S)-5-chloro-1-(1-(2-cyclohexyl-2-fluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.60): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a white solid (15.9 mg, 84%), which was determined to be >97% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 10.0 min, t_R (minor) = 13.6 min). R_f = 0.61 (10% MeOH/CH_2Cl_2); IR (neat) 3004, 2924, 1697, 1487, cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 10.4 (s, 1H) 7.19 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 7.01 (br d, *J* = 8.4 Hz, 1H), 4.45-4.53 (dm, *J* = 49.8 Hz, 1H), 4.36 (br m, 1H), 3.17 (br m, 2H), 2.71 (m, 1H), 2.48 (br m, 2H), 2.33 (br m, 2H), 1.77-1.83 (m, 5H), 1.68 (m, 2H) 1.57 (br m, 1H), 1.07-1.27 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.2, 128.9, 127.4, 126.8, 121.0, 110.2 (d, *J* = 36.2 Hz), 95.6 (d, *J* = 172.0 Hz), 60.0 (d, *J* = 21.1 Hz), 53.6, 53.5, 50.4, 41.0 (d, *J* = 20.1 Hz) 29.6, 28.9, 28.6 (d, *J* = 4.0 Hz), 27.1 (d, *J* = 6.0 Hz), 26.1, 25.9, 25.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –183.9; HRMS (TOF, ES+) $C_{20}H_{27}FN_3OCl$ $[M+H]^+$ calc'd 380.1905, found 380.1891.



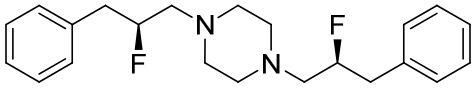
2.61

(S)-1-(1-(2-fluoro-2-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.61): The product was prepared according to the general procedure (except that (S)-5-(pyrrolidin-2-yl)-1H-tetrazole **2.65** was used as the catalyst) and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a yellow solid (13.1 mg, 74%), which was determined to be 40% ee by chiral HPLC analysis. (Chiralcel® AD, 100% MeOH/0.1 DEA, t_R (major) = 6.4 min, t_R (minor) = 7.4 min). R_f = 0.60 (50% EtOAc/hexanes); IR (neat) 3005, 2926, 1694, 1484, 1376 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 10.4 (s, 1H), 7.26-7.45 (m, 6H), 7.06 (m, 3H), 4.07 (br s, 1H), 3.77 (m, 2H), 3.52 (m, 2H), 2.98 (m, 4H) 1.95 (br d, *J* = 12.0 Hz, 2H), 1.89 (d, *J* = 22.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.7, 140.2 (d, *J* = 21.1 Hz), 129.2, 128.9, 128.7, 127.8, 127.6, 126.7, 123.8 (d, *J* = 9.0 Hz), 121.7 (d, *J* = 9.0 Hz), 109.8, 95.8 (d, *J* = 178.1 Hz), 53.9, 52.8 (d, *J* = 5.0 Hz), 50.3, 46.8, 25.6 (d, *J* = 23.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –145.4; HRMS (TOF, ES+) $C_{21}H_{24}N_3OF$ $[M+Na]^+$ calc'd 376.1801, found 376.1792.



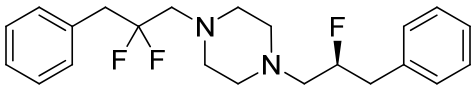
2.62

***tert*-butyl-4-(((1S,2S,4S)-2-fluorobicyclo[2.2.1]hept-5-en-2-yl)methyl)piperazine-1-carboxylate (2.62)**: The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a yellow solid (10.8 mg, 70%), which was determined to be >15% ee by chiral HPLC analysis. (Chiralcel® AD, Isocratic 5% *i*-PrOH/Hexanes, t_R (major) = 10.6 min, t_R (minor) = 11.9 min). R_f = 0.78 (50% EtOAc/hexanes); IR (neat) 2988, 1685, 1459, 1275, 1260 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 6.21 (m, 1H), 6.01 (m, 1H), 3.42 (m, 4H), 3..02 (m, 1H), 2.88 (brs, 1H), 2.57 (m, 3H), 2.42 (m, 3H), 1.88 (m, 1H), 1.80 (m, 1H) 1.64 (m, 1H), 1.45 (s, 9H), 1.39 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.76, 140.1 (d, J = 4.0 Hz), 133.2 (d, J = 9.0 Hz), 108.1, 106.2, 79.3, 79.5, 64.0 (d, J = 22.1 Hz), 54.0 (d, J = 3.0 Hz), 50.3 (d, J = 23.1 Hz) 47.5, 40.8, 39.2 (d, J = 21.1 Hz), 28.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): 139.0 (major), -143.0 (minor);; HRMS (TOF, ES+) $C_{17}H_{27}FN_2O_2$ $[M+H]^+$ calc'd 311.2135, found 311.2125.



2.63

1,4-bis((S)-2-fluoro-3-phenylpropyl)piperazine (2.63): The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as yellow oil (10.3 mg, 58%). Compound was also isolated as yellow oil. R_f = 0.69 (50% EtOAc/hexanes); IR (neat) 2921, 1453, 1274, 1158 cm^{-1};^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.34 (m, 4H), 7.29 (m, 2H), 7.19 (d, *J* = 7.2 Hz, 4H), 5.19 (dm, *J* = 49.5 Hz, 2H), 3.47 (br s, 4H), 3.35 (br m, 4H), 3.15 (m, 2H), 3.01 (m, 6H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 134.2 (d, *J* = 4.6 Hz), 129.2, 128.8, 127.4, 90.0 (d, *J* = 174.7 Hz), 59.6 (d, *J* = 20.6 Hz), 50.2, 39.2 (d, *J* = 21.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –175.7; HRMS (TOF, ES+) $C_{22}H_{28}F_2N_2$ $[M+H]^+$ calc'd 359.2299, found 359.2293.

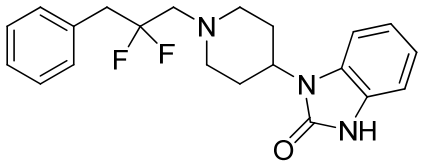


(S)-1-(2,2-difluoro-3-phenylpropyl)-4-(2-fluoro-3-phenylpropyl)piperazine:

Isolated alongside compound monofluorinated piperazine as a yellow solid. R_f = 0.74 (50% EtOAc/hexanes); IR (neat) 2921, 1454, 1275, 1261, 1158, 1096 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.25-7.34 (m, 10H), 4.95 (dm, *J* = 48.0 Hz, 1H), 3.27 (t, *J* = 16.2 Hz, 2H), 3.00 (m, 2H), 2.53-2.66 (m, 12H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 136.8 (d, *J* = 4.9 Hz), 133.6 (t, *J* = 4.6 Hz), 130.4, 129.3, 128.4, 128.3, 127.1, 126.6 124.4 (t, *J* = 243.7 Hz) 92.7 (d, *J* = 173.0 Hz), 61.2 (d, *J* = 20.9 Hz), 60.0 (t, *J* = 28.3 Hz), 53.8 (d, *J* = 5.8 Hz), 40.8 (t, *J* = 24.8 Hz), 39.7 (d, *J* = 21.5 Hz), 29.6; ^{19}F NMR

(282 MHz, $CDCl_3$) δ (ppm): –176.4, -94.4; HRMS (TOF, ES+) $C_{22}H_{27}F_3N_2$ $[M+H]^+$ calc'd 377.2205, found 377.2204.

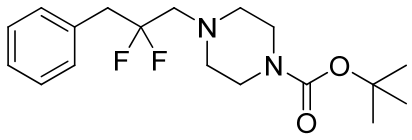
General Procedure for β,β -Difluoroamines Synthesis: A solution of D,L-Proline (0.4 equiv) and *N*-fluorobenzenesulfonimide **33** (2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature and treated with aldehyde substrate **32** (1 equiv). The reaction mixture was stirred at this temperature for 24 h, and then cooled to -78 °C, diluted with 10 mL Et_2O and filtered through a pad of Davisil® Silica Gel, eluting with Et_2O. Me_2S (5.0 mL) was added, washed with Sat. $NaHCO_3$ (3X) and brine (1X) and then dried over $MgSO_4$. Filtration and concentration afforded the crude oil which was dissolved in DCE, followed by the addition of amine *(*1.0 equiv), and $NaBH(OAc)_3$. The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. $NaHCO_3$ and extracted thrice with EtOAc and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds.



2.70

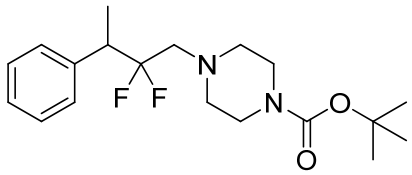
1-(1-(2,2-difluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (2.70): The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% $MeOH/CH_2Cl_2$) to afford the product as a white solid (11.8 mg, 64%). R_f = 0.57 (10% $MeOH/CH_2Cl_2$); IR (neat) 3003, 2925, 1691, 1481, 1377 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H) 7.46 (d, *J* = 6.8 Hz, 1H), 7.37 (m, 2H),

7.28 (m, 3H), 7.13 (m, 3H), 4.63 (br s, 1H), 3.71 (d, J = 11.6 Hz, 2H), 3.36 (m, 3H), 3.03 (m, 4H), 2.74 (m, 1H), 1.98 (d, J = 11.2 Hz, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 154.6, 130.6, 130.3, 130.1, 128.9, 128.2, 126.6, 122.0, 120.7 (t, J = 245.9 Hz), 110.2, 57.6 (t, J = 27.3 Hz), 53.61, 47.1, 42.6 (t, J = 24.1 Hz) 25.7, 24.0 (t, J = 25.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –94.4; HRMS (TOF, ES+) $C_{21}H_{23}F_2N_3O$ $[M+H]^+$ calc'd 372.1887, found 372.1888.



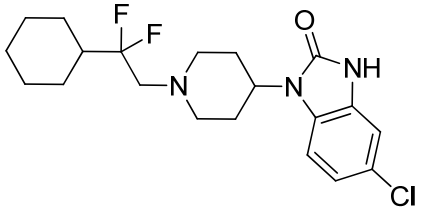
2.71

***tert*-butyl 4-(2,2-difluoro-3-phenylpropyl)piperazine-1-carboxylate (2.71)**: The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a white solid (11.4 mg, 67%), R_f = 0.78 (50% EtOAc/hexanes); IR (neat) 2927, 1690, 1475, 1373 cm^{-1}; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.27-7.34 (m, 5H), 3.45 (m, 4H), 3.28 (t, J = 16.2 Hz, 2H), 2.56 (t, J = 13.2 Hz, 2H), 2.49 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.6, 133.5 (t, J = 5.0 Hz), 130.3, 128.2, 127.1, 124.3 (t, J = 243.4 Hz), 79.6, 60.1 (t, J = 28.1 Hz), 53.6, 40.9 (t, J = 24.1 Hz), 28.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –94.4; HRMS (TOF, ES+) $C_{18}H_{26}F_2N_2O_2$ $[M+H]^+$ calc'd 341.2041, found 341.2040.



2.72

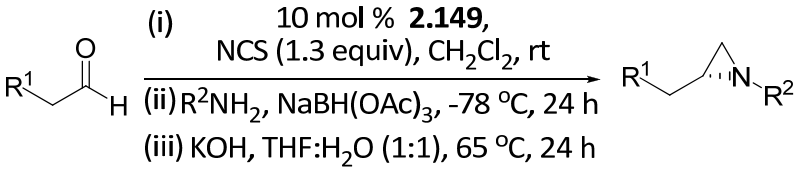
***Tert*-butyl 4-(2,2-difluoro-3-phenylbutyl)piperazine-1-carboxylate (2.72)**: The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a white solid (12.0 mg, 68%), R_f = 0.78 (50% EtOAc/hexanes); IR (neat) 2927, 1691, 1477, 1373 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.25-7.33 (m, 5H), 3.49 (m, 1H), 3.41 (br s, 4H), 2.53 (m, 3H), 2.42 (m, 1H), 2.27 (m, 2H), 1.46 (s, 9H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.6, 140.0 (d, *J* = 7.0 Hz), 128.7, 128.2, 127.1, 125.2 (t, *J* = 246.4 Hz), 79.5, 59.9 (dd, *J* = 6.0, 57.3 Hz), 53.6, 43.9 (dd, *J* = 3.0, 46.2 Hz), 28.3, 14.3 (t, *J* = 4.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –98.7, –99.6, –106.1, –106.9; HRMS (TOF, ES+) $C_{19}H_{28}F_2N_2O_2$ $[M+H]^+$ calc'd 355.2186, found 355.2194.



5-chloro-1-(1-(2-cyclohexyl-2,2-difluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one: The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/CH_2Cl_2) to afford the product as a white solid (15.2 mg, 77%). R_f = 0.62 (10% MeOH/CH_2Cl_2); IR (neat) 3003, 2924, 1691, 1481, 1377 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 9.83 (s, 1H) 7.13 (m, 2H), 7.04 (dd, *J* = 1.8, 8.4 Hz, 1H), 4.31 (br m, 1H), 3.11 (m, 2H), 2.76 (t, *J* = 15.0 Hz, 2H), 2.42 (m, 4H), 1.97 (m,

1H), 1.82 (m, 5H), 1.72 (d, J = 13.2 Hz, 1H), 1.22 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.9, 128.8, 127.7 (t, J = 231.4 Hz), 126.8, 125.5, 121.0, 110.0 (d, J = 22.1 Hz), 68.1, 59.3 (t, J = 28.1 Hz), 54.3, 50.8, 42.2 (t, J = 22.1 Hz) 29.6, 29.3, 25.7 (t, J = 25.1 Hz), 25.4 (t, J = 4.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –104.26; HRMS (TOF, ES+) $C_{20}H_{26}FN_3OCl$ $[M+H]^+$ calc'd 398.1811, found 398.1796.

One-Pot Procedure for Chiral Aziridine Synthesis

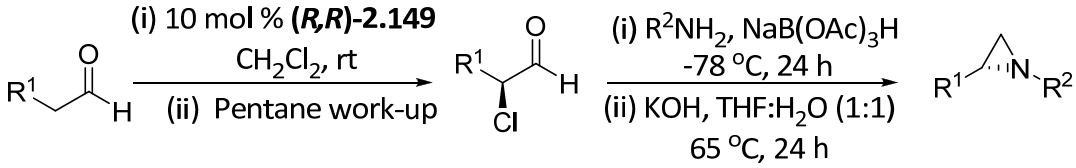


To a solution of aldehyde (1.0 eq.) and (2*R*,5*R*)-2,5-diphenylpyrrolidine (0.1 eq.) in CH_2Cl_2, was added *N*-chlorosuccinimide (1.3 eq.) at -78 °C. This mixture was allowed to stir and warm to room temperature over a period of 1.5 – 2.0 hrs after which ground molecular sieves were added. The reaction mixture was then cooled to -78 °C and a solution of amine (1.0 eq.) in 2 mL of CH_2Cl_2 at -78 °C was added. This solution stirred at -78 °C for an additional 1.5 – 2.0 hrs followed by addition of sodium triacetoxyborohydride (1.2 eq.) and stirring overnight at -78 °C. The reaction mixture was filtered through a pad of Celite eluting with CH_2Cl_2 and concentrated *in vacuo* resulting in a crude oil which was then dissolved in 1:1 THF/H_2O along with KOH (6.5 eq.) and stirred overnight at 65 °C. The reaction mixture was extracted with EtOAc (5x), dried over $MgSO_4$, and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the title compounds.

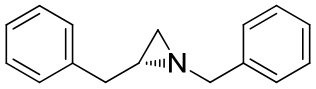
The enantiomeric excess was determined either by chiral HPLC or SFC analysis.

The diastereomeric ratio was determined by NMR experiments using chiral solvating agents.

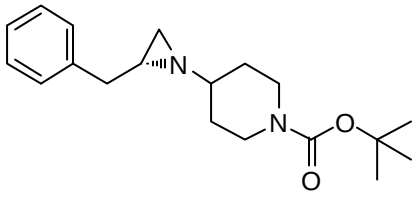
Two-Pot Procedure for Chiral Aziridine Synthesis



To a solution of aldehyde (1.0 eq.) and (2*R*,5*R*)-2,5-diphenylpyrrolidine (0.1 eq.) in CH_2Cl_2, was added *N*-chlorosuccinimide (1.3 eq.) at -78 ^oC. This mixture was allowed to stir and warm to room temperature over a period of 1.5 – 2.0 hrs. The reaction was quenched by the addition of excess pentane followed by filtration and concentration of the filtrate *in vacuo*. The crude product was redissolved in CH_2Cl_2 and ground molecular sieves were added. The reaction mixture was then cooled to -78 ^oC and a solution of amine (1.0 eq.) in 2 mL of CH_2Cl_2 at -78 ^oC was added. This solution stirred at -78 ^oC for an additional 1.5 – 2.0 hrs followed by addition of sodium triacetoxyborohydride (1.2 eq.) and stirring overnight at -78 ^oC. The reaction mixture was filtered through a pad of Celite eluting with CH_2Cl_2 and concentrated *in vacuo* resulting in a crude oil which was then dissolved in 1:1 THF/H_2O along with KOH (6.5 eq.) and stirred overnight at 65 ^oC. The reaction mixture was extracted with EtOAc (5x), dried over $MgSO_4$, and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the title compounds. The enantiomeric excess was determined either by chiral HPLC or SFC analysis.

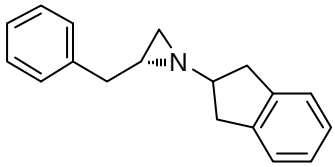


(*R*)-1,2-dibenzylaziridine: The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear, yellow oil (167.5 mg, 75%), which was determined to have an ee of 94% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 7.8 min, t_R (minor) = 6.8 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.29-7.25 (m, 3H); 7.24-7.18 (m, 4H); 7.18-7.13 (m, 3H); 3.40 (d, J = 1.65 Hz, 2H); 2.81 (dd, J_1 = 5.88 Hz, J_2 = 14.64 Hz, 1H); 2.60 (dd, J_1 = 5.84 Hz, J_2 = 14.64 Hz, 1H); 1.76-1.68 (m, 2H); 1.43 (d, J = 6.10 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.75, 139.35, 128.81, 128.47, 128.22, 127.11, 126.30, 64.90, 40.82, 39.48, 33.95. HRMS (TOF, ES+) $C_{16}H_{17}N$ $[M+H]^+$ calc. mass 224.1439, found 224.1432. Specific rotation $[\alpha]_D^{25}$ = +32.96° (c = 4.733, $CHCl_3$).

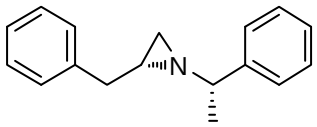


(*R*)-tert-butyl 4-(2-benzylaziridin-1-yl) piperidine-1-carboxylate (Table 1, Entry 1): The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (145.6 mg, 46%), which was determined to have an ee of 91% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R (major) = 27.3 min, t_R (minor) = 30.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31 (m, 2H); 7.24 (m, 3H); 3.92 (br d, J = 31.2 Hz, 2H); 2.84-2.56 (m, 4H); 1.72 (m, 2H); 1.59 (m, 1H); 1.45 (m, 1H); 1.45 (s, 9H); 1.35 (d, J = 6.4 Hz, 2H); 1.24 (m, 2H).

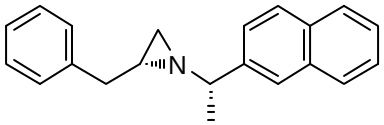
^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.98, 139.93, 128.92, 128.50, 126.40, 79.49, 66.75, 40.35, 39.86, 32.67, 31.89, 31.44, 28.56. HRMS (TOF, ES+) $C_{19}H_{29}N_2O_2$ $[M+H]^+$ calc. mass 317.2229, found 317.2233. Specific rotation $[\alpha]_D^{25}$ = +21.82° (c = 5.133, $CHCl_3$).



(*R*)-2-benzyl-1-(2,3-dihydro-1H-inden-2-yl) aziridine (Table 1, Entry 2): The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a dark brown oil (127.1 mg, 51%), which was determined to have an ee of 90% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 7.8 min, t_R (minor) = 6.2 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.25 (m, 2H); 7.24-7.13 (m, 4H); 7.12-7.04 (m, 3H); 3.02-2.90 (m, 2H); 2.80 (dd, J_1 = 6.70 Hz, J_2 = 15.93 Hz, 1H); 2.68 (dd, J_1 = 5.51 Hz, J_2 = 14.14 Hz, 1H); 2.63-2.54 (m, 2H); 2.24 (p, J = 5.51 Hz, 1H); 1.70 (d, J = 3.27, 1H); 1.66-1.59 (m, 1H); 1.39 (d, J = 6.31 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 141.98, 141.66, 140.05, 128.94, 128.45, 126.39, 126.33, 124.89, 124.64, 70.92, 40.86, 39.67, 39.60, 39.35, 33.51. HRMS (TOF, ES+) $C_{17}H_{19}N$ $[M+H]^+$ calc. mass 250.1596, found 250.1596. Specific rotation $[\alpha]_D^{25}$ = +32.96° (c = 4.733, $CHCl_3$). Specific rotation $[\alpha]_D^{25}$ = +7.19° (c = 4.867, $CHCl_3$).

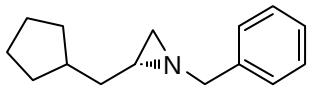


(*R*)-2-benzyl-1-((S)-1-phenylethyl) aziridine (Table 1, Entry 3): The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (151.9 mg, 64%), which was determined to have a dr of >10:1 by NMR with the chiral solvating agent *R*(-)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.33-7.24 (m, 8H); 7.21-7.15 (m, 2H); 2.78 (dd, J_1 = 6.51 Hz, J_2 = 14.15 Hz, 1H); 2.67 (dd, J_1 = 6.06 Hz, J_2 = 14.14 Hz, 1H); 2.34 (q, J = 6.59 Hz, 1H); 1.66 (dq, J_1 = 3.51 Hz, J_2 = 6.34 Hz, 1H); 1.57 (d, J = 3.51 Hz, 1H); 1.28 (d, J = 6.35 Hz, 1H); 1.21 (d, J = 6.63 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 144.73, 139.98, 129.01, 128.44, 128.38, 127.02, 126.93, 126.34, 69.98, 41.80, 39.89, 33.60, 23.39. HRMS (TOF, ES+) $C_{17}H_{19}N$ $[M+H]^+$ calc. mass 238.1596, found 238.1596. Specific rotation $[\alpha]_D^{25}$ = -32.67° (c = 8.600, $CHCl_3$).

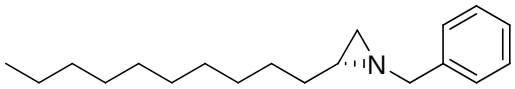


(*R*)-2-benzyl-1-((S)-1-(naphthalen-2-yl)ethyl) aziridine (Table 1, Entry 4): The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear orange oil (163.8 mg, 57%), which was determined to have a dr of >10:1 by NMR with the chiral solvating agent R(-)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol). ^{1}H NMR (400.1 MHz,

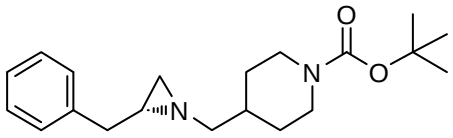
$CDCl_3$) δ (ppm): 7.76-7.70 (m, 4H); 7.45-7.41 (m, 1H); 7.36 (m, 2H); 7.26 (d, J = 4.32 Hz, 3H); 7.20-7.13 (m, 2H); 2.79 (dd, J_1 = 6.50 Hz, J_2 = 14.15 Hz, 1H); 2.67 (dd, J_1 = 6.09 Hz, J_2 = 14.15, 1H); 2.47 (q, J = 6.59 Hz, 1H); 1.69 (dq, J_1 = 3.58 Hz, J_2 = 6.31 Hz, 1H); 1.58 (d, J = 3.58 Hz, 1H); 1.29 (d, J = 6.31 Hz, 1H); 1.25 (d, J = 6.59 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 142.27, 140.01, 133.54, 132.85, 129.05, 128.50, 128.06, 127.97, 127.75, 126.40, 126.03, 125.60, 125.51, 125.28, 70.21, 42.00, 39.94, 33.73, 23.47. HRMS (TOF, ES+) $C_{21}H_{21}N$ $[M+H]^+$ calc. mass 288.1752, found 288.1746. Specific rotation $[\alpha]_D^{25}$ = -23.72° (c = 4.933, $CHCl_3$).



(*R*)-1-benzyl-2-(cyclopentylmethyl) aziridine (Table 1, Entry 5): The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (116.3 mg, 54%), which was determined to have an ee of 95% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 5.2 min, t_R (minor) = 4.6 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.22 (m, 1H); 3.47 (d, J = 13.20 Hz, 1H); 3.36 (d, J = 13.20 Hz, 1H); 1.85-1.75 (m, 1H); 1.75-1.62 (m, 2H); 1.60 (d, J = 3.15 Hz, 1H); 1.59-1.52 (m, 2H); 1.51-1.40 (m, 4H); 1.39 (d, J = 6.00 Hz, 1H); 1.33 (q, J = 7.90 Hz, 1H); 1.15-1.00 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.64, 128.43, 128.36, 127.10, 65.18, 39.42, 39.28, 38.87, 34.43, 32.85, 32.53, 25.24, 25.12. HRMS (TOF, ES+) $C_{15}H_{22}N$ $[M+H]^+$ calc. mass 216.1752, found 216.1752. Specific rotation $[\alpha]_D^{25}$ = +6.29° (c = 7.000, $CHCl_3$).

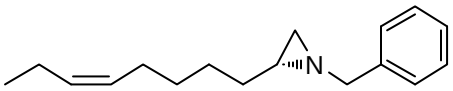


(*R*)-1-benzyl-2-decylaziridine (Table 1, Entry 6): The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (177.7 mg, 65%), which was determined to have an ee of 94% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 4.5 min, t_R (minor) = 4.1 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.22 (m, 1H); 3.50 (d, *J* = 13.25 Hz, 1H); 3.32 (d, *J* = 13.25 Hz, 1H); 1.61 (d, *J* = 3.23 Hz, 1H); 1.49-1.16 (m, 20H); 0.88 (t, *J* = 6.67 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.64, 128.43, 128.32, 127.09, 65.20, 39.98, 34.24, 33.19, 32.07, 29.76, 29.73, 29.53, 29.49, 27.60, 22.84, 14.27. HRMS (TOF, ES+) $C_{19}H_{31}N$ $[M+H]^+$ calc. mass 274.2535, found 274.2527. Specific rotation $[\alpha]_D^{23}$ = +7.42° (c = 6.467, $CHCl_3$).

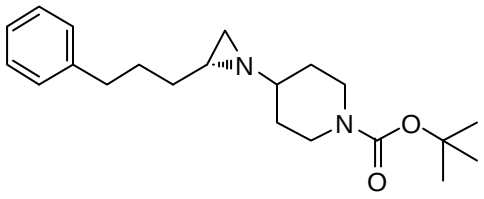


(*R*)-tert-butyl 4-((2-benzylaziridin-1-yl)methyl) piperidine-1-carboxylate (Table 1, Entry 7): The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (177.7 mg, 65%), which was determined to have an ee of 86% by SFC analysis (Chiralcel® OJ, 5% IPA/CO_2, t_R (major) = 3.2 min, t_R (minor) = 3.7 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.34-7.17 (m, 5H); 4.15-3.95 (br, 2H); 2.73 (dd, J_1 = 5.60 Hz, J_2 = 14.25 Hz, 1H); 2.64 (dd, J_1 = 7.00 Hz, J_2 = 14.25 Hz, 1H); 2.60-2.46 (m, 2H);

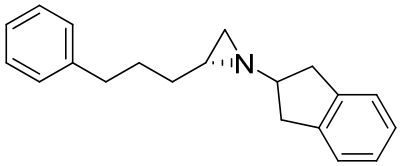
2.28 (dd, J_1 = 7.81 Hz, J_2 = 11.76 Hz, 1H); 1.91 (dd, J_1 = 5.70 Hz, J_2 = 11.76 Hz, 1H); 1.76 (d, J = 12.82 Hz, 1H); 1.71 (d, J = 3.34, 1H); 1.57-1.48 (m, 3H); 1.46 (s, 9H); 1.30 (d, J = 6.25, 1H); 1.06 (pd, J_1 = 4.15 Hz, J_2 = 12.27 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.96, 139.92, 128.86, 128.49, 126.38, 79.29, 67.36, 40.97, 39.64, 37.23, 34.32, 30.67, 30.54, 28.58. HRMS (TOF, ES+) $C_{20}H_{30}N_2O_2$ $[M+H]^+$ calc. mass 331.2386, found 331.2387. Specific rotation $[\alpha]_D^{25}$ = +32.15° (c = 0.933, $CHCl_3$).



(*R*,*Z*)-1-benzyl-2-(oct-5-en-1-yl) aziridine (Table 1, Entry 8): The compound was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (146.0 mg, 60%), which was determined to have an ee of 96% by chiral HPLC analysis using the (2R,5R)-2,5-diphenylpyrrolidine catalyst (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 5.2 min, t_R (minor) = 4.7 min). When the compound was prepared using the (2S,5S)-2,5-diphenylpyrrolidine catalyst, the product had an ee of 94% (Chiralcel® OD, Isocratic 2% IPA/hexane, tR (major) = 4.7 min, tR (minor) = 5.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.23 (m, 1H); 5.39-5.23 (m, 2H); 3.49 (d, J = 13.25, 1H); 3.32 (d, J = 13.25, 1H); 2.06-1.93 (m, 4H); 1.61 (d, J = 3.06 Hz, 1H); 1.49-1.24 (m, 8H); 0.94 (t, J = 7.54 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.61, 131.79, 129.23, 128.44, 128.31, 127.10, 65.19, 39.88, 34.26, 33.09, 29.62, 27.22, 27.18, 20.64, 14.53. HRMS (TOF, ES+) $C_{17}H_{25}N$ $[M+H]^+$ calc. mass 244.2065, found 244.2055. Specific rotation $[\alpha]_D^{25}$ = -18.19° (c = 7.200, $CHCl_3$).

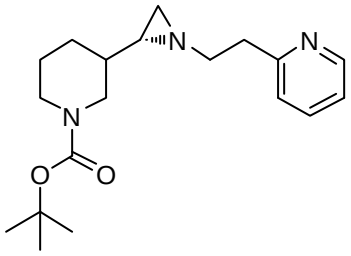


(*R*)-tert-butyl 4-(2-(3-phenylpropyl)aziridin-1-yl)piperidine-1-carboxylate (Table 1, Entry 9): The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (179.1 mg, 52%), which was determined to have an ee of 90% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R (major) = 68.8 min, t_R (minor) = 81.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.24 (m, 2H); 7.21-7.14 (m, 3H); 4.12-3.91 (br, 2H); 2.80-2.68 (m, 2H); 2.64 (t, *J* = 7.87 Hz, 2H); 1.89-1.59 (m, 5H); 1.59-1.50 (m, 3H); 1.45 (s, 9H); 1.38-1.17 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.03, 142.49, 128.54, 128.46, 125.88, 79.54, 66.95, 38.55, 36.01, 33.09, 32.71, 32.18, 31.61, 29.89, 28.58. HRMS (TOF, ES+) $C_{21}H_{32}N_2O_2$ $[M+H]^+$ calc. mass 345.2542, found 345.2537. Specific rotation $[\alpha]_D^{25}$ = +3.08° (c = 7.467, $CHCl_3$).



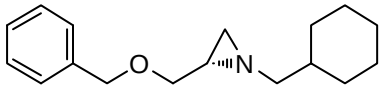
(*R*)-1-(2,3-dihydro-1H-inden-2-yl)-2-(3-phenylpropyl) aziridine (Table1, Entry 10): The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a dark brown oil (155.3 mg,

56%), which was determined to have an ee of 92% by chiral HPLC analysis (Chiralcel® OD-Cl (Cellulose-2), 4% EtOH/hexane, t_R (major) = 6.0 min, t_R (minor) = 5.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.24 (m, 2H); 7.22-7.15 (m, 5H); 7.15-7.09 (m, 2H); 3.11-2.94 (m, 4H); 2.65 (t, *J* = 7.97 Hz, 2H); 2.32 (p, *J* = 6.12 Hz, 1H); 1.92-1.68 (m, 2H); 1.56 (d, *J* = 3.32 Hz, 1H); 1.54-1.40 (m, 2H); 1.39-1.28 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 142.58, 141.87, 141.84, 128.58, 128.46, 126.54, 126.50, 125.87, 124.92, 124.75, 71.21, 39.88, 39.38, 35.99, 33.44, 32.95, 29.87. HRMS (TOF, ES+) $C_{20}H_{23}N$ $[M+H]^+$ calc. mass 278.1909, found 278.1906. Specific rotation $[\alpha]_D^{25}$ = +0.42° (c = 7.067, $CHCl_3$).



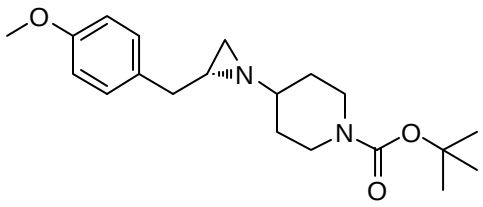
***Tert*-butyl 3-((R)-1-(2-(pyridin-2-yl)ethyl)aziridin-2-yl) piperidine-1-carboxylate (Table 1, Entry 11):** The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N followed by 1:1 MeOH/CH_2Cl_2 with 0.1% Et_3N) to afford the product as an orange oil (175.7 mg, 53%), which was determined to have an ee of 77% by chiral HPLC analysis using the (2R,5R)-2,5-diphenylpyrrolidine catalyst (Chiralcel® OD, Isocratic 5% IPA/hexane, t_R (major) = 15.1 min, t_R (minor) = 23.0 min). When the compound was prepared using the (2S,5S)-2,5-diphenylpyrrolidine catalyst, the product had an ee of 74% (Chiralcel® OD, Isocratic 2% IPA/hexane, tR (major) = 15.7 min, tR (minor) = 21.9 min). ^{1}H NMR (400.1 MHz,

$CDCl_3$) δ (ppm): 8.50 (d, J = 4.63 Hz, 1H); 7.58 (td, J_1 = 1.66 Hz, J_2 = 7.68 Hz, 1H); 7.19 (d, J = 7.83 Hz, 1H); 7.10 (m, 1H); 4.23-3.96 (br, 2H); 3.10-2.94 (m, 2H); 2.82-2.72 (m, 1H); 2.71-2.55 (br, 2H); 2.53-2.43 (m, 1H); 1.81 (d, J = 12.69, 1H); 1.64-1.54 (m, 2H); 1.45 (s, 9H); 1.31-1.14 (m, 4H); 1.08-0.96 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 159.93, 155.01, 149.42, 136.50, 123.45, 121.42, 79.42, 61.14, 44.36, 39.72, 38.89, 32.97, 30.39, 29.46, 28.60. HRMS (TOF, ES+) $C_{19}H_{29}N_3O_2$ $[M+H]^+$ calc. mass 332.2338, found 332.2336 $[M+H\text{-}Boc]^+$ calc. mass 232.1814, found 232.1808. (*R*)-enantiomer specific rotation $[\alpha]_D^{25}$ = -9.58° (c = 5.533, $CHCl_3$). (*S*)-enantiomer specific rotation $[\alpha]_D^{25}$ = +8.24° (c = 6.800, $CHCl_3$).

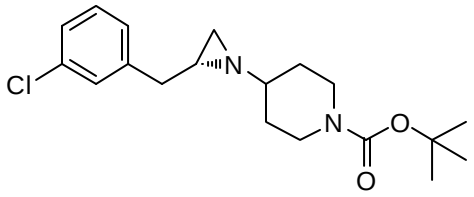


(*S*)-2-((benzyloxy)methyl)-1-(cyclohexylmethyl) aziridine (Table 1, Entry 12): The product was prepared according to the one-pot procedure using (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (5o) as the catalyst and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (103.8 mg, 56%), which was determined to have an ee of 56% by SFC analysis (Chiralpak® IA, 15% IPA/CO_2, t_R (major) = 1.5 min, t_R (minor) = 1.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.28-7.22 (m, 4H); 7.21-7.16 (m, 1H); 4.47 (q, J = 11.94 Hz, 2H); 3.40 (dd, J_1 = 5.18 Hz, J_2 = 10.73 Hz, 1H); 3.34 (dd, J_1 = 6.04 Hz, J_2 = 10.36 Hz, 1H); 2.08 (dd, J_1 = 7.44 Hz, J_2 = 11.80 Hz, 1H); 1.97 (dd, J_1 = 6.16 Hz, J_2 = 11.71 Hz, 1H); 1.85-1.77 (m, 1H); 1.75-1.67 (m, 1H); 1.66-1.44 (m, 6H); 1.23-1.03 (m, 4H); 0.92-0.78 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 138.48, 128.45, 127.74, 127.65, 73.11, 72.87, 68.16, 38.85,

38.30, 32.02, 31.71, 31.68, 26.73, 26.18. HRMS (TOF, ES+) $C_{17}H_{25}NO$ $[M+H]^+$ calc. mass 260.2014, found 260.2014. Specific rotation $[\alpha]_D^{25}$ = +32.96° (c = 4.733, $CHCl_3$). Specific rotation $[\alpha]_D^{25}$ = +8.27° (c = 6.533, $CHCl_3$).



(*R*)-*tert*-butyl 4-(2-(4-methoxybenzyl)aziridin-1-yl) piperidine-1-carboxylate (Table 1, Entry 13): The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane) to afford the product as a clear, yellow oil (180.1 mg, 52%), which was determined to have an ee of 92% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$/acetonitrile, t_R (major) = 28.1 min, t_R (minor) = 31.8 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.17 (d, *J* = 8.48 Hz, 2H); 6.85 (d, *J* = 8.48 Hz, 2H); 4.05-3.85 (br, 2H); 3.80 (s, 3H); 2.84-2.72 (m, 1H); 2.68 (dd, J_1 = 5.15 Hz, J_2 = 14.21 Hz, 2H); 2.53 (dd, J_1 = 7.34 Hz, J_2 = 14.21 Hz, 1H); 1.77-1.69 (m, 1H); 1.67 (d, *J* = 3.36 Hz, 1H); 1.58-1.40 (m. 3H); 1.45 (s, 9H); 1.33 (d, *J* = 6.34 Hz, 2H); 1.25-1.17 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 158.25, 155.02, 132.08, 129.86, 113.90, 79.50, 66.83, 55.38, 40.58, 38.98, 32.61, 31.98, 31.48, 28.58. HRMS (TOF, ES+) $C_{20}H_{30}N_2O_3$ $[M+H]^+$ calc. mass 347.2335, found 347.2325. Specific rotation $[\alpha]_D^{25}$ = +33.20° (c = 3.133, $CHCl_3$).



(*R*)-tert-butyl 4-(2-(3-chlorobenzyl)aziridin-1-yl) piperidine-1-carboxylate (Table 1, Entry 14): The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane) to afford the product as a clear, orange oil (171.9 mg, 49%), which was determined to have an ee of 95% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R (major) = 45.4 min, t_R (minor) = 49.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.28-7.18 (m, 3H); 7.15-7.11 (m, 1H); 4.04-3.79 (br, 2H); 2.87-2.66 (m, 3H); 2.55 (dd, J_1 = 7.37 Hz, J_2 = 14.08 Hz, 1H); 1.76-1.69 (m, 1H); 1.68 (d, J = 3.38 Hz, 1H); 1.62-1.52 (m, 1H); 1.52-1.38 (m, 2H); 1.45 (s, 9H); 1.36 (d, J = 6.37 Hz, 1H); 1.34-1.27 (m, 1H); 1.27-1.18 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.99, 141.93, 134.20, 129.75, 129.01, 127.17, 126.61, 79.51, 66.67, 39.96, 39.47, 32.65, 31.87, 31.42, 28.56. HRMS (TOF, ES+) $C_{19}H_{28}N_2O_2Cl$ $[M+H]^+$ calc. mass 351.1839, found 351.1832. Specific rotation $[\alpha]_D^{25}$ = +13.26° (c = 21.867, $CHCl_3$).

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CHAPTER III

TOTAL SYNTHESIS OF BREVISAMIDE

3.1. Introduction

In recent years, natural marine toxins are becoming more prevalent around the world, affecting an estimated 500,000 individuals annually, and having deleterious impacts on health resulting in a global mortality rate of 1.5%.[2] These toxins, which poison wildlife as well as humans are known to be produced by a very large and diverse group of eukaryotic algae in the marine ecosystem, dinoflagellates during the course of harmful algal blooms (also known as the red tides).[1] Interestingly, many marine toxins are known to have fascinating complex structures. In particular, the dinoflagellate toxins are structurally and functionally diverse, usually possessing multiple cyclic-ether rings which are often aligned in a ladder frame, and in a long carbon chain backbone bearing many hydroxyl groups.[3] These polycyclic ether marine natural products have shown unique and extreme potent biological activities such as neurotoxicity, anticancer and antifungal properties.[3]

Karenia brevis is a marine dinoflagellate known for producing complex fused polyethers is found in the Gulf of Mexico, Caribbean Sea and along New Zealand coasts. This organism is responsible for the blooms along the coasts of Florida and Texas.[4] Brevetoxin A (**3.1**), B (**3.2**) and hemibrevetoxin B (**3.3**) (Figure 3.1) were isolated from the red tide dinoflagellates, *Karenia brevis*, and they are the first members of this class of natural product to be structurally elucidated.[5] This group of natural products consists of a

lactone ring fused to 9 to 10 contiguous trans-fused cyclic ether rings. The brevetoxins bind with high affinity to site 5 of the voltage-sensitive sodium channel (VSSC) in neurons, responsible for the passage of sodium ions through a cell's plasma membrane. These voltage-sensitive channels are responsible for inducing a channel mediated sodium ion reflux, nerve membrane depolarization, and spontaneous firing. This process causes the disruption of the neurological activities leading to illness known as neurotoxic shellfish poisoning (NSP). Brevetoxins are easily absorbed into the body due to their lipid-solubility properties and can pass through cell membranes including the blood brain barrier (BBB).[6]

Nicolaou and co-workers reported the first total syntheses of brevetoxin A (**3.1**) and B (**3.2**) in 1995 and 1998 respectively.[7] Nakata's, Yamamoto/Kadota's and Crimmins's group have also completed syntheses of either brevetoxin A (**3.1**) or B (**3.2**).[8]

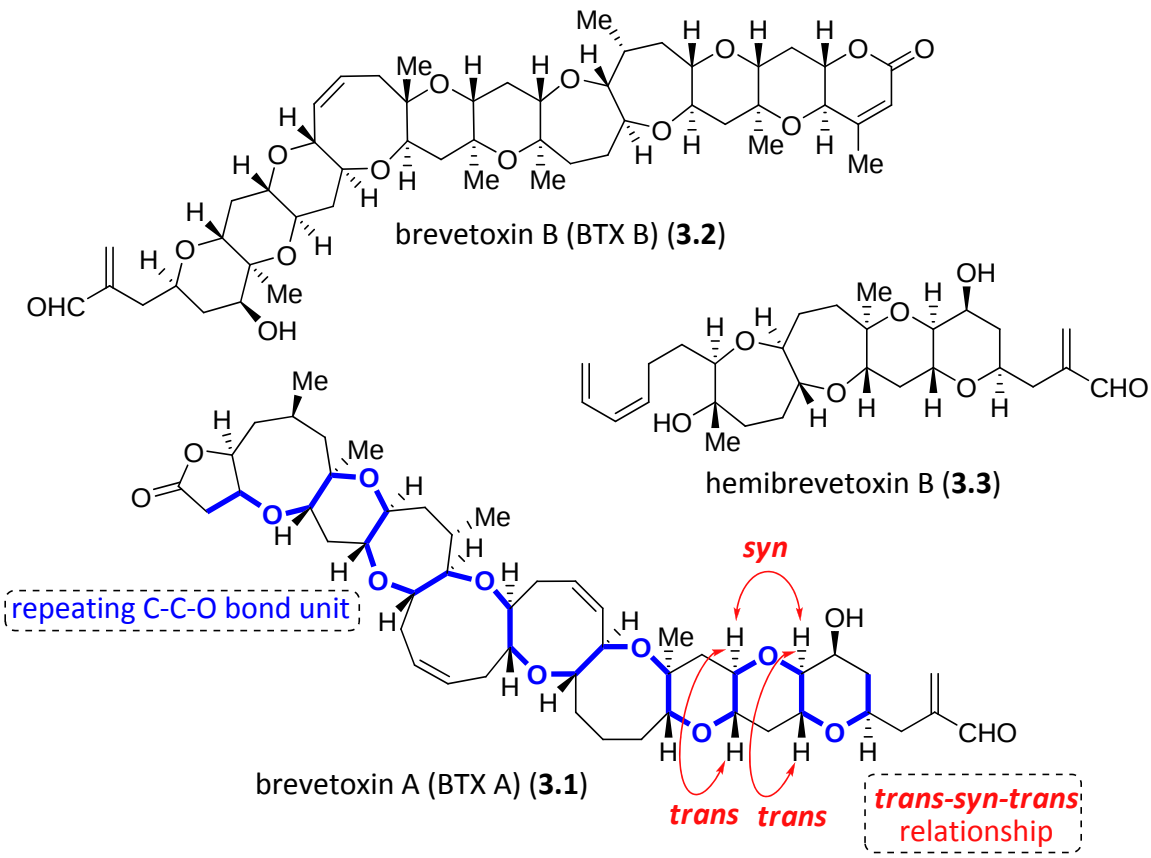


Figure 3.1. Structures of brevetoxin A (**3.1**), B (**3.2**) and hemibrevetoxin B (**3.3**).

Gambierdiscus toxicus another marine dinoflagellate is considered to produce some of the most poisonous toxins, including ciguatoxin (CTX-3C) (**3.4**), gambierol (**3.5**), gambieric acid A-D (**3.6-3.9**) (Figure 3.3) and maitotoxin (**3.10**) (Figure 3.4).

Other known marine toxins include gymnocin A (**3.11**), gymnocin B (**3.12**) (isolated from *Gymnodinium mikimotoi*) and yessotoxin (**3.13**) which was isolated from the marine dinoflagellate *Protoceratium reticulatum* (Figure 3.2).

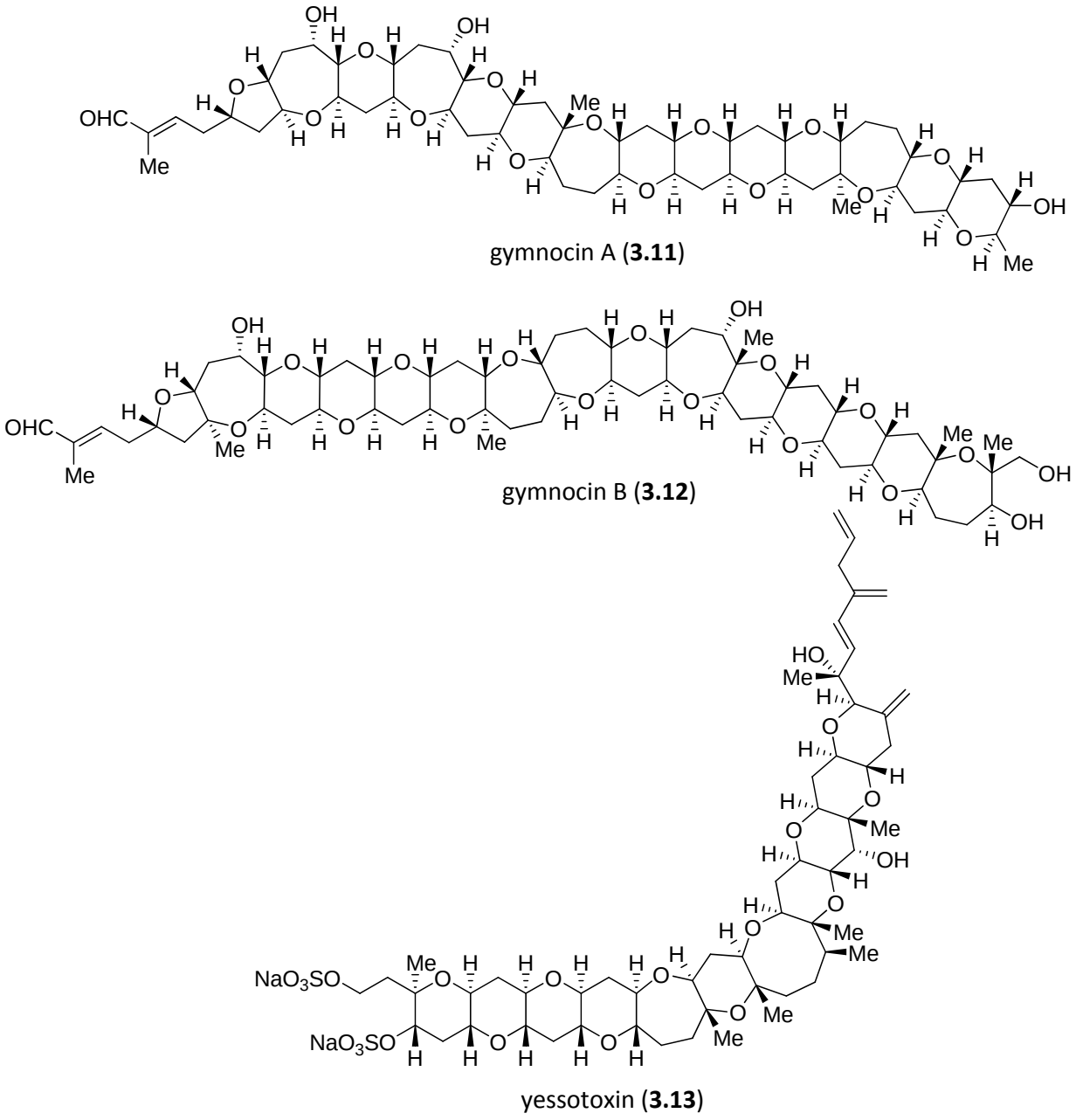


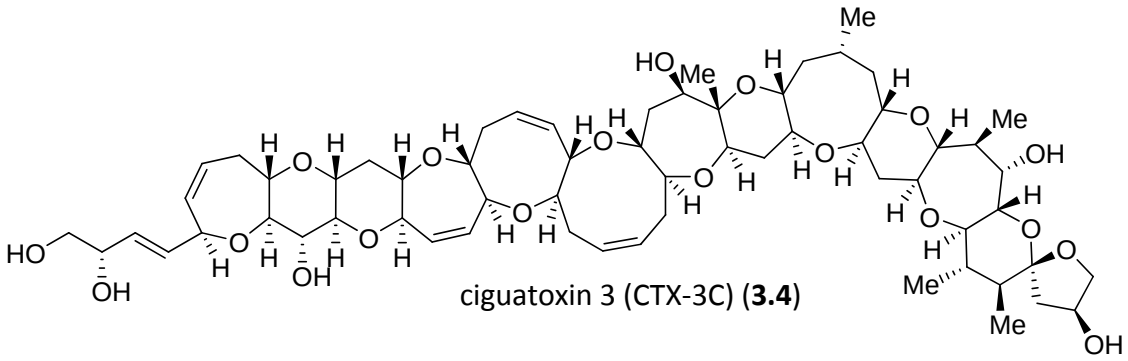
Figure 3.2. Structures of gymnocin A (**3.11**), gymnocin B (**3.12**) and yessotoxin (**3.13**).

Ciguatera, a type of seafood poisoning caused by ciguatoxins is estimated to affect approximately 20,000 people annually.[9] Ciguatoxins are lipophilic polycyclic ethers with 13 five- to nine membered fused cyclic ether rings. Similar to brevetoxin,

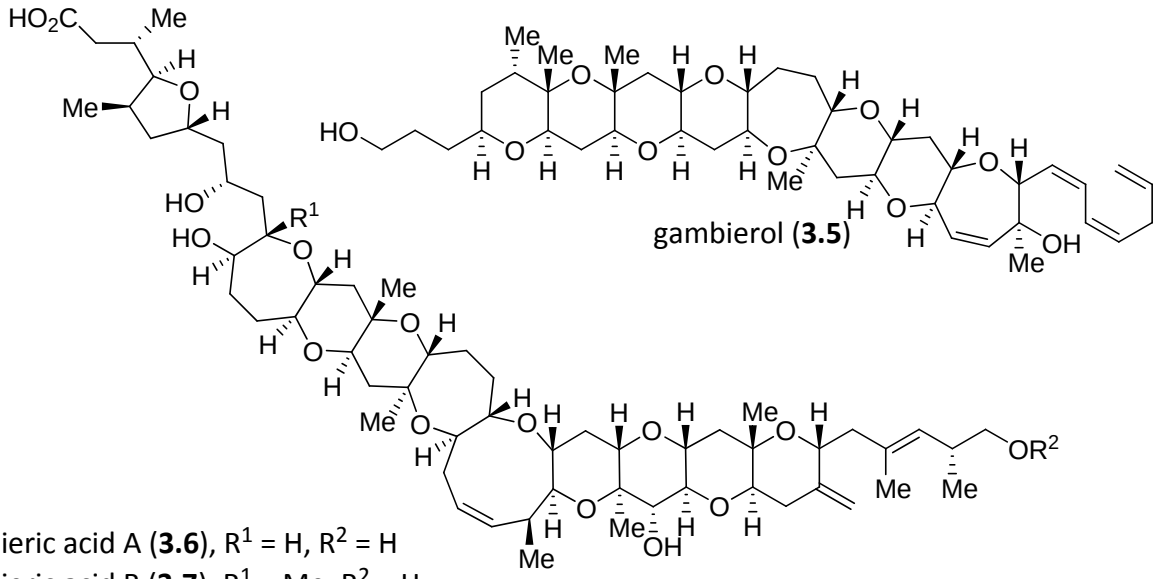
ciguatoxins are extremely potent neurotoxins that lower the threshold for opening voltage-gated sodium channels, thus causing membrane depolarization.[10] These effects could cause heart contractions and paralysis. In 1984, Scheuer's group reported the isolation of ciguatoxin and later Yasumoto and co-workers disclosed its structure. In 2001, the first total synthesis of ciguatoxin congener CTX-3C (**3.4**) (Figure 3.3) was accomplished by Hirama and co-workers.[11]

Gambierol (**3.5**) (Figure 3.3), a polycyclic ether family of marine neurotoxin was isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* in 1993.[12] Structurally, gambierol consists of 8 ether rings, 18 stereocenters, and 2 pyranyl rings. Similar to ciguatoxins, gambierol (**3.5**) is responsible for ciguatera seafood poisoning, showing potent toxicity in mice at LD_{50} 50 μg/kg (ip). It is believed that gambierols bind to ion channels like other similar neurotoxins. In 2003, Yasumoto, Hirama, and co-workers reported that gambierol inhibits the binding of brevetoxin PbTx-3 to its target, site 5 of voltage gated sodium channels, thus acting as a competitive antagonist of PbTx-2.[13] Later, Bigiani and co-workers reported that gambierol (**3.5**) is also capable of binding to potassium channels.[14] The first total synthesis of gambierol (**3.5**) was accomplished by Sasaki and co-workers in 2002.[15] Yamamoto/Kadota and Rainier groups have also completed the synthesis of the natural product.[16]

In 1992, gambieric acids A-D (**3.6**-**3.9**) (Figure 3.3) were isolated from *Gambierdiscus toxicus* which were shown to inihibit the growth of *Aspergillus niger* showing potency that exceeds amphotericin B by 2000-fold.[17] A competitive inhibition assay performed by Hirama and co-workers showed that gambieric acid-A (**3.6**) inhibits the binding of isotope-labeled dihydro-brevetoxin ([^{3}H]-PbTx-3).[18]



ciguatoxin 3 (CTX-3C) (**3.4**)



gambierol (**3.5**)

gambieric acid A (**3.6**), R^1 = H, R^2 = H
gambieric acid B (**3.7**), R^1 = Me, R^2 = H
gambieric acid A (**3.8**), R^1 = H, R^2 = (R)-$COCH_2CH(Me)CH_2CO_2H$
gambieric acid A (**3.9**), R^1 = Me, R^2 = (R)-$COCH_2CH(Me)CH_2CO_2H$

Figure 3.3. Structures of ciguatoxin (**3.4**), gambierol (**3.5**) and gamberic A-D (**3.6-3.9**).

Maitotoxin (**3.10**) the largest molecule made by nature (excluding bio-polymers) was first discovered from the surgeon fish *Ctenochaetus striatus* [19] and later isolated from cultured cells of *Gambierdiscus toxicus*.[20] The structure of maitotoxin (**3.10**) contains 32 rings and 98 stereogenic centers (Figure 3.4). Maitotoxin (**3.10**) is extremely potent and the most poisonous marine toxin known, showing lethality (LD_{50}) value of 50 ng/kg against mice.[21]

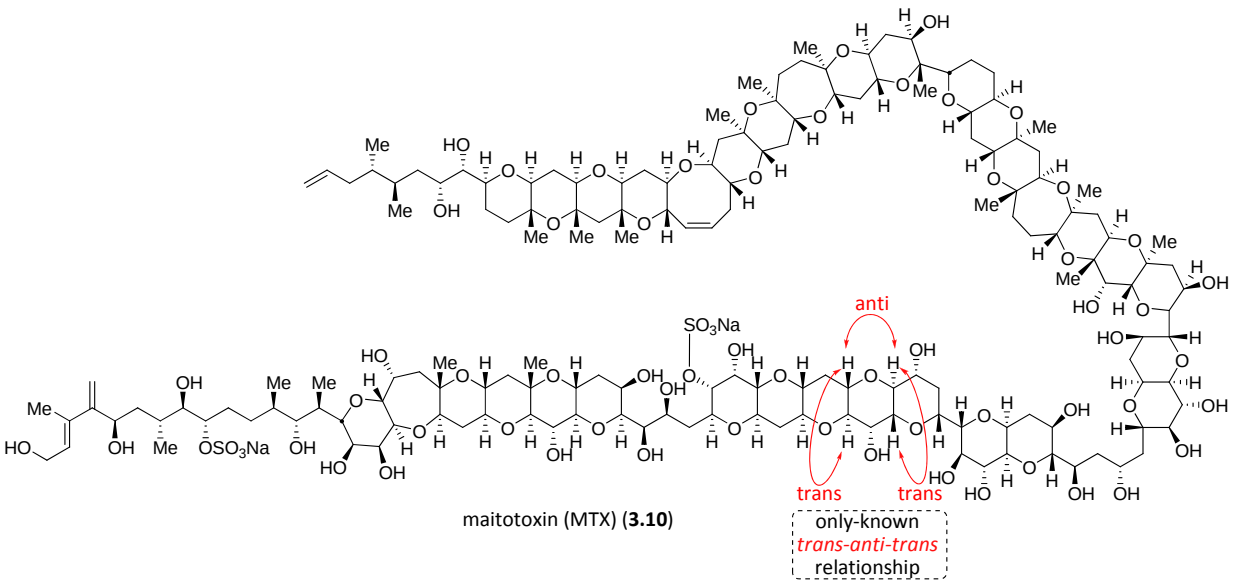


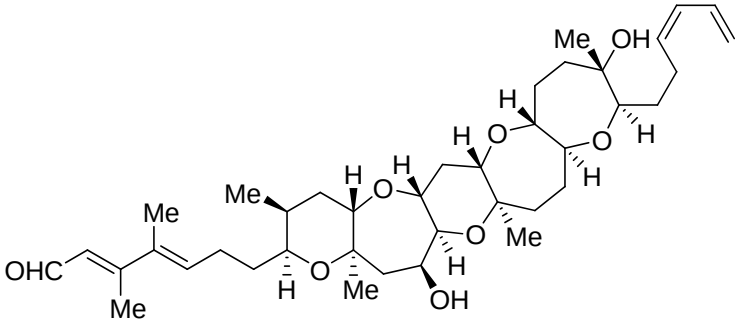
Figure 3.4. Structure of Maitotoxin (**3.10**).

In 2005, Baden, Bourdelais and co-workers isolated a new member of polycyclic ether from the culture of *Karenia brevis* called brevenal (**3.14**) (Figure 3.5), a smaller, ladder-frame polycyclic ether that competitively displaced brevetoxin from its binding site in rat brain synaptosomes.[22] Brevenal (**3.14**) was shown to displace ([^{3}H]-PbTx-3) from receptor site 5 of VSSC. Also recently, it has been demonstrated that brevenal (**3.14**) is a potent antagonist of PbTx-2-induced Ca^{2+} influx in neurons.[23] Molgo and co-workers have recently shown that brevenal (**3.14**) can potently inhibit ciguatoxin's stimulatory effect on exocytosis and can be used as the first treatment of ciguatera.[24] For the treatment of cystic fibrosis and neurotoxic shellfish poisoning, brevenal (**3.14**) has been identified as a lead compound.

