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Article

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Application of Ru(II)-catalyzed Enyne Cyclization in the Synthesis of Brefeldin A

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ABSTRACT: The approach to brefeldin A described herein hinges on Ru(II)-catalyzed cycloisomerization of an enyne obtained by the reaction of an alkynylzinc reagent with an α-chlorosulfide. Other key steps include Mislow-Evans rearrangement, cross-metathesis, macrocyclization using Roush-Masamune protocol.

INTRODUCTION

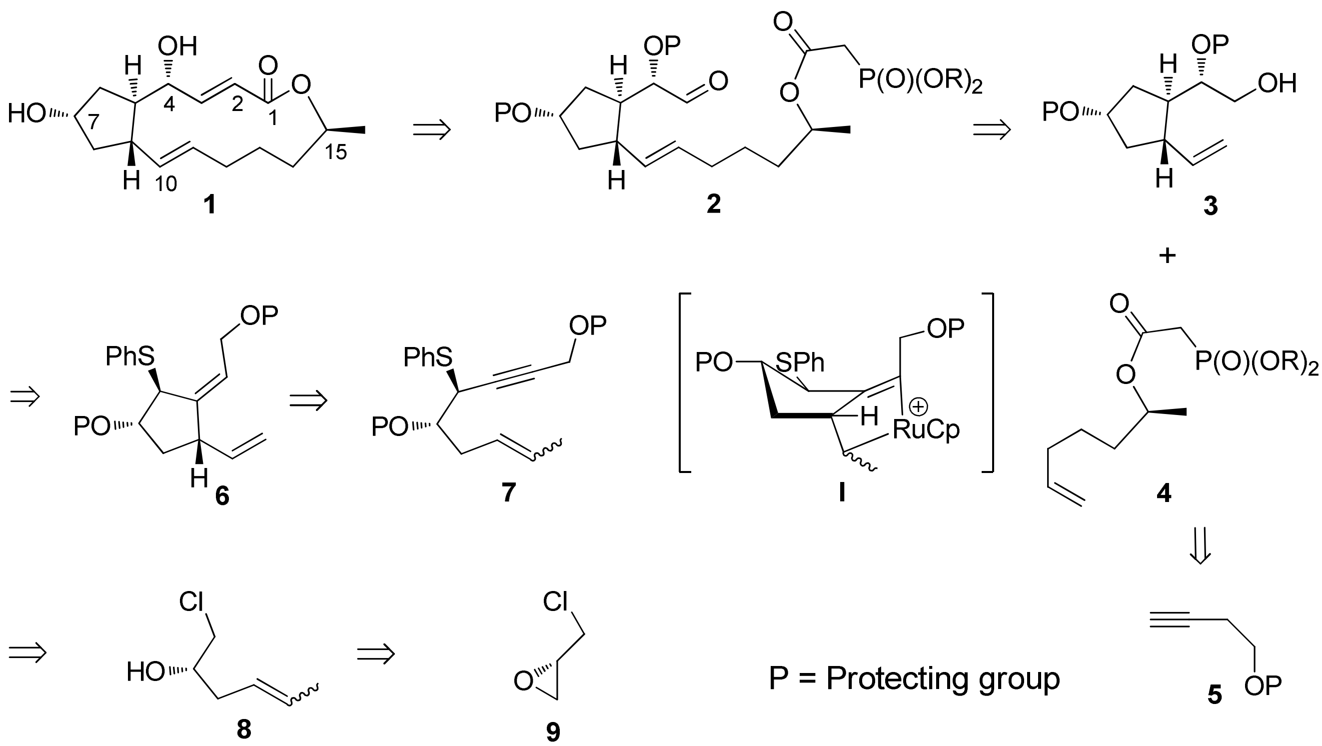
Brefeldin A (**1**) was isolated in 1958 from *Penicillium decumbens*[1] and later from other fungal strains such as *Penicilium brefeldianum* and *Phyllosticta mediaginis*. Its structure was established in 1971.[2] Brefeldin A has been shown to possess a range of biological activities including antiviral, antibiotic, antifungal and antimitotic activities.[3] Brefeldin A has been shown to disassemble Golgi complex, redistribute into endoplasmic reticulum and inhibit protein transport to post-Golgi compartment in the cell.[4] At the molecular level, Brefeldin A inserts at the interface of two proteins that regulate vesicle building and transport *viz*. guanine exchange factor (GEF) and adenosine ribosylation factor 1 (ARF1) thereby bringing the GDP/GTP exchange which is critical for the proper functioning of the ARF1GTPase to a halt.[5]

The combination of wide biological activity and unique structural features has made brefeldin A an attractive synthetic target. Impressive strategies and routes designed for the assessment of new synthetic methods have been reported by several groups.[6] Many of the approaches include macrolactonization for the formation of the 13-membered ring. Herein, we report the total synthesis of brefeldin A utilizing the HWE-olefination to form the macrocycle, cross-metathesis to create the C10-

C11 alkene in much the same way as Romo- and co-workers utilized these reactions in their synthesis of brefeldin A and Ru(II)-catalyzed enyne cyclization to construct the five-membered ring.

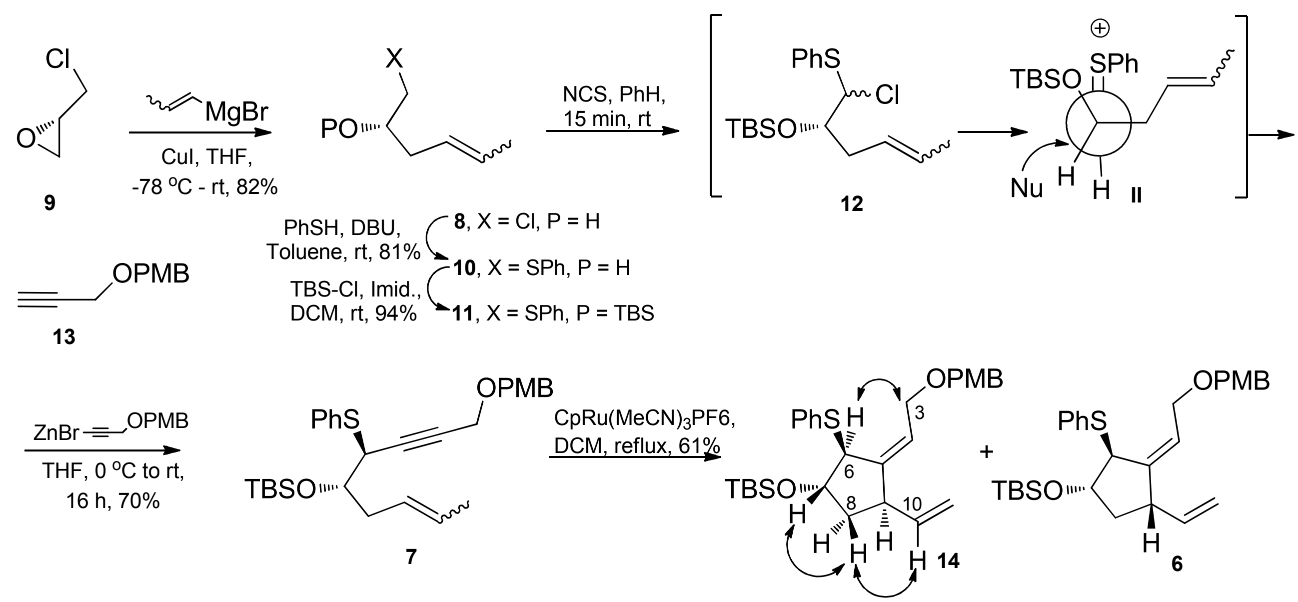
RESULTS AND DISCUSSION

The retrosynthetic analysis is depicted in Scheme 1. Brefeldin A was envisioned to be obtained from the phosphonate ester **2**, obtained by the cross-metathesis of terminal alkenes **3** and **4**. The alkene **4** can be derived from homopropargylic ether **5**. The alkene **3** can be obtained by a [2,3]-sigmatropic rearrangement from the sulfoxide derived from compound **6** followed by chemo- and stereoselective reduction of the internal double bond by C-7 hydroxyl-directed reduction. Sulfide **6** was envisioned to be obtained by Ru(II)-catalyzed cyclization of enyne **7** in its most stable ground-state conformation via putative transition state I. Enyne **7** can be obtained from chlorohydrin **8** which can readily be prepared from commercially available epichlorohydrin **9**.



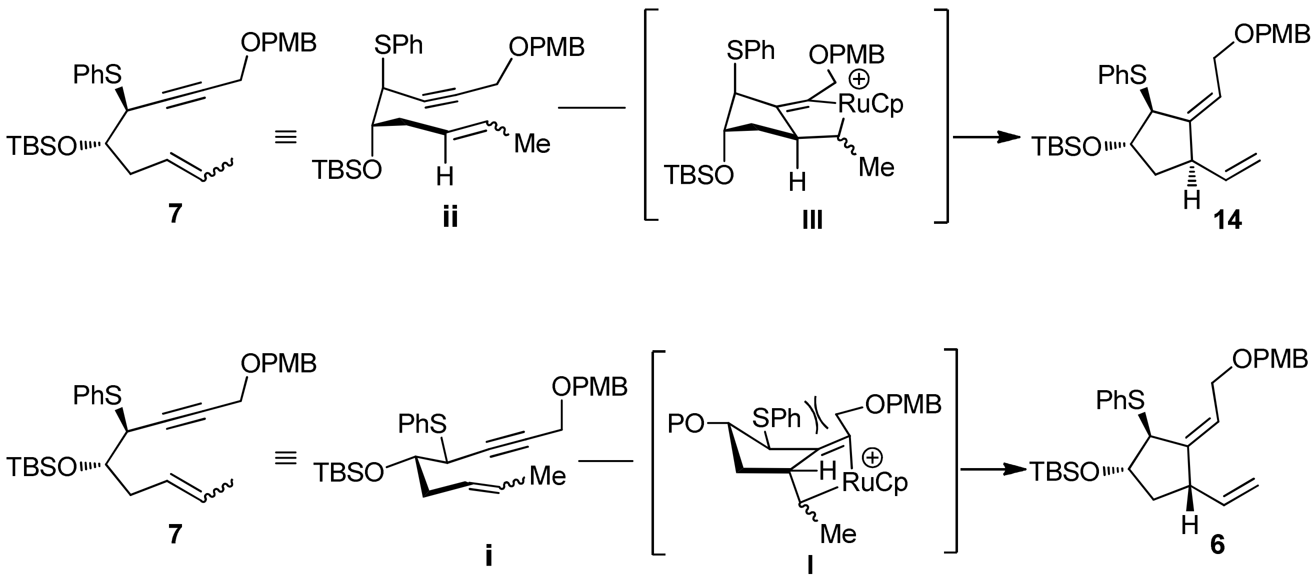
Scheme 1. Retrosynthetic Disconnection of Brefeldin A.

