Enantioselective synthesis of C1-C4 and C5-C14 fragments of cytospolide D

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Dedicated to Prof. Peter Alan Jacobi in recognition of his seminal contributions to so many aspects of organic chemistry

Abstract

A convergent approach for the synthesis of the two key fragments (C1-C4 and C5-C14) of cytospolide D is described. Key transformations include MacMillan’s crossed aldol, Sharpless asymmetric dihydroxylation (AD) and Mitsunobu inversion reactions.

Keywords: Cytospolide, Sharpless AD, MacMillan’s crossed aldol, Mitsunobu inversion, Yamaguchi esterification.
Introduction

Over the recent years, decanolides (nonenolides) have been recognized as a rich source of bioactive natural products with fascinating chemical structures. The novel decanolide compounds, cytospolide A-E (1-5) along with other thirteen natural product analogues (cytospolides M-Q and decytospolides A and B) were isolated by Zhang and co-workers from leaves of endophytic fungus shrub Ilex canariensis found mainly in the island of Gomera, Spain (Figure 1). A number of cytospolides showed cytotoxic effects to various human carcinoma cell lines. The C-2 methyl group inversion in cytospolide E 5 from 2R of 4 to 2S of 5 was found to lead to a surprise increase in cytotoxic activity against the A-549 tumor cell lines. The structure of all the cytospolides were determined by extensive studies of chemical, spectroscopic and single crystal X-ray analysis. Cytospolide D 4 has been a synthetic target of considerable interest due to its bioactivities and unique structure with an array of functionalities. Various methods for the synthesis of cytospolide D 4 based on the chiral pool approaches have been documented in the literature. As part of our ongoing program towards the syntheses of bioactive natural products, we became interested in developing a simple and flexible route to the key fragments of cytospolide D 4. Herein, we are reporting a new and efficient enantioselective synthesis of key fragments C1-C4 and C5-C14 for the cytospolide D 4 employing the MacMillan’s crossed aldol, Sharpless AD and Mitsunobu inversion reaction as key steps.

![Figure 1. Some representative structures of cytospolide.](image)

Results and Discussion

Our retrosynthetic analysis for the synthesis of both the fragments of cytospolide D 4 is displayed in Scheme 1. We envisaged that the cytospolide D 4 in its E-form could be synthesized from the key precursor bis-olefin derivative 10 via Grubbs RCM reaction followed by deprotection of protecting groups. The bis-olefin derivative 10 could be accessed from the olefinic alcohol fragment 11 (C5-C14) and acid fragments 12 (C1-C4) by intermolecular Mitsunobu esterification. The alcohol derivative 11 in turn could be synthesized from easily
accessible trans-olefinic ester 14 via Sharpless AD followed by standard organic transformation. The olefinic acid fragment 12 could be assembled from alcohol derivative 13 by employing PMB protection of primary alcohol, silyl ether cleavage, regioselective primary hydroxyl o-tosylation, base treatment to get terminal epoxide, one carbon homologation, TBS protection and PMB deprotection followed by oxidation. The 1,3-diol derivative 13 in turn could be obtained from the aldehyde intermediate of monosilylated ethylene glycol derivative 15 via asymmetric MacMillan’s crossed aldol reaction followed by in-situ aldehyde reduction.