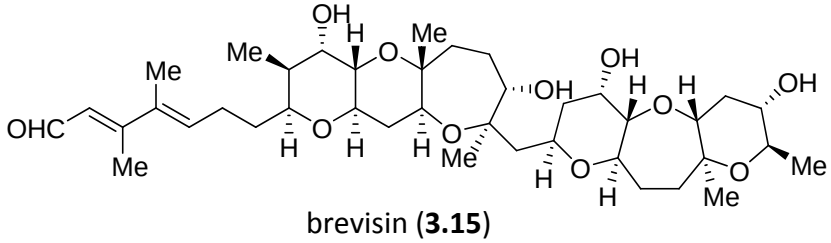
Three total syntheses have been reported since the isolation of brevenal (**3.14**). The first of the syntheses was accomplished by Sasaki and co-workers in 2006.[25] In 2009,

the second synthesis was reported by Kadota/Yamamoto and co-workers.[26] Another synthesis was recently reported by Rainier and co-workers.[27]

Brevisin (**3.15**) a polycyclic ether, was isolated from the dinoflagellate *karenia brevis* by Wright and co-workers in 2008. It contains two separate fused polyether rings linked by a methylene group. One of the polyether rings contains the same conjugated aldehyde side chain found in brevenal (**3.14**) (Figure 3.5).[28] Thus, this unprecedented polycyclic ether could provide more insight into the biogenesis of fused polyether ring systems. Wright and co-workers reported that brevisin (**3.15**) inhibits the binding of [^{3}H]-PhTx-3 to its binding site on the voltage -sensitive sodium channels in rat synaptosomes. In 2011, the total synthesis was reported by the Satake group, who were involved in the isolation of this polycyclic ether natural product.[29]



brevenal (**3.14**)



brevisin (**3.15**)

Figure 3.5. Structures of brevenal (**3.14**) and brevisin (**3.15**).

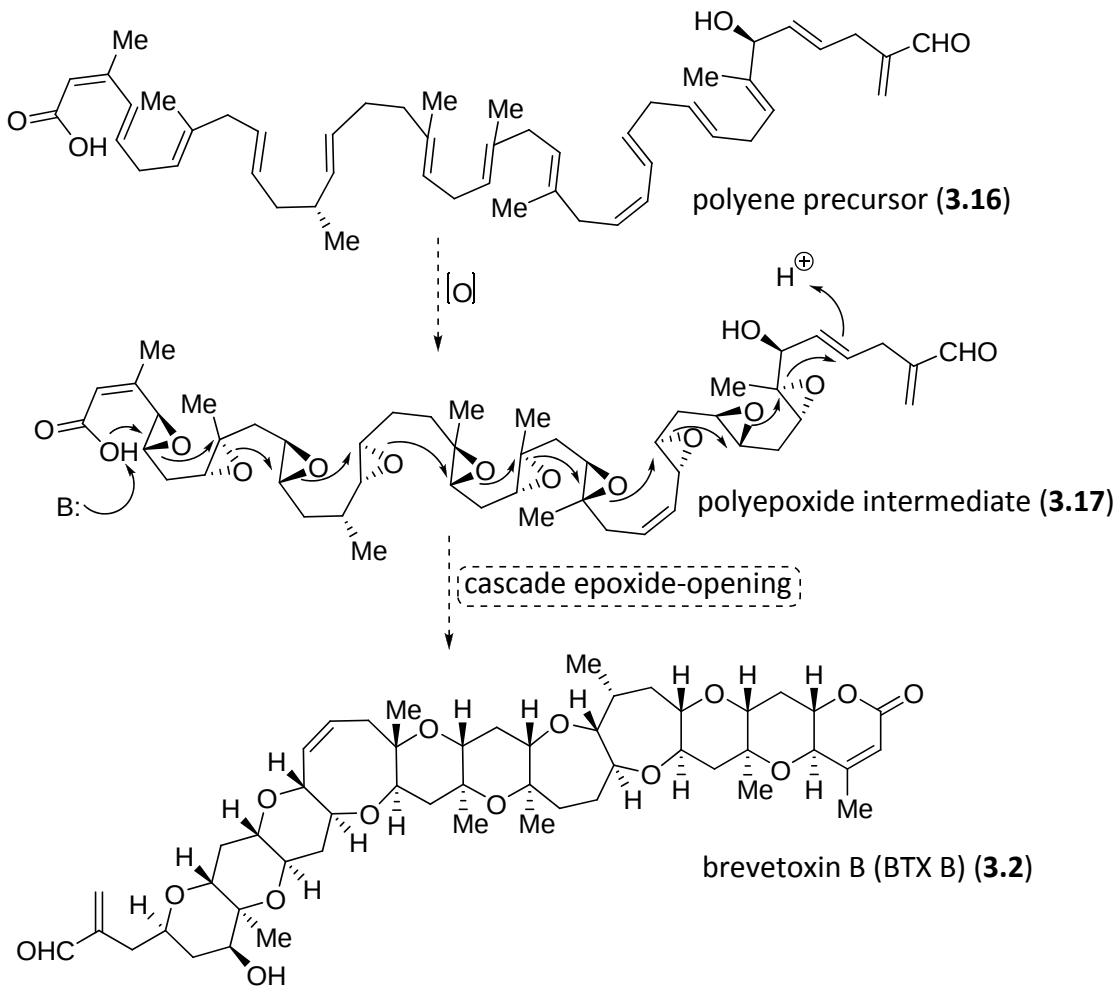
3.2. Biosynthesis of ladder polyethers

Complex ladder polyethers possess many structural and stereochemical similarities. Structurally, a carbon-carbon-oxygen unit is present through the length of the polycyclic ether ladder. As seen in the structure of maitotoxin (**3.10**) and other polyether toxins, the repeating C-C-O units is independent of the substitution, ladder length and ether ring size. The relative stereochemistry of the ladder ring function possesses a *trans-syn-trans* relationship (Figure 3.1) except for maitotoxin (**3.10**) ((Figure 3.4) which contains a *trans-anti-trans* relationship).[30,31,32]

In 1985, after the discovery and structural determination of brevetoxin B (**3.2**), Nakanishi proposed that the structural and stereochemical features of the ladder-frame polyethers could arise through a cascade of successive endotet epoxide openings of a polyepoxide precursor.[33] Therefore, each epoxide opening must proceed stereospecifically with complete inversion of stereochemistry. A similar proposal has been suggested independently by Shimizu[34] and Nicolaou.[35,36] Specifically, Nakanishi proposed that brevetoxin B (**3.2**) is assembled from a polyepoxide precursor (**3.17**) via a cascade of S_N2 epoxide openings and further proposed that the polyepoxide precursors could arise from epoxidation of polyene **3.16** (Scheme 3.1).[33] Recently, Rein and co-workers reported the first evidence of resident polyketide synthase (PKS) genes in *Karenia brevis* or other dinoflagellate.[37] This work corroborates the proposal of Nakanishi that polyketides are the origin of the carbon skeleton in ladder polyethers.[33]

In 2006, Gallimore and Spencer showed that contiguous rings in any single polyether can be derived from stereochemically identical *trans* epoxides. Therefore, there is a stereochemical regularity at the ether ring junctures which supports the previous

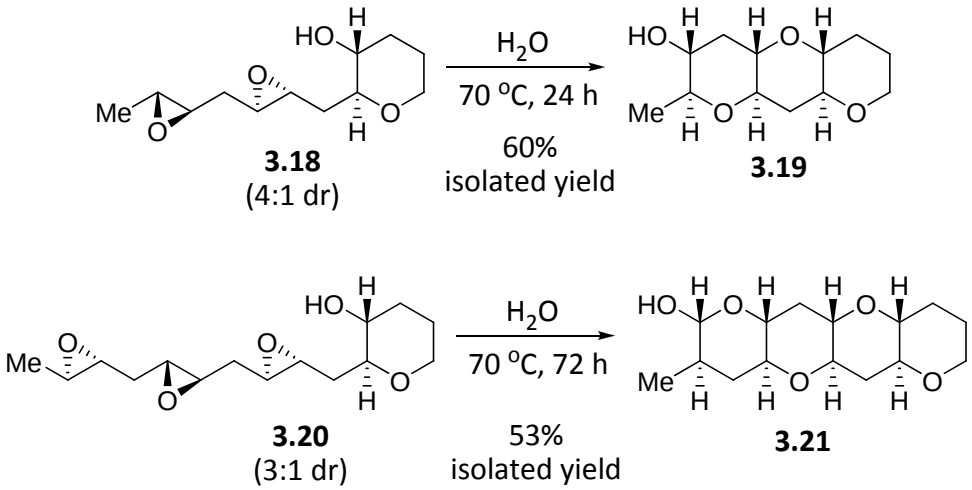
hypothesis by Nakanishi. Furthermore, they suggested that a single epoxidase is likely responsible for the selective and uniform epoxidation of the *trans* polyene precursor.[38]



Scheme 3.1. Nakanishi's proposed biosynthesis of brevetoxin B (**3.2**).

Recently, an important breakthrough in understanding the formation of ladder polyether marine natural products was reported by Jamison's group. Their work explained the importance of the first ring towards the cascade formation of multiple ether rings present in the ladder frame polyethers. It was reported that the endo-tet cyclization of a polyepoxide precursors for the formation of ladder-frame polyethers can only

proceed in aqueous media of neutral pH, and an initial 3-hydroxy-tetrahydropyranyl ring moiety must be built into the polyepoxide intermediate (Scheme 3.2).[39] Jamison's work suggests that after enzyme catalyzed formation of the first ether ring, the cascade polyepoxide opening should proceed spontaneously, relying on the spatial and configurational properties of the epoxide-intermediate.[39,40]



Scheme 3.2. Water-promoted epoxide-opening casacade.

3.3. Isolation of brevisamide

In 2008, Satake, Tachibana, Wright, and co-workers reported the isolation and characterization of brevisamide (**3.22**), an unprecedented monocylic ether alkaloid, from the dinoflagellate *Karenia brevis*. The extraction of 400 L of cultured cells lead to 0.2 mg of brevisamide (**3.22**) as an amorphous solid.[41] Brevisamide (**3.22**), which displayed similar UV data to brevenal (**3.14**), had a very distinctive ^{1}H NMR spectra compared to other known brevetoxins. The structural assignment was elucidated by 500 MHz 2D-

NMR experiments including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC, TOSCY, HSQC and NOE experiments.

Brevisamide (**3.22**), contains the same conjugated 3,4-dimethyl-2,4-dienal side chain as the more complex polycylic ether brevenal (**3.14**) and brevisin (**3.15**) (Figure 3.6). Thus, brevisamide (**3.22**) is believed to be a biosynthectic precursor for these complex polyether natural products **3.14** & **3.15**.[22] Interestingly, the brevisamide (**3.22**) skeleton matches well with Jamison's template ring system in the formation of ladder polyethers (Scheme 3.2), with the ether ring oxygen *anti* to the hydroxyl oxygen and a carbon-carbon-oxygen unit.[39,40] These features are consistent with the structural and stereochemical trend found in complex ladder polyethers such as brevetoxins. Brevisamide (**3.22**) might prove the existence of the tetrahydropyran template in nature.[41] Wright, and co-workers suggested that based on the established biosynthesis pathway of other dinoflagellate metabolites, glycine could be the source of the amide nitrogen of brevisamide (**3.22**) and acts as a starter unit in a NRPS/PKS hybrid pathway.[41]

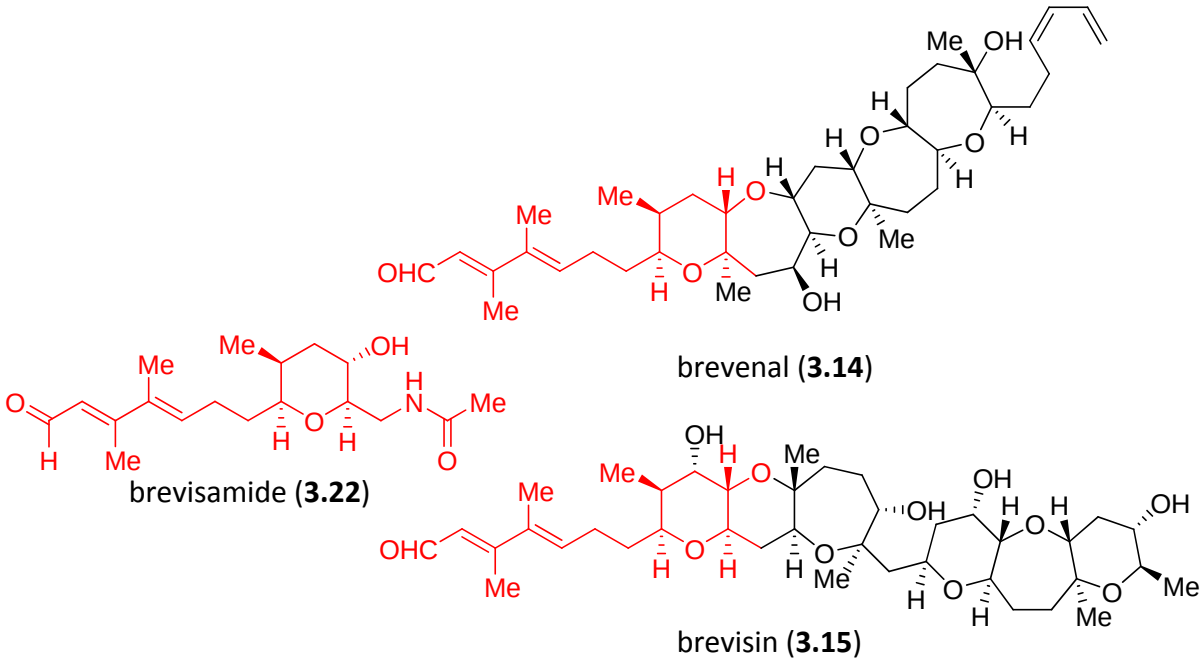
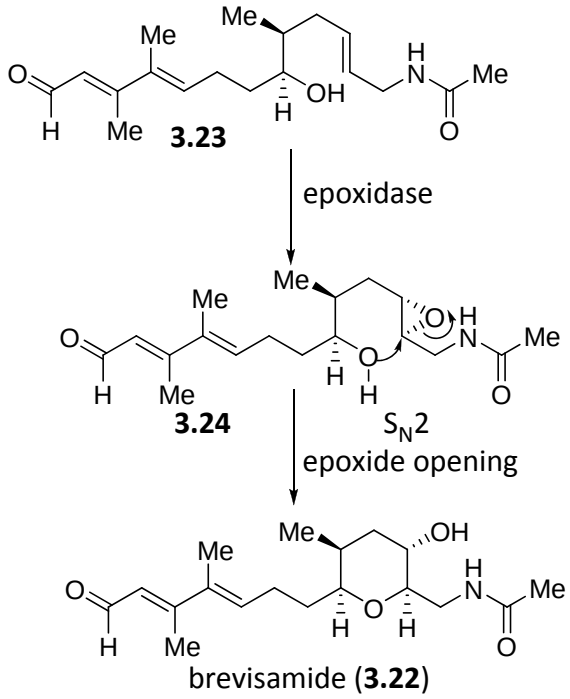


Figure 3.6. Structures of brevenal A (**3.14**), brevisin (**3.15**) and brevisamide (**3.22**).

3.4. Proposed biosynthesis of brevisamide

An epoxide based biosynthetic mechanism for the formation of the ether ring of brevisamide was proposed by Wright and co-workers (Scheme 3.3). It involves epoxidation of polyketide olefin chain **3.23** to give hydroxyl epoxide intermediate **3.24**, which undergoes intramolecular S_N2 cyclization of the β-hydroxy group on a flow from left to right-opposite the flow of polyketide chain assembly to provide brevisamide (**3.22**).[41] Consequently, the isolation of brevisamide as the smallest known ether-containing metabolite produced by dinoflagellate provides further support for the model of ladder-frame initiation in the biosynthesis of polycyclic ether natural products.



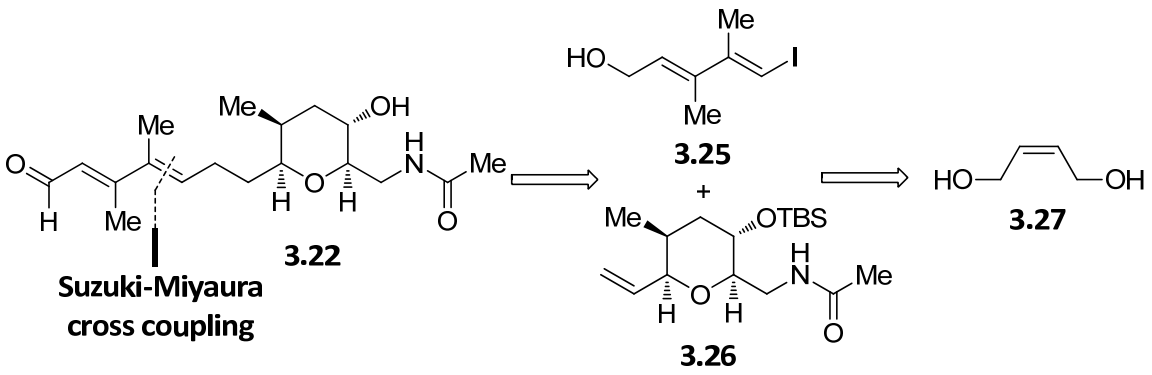
Scheme 3.3. Proposed biosynthetic mechanism for the formation of brevisamide (**3.22**).

Due to the unique role brevisamide (**3.22**) could play in further understanding the biogenetic origin of fused, ladder-frame polyether marine natural products, it has garnered a great deal of interest among the synthetic community, with five total syntheses and two formal syntheses reported.

3.5. Other total synthesis of brevisamide

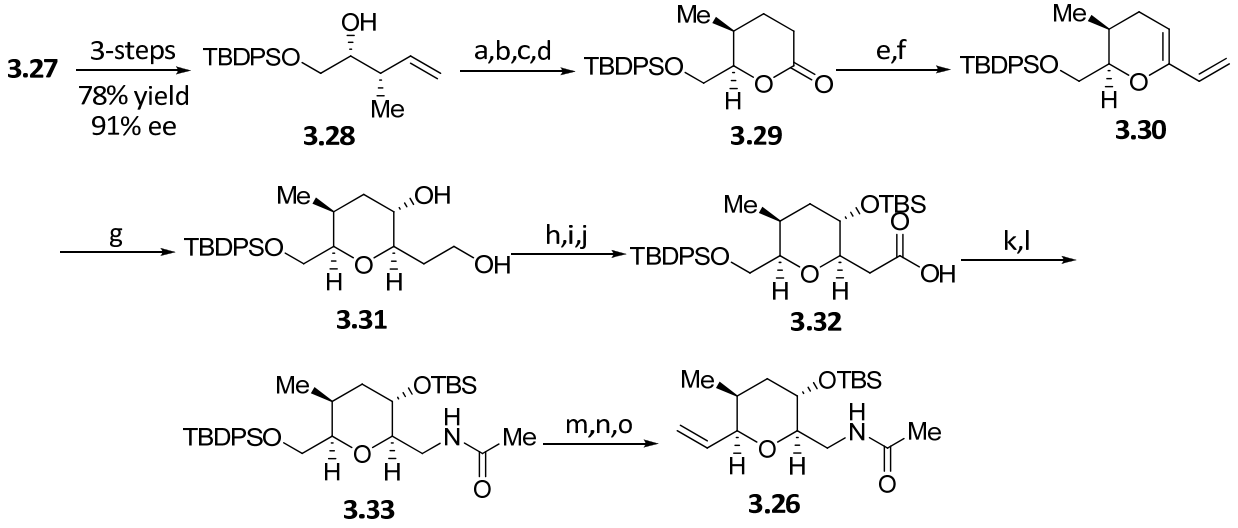
Within months of the publication of the isolation and characterization of brevisamide (**3.22**) by Satake, Tachibana, Wright, and co-workers, the first total synthesis and structural confirmation of brevisamide was reported by the same group.[42] Satake's strategy involves Suzuki-Miyaura coupling of iodide **3.25** and amino cyclic ether

fragment **3.26** (Scheme 3.4). Both fragments can be obtained from a commercially available starting material, cis-but-2-ene-1,4-diol **3.27** (Scheme 3.4).



Scheme 3.4. Satake and Tachibana's retrosynthesis of brevisamide (**3.22**).

The synthesis of amino cyclic ether **3.26** began from optically active homoallylic alcohol **3.28**, which was prepared in three steps (silyl-monoprotection, ozonolysis and brown crotylation) from diol **3.27** (78 % yield, 91% ee). Ozonolysis of the homoallylic alcohol **3.28**, Wittig reaction of the resulting aldehyde, hydrogenation and transesterification of the enoate gave lactone **3.29** in 71% after four steps. Ketene acetal triflate generation from **3.29**, followed by Stille coupling generated the dienol ether **3.30**, which was further subjected to hydroboration conditions to give the pyran ring **3.31**. TBS-protection of the diol, followed by selective deprotection of the primary silyl-alcohol and TEMPO oxidation gave carboxylic acid **3.32** in 80% yield for three steps (Scheme 3.5).

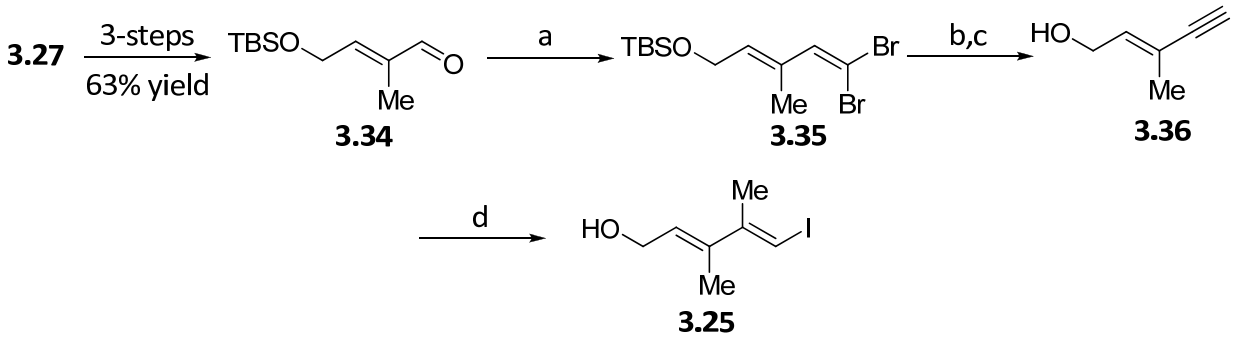


Scheme 3.5. Synthesis of Suzuki-Miyaura coupling fragment amino cyclic ether **3.26**. *Reagents and conditions:* (a) O_3, CH_2Cl_2, -78 ^oC; PPh_3, rt; (b) $Ph_3P{=}CHCO_2Me$, THF, rt; (c) H_2, Pd/C, EtOAc, rt; (d) PPTS, benzene, reflux (71% yield for 4-steps). (e) KHMDS, Tf_2NPh, DMPU, THF, -78 ^oC; (f) $CH_2{=}CHSn$*n*-Bu_3, $Pd(PPh_3)_4$, LiCl, THF, reflux (85% yield for 2-steps); (g) thexylborane, THF, 0 ^oC, 30% H_2O_2, sat. $NaHCO_3$ aq, rt; (h) TBSCl, imidazole, DMF, rt; (i) CSA, MeOH-CH_2Cl_2, 0 ^oC; (j) TEMPO, NaOCl, KBr, TBAC, NaCl, $NaHCO_3$, CH_2Cl_2-H_2O, 0 ^oC, (80% yield for 3-steps). (k) DPPA, Et_3N, toluene, 80 ^oC, 4 N LiOH, THF, rt, 1 h, 85%; (l) Ac_2O, pyridine, quant; (m) TBAF, AcOH, THF, 0 ^oC to rt, 83%; (n) SO_3-pyridine, Et_3N, CH_2Cl_2-DMSO, 0 ^oC; (o) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, -78 ^oC to rt; (56% yield for 2-steps).

Curtius rearrangement of pyran acid **3.32** generated the terminal amino group of the pyran ring and subsequent acetylation delivered the desired amide **3.33**. Selective deprotection of the silylether, Parikh-Doering oxidation and Wittig reaction of the resulting aldehyde furnish the desired key ether ring fragment **3.26** (Scheme 3.5).

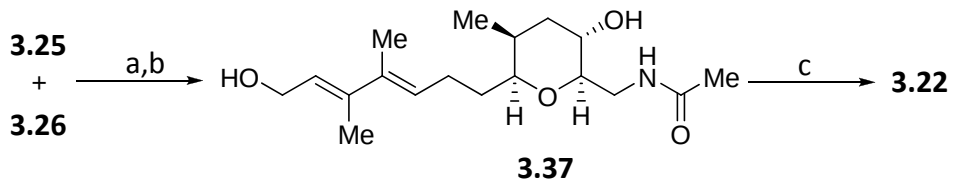
Unsaturated aldehyde **3.34** was prepared from diol **3.27** in three steps was subjected to Corey-Fuchs type reaction to generate dibromoolefin **3.35**. Desilylation with

TBAF and debromination afforded enynol **3.36**. Subsequent methylalumination-iodination of **3.36** proceeded by syn-addition to afford the iodide side chain fragment **3.25** with the desired *E*,*E* geometry (Scheme 3.6).



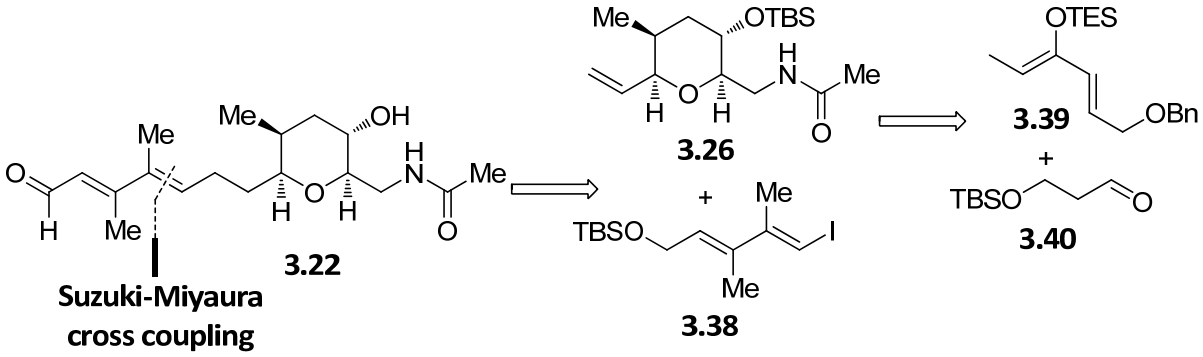
Scheme 3.6. Synthesis of Suzuki-Miyaura coupling fragment iodide **3.25**.
Reagents and conditions: (a) CBr_4, PPh_3, Et_3N, CH_2Cl_2, -40 to 0 ^oC (b) TBAF, THF, 45 ^oC;
(c) *n*-BuLi, Et_2O, -78 ^oC; H_2O, rt (66% yield for 2-steps); (d) Me_3Al, $ZrCp_2Cl_2$, CH_2Cl_2-heptane, rt; I_2, THF, -78 to 0 ^oC, 38%.

Hydroboration of the terminal olefin in amino cyclic ether fragment **3.26** afforded the alkylborane, which was coupled with iodide side chain fragment **3.25** (Cs_2CO_3, cat. $PdCl_2$(dppf), DMF, 45 ^oC) to give the cross-coupled product. TBAF deprotection of the crude product gave diol **3.37** in 40% yield for the two steps. Finally, selective allylic oxidation with MnO_2 provided the first synthetic brevisamide **3.22** in 55% yield (Scheme 3.7).



Scheme 3.7. Satake and Tachibana's synthesis of brevisamide (**3.22**).
Reagents and conditions: (a) 9-BBN, THF, rt; 3 M, Cs_2CO_3, $PdCl_2$(dppf), DMF, 45 ^oC; (b) TBAF, THF, 0 ^oC (40% yield for 2-steps); (c) MnO_2, CH_2Cl_2, rt 55%.

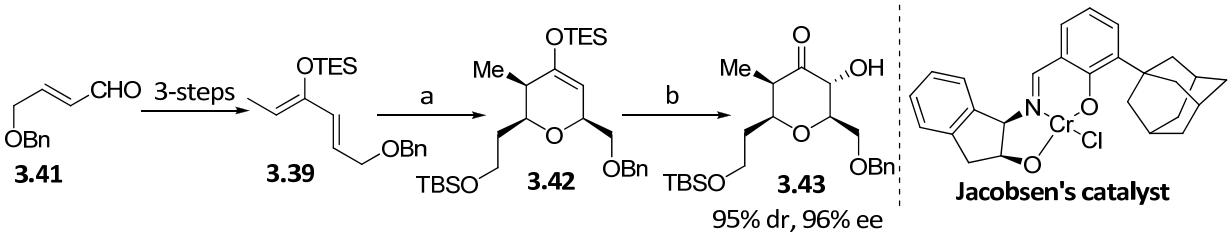
Ghosh and Li reported the total synthesis of brevisamide based on the same coupling strategy reported by Satake and co-workers.[43] The synthesis features a Suzuki-Miyaura coupling of pyran **3.26** and iodide **3.38**. The pyran ring **3.26** was accessed using Jacobsen's asymmetric hetreo-Diels-Alder reaction and iodide **3.38** was constructed via Negishi's zirconium-catalyzed carboalumination-iodination reaction (Scheme 3.8).



Scheme 3.8. Ghosh and Jianfeng's retrosynthesis of brevisamide (**3.22**).

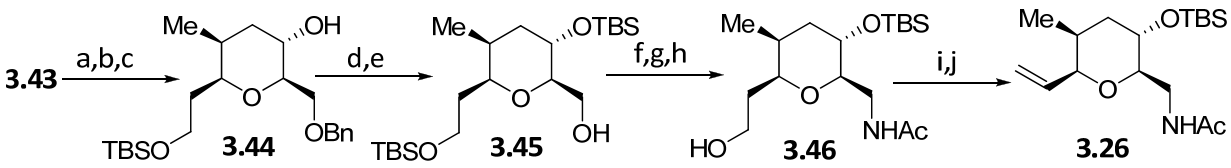
The synthesis of pyran ring **3.26** began from triethylsilyl diene **3.39**, which was prepared in three steps (monoprotection, ozonolysis and brown crotylation) from aldehyde **3.40**. Asymmetric hetero-Diels-Alder reaction of triethylsilyl diene **3.39** and

aldehyde **3.40** in the presence of 10 mol % Jacobsen's catalyst **3.41**, afforded the desired cycloadduct **3.42** in 52% yield (95% dr, 96% ee). Rubottom oxidation of **3.42** with m-CPBA in the presence of aqueous $NaHCO_3$ buffer gave alcohol **3.43** in 60% yield (Scheme 3.9).

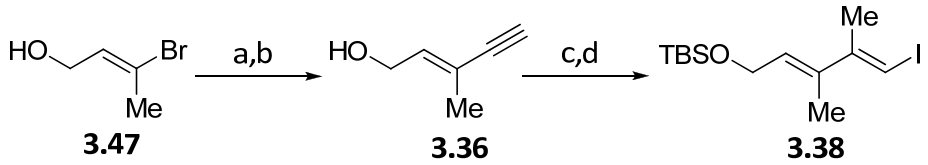


Scheme 3.9. Synthesis of alcohol **3.43**. *Reagents and conditions:*
(a) **3.40**, 10 mol% Jacobsen's catalyst, 52%; (b) *m*-CPBA, $NaHCO_3$, 60%.

Wolff-Kishner ketone reduction in a three step protocol afforded alcohol **3.44** (76% yield for three steps). Silyl protection of the alcohol, followed by removal of the benzyl ether provided the alcohol **3.45** in 82% yield for the two steps. Azide formation via Mitsunobu reaction of alcohol **3.45**, followed by reduction of the azide, acetylation of the resulting amine and selective desilylation of the primary TBS-ether gave acetamide **3.46**. Two step conversion of the primary alcohol gave key olefin fragment **3.26** (50% yield for two steps) (Scheme 3.10).



Scheme 3.10. Synthesis of Suzuki-Miyaura coupling fragment amino cyclic ether **3.26**. *Reagents and conditions:* (a) $TsNHNH_2$; (b) $NaBH_3CN$; (c) NaOAc, EtOH, (73% yield for 3-steps); (d) TBSOTf, Et_3N, 0 ^oC; (e) H_2, Pd-C (f) PPh_3, DIAD, NH_3, 0 ^oC, 94%; (g) H_2, Pd-C, Ac_2O, $NaHCO_3$; (h) PPTS, EtOH, (77% yield for 2-steps); (i) 2-NO2PhSeCN, n-Bu_3P; (j) m-CPBA, Na_2HPO_4, *i*-Pr_2NH (50% yield for 2-steps).

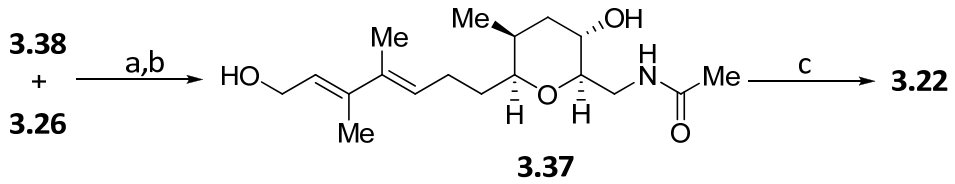


Scheme 3.11. Synthesis of Suzuki-Miyaura coupling fragment iodide **3.25**. *Reagents and conditions:* (a) trimethylsilylacetylene, $Pd(PPh_3)_4$, 20 mol% CuI, DIPEA 96%; (b) K_2CO_3, MeOH, 82 %; (c) Me_3Al, -78 to 0 ^oC, $ZrCp_2Cl_2$, 23 ^oC, then I_2, 0 ^oC, 39%. (d) TBSCl, imidazole, 87%.

The iodide fragment **3.38** was accomplished starting from previously known *E*-bromocrotyl alcohol **3.47**. Enynol **3.36** was generated by reacting alcohol **3.47** with trimethylsilylacetylene (in the presence of diisopropylethylamine and a cat. $Pd(PPh_3)_4$ and CuI) and desilylation with K_2CO_3. Similar to Satake's approach, iodide fragment **3.38** was achieved from Negishi's zirconium-catalyzed carboalumination-iodination reaction of enynol **3.36** and silylation of the resulting alcohol (Scheme 3.11).

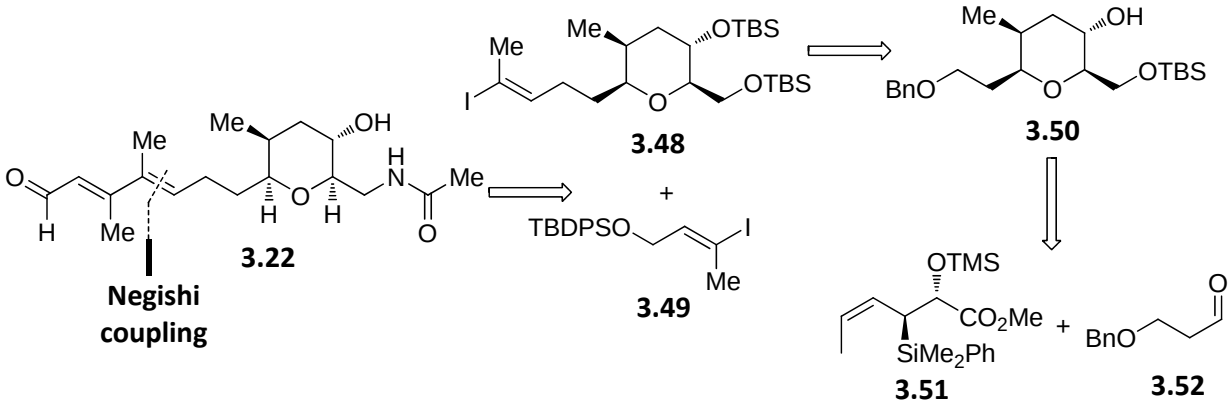
Suzuki-Miyaura coupling of the two fragments, followed by desilylation gave alcohol **3.37**, a two step protocol similar to that reported by Satake and co-workers.

Chemoselective oxidation with TEMPO of the allylic alcohol **3.37** gave brevisamide (**3.22)** (Scheme 3.12).



Scheme 3.12. Ghosh and Jianfeng's synthesis of brevisamide (**3.22**).
Reagents and conditions: (a) 9-BBN, then aq. Cs_2CO_3, $PdCl_2(dppf)$-CH_2Cl_2; (b) TBAF, THF, (40% yield 2-steps); (c) TEMPO, $PhI(OAc)_2$, 87%.

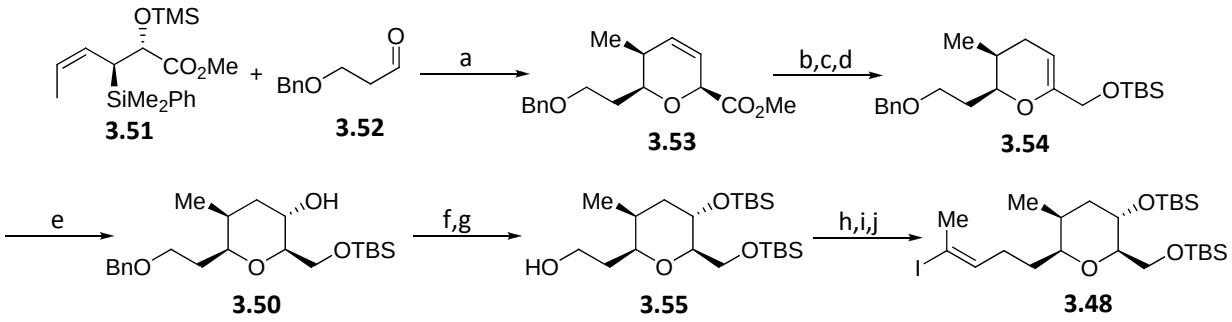
Another synthesis of brevisamide was reported by Lee and Panek.[44] Their synthesis utilized a modified Negishi cross-coupling of fragments **3.48** and **3.49**. The (*E*)-vinyl iodide of pyran ring **3.48** was installed through S_N2-type propynl substitution and hydrozirconation-iodination (Scheme 3.13).



Scheme 3.13. Lee and Panek's retrosynthesis of brevisamide (**3.22**).

The synthesis began with the preparation of pyran ring **3.48** (Scheme 3.14). Utilizing Panek's silicon-directed [4 + 2]-annulation reaction, (Z)-crotylsilane **3.51** was

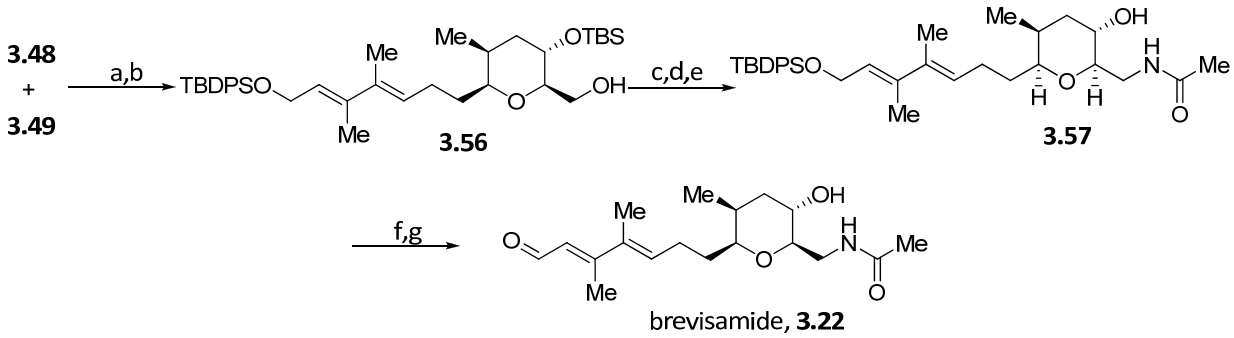
reacted with aldehyde **3.52** in the presence of TMSOTf to give 5,6-*cis*-dihropyran **3.53** in 70% (10:1 *dr*). Isomerization of the olefin with DBU, reduction of the ester with LAH and silyl protection of the alcohol gave allylic silyl-ether **3.54**. Hydroboration of the allylic silyl-ether **3.54** with $BH_3{\cdot}SMe_2$ gave the desired key tetrahydropyranol **3.50** in 90% yield and high diastereoselectivity (>11:1 dr). Silyl-ether protection of the tetrahydropyranol and deprotection of the benzyl ether gave primary alcohol **3.55** in excellent yield. Triflation of the alcohol, followed by S_N2 displacement with 1-propynyllithium and hydrozirconation of the internal alkyne using Schwartz reagent, followed by trapping of the organozirconium intermediate with iodine furnished the coupling precursor (*E*)-iodoalkene **3.48** (E/Z =10:1) (Scheme 3.14).



Scheme 3.14. Synthesis of Negishi coupling fragment pyran ring **3.58**.

Reagents and conditions: (a) TMSOTf, CH_2Cl_2, PhH, -50 ^oC, 70% yield, 10:1 *dr*; (b) DBU, THF, rt, 86%; (c) $LiAlH_4$, Et_2O, 0 ^oC; (d) TBSCl, imidazole, DMF, rt, (84% yield for 2-steps); (e) $BH_3.SMe_2$, THF, 0 ^oC to rt, H_2O_2, 1 N NaOH, 90% yield, >11:1 *dr*; (f) TBSOTF, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 98%; (g) Pd/C, H_2, EtOAc, rt quant; (h) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 oC; (i) 1-propynylithium, THF, -78 ^oC to rt, (78% yield for 2-steps); (j) Cp_2ZrHCl, THF, 50 ^oC, I_2/THF, 0 oC, 88%.

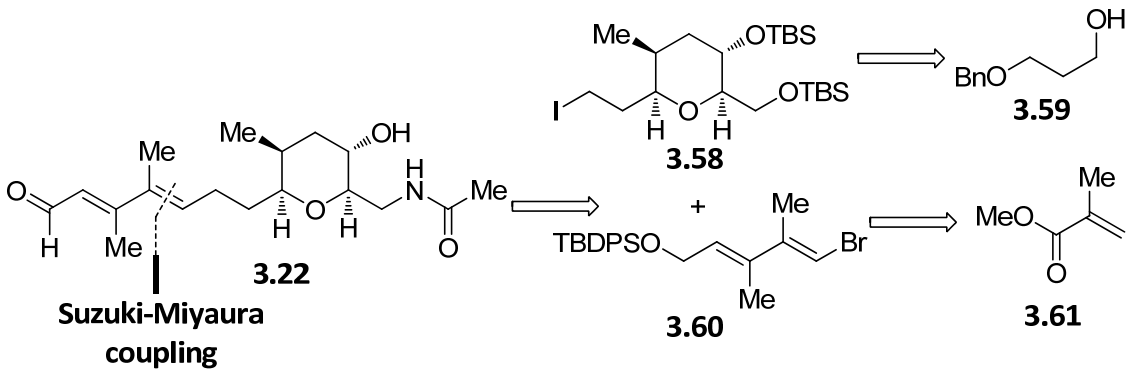
Modified Negishi coupling of fragment **3.48** and **3.49** in the presence of 10 mol% $Pd(PPh_3)_4$ and selective desilylation afforded diene **3.56** in 58% for two steps. Completion of the synthesis was acheieved by subjecting diene **3.56** to Mitsunobu conditions (80% yield), azide reduction and acetylation of the resulting amine to afford amide **3.57** in 83% yield over three steps. Desilylation of **3.57** with TBAF and chemoselective oxidation of the allylic alcohol with MnO_2 provided brevisamide (**3.22**) (Scheme 3.15).



Scheme 3.15. Lee and Panek's completion of the synthesis of brevisamide (**3.22**). *Reagents and conditions:* (a) *t*-BuLi, $ZnCl_2$, THF, -78 ^oC to 0 ^oC, $Pd(PPh_3)_4$; (b) CSA, MeOH, CH_2Cl_2, (58% yield 2-steps); (c) DIAD, PPh_3, DPPA, THF, 80%; (d) PPh_3, NH_4OH, dioxane/MeOH, rt; (e) Ac_2O, DMAP, TEA, CH_2Cl_2, rt, (83% yield 2-steps); (f) TBAF, THF, 83%; (g) MnO_2, CH_2Cl_2, rt, 66%.

Recently, Satake and co-workers reported an improved synthesis of brevisamide, in an aim to develop a more efficinet route to the ether ring fragment and improve the yield of their key step (Suzuki-Miyaura coupling reaction).[45] In their current strategy, the Suzuki-Miyaura coupling pyran ring iodide fragment **3.58** was prepared from 3-

benzyloxy-propan-1-ol **3.59**, while bromodienol fragment **3.60** was prepared from methacrylate **3.61** (Scheme 3.16).

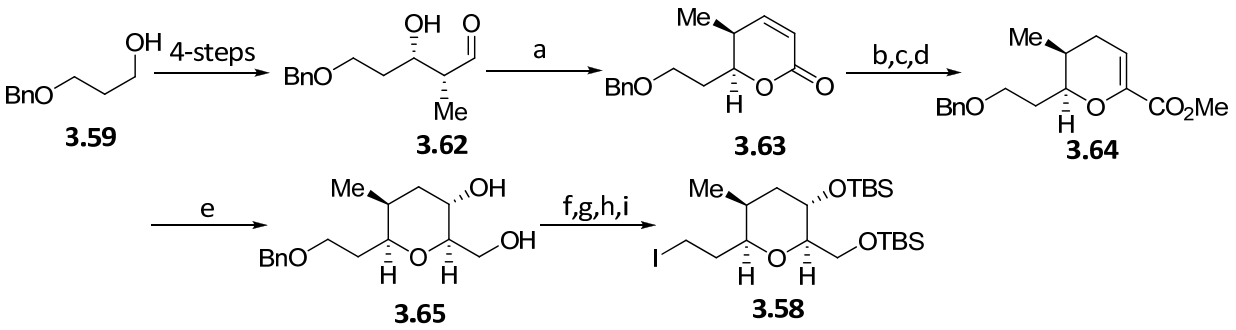


Scheme 3.16. Satake and Tachibana's new retrosynthesis of brevisamide (**3.22**).

The synthesis of pyran ring **3.58** began from β-hydroxyaldehyde **3.62** which was preapred in four steps from 3-benzyloxy-propan-1-ol **3.59**. Horner-Wadsworth-Emmons (HWE) reaction of **3.62** with $(PhO)_2P(O)CH_2CO_2Me$ in the presence of excess NaH afforded α,β-unsaturated lactone **3.63** in 71% yield. Hydrogenation, triflation and palladium catalyzed carbonylation gave oxene carboxylate **3.64**. DIBALH reduction and subsequent hydroboration gave diol **3.65** as single isomer. Bis-silylation of the diol with TBSCl, followed by benzyl deprotection and conversion of the primary alcohol gave the desired iodide fragment **3.58** (Scheme 3.17).

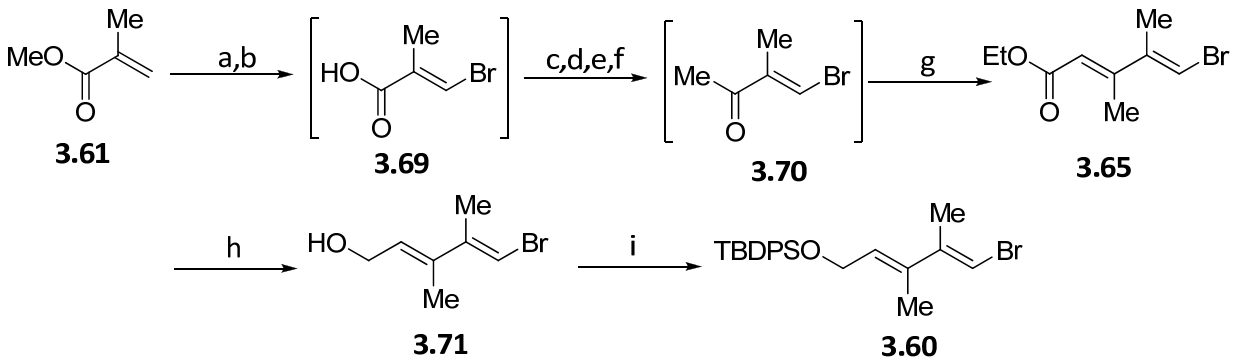
Bromodienol fragment **3.60** was prepared from methyl methacrylate **3.61** (Scheme 3.18). Bromination, dehydrobromination, hydrolysis, allylic oxidation, Grignard addition, MnO_2 allylic oxidation and finally Horner-Wadsworth-Emmons (HWE) reaction gave the desired (*E*,*E*)-dienoate **3.65** in 31% from **3.61** without purification.

DIBALH reduction of the (*E*,*E*)-dienoate **3.65**, followed by silyl protection of the resulting alcohol gave the bromodienol side chain fragment **3.60** in excellent yield.



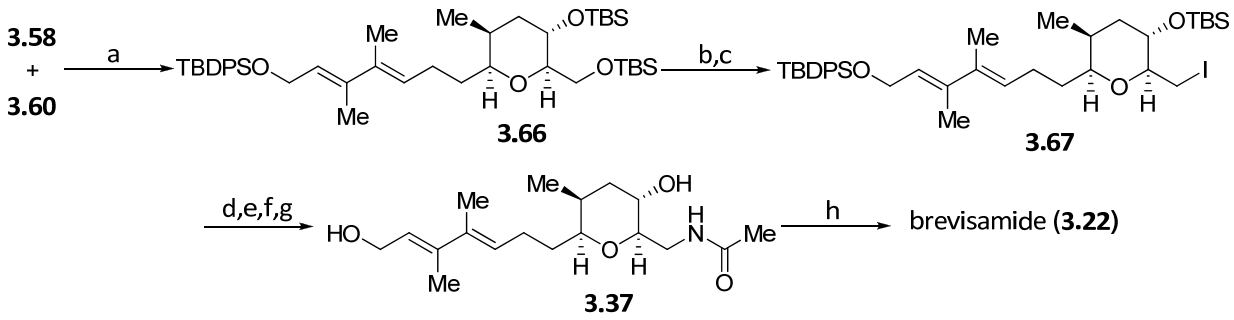
Scheme 3.17. Synthesis of Suzuki-Miyaura coupling fragment pyran ring **3.58**.

Reagents and conditions: (a) $(PhO)_2P(O)CH_2CO_2Me$ (1.2 equiv), NaH (1.5 equiv), THF, -78 to 0 ^oC, 71%.; (b) H_2, Pd/C, EtOAc, rt, 98%; (c) $PhNTf_2$, KHMDS, DMPU, THF, -78 to 0 ^oC; (d) CO, Et_3N, $Pd(PPh_3)_4$, DMF/MeOH, rt, 88% for two steps; (e) DIBALH, CH_2Cl_2, -78 to 0 ^oC, 88%; (f) $BH_3.SMe_2$, THF, 0 ^oC; then 3 M NaOH aq, 30% H_2O_2 aq, 45 ^oC, 86%; (g) TBSCl, imidazole, DMF, rt, 95%; (h) LiDBB, THF, -78 ^oC, 82%; (i) I_2, PPh_3, imidazole, toluene, 91%.



Scheme 3.18. Synthesis of Suzuki-Miyaura coupling fragment bromodienol **3.60**. (a) Br_2, CCl_4, 0 ^oC to rt; (b) NaOH, THF/H_2O, 0 ^oC to rt; (c) $LiAlH_4$, ether, 0 ^oC to rt; (d) MnO_2, ether, rt, (e) MeMgBr, ether, 0 ^oC; (f) MnO_2, ether, rt; (g) $(EtO)_2P(O)CH_2COOEt$, *n*-BuLi, THF, 0 ^oC to rt, **3.65** 31%, for seven steps; (h) DIBALH, CH_2Cl_2, -78 ^oC, 98%; (i) TBDPSCl, imidazole, DMF, 0 ^oC to rt, 99%.

Suzuki-Miyaura coupling of fragments **3.60** and **3.58** gave the desired cross-coupled product **3.66** in 64% yield. Selective desilylation of **3.66**, followed by treatment with I_2 in the presence of PPh_3 and imidazole gave the desired iodide **3.67**. Conversion of iodide to azide, followed by reduction to amine, acetylation and desilylation gave dienol **3.37** in 89% yield over four steps. Finally, oxidation of the allylic alcohol with TEMPO and $PhI(OAc)_2$ gave brevisamide **3.22** in 88% yield (Scheme 3.19). Brevisamide (**3.22**) was screened against mouse lymhoid P388 cells. It showed only weak cytotoxity at 30 μg/mL and no symptoms were noticed against the mice even at 3 mg/kg.



Scheme 3.19. Satake and Tachibana's second synthesis of brevisamide (**3.22**). *Reagents and conditions:* (a) B-OMe-9-BBN, *t*-BuLi, Et_2O/THF, -78 ^oC to rt, then 3 M, Cs_2CO_3, $PdCl_2$(dppf), aq. DMF, 64%; (b) CSA, CH_2Cl_2/MeOH, 0 ^oC, 85% brsm; (c) I_2, PPh_3, imidazole, toluene, rt, 90%; (d) NaN_3, DMF, rt; (e) PPh_3, THF, rt; then H_2O, 50 ^oC; (f) Ac_2O, pyridine, rt; (g) TBAF, THF, 0 ^oC to rt, 89% for four steps; (h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 88%.

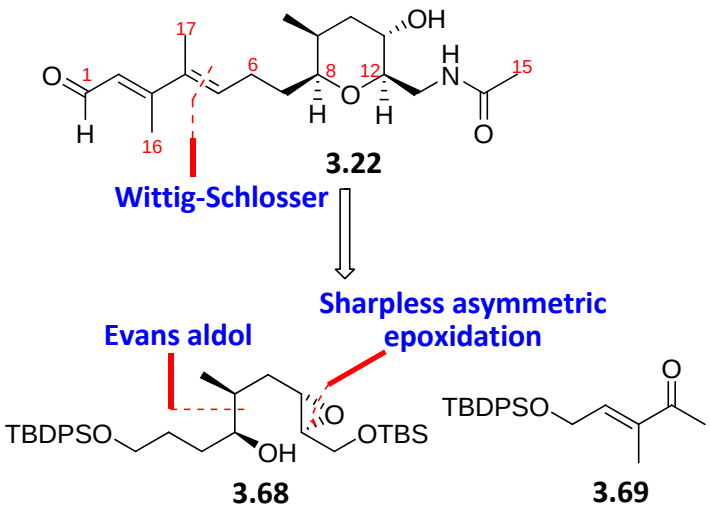
Due to the unique properties of marine polycyclic ether natural products and the crucial role of brevisamide (**3.22**) could play in understanding the process of initiation of ladder frame formations. We have embarked on the total synthesis of brevisamide (**3.22**). In addition, we plan to employ feeding experiments, where we intend to utilize isotopic labeled brevisamide as a precursor to better understand the formation or the biosynthesis of these complex toxin structures. We also envisioned that pharmacological screening could be performed on this congener as well as unnatural analogs that we plan to synthesize.

Shortly, after we initiated our campaign towards the total synthesis of brevisamide (**3.22**), Satake and co-workers who reported the isolation disclosed the first total synthesis and structural confirmation, within months of the publication. Their synthesis proceeded in 28 total synthetic steps, with the linear sequence of 21 steps, for an overall yield of

0.23% from cis-but-2-ene diol. From our perspective a more concise approach and improved overall yield to brevisamide (**3.22**) is required.

3.6. Retrosynthetic analysis

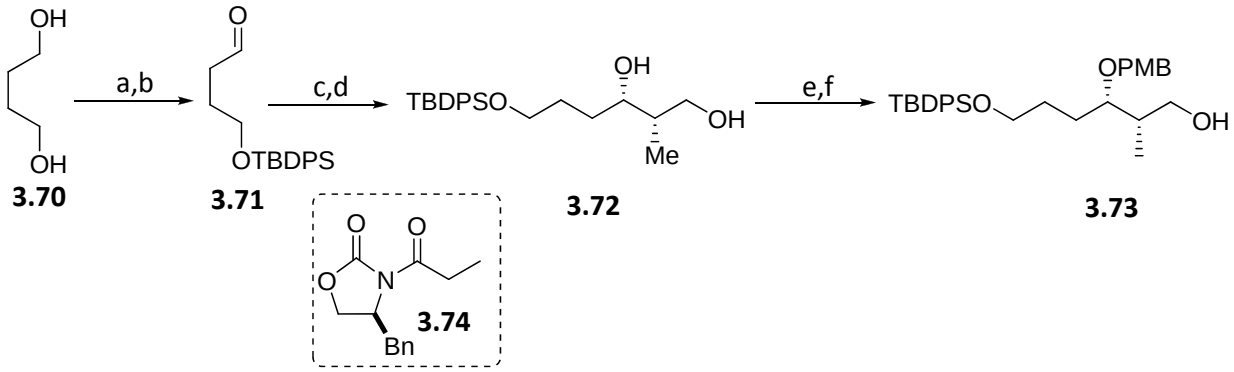
The biosynthetic hypothesis proposed by by Satake and co-workers guided the retrosynthetic analysis of brevisamide (**3.22**).[41] The approach involves an intramolecular S_N2 cyclization of the hydroxyl group into the epoxide of alcohol **3.68** and Wittig-Schlosser reaction to generate the E-geometry of C_4-C_5 of brevisamide **3.22** (Scheme 3.20). The hydroxyl group could be installed via an Evans aldol reaction[46] and the epoxide via Sharpless asymmetric epoxidation[47] (Scheme 3.20).



Scheme 3.20. Restrosynthetic analysis of brevisamide (**3.22**) based on proposed biosynthesis.

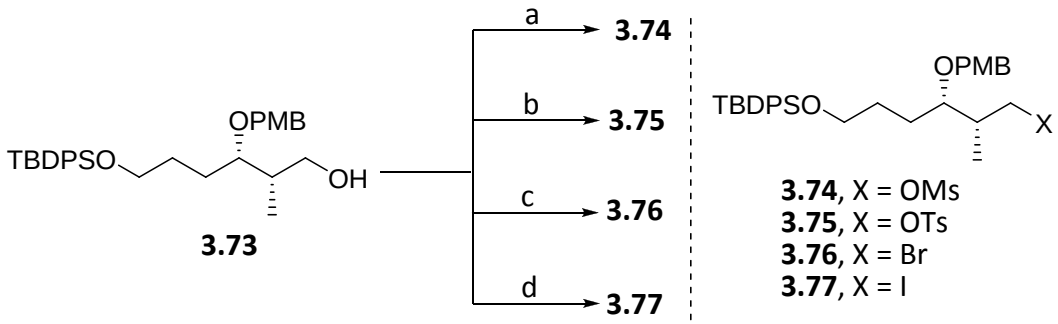
The synthesis of **3.68** began with the monoprotection of diol **3.70**, followed by Swern oxidation to give aldehyde **3.71**. Evans aldol reaction[46] of the aldehyde **3.71** and oxazolidinone **3.72** provided the desired *syn*-aldol adduct auxillary in 89% yield, which

was reductively removed with $LiBH_4$ to give diol **3.72** in 93% yield. The diol was protected as the *p*-methoxybenzylidene acetal, and later reduced regioselectively with DIBALH to afford primary alcohol **3.73** in 91% yield for the two steps (Scheme 3.21).[25]

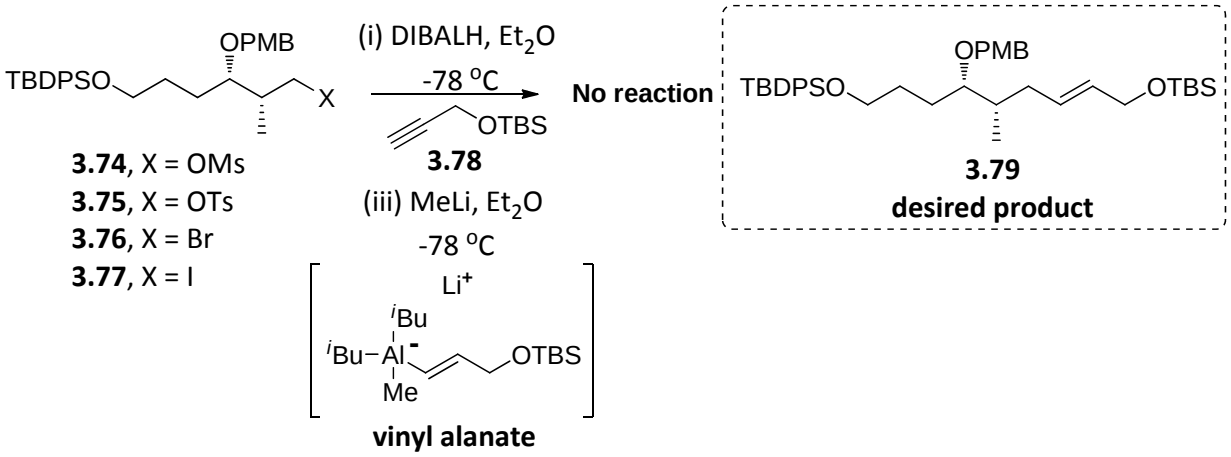


Scheme 3.21. Synthesis of alcohol **3.73**. *Reagents and conditions:* (a) TBDPSCl, Imidazole, DMF, 0 ^oC, 3 h; (b) $(COCl)_2$, Me_2SO Et_3N, CH_2Cl_2, -78 ^oC, (c) 92 %; **3.74**, *n*-Bu_2BOTf, Et_3N, 89%; (d) $LiBH_4$, THF, 93%; CH_2Cl_2 -78 to 0 ^oC; (e) *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, rt;
(f) DIBALH, CH_2Cl_2 -78 to 0 ^oC

At this juncture, we envisioned to install a silyl propargyl ether by displacement of a leaving group. To that end the C_{17} hydroxyl group was functionalized to different leaving groups (**3.74-3.77**) (Scheme 3.22). Our first approach towards the displacement of the leaving group utilizes carbo-alumination reaction. It was thought that the vinyl ate-complex generated from alkyne **3.78** would cause the displacement to proceed smoothly. Unfortunately, all attempts for form the desired product **3.79** via carbo-alumination reaction were unsuccessful (Scheme 3.23).



