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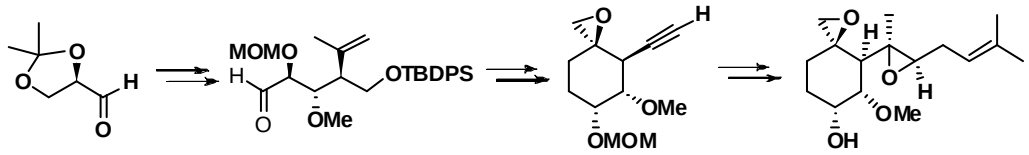
Graphics for TOC



A stereoselective formal synthesis of fumagillol is disclosed. The key steps include stereoselective carbonyl-ene reaction, Barton-McCombie radical deoxygenation, one-pot stannyl cupration of an alkyne, methylation of the resultant alkenyl copper and further Stille-coupling of the alkenyl stannane.

Stereoselective Formal Synthesis of (-)-Fumagillol

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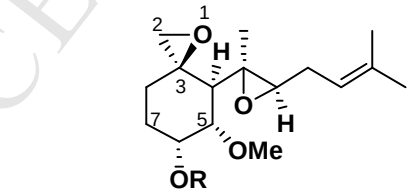
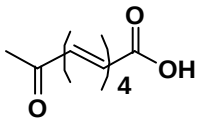
Abstract: A formal synthesis of fumagillol, a congener of fumagillin that possesses varied biological activity, is disclosed. Initial attempts at preparing an allylic sulfide via an α-chloro sulfide met with failure. The successful route involves a carbonyl-ene reaction, one-pot stannyl cupration, methylation of resulting alkenyl copper and further Stille-coupling of the alkenyl stannane as the key steps.

Introduction

Fumagillin **1** was isolated in 1949 by Elbe and Hanson[1] from the fungus *Aspergillus fumigatus*. It was originally shown to display antibiotic activity, later it was found to be useful for the treatment of nosema disease in honey bees, amoebiasis in humans,[2] microsporidial keratoconjunctivitis[3] of the eye, malaria, leishmania[4] and microsporidiosis in HIV-infected patients.[5] Folkmann and co-workers discovered the notable capacity of fumagillin **1** to inhibit angiogenesis in tumor cells.[6] This activity was hypothesized to be related to the inhibition of endothelial cell proliferation as a result of binding and inhibiting methionine aminopeptidase type 2 (metAP-2).[7, 8]



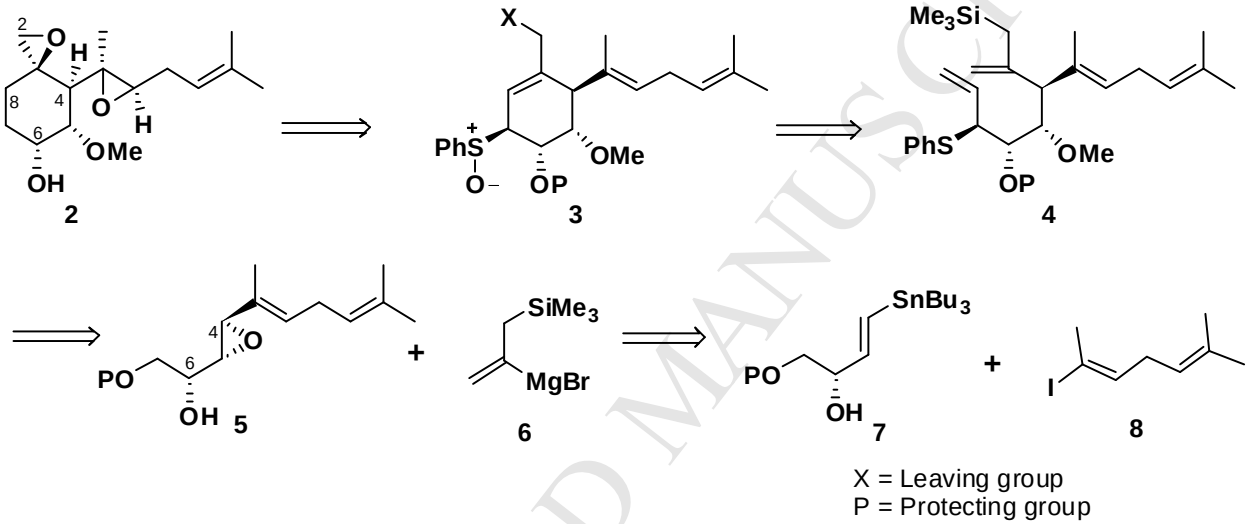
R = 

Fumagillin **(1)**

R = H Fumagillol **(2)**

Figure 1. Structure of Fumagillin and its Congener, Fumagillol.

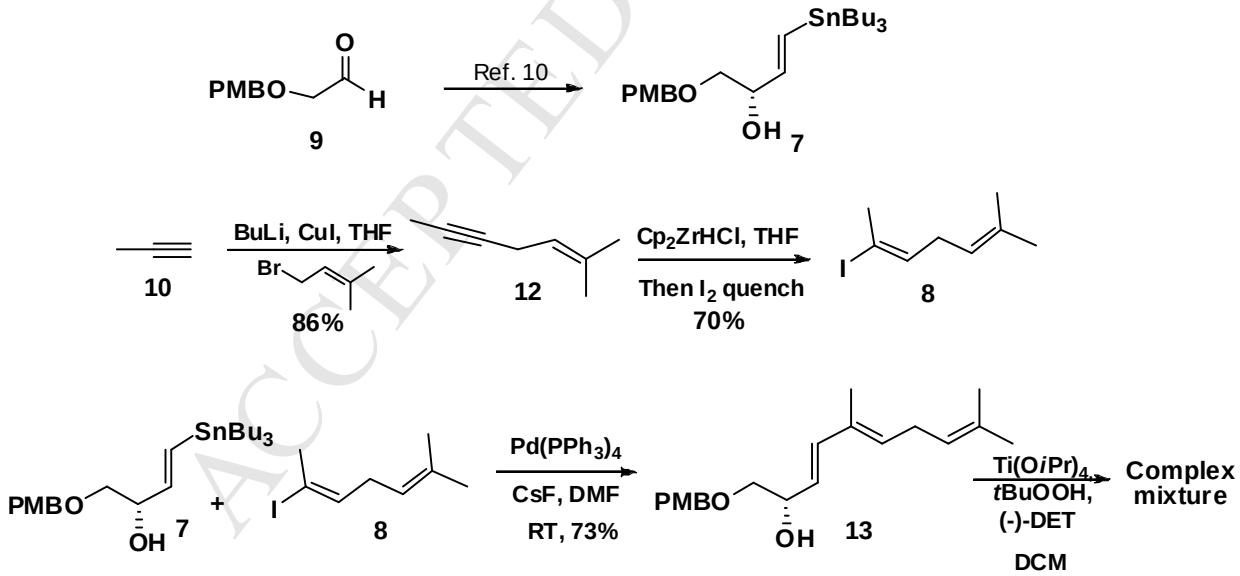
Fumagillin has a highly functionalized cyclohexane ring and five contiguous chiral centers. Due to its varied biological activity and its rare carbon skeleton a number of synthetic studies have been reported both for fumagillin and fumagillol.[9] Herein, we describe initially, our frustrated attempts to prepare an allylic sulfide from an α-chloro sulfide, envisioned as a key intermediate to fumagillol and later a successful route taking advantage of an intramolecular carbonyl-ene reaction resulting in the formal synthesis of fumagillol. The original retrosynthetic disconnection is depicted in Scheme 1.



Scheme 1. Retrosynthetic Disconnection of Fumagillol.

