DISSERTATION

TOTAL SYNTHESIS OF HAPALINDOLES J AND U, FORMAL SYNTHESIS OF HAPLAINDOLE O, SYNTHESIS OF THE PROPOSED BIOSYNTHETIC PRECURSOR TO HAPALINDOLE K AND WORK TOWARDS THE AMBIGUINE FAMILY OF ALKALOIDS

Submitted by

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ABSTRACT

TOTAL SYNTHESIS OF HAPALINDOLES J AND U, FORMAL SYNTHESIS OF HAPLAINDOLE O, SYNTHESIS OF THE PROPOSED BIOSYNTHETIC PRECURSOR TO HAPALINDOLE K AND WORK TOWARDS THE AMBIGUINE FAMILY OF ALKALOIDS

Herein I discussed the total synthesis of hapalindoles J and U, the formal synthesis of hapalindole O, the proposed biosynthetic precursor to hapalindole K and efforts towards other hapalindole and ambiguine families of alkaloids. The hapalindoles and ambiguines both possess a highly functionalized 6:6:6:5, which I accessed over six synthetic steps via a developed silyl strategy with an overall 54% yield. Hapalindole J was synthesized in an overall 11% yield over eleven synthetic steps and hapalindole U in an overall 25% yield over thirteen synthetic steps from commercially available materials utilizing the silyl strategy developed. A formal synthesis of hapalindole O, intercepting Natsume's total synthesis, was accomplished as well via the developed silyl strategy. In addition, the synthesis of the proposed biosynthetic precursor to hapalindole K was accessed. Currently, this newly developed silyl strategy is being employed in accessing some of the more functionalized hapalindoles (such as K) as well as the complex ambiguine core.

ACKNOWLEDGEMENTS

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Finally, to my wonderful wife and best-friend Heather: no words can fully express my love for you. None of this work could have been accomplished without your endless support, love, kindness and patients. Thank you for supporting me, not only in this dissertation, but in our move to Illinois for my post-doc. I owe you so much!!! I can't wait to be done with this process and to enjoy every day with you. I love you so very much!!

Dedicated to

Joan Rafferty (Mother)

&

Heather Rafferty (Wife)

(The two most important women in my life)

TABLE OF CONTENTS

List of Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	Azobis(isobutyronitrile)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
Bu	Butyl
n-BuLi	Butyllithium
s-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butyllithium
t-BuOK	Potassium *tert*-butoxide
Cbz	Benzyloxycarbonyl
CSA	Camphorsolfonic acid
COSY	Correlation spectroscopy
DCM	Dichloromethane
DEAD	Diethyl azocarboxylate
DIBAl-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
eq	equivalents
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamine
LiHMDS	Lithium (bis)trimethylsilyl amide
2,6-lutidine	2,6-Dimethylpyridine
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeI	Methyl iodide
MeOH	Methanol
MOM	Methoxymethyl

Ms	Methanesulfonyl (mesylate)
NaHMDS	Sodium (bis)trimethylsilyl amide
NCS	*N*-Chlorosuccinamide
NBS	*N*-Bromosuccinamide
NMM	*N*-Methyl morpholine
NOSEY	Nuclear Overhauser effect spectroscopy
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium p-toluenesolfonate
i-Pr	Isopropyl
Py. or Pyr	Pyridine
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenlsilyl
TBS	*tert*-Butyldimetylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
pTSA	*para*-Toluenesulfonic acid

Chapter 1: Introduction and Isolation

1.1 Introduction

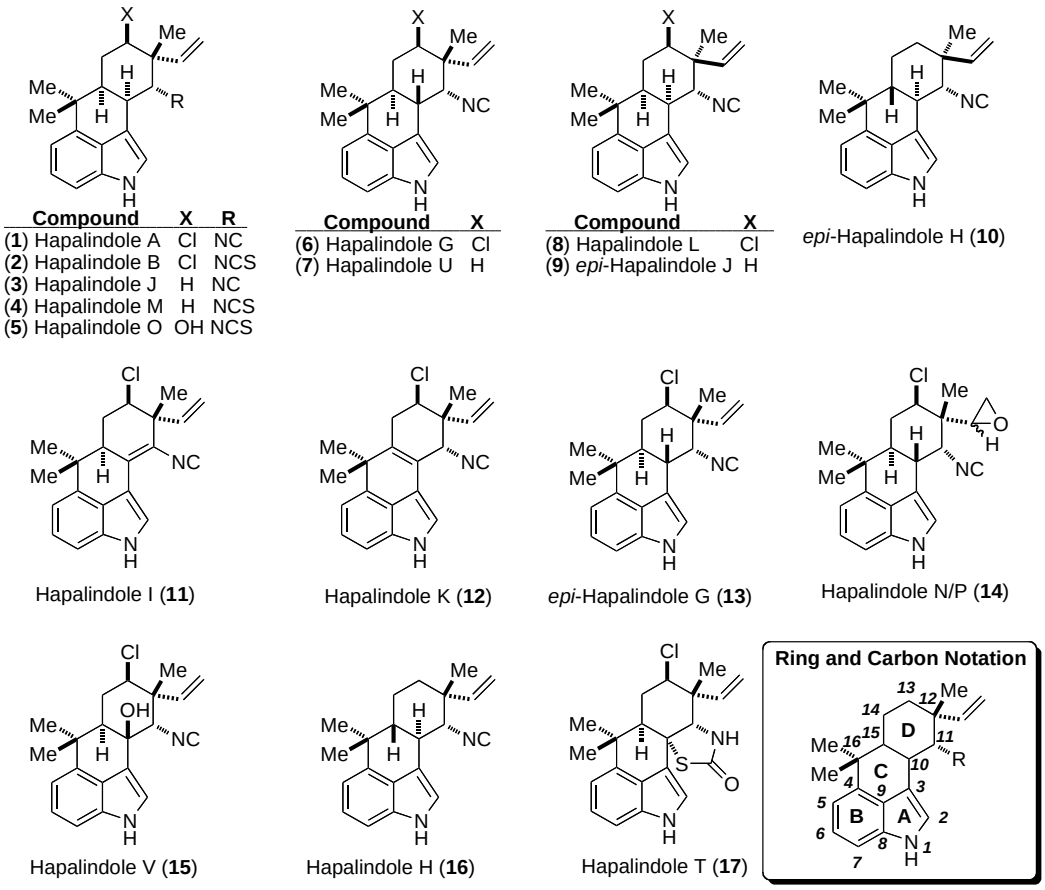
Herein will be discussed the hapalindole and ambiguine alkaloid families of natural products. Their structural relationships, isolations, previous syntheses and current work on their total synthesis will be discussed.

1.2 Structure and Ring & Carbon Notation

The family of alkaloids, tetracyclic hapalindoles and ambiguines contain several structural similarities that will be used in the efforts to gain access to the ambiguines. One key difference between the two families is the presence of a reverse prenyl group in the ambiguines on carbon 2 of the indole that the tetracyclic hapalindoles lack. This reverse prenyl group can be untethered to the carbon core or tethered to the 11 position of the ambiguines.

1.2.1 Hapalindoles

As of 2011, 10 tricyclic hapalindoles and 17 tetracyclic hapalindoles have been isolated and characterized.[1] The tetracyclic hapalindoles are of interested in the efforts towards the ambiguine family of natural products, due to the structural similarity of the two natural product families. Tetracyclic hapalindoles all posses a quaternary carbon at position 12, isonitrile or isothiocyanate at position 11, a fused 5:6:6:6 ring system, gem-dimethyl groups at position 16, many containing a chlorine at position 13, and a variety stereo-centers of multiple assignments. (Scheme 1).

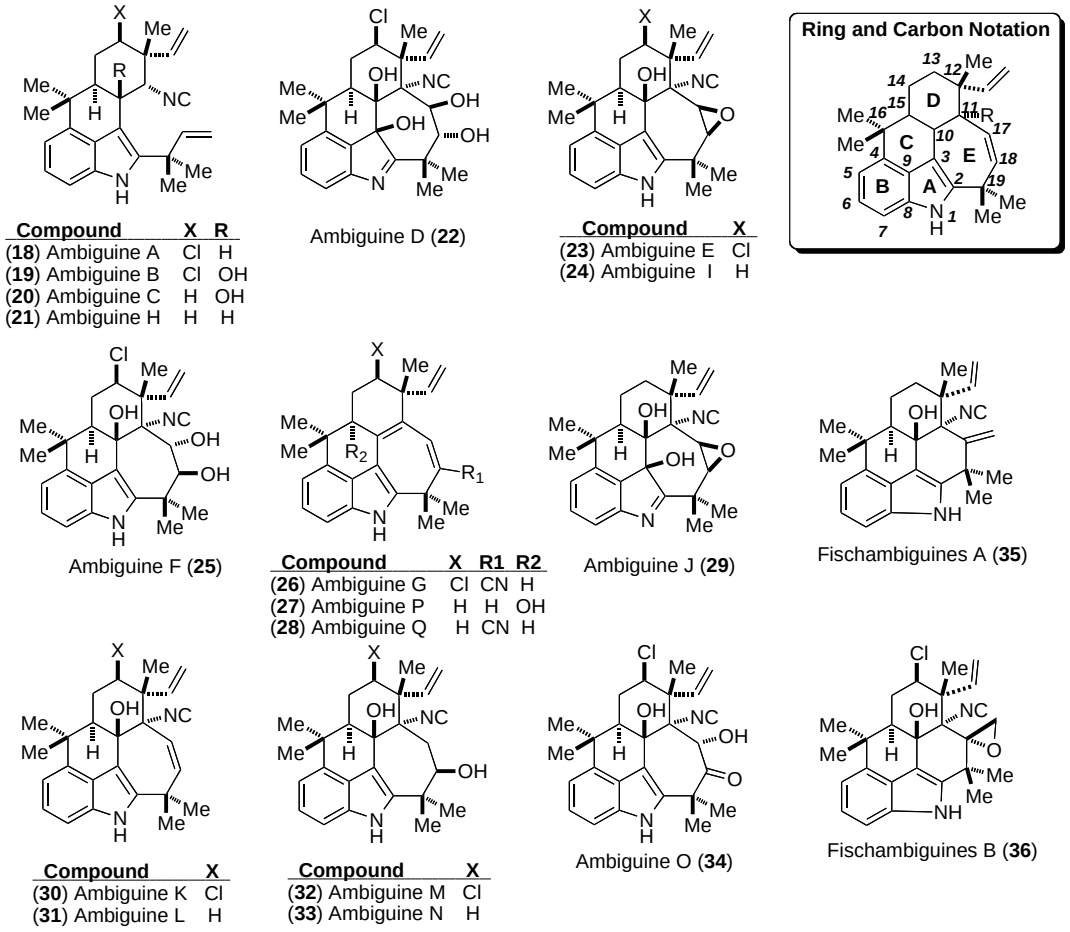


Scheme 1. Tetracyclic hapalindole family.

1.2.2 Ambiguines

As of 2011 there have been 17 ambiguines and 2 fischambiguines (structural similar to the ambiguines) isolated and characterized, Scheme 2.[2] All of the ambiguines have a quaternary center of the same stereochemistry at C12, a similar tetracyclic ring system (rings ABCD), gem-dimethyls at C16 and C19, and most of them contain an isonitrile at C11, two contain a nitrile and one contains neither. In roughly half of the ambiguines a chlorine is present at C13 and in more than half of the family a OH is present at C10, as well as combinations of the two. All of the ambiguines posses a reverse prenyl group at the C2 position of the indole, all of the ambiguines expect 4 have

the reverse prenyl group tethered to the C11 position forming a seven-membered ring. The fischambiguines are considered part of the ambiguine family of alkaloids due to a presence of a six-membered ring rather than a seven-membered ring with the same gem-dimethyl groups like that of the ambiguines.



Scheme 2. Ambiguine and Fischambiguine family.

1.3 Isolation

1.3.1 Hapalindoles

Seventeen tetracycle hapalindoles were isolated and characterized by Moore and co-workers in 1986 from cultured blue-green algae cyanophyte *Hapalosiphon fontinalis*.[1c] The algae, *Hapalosiphon fontinalis*, a member of the Stigonemataceae

family, was isolated from a soil sample from the Marshall Islands in 1982, which was massed cultured in the laboratory shortly after. Clonal cultures were prepared by repeated subculture on solidified media, after which the algae was cultured in 25-L glass bottles containing the appropriate media (MOPS and A3M7-salt). All cultures prepared were illuminated with a constant incident intensity of 330 μeinstein m^{-2} s^{-1} via banks of cool-white fluorescent tubes, while at the same time being vigorously aerated with ~1% CO_2 in air with an incubation temperature of 24 ±1 ℃. The algae were harvested 24 days later by filtration and the lyophilized cells range from 0.4 to 0.5 g/L of culture.

The freezed-dried algae were then extracted with a 1:1 CH_2Cl_2/2-propanol solution over night at approximately 8 ℃ with constant stirring. The filtered extracts were then combined and concentrated to give a dry green solid. Approximately 11 g of extract was dissolved in 1 L of CH_2Cl_2 and loaded onto a 4.5 cm x 10 cm diameter silica gel column (EM Science Kieselgel 60; 230-400 mesh) that was pre-equilibrated with the same solvent. Eluting with CH_2Cl_2 for the first 400 mL constituted the first fraction, which was subsequently discarded, followed by a 600 mL second fraction with the same effluent which was collected and concentrated to give 1.15 g of a solid. The column was then eluted with 1:1 CH_2Cl_2/heptane (1 L), $CHCl_3$ (600 mL) and lastly 1:1 CH_2Cl_2/EtOAC (2 L). Each different effluent composition was collected separately and concentrated to give 4.8, 0.6 and 1.72 g of solid, respectively.

The first two collect fractions, 1.15 g and 4.8 g, were combined and treated with 1:1 cyclohexane/CH_2Cl_2 to afford hapalindole A. A portion of the mother liquor was dissolved into EtOAc and loaded onto a Prep-Pak-500 silica cartridge in a Water Prep LC 500A system. The sample was eluted using 8 L of a hexane to 85:15 hexane/EtOAc

gradient, during which fractions were combined based upon TLC analysis (1:4 EtOAc:hexane). Further purification via a 1 x 50 cm stainless steal HPLC column containing Whatman LPS-1 silica gel (13-24 μM) at 2.5 mL/min was then performed utilizing the following solvent system: (1) hapalindoles Q, D and F with 1:1 CH_2Cl_2/heptane, (2) M, U, Q, C, E, H and I using 2:1 CH_2Cl_2/heptane, (3) B using 2.5:1 CH_2Cl_2/heptane, (4) B, K using 4:1 CH_2Cl_2/heptane, (5) G, L, J and K using 3:1 CH_2Cl_2/heptane and (6) A using 2:1 CH_2Cl_2/heptane.

The last fraction (CH_2Cl_2/EtOAc) from the initial column was re-chromatographed via a gravity-flow column (5 x 12 cm) consisting of silica gel (Merck; 200-400 mesh) equilibrated with 2:1 CH_2Cl_2/cyclohexane, via a gradient from 2:1 CH_2Cl_2/cyclohexane to 100:1 CH_2Cl_2/MeOH. Said chromatography afforded hapalindoles N, O, P, T and V.

1.3.2 Ambiguines

In the search of alkaloids with antifungal activity, Moore and Patterson isolated ambiguines A-F from the blue-green algae *Fischerella ambigua*, member of the Stigonemataceae family, in 1992.[2a] The family Stigonemataceae contains other alkaloids, structurally and biosynthetically related, of which are: tricyclic hapalindoles, tetracyclic hapalindoles, welwitindolinone and fischerindoles. *Fisherella ambigua* was obtained from the University of Texas Collection and grown on liquid medium in 20-L glass bottles. The axenic algae was harvested, after 25-30 days of growth, by filtration, and freeze-dried to afford typically 0.39 g/L of algae. The algae was extracted with a 1:1 solution of CH_2Cl_2/2-propanol, to which the extracts were chromatographed on a 1.1 m x 5 cm column of Sephadex LH-20 using MeOH as the eluent. Fractions that were active

against *C. albicans* by disk assay were combined into two pools and evaporated. The residue from pool 1 was dissolved in MeOH, filtered, chromatographed on a 30 x 2.5 cm column of C18 silica using a linear gradient of 80-100% MeOH in water. Fractions that possessed fungicidal properties were combined and evaporated to give ambiguine A and a residue that was further purified by pTLC to give ambiguine D, ambiguine B and C. The residue in pool 2 was purified in a similar fashion to give ambiguines E and F. Ambiguine A was isolated as white needles, ambiguine B as an amorphous solid, ambiguine C as an amorphous solid, ambiguine D as crystals, ambiguine E as white needles, and ambiguine F as an amorphous solid. Ambiguines A-F were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, ^{1}H-NOE, ^{1}H-HMBC and ambiguine D were analyzed via X-ray crystallography to determine absolute stereochemistry that was used to elucidate the other ambiguines.

Moore and Patterson isolated Ambiguine G in 1998 from the cyanophyte *Hapalosiphon delicatulus* in a 0.0064% yield. The cyanophyte was cultured in an autoclaved 20-L glass carboy containing an inorganic medium adjusted to pH 7.0 with MOPS and were continuously illuminated with an incident intensity of 80-200 μ mol photos m^{-2} s^{-1}. After 38 days the algae was harvested by filtration, freeze-dried, and extracted twice with 1-L portions of 1:1 CH_2Cl_2/2-propanol overnight. The crude product was dissolved in MeOH and chromatographed on a Sephadex LH20-120 column using MeOH as the eluent. Fractions 4 and 5 were collected and further purified to give ambiguines A and G. Ambiguine G was characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, ^{1}H-NOE, and ^{1}H-HMBC.

The ambiguine family was expanded again 2007 when Raveh and Carmeli isolated and characterized ambiguines H, I and J from *Fischerella ambigua*, along with five previously isolated ambiguines and *epi*-hapalindole H. The cyanobacterium was cultured in 20 L glass bottles containing a modified BG-11 medium and illuminated with an intensity of 100 μ mol photons/M^2/s from fluorescent tubes and aerated with 0.5% carbon dioxide at an incubation temperature of 25 °C for 30-35 days and harvested by filtration and freeze-dried. The freeze-dried cells were extracted with 7:3 MeOH/H_2O, the crude extract was purified by an ODS-column with increasing MeOH concentration in H_2O. Fractions 9 and 10, selected by a bioassay-guided technique, were combined and separated on a Sephadex LH-20 gel-filtration column with 1:1 CH_2Cl_2/MeOH eluent to afford five fractions on the basis of proton NMR data. Fractions 2, 3 and 4 were combined and further separated on a HiBar Select B column with 85:15 MeCN/H_2O to afford 12-*epi*-hapalindole H, ambiguines I, E, H, A, D, J, B and F. Ambiguine H was isolated as a white solid, ambiguine I as a white solid and ambiguine J as a transparent solid. Ambiguines H, I and J were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, ^{1}H-NOE, and ^{1}H-HMBC.

Ambiguines K, L, M, N and O were isolated and characterized in 2009 by Mo, Orjala and co-workers from *Fischerella ambigua*. The cyanobacterium was grown in 2.8 L Fernbach flasks containing 1 L of inorganic medium (Allen medium), illuminated with fluorescent lamps at 1.93 klx with an 18/6 h light/dark cycle. The culture room temperature was maintained at 22 ℃ and after 6-8 weeks the biomass was harvested by centrifugation and then freeze-dried. Extraction of the freeze-dried biomass with CH_2Cl_2/MeOH (1:1) afforded 691.1 mg of crude extract, which showed potent inhibitory

activity against the TB pathogen *Mycobacterium tuberculosis*. Separation on a Sephadex LH-20 column with MeOH gave two sub-fractions. The first sub-fraction was purified by RP-HPLC eluting with MeCN/H_2O (75:25) to afford ambiguine K, L and hapalindole G. The second sub-fraction was purified in the same fashion to afford ambiguines M, N and O. Ambiguine K was isolated as colorless crystals, ambiguine L as a white amporphous powder, ambiguine M as a white amorphous powder, ambiguine N as white amorphous powder and ambiguine O as a white amorphous powder. Ambiguines K, L, M, N and O were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, ^{1}H-NOE, and ^{1}H-HMBC.

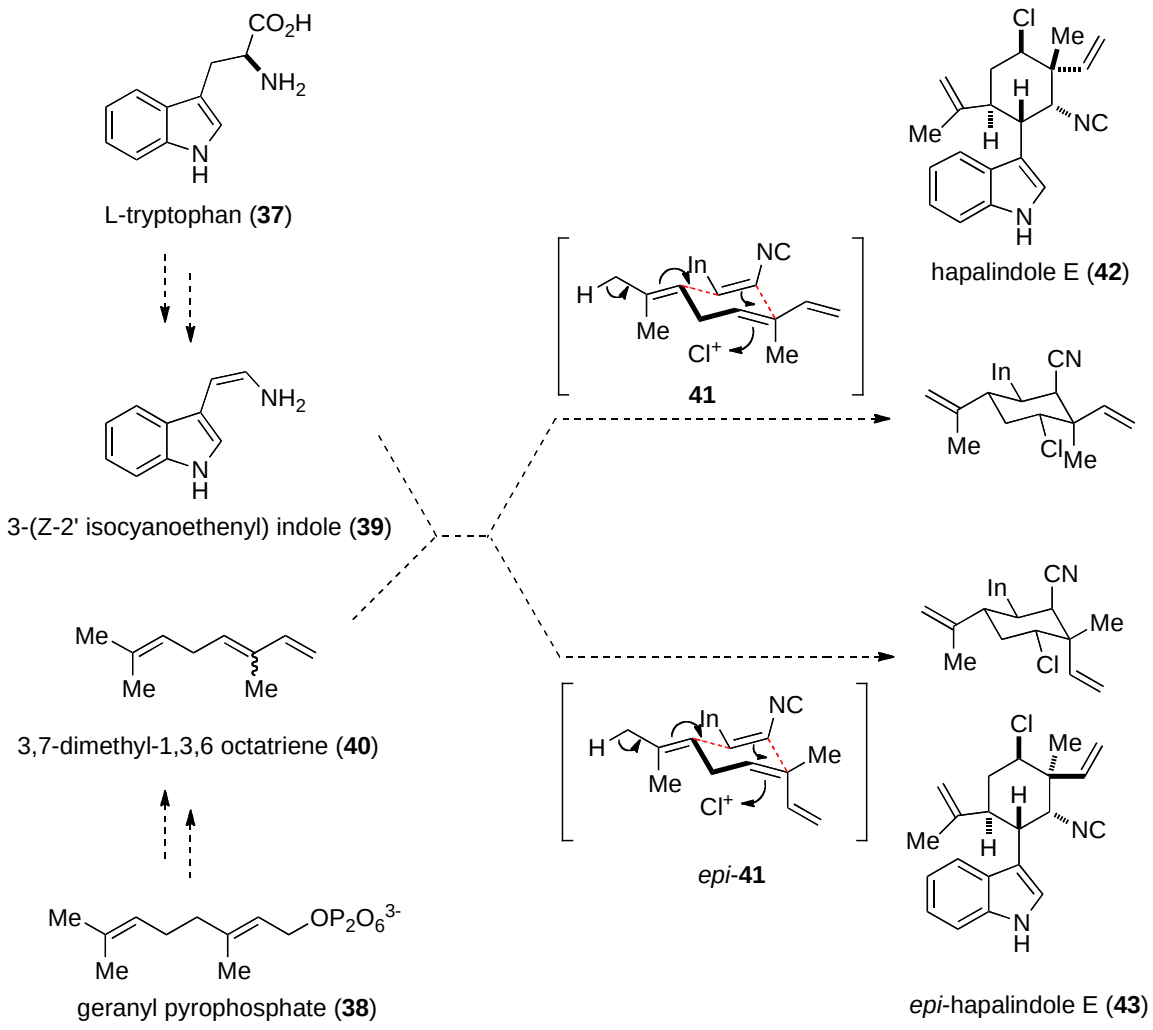
In 2010, the ambiguine family grew once again bring the family to 17 members along with 2 fischambiguines. Orjala and co-workers returned to *Fisherella ambigua* to isolated and characterized ambigiunes P and Q as well as fischambiguines A and B. A freeze-dried biomass was obtained as previously described for the isolated of ambiguines K-O, extracted with CH_2Cl_2/MeOH (1:1) to yield 691.1 mg of crude extract which was fractionated on silica gel using a gradient with increasing MeOH in CH_2Cl_2 to afford 18 fractions. Fraction 2, TB active, was further fractionated using a Sephadex LH-20 column with MeOH as the eluent to obtain 9 fractions. Fractions 2-8 were subjected to RP-HPLC using a MeOH/H_2O (85:15) to afford fischambiguine B and a mixture. The mixture was further purified by RP-HPLC using a MeCN/H_2O (75:25) to afford fischambiguine A.

A second freeze-dried biomass from 5 L of culture algae were extracted by repeated maceration with CH_2Cl_2/MeOH (1:1) to yield 178 mg of crude extract. Purification by an open silica gel column with a gradient of increasing MeOH in CH_2Cl_2 gave 9 fractions. Fraction 3 was purified by RP-HPLC with a linear solvent gradient of MeOH/H_2O (6:4)

to MeOH/H_2O (9:1) over 15 min to give ambiguine P and Q. Ambiguine P was isolated as a white amorphous powder, ambiguine Q nitrile as a yellow amorphous powder, fischambiguine A as colorless crystals, and fischambiguine B as white amorphous powder. Ambiguines P and Q and fischambiguines A and B were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, ^{1}H-NOE, and ^{1}H-HMBC.

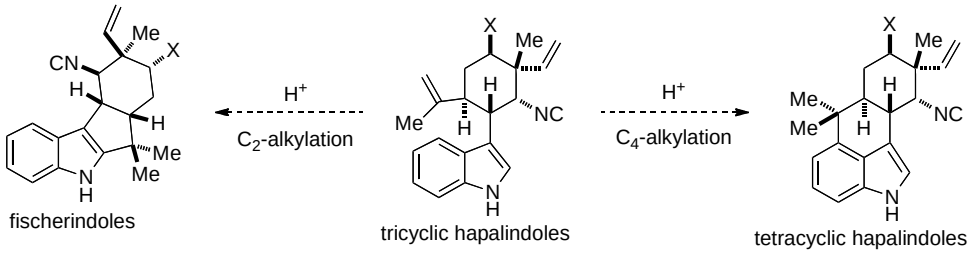
1.4 Biosynthesis

It is proposed that the hapalindoles and ambiguines share a similar biosynthetic pathway that starts with L-tryptophan (**37**) and geranyl pyrophosphate (**38**).[3] The proposed biogenetic pathway to the hapalindoles involves a chloronium ion-induced enzyme-mediated π-cation cyclization that affords the six-membered ring containing the chlorine atom, vinyl substituted quaternary center, isonitrile functionality, indole ring and isopropene group (Scheme 3). Suitable materials that could allow for this cyclization could be 3-(Z-2' isocyanoethenyl) indole (**39**), which could come from L-tryptophan (**37**), and 3,7-dimethyl-1,3,6-octatriene (**40**) which is known to come from geranyl pyrophosphate (**38**). Triene (**40**) in the presence of a chloronium ion can then undergo a [4+2] annulation with the olefin in (**39**) via a six-membered transition state (**41** or *epi*-**41**) to result in hapalindole E (**42**) or *epi*-hapalindole E (**43**), both tricyclic hapalindoles. This proposed pathway does allow the *epi* geometry about the quaternary center at C12 that is observed in the hapalindole family of alkaloids. The isonitrile functionality is derived from glycine and cyanide. For those hapalindoles that posses the thiocyanate group, the biosynthesis is not known, but is thought to arise from an inorganic thiocyanate ion.



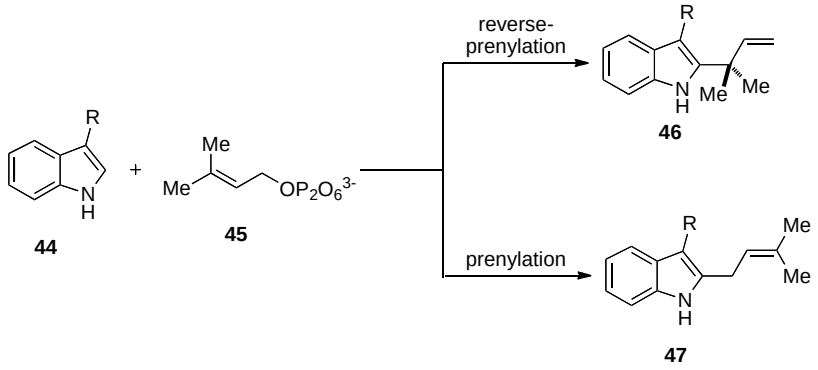
Scheme 3. Proposed biogenetic pathway to hapalindoles via a π-cation cyclization.

The tricyclic hapalindole can be transformed, via enzyme-mediated reactions, to either the fisherindoles or tetracyclic hapalindoles (Scheme 4). It's well documented that the tricyclic hapalindoles can be converted to fischerindoles under acidic conditions as well as tetracyclic hapalindole, with the former in higher yields due to electronics.[4] In the presence of a cellular matrix, both C2 and C4 alkylation occur at the same rate.



Scheme 4. Fischerindoles and tetracyclic hapalindole formation from tricyclic core

Both prenylation and reverse prenylation of indoles is well known (Scheme 5).[3] *In vivo*, reverse prenylation occurs via S_n2' displacement of the pyrophosphate on dimethylallylpyrophosphate (**45**) to afford C2-reverse prenylated indole (**46**). Prenylation occurs via nucleophilic displacement of the pyrophosphate on (**45**) via a S_n2 displacement to afford C2-prenylated indole (**47**). Formation of dimethylallylpyrophosphate, is known, from acyl-CoA via mevalonic acid as an intermediate. It is through this reverse-prenylation that the ambiguines are thought to arise from.



Scheme 5. Prenylation & reverse prenylation of indole

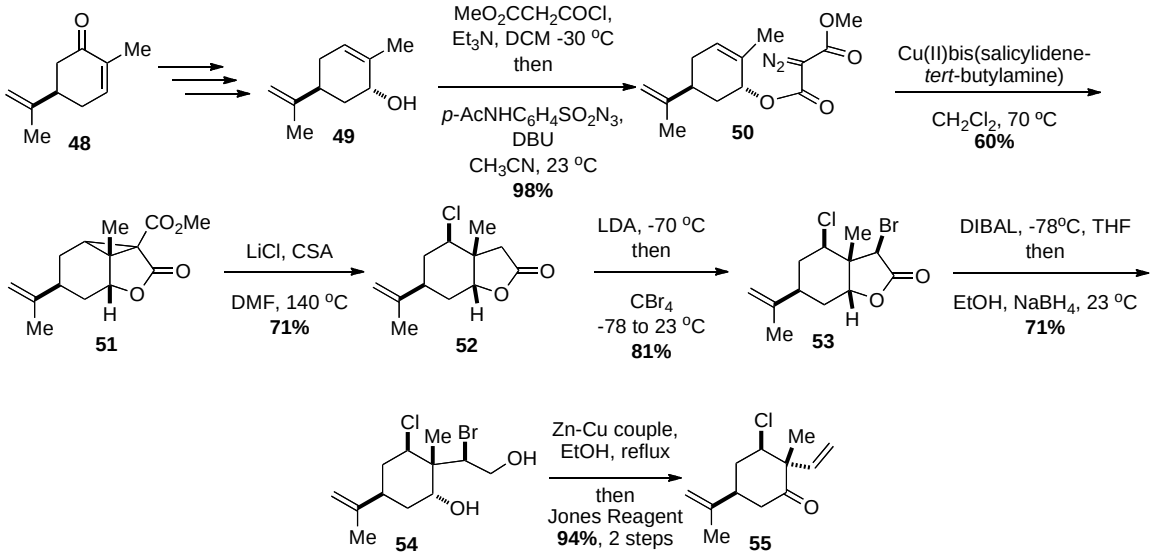
Chapter 2: Previous Synthetic Work on the Tetracyclic Hapalindoles and Ambiguines

2.1: Introduction

Previous total syntheses of several hapalindoles and ambiguine H will be reported, but other groups are currently working towards total syntheses as well, but will not be reported in this body of work.

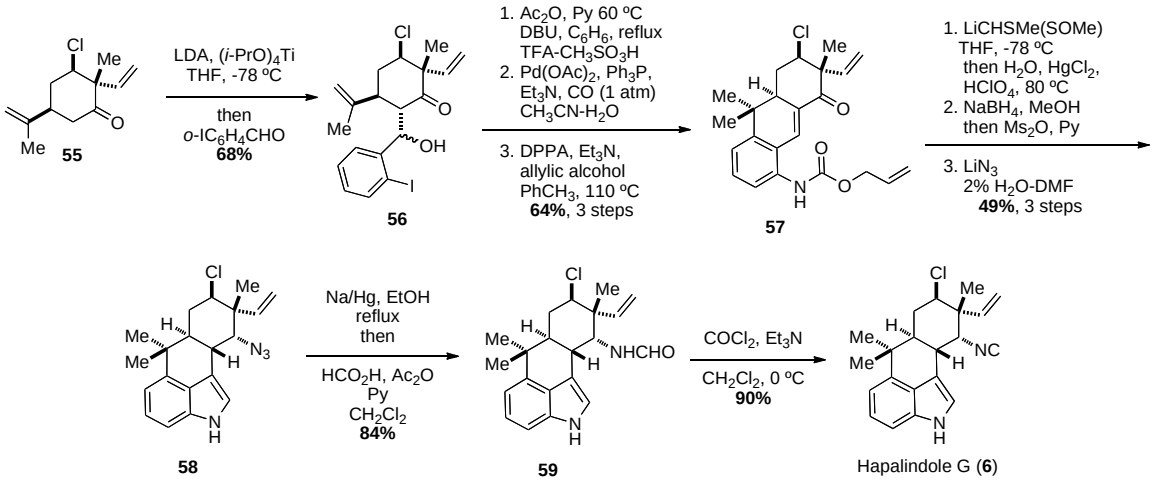
2.2: Fukuyama's Asymmetric Total Synthesis of Hapalindole G

Fukyama and co-workers accomplished their asymmetric total synthesis of hapalindole G in 1994.[5] Starting from (R)-carvone (**48**) transformation into the desired *trans*-carveol (**49**) in two synthetic steps, scheme 6. Treating (**49**) with methyl(chloroformyl)acetate followed by a diazo transfer afforded diazomalonate (**50**) in 98% yields in one pot. Subjecting **50** to copper(II) bis(salicylidene-*t*-butylamine) in DCM catalyzed an intramolecular cyclopropanation event furnishing **51** in modest yields. Krapcho decarboxylation conditions afforded **52** from **51** in 71% yield, which was subsequently brominated with CBr_4 via a lithium-enolate to afford **53** in 81% yields. Back-to-back reductions with DIBAl-H followed by $NaBH_4$ gave access to **54** which was subjected Zn-Cu in EtOH to furnish the desired vinyl functionality, followed by a Jones oxidation to afford the functionalized northern cyclohexyl ring of hapalindole G in 94% yield over two-steps.



Scheme 6. Elaboration of (R)-carvone into functionalized cyclohexyl **55**.

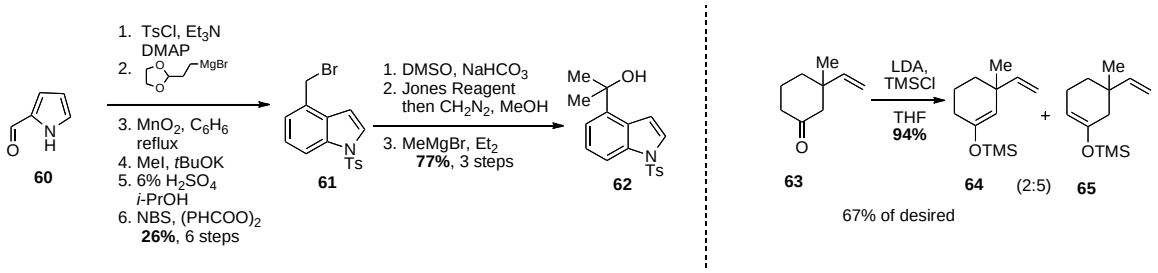
The lithium-enolate of **55** was then subjected to an aldol condensation with *o*-iodobenzaldehyde catalyzed by titanium(IV) isopropoxide to give an epimeric mixture of β-hydroxy-ketone **57**, scheme 7. Enone **57** was accessed via acetylation of the benzylic alcohol followed by elimination of the same alcohol with DBU with subsequent treatment with TFA and methanesulfonic acid. The resulting enone material was converted to its corresponding carboxylic acid via a palladium-mediated carbonylation, followed by conversion to the allyl urethane under conditions outlined by Shiori-Yamada. Treatment of **57** with lithiated methyl (methylthio)methyl sufloxide resulted in conjugate addition, and upon treatment with $HgCl_2$ afforded the request indole for the hapalindole family. Reduction with $NaBH_3$, mesylation, followed by S_N2 displacement with LiN_3 furnished tetracycle **58**. Azide reduction was accomplished via heating **58** with sodium amalgam in EtOH, which was formylated with formic acid, acetic anhydride and pyridine in DCM to afford **59** in 84% yield. Treating **59** with phosgene and NEt_3 afforded hapalindole G in 90% yield from **59**, with an overall yield of 4% over 15 synthetic steps.



Scheme 7. Fukuyama's route accessing hapalindole G.

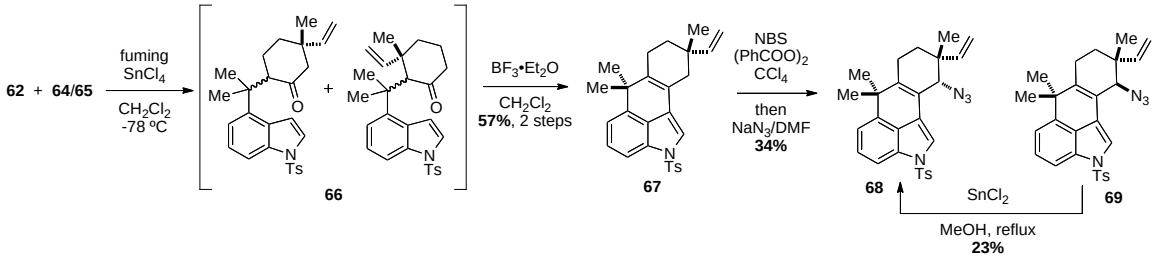
2.3: Natsume's Racemic Total Syntheses of Hapalindoles J, M, H and U

Natsume and co-workers developed a route accessing hapalindoles J, M, H and U racemically in 1990.[6] Outling in scheme 8, starting from 2-carbaldehyde-pyrrole (**60**) accessing 4-(bromomethyl)-*N*-tosyl-indole (**61**) was accomplished in six synthetic steps. Tosylation of **60** was achieved with TsCl, Et_3N and DMAP in DCM. Subjecting the tosylated product to (2-(1,3-dioxolan-2-yl)ethyl) Grignard, oxidation back to the ketone functionality with MnO_2, methylation with MeI followed by treatment with 6% sulfuric acid afforded 4-methyl-*N*-tosyl-indole. Treating said indole with NBS with benzoyl peroxide furnished **61** in an overall 26% yield from **60**. Compound **61** was further functionalized to **62** via oxidation, diazomethane along with methanol for ester formation, with subsequent treatment with methyl Grignard to furnish **62** in an overall 77% yield over three synthetic steps. Treating **63** with LDA in THF at -78 ℃ gave access to the two diastereomeric lithium-enolates, to which TMSCl was added to give access to TMS-enol ethers **64** and **65** (2:5, undesired:desired ratio) in 94% yield. Compounds **64** and **65** were not separated and carried on as a mixture of diastereomers.



Scheme 8. Natsume's route accessing indole **62** and TMS-enol ethers **64**/**65**.

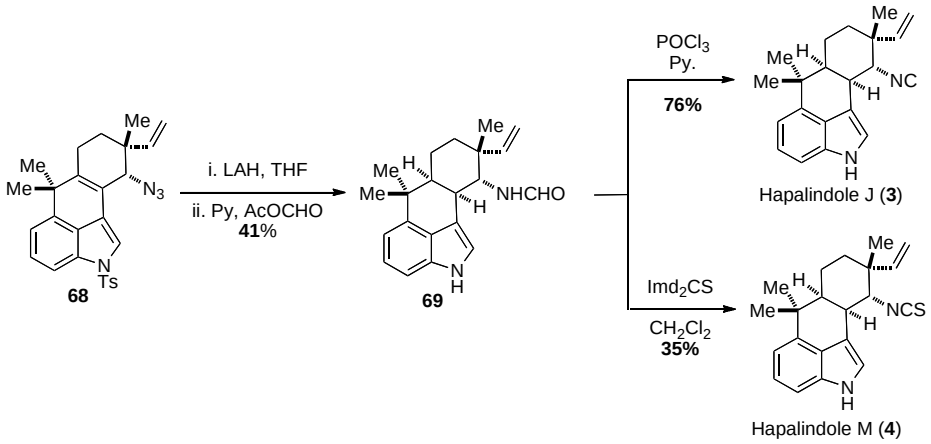
Treating indole **62** and TMS-enol ethers **64**/**65** in DCM at -78 ℃ with tin(IV) chloride furnished the two isomers **66a** and **66b**, which was subsequently treated with BF_3•etherate in DCM to afford tetracycle **67** in 57% over two steps, scheme 9. Natsume and co-workers were able to perform a radical bromination upon tetracycle **67** which they immediately took up in DMF and treated with NaN_3 to furnish azides **68** and **69** in 34% and 29% respectively. Azide **69** was converted into azide **68** via treatment with tin(II) chloride in MeOH at reflux in 23% yields.



Scheme 9. Lewis acid-mediate coupling and elaboration onto azide **68**.

Azide **68** was treated with LAH in THF to effectively reduce the tetra-substituted olefin in a non-facially selectively manner as well as the azide to the corresponding amine, scheme 9. The amine in the crude material was then treated with pyridine and acetic formyl anhydride to afford the desired formamide **69** in 41% yield in a one-pot procedure. Subjecting **69** to phosphorous oxychloride in pyridine gave access to racemic hapalindole J (**3**) in 79% yield. Likewise, treating **69** with 1,1'-thiocarbonyldiimidazole

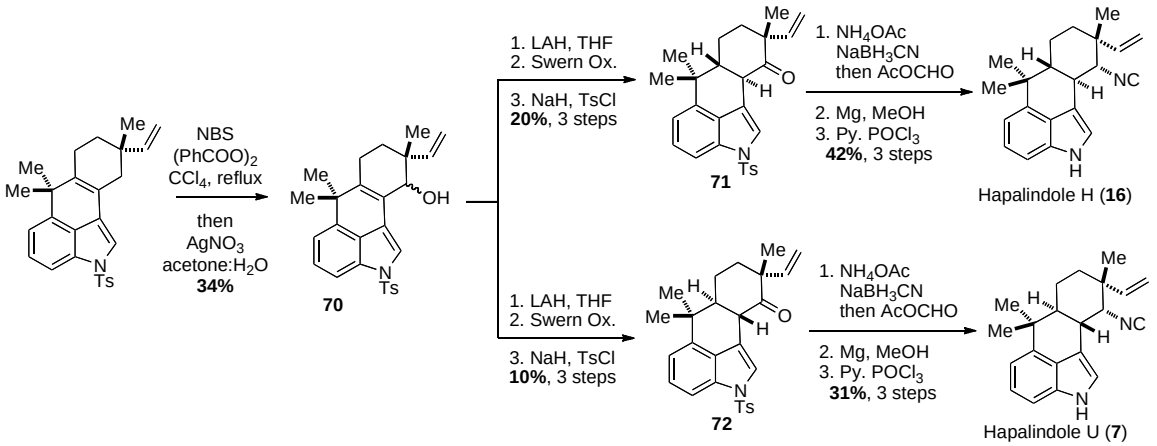
in DCM at 0 ℃ for 18h afforded racemic hapalindole M (**4**) in 35% yield. Natsume and co-workers were able to racemically synthesized hapalindole J and M in an overall 11% and 5% yield, respectively, over 15 steps, many of which were multiple steps performed in a one-pot method.



Scheme 10. Natsume's Total Syntheses of Hapalindole J and M.

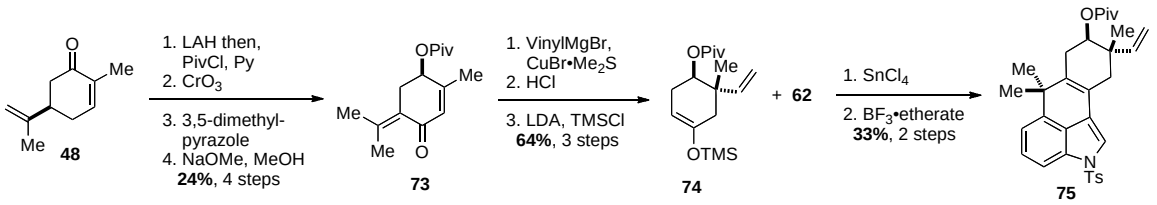
Intercepting their dehydrated tetracycle **67**, Natsume and co-workers were able to access hapalindoles H and U in a racemic fashion, Scheme 11. Subjecting **67** to the radical bromination conditions described above followed by treatment with silver nitrate in acetone/H_2O accessed allylic alcohol **70** in 34% yields. Treating **70** with LAH in THF afforded two diastereomers possessing *cis*-geometries about the former olefin. The resulting diastereomers were isolated, oxidized under Swern conditions and protected as the *N*-tosyl with NaH and TsCl to furnish **71** and **72** in 20% and 10% yields, respectively. Subjecting both to reductive amination conditions with ammonium acetate and sodium cyanoborohydride followed by formylation with acetate formyl anhydride furnished the respective formamide tetracycles. Treatment with phosphorous oxychloride in pyridine afforded racemic hapalindoles H (**16**) and U (**7**) in 42% and 31% yields, respectively. Natsume and co-workers were able to racemically synthesized hapalindole H and U in an

overall 0.2% and 0.1% yield, respectively, over 19 steps, many of which were multiple steps performed in a one-pot method.



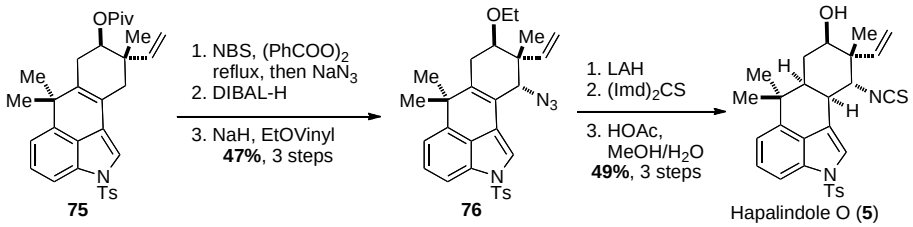
Scheme 11. Natsume's total synthesis of hapalindoles H and U.

Natusme and co-workers completed an enantio-specific total synthesis of hapalindole O. Treating (R)-carvone (**48**) with LAH afford the corresponding carveol species that was subsequently protected with a Piv group, scheme 12. Using chromium trioxide effectively oxidized the allylic position as well as oxidized the resulting alcohol to the corresponding enone. Subjecting the enone to NaOMe in MeOH furished the di-enone species **73** in 24% yield over four steps. Vinyl cuprate addition upon **73** followed by treatment with HCl afforded the desired quaternary carbon center with isopropene elimination. Treatments with LDA followed by TMSCl afford the desired TMS-enol ether **74** in 64% yields over three steps. Employing the same lewis acid-mediate coupling previously used afforded dehydrated tetracycle **75** in 33% yield over two steps.



Scheme 12. Natsume's enantio-specific approach to hapalindole O.

Employing the same radical bromination followed by sodium azide conditions afford the azide counterpart of **75**, scheme 13. De-protection of the Piv group was accomplished under reductive conditions using DIBAL, and the resulting alcohol was protected as the ethyl ether to give **76** in 47% over three steps. Reduction of the tetra-substituted olefin and azide was accomplished with LAH, and the resulting amine was transformed into the desired isothiocyante followed by de-protection of the ethyl ether to give hapalindole O (**5**) in 49% yield over 3 steps. In summary, Natsume and co-workers successfully accessed hapalindole O in an enantio-specific fashion in an overall 0.2% yield over 24 steps.

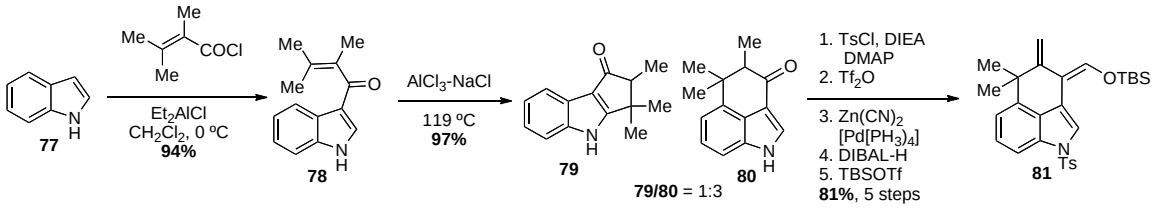


Scheme 13. Natsume's total synthesis of hapalindole O.

2.4: Johnston's Asymmetric Total Syntheses of Hapalindoles K, A and G

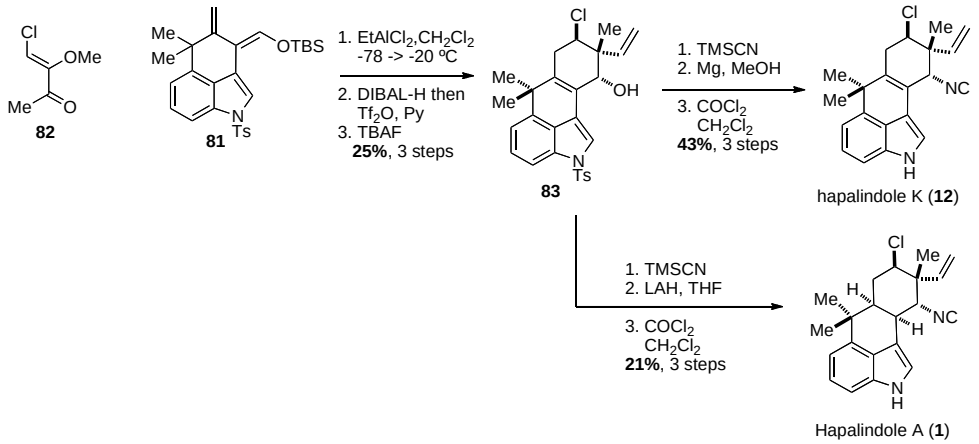
Chandra and Johnston achieved the total syntheses of hapalindole K, A and G in 2011 via a novel Diels-Alder reaction and a late-stage Ritter reaction accessing the functionalized core of these three natural products.[7] Treating indole **77** with α-methyl tiglic acid chloride with Et_2AlCl resulted in a Friedel-Crafts acylation reaction to occur affording **78** in 94% yields, scheme 14. Subjecting **78** to a molten solution of $AlCl_3$-NaCl effectively accessed **80** as the major product, but when heated at higher temperatures the undesired **79** was obtained as the major product. The indole nitrogen was tosyl protected with TsCl, Huing's base with catalytic DMAP. The resulting protected species was converted to its enol triflate with triflic anhydride and treated with

$Zn(CN)_2$ and $[Pd(PPh_3)_4]$ followed by nitrile reduction with DIBAL-H and TBSOTf treatment to afford the desired diene **81**.



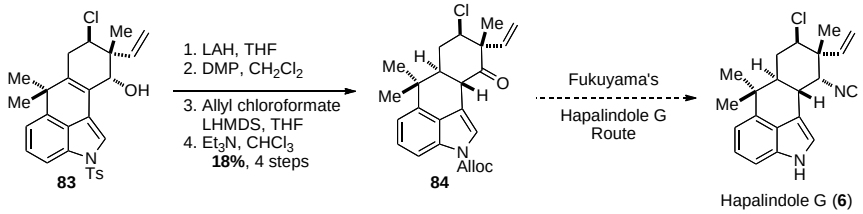
Scheme 14. Johnston's Assembly of Pre-D.A. substrate **81**.

Treating a solution of dienophile **82** and diene **81** in DCM with ethyl aluminum dichloride successfully formed the desired Diels-Alder product in 59% yields, scheme 15. Reduction of the ketone with DIBAL-H followed by triflation of the resulting alcohol furnished the required vinyl group. De-protection of the TBS group was achieved with TBAF to afford **83** in an overall 25% over three steps from **81** and **82**. A Ritter reaction was performed on **83** with TMSCN in acetic/sulfuric acid to furnish the resulting formamide, which was subsequently treated with phosgene to afford hapalindole K (**12**) in 43% yield over three steps. Likewise, performing another Ritter reaction upon **83** followed by LAH resulted in the reduced decalin system and upon treatment with phosgene afforded hapalindole A (**1**) in 21% over three steps.



Scheme 15. Johnston's total syntheses of hapalindoles K and A.

Johnston also accessed hapalindole G with a formal synthesis employing Fukuyama's chemistry previously delineated, scheme 16. Reduction of **81** with LAH followed by oxidation with DMP afford the *trans*-decalin ring system, which was subsequently Alloc protected to furnish **84**, which is an intermediated employed by Fukuyama in his route to hapalindole G (**6**).

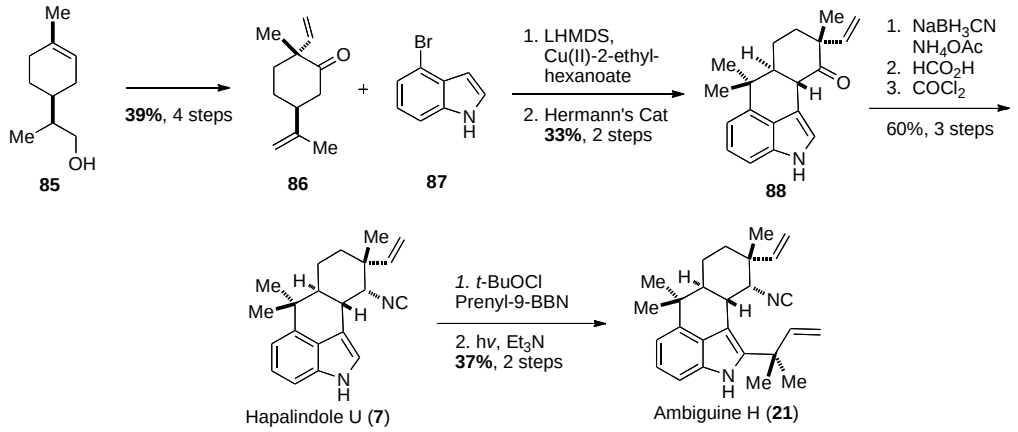


Scheme 16. Johnston's formal synthesis of hapalindole G.

2.5: Baran's Asymmetric Total Syntheses of Hapalindoles U and Ambiguine H

Baran and co-workers achieved the asymmetric total syntheses of hapalindole U and ambiguine H in 2007.[8] Starting from commercially available, but highly expensive, **85** was elaborated into **86** in an overall 39% yield over four synthetic steps, scheme 17. Ketone **86** was successfully coupled to 4-bromoindole (**87**) utilizing a radical approached, previously employed in the total synthesis of fisherindoles, followed by treatment with Hermanns catalyst as the palladium source to induce a Mannich reaction giving access to tetracyclic **88** in 33% yield over two steps. Reductive amination with ammonium acetate and sodium cyanoborohydride, followed by formamide formation via coupling with formic acid with subsequent dehydration with phosgene furnished hapalindole U in an overall 7% yield over nine synthetic steps from commercially available materials. Treating hapalindole U to *t*-BuOCl followed by prenyl 9-BBN, according to the protocol developed by Danishefsky, afforded a pentacyclic chloroimidate crystalline solid.

Irradiation of this crystalline solid for 5 h resulted in a Norris-type cleavage affording ambiguine H in 37% over two steps, and in an overall 3% yields over 11 synthetic steps.



Scheme 17. Baran's total synthesis of hapalindole U and ambiguine H.

Chapter 3: Previous and Current Synthetic Work

3.1: General Synthetic Strategy

In designing a route to access the tetracyclic hapalindoles and ambiguines several key points were essential in the design. Firstly, we wanted a route that was highly convergent in that it would allow for the total synthesis of both alkaloid families through similar starting materials utilizing the same or slightly modified chemistry. As both families contain a similar 5:6:6:6 ring system, quaternary carbon center at C12, geminal dimethyl groups off C4 of the indole ring as well as an isonitrile moiety at C11 a convergent synthesis for these families should be fairly easy to develop.

Second, keeping in mind the previous syntheses[5-8] and efforts towards these families of alkaloids, we desired to formulate a new route to access them that enhances this area of natural product synthesis. To this end, our route designed will be driven to access the family in the fewest steps possible, introducing stereo-centers early, and maximizing atom economy as much as possible. We also desire to develop a route that allows for functionality to be installed at multiple points throughout the synthesis, to help circumvent any problems that might arise during the synthesis.

Lastly, the route must be flexible to allow for possible analogs to be synthesized, at a variety of points in the synthetic route. The quaternary carbon at C12 of the D ring system is of main interest for possibly analog formation. Any synthetic route needs to allow for diversity in the alkyl groups that can be used at this stereogenic carbon. The

gem dimethyl groups off of the C4 carbon of indole are also of interested for future potential analogs as well as the C13 carbon and its methylene or halide carbon.

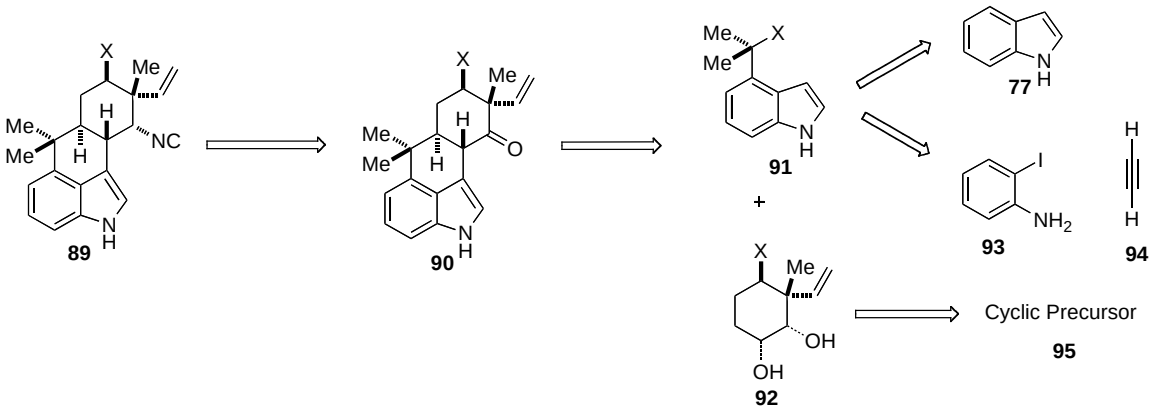
3.1.1: Retrosynthetic Analysis

With the structural similarities of the tetracyclic hapalindoles and ambiguines, along with the criteria outlined above, we believed that a common retrosynthetic route could be used to access the tetracyclic (5:6:6:6) carbon core that both alkaloids posses. Modification of the indole at C2 could allow for the reverse prenyl group that is seen in the ambiguines. The two-retrosynthetic routes shown below, while not extremely detailed at this point, give the general route that was used to access both families of alkaloids and their cores.

3.1.2: Tetracyclic 5:6:6:6 Carbon Core for Tetracyclic Hapalindoles

It is thought that the tetracyclic carbon core **89** of the hapalindoles could come from the ketone containing tetracyclic core **90** via reductive amination, peptide coupling and dehydration (Scheme 18). Tetracycle **90** is envisioned to come about through a double carbon-carbon bond formation event, either in parallel or in a step-wise process. Functionalized indole **91** and cyclohexyl **92** have been envisioned to be coupled either through some type of palladium-enolate reaction to form the C3-C10 bond followed by a ring closing event to form C4-C16. Likewise, the C4-C16 bond could be formed via a metal-mediated carbon-carbon bond formation via **91** and **92**. Functionalized indole **c** can be accessed either directly from indole **77** via standard indole chemistry or from *o*-iodoaniline **93** and alkyne **94** through a Larock indole synthesis[9] or a Sonogashira[10] coupling followed by a copper mediated ring closure. It is thought that he cyclohexyl

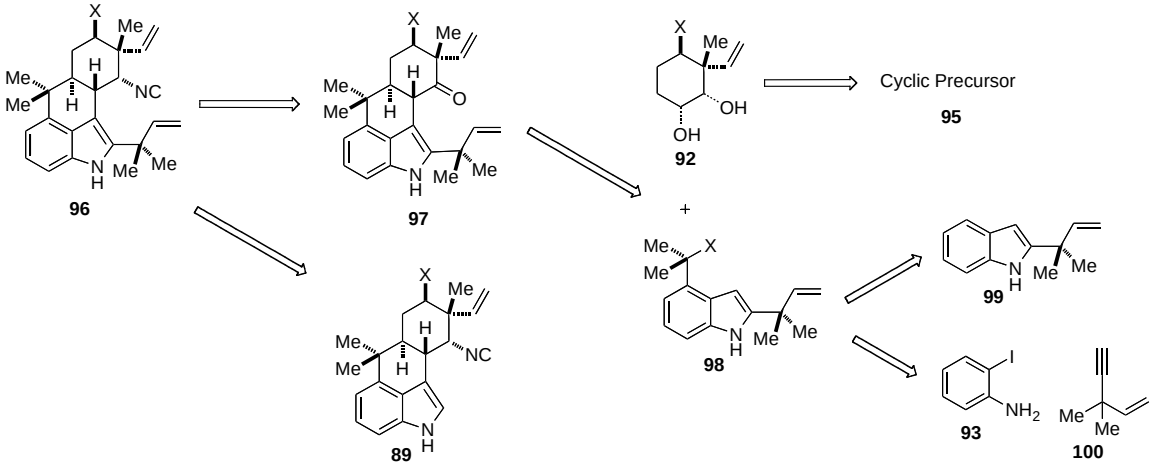
unit **92** could be accessed via a variety of cyclic precursors that allow for both the setting of the quaternary center at C12 as well as the possibly incorporation of a halide at C13.



Scheme 18. Retrosynthetic analysis for the tetracyclic hapalindoles.

3.1.3: Ambiguines – Non-Tethered Reverse Prenylated E-Ring

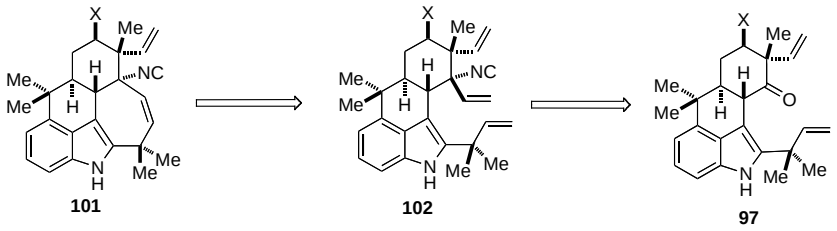
The non-tethered E ring system of the ambiguines were thought to be accessed directly from the tetracycle core **89** (Scheme 18) or from installation of the reverse prenyl group earlier in the synthesis (Scheme 19). Functionalized reverse-prenylated **98** could arise from either a reverse-prenylated indole utilizing standard indole chemistry, from a LaRock indole synthesis or Sonogashira coupling followed by a copper mediated ring closure.



Scheme 19: Retrosynthetic analysis for the ambiguines.

3.1.4: Ambiguines – Tethered Reverse Prenylated E-Ring

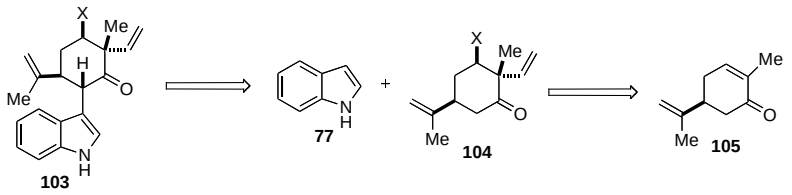
To gain access the tethered reverse-prenylated ambiguines, ring E, we envisioned that tetracycle **97** could be used (Scheme 20). Condensing hydroxyl amine onto ketone **97** followed by 1,2 addition of vinyl Grignard should give access to **102**. Performing a Ring-Close-Metathesis reaction should give access to pentacycle **101** that can be elaborated to the pentacyclic ambiguines. Functional group manipulations could take **101** and give access to the functionalized pentacyclic ambiguines.



Scheme 20: Retrosynthetic analysis of the pentacyclic ambiguines.

3.2: Synthesis of D-Ring

Searching for a cyclic compound that could be used as a starting point to gain access to ring D, two key features were sought after. First, the cyclic compound must allow for the quaternary center to be installed along with the future opportunity for analogs to be made about this carbon. Lastly, the cyclic compound must allow for installation of the quaternary center asymmetrically, or at least have the ability to a-symmetrize the compound at a later point. (S)-Carvone was chosen as the cyclic precursor for elaboration into quaternary center containing compound **104**, which could be coupled to indole **77** to give tricycle **103** (Scheme 21).

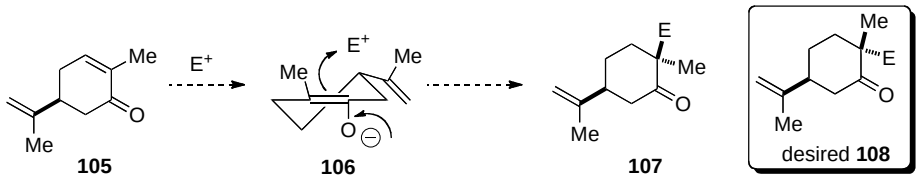


Scheme 21: Retrosynthetic analysis using carvone as the cyclic precursor.

3.2.1: Carvone: Attempts at Quaternary Center Formation

(S)-Carvone (**105**) was chosen as the cyclic precursor for two main reasons. First, due to its inherit stereochemistry about the isopropene carbon, which is desired for both family of alkaloids. Lastly, the enone allows for a handle for the installation of the quaternary center at C12 as well as the possibility for the halide incorporation at C13, which is required for roughly half of each family of alkaloids.

One of the main limitations to (S)-carvone (**105**) as the cyclic precursor is its pre-disposed selectivity about carbon C3, the future C12 carbon quaternary center. Once the enone of carvone is either transformed or temporally converted into enolate **106**, all electrophiles being added will favor addition to the same face as the isopropene group to give **107** rather than desired **108** (Scheme 22). Three approaches will be described that attempt to use (S)-carvone and elaborate it into the desired quaternary compound **108** by functionalizing **105** so that any addition affords **108** as the sole stereo-chemical product.

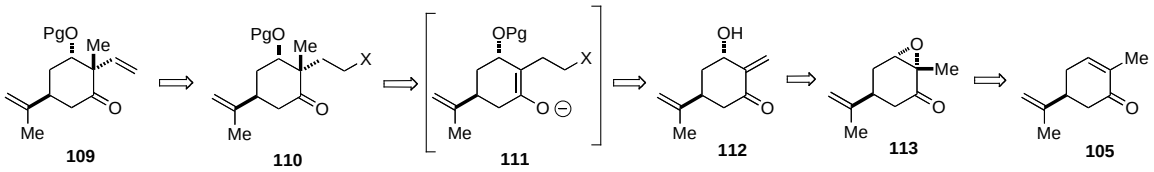


Scheme 22: Electrophilic addition upon carvone and predicted stereochemistry.

3.2.1.1: Exo-Cyclic Enone for Quaternary Center Formation

Due to the nature of electrophilic additions onto (S)-carvone (**105**) giving the opposite selectivity that is desired for both the tetracyclic hapalindoles and ambiguines, it was thought that this pre-disposed selectivity could be taken advantage of. All electrophilic additions will add to the same face of the isopropene group, therefore the methyl group rather than the vinyl group of the future C12 quaternary center needs to be added first. Therefore, the methyl group of carvone needs to be transformed into the required vinyl group or a group that be converted into a vinyl system at a later stage.

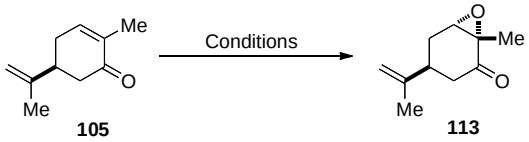
Retro-synthetically, the functionalized northern cyclohexyl D ring, **109**, could arise from the pre-vinyl compound **110**, via an E2 pathway to afford **109**. The methyl group of the quaternary carbon could be installed via standard enolate condition using a methyl halide substrate via **111**. Formation of **111** could come about from a cuprate addition onto the exo-cyclic enone **112**, which is proposed to come from the epoxy-(S)-carvone, **113** (Scheme 23).



Scheme 23: Retrosynthetic analysis to quaternary center via exo-olefin approach.

There is much precedence for the epoxidation of enones in the literature using nucleophilic epoxidizing agents.[11] Scheme 24 outlines the attempts at the formation of epoxy-(S)-carvone **113**. Epoxide formation using *t*-BuOOH in toluene has been well shown to give epoxides in descent to good yields on mono-β-substituted enones. While it is unfortunate that these conditions failed to give only a trace amount of product, it was not surprising or unexpected. Di-β,β-substituted enones generally require smaller

nucleophilic epoxidizing agents, such as H_2O_2. It was found that subjecting carvone in methanol to a 30% H_2O_2 solution with 1 eq. of sodium hydroxide at 10 ℃ over 5 h gave access to the desired epoxy-carvone **113** in 78% yield, which could be further elaborated to exo-cyclic enone **112**.

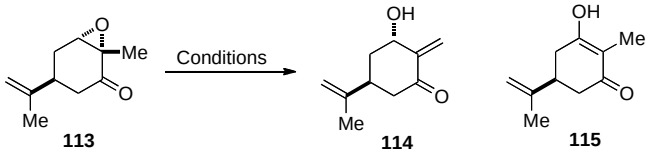


105 **113**

Conditions	Yields of 113
t-BuOOH (1.1 eq.), $PhCH_3$, rt (16 h)	trace
t-BuOOH (2.0 eq.), $PhCH_3$, rt (16 h)	trace
H_2O_2 (1.1 eq.), NaOH (0.3 eq.), MeOH, rt (2 h)	2.0%
H_2O_2 (1.1 eq.), NaOH (1.0 eq.), MeOH, rt (2 h)	6.3%
H_2O_2 (2.0 eq.), NaOH (1.0 eq.), MeOH, rt (2 h)	7.2 %
H_2O_2 (1.1 eq.), NaOH (0.3 eq.), MeOH, 10 ^oC (5 h)	21%
H_2O_2 (1.1 eq.), NaOH (1.0 eq.), MeOH, 10 ^oC (5 h)	24%
H_2O_2 (2.0 eq.), NaOH (1.0 eq.), MeOH, 10 ^oC (5 h)	25%
H_2O_2 (3.0 eq.), NaOH (1.0 eq.), MeOH, 10 ^oC (5 h)	78%
H_2O_2 (3.0 eq.), NaOH (1.0 eq.), MeCN, 10 ^oC (2 h)	14%

Scheme 24: Epoxidation conditions screened to formation of **113**.

With epoxy-(S)-carvone **113** in hand, attention was placed towards the formation of the exo-cyclic enone **114** which is to be used to generate the vinyl group or vinyl group derivative. Epoxides have been used to generate allylic alcohols via strong base de-protonation in good to average yields.[12] Treating **113** in THF with LDA at -78 ℃ over 3 h failed to give any of the desired exo-cyclic enone (**114**), but rather a 55% of the vinylogous acid **115** (Scheme 25). Attempting the reaction with LDA in a variety of temperatures as well as reaction times failed to afford any of the desired product, but only the vinylogous acid.



113 **114** **115**

Conditions	Temp (ºC)	Time	Yields (114:115)
LDA, THF	-78	3 h	0% : 55%
LDA, THF	-78	2 h	0% : 57%
LDA, THF	0	1 h	0% : 21%
LDA, THF	25	1 h	0% : 25%
LDA, THF	25	3 h	0% : 10%
LHMDS, THF	-78	1 h	0% : 76%
LHMDS, THF	-44	1 h	0% : 58%
LHMDS, THF	25	1 h	0% : 31%
BuLi, THF	-78	30 min	decomp
BuLi, THF	-44	30 min	decomp
DBN, TMSI, THF	-78	1 h	2% : 65%
DBN, TMSI, THF	0	1 h	5%: 82%

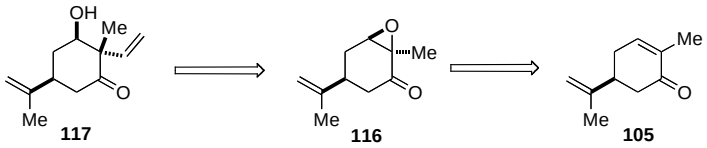
Scheme 25: Attempts at exo-cyclic enone formation.

Switching the base to LHMDS was then attempted to screen if steric bulk of the base could be restricting the reaction. A 10-20% increase in yields was observed when using LHMDS, but unfortunately to the undesired vinylogous acid. At this point, we knew that the exo-cyclic enone **114** was forming, as the hydrogens on the methyl group are the only hydrogens that can be used to rationalize **115** formation. For both LDA and LHMDS, de-protonation was occurring as observed via color change of the base upon addition to the epoxy-carvone solution; light yellow color to clear. It is thought that **114** did in fact form under the reaction conditions, but then underwent a tautomerization event to give the more thermodynamic product **115** either intra-molecularly or through a proton transfer from the solution or base. To explore this, a solution of LDA was quenched with deuterated water to afford the deuterated diisopropylamine, which was then added to a solution of the epoxy-carvone in THF, cooled to -78 ℃ and treated with LDA. The methyl group on the vinylogous acid did have partial incorporation of deuterium, which supports the theory that a rapid tautomerization event occurs giving the thermodynamic product **115**.

The deuterated diisopropyl amine study gave evidence of either a proton source form the base or from the solution could justify the vinylogous acid formation from the exo-cyclic enone. It was thought that the use of an even stronger base would prevent this proton transfer, to this end *n*-BuLi was used, but only gave decomposition of the starting matieral. A variety of other strong bases were screened in the attempts at preventing tautomerization to the undesired vinylogous with no success. Employing TMSI did give access to desired **114**, but only on small-scale attempts (<20 mg), thus making it prohibitive for natural product synthesis in this early stage.

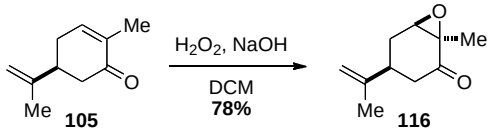
3.2.1.2: Epoxide Opening Quaternary Center Formation

The next approach to gaining access to the quaternary carbon center **117** was envisioned to be through the epoxy-carvone species **116** (Scheme 26). There is much precedence in ring opening epoxides on the more hinder carbon using Lewis acids or acidic conditions.[13] Here, it is thought that the epoxy-carvone could be treated with vinyl Grignard under Lewis acid conditions to afford the desired quaternary center-containing compound **117**. The epoxy-carvone compound could come from carvone using standard nucleophilic epoxidizing conditions.



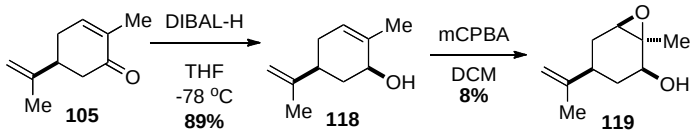
Scheme 26: Retro-synthetic Approach to Quaternary Center Via Epoxide Opening

(S)-Carvone was chosen due to its inherit stereochemistry already present in the compound, about the isopropene groups carbon in the cyclohexenone ring. Epoxidizing (S)-carvone **105** with a 30% hydrogen peroxide solution and sodium hydroxide in DCM was performs in a 78%. Having accessed the desired epoxy-carvone species the next step was to reduce the ketone to the corresponding alcohol. Reduction is required as vinyl Grignard is to be used for setting the quaternary carbon center, and the presence of the ketone will prevent mono-vinylation from occurring. Unfortunately, all attempts at reducing **116** failed to afford the reduced ketone. Majority of the conditions attempts resulted in partial ketone reduction as well as epoxide ring opening.



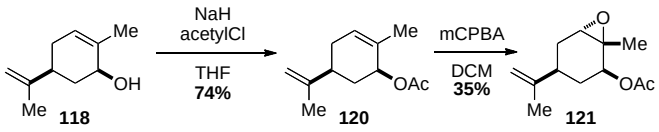
Scheme 27: Epoxidation of (S)-carvone.

It was thought that the reduction of the ketone should be performed early stage, given the failed reduction of the epoxide species. Facial reduction of (S)-carvone was accomplished using DIBAL-H in DCM to give the corresponding (S,S)-carvonol **118** in 89% yields (Scheme 28). Epoxidation of **118** with *m*CPBA in DCM afforded the desired epoxide (**119**), but in extremely low yields.



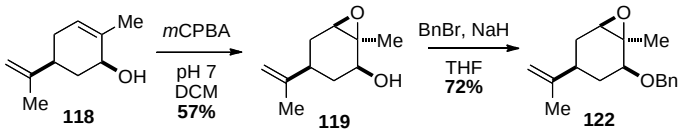
Scheme CC: Epoxidation of (S,S)-carvonol **118**.

Using *m*CPBA for epoxidation is quite common,[14] but using it by itself for directed epoxidation is not as well documented. It is thought that the required "butterfly" confirmation that *m*CPBA must adopt for epoxidation is being interrupted by the free alcohol in **118**. Therefore, protection of the free hydroxyl group should eliminate this effect. Acetylation of the alcohol in **118** was accomplished in 74% yields to give **120** via deprotonation with NaH and the addition of acetyl chloride in THF (Scheme 29). Epoxidation of **120** with *m*CPBA in DCM afforded the epoxide **121** in 35% yields. While the acetyl protected alcohol did allow epoxidation to occur, it failed to give the desired facial-selective product. While the early stage installation of the acetyl group failed to give the desired epoxided, future vinyl Grignard addition would have been affected by the presence of the acetyl group; in that vinyl addition would occur in a 1,2 fashion.



Scheme 29: Facially selective epoxidation of **120**.

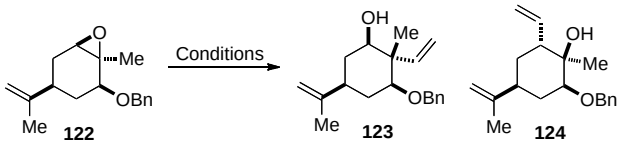
Previously **118** was epoxidized with *m*CPBA in DCM to afford **119**, but sadly in a 8% yield thus making it non-scalable for natural product synthesis. Conducting the reaction again with *m*CPBA along with a 15:1 (v:v) DCM:pH 7 phosphate buffer gave the desired epoxy-carvone **119** in 57% yields (Scheme 30). To our surprise, screening different temperatures failed to afford any increase in yields. With **119** in hand benzylation of the alcohol was performed using NaH and benzyl bromide in THF to give **122** in 72% yields.



Scheme 30: Epoxidation of (S,S)-carvonol and subsequent benzylation.

With **122** in hand, the Lewis acid mediated vinyl group addition was to be performed. Scheme 31 outlines the attempts at ring opening the epoxy-carvonol **122** under a variety of conditions. Treating **122** with the vinyl Grignard in THF at -78 ℃ failed to give any of the desired or non-desired materials, but rather just decomposition of the material with a variety of temperature profiles. Using 1.5 eq of magnesium bromide as a Lewis acid to coordinate to the epoxide for hopeful addition of the vinyl Grignard to the more hinder carbon failed to give any of the desired regio-selectivity, but rather 2% of the undesired. Increasing the Lewis acid eq. failed to give access to any vinyl addition, until 10 eq. of the Lewis acid was used. Swamping the system with an enormous about of magnesium bromide failed to increase the yield of the desired product **123**, but did increase the production of the non-desired regio-product **124**. Using titanium (IV) isopropoxide as the Lewis acid also failed to give rise to the desired addition product **123**, likewise was observed when using BF_3 etherate as the Lewis acid.

Multiple temperatures and temperature profiles were screened for the conditions outlines in the table in Scheme 31, all of which failed to give any improved yield of desired compound **123**. Other solvents were also attempted, but failed to give any trace amounts of desired **123**, but rather **124** as well as decomposition of the starting material.

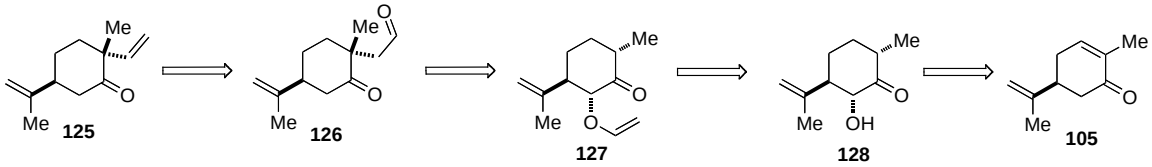


Reagents	Conditions	Time	Yield (123: 124)
vinylMgBr, THF	-78 ºC to RT	5 h	decomposition
vinylMgBr, THF	-78 ºC to 30 ºC	5 h	decomposition
vinylMgBr, $MgBr_2$ (1.5 eq.), THF	-78 ºC to RT	8 h	0% : 2%
vinylMgBr, $MgBr_2$ (3 eq.), THF	-78 ºC to RT	8 h	0% : 5%
vinylMgBr, $MgBr_2$ (10 eq.), THF	-78 ºC to RT	8 h	1% : 4%
vinylMgBr, Ti(*i*OPr)$_4$, THF	-78 ºC to RT	6 h	0% : 46%
vinylMgBr, BF_3•Et_2O, THF	-78 ºC to RT	8 h	0% : 22%
vinylMgBr, BF_3•Et_2O, THF	-78 ºC to reflux	8 h	0% : 20%

Scheme 31: Attempts at epoxide opening with vinyl Grignard.

3.2.1.3: Quaternary Center Formation via a Claissen Reaction

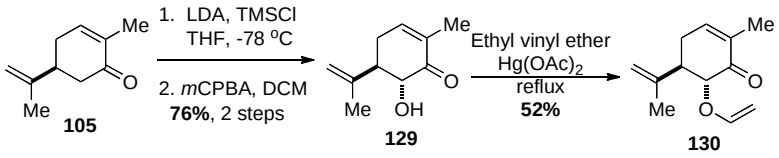
Gaining access to quaternary center containing **125** was next envisioned to come from a vinyl surrogate, possibly an aldehyde **126**, which was proposed to come about via a Claissen rearrangement[15] from **127** (Scheme 32). The required vinyl ether was to be installed from the α-hydroxy-ketone **128**, which would be accessed via a Rubottom oxidation[16] of (S)-carvone **105**.



Scheme 32: Retrosynthetic analysis for Claissen route to quaternary center.

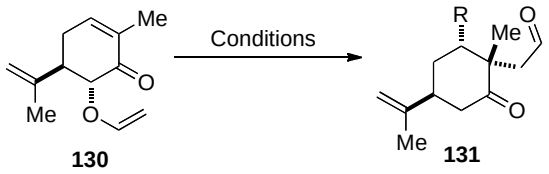
To access the needed Claissen substrate, (S)-carvone (**105**) was subjected to Rubottom oxidation conditions to afford **129** in 76% yields over two steps (Scheme 33). Treatment of **129** with neat ethyl vinyl ether and $Hg(OAc)_2$ under refluxing conditions

gave **130** in 52% yields. With **130** in hand, the next step was to perform the Claissen to give access to the quaternary center.



Scheme 33: Accessing α-vinylether (S)-carvone.

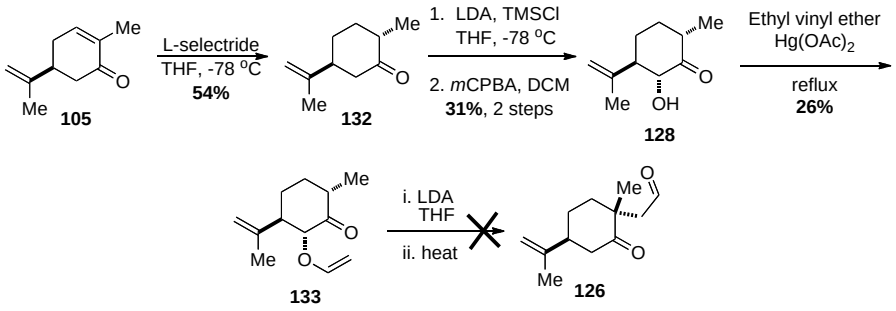
At this point, it was thought that using a soft nucleophile could add in a 1,4 fashion into the enone, forming the required enolate that could then undergo a subsequent Claissen reaction to give access to the desired quaternary center compound **131**. Pyrrolidine was selected as it could give a handle for further modification about the β carbon for halide installation. Pyrrolidine was added to a solution of **130** in toluene and brought to reflux for 24h, to our surprise, after this time only starting material was present in the reaction mixture (Scheme 34). Letting the reaction proceed for a longer duration gave decomposition of the material. Likewise, increasing the equivalents of pyrrolidine only gave decomposition of the starting material. Morpholine was then attempted as the soft nucleophile under the same conditions, but unfortunately also failed to give any desired product but only starting material and decomposition of the material.



Conditions	Time	Results
Pyrrolidine (1.1 eq) $PhCH_3$, reflux	24 h	Starting Material
Pyrrolidine (1.1 eq) $PhCH_3$, reflux	48 h	Decomposition
Pyrrolidine (1.1 eq) $PhCH_3$, 40 ºC	48 h	Decomposition
Pyrrolidine (2.0 eq) $PhCH_3$, reflux	24 h	Decompositions
Pyrrolidine (2.0 eq) $PhCH_3$, 40 ºC	48 h	Decomposition
Morpholine (1.1 eq) $PhCH_3$, 40 ºC	12 h	Starting Material
Morpholine (2.0 eq) $PhCH_3$, reflux	2 h	Decomposition
Morpholine (1.1 eq) $PhCH_3$/DMF MW	10 min	Decomposition

Scheme 34: Attempted Claissen at quanternary carbon center formation.

With the results in Scheme 34, two theories as to the failed result can be concluded: (1) the Claissen reaction can not occur on this system or (2) the soft nucleophile, once added to the enone can undergo a reverse 1,4 reaction more rapidly than the desired Claissen reaction. To exam if the Claissen reaction is a viable pathway on this system, removal of the soft nucleophile and direct enolization was to be performed. (S)-Carvone (**105**) was reduced with L-selectride in THF in modest yields of 54% to give **132** (Scheme 35). Rubottom oxidation conditions were employed to give **128** in 31% over two steps, followed by formation of the vinyl ether using conditions previously described to give **133** in 26% yields. Treating **133** with LDA followed by gentle heat failed to give any of the desired Claissen product. Modification in temperature and/or solvent conditions failed to afford the desired product as well. It is of interest to note that the enolization did occur, as quenching the reaction with deuterated water did show incorporation of deuterium on the α-carbons. Due to the failure of a Claissen reaction to occur on this system where the enolate was directly formed with little chance of reversibility, it was determined that the system doesn't seem to allow a Claissen reaction to occur.

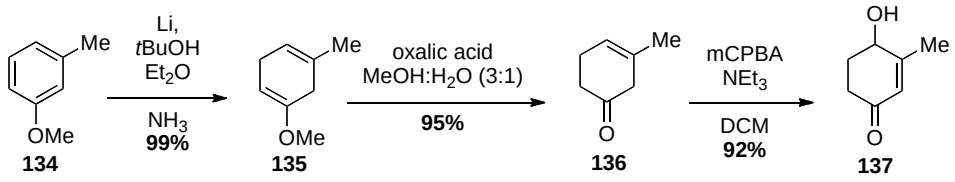


Scheme 35: Direct enolate formation for Claissen reaction.

3.2.2: Current Quaternary Center Formation Strategy – *m*-methylanisole

With the precedence of the previously described approaches using carvone as the cyclic precursor for ring D, it was decided to approach the access of the D ring in a different fashion that didn't utilizing carvone. Carvone did bring in a degree of complexity already installed, the stereochemistry about the isopropene group, but the challenges it bought along clearly out weighted all the benefits.

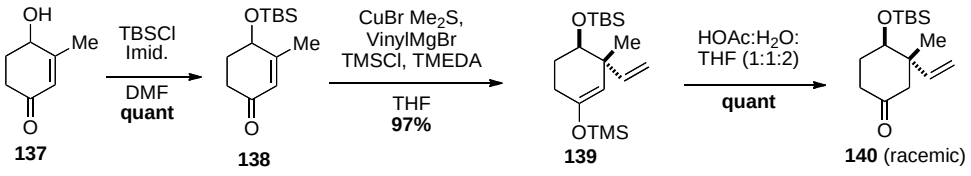
Commerically avaialable *m*-methylanisole **134** was converted to its corresponding Birch reduction diene product **135** in near quantitative yields using *t*BuOH as the proton source in liquid ammonia and lithium metal as the reductant (Scheme 36). Treatment of **135** with oxalic acid in a MeOH:H_2O (3:1) clipped the methyl ether to afford **136** in a 95% yield.[17] Epoxidation of **136** with *m*CPBA in DCM followed by addition of TEA gave access to the enone allylic alchol **137** in 92% yields.



Scheme 36: Approach to access enone allylic alcohol **137.**

Secondary alcohol **137** was protected as the TBS ether using TBSCl and imidazole in DMF to afford the protected alcohol **138** in quantitative yields (Scheme 37).

Setting the quaternary center has been envisioned to come about through a Michael addition with vinyl Grignard, using the TBS protected alcohol to give facial selectivity. The standard procedure, for this body of work, to set this center required copper (I) bromide to be added to THF and cooled to -78 ℃ followed by slow addition of vinyl Grignard over 20 min and left to stir. After 1 h, TMEDA followed by TMSCl was added and stirred for 10 min, then **138** in THF was added, left to stir for 2.5 h and worked-up to afford quaternary center containing compound **139** as a racemic mixture. Cleavage of the TMS-enol ether was accomplished over 1 h with a HOAc:H_2O:THF (1:1:2) mixture to give access to the racemic functionalized northern cyclohexyl ring D **140** for both the tetracyclic hapalindoles and ambiguines. With this compound in hand, it gives not only the desired and required quaternary center for both families, but a handle that can be used for the installation of the halide that is present in many of the alkaloids in these families. It is of note to mention that use of a TBS group for the protection of the alcohol gave, not only the best yields but also the best facial selectivity for access to **139**. When smaller silyl groups or alkyl protecting groups were attempted yields in the cuprate addition dropped by 20-55% and facial selectivity was nearly destroyed. The use of larger protecting groups gave similar facial selectivity, but also gave lower yields, which was thought to be from the excess bulk about the protected alcohol center.



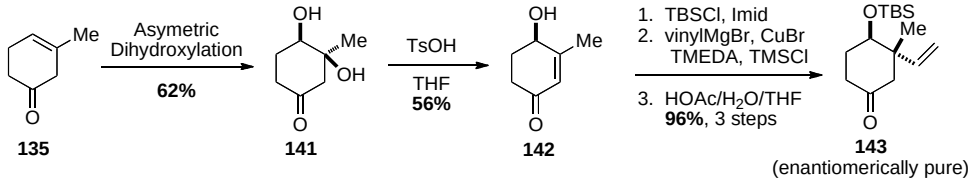
Scheme 37: Formation of racemic quaternary carbon center.

3.2.2.1 Accessing the Quaternary Center Asymmetrically

Having accessed **140** allowed the progression of the project towards the total syntheses of tetracyclic hapalindoles as well as the ambiguines, but a problem still needed to be addressed. The route to access **140** from commercial starting materials, while great in steps and yields, still gives the product as a racemic mixture. While the use of this material to access natural products is still viable, and was used for total syntheses, it only allows for a racemic synthesis that could be purified at the end of the synthesis via HPLC. The question then was asked on how could this route be adapted to give asymmetric **140**.

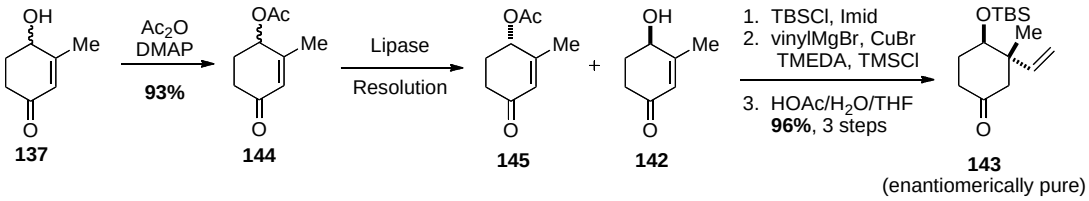
In the racemic route **136** is treated with *m*CPBA and NEt_3 to give the enone allylic alcohol **137** in great yields, but unfortunately with no facial selectivity. Performing an asymmetric dihydroxylation[18] on **136** allowed access to diol **141** with the proper stereochemistry about the secondary alcohol in modest to good yields (Scheme 38). Treating diol **141** with TsOH in THF at room temperature afforded **142** as a single enantiomer as confirmed by chiral HPLC. Having accessed **142** asymmetrically the following steps of TBS protection, cuprate addition and silyl hydrolysis as performed previously gave access to the same quaternary center containing compound **143** which could be used for asymmetric total syntheses once a route is established. While this route does give access to the material asymmetrically, there are several shortfalls that need to be addressed. Firstly, the asymmetric dihydroxylation can only be performed on small scales (80-120 mg), any attempts at increasing the scale resulted in return of starting material, decomposition, and a sharp decrease in yields. Lastly, the TsOH mediated dehydration is not a reproducible step. The yield shown in Scheme 38 is an

average of multiple attempts. Yields on this step could range from 84-23%, even when run on the same scale.



Scheme 38: Asymmetric dihydroxylation to gain access of enantiomeric **143**.

Given the problems of scale and reproducibility of the route show in Scheme 38 an enzymatic resolution was then attempted. Acetylation of enone allylic alcohol **137** with acetic anhydride, DMAP in THF afforded **144** in great yields (Scheme 39). Taking this racemic compound **144** and subjecting it to pig lipase resolution[19] afforded a mixture of acetylated and de-acetylated **145** and **142** respectively. Comparing the optical rotation of **142** obtained in the resolution to **142** obtained from the dihydroxylation gave the same value. Using chemistry previously employed gave access to **143** asymmetrically with no shortfalls.



Scheme 39: Lipase resolution accessing **143.**

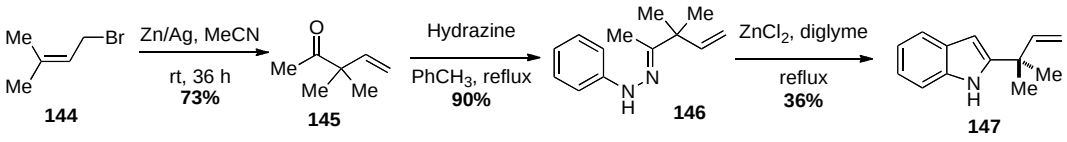
The asymmetric quaternary carbon compound **143** will be used once an established route to either the tetracyclic hapalindoles and/or ambiguines has been developed. Until that point the racemic compound **140** was used in the efforts to gain access to a route that accesses the natural products.

3.3 Reverse Prenylated Indole and 4-Bromo-Indole

Having accessed ring D of both family of alkaloids in both a symmetric and asymmetric fashion, attention was shifted towards gaining access to C2 reverse prenylated indole. As it will be become clear later in this body of work, two different C2 reverse prenylated indoles were targeted for synthesis. Those being the C2 reverse prenylated indole, no substitutions upon the indole except for the C2 alkyl group, and 4-bromo-2-reverse prenyl-indole.

3.3.1 Synthesis of C2 Reverse Prenylated Indole

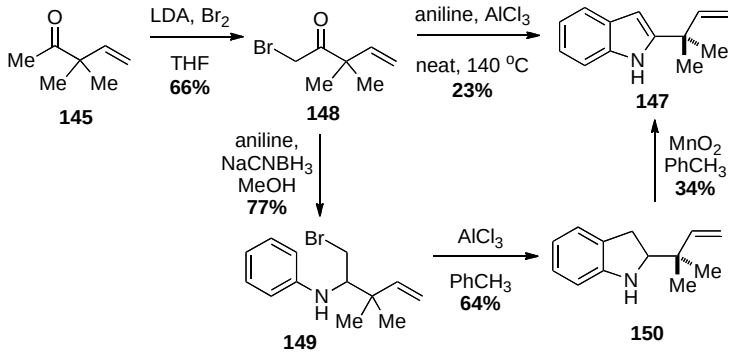
Three different strategies were employed in gaining access to C2 reverse prenylated indole: Fisher Indole,[20] Friedel Craft,[21] and Hydroboration.[22] Starting with commercially available 3-methyl-1-bromo-2-butene (**144**), formation of ketone **145** was obtained by treating **144** with a Zn/Ag in MeCN at room temperature for 36 h to afford product **145** in 62% yield, (Scheme 40). Subjecting **145** and phenyl hydrazine refluxing conditions in toluene for 3 h afforded **146** in good yields. Refluxing **146** in diglyme with zinc (II) chloride gave access to C2 reverse prenylated indole **147** in 36% yield. While this route does give access to the desired product, the overall yields of the sequence are lower but are scalable.



Scheme 40: Fisher indole synthesis for synthesis of reverse prenylate indole **147**.

In an attempt to improve the yields in gaining access to C2 reverse prenylated indole **147**, and noting that the zinc (II) chloride step in Scheme 40 is the bottle neck step, a Friedel-Crafts strategy was attempted. Bromination of **145** was accomplished by

deprotonation with LDA followed by diatomic bromine addition to give **148** in good yields (Scheme 41). To ketone **148** was added aniline and brought to reflux for 1 h, at which time $AlCl_3$ was added and returned to reflux. Workup of the reaction gave C2 reverse prenylated indole **147**, but in a rather low yield. Modifications on this synthetic step failed to give any increase in yields, which is unfortunately lower than the [3+3] step in the Fisher Indole synthesis.

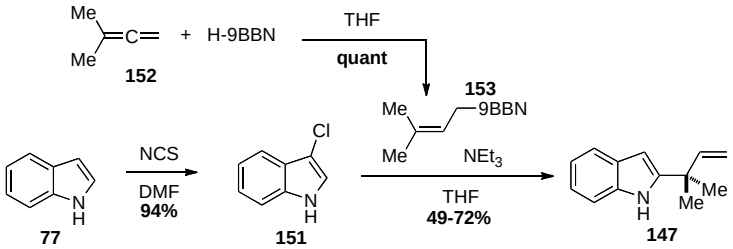


Scheme 41: Friedel-Crafts alkylation strategy accessing reverse-prenylation indole **147**.

It was realized that the Friedel-Craft step outlined in Scheme 41 is dependent upon many variables; such as reversibility of the iminium, tautomerization of the resulting iminium that is formed, and Friedel-Crafts alkylation occurring before condensation of the amine and ketone. To explore if this reaction was problematic, or just not an improve route to gain access to the desired indole the order of synthetic events were modified. Ketone **148** and aniline were subjected to reductive animation conditions to give **149** in modest yields. Performing this synthetic step allowed for probing into whether or not the iminium in the previous strategy was too unstable or if tautomerization was a cause of the low yielding step. Treating **149** with $AlCl_3$ in toluene at reflux for 4 h afforded **150** in a 64% yield, which was remarkably greater than previous seen in the one-pot route, thus suggesting either instability of the iminium or

rapid tautomerization to the corresponding enamine. Oxidation of **150** to the C2 reverse prenylated indole was accomplished with manganese dioxide in DCM at reflux in a 65% yield. Utilizing a Friedel-Craft alkylation rather than the Fisher indole synthesis does give access to the needed reverse prenylated indole in greater yields, but in a longer linear sequence as well as a greater financial expense.

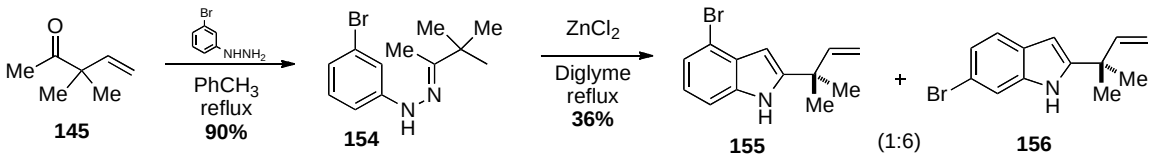
Reverse prenylation of indoles is well shown in the literature, mostly through the hydroboration of indole itself.[22] Previously in the Williams' group gaining access to C2 reverse prenylated indole was accomplished through hydroboration. Scheme 42 outlines the group chemistry that was employed to gain access to the desired indole **147**. The formation of the 9BBN-alkyl species as well as the chlorination of indole were both performed in excellent yields, however, the actual hydroboration step proved to be problematic as generally seen throughout its use in the Williams' group and outside of it. The yields of the hydroboration have not been reproducible, even when conducted on the same scale, as well as the small flasks and stir bars. Fortunately, when the yields of the reaction are poor recover of the indole starting material is possibly, but the 9BBN-alkyl species (**153**) was not recovered. This variability causes hydroboration to be a troublesome step in gaining access to reverse prenylated indoles, but while it is variable and problematic it is extremely scalable and thus has been used for gaining access to reverse prenylated indoles.



Scheme 42: Hydroboration for accesing reverse-prenylated indole **147**.

3.3.2 Synthesis of 4-Bromo-2-Reverse Prenyl Indoles

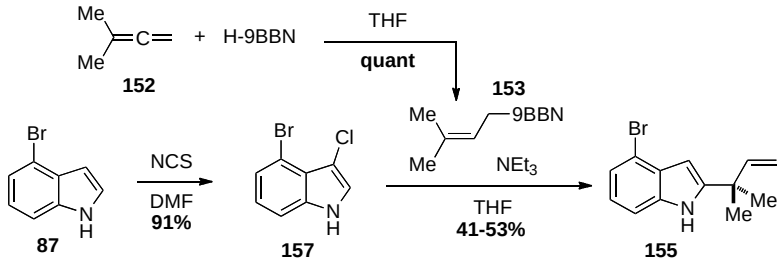
With the access of C2 reverse prenylated indoles, efforts were focused upon the synthesis 4-bromo-2-reverse prenyl-indoles, as previously stated this will become clear later in this body of work. Of the previously used routes, the Fisher indole synthesis was employed first. Ketone **145**, previously described, was added to *m*-bromo-phenyl hydrazine in toluene and refluxed to afford **154** in a 90% yield, (Scheme 43). Refluxing **154** in diglyme with zinc (II) chloride allowed the [3+3] rearrangement to occur in a 36% yield. The rearrangement gave both regio-isomers **155** and **156** in a 1:6 ratio, while this was not unexpected due to sterics it was unfortunate that the reaction favored the undesired isomer to such a large extreme. The Friedel-Crafts route was not explored as a possibly means to gain access to these reverse prenylated indoles as precedence in these types of reactions rarely give alkylation between two substituents, but rather almost exclusively on the less hindered side.



Scheme 43: Fisher indole synthesis accessing **155**.

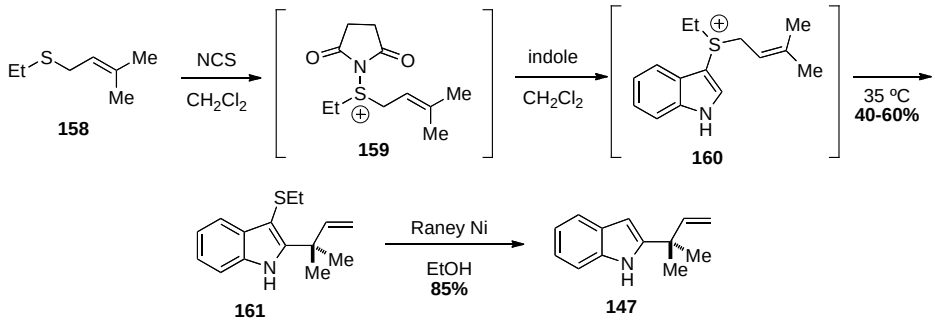
With the regio-selectivity issues with attempting to form the 4-bromo-2-reverse prenylated indoles it was concluded that forming the indole ring with this substitution pattern in mind are not viable routes to these systems; thus an established indole ring must be used with the desired substitution pattern. Installation of the reverse-prenyl group via hydroboration was the best option based upon the results of the Fisher indole synthesis attempts. The 4-bromoindole, which is commercially available although at $60/1g, was synthesized from 2-nitro-6-bromo-toluene via a Leimgruber-Batcho indole

synthesis. Formation of the 9BBN-alkyl species was accomplished as previously described. As seen with the 3-chloroindole, the 4-bromo-3-chloroindole also had variable yields under the hydroboration conditions to gain access to **155**, Scheme 44.



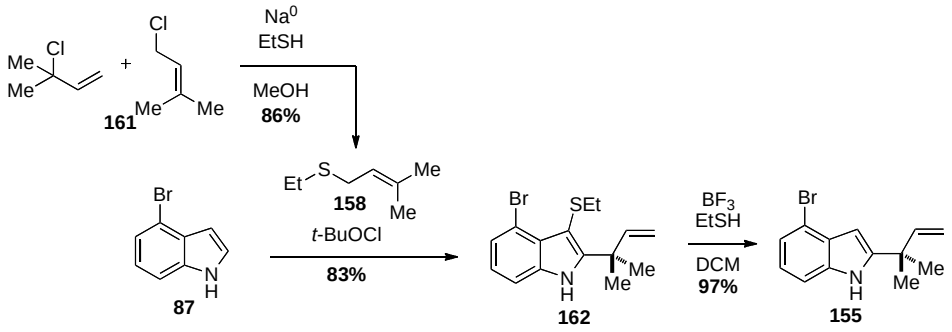
Scheme 44: Hydroboration accessing indole **155**.

Tomita and coworkers[23] showed that C2 reverse prenylated indoles could be accessed through a thio-Claisen reaction, (Scheme 45). Ethyl prenyl sulfide (**158**) was treated with NCS to form the reactive alkylprenylsulfonium ion (**159**), which upon treatment with indole undergoes a C3 nucleophilic attack upon the sulfonium to give the 3-(ethylprenylsulfonium) indole (**160**). Warming the reaction to 35 ℃ allows for a thio-Claisen reaction to occur to give C2 reverse prenyl indole ethyl sulfide (**161**). The ethyl sulfide was removed under reducing conditions with Raney Nickel or Zn/acetic acid to afford C2 reverse prenylated indole **147**.



Scheme 45: Tomita and coworkers thio-Claisen approach to **147**.

Freshly prepared sodium methoxide, prepared from sodium metal and methanol, was treated with ethane thiol and a mixture of prenyl chloride and reverse prenyl chloride (**161**) to give ethyl prenyl sulfide (**158**) in 86% yield, (Scheme 46).[24] Sulfide **158** was treated with NCS at -30 ℃ followed by slow addition of 4-bromoindole (**87**), the mixture was allowed to warm to room temperature and then heated to 35 ℃ over one hour. Upon workup and chromatography reverse prenylated ethyl sulfide **162** was isolated, however in only a 42% yield. Switching to *t*-BuOCl under the same conditions afforded indole **162** in an 83% yield. Reduction of the ethyl sulfide with Raney Nickel or Zn/acetic acid gave 11-19% of **155**, but mostly decomposition. To ethane thiol was added BF_3 etherate followed by indole **162** and left to stir for 20 h to afford indole **155** in a 97% yield.

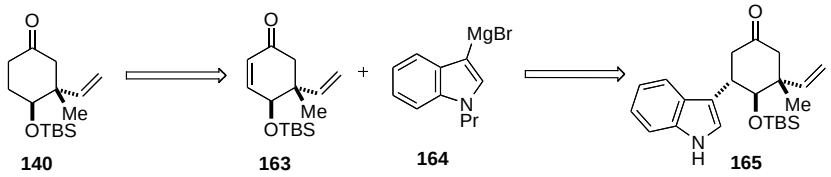


Scheme 46: Thio-Claissen approach accessing **162**.

3.4 Indole or Pre-indole Addition into Enone

Having accessed the D ring, installation of the indole ring either directly, or via a masked functional group for later elaboration into the indole, was the next obstacle. The envisioned route to introduce a functionalized indole (**164**), as outlined in Scheme 47, through a 1,4 Michael addition onto the enone (**163**) using the TBS protected alcohol for facial selectivity. Indole (**77**) could be converted to the 3-MgBr-indole (**164**) for direct addition or a compound that can be elaborated into indole later could be added via the

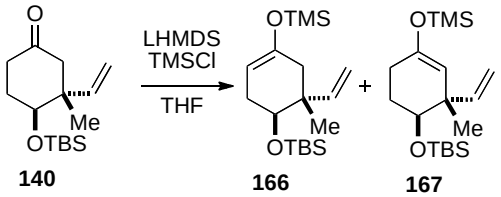
same 1,4 addition. Enone (**163**) could arise from oxidation of previously synthesized quaternary center (**140**).



