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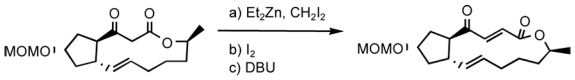
Formal Synthesis of (+)-Brefeldin A: Application of a Zinc-mediated Ring Expansion Reaction

Weimin Lin and **Charles K. Zercher***
Department of Chemistry, University of New Hampshire, Durham, NH 03824

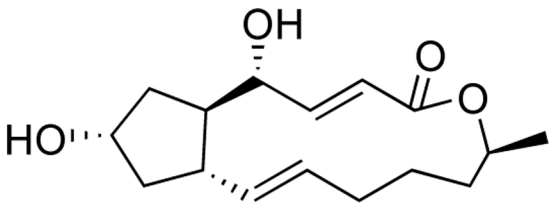
Abstract



An efficient formal synthesis of (+)-brefeldin A was accomplished through a synthetic approach that relied upon three keys steps. The five-membered ring was generated in a stereocontrolled fashion through application of a tandem conjugate addition-intramolecular cyclization method developed by Toru. Ring-closing metathesis provided access to a twelve-membered β-keto lactone, which was ring-expanded to the α,β-unsaturated-γ-keto lactone through a zinc carbenoid-mediated reaction. Conversion of this lactone to (+)-brefeldin A has been reported previously.

Introduction

(+)-Brefeldin A is a bicyclic compound that possesses a 13-membered macrocyclic lactone. Although the isolation of (+)-brefeldin A from fungal sources (such as *Penicillium decumbens, P. brefeldianum, and Phyllosticta medicaginis*) was reported in 1958,[1] the structure of this fungal metabolite was not established until 1971.[2]



1 (+)-Brefeldin A

A wide range of biological properties has been attributed to this molecule, including antiviral, cytostatic, and antibiotic activities. [3] Furthermore, a recent study has demonstrated that (+)-brefeldin A can drive Golgi complex disassembly and redistribution to the endoplasmic reticulum, and can inhibit protein transport to post-Golgi compartments in the cell. [4] (+)-Brefeldin A has received attention due to its potential service as an anticancer agent[5] and as an immunosuppressive agent.[6]

*ckz@cisunix.unh.edu.

This combination of wide ranging biological activity and unusual structural features has made (+)-brefeldin A an attractive synthetic target. An impressive array of synthetic approaches has been described for this molecule, including a number of approaches that are noteworthy due to their efficiency and brevity.[7] Many of these approaches have used the natural product as a proving ground for the development and assessment of new synthetic methods. Macrocyclic lactonization methods and strategies for the stereoselective formation of five-membered rings have dominated this methodology development.

Our interest in (+)-brefeldin A was based upon the presence of the γ-oxygenated α,β-unsaturated lactone. We recently reported a tandem chain extension-oxidation-elimination reaction in which β-keto esters are converted in a single step to γ-keto-α,β-unsaturated esters through treatment with a zinc carbenoid.[8] We further demonstrated that the reaction facilitates efficient formation of macrocyclic β-keto lactones with ring sizes of 13 or greater,[9] although smaller macrocylic rings proved to be more resistant to the ring expansion. The chain extension (ring expansion) reaction is performed through treatment of the β-keto carbonyl with the Furukawa-modified Simmons-Smith reagent derived from diethylzinc and diiodomethane.[10] A traditional use of this electrophilic carbenoid has been in the cyclopropanation of olefinic functionalities, usually those possessing allylic oxygenation. The presence of both the electron-rich alkene and the ring-fused thirteen-membered ring lactone in (+)-brefeldin A presented challenges to the application of the zinc-carbenoid-mediated ring expansion protocol.

Results and Discussion

The key step in our synthetic approach to (+)-brefeldin A was, therefore, the conversion of the β-keto lactone to the γ-keto-α,β-unsaturated lactone. Since Bartlett,[11] and more recently Kim,[12] reported a synthesis of (+)-brefeldin A through intermediate **2**, we targeted the formation of **3** as the penultimate compound in our approach to (+)-brefeldin A. Our previous studies had established that ring-closing metathesis (RCM) of β-keto esters could provide useful amounts of the corresponding β-keto lactones. While alkene-stereoselectivity was inconsequential in our earlier studies, (+)-brefeldin A presented a synthetic target in which control of olefin geometry was required. Assuming that the ring-closing metathesis reaction of **4** could provide the necessary *E*-alkene **3**, we anticipated that the metathesis precursor could be prepared through a mixed Claisen condensation involving the activation of carboxylic acid **5**. Formation of the substituted cyclopentane **5** was anticipated to be available from α,β-unsaturated ester **6**, derivable from the optically active triol **7**.

Enantiomerically pure (*S*)-1,2,4-butanetriol (**7**) was converted to the unsaturated diol **8** in four steps via the route reported by Labelle.[13] The starting material is commercially available, although it can also be prepared conveniently through reduction of (*S*)-malic acid with borane.[14] Two different approaches were utilized for the preparation of compound **6** from the diol. An indirect route involved formation of the tosylate **9** from the diol,[15] followed by protection of the secondary alcohol with a methoxymethyl group. Substitution of the tosylate with bromide provided the ethyl (5*S*,2*E*) 6-bromo-5-(methoxymethoxy)hex-2-enoate **6**. (Scheme 2).

A more direct approach to compound **6** was developed in which the primary alcohol was selectively brominated using triphenylphosphine and carbon tetrabromide. [16] Reaction between compound **11** and methoxymethyl chloride using *N*,*N*-diisopropylethylamine (DIEA) as the base provided the targeted electrophile **6**.