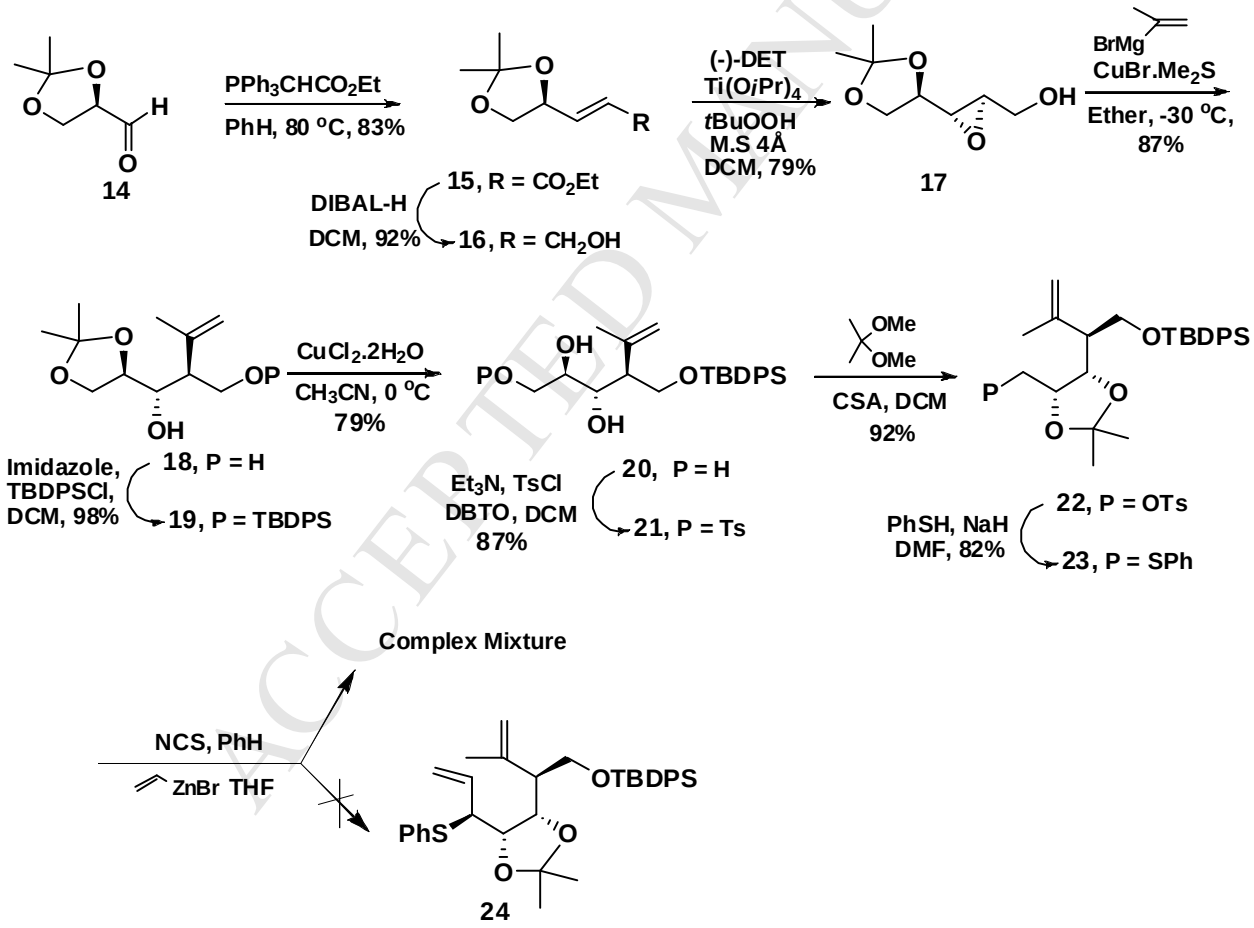
Fumagillol was envisioned to be obtained from allylic sulfoxide **3** by [2,3] sigmatropic rearrangement to introduce the hydroxyl at C3 (fumagillol numbering) followed by introduction of the epoxide moieties. The cyclohexene **3** was expected to be obtained by a ring-closing metathesis of tetraene **4**. Compound **4** was envisaged to be obtained by the regioselective opening of epoxide **5** at C4 (fumagillol numbering) by Grignard reagent **6** and eventually from the chloro sulfide derived from the primary hydroxyl at C7 in the ensuing product. Epoxide **5** itself was imagined to be obtained by coupling stannane **7** and iodo alkene **8** followed by Sharpless' asymmetric epoxidation.

The synthesis began with the preparation of stannane **7**, from aldehyde **9** in four steps, following the procedure reported in the literature,[10] without incident. The enyne **12**, obtained by a copper catalyzed addition[11] of lithio propyne with prenyl bromide, on regioselective hydrozirconation[12] followed by iodine quench yielded iodo alkene **8**. Stille-coupling[13] of stannane **7** and iodo alkene **8** proceeded in good yield to afford the trienol **13**. Attempted Sharpless' epoxidation[14] however, failed to yield any of the desired epoxide **5**, no reaction was observed at -20 ^{o}C and on rising the temperature to 0 ^{o}C, a complex mixture resulted after an extended period of time, Scheme 2. It is reasonable to assume that the adjoining trisubstituted alkene probably hinders the approach of the reagent to the substrate at low temperature and probably, after the epoxide was formed at higher temperature, Lewis acid promoted opening of the epoxide results in a complex mixture. Having been unsuccessful in preparing the epoxide **5**, it was decided to introduce the side chain at C4 late in the synthesis. By a revised analysis, the retron **24**, resembling **4**, possessing a hydroxymethyl residue in the place of the dienyl side chain was envisaged as the key intermediate.



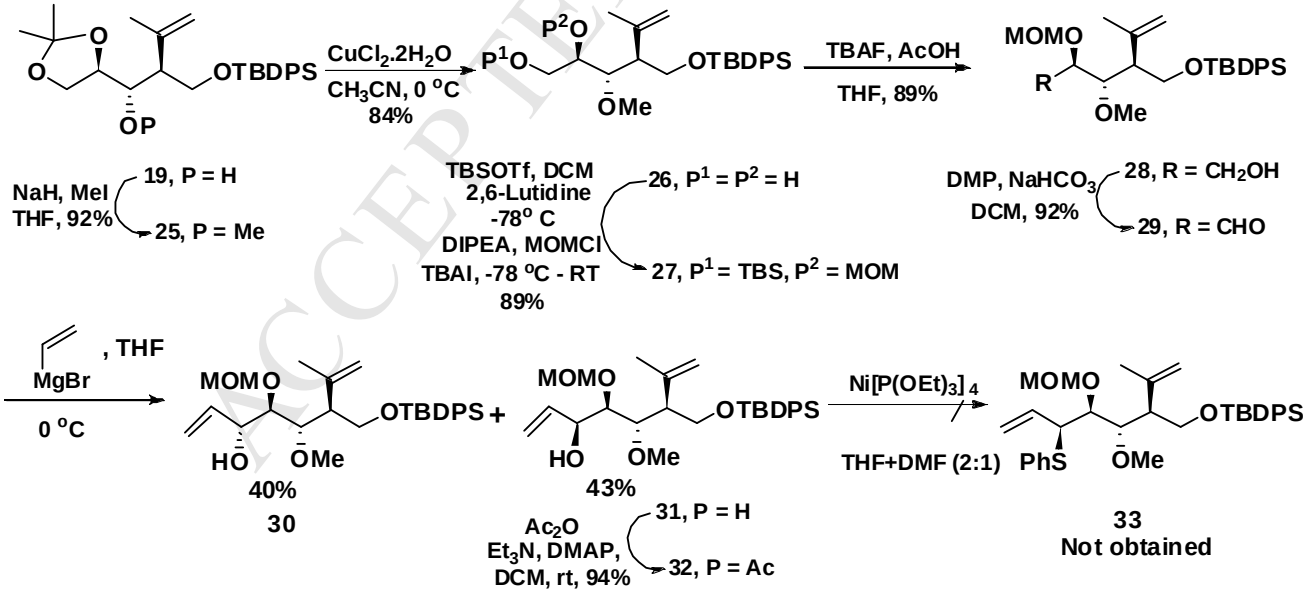
Scheme 2. Attempted Synthesis of Diene Epoxide **5**.