Scheme 47: Indole incorporation via 1,4 Michael addition.

3.4.1 Enone Formation from Quaternary Center Ring D

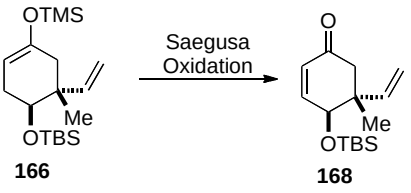
Transformation of ketones into enone has great precedence in the literature through a variety of different conditions. While a variety of conditions were employed in the installation of the desired enone; the best conditions were that of a Saegusa oxidation[25] as well as IBX oxidation conditions.[25b] Generation of the needed TMS-enol ether **166**, Scheme 48, is in direct competition with TMS-enol ether **167**, has neither is thermodynamically or kinetically favored. Treating **140** with TMSOTf under standard conditions gives a 1:1 ratio of **166**:**167**, has expected with the known mechanism of enolization with silyl triflates. Cooling **140** in THF to -15 ℃ followed by LHMDS, to which TMSCl was added 45 min later and workup gave a 2:1 **166**:**167** ratio. Screening a variety of temperature conditions, it was found that performing this reaction at -78 ℃ gave a 98% yield of the desired TMS-enol ether **166** exclusively.



Scheme 48: TMS-enol ether formation.

3.4.1.1 Saegusa Oxidation

Subjecting TMS-enol ether **166** to Saegusa Oxidation conditions did give access to enone **168**, but with limitations, (Scheme 49). Performing the oxidation under the original conditions of catalytic palladium (II) acetate did give access to the desired enone in modest to good yields, but did required the use of benzoquinone as a re-oxidant. Rather than benzoquinone, oxygen gas was also used in the oxidation and also afforded the desired enone **168**. The use of oxygen gas was favored for two primary reasons: it was more efficient based on atom economy as well as giving better yields. It is of note to mention, accessing enone **168** under Saegusa oxidation conditions is only viable on small scale (100 mg or less). It was observed that when attempted the oxidation on scales larger than 100 mg yields drops drastically. While the Saegusa oxidation does give access to enone **168**, it only does so on small scale, thus limiting its use for natural product synthesis this earlier in the route.



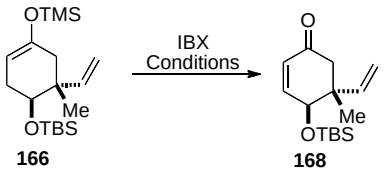
Conditions	Results
$Pd(OAc)_2$, *p*-BQ (10mg scale)	72%
$Pd(OAc)_2$, *p*-BQ (50mg scale)	68%
$Pd(OAc)_2$, *p*-BQ (100mg scale)	59%
$Pd(OAc)_2$, *p*-BQ (400mg scale)	42%
$Pd(OAc)_2$, O_2, DMSO (10mg)	85%
$Pd(OAc)_2$, O_2, DMSO (52mg)	**QUANT**
$Pd(OAc)_2$, O_2, DMSO (150mg)	65%

Scheme 49: Saegusa oxidation conditions for enone **168** formation.

3.4.1.2 IBX (2-Iodoxybenzoic acid) Oxidation

Noting the scale limitations of the Saegusa oxidation, attention was shifted towards enone formation through an IBX oxidation. It was found that using 3 equivalents of IBX gave the best yields in a variety of DCM:DMSO solvent mixtures, Scheme 50. Likewise, the optimal solvent mixture was found to be a DCM:DMSO ratio of 1:4 to give 86% yields in the oxidization. Unlike the Saegusa oxidation, the use of

IBX is optimal on large scale (1 g or larger), but it fails to give yields greater than 35% when performed on scales lower than 300 mg.

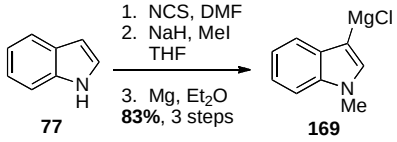


Conditions	Results
IBX (1 eq), DCM:DMSO (2:1)	12%
IBX (1.5 eq), DCM:DMSO (2:1)	15%
IBX (2 eq), DCM:DMSO (2:1)	19%
IBX (2.5 eq), DCM:DMSO (2:1)	23%
IBX (3 eq), DCM:DMSO (2:1)	30%
IBX (4 eq), DCM:DMSO (2:1)	31%
IBX (8 eq), DCM:DMSO (2:1)	29%
IBX (3 eq), DCM:DMSO (1:1)	42%
IBX (3 eq), DCM:DMSO (1:2)	49%
IBX (3 eq), DCM:DMSO (1:4)	**86%**
IBX (1 eq), DCM:DMSO (1:4)	33%
IBX (3 eq), DMSO	13%

Scheme 50: IBX oxidation conditions for enone **168** formation.

3.4.2 Michael Addition into Enone for Tricycle Access

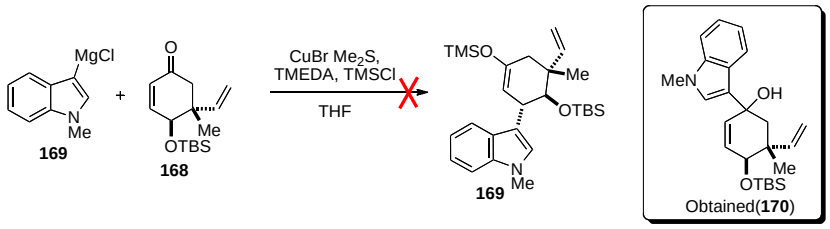
Indole (**77**) was chlorinated with NCS in DMF to give 3-chloro-indole, which was subsequently *N*-methylated with NaH and iodomethane. The chlorinated indole was azeotroped three-times from benzene to fully remove any traces of water. The azeotroped indole was then dissolved in ether to which magnesium metal with a trace of iodine was added to afford 3-MgBr-N-methylindole **169**, Scheme 51.



Scheme 51: Formation of 3-MgBr-*N*-methylindole **169**.

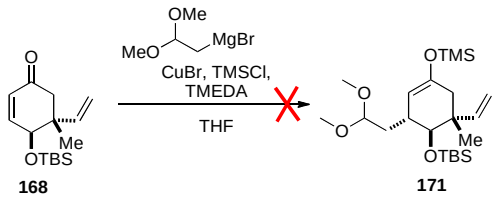
Grignard indole **169** and enone **168** was subjected to the same 1,4 additions conditions that were used to install the vinyl group of the quaternary center previously discussed, Scheme 52. These cuprate conditions previously allowed for the installation of vinyl Grignard thourgh an enone addition, but on enone **168** failed to give any addition via 1,4 but rather through a 1,2 pathway in 45% yields. Attempts were made at changing the 1,4 addition procedures, including temperature, addition order, reaction

times and a combination of each of these. Unfortunately, all attempts at adding the Grignard indole into enone **168** failed to give any of the desired 1,4 addition product.



Scheme 52: Attempted indole-Grignard addition into enone

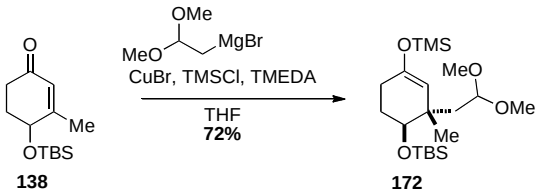
While it is unfortunate that the addition of indole into enone **168** failed, the result was not completely unexpected. Michael additions of indole into enones have always proven to be problematic in the literature, and with the complexity of enone **168** the expectations of indole addition was not that high. Since indole (**168**) could not be added directly, focus was shifted towards adding a compound that could later be transformed into an indole. For this, a smaller Grignard with a masked aldehyde as a dimethyl acetal was chosen for addition to the enone, Scheme 53. Using the standard cuprate conditions for 1,4 addition, the masked aldehyde failed to added. Screening multiple conditions, as done with for the indole system, still failed to give any of the desired, and undesired 1,2 addition products.



Scheme 53: Attempted masked aldehyde addition onto enone

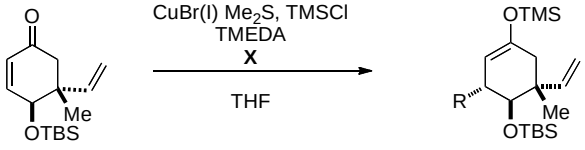
At this point, the question had to be asked if it is the cuprate alkyl species that is not adding to the enone, or is it the enone in **168** that is preventing addition. To test this, the masked aldehyde previously attempted on enone **168** was taken and subjected to

standard cuprate additions but to the enone previously used in the formation of the quaternary center compound **138**, Scheme 39. Surprisingly, the masked aldehyde added in a 1,4 fashion to enone **138** affording **172** in 72% yield, thus suggesting that it is not the cuprate alkyl species, directly, preventing addition on enone **168**.



Scheme 54: Investigation into alkyl cuprate addition issues upon enones.

Screening of different alkyl cuprate additions upon enone **168** was undertaken as outlined in Scheme 55. When subjecting enone **168** to the same conditions, vinyl Grignard as well, only 1,2 addition was observed. The same result was also observed when taking vinyl bromide performing a lithium-halogen exchange followed by CuBr Me_2S to form a lithium cuprate alkyl species. This result gives support that enone **168** is the cause for the failure of 1,4 addition. Screening other type of alkyl groups was also performed to determine if the anion strength of the alkyl system could be attributed to the lack of addition. Alkynyl, phenyl, and benzyl Grignards and halides were also screened for 1,4 addition with no success as well.

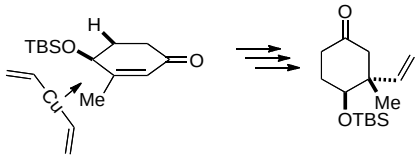


X	Conditions	Results
VinylMgBr	Standard	1,2
VinylBr	*t*BuLi then Std	1,2
HCCMgBr	Std	1,2
TMSCCH	*n*-BuLi, Std	X
PhenylMgBr	Std	X
PhenylBr	*t*BuLi, Std	X
BenzylMgBr	Std	8%
BenzylBr	*t*BuLi, Std	7%

Scheme 55: Screening of alkyl species for 1,4-addition.

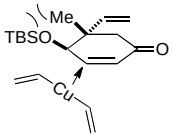
With the failed addition of vinyl Grignard under the same conditions that installed quaternary carbon center on the opposite side of the molecule, the mechanism

of cuprate addition was investigated. When setting the quaternary carbon center with vinyl cuprate, coordination of the copper species to the β carbon is required. The TBS protected alcohol gives facial selectivity, forcing the cuprate to the opposite site. As the cuprate coordinates the bulk forces the TBS protected alcohol to be push towards the sp^3-hybridized carbon, giving enough room for the coordination and vinyl addition, Scheme 56.



Scheme 56. Vinyl cuprate coordination for 1,4-addition.

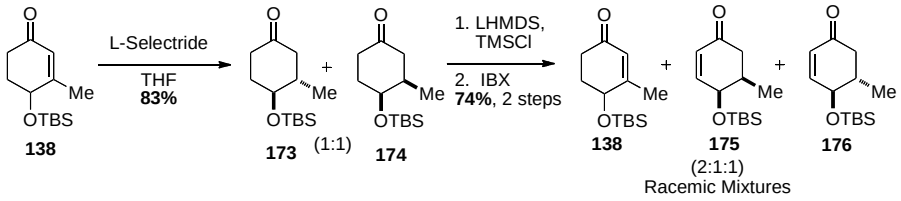
In the case of the enone with the quaternary center already installed coordination can still occur, has observed based upon color change in the solution. Coordination in this case, unfortunately, is not strong enough to the β carbon to allow addition of the vinyl species. This is thought to be due to the fact that the TBS protected alcohol has no room to be pushed slightly away due to the presence of the methyl group on the same face, Scheme 57. It is of note to mention, that the TBS group can switched for a smaller protecting group which does allow for cuprate addition, but does eliminate facial selectivity in the 1,4 addition.



Scheme 57: Steric factors preventing alkyl cuprate addition.

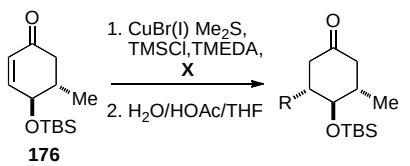
3.4.2.1 Investigation into the failed 1,4 addition upon enone 168.

To fully explore if the TBS protected alcohols inability to be pushed away from the β-carbon was the reason for alkyl addition failure another experiment was conducted. It was thought, to probe this problem the order of alkyl addition needed to be investigated, therefore the indole or indole synthon was to be added before the vinyl group. To this end, enone **138** was reduced with L-Selectride to the corresponding cis/trans (1:1 ratio) of **173** and **174**, Scheme 58. The reduced mixture was subjected to enone formation conditions, via a TMS-enol ether, previously described to afford a mixture of separable enones **138**, **175**, and **176** (2:1:1 ratio).



Scheme 58: Enone transposition via reduction and IBX-oxidation.

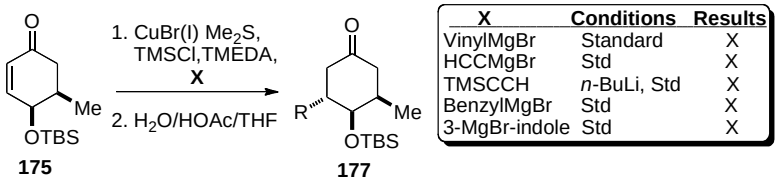
To explore the effects of the TBS protected alcohol on cuprate addition, *trans* enone **176** was subjected to a variety of alkyl cuprates, Scheme 59. Vinyl addition onto the β-carbon proceeded in a 78%, compared to the lack of addition on the quaternary carbon center enone. A variety of other types of alkyl compounds were added via cuprate addition, previously attempted with no success, on the trans enone. To our delight, 3-MgBr-N-Methylindole was added in a 43% yield onto **176**, thus giving further proof that the presence of the quaternary carbon center hinders 1,4-addition onto this TBS protected enone system.



X	Conditions	Results
VinylMgBr	Standard	78%
HCCMgBr	Std	82%
TMSCCH	*n*-BuLi, Std	85%
BenzylMgBr	Std	52%
3-MgBr-indole	Std	43%

Scheme 59: 1,4-Addition of various alkyl/arenyl cuprates onto *trans*-enone **176**.

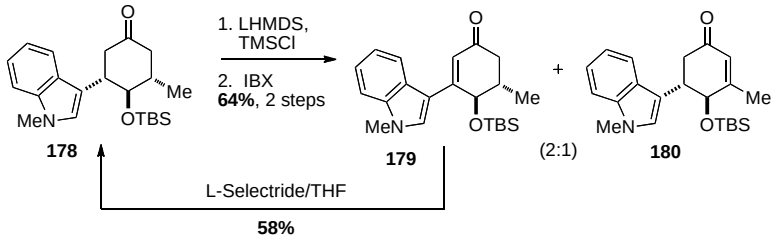
Trans-enone **176**, Scheme 59, does give evidence to the fact that the quaternary carbon center does effect the addition, but it does not address if it is the methyl and TBS group's syn relationship that causes the cuprate additions to fail. To explore this, the *cis*-enone **175** was subjected to the same alkyl/arenyl cuprate additions that were successful for the *trans*-enone **176**, Scheme 60. All cuprate additions upon **175** failed to give any 1,4 addition. Thus supporting the theory that it is the presence of the methyl group on the same face as the TBS protected alcohol that prevents addition due to steric congestion.



X	Conditions	Results
VinylMgBr	Standard	X
HCCMgBr	Std	X
TMSCCH	*n*-BuLi, Std	X
BenzylMgBr	Std	X
3-MgBr-indole	Std	X

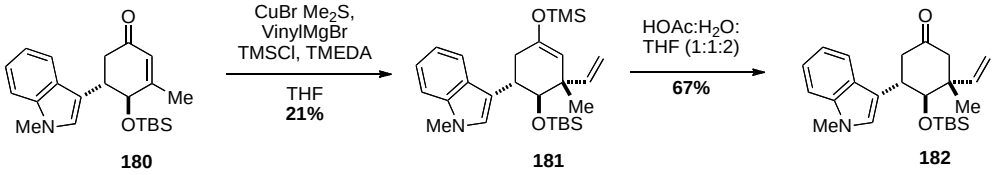
Scheme 60: 1,4-Addition of various alkyl/arenyl cuprates onto *cis*-enone **175**.

Having accessed the indole addition product **178**, attention was shifted towards setting the quaternary carbon center. To this end, tricycle **178** was subjected to TMS-enol ether formation conditions followed by IBX for enone installation to give both regio-isomers **179** and **180** in a 64% yield, Scheme 61. Separation of the isomers gave a 2:1 ratio of undesired **179** to desired **180**. The undesired enone **179** was recycled to the **178** via L-Selectride reduction in 58% yields.



Scheme 61: Enone formation upon tricycle **178**.

Having indole added onto the pre-D ring as well as having accessed the desired enone **180,** treatment under standard cuprate formation and addition conditions were performed. To our delighted, vinyl Grignard was successively added in a 21% yield to give the desired quaternary carbon center **181**, Scheme 62. Vinyl addition was expected to occur as based on the theory of the trans relationship of the indole and TBS protected alcohol. Previously, setting the quaternary center without any indole or pre-indole was accomplished in 97% yields, a 76% greater yield than the indole containing enone **180**. While eliminating the steric congestion as seen with the *cis* relationship of large bulky center allowed for access to the tricycle with quaternary center installed, the *trans* relationship did in fact create another steric congestion on the indole and cuprate, which unfortunately could not be remedied. TMS-enol ether was cleaved with an acetic acid:water:THF mixture to furnish **182** in 67% yields.

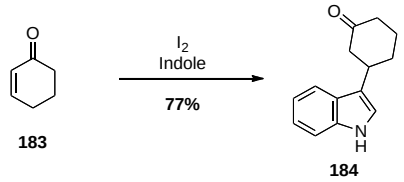


Scheme 62: Vinyl cuprate addition upon tricycle **180**.

3.4.2.2 I_2 Mediated Enone Addition

Gaining access to tricycle **182** does allow for elaboration into the tetracyclic system with isopropene addition, but it requires a 10 linear steps sequence that gives a 0.21% overall yield. No further attempts at optimizations of any of the steps resulted in an increase in overall yields, thus limiting this route for natural product synthesis. The limiting steps in the route involve the cuprate addition into an enone, whether pre or post indole incorporation due to steric congestion. Accessing the functionalized D ring is accomplished in 6 linear steps in an overall 84% yield, with subsequent enone formation

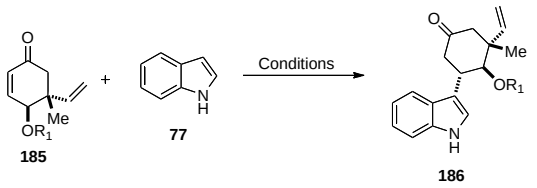
in 2 additional steps with an overall 71% yield from the commercially availably starting material. Focus was shifted towards different 1,4 addition pathways that could allow for direct indole addition that do not involve cuprates, as it was observed cuprates require sterically accessible systems to work in descent to good yields. Banik and co-workers[26] showed in 2005 that I_2 could be employed for indole addition via a 1,4 addition pathway onto enone **183** to afford **184** in 77% yields, Scheme 63. This chemistry was repeated on the same starting materials and similar yields, 78%, were obtained. It is of note to mention that when metal triflates were used the same product was observed, but in slightly lower yields (62-67%).



Scheme 63. I_2-Mediated indole addition onto enone **183**.

With the successful addition of indole onto cyclohexenone, addition of indole onto the enone of the D ring was then attempted, Scheme 64. When treating indole with the TBS protected alcohol of **185** with I_2 a 12% yield of desired **186** as well as the TBS de-protected protected in 8% yields. The de-protected product was successively re-protected as the TBS alcohol using NaH, TBSCl in THF over a 12 h in 82% yields. De-protection of TBS groups with I_2 is well known, but usually on scales of hours not min. It was thought, that coordination to the TBS ether could be hindering this reaction. To overcome this possible interaction, the reaction was attempted with the free allylic alcohol enone **185** and indole (**77**), but unfortunately gave no product and only recovered starting material over a 24 h period. When attempting the addition with a variety of metal triflates[27] on the TBS protected enone, only de-protection of the TBS

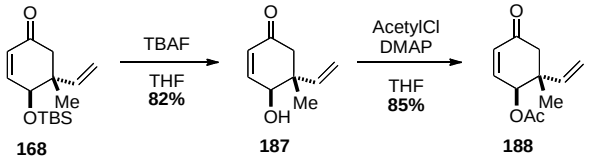
group was observed, no addition product. Likewise, when using the de-protected enone of **185** with the metal triflates only starting material was observed over a 24 h period.



R1	Conditions	Time	Results
TBS	I_2	30 min	Desired (12%) & Desired (-TBS, 8%)
H	I_2	0.5-24h	Starting Material
TBS	$Sc(OTf)_3$	4-6 h	TBS Deprotection
	$Yb(OTf)_3$		
	$Zn(OTf)_3$		
	$In(OTf)_3$		
	$Cu(OTf)_2$		
	$Bi(OTf)_3$		
H	$Sc(OTf)_3$	>24 h	Starting Material
	$Yb(OTf)_3$		
	$Zn(OTf)_3$		
	$In(OTf)_3$		
	$Cu(OTf)_2$		
	$Bi(OTf)_3$		

Scheme RR. I_2-Mediated coupling of indole into enone **185**.

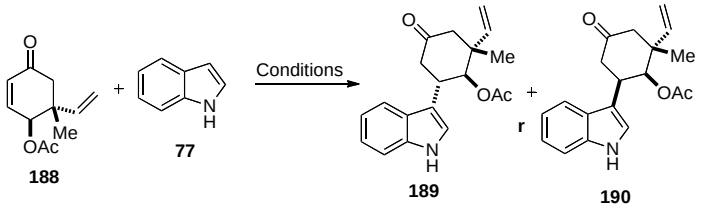
While the free alcohol prevented any 1,4 addition onto the enone, and the TBS protected enone failed to give any respectable yields a protecting group switch was performed. Silyl protecting groups were not considered due to the problems encountered with the TBS group. Alkyl groups, as seen during the attempts of setting the quaternary carbon center failed to give facial selectivity. With this, an acetyl group was chosen in the hopes that the planar nature of the ester along with free rotation could generate enough facial selectivity for the indole addition. Treating **168** with TBAF in THF afforded free alcohol **187**, which upon treatment with acetyl chloride and DMAP in THF gave the acetyl-protected enone **188** in a 70% yield over the 2-steps, Scheme 65.



Scheme 65: Protecting group swap-TBS to acetyl protecting group.

With acetyl protected enone **188** in hand, treatment of I_2 onto a pre-mixed enone indole solution was attempted, Scheme 66. As previously done with the TBS protected indole, the reaction was run for 30 min, but failed to give any desired product and only

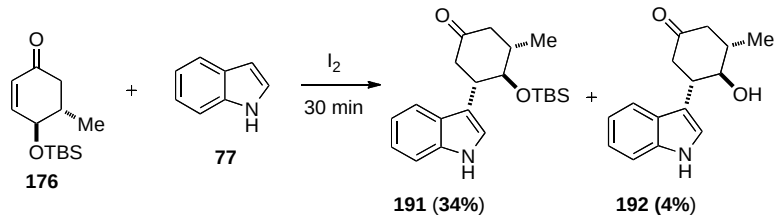
starting material was recovered. When the reaction was run for 2 h, it did proceed to product in a 22% yield, but unfortunately in a 2:3 desired to undesired facial selectivity. Running the reaction with metal triflates gave recovered starting material, except in the case of $Sc(OTf)_3$ which afforded products **189**:**190** in 2% yields in a 1:3 (desired:undesired) facial selectivity ratio.



Conditions	Time	Results % (189:190)
I_2	30 min	Starting Material
I_2	2 h	22% (1:1.5)
$Sc(OTf)_3$		2% (1:3)
$Yb(OTf)_3$		Starting Material
$Zn(OTf)_3$	4-6 h	Starting Material
$In(OTf)_3$		Starting Material
$Cu(OTf)_2$		Starting Material
$Bi(OTf)_3$		Starting Material

Scheme 66: I_2 Mediated addition of indole onto acetyl protected enone **188**.

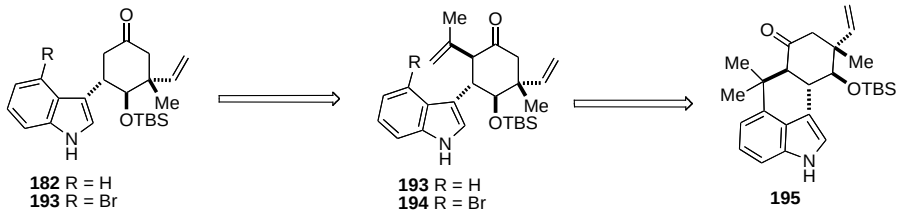
Recalling the issue of cuprate addition onto the same enone being of steric congestion, the same theory was explored for the I_2 mediated coupling. Treating the trans enone **176** (Scheme 58), previously employed and described above, with indole and I_2 over a 30 min period afforded 1,4 addition products **191**:**192** in 38% yields in a 9:1 (TBS protected:TBS de-protected) ratio, Scheme 67. When letting the reaction run longer than 30 min, the yield of reaction did not increase nor decrease, but the ratio of TBS protected to de-protected ratio shifted towards de-protection. The yields of the I_2 mediated addition are comparable to the cuprate addition conditions previously shown. When attempting the I_2 mediated addition on the cis enone, no indole addition was observed, as with the case when cuprates were employed. Given the fact that both the cuprate and I_2 mediated conditions both had similar yields on given substrates, it was determined that steric congestion would pose a problem for any type of 1,4 addition onto the D ring.



Scheme 67: I_2 Mediated indole addition onto *trans*-enone **176.**

3.4.3 Isopropene Incorporation

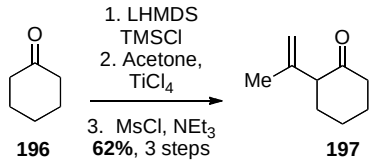
Accessing tricycle **182**, while low yielding, did allow for further elaboration into the core of both the tetracyclic hapalindoles and ambiguine family of alkaloids. In addition to having accessed tricycle **182**, accessing the 4-bromoindole analog (**192**) was also achieved via the same chemistry previously described, but with 4-bromoindole. It was envisioned that tricycle **182** or **193** could be functionalized to allow for isopropene addition, with stereochemistry governed by the indole ring, Scheme 68. Via either an acid-catalyzed ring closing event via **193** or through a Heck reaction upon **194** tetracycle **195** could be accessed for both families of alkaloids.



Scheme 68: Retro-synthetic route to tetracycle core.

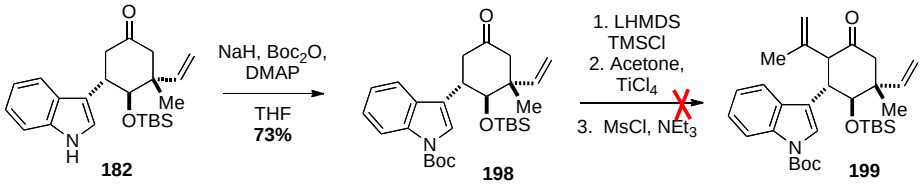
Installation of the required isopropene group was first done on a model system to ensure such addition could take place. Cyclohexanone (**196**) was treated with LHMDS and TMSCl to afford the corresponding TMS-enol ether, which was subjected to Mukaiyama Aldol reaction conditions[28] with acetone to afford the β-hydroxyketone. Mesylation of the alcohol with MsCl and NEt_3 at -44 ℃ gave the eliminated product (**197**) in 62% yields over three steps, Scheme 69. It is of note to mention that if the

mesylated product was allowed to warm to room temperature before quenching the reaction, the enone product was formed almost exclusively.



Scheme 69: Isopropene addition upon cyclohexeneone (**196**).

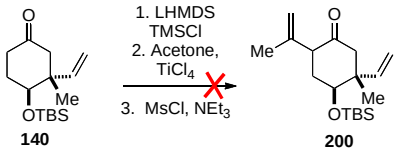
Having successfully added an isopropene group to cyclohexanone, tricycle **182** was treated with NaH, Boc_2O and DMAP in THF to give the Boc protected indole in 73% yields. Treating **198** under the same condition used for isopropene addition upon cyclohexanone failed to give any of the desired product **199**. Formation of the TMS-enol ether was observed, as seen by ^{1}H-NMR and TLC. All attempts at modifying the Mukaiyama Aldol reaction failed to give any of the desired β-hydroxyketone. Addition of catalytic as well as stoichiometric amounts of CsF also failed to give any of the desired β-hydroxyketone.



Scheme 70: Attempted isopropene incorporation upon tricycle **182**.

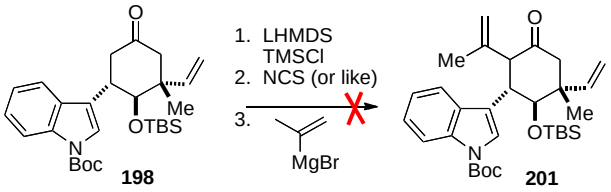
With the failed isopropene addition onto tricycle **198**, it was thought that perhaps sterics once again was the factor in the failed addition. To examine this, the quaternary carbon center **140** was treated with LHMDS and TMSCl to give the corresponding TMS-enol ether in quantitative yields, Scheme 71. Subjecting the TMS-enol ether to Mukaiyama Aldol conditions, previously used for the installation of the isopropene

group, also failed to give any of the addition product. All modifications to the conditions failed to give any of the desired β-hydroxyketone.



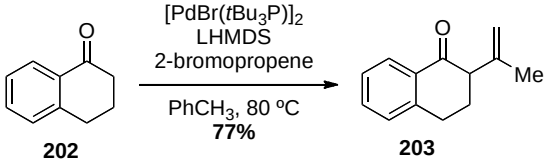
Scheme 71: Attempted isopropene addition upon **140**.

With the failure of the Mukaiyama Aldol reaction for isopropene installation, but validation of the TMS-enol ether formation an S_N2 route was envisioned, Scheme 72. From the TMS-enol ether, halogenation of the α-carbon was thought to possible followed by direct displacement with isopropene Grignard. Unfortunately, the three step procedure failed to give any of the desired isopropene product **201**. The TMS-enol ether was validated by ^{1}H-NMR, but halogenation was never observed using a variety of halogenation reagents (NCS, NBS, NIS and Br_2).



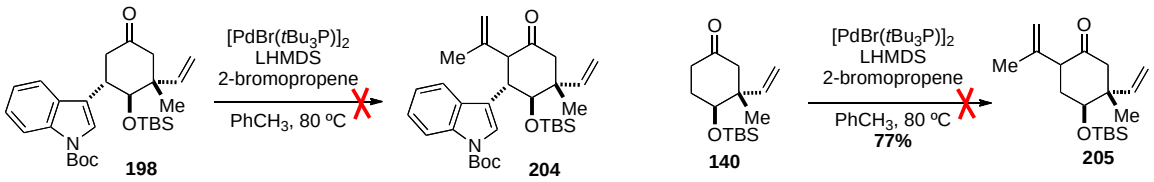
Scheme 72: Attempted S_N2 addition of isopropene upon tricycle **198**.

Huang[29] showed in 2007 the direct incorporation of an isopropene group upon a cyclic ketone species via a S_N2 displacement by a palladium enolate species (Scheme 73). Treating the cyclic ketone (**202**) with LHDMS in toluene followed by addition of the palladium catalyst with subsequent addition of 2-bromopropene at reflux afforded the desired isopropene incorporated species.



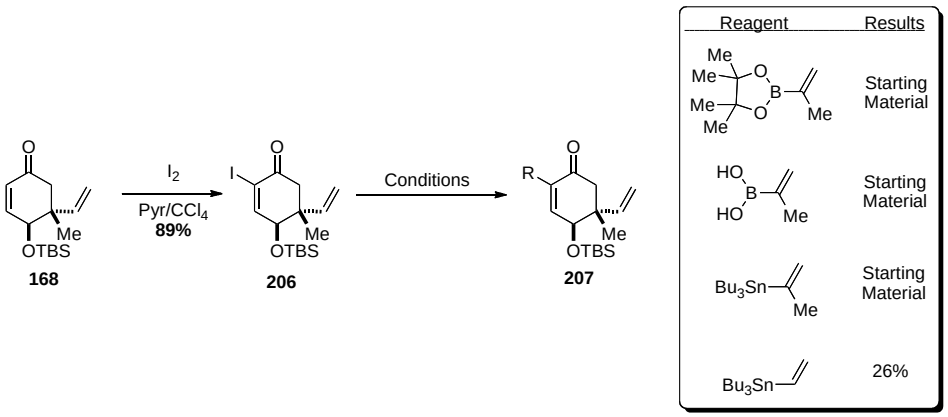
Scheme 73: Palladium mediated isopropene addition.

With the successful isopropene addition upon both the literature starting material as well as cyclohexanone, the methodology was then applied substrates for both the tetracyclic hapalindoles and ambiguines, Scheme 74. Unfortunately, isopropene addition was not observed on tricycle **198** or **140** using the same conditions as outlined in Scheme 73. Employing different palladium catalysts, different phosphine ligands and solvents failed to give any of the desired products and just returned starting material under all conditions. There is much precedence in the literature for palladium mediated reactions for alkyl additions, both with and without silyl protected alcohols. Given that the TBS protected alcohol gave problems earlier with the 1,4 addition, it was thought that perhaps this group is effecting isopropene addition. To explore this, 3-methylcyclohexenone was subjected to vinyl cuprate additions and TMS-enol ether cleavage conditions to give **140** without the TBS protected alcohol. Subjecting this to the literature conditions as outlined in Scheme 73, did afford isopropene addition in 34% yields. Thus, validating that the TBS protected alcohol once again is restricting addition upon the functionalized D-ring. Palladium-enolate addition reactions, while having precedence, are problematic reactions. To this end, efforts were focused on more traditional palladium mediated reactions.



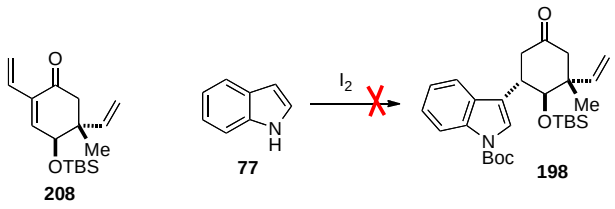
Scheme 74: Attempted palladium-mediated isopropene additions upon **198** and **140**.

In light of the failed attempts at incorporation of an isopropene group and that said attempts were performed on a sp^3 hydridized carbon, it was thought that more traditional sp^2 hydridized metal-mediated coupling should be explored. Enone **168**, described previously, was treated with diatomic iodide in a 1:1 pyridine/CCl_4 to give iodinated enone **206** via a modified Baylis-Hillman reaction (Scheme 75). Subjecting enone **206** to Suzuki coupling conditions with both the boric ester and boric acid isopropene failed to give any of the desired isopropene incorporation and only returned starting material. To our disappointment, screening different solvents, palladium sources and types resulted in the return of starting material. Attempts at employing Stille coupling conditions with the freshly prepared isopropenetributyltin also failed to give any desired product and returned starting material only. All optimiziation attempts failed to give any change. When attempting a Stille coupling upon **206** with vinyltributyltin incorporation of the vinyl group was obtained in 26% yield, and when a Suzuki coupling was attempted with the vinyl boric ester incorporation was observed with a 16% yield. Further investigation into Suzuki or Stille couplings upon **206** showed that one or two carbon tin or boron reagents (sp^3, sp^2 and sp) can successfully be added, but when three or more carbon, independent of hydridization, are employed no incorporation is observed. Interestingly, when the same enone as **206** with the TBS ether replaced with a H all Suzuki and Stille couplings attempted in Scheme 75 afforded the anticipated products. Thus showing once again the direct effects of the TBS ether upon reactivity towards alkylation onto the cyclohexyl system in this case.



Scheme 75: Baylis-Hillman and subsequent attempted Stille and Suzuki couplings.

While isopropene addition to iodinated enone **206** failed to give any product, vinyl incorporation was achieved and also was optimized to allow for 700-900 mg scale reactions to be performed. With **208** in hand it was decided to attempt indole addition via I_2-mediated reaction, shown previously, to access a modified version of desired tricycle **198**, which was thought could be elaborated into the desired tricycle. When subjecting **208** to indole (**77**) and I_2 no addition product was observed, but only starting material (Scheme 76).



Scheme 76: Attempted I_2 mediated indole addition onto functionalized enone **208**.

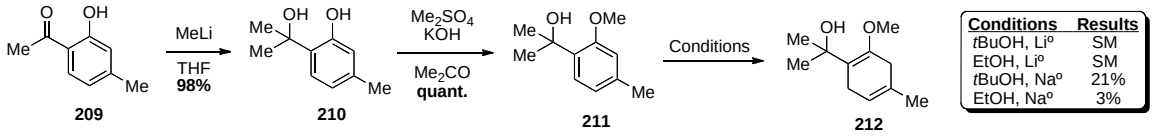
3.5 Early Stage Installation of Isopropene Group

Given the failures described above in attempting the late stage incorporation of the desired isopropene group, thought was given to the stage at which the isopropene group should be installed. From the results observed, the only chance of installing the

isopropene group was determined to be early in the synthesis. Recalling, that once the TBS ether is installed all attempts at isopropene addition failed thus suggesting that the installation must be prior to the TBS ether formation. All attempts at installing the isopropene group upon the allylic alcohol species resulted in re-aromatization of the ring. With this, it was determined that any early attempts at introducing the isopropene group would need to be performed either prior or immediately after the Birch reduction.

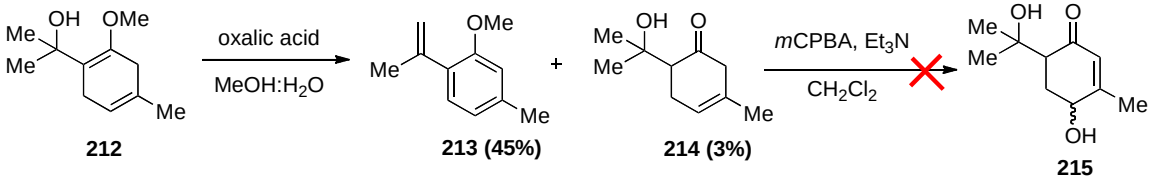
3.5.1 Employing 2'-hydroxyl-4'-methylacetophenone

Rather than starting with *m*-methylanisole, as outlined in Scheme 36, 2'-hydroxy-4'-methylacetophenone (**209**) was used due to the presence of the methyl ketone that could be elaborated into the desired isopropene, which was previously unattainable. Treating **209** with methyllithium in THF afforded tertiary alcohol **210** in 98% yields, Scheme 77. Selective methylation of the phenol was accomplished with dimethyl sulfate and potassium hydroxide in acetone in quantitative yields furnishing **211**. Unfortunately, subjecting **211** to Birch conditions previously employed in Scheme 36 failed to afford any of the desired reduced product **212** utilizing both *t*BuOH and EtOH as the proton sources. When using sodium metal rather than lithium metal the desired reduced compound **212** was obtained in 21% yields with *t*BuOH as the proton source and in 3% yields with EtOH as the proton source. In both proton sources that major product was of the strene derivative of **211**.



Scheme 77: Initial trials at early stage isopropene incorporation.

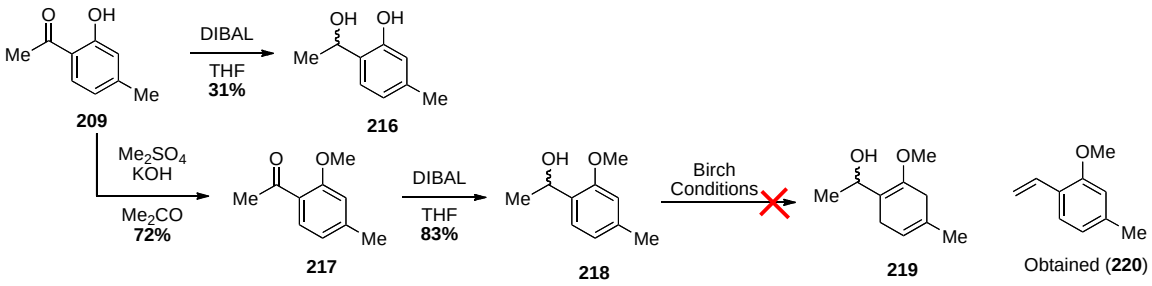
With **212** in hand, cleavage of the methyl ether as shown in Scheme 78, was performed utilizing the same conditions employed in Scheme 36. To our surprise, only 3% of desired **214** was obtained with most of the material recovered being that of a styrene analog **213** in 45% yields. Upon analysis, treating **212** with any acid source should promote conversion to **213** to due protonation of the tertiary alcohol followed by elimination and then re-aromatization. Unfortunately, all attempts at de-methylating **212** under various conditions failed to give any of the desired compound **214**. All attempts at optimization towards the access of **214** via acid-catalysis failed to enhance the yields. Attempted *m*CPBA oxidation and subsequent enone formation under previously employed conditions failed to give any of desired **215**.



Scheme 78: Attempted access to isopropene surrogate prior to TBS protection.

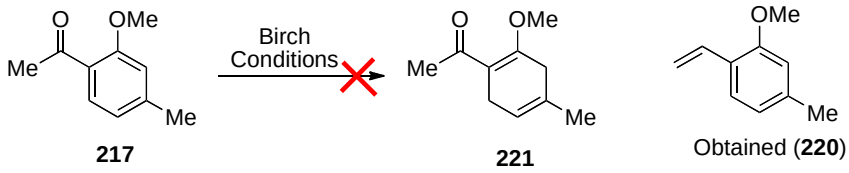
Given the low yields in the both the Birch reduction and oxalic acid steps in Scheme 77 and 78, mostly thought due to the presence of the tertiary alcohol, it was decided to attempt the same methods as in Scheme 77 and 78, but with a secondary alcohol instead. It was thought that the secondary alcohol would be less prone to elimination as the tertiary alcohol proved to be. Reduction of the ketone in **209** was accomplished with DIBAL in THF to afford **216** in 31% yields, Scheme 79. Methylation of the phenol to afford **218** was unattainable. To this end, methylation of **209** with dimethyl sulfuate in acetone afforded **217** in 72% yields, which was then reduced with DIBAL to afford **218** in 83% yields. Subjecting **218** to Birch conditions

failed to afford desired **219**, but only furnished styrene "like" **220**. Subjecting **216** to Birch conditions were attempted as well, but only furnished the free phenol analog of **220**.



Scheme 79: Attempts at isopropene surrogate via a secondary benzylic alcohol.

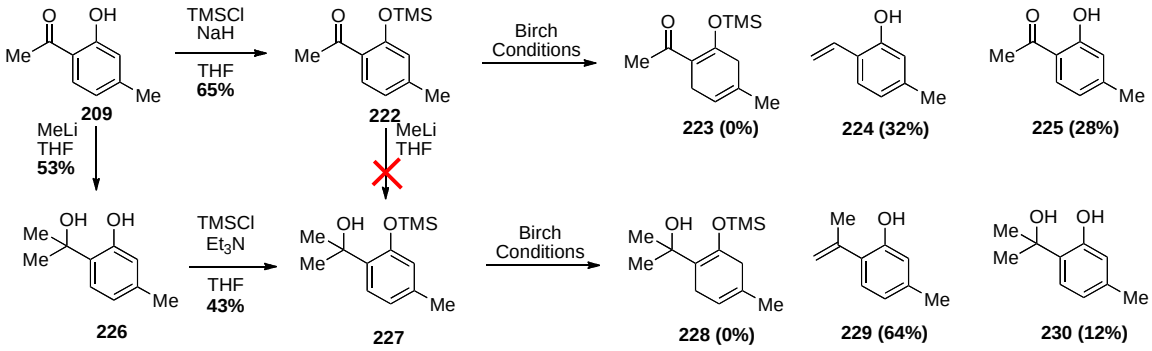
Given the issues arising from employing any type of benzylic alcohols, it was then decide to subject **217** to Birch conditions in the hopes that the ketone would prevent the undesired vinyl group formation. Subjecting **217** to Birch conditions failed to afford desired **221**, but rather furnished **220**, Scheme 80.



Scheme 80: Attempts at isopropene surrogate formation via benzylic ketone **217**.

Birch reduction with the tertiary alcohol in place for later isopropene elaboration was achieved, albeit in low yields of 21%, as outlined in Scheme 77, from **211** to **212**. Given the cost of the starting materials and reagents, the low yield was not a limiting factor. The cleavage of the methyl ether, as outlined in Scheme 78, is the major concern. It was thought that if, rather than a methyl protected phenol, a silyl protecting group was employed, accessing desired **215** (Scheme 78) could be accomplished. It is of note to mention, that all attempted Birch reductions on free phenols failed to give any desired

products and mostly recovered starting material. TMS-Protection of **209** was accomplished with TMSCl and NaH in THF to afford **222** in 65% yields, Scheme 81. Subjecting **222** to Birch reduction conditions failed to afford any of desired **223**, but did afford eliminated **224** in 32% yields and de-protected phenol **225** in 28% yields. Methylation of **222** with MeLi in THF failed to afford desired **227**, but did afford **209** in 82%. Given the sensitivity of TMS groups to strong bases, **209** was methylated first with MeLi in THF to afford **226** in 53% yields followed by TMS protection of the phenol with TMSCl and Et_3N in THF to furnish **227** in 43% yields. Subjecting **227** to Birch conditions failed to afford any of desired **228**, but did afford undesired olefin **229** in 64% yields and de-protected phenol **230** in 12% yields. Swapping TMS for a TBS TIPS or TES group with the chemistry delineated in Scheme 81 failed to afford any of desired **228**.

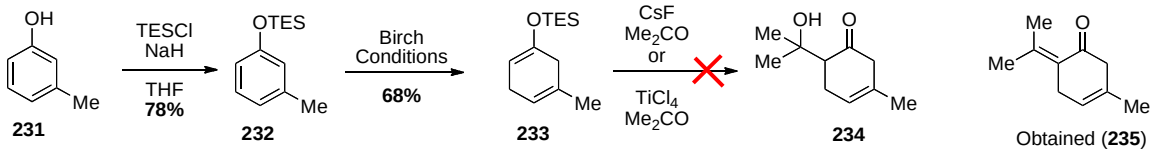


Scheme 81: Attempted Birch reductions with TMS-protected **209** and **224**.

3.5.2 Employing *m*-Cresol

Given the inability to successfully subject any isopropene group or surrogate upon an arene system to Birch or oxalic acid conditions, it was thought to utilized a silyl protected intermediate to invoke a 1,2 addition upon acetone to give rise to the desired material. Treating *m*-cresol to TESCl and NaH in THF furnished **232** in 78% yields,

Scheme 82, to which was subjected to Birch conditions afforded **233** in 68% yields. Unfortunately, subjecting **233** to cesium fluoride, to remove the TES group, followed by addition with acetone failed to give anticipated **234** but rather afforded enone **235** in 72% yields. Similar results were obtained when attempting to subject **233** to Mukaiyama aldol conditions with $TiCl_4$ in DCM with acetone.



Scheme 82: Silyl enol ether approach at accessing **234.**

3.6 Current Strategy for Accessing the Tetracyclic Hapalindole and Ambiguines

Given the inability to directly add an isopropene group upon **140**, **182**, **186**, **191**, **192**, and **198** or upon arene's **210**, **218**, **217**, **218**, **222**, **227** and **233** attention was directed towards the addition of a group later in the synthesis that could be elaborated into either an isopropene group or another functionalized useful species.

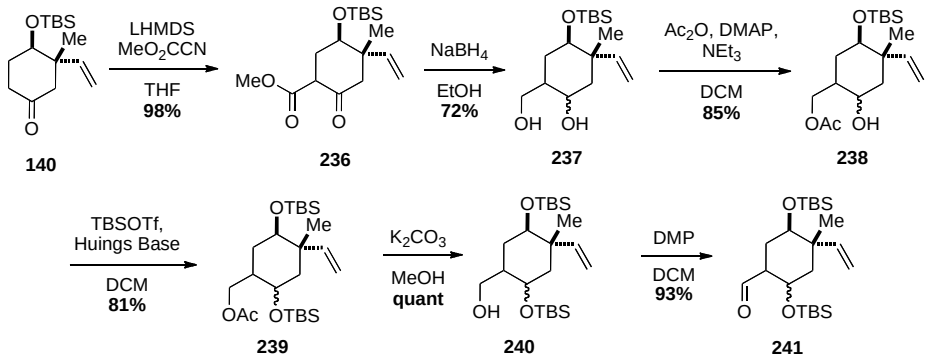
3.6.1 Aldehyde Addition upon 140

Attempts were made at the addition of ethanal to **140** in the hopes of obtaining a β-hydroxy-ketone that could be elaborated into an isopropene group or another functionalized system. All attempts upon adding aldehydes upon **140** resulted in olefin formation in low to poor yields.

3.6.2 Oxidation/Reduction Strategy for Tricycle Access

Given the inability to directly add an aldehyde onto **140** in anything but poor yields, it was decided to attempt an ester incorporation that could be reduced to the desired exocyclic aldehyde. Compound **140** was treated with LHMDS in THF followed

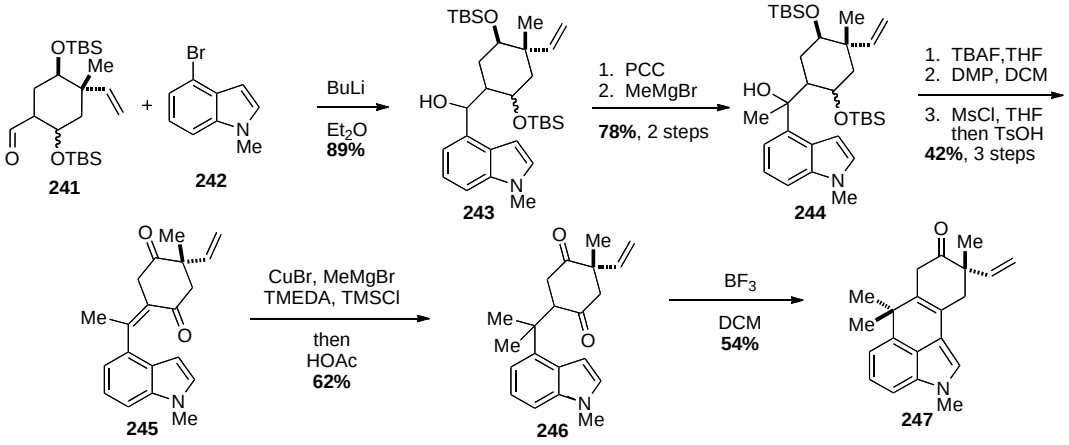
by addition of Mander's reagent to afford ester **236** in 98% yield (Scheme 83). Unfortunately, all attempts at exclusive reduction of the ester failed in favor of ketone reduction. Due to the inability to selectivity reduce the ester a multiple step conversion was undertaken to gain access to the desired exocyclic aldehyde. Ester **236** was dissolved in EtOH and subjected to reduction with $NaBH_4$ over 12 h to afford diol **237** in 72% yield. Selective oxidative of the primary alcohol was attempted, but was never successful beyond a 5% yield. To this end, the primary alcohol was acetylated to give **238**, which was subjected to TBSOTf for protection of the secondary alcohol as the TBS ether to afford **239**. The acetyl group was removed with K_2CO_3 in MeOH to give primary alcohol **240** in quantitative yields, which was subsequently oxidized with DMP in CH_2Cl_2 to give the desired aldehyde **241** in 93% yield (45% yield from quaternary center compound **140** over six steps).



Scheme 83: Oxidation/Reduction strategy accessing **241**.

N-Methylindole **242** was treated with *t*BuLi in Et_2O to which aldehyde **241** was added to afford tricycle **243** in good yields, Scheme 84. Oxidation of the secondary alcohol was accomplished with PCC, and was subsequently treated with MeMgBr to afford the tertiary alcohol **244**. Global deprotection of the TBS ethers was accomplished with TBAF in THF, followed by oxidation to the diketone species with DMP in DCM.

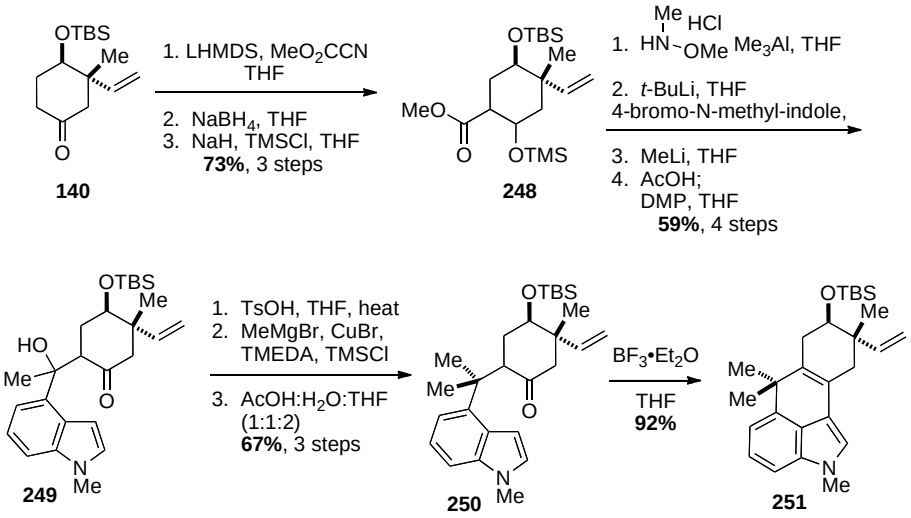
Mesylation of the tertiary alcohol within the di-ketone compound with subsequent TsOH treatment gave rise to enone **245** in modest yields over three steps. Formation of the gem-dimethyl compound **246** was accomplished by employing standard cuprate conditions with methyl Grigand followed by cleavage of the TMS-enol ether with acetic acid:H_2O:THF. Treating **246** with BF_3•etherate in DCM gave the corresponding dehydrated tetrayclic compound **247** (10% yield from **241** and **242** over nine synthetic steps, or 4% yield from **140** over 15 synthetic steps).[30] Given the overall poor yield in accessing tetracycle **247** as well as the number of synthetic steps, efforts were directed towards optimizing and shortening the step count towards accessing **247**.



Scheme 84: Access of tetracyclic core **247**.

Assembly of tetracycle **251** began with treating racemic **140** with LHMDS and Mander's reagent to give the β-ketoester (Scheme 86). Reduction of the ketone with $NaBH_4$ followed by TMS protection of the resulting alcohol gave **248** in good yields. Treatment of **248** with N-methoxy-methylamine hydrochloride and Me_3Al in THF afforded the Weinreb amide. Subjecting 4-bromo-*N*-methylindole to lithium-halogen exchange conditions resulted in the corresponding 4-lithium species that was added to the Weinreb amide and worked up under acid conditions and carried on without further

purification. Methyl lithium was added to the crude material at -78 ℃ in THF, warmed to room temperature, and worked up under acidic conditions to afford a 2.5:1 mixture of the secondary alcohol and its corresponding TMS ether. The crude mixture was treated with acetic acid for 45 min, concentrated, and taken into THF and oxidized with Dess-Martin Periodinane to afford **249** in good yields. Dehydration of **249** with TsOH gave the β-methyl,β-indole-exocyclic enone that was subjected to methyl cuprate Michael conditions to afford tricycle **250**. Subjecting **250** to BF_3-etherate afforded tetracycle **251** in an overall yield of 27% from **140** over 11 synthetic steps.[30]



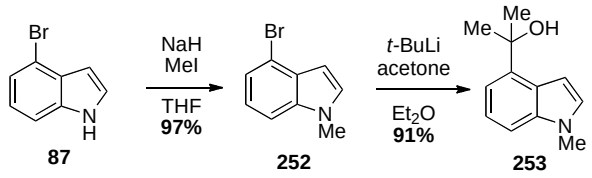
Scheme 86: Optimization accessing tetracyclic core **251**.

3.6.3 Lewis-Acid Mediated Coupling for Tricycle Access

Accessing tetracycles **247** and **251** were of great importance, as prior to this oxidation/reduction strategy no routes allowed access to such tetracycles. Natsume and co-workers accessed similar tetracycles in their total syntheses of hapalindole J, M, H and U as delineated in Schemes 8 through 13. Given the step count to access **247** and

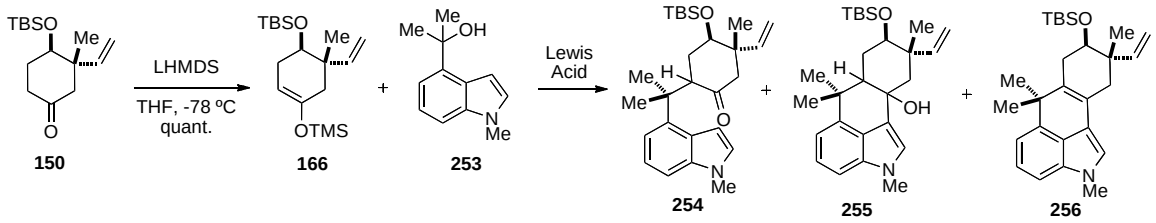
251, it was decided to employ Natsume's Lewis-acid strategy at accessing the same type of tetracycles.

Accessing the required 4-(2-hydroxyl-2-propyl)-N-methyl-indole (**253**) for the tin-mediated coupling was accomplished from 2-bromo-6-nitrotoluene under Leimgruber-Batcho[31] conditions to afford **87** in high yields, (Scheme 87). *N*-Methylation of **87** was performed with NaH and methyl iodide in THF to afford **252**. Treatment of **252** under lithium-halogen exchange conditions followed by acetone addition furnished **253** in 91% yield.



Scheme 87: Synthesis of indole **253.**

Treatment of **140** with LHMDS followed by TMSCl gave the required TMS-enol ether **166**. A variety of conditions were probed to optimize the coupling of **166** to **253** (Scheme 88 and Table 1). In the event, it was observed that treating indole **253** and TMS-enol ether **266** with fuming tin (IV) chloride in DCM gave the tetracyclic species **255** in good yields. While we were anticipating the tricycle **256**, synthesis of **255** gives the carbon core along with the desired tertiary alcohol at the C10, which is present in several the tetracyclic hapalindoles and ambiguines.[30]

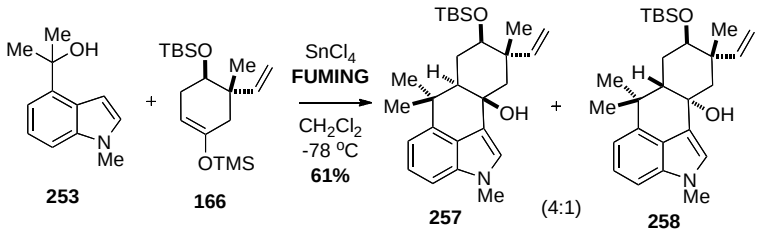


Scheme 88: Lewis acid coupling of **166** and **253.**

Table 1: Lewis-acid and conditions screened for scheme 88.

Lewis Acid	Conditions	Product		
		254	**255**	**256**
$TiCl_4$ (fuming)	$PhCH_3$, -78 ℃	7%	X	X
$TiCl_4$ (fuming)	$PhCH_3$, -44 ℃	X	X	5%
$TiCl_4$ (1 M $PhCH_3$)	$PhCH_3$, -78 ℃	X	X	X
$TiCl_4$ (1 M $PhCH_3$)	$PhCH_3$, -44 ℃	X	X	X
$TiCl_4$ (1 M CH_2Cl_2)	CH_2Cl_2, -78 ℃	13%	X	X
$TiCl_4$ (1 M CH_2Cl_2)	CH_2Cl_2, -44 ℃	X	X	X
$TiCl_4$ (fuming)	CH_2Cl_2, -78 ℃	X	X	36%
$TiCl_4$ (fuming)	CH_2Cl_2, -44 ℃	X	X	13%
$SnCl_4$ (1 M $PhCH_3$)	$PhCH_3$, -78 ℃	15%	24%	X
$SnCl_4$ (1 M $PhCH_3$)	$PhCH_3$, -44 ℃	X	X	X
$SnCl_4$ (1 M CH_2Cl_2)	CH_2Cl_2, -78 ℃	83%	X	X
$SnCl_4$ (1 M CH_2Cl_2)	CH_2Cl_2, -44 ℃	54%	X	X
$SnCl_4$ (fuming)	CH_2Cl_2, -78 ℃	5%	61%	X
$SnCl_4$ (fuming)	CH_2Cl_2, -44 ℃	13%	8%	42%

Further studies into the coupling of **166** and **253** with fuming tin (IV) chloride revealed that the reaction afforded diastereomeric tetracycles **257** and **258** (4:1 ratio) (Scheme 89), but not the dehydrated tetracycle as seen in Scheme 88. Quenching the fuming tin (IV) chloride reaction at -78 ℃ proved to be essential in forming the tertiary alcohol. When quenching the reaction at any temperate above -50 ℃ formation of the dehydrated tetracycle **256** was observed. When **166** and **253** were treated with the 1M tin (IV) chloride solution a similar tricyle as seen in Scheme 88 was formed. Subjecting this tricycle to BF_3-etherate afforded the dehydrated tetracycle **256**. When performing the same procedure with *N*-Boc protecting group only the dehydrated tetracycle was observed. Interestingly, when attempting the reaction on a substrate bearing the *N*-tosyl group under the same conditions, only the tricycle was obtained. Other alkyl protecting groups such as PMB or benzyl groups can be used with the current methodology, however the yields from the coupling reactions are significantly lower, 19% and 24% respectively.

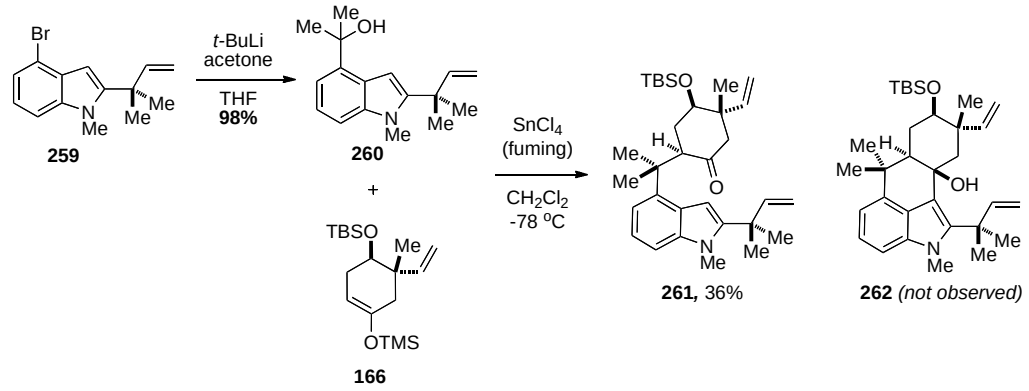


Scheme 89: Fuming $SnCl_4$-mediated tetracycle formation.

Unfortunately none of the hapalindoles, tri- or tetra-, nor the ambiguines contain a *N*-methylated indole, thus while the fuming tin (IV) chloride reaction gives access to a highly functionalized ring system the presence of the *N*-methylated indole requires further functionalization. There is precedence in the literature for the removal of methyl groups upon amines,[32] but not aromatic amines such as indoles, via the von-Brown reaction. Reduction of indoles to indolines is well documented in the literature, which also has been shown to be demethylated under von-Brown conditions.[33] Reduction of **257** and **258** to their corresponding indoline was unsuccessful under a variety of conditions. Therefore, the next course of action is to place a protecting group upon the indole nitrogen that is cleavable.

While the *N*-methylated indole accessed in scheme 89 could not be deprotected, attempts at accessing the reverse-prenylated counterpart was attempted under the conditions delineated above. C2-Reverse-prenylated-4-bromoindole **259** was successfully transformed into the tertiary alcohol **260** via lithium-halogen exchange conditions, previously described, scheme 90. The coupling of **260** and **166** with fuming tin (IV) chloride was attempted as described previously in Table 1. Unfortunately, no tetracyclic product was observed when subjecting **260** and **166** to any of the previous coupling conditions. Furthermore, only fuming tin (IV) chloride allowed access to the tricycle **261** in 36% yield (Scheme 90). Treating tricycle **261** with BF_3-

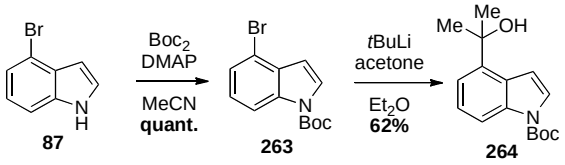
etherate at room temperature for 24 hours failed to give the desired tetracycle **262**, but rather the dehydrated tetracyclic system. Similar results were obtained when attempting the same methodology on methyl, ethyl, vinyl, and propyl C-2 substituted indoles.



Scheme 90: Attempts at gaining access to reverse prenylated tetracycle.

Boc Protected Indole

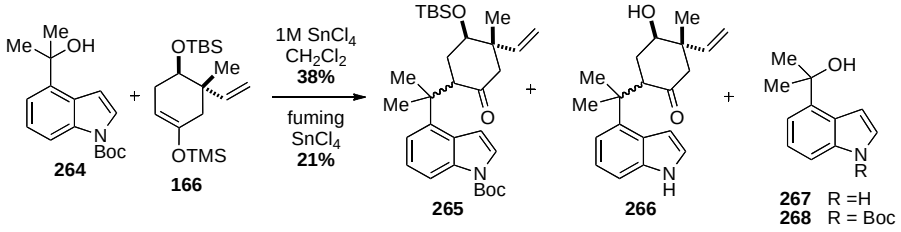
With the inability to deprotect the methyl group upon the indole in scheme 89, efforts were directed towards installing a group that can be cleaved easily. Given the precedence in the literature for indole protecting groups a *t*-butyl carbamate group (Boc) was chosen. 4-Bromoindole **87** was subjected to Boc protection conditions with Boc anhydride and DMAP in MeCN to give access to **263** in quantitative yields. Subjecting **263** to lithium-halogen exchange conditions delineated above afforded **264** in 62% yields, scheme 91.



Scheme 91: Synthesis of 4-(2-hydroxy-2-propyl)-*N*-Boc-indole (**264**).

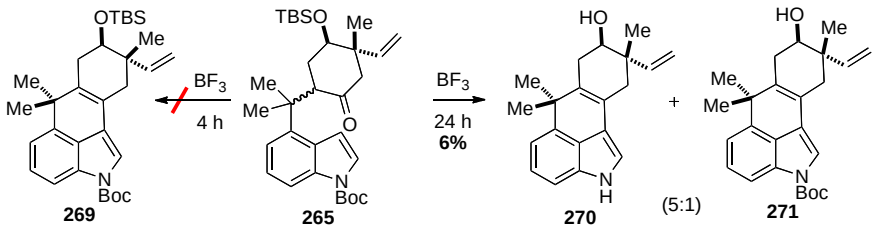
With **264** in hand, coupling to **166** was undertaken with the previously employed conditions, scheme 92. Initially, a 1 M tin (IV) chloride in DCM was used for the

coupling, due to the sensitive of Boc groups towards Lewis acids. Subjecting **264** and **166** to the dilute Lewis acid conditions failed to give any of the desired functionalized tetracyclic core, but did give rise to tricycles **265** and **266** as well as indoles **267** and **268** in a 2:3:6:3 ratio. With the lack of any of the functionalized tetracyclic core being observed with the diluted tin (IV) chloride, the reaction was attempted again utilizing fuming tin (IV) chloride, but unfortunately no tetracycle was observed and a decreased yield was obtained with the same product distribution. Compound **266** could be converted into **265** with TBSCl and DMAP in DMF for TBS protection of the alcohol followed by Boc anhydride and DMAP in MeCN to give **265** in 67% yields over the two steps.



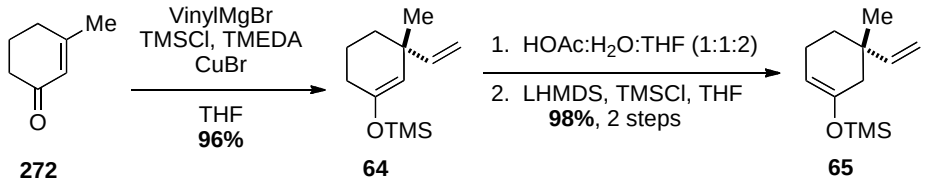
Scheme 92: Lewis-acid coupling with *N*-Boc protected indole.

Tricycle **265** was treated with BF_3•etherate for 4 hours, as done in Scheme 86, but failed to give any product, Scheme 93. Allowing the reaction to run for 24 h afforded tetracyclic **270** and **271** in a 5:1 ratio in 6% yields. Unfortunately, all optimization conditions failed to give any increase in tetracycle yields. TBS protected alcohols can be deprotected utilizing BF_3•etherate, and given the complexes they can form with the resulting alkoxide ion, it was thought that this complex was causing the reaction to shut down. To this end, it was envisioned to synthesize an analog of tricycle **265** that replaced the alcohol with a hydrogen, thus removing the problematic functional group in the BF_3•etherate closure step.



Scheme 93: BF_3•etherate ring closure to tetracycles **270** and **271**.

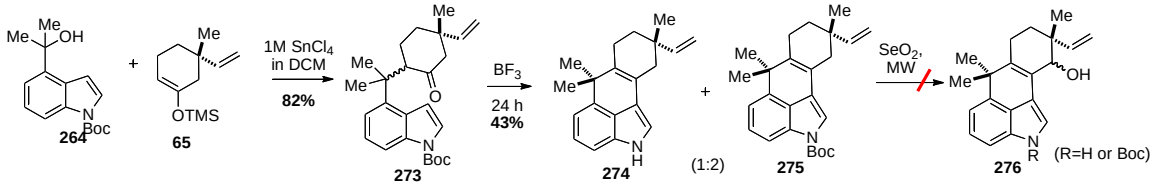
Accessing the analog of **265** with a hydrogen substituted for the TBS protected alcohol was envisioned to come about from a modified route gaining access to the northern cyclohexyl ring system. Starting from commercially available 3-methylcyclohexenone **272**, the quaternary carbon center was installed to afford **264** via the same cuprate chemistry previously described above for the formation of the TBS ether analog system, scheme 94. The TMS-enol ether was cleaved with acetic acid:water:THF mixtures to afford the resulting ketone, which was enolized with LHMDS and treated with TMSCl to afford the desired regio-isomer TMS-enol enolated **65** in great yields.



Scheme 94: Accessing quaternary carbon center devoid of TBS protected alcohol.

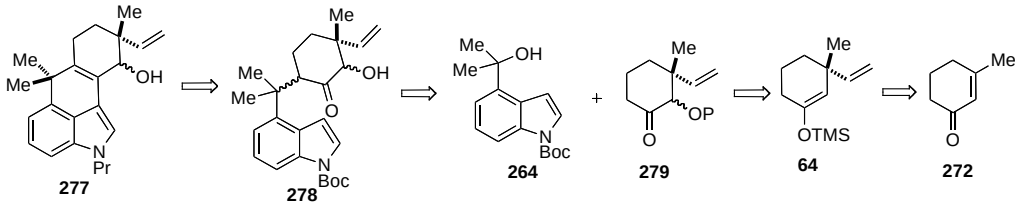
Coupling of **264** and **65** was accomplished with a dilute tin (IV) chloride (1M) solution, rather than the fuming due to the observed decrease in yields with the Boc protected indole, to afford tricycle **273** in 82% yields, Scheme 95. Previously when treating this tricycle with the TBS protected alcohol with BF_3•etherate a dismal 6% yield was obtained, which was thought to be due to the reactivity of the resulting alkaloid ion formed *in situ*, but in the system it resulted in a 43% yield of **274** and **275** in

a 1:2 ratio. These two dehydrated tetracycles were separated and subjected to Riley oxidation conditions in the attempts to install the desired allylic alcohol for future isonitrile incorporation. Unfortunately, both the free indole **274** and the Boc protected indole **275** failed to give any of the desired allylic alcohol (**276**) and resulted in decomposition and the recovery of less than 5% of the starting matieral.



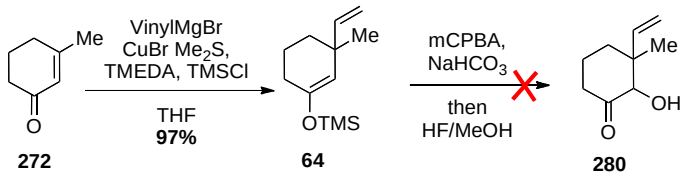
Scheme 95: Attempts at gaining access to allylic alcohol **276**.

With the Riley oxidation failing to give the desired allylic alcohol **276**, gaining access to this system was re-examined, Scheme 96. Rather than installing the allylic alcohol **277**, it was envisioned to have said alcohol already installed prior to tetracycle access via tricycle **278**. Compound **278** could be accessed from the Lewis-acid coupling of functionalized indole **264** and alcohol containing cyclohexyl compound **279**. Accessing the alcohol containing system could be achieved during the quaternary carbon center formation by trapping the TMS-enol ether **64** and performing a Rubottom oxidation to access **279**. Compound **64** could be accessed from the previously utilizing 3-methyl-cyclohexenone **272**.



Scheme 96: Retrosynthetic analysis for gaining access to allylic alcohol **272**.

Previously, the method of cuprate addition for quaternary carbon center formation was delineated in detail. Employing these same conditions afforded **64** in 97% yields, previously accessed as well, Scheme 97. Subjecting TMS-enol ether **64** to standard Rubottom conditions, treatment with *m*CPBA in DCM followed by silyl cleavage with TBAF or HF, was attempted. To our surprise, rather than obtaining any of the desired α-hydroxyketone **280**, only cleavage of the TMS group was observed giving the resulting ketone species exclusively.

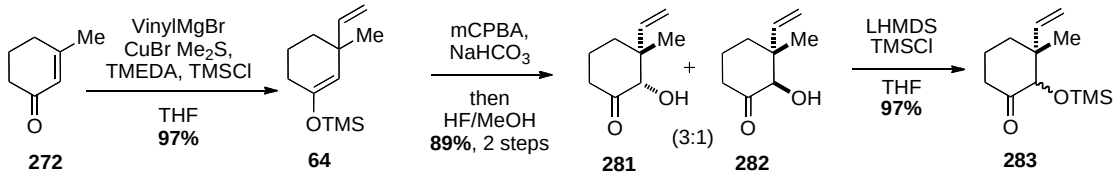


272 **64** **280**

Scheme 97: Attempted Rubottom oxidation via previous cuprate strategy.

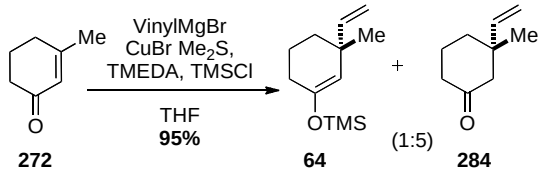
Standard workup conditions from the vinyl cuprate addition upon **272** was washing the reaction mixture with a saturated $NaHCO_3$ until the aqueous layer was devoid of any blue color, which is indicative of copper species. Using these standard workup conditions did result in a clear aqueous layer after multiple sodium bicarbonate washes, but it is believed that trace amount of copper were still present within the mixture which complexes with *m*CPBA shutting down the oxidation of the TMS-enol ether. This was visual supported as upon addition of the oxidant a bluish tint appears in the reaction when attempting to access **280**. To this end, rather than employing a sodium bicarbonate wash for copper removal, metal chelating agents were attempted. Treating **272** under standard cuprate addition conditions was performed, but rather than rinsing with sodium bicarbonate a 0.1 M phosphate buffer at a pH of 7 was used followed by further washing of the organic layer with a 1 M EDTA solution three times, Scheme 98. Concentration of the organic layer, post-drying, resulted in **64**. Treating

compound **64** to Rubottom conditions afforded a mixture of alcohols **281** and **282** in a 3:1 ratio. The alcohol was protected as the TMS ether via treatment of the alcohol mixture with LHMDS in THF followed by TMSCl addition to afford **283** in 97% yields.



Scheme 98: Synthesis of TMS protected α-hydroxyketone species **283.**

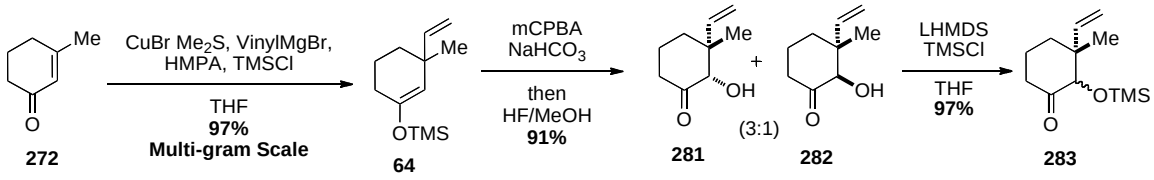
Washing the organic layers of the vinyl cuprate addition reaction with both the phosphate buffer as well as the EDTA did successful remove all of the copper, thus giving access to the desired TMS protected α-hydroxyketone species **283**. The reaction worked great on scales less than 150 mg of starting material **272**, but when running the reaction with the new workup conditions on scales larger than 150 mg rather than obtaining the desired TMS-enol ether **64** exclusively, ketone **284** was also obtained in a 1:5 ratio, respectively, Scheme 99. Thus, while the phosphate and EDTA washes do allow for copper removal, the subsequent Rubottom oxidation can only be performed on scales less than 150 mg.



Scheme 99: Scale-up issues for accessing pre-Rubottom oxidation substrate.

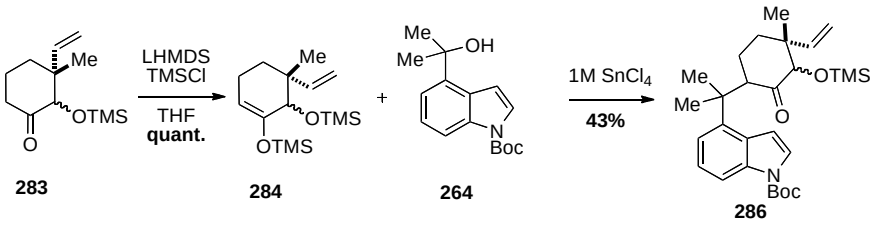
Given the scale limitations with the standard cuprate addition workup conditions, it was deemed that the conditions for vinyl cuprate addition should be revisited. Multiple conditions, order of addition, concentration and reaction durations were screened. The following conditions were observed to give optimized results: vinyl

Grignard was cooled to -78 ℃ to which a pre-mixed solution of copper bromide•dimethyl sulfide in HMPA (0.25 M) was added over 5 min and left to stir for 30 min, followed by slow addition of **272** and TMSCl in THF (1 M to **272**) over 30 min at the same temperature, after 2.5 h triethyl amine (20 eq. to **272**) was added and the reaction allowed to warm to room temperature, and washed twice with 2 volume eq. of water and one volume eq. of a saturated ammonium chloride solution to afford **64** in excellent yields and on a multi-gram scale (up to 10 g), Scheme 100. While accessing a multi-gram route to **64** was achieved, the subsequent Rubotttom oxidation was in question as to where or not all of the copper was removed under these new conditions. To our delight, subjecting **64** to *m*CPBA in DCM followed by HF in MeOH afforded disastereomer alcohols **281** and **282** in the same ratio's previously observed, which was elaborated into **283** in 97% yields.



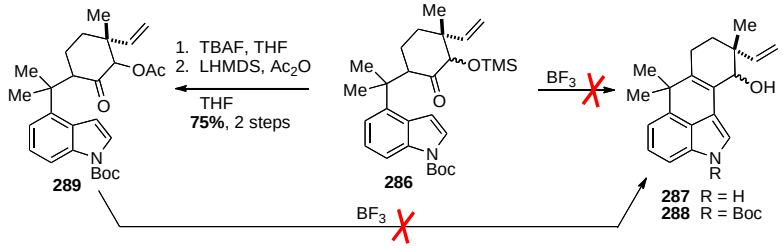
Scheme 100: Optimized cuprate addition route to access **283.**

Having accessed **283**, the next step was to couple it to *N*-Boc-indole and attempt the ring closure to the desired tetracycle for the hopeful access of the allylic alcohol dehydrated tetracycle. Compound **283** was transformed into its corresponding TMS-enol ether in quantitative yields, Scheme 101. Coupling of **284** to **264** was successfully performed using a 1 M tin (IV) chloride solution accessing tricycle **286**, it is of note to mention that using fuming tin (IV) chloride gave significantly lower yields.



Scheme 101: Coupling TMS-α-hydroxyketone to indole accessing tricycle **286.**

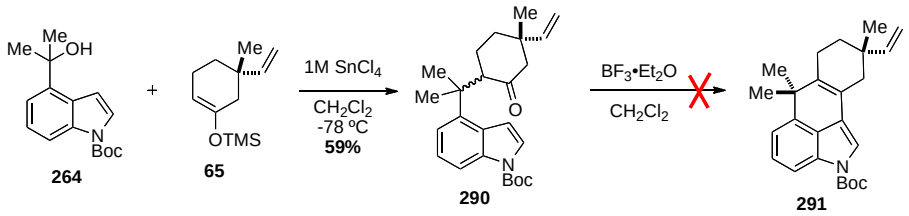
With TMS-protected alcohol **286** in hand, the next step was to close the tricycle to the anticipated tetracycle with allylic alcohol, or TMS protected alcohol, in place. Treating **286** with BF_3•etherate, as previously done for tetracycle access in both 4 and 24 h, failed to give any of the desired tetracycle **287** or **288**, Scheme 102. Interestingly enough what was observed was deprotection of the TMS group and nothing more. Given the trouble of silyl groups in the presence of BF_3•etherate previously encountered, the TMS group was removed with TBAF in THF and acetylated to give **289**. Treating **289** with BF_3•etherate failed to give any of the desired tetracycle and resulted in decomposition of the material.



Scheme 102: Attempted tetracycle formation via *N*-Boc tricycle.

With the results presented in Scheme 102 in mind, it was decided to investigate which group, either the protected alcohol or Boc protected nitrogen, could be interfering with the ring closure to the desired tetracyclic core. To examine this, it was decided to build an analog of tricycle **286** that has hydrogen substituted for the alcohol moiety. To this end TMS-enol ether **65**, delineated in Scheme 94, was coupled to indole **264** with 1

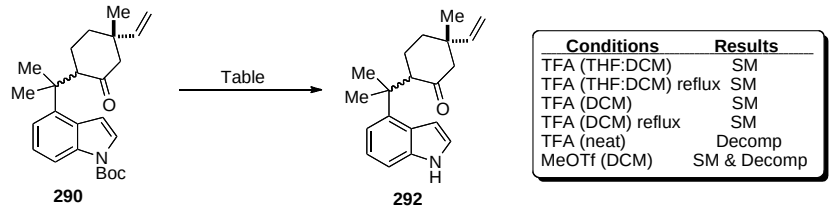
M tin(IV) chloride in DCM at -78 ℃ to afford tricycle **290** in 59% yields, Scheme 103. Treating **290** with BF_3•etherate should give insight into the effect of tetracycle formation of the protected alcohol in Scheme 102. To our surprise, treating **290** with BF_3•etherate failed to give any of the desired tetracycle **291**, but afforded starting material (<24%) and decomposed material. Thus suggesting that the protected alcohol might not be the cause in tetracycle access from the corresponding tricycles. With this result in hand, it was decided to screen the effects of the Boc group upon the ring closure.



Scheme 103: Screening effects upon protected alcohol substitution.

With the *N*-Boc tricycle **290** in hand, deprotection of the Boc group was chosen as the next course of action to either attempt tetracycle formation with the free amine or placement of a different protecting group for ring closure attempts. Scheme 104 outlines the conditions attempted at the removal of the Boc group upon the indole nitrogen. Treating tricycle **290** with TFA in THF:DCM, fairly standard conditions for such a reaction, at both room temperature and at reflux failed to afford any of the desired tricycle **292**. Attempting the same deprotection with TFA in only DCM both at room temperature and at reflux still only returned starting material. It is of note to mention, that these four conditions were run for over 2 weeks, solvent was replaced to maintain solvent levels in the refluxing reactions. Next, **290** was taken up in neat TFA and left to stir. Monitoring the reaction every 5 minutes by TLC showed no consumption of starting material. Nearly 2 h after the reaction began the material started to decompose

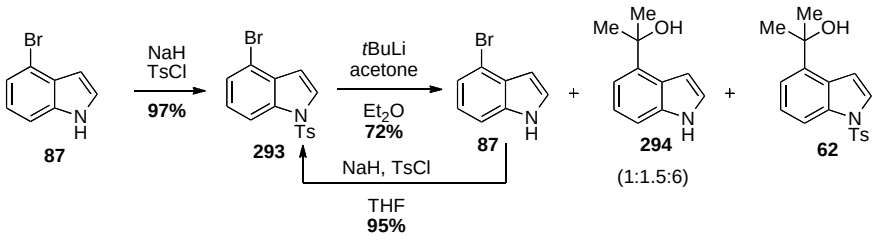
as monitored by TLC analysis and confirmed by NMR analysis. Lastly, treating **290** with MeOTf[34] failed to afford any of the desired material but returned starting material (34%) and decomposition of starting material.



Scheme 104: Attempted conditions at Boc removal of tricycle **290.**

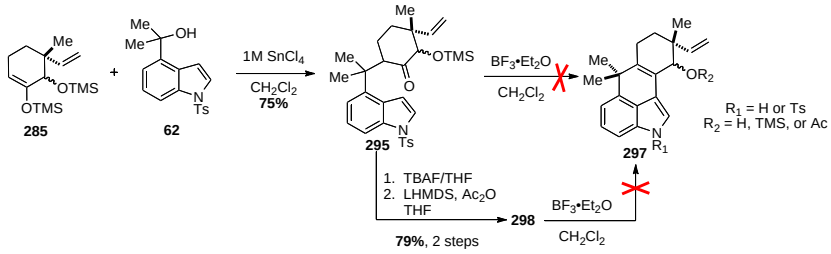
Tosyl Protected Indole

Given the inability to remove the Boc group upon tricycle **290**, it was thought to bring the new protecting group into the synthesis from 4-bromo-indole. Natsume successfully utilized a Tosyl group upon the indole nitrogen for his synthesis of hapalindoles, but as described in chapter 2, was extremely lengthy and in low yields. Starting form 4-bromoindole **87**, accessing the tosylated indole **293** was accomplished with NaH and freshly purified TsCl in THF in 97% yields, Scheme 105. Subjecting *N*-Ts-indole **293** to the same lithium-halogen conditions, delineated in Scheme 91, furnished desired indole **62**, along with de-protected indoles **87** and **294** in a 1:1.5:5 ratio (**87:294:62**) ratio and in 95% yield. The returned 4-bromoindole **87** was successfully re-protected with NaH and TsCl in THF to give **293** in 95% yield. Unfortunately, the de-protected tertiary alcohol indole **294** could not be efficiently recycled to afford desired indole **62**.



Scheme 105: Synthesis of functionalized indole **62.**

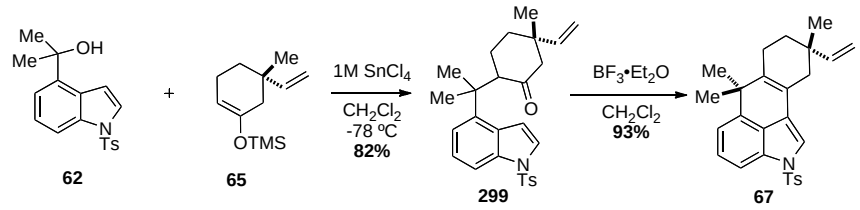
With *N*-tosyl-indole **62** in hand, it was decided to couple said indole with the TMS protected alcohol TMS-enol ether (**285**) to examine what effect the replacement of the Boc group has upon tetracycle formation. Treating a solution of **285** and **62** in DCM at -78 ℃ with 1 M tin(IV) chloride in DCM afforded **295** in 75% yield, Scheme 106. As with previous systems, treating tricycle **295** with BF_3•etherate failed to afford desired tetracycle **297** in any forms. De-protection of the TMS protected alcohol is once again suspect as occurring more rapidly than the anticipated 1,2 addition with subsequent dehyration accessing **297**. Given the same conditions as in Scheme 102, the TMS group was de-protected with TBAF in THF and the resulting alcohol acetylated with LHMDS and Ac_2O in THF to afford **298** in 79% yields. Treating the acetyl protected alcohol **298** with BF_3•etherate in DCM also failed to give desired tetracycle **297**.



Scheme 106: Attempts at accessing tetracyclic core via *N*-Tosyl protected indole.

Given the trouble encountered with the protected alcohol upon ring closure accessing the desired tetracycle with both the *N*-tosyl and Boc protected indole, efforts were direct towards accessing a tetracyclic core in which said alcohol could be installed

late stage similar to the strategy employed by Natsume. Treating a solution of indole **62** with TMS-enol ether **65** in DCM at -78 ℃ with a 1 M tin(IV) chloride in DCM afforded tricycle **299** in 82% yield, Scheme 107. Subjecting tricyle **299** to BF_3•etherate in DCM gave dehydrated tetracycle **67** in 93% yield.



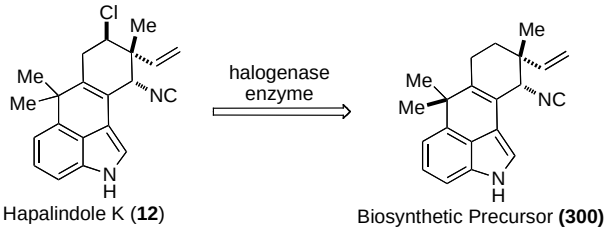
Scheme 107: Lewis acid coupling of **62** and **65** and ring closure to **67.**

Natsume and co-workers previously accessed the same tetracycle in the same fashion, from **62** and **65** affording **66** then elaborating onto **67**, but their synthetic route to **62** and **65** are lengthy and low yielding. Accessing **62** was accomplished from 1H-pyrrole-2-carbaldehyde, shown in chapter 2, in nine synthetic steps in an overall 20% yield. TMS-enol ether **65** was accessed in three synthetic steps with an overall 43% yield, but in their total synthesis paper it was reported as an 67% yield with a mixture of TMS-enol ether isomers in a 5:1 (desired:undesired) ratio. Whereas in our current route, accessing indole **62** is accomplished in two synthetic steps in an overall 51% yield and accessing TMS-enol ether **65** is accomplished in two synthetic steps in an overall 94% yield and more importantly with only formation of the desired enol compound.[30]

3.6.3.1 Total Synthesis of proposed biosynthetic precursor to Hapalindole K

The proposed biogenetic pathway to the hapalindoles involves a chloronium ion-induced enzyme-mediated π-cation cyclization to afford a six-membered ring containing the chlorine atom, vinyl substituted quaternary center, isonitrile functionality, indole ring,

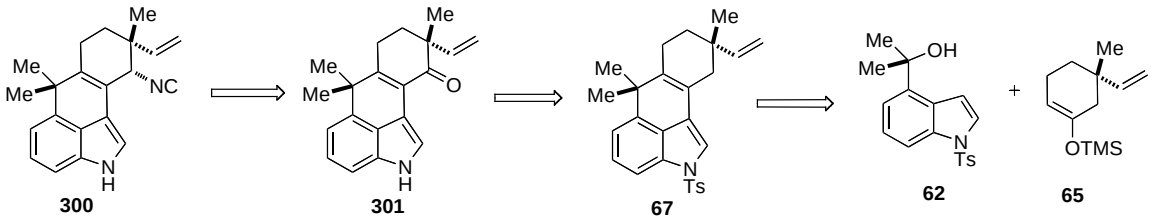
and isopropene group, as delineated in chapter 1 scheme 3. This proposed pathway does allow for the *epi* C12 geometry observed in the hapalindole alkaloid family. While the proposed biosynthetic route provides a feasible means of gaining access to the hapalindole tricyclic core, the stage of halide installation is debatable. Half of the hapalindoles possess identically stereo-configured chlorine atoms at C13, while the other half do not, despite being otherwise structurally identical, as in the cases of hapalindoles A and J, B and M, G and U and L and *epi*-J. This fact may indicate late-stage installation of the halogen atom via a halogenase enzyme; for if the chlorine were installed through the aforementioned chloronium ion-induced cyclization, scrambling of the stereochemistry at C13 would be anticipated, especially when considering the possible *epi* pathway. We accordingly propose hapalindole K to arise from its non-halogenated precursor (**300**), which we purpose to be an as-yet undiscovered natural product (Scheme 108).



Hapalindole K (**12**) Biosynthetic Precursor **(300)**

Scheme 108: Proposed biosynthetic halogenase for chlorine installation.

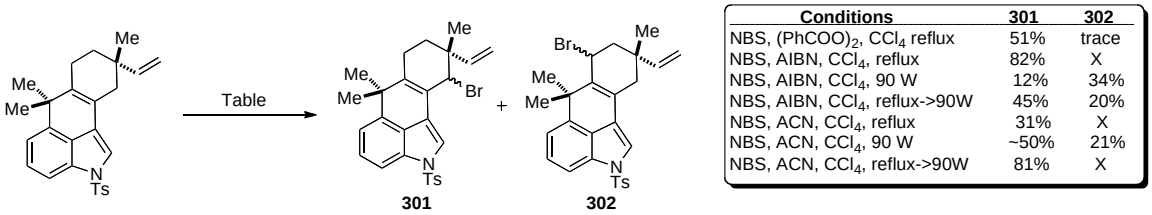
We envisioned that the proposed hapalindole K precursor (**300**) could arise from the reductive amination of **301** followed by coupling with formic acid with subsequent dehydration with Burgess reagent, Scheme 109. Tetracycle **301** could be accessed from **67** employing a route similar to Natsume via radical bromination of **67** with subsequent alcohol formation via S_N^2 displacement followed by oxidation to give **301**. Tetracycle **67** has already been access given chemistry previously described above.



Scheme 109: Retrosynthetic analysis to proposed hapalindole K biosynthetic precursor.

Natsume and co-workers employed radical bromination via NBS and benzoyl peroxide in CCl_4 at reflux to access **301**, as seen in Scheme 110. While it was our plan as well to install a bromine via radical bromination, we wished to optimize said bromination. Scheme 110 outlines the attempted conditions to access desired brominated tetracycle **301**. Employing the same conditions used by Natsume afforded **301** in 51% yield with trace amount of the undesired brominated product. Switching the radical initiator from benozyl peroxide to AIBN increased yields of **301** by 31% with no observed formation of the undesired product **302**. Employing light rather than heat unfortunately did not result in increased yields, but in fact decreased yields of **301** to 12% with 34% formation of undesired **302**. Attempting a combination of heat and light also failed to give any increase in yields. Switching the initiator to ACN also failed to give improved yield with just reflux or light alone. But, using ACN with a combination of heat and light afford **301** in 81% yields with no observed formation of undesired **302**. It is of note to mention that if the NBS was not freshly purified prior to the reaction yields were observed to be depressed by more than 20% in all conditions screened. Also, CCl_4 proved to be the best solvent of choice for this reaction, attempts at utilizing different solvents gave depressed yields of nearly 40%. Likewise, NBS was the only brominating agent that afforded the desired product. Therefore, subjecting **67** to NBS

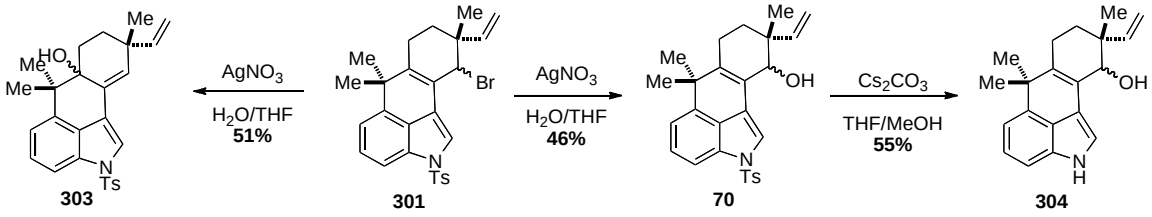
and AIBN in CCl_4 at reflux for 20 min affords desired brominated tetracycle **301** in 82% yield, 31% greater than the method employed by Natsume.



Conditions	301	302
NBS, $(PhCOO)_2$, CCl_4 reflux	51%	trace
NBS, AIBN, CCl_4, reflux	82%	X
NBS, AIBN, CCl_4, 90 W	12%	34%
NBS, AIBN, CCl_4, reflux->90W	45%	20%
NBS, ACN, CCl_4, reflux	31%	X
NBS, ACN, CCl_4, 90 W	~50%	21%
NBS, ACN, CCl_4, reflux->90W	81%	X

Scheme 110: Screened radical bromination conditions for accessing **301**.

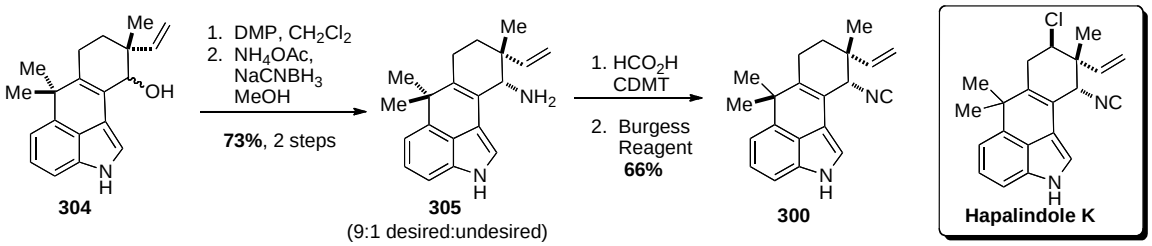
To a solution of **301** in THF was added a pre-mixed 1 M $AgNO_3$ in H_2O and allowed to stir for 24h affording **70** in 46% yields, Scheme 111. Unfortunately, this was 20% lower than the method used by Natsume that employed acetone rather than THF. It was found that when acetone was used as the organic solvent a S_N2' was observed affording **303** in 51% yield. Tosyl group removal was deemed optimal at this stage, rather than later in the synthesis, due to the anticipated reactivity of the impending isonitrile. Treating a solution of **70** in THF/MeOH (1:1 v/v) with cesium carbonate afforded **304** in 55% yield.[35]



Scheme 111: Elaboration of **301** into allylic alcohol tetracycle **304**.

Having accessed tetracycle **304**, elaboration to the biosynthetic precursor was undertaken, Scheme 112. Oxidation of **304** to the corresponding enone was accomplished with Dess-Martin periodinane in DCM. The amine was installed via reductive amination using ammonium acetate in MeOH with $NaCNBH_3$ to give **305** (9:1 diastereomeric mixture ratio, desired:undesired) in 73% yield over two steps. Formic

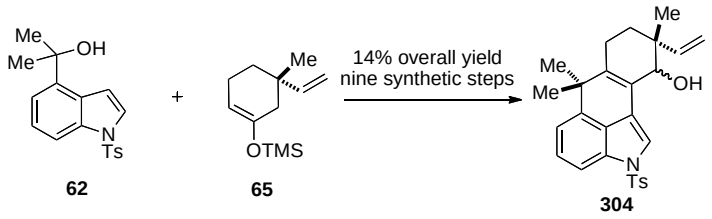
acid was then coupled to amine **305** using CDMT to give the corresponding formamide, which was dehydrated with Burgess reagent to provide isonitrile **300** in 66% yield over two steps.



Scheme 112: Synthesis of proposed hapalindole K biosynthetic precursor **300**.

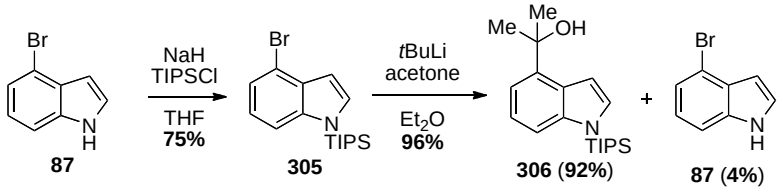
3.6.3.2 Silyl Strategy for Accessing Allylic Alcohol Tetracycle

At this point, a route has been established that allows for access to allylic alcohol tetracycle **304**, Scheme 113, for further elaboration onto other hapalindole tetracycles as well as possibly the ambiguines. Accessing **304** was achieved in an overall 29% yield in four synthetic from functionalized indole **62** and TMS-enol ether **65**, but if considering from the commercially available starting material **304** is accessed in an overall 14% yield in nine synthetic steps. Granted this route does give access to the desired tetracycle, the steps required from said cycle is expected to be numerous for accessing tetracyclic hapalindole and/or ambiguine natural products. Thus, the step-count needs to be reduce as well as the yield increased. Two key areas that could be improve are the formation of the functionalized indole **62** and the installation of the required allylic alcohol, either early or late stage. To this end, efforts were directed towards improving the yields on the functionalized indole moiety.



Scheme 113: Synthetic route accessing allylic alcohol tetracycle **304.**

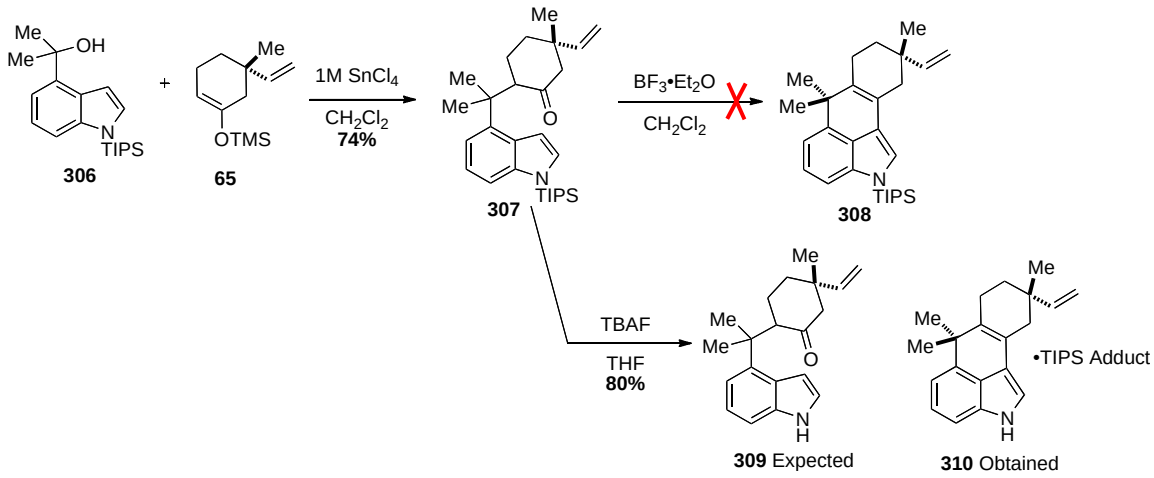
Given the instability of Tosyl groups towards alkaline conditions, and noting that a lithium-halogen exchange via *t*-BuLi is utilized in accessing the functionalized indole moiety, silyl analogs were sought after due to their relative stability to alkaline conditions as well as their ease of acid-mediated removal. Initially, efforts were directed towards triisopropylsilane (TIPS) as a protecting group due to its size and high alkaline stability. Treating 4-bromoindole **87** with NaH and TIPSCl in THF afforded **305** in 75% yield as shown in Scheme 114. As previously delineated, treatment of **305** with lithium-halogen exchange conditions afforded a 23:1 (**306**:**87**) ratio in 96% yields. Recovered **87** was successfully recycled to **305** in 73% yields. TIPS protected indole **306** was successfully accessed in a 18% greater yield than its tosyl protected counterpart, but unfortunately with no decrease in synthetic steps.



Scheme 114: Synthesis of TIPS functionalized indole **306.**

TMS-enol ether **65** and indole **306** in DCM at -78 ℃ were next treated with 1 M tin(IV) chlorie in DCM to give tricycle **307** in 74% yields, Scheme 115. The TIPS protected tricycle **307** was therefore accessed in six-synthetic steps with an overall 48% yield, 19% greater than the tosyl analog. Treating **307** with BF_3•etherate in DCM

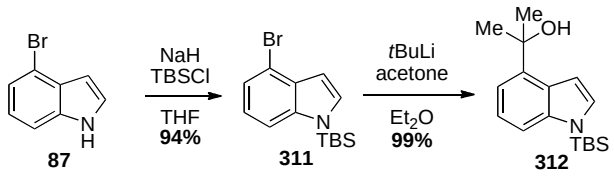
afforded only decomposed material and failed to afford any of the desired tetracycle **308**. De-protection of the TIPS groups was thought to be the best course of action, after which cyclization could be attempted upon the free indole nitrogen species. Subjecting **307** to TBAF in THF failed to afford any of the expected de-protected tricycle **309**, but produce a single new compound. Upon NMR and MS analysis the newly formed product was in fact tetracycle **310**, but unfortunately is possessed a TIPS adduct that could not be purified or removed under a variety of conditions (column chromatography, HF adsorbed chromatography, benzene azeotrope and high vacuum pump removal). Given the rapid access to tetracycle core **310** under these conditions, further investigation was required to elucidate the silyl adduct or how to possibly cirvumvent it.



Scheme 115: Efforts for tetracycle access via TIPS protected indole.

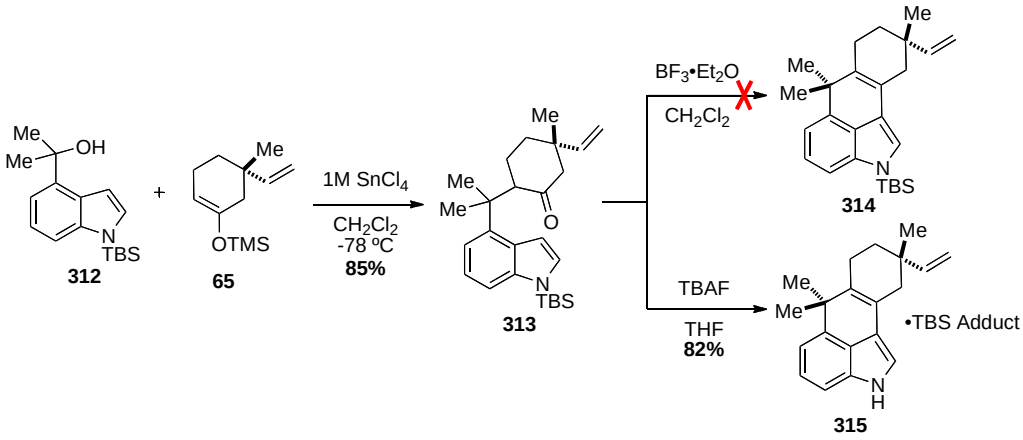
Hypothesizing that they size of the TIPS group might be responsible for the adduct formation, TBS was used rather than TIPS for indole protection. TBS was also chosen due to its ease of removal post TBSCl protection of alcohols, remaining TBSCl or the resulting TBSOH can easily be removed via high vac pumping at 35 ℃ or HF adsorbed chromatography. Substituting TBSCl or TIPSCl the same synthetic sequence

outlined in Scheme 114 was undertaken to afford **311** in 94% yield and then **312** in 99% yield as shown in Scheme 116.



Scheme 116: Synthesis of TBS functionalized indole **312.**

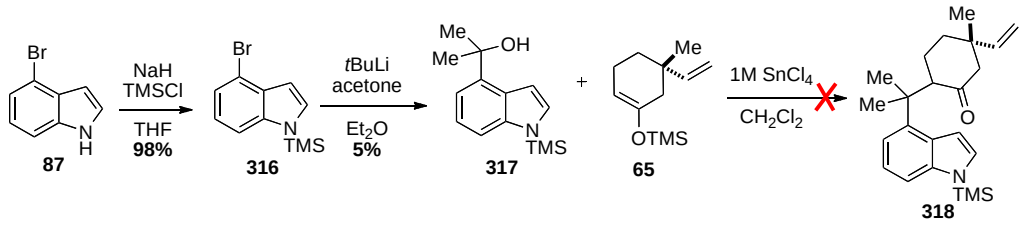
Treating a solution of **312** and **65** in DCM at -78 ℃ with 1 M tin(IV) chloride in DCM afforded tricycle **313** in 85% yields, 11% greater than the TIPS analog, Scheme 117. Treating tricycle **313** with BF_3•etherate failed to furnish tetracycle **314**, which was not unexpected just performed for screening purposes. Treating **313** with TBAF in THF did afford the desired tetracycle, but unfortunately as the TBS adduct (**315**) as confirmed by NMR and MS analysis. All attempts at removing the silyl adduct, as in the case of the TIPS analog, failed to furnish purified tetracycle.



Scheme 117: Efforts for tetracycle access via TIPS protected indole.