Scheme 3.22. Synthesis of **3.74-3.77**. *Reagents and conditions:* (a) MsCl, Pyridine, 96%; (b) TsCl, Pyridine, 92%; (c) NBS, CH_2Cl_2, 86%; (d) I_2, PPh_3, 83%.

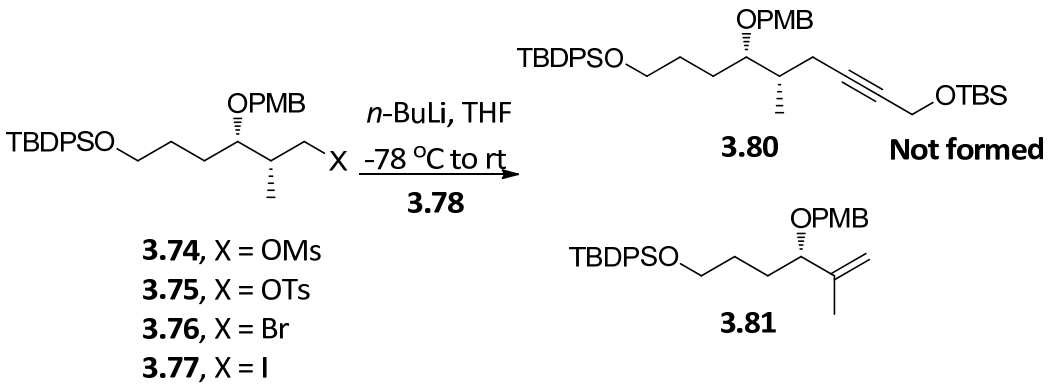


Scheme 3.23. Synthesis of allylic alcohol **3.79** via carbo-alumination reaction.

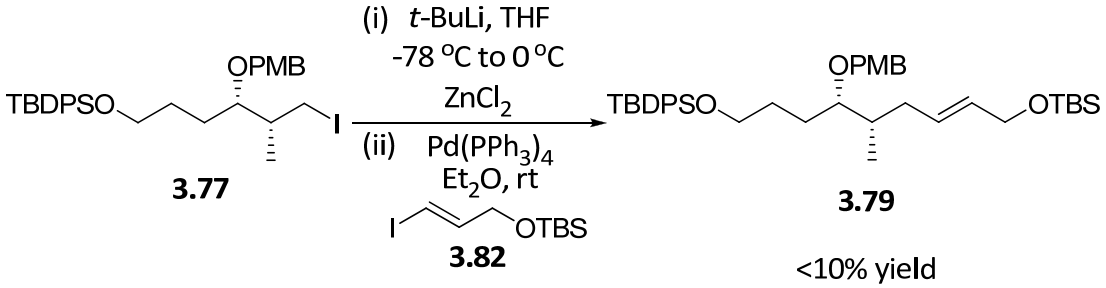
We then attempted to form **3.79** by simple displacement using lithiated alkyne **3.78** and subsequent reduction of the alkyne **3.80**. In all cases the desired product was not formed, only trace amounts of the eliminated side-product **3.81** or complex mixtures were observed (Scheme 3.24).

Since the displacement proved difficult, we decided to install the silyl propargyl ether via Negishi coupling.[48] We relied on the single one-pot procedure of Negishi coupling involving transmetallation to Zn^{II} species of lithiated **3.77** followed by Pd(0)-mediated coupling of vinyl halide **3.82** to give **3.79**. Subjecting 3.77 and 3.82 to Negishi

coupling conditions provide the desired product but in low yield (<10% yield) (Scheme 3.25).



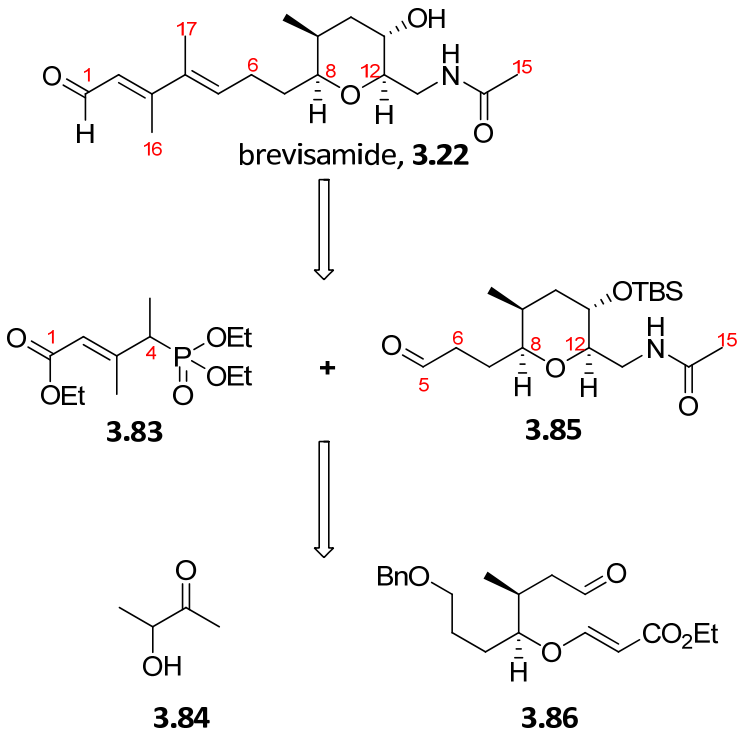
Scheme 3.24. Synthesis of allylic alcohol **3.79** via S_N2 displacement.



Scheme 3.25. Synthesis of allylic alcohol **3.79** via Negishi coupling reaction.

Due to the failed attempts to incorporate the silyl propargyl ether, a revised retrosynthetic plan was developed. Scheme 3.26 illustrates a revised retrosynthetic plan inspired by the synthesis of brevenal by Takamura and co-worker.[49] We envisioned the western C_1-C_4 side chain would be installed through a Horner-Emmons-Wadsworth reaction[50] utilizing **3.83**, prepared from commercially available **3.84**. Key pyran **3.85**, the

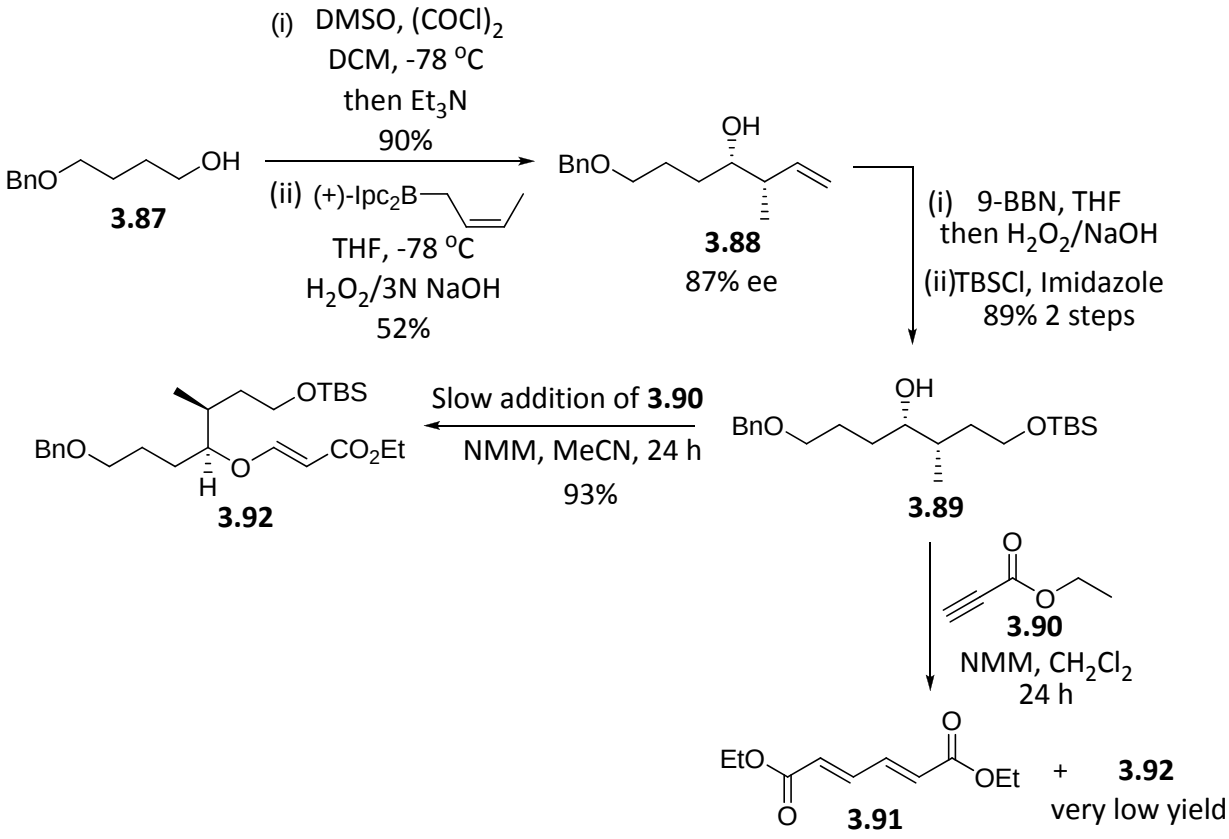
C_5-C_{15} fragment, was conceived to be derived from **3.86** through a SmI_2-mediated reductive cyclization reaction.[51]



Scheme 3.26. Revised retrosynthetic analysis of brevisamide (**3.22**)

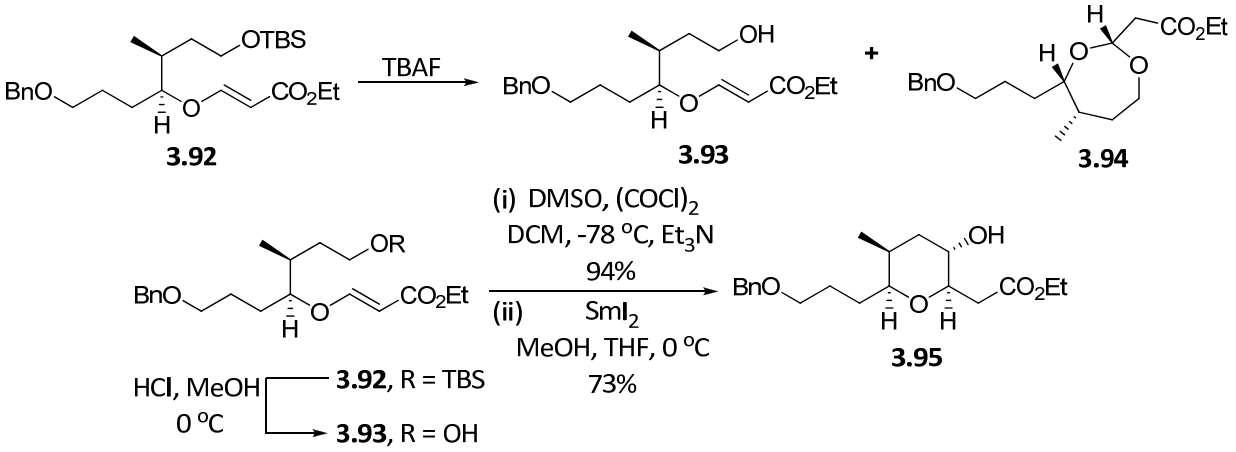
The synthesis of pyran **3.85** began with the Swern oxidation of monobenzyl protected-1,4-butane diol **3.87** to the corresponding aldehyde which was then subjected to a Brown crotylation reaction to afford **3.88** as a single diastereomer in 87% ee (Scheme 3.27).[52] Hydroboration and chemoselective TBS protection of the primary alcohol provided **3.89** in 89% yield for the two steps. 1,4-addition of alcohol **3.89** to ethyl propiolate **3.90** proved difficult, resulting in complex product mixtures and dienedioate **3.91** under a number of reaction conditions.[53] Ultimately, slow addition of ethyl

propiolate **3.90** via syringe pump over 24 h delivered the key intermediate **3.92** in 93% isolated yield (Scheme 3.27).[54]



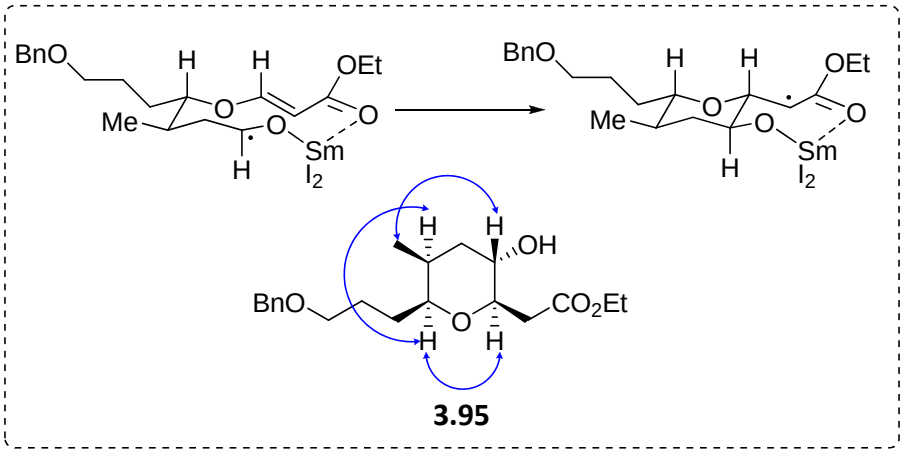
Scheme 3.27. Synthesis of acrylate **3.92**.

Removal of the TBS group proved equally problematic. Upon exposure to TBAF, a 1:1 mixture of the desired **3.93** and an unanticipated 1,3-dioxepane **3.94** formed. While separable, this undesired side product was detrimental at this stage of the synthesis. After surveying a variety of reaction conditions, we found that addition of a few drops of concentrated HCl in MeOH at 0 °C smoothly delivered the alcohol **3.93** in quantitative yield. Swern oxidation proceeded uneventfully delivering the key template **3.86** for the reductive cyclization in 94% yield (Scheme 3.28).[51]



Scheme 3.28. Synthesis of tetra-substituted pyran **3.95**.

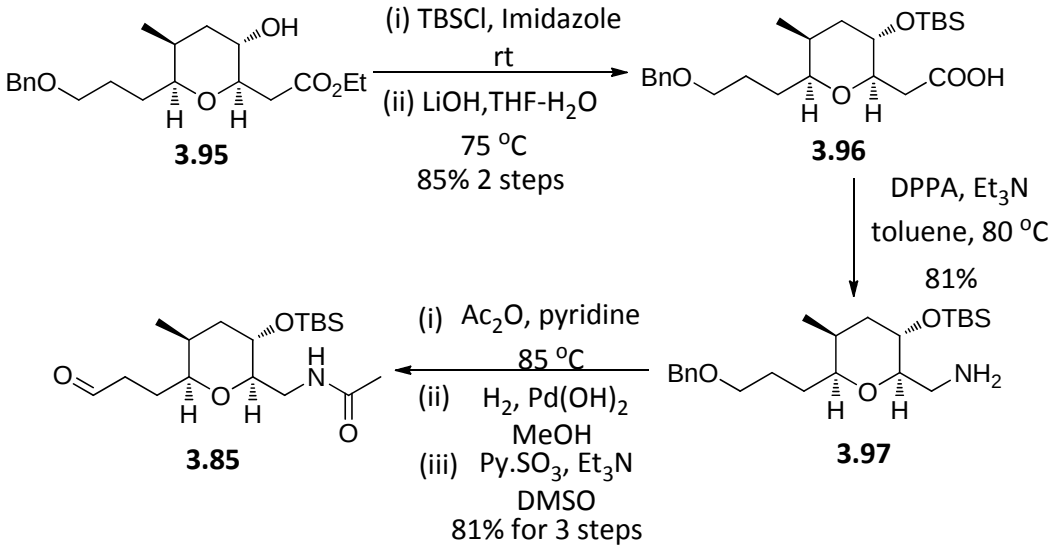
Exposure of the key hydroxy ester **3.86** to SmI_2 provided the desired pyran **3.95** in 73% yield. The relative stereochemistry of **3.95** was assigned by NMR and NOE analysis and in agreement with literature precedent (Scheme 3.29).[51]



Scheme 3.29. NOE Analysis of Pyran **3.95**.

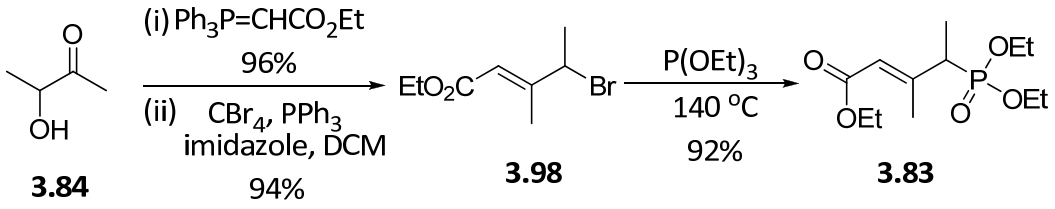
Once in hand, the secondary alcohol of **3.95** was protected and the ester hydrolyzed to produce acid **3.96** in 85% yield for the two steps. Curtius rearrangement with $(PhO)_2P(O)N_3$ (DPPA) provided the aminomethyl congener **3.97** in 81% yield

(Scheme 3.30).[55] Finally, an acetylation, benzyl deprotection, and oxidation sequence afforded target pyran **3.85**, the C_5-C_{15} fragment, in 81% yield for the three steps (Scheme 3.30).[54]



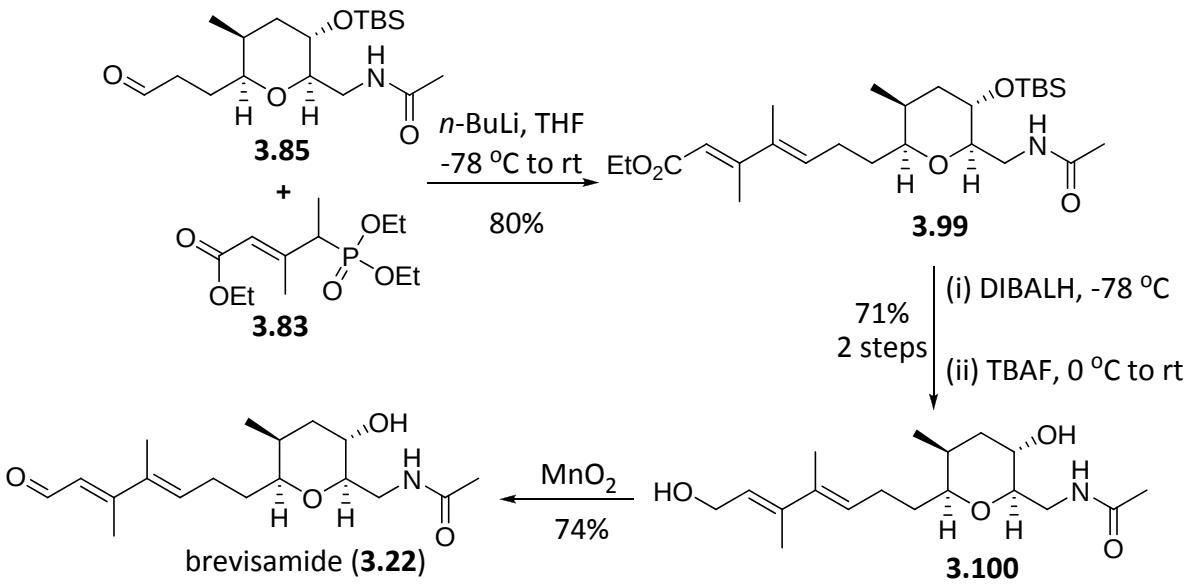
Scheme 3.30. Synthesis of key Horner-Emmons-Wadsworth fragment pyran **3.85**.

Attention now focused on the synthesis of phosphonate ester **3.83**.[49] As shown in Scheme 3.31, a Wittig reaction[56] with 3-hydroxybutan-2-one **3.84**, and subsequent bromination, generated the secondary bromide **3.98** in 94% yield. Application of an Arbuzov reaction delivers the key phosphonate ester **3.83**, the C_1-C_4 side chain, in 92% yield.[49,57]



Scheme 3.31. Synthesis of phosphonate ester **3.83**.

The Horner-Wadsworth-Emmons reaction[50] between the C_1-C_4 fragment **3.83** and the C_5-C_{15} fragment **3.85** proceeded well, installing the conjugated 3,4-dimethyl-2,4-dienal moiety and delivering **3.99** in 78% yield (Scheme 3.32). DIBALH reduction of the ester to the corresponding allylic alcohol[49] and TBAF-mediated deprotection of the secondary TBS ether delivered **3.100**, the direct precursor to brevisamide **3.22**, in 71% yield for the two steps. A final MnO_2 oxidation of the allylic alcohol produced the natural product brevisamide **3.22** in 74% yield (Scheme 3.32). The synthetic **3.22** exhibited physical and spectroscopic data identical to that of the natural brevisamide and that of the previously prepared synthetic brevisamide **3.22**.[41,58]

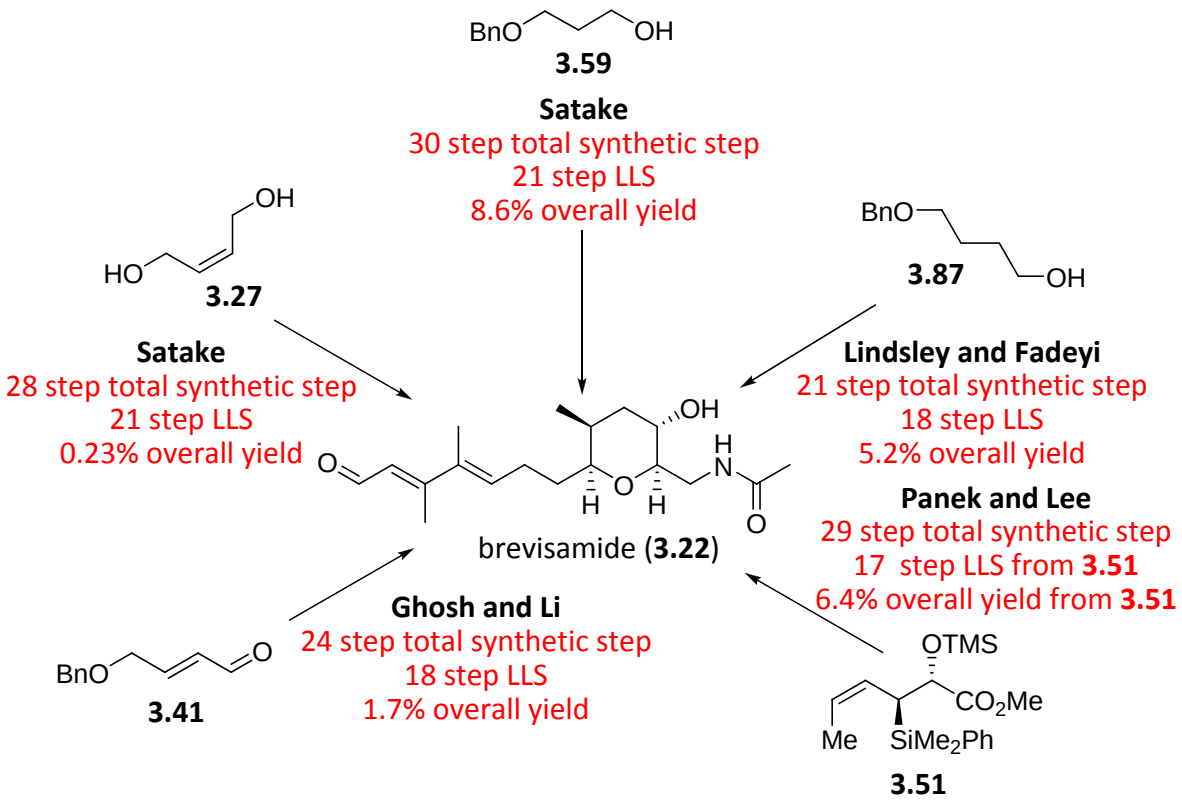


Scheme 3.32. Completion of the synthesis of brevisamide (**3.22**).

3.7. Conclusion

Thus, the second total synthesis of brevisamide (**3.22**) has been accomplished in 21 synthetic steps, with 18 steps longest linear sequence, and an overall yield from monobenzyl protected-1,4-butane diol **3.87** of 5.2%. Noteworthy synthetic steps from this route include a SmI_2 reductive cyclization to generate the highly functionalized pyran **3.95** and a Horner-Wadsworth-Emmons reaction to assemble the western C_1-C_4 **3.83** and eastern C_5-C_{15} **3.85** fragments.

As discussed earlier, Satake, Ghosh and Panek have independently completed the synthesis of brevisamide (**3.22**). As shown below in Scheme 3.33 our route this route appears to be the most efficient, with fewer steps and highest overall yield (Scheme 3.33).



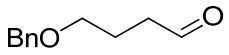
Scheme 3.33. Summary of the synthesis of brevisamide (**3.22**).

Experimental Methods

General. All ^{1}H & ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz)**,** Bruker AV-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). IR spectra were recorded as thin films and are reported in wave-numbers (cm^{-1}). Low resolution mass spectra were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra were recorded on a Waters Qtof-API-US plus Acquity system. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(ME - MT)/ MT] \times 10^6$, where ME is the experimental mass and MT is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference. Analytical thin layer chromatography was performed on 250 μM silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. Analytical HPLC was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral HPLC was performed on an Agilent 1200 Series HPLC utilizing a Chiracel OD, OJ or Chiralpak AD columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical

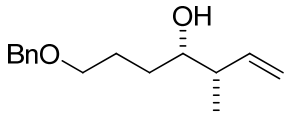
Co. and were used without purification. All polymer-supported reagents were purchased from Biotage, Inc. Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Mass spectra were obtained on a Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data.

Experimental Section for Brevisamide



4-(benzyloxy)butanal.

Oxalyl chloride (14 mL, 161.3 mmol) was dissolved in 300 mL of CH_2Cl_2 at -78°C. DMSO (14.6 mL, 205 mmol) in 75 mL CH_2Cl_2 was added dropwise. The mixture was stirred for 20 minutes at -78°C. 4-benzyloxy-butan-1-ol **3.87** (13.2 g, 73.3 mmol) was added drop-wise. After stirring for 20 minutes, triethylamine (48.2 mL, 354.2 mmol) was added dropwise via syringe. The cooling bath was removed after 5 minutes, and the reaction was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc and washed NH_4Cl and then brine, the combine organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification through a short plug of silica gel (EtOAc/hexanes 1:4) yielded 11.7 g (90%) 4-(benzyloxy)-butanal **66** as a clear oil. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 9.78 (d, J = 1.6 Hz, 1H) 7.36-7.26 (m, 5H), 4.49 (s, 2H), 3.51 (t, J = 6.0 Hz, 2H), 2.55 (dt, J = 7.2, 1.6 Hz, 2H), 1.98-1.92 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 202.2, 138.2, 128.3, 127.5, 72.9, 69.1, 40.8, 22.5; HRMS (TOF, ES+) $C_{11}H_{14}O_2$ $[M+H]^+$ calc'd 179.1072, found 179.1072.

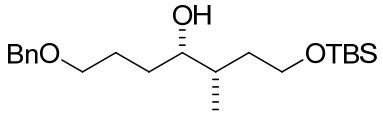


(3S,4S)-7-(benzyloxy)-3-methylhept-1-en-4-ol (3.88).

To a solution of potassium *tert*-butoxide (4.3 g, 38.3 mmol) in THF (20 mL) was added Z-butene (5 mL, 100 mmol) *via* a cannula at -78°C. ^{n}BuLi (16 mL, 1.6 M in hexane, 25.6 mmol) was added and the reaction was stirred at -78°C for 5 minutes and then stirred at -45°C for 15 minutes. The reaction was then cooled back to -78°C and (+)-B-methoxydi-isopinocampheylborane (12.5 g, 34.3 mmol) in Et_2O (30 mL) *via* syringe pump. After stirring for 30 minutes, $BF_3 \cdot Et_2O$ (6.25 mL, 49.3 mmol) was added, followed by a solution of aldehyde (6.0 g, 33.7 mmol) in THF (18 mL) *via* syringe pump. The reaction mixture was allowed to stir at -78°C for 3 h before 3 M solution of NaOH (15 mL) and 15 mL of 30% H_2O_2 were slowly added, and the mixture was allowed to stir overnight at room temperature.

The mixture was then extracted Et_2O (5 x 30 mL) and the combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Caranol was removed through distillation under full vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes) to give homoallylic alcohol **3.88** as colorless oil (4.1 g, 52%). The optical purity was assessed to be 87% *ee* by derivation to the corresponding MPTA ester. $[\alpha]_D^{20}$ -22.5 (*c* 0.2, $CHCl_3$); R_f = 0.75 (4:1 hexanes/EtOAc); IR (neat) 3600-3200 (brs), 3066, 3031, 2926, 2867, 1811, 1639, 1454, 1364, 1099, 997, 912, 736, 697 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.36-7.26 (m, 5H), 5.79 (m, 1H), 5.09-5.04 (m, 2H), 4.52 (s, 2H), 3.51 (t, *J* = 5.9 Hz 2H), 3.48-3.46 (m, 1H), 2.31-2.23 (m,

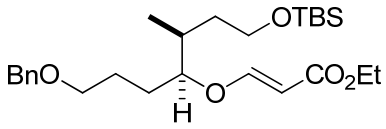
1H), 2.15 (brs, 1H), 1.84-1.63 (m, 3H), 1.46-1.37 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 141.1, 138.2, 128.3, 127.6, 127.6, 114.9, 74.5, 72.9, 70.4, 43.6, 31.3, 26.5, 14.5; HRMS (TOF, ES+) $C_{15}H_{22}O_2$ $[M+H]^+$ calc'd 235.1698, found 235.1689.



(3S,4S)-7-(benzyloxy)-1-(tert-butyldimethylsilyloxy)-3-methylheptan-4-ol (3.89).

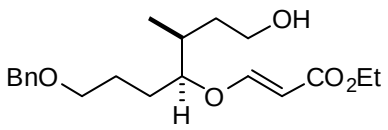
To a solution of **3.88** (4.0 g, 17.1 mmol) at 0^{o}C was added 9-BBN (89 mL, 0.5 M in THF, 44.5 mmol) slowly. The reaction was allowed to stir at rt overnight. The reaction was cooled in ice-bath and 3 M NaOH (24 mL) was added dropwise followed by 30% H_2O_2 (24 mL) added dropwise. The mixture was stirred at 0^{o}C for 1 h and overnight at room temperature. The reaction was diluted with water and extracted with EtOAc (5 x 30 mL) and the combined organic layer was washed with sat. $NaHCO_3$, brine dried over Na_2SO_4 and concentrated to give the crude diol. To a solution of the crude diol in CH_2Cl_2 (250 mL) at 0^{o}C was added imidazole (2.33 g, 34.2 mmol) and TBSCl (2.6 g, 17.0 mmol). After stirring at rt for 2 h, water was added. The organic was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by SiO_2 chromatography (4:1 to 1:1 EtOAc/hexanes) affords the alcohol **3.89** as colorless oil (5.57 g, 89%). $[\alpha]_D^{20}$ -8.4 (*c* 0.2, $CHCl_3$); R_f = 0.31 (4:1 EtOAc/hexanes); IR (neat) 3435, 2954, 2929, 2857, 1474, 1454, 1255, 1096 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.34-7.26 (m, 5H), 4.51 (s, 2H), 3.77-3.71 (m, 1H), 3.67-3.61 (m, 1H), 3.56-3.47 (m, 3H), 2.75 (brs, 1H), 1.87-

1.78 (m, 1H), 1.76-1.64 (m, 3H), 1.59-1.43 (m, 3H), 0.89 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 128.3, 127.6, 127.5, 74.1, 72.8, 70.5, 61.4, 36.4, 36.2, 30.9, 26.8, 25.8, 13.8, -5.5; HRMS (TOF, ES+) $C_{21}H_{38}O_3Si$ $[M+H]^+$ calc'd 367.2668, found 367.2668.



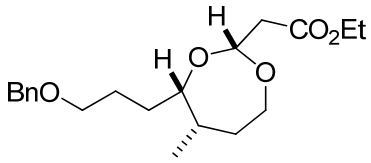
(E)-ethyl-3-((3S,4S)-7-(benzyloxy)-1-(tert-butyldimethylsilyloxy)-3-methylheptan-4-yloxy)acrylate (3.92).

To a solution of secondary alcohol **3.89** (1.2 g, 3.28 mmol) in CH_3CN (3.5 mL) was added N-methyl morpholine (72 μL, 0.656 mmol). To the stirred solution was added slowly ethyl propiolate *via* syringe pump over 24 h at room temperature. Concentration and flash chromatography on silica gel (Hex/EtOAc, 4:1) afforded β-alkoxyacrylate **3.92** (1.41 g, 93%). $[\alpha]_D^{20}$ -1.8 (*c* 0.2, $CHCl_3$); R_f = 0.5 (4:1 hexanes/EtOAc); IR (neat) 3031, 2929, 2862, 1707, 1648, 1487, 1375, 1132, 1095, 1072 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J* = 12.4 Hz, 1H), 7.37-7.28 (m, 5H), 5.23 (d, *J* = 12.4 Hz, 1H), 4.50 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.82-3.80 (m, 1H), 3.69-3.57 (m, 2H), 3.48-3.43 (m, 2H), 1.97-1.85 (m, 1H), 1.73-1.58 (m, 5H), 1.37-1.31 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 168.2, 163.3, 138.4, 128.3, 127.6, 127.5, 96.8, 88.2, 72.9, 69.8, 60.8, 59.5, 35.3, 33.2, 27.9, 25.9, 25.8, 18.2, 14.3, 14.2, -5.3, -5.4; HRMS (TOF, ES+) $C_{26}H_{44}O_3Si$ $[M+H]^+$ calc'd 465.3036, found 465.3037.



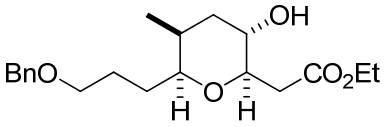
(E)-ethyl 3-((3S,4S)-7-(benzyloxy)-1-hydroxy-3-methylheptan-4-yloxy)acrylate (3.93).

To a solution of β-alkoxyacrylate **3.92** (1.0 g, 2.15 mmol) in MeOH (10 mL) at 0°C was added conc. HCl (3 drops). After stirring for 1 h at 0°C, the reaction mixture was neutralized with Et_3N (0.5 mL) and concentrated in vacuo. The solid was dissolved in EtOAc and washed with sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product purified by SiO_2 chromatography (1:1 EtOAc/Hex) to give alcohol **3.93** as a colorless liquid (751 mg, 99.8%). $[\alpha]_D^{20}$ -5.5 (*c* 0.2, $CHCl_3$); R_f = 0.39 (1:1 hexanes/EtOAc); IR (neat) 3449, 3030, 2929, 2862, 1707, 1450, 1369, 1305, 1262, 1180, 1087, 739 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J* = 12.4 Hz, 1H), 7.37-7.26 (m, 5H), 5.24 (d, *J* = 12.4 Hz, 1H), 4.49 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.86-3.82 (m, 1H), 3.74-3.62 (m, 2H), 3.51-3.45 (m, 2H), 1.95.1.88 (m, 1H), 1.72-1.55 (m, 5H), 1.46-1.37 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.9, 138.5, 128.3, 127.6, 127.4, 98.6, 80.9, 72.8, 70.1, 60.4, 60.3, 40.4, 36.4, 35.1, 30.1, 26.6, 14.1, 12.6; HRMS (TOF, ES+) $C_{20}H_{30}O_5$ $[M+Na]^+$ calc'd 373.1991, found 373.1992.



ethyl 2-((2R,4S,5S)-4-(3-(benzyloxy)propyl)-5-methyl-1,3-dioxepan-2-yl)acetate (3.94).

$[\alpha]_D^{20}$ -1.0 (*c* 0.2, $CHCl_3$); IR (neat) 3031, 2939, 1738, 1636, 1368, 1051 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.34-1.26 (m, 5H), 5.11 (t, *J* = 6.0 Hz, 1H), 4.49 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.91-3.85 (m, 1H), 3.7-3.59 (m, 2H), 3.53-3.42 (m, 2H), 2.65-2.55 (m, 2H), 1.91-1.85 (m, 2H), 1.77-1.71 (m, 1H), 1.69-1.55 (m, 2H), 1.53-1.42 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.9, 138.5, 128.3, 127.6, 127.4, 98.6, 80.9, 72.8, 70.1, 60.4, 60.3, 40.4, 36.4, 35.1, 30.1, 26.6, 14.1, 12.6; HRMS (TOF, ES+) $C_{20}H_{30}O_5$ $[M+Na]^+$ calc'd 373.1991, found 373.1992.



ethyl 2-((2R,3S,5S,6S)-6-(3-(benzyloxy)propyl)-3-hydroxy-5-methyltetrahydro-2H-pyran-2-yl)acetate (3.95).

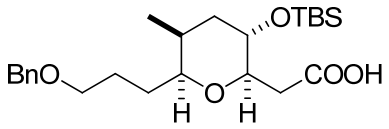
Oxalyl chloride (0.27 mL, 3.15 mmol) was dissolved in 2 mL of CH_2Cl_2 at -78°C. DMSO (0.3 mL, 0.34 mmol) in 1 mL CH_2Cl_2 was added dropwise. The mixture was stirred for 20 minutes at -78°C. Alcohol **3.93** (500 mg, 1.43 mmol) was added drop-wise. After stirring for 20 minutes, triethylamine (0.96 mL, 6.91 mmol) was added dropwise via syringe. The cooling bath was removed after 5 minutes, and the reaction was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc and washed

NH_4Cl and then brine, the combine organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification through a short plug of silica gel (EtOAc/hexanes 1:1) yielded the desired aldehyde (467.7 mg, 94%).

$[\alpha]_D^{20}$ -17.7 (*c* 0.2, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 9.73 (s, 1H) 7.46 (d, *J* = 12.4 Hz, 1H), 7.35-7.26 (m, 5H), 5.25 (d, *J* = 12.4 Hz 1H), 4.49 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.89-3.85 (m, 1H), 3.53-3.43 (m, 2H), 2.57-2.51 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.44-2.39 (m, 1H), 2.35-2.29 (ddd, *J* = 16.4, 8.0, 1.6 Hz, 1H), 1.73-1.57 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 201.6, 167.9, 162.5, 138.3, 128.3, 127.6, 127.5, 97.5, 86.7, 72.9, 69.5, 59.7, 46.6, 31.2, 27.6, 25.9, 14.7, 14.3; HRMS (TOF, ES+) $C_{20}H_{28}O_5$ $[M+Na]^+$ calc'd 371.1834, found 371.1831.

To a solution aldehyde (100 mg, 0.28 mmol) in dried THF 10 mL under argon was added anhydrous MeOH (0.13 mL), the mixture was cooled to 0°C and 0.1 M SmI_2 in THF (8.3 mL, 8.4 mmol) was added dropwise. After stirring for 30 minutes at 0°C, the reaction was quench with 1:1 mixture of sat. $NaHCO_3/Na_2SO_3$. The mixture was concentrated, extracted with EtOAc and the combined organic layer was dried over Na_2SO_4. Flash chromatography on silica gel (Hex/EtOAc, 4:1) afforded pyran **3.95** (71.5 mg, 73%). $[\alpha]_D^{20}$ -5.3 (*c* 0.2, $CHCl_3$); R_f = 0.4 (1:1 hexanes/EtOAc); IR (neat) 3449, 3030, 2929, 2862, 1738, 1636, 1369, 1305, 1262, 1180, 1087, 739 cm^{-1}; ^1H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.35-7.31 (m, 4H), 7.29-7.26 (m, 1H), 4.49 (s, 2H), 4.15 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.57-3.51 (m, 1H), 3.50-3.43 (m, 3H), 3.42-3.39 (m, 1H), 2.81-2.78 (dd, *J* = 15.0, 4.8 Hz, 1H), 2.51-2.48 (dd, *J* = 15.0, 7.8 Hz, 1H), 1.99-1.96 (dm, 1H), 1.88-1.84 (m, 1H), 1.75-1.68 (m, 1H), 1.61-1.57 (m, 2H), 1.54-1.49 (m, 1H), 1.43-1.38

(m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 172.1, 138.6, 128.3, 127.5, 127.4, 79.8, 79.6, 72.7, 70.1, 67.0, 40.8, 46.6, 38.7, 32.9, 29.1, 26.4, 14.1, 12.6; HRMS (TOF, ES+) $C_{20}H_{30}O_5$ $[M+H]^+$ calc'd 351.2171, found 351.2174.

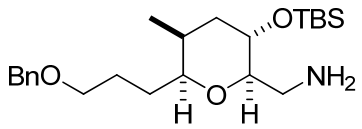


2-((2R,3S,5S,6S)-6-(3-(benzyloxy)propyl)-3-(tert-butyldimethylsilyloxy)-5-methyltetrahydro-2H-pyran-2-yl)acetic acid (3.96).

To a solution of pyran **3.95** (42.7 mg, 0.12 mmol) in DMF (1.5 mL) was added TBSCl (56.8 mg, 0.38 mmol) and imidazole (25.7 mg, 0.38 mmol). The reaction mixture was stirred at rt overnight, quench with H_2O and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated to give TBS-protected ester. To a solution of the crude ester in THF (1.5 mL) and H_2O (1.5 mL) was added $LiOH \cdot H_2O$ (11.8 mg, 0.49 mmol). After stirring overnight at 75 °C, an additional amount of $LiOH \cdot H_2O$ (5.9 mg, 0.24 mmol) was added to the reaction mixture, and stirred overnight at the same temperature. The reaction mixture was cooled to 0^{o}C, diluted with EtOAc and carefully neutralized with 0.5 N HCl. The organic layer was combined and washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give the crude carboxylic acid. Purification by SiO_2 chromatography (10% EtOAc/Hex containing 0.5% AcOH) afforded carboxylic acid (**3.96**) as a colorless liquid (44.4 mg, 85% for 2 steps).

$[\alpha]_D^{20}$ 15.1 (*c* 0.2, $CHCl_3$); R_f = 0.297 (10% EtOAc/Hex containing 0.5% AcOH); IR (neat) 2929, 2856, 2360, 1714, 1421, 1111 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm):

7.39-7.2 (m, 5H), 4.51 (s, 2H), 3.58-3.44 (m, 5H), 2.87-2.83 (dd, J = 16.0, 3.2 Hz, 1H), 2.50-2.44 (dd, J = 16.0, 8.4 Hz, 1H), 1.88-1.87 (m, 2H), 1.74-1.44 (m, 4H), 1.36-1.32 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H); 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.2, 138.4, 128.3, 127.6, 127.4, 80.3, 79.3, 72.8, 69.9, 67.0, 40.7, 37.3, 32.6, 29.1, 26.3, 25.6, 17.8, 12.6, -4.2, -4.8; HRMS (TOF, ES+) $C_{24}H_{40}O_5Si$ $[M+H]^+$ calc'd 437.2723, found 437.2716.

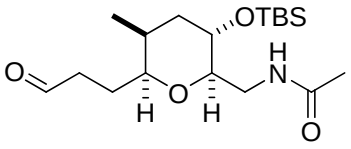


((2R,3S,5S,6S)-6-(3-(benzyloxy)propyl)-3-(tert-butyldimethylsilyloxy)-5-methyltetrahydro-2H-pyran-2-yl)methanamine (3.97).

To a solution of carboxylic acid **3.96** (250 mg, 0.57 mmol) in toluene (5 mL) were added Et_3N (0.25 mL, 1.79 mmol) and diphenyl phosphorazidate (DPPA) (0.25 mL, 1.16 mmol) and the mixture was stirred at rt for 30 min, then stirred at 80 °C for 4 h. The reaction mixture was concentrated and re-dissolved in THF (5 mL), 4N LiOH (2.8 mL) in H_2O was added and stirred for 1 h at rt. The mixture was diluted with water, extracted EtOAc. The organic layer was dried over Na_2SO_4, concentrated and purified by chromatography on silica gel (10% MeOH/CH_2Cl_2, containing 0.5% of Et_3N) to give amine **3.97** (188 mg, 81%) as a colorless oil.

$[\alpha]_D^{20}$ 15.8 (*c* 0.2, $CHCl_3$); R_f = 0.57 (10% MeOH/CH_2Cl_2); IR (neat) 3073, 2929, 2856, 1598, 1473, 1102 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm) 7.35-7.28 (m, 5H), 4.50 (s, 2H), 3.41-3.33 (m, 3H), 3.30-3.28 (m, 1H), 3.16-3.13 (m, 1H), 3.03 (dd, J = 12.6, 2.6 Hz, 1H), 2.48 (m, 1H), 1.85-1.73 (m, 2H), 1.70-1.63 (m, 1H), 1.57-1.44 (m, 2H), 1.41-

1.38 (m, 1H), 1.33-1.25 (m, 1H), 0.88 (d, J = 7.2 Hz, 3H), 0.85 (s, 9H), 0.03 (d, J = 4.4 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 138.4, 129.1, 128.3, 127.7, 127.5, 120.4, 79.4, 72.8, 70.2, 66.1, 40.7, 32.4, 28.9, 26.2, 25.7, 25.6, 17.8, 12.6, -4.2, -4.8; HRMS (TOF, ES+) $C_{23}H_{41}NO_3Si$ $[M+H]^+$ calc'd 408.2934, found 408.2935.

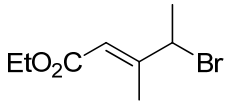


N-(((2R,3S,5S,6S)-3-(tert-butyldimethylsilyloxy)-5-methyl-6-(3-oxopropyl)tetrahydro-2H-pyran-2-yl)methyl)acetamide (3.85).

To a solution of amine **3.97** (90.3 mg, 0.22 mmol) in pyridine (2 mL) was added $(CH_3CO)_2O$, the mixture was warmed to 85^{o}C for 1 h. The reaction mixture was concentrated and purified by SiO_2 chromatography (Hex/EtOAc, 4:1) to afford the desired amide (93.8 mg, 95%). $[\alpha]_D^{20}$ 12.5 (c 0.2, $CHCl_3$); R_f = 0.29 (Hex/EtOAc, 4:1); IR (neat) 3437, 3073, 2929, 2856, 1653, 1589, 1104, 836, 776 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm) 7.36-7.26 (m, 5H), 5.82 (brs, 1H), 4.51 (s, 2H), 3.79-3.73 (m, 1H), 3.56-3.44 (m, 3H), 3.42-3.39 (m, 1H), 3.14-3.06 (m, 2H), 1.95 (s, 3H), 1.88-1.82 (m, 2H), 1.75-1.67 (m, 2H), 1.64-1.53 (m, 2H), 1.44-1.38 (m, 1H), 0.93 (d, J = 7.2 Hz, 3H) 0.88 (s, 9H), 0.06 (d, J = 9.2 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.7, 138.4, 128.3, 127.6, 127.5, 81.1, 79.5, 72.9, 70.1, 65.6, 41.4, 40.8, 32.5, 29.3, 26.5, 25.7, 23.3, 17.8, 12.6, -4.2, -4.9; HRMS (TOF, ES+) $C_{25}H_{43}NO_4Si$ $[M+H]^+$ calc'd 450.3040, found 450.3036.

To a solution of the benzyl ether (93.8 mg, 0.21 mmol) in MeOH (4 mL) was added $Pd(OH)_2/C$ (95 mg) and the mixture was stirred under H_2 atmosphere at room

temperature overnight. The catalyst was filtered off through a short silica gel column (EtOAc) and the filtrate was concentrated and purified on a short silica gel column to give the desired alcohol. $[\alpha]_D^{20}$ 47.5 (*c* 0.2, $CHCl_3$); IR (neat) 3437, 3345, 2927, 2856, 1633, 1599, 1109 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ 5.82 (brs, 1H), 3.87-3.82 (dm, 1H), 3.68-3.65 (m, 2H), 3.57-3.51 (m, 1H), 3.45-3.43 (m, 1H), 3.19-3.13 (m, 1H), 3.08-3.02 (m, 1H), 1.98 (s, 3H), 1.90-1.83 (m, 2H), 1.71-1.50 (m, 4H), 1.48-1.42 (m, 1H), 0.93 (d, *J* = 7.2 Hz, 3H) 0.88 (s, 9H), 0.06 (d, *J* = 9.2 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.8, 81.6, 80.1, 65.5, 62.4, 41.4, 40.8, 33.1, 29.8, 29.2, 25.7, 23.2, 17.9, 12.7, -4.2, -4.9; HRMS (TOF, ES+) $C_{18}H_{37}NO_4Si$ $[M+H]^+$ calc'd 360.2570, found 360.2565. To a solution of alcohol (75.2 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) and DMSO (2 mL) at 0 °C was added Et_3N (0.15 mL, 1.05 mmol) and SO_3·pyr. (133.7 mg, 0.84 mmol), and stirred for 1 hour at 0 °C. The mixture was diluted with EtOAc, and washed with sat. NH_4Cl, water and brine. Concentration gave the crude aldehyde **3.85** (63.6 mg, 81% for 3 steps), which was used for the next reaction directly.

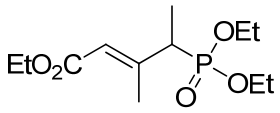


(E)-ethyl 4-bromo-3-methylpent-2-enoate (3.98).

A mixture of 3-hydroxy-2-butanone **3.84** (1 g, 11.3 mmol) and $Ph_3P{=}CHCO_2Et$ (4.72 g, 13.6 mmol) in toluene (15 mL) was refluxed overnight. The mixture was concentrated and purified by chromatography (hexane/EtOAc, 4:1 to 1:1) to give the desired ester (1.7 g, 96%) as yellow oil. R_f = 0.37 (1:1 EtOAc/hexanes); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.95 (d, *J* = 1.2 Hz, 1H), 4.26 (q, *J* = 6.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.12

(s, 3H), 1.31 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 166.9, 161.1, 113.9, 72.3, 59.7, 21.7, 14.8, 14.2; HRMS (TOF, ES+) $C_8H_{14}O_3$ $[M+H]^+$ calc'd 159.1021, found 159.1021. To a stirred solution of the hydroxyl ester (1.7 g, 10.8 mmol) obtained above, imidazole (1.03 g, 15.1 mmol) and PPh_3 (4.23 g, 16.1 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added CBr_4 (5.0 g, 15.1 mmol). After stirring for 1 hour at room temperature, the reaction was quenched with sat. Na_2SO_3, diluted with Et_2O, and washed with water and brine.

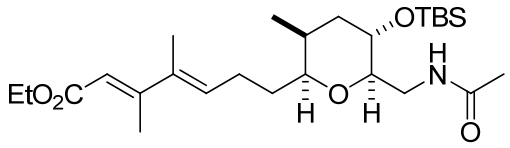
Concentration and chromatography (hexane/EtOAc, 20:1 to 4:1) gave bromide **3.98** (2.2 g, 90% for 2 steps): colorless oil; R_f = 0.58 (Hexane/EtOAc, 2:1); IR (neat) 2951, 1721, 1655, 1101, 1077 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.91 (s, 1H), 4.65 (q, J = 6.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.27 (d, J = 0.8 Hz, 3H), 1.80 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 156.7, 116.7, 60.0, 53.3, 23.7, 14.9, 14.2; HRMS (TOF, ES+) $C_8H_{14}O_2Br$ $[M+H]^+$ calc'd 221.0177, found 221.0177.



(E)-ethyl 4-(diethoxyphosphoryl)-3-methylpent-2-enoate (3.83).

Bromide **3.98** (597 mg, 2.71 mmol) was heated to 140^{o}C in triethyl phosphite (0.4 mL, 2.45 mmol) overnight. The mixture was cooled to room temperature and purified on silica gel chromatography (1:2 Hex/EtOAc) to give phosphate **3.83** (694 mg, 92%): colorless oil; R_f = 0.27 (Hexane/EtOAc, 1:2); IR (neat) 3470, 2990, 1655 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.81 (d, J = 4.8 Hz, 1H), 4.18-4.06 (m, 6H), 2.71 (dq, J =

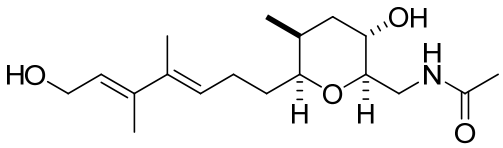
24.0, 7.2 Hz, 1H), 2.27 (d, J = 2.8 Hz, 3H), 1.41-1.26 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 166.3, 155.5, 155.4, 118.8, 118.7, 62.3, 62.2, 62.2, 62.1, 59.7, 43.0, 41.7, 18.2, 16.4, 16.3, 14.2, 13.7, 13.6; HRMS (TOF, ES+) $C_{12}H_{23}O_5P$ $[M+H]^+$ calc'd 279.1361, found 279.1361.



(2E,4E)-ethyl-7-((2S,3S,5S,6R)-6-(acetamidomethyl)-5-(tert-butyldimethylsilyloxy)-3-methyltetrahydro-2H-pyran-2-yl)-3,4-dimethylhepta-2,4-dienoate (3.99).

To a solution of phosphate **3.83** (24.6 mg, 0.088 mmol) in THF (0.7 mL) cooled to -78^{o}C was added ^{n}BuLi (50 μL, 0.0752 mmol) dropwise. The mixture was stirred at -78^{o}C for 10 minutes, warmed to 0^{o}C and stir for 50 minutes. The mixture was re-cooled to -78^{o}C and a precooled (-78^{o}C) solution of aldehyde **3.85** (26.8 mg, 0.0752 mmol) in THF (0.5 mL) was added dropwise. The mixture was then warmed to room temperature over 1 h and stir overnight. The reaction mixture was quenched with sat. NH_4Cl diluted with EtOAc and washed with H_2O and brine. Organic layer was dried over Na_2SO_4, concentrated and purified by SiO_2 chromatography (1:1 EtOAc/hexanes) to give ester **3.99** (33 mg, 78%). $[\alpha]_D^{20}$ 11.7 (*c* 1.30, $CHCl_3$); R_f = 0.46 (1:1 EtOAc/hexanes); IR (neat) 2929, 1721, 1619, 1599, 1089 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) 5.89 (t, J = 7.2 Hz, 1H), 5.84 (s, 1H), 5.79 (brs, 1H), 4.16 (q, J = 7.2 Hz, 2H) 3.78-3.70 (m, 1H), 3.57-3.51 (m, 1H), 3.40-3.37 (m, 1H), 3.18-3.07 (m, 2H), 2.31 (s, 3H), 2.26-2.21 (q, J = 7.2 Hz, 2H), 2.04 (s, 3H), 1.89-1.84 (m, 2H), 1.81 (s, 3H), 1.66-1.58 (m, 2H), 1.43-1.35 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H) 0.94 (d, J = 7.2 Hz, 3H) 0.87 (s, 9H), 0.06 (d, J = 8.8 Hz, 6H);

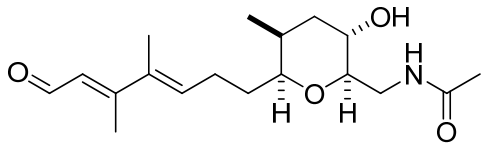
^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.6, 167.4, 155.9, 136.6, 132.3, 114.7, 81.2, 78.9, 65.6, 59.6, 41.4, 40.8, 32.6, 32.1, 25.7, 25.5, 23.2, 17.8, 15.3, 14.3, 13.9, 12.7, -4.2, -4.9; HRMS (TOF, ES+) $C_{26}H_{47}NO_5Si$ $[M+Na]^+$ calc'd 504.3121, found 504.3123.



N-(((2R,3S,5S,6S)-3-hydroxy-6-((3E,5E)-7-hydroxy-4,5-dimethylhepta-3,5-dienyl)-5-methyltetrahydro-2H-pyran-2-yl)methyl)acetamide (3.100).

To a solution of ester **3.99** (27 mg, 0.056 mmol) in CH_2Cl_2 (2 mL) at -78oC was added DIBAL-H (212.8 μL, 0.213 mmol, 1.0 M solution in hexane). After stirring for 15 min, the reaction was quenched with MeOH and diluted with Et_2O. The mixture was filtered through a short silica gel column (Et_2O and then EtOAc), and the filtrate was concentrated to give the crude allyl alcohol, which was used for the next reaction directly. To a solution of the crude allyl alcohol in THF at 0^{o}C was added TBAF (0.06 mL, 0.056 mmol, 1.0 M solution in THF). The reaction mixture was warmed to room temperature and stir for 1 h. The mixture was quenched with NH_4Cl, extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated. Purification by SiO_2 chromatography (5% MeOH/$CHCl_3$) gave diol **3.100** (12.9 mg, 71% for 2 steps) as a light yellow oil. $[\alpha]_D^{20}$ -8.0 (*c* 0.2, MeOH); R_f = 0.2 (5% MeOH/$CHCl_3$); IR (neat) 3313, 2924, 2853, 2360, 1653, 1559, 1537, 1457, 1375, 1106, 1020, 797, 668 cm^{-1}; ^{1}H NMR (400.1 MHz, CD_3OD) δ (ppm): 5.65 (dd, *J* = 6.4, 6.0 Hz, 1H), 5.61 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.22 (d, *J* = 6.4 Hz, 2H), 3.58-3.53 (m, 1H), 3.45–3.32 (m, 3H), 3.07 (ddd, *J* = 9.6, 6.8, 2.8 Hz, 1H), 2.35–2.16 (m, 2H), 1.97 (s, 3H), 1.94-1.89 (dm, 1H), 1.86–1.83 (m, 1H), 1.81 (s, 3H), 1.80 (s,

3H), 1.67–1.57 (m, 2H), 1.44–1.34 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.9, 136.1, 126.9, 124.1, 82.4, 79.6, 61.9, 69.9, 40.9, 38.3, 32.6, 32.5, 29.6, 25.2, 22.9, 14.1, 12.6; HRMS (TOF, ES+) $C_{18}H_{31}NO_4$ $[M+Na]^+$ calc'd 348.2151, found 348.2151.



Brevisamide (3.22).

To a solution of diol **3.100** (7.0 mg, 0.0215 mmol) in CH_2Cl_2 (1.5 mL) was added MnO4 (141 mg, 1.615 mmol) and the mixture was stirred at room temperature for 1.5 h. After stirring for 1 hour, the mixture was filtered through a short silica gel column (EtOAc), and the filtrate was concentrated. Purification by SiO_2 chromatography (5% MeOH/$CHCl_3$) gave brevisamide **3.22** (5.1 mg, 74%) as colorless oil. $[\alpha]_D^{20}$ -7.7 (*c* 0.2, MeOH); R_f = 0.2 (5% MeOH/$CHCl_3$); IR (neat) 3330, 2924, 2853, 2360, 1653, 1550, 1457, 1375, 1106, 1060, 795cm^{-1}; ^{1}H NMR (500.1 MHz, CD_3OD) δ (ppm): 10.1 (d, J = 8.0 Hz, 1H), 6.23 (dd, J = 7.5, 7.0 Hz, 1H), 6.04 (d, J = 8.0 Hz, 1H), 3.54 (dd, J = 14.0, 3.0 Hz, 1H), 3.45–3.37 (m, 2H), 3.34 (dd, J = 14.0, 7.0 Hz, 1H), 3.08 (ddd, J = 9.5, 6.7, 2.7 Hz, 1H), 2.38–2.36 (m, 1H), 2.34 (s, 3H), 1.96 (s, 3H), 1.92 (ddd, J = 2.5, 2.5, 12.5 Hz, 1H), 1.87 (s. 3H), 1.87–1.81 (m, 1H), 1.69–1.54 (m, 2H), 1.48–1.38 (m, 1H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 194.3, 173.8, 160.9, 137.3, 136.8, 126.2, 83.1, 80.3, 64.9, 42.5, 40.8, 34.2, 33.2, 26.9, 22.4, 14.5, 13.9, 13.0; HRMS (TOF, ES+) $C_{18}H_{29}NO_4$ $[M+H]^+$ calc'd 324.2175, found 324.2174.