The synthesis following a revised strategy began with (D)-glyceraldehyde acetonide[15] **14** which was converted by a two step sequence into alcohol **16**. Sharpless asymmetric epoxidation afforded epoxide **17**[15] that on treatment with 2-propenylmagnesium bromide[16] in the presence of $CuBr.Me_2S$ yielded diol **18**, Scheme 3. Selective protection of the primary hydroxyl as its silyl ether afforded compound **19**. Deprotection of the acetonide using $CuCl_2$[17] yielded the triol **20** which was converted to tosylate **21**. Protection of diol as its acetonide furnished compound **22**. Displacement of the tosylate by sodium thiophenoxide in anhydrous DMF afforded sulfide **23**.[18] Reaction of sulfide **23** with *N*-chlorosuccinimide in benzene yielded the α-chloro sulfide which without isolation was reacted with vinylzinc bromide only to obtain a complex mixture of products and none of the desired diene **24**.



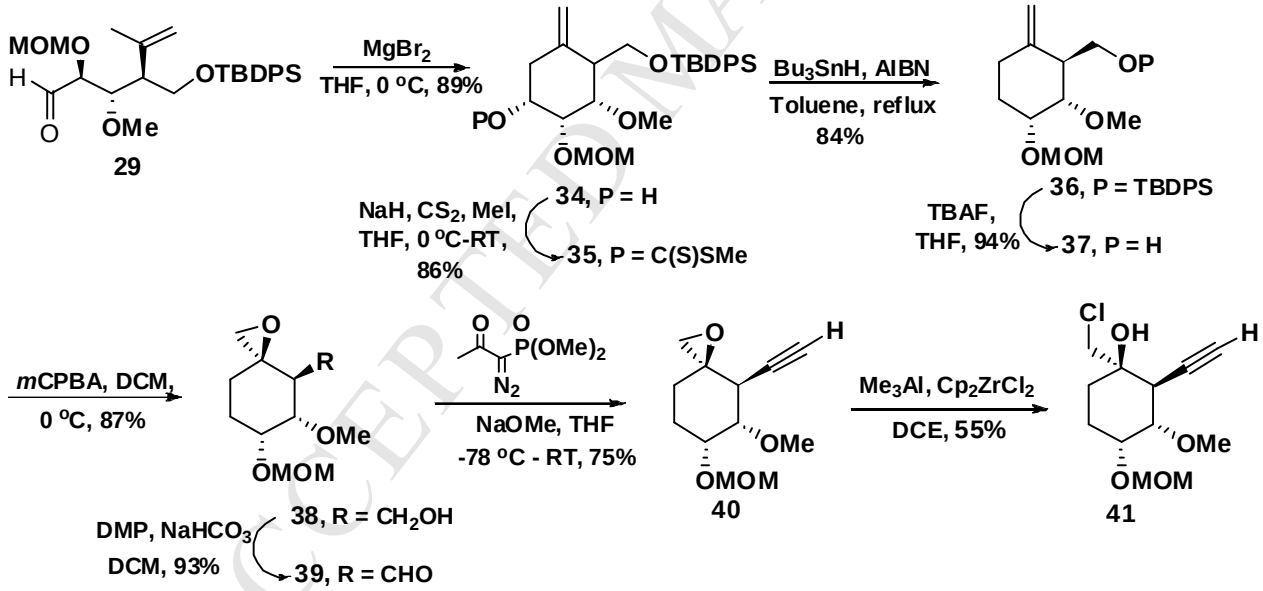
Scheme 3. Attempted Synthesis of Allylic Sulfide **24**.

A subsequent attempt was made to prepare the allylic sulfide following Takeda's protocol[19] by a Ni(0)-catalysed reaction of an allylic acetate with thiophenol. The requisite substrate was prepared as detailed in Scheme 4. Acetonide **19** was converted to the methyl ether **25** under standard conditions. Deprotection of the acetonide afforded diol **26** that was converted to the MOM ether **27** in a one-pot operation by selective protection of the primary hydroxyl using TBSOTf and further treatment of the ensuing silyl ether with MOM-Cl in the presence of Hunig's base. Selective deprotection of the primary TBS ether with TBAF buffered with acetic acid afforded alcohol **28**, that was oxidized to aldehyde **29** using DMP.[20] Reaction of aldehyde **29** with vinylmagnesium bromide proceeded with poor diastereoselectivety to furnish allylic alcohols **30** and **31** in nearly equimolar ratio. The structure was assigned to alcohols **30** and **31** following Trost's protocol[21] by preparation of α-methoxyphenylacetic esters. We decided to address the issue of poor stereoselectivety in the addition to the aldehyde after securing the allylic sulfide **33**. Thus alcohol **31** was converted to acetate **32** and subjected to treatment with PhSH in the presence of $Ni[P(OEt)_3]_4$ in the presence of 2,6-di-*tert*-butyl phenol. The allylic sulfide **33** was not obtained, after prolonged reaction time, only the hydrolyzed alcohol **31** could be isolated. Thus our attempts at securing the allylic sulfide were frustrated again.



Scheme 4. Attempted Route for the Synthesis of Allylic Sulfide **33**.

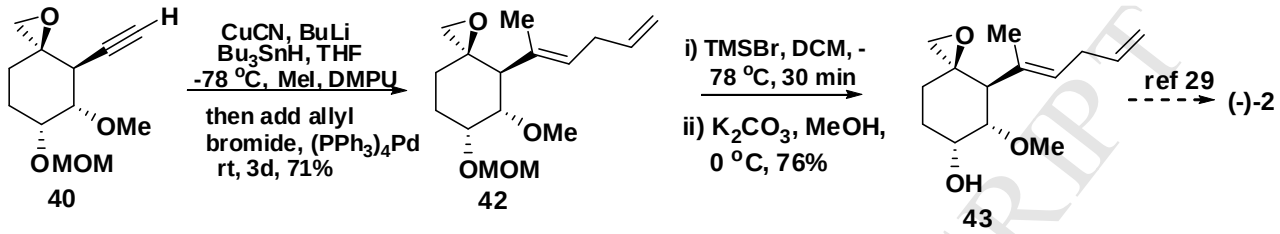
In our attempts to improve the selectivity in the preparation of allylic alcohol **31**, $MgBr_2$ was introduced to chelate the aldehyde carbonyl and the MOM ether groups. Addition of vinylmagnesium bromide to aldehyde **29** in the presence of $MgBr_2$ did not afford the alcohol **31** but the cyclohexenol **34** by an intramolecular carbonyl-ene reaction thus opening a way to fumagillol quite by an accident. Although a single isomer was obtained, the structure of **34** was not rigorously established since the carbinol stereocenter was to be destroyed subsequently.[22] The alcohol was converted to xanthate **35** and radical deoxygenation[23] with nBu$_3$SnH and catalytic AIBN afforded cyclohexene **36**. Deprotection of silyl ether using TBAF furnished alcohol **37**, Scheme 5. Hydroxyl directed epoxidation with *m*CPBA proceeded stereoselectively[24] to furnish epoxide **38**. Oxidation of alcohol to aldehyde **39** using DMP proceeded cleanly. Subjecting aldehyde **39** to reaction with Ohira-Bestmann reagent[25] in the presence of NaOMe furnished alkyne **40** cleanly. Attempted carboalumination using Negishi's protocol[26] did not yield the desired product but the chlorohydrin **41**.