Formation of compound **13** through the conjugate addition of the α-sulfinyl carbanion derived from a chiral tolylsulfoxide to compound **6** was investigated (Scheme 3). The stereoselective cyclization method,[17] developed by Toru, was particularly attractive due to the strong preference for trans stereochemistry on the five-membered ring and for the ease by which the

vinyl group can be generated through fluoride-mediated elimination of the sulfinic acid. Toru's studies had established that the absolute stereochemistry of the newly formed stereocenters is controlled by the chiral sulfoxide. Formation of the stereocenters in (+)-brefeldin A required the utilization of the (*S*)-sulfoxide **12**, which could be prepared via the (*D*)-menthyl tolylsulfinate.[18,19] Due to its remote position, the existing stereocenter on compound **6** was not anticipated to influence the stereoselective formation of the cyclopentane.

Upon exposure of the carbanion of **12** to the unsaturated bromide **6**, one predominant diastereomer **13** (*de* >95%) was detected by analysis of the ^{13}C NMR spectrum, although the stereochemistry could not be assigned. The configuration of the newly generated stereocenters was clarified after tetrabutylammonium fluoride (TBAF) induced elimination and lithium aluminum hydride (LAH) reduction of the ester (Scheme 3). Treatment with TBAF immediately after purification of **13** was necessary due to rapid decomposition of **13**, presumably through syn-elimination of the arylsulfinic acid. A comparison of the spectroscopic data of the alcohol **15** to those reported in the literature[20] confirmed that the homoallylic primary alcohol possessed the necessary relative stereochemistry for approaching (+)-brefeldin A. Saponification of **14** with 3M lithium hydroxide produced the targeted homoallylic carboxylic acid **5** in an excellent yield with no epimerization.

With the successful formation of the key intermediate **5**, a simple two-step reaction sequence[9] was performed to prepare compound **17**, the precursor for the modified Claisen condensation (Scheme 4). Generation of the cuprate from 1-bromo-3-butene (**16**) and addition to (*S*)-propylene oxide provided an intermediate alkoxide that could be acetylated in almost quantitative yield. After treatment of compound **17** with LDA, a solution of an acyl imidazole was transferred to the enolate solution by cannula. Compound **4** was generated in higher than 80% yield without detectable epimerization.

After obtaining the unsaturated β-keto ester **4**, Grubbs' first generation catalyst was used to prepare the unsaturated β-keto macrolide **3** through a ring closing metathesis (RCM) reaction (Scheme 5). Dichloromethane proved to be a better solvent than toluene for full conversion of the starting material to the targeted compound **3**, although addition of a second portion of catalyst to the refluxing solution was necessary. Two macrolides **3A** and **3B**, separable by column chromatography, were formed with an *E*:*Z* ratio = 3.5:1. The stereochemistry was assigned by ^{1}H NMR and 1D NOE analysis of the crude reaction mixture. Iodine-catalyzed double bond isomerization in the macrocyclic compound was unsuccessful for converting compound **3B** to compound **3A**. However, isomerization of the *Z* to the *E* double bond was accomplished by treatment with thiophenol in the presence of AIBN at 80 °C.[20]

Before a full investigation of the zinc-mediated chain extension-oxidation-elimination reaction for the preparation of compound **2** was performed, the efficiency of the simple chain extension reaction was studied.[21] Following generation of the zinc-carbenoid (7.5 equiv), the macrolide **3A** was added to the solution and allowed to react for 30 min. In addition to product formation, starting material was still observed under these conditions even after the reaction time was extended from 30 min to 2 h. The reason for the presence of unreacted starting material is unknown, although slow deprotonation of β-keto macrocyclic compounds, as observed in earlier studies,[9] and decomposition of the carbenoid[22] over time may be factors. Increasing the equivalents of carbenoid from 7.5 to 10 did result in more efficient chain extension, although minor amounts of inseparable cyclopropanated products appeared to form under these conditions. The location and stereochemistry of the cyclopropane were investigated no further.

A modification of the reaction was performed, in which carbenoid (overall 7.5 equiv) was added in two portions (Scheme 6). After treatment of the β-keto macrolide **3A** for 30 min with 5 equivalents of carbenoid prepared in advance, second portions of diethyl zinc and 1,1-

diiodomethane (2.5 equiv) were added sequentially. After an additional thirty minutes of reaction time, complete conversion to the ring expanded product **18** was accomplished.

These conditions were repeated and excess iodine was added to the solution to trap the intermediate formed in the chain extension reaction (Scheme 6). After elimination of iodide by treatment with DBU, the targeted α,β-unsaturated-γ-keto-macrolide was produced. The newly formed double bond, generated from the zinc-mediated chain extension-oxidation-elimination reaction, was assigned the *E*-configuration based on ^{1}H-^{1}H coupling constant (J = 16.0 Hz), as well as through comparison to the known literature data.[12] The spectroscopic data of the material in the chain extension-oxidation-elimination sequence was identical to that reported in the literature. Therefore, the successful preparation of **2** completed the formal synthesis of (+)-brefeldin A.

In summary, an efficient approach to (+)-brefeldin A was developed, in which a zinc-mediated chain extension-oxidation-elimination reaction was used as a key step. Combination of this twelve step linear sequence with the reduction and deprotection steps reported in the literature provides, to the best of our knowledge, the shortest synthetic route to (+)-brefeldin reported to date. This efficient synthetic approach demonstrates the power and utility of Toru's cyclopentane-formation method and of the zinc-mediated chain extension reaction.