Comparison of NMR data of natural and synthetic brevisamide

entry	Natural δ_H (mult, J in Hz)	Synthetic δ_H (mult, J in Hz)	Natural δ_C (mult)	Synthetic δ_C (mult)
1	10.10 (d, 7.9)	10.1 (d, 8.0)	194.4	194.3
2	6.04 (d, 7.9)	6.04 (d, 8.0)	126.3	126.2
3			160.9	160.9
4			137.2	137.3
5	6.23 (t, 7.1)	6.23 (dd, 7.0, 7.5)	136.8	136.8
6	2.34 m	2.35 m	26.9	26.9
7	1.65 m	1.64 m	33.2	33.2
8	1.44 m	1.43 m		
9	3.39 m	3.40 m	80.3	80.3
10	1.85 m	1.84 m	34.3	34.2
11	1.90 m	1.92 (ddd, 2.5, 2.5, 12.5)	40.9	40.8
12	1.65 m	1.64 m		
13	3.42 m	3.43 m	65.0	64.9
14	3.08 (ddd, 2.6, 7.0, 9.3)	3.08 (ddd, 2.7, 6.7, 9.5)	83.1	83.1
15	3.53 (dd, 2.6, 14.0)	3.54 (dd, 3.0, 14.0)	42.5	42.5
16	3.32 (dd, 7.1, 14.0)	3.34 (dd, 7.0, 14.0)		
17			173.7	173.8
18	1.95 s	1.96 s	22.5	22.4
19	2.33 s	2.34 s	14.6	14.5
20	1.86 s	1.87 s	14.0	13.9
21	0.95 (d, 6.9)	0.97 (d, 7.2)	13.1	13.0

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CHAPTER IV

A GENERAL APPROACH FOR THE CONSTRUCTION OF AZABICYCLIC RING-CONTAINING ALKALOIDS: PROGRESS TOWARDS THE TOTAL SYNTHESIS OF STEMAPHYLLINE AND GRANDISINES A, D & G.

4. 1. Introduction

Azabicyclic ring skeletons are common structural subunits present in numerous alkaloid natural products and serve as important scaffolds in biologically active and pharmaceutically significant compounds.[1-4] Pyrrolizidine, indolizidine, pyrrolo[1,2-a]azepine, and pyrrolo[1,2-a]azocine are common examples of the azabicyclic ring system (Figure 4.1). Due to the importance of azabicyclic skeletons, the synthesis of these ring systems constitutes an area of current interest among synthetic chemists.

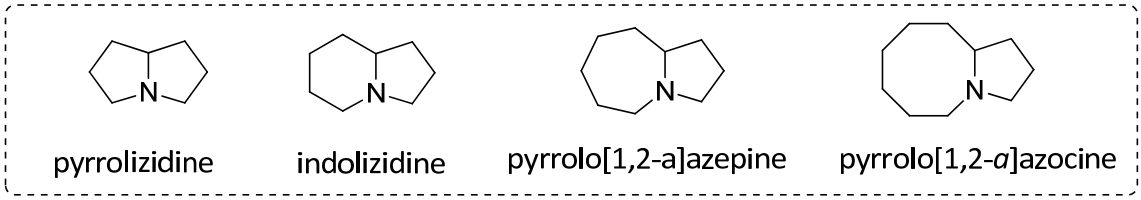


Figure 4.1. Azabicylic ring systems.

The purpose of our research in this area is to develop a general approach for the construction of azabicyclic ring systems and the application of the methodology towards the synthesis of indolizidine and stemona alkaloids. Therefore a brief introduction of *Stemona* and indolizidine alkaloids is warranted.

4.2. *Stemona* alkaloids

The *Stemona* plants primarily grow in southern Asia, Malaysia and northern Australia in dry vegetation and have been used for centuries in traditional Japanese and Chinese folk medicine.[2] Many of the secondary metabolites of *stemona* plants roots possess potentially significant biological activities. The water extract from these roots is used for both insecticidal and medicinal purposes, such as treatment of respiratory diseases (pulmonary tuberculosis, bronchitis) and as anthelmintics (anti-parasitic for both human and cattle use).[2]

Stemona alkaloids represent a class of approximately 100 biogenetically intriguing and structurally unique natural products. They are isolated from plants of the *Stemona* genus (Stemonaceae family) and are well-known to contain chemically diverse alkaloids with a pyrrolo[1,2-*a*]azepine (also 4-azazulene) nucleus. The *Stemona* alkaloids are divided into 8 major groups: stenine, stemoamide, tuberostemospirone, stemonamine, stemofoline, stemocurtisine, parvistemoline and miscellaneous groups (contains stemona alkaloids with cleaved pyrrolo[1,2-*a*]azepine nucleus) (Figure 4.2).[3] Examples of *Stemona* alkaloids (**4.1**-**4.8**) for each group are shown in Figure 4.2.

Due to their structural and stereochemical challenges and interesting biological activities, the synthesis of Stemona alkaloids has attracted considerable interest from the synthetic community.

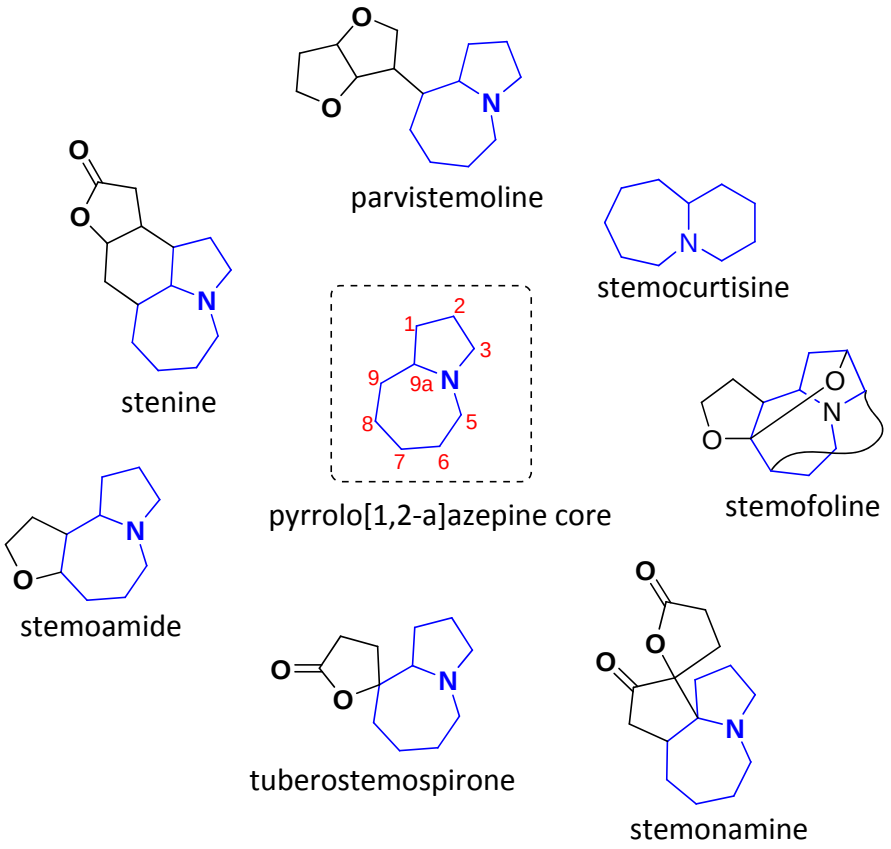


Figure 4.2. *Stemona* alkaloid groups.

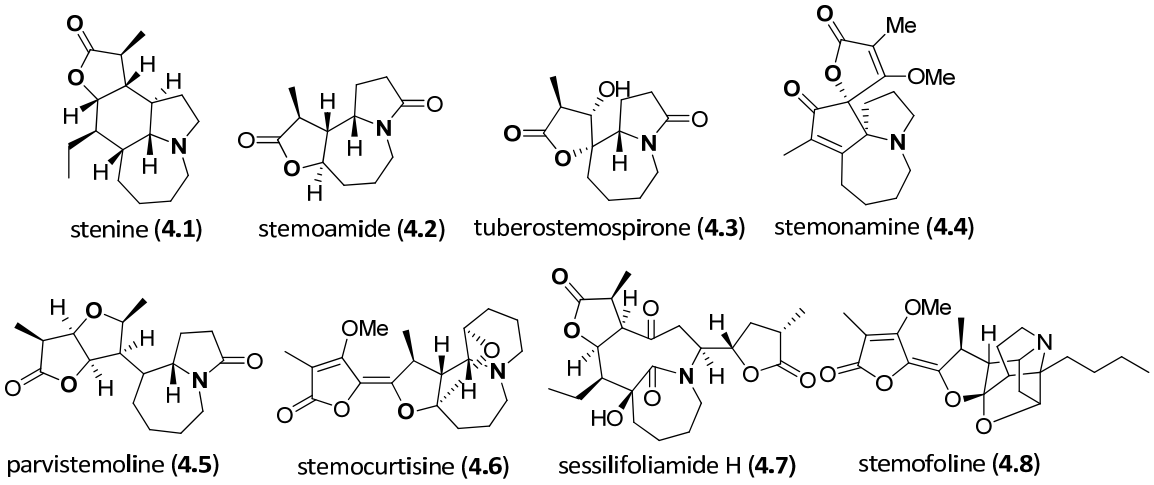
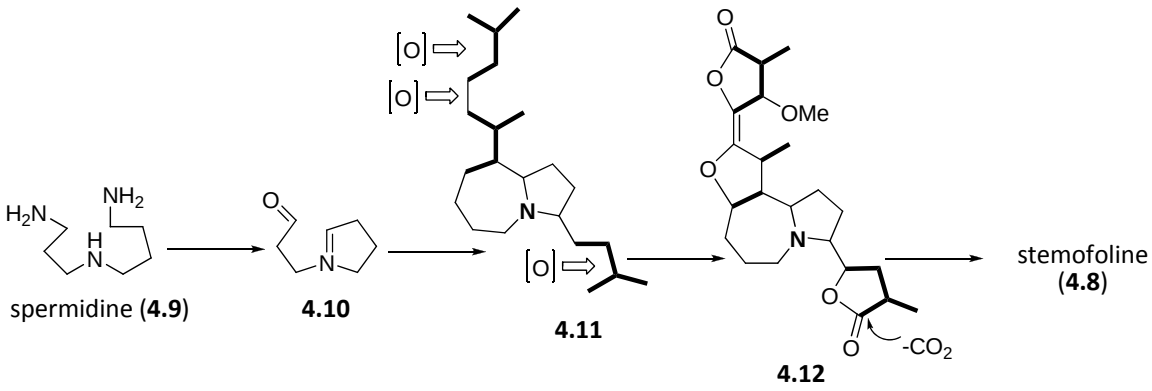


Figure 4.3. Examples of *Stemona* alkaloids.

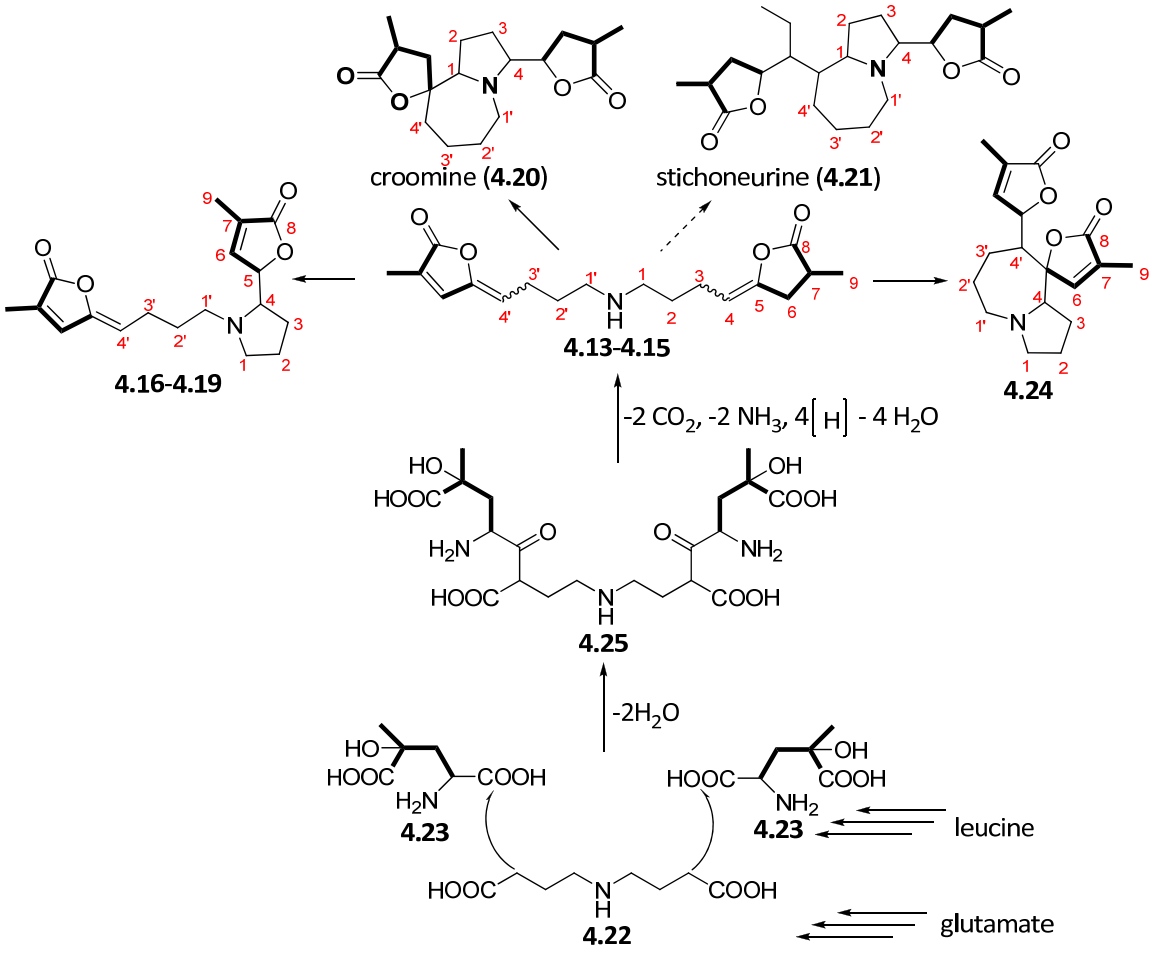
4.3. Biosynthesis of *Stemona* alkaloids

The biosynthetic origin of Stemona alkaloids is not well established. Seger and co-workers proposed that the formation of Stemona alkaloids is similar to that of the pyrrolizidinealkaloids, which utilize a homospermidine precursor. The proposal involves conversion of spermidine **4.9** to iminium **4.10**, which then undergoes cyclization to give 7,5-member-fused ring system of the pyrrolo[1,2-a] azepine system. Further oxidation of azepine **4.11**, opening of the lactone ring **4.12** and several ring closures result in stemofoline **4.8** (Scheme 4.1).[4]



Scheme 4.1. Proposed biosynthesis of *Stemona* alkaloids.

In 2009, Greger and co-workers isolated Pandanus alkaloid (pandanamine **4.13-4.15** and pandamarilactonines A-D (**4.16-4.19**)) from *Stichoneuron calcicola* of the family stemonaceae. Thus, co-occurrence of pandanamines and croomine **4.20** in the family of stemonaceae represents a new biogentic origin argument of *Stemona* alkaloids. It was proposed that pandanamines, which originate from leucine and glutamate are a biogentic precursor to croomine **4.20**, stichoneurine **4.21** and unnamed pyrroloazepine derivative **4.24** (Scheme 4.2).[5]



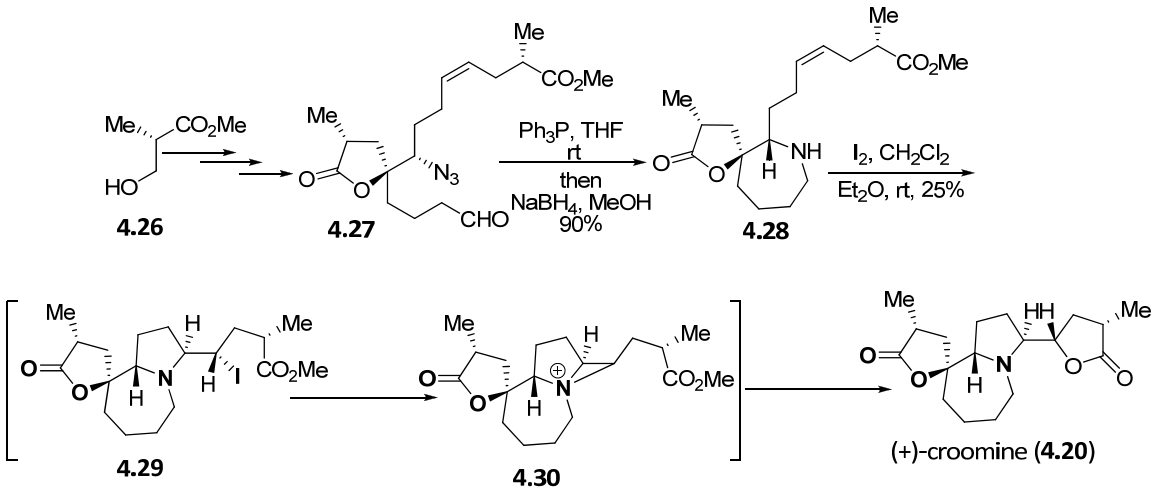
Scheme 4.2. Possible biosynthetic pathway of pandanamines and structural relation to *Stemona* alkaloids.

4.4 Synthetic approach to Stemona alkaloids

4.4.1 Azepine formation by Staudinger-Aza-Wittig reaction

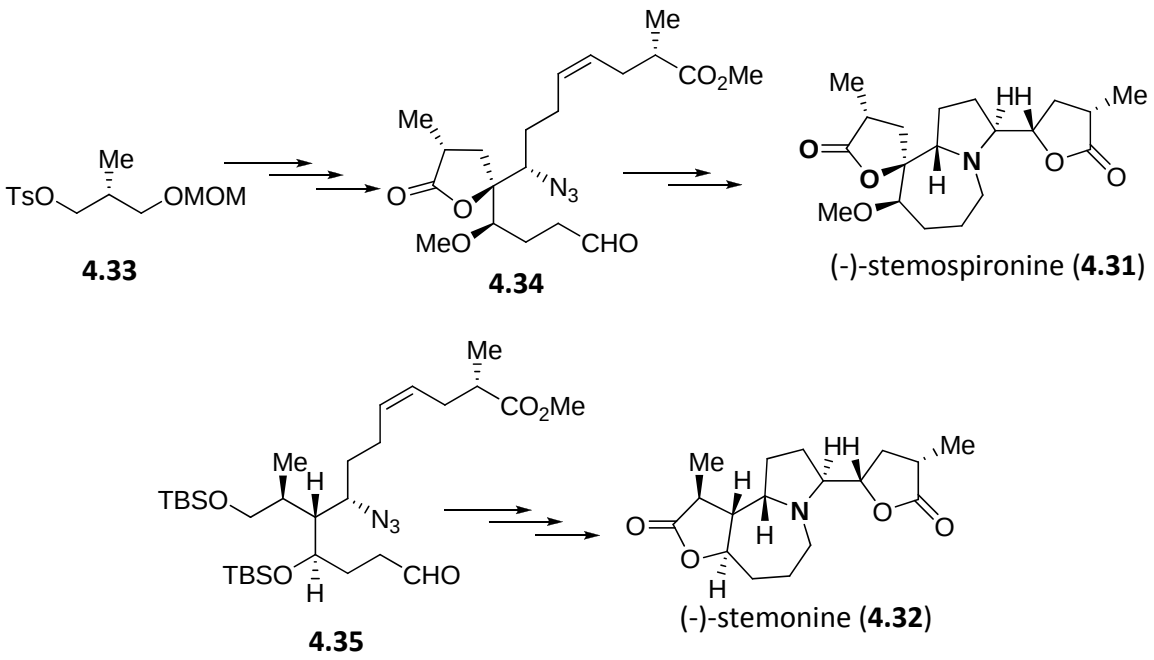
Williams and co-workers in 1989 completed the first total synthesis of a stemona alkaloid. The total synthesis of (+)-croomine was accomplished in 24 steps from (2*S*)-3-(hydroxymethyl) propionate **4.26**. Their strategy utilizes azidoaldehyde **4.27** in a Staudinger-Aza-Wittig reaction to generate azepine ring **4.28**. The pyrrolidino-butyrolactone unit of croomine **4.20** was achieved in a single step which involves

iodoamination, followed by intramolecular cyclization to give aziridinium salt, and a second cyclization for the formation of the lactone ring (Scheme 4.3).[6]



Scheme 4.3. Staundinger-Aza-Wittig approach for the synthesis of (+)-croomine (**4.20**).

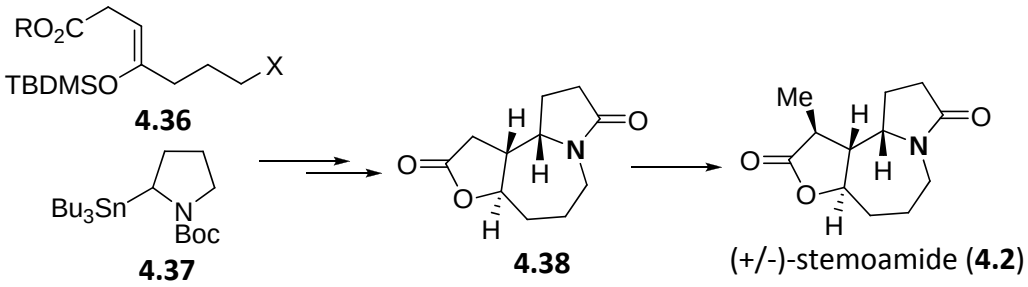
Similar to the approach used in the total synthesis of croomine (**4.20**), Williams and co-workers also accomplished the total synthesis of (-)-stenospironine (**4.31**) and (-)-stenomine (**4.32**) via a Staundinger-Aza-Wittig reaction and iodine-induced double cyclization process (Scheme 4.4).[7]



Scheme 4.4. Staundinger-Aza-Wittig approach for the synthesis of **4.31** and **4.32**.

4.4.2. Azepine formation by 7-*exo*-*tet*-cyclization

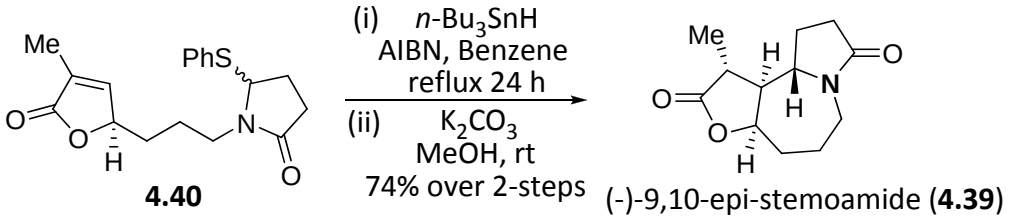
Narasaka and co-workers reported a 12-linear step racemic synthesis of stemoamide; the key-step utilizes an oxidative coupling reaction of silylenol ether **4.36** and acyliminium ion generated from stannyl **4.37** (Scheme 4.6).[8]



Scheme 4.5. Azepine formation by 7-*exo*-*tet*-cyclization.

4.4.3. Azepine formation through intramolecular radical coupling

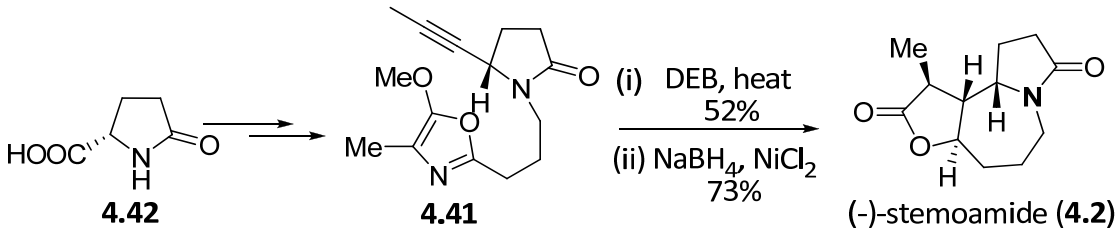
Khim and co-workers constructed the azepine ring of 9,10-*bis*-*epi*-stemoamide (**4.39**) via a 7-exo-trig radical cyclization reaction of phenylthiolactam **4.40** (Scheme 4.6).[9]



Scheme 4.6. Azepine formation through intramolecular radical coupling.

4.4.4. Azepine formation by [4+2] cycloaddition

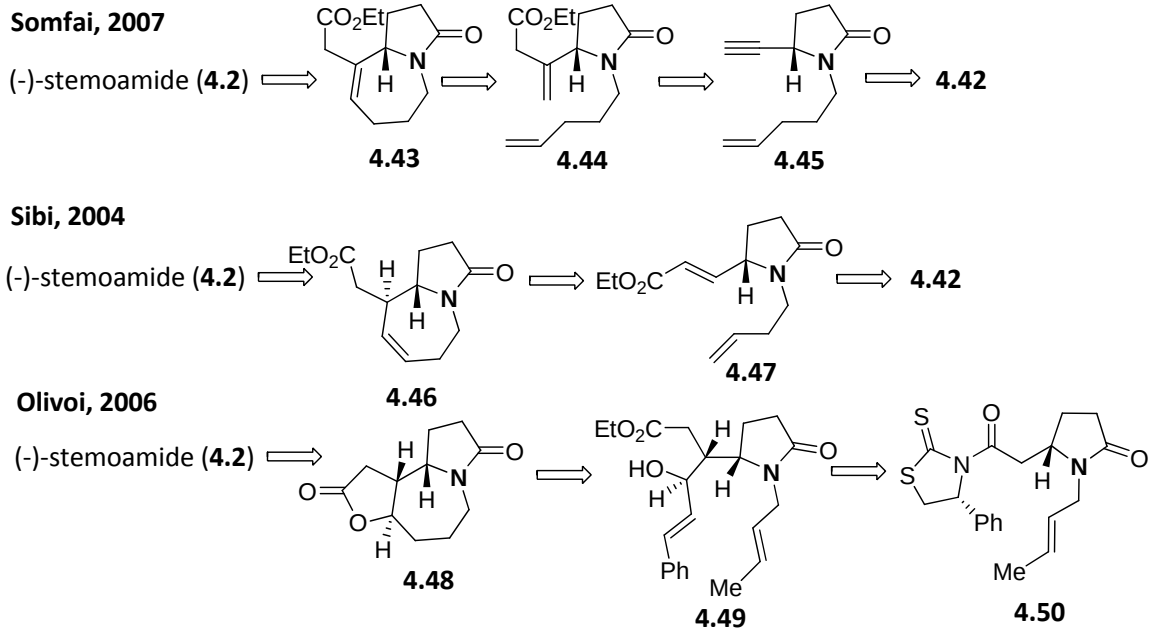
Construction of stemoamide (**4.2**) azepine ring was accomplished through an intramoleclar Diels-Alder/retro Diels-Alder protocol. Thermolysis of alkyne **4.41** followed by reduction afforded stemoamide (**4.2**) in good yield (Scheme 4.7).[10]



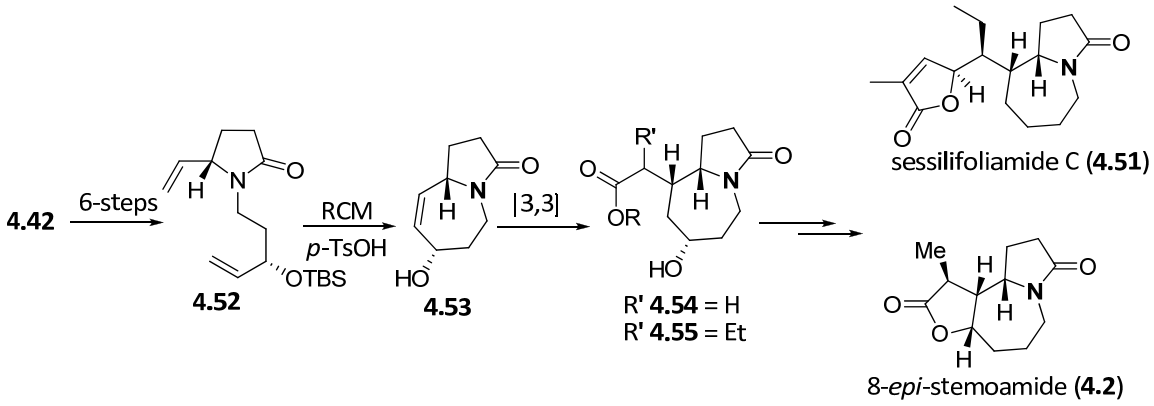
Scheme 4.7. Azepine formation by [4+2] cycloaddition.

4.4.5. Azepine formation by ring-closing metathesis (RCM)

The formation of the azepine ring of (-)-stemoamide has been accomplished by several groups using the ring closing metathesis approach as shown in Scheme 4.8.[11] Peter Wipf recently reported the total synthesis of sessilifoliamide C and (-)-8-epi-stemoamide in 21-synthetic steps. The synthesis utilizes a [3,3]-sigmatropic rearrangement to install stereocenters at C_9-C_{10} and a RCM to construct the azepine ring (Scheme 4.9).[12]



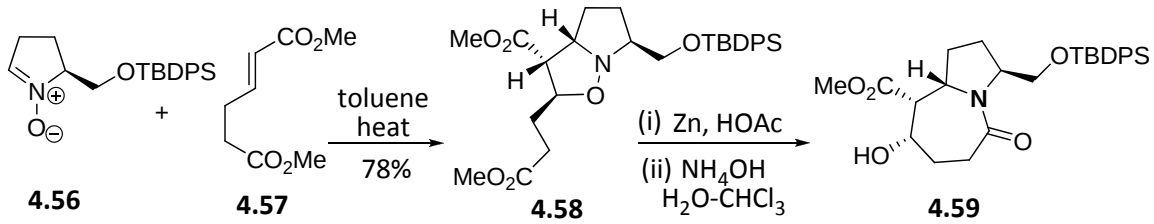
Scheme 4.8. Strategies using an RCM process.



Scheme 4.9. Wipf's total synthesis of sessilifoliamide C and (-)-8-*epi*-stemoamide.

4.4.6. Cyclic nitrone strategy

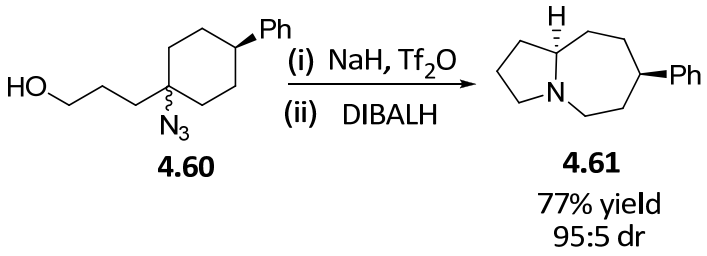
Figueredo and co-workers reported a general approach to the azepine ring of stemona alkaloids. Their approach employ a 1,3-dipolar cycloaddition of cyclic nitrones, followed by N-O reductive cleavage and azepine closure (Scheme 4.10).[13]



Scheme 4.10. Formation of azabicyclo intermediates from chiral nitrones.

4.4.7. Intramolecular Schmidt rearrangement

In 2009, Renaud and co-workers utilized a previously developed intramolecular Schmidt rearrangement in the synthesis of the azepine ring. Subjecting alcohol **4.60** to NaH, triflic anhydride followed by DIBALH gave azepine **4.61** (77% yield, 95:5 *dr*).[14]



Scheme 4.11. Azepine via intramolecular Schmidt rearrangement.

Other very important type of azabicyclic ring system is the indolizidine ring system. Discussed in the next section is a brief background on indolizidine containing alkaloids and synthetic approach towards them.

4.5. Indolizidine alkaloids

Indolizidine alkaloids are usually isolated from a myriad of sources including ants, frog, fungi and trees. Indolizidine alkaloids have shown interesting biological activities including insecticidal, antibacterial, antifungal, antiviral, antiinfective, antiparasitic, antimalaria and anticancer activities.[15]

Indolizidine alkaloids are defined by 1-aza-bicyclo-[**4.3.0**]-octane core similar to the stemona alkaloids, different approaches have been utilized in the synthesis of indolizidine alkaloids. Shown in Figure 4.3 are some examples of indolizidine containing natural products. Outlined below are few approaches to the construction of indolizidine ring systems.

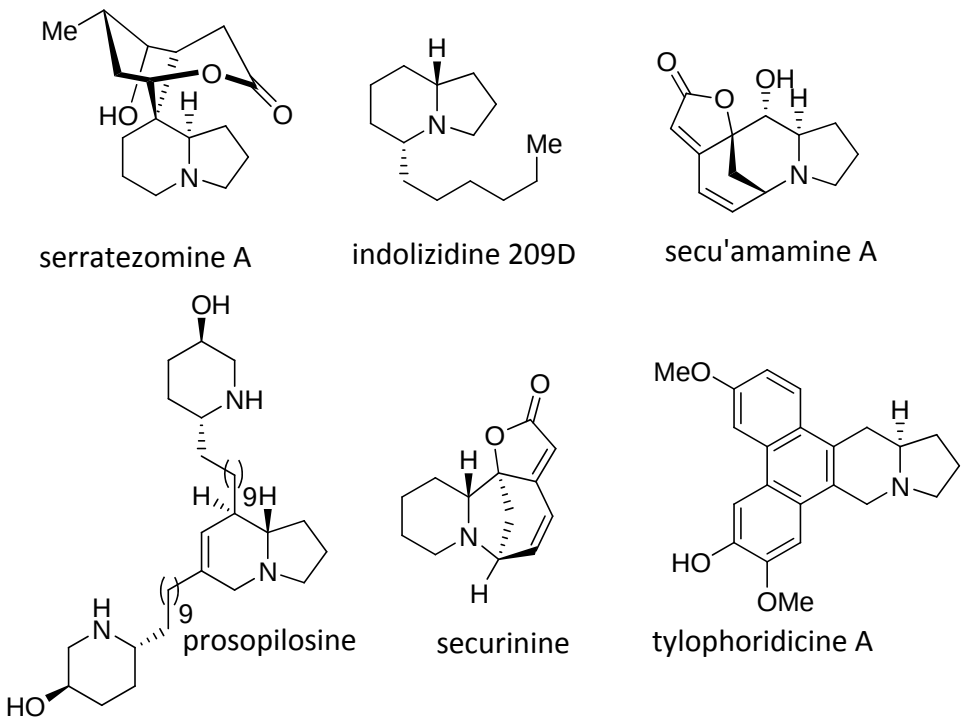


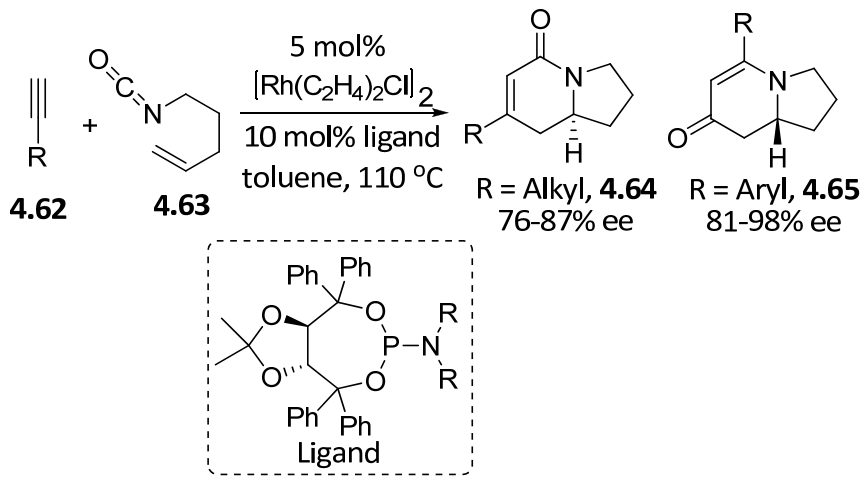
Figure 4.4. Examples of indolizidine containing natural products.

4.6. Synthetic approach for the construction of indolizidine ring systems

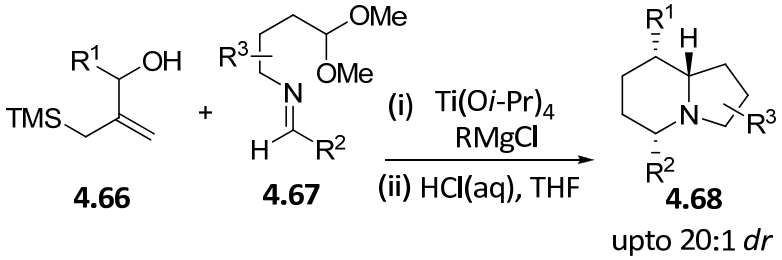
In 2006, Rovis and co-workers reported a regioselective/enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkyne **4.62** and akenylisocyanates **4.63** to access indolizidine frameworks **4.64** and **4.65** in good to excellent yields and up to 98% ee (Scheme 4.12).[16]

Micalizio and co-workers developed a diastereoselective synthesis of indolizidine frameworks through a chemoselective coupling of 2-hydroxymethyl-substituted allylic silanes **4.66** with amines **4.67** followed by acid induced cyclization (Scheme 4.13).[17]

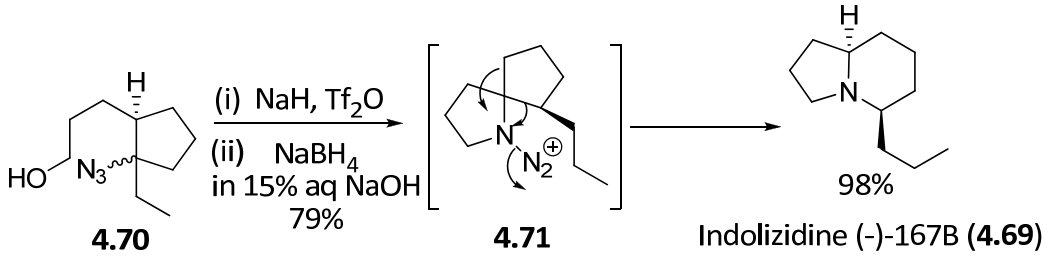
Similar to their approach towards Stemona alkaloids, Renaud and co-workers also reported the synthesis of indolizidine (-)-167B (**4.69**) via an intramolecular Schmidt rearrangement reaction of primary azido alcohols **4.70** (Scheme 4.14).[14]



Scheme 4.12. Rovis's indolizidine ring system via rhodium-catalyzed [2+2+2] cycloaddition.

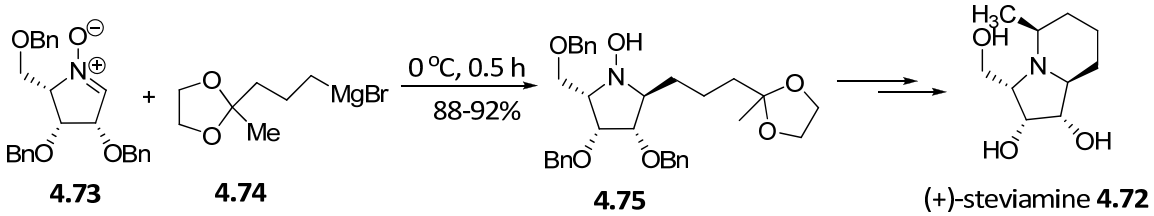


Scheme 4.13. Diastereoselective synthesis of indolizidine ring system.



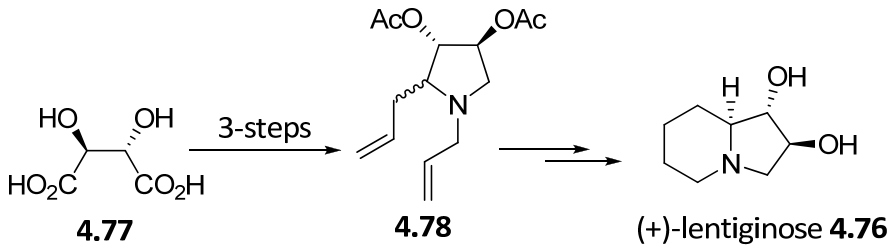
Scheme 4.14. Indolizidine (-)-167B via intramolecular Schmidt rearrangement.

Recently, Yu and co-workers reported the total synthesis of (+)-steviamine **4.72** via a cyclic nitrone strategy. The synthesis was achieved from readily available D-ribose-derived cyclic nitrone **4.73** (Scheme 4.15).[18]



Scheme 4.15. Synthesis of (+)-steriamine **4.72** via a cyclic nitrone strategy.

Several laboratories have utilized the ring closing metathesis in the construction of the indolizidine ring of different natural product alkaloids. An example is the total synthesis of (+)-leutiginose **4.76** reported by Pilli and co-workers (Scheme 4.16).[19]



Scheme 4.16. Synthesis of (+)-leutiginose **4.76** via ring closing metathesis (RCM).

An important example of indolizidine containing natural products is the grandisine alkaloids. Discussed in the next section is the isolation and synthetic approach to this unique natural product.

4.7. Isolation of grandisines A-G

Grandisines A-G are indolizidine alkaloids, isolated by Carroll and co-workers from the leaves of the Australian rain forest tree *Elaeocarpus grandis*. These alkaloids display selective human δ-opioid receptor affinity. Selective activation of the δ-opioid receptor is an attractive strategy for the development of new analgesics, thus grandisines are potential potent analgesic agents.[20]

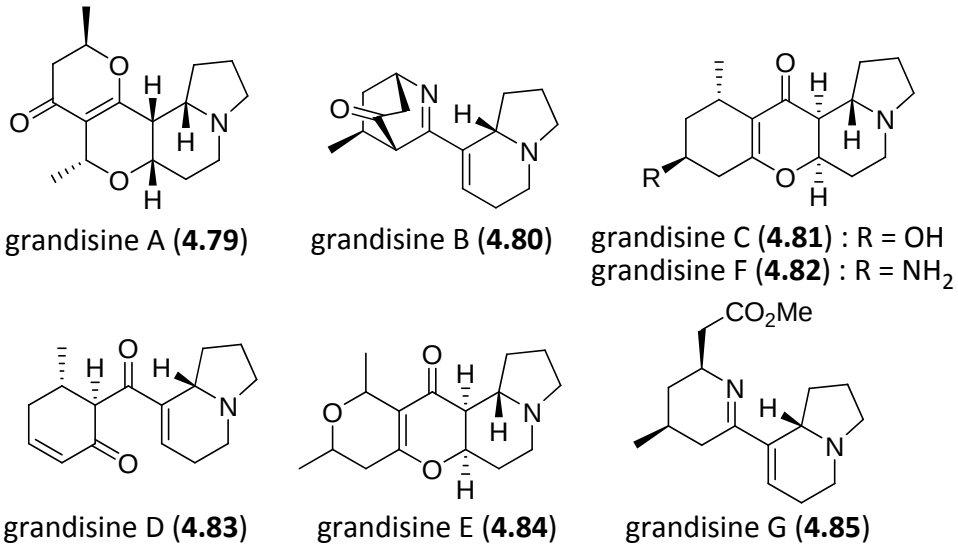
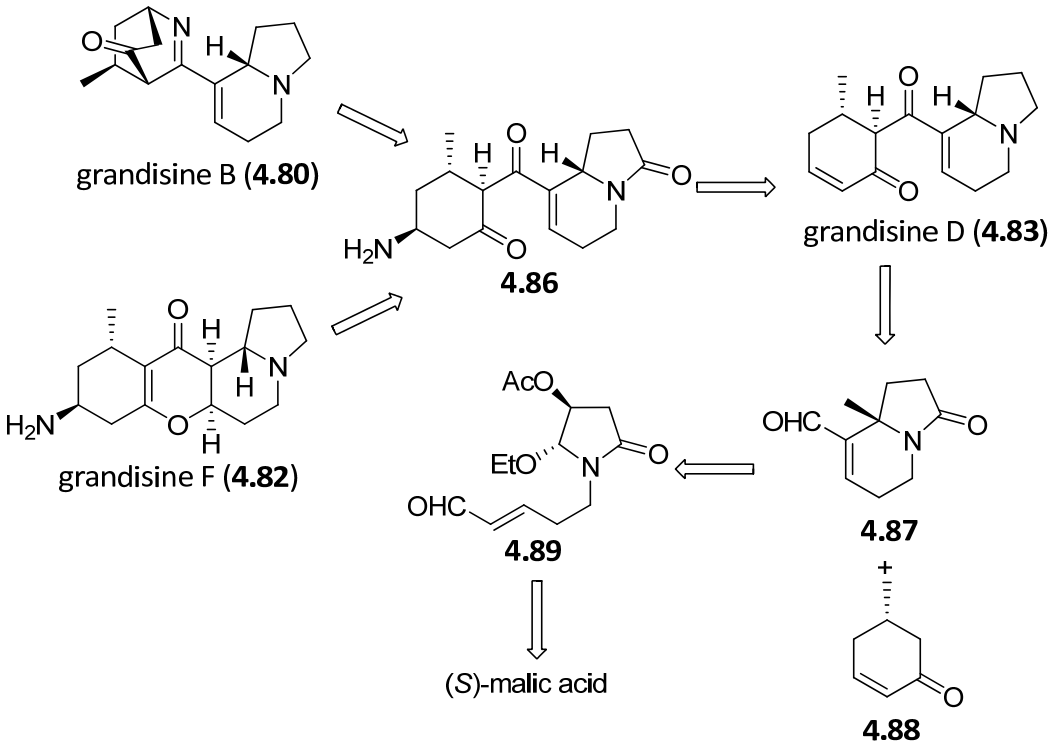


Figure 4.5. Structures of grandisines.

4.8. Total synthesis of grandisines B, D, and F

Tamura and co-workers have reported the first total synthesis of grandisine alkaloids, grandisines B, D, and F (**4.80**, **4.83** and **4.82**). Key steps in their syntheses involve the construction of the isoquinuclidinone moiety of grandisine B **4.80** by intramolecular imine formation, and the tetracyclic ring system of grandisine F **4.82** by stereoselective ring closure of the enolate of amine **4.82** generated by amination of grandisine D **4.83**. Grandisine D (**4.83**) was achieved by a Brønsted acid mediated

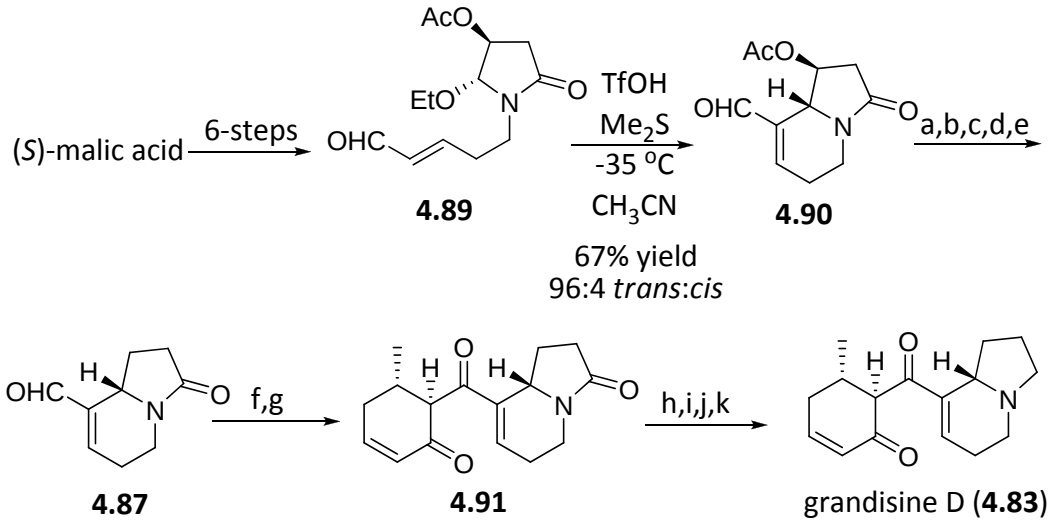
Morita-Baylis-Hillman (MBH) ring-closure reaction and stereoselective aldol reaction with (*S*)-5-methylcyclohexenone (9) as key steps.[21,22]



Scheme 4.17. Tamura's restrosynthetic analysis for grandisines B, D, and F.

Tamura's synthesis of grandisine D began with the synthesis of aminal **4.89** from commercially available (*S*)-malic acid in 6 steps. Subjecting aminal **4.89** to Morita-Baylis-Hillman (MBH) ring-closure reaction in the presence of TfOH, Me_2S in CH_3CN gave the desired MBH product **4.90** in good yield and high stereoselectivity (*trans*:*cis* = 96:4). Acetal protection of the conjugated aldehdye followed by deacetylation, deoxygenation and subsequent deprotection of the aldehyde gave key aldehyde **4.87**. Aldol reaction of enone **4.88** with aldehyde **4.87** followed by Dess Martin oxidation gave α,β-unsaturated ketone of **4.91**. Reduction of the lactam carbonyl group gave the first

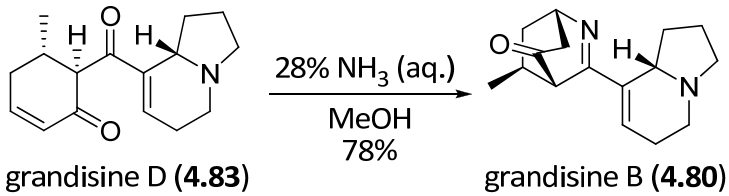
total synthesis of grandisine D. The synthesis was accomplished in 26 synthetic steps, with 20 steps longest linear sequence (Scheme 4.18).[21,22]



Scheme 4.18. Total synthesis of grandisine D.

Reagents and conditions: (a) $HO(CH_2)_2OH$, *p*-TsOH (cat.) 96%; (b) NaOEt, EtOH, 70%; (c) ClCSOPh, DMAP, CH_2Cl_2 (d) Bu_3SnH, AIBN, C_6H_6 (96% 2 steps); (e) *p*-TsOH, acetone-H_2O, 97%; (f) **4.88**, $^{n}Bu_2BOTf$, $^{i}Pr_2NEt$, CH_2Cl_2, quant; (g) DMP, CH_2Cl_2, 88%; (h) PhSH $HClO_4$, MeOH, 93%; (i) Lawesson's reagent; (j) $Me_3O^{+}B^{-}F_4$; (k) $NaBH_3CN$, 63% (2 steps)

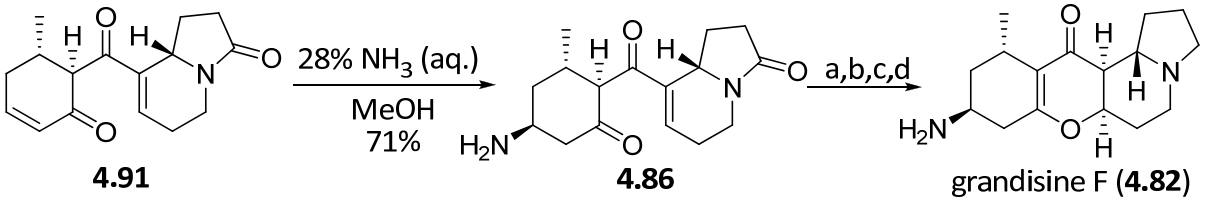
According to previously proposed biosynthesis of grandisines B, the total synthesis was achieved from grandisine D (**4.83**) on treatment with ammonia. The synthesis involves an intermolecular 1,4-addition of ammonia and intramolecular imine formation to afford grandisine B (**4.80**).[22]



grandisine D (**4.83**) grandisine B (**4.80**)

Scheme 4.19. Total synthesis of grandisine B.

Grandisine F was synthesized by treatment of diketone **4.91** with ammonia solution to give tetracyclic amine **4.86** as a single isomer. Further 4-step to reduce the amide carbonyl group gave grandisine F (Scheme 4.20).[22]

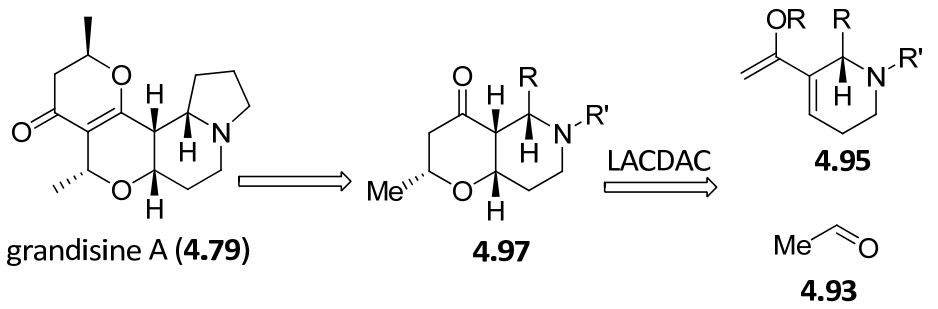


4.91 **4.86** grandisine F (**4.82**)

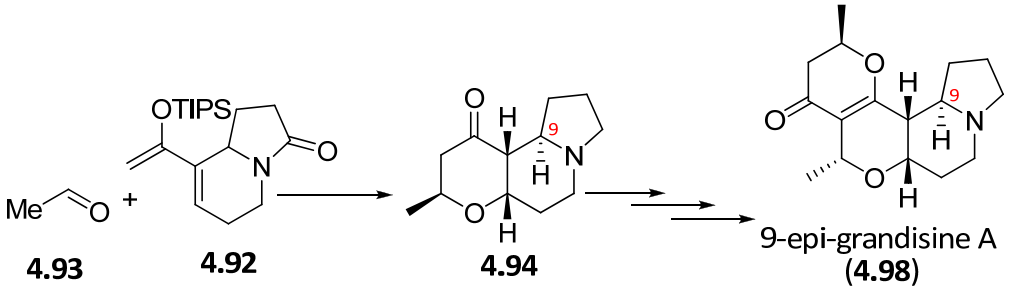
Scheme 4.20. Total synthesis of grandisine F. *Reagents and conditions:* (a) Boc_2O, CH_3CN, 99%; (b) Lawesson's reagent, 99%; (c) Raney Ni, THF, 80% (d) TFA, CH_2Cl_2,

4.9. Total synthesis of grandisine A

Danishefsky and Maloney disclosed the total synthesis of grandisine A in 2007. The key step in their synthesis employed a stereo-controlled Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) reaction (Scheme 4.22). In their previous effort, the LACDAC reaction of lactam **4.92** and acetaldehyde **4.93** yielded **4.94**, in which cycloaddition of the acetaldehyde had occurred in an *anti* fashion to give the undesired stereochemistry at C9 (Scheme 4.23).[23] An alternate approach was then developed, where a siloxyvinyl **4.95** would replace lactam **4.92** in the LACDAC reaction.



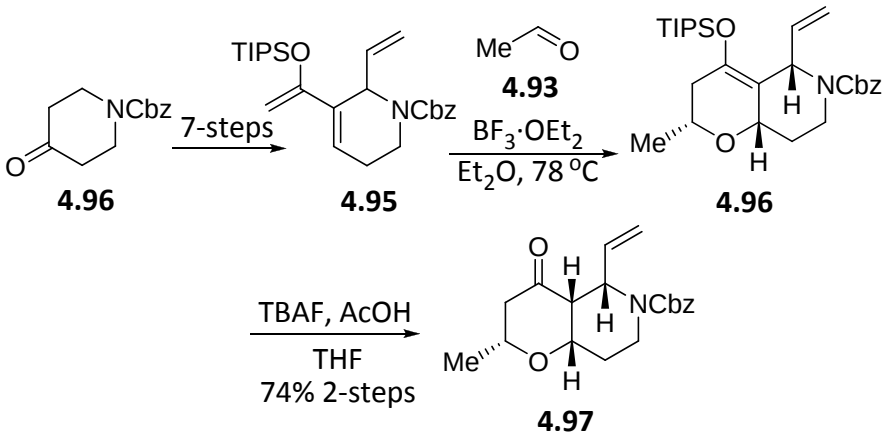
Scheme 4.21. Danishefsky's restrosynthetic analysis for grandisine A.



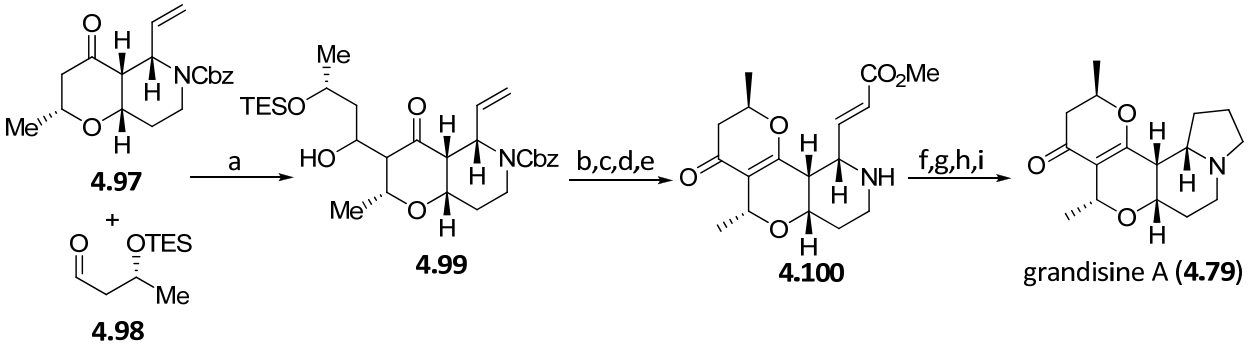
Scheme 4.22. LACDAC strategy to 9-*epi*-grandisine A.

The synthesis of key cyclocondensation precursor **4.95** was accomplished from dihydropyridone **4.96** in 7 steps. Subjecting diene **4.95** and acetaldehyde **4.93** to $BF_3 \cdot OEt_2$ delivered the desired Diels-Alder product *endo*-bicyclic ring **4.96**, which upon deprotection gave racemic **4.97** (Scheme 4.23).

Chiral HPLC separation of rac-**4.97** gave enantiopure (+)-**4.97**, which was subjected to aldol reaction with (*R*)-3-(triethylsilyloxy)butanal **4.98** to give hydroxyketone **4.99**. 4-step transformation of **4.99** gave α,β-unsaturated ester **4.100**, which was subjected to double bond reduction, cleavage of the Cbz group, lactamization and reduction of the lactam carbonyl group to give the first synthesis of grandisine A (**4.79**) (Scheme 4.24).[24]



Scheme 4.23. Synthesis of vinyl **4.97**.

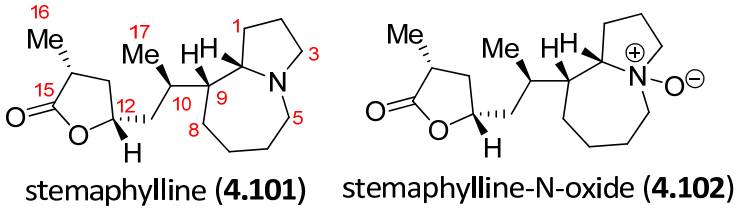


Scheme 4.24. Total synthesis of grandisine A. *Reagents and conditions:* (a) LiHMDS, $ZnCl_2$, THF, -78 °C, then **4.98**, -78 °C to -50 °C, 3.5 h; (b) Dess–Martin periodinane, CH_2Cl_2; (c) TFA, CH_2Cl_2, 73% over 3 steps; (d) O_3, MeOH, Sudan III (indicator), -78 °C, then Me_2S, -78 °C to 25 °C; (e) methyl (triphenylphosphoranylidene)acetate, benzene, 60 °C to 40 °C, 9.5 h, 80% over 2 steps; (f) 10% Pd/C, H_2 (1 atm), MeOH; (g) PhMe, reflux, 24 h, 98% over 2 steps; (h) Lawesson's reagent, PhMe, 65 °C, 98%; (i) Raney nickel, THF, 25 °C, 94%.

4.10. Isolation of stemaphylline and stemaphylline-*N*-oxide

Recently in 2009, stemaphylline (**4.101**) and stemaphylline-*N*-oxide (**4.102**) (Figure 4.5) were isolated from the root extracts of *Stemona aphylla* (Stemonaceae) that were collected at Mae Hong Son, Thailand, by Pitchaya and co-workers.[25] The structures were elucidated by extensive NMR analysis. Stemaphylline showed moderate acetylcholinesterase (AChE) inhibitory activities, pronounced insecticidal activity, and weak antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas auruginosa* and *Candida albicans* (MIC 62.5-125 μg/mL).[25]

To date, there have been no synthetic efforts directed toward the total synthesis of stemaphylline (**4.101**) and stemaphylline-*N*-oxide (**4.102**) (Figure 4.6).



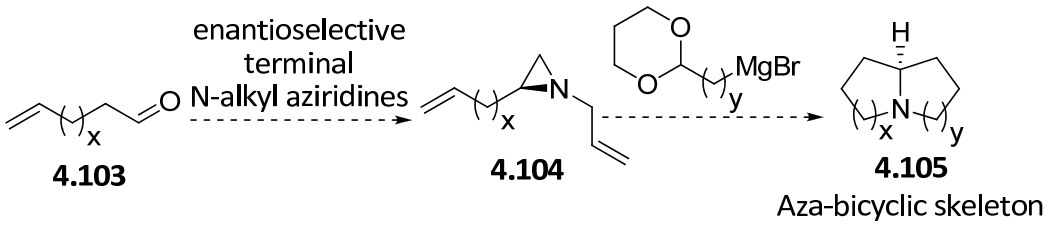
stemaphylline (**4.101**) stemaphylline-N-oxide (**4.102**)

Figure 4.6. Stemaphylline (**4.101**) and stemaphylline-*N*-oxide (**4.102**).