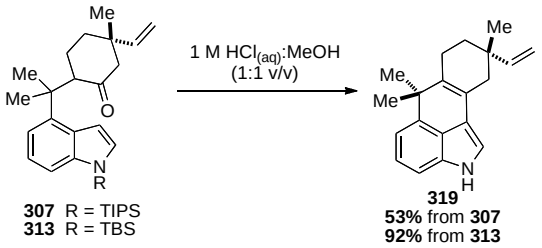
Given the inability to remove the TIPS and TBS adduct from the tetracycle it was thought to use TMS as the protecting group due to its characteristic liable nature, which was thought to aid in removal of the adduct product. Functionalized indole **317**

was access from **87** via treatment with NaH and TMSCl in THF to furnish **316** which was subsequently subjected to lithium-halogen conditions affording **317** a 5% yield, thought to be due to TMS groups liable nature. Unfortunately, all attempts at coupling **317** and **65** failed to give **318**, but rather decomposition of material as well as TMS de-protected **317**.



Scheme 118: Attempted TMS protection for tetracycle formation.

Given the silyl adduct formed under alkaline conditions with TBAF it was decided to screen acid conditions to remove the silyl group upon their corresponding tricycles to afford de-protected tricycles that could hopefully be elaborated into tetracycles efficiently. As outlined in Scheme 119, treating both the TIPS and TBS protected tricycles **307** and **313**, respectively, with a pre-mixed 1 M HCl:MeOH (1:1 v/v) failed to afford the anticipated de-protected tricycle, but to our delighted furnished the sought-after tetracycle **319** in 53% yield from the TIPS tricycle and 92% from the TBS tricycle. It is thought that not only does the HCl act as a means to de-protected the silyl group it allows actives the carbonyl via protonation which allows the C3 position of the indole ring to attack the carbonyl carbon in a Fridel-Crafts acylation like pathway. Dehydrated tetracycle **319** can be accessed in an overall 68% yield in seven synthetic steps.

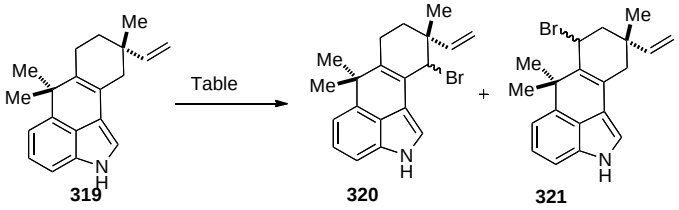


307 R = TIPS
313 R = TBS

319
53% from **307**
92% from **313**

Scheme 119: Acid-mediated de-protection tandem ring closure to tetracycle **319.**

With dehydrated tetracycle **319** in hand, focus was directed towards installation of the allylic alcohol. Employing the same conditions previously used for radical bromination of the tosyl protected tetracycle, previously described, no brominated product was observed, but only decomposition and recovered starting material as outlined in Scheme 120. Given this result, it can be concluded the indole nitrogen must be protected for the radical bromination to be performed.

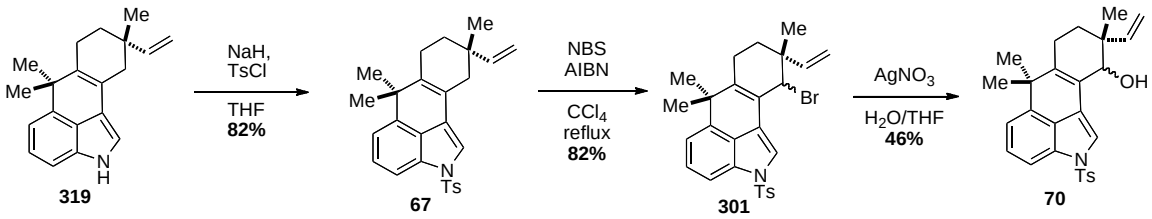


319 **320** **321**

Conditions	Yield (% 320:321)
NBS, $(PhCO)_2O$, CCl_4 reflux	Decomp
NBS, AIBN, CCl_4, reflux	Decomp
NBS, AIBN, CCl_4, 90 W	S.M.
NBS, AIBN, CCl_4, reflux->90W	S.M.
NBS, ACN, CCl_4, reflux	S.M.
NBS, ACN, CCl_4, 90 W	S.M.
NBS, ACN, CCl_4, reflux->90W	S.M.

Scheme 120: Attempted radical brominations upon tetracycle **319**.

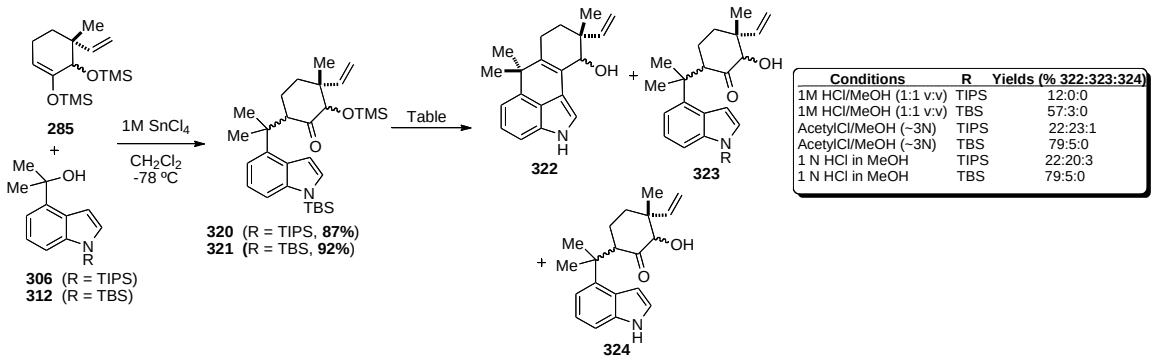
Treating a solution of **320** in THF with NaH followed by TsCl gave access to **67** in 82% yields. Elaboration of **67** into the desired allylic alcohol tetracycle has previously been described above, as outlined in Scheme 121. Employing TBS rather than a tosyl protecting group does give access to the same allylic alcohol **70** and does so in an overall yield of 21%, 7% greater than the tosyl route, but does so in ten synthetic steps, one step longer than the tosyl strategy. While the TBS route is one step longer is does allow for an extra 6% overall increase in yield accessing **70**, thereby validating the extra synthetic step.



Scheme 121: Accessing allylic alcohol **70**.

Switching the tosyl group for a TBS does enhance the synthetic route accessing **70**, but does so by increasing the step count by one, which comes about from the need to protect the indole nitrogen after the acid-mediated ring closure. With this, it was thought to re-approach the idea of installing the alcohol *early* stage rather than *late* stage that causes the current problem. Treating a solution of **285** and TIPS or TBS indoles **306** and **312**, respectively in DCM at -78 ℃ with 1 M tin(IV) chloride in DCM afforded tricycles **320** and **321**, 87% and 92% respectively, Scheme 122. Subjecting **320** to 1 M HCl in MeOH (1:1, v/v) afforded desired allylic alcohol tetracycle **322** in 12% and subjecting **321** to the same conditions afforded 57% yield of **322** along with 3% of the TMS de-protected tricycle **323**. It is of note to mention that the TBS tricycle **323** when subjected to the same acid-mediated conditions failed to afford any of the desired **322**, but only returned started material. In both the TIPS and TBS reactions trace amounts of a non-dehydrated di-hydroxy product was observed, thus suggesting a hydro-halogenation reaction occurring upon the formation of **322** or en-route to **322**. To explore this, rather than employing aqueous HCl in MeOH to promote ring closure to **322** methanolic HCl (dry HCl in MeOH) was used instead. Treating **320** with methanolic HCl afforded **322** in 22% yields, but also gave **323** in 23%. To our delight, treatment of **321** with methanolic HCl afforded tetracycle **322** in 79% yields, with only 5% yield of tricycle **323** that could be easily converted to **322** with additional methanolic

HCl. It is of note to mention that these results for accessing **322** from **320** or **321** could be accomplished using methanolic HCl commercially available, or by preparing it fresh via two methods: (1) dissolving $HCl_{(g)}$ in MeOH, and (2) addition of dry acetyl chloride into MeOH. Thus, the allylic alcohol tetracycle **322** can be accessed in an overall 54% yield in six synthetic steps from commercially available materials, far greater than the previous tosyl route of 14% in nine steps. The only drawback with this silyl strategy is scale. The closure of tricycle **320** to **322** can only be performed on scales less that 75 mg, upon attempting the reaction with greater than 75 mg of **320** mostly **323** is obtained. Multiple separate reactions of **320** being converted to **322** can be performed simultaneously and post saturated $NaHCO_3$ quenched can be combined and purified with no decrease in yield in comparison to a single reaction on scales less than 75 mg.



Conditions	R	Yields (% 322:323:324)
1M HCl/MeOH (1:1 v:v)	TIPS	12:0:0
1M HCl/MeOH (1:1 v:v)	TBS	57:3:0
AcetylCl/MeOH (~3N)	TIPS	22:23:1
AcetylCl/MeOH (~3N)	TBS	79:5:0
1 N HCl in MeOH	TIPS	22:20:3
1 N HCl in MeOH	TBS	79:5:0

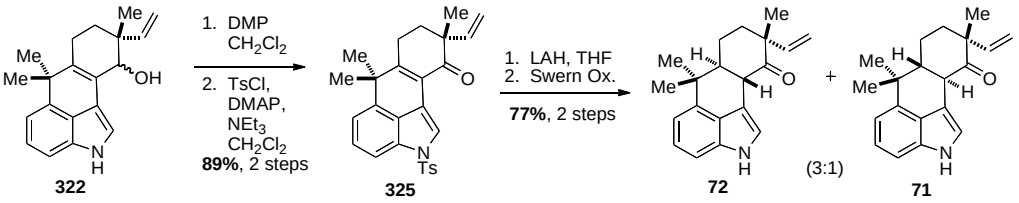
Scheme 122: Silyl strategy accessing functionalized allylic alcohol tetracycle **322**.

3.6.3.3 Total Synthesis of Hapalindole U

Having established an efficient and high yielding route to the functionalized tetracycle core **322**, efforts were directed towards utilizing said chemistry for the total synthesis of a hapalindole, namely hapalindole U (**7**).

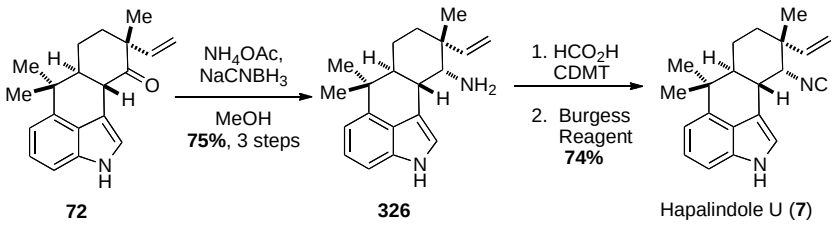
Subjecting **322** to oxidation with Dess-Martin Periodionate in CH_2Cl_2 gave the corresponding ketone, which was subsequently treated with TsCl, NEt_3, and catalytic

DMAP in CH_2Cl_2 at reflux to furnish compound **325** in 89% yield over the two synthetic steps as shown in Scheme 123. Treating **325** with LAH in THF over 12 h afforded the reduced cis-declin system in a 3:1 ratio of desired to undesired, which was then subjected to Swern oxidization conditions to afford the trans-decalin **72** and **71** (3:1 ratio) systems in a 77% yield. Purification of the oxidized mixture resulted in the isolation of desired **72** in 58% yield and the undesired **71** in 19% yield from **325** over the two steps.



Scheme 123: Reduction and oxidization accessing ketone **722**.

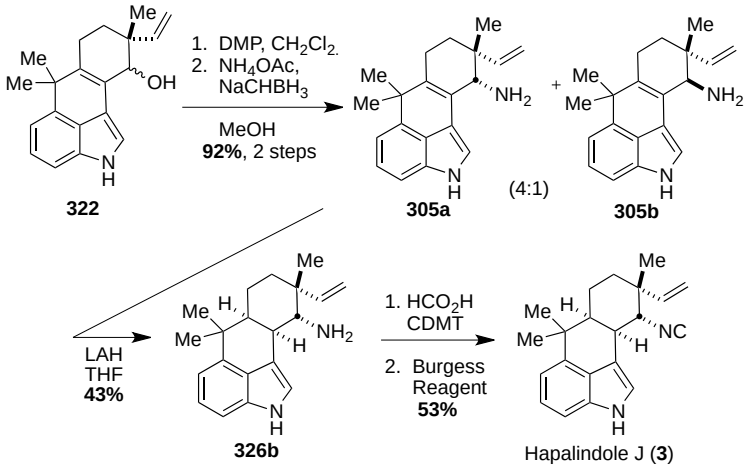
Reductive animation upon **72** with ammonium acetate and $NaCNBH_3$ in MeOH gave access to desired **326** in 75% yield, with only a 10% yield of the undesired diastereomer of the resulting amine, Scheme 124. Foramide formation was accomplished by the treatment of **326** and formic acid with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), catalytic DMAP and *N*-methyl-morpholine in CH_2Cl_2 which was subsequently dehydrated with Burgess reagent in benzene to afford hapalindole U (**7**) in 74% yield from **326**. With the newly developed silyl strategy, the total synthesis of hapalindole U (**7**) has been accomplished convergently over twelve synthetic steps, with an overall 16% yield from commercial available materials.



Scheme 124: Total synthesis of hapalindole U (**7**).

3.6.3.4 Total Synthesis of Hapalindole J (Completed post-dissertation submission)

Accessing hapalindole J was accomplished via compound **322** as shown in Scheme 124b. Oxidation of allylic alcohol **322** with DMP in CH_2Cl_2 followed by reductive amination with ammonium acetate and $NaCNBH_3$ in MeOH afforded allylic amines **305a** and **305b** (4:1 ratio) in 92% yield. Purification of the mixture provided the desired isomer **305a**, as well as undesired **305b**, in 74% and 18% yields, respectively, over the two steps from **322**.



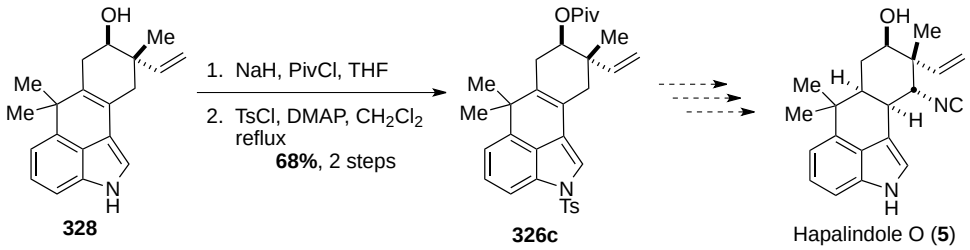
Scheme 124b. Elaboration of **322** into Hapalindole J.

Subjecting allylic amine **305a** to reduction conditions with LAH in THF allowed for a face-selective reduction of the tetra-substituted alkene giving access to **326b** in 43% yield. Coupling formic acid to **326b** was accomplished with CDMT, catalytic DMAP, and *N*-methyl-morphholine in CH_2Cl_2 affording the resulting formamide compound (not shown). Treating the incipient formamide with Burgess reagent in benzene afforded Hapalindole J in 53% yield from **326b**.

3.6.3.5 Formal Synthesis of Hapalindole O (Completed post-dissertation submission)

The formal synthesis of hapalindole O was completed after this dissertation was submitted to the committee, as such numbering and current work compounds will be

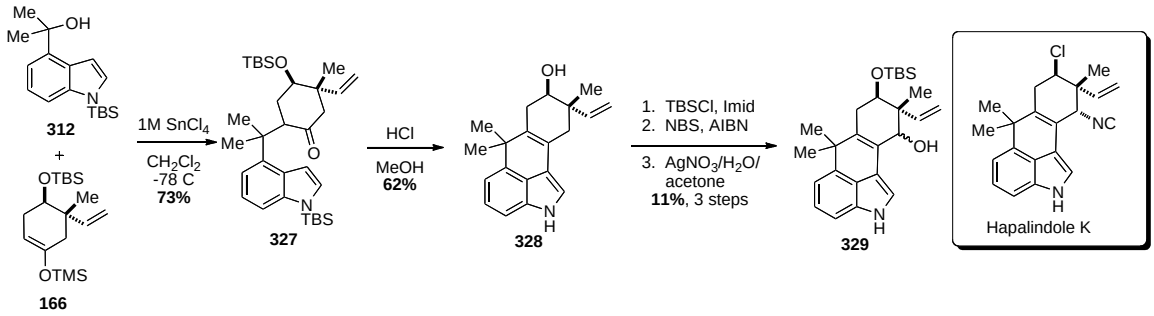
used. Further elaboration of **328**, described in scheme 125 in current work section, via NaH and PivCl protected the secondary alcohol followed by tosyl protection of the indole nitrogen gave access to **326c** (Scheme 124c). Compound **326c** directly intercepts Natsume's total synthesis of hapalindole O as described in scheme 13 in this body of work.



Scheme 124c. Formal Synthesis of Hapalindole O from **328**.

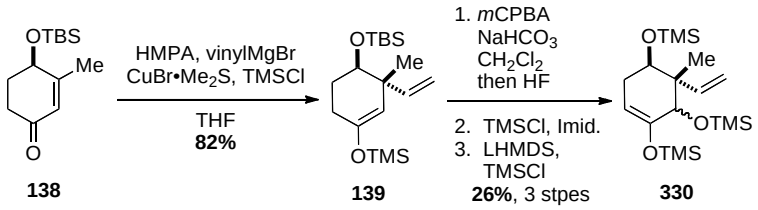
3.7 Current Synthetic Efforts

Having accessed hapalindole U via the developed silyl strategy, attention was directed towards accessing a similar allylic alcohol tetracyclic core that allows for the possible halide installation present in many of the tetracyclic hapalindoles and most of the ambiguines. Treating a solution of indole **312** and TMS-enol ether **166** in DCM at -78 ℃ to a solution of 1 M tin(IV) chloride in DCM afforded tricycle **327** in 73% yields, Scheme 127. Subjecting **327** to methanolic HCl afforded **328** in 62% yields, but as in previous silyl systems no there was no observed scale issue. The alcohol was protected as the TBS ether with TBSCl and the resulting compound was subjected to radical bromination conditions, as delineated in Scheme 110, to afford **329** in 11% yield over three synthetic steps. Unfortunately, the radical bromination reaction was only successful on scales less than 10 mg, thus greatly limiting material needed to continue with this route.



Scheme 125: Accessing tetracycle with halide handle installed.

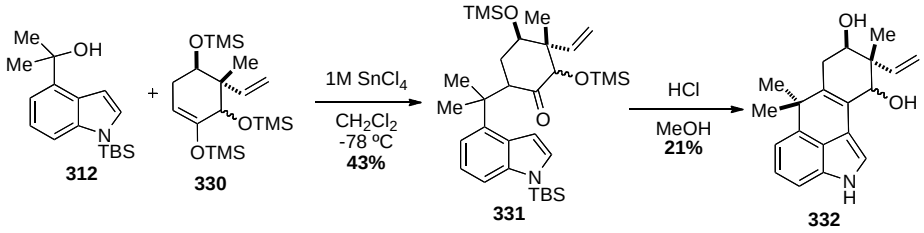
With the radical bromination conditions failing to give **329** on scales that are useful, it was decided to employ a similar route to access **329** as utilized in the total synthesis of hapalindole U. Accessing the required TMS-enol ether **330** was accomplished from **138** via the newly developed cuprate addition conditions that allow for the purification of **139** that is devoid of any copper species, Scheme 126. Subjecting **139** to Rubottom conditions afforded the corresponding α-hydroxyketone species, with the free alcohol at the northern position due to the need of employing HF in the reaction. The diol was di-TMS protected with TMSCl and imidazole and the resulting compound was transformed into the desired TMS-enol ether **330** via LHMDS and TMSCl in 26% yields over three synthetic steps.



Scheme 126: Accessing **330** for halide handle as well as allylic alcohol formation.

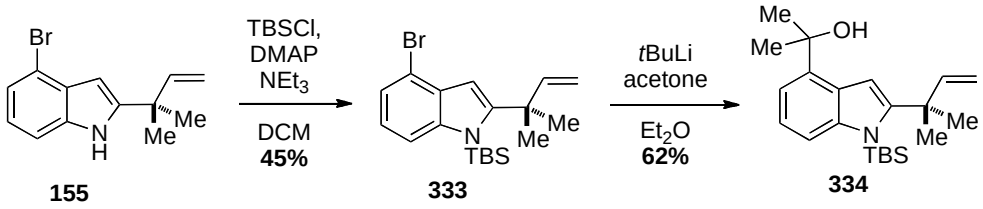
Treating a solution of indole **312** and TMS-enol ether **330** in DCM at -78 ℃ with a 1 M solution of tin(IV) chloride solution afforded tricycle **331** in 43% yields, Scheme 127. Treating **331** with methanolic HCl afforded **332** in 21% yields, but as in

the analogous system in Scheme 122 scales were limited. In this system, attempting the reaction with greater than 25 mg of **331** resulted in obtaining an analog of **331** with its free diol's, similar to **322**.



Scheme 127: Accessing tetracyclic diol **332**.

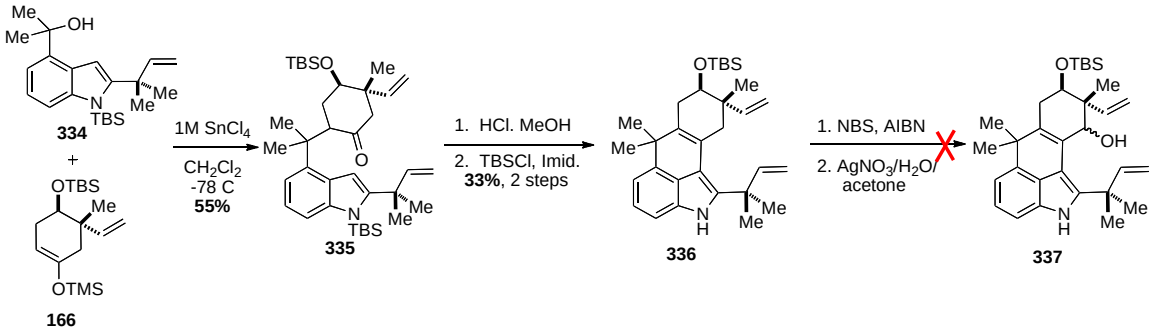
Having accessed the core of the tetracyclic hapalindoles, direction was then placed upon accessing the core of the ambiguines utilizing the same silyl strategy previously delineated. To this end, accessing the functionalized C2-reverse prenylated tertiary alcohol **334** was undertaken. Protection of the indole nitrogen with a TBS groups was accomplished with TBSCl, DMAP and Et_3N in DCM at reflux to afford **333** in 45% yields, Scheme 128. Subjecting **333** to same lithium-halogen conditions previously employed afforded **334** in 62% yield.



Scheme 128: Accessing functionalized indole **334**.

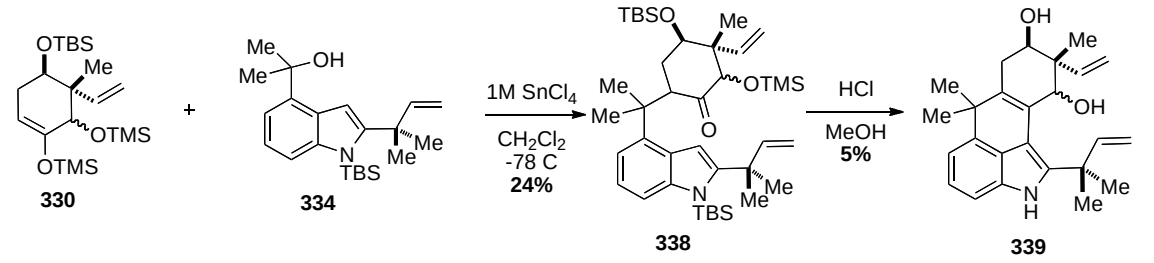
Coupling of **334** to **166** was accomplished under the same chemistry previously described and employed to afford tricycle **335** in 55% yields, Scheme 130. Treating **335** with methanolic HCl followed by TBS protection with TBSCl and imidazole afforded **336** in 33% yields over two synthetic steps. The ring closure of **335** to **336** was found to

have no scale limitations, as previously seen with similar systems. Unfortunately, all installation attempts of the hydroxyl group to access **337** via radical bromination failed.



Scheme 130: Attempted **337** accessed via radical bromination.

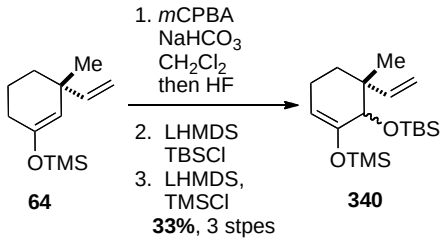
Given that all attempts at radical bromination failed, it was decided to employ our silyl chemistry. Coupling **330** to **334** was accomplished with a 1 M solution of tin(IV) chloride to afford **334** in 24% yields, Scheme 131. Ring closure of **338** to tetracycle **339** was accomplished with methanolic HCl in 5% yields, and as previously observed was scale dependent. The reaction failed to give any desired product **339** when attempted on scales greater than 8 mg.



Scheme 131: Accessing **339** via silyl chemistry.

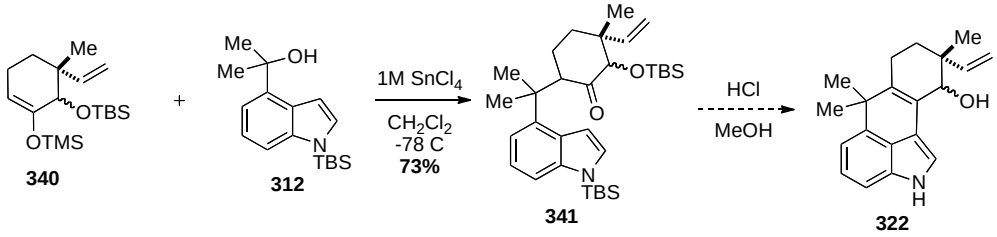
Given the scale dependences observed for all attempted systems with the α-TMSO-ketone, as well as the acid sensitivity of TMS groups, it was decided to employ a less sensitive silyl group, TBS. To screen the effect of the TBS group upon the silyl chemistry, the simplest system was chosen, namely **340** and indole **312**. Accessing the

TBS protected cyclohexyl system was accomplished from **64** employing the same conditions previously used with the exception of the TBS rather than TMS ether installation, Scheme 132.



Scheme 132: Formation of TBS protected alcohol of **340**.

Coupling **340** to indole **312** was undertaken via the same methodology previously discussed to afford tricycle **341** in 73% yields, which is only 14% lower when employing the TMS ether analog of **340**. As of date, subjecting **341** to methanolic HCl has only afforded **322** once with a less than 1% yield employing the same conditions outlined in Scheme 122.



Scheme 133: Attempts at accessing **322** via TBS protected alcohol rather than TMS.

3.8 Total Synthesis Summary

In summary, the symmetric total syntheses of *D,L*-hapalindoles J and U have been accomplished in 11% over eleven synthetic steps and 25% yield over thirteen synthetic steps, respectively, using a novel silyl strategy to access to the 6:5:6:6 tetracyclic carbon core. The route delineated gaining access to hapalindole J, in this body of work, is six

steps shorter, as well as 22-fold greater than the route Natsume employed in accessing the compound previously, and to date no other total syntheses have been reported.

From the perspective of the two previous syntheses of hapalindole U: Natsume's racemic synthesis of over twenty steps, with an overall 0.2% yield,[3] and the beautiful enantioselective effort by Baran over nine steps, with an overall 7.5% yield[4]), our work constitutes an efficient approach to the natural product. Although our strategy is similar to that of Natsume's route, it requires eight fewer steps and gives an eighty-fold greater yield, mostly due to the greatly enhanced efficiency of accessing the functionalized tetracycle core. Current efforts are being directed toward harnessing this approach to make isotopically labeled biosynthetic intermediates that we are presently investigating in the context of the biogenesis of these substances.

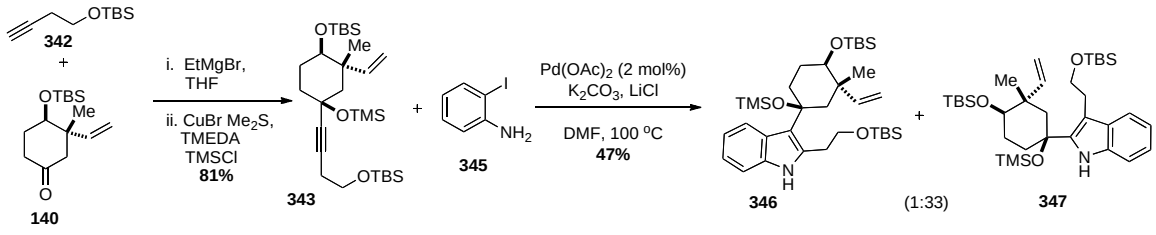
Chapter 4: Summary and Concluding Remarks

6.1: Summary of Progress

In our progress towards the total synthesis of tetracyclic hapalindoles and the ambiguines, we have shown that accessing a functionalized tetracyclic 5:6:6:6 core is problematic, mostly in regards to scale. The silyl chemistry approach that was developed does give rapid access to the desired allylic alcohol tetracyclic core, but is scale dependent. In the best case the reaction can be run on 75 mg of material (**320** to **322**), but in the worst case it can only be done on 8 mg of material (**338** to **339**). The suspected cause of this scale limitation is the TMS protected alcohol alpha to the ketone in the cyclohexyl species. The TMS group was chosen for its labile nature against acids so that a one-pot ring closure and deprotection could be performed, but it is that same labile nature that is proposed to be resulting in the scale restrictions. Given the scale limitations, the silyl strategy described in this body of work did allow for rapid access to **322** which was elaborated onto hapalindole U with an overall 16% yield over twelve synthetic steps from commercial available materials. In addition, this silyl strategy has allowed for highly functionalized tetracycles to be access, a proposed three steps from hapalindole K, as well as the ambiguine-functionalized core.

Multiple synthetic routes were attempted in gaining access to the tetracyclic core of the hapalindoles, many of which were not discussed in this body of work. To help reduce overlap in synthetic work, a brief summary of two key routes will be presented.

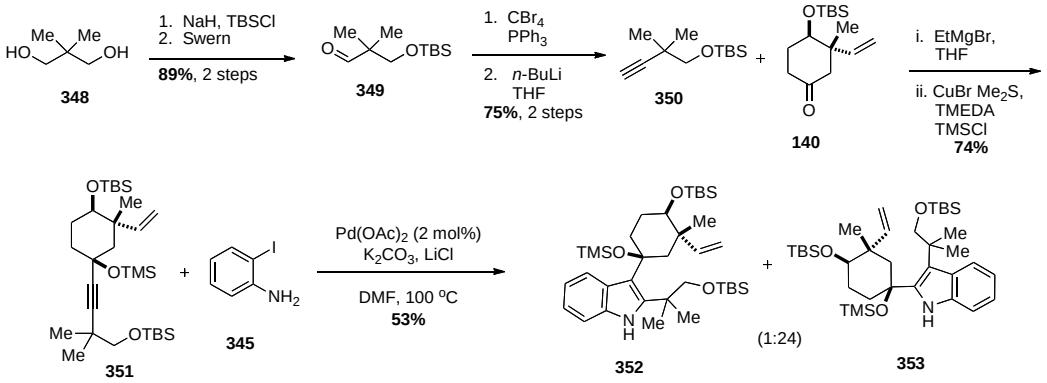
Prior to starting the oxidation/reduction (Section **3.2.6**) it was thought that the tetracyclic ring system could be assembled through a Larock indole synthesis,[9] in which an alkyne and *o*-iodoaniline are coupled to afford indole via a palladium reaction. While there is much precedence in the literature regarding Larock indole syntheses, it is also well known that when conducting this reaction the large substituent upon the alkyne will always end up at the C2 position of the indole ring being formed. This is due to the palladium species that is formed post-oxidative insertion onto *o*-iodoaniline to relieve steric congestion upon the species. With this, it was still thought to attempt the Larock indole synthesis upon alkyne **342** and *o*-iodoaniline (**345**). To this end, TBS protected alkyne **342** was added in a 1,2 fashion to **140** under standard cuprate conditions to afford **343** in 81% yields, Scheme 134. With **343** in hand, the Larock indole synthesis[9] was attempted with **345** under standard Larock conditions. The reaction did produce the desired tricycle **346**, but also formed the undesired regio-isomer product **347** in a 1:33 ratio (desired:nondesired). While it was expected that **347** would be the major product, due the substituent effect upon alkyne **343** in the Larock indole synthesis reaction, it was not expected to be 1:33.



Scheme 134: Intermolecular Larock indole synthesis attempt.

Given the poor selectively in the Larock indole synthesis shown in Scheme 134 it was thought that if addition "bulk" was placed upon the TBS ether side of the alkyne that the selectivity of the Larock method could be directed to give more of the desired regio-

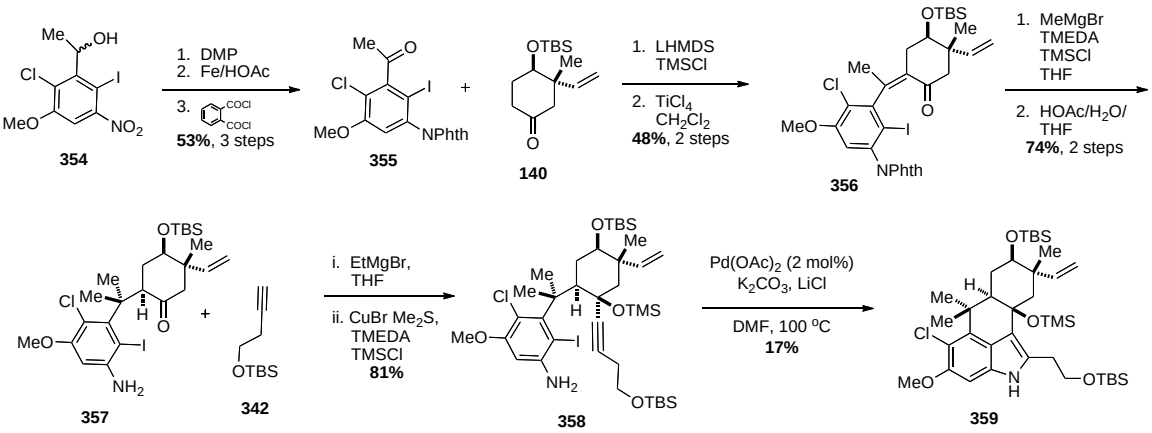
isomer, still noting that it was expected to form the undesired isomer just in a hopeful smaller ratio. Given that the ambiguines require a reverse prenyl group upon the C2 of the indole ring it was decided to place the gem-dimethyls earlier to help add the desired "bulk" to the alkyne. Selective mono TBS protection of **348** was accomplished via NaH and the use of 1.01 eq of TBSCl, to which the resulting compound was subjected to Swern oxidation conditions to afford **349** in 89% yield over two steps, Scheme 135. The aldehyde was elaborated into the desired alkyne under Corey-Fuchs conditions to afford **350** in 75% yields over two steps, employing the Ohira-Bestmann reagent could also be used for the same transformation in similar yields of 74%. Alkyne **350** was converted into the corresponding Grignard with EtMgBr, to which it was subjected to standard cuprate addition conditions to give 1,2 addition upon **140** to afford **351** in 74% yields. Alkyne **351** and **345** were subjected to LaRock indole synthesis conditions to afford the desired product **352** and undesired **353** in an overall 53% yield. Unfortunately, the additional two-methyl groups did not add sufficient "bulk" to the alkyne to sufficiently sway the isomer ratio to the desired in an amount that was productive.



Scheme 135: Second intermolecular LaRock indole synthesis attempt.

With the poor selectivity observed from the two attempted intermolecular LaRock indole syntheses, from the steric congestion inherit in the transition state, it was thought

to employ an intramolecular LaRock with a tethered systems that could only give the desired product. To this end, it was thought that an Mukaiyama aldol reaction could be employed to attach the required *o*-iodoaniline species, along with the required gem-dimethyls, to which the desired alkyne could be added upon the ketone to give the tethered system required for an intramolecular LaRock indole synthesis attempt. Starting from available material **354**, oxidation to the benzylic ketone was accomplished with DMP, followed by nitro reduction to the amine with subsequent phthalimide formation to afford **355** in 53% yields over three steps, Scheme 136. Treating **140** with LHDMS followed by TMSCl afforded the required TMS-enol ether to which a Mukaiyama aldol reaction upon ketone **355** was conducted to afford **356** in 48% yields over two steps. Methyl cuprate addition followed by TMS-enol ether cleavage afforded **357** in 74% yields overs two steps. Alkyne **342** was added in a 1,2 fashion to afford **358** which was subjected to an intramolecular LaRock to afford tetracycle **359** in 17% yields. Upon obtaining this result, the Lewis-acid coupling approach in section **3.6.3** began to give access to the tetracycle desired in fewer steps and greater yields, thus this route was tabled in favor of the Lewis-acid approach.



Scheme 136: Intramolecular LaRock indole synthesis.

6.2: Concluding Remarks

Given the problematic nature of the TMS protected α-hydroxyketone, attention should be efforts should be placed towards screening TBS in this roll for possible allylic alcohol tetracycle formation. Likewise, employing a protecting group that is not acid liable should be explored to protect the α-hydroxyketone, such as a PMB or MOM group. Employing such groups should still allow for the methanolic HCl ring closure to the tetracylic with protected alcohol that could be de-protected to return the desired allylic alcohol. The advanced substrates discussed in section **3.7** need to be elaborated onto their corresponding natural products, which should be accessible with the chemistry outlined in this body of work: compound **339** to ambiguine A, **332** to hapalindoles A, B, O, epi G and L, and **329** to hapalindole K. Also, attention should be placed upon the intramolecular Indole synthesis route described in this chapter. This route does allow for access to highly functionalized systems. Synthesis of the desired **354**, containing no Cl or methoxy, should be made and coupled to **140**. Continuing the efforts delineated in this body of work with the methodologies described should afford multiple natural product synthesis in addition to the ones presented.

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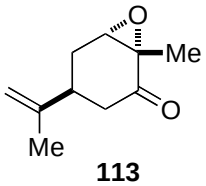
Chapter 5: Experimentals

7.1: General Considerations

^{1}H and ^{13}C NMR spectra were recorded on Varian DPX-300 spectrometer or a Varian DPX-400 spectrometer where indicated. Low-resolution mass spectra (MS) were obtained at 50-70 eV by electron impact (EI). Chemical ionization mass spectra (CIMS) were obtained using isobutane as a carrier gas. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. Intensities of signals were estimated as vs = very strong, s = strong, m =medium, w = weak, b = broad. Chemical shifts (ppm) are relative to TMS used as an internal standard. The multiplicity were marked as s =singlet, d = dublet, t = triplet, q = quartet, qu quintet, m = multiplet. Melting points are uncorrected. Flash column chromatography was carried out using Sorbent Technologies stand grade silica gel (230 x 400 mesh). Analytical and preparative thin-layer chromatography (TLC) were performed on EM Science silica gel 60 PF_{254} plates. All non-aqueous reactions were performed under an inert atmosphere of argon in flame-dried glassware, containing a stir bar, unless otherwise noted. Anhydrous diethyl ether (Et_2O), toluene (PhMe), *N*,*N*-dimethylforamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), methanol (MeOH), benzene, triethylamine (TEA), diisopropylamine, acetonitrile and tetrahydrofuran (THF) were obtained via a dual column solvent purification system

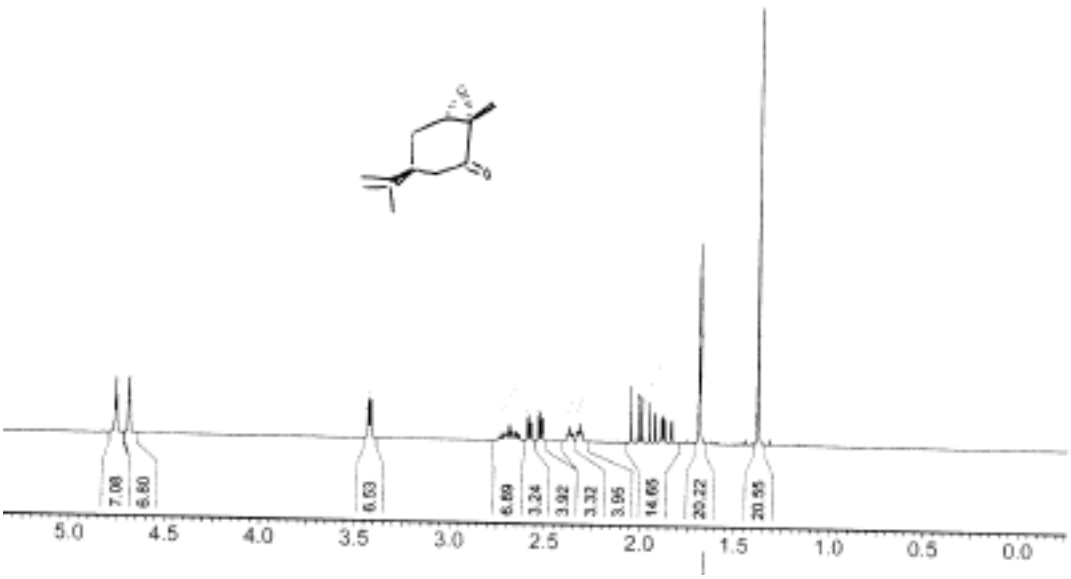
(J.C. Meyer of Glass Contour). All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Organic extracts were dried with Na_2SO_4 (unless otherwise noted) before filtration and concentration under reduced pressure.



113

(S)-epoxy-(S)-carvone (113). To a 25 mL round bottom flask sodium hydroxide (114 mg, 2.87 mmol, 0.9 eq.) was added to methanol (1 mL) and stirred. Once a majority of the sodium hydroxide dissolved the flask was placed into a water bath and H_2O_2 (4.60 mL, 47.85 mL, 15 eq) was added drop wise and left to stir for 10 min. Carvone (0.5 mL, 5.19 mmol, 1 eq.) was added via syringe and left to stir at rt for 5 h. The reaction was quenched with brine and extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc in hexane) to afford product **113** in 78% yields (260 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 4.70 (d, 2H), 2.70 (d, 1H), 2.5 (m, 2H), 2.00 (m, 2H), 1.70 (s, 3H), 1.45 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 205, 150, 110, 61, 60, 41, 38, 30, 21, 18; **HMRS-FAB**: [M+H] calcd for $C_{10}H_{14}O_2$, 167.10; found, 167.10648.


7.08
6.80
6.03
6.89
3.24
3.92
3.32
3.95
14.65
20.22
20.55
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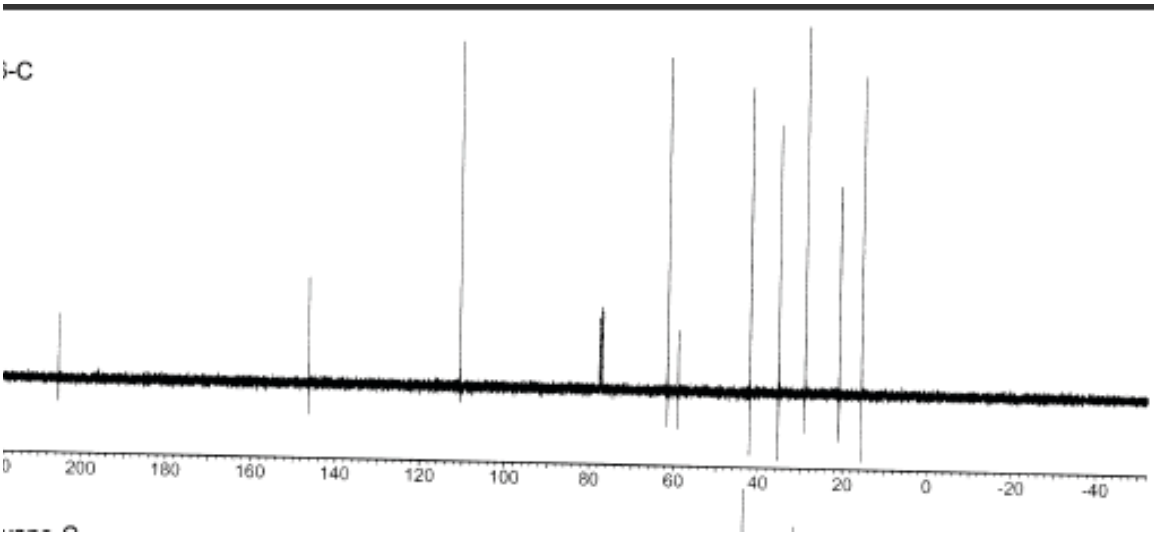
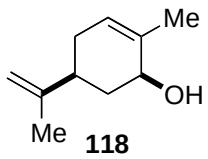
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

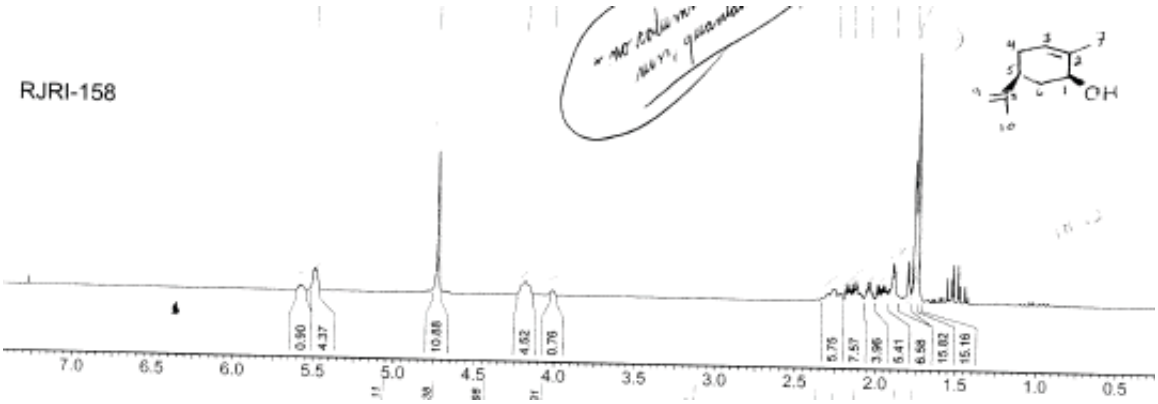

200
180
160
140
120
100
80
60
40
20
0
-20
-40



118

(S)-Carveol (118). To a 50 mL round bottom flask THF (10 mL) cooled to -78 ℃ and (S)-carvone (1.09 mL, 7.00 mmol, 1 eq.) was added. After being stirred for 5 min DIBAL-H (1 M THF solution, 14.0 mL, 14 mmol, 2 eq.) was added drop wise via syringe and stirred at -78 ℃ for 4 h. The reaction was quenched with 1.0 M HCl and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 89% yields (980 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ See below; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 150, 138, 122, 110, 71, 38, 35, 21, 20.


RJRI-158
OH
0.90
4.37
10.88
4.62
0.76
5.75
7.57
3.96
5.41
6.58
15.82
15.16
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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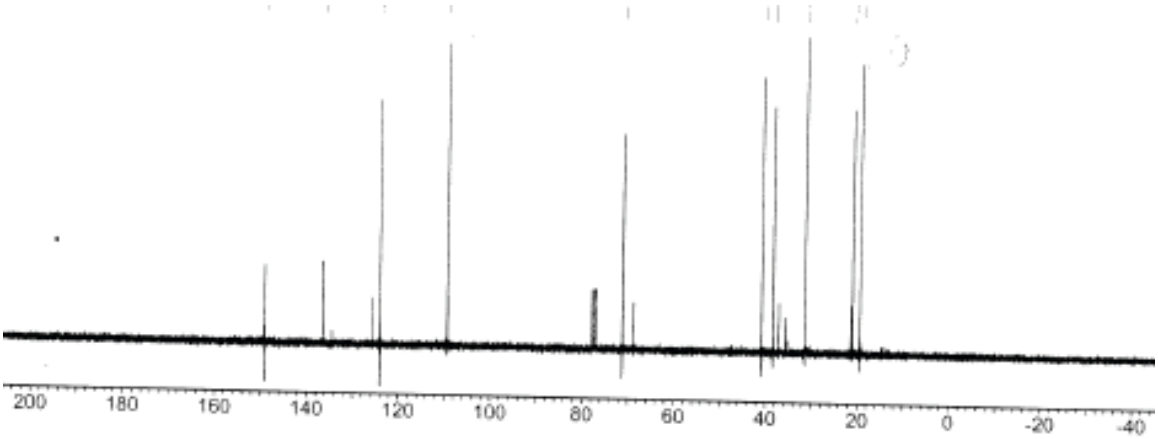
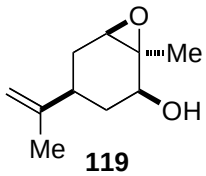
3.0
2.5
2.0
1.5
1.0
0.5

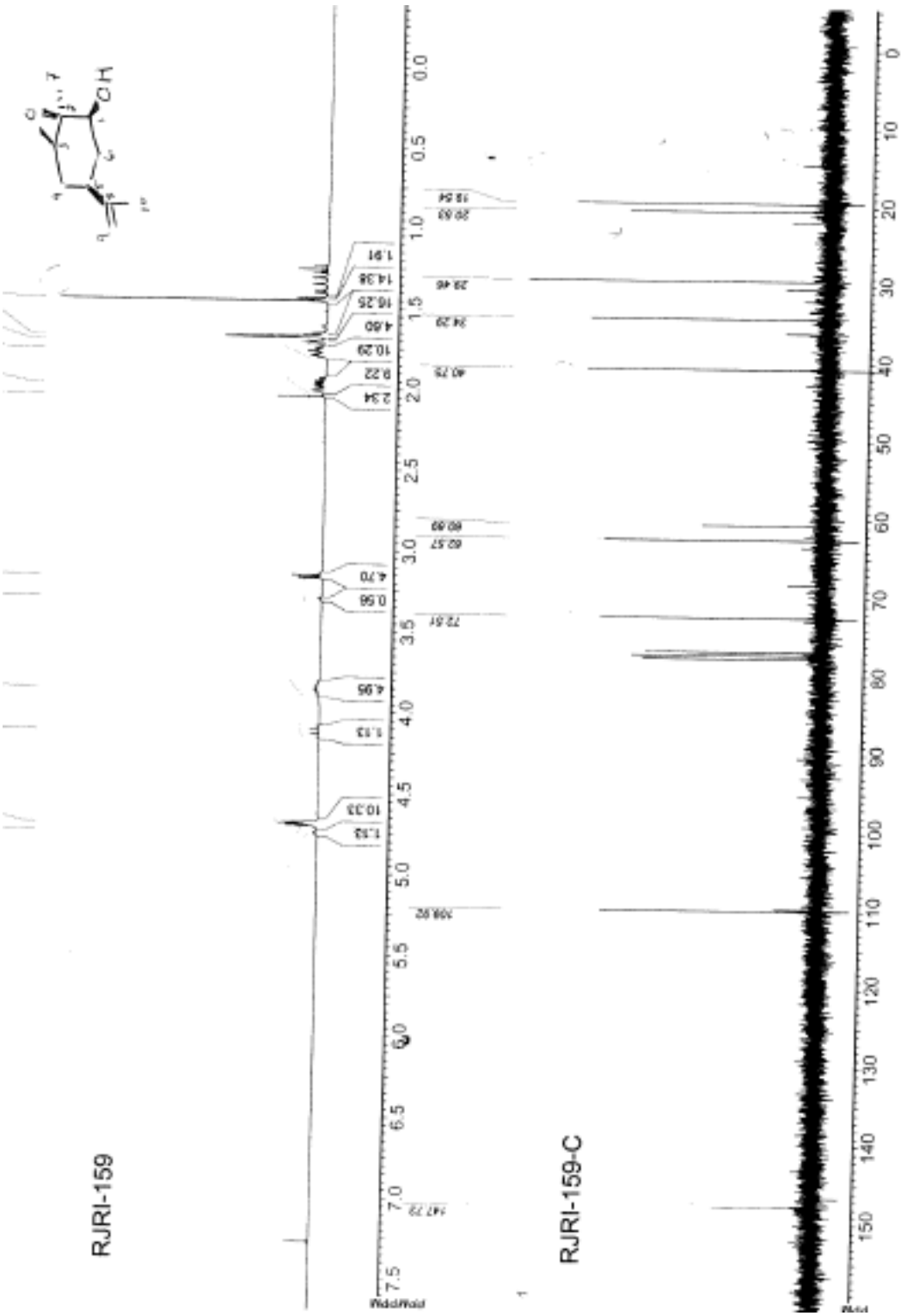

200
180
160
140
120
100
80
60
40
20
0
-20
-40



119

Cis-epoxy-cis-(S)-carveol (119). In a 10 mL round bottom flask (S)-carveol **(118)** (50 mg, 0.33 mmol, 1 eq.) was added to methylene chloride (2 mL). After stirring for 5 min mCPBA (87 mg, 0.39 mmol, 1.2 eq.) was added and stirred at rt for 5 h. The reaction was quenched with saturated $Na_sS_sO_3$ and extracted with methylene chloride (2 x 5 mL). The organic layers were combined, washed with potassium carbonate, brine and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 8% yields (5 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ See below; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ See below.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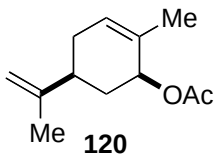
RJRI-159-C

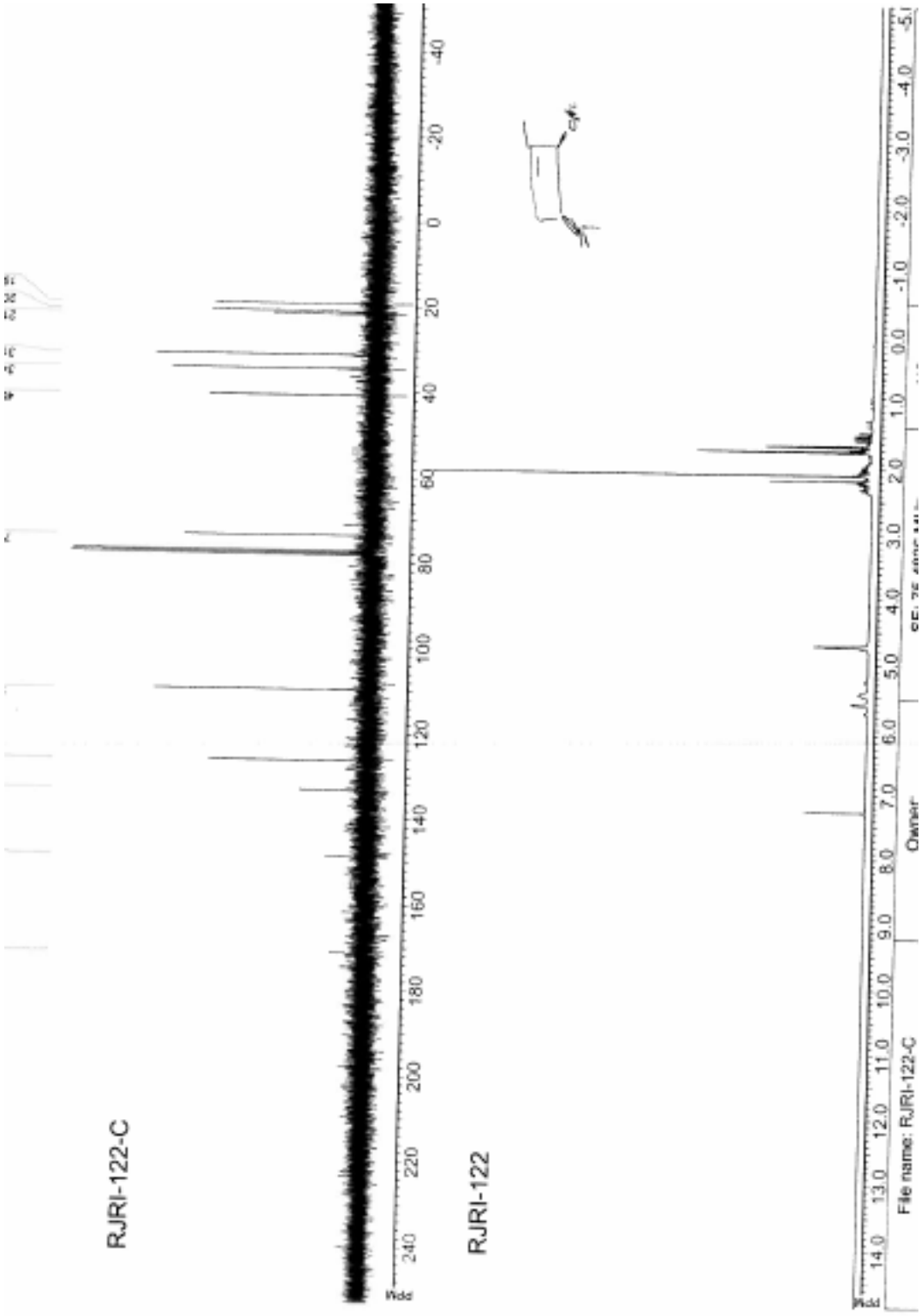


120

Cis-O-acetyl-cis-(S)-carveol (Route 1) (120). In a 100 mL round bottom flask (S,S)-carveol (1.00 g, 6.57 mmol, 1 eq.) was added to THF (40 mL). After stirring for 5 min NaH (289 mg, 7.23 mmol, 1.1 eq.) was added. After stirring for one-hour acetyl chloride (1.88 mL, 26.28 mmol, 4 eq.) was added and stirred at rt for 48 h. The reaction was quenched with 1.0 M HCl and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc in hexane) to afford a clear oil product in 65% yields (845 mg).

Route B (f): In a 5 mL round bottom flask (S,S)-carveol (30 mg, 0.197 mmol, 1 eq.) was added to THF (2 mL). After stirring for 5 min NaH (8.68 mg, 0.217 mmol, 1.1 eq.) was added. After stirring for one-hour acetic anhydride (0.07 mL, 0.788 mmol, 4 eq.) was added and stirred at rt or 48 h. The reaction was quenched with 1.0 M HCl and extracted with EtOAc (3 x 4 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc in hexane) to afford a clear oil product in 74% yields (28 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ Only crude taken; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 170.2, 148.5, 135.8, 122.7, 74.3, 32.0, 31.8, 22.1, 20.8; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{12}H_{18}O_2$, 195.13; found, 195.1209.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RJRI-122
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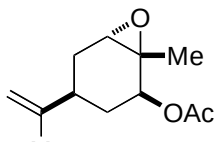
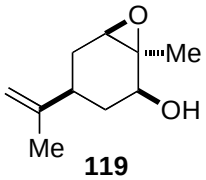


121

To a solution of **120** (20 mg, 0.103 mmol, 1.0 eq.) in DCM (5 mL) was added *m*CPBA (77% pure, 28 mg, 0.13 mmol, 1.2 eq.) and stirred at rt. The reaction was quenched 24 h later with saturated $Na_2S_2O_3$, extracted with DCM, washed with brine, dried and concentrated. The material was purified via flash silica gel chromatography (1:8 EtOAc:hexane) to afford product in 35% yields (8 mg).

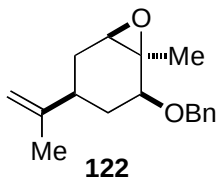
^{1}HNMR: (300 MHz, $CDCl_3$) δ 4.70 (d, 2H), 2.70 (d, 1H), 2.5 (m, 2H), 2.00 (m, 2H), 1.70 (s, 3H), 1.45 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 205, 150, 110, 61, 60, 41, 38, 30, 21, 18.



119

To a solution of **118** (50 mg, 0.33 mmol, 1.0 eq.) in DCM (2 mL) was added *m*CPBA (77% pure, 87 mg, 0.39 mmol, 1.2 eq.) and left to stir at rt. The reaction was quenched 3 h later with saturated $Na_2S_2O_3$, washed with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 57% yields (31 mg).

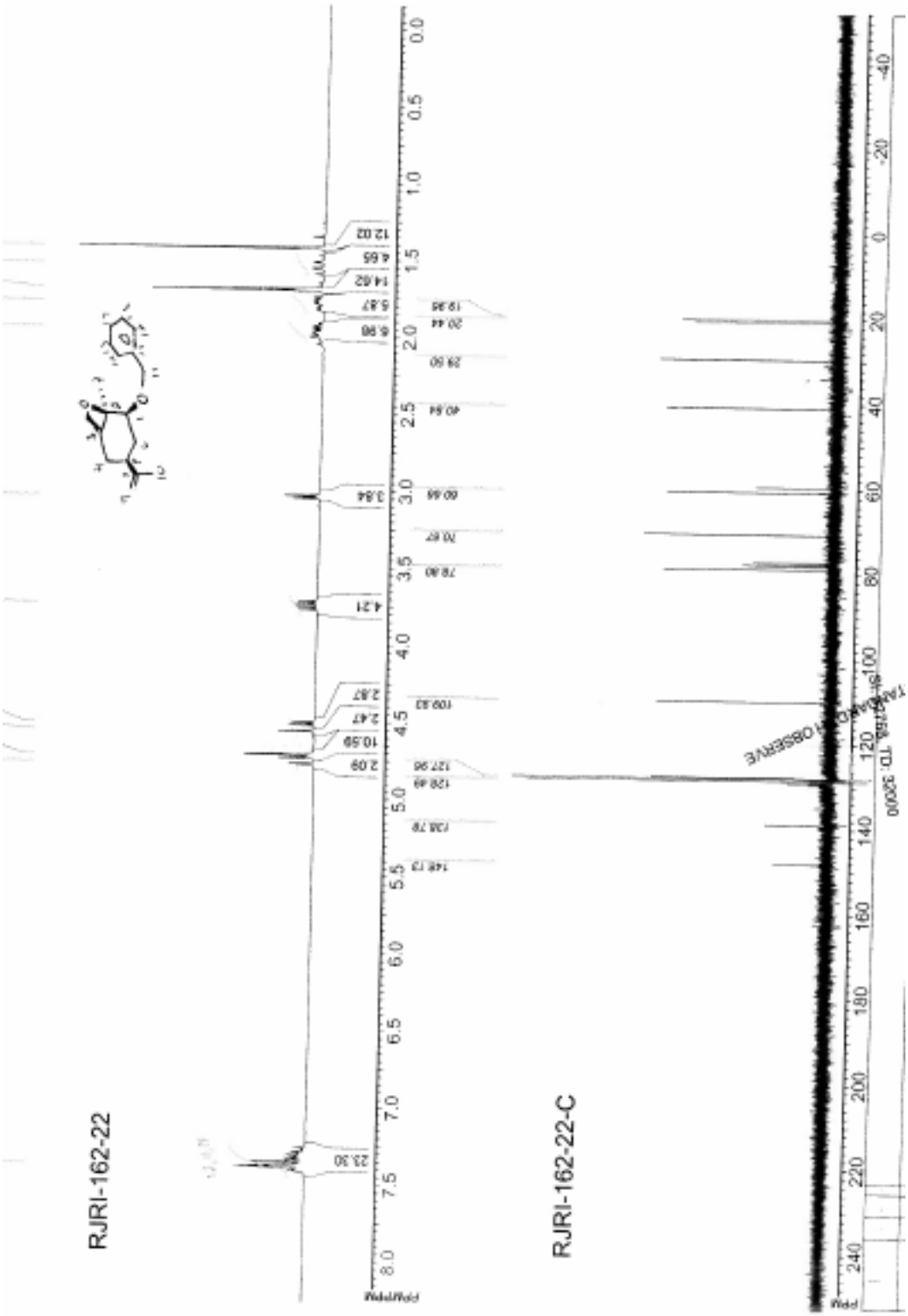
^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.09-4.89 (m, 2H), 3.6 (bs, 1H), 3.49 (t, 1H), 2.98 (t, 1H), 2.25 (m, 1H), 1.92 (s, 3H), 1.81-1.46 (m, 4H), 1.30 (s, 3H).

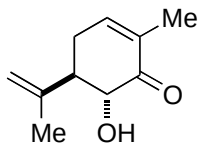


122

O-Benzyl-(R)-epoxy-(*S*,*S*)-carveol (15). In a 10 mL round bottom flask containing THF (4 mL) and DMF (0.5 mL) was added (**119**) (60 mg, 0.357 mmol, 1 eq.). Sodium hydride (17.12 mg, 0.428 mmol, 1.2 eq.) was added to the stirring solution and left to stir at rt for 2.5 h. Benzyl chloride (0.051 mL, 0.428 mmol, 1.2 eq.) was then added and left to stir at rt for 5 h. The reaction was quenched with brine, extracted with EtOAc, washed with water then brine, dried and concentrated. The crude liquid was purified by flash silica chromatography (1:4 EtOAc:hexane) to afford product in 72% yields (66 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ See below; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ See below; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{17}H_{22}O_2$, 259.17; found, 259.1604.

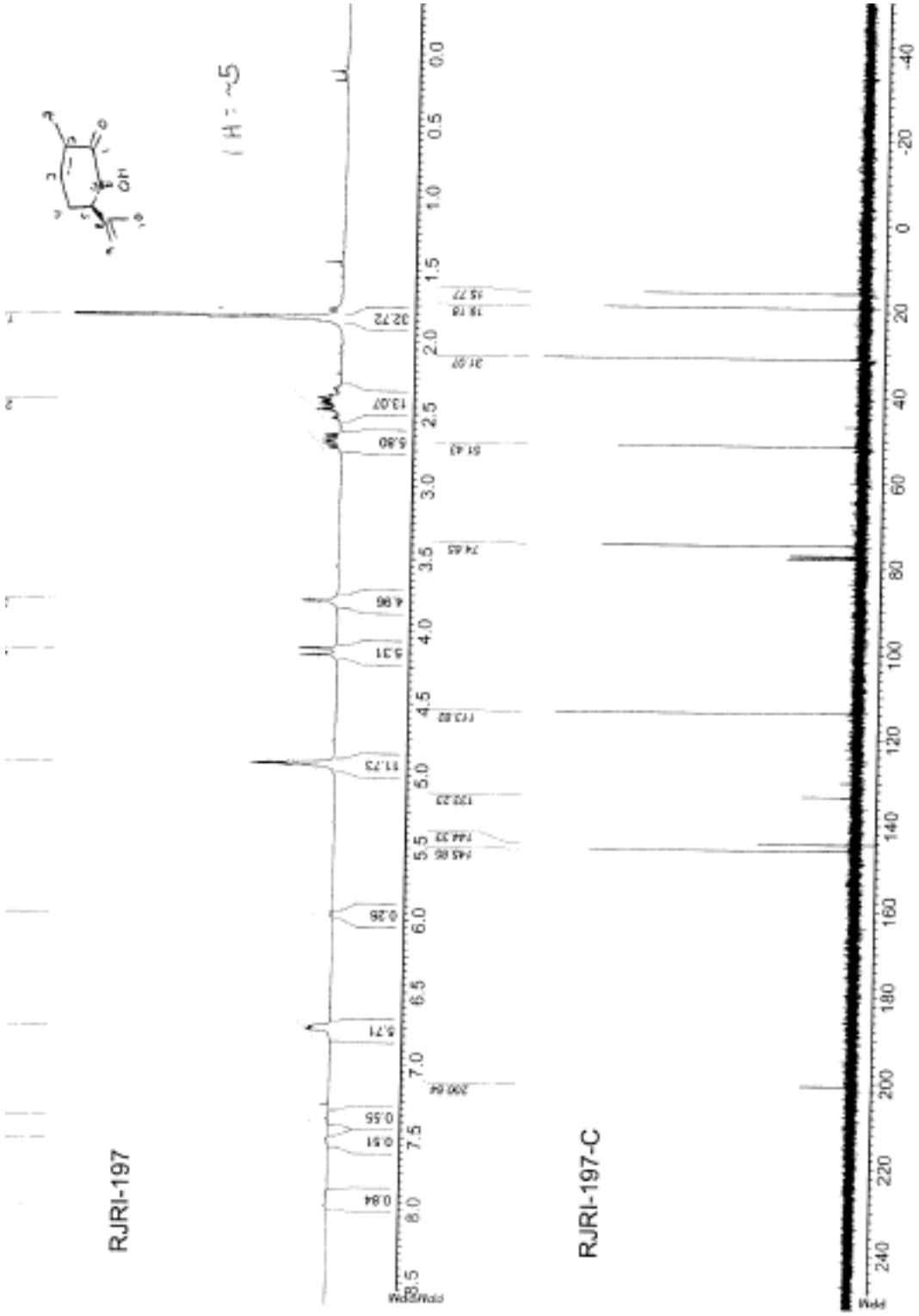

RJRI-162-22
RJRI-162-22-C

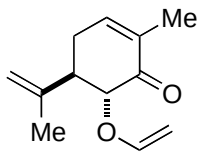


129

Compound 129: To a cooled solution -78 ℃ of **(105**) (1 mL, 6.4 mmol, 1.0 eq.) in THF (40 mL) was added LHMDS (1 M in THF, 7.7 mL, 7.7 mmol, 1.2 eq.) and stirred at the same temperature. After 1 h TMSCl (0.97 mL, 7.7 mmol, 1.2 eq.) was added and left to stir, 45 min later the reaction quenched with the addition of brine, poured onto a pre-mixed brine:hexane (50 mL, 1:1), and extracted with hexane. The organic layers were combined, washed with brine, dried and concentrated. The crude material (1.36 g, 6.2 mmol, 1.0 eq.) was dissolved in DCM (40 mL) and cooled to 0 ℃ to which *m*CPBA (77% pure, 1.64 g, 7.4 mmol, 1.2 eq.) was added. The reaction was quenched 2 h later with saturated $Na_2S_2O_3$, extracted with DCM, washed with saturated $NaHCO_3$, water and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:5 EtOAc:hexane) to afford product in 76% yields (808 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ See below; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ See below.

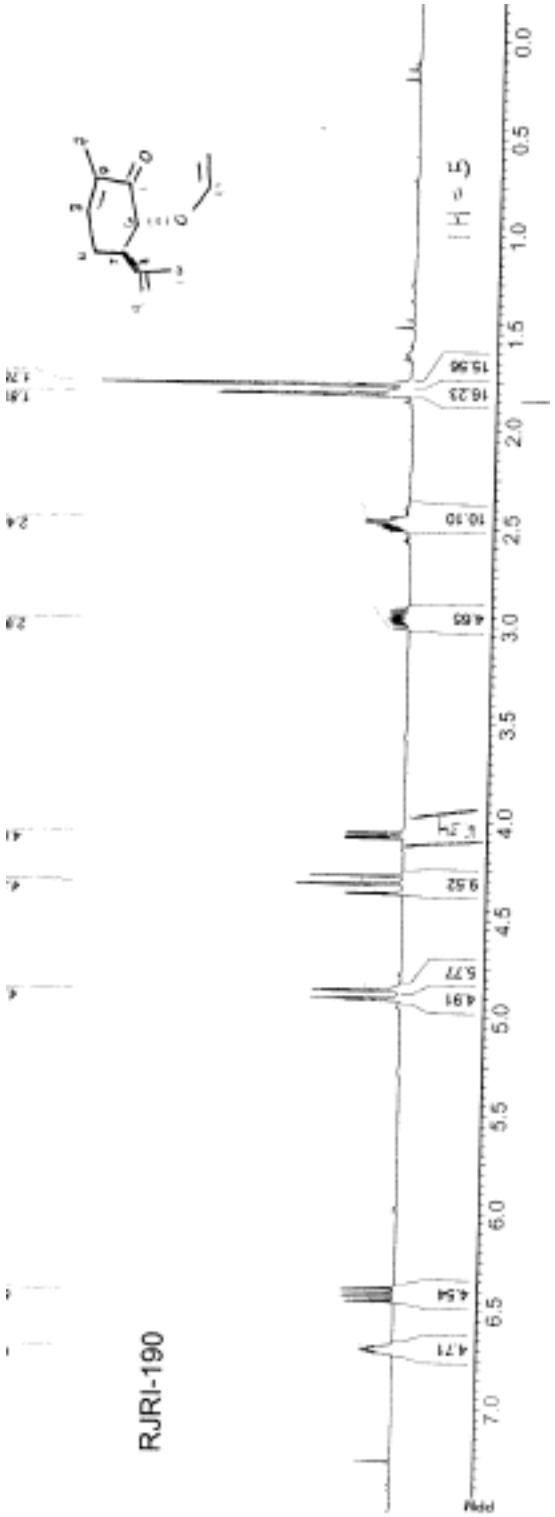

RJRI-197
RJRI-197-C



130

To a solution of **129** (500 mg, 3.01 mmol, 1.0 eq.) in neat ethylvinyl ether (22 mL, 2.0 eq.) was added freshly recrystallized $Hg(OAc)_2$ (978 mg, 3.1 mmol, 1.02 eq.) and brought to reflux. After 14 h, the reaction was cooled and glacial acetic acid (0.1 mL) was added followed by 5% KOH solution (50 mL) and Et_2O (150 mL), extracted with Et_2O, washed with water and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 52% yields (300 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ See below; **^{13}CNMR:** (75 MHz, $CDCl_3$) δ See below.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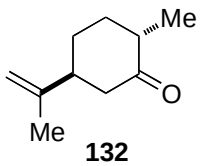
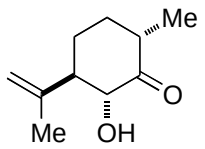
4.71
PPM



132

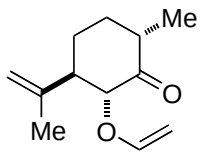
Reduced carvone (**132**). To a 50 ml round bottom flask was added THF (20 mL) and S-carvone (0.30 mL, 1.92 mmol, 1 eq.) and left to stir while cooling to -78℃. To this was added L-selectride (2.02 mL, 2.02 mmol, 1.05 eq.) dropwise over a 15 min period and left to stir at -78℃. After 3 hours 10 mL of a 1:1 (30%H_2O_2/2N NaOH) solution was added to the reaction and was left to stir. The resulting solution was left to stir until it reached rt, over the course of 12h, and was diluted with EtOAc, washed with 1 N HCl, sat'd $NaHCO_3$ and brine. The organic layer was dried and concentrated to afford a 4:1 mixture of diastereomers. The resulting crude oil was used without purification (292 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.2-4.9 (dd, 2H), 2.62-1.93 (m, 7H), 1.82 (s, 3H), 1.79-1.62 (m, 1H), 1.11 (d, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 208.2, 147.8, 115.2, 47.3, 46.1, 45.9, 35.6, 30.3, 21.7, 15.0.



128

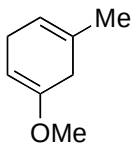
(S)-6-Hydroxyl-reduced carvone (**132**) To a 100 mL round bottom flask was added THF (0.1 M) and diisopropylamine (## mL, ## mmol, 1.2 eq.) and left to stir while cooling to -78℃. To this was added 1.6 M n-BuLi (## mL, ## mmol, 1.2 eq.) dropwise over 10 min and left to stir at 078℃ for 15 min. Compound **132** (## mL, ## mmol, 1.0 eq.) was added via syringe to the flask, after 40 min TMSCl (## mL, ## mmol, 1.5 eq.) was added and left to stir for 30 min. To the reaction brine (20 mL) was added and then the reaction was immediately poured into a separatory funnel containing 100 mL of 1:1 brine/hexane. The organic layer was washed with water once and dried over anhydrous $MgSO_4$ and concentrated. To another 100 mL round bottom flask containing DCM (## mL) the crude oil was dissolved and stirred for 10 min. While stirring at rt mCPBA (## mg, ## mmol, 1.8 eq.) was added and left to stir until there was no presence of starting material present by TLC. The reaction was quenched with brine and the aqueous layer extracted with DCM. The organic layers were combined, washed with water (2 x 20 mL), sat'd $NaHCO_3$ and brine, and dried with anhydrous $MgSO_4$ and concentrated. The resulting crude oil was purified by flask silica gel chromatography (1:4 EtOAc:hexane) to afford product in 31% yield over 2 steps.



133

(*S*)-6-Vinyl ether-reduced carvone (**133**) To a 50 mL 2-neck flask was added ethyl vinyl ether (22 mL, 3.07 mmol, 1.02 eq.) and (**128**) (500 mg, 3.01 mmol, 1 eq.) and left to stir at rt for 2 h. Mercury (II) acetate (978 mg, 3.07 mmol, 1.02 eq.) was added to the reaction flask and brought to reflux for 20 h. The flask was removed from heat and allowed to cool to rt, then glacial acetic acid (0.07 mL) was added and left to stir for 3 h. The reaction was then poured into a separatory funnel containing 5% KOH (50 mL) and diethyl ether (150 mL). The aqueous layer was extracted with ether (2 x 10 mL). The organic layers were combined, washed with water (3 x 20 mL) and brine, and then dried with anhydrous $MgSO_4$ then concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford the desired product in 26% yields (152 mg).

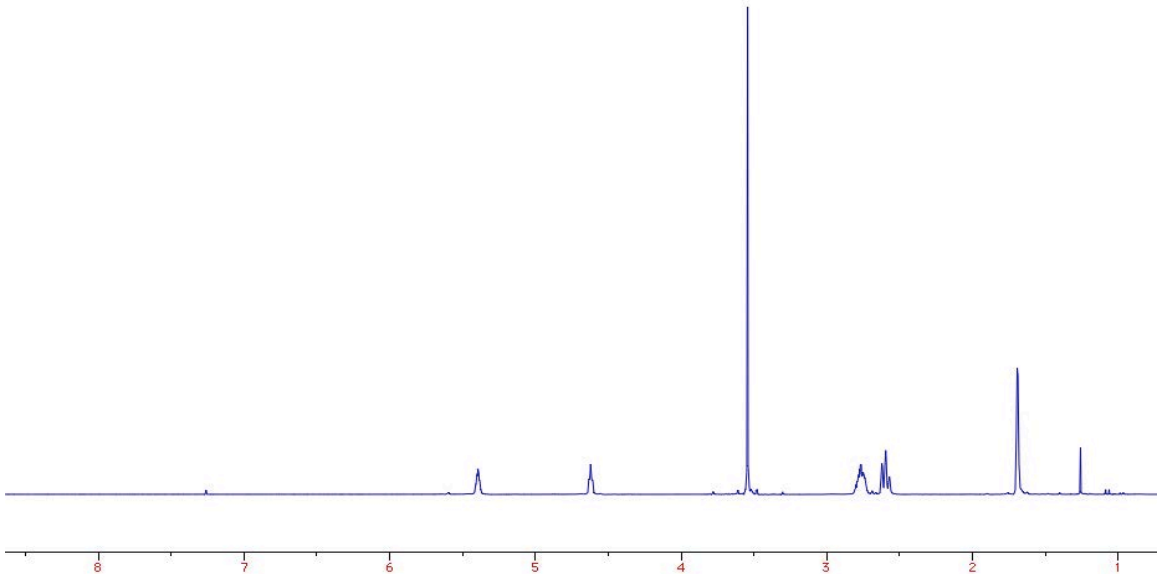
^{1}HNMR: (300 MHz, $CDCl_3$) δ 6.20 (dd, 1H), 5.21-4.92 (dd, 1H), 4.90-4.82 (dd, 2H), 4.25 (d, 1H), 2.78-2.41 (m, 2H), 2.01-2.45 (m, 2H), 1.82 (s, 3H), 1.72-1.50 (m, 2H), 1.11 (d, 3H).



135

1-Methoxy-5-methylcyclohexa-1,4-diene (**135**) A 500 mL 3-necked round bottom flask equipped with a dry-ice condenser was purged with argon and cooled to -78℃ after which ammonia (193 mL, 7728 mmol, 120 eq.) was condensed into said flask. *m*-Methylanisole (8.11 mL, 64.4 mmol, 1 eq.) in ether (80.2 mL, 772.8 mmol, 12 eq.) was added to the flask followed by *t*-butanol (82 ml, 869 mmol, 13.5 eq.) and left to stir at -78℃ for 10 min. Lithium wire (2.2 g, 322 mmol, 5 eq.) was added to the solution over a 30 min period and left to stir at -78℃ for 6 h. The reaction was quenched with solid ammonium chloride and stirred for 2 h. Gentle heating, 33℃, of the reaction evaporated the ammonia. Once the ammonia was removed, the resulting solution was diluted with 150 mL of pentane and then poured onto 200 mL of 1:1 water:pentane. The pentane layer was washed with water (3 x 50 mL), dried with anhydrous $MgSO_4$ and concentrated to afford product in 99% yields (7.9 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.41-5.38 (m, 1H), 4.63-4.61 (m, 1H), 3.54 (s, 3H), 2.80-2.73 (m, 2H), 2.59 (t, 8.2, 7.5 Hz, 2H), 1.69 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 153.1, 130.7, 118.9, 90.5, 53.9, 33.4, 27.0, 23.0.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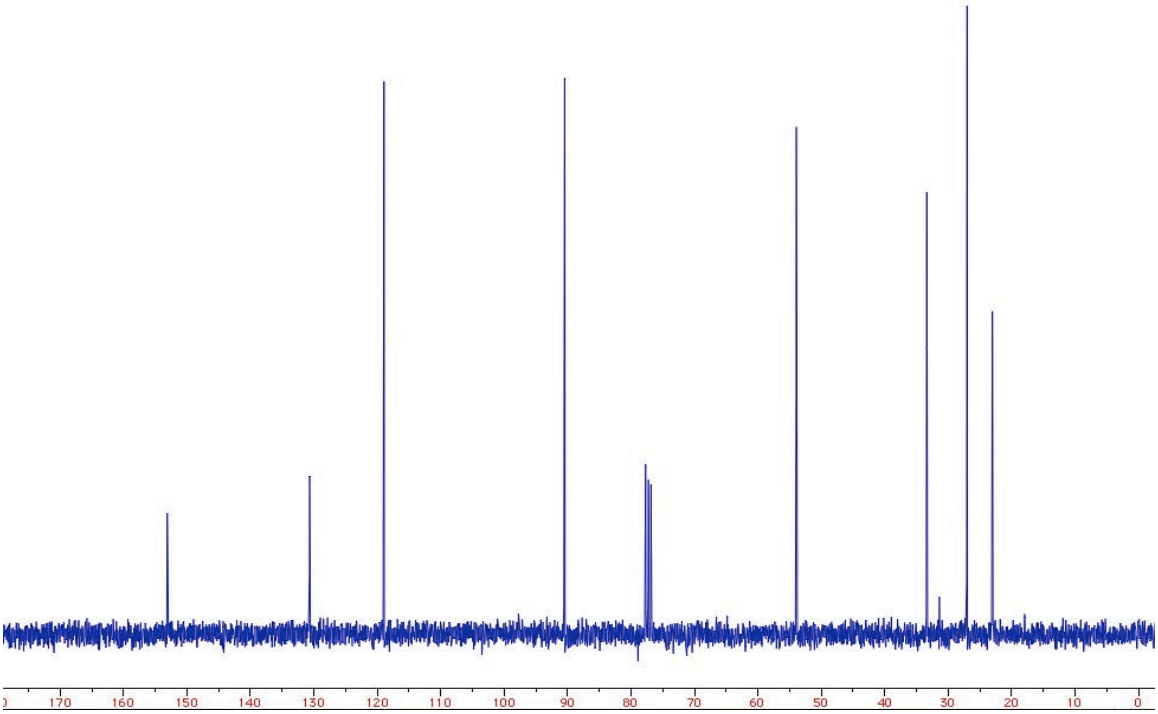
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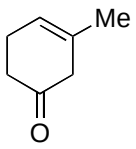
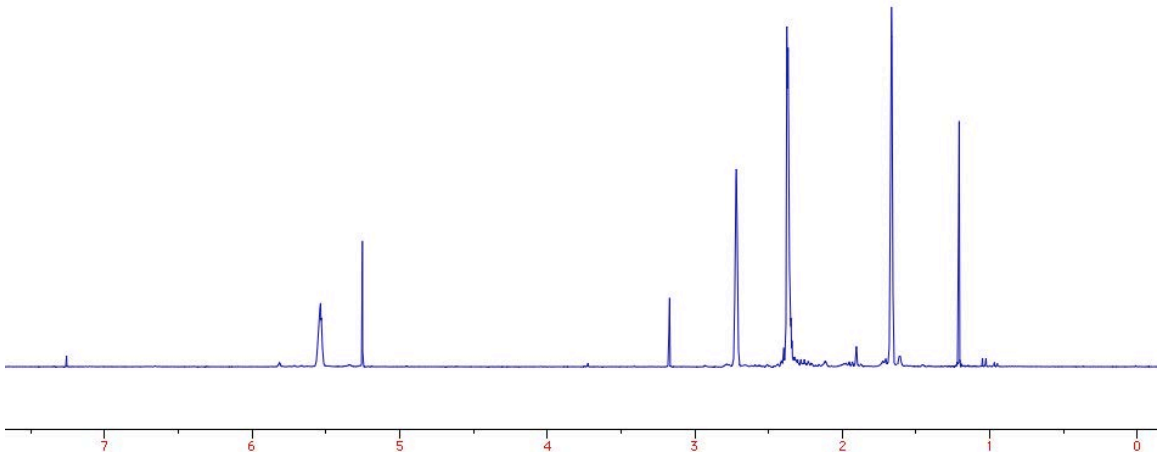


136

3-Methylcyclohex-3-enone (**c**) To a 25 mL round bottom flask was added 32 mL of 3:1 methanol:water and oxalic acid (64 mg, 0.704 mmol, 0.044 eq.) and stirred at rt for 5 min. (#) (2 g, 16 mmol, 1 eq.) was added and left to stir at rt. After 1 h the reaction was diluted with water and extracted with DCM (3 x 20 mL), washed with water, dried over anhydrous $MgSO_4$ and concentrated. The resulting oil was used without purification, with 95% yields (1.7 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.541 (bs, 1H), 2.719 (bs, 2H), 2.397-2.341 (m, 4H), 1.665 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 210.9, 132.3, 121.1, 44.6, 38.5, 25.2, 22.9; **IR:** (Thin Film) 1634; **HMRS-FAB**: $[M+H]^+$ calcd for $C_7H_{10}O$, 110.07; found, 110.0743.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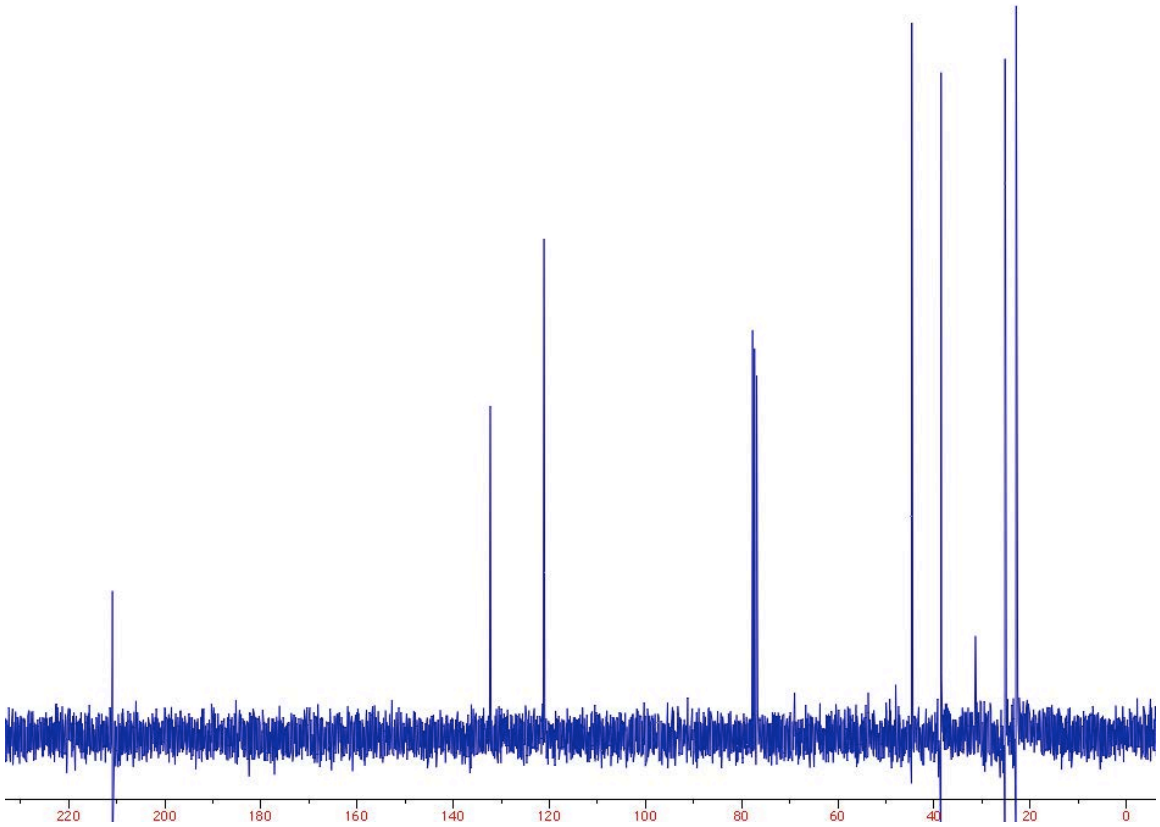
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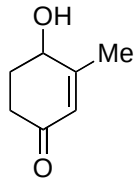
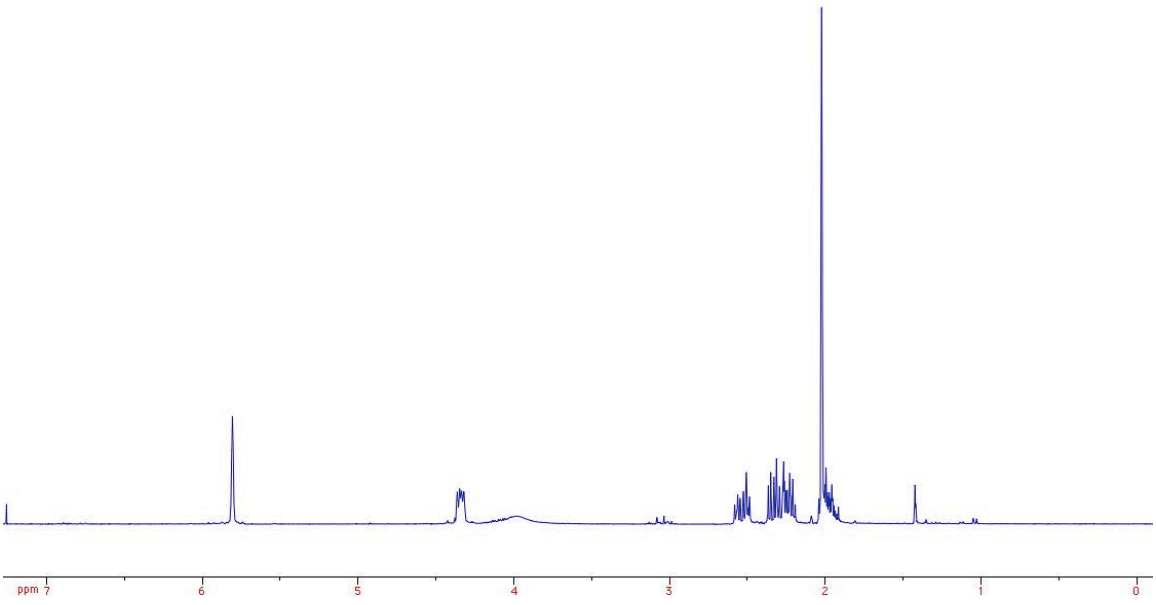


137

4-Hydroxyl-3-methylcyclohex-2-enone (**137**) To a 500 mL round bottom flask was added DCM (190 mL), (**136**) (2.1 g, 19.06 mmol, 1 eq.) then mCPBA (5.11 g, 22.87 mmol, 1.2 eq.) and stirred at rt for 3 h. The reaction is quenched with 100 mL of a 50% $NaCO_3$ solution. The organic layer is separated and placed back into the same round bottom flask and triethyl amine (5.3 mL, 38.12 mmol, 2 eq.) is added and stirred at rt for 3.5 h. The reaction is quenched with brine (50 mL) and extracted with DCM (2 x 50 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, concentrated and purified by flash silica gel chromatography (1:1 EtOAc:hexane) to afford product in 92% yields (2.2 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.806 (bs, 1H), 4.363-4.321 (m, 1H), 3.994 (bs, 1H), 2.581-2.485 (m, 1H), 2.366-2.193 (m, 2H), 2.024 (s, 3H), 2.003-1.915 (m, 1H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 199.9, 164.8, 126.9, 68.7, 35.1, 32.1, 20.9; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+Na]^+$ calcd for $C_7H_{10}O_2Na$, 149.06; found, 149.0614.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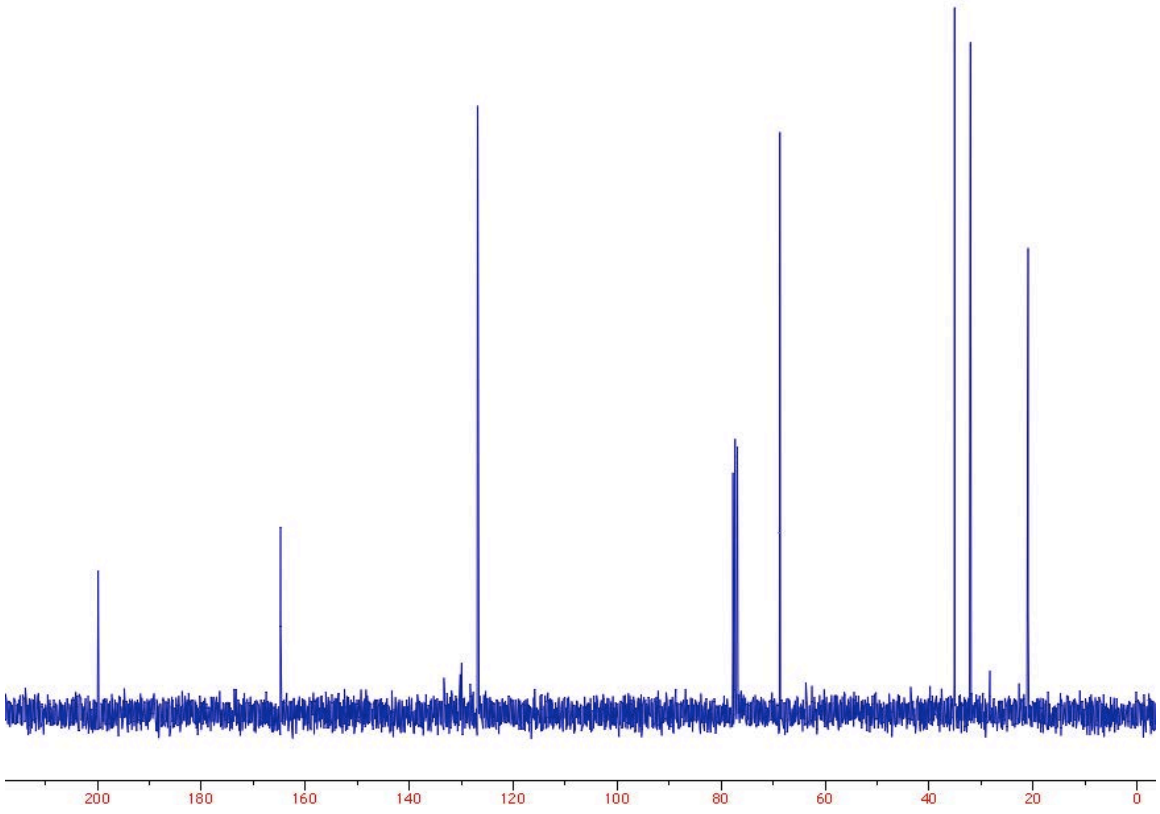
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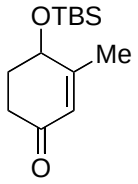
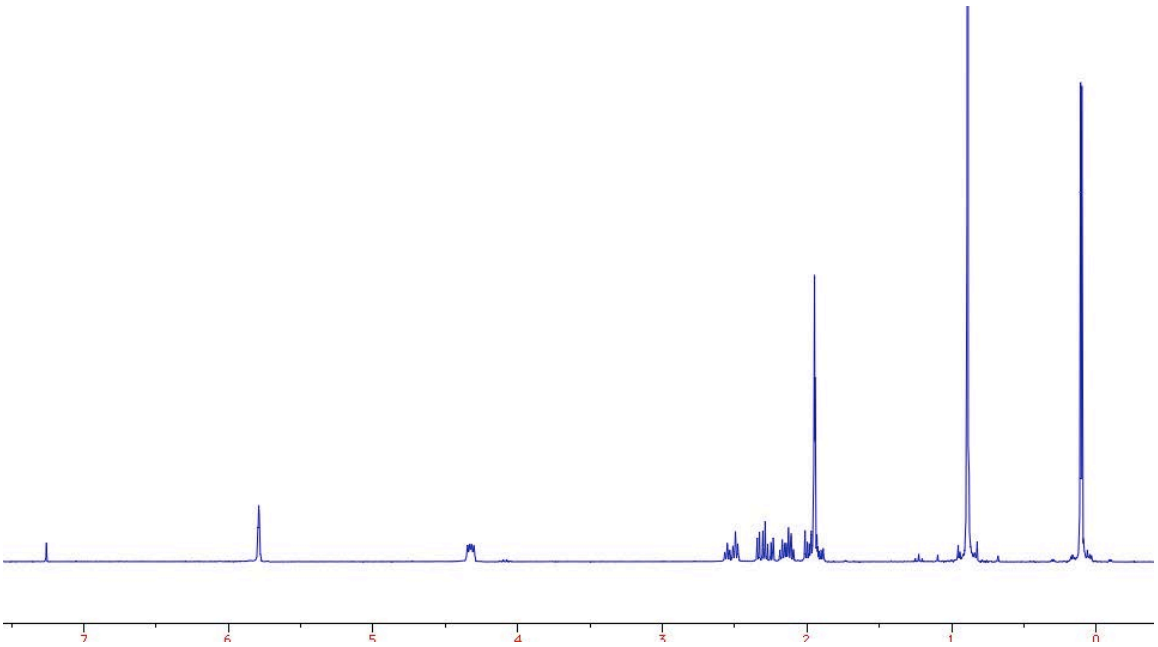


138

4-(*t*-Butyldimethylsilyloxy)-3-methylcyclohex-2-enone (**138**) To a 250 mL round bottom flask was added DMF (125 mL), (**137**) (2.38 g, 19.06 mmol, 1 eq.), imidazole (1.6 g, 22.87 mmol, 1.2 eq.) and TBSCl (3.4 g, 22.87 mmol, 1.2 eq.). The reaction was left to stir until the disappearance of all starting material, monitored by TLC (typically between 20 and 26 h). The reaction was quenched with brine and extracted with hexane (3 x 75 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in quantitative yields (4.6 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.791 (s, 1H), 4.346-4.303 (m, 1H), 2.568-2.479 (m, 1H), 2.344-2.234 (m, 1H), 2.186-2.094 (m, 1H), 2.013-1.970 (m, 1H), 1.948 (s, 3H), 0.889 (s, 9H), 0.109 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 198.9, 164.5, 126.8, 69.8, 35.3, 32.8, 25.9, 21.3, 18.3, -4.1; **IR:** (Thin Film) 1721; **HMRS-FAB**: $[M]^+$ calcd for $C_{13}H_{24}O_2Si$, 240.15; found, 240.1576.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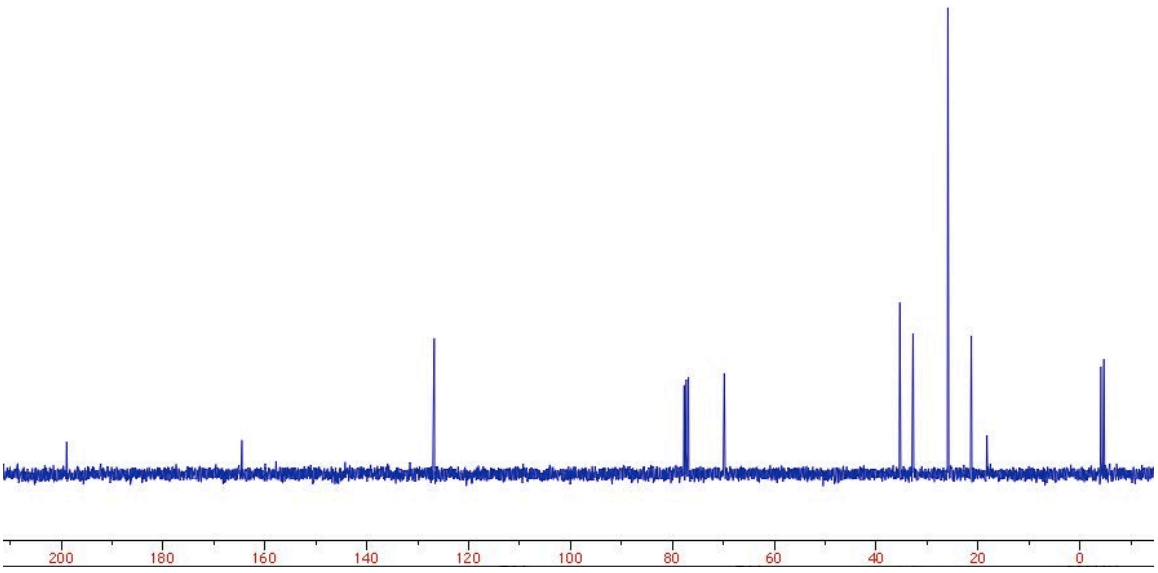
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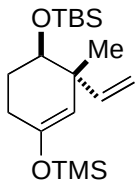


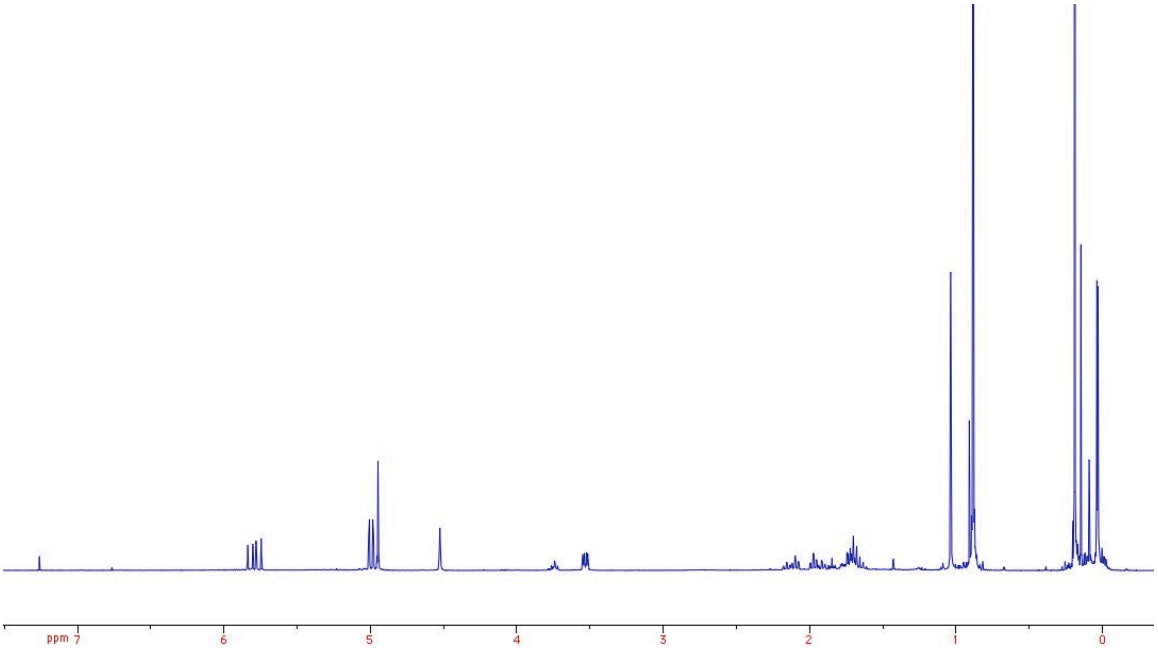
139

Racemic 1-(TBSO)-(2-methyl-4-(TMSO)-2-vinylcycylohex-3-enyloxy)silane (Route 1) (**139**) To a 25 mL round bottom flask was added THF (2 mL) and vinyl bromide (0.44 mL, 0.44 mmol, 2.1 eq.) and cooled to -78°C. Over a 10 min period *t*-BuLi (0.51 mL, 0.88 mmol, 4.2 eq.) was added drop wise. After 15 min add CuBr•Me_2S (58 mg, 0.23 mmol, 1.1 eq) was added and left to stir for 20 min. Then TMEDA (0.## mL, ## mmol, 6 eq.), TMSCl (0.## mL, ## mmol, 3 eq.) and (**138** (100 mg, 0.42 mmol, 1 eq.) in THF (0.4 mL) was added. The reaction was left to stir at -78°C for 4 h, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried over anhydrous $MgSO_4$ and concentrated. No chromatography was performed on the crude oil, which was obtained in 71% yields.

Route 2: To a 250 mL round bottom flask was added THF (80 mL) and CuBr•Me_2S (3.13 g, 12.48 mmol, 1.5 eq.) and stirred while cooling to -78°C. Over a 15 min period vinyl Grignard (24.96 mL, 24.96 mmol, 1.5 eq.) was added and left to stir for 30 min. TMEDA (2.89 mL, 24.96 mmol, 3 eq.), TMSCl (3.17 mL, 24.96 mmol, 3 eq.) and (**138**) (2 g, 8.32 mmol, 1 eq.) in THF (8mL) was added. The reaction was left to stir at -78°C for a 4 h period, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane,

washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried over anhydrous $MgSO_4$ and concentrated. No chromatography was performed on the crude oil, which was obtained in 97% yields (2.7 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.791 (dd, 10.57, 10.57, 1H), 4.981 (dd, 8.50, 10.49 Hz, 2H), 4.524 (s, 1H), 3.532 (dd, 3.05, 3.05 Hz, 1H), 2.180-2.078 (m, 1H), 1.997-1.899 (m, 1H), 1.745-1.634 (m, 2H), 1.037 (s, 3H), 0.884 (s, 9H), 0.191 (s, 9H), 0.039 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 149.6, 147.6, 113.2, 110.4, 73.3, 44.2, 27.2, 27.1, 26.0, 25.8, 23.0, 18.4, 1.6, 0.5, -4.1, -4.6.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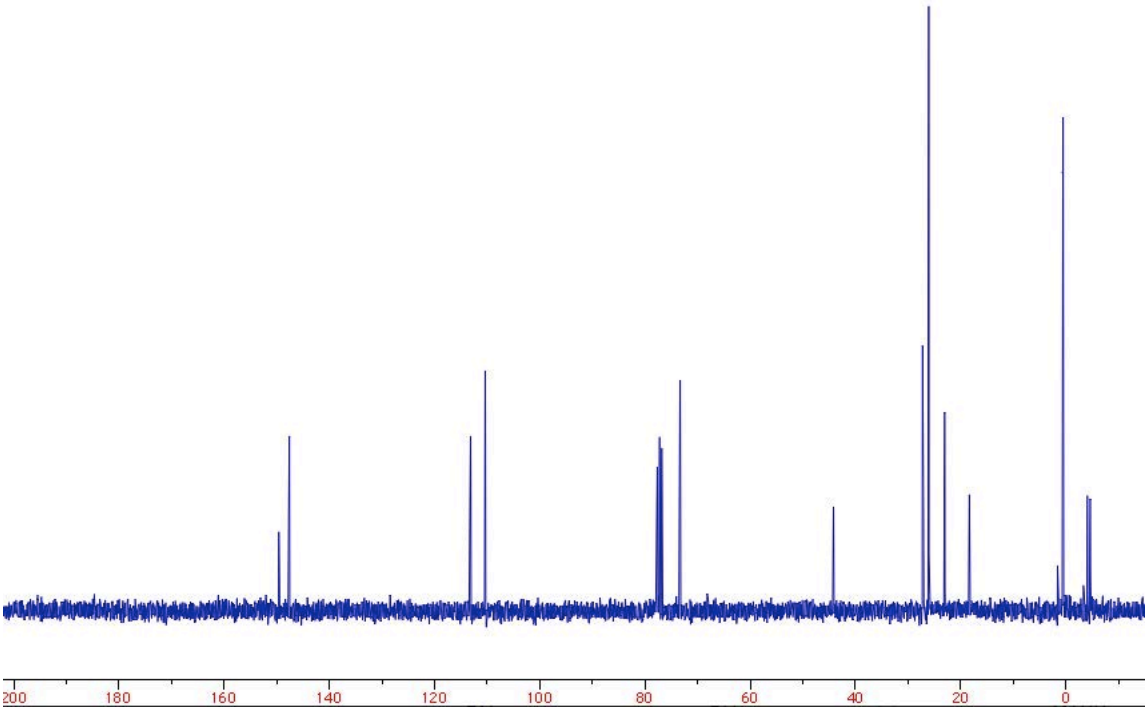
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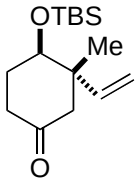
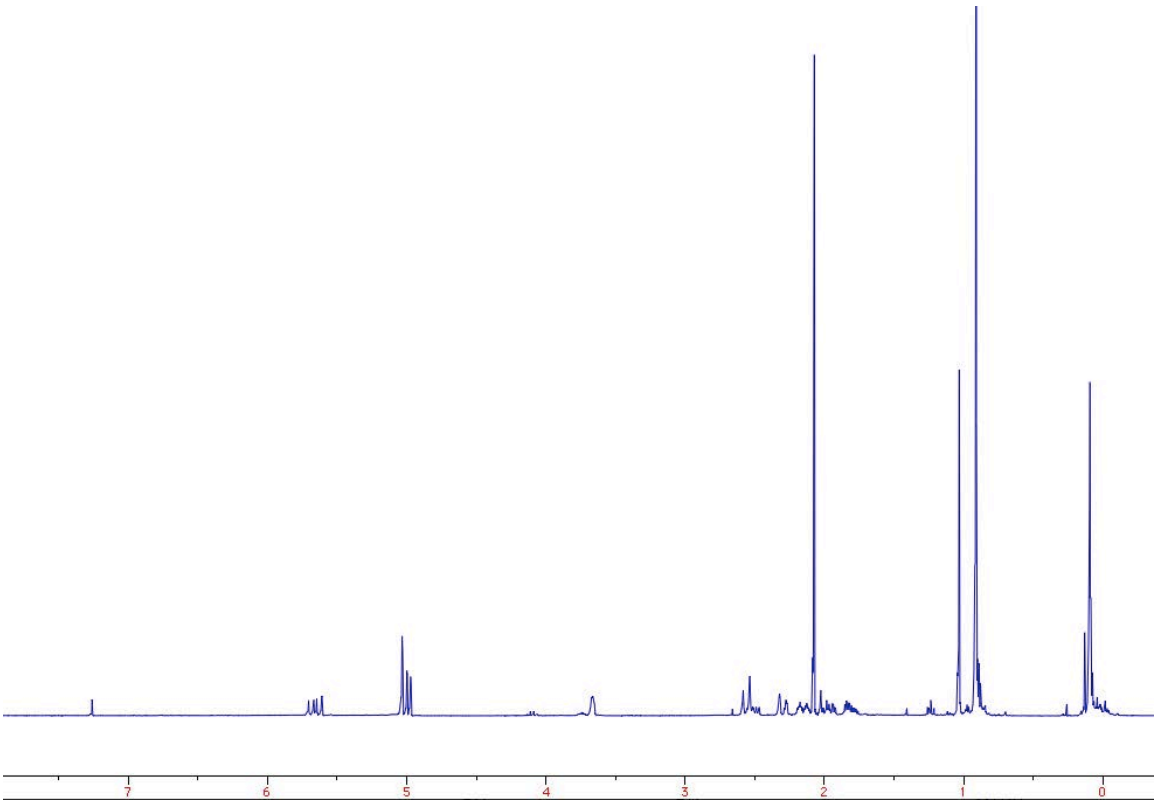


140 (racemic)

Racemic 4-*t*-Butyldimethylsilyloxy-3-methyl-3-vinylcyclohexanone (**140**) To a 100 mL round bottom flask was added THF (20 mL), 1:1 AcOH:Water (20 mL) and (**139**) (2.45 g, 7.19 mmol, 1 eq.) and stirred at rt for 1 h. The reaction was diluted with EtOAc, washed with sat'd $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in quantitative yields (1.9 g).

