Title
Synthetic studies of the Thio-Nazarov Cyclization, Biomimetic Total Syntheses of Shimalactones and Exiguamines, and Synthesis of Photoswitchable Dopamine Analogs

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Biomimetic Total Syntheses of Shimalactones and Exiguamines

Synthesis of Photoswitchable Dopamine Analogs

by

Vladimir Sofiyev

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Robert Bergman, Chair
Professor Dirk Trauner, Co-chair
Professor Richmond Sarpong
Professor Chris Vulpe

Fall 2010

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Abstract

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Biomimetic Total Syntheses of Shimalactones and Exiguamines

Synthesis of Photoswitchable Dopamine Analogs

Vladimir Sofiyev

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Robert Bergman, Chair

Professor Dirk Trauner, Co-Chair

Part 1 of this thesis describes progress towards thio-Nazarov electrocyclization utilizing substrates with a removable docking group, such as alkyl sulfides, for Lewis acid coordination. This work builds on the successful asymmetric catalysis of Nazarov electrocyclization using non-removable docking groups for coordination of Lewis acids.

Parts 2 and 3 of this thesis describe the biomimetic syntheses of the natural products shimalactones and exiguamines respectively. While the synthesis of alkaloids exiguamines A and B is an improvement of our previous work, the synthesis of polyketides shimalactones A and B is their first synthesis and describes a novel intramolecular addition of a β-ketolactone across a diene. Both syntheses feature pericyclic reactions in their key step biomimetic cascade reactions.

Part 4 of this thesis describes the synthesis of photoswitchable derivatives of dopamine, containing azobenzenes.

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Finally, I would like to extend special thanks to Emine Kaya for making my last year in graduate school the best time of my life. Your love, companionship, and motivation mean everything to me. You have given this work and my life a greater meaning.

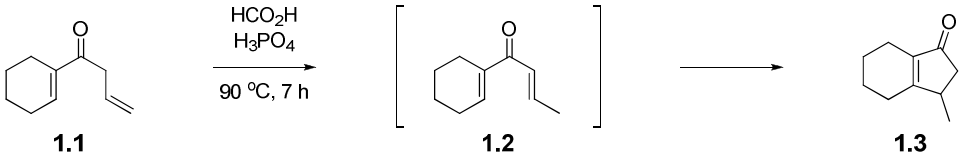
Berkeley, California, July 13, 2010.

Chapter 1. Progress Towards Thio-Nazarov Electrocyclization

1.1 Introduction

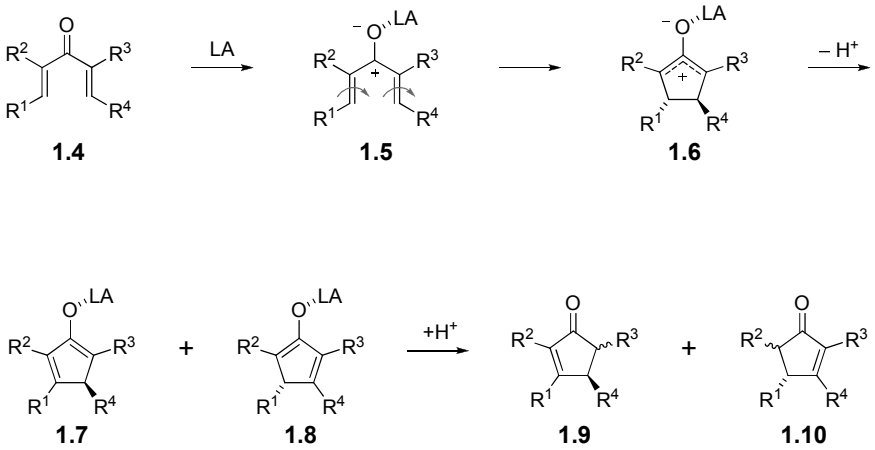
Over 60 years ago, Nazarov and coworkers discovered that in acidic media, allylvinyl ketone **1.1** could undergo an isomerization to divinyl ketone **1.2**, which could further cyclize to produce cyclopentenone **1.3** (Scheme 1.1).[1] This interesting acid catalyzed transformation of divinyl ketones to cyclopentenones drew a lot of attention from the synthetic community and was named the Nazarov cyclization.

Scheme 1.1. Discovery of the Nazarov cyclization.



Mechanistically, the Nazarov cyclization is a pericyclic 4π electrocyclization that results in conrotatory ring-closure under protic acid or Lewis acid catalysis (Scheme 1.2). Coordination of a proton or Lewis acid (LA) to the dienone substrate **1.4** triggers the electrocyclization of the pentadienyl cation **1.5**, followed by loss of a proton (**1.6** → **1.7** and **1.8**) and reprotonation of the resulting enolate (**1.7**, **1.8** → **1.9**, **1.10**).

Scheme 1.2. Mechanism of the Nazarov cyclization.

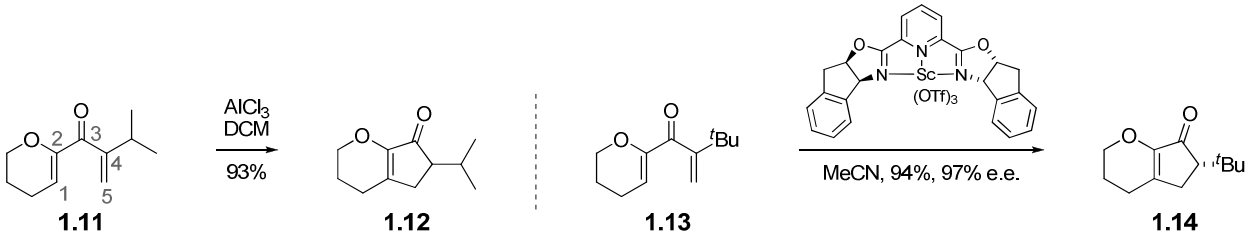


Ever since its discovery, the Nazarov cyclization has been developed into a very useful synthetic tool. It became one of the most versatile methods for the synthesis of five-membered carbocycles and has been used in the construction of numerous complex target molecules, including polyquinane natural products and prostanoids.[2] Modern variants are based on the directing effect of silicon containing substrates,[3] the interception of cationic intermediates,[4] or the use of highly reactive allene substrates.[5] There are also examples of the reverse reaction.[6]

1.2 Background

Our group became interested in the Nazarov cyclization during our work with guanacastepene antibiotics.[7] Previously we established the classes of substrates such as 2-alkoxy-1,4-pentadien-3-ones **1.11** and **1.13**, most of which contained a dihydropyran moiety, that participate in a Nazarov electrocyclization (Scheme 1.3).[8] This transformation was prone to catalysis by Lewis acids such as $AlCl_3$ and, in an asymmetric variant, a -scandium indane pybox in CH_2Cl_2 or MeCN solvent yielding cyclopentenones **1.12** and **1.14**.[9] Alkoxy substitution at the 2 position of the 1,4-pentadien-3-ones assured that good regioselctivity was obtained in the Nazorov reaction, i.e. double bond in the product is between carbon 1 and 2, not 4 and 5. In addition, good asymmetric induction in the proton transfer step was observed most probably due to a bidentate coordination of the substrates to the Lewis acid catalyst.

Scheme 1.3. 2-Alkoxy-1,4-pentadien-3-ones as Nazarov substrates.



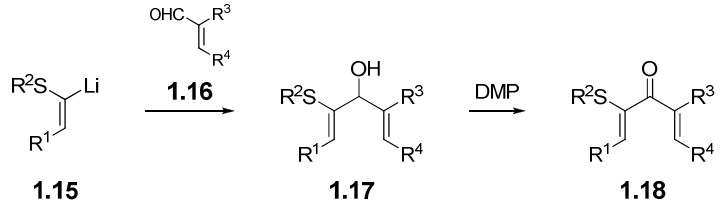
Motivated by these results, we envisaged that the oxygen atom in the alkoxy substituent could potentially be replaced by a sulfur. This would, in theory, still allow for coordination of the Lewis acids to the substrate in a bidentate fashion, controlling both the regio- as well as the enantioselectivity of the reaction. In addition, the ease with which carbon-sulfur bonds can be cleaved, for example, with Raney nickel,[10] without competitive reduction of double bonds would allow access to a wider range of targets.

1.3 Results and Discussion

1.3.1 Thio-Nazarov electrocyclization

To investigate the thio-Nazarov cyclization of 2-sulfido-1,4-pentadien-3-ones, a series of substrates were prepared based on a general synthetic strategy (Scheme 1.4). Addition of a lithiated vinyl sulfide **1.15**, such as ethyl vinyl sulfide, to an unsaturated aldehyde **1.16** readily afforded divinylcarbinol **1.17**. Subsequent oxidation using Dess-Martin periodinane (DMP) gave dienones **1.18**. Combined yields for the addition and oxidation steps are shown in Figure 1.1.

Scheme 1.4. General synthesis of 2-sulfido-1,4-pentadien-3-ones.



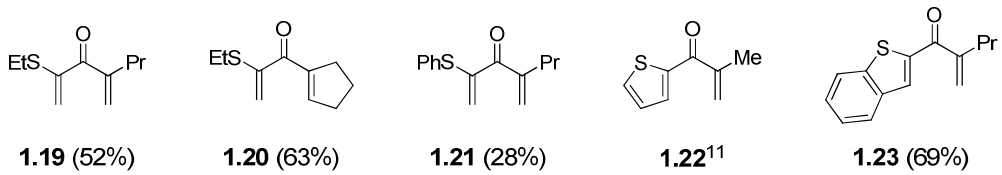
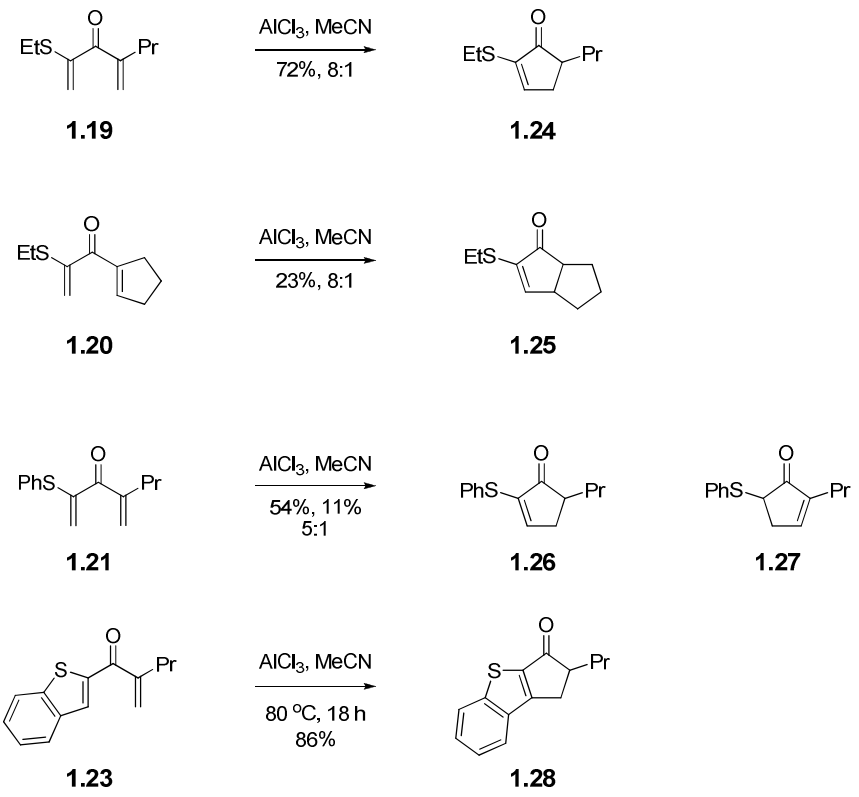


Figure 1.1. 2-sulfido-1,4-pentadien-3-one substrates synthesized.

A variety of Lewis and Brønsted acids were screened, such as $AlCl_3$, $Cu(OTf)_2$, $CuCl_2$, $Sc(OTf)_3$, [Cu(box)]$(OTf)_2$, [Cu(box)]$(SbF_6)_2$, $SnCl_4$, $TiCl_4$, $Ti(OiPr)_4$, $FeCl_3$, [Sc(indo-pybox)]$(OTf)_3$, [Fe(box)]Cl_3, [Fe(box)I_2]I_3,[12] Tf_2O, TfOH, and H_2SO_4. The Lewis acids that were found to be efficient in catalyzing the cyclization of 2-alkoxy-1,4-pentadien-3-ones in the previous work were also effective in this work. The $AlCl_3$-catalyzed reaction was the fastest and gave the best yields in the electrocyclization in both CH_2Cl_2 and MeCN solvents, while [Sc(indo-pybox)]$(OTf)_3$ resulted in slower reactions with lower yields. Scheme 1.5 shows the isolated products with the best yields and ratios of products. It became apparent that while sulfide substitution allowed us to predict the major product in the electrocyclization consistently, the ratios were not satisfactory, except for benzothiophenyl substrate **1.23** where the propensity to rearomatize resulted in a single isolated product **1.28**. Interestingly, previously known thiophenyl substrate **1.22** did not display the same reactivity and tended to polymerize, unless strongly acidic conditions, such as H_2SO_4, were used.[11] In that case the stepwise Friedel-Crafts mechanism is most likely at work instead of the concerted Nazarov electrocyclization.

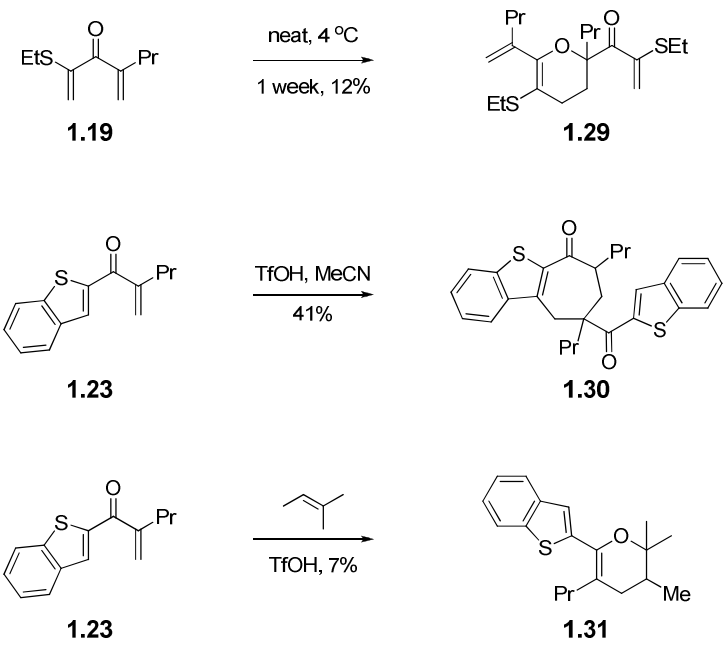
Scheme 1.5. Thio-Nazarov electrocyclizations.



1.3.2 Stability of thio-Nazarov substrates

During our initial work with the thio-Nazarov substrates we discovered that the yields in the electrocyclizations decreased as the age of the substrates increased. For example, freshly prepared **1.19** could be cyclized to **1.24** (Scheme 1.5) in 72% yield, while a day-old material would result in 37% yield. The decomposition was apparently quicker for **1.20** and **1.21**, which could not be stored for any length of time and had to be used immediately to obtain any of the products **1.25**, **1.26**, and **1.27** from the Nazarov reaction. As previously mentioned, thiophene-containing substrate **1.22** polymerized very quickly and could only be immediately treated with H_2SO_4 to undergo intramolecular Friedel-Crafts reaction. We were able to characterize the product of the major decomposition pathway for **1.19**. Upon storage this compound tends to form hetero Diels-Alder homodimer **1.29** (Scheme 1.6).

Scheme 1.6. Representative byproducts.



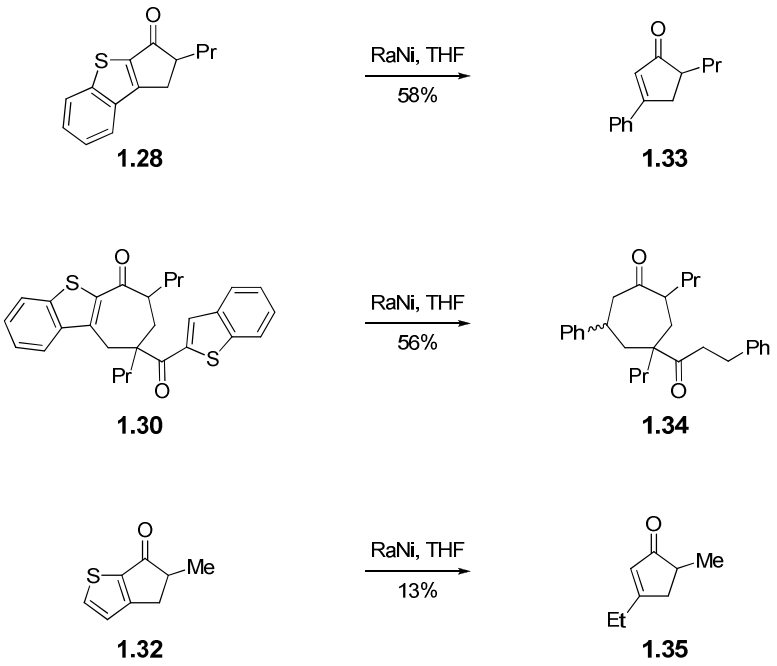
Surprisingly, benzothiophene-based substrate **1.23** was found to be rather stable. This compound did not show any signs of decomposition upon prolonged storage and required elevated temperatures and prolonged reaction times for conversion to cyclopentenone **1.28** (Scheme 1.5). However, when treated with triflic acid in an attempt to speed up the conversion of **1.23** to **1.28** the homodimer **1.30** was isolated along with the desired Nazarov product **1.28** (Scheme 1.6). This unusual product is presumably the result of [5+2] cycloaddition or interrupted Nazarov reaction. Although, this compound was isolated as a single diastereomer, the relative stereochemistry could not be determined. In order to explore this unprecedented mode of reactivity, we repeated this reaction in 2-methyl-2-butene and butyl vinyl ether as solvents. We were anticipating the isolation of the corresponding [5+2] cycloaddition products. However, the only isolable material was the hetero Diels-Alder product **1.31** obtained in low yield. It is evident that a polar solvent such as MeCN is required for this transformation.

1.3.3 Desulfurization

One of the primary goals of the project was to establish whether it was possible to cleave the carbon-sulfur bonds of the thio-Nazarov products using reagents such as Raney nickel in a robust and reproducible fashion. Scheme 1.7 illustrates the products isolated during this study. Desulfurization of **1.28** and **1.30** using Raney nickel resulted in isolation of **1.33** and **1.34** in modest yields. The latter was isolated as a separable mixture of diastereomers around the newly created stereocenter, the relative stereochemistry of which could not be determined. While cyclopentenone **1.35** was obtained in low yield from **1.32**, no isolable products could be obtained from the desulfurization attempts of **1.24**-**1.27**. This could be due to the high volatility of the desired compounds or due to the inability to visualize them by TCL on the small scales on which these experiments were performed. In addition to unsatisfactory yields, reactivity of Raney

nickel towards double bonds appeared unpredictable (Scheme 1.7, compare **1.33** to **1.34**). Another method for desulfurization of α-(alkylthio)ketones by the reaction with a thiolate anion was unsuccessful in our hands.[13]

Scheme 1.7. Desulfurization.



1.3.4 Asymmetric thio-Nazarov attempts

During the initial screening of Lewis acids we identified [Sc(indo-pybox)](OTf)$_3$ as the only chiral Lewis acid capable of catalyzing the Nazarov reaction. It was tested against substrates **1.19** and **1.23**. While for substrate **1.19** 10 to 18 days were required for the consumption at RT with maximum yield of 36% for the Nazarov product, benzothiophene-containing substrate **1.23** could only be converted to the corresponding Nazarov product **1.28** in 2% yield after heating the reaction mixture in a sealed tube at 180 ^{o}C for 14 h. We were able to confirm the transfer of chiral information (e.e. = 29% for **1.24** and e.e. = 3.7% for **1.28**) with the help of chiral HPLC analysis. However, due to the long reaction times, the starting materials decomposed quicker than the reaction proceeded, resulting in low yields. Thus, the [Sc(indo-pybox)](OTf)$_3$-catalyzed Nazarov reaction proved to be completely impractical.

1.3.5 Conclusions

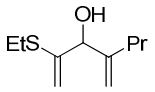
Preliminary studies of the thio-Nazarov reaction were undertaken using substrates **1.19**-**1.23**. We found that the racemic version of the reaction using $AlCl_3$ as a catalyst could be a useful synthetic tool. However, due to the instability of the substrates, the thio-Nazarov reaction needs to always be carried out using freshly prepared substrates. While carbon-sulfur bond cleavage with Raney nickel can be used in synthesis, it is by no means a robust method. Special care must be exercised with substrates where competitive reduction of double bonds can occur.

Finally, a cursory study of the asymmetric thio-Nazarov reaction using [Sc(indo-pybox)](OTf)$_3$ as a Lewis acid catalyst proved it to be impractical for organic synthesis. Further investigations are required in order to make the thio-Nazarov reaction a practical synthetic tool.

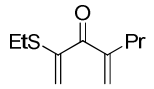
1.4 Experimental

1.4.1 Synthetic Procedures

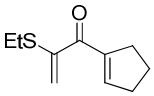
General methods. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} TLC plates and visualized using charring solutions of potassium permanganate or 2,4-dinitrophenylhydrazine. Reactions were carried out under inert atmosphere in oven-dried glassware and were magnetically stirred. Ether and THF were purified by passage over activated alumina according to the procedure described by Bergman.[14] MeCN was distilled from CaH_2 immediately prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried over $MgSO_4$ unless otherwise indicated. NMR spectra were measured using Brüker AV 300, AVQ 400, AVB 400, and DRX 500 spectrometers in $CDCl_3$ and calibrated from residual solvent signal (7.26 for ^{1}H and 77.23 for ^{13}C). IR spectra were measured using Genesis FT-IR spectrometer by evaporative thin film on a NaCl plate. Low and high resolution mass spectra (LRMS and HRMS) were obtained using the Micro-Mass Facility operated by the College of Chemistry, University of California, Berkeley on VG ProSpec Mass Spectrometer by electron impact (EI) at 70 eV. Enantiomeric excess was determined on a Shimadzu VP Series Chiral HPLC, using the Chiral PAK AD-H, Chiral PAK OD-H, or Regis Technologies WHELK-O 1 columns, eluting with a flow-rate of 1 mL/min.



1.17a. To a solution of ethyl vinyl sulfide (1.90 mL, 18.7 mmol) in THF (72 mL) and HMPA (8.0 mL) at –70 °C was added dropwise a 1.4 M solution of *s*-BuLi in hexanes (16.0 mL, 22.4 mmol). After 30 min 2-propyl-crotonal (2.2 mL, 18.8 mmol) was added dropwise. The reaction mixture was stirred for 30 min at –70 °C, warmed to RT in 30 min, quenched with water (100 mL), and extracted with ether (60 mL and 2 x 30 mL). The combined organic extracts were washed with brine (40 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) afforded **1.17a** (2.41 g, 69%) as a yellow oil. Data for **1.17a**: R_f 0.15 (10% EtOAc/hexanes); IR 3411, 2260, 2341 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.42 (s, 1H), 5.21 (s, 1H), 4.98 (s, 1H), 4.91 (s, 1H), 4.62 (d, 1H, *J* = 4.9 Hz), 2.73 (q, 2H, *J* = 7.4 Hz), 2.21 (d, 1H, *J* = 4.5 Hz), 2.05 – 1.90 (m, 2H), 1.49 (m, 2H), 1.29 (t, 3H, *J* = 7.4 Hz), 0.91 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz) δ 148.6, 147.0, 111.0, 108.3, 78.1, 34.0, 25.6, 21.1, 14.1, 13.4; HRMS (EI) calculated for $C_{10}H_{18}OS$ $(M)^+$: 186.1078, found: 186.1075.

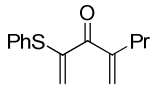


1.19. To a solution of alcohol **1.17a** (282 mg, 1.51 mmol) in CH_2Cl_2 (10 mL) and pyridine (1.0 mL) was added Dess-Martin periodinane (776 mg, 1.83 mmol) followed by a second portion of DMP (160 mg, 0.377 mmol) after 15 min. After 10 min the reaction mixture was poured onto a mixture of water/saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (10/10/10 mL) and stirred for 15 min. Phases were allowed to separate and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.19** (212 mg, 76%) as a yellow oil. Data for **1.19**: R_f 0.30 (5% EtOAc/hexanes); IR 1658 cm^{-1}; ^1H NMR (400 MHz) δ 5.79 (s, 1H), 5.70 (s, 1H), 5.67 (s, 1H), 5.52 (s, 1H), 2.68 (q, 2H, *J* = 7.4 Hz), 2.27 (t, 2H, *J* = 7.6 Hz), 1.40 (sextet, 2H, *J* = 7.5 Hz), 1.25 (t, 3H, *J* = 7.4 Hz), 0.86 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz) δ 196.0, 147.2, 145.3, 125.3, 118.8, 34.0, 25.4, 21.3, 13.8, 13.3; HRMS not obtained (compound unstable under conditions).



1.20. To a solution of ethyl vinyl sulfide (1.60 mL, 15.8 mmol) in THF (54 mL) and HMPA (6.0 mL) at –70 °C was added dropwise a 1.4 M solution of *s*-BuLi in hexanes (13.5 mL, 18.9 mmol). After 30 min 1-formyl-cyclohexene (1.43 mL, 14.8 mmol) was added dropwise. The reaction mixture was stirred for 30 min at –70 °C, warmed to RT in 30 min, quenched with water (70 mL), and extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried, filtered, and concentrated to afford 4.0 g of orange oil that was used without further purification.

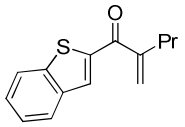
To a solution of foregoing alcohol in CH_2Cl_2 (80 mL) and pyridine (8.0 mL) was added Dess-Martin periodinane (8.65 g, 20.4 mmol) followed by a second portion of DMP (835 mg, 1.97 mmol) after 20 min. After 40 min the reaction mixture was poured onto a solution of NaOH (1 M, 100 mL) and stirred for 15 min. The phases were allowed to separate and the aqueous layer was removed and extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (20 mL) and then dried, filtered, and concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes) afforded **1.20** (1.71 g, 63% over two steps) as a light-yellow oil. Data for **1.20**: R_f 0.39 (10% Et_2O/pentane); IR 1642 cm^{-1}; ^1H NMR (300 MHz) δ 6.57 (s, 1H), 5.66 (s, 1H), 5.34 (s, 1H), 2.57 (q, 2H, *J* = 7.4 Hz), 2.44 (m, 4H), 1.79 (m, 2H), 1.14 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz) δ 191.3, 146.8, 145.3, 143.1, 116.8, 34.0, 31.3, 25.1, 22.5, 13.2; HRMS (EI) calculated for $C_{10}H_{14}OS$ $(M)^+$: 182.0765, found: 182.0764.



1.21. To a solution of TMEDA (0.59 mL, 3.91 mmol) in THF (12 mL) was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (1.9 mL, 4.75 mmol) and the reaction mixture was cooled to –78 °C. Phenyl vinyl sulfide (0.50 mL, 3.91 mmol) was added slowly; the reaction mixture was warmed to RT over 30 min, and cooled back to –78 °C. 2-Propyl-crotonal (0.50 mL, 4.28 mmol) was added and the reaction mixture was warmed to RT over 15 min when it was quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded alcohol intermediate (531 mg, 58%) as a colorless oil that was immediately used in the next step.

To a solution of alcohol (531 mg, 2.26 mmol) in CH_2Cl_2 (20 mL) and pyridine (2.0 mL) was added Dess-Martin periodinane (1.53 g, 3.61 mmol). After 15 min at RT the reaction mixture was poured onto 1 M solution of NaOH (20 mL) and stirred for 3 h. Phases were allowed to separate and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), brine (20 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.21** (251 mg, 48%) as a yellow oil.

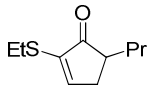
Data for **1.21**: R_f 0.61 (5% EtOAc/hexanes); IR 1705, 1666 cm^{-1}; ^1H NMR (500 MHz) δ 7.47 (m, 2H), 7.35 (m, 3H), 5.86 (s, 1H), 5.77 (s, 1H), 5.70 (s, 1H), 5.41 (s, 1H), 2.28 (t, 2H, J = 7.6 Hz), 1.39 (sextet, 2H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz) δ 195.4, 147.3, 146.7, 134.6, 131.4, 129.7, 129.0, 125.1, 122.0, 34.2, 21.3, 13.9; HRMS (EI) calculated for $C_{14}H_{16}OS$ $(M)^+$: 232.0922, found: 232.0926.



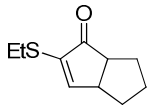
1.23. To a solution of benzothiophene (2.02 g, 15.0 mmol) in ether (10 mL) at 0 °C was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (7.5 mL, 18.8 mmol). The reaction mixture was heated to reflux for 1.5 h, cooled to 0 °C, and 2-propyl-crotonal (1.48 g, 15.1 mmol) was added as a solution in ether (10 mL). The reaction mixture was stirred for 40 h at RT, quenched with saturated aqueous NH_4Cl (20 mL), and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried, filtered, and concentrated to afford 3.54 g of orange oil that was used without further purification.

To a solution of crude alcohol in CH_2Cl_2 (50 mL) and pyridine (5.0 mL) at 0 °C was added Dess-Martin periodinane (10.0 g, 23.6 mmol). After 30 min at RT the reaction mixture was poured onto 1 M solution of NaOH (65 mL) and stirred for 1 h. Phases were allowed to separate and the aqueous phase was extracted with DCM (2 x 20 mL). Combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), brine (20 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.23** (2.38 g, 69% over

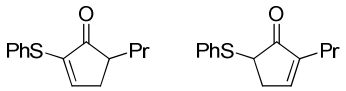
two steps) as a yellow oil. Data for **1.23**: R_f 0.23 (5% EtOAc/hexanes); IR 1639 cm^{-1}; ^1H NMR (400 MHz) δ 7.88 (s, 1H), 7.84 (m, 2H), 7.40 (m, 2H), 5.82 (s, 1H), 5.76 (s, 1H), 2.47 (t, 2H, J = 7.5 Hz), 1.54 (sextet, 2H, J = 7.5 Hz), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz) δ 191.4, 148.3, 143.4, 142.7, 139.0, 131.2, 127.4, 126.1, 125.0, 123.2, 122.9, 34.9, 21.4, 13.8; HRMS (EI) calculated for $C_{14}H_{14}OS$ $(M)^+$: 230.0765, found: 230.0767.



1.24. A solution of dienone **1.19** (56.8 mg, 0.308 mmol) in MeCN (2.0 mL) was added to a solution of $AlCl_3$ (8.9 mg, 0.067 mmol) in MeCN (2.0 mL) and stirred for 1 h at RT. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (10 mL and 2 x 5 mL). Combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.24** (41.1 mg, 72%) as a yellow oil. Data for **1.24**: R_f 0.36 (10% EtOAc/hexanes); IR 1704 cm^{-1}; ^1H NMR (400 MHz) δ 7.10 (t, 1H, J = 3.0 Hz), 2.84 (m, 3H), 2.44 (m, 1H), 2.32 (dt, 1H, J_d = 18.8 Hz, J_t = 2.6 Hz), 1.80 (m, 1H), 1.37 (m, 3H), 1.31 (t, 3H, J = 7.4 Hz), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz) δ 208.2, 151.4, 141.3, 45.5, 34.7, 33.8, 25.0, 20.6, 14.2, 14.1; HRMS (EI) calculated for $C_{10}H_{16}OS$ $(M)^+$: 184.0922, found: 184.0925.



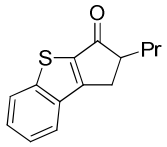
1.25. A solution of dienone **1.20** (111 mg, 0.610 mmol) in MeCN (2.0 mL) was added to a solution of $AlCl_3$ (81.4 mg, 0.610 mmol) in MeCN (4.0 mL) and the bright-yellow reaction mixture was stirred over night at RT. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (10 mL and 2 x 5 mL). Combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **1.25** (25.6 mg, 23%) as a yellow oil. Data for **1.25**: R_f 0.38 (15% EtOAc/hexanes); IR 1708 cm^{-1}; ^1H NMR (400 MHz) δ 6.95 (s, 1H), 3.31 (m, 1H), 2.83 (m, 3H), 1.95 (m, 1H), 1.76 – 1.55 (m, 5H), 1.29 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz) δ 209.3, 155.8, 142.1, 50.3, 45.4, 30.5, 30.3, 25.1, 23.8, 14.0; HRMS (EI) calculated for $C_{10}H_{14}OS$ $(M)^+$: 182.0765, found: 182.0766.



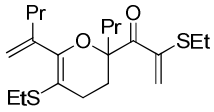
1.26 and **1.27**. A solution of dienone **1.21** (67.0 mg, 0.288 mmol) in MeCN (2.0 mL) was added to a solution of $AlCl_3$ (7.0 mg, 0.052 mmol) in MeCN (2.0 mL) and the bright-yellow reaction mixture was stirred over night at RT. The reaction mixture was quenched with saturated aqueous solution of Rochelle salt (5 mL), stirred for 2 h, and extracted with EtOAc (3 x 10 mL). Combined organic extracts were washed with brine (10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.26** (36.5 mg, 54%) and **1.27** (7.6 mg, 11%) as yellow oils.

Data for **1.26**: R_f 0.40 (5% EtOAc/hexanes); IR 1704 cm^{-1}; ^1H NMR (400 MHz) δ 7.46 (m, 2H), 7.34 (m, 3H), 6.90 (t, 1H, J = 3.0 Hz), 2.77 (ddd, 1H, J_1 = 19.0 Hz, J_2 = 6.5 Hz, J_3 = 3.1 Hz), 2.49 (m, 1H), 2.26 (dt, 1H, J_d = 19.1 Hz, J_t = 2.5 Hz), 1.81 (m, 1H), 1.37 (m, 3H), 0.92 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 207.1, 154.1, 142.4, 133.6, 131.3, 129.6, 128.6, 45.8, 34.5, 33.7, 20.5, 14.2; HRMS (EI) calculated for $C_{14}H_{16}OS$ $(M)^+$: 232.0922, found: 232.0921.

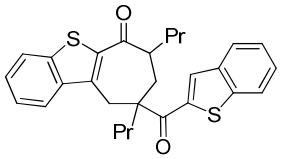
Data for **1.27**: R_f 0.33 (5% EtOAc/hexanes); IR 1705 cm^{-1}; ^1H NMR (400 MHz) δ 7.45 (m, 2H), 7.27 (m, 3H), 7.18 (s, 1H), 3.75 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 3.08 (m, 1H), 2.58 (m, 1H), 2.15 (m, 2H), 1.48 (m, 2H), 0.89 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz) δ 205.6, 155.5, 145.6, 133.3, 132.6, 129.1, 127.9; HRMS (EI) calculated for $C_{14}H_{16}OS$ $(M)^+$: 232.0922, found: 232.0922.



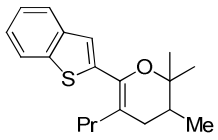
1.28. A solution of enone **1.23** (68.8 mg, 0.299 mmol) in MeCN (3.0 mL) was added to a solution of $AlCl_3$ (46.8 mg, 0.351 mmol) in MeCN (3.0 mL) and the bright-yellow reaction mixture was heated to 80 °C for 18 h. The reaction mixture was quenched with saturated aqueous solution of Rochelle salt (5 mL) and stirred for 2.5 h. The mixture was then extracted with EtOAc (2 x 10 mL), and combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.28** (58.9 mg, 86%) as a yellow oil. Data for **1.28**: R_f 0.33 (10% EtOAc/hexanes); IR 1699 cm^{-1}; ^1H NMR (400 MHz) δ 7.86 (m, 2H), 7.46 (m, 2H), 3.35 (dd, 1H, J_1 = 17.4 Hz, J_2 = 6.7 Hz), 3.03 (m, 1H), 2.85 (dd, 1H, J_1 = 17.4 Hz, J_2 = 2.5 Hz), 1.97 (m, 1H), 1.48 (m, 3H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz) δ 201.2, 163.8, 148.4, 140.6, 134.4, 128.3, 125.2, 124.6, 123.7, 51.6, 34.1, 29.9, 20.6, 14.2; HRMS (EI) calculated for $C_{14}H_{14}OS$ $(M)^+$: 230.0765, found: 230.0768.



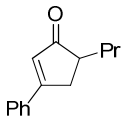
1.29. Dienone **1.19** (98.6 mg) was stored neat at 4 °C for 1 week. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.29** (12.2 mg, 12%) as a yellow oil. Data for **1.29**: R_f 0.30 (5% EtOAc/hexanes); IR 1678 cm^{-1}; ^1H NMR (400 MHz) δ 6.38 (s, 1H), 5.70 (s, 1H), 5.21 (s, 1H), 5.09 (s, 1H), 2.62 – 2.51 (m, 4H), 2.31 – 2.19 (m, 4H), 1.49 – 1.41 (m, 4H), 1.25 – 1.15 (m, 10H), 0.95 – 0.85 (m, 6H); ^{13}C NMR (100 MHz) δ 197.1, 152.8, 145.3, 143.3, 125.1, 118.5, 103.4, 88.6, 37.2, 35.7, 29.9, 29.5, 26.3, 24.6, 23.7, 21.8, 21.0, 15.0, 14.3, 14.1, 14.0; HRMS (EI) calculated for $C_{20}H_{32}O_2S_2$ $(M)^+$: 368.1844, found: 368.1850.



1.30. A solution of enone **1.16** (104 mg, 0.451 mmol) in MeCN (5.0 mL) was treated with triflic acid (70 μL, 0.79 mmol) and the golden-yellow reaction mixture was stirred at RT for 40 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (6 mL) and stirred for 15 min. The biphasic mixture was then extracted with EtOAc (3 x 10 mL), and combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.28** (61.6 mg, 59%) along with **1.30** (42.1 mg, 41%) as yellow oils. Data for **1.30**: R_f 0.25 (10% EtOAc/hexanes); IR 1693, 1651 cm^{-1}; ^1H NMR (400 MHz) δ 7.46 (d, 1H, J = 7.8 Hz), 7.36 (m, 3H), 7.19 (m, 2H), 7.11 (s, 1H), 6.96 (m, 2H), 3.18 (m, 1H), 2.93 (d, 1H, J = 18.4 Hz), 2.87 (d, 1H, J = 18.4 Hz), 2.48 (dd, 1H, J_1 = 13.8 Hz, J_2 = 10.9 Hz), 1.98 (dd, 1H, J_1 = 13.8 Hz, J_2 = 1.8 Hz), 1.64 (m, 3H), 1.45 (m, 1H), 1.26 (m, 4H), 0.88 (t, 3H, J = 7.2 Hz), 0.80 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz) δ 203.5, 199.9, 164.4, 147.8, 144.3, 142.5, 140.7, 138.7, 133.6, 128.5, 128.2, 127.2, 126.1, 124.7, 124.6, 123.5, 123.2, 122.5, 58.3, 44.0, 41.9, 41.5, 38.5, 34.0, 20.8, 17.7, 14.8, 14.3; HRMS (EI) calculated for $C_{28}H_{28}O_2S_2$ $(M)^+$: 460.1531, found: 460.1539.

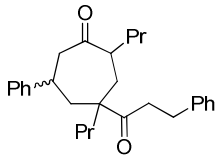


1.31. A solution of enone **1.23** (32.1 mg, 0.139 mmol) in 2-methyl-2-butene (0.50 mL, 4.7 mmol) was treated with triflic acid (30 μL, 0.34 mmol) and the dark-red reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and quenched with saturated aqueous $NaHCO_3$ (6 mL). The aqueous phase was then extracted with EtOAc (2 x 10 mL), and combined organic extracts were washed with brine (10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (4% EtOAc/hexanes) afforded **1.31** (2.4 mg, 7%) as a yellow oil. Data for **1.31**: R_f 0.64 (10% EtOAc/hexanes); ^1H NMR (400 MHz) δ 7.75 (m, 2H), 7.29 (m, 3H), 2.24 (m, 3H), 1.84 (m, 2H), 1.53 (sextet, 2H, J = 7.5 Hz), 1.35 (s, 3H), 1.17 (s, 3H), 0.98 (d, 3H, J = 6.6 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz) δ 143.4, 140.2, 139.82, 139.77, 124.2, 123.6, 122.3, 122.2, 112.6, 106.8, 100.4, 36.1, 34.7, 32.8, 27.3, 22.0, 19.3, 16.8, 14.3; HRMS (EI) calculated for $C_{19}H_{24}OS$ $(M)^+$: 300.1548, found: 300.1544.



1.33. A solution of cyclopentenone **1.28** (53.5 mg, 0.232 mmol) in THF (5.0 mL) was treated with slurry of Raney Nickel in water (tip of the spatula) and stirred at RT for 16 h when no changes could be observed by TLC. Reaction mixture was passes through a silica plug and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) afforded **1.33**

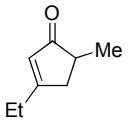
(26.8 mg, 58%) as a colorless oil. Data for **1.33**: R_f 0.20 (10% EtOAc/hexanes); IR 1691 cm^{-1}; ^1H NMR (500 MHz) δ 7.64 (m, 2H), 7.45 (m, 3H), 6.53 (t, 1H, J = 3.4 Hz), 3.21 (ddd, 1H, J_1 = 18.0 Hz, J_2 = 6.8 Hz, J_3 = 1.7 Hz), 2.70 (dt, 1H, J_d = 18.1 Hz, J_t = 2.1 Hz), 2.57 (m, 1H), 1.86 (m, 1H), 1.44 (m, 3H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz) δ 211.8, 172.6, 134.2, 131.4, 129.1, 127.0, 126.9, 46.3, 35.6, 34.0, 20.7, 14.3; HRMS (EI) calculated for $C_{14}H_{16}O$ $(M)^+$: 200.1201, found: 200.1202.



1.34a and **1.34b.** A solution of dimer **1.30** (74.7 mg, 0.179 mmol) in THF (5.0 mL) was treated with slurry of Raney Nickel in water (tip of the spatula) and stirred at RT for 18 h when no changes could be observed by TLC. Reaction mixture was passes through a silica plug and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **1.34a** (17.2 mg, 26%) and **1.34b** (19.8 mg, 30%) as a colorless oils.

Data for **1.34a**: R_f 0.20 (10% EtOAc/hexanes); IR 1732, 1709 cm^{-1}; ^1H NMR (400 MHz) δ 7.41 – 7.21 (m, 10H), 3.69 (m, 1H), 2.94 – 2.73 (m, 6H), 2.48 (dd, 1H, J_1 = 14.3 Hz, J_2 = 10.2 Hz), 2.22 (dd, 1H, J_1 = 18.8 Hz, J_2 = 11.8 Hz), 2.15 (ddd, 1H, J_1 = 12.8 Hz, J_2 = 6.4 Hz, J_3 = 2.1 Hz), 1.98 (t, 1H, J = 12.4 Hz), 1.59 – 1.13 (m, 9H), 0.96 (t, 3H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz) δ 212.7 (two signals), 143.8, 141.8, 128.8, 128.7, 128.6, 127.1, 126.7, 126.1, 53.1, 46.4, 46.3, 44.34, 44.25, 37.7, 37.1, 35.7, 35.5, 29.6, 20.5, 17.8, 14.9, 14.3; HRMS (EI) calculated for $C_{28}H_{32}O_2$ $(M)^+$: 404.2715, found: 404.2719.

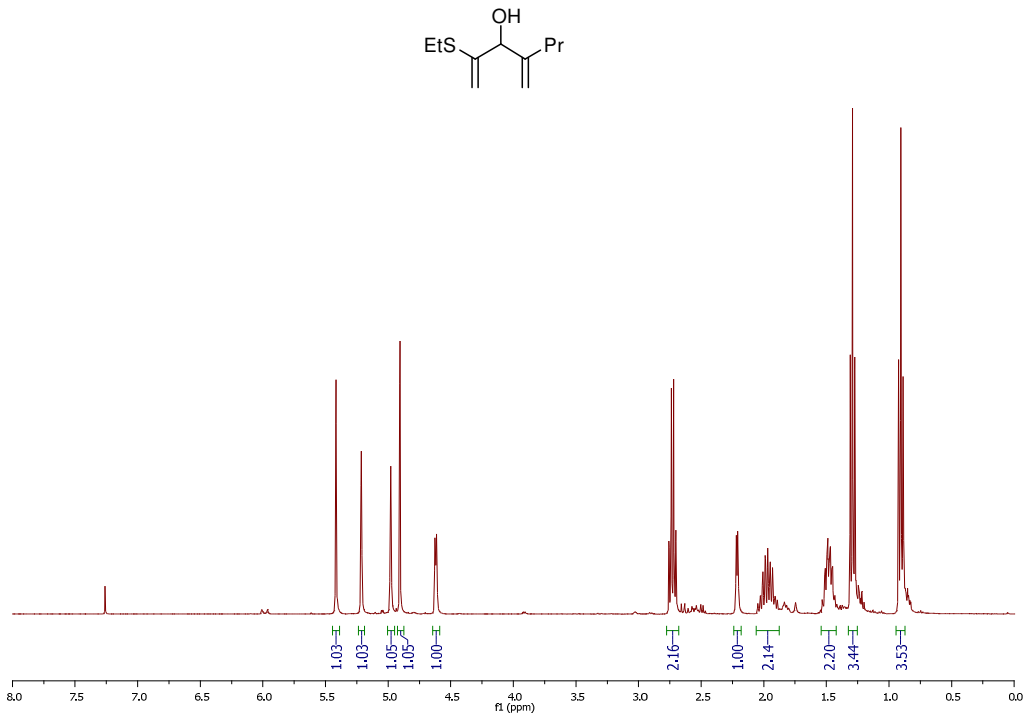
Data for **1.34b**: R_f 0.18 (10% EtOAc/hexanes); IR 1734, 1711 cm^{-1}; ^1H NMR (400 MHz) δ 7.41 – 7.20 (m, 10H), 3.39 (m, 1H), 2.94 – 2.72 (m, 5H), 2.54 (m, 1H), 2.46 (dd, 1H, J_1 = 18.2 Hz, J_2 = 12.2 Hz), 2.30 (ddd, 1H, J_1 = 13.1 Hz, J_2 = 6.7 Hz, J_3 = 1.9 Hz), 2.18 (dd, 1H, J_1 = 14.4 Hz, J_2 = 9.1 Hz), 1.73 (t, 1H, J = 12.5 Hz), 1.61 (dd, 1H, J_1 = 14.4 Hz, J_2 = 2.6 Hz), 1.51 – 1.22 (m, 8H), 0.96 (t, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 212.7 (two signals), 143.6, 141.5, 128.9, 128.62, 128.59, 126.9 (two signals), 126.2, 53.1, 48.5, 46.0, 43.9, 42.9, 38.2, 38.0, 36.4, 35.9, 29.8, 20.5, 17.6, 14.9, 14.3; HRMS (EI) calculated for $C_{28}H_{32}O_2$ $(M)^+$: 404.2715, found: 404.2716.



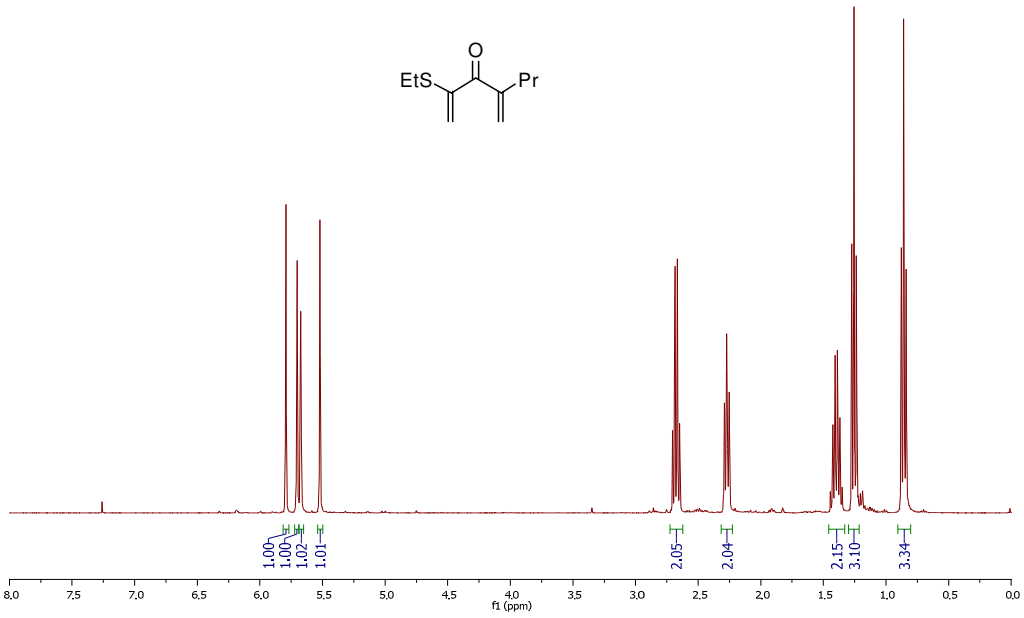
1.35. A solution of cyclopentenone **1.32** (69.6 mg, 0.457 mmol) in Et_2O (5.0 mL) was treated with slurry of Raney Nickel in water (tip of the spatula) and stirred at RT for 2 h when no further changes could be observed by TLC. Reaction mixture was passes through a Celite plug and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) afforded **1.35** (7.4 mg, 13%) as a colorless oil. Data for **1.35**: R_f 0.15 (10% EtOAc/hexanes); IR 1705, 1616 cm^{-1}; ^1H NMR (400 MHz) δ 5.90 (t, 1H, J = 1.5 Hz), 2.82 (m, 1H), 2.40 (m, 3H), 2.17 (m, 1H),

1.18 (m, 6H); ^{13}C NMR (100 MHz) δ 212.9, 182.8, 127.5, 40.9, 40.5, 26.9, 16.7, 11.6; HRMS (EI) calculated for $C_8H_{12}O$ $(M)^+$: 124.0888, found: 124.0889.

1.4.2 Selected NMR Spectra 1.17a



1.19


O
EtS
Pr
1.00
1.00
1.02
1.01
2.05
2.04
2.15
3.10
3.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
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f1 (ppm)

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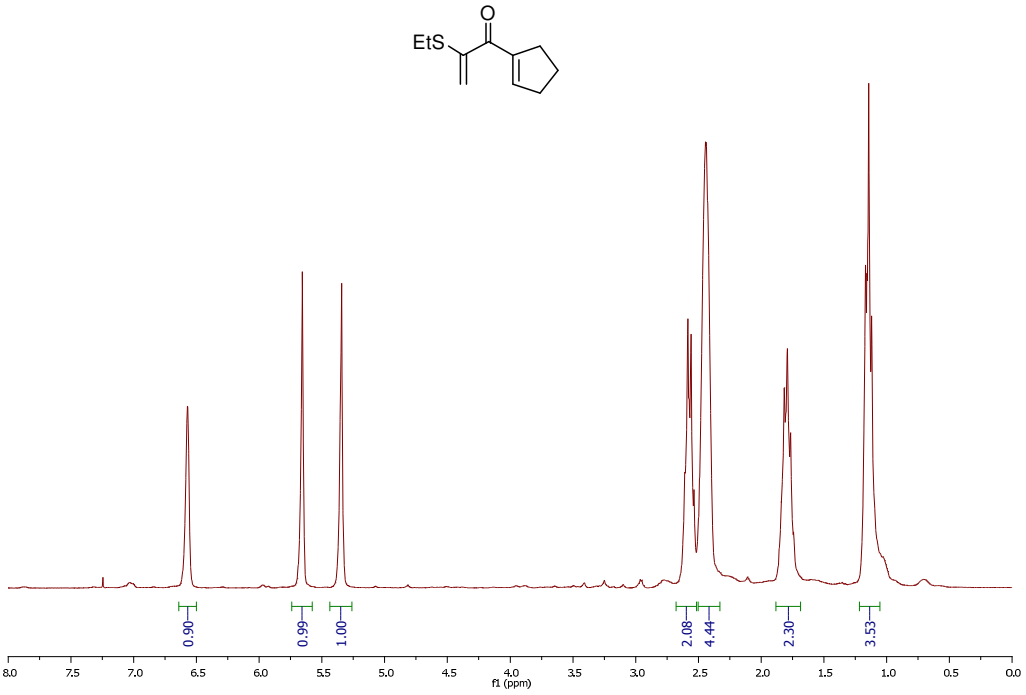
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EtS
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0.99
1.00
2.08
4.44
2.30
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.0
1.5
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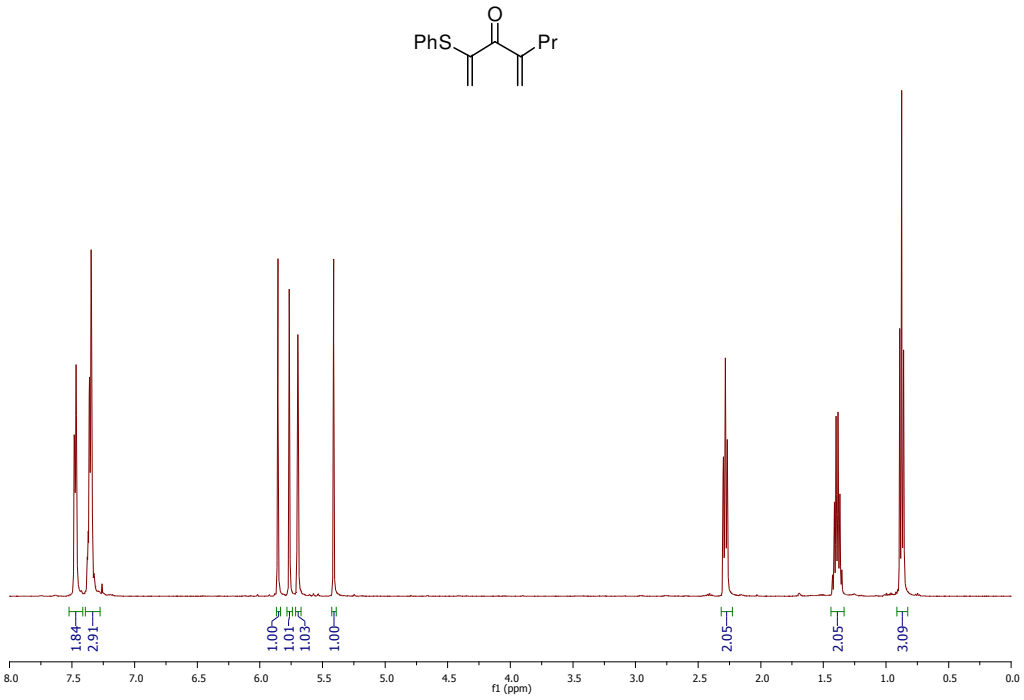
f1 (ppm)

1.21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O
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2.05
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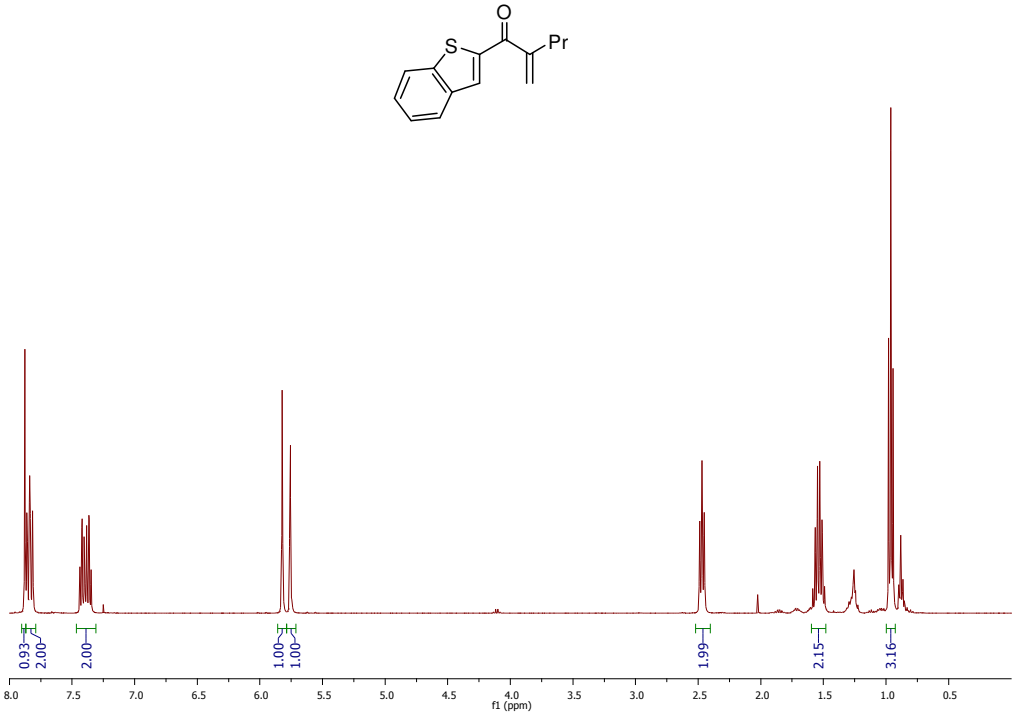
f1 (ppm)

1.23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O
Pr
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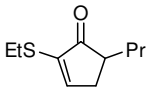
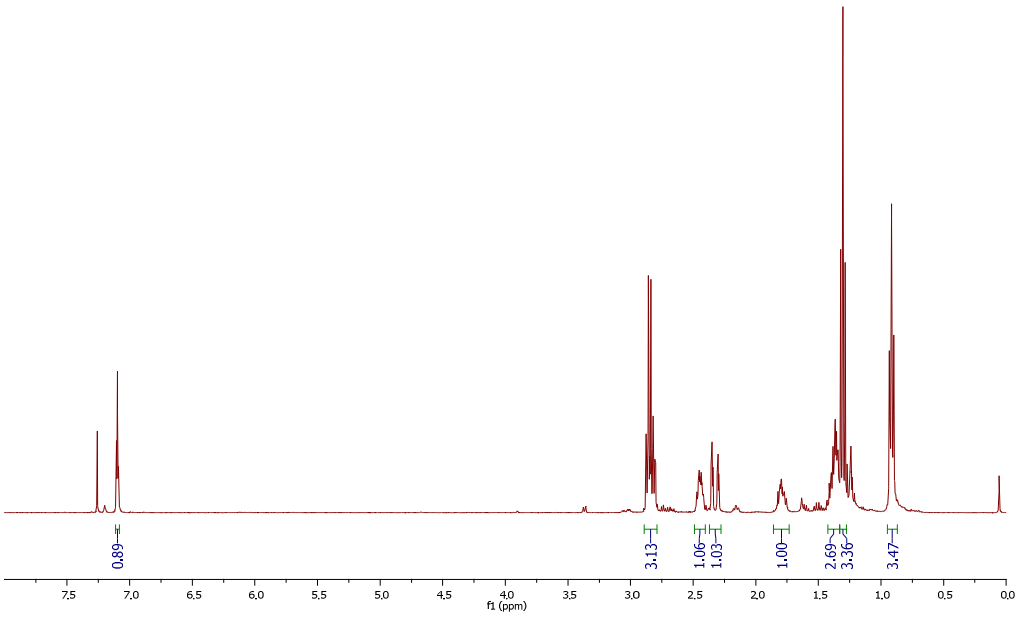
1.00
1.99
2.15
3.16
f1 (ppm)