4.11. A general approach for the construction of azabicyclic ring systems and progress towards the total synthesis of stemaphylline

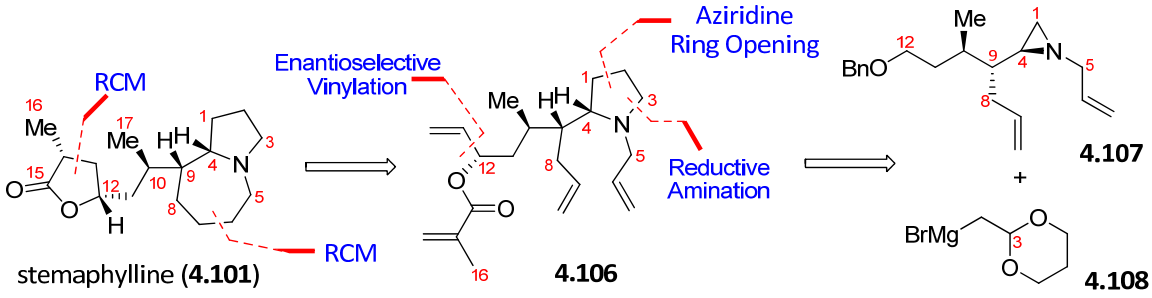
Due to the unique properties of azepine and indolizidine containing natural products, we have embarked on the development of a general and asymmetric synthesis for the construction of azabicyclic ring systems and its application towards the total synthesis of stemaphylline and grandisines. Relying on our previous work on the enantioslective synthesis of *N*-alkyl aziridines, we envisioned a Lewis acid mediated

aziridine ring opening/reductive amination protocol of aziridine **4.104** to access various ring size of the azabicylic skeleton (Scheme 4.25).



Scheme 4.25. Azabicyclic ring skeleton via *N*-alkyl aziridines.

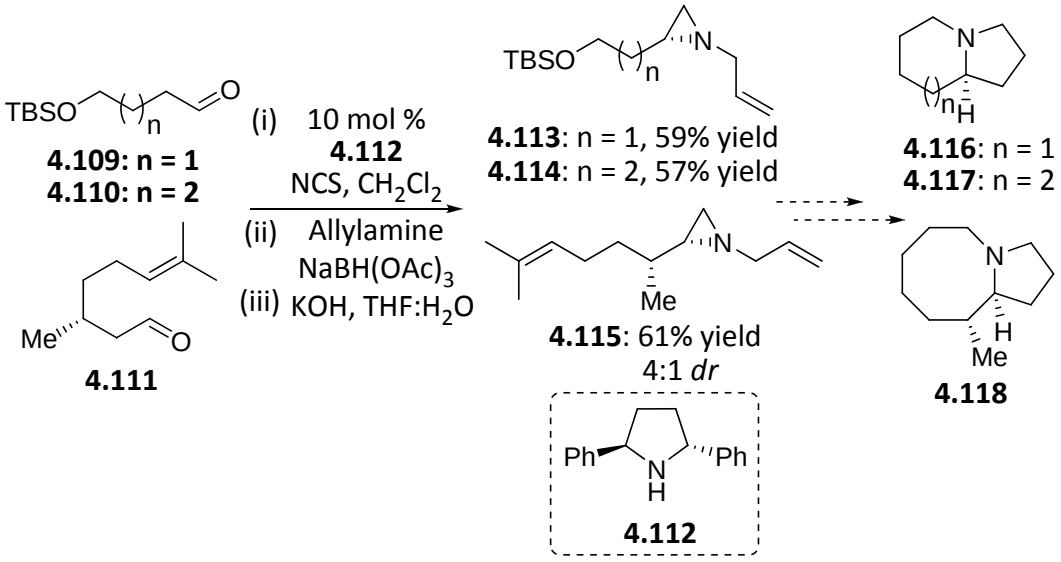
Based on the proposed approach to azabicyclic ring systems, we then developed a retrosynthesis for stemaphylline (**4.101**). The retrosynthetic analysis is outlined in Scheme 4.26. The lactone and 7-membered azepine rings could be installed via RCM. The pyrrolindine ring **4.106** would be constructed by ring opening of aziridine **4.107** and subsequent reductive amination.



Scheme 4.26. Retrosynthetic analysis of stemaphylline (**4.101**).

To test the viability of the above strategy, aldehydes **110-112** were chosen, which are commercially available or prepared from corresponding alcohols. In the presence of

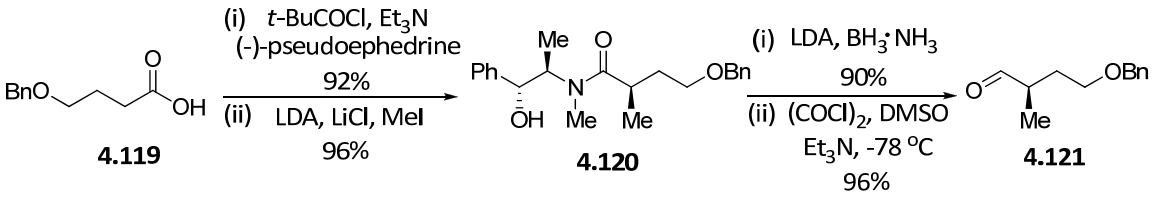
the organocatalyst **4.112**, aldehyde (**4.109**-**4.110**) reacted with *N*-chlorosuccinimde (NCS) to give α-chlorination product, which was subsequently subjected to reductive amination with allyamine and finally treated with KOH to give the desired aziridines (**4.113**–**4.115**) (Scheme 4.27). With the aziridine in hand, Lewis acid mediated aziridine ring opening/reductive amination protocol was envisioned. Finally, functional group interconversion (in the case of **4.114** and **4.115**) and RCM/hydrogenation should give the desired azabicyclic ring skeletons products **4.116**-**4**.**118** (Scheme 4.27).



Scheme 4.27. Synthesis of enantioenriched azabicyclic rings.

With model aziridines (**4.113**-**4.115**) in hand, we then attempted to synthezise the required aziridine **4.107** for the synthesis of stemaphylline (Scheme 4.26). The synthesis started from carboxylic acid **4.119**. Acylation of pseudoephedrine with the mixed anhydrides of carboxylic acid **4.119** derived from pivaloyl chloride followed by

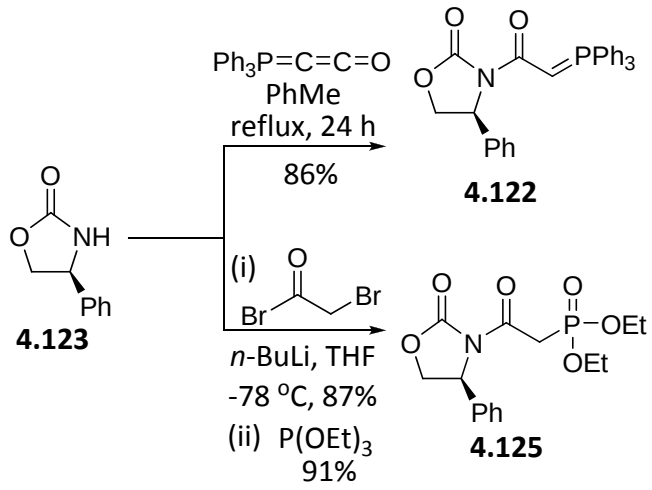
asymmetric alkylation gave the desired alkylated product **4.120** in 96% yield (Scheme 4.28).[26]



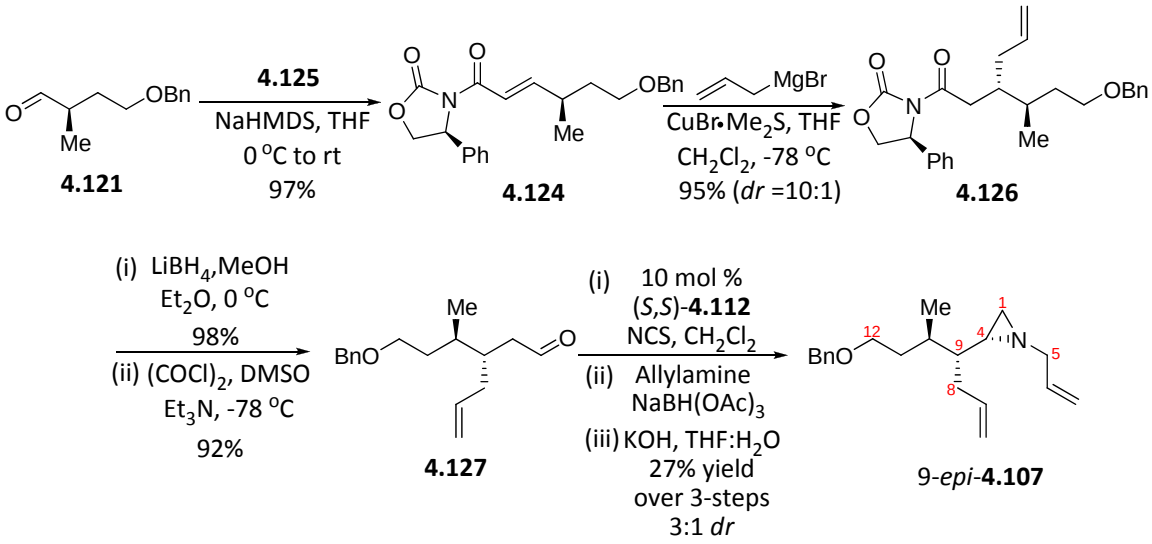
Scheme 4.28. Synthesis of aldehyde **4.121**.

Semi-reduction of amide **4.120** with Brown's lithium triethoxyborohydride[27] to aldehyde **4.121** proved problematic on a large scale synthesis. However a 2 step protocol involving reduction with lithium amidotrihydroborate (LiH_2NBH_3, LAB) followed by oxidation proceeded to give aldehyde **4.121** in 96% yield (Scheme 4.28).

Standard Wittig reaction of aldehyde **4.121** with ylide **4.122** (prepared from oxazolidinone **4.123**, Scheme 4.29)[28] gave the desired product **4.124** in low yield and about 1.5:1 mixture of *E*/*Z*-olefin. Alternatively the aldehyde **4.121** was subjected to Horner-Emmons-Wadsworth reaction[29] with chiral imide **4.125** (prepared from oxazolidinone **4.123**, Scheme 4.29)[30] to give *E*-enone **4.124** in 97% yield.[31] 1,4-Conjugate addition of **4.124** with allyl cuprate afforded desired product **4.126** in 95% yield (*dr* =10:1).[32] At this point, reduction of oxazolidinone **4.124** with $LiBH_4$ gave the desired primary alcohol in 98% yield. Swern oxidation of the alcohol gave the required aldehyde **4.127** in 92% yield. Application of the 3-steps one-pot protocol using (*S*,*S*)-**4.112** provides aziridine 4-*epi*-**4.107** in 27% yield (3:1 *dr*) (Scheme 4.30).



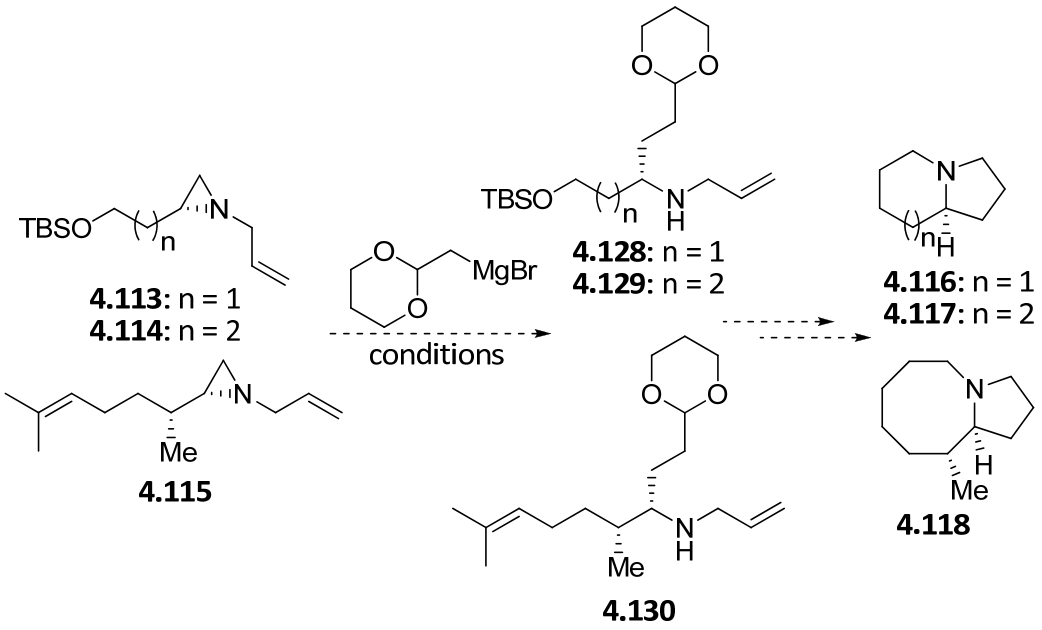
Scheme 4.29. Synthesis of ylide **4.122** and chiral imide **4.125**.



Scheme 4.30. Synthesis of aziridine 4-*epi*-**4.107**.

Encouraged by the progress in the synthesis of the key aziridine precursor 9-*epi*-**4.107** towards the synthesis of stemaphylline (**4.101**), we moved to advance the model studies aziridines **4.113**–**4.115** to the azabicyclic frameworks **4.116**-**4.118** (Scheme 4.31). Regrettably, every attempt to open the aziridine rings **4.113**–**4.115** to amines **4.128**-**4.130** led to complex mixtures under established conditions. Additionally, using various Lewis

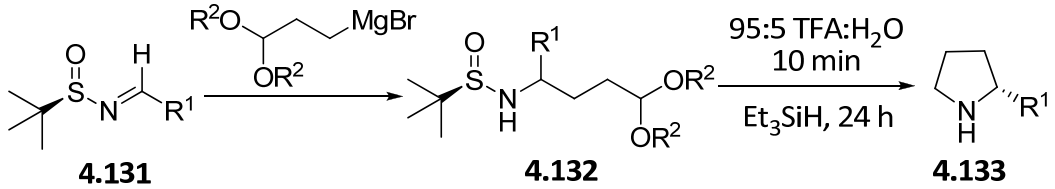
acids catalyst failed to give the desired product (Scheme 4.31). Since the aziridine route proved to be problematic, it was decided to switch to an alternate route.



Scheme 4.31. Failed aziridine ring opening.

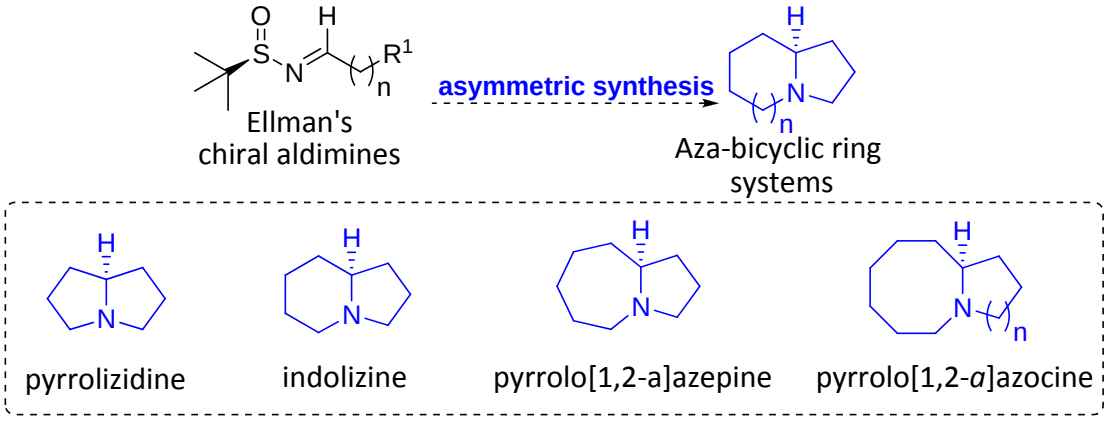
4.12. Approach to azabicyclic ring systems via chiral sulfinamides

Our new route was inspired by Ellman's synthesis of chiral 2-substituted pyrrolidines **4.133** that proceeds with high yields and diastereoselectivities (Scheme 4.32).[33]



Scheme 4.32. Synthesis of chiral 2-substituted pyrrolidines.

We envisioned a protocol involving asymmetric Grignard addition or Indium-mediated allylation, *N*-alkylation, ring closing metathesis (RCM), and finally an intramolecular reductive amination or cyclization to afford enantiopure azabicyclic ring skeleton. Our new approach to azabicyclic rings is outlined in Scheme 4.33.

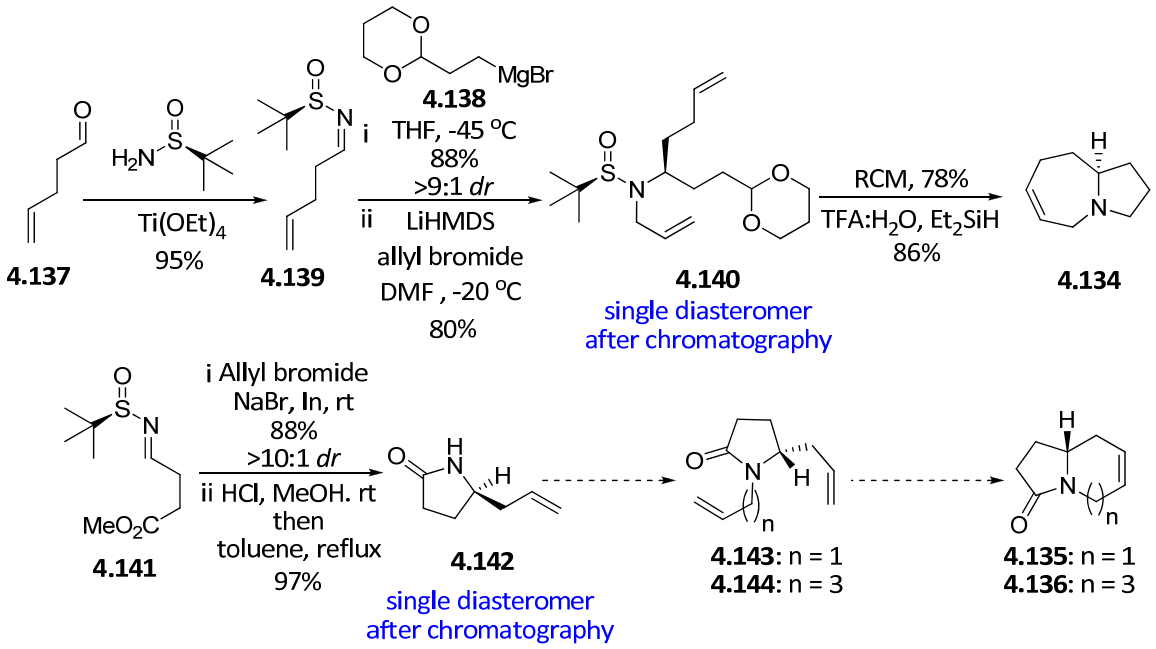


Scheme 4.33. Enantioenriched azabicyclic rings via chiral sulfinamides.

To test the viability of the above strategy, azepine ring **4.134** and lactam **4.141** were prepared in excellent enantiopurity starting from 4-propenal **4.137** and methyl 4-oxobutanoate, respectively (Scheme 4.34). The *N*-Sulfinyl aldimines were prepared by condensation of the aldehydes in the presence of $Ti(OEt)_4$.

Addition of Grignard reagent **4.138** into *N*-sulfinyl aldimine **4.139** gave the desired sulfinamide in 88% yield and high diastereoselectivity (9:1 *dr*). The sulfinamide was isolated as a single diastereomer after silica-gel column chromatography. *N*-alkylation with allyl bromide gave acetal **4.140** as single diastereomer. As previously noticed by Ellman, the addition of the acetal Grignard reagent **4.138** to *N*-sulfinyl aldimine **4.139** proceeds with the opposite sense of induction compared to that observed

for other Grignard reagents. Ellman suggested that the reversal in selectivity is likely due to the intramolecular chelation of the acetal of **4.138**.[33] RCM followed by acidic deprotection of the sulfinamide protecting group and acetal cleavage effected the cyclization, which upon reduction of the resulting iminium ion with triethyl silane gave the desired azepine ring **4.134** in 86% yield (Scheme 4.34).



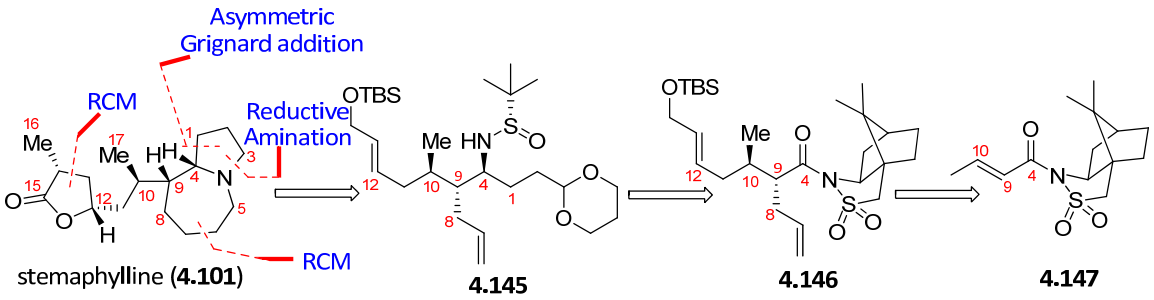
Scheme 4.34. Approach towards azabicyclic ring systems.

Xu and co-workers reported the asymmetric synthesis of chiral homoallylic amines by In-mediated allylation of N-sulfinyl imines in saturated NaBr solution.[34] Applying the conditions, indium mediated allylation of chiral *N-tert*-butanesulfinylimine **4.141** in saturated aqueous NaBr solution at room temperature gave the desired *N*-sulfinyl-amino ester product in 88% yield as 10:1 diastereoslectivity (only the major diastereomer was isolated after column chromatography).[34] *N*-sulfinyl cleavage with HCl

in MeOH, followed by refluxing in toluene resulted in the subsequent lactamization to give lactam **4.142** in 97% yield. Further *N*-alkylation and RCM will afford indolizidine ring **4.135** and azozine ring **4.136** (Scheme 4.34).

4.13. Progress towards the total synthesis stempahylline via chiral sulfinamides

With the model ring systems in place, we moved to apply the new methodology to the total synthesis of stemphylline **4.102** and grandisines alkaloids (**4.79**, **4.83** and **4.89**). Outlined in Scheme 4.35 is our new retrosynthetic analysis of stemaphylline **4.101**.



Scheme 4.35. New retrosynthetic analysis of stemaphylline (**4.101**).

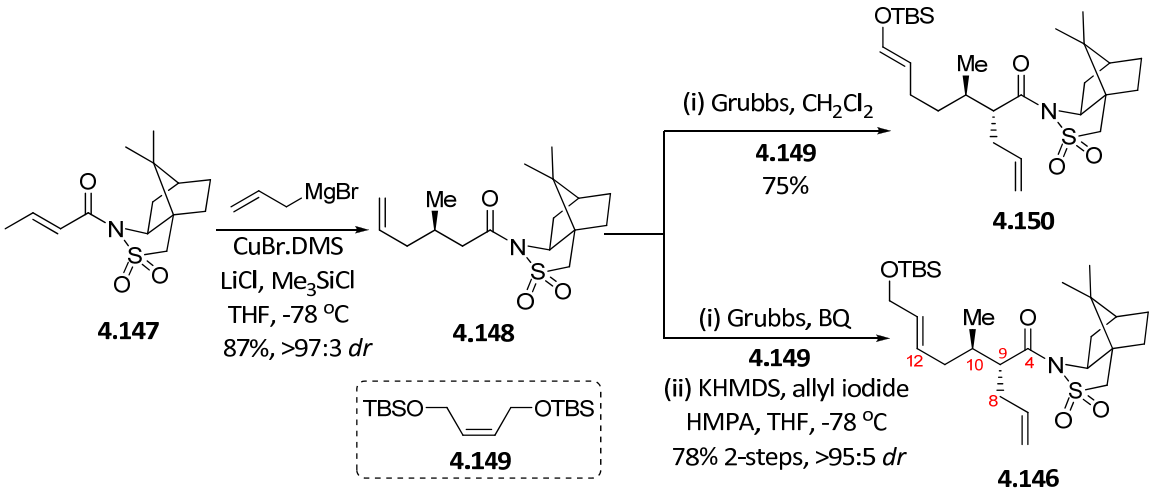
In the new approach, the 5-membered ring of the azepine ring would be installed via asymmetric Grignard addition and acid mediated auxiliary deprotection/intramolecular reductive amination protocol (Scheme 4.35). Sulfinamide **4.145** would be obtained from diene **4.146**, while the C10 and C9 stereochemistry will be installed by asymmetric 1,4-conjugate addition and allylation of commercially available chiral camphor sultam **4.147**.

Conjugate addition of allyl cuprate in the presence of lithium chloride and chlorotrimethylsilane provided **4.148** in 87% yield and high diastereoselectivity (97:3 *dr*).

Cross metathesis of **4.148** with bis-silyl diol **4.149** in the presence of Grubbs' second generation catalyst gave exclusively the isomerised product **4.150** in 75% (Scheme 4.36).

Recently, Grubbs and co-workers reported that using 10 mol% 1,4-benzoquinone as an additive prevents olefin isomerization of a number of allylic ethers and long-chain aliphatic alkenes during olefin metathesis reactions with ruthenium catalysts. Thus performing the reaction in the presence of 10 mol% 1,4-benzoquinone gave the desired cross metathesis product, which was subsequently subjected to stereoselective α-allylation in the KHMDS and HMPA to give diene **4.146** in 78% for 2 steps (Scheme 4.36). The high diastereomeric purity of **4.146** (>95% *dr*) is most likely due to the cooperative contributions arising from the stereocenter at C10 and that of the auxillary.

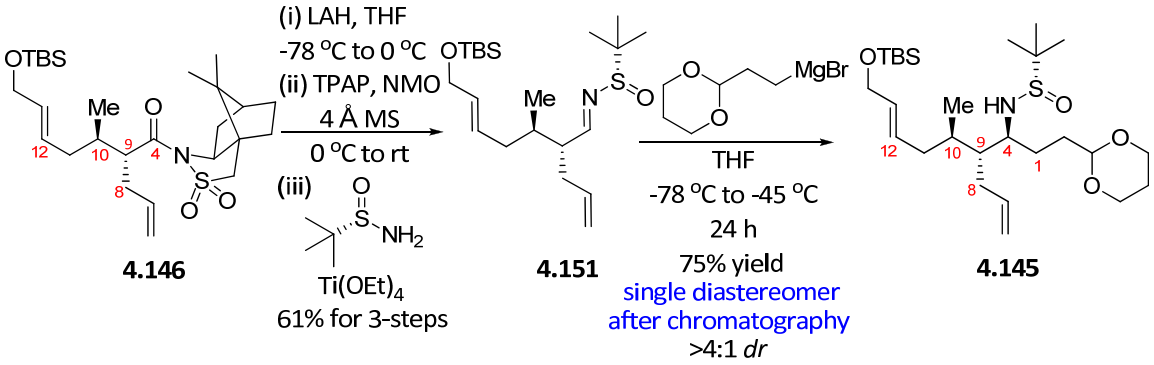
The sultam was reductively cleaved with LAH and oxidation of the resulting primary alcohol with Ley reagent furnished the desired aldehyde. *N*-Sulfinyl aldimine **4.151** was prepared by condensation with (*S*)-tert-butanesulfinamide in the presence of $Ti(OEt)_4$ (Scheme 4.36).



Scheme 4.36. Synthesis of sultam **4.146**.

Grignard addition into the *N*-sulfinyl aldimine **4.151** furnished the desired sulfinamide **4.145** in 4:1 diastereomeric ratio, which upon chromatography gave a single diastereomer of **4.145** in 75% yield (Scheme 4.37).

The configuration at C4 of **4.145** is assigned according to literature precedent.[33]

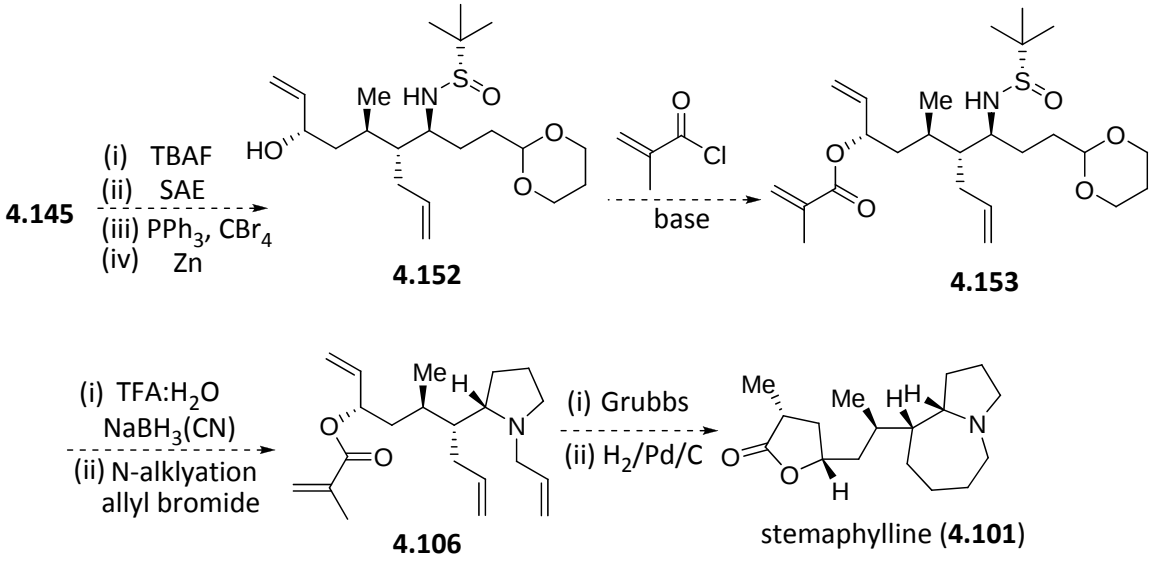


Scheme 4.37. Synthesis of sulfinamide **4.145**.

The final stages of the synthesis would involve generation of the key vinyl alcohol **4.152** through sharpless epoxidation of the resulting allylic alcohol after TBAF deprotection. We anticipate that Appel reaction on the resulting hydroxyl epoxide will provide the required bromide to initiate zinc-mediated ring opening of the epoxide. Exposure of the vinyl alcohol to methacryloyl chloride should provide the acylated product **4.153**.

Acid-mediated intramolecular reductive amination of the resulting sulfinamide should deliver the pyrrolidine ring. Subsequently, *N*-alkyaltion with allyl bromide will give pyrrolidine ring **4.106**, which will set the stage for the double RCM reaction to generate the azepine and the lactone rings. Finally, we anticipate that global

hydrogenation of the double bonds will yield stemaphylline **4.101** with the desired C14 stereochemistry (Scheme 4.38).

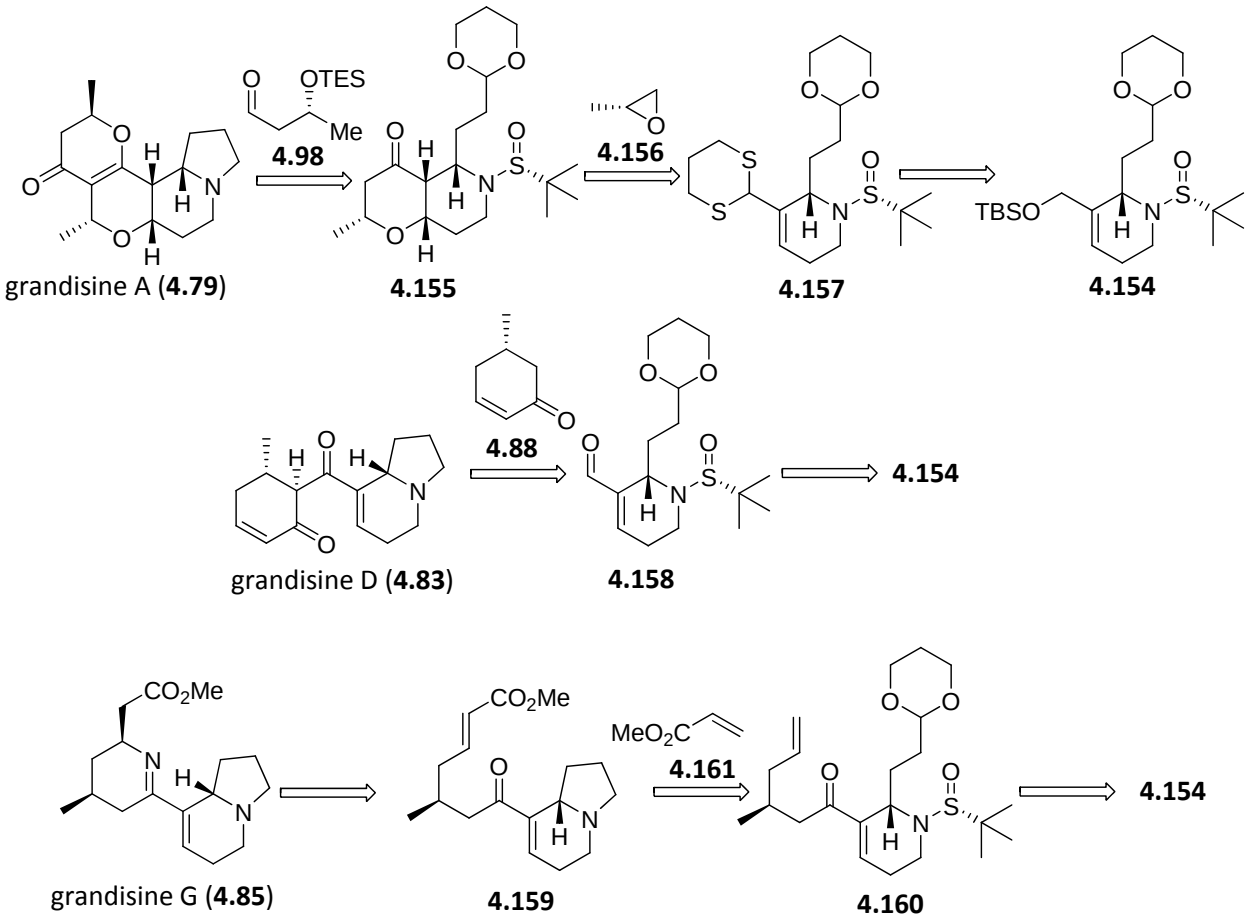


Scheme 4.38. Completion of the total synthesis of stemaphylline **4.101**.

4.14. Progress towards the Total Synthesis of Grandisines A, D, and G

Our interest in the total synthesis of grandisines A, D and G (**4.79**, **4.83**, and **4.85**) was inspired by the successful progress achieved in the application of our new methodology towards the total synthesis of stemophylline (**4.101**).

We envisioned a common intermediate tetrahydropyridine **4.154** in the construction of these indolizidine alkaloids. The retrosynthetic analysis of grandisines A, D, and G (**4.79**, **4.83**, and **4.85**) is summarized in Scheme 4.39.

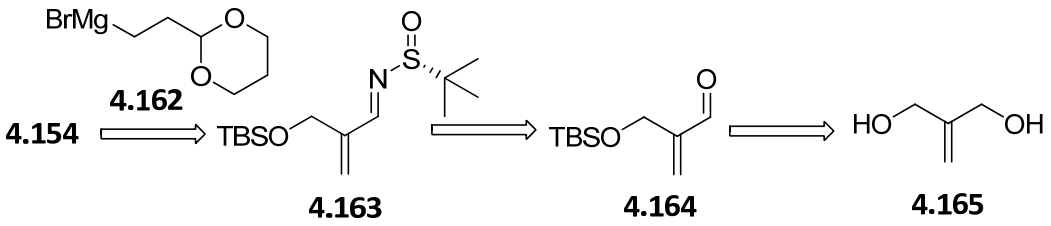


Scheme 4.39. Retrosynthetic analysis of grandisine A, D and G.

Similar to Danishefsky's approach,[24] grandisine A (**4.79**) would be obtained by an aldol reaction of (*R*)-3-(triethylsilyloxy)-butanal **4.98** with pyranone **4.155** prepared from ring opening of commercially available epoxide **4.156** by dithiane **4.157**. We envisage that **4.157** can be prepared from tetrahydropyridine **4.154** (Scheme 4.40). Grandisine D (**4.83**) was seen to arise from aldol reaction of previously known enone **4.88** and α, β-unsaturated aldehyde **4.158**, readily prepared from common intermediate **4.154**. Our retrosynthetic analysis of grandisine G (**4.85**) envisaged an intramolecular Michael

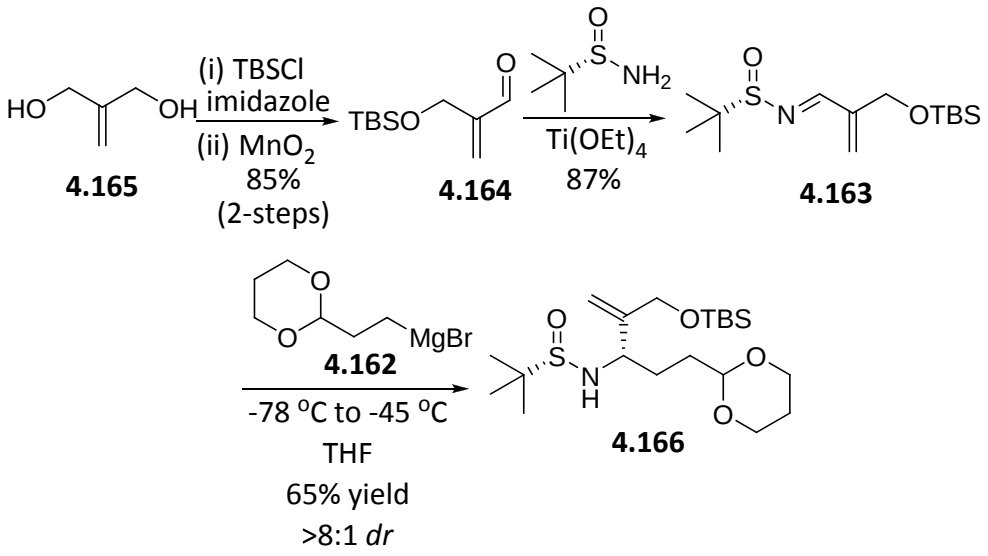
addition reaction of ketimine **4.159**. Cross metathesis of olefin **4.160** and α, β-unsaturated ester **4.161**, followed by ketimine formation will provide **4.159**.

Based on the developed methodology, the key tetrahydropyridine ring **4.154** would be installed via asymmetric Grignard addition of acetal reagent **4.162** into *N*-sulfinyl aldimine **4.163**. The precursor to this key transformation, aldehyde **4.164** would be accessible by mono-protection and allylic oxidation of diol **4.165** (Scheme 4.40).



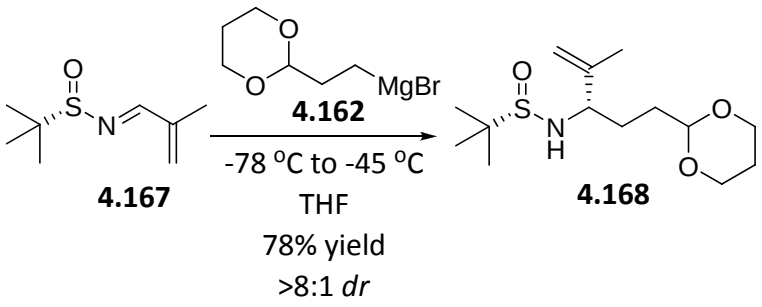
Scheme 4.40. Approach to common intermediate for grandisines A, D and G.

We propose to approach the synthesis of **4.154** or similar intermediate **4.158** via two similar substrates. The synthesis of **4.154** began from diol **4.165**; mono-protection with TBSCl followed by MnO_2 oxidation gave desired aldehyde **4.164** in 75% yield for 2-steps. Condensation with (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ gave the desired *N*-sulfinyl aldimine **4.163**. Grignard addition reaction furnished the desired sulfinamide **4.166** in >8:1 diastereomeric ratio, which upon chromatography gave a single diastereomer in 65% yield (Scheme 4.41).



Scheme 4.41. Synthesis of sulfinamide **4.166**.

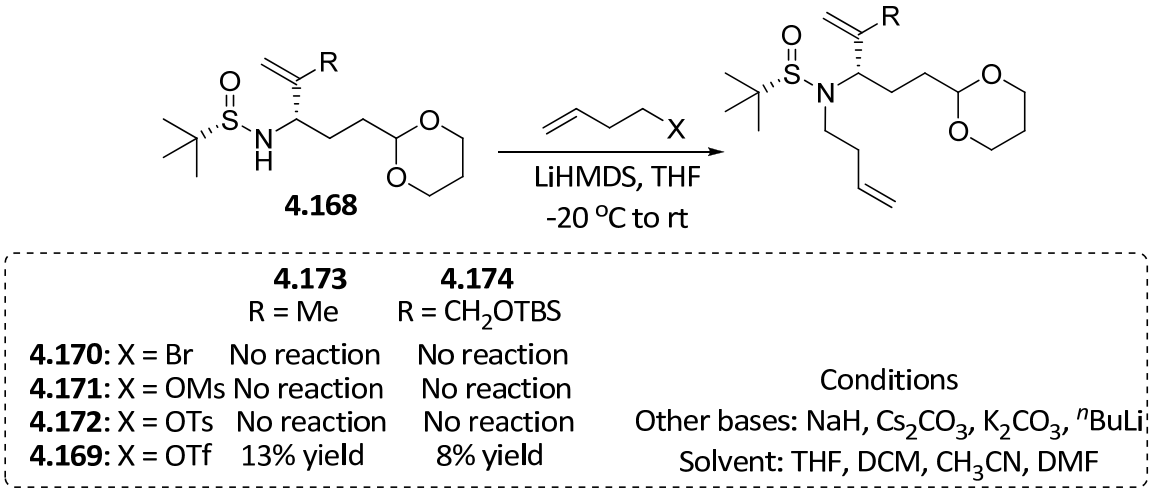
At this point, we decided to approach aldehyde **4.158** via a similar approach. Grignard addition into aldimine **4.167** generated from commercially available methacrolein, gave sulfinamide **4.168** in 78% yield (>8:1 *dr*) (Scheme 4.42).



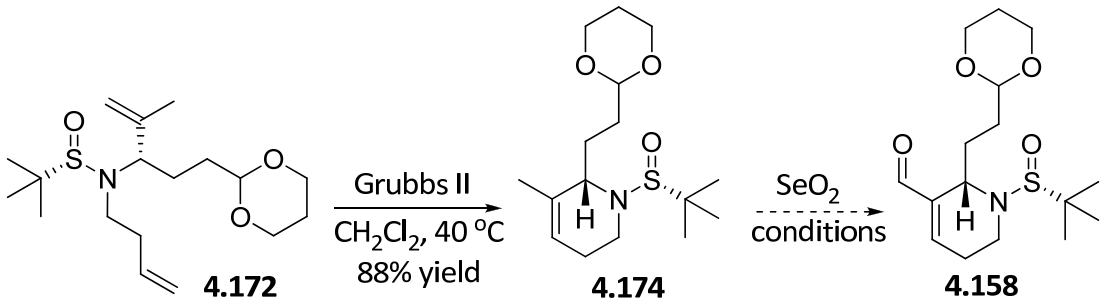
Scheme 4.42. Synthesis of sulfinamide **4.168**.

Surprisingly, *N*-alkylation of these substrates proved to be problematic. A variety of base and leaving groups were utilized as shown in Scheme 4.43. Only triflate **4.169** gave the desired *N*-alkylated products **4.173** and **4.174** in poor yields. It is noteworthy to

mention that *N*-alkylation with the bromides such as allyl bromide and 5-bromopentene proceed smoothly to give their corresponding *N*-alkylated products. We thought that the ease for **4.169**-**4.172** to eliminate to butadiene might be the reason for the low yield or lack of reactivity in the case of **4.173** or **4.174**. Although, there is literature precedent for this type of *N*-alkylation using **4.169**-**4.172**,[35] unfortunately these conditions did not work in our hands.



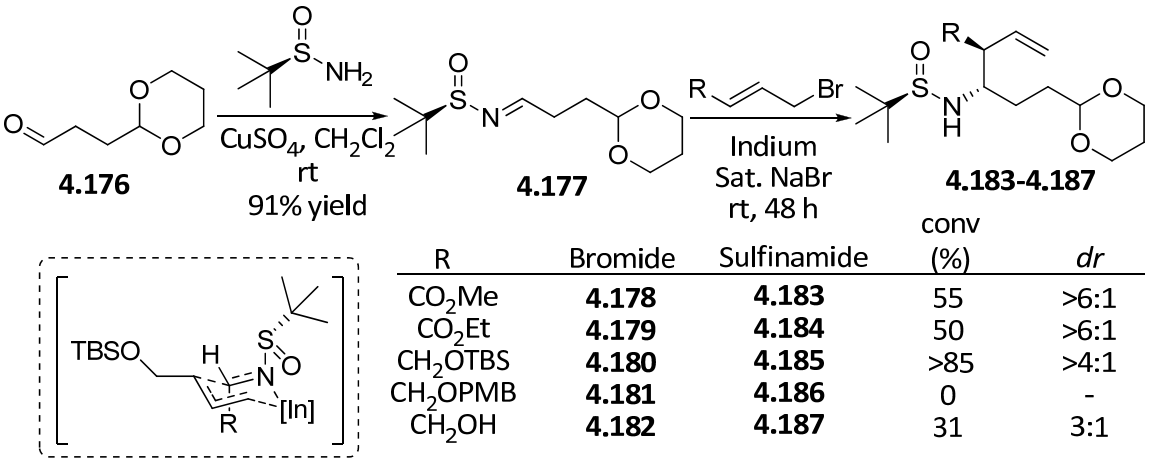
Scheme 4.43. *N*-alkylation of sulfinamide **4.168**.



Scheme 4.44. Failed route to **4.158**.

RCM of **4.174** furnished the desired tetrahydropyridine ring **4.175** in 88% yield. Unfortunately, oxidation of the allylic methyl group to give key aldehyde **4.158** failed using established conditions (Scheme 4.45). Due to these unexpected results, we decided to construct the tetrahydropyridine ring **4.158** via an alternative route.

The synthesis began from aldehyde **4.176**, which undergoes condensation with (*R*)-tert-butanesulfinamide to give aldimine **4.177**. Initial investigations focused on performing indium-mediated allylation of **4.177** using a variety of bromides (**4.178**-**4.182**), and the results are summarized in Scheme 4.46. Utilizing bromo-ester **4.178** and **4.179** gave the desired homoallylic sulfinamide **4.183** and **4.184** in 50-55% conversions. These results were promising as revealed by the bromo-esters. Using free alcohol **4.182** led to lower conversion and diastereoselectivity, while no reaction occurred when PMB-ether **4.181** was used. An increase of the reaction conversion to product and moderate diastereoselectivity was observed when TBS-ether **4.180** was used (>85% conversion, >4:1 *dr*) (Scheme 4.45).

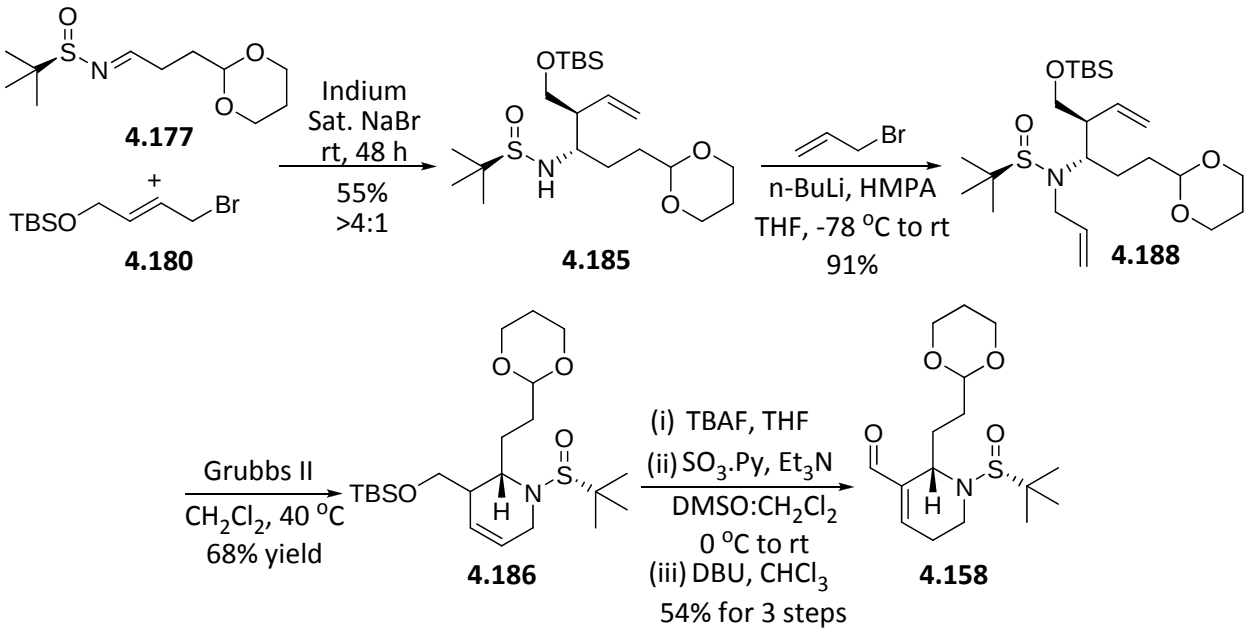


R	Bromide	Sulfinamide	conv (%)	*dr*
CO_2Me	**4.178**	**4.183**	55	>6:1
CO_2Et	**4.179**	**4.184**	50	>6:1
CH_2OTBS	**4.180**	**4.185**	>85	>4:1
CH_2OPMB	**4.181**	**4.186**	0	-
CH_2OH	**4.182**	**4.187**	31	3:1

Scheme 4.45. Indium-mediated allylation aldimine **4.177**.

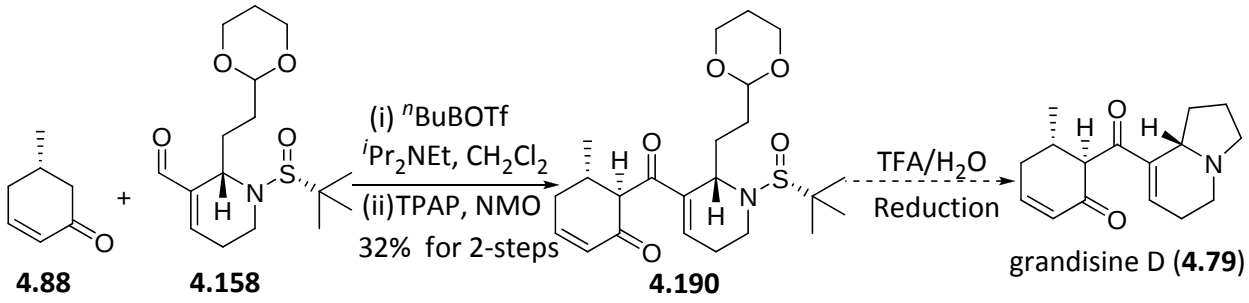
The *syn*-configuration was assigned according to literature precedent and the six-membered chair transition state model (Scheme 4.46).[34] These reactions were all performed at 0.05 mmol scale of **4.177**. Surprisingly, upon scaling up the synthesis (even at 0.25mmol scale of **4.177**) only 20% conversion to the desired product was observed. After surveying a variety of reaction conditions, we found that pre-mixing by stirring and sonication of the indium metal and bromide before adding the aldimine was crucial to deliver homoallylic sulfinamide **4.185**.

N-alkylation proceeded uneventfully delivering key diene **4.188** for RCM reaction. Exposure to second generation Grubbs catalyst provided the desired tetrahydropyridine ring **4.189**. Once in hand, the TBS-ether was deprotected, oxidized and the double bond was isomerized with DBU to produce the desired α, β-unsaturated aldehyde **4.158** in 55% yield over 3-steps (Scheme 4.46).



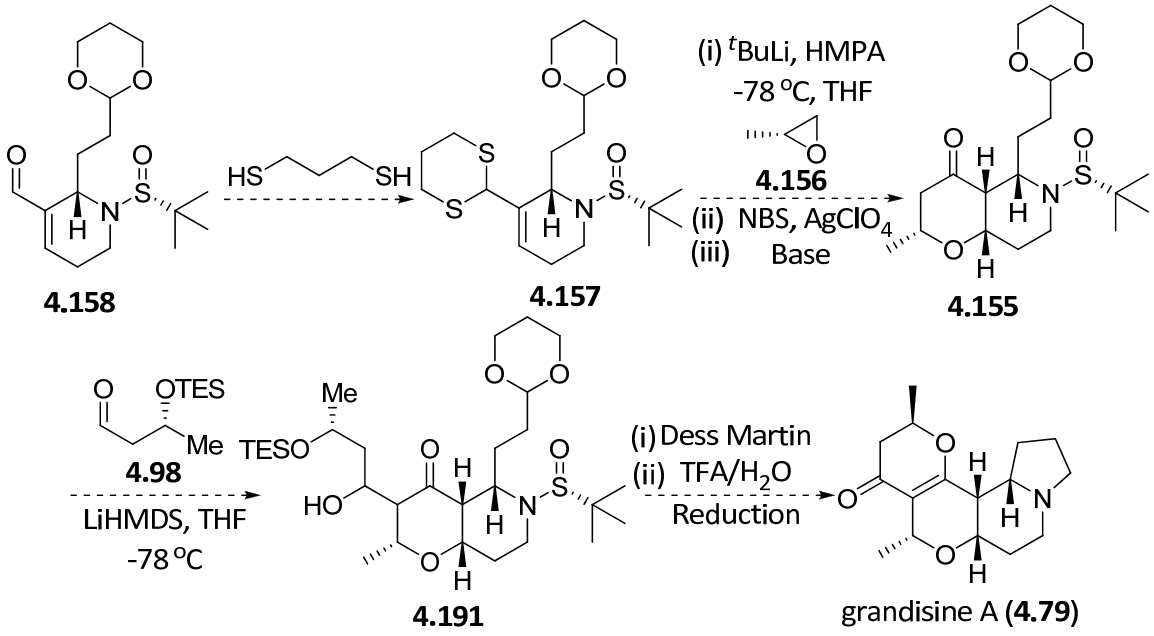
Scheme 4.46. Synthesis of α, β-unsaturated aldehyde **4.158**.

Aldol reaction of previously known enone **4.88** and aldehyde **4.158** followed by Ley oxidation furnished α, β-unsaturated ketone **4.190**, the direct precursor to grandisine D (**4.83**). At this point, we are hopeful that subjecting **4.190** to acid would mediate *N*-sulfinyl and acetal deprotection and intramolecular reductive amination after reduction of the resulting iminiun ion to provide grandisine D **4.83** (Scheme 4.47).



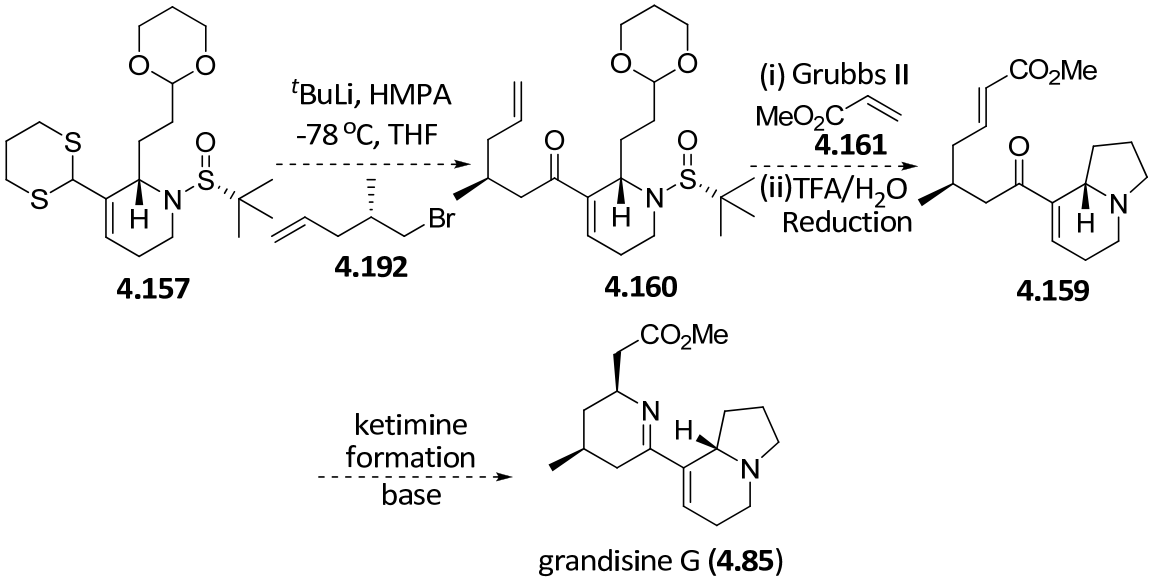
Scheme 4.47. Completion of synthesis of grandisine D **4.83**.

Grandisine A (**4.79**) will be accomplished as follows (Scheme 4.48). Protection of the aldehyde **4.158** as 1,3-dithiane, lithiation of **4.157** followed by epoxide ring opening, deprotection of the dithiane group of the resulting alcohol and 1,4-conjugate addition of the resulting ketone will give rise to tetrahydro-*cis*-fused pyranone **4.155**. Aldol reaction of pyranone **4.155** and aldehyde **4.98** should proceed smoothly. The resulting β-hydroxy ketone **4.191** will be oxidized and subsequent acid-mediated global deprotection and double cyclization would provide grandisine A (**4.79**) after reduction of the resulting iminium ion.



Scheme 4.48. Synthesis of grandisine A **4.79**.

Grandisine G (**4.85**) would be achieved as follows (Scheme 4.49). Starting from dithiane **4.157**, we envisioned S_N2 displacement of olefin **4.192**, followed by deprotection of the dithiane. Cross metathesis of the resulting α,β-unsaturated ketone **4.160** will furnish α,β-unsaturated ester **4.159**. We anticipate that ketimine formation will occur, which should rapidly undergo intramolecular Michael addition into the α,β-unsaturated ester to provide grandisine G (**4.85**). We anticipate an intramolecular Michael addition reaction to occur from the desired face to give the correct configuration due to the stereochemistry of the methyl substituent (Scheme 4.49).



Scheme 4.49. Synthesis of grandisine G **4.85**.

4.15. Conclusion

In conclusion, two independent approaches towards the construction of the azabicyclic ring system were studied. The aziridine ring opening proved problematic but current studies are underway to effect this transformation which is precedent in the literature.

We have developed a powerful extension of Ellman asymmetric synthesis of pyrrolidine rings for the general construction of azabicyclic ring systems in good yields and diastereoselectivity. Moreover, the new methodology allows the asymmetric synthesis of key intermediates towards the total synthesis of stemaphylline, grandisine A, D and G. Overall, these novel strategies for the synthesis of azabicyclic ring systems found in numerous alkaloids and drug molecules from readily available precursors, represent a significant improvement in the art to access these therapeutically relevant alkaloid scaffolds.

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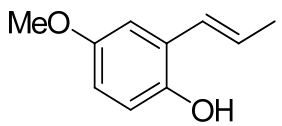
Appendix A1:

Spectra Relevant to Chapter I.