The synthesis began with (*S*)-epichlorohydrin **9**, obtained by hydrolytic kinetic resolution[7] of *rac*-epichlorohydrin, which on reaction with the commercially available 1-propenylmagnesium bromide (mixture of *E*- and *Z*-isomers) in the presence of copper-(I) Iodide furnished chlorohydrins **8** as an inseparable mixture of (*E*)- and (*Z*)-isomers in a 4.5:5.5 ratio. Displacement of chlorine in compound **8** by treatment with thiophenol in the presence of DBU yielded sulfide **10**. The hydroxyl group was protected under standard conditions to afford the silyl ether **11**. Reaction of sulfide **11** with *N*-chlorosuccinimide in anhydrous benzene afforded the α-chlorosulfide **12**, which without isolation[8] was reacted with the alkynylzinc bromide, prepared form propargylic ether **13** via reaction with *i*-PrMgCl·LiCl followed by transmetalation with $ZnBr_2$, to yield sulfide **7** highly stereoselectively. The structure assigned to compound **7** was based on precedent and was supported by NOE studies on the diene **14** resulting from cycloisomerization. The reaction outcome can be rationalized by invoking the putative transition state **II** where in the sulfenium ion, resulting from the reaction of chlorosulfide **12** with $ZnBr_2$, is eclipsed by the -OTBS group and the alkynylzinc nucleophile attacks it from the face opposite to the bulky alkenyl residue. The *E*/*Z*-mixture of propargylic sulfides was inseparable at this stage also and was taken ahead to the next step. The cycloisomerization of the 1,6-enyne[9] proceeded cleanly in the presence of 8 mol% of $CpRu(MeCN)_3PF_6$ in refluxing dichloromethane to furnish dienes **14** and **6** in a 13:1 ratio as an inseparable mixture, Scheme 2.



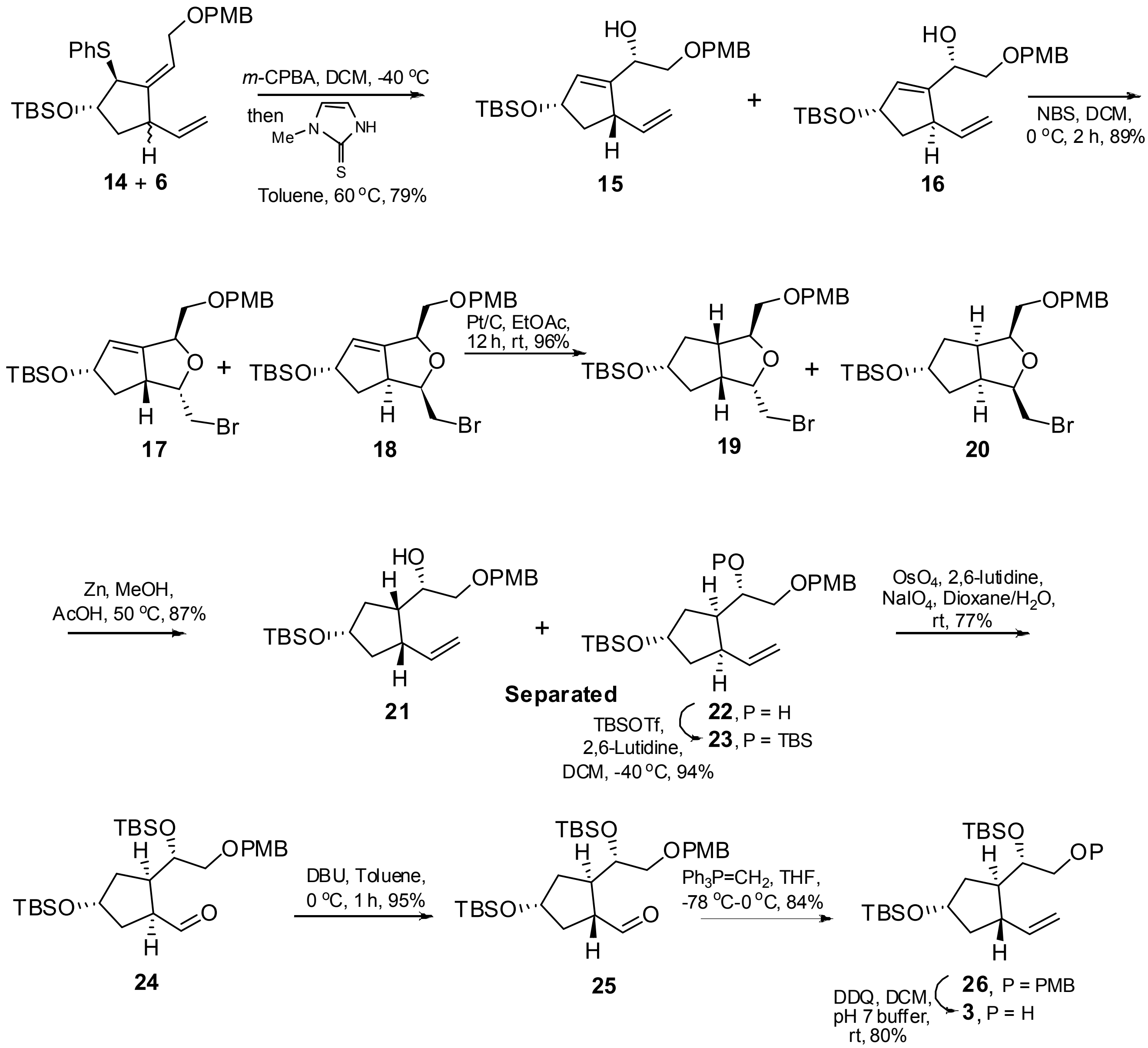
Scheme 2. Ru(II)-catalyzed Enyne Cyclization.

Solvents capable of coordinating to the ruthenium catalyst, such as acetone and DMF, were found to be unsatisfactory as very little conversion was observed. It is noteworthy that the olefin geometry of enyne **7** did not influence the outcome of cycloisomerization. The structure was assigned to the diene **14** based on NOE studies. Charecteristic NOE was observed between C10H and C8Hβ, C8Hβ and C7H and C6H and C3H. It was disappointing to note that the desired diene **6**, which was expected to be the predominant if not the sole product from the cycloisomerization, was only obtained as the minor product. The outcome can be rationalized by the reaction proceeding from the ground state conformation **ii** through the putative transition state **III**, to furnish diene **14**. The transition state **I**, that would result from the preferred, low energy ground state conformer **i**, probably suffers from A-1,3-interactions between the -SPh and -CH_2OPMB groups and therefore, diene **6** is obtained as the minor product, Scheme 3. Thus, the transition state energies are more important than ground state energies and dictate product outcome. The inseparable mixture of dienes was carried forward with the hope of separating the isomers at a later stage.



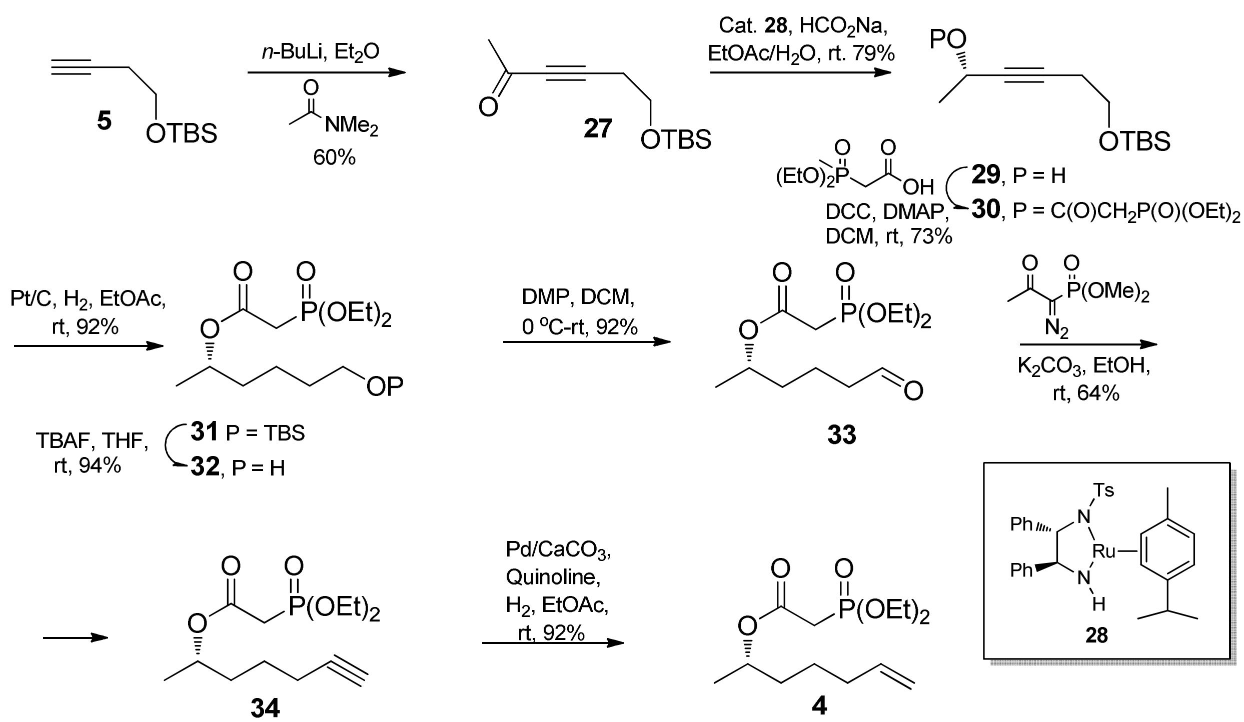
Scheme 3. Stereochemical Analysis of Enyne Cyclization.