1.24


O
EtS
Pr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1.00
2.69
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3.47
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7.0
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5.5
5.0
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4.0
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3.0
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2.0
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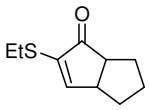
0.5
0.0
f1 (ppm)

1.25


O
EtS

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1.00
3.20
1.23
4.86
3.78
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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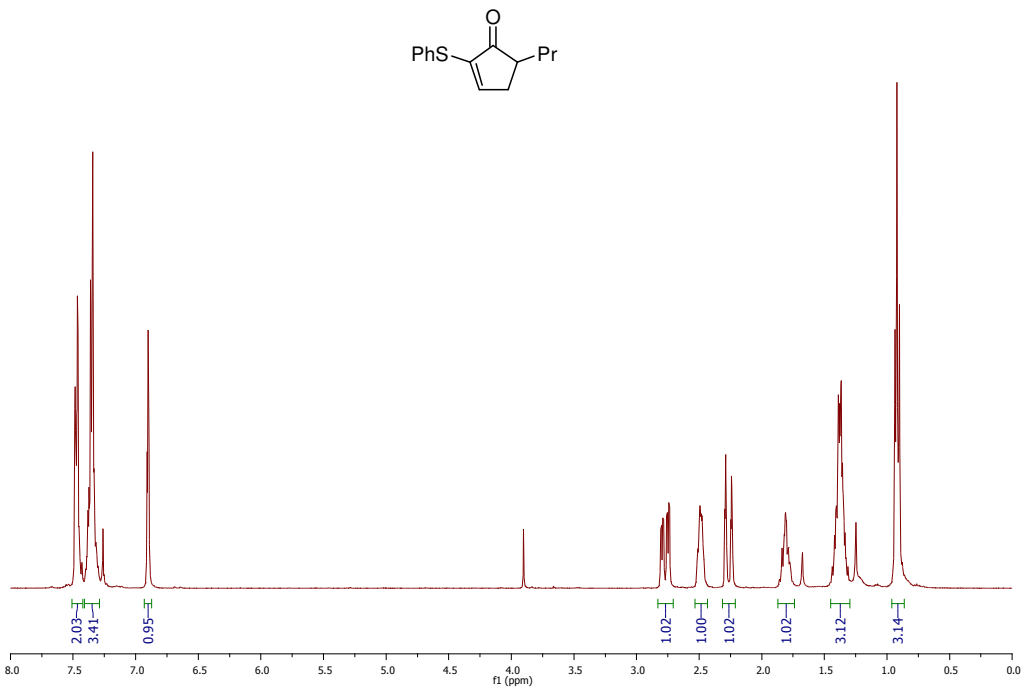
1.0
0.5
0.0
f1 (ppm)

1.26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PhS
Pr
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3.12
3.14
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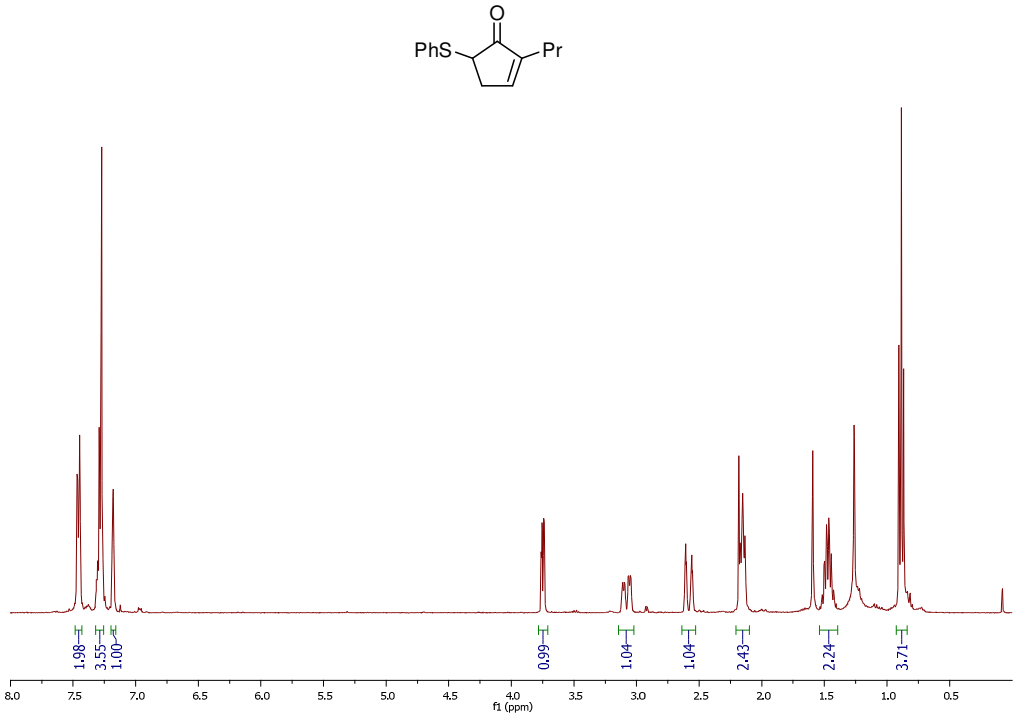
1.27


O
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Pr
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0.99
1.04
1.04
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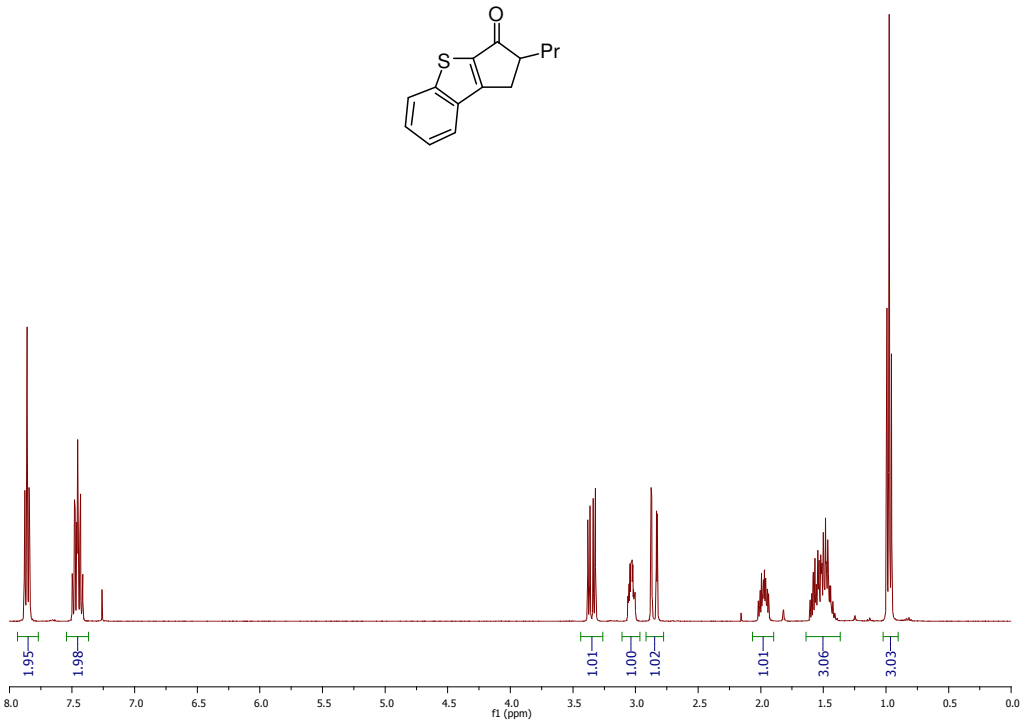
f1 (ppm)

1.28


O
S
Pr
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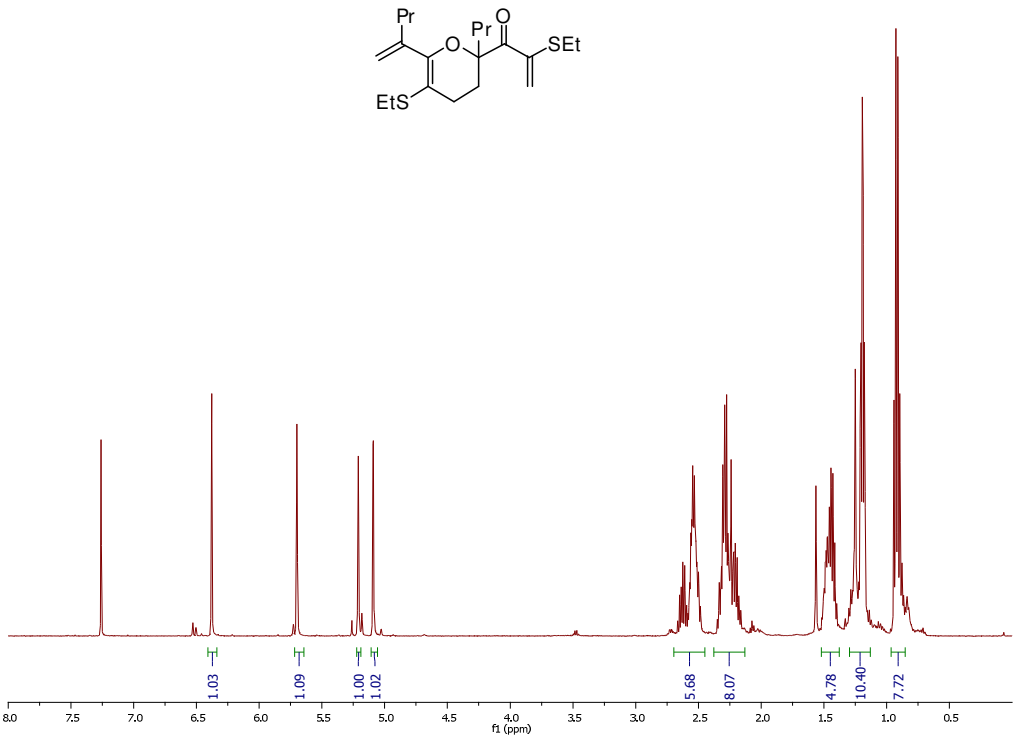
1.98
1.01
1.00
1.02
1.01
3.06
3.03
f1 (ppm)

1.29


Pr
Pr
O
O
SEt
EtS
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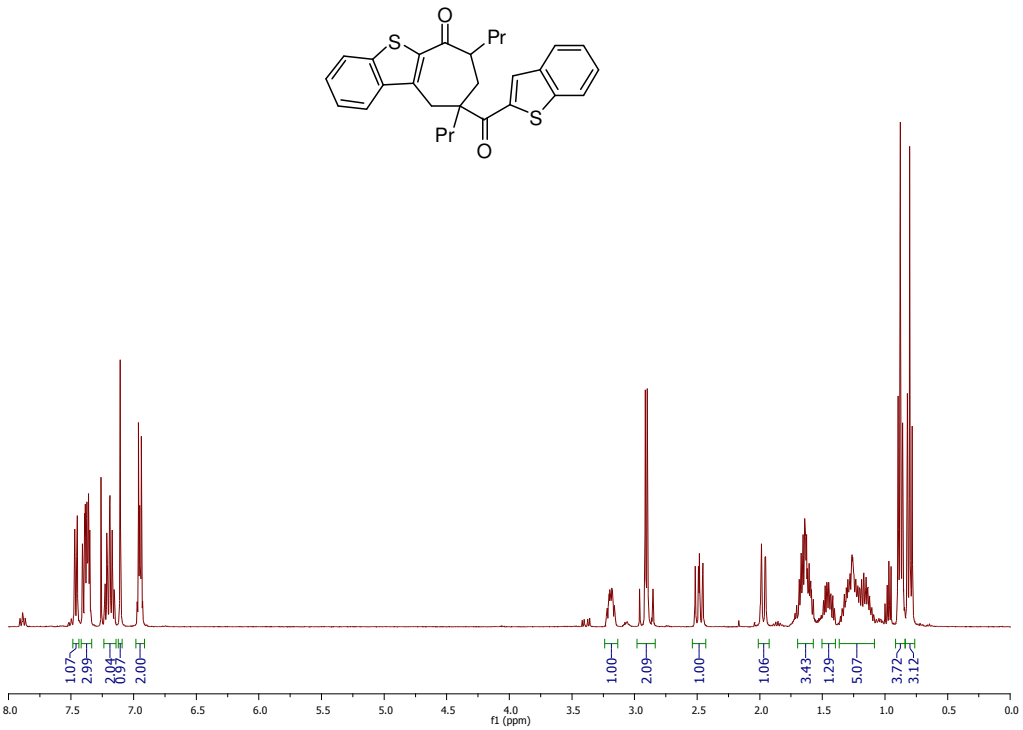
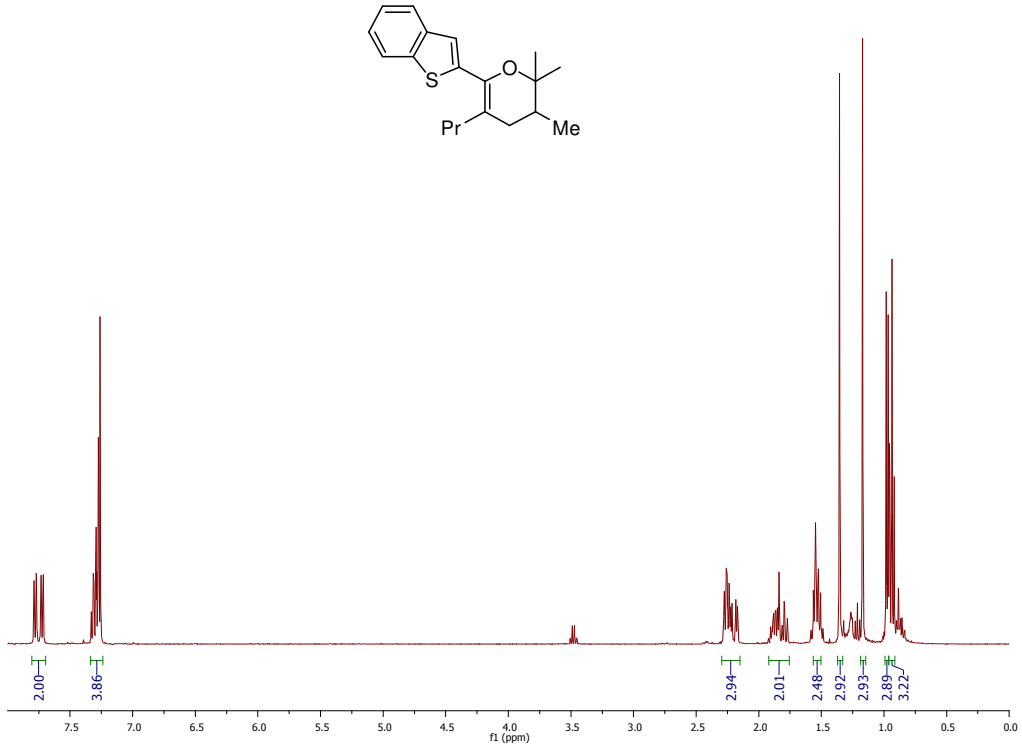
1.00
1.02
5.68
8.07
4.78
10.40
7.72
f1 (ppm)

1.30


O
S
Pr
Pr
S
O
1.07
2.99
2.04
0.97
2.00
1.00
2.09
1.00
1.06
3.43
1.29
5.07
3.72
3.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

1.31


S
O
Pr
Me
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2.94
2.01
2.48
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2.89
3.22
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6.5
6.0
5.5
5.0
4.5
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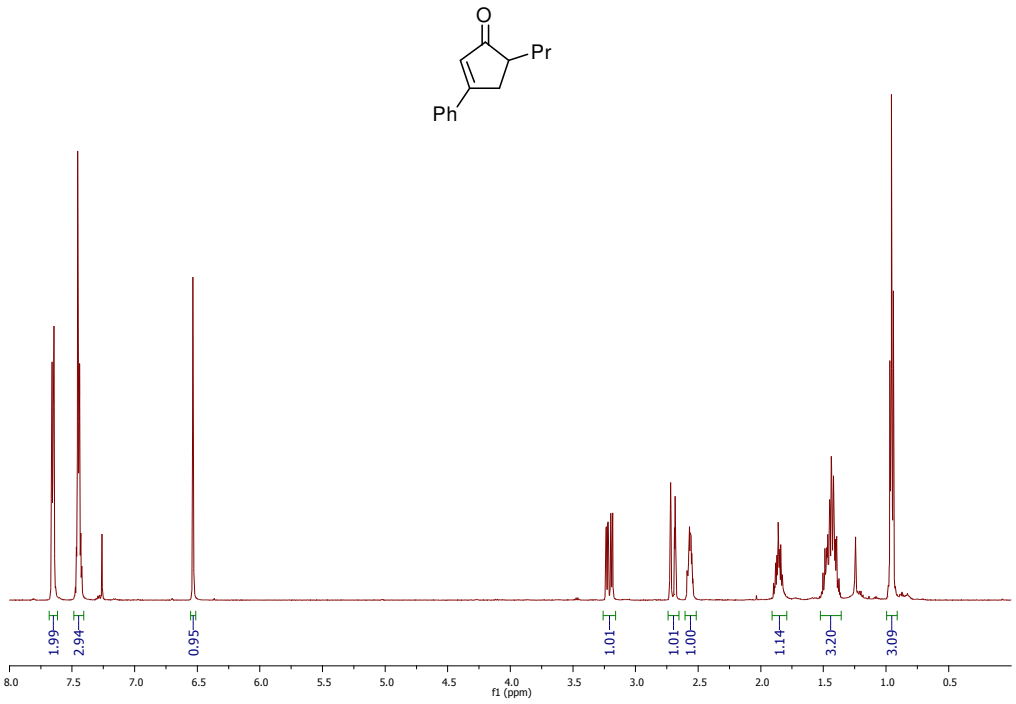
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

1.33


O
Pr
Ph
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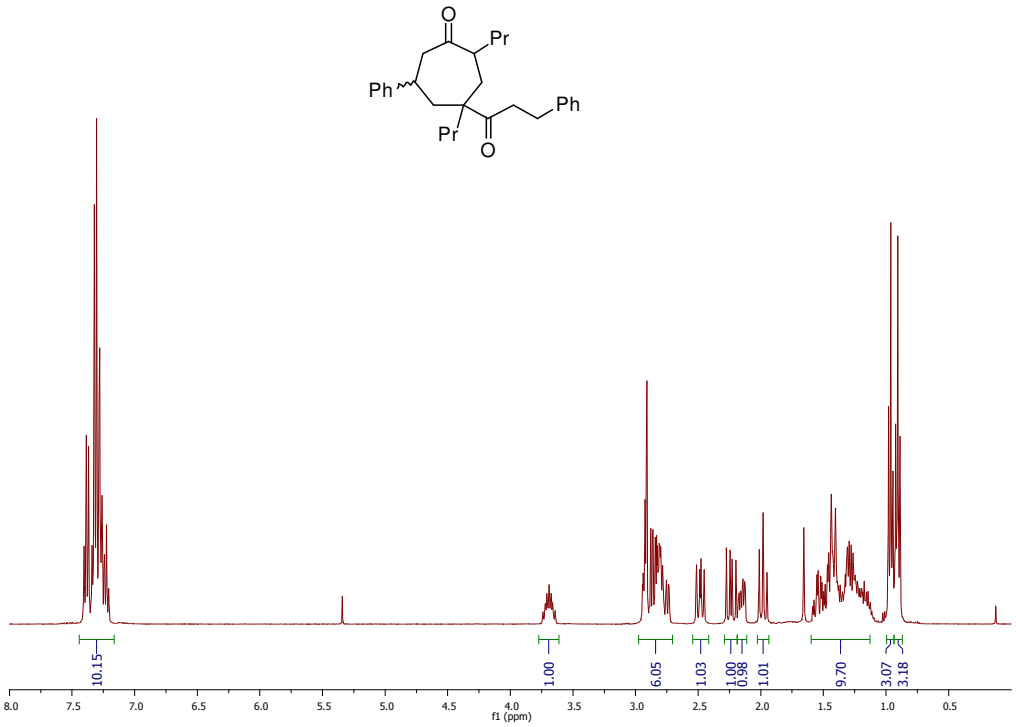
3.09
f1 (ppm)

1.34a


O
Pr
Ph
Ph
Pr
O
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1.00
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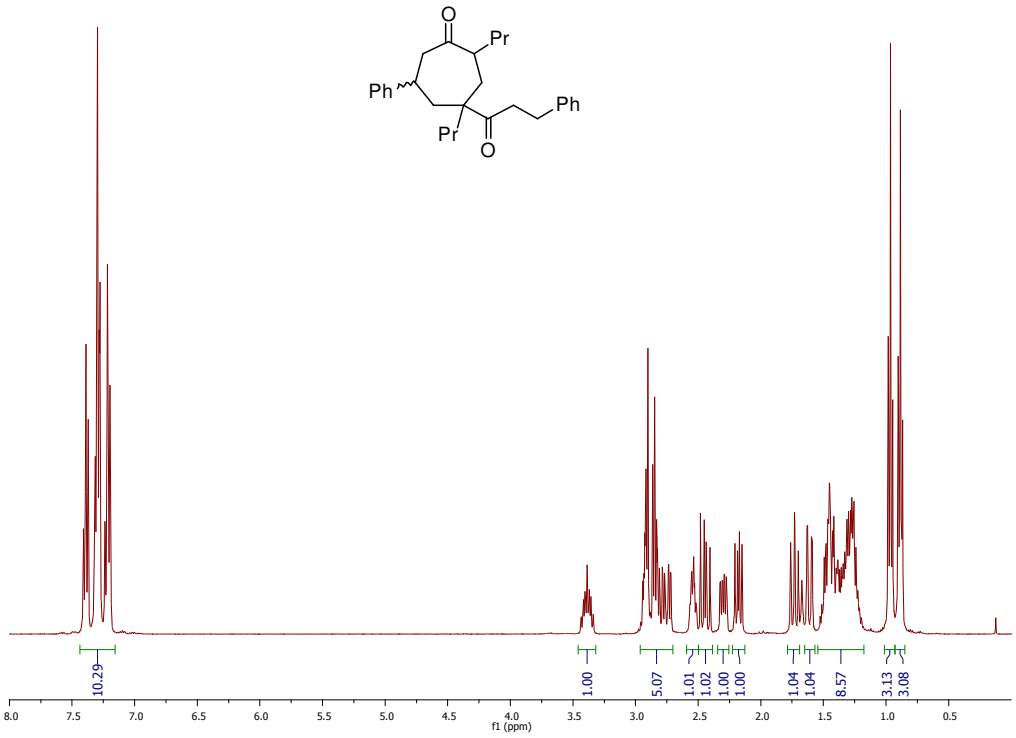
9.70
3.07
3.18
f1 (ppm)

1.34b


O
Pr
Ph
Ph
Pr
O
10.29
1.00
5.07
1.01
1.02
1.00
1.00
1.04
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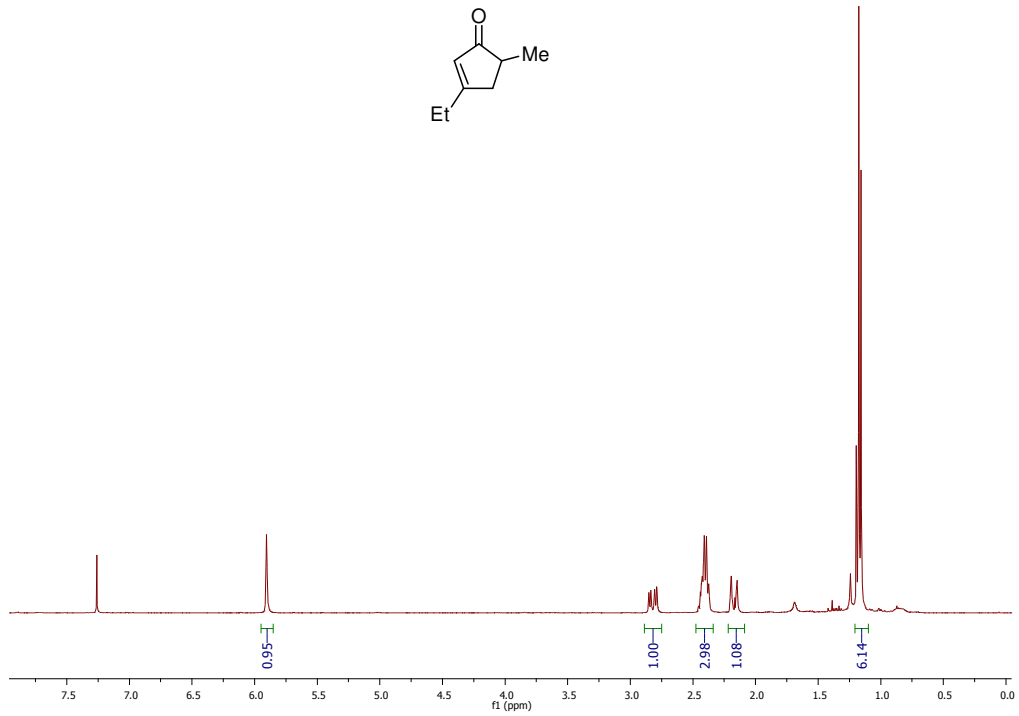
8.57
3.13
3.08
f1 (ppm)

1.35


O
Me
Et
0.95
1.00
2.98
1.08
6.14
f1 (ppm)

1.5 References

1. Nazarov, I. N. *Usp. Khim.* **1949**, *18*, 377–401; (b) Nazarov, I. N. *Usp. Khim.* **1951**, *20*, 71–103.

2. (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N. Y.)* **1994**, *45*, 1. (b) Krohn, K. *Org. Synth. Highlights* **1991**, 137. (c) Santellirouvier, C.; Santelli, M. *Synthesis* **1983**, *6*, 429–442. (d) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *11*, 2193–2206. (e) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (f) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.

3. (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642–2645. (b) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168–194.

4. Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 1970–1973.

5. (a) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290. (b) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328–5329.

6. Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328–14329.

7. Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113–4115.

8. Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934.

9. Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545.

10. Troin, Y.; Diez, A.; Bettiol, J. L.; Rubiralta, M.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1991**, *32*, 663–668.

11. Blanchard, P.; Brisset, H.; Illien, B.; Riou, A.; Roncali, J. *J. Org. Chem.* **1997**, *62*, 2401–2408.

12. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729.

13. Oki, M.; Funakoshi, W.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 828–832.

14. Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64–64.

Chapter 2. Total Synthesis of Shimalactones A and B

2.1 Introduction

Shimalactones A and B (**2.1**, **2.2**) were isolated and their structures were elucidated by the Kobayashi group from a cultured marine fungus *Emericella variecolor* GF10 in 2005 (Figure 2.1).[1,2] These highly unsaturated polyketides induce the neuritogenesis of neuroblastoma Neuro 2A cells at 10 mg/mL. The molecules consist of a bicyclo[4.2.0]octadiene moiety as well as a novel oxabicyclo[2.2.1]heptane unit tethered by an *E*-configured olefin. The molecules also feature nine stereocenters, five of which are contiguous and four of which are quaternary. We were attracted to the shimalactones because of their biological activity and complex architecture.

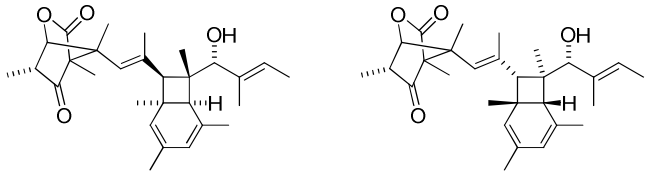


Figure 2.1. Shimalactones A and B.

2.2 Background

The total syntheses of several other highly unsaturated polyketides completed by our group (Figure 2.2), such as ocellapyrones A and B (**2.3** and **2.4**), elysiapyrones A and B (**2.5** and **2.6**), and SNF4435 C and D (**2.7** and **2.8**), have shown that the bicyclo[4.2.0]octadiene portion of shimalactones can be accessed by a biomimetic 8π-6π electrocyclization cascade of an *E,Z,Z,E*-configured octatetraene, such as **2.9** (Scheme 2.1).[3,4,5,6,7] The shimalactones were isolated as a pair of diastereomers in a 3:1 ratio with only the stereocenters of the cyclobutane inverted.[2,7] Previous studies on **2.3**-**2.8** indicate that these diastereomers could arise from a nonselective 8π electrocyclization followed by a stereoselective 6π electrocyclization. Thus, only two diastereomers are found in nature instead of the possible four.

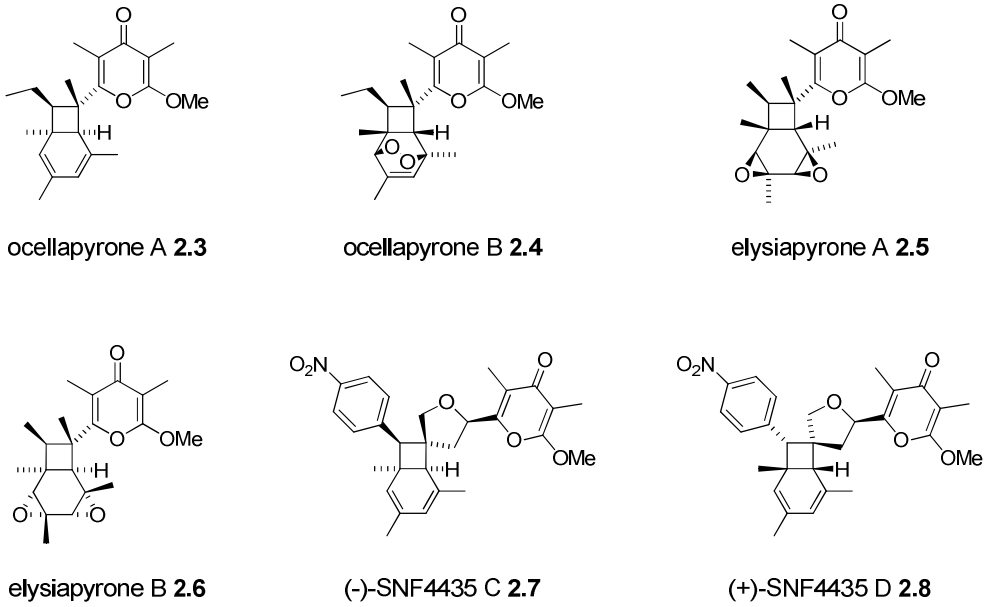
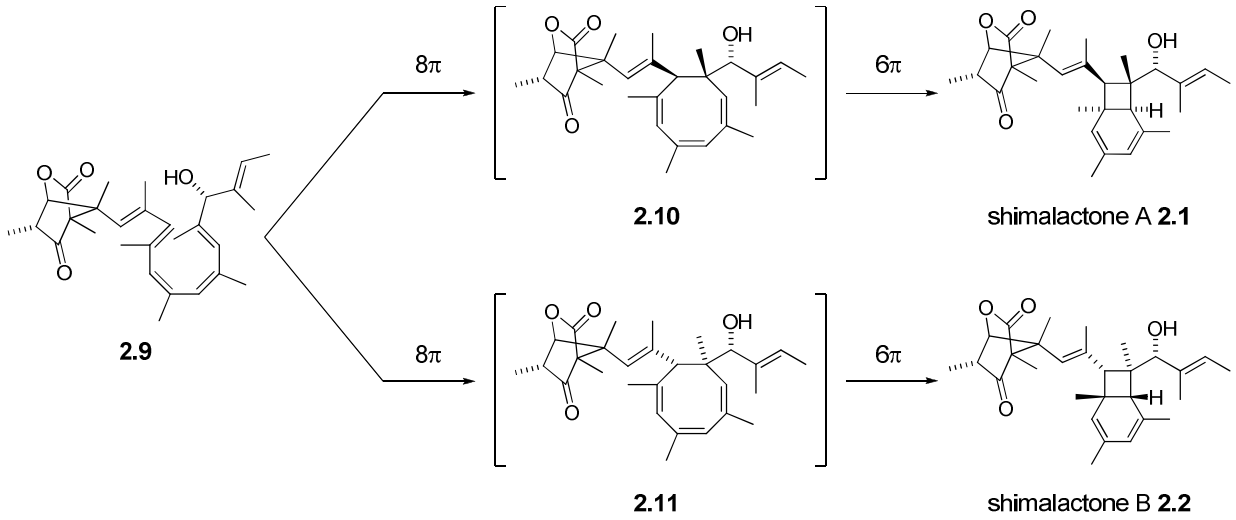


Figure 2.2. Highly unsaturated polyketides containing a bicyclo[4.2.0]octadiene moiety.

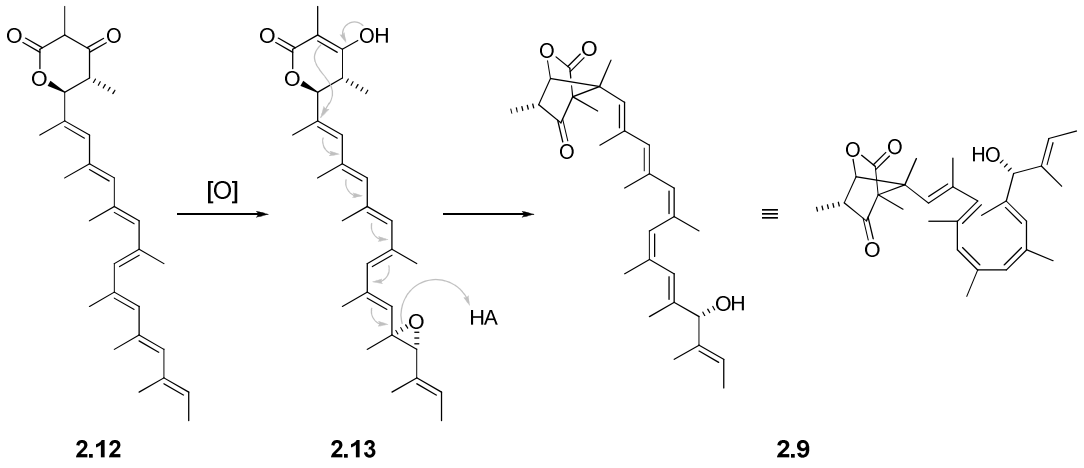
Scheme 2.1. Biomimetic 8π-6π electrocyclization cascade.



A likely biosynthesis of the shimalactones proceeds through an all-*E* heptaene **2.12** intermediate containing a dihydropyrone moiety (Scheme 2.2).[7a] The presence of the dihydropyrone is one of the main structural differences between the shimalactones and natural products **2.3**-**2.8** that have a pyrone in their precursors. One of the double bonds of the polyene **2.12** is enzymatically epoxidized which starts the cascade of cyclizations. An intramolecular conjugate epoxide opening of **2.13** forms a skipped hexaene in addition to the oxabicyclo[2.2.1]heptane unit of **2.9**. The conjugated portion of the polyene may subsequently isomerize until it achieves *E*,*E*,*Z*,*Z*,*E*-configuration required for the 8π-6π electrocyclization

cascade, which would follow immediately afterward. Our retrosynthesis of shimalactones is drawn from this proposed biosynthesis.

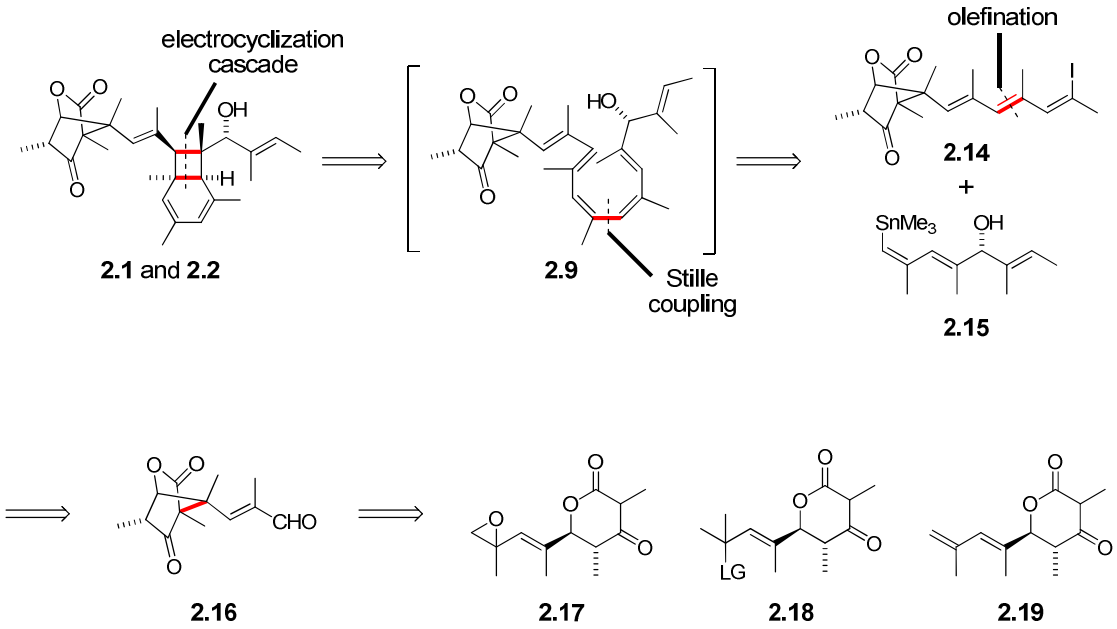
Scheme 2.2. Possible biosynthesis of the shimalactones.



2.3 Results and Discussion

Herein we report our biomimetic, convergent, and protection group-free total synthesis of shimalactones A and B.[8] While staying close to the proposed biosynthesis of the shimalactones was one of our goals, we wanted to use it to simplify our strategy and make it more efficient. Thus, we chose to forgo the polyene **2.12** due to potential difficulties with handling such an intermediate as well as presumed selectivity issues in the epoxidation step. Instead, we decided to intercept this hypothetical biosynthesis at the intermediate **2.9**, which we knew could be disconnected by means of Stille coupling, as demonstrated in syntheses of polyketides **2.3**-**2.8**, into an iodotriene **2.14** and stannane **2.15** (Scheme 2.3). While we envisaged disconnecting **2.14** at the central double bond, the central objective of the project became the synthesis of the bicyclic lactone **2.16**. The biomimetic disconnection of **2.16** to install the bond between two quaternary carbons has not been precedented in the literature and appeared to be the most formidable step of the synthesis.

Scheme 2.3. Retrosynthetic analysis of the shimalactones.

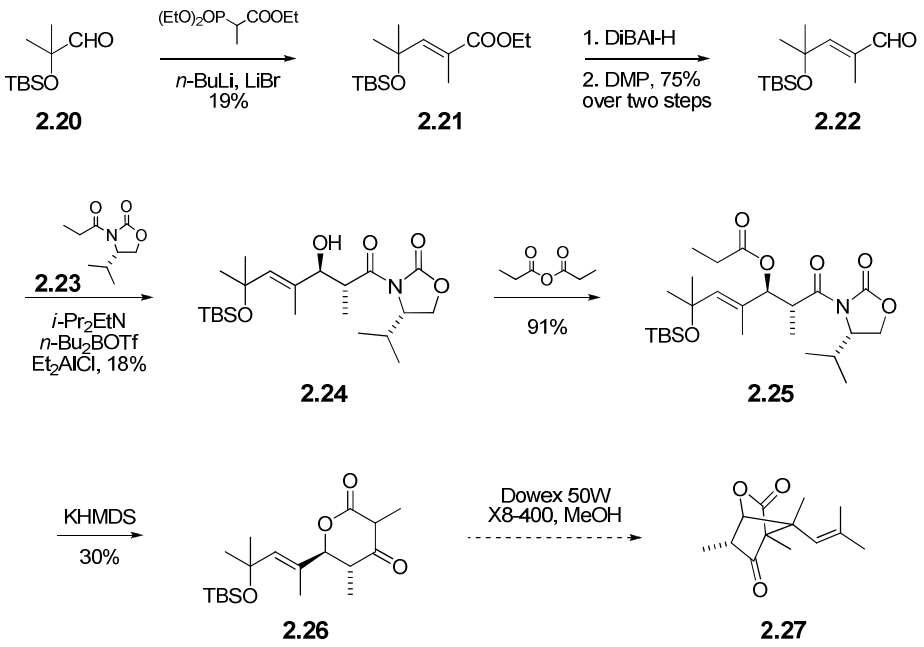


We considered several approaches to the oxabicyclo[2.2.1]heptane **2.16** (Scheme 2.3). The most obvious approach uses epoxide **2.17**, a shorter version of **2.13**, that can be opened by the nucleophilic β-ketolactone in a conjugate fashion. The second strategy features an allylic leaving group **2.18** that can be displaced by the β-ketolactone, while the third relies on diene **2.19** which can be easily protonated, creating an allylic carbocation that is delocalized between two tertiary carbons. Under acidic conditions, the β-ketolactone would undergo rapid keto-enol equilibrium and would be able to trap the positive charge.

2.3.1 Leaving group strategy

At first, we decided to focus on the second strategy with the leaving group being a protected alcohol that can be deprotected and ionized under acidic conditions. We made this choice to gain quick access to the precursor for the key cyclization as well as to evaluate the stereochemistry at the resulting quaternary stereocenter in the oxabicyclo[2.2.1]heptane fragment. The synthetic route to β-ketolactone **2.18** is detailed in Scheme 2.4. Starting with known aldehyde **2.20**, which is available from methyl-2-hydroxyisobutyrate in three steps,[9] a Horner-Wadsworth-Emmons olefination afforded ester **2.21**. Reduction with DiBAl-H and reoxidation with Dess-Martin periodinane yielded aldehyde **2.22**. The modest yield in the HWE olefination can be attributed to the large steric bulk at the α-position of aldehyde **2.20**. Treatment of **2.22** with two equivalents of Et_2AlCl and one equivalent of *n*-Bu_2BOTf in presence of propionyl-oxazolidinone **2.23** yielded *anti*-aldol product **2.24** in 4:1 ratio with *syn*-aldol product (not shown).[10] This yield was poor even after extensive optimization, while other methods failed to give any of the desired aldol adduct altogether.[11,12] Acylation of alcohol **2.24** with propionic anhydride afforded propionate **2.25**, which was subsequently cyclized to β-ketolactone **2.26** using an unusual Dieckmann cyclization developed by Brandwänge and Leijonmark.[13]

Scheme 2.4. Synthesis of the precursor for the key cyclization.



An initial cyclization attempt of **2.26** using acidic Dowex resin did not afford the desired bicyclic lactone **2.27**. Based on the crude NMR, we think that 1,4-elimination of the deprotected allylic alcohol took place instead of intramolecular attack to afford a diene. In addition, MeOH is believed to have participated, converting the β-ketolactone into a vinylogous methyl carbonate. However, a stable product could not be isolated. We realized from these efforts that compound **2.26** may not be an appropriate precursor for **2.27**. Synthetic difficulties in making **2.26** caused us to divert from this strategy.

2.3.2 Epoxide and Diene strategies

We turned our attention to the synthesis of epoxide **2.17** and diene **2.19** assuming that they could be made from a common precursor. Known alcohol **2.28** was prepared in three straightforward steps from diethyl methyl malonate, then oxidized with MnO_2 and immediately used in the aldol reaction with **2.23** (Scheme 2.5).[14] Compared to the aldol with aldehyde **2.22**, Heathcock's conditions resulted in slightly higher yield and similar diastereoselectivity (32%, 4:1 *anti*:*syn*).[10] However, conditions reported by Evans proved to be better.[12] On 1 mmol scale, the *anti*-aldol with propionyl-oxazolidinone **2.23** in the presence of $MgCl_2$, Et_3N, and TMSCl afforded **2.29** in moderate yield and excellent diastereoselectivity (42%, 56:1 *anti*:*syn*). Surprisingly, when scaled up to 45 mmol scale, the anti- **2.29** and syn-aldol **2.30** adducts were obtained with the same combined yield (42%), but much poorer diastereoselectivity (55:45 *anti*:*syn*). Alcohols were separated and a crystal structure of compound **2.29** was obtained in order to verify the relative stereochemistry (Figure 2.3).

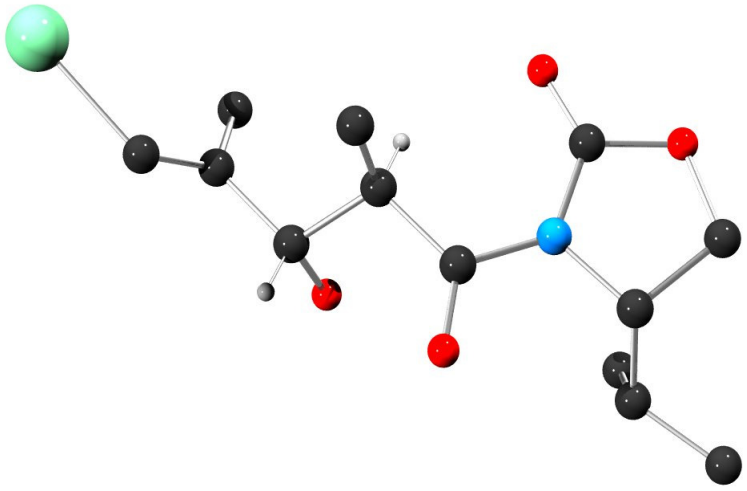
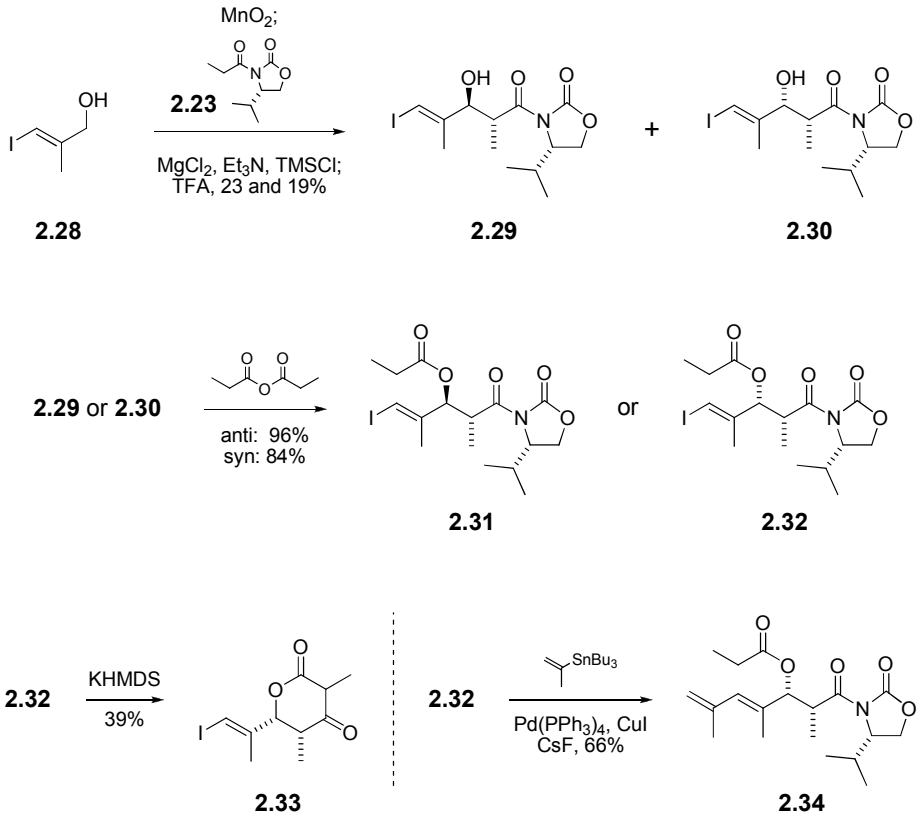


Figure 2.3. X-ray structure of the *anti* aldol **2.29** showing two new stereocenters.

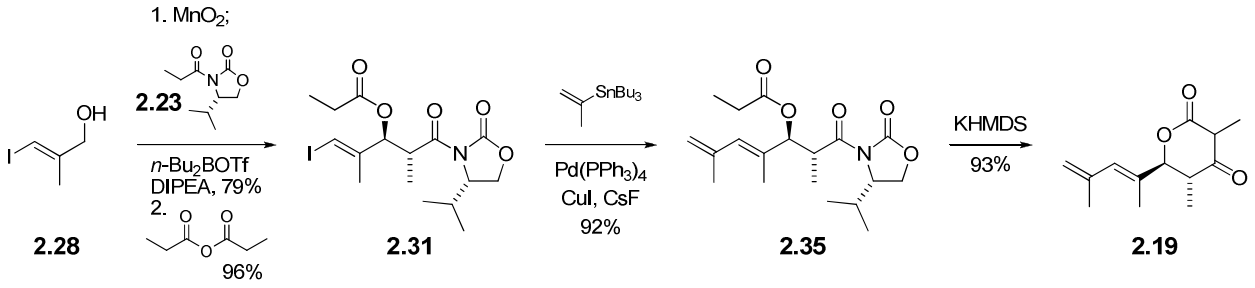
Scheme 2.5. Synthesis of diene **2.19** – initial attempts.



Both alcohols were converted to propionates **2.31** and **2.32** respectively in excellent yield (Scheme 2.5). As the Dieckmann cyclization of **2.31** failed to give any isolable product, *syn* diastereomer **2.32** was used to test the next set of reactions in order to conserve the desired *anti*

aldol adduct **2.31**. *Syn* propionate **2.32** could be successfully cyclized to β-ketolactone **2.33** and underwent Stille cross-coupling to afford diene **2.34**. Unfortunately, both compounds consistently decomposed when subjected to the next step in the synthesis (correspondingly Stille cross-coupling for **2.33** and Dieckmann cyclization for **2.34**). When **2.34** was subjected to the cyclization conditions, a β-ketolactone moiety was spectroscopically observed based on a characteristic ketone carbonyl signal at 205.2 ppm in the ^{13}C NMR. The target could also be seen by TLC, but resisted attempts to isolate it. Decomposition of the product on silica gel, Et_3N-treated silica gel, and alumina columns indicated that it is highly unstable.

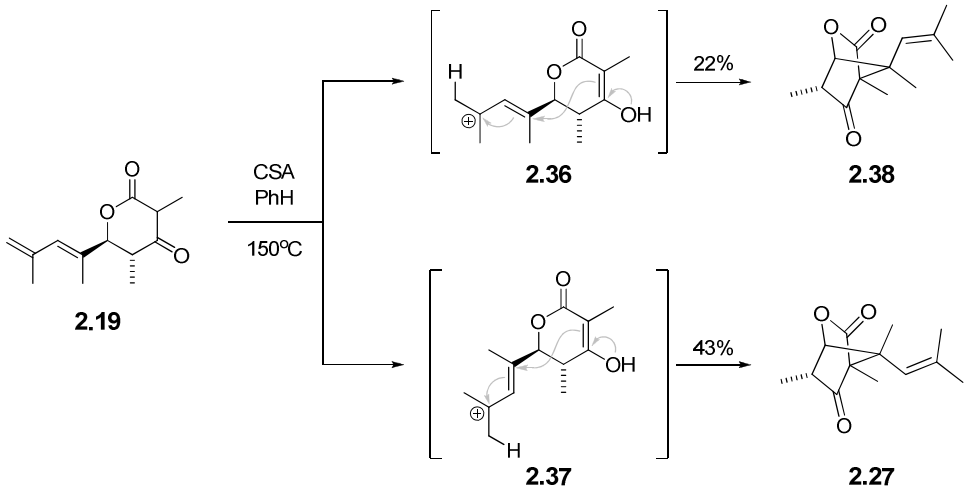
Scheme 2.6. Synthesis of diene **2.19**.



To our great surprise, *anti* propionate **2.31** underwent the Stille cross-coupling to afford diene **2.35**, which could be smoothly cyclized to β-ketolactone **2.19** in excellent yield (Scheme 2.6). We were also pleased to find that the use of two equivialents of *n*-BuBOTf in the *anti*-selective aldol gave **2.29** as a single diastereomer in good yield.[11] All attempts to perform selective epoxidation or dihydroxylation of the terminal double bond of **2.19** failed. We abandoned the use of the vinyl epoxide **2.17** as our retrosynthetic strategy and instead proceeded with a robust route to **2.19**, turning our attention to the key cyclization.

A variety of acids and organometallic catalysts were screened in attempt to convert diene **2.19** to bicyclic lactone **2.27** (Scheme 2.7). Relatively harsh conditions were required to perform this transformation – camphorsulfonic acid in benzene or toluene in a sealed tube heated to 120 to 180 ^oC. Presumably, the cyclization proceeds through the intermediacy of an allylic carbocation that can be attacked by the β-ketolactone from either of the two faces **2.36** or **2.37**, giving rise to the undesired diastereomer **2.38** and the desired **2.27** respectively. While the best yields were obtained in benzene at 150 ^oC, the yield proved to be very concentration sensitive and the ratio between the diastereomers could not be altered. This was the first instance of the synthesis of an oxabicyclo[2.2.1]heptane moiety.

Scheme 2.7. Key cyclization.



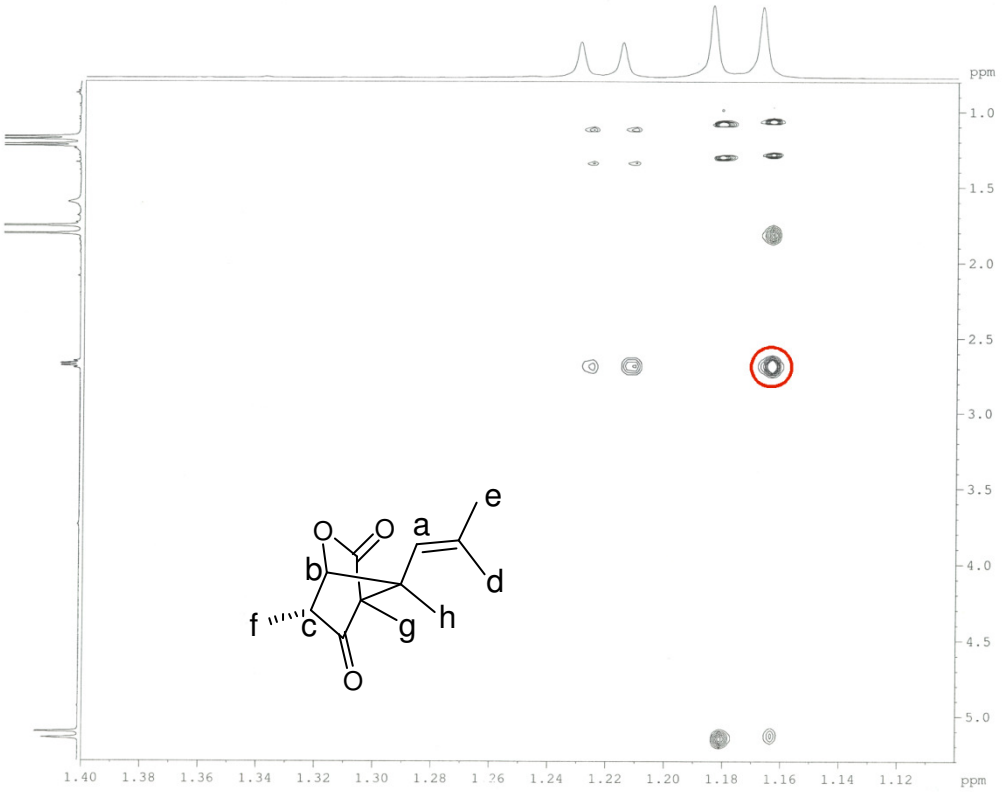


Figure 2.4. NOESY spectrum of the undesired bicyclic lactone **2.38**.

The determination of the relative stereochemistry of **2.27** and **2.38** was initially investigated on the basis of detailed ^{1}H NMR measurements. The results of 2-dimensional nuclear Overhauser effect spectroscopy (NOESY) for **2.38** are shown in Figure 2.4 and reveal

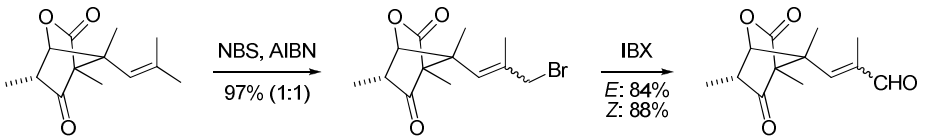
correlations between H_c and H_h. These findings support a relative stereochemistry that is consistent with **2.38**. Analogous analysis was conducted for **2.27**.

2.3.3 Elongation of the polyene chain

With the key step cyclization completed, we needed to extend the polyene chain in order to get to the iodotriene **2.14**. Unlike the case of an epoxide opening, cyclization of **2.19** left us with no functional handle, such as an OH group, that has been traditionally used for olefination chemistry in its oxidized form. At first, this did not appear to be a major difficulty, because it is well known that SeO_2 is capable of oxidizing unfunctionalized allylic C-H bonds to the alcohol or aldehyde oxidation states.[15] However, bicyclic lactone **2.27** proved to be inert to most of the allylic functionalization conditions using SeO_2 that are described in the literature and decomposed under harshly acidic ones. It became apparent to us that the steric bulk of the oxabicyclo[2.2.1]heptane group next to the allylic system interfered with this reaction and we decided to resort to another strategy.

Under classical radical bromination conditions, **2.27** was converted to a 1:1 mixture of *E* (**2.39**) and *Z* (**2.40**) bromides in excellent yield (Scheme 2.8). We initially assumed that the allylic bromide **2.39** could be oxidized to enal **2.17** using a variety of conditions, including Kornblum oxidation with modifications[16,17] or the Ganem oxidation also with modifications.[18,19] However, after an extensive screen of conditions, it became obvious that the bicyclic system is highly unstable under the basic conditions required for all of these reactions. We were delighted to find that, at the time, recently published neutral conditions that used IBX for the oxidation of benzylic bromides to aldehydes worked in our hands.[20] Both **2.39** and **2.40** were separately converted to the *E* (**2.17**) and *Z* (**2.41**) enals respectively in good yield.

Scheme 2.8. Allylic oxidation.



X-ray quality crystals of **2.17** were grown and the crystal structure determined to verify the stereochemistry at the one-carbon bridge as well as the double bond geometry (Figure 2.5). At this point, it became very apparent why the oxabicyclo[2.2.1]heptane framework is so base-sensitive. The proton α to the keto carbonyl in the bicycle is aligned antiperiplanar to the carbon-oxygen bond of the lactone. Thus it is perfectly set-up for elimination of CO_2 and expulsion of a different enolate (**2.42**). The cyclopentenone product of this elimination **2.43** was isolated as a 2:1 mixture of diastereomers during one of the initial attempts to olefinate **2.17** (Scheme 2.9).