**Scheme 1.** Retrosynthetic analysis of cytopolide D 4.

**Synthesis of the C5-C14 Fragment (11).**
The synthesis of the key fragment olefinic alcohol 11 is depicted in Scheme 2. The synthesis started from readily available α, β-unsaturated ester 14 by treatment with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of (DHQ)2PHAL (hydroquinine 1,4-phthalazinediyli diether) under Sharpless asymmetric conditions to afford the diol derivative 16 in 92% yield with >98% ee [(α)D -14.37 (c 1.00, EtOH), Lit19-20 -14.40 (c 1.00, EtOH)]. The diol derivative 16 on LiAlH4 reduction afforded triol intermediate, which on regioselective primary alcohol o-tosylation by TsCl and Et3N in the presence of catalytic amount of Bu2SnO2 (dibutyltin(IV) oxide) followed by base treatment afforded the epoxy alcohol derivative 17 as the sole product in 80% yield. The free secondary hydroxyl group of 17 was subjected to imidazole-promoted protection with TBSCl which furnished the TBS protected epoxide 18 in 90% yield. The protected epoxide derivative 18 was then subjected to copper-catalyzed (CuI) regioselective ring opening with allylMgBr to give the alkenol derivative 19 in excellent yield. The free hydroxyl group of alkenol derivative 19 on p-methoxybenzyl chloride (PMBCl) protection in the presence of NaH and selective desilylation of the TBS ether with TBAF (tetrabutylammonium fluoride) furnished the alkenol derivative 11 in excellent yield.
Scheme 2. Reagents and conditions: (a) 0.005 mol% OsO₄, 0.1 mol% (DHQ)₂PHAL, K₃[Fe(CN)₆], CH₃SO₂NH₂, K₂CO₃, t-BuOH:H₂O 1:1 v/v, 0 °C, 24 h, 92%; (b) i) LiAlH₄, dry THF, 0 °C, 2 h; ii) TsCl, Et₃N, Bu₂SnO (cat), dry CH₂Cl₂, 0 °C to rt, 2 h, 80% (over three steps). (c) TBSCI, imidazole, DMAP, CH₂Cl₂, 0 °C to rt, 2 h, 90%; (d) C₃H₅MgBr, Cul (cat.), dry THF, 0 °C, 2.5 h, 85%. (e) PMBCl, NaH, TBAI (cat.), THF, 0 °C to rt, 3 h, 76%. (f) TBAF, THF, 0 °C to rt, 1 h, 95%; (g) (i) p-nitrobenzoic acid, DIAD, Ph₃P, toluene, 0 °C to rt, 2.5 h; (ii) K₂CO₃, MeOH, 0 °C to rt, 45 min, 82%.

Synthesis of the C₁-C₄ Fragment (12)
The synthesis of olefinic acid fragment 12 (C₁-C₄) is illustrated in Scheme 3. The 1,3-Diol 13 was synthesized from readily available monosilylated ethylene glycol derivative 15 via MacMillan’s crossed aldol reaction with propenal catalyzed by D-proline and subsequent NaBH₄ reduction in 86% yield with >99% ee and anti:syn 98:2 ratio. Treatment of 1,3-diol 13 with K₂CO₃ and PMBCl in acetone under reflux conditions successfully furnished the regioselective primary alcohol PMB protected derivative 21 in 83% yield. The synthesis of the epoxide derivative 22 from alcohol 21 was carried out by a process including silyl deprotection and selective primary alcohol tosylation by TsCl and Et₃N in the presence of catalytic amount of Bu₂SnO followed by base treatment in 89% yield (over three steps). The epoxide derivative 22 on one-carbon homologation with dimethylsulfonium methylide in the presence of n-BuLi furnished the allyl alcohol derivative 23 in 91% yield. With allyl alcohol derivative 23 in hand, we then subjected it to imidazole-promoted protection with TBSCI and selective deprotection of the PMB ether with DDQ to afford the primary alcohol derivative 25 in excellent yield. Finally, TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl]/BIAB [(diacetoxyiodo)benzene] mediated oxidation of the primary alcohol 25 furnished the key fragment 12 in 87% yield.
Scheme 3. Reagents and conditions: (a) i) (COCl)$_2$, DMSO, Et$_3$N, dry CH$_2$Cl$_2$, -78 °C to rt, 2 h; ii) propionaldehyde, 10 mol % D-proline, 1,4 dioxane, 4 °C, 24 h; iii) NaBH$_4$, CH$_3$OH, 30 min, 86% (three steps). (b) PMBCl, K$_2$CO$_3$, TBAI, acetone, 70 °C, 18 h, 83%. (c) i) TBAF, THF, rt, 90 min; ii) TsCl, Bu$_2$SnO, Et$_3$N, dry DCM, 0 °C to rt, 30 min; iii) KOH, Et$_2$O, rt, 2 h, 89% (three steps). (d) trimethylsulphonium iodide, n-BuLi, dry THF, -10 to 0 °C, 3h, 91%. (e) TBSCI, imidazole, DMAP, dry CH$_2$Cl$_2$, 0 °C to rt, 2.5 h, 95%. (f) DDQ, dry CH$_2$Cl$_2$, rt, 45 min, 93%. (g) TEMPO, (diacetoxyiodo)benzene, CH$_2$Cl$_2$: H$_2$O, 3:1, rt, 24 h, 87%.