Scheme 5. Attempted Synthesis of a Trisubstituted Alkene by Carboalumination.

Stannyl cupration could however, be effected by the Lipshutz protocol,[27] treatment of the resulting alkenyl copper with MeI afforded the trisubstituted alkenyltin derivative which was subjected

to Stille-coupling with allyl bromide in the presence of $Pd(PPh_3)_4$[28] to yield the diene **42** in 71% yield. Deprotection of MOM ether, achieved using TMS-Br at low temperature, followed by treatment of the crude product with K_2CO_3 afforded alcohol **43** which has been prepared by Kim and co-workers[29] en route to fumagillol and thus completing the formal synthesis of fumagillol, Scheme 6.



Scheme 6. Formal Synthesis of Fumagillol.

Conclusion

In summary, a stereoselective route to fumagillol was developed. The key steps of the synthesis include the C-C bond formation using intramolecular carbonyl-ene reaction to construct cyclohexane framework, Ohira-Bestmann reaction, stannyl cupration, methylation and Stille-coupling reaction to introduce the side chain. Attempts to prepare an allylic sulfide from an allylic acetate by a Ni-catalyzed reaction and from a sulfide via the chloro sulfide did not fructify.

Experimental procedure

The stannane **7** was prepared following a reported procedure.[10]

(*S*,*E*)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (15): To a stirred solution of diacetonide derivative of D-Mannitol (2 g, 8 mmol) in DCM (40 mL) cooled to 0 ^oC was added $NaHCO_3$ (1.3 g, 16 mmol) and $NaIO_4$ (3.4 g, 16 mmol). The reaction mixture was stirred for 2 h at the same temperature, the solids were filtered and the filtrate was washed with water. The aq layer was extracted with DCM (3x20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude aldehyde **14** (2 g, 16 mmol) was reacted with (ethoxycarbonylmethyl)triphenylphosphonium bromide (6.78 g, 16 mmol) in refluxing benzene (53 mL) for 12 h. The solvent was evaporated and the crude mixture was washed

with 15% ethyl acetate/hexane (v/v) to precipitate triphenylphosphine oxide. The filtrate was evaporated in vacuo and the residue was purified by column chromatography using 10% ethyl acetate/hexane (v/v) to give pure compound **15** (2.64 g, 13.2 mmol) in 83% yield as a liquid. TLC: R_f 0.6 (8:2, hexanes:ethyl acetate). IR (neat): 2986, 2934, 1720, 1261, 1216, 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (dd, *J* = 15.5, 5.6 Hz, 1H), 6.08 (dd, *J* = 15.5, 1.4 Hz, 1H), 4.67-4.62 (m, 1H), 4.21-4.15 (m, 3H), 3.66 (dd, *J* = 8.2, 7.1 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 144.4, 122.1, 109.9, 74.7, 68.5, 60.3, 26.2, 25.5, 13.9. MS (ESI): *m/z* 223 $[M+Na]^+$.

(*S,E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1ol (16): To a solution of ester **15** (2.6 g, 13 mmol) in DCM (43 mL) cooled to -78 ^oC was added DIBAL-H (1.2 M in toluene, 23.8 mL, 28.6 mmol). The reaction mixture was stirred at the same temperature for 1h and then quenched with aq saturated sodium potassium tartarate (25 mL). The temperature was warmed to rt and stirring continued for 1 h. The layers were separated and the aq layer was extracted with DCM (3x25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using 20% ethyl acetate/hexane (v/v) to give pure compound **16** in 92% yield (1.89 g, 12 mmol) as a pale yellow liquid. TLC: R_f 0.3 (8:2, hexanes:ethyl acetate). IR (neat): 3413, 2988, 2934, 2875, 1154, 1099, 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.98-5.9 (m, 1H), 5.73-5.66 (m, 1H), 4.55-4.48 (m, 1H), 4.14 (d, *J* = 5.0 Hz, 2H), 4.08 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.5 (dd, *J* = 8.1, 7.1 Hz, 1H), 2.0-1.88 (brt, 1H), 1.41 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 127.3, 108.8, 76.0, 68.7, 61.4, 26.1, 25.3; MS (ESI):*m/z* 181 $[M+Na]^+$. HRMS (ESI): calcd for $C_8H_{14}O_3Na$: 181.0835, found: 181.0829.

((*2R,3S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol (17): A suspension of finely powdered activated molecular sieves (4Å, 1.9 g) in anhydrous DCM (80 mL) maintained under nitrogen atmosphere was cooled to -20 ^oC. Neat $Ti(O^iPr)_4$ (3.57 mL, 11.8 mmol) and a solution of D-(-)-diethyl tartrate (2.2 mL, 13 mmol) in anhydrous DCM (13 mL) were added successively. The mixture was stirred for 20 min and allylic alcohol **16** (1.86 g, 11.8 mmol) in anhydrous DCM (12 mL) was added

over 15 min. After stirring for 30 min a solution of *tert*-butyl hydroperoxide (5 M in toluene, 3.5 mL, 17.7 mmol) was added dropwise. The mixture was maintained at -20 ^{o}C overnight. The reaction was quenched by adding an aq solution of $FeSO_4.7H_2O$ (2 g) and tartaric acd (1.2 g) in water (20 mL) at 0 ^{o}C. After stirring for 10 min the mixture was filtered and the residue was washed with DCM (25 mL). The filtrate was separated and the aq layer was extracted with DCM (3x50 mL). The combined organic layers were stirred at 0 ^{o}C for 1 h with 30% NaOH (w/v) solution in saturated brine (10 mL), after which the layers were separated and the aq layer was washed with ether (3x20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using 30% ethyl acetate/hexane (v/v) to give pure compound **17** (1.6 g, 9.3 mmol) in 79% yield as a pale yellow liquid. TLC: R_f 0.3 (7:3, hexanes:ethyl acetate). IR (neat): 3449, 2988, 2927, 1152, 1060 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.98-3.93 (m, 2H), 3.9 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.67 (ddd, *J* = 12.5, 6.2, 4.1 Hz, 1H), 3.12-3.07 (m, 2H), 1.89 (br, 1H), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.6, 75.0, 66.5, 60.9, 57.0, 55.1, 26.2, 24.9; MS (ESI): *m/z* 197 $[M+Na]^+$. HRMS (ESI): calcd for $C_8H_{14}O_4Na$: 197.0784, found: 197.0777.

(*1S,2S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(prop-1-en-2-yl)propane-1,3-diol (18): A freshly prepared solution of isopropenylmagnesium bromide in THF (1.0 M, 78.3 mL) was added over a period of 20 min to a slurry of $CuBr.Me_2S$ (6.4 g, 31.2 mmol) in anhydrous ether (120 mL) cooled to -50 °C. The mixture was stirred for 10 min at -20 °C, after which time a solution of the epoxide **17** (1.56 g, 9 mmol) in anhydrous ether (37 mL) was added over a period of 10 min. The mixture was stirred at -20 °C for 36 h. The reaction mixture was quenched by adding aq saturated aqueous NH_4Cl (37 mL) and brine (18 mL). The layers were separated and the aq layer was extracted with ether (3x30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography to yield the diol **18** as white crystals (1.69 g, 7.83 mmol) in 87% yield. TLC: R_f 0.25 (7:3, hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +21 (*c*, 1, $CHCl_3$); mp 50-51^{o}C; IR (neat): 3413, 2984, 2926, 1156,

1064 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.94-4.92 (brs, 1H), 4.84-4.82 (brs, 1H), 4.16-4.06 (m, 2H), 3.98-3.94 (m, 2H), 3.92 (dd, *J* = 9.1, 8.0 Hz, 1H), 3.71-3.65 (m, 1H), 2.23-2.17 (m, 1H), 1.73 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3, 114.2, 108.7, 76.5, 71.9, 64.3, 63.5, 50.7, 26.2, 25.0, 20.9; MS (ESI): *m/z* 239 $[M+Na]^+$. HRMS (ESI): calcd for $C_{11}H_{20}O_4Na$: 239.1253, found: 239.1242.