^{1}HNMR: (300 MHz, CDCl3) δ 5.672 (dd, 17.4, 11.2 Hz, 1H), 5.018 (dd, 3, 14 Hz, 2H), 3.673 (t, 3.6 Hz, 1H), 2.594-1.772 (comp, 6H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 211.6, 143.9, 114.4, 72.8, 46.7, 35.9, 29.9, 26.0, 24.9, 18.3, -4.2; **IR:** (NaCl Film) 1623 cm^{-1}; **HMRS-FAB:** [M+H]+ calcd for $C_{15}H_{28}O_2Si$, 269.19; found, 269.1979.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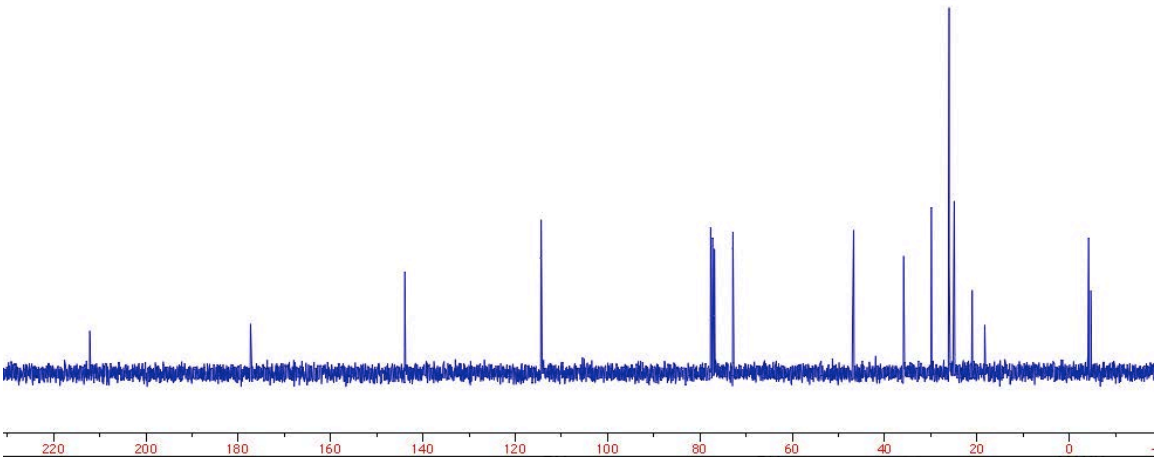
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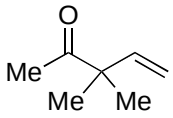
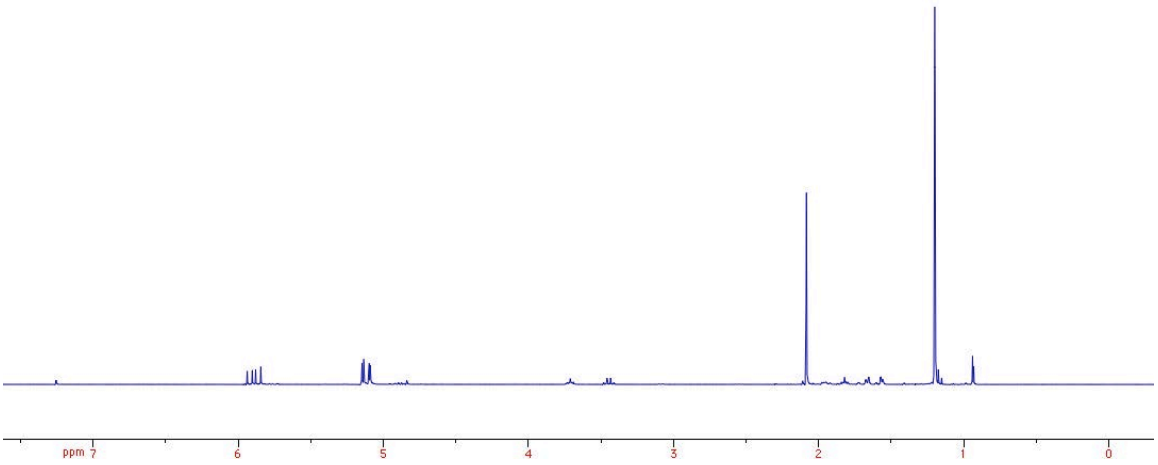
Zn/Ag Couple. Coupling agent was prepared by adding glacial acetic acid (100 mL) and silver acetate (50 mg) to a 250 mL 3-necked round bottom flask fitted with a condenser. The mixture was brought to reflux, let sit at reflux for 15 min and then Zn powdered (50 g) was added. The solution was allowed to stir at reflux for 30 seconds, and then was cooled in an ice-bath. The solution was filtered with Celite (washed with anhydrous THF previously) to afford the crude couple product, which was washed with anhydrous ether (4 x 30 mL) and dried under vacuum for 36 h prior to use. Reaction afforded the Zn/Ag couple (50 g, 100%).



145

3,3-Dimethyl-pent-2-on-4-ene (145): To a 250 mL 3-neck flask was added MeCN (10.06 mL, 192.76 mmol, 0.75 eq.), Zn(Hg) (16.8 g) and THF (46 mL). While stirring vigorously at rt 3-methyl-1-bromo-but-2-ene (30 mL, 257.64 mmol, 1.0 eq) was added slowly over 12 h. The reaction was cooled to 0 ℃ to which a pre-cooled saturated NH_4Cl solution (20 mL) was added and left to stir for 10 min, then poured onto an additional 50 mL of NH_4Cl, extracted with Et_2O, washed with brine, dried and distilled under vacuum to afford product in 73% yields (21 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 6.1-5.9 (m, 1H), 5.2-4.9 (m, 2H), 2.1 (s, 3H), 1.2 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 211.2, 148.7, 121.2, 51.3, 40.9, 25.9; **IR:** (NaCl Film) 1643 cm^{-1}.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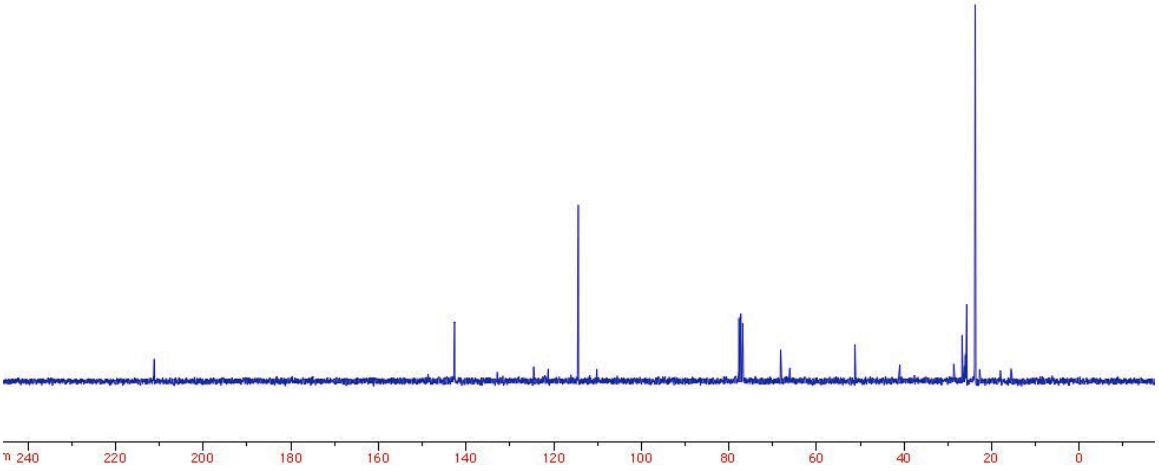
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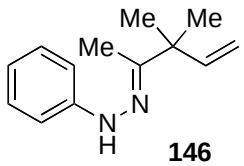
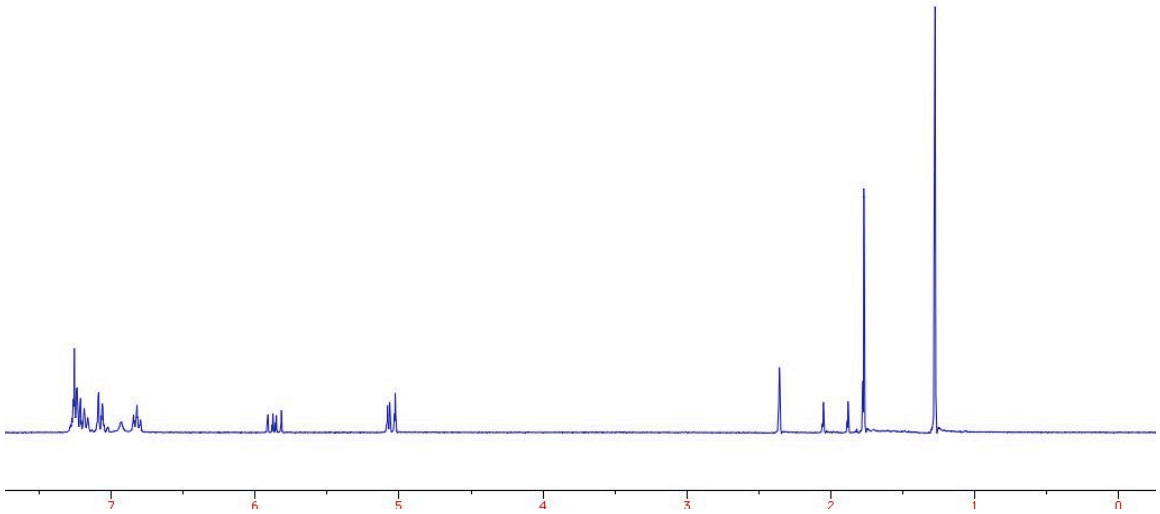


146

2-(2-methylbut-3-en-2-yl)-indole (3). To a 50 mL round bottom flask toluene (12 mL) was added followed by phenyl hydrazine (1.75 mL, 17.8 mmol, 1 eq.) via syringe. After the solution was stirred was 10 min the ketone **145** (2 g, 17.8 mmol, 1 eq.) was added. The flask was fitted with a short path distillation set and refluxed/distilled for 30 min, while the water was removed. The solvent was removed *in vacuo*, additional toluene (5 mL) was added, stirred thoroughly and removed *in vacuo*. The hydrazone was obtained as an orange oil (3.24 g, 90.2%), which was dried thoroughly over 24 h (under vacuum over phosphorus pentaoxide).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.4-6.9 (m, 5H), 5.9-5.7 (m, 1H), 5.2-5.1 (m, 2H), 2.1 (s, 1H), 1.8 (s, 6H), 1.3 (s, 3H).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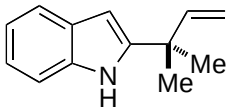
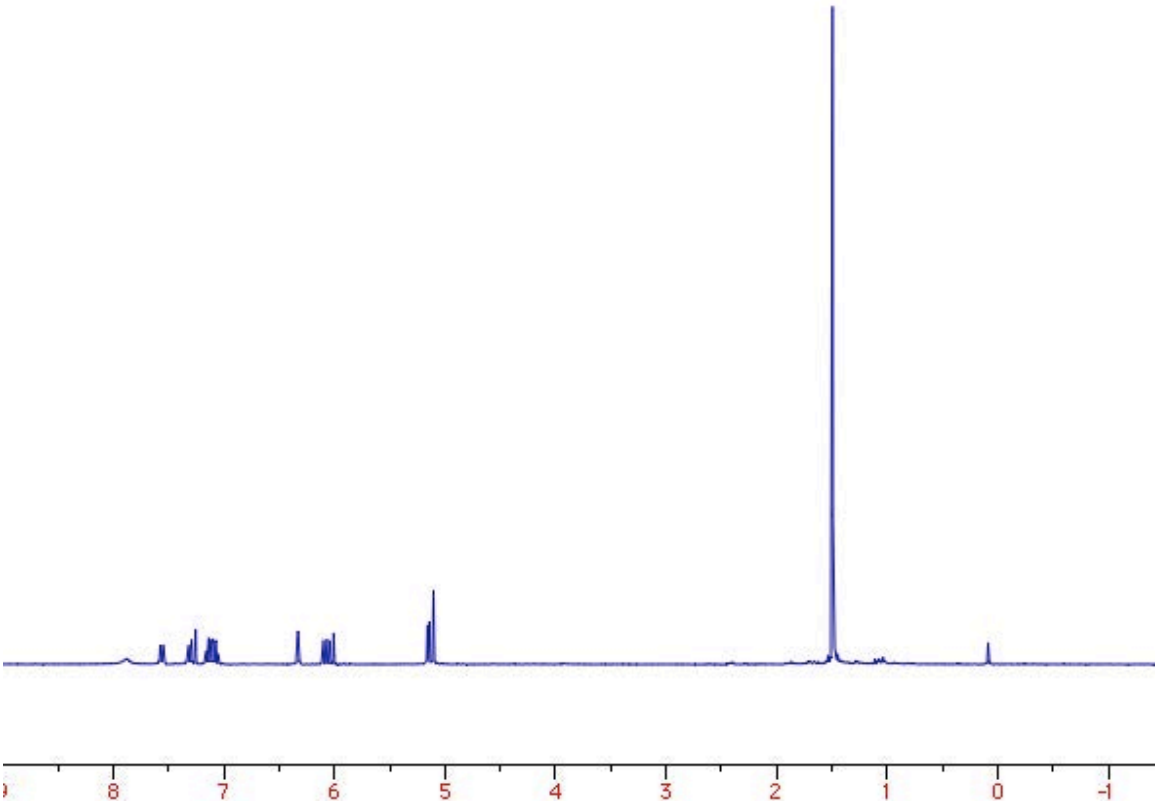


147

2-(2-Methylbut-3-en-2-yl)-1*H*-indole (147): To a 100 mL 2-necked round bottom flask, fitted with a reflux condenser, was added dried $ZnCl_2$. System was purged, flushed with argon and repeated two additional times to ensure atmospheric water was removed. Via syringe digylme (20 mL) was added and allowed to stir for 15 min. Hydrazone **146** (3.24 g, 16.1 mmol, 1 eq.), filtered through Celite to remove drying agent prior to use and placed on high vacuum line for 1 h, was added via syringe. The reaction was refluxed for 11 h. To the hot solution was added hot toluene (10 mL) and stirred with a glass rod until it was at rt. Diglyme was removed using a short path set at reduced pressure. The resulting crude product was purifed by flash silica gel chromatography (toluene) to afford the product in 36% yields (1.1 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 1.51(s, 6H), 5.12 (s, 1H), 5.17 (dd, 1H), 6.10 (d, 1 H), 6.34 (dd, 1H), 7.12 (dd, 2H), 7.33 (d, 1H), 7.57 (d, 1H), 7.89 (br. s, 1H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.17, 136.10, 128.64, 121.42, 120.24, 119.74, 112.37, 98.12, 38.47, 27.72.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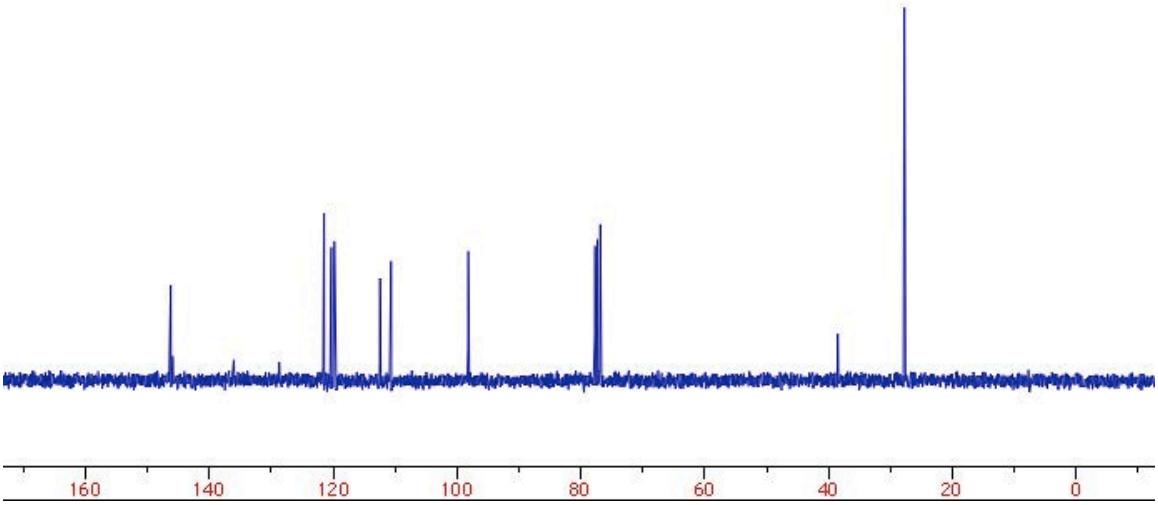
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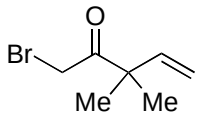
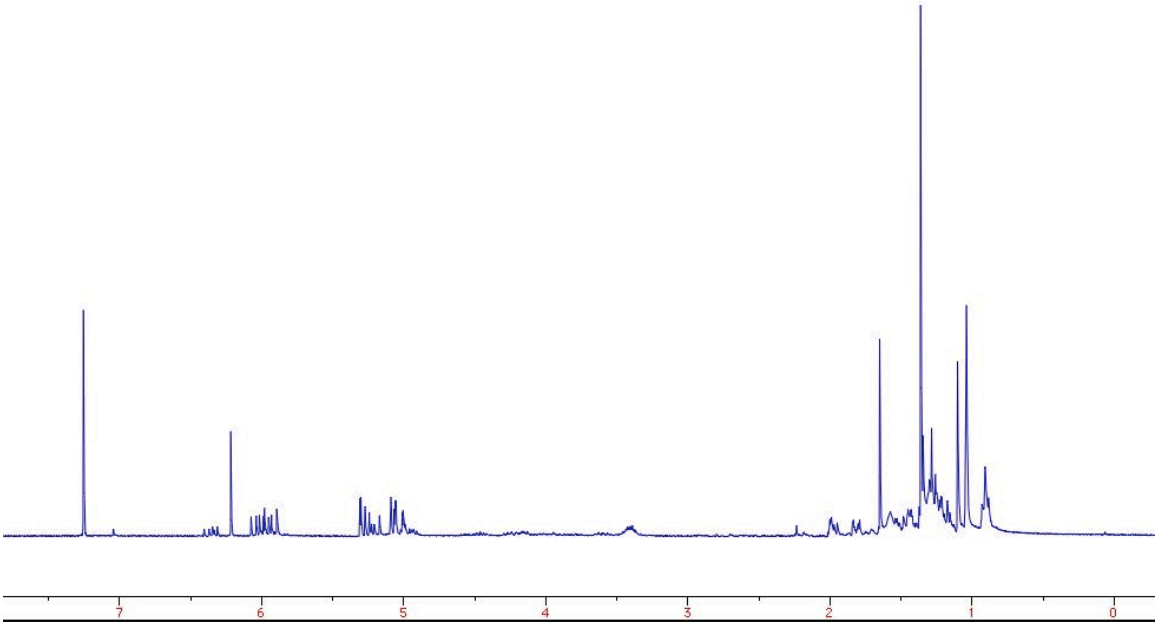
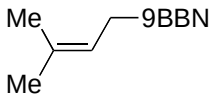


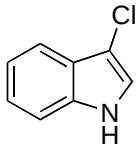
148

1-Bromo-3,3-dimethyl-4-penten-2-one (148). To a 25 mL round bottom flask was added THF (3 mL) and isopropyl amine (0.38 mL, 4.46 mmol, 1 eq.). The solution was left to stir while cooling to -78 ℃. Upon standing for 10 min at -78 ℃ BuLi (3.3 mL, 4.46 mmol, 1 eq.) was added slowly over 5 min and then left to stir for 15 min at -78 ℃. To this solution was added ketone **145**, and stirred thoroughly for 2 min at -78 ℃ at which point it was transferred to a 0 ℃ ice-water bath. After stirring for 15 min Br_2 (0.27 mL, 5.35 mmol, 1.2 eq.) was added to the reaction via syringe, and left to stir vigorously for 1 h. To the reaction was added water (1.8 mL) then 1.0 M HCl (1.0 mL) and extracted with EtOAc (3 x 2 mL). The organic layers were combined and concentrated to afford product in 60% yields (511 mg).





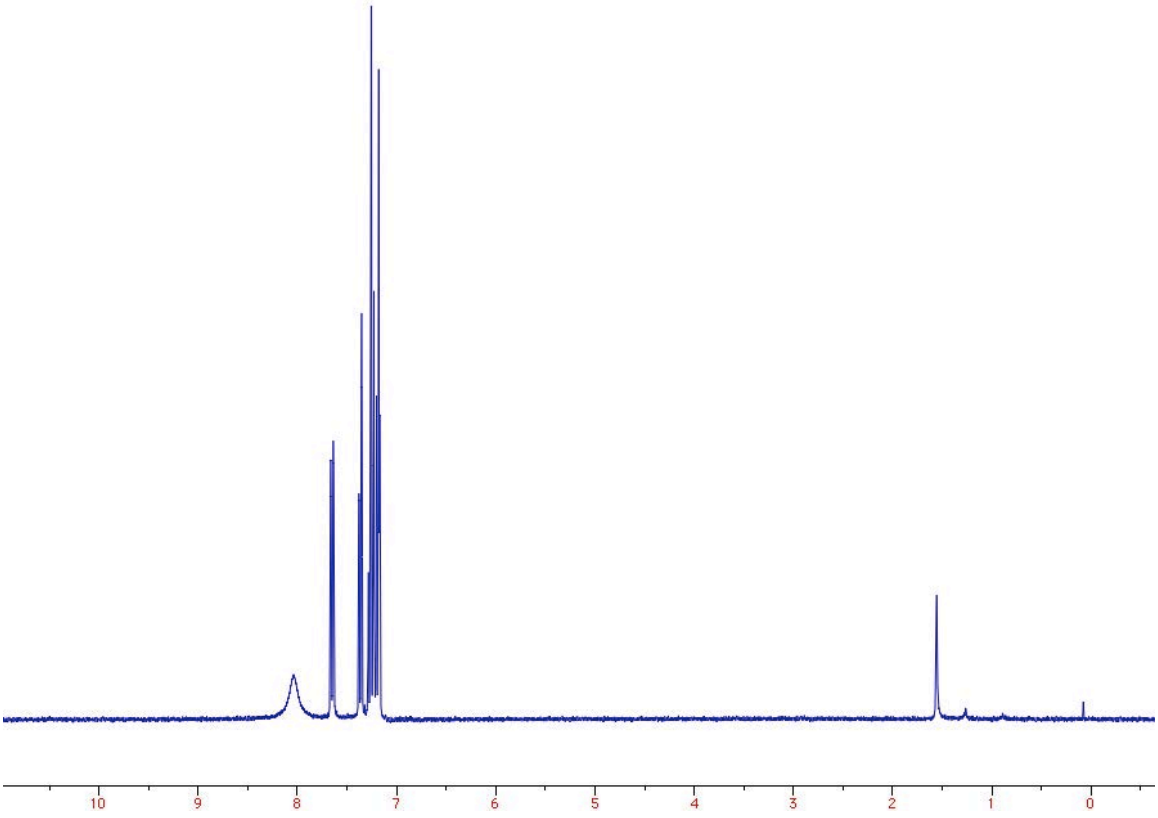
4-9BBN-2-methyl-2-butene or prenyl-9BBN (153). To a 5 mL round bottom flask was added 9-BBN (0.5 M in THF, 1.8 mL, 13.2 mmol, 1.0 eq.). The solution was concentrated (~1 mol/L) by THF evaporation with an argon line. Once the 9-BBN solution volume was reduced by half, 2-methyl-2,3-butadiene (1.31 mL, 13.2 mmol, 1.0 eq.) was added via syringe. Gas lines were removed, the flask was parafilmed and left to stir at rt for 12 h.



151

3-Chloroindole (151). To a 100 mL round bottom flask indole (**77**) (0.9 g, 7.68 mmol, 1.0 eq.) was added to DMF (40 mL). The solution was stirred vigorously at rt till the indole was completely dissolved, then NCS (1.23 g, 9.22 mmol, 1.2 eq.) was added. The reaction was left to stir at rt for 12 h; then brine (40 mL) was added. The solution was then transferred to a separatory funnel and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (20 mL), water (30 mL) and then dried over anhydrous Na_sSO_4 and concentrated. The crude oil obtained was purified by flash silica gel chromatography (1:9 EtOAc:hexane) to afford the desired 3-chloroindole (0.63 g, 54%) as a yellow crystalline solid.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.20 (m, 2H), 7.37 (dd, 1H), 7.67 (dd, 1H), 8.05 (br. s, 1H); **^{13}CNMR**: (75 MHz, $CDCl_3$) δ 133.38, 125.75, 123.33, 121.34, 118.04, 111.01, 104.05.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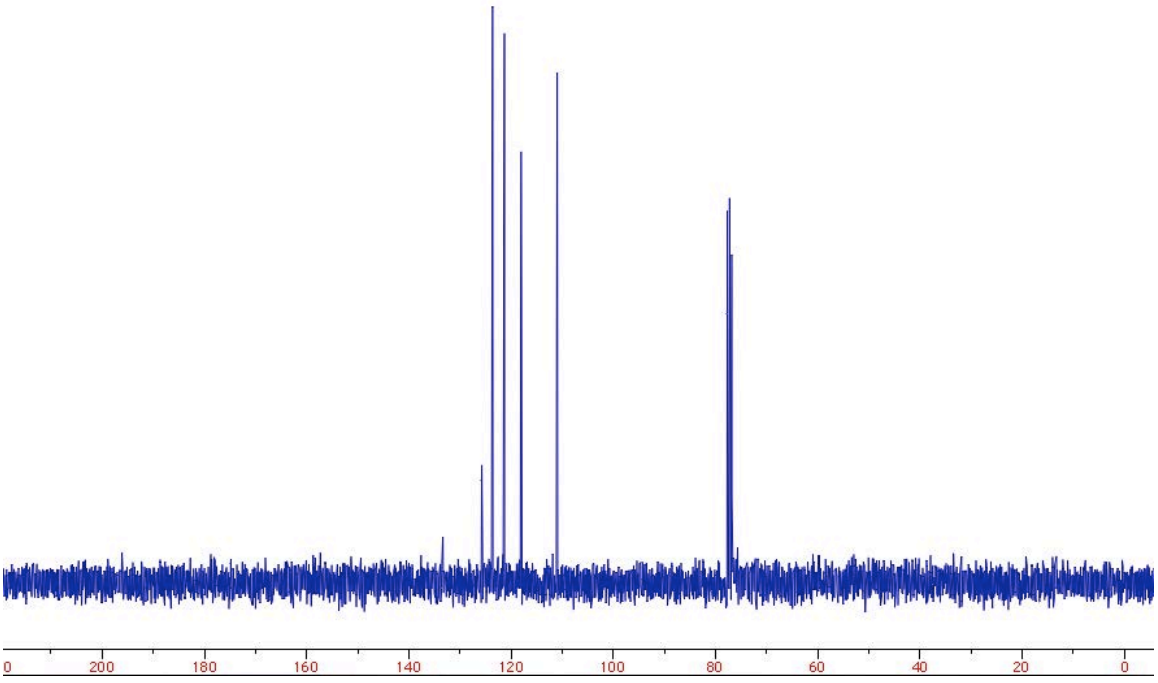
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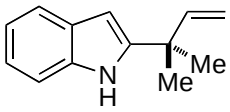
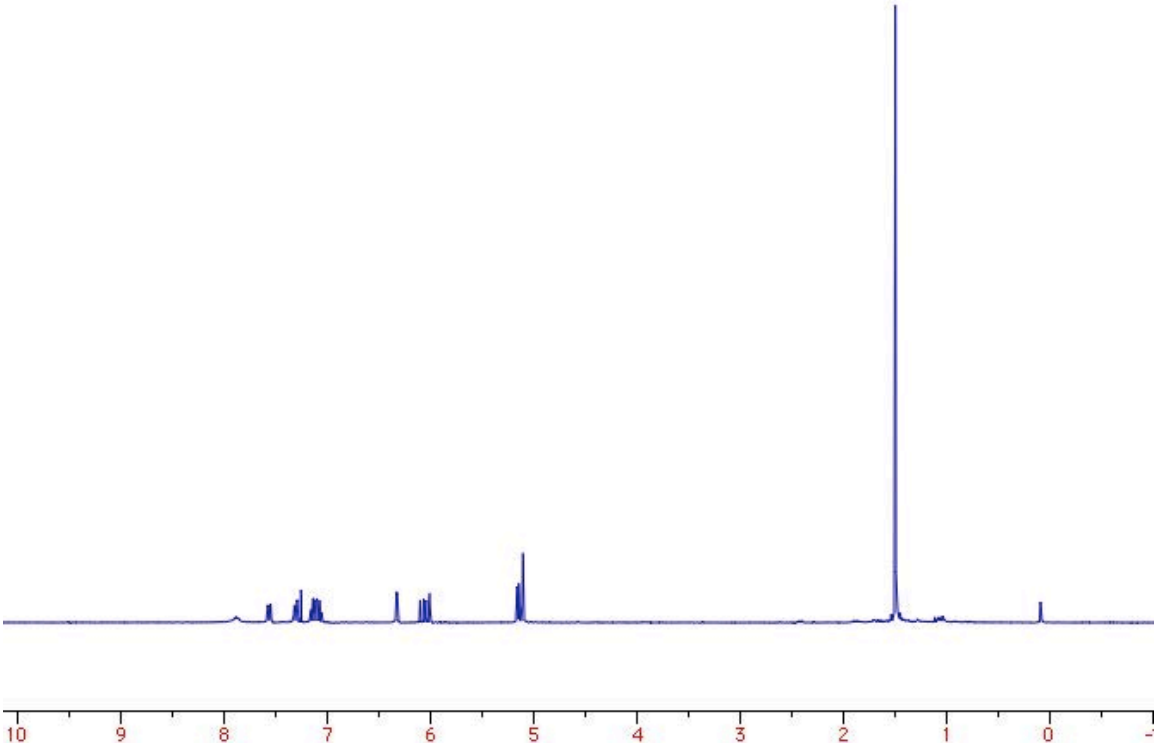


147

2-(2-methylbut-3-en-2-yl)-indole (147) (Route 2). To a 25 mL round bottom flask 3-chloroindole **151** (0.5 g, 3.3 mmol, 1.0 eq.) was added to THF (9 mL). To the stirring solution was added triethylamine (0.9 mL, 6.6 mmol, 2.0 eq.) via syringe. The ethereal solution was stirred at rt for 10 min after which, the prenyl-9BBN (6.6 mmol, 2.0 eq.) was added. Gas lines removed 5 min after addition and the flask was parafilmed and left to stir at rt for 12 h. Solution was concentrated then purified by flash silica gel chromatography (1:9 EtOAc:hexane) to afford the reverse prenylated indole in a 49-72% yield range as a yellow-amber liquid.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 1.51(s, 6H), 5.12 (s, 1H), 5.17 (dd, 1H), 6.10 (dd, 1 H), 6.34 (dd, 1H), 7.12 (dddd, 2H), 7.33 (d, 1H), 7.57 (d, 1H), 7.89 (br. s, 1H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.17, 136.10, 128.64, 121.42, 120.24, 119.74, 112.37, 98.12, 38.47, 27.72; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{13}H_{15}N$, 185.12; found, Need.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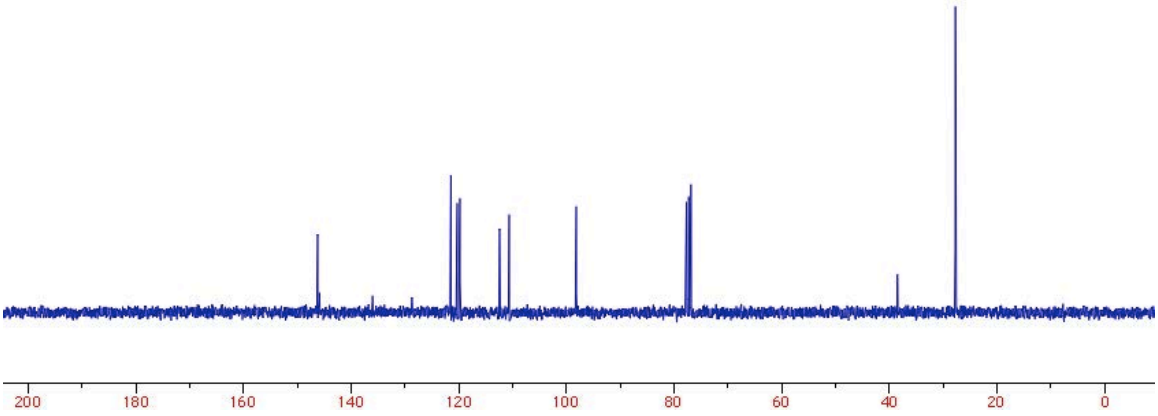
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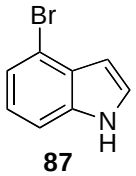
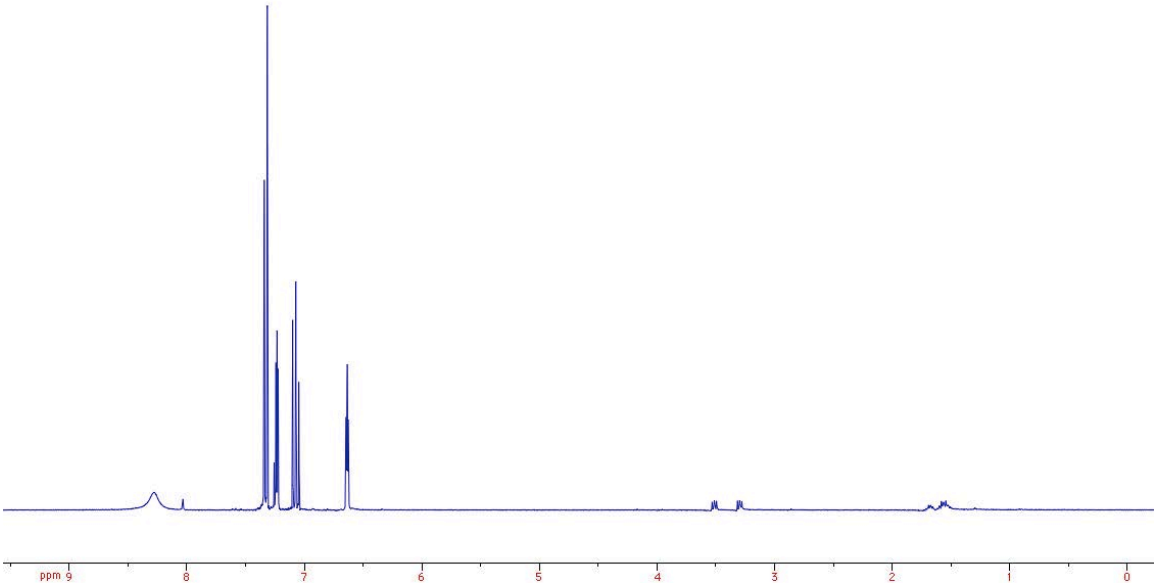


87

4-Bromo-indole (**87**) To a 250 mL round bottom flask was added DMF (24 mL), DMF•DMA (0.92 mL, 6.93 mmol, 3 eq.), pyrrolidiine (0.19 mL, 2.31 mmol, 1 eq.), and 1-bromo-2-methyl-3-nitrobenzene (500 mg, 2.31 mmol, 1 eq.). The reaction was stirred for 2 h at 110°C, then allowed to cool to rt, and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether, the organic layer combined, dried over anhydrous $MgSO_4$ and concentrated. The crude oil was not purified, nor characterized, and was carried on to the next reaction. To a 250 mL round bottom flask was added glacial acetic acid (12 mL) and the crude material (2.31 mmol, 1 eq.) and heated to 75°C while stirring. Once at 75°C for 10 min zinc (1.3 g, 20.79 mmol, 9 eq.) was added over a 10 min period then the temperature was raised to 85°C. After 4 h the reaction was removed from heat, diluted with ether, the organic layer washed with sat'd $NaHCO_3$ and water several times, dried over anhydrous $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 94% yields (425 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 7.33 (s, 2H), 7.23 (t, 2.88, 2.85 Hz, 1H), 7.07 (t, 7.97, 7.77 Hz, 1Hz), 6.63 (t, 3.04, 2.72 Hz, 1H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 161.3, 136.2, 128.9, 125.0, 122.9, 114.9, 110.5, 103.2.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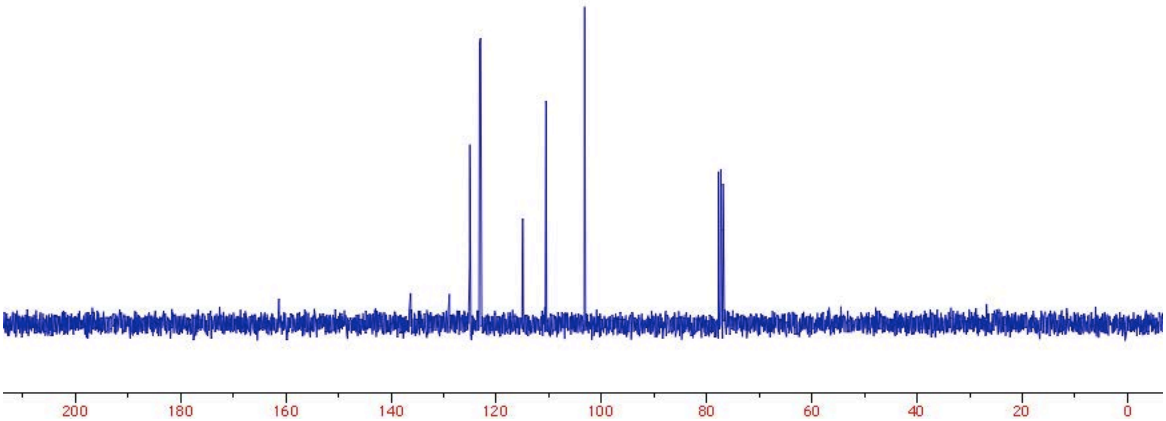
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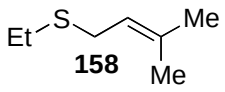
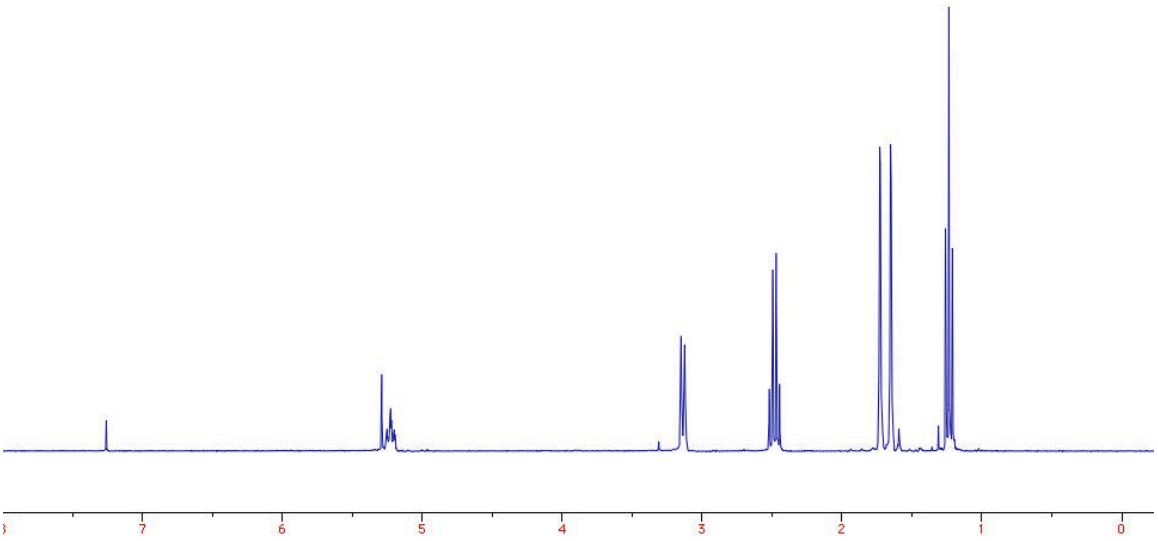


158

Ethyl(3-methylbut-2-en-1-yl)sulfane (158). Naº (1.96 g, 85.34 mmol, 1.05 eq) was added slowly to MeOH (40 mL) at 0 ºC and allowed to stir until all Naº was dissolved. EtSH (6.1 mL, 82.90 mmol, 1.02 eq) was added to the solution drop wise over a period of 2 h. A mixture of **161** (8.5 g, 81.27 mmol, 1 eq) was added to the reaction mixture at a drop wise pace, upon addition the reaction was allowed to stir for 30 min. The mixture was poured into a separation funnel containing H_2O (50 mL) and extracted with DCM. The organic layers were combined and concentrated under reduced pressure to afford product in 86% yield (9.1 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.20 (t, 7.5 Hz, 1 H), 3.09 (d, 7.5 Hz, 2 H), 2.44 (q, 7.4 Hz, 2 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.20 (t, 7.3 Hz, 3 H).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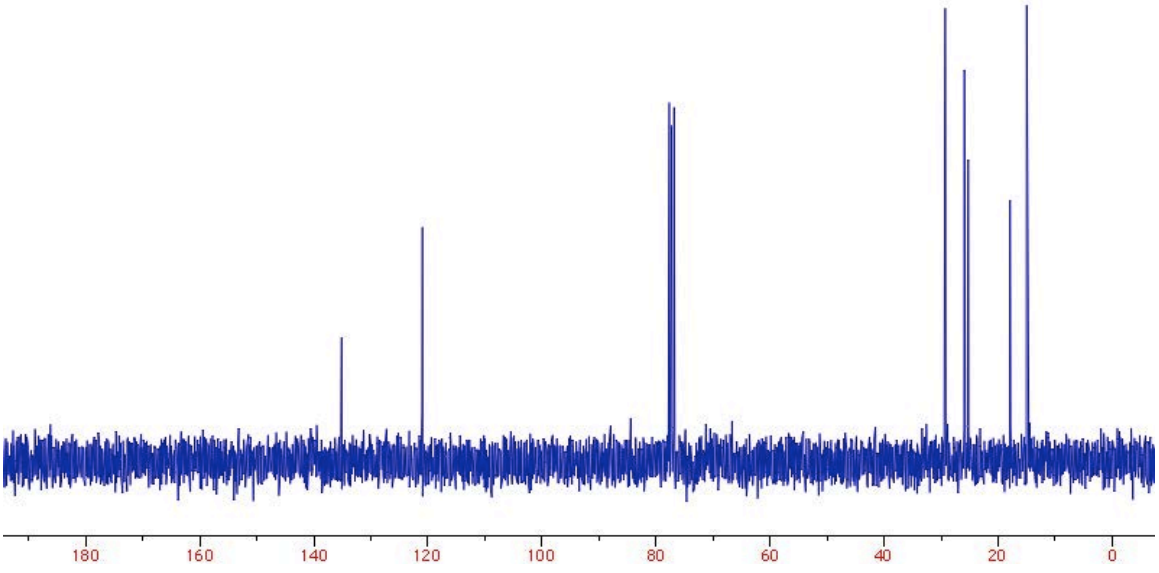
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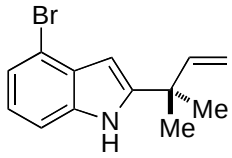
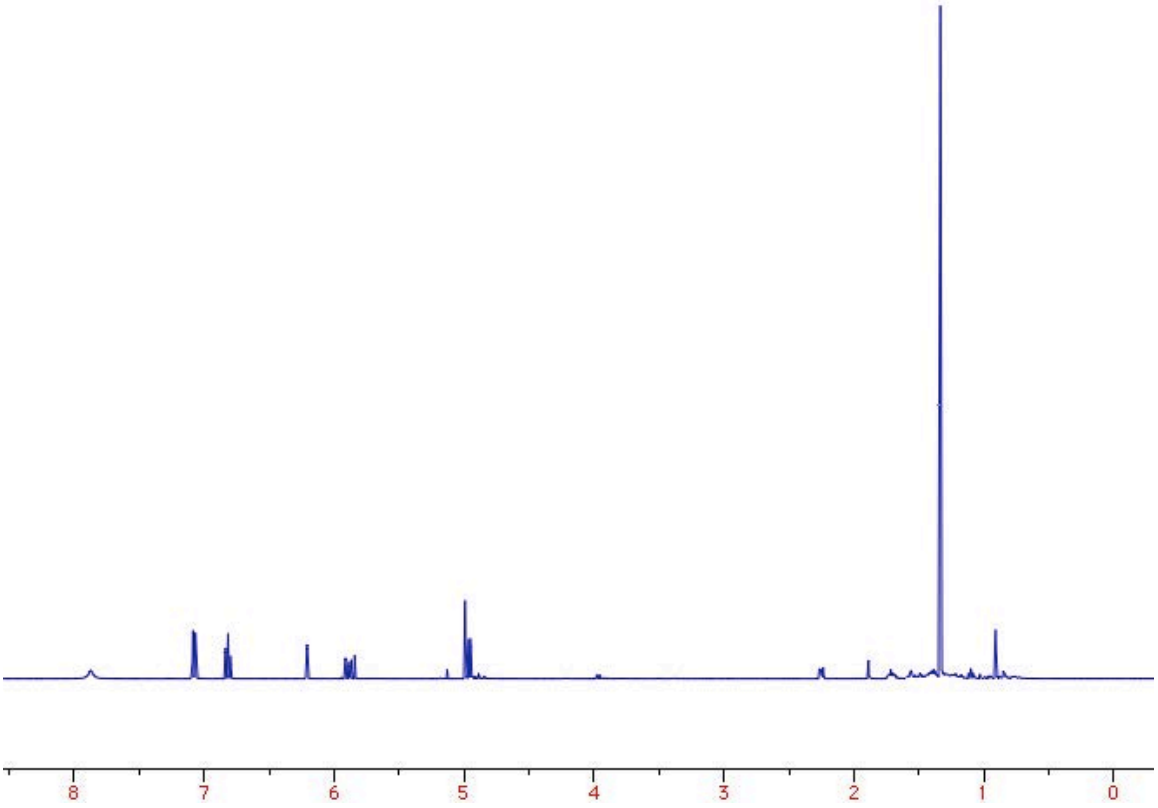


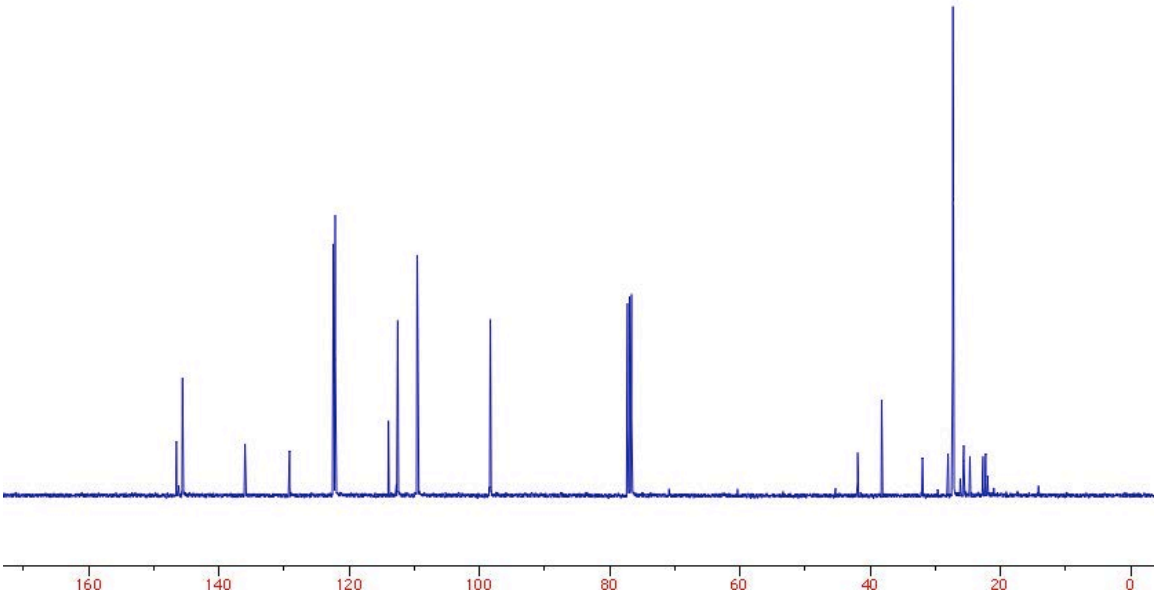
155

To a solution of **87** (97 mg, 0.53 mmol, 1 eq) and **158** (102 mg, 0.58mmol, 1.1 eq) in DCM (5 mL) at -78ºC was added *t*-BuOCl (66 µL, 0.58 mmol, 1.1 eq). The reaction mixture was allowed to stir at -78ºC for 1 h., at which point it was allowed to warm to room temperature where it remained for 18 h. H_2O was added and the two phases separated. The organic layer was washed with 1 M HCl, H_2O, brine and dried. Filtration and concentration under reduced pressure provided crude **162**. The crude material was used without further purification. To a solution of BF_3•etherate (185 µL, 1.47 mmol, 1 eq) in DCM (15 mL) at 0ºC was added EtSH (545 µL, 7.35 mmol, 5 eq). The reaction stirred for 5 min. at 0ºC at which time a solution the crude material (461 mg, 1.47 mmol, 1 eq) in DCM (3 mL) was added to the mixture. Upon warming to room temperature the mixture continued to stir for 18 h. The mixture was then poured in to a cold solution of sat. $NaHCO_3$ and allowed to stir for 15 min. The solution was diluted with DCM and separated. The organic layer was washed with 1 M NaOH, H_2O, brine and dried. Filtration through a pad of Celite and concentration under reduced pressure provided crude product. The material was purified via flash silica gel chromatography (1.8 EtOAc:hexane) to afford product in 81% yield (113 mg) over 2 steps.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.87 (bs, 1H), 7.07 (d, 8.5 Hz, 2H), 6.82 (t, 7.7, 8.0 Hz, 1 H), 6.21 (s, 1H), 5.877, dd, 10.3, 10.3 Hz, 1H), 4.97 (dd, 11.4, 5.2 Hz, 2H), 1.35 (s, 6H);

^{13}CNMR: (75 MHz, $CDCl_3$) δ 146.5, 145.6, 136.0, 129.2, 122.4, 122.1, 113.9, 112.6, 109.6, 98.3, 41.9, 38.2, 27.3; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{13}H_{14}BrN$, 264.03; found, 264.0377.

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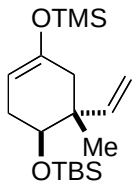
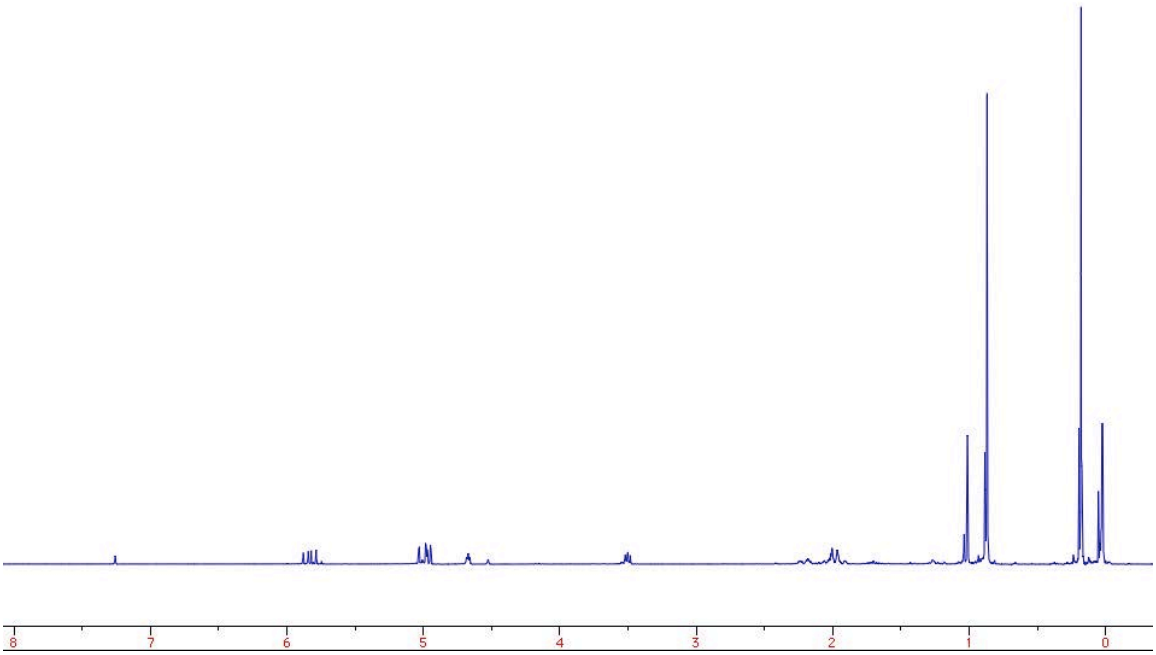


166

***t*-Butyldimethyl(6-methyl-4-(trimethylsilyloxy)-6-vinylcyclohex-3-enyloxy)-silane** (**166**): To a solution of **140** (100 mg, 0.37 mmol, 1.0 eq.) in THF at -78 ℃ was added LHMDS (1 M in THF, 0.41 mL, 0.41 mmol, 1.1 eq.) to which 45 min later TMSCl (53 mg, 0.447 mmol, 1.2 eq.) was added and left to stir at the same temperature. The reaction was quenched 45 min later with the addition of brine (1 vol. eq.) then poured onto a 1:1 brine:hexane (2 vol. eq.), and extracted with hexane. The organic layers were combined, dried and concentrated. The product was used without further purification and obtained in 98% yields (123 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.83 (dd, 1H), 4.99 (dd, 2H), 4.67 (bs, 1H), 3.52-3.48 (m, 1H), 2.26-1.89 (m, 4H), 1.01 (s, 3H), 0.87 (s, 9H), 0.180 (s, 9H), 0.021 (s, 6H).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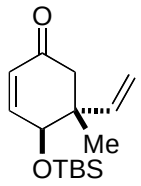


168

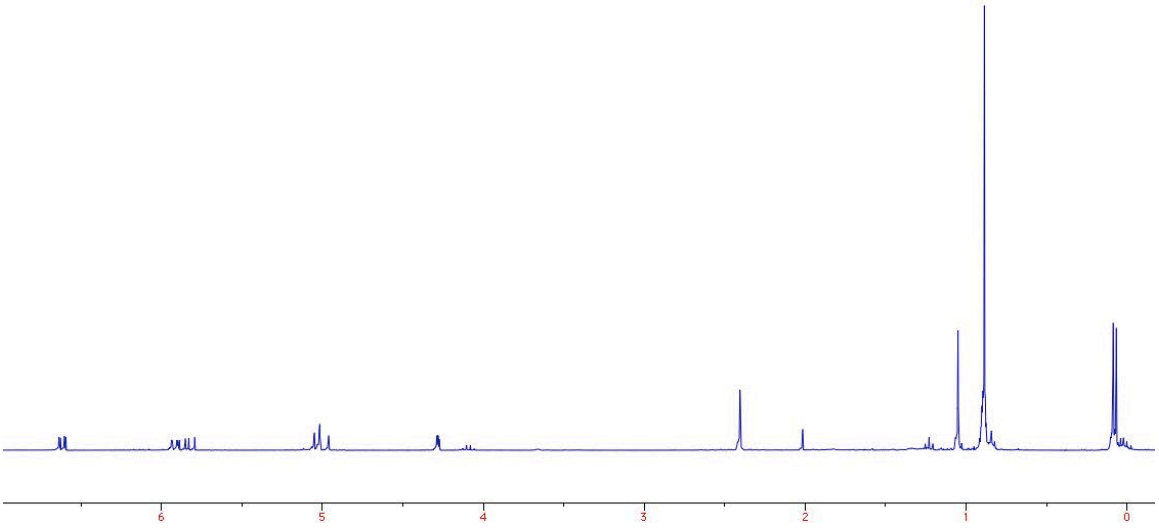
(Route 1) 4-(*t*-Butyldimethylsilyloxy)-5-methyl-5-vinylcyclohex-2-enone (168) Palladium (II) acetate (151 mg, 0.67 mmol, 0.5 eq.) and *p*-benzoquinone (73 mg, 0.67 mmol, 0.5 eq.) was added to MeCN (20 mL) and stirred until mostly all solutes were dissolved. TMS-enol ether (**166**) (460 mg, 1.35 mmol, 1.0 eq.) in MeCN (0.5 mL) was added and left to stir at RT. After 24 h the reaction was quenched with NH_4Cl and extracted with hexanes. The combined organic fractions were washed with $NaHCO_3$ (sat'd) and brine, dried ($MgSO_4$) and concentrated, and then purified by flash silica gel chromatography (1:9 EtOAc:hexane) to afford product in 41% yields (147 mg).

(Route 2) TMS-enol ether (166) (91 mg, 0.27 mmol, 1.0 eq.) was added to DMSO (5 mL) and stirred to which palladium (II) acetate (5.61 mg, 0.025 mmol, 10% mol) was added. The reaction was stirred at RT under an O_2 atmosphere. After 72 h the reaction was quenched with NH_4Cl, filtered to remove the palladium, and extracted with hexanes. The combined organic layers were washed with $NaHCO_3$ (sat'd, x2), dried and concentrated, and then purified by flash silica gel chromatography (1:9 EtOAc:hexane) to afford product.

(Route 3) To a 100 mL round bottom flask was added DCM (24 mL), DMSO (12 mL), and (**166**) (1 g, 3.72 mmol, 1 eq.). IBX (3.6 g, 13.02 mmol, 3.5 eq.) was then added

and heated to 65℃ for 36 h. The reaction was then diluted with diethyl ether, the organic layer washed with sat'd $NaHCO_3$ (2 x 20 mL), water and brine, dried with anhydrous $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc:hexane) to afford product in 86% yields (852 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 6.62 (dd, 2.7, 2.7, 1H), 5.94-5.79 (m, 4H), 5.01 (dd, 10.6, 17.3 Hz, 2H), 4.28 (t, 1.9, 1.9 Hz, 1H), 2.41 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.09 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 151.2, 128.6, 113.5, 73.3, 47.2, 35.9, 29.9, 25.9, 18.5, 18.3, -4.1, -4.2.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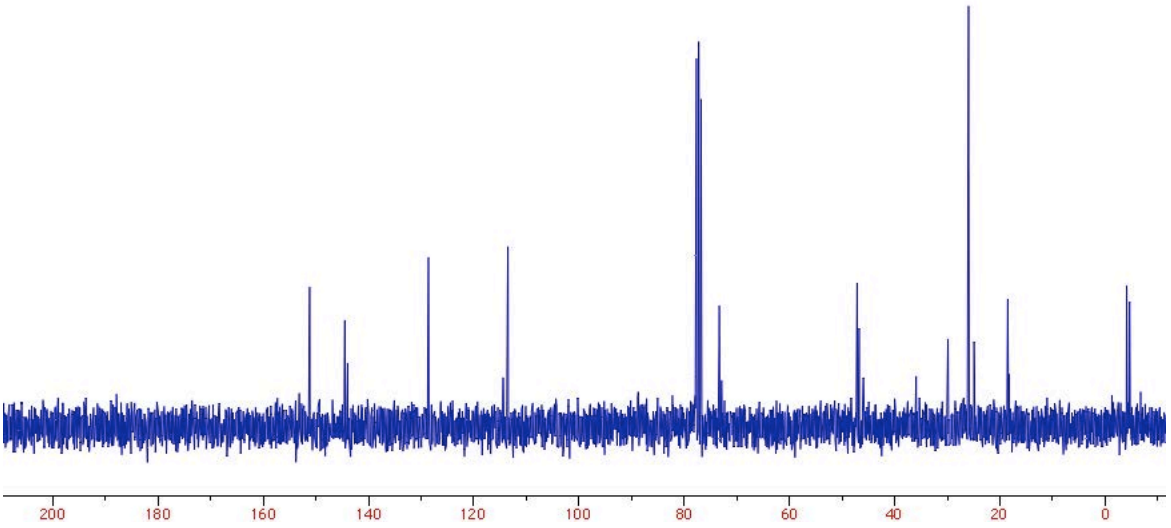
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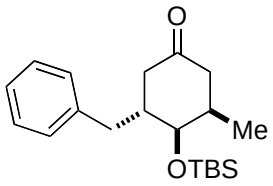
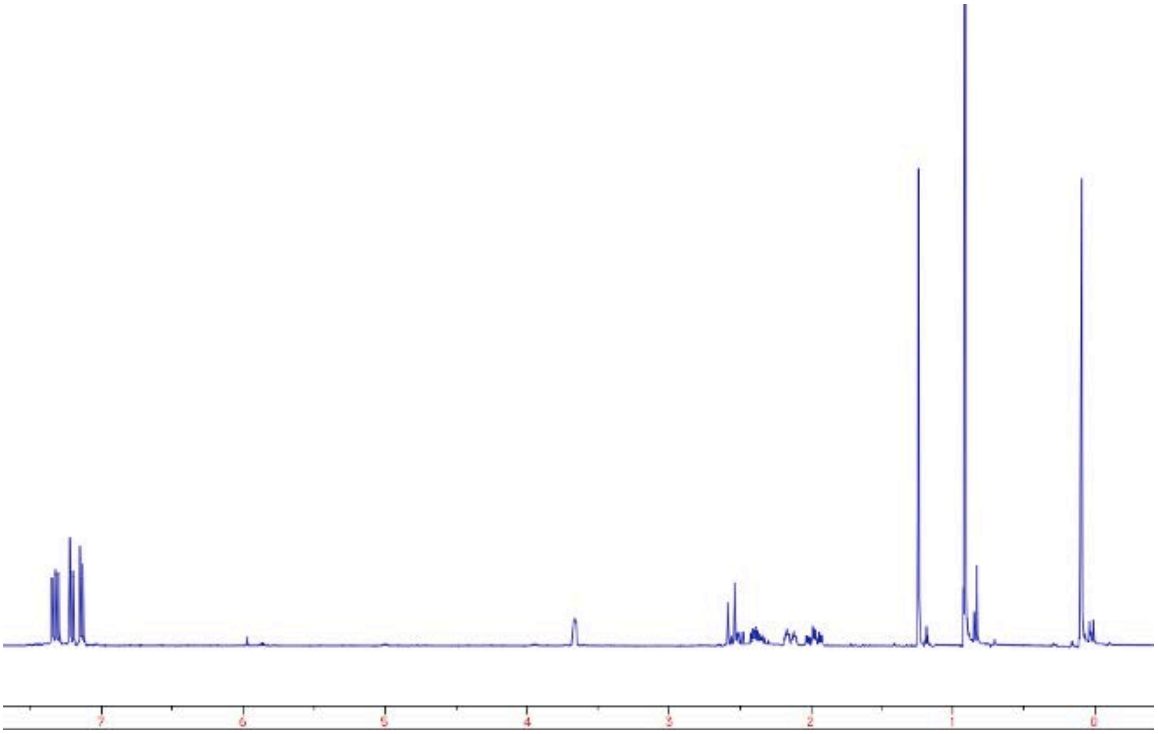


3-Benzyl-4-(*tert*-butyldimethylsilyloxy)-5-methyl-5-vinylcyclohex-1-enyloxy)tri-methylsilane: To a 5 mL round bottom flask was added THF and copper (I) bromide dimethylsulfide (24 mg, 0.094 mmol, 0.5 eq.) and cooled while stirring to -78 ℃. To the stirring solution was added benzyl Grignard (0.282 mL, 0.564 mL, 3 eq.) dropwise. Once 30 min elapsed TMSCl (0.1 mL, 0.752 mmol, 4 eq.), TMEDA (0.05 mL, 0.47 mmol, 2.5 eq.) and (**168**) (50 mg, 0.188 mmol, 1 eq.) in 0.2 mL THF was added and was left to stir at -78 ℃ for 6 h. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ (2 x 2 mL) and water, brine, dried over $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 8% yields.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.29 (m, 2H), 7.20 (d, 1H), 3.51 (t, 1H), 2.63-2.00 (m, 8H), 1.23 (s, 3H), 0.92 (s, 9H), 0.24 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 156.5, 150.7, 140.4, 129.6, 129.4, 124.8, 110.2, 107.3, 87.3, 41.1, 36.7, 35.4, 34.3, 25.3, 18.5, 17.9, 0.2; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{25}H_{42}O_2Si_2$, 430.27; found, 430.2635.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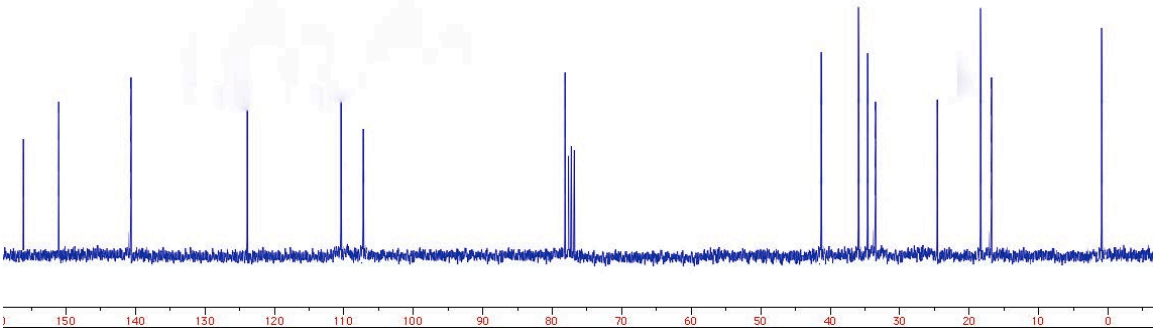
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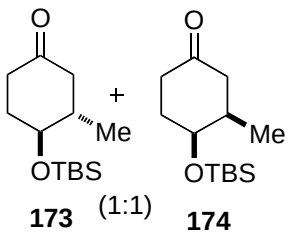
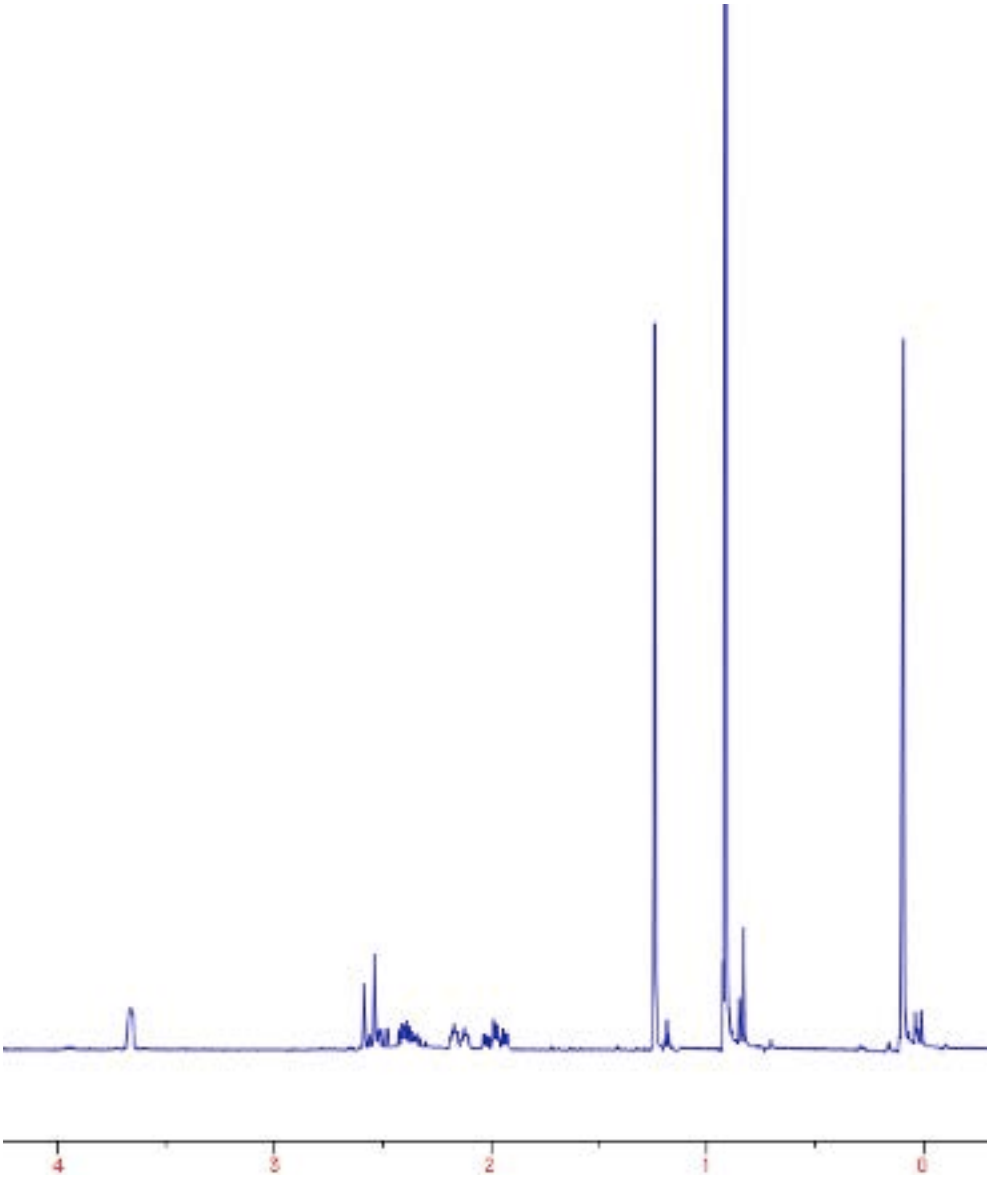


173 (1:1) **174**

Mixture of cis/trans isomers of 3-methyl-4-TBSoxy-cyclohexanone (173/174): To a solution of **138** (## mg, ## mmol, ## eq.) in THF at -78 ℃ was added L-selectride (1 M in THF, ## mL, ## mmol, 1.2 eq.). The reaction was quenched once starting material was consumed by TLC analysis with a saturated NH_4Cl solution, and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:3 EtOAc:hexane) to afford product in 83% yield (1:1 ratio).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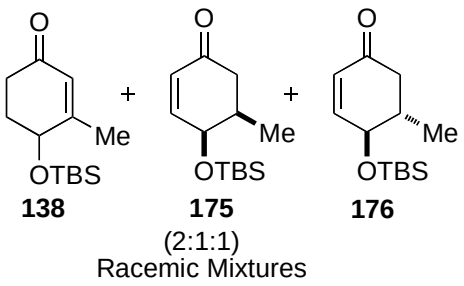
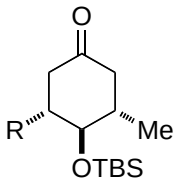
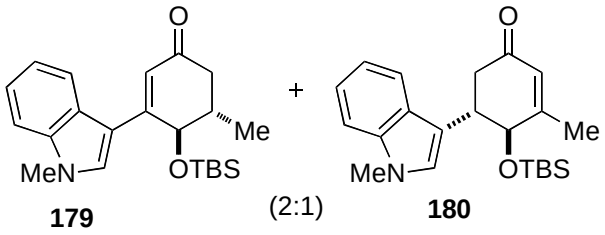


Compounds 138, 175, 176: To a solution of **173/174** (## mg, ## mmol, 1.0 eq.) in THF at -78 ℃ was added LHMDS (1 M in THF, ## mL, ## mmol, 1.1 eq.) to which 45 min later TMSCl (## mg, ## mmol, 1.2 eq.) was added and left to stir at the same temperature. The reaction was quenched 45 min later with the addition of brine (1 vol. eq.) then poured onto a 1:1 brine:hexane (2 vol. eq.), and extracted with hexane. The organic layers were combined, dried and concentrated. The product was used without further. The crude material was added to a pre-mix solution of DCM (24 mL) and DMSO (12 mL). IBX (## g, ## mmol, 3.5 eq.) was then added and heated to 65℃ for 36 h. The reaction was then diluted with diethyl ether, the organic layer washed with sat'd $NaHCO_3$ (2 x 20 mL), water and brine, dried and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc:hexane) to afford a mixture of products in 74% yields.



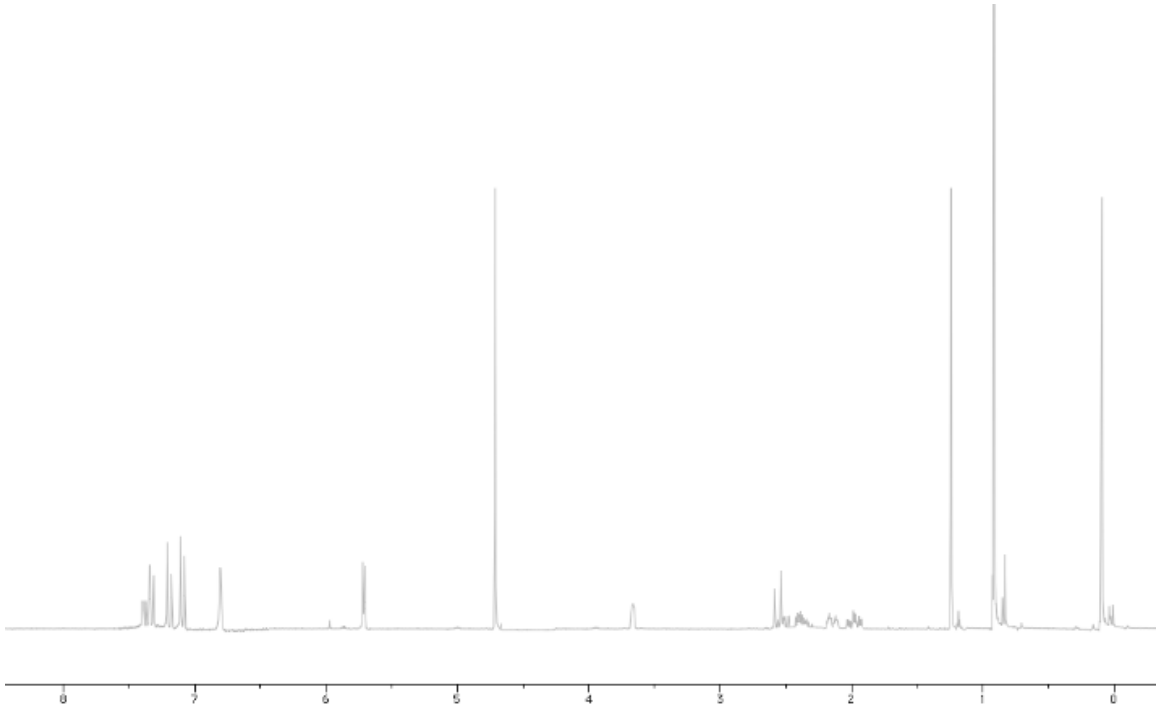
X	Conditions	Results
VinylMgBr	Standard	78%
HCCMgBr	Std	82%
TMSCCH	*n*-BuLi, Std	85%
BenzylMgBr	Std	52%
3-MgBr-indole	Std	43%

Compounds: To a 250 mL round bottom flask was added THF 0.1 M) and CuBr•Me_2S (1.5 eq.) and stirred while cooling to -78°C. Over a 15 min period Grignard X (1.5 eq.) was added and left to stir for 30 min. TMEDA (3 eq.), TMSCl (3 eq.) and (**176**) (1 eq.) in THF was added. The reaction was left to stir at -78°C for a 4 h period, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried and concentrated. No chromatography was performed on the crude oil.



179 (2:1) **180**

Compound 180: To a solution of **178** (## mg, ## mmol, 1.0 eq.) in THF at -78 ℃ was added LHMDS (1 M in THF, ## mL, ## mmol, 1.1 eq.) to which 45 min later TMSCl (## mg, ## mmol, 1.2 eq.) was added and left to stir at the same temperature. The reaction was quenched 45 min later with the addition of brine (1 vol. eq.) then poured onto a 1:1 brine:hexane (2 vol. eq.), and extracted with hexane. The organic layers were combined, dried and concentrated. The product was used without further. The crude material was added to a pre-mix solution of DCM (24 mL) and DMSO (12 mL). IBX (## g, ## mmol, 3.5 eq.) was then added and heated to 65 ℃ for 36 h. The reaction was then diluted with diethyl ether, the organic layer washed with sat'd $NaHCO_3$ (2 x 20 mL), water and brine, dried and concentrated. The crude oil was purified by flash silica gel chromatography (5% EtOAc:hexane) to afford a mixture of products in 64% yields (2:1 ratio of undesired:desired).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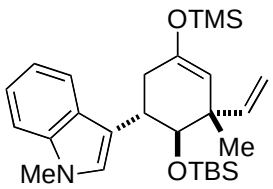
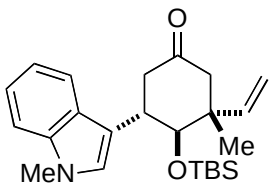


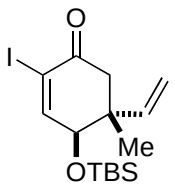
181

Compound 181: To a 250 mL round bottom flask was added THF (0.1 M) and CuBr•Me_2S (1.5 eq.) and stirred while cooling to -78°C. Over a 15 min period vinyl Grignard X (1.5 eq.) was added and left to stir for 30 min. TMEDA (3 eq.), TMSCl (3 eq.) and (**180**) (1 eq.) in THF was added. The reaction was left to stir at -78°C for a 4 h period, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried and concentrated. No chromatography nor NMR analysis was performed on the crude oil, it was obtained in a 21% yield.



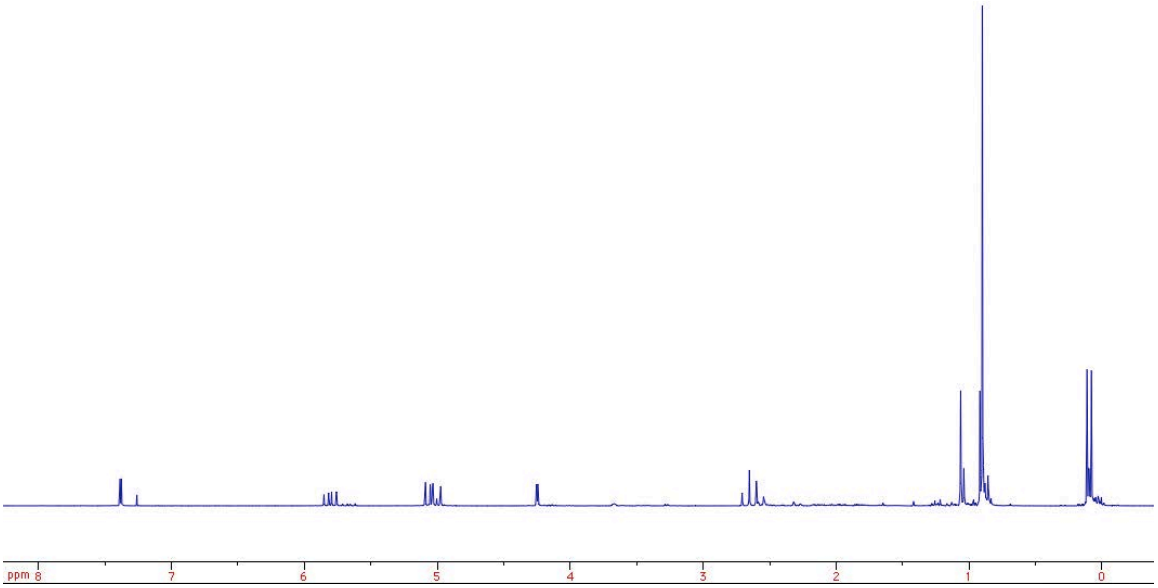
182

Racemic 4-*t*-Butyldimethylsilyloxy-3-methyl-3-vinylcyclohexanone (**182**) To a 100 mL round bottom flask was added THF (## mL), 1:1 AcOH:Water (## mL) and (**181**) (## g, ## mmol, 1 eq.) and stirred at rt for 1 h. The reaction was diluted with EtOAc, washed with saturated $NaHCO_3$ and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 67% yields.



Compound (206): To a pre-mixed solution of Pyr:CCl_4 (1:1, 4 mL) was added **168** (400 mg, 1.5 mmol, 1.0 eq.) and cooled to 0 ℃ at which point I_2 (1.55 g, 6.00 mmol, 4 eq.) in Pyr:CCl_4 (1:1, 6 mL) was added dropwise. The reaction was diluted with Et_2O 12 h later, washed with H_2O, 1 N HCl, H_2O again, saturated $Na_2S_2O_3$, dried and concentrated. The crude material was purified via flash silica gel chromatography to afford product in 89% yields (523 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.38 (d, 3.3 Hz, 1H), 5.81 (dd, 10.8, 10.8 Hz, 1H), 5.03 (dd, 10.8, 17.5 Hz, 2H), 4.25 (d, 3.1 Hz, 1H), 2.65 (t, 2H), 1.06 (s, 3H), 0.9 (s, 9H), 0.11 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 159.4, 143.4, 114.2, 75.7, 46.4, 45.2, 35.9, 26.1, 25.9, 25.8, 18.8, 18.3, -4.1, -4.2.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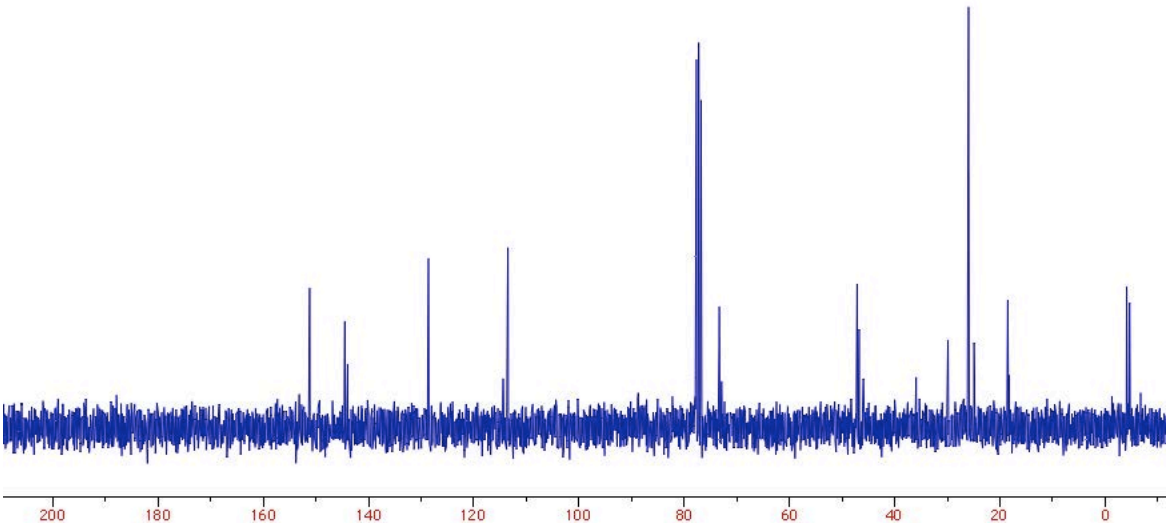
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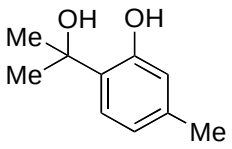
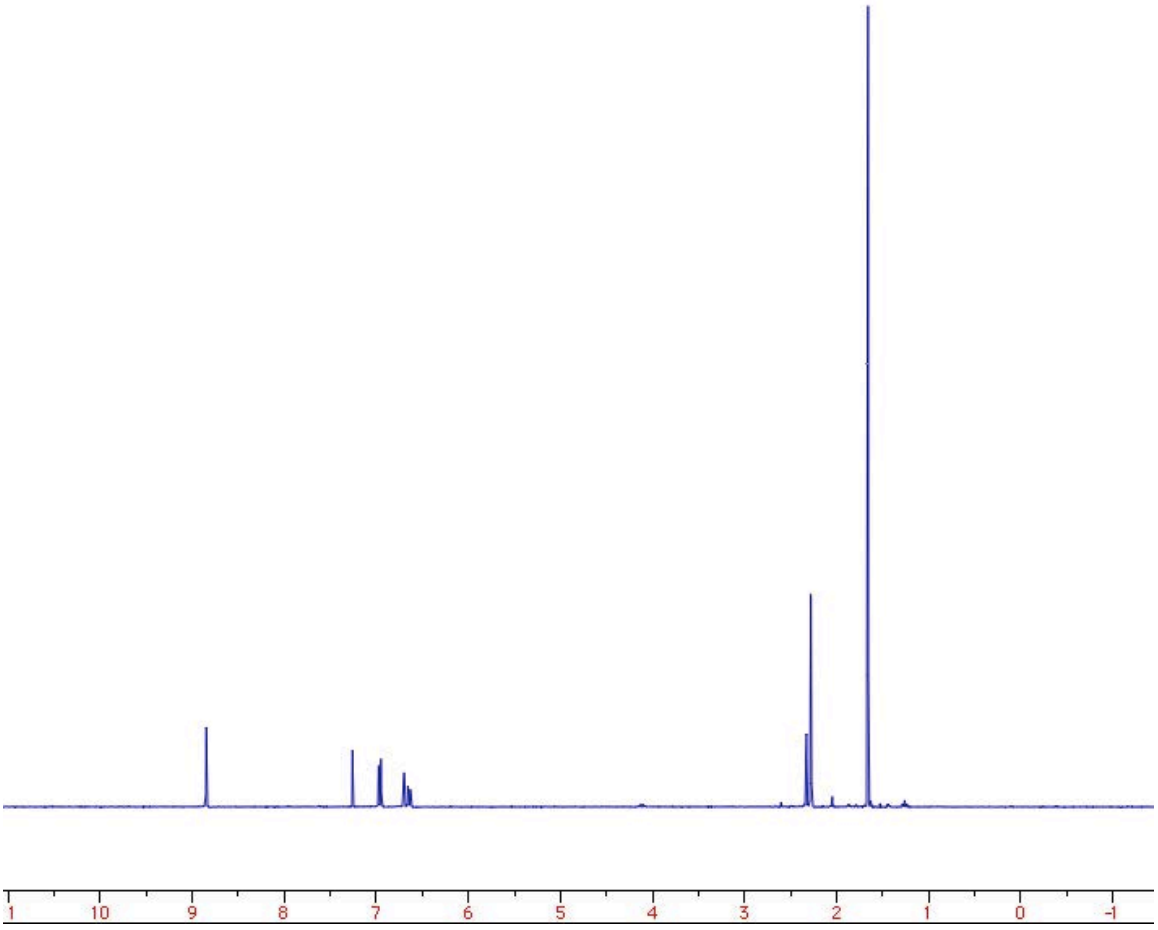


210

Compound 210: To a solution of **209** (10 mL, 71.91 mmol, 1.0 eq) in THF (600 mL) at -78 ℃ was added MeLi (1.6 M, 94 mL, 151 mmol, 2.1 eq) and left to stir at the same temperature. The reaction was quenched 8 h later with a saturated NH_4Cl solution and extracted with hexane. The organic layers were combined, washed with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:3 EtOAc:hexane) to afford product in 98% yields (11.7 g).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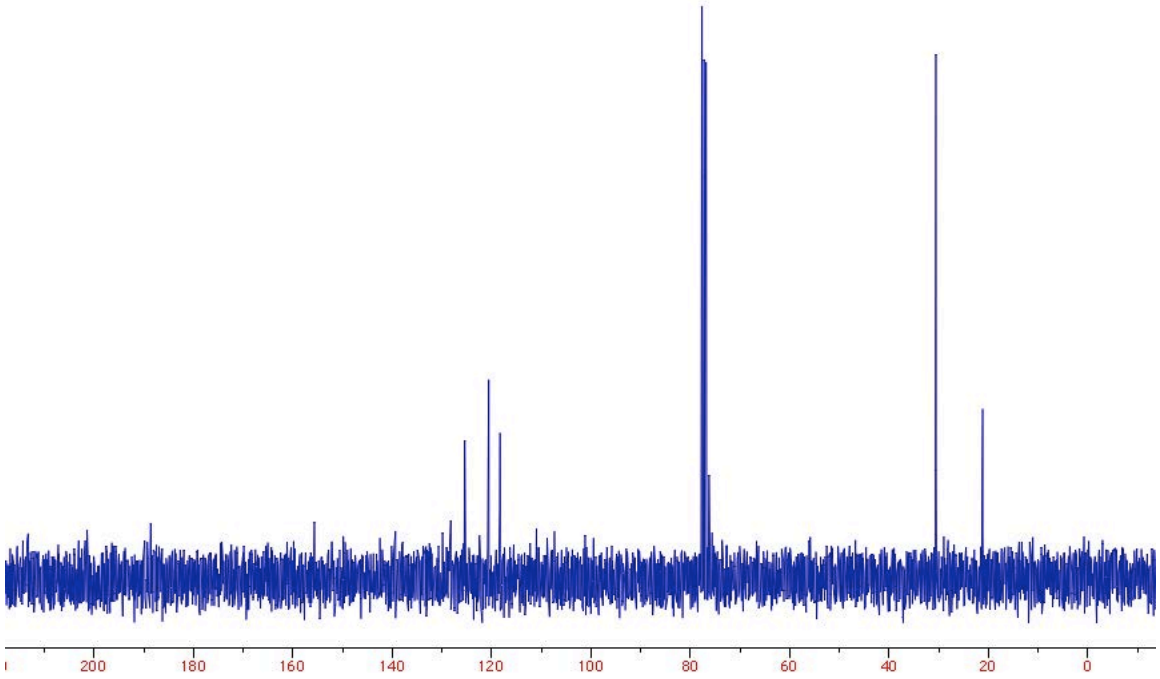
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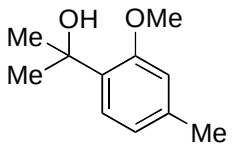
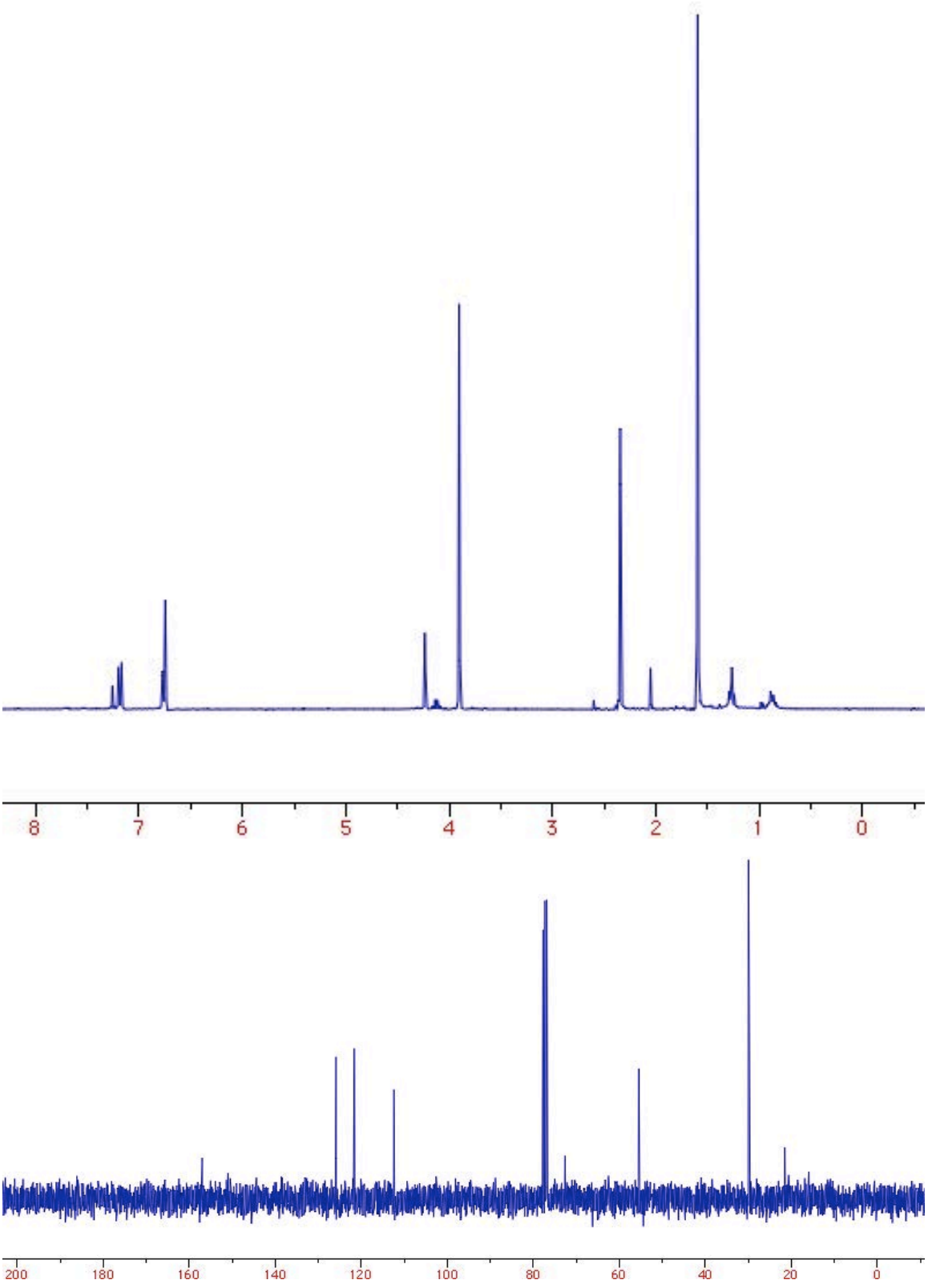


211

Compound 211: To a solution of **217** (71.91 mmol, 1.0 eq) in THF (700 mL) at -78 ℃ was added MeLi (58 mL, 93.48 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was warmed to room temperature after 4 h and then quenched with a saturated NH_4Cl solution and extracted with hexanes. The organic layers were combined, washed with $NaHCO_3$ and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:3 EtOAc: hexane) to afford product in quantitative yields (12.9 g).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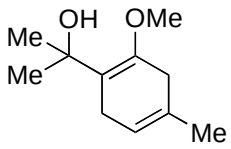
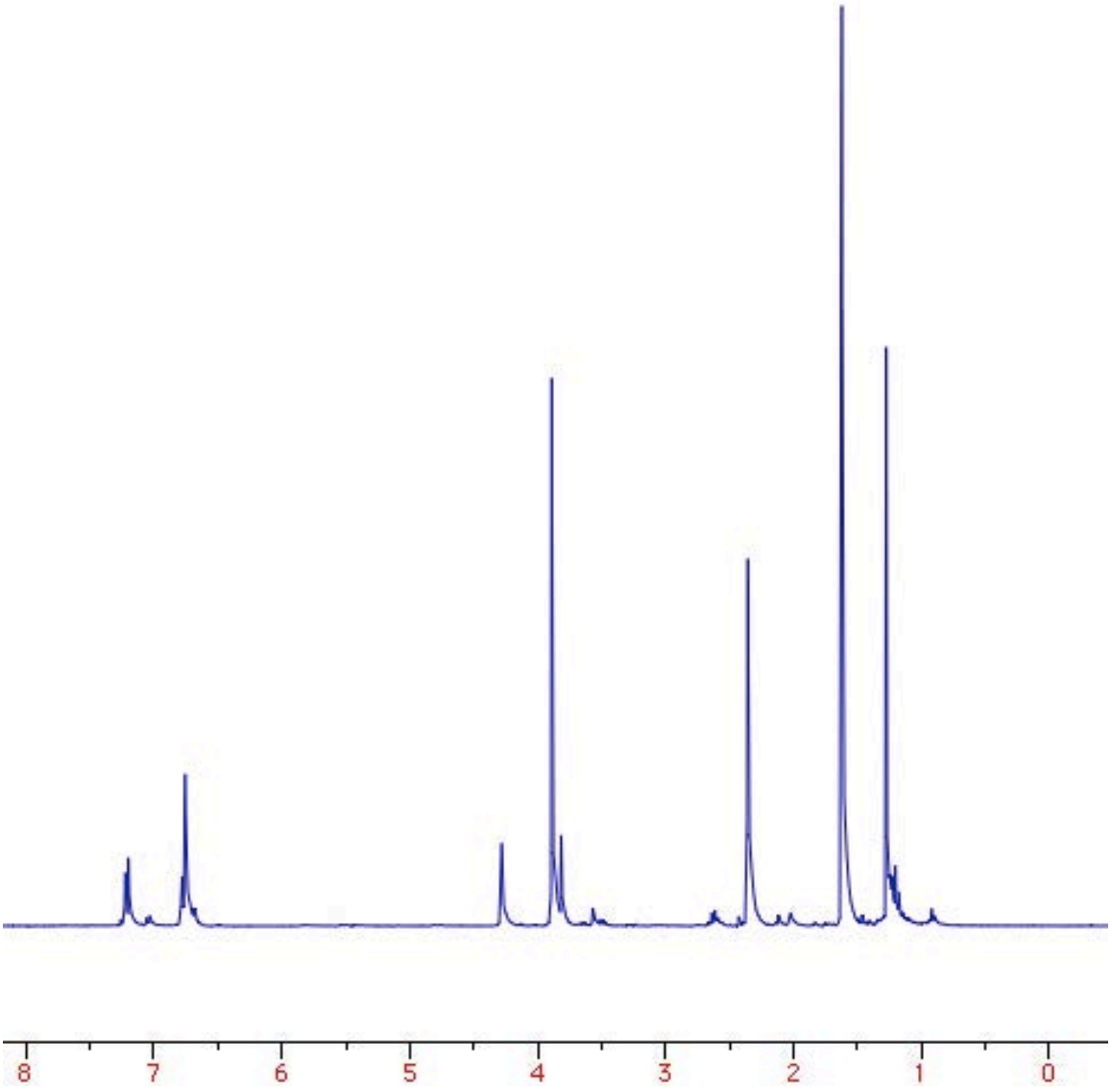


212

Compound 212: A 500 mL 3-necked round bottom flask equipped with a dry-ice condenser was purged with argon and cooled to -78℃ after which ammonia (50 mL, 1897 mmol, 60 eq.) was condensed into said flask. Compound **211** (5.7 g, 31.6 mmol, 1 eq.) in ether (33 mL, 316 mmol, 10 eq.) was added to the flask followed by *t*-butanol (18 ml, 189 mmol, 6 eq.) and left to stir at -78℃ for 10 min. Sodium metal (2.2 g, 94.9 mmol, 3 eq.) was added to the solution over a 30 min period and left to stir at -78℃ for 6 h. The reaction was quenched with solid ammonium chloride and stirred for 2 h. Gentle heating, 33℃, of the reaction evaporated the ammonia. Once the ammonia was removed, the resulting solution was diluted with 150 mL of pentane and then poured onto 200 mL of 1:1 water:pentane. The pentane layer was washed with water (3 x 50 mL), dried with anhydrous $MgSO_4$ and concentrated to afford product in 21% yields (1.2 g).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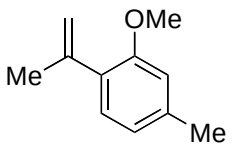
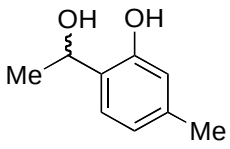


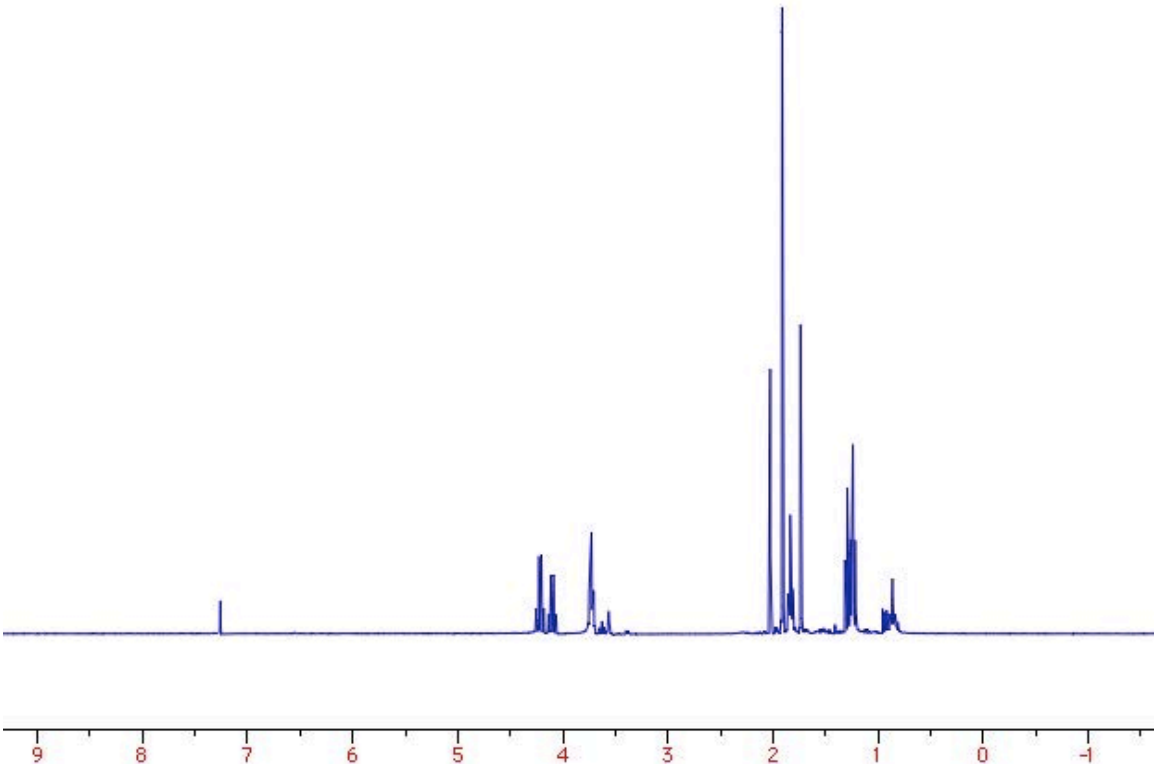
213

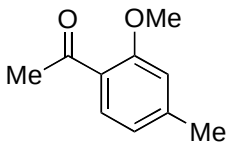
Compound 213: To compound **212** (25.5 mmol, 1.0 eq.) was added a pre-mixed solution of MeOH:H_2O (3:1, 50 mL) followed by oxalic acid (102 mg, 1.1 mmol, 0.044 eq). The reaction was stirred for 1h, quenched with brine, extracted with DCM and dried.



216

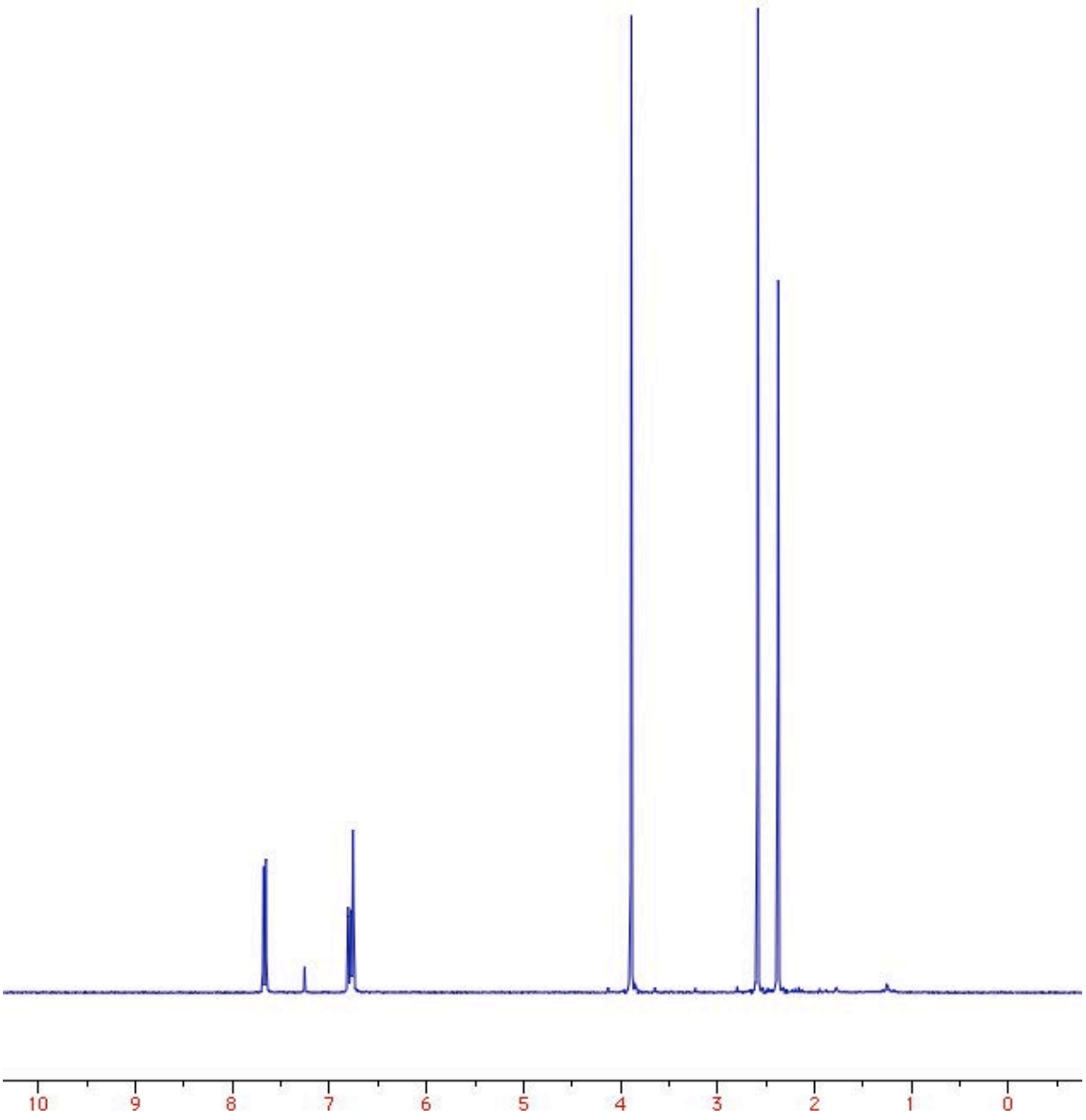
Compound 216: To a solution of **209** (1 mL, 7.2 mmol, 1.0 eq) in THF at -78 ℃ was added DIBAl-H (1 M in THF, 15.8 mL, 15.8 mmol, 2.2 eq.) and left to stir at the same temperature. The reaction was warmed to rt 4 h later at which point MeOH (20 mL) was added followed by Rochelle's salt and stirred overnight. The reaction was extracted with Et_2O, washed with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 31% yields (339 mg).