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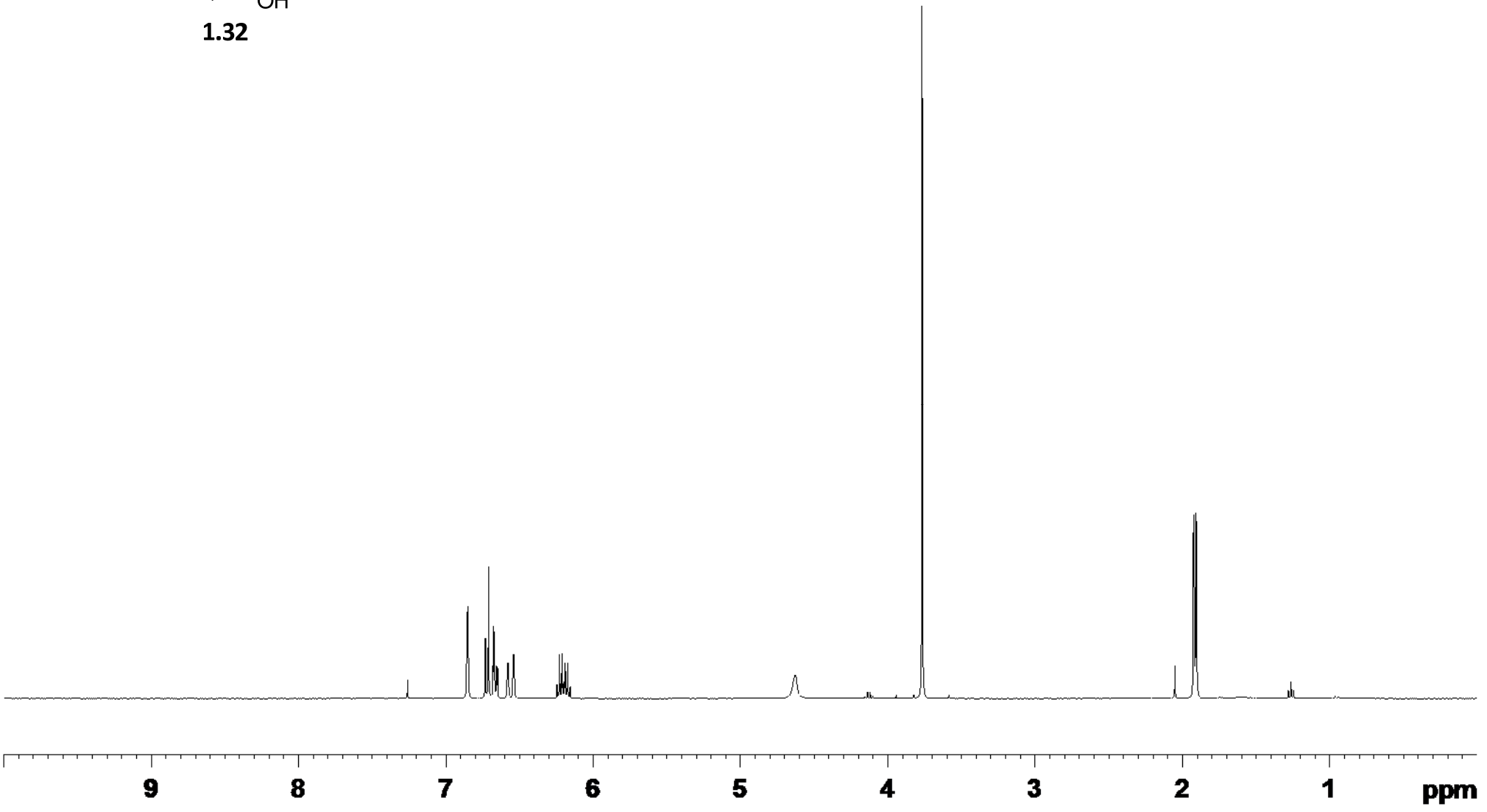

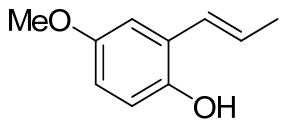

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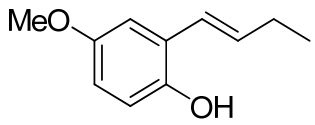

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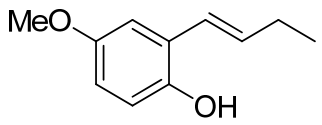

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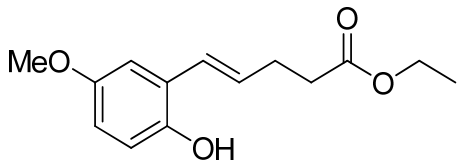

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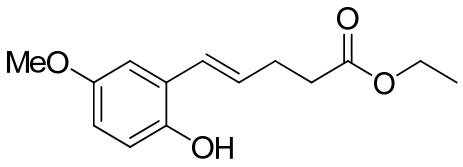

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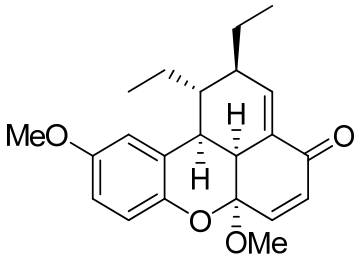

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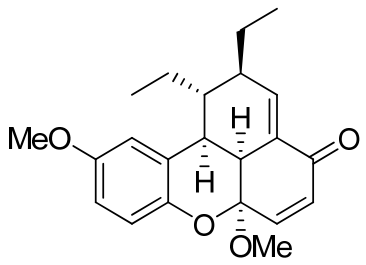

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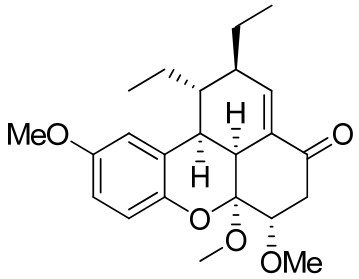

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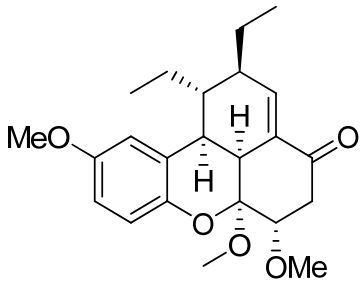

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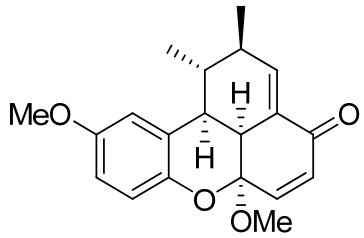

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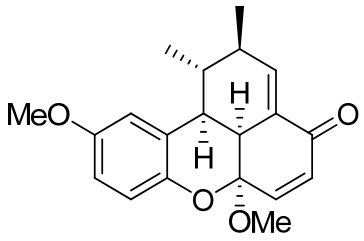

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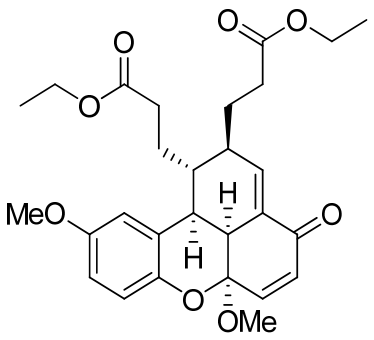

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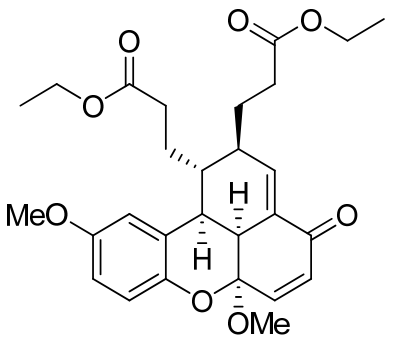

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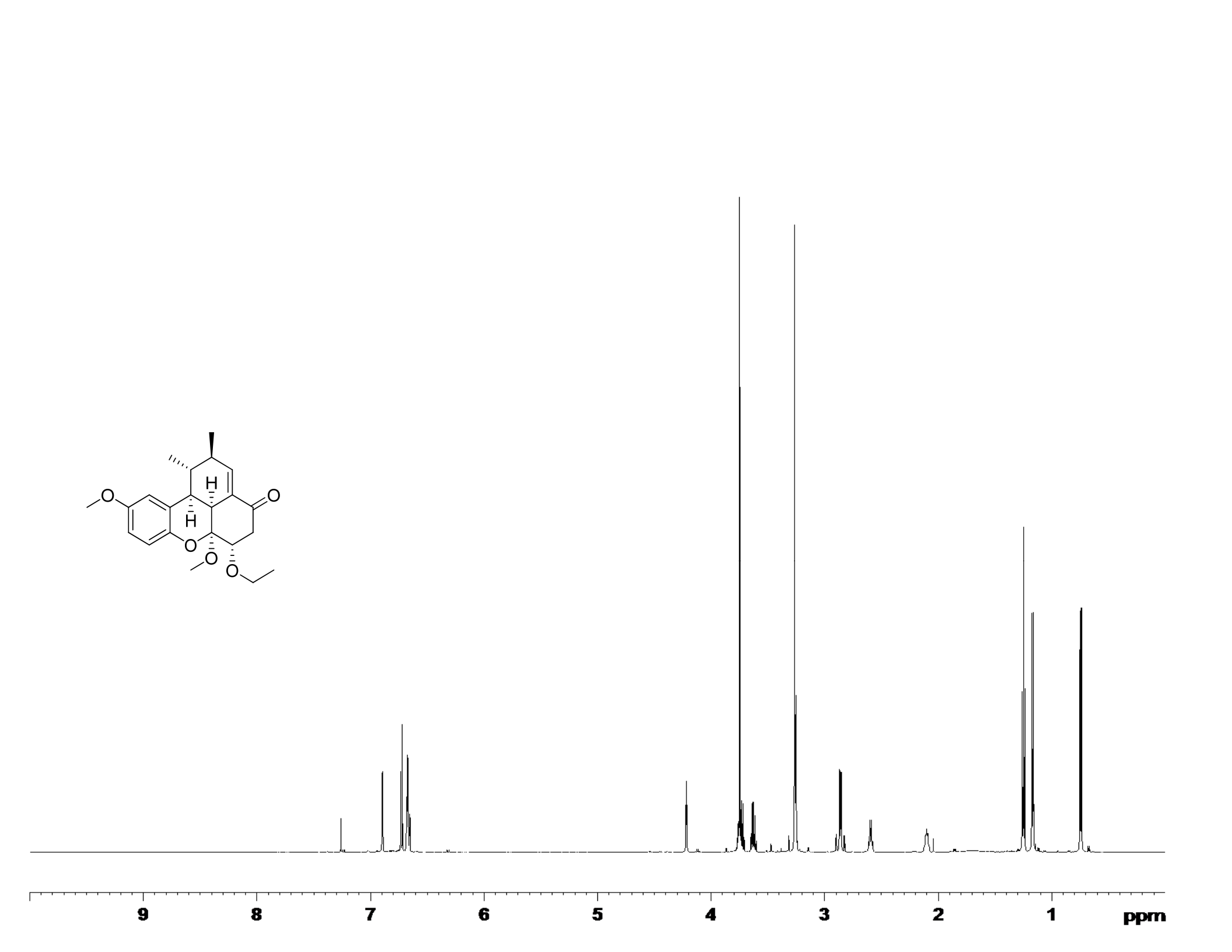
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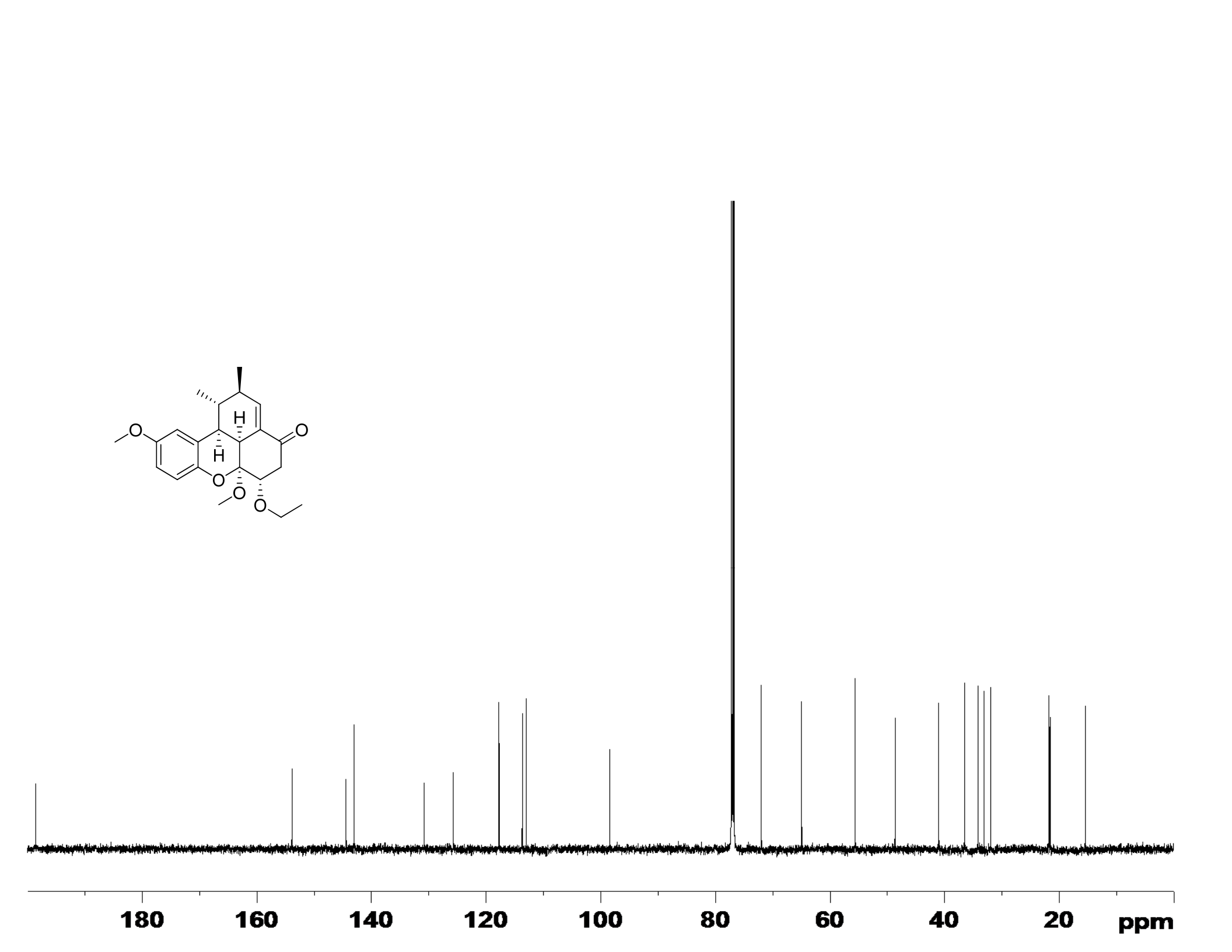
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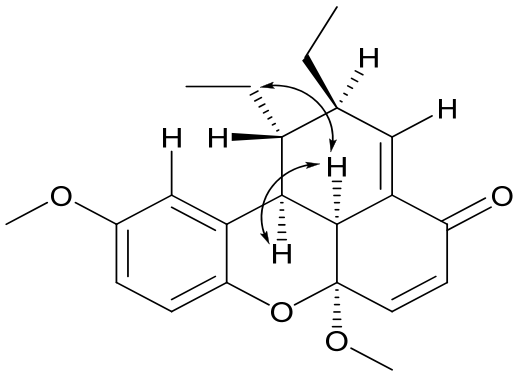
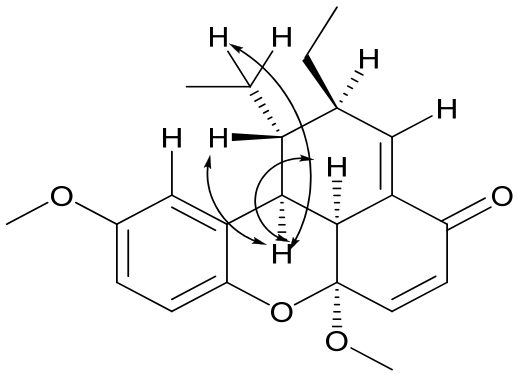
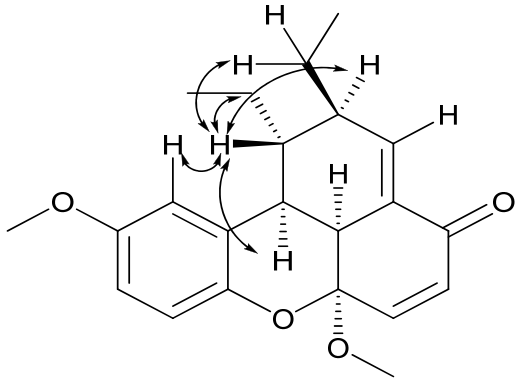
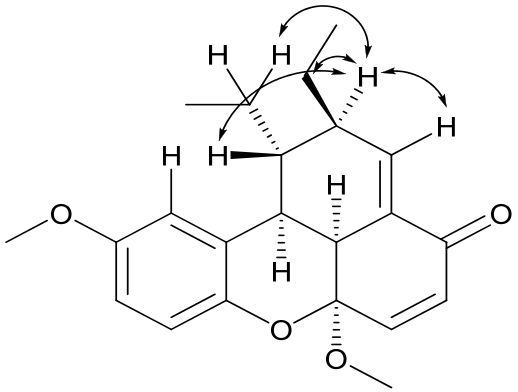
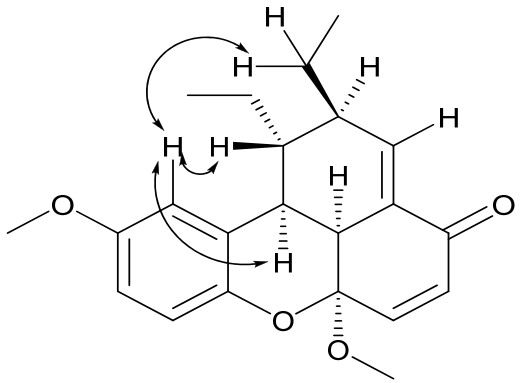
nOe correlations observed for **1.35** to confirm relative stereochemistry

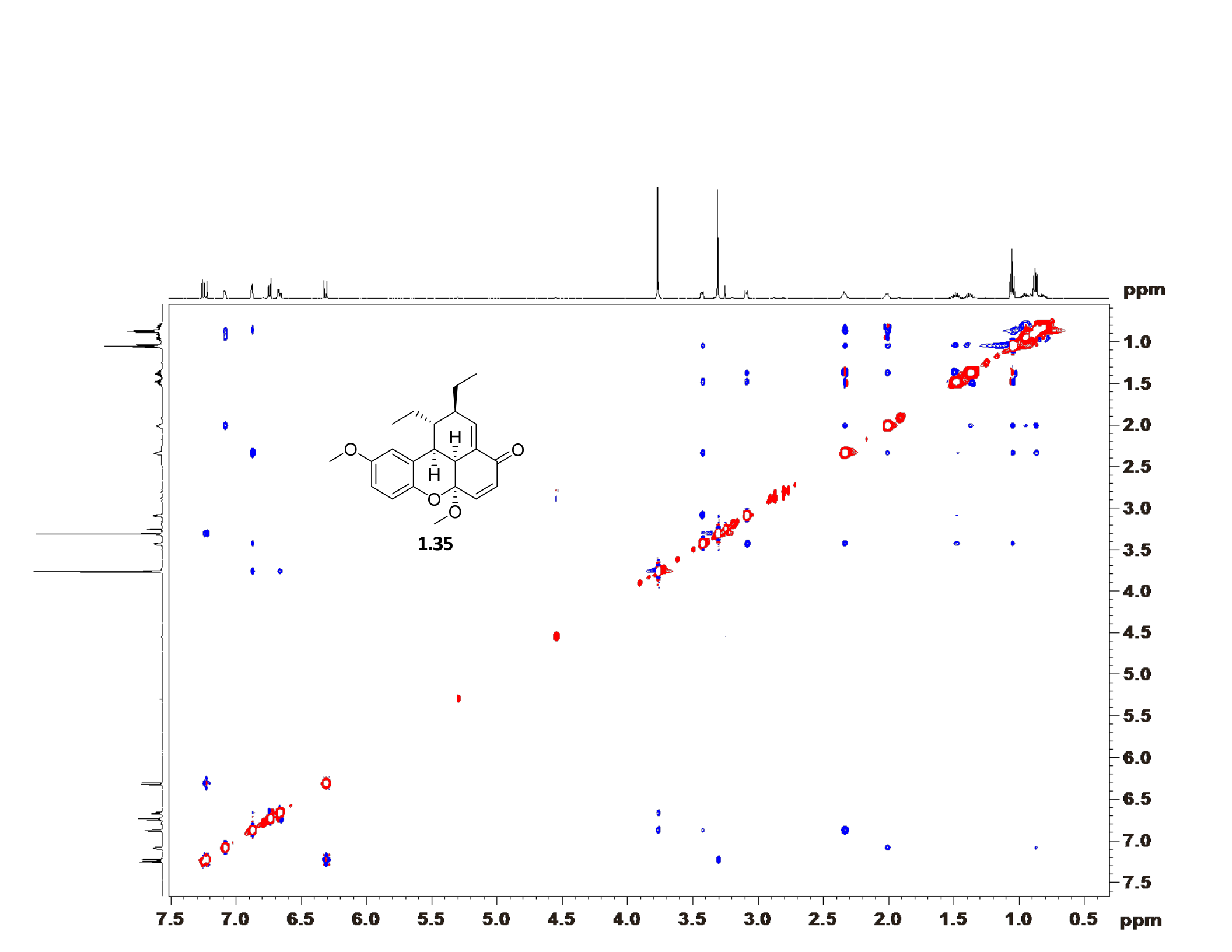








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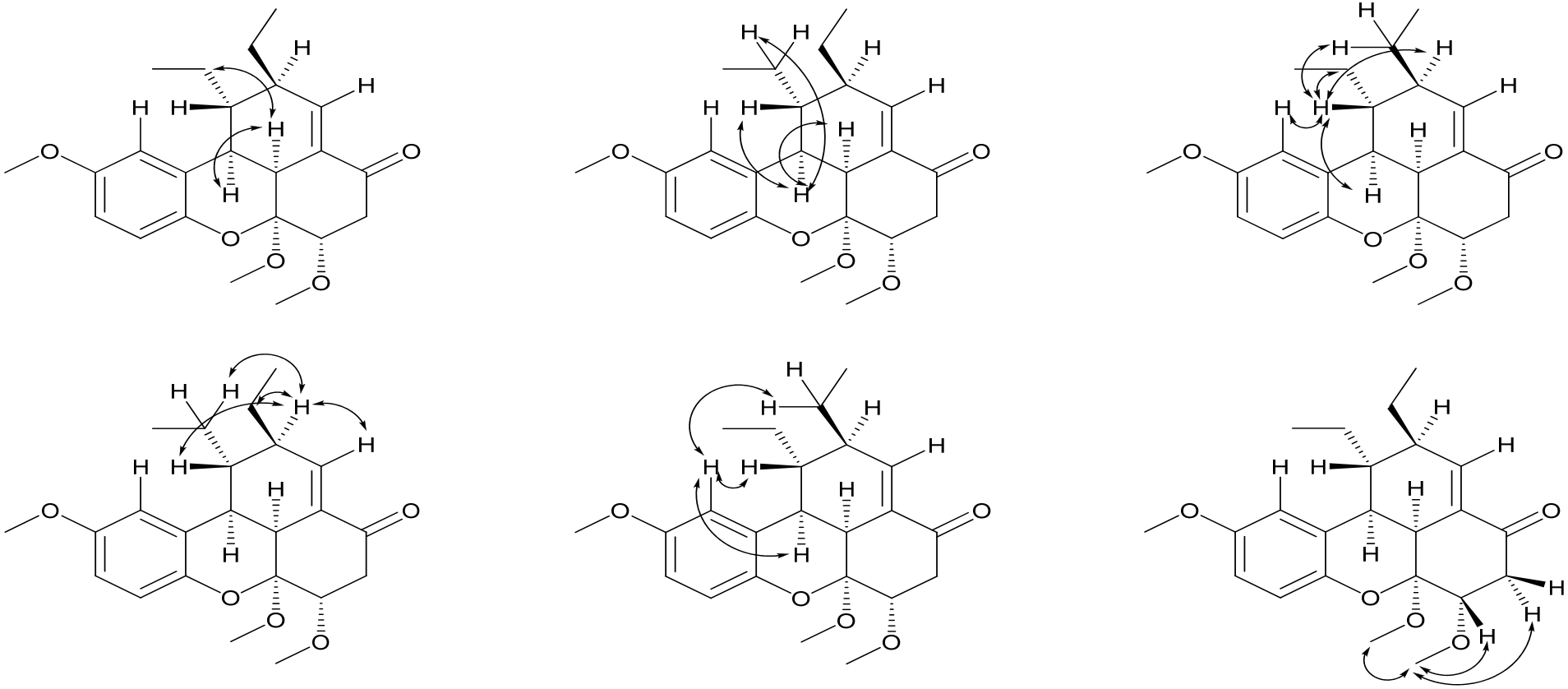
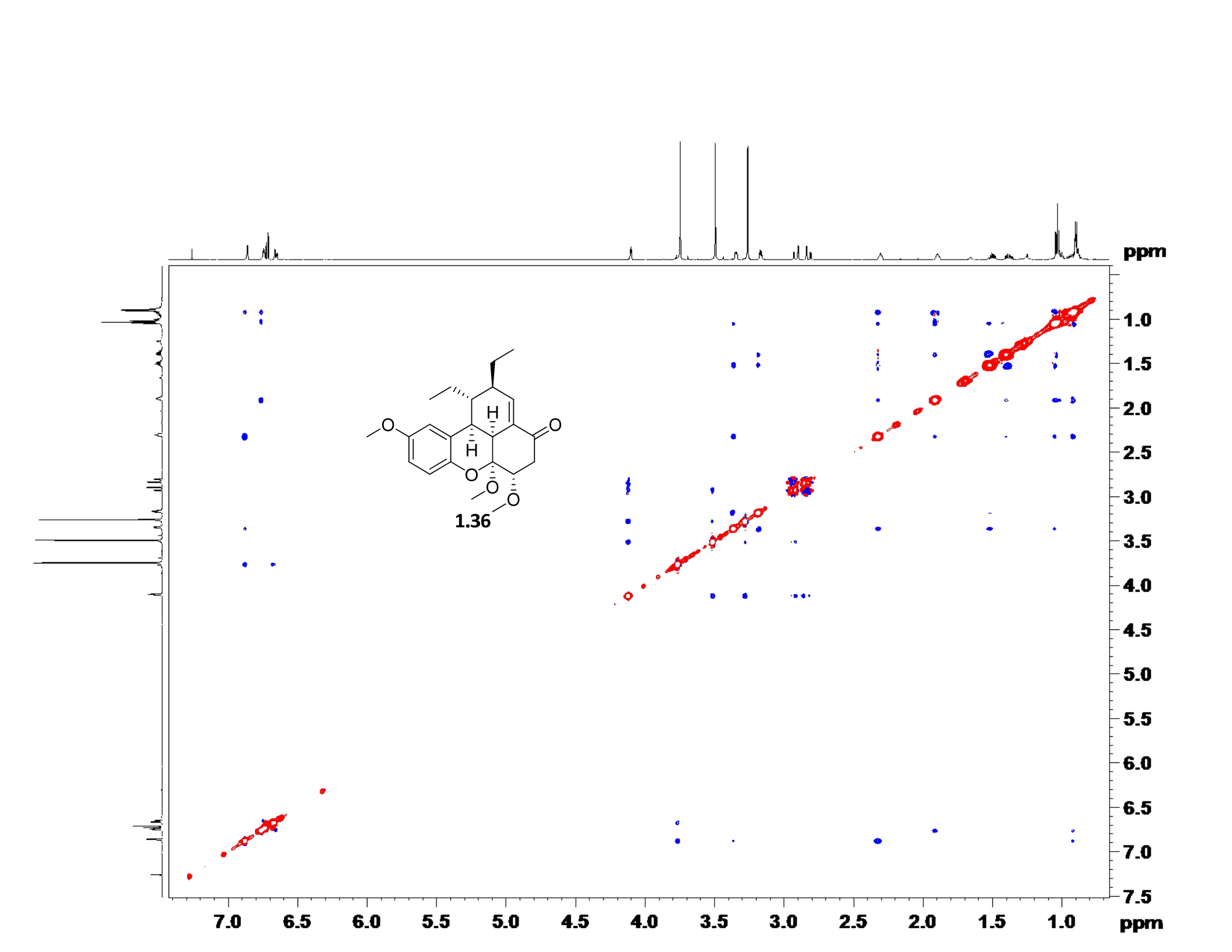
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
H
H
O
O
O
O
1.35

nOe correlations observed for **1.36** to confirm relative stereochemistry

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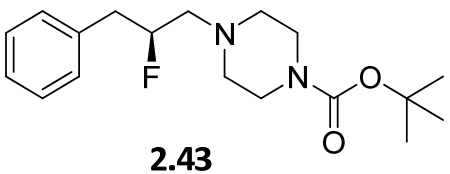
3.5
3.0
2.5
2.0
1.5
1.0
ppm
H
H
O
O
O
O
O
1.36

Appendix A2:

Spectra Relevant to Chapter II.



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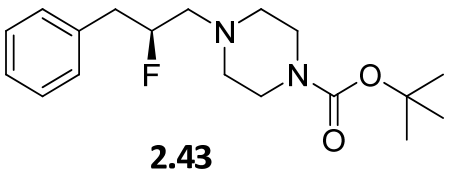

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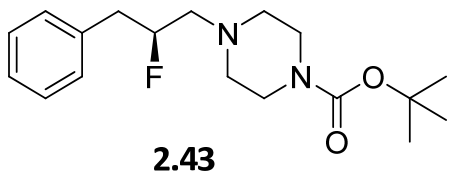

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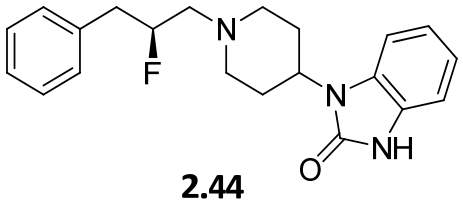

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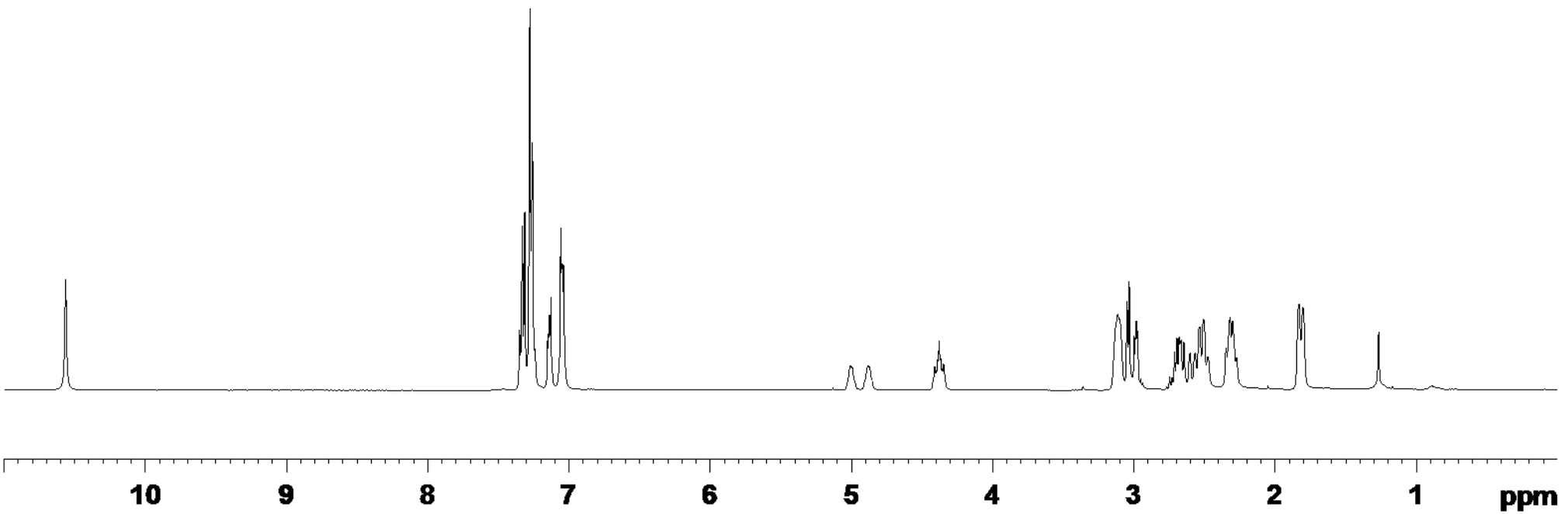

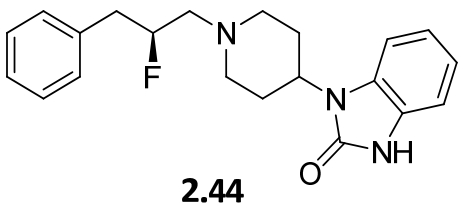

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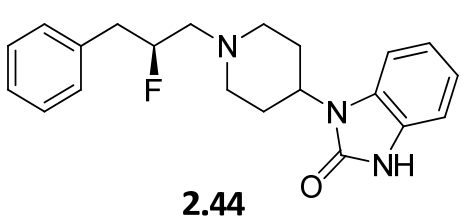

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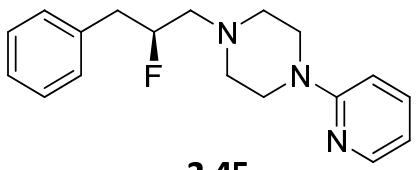

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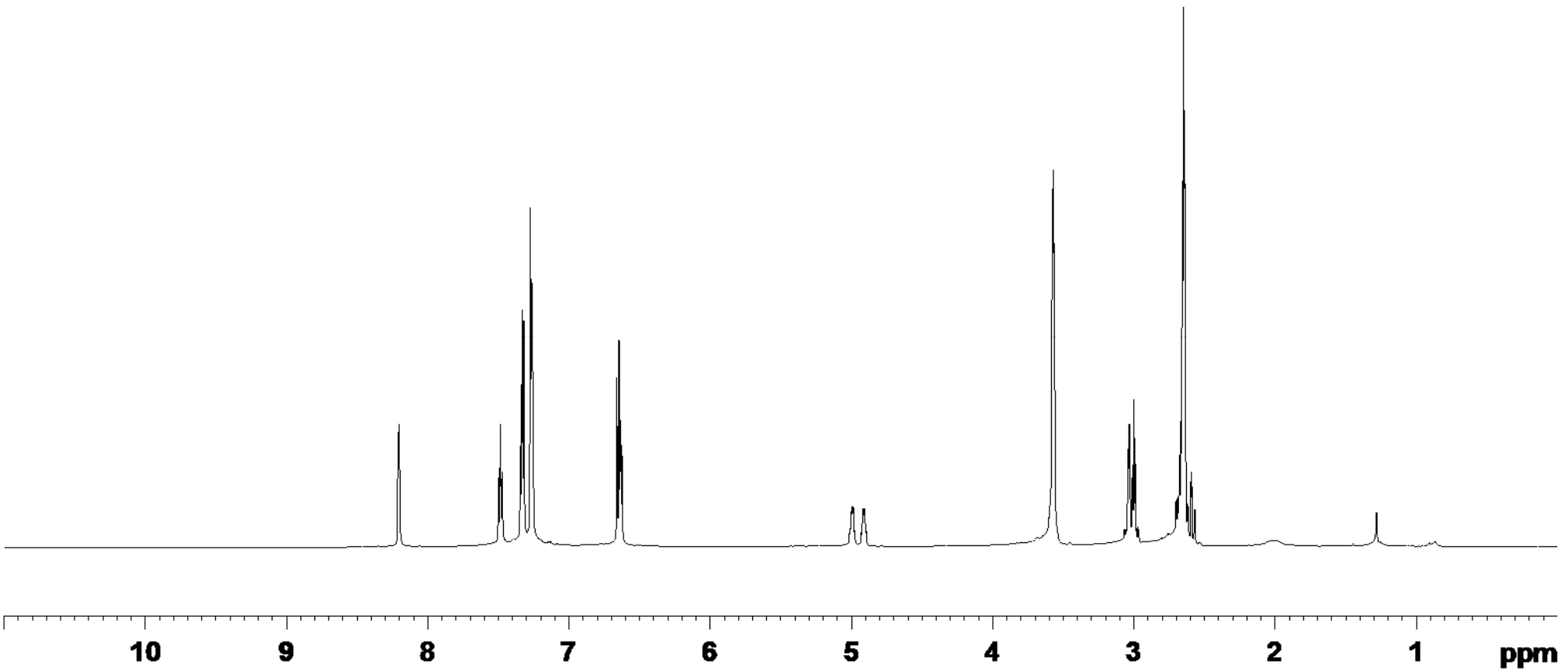

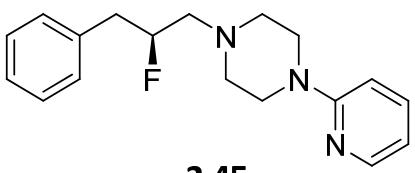

2.45

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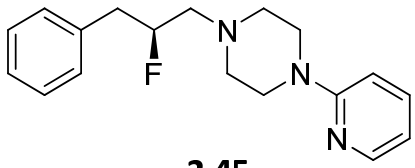

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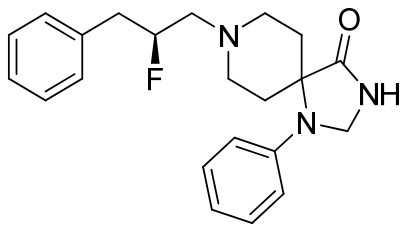

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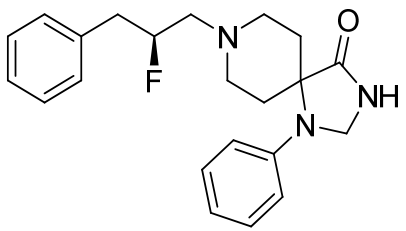

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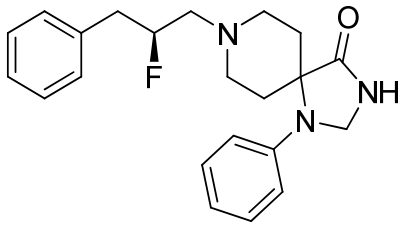

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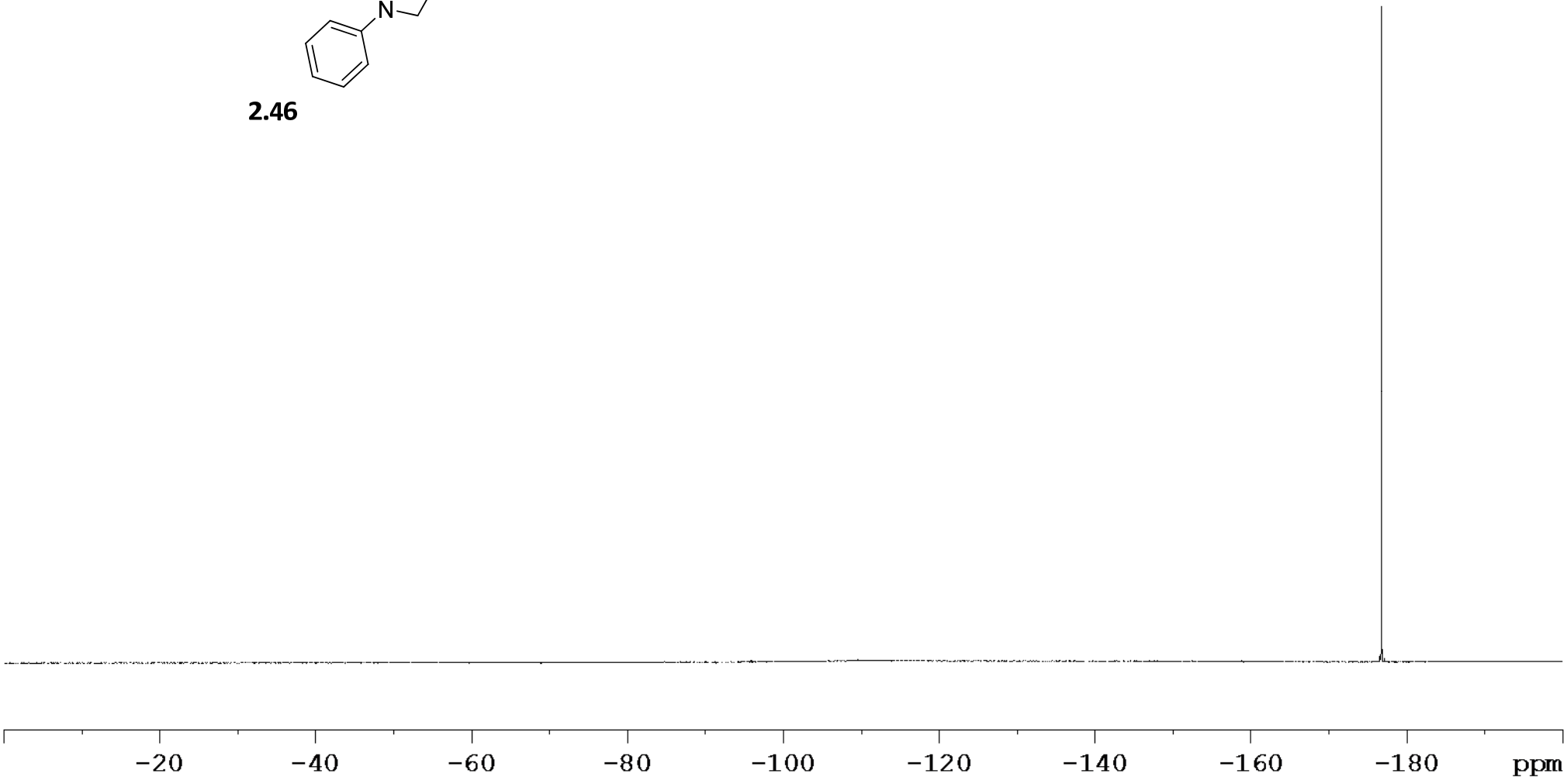

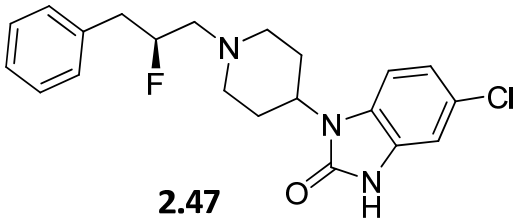

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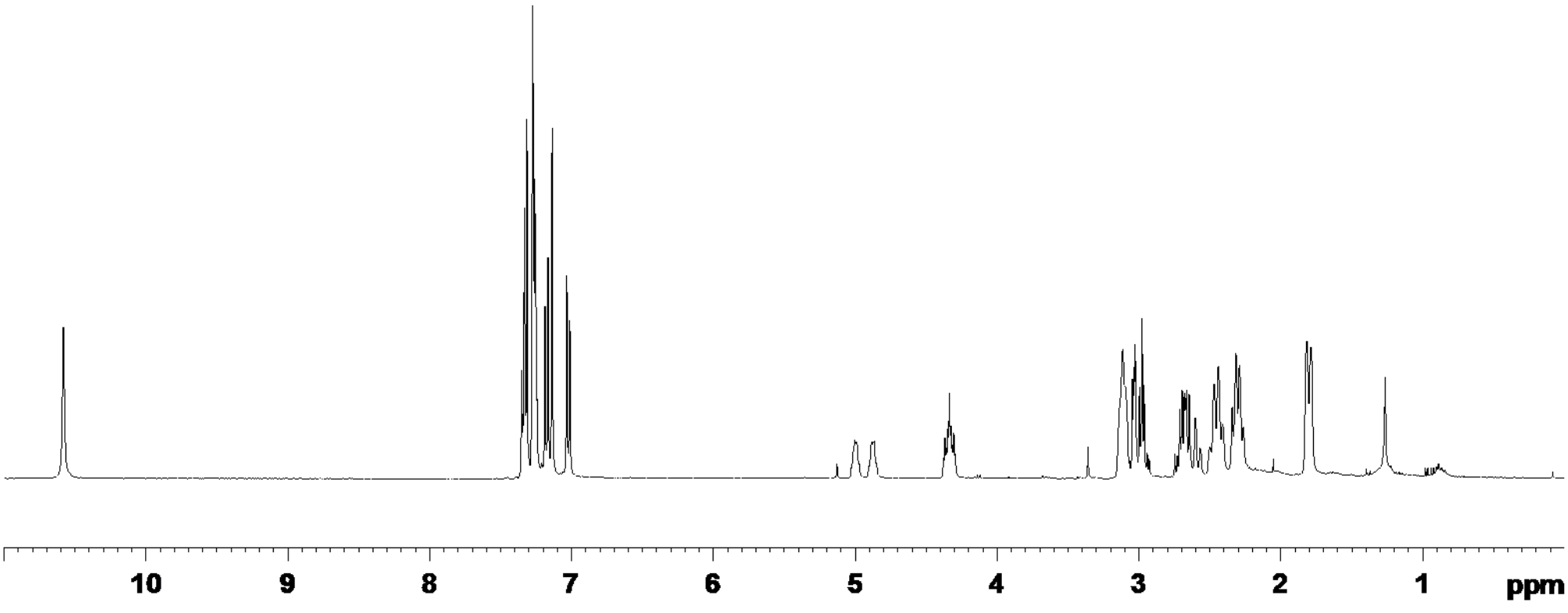

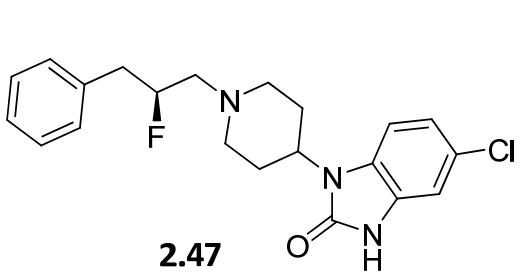

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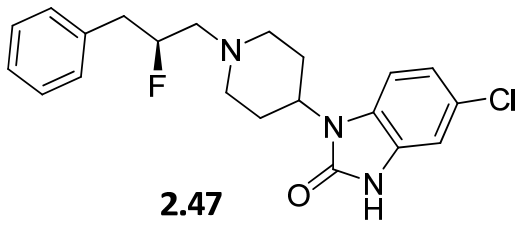

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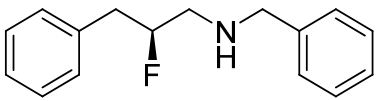

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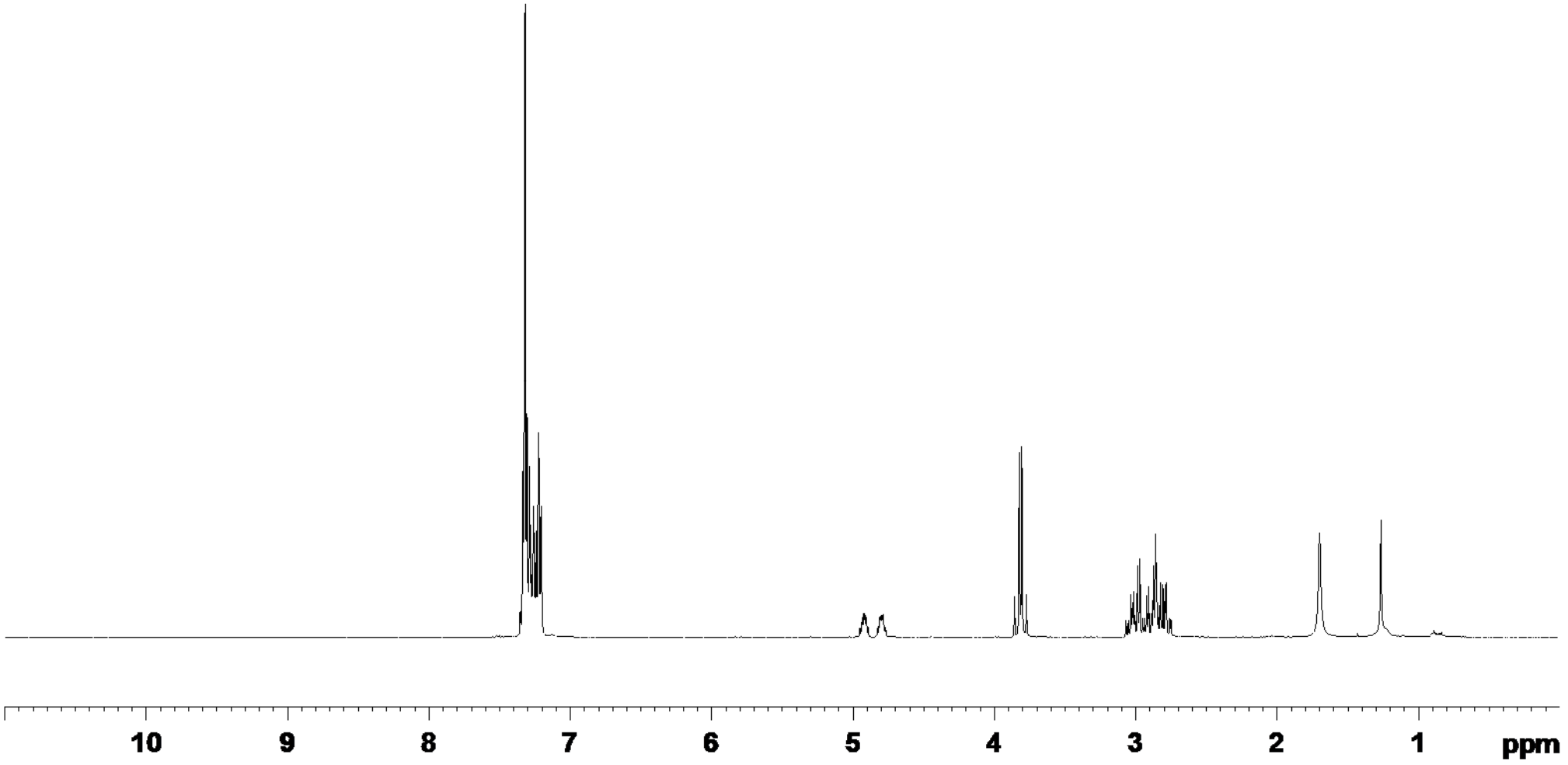

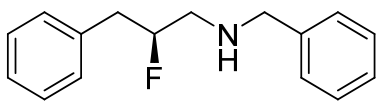

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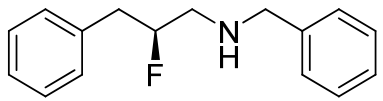

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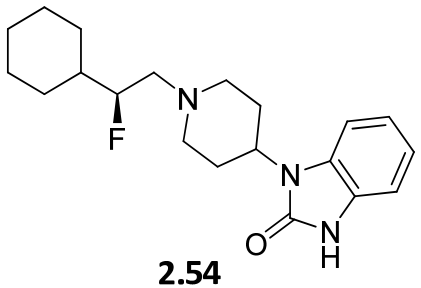

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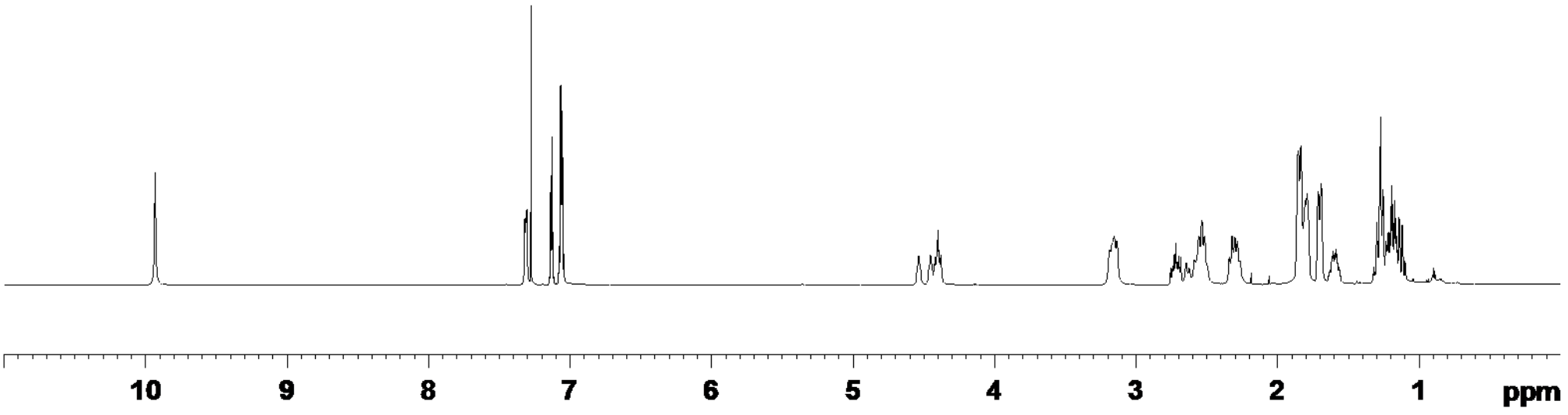

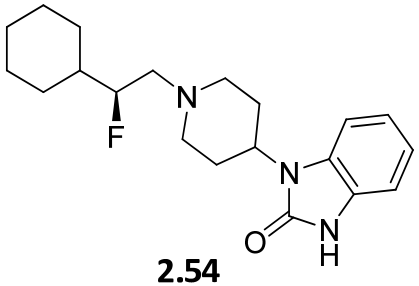

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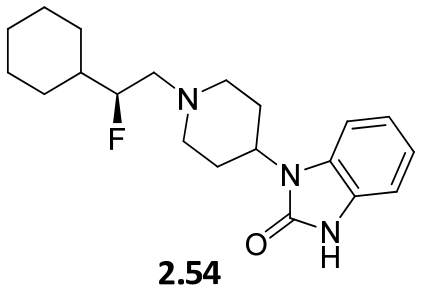

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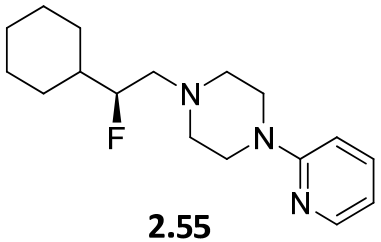

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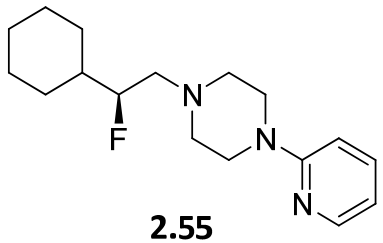

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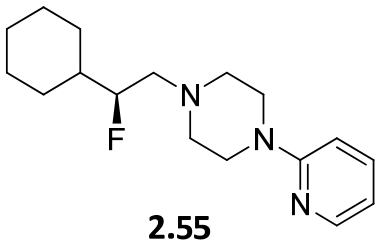

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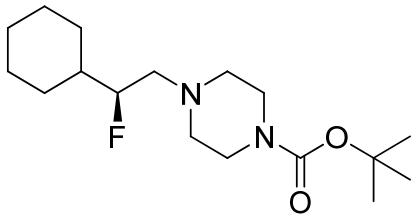

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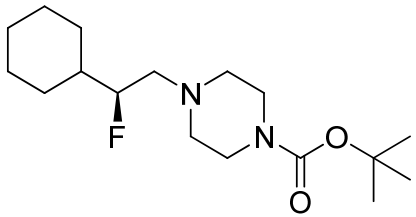

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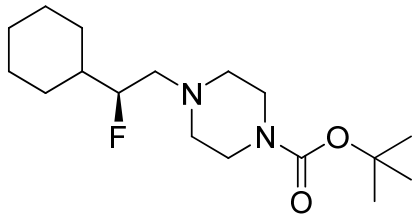

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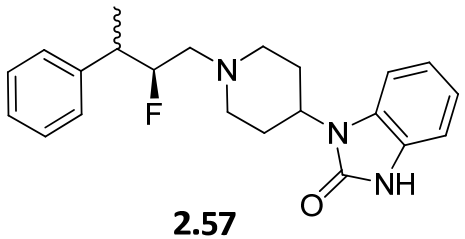

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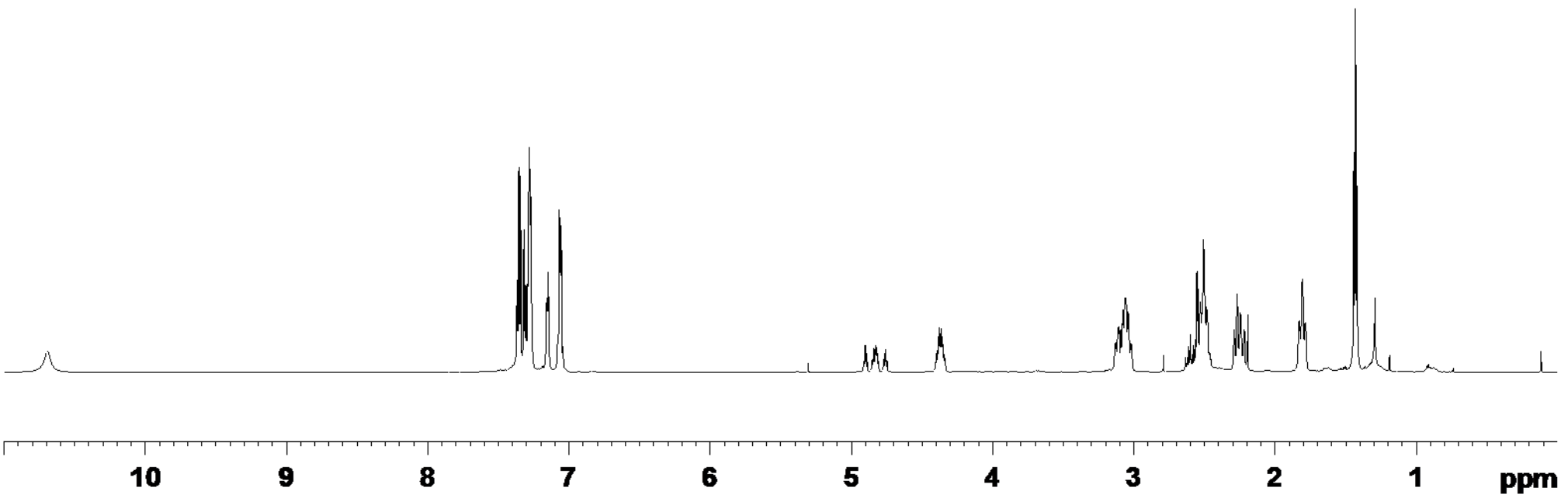

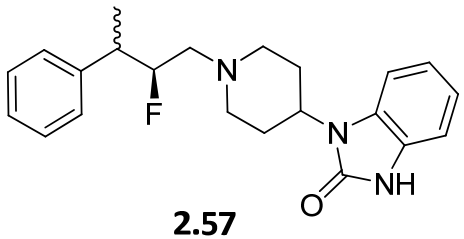

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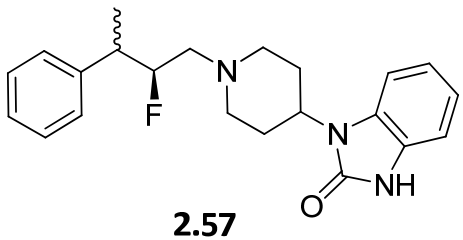

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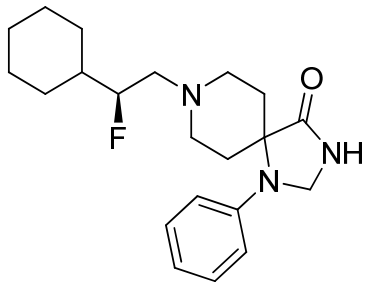

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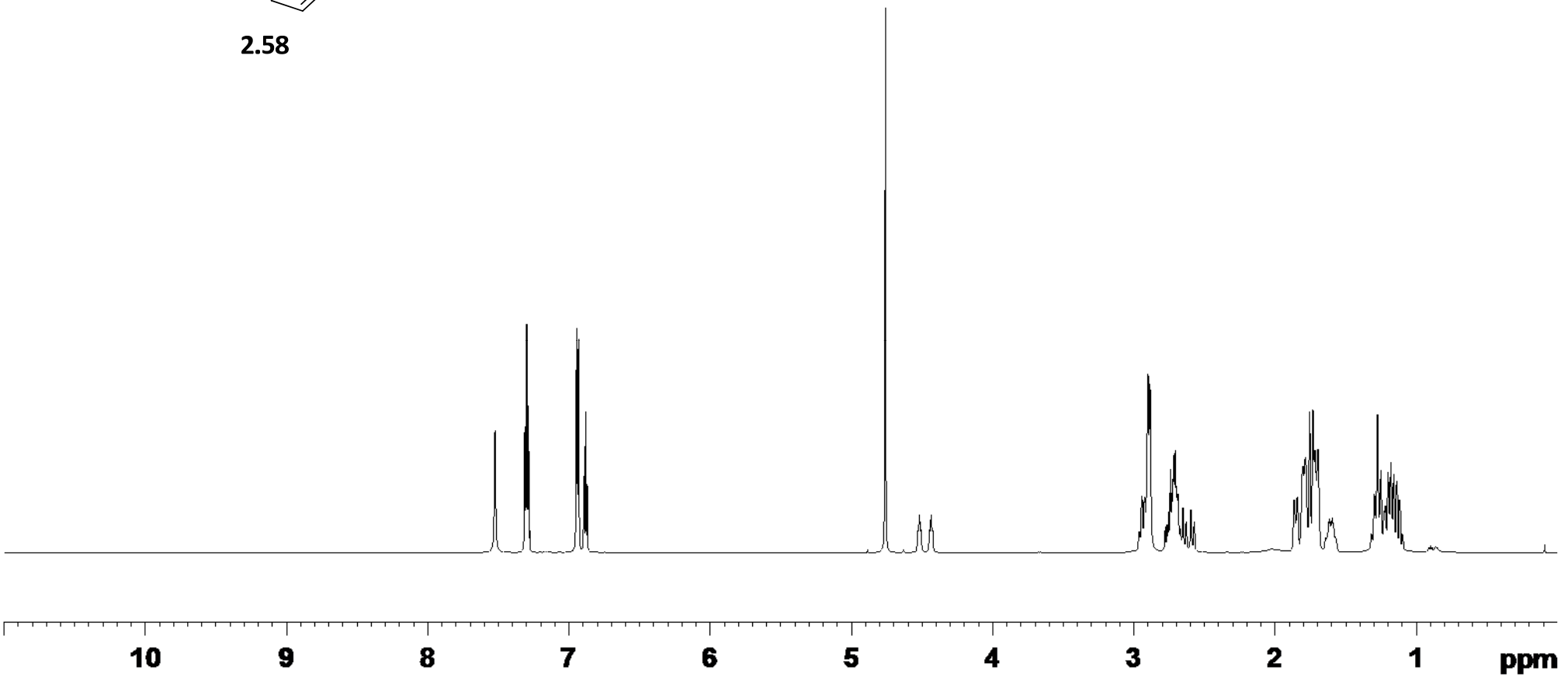