(1*S*,2*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylbut-3-en-1-ol (19): To a solution of compound **18** (1.66 g, 7.7 mmol) in anhydrous DCM (30 mL) cooled to 0 °C was added imidazole (1.04 g, 15.4 mmol) followed by TBDPS-Cl (2 mL, 7.7 mmol). The reaction mixture was warmed to rt and stirred for 10 h. The reaction mixture was quenched by the addition of water (10 mL) and diluted with DCM (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 10% ethyl acetate/hexane (v/v) to give pure TBDPS ether **19** (3.42 g, 7.54 mmol) in 98% yield as a gummy oil. TLC: R_f 0.4 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +42 (*c*, 0.6, $CHCl_3$), IR (neat): 3485, 3071, 2932, 2860, 1157, 1109, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.7-7.64 (m, 4H), 7.45-7.36 (m, 6H), 4.89 (s, 1H), 4.84 (s, 1H), 4.15-4.05 (m, 2H), 4.2 (ddd, *J* = 8.3, 4.1, 3.0 Hz, 1H), 3.98-3.92 (m, 2H), 3.87 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.0 (d, *J* = 2.9 Hz, 1H), 2.2-2.16 (m, 1H), 1.7 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 135.6, 133.1, 129.7, 127.6, 114.1, 108.7, 76.9, 71.0, 64.4, 64.4, 50.5, 26.8, 26.4, 25.3, 21.3, 19.1; MS (ESI): *m/z* 477 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{38}O_4NaSi$: 477.2431, found: 477.2405.

***tert*-Butyl((*S*)-2-((*S*)-2-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxalan-4-yl)(methoxy)methyl)-3-methylbut-3-enyloxy)diphenylsilane (25):** A solution of compound **19** (2.95 g, 6.5 mmol) in anhydrous THF (13 mL) was added dropwise to a suspension of NaH (60% in Nujol, 312 mg, 7.8 mmol) in anhydrous THF (13 mL) maintained at 0 ^oC. After stirring at rt for 1 h the mixture was cooled to 0 ^oC and MeI (0.8 mL,

13 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 12 h. The reaction mixture was quenched with aq saturated NH_4Cl solution (10 mL). The layers were separated and the aq layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using 8% ethyl acetate/hexane (v/v) to give pure compound **25** (2.8 g, 6 mmol) in 92% yield as a liquid. TLC: R_f 0.5 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +35 (*c*, 0.5, $CHCl_3$), IR (neat): 3070, 2932, 2859, 1106 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.7-7.64 (m, 4H), 7.44-7.34 (m, 6H), 4.9 (s, 1H), 4.79 (s, 1H), 4.17 (td, *J* = 7.0, 3.2 Hz, 1H), 3.94-3.87 (m, 2H), 3.84 (d, *J* = 5.6 Hz, 2H), 3.63 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.45 (s, 3H), 2.15 (dt, *J* = 8.8, 5.6 Hz, 1H), 1.67 (s, 3H), 1.42 (s, 3H), 1.27 (s, 3H), 1.2 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 135.5, 133.5, 129.4, 127.4, 113.8, 108.4, 79.2, 77.3, 64.3, 62.9, 60.7, 51.4, 26.8, 26.1, 25.4, 21.4, 19.1; MS (ESI): *m/z* 491 $[M+Na]^+$. HRMS (ESI): calcd for $C_{28}H_{40}O_4NaSi$: 491.2588, found: 491.2564.

(*2R,3S,4S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methoxy-5-methylhex-5-ene-1,2-diol (26): Acetonide **25** (2.76 g, 5.9 mmol) was deprotected following the same procedure detailed for the preparation of **20** to afford diol **26** (2.12 g, 4.96 mmol) in 84% yield. $[\alpha]^{25}_D$ = +5 (*c*, 0.4, $CHCl_3$), TLC: R_f 0.3 (7:3 hexanes:ethyl acetate). IR (neat): 3448, 3071, 2930, 2857, 1108, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.7-7.64 (m, 4H), 7.46-7.36 (m, 6H), 4.88-4.85 (brs, 1H), 4.77-4.74 (brs, 1H), 3.92 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.8-3.67 (m, 4H), 3.52 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.42 (s, 3H), 2.41 (dt, *J* = 7.5, 5.6 Hz, 1H), 1.72 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 135.6, 133.1, 129.7, 127.6, 113.7, 83.0, 71.9, 63.4, 62.9, 60.7, 50.3, 26.8, 21.8, 19.1. MS (ESI): *m/z* 451 $[M+Na]^+$. HRMS (ESI): calcd for $C_{25}H_{36}NaO_4Si$: 451.2275, found: 451.2294.

(*6R,7S,8S*)-7-Methoxy-6-(methoxymethoxy)-2,2,3,3,12,12-hexamethyl-11,11-diphenyl-8-(prop-1-en-2-yl)-4,10-dioxa-3,11-disilatridecane (27): To a solution of compound **26** (2.11 g, 4.94 mmol) in anhydrous DCM (25 mL) cooled to -78 ^oC was added 2,6-lutidine (1.14 mL, 10 mmol) and TBSOTf (1.14 mL, 5 mmol). The solution was stirred at the same temperature for 30 min subsequently, DIPEA

(1.74 mL, 10 mmol), MOMCl (0.43 mL, 6 mmol) and TBAI (157 mg, 0.49 mmol) in DCM (0.5 mL) were added at the same temperature. The reaction mixture was warmed to rt, stirred for 12 h and quenched by the addition of water (10 mL). The reaction mixture was diluted with DCM (10 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 compund **27** (2.57 g, 4.4 mmol) in 89% yield as a gummy oil. TLC: R_f 0.7 (9.5:0.5 hexanes:ethyl acetate)**.** $[\alpha]^{25}_D$ = -50 (*c*, 0.6, $CHCl_3$), IR (neat): 3071, 2930, 2857, 1108, 1038 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.7-7.64 (m, 4H), 7.44-7.34 (m, 6H), 4.95-4.93 (brs, 1H), 4.86-4.84 (brs, 1H), 4.74 (d, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 3.84-3.81 (m, 2H), 3.77-3.72 (m, 3H), 3.6-3.56 (m, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 2.36-2.31 (m, 1H), 1.77 (s, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 135.6, 133.7, 129.4, 127.4, 114.1, 96.8, 81.4, 80.1, 63.2, 62.7, 60.0, 55.2, 51.2, 26.8, 25.9, 21.2, 19.2, 18.2, -5.3, -5.4; MS (ESI): *m/z* 609 $[M+Na]^+$. HRMS (ESI): calcd for $C_{33}H_{54}NaO_5Si_2$: 609.3402, found: 609.3394.

(*2R,3S,4S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methoxy-2-(methoxymethoxy)-5-methylhex-5-en-1-ol (28): To a solution of compound **27** (2.46 g, 4.2 mmol) in THF (2.1 mL) cooled to 0 ^oC, TBAF (1M in THF, 4.2 mL, 4.2 mmol) in acetic acid (0.24 mL, 4.2 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 12 h. The solvent was evaporated under reduced pressure to afford a crude compound, which was purified by column chromatography using 15% ethyl acetate/hexane (v/v) to give pure compund **28** (1.76 g, 3.72 mmol) in 89% yield as a gummy oil. TLC: R_f 0.25 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -10 (*c*, 0.4, $CHCl_3$), IR (neat): 3457, 3065, 2934, 1104, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.63 (m, 4H), 7.45-7.34 (m, 6H), 4.95-4.92 (brs, 1H), 4.84-4.82 (brs, 1H), 4.7 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 3.87-3.7 (m, 4H), 3.68-3.64 (m, 1H), 3.6 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 2.34 (ddd, *J* = 9.5, 6.4, 4.1 Hz, 1H), 1.74

(s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 135.6, 133.6, 129.5, 127.5, 114.2, 96.7, 82.2, 81.5, 62.9, 62.0, 60.5, 55.5, 51.2, 26.8, 21.4, 19.2; MS (ESI): *m/z* 495 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{40}NaO_5Si$: 495.2357, found: 495.2557.