The oxidation of the sulfide with *m*CPBA at low temperature furnished an equimolar epimeric mixture of sulfoxides which without isolation, upon warming in the presence of 2-thio-1-methylimidazole suffered Mislow-Evans rearrangement[10] to afford an inseparable mixture of allylic alcohols **15** and **16**. Thus the C-6 configuration is efficiently transferred to C-4. The outcome is independent of the configuration at sulfur since the epimeric mixture of sulfoxides give a single product. The next objective in the synthesis was the selective hydrogenation of the trisubstituted internal alkene by a hydroxyl directed hydrogenation. Toward this end, the hydroxyl group in **15** and **16** were protected under standard conditions to furnish the corresponding MOM ethers followed by deprotection of the silyl ether to furnish the required substrate. Attempted hydrogenation using Crabtree's catalyst[11] did not bear fruit. It was observed that both the alkenes were reduced when the reaction was allowed to proceed to completion and when the reaction was stopped midway, the terminal olefin was preferentially reduced. It is likely that the -OMOM/OPMB group coordinates with the Crabtree catalyst to reduce the terminal olefin. In another trial, we attempted to take advantage of steric factors in the selective dihydroxylation of the terminal alkene. If successful, the internal alkene **16** could be stereoselectively reduced by a hydroxyl directed hydrogenation, further oxidative cleavage of the diol would then afford an aldehyde which can be isomerised by a base to correct the configuration at C-9. Attempted selective dihydroxylation using either AD-mix-α[12] or AD-mix-β resulted in the dihydroxylation of the internal alkene in preference to the terminal alkene. Thus selective hydrogenation of the internal alkene and selective dihydroxylation of the terminal alkene were unsuccessful. We therefore, resorted to the bromoetherification reaction using C-4 hydroxyl group to protect the terminal double bond. Treatment of the mixture of alcohols **15** and **16** with *N*- bromosuccinimide in anhydrous dichloromethane proceeded cleanly to afford bromohydrins **17** and **18**. The configuration of the newly created stereogenic centers in bromohydrins **17** and **18** was not established since it was to be destroyed subsequently. The structure is assumed to be as depicted in Scheme 4. Hydrogenation of the alkene using Pt/C proceeded chemoselectively without hydrogenolysis of C-Br bond and -OPMB ether to yield bicyclic ethers **19** and **20**. Reductive cleavage using Vasella's protocol[13] yielded a separable mixture of terminal alkenes **21** and **22**. It is noteworthy that the synthesis was not any lengthier because the hydroxyl directed hydrogenation did not proceed as expected. It would have required theoretically, a) silyl ether deprotection, b) hydroxyl directed hydrogenation and c) reprotection of C-7 hydroxyl group to convert to convert the MOM ether of **16** to MOM ether of **22**. In the actual synthesis it required the same three steps a) bromoetherification, b) hydrogenation and c) reductive cleavage to convert compound **16** to compound **22**. Proceeding, the hydroxyl group in **22** was protected as its TBS ether **23** employing standard conditions. Oxidative cleavage of the alkene using Jin's protocol[14] furnished the aldehyde **24**. It is worthwhile to note that partial epimerization at C-9 was observed if the reaction was allowed to proceed for longer periods of time. Attempted one pot transformation of alkene **23** to the isomerized aldehyde **25** using pyridine in lieu of 2,6-lutidine for the oxidative cleavage, did not result in complete epimerization. In the event oxidative cleavage proceeded cleanly using 2,6-lutidine when the reaction was terminated after 12 h, subsequent epimerization using DBU afforded aldehyde **25** cleanly. One carbon homologation furnished the alkene **26**. Selective deprotection of the PMB group using DDQ under buffered conditions[15] furnished the key intermediate **3**, Scheme 4.



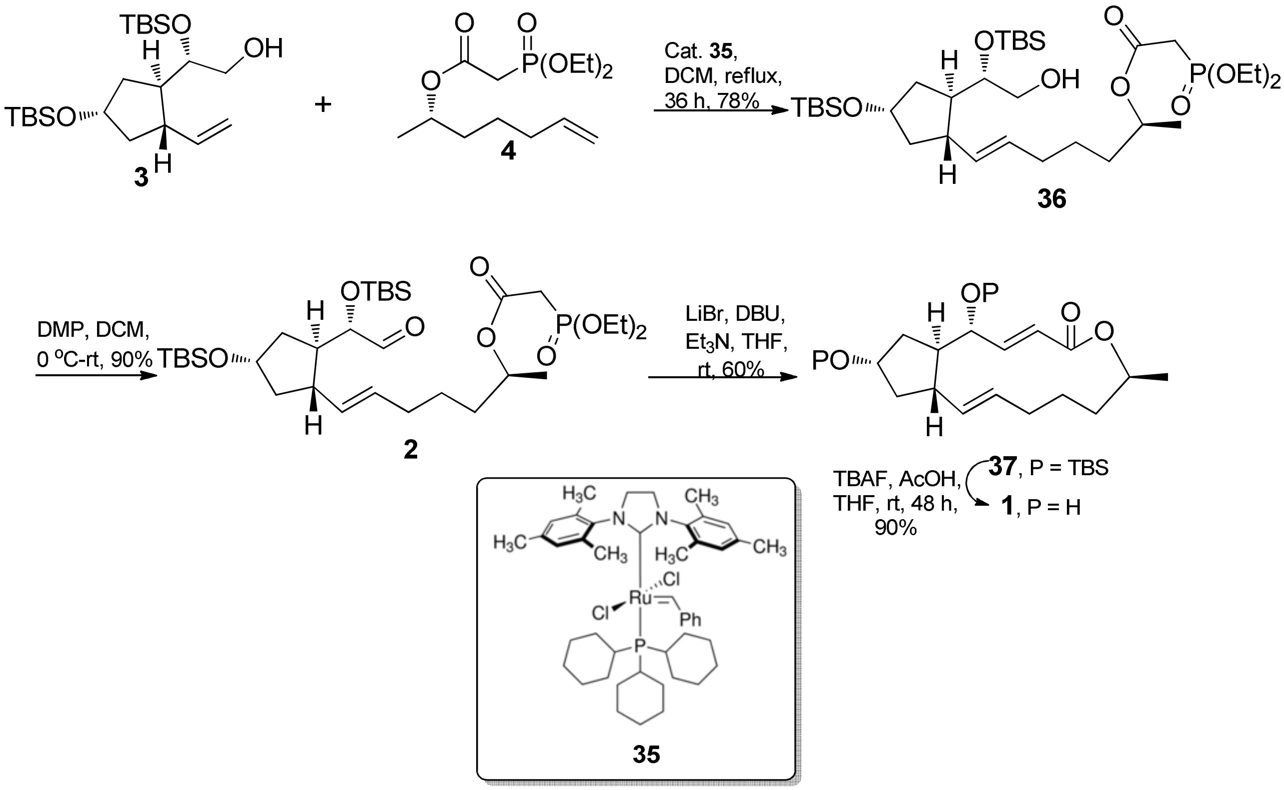
Scheme 4. Synthesis of Key Intermediate **3**.

The synthesis of the cross-metathesis partner **4** began from homopropargyl ether **5**. Reaction of the lithium acetylide of **5** with *N*,*N*-dimethylacetamide afforded the propargylic ketone **27**. Reduction[16] of the ketone using Noyori's catalyst **28** furnished alcohol **29** (93% ee). The enantiomeric purity of the alcohol **29** was ascertained by conversion to methoxymandelate ester following Trost's protocol.[17] The phosphonate ester **30** was prepared readily under standard conditions using DCC and catalytic DMAP. The triple bond in **30** was chemoselectively reduced without hydrogenolysis of the propargylic ester using Pt/C to yield silyl ether **31**. Deprotection of the silyl ether using TBAF afforded the alcohol **32** which on oxidation using Dess-Martin periodinane[18] yielded the aldehyde **33**. Alkynylation using Ohira-Bestman's protocol[19] furnished alkyne **34** cleanly. It is noteworthy that homologation of the aldehyde could be effected using K_2CO_3/EtOH without complications due to transesterification of the phosphonate ester. Partial reduction of the triple bond using Lindlar's catalyst yielded the alkene **4**,[20] scheme 5.



Scheme 5. Synthesis of Cross-metathesis Partner **4**.

With both the partners **3** and **4** becoming available, the cross-metathesis reaction was attempted using Grubbs' II generation catalyst[21] **35** to yield the alcohol **36** in an excellent yield (78%). The success of the cross-metathesis was all the more interesting in the context of the failure to effect cross-metathesis between a terminal alkene and methyl acrylate by Hale and co-workers.[6a] Oxidation using Dess-Martin periodinane yielded aldehyde **2** which was subjected to the Roush-Masamune modification[22] of the HWE olefination[20,23] to furnish the silyl ether of brefeldin, **37**. Deprotection of the silyl ethers under acidic conditions furnished brefeldin A, with physical characteristics in excellent agreement with those reported in the literature,[24] Scheme 6.



Scheme 6. Synthesis of Brefeldin A.

CONCLUSIONS

In summary, a stereoselective synthesis of brefeldin A is disclosed. The key steps of the synthesis include the stereoselective preparation of a propargylic sulfide using an α-chloro sulfide intermediate, stereoselective enyne cycloisomerization using a Ru(II) catalyst, Mislow-Evans rearrangement to create the C-4 carbinol center, selective reduction of an internal alkene by bromoether formation, cross-metathesis for the creation of C10-C11 double bond and macrolactonization by HWE olefination.

EXPERIMENTAL

Dry reactions were performed under an inert atmosphere using argon or nitrogen. All glassware apparatus used for reactions were perfectly oven dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; DCM, Toluene from CaH_2; MeOH from Mg cake; Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (100−200 mesh). Analytical thin-layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Optical rotations $[\alpha]^D$ were measured on a polarimeter and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in neat/KBr (as mentioned) and reported in wavenumber (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. ^1H NMR spectra were recorded at 300 or 400 or 500 MHz and ^{13}C NMR spectra at 75 or 100 or 125 MHz in $CDCl_3$ with the residual solvent signal as internal standard unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*S,Z*)-1-Chlorohex-4-en-2-ol and (*S,E*)-1-Chlorohex-4-en-2-ol (8): A solution of 1-propenylmagnesium bromide (0.5 M in THF, 24 mL, 12 mmol) was added dropwise to a suspension of CuI (228 mg, 1.2 mmol) in anhydrous THF (44 mL) maintained at -10 °C in a rb flask. After stirring at the same temperature for 45 min the mixture was cooled to -78 °C, and the solution of (*S*)-epichlorohydrin **9** (736 mg, 8 mmol) in anhydrous THF (8 mL) was slowly added to the above. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was quenched with saturated aq NH_4Cl solution (16 mL). The layers were separated and the aq layer was extracted with Et_2O (3x20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure to give **8** as a colourless liquid (879 mg, 6.56 mmol) in 82% yield. B.P 78-80 °C/20 mm of Hg, TLC: R_f 0.55 (9:1, hexanes:ethyl acetate). IR (neat): 3386, 3019, 2920, 1047, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.7-5.55 (m, 2H), 5.44-5.38 (m, 2H), 3.9-3.78 (m, 2H), 3.64 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.61 (dd, *J* = 11.1, 3.8 Hz, 1H), 3.51 (dd, *J* = 11.1, 6.7 Hz, 1H), 3.49 (dd, *J* = 11.1, 6.7 Hz, 1H), 2.38-2.34 (m, 2H), 2.28-2.24 (m, 2H), 1.69 (d, *J* = 6.2 Hz, 3H), 1.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.1, 127.4, 125.4, 124.4, 70.9, 70.8, 49.2, 49.0, 37.3, 31.6, 17.8, 12.7. MS (ESI): *m/z* 133 $[M-H]^+$.