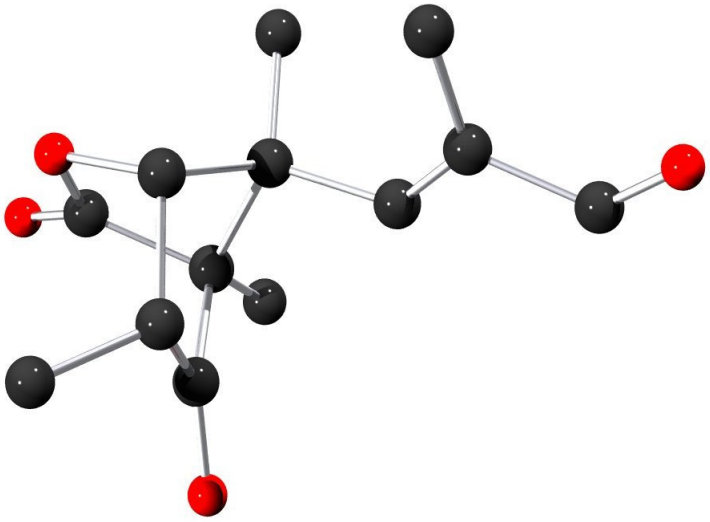
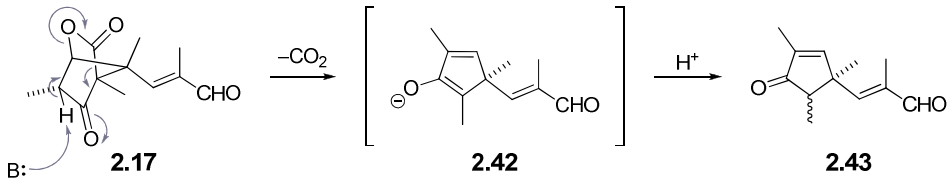


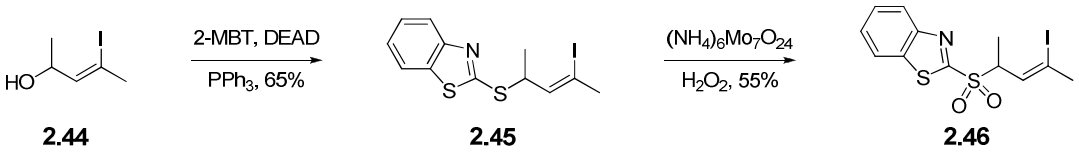
Figure 2.5. X-ray structure of the enal **2.17**.

Scheme 2.9. Elimination of CO_2 from enal **2.17** under basic conditions.



As foreshadowed by the previous paragraph, conversion of the enal **2.17** to the iodotriene **2.14** posed a serious challenge due to the base sensitivity of the enal. Our initial plan involved Julia olefination with sulfone **2.46**, which was prepared by a Mitsunobu reaction of the known alcohol **2.44** with 2-mercaptobenzothiazole followed by oxidation of the resulting sulfide **2.45** with ammonium heptamolybdate (Scheme 2.10).[21] Sulfone **2.46** failed to react with a variety of commercially available aldehydes, not to mention enal **2.17**. Likewise, a variety of other olefination reagents, no matter how mild, failed to react with **2.17**. In addition, it was determined that exposure of **2.17** to a variety of organic amines for even 5 minutes completely destroyed the material.

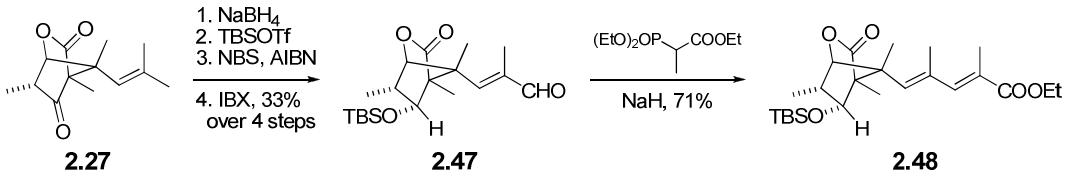
Scheme 2.10. Synthesis of sulfone **2.46**.



With this information in hand, we considered "silencing" the ketone that was contributing to the acidity of the α proton of **2.17**. Several attempts to convert it to a ketal failed to give any product. Presumably, this is due to the increased steric demands of a ketal as compared to a

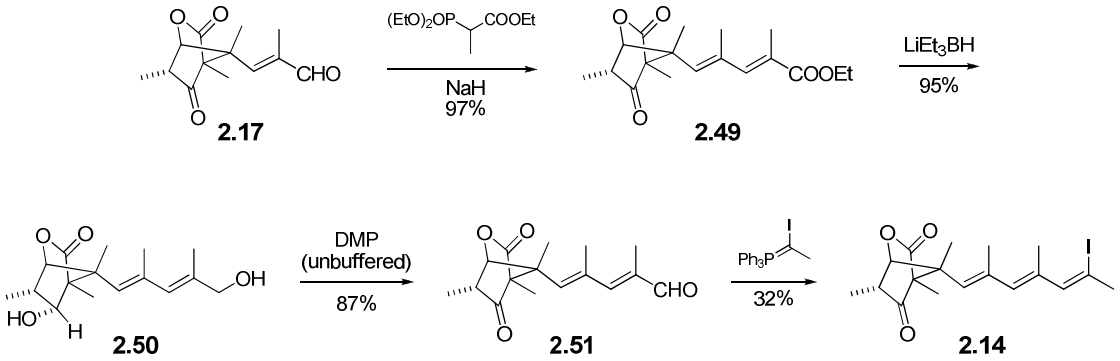
ketone. The next best solution to the problem was to reduce the ketone to an alcohol and protect it as a silyl ether. Scheme 2.11 details this strategy. Bicyclic lactone **2.27** was reduced with $NaBH_4$, protected as a TBS ether, and the allylic position was oxidized as before to give enal **2.47**. Complete stereocontrol was achieved in the reduction of **2.27** using super hydride. However, with $NaBH_4$ a diastereomeric ratio of only 4:1 was obtained in favor of the product shown. As expected, Horner-Wadsworth-Emmons olefination furnished dienoate **2.48** in good yield even after 1.5 h exposure of the enal **2.47** to the reaction conditions. However, to our disappointment, the silyl protecting group could not be removed under a variety of conditions.

Scheme 2.11. Olefination of the reduced and protected ketone.



Inspired by Phil Baran's seminar on protection group free total syntheses, we set out to perform the same transformation on the unprotected substrate **2.17**.[22] Considering the sensitivity of the substrate, the reaction times were kept under 2 min. To our great surprise, HWE olefination of **2.17** furnished dienoate **2.49** in 97% yield (Scheme 2.12). Interestingly, the yield dropped to 48% if the reaction time was extended to 10 min. By keeping the reaction times very short, **2.49** was reduced to diol **2.50**, which was subsequently reoxidized to dienal **2.51** in excellent yield. Finally, Stork-Zhao olefination gave iodotriene **2.14**. Being considerably slower, this transformation could not be optimized beyond 32% yield.

Scheme 2.12. Synthesis of iodotriene **2.14**.

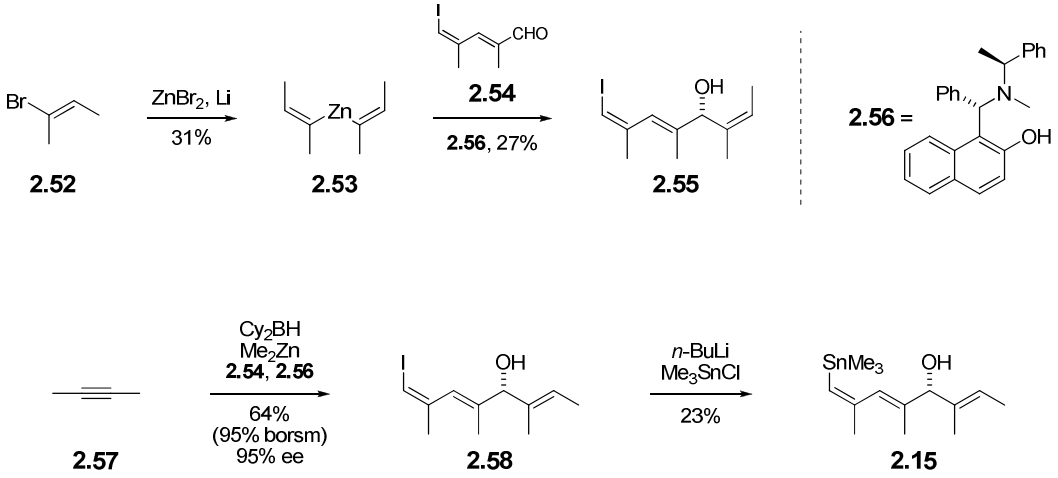


2.3.4 Synthesis of stannane 2.15 and endgame

With the iodotriene **2.14** in our hands, we turned our attention to its coupling partner – stannane **2.15**. We envisioned setting the carbinol stereocenter by an enantioselective addition of an organozinc reagent to the known aldehyde **2.54** (Scheme 2.13), which is available in six straightforward steps from propargyl alcohol.[23] It is known from the literature that dialkenyl zinc compounds can be prepared and isolated in spite of their instability in air.[24] Following the

Soai protocol to make the corresponding dialkenyl zinc compound from *E*-2-butene **2.52**, we obtained **2.53** instead, where the double bond geometry isomerized cleanly under the reaction conditions. We discovered this when addition of **2.53** to aldehyde **2.54** in presence of Chan ligand **2.56** gave us alcohol **2.55**,[25] the NOESY spectrum of which revealed the discrepancy (Figure 2.6). Curiously, this has not been noted in the literature since both examples in the Soai paper have the same substituents at the terminus of the double bond (either two protons or two methyl groups).

Scheme 2.13. Synthesis of stannane **2.15**.



Since the addition step (**2.53** → **2.55**) worked in our hands, we decided to generate the required alkenyl zinc species in situ. Following Chan's example, this was performed by hydroboration of 2-butyne (**2.57**) with dicyclohexyl borane, followed by transmetallation to dimethylzinc and addition to the unsaturated aldehyde **2.54** in presence of ligand **2.56** (Scheme 2.13). While the yield was much higher than when isolated dialkenyl zinc was used, **2.58** was obtained in excellent 95% enantiomeric excess. The determination of the relative stereochemistry of **2.55** and **2.58** was investigated on the basis of 2-dimensional nuclear Overhauser effect spectroscopy (NOESY). Figure 2.6 shows correlations between H_c and H_g as well as between H_d and H_f for **2.55**, while for the desired iodide **2.58** the correlations between H_c and H_d as well as between H_g and H_f were observed.

After exchanging the iodide for trimethyltin we were delighted to obtain stannane **2.15**. Finally, Stille-Liebeskind cross-coupling of **2.14** and **2.15** generated intermediate **2.9**,[26] which in turn underwent an 8π-6π electrocyclization cascade giving shimalactones A (**2.1**) and B (**2.2**) in 55 and 11% yield respectively (Scheme 2.14). While shimalactones are isolated in 3:1 ratio from the natural sources, we were thrilled to obtain them in a very similar ratio of 5:1. This is another piece of evidence that the biosynthesis proceeds through intermediacy of pentaene **2.9**.

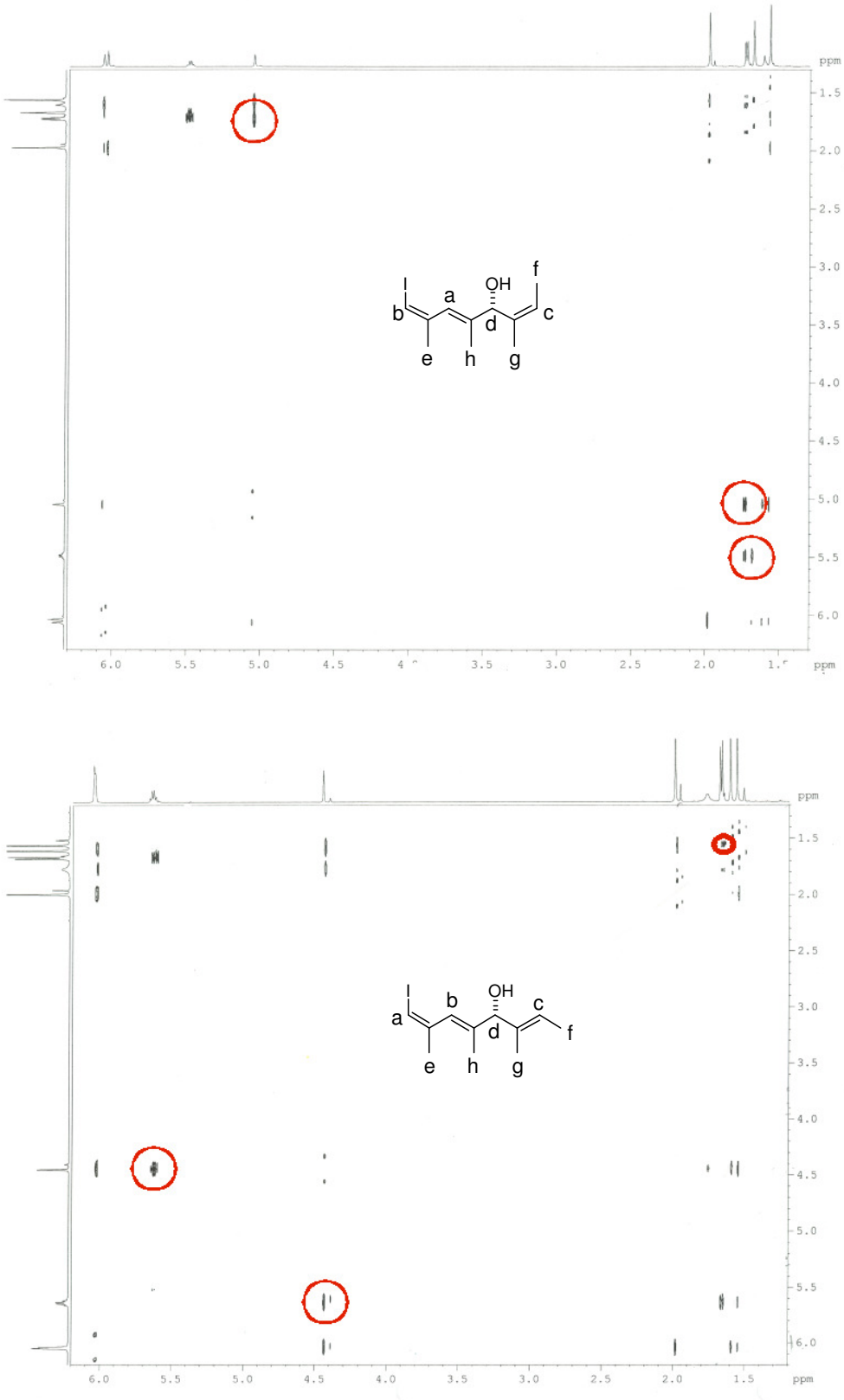
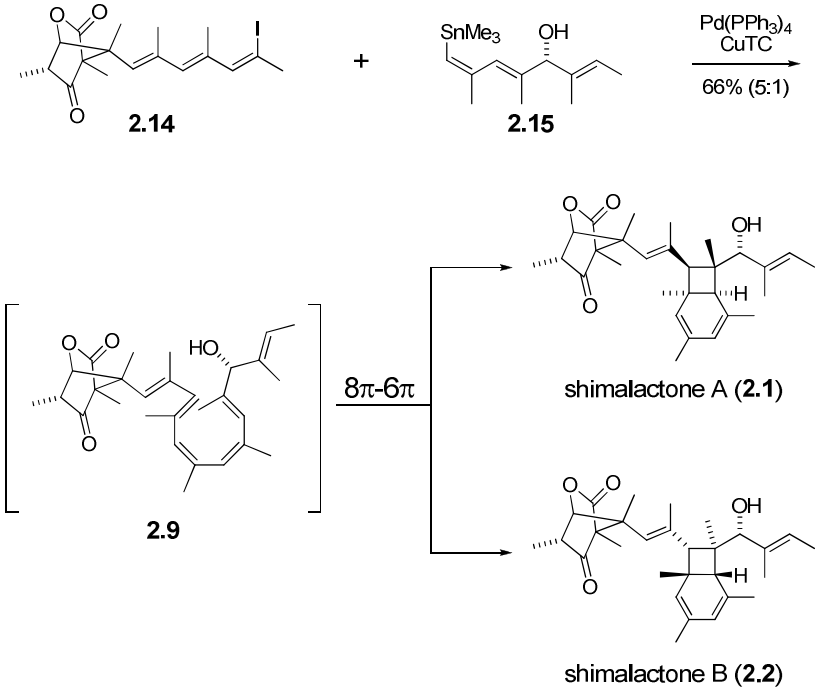


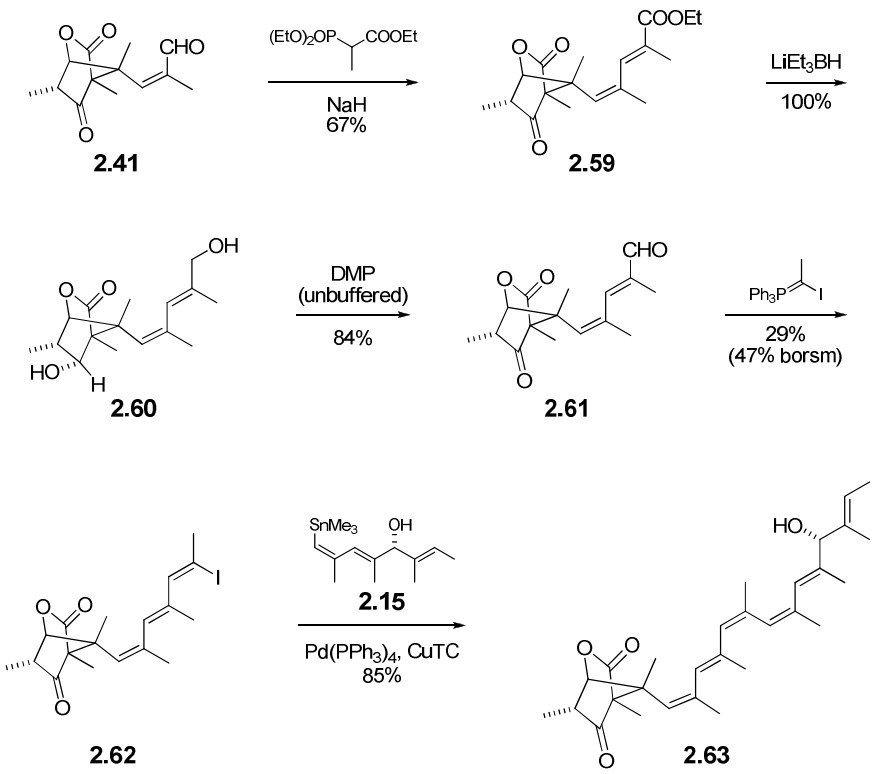
Figure 2.6. NOESY spectra of the undesired iodide **2.55** (top) and the desired iodide **2.58**.

Scheme 2.14. Stille cross-coupling/8π-6π electrocyclization cascade.



The electrocyclization cascade presumably proceeds through *E*,*E*,*Z*,*Z*,*E*-polyene **2.9**, which could never be isolated. Previous studies by Baldwin and our group have shown that polyenes of this type undergo facile isomerizations of their trisubstituted double bonds.[7a,27] Therefore, we decided to advance compound **2.41** to the pentaene stage (Scheme 2.15). A sequence analogous to the one shown in Scheme 2.12 gave iodotriene **2.62**, which underwent cross coupling with stannane **2.15** to afford *Z*,*E*,*Z*,*Z*,*E*-pentaene **2.63**. Remarkably, this compound was found to resist 8π electrocyclization and could be isolated. Presumably, the bulk of the oxabicyclo[2.2.1]heptaenyl substituent, which would be positioned endo in an 8π transition state, prevents **2.63** from undergoing the cyclization, in stark contrast to its isomer **2.9**. However, despite repeated attempts, **2.63** could not be isomerized to the shimalactones.

Scheme 2.15. Synthesis of stable pentane **2.62**.



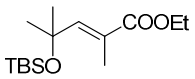
2.3.5 Conclusions

In summary, we have achieved a convergent and protecting group-free synthesis of the shimalactones, which supports our biosynthetic hypothesis on the origin of these compounds. To this end, we have developed a new acid-catalyzed key cyclization (**2.19 → 2.27, 2.38**), which generates two adjacent quaternary stereocenters in a strained bicyclic ring system. We have also added another Stille cross-coupling/8π-6π electrocyclization cascade to our portfolio of cascade reactions in the total synthesis of natural products.[28,29]

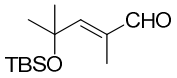
2.4 Experimental

2.4.1 Synthetic Procedures

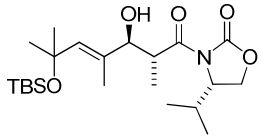
General methods. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} TLC plates and visualized using charring solutions of potassium permanganate or 2,4-dinitrophenylhydrazine. Reactions were carried out under inert atmosphere in oven-dried glassware and reaction solutions were magnetically stirred. Et_2O, THF, and CH_2Cl_2 were purified by passage over activated alumina according to the procedure described by Bergman.[30] MeCN, Et_3N, *i*-Pr_2EtN, and TMSCl were distilled from CaH_2 immediately prior to use. EtOAc was distilled from $MgSO_4$ and stored over 4Å molecular sieves under argon. Hexane was distilled from NaH and stored under argon. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried over $MgSO_4$ unless otherwise indicated. NMR spectra were measured using Brüker AV 300, AVQ 400, AVB 400, AV 500, and DRX 500 spectrometers in $CDCl_3$ and calibrated from residual solvent signal (7.26 for ^1H and 77.23 for ^{13}C). IR spectra were measured using Genesis FT-IR spectrometer by evaporative thin film on a NaCl plate. Low and high resolution mass spectra as well as elemental analyses (LRMS, HRMS, and EA) were obtained using the Micro-Mass Facility operated by the College of Chemistry, University of California, Berkeley. Mass spectra were measured on VG ProSpec Mass Spectrometer by either electron impact (EI) at 70 eV or with fast atom bombardment (FAB) as noted. Melting points were determined with an electrothermal apparatus and are uncorrected. Optical rotation was determined using a Perkin-Elmer 241 polarimeter equipped with a 589 nm sodium lamp. Enantiomeric excess was determined on a Shimadzu VP Series Chiral HPLC, using the Chiral PAK AD-H, Chiral PAK OD-H, or Regis Technologies WHELK-O 1 columns, eluting with a flow-rate of 1 mL/min.



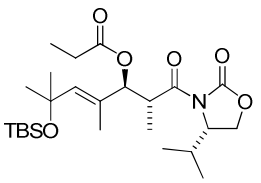
Ester 2.21. A solution of LiBr (1.55 g, 17.9 mmol) was prepared in MeCN (30 mL) and stirred for 10 min. Triethylphosphonopropionate (2.90 mL, 13.3 mmol) was then added dropwise and stirred for another 10 min. The reaction mixture was cooled to 0 ^oC and *n*-BuLi (2.5 M in hexanes, 6.0 mL, 15 mmol) was added, followed by a solution of **2.20** (1.82 g, 9.01 mmol) in MeCN (5 mL). The mixture was stirred overnight at RT. The reaction was then quenched with 1 M HCl (25 mL). The aqueous phase was separated and extracted with Et_2O (3 x 30 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (4% Et_2O/pentane) afforded **2.21** (490 mg, 19%) as a colorless oil. Data for **2.21**: R_f 0.53 (5% Et_2O/pentane); IR 1713 cm^{-1}; ^1H NMR (400 MHz) δ 6.76 (s, 1H), 4.12 (q, 2H, *J* = 7.2 Hz), 1.95 (s, 3H), 1.37 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz), 0.82 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz) δ 169.1, 148.7, 127.7, 73.5, 60.7, 31.0, 26.0, 18.3, 14.4, 13.5, –2.0; HRMS (EI) calculated for $C_{15}H_{30}O_3Si$ $(M)^+$: 286.1964, found: 286.1966.



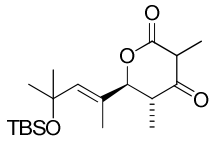
Aldehyde 2.22. A solution of **2.21** (906 mg, 3.16 mmol) in hexanes (22 mL) was cooled to –78 ^{o}C and DiBAl-H (1.0 M in hexanes, 7.0 mL, 7.0 mmol) was added dropwise. The reaction mixture was stirred overnight while gradually warming to RT. It was then quenched with saturated aqueous sodium potassium tartrate (40 mL) and stirred for 5 h. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated to afford the allylic alcohol (766 mg) as a colorless oil. The crude oil was taken up in CH_2Cl_2 (30 mL) and pyridine (3 mL) followed by addition of Dess-Martin periodinane (2.15 g, 5.07 mmol). After being stirred for 20 min, the reaction mixture was quenched with 1 M NaOH (40 mL) and stirred for 1 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **2.22** (571 mg, 75%) as a colorless oil. Data for **2.22**: R_f 0.38 (5% EtOAc/hexanes); IR 1693 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.30 (s, 1H), 6.42 (s, 1H), 1.86 (s, 3H), 1.45 (s, 6H), 0.85 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz) δ 196.4, 162.0, 137.8, 74.0, 30.5, 26.0, 18.3, 10.1, –1.9; HRMS (EI) calculated for $C_{13}H_{25}O_2Si$ $(M–H)^+$: 241.1624, found: 241.1626.



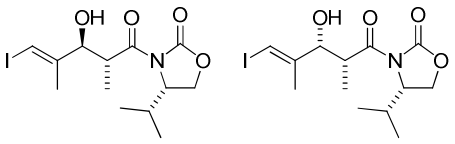
***Anti*-aldol adduct 2.24.** *i*-Pr_2EtN (0.10 mL, 0.57 mmol) was added to a solution of propionyloxazolidinone **2.23** (94.5 mg, 0.510 mmol) in CH_2Cl_2 (2 mL) which was subsequently cooled to 0 ^{o}C. *n*-Bu_2BOTf (0.12 mL, 0.48 mmol) was added dropwise and, after being stirred for 45 min, the mixture was cooled to –78 ^{o}C. In a separate flask Et_2AlCl (1 M in hexanes, 0.85 mL, 0.85 mmol) was added to a solution of **2.22** (99.6 mg, 0.411 mmol) in CH_2Cl_2 (2 mL). After being stirred for 5 min, the mixture was cooled to 0 ^{o}C and added to the above solution by cannula. The reaction mixture was stirred at –78 ^{o}C for 4.5 h and quenched with 5:1 MeOH:30% aqueous H_2O_2 (10 mL). After 10 min at –78 ^{o}C the reaction mixture was warmed to RT and stirred for 2 h. It was then diluted with water and extracted with Et_2O (2 x 10 mL). The organic extracts were washed with dilute $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated. Purification by silica gel chromatography (10% to 25% EtOAc/hexanes) afforded **2.24** (31.6 mg, 18%) as a colorless oil. Data for **2.24**: R_f 0.53 (25% EtOAc/hexanes); IR 3480, 1783, 1687 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.54 (s, 1H), 4.25 (m, 1H), 4.23 – 3.92 (m, 4H), 2.39 (m, 1H), 1.80 (s, 3H), 1.34 (s, 6H), 1.01 (d, 3H, *J* = 7.2 Hz), 0.88 (t, 6H, *J* = 7 Hz), 0.83 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz) δ 176.8, 154.9, 138.7, 134.6, 82.8, 73.4, 63.6, 59.3, 40.7, 31.7, 28.7, 26.1, 18.3, 18.2, 14.9, 14.8, 11.6, –1.8, –1.9; HRMS not obtained (compound unstable under conditions).



Propionate 2.25. Propionic anhydride (80 μL, 0.62 mmol), Et_3N (80 μL, 0.58 mmol), and DMAP (4.7 mg, 0.038 mmol) were added to a solution of alcohol **2.24** (61.6 mg, 0.144 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was heated at reflux for 13 h. The reaction mixture was then cooled to RT, diluted with EtOAc (20 mL), and washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The solution was dried and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **2.25** (63.5 mg, 91%) as a colorless oil. Data for **2.25**: R_f 0.54 (25% EtOAc/hexanes); IR 1785, 1743, 1702 cm^{-1}; ^1H NMR (400 MHz) δ 5.73 (s, 1H), 5.32 (d, 1H, *J* = 10.4 Hz), 4.44 (m, 1H), 4.28 – 4.17 (m, 3H), 2.30 (m, 1H), 2.17 (m, 2H), 1.79 (s, 3H), 1.34 (s, 6H), 1.05 (t, 3H, *J* = 7.6 Hz), 1.01 (d, 3H, *J* = 7.2 Hz), 0.88 (m, 6H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz) δ 175.0, 172.8, 153.9, 141.0, 131.1, 82.2, 73.1, 63.2, 58.7, 39.5, 31.8, 31.6, 28.4, 27.8, 26.1, 18.3, 18.1, 14.7, 14.5, 12.6, 9.3, –1.8, –2.1; HRMS not obtained (compound unstable under conditions).



β-ketolactone 2.26. KHMDS (0.50 M in toluene, 1.0 mL, 0.50 mmol) was added to a solution of propionate **2.25** (61.5 mg, 0.127 mmol) in THF (8 mL) at –78 °C and the reaction mixture was stirred for 2 h. It was then quenched at –78 °C with saturated aqueous NH_4Cl/MeOH/H_2O mixture (1:1:1, 30 mL), warmed to 0 °C, and stirred for 30 min. The mixture was extracted with EtOAc (20 mL). The aqueous phase was acidified to pH 2 with 1 M HCl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **2.26** (13.3 mg, 30%) as a colorless oil. Data for **2.26**: R_f 0.52 (25% EtOAc/hexanes); IR 1765, 1722 cm^{-1}; ^1H NMR (500 MHz, keto tautomer) δ 5.68 (s, 1H), 4.60 (d, 1H, *J* = 10.8 Hz), 3.52 (q, 1H, *J* = 6.5 Hz) 2.49 (m, 1H), 1.85 (s, 3H), 1.41 (s, 3H), 1.39 (s, 1H), 1.38 (d, 3H, *J* = 6.5 Hz), 1.08 (d, 3H, *J* = 7.0 Hz), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz) δ 204.4, 170.0, 142.5, 129.5, 86.7, 73.3, 50.4, 44.5, 31.5, 31.3, 26.1, 18.3, 11.9, 11.5, 8.5, –1.7, –1.8; HRMS not obtained (compound unstable under conditions).



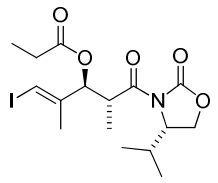
***Anti*- and *syn*-aldol adducts 2.29 and 2.30.** Procedure A: Activated manganese dioxide (40.1 g, 461 mmol) was added to a solution of iodoalcohol **2.28** (9.00 g, 45.5 mmol) in CH_2Cl_2 (150 mL) and the resulting suspension was stirred for 9 h. The reaction mixture was filtered through a

Celite/$MgSO_4$ plug and washed with dry CH_2Cl_2 (450 mL). The filtrate was concentrated and immediately redissolved in dry EtOAc (40 mL). This solution was then transferred via cannula to a flask containing a heterogeneous mixture of $MgCl_2$ (2.03 g, 21.3 mmol), propionyloxazolidinone **2.23** (8.41 g, 45.4 mmol), and Et_3N (12.5 mL, 90.2 mmol) in EtOAc (25 mL). Then TMSCl (11.5 mL, 90.6 mmol) was added and the reaction mixture was stirred at RT for 72 h. The reaction mixture was filtered through a silica gel plug and washed with ether (300 mL). The solution was concentrated, redissolved in methanol (50 mL), and three drops of TFA were added. After being stirred for 10 min the mixture was concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.29** (4.04 g, 23%) as a white solid along with *syn*-aldol diastereomer **2.30** (3.32 g, 19%) as a colorless oil.

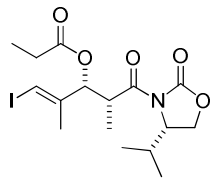
Procedure B: Activated manganese dioxide (1.22 g, 14.0 mmol) was added to a solution of iodoalcohol **2.28** (200 mg, 1.01 mmol) in Et_2O (4 mL) and the resulting suspension was stirred for 1 h. The reaction mixture was filtered through a Celite plug under argon and washed with dry Et_2O (8 mL). The filtrate was dried over 3 Å molecular sieves (powder, 200 mg) for 30 min and cooled to –78 ^oC. In a separate flask propionyloxazolidinone **2.23** (128 mg, 0.691 mmol) was dissolved in Et_2O (2 mL) and cooled to 0 ^oC. *n*-Bu_2BOTf (0.35 mL, 1.40 mmol) was added dropwise to this solution followed by *i*-Pr_2EtN (0.14 mL, 0.804 mmol) and after being stirred for 45 min the mixture was cooled to –78 ^oC. The solution containing the aldehyde was cannulated into this solution over 10 min and the resulting mixture was stirred for 6 h. The reaction mixture was then quenched with tartaric acid (0.52 g) and allowed to warm to RT overnight. Water (20 mL) was then added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and cooled to 0 ^oC. A mixture of 5:1 MeOH:30% aqueous H_2O_2 (12 mL) was added and the mixture was stirred at RT for 30 min. It was then washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried, and concentrated. The resulting biphasic mixture was pushed through a plug of silica using 20% EtOAc/hexanes. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.29** (208 mg, 79%). Suitable crystals for the X-ray analysis were grown by evaporation from hexanes/Et_2O (1:1) with trace MeOH (see the CIF file for experimental details).

Data for **2.29**: R_f 0.33 (25% EtOAc/hexanes); IR 3473, 1781, 1693 cm^{-1}; ^1H NMR (500 MHz) δ 6.33 (s, 1H), 4.42 (m, 1H), 4.29 – 4.18 (m, 4H), 3.19 (d, 1H, *J* = 6.5 Hz), 2.34 (m, 1H), 1.85 (s, 3H), 1.08 (d, 3H, *J* = 6.5 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.87 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz) δ 176.2, 154.5, 147.7, 80.8, 79.9, 63.6, 59.0, 40.2, 28.6, 19.6, 18.1, 14.9, 14.8; HRMS not obtained (compound unstable under conditions); M.P. = 116.0 – 116.5 ^oC; $[\alpha]_D^{23}$ = + 44.7^o (c = 1.00, $CHCl_3$); anal. calcd for $C_{13}H_{20}INO_4$: C, 40.96; H, 5.29; N, 3.67, found: C, 41.25; H, 5.27; N, 3.80.

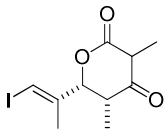
Data for **2.30**: R_f 0.28 (25% EtOAc/hexanes); IR 3481, 1778, 1700 cm^{-1}; ^1H NMR (400 MHz) δ 6.36 (s, 1H), 4.52 – 4.08 (m, 5H), 2.82 (s, 1H), 2.30 (m, 1H), 1.83 (s, 3H), 1.08 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 7.2 Hz), 0.86 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz) δ 175.8, 153.9, 146.5, 79.6, 76.0, 63.5, 58.6, 40.39, 28.6, 21.3, 18.1, 14.9, 10.6; HRMS not obtained (compound unstable under conditions).



Propionate 2.31. Propionic anhydride (1.80 mL, 14.0 mmol), Et_3N (1.80 mL, 13.0 mmol), and DMAP (360 mg, 2.94 mmol) were added to a solution of alcohol **2.29** (4.04 g, 10.6 mmol) in CH_2Cl_2 (100 mL) and the resulting solution was stirred for 1 h. The reaction mixture was then cooled to RT, diluted with CH_2Cl_2 (100 mL) and washed with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The solution was dried and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) gave **2.31** (4.46 g, 96%) as a white solid. Data for **2.31**: R_f 0.38 (25% EtOAc/hexanes); IR 1778, 1738, 1703 cm^{-1}; ^1H NMR (400 MHz) δ 6.55 (s, 1H), 5.56 (d, 1H, *J* = 10.8 Hz), 4.45 – 4.19 (m, 4H), 2.33 – 2.15 (m, 3H), 1.82 (s, 3H), 1.07 (t, 3H, *J* = 7.6 Hz), 1.02 (d, 3H, *J* = 7.2 Hz), 0.89 (m, 6H); ^{13}C NMR (100 MHz) δ 174.1, 172.8, 153.8, 143.2, 84.6, 79.2, 63.4, 58.7, 39.6, 28.5, 27.6, 19.4, 18.1, 14.8, 14.4, 9.1; HRMS (FAB) calculated for fragment $C_{13}H_{19}NO_3I$ $(M\text{-}EtCO_2)^+$: 364.0410, found: 364.0419, M.P. = 125.5 – 126.5 °C; $[\alpha]_D^{23}$ = + 9.9° (c = 1.00, $CHCl_3$); anal. calcd for $C_{16}H_{24}INO_5$: C, 43.95; H, 5.53; N, 3.20, found: C, 44.18; H, 5.53; N, 3.35.

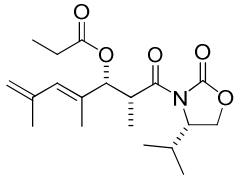


Propionate 2.32. Propionic anhydride (1.30 mL, 10.1 mmol), Et_3N (1.40 mL, 10.1 mmol), and DMAP (204 mg, 1.76 mmol) were added to a solution of alcohol **2.30** (3.19 g, 8.37 mmol) in CH_2Cl_2 (50 mL) and heated at reflux for 2 h. The reaction mixture was then cooled to RT, diluted with CH_2Cl_2 (50 mL) and washed with 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The solution was dried and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) gave **2.32** (3.07 g, 84%) as a white solid. Data for **2.32**: R_f 0.44 (25% EtOAc/hexanes); IR 1778, 1743, 1701 cm^{-1}; ^1H NMR (400 MHz) δ 6.30 (s, 1H), 5.66 (d, 1H, *J* = 6.4 Hz), 4.39 (m, 1H), 4.20 (m, 3H), 2.31 (q, 2H, *J* = 7.6 Hz), 2.15 (m, 1H), 1.84 (s, 3H), 1.09 (m, 6H), 0.85 (d, 3H, *J* = 6.8 Hz), 0.81 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz) δ 173.1, 154.0, 143.9, 81.5, 76.7, 63.5, 58.6, 40.1, 28.5, 27.8, 21.0, 18.2, 14.9, 12.3, 9.3; HRMS (FAB) calculated for fragment $C_{13}H_{19}NO_3I$ $(M\text{-}EtCO_2)^+$: 364.0410, found: 364.0416; M.P. = 77.5 – 78.0 °C; $[\alpha]_D^{23}$ = + 54.5° (c = 1.00, $CHCl_3$); anal. calculated for $C_{16}H_{24}INO_5$: C, 43.95; H, 5.53; N, 3.20, found: C, 43.69; H, 5.62; N, 3.24.

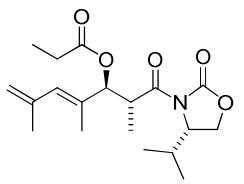


β-ketolactone 2.33. KHMDS (0.50 M in toluene, 5.4 mL, 2.7 mmol) was added to a solution of propionate **2.32** (295 mg, 0.675 mmol) in THF (5 mL) at –78 °C and the reaction mixture was

stirred for 2 h. It was then quenched at –78 °C with saturated aqueous NH_4Cl/MeOH/H_2O mixture (1:1:1, 30 mL), warmed to 0 °C and stirred for 30 min. The mixture was extracted with EtOAc (20 mL). The aqueous phase was acidified to pH 2 with 1 M HCl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried, and concentrated. Purification by silica gel chromatography (35% EtOAc/hexanes) afforded **2.33** (81.4 mg, 39%) as a white solid. Data for **2.33**: R_f 0.40 (35% EtOAc/hexanes); IR 1625 cm^{-1}; ^1H NMR (400 MHz, keto tautomer) δ 6.57 (s, 1H), 4.82 (s, 1H), 3.71 (m, 1H), 2.69 (m, 1H), 1.79 (m, 6H), 1.01 – 0.89 (m, 3H); (enol tautomer) 9.15 (br, 1H), 6.66 (s, 1H), 5.26 (s, 1H), 2.81 (m, 1H), 1.79 (m, 3H), 1.35 (d, 3H, *J* = 6.4 Hz), 1.01 – 0.89 (m, 3H); ^{13}C NMR (100 MHz, both tautomers) δ 204.1, 171.7, 169.9, 169.0, 140.8, 139.2, 97.8, 80.9, 80.3, 80.2, 79.0, 50.6, 43.4, 35.4, 21.9, 21.8, 11.4, 10.4, 8.7, 8.4; HRMS (FAB) calculated for $C_{10}H_{14}O_3I$ $(M+H)^+$: 308.9988, found: 308.9998; $[\alpha]_D^{23}$ = + 162.8° (c = 1.05, $CHCl_3$), decomp. above 120 °C.

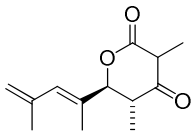


Propionate 2.34. A solution of isopropenyl-tri-*n*-butylstannane (854 mg, 2.58 mmol) and propionate **2.32** (1.02 g, 2.33 mmol) in DMF (6 mL) was evacuated and purged with Ar three times. Then CuI (45.5 mg, 0.239 mmol), $Pd(PPh_3)_4$ (133 mg, 0.115 mmol), and CsF (691 mg, 4.55 mmol) were added. The reaction mixture was stirred at 45 °C for 2 h and at RT overnight. It was then diluted with water (40 mL), filtered through a plug of Celite, and washed with Et_2O (100 mL). The phases were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried, concentrated, and filtered through a silica gel plug. Purification by silica gel chromatography (15% to 30% EtOAc/hexanes) afforded **2.34** (536 mg, 66%) as a light-yellow oil, which solidified upon storage at –30 °C. Data for **2.34**: R_f 0.43 (25% EtOAc/hexanes); IR 1779, 1740, 1702 cm^{-1}; ^1H NMR (400 MHz) δ 5.89 (s, 1H), 5.56 (d, 1H, *J* = 6.4 Hz), 4.97 (s, 1H), 4.79 (s, 1H), 4.44 – 4.41 (m, 1H), 4.29 – 4.17 (m, 3H), 2.34 (q, 2H, *J* = 7.6 Hz), 2.18 (m, 1H), 1.85 (s, 3H), 1.81 (s, 3H), 1.15 – 1.11 (m, 6H), 0.86 (d, 3H, *J* = 7.2 Hz), 0.80 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz) δ 173.8, 173.3, 154.0, 141.2, 132.9, 130.1, 116.1, 78.2, 63.3, 58.6, 40.2, 28.5, 27.9, 23.7, 18.1, 14.8, 14.7, 12.4, 9.4, HRMS not obtained (compound unstable under conditions); M.P. = 46.5 – 48.0 °C; $[\alpha]_D^{23}$ = + 63.3° (c = 1.00, $CHCl_3$).

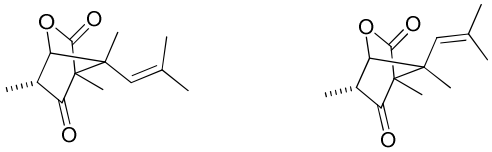


Diene 2.35. A solution of isopropenyl-tri-*n*-butylstannane (454 mg, 1.37 mmol) and propionate **2.31** (500 mg, 1.14 mmol) in DMF (3 mL) was lyophilized three times. Then CuI (50 mg, 0.26 mmol), $Pd(PPh_3)_4$ (95 mg, 0.082 mmol), and CsF (350 mg, 2.3 mmol) were added. The reaction mixture was stirred at 45 °C for 6.5 h in the dark. It was then diluted with Et_2O (30 mL) and water (40 mL), filtered through a plug of Celite, and washed with Et_2O (100 mL). The phases

were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were washed with 10% aqueous NaCl (2 x 30 mL) and brine (30 mL), then dried and concentrated. Purification by silica gel chromatography (2% TEA, 25% EtOAc, 73% hexanes) afforded **2.35** (370 mg, 92%) as a light-yellow oil, which solidified upon storage at 0 °C. Data for **2.35**: R_f 0.50 (25% EtOAc/hexanes); IR 2968, 1782, 1741, 1701 cm^{-1}; ^1H NMR (400 MHz) δ 6.06 (s, 1H), 5.40 (d, 1H, *J* = 10.4 Hz), 5.02 (s, 1H), 4.86 (s, 1H), 4.47 – 4.44 (m, 1H), 4.32 – 4.18 (m, 3H), 2.33 (m, 1H), 2.20 (m, 2H), 1.85 (s, 3H), 1.79 (d, 3H, *J* = 1.2 Hz), 1.09 – 1.04 (m, 6H), 0.91 – 0.88 (m, 6H); ^{13}C NMR (100 MHz) δ 174.9, 173.0, 153.9, 141.1, 133.7, 131.8, 116.5, 82.0, 63.3, 58.7, 39.8, 28.5, 27.8, 23.6, 18.1, 14.8, 14.6, 13.3, 9.2, HRMS (FAB) calculated for $C_{13}H_{19}NO_3ILi$ $(M+Li)^+$: 358.2206, found: 358.2202; M.P. = 48.0 – 51.0 °C; $[\alpha]_D^{23}$ = + 79.9° (c = 1.00, $CHCl_3$); anal. calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99, found: C, 65.02; H, 8.28; N, 3.91.



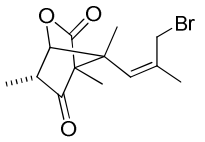
β-ketolactone 2.19. KHMDS (0.885 M in THF, 8.6 mL, 7.6 mmol) was added to a solution of diene **2.35** (670 mg, 1.9 mmol) in THF (40 mL) at –78 °C and the reaction mixture was stirred for 2 h. It was then quenched at –78 °C with saturated aqueous $NH_4Cl/MeOH/H_2O$ mixture (1:1:1, 60 mL) and warmed to RT. The mixture was acidified to pH 3 with 1 M HCl and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.19** (389 mg, 93%) as a white solid. Data for **2.19**: R_f 0.28 (25% EtOAc/hexanes); IR 1746, 1715 cm^{-1}; ^1H NMR (400 MHz) δ 6.01 (s, 1H), 5.11 (t, 1H, *J* = 1.6 Hz), 4.91 (s, 1H), 4.71 (d, 1H, *J* = 10.8 Hz), 3.55 (q, 1H, *J* = 6.8 Hz), 2.53 (m, 1H), 1.88 (s, 3H), 1.85 (d, 3H, *J* = 1.2 Hz), 1.38 (d, 3H, *J* = 6.8 Hz), 1.10 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz) δ 204.4, 169.7, 140.4, 134.6, 130.2, 117.2, 86.1, 50.2, 44.4, 23.2, 12.1, 11.8, 8.3; HRMS (FAB) calculated for $C_{13}H_{18}O_3$ $(M)^+$: 222.1256, found: 222.1255; M.P. = 83.0 – 84.0 °C; $[\alpha]^{23}$ = – 60.7° (c = 1.00, $CHCl_3$, 436 nm Hg); anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16, found: C, 70.01; H, 8.30.

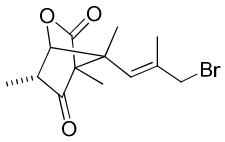


Bicyclic lactones 2.27 and 2.38. To a solution of β-ketolactone **2.19** (501 mg, 2.25 mmol) in benzene (64 mL) was added 10-camphorsulfonic acid (522 mg, 2.25 mmol). The reaction tube was sealed and heated to 150 °C for 3.25 hr. The reaction mixture was then cooled to RT, partially concentrated, filtered through a plug of silica, and washed with 50% Et_2O/hexane (15 mL). The resulting solution was concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes) afforded **2.27** (214 mg, 43%) as a light-yellow solid and its diastereomer **2.38** (113 mg, 22%).

Data for **2.27**: R_f 0.53 (25% EtOAc/hexanes); IR 1794, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 5.10 (d, 1H, J = 2.5 Hz), 4.94 (s, 1H), 2.70 (qd, 1H, J_q = 7.5 Hz, J_d = 2.0 Hz), 1.74 (d, 3H, J = 0.5 Hz), 1.69 (d, 3H, J = 1.0 Hz), 1.34 (s, 3H), 1.21 (d, 3H, J = 7.0 Hz), 1.19, (s, 3H); ^{13}C NMR (126 MHz) δ 208.3, 172.0, 138.4, 121.7, 85.4, 70.4, 57.7, 44.3, 26.9, 20.1, 17.1, 11.8, 4.9; HRMS (EI+) calculated for $C_{13}H_{18}O_3$ $(M)^+$: 222.1256, found: 222.1257; M.P. = 73.0 – 74.0 °C; $[\alpha]_D^{23}$ = –77.9° (c = 1.03, $CHCl_3$); anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16, found: C, 70.50; H, 7.98.

Data for **2.38**: R_f 0.41 (25% EtOAc/hexanes); IR 1793, 1750 cm^{-1}; ^1H NMR (400 MHz) δ 5.15 (t, 1H, J = 1.4 Hz), 5.10 (d, 1H, J = 2.4 Hz), 2.67 (qd, 1H, J_q = 7.4 Hz, J_d = 2.2 Hz), 1.81 (d, 3H, J = 1.2 Hz), 1.76 (d, 3H, J = 1.2 Hz), 1.22 (d, 3H, J = 7.2 Hz), 1.19 (s, 3H), 1.17, (s, 3H); ^{13}C NMR (126 MHz) δ 208.4, 172.3, 138.2, 121.3, 85.0, 70.1, 57.1, 43.3, 27.5, 20.1, 17.7, 11.6, 5.2; HRMS (EI+) calculated for $C_{13}H_{18}O_3$ $(M)^+$: 222.1256, found: 222.1257; M.P. = 63.0 – 64.0 °C; $[\alpha]_D^{23}$ = +76.8° (c = 1.00, $CHCl_3$); anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16, found: C, 70.11; H, 8.28.

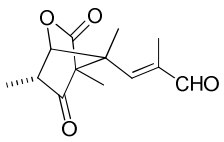




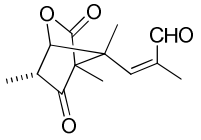
***E* and *Z* bromides 2.39 and 2.40.** To a solution of bicyclic lactone **2.27** (288 mg, 1.29 mmol) in carbon tetrachloride (5.0 mL) were added NBS (236 mg, 1.32 mg) and AIBN (21.0 mg, 0.128 mmol). The reaction mixture was heated to reflux for 1.5 hr, filtered through a plug of silica, and washed with Et_2O/hexanes (1:1, 15 mL). The resulting solution was concentrated. Purification by silica gel chromatography (gradient from 10% to 15% EtOAc/hexanes) afforded *Z*-bromide **2.40** (182 mg, 47%) and *E*-bromide **2.39** (194 mg, 50%) as white solids.

Data for *Z*-bromide **2.40**: R_f 0.55 (25% EtOAc/hexanes); IR 1787, 1753 cm^{-1}; ^1H NMR (500 MHz) δ 5.15 (d, 1H, J = 1.5 Hz), 5.14 (d, 1H, J = 2.0 Hz), 4.08 (d, 1H, J = 10.0 Hz), 3.82 (d, 1H, J = 10.0 Hz), 2.83 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 1.84 (d, 3H, J = 1.5 Hz), 1.37 (s, 3H), 1.18 (m, 6H); ^{13}C NMR (126 MHz) δ 207.8, 171.4, 137.7, 127.3, 85.0, 70.4, 57.6, 44.8, 31.6, 23.0, 17.9, 11.5, 4.9; HRMS (FAB) calculated for $C_{13}H_{18}O_3{}^{79}Br$ $(M+H)^+$: 301.0439, found: 301.0442; M.P. = 117.0 – 118.0 °C; $[\alpha]_D^{23}$ = +139.9° (c = 1.04, $CHCl_3$); anal. calcd for $C_{13}H_{17}O_3Br$: C, 51.84; H, 5.69, found: C, 51.65; H, 5.92.

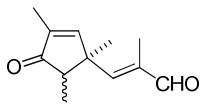
Data for *E*-bromide **2.39**: R_f 0.53 (25% EtOAc/hexanes); IR 1783, 1749 cm^{-1}; ^1H NMR (500 MHz) δ 5.35 (s, 1H), 5.10 (d, 1H, J = 2.0 Hz), 3.83 (s, 2H), 2.61 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 1.89 (d, 3H, J = 1.0 Hz), 1.34 (s, 3H), 1.18 (m, 6H); ^{13}C NMR (126 MHz) δ 207.5, 171.3, 138.2, 126.9, 84.8, 70.0, 57.5, 44.3, 40.0, 17.0, 16.5, 11.8, 4.9; HRMS (FAB) calculated for $C_{13}H_{18}O_3{}^{79}Br$ $(M+H)^+$: 301.0439, found: 301.0444; M.P. = 82.0 – 83.0 °C; $[\alpha]_D^{23}$ = –53.5° (c = 1.07, $CHCl_3$); anal. calcd for $C_{13}H_{17}O_3Br$: C, 51.84; H, 5.69, found: C, 52.01; H, 5.81.



Enal 2.16. To a solution of *E*-bromide **2.39** (29.6 mg, 98.3 μmol) in DMSO (0.5 mL) was added IBX (55.4 mg, 198 μmol). The reaction mixture was heated to 50 °C for 1 hr, diluted with Et_2O/hexanes (30 mL 1:1), and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.16** (19.6 mg, 84%) as a white solid. Suitable crystals for the X-ray analysis were grown by evaporation from EtOAc/Et_2O (9:1) with trace MeOH (see the CIF file for experimental details). Data for **2.16**: R_f 0.26 (25% EtOAc/hexanes); IR 1797, 1752, 1692 cm^{-1}; ^1H NMR (500 MHz) δ 9.32 (s, 1H), 6.18 (d, 1H, J = 1.0 Hz), 5.20 (d, 1H, J = 2.0 Hz), 2.52 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 1.88 (d, 3H, J = 1.5 Hz), 1.44 (s, 3H), 1.29 (s, 3H), 1.22 (d, 3H, J = 7.0 Hz); ^{13}C NMR (126 MHz) δ 206.6, 193.8, 170.5, 147.2, 142.3, 84.2, 69.7, 58.3, 44.8, 16.1, 11.8, 11.1, 4.9; HRMS (FAB) calculated for $C_{13}H_{17}O_4$ $(M+H)^+$: 237.1127, found: 237.1124; M.P. = 139.5 – 140.5 °C; $[\alpha]_D^{23}$ = –99.5° (c = 1.00, $CHCl_3$); anal. calcd for $C_{13}H_{17}O_3Br$: C, 66.09; H, 6.83, found: C, 65.79; H, 6.90.

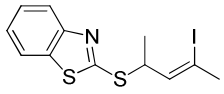


Enal 2.41. To a solution of *Z*-allylic bromide **2.40** (97.6 mg, 0.324 mmol) in DMSO (1.0 mL) was added IBX (182 mg, 0.650 μmol). The reaction mixture was heated to 50 °C for 1 hr, diluted with Et_2O/hexanes (30 mL 1:1), and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.41** (67.4 mg, 88%) as a white solid. Data for **2.41**: R_f 0.38 (25% EtOAc/hexanes); IR 1797, 1753, 1681 cm^{-1}; ^1H NMR (500 MHz) δ 10.08 (s, 1H), 6.07 (d, 1H, J = 1.0 Hz), 5.22 (d, 1H, J = 1.5 Hz), 2.65 (qd, 1H, J_q = 7.0 Hz, J_d = 2.0 Hz), 1.87 (d, 3H, J = 1.0 Hz), 1.51 (s, 3H), 1.26 (s, 3H), 1.21 (d, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz) δ 207.0, 190.6, 170.5, 141.1, 139.6, 86.3, 70.6, 58.0, 44.8, 19.6, 18.0, 11.8, 4.9; HRMS (FAB) calculated for $C_{13}H_{17}O_4$ $(M+H)^+$: 237.1127, found: 237.1124; M.P. = 108.9 – 109.0 °C; $[\alpha]_D^{23}$ = –61.0° (c = 0.83, $CHCl_3$); anal. calcd for $C_{13}H_{17}O_3Br$: C, 66.09; H, 6.83, found: C, 66.14; H, 6.97.

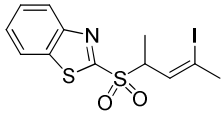


Cyclopentenone 2.43. To a solution of diethylphosphonopropanal (24.9 mg, 128 μmol) and DBU (30 μL, 201 μmol) in toluene (1.0 mL) at 0 °C was added *E*-enal **2.16** (19.5 mg, 82.5 μmol) as a solution in toluene (1.0 mL) using more toluene (2 x 0.5 mL) to wash the cannula. After 15 min the reaction mixture was warmed to RT, quenched with water (5.0 mL), extracted with Et_2O (40 mL), washed with brine (5.0 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes, pretreated with TEA) afforded an inseparable 2:1 mixture of diastereomers **2.43** (14.4 mg, 91%) as a colorless oil. Data for **2.43**: R_f 0.49 (25%

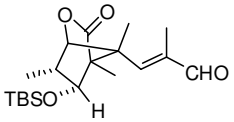
EtOAc/hexanes); ^{1}H NMR (500 MHz) δ 9.37 (s, 1H, minor), 9.35 (s, 1H, major), 7.24 (d, 1H, *J* = 1.0 Hz, major), 7.21 (d, 1H, *J* = 1.2 Hz, minor), 6.49 (d, 1H, *J* = 1.1 Hz, major), 6.28 (d, 1H, *J* = 1.1 Hz, minor), 2.50 (q, 1H, *J* = 7.4 Hz, major), 2.33 (q, 1H, *J* = 7.6 Hz, minor), 1.82 (d, 3H, *J* = 1.3 Hz, minor), 1.81 (d, 3H, *J* = 1.3 Hz, major), 1.76 (d, 3H, *J* = 1.1 Hz, major), 1.70 (d, 3H, *J* = 1.1 Hz, minor), 1.46 (s, 3H, minor), 1.26 (s, 3H, minor), 1.19 (d, 3H, *J* = 7.5 Hz, major), 1.04 (d, 3H, *J* = 7.6 Hz, minor); ^{13}C NMR (126 MHz) δ 210.2, 209.5, 195.7 (2 signals), 162.0, 161.5, 158.0, 155.7, 140.3, 139.5, 139.2, 139.0, 53.3, 51.5, 48.5, 47.4, 28.6, 24.3, 12.5, 10.8, 10.6, 10.3 (two signals), 10.1; HRMS (FAB) calculated for $C_{12}H_{16}O_2$ $(M)^+$: 192.1150, found: 192.1154.



Sulfide 2.45. DEAD (1.20 mL, 7.62 mmol) was added dropwise to a solution of iodoalcohol **2.44** (866 mg, 4.09 mmol), PPh_3 (1.62 g, 6.17 mmol), and 2-mercaptobenzothiazole (1.39 g, 8.29 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm up to RT and was stirred for 72 h. It was then filtered through a plug of silica gel, washed with Et_2O/hexane (50%, 100 mL), and concentrated. Purification by silica gel chromatography (5% EtOAc/hexane) afforded **2.45** (959 mg, 65%) as a colorless oil. Data for **2.45**: R_f 0.58 (10% EtOAc/hexane); IR 1456, 1426, 991, 776 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.93 (d, 1H, *J* = 8.5 Hz), 7.76 (d, 1H, *J* = 7.5 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 5.62 (dq, 1H, *J* = 9 Hz, 1.5 Hz), 4.53 (dq, 1H, *J* = 9 Hz, 7 Hz), 2.51 (d, 3H, *J* = 1.5 Hz), 1.58 (d, 3H, *J* = 7 Hz); ^{13}C NMR (126 MHz) δ 164.9, 153.4, 136.0, 135.9, 126.1, 124.5, 122.1, 121.0, 103.7, 50.5, 33.7, 20.7; HRMS (EI) calculated for $C_{12}H_{12}INS_2$ $(M)^+$: 360.9456, found: 360.9450.