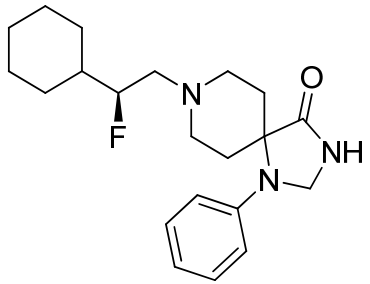

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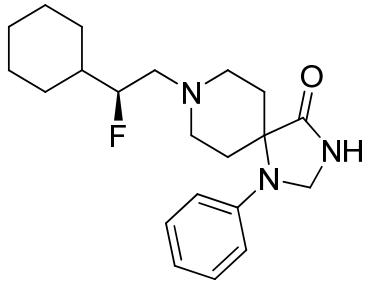

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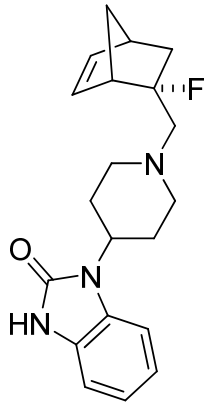

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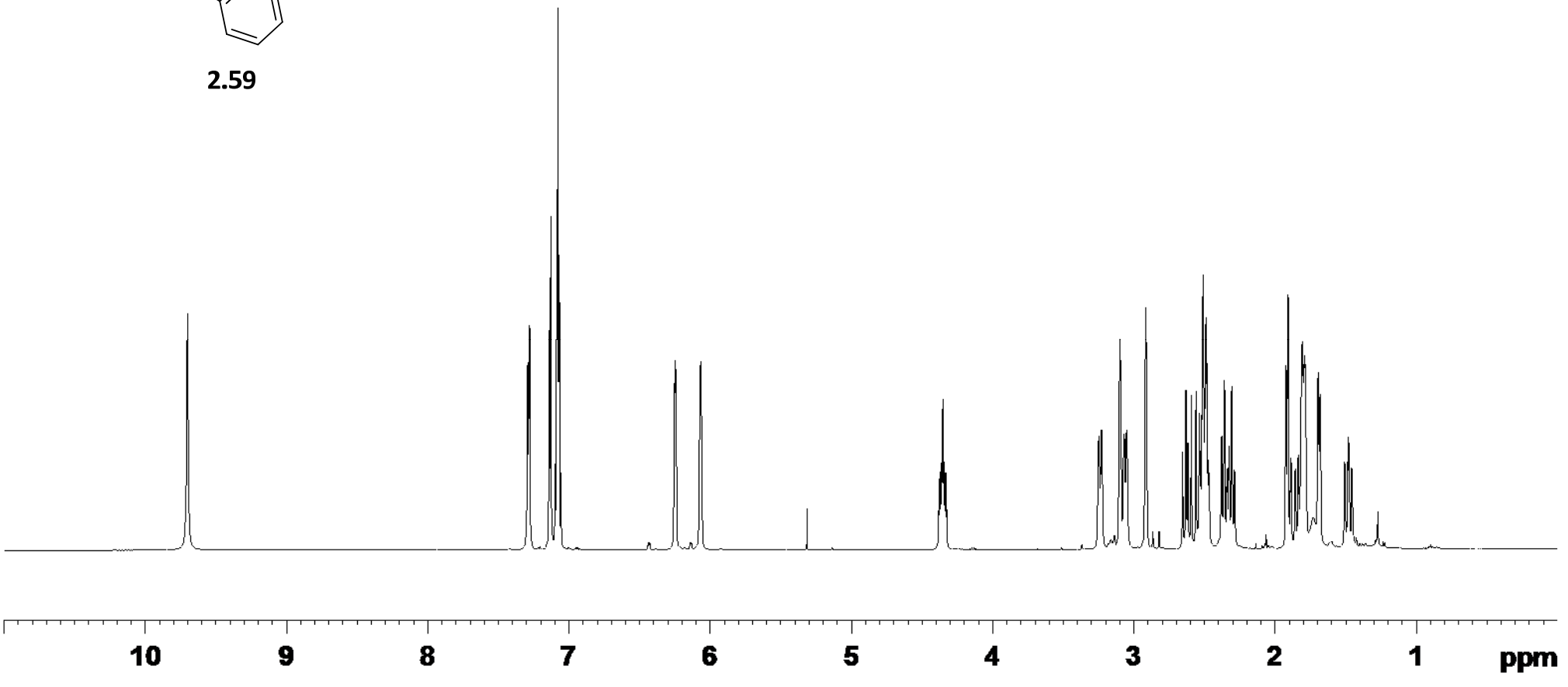

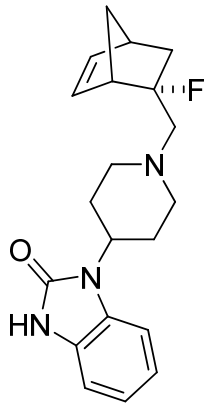

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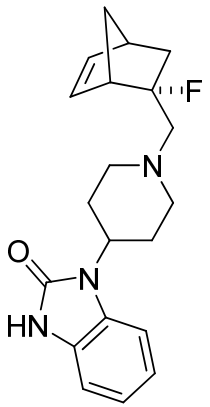

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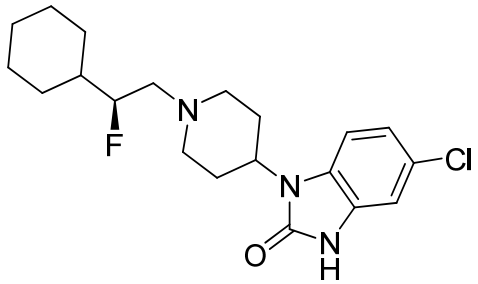

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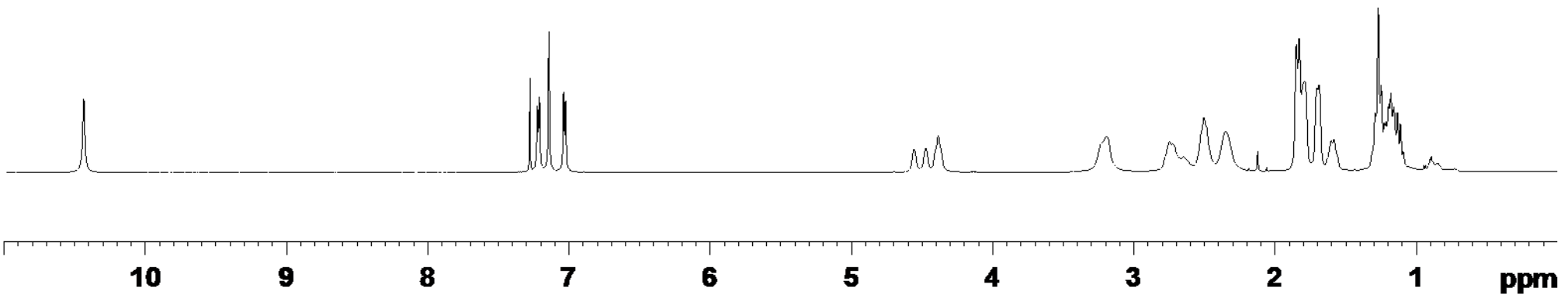

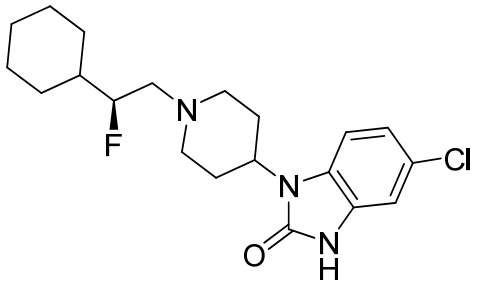

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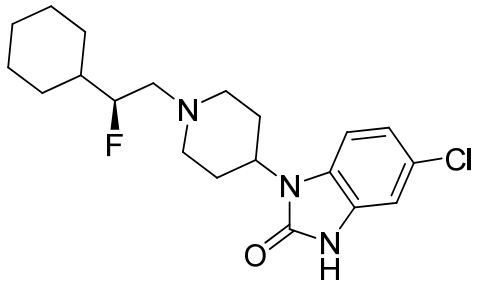

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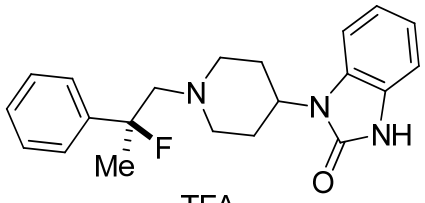

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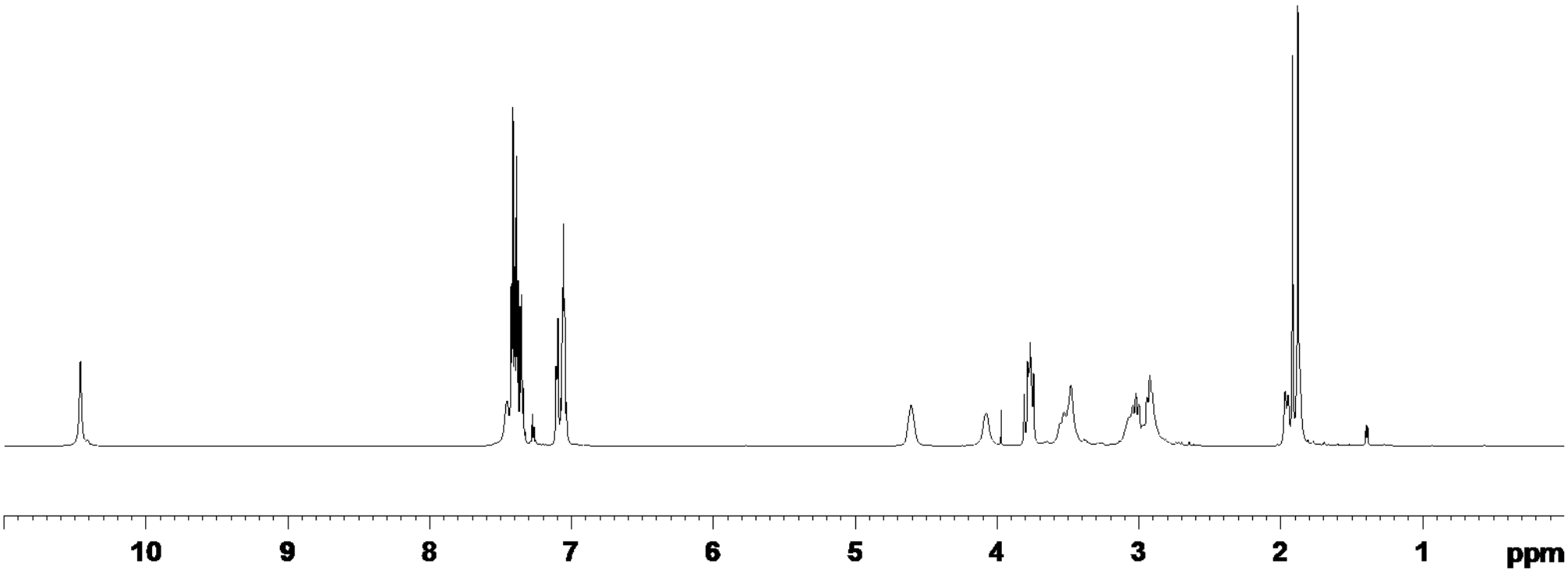

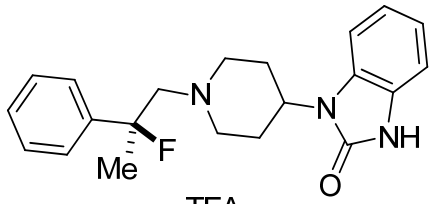

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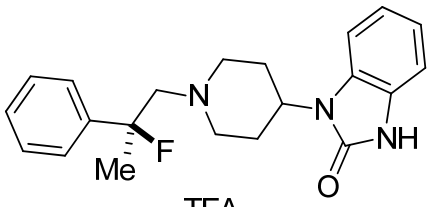

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TFA

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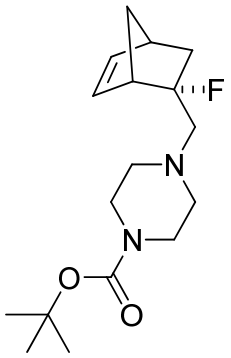

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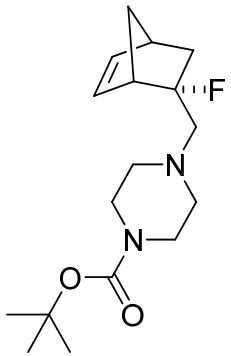

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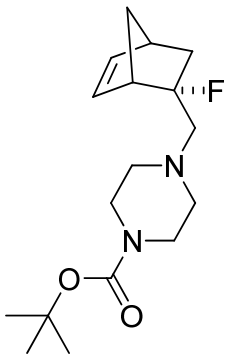

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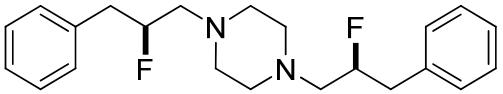

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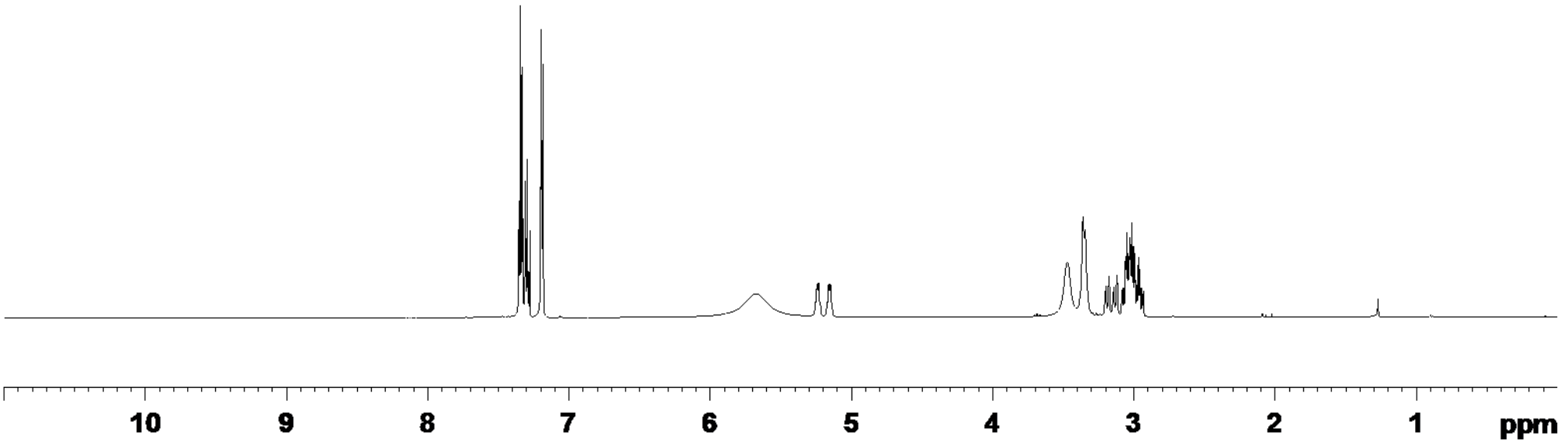

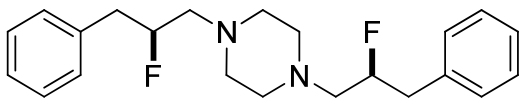

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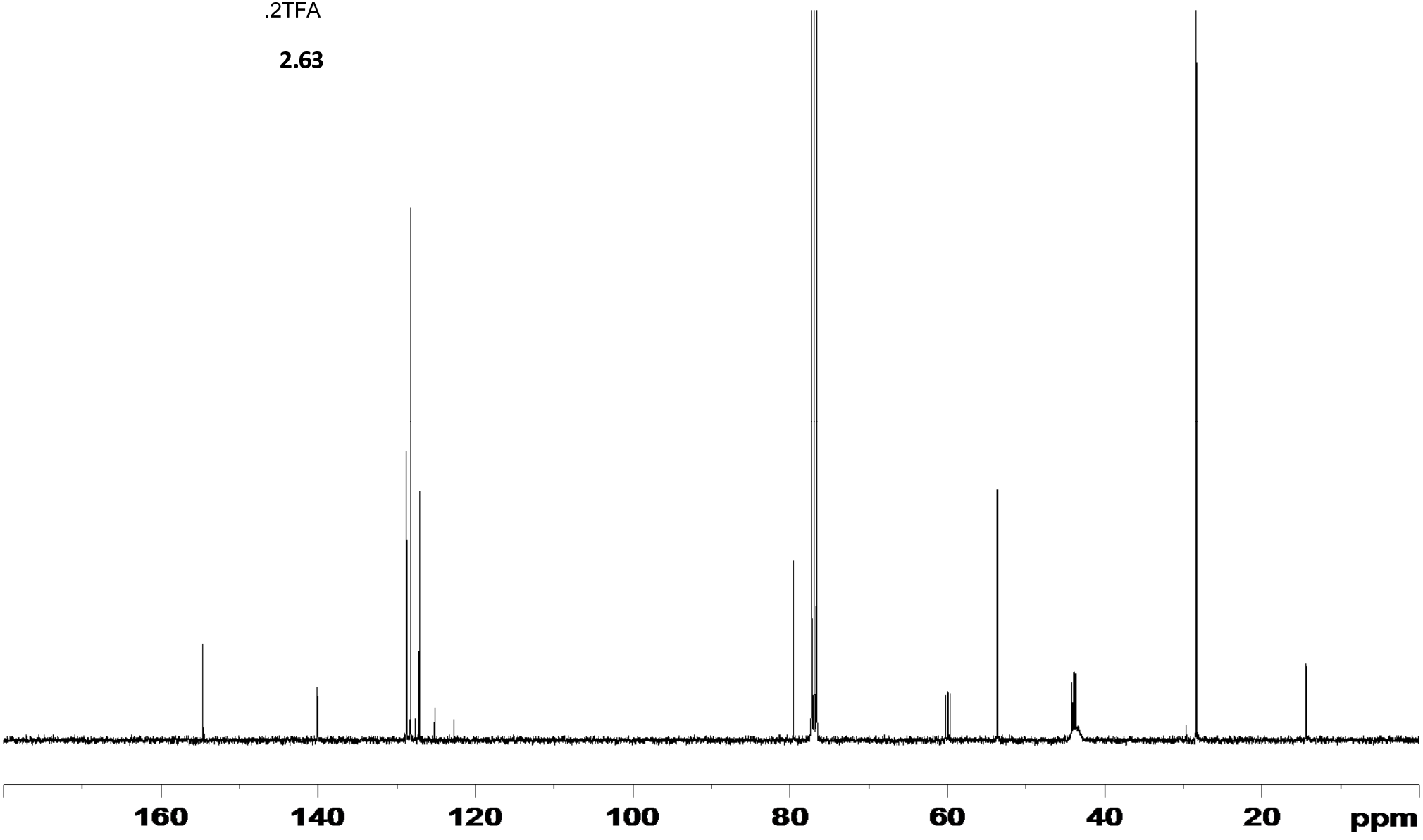

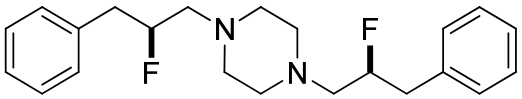

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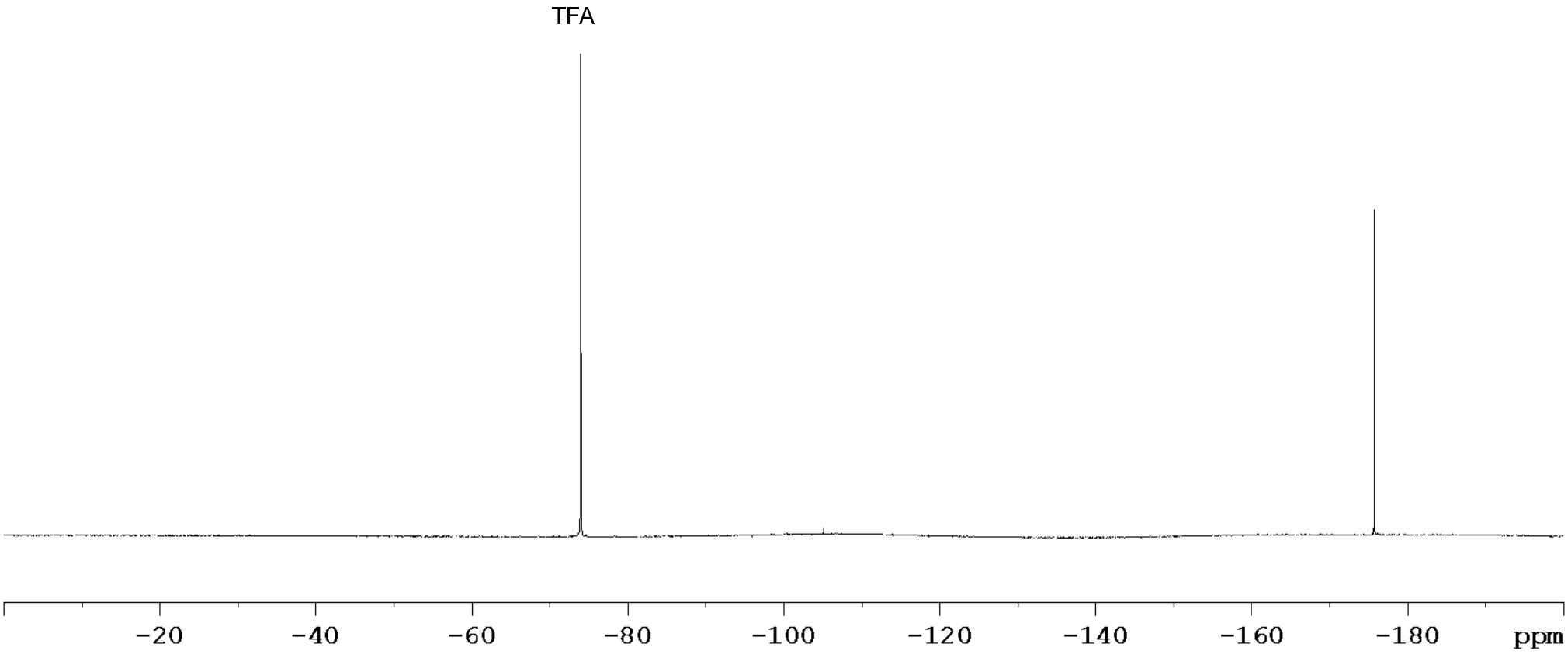

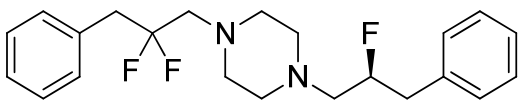
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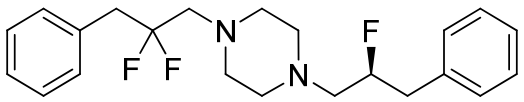
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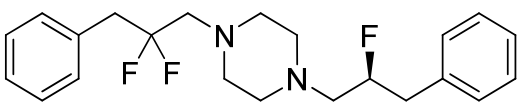
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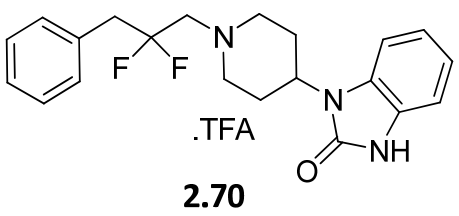

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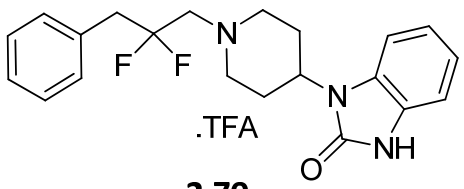

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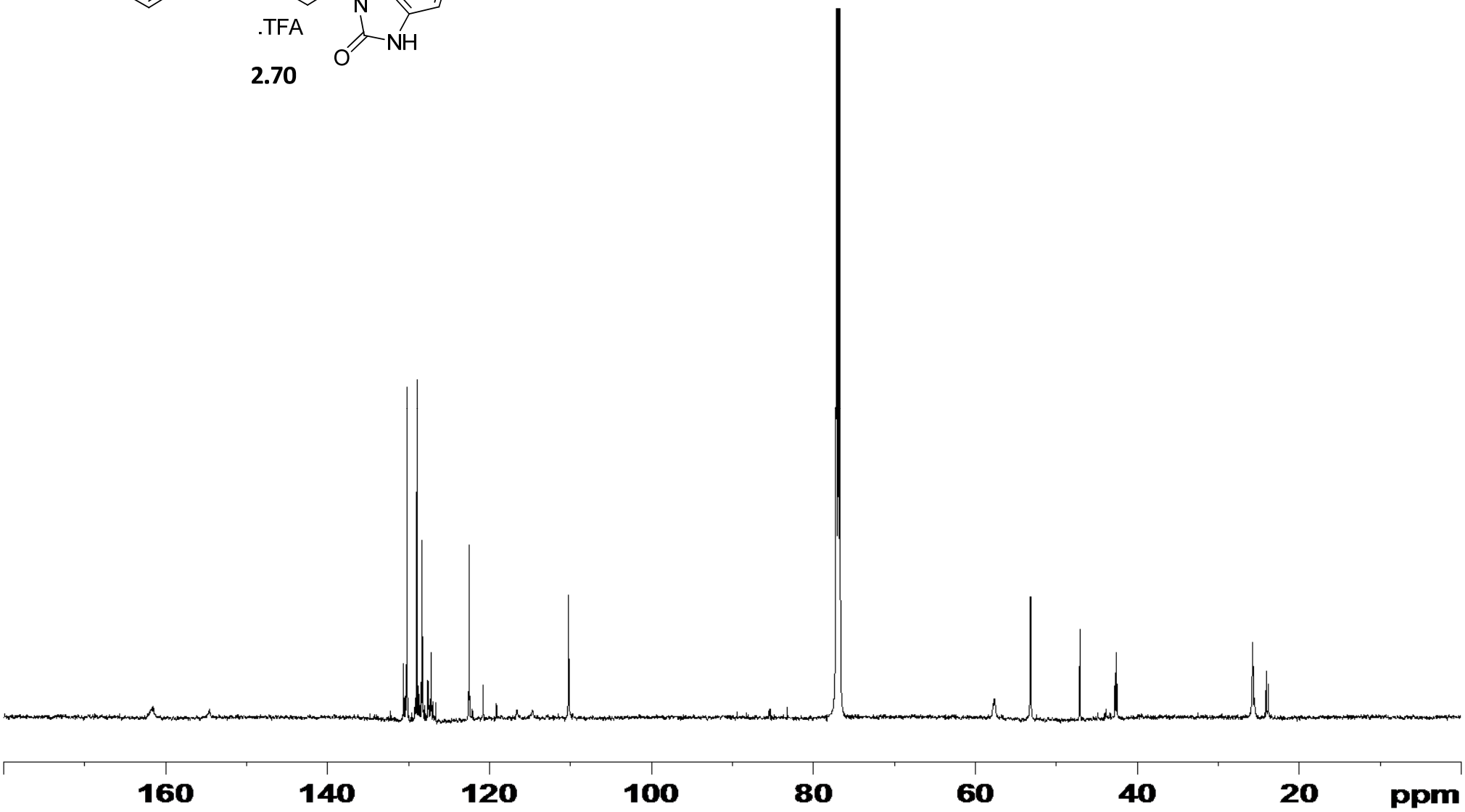

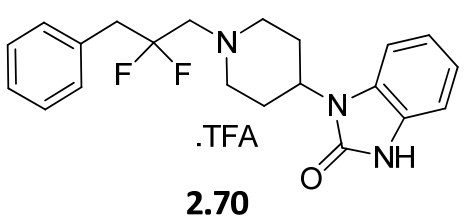

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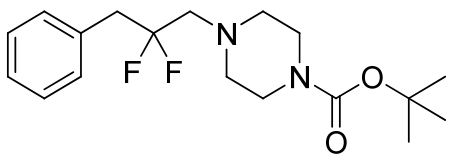

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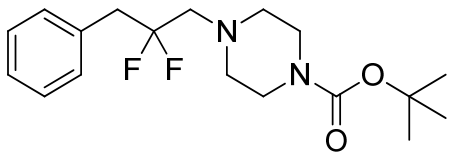

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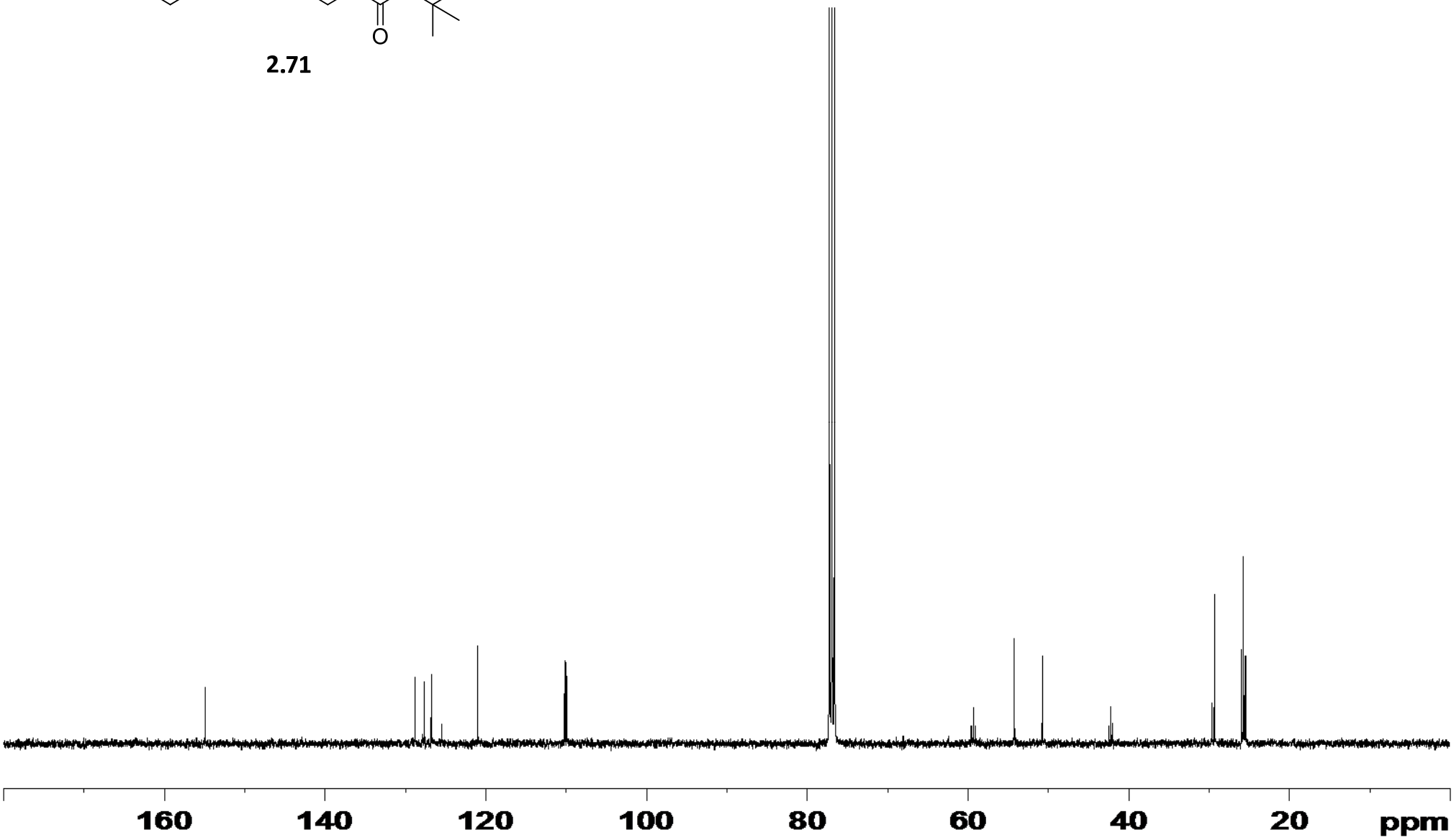

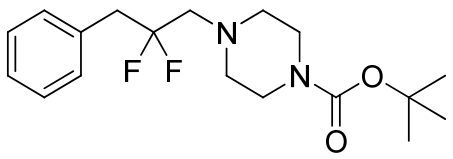

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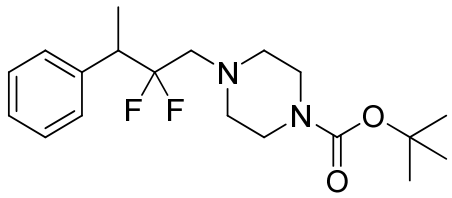

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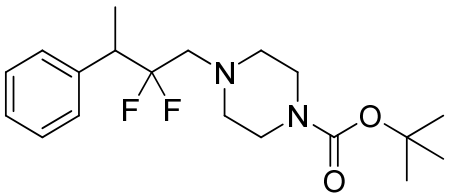

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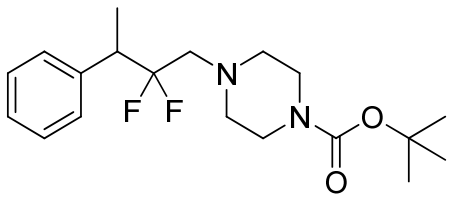

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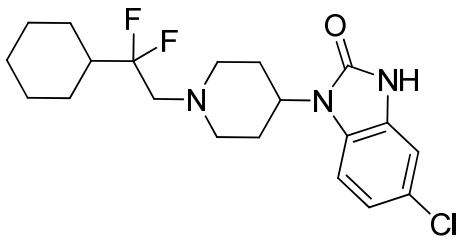
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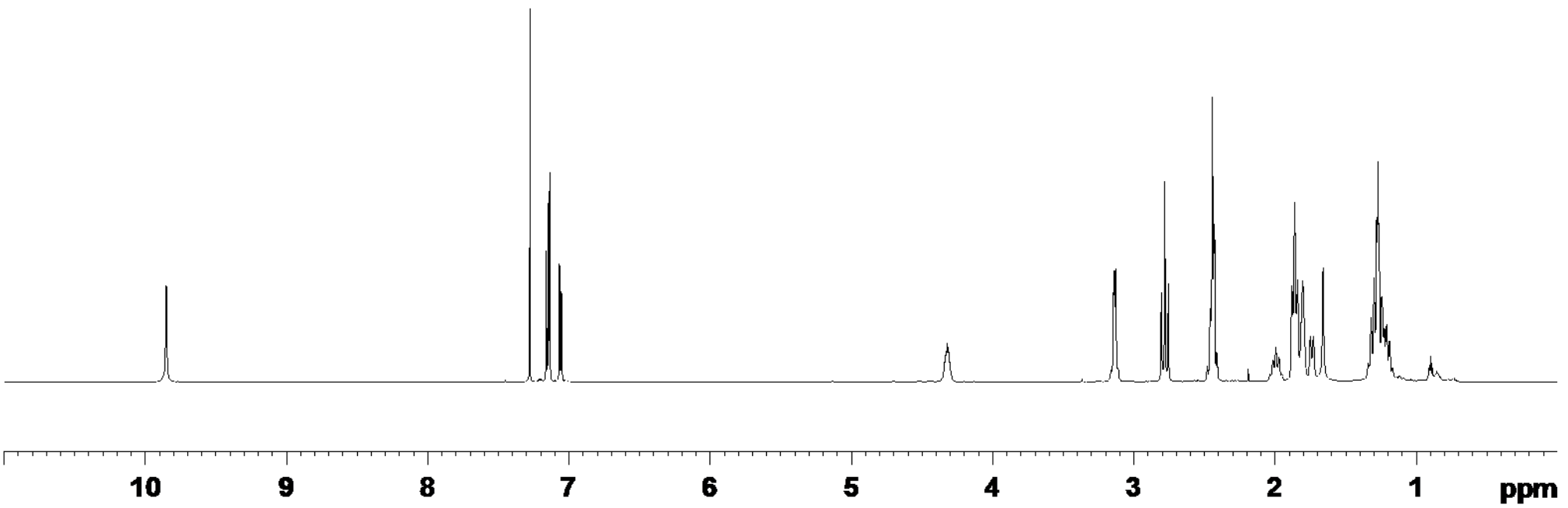
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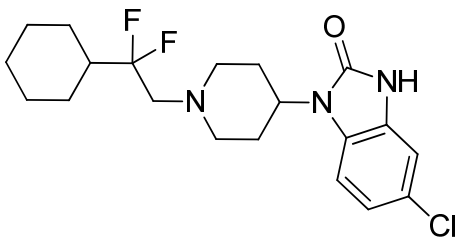
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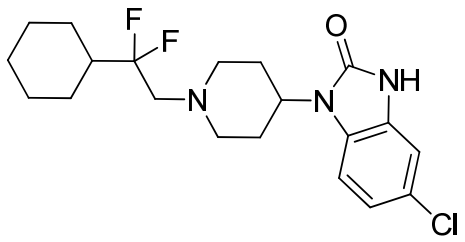
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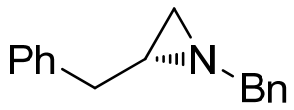

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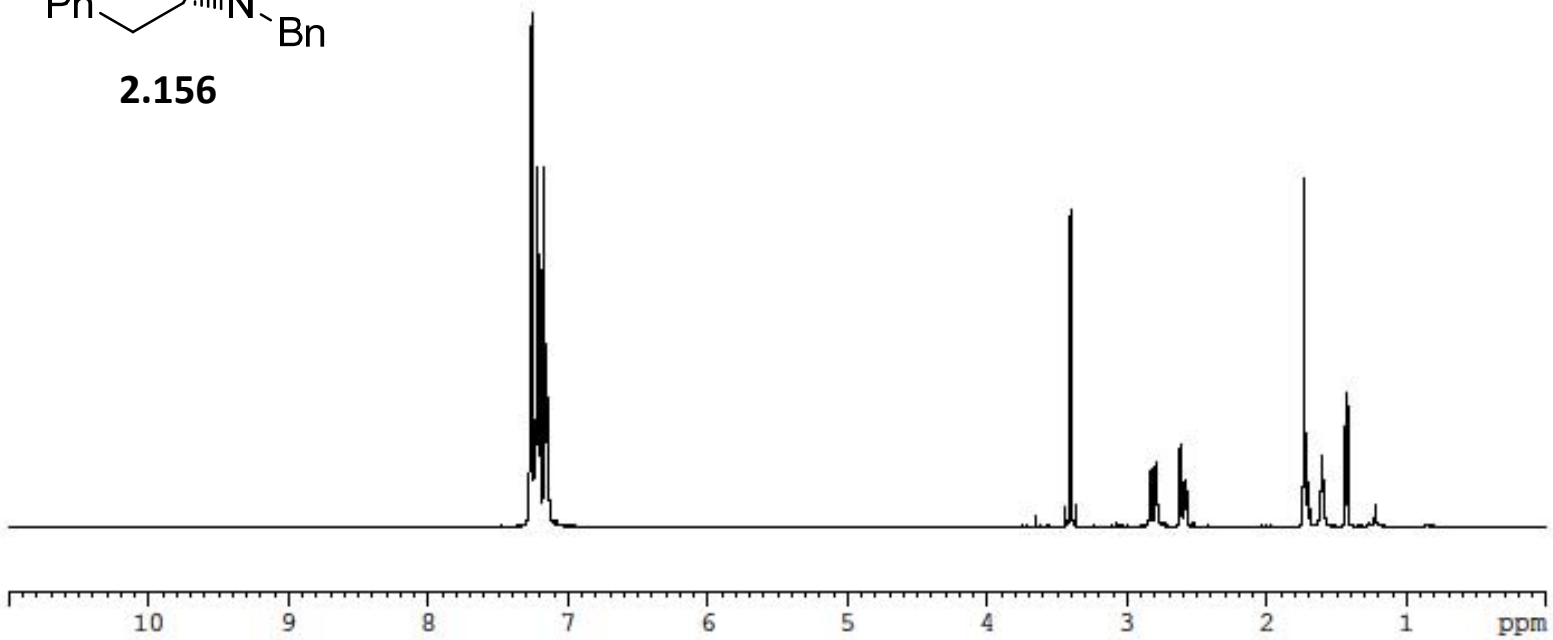

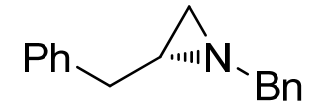

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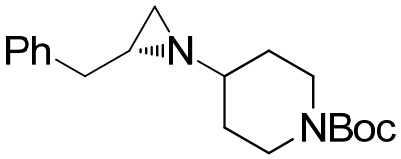


Table 2.11, Entry 1

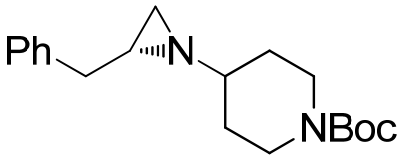
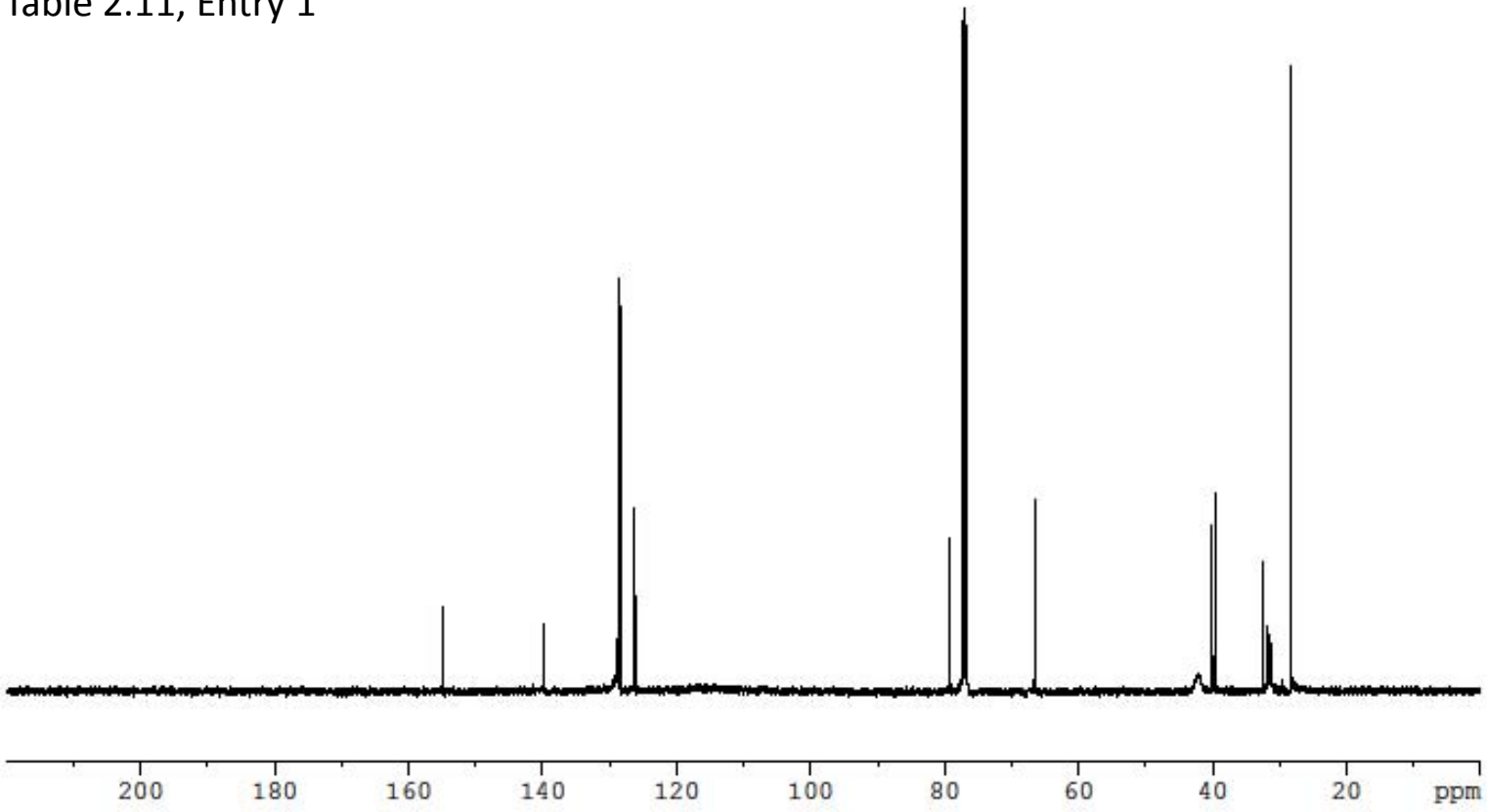
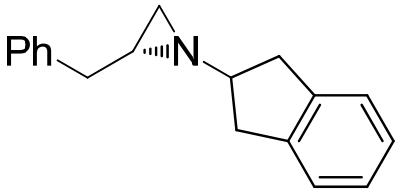


Table 2.11, Entry 1





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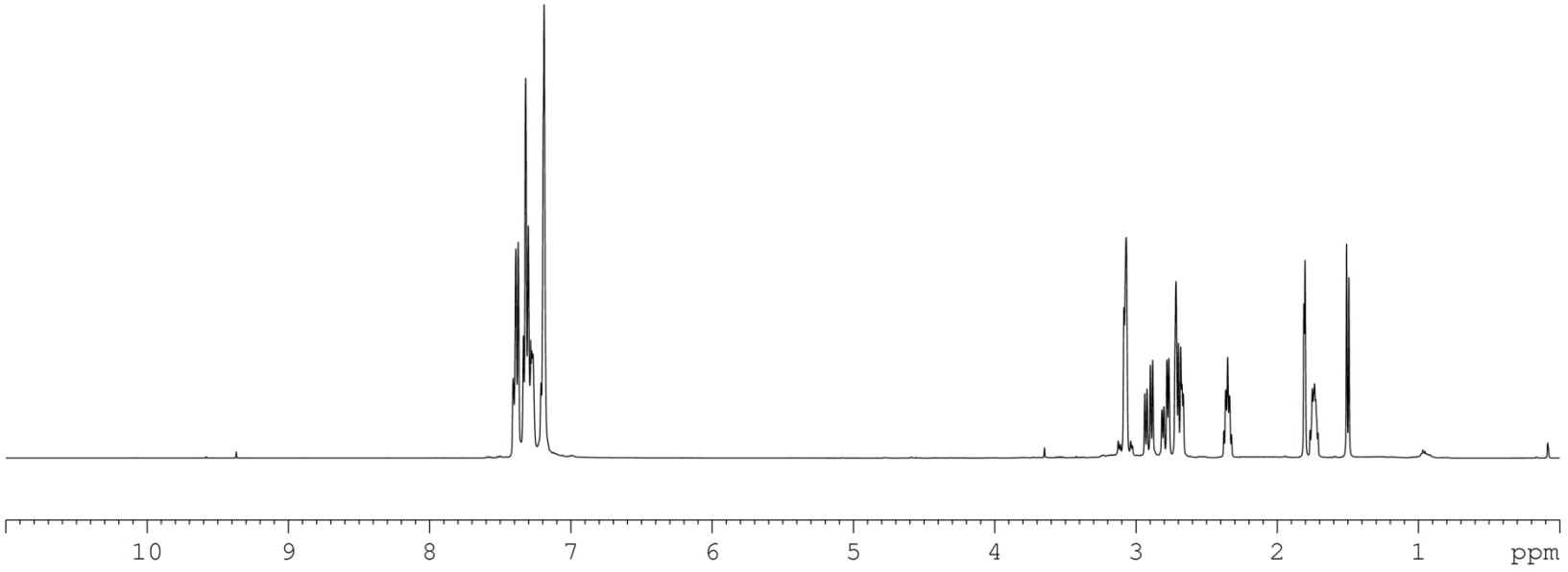

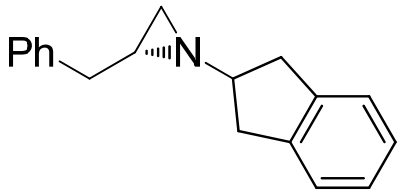

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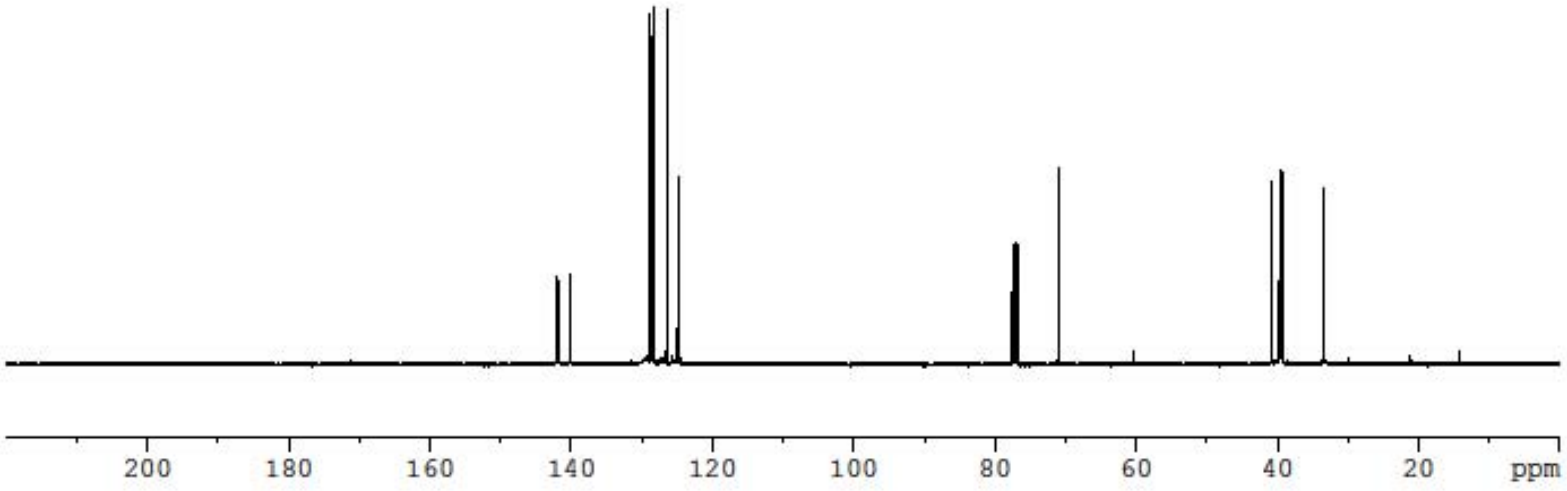

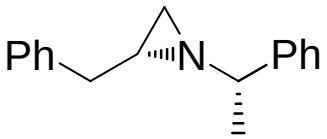

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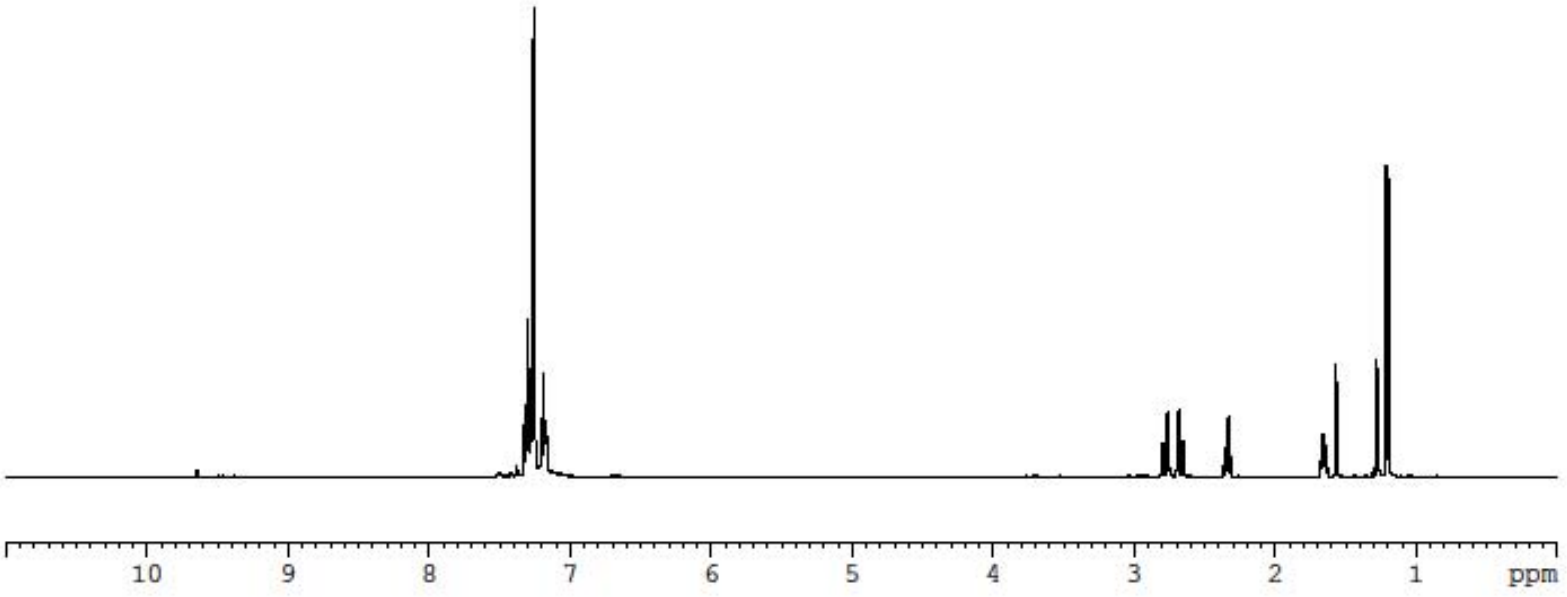

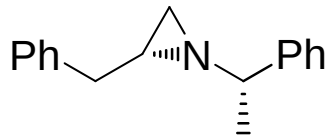

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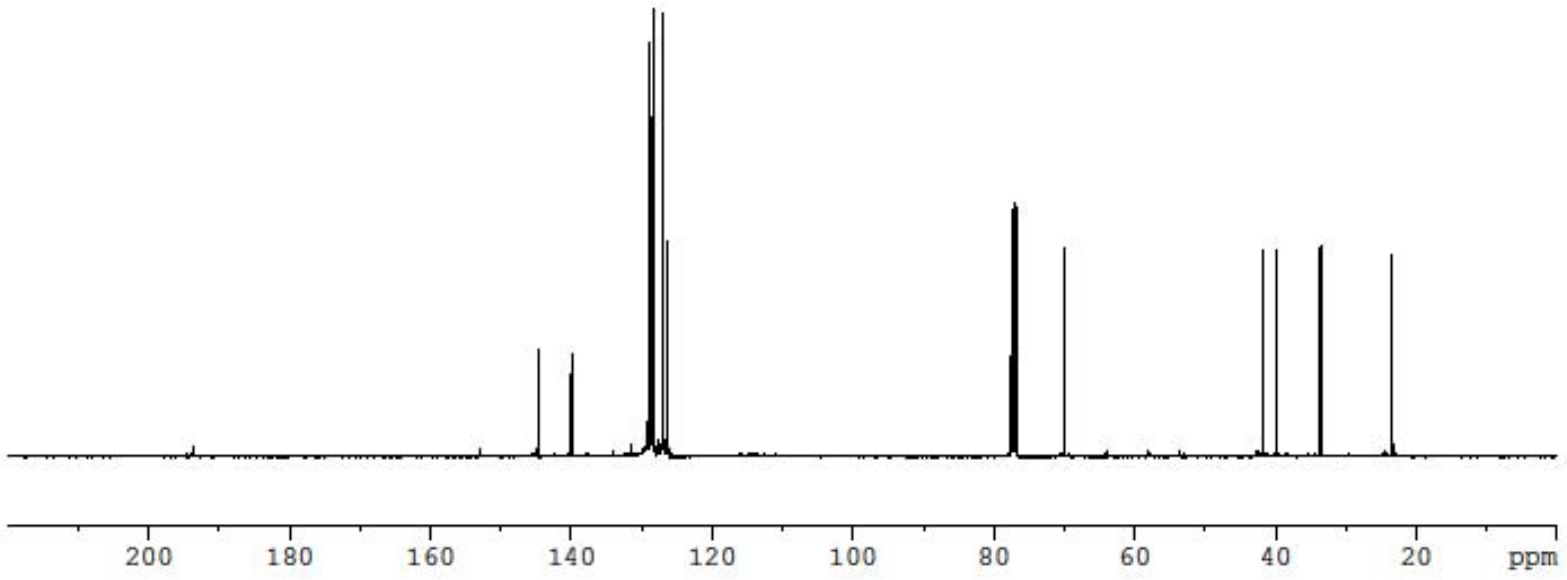

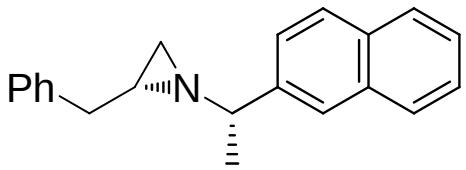

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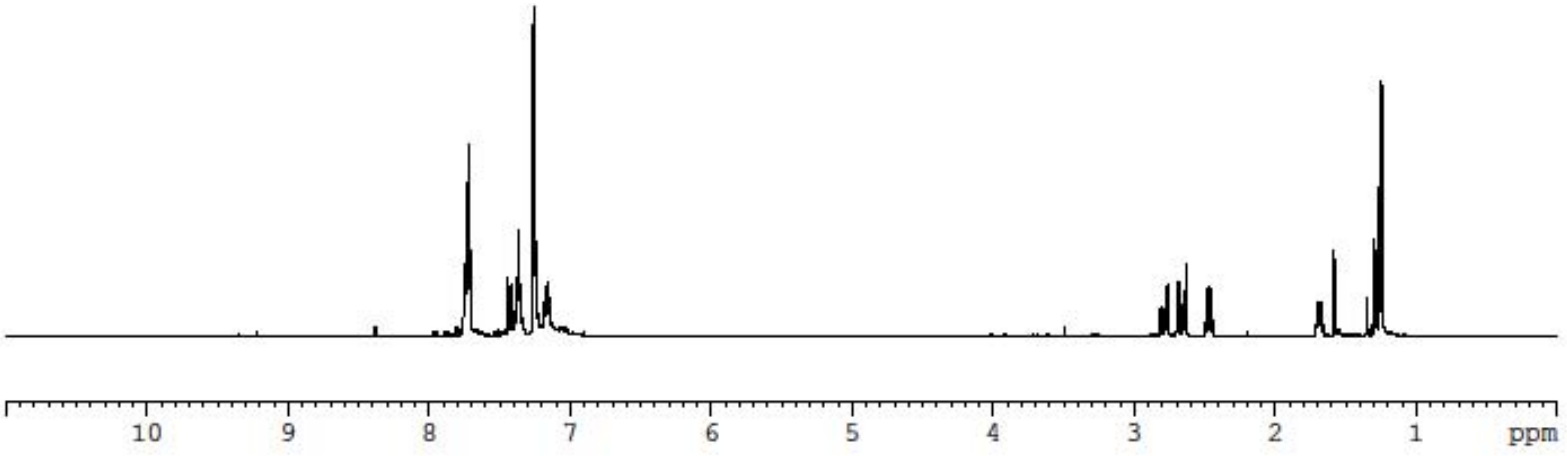