217

Compound 217: To a solution of **209** (15 mL, 108 mmol, 1.0 eq) in acetone (250 mL) was added KOH (24 g, 4.0 eq) and dimethyl sulfate (31 mL, 324 mmol, 3.0 eq.). The reaction was stirred for 12 h, quenched with saturated NH_4Cl, extracted with hexane, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 72% yields (12.8 g).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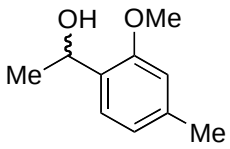
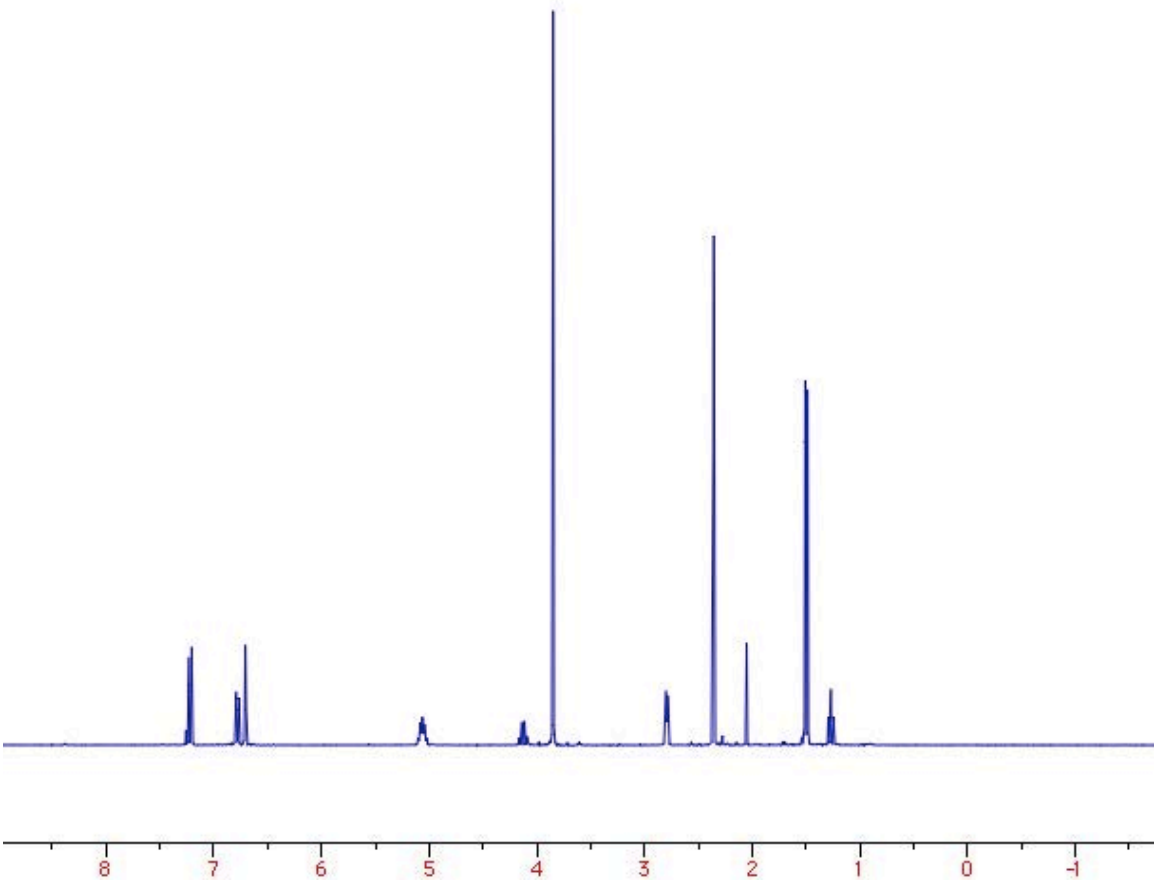


218

Compound 218: To a solution of **217** (1 g, 6.1 mmol, 1.0 eq) in THF (60 mL) at -78 ℃ was added DIBAl-H (1 M in THF, 13.4 mL, 13.4 mmol, 2.2 eq). The reaction was warmed to 0 ℃ 4 h later at which time MeOH (30 mL) was added followed by Rochelle's salt (60 mL) and stirred overnight. The reaction was extracted with Et_2O, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 83% yields (840 mg).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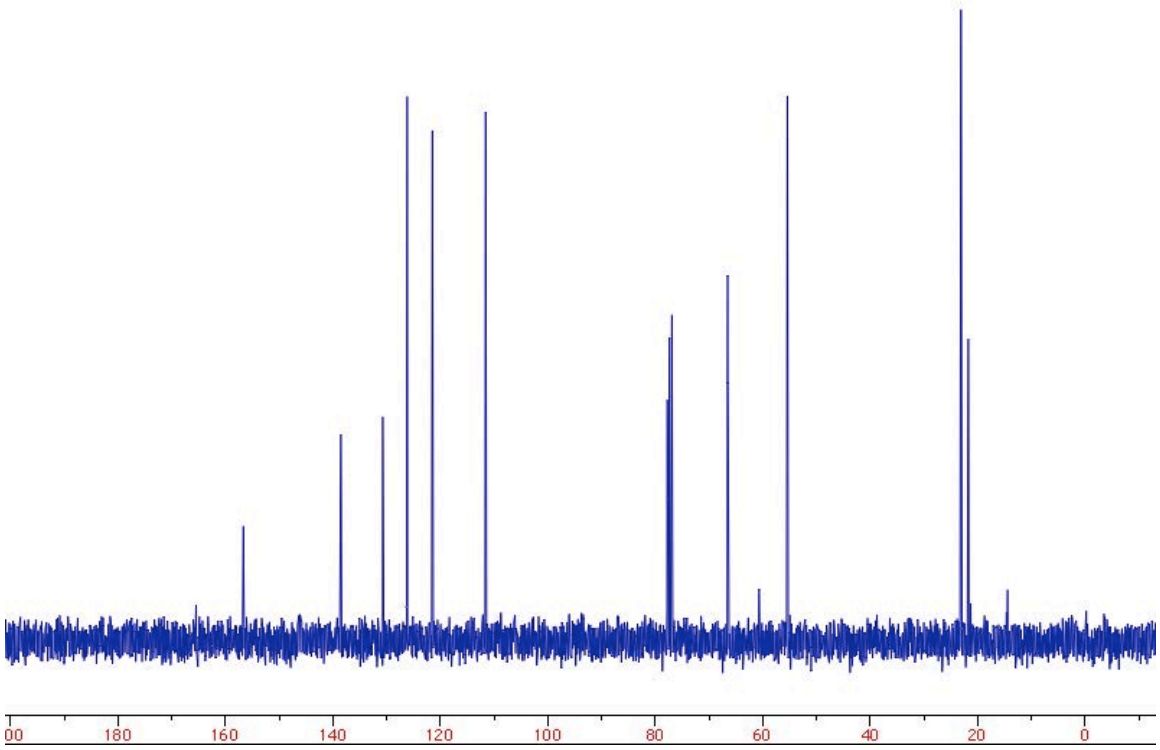
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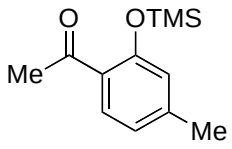
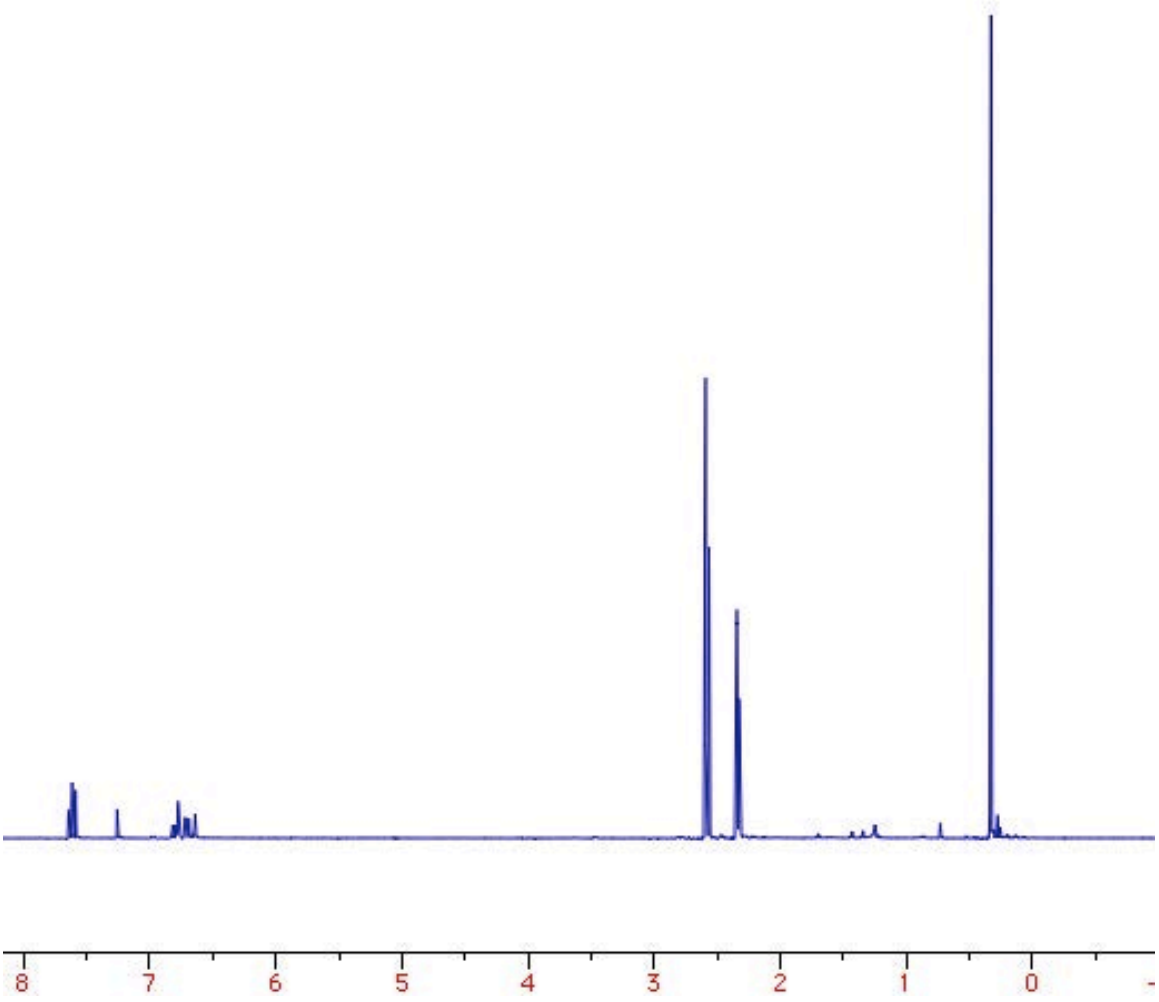


222

Compound 222: To a solution of **209** (0.1 mL, 0.72 mmol, 1.0 eq) in Et_2O (2 mL) was added TMSCl (0.11 mL, 0.86 mmol, 1.2 eq.) and Et_3N (0.14 mL, 1.01 mmol, 1.4 eq). The reaction was quenched, 12 h later, with a saturated NH_4Cl solution, extracted with hexane, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 65% yields (104 mg).

See III-075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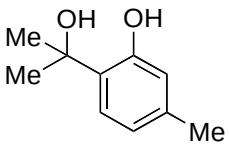
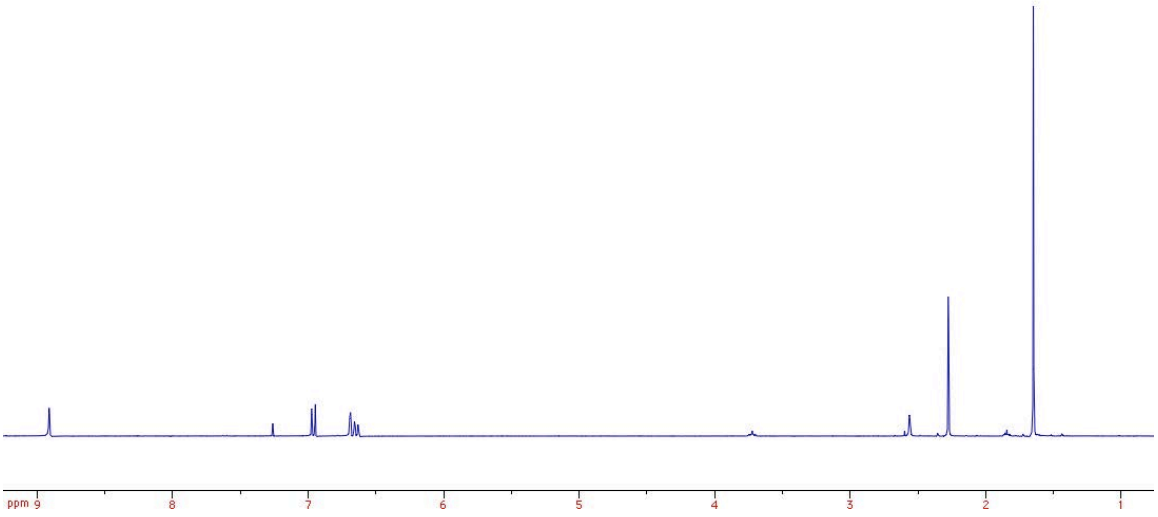
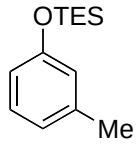


226

Compound 226: To a solution of **209** (10 mL, 71.9 mmol, 1.0 eq) in THF (600 mL) at -78 ℃ was added MeLi (1.6 M, 94 mL, 151 mmol, 2.1 eq.) and left to stir at the same temperature. The reaction was quenched, 12 h later, with a saturated NH_4Cl solution and extracted with hexanes. The organic layers were combined, washed with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 53% yields (6.3 g).

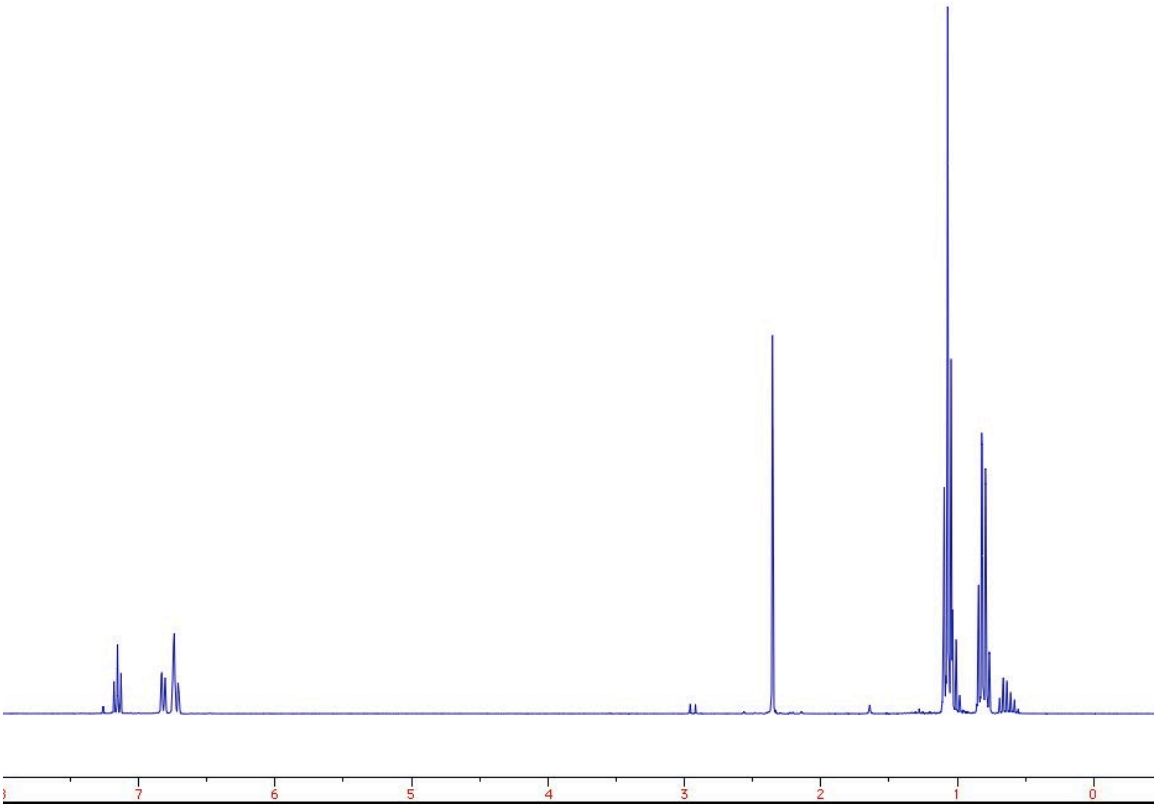
See III-074

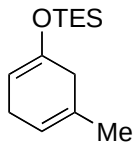




232

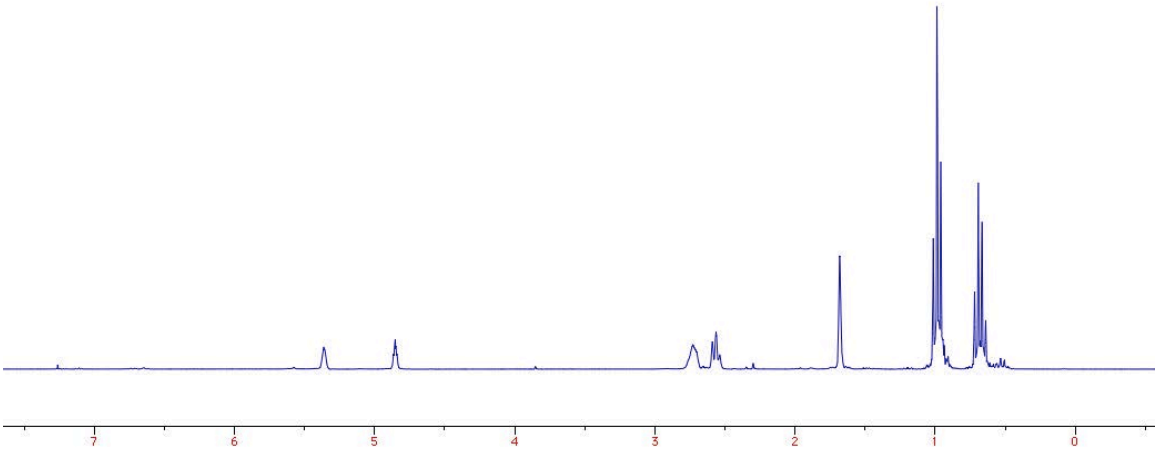
Compound 232: To a solution of **231** (2 mL, 19.1 mmol, 1.0 eq) in DMF (20 mL) was added TESCl (3.8 mL, 2.94 mmol, 1.2 eq.) and imidazole (3.25 g, 47.8 mmol, 2.5 eq) and brought to 60 ℃. The reaction poured onto pentanes 12 h later, washed once with a saturated solution of $NaHCO_3$, extracted with DCM, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 78% yields (1.4 g).





233

Compound 233: A 500 mL 3-necked round bottom flask equipped with a dry-ice condenser was purged with argon and cooled to -78 ℃ after which ammonia (14 mL, 539 mmol, 60 eq.) was condensed into said flask. Compound **232** (2 g, 8.99 mmol, 1 eq.) in ether (9.3 mL, 89 mmol, 10 eq.) was added to the flask followed by *t*-butanol (5.1 ml, 53.96 mmol, 6 eq.) and left to stir at -78 ℃ for 10 min. Lithium wire (189 mg, 26.8 mmol, 3 eq.) was added to the solution over a 30 min period and left to stir at -78 ℃ for 6 h. The reaction was quenched with solid ammonium chloride and stirred for 2 h. Gentle heating, 33 ℃, of the reaction evaporated the ammonia. Once the ammonia was removed, the resulting solution was diluted with 150 mL of pentane and then poured onto 200 mL of 1:1 water:pentane. The pentane layer was washed with water (3 x 50 mL), dried with anhydrous $MgSO_4$ and concentrated to afford product in 68% yields (569 mg).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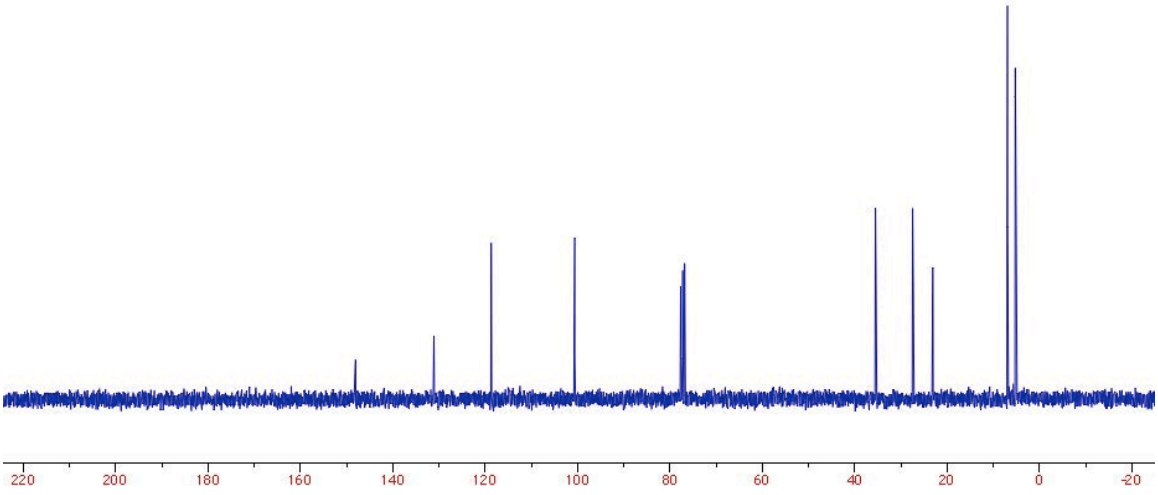
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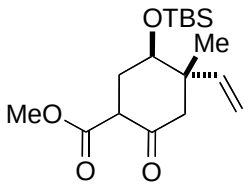
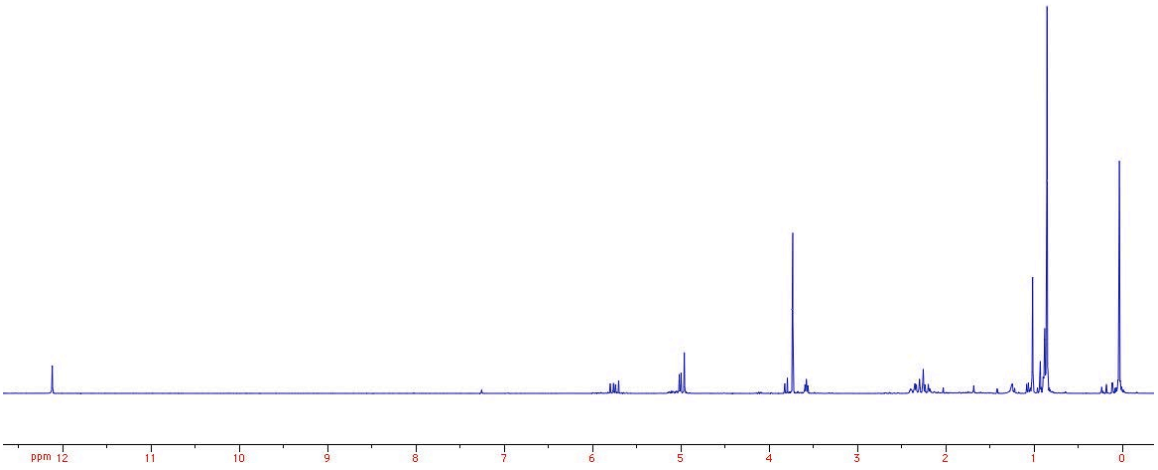


236

Compound 236: To a flamed dried 100 mL RBF was added THF (37 mL) and (**140**) (1.0 g, 3.72 mmol, 1.0 eq.) and cooled to -78 ℃. To the cooled solution was added LHMDS (4.10 mL, 4.09 mL, 1.1 eq.) and left to stir for 1 h to which methylcyanoformate (0.44 mL, 5.58 mmol, 1.5 eq.) was added. Once added the reaction was allowed to warm to RT gradually at which point NH_4Cl was added to quench and extracted with hexanes. The organic layers were combined, washed with water and brine, dried and concentrated. Purification by flash silica gel chromatography (5% EtOAc in Hexane) afforded product in 94% yields (1.1 g)

^{1}HNMR: (300 MHz, $CDCl_3$) δ 12.12 (s, 1H), 5.75 (dd, 10.6, 10.7 Hz, 1H), 4.99 (dd, 5.5, 11.4 Hz, 2H), 3.73 (s, 1H), 3.58 (t, 4.8, 5.0 Hz, 1H), 2.41-2.18 (m, 4H), 1.02 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 172.9, 170.9, 144.0, 112.8, 93.9, 72.3, 51.6, 41.4, 37.0, 31.8, 29.5, 26.0, 22.8, 21.4, 18.2, -4.0, -4.7.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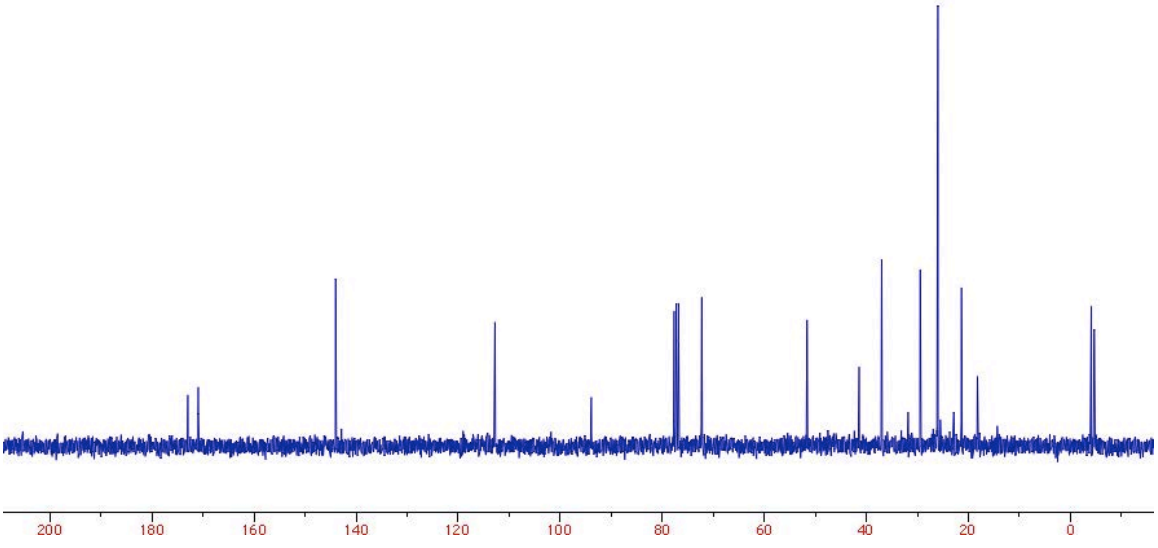
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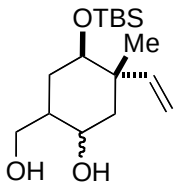
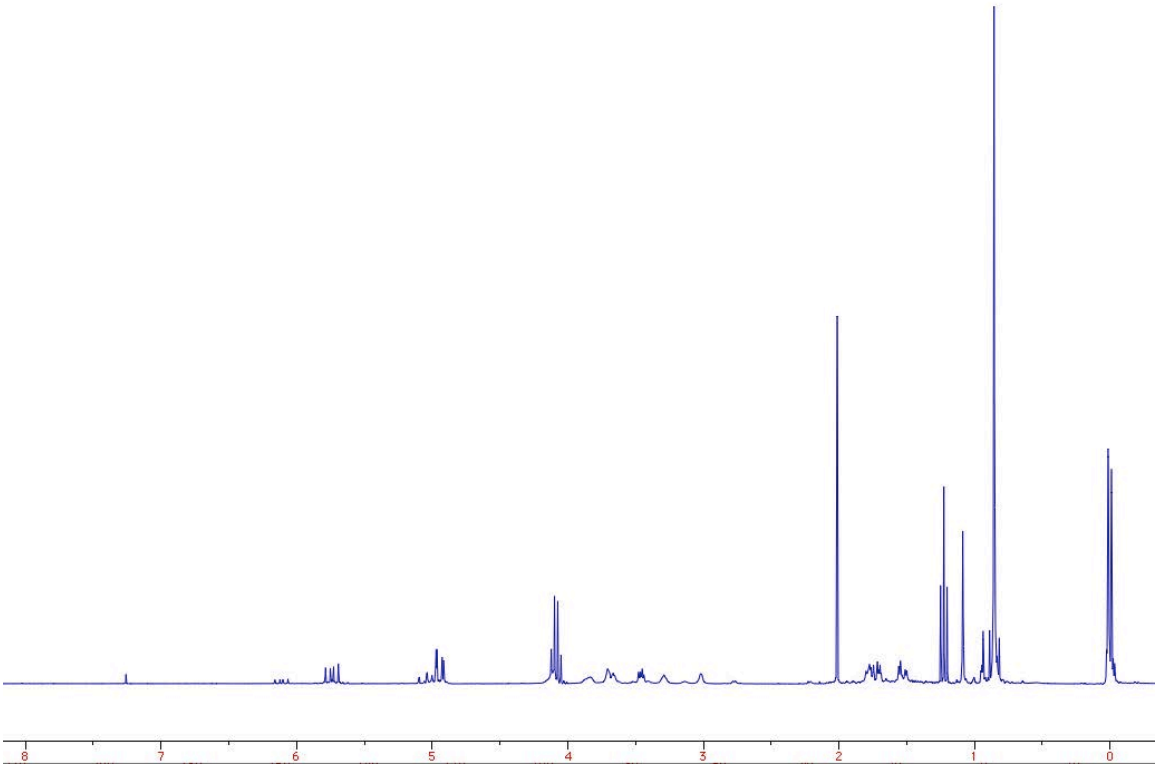


237

Compound 237: To a flamed dried 50 mL RBF was added EtOH (18 mL) followed by $NaBH_4$ (278 mg, 7.35 mmol, 4 eq.) and stirred for 10 min, after which (**236**) (600 mg, 1.84 mmol, 1.0 eq.) was added. After 7 h of stirring the solvent was removed, taken up in EtOAc, washed with H_2O and brine, dried and concentrated. Purification by flash silica gel chromatography (1:4 EtOAc:Hexanes) afford product as a mixture of 4 diastereomers in 85% yields.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 6.16-5.69)m 1H), 5.09-4.91 (m, 2H), 4.12-4.05 (m, 2H), 3.85-3.02 (m, 6H), 1.80-1.49 (m, 4H), 1.08-0.94 (3H), 0.85 (s, 9H), 0.02 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 147.7, 112.6, 112.0, 75.4, 73.2, 70.7, 69.1, 65.8, 65.7, 60.7, 42.3, 41.4, 39.4, 30.3, 26.1, 26.0, 26.0, 21.3, 18.3, 14.4, -3.8, -4.1, -4.7.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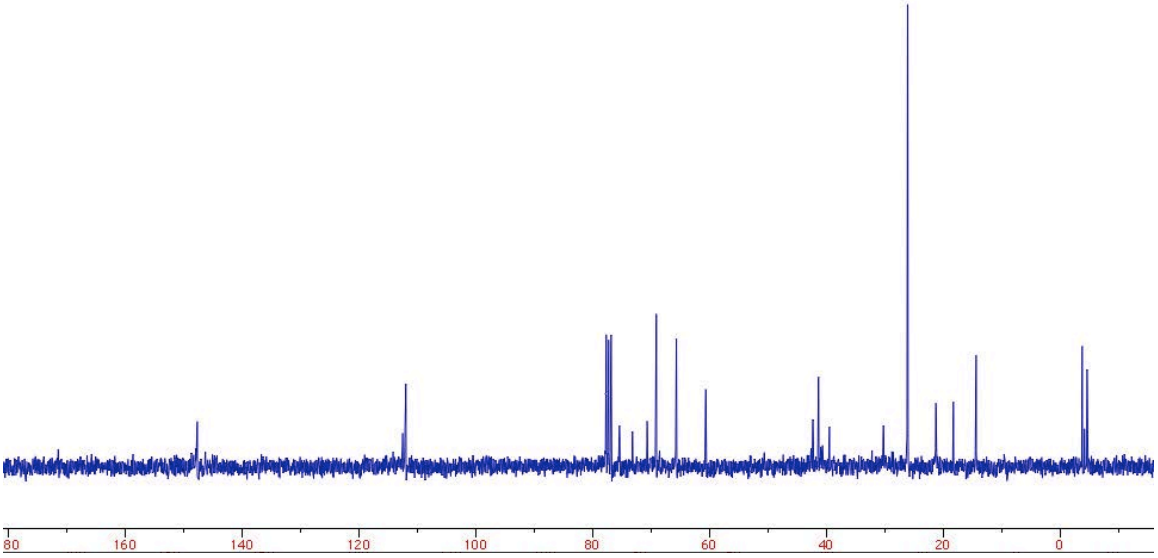
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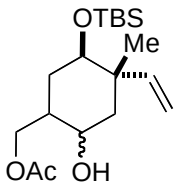
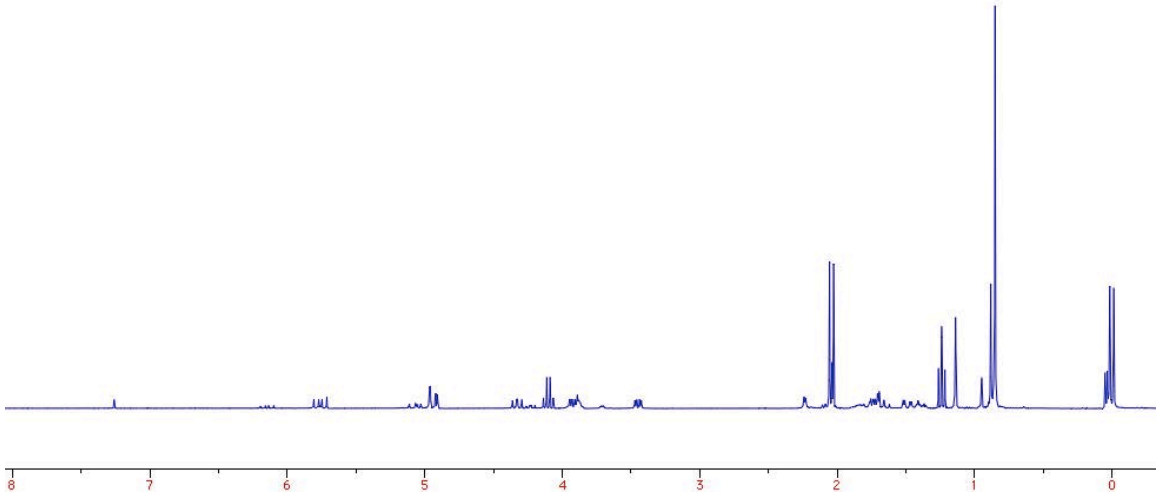


238

Compound 238: To a flamed dried 15 mL RBF was added DCM (3.5 mL), Ac_2O (0.032 mL, 0.34 mmol, 1.02 eq.), DMAP (20 mg, 0.17 mmol, 0.5 eq.) and (**237**) (100 mg, 0.33 mmol, 1.0 eq.) and stirred at RT. After 3h the reaction was quenched with NH_4Cl, extracted with EtOAc, the combined organic layers washed with brine, dried and concentrated. Purification by flash silica gel chromatography (2:3 EtOAc:hexanes) afforded product as a mixture of diastereomers in 78% yields (88 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 6.20-5.71 (m, 1H), 5.12-4.91 (m, 3H), 4.36-4.19 (m, 2H), 3.95-3.89 (m, 3H), 3.72-3.71 (m, 1H), 3.47-3.43 (m, 1H), 2.24-2.23 (m, 1H), 2.06 (s, 3H), 1.86-1.37 (m, 7H), 1.14 (s, 3H), 0.96-0.88 (m, 3H), 0.85 (s, 9H), 0.05-0.01 (m, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 171.9, 148.6, 147.5, 112.6, 111.7, 75.9, 72.9, 67.5, 65.8, 65.6, 60.6, 42.1, 41.2, 41.1, 40.6, 39.1, 29.0, 26.0, 21.3, 21.2, 18.2, 14.4, -3.8, -4.5.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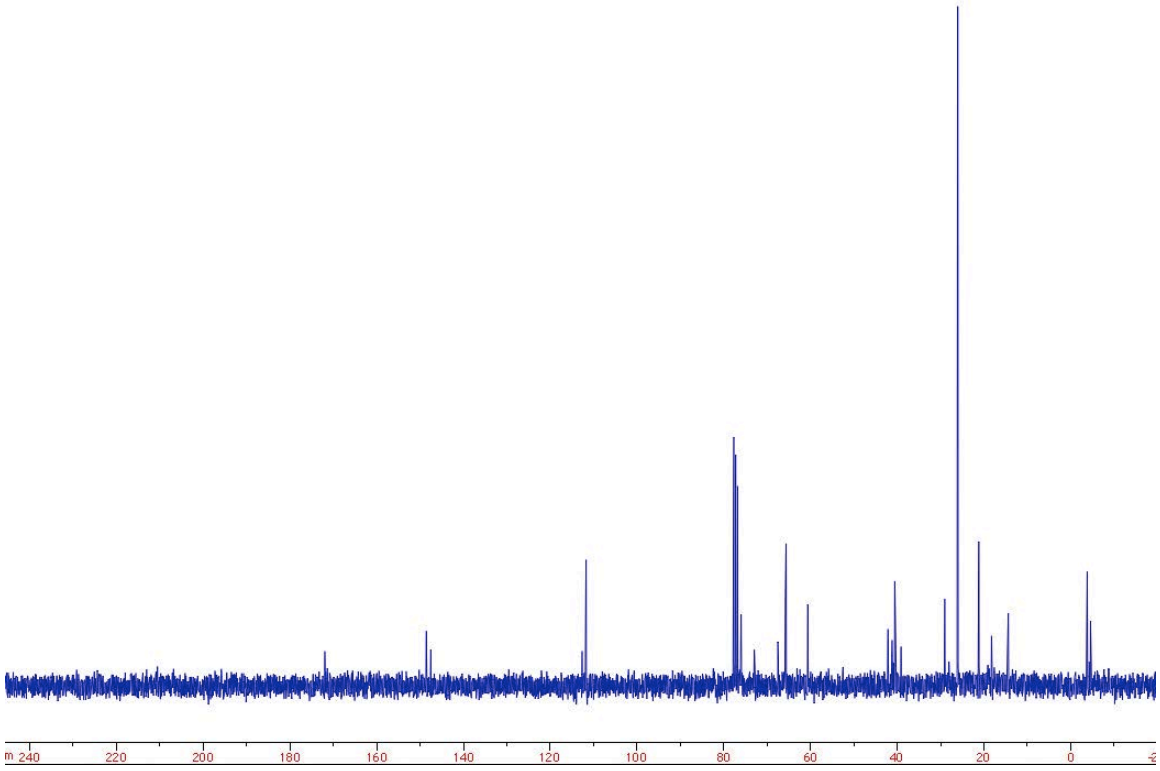
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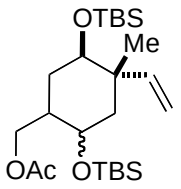
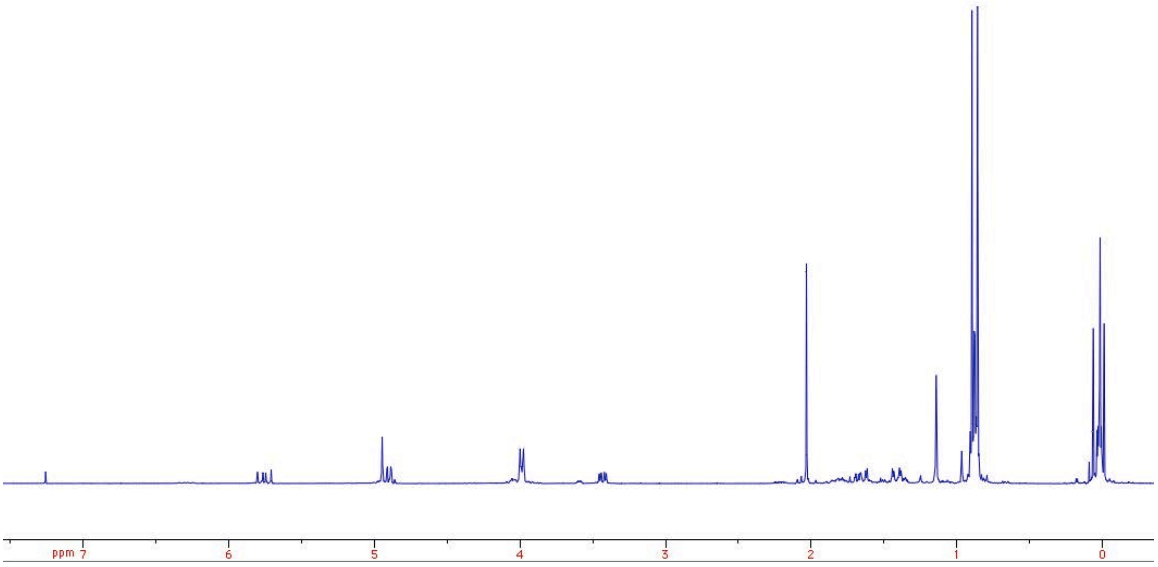


239

Compound 239: To a solution of (**238**) (110 mg, 0.32 mmol, 1.0 eq.) in DCM (0.04 M, 6 mL) was added diisopropylethylamine (0.33 mL, 1.93 mmol, 6.0 eq.) and cooled to -78 ℃. In a separate RBF was added TBSOTf (0.29 mL, 1.28 mmol, 4.0 eq.), diisopropylethylamine (0.11 mL, 0.64 mmol, 2.0 eq.) and DCM (0.17 M, 8 mL) and cooled to -78 ℃, at which point the TBSOTf solution was added via cannula to the previous solution. The reaction was quenched with brine and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 81% yields (118 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.76 (dd, 11.2, 11.2 Hz, 1H), 4.92 (dd, 1.2, 17.6 Hz, 2H), 3.99 (d, 7.1 Hz, 1H), 3.46-3.41 (m, 1H), 2.03 (s, 3H), 1.90-1.34 (m, 6H), 1.14 (s, 3H), 0.89-0.86 (m, 18H), 0.06-0.01 (m, 12H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ171.2, 149.1, 147.8, 111.5, 67.8, 66.5, 65.7, 42.3, 42.0, 40.9, 40.7, 29.0, 26.2, 26.1, 26.1, 25.9, 21.3, 18.8, 18.3, -3.6, -4.5, -5.1; **HMRS-FAB:** [M+H]+ calcd for $C_{24}H_{49}O_4Si_2$, 457.31; found, 457.3158.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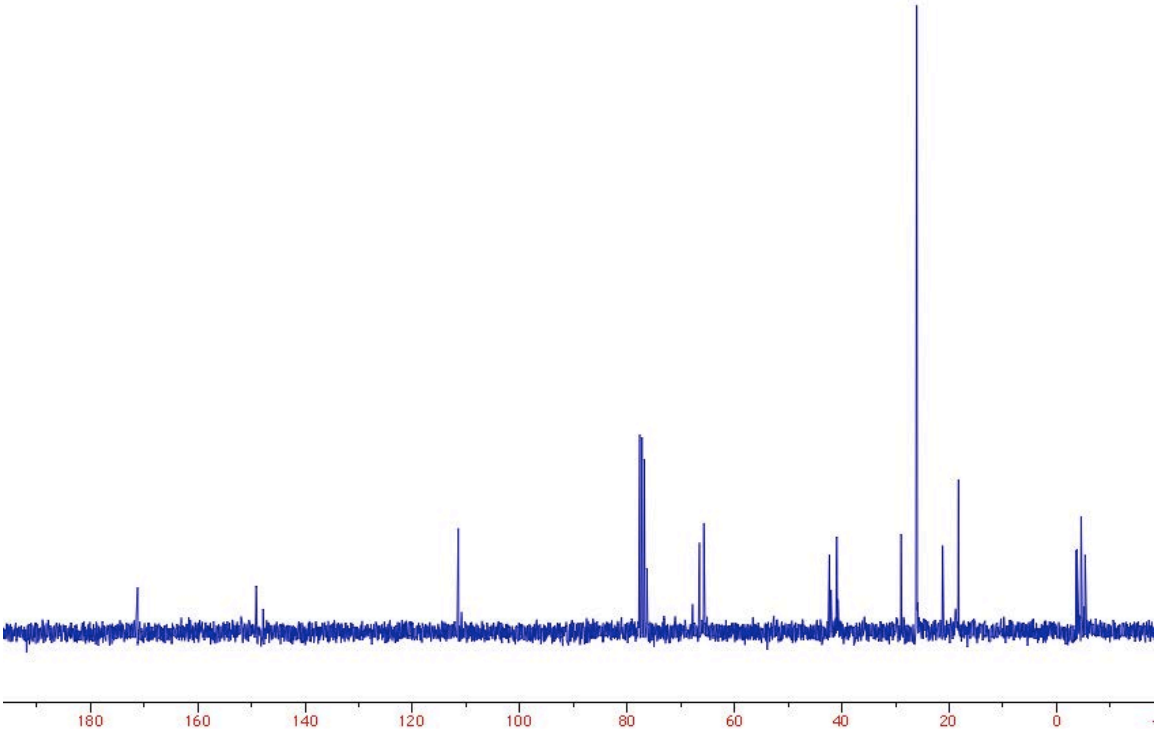
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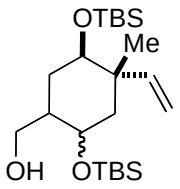
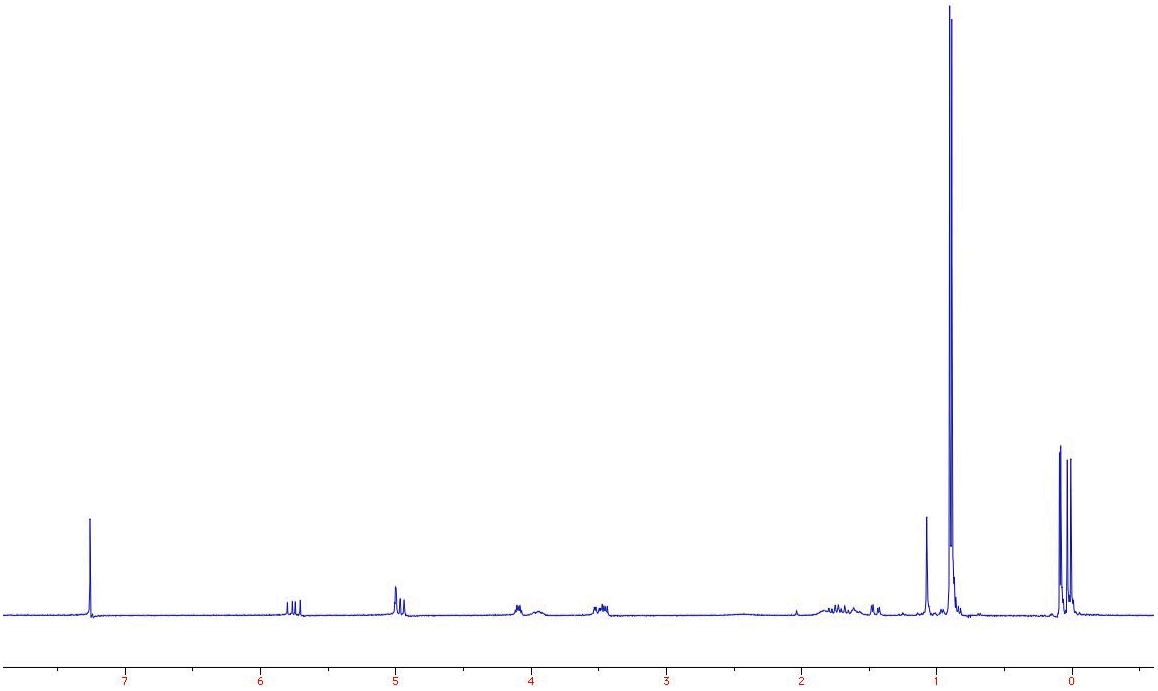


240

Compound 240: To a solution of (**239**) (0.11 mmol, 1.0 eq.) in MeOH (1 mL) was added K_2CO_3 (30 mg, 0.22 mmol, 2.0 eq.) and left to stir. The reaction was quenched with the addition of saturated NH_4Cl 3 h later and extracted with hexane. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in quantitative yields (46 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.75 (dd, 11.1, 11.1 Hz, 1H), 4.97 (dd, 8.1, 9.9 Hz, 2H), 4.12-4.07 (m, 1H), 3.99-3.91 (m, 1H), 3.53-3.44 (m, 2H), 1.85-1.43 (m, 6H), 1.08 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H), 0.04 (s, 6H).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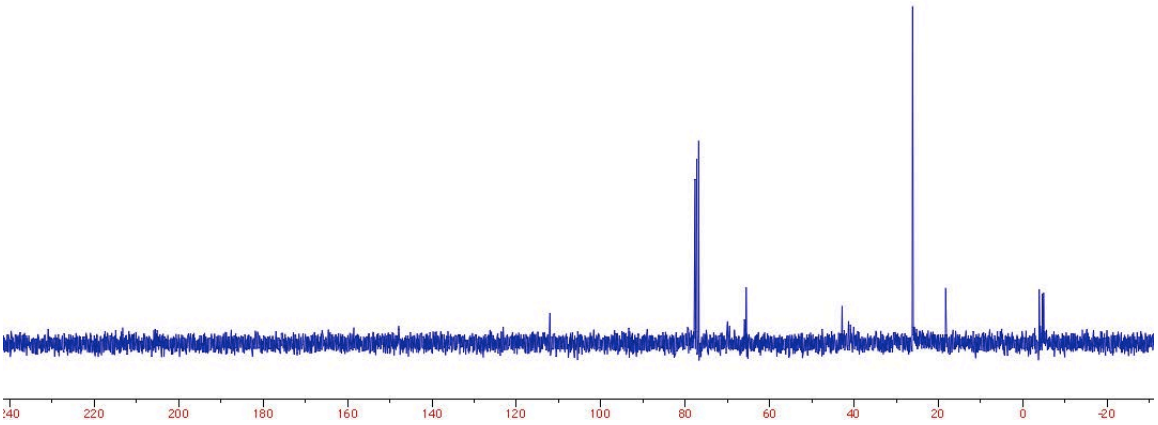
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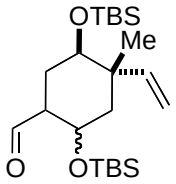
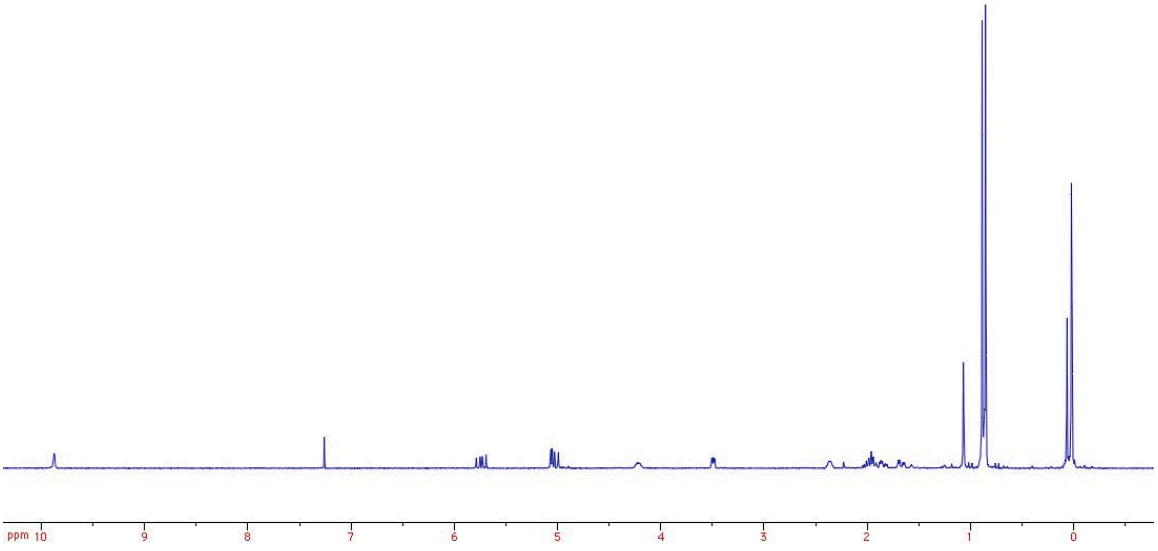


241

Compound 241: To a solution of (**240**) (8 mg, 0.02 mmol, 1.0 eq.) in DCM (0.4 mL) was added DMP (24 mg, 0.06 mmol, 3.0 eq.) and left to stir for 4 h. The reaction was quenched with the addition of saturated $Na_2S_2O_3$ and left to stir for an additional 30 min, after which it was washed with saturated $NaHCO_3$ (x3) and $Na_2S_2O_3$, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:3 EtOAc:hexane) to afford product in 93% yields (8 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 5.73 (dd, 11.0, 11.1 Hz, 1H), 5.03 (dd, 4.1, 11.2, Hz, 2H), 4.25-4.19 (m, 1H), 3.51-3.48 (m, 1H), 2.39-2.33 (m, 1H), 2.04-1.57(m, 4H), 1.07 (s, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.02 (s, 6H).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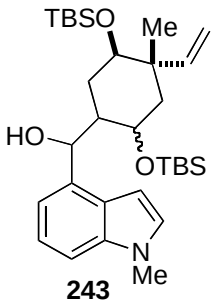
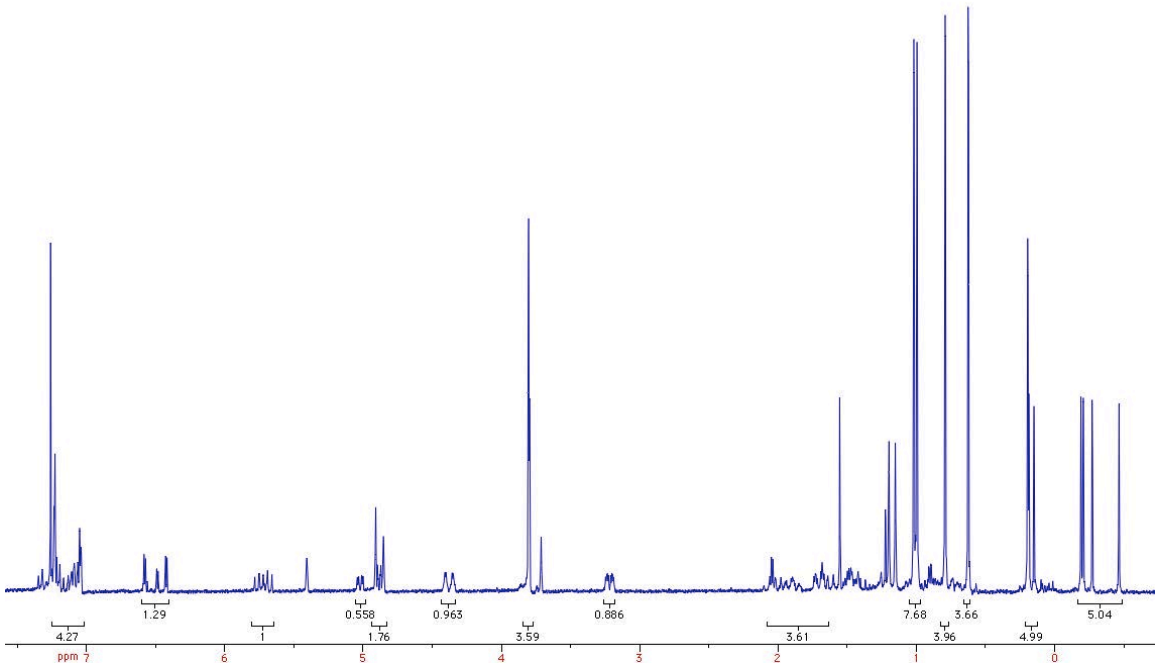


243

Compound 243: To a solution of n-methyl-4bromoindole (62 mg, 0.29 mmol, 1.1 eq.) in Et_2O (5 mL) at -78 ℃ was added slowly *t*BuLi (1.7 M in pentane, 0.34 mL, 0.59 mmol, 2.2 eq.) and left to stir at the same temperature. A solution of **241** (110 mg, 0.27 mmol, 1.0 eq.) in Et_2O (2 mL) was added 10 min later, and left to stir for 1 h, then quenched with saturated NH_4Cl, washed with saturated $NaHCO_3$ and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:5 EtOAc:hexane) to afford product in 89% yield (131 mg).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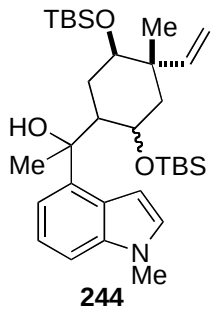
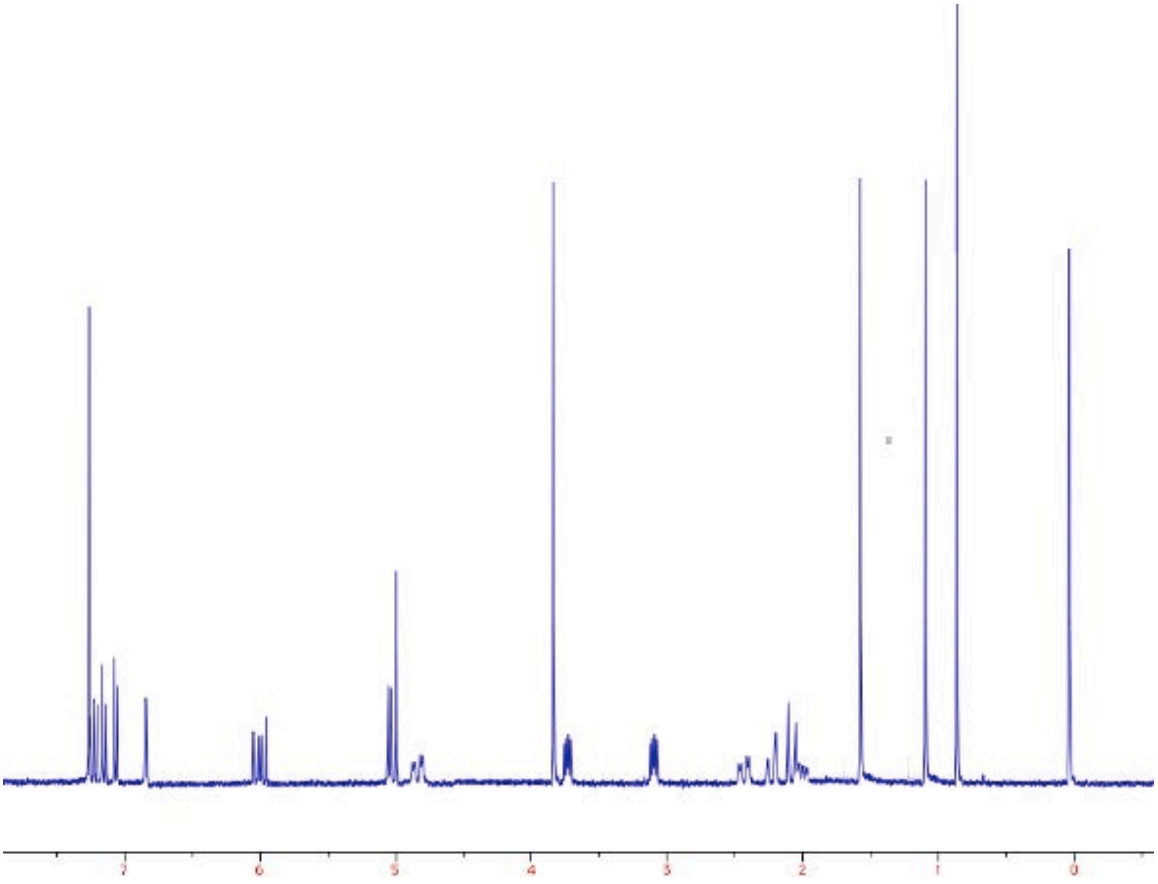


244

Compound 244: To a solution of (**243**) (1.0 eq.) in DCM (0.1 M) was added DMP (3.0 eq.) and left to stir for 3 h. The reaction was quenched with the addition of saturated $Na_2S_2O_3$ and left to stir for an additional 30 min, after which it was washed with saturated $NaHCO_3$ (x3) and $Na_2S_2O_3$, dried and concentrated to afford crude material. The crude material was taken up in THF and cooled to -78℃ to which methyl Grignard (1 M in THF, 1.05 eq.) was added and left to stir for 45 min. The reaction was quenched with a solution of NH_4Cl and extracted with hexane. The organic layers were concentrated, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:5 EtOAc:hexane) to afford product in 78% yield over 2 steps.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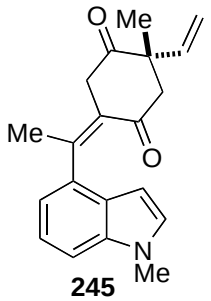
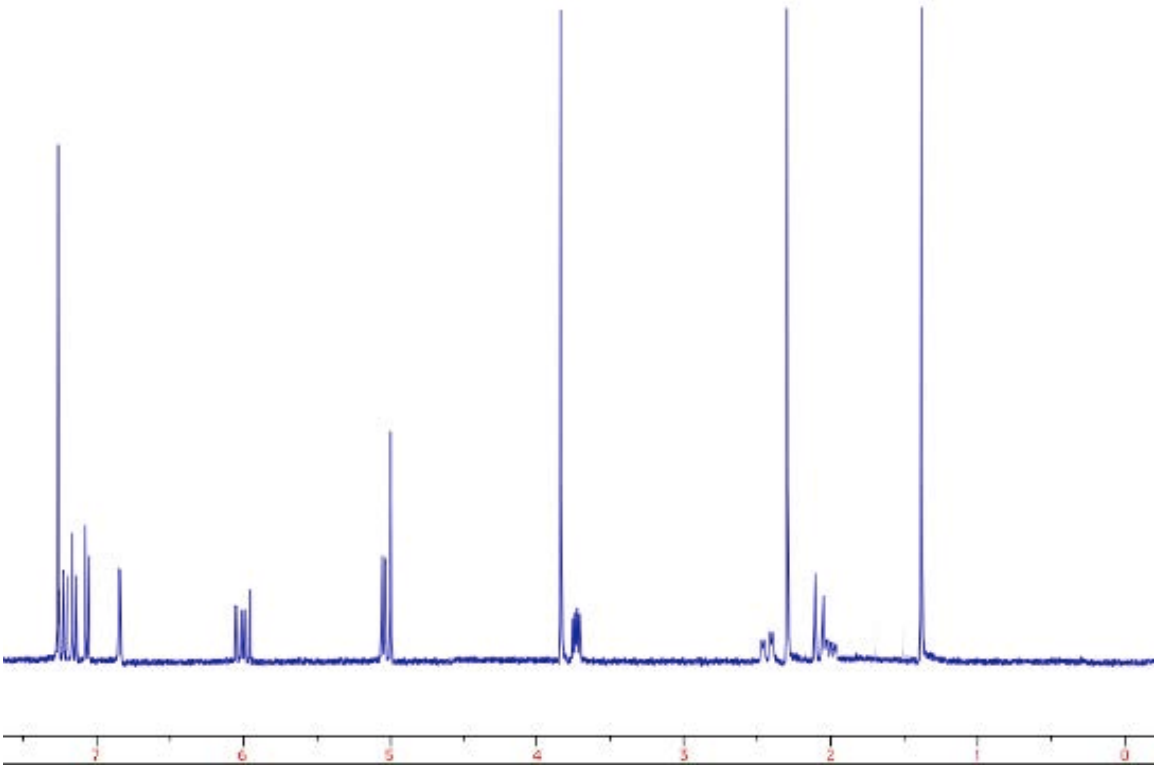


245

Compound 245: To a solution of (**244**) (1.0 eq.) in THF (0.1 M) was added TBAF (1 M in THF, 4.5 eq.) and left to stir for 3 h. The reaction was concentrated and filtered through a silica plug to afford crude material. The crude material was taken up in DCM (0.2 M), to which DMP (5 eq.) was added and left to stir for 5 h. The reaction was quenched with the addition of saturated $Na_2S_2O_3$ and left to stir for an additional 30 min, after which it was washed with saturated $NaHCO_3$ (x3) and $Na_2S_2O_3$, dried and concentrated to afford the desired crude di-keto-mono-alcohol compound. The crude product was taken up in THF, treated with NaH (1.5 eq.) followed by MsCl (2.3 eq.). After 2 h, TsOH (excess) was added and left to stir for 12 h. The reaction was quenched with brine and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 42% over three synthetic steps.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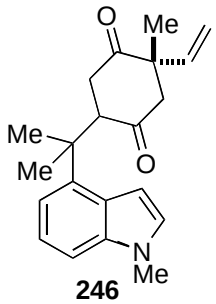
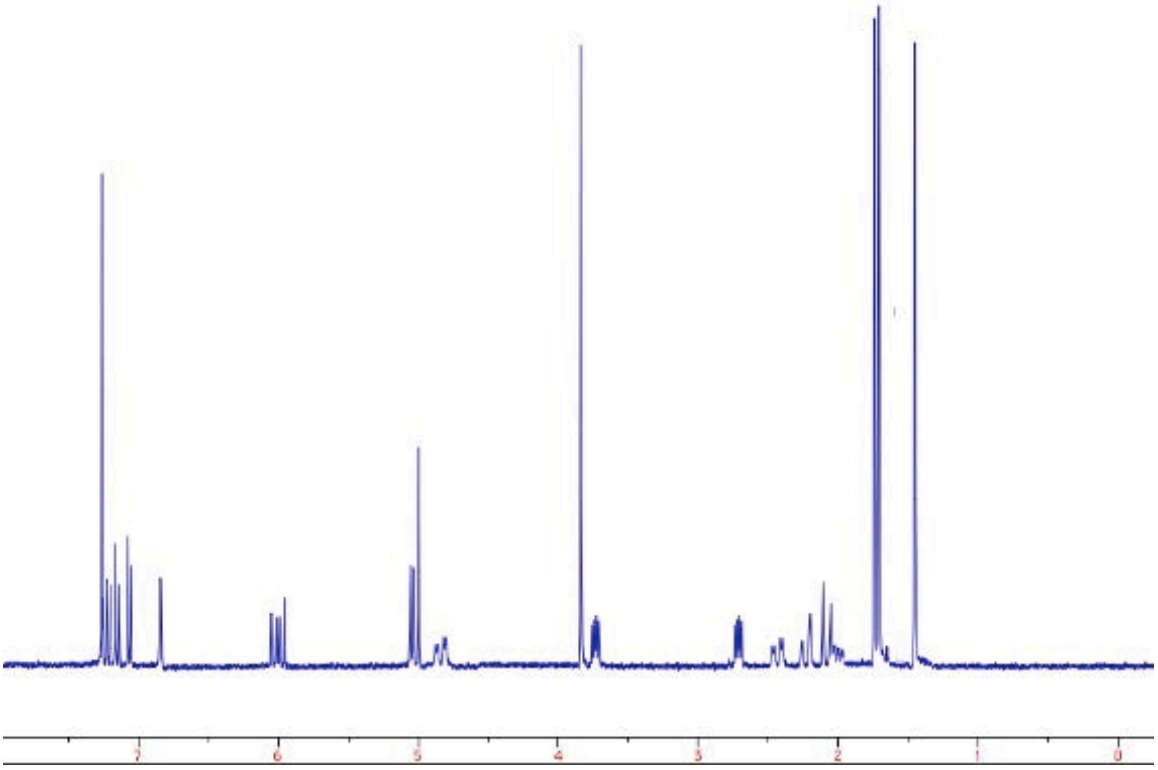


246

Compound 246: To a RBF was added THF (0.1 M) and CuBr•Me_2S (0.2 eq.) and stirred while cooling to -78°C. Over a 15 min period methyl Grignard (3.0 eq.) was added and left to stir for 30 min. TMEDA (4 eq.), TMSCl (2.5 eq.) and (**245**) (1 eq.) in THF was added. The reaction was left to stir at -78°C for a 4 h, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried over anhydrous $MgSO_4$ and concentrated. The crude material was added to a pre-mixed solution of THF:AcOH:Water (2:1:1, 0.1 M) and stirred at rt for 1 h. The reaction was diluted with EtOAc, washed with saturated $NaHCO_3$ and water, dried and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 62% yields.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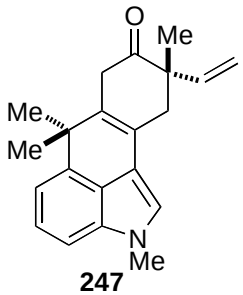
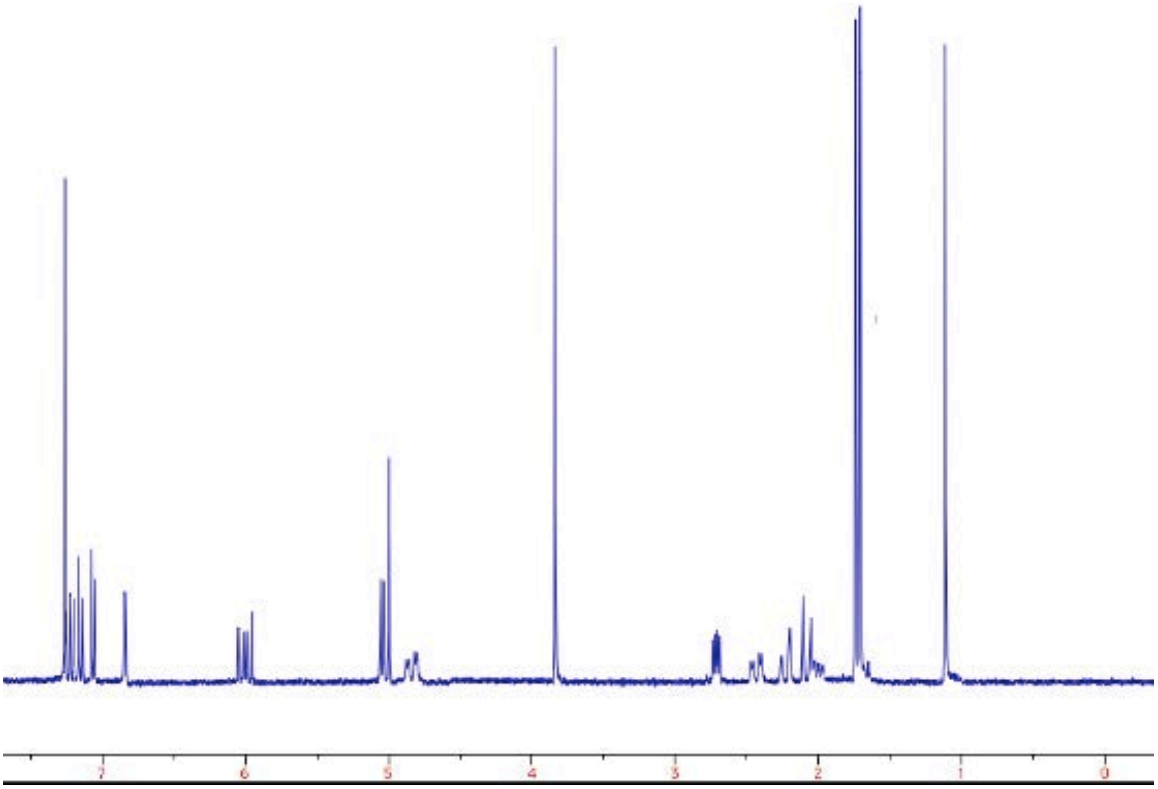


247

Compound 247: To a solution of **246** (1.0 eq.) in DCM (0.1 M) was added BF_3-etherate (1.05 eq.) and left to stir at rt for 2 h. The reaction was concentrated and purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 54% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.24-7.23 (m, 3H), 6.83 (s, 1H), 6.09 (dd, 17.2, 10.5 Hz, 1H), 5.08 (dd, 21.5, 10.6 Hz, 2H), 3.74 (s, 3H), 2.59-1.87 (comp, 4H), 1.56 (s, 6H), 1.05 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 145.3, 144.2, 141.3, 123.8, 121.7, 120.8, 115.1, 114.4, 107.3, 99.2, 73.2, 72.8, 46.7, 38.8, 35.9, 32.2, 31.2, 28.4, 26.0, 25.1, 18.2, -3.0.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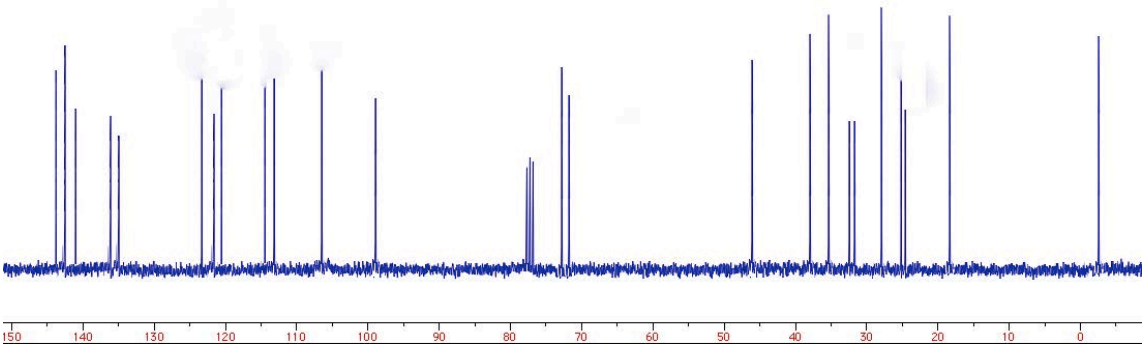
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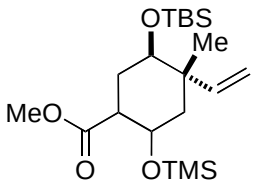
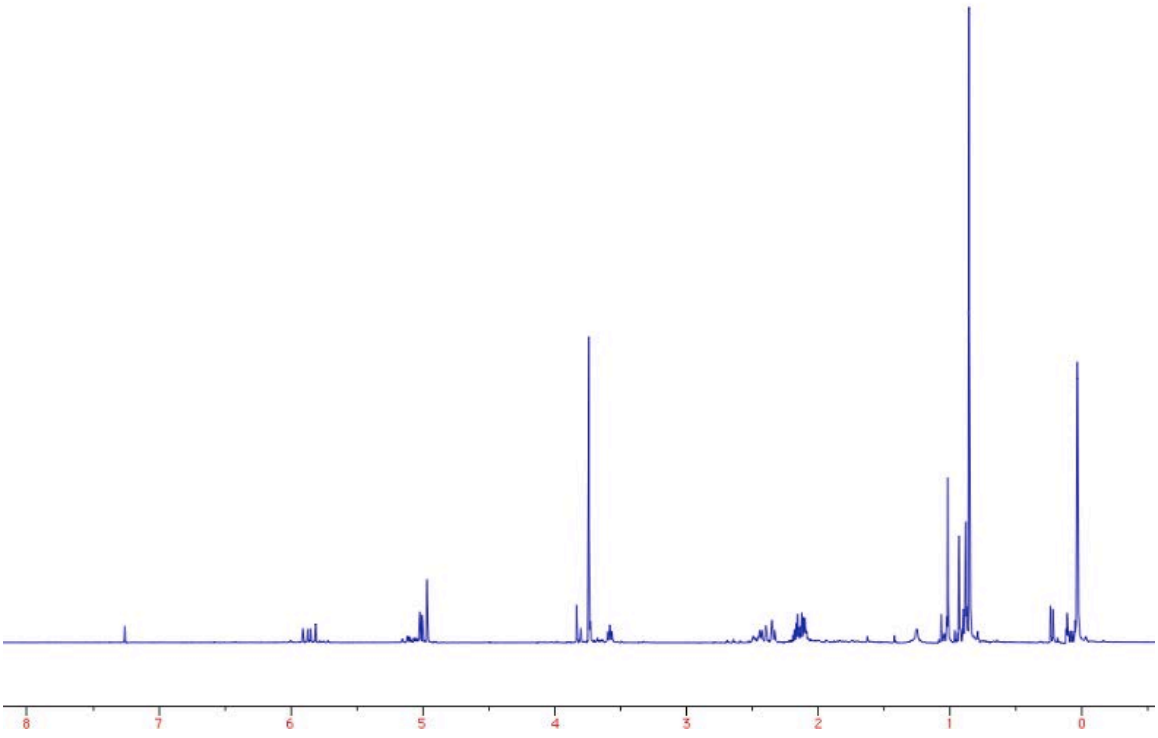
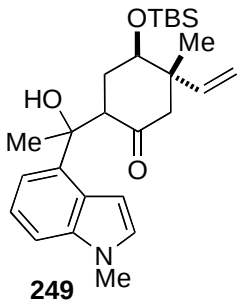


248

Compound 248: To solution of THF (37 mL) compound **140** (1.0 g, 3.72 mmol, 1.0 eq.) was added and cooled to -78 ℃. To the cooled solution was added LiHMDS (4.10 mL, 4.09 mL, 1.1 eq.) and left to stir for 1 h to which methylcyanoformate (0.44 mL, 5.58 mmol, 1.5 eq.) was added. Once added the reaction was allowed to warm to RT gradually at which point NH_4Cl was added to quench and extracted with hexanes. The organic layers were combined, washed with brine and water, dried and concentrated. Purification by flash silica gel chromatography (5% EtOAc in Hexane) afforded product. The product (100 mg, 0.306 mmol) was added to THF (3 mL) and cooled to 0 ℃, to which $NaBH_4$ (23 mg, 0.61 mmol, 2 eq.) added in one portion. The reaction was concentrated after 1 h and purified by flash silica gel chromatography (1:4 EtOAc:Hexane). NaH (44 mg, 1.09 mmol, 1.2 eq.) was added to THF (10 mL) and cooled to 0 ℃, to which the product (300 mg, 0.91 mmol) was added dropwise over 10 min and left to stir for 30 min. The reaction was brought to rt and TMSCl (0.16 mL, 1.27 mmol, 1.4 eq.) was added and left to stir for 1 h. The reaction was quenched with brine and extracted with hexanes (x2). The organic layers were combined washed with water and brine, dried and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 73% yield (1.08 g, 3 steps).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.76 (dd, 17.7 Hz, 1H), 5.00 (dd, 3.1 Hz, 2H), 3.74 (s, 3H), 3.58 (t, 4.8 Hz, 1H), 2.55-2.182 (m, 6H), 1.020 (s, 3H), 0.849 (s, 9H), 0.038 (s, 6H), 0.025 (s, 9H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 170.9, 144.0, 112.8, 78.1, 72.2, 51.7, 46.3, 41.6, 36.9, 29.5, 26.0, 21,4, 18.2, 4.6, 3.9; **IR:** (NaCl Film) 1632, 1243 cm^{-1}; **HMRS-FAB**: [M] calcd for $C_{20}H_{40}O_4Si_2$, 400.25; found, 400.2563.



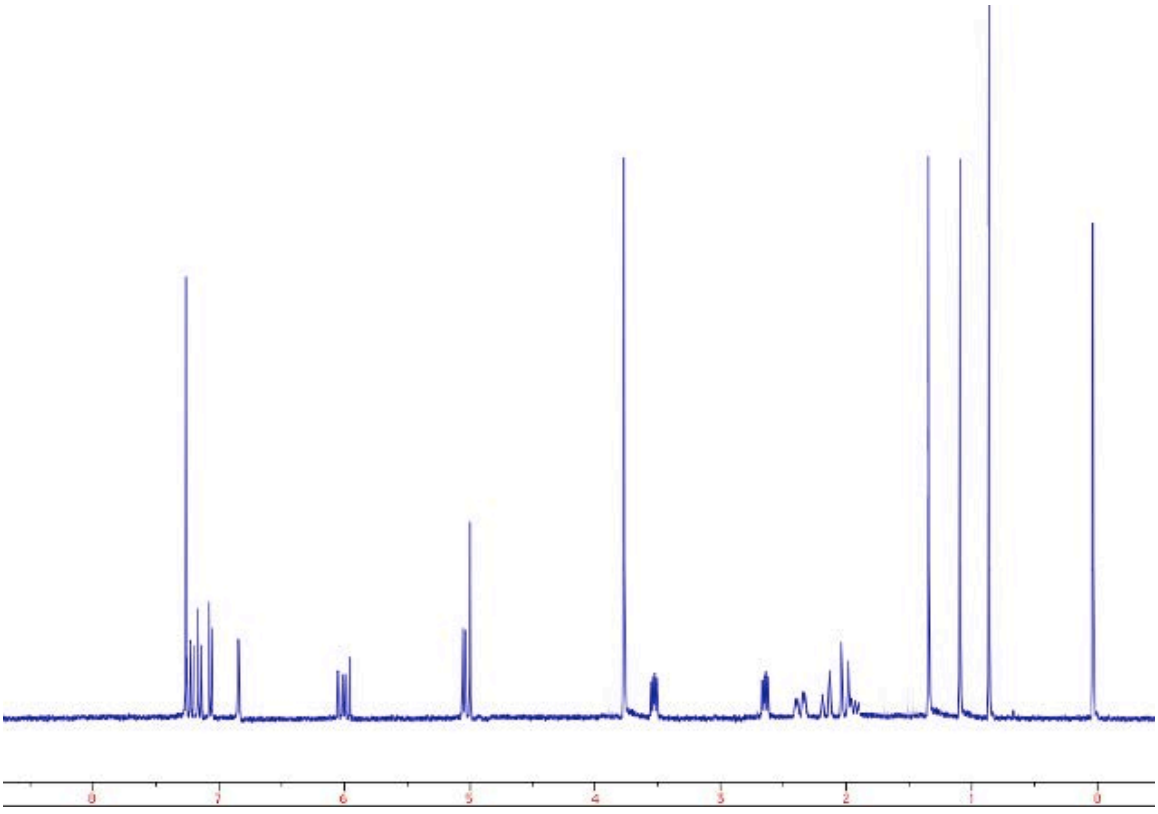


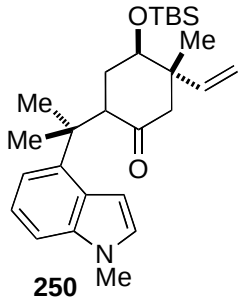
249

Compound 249: To a solution of *N*-methoxy-methylamine hydrochloride (59 mg, 0.6 mmol, 2 eq.) in CH_2Cl_2 (4 mL) at -78 ℃, dimethyl aluminium chloride (0.04 mL, 0.36 mmol, 1.2 eq.) was added and the mixture was stirred for 1 h. Compound **248** (121 mg, 0.30 mmol) was added and the mixture was stirred at -78 ℃ for 30 min. The reaction mixture was then stirred at rt for 4 h. The reaction was quenched with excess HCl (1 M) and diluted with EtOAc. The mixture was filtered through celite, washed with HCl (1 M), $NaHCO_{3\ (sat'd)}$, and extracted with EtOAc (x2). The organic layers were combined, dried over $MgSO_4$ and concentrated. The crude material was taken up in THF (8 mL), cooled to -78 ℃ and then MeLi (1.6 M in Et_2O 0.23 mL, 0.36 mmol, 1.2 eq.) was added and left to stir for 1 h. The reaction was quenched with NH_4Cl and extracted with hexane (x2). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product. To THF (10 mL) was added the product (100 mg, 0.19 mmol), cooled to 0 ℃ and AcOH (0.02 mL, 0.29 mmol, 1.5 eq.) was added. The reaction was quenched with brine after 45 min and concentrated. The crude material was taken up in THF (4 mL) and DMP (322 mg, 0.76 mmol, 4 eq.) was added and left to stir for 2 h. To the reaction was added $Na_2S_2O_{3\ (sat'd)}$, left to stir for 30 min, washed with $Na_2S_2O_{3\ (sat'd)}$ (x2),

$NaHCO_{3\ (sat'd)}$ then brine, dried over $MgSO_4$ and concentrated. The crude material was purifed by flash silica gel chromatography (1:3 EtOAc:hexane) to afford product **7** in a 59% yield (78 mg, 4 steps).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.245-7.232 (m, 4H), 6.831 (s, 1H), 6.091 (dd, 17.2, 10.5 Hz, 1H), 5.079 (dd, 21.5, 10.6 Hz, 2H), 3.740 (s, 3H), 3.673 (t, 3.6 Hz, 1H), 3.569 (s, 1H), 2.792 (t, 3.6 Hz, 1H), 2.594-1.872 (comp, 4H), 1.354 (s, 3H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 198.6, 145.3, 144.2, 141.3, 123.8, 120.8, 115.1, 114.4, 107.3, 99.2, 73.2, 72.8, 71.6, 46.7, 38.8, 35.9, 31.2, 28.4, 26.0, 23.7, 18.2, -3.0; **IR:** (NaCl Film) 3297, 1654 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{26}H_{39}NO_3Si$, 442.27; found, 442.2742.

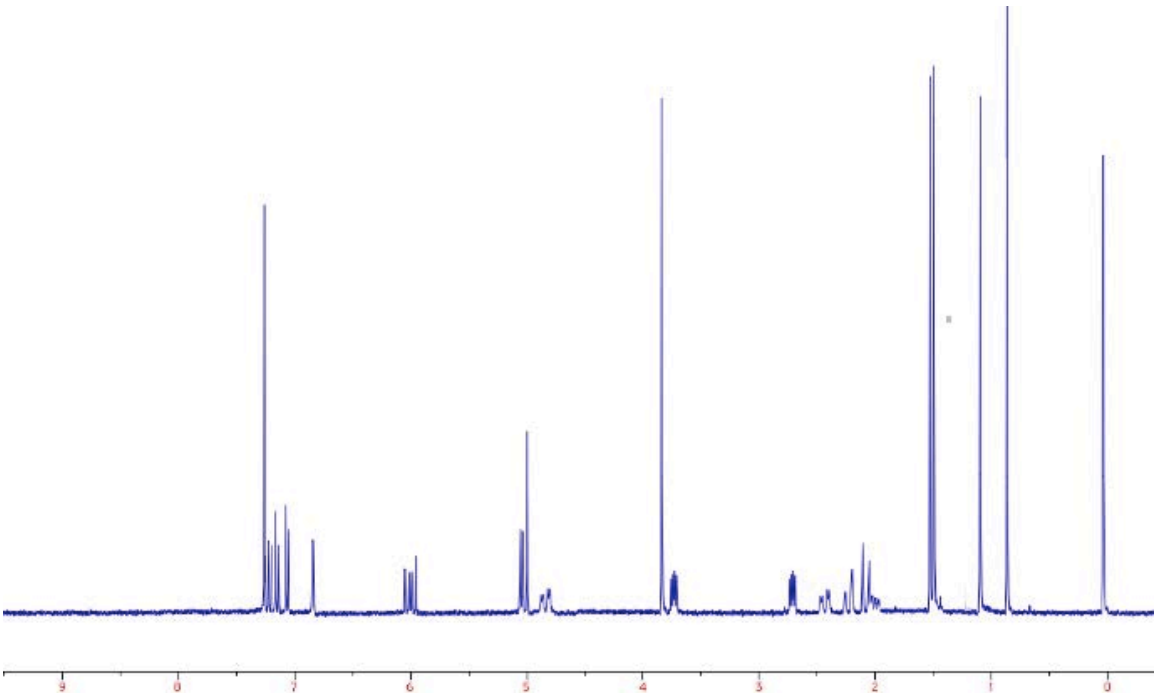




250

Compound 250: To a solution of THF (8 mL) and **249** (300 mg, 0.68 mmol) was added TsOH (cat'l) and refluxed for 1 h. The reaction was concentrated and purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford the exo-cyclic enone. Solid CuBr•Me_2S (49 mg, 0.18 mmol, 0.2 eq.) was added to a solution of THF (40 mL) and stirred while cooling to -78°C. Methylmagnesium bromide (1M in THF, 2.82 mL, 2.82 mmol, 3 eq.) was added over a 20 minute peiod and left to stir for an additional hour at the same temperature. TMEDA (0.44 mL, 3.76 mmol, 4 eq.), TMSCl (0.36 mL, 2.82 mmol, 3 eq.) and the product (400 mg, 0.944 mmol, 1 eq.) in THF (10 mL) was added. The reaction was left to stir at -78°C for a 4 h period, no additional dry-ice was added to the bath to allow the reaction to reach rt over this period. The reaction was diluted with hexane, washed with sat'd $NaHCO_3$ and water until the aqueous layer was no longer blue in color, dried over anhydrous $MgSO_4$ and concentrated. The crude oil was added to a pre-mixed solution (10 mL) of THF:H_2O:HOAc (2:1:1) and stirred at rt for 1 h. The reaction was diluted with EtOAc, washed with sat'd $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product **8** in 67% yield (200 mg, 3 steps).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.245-7.232 (m, 4H), 6.831 (s, 1H), 6.091 (dd, 17.2, 10.5 Hz, 1H), 5.079 (dd, 21.5, 10.6 Hz, 2H), 5.018 (dd, 3, 14 Hz, 2H), 3.740 (s, 3H), 3.673 (t, 3.6 Hz, 1H), 2.712 (t, 3.6 Hz, 1H), 2.594-1.872 (comp, 5H), 1.555 (s, 6H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 198.6, 145.3, 144.2, 141.3, 123.8, 120.8, 115.1, 114.4, 107.3, 99.2, 73.2, 72.8, 46.7, 38.8, 35.9, 32.2, 31.2, 28.4, 26.0, 25.1, 18.2, -3.0; **IR:** (NaCl Film) 1654 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{27}H_{41}NO_2Si$, 440.29; found, 440.2895.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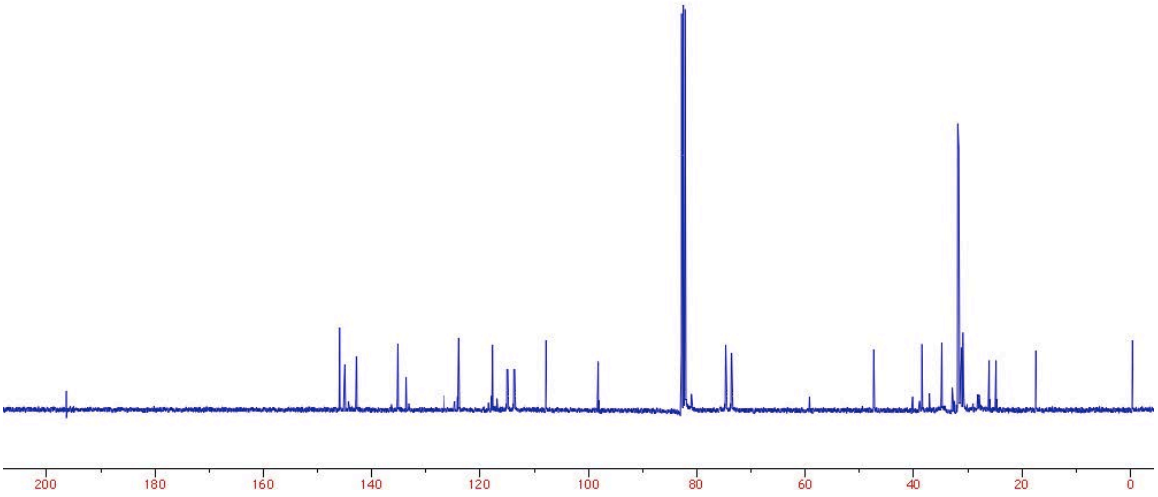
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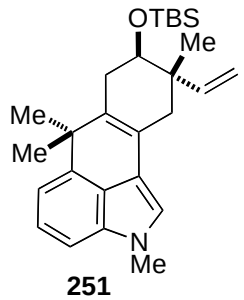
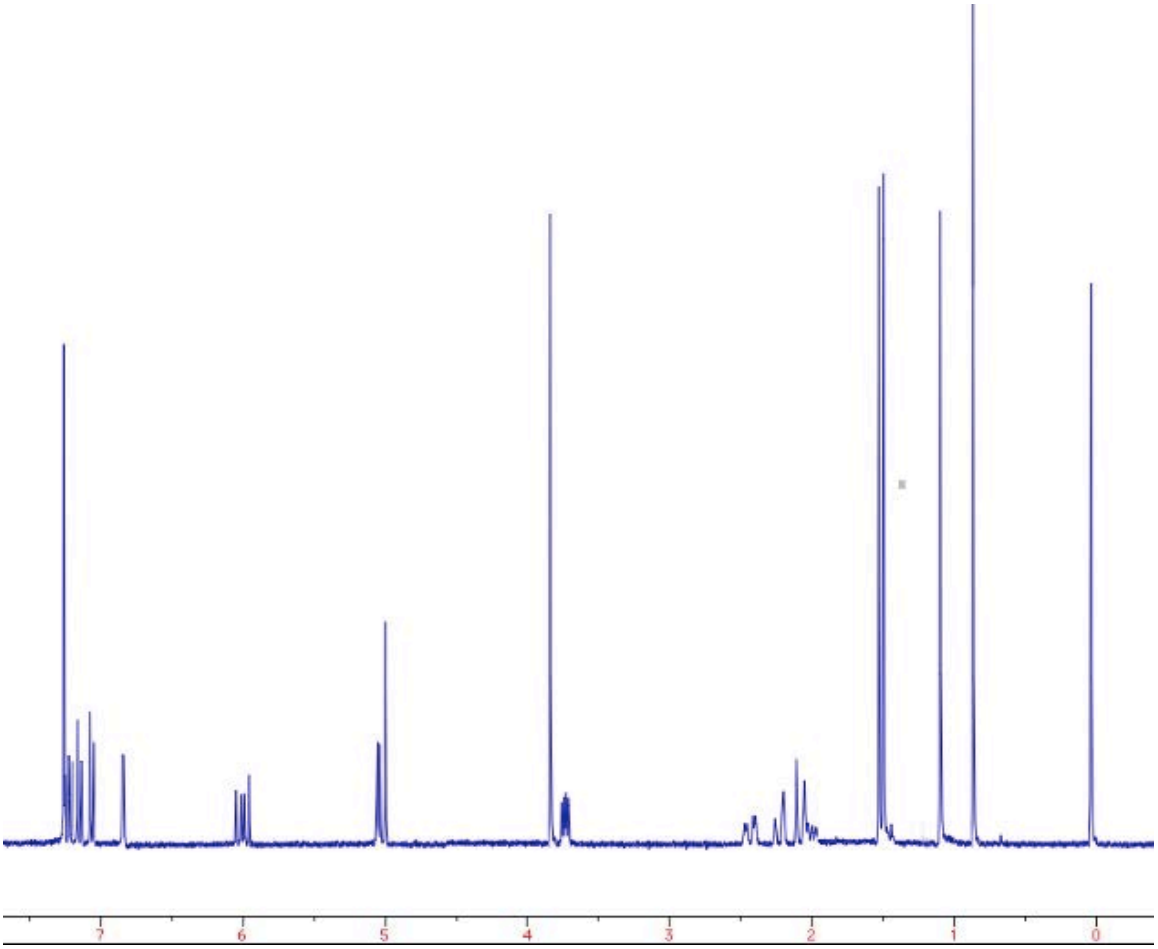


251

Compound 251: To a solution of THF (8 mL) and **250** (350 mg, 0.80 mmol) was added BF_3-etherate (0.10 mL, 0.84 mmol, 1.05 eq.) and left to stir at rt for 2 h. The reaction was concentrated and purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 92% yield (310 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.24-7.23 (m, 3H), 6.831 (s, 1H), 6.091 (dd, 17.2, 10.5 Hz, 1H), 5.079 (dd, 21.5, 10.6 Hz, 2H), 3.740 (s, 3H), 3.673 (t, 3.6 Hz, 1H), 2.594-1.872 (comp, 4H), 1.555 (s, 6H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 145.3, 144.2, 141.3, 123.8, 121.7, 120.8, 115.1, 114.4, 107.3, 99.2, 73.2, 72.8, 46.7, 38.8, 35.9, 32.2, 31.2, 28.4, 26.0, 25.1, 18.2, -3.0; **HMRS-FAB**: [M] calcd for $C_{27}H_{39}NOSi$, 421.28; found, 421.2785.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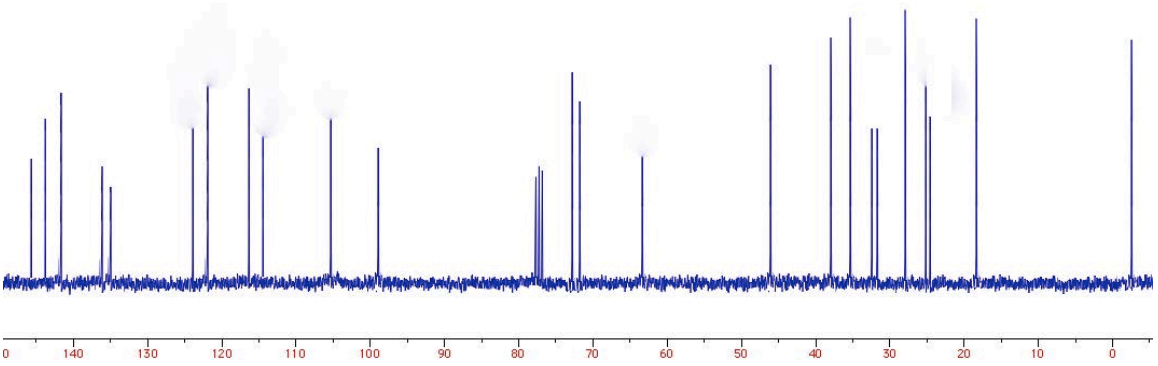
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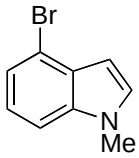
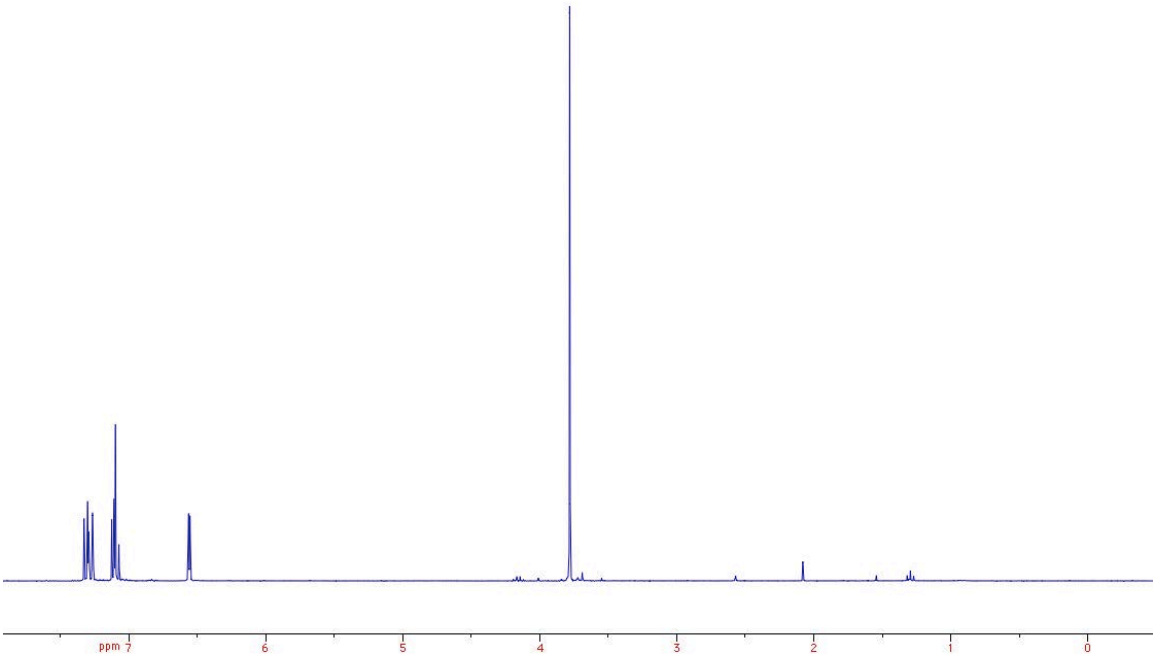


252

4-bromo-1-methyl-1H-indole (252): To a solution of THF (50 mL) was added NaH (263 mg, 6.58 mmol, 1.2 eq.) at rt, to which compound **87** (0.7 mL, 5.48 mmol) was added drop wise and allowed to stir. After 30 min, methyl iodide (0.48 mL, 7.67 mmol, 1.4 eq.) was added and allowed to stir for 5 h. The reaction was quenched with brine and extracted with hexane (x2). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 97% yield (1.1 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.327 (dd, 0.03, 0.8 Hz, 1H), 7.282 (dt, 8.2, 0.8 Hz, 1H), 7.109 (m, 2H), 6.569 (dd, 0.04, 0.8 Hz, 2H), 3.778 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 141.2, 131.3, 128.4, 124.6, 122.6, 113.3, 108.9, 101.9, 34.1.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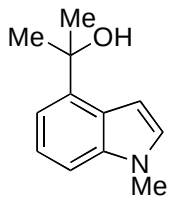
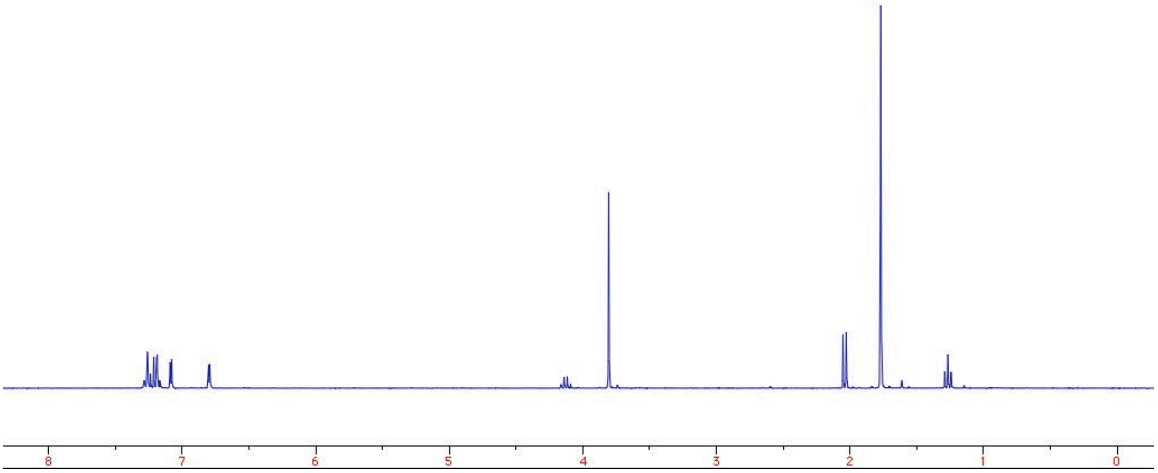


253

2-(1-methyl-1H-indol-4-yl)propan-2-ol (253): To a stirring solution of **252** (300 mg, 1.43 mmol) in Et_2O (28 mL) at -78 ℃ was slowly added *t*BuLi (1.7 M in pentane, 1.68 mL, 2.86 mmol, 2 eq.) and left to stir for 15 min. Acetone (0.12 mL, 1.57 mmol, 1.1 eq.) in Et_2O (14 mL) was added, and the resultant mixture was allowed to stir for 1h. The reaction was quenched with NH_4Cl $_{(sat'd)}$ and extracted with hexanes (x3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 91% yield (246 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.291-7.166 (m, 3H), 7.087 (d, 3.2 Hz, 1H), 6.801 (d, 3.2 Hz, 1H), 3.808 (s, 3H), 2.049 (s, 1H), 1.774 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 128.4, 125.1, 121.5, 114.9, 108.8, 102.0, 73.8, 33.2, 31.1.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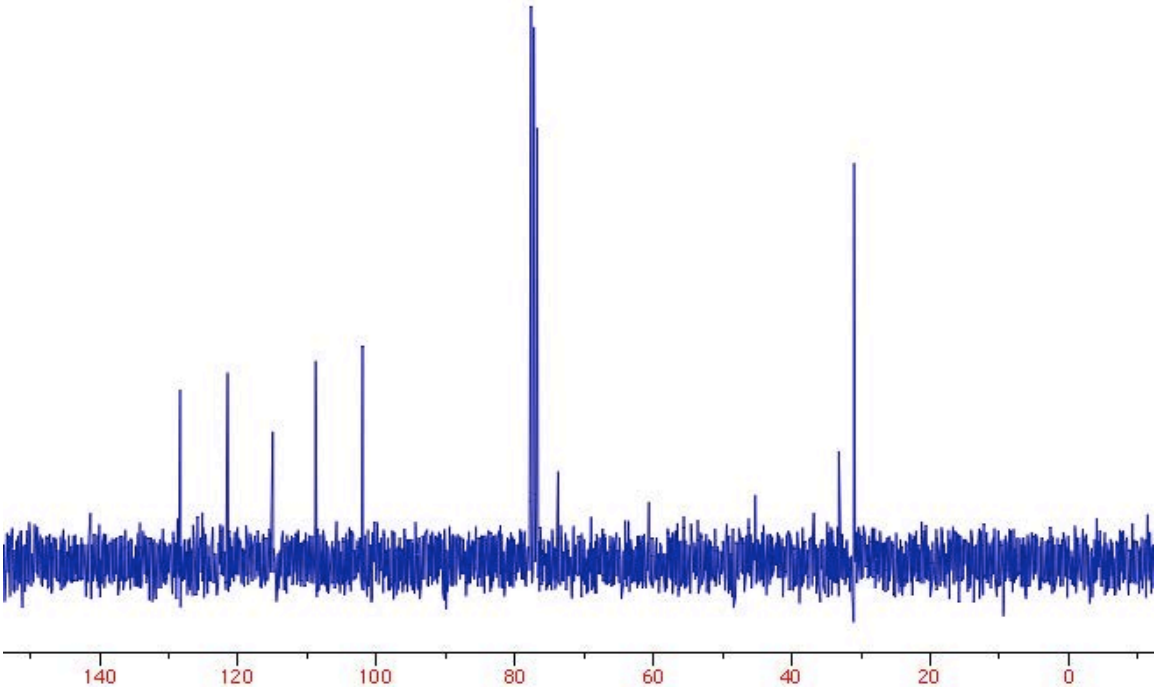
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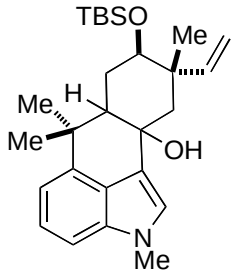


255

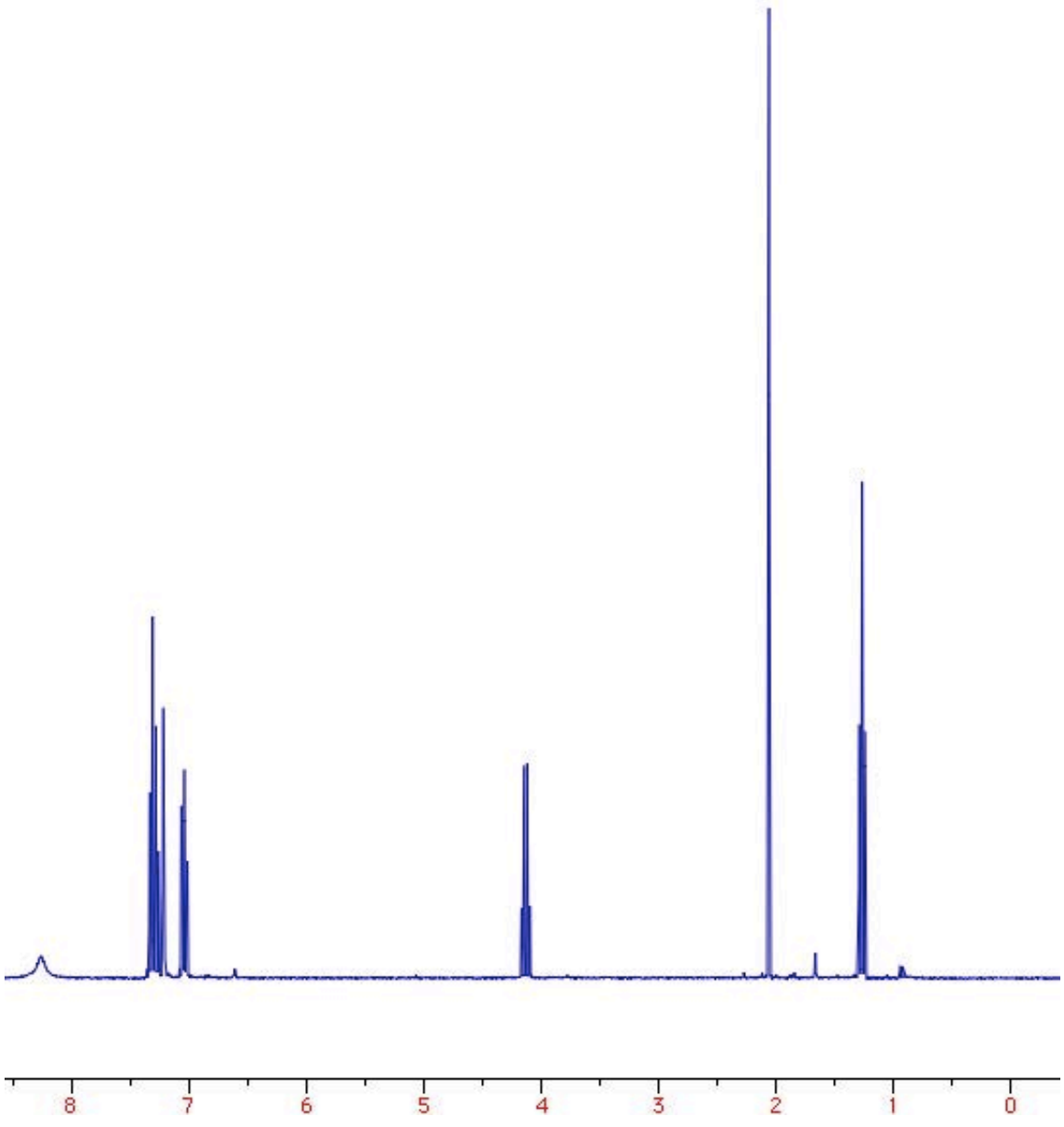
Compound 255: Compound **140 (**200 mg, 0.75 mmol) was added to THF (7 mL) and cooled to -78 ℃, to which LHMDS (1 M in THF, 0.82 mL, 0.82 mL, 1.1 eq.) was added. After 45 min at -78 ℃, TMSCl (0.11 mL, 0.89 mL, 1.2 eq.) was added and left to stir for 45 min at the same temperature. The reaction was quenched with brine, poured onto a brine:hexane (1:1) mixture and extracted with hexanes (x2). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated to afford product **17** that was used without further purification. To a solution of **166** (150 mg, 0.44 mmol, 1.2 eq.) in DCM (2 mL) was added **253** (69 mg, 0.37 mmol), cooled to -78 ℃, and after stirring for 5 min was added fuming tin (IV) chloride in DCM (0.41 mmol, 1.1 eq.) and left to stir for 15 min. The reaction was quenched with $NaHCO_{3\,(sat'd)}$ at the same temperature and extracted with DCM (x3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 83% yield (135 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.245-7.232 (m, 4H), 6.972 (s, 1H), 6.091 (dd, 17.2, 10.5 Hz, 1H), 5.032 (dd, 21.5, 10.6 Hz, 2H), 4.976 (dd, 3, 14 Hz, 2H), 3.740 (s, 3H), 3.673 (t,

3.6 Hz, 1H), 2.734 (m, 1H), 2.594-1.872 (comp, 5H), 1.731 (s, 6H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 145.3, 144.2, 141.3, 123.8, 121.7, 120.8, 115.1, 114.4, 107.3, 99.2, 75.3, 73.6, 46.2, 38.8, 35.9, 33.2, 31.5, 28.4, 26.0, 25.1, 18.2, -3.0; **IR:** (NaCl Film) 3389 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{27}H_{41}NO_2Si$, 440.29; found, 440.2904.