(*S,Z*)-1-(Phenylthio)hex-4-en-2-ol and (*S,E*)-1-(Phenylthio)hex-4-en-2-ol (10): To a stirred mixture of DBU (0.94 mL, 6.3 mmol) and thiophenol (0.64 mL, 6.3 mmol) in toluene (12 mL) was added a solution of chloride **8** (844 mg, 6.4 mmol) in toluene (4 mL), and the resulting reaction mixture was stirred at rt for 12 h. The precipitated DBU.HCl salt was removed by filtration. The filtrate was washed with water (4 mL) and dried over anhydrous Na_2SO_4. Toluene was evaporated in vacuo and the residue was purified by column chromatography using 3% ethyl acetate/hexane (v/v) to give pure sulfide **10** in 81% yield (1.06 g, 5.1 mmol) as a colourless liquid. TLC: R_f 0.6 (9:1 hexanes:ethyl acetate). IR (neat): 3419, 3060, 3018, 1582, 1478, 1436, 1029, 692, 740 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.1 Hz, 4H), 7.28 (t, *J* = 7.1 Hz, 4H), 7.2 (t, *J* = 7.1 Hz, 2H), 5.68-5.56 (m, 2H), 5.46-5.39 (m, 2H), 3.78-3.76 (m, 2H), 3.16 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.12 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.9 (dd, *J* = 13.7, 8.0 Hz, 2H), 2.37-2.2 (m, 4H), 1.69 (d, *J* = 6.4 Hz, 3H), 1.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.4, 135.3, 129.9, 129.7, 128.9, 127.2, 126.3, 126.1, 125.1, 69.2, 69.0, 41.0, 40.9, 39.1, 33.4, 17.9, 12.9; MS (ESI): *m/z* 231 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{16}NaOS$: 231.0814, found: 231.0807.

(*S,Z*)-*tert*-Butyldimethyl(1-(phenylthio)hex-4-en-2-yloxy)silane and (*S,E*)-*tert*-Butyldimethyl(1-(phenylthio)hex-4-en-2-yloxy)silane (11): To a solution of alcohol **10** (1.01 g, 4.9 mmol) in anhydrous dichloromethane (16 mL) cooled to 0 °C was added imidazole (666 mg, 9.8 mmol) followed by TBS-Cl (735 mg, 4.9 mmol). The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was quenched by the addition of water (10 mL) and diluted with dichloromethane (20 mL). The layers were separated and the organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 1% ethyl acetate/hexane (v/v) to give the pure silyl ether **11** (1.48 g, 4.6 mmol) in 94% yield as a gummy oil. TLC: R_f 0.7 (9.5:0.5 hexanes:ethyl acetate). IR (neat): 2954, 2857, 1253, 1089, 775, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.4 Hz, 4H), 7.27 (t, *J* = 7.4 Hz, 4H), 7.16 (t, *J* = 7.4 Hz, 2H), 5.61-5.36 (m, 4H), 3.9-3.8 (m, 2H), 3.05-2.95 (m, 4H), 2.45-2.31 (m, 3H), 2.25 (dt, *J* = 13.8, 6.4 Hz, 1H), 1.66 (d, *J* = 5.7 Hz, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 18 H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 128.9, 128.7, 128.1, 126.7, 126.3, 125.7, 125.6, 71.4, 71.3, 40.2, 39.6, 33.9, 25.8, 18.0, 13.0, -4.5; MS (ESI): *m/z* 345 $[M+Na]^+$. HRMS (ESI): calcd for $C_{18}H_{31}OSSi$: 323.1859, found: 323.1871.

***tert*-Butyl(5*S*,6*S*,*Z*)-9-(4-methoxybenzyloxy)-6-(phenylthio)non-2-en-7-yn-5-yloxy)dimethyl silane and *tert*-Butyl(5*S*,6*S*,*E*)-9-(4-methoxybenzyloxy)-6-(phenylthio)non-2-en-7-yn-5-yloxy)dimethylsilane (7):** To a solution of alkyne (2.32 g, 13.2 mmol) in anhydrous THF (4.4 mL) cooled to 0 °C was added *i*-PrMgCl·LiCl (1.5 M in THF, 8.8 mL, 13.2 mmol) and the mixture was stirred for 30 min at the same temperature. To the so generated Grignard reagent, $ZnBr_2$ (1.5 M in THF, 9.6 mL, 14.4 mmol) was added at 0 °C and stirred for 30 min. To the above organozinc reagent maintained at 0 °C was added a solution of chlorosulfide (4.4 mmol) in anhydrous benzene (44 mL), prepared by the dropwise addition of a solution of the sulfide **11** (1.41 g, 4.4 mmol) in anhydrous benzene (22 mL) to the solution of *N*-chlorosuccinimide (585 mg, 4.4 mmol) in benzene (22 mL) at ambient temperature and stirring for a period of 15 min. The reaction mixture was stirred gradually allowing it to attain rt and stirred further for a period of 5 h when TLC examination indicated complete consumption of the chlorosulfide **12**. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated aq NH_4Cl solution (10 mL). It was allowed to warm to rt and diluted with Et_2O (15 mL), the layers were separated and the aq layer extracted with Et_2O (3×10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using 2% ethyl acetate/hexane (v/v) as the eluent to afford the pure product **7** (1.48 g, 3 mmol) in 70% yield as a liquid.

TLC: R_f 0.5 (9.5:0.5 hexanes:ethyl acetate). IR (neat): 2930, 2855, 1611, 1512, 1465, 1249, 1085, 1035, 832 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 8.3, 1.2 Hz, 4H), 7.32-7.28 (m, 4H), 7.25-7.21 (m, 6H), 6.86 (d, *J* = 8.5 Hz, 4H), 5.62-5.4 (m, 4H), 4.46 (d, *J* = 11.5 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 2H), 4.15-4.13 (m, 4H), 4.1-3.98 (m, 2H), 3.95-3.85 (m, 2H), 3.8 (s, 6H), 2.7-2.4 (m, 4H), 1.66 (d, *J* = 6.2 Hz, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 0.9 (s, 18H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 159.1, 134.8, 132.0, 131.9, 129.6, 129.4, 128.7, 128.3, 127.1, 126.7, 126.5, 125.7, 113.6, 84.6, 84.5, 81.2, 74.1, 74.0, 70.5, 56.9, 55.0, 45.6, 37.4, 31.8, 25.7, 18.0, 13.0, -4.5, -4.6, -4.7; MS (ESI): *m/z* 497 $[M+H]^+$. HRMS (ESI): calcd for $C_{29}H_{44}O_3NSSi$: 514.2 805, found: 514.2798.

***tert*-Butyl((1*S*,2*S*,4*R*,*Z*)-3-(2-(4-methoxybenzyloxy)ethylidine)-2-(phenylthio)-4-vinylcyclopentyloxy)dimethylsilane (14) and *tert*-Butyl((1*S*,2*S*,4*S*,*Z*)-3-(2-(4-methoxybenzyloxy)ethylidine)-2-(phenylthio)-4-vinylcyclopentyloxy)dimethylsilane (6):** To a solution of the enyne **7** (1.43 g, 2.9 mmol) in anhydrous dichloromethane (29 mL) under nitrogen was added $CpRu(CH_3CN)_3PF_6$ (98.6 mg, 0.23 mmol, 8 mol%). The resulting mixture was stirred at reflux for 24 h. The solvent was removed under reduced pressure, the residue was diluted with a minimum amount of DCM /Et_2O (1:1) and passed through a small plug of silica gel using ether as the eluent. The filtrate was concentrated under reduced pressure, and the residue was further purified by column chromatography using 2% ethyl acetate/hexane (v/v) to afford the cyclic product **14** and **6** as an inseparable mixture in a 13:1 ratio (934 mg, 1.88 mmol) in 61% yield as a liquid. TLC: R_f 0.55 (9.5:0.5 hexanes:ethyl acetate). IR (neat): 3070, 2930, 2855, 1614, 1512, 1467, 1359, 1249, 1067, 999, 833 cm^{-1}. ^1H NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$): δ 7.34-7.24 (m, 14H), 6.87 (d, *J* = 8.6 Hz, 4H), 5.7-5.62 (m, 2H), 5.6-5.51*(m, 2H), 5.1-5.03 (m, 2H), 5.02-4.97* (m, 2H), 4.5 (d, *J* = 11.5 Hz, 2H), 4.46 (d, *J* = 11.5 Hz, 2H), 4.25-4.2 (m, 4H), 4.14* (d, *J* = 2.1 Hz, 1H) 4.12 (d, *J* = 3.3 Hz, 1 H), 3.98-3.96 (m, 2H), 3.8 (s, 6H), 3.44-3.36 (m, 1H), 3.18-3.12* (m, 1H), 2.08-2.0 (m, 2H), 1.83 (ddd, *J* = 12.9, 7.3, 1.8 Hz, 2H), 0.82* (s, 9H) 0.8 (s, 9H), -0.08* (s, 3H), -0.11* (s, 3H), -0.149 (s, 3H), -0.151 (s, 3H); ^{13}C NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 100 MHz, $CDCl_3$): δ 159.1, 145.5, 144.8*, 141.4*, 140.7, 135.3, 133.4*, 132.5*, 131.9*, 131.6, 130.5, 129.7*, 129.4, 128.9, 128.6*, 127.7*, 127.1, 125.6, 124.7*, 115.4, 113.7, 76.9, 72.4*, 71.6, 67.3, 67.1*, 57.0*, 56.4*, 55.8, 55.2, 47.0*, 46.6, 39.8*, 38.9, 25.7*, 25.6, 17.8, -4.9; MS (ESI): *m/z* 519 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{44}O_3NSSi$: 514.2805, Found: 514.2782.