Experimental Section

Ethyl (1*R*,2*R*,4*R*)-4-(methoxymethoxy)-2-((1*R*)-1-(*p*-tolylsulfinyl)-2-(trimethylsilyl)-ethyl) cyclopentanecarboxylate (13)

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (3 mL), and diisopropylamine (0.1 mL, 0.75 mmol) in order. After the solution was cooled to 0 °C, *n*-BuLi (2.0 M in hexanes, 0.37 mL, 0.75 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was cooled to −78 °C using dry ice in acetone, compound **12** (0.06 g, 0.25 mmol, in 0.5 mL of THF) was added. After the solution was allowed to stir for 15 min, compound **6** (0.09 g, 0.33 mmol, in 0.33 mL of THF) was added in one portion. The solution was allowed to stir for 15 min at −78 °C and then warm to 0 °C. After TLC analysis (hexanes:ethyl acetate = 3:1; R_f = 0.20) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3×5 mL), washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexane: ethyl acetate = 3:1, R_f = 0.15) to offer 88 mg (80%) of **13** as a colorless liquid. (In order to prevent decomposition of the product, treatment with TBAF was performed immediately after characterization data was obtained.) $[\alpha]^{25}_{D} = -52$ (c = 0.003 g/mL, THF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (d, 2H, J = 8.0 Hz), 7.50-7.48 (d, 2H, J = 8.0 Hz), 4.90 (dd, 1H, J = 6.9 Hz), 4.84 (d, 1H, J = 6.9 Hz), 4.44 (m, 1H), 4.41-4.37 (q, 2H, J = 7.1, Hz), 3.66-3.54 (m, 2H), 3.58 (s, 3H), 3.02 (m, 1H), 2.69 (m, 1H), 2.60 (s, 3H), 2.60-2.34 (m, 3H), 1.52-1.49 (t, 3H, J = 7.1 Hz), 0.99-0.97 (m, 2H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 141.8, 141.8, 131.0, 125.4, 96.4, 77.1, 66.8, 62.2, 56.9, 47.4, 47.0, 37.9, 35.0, 22.7, 15.8, 10.6, 0.0. IR (neat, cm^{-1}): 2964, 2882, 1727, 1614, 1596.

Ethyl (1*R*,2*S*,4*S*)-4-(methoxymethoxy)-2-vinylcyclopentanecarboxylate (14)

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (5 mL) and compound **13** (0.09 g, 2 mmol, in 2 mL of tetrahydrofuran) in order. After the solution was cooled to 0 °C in the ice bath, TBAF (1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol) was added in one portion.

After TLC analysis (hexanes:ethyl acetate = 3:1; R_f = 0.15) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (3 mL). The mixture was extracted with diethyl ether (2×5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 10:1, R_f = 0.25) to offer 0.39 g (85%) of **14** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.04 (dd, 1H, *J* = 0.9, 16.4 Hz), 4.98 (dd, 1H, *J* = 1.0, 10.1 Hz), 4.62 (s, 2H), 4.23 (m, 1H), 4.18-4.10 (m, 2H), 3.36 (s, 3H), 2.76-2.68 (m, 2H), 2.30 (m, 1H), 2.08-2.02 (m, 2H), 1.58 (m, 1H), 1.26-1.23 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 140.6, 114.8, 95.5, 66.1, 60.6, 55.6, 48.4, 46.6, 39.7, 37.2, 14.5. IR (neat, cm^{-1}): 3035, 2964, 2954, 1723, 1642. $[\alpha]^{25}_D$ = −35 (c = 0.001 g/mL, $CHCl_3$); HRMS (FAB^+) *m/z* Calcd for $C_{12}H_{21}O_4$ (M+1): 229.1440. Found 229.1425.

((1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-2-vinylcyclopentyl)methanol (15)

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (3 mL), lithium aluminum hydride (15 mg, 0.4 mmol) and compound **14** (18 mg, 0.075 mmol) in the indicated order. The solution was refluxed till TLC analysis (hexanes:ethyl acetate = 3:1; R_f = 0.20) indicated that the starting material was consumed. The solution was cooled to room temperature and quenched by cautious and sequential addition of water (1 mL), 10% aqueous sodium hydroxide (1 mL), and water (3 mL). After stirred for 10 min, the solution was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1, R_f = 0.10) to offer 7 mg (50%) **15** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.04 (dd, 1H, *J* = 1.0, 17.1 Hz), 4.96 (dd, 1H, *J* = 1.7, 10.1 Hz), 4.63 (s, 2H), 4.16 (m, 1H), 3.68 (dd, 1H, *J* = 5.4, 10.8 Hz), 3.54 (dd, 1H, *J* = 6.1, 10.8 Hz), 3.36 (s, 3H), 2.27-2.18 (m, 3H), 2.05 (m, 1H), 1.92 (m, 1H), 1.67 (m, 1H), 1.56 (m, 1H); $[\alpha]^{25}_D$ = −39 (c = 0.001 g/mL, $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 114.5, 95.5, 76.9, 65.7, 55.5, 46.0, 45.8, 40.4, 36.2. IR (neat, cm^{-1}): 3450, 2960, 1621. HRMS (FAB^+) *m/z* Calcd for $C_{10}H_{19}O_3$ (M+1): 187.1334. Found 187.1341.

(1*R*,2*S*,4*S*)-4-(Methoxymethoxy)-2-vinylcyclopentanecarboxylic acid (5)

Compound **14** (0.46 g, 2.0 mmol) was dissolved in a 25-mL round-bottomed flask with 4 mL of THF. Water (4 mL), and lithium hydroxide monohydrate (0.38 g, 8.0 mmol) were added to the solution in the indicated order. The mixture was allowed to stir for overnight at room temperature and the solution was brought to pH = 1.0 with 1M HCl, then extracted with diethyl ether (3×5 mL). The combined organic layers were dried carefully over anhydrous sodium sulfate and concentrated *in vacuo* to yield 0.32 g (80%) of **5** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.09 (d, 1H, *J* = 17.2 Hz), 5.01 (d, 1H, *J* = 10.2 Hz), 4.63 (s, 2H), 4.25 (m, 1H), 3.36 (s, 3H), 2.78-2.76 (m, 2H), 2.32 (m, 1H), 2.12-2.10 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 140.4, 115.1, 95.5, 55.6, 48.2, 46.3, 39.7, 37.2. IR (neat, cm^{-1}): 3300, 2960, 1710. $[\alpha]^{25}_D$ = −40 (c = 0.002 g/mL, $CHCl_3$). HRMS (FAB^+) *m/z* Calcd for $C_{10}H_{17}O_4$ (M+1): 201.1127. Found 201.1131.