(*2S,3S,4S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methoxy-2-(methoxymethoxy)-5-methylhex-5-enal (29): To a solution of alcohol **28** (1.7 g, 3.6 mmol) in anhydrous DCM (14 mL) was added Dess-Martin periodinane (1.9 g, 4.3 mmol). After being stirred at rt for 30 min, the reaction mixture was quenched with aq saturated $Na_2S_2O_3$ (5 mL) and aq saturated $NaHCO_3$ solution (5 mL). The aq phase was extracted with DCM (3x10 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 5% ethyl acetate/hexane (v/v) to afford compound **29** (1.55 g, 3.3 mmol) in 92% yield as a liquid. TLC: R_f 0.65 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = +10 (*c*, 0.6, $CHCl_3$), IR (neat): 3071, 2932, 2892, 1729, 1109, 1040 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (d, *J* = 0.9 Hz, 1H), 7.69-7.63 (m, 4H), 7.44-7.35 (m, 6H), 5.02-4.99 (brs, 1H), 4.94-4.92 (brs,1H), 4.72 (s, 2H), 4.19-4.17 (m, 1H), 3.86 (dd, *J* = 9.9, 6.7 Hz, 1H), 3.8 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.75 (dd, *J* = 10.5, 1.6 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.62 (ddd, *J* = 10.5, 6.7, 3.5 Hz, 1H), 1.7 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 143.5, 135.6, 133.6, 129.5, 127.5, 116.0, 96.9, 83.1, 82.3, 62.7, 58.8, 55.7, 49.4, 26.8, 21.6, 19.2; MS (ESI): *m/z* 493 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{38}O_5NaSi$: 493.2380, found: 493.2368.

(*1R,2R,3S,4S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methoxy-2-(methoxymethoxy)-5-methylenecyclohexanol (34): A solution of aldehyde **29** (1.3 g, 2.8 mmol) in anhydrous THF was added to magnesium bromide (1M in diethyl ether, 2.8 mL, 2.8 mmol) at 0 ^oC. The reaction mixture was stirred for 30 min at 0 ^oC. The reaction was quenched by the addition of an aq saturated NH_4Cl solution (10 mL), allowed to warm to rt and diluted with Et_2O (10 mL). The layers were separated and the aq layer was extracted with Et_2O (3x10 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 10% ethyl acetate/hexane (v/v) to yield compound **34** (1.18 g, 2.5 mmol) in 89% yield. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -20 (*c*, 0.4, $CHCl_3$), IR (neat): 3447, 3070, 2930, 2890, 1647, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.7-7.64 (m, 4H), 7.46-7.36 (m, 6H), 4.99-4.97 (brs, 1H), 4.97-4.95 (brs, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 3.93-3.91 (m, 1H), 3.85-3.8 (m, 3H), 3.72-3.69 (m, 1H), 3.45 (s, 3H), 3.37 (s, 3H), 2.74 (q, *J* = 5.6 Hz, 1H), 2.41 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.31 (dd, *J* = 13.7, 3.0 Hz, 1H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 135.6, 133.3, 129.7, 127.6, 115.1, 96.1, 80.6, 75.3, 69.7, 62.5, 57.4, 55.6, 47.4, 39.4, 26.8, 19.2; MS (ESI): *m/z* 493 $[M+Na]^+$.

***O*-(1*R*,2*R*,3*S*,4*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methoxy-2-(methoxymethoxy)-5-methylenecyclohexyl *S*-methyl carbonodithioate (35):** To a suspension of NaH (60% in Nujol, 192 mg, 4.8 mmol) in anhydrous THF (10 mL) cooled to 0 ^oC was added alcohol **34** (1.13 g, 2.4 mmol) dissolved in anhydrous THF (10 mL) under nitrogen atmosphere, the mixture was stirred for 30 min at room temperature. To the above alkoxide carbon disulfide (0.24 mL, 3.6 mmol) was added at 0 °C, and the mixture was stirred for 30 min. Methyl iodide (0.26 mL, 4.3 mmol) was added, and the mixture was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched with ice pieces at 0 °C and diluted with ethyl acetate (25 mL) and water (10 mL). The layers were separated and the aq layer was extracted with EtOAc (3x10 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 8% ethyl acetate/hexane (v/v) to yield compound **35** (1.15 g, 2.06 mmol) in 86% yield. TLC: R_f 0.5 (9:1 hexanes:ethyl acetate). IR (neat): 3070, 3048, 2929, 2890, 2856, 1648, 1211, 1147, 1112, 1063 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.7-7.65 (m, 4H), 7.46-7.36 (m, 6H), 5.48 (ddd, *J* = 11.9, 4.8, 2.5 Hz, 1H), 5.07 (s, 1H), 5.01 (s,1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.57-4.53 (m, 1H), 4.07 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.98 (dd, *J* = 10.3, 1.8 Hz, 1H), 3.44 (s, 3H), 3.31 (s, 3H), 3.3-3.26 (m, 1H), 2.8-2.72 (m, 1H), 2.59 (s,

3H), 2.57-2.48 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215, 139.8, 135.6, 133.4, 129.4, 127.5, 112.9, 96.7, 80.8, 78.9, 70.3, 60.2, 56.5, 55.5, 44.0, 35.3, 26.9, 19.3,19.0. MS (ESI): *m/z* 583 $[M+Na]^+$. HRMS (ESI): calcd for $C_{29}H_{40}O_5SiS_2$: 561.2159, found: 561.2185.

***tert*-Butyl(((1*S*,2*S*,3*R*)-2-methoxy-3-(methoxymethoxy)-6-methylenecyclohexyl)methoxy) diphenylsilane (36):** To a solution of compound **35** (1.13 g, 2.01 mmol) in toluene (15 mL), Bu_3SnH (914 mg, 3.0 mmol), catalytic amount of AIBN (33 mg, 0.2 mmol) were added under a nitrogen atmosphere and the mixture was heated at reflux for 8 h. Toluene was removed under reduced pressure and the residual product was purified by column chromatography using 8% ethyl acetate/hexane (v/v) to yield compound **36** (771 mg, 1.7 mmol) in 84% yield. TLC: R_f 0.4 (9:1 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -5 (*c*, 0.6, $CHCl_3$), IR (neat): 2925, 1219, 1105, 1043, 771, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.7-7.66 (m, 4H), 7.46-7.36 (m, 6H), 4.84 (s, 1H), 4.8 (s, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.7 (d, *J* = 6.9 Hz, 1H), 3.96 (dt, *J* = 9.0, 3.2 Hz, 1H), 3.83-3.77 (m, 2H), 3.61 (dd, *J* = 5.4, 2.6 Hz, 1H), 3.4 (s, 3H), 3.39 (s, 3H), 2.75 (q, *J* = 5.8 Hz, 1H), 2.27 (ddd, *J* = 13.8, 6.2, 4.7 Hz, 1H), 2.07 (ddd, *J* = 13.8, 9.9, 4.7 Hz, 1H), 1.96-1.88 (m, 1H), 1.64-1.61 (m, 1H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 135.6, 133.5, 129.6, 127.6, 111.7, 95.1, 79.8, 72.4, 62.9, 57.0, 55.2, 47.8, 30.1, 27.6, 26.8, 19.2; MS (ESI): *m/z* 477 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{38}O_4Si$: 455.2612, found: 455.2629.