The fragments alkenol derivative 11 and acid fragment 12 could be used for the coupling reactions to accomplish the synthesis of key precursor bis-olefin derivative 10 which could be used for the total synthesis of cytospolide D 4 as shown in Scheme 4. The ester derivative 10 could be prepared by coupling of alcohol fragment 11 and acid fragment 12 under Mitsunobu conditions. Alternatively, to access the key precursor bis-olefin, the Yamaguchi esterification$^{28-30}$ could be attempted. Therefore, alkenol derivative 11 was subjected to Mitsunobu inversion in the presence of p-nitrobenzoic acid, Ph$_3$P, and DIAD followed by K$_2$CO$_3$ treatment in MeOH to afford required alkenol derivative 11a in 82% yield (Scheme 2). The Yamaguchi esterification of acid fragment 12 and alkenol derivative 11a could also lead to the required bis-olefin derivative 10.$^{31}$ The bis-olefin derivative 10 could then be converted into the target compound cytospolide D 4 by the Grubbs RCM and deprotection of both protecting group following the standard organic transformations. Ramana et al. reported the synthesis of Cytospolide E 5 with similar fragments with different stereochemistry.$^{32}$ We can expect to get E geometry with the current stereochemistry and would be investigated.

Scheme 4. Coupling of fragments for cytospolide D.
Conclusions

We have developed a new and efficient enantioselective approach to the synthesis of the two key fragments (C1-C4 and C5-C14) of cytopolide D employing MacMillan’s crossed aldol, Sharpless AD and Mitsunobu inversion reactions as key steps. The synthetic approach described has significant potential for stereochemical variations in all the positions and further extension to other stereoisomers and analogues. Currently, the efforts are in progress and the results will be disclosed in due course.

Experimental Section

General. All reactions were carried out under argon or nitrogen in oven dried glassware using standard glass syringes and septa. The solvents and chemicals were purchased from Merck and Sigma Aldrich Company. Solvents and reagents were purified and dried by standard methods prior to use. Progress of the reactions was monitored by TLC using precoated aluminium plates of Merck kiesel gel 60 F254. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of n-hexane/ethyl acetate and Dichloromethane/MeOH. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam condensing ATR accessory. \(^1\)H and \(^{13}\)C NMR spectra were recorded in CDCl\(_3\) (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. Chemical shifts are reported in \(\delta\) (ppm), referenced to TMS. HRMS were recorded on Agilent 6530 Accurate-Mass Q-TOF using Electron Spray Ionization. Optical rotations were measured on automatic polarimeter AA-65.

(2R,3S)-Ethyl 2,3-dihydroxyoctanoate (16). To a solution of tert-butyl alcohol and water (1:1, 160 mL) at room temperature, \(K_2\)Fe(CN)\(_6\) (23.26 g, 70.58 mmol), \(K_2\)CO\(_3\) (9.79 g, 70.58 mmol) and (DHQ)\(_2\) PHAL (183 mg, 0.23 mmol or 0.1 mol %) were added sequentially. The resulting mixture was cooled to 0°C followed by addition of OsO\(_4\) (1.16 mL, 0.1 M solution in toluene, 0.005 mol%) and methanesulfonamide (2.23 g, 23.52 mmol). After being stirred for 2 min at 0°C, the olefin 14 (4.0 g, 23.52 mmol) was added in one portion and resulting mixture was further stirred at 0°C for 24 h. The reaction was quenched with solid sodium sulfite (8.0 g) and stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 30 mL), dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Silica gel column chromatography (hexane/EtOAc 3:1 v/v) of the residue afforded diol 16 (4.40 g, 92%) as a white solid. Mp 42-43°C; [\(\alpha\)]\(^{25}\) -14.37 (c 1.00, EtOH); IR (CH\(_2\)Cl\(_2\)) \(\nu\): 3470, 2875, 1736, 1482, 1260 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 4.35-4.27 (m, 2H), 4.09 (d, J 2.0 Hz, 1H), 3.89 (td, J 7.4, 1.7 Hz, 1H), 3.09 (brs, 1H), 1.66-1.54 (m, 5H), 1.53-1.31 (m, 8H), 0.90 (t, J 6.9 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 173.9, 73.1, 72.7, 62.3, 34.0, 31.8, 25.6, 22.7, 14.3, 14.2.