(*S*)-Hept-6-en-2-yl acetate (17)

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with magnesium turnings (0.6 g, 25 mmol), THF (30 mL) and a crystal of iodine. 1-Bromo-3-butene (**16**) (1.3 mL, 13 mmol) was dissolved in tetrahydrofuran (10 mL). A portion of the bromobutene solution (1 mL) was added and the mixture was allowed to stir until the brown color of the mixture disappeared. The solution was allowed to stir for an additional 10 min, then 4-bromo-1- butene solution was added dropwise

over a 1-h period using a syringe pump. The mixture was allowed to stir for an additional 1 h and was brought to −40 °C and copper(I) iodide (50 mg, 0.26 mmol) was added. The resulting light green mixture was allowed to stir for an additional 10 minutes, at which time (*S*)-propylene oxide (0.35 mL, 5 mmol) was added in a single portion. The mixture was allowed to warm to −15 °C and allowed to stir for an additional 2.5 hours, then quenched with saturated aqueous ammonium chloride (10 mL). The layers were separated and the organic layer was washed with H_2O (10 mL) and brine (10 mL). The layers were separated and the combined aqueous layers were extracted with diethyl ether (3×50 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solution was filtered and concentrated under reduced pressure. The resulting crude residue was dissolved in a 25-mL oven-dried round-bottomed flask with 8 mL diethyl ether. Acetyl chloride (0.71 mL, 10 mmol, freshly distilled) was added to the solution followed with addition of pyridine (0.80 mL, 10 mmol). The solution was allowed to reflux till TLC analysis (hexane: ethyl acetate = 3:1; R_f = 0.10) indicated that the starting material was consumed. After cooling to the room temperature, the solution was washed with 1M HCl (3×10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 15:1, R_f = 0.15) to yield 0.66 g (85%) of **17** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (m, 1H), 4.93 (dd, 1H, *J* = 1.7, 17.1 Hz), 4.88 (dd, 1H, *J* = 0.9, 11.2 Hz), 4.83 (m, 1H), 2.01-1.96 (m,2H), 1.95 (s, 3H), 1.56-1.18 (m, 4H), 1.14 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 137.4, 113.7, 69.8, 34.3, 32.5, 23.7, 20.2, 18.9. IR (neat, cm^{-1}): 3052, 2975, 1740. HRMS (FAB^+) *m/z* Calcd for $C_9H_{17}O_2$ (M+1): 157.1229. Found 157.1232.

(*S*)-Hept-6-en-2-yl 3-((1*R*,2*S*,4*S*)-4-(methoxymethoxy)-2-vinylcyclopentyl)-3-oxopropanoate (4)

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with anhydrous THF (2 mL), compound **5** (0.10 g, 0.5 mmol, in 1 mL of THF), and 1,1-dicarbonylimidazole (0.10 g, 0.6 mmol) in the indicated order. In a separate 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (8 mL), and diisopropylamine (0.28 mL, 2 mmol) in order. After the solution was cooled to 0 °C in the ice bath, *n*-BuLi (2.0 M in hexanes, 1.0 mL, 2.0 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was cooled to −78 °C, compound **17** (0.31 g, 2 mmol, in 3 mL of THF) was added in 1 h using syringe pump. The acyl imidazole solution was transferred to the enolate solution by cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (2 mL). The solution was extracted with diethyl ether (3×5 mL) and the combined organic layers were washed by brine (5 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica (hexanes:ethyl acetate = 10:1, R_f = 0.20) to yield 0.14 g (85%) of **4** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87-5.74 (m, 2H), 5.08-4.93 (m, 4H), 4.62 (s, 2H), 4.17 (m, 1H), 3.44 (s, 2H), 3.35 (s, 3H), 3.04 (dd, 1H, *J* = 8.9, 17.6 Hz), 2.70 (m, 1H), 2.26 (m, 1H), 2.11-1.96 (m, 4H), 1.64-1.35 (m, 6H), 1.23 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 167.0, 141.8, 138.6, 115.4, 115.0, 95.5, 77.4, 72.4, 55.7, 55.6, 49.9, 45.8, 40.0, 36.1, 35.4, 33.6, 24.8, 20.1. $[\alpha]^{25}_D$ = −26 (c = 0.001 g/mL, $CHCl_3$); HRMS (FAB^+) *m/z* Calcd for $C_{19}H_{31}O_5$ (M+1): 339.2195. Found 339.2171.