((1*S*,2*S*,3*R*)-2-Methoxy-3-(methoxymethoxy)-6-methylenecyclohexyl)methanol (37): To a solution of compound **36** (726 mg, 1.6 mmol) in THF (1.6 mL) cooled to 0 ^oC, TBAF (1M in THF, 1.6 mL, 1.6 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 12 h. The solvent was evaporated under reduced pressure to afford a crude compound, which was purified by column chromatography using 30% ethyl acetate/hexane (v/v) to give pure compund **37** (324 mg, 1.5 mmol) in 94% yield as a gummy oil. TLC: R_f 0.3 (7:3 hexanes:ethyl acetate)**.** $[\alpha]^{25}_D$ = +15 (*c*, 0.6, $CHCl_3$), IR (neat): 3450, 2927, 1149, 1100, 1037 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.65 (s, 1H), 4.11-4.08 (m, 1H), 3.9 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.84

(dd, *J* = 10.9, 6.7 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.24 (dd, *J* = 6.5, 2.7 Hz, 1H), 2.8-2.74 (m, 1H), 2.42-2.34 (m, 1H), 2.1 (dt, *J* = 13.6, 4.7 Hz, 1H), 2.05-1.98 (m, 1H), 1.47-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 108.7, 95.2, 84.6, 70.5, 62.8, 56.6, 55.2, 45.3, 30.1, 28.6; MS (ESI): *m/z* 239 $[M+Na]^+$. HRMS (ESI): calcd for $C_{11}H_{20}NaO_4$: 239.1254, found: 239.1270.

((3*R*,4*S*,5*S*,6*R*)-5-Methoxy-6-(methoxymethoxy)-1-oxaspiro[2.5]octan-4-yl)methanol (38): To a solution of compound **37** (302 mg, 1.4 mmol) in DCM (7 mL) cooled to 0 ºC was added *m*CPBA (393 mg, 1.6 mmol). The reaction mixture was stirred at the same temperature for another 30 min and then quenched by adding aq saturated Na_2SO_3 (3 mL). The mixture was diluted with DCM (10 mL) and the layers separated. The combined organic layers were washed successively with aq saturated $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 40% ethyl acetate/hexanes (v/v) as the eluent to afford the product **38** (283 mg, 1.22 mmol) in 87% yield as a liquid. TLC: R_f 0.2 (7:3 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -50 (*c*, 0.6, $CHCl_3$), IR (neat): 3447, 2929, 1148, 1102, 1036 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.77 (d, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.27-4.24 (m, 1H), 3.75 (dd, *J* = 11.9, 3.3 Hz, 1H), 3.64 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.58 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 3.19 (d, *J* = 3.8 Hz, 1H), 2.65 (d, *J* = 3.8 Hz, 1H), 2.36 (dt, *J* = 10.8, 3.3 Hz, 1H), 2.23 (td, *J* = 13.5, 4.4 Hz, 1H), 2.04-1.98 (m, 1H), 1.75-1.67 (m, 1H), 1.11 (dt, *J* = 14.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.6, 79.5, 69.9, 61.1, 58.9, 57.2, 55.3, 51.2, 40.4, 28.4, 25.5; MS (ESI): *m/z* 255 $[M+Na]^+$. HRMS (ESI): calcd for $C_{11}H_{20}NaO_5$: 255.1203, found: 255.1226.

(3*R*,4*S*,5*S*,6*R*)-5-Methoxy-6-(methoxymethoxy)-1-oxaspiro[2.5]octane-4-carbaldehyde (39): To a solution of alcohol **38** (259 mg, 1.12 mmol) in DCM (5.6 mL) was added Dess-Martin periodinane (560 mg, 1.23 mmol). After being stirred at rt for 30 min, the reaction mixture was quenched with aq saturated $Na_2S_2O_3$ (2 mL) and aq saturated $NaHCO_3$ solution (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 30% ethyl acetate/hexane (v/v) to afford compound **39** (239 mg, 1.04 mmol) in 93% yield as a liquid. TLC: R_f 0.5 (7:3 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -35 (*c*, 0.6, $CHCl_3$), IR (neat): 2932, 1726, 1150, 1096, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.42 (d, *J* = 3.6 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.3-4.27 (m, 1H), 3.97 (dd, *J* = 10.3, 2.7 Hz, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 2.94 (dd, *J* = 10.3, 3.6 Hz, 1H), 2.72 (d, *J* = 3.8 Hz, 1H), 2.63 (d, *J* = 3.8 Hz, 1H), 2.18-2.1 (m, 1H), 2.07-2.0 (m, 1H), 1.82-1.74 (m, 1H), 1.17 (dt, *J* = 14.0, 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 95.5, 79.2, 68.8, 58.0, 56.9, 55.4, 52.3, 51.2, 27.9, 25.5; MS (ESI): *m/z* 253 $[M+Na]^+$. HRMS (ESI): calcd for $C_{11}H_{18}NaO_5$: 253.1046, found: 253.1050.

(3*R*,4*S*,5*S*,6*R*)-4-Ethynyl-5-methoxy-6-(methoxymethoxy)-1-oxaspiro[2.5]octane (40): To a solution of Ohira-Bestmann reagent (422 mg, 2.2 mmol) in anhydrous THF (2 mL) cooled to -78 ^oC was added NaOMe (5.4 M in Methanol, 0.37 mL, 2 mmol) in anhydrous THF (2 mL). The mixture was stirred for 10 min and then the solution of aldehyde **39** (230 mg, 1 mmol) in anhydrous THF (1 mL) was added slowly at -78 ^oC. The reaction mixture was gradually warmed to 0 ^oC and stirred for 12 h at the same temperature and then warmed to rt. The reaction was quenched by adding aq saturated NH_4Cl solution (2 mL) at 0 ^oC. It was allowed to warm to rt and diluted with Et_2O (5 mL), the layers were separated and the aq layer was extracted with Et_2O (3x5 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 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 20% ethyl acetate/hexane (v/v) to yield compound **40** (169 mg, 0.75 mmol) in 75% yield. TLC: R_f 0.3 (8:2 hexanes:ethyl acetate). $[\alpha]^{25}_D$ = -25 (*c*, 0.6, $CHCl_3$), IR (neat): 2927, 2855, 2101, 1735, 1251, 1110, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.75 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.22-4.19 (m, 1H), 3.52-3.5 (m, 1H), 3.48 (s, 3H), 3.4 (s, 3H), 3.16 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.07 (d, *J* = 4.7 Hz, 1H), 2.66 (d, *J* = 4.7 Hz,

1H), 2.12 (d, *J* = 2.4 Hz, 1H), 2.0-1.9 (m, 2H), 1.8-1.72 (m, 1H), 1.54-1.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.6, 82.0, 80.2, 71.5, 70.6, 58.0, 57.5, 55.3, 52.5, 36.1, 26.8, 25.6; MS (ESI): *m/z* 249 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{18}NaO_4$: 249.1097, found: 249.1088.