(*S*)-1-((3*S*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-vinylcyclopent-1-enyl)-2-(4-methoxybezyl oxyethanol (15) and (*S*)-1-((3*S*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-vinylcyclopent-1-enyl)-2-(4-methoxybezyl oxyethanol (16): To a solution of **14** and **6** (793 mg, 1.6 mmol) in dichloromethane (7 mL) cooled to -40 ºC was added *m*CPBA (393 mg, 1.6 mmol) and the reaction mixture stirred at the same temperature for another 30 min. Toluene (7 mL) and 2-mercapto-1-methyl-imidazole (218 mg, 1.92 mmol) were added. The reaction mixture was stirred at 60 ^{o}C for 2 h and then quenched by adding saturated aq $NaHCO_3$ (3 mL). The mixture was diluted with dichloromethane (10 mL) and the layers separated. The combined organic layers were washed successively with water (10 mL), brine (10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 10% ethyl acetate/hexanes (v/v) as the eluent to afford the product **15** and **16** as an inseparable mixture (509 mg, 1.26 mmol) in 79% yield as a liquid. TLC: R_f 0.3 (8.8:1.2 hexanes:ethyl acetate); IR (neat): 3449, 2927, 2856, 1612, 1512, 1463, 1357, 1249, 1174, 1045, 1001, 834 cm^{-1}. ^1H NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 5.81 (dd, *J* = 3.5, 1.8 Hz, 2H), 5.75-5.65* (m, 1H), 5.57 (ddd, *J* = 16.8, 9.9, 9.1 Hz, 1H), 5.14-5.05* (m, 2H), 4.98 (dd, *J* = 16.8, 1.5, Hz, 1H), 4.96 (dd, *J* = 9.9, 1.5 Hz, 1H), 4.94-4.89 (m, 2H), 4.51 (d, *J* = 11.7 Hz, 2H), 4.48 (d, *J* =11.7 Hz, 2H), 4.34 (brd, *J* = 7.0 Hz, 2H), 3.8 (s, 6H), 3.65* (dd, *J* = 9.6, 3.1 Hz, 1H), 3.6 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.46* (dd, *J* = 9.6, 8.1 Hz, 1H), 3.4 (dd, *J* = 9.7, 8.0 Hz, 1H), 3.33-3.24 (m, 2H), 2.52 (d, *J* = 2.4 Hz, 2H), 2.03-1.97 (m, 4H), 0.88 (s, 18H), 0.06 (s, 12H); ^{13}C NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 126 MHz, $CDCl_3$): δ 159.3, 147.3, 141.4*, 140.9, 129.9, 129.4, 115.2*, 115.0, 113.8, 76.2, 73.0*, 72.8, 72.2, 68.9, 55.2, 49.2*, 48.9, 42.0, 41.3*, 25.9, 18.2, -4.5, -4.6; MS (ESI): *m/z* 427 $[M+Na]^+$. HRMS (ESI): calcd for $C_{23}H_{36}O_4NaSi$: 427.2275; found; 427.2245.

((3*aR*,5*S*)-3-(Bromoethyl)-1-((4-methoxybenzyloxy)methyl)-3,3*a*,4,5-tetrahydro-1H-cyclo penta(*c*)furan-5-yloxy)(*tert*-butyl)dimethyisilane (17) and ((3*aS*,5*S*)-3-(Bromoethyl)-1-((4-methoxybenzyloxy)methyl)-3,3*a*,4,5-tetrahydro-1H-cyclopenta(*c*)furan-5-yloxy)(*tert*-butyl)dimethyisilane (18): To a stirred solution of the mixture of alcohols **15** and **16** (464 mg, 1.15 mmol) in anhydrous dichloromethane (12 mL) maintained at 0 ^{o}C under N_2 atmosphere was added recrystallised *N*-bromosuccinimide (204 mg, 1.15 mmol) and the resulting mixture was stirred for 1 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography using 10% ethyl acetate/hexane (v/v) as the eluent to afford the product **17** and **18** (491 mg, 1.02 mmol) as an inseparable mixture of diastereomers in 89% yield as a liquid. TLC: R_f 0.5 (8.8:1.2 hexanes:ethyl acetate); IR (neat): 2929, 2856, 1611, 1546, 1513, 1463, 1249, 1171, 1077, 1041, 831 cm^{-1}. ^{1}H NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 5.58-5.52 (m, 2H), 5.12-5.08* (m, 1H), 5.07-5.03 (m, 1H), 4.75-4.7 (m, 1H), 4.69-4.66* (m, 1H), 4.56 (d, *J* = 11.8 Hz, 2H), 4.49 (d, *J* = 11.8 Hz, 2H), 3.81 (s, 6H), 3.6-3.37 (m, 12H), 1.99 (dd, *J* = 13.5, 6.7 Hz, 2H), 1.83 (dt, *J* = 13.5, 6.6 Hz, 2H), 0.89* (s, 9H), 0.88 (s, 9H), 0.10* (s, 3H), 0.09* (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 100 MHz, $CDCl_3$): δ 159.1, 154.8, 130.1*, 130.0, 129.3, 129.1*, 122.8, 113.7, 83.1*, 83.0, 81.7, 75.8*, 74.7, 73.0*, 72.9, 71.9*, 71.2, 55.2, 55.0, 53.1*, 38.8, 34.1*, 34.0, 25.9, 18.3, 18.2*, -4.6, -4.7; MS (ESI): *m/z* 505/507 $[M+Na]^+$. HRMS (ESI): calcd for $C_{23}H_{39}O_4NBrSi$: 500.1826, found: 500.1827.

(3*aR*,5*R*,6*aR*)-1-(Bromoethyl)-3-((4-methoxybenzyloxy)methyl)hexahydro-1H-cyclopenta(*c*)furan-5-yloxy)*tert*-butyl)dimethylsilane (19) and (3*aR*,5*R*,6*aS*)-1-(Bromoethyl)-3-((4-methoxybenzyloxy)methyl)hexahydro-1H-cyclopenta(c)furan-5-yloxy)*tert*-butyl)dimethylsilane (20): To a solution of the mixture of bromoethers **17** and **18** (457 mg, 0.95 mmol) in ethyl acetate (9.5 mL), Pt/C (46 mg, 10% w/w) was added. The resulting suspension was placed under a hydrogen atmosphere (balloon) and stirred vigorously for 12 h at rt. The solution was then filtered through Celite and the filtrate was evaporated under reduced pressure to afford compounds **19** and **20** (438 mg, 0.91

mmol) as an inseparable mixture in 96% yield as a liquid. TLC: R_f 0.6 (8.8:1.2 hexanes:ethyl acetate); IR (neat): 2960, 2856, 1614, 1512, 1464, 1363, 1258, 1173, 1038, 801 cm^{-1}. ^{1}H NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.3 Hz, 4H), 6.85 (d, *J* = 8.3 Hz, 4H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.52* (d, J = 11.5 Hz, 1H), 4.5* (d, J = 11.5 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.34 (quintet, *J* = 3.8 Hz, 2H), 4.28-4.23 (m, 1H), 4.22-4.18* (m, 1H), 3.91-3.87 (m, 2H), 3.8 (s, 6H), 3.51 (dd, *J* = 9.9, 6.8 Hz, 2H), 3.46 (dd, *J* = 9.9, 4.7 Hz, 2H), 3.42 (dd, *J* = 9.6, 5.3 Hz, 2H), 3.29 (dd, *J* = 9.6, 8.0 Hz, 2H), 2.94 (ddd, *J* = 14.4, 8.3, 6.2 Hz, 1H), 2.76 (ddd, *J* = 12.9, 4.6, 4.1 Hz, 1H), 2.50-2.44* (m, 1H), 2.36-2.27* (m, 1H), 1.93 (ddd, *J* = 12.9, 8.5, 2.8 Hz, 2H), 1.67 (dt, *J* = 14.4, 4.8 Hz, 2H), 1.57-1.5 (m, 4H), 0.9 (s, 18H), 0.03 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (13:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 126 MHz, $CDCl_3$): δ 159.1, 130.0, 129.3, 129.1*, 113.7, 85.6, 79.1, 75.1, 73.0, 69.8, 55.1, 47.4, 45.3, 42.3, 35.4, 35.1*, 34.9, 25.8, 18.0, -4.7, -4.8; MS (ESI): *m/z* 507/509 $[M+Na]^+$. HRMS (ESI): calcd for $C_{23}H_{41}O_4N$ BrSi: 502.1982, found: 502.1978.

(*S*)-1-((1*R*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-vinylcyclopentyl)-2-(4-methoxybenzyloxy)ethanol (22): The mixture of compounds **19**, **20** (411 mg, 0.85 mmol) and activated Zn dust (1.37 g, 21.2 mmol) in MeOH (8.5 mL), AcOH (0.85 mL) was stirred at 50 °C for 1 h and then filtered through Celite. The filtrate was poured into saturated aq $NaHCO_3$ solution (5 mL) and extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane(v/v) to afford the alcohol **22** (276 mg, 0.68 mmol) in 80% yield as a liquid and subsequently **21** (21 mg, 0.05 mmol, 6%) as a liquid. **22** TLC: R_f 0.35 (8.8:1.2 hexanes:ethyl acetate); $[\alpha]^{25}_D$ = +0.22 (*c* 0.4, $CHCl_3$). IR (neat): 3450, 2928, 2855, 1614, 1513, 1464, 1362, 1249, 1062, 1045, 963, 831 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.87-5.8 (m, 1H), 4.97-4.93 (m, 2H), 4.46 (s, 2H), 4.39-4.35 (m, 1H), 3.8 (s, 3H), 3.82-3.78 (m, 1H), 3.48 (dd, *J* = 9.3, 3.0 Hz, 1H) , 3.29 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.83-2.76 (m, 1H), 2.3-2.23 (m, 1H), 1.88 (ddd, *J* = 13.4, 9.7, 6.1 Hz, 1H), 1.78-1.74 (m, 2H), 1.71 (ddd, *J* = 13.4, 7.9, 0.9 Hz, 1H), 0.9 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2, 139.8, 130.1, 129.3, 114.7, 113.7, 73.0, 72.8, 72.7, 70.7, 55.2, 44.3, 42.9, 42.7, 36.6, 25.8, 18.1, -4.7; MS (ESI): *m/z* 424 $[M+NH_4]^+$. HRMS (ESI): calcd for $C_{23}H_{38}O_4NaSi$: 429.2431, found: 429.2422.