Sulfone 2.46. A solution of $(NH_4)_6Mo_7O_{24}\cdot(H_2O)_4$ (637 mg, 0.516 mmol) in 30% aqueous H_2O_2 (3 mL) was added dropwise to a solution of **2.45** (927 mg, 2.57 mmol) in EtOH (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h. Then water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (25 mL x 3). The combined organic extracts were dried and concentrated. Purification by silica gel chromatography (15% EtOAc/hexane) afforded **2.46** (557 mg, 55%) as a colorless oil. Data for **2.46**: R_f 0.24 (10% EtOAc/hexane); IR 1470, 1330, 1149 cm^{-1}; ^{1}H NMR (400 MHz) δ 8.25 (m, 1H), 8.01 (m, 1H), 7.61 (m, 2H), 5.61 (dq, 1H, *J* = 9.8 Hz, 1.4 Hz), 4.46 (dq, 1H, *J* = 9.8 Hz, 7.0 Hz), 2.47 (d, 3H, *J* = 1.2 Hz), 1.59 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz) δ 164.5, 153.0, 137.6, 128.5, 128.2, 127.8, 125.8, 122.4, 109.5, 68.2, 34.3, 12.8; HRMS (FAB) calculated for $C_{12}H_{12}IO_2NS_2$ $(M+H)^+$: 393.9432, found: 393.9443.



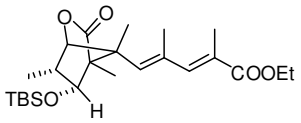
Enal 2.47. $NaBH_4$ (98.8 mg, 2.61 mmol) was added to a solution of bicyclic lactone **2.27** (285 mg, 1.28 mmol) in dry MeOH (5.0 mL) at –20 °C. The reaction mixture was warmed to room

temperature and quenched with AcOH (0.02 mL) after 30 min. The crude reaction mixture was then filtered through a plug of silica and concentrated.

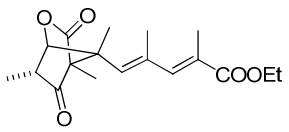
The resulting oil was taken up in dry THF (5.0 mL) and TEA (0.25 mL, 1.8 mmol) followed by TBSOTf (0.35 mL, 1.5 mmol) were added. After 70 min the crude reaction mixture was filtered through a plug of silica and concentrated to afford crude oil (441 mg).

To the crude oil in carbon tetrachloride (5.0 mL) were added NBS (228 mg, 1.28 mg) and AIBN (17.5 mg, 0.107 mmol). The reaction mixture was heated to reflux for 80 min, filtered through a plug of silica, washed with Et_2O/hexanes (1:1, 15 mL), and concentrated to afford crude oil (603 mg).

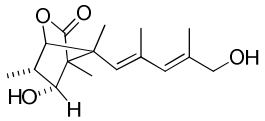
To the crude oil in DMSO (2.0 mL) was added IBX (720 mg, 2.57 mmol). The reaction mixture was heated to 50 ^oC for 1 hr, diluted with Et_2O/hexanes (30 mL 1:1), washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.47** (150 mg, 33% over 4 steps) as a white solid along with other diastereomers. Data for **2.47**: R_f 0.46 (25% EtOAc/hexanes); ^1H NMR (500 MHz) δ 9.41 (s, 1H), 6.31 (d, 1H, *J* = 1.0 Hz), 4.67 (s, 1H), 3.98 (d, 1H, *J* = 8.8 Hz), 2.26 (m, 1H), 1.81 (d, 3H, *J* = 1.1 Hz), 1.22 (s, 3H), 1.19 (s, 3H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz) δ 194.5, 175.2, 149.9, 140.9, 85.4, 74.9, 60.5, 54.8, 37.3, 25.8, 18.3, 15.9, 10.6, 10.3, 8.6, –4.2, –4.5; HRMS (FAB) calculated for $C_{19}H_{33}O_4Si$ $(M+H)^+$: 353.2148, found: 353.2141; M.P. = 134.0 – 135.0 ^oC.



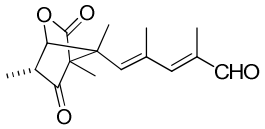
Dienoate 2.48. Sodium hydride (60% in mineral oil, 32.0 mg, 0.80 mmol) was added to a solution of triethylphosphonopropionate (163 mg, 0.686 mmol) in THF (2.0 mL). After 15 min enal **2.47** (150 mg, 0.426 mmol) was added via a cannula as a solution in THF (2.0 mL) using THF (1.0 mL) to aid the transfer. After 1.5 h the crude reaction mixture was filtered through a plug of silica and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **2.48** (131 mg, 71%) as a colorless oil along with the unreacted starting material. Data for **2.48**: R_f 0.59 (25% EtOAc/hexanes); ^1H NMR (400 MHz) δ 7.03 (s, 1H), 5.36 (s, 1H), 4.62 (s, 1H), 4.20 (q, 2H, *J* = 7.1 Hz), 4.00 (d, 1H, *J* = 8.8 Hz), 2.41 (m, 1H), 1.95 (s, 3H), 1.83 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz), 1.14 (s, 3H), 1.10 (s, 3H), 0.95 (d, 3H, *J* = 7.2 Hz), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz) δ 176.1, 168.7, 142.3, 135.3, 132.2, 127.4, 86.2, 75.0, 61.1, 60.9, 54.3, 37.1, 25.8, 18.2, 17.9, 16.5, 14.5, 14.2, 10.4, 8.5, –4.3, –4.6; HRMS (FAB) calculated for $C_{24}H_{40}O_5SiLi$ $(M+Li)^+$: 443.2805, found: 443.2810.



Dienoate 2.49. Sodium hydride (60% in mineral oil, 32.2 mg, 0.805 mmol) was added to a solution of triethylphosphonopropionate (220 mg, 0.924 mmol) in THF (1.0 mL) at –30 °C. After 15 min enal **2.16** (105 mg, 0.443 mmol) was added via a cannula as a solution in THF (1.0 mL) using THF (1.0 mL) to aid the transfer. The reaction was quenched with saturated aqueous NH_4Cl (3.0 mL) after 2 min. The mixture was extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **2.49** (138 mg, 97%) as a colorless oil that solidified upon storage at 4°C. Data for **2.49**: R_f 0.37 (25% EtOAc/hexanes); IR 1797, 1753, 1709 cm^{-1}; ^1H NMR (500 MHz) δ 6.95 (s, 1H), 5.25 (d, 1H, *J* = 1.0 Hz), 5.16 (d, 1H, *J* = 2.5 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 2.69 (qd, 1H, J_q = 7.3 Hz, J_d = 2.0 Hz), 1.92 (d, 3H, *J* = 1.0 Hz), 1.88 (d, 3H, *J* = 1.0 Hz), 1.40 (s, 3H), 1.28 (t, 3H, *J* = 7.3 Hz), 1.20 (d, 3H, *J* = 7.5 Hz), 1.18 (s, 3H); ^{13}C NMR (126 MHz) δ 207.5, 171.3, 168.4, 141.0, 137.5, 129.9, 128.6, 84.9, 70.2, 61.2, 58.2, 44.5, 18.7, 16.8, 14.4, 14.2, 11.8, 4.9; HRMS (FAB) calculated for $C_{18}H_{25}O_5$ $(M+H)^+$: 321.1702, found: 321.1697; M.P. = 65.5 – 66.5 °C; $[\alpha]_D^{23}$ = –29.6° (c = 0.90, $CHCl_3$).

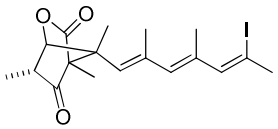


Diol 2.50. $LiEt_3BH$ (1.0 M in THF, 0.60 mL, 0.60 mmol) was added to a solution of dienoate **2.49** (46.4 mg, 0.145 mmol) in THF (1.0 mL) at –78 °C. The reaction was quenched with saturated aqueous NH_4Cl (3.0 mL) after 10 min. The mixture was extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (50% EtOAc/hexanes) afforded **2.50** (38.4 mg, 95%) as a colorless oil. Data for **2.50**: R_f 0.18 (50% EtOAc/hexanes); IR 3426, 1777, 1765 cm^{-1}; ^1H NMR (500 MHz) δ 5.83 (s, 1H), 5.17 (s, 1H), 4.67 (s, 1H), 4.11 (d, 1H, *J* = 9.5 Hz), 4.04 (s, 2H), 2.54 (m, 1H), 2.11 (bs, 1H), 1.79 (bs, 1H), 1.75 (s, 6H), 1.19 (s, 3H), 1.15 (s, 3H), 1.02 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz) δ 177.4, 136.03, 135.97, 128.7, 127.5, 86.9, 74.6, 68.8, 61.0, 54.4, 36.6, 18.7, 16.6, 15.5, 9.4, 8.0; HRMS (FAB) calculated for $C_{16}H_{24}O_4Li$ $(M+Li)^+$: 287.1835, found: 287.1832; $[\alpha]_D^{23}$ = –12.5° (c = 1.05, $CHCl_3$).

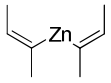


Dienal 2.51. Dess-Martin periodinane (422 mg, 0.995 mmol) was added to a solution of the diol **2.50** (86.2 mg, 0.307 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 20 min the reaction mixture was diluted with Et_2O (5 mL) and quenched with a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (5.0 mL, 1:1). After 15 min the phases were separated and the aqueous phase was extracted with Et_2O (5 x 2 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (20%

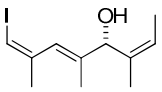
EtOAc/hexanes) afforded **2.51** (73.7 mg, 87%) as a colorless oil that solidified upon storage at 4°C. Data for **2.51**: R_f 0.19 (25% EtOAc/hexanes); IR 1797, 1753, 1678 cm^{-1}; ^1H NMR (500 MHz) δ 9.38 (s, 1H), 6.61 (s, 1H), 5.50 (s, 1H), 5.20 (d, 1H, J = 2.0 Hz), 2.68 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 2.07 (s, 3H), 1.87 (s, 3H), 1.43 (s, 3H), 1.22 (m, 6H); ^{13}C NMR (126 MHz) δ 207.5, 195.8, 171.3, 152.4, 138.5, 137.9, 133.7, 85.0, 70.4, 58.5, 44.9, 18.7, 16.8, 12.1, 11.3, 5.2; HRMS not obtained (compound unstable under conditions); M.P. = 118.5 – 120.0 °C; $[\alpha]_D^{23}$ = –41.6° (c = 1.45, $CHCl_3$).



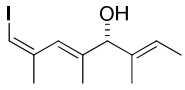
Iodotriene 2.14. *n*-BuLi (2.5 M in hexanes, 0.10 mL, 0.25 mmol) was added to a solution of (ethyl)triphenylphosphonium iodide (98.5 mg, 0.235 mmol) in THF (1.0 mL) at RT. The mixture was stirred for 20 minutes and then transferred into a solution of I_2 (63.3 mg, 0.249 mmol) in THF (0.5 mL) at –78 °C. The reaction mixture became very viscous. The temperature was then elevated to –20 °C, and KHMDS (0.91 M in THF, 0.23 mL, 0.21 mmol) was added. The mixture turned a deep red color. Dienal **2.51** (31.6 mg, 0.114 mmol) in THF (1.0 mL) was added to the reaction mixture via a cannula using THF (1.0 mL) to aid the transfer. The reaction was quenched with saturated aqueous NH_4Cl (3.0 mL) after 10 min. The mixture was extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes) afforded **2.14** (15.3 mg, 32%) as a light-yellow oil. Data for **2.14**: R_f 0.21 (10% EtOAc/hexanes); IR 1797, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 5.96 (s, 1H), 5.80 (s, 1H), 5.16 (d, 1H, J = 2.0 Hz), 5.11 (s, 1H), 2.76 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 2.56 (d, 3H, *J* = 1.5 Hz), 1.87 (d, 3H, *J* = 1.0 Hz), 1.78 (d, 3H, *J* = 0.5 Hz), 1.41 (s, 3H), 1.22 (d, 3H, *J* = 7.0 Hz), 1.20 (s, 3H); ^{13}C NMR (126 MHz) δ 207.9, 171.7, 137.97, 137.91, 136.1, 133.6, 126.2, 98.7, 85.2, 70.3, 58.3, 44.4, 35.2, 19.2, 18.0, 17.0, 11.9, 5.0; HRMS (FAB) calculated for $C_{18}H_{24}IO_3$ $(M+H)^+$: 415.0770, found: 415.0758; $[\alpha]_D^{23}$ = +12.8° (c = 0.77, $CHCl_3$).



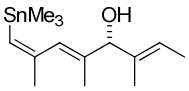
Dialkenyl zinc 2.53. *E*-2-butenyl bromide (1.80 mL, 17.7 mmol) followed by small pieces of lithium (270 mg, 38.5 mmol) were added to a suspension of $ZnBr_2$ (2.00 g, 8.88 mmol) in Et_2O (15.0 mL) in a 100 mL Schlenk flask and the reaction mixture was sonicated for 1.5 h at 0 °C. Et_2O was removed with a high vacuum pump, and the remaining black viscous mixture was extracted with toluene (2 x 10 mL) and concentrated with a high vacuum pump. Purification of the resulting black tar by sublimation (0.3 mmHg, 40 °C) afforded **2.53** (476 mg, 31%) as a white crystalline solid that is extremely moisture-sensitive. Data for **2.53**: ^1H NMR (400 MHz) δ 6.24 (qq, 1H, J_1 = 6.3 Hz, J_1 = 1.6 Hz), 1.87 (quintet, 3H, *J* = 1.6 Hz), 1.74 (dq, 3H, J_d = 6.3 Hz, J_q = 1.5 Hz); ^{13}C NMR (100 MHz) δ 150.1, 136.1, 26.3, 22.9; anal. calcd for $C_8H_{14}Zn$: C, 54.72; H, 8.04, found: C, 54.56; H, 8.13.



Dialkenyl carbinol 2.55. To a solution of dialkenyl zinc **2.53** (101 mg, 0.574 mmol) in toluene (2.0 mL) was added a solution of ligand **2.56** (211 mg, 0.574 mmol) in toluene (4.0 mL) and the reaction mixture was cooled to –30 °C. After 20 min the aldehyde **2.54** (79.3 mg, 0.336 mmol) was added via a cannula as a solution in toluene (2.0 mL). After 24 h the reaction mixture was quenched with water (5.0 mL) and extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **2.55** (21.6 mg, 27%) as a light-yellow oil. Data for **2.55**: R_f 0.28 (10% EtOAc/hexanes); IR 3385 cm^{-1}; ^1H NMR (500 MHz) δ 6.06 (s, 1H), 6.04 (s, 1H), 5.48 (q, 1H, J = 6.6 Hz), 5.05 (s, 1H), 1.97 (s, 3H), 1.73 (dd, 3H, J_1 = 6.9 Hz, J_2 = 1.3 Hz), 1.68 (s, 3H), 1.60 (br s, 1H), 1.57 (s, 3H); ^{13}C NMR (100 MHz) δ 145.4, 139.3, 135.4, 125.9, 123.7, 76.9, 72.5, 24.9, 17.7, 15.3, 13.6; HRMS (FAB) calculated for $C_{11}H_{16}I$ $(M–OH)^+$: 275.0297, found: 275.0293; $[\alpha]_D^{23} = –80^o$ (c = 0.76, $CHCl_3$).

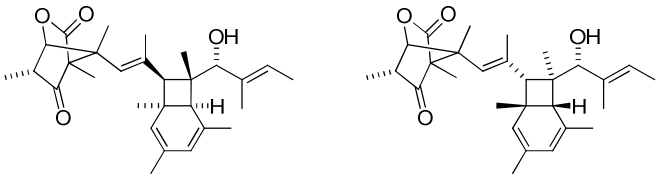


Dialkenyl carbinol 2.58. 2-Butyne **2.57** (0.10 mL, 1.3 mmol) was added dropwise to a slurry of dicyclohexylborane (151 mg, 0.848 mmol) in toluene (0.5 mL) at RT and the reaction mixture became clear within 2 min. After 1 hr the reaction mixture was cooled to –78 °C and Me_2Zn (2.0 M in toluene, 0.5 mL, 1.0 mmol) was added. After 1 hr the ligand **2.56** (46.8 mg, 0.127 mmol) in toluene (1.5 mL) was added to the reaction mixture via a cannula. Then the temperature was increased to –30 °C over a period of 0.5 h, the aldehyde **2.54** (106 mg, 0.449 mmol) was added, and the final mixture was allowed to stir for 10 h at –30 °C. The reaction was quenched with water (5.0 mL) and the resulting mixture extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexanes) afforded **2.58** (83.8 mg, 64%) as a light-yellow oil along with recovered **2.54** (34.7 mg). Data for **2.58**: R_f 0.28 (10% EtOAc/hexanes); IR 3384 cm^{-1}; ^1H NMR (500 MHz) δ 6.04 (s, 2H), 5.63 (q, 1H, J = 6.5 Hz), 4.44 (s, 1H), 1.98 (d, 3H, J = 0.5 Hz), 1.68 (bs, 1H), 1.66 (d, 3H, J = 6.0 Hz), 1.59 (s, 3H), 1.55 (d, 3H, J = 1.0 Hz); ^{13}C NMR (126 MHz) δ 145.2, 139.4, 135.7, 127.3, 122.2, 81.6, 77.1, 24.9, 14.7, 13.5, 12.0; HRMS (FAB) calculated for $C_{11}H_{16}I$ $(M–OH)^+$: 275.0297, found: 275.0293; $[\alpha]_D^{23} = –23.8^o$ (c = 1.03, $CHCl_3$). Analysis of enantiomers by chiral HPLC (Chiralcel AD, flow rate 1.0 mL/min, 99:1 hexanes:ethanol, T_r minor 12.72, major 13.08 min) determined the e.e. to be 95%.



Stannane 2.15. *n*-BuLi (2.19 M in hexanes, 2.70 mL, 5.91 mmol) was added to a solution of iodide **2.58** (832 mg, 2.85 mmol) in THF (6.0 mL) at –78 °C. After 10 min trimethyltin chloride (1.0 M in THF, 6.0 mL, 6.0 mmol) was added. The reaction was quenched with water (10 mL) after 10 min and the resulting mixture extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel

chromatography (5% EtOAc/hexanes) afforded **2.15** (212 mg, 23%) as a light-yellow oil. Data for **2.15**: R_f 0.26 (10% EtOAc/hexanes); IR 3385 cm^{-1}; ^1H NMR (500 MHz) δ 6.16 (s, 1H), 5.80 (s, 1H, $^2J_{Sn}$ = 79.8 Hz), 5.58 (q, 1H, *J* = 5.5 Hz), 4.36 (s, 1H); 2.02 (d, 3H, *J* = 1.0 Hz), 1.64 (d, 3H, *J* = 6.5 Hz), 1.60 (d, 3H, *J* = 1.0 Hz), 1.52 (s, 3H), 0.10 (s, 9H, $^2J_{119Sn}$ = 55.0 Hz, $^2J_{117Sn}$ = 52.5 Hz); ^{13}C NMR (126 MHz) δ 152.3, 137.1, 136.0, 130.5, 129.4, 121.6, 81.9, 27.7, 14.3, 13.4, 11.9, –8.74 ($^1J_{119Sn}$ = 348 Hz, $^1J_{117Sn}$ = 331 Hz); HRMS (FAB) calculated for $C_{14}H_{25}{}^{120}Sn$ $(M–OH)^+$: 313.0978, found: 313.0981; $[\alpha]_D{}^{23}$ = –19.0° (c = 0.98, $CHCl_3$).



Shimalactones A and B 2.1 and 2.2. To a solution of **2.15** (31.3 mg, 95.1 μmol) and **2.14** (12.5 mg, 30.2 μmol) in DMF (0.5 mL) was added tetrakis-triphenylphosphine palladium (5.0 mg, 4.3 μmol) and copper(I) thiophene-2-carboxylate (10.2 mg, 53.5 μmol). The reaction mixture was stirred at RT. After 1 hr it was diluted with a mixture of Et_2O:hexane (4 mL 1:1), pushed through a plug of silica, and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) afforded a mixture of shimalactone A and B (9.0 mg, 66%, 5:1 d.r.) as a colorless oil. While shimalactone A (3.0 mg) was purified by reverse phase HPLC (econocil C18, MeOH/H_2O), shimalactone B was characterized as a mixture with shimalactone A.

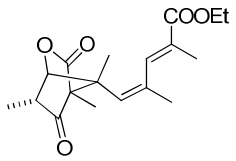
Data for shimalactone A **2.1**: R_f 0.48 (25% EtOAc/hexanes); IR 3527, 2936, 1795, 1750 cm^{-1}; HRMS (FAB) calculated for $C_{29}H_{40}O_4Li$ $(M+Li)^+$: 459.3087, found: 459.3101; $[\alpha]_D{}^{23}$ = +10.9° (c = 0.58, MeOH).

^1H NMR isolation from natural sources	^1H NMR current synthesis (500 MHz)	^{13}C NMR isolation	^{13}C NMR current
5.49 (q, 1H, *J* = 6.6 Hz)	5.49 (q, 1H, *J* = 6.5 Hz)	207.6	207.6
5.46 (s, 1H)	5.46 (s, 1H)	171.8	171.7
5.27 (s, 1H)	5.27 (s, 1H)	138.2	138.2
5.10 (d, 1H, *J* = 2.2 Hz)	5.11 (d, 1H, *J* = 2.5 Hz)	136.5	136.5
4.83 (s, 1H)	4.83 (s, 1H)	132.5	132.6
3.84 (s, 1H)	3.85 (s, 1H)	129.4	129.4
2.68 (s, 1H)	2.68 (s, 1H)	123.9	123.85
2.60 (qd, 1H, *J* = 7.2 Hz, *J* = 2.2 Hz)	2.60 (qd, 1H, *J* = 7.3 Hz, *J* = 2.3 Hz)	123.8	123.80
2.39 (s, 1H)	2.40 (s, 1H)	123.5	123.5
1.71 (s, 3H)	1.71 (s, 3H)	122.5	122.5
1.65 (s, 6H)	1.66 (s, 6H)	86.3	86.3
1.60 (d, 3H, *J* = 6.6 Hz)	1.61 (d, 3H, *J* = 7.0 Hz)	85.2	85.1
1.55 (s, 3H)	1.55 (s, 3H)	70.1	70.1
1.34 (s, 3H)	1.34 (s, 3H)	60.7	60.7
1.19 (d, 3H, 7.2 Hz)	1.19 (d, 3H, 7.5 Hz)	58.3	58.2

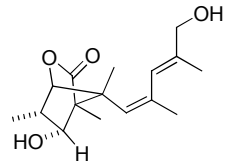
1.15 (s, 3H)	1.16 (s, 3H)	51.7	51.7
1.10 (s, 3H)	1.10 (s, 3H)	49.6	49.6
1.01 (s, 3H)	1.01 (s, 3H)	44.0	44.0
		41.2	41.2
		31.9	31.9
		23.3	23.3
		22.1	22.0
		20.6	20.5
		16.8	16.8
		14.4	14.4
		13.2	13.2
		13.1	13.1
		11.6	11.6
		4.7	4.7

Data for shimalactone B **2.2**: R_f 0.48 (25% EtOAc/hexanes). As shimalactone B was obtained as a mixture with shimalactone A and thus was not characterized beyond ^{1}H NMR.

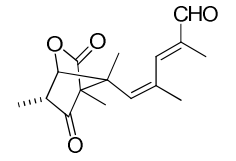
^{1}H NMR isolation from natural sources	^{1}H NMR current synthesis (500 MHz)
5.46 (s, 1H)	5.46 (s, 1H)
5.42 (q, 1H, *J* = 6.6 Hz)	5.41 (q, 1H, *J* = 6.5 Hz)
5.28 (s, 1H)	5.27 (s, 1H)
5.12 (d, 1H, *J* = 1.9 Hz)	5.13 (s, 1H)
4.76 (s, 1H)	4.75 (s, 1H)
3.66 (s, 1H)	3.66 (s, 1H)
3.03 (s, 1H)	3.03 (s, 1H)
2.77 (qd, 1H, *J* = 7.4 Hz, *J* = 1.9 Hz)	2.77 (qd, 1H, *J* = 7.3 Hz, *J* = 2.3 Hz)
2.68 (s, 1H)	2.68 (s, 1H)
1.77 (s, 3H)	1.77 (s, 3H)
1.66 (s, 3H)	1.66 (s, 3H)
1.58 (d, 3H), 1.57 (s, 3H)	1.57 (m, 6H)
1.50 (s, 3H)	1.49 (s, 3H)
1.32 (s, 3H)	1.32 (s, 3H)
1.21 (d, 3H, 7.4 Hz)	1.20 (d, 3H, 7.5 Hz)
1.15 (s, 3H)	1.16 (s, 3H)
1.13 (s, 3H)	1.13 (s, 3H)
0.98 (s, 3H)	0.97 (s, 3H)



Dienoate 2.59. Sodium hydride (60% in mineral oil, 124 mg, 3.10 mmol) was added to a solution of triethylphosphonopropionate (842 mg, 3.53 mmol) in THF (3.0 mL) at –10 °C. After 15 min enal **2.41** (419 mg, 1.77 mmol) was added via a cannula as a solution in THF (3.0 mL) using THF (2.0 mL) to aid the transfer. The reaction was quenched with saturated aqueous NH_4Cl (5.0 mL) after 2 min. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (15 mL), dried, and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) afforded **2.59** (381 mg, 67%) as a colorless oil. Data for **2.59**: R_f 0.49 (25% EtOAc/hexanes); IR 1799, 1752, 1714 cm^{-1}; ^1H NMR (500 MHz) δ 7.22 (s, 1H), 5.20 (d, 1H, J = 1.0 Hz), 4.94 (d, 1H, J = 2.0 Hz), 4.25 (q, 2H, J = 7.2 Hz), 2.65 (qd, 1H, J_q = 7.0 Hz, J_d = 2.0 Hz), 1.88 (d, 3H, J = 1.0 Hz), 1.84 (s, 3H), 1.33 (t, 3H, J = 7.0 Hz), 1.29 (s, 3H), 1.18 (s, 3H), 1.16 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz) δ 207.9, 171.6, 167.6, 137.2, 137.1, 130.9, 126.8, 85.0, 70.1, 61.4, 58.0, 44.2, 24.0, 16.9, 14.4 (2C), 11.7, 4.8; HRMS (FAB) calculated for $C_{18}H_{25}O_5$ $(M+H)^+$: 321.1702, found: 321.1700; $[\alpha]_D^{23}$ = –17.1° (c = 1.46, $CHCl_3$).

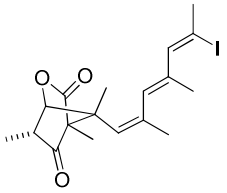


Diol 2.60. $LiEt_3BH$ (1.0 M in THF, 4.8 mL, 4.8 mmol) was added to a solution of ester **2.59** (381 mg, 1.19 mmol) in THF (3.0 mL) at –78 °C. The reaction was quenched with saturated aqueous NH_4Cl (3.0 mL) after 10 min. The mixture was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (50% EtOAc/hexanes) afforded **2.60** (332 mg, 99.6%) as a colorless oil. Data for **2.60**: R_f 0.26 (50% EtOAc/hexanes); IR 3425, 1765 cm^{-1}; ^1H NMR (400 MHz) δ 6.00 (s, 1H), 5.18 (s, 1H), 4.54 (s, 1H), 4.09 (d, 1H, J = 12.5 Hz), 4.05 (s, 2H), 2.51 (m, 1H), 2.27 (bm, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.95 (d, 3H, J = 9.5 Hz); ^{13}C NMR (100 MHz) δ 178.1, 138.1, 136.4, 125.8, 122.9, 87.2, 74.5, 67.5, 60.9, 54.4, 36.1, 25.2, 16.4, 15.5, 9.3, 7.9; HRMS (FAB) calculated for $C_{16}H_{24}O_4Li$ $(M+Li)^+$: 287.1835, found: 287.1829; $[\alpha]_D^{23}$ = +15.2° (c = 1.52, $CHCl_3$).

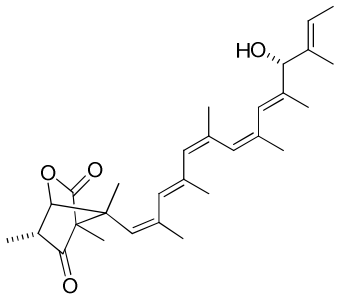


Dienal 2.61. Dess-Martin periodinane (189 mg, 0.446 mmol) was added to a solution of the diol **2.60** (38.4 mg, 0.137 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 20 min the reaction mixture was diluted with Et_2O (5 mL) and the reaction was quenched with a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (5.0 mL, 1:1). After 15 min the phases were separated

and the aqueous phase was extracted with Et_2O (5 x 2 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded **2.61** (31.6 mg, 84%) as a white solid. Data for **2.61**: R_f 0.32 (25% EtOAc/hexanes); IR 1790, 1750, 1681 cm^{-1}; ^1H NMR (500 MHz) δ 9.54 (s, 1H), 6.98 (s, 1H), 5.32 (s, 1H), 4.97 (d, 1H, J = 2.0 Hz), 2.66 (qd, 1H, J_q = 7.3 Hz, J_d = 2.3 Hz), 1.96 (d, 3H, *J* = 0.5 Hz), 1.86 (d, 3H, *J* = 1.0 Hz), 1.35 (s, 3H), 1.21 (s, 3H), 1.17 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz) δ 207.5, 194.5, 171.2, 146.5, 140.8, 136.8, 129.4, 84.9, 70.3, 57.9, 44.3, 24.2, 17.1, 11.7, 11.3, 4.9; HRMS (FAB) calculated for $C_{16}H_{20}O_4Li$ $(M+Li)^+$: 283.1522, found: 283.1524; M.P. = 95.5 – 97.0 °C; $[\alpha]_D^{23}$ = –19.3° (c = 1.02, $CHCl_3$).



Iodotriene 2.62. *n*-BuLi (2.5 M in hexanes, 0.52 mL, 1.3 mmol) was added to a solution of (ethyl)triphenylphosphonium iodide (549 mg, 1.31 mmol) in THF (2.0 mL) at RT. The mixture was stirred for 20 minutes and then transferred into a solution of I_2 (334 mg, 1.33 mmol) in THF (1.0 mL) at –78 °C. The reaction mixture became very viscous. The temperature was then elevated to –20 °C, and NaHMDS (2.0 M in THF, 0.61 mL, 1.22 mmol) was added. The mixture turned a deep red color. Aldehyde **2.61** (181 mg, 0.655 mmol) in THF (1.0 mL) was added to the reaction mixture via a cannula using THF (1.0 mL) to aid the transfer. The reaction was quenched with saturated aqueous NH_4Cl (3.0 mL) after 6 min. The mixture was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes) afforded **2.62** (77.3 mg, 29%, 47% b.o.r.s.m.) as a light-yellow oil along with the starting aldehyde (70.9 mg). Data for **2.62**: R_f 0.43 (10% EtOAc/hexanes); IR 1793, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 6.10 (s, 1H), 6.06 (s, 1H), 5.19 (S, 1H), 5.13 (s, 1H), 2.72 (q, 1H, *J* = 7.0 Hz), 2.62 (s, 3H), 1.85 (s, 3H), 1.80 (s, 3H), 1.33 (s, 3H), 1.17 (m, 6H); ^{13}C NMR (126 MHz) δ 208.4, 172.1, 138.4, 137.9, 137.1, 128.5, 125.4, 99.2, 85.3, 70.3, 58.1, 44.2, 35.3, 25.2, 18.5, 16.9, 11.8, 4.9; HRMS (FAB) calculated for $C_{18}H_{24}IO_3$ $(M+H)^+$: 415.0770, found: 415.0763; $[\alpha]_D^{23}$ = +4.6° (c = 0.61, $CHCl_3$).



Pentaene 2.63. To a solution of **2.62** (77.3 mg, 0.187 mmol) and **2.15** (103 mg, 0.313 μmol) in DMF (0.5 mL) was added tetrakis-triphenylphosphine palladium (10.6 mg, 9.17 μmol) and copper(I) thiophene-2-carboxylate (52.0 mg, 0.273 mmol). The reaction mixture was stirred at RT. After 1 hr it was diluted with a mixture of Et_2O:hexane (4 mL 1:1), pushed through a plug

of silica, and concentrated. Purification by silica gel chromatography (8% EtOAc/hexanes) afforded **2.63** (72.2 mg, 85%) as a light-yellow oil. Data for **2.63**: R_f 0.43 (25% EtOAc/hexanes); IR 3535, 1797, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 6.16 (s, 1H), 6.12 (s, 1H), 5.93 (s, 1H), 5.72 (s, 1H), 5.58 (q, 1H, J = 7.0 Hz), 5.06 (s, 1H), 5.01 (d, 1H, J = 2.0 Hz), 4.39 (s, 1H), 2.69 (qd, 1H, J_q = 7.5 Hz, J_d = 2.0 Hz), 1.89 (s, 3H), 1.85 (s, 3H), 1.83 (s, 3H), 1.76 (s, 3H), 1.64 (d, 3H, J = 6.5 Hz), 1.51 (s, 6H), 1.28 (s, 3H), 1.16 (s, 3H), 1.13 (d, 3H, J = 5.0 Hz); ^{13}C NMR (126 MHz) δ 208.4, 172.1, 139.2, 137.6, 137.4, 136.3, 135.9, 135.6, 131.2, 128.7, 127.9, 125.8, 124.8, 121.9, 85.4, 81.8, 70.2, 58.1, 44.1, 25.5, 25.3, 24.5, 19.4, 16.7, 14.4, 13.4, 11.9, 11.7, 4.8; HRMS (FAB) calculated for $C_{29}H_{40}O_4Li$ $(M+Li)^+$: 459.3087, found: 459.3078; $[\alpha]_D^{23}$ = –14.9° (c = 1.24, $CHCl_3$).

2.4.2 Crystallographic analysis of 2.29 and 2.16

Crystallographic analysis was performed at the Chexray Facility operated by the College of Chemistry, University of California, Berkeley using Bruker SMART CCD (charge coupled device)-based diffractometer with graphite monochromated Mo-Kα radiation. A fragment of a crystal of **2.29** or **2.16** was mounted on a Kapton loop using Paratone N hydrocarbon oil. The data were collected at a temperature of -115 ± 1 °C. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 20.0 seconds per frame.

Experimental details for **2.29**:

Empirical Formula	$IO_4NC_{13}H_{20}$
Formula weight	381.21
Crystal Color, Habit	colorless, rodlike
Crystal Dimensions	0.06 x 0.14 x 0.15 mm
Crystal System	monoclinic
Lattice Type	primitive
Lattice Parameters	a = 11.421 (2) Å b = 6.152 (1) Å c = 12.301 (2) Å β = 115.108 (2) Å V = 782.6 (2) $Å^3$
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.618 g/cm^3
F_{000}	380.00
μ (MoKα)	20.56 cm^{-1}
Radiation	0.71069 Å
Detector Position	60.00 mm
Exposure Time	20.0 seconds per frame
Scan Type	ω (0.3° per frame)
$2\theta_{max}$	52.7°
No. of Reflections Measured	Total: 4869 Unique: 2513 (R_{int} = 0.014)

Corrections	Lorentz-polarization
	Absorption (Tmax = 1.00 Tmin = 0.88)
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	2142
No. Variables	171
Reflection / Parameter Ratio	12.53
Residuals: R; Rw; Rall	0.023; 0.028; 0.030
Goodness of Fit Indicator	1.27
Max Shift / Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.53 e^- / $Å^3$
Minimum peak in Final Diff. Map	-0.30 e^- / $Å^3$

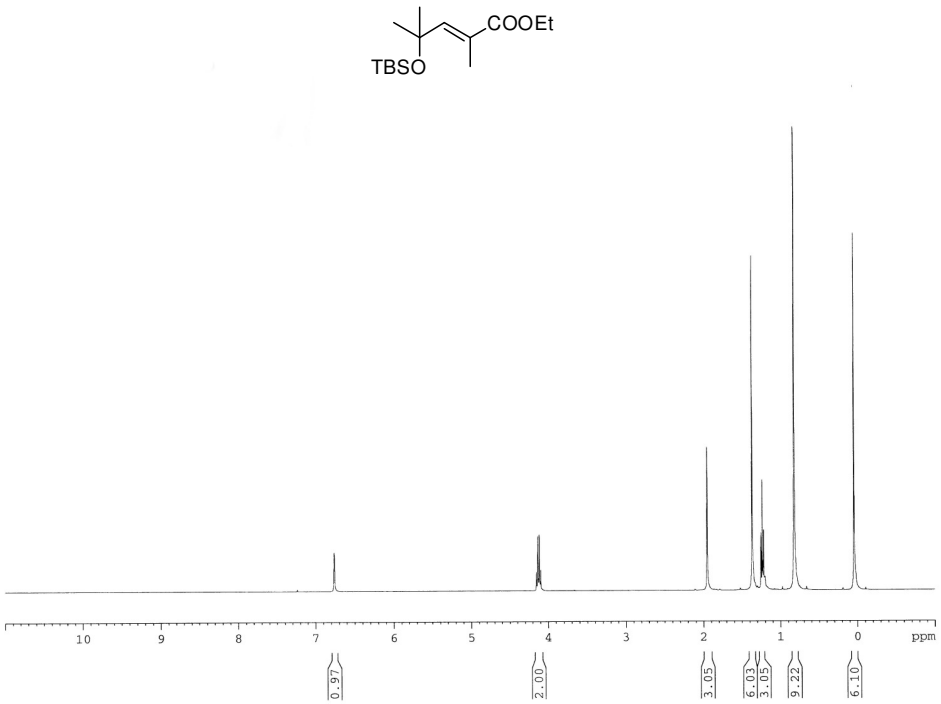
Experimental details for **2.16**:

Empirical Formula	$O_4C_{13}H_{16}$
Formula weight	236.27
Crystal Color, Habit	colorless, blocky
Crystal Dimensions	0.3 x 0.27 x 0.24 mm
Crystal System	orthorhombic
Lattice Type	primitive
Lattice Parameters	a = 9.053 (2) Å
	b = 11.263 (2) Å
	c = 11.950 (2) Å
	$\beta = 90^o$
	V = 1218.5 (4) $Å^3$
Space Group	P 21 21 21
Z value	4
D_{calc}	1.288 g/cm^3
F_{000}	504.00
μ (MoKα)	20.56 cm^{-1}
Radiation	0.7107 Å
Detector Position	60.00 mm
Exposure Time	20.0 seconds per frame
Scan Type	ω (0.3° per frame)
$2\theta_{max}$	52.7°
No. of Reflections Measured	Total: 5924
	Unique: 1389 (R_{int} = 0.0334)
Corrections	Lorentz-polarization
	Absorption (Tmax = 1.00 Tmin = 0.88)
Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$

p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I > 3.00σ(I))	2142
No. Variables	154
Reflection / Parameter Ratio	12.53
Residuals: R; Rw; Rall	0.0334; 0.0415; 0.0405
Goodness of Fit Indicator	2.023
Max Shift / Error in Final Cycle	0.0003
Maximum peak in Final Diff. Map	0.14 e^- / $Å^3$
Minimum peak in Final Diff. Map	-0.11 e^- / $Å^3$

2.4.3 Selected NMR Spectra

2.21



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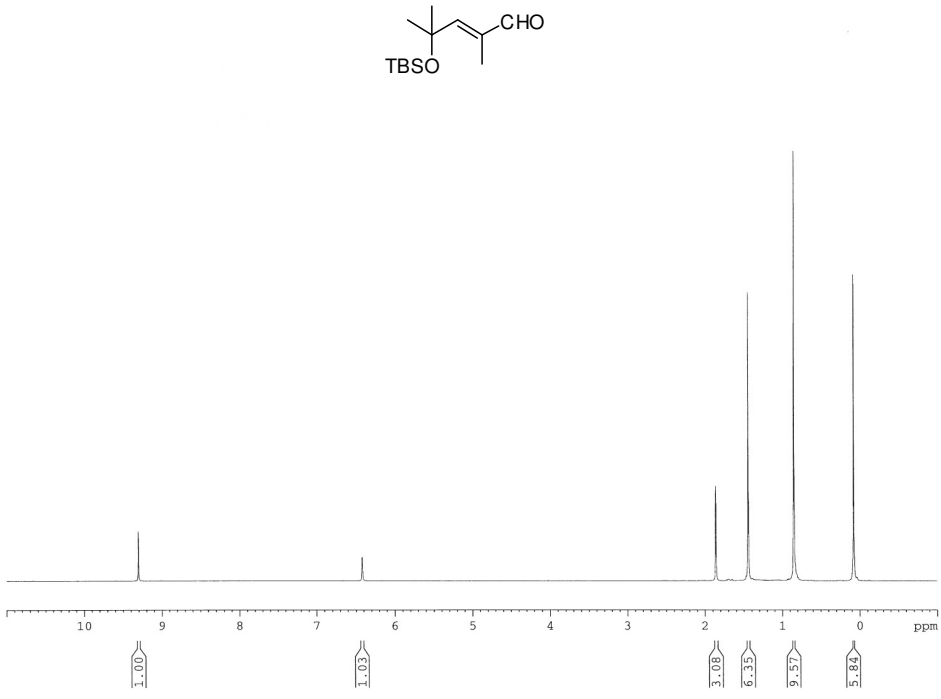

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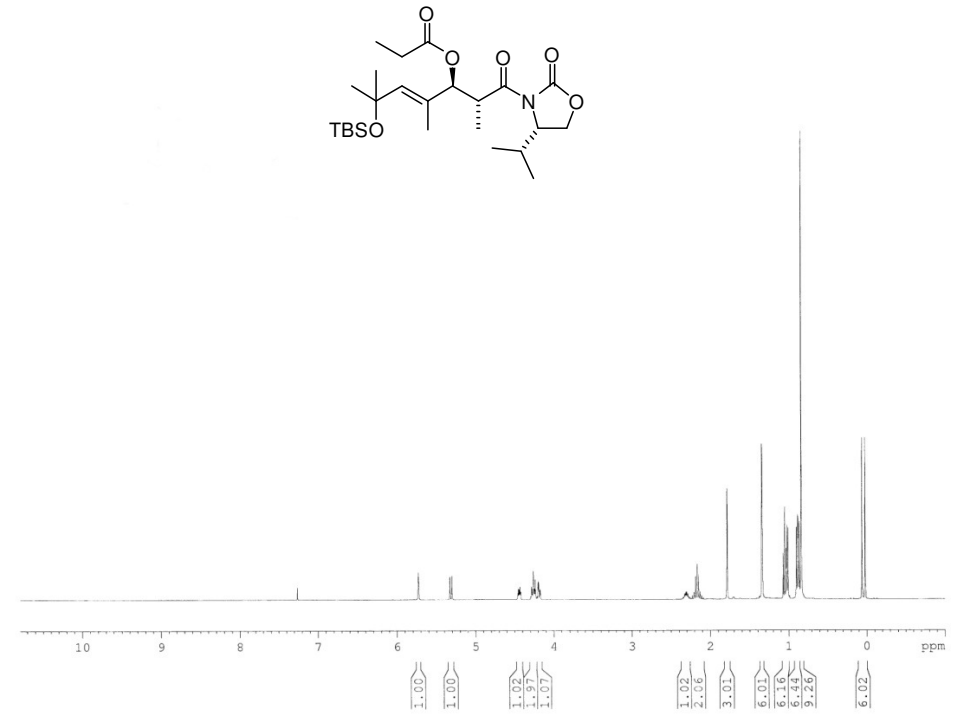
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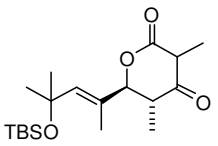
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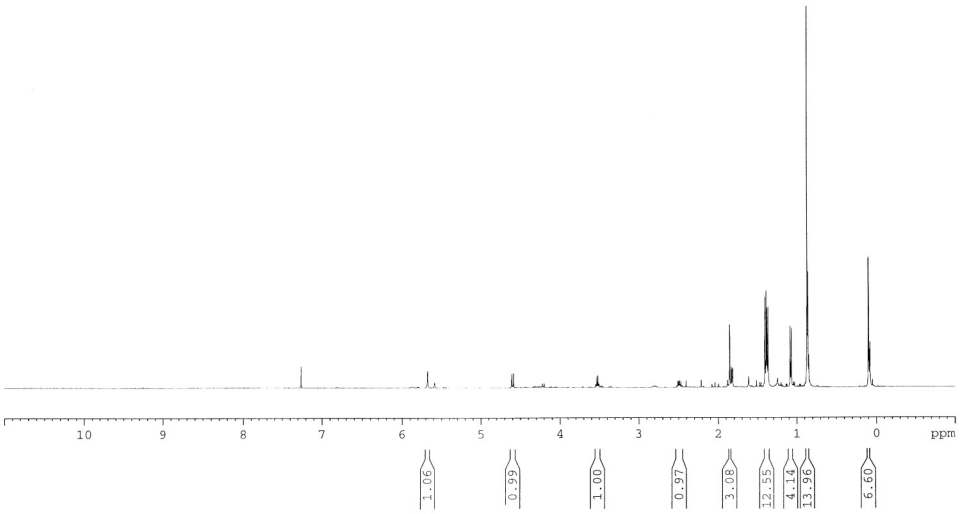
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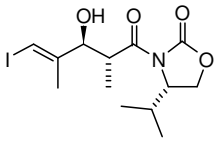
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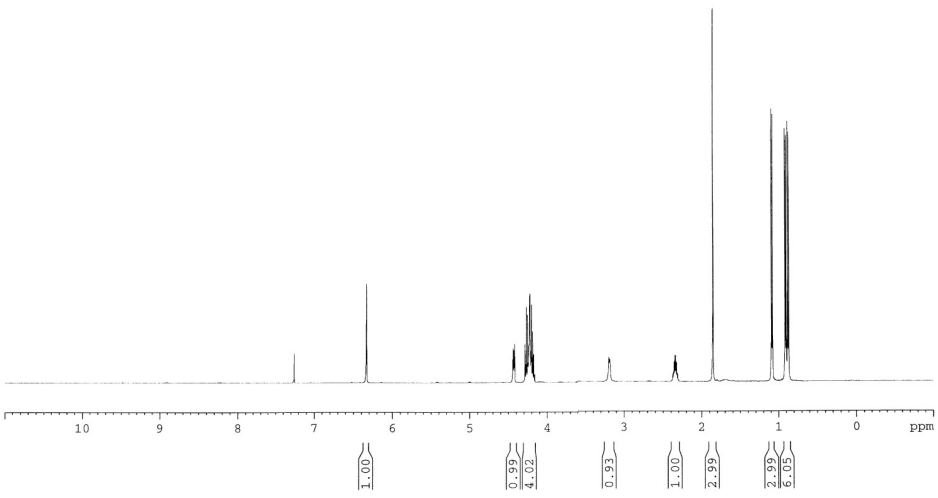
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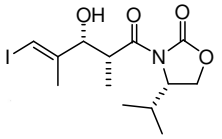
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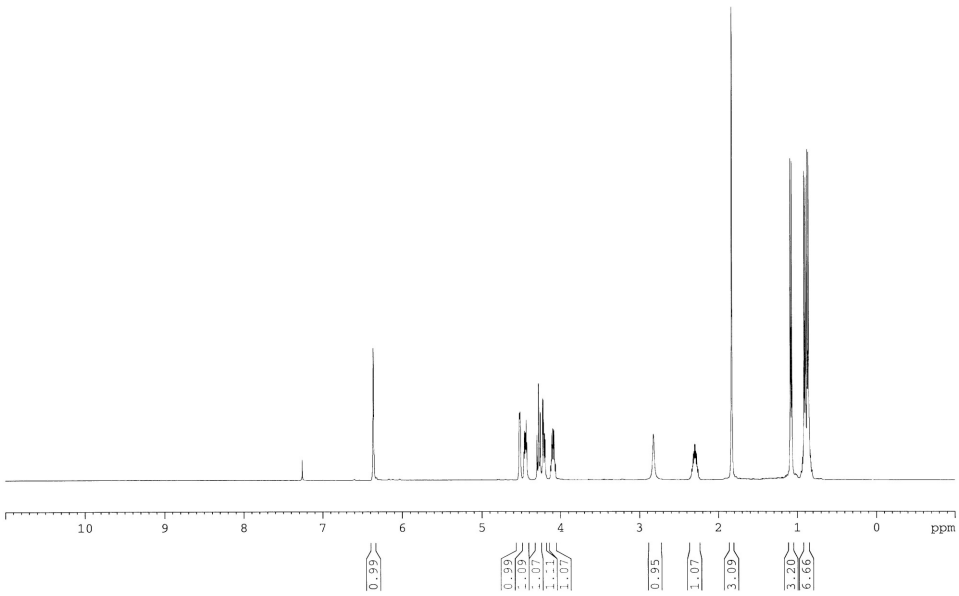
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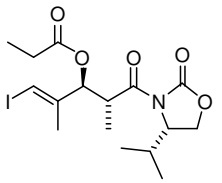
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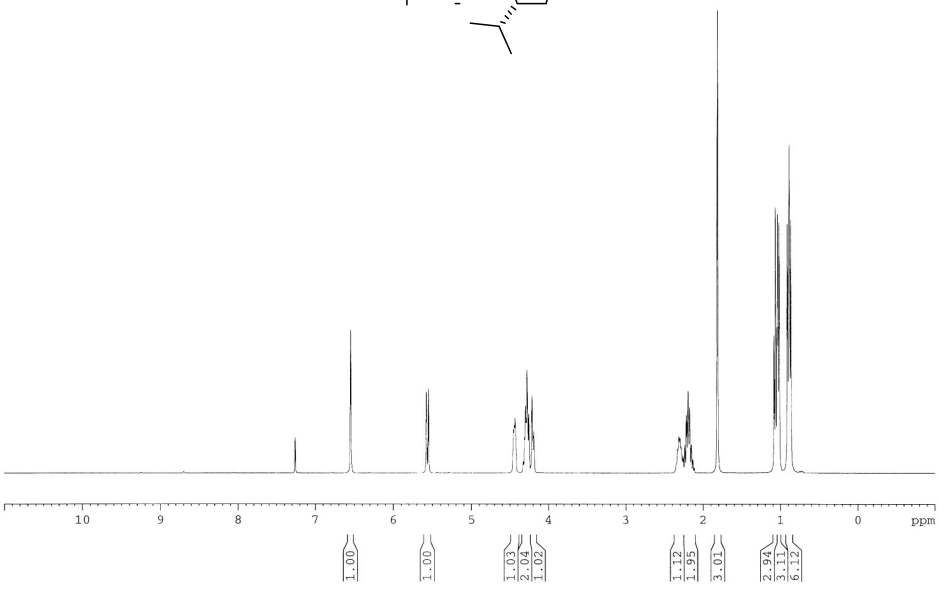
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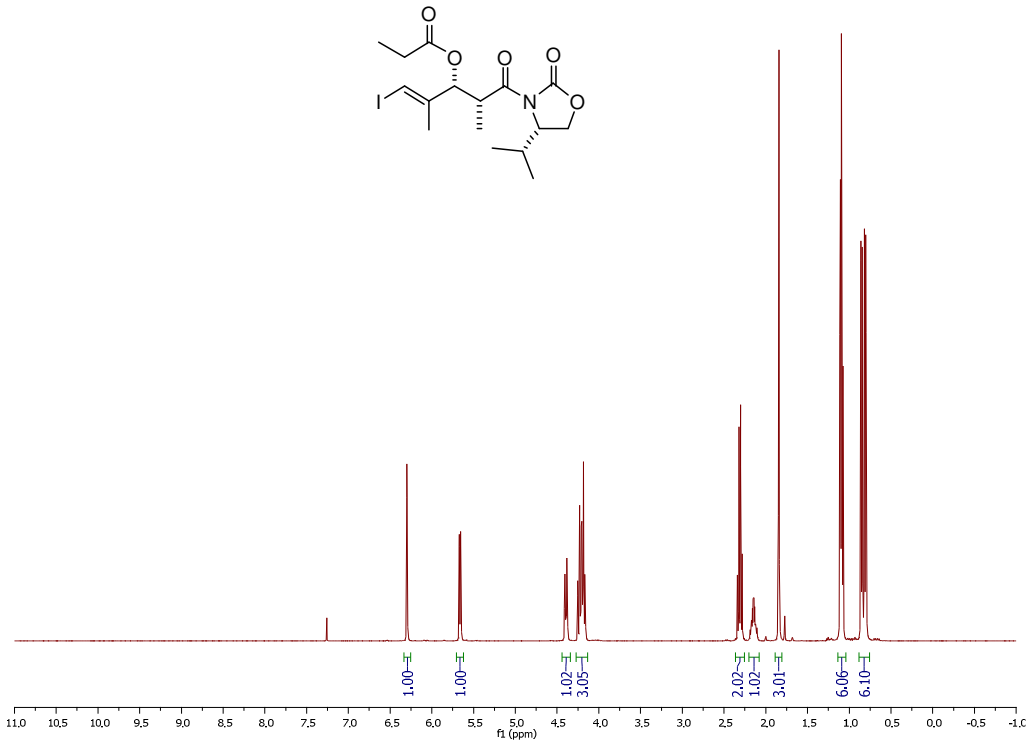
2.32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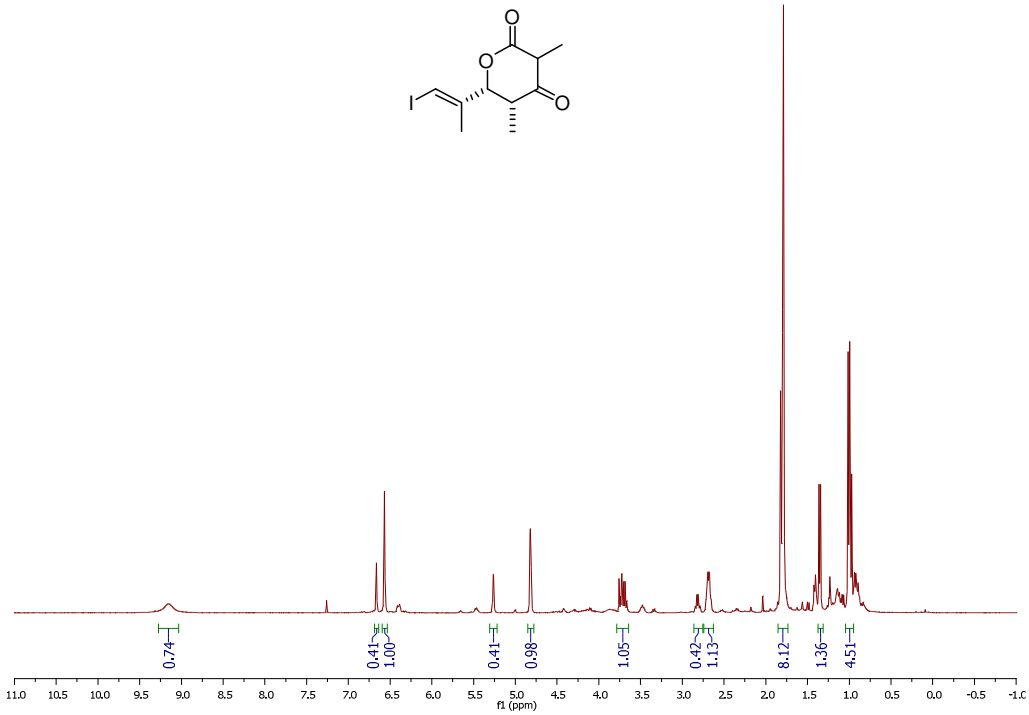
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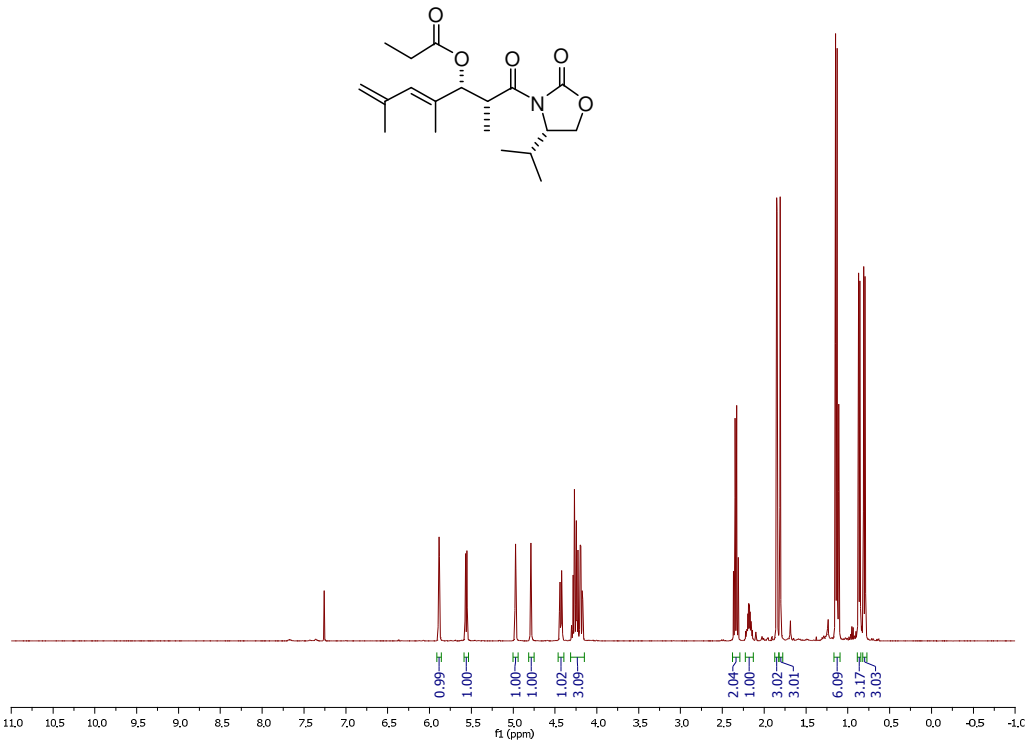
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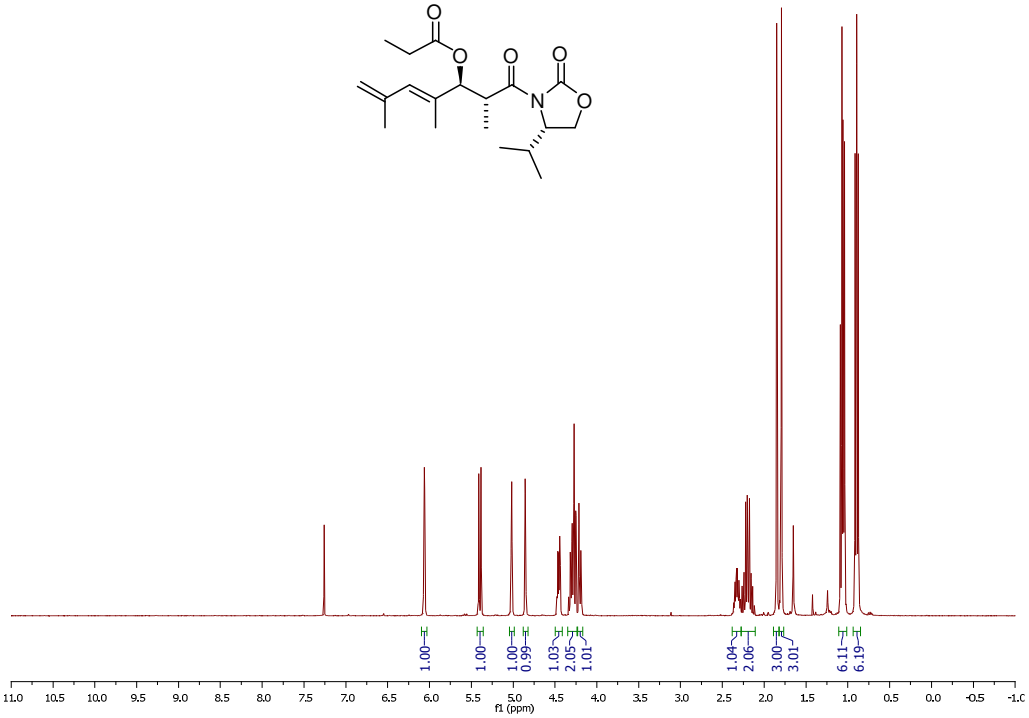
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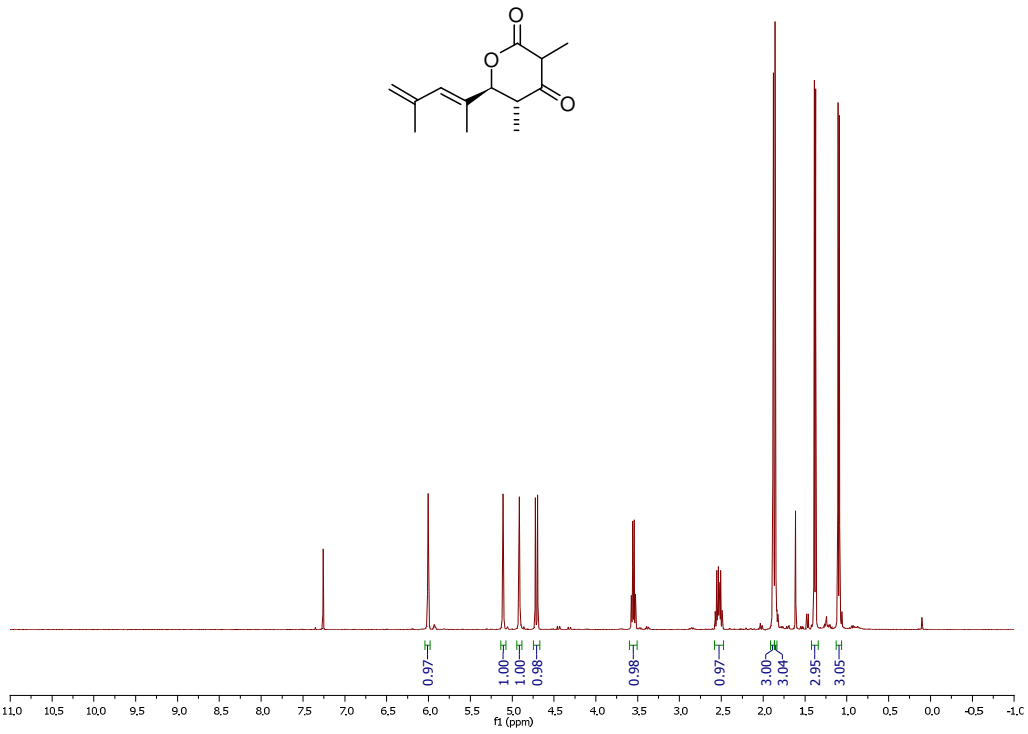
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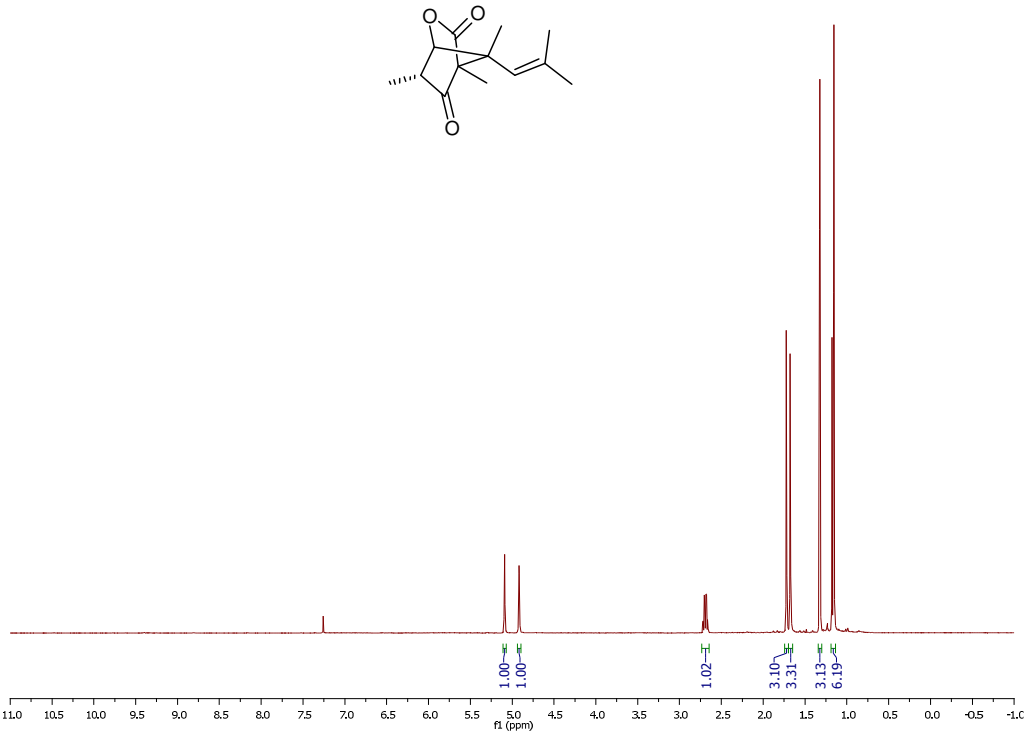
f1 (ppm)