4-bromo-3-chloro-1H-indole (258a): To DMF (20 mL) was added 4-bromoindole (0.5 mL, 3.97 mmol) and stirred vigorously at rt till the indole was completely dissolved, then NCS (530 mg, 3.97 mmol, 1 eq.) was added. The reaction was left to stir at rt for 12 h and then quenched with brine and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine and water, dried over $MgSO_4$ and concentrated. The crude oil obtained was purified by flash silica gel chromatography (1:9 EtOAc:hexane) to afford the product in a 91%.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.20 (m, 2H), 7.37 (dd, 1H), 7.67 (dd, 1H), 8.05 (br. s, 1H); **^{13}CNMR**: (75 MHz, $CDCl_3$) δ 133.38, 125.75, 123.33, 121.34, 118.04, 111.01, 104.05; **IR:** (Thin Film) Need; **HMRS-FAB**: $[M+H]^+$ calcd for C_8H_5BrClN, 228.93; found, 228.9217.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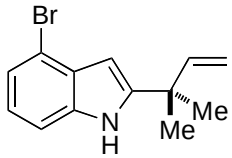

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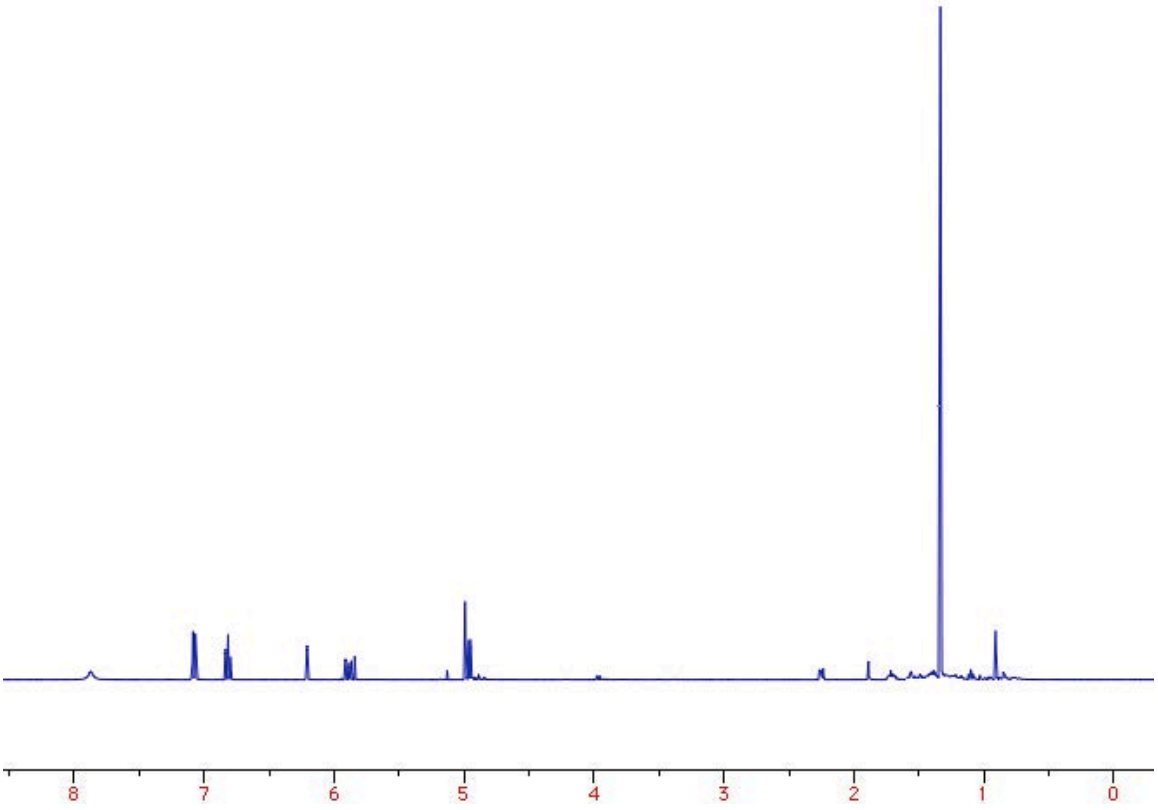
4-bromo-1-methyl-2-(2-methylbut-3-en-2-yl)-1H-indole (258b): To THF (8 mL) was added **258a** (200 mg, 0.867 mmol) and cooled to 0 ℃, to which Et_3N (0.42 mL, 3.03 mmol, 3.5 eq.) was added then a preformed solution of 2-methyl-2,3-butadiene (1.31 mL, 13.2 mmol, 2.0 eq.) in THF and 9-BBN (0.5 M in THF, 1.8 mL, 13.2 mmol, 2.0 eq.). The reaction was left to stir for 2 h and then poured onto 1 M NaOH:Et_2O (1:1) and washed with water (x2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in a variable yield of 41-53%.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.87 (bs, 1H), 7.07 (d, 8.5 Hz, 2H), 6.82 (t, 7.7, 8.0 Hz, 1 H), 6.21 (s, 1H), 5.877, dd, 10.3, 10.3 Hz, 1H), 4.97 (dd, 11.4, 5.2 Hz, 2H), 1.35 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.5, 145.6, 136.0, 129.2, 122.4, 122.1, 113.9, 112.6, 109.6, 98.3, 41.9, 38.2, 27.3; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{13}H_{14}BrN$, 264.03; found, 264.0377.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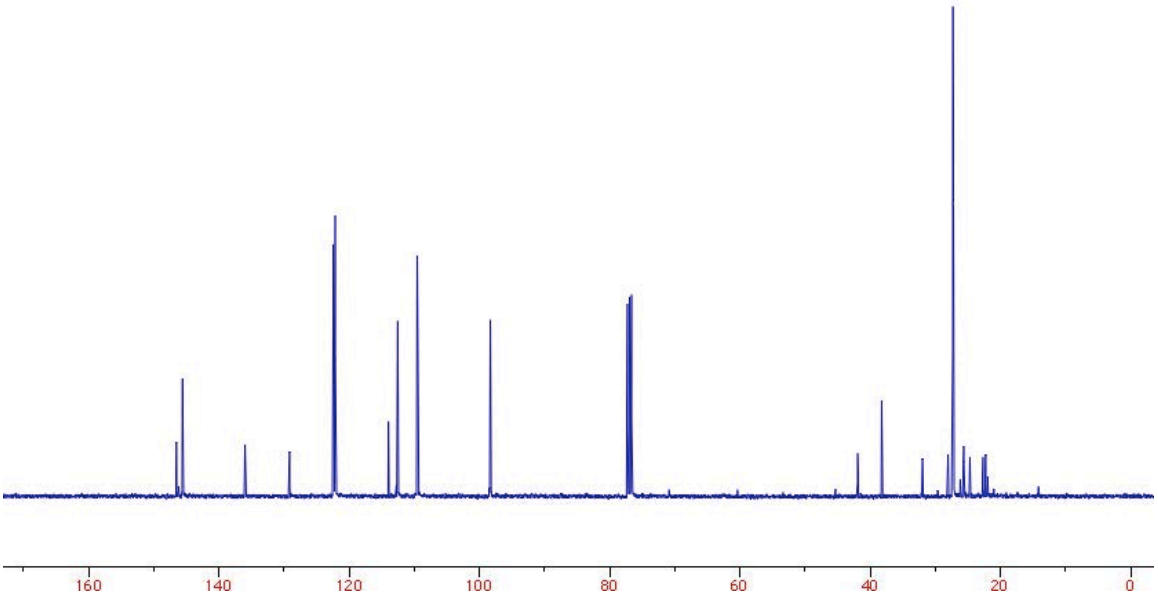
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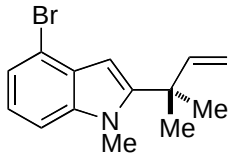
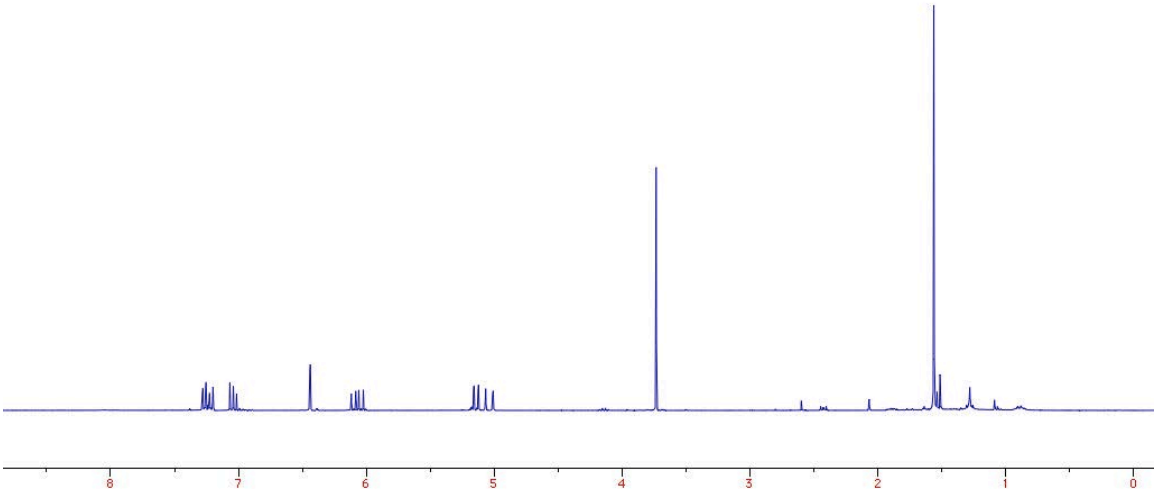


259

4-bromo-1-methyl-2-(2-methylbut-3-en-2-yl)-*N*-methyl-indole (259): To a solution of THF (4 mL) was added NaH (18 mg, 0.45 mmol, 1.2 eq.) at rt, to which the **258b** (100 mg, 0.378 mmol) was added drop wise and allowed to stir. After 30 min, methyl iodide (0.03 mL, 0.53 mmol, 1.4 eq.) was added and allowed to stir for 5 h. The reaction was quenched with brine and extracted with hexane (x2). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 98% yield (103 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.281-7.199 (m, 2H), 7.042 (t, 7.5 Hz, 1H), 6.440 (s, 1H), 6.069 (dd, 17.4, 10.6 Hz, 1H), 5.082 (dd, 30.1, 10.6, 2H), 3.732 (s, 3H), 1.561 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 147.6, 145.9, 139.0, 127.9, 122.3, 122.0, 114.4, 113.1, 108.1, 99.4, 38.9, 32.6, 28.5; **IR:** (NaCl Film); **HMRS-FAB**: $[M+H]^+$ calcd for $C_{14}H_{16}BrN$, 277.05; found, 277.0493.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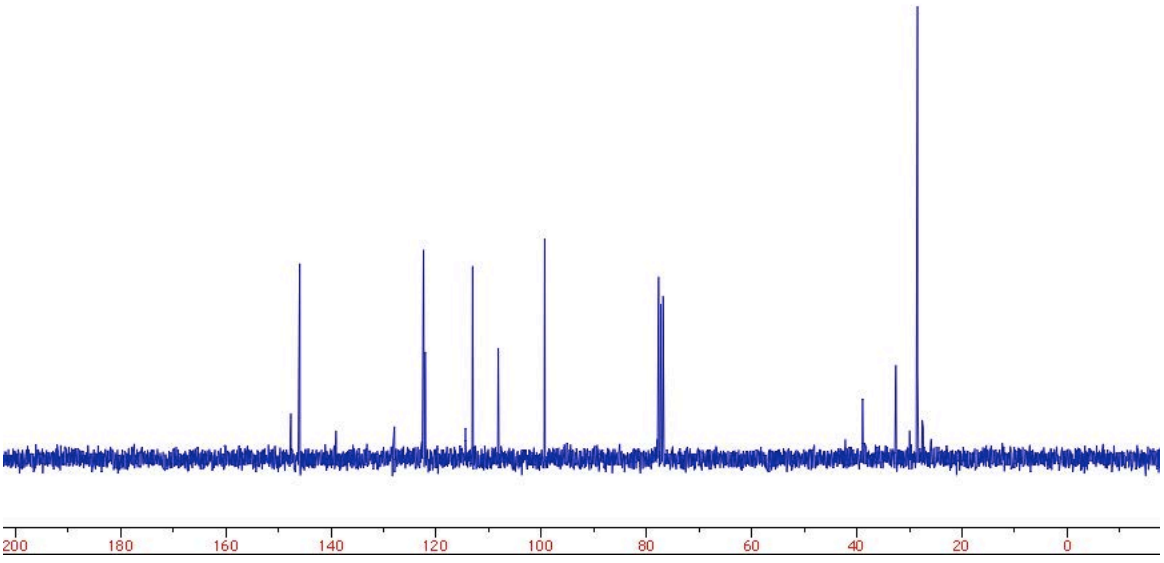
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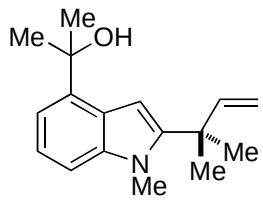

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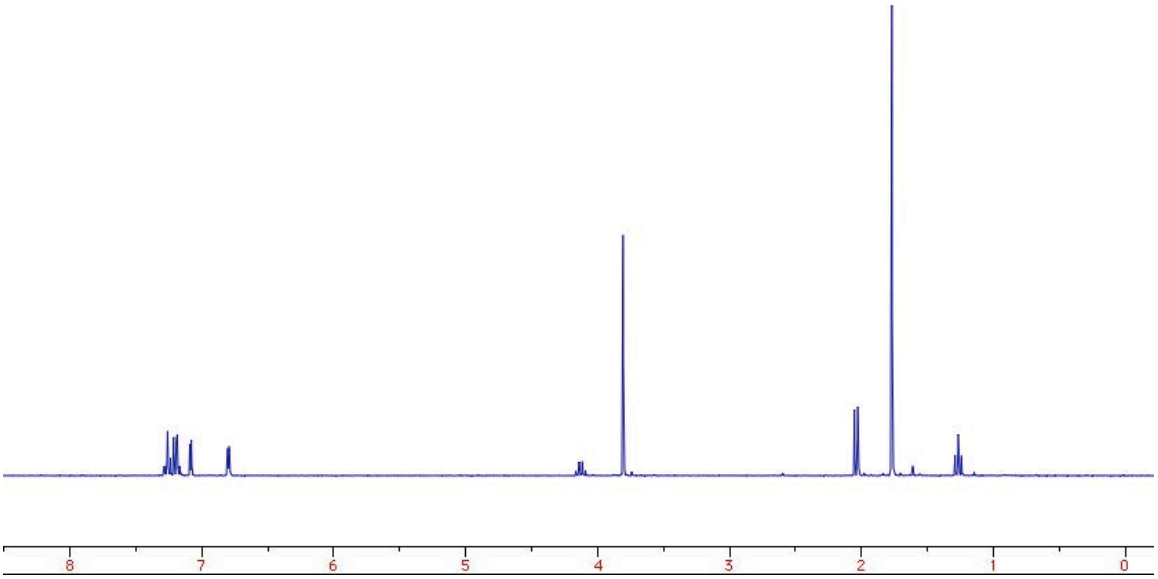
2-(1-methyl-2-(2-methylbut-3-en-2-yl)-1H-indol-4-yl)propan-2-ol (260): To a stirring solution of **259** (81 mg, 0.29 mmol) in Et_2O (2 mL) at -78 ℃ was slowly added *t*BuLi (1.7 M in pentane, 0.34 mL, 0.58 mmol, 2 eq.) and left to stir for 15 min. Acetone (0.02 mL, 0.29 mmol, 1 eq.) in Et_2O (2 mL) was added, and the resultant mixture was allowed to stir for 1h. The reaction was quenched with saturated NH_4Cl and extracted with hexanes (x3). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 98% yield (73 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.227-7.140 (m, 3H), 6.690 (s, 1H), 6.086 (dd, 17.4, 10.6 Hz, 1H), 5.077 (dd, 21.7, 10.6 Hz, 2H) 3.740 (s, 3H), 2.055 (s, 1H), 1.775 (s, 6H), 1.555 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.4, 145.9, 140.5, 123.9, 120.9, 115.1, 112.7, 108.4, 99.7, 73.8, 38.8, 32.2, 28.6; **IR:** (NaCl Film) 3306 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{17}H_{23}NO$, 258.18; found, 258.1802.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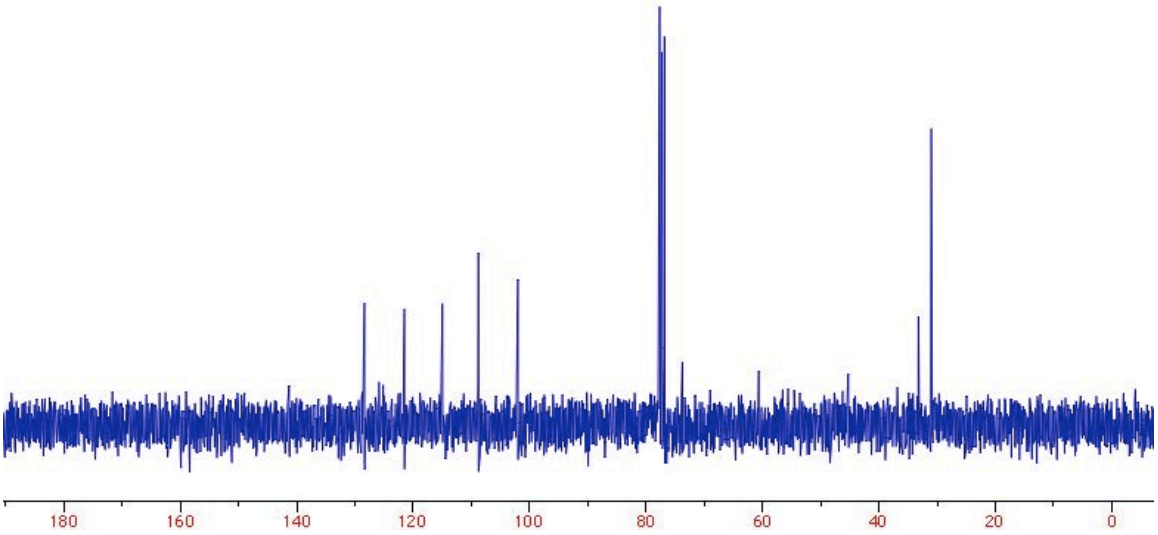
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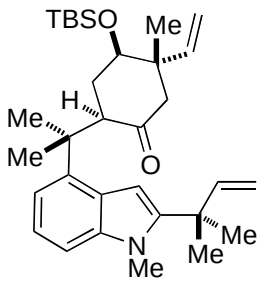

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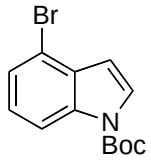
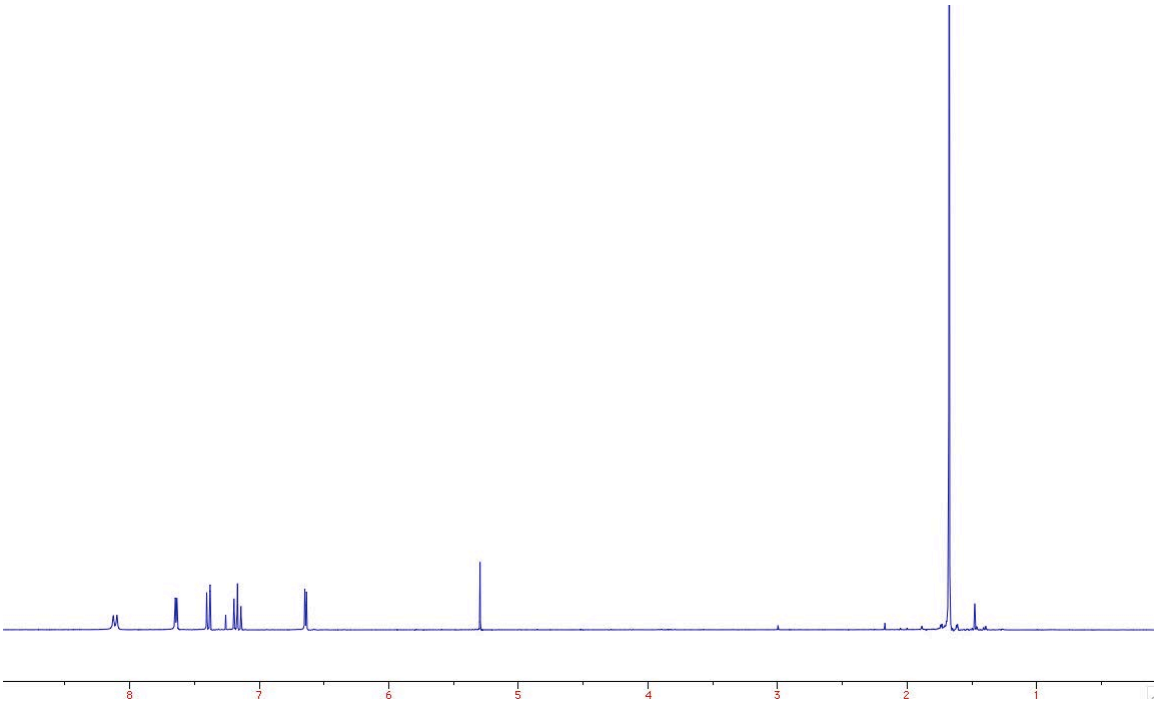
(2R,4R,5*S*)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-2-(2-(1-methyl-2-(2-methylbut-3-en-2-yl)-1H-indol-4-yl)propan-2-yl)-5-vinylcyclohexanone (261): To a solution of **166** (69 mg, 0.326 mmol, 2.1 eq.) in DCM (2 mL) was added **260** (40 mg, 0.155 mmol, 1.0 eq.), cooled to -78 ℃, and after stirring for 5 min was added fuming tin (IV) chloride in DCM (0.16 mL, 1.05 eq.) and left to stir for 15 min. The reaction was quenched with saturated $NaHCO_3$ at the same temperature and extracted with DCM (x3). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 61% yield (48 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.245-7.232 (m, 3H), 6.701 (s, 1H), 6.092 (dd, 17.3, 10.5 Hz, 1H), 6.710 (dd, 17.2, 10.9 Hz, 1H), 6.091 (dd, 17.2, 10.5 Hz, 1H), 5.079 (dd, 21.5, 10.6 Hz, 2H), 5.018 (dd, 3, 14 Hz, 2H), 3.740 (s, 3H), 3.673 (t, 3.6 Hz, 1H), 2.712 (t, 3.6 Hz, 1H), 2.594-1.872 (comp, 5H), 1.775 (s, 6H), 1.555 (s, 6H), 1.046 (s, 3H), 0.925 (s, 9H), 0.108 (s, 6H); **^{13}CNMR:** (75 MHz, CDCl3) δ 198.6, 145.3, 145.1, 144.2, 141.3, 123.8, 120.8, 115.1, 114.4, 112.6, 107.3, 99.2, 73.2, 72.8, 46.7, 38.8, 35.9, 32.2, 31.2, 28.4, 26.0, 25.1, 18.2, -3.0; **IR:** (NaCl Film) 1654 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{32}H_{49}NO_2Si$, 507.35; found, 507.3546.



263

Compound 263: 4-Bromoindole (**87**) (1 mL, 7.8 mmol, 1.0 eq.) was added to MeCN (0.6 M, 13 mL) followed by Boc_2O (1.9 g, 9.8 mmol, 1.12 eq) and DMAP (86 mg, 0.71 mmol, 0.09 eq) and left to stir at rt for 12 h. The reaction was concentrated, taken up in DCM, washed with saturated $NaHCO_3$, saturated NH_4Cl and water, dried and concentrated to afford product in quantitative yields (2.3 g). No purification was required. **^{1}HNMR:** (300 MHz, $CDCl_3$) δ 8.112 (d, 8.26 Hz, 1H), 7.642 (d, 3.77 Hz, 1H), 7.392 (s, 7.77 Hz, 1H), 7.530 (t, 7.99, 8.11 Hz, 1H), 6.506 (s, 3.78 Hz, 1Hz), 1.676 (s, 9 H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 126.7, 125.8, 125.4, 114.9, 114.5, 107.3, 84.5, 28.4; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{13}H_{14}BrNO_2$, 295.02; found, 295.0218 & 297.0215.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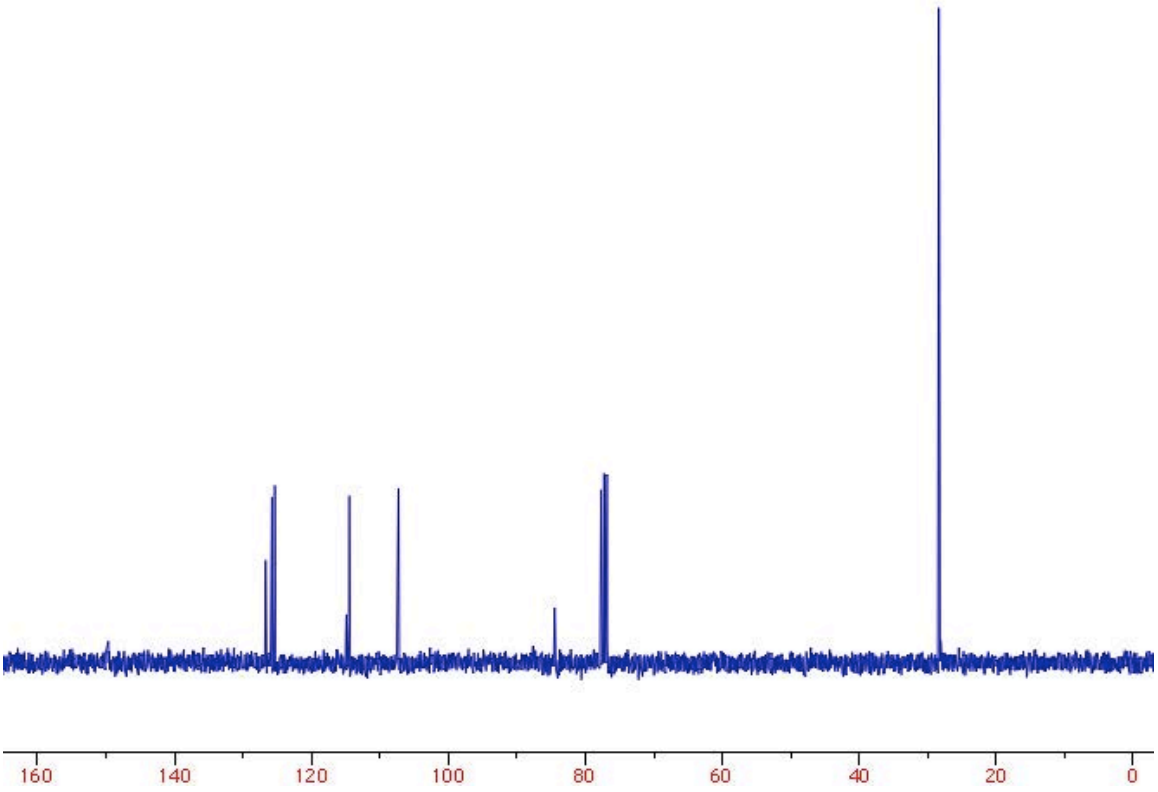
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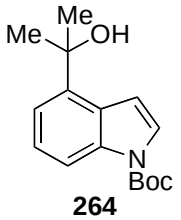
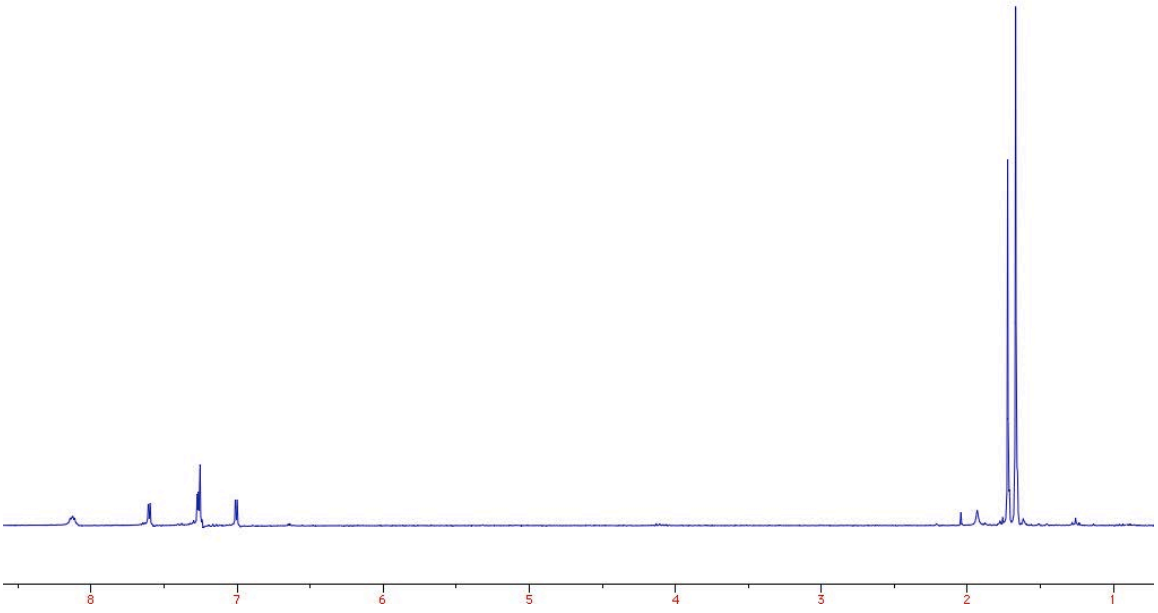


264

Compound 264: Compound (**263**) (1 g, 3.8 mmol, 1.0 eq.) was added to a Et_2O (0.05 M, 70 mL) and cooled to -78 ℃. *t*BuLi (1.7 M in pentane, 3.97 mL, 6.8 mmol, 2.0 eq.) was added over the course of 3 min and left to stir for 5 min at the same temperature. To this solution was added acetone (0.28 mL, 3.78 mmol, 1.0 eq.) in Et (0.2 M, 15 mL) via cannula. The reaction was left to stir for 15 min, quenched with $NH_4Cl_{(s)}$, extracted with hexane, washed with water and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 ethyl acetate:hexane) to afford product in 62% yields (649 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.128 (t, 5.017, 4.002 Hz, 1H), 7.603 (d, 3.805 Hz, 1H), 7.266 (m, 2H), 7.007 (d, 3.811 Hz, 1H), 1.933 (bs, 1H), 1.725 (s, 6H), 1.670 (s, 9H); **IR:** (NaCl Film) 3354 cm^{-1}.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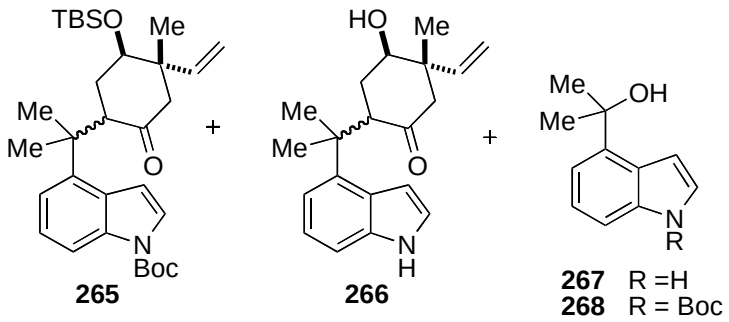
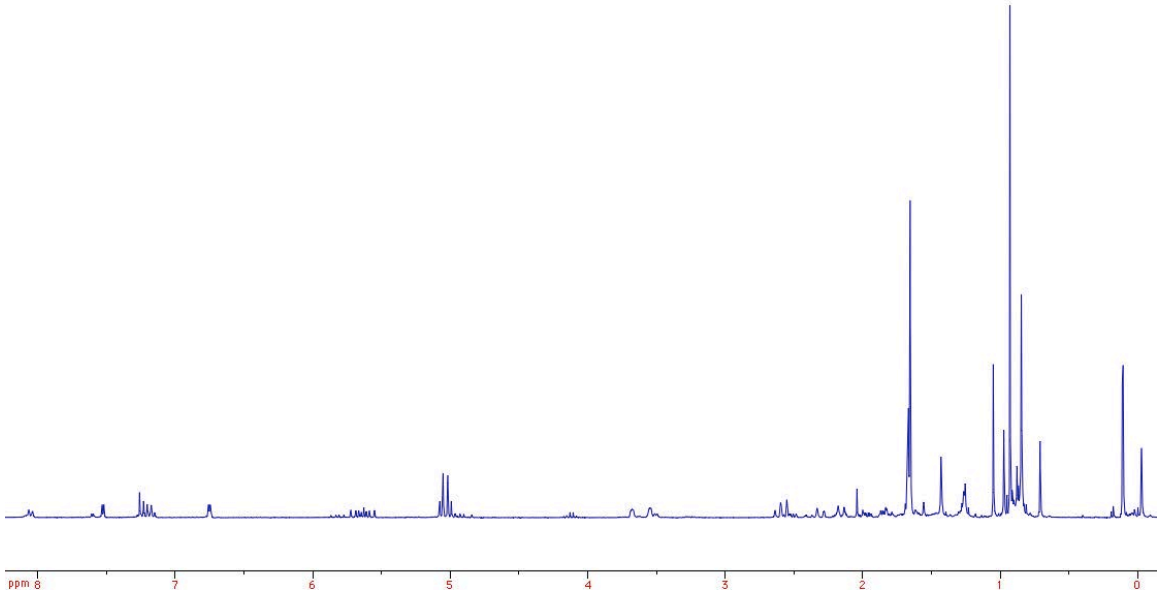


Compound 265: Compound **264** (1.18 g, 4.3 mmol, 1.0 eq) taken up in DCM (100 mL) to which **enolether** (2.72 g, 8.6 mmol, 2.0 eq.) was added. The mixture was cooled to -78 ℃ and $SnCl_4$ (1 M, 4.5 mL, 4.5 mmol, 1.05 eq.) was added slowly. After 30 min the reaction was poured onto saturated $NaHCO_3$ (200 mL), stirred for 30 min, and extracted with DCM. The organic layers were combined, washed once with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography to afford product (21% total yield of 4 products, 3% yield of **265** as a diastereomeric mixture).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.088-8.037 (m, 1H), 7.607-7.518 (m, 1H), 7.259-7.255 (m, 2H), 6.750 (d, 3.57 Hz, 1H), 5.867-5.551 (m, 2H), 5.075-4.850 (m, 4H), 3.674-3.494 (m, 2H), 2.637-1.775 (m, 10H), 1.675-1.655 (m, 13H), 1.051-1.811 (m, 28H), 0.112-0.028 (m 9H); **^{13}CNMR:** (75 MHz, CDCl3) δ 143.9, 143.7, 124.8, 123.9, 120.6, 114.8, 114.4, 113.4, 108.4, 83.7, 73.3, 72.9, 50.4, 48.1, 47.9, 46.9, 46.8, 35.9, 33.1, 29.8, 28.4, 28.3, 26.2, 25.9, 25.7, 24.9, 23.3, 18.3, 18.2, -4.2, -4.7, -4.9; **IR:** (NaCl Film) 1634 cm^{-1}; **HMRS-FAB**: $[M+Na]^+$ calcd for $C_{31}H_{47}NO_4Si$, 548.78; found, 548.3167.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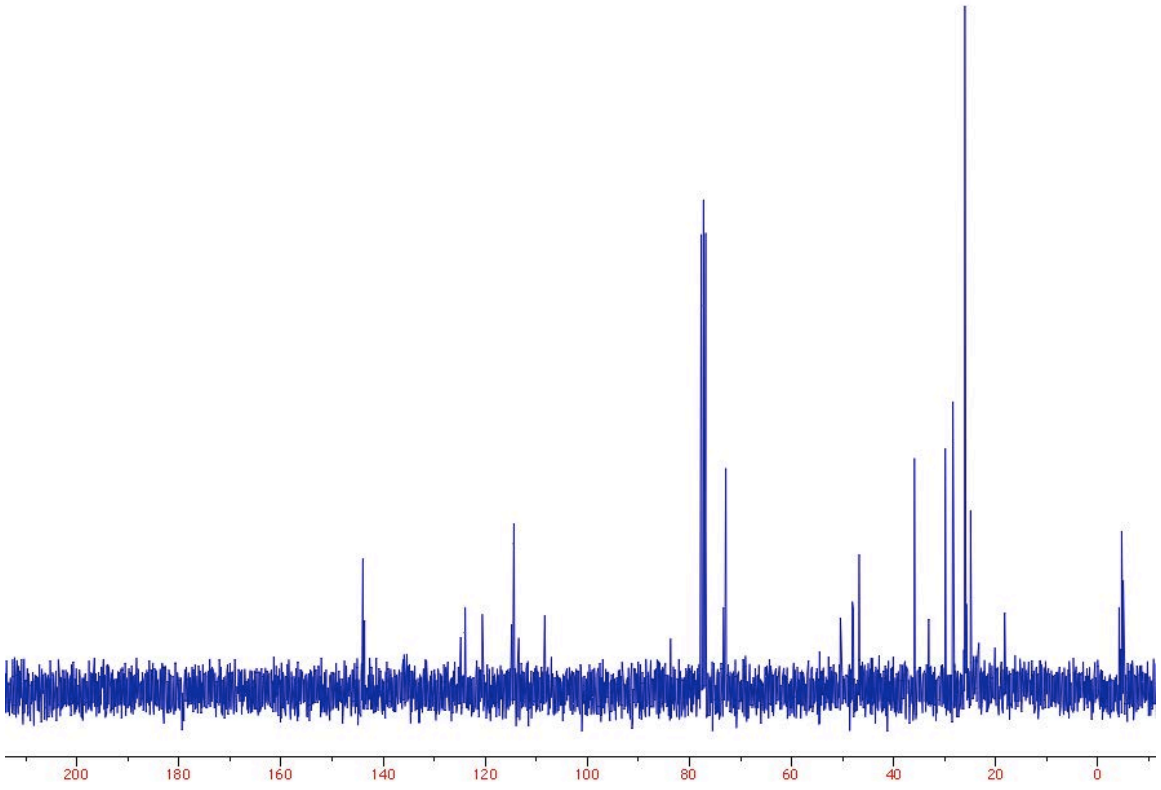
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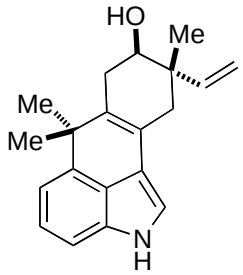
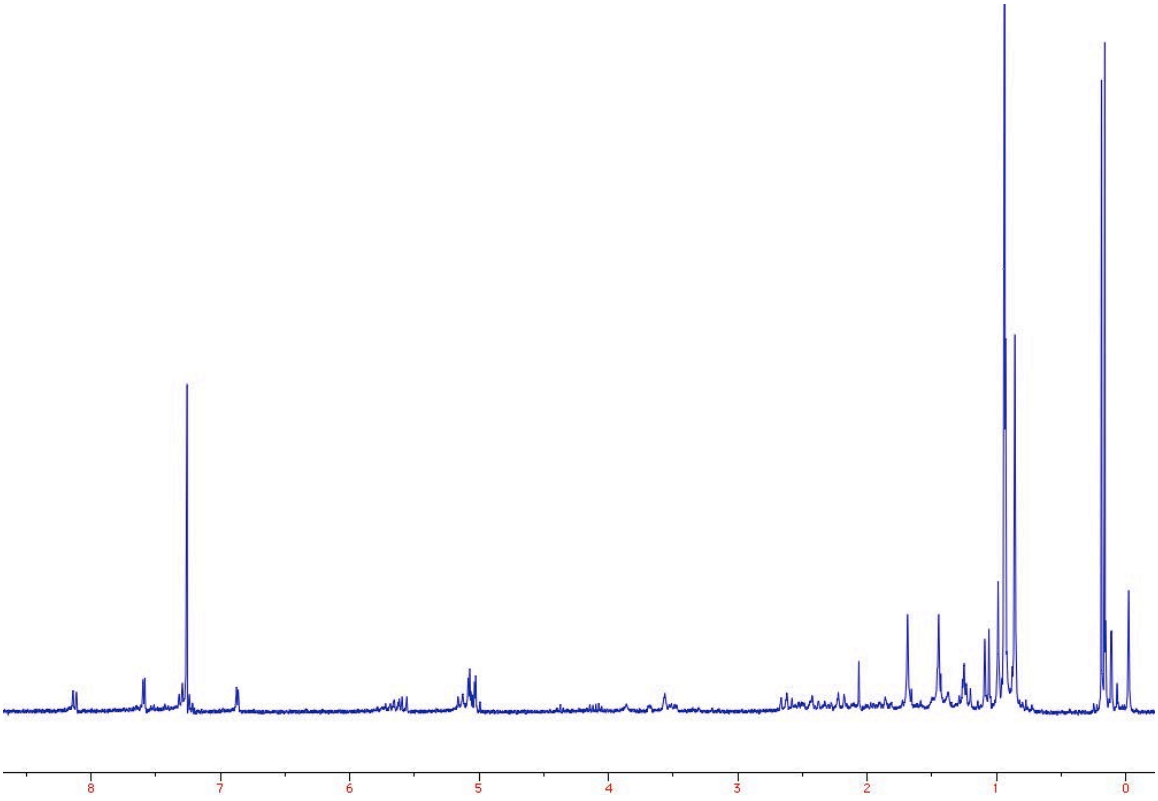


270

Compound 270: Compound **265** (58 mg, 0.11 mmol, 1.0 eq.) was taken up in THF (2 mL) and cooled to 0 ℃. To which BF_3•etherate was added slowly and allowed to warm to rt. After 3 h the reaction was concentrated, taken up in DCM (0.5 mL), filtered through silica to remove the boron and concentrated. The crude material was purified via flash silica gel chromatography (1:9 ethyl acetate:hexane) to afford product in 6% yields (2 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.127 (d, 7.930 Hz, 1H), 7.592 (d, 3.95 Hz, 1H), 7.293 (t, 7.53, 7.98 Hz, 1H), 6.869 (d, 4.39, 1H), 5.663-5.559 (m, 1H), 5.085-4.993 (m, 2H), 3.563 (s, 1H), 2.664-2.063 (m, 8H), 1.686 (s, 3H), 1.446 (s, 3H), 1.262-1.201 (m, 2H), 1.074 (d, 9.78, 2H), 0.937 (s, 15H), 0.857 (s, 6H), 0.187-0.115 (m, 8H); **IR:** (NaCl Film) 1202 cm^{-1}.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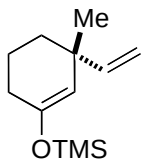
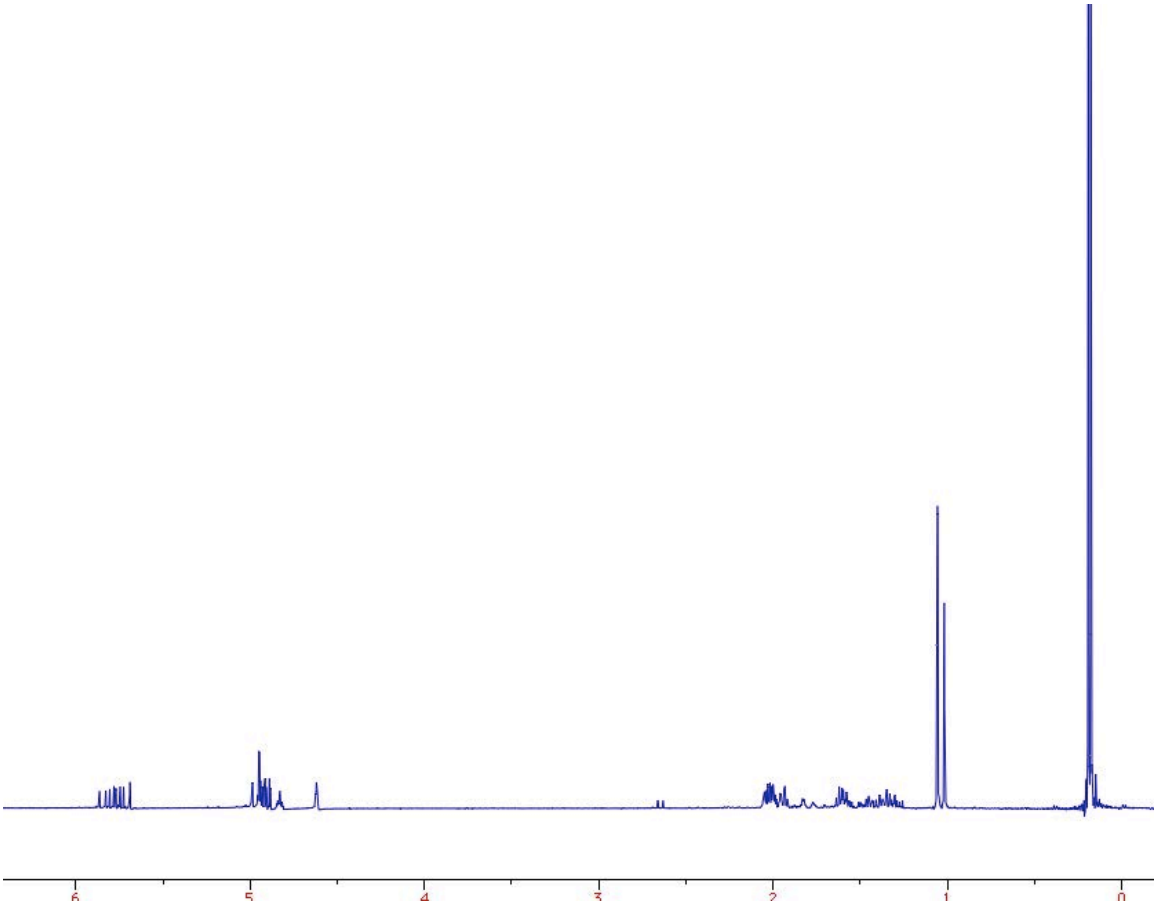


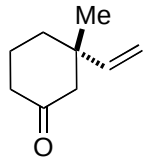
64

Compound 64: Route A: Copper (I) bromide•dimethyl sulfide (1.09 g, 5.3 mmol, 0.2 eq.) was taken up in THF (250 mL) and cooled to -78 ℃. To this cooled solution was added, slowly, via cannula vinyl Grignard (1 M in THF, 79 mL, 79.3 mmol, 3.0 eq.) and left to stir for 30 min at the same temperature. TMEDA (12.3 mL, 105.8 mmol, 4.0 eq.) followed by TMSCl (8.4 mL, 66.1 mmol, 2.5 eq.) was added and left to stir for 5 min, to which 3-methyl-cyclohexenone (3 mL, 26.4 mmol, 1.0 eq.) in THF (1 M, 26 mL) was added. After being stirred at -78 ℃ for 2 h the reaction was allowed to warm to rt, and left to stir for 30 min at which time one volume equivalent of hexane was added. The mixture was washed several times with a saturated $NaHCO_3$ solution, until the aqueous layer was devoid of any blue color and/or tint. The organic layer was dried and concentrated to give product. The product was used without further purification.

Route B: Vinyl Grignard (1 M in THF, 106 mL, 105.8 mmol, 1.5 eq.) was added to a RBF and cooled to -78 ℃ to which a pre-mixed solution of CuBr•Me_2S (1.8 g, 7.1 mmol, 0.1 eq.) in HMPA (0.25 M) was added over 5 min and left to stir at the same temperature. After 30 min, a pre-mixed solution of TMSCl (18 mL, 141 mmol, 2.0 eq.) and 3-methylcyclohexenone (8 mL, 70.2 mmol, 1.0 eq.) in THF (1 M, 70 mL) was added over 30 min and left to stir at the same temperature for 3 h. TEA (40 mL) was added and the reaction was warmed to rt and diluted with hexane. The mixture was washed with water (100 mL x 2), once with a saturated NH_4Cl (200 mL), dried and concentrated to give product in 96% yields. The product was used without further purification.

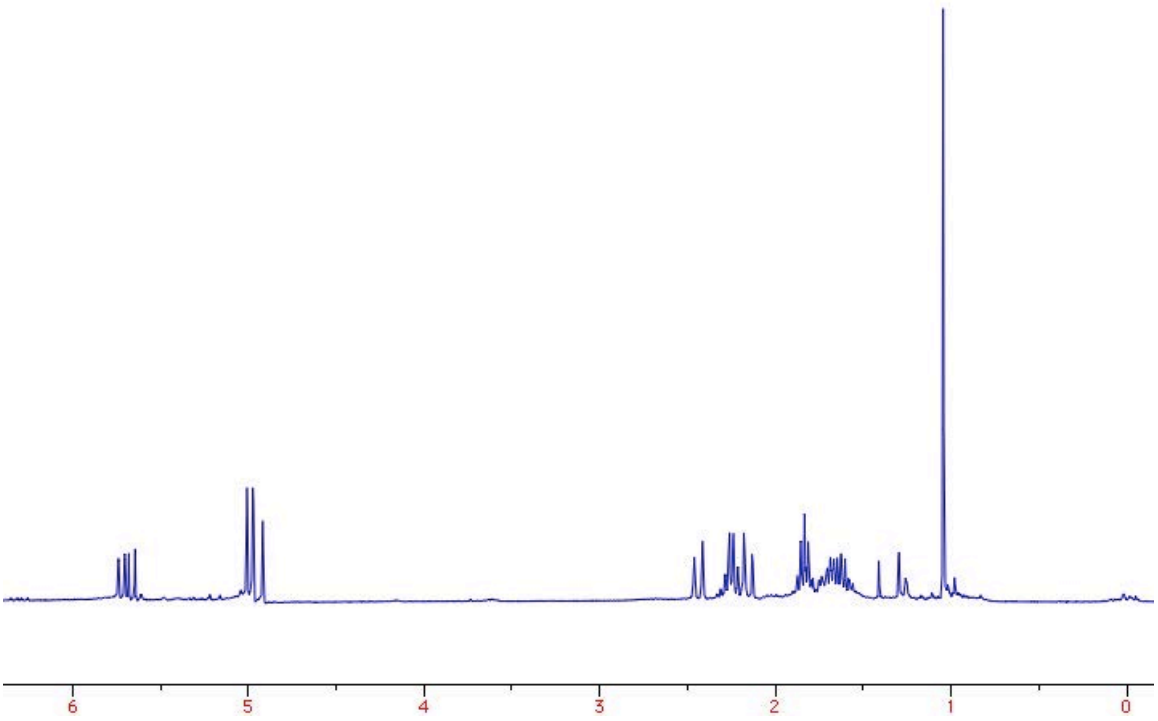
^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.864-5.689 (m, 1H), 4.949-4.872 (m, 2H), 4.620 (s, 1H), 2.058-1.258 (m, 6H), 1.061-1.011 (m, 3H), 0.173 (s, 9H).





Compound 284: To compound **64** (52.9 mmol) was added a pre-mix solution of acetic acid:water:THF (500 mL) (0.1 M, 1:1:2) and left to stir. After 1 h, one volume equivalent of saturated $NaHCO_3$ was slowly added. The layers were separated, washed with additional saturated $NaHCO_3$ till gases ceased evolving. The organic layer was dried and concentrated to give product in quantitative yields. The product was used without further purification.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.692 (dd, 10.87, 10.86 Hz, 1H), 4.963 (dd, 10.04, 16.29 Hz, 2H), 2.438 (d, 13.98 Hz, 1H), 2.334-2.213 (m, 2H), 2.155 (d, 14 Hz, 1H), 1.873-1.786 (m, 2H), 1.748-1.585 (m, 2H), 1.045 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 211.7, 192.9, 145.9, 112.9, 51.8, 41.1, 36.7, 27.5, 22.3; **IR:** (NaCl Film) 1624 cm^{-1}.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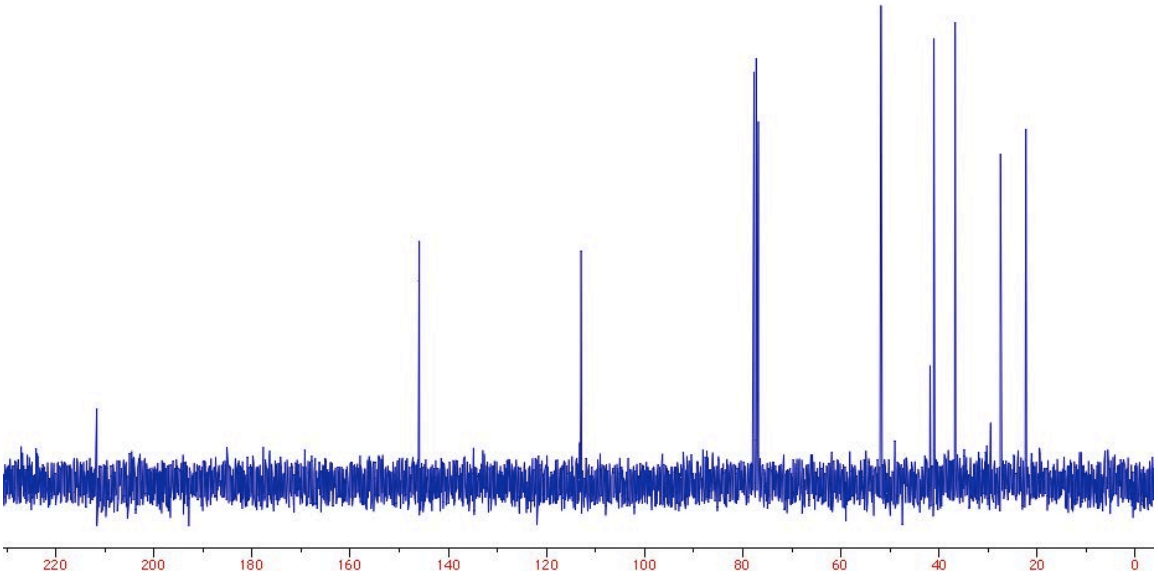
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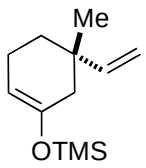
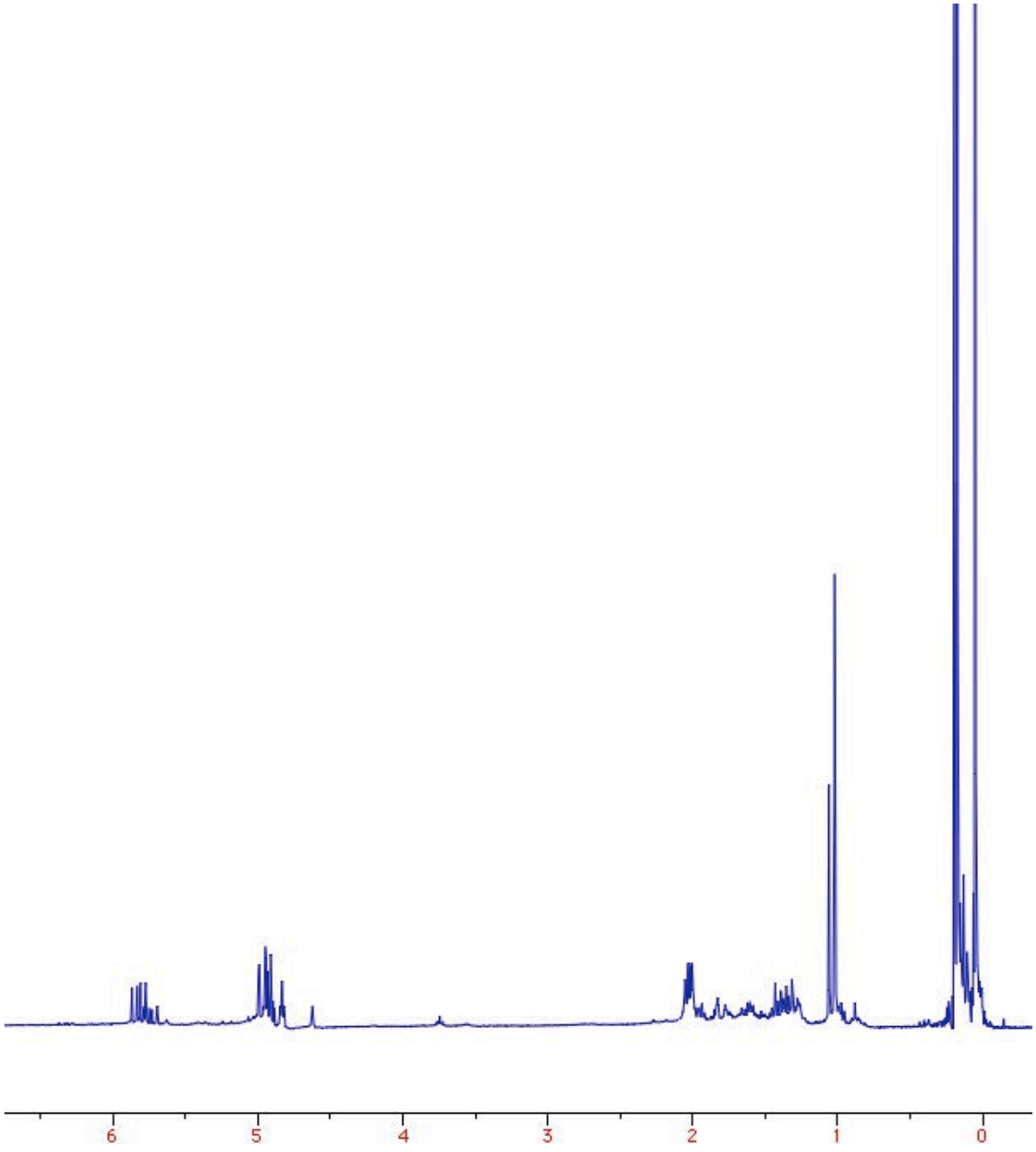


65

Compound 65: Compound **284** (1.5 g, 10.9 mmol, 1.0 eq.) was taken up in THF (110 mmL) and cooled to -78 ℃, to which LHMDS (1 M in THF, 12 mL, 11.9 mmol, 1.1 eq.) was added and left to stir at the same temperature. After 45 min, TMSCl (1.65 mL, 13.0 mmol, 1.2 eq.) was added and left to stir at -78 ℃ for an additional 45 min. The reaction was quenched with the addition of brine (100 mL), poured onto a hexane:brine (100 mL, 1:1) mixture, extracted with hexane, dried and concentrated to afford product in 98% yields (2.2 g). The product was used without further purification.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.867-5.692 (m, 1H), 4.994-4.889 (m, 2H), 4.620-4.618 (m, 1H), 2.061-1.768 (m, 3H), 1.624-1.256 (m, 3H), 1.059-1.021 (m, 3H), 0.175 (s, 9H).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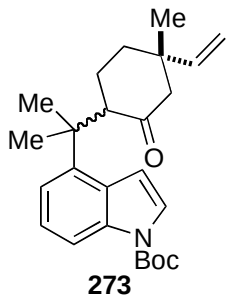
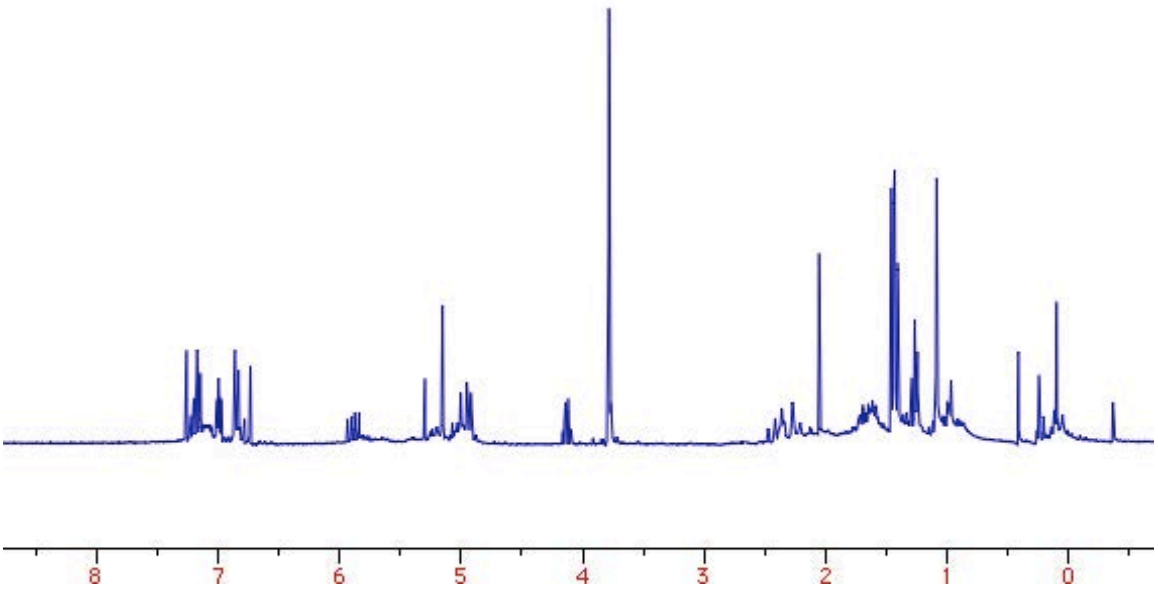
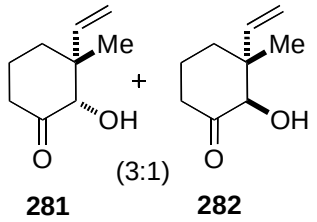


273

Compound 273: Compound **264** (223 mg, 0.76 mmol, 1.0 eq) taken up in DCM (10 mL) to which **65** (334 mg, 1.59 mmol, 2.0 eq.) was added. The mixture was cooled to -78 ℃ and $SnCl_4$ (1 M, 0.79 mL, 0.79 mmol, 1.05 eq.) was added slowly. After 30 min the reaction was poured onto saturated $NaHCO_3$ (200 mL), stirred for 30 min, and extracted with DCM. The organic layers were combined, washed once with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography to afford a diastereomeric mixture of products in 82% yield (255 mg).

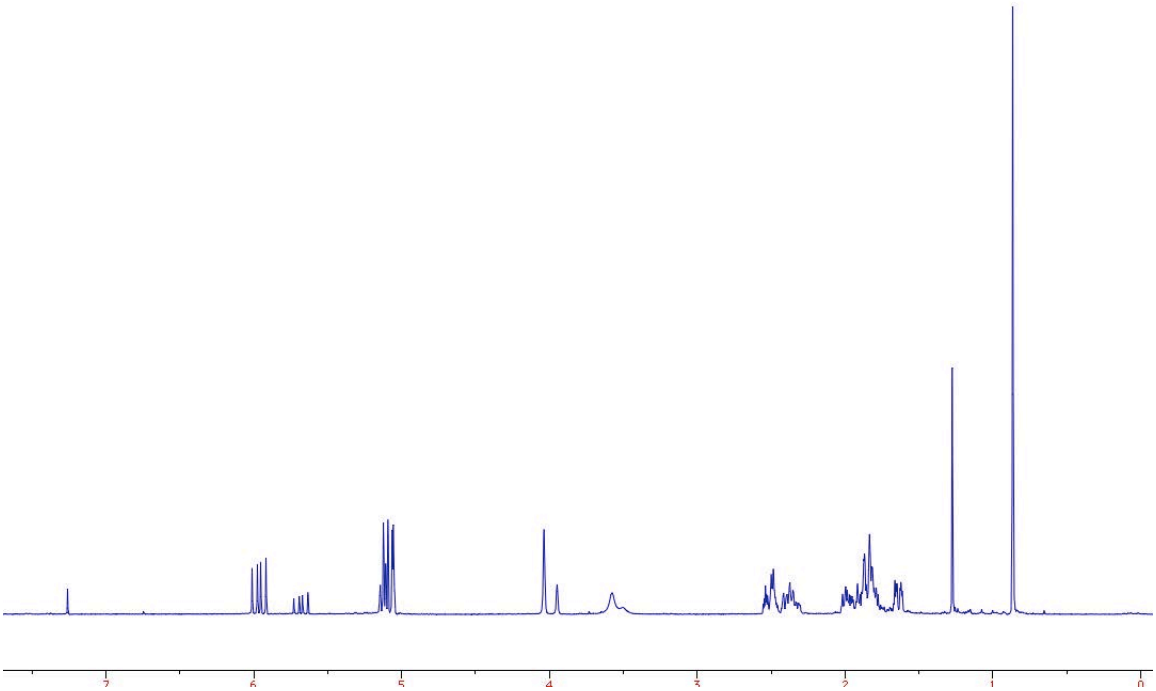


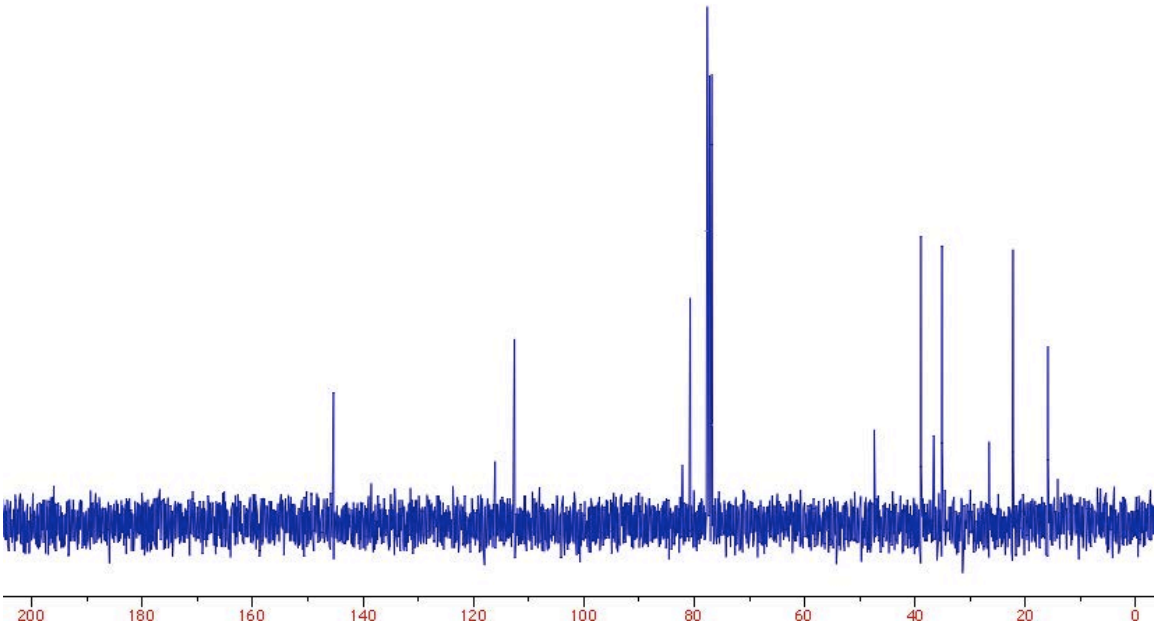


281 **282**

Compounds 281 & 282: Compound **64** (10.2 g, 48.5 mmol, 1.0 eq.) is added to DCM (0.2 M, 240 mL) and cooled to 0 ℃, at which time $NaHCO_3$ (4.9 g, 58.18 mmol, 1.2 eq.) is added. To this solution freshly purified *m*CPBA (10 g, 58.2 mmol, 1.2 eq.) in DCM (0.6 M, 100 mL) is added at the same temperature. Upon addition of the *m*CPBA the reaction is allowed to warm to rt and left to stir. After 2 h the reaction is filtered through a pad of celite, concentrated, taken up in pentane, filter through another pad of celite and concentrated once more. The crude greenish-yellow oil is dissolved into MeOH (100 mL) to which HF (48% in H_2O, 1.69 mL, 97 mmol, 2.0 eq.) is added. After 1 h $NaHCO_{3(s)}$ is added, followed by H_2O and then diluted with EtOAc. The aqueous layer is extracted several times with EtOAc, the organic layer combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford a diastereomeric mixture of products in 89% yield (6.7 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.964 (dd, 10.76, 10.75 Hz, 3H), 5.681 (dd, 11.16, 11.13 Hz, 1H), 5.143-5.056 (m, 7H), 4.036 (s, 3H), 3.948 (s, 1H), 2.553-2.302 (m, 8H), 2.017-1.613 (m, 17H), 1.275 (s, 3H), 0.866 (s, 8H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 145.4, 116.1, 112.6, 82.1, 80.7, 47.4, 38.9, 38.8, 36.6, 35.1, 35.0, 31.3, 26.6, 22.2, 15.9, 14.1; **IR:** (NaCl Film) 1644 cm^{-1}; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{\#\#}H_{\#\#}NO_{\#}Si$, 442.27; found, ####.

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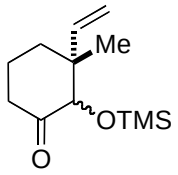
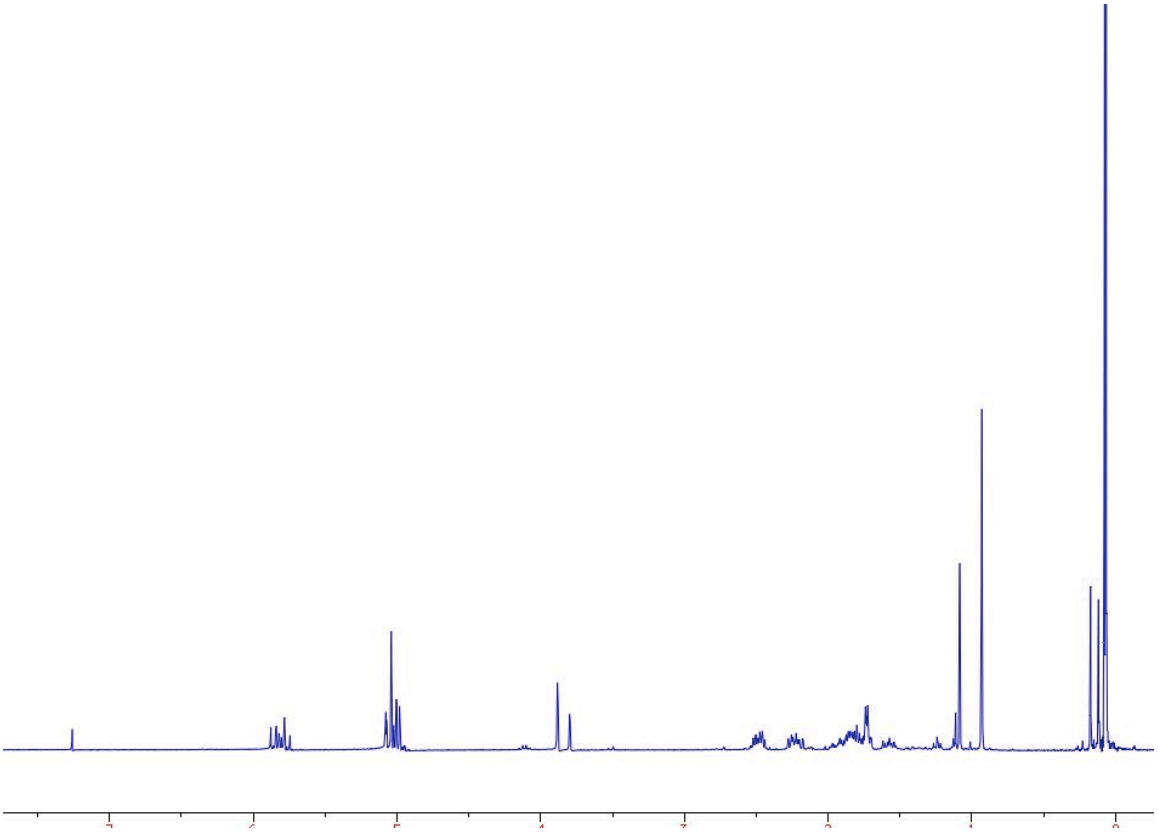
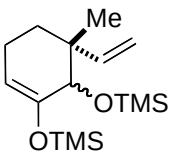


283

Compound 283: Compound **281&282** (500 mg, 3.24 mmol, 1.0 eq.) in THF (30 mL) was cooled to -78℃ to which LHMDS (1 M in THF, 3.4 mL, 3.4 mmol, 1.05 eq.) was added. The solution was warmed to 0 ℃ after 15 min and left to equilibrate. After 20 min TMSCl (0.54 mL, 4.2 mmol, 1.3 eq.) was added and left to stir for 1 h at the same temperature, then warmed to rt. The reaction was quenched with the addition of brine (50 mL), extracted with hexane, dried and concentrated. The crude oil was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford diastereomeric mixture of products in 97% yield (711 mg).

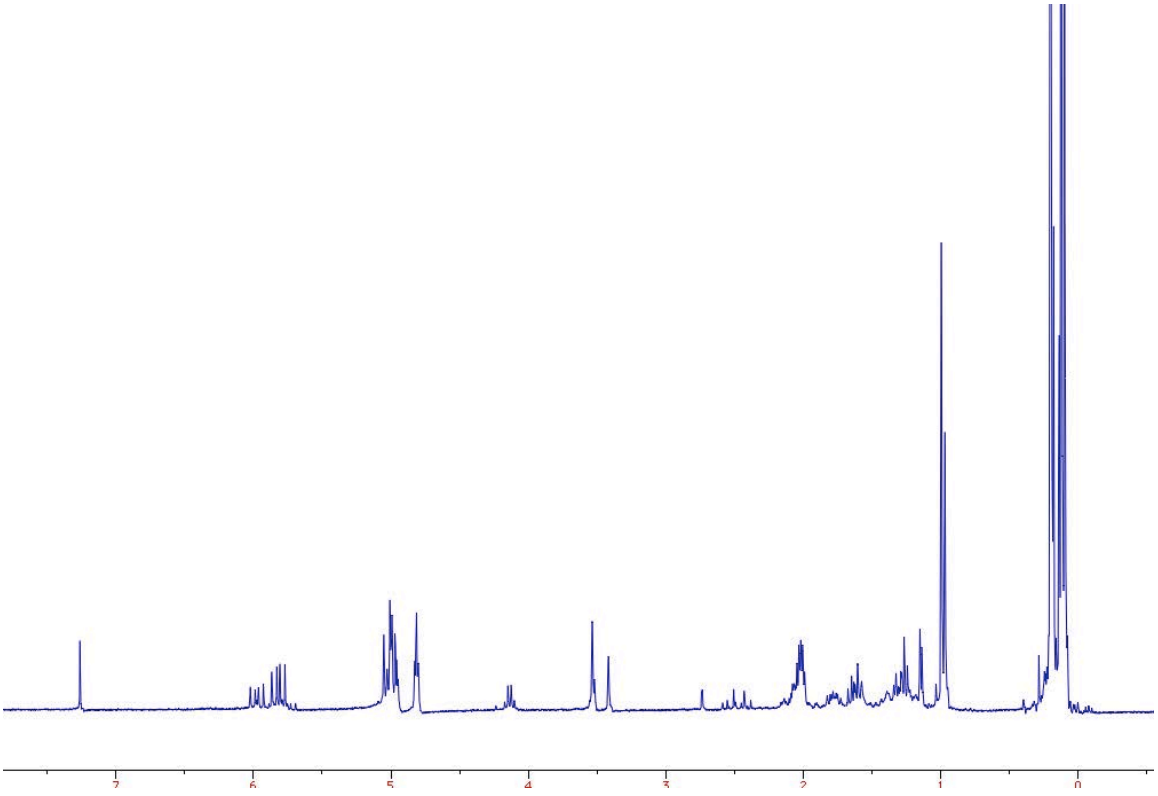
^{1}HNMR: (300 MHz, $CDCl_3$) δ 5.877-5.743 (m, 1H), 5.077-4.978 (m, 2H), 3.883-3.798 (m, 1H), 2.521-1.541 (m, 6H), 1.085 (s, 1H), 0.931 (s, 2H), 0.066 (s, 9H).

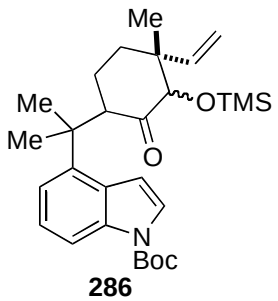




284

Compound 284: To a solution of **283** (268 mg, 1.18 mmol, 1.0 eq.) in THF (11 mL) at -78 ℃ was added LHMDS (1 M in THF, 1.3 mL, 1.3 mmol, 1.1 eq.). TMSCl (0.17 mL, 1.32 mmol, 1.2 eq.) was added 45 min later and left to stir at the same temperature. One hour later the reaction was quenched with brine, poured onto brine:hexane (50 mL, 1:1), extracted with hexanes, dried and concentrated to afford product in quantitative yields (352 mg). The product was used without further purification.

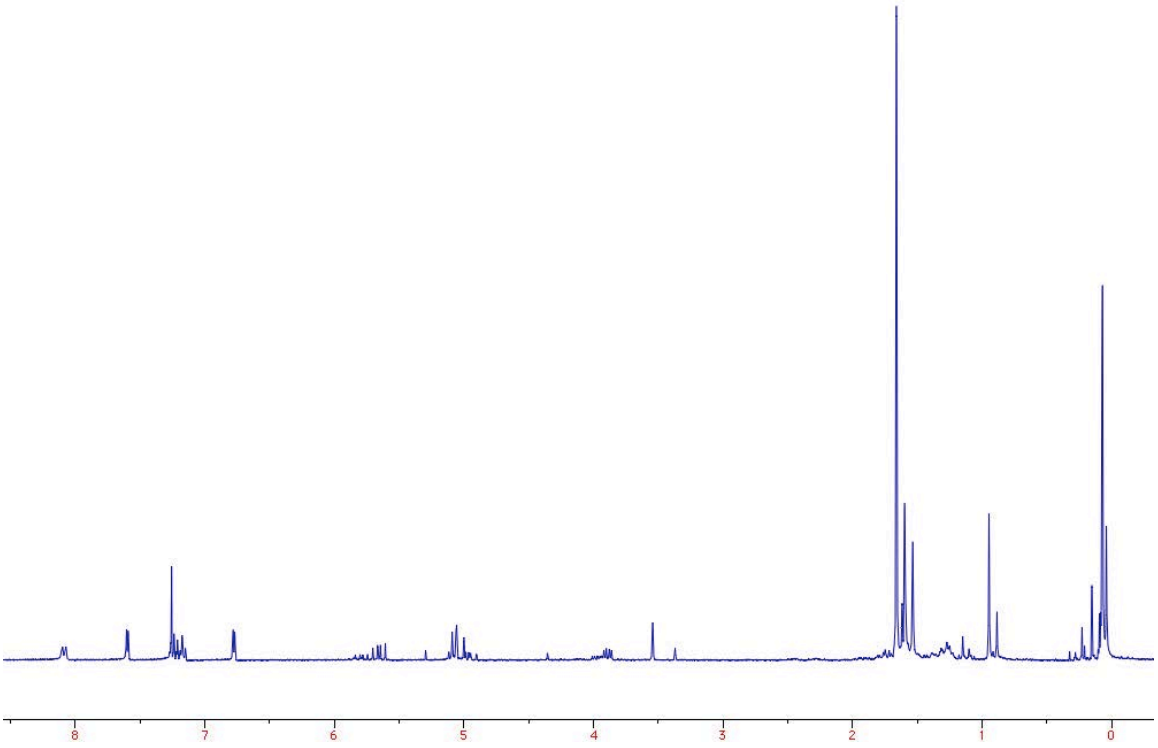




286

Compound 286: To a solution of **264** (765 mg, 2.8 mmol, 1.0 eq.) in DCM (50 mL) was added **284** (1.66 g, 5.56 mmol, 2.0 eq.) and cooled to -78 ℃ to which $SnCl_4$ (1 M in DCM, 3 mL, 2.94 mmol, 1.05 eq.) was added slowly. The reaction was brought to rt 15 min later, poured onto a saturated $NaHCO_3$ (50 mL) and extracted with DCM. The organic layers were combined, washed with brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (5% EtOAc in hexane) to afford a diastereomeric mixture of products in 43% yields (582 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.086 (d, 7.69 Hz, 1H), 7.599 (d, 3.86 Hz, 1H), 7.237-7.150 (m, 2H), 6.776 (d, 3.86 Hz, 1H), 5.803-5.607 (m, 1H), 5.117-4.901 (m, 2H), 4.010-3.861 (m, 1H), 3.543-3.371 (m, 1H), 1.663 (s, 9H), 1.599 (s, 3H), 1.536 (s, 3H), 1.392-1.063 (m, 4H), 0.948-0.886 (m 3H), 0.073 (s, 9H); **HMRS-FAB**: $[M+Na]^+$ calcd for $C_{28}H_{41}NO_4Si$, 506.27; found, 506.2712.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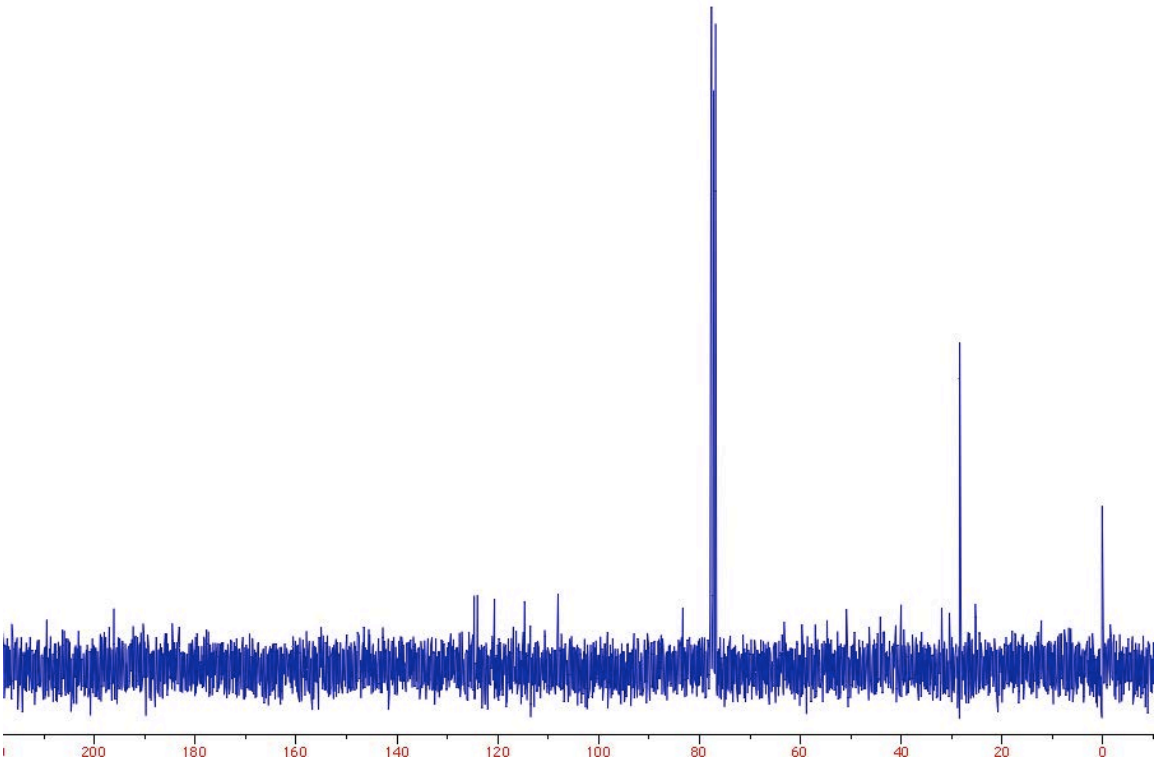
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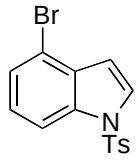
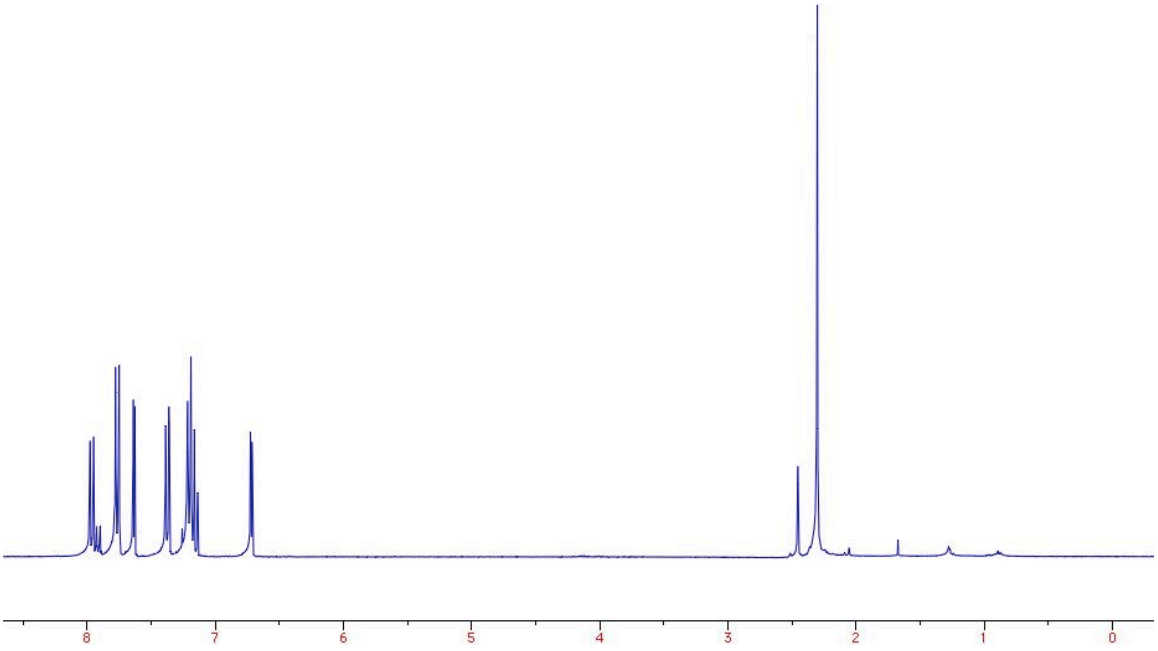


293

***N*-tosyl-4-bromo-indole (293):** To a solution of THF (240 mL) and NaH (1.05 g, 26.3 mmol, 1.1 eq.) was added 4-bromoindole (3 mL, 23.9 mmol, 1.0 eq.). After 1 h TsCl (5.5 g, 28.7 mmol, 1.2 eq.) was added and left to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 97% yield (8.1 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.945 (d, 8.3 Hz, 1H), 7.758 (d, 8.4 Hz, 2H), 7.624 (d, 3.8 Hz, 1H), 7.383 (d, 8.5 Hz, 1H), 7.241-7.139 (m, 3H), 6.722 (d, 4.4 Hz, 1H), 2.339 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 139.4, 138.1, 134.8, 130.4, 130.0, 130.0, 128.1, 128.1, 123.2, 122.4, 118.1, 113.5, 112.8, 102.4, 21.3; **HMRS(ESI-APCI)**: [M] calcd for $C_{15}H_{12}BrNO_2S$, 348.98; found, 348.9804.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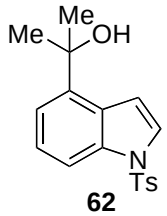
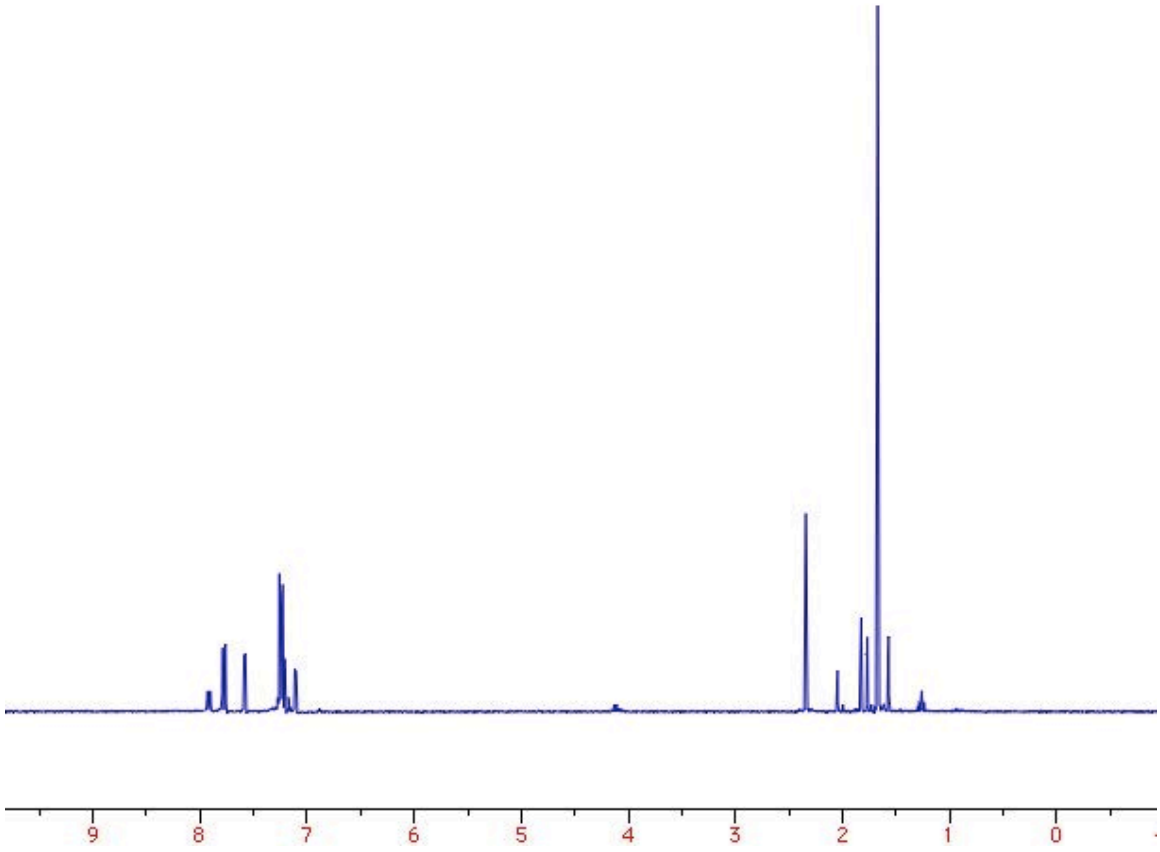


62

4-(2-hydroxy-2-propyl)-*N*-tosyl-indole (62): Compound **293** (8.4 g, 23.9 mmol, 1eq.) was taken up in Et_2O (400 mL) and cooled to -78 ℃. To the cooled solution was added *t*BuLi (28 mL, 47.9 mmol, 2 eq.) slowly and left to stir for 15 min to which a solution of acetone (1.8 mmol, 23.9 mmol, 1 eq.) in Et_2O (100 mL) was added. After 45 min the reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x2). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 51% yield (4.0 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.912 (d, 9.9 Hz, 1H), 7.747 (d, 8.4 Hz, 2H), 7.559 (d, 3.8 Hz, 1H), 7.218-7.145 (m, 4H), 7.084 (d, 4.5 Hz, 1H), 2.281 (s, 3H), 2.229 (s, 1H), 1.624 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 139.4, 138.6, 134.8, 132.2, 130.0, 130.0, 128.2, 128.2, 127.3, 122.3, 121.2, 113.7, 111.7, 104.9, 74.9, 32.0, 32.0, 21.3; **HMRS(ESI-APCI)**: [M] calcd for $C_{18}H_{19}NO_3S$, 329.11; found, 329.0978.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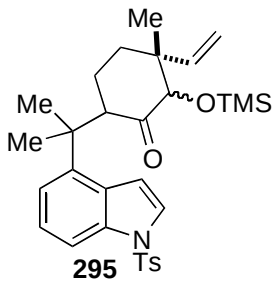
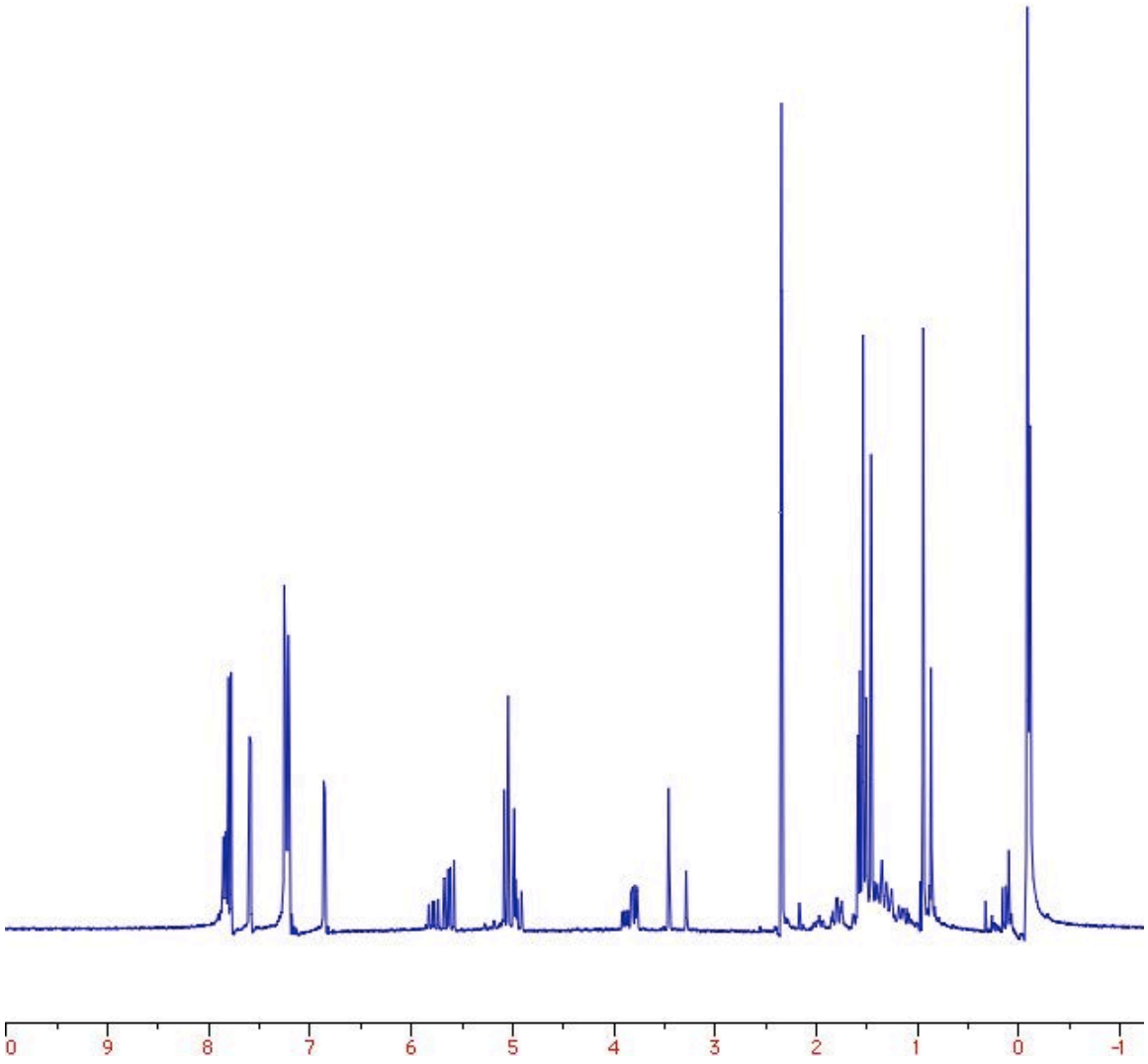


295

(Racemic)-Compound (295): To a solution of **285** (399 mg, 1.37 mmol, 2.0 eq.) in DCM (7 mL) was added **62** (220 mg, 0.67 mmol, 1.0 eq.), cooled to -78 ℃, and after stirring for 5 min 1 M tin (IV) chloride in DCM (0.87 mL, 0.87 mmol, 1.3 eq.) was added and left to stir for 15 min. The reaction was then allowed to warm to room temperature and was then poured onto a 1:1 solution of aqueous $NaHCO_3$:DCM and left to stir for 12 h. The mixture was extracted with DCM (x3), the organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 75% yield (270 mg).