(10a*S*,13a*R*,*E*)-5,6,7,8,11,12,13,13a-Octahydrocyclopenta[e][1]oxacyclododecine-1,3(2H, 10aH)-dione (3A) and (10a*S*,13a*R*,*Z*)-5,6,7,8,11,12,13,13a-Octahydrocyclopenta[e][1] oxacyclododecine-1,3(2H,10aH)-dione (3B)

A 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (100 mL), compound **4** (0.16 g, 0.6 mmol, in 1 mL of dichloromethane) and bis(cyclohexylphosphine)benzylidine

ruthenium (IV) dichloride (20 mg, 0.024 mmol) in the indicated order. This solution was heated to reflux for 8 hours and another portion of catalyst was added (20 mg, 0.024 mmol). Reflux was continued for an additional 8 hours till TLC analysis (hexanes:ethyl acetate = 15:1, R_f = 0.20) indicated that the starting material was consumed. The solution was allowed to cool and concentrated *in vacuo*. The residue was chromatographed on silica to yield 100 mg (64 %) of two isomers **3A** (50%) and **3B** (14%). The compounds were produced in *E*:*Z* = 3.5:1 ratio (based on ^{1}H NMR of the crude reaction mixture). ***E*-isomer (3A):** (hexanes:ethyl acetate = 10:1, R_f = 0.20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (m, 1H), 5.30 (dd, 1H, *J* = 8.5, 16.2 Hz), 5.04 (m,1H), 4.61 (s, 2H), 4.15 (m, 1H), 3.44 (m, 1H), 3.40-3.38 (m, 2H), 3.36 (s, 3H), 2.59 (m, 1H), 2.26-2.15 (m, 2H), 2.04-1.92 (m, 2H), 1.72-1.52 (m, 5H), 1.33 (m, 1H), 1.19 (d, 3H, *J* = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 205.4, 167.3, 133.6, 131.7, 95.4, 77.4, 71.6, 55.6, 53.9, 50.8, 46.0, 40.3, 36.0, 32.0, 31.6, 20.7, 18.5. IR (neat, cm^{-1}): 3036, 2956, 1740, 1713. $[\alpha]^{25}_D$ = +4 (c = 0.001 g/mL, $CHCl_3$). HRMS (FAB^+) *m/z* Calcd for $C_{17}H_{27}O_5$ (M+1): 311.1858. Found 311.1841. ***Z*-isomer (3B)** (hexanes:ethyl acetate = 7:1, R_f = 0.15); ^{1}H NMR (500 MHz, CDCl3) δ 5.42 (ddd, 1H, *J* = 1.4, 5.4, 5.4 Hz), 5.30 (ddd, 1H, *J* = 1.4, 5.4, 5.4 Hz), 5.05 (m, 1H), 4.62 (s, 2H), 4.24 (m, 1H), 3.50 (d, 1H, *J* = 14.0 Hz), 3.38 (d, 1H, *J* = 14.2 Hz), 3.35 (s, 3H), 3.16 (m, 1H), 2.98 (dd, 1H, *J* = 8.2, 16.4 Hz), 2.37-2.22 (m, 2H), 2.04-1.74 (m, 5H), 1.58-1.43 (m, 3H), 1.23 (d, 3H, *J* = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 203.8, 165.0, 132.1, 129.8, 94.4, 76.7, 72.0, 56.5, 54.4, 47.8, 39.3, 38.8, 35.2, 30.7, 25.8, 22.9, 17.8. $[\alpha]^{25}_D$ = +53 (c = 0.011 g/mL, $CHCl_3$). HRMS (CI^+) *m/z* Calcd for $C_{17}H_{27}O_5$ (M+1): 311.1856. Found 311.1841.

Isomerization of 3B to 3A

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound **3B** (10 mg, 0.04 mmol), thiophenol (0.014 mL, 0.14 mmol) and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for 8 hours. The mixture was concentrated *in vacuo*, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 10:1, R_f = 0.20) to give 6 mg (60%, based on 75% conversion) of **3A**.

(6*S*,11a*S*,13*S*,14a*R*,*E*)-13-(Methoxymethoxy)-6-methyl-2,3,6,7,8,9,12,13,14,14a-decahydro-1H-cyclopenta[f][1]oxacyclotridecine-1,4(11aH)-dione (18)

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 3 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 1.0 mL, 1.0 mmol). The solution was cooled to 0 °C and compound **3A** (62 mg, 0.2 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, methylene iodide (0.08 mL, 1.0 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Diethyl zinc (1.0 M in hexanes, 0.5 mL, 0.5 mmol) was added to the solution at room temperature and after 10 minutes, methylene iodide (0.04 mL, 0.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate =7:1; R_f = 0.20) to offer 49 mg (75%) of 1**8** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (ddd, 1H, *J* = 5.0, 10.0, 15.0 Hz), 5.31 (dd, 1H, *J* = 8.8, 15.2 Hz), 4.78 (m, 1H), 4.62 (s, 2H), 4.21 (m, 1H), 3.36 (s, 3H), 3.01-2.91 (m, 2H), 2.80 (m, 1H), 2.66-2.54 (m, 2H), 2.39-2.28 (m, 2H), 2.05-1.81 (m, 4H), 1.64-1.46 (m, 2H), 1.28-1.10 (m, 3H), 1.19 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 172.9, 133.2, 132.2, 95.5, 71.8, 56.6, 55.6, 46.7, 40.3, 38.8, 36.6, 32.6, 31.1, 29.5, 24.2, 19.6.

IR (neat, cm^{-1}): 3040, 2980, 1750, 1720. $[\alpha]^{25}_{D}$ = +22.5 (c = 0.002 g/mL, $CHCl_3$). HRMS (FAB^+) *m/z* Calcd for $C_{18}H_{29}O_5$ (M+1): 325.2015. Found 325.2020.