2.27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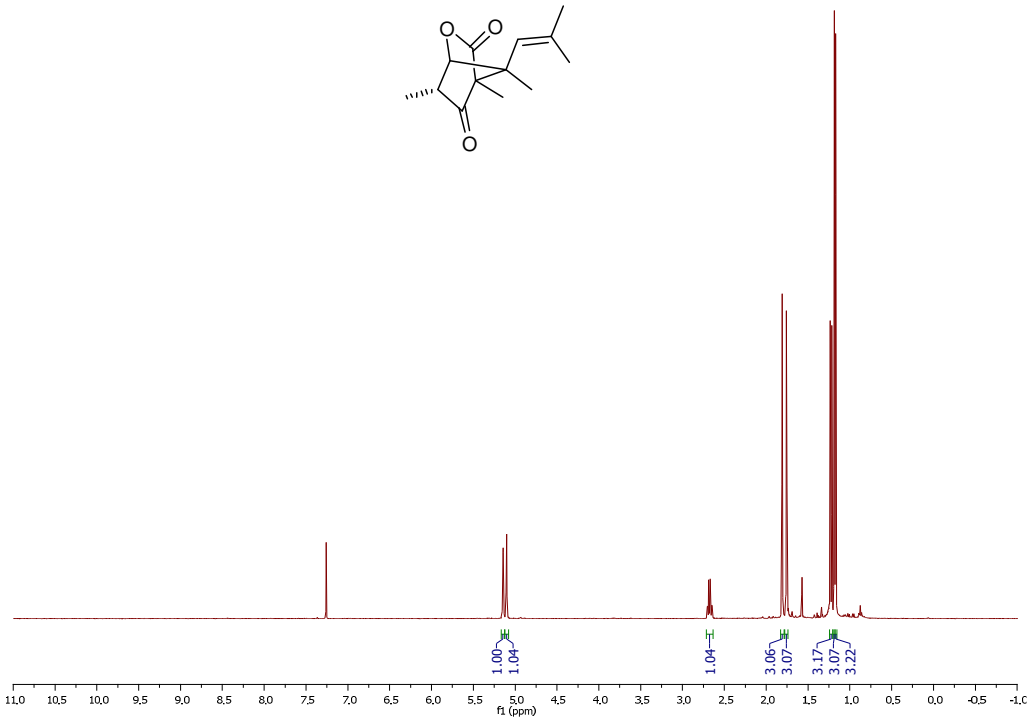
1.00
1.02
3.10
3.31
3.13
6.19
f1 (ppm)

2.38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O
O
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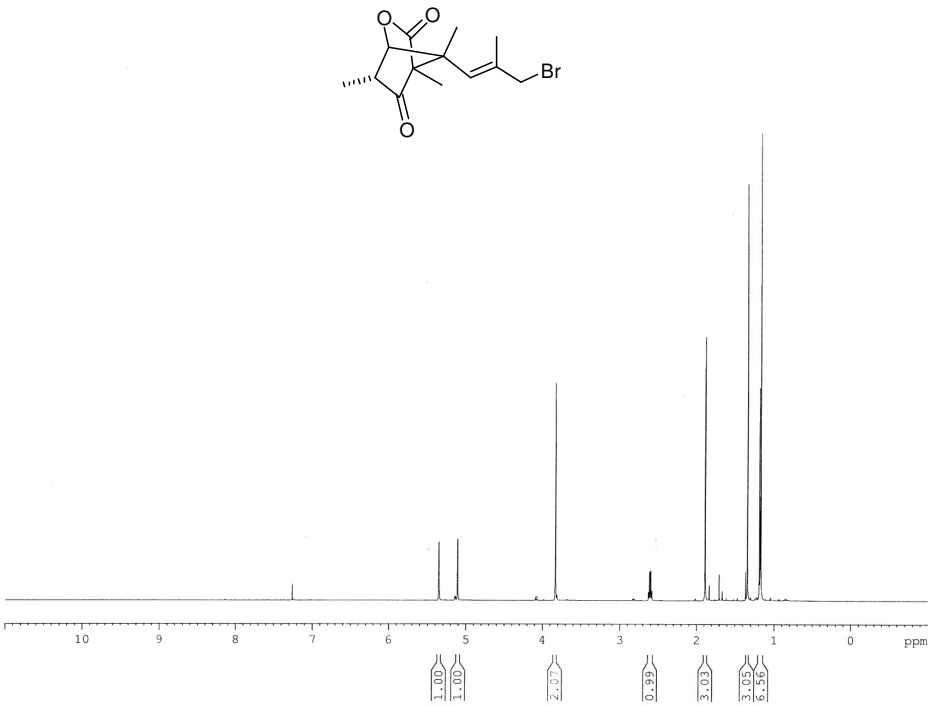
1.04
1.04
3.06
3.07
3.17
3.07
3.22
f1 (ppm)

2.39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O
Br
ppm
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1.00
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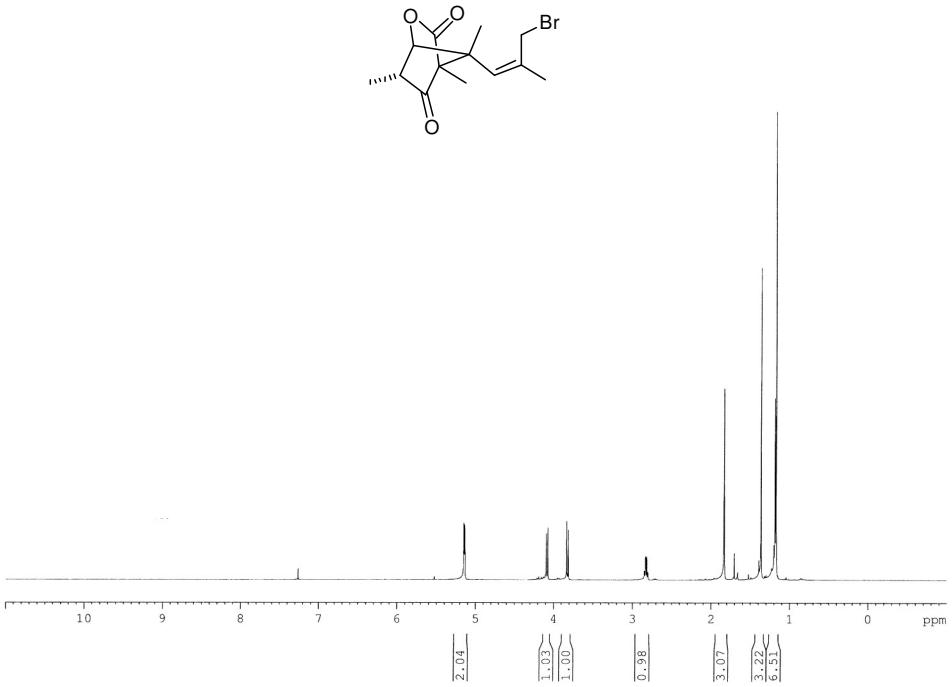
0.99
3.03
3.05
6.56

2.40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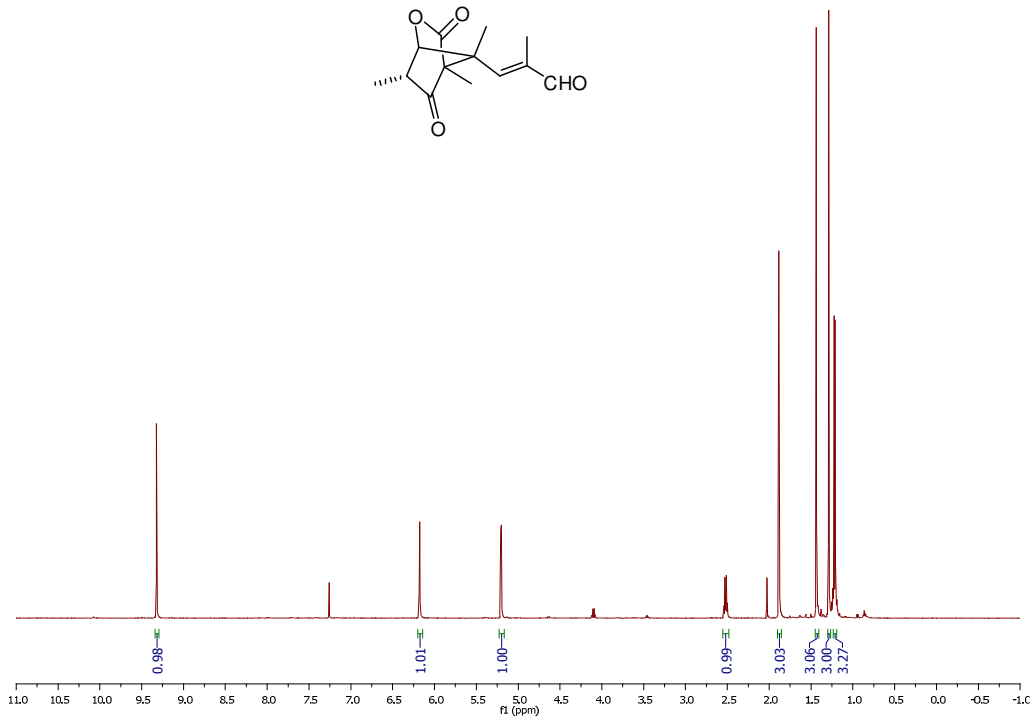
O
Br
O
10
9
8
7
6
5
4
3
2
1
0
ppm
2.04
1.03
1.00
0.98
3.07
3.22
6.51

2.16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3.00
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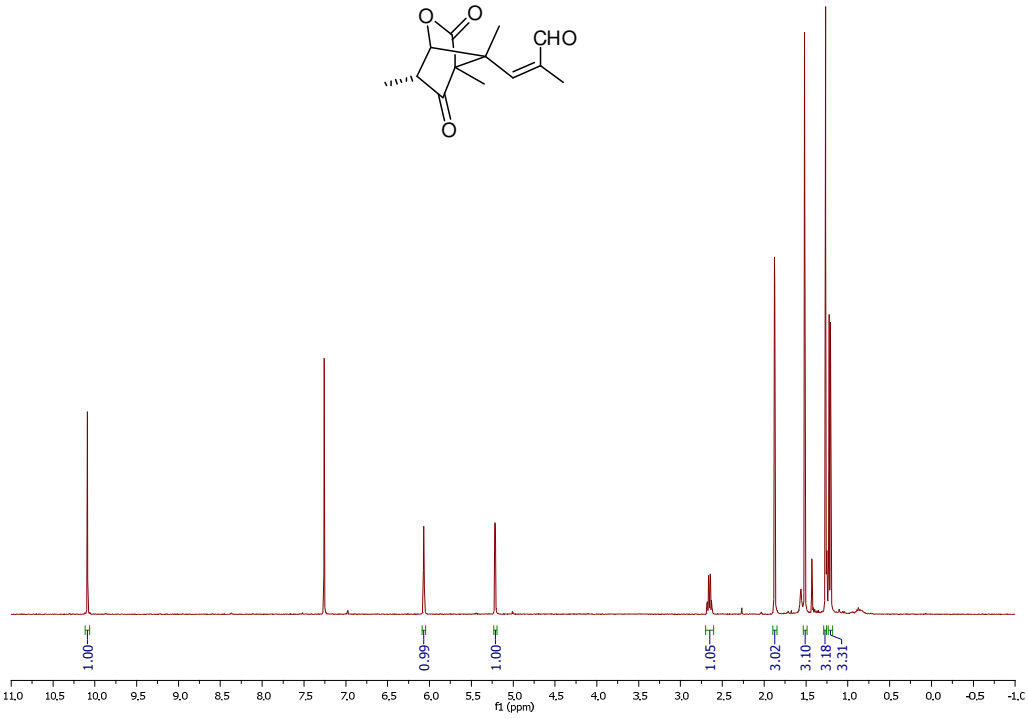
f1 (ppm)

2.41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O
CHO
O
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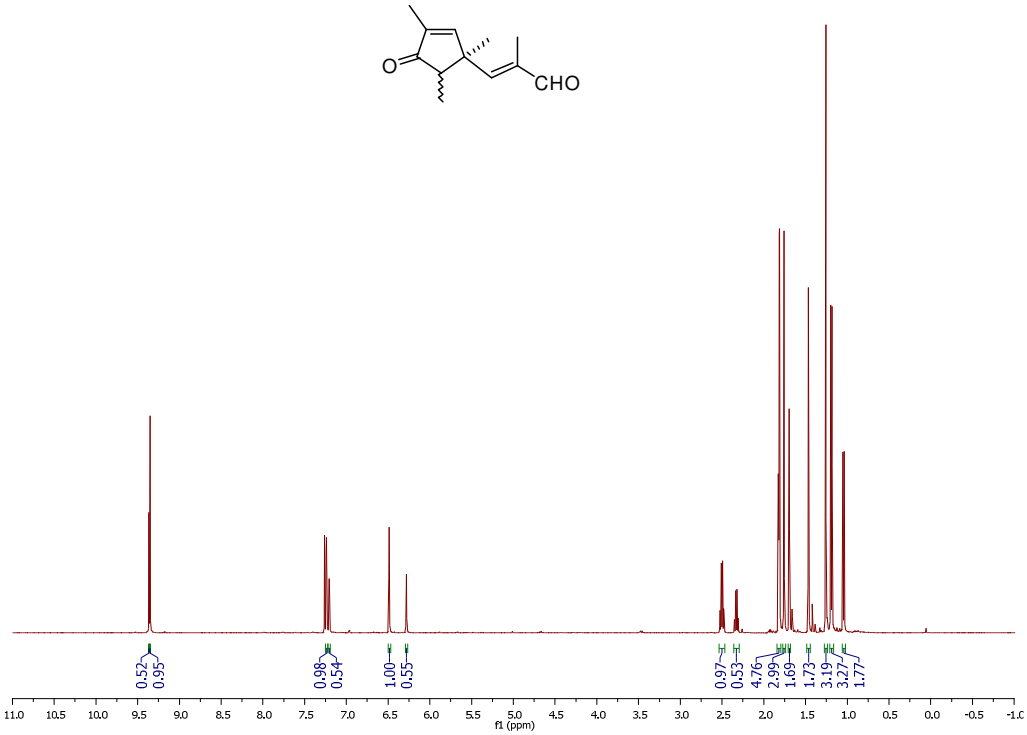
3.02
3.10
3.18
3.31
f1 (ppm)

2.43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0.98
0.54
1.00
0.55
0.97
0.53
4.76
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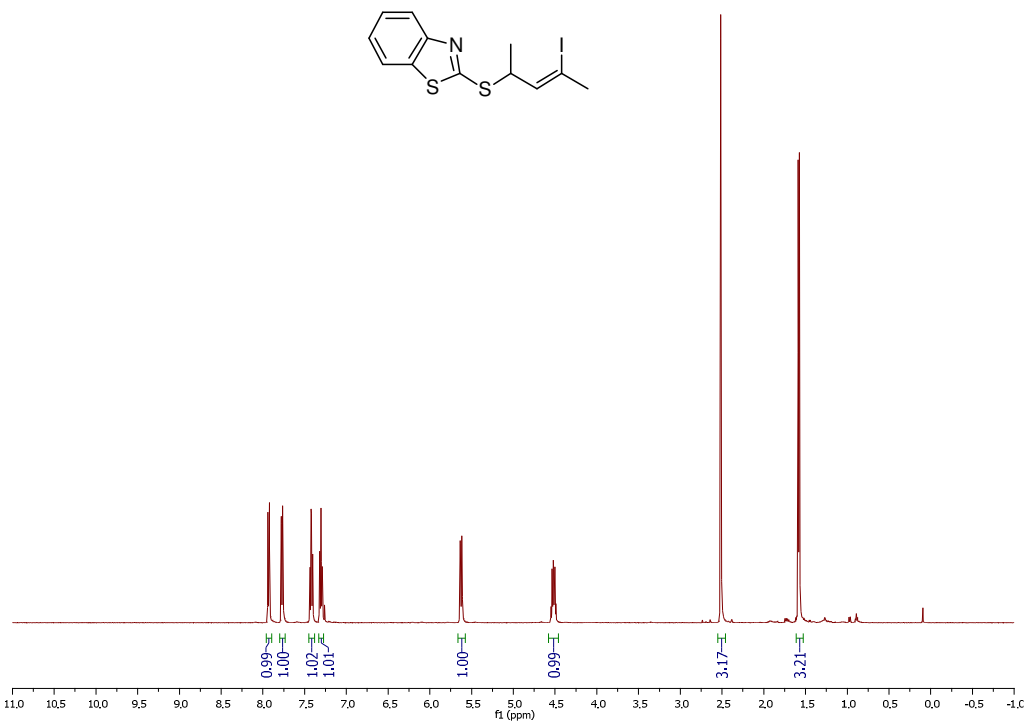
1.73
3.19
3.27
1.77
f1 (ppm)

2.45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S
S
I
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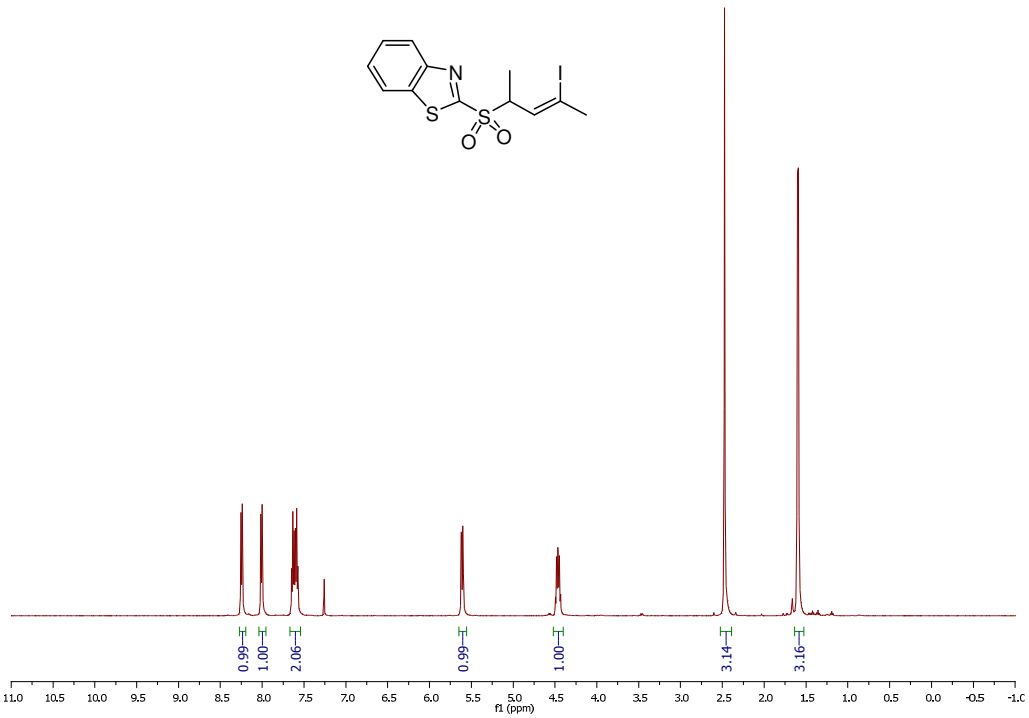
1.02
1.01
1.00
0.99
3.17
3.21
f1 (ppm)

2.46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S
S
O
O
I
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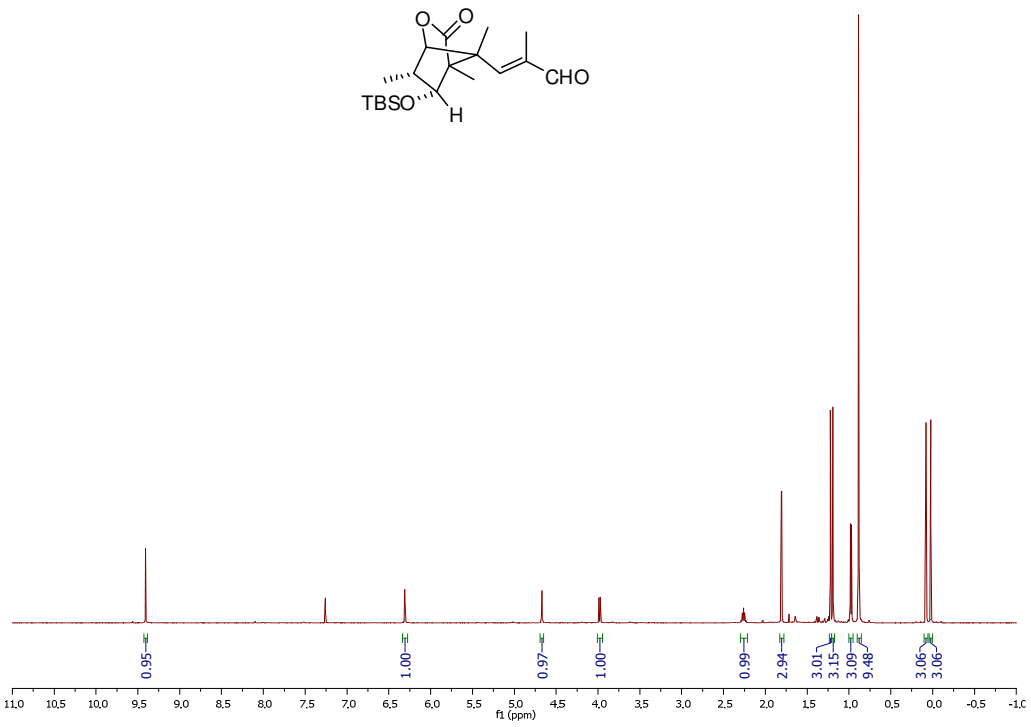
1.00
2.06
0.99
1.00
3.14
3.16
f1 (ppm)

2.47


O
O
CHO
TBSO
H
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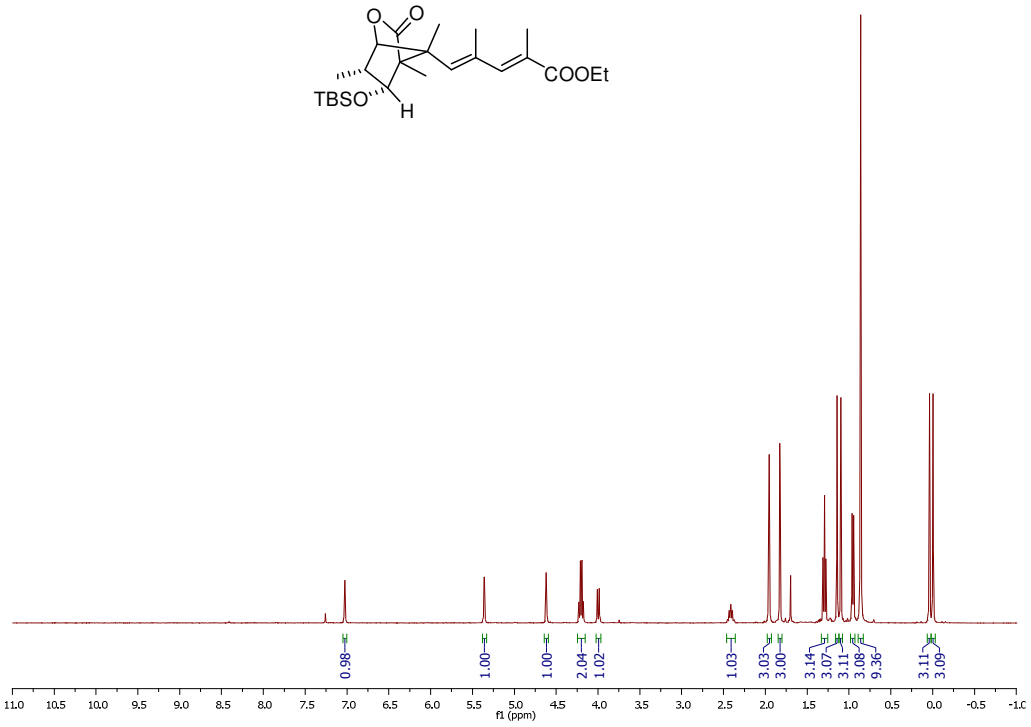
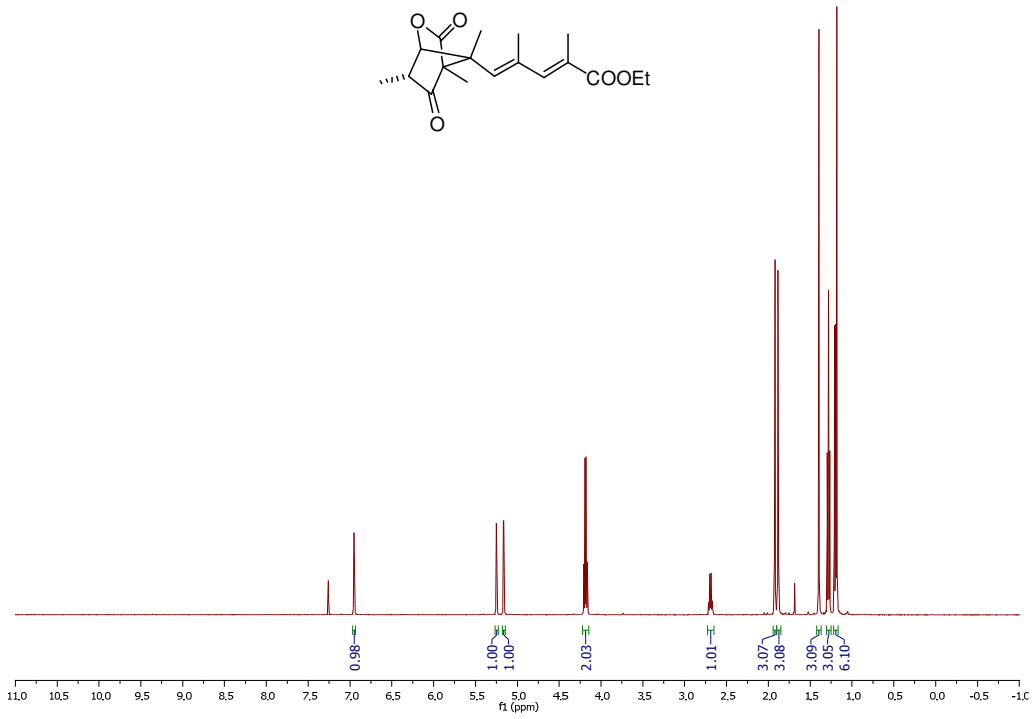
1.00
0.97
1.00
0.99
2.94
3.01
3.15
3.09
9.48
3.06
3.06
f1 (ppm)

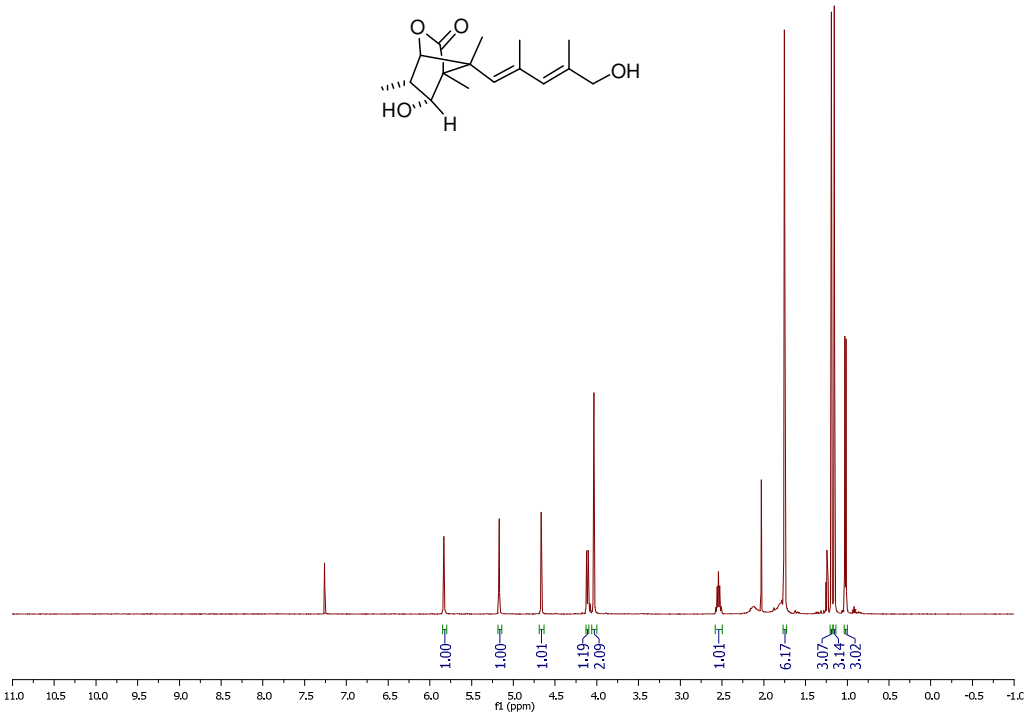
2.48


O
O
COOEt
TBSO
H
0.98
1.00
1.00
2.04
1.02
1.03
3.03
3.00
3.14
3.07
3.11
3.08
9.36
3.11
3.09
f1 (ppm)

2.49


O
O
COOEt
O
0.98
1.00
1.00
2.03
1.01
3.07
3.08
3.09
3.05
6.10
f1 (ppm)

2.50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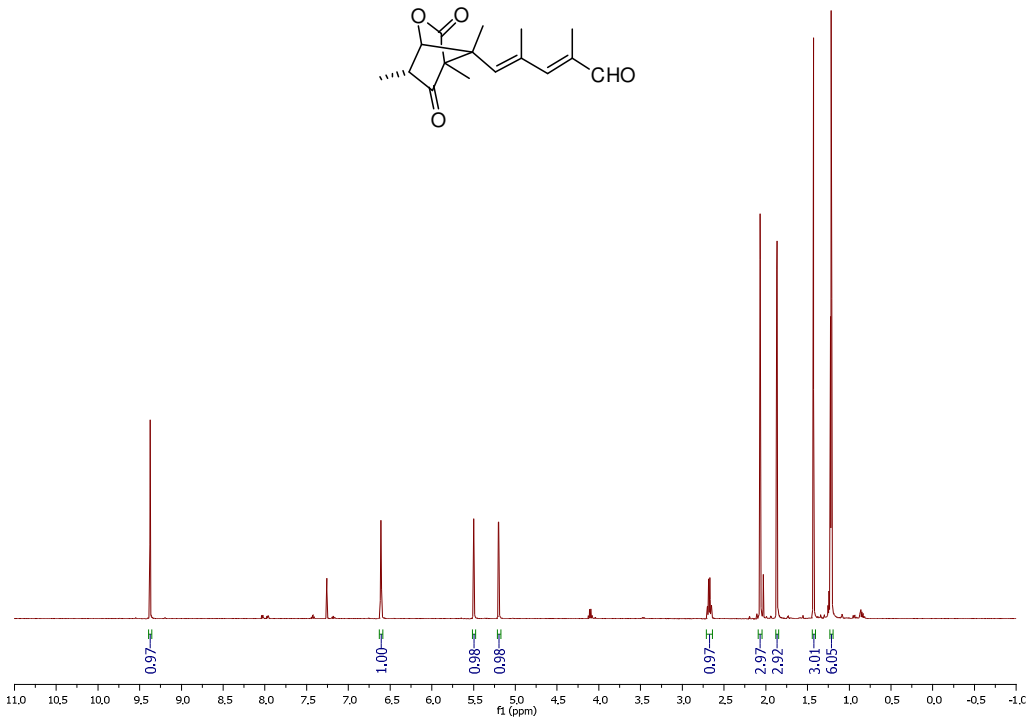
O
OH
HO
H
1.00
1.00
1.01
1.19
2.09
1.01
6.17
3.07
3.14
3.02
f1 (ppm)

2.51


O
O
CHO
O
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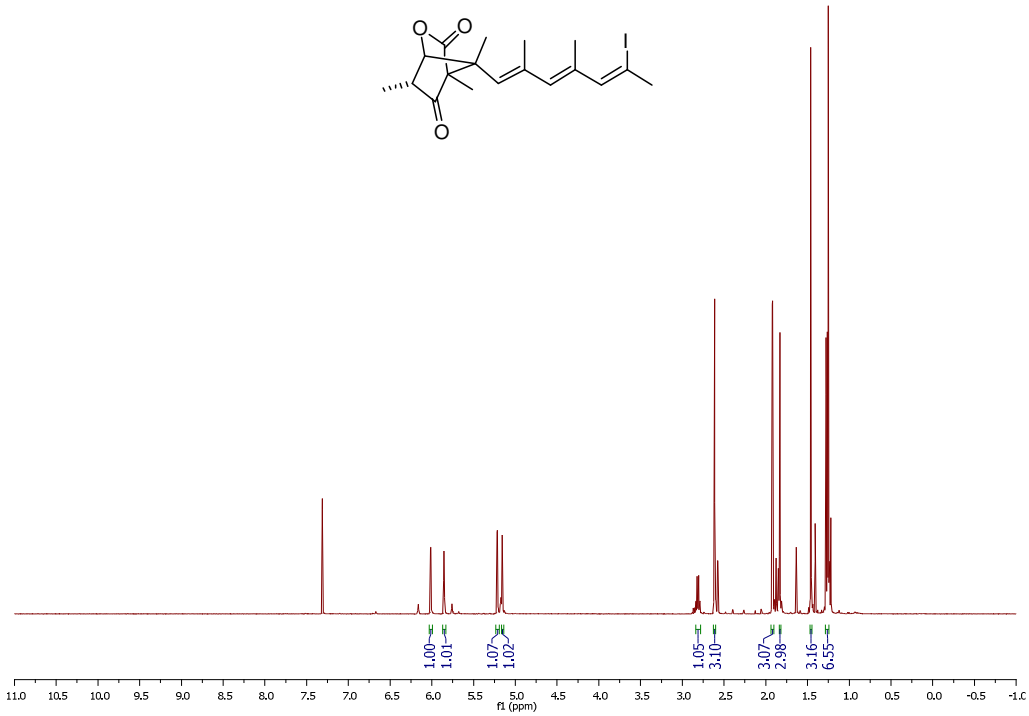
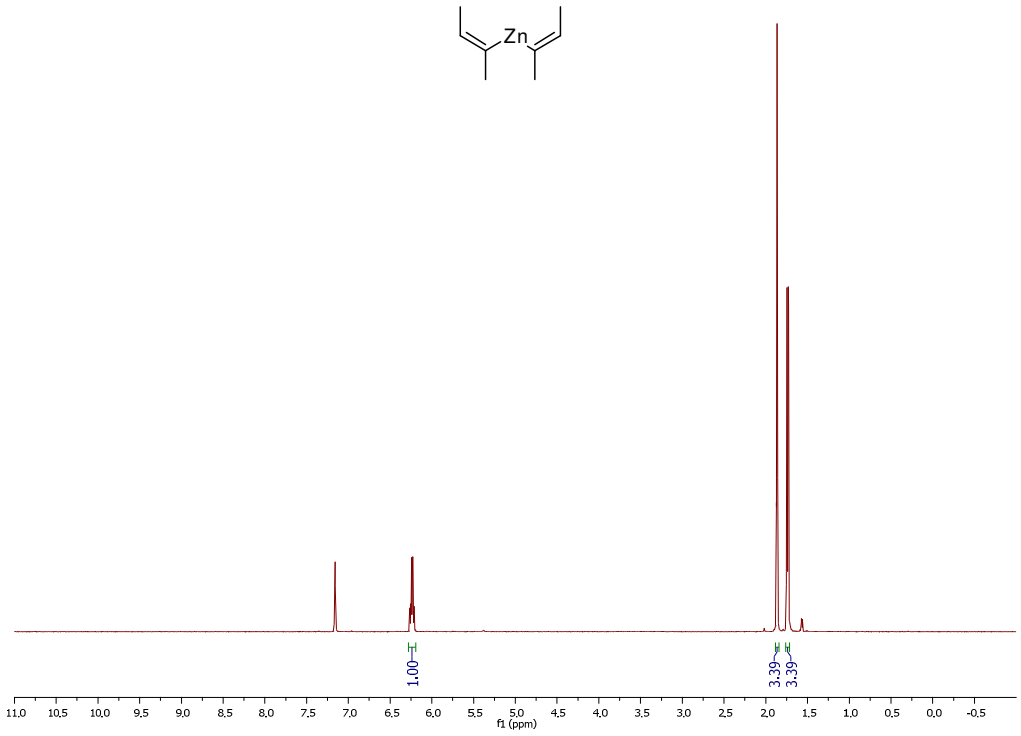
1.00
0.98
0.98
0.97
2.97
2.92
3.01
6.05
f1 (ppm)

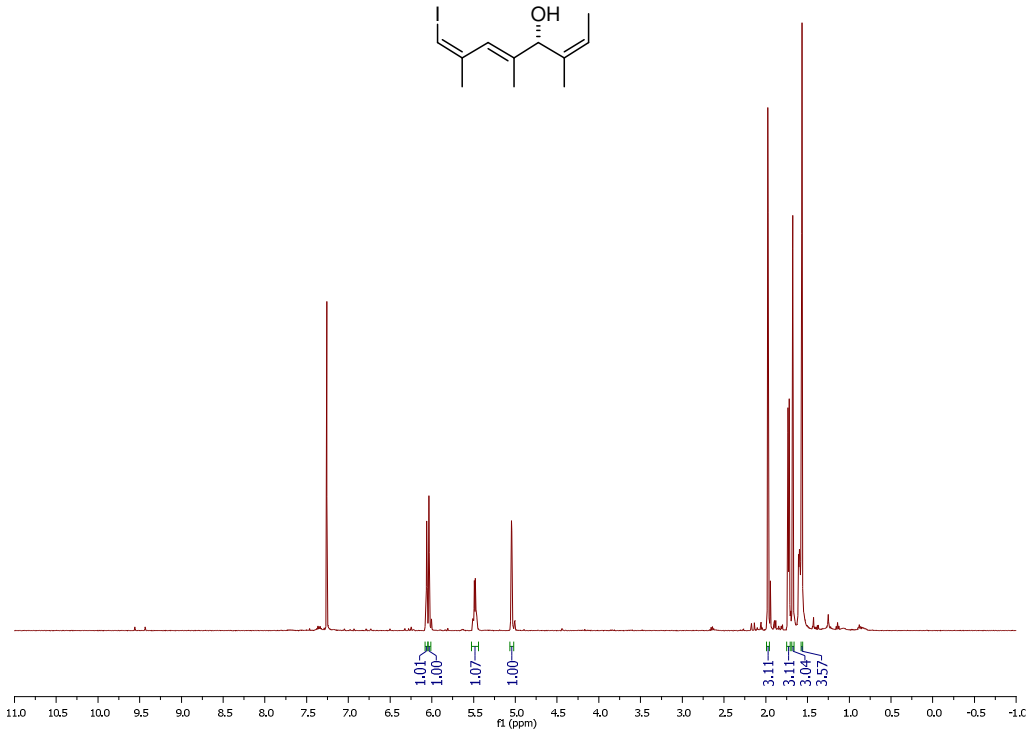
2.14


O
O
I
O
1.00
1.01
1.07
1.02
1.05
3.10
3.07
2.98
3.16
6.55
f1 (ppm)

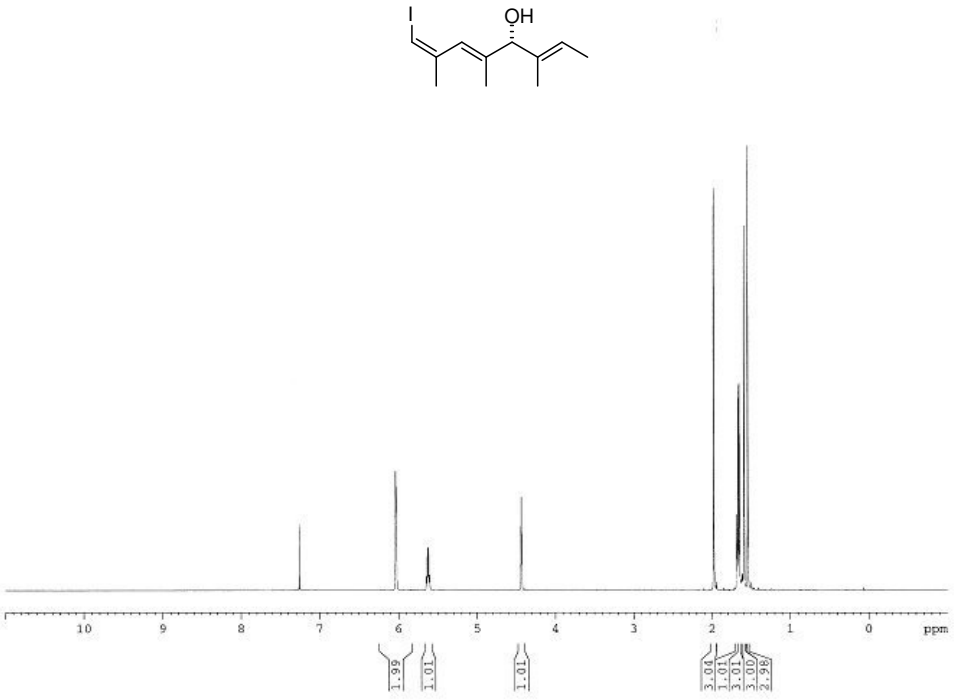
2.53



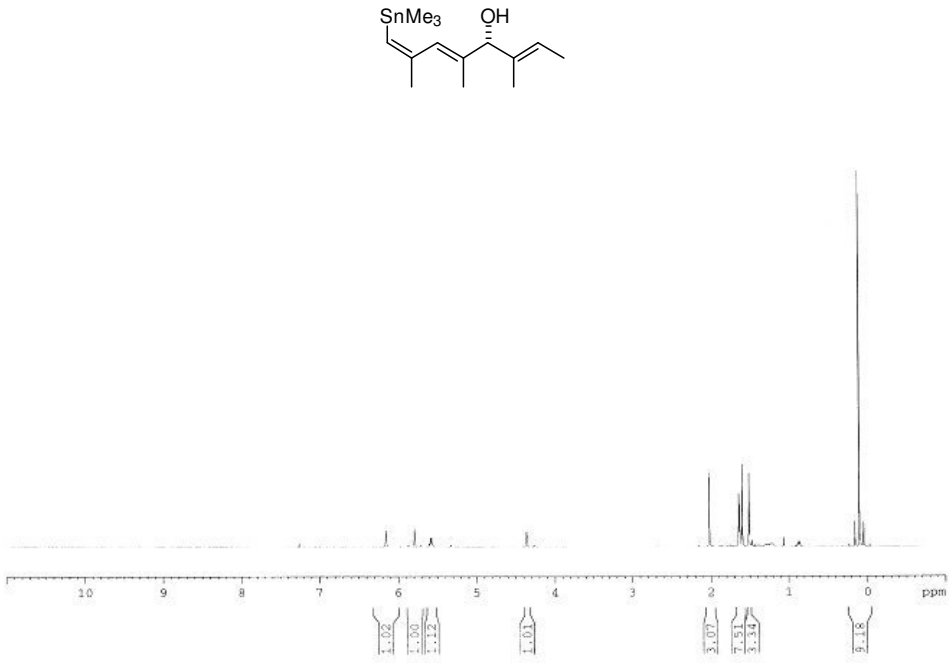
2.55



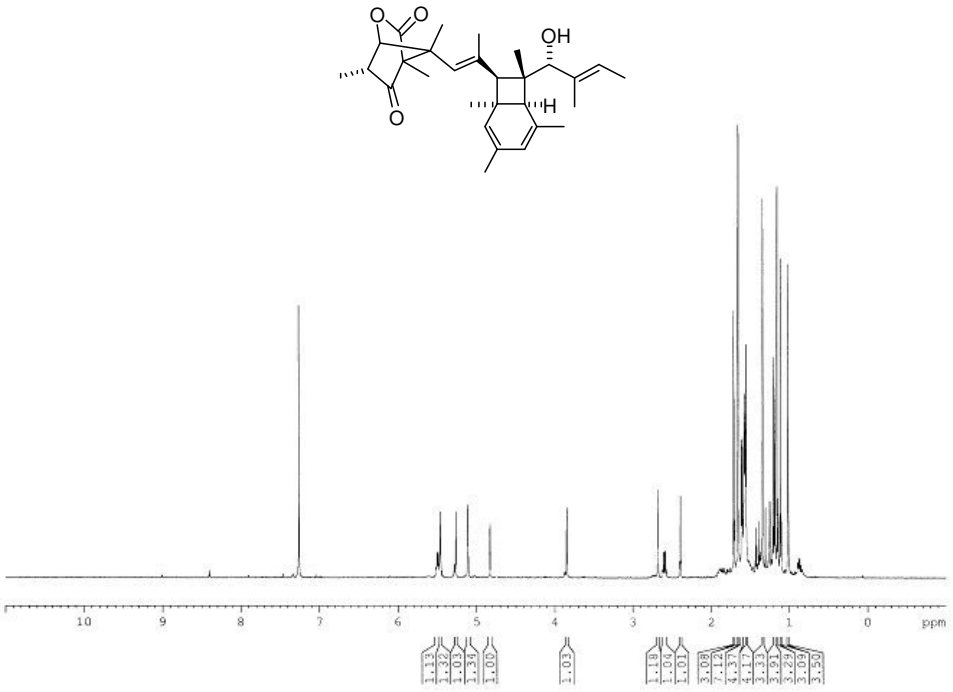
2.58


I
OH
10
9
8
7
6
5
4
3
2
1
0
ppm
1.99
1.01
1.01
3.04
1.01
3.01
3.00
2.98

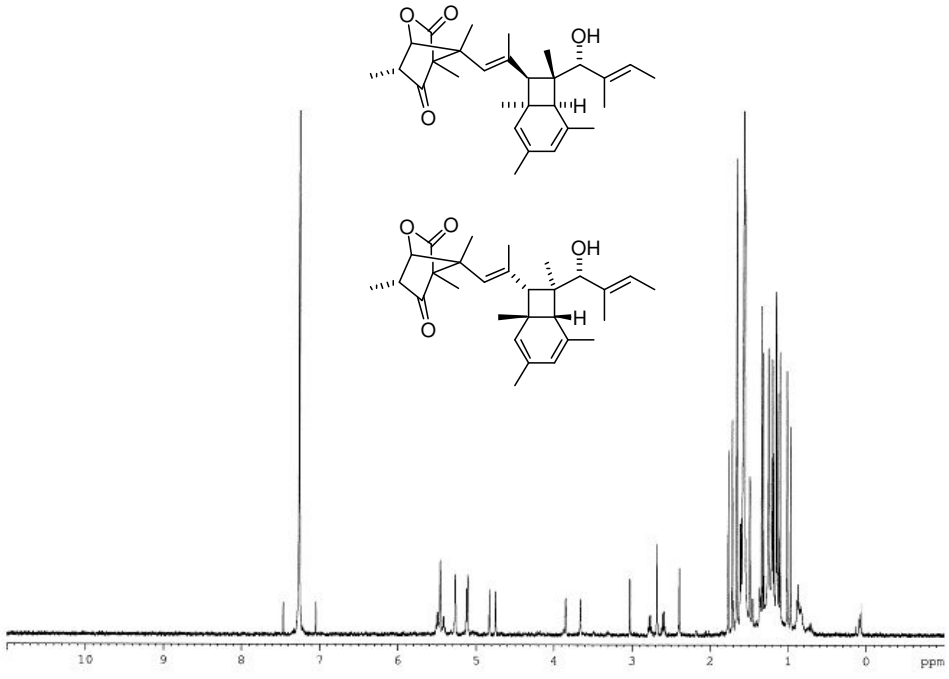
2.15


SnMe3
OH
10
9
8
7
6
5
4
3
2
1
0
ppm
1.02
1.00
1.12
1.01
3.07
7.51
3.34
9.18

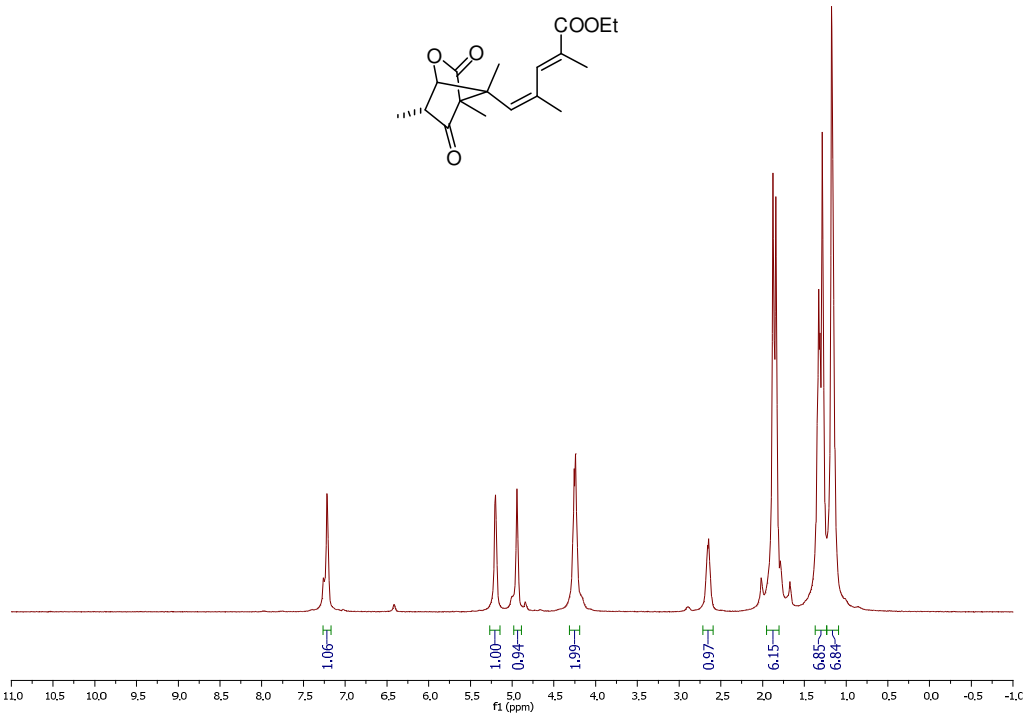
2.1



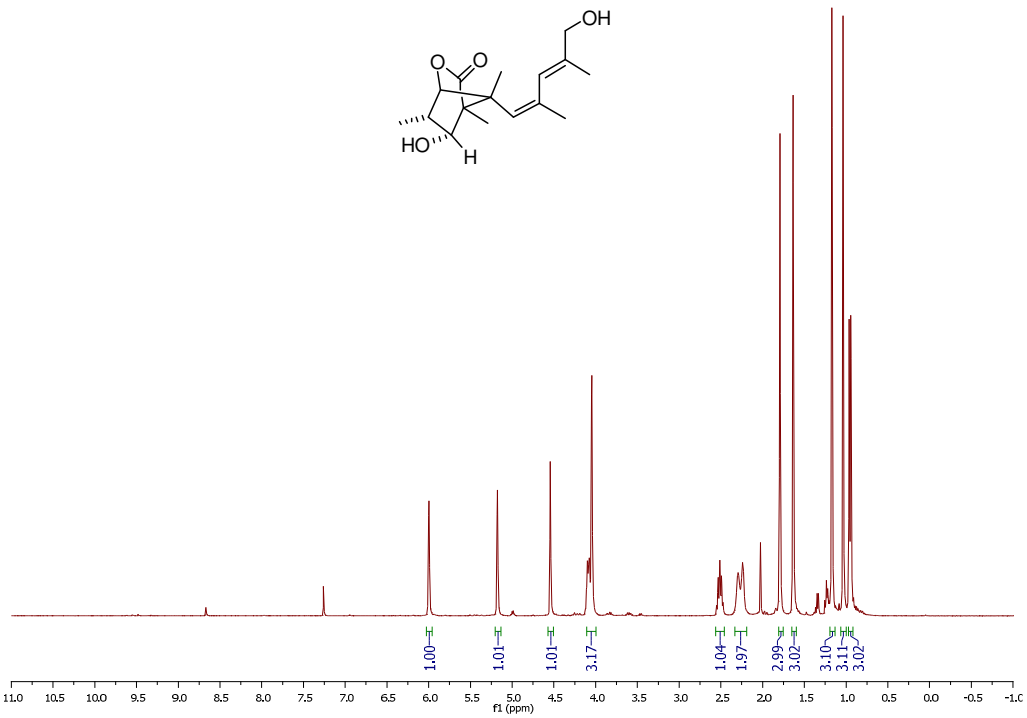
2.1 and **2.2**



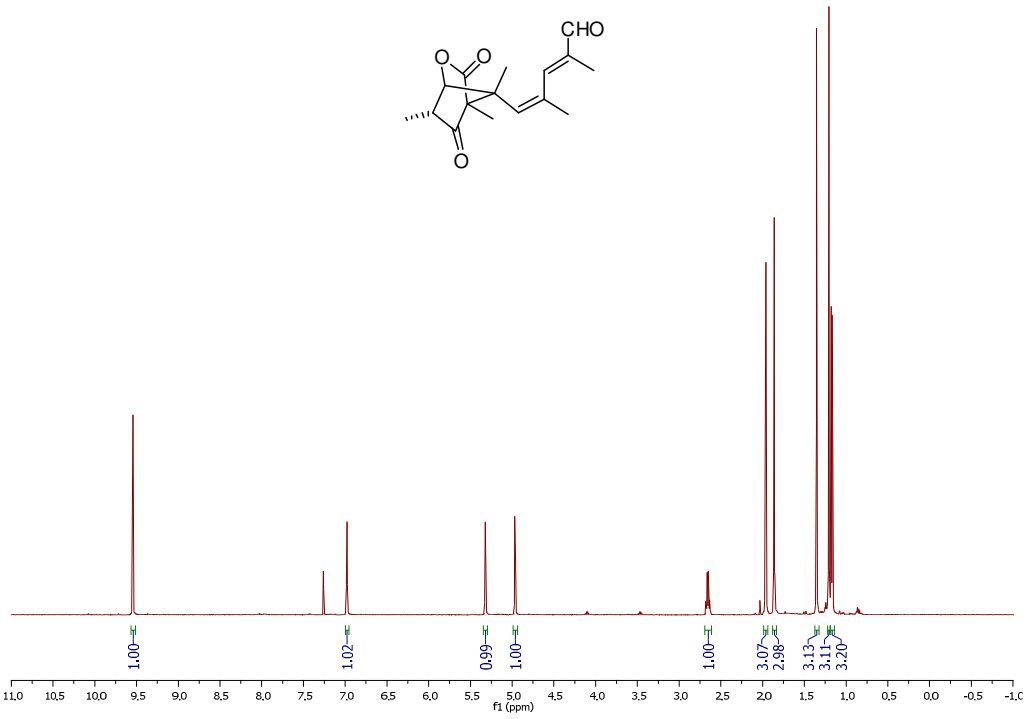
2.59


COOEt
O
O
O
1.06
1.00
0.94
1.99
0.97
6.15
6.85
6.84
f1 (ppm)

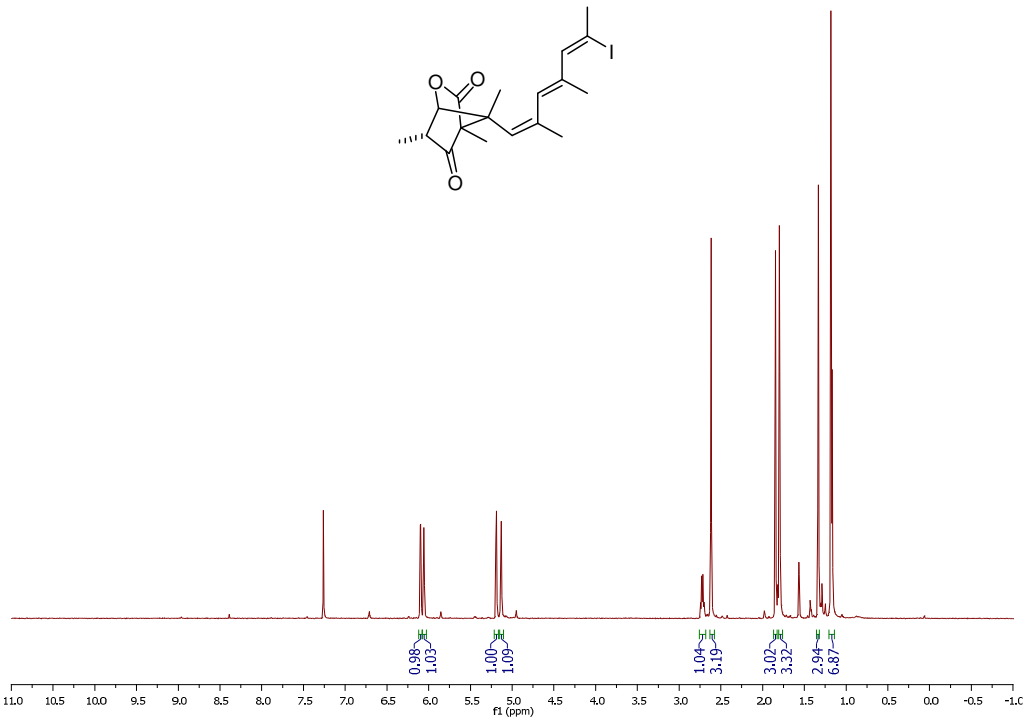
2.60


OH
O
O
HO
H
1.00
1.01
1.01
3.17
1.04
1.97
2.99
3.02
3.10
3.11
3.02
f1 (ppm)

2.61


CHO
O
O
O
1.00
1.02
0.99
1.00
1.00
3.07
2.98
3.13
3.11
3.20
f1 (ppm)

2.62


I
O
O
O
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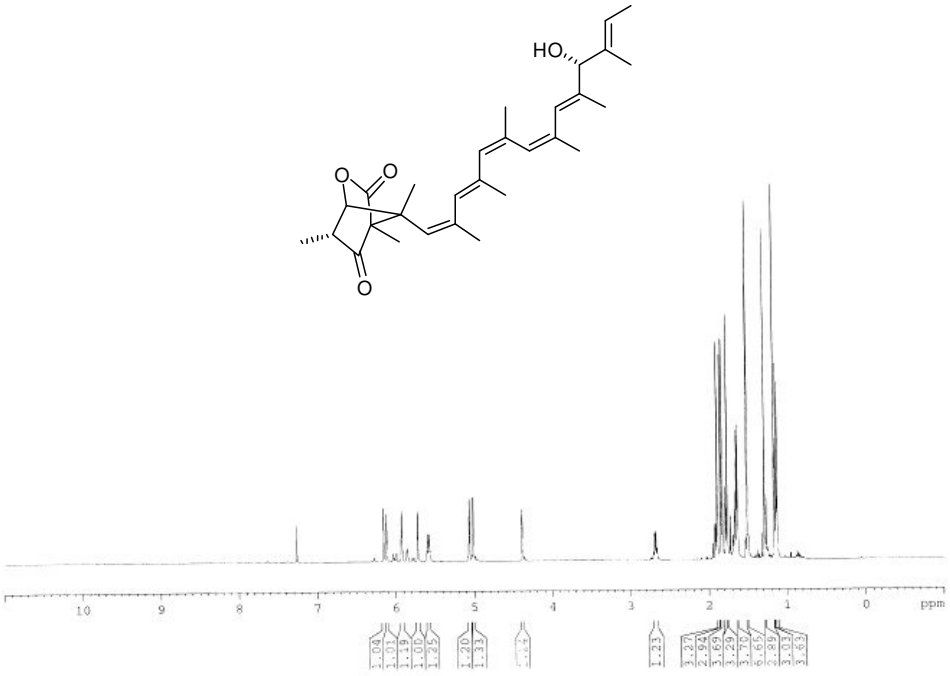
2.94
6.87
f1 (ppm)

2.63



2.5 References

1. Wei, H.; Itoh, T.; Konishita, M.; Kotoku, N.; Aoki, S.; Kobayashi, M. *Tetrahedron* **2005**, *61*, 8054–8058.
2. Wei, H.; Itoh, T.; Konishita, M.; Kotoku, N.; Kobayashi, M *Heterocycles* **2006**, *68*, 111–123.
3. Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221–2224.
4. Barbarow, J. E.; Miller, A. K.; Trauner, D. Org. Lett. 2005, 7, 2901–2903.
5. Beaudry, C. M.; Trauner, D. Org. Lett. 2005, 7, 4475–4477.
6. Miller, A. K.; Trauner, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4602–4606.