(*S*)-1-((1*S*,2*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-vinylcyclopentyl)-2-(4-methoxybenzyloxy)ethanol (21): TLC: R_f 0.25 (8.8:1.2 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -11.2 (*c* 0.4, $CHCl_3$). IR (neat): 3450, 2928, 2855, 1614, 1513, 1464, 1362, 1249, 1062, 1045, 963, 831 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.84 (ddd, *J* = 17.2, 10.2, 9.0 Hz, 1H), 5.1-5.0 (m, 2H), 4.5 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.4-4.35 (m, 1H) 3.81 (s, 3H), 3.67-3.62 (m, 1H), 3.49 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.34 (dd, *J* = 9.4, 7.7 Hz, 1H), 3.02-2.95 (m, 1H), 2.42-2.34 (m, 1H), 1.91-1.86 (m, 1H), 1.79-1.74 (m, 1H), 1.53-1.47 (m, 2H), 0.9 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 139.4, 130.1, 129.2, 114.9, 113.7, 73.5, 73.0, 72.5, 71.5, 55.2, 44.3, 43.7, 42.1, 37.1, 25.8, 18.0, -4.7; MS (ESI): *m/z* 424 $[M+NH_4]^+$. HRMS (ESI): calcd for $C_{23}H_{38}NaO_4Si$: 429.2431, found: 429.2418.

***tert*-Butyl((1*S*,3*R*,4*R*)-3-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)ethyl-4-vinylcyclopentyloxy)dimethylsilane (23):** To a solution of alcohol **22** (243 mg, 0.6 mmol) in anhydrous dichloromethane (6 mL) cooled to -40 ^{o}C was added 2,6-lutidine (64 mg, 0.6 mmol) followed by TBSOTf (158 mg, 0.6 mmol). The reaction mixture was stirred at the same temperature for 30 min, quenched by the addition of water (5 mL) and diluted with dichloromethane (5 mL). The layers were separated and the organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 1% ethyl acetate/hexane (v/v) to give pure silyl ether **23** (291 mg, 0.56 mmol) in 94% yield as a gummy oil. TLC: R_f 0.7 (9.5:0.5 hexanes:ethyl acetat e). $[\alpha]^{25}_D$ = -3.63 (*c* 0.4, $CHCl_3$). IR (neat): 2954, 2927, 2855, 1637, 1512, 1463, 1380, 1250, 1101, 1040 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.8-5.72 (m, 1H), 4.94-4.88 (m, 2H), 4.41 (s, 2H), 4.37-4.32 (m, 1H), 3.8 (s, 3H), 3.79- 3.75 (m, 1H), 3.37 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.32 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.8-2.72 (m, 1H), 2.47-2.39 (m, 1H), 1.85-1.68 (m, 4H), 0.88 (s, 9H), 0.86 (s, 9H) 0.04 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 139.7, 130.5, 129.2, 114.7, 113.6, 73.5, 72.7, 72.6, 72.5, 55.2, 44.4, 43.9, 43.2, 37.5, 26.0, 25.9, 18.2, 18.1, -3.6, -4.5, -4.7; MS (ESI): *m/z* 543 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{53}O_4Si_2$: 521.3477, found: 521.3482.

(1*S*,2*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)ethyl)cyclopentanecarbaldehyde (24): To a solution of compound **23** (270 mg, 0.52 mmol) in dioxane-water (3:1, 5.2 mL) were added 2,6-lutidine (0.12 mL, 1.04 mmol), OsO_4 (0.04 M in toluene, 0.26 mL, 0.01 mmol) and $NaIO_4$ (443 mg, 2.08 mmol). The reaction was stirred at 25 °C for 12 h. After the reaction was completed, water (7 mL) and dichloromethane (14 mL) were added. The organic layer was separated and the aq layer was extracted using dichloromethane (3x7 mL). The combined organic layer were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography using 3% ethyl acetate/hexane (v/v) to afford aldehyde **24** (208 mg, 0.4 mmol) in 77% yield as a colorless oil. TLC: R_f 0.4 (9.5:0.5 hexanes:ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (d, *J* = 2.5 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.4 (d, *J* = 11.4 Hz, 1H), 4.4-4.35 (m, 1H), 4.13-4.09 (m, 1H), 3.8 (s, 3H), 3.41 (dd, *J* = 9.4, 5.0 Hz, 1H), 3.33 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.05-2.98 (m, 1H), 2.89-2.81 (m, 1H), 2.13 (ddd, *J* = 13.1, 6.7, 5.4 Hz, 1H), 1.8-1.66 (m, 3H), 0.87 (s, 9H), 0.83 (s, 9H) , 0.04 (s, 3H), 0.036 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 159.1, 130.1, 129.2, 113.7, 73.4, 72.9, 72.3, 70.8, 55.2, 51.4, 44.5, 36.9, 36.8, 25.9, 25.8, 18.1, 18.0, -4.7; MS (ESI): *m/z* 545 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{50}O_5NaSi_2$: 545.3089 found: 545.3093.

(1*R*,2*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)ethyl)cyclopentanecarbaldehyde (25): To a solution of aldehyde **24** (187 mg, 0.36 mmol) in toluene (1.8 mL) cooled to 0 °C was added DBU (6 mg, 0.036 mmol) and the solution was stirred for 1 h. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 3% ethyl acetate/hexane (v/v) to give pure aldehyde **25**

(177 mg, 0.34 mmol) in 95% yield as a liquid. TLC: R_f 0.4 (9.5:0.5 hexanes:ethyl acetate). $[\alpha]^{25}_D = +1.6$ (*c* 0.4, $CHCl_3$). IR (neat): 2954, 2930, 2856, 1723, 1615, 1513, 1466, 1361, 1251, 1092, 1040, 834 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.61 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.32-4.28 (m, 1H), 3.89 (td, *J* = 5.7, 3.8 Hz, 1H), 3.8 (s, 3H), 3.35 (dd, *J* = 9.6, 5.7, Hz, 1H), 3.32 (dd, *J* = 9.6, 5.7 Hz, 1H), 2.78 (dddd, *J* = 11.9, 7.9, 3.8, 2.4 Hz, 1H), 2.54 (ddt, *J* = 11.9, 6.2, 2.4 Hz, 1H), 1.96-1.88 (m, 2H), 1.72 (ddd, *J* = 12.6, 9.6, 4.2 Hz, 1H), 1.65-1.59 (m, 1H), 0.86 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.025 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 159.1, 130.2, 129.2, 113.6, 73.6, 73.3, 72.8, 72.5, 55.2, 52.1, 41.3, 37.8, 35.8, 25.8, 25.7, 18.1, 17.9, -3.9, -4.8, -4.9; MS (ESI): *m/z* 545 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{50}O_5NaSi_2$: 545.3089 found: 545.3092.

***tert*-Butyl((1*S*,3*R*,4*S*)-3-((S)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)ethyl-4-vinylcyclopentyloxy)dimethylsilane (26):** *n*-Butyl lithium (2.5 M in hexane, 0.24 mL, 0.6 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (224 mg, 0.63 mmol) in anhydrous THF (3 mL) cooled to -78 ºC. After stirring the mixture for 1.5 h at 0 ºC, a solution of aldehyde **25** (156 mg, 0.3 mmol) in THF (2 mL) was added to the orange colored ylide solution at -78 ºC. The solution was warmed to 0 ºC, stirred for 0.5 h and then quenched with saturated aq NH_4Cl (2 mL). The mixture was diluted with water (5 mL) and extracted with EtOAc (3x5 mL). The combined organic layers were dried over Na_2SO_4. Purification by silica gel column chromatography using 1% ethyl aceta te/hexane(v/v) afforded compound **26** as a liquid (130 mg, 0.25 mmol) in 84% yield. TLC: R_f 0.7 (9.5:0.5 hexanes:ethyl acetate). $[\alpha]^{25}_D = -18.3$ (*c* 0.4, $CHCl_3$). IR (neat): 2954, 2927, 2855, 1637, 1512, 1463, 1380, 1250, 1101, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.75 (ddd, *J* = 17.0, 10.0, 1.5 Hz, 1H), 4.94 (dd, *J* = 17.0, 1.9 Hz, 1H), 4.89 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.23-417 (m, 1H), 3.85-3.81 (m, 1H), 3.8 (s, 3H), 3.32 (dd, *J* = 9.4, 6.2, Hz, 1H), 3.27 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.39-2.31 (m, 1H), 2.1-2.0 (m, 2H), 1.9-1.83 (m, 1H), 1.51-1.4 (m, 2H) 0.87 (s, 9H), 0.88 (s, 9H) 0.05 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0, 142.9, 130.4, 129.1, 113.6, 113.4, 74.1, 73.3, 72.8, 70.4, 55.2, 46.1, 43.8, 42.9, 34.5, 25.9, 18.2, 18.1, -3.7, -4.7, -4.8; MS (ESI): *m/z* 543 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{53}O_4Si_2$: 521.3477, found: 521.3482.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-((1*R*,2*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-2-vinyl cyclopeantyl)ethanol (3): To a solution of alkene **26** (104 mg, 0.2 mmol) in dichloromethane (1.8 mL) and pH 7 buffer (0.2 mL) cooled to 0 °C was added DDQ (68 mg, 0.3 mmol). The reaction mixture was stirred at the same temperature for 1 h and then diluted with water (5 mL). The aq phase was extracted with EtOAc (3x5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 15% ethyl acetate/hexane (v/v) afforded **3** (64 mg, 0.16 mmol) in 80% yield as a colorless oil. TLC: R_f 0.25 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -23.2 (*c* 0.4, $CHCl_3$). IR (neat): 2955, 2930, 2891, 2857, 1639, 1466, 1254 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddd, *J* = 17.0, 10.0, 1.5 Hz, 1H), 4.95 (dd, *J* = 17.2, 1.9 Hz, 1H), 4.92 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.24-4.19 (m, 1H), 3.71 (td, *J* = 5.0, 3.5 Hz, 1H), 3.52 (d, *J* = 5.0 Hz, 2H), 2.34-2.26 (m, 1H), 2.1-2.0 (m, 2H), 1.82 (ddd, *J* = 13.1, 9.0, 6.5 Hz, 1H), 1.65-1.58 (m, 1H), 1.45 (ddd, *J* = 12.8, 8.6, 5.6 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H) 0.03 (s, 6H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.1, 113.5, 73.2, 73.1, 66.3, 46.2, 44.3, 42.9, 36.1, 25.9, 25.8, 18.1, -3.9, -4.5, -4.7; MS (ESI): *m/z* 423 $[M+Na]^+$. HRMS (ESI): calcd for $C_{21}H_{44}O_3NaSi_2$: 423.2721 found: 423.2730.