(5S)-1-((S)-Oxiran-2-yl)hexan-1-ol (17). To a solution of LiAlH\(_4\) (1.56 g, 41.12 mmol) in dry THF (20 mL) at 0°C was added a solution of 16 (4.20 g, 20.56 mmol) in dry THF (40 mL) dropwise. The resulting mixture was stirred at 0°C for 2 h. After this 10%aq NaOH (20 mL) solution was added slowly to quench the reaction. The mixture was extracted with EtOH (2 x 30 mL), the combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo to get the triol intermediate which is used for the next step without further purification.

To a solution of above triol in dry DCM (40 mL), was added Et\(_3\)N (2.86 mL, 20.56 mmol), TsCl (3.91 g, 20.56 mmol), and Bu\(_2\)SnO (1.02 g, 4.11 mmol) sequentially. The resulting solution was stirred for 30 min and quenched with H\(_2\)O (20 mL). The aqueous layer extracted with DCM (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude mono tosylated derivative was formed and was used as such in next reaction without further purification.
To a solution of Mono tosylated derivative formed in the above reaction in ether (40 mL) at 0 °C was added KOH (3.46 g, 61.68 mmol). The resulting solution was stirred for 2 hours at room temperature and after which the turbid solution was quenched with H₂O (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), organic layer separated, washed with brine dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc 3:1 v/v) afforded the epoxide 17 (2.36 g, 80%) as colorless liquid. [Rf 0.5, EtOAc/hexane 1:4 v/v]; [α]₂⁰⁺ +4.38 (c 1.0, CHCl₃); IR (CH₂Cl₂) ν: 3446, 2931, 2878, 1108, 870 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 3.49-3.39 (m, 1H), 2.99 (ddd, J 4.9, 4.2, 2.8 Hz, 1H), 2.83 (t, J 4.8 Hz, 1H), 2.72 (dd, J 4.9, 2.8 Hz, 1H), 1.93 (brs, 1H), 1.71-1.59 (m, 2H), 1.53-1.25 (m, 6H), 0.90 (t, J 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 71.8, 55.5, 45.3, 34.5, 31.9, 25.1, 22.6, 14.1; HRMS (ESI), calcd for C₁₆H₂₀O₂Na [M+Na]⁺ 259.1042; found 259.1039.

**Tert-Butylidimethyl((S)-1-((S)-oxiran-2-yl)hexyloxy)silane (18).** To an ice-cold solution of 17 (2.0 g, 13.8 mmol) in dry CH₂Cl₂ (30 mL) under nitrogen at 0 °C, imidazole (1.42 g, 20.70 mmol), TBSCI (2.71 g, 18.02 mmol) and DMAP (337 mg, 2.76 mmol) were added sequentially and mixture was stirred for 2 hours before quenching of the reaction with saturated aqueous NH₄Cl (20 mL). The reaction mixture was extracted with CH₂Cl₂, washed with brine and dried over Na₂SO₄, concentrated in vacuo and purified on silica gel (hexane/EtOAc 19:1 v/v) to afford TBS protected epoxide 18 (3.20 g, 90%) as a colorless oil. [Rf 0.7, EtOAc/hexane 1:9 v/v]; [α]₂⁰⁺ +6.61 (c 1.0, CHCl₃); IR (CH₂Cl₂) ν: 3449, 2935, 2861, 1070, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 3.25 (dd, J 12.4, 6.8 Hz, 1H), 2.91 (ddd, J 6.8, 4.1, 2.8 Hz, 1H), 2.77 (t, J 5.12 Hz, 1H), 2.55 (dd, J 5.0, 2.7 Hz, 1H), 1.61-1.45 (m, 2H), 1.42-1.20 (m, 6H), 0.90 (s, 9H), 0.87 (t, J 7.0 Hz, 3H), 0.11 (s, 3H), 0.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 74.8, 56.2, 45.1, 34.8, 32.0, 26.0, 25.1, 22.7, 18.3, 14.2, -4.2, -4.9; HRMS (ESI), calcd for C₁₄H₃₂O₂Si [M+H]⁺ 259.2088; found 259.2091.