Mixture of diastereomers: ^{1}**HNMR:** (300 MHz, $CDCl_3$) δ 7.846 (d, 1H), 7.795 (d, 2H), 7.573 (d, 1H), 7.244-7.204 (m, 4H), 6.861 (d, 1H), 5.705 (1H), 4.995 (1H), 3.845 (1H), 3.458 and 3.285 a total of 1H, 2.343 (s, 3H), 1.609 (s, 6H), 1.621-1.431 (m, 4H), 0.943 and 0.865 total of 3 H), 0.017 (s, 9H); **HMRS(ESI-APCI)**: $[M]^+$ calcd for $C_{30}H_{39}NO_4SSi$, 537.24; found, 537.2417.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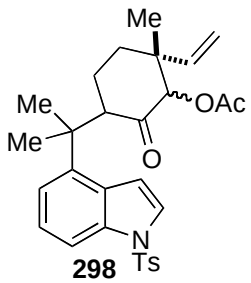
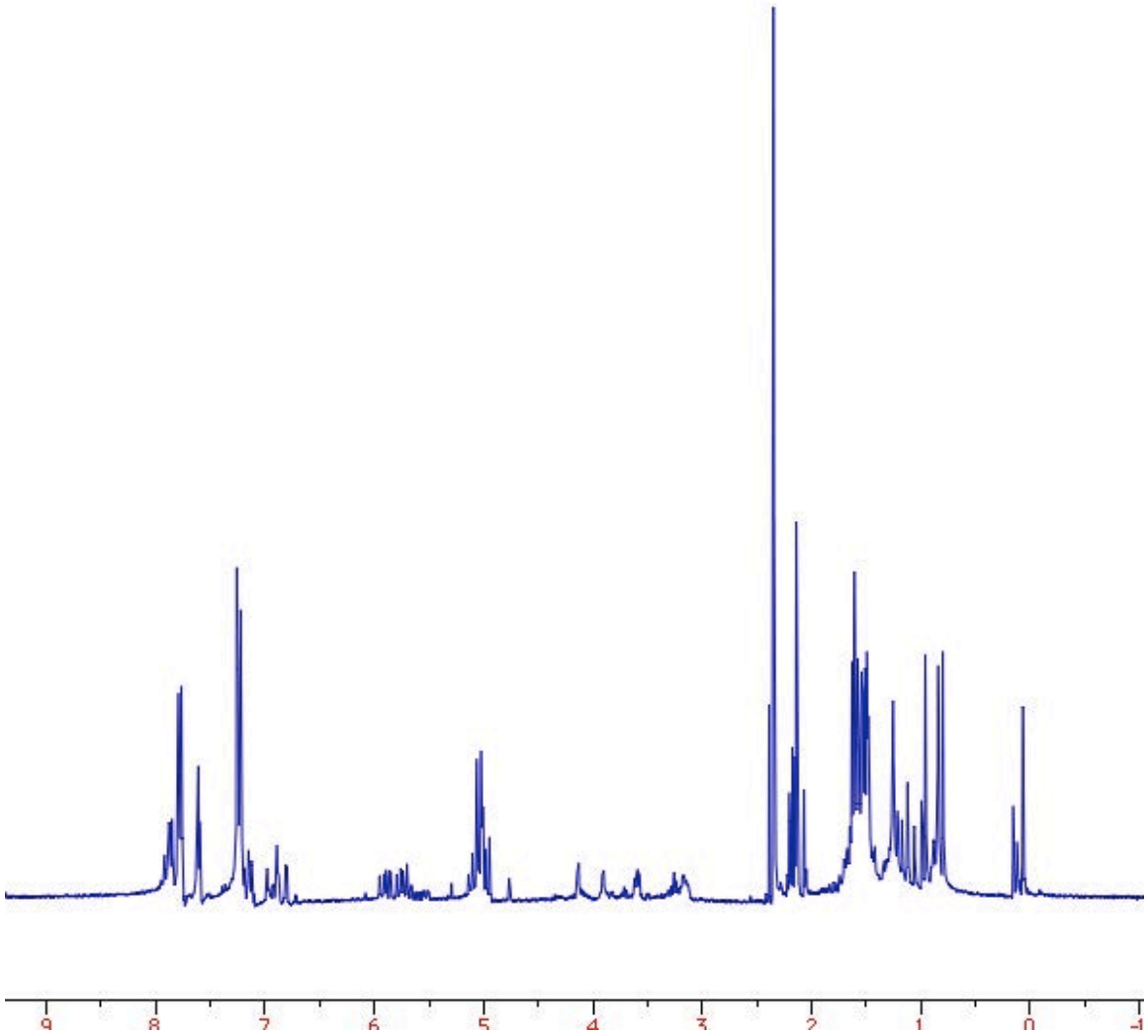


298

Compound 298: To a solution of **295** (130 mg, 0.24 mmol, 1.0 eq) in THF (3 mL) was added a 1 M solution of TBAF in THF (0.48 mL, 0.48 mmol, 2.0 eq) and left to stir. The reaction was quenched, 5 h later, with a saturated solution of NH_4Cl, extracted with hexane, washed with brine, dried and concentrated. The crude material (91 mg, 0.195 mmol) was taken up in THF (2 mL), cooled to 0 ℃ at which time LHMDS (1 M in THF, 0.21 mL, 0.21 mmol, 1.1 eq.) was added. Acetyl chloride (0.02 mL, 0.205, 1.05 eq) was added 15 later, quenched with a saturated NH_4Cl solution, 45 min later, extracted with hexane, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 79% yield (96 mg) over two steps.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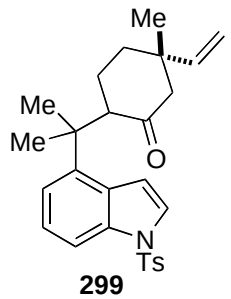
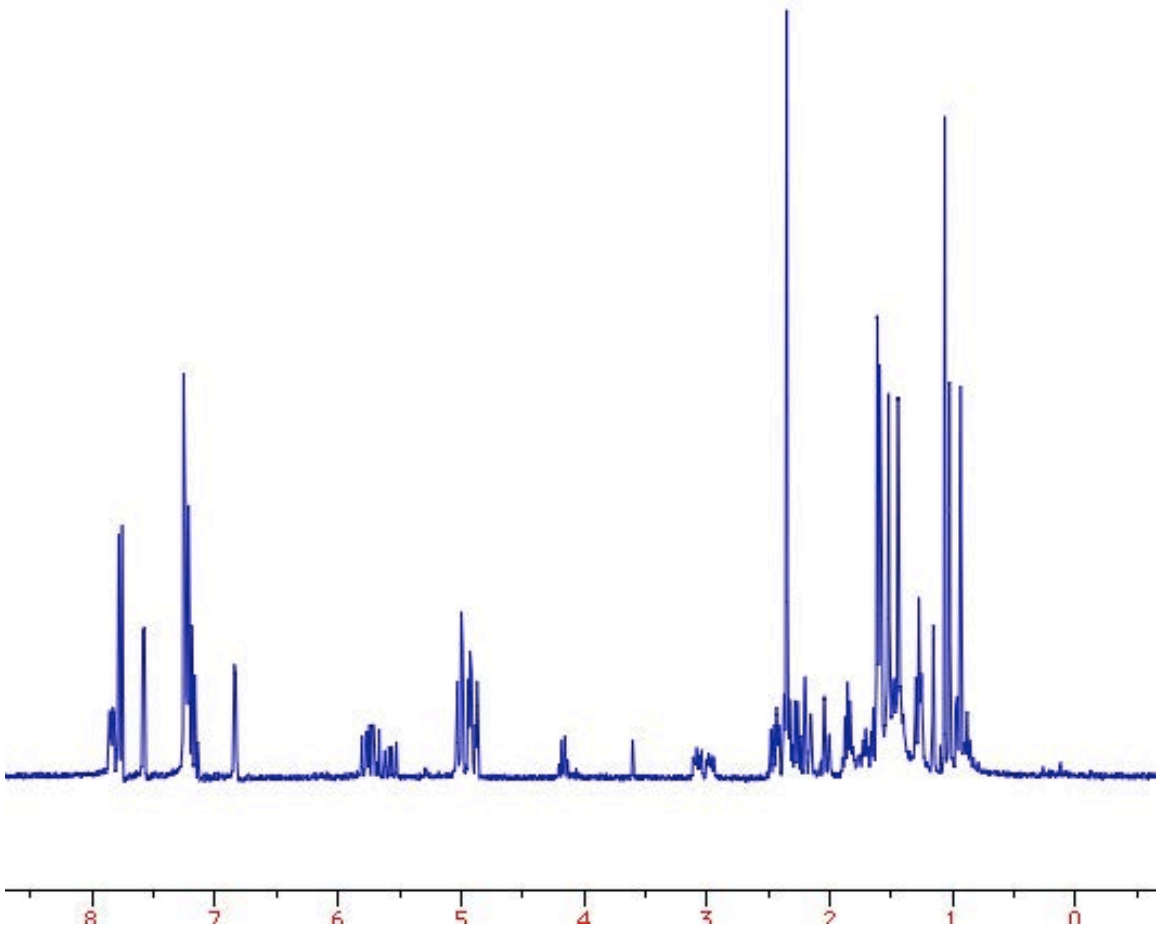


299

(Racemic)-Compound 299: To a solution of **65** (1.4 g, 6.65 mmol, 2.0 eq.) in DCM (30 mL) was added **62** (1.1 g, 3.3 mmol), cooled to -78 ℃, and after stirring for 5 min was added 1 M tin (IV) chloride in DCM (4.3 mL, 4.3 mmol, 1.3 eq.) and left to stir for 15 min at the same temperature. The reaction was then allowed to warm to room temperature and was then poured onto a 1:1 solution of aqueous $NaHCO_3$:DCM and left to stir for 12 h. The mixture was extracted with DCM (x3), the organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 82% yield (1.2 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.863-7.822 (d, 1H), 7.786-7.758 (d, 2H), 7.589-7.576 (d, 1H), 7.246-7.139 (m, 4H), 6.834-6.831 (d, 1H), 5.807-5.524 (dd, 1 H), 5.036-4.864 (dd, 2H), 3.112-2.943 (dd, 1H), 2.348 (s, 3H), 2.282-1.631 (m, 4H), 1.601 (s, 6H), 1.067 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 211.5, 147.5, 139.7, 139.4, 134.8, 132.1, 130.0, 130.0, 128.2, 128.2, 127.3, 122.2, 120.1, 114.2, 112.6, 111.4, 104.9, 67.6, 54.8, 42.4, 35.8, 31.9, 24.4, 24.4, 22.5, 21.3, 19.3; **HMRS(ESI-APCI)**: $[M]^+$ calcd for $C_{27}H_{31}NO_3S$, 449.20; found, 449.2065.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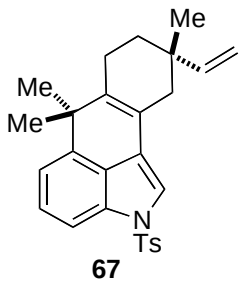
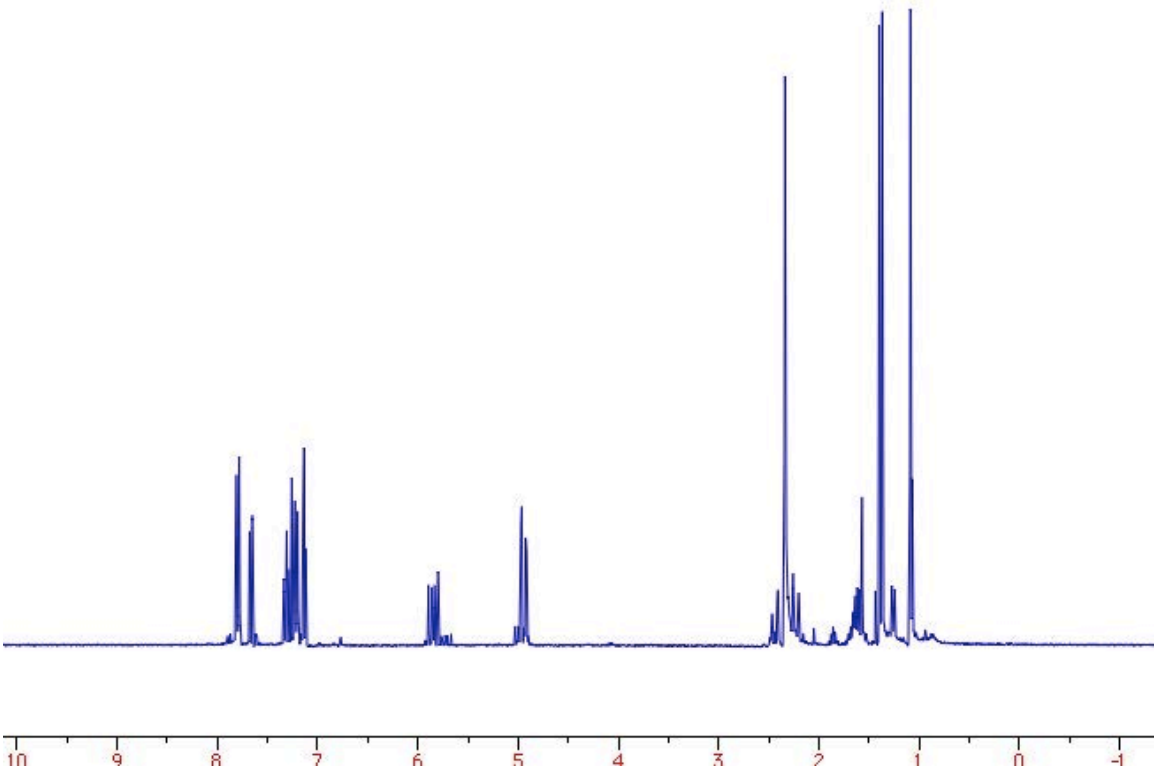


67

(Racemic)-Compound 67: Compound **299** (392 mg, 0.87 mmol, 1.0 eq.) was added to DCM (10 mL) and cooled to 0 ℃. To the cooled solution BF_3•Et_2O (0.19 mL, 1.48 mmol, 1.7 eq.) was added and left to stir until the starting material was consumed as monitored by TLC. The reaction was poured onto aqueous $NaHCO_3$ at 0 ℃ and extracted twice with DCM. The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 93% yield (349 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.809 (d, 8.4 Hz, 2H), 7.707 (d, 8.1 Hz, 1H), 7.334 (t, 7.7, 8.0 Hz, 1H), 7.187-7.136 (m, 4H), 5.868 (dd, 11, 18 Hz, 1H), 4.970 (dd, 9, 18 Hz, 2H), 2.473 (d, 17 Hz, 1H), 2.295 (s, 3H), 2.201 (d, 19 Hz, 1H), 1.880-1.569 (m, 4H), 1.406 (s, 3H), 1.380 (s, 3H), 1.109 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 146.9, 144.8, 141.1, 140.5, 135.8, 133.6, 130.0, 127.2, 126.5, 121.3, 119.4, 118.9, 115.5, 113.0, 111.3, 110.9, 41.1, 36.9, 34.8, 34.6, 30.3, 30.1, 27.5, 26.4, 22.8, 22.3, 21.8; **HMRS(ESI-APCI)**: $[M]^+$ calcd for $C_{27}H_{29}NO_2S$, 431.19; found, 431.1942.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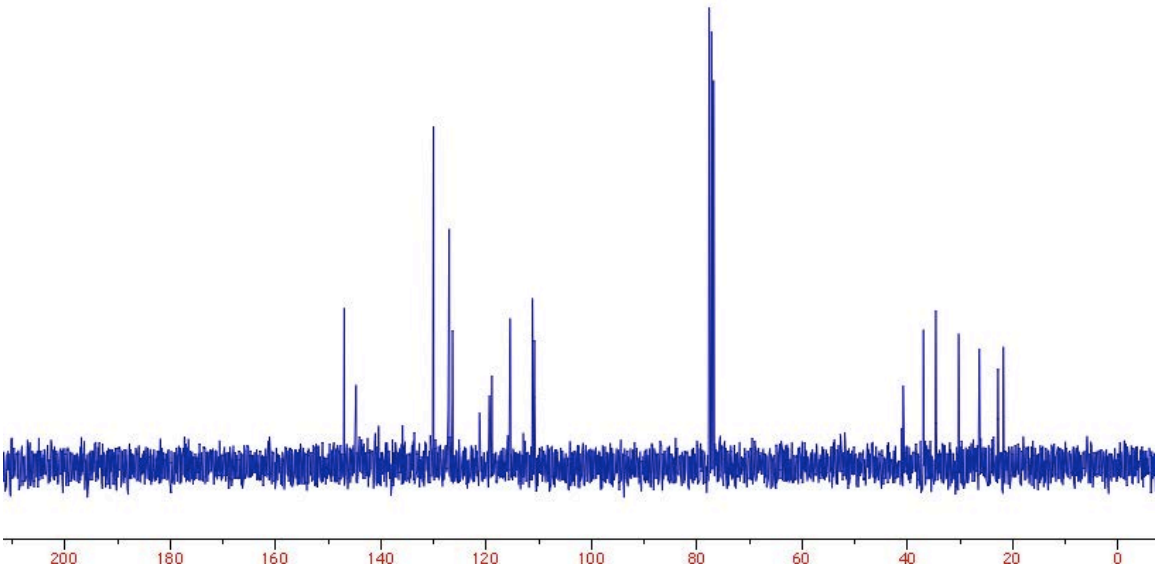
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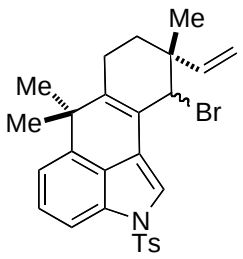
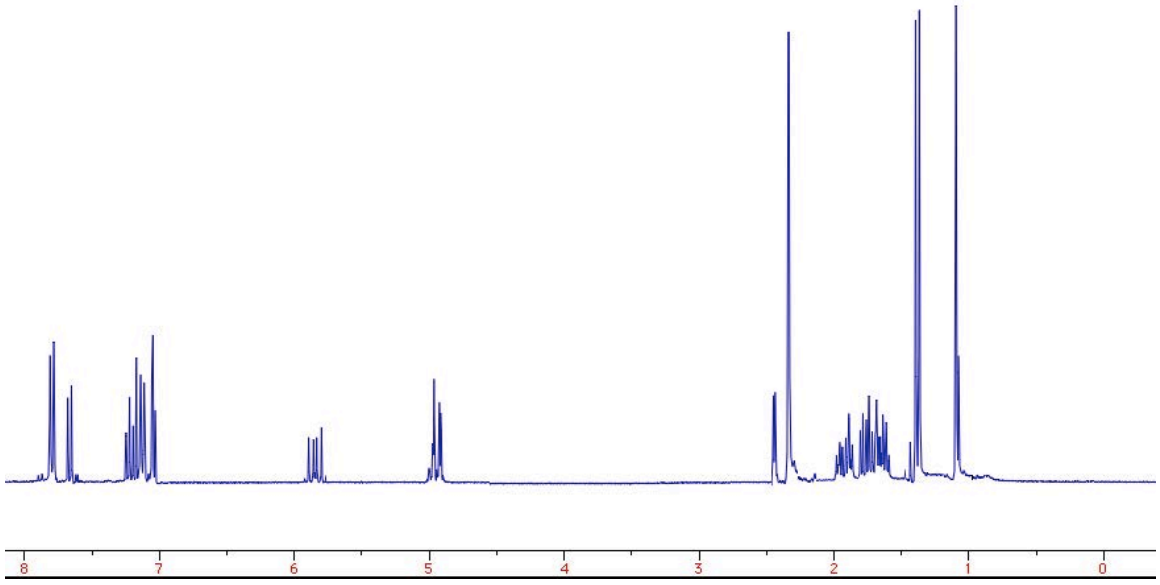


301

(Racemic)-Compound 301: To CCl_4 (1 mL) was added compound **67** (37 mg, 0.086 mmol, 1.0 eq.) followed by NBS (16.6 mg, 0.093 mmol, 1.09 eq.) and AIBN (3.11 mg, 0.019 mmol, 0.23 eq.) and brought to reflux. After 45 min the reaction was cooled to 0 ℃ to which aqueous $NaHCO_3$ was added and extracted with DCM (3x2 mL). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 82% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.81 (d, 8.4 Hz, 2H), 7.71 (d, 8.1 Hz, 1H), 7.33-7.136 (m, 5H), 5.868 (dd, 11, 18 Hz, 1H), 4.970 (dd, 9, 18 Hz, 2H), 2.473 (d, 17 Hz, 1H), 2.295 (s, 3H), 1.880-1.569 (m, 4H), 1.406 (s, 3H), 1.380 (s, 3H), 1.109 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 146.9, 144.8, 141.1, 140.5, 135.8, 133.6, 130.0, 127.2, 126.5, 121.3, 119.4, 118.9, 115.5, 113.0, 111.3, 110.9, 41.1, 36.9, 34.8, 34.6, 30.3, 30.1, 27.5, 26.4, 22.8, 22.3, 21.8; **HMRS(ESI-APCI)**: $[M+H]^+$ calcd for $C_{27}H_{28}BrNO_2S$, 511.10; found, 511.1043.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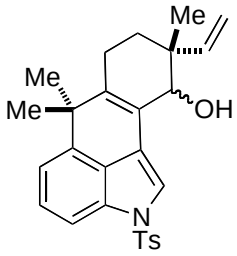
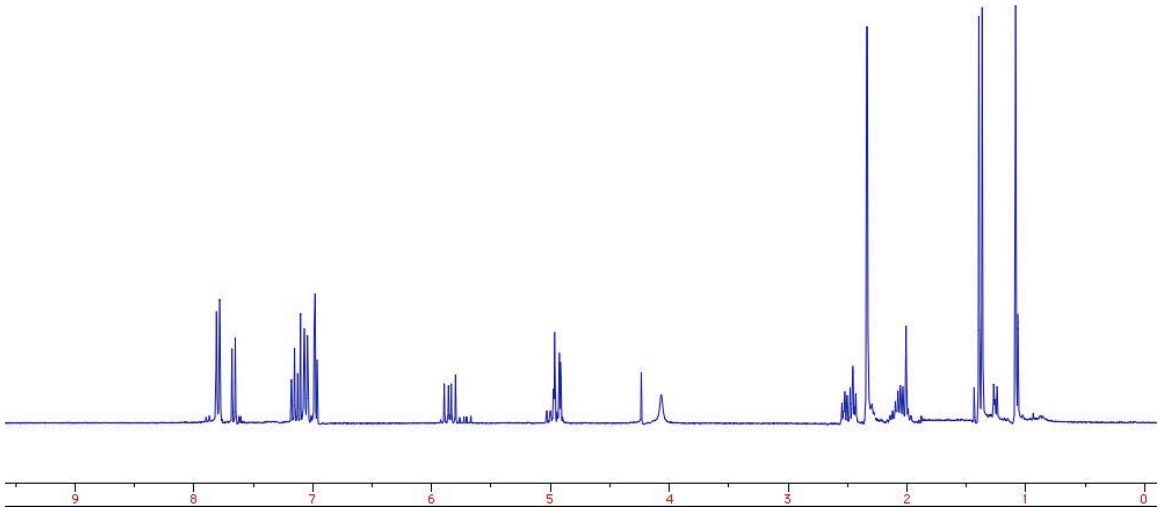


70

(Racemic)-Compound 70: Compound **301** (0.086 mmol, 1.0 eq.) was added to acetone (1 mL) to which $AgNO_3$ (27 mg, 0.159 mmol, 1.6 eq.) in H_2O (1 mL) was added and left to stir for 12 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM (x2). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 46% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.51-7.87 (m, 3H), 7.37-6.97 (m, 5H), 5.78 (dd, 18 Hz, 1H), 5.29-4.87 (m, 2H), 4.27 (s, 1H), 4.13 (br s, 1H), 2.51-2.31 (m, 2H), 2.29 (s, 3H), 2.2-1.9 (m, 2H), 1.39 (s, 6H), 1.06 (s, 3H); **HMRS(ESI-APCI)**: [M] calcd for $C_{27}H_{29}NO_3S$, 447.19; found, 447.1901.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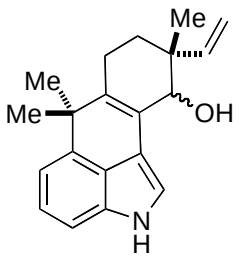
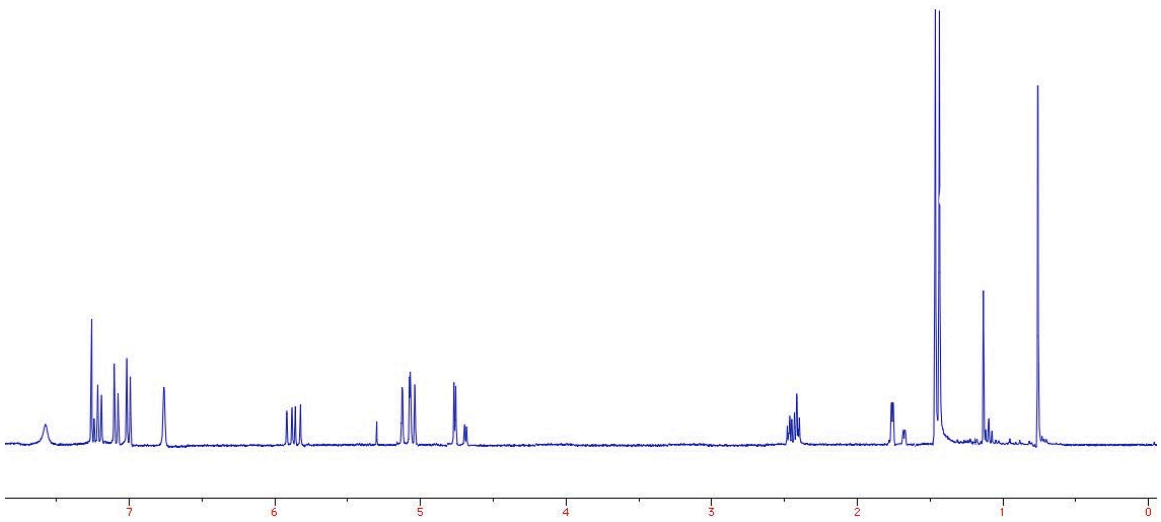


304

(Racemic)-Compound 304: To a mixture of THF (2 mL) and MeOH (1 mL) was added compound **70** (100 mg, 0.22 mmol, 1.0 eq.) at RT followed by cesium carbonate (215 mg, 0.66 mmol, 3.0 eq.) and left to stir. After 14 h the reaction was concentrated and re-dissolved in water (2 mL) and stirred for 10 min. The solids were filtered off, washed with water and dried. The crude solid was purified by flash silica gel chromatography (1:3 EtOAc:hexane) to afford product in 55% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.3-76.9 (m, 3H), 6.7 (s, 1H), 5.78 (dd, 18 Hz, 1H), 5.21-4.92 (m, 2H), 4.81-4.65 (m, 1H), 2.51-2.19 (m, 4H), 1.62-1,53 (m, 1H), 1.39 (s, 6H), 1.06-0.76 (m, 3H); **HMRS(ESI-APCI)**: [M] calcd for $C_{20}H_{23}NO$, 293.18; found, 293.1845.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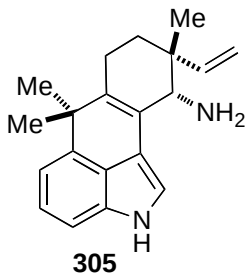
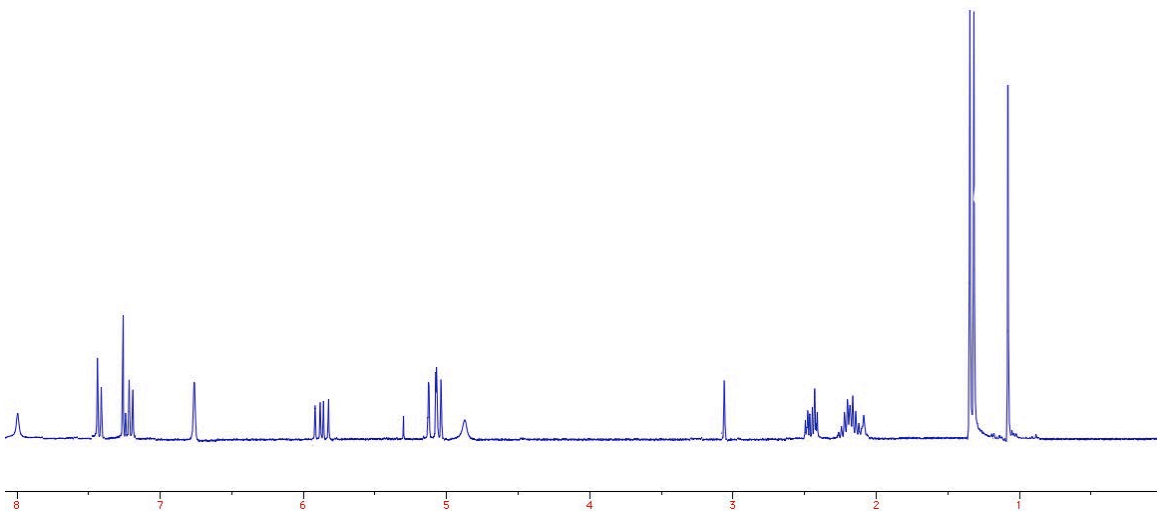


305

(Racemic)-Compound 305: To DCM (2 mL) was added compound **304** (55 mg, 0.19 mmol, 1.0 eq.) and DMP (157 mg, 0.37 mmol, 2.0 eq.) and left to stir for 2 h. The reaction was quenched with aqueous NaS_2O_3 (4 mL) and left to stir for 45 min, washed with aqueous $NaHCO_3$ (x2), once with aqueous NaS_2O_3, water and brine, dried over $MgSO_4$ and concentrated. The crude material was dissolved in THF (0.5 mL, 0.5 M) and added to a solution of ammonium acetate (586 mg, 7.6 mmol, 40 eq.), $NaCNBH_3$ (119 mg, 1.9 mmol, 10 eq.) in MeOH (70 mL) and left to stir for 48 h at RT. The reaction was quenched with aqueous $NaHCO_3$ and extracted with Et_2O (x3). The organic layers were combined, washed with 1 N HCl, and the organic and aqueous layer was separated. The aqueous layer was brought to above pH 8 with 2 N NaOH and extracted with EtOAc. The organic layers were combined, washed with brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:5 EtOAc:hexane) to afford product in 92% yield (total ##% include compounds diastereomer).

^{1}HNMR: (300 MHz, $CDCl_3$) δ7.5-7.2 (m, 3H), 6.7 (s, 1H), 5.78 (dd, 18 Hz, 1H), 5.29-4.97 (m, 2H), 4.92 (br s, 2H), 2.98 (s, 1H), 2.51-2.19 (m, 4H), 1.39 (s, 6H), 1.06 (s, 3H); **HMRS-FAB**: $[M+H]^+$ calcd for $C_{20}H_{25}N_2$, 293.20; found, 293.2017.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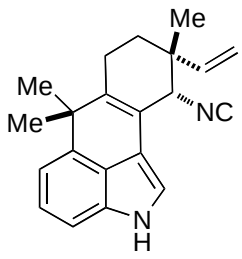
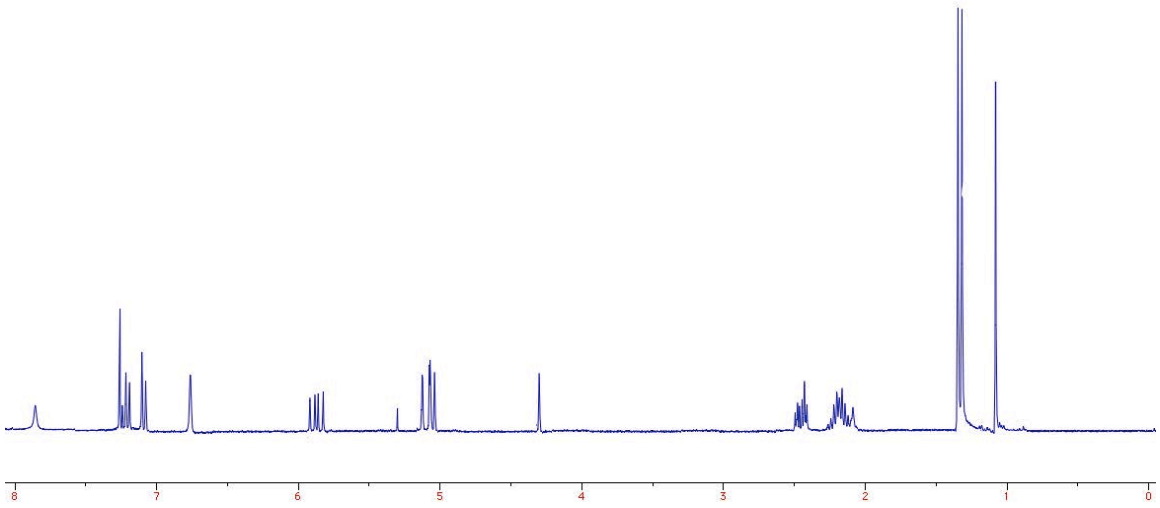


300

(Racemic)-Compound 300: Compound **305** (10 mg, 0.034 mmol, 1.0 eq.) was dissolved in DCM (1 mL), to which was added sequentially: formic acid (0.003 mL, 0.068 mmol, 2.0 eq.), 2-chloro-4,6-dimethoxy-1,3,5-triazine (65 mg, 0.08 mmol, 2.2 eq.), DMAP (0.2 mg, 0.002 mmol, 0.06 eq.), and *N*-methyl morpholine (0.008 mL, 0.08 mmol, 2.2 eq.). The mixture was stirred for 2 h, diluted with DCM and poured onto saturated $NaHCO_3$. The aqueous layer was extracted with DCM (x5). The organic layers were combined, washed with 1 N HCl, brine, dried and concentrated. The crude material was dissolved in benzene (14 mL, 0.01 M) and Burgess reagent (32 mg, 0.14 mmol, 4.0 equiv.) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed *in vacuo* and the crude material was purified by flash silica gel chromatography (1:3 EtOAc:hexane) to afford product in 66% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.8 (bs, 1H), 7.4-7.1 (m, 3H), 6.7 (s, 1H), 5.82 (dd, 18 Hz, 1H), 5.31-4.92 (m, 2H), 4.34 (d, 1H), 2.51-2.19 (m, 4H), 1.39 (s, 6H), 1.06 (s, 3H); **^{13}CNMR:** (75 MHz, CDCl3) δ 157.8, 155.9, 149.1, 142.3, 138.1, 136.5, 135.1, 132.1, 121.9, 118.0, 110.2, 108.4, 108.1, 63.6, 42.8, 39.6, 38.4, 31.3, 31.2, 23.5, 20.4; **HMRS-FAB**: $[M+H]^+$ calcd for $C_{21}H_2N_2$, 303.18; found, 303.1872.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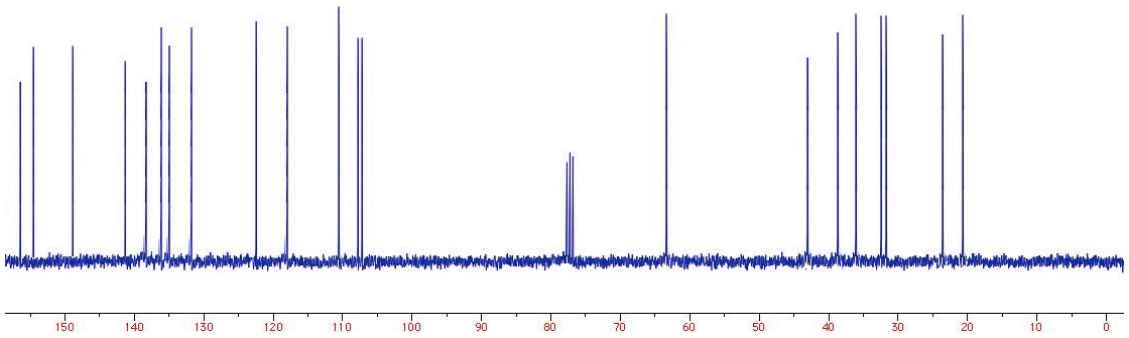
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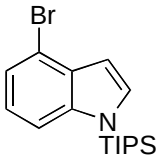
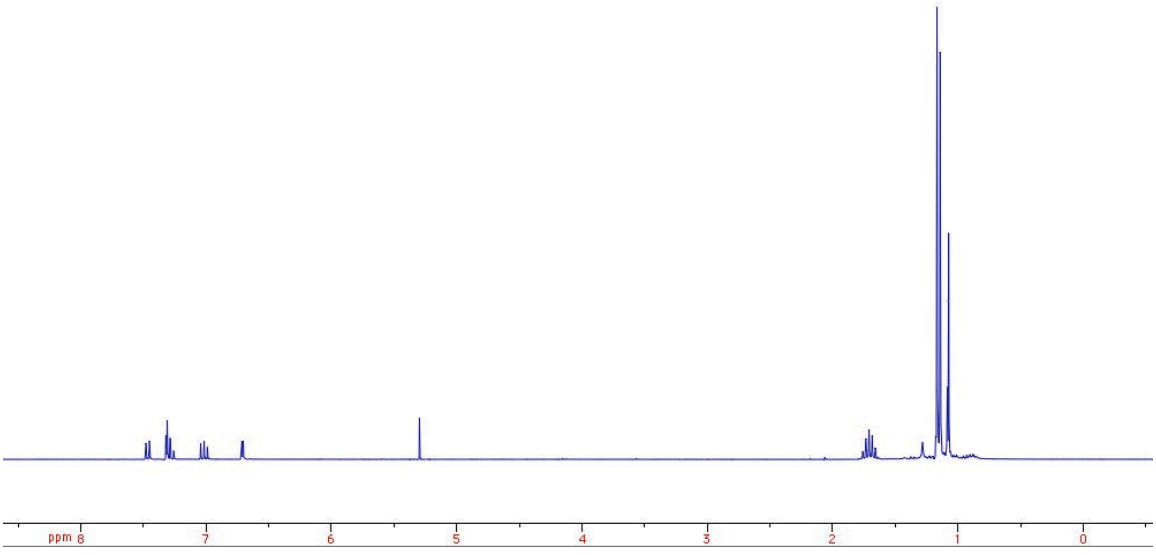
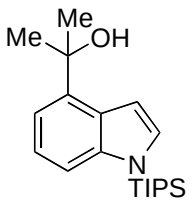


305

***N*-TIPS-4-bromo-indole (305):** To a solution of THF (200 mL) and NaH (2.5 g, 62.6 mmol, 1.1 eq.) was added 4-bromoindole (4 mL, 31.3 mmol, 1.0 eq.). After 1 h TIPSCl (8.6 g, 40.7 mmol, 1.2 eq.) was added and left to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x3). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 75% yield (8.3 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.47 (d, 8.3 Hz, 1H), 7.30 (t, 3.1, 6.8 Hz, 2H), 7.02 (t, 8.2, 7.7 Hz, 1H), 6.71 (d, 3.3 Hz, 1H), 1.79-1.6 (m, 3H), 1.16 (s, 18H); **HMRS-FAB**: $[M+H]^+$ calcd for $C_{17}H_{27}BrNSi$, 353.10; found, 353.1054.

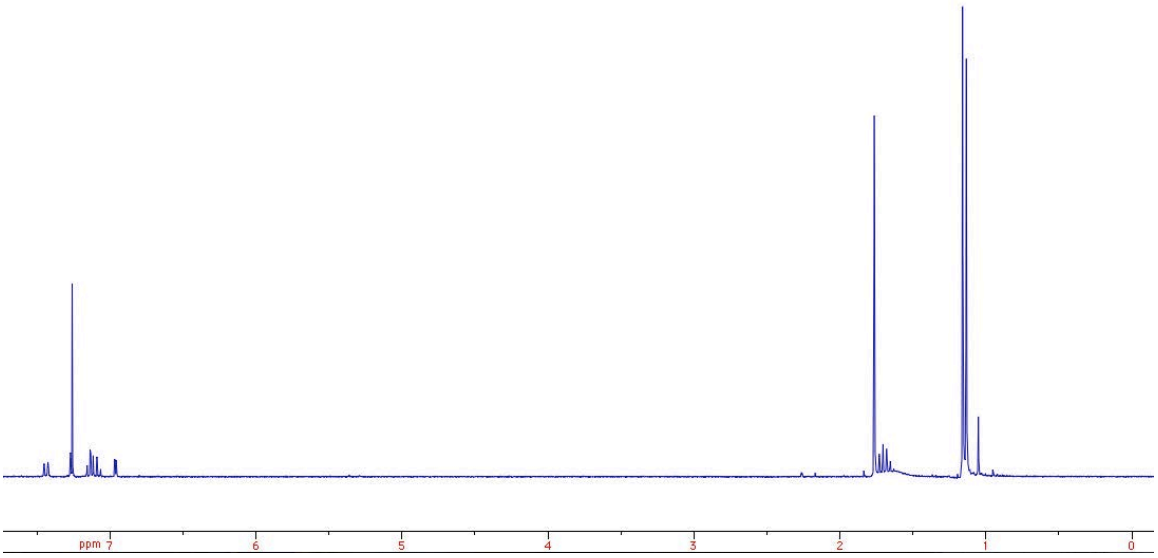


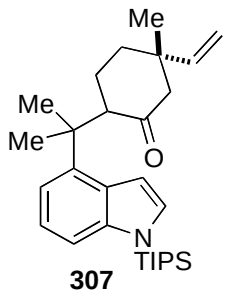


306

4-(2-hydroxy-2-propyl)-*N*-TIPS-indole (306): Compound (**305**) (1.79 g, 5.08 mmol, 1eq.) was taken up in Et_2O (100 mL) and cooled to -78 ℃. To the cooled solution was added *t*BuLi (1.7 M in pentane, 5.98 mL, 10.16 mmol, 2 eq.) slowly and left to stir for 15 min to which a solution of acetone (0.37 mL, 5.08 mmol, 1 eq.) in Et_2O (25 mL) was added. After 45 min the reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x2). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 92% yield (1.5 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ7.45 (d, 7.9 Hz, 1H), 7.27 (t, 3.3, 3.1 Hz, 1H), 7.19-7.07 (m, 2H), 8.47 (d, 3.2 Hz, 1H), 2.05 (s, 1H), 1.78 (s, 6H), 1.74-1.67 (m, 3H), 1.16 (s, 18H).

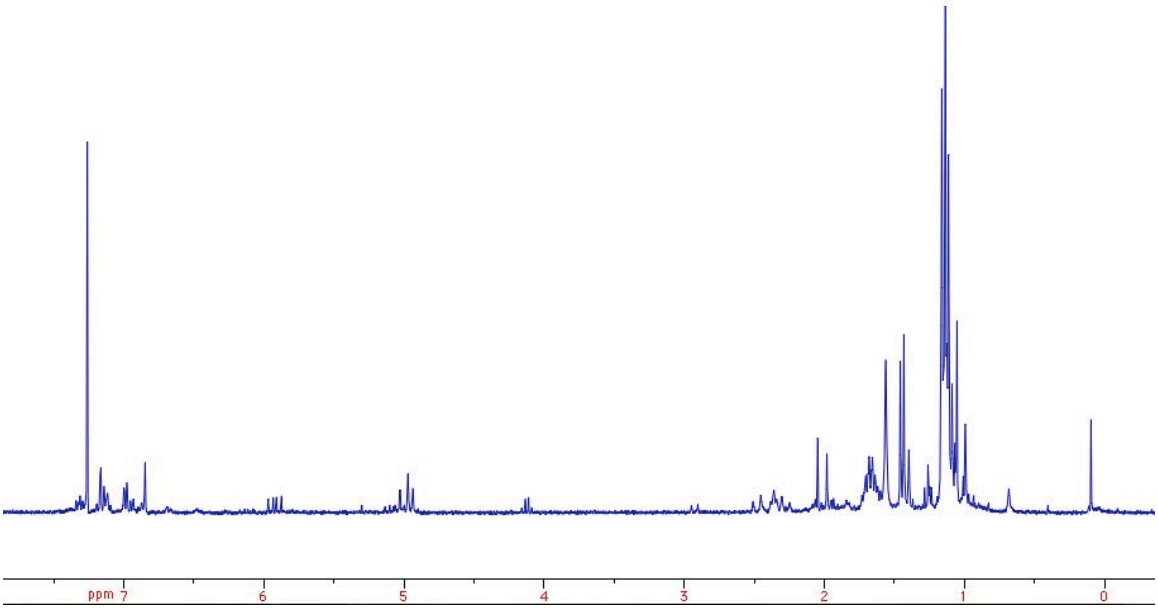




307

(Racemic)-Compound 307: To a solution of **306** (683 mg, 2.06 mmol, 1.0 eq.) in DCM (40 mL) was added **65** (564 mg, 2.68 mmol, 1.3 eq.), cooled to -78 ℃, and after stirring for 5 min 1 M tin (IV) chloride in DCM (2.2 mL, 2.2 mmol, 1.3 eq.) was added and left to stir for 15 min. The reaction was then allowed to warm to room temperature and was then poured onto a 1:1 solution of aqueous $NaHCO_3$:DCM and left to stir for 12 h. The mixture was extracted with DCM (x3), the organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 74% yield (688 mg).

Mixture of diastereomers: ^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 7.22-7.21 (m, 2H), 7.08-7.06 (m, 1H), 6.77-6.76 (m, 1H), 5.87-5.63 (m, 1H), 5.09-4.92 (m, 2H), 4.15-4.00 (m, 1H), 3.50-3.32 (m, 1H), 1.98-1.92 (m, 1H), 1.75-1.53 (m, 8H), 1.23-0.89 (m, 21H), 0.19-0.09 (m, 3H), 0.04 (s, 6H).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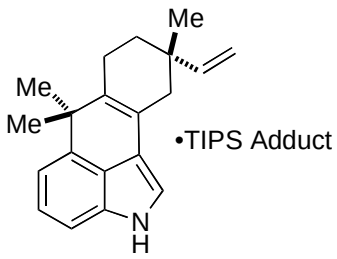
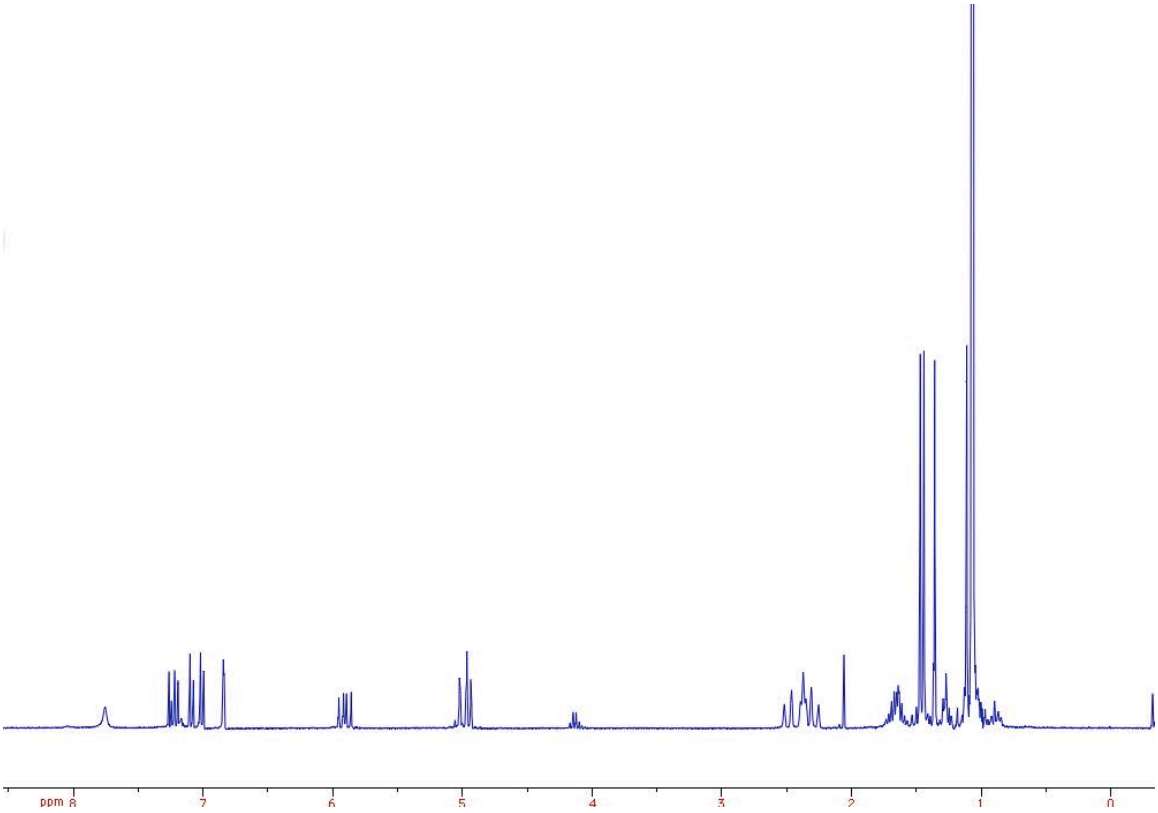
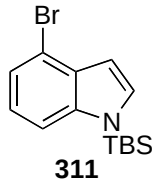


310 Obtained

(Racemic)-Compound 310: To a solution of **307** (414 mg, 0.92 mmol, 1.0 eq) in THF (10 mL) was added a 1 M solution of TBAF in THF (1.8 mL, 1.8 mmol, 2.0 eq). The concentrated upon consumption of the starting material as monitored by TLC analysis taken up in DCM and subjected to flash silica gel chromatography (1:2 EtOAc:hexane) to afford product in 80% yields.

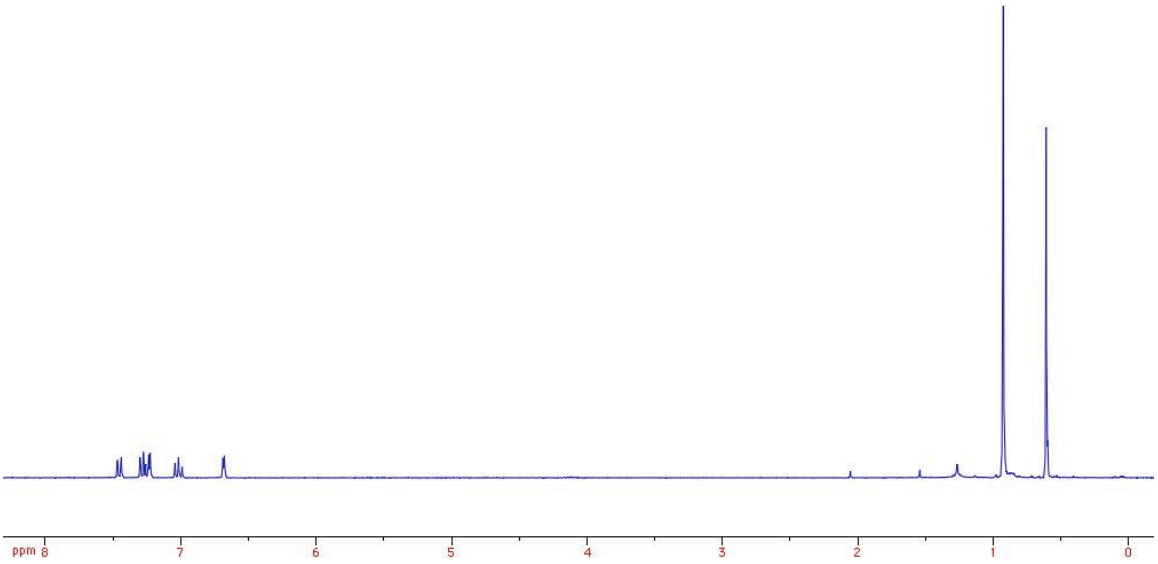




311

***N*-TBS-4-bromo-indole (311):** To a solution of THF (600 mL) and NaH (2.46 g, 61.4 mmol, 1.1 eq.) was added 4-bromoindole (7 mL, 55.81 mmol, 1.0 eq.). After 1 h TBSCl (10.1 g, 66.97 mmol, 1.2 eq.) was added and left to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x3). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 94% yield (16.3 g).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.482 (d, 8.3 Hz, 1H), 7.296 (d, 7.6 Hz, 1H), 7.239 (d, 3.3 Hz, 1H), 7.025 (t, 7.8, 8.1 Hz, 1H), 6.692 (d, 4.1 Hz, 1H), 1.277 (s, 1H), 0.935 (s, 9H), 0.617 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 141.4, 132.2, 131.8, 122.9, 122.5, 114.7, 113.2, 105.3, 26.5, 19.7, 3.7; **HMRS(ESI-APCI)**: [M] calcd for $C_{14}H_{39}NO_4SSi$, 310.06; found, 310.0619.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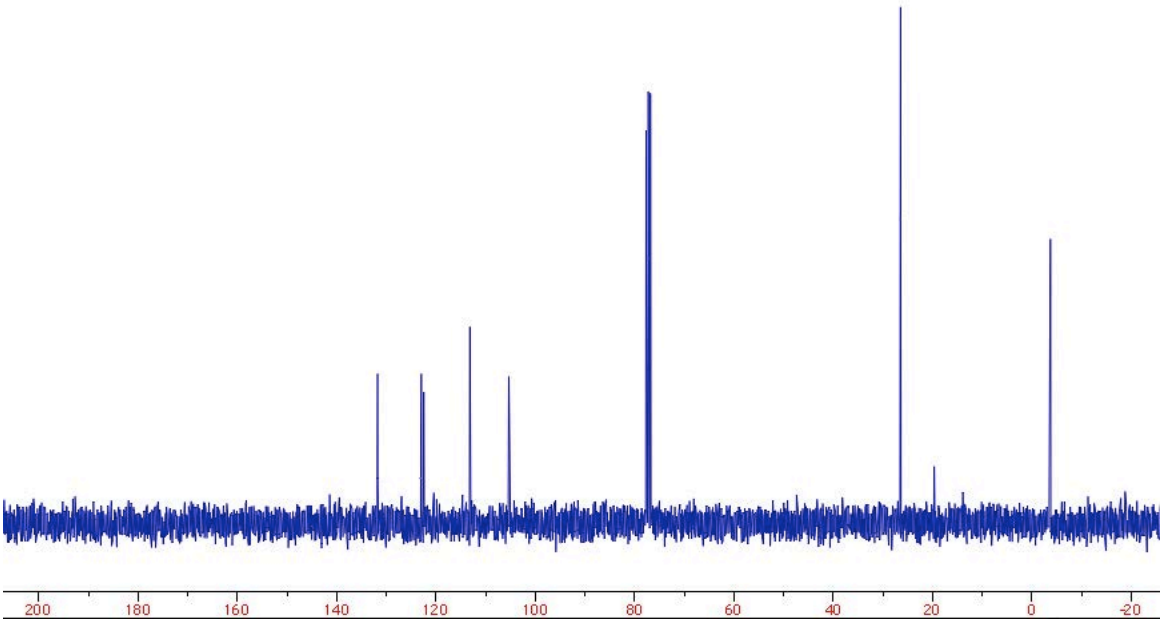
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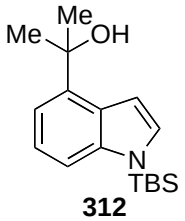
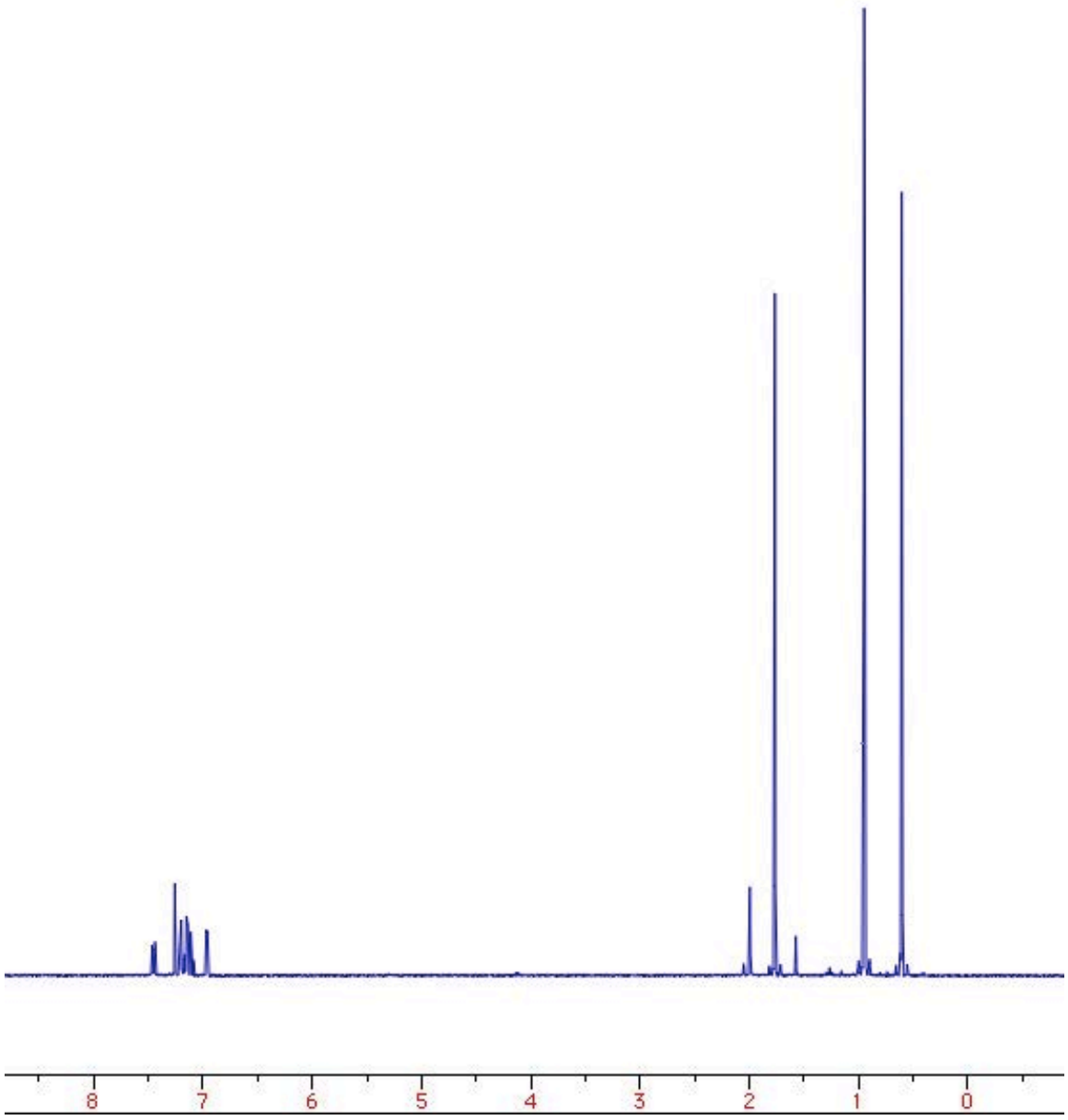


312

4-(2-hydroxy-2-propyl)-*N*-TBS-indole (312): Compound (**311**) (1.0 g, 3.22 mmol, 1eq.) was taken up in Et_2O (60 mL) and cooled to -78 ℃. To the cooled solution was added *t*BuLi (3.79 mL, 6.44 mmol, 2 eq.) slowly and left to stir for 15 min to which a solution of acetone (0.24 mL, 3.22 mmol, 1 eq.) in Et_2O (15 mL) was added. After 45 min the reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x2). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 99% yield (923 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.452 (d, 7.8 Hz, 1H), 7.205 (d, 3.3 Hz, 1H), 7.176-7.088 (m, 2H), 6.965 (d, 3.3 Hz, 1H), 1.992 (s, 1H), 1.763 (s, 6H), 0.946 (s, 9H), 0.603 (s, 6H); **HMRS(ESI-APCI)**: [M] calcd for $C_{17}H_{27}NOSi$, 289.19; found, 289.1943.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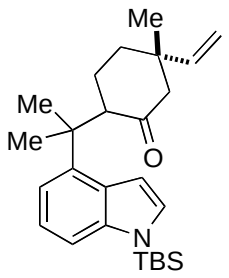
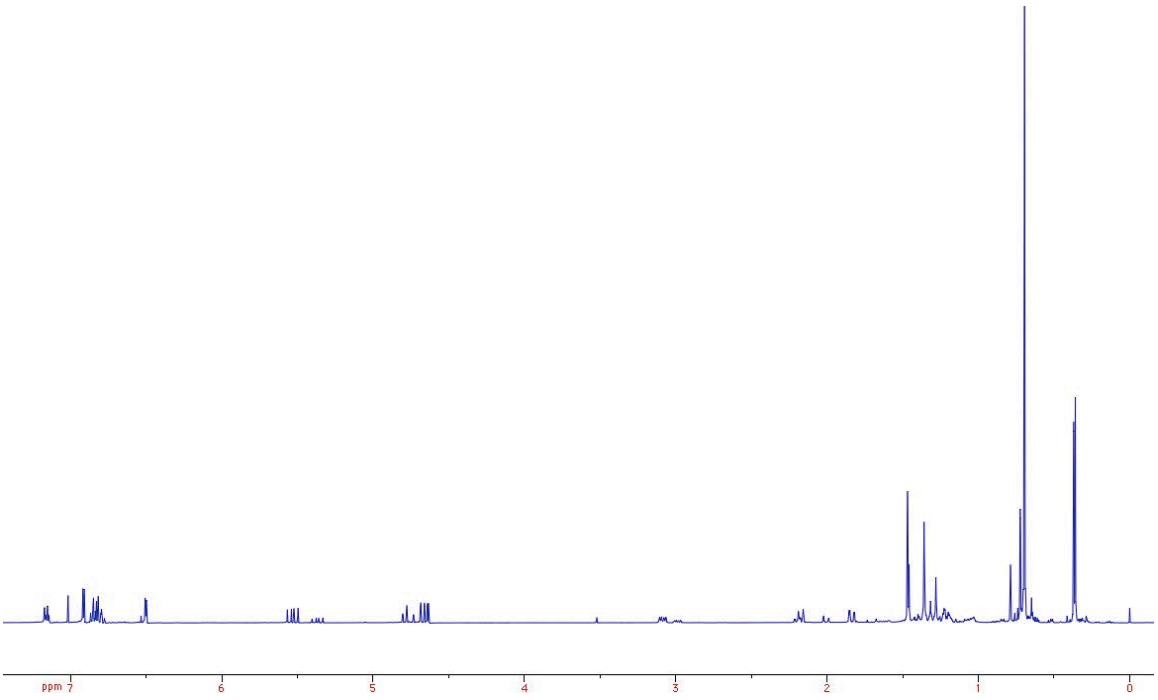


313

(Racemic)-Compound 313: To a solution of 312 (1.57 g, 5.4 mmol, 1.0 eq.) and 65 (2.05 g, 9.74 mmol, 1.8 eq.) in DCM (50 mL) at -78 ℃ was added a 1 M tin(IV) chloride solution (7 mL, 7,0 mmol, 1.3 eq.) and left to stir for 15 min. The reaction was poured onto a saturated $NaHCO_3$ solution and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (5% EtOAc in hexane) to afford product in 85% yield (1.9 g).

Mixture of diastereomers: ^{1}**HNMR:** (300 MHz, $CDCl_3$) δ 7.17-7.14 (m, 1H), 6.91 (d, 3.3 Hz, 1H), 6.87-6.77 (m, 2H), 6.50 (d, 3.3 Hz, 1H), 5.57-5.33 (m, 1H), 4.80-4.63 (m, 2H), 3.11-2.97 (m, 1H), 2.22-2.16 (m, 1H), 2.02-1.82 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 1.32-1.03 (m, 4H), 0.79-0.72 (m, 3H), 0.69 (s, 9H), 0.36 (s, 6H); ^{13}**CNMR:** (75 MHz, $CDCl_3$) δ 215.2, 151.6, 148.5, 145.8, 145.4, 133.5, 133.4, 131.8, 124.6, 121.2, 121.1, 117.6, 116.1, 116.0, 113.9, 109.2, 60.1, 58.1, 57.2, 46.3, 46.1, 44.5, 44.4, 41.7, 40.4, 33.7, 30.6, 30.5, 30.1, 29.1, 26.8, 26.7, 26.3, 23.3, 17.9, -0.01, -0.04.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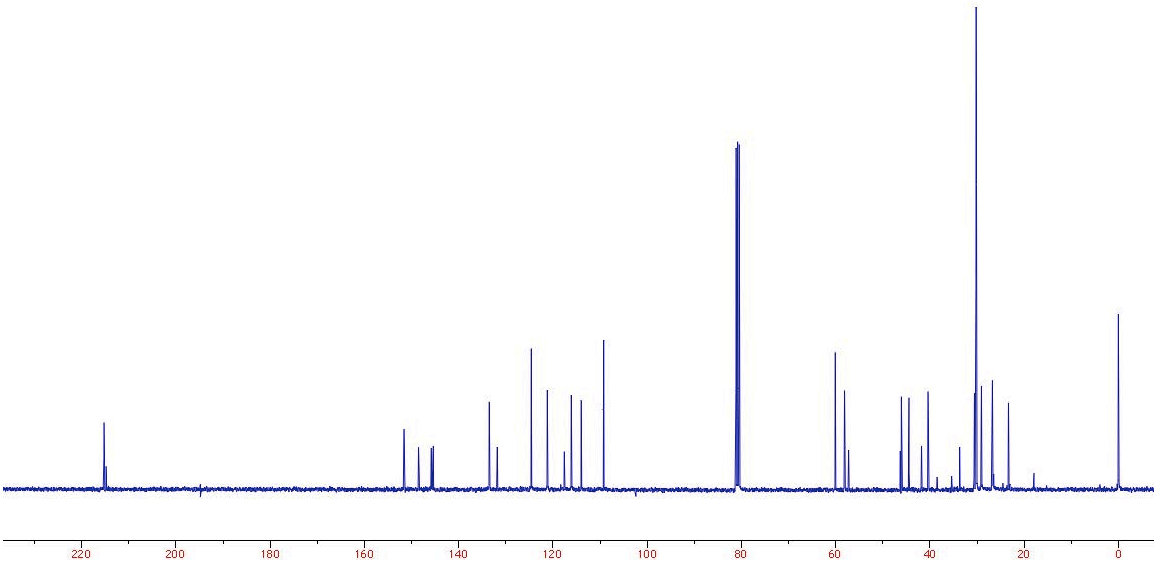
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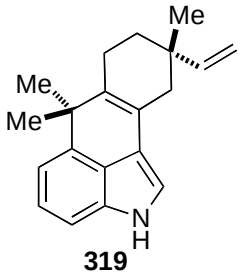
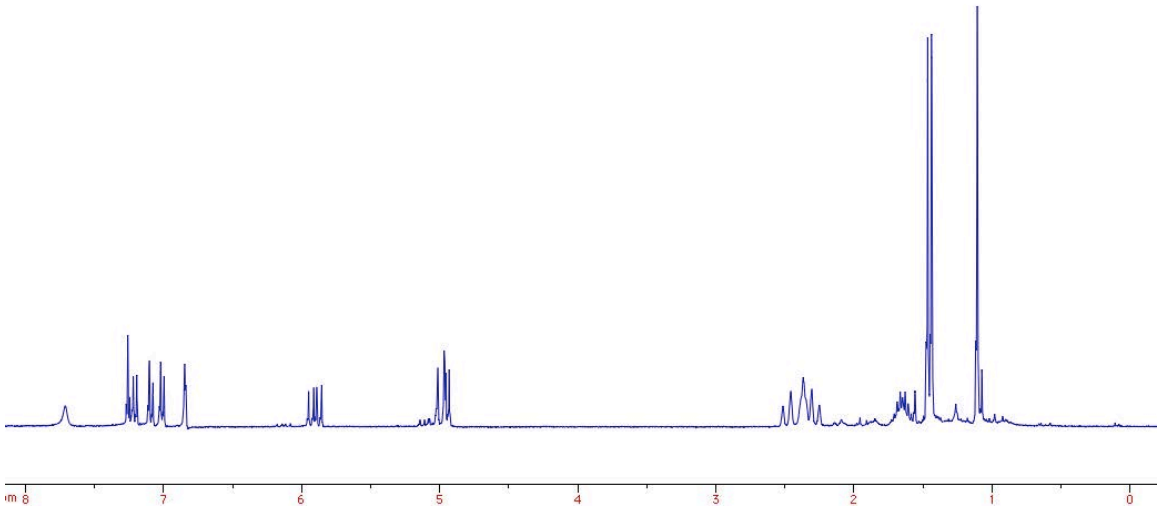


319
53% from **307**
92% from **313**

(Racemic)-Compound 319: To a solution of 313 (94 mg, 0.23 mmol, 1.0 eq.) in MeOH (3 mL) was added an aqueous 1 M HCl solution (3 mL) and left to stir until starting material was consumed as monitored via TLC analysis. The reaction was poured onto a saturated $NaHCO_3$ solution and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated to afford crude material. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 53% yield from the TIPS tricycle and in 92% yield from the TBS tricycle (59 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.21 (d, 7.6 Hz, 1H), 7.09 (d, 7.7 Hz, 1H), 7.01 (d, 7.3 Hz, 1H), 6.85 (s, 1H), 5.90 (dd, 10.7, 17.5 Hz, 1H), 4.97 (dd, 10.7, 13.8 Hz, 2H), 2.49 (d, 17.4 Hz, 1H), 2.38-2.35 (m, 2H), 2.28 (d, 16 Hz, 1H), 1.73-1.56 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H), 1.11 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 147.6, 144.3, 141.0, 135.7, 124.8, 124.4, 120.3, 114.7, 114.4, 110.9, 107.9, 107.6, 99.1, 71.2, 40.8, 37.4, 35.0, 34.9, 30.6, 30.5, 26.1, 25.9, 22.6.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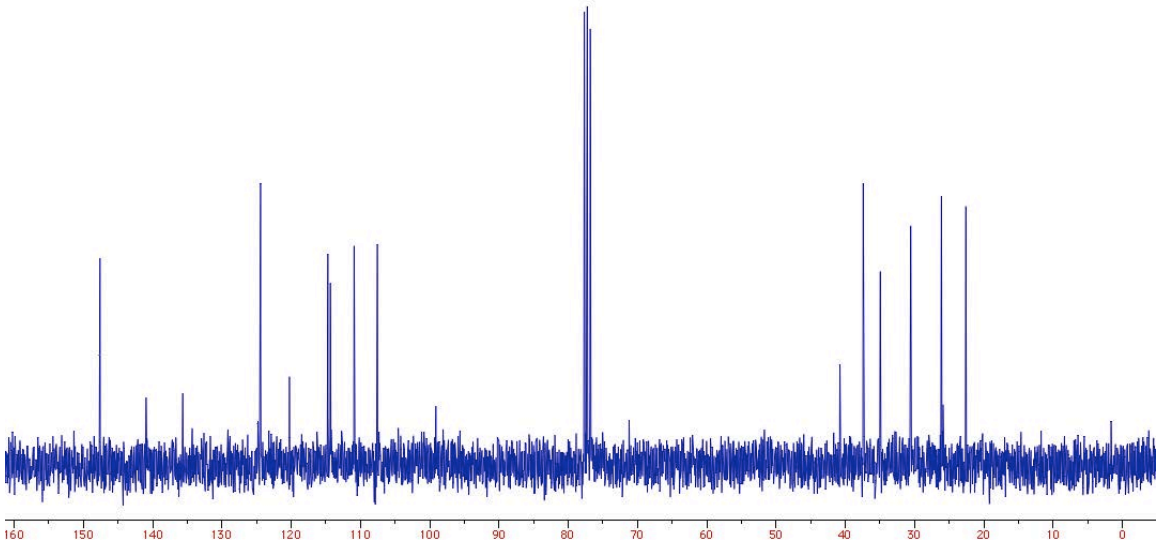
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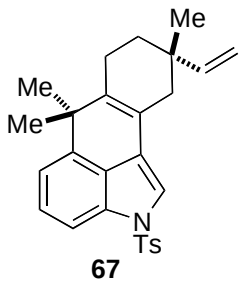
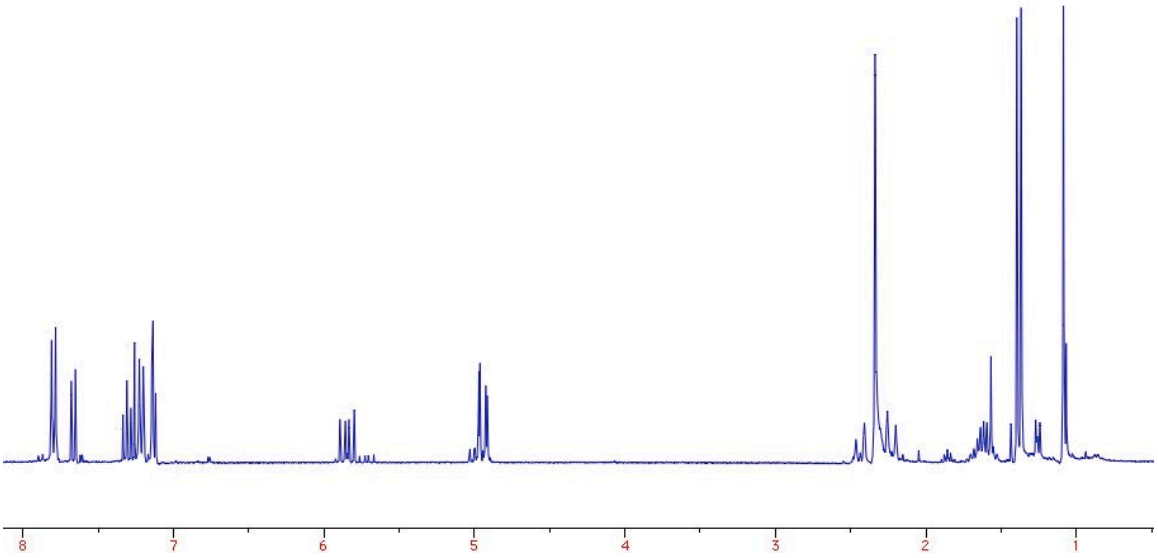


67

(Racemic)-Compound 67: To a solution of **319** (240 mg, 0.87 mmol, 1.0 eq.) in DCM (10 mL) was added TsCl (247 mg, 1.29 mmol, 4 eq.) and DMAP (0.2 eq.) was added and brought to reflux. After 12 h the reaction was quenched with saturated NH_4Cl and extracted with DCM. The organic layers were combined were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:8 EtOAc:hexane) to afford product in 82% yield (3.08 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.79 (d, 8.4 Hz, 2H), 7.67 (s, 1H), 7.31 (t, 7.8, 7.9 Hz, 1H), 7.21 (d, 8.0 Hz, 2H), 7.15-7.12 (m, 2H), 5.85 (dd, 10.5, 10.5 Hz, 1H), 4.94 (dd, 2.8, 14.1 Hz, 2H), 2.44 (d, 16.7 Hz, 1H), 2.34 (s, 3H), 2.23 (d, 16.5 Hz, 1H), 1.90-1.57 (m, 4H), 1.40 (s, 3H), 1.37 (s, 3H), 1.09 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.9, 1344.7, 140.4, 135.9, 130.0, 127.2, 126.4, 121.3, 119.4, 118.9, 115.4, 111.2, 110.8, 40.8, 37.0, 36.8, 34.7, 34.6, 34.5, 30.2, 30.1, 26.3, 23.6, 22.8, 21.8.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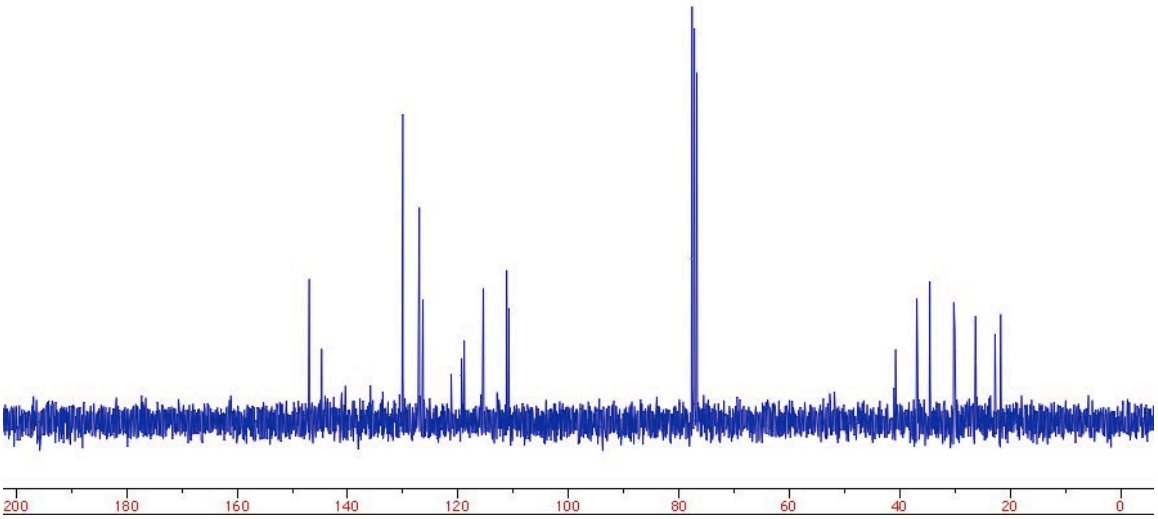
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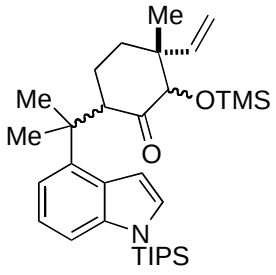
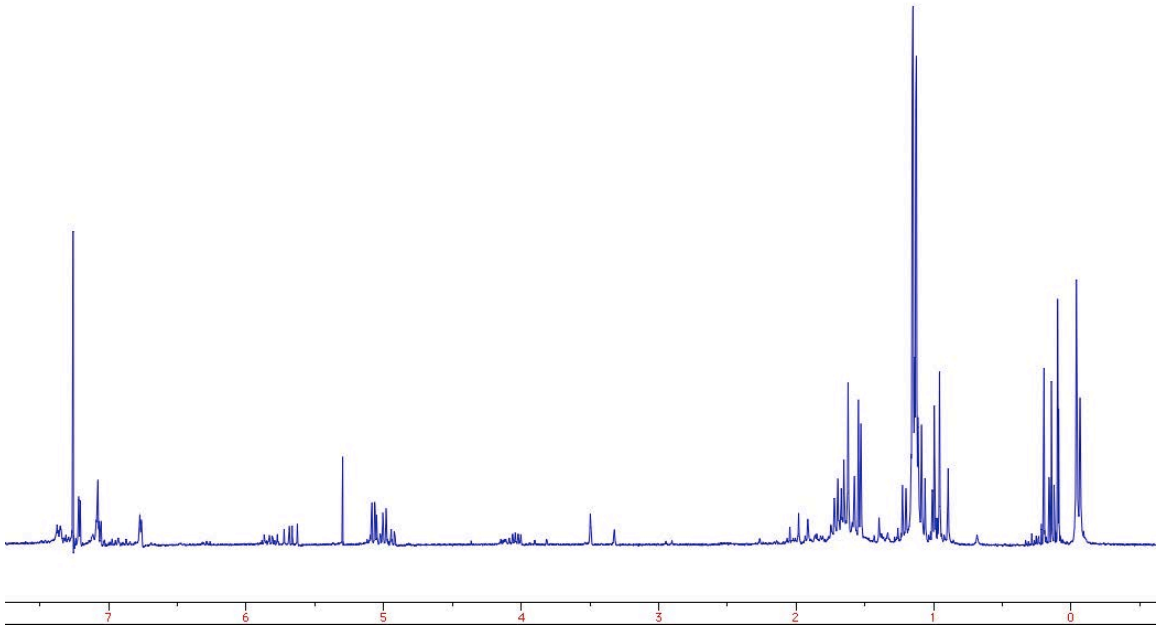


320

(Racemic)-Compound 320: To a solution of **306** (407 mg, 1.23 mmol, 1.0 eq) in DCM (15 mL) was added **285** (550 mg, 1.84 mmol, 1.5 eq) and cooled to -78 ℃ at which a 1 M solution in DCM of tin(IV) chloride (1.3 mL, 1.29 mmol, 1.05 eq) was added and left to stir for 15 min. The reaction was poured onto a saturated $NaHCO_3$ solution and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (5% EtOAc in hexane) to afford product in 87% yield (578 mg).

Mixture of diastereomers: ^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 7.22-7.21 (m, 2H), 7.08-7.06 (m, 1H), 6.77-6.76 (m, 1H), 5.87-5.63 (m, 1H), 5.09-4.92 (m, 2H), 4.15-4.00 (m, 1H), 3.50-3.32 (m, 1H), 1.98-1.92 (m, 1H), 1.75-1.53 (m, 8H), 1.23-0.89 (m, 21H), 0.19-0.09 (m, 3H), 0.04 (s, 6H).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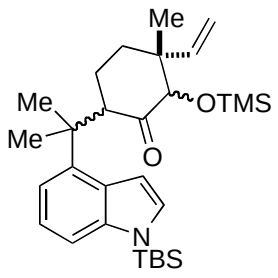
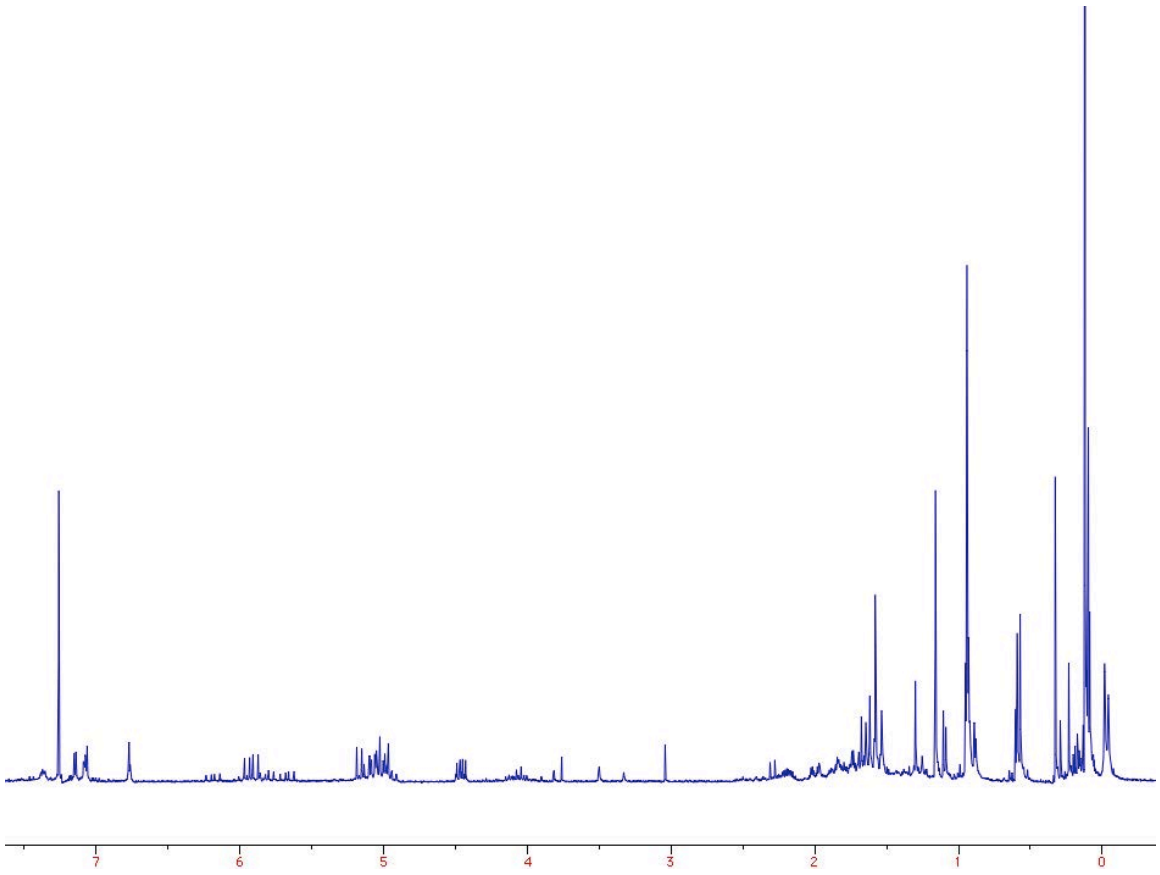


321

(Racemic)-Compound 321: To a solution of 312 (76 mg, 0.26 mmol, 1.0 eq.) and 285 (141 mg, 0.47 mmol, 1.8 eq.) in DCM (3 mL) at -78 ℃ was added a solution of 1 M tin(IV) chloride in DCM (0.34 mL, 0.34 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was poured onto a saturated $NaHCO_3$ solution 15 min later and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated to afford crude material. The crude material was purified via flash silica gel chromatography (10% EtOAc in hexane) to afford product in 92% yield (119 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.39-7.35 (m, 1H), 7.16-7.15 (m, 1H), 7.09-7.07 (m, 2H), 6.78-6.77 (m, 1H), 5.72-5.62 (m, 1H), 5.09-5.00 (m, 2H), 4.07-4.01 (m, 1H), 3.50-3.33 (m, 1H), 1.65-1.26 (m, 10H), 0.95 (s, 9H), 0.89-0.88 (m, 3H), 0.59 (s, 9H), 0.01 (s, 6H).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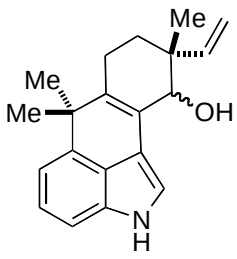
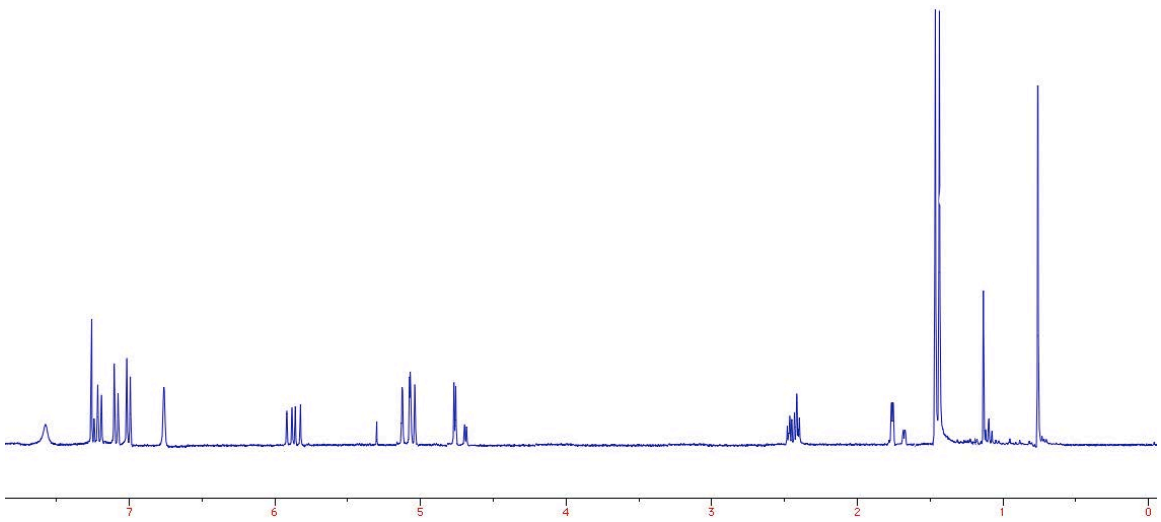


322

(Racemic)-Compound 322: (Route 1): To compound **320** (75 mg, 0.15 mmol, 1.0 eq.) was added MeOH (2 mL) followed by 1 N $HCl_{(aq)}$ (1.35 mL, 1.35 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (10 mL) and stirred for 1 h and extracted with DCM. The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 57% yield (12% yield for the TIPS tricycle analog).

(Route 2): To compound **320** (75 mg, 0.15 mmol, 1.0 eq.) was added MeOH (2 mL) followed by 3 N methanolic HCl (3 N HCl in MeOH, 0.5 mL, 1.51 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (10 mL) and stirred for 1 h and extracted with DCM. The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 79% yield (22% yield for the TIPS tricycle analog).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.3-76.9 (m, 3H), 6.7 (s, 1H), 5.78 (dd, 18 Hz, 1H), 5.21-4.92 (m, 2H), 4.81-4.65 (m, 1H), 2.51-2.19 (m, 4H), 1.62-1,53 (m, 1H), 1.39 (s, 6H), 1.06-0.76 (m, 3H); **HMRS(ESI-APCI)**: [M] calcd for $C_{20}H_{23}NO$, 293.18; found, 293.1845.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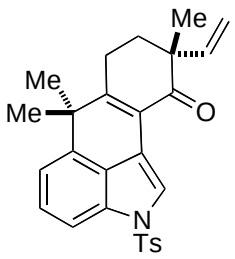
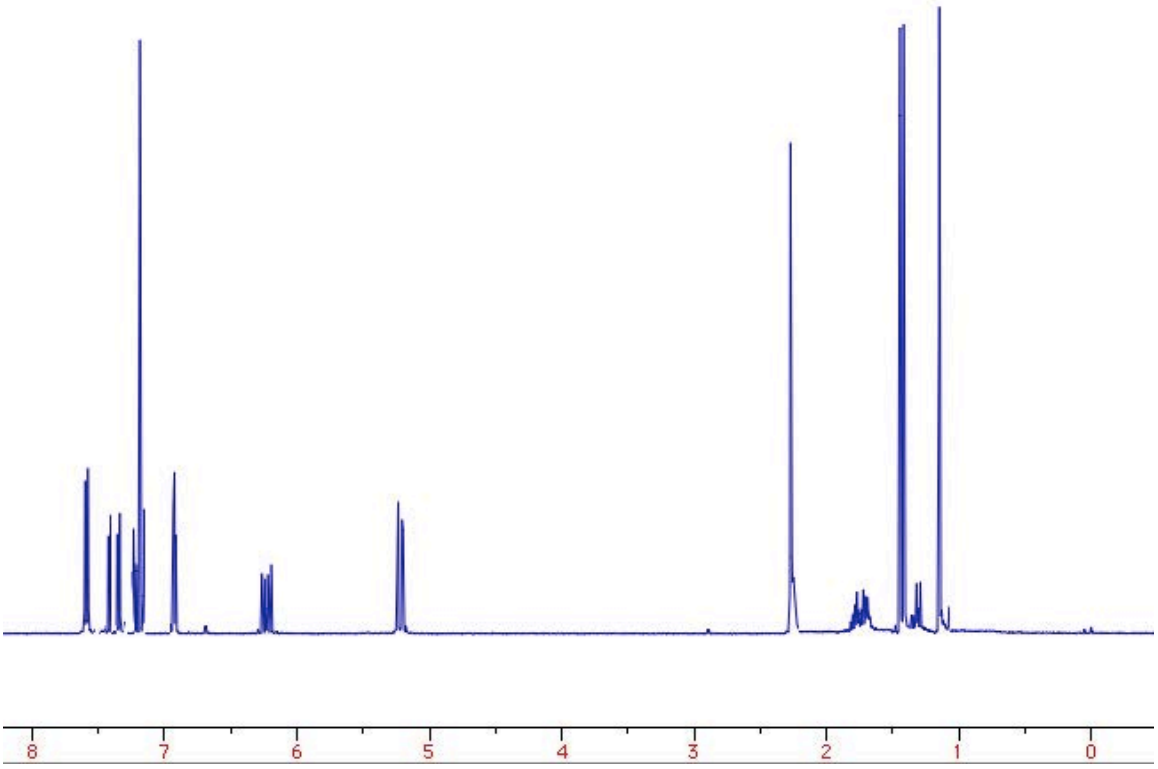


325

(Racemic)-Compound 325: To DCM (2 mL) was added compound **322** (55 mg, 0.19 mmol, 1.0 eq.) and DMP (157 mg, 0.37 mmol, 2.0 eq.) and left to stir for 2 h. The reaction was quenched with aqueous NaS_2O_3 (4 mL) and left to stir for 45 min, washed with aqueous $NaHCO_3$ (x2), once with aqueous NaS_2O_3, water and brine, dried over $MgSO_4$ and concentrated. The crude material was dissolved in DCM (2 mL) to which TsCl (145 mg, 0.76 mmol, 4 eq.) and DMAP (5 mg, 0.04 mmol, 0.2 eq.) was added and brought to reflux. After 12 h the reaction was quenched with saturated NH_4Cl and extracted with DCM. The organic layers were combined were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:8 EtOAc:hexane) to afford product an overall 89% yield (84 mg) over 2 steps.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.53 (t, 2.1 Hz, 1H), 7.49-7.29 (m, 4H), 7.05-7.02 (m, 2H), 6.99 (s, 1H), 6.31 (dd, 10.5, 16.3 Hz, 1H), 5.11 (dd, 10.4, 16.1 Hz, 2H), 2.43 (s, 3H), 1.92-2.11 (m, 4H), 1.49 (s, 3H), 1.42 (s, 3H), 1.18 (s, 3H).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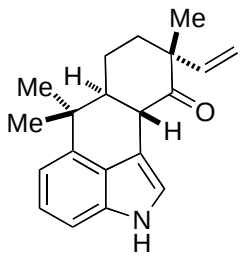
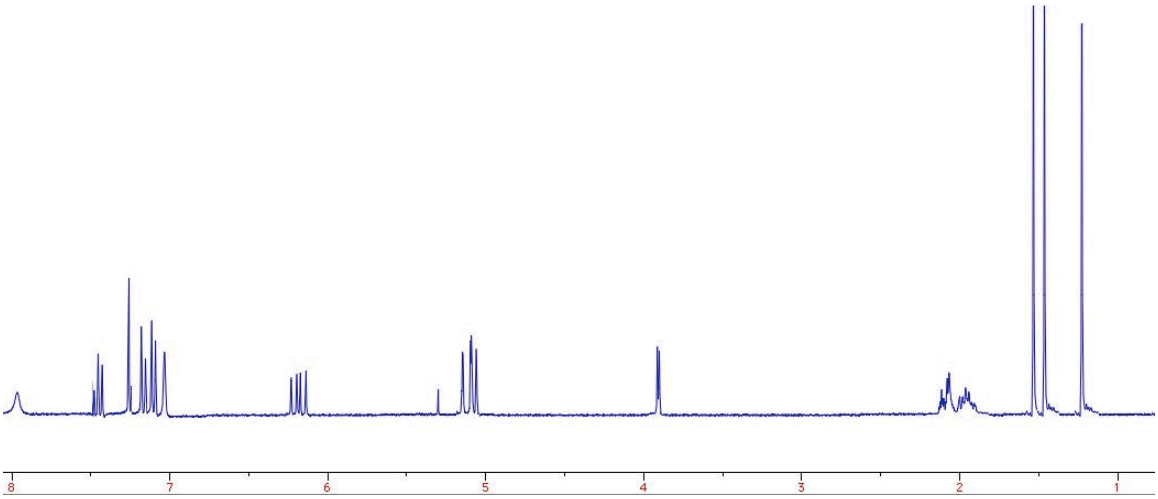


72

(Racemic)-Compound 72: To a solution of compound **325** (175 mg, 0.39 mmol, 1.0 eq.) in THF (5 mL) was added LAH (30 mg, 0.79 mmol, 2.0 eq.) and left to stir at rt. After 14 h Rochelle's salt (10 mL) was added and left to stir for an additional 2 h, extracted and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried and concentrated. To oxalic chloride (0.04 mL, 0.47 mmol, 1.2 eq.) in DCM (1 mL) was added DMSO (0.07 mL, 0.94 mmol, 2.4 eq.) at -78 ℃ and left to stir for 25 min at the same temperarture, to which crude alcohol in DCM (1 mL) was added at the same the temperature. Triethyl amine (0.27 mL, 1.95 mol, 5.0 eq.) was added 20 min later and allowed to warm to rt. The reaction diluted with H_2O and extracted with hexane. The organic layers were combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 58% yield (77% yield including the diastereomer).

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.49 (t, 1.9 Hz, 1H), 7.20-7.15 (m, 2H), 7.03 (s, 1H), 6.21 (dd, 10.7, 17.2 Hz, 1H), 5.15 (dd, 10.7, 17.3 Hz, 1H), 3.92 (dd, 1.0, 11.5 Hz, 1H) 1.92-2.11 (m, 5H), 1.51 (s, 3H), 1.48 (s, 3H), 1.24 (s, 3H); **^{13}C NMR:** (75 MHz, $CDCl_3$) δ 212.2, 142.8, 139.7, 133.6, 125.3, 122.4, 121.0, 112.3, 112.2, 108.6, 107.9, 51.6, 50.3, 44.1, 38.0, 37.5, 24.7, 24.1, 23.0, 21.3; **HMRS-FAB:** $[M+H]^+$ calcd for $C_{20}H_{24}NO$, 294.1852; found, 294.1847.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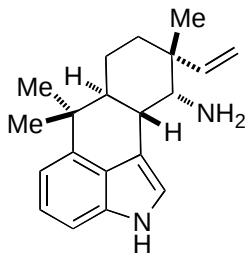
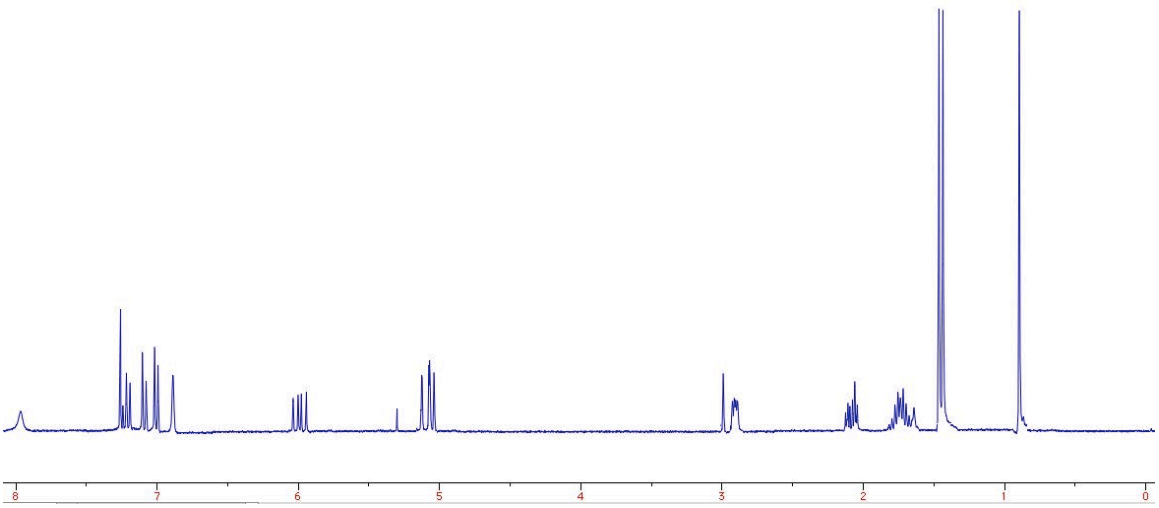


326

(Racemic)-Compound 326: Compound **72** (100 mg, 0.34 mmol, 1.0 eq.) was dissolved in THF (0.8 mL, 0.5 M) and added to a solution of ammonium acetate (1.05 g, 13.6 mmol, 40 eq.), $NaCNBH_3$ (214 mg, 3.4 mmol, 10 eq.) in MeOH (4 mL) and left to stir for 48 h at RT. The reaction was quenched with aqueous $NaHCO_3$ and extracted with Et_2O (x3). The organic layers were combined, washed with 1 N HCl, and the organic and aqueous layer was separated. The aqueous layer was brought to above pH 8 with 2 N NaOH and extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude material was purified by flash silica gel chromatography (1:5 EtOAc:hexane) to afford product in 75% yield (75 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.25-6.98 (m, 3H), 6.87 (s, 1H), 6.01 (dd, 10.5, 16.9 Hz, 1H), 5.06 (dd, 10.6, 15.9 Hz, 2H), 3.01 (s, 1H), 2.89 (bs, 1H), 2.21-2.05 (m, 2H), 1.82-1.53 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H), 0.98 (s, 3H) ;**^{13}C NMR:** (75 MHz, $CDCl_3$) δ NEED; **HRMS-FAB:** $[M+H]^+$ calcd for $C_{20}H_{27}N_2$, 295.21; found, 295.2175.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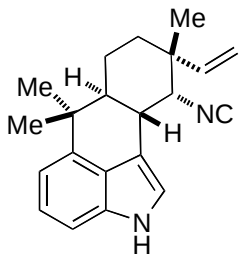
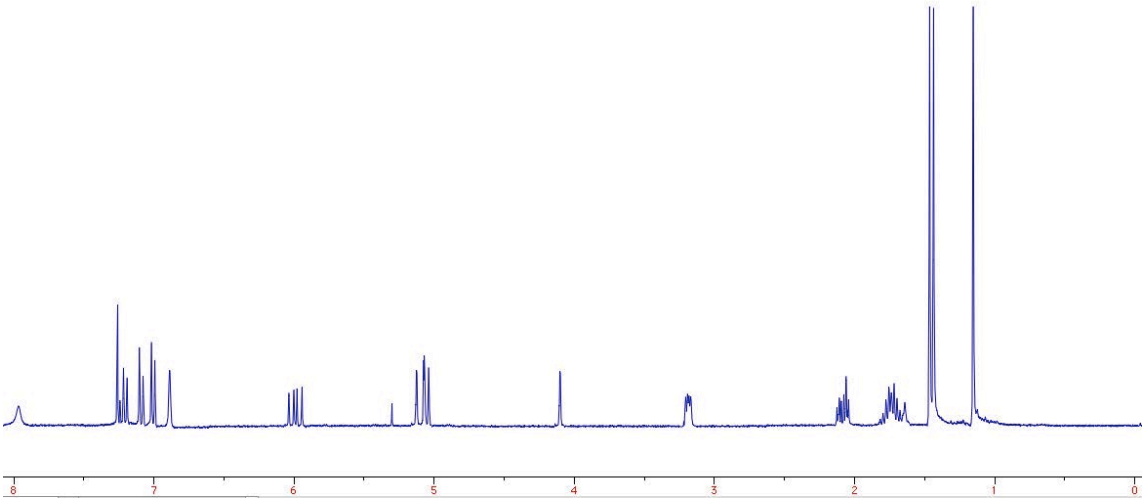


Hapalindole U (**7**)

(Racemic)-Hapalindole U: Compound **326** (22 mg, 0.07 mmol, 1.0 eq.) was dissolved in DCM (1.0 mL), to which was added sequentially: formic acid (0.006 mL, 0.15 mmol, 2.0 eq.), 2-chloro-4,6-dimethoxy-1,3,5-triazine (26 mg, 0.15 mmol, 2.2 eq.), DMAP (0.5 mg, 0.004 mmol, 0.06 eq.), and *N*-methyl morpholine (0.002 mL, 0.15 mmol, 2.2 eq.). The mixture was stirred for 2 h, diluted with DCM and poured onto saturated $NaHCO_3$. The aqueous layer was extracted with DCM (x5). The organic layers were combined, washed with 1 N HCl, brine, dried and concentrated. The crude material was dissolved in benzene (0.01 M) and Burgess reagent (67 mg, 0.28 mmol, 4.0 equiv.) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed in vacuo and the crude material was purified by flash silica gel chromatography (1:3 EtOAc:hexane) to afford hapalindole U in 74% yields over two steps (16 mg).

^{1}HNMR: (300 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.18-7.19 (m, 2H), 7.03-7.04 (m, 1H), 6.90 (bt, 1H), 6.05 (dd, 10.8, 17.3 Hz, 1H), 5.19 (dd, 10.9, 17.4 Hz, 2H), 4.11 (bd, 1H), 3.29-3.26 (m, 1H), 2.07-1.93 (m, 3H), 1.70-1.66 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.20 (s, 3H); **^{13}C NMR:** (75 MHz, $CDCl_3$) δ 156.1, 145.7, 141.1, 133.9, 125.8, 122.8, 116.0, 113.1, 113.0, 112.6, 108.2, 63.1, 43.2, 39.6, 37.4, 33.7, 30.0, 25.4, 24.4, 21.6, 21.0; **HRMS-FAB:** $[M+Na]^+$ calcd for $C_{21}H_{24}NaN_2$, 327.18; found, 327.1846.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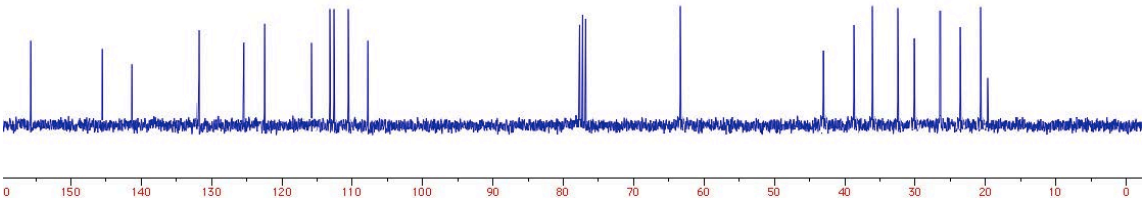
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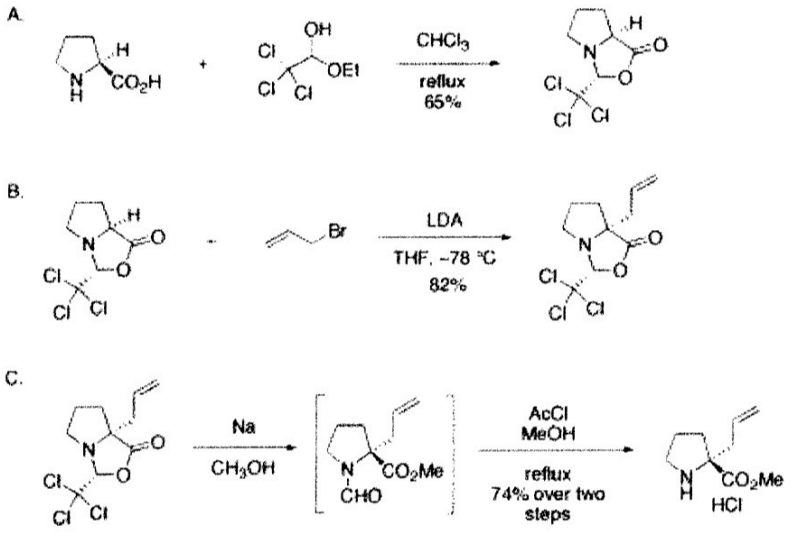
(3*R*,7*aS*)-3-(TRICHLOROMETHYL)TETRAHYDROPYRROLO[1,2-*C*]OXAZOL-1(3*H*)-ONE: AN AIR AND MOISTURE STABLE REAGENT FOR THE SYNTHESIS OF OPTICALLY ACTIVE α-BRANCHED PROLINES



Submitted by Gerald D. Artman III, Ryan J. Rafferty, and Robert M. Williams.[1]
Checked by Gregory L. Aaron, Matthew M. Davis, and Kay M. Brummond.

1. Procedure

A. (3R,7aS)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one. To a suspension of L(-)-proline (11.55 g, 100.3 mmol) (Note 1) in chloroform (500 mL) (Note 2) in a 1000-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar is added 2,2,2-trichloro-1-ethoxyethanol (23.27 g, 120.3 mmol) (Note 3 and 4). A 25-mL Dean-Stark trap topped with a reflux condenser, fitted with an argon adapter, is attached to the reaction vessel and the reaction mixture is heated at reflux using a heating mantle until L(-)-proline is no longer visibly suspended and consumption is observed by reverse phase TLC (Note 5). Heating is

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discontinued and the volatile organics are removed under reduced pressure on a rotary evaporator (40 °C, 20–25 mmHg). The resulting brown, crystalline solid is recrystallized from ethanol. Boiling ethanol (30 mL) is added to the crude residue in the reaction flask warmed to 50 °C (bath temperature). The resultant mixture is stirred magnetically with heating on a hot plate until the mixture becomes homogenous. The solution is quickly poured into a 125-mL Erlenmeyer flask. The flask is fitted loosely with a septa and cooled slowly to room temperature then in an ice/water bath for 1 h. The resulting crystals are collected by suction filtration on a Büchner funnel and washed with 15 mL of ice-cold ethanol. The crystals are then transferred to a round-bottomed flask and dried overnight at 0.06 mmHg to provide *(3R,7aS)*-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (15.19–15.96 g, 62–65%) as colorless to light brown crystals (Note 6, 7, 8).

B. (3R,7aR)-7a-Allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one. A flame-dried, 500-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar and an adaptor with an argon inlet, is charged with *N,N*-diisopropylamine (10.0 mL, 71.4 mmol) (Note 9) and tetrahydrofuran (THF, 140 mL) (Note 10). The reaction vessel is cooled to –78 °C before *n*-butyllithium in hexane (1.6M, 46.0 mL, 73.6 mmol) (Note 11) is added via syringe. The reaction mixture is stirred for an additional 30 min at –78 °C. In a separate 250-mL single-necked, round-bottomed flask equipped with a magnetic stirbar under argon, (3*R*,7*aS*)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (12.2 g, 49.9 mmol) is dissolved in THF (100 mL). This solution is cooled to 0 °C and stirred for 10 min. A cannula is used to rapidly deliver this THF solution to the LDA solution at –78 °C under argon over 5 min (Note 12). The resulting solution is stirred for an additional 30 min at –78 °C before the addition of allyl bromide (7.8 mL, 90 mmol) (Note 13) via syringe in a single portion. The reaction mixture is placed in a CO_2/CH_3CN bath to warm to –40 °C, where it is maintained for an additional 30 min (Note 14). The reaction mixture is then poured into a 1-L separatory funnel containing 300 mL of water. The aqueous solution is extracted with chloroform (3 x 300 mL). The combined organic extracts are dried over Na_2SO_4 and concentrated using a rotary evaporator (40 °C, 20–25 mm Hg) to afford (*3R,7aR*)-*7a*-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (11.34–11.92 g, 80–82%) as a brown oil (Note 15).

C. (R)-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a reflux condenser fitted with an argon inlet, a 300-mL pressure-equalizing additional funnel fitted with a rubber septum, and a glass stopper. The glass stopper is removed and the flask is charged with (*3R,7aR*)-7a-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3*H*)-one (8.20 g, 29.0 mmol) and methanol (100 mL) (Note 16). Sodium metal (420 mg, 18.3 mmol) (Note 17) is added slowly (~1 piece every 2 min) over 30 min by removal of the glass stopper. The reaction mixture is stirred for an additional 30 min until sodium pieces are no longer visible (Note 18). The reaction vessel is cooled in an ice/water bath and the pressure-equalizing addition funnel is charged with acetyl chloride (40 mL, 563 mmol) (Note 19), which is added dropwise into the reaction mixture over 1 h (Note 20). The funnel is removed and replaced with a glass stopper and both stoppers are secured using Keck® clips. The resulting milky brown solution is heated to reflux until only baseline material is evident by thin layer chromatography (Note 21). The volatile organics are then removed using a rotary evaporator (40 °C, 20–25 mm Hg). The resulting oily solid is diluted with methylene chloride (50 mL). The precipitated sodium chloride is removed via filtration through a Büchner funnel washing with additional methylene chloride (10 mL). The filtrate is concentrated under reduced pressure by rotary evaporation (40 °C, 20–25 mm Hg) This process is repeated two additional times to afford (*R*)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride as an oil. Purification of the crude hydrochloride salt is achieved using flash silica gel chromatography eluting with a gradient of 95:5→90:10 CH_2Cl_2:MeOH (Note 22) to afford (*R*)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (4.16–4.44 g, 71–74%) as an oil, which solidifies under reduced pressure (Note 23). An enantiomeric excess of >99% for the desired product was determined through synthesis of the Mosher amide under Schotten-Baumann conditions followed by NMR spectroscopy and HPLC analysis (Note 24).

2. Notes

1. L(-)-Proline (99+%) was used as received from Acros Organics.
2. Chloroform (ACS grade) was used without further purification from Fisher Scientific.

3. The original procedure reported by Germanas employed trichloroacetaldehyde or chloral. However, this reagent is regulated and difficult to obtain. The submitters have found that commercially available 2,2,2-trichloro-1-ethoxyethanol can be used as a masked form of chloral.

4. 2,2,2-Trichloro-1-ethoxyethanol (98%) was used as commercially available and was obtained from Alfa Aesar.

5. Disappearance of L(-)-Proline (R_f = 0.89) and formation of (3*R*,7a*S*)-3-(trichloromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3*H*)-one (R_f = 0.26) was observed via reverse phase thin layer chromatography performed on Partisil® KC18 Silica Gel 60Å (200 μm thickness) on glass backed plates (1:1 H_2O/CH_3CN) visualizing with $KMnO_4$ TLC Stain (yellow spots). The reaction requires 15–19 h to reach completion, during which time a color change from a milky opaque to an orange solution is observed.

6. *(3R,7aS)*-3-(Trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one[2,3] displays the following physical and spectral characteristics: mp 108–109 °C (lit.[3] 107–109 °C); optical rotation: $[\alpha]_D$ = +34.0 (*c* 2, C_6H_6), lit.[3] $[\alpha]_D$ = +33 (*c* 2, C_6H_6); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.70–1.79 (m, 1 H), 1.90–1.97 (m, 1 H), 2.08–2.14 (m, 1 H), 2.19–2.27 (m, 1 H), 3.11–3.15 (m, 1 H), 3.42 (ddd, *J* = 11, 7.5, 6 Hz, 1 H), 4.12 (dd, *J* = 9, 4.5 Hz, 1 H), 5.17 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 29.9, 57.9, 62.4, 100.6, 103.6, 175.5; IR (thin film) 2978, 2962, 2899, 2871, 1782, 1327, 1178, 1009, 959, 815, 791, 744 cm^{-1}; Anal. Calcd for $C_7H_8Cl_3NO_2$: C, 34.39; H, 3.30; N, 5.73. Found: C, 34.47; H, 3.28; N, 5.65.

7. Unlike the Seebach pivaldehyde/proline condensate, this product is air- and moisture-stable and can be stored upon the bench top with no decomposition by NMR spectroscopy after more than 30 days.

8. Following the submission of this procedure, *(3R,7aS)*-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one is now commercially produced by AK Scientific, California, USA.

9. *N,N*-Diisopropylamine (99%) was purchased from Fisher Scientific and was freshly distilled from $CaCl_2$ prior to use.

10. Tetrahydrofuran (THF, 99.5%) was purchased from Sigma-Aldrich and was purified via a Sol-Tek ST-002 solvent purification system.

11. 1.6 M *n*-Butyllithium in hexanes was purchased from Sigma-Aldrich and freshly titrated using the method developed by Love and Jones.[4]

12. A color change is apparent as the enolate is formed. The LDA solution changes from light yellow, to dark red, to dark brown upon the addition of the oxazolinone.

20. The addition of acetyl chloride must be conducted at a slow rate to avoid an exothermic reaction and loss of HCl gas. The submitters observed that if the addition is too fast, an additional quantity of acetyl chloride (~20 mL) generally has to be added to the reaction mixture once the solution is brought to reflux.

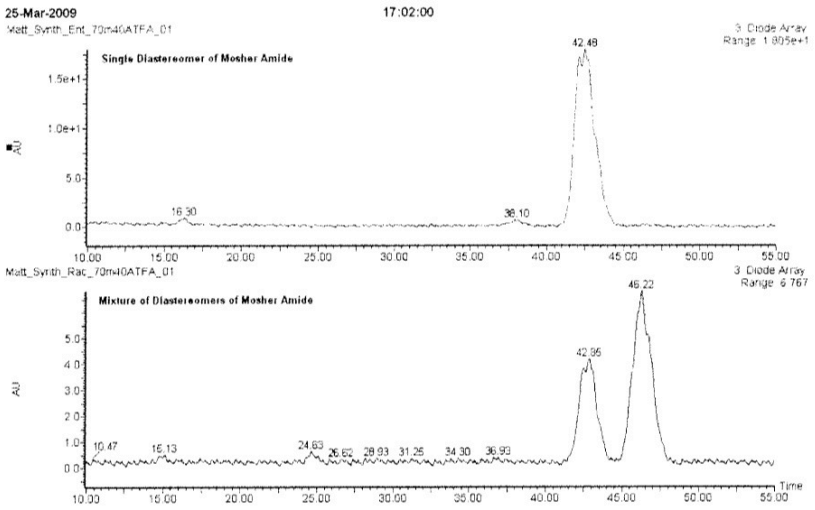
21. The reaction was monitored by TLC using silica gel F_{254} (200 μm thickness) glass backed plates, 1:1 EtOAc:hexanes, $KMnO_4$ TLC stain, (yellow spots) for the disappearance of the intermediate *N*-formyl ester (R_f = 0.25), and other intermediate compounds until only the hydrochloride salt (R_f = 0.00) remains.

22. Flash silica gel chromatography of the final product employed a column with specifications of: inner diameter: 2.5 inches; packed length: 6 inches. Fractions of ~27 mL were collected in 16 x 150 mm test tubes. Fractions containing the desired product (R_f = 0.47) were determined by TLC (90:10 CH_2Cl_2:MeOH) with $KMnO_4$ TLC staining. These fractions were combined and concentrated under reduced pressure (40 °C, 20–25 mm Hg).