6-(*tert*-Butyldimethylsilyloxy)hex-3-yn-2-one (27): To a solution of silyl ether **5** (1.47 g, 8 mmol) in anhydrous Et_2O (26 mL) cooled to -78 °C was added *n*BuLi (2.5 M in hexanes, 3.2 mL, 8 mmol). The reaction mixture was stirred for 30 min before addition of *N*,*N*-dimethylacetamide (0.93 mL, 10 mmol) in 7 portions over 35 min. The reaction was then warmed to 0 °C and stirred for 3 h before being quenched with water (20 mL) and acidified with aq NH_4Cl (6 mL). The reaction mixture was then extracted with Et_2O (2x15 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography using 5% ethyl acetate/hexane (v/v) to afford pure ketone **27** (1.08 g, 4.8 mmol) in 60% yield as a yellow liquid. TLC: R_f 0.25 (9.5:0.5 hexanes:ethyl acetate). IR (neat): 2931, 2859, 2213, 1679, 1109 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.77 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 0.9 (s, 9H), 0.07 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.6, 90.9, 81.9, 60.7, 32.6, 25.7, 23.2, 18.2, -5.3; MS (ESI): *m/z* 249 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{23}O_2Si$: 227.1461 found: 227.1456.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)hex-3-yn-2-ol (29): To a solution of sodium formate (6.6 g, 97 mmol) in water (66 mL) was added the solution of freshly prepared ketone **27** (994 mg, 4.4 mmol) in ethyl acetate (66 mL) followed by Ru[(1*S*,2*S*)-*p*TsNCH(Ph)CH(Ph)NH] (η6-*p*-cymene) **28** (0.108 g, 2 mol%) and ionic liquid (2-3 drops) at rt. The reaction was stirred for 20 h and the aq phase was extracted with EtOAc (2x50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After purification on silica gel column chromatography using 10% ethyl acetate/hexane (v/v) compound **29** was obtained as a liquid (791 mg, 3.47 mmol) in 79% yield. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -25.2 (*c* 0.4, $CHCl_3$). IR (neat): 3336, 2932, 2859, 1106 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.49 (qt, *J* = 6.5, 1.9 Hz, 1H), 3.7 (t, *J* = 7.1 Hz, 2H), 2.41 (td, *J* = 7.1, 1.9 Hz, 2H), 1.9 (bs, 1H, OH), 1.41 (d, *J* = 6.5 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 83.4, 80.6, 61.6, 57.8, 25.6, 24.3, 22.7, 18.0, -5.5; MS (ESI): *m/z* 251 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{28}O_2NSi$: 246.1883 found: 246.1872.

(2*R*)-6-(*tert*-Butyldimethylsilyloxy)hex-3yn-2yl-2-methoxy-2-phenylacetate (29a): To a soluti on of racemic alcohol (11.4 mg, 0.05 mmol), obtained by treatment of compound **27** with $NaBH_4$, in dichloromethane (0.5 mL) was added (*R*)-(-)-α-methoxyphenylacetic acid (9.1 mg, 0.055 mmol), DMAP (1 mg, 15 mol%) and DCC (11.3 mg, 0.05 mmol) at 0 °C. The reaction mxiture was stirred for 2 h at rt and the solvent was evaporated in vacuo**.** The crude product was triturated with cold ether (2 mL) to afford compound **29a** in 90% yield as a liquid. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (t, *J* = 6.2 Hz, 4H), 7.37-7.33 (m, 6H), 5.52-5.45 (m, 2H), 4.77 (s, 1H), 4.76 (s, 1H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.6 (t, *J* = 7.0 Hz, 2H), 3.41 (s, 6H), 2.4 (td, *J* = 7.0, 1.8 Hz, 2H), 2.32 (td, *J* = 7.1, 1.9 Hz, 2H), 1.46 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.9 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.04 (s, 6H).

(*R*)-((*S*)-6-(*tert*-Butyldimethylsilyloxy)hex-3yn-2yl)2-methoxy-2-phenylacetate (29b): To a solution of alcohol **29** (11.4 mg, 0.05 mmol) in DCM (0.5 mL) was added (*R*)-(-)-α-methoxyphenylacetic acid (9.1 mg, 0.055 mmol), DMAP (1 mg, 15 mol%) and DCC (11.3 mg, 0.05 mmol) at 0 ^{o}C. The reaction mxiture was stirred for 2 h at rt and the solvent was evoparated in vacuo. The crude product was triturated with cold ether to afford compound **29b** in 90% yield as a liquid. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.37-7.33 (m, 3H), 5.52-5.45 (m, 1H), 4.76 (s, 1H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.41 (s, 3 H), 2.4 (td, *J* = 7.0, 1.8 Hz, 2H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.9 (s, 9H), 0.07 (s, 6H).

(*S*)-6-(*tert*-Butyldimethylsilyloxy)hex-3-yn-2-yl-2-(diethoxyphosphoryl)acetate (30): To a solution of the mixture of alcohol **29** (768 mg, 3.37 mmol), 2-(diethoxyphosphoryl)acetic acid (990 mg, 5 mmol, 1.5 equiv), DMAP (82 mg, 0.67 mmol, 0.2 equiv) in dichloromethane (33 mL) at rt was added DCC (1 g, 5 mmol) and the mixture was stirred for 12 h. The mixture was concentrated under reduced pressure and the crude material was triturated with ether and filtered through Celite. Ether was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel using 50% ethyl acetate/petroleum ether (v/v) as the eluent to afford ester **30** (998 mg, 2.46 mmol) in 73% yield as a liquid. TLC: R_f 0.3 (0.6:0.4 hexanes:ethyl acetate). $[\alpha]^{25}_{D}$ = -20 (*c* 0.36, $CHCl_3$). IR (neat): 2934, 2860, 1742, 1260, 1109, 1027 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (qt, *J* = 6.7, 1.8 Hz, 1H), 4.2-4.1 (m, 4H), 3.67 (t, *J* = 7.1 Hz, 2H), 2.94 (d, $J_{h\text{-}p}$ = 21.6 Hz, 2H), 2.38 (td, *J* = 7.1, 1.8 Hz, 2H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 6H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6, 82.8, 78.9, 62.6, 61.8, 61.4, 34.7, 25.7, 22.9, 21.4, 18.2, 16.2, -5.3; MS (ESI): *m/z* 429 $[M+Na]^+$. HRMS (ESI): calcd for $C_{18}H_{36}O_6PSi$: 407.2013 found: 407.2003.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)hex-3-an-2-yl-2-(diethoxyphosphoryl)acetate (31): To a solution of compound **30** (893 mg, 2.2 mmol) in ethyl acetate (20 mL), Pt/C (90 mg, 10% w/w) was added. The resulting suspension was placed under a H_2 atmosphere (balloon) and stirred vigorously for 9 h at rt. The solution was then filtered through Celite, and the solvent was evaporated to afford the compound **31**

(828 mg, 2.02 mmol) in 92% yield as a liquid. TLC: R_f 0.35 (0.6:0.4 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +0.49 (*c* 1.02, $CHCl_3$); IR (neat): 2935, 2860, 1733, 1264, 1102, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.97-4.9 (m, 1H), 4.2-4.12 (m, 4H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.92 (d, J_{h-p}= 21.6 Hz, 2H), 1.8-1.7 (m, 1H), 1.68-1.58 (m, 1H), 1.56-1.45 (m, 3H), 1.44-1.36 (m, 1H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 72.3, 62.6, 62.4, 62.3, 35.3, 33.4, 32.3, 25.7, 21.4, 19.5, 18.1, 16.2, 16.1, -5.4; MS (ESI): *m/z* 433 $[M+Na]^+$. HRMS (ESI): calcd for $C_{18}H_{40}O_6PSi$: 411.2326 found: 411.2313.

(*S*)-6-Hydroxyhexan-2-yl-2-(diethoxyphosphoryl)acetate (32): To a stirred solution of phosphonate ester **31** (787 mg, 1.92 mmol) in THF (2.9 mL) was added TBAF (1.0 M in THF, 2.9 mL, 2.9 mmol). The resulting solution was stirred for 3 h, quenched with aq NH_4Cl solution (3 mL) and extracted with EtOAc (3x3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using 60% ethyl acetate/hexane (v/v) to afford the compound **32** (532 mg, 1.8 mmol) in 94% yield as a liquid. TLC: R_f 0.2 (1:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -0.21 (*c* 1.02, $CHCl_3$). IR (neat): 3422, 2982, 2934, 2865, 1730, 1276, 1025, 1116 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.03-4.96 (m, 1H), 4.2-4.1 (m, 4H), 3.63 (t, *J* = 6.1 Hz, 2H), 2.93 (d, J_{h-p}= 21.6 Hz, 2H), 1.6-1.4 (m, 6H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.25 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 72.2, 62.7, 62.6, 62.0, 35.3, 35.1, 32.1, 21.2, 19.7, 16.1; MS (ESI): *m/z* 319 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{26}O_6P$: 297.1461 found: 297.1452.

(*S*)-6-Oxohexan-2-yl-2-(diethoxyphosphoryl)acetate (33): To a solution of alcohol **32** (476 mg, 1.62 mmol) in DCM (6.5 mL) was added Dess-Martin periodinane (755 mg, 1.7 mmol). After being stirred at rt for 30 min, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (2 mL) and saturated aq $NaHCO_3$ (2 mL). The aq phase was extracted with DCM (3x4 mL), The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 60% ethyl acetate/hexane (v/v) to afford compound **33** (441 mg, 1.5 mmol) in 92% yield as a liquid. TLC: R_f 0.23 (1:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -8.3 (*c* 1.02, $CHCl_3$).

IR (neat): 2982, 2934, 2865, 1730, 1273, 1024, 1117, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.7 (t, *J* = 1.5 Hz, 1H), 5.0- 4.94 (m, 1H), 4.2-4.13 (m, 4H), 2.94 (d, J_{h-p}= 21.6 Hz, 2H), 2.49-2.44 (m, 2H), 1.75-1.6 (m, 4H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.26 (d, *J* = 6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.9, 165.2, 72.0, 62.7, 43.3, 34.9, 34.8, 33.6, 19.7, 16.2; MS (ESI): *m/z* 333 $[M+K]^+$. HRMS (ESI): calcd for $C_{12}H_{24}O_6P$: 295.1305 found: 295.1292.