**(S,S)-6-(Tert-Butylidimethylsiloxy)undec-1-en-5-ol (19).** To a stirred solution of TBS protected epoxide 18 (3.0 g, 11.60 mmol) in dry THF (30 mL) at 0 °C, added Cul (110 mg, 0.58 mmol) followed by dropwise addition of 17.41 mL of 1.0 M solution of allylMgBr (17.41 mmol) in diethylether. After addition was complete, the reaction mixture was stirred for 2 hours at the same temperature and quenched with saturated aqueous NH₄Cl (30 mL) and the mixture was stirred for 20 minutes at 0 °C, and the layers were separated, aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na₂SO₄, organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/EtOAc 9:1 v/v) to afford secondary alcohol 19 (2.95 g, 85%) as pale yellow oil. [Rf 0.6, EtOAc/hexane, 1:9 v/v]; [α]₂⁰⁺ -17.91 (c 1.00, CH₂Cl₂); IR (CH₂Cl₂) ν: 3423, 2929, 2850, 1435, 1217 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 3.39 (m, 1H), 5.04 (ddd, J 17.2, 3.5, 1.7 Hz, 1H), 4.96 (ddd, J 2.9, 2.4, 1.2 Hz, 1H), 3.52-3.43 (m, 2H), 2.31-2.19 (m, 1H), 2.17-2.07 (m, 2H), 1.55-1.38 (m, 3H), 1.33-1.22 (m, 7H), 0.90 (s, 9H), 0.87 (t, J 7.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 138.7, 114.8, 75.3, 72.1, 34.0, 33.6, 32.2, 30.4, 26.0, 24.8, 22.8, 18.3, 14.2, -4.0, -4.46; HRMS (ESI), calcd for C₁₇H₃₅O₂SiNa [M+Na]⁺ 323.2377; found 323.2386.

tert-Butyl((S,S)-5-(4-methoxybenzoyloxy)undec-1-en-6-xyloxy)dimethylsilane (20). To a stirred suspension of NaH (431 mg, 17.96 mmol) in dry THF (10 mL) was added dropwise a solution of secondary alcohol 19 (2.7 g, 8.98 mmol) taken in anhydrous THF (20 mL) over a period of 10 min at 0 °C. The reaction mixture was stirred for 1 hour at same temperature then p-methoxybenzyl chloride (1.46 mL, 10.77 mmol) was added at 0 °C over a period of 10 min, followed by addition of TBAI (164 mg, 0.44 mmol) and the resultant reaction mixture was warmed to room temperature and stirred for 2 hours followed by addition of cold water (20 mL) to quench the reaction mixture. Aqueous layer was extracted with ethyl acetate (3 x 30 mL), combined organic extracts were dried over Na₂SO₄ concentrated in vacuo and purified by silica gel column chromatography (hexane/EtOAc 97:3 v/v) to afford p-methoxybenzyl ether compound 20 (2.86 g, 76%) as colorless liquid. [Rf 0.5, EtOAc/hexane 1:19 v/v]; [α]₂⁰⁺ +11.21 (c 1.0, CHCl₃); IR (CH₂Cl₂) ν: 2956, 2857, 1653, 1429, 1217 cm⁻¹; ¹H
NMR (400 MHz, CDCl₃) δ: 7.26-7.22 (m, 2H), 6.87 (dd, J 8.6, 0.7 Hz, 2H), 5.88-5.72 (m, 1H), 5.04-4.91 (m, 2H), 4.47 (dd, J 33.7, 11.3 Hz, 2H), 3.80 (s, 3H), 3.76-3.71 (m, 1H), 3.31-3.28 (m, 1H), 2.25-2.13 (m, 1H), 2.07-1.95 (m, 1H), 1.76-1.62 (m, 1H), 1.51-1.39 (m, 2H), 1.32-1.15 (m, 7H), 0.05 (s, 12H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ: 159.3, 139.1, 131.2, 129.5, 114.7, 114.4, 113.9, 81.9, 81.2, 72.0, 55.4, 32.1, 31.1, 30.7, 30.5, 28.7, 28.1, 26.0, 18.2, 14.2, -4.14, -4.43; HRMS (ESI), calcd for C₂₃H₄₄O₃SiNa [M+Na]⁺ 443.2952; found 443.2950.