7. (a) Miller, A. K.; Trauner, D. *Synlett* **2006**, *14*, 2295–2316. (b) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541–547. (c) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548–553.
8. Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149–152.
9. Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837–8847.
10. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750.
11. Raimundo, B. C.; Heathcock, C. H. *Syn. Lett.* **1995**, 1213–1214.
12. Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.
13. (a) Brandwänge, S.; Leijonmark, H. *Tetrahedron Lett.* **1992**, *33*, 3025–3028. (b) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorenson, E. J. *Org. Lett.* **1999**, *1*, 645–648. (c) Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001**, *42*, 8643–8645.
14. Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans. 1* **1990**, *9*, 47–65.
15. Fürstner, A.; Gastner, T. *Org. Lett.* **2000**, *2*, 2467–2470.
16. (a) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J.; Powers, J. W.; Larson, H. O.; Levand, O.; Wraver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562–6562.
17. Dave, P.; Byun, H. S.; Engel, R. *Synth. Commun.* **1986**, *16*, 1343–1346.
18. Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825–4826.
19. Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D. *Synth. Commun.* **1992**, *22*, 1967–1971.
20. Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2006**, *47*, 1757–1761.
21. Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529–1532.

22. Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193–205.

23. Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901–2903.

24. Shibata, T.; Nakatsui, K.; Soai, K. Inorganica Chimica Acta 1999, 296, 33–36.

25. Ji, J.; Qiu, L.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589–1590.

26. (a) Espinet, P.; Echavarren, A. M. *Angew. Chem.* **2004**, *116*, 4808–4839. (b) *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.

27. Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675–1689.

28. Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778.

29. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

30. Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64–64.

Chapter 3. Second-Generation Synthesis of Exiguamines A and B

3.1 Introduction

Exiguamines A (**3.1**) and B (**3.2**) are polycyclic alkaloids that were isolated from a marine sponge *Neopetrosia exigua* and quickly got the attention of the synthetic and medicinal community when they were first described in the literature in 2006 (Figure 3.1).[1,2] Structurally, the natural products feature multiple polar functional groups, including a quaternary ammonium center, densely packed into the axially chiral hexacyclic framework. At the time of isolation, the compounds were found to be the most potent inhibitors (K_i of 41 ± 3 nM) of idoleamine-2,3-dioxigenase (IDO) that had been identified to date.[1]

IDO is a heme-containing, monomeric oxidoreductase that catalyzes the first and rate-limiting step in the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Tryptophan depletion, as well as the accumulation of its metabolites, results in a strongly inhibitory effect on the development of immune responses. This effect is exerted by blocking T cell activation, inducing T cell apoptosis and promoting differentiation of naive T cells into those with a regulatory phenotype.[3] Thus IDO has recently been acknowledged as one of the promising targets for cancer therapy.[3,4]

Although several derivatives of tryptophan have provided important proof-of-principle demonstrations for the use of IDO inhibitors in cancer chemotherapy, none of them are potent enough to be true drug development candidates. In the last few years there has been an explosion in the discovery of more potent IDO inhibitors from natural sources led largely by the Andersen group.[1,2,5,6] Exiguamines are now part of the growing group of identified natural product-based IDO inhibitors that also includes annulin B (**3.3**), annulin C (**3.4**), and plectosphaeroic acid A (**3.5**) (Figure 3.1). In spite of a growing effort to identify more efficaceous IDO inhibitors, exiguamines still stand out as some of the most potent inhibiting agents.

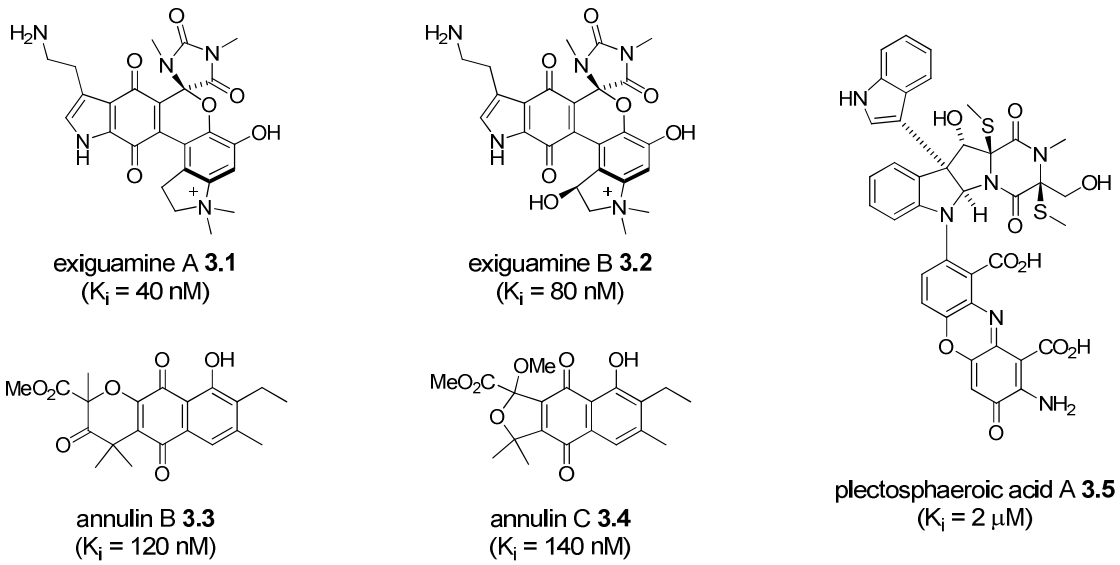
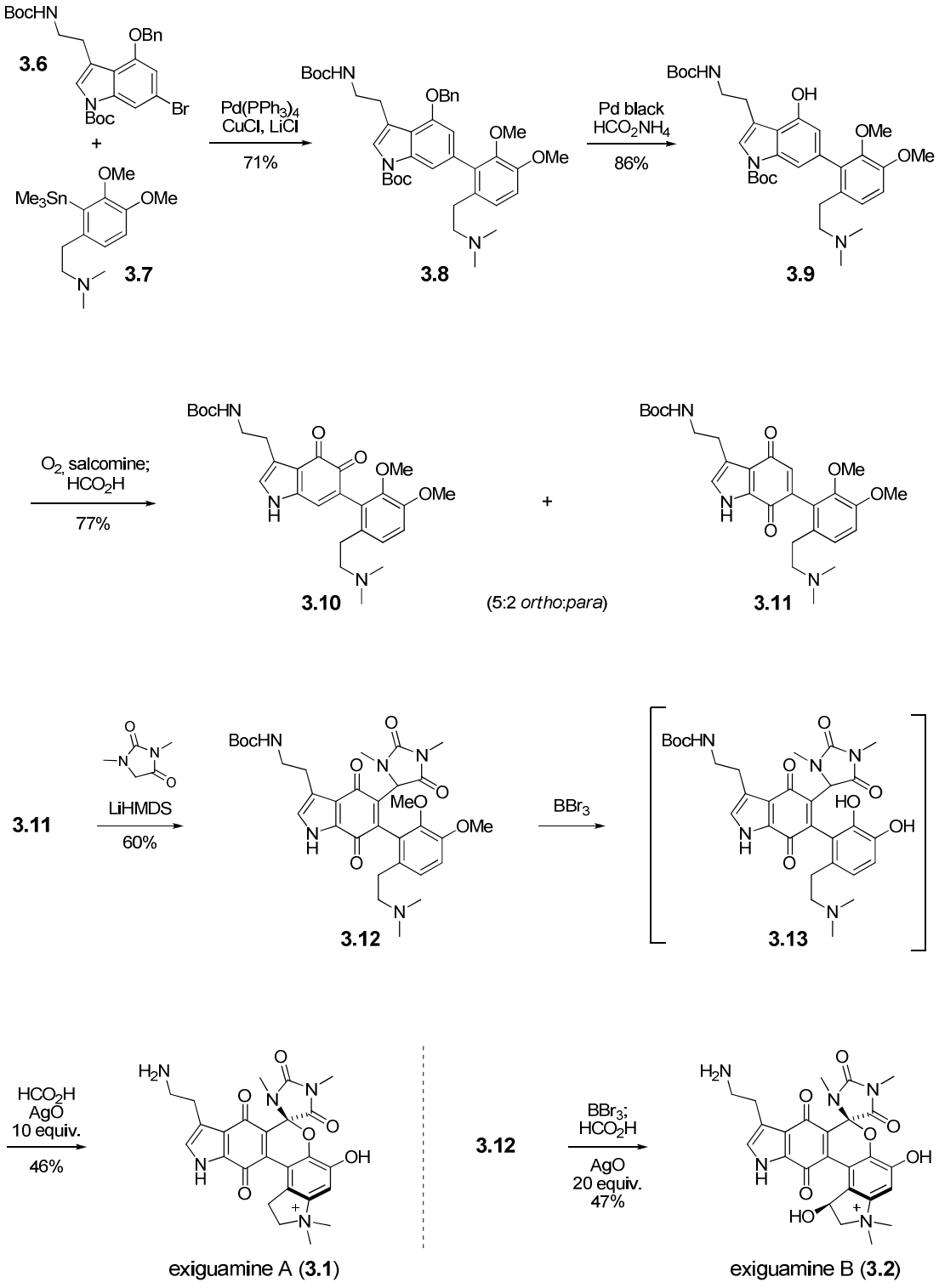


Figure 3.1. Natural products with IDO-inhibiting properties.

3.2 Background

In 2008 the work within the Trauner group resulted in a biomimetic approach to exiguamine A and the discovery of exiguamine B. The approach brought together the tryptamine fragment **3.6**, made in eleven steps from *meta*-bromophenol, and the phenethylamine fragment **3.7**, available in two steps, via a Stille cross-coupling (Scheme 3.1). The synthesis hinged upon the use of the oxa-6π electrocyclization in the final biomimetic cascade (**3.13** → **3.1** or **3.2**).[2] While the endgame of the synthesis worked as had been envisioned, the early stages of the route had potential for improvement. Specifically, the oxidation of phenol **3.9** to *para*-quinone **3.11** proceeded with unfavorable regioselectivity and provided the desired product **3.11** along with the unwanted *ortho*-quinone **3.10** in 22% and 55% yields, respectively. Thus, this chapter will deal with the improvements that have been made to the earlier part of the synthesis.

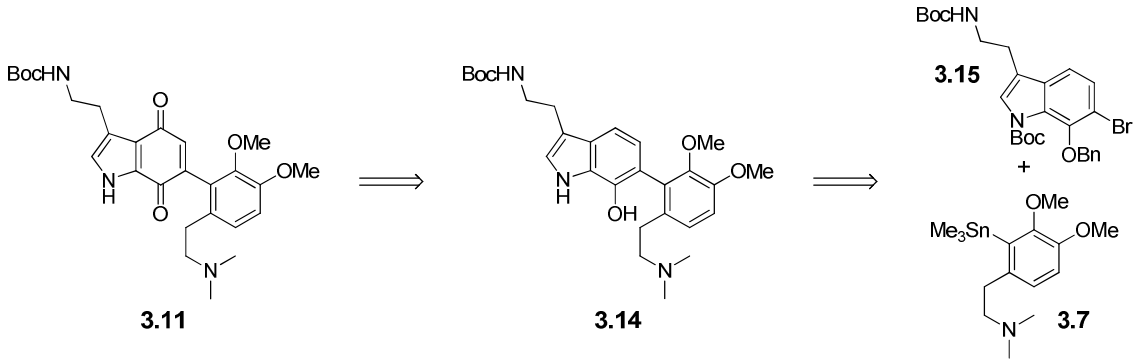
Scheme 3.1. First total synthesis of the exiguamines by the Trauner group.[2]



3.3 Results and Discussion

Based on the knowledge gained through our first-generation total synthesis, the need for improvement in two areas was recognized. Firstly, we anticipated the development of a more efficient and easily scalable synthesis of the tryptamine fragment. Secondly, we hoped to eliminate the formation of the unwanted *ortho*-quinone **3.10** that required tedious HPLC separation from the desired *para*-quinone **3.11**. Thus, the initial goal was a route to phenol **3.14**, which can in principle be oxidized to the *para*-quinone **3.11** avoiding potential byproducts due to the lack of free *ortho* positions (Scheme 3.2). Following the original synthetic route, we envisioned constructing **3.14** via a biaryl cross-coupling between the protected tryptamine **3.15** and stannane **3.7**.

Scheme 3.2. Retrosynthetic plan for the second generation synthesis.



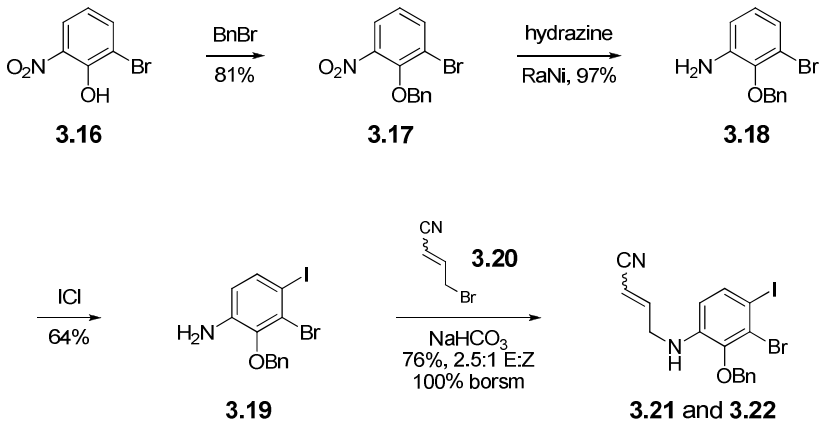
3.3.1 Heck approach to the tryptamine fragment

While many approaches are known to the synthesis of indole alkaloids,[7] only a few are suitable for the synthesis of such highly-substituted fragments as compound **3.15**. In the first route to the exiguamines we have employed the Hemetsberger synthesis to obtain tryptamine **3.6**.[8] In the synthesis described here we saw an opportunity to employ Heathcock's work with discorhabdin alkaloids, which featured a Heck reaction in the construction of the indole nucleus.[9]

The synthesis of the tryptamine fragment is shown in Scheme 3.3 and begins with benzyl protection of the commercially-available 2-bromo-6-nitrophenol (**3.16**) to afford benzyl ether **3.17**. Subjection of this material to hydrazine/Raney nickel reduction supplied aniline **3.18** in excellent yield (Scheme 3.3).

We then aimed at introducing an iodine in the *ortho* position of the aniline in order to utilize the resulting aryl iodide in the foreseen intramolecular Heck reaction-mediated construction of the 5-membered ring of the indole. This iodination was precedented in the above-mentioned work of Heathcock using a substrate, which had a methoxy group in place of our bromide. However, in our hands the iodination proceeded in the *para* position to afford iodoaniline **3.19** using a variety of electrophiles. This discrepancy was clear after **3.19** was alkylated with bromocrotononitrile (**3.20**) and the resulting *E*/*Z*-mixture of cyanides **3.21** and

Scheme 3.3. Heck approach to the tryptamine fragment.



3.22 was subjected to nuclear Overhauser effect spectroscopy (NOESY). Figure 3.2 highlights the through-space correlation between the pair of allylic protons, H_g, and the doublet H_c on the phenyl ring, which is consistent with structure **3.21**. Thus, the Heck approach to the indole nucleus turned out to be not applicable and we turned our attention to another strategy, described in the following section.

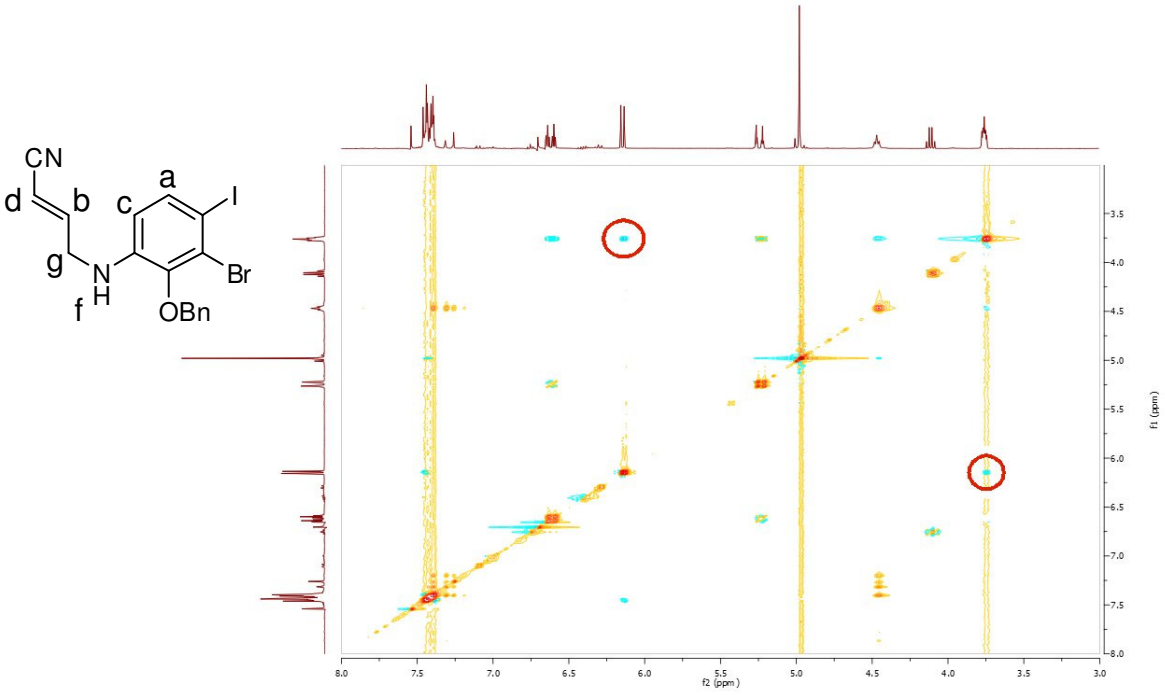
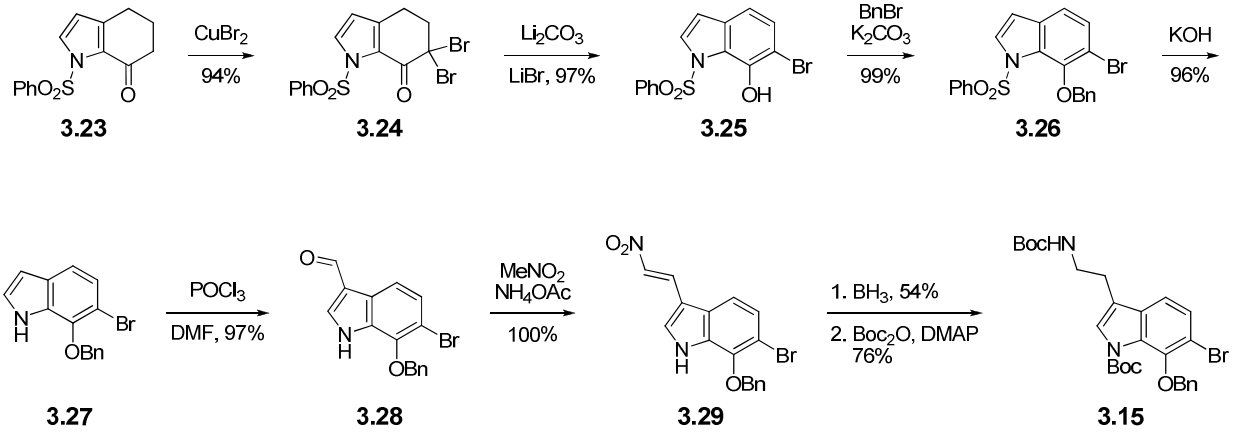


Figure 3.2. NOESY spectrum of the unexpected regioisomer **3.21**.

3.3.2 Revised synthesis of the tryptamine fragment

Our revised synthesis began with tetrahydroindole **3.23** (Scheme 3.4), which is readily available in multigram quantities from pyrrole in six straightforward steps.[10] Bromination at the α position gave dibromide **3.24**, while elimination and subsequent tautomerization furnished the aromatized product **3.25** in excellent yield.[10b] This phenol was subsequently protected as a benzyl ether **3.26** and the phenyl sulphonyl group was removed under alkaline conditions to afford indole **3.27** also in excellent yield.[11] We then set out to install the ethylamine side chain of the tryptamine using a strategy that relied on the previous synthesis. Thus, Vilsmeier-Haack formylation yielded formyl indole **3.28**, and the subsequent Henry reaction furnished nitrovinylindole **3.29** in quantitative yield.

Scheme 3.4. Synthesis of the tryptamine **3.15**.



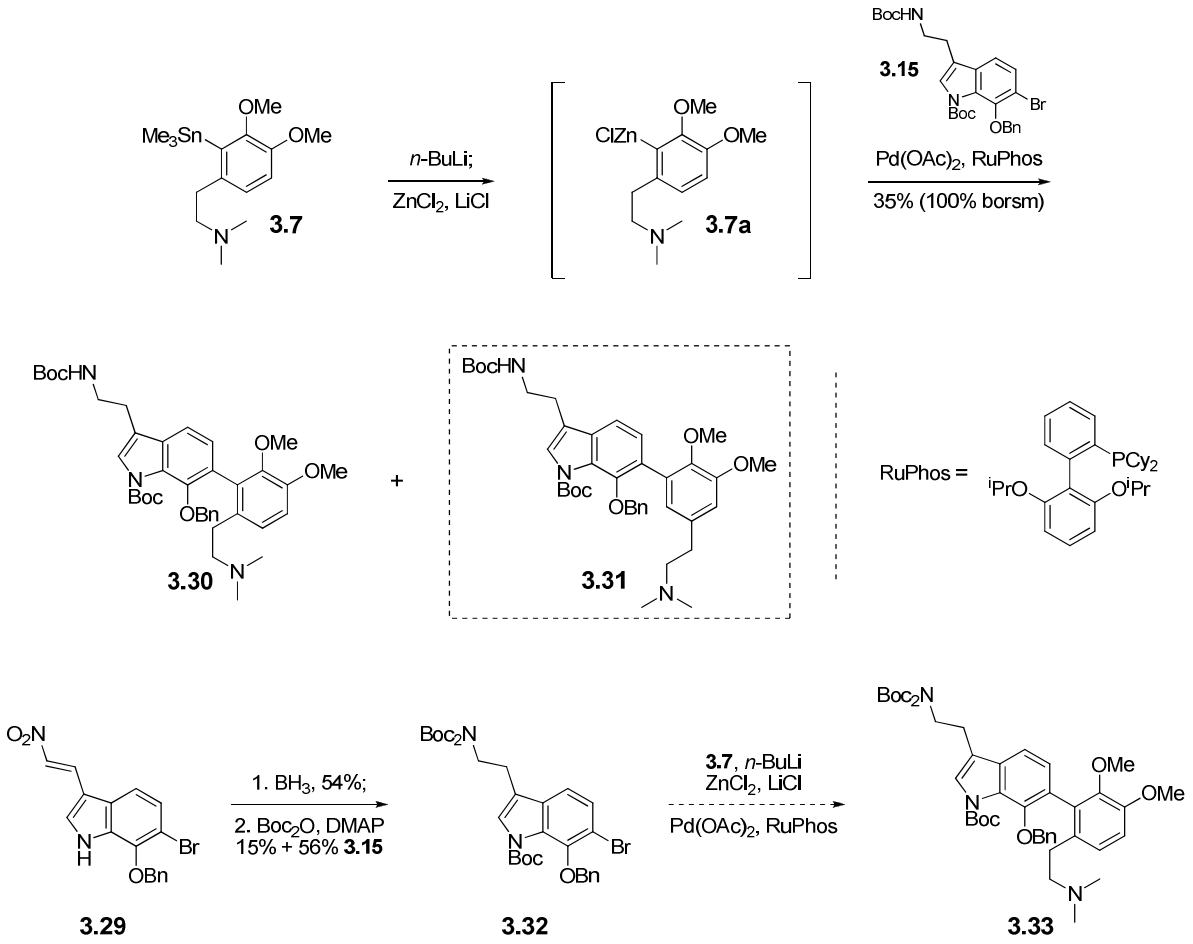
The next envisaged step was the exhaustive reduction of the nitroalkene. However, during the reduction of **3.29** with lithium aluminum hydride the bromine functionality was lost. This was not surprising, as a number of other research groups have had similar problems when an *ortho*-docking group was present on the phenyl ring.[12] Upon screening a variety of alternative conditions it was found that the only suitable method was reduction with borane, which afforded the desired tryptamine in moderate yield (Scheme 3.4). The ensuing unstable tryptamine had to be immediately bis-Boc protected to give the target building block, **3.15**.

3.3.3 Cross-coupling of the tryptamine and phenethylamine fragments

In contrast to the prior synthesis, the bromide **3.15** failed to engage in a Stille cross-coupling with the previously described stannane **3.7**, presumably due to the increased steric hindrance imposed by the *ortho*-benzyl ether group. Fortunately, it was found that a Negishi cross-coupling of the corresponding aryl zinc species **3.7a** with compound **3.15** was possible under carefully optimized conditions (Scheme 3.5).[13] By such means biaryl **3.30** was generated in moderate yield. It was found to be crucial to perform the lithiation of the stannane **3.7** at – 10 ^{o}C, otherwise unwanted regioisomer **3.31** (Scheme 3.5) was isolated and required tedious

separation by HPLC. Additionally, the coupling reaction was successful only when the aryl zinc species was added as slowly as possible to the refluxing solution of bromide **3.15** and active catalyst in THF. Unfortunately, aryl zinc species **3.7a** had to be generated by lithiation of the stannane **3.7** and could not be obtained from direct lithiation of tetramethyldopamine. Nevertheless, we were delighted to discover that the unreacted starting material **3.15** could be isolated and resubjected to the cross-coupling conditions. Presumably, the source of the problem was the pendant Boc carbamate and/or its conjugate base due to its affinity towards Lewis-acidic palladium. Moreover, the corresponding *tris*-Boc protected compound **3.32**, which had been occasionally obtained as a result of overprotection, showed complete lack of activity in the cross-coupling reaction, most likely also due to a strong chelation and thus inhibition of the active palladium catalyst (Scheme 3.5). The structure of **3.32** was verified by X-ray analysis (Figure 3.3).

Scheme 3.5. Cross-coupling of tryptamine **3.15**.



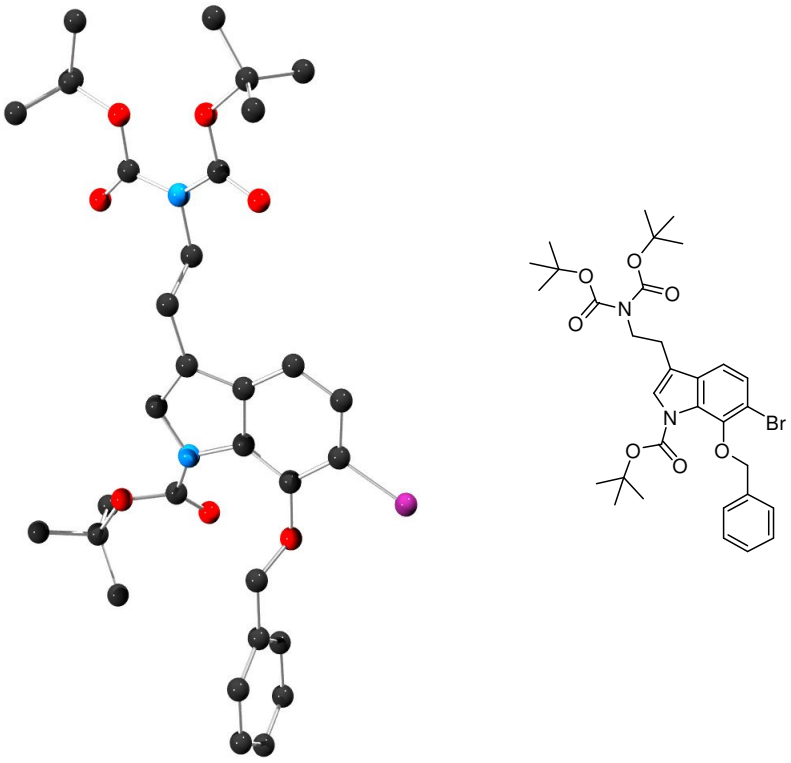
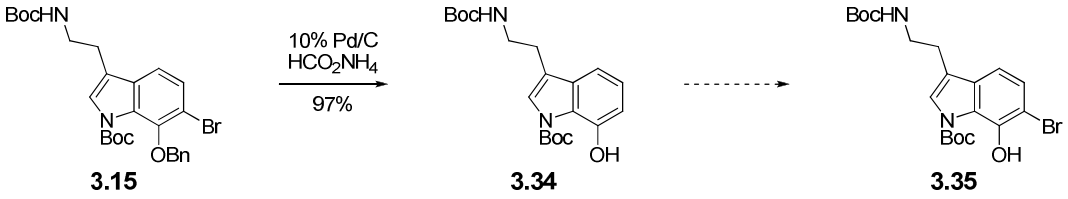


Figure 3.3. ORTEP diagram derived from the single-crystal X-ray analysis of the *tris*-Boc protected tryptamine **3.32**.

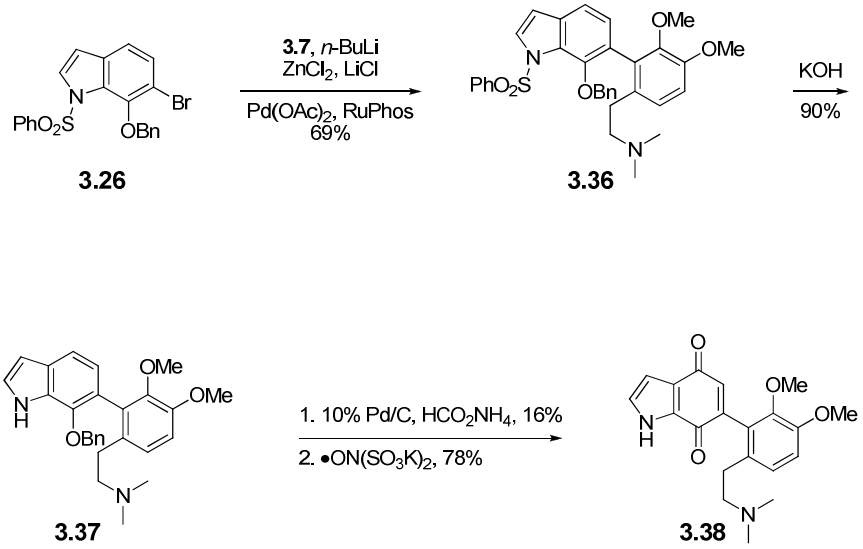
In light of the unsatisfactory yields of the Negishi cross-coupling and the steric hindrance of the aryl bromide **3.15**, we decided to remove the benzyl protecting group at this stage and investigate the Stille cross-coupling using bromophenol **3.35** (Scheme 3.6).[14] To our disappointment, all the attempted reaction conditions resulted in reductive debromination, yielding phenol **3.34**. We proposed that **3.35** can be made through directed *ortho*-bromination of phenol **3.34**. Unfortunately, none of the conditions known for selective *ortho*-bromination of phenols, such as Br_2/*t*-BuNH_2, pyridine hydrobromide perbromide, or 2,4,4,6-tetrabromocyclohexa-2,5-dieneone,[15] resulted in formation of the desired product. The *para*-brominated product was isolated exclusively.

Scheme 3.6. Attempted synthesis of the free bromophenol.



Another logical solution to the difficulties in the cross-coupling step and the installation of the ethylamine sidechain of **3.15** would be to reverse the order of steps. This would ensure that the problematic Boc carbamate functional group would not be there during the cross-coupling, while the labile bromine would not interfere with the reduction of the nitroalkene. In the event, the Negishi cross-coupling of aryl bromide **3.26** with the stannane **3.7** proceeded smoothly, yielding biaryl **3.36** in 69% yield. This last compound was deprotected to afford free indole **3.37** in excellent yield (Scheme 3.7). However, the previously robust Vilsmeier-Haack formylation/Henry reaction sequence resulted in complex mixtures of products. Screening of other literature-known conditions for the installation of the ethylamine sidechain of the tryptamine such as opening of an aziridine, reaction with 1-(dimethylamino)-2-nitroethylene (DMANE), nucleophilic addition of cyanide to gramine, as well as bromination of the indole at the 3 position proved futile.[16] The benzyl group of compound **3.37** was removed and the ensuing phenol was then oxidized to *para*-quinone **3.38** using Fremy's radical[17] to test the oxidation conditions.

Scheme 3.7. Cross coupling of the aryl bromide **3.26**.

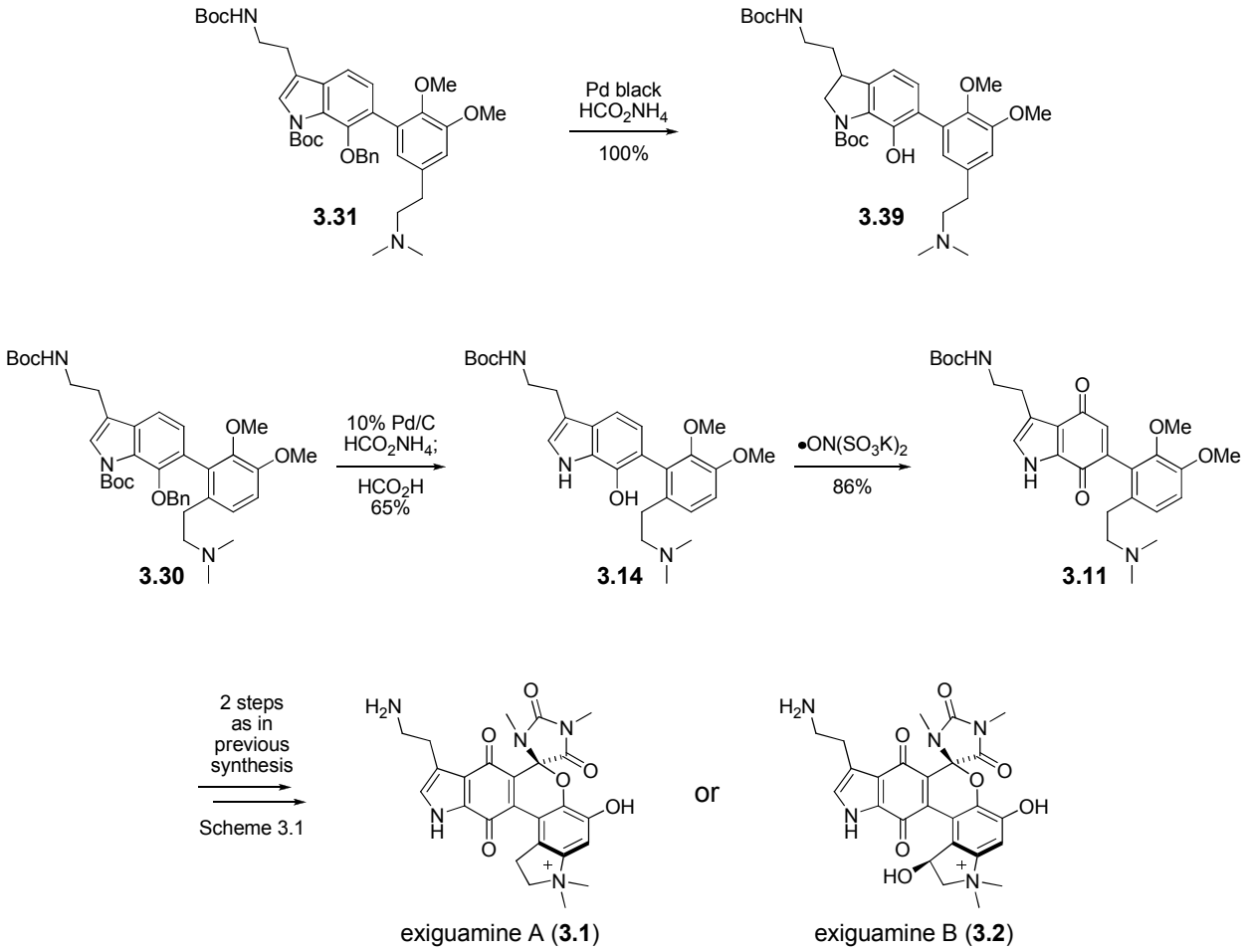


3.3.4 Endgame: oxidation and conversion to exiguamines

Since the Fremy's radical-mediated oxidation (**3.37** → **3.38**) worked well and gave no sideproducts, we focused our attention on the deprotection and oxidation of biaryl **3.30** (Scheme 3.8). Some difficulties were immediately encountered in the deprotection step. Reduction of the C_2-C_3-double bond of indole was invariably observed upon submission of either **3.30** or **3.31** to deprotection conditions such as palladium black or large excess of ammonium formate. However, when fewer equivalents of ammonium formate were used the reaction did not proceed at all. Optimal conditions were found to be 10% Pd/C and seven equivalents of ammonium formate. The indole Boc protecting group was immediately removed to give free indole **3.14** in good yield. While both the benzyl group and the indole Boc of **3.30** could be cleaved in one pot using lithium di-*tert*-butylbiphenylide without affecting the indole double bond,[18] the yields did not exceed those obtained using transfer hydrogenation conditions described above. Fremy's

radical oxidation proceeded smoothly to furnish *para*-quinone **3.11** in excellent yield. Curiously, the oxidation did not take place unless the indole Boc was removed, most likely due to the steric hindrance around the reaction site. The newly-formed *para*-quinone **3.11** was then converted to exiguamines A and B using the reaction conditions utilized in the first total synthesis[2] (see Scheme 1).

Scheme 3.8. Endgame of the second-generation synthesis of exiguamines.



3.3.5 Summary and conclusions

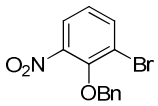
A second-generation synthesis of exiguamines has been achieved. While the original synthesis allowed us to obtain a common precursor to exiguamines A and B and showcase a biomimetic cascade reaction affording either natural product, the synthetic efforts described herein have resulted in a scalable and efficient route to these compounds. It is anticipated that the material obtained through this work will be used for research efforts aimed at addressing some of the many unsolved questions still surrounding idoleamine-2,3-dioxigenase and its role in cancer.

3.4 Experimental

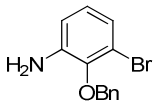
3.4.1 Synthetic Procedures

General Methods: Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60Å silica gel, Waters Preparative C18 125 Å 55-105 μm silica gel (reversed phase), or preparative HPLC on a Zorbax 21.2 × 250 mm, 7 μm SB-C18 column, 22.0 mL/min flow rate (reversed phase HPLC), as indicated. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} TLC plates and visualized using charring solutions of potassium permanganate. Reactions were carried out under inert gas atmosphere in oven-dried glassware and reaction solutions were magnetically stirred. THF was distilled from benzophenone ketyl prior to use. EtOAc was distilled on a rotary evaporator, dried over activated 3 Å molecular sieves, and degasses by sparging with a stream of dry N_2 for 20 min. All other reagents and solvents were used without further purification from commercial sources unless otherwise noted.

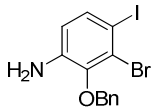
NMR spectra were measured by the LMU NMR facility on Brüker AC (300 MHz), Varian XL (400 MHz), or Brüker AMX 600 (600 MHz) and calibrated using residual solvent signal. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad. Where consistent coupling constants have been observed in the NMR spectrum, the apparent multiplicity of the proton signal concerned is reported. High resolution mass spectra (HRMS) were obtained by the LMU Mass Spectroscopy facility using fast atom bombardment (FAB) or electrospray ionization (ESI). Melting points were determined with an electrothermal apparatus and are uncorrected.



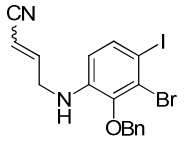
Benzyl ether 3.17. To a solution of 2-bromo-6-nitrophenol (**3.16**; 1.04 g, 4.75 mmol) in DMF (20 mL) was added benzyl bromide (0.57 mL, 4.8 mmol) and K_2CO_3 (1.97 g, 14.3 mmol). The resulting suspension was stirred at 90 °C for 3 h. After being cooled to ambient temperature, the reaction mixture was diluted with water (50 mL), and extracted with Et_2O (50 mL) and then with EtOAc (2 x 40 mL). The combined organic phases were washed with 10% aqueous NaCl (2 x 40 mL), brine, dried, filtered, and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **3.17** (1.18 g, 81%) as an off-white solid. Data for **3.17**: R_f 0.56 (25% EtOAc/hexanes); IR 1526, 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.83 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.79 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.55 (m, 2H), 7.40 (m, 3H), 7.16 (t, 1H, J = 8.0 Hz), 5.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.4, 138.1, 135.7, 129.0, 128.9, 128.8 (two overlapping signals), 125.5, 124.7, 120.5, 76.8; HRMS not obtained (compound unstable under conditions); m.p. = 61.0 – 62.0 °C.



Aniline 3.18. To a solution of benzyl ether **3.17** (135 mg, 0.438 mmol) in THF (5.0 mL) was added Raney Nickel (~100 mg, suspension in water) and the resulting mixture was stirred at RT for 30 min. The suspension was filtered through a pad of Celite and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **3.18** (118 mg, 97%) as a colorless oil. Data for **3.18**: R_f 0.48 (25% EtOAc/hexanes); IR 1475, 1453, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (m, 2H), 7.45 (m, 3H), 6.98 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 6.84 (t, 1H, J = 8.0 Hz), 6.68 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 5.02 (s, 2H), 3.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.1, 141.9, 137.1, 128.7, 128.49, 128.45, 126.0, 122.5, 117.6, 115.2, 74.0; HRMS (FAB) calculated for $C_{13}H_{12}{}^{79}BrNO$ $(M)^+$: 277.0102, found: 277.0097.



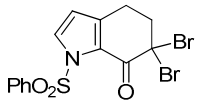
Iodidoaniline 3.19. A biphasic mixture of Et_2O (6.0 mL), saturated aqueous Na_2CO_3 (1.5 mL), aniline **3.18** (357 mg, 1.28 mmol), and ICl (570 mg, 3.51 mmol) was stirred in the dark for 2.5 h. The reaction mixture was diluted with Et_2O (30.0 mL) and washed with saturated aqueous Na_2SO_3 (3 x 10 mL), dried, filtered, and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **3.19** (334 mg, 64%) as a colorless oil. Data for **3.19**: R_f 0.46 (25% EtOAc/hexanes); IR 1604, 1458, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (m, 2H), 7.40 (m, 4H), 6.49 (d, 1H, J = 8.4 Hz), 4.95 (s, 2H), 3.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.0, 141.7, 136.8, 135.7, 128.0, 128.7, 128.5, 125.2, 116.8, 86.2, 74.0; HRMS (FAB) calculated for $C_{13}H_{11}{}^{79}BrINO$ $(M)^+$: 402.9069, found: 402.9061.



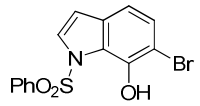
***Z*-cyanide 3.21 and *E*-cyanide 3.22**. To a solution of iodoaniline **3.19** (108 mg, 0.267 mmol) in acetone (4.0 mL) was added bromocrotononitrile (**3.20**; 141 mg, 0.966 mmol) as a mixture of *E*- and *Z*-isomers followed by $NaHCO_3$ (234 mg, 2.79 mmol). The resulting mixture was stirred at 56 °C. After 1h, another portion of crotononitrile (50 mg, 0.34 mmol) was added, and this was repeated after additional hour. After 10 h at 56 °C, the reaction mixture was cooled to RT, then filtered and concentrated. Purification by silica gel chromatography (15% EtOAc/hexanes) afforded **3.21** (42.7 mg, 34%) and **3.22** (68.9 mg, 55%) as a colorless oils.

Data for *Z*-cyanide **3.21**: R_f 0.39 (25% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 6H), 6.31 (m, 2H), 5.44 (dt, 1H, J_d = 11.1 Hz, J_t = 1.8 Hz), 4.96 (s, 2H), 4.51 (t, 1H, J = 6.3 Hz), 3.97 (td, 2H, J_t = 6.3 Hz, J_d = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4, 143.9, 142.0, 136.7, 136.0, 128.91, 128.86, 128.6, 124.8, 115.3, 112.0, 101.5, 85.9, 74.5, 43.8; HRMS (FAB) calculated for $C_{17}H_{14}{}^{79}BrIN_2O$ $(M)^+$: 467.9334, found: 467.9330.

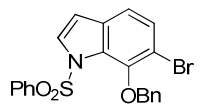
Data for *E*-cyanide **3.22**: R_f 0.55 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 6H), 6.62 (dt, 1H, J_d = 16.3 Hz, J_t = 4.0 Hz), 6.15 (d, 1H, J = 8.6 Hz), 5.24 (dt, 1H, J_d = 16.3 Hz, J_t = 2.2 Hz), 4.98 (s, 2H), 4.47 (t, 1H, J = 6.0 Hz), 3.76 (ddd, 2H, J_1 = 6.1 Hz, J_2 = 4.0 Hz, J_3 = 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0, 143.7, 141.9, 136.6, 135.9, 128.98, 128.95, 128.7, 124.7, 117.1, 112.0, 100.6, 85.9, 74.7, 45.0; HRMS (FAB) calculated for $C_{17}H_{14}{}^{79}BrIN_2O$ $(M)^+$: 467.9334, found: 467.9336.



Dibromide 3.24. A mixture of ketone **3.23** (1.35 g, 4.90 mmol) and cupric bromide (6.58 g, 29.5 mmol) in dry, degassed EtOAc (20 mL) was refluxed for 16 h under an argon atmosphere, cooled to RT, and filtered through a silica plug that was subsequently washed with EtOAc (100 mL). The combined filtrates (green solution) were washed with brine (100 mL) and concentrated. Trituration with MeOH afforded dibromide **3.24** (1.99 g, 94%) as a white solid. Data for **3.24**: R_f 0.37 (25% EtOAc/*iso*-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (m, 2H), 7.84 (d, 1H, J = 3.2 Hz), 7.61 (m, 1H), 7.52 (m, 2H), 6.28 (d, 1H, J = 3.2 Hz), 2.96 (t, 2H, J = 5.8 Hz), 2.83 (t, 2H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 142.2, 137.6, 135.0, 132.7, 129.1, 128.7, 121.8, 110.8, 67.5, 47.0, 24.2; HRMS (ESI) calculated for $C_{14}H_{15}{}^{79}Br_2N_2O_3S$ $(M+NH_4)^+$: 448.9170, found: 448.9156; m.p. = 180.4 – 180.9 °C.

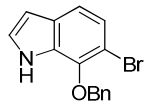


Phenol 3.25. A mixture of dibromide **3.24** (4.37 g, 10.1 mmol), lithium carbonate (830 mg, 11.2 mmol), and lithium bromide (967 mg, 11.1 mmol) in dry DMF (45 mL) was stirred for 45 min at 110 °C. After cooling to ambient temperature, the mixture was diluted with EtOAc (250 mL), washed with saturated aqueous NH_4Cl (150 mL), 10% aqueous NaCl (2 x 150 mL), and brine (50 mL) then concentrated. Purification by silica gel chromatography (product loaded in silica; eluted with 20% → 25% EtOAc/*iso*-hexanes) afforded phenol **3.25** (3.44 g, 97%) as a tan solid. Data for **3.25**: R_f 0.63 (25% EtOAc/*iso*-hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.21 (s, 1H), 7.79 (m, 2H), 7.53 (m, 1H), 7.46 (m, 3H), 7.38 (d, 1H, J = 8.3 Hz), 6.90 (d, 1H, J = 8.3 Hz), 6.63 (d, 1H, J = 3.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.7, 137.0, 134.6, 134.0, 129.8 (two overlapping signals), 128.5, 127.0, 123.4, 114.0, 111.7, 107.6; HRMS (ESI) calculated for $C_{14}H_9{}^{79}BrNO_3S$ $(M–H)^–$: 349.9487, found: 349.9491; m.p. = 125.6 – 127.1 °C.

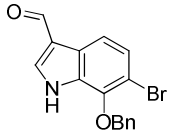


Benzyl ether 3.26. A mixture of phenol **3.25** (508 mg, 1.44 mmol), potassium carbonate (608 mg, 4.40 mmol), and benzyl bromide (0.20 mL, 1.7 mmol) in dry DMF (10 mL) was stirred at 90 °C for 1.5 h. After cooling, the mixture was diluted with EtOAc (100 mL), washed with dilute

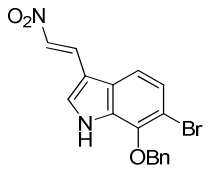
aqueous NH_4Cl (50 mL), 10% aqueous NaCl (50 mL), and brine (30 mL) then concentrated. Purification by silica gel chromatography (10% EtOAc/*iso*-hexanes) afforded **3.26** (628 mg, 98%) as a colorless oil, which solidified upon storage at 0 °C. Data for **3.26**: R_f 0.67 (25% EtOAc/*iso*-hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, 1H, *J* = 3.7 Hz), 7.77 (m, 2H), 7.60 (m, 2H), 7.51 – 7.42 (m, 5H), 7.22 (m, 3H), 6.69 (d, 1H, *J* = 3.7 Hz), 5.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 138.4, 137.4, 134.0, 133.6, 129.8, 129.1, 129.0, 128.9, 128.7, 128.3, 128.2, 127.9, 118.2, 113.9, 107.8, 75.2; HRMS (ESI) calculated for $C_{21}H_{20}{}^{79}BrN_2O_3S$ $(M+NH_4)^+$: 459.0378, found: 459.0360; m.p. = 94.5 – 95.9 °C.



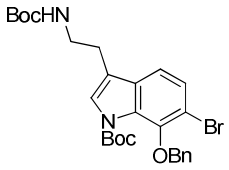
Indole 3.27. A mixture of benzyl ether **3.26** (1.24 g, 2.80 mmol) and potassium hydroxide (2.97 g, 52.9 mmol) in DME/MeOH/H_2O (15 mL of a 1:1:1 v/v/v mixture) was stirred at 80 °C for 1 h. Upon cooling to ambient temperature, the cherry-red mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (150 mL). The separated organic phase was washed with brine (50 mL) and concentrated. Purification by silica gel chromatography (10% EtOAc/*iso*-hexanes) afforded **3.27** (809 mg, 96%) as a viscous yellow oil. Data for **3.27**: R_f 0.66 (25% EtOAc/*iso*-hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (br. s, 1H), 7.51 (m, 2H), 7.41 (m, 3H), 7.31 (s, 2H), 7.02 (t, 1H, *J* = 2.8 Hz), 6.52 (t, 1H, *J* = 2.7 Hz), 5.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 137.4, 131.0, 129.5, 128.9, 128.6, 128.5, 124.9, 124.5, 117.9, 108.6, 103.3, 75.8; HRMS (ESI) calculated for $C_{15}H_{11}{}^{79}BrNO$ $(M–H)^–$: 300.0024, found: 300.0028.



Aldehyde 3.28. Freshly-distilled $POCl_3$ (260 μL, 2.84 mmol) was added dropwise to dry DMF (3 mL) at 0 °C, stirred for 15 min then transferred via a cannula to a solution of indole **3.27** (693 mg, 2.29 mmol) in DMF (3 mL). The reaction mixture was stirred at 0 °C for 30 min, then at 40 °C for 1 h. The resulting yellow mixture was cooled to 0 °C then basified with a 1 N solution of NaOH before being heated to reflux. After 20 min, the reaction mixture was cooled to ambient temperature, then diluted with EtOAc (150 mL), washed with 10% aqueous NaCl (50 mL), brine (50 mL) and concentrated. Purification by silica gel chromatography (40% EtOAc/*iso*-hexanes) afforded **3.28** (738 mg, 97%) as a white solid. Data for **3.28**: R_f 0.49 (50% EtOAc/*iso*-hexanes); ^{1}H NMR (Acetone-d_6, 400 MHz) δ 11.52 (br. s, 1H), 10.02 (s, 1H), 8.17 (s, 1H), 7.93 (d, 1H, *J* = 8.4 Hz), 7.58 (m, 2H), 7.44 (d, 1H, *J* = 8.4 Hz), 7.42 – 7.33 (m, 3H), 5.19 (s, 2H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 185.4, 142.8, 138.2, 137.8, 132.7, 129.2, 129.1, 129.0, 127.7, 127.2, 120.6, 119.4, 111.0, 76.0; HRMS (ESI) calculated for $C_{16}H_{11}{}^{81}BrNO_2$ $(M–H)^–$: 329.9953, found: 329.9957; m.p. = 152.1 – 152.6 °C.