(*S*)-Hept-6-yn-2-yl-2-(diethoxyphosphoryl)acetate (34): To a solution of Ohira-Bestmann reagent (403 mg, 2.1 mmol) in ethanol (7 mL) cooled to 0 °C was added K_2CO_3 (276 mg, 2 mmol). The solution of aldehyde **33** (411 mg, 1.4 mmol) in ethanol (1.4 mL) was added to the above mixture allowing the temperature to rise from 0 °C to rt and the mixture was stirred for 2 h. The solution was filtered through Celite and the filtrate was evaporated in vacuo. The crude product was dissolved in ethyl acetate (20 mL) and washed with water (20 mL). The aq phase was extracted with EtOAc (2x20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 30% ethyl acetate/hexane (v/v) to afford compound **34** (261 mg, 0.9 mmol) in 64% as a liquid. TLC: R_f 0.45 (1:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +18.4 (*c* 0.4, $CHCl_3$). IR (neat): 3463, 2983, 2936, 1731, 1272, 1117, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02-4.93 (m, 1H), 4.21-4.13 (m, 4H), 2.94 (d, J_{h-p}= 21.6 Hz, 2H), 2.2 (td, *J* = 6.8, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.76-1.5 (m, 4H,), 1.34 (t, *J* = 7.0, 6H), 1.25 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 83.7, 71.8, 68.6, 62.6, 62.5, 35.1, 34.7, 24.0, 19.7, 18.1, 16.2; MS (ESI): *m/z* 313 $[M+Na]^+$. HRMS (ESI): calcd for $C_{13}H_{24}O_5P$: 291.1355 found: 291.1351.

(*S*)-Hept-6-en-2-yl-2-(diethoxyphosphoryl)acetate (4): To the solution of compound **34** (232 mg, 0.8 mmol) in ethyl acetate (8 mL), Lindlar's catalyst (24 mg, 10% w/w) was added. The resulting suspension was placed under a hydrogen atmosphere (balloon) and stirred vigorously for 16 h at rt. The solution was filtered through Celite and the filtrate was evaporated under reduced pressure to afford the compound **4** (217 mg, 0.74 mmol) in 92% yield as a liquid. TLC: R_f 0.5 (1:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -10.2 (*c* 0.6, $CHCl_3$). IR (neat): 2981, 2934, 1732, 1271, 1116, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82-5.73 (m, 1H), 5.0-4.93 (m, 3H), 4.2-4.14 (m, 4H), 2.94 (d, J_{h-p} = 21.6 Hz, 2H), 2.08-2.01

(m, 2H), 1.54-1.38 (m, 4H), 1.34 (t, *J* = 7.1 Hz, 6H), 1.24 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 138.2, 114.7, 72.3, 62.6, 62.5, 35.2, 35.1, 33.3, 24.4, 19.7, 16.3, 16.2; MS (ESI): *m/z* 315 $[M+Na]^+$. HRMS (ESI): calcd for $C_{13}H_{26}O_5P$: 293.1512 found: 293.1508.

(*S,E,)*-7-((1*S*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-hydroxyethyl)cyclopentyl)hepta-3,6-dien-2-yl-2-(diethoxyphosphoryl)acetate (36): To a solu tion of phosphonate **4** (70 mg, 0.24 mmol) and alkene **3** (48 mg, 0.12 mmol) in anhydrous dichloromethane (1.2 mL), Grubbs' II generation catalyst **35** (2.5 mg, 0.003 mmol) was added as a solid in one portion and the reaction mixture was refluxed for 36 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 25% ethyl acetate/hexane (v/v) to afford compound **36** (61 mg, 0.093 mmol) in 78% yield as a liquid. TLC: R_f 0.5 (4:6 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = - 4.7 (*c 0.4* , $CHCl_3$). IR (neat): 3425, 2954, 2929, 2856, 1735, 1257, 1112, 1028 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39-5.3 (m, 2H), 4.98-4.9 (m, 1H), 4.2-4.13 (m, 5H), 3.68 (td, *J* = 5.1, 3.2 Hz, 1H), 3.5 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.46 (dd, *J* = 11.1, 5.1 Hz, 1H), 2.93 (d, J_{h-p}= 11.6 Hz, 2H), 2.3-2.2 (m, 1H), 2.05-1.95 (m, 4H), 1.83 (ddd, *J* = 12.9, 8.5, 7.0 Hz, 1H), 1.56-1.36 (m, 6H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.9 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 135.2, 129.1, 73.1, 73.0, 72.4, 66.3, 62.5, 46.3, 43.4, 43.1, 35.5, 35.2, 35.0, 32.1, 25.9, 25.1, 19.7, 18.1, 16.3, -3.8, -4.5, -4.7; MS (ESI): *m/z* 687 $[M+Na]^+$. HRMS (ESI): calcd for $C_{32}H_{65}O_8NaPSi_2$: 687.3847 found: 687.3856.

(*S,E*)-7-((1*S*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)-2-oxoethyl)cyclopentyl)hepta-3,6-dien-2-yl2-(diethoxyphosphoryl)acetate (2): To a solution of alcohol **36** (46 mg, 0.07 mmol) in dichloromethane (0.7 mL) was added Dess-Martin periodinane (35.6 mg, 0.084 mmol). After being stirred at rt for 30 min, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (1 mL) and saturated aq $NaHCO_3$ (1 mL). The aq phase was extracted with dichloromethane (3x3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography on silica gel using 55% ethyl acetate/hexane (v/v) to afford compound **2** (41.7 mg, 0.063 mmol) in 90% yield as a liquid. TLC: R_f 0.25 (1:1 hexanes:ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.56 (d, *J* = 1.3 Hz, 1H), 5.36-5.33 (m, 2H), 4.98-4.9 (m, 1H), 4.2-4.13 (m, 5H), 3.4 (dd, *J* = 2.2, 1.3 Hz, 1H), 2.94 (d, $J_{h\text{-}p}$= 21.6 Hz, 2H), 2.4-2.3 (m, 1H), 2.2 (ddd, *J* = 18.0, 8.8, 2.5 Hz, 1H), 2.08-1.92 (m, 3H), 1.83 (ddd, *J* = 12.9, 8.8, 7.0 Hz, 1H), 1.56-1.36 (m, 6H), 1.34 (t, *J* = 7.1, 6H), 1.24 (d, *J* = 6.2 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 204.1, 165.4, 133.8, 130.3, 73.0, 72.3, 62.5, 60.3, 45.8, 42.9, 42.8, 35.2, 35.1, 34.5, 32.2, 25.8, 25.7, 25.1, 19.8, 18.1, 18.0, 16.3, -4.2, -4.8, -5.0; MS (ESI): *m/z* 685 $[M+Na]^+$. HRMS (ESI): calcd for $C_{32}H_{64}O_8PSi_2$: 663.3871 found: 663.3860.

(1*R*,2*E*,6*S*,10*E*,11*aS*,13*S*,14*aR*)-1,13-bis(*tert*-Butyldimethylsilyloxy)-6-methyl-6,7,8,9,12,13, 14,14*a*-octahydro1H(*f*)(1)oxacyclotridecin-4-(11*a*H)-one (37): To a stirred suspension of LiBr (74 mg, 0.85 mmol), DBU (19 μL, 0.13 mmol) and Et_3N (90 μL, 0.65 mmol) in anhydrous THF (3.3 mL) was added the solution of phosphonate **2** (33 mg, 0.05 mmol) in THF (3.3 mL) via a syringe pump over 20 h. The reaction mixture was stirred for 7 h after addition. After concentration of the solvent, the residue was redissolved in pentane (5 mL) and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel using 3% diethyl ether/pentane (v/v) gave the known bis-silyl brefeldin A **37** (15 mg, 0.029 mmol) in 60% yield as a colorless oil. TLC: R_f 0.5 (9.8:0.2 hexanes:ethyl acetate); $[\alpha]^{25}_D$ = +20.9 (*c*, 0.4, $CHCl_3$), lit[24] $[\alpha]^{23}_D$ = +22 (*c*, 0.72, $CHCl_3$). IR (neat): 2933, 2857, 1711, 1256, 1218, 1119 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3 (dd, *J* = 15.5, 3.0 Hz, 1H), 5.87 (dd, *J* = 15.5, 1.8 Hz, 1H), 5.62 (ddd, *J* = 15.2, 10.2, 4.4 Hz, 1H), 5.26 (dd, *J* = 15.3, 9.4 Hz), 4.92-4.84 (m, 1H), 4.22-4.15 (m, 1H), 4.05-3.98 (m, 1H), 2.3-2.2 (m, 1H), 2.08-1.9 (m, 4H), 1.86-1.67 (m, 4H), 1.53-1.4 (m, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.015 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 152.5, 137.3, 129.2, 118.0, 76.3, 72.8, 71.3, 52.8, 43.8, 43.6, 42.0, 34.0, 31.8, 26.7, 25.8, 20.9, 18.1, 18.0, -4.1, -4.7, -4.8; MS (ESI): *m/z* 531 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{53}O_4Si_2$: 509.3477 found: 509.3499.

(1*R*,2*E*,6*S*,10*E*,11*aS*,13*S*,14*aR*)-1,13-Dihydroxy-6-methyl-6,7,8,9,12,13,14,14*a*-octahydro-1H (*f*)(1)oxacyclotridecin-4-(11*a*H)-one (1): To a solution of compound **37** (10 mg, 0.019 mmol) in THF (0.8 mL) and water (0.8 mL), HCl (2 M in water, 0.2 mL) was added and the resulting mixture was stirred for 39 h at ambient temperature. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (1 mL) and the aq layer extracted with ether (3 x 5 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated and the residue was purified by flash chromatography on silica gel using 60% ethyl acetate/hexane (v/v) to give (+)-brefeldin A as a white solid (3.5 mg, 0.017 mmol) in 88% yield. M.p. = 202-204 °C TLC: R_f 0.2 (50:50 hexanes: ethyl acetate); IR (KBr): 3448, 2925, 2853, 1632, 1403, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 15.6, 3.9 Hz, 1H), 5.9 (dd, *J* = 15.6, 2.0 Hz, 1H), 5.7 (ddd, *J* = 15.5, 10.7, 5.0 Hz, 1H), 5.28 (dd, *J* = 15.4, 10.3 Hz, 1H), 4.9-4.84 (m, 1H), 4.36-4.3 (m, 1H), 4.14-4.08 (m, 1H), 2.38-2.3 (m, 1H), 2.2 (ddd, *J* = 13.8, 9.7, 5.5 Hz, 1H), 2.1-1.7 (m, 9H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.88-0.82 (m, 1H), MS (ESI): *m/z* 281 $[M+H]^+$. HRMS (ESI): calcd for $C_{16}H_{25}O_4$: 281.1747 found: 281.1739.

Supporting Information

Spectroscopic characterization data. This material is available free of charge via the internet at http://pubs.acs.org.

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