(5S,6S)-5-(4-Methoxybenzylloxy)undec-1-en-6-ol (11). To a solution of 20 (2.50 g, 5.94 mmol) in dry THF (20 mL) at 0 °C was added TBAF (1.0 M in THF, 8.91 mL, 8.91 mmol), and resulting solution was stirred for 1 hour at room temperature. Saturated solution of NH₄Cl was added to quench the reaction. The aqueous phase is extracted with EtOAc (3 x 30 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄ (3.66 mL, 11 mmol) in dry THF (20 mL) at 0 °C. The volatiles were removed in vacuo to give the crude aldehyde, which was used for the next step without further purification.

The solution of ester (13.0 g, 29.5 mmol) in dry toluene (20 mL) was added dropwise to a precooled (-78 °C) solution of oxalyl chloride (2.11 mL, 24.96 mmol) in dry CH₂Cl₂ (20 mL). After stirring the reaction mixture at the same temperature for 30 min, a solution of the monosilylated ethylene glycol 15 (5.0 g, 16.64 mmol) in CH₂Cl₂ (40 mL) was added slowly, and stirred for another 30 min at -78 °C. A solution of Et₃N (10.18 mL, 73.21 mmol) in CH₂Cl₂ (40 mL) was added at -78 °C and the stirring was continued for additional 1 hour at the room temperature. The mixture was partitioned between water and CH₂Cl₂ and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude aldehyde, which was used for the next step.
To a stirred solution of above aldehyde and D-proline (192 mg, 1.66 mmol) in dioxane (17 mL) at 4 °C was added dropwise a pre-cooled (4 °C) solution of propionaldehyde (5.95 mL, 83.20 mmol) in dioxane (17 mL) over 24 hours via syringe pump. The mixture was continuously stirred for an additional 24 hours at the same temperature. After completion, the reaction was diluted with ethyl acetate washed with brine and organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude aldehyde obtained was directly used for the next reaction.

To a stirred suspension of above aldehyde in dry MeOH (40 mL) was added NaBH$_4$ (1.26 g, 33.28 mmol) in small lots at 0 °C. After stirring the mixture at room temperature for 30 min, reaction mixture was quenched with water (20 mL). The aqueous layer extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated under vacuum. Silica gel column chromatography (hexane/ EtOAc 4:1 v/v) of the residue afforded 1,3-diol 13 (5.10 g, 86%) as a thick colorless liquid. $[\alpha]_D^{25} +4.48$ (c 1.0, MeOH); IR (CHCl$_3$) ν: 3458, 2935, 1452, 1110, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.67-7.65 (m, 4H), 7.46-7.37 (m, 6H), 3.95-3.71 (m, 1H), 3.67-3.57 (m, 4H), 3.06-3.00 (brs, 2H), 1.81-1.74 (m, 1H), 1.07 (s, 9H), 0.75 (d, J 6.88 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 135.5, 132.9, 129.9, 127.8, 77.1, 67.5, 66.4, 37.1, 26.8, 19.2, 13.4; HRMS (ESI), calcd for C$_{21}$H$_{30}$O$_3$SiNa $[M+Na]^+$ 381.1856; found 381.1857; HPLC: Chiralcel OD-H (250 x 45 mm), EtOH:n-hexane (01:99) v/v, flow rate 1.0 ml/min, $\lambda_{max} = 220$ nm, $t_R = 10.83$, $t_R = 12.05$, $t_R = 13.55$ and $t_R = 14.91$, > 99% ee, *anti*syn 98:2.7.