(1*R*,2*S*,3*S*,4*R*)-1-(Chloromethyl)-2-ethynyl-3-methoxy-4-(methoxymethoxy)cyclohexanol (41): To a solution of Cp_2ZrCl_2 (27 mg, 0.09 mmol) in DCE (0.5 mL) cooled to 0 ^oC was added Me_3Al (2 M in toluene, 0.15 mL, 0.3 mmol) slowly. After stirring for 15 min, alkyne **40** (22.6 mg, 0.1 mmol) was added at the same temperature and stirring was continued for 30 min. Prenyl bromide (0.01 mL, 0.1 mmol) followed by solution of Pd $(PPh_3)_4$ (0.005 mmol, 5 mg) in DCE (0.2 mL) was added. The reaction was stirred for 6 h at rt, there upon quenchend by the addition of an aq saturated citric acid solution (1 mL) at 0 ^oC. It was allowed to warm to rt and diluted with DCM (3 mL), the layers were separated and aq layer extracted with DCM (3x3 mL). The combined organic layers were washed with H_2O (3 mL), brine (5 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 hexane to yield a chloron alcohol **41** (14 mg, 0.055 mmol) in 55% yield. TLC: R_f 0.2 (8:2 hexanes:ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (d, *J* = 6.8 Hz, 1H), 4.7 (d, *J* = 6.8 Hz, 1H), 4.15-4.12 (m, 1H), 3.7 (d, *J* = 11.0 Hz, 1H), 3.63 (d, *J* = 11.0 Hz, 1H), 3.5 (s, 3H), 3.44 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.4 (s, 3H), 3.14 (dd, *J* = 10.5, 2.2 Hz, 1H), 2.4 (d, *J* = 2.2 Hz, 1H), 2.16-2.14 (brs, 1H), 1.95-1.8 (m, 2H) 1.74-1.65 (m, 2H). MS (ESI): *m/z* 285 $[M+Na]^+$.

(3*R*,4*S*,5*S*,6*R*)-4-((*E*)-Hexa-2,5-dien-2-yl)-5-methoxy-6-(methoxymethoxy)-1-oxaspiro[2.5]octane (42): To a solution of CuCN (36 mg, 0.4 mmol) in anhydrous THF (1 mL) cooled to -78 ^oC was added *n*-BuLi (2.5 M in THF, 0.32 mL, 0.8 mmol). The reaction mixture was warmed to -65 ^oC to get clear solution. After 15 min cooled to -78 ^oC and tributyltinhydride (0.21 mL, 0.8 mmol) was added slowly, the reaction mixture became yellowish and bubbles of hydrogen gas were evolved. After 10 min alkyne **40** (45 mg, 0.2 mmol) in THF (0.5 mL) was added, stirring was continued for 30 min followed by MeI

(0.06 mL, 2 mmol) and DMPU (0.2 mL) were added. The reaction mixture was slowly warmed to 0 ^{o}C then allyl bromide (0.035 mL, 0.4 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added. The reaction mixture was stirred at rt for 3 days and quench with aq saturated NH_4Cl solution (1 mL) at 0 ^{o}C. It was allowed to warm to rt and diluted with Et_2O (2 mL), the layers were separated and aq layer extracted with Et_2O (3x2 mL). The combined organic layers were washed with H_2O (2 mL), brine (2 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 20% ethyl acetate/hexane (v/v) to yield diene **42** (40 mg, 0.14 mmol) in 71% yield. TLC: R_f 0.25 (8:2 hexanes:ethyl acetate). $[\alpha]^{25}_{D}$ = -55 (*c*, 0.6, $CHCl_3$), IR (neat): 2953, 2924, 2855, 1434, 1152, 1100, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83-5.72 (m, 1H), 5.27 (t, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.94 (d, *J* = 10.1 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.32-4.28 (m, 1H), 3.51 (dd, *J* = 11.2, 2.7 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 2.97 (d, *J* = 11.2 Hz, 1H), 2.86-2.72 (m, 2H), 2.66 (d, *J* = 5.0 Hz, 1H), 2.45 (d, *J* = 5.0 Hz, 1H), 2.23 (td, *J* = 13.7, 4.4 Hz, 1H), 2.04-1.96 (m, 1H), 1.72 (tdd, *J* = 13.9, 4.4, 2.2 Hz, 1H), 1.57 (d, *J* = 3.3 Hz, 3H), 1.1 (ddd, *J* = 13.7, 4.4, 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 130.4, 127.7, 114.4, 95.8, 80.6, 69.5, 56.7, 55.3, 51.3, 48.6, 37.9, 32.2, 28.6, 26.0, 21.4. MS (ESI): *m/z* 305 $[M+Na]^+$. HRMS (ESI): calcd for $C_{16}H_{26}NaO_4$: 305.1729, found: 305.1730.

(3*R*,4*S*,5*S*,6*R*)-4-((*E*)-Hexa-2,5-dien-2-yl)-5-methoxy-1-oxaspiro[2.5]octan-6-ol (43): To a solution of compound **42** (28.2 mg, 0.1 mmol) in DCM (1 mL) cooled to -78 ^{o}C, TMSBr (0.03 ml, 0.3 mmol) was added. The reaction mixture was stirred for 30 min and quenched with aq saturated $NaHCO_3$ solution (0.5 mL). It was allowed to warm to rt and diluted with DCM (2 mL), the layers were separated and aq layer extracted with DCM (3x2 mL). The combined organic layers were washed with H_2O (2 mL), brine (2 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford a crude bromo compound. TLC: R_f 0.15 (8:2 hexanes:ethyl acetate). To the solution of crude compound in methanol (5 mL) at room temperature was added solid potassium carbonate (27 mg, 0.2 mmol). After

stirring for 1 h at the same temperature, methanol was removed in vacuo. The residue was partitioned between brine (2 mL) and ethyl acetate (6 mL). The organic layer separated and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with H_2O (2 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 30% ethyl acetate/hexane (v/v) to yield compound **43** (18 mg, 0.076 mmol) in 76% yield. TLC: R_f 0.2 (8:2 hexanes:ethyl acetate). IR (neat): 3464, 2930, 2362, 1638, 1445, 1377, 1324, 1214, 1103 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.86-5.76 (m, 1H), 5.42-5.26 (brs, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.28-4.26 (m, 1H), 3.7-3.5 (m, 2H), 3.37 (s, 3H), 3.32 (d, *J* = 10.0 Hz, 1H), 2.9-2.8 (m, 2H), 2.52 (d, *J* = 5.0 Hz, 1H), 2.27-2.22 (brs, 1H), 1.93-1.75 (m, 3H), 1.7-1.66 (m, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 132.7, 127.0, 114.5, 80.9, 64.4, 60.7, 56.9, 51.2, 47.9, 32.1, 29.7, 27.8, 26.6. MS (ESI): *m/z* 261 $[M+Na]^+$. HRMS (ESI): calcd for $C_{14}H_{23}O_6$: 239.1647, found: 239.1633.

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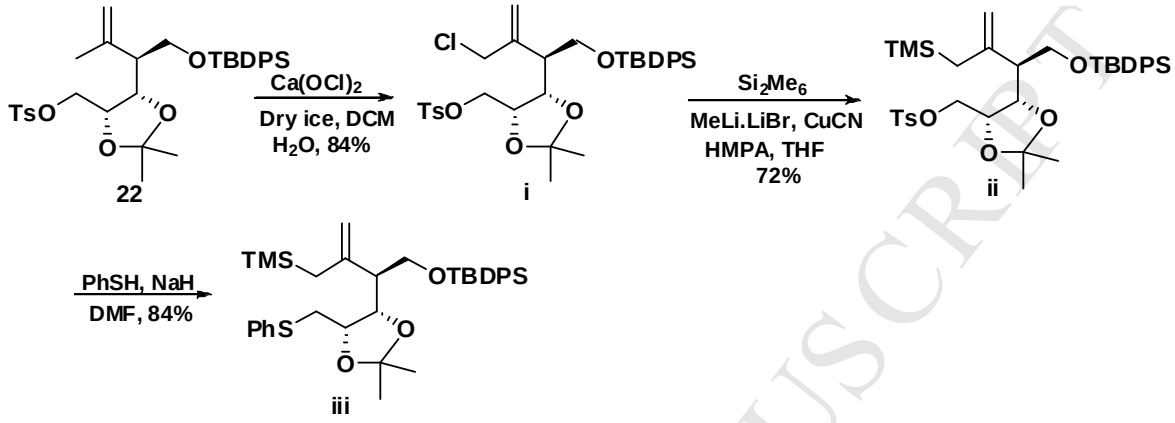

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