Nitro indole 3.29. To a stirred solution of aldehyde **3.28** (961 mg, 2.91 mmol) in nitromethane (35 mL) was added NH_4OAc (238 mg, 3.09 mmol) at RT. The yellow solution was then heated to reflux for 1.5 h before being cooled to RT. Concentration and purification by silica gel chromatography (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH) afforded **3.29** (1.08 g, 100%) as an orange solid. Data for **3.29**: R_f 0.44 (25% EtOAc/*iso*-hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.54 (s, 1H), 8.39 (d, 1H, *J* = 13.5 Hz), 8.29 (s, 1H), 8.03 (d, 1H, *J* = 13.5 Hz), 7.72 (d, 1H, *J* = 8.6 Hz), 7.61 (m, 2H), 7.44 – 7.37 (m, 4H), 5.12 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 141.8, 136.4, 136.2, 133.7, 132.2, 131.8, 128.5, 128.20, 128.18, 126.7, 125.9, 117.7, 109.7, 108.9, 74.9; HRMS (ESI) calculated for $C_{17}H_{12}{}^{79}BrN_2O_3$ $(M–H)^-$: 371.0031, found: 371.0057; m.p. = 198.1 – 198.4 °C.

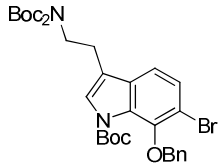


Tryptamine 3.15. To a stirred solution of nitro indole **3.29** (1.11 g, 2.98 mmol) in THF (30 mL) was slowly added a 1.0 M solution of BH_3 in THF (18.0 mL, 18.0 mmol). The resulting mixture was stirred at 70 °C for 1.5 h. The reaction mixture was cooled to 0 °C then slowly quenched by addition of small pieces of ice followed by 1.0 M HCl (100 mL). The mixture was then stirred at 60 °C for 1 h, cooled to 0 °C and basified with a 2.5 M solution of NaOH (50 mL). The reaction mixture was saturated with NaCl, then extracted with diethyl ether (150 mL). The separated organic phase was dried, filtered, and concentrated. Purification by silica gel chromatography ([90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH] → 4:1 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:MeOH) afforded unprotected tryptamine (555 mg, 54%) as a brown oil, which was used immediately in the next step.

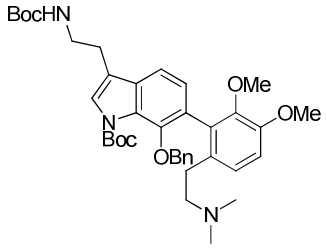
To a stirred solution of ensuing unprotected tryptamine (864 mg, 2.50 mmlol) in THF (40 mL) were added Boc_2O (1.10 mL, 5.14 mmol), triethylamine (0.70 mL, 5.0 mL), and DMAP (63.0 mg, 0.516 mmol) at RT. After 16 h the reaction mixture was diluted with EtOAc (200 mL), washed with a saturated solution of $NaHCO_3$ (100 mL) then brine (50 mL). The separated organic phase was concentrated. Purification by silica gel chromatography (15% EtOAc/*iso*-hexanes) gave tryptamine **3.15** (1.04 g, 76%) as a clear oil that solidified upon prolonged storage at 0 °C.

Data for **3.15**: R_f 0.30 (15% EtOAc/*iso*-hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (m, 2H), 7.45 (d, 1H, *J* = 8.3 Hz), 7.35 (m, 4H), 7.16 (d, 1H, *J* = 8.3 Hz), 5.02 (s, 2H), 4.73 (br. s, 1H), 3.42 (app. q, 2H, *J* = 6.2 Hz), 2.84 (t, 2H, *J* = 6.9 Hz), 1.57 (s, 9H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 148.4, 144.0, 137.0, 133.5, 129.5, 128.9, 128.6, 128.3, 128.1, 126.2,

117.6, 115.8, 114.9, 83.8, 79.4, 75.5, 40.3, 28.6, 28.1, 25.6; HRMS (ESI) calculated for $C_{27}H_{28}{}^{79}Br^{35}Cl\,N_2O_5$ $(M+Cl)^-$: 579.1261, found: 579.1293; m.p. = 114.3 – 114.5 °C.

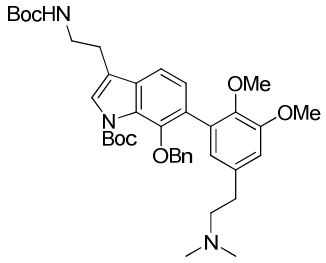


Tris-Boc carbamate 3.32. To a stirred solution of unprotected tryptamine (obtained as described above; 288 mg, 0.834 mmol) in MeCN (20 mL) were added Boc_2O (370 mg, 1.70 mmol), *i*-Pr_2EtN (0.18 mL, 1.03 mL), and DMAP (59.5 mg, 0.488 mmol) at RT. After 3 days the reaction mixture was diluted with EtOAc (200 mL), washed with saturated solution of $NaHCO_3$ (100 mL), and brine (50 mL). The organic phase was concentrated. Purification by silica gel chromatography (15% EtOAc/*iso*-hexanes) gave tris-Boc carbamate **3.32** (78.6 mg, 15%) as a clear oil that solidified upon prolonged storage at 0 °C, along with tryptamine **3.15** (256 mg, 56%). Data for **3.32**: R_f 0.58 (15% EtOAc/*iso*-hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (m, 2H), 7.48 (d, 1H, *J* = 8.3 Hz), 7.34 (m, 4H), 7.27 (d, 1H, *J* = 8.3 Hz), 5.00 (s, 2H), 3.85 (m, 2H), 2.95 (m, 2H), 1.57 (s, 9H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 148.4, 144.0, 137.1, 133.7, 129.4, 128.9, 128.4, 128.18, 128.16, 126.4, 117.5, 116.0, 114.8, 83.8, 82.6, 75.5, 46.3, 28.2, 28.1, 24.6; HRMS (ESI) calculated for $C_{32}H_{41}{}^{79}BrN_2NaO_7$ $(M+Na)^+$: 667.1995, found: 667.1990; no distinct m.p., decomp. above 150 °C.

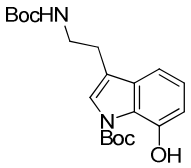


Biaryl 3.30. A solution of stannane **3.7** (130 mg, 0.349 mmol) in THF (2 mL) was treated with a 2.5 M solution of *n*-BuLi in hexanes (150 μL, 0.38 mmol) at –10 °C. After 15 min, a 1.0 M solution of $ZnCl_2$ in THF, that is 2.3 M in LiCl, (420 μL, 0.42 mmol) was added dropwise, and the reaction mixture was allowed to slowly warm to RT. After another 15 min the reaction mixture was transferred, dropwise and via a cannula to a stirred mixture of tryptamine **3.15** (120 mg, 0.220 mmol), $Pd(OAc)_2$ (9.3 mg, 41 μmol), and RuPhos (39.8 mg, 85.3 μmol) in THF (2 mL) at 70 °C. The reaction mixture was stirred overnight then concentrated. Purification by silica gel chromatography (1:1 → 1:0 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded biaryl **3.30** (51.9 mg, 35%) as a colorless oil along with unreacted tryptamine **3.15** (77.7 mg, 65%), which could be recycled. Data for biaryl **3.30**: R_f 0.35 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.37 (d, 1H, *J* = 7.9 Hz), 7.34 (s, 1H), 7.14 (m, 3H), 7.09 (d, 1H, *J* = 7.9 Hz), 7.06 (d, 1H, *J* = 8.5 Hz), 6.94 (d, 1H, *J* = 8.5 Hz), 6.87 (m, 2H), 4.82 (d, 1H, *J* = 10.1 Hz), 4.76 (br. s, 1H), 4.53 (d, 1H, *J* = 10.1 Hz), 3.88 (s, 3H), 3.70 (s, 3H), 3.48 (m, 2H), 2.90 (t, 2H, *J* = 6.4 Hz), 2.84 (m, 2H), 2.57 (m, 2H), 2.23 (s, 6H), 1.54 (s, 9H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.1, 151.9, 148.8, 147.3, 144.5, 137.5, 133.9, 129.1, 128.6, 128.5, 128.1, 128.0, 127.8, 127.5, 126.8, 126.3, 125.0, 117.9, 114.7,

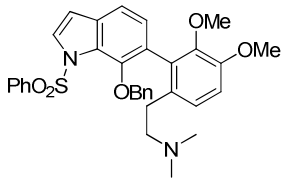
112.2, 83.5, 79.5, 75.2, 61.0, 59.0, 56.1, 43.5, 40.4, 29.3, 28.6, 28.2, 25.8; HRMS (ESI) calculated for $C_{39}H_{52}N_3O_7$ $(M+H)^+$: 674.3805, found: 674.3804.



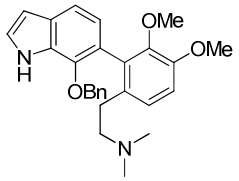
Biaryl isomer 3.31. The compound was isolated as an impurity from the reaction described above when the lithiation was carried out above 0 °C. Data for biaryl isomer **3.31**: R_f 0.35 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.38 (s, 1H), 7.34 (d, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.19 (m, 3H), 6.98 (m, 2H), 6.82 (d, 1H, *J* = 1.8 Hz), 6.79 (d, 1H, *J* = 1.9 Hz), 4.67 (m, 3H), 3.93 (s, 3H), 3.69 (s, 3H), 3.47 (m, 2H), 2.91 (m, 6H), 2.72 (s, 6H), 1.59 (s, 9H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.2, 153.6, 148.8, 146.3, 144.6, 137.8, 133.8, 133.6, 130.7, 129.1, 128,62, 128.57, 128.2, 127.8, 126.9, 126.3, 124.2, 117.7, 114.5, 112.3, 83.5, 79.6, 75.4, 60.9, 59.2, 56.2, 43.2, 40.4, 30.9, 28.6, 28.2, 25.8; HRMS (ESI) calculated for $C_{39}H_{52}N_3O_7$ $(M+H)^+$: 674.3805, found: 674.3799.



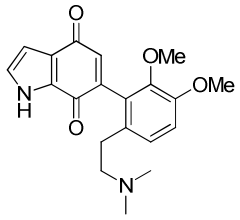
Phenol 3.34. To a solution of tryptamine **3.15** (195 mg, 0.357 mmol) in EtOH (10 mL) was added NH_4HCO_2 (134 mg, 2.12 mmol) followed by 10% Pd/C (39.2 mg). The reaction mixture was stirred at 40 °C for 30 min, cooled to RT then filtered through a silica plug that was washed with CH_2Cl_2. The combined filtrates were concentrated and the resulting mixture was then suspended in CH_2Cl_2, filtered, and concentrated. Purification by silica gel chromatography (15% EtOAc/*iso*-hexanes) afforded the free phenol **3.34** (131 mg, 97%) as a colorless oil. Data for **3.34**: R_f 0.30 (15% EtOAc/*iso*-hexanes); ^1H NMR ($CDCl_3$, 600 MHz) δ 10.85 (br. s, 1H), 7.24 (s, 1H), 7.15 (t, 1H, *J* = 7.8 Hz), 6.97 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.9 Hz), 6.86 (dd, 1H, J_1 = 7.9 Hz, J_2 = 0.6 Hz), 4.63 (br. s, 1H), 3.43 (m, 2H), 2.83 (t, 2H, *J* = 6.9 Hz), 1.65 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 152.5, 145.0, 133.5, 125.4, 123.8, 123.4, 119.8, 113.1, 110.1, 86.0, 79.4, 40.1, 28.6, 28.2, 25.8; HRMS (ESI) calculated for $C_{20}H_{28}N_2NaO_5$ $(M+H)^+$: 399.1896, found: 399.1896.



Biaryl 3.36. A solution of stannane **3.7** (512 mg, 1.38 mmol) in THF (4 mL) was treated with a 2.5 M solution of *n*-BuLi in hexanes (580 µL, 1.45 mmol) at RT. After 15 min, a 1.0 M solution of $ZnCl_2$ in THF (1.55 mL, 1.55 mmol) was added dropwise. After another 15 min the reaction mixture was transferred, dropwise and via a cannula, to a stirred mixture of benzyl ether **3.26** (475 mg, 1.07 mmol), $Pd(OAc)_2$ (12.3 mg, 54.8 µmol), and RuPhos (50.1 mg, 107 µmol) in THF (4 mL). The reaction mixture was stirred for 16 h then concentrated. Purification by silica gel chromatography (1:1 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded **3.36** (425 mg, 69%) as a pale-yellow viscous oil. Data for **3.36**: R_f 0.33 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O: NH_4OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, 1H, *J* = 3.7 Hz), 7.48 (m, 2H), 7.37 (m, 2H), 7.23 (m, 3H), 7.15 (m, 2H), 7.03 (d, 1H, *J* = 8.0 Hz), 6.99 (d, 1H, *J* = 8.5 Hz), 6.89 (m, 3H), 6.71 (d, 1H, *J* = 3.7 Hz), 4.85 (d, 1H, *J* = 9.6 Hz), 4.68 (d, 1H, *J* = 9.6 Hz), 3.82 (s, 3H), 3.58 (s, 3H), 2.29 – 2.00 (m, 4H), 1.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.4, 147.0, 143.7, 139.3, 137.5, 133.8, 133.2, 132.9, 132.3, 129.3, 128.9, 128.7, 128.6, 127.9, 127.8, 127.6, 127.5, 124.5, 116.7, 112.4, 107.6, 75.4, 60.6, 60.4, 56.0, 44.7, 30.3 (one signal in the aromatic region is obscured or overlapping); HRMS (ESI) calculated for $C_{33}H_{35}N_2O_5S$ $(M+H)^+$: 571.2267, found: 571.2249.



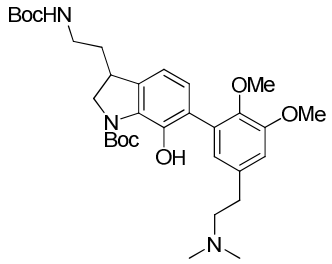
Free indole 3.37. A mixture of biaryl analog **3.36** (789 mg, 1.38 mmol) and potassium hydroxide (2.81 g, 50.1 mmol) in DME/MeOH/H_2O (21 mL of a 3:3:1 v/v/v mixture) was stirred for 30 min at 80 °C. After cooling to ambient temperature, the pink mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (150 mL). The separated organic phase was washed with brine (50 mL) and concentrated. Purification by silica gel chromatography (1:1 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded **3.37** (538 mg, 90%) as a pink viscous foam. Data for **3.37**: R_f 0.35 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (br. s, 1H), 7.41 (d, 1H, *J* = 8.0 Hz), 7.26 (m, 3H), 7.15 (m, 2H), 7.09 (t, 1H, *J* = 2.7 Hz), 7.06 (d, 1H, *J* = 8.4 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 6.90 (d, 1H, *J* = 8.0 Hz), 6.54 (m, 1H), 4.76 (s, 2H), 3.89 (s, 3H), 3.69 (s, 3H), 2.57 – 2.30 (m, 4H), 2.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4, 147.2, 142.5, 138.3, 134.1, 132.7, 130.4, 129.6, 128.61, 128.13, 128.07, 124.6, 124.3, 123.6, 121.9, 115.9, 112.0, 103.1, 75.2, 61.0, 60.6, 56.1, 45.0, 30.7; HRMS (ESI) calculated for $C_{27}H_{31}N_2O_3$ $(M+H)^+$: 431.2335, found: 431.2314.



***Para*-quinone 3.38**. To a solution of free indole analog **3.37** (610 mg, 1.42 mmol) in EtOH (40 mL) was added NH_4HCO_2 (1.25 g, 19.8 mmol) followed by 10% Pd/C (270 mg). The reaction mixture was stirred at 45 ^oC for 10 min then cooled to RT, and filtered through a plug of Celite, which was washed with CH_2Cl_2. Concentration of filtrates and purification by silica gel chromatography (1:1 → 1:0 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded the free phenol (77.9 mg, 16%) as a pale-yellow oil.

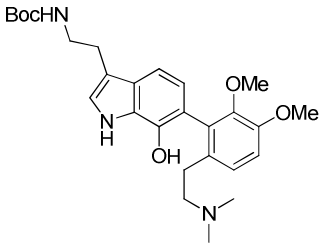
To a solution of ensuing phenol (77.9 mg, 229 μmol) in EtOAc (3 mL) was added Fremy's radical •$ON(SO_3K)_2$ (250 mg, 939 μmol) as a solution in neutral aqueous phosphate buffer (6 mL, prepared from 2.31 g H_2KPO_4, 0.52 g K_2HPO_4 and 100 mL H_2O) at RT and with rapid stirring. Upon mixing, the reaction mixture turned orange. After 30 min the reaction mixture was diluted with brine (30 mL), extracted with EtOAc (2 x 50 mL), and concentrated. Purification by silica gel chromatography (1:1 → 1:0 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]: CH_2Cl_2) afforded **3.38** (63.1 mg, 78%) as an orange oil.

Data for **3.38**: R_f 0.33 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96 (d, 1H, J = 2.7 Hz), 6.83 (d, 1H, J = 2.0 Hz), 6.63 (d, 1H, J = 2.7 Hz), 6.61 (d, 1H, J = 2.0 Hz), 6.55 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.77 (m, 2H), 2.65 (m, 2H), 2.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.5, 176.4, 152.5, 145.8, 145.4, 136.2, 136.0, 131.7, 128.1, 126.0, 125.8, 122.1, 114.4, 108.0, 61.2, 61.0, 56.0, 45.3, 33.8; HRMS (ESI) calculated for $C_{20}H_{23}N_2O_4$ $(M+H)^+$: 355.16.58, found: 355.1651.

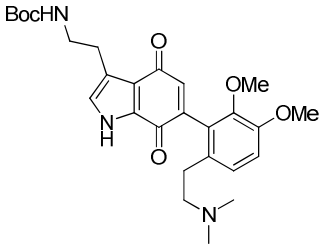


Phenol 3.39. To a solution of free biaryl isomer **3.31** (33.5 mg, 46.5 μmol) in EtOH (4 mL) was added NH_4HCO_2 (60.8 mg, 964 μmol) followed by 10% Pd/C (12.2 mg). The reaction mixture was stirred at 45 ^oC for 3 h, cooled to RT, filtered, concentrated, suspended in CH_2Cl_2 then filtered again, and concentrated. Purification by silica gel chromatography (1:1 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded the free phenol (27.1 mg, 100%) as a colorless oil. Data for **3.39**: R_f 0.43 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^1H NMR (Acetone-d_6, 400 MHz) δ 10.99 (s, 1H), 7.00 (d, 1H, J = 2.1 Hz), 6.86 (d, 1H, J = 7.6 Hz), 6.76 (d, 1H, J = 7.6 Hz), 6.72 (d, 1H, J = 2.1 Hz), 6.10 (br. s, 1H), 4.27 (dd, 1H, J_1 = 11.4 Hz, J_2 = 9.2 Hz), 3.86 (s, 3H), 3.81 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.4 Hz), 3.62 (s, 3H), 3.37 (m, 3H), 3.23 (q, 2H, J = 6.7

Hz), 3.10 (m, 2H), 2.92 (s, 6H), 2.03 (m, 1H, obscured by the residual acetone signal), 1.73 (m, 1H), 1.57 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 156.8, 156.1, 153.8, 147.0, 143.9, 138.1, 134.5, 132.7, 128.8, 128.5, 128.2, 124.4, 115.1, 113.3, 83.5, 78.6, 60.4, 59.2, 56.1 (two overlappling signals), 42.8, 39.0, 38.3, 36.0, 31.1, 28.7, 28.5; HRMS (ESI) calculated for $C_{32}H_{48}N_3O_7$ $(M+H)^+$: 586.3492, found: 586.3486.



Phenol 3.14. To a solution of biaryl **3.30** (61.2 mg, 90.8 μmol) in EtOH (4 mL) was added NH_4HCO_2 (42.0 mg, 0.666 mmol) followed by 10% Pd/C (27.1 mg). The reaction mixture was stirred at 45 °C for 30 min then cooled to RT, and filtered through a plug of Celite, which was washed with CH_2Cl_2. The filtrates were concentrated then redissolved in CH_2Cl_2, filtered again through a plug of Celite to remove excess NH_4HCO_2, and concentrated. The crude mixture thus obtained was dissolved in 5 mL of 1% aqueous formic acid and stirred for 12 hrs. Removal of solvent followed by purification by silica gel chromatography (1:1 → 1:0 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded **3.14** (28.6 mg, 65%) as a colorless oil. Data for **3.14**: R_f 0.34 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^{1}H NMR (Acetone-d_6, 400 MHz) δ 7.19 (d, 1H, J = 8.1 Hz), 7.13 (s, 1H), 7.05 (d, 1H, J = 8.6 Hz), 6.99 (d, 1H, J = 8.5 Hz), 6.68 (d, 1H, J = 8.0 Hz), 3.85 (s, 3H), 3.48 (s, 3H), 3.41 (t, 2H, J = 7.1 Hz), 2.94 (t, 2H, J = 7.5 Hz), 2.60 – 2.45 (m, 4H), 2.05 (s, 6H, hidden under residual acetone signal), 1.42 (s, 9H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 156.6, 152.3, 148.6, 141.2, 135.0, 134.3, 129.9, 129.3, 125.3, 122.8, 122.7, 118.1, 113.8, 112.9, 111.1, 78.4, 62.1, 60.3, 56.1, 45.6, 42.0, 31.4, 28.7, 26.9; HRMS (ESI) calculated for $C_{27}H_{38}N_3O_5$ $(M+H)^+$: 484.2811, found: 484.2805.



***Para*-quinone 3.11**. To a vigorously-stirred solution of phenol **3.14** (8.6 mg, 17.8 μmol) in EtOAc (1 mL) was added Fremy's radical •$ON(SO_3K)_2$ (18.0 mg, 67.1 μmol) as a purple solution in neutral aqueous phosphate buffer (2 mL, prepared from 2.31 g H_2KPO_4, 0.52 g K_2HPO_4 and 100 mL H_2O) at RT. Upon addition, the reaction mixture turned orange. After 30 min the reaction mixture was diluted with brine (30 mL), extracted with EtOAc (2 x 50 mL), and concentrated. Purification by silica gel chromatography (1:1 → 1:0 [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH]:CH_2Cl_2) afforded **3.11** (7.6 mg, 86%) as an orange oil. Data for **3.11**: R_f 0.25 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.98 (d, 1H, J = 8.5 Hz), 6.91 (d, 1H, J = 8.5 Hz), 6.81 (s, 1H), 6.40 (s, 1H), 4.93 (t, 1H, J = 5.7 Hz),

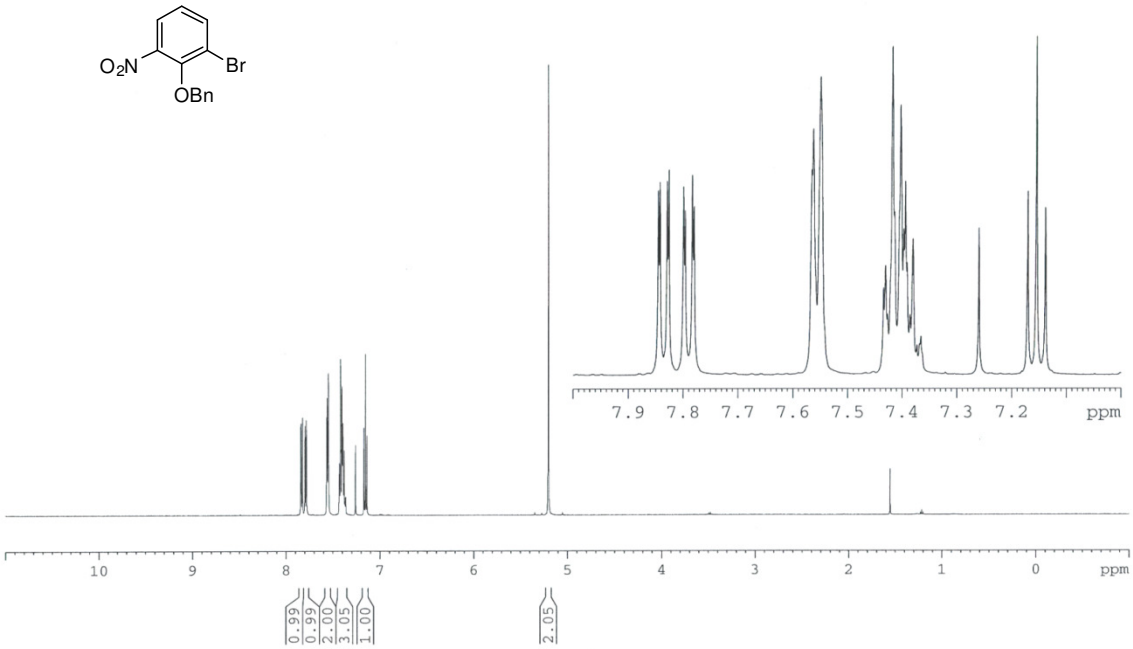
3.85 (s, 3H), 3.68 (s, 3H), 3.41 (m, 2H), 2.97 (m, 1H), 2.93 (m, 1H), 2.74 (m, 1H), 2.63 (m, 1H), 2.53 (m, 2H), 2.29 (s, 6H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 184.1, 176.4, 156.3, 151.0, 146.9, 144.5, 137.1, 131.7, 130.4, 128.4, 124.9, 124.6, 123.8, 123.2, 113.3, 79.3, 61.0, 60.7, 56.0, 44.8, 40.8, 30.5, 28.7, 26.3; HRMS (ESI) calculated for $C_{27}H_{36}N_3O_6$ $(M+H)^+$: 498.2604, found: 498.2598.

Table 3.1. Comparison of the NMR chemical shifts for *para*-quinone **3.11** from the current and previous syntheses.[2]

^{1}H NMR literature (500 MHz)	^{1}H NMR current (600 MHz)	^{13}C NMR literature	^{13}C NMR current
9.95 (br. s, 1H)	-	184.0	184.1
6.98 (d, 1H, *J* = 9 Hz)	6.98 (d, 1H, *J* = 8.5 Hz)	176.1	176.4
6.92 (d, 1H, *J* = 9 Hz)	6.91 (d, 1H, *J* = 8.5 Hz)	156.1	156.3
6.89 (s, 1H)	6.81 (s, 1H)	150.7	151.0
6.41 (br. s, 1H)	6.40 (s, 1H)	146.6	146.9
4.90 (br. s, 1H)	4.93 (t, 1H, *J* = 5.7 Hz)	144.4	144.5
3.86 (s, 3H)	3.85 (s, 3H)	136.8	137.1
3.70 (s, 3H)	3.68 (s, 3H)	131.5	131.7
3.42 (m, 2H)	3.41 (m, 2H)	130.8	130.4
2.95 (m, 2H)	2.97 (m, 1H), 2.93 (m, 1H)	128.1	128.4
2.70 (m, 1H)	2.74 (m, 1H)	124.6	124.9
2.56 (m, 1H)	2.63 (m, 1H)	124.0	124.6
2.44 (t, 2H, *J* = 8 Hz)	2.53 (m, 2H)	123.6	123.8
2.20 (s, 6H)	2.29 (s, 6H)	123.0	123.2
1.43 (s, 9H)	1.42 (s, 9H)	113.1	113.3
		79.1	79.3
		60.9	61.0
		60.8	60.7
		55.8	56.0
		45.0	44.8
		40.6	40.8
		30.8	30.5
		28.4	28.7
		26.1	26.3

3.4.2 Selected NMR Spectra

3.17



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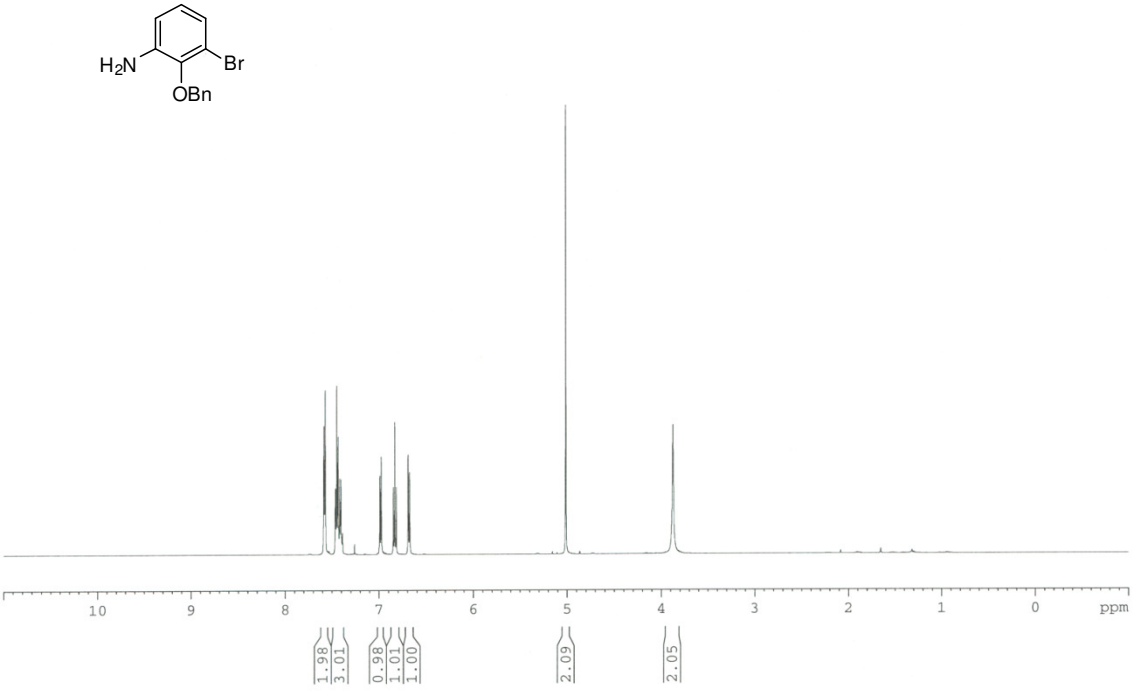

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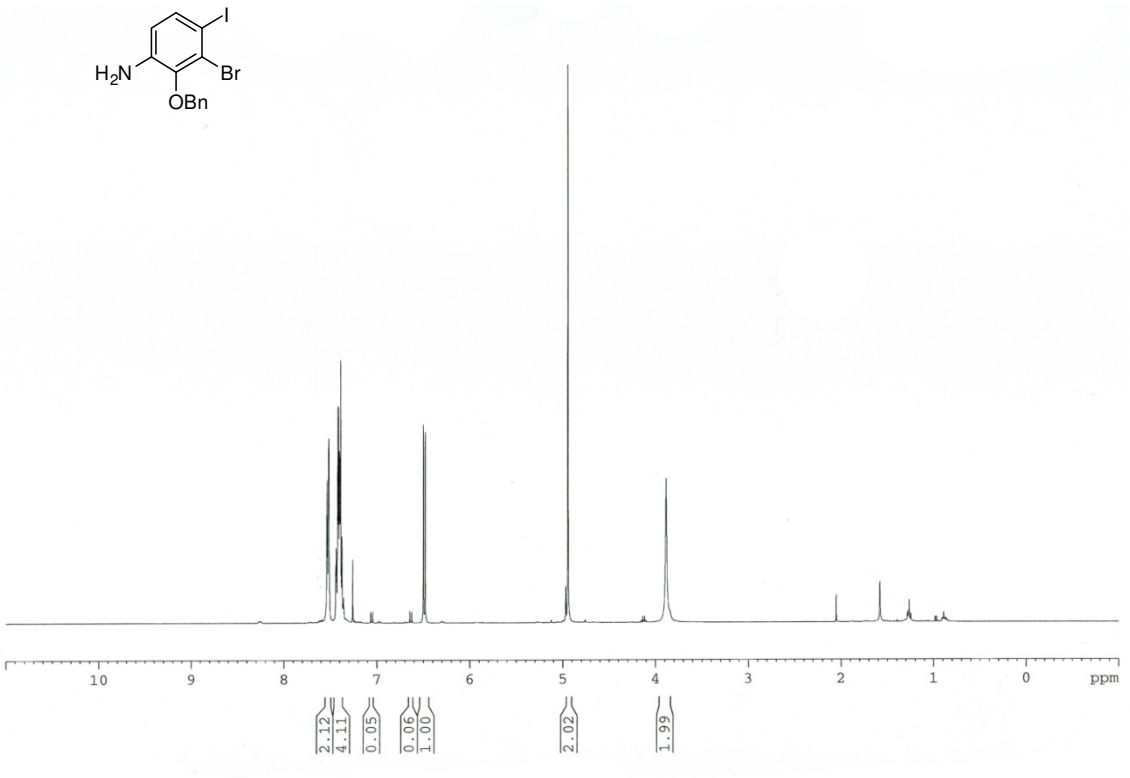
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Br
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9
8
7
6
5
4
3
2
1
0
ppm
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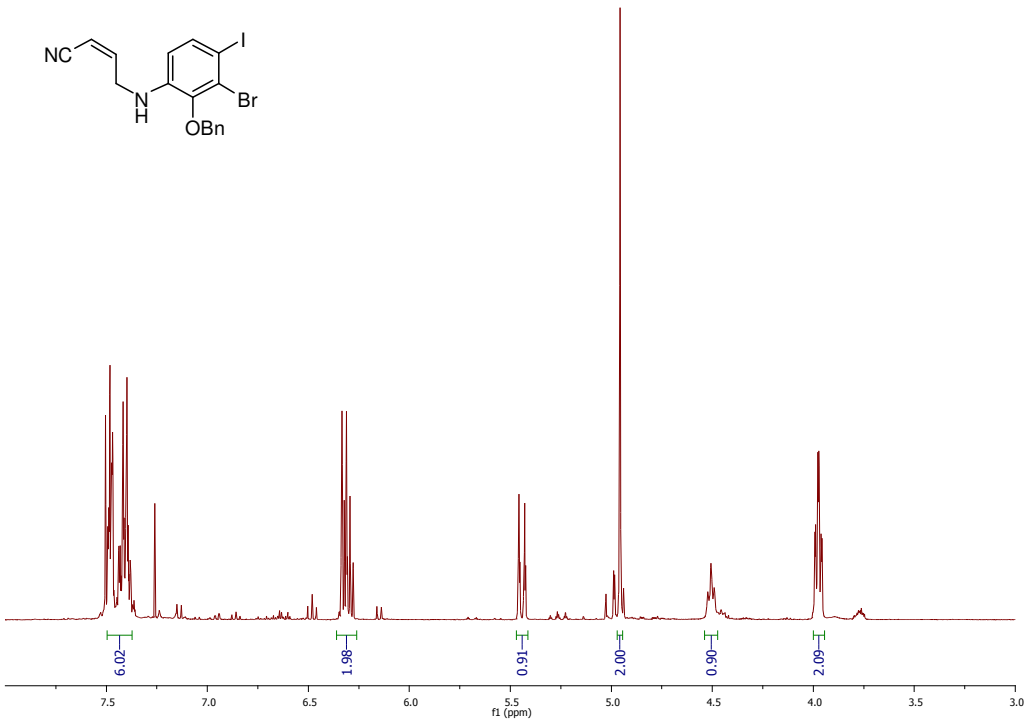
0.05
0.06
1.00
2.02
1.99

3.21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H
Br
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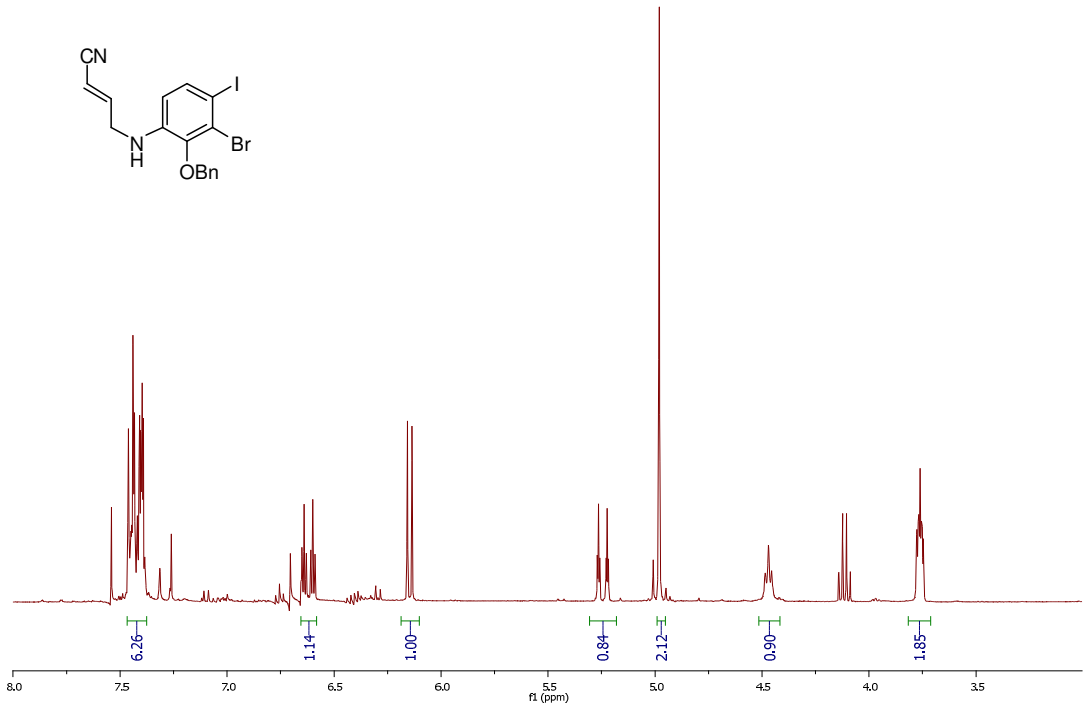
4.5
4.0
3.5
3.0
f1 (ppm)

3.22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H
Br
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6.0
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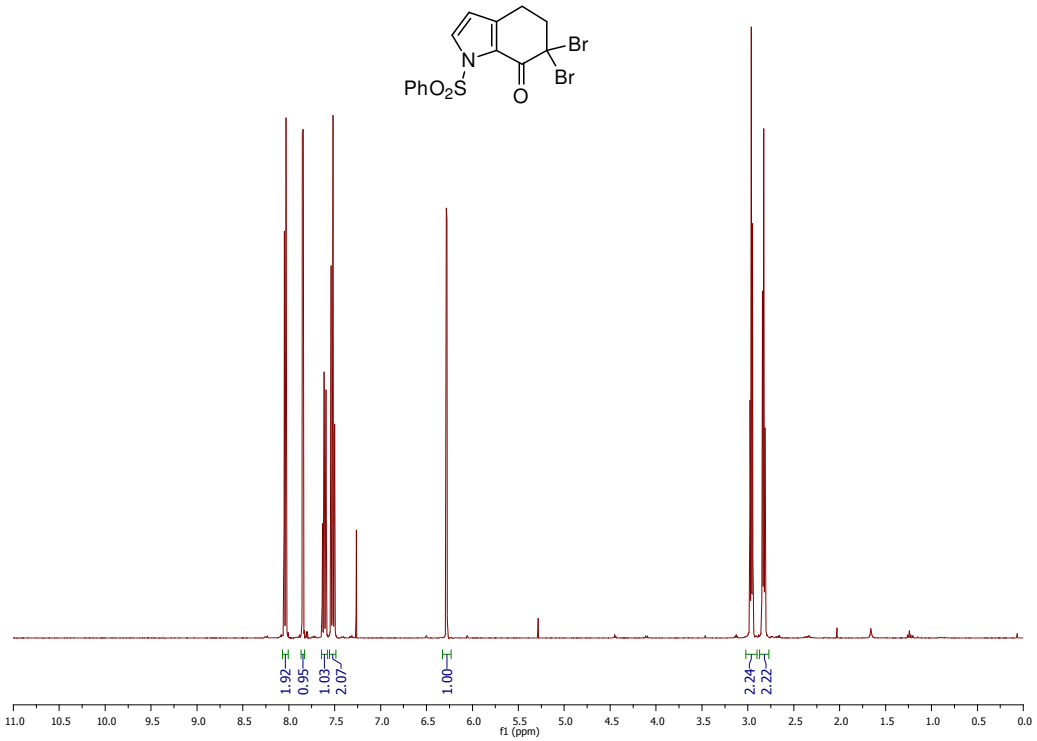
4.5
4.0
3.5
f1 (ppm)

3.24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7.5
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5.5
5.0
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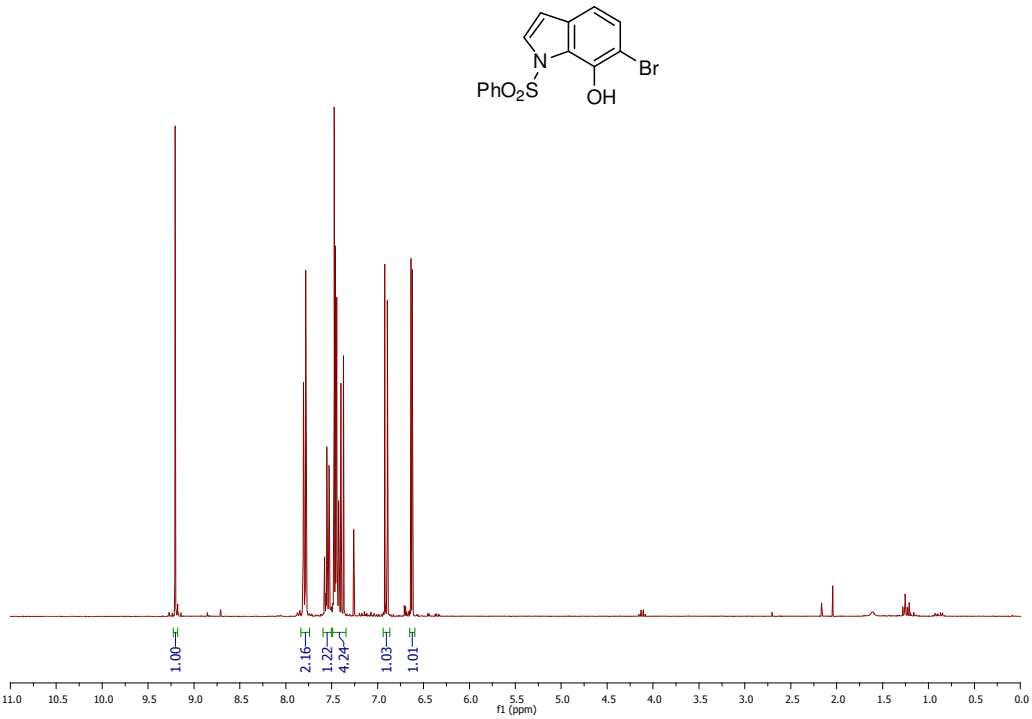
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1.01
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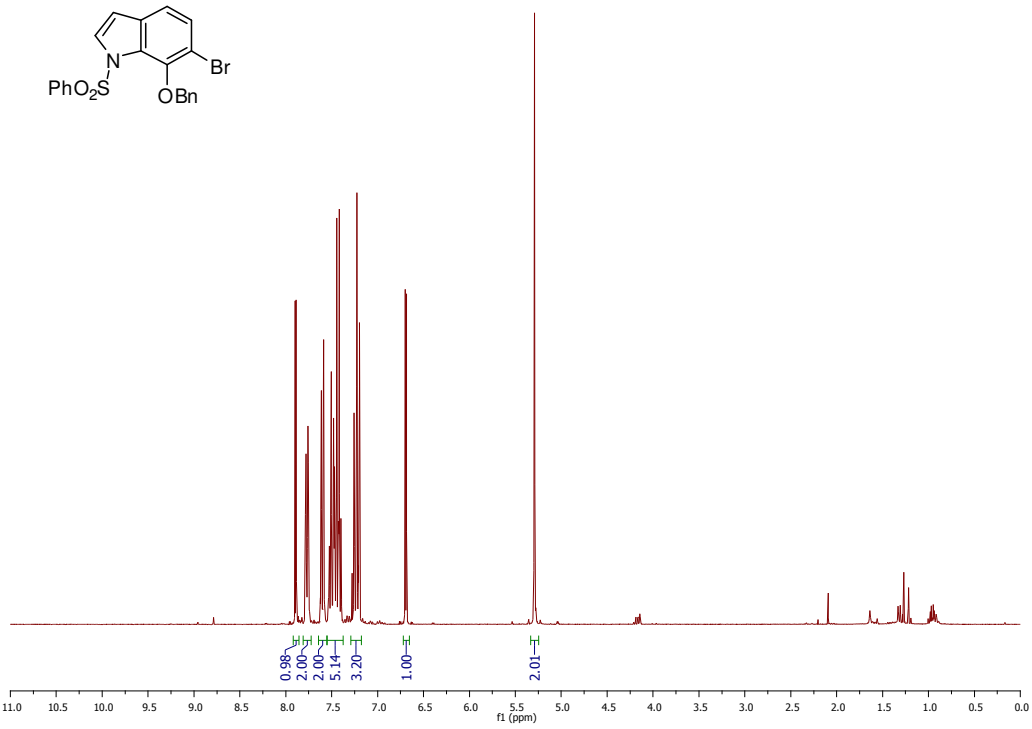
f1 (ppm)

3.26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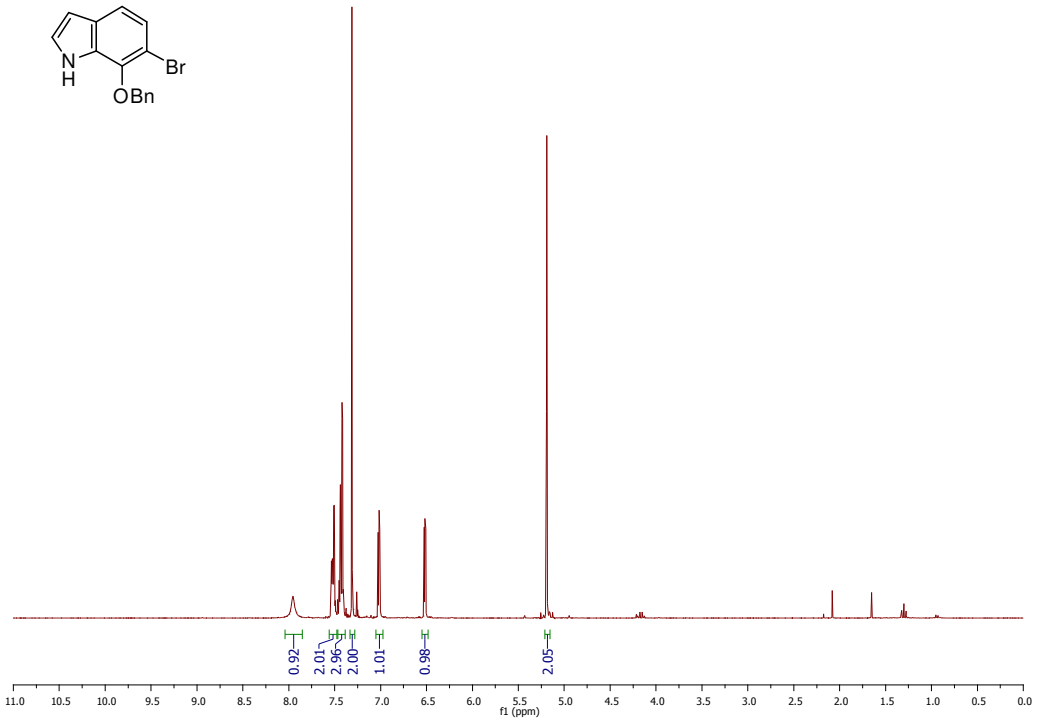
f1 (ppm)

3.27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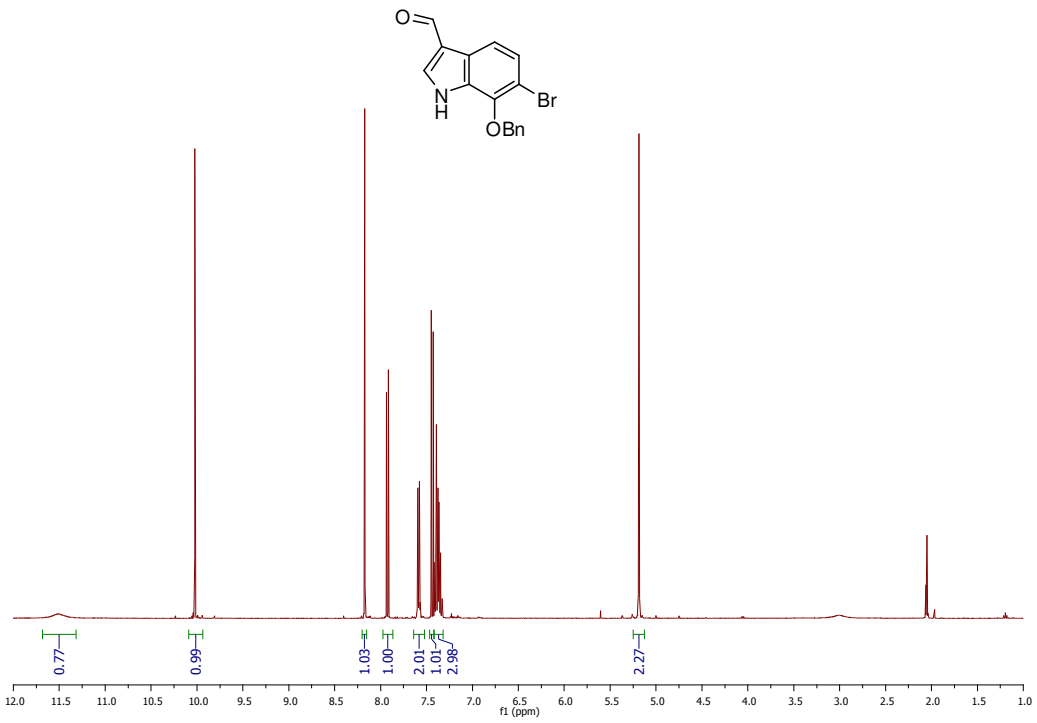
f1 (ppm)

3.28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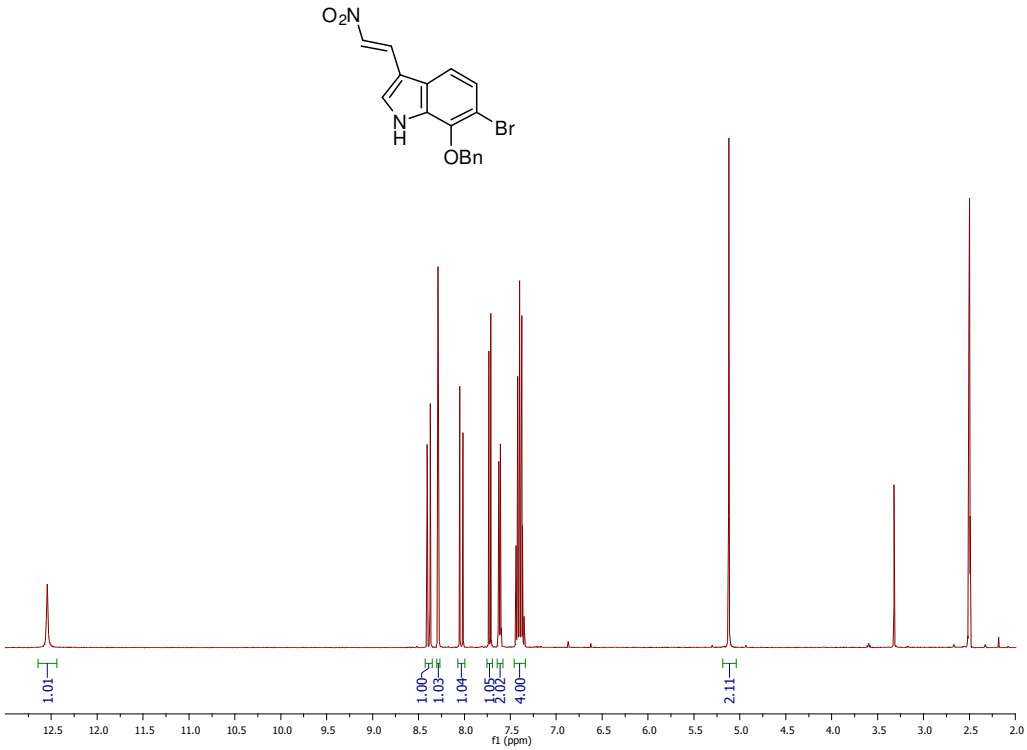
3.29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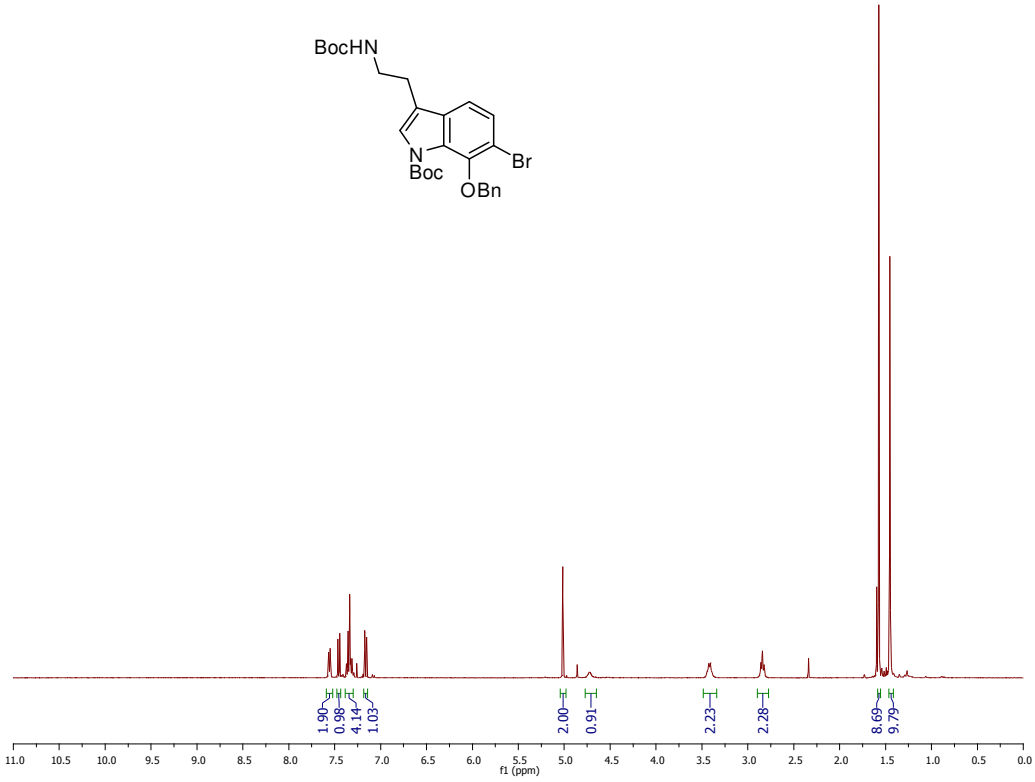
3.15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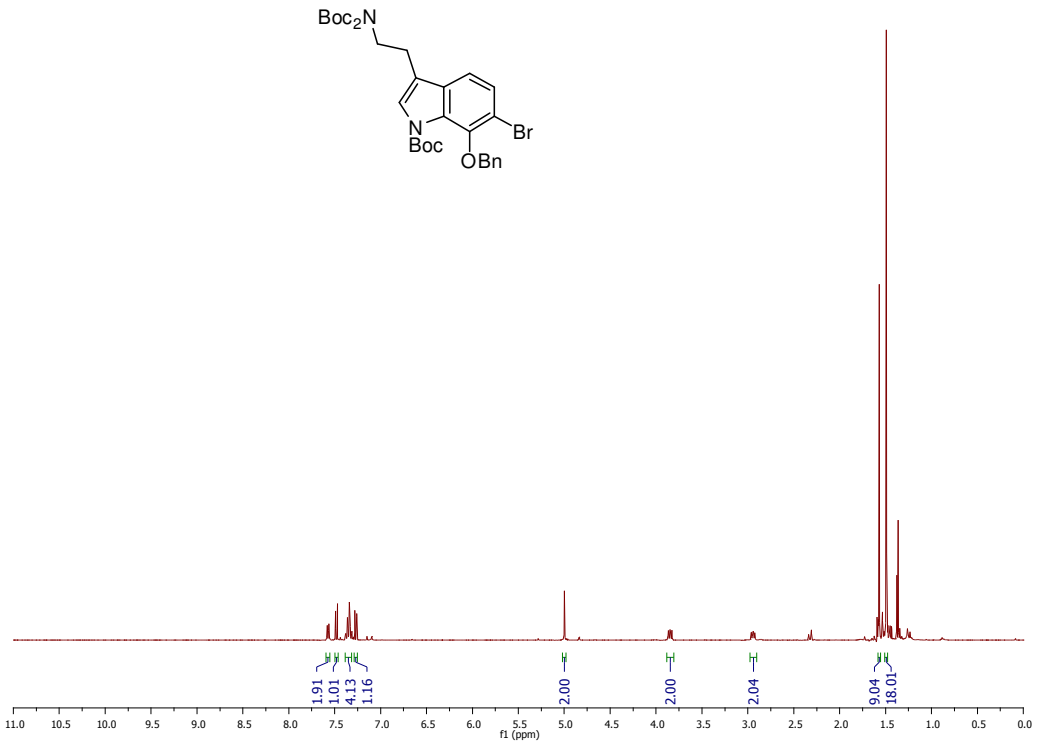
3.32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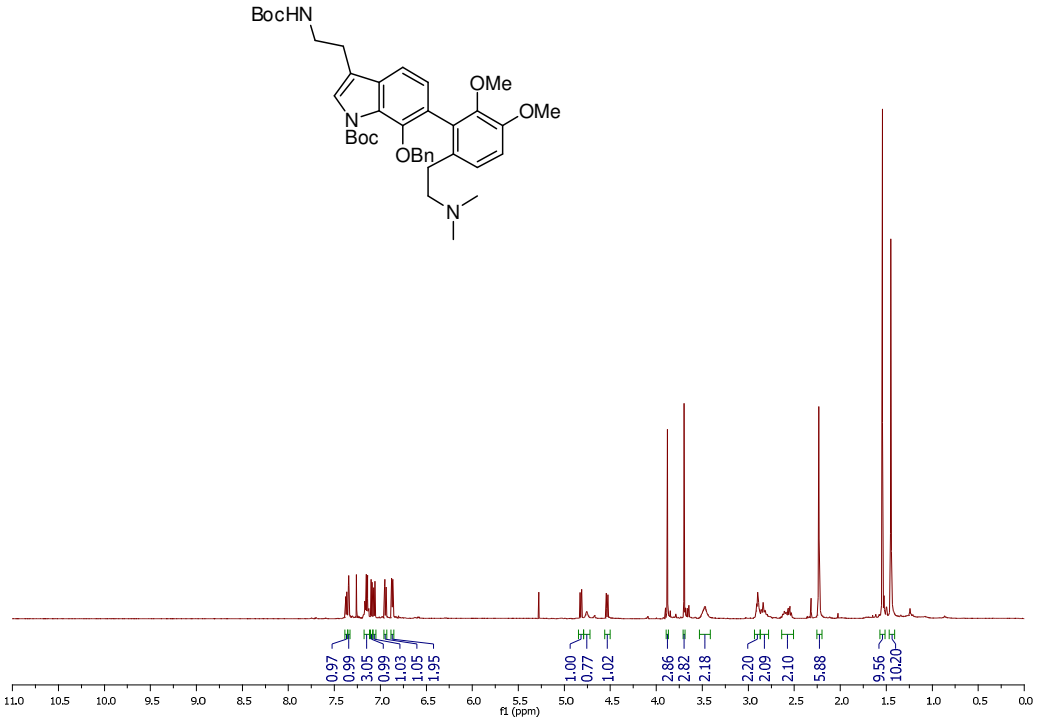
f1 (ppm)