(2*E*,6*S*,10*E*,11a*S*,13*S*,14a*R*)-13-(Methoxymethoxy)-6-methyl-6,7,8,9,12,13,14,14a-octahydro-1H-cyclopenta[f][1]oxacyclotridecine-1,4(11aH)-dione (2)

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 3 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 0.5 mL, 0.5 mmol). The solution was cooled to 0 °C and compound **3A** (25 mg, 0.08 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, methylene iodide (0.02 mL, 0.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Diethyl zinc (1.0 M in hexanes, 0.25 mL, 0.25 mmol) was added to the solution at room temperature and after 10 minutes, methylene iodide (0.02 mL, 0.25 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Iodine (0.5 g, 2.0 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 seconds. A saturated solution of sodium thiosulfate (2 mL) was added and the mixture was stirred until the pink color had disappeared. To this solution was added DBU (0.15 mL, 1.0 mmol) and the mixture was stirred for 1 minute, washed with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3×5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica (hexanes:ethyl acetate =7:1; R_f = 0.25) to yield 12 mg (46%) of **2** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 1H, *J* = 16.0 Hz), 6.44 (d, 1H, *J* = 15.8 Hz), 5.86 (ddd, 1H, *J* = 4.1, 10.9, 15.1 Hz), 5.52 (ddd, 1H, *J* = 1.3, 9.6, 15.2 Hz), 4.56 (m, 1H), 4.63 (s, 2H), 4.10 (m, 1H), 3.36 (s, 3H), 2.88 (q, 1H, *J* = 9.1 Hz), 2.56 (q, 1H, *J* = 9.1 Hz), 2.30-2.21 (m, 2H), 2.14 (m, 1H), 2.02 (m, 1H), 1.96-1.88 (m, 2H), 1.80 (m, 1H), 1.68-1.58 (m, 2H), 1.33 (d, 3H, *J* = 6.1 Hz), 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.1, 140.2, 135.7, 132.9, 128.3, 95.2, 77.2, 73.7, 56.0, 55.3, 45.2, 40.3, 34.2, 32.7, 32.2, 25.6, 20.2. $[\alpha]^{25}_{D}$ = −20 (c = 0.001 g/mL, $CHCl_3$). Lit[12] $[\alpha]^{25}_{D}$ = −18.5 (c = 0.50 g/mL, CH_3OH). HRMS (FAB^+) *m/z* Calcd for $C_{18}H_{27}O_5$ (M +1): 323.1859. Found 323.1852.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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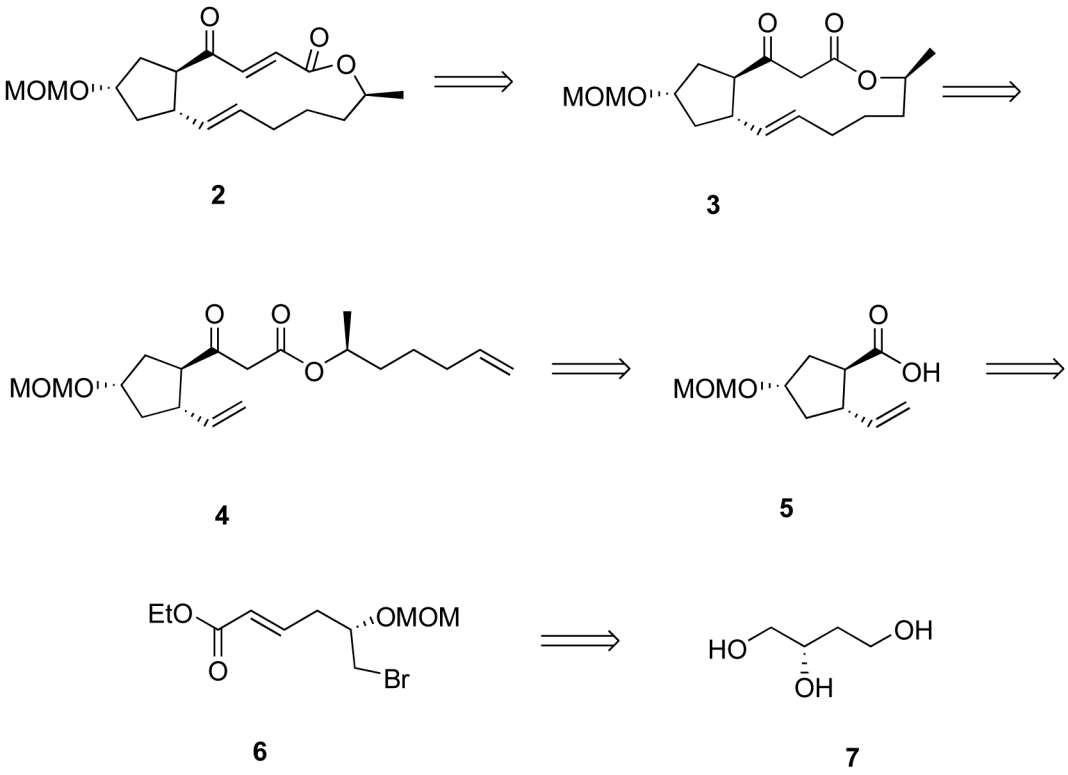
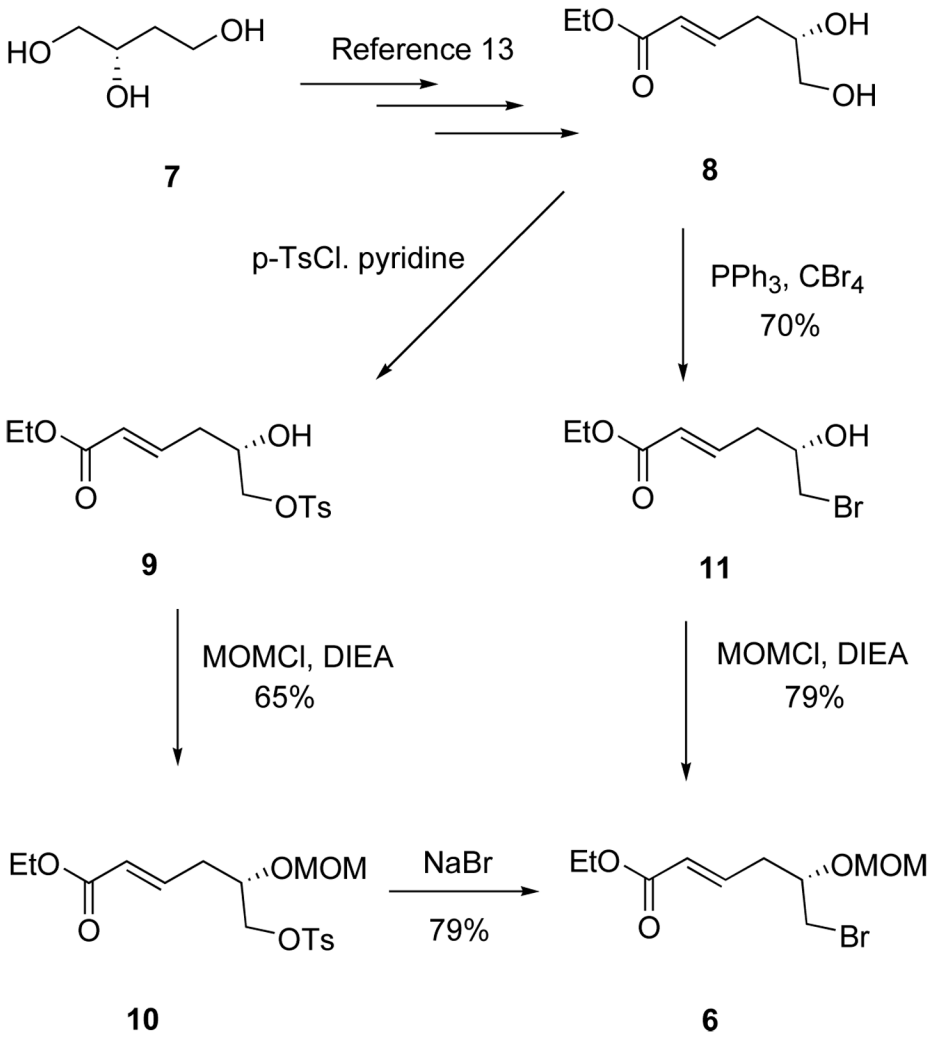
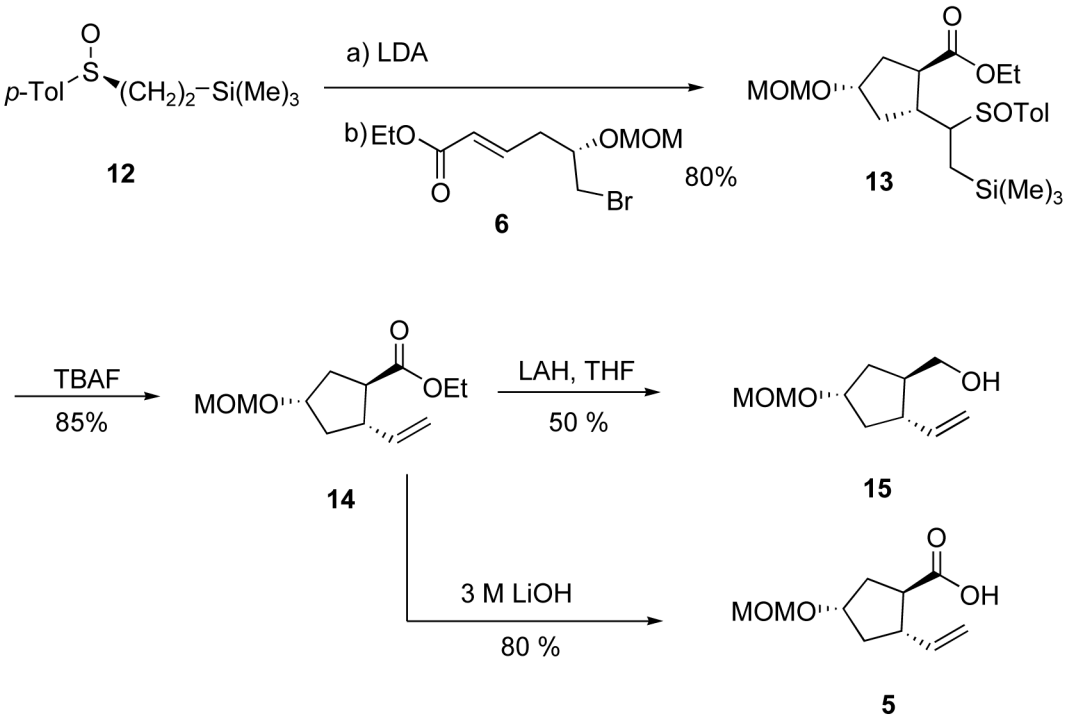