(2S,3S)-1-(tert-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-3-methylbutan-2-ol (21). To a solution of diol 13 (5.0 g, 13.99 mmol) in acetone (60 mL) were added K$_2$CO$_3$ (5.78 g, 41.82 mmol), TBAI (50 mg) and p-methoxy benzyl chloride (2.27 mL, 16.73 mmol) sequentially. The resulting mixture was refluxed for 18 hours. The reaction mixture was then concentrated under reduced pressure, the crude wa instilled to quench the reaction. The aqueous phase was extracted with EtOAc (3 x 40 mL), dried over anhydrous Na$_2$SO$_4$, and evaporated under vacuum. Silica gel column chromatography (hexane/ EtOAc 9:1 v/v) to obtain 21 (5.48 g, 83%) as a colourless liquid. $[\alpha]_D^{25} +7.26$ (c 1.0, CHCl$_3$); IR (CHCl$_3$) ν: 3433, 2932, 2860, 1430, 1105, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.66 (dt, J 8.0, 1.2 Hz, 4H), 7.46-7.31 (m, 6H), 7.20 (d, J 8.6 Hz, 2H), 6.85 (d, J 8.6 Hz, 2H) 4.39 (s, 2H), 3.79 (s, 3H), 3.75-3.58 (m, 3H), 3.51-3.34 (m, 2H), 3.06 (d, J 3.4 Hz, 1H), 2.06-1.86 (m, 1H), 1.05 (s, 9H), 0.91 (d, J 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 159.3, 133.7, 133.4, 130.5, 129.9, 129.4, 127.9, 113.9, 75.0, 73.0, 66.3, 55.4, 35.8, 27.0, 19.4, 14.1; HRMS (ESI), calcd for C$_{29}$H$_{38}$O$_3$SiNa $[M+Na]^+$ 501.2431; found 501.2432

3(S)-2(2S)-1-(4-Methoxybenzyloxy)propan-2-yl)oxirane (22). To a stirred solution of 21 (5.0 g, 10.4 mmol) in dry THF (50 mL), TBAF (1.0 M in THF, =15.66 mL, 15.66 mmol) was added, and resulting solution was stirred for 1.5 hours at room temperature. Saturated solution of NH$_4$Cl was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to get the diol. The crude residue was taken for the next reaction without further purification.

To a solution of above diol at 0 °C in dry DCM (20 mL), was added Et$_3$N (1.73 mL, 12.48 mmol), TsCl (2.37 g, 12.48 mmol) and Bu$_2$SnO (517 mg, 2.08 mmol) sequentially. The resulting solution was stirred for 30 min at room temperature and quenched with water (20 mL). The aqueous layer extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude monotosylated derivative formed was utilized for the next reaction without further purification.

To a solution of monotosylated derivative formed in the above reaction in ether (20 ml) was added KOH (1.75 g, 31.2 mmol). The resulting solution was stirred for 2 hours at room temperature and after which the turbid solution was quenched with H$_2$O (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), organic layer separated, washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure.
Purification by silica gel chromatography (hexane/EtOAc 19:1 v/v) afforded the epoxide 22 (2.05 g, 89%) as colorless liquid. [Rf 0.7, EtOAc/hexane 1:9 v/v]; [α]D25 +14.30 (c 1.0, CHCl3); IR (CH2Cl2) ν: 2929, 2858, 1612, 1246, cm−1; 1H NMR (400 MHz, CDCl3) δ: 7.27 (d, J 8.6 Hz, 2H), 6.88 (d, J 8.7 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.52-3.38 (m, 2H), 2.90-2.84 (m, 1H), 2.77-2.72 (m, 1H), 2.54 (dd, J 5.2, 2.8 Hz, 1H), 1.72-1.66 (m, 1H), 0.99 (d, J 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ: 159.2, 130.7, 129.3, 113.9, 79.2, 72.5, 55.4, 54.4, 45.9, 36.7, 13.3; HRMS (ESI), calcd for C13H18O3Na [M+N]+ 245.1148; found 245.1157.