23. *(R)*-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride displays the following physical and spectral characteristics: brown oil that slowly solidifies to a brown solid (99 % *ee*); optical rotation: $[\alpha]_D$ = -83 (*c* 2, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.93 (bs, 1 H), 2.14 (bs, 2 H), 2.45 (bs, 1 H), 2.83–2.90 (m, 1 H), 3.03–3.10 (m, 1 H), 3.54 (bs, 1 H), 3.62 (bs, 1 H), 5.22 (d, *J* = 9.8 Hz, 1 H), 5.32 (d, *J* = 16.8 Hz, 1 H), 5.83-5.92 (m, 1 H), 9.55 (bs, 1 H), 10.64 (bs, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ: 22.4, 34.5, 39.2, 45.6, 53.7, 72.5, 121.4, 130.2, 170.0; IR (thin film) 3404, 2956, 2719, 2491, 1745, 1642, 1452, 1236 cm^{-1}; Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.56; H, 7.84; N, 6.81; Found: C: 52.24; H: 7.69; N: 6.66.

24. The *ee* of the final product was determined via conversion of the final product to the Mosher amide using commercially available (*S*)-(+)-α-methoxy-α-trifloromethylphenylacetyl chloride (Note 25) under Schotten-Baumann conditions: In a 5-mL round-bottomed flask with a magnetic stir bar, (*R*)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (26 mg, 0.15 mmol) was partitioned between CH_2Cl_2 (0.75 mL) and water (0.75 mL). NaOH (30 mg, 0.75 mmol) was added followed by commercially available (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.03 mL, 0.16 mmol). The reaction mixture was stirred open to the air for 1 h before being transferred to a 30-mL separatory funnel using CH_2Cl_2 (20 mL) and diluted with H_2O. The aqueous layer was separated and the resulting organic layer

was washed with saturated $NaHCO_3$ (10 mL), 2 M HCl (10 mL), and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude product (47 mg) was analyzed by NMR spectroscopy and HPLC. ^{1}H NMR spectroscopy of the crude material observed a single amide rotamer at room temperature. An analytical sample was obtained by purifying the crude material via flash silica gel chromatography (Inner diameter 1 cm; Packed Length 11.5 cm) eluting 2.5:97.5 to 10:90 EtOAc/hexanes to afford 25 mg of the Mosher amide. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.59–1.71 (m, 2 H), 1.88 (ddd, J = 13.3, 7.0, 4.9 Hz, 1 H), 2.03 (ddd, J = 13.3, 9.8, 7.0 Hz, 1 H), 2.83 (dd, J = 14.0, 7.0 Hz, 1 H), 3.07 (ddd, J = 11.2, 7.0, 4.2 Hz, 1 H), 3.18 (dd, J = 14.0, 7.7 Hz, 1 H), 3.32 (ddd, J = 11.2, 8.4, 6.3 Hz, 1 H), 3.71 (s, 3 H), 3.79 (s, 3 H), 5.15 (dd, J = 9.8, 0.7 Hz, 1 H), 5.20 (d, J = 16.8 Hz, 1 H), 5.81 (ddt, J 17.5, 9.8, 7.0 Hz, 1 H), 7.40–7.41 (m, 3 H), 7.58–7.60 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ: 24.0, 34.1, 37.8, 48.7, 52.2, 55.4, 69.7, 84.5 (q, J = 25.0 Hz), 119.7, 123.5 (q, J = 290.4 Hz), 127.3, 127.9, 129.3, 132.8, 132.9, 164.4, 173.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –69.8; HPLC purity of the amide was determined by dissolving a sample in CH_3CN and passing it through a Phenomenex Luna 3 micron particle size C18 column (Length 100 mm; Diameter 4.6 mm) using a 60:40 solution of 0.1 % TFA in H_2O and 0.01% TFA in CH_3CN at 1 mL/min over 70 min. The desired product was observed as a single peak at 42.48 min (>99% pure) that was compared to a mixture of both Mosher amide diastereomers (Note 26). See attached chromatograph below.



25. (*S*)-(+)-α-Methoxy-α-triflоromethylphenylacetyl chloride (>99.5% *ee*) was purchased from Aldrich and used without further purification.

26. The amine L-proline methyl ester hydrochloride was protected as the *tert*-butyloxycarbamate using di-*tert*-butyl dicarbonate and triethylamine. Subsequent alkylation and epimerization was accomplished by deprotonating with lithium diisopropylamide followed by addition of allyl bromide. The amine was liberated by treatment with trifluoroacetic acid. The amine was converted to the Mosher amide under Schotten-Baumann conditions.

Waste Disposal Information

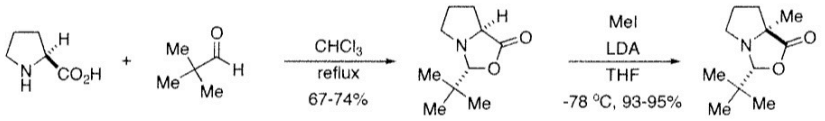
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The synthesis of optically active amino acids and derivatives continues to be an important area of research for academic laboratories and the pharmaceutical industry. In 1995, Seebach reported an *Organic Syntheses* procedure for the synthesis of a proline/pivaldehyde condensate

(**3**), which could be employed for the synthesis of optically active α-branched proline amino acids (*cf.* **4**).[5] However, difficulties are often encountered during the preparation of **3**. The condensation of proline (**1**) and pivaldehyde (**2**) requires long reaction times in a low boiling solvent, which systematically needs to be replaced over 3-7 days. Since product **3** is extremely sensitive to air and moisture, rigorously anhydrous conditions are required to ensure that no moisture enters the system. In addition, pivaldehyde (**2**) is required in large excess (~6-7 equivalents) making this procedure economically prohibitive due to its high cost.

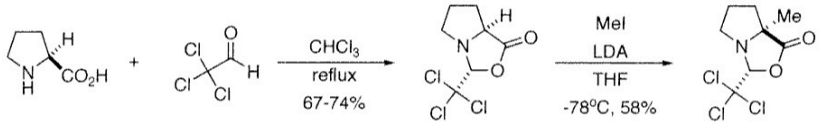
Scheme 1



1 **2** **3** **4**

Interestingly, Germanas and Wang reported an alternative to the Seebach oxazolinone, (3*R*,7*aS*)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**6**), to generate optically active α-branched proline derivatives in good yields (*cf.* **7**).[2b] Unlike the Seebach compound **3**, the trichloro oxazolinone **6** is an air- and moisture-stable crystalline solid, which can be stored on the bench top for greater than 1 month with no decomposition or observed loss of optical purity. Furthermore, the preparation of **6** requires only a small excess of a chloral (**5**) or chloral hydrate.

Scheme 2



1 **5** **6** **7**

Despite the advantages of the trichloro oxazolinone **6** over the Seebach compound **3**, it has seen little use in synthesis.[3,6] Chloral (**5**) is a regulated substance greatly limiting its commercially availability even for small (10–20 g) quantities. Secondly, the cleavage of the trichloro auxiliary from **7**, though reported by Germanas to proceed in high yield is generally

reported by other groups to require >24h and proceeds in moderate to low yields.

As such, we have found that 2,2,2-trichloro-1-ethoxyethanol, which is commercially available, can be used as a chloral synthon resulting in a scalable procedure for the synthesis of the oxazolinone **6**. In addition, we have discovered that the initial opening of the lactone to the *N*-formyl methyl ester intermediate is slow when using refluxing HCl in methanol. By employing the one-pot procedure described, exposure of the alkylated product (*cf.* **7**) to sodium methoxide results in rapid conversion to the *N*-formyl methyl ester at room temperature. This compound is much more amenable to cleavage of the *N*-formyl group under refluxing HCl in methanol to reproducibly afford the desired *R*-allyl prolinate hydrochloride salt on a multigram scale.

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523-1872.
2. (a) Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Bombieri, G.; Benetollo, F. *J. Heterocyclic Chem.* **1989**, *26*, 837-841. (b) Wang, H.; Germanas, J. P. *Synlett* **1999**, 33-36.
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6. (a) Hoffman, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew Chem., Int. Ed.* **2001**, *40*, 3361-3364. (b) Bittermann, H.; Einsiedel, J.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2004**, *47*, 5587-5590. (c) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97-102.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-Proline; (147-85-3)
2,2,2-Trichloro-1-ethoxyethanol; (515-83-3)
(3*R*,7*aS*)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one; (97538-67-5)
n-Butyllithium; (109-72-8)
N,N-Diisopropylamine; (108-18-9)
Allyl bromide; (106-95-6)
(3*R*,7*aR*)-7*a*-Allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (220200-87-3)
Sodium; (7440-23-5)
Acetyl chloride; (75-36-5)
(*R*)-Methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (112348-46-6)

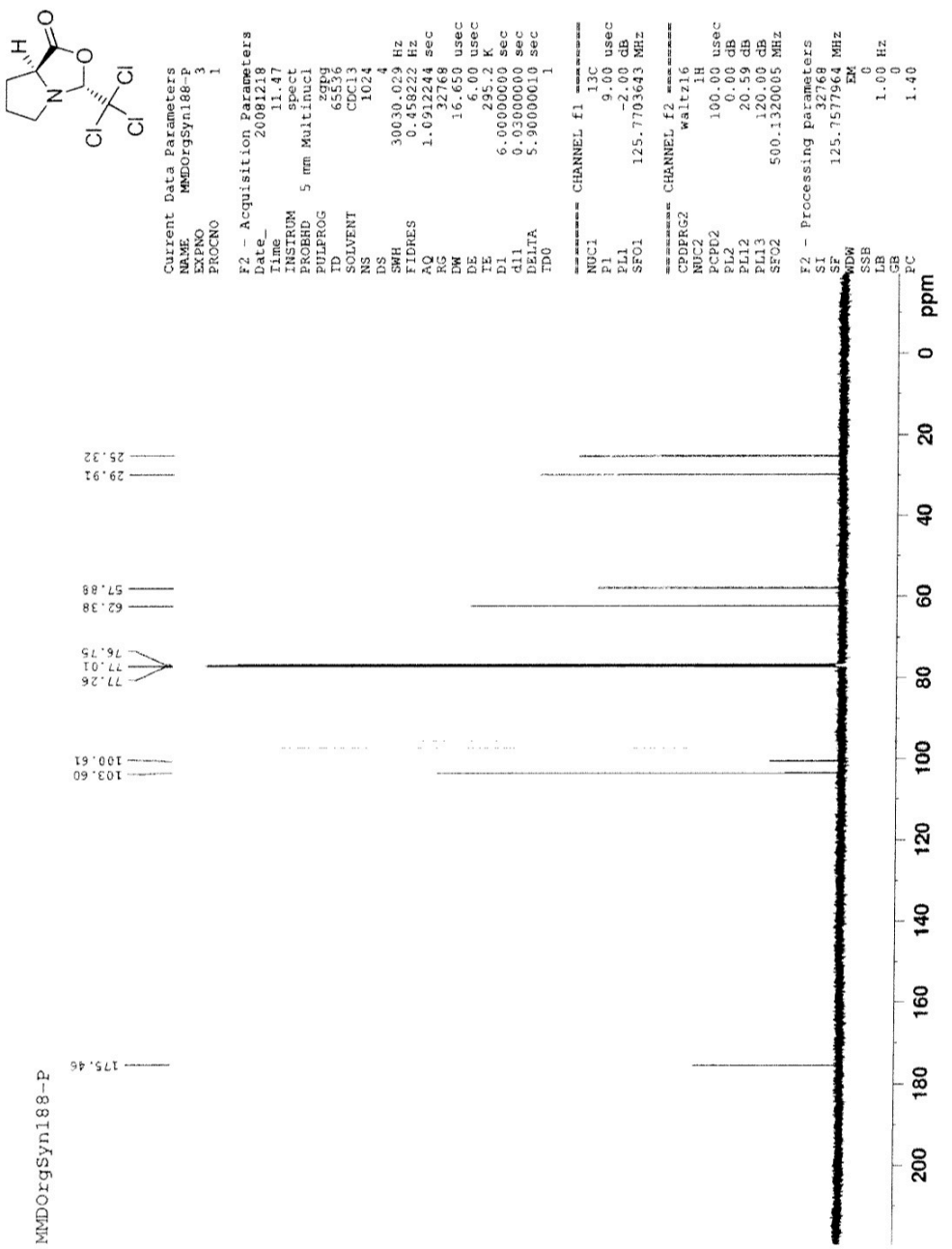
Robert M. Williams was born in New York in 1953 and attended Syracuse University where he received the B.A. degree in Chemistry in 1975. He obtained the Ph.D. degree in 1979 at MIT (W.H. Rastetter) and was a post-doctoral fellow at Harvard (1979-1980; R.B. Woodward/Yoshito Kishi). He joined Colorado State University in 1980 and was named a University Distinguished Professor in 2002. His interdisciplinary research program (over 250 publications) at the chemistry-biology interface is focused on the total synthesis of biomedically significant natural products, biosynthesis of secondary metabolites, studies on antitumor drug-DNA interactions, HDAC inhibitors, amino acids and peptides.

Gerald Artman III was born in Michigan in 1978. He received his B.Sc. in Chemistry from Eastern Michigan University in 1999. Gerald moved to the Pennsylvania State University at University Park for his graduate studies. Under the guidance of Professor Steven Weinreb, he explored new methodology development and alkaloid total synthesis. As a NIH Postdoctoral Fellow in the lab of Professor Robert M. Williams, Gerald completed the total synthesis of the stephacidin alkaloids. Since 2007, he has been employed at the Novartis Institutes for BioMedical Research in Cambridge, MA.

Ryan J. Rafferty was born in Denver, CO in 1976. He received his B.Sc. in Chemistry (Biochemistry Emphasis) from the University of Northern Colorado in 2000, where he remained to receive this B.Sc. in Biology and M.Sc. in Biochemistry under the supervision of Prof. Richard Hyslop. His master's degree focused on the toxicology and kinetic studies and development of metabolite assays of 6-thiopurine and its analogs. He is currently pursuing his Ph.D. at Colorado State University under the supervision of Prof. Robert M. Williams. His research is focused on the total synthesis of the antifungal alkaloid ambiguine family.

Gregory Aaron was born in 1985 in Franklin, Pennsylvania. In 2008 he received his B.S. degree in chemistry from the University of Pittsburgh. While pursuing his undergraduate degree he carried out research on a number of projects under the supervision of Prof. Kay Brummond.

Matthew Davis was born in 1981 in Park Forest, Illinois. In 2004 he received his B.S. degree in chemistry from Hope College in Holland, Michigan. He is currently pursuing graduate studies at the University of Pittsburgh, under the guidance of Prof. Kay Brummond. His research currently focuses on expanding the scope of the Rh(I)-catalyzed cyclocarbonylation reaction of allene-ynes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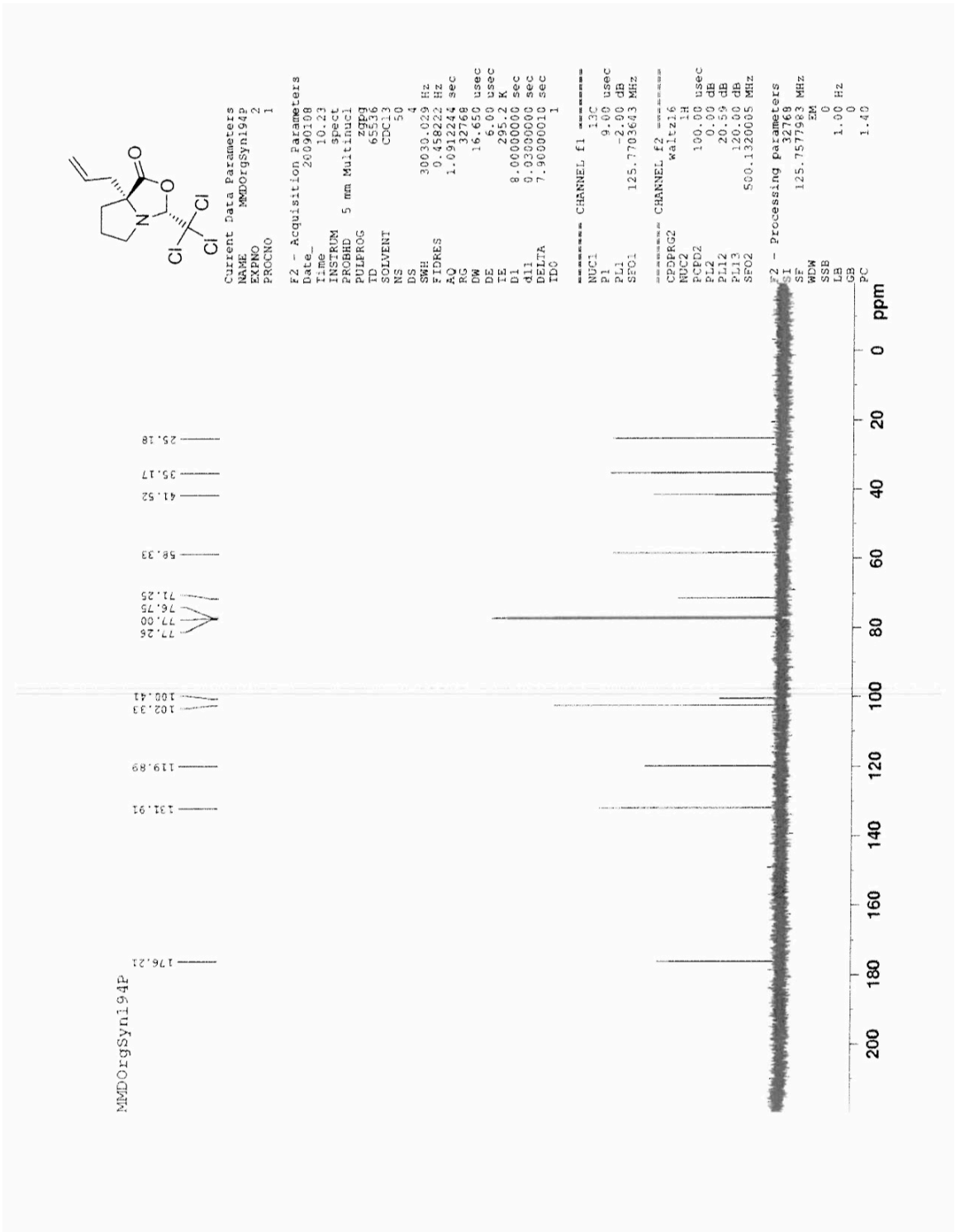
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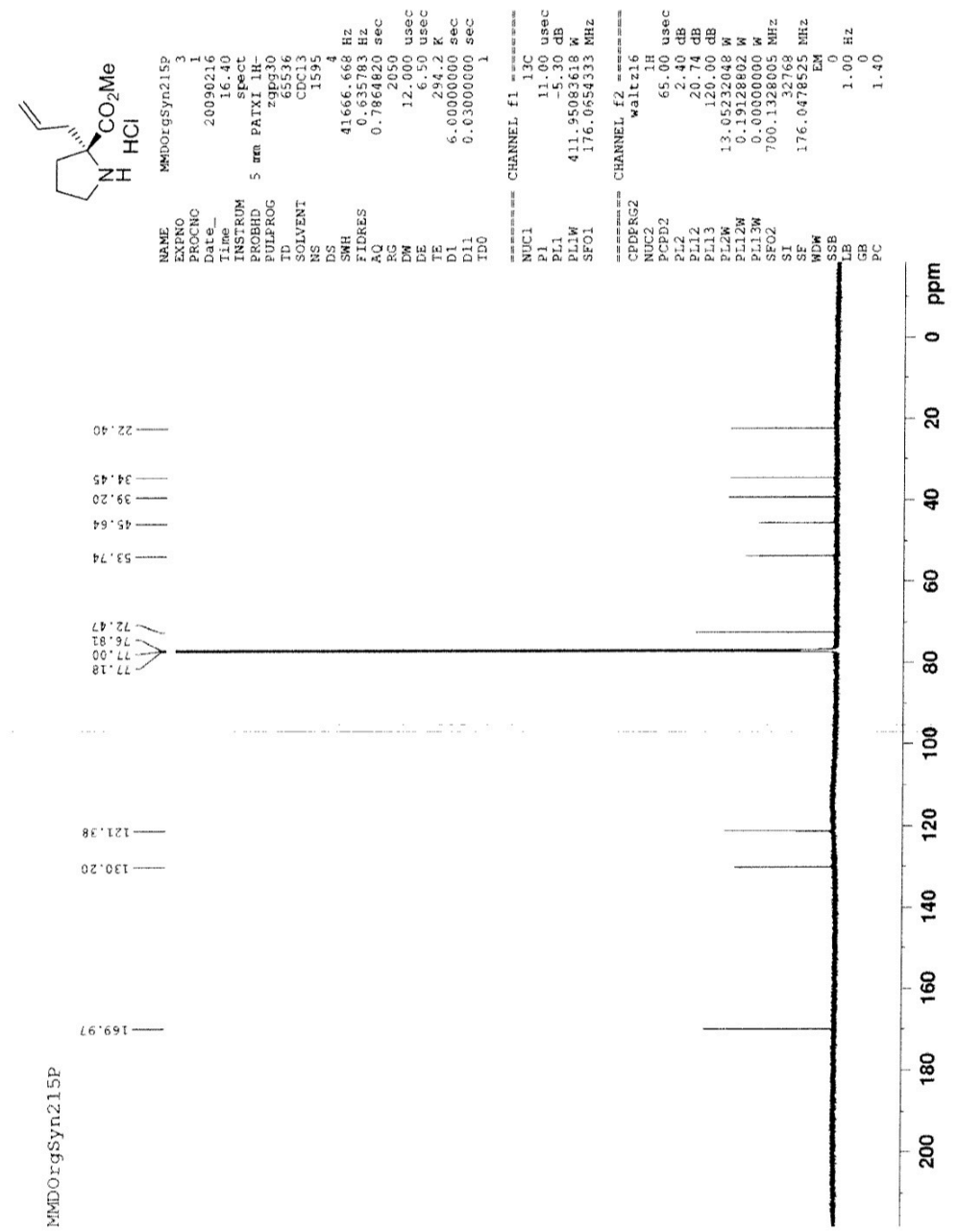
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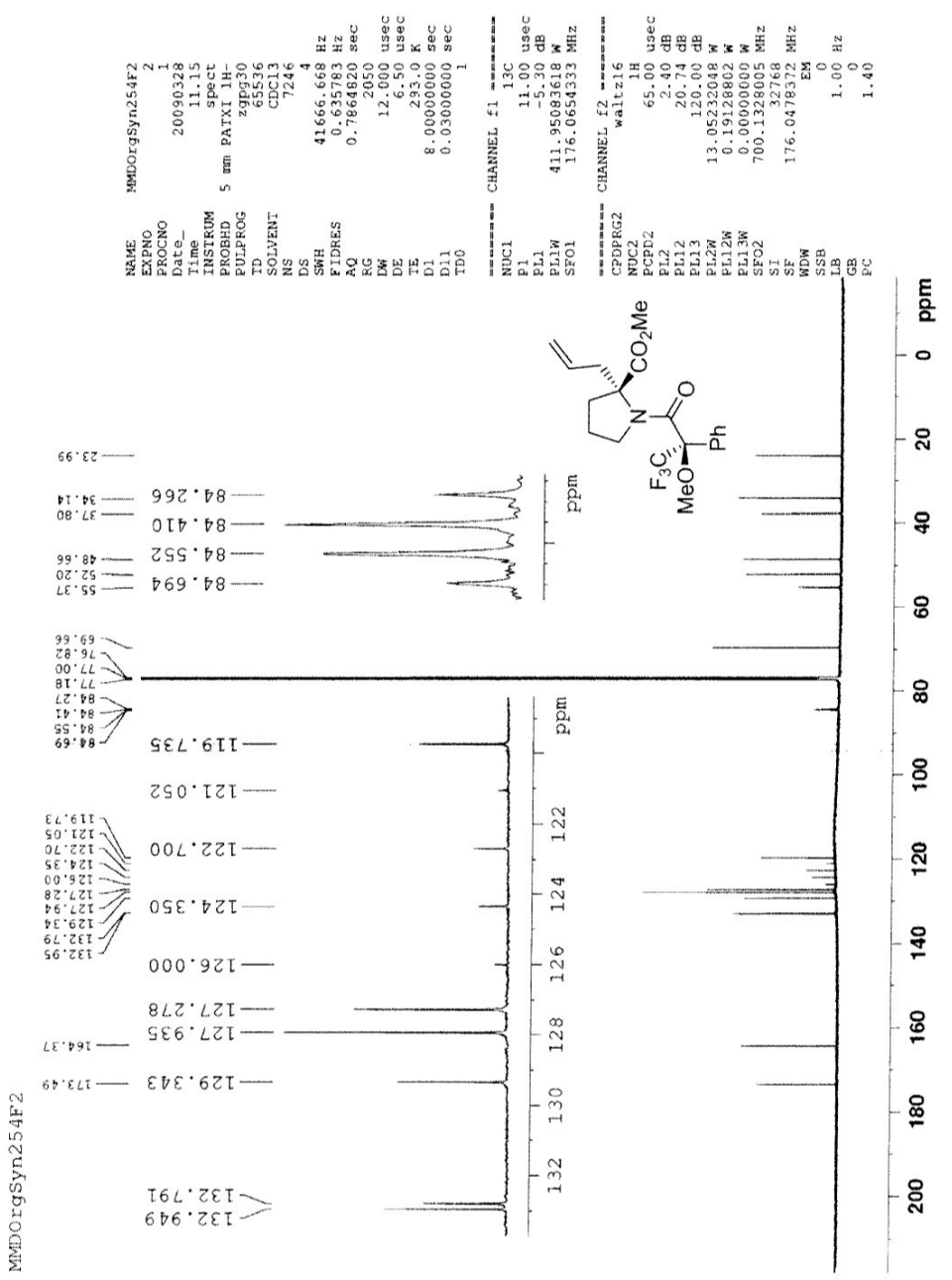
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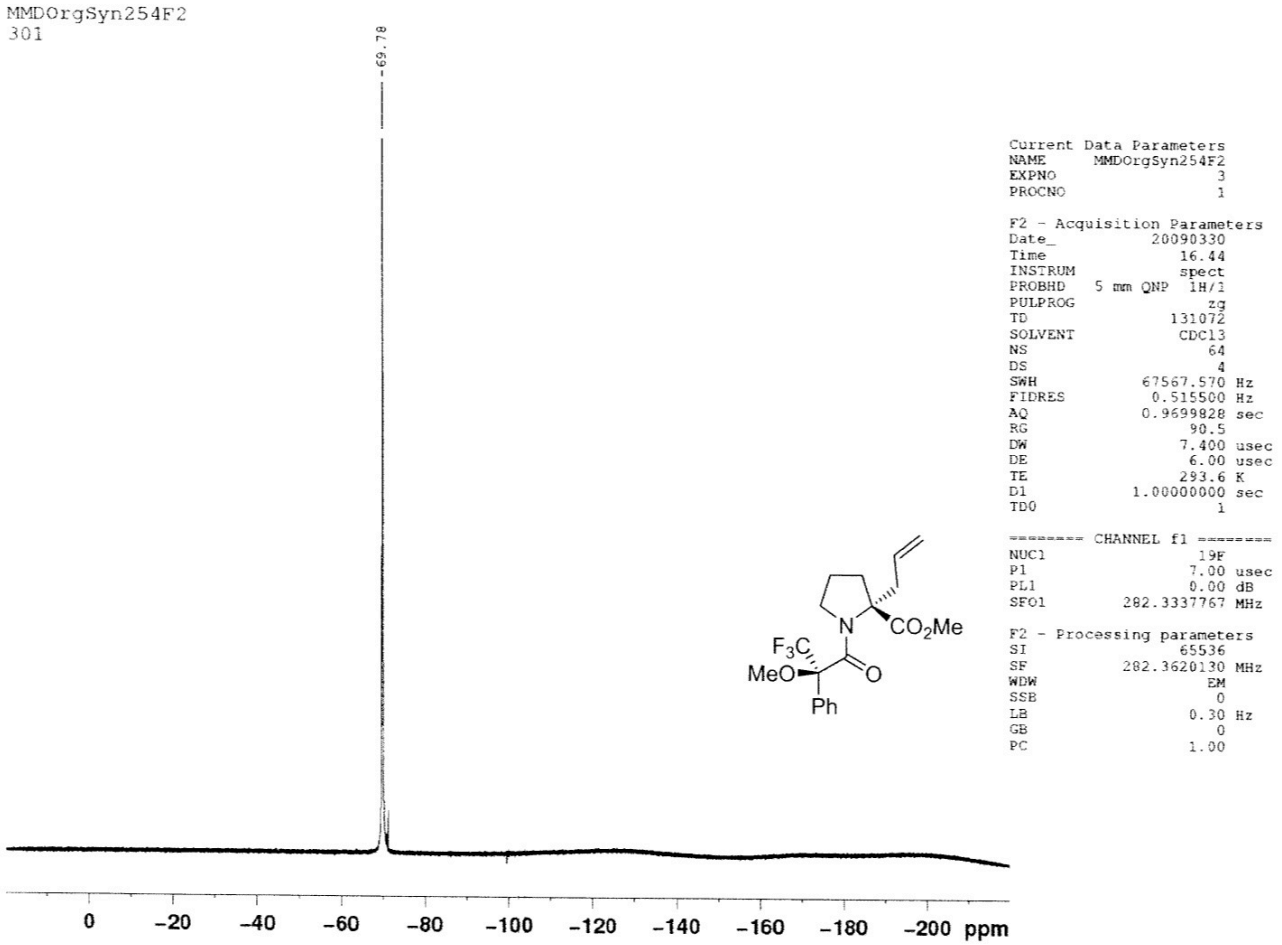
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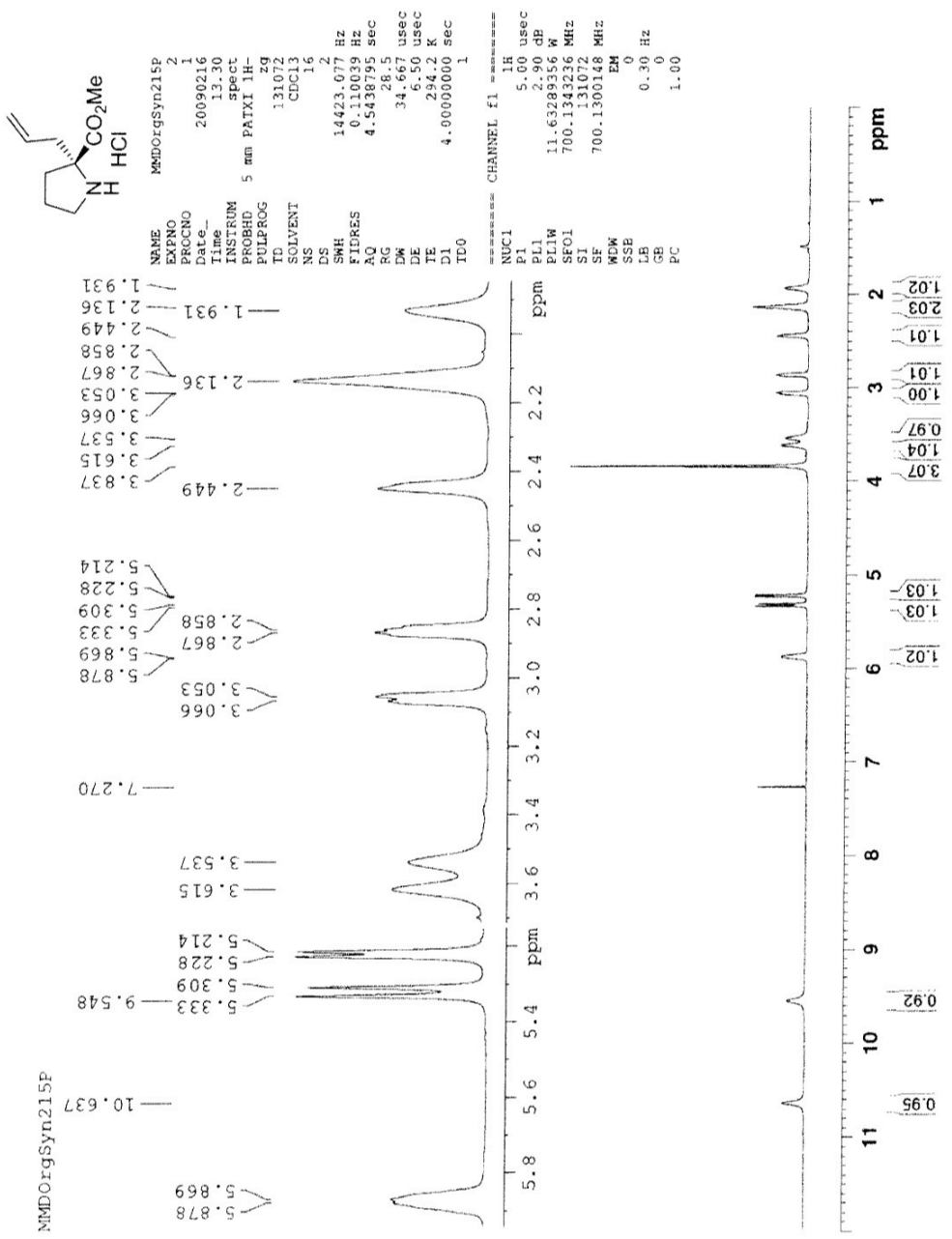
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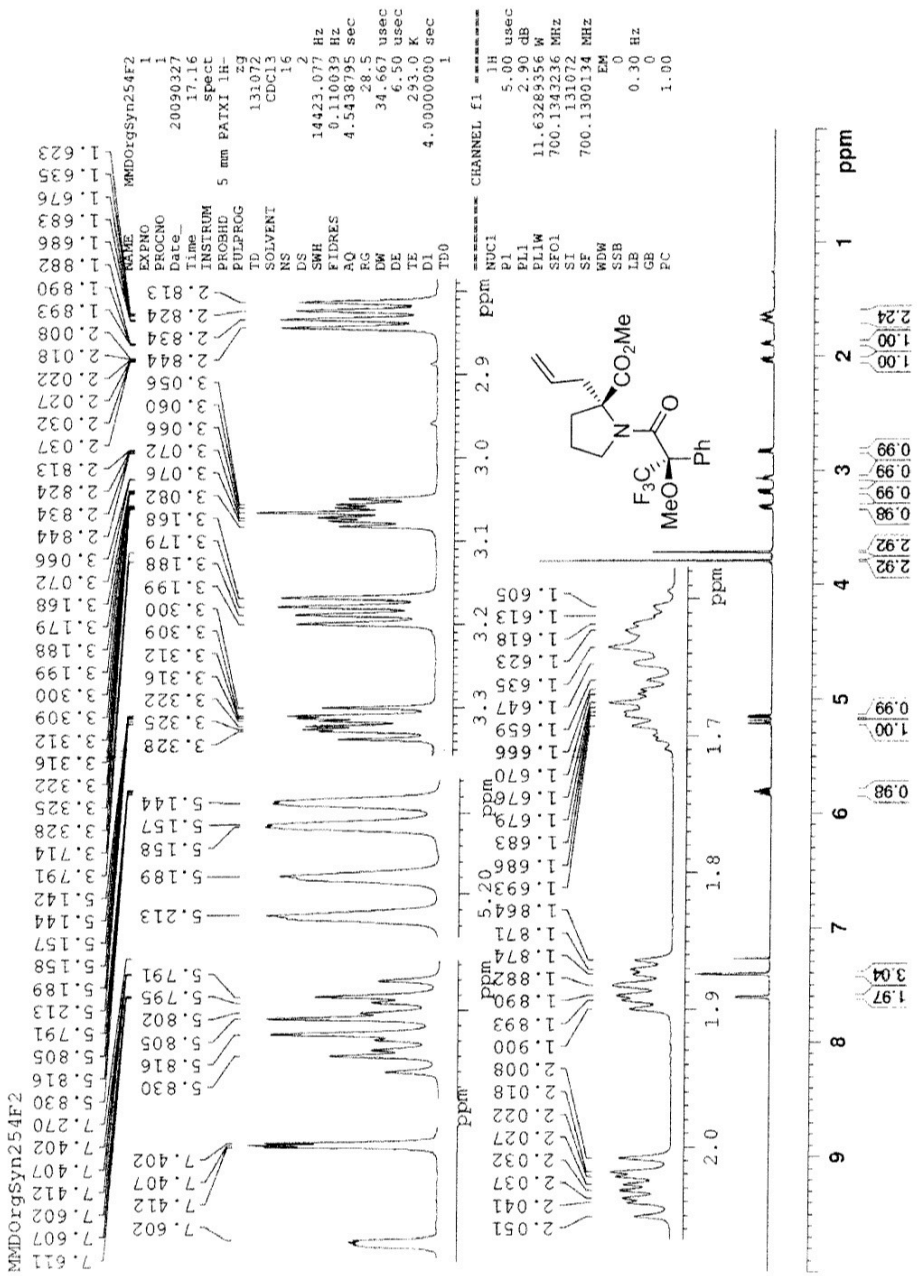
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Synthetic studies on the ambiguine family of alkaloids: construction of the ABCD ring system

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ABSTRACT

A racemic synthesis of the ABCD ring core of the ambiguines that preserves the tertiary alcohol has been accomplished in a convergent synthesis in 10 synthetic steps, in an overall yield of 46% from commercially available 4-bromoindole and *m*-methylanisole.

The ambiguines[1–3] are a family of indole alkaloids that were first isolated in 1991. They are structurally related to the hapalindoles[4,5] family of alkaloids (Fig. 1). To date, the ambiguine family has 15 members (Ambiguines A–O) that are broken down into two subclasses; the tetracyclic and pentacyclic systems.

The tetracyclic ambiguines are structurally same as the hapalindoles with the exception of the presence of a reverse-prenyl group on C2 of the indole ring. Pentacyclic ambuguines contain a seven-membered ring, which contains either an epoxide, diol, vinyl cyanide, α-hydroxyl ketone or diene functionality. Carbon-13 of ring D, in both families, can either have a methylene carbon (R_1) or chlorine-containing carbon. Likewise, both can either have a hydrogen at the C10 position (R_2) or possess an alcohol at said carbon. The common core for both the hapalindole and ambuguine families for most of their members contains the C13 chlorine containing stereocenter as well as the C10 tertiary alcohol.

The structural complexity and densely functionalized core have attracted considerable synthetic attention and to date only ambiguine H has been conquered by total synthesis.[6] We report herein, our own preliminary efforts on the synthesis of these intriguing substances.

We envisioned that the pentacyclic core **1** of the ambiguines could arise from an intra-molecular RCM reaction of **2**, which could be assembled through a Mannich reaction with vinyl Grignard and ammonium acetate followed by isonitrile formation from **3** (Scheme 1). Formation of the tetracyclic core **3** was anticipated to arise from the manipulation of **4** and **5**. The C12 quaternary center was envisioned to arise from compound **5**, which could be accessed from commercially available *m*-methylanisole and functionalized indole **4** from 2-bromo-6-nitrotoluene.

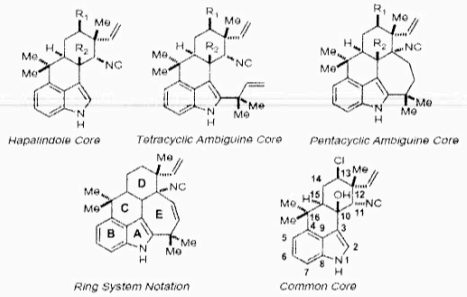

Figure 1. Hapalindole, tetracyclic and pentacyclic ambiguine cores.

Following the protocol of Rubottom and Gruber,[7] commercially available *m*-methylanisole was converted into **7** utilizing a Birch reduction followed by hydrolysis (Scheme 2). Secondary alcohol **7** was protected with TBSCl and imidazole, followed by treatment with vinylmagnesium bromide to afford the quaternary center substrate as the corresponding TMS-enol ether. Cleavage of the TMS-enol ether with an acetic acid/water/THF mixture afforded racemic **5** in an overall 86% yield for the six steps.

Assembly of tetracycle **11** began with treating of racemic **5** with LHMDS and Mander's reagent to give the β-ketoester (Scheme 3).

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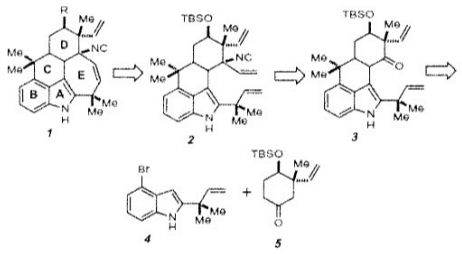
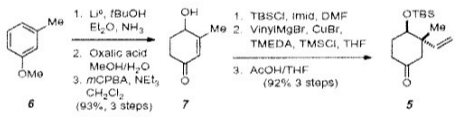
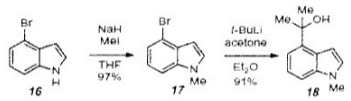


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of substrate **5**.

Reduction of the ketone with $NaBH_4$ followed by TMS protection of the resulting alcohol gave **8** in good yields. Treatment of **8** with *N*-methoxy-methylamine hydrochloride and Me_3Al in THF afforded the Weinreb amide. Subjecting 4-bromo-*N*-methylindole to lithium–halogen exchange resulted in the corresponding 4-lithium species that was added to the Weinreb amide and worked up under acid conditions and carried on without further purification. Methyl lithium was added to the crude material at −78 °C in THF, warmed to room temperature, and worked up under acidic conditions to afford a 2.5:1 mixture of the secondary alcohol and its corresponding TMS ether. The crude mixture was treated with acetic acid for 45 min, concentrated, and taken into THF and oxidized with Dess–Martin Periodinane to afford **9** in good yields. Dehydration of **9** with TsOH gave the β-methyl, β-indole-exocyclic enone that was subjected to methyl cuprate Michael conditions to afford tricycle **10**. Subjecting **10** to BF_3-etherate afforded tetracycle **11** in an overall yield of 27% from **5** in 11 steps.



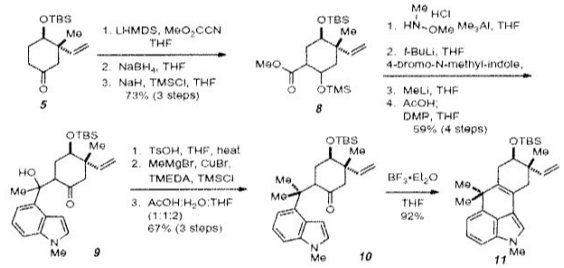
Scheme 5. Synthesis of indole **18**.

Muratake and Natsume[8,9] in their total synthesis of hapalindole U employed a dilute (1 M) tin(IV) chloride-mediated coupling to form **14**. Treating TMS-enol ether **12** with 4-(2-hydroxy-2-propyl)-*N*-tosyl-indole **13** with 1 M $SnCl_4$ at −78 °C afforded tricyle **14** when quenched at −78 °C (Scheme 4).

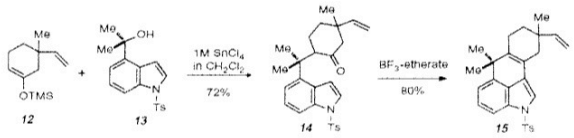
Murataka's tricycle **14** and our tricyle **10** are similar in structure, with ours being more functionalized. Both routes close the tricycle with BF_3-etherate in THF to give rise to similar tetracycles. Tetracycle **15** was formed in 58% over two steps, whereas tetracycle **11** was formed in 27% over 11 steps clearly showing the advantage of the tin-mediated chemistry. It was thought that utilizing this methodology, which has been used in a variety of alkaloid syntheses,[10–13] we could gain rapid access to the ABCD ring system of the ambigiunes in a more efficient manner than that extant.

Accessing the required 4-(2-hydroxyl-2-propyl)-*N*-methylindole for the tin-mediated coupling was accomplished from 2-bromo-6-nitrotoluene under Leimgruber–Batcho[14] conditions to afford **16** in high yields (Scheme 5). N-Methylation of **16** was performed with NaH and methyl iodide in THF to afford **17**. Treatment of **17** under lithium–halogen exchange conditions followed by acetone addition furnished **18** in a 91% yield.

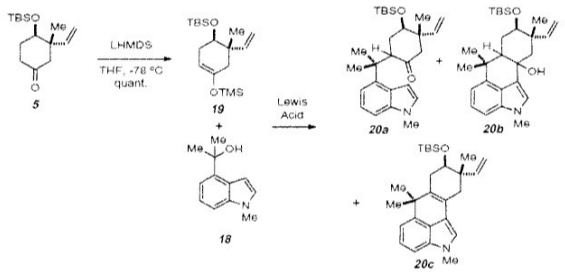
Treatment of **5** with LHMDS followed by TMSCl gave the required TMS-enol ether **19**. A variety of conditions were probed to optimize the coupling of **18** to **19** (Scheme 6 and Table 1). In the event, it was observed that treating indole **18** and TMS-enol ether **19** with fuming tin(IV) chloride in DCM gave the tetracyclic species **20b** in good yields. While we were anticipating the tricycle **20a**,



Scheme 3. Weinreb amide route to tetracycle **11**.



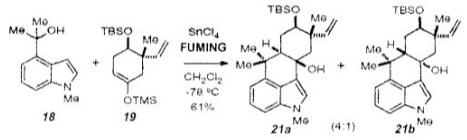
Scheme 4. Muratake and Natsume tricycle formation.



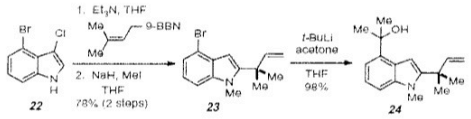
Scheme 6. Lewis acid-mediated coupling of **18** + **19**.

Table 1
Lewis-acid and conditions screened for Scheme 6

Lewis acid	Conditions	Product		
		20a	**20b**	**20c**
$TiCl_4$ (fuming)	Toluene, −78 °C	7%	X	X
$TiCl_4$ (fuming)	Toluene, −44 °C	X	X	5%
$TiCl_4$ (1 M $PhCH_3$)	Toluene, −78 °C	X	X	X
$TiCl_4$ (1 M $PhCH_3$)	Toluene, −44 °C	X	X	X
$TiCl_4$ (1 M DCM)	DCM, −78 °C	13%	X	X
$TiCl_4$ (1 M DCM)	DCM, −44 °C	X	X	X
$TiCl_4$ (fuming)	DCM, −78 °C	X	X	36%
$TiCl_4$ (fuming)	DCM, −44 °C	X	X	13%
$SnCl_4$ (1 M $PhCH_3$)	Toluene, −78 °C	15%	24%	X
$SnCl_4$ (1 M $PhCH_3$)	Toluene, −44 °C	X	X	X
$SnCl_4$ (1 M DCM)	DCM, −78 °C	83%	X	X
$SnCl_4$ (1 M DCM)	DCM, −44 °C	54%	X	X
$SnCl_4$ (fuming)	DCM, −78 °C	5%	61%	X
$SnCl_4$ (fuming)	DCM, −44 °C	13%	8%	42%



Scheme 7. Fuming $SnCl_4$-mediated tetracycle formation.



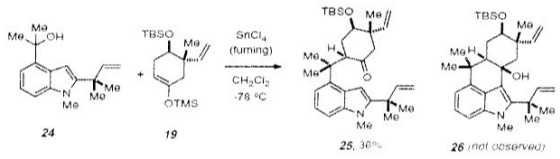
Scheme 8. Synthesis of indole **24**.

synthesis of **20b** gives the carbon core along with the desired tertiary alcohol at the C10, which is present in several ambiguines.

Further studies into the coupling of **18** and **19** with fuming tin(IV) chloride revealed that the reaction afforded diastereomeric tetracycles **21a** and **21b** (4:1 ratio) (Scheme 7), but not the dehydrated tetracycle as seen in Scheme 4. Quenching the fuming tin(IV) chloride reaction at −78 °C proved to be essential in forming the tertiary alcohol. When quenching the reaction at any temperate above −50 °C formation of the dehydrated tetracycle **20c** was observed. When **18** and **19** were treated with the 1 M tin(IV) chloride solution a similar tricyle as seen in Scheme 4 was formed. Subjecting this tricycle to BF_3-etherate afforded the dehydrated tetracycle **20c**. When performing the same procedure with either the corresponding *N*-Boc or *N*-silyl (TMS, TBS, or TIPS) protecting groups only dehydrated tetracycles were observed. Interestingly, when attempting the reaction on a substrate bearing the *N*-tosyl group under the same conditions, only the tricycle was obtained. Other alkyl protecting groups such as PMB or benzyl groups can be used with the current methodology, however the yields from the coupling reactions are significantly lower, 7% and 11%, respectively.

Having accessed the ABCD ring system of the ambiguines, along with the tertiary alcohol at C10, efforts were directed toward gaining access to the same ABCD system with the reverse-prenyl group on C-2 of the indole. Chlorination of the previously described 4-bromoindole with NCS in DMF afforded **22** in excellent yields (Scheme 8). Installation of the reverse-prenyl group was accomplished using Danishefsky chemistry[15] followed by N-methylation of the indole nitrogen to afford **22**. Subjecting **22** to lithium–halogen exchange conditions followed by acetone gave access to **24** in 98% yield.

The coupling of **24** and **19** with fuming tin(IV) chloride was attempted as described previously in Table 1. Unfortunately, no tetracyclic product was observed when subjecting **24** and **19** to any of the previous coupling conditions. Furthermore, only fuming tin(IV) chloride allowed access to the tricycle **25** in 36% yield (Scheme 9). Treating tricycle **25** with BF_3-etherate at room temperature for



Scheme 9. Attempted tetracycle formation.

24 h failed to give the desired tetracycle, but rather the dehydrated tetracyclic system. Similar results were obtained when attempting the same methodology on methyl, ethyl, vinyl, and propyl C2 substituted indoles.

In summary, we have shown two methods of accessing the ABCD cores of both the hapalindoles and ambiguines. Utilizing fuming tin(IV) chloride-mediated coupling of tertiary benzylic alcohols of indoles and TMS-enol ethers we have also gained access to more functionalized tetracyclic cores. Current efforts to deploy this methodology for the concise total synthesis of several members of this family of alkaloids are under investigation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.086.

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Total Synthesis of Hapalindole U

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ABSTRACT

A racemic total synthesis of hapalindole U has been accomplished convergently over twelve synthetic steps, with an overall yield of 16% from commercially available materials. The route employs a novel silyl strategy for accessing the 6:5:6:6 ring system of the hapalindoles rapidly and in good yields.

Keywords:
Hapalindole U
Tin (IV) chloride
Silyl Ring Closure

The hapalindoles were first isolated in 1984 by Moore and Patterson.[1,2] Since that time, the family has expanded to include 29 members, which comprise both tri- and tetracyclic variants (Figure 1). The tetracyclic hapalindoles differ structurally from their tricyclic counterparts only by the presence of their C4-C16 bond, with stereocenters' absolute configurations remaining otherwise mostly identical. Both hapalindole types contain a quaternary carbon center at C12 and an isonitrile or isothiocyanate at C11. Additionally, both structure types possess a hydrogen or alcohol at C10 (R2) and a hydrogen or chlorine at C13 (R1).

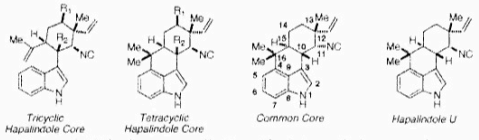
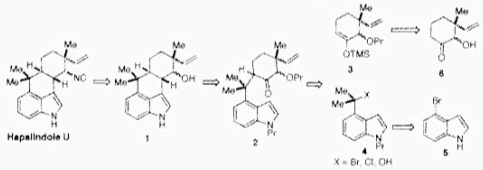


Figure 1. Tri- & tetracyclic hapalindole and ring notation.

To date, most of the hapalindoles have been conquered by total synthesis, many racemically and a few asymmetrically. Of these syntheses, hapalindole U (Figure 1), isolated in 1986 from the cultured cyanophyte *Hapalosiphon fontinalis*, has been conquered both racemically and asymmetrically by Natsume and Baran, respectively. Natsume's total synthesis was accomplished over 20 synthetic steps in an overall yield of 0.2%,[3] and Baran's in nine synthetic steps from commercially available material in 7% overall yield.[4] Herein, we report our racemic route to hapalindole U, which should also allow for analogs to be synthesized for possible biosynthetic studies.

We envisioned that hapalindole U could arise from the oxidation of alcohol **1**, followed by reductive amination, formylation, and dehydration, as Scheme **1** depicts. Tetracycle **1** could be accessed from the ring closure of tricycle **2**, which in turn could arise from the Lewis acid mediated coupling of TMS-enol ether **3** and functionalized indole **4**. Compound **3** could be accessed via alcohol protection and enolization of **6**, which could be formed through a Rubottom oxidation following vinyl cuprate addition upon 3-methylcyclohexenone. Functionalized indole **4** could be accessed from 4-bromoindole (**5**).



Scheme 1. Retrosynthetic analysis for hapalindole U.

Our route to α-hydroxy-ketone **6** began by subjecting commercially available 3-methylcyclohexenone (**7**) to Michael conditions utilizing vinyl Grignard, $CuBr{\bullet}Me_2S$, TMEDA and TMSCl to generate TMS-enol ether **8**, as shown in Scheme 2. Cleavage of the TMS-enol ether with an acetic

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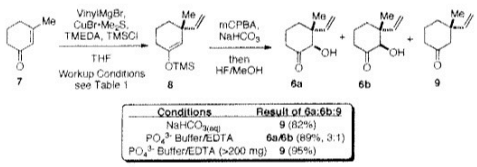
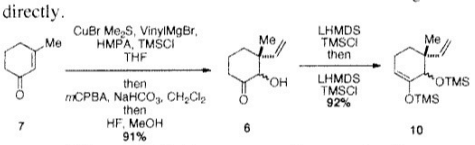
acid/water/THF mixture accessed **9**, which has been used in previous synthetic routes to hapalindole derivatives. Subjecting **8** to Rubottom oxidation conditions, according to related literature precedent,[5] failed to give any α-hydroxy-ketone **6a/6b**, but did afford **9** in 82% yield. Workup conditions for the cuprate reaction involved washing with aqueous $NaHCO_3$ until the aqueous layer became colorless. It is thought that these conditions might not fully remove the copper from the TMS-enol ether species, ultimately contributing to the failed oxidation with *m*CPBA. Modification of the workup conditions (washing the crude material sequentially with a 0.1 M phosphate buffer at pH 7, followed by 1.0 M EDTA solution) completely removed the copper from the TMS-enol ether. Ensuing treatment of **8** with *m*CPBA, followed by TMS cleavage with HF in MeOH, gave a 3:1 diastereomeric mixture of α-hydroxy-ketones **6a**:**6b**. Unfortunately, it was found that the phosphate buffer and EDTA quench conditions only worked on scales of up to 200 mg. On larger scales these conditions preferentially cleaved the TMS-enol ether to afford ketone **9**. Further modifications failed to circumvent this result.

Scheme 2. Accessing **6a-b** via a Rubottom oxidation.

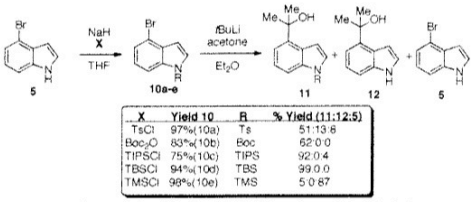


Attention was then directed towards modifying the cuprate addition (Scheme 3). Slowly adding CuBr•Me_2S in HMPA to vinylmagnesium bromide at –78 °C over 5 min, followed by TMSCl and **7** in THF (1M) over 30 min, gave the desired TMS-enol ether in excellent yields. Subjecting said enol ether to Rubottom oxidation conditions then afforded **6** in 91% in one pot (3:1 ratio as in Scheme 2). TMS protection of the secondary alcohol was accomplished with LHMDS and TMSCl; sequential treatment with more LHMDS/TMSCl in one pot then furnished desired TMS-enol ether **10** in 92%. This route gives multiple grams of product **10**, starting from **7**. Surprisingly, treatment of **6** with more than 2.0 equivalents of LHMDS/TMSCl or excess TMSOTf failed to give **10** directly.



Scheme 3. Multi-gram route for accessing **6**.

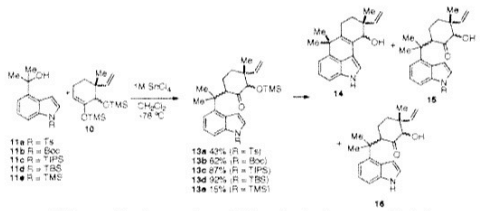
Our route to **11** began by converting 2-bromo-6-nitrotoluene (not shown) to indole **5** in high yield.[6] This intermediate was then protected with Boc anhydride, tosylchloride, and various silylchlorides to afford compounds **10a-e** (Scheme 4). Subjection to lithium-halogen exchange conditions, followed by acetone, then furnished products **11**, **12**, and **5** with the various ratios indicated. In this conversion, compounds **10a**, **10c** and **10e** regenerated differing amounts of **5**, which was easily re-protected. Derivative **12a**, however, could not be efficiently converted to **11a**.



Scheme 4. Synthesis of various functionalized indoles.

Subjecting indole **11** and TMS-enol ether **10** to 1 M tin(IV) chloride in CH_2Cl_2 at –78 °C afforded the corresponding tricycles **13** in low to excellent yields, as shown in Scheme 5.[7] Of the various protected indoles screened, the TBS and TIPS analogs faired best in Lewis acid-mediated couplings, while the TMS variant proved too labile. Closure of tricycle **13** to the corresponding tetracycle **14** was attempted under a variety of conditions, as Table 1 illustrates. Treatment of the five different *N*-protected tricycles with BF_3•Et_2O gave poor yields of **14**. Treatment of **13a-b** with BF_3•Et_2O afforded only the de-silylated tricycle, with no tetracycle formation. Given the known reactivity of Lewis acids towards silyl groups, this result was not completely unexpected, though it was anticipated that at least one-third of the material would close to **14**. To circumvent this complication, the TMS groups in **13a** and **13b** were removed with TBAF to give free alcohols **15a-b**. These disappointingly failed to provide **14** when treated with BF_3•Et_2O, as did their acetylated counterparts (not shown). *N*-Silylated tricyles **15c-e** gave trace amounts of **14** upon treatment with BF_3•Et_2O, but primarily afforded tricyle **16** in good to average yields. At this stage it was anticipated that tricycles **13** might be more efficiently cyclized to **14** by subjecting them to TBAF in THF, particularly in the cases of **13c-e**. Treatment of **13a-b** with TBAF gave tricycles **15a-b** exclusively. By comparison, *N*-Silylated intermediates **13c-d** afforded tetracyclic products that resembled **14**, but contained the corresponding silyl groups as unidentifiable adducts on the carbon core. It is proposed that the alkaline nature of TBAF caused a base-induced side reaction to give the observed adducts.

Given the poor performance of **13a**, **13b**, and **13e**, as well as the promising conversion of **13c-d** to products that resembled **14**, it was decided to screen *acidic* conditions for silyl deprotection. This led us to subject **13c-d** to a 1:1 aqueous mixture of HCl:MeOH, which afforded **14** in 12% and 57% yields, respectively, without any observed silyl adduct formation. Trace amounts of a non-dehydrated di-hydroxy product were observed in both cases, thus suggesting a hydro-halogenation reaction occurring during formation of **14**. To circumvent this outcome, methanolic HCl was employed instead of aqueous HCl. Under these conditions, **13b** afforded **14** with a slightly improved 22% yield, along with a 23% yield of **15b**. In contrast, treatment of **13c** with methanolic HCl pleasingly gave **14** in 79% yield, with a modest 5% yield of tricycle **15c**, which could be converted to **14** by subjection to additional methanolic HCl. It is noteworthy that **13c-d** can be converted to **14** by any of the following means: (1) employing commercially available methanolic HCl; (2) dissolving $HCl_{(g)}$ in MeOH; or (3) adding dry acetyl chloride to methanol. The allylic-hydroxy-tetracycle **14** is thereby accessed in 54% yield over six synthetic steps from commercially available materials.



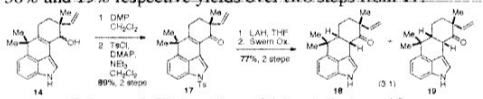
Scheme 5. Accessing allylic alcohol tetracycle **14**.

Table 1. Conditions screened for **13a-e** closure to **14a-e**.

Compound	Conditions/Yields (%:**14**:**15**:**16**)			
	BF_3•Et_2O	TBAF	$HCl_{(aq)}$	Methanolic HCl
23a	0:46:0	0:62:0	2:21:0	7:16:0
23b	0:53:21	0:49:0	0:7:5	0:0:1
23c	3:0:31	53*:1:7	12:0:0	22:23:1
23d	5:0:25	61*:0:10	57:3:0	79:5:0
23e	0:0:45	0:0:7	1:0:0	0:0:0

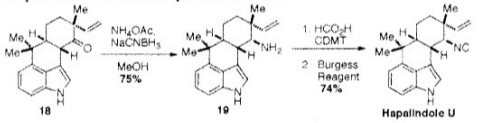
*Isolation of compound **14** was of a silyl adduct upon said ring system.

Oxidizing **14** with Dess-Martin Periodionane in CH_2Cl_2 gave the corresponding ketone, which was subsequently treated with TsCl, NEt_3, and catalytic DMAP at reflux to furnish compound **17** in 89% yield over the two synthetic steps (Scheme 6). Treating **17** with LAH in THF over 12 h afforded the reduced *cis*-decalin system in a 3:1 ratio favoring the desired isomer, which was then subjected to Swern oxidization conditions to afford *trans*-decalins **18** and **19** (3:1 ratio) in 77% yield. Purification of the oxidized mixture provided the desired isomer **18**, as well as undesired **19**, in 58% and 19% respective yields over two steps from **17**.



Scheme 6. Elaboration of **14** onto ketone **18**.

Reductive amination of **18** with ammonium acetate and $NaCNBH_3$ in MeOH gave desired **19** in 75% yield, with only a 10% yield of the undesired diastereomer (Scheme 7). Formamide assembly was accomplished by treating **19** with formic acid, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), catalytic DMAP, and *N*-methyl-morpholine in CH_2Cl_2.[4] The resulting intermediate (not shown) was subsequently dehydrated with Burgess reagent in benzene to afford Hapalindole U in 74% yield from **19**.



Scheme 7. Accessing Hapalindole U.

In summary, the symmetric total synthesis of (+/–) hapalindole U has been accomplished in 16% yield over twelve synthetic steps using a novel silyl strategy to access to the 6:5:6:6 tetracyclic carbon core. When considering the two previous syntheses of hapalindole U (one racemic by Natsume over 20 steps, with an overall 0.2% yield,[3] and one asymmetric by Baran over nine steps, with an overall 7.5% yield[4]), our work provides a higher-yielding approach to the natural product. Although our strategy is similar to Natsume's route, it requires eight fewer steps and gives an eighty-fold greater yield, mostly due to our enhanced means of accessing the functionalized tetracycle core. While Baran's route requires three fewer steps, it suffers from a 2.1-fold lower yield. Given that the route presented here is racemic and that Baran's is asymmetric, however, our higher yield is negated upon considering the 50:50 ratio of enantiomers produced. One advantage our approach, however, is that it allows for analog studies to be conducted at multiple stages. Current efforts are being directed toward an asymmetric route, which may center on the stereoselective reduction of **17** to **18** using various chiral reductants.

Acknowledgments. We gratefully acknowledge financial support from the National Institutes of Health Grant ??????.

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7. Rafferty, R. J.; Williams, R. M.; *Tetrahedron Let.* **2011,** *52*, 2037-2040.

Total Synthesis of Veraguamides A-C and H-L and Analogs
Research Proposal

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Abstract: The total syntheses of veraguamides A-C and H-L have been proposed. Veraguamide A (**1**) has been shown to possess potent cytotoxicity towards the H-460 human lung cancer cell line (LD_{50} = 141 nM). Upon developing a synthetic route, analogs of particularly **1** as well as the other seven members will be undertaken in efforts to increase the potency towards the H-460 human lung cancer cell line. Synthetically, formation of the different β-hydroxyacid in the veraguamide family is of key interest and the proposed route to access the variants is via a crotylation and/or Evan's auxiliary approach.

The veraguamide family was isolated and characterized in 2010 by the Panama International Cooperative Biodiversity Group (ICBG) from a collection of cf. *Osillatoria margaritifera* from the Coiba National Park (CNP), Panama.[1] The veraguamide family is thought to arise biosynthetically from polyketide synthases (PKS's) and nonribosomal peptide synthetase (NRPS) derivatized portions given natural amino acids as wells as the wealth of oxygen, nitrogen, and carbon rich supplies within these cyanobacteria. In 2010, multiple filamentous forming species of marine cyanobacteria were collected from the CNP as part of the ICGB in Panama. The extracts of said isolates' were screened against numerous biological assays, and it was found that *Osillatoria margaritifera* was highly cytotoxic towards the H-460 human lung cancer cells in vitro. Upon further investigation, via a bioassay-guided fractionation process, the veraguamide were discovered, Figure 1. It was found that veraguamide A (**1**), the major compound in the isolate, was highly

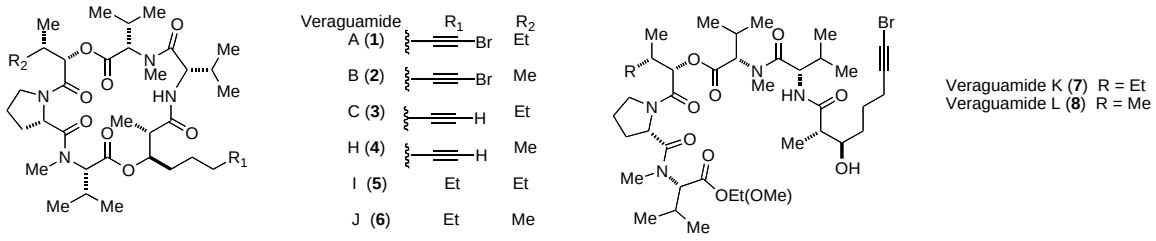


Figure 1. Veraguamide Family

potent towards H-460 cells with a LD_{50} value of 141 nM, the other seven members

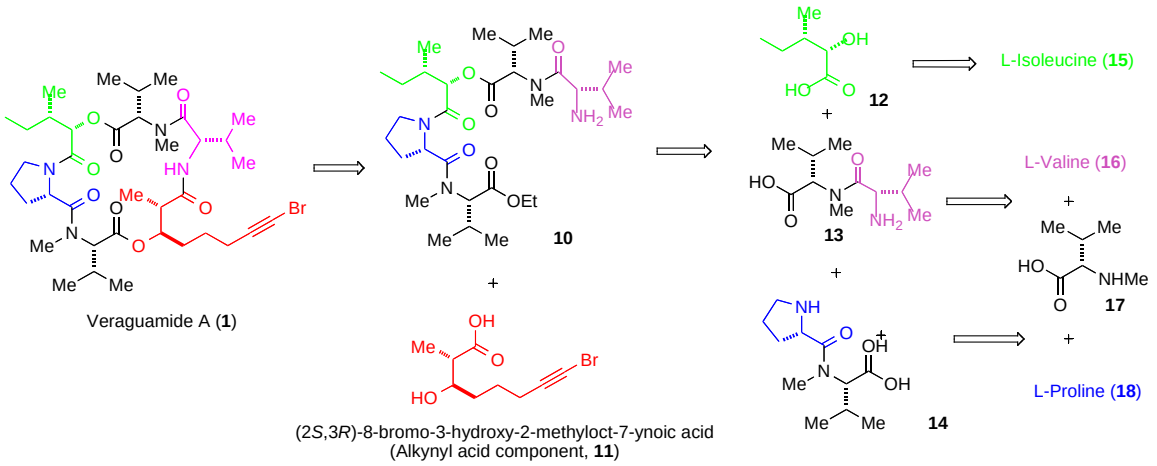
cytotoxicity is unfortunately not nearly as potent, in the mid to high μM range. It is proposed that the presence of the terminal alkyne gives the veraguamides their cytotoxicity, but said alkyne functionality is not limited to this family in cyanobacteria. Multiple other cyclic and acyclic compounds have been isolated form cyanobacertia that also possess a terminal alkyne including: carmabin A,[2] georgamide,[3] pitipeptolide A,[4] yanucamides,[5] antanapeptin,[6] trugapeptin A,[7] hantupeptin,[8] wewakpeptins,[9] dragonamide,[10] and viridamide A.[11] Unlike **1**, these compounds have little to no cytotoxicity towards human cancer lines, but rather have antimalarial, antibacterial and antifungal activities. Thus, the terminal alkyne claim for **1**'s cytotoxicity cannot be concluded at this time, mode of action studies are required to elucidate the mode of cytotoxicity of **1**.

Proposed Area of Research

As of date no synthetic work as been report on the veraguamides family of natural products, and given the potent cytotoxicity of **1** effort should be directed towards accessing this newly isolated possible anticancer agents. This proposal therefore, will delineate efforts towards: (1) gaining access to veraguamide A (**1**) and the other seven members, (2) synthesizing analogs of **1**, and (**3**) attempts at elucidating the mode of action of **1** will be undertaken in the Hergenrother Laboratories once at the University of Illinois, Champaign-Urbana.

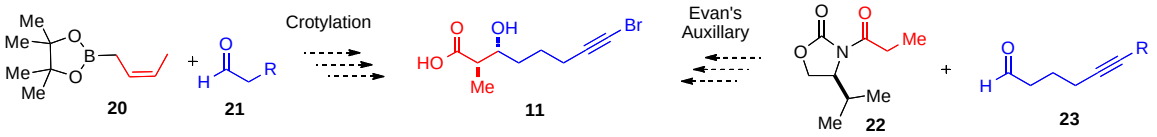
RETROSYNTHESIS

Retrosynthetically, veraguamide A has been envisioned to arise from multiple peptide and esterification reactions from various standard L-amino acids, derivatized amino acids and an alkynyl acid component, scheme 1. The total synthesis of **1** will be accomplished via peptide coupling and esterification of alkynyl acid **11** to pentapetide **10**. The proposed route to access **11** will be discussed shortly. Penta-peptide **10** will arise from the esterification of α-hydroxyacid **12**, which will be accessed from L-isoleucine, to dipeptide **13** and the peptide coupling of the N-terminus of **13** to the C-terminus of dipeptide **14**. Di-peptide **13** will be accessed from the peptide coupling of the N-terminus of L-valine (**16**) to the C-terminus of *N*-methyl-L-valine (**17**), which will be accessed from L-valine (**19**). Peptide coupling of the N-terminus of **17** with the C-terminus of L-proline (**18**) will give di-peptide **18**.



Scheme 1. Retrosynthetic Analysis for Veraguamide A Access.

Accessing the alkynyl acid **11** for the total synthesis of veraguamide A as well as other members of the family will be the key synthetic challenge in the project. Two routes will be proposed for accessing this key component of the veraguamide family. A crotylation strategy as well as employing the Evan's auxiliary will be used in accessing this key component, scheme 2.

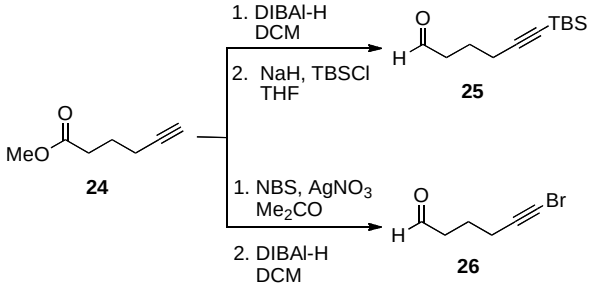


Scheme 2. Retrosynthetic Analysis for Alkynyl Acid **11** Access.

PROPOSED SYNTHESIS FOR ACCESSING THE VERAGUAMIDE FAMILY

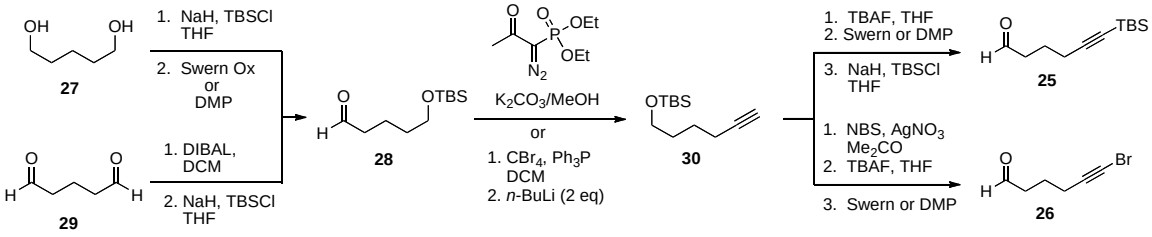
*Aldehyde **21** and **23** Access*

The two strategies envisioned for accessing **11** involve an aldehyde, which ideally would contain the alkynyl bromide functionality. Noting the reactivity of said functional group, two aldehyde compounds will be made that could be elaborated into the desired alkynyl bromide at a later stage. Commercially available methyl-hex-5-yn-onate (**24**) could be transformed into both the desired alkynyl bromide **26** and a TBS-alkynyl **25** compound for future deprotection and bromide installation, scheme 3. Reduction of **24** with DIBAl-H followed by treatment with NaH and TBSCl would afford **25** in anticipated good yields. Desired **26** could be access from **24** with NBS and $AgNO_3$ in acetone[12] followed by DIBAl-H reduction. The only limitation to these two routes is the starting material **24**, which costs $104/5g.



Scheme 3. Synthesis of TBS and Bromide Alkynyl Aldehydes.

An alternative route for accessing both **25** and **26**, with the option of additional aldehyde analogs as well as reducing cost, is from commercially available diol **27** ($35.90/100g) and dialdehyde **29** ($27.80/25g), scheme 4. Mono-TBS protection of **27** could be accomplished with NaH and TBSCl (1.1 eq.) in THF, which could be oxidized with either Swern conditions or with Dess-Martin periodinane (DMP) affording **28**. Likewise, **29** could be selectivity reduced to the mono-alcohol with DIBAl-H and subsequently protected as the TBS ether **28**. Accessing **28** does give an additional aldehyde to be utilized during attempts at accessing the alkynyl acid **11**. Compound **28** could be elaborated into the terminal alkyne under Ohira-Bestmann[13] or Corey-Fuchs[14] conditions to give **30**, and another aldehyde for screening in route to **11**. From **30**, both **25** and **26** can be accessed, previously shown from the methyl ester, in a more cost effective manner. Compound **25** can access from **30** via TBS deprotection with TBAF followed by either Swern or DMP oxidation with subsequent TBS addition with NaH and TBSCl. Treatment of **30** with NBS and $AgNO_3$ in acetone will give the alkynyl bromide. TBS deprotection can be accomplished with TBAF in THF, and then transformed into **26** via oxidation with either Swern or DMP conditions.

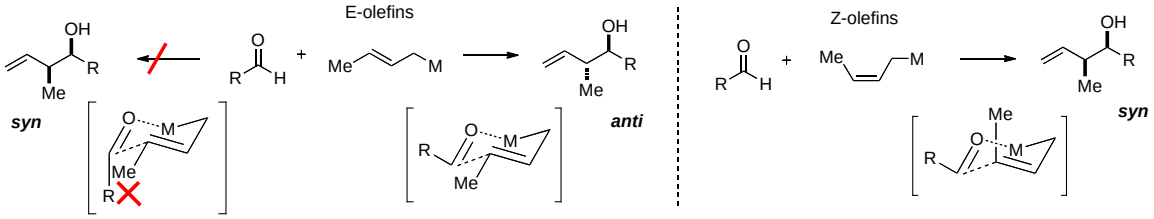


Scheme 4. Accessing Aldehydes **25**, **26**, and **28** for Future Elaboration.

Once accessing the multiple aldehyde variants, efforts will be direct towards elaboration of said aldehydes to **11**. Two possible strategies that are being proposed are via crotylation and utilizing the Evan's auxiliary.

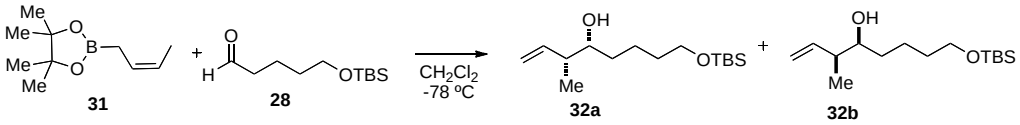
*Crotylation Strategy for Alkynyl Acid **11** Access*

Crotylation has been well documented in the literature in forming carbon-carbon bonds with concurrent stereo-center installation, giving either *syn* or *anti* relationships.[15] Depending upon the geometry of the alkenyl species either *syn* or *anti* products can be obtained, as predicted through a closed transition state, scheme 5. Crotyl E-olefins give rise to *anti* selectivity, as predicted through the transition state, and crotyl Z-olefins *syn* selectivity.



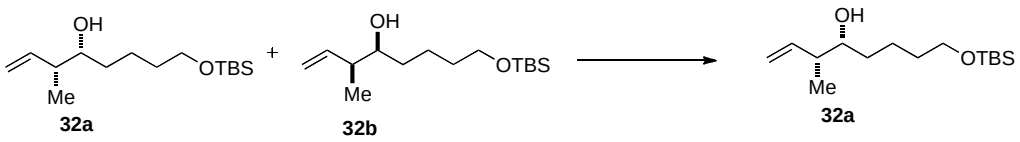
Scheme 5. Anti verses Syn Selectivity in Crotylation Reactions

In order to access the *syn* relationship in **11** via a crotylation strategy, the use of the cis-2-butenyl metal species will be employed. The use of the metal for the crotylation species is of key importance, as many of the metal species tend to isomerize, which as illustrated above govern the *syn* and *anti* selectivity. Pinacol boronic ester was chosen due to its resistance to isomerization, unlike the lithium and chromium species.[15] Other types of metal species can be utilized, such as silyl and tin, but boron was chosen for its economical aspects as well as its waste disposal.[15] Pinacol boronic ester **31**, which is both commercially available and synthetic accessible[16], could be treated with aldehyde **28** in DCM at -78 ℃ to afford a racemic mixture of **32**, scheme 6. It is of note to mention that only aldehyde **28** will be carried through this type of crotylation strategy, as a late stage ozonolysis reaction will be performed and alkynes have been noted to react under ozonolysis conditions.[17]



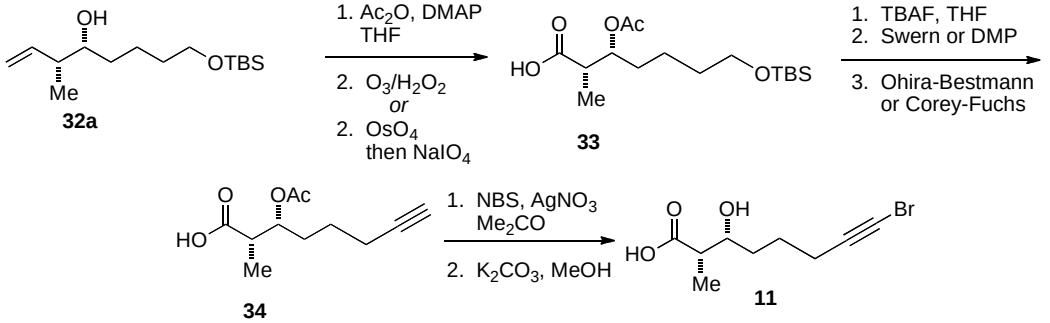
Scheme 6. Crotylation for Access to Racemic **32**.

Resolution of the racemic alcohol mixture could be accomplished in either of two methods: (1) esterification with a chiral carboxylic acid for separation[18] or (2) an enzymatic resolution with a lipase and vinyl acetate, scheme 7.



Scheme 7. Resolution

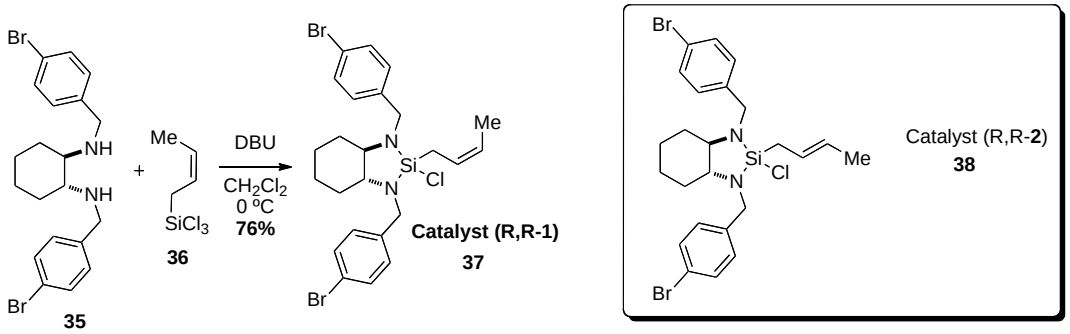
With enantiomerically pure **32** in hand, the secondary alcohol could be acetylated with acetic anhydride and DMAP. The resulting compound will be subjected to either ozonolysis under oxidative workup conditions or dihydroxylation followed by diol cleavage with sodium periodate to give compound **33**, scheme 8. Deprotection of the TBS ether with TBAF followed by oxidation under Swern or DMP conditions should give the corresponding aldehyde which can be transformed into the alkyne using either the Ohira-Bestmann reagent or under Corey-Fuchs conditions to give compound **34**. Treating **34** with NBS and $AgNO_3$ in acetone should give the alkynyl bromide followed by K_2CO_3 in methanol to remove the acetyl group should give access to compound **11**. Prior to elaboration to the alkynyl species, the free acid can be protected as the methyl ester if problems arise from the alkynyl installation with the free acid in place. While this strategy does give access to desired **11** asymmetrically, there are several points of concern: (1) the route is lengthy involving nine synthetic steps from the previously described aldehyde compounds, (2) the resolution step requires the lost of at least 50% of the synthesized material, (3) the ozonolysis and/or dihydroxylation/cleavage sequence will not tolerate the presence of the desired alkyne thus requiring further synthetic elaboration, and (4) the anticipated yields and cost of the multiple synthetic steps can be higher than expected.



Scheme 8. Access of Alkynyl Acid **11**

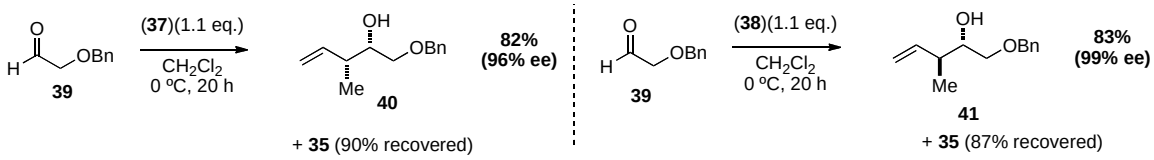
To circumvent the resolution of racemic **32**, shown above, employing enantio-selective crotylation conditions can be performed. Modification of the pinacol boronic

ester portion of the crotyl compound can be undertaken to install a chiral backbone[19], but it is shown in the literature that the use of chiral silyl crotylation reagents give not only better yields but enhanced ee's. Leighton and co-workers[20] in 2004 demonstrated the use of a chiral crotylsilane reagent to give enantiomerically pure products. The authors showed how the chiral crotylsilane reagent could be prepared from commercially available **35** and **36** with treatment of DBU in DCM to afford catalyst **37** in 76% yields, scheme 9. The E-olefin can be prepared in the same fashion. It is of note to mention that the (S,S) catalyst can also be prepared from the corresponding (S,S) enantiomer of **35**.



Scheme 9. Synthesis of Chiral crotylsilane reagents.

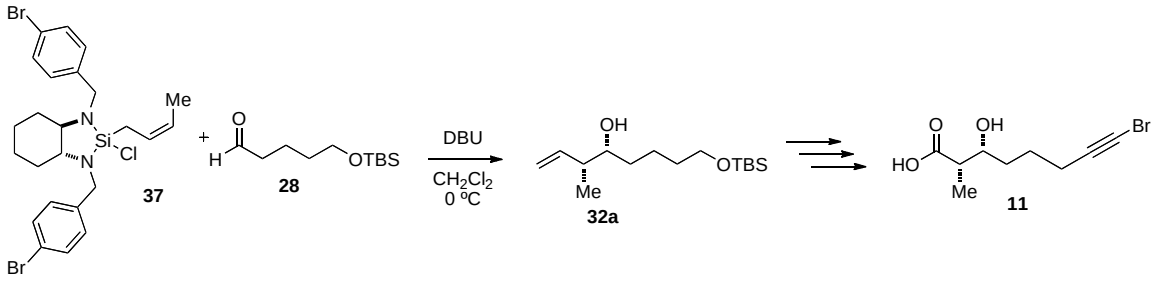
Leighton and co-workers[20] demonstrated the synthetic utility of their chiral crotylsilane catalyst via the crotylation of *O*-benzyl-ethan-2-ol-al, scheme 10. Governed by the close transition state, as described in scheme 5, the geometry of the olefin directs the *syn* and *anti* selectivity, but now with this crotylsilane catalyst it also directs enantioselectivity as seen in scheme 10.



Scheme 10. Chiral crotylation via chiral crotylsilane catalyst.

Given the precedence, as outlined in scheme 10, it is thought that the same crotylsilane catalyst **37** can be employed along with aldehyde **28** in DCM with DBU at 0 ℃ to give the desired enantiomerically pure alcohol **32a**, scheme 11. Once enantiomically pure **32a** is accessed, the same transformations as outlined in scheme 8 can be performed to gain access to **11**. Limitations to this synthetic strategy still include: (1) length of the route, (2) ozonolysis and/or dihydroxylation/cleavage sequence will not

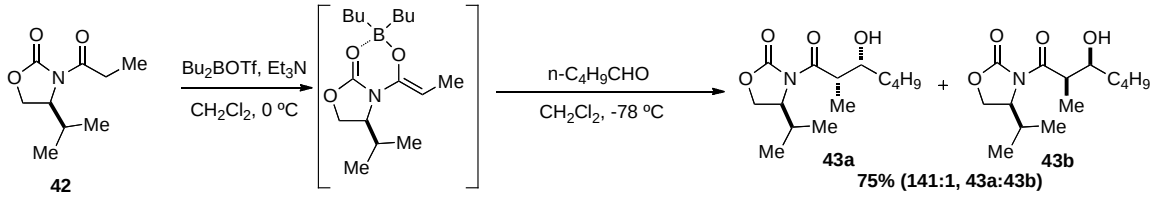
tolerate the presence of the desired alkyne thus requiring further synthetic elaboration, and (3) the anticipated yields and cost of the multiple synthetic steps can be higher than expected, but no longer include resolution and loss of 50% (at least) of material. The last strategy to gain access to **11** will reduce not only the length of the route, but also will allow the use of the alkynyl aldehyde **25** or **26** directly.



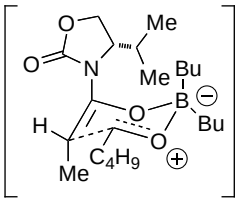
Scheme 11. Asymmetric Synthesis of Alkynyl Acid **11**.

*Evan's Auxiliary Strategy for Alkynyl Acid **11** Access*

Given the limitations of the crotylation strategy delineated above, specifically in regards to the inability to utilize the alkynyl aldehydes **25** and **26**, it is envisioned to employ the Evan's auxiliary,[21] which can tolerate a variety of functionality on both the attached carbonyl as well as the aldehyde being added onto, to access alkynyl acid **11**. Addition of propionyl chloride onto aldehyde **25** or **26** via Evan's auxiliary will give the carbon core, along with the desired stereocenters of **11**. Evan's and co-workers[21] showed the addition of a propionyl group, via the (S)-auxiliary, onto pentanal giving the desired *syn* selectivity with a 141:1 enantiomeric excess of desired to undesired as governed by the closed transition state, scheme 12 and 13, respectively.

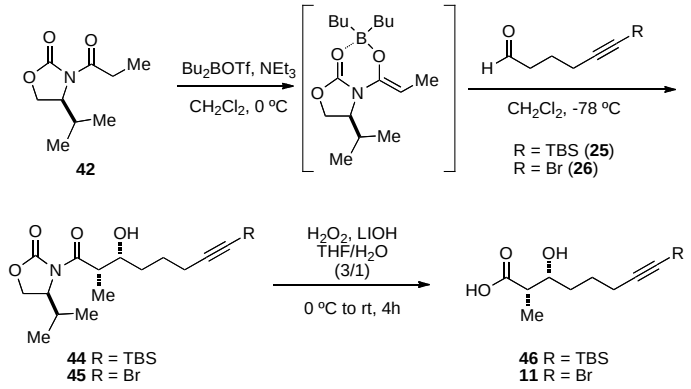


Scheme 12. Illustration of the use of Evan's Auxiliary.



Scheme 13. Closed Transition State for Enantiomeric and *Syn* Selectivity

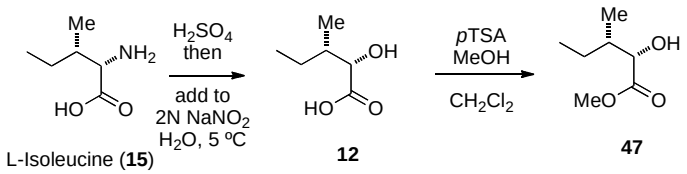
Starting from (S)-valinol oxazolidinone **42** can be accessed via treatment with diethyl carbonated, K_2CO_3 and sodium ethoxide followed by heating at 129 ℃.[22] Once the oxazolidinone is purified, it can be treated with *n*-BuLi in THF followed by addition of propionyl chloride to afford **42**[21], scheme 14. Treating **42** with *n*-Bu_2BOTf and Et_3N in DCM will result in the boron enolate to which aldehyde **25** or **26** in DCM will be added to afford **44** or **45**[21]. The auxiliary can be removed to furnish the carboxylic acid by treatment of **44** or **45** with hydrogen peroxide, lithium hydroxide in a mixture of THF/H_2O (3/1) to give **46** or **11**.[23] Accessing the alkynyl bromide **11** or alkynyl TBS **46** can be performed utilizing the Evan's auxiliary with little expected problems. This current route does allow the use of the desired aldehyde portion for **11**, unlike the crotylation strategy. While the crotylation strategy is still concerned a viable route for accessing **11**, the Evan's auxiliary route is planned on being the main route and the crotylation strategy a means to gaining access to aldehyde derivatives and as a backup route for accessing **11**.



Scheme 14. Evan's auxiliary strategy for proposed access of **11** and **46**.

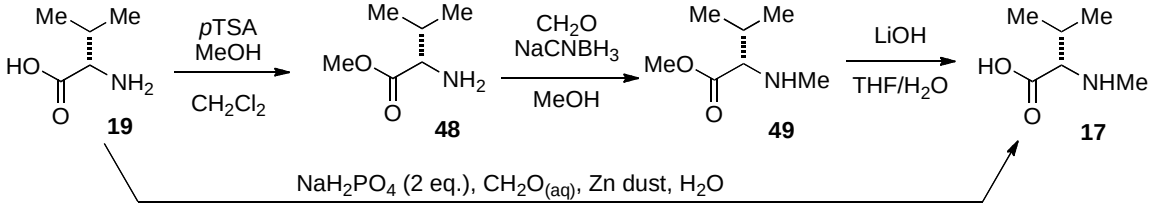
*Strategy for Accessing α-Hydroxyacid **12** and N-Methyl-Valine **17***

α-Hydroxyacid **12** can be synthesized from L-isoleucine **15** in a single step.[24] L-Isoleucine can take taken up into 2 N sulfuric acid and cooled to 0 ℃, to which a 2 N $NaNO_2$ solution will be added and stirred for 24 h to afford **12**, scheme 15. While it is anticipated that **12** can be directly esterified to di-peptide **13**, the free carboxylic acid might interfere, thus the methyl ester will also be prepared. The methyl ester can be formed by treatment of **12** with *p*TSA and methanol to afford **47**, or done prior to the amine-hydroxyl exchange.



Scheme 15. Synthesis of α-hydroxyacid **12** and methyl ester **47**.

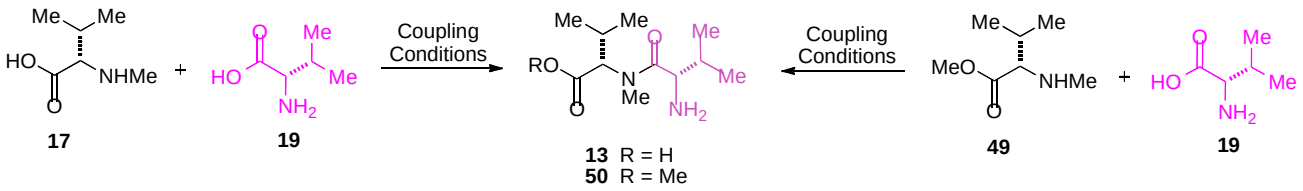
N-Methyl-valine is available commercially, at a cost of $27 for 100mg ($270/1g), making it extremely cost ineffective to purchase it. Synthesis of **17** can start from the methyl ester of valine (**48**), at a cost of $54.30 for 10 g ($5.4/1g), via reductive animation with formaldehyde and sodium cyanoborohydride in MeOH to give **49**, scheme 16. The methyl ester can be transformed to the free acid with LiOH in THF/H_2O to give **17**. While it is anticipated that the coupling of **17** to both L-proline and **12** should proceed smoothly, having the corresponding methyl ester might be required in the coupling previously stated and therefore is beneficial to have a route accessing it. To further reduce the cost of accessing **17**, rather than using the methyl ester of valine at a cost of $5.4/1g, L-valine can be used at a cost of $0.97/1g and can be transformed into the methyl ester via *p*TSA and MeOH. L-Valine can also be directly converted to *N*-methyl-valine by treating **19** under reductive conditions as employed by Bieber[25].



Scheme 16. Synthesis of **17** and derivatives.

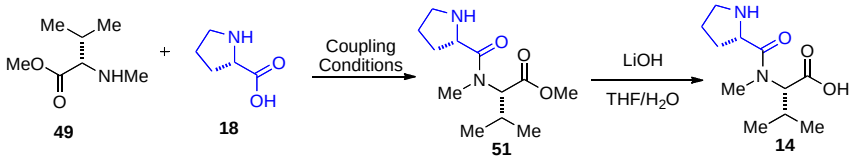
*Synthesis of di-peptides **13** and **14***

Di-peptide **13** or its methyl ester counterpart **50** can arise from **17** and **19** or **49** and **19**, respectively. Standard peptide coupling conditions will be employed for all peptide couplings, ideally EDCI[26] or PyBOP[27] couplings will be undertaken for their general ease and cost effectiveness, but other peptide coupling reagents[28] can also be employed if problems ensue. Amino acids **17** and **19** can be coupled to afford desired **13**, but in addition **50** will be accessed from **49** and **19** to afford the methylated peptide to aid in any problems that might arise from the unprotected C-terminus of **13** in subsequent couplings, scheme 17.



Scheme 17. Access of di-peptide **13** and its methyl ester **50**.

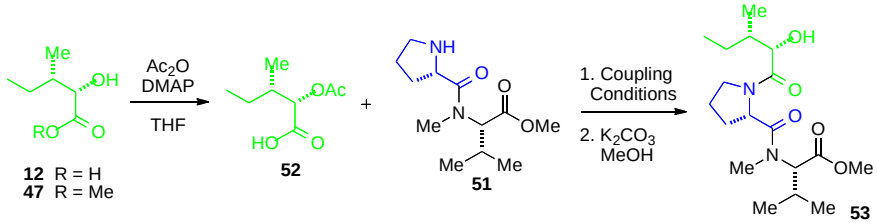
Coupling of **49** and **18** under standard peptide coupling conditions will afford the methyl ester di-peptide **51**, which upon treatment with LiOH in THF/H_2O will give desired di-peptide **14**, scheme 18. As described above, both the free C-terminus and the methyl ester will be synthesized to help account for any problems that might arise durning the coupling to the penta-peptide (**10**) as well as the macro-cyclization towards **1**. The cyclic amine of **18** can be Boc protected if issued arise from the coupling of **49** to **18** and subsequently removed with TFA in THF or DCM.



Scheme 18. Access of di-peptide **14** and its methyl ester **51**.

*Synthesis of penta-peptide **10** and Veraguamide A (**1**)*

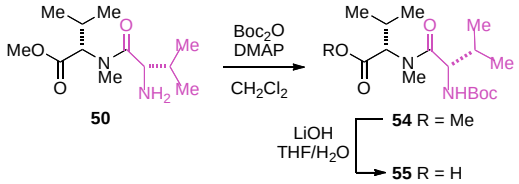
Accessing penta-peptide **10** is envisioned to start with the coupling of **52** with di-peptide **51**. Acetylation of either **12** or **47** can accomplished with acetic anhydride and catalytic DMAP in THF. The acetylated derivative of **47** could then be treated with LiOH in THF/H_2O to afford **52**, scheme 19. Coupling **52** to **51** will be accomplished with standard peptide coupling conditions to afford the tri-peptide, followed by treatment with K_2CO_3 in MeOH, for acetyl removal, to afford tri-peptide **53**.



Scheme 19. Synthesis of tri-peptide **53**

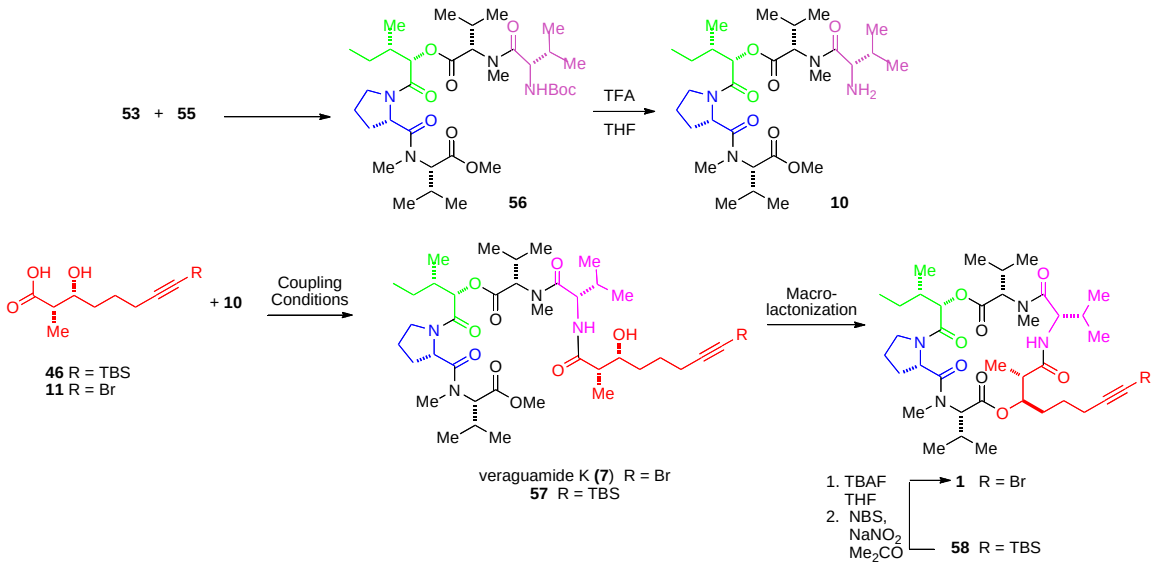
Prior to forming the penta-peptide **10**, Boc protection of the N-terminus of **50** could be undertaken via treatment with Boc anhydride and catalytic DMAP in DCM to give **54**, scheme 20. Transformation into the free acid on the C-terminus could be

performed via LiOH in THF/H_2O to afford **55**. Boc protection of **50** will be done to help decrease any problems that might arise from the coupling of di-peptide **50** with the other half of penta-peptide **10**. While it will be attempted to perform the coupling of **13** with **12**, it is not expected to deliver good to great yields, thus the Boc strategy being implemented. If any issues arise in Boc protection the N-terminus of **50**, the Boc group will be introduced earlier in the synthesis prior to formation of the di-peptide **50**.



Scheme 20. Synthesis of di-peptide **54** and **55**.

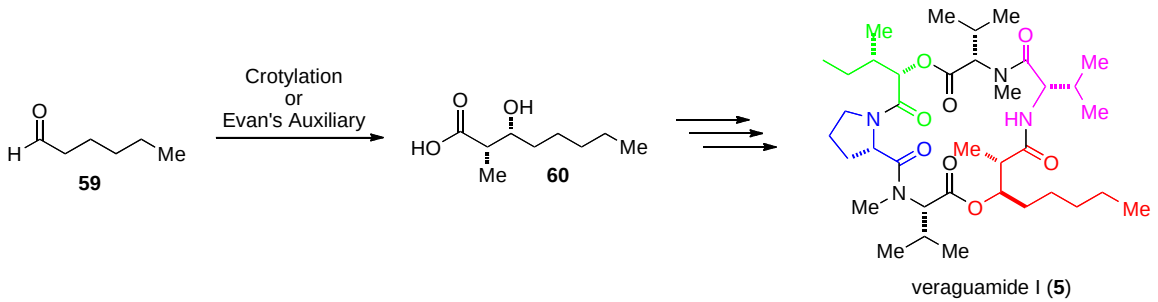
Esterification of **53** to **55** can be accomplished with DCC and catalytic DMAP to afford penta-peptide **56**, scheme 21. Deprotection of the Boc group can be accomplished with TFA in THF or a THF/DCM mixture to give **10**. Having accessed penta-peptide **10**, introduction of either alkynylacid **11** or **46** can be undertaken. Standard peptide coupling conditions will be employed for the coupling of the alkynyl acid **11** or **46** to **10**, in the event the β-hydroxyl group interferes with the coupling, said alcohol can be acetylated with Ac_2O and catalytic DMAP, coupled to **10**, treated with K_2CO_3 in MeOH to de-acetylate to access either veraguamide K (**7**) or **57**. Prior to macrolactonization the hexa-peptide will be treated with LiOH in THF/H_2O to de-protect the methyl ester of the *N*-methyl-valine. Treating this free C-terminus under standard macrolactonization conditions, either DCC and DMAP (Keck conditions[29]), Corey-Nicoloau[30] conditions, DEAD and triphenylphospine (Mitsunobu[31] conditions), Mukaiyama conditions, or Yamaguchi[32] conditions will afford veraguamide A (**1**) or **58**. The alkynyl TBS (**58**) can be converted into **1** via TBS deprotection with TBAF in THF followed by NBS and $NaNO_2$ in acetone. It is of note to mention that if the alkyne group in **11** or **46** gives rise to any problems in the construction of the cyclic core, aldehyde **28** could be employed at elaborated into the desired alkynyl functionality at the end of the synthesis.



Scheme 21. Access of Veraguamide A (**1**).

Synthesis of Veraguamides C and I

Veraguamide C (**3**) can be accessed directly from **58** via treatment with TBAF in THF followed by an acidic workup to give the terminal alkyne of **3**. Veraguamide I (**5**) can also be accessed utilizing the chemistry outlined in scheme 21, with the replacement of **11** or **46** with **60**. Compound **60** can be accessed from aldehyde **59** ($0.30/1g) via the crotylation or Evan's auxiliary strategy delineated above, scheme 22.



Scheme 22. Synthesis of alkynyl acid **60** for access of veraguamide I (**5**).

Synthesis of Veraguamides B, H, J and L

Replacing L-isoleucine (**15**) in scheme 17 with L-valine will allow for access to veraguamides B (**2**), H (**4**), J (**6**) and L (**8**) using the same strategy to access (**1**), (**3**), (**5**) and (**7**), respectively.

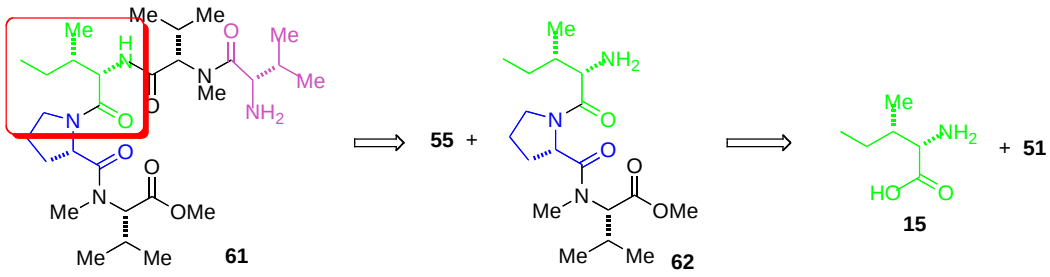
ANALOG SYNTHESIS

Synthesis of analogs of veraguamide A (**1**) is the primary target, due to its potent cytotoxicity, but once accomplished the same strategies could be applied to the other

members of the family for analog synthesis. Two type of analog proposed are: (1) removal of the esters within **1** in favor of amide bonds to determine the effect of said group upon cytotoxicity and (2) modification of proline. Synthesis of the enantiomer of **1** is also of interest, but will not be discussed at this time.

Amide Replacement

With the chemistry previously described the only variant in accessing **10** is the removal of the ester in the northwestern portion of **10** to the amide functionality to give **61**, scheme 23, as indicated by the red box. Compound **61** could be accessed from the coupling of **55**, previously delineated, to the newly synthesized tri-peptide **62**. Tri-peptide **62** can arise from the coupling of **51**, previously described, with L-isoleucine once Boc protection has been accomplished. Substituting **61** for **10** in scheme 21 will give access to one of the analogs to be screen for cytotoxicity.

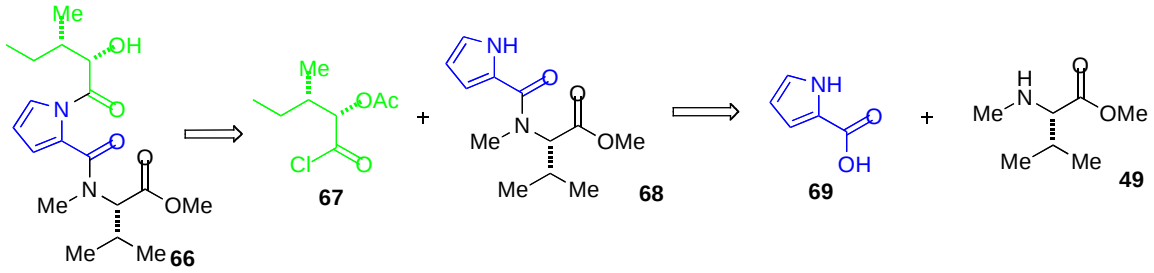


Scheme 23. Accessing the amide replacement **61** for **10**.

Substitution of the ester linkage in the southeastern portion of **1** is another analog of interest, keeping the northwestern ester. It is anticipated that this analog can come about via the Evan's auxiliary approach to **11**. Formation of the E-olefin should afford the *anti* analog of either **44** or **45**. Mesylation of the alcohol followed by either direct sodium amide or a protected amine source would give access to the desired *syn* amino species that can be further elaborated into the amino forms of **11** and **46**, referred to as **63** and **64** respectively. Replacing **11** or **46** in scheme 21 with either **63** or **64** will afford the southeastern amide analog of **1**.

Lastly, substituting both ester linkages for the amides will also be undertaken. It is anticipated that the chemistry outlined above can be utilized to access this "true" amide linked cyclic peptide **65**. The same type of amide substitution can also be employed in the analog synthesis of the other seven members of this family.

Substitution of the pyrrolidine ring with a more ridged pyrrole ring is also an analog of interest for cytotoxicity screening. Assessing **1** with this substitution is envisioned to come from **66**, scheme 24, which upon forming can be inserted in scheme 21 for elaboration into pyrrole analog **70** of veraguamide A (**1**). It is thought that **66** can arise from the addition of **68**, post NaH treatment, to the acid chloride of **67** to afford **66**. Compound **68** can be accessed from the coupling of **69**, commercially available, and **49**. In addition to the analogs outlined above, it is hoped that functional group "knock out" analogs can also be synthesized to help elucidate how **1** causes it cytotoxicity.



Scheme 24. Accessing pyrrole analog portion for pyrrole analog of **1**.

CYTOTOXICITY AND MODE OF ACTION STUDIES

Mode of action studies as well as all cytotoxicity evaluations will be conducted in Prof. Paul Hergenrother's Laboratory (during my Post-Doctoral Fellowship).

Conclusion

It is proposed that the total synthesis of the veraguamide family of natural products, which have been determined to have modest to potent cytotoxicity towards H-460 human lung cancer cell lines, as well as analogs can be accomplished via multiple peptide couplings as well as the synthesis of small molecules. The alkynyl acid compound required for the total synthesis has been proposed to arise from either a crotylation strategy or via the use of Evan's auxiliary. It is the authors hope that the analogs accessed, and/or functional group "knock out" studies can give insight to how these compounds cause their cytotoxicity as well as to help enhance their cytotoxicity.

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