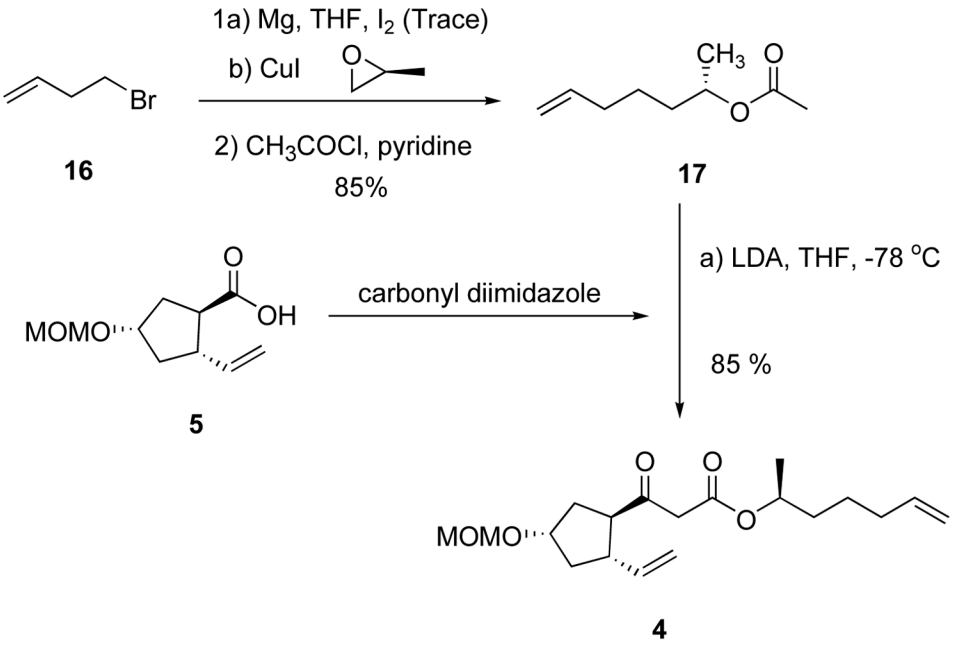
Scheme 1.
Retrosynthetic Analysis



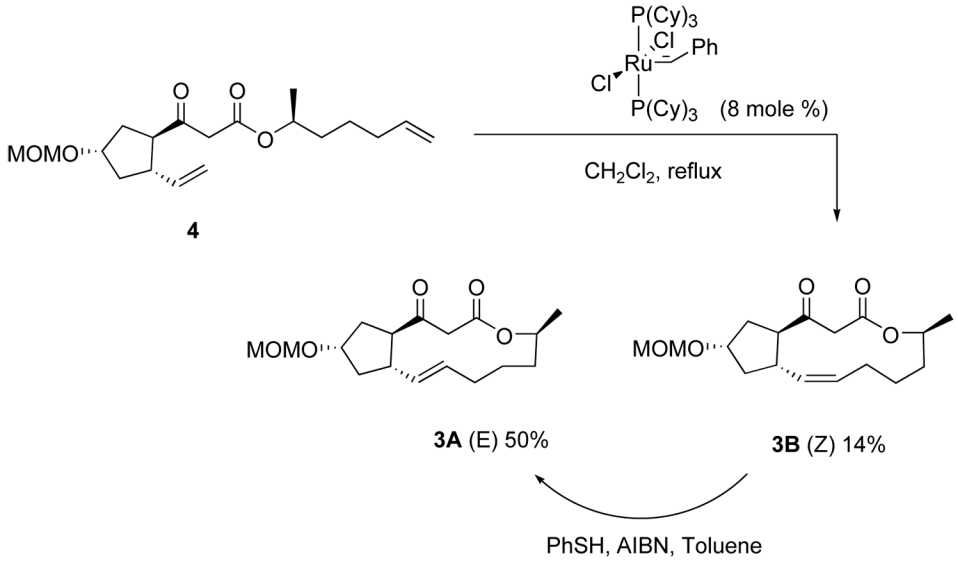
Scheme 2.
Preparation of **6**



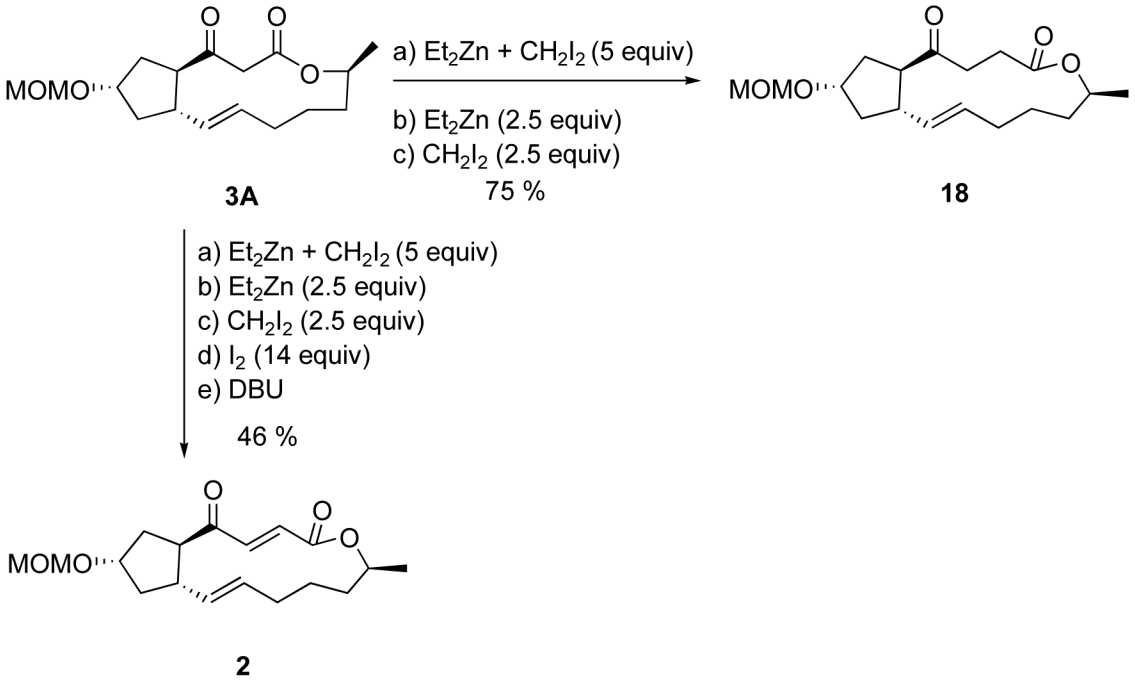
Scheme 3.
Cyclization to the Cyclopentane



Scheme 4.
Preparation of Compound **17**



Scheme 5.
Ring Closing Metathesis (RCM) for the Preparation of **3A** and **3B**



Scheme 6.
Ring Expansion Reactions of Compound **3A**