3.30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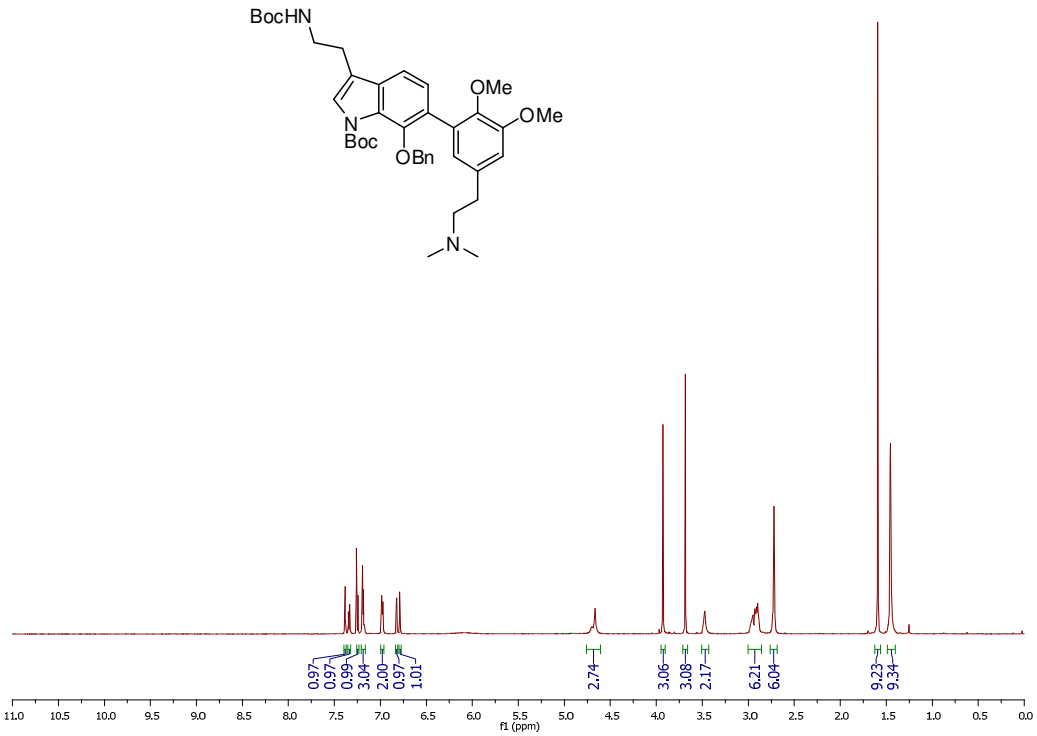
f1 (ppm)

3.31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9.23
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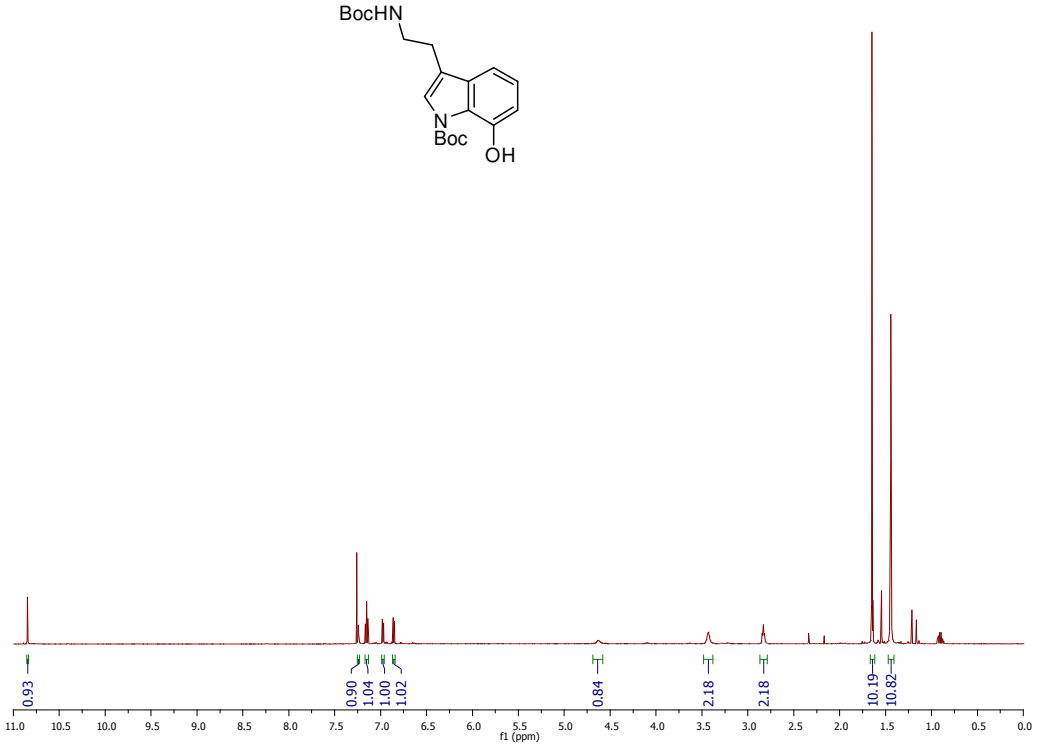
f1 (ppm)

3.34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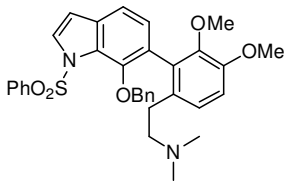
f1 (ppm)

3.36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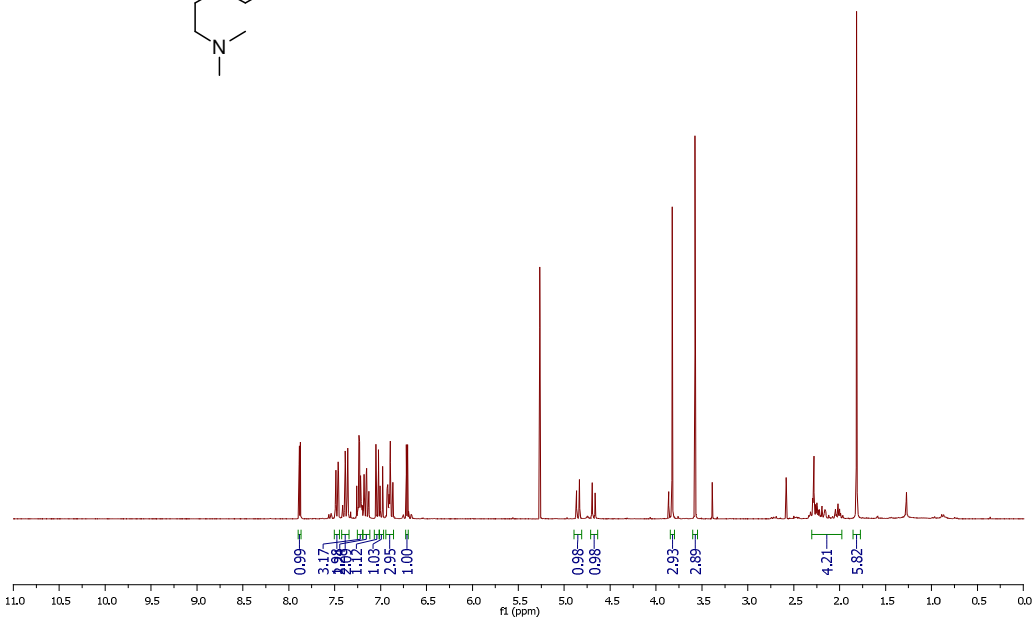
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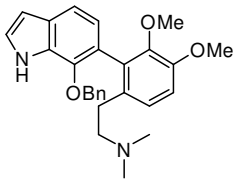
f1 (ppm)

3.37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OMe
N
H
OBn
N

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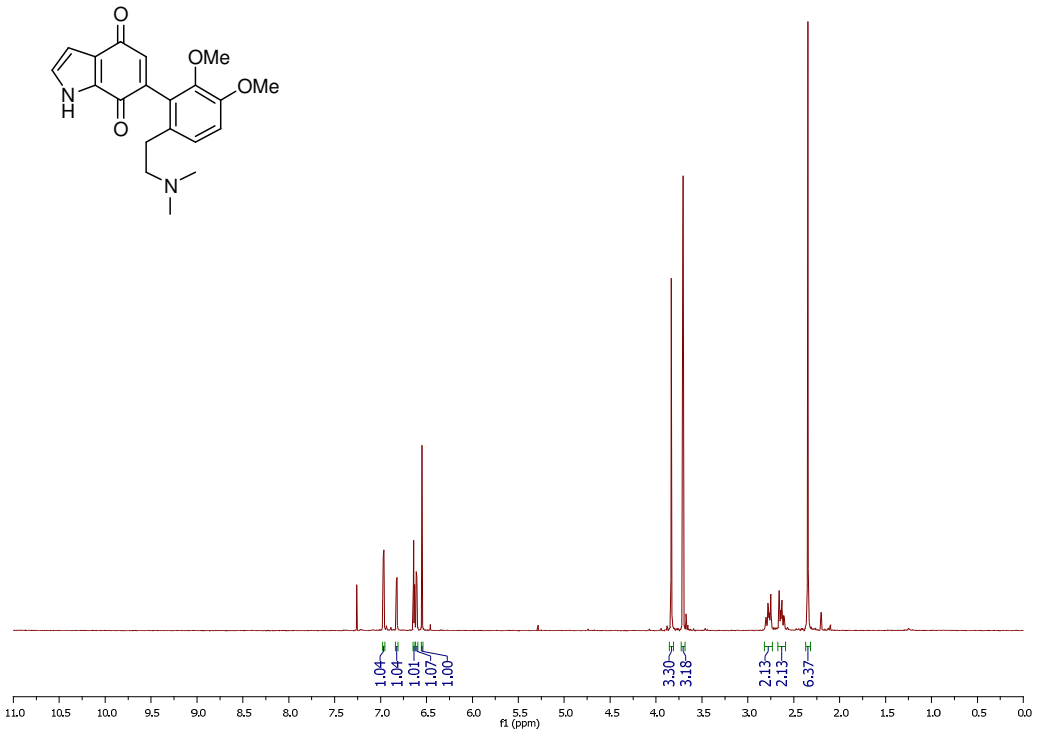
3.38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H
O
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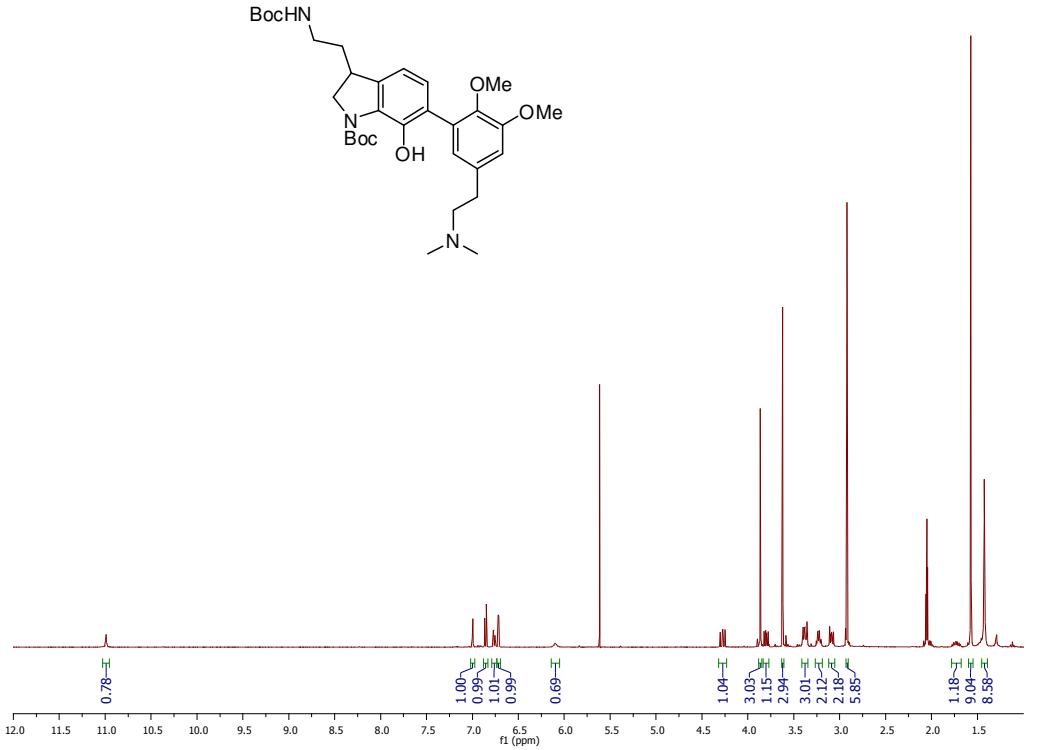
2.13
6.37
f1 (ppm)

3.39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Boc
OH
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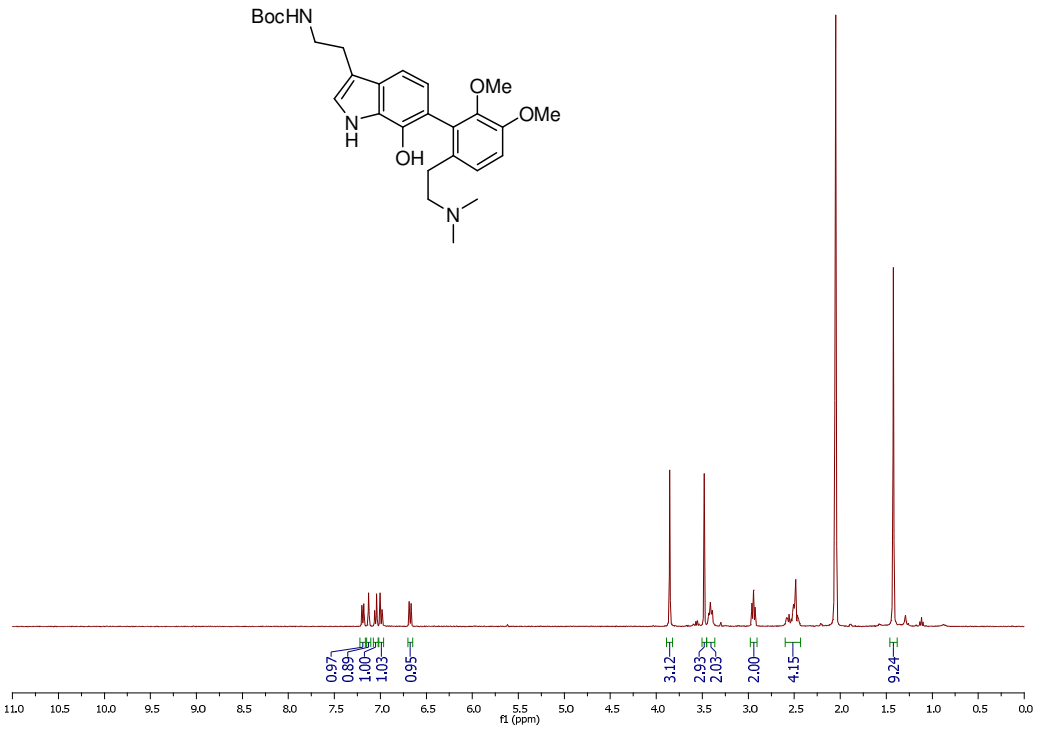
f1 (ppm)

3.14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OH
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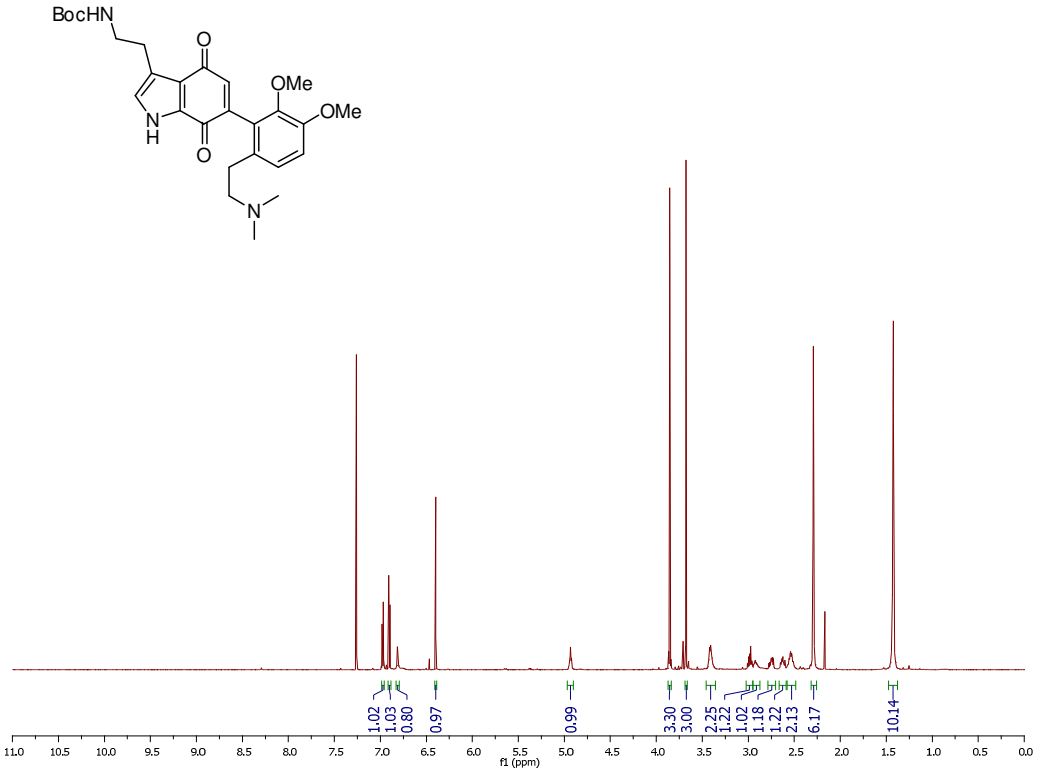
3.11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3.30
3.00
2.25
1.22
1.02
1.18
1.22
2.13
6.17
10.14
f1 (ppm)

3.5 References

1. Brastianos, H. C.; Vottero, E.; Partick, B. O.; Van Soest, R.; Matainaho, T.; Mauk, A. G.; Andersen, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 16046–16047.
2. Volgraf, M.; Lumb, J.-P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Münzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Bio.* **2008**, *4*, 535–537.
3. Opitz, C. A.; Wick, W.; Steinman, L.; Platten, M. *Cell. Mol. Life Sci.* **2007**, *64*, 2542–2563.
4. (a) Liu, X.; Newton, R. C.; Friedman, S. M.; Scherle, P. A. *Curr. Cancer Drug Tar.* **2010**, *9*, 938–952. (b) Loeb, S.; Koenigsrainer, A.; Rammensee, H.-G.; Opelz, G.; Terness, P. *Nat. Rev. Cancer* **2009**, *9*, 445–452.
5. Pereira, A.; Vottero, E.; Roberge, M.; Mauk, A. G.; Andersen, R. J. *J. Nat. Prod.* **2006**, *69*, 1496–1499.
6. Carr, G.; Tay, W.; Bottriell, H.; Andersen, S. K.; Mauk, A. G.; Andersen, R. J. *Org. Lett.* **2009**, *11*, 2996–2999.
7. Gribble, G. W. *J. Chem. Soc. Perkin Trans. 1* **2000**, *7*, 1045–1075.
8. Adams, R. E.; Press, J. B.; Degan, E. G. *Syn. Comm.* **1991**, *12*, 675–681.
9. Aubart, K. M.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 16–22.
10. Best route to the tetrahydraindole follows the first 4 steps from (a) Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379–3380; and steps 5 and 6 adapted from (b) Tani, M.; Ariyasu, T.; Ohtsuka, M.; Koga, T.; Ogawa, Y.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1996**, *44*, 55–61. The compound was previously described in (c) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214–3219.

11. For removal of phenyl sulphonyl group see: Jackson, P. M.; Moody, C. J. *Tetrahedron* **1992**, *48*, 7447–7466.

12. For alternatives to the standard LAH reduction of the nitrovinyl indole see: (a) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283–1289; (b) Schumaker, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935–942.

13. Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765–2768.

14. Ouchi, H.; Kawata, Y.; Ono, M.; Morita, Y.; Yamamoto, Y.; Takahata, H. *Heterocycles* **2004**, *62*, 491–502.

15. For use of Br_2/*t*-$BuNH_2$ see (a) Pearson, D. E.; Wyson, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358–2360. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806–810. For use of pyridine hydrobromide perbromide see (c) Yamada, F.; Tamura, M.; Hasegawa, A.; Somei, M. *Chem. Pharm. Bull.* **2002**, *50*, 92–99. For use of 2,4,4,6-tetrabromocyclohexa-2,5-dieneone see (d) Calo, V.; Lopez, L.; Pesce, G.; Ciminale, F.; Todesco, P. E. *J. Chem. Soc. Perkin Trans. 2* **1974**, *10*, 1189–1191.

16. For aziridine opening see: (a) Reinhart, K. L. Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387. For DMANE see 5(a) and references therein. For use of gramines as intermediates see: (b) Leclerc, V.; Yous, S.; Delagrange, P.; Boutin, J. A.; Renard, P.; Lesieur, D. *J. Med. Chem.* **2002**, *45*, 1853–1859.

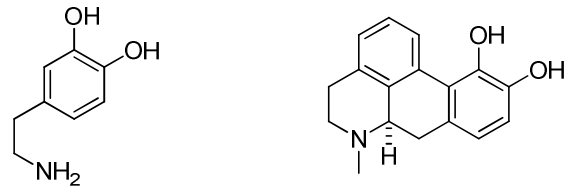
17. Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229–246.

18. Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534–2542 and references therein.

Chapter 4. Synthesis of Photoswitchable Dopamine Analogs

4.1 Introduction

Dopamine is a catecholamine neurotransmitter, first identified by Arvid Carlsson in 1959 (**4.1** in Figure 4.1).[1] It occurs in vertebrates and invertebrates and is produced in several areas of the brain, such as the *substantia nigra* and the ventral tegmental area. Despite its scarce abundance (only 1/100,000 of all neurons are dopaminergic neurons), dopamine plays an important role in regulating basic brain functions such as behavior, cognition, voluntary movement, motivation, reward sleep, mood, attention, and learning.[2] It interacts with five types of dopamine receptors: D_1, D_2, D_3, D_4, and D_5, and their variants. All dopamine receptors can be assigned to two major classes: the D_1–like class of dopamine receptors which includes D_1 and D_5 and the D_2–like class, encompassing $D_{2/3/4}$ receptors. All receptors belonging to both the D_1– and D_2–like classes are trimeric G-protein coupled receptors (GPCRs). However, whilst stimulation of D_1–like receptors activates adenylyl cyclase and leads to upregulation of the secondary messenger cyclic adenosine monophosphate (cAMP), in contrast, activation of D_2-like receptors inhibits adenylyl cyclase function and brings about a reduction in cAMP concentration.[3]



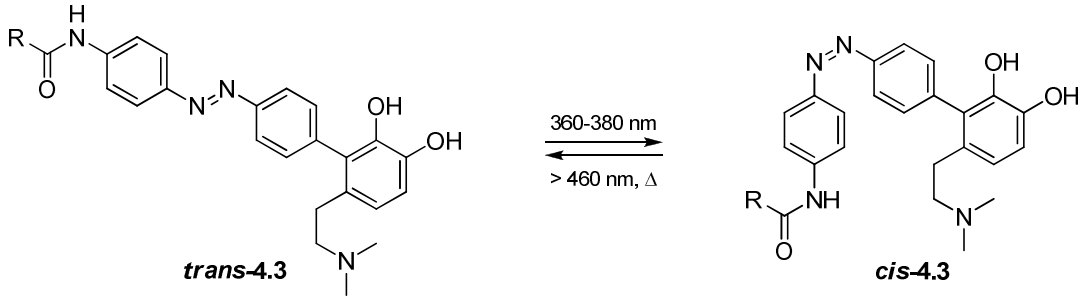
dopamine (**4.1**) apomorphine (**4.2**)

Figure 4.1. Dopamine and apomorphine.

Dopamine receptor agonists are compounds which can activate these receptors in the absence of dopamine. In terms of their selectivity, dopamine agonists can be classified as $D_{1/5}$ or $D_{2/3/4}$ dopamine receptor agonists, with only $D_{2/3/4}$ dopamine receptor agonists having therapeutic relevance. Indeed, some of them have already found application in the treatment of Parkinson's disease, restless leg syndrome, or special tumors. For example, apomorphine (**4.2** in Figure 4.1) – a partial agonist at the $D_{2/3/4}$ receptors with K_i values in the low nM range – is used as effective therapy for the Parkinson's disease and erectile dysfunction.[4]

In light of the already well–precedented applications of analogs of dopamine, the prospects of developing a new class of dopamine agonists have been a long standing interest to us. Recently, the Trauner group has developed a range of molecules capable of modulating the function of sodium and potassium ion channels by means of light,[5] and we were now keen on extending this concept to analog of dopamine **4.3** (Scheme 4.1), the ability of which to activate dopamine receptors would be controlled by simple illumination with light.

Scheme 4.1. Dopamine analog in *trans* and *cis* states (where R could be any substituent).



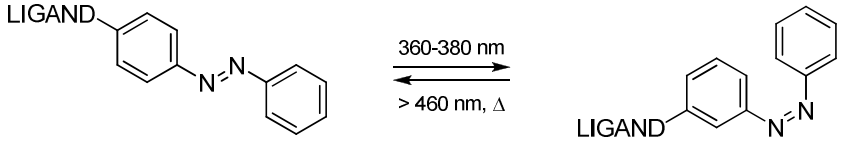
***trans*-4.3** **cis-4.3**

However, before the results which have come out of these project aims can be discussed, a brief description of photoswitchable receptor agonists and antagonists is warranted in order to put our work into context. This follows in the next section and focuses specifically on azobenzene-containing photoswitches.

4.2 Background

The line of research undertaken by our group involves the design, synthesis, and evaluation of photoswitchable ligands tailored to target a specific type of enzyme, ion channel, or receptor. There are multiple reasons for the choice of azobenzenes as photoswitches (Scheme 4.2). Azobenzenes are used because of their large change in length and geometry upon *cis–trans* isomerization ($\Delta L \approx 7$ Å). Due to this change the azobenzene photoswitches bind to their targets in only one state and produce no response in the other state. In most examples the *trans* state functions as the "on" state and *cis* as "off" due to either the increased steric bulk in the *cis* state or to inability to reach the binding site by the photoswitchable ligand in the *cis* state. However, reversed examples are known as well.

Scheme 4.2. Azobenzene as a photoswitch.



***trans*-4.4** ***cis*-4.4**

In order to achieve rapid and complete on/off control of protein function, any photoswitchable ligand should meet several general criteria. Firstly, photoswitching must occur on the time scale of protein and cellular function, generally somewhere between micro- and milliseconds using light intensities that are not harmful to cells. Secondly, it is important to achieve high photoconversion between isomers, which relies on the ability to selectively excite one form or the other using different wavelength of light. While azobenzenes satisfy both of the above criteria, they can also thermally relax or be rapidly converted to the "off" state with light.

The photoswitchable ligands which have to date been developed can be subdivided into two categories: photochromic ligands (PCLs) and photoswitchable tethered ligands (PTLs). The major difference between the two is the need for the PTLs to be covalently attached to the protein of interest, which often requires genetic modification of the native protein to engineer a site of attachment, such as a nucleophilic cysteine, while PCLs are not covalently linked and are thus able to operate on native proteins. For example, Figure 4.2 illustrates how both the PCL and PTL approaches can be used to reversibly block potassium channels.[5d] In the case of PTL, the covalently attached ligand blocks the potassium channel only when the azobenzene is in the *trans* state since, when the *cis* geometry is adopted, the ligand physically cannot reach the pore of the channel. Similarly, a photochromic ligand (PCL), which is not covalently attached to the receptor, has also been designed and successfully shown that binding to the receptor is possible only when the *trans* configuration of the azobenzene is adopted and that no blocking is achieved when in the *cis* form. Indeed, PTL and PCL approaches have now also been successfully extended to sodium channels, ionotropic and metabotropic glutamate receptors, carbonic anhydrase, and AMPA receptor.[5]

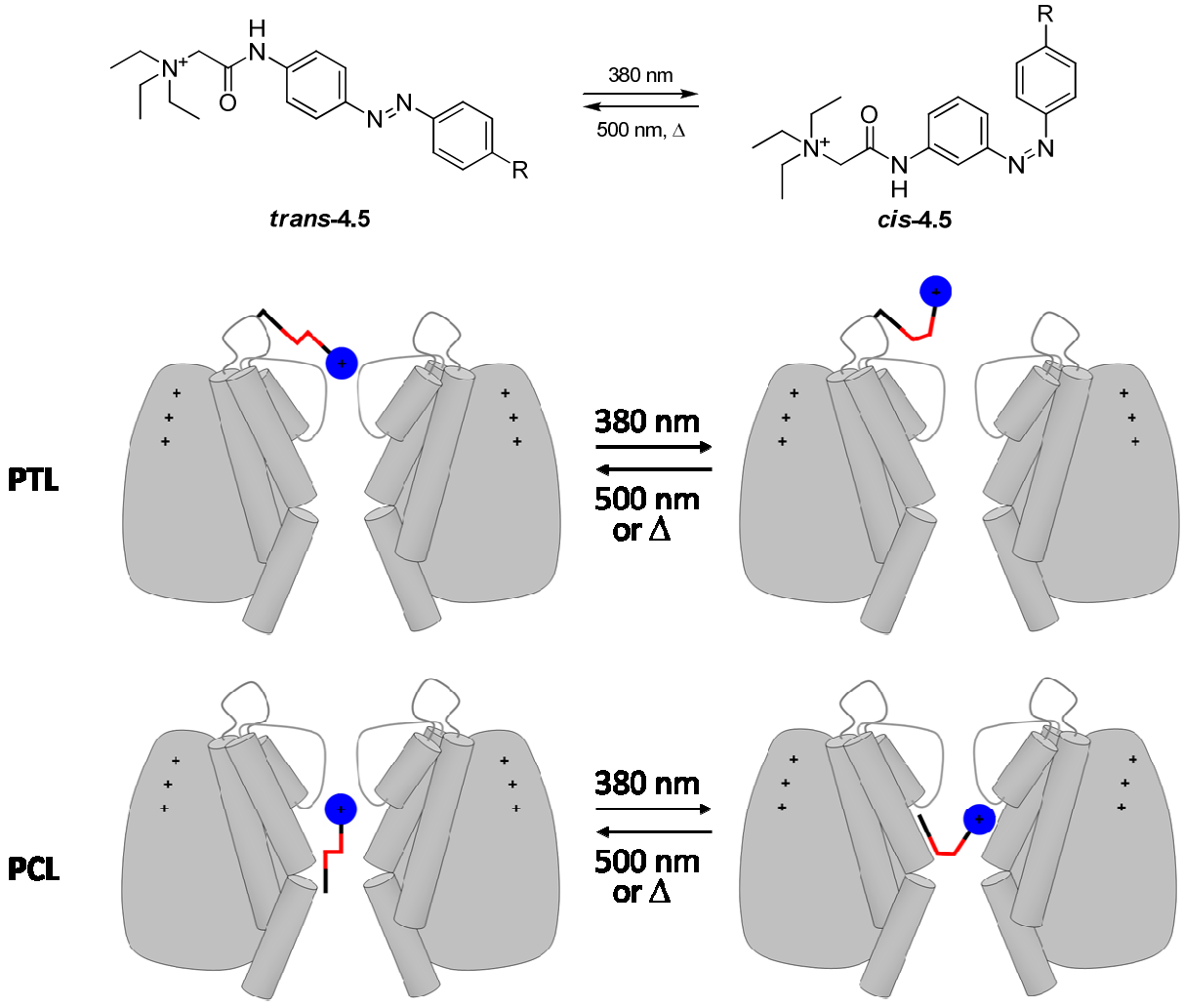


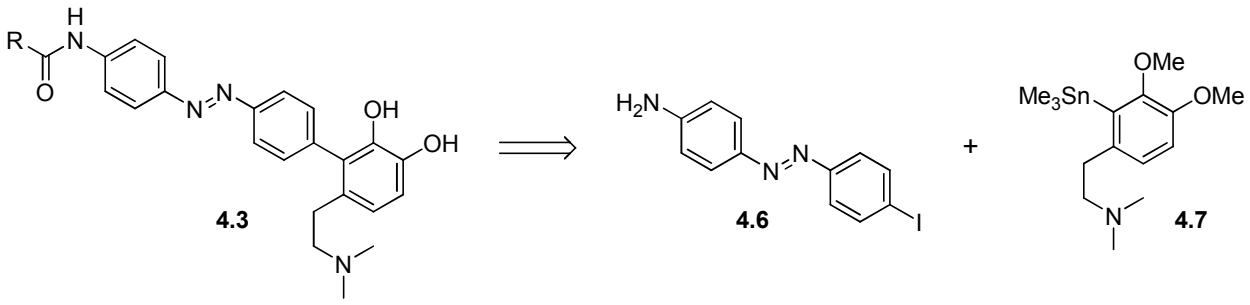
Figure 4.2. PTL and PCL approaches applied to potassium channels (R = H or var. amides).[5d]

Following such great success with the development of a range of photoswitchable ligands capable of modulating a number of biological targets our attention was turned to dopamine receptors and specifically, the synthesis and evaluation of a photoswitchable dopamine analog (*vide supra*, Scheme 4.1, page 115). The results which have been generated towards this goal are described next.

4.3 Results and Discussion

The ability of naturally occurring dopamine receptors to command biological function would be even greater if one could equip them with additional artificial photosensitive control mechanisms. Based on the structure of apomorphine (**4.2**, *vide supra*, Figure 4.1, page 116) we have realized the potential to adapt our azobenzene photoswitch strategy to the dopamine receptor. In particular, we decided to replace the phenyl group of apomorphine (**4.2**) with an azobenzene moiety and in this way generate dopamine analog **4.3** (Scheme 4.3, were R could be any substituent). Photoisomerization of **4.3** between *cis* and *trans* states should result in a change in affinity for the dopamine receptor. Specifically, it was thus postulated that introduction of a sterically demanding group at the azobenzene terminus would drastically diminish the ability of the *cis* form of **4.3** to insert into the binding pocket of the dopamine receptor and, ultimately, attenuate its activity. We envisaged that photoswitch **4.3** could be disconnected in a convergent manner along the biaryl bond using a Stille cross-coupling to previously described iodoazobenzene **4.6** and stannane **4.7**.[6,7]

Scheme 4.3. Design and retrosynthesis of photoswitchable dopamine analogs.

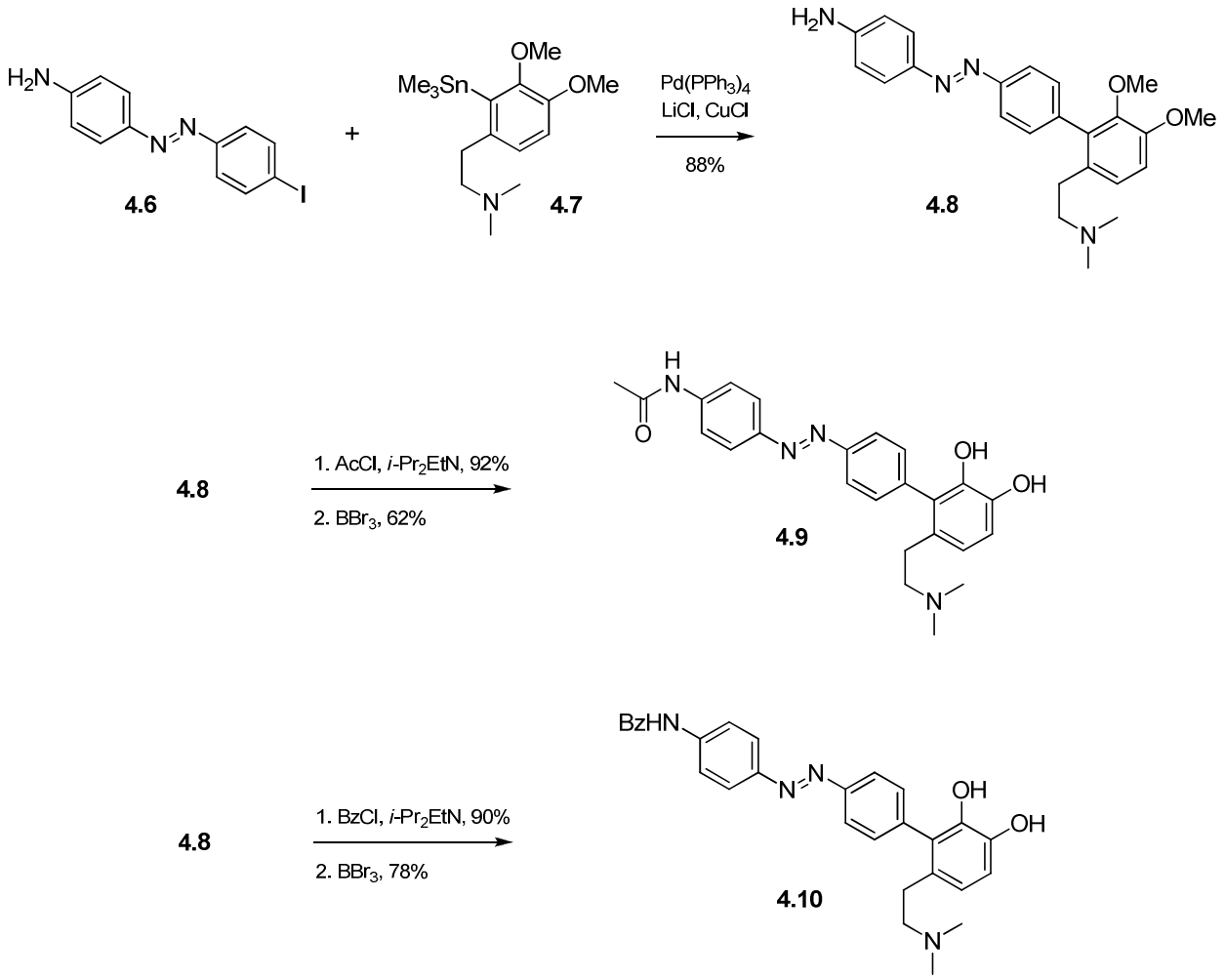


4.3.1 Synthesis

Based on the restrosynthetic strategy shown in Scheme 4.2 we have prepared two new photoswitchable ligands – acyl catecholamine **4.9** and benzoyl catecholamine **4.10** (Scheme 4.4). The best yields have been achieved when iodobenzene **4.6** was coupled to the stannane **4.7** using the Stille cross-coupling prior to the formation of the amide bond. While the Stille cross-coupling with such a sterically demanding coupling partner as stannane **4.7** proved to be challenging, it was precedented in our previous work with alkaloids exiguamines A and B (see Chapter 3) and was overcome employing similar coupling conditions.[7] The resulting aniline **4.8** was then converted to intermediate acetamide and the catechol moiety was deprotected using BBr_3 to afford acyl catecholamine **4.9**. Alternatively, aniline **4.8** could be converted to an amide with benzoyl chloride and, following BBr_3 deprotection, afford the desired benzoyl

catecholamine photoswitch **4.10**. The ability of catecholamines **4.9** and **4.10** to photoswitch between the *cis* and *trans* states has been verified using UV-Visible Spectroscopy experiments.

Scheme 4.4. Synthesis of photoswitchable dopamine analogs.



4.3.2 D_2 dopamine Receptor Binding and Efficacy

Binding affinity of the prepared compounds for the D_2 dopamine receptor has been investigated by our collaborators – Dr. Georg Höfner in the group of Prof. Wanner (pharmaceutical chemistry, LMU). In the Malmberg assay used,[8] a potential dopamine receptor agonist competes with a radioactively labeled ligand, such as [^{3}H]-spiperone, also an agonist, and the level by which the radioactivity is attenuated provides an indication of binding affinity. In this context, both **4.9** and **4.10** were incubated with the homogenates of HEK 293 cells that stably express the D_2 dopamine receptor. Three independent competition experiments (each carried out in triplicate with six concentrations of the test compound) were used to calculate IC_{50} values, which were transformed to pK_i values according to the Cheng-Prusoff equation[9] (based on a K_d value for [^{3}H]-spiperone of 41.0 pM, pre-determined in saturation experiments). Haloperidol and apomorphine (**4.2**), having known pK_i values towards the D_2 dopamine receptor,

were used as control compounds. The results are shown in Table 4.1 and clearly show that both **4.9** and **4.10** indeed possess affinity for the D_2 dopamine receptor, and that this affinity is comparable to that of the antagonist apomorphine and higher than that of the antagonist haloperidol.

Table 4.1. pK_i values determined for **4.9** and **4.10** through the Malmberg displacement assay.

Compound	pK_i 1	pK_i 2	pK_i 3	mean pK_i	SEM
haloperidol	9.059	8.978	9.206	9.081	0.067
apomorphine	6.963	6.765	6.977	6.902	0.068
4.9	6.788	6.501	6.588	6.626	0.085
4.10	6.486	6.252	6.563	6.434	0.093

Following promising results that both **4.9** and **4.10** have high affinity for the D_2 dopamine receptor, the stage was set to investigate their utility as photoswitchable ligands and evaluate their potential to modulate the activity of dopamine receptors by means of light. These investigations are currently in progress at Prof. Javitch group (Columbia University) and will be reported in due course. However, preliminary assays using a Ca^{2+}-sensitive luminescent protein aequorin as a reporter show that compounds **4.9** and **4.10** are D_2 dopamine receptor agonists in the dark-adapted state (*trans*) in the low μM range.

4.3.3 Conclusions and Future Work

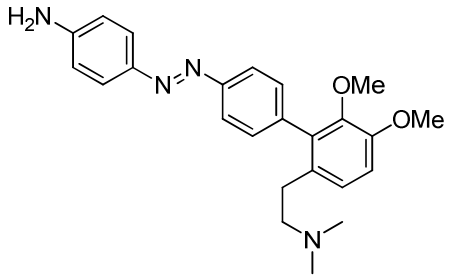
Two new compounds **4.9** and **4.10**, containing a catecholamine and an azobenze moiety, were synthesized based on structural similarity to the known D_2 dopamine receptor apomorphine (**4.2**, *vide supra*, Figure 4.1, page 115). Their ability to photoswitch between the *cis* and *trans* states has been verified using UV-Vis experiments. Additionally, both compounds were shown to have a strong affinity for the D_2 dopamine receptor using the Malmberg displacement assay. Currently the compounds are investigated through collaboration with the Prof. Javitch group (Columbia University). We expect to observe a change in the affinity of the compounds towards the D_2 dopamine receptor based in response to irradiation with either 380 or 500 nm light. However, it was already shown in the preliminary experiments that both new compounds **4.9** and **4.10** are D_2 dopamine receptor agonists in the low μM range in their *trans* form.

4.4 Experimental

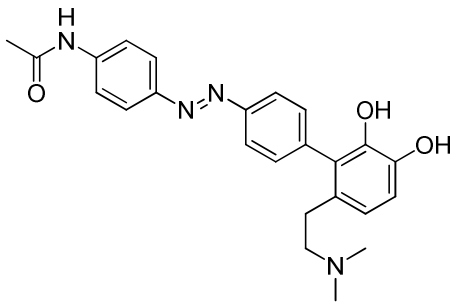
3.4.1 Synthetic Procedures

General Methods: Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60Å silica gel, Waters Preparative C18 125 Å 55-105 μm silica gel (reversed phase), or preparative HPLC on a Zorbax 21.2 × 250 mm, 7 μm SB-C18 column, 22.0 mL/min flow rate (reversed phase HPLC), as indicated. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} TLC plates and visualized using charring solutions of potassium permanganate. Reactions were carried out under inert atmosphere in oven-dried glassware and reaction solutions were magnetically stirred. THF was distilled from benzophenone ketyl prior to use. All other reagents and solvents were used without further purification from commercial sources unless otherwise noted.

NMR spectra were measured by the LMU NMR facility on Brüker AC (300 MHz), Varian XL (400 MHz), or Brüker AMX 600 (600 MHz) instruments and calibrated to residual solvent signal. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad. High resolution mass spectra (HRMS) were obtained by the LMU Mass Spectroscopy facility using electrospray ionization (ESI) on a Thermo Finnigan LTQ FT mass spectrometer. UV-vis spectroscopy was performed using Varian Cary® 50 spectrophotometer.



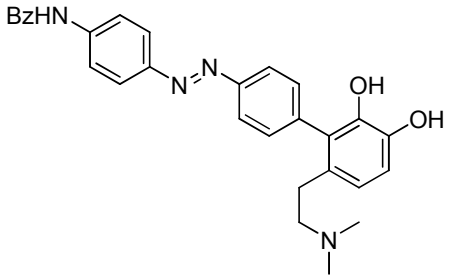
Aniline 4.8. To a flask containing LiCl (62.8 mg, 1.48 mmol), CuCl (53.7 mg, 543 μmol), and $Pd(PPh_3)_4$ (57.1 mg, 49.4 μmol) was added a degassed solution of azobenzene **4.6** (79.7 mg, 247 μmol) and stannane **4.7** (110 mg, 296 μmol) in DMSO (3.0 mL). The reaction mixture was stirred at 65 °C for 17 h. After cooling to RT the mixture was diluted with EtOAc (30 mL) and aqueous NaCl (10%, 20 mL), then filtered through a plug of Celite. The separated aqueous phase was extracted with EtOAc (30 mL), then the combined organic phases were washed with brine (20 mL) and concentrated in vacuo. Purification by silica gel chromatography (CH_2Cl_2 : [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH] 1:1) afforded aniline **4.8** (88.0 mg, 88%) as a brown oil. Data for **4.8**: R_f 0.25 (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90 (d, 2H, *J* = 8.4 Hz), 7.81 (d, 2H, *J* = 8.6 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 6.72 (d, 2H, *J* = 8.6 Hz), 4.16 (br. s, 2H), 3.87 (s, 3H), 3.53 (s, 3H), 2.61 (m, 2H), 2.34 (m, 2H), 2.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.0, 151.3, 149.9, 146.8, 145.6, 138.8, 136.3, 131.0, 130.7, 125.3, 125.0, 122.1, 114.7, 112.0, 60.9, 60.8, 56.0, 45.0, 30.6; HRMS (ESI) calculated for $C_{24}H_{29}N_4O_2$ $(M+H)^+$: 405.2291, found: 405.2277.



Catecholamine 4.9. To a solution of **4.8** (97.6 mg, 242 μmol) in THF (4.0 mL) were added *i*-Pr_2EtN (50 μL, 290 μmol) and acetyl chloride (20 μL, 240 μmol). The resulting mixture was stirred for 30 min at RT and concentrated. Purification by silica gel chromatography (90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH) afforded an orange oil (99.8 mg, 92%).

To a solution of the foregoing acetamide (65.0 mg, 145 μmol) in CH_2Cl_2 (4.0 mL) at – 78 °C was added a solution of BBr_3 (1.0 M in heptane, 1.02 mL, 1.02 mmol). The resulting red reaction mixture was stirred at – 78 °C for 10 min, warmed to RT and stirred at this temperature for another 2 h. The reaction mixture was then concentrated in vacuo, suspended in aqueous formic acid (0.1%, 20 mL), and filtered. The filtrate was washed with MeOH (15 mL) and dried in vacuo to afford catecholamine **4.9 (**37.8 mg, 62%) as a brown powder.

Data for **4.9**: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (d, 2H, *J* = 8.5 Hz), 7.86 (d, 2H, *J* = 9.0 Hz), 7.72 (d, 2H, *J* = 8.9 Hz), 7.42 (d, 2H, *J* = 8.6 Hz), 6.79 (d, 1H, *J* = 8.2 Hz), 6.72 (d, 1H, *J* = 8.2 Hz), 3.00 (m, 2H), 2.77 (m, 2H), 2.61 (s, 6H), 2.12 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.0, 153.3, 150.2, 146.1, 144.6, 143.2, 141.3, 132.6, 130.3, 126.2, 124.9, 123.9, 121.8, 121.2, 115.9, 59.7, 43.5, 29.1, 24.2; HRMS (ESI) Calc. for $C_{24}H_{27}N_4O_3$ $(M+H)^+$: 419.2083, found: 419.2069.



Catecholamine 4.10. To a solution of **4.8** (45.3 mg, 110 μmol) in THF (4.0 mL) were added *i*-Pr_2EtN (23 μL, 130 μmol) and benzoyl chloride (13 μL, 110 μmol). The resulting mixture was stirred for 90 min at RT and concentrated in vacuo. Purification by silica gel chromatography (CH_2Cl_2 : [90:10:0.6:0.6 CH_2Cl_2:MeOH:H_2O:NH_4OH] 1:1) afforded a red oil (49.0 mg, 90%).

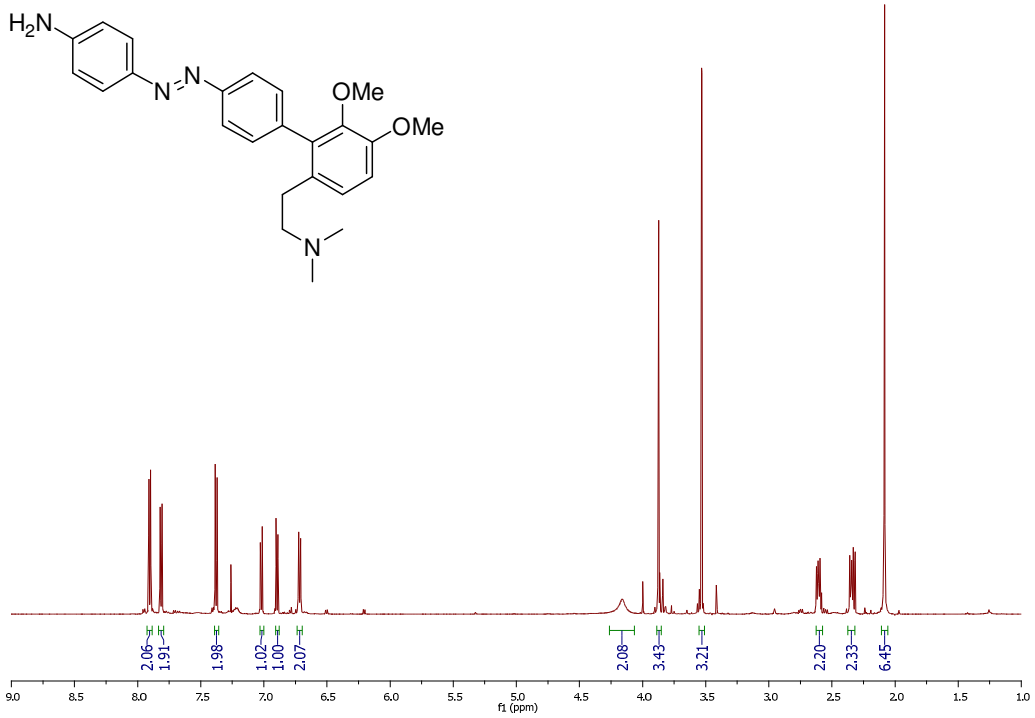
To a solution of foregoing amide (49.0 mg, 96.3 μmol) in CH_2Cl_2 (4.0 mL) at – 78 °C was added a solution of BBr_3 (1.0 M in heptane, 0.80 mL, 800 μmol). The resulting red reaction mixture was stirred at – 78 °C for 10 min, warmed to RT and stirred at this temperature for another 2 h. The reaction mixture was then concentrated, suspended in aqueous formic acid (0.1%, 20 mL),

and filtered. The filtrate was washed with MeOH (15 mL) and dried in vacuo to afford catecholamine **4.10** (35.8 mg, 78%) as a brown powder.

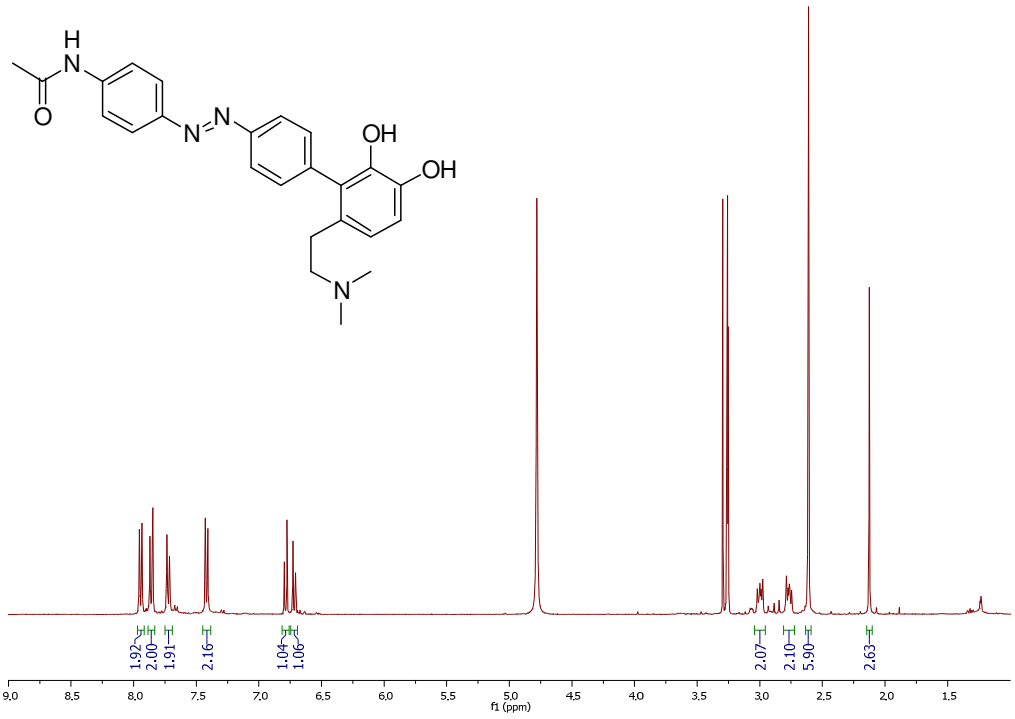
Data for **4.10**: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.87 (m, 8H), 7.53 – 7.38 (m, 5H), 6.76 (d, 1H, *J* = 8.2 Hz), 6.69 (d, 1H, *J* = 8.2 Hz), 2.95 (m, 2H), 2.76 (m,2H), 2.58 (s, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 169.1, 153.3, 150.5, 146.0, 144.6, 143.2, 141.3, 136.2, 133.3, 132.6, 130.2, 129.8, 128.9, 126.2, 124.8, 124.0, 122.3, 121.9, 115.9, 59.7, 43.5, 29.1; HRMS (ESI) calculated for $C_{29}H_{29}N_4O_3$ $(M+H)^+$: 481.2240, found: 481.2235.

3.4.2 Selected NMR Spectra

4.8



4.9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N
O
N
N
OH
OH
N
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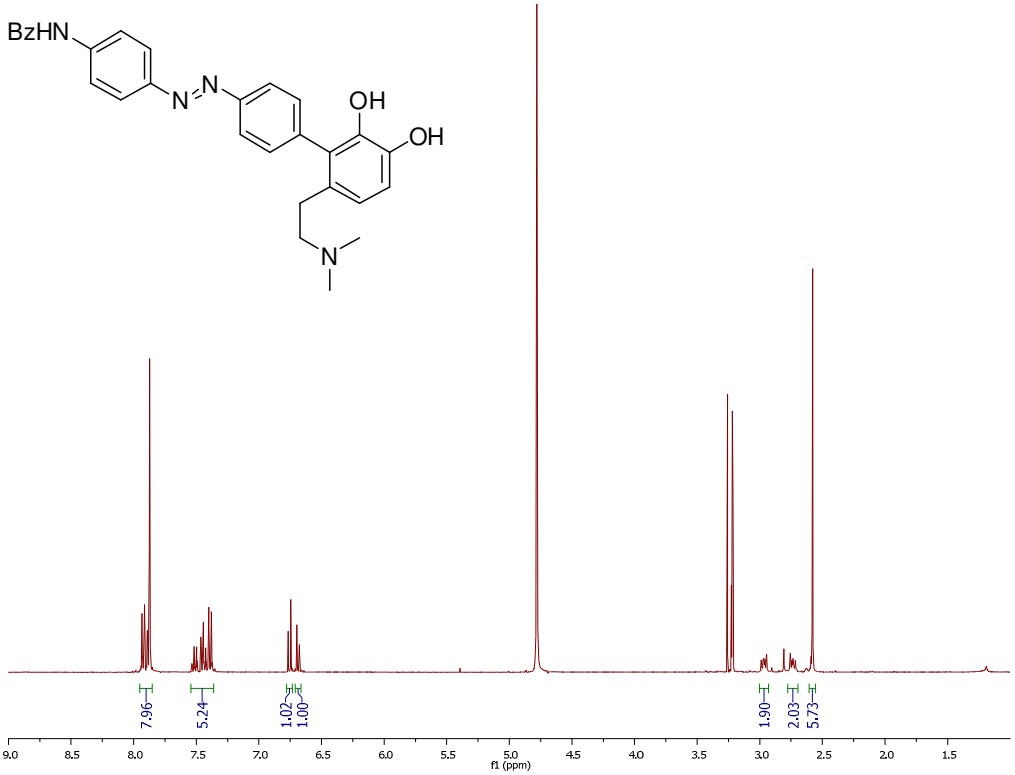
2.00
1.91
2.16
1.04
1.06
2.07
2.10
5.90
2.63
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

4.10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OH
OH
N
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1.02
1.00
1.90
2.03
5.73
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

4.5 References

1. Carlsson, A. *Pharmacol. Rev.* **1959**, *11*, 490–493.
2. Girault, J.; Greengard, P. *Arch. Neurol.* **2004**, *61*, 641–644.
3. Missale, C.; Nash, S. R.; Robinson, S. W.; Jaber, M.; Caron, M. G. *Physiol. Rev.* **1998**, *78*, 189–225.
4. Schwab, R.; Amador, L.; Lettvin, J. *T. Am. Neurol. Assoc.* **1951**, *56*, 251–253.
5. (a) Banghart, M. R.; Volgraf., M.; Trauner, D. *Biochemistry* **2006**, *45*, 15129–15141. (b) Volgraf, M.; Gorostiza, P.; Szobota, S.; Helix, M. R.; Isacoff, E. Y.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 260–261. (c) Harvey, J. H.; Trauner, D. *Chembiochem.* **2008**, *9*, 191–193. (d) Banghart, M. R.; Mourot, A.; Fortin, D. L.; Yao, J. Z.; Kramer, R. H.; Trauner, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 1–6.
6. Masuyama, S. *Nippon Kagaku Zasshi* **1950**, *71*, 47–48.
7. Volgraf, M.; Lumb, J.-P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Münzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Bio.* **2008**, *4*, 535–537.
8. Malmberg, A.; Jerning, E.; Mohell, N. *European Journal of Pharmacology* **1996**, *303*, 123–128.
9. Cheng, Y. C.; Prussoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
10. Knight, P. J. K.; Pfeifer, T. A.; Grigliatti, T. A. *Anal. Biochem.* **2003**, *320*, 88–103.