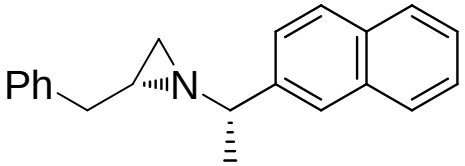

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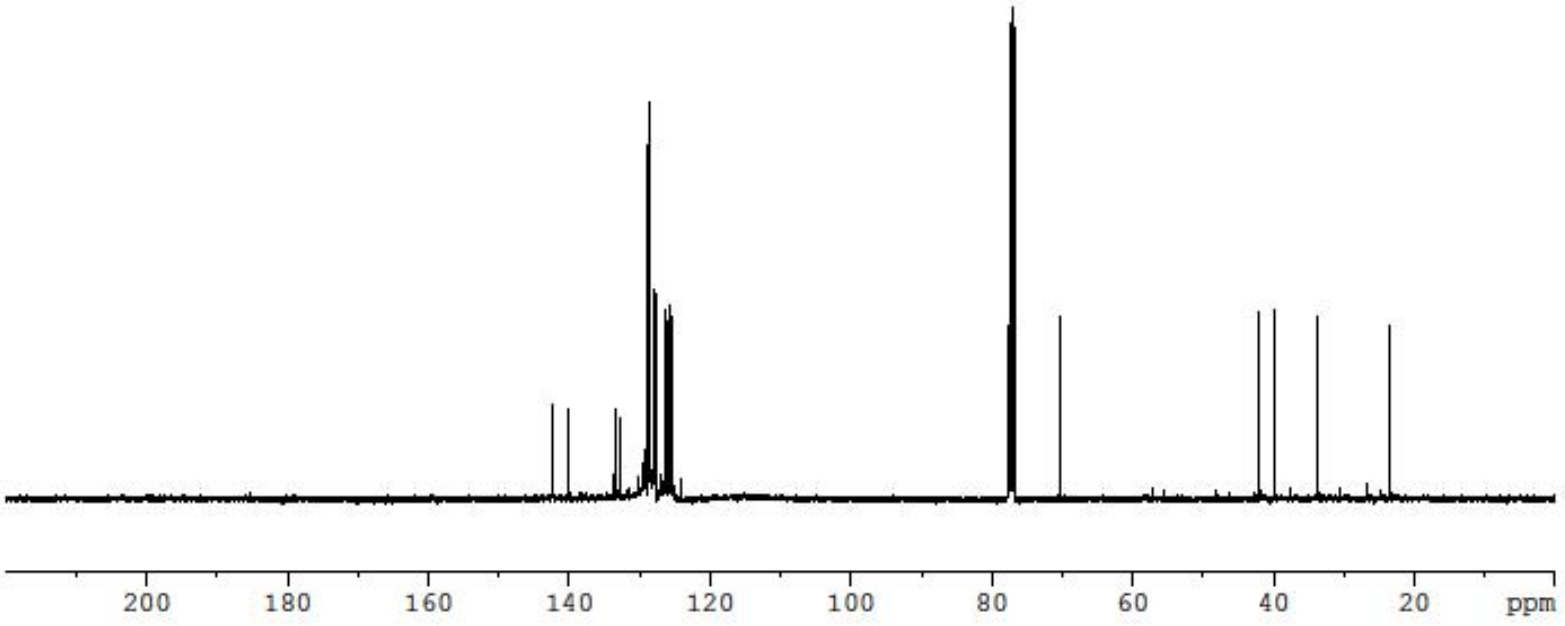

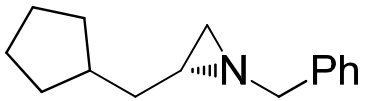

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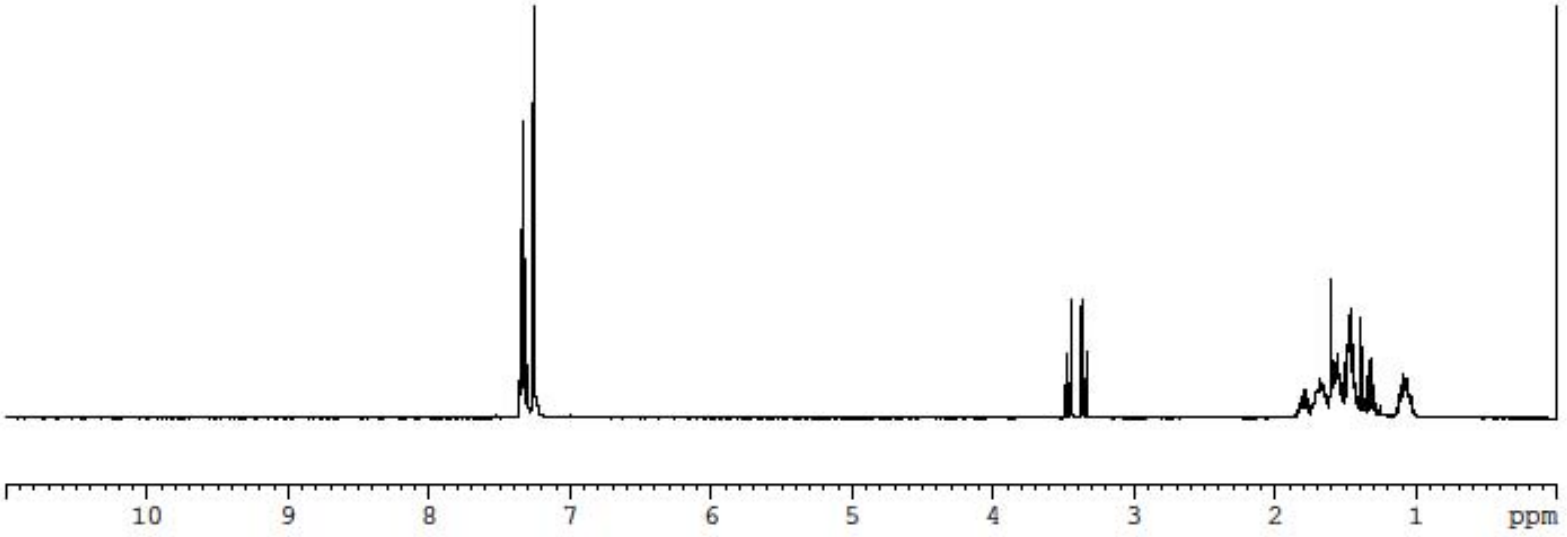

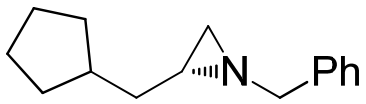

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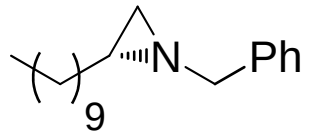

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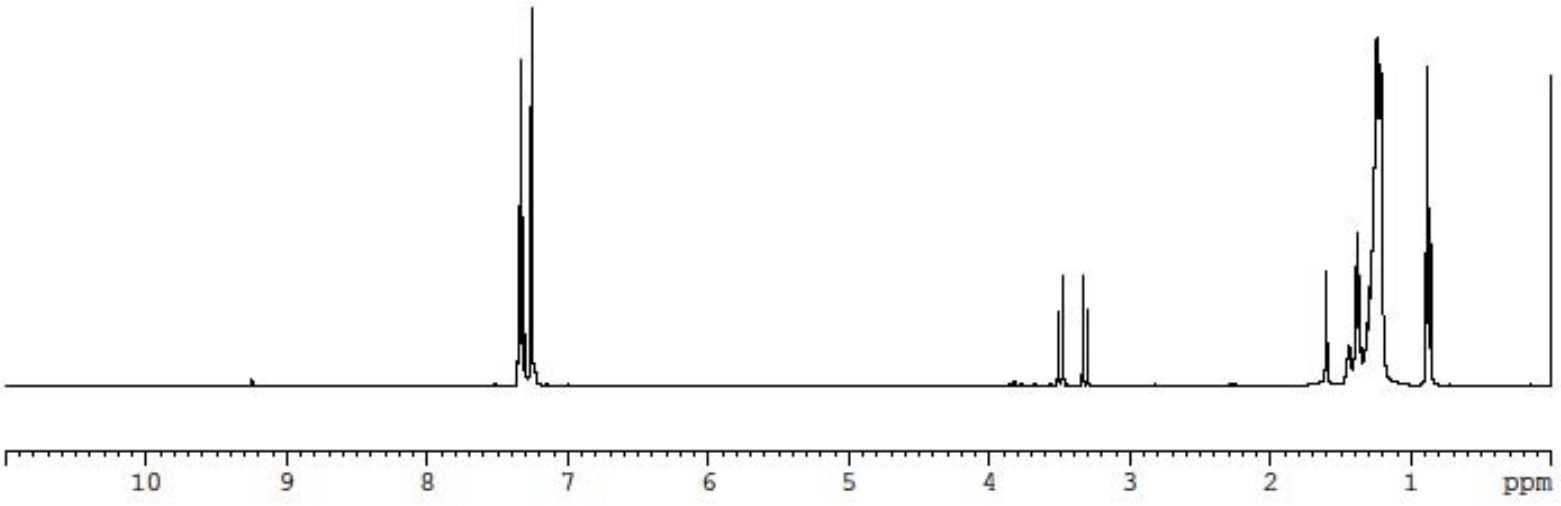

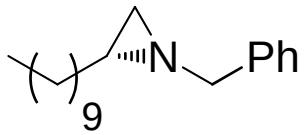

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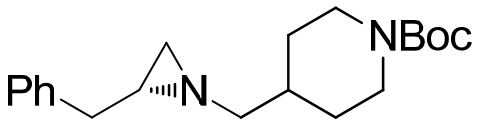

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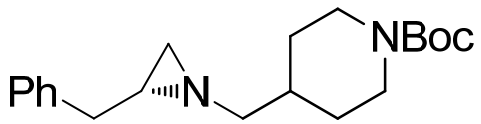

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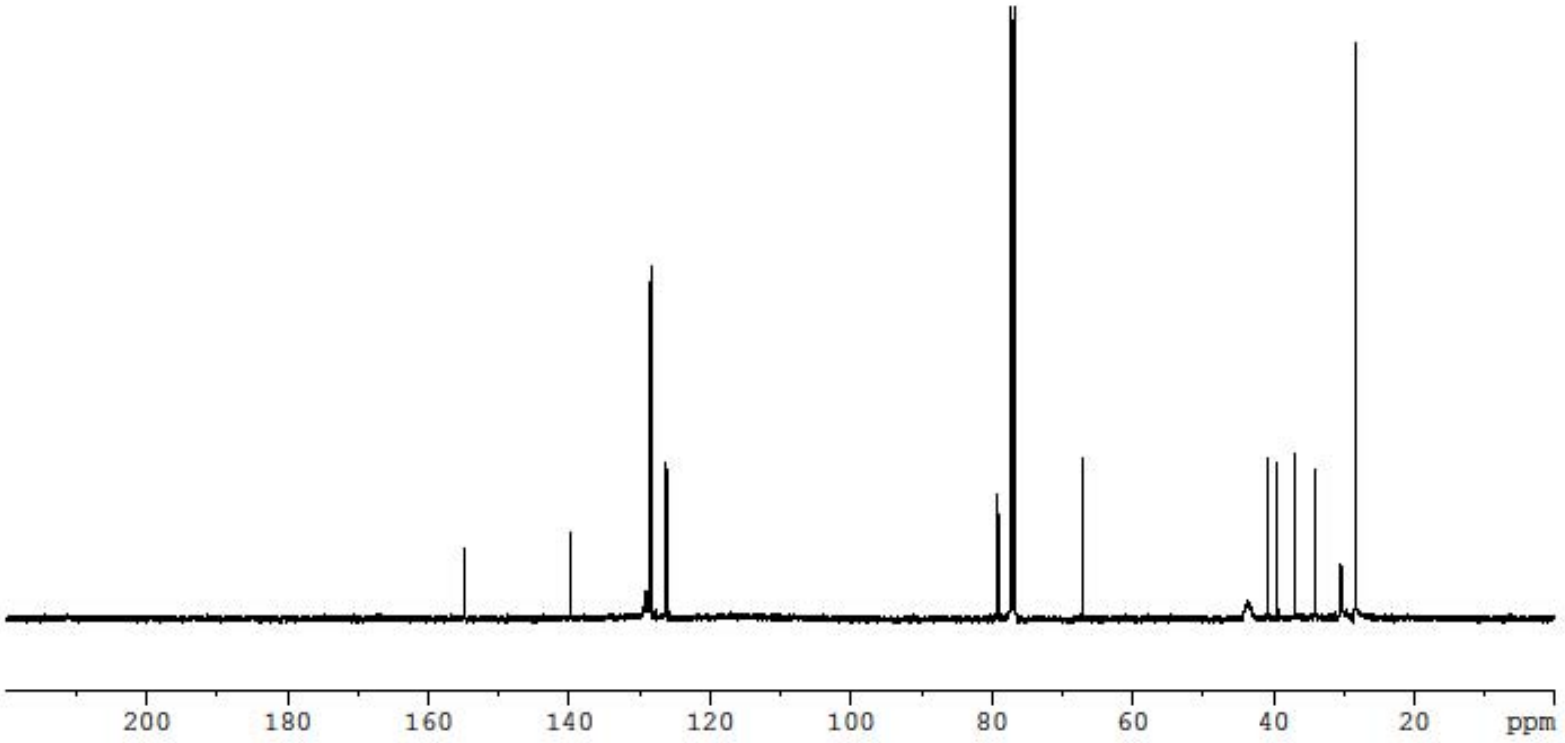

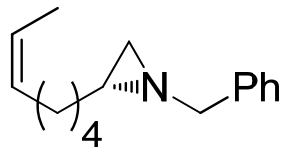

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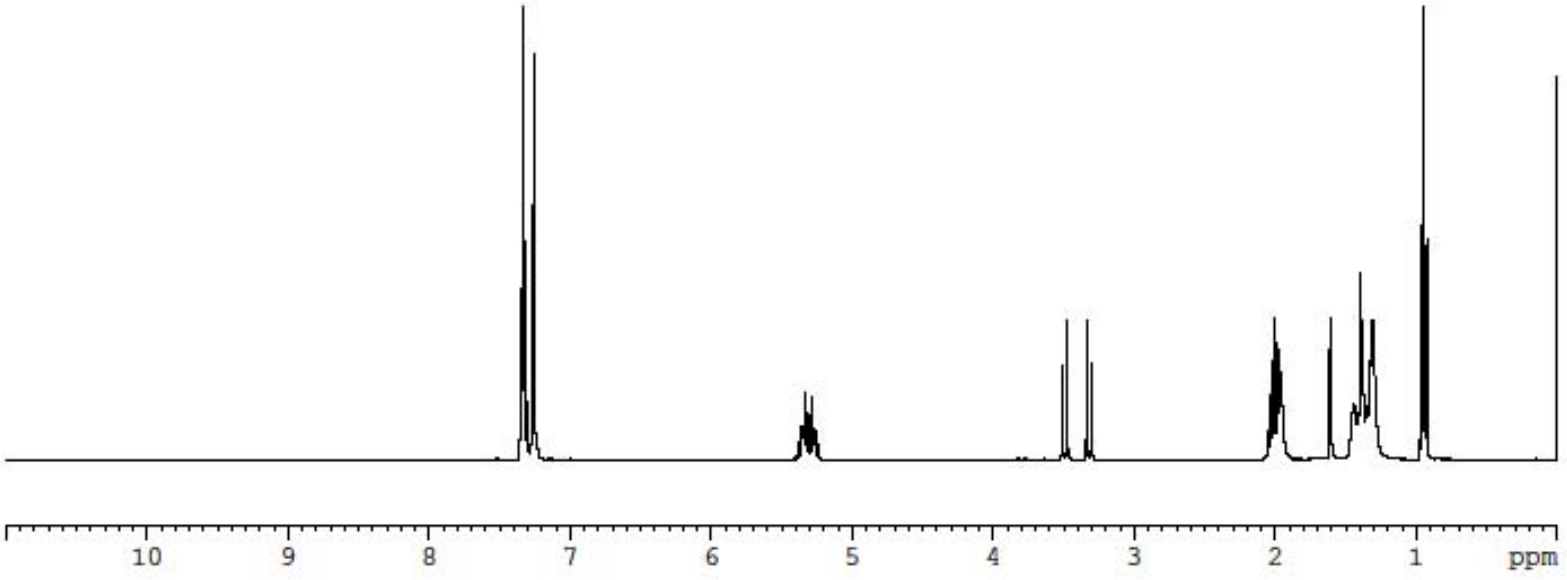

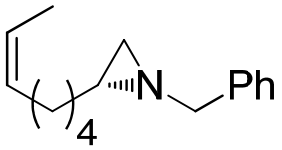

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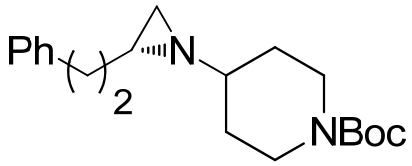

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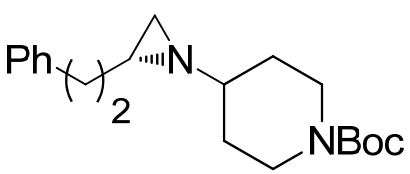

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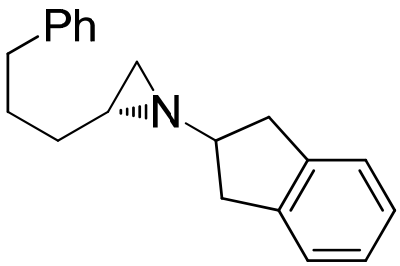

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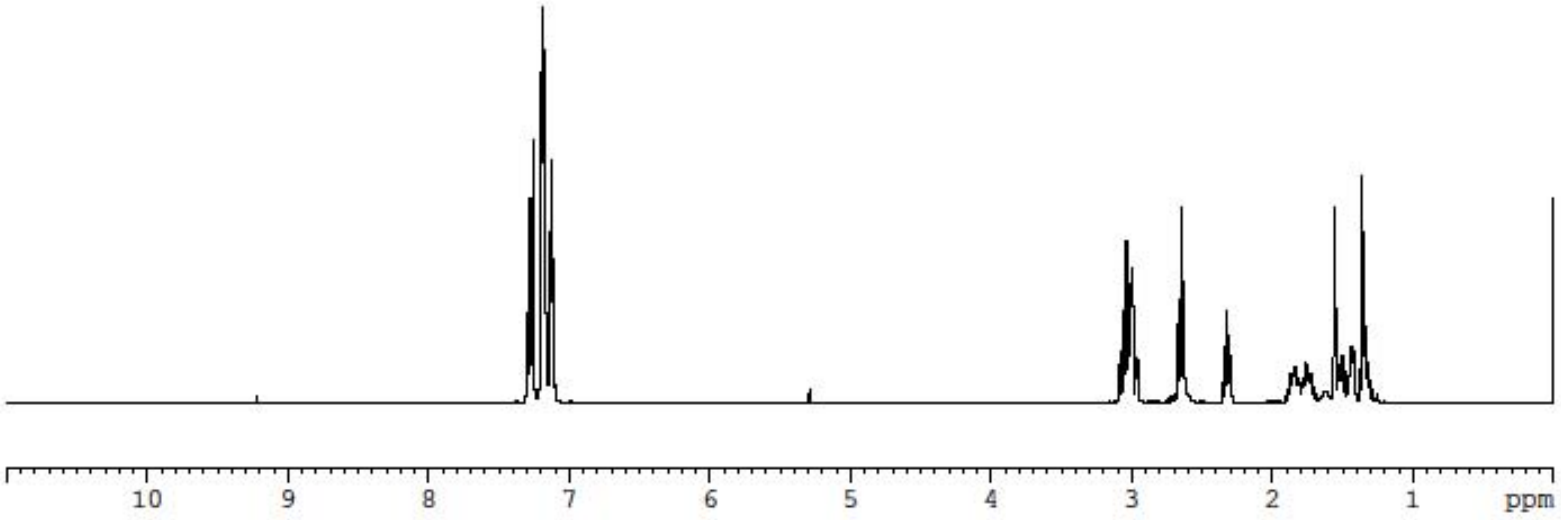

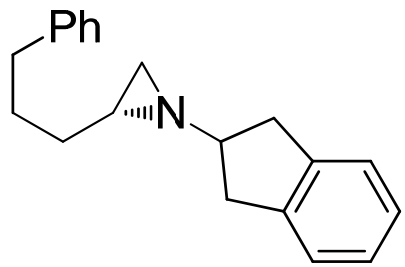

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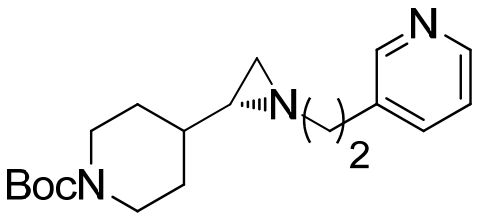

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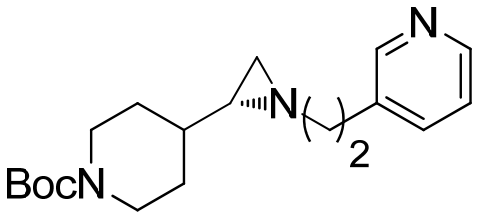

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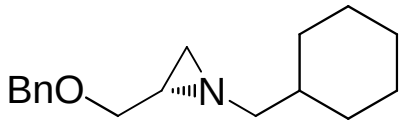

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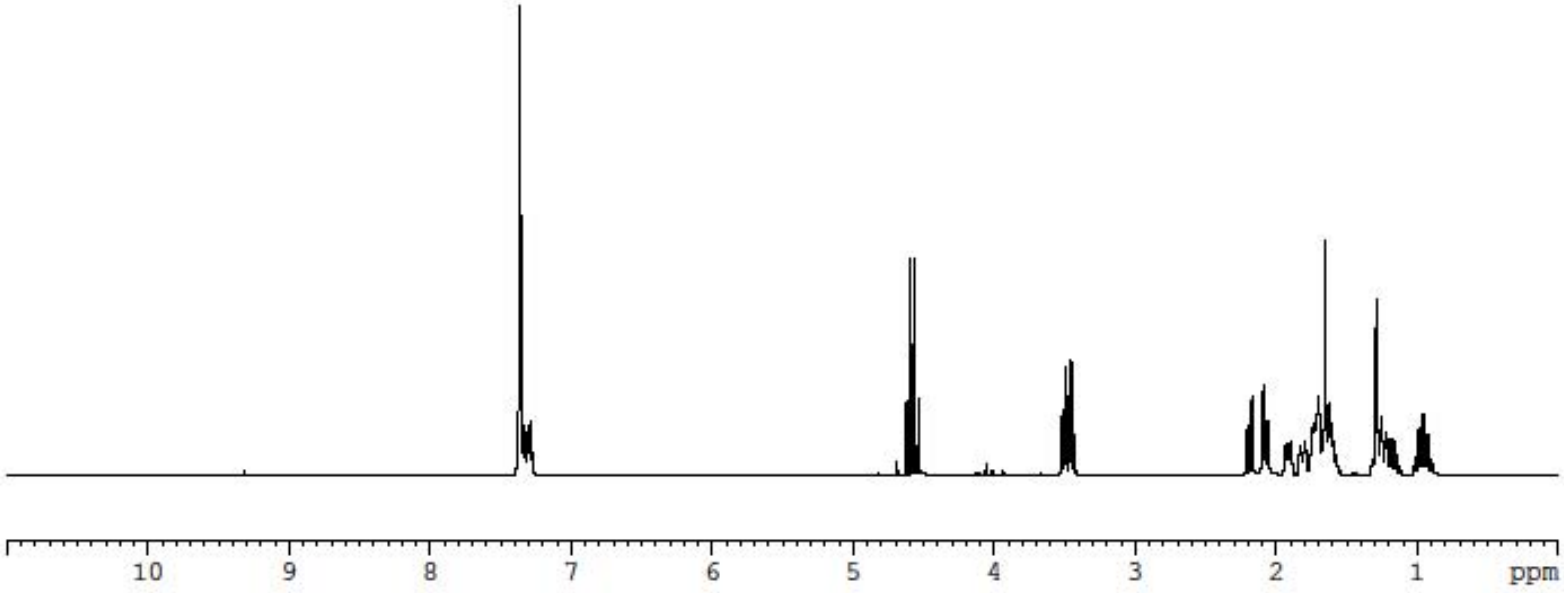

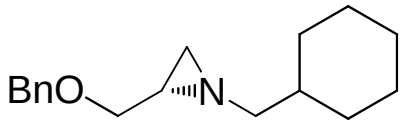

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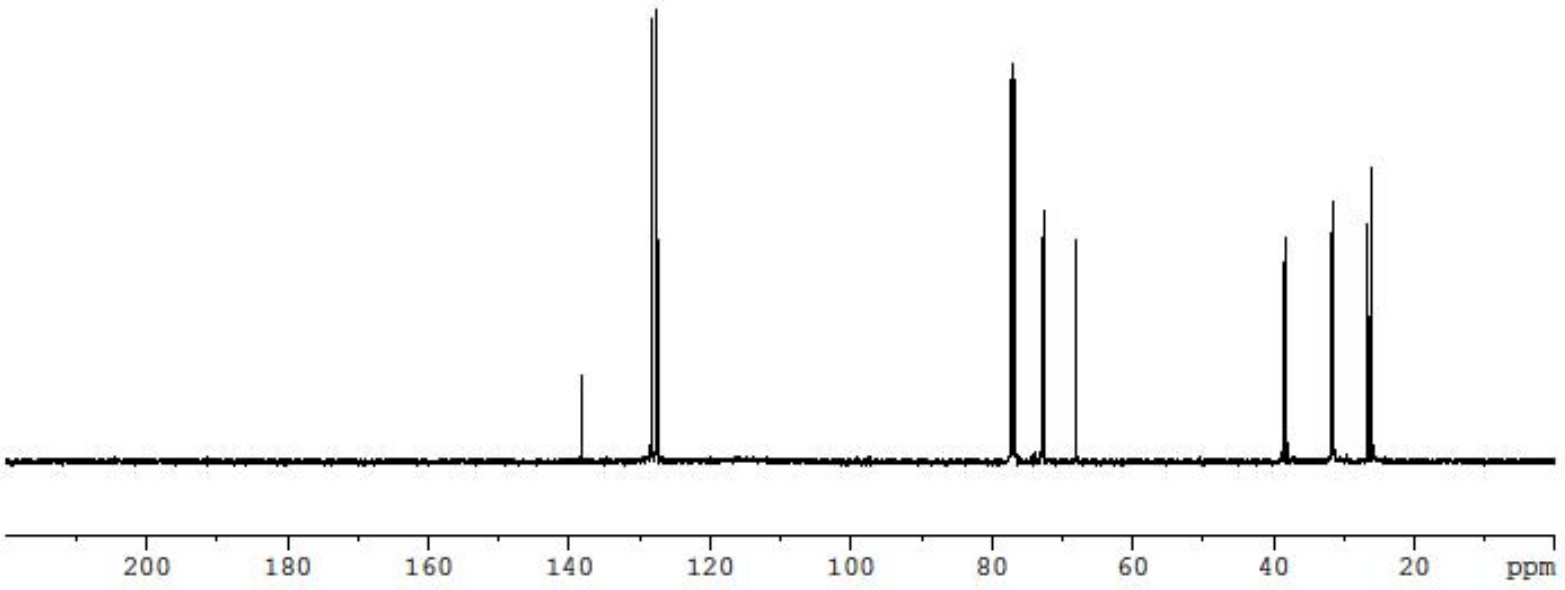

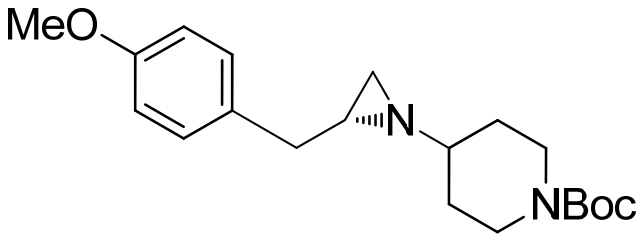

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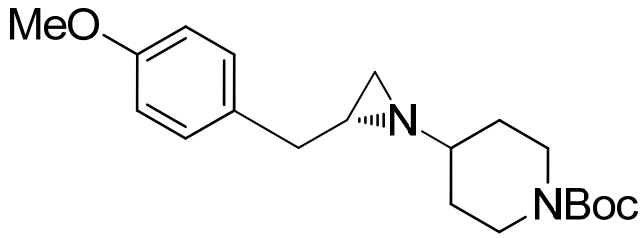

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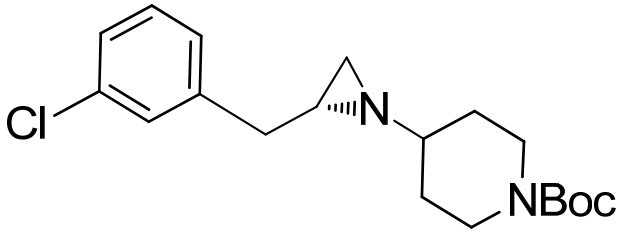

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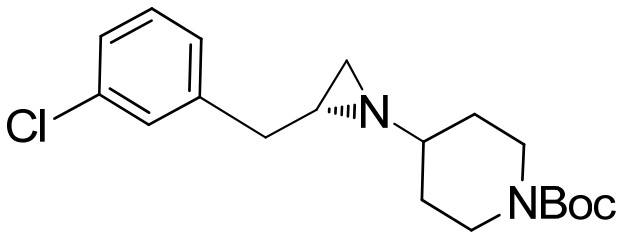
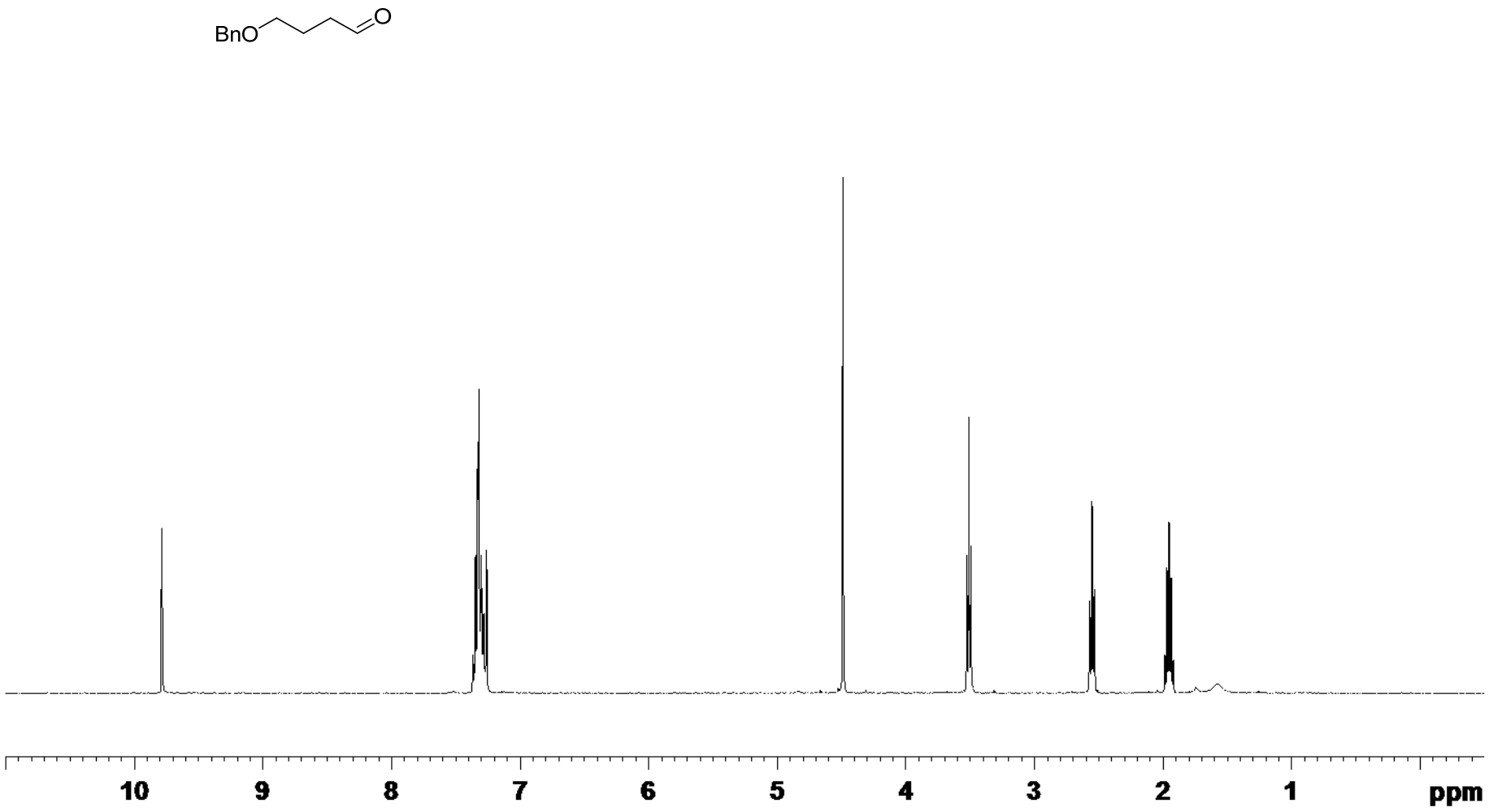


Table 2.11, Entry 14

Appendix A3:

Spectra Relevant to Chapter III.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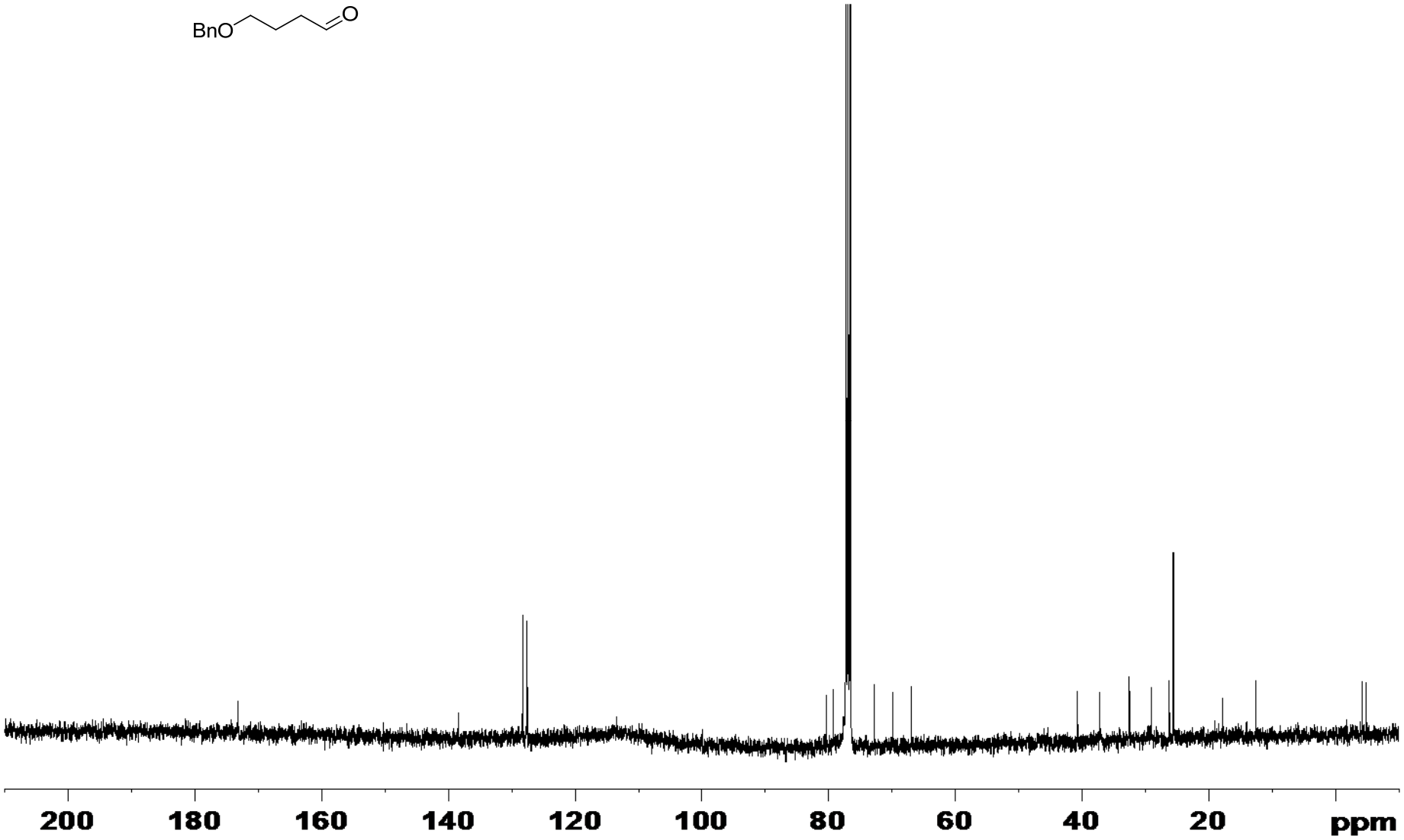
7
6
5
4
3
2
1
ppm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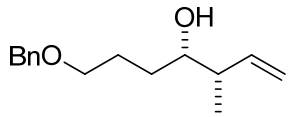

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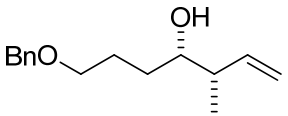

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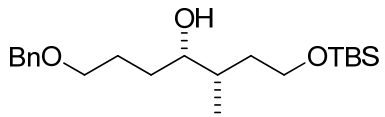

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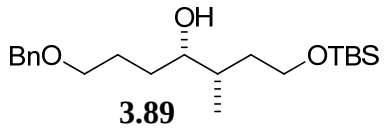

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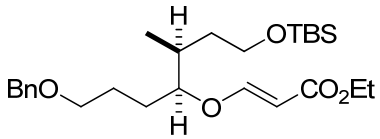

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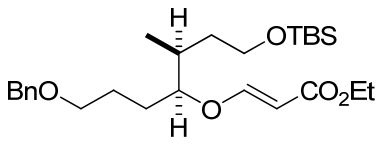

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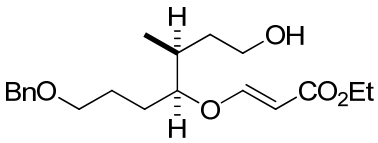

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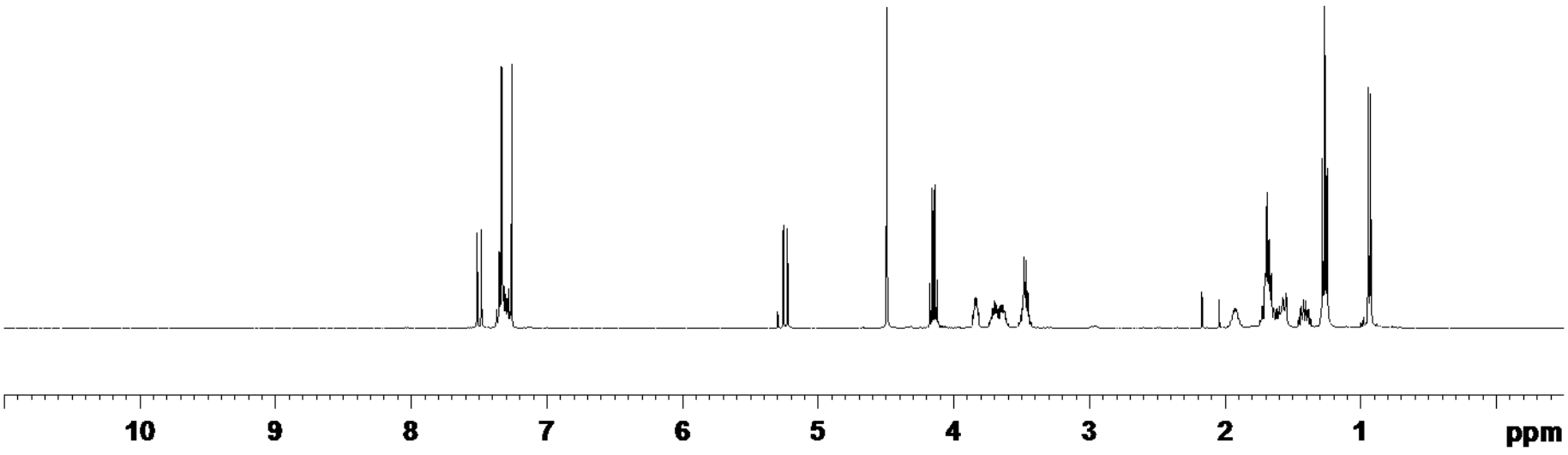

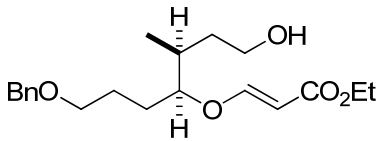

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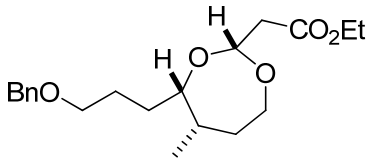

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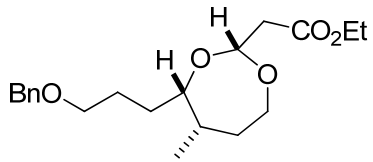

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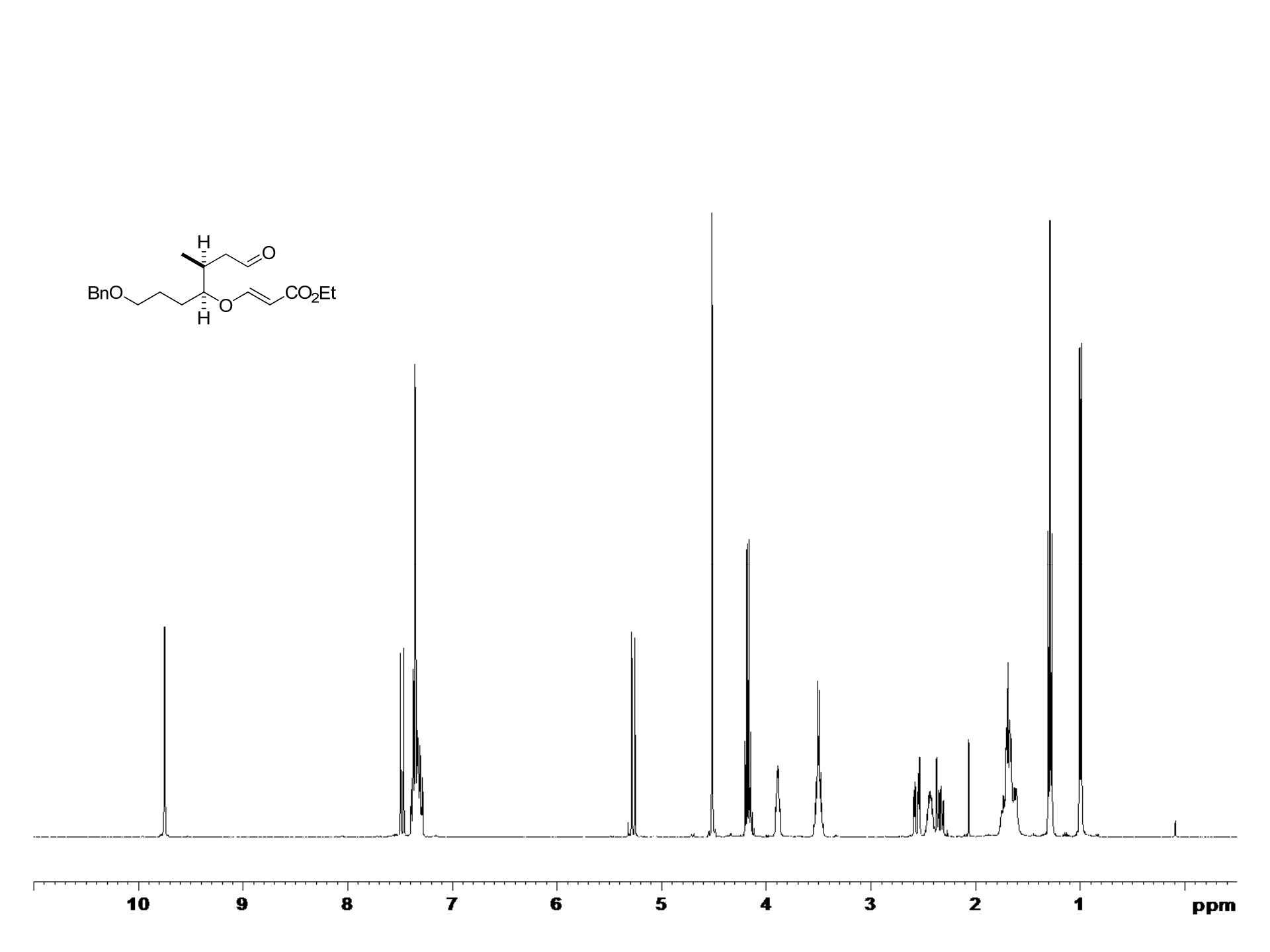
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BnO
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CO2Et
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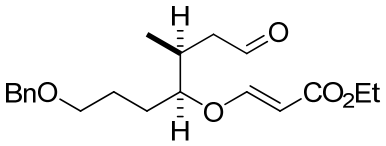
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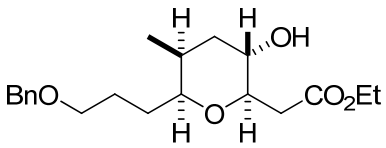

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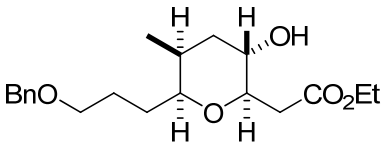

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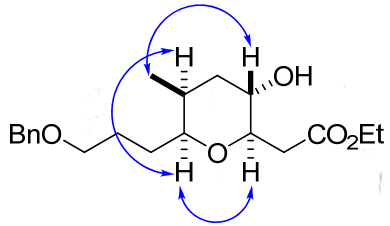
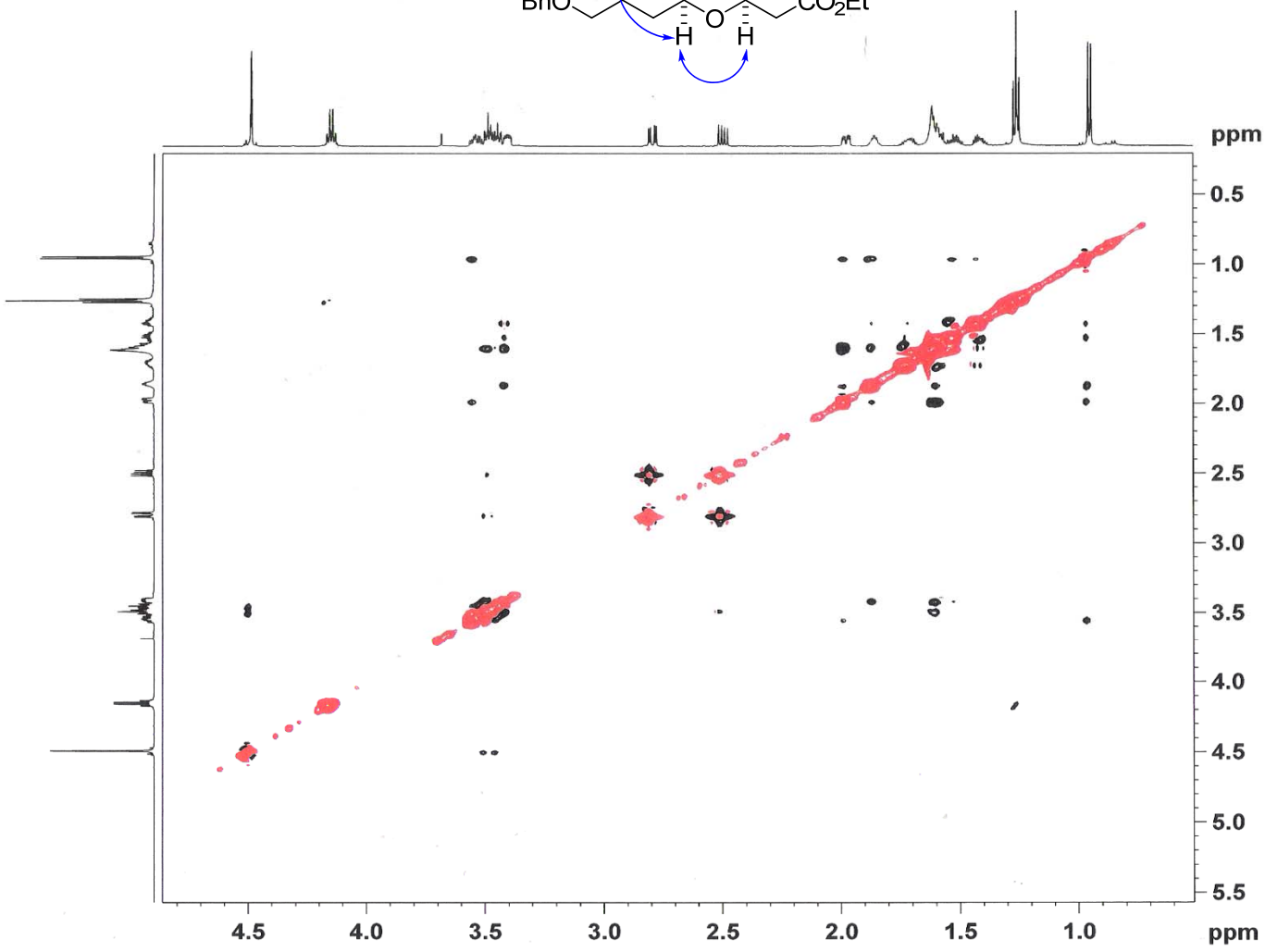
1HNMR NOE





Current Data Parameters
NAME NO-1-135
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090409
Time 10.48
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 8
DS 16
SWH 7812.500 Hz
FIDRES 3.814697 Hz
AQ 0.1311220 sec
RG 128
DW 64.000 usec
DE 6.00 usec
TE 298.0 K
D0 0.00005294 sec
D1 1.49689199 sec
D8 0.60000002 sec
D16 0.00020000 sec
IN0 0.00012800 sec

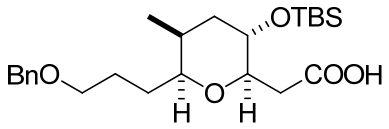
======== CHANNEL f1 ========
NUC1 1H
P1 8.69 usec
P2 17.38 usec
PL1 3.00 dB
PL1W 6.35607052 W
SFO1 600.1330006 MHz

======= GRADIENT CHANNEL =====
GPNAM1 SMSQ10.100
GPNAM2 SMSQ10.100
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec

F1 - Acquisition parameters
ND0 1
TD 422
SFO1 600.133 MHz
FIDRES 18.512983 Hz
SW 13.919 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI 1024
SF 600.1300000 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.40

F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300000 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0



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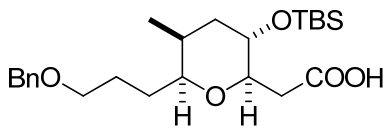

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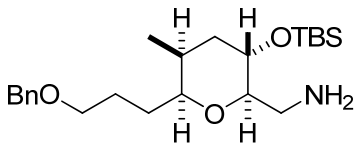

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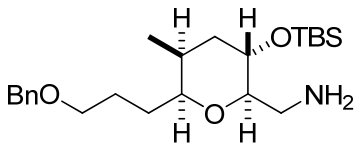

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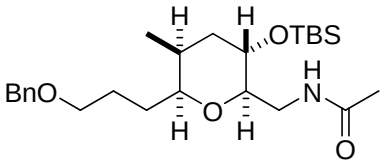

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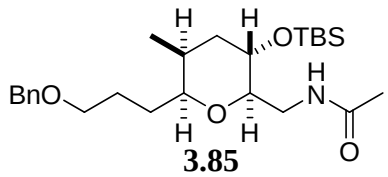

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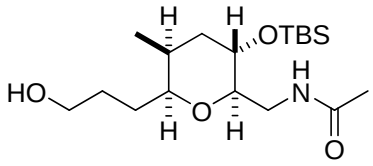
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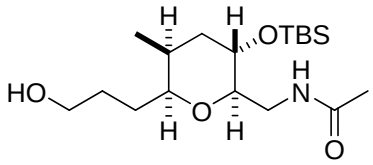
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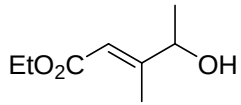
ppm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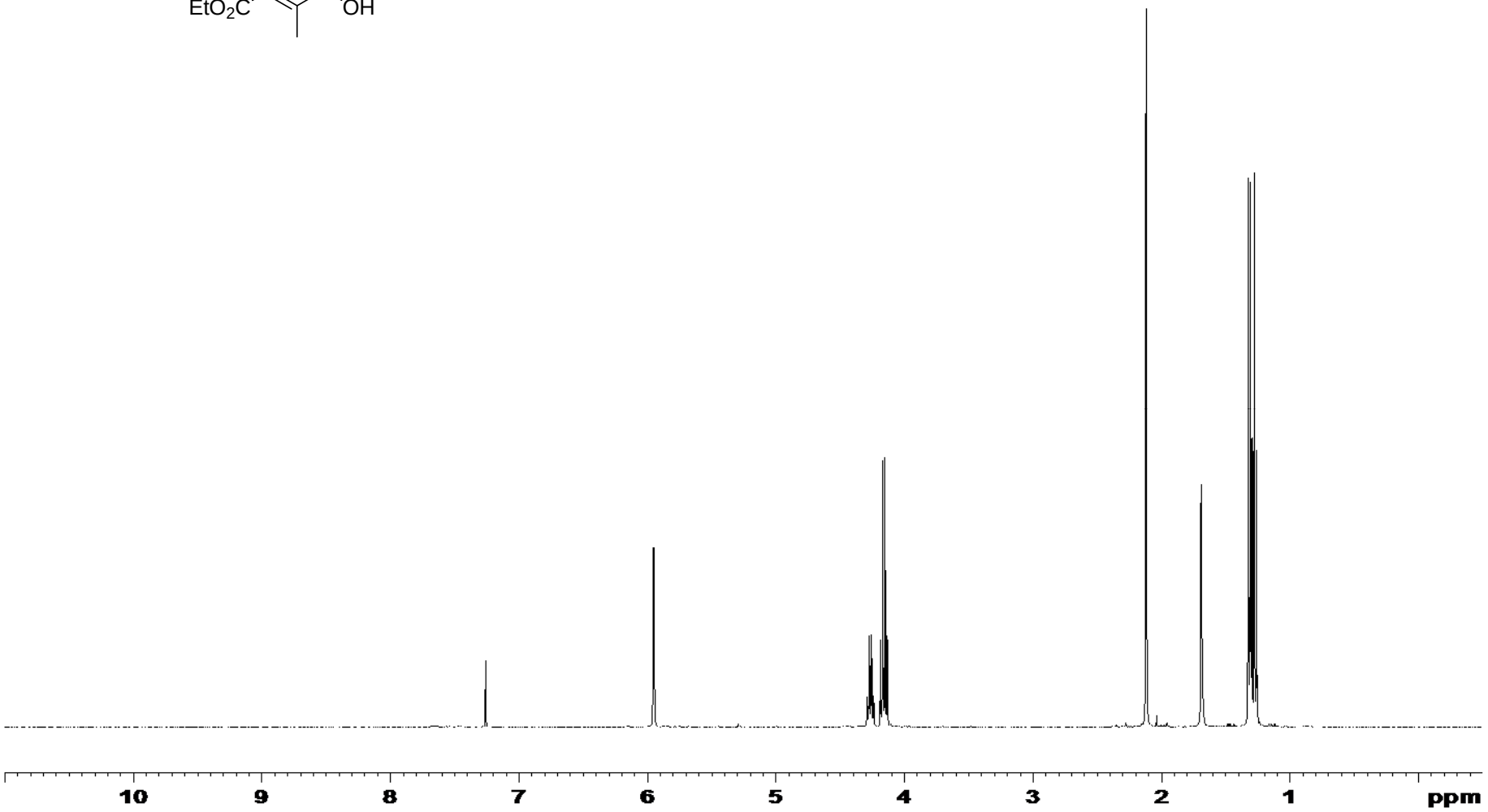
OH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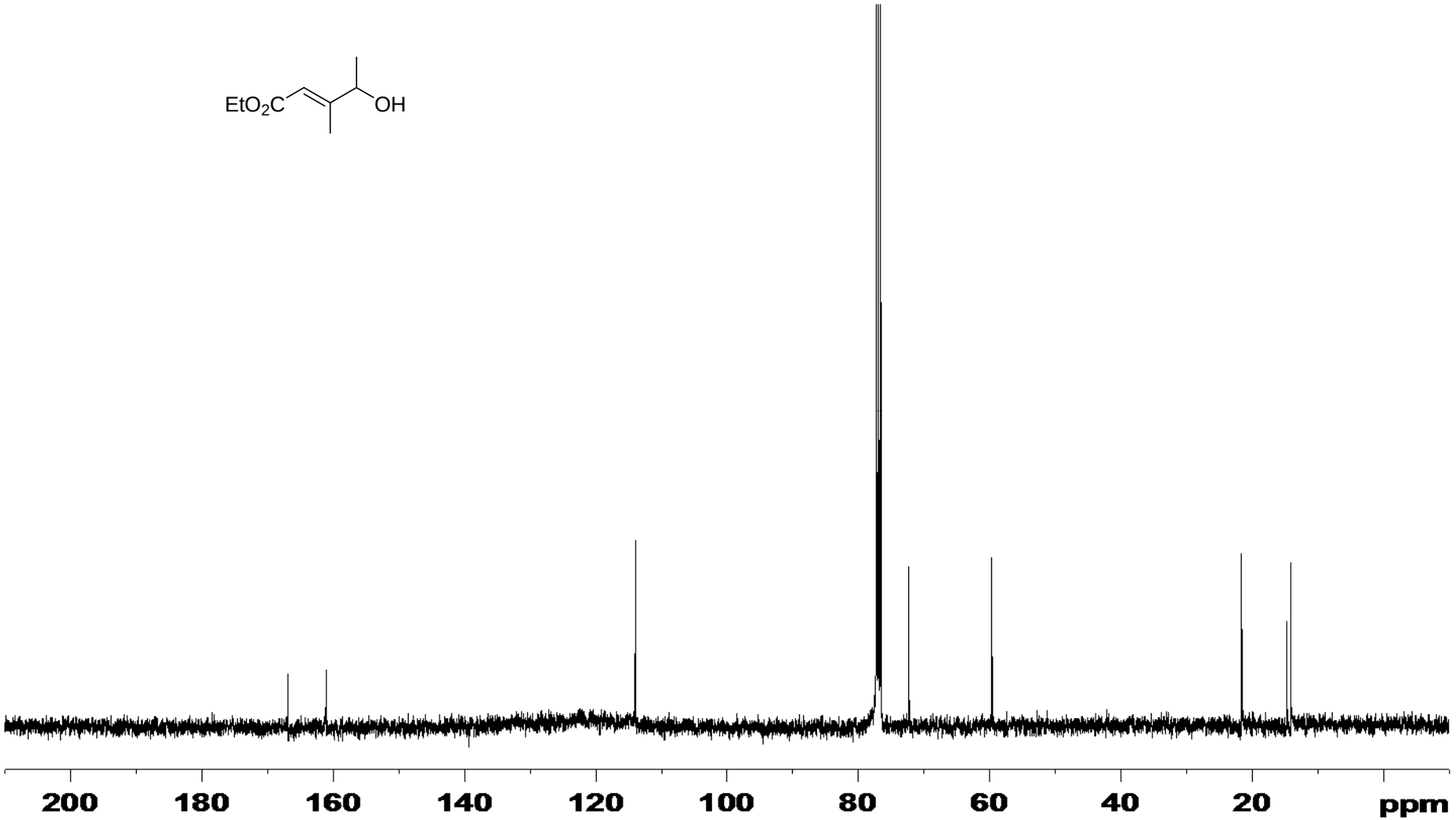
ppm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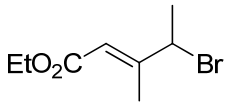

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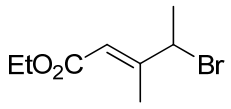

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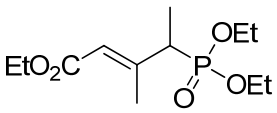

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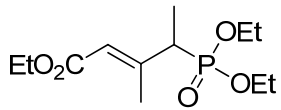

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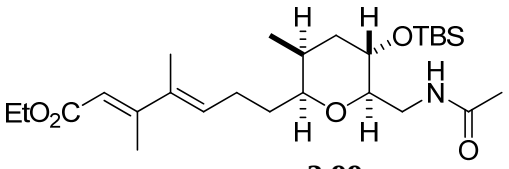

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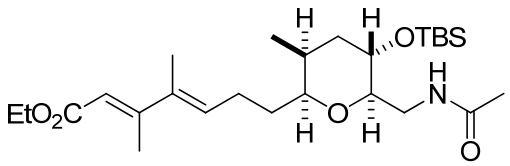

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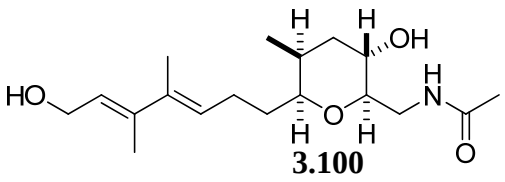

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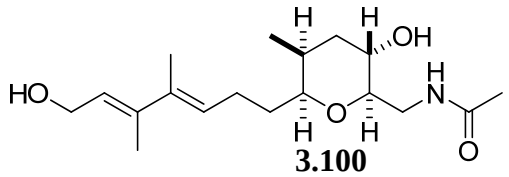

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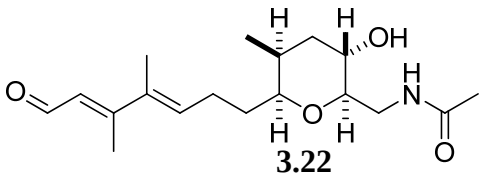

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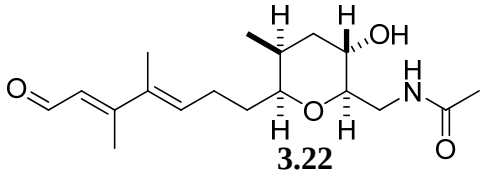

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