*(3R,4S)-5-(4-Methoxybenzoxiloxy)-4-methylpent-1-en-3-ol (23).* To a -10 °C suspension of trimethylsulphonium iodide (7.33 g, 35.96 mmol) in THF (70 mL) was added n-BuLi (2.5 M hexane solution, 13.31 mL, 33.26 mmol). After 30 min a solution of epoxide 22 (2.0 g, 8.99 mmol) in THF (20 mL) was added dropwise and the reaction was continued at 0 °C for 1 h then mixture was stirred at room temperature for further 1.5 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel column chromatography (hexane/EtOH 1:4 v/v) to give the desired allylic alcohol (1.92 g, 91%) 23 as colourless liquid. [Rf 0.4, EtOAc/hexane 1:9 v/v]; [α]D25 18.3 (c 0.125, MeOH); IR (CH2Cl2) ν: 3450, 2930, 2858, 1612, 1246, cm−1; 1H NMR (400 MHz, CDCl3) δ: 7.25 (dt, J 0.8, 6.4 Hz, 2H), 6.88 (dt, J 6.8, 2.8 Hz, 2H), 5.83 (ddd, J 17.1, 10.4, 6.6 Hz, 1H), 5.25 (dt, J 17.2, 1.6 Hz, 1H), 5.16-5.13 (m, 1H), 4.45 (s, 2H), 3.99 (td, J 7.2, 3.2 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, J 9.6, 4.4 Hz, 1H), 3.48-3.41 (m, 2H), 1.93-1.83 (m, 1H), 0.88 (d, J 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ: 159.4, 139.6, 1230, 129.5, 115.9, 114.0, 77.9, 74.5, 73.2, 55.4, 38.6, 13.9; HRMS (ESI), calcd for C14H20O2Na [M+Na]+ 259.1304; found 259.1309.

tert-Butyl(3R,4S)-5-(4-methoxybenzoxiloxy)-4-methylpent-1-en-3-xylo)dimeylsilane (24). To an ice-cold solution of 23 (1.70 g, 7.19 mmol) in dry CH2Cl2 (20 mL) under nitrogen, imidazole (741 mg, 10.78 mmol), TBSCI (1.46 g, 9.3 mmol) and DMAP (175 mg, 0.20 mmol) were added sequentially and mixture was stirred for 2.5 hours before quenching the reaction mixture with saturated aqueous NH4Cl (10 mL). The reaction mixture was extracted with CH2Cl2, washed with brine and dried over Na2SO4, concentrated in vacuo and purified on silica gel column chromatography (hexane/EtOAc 24:1 v/v) to furnish TBS protected compound 24 (2.39 g, 95%) as a colorless oil. [Rf 0.6, EtOAc/hexane 1:9 v/v]; [α]D25 +4.22 (c 1.0, CHCl3); IR (CH2Cl2) ν: 2929, 2856, 1615, 1511, 1248 cm−1; 1H NMR (400 MHz, CDCl3) δ: 7.25 (td, J 6.4, 2.8 Hz, 2H), 6.87 (d, J =8.7 Hz, 2H), 5.76 (ddd, J 17.1, 7.4, 4.1 Hz, 1H), 5.17-5.02 (m, 2H), 4.41 (q, J 21.2, 11.6 Hz, 2H), 4.17 (q, J 7.2, 4.0 Hz, 1H), 3.80 (s, 3H), 3.43 (dd, J 9.1, 6.0 Hz, 1H), 3.31-3.21 (m, 1H), 1.92-1.79 (m, 1H), 0.95-0.87 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H); 13C NMR (100 MHz, CDCl3) δ: 159.2, 139.6, 131.0, 129.3, 115.3, 113.8, 75.4, 72.8, 72.2, 55.4, 40.1, 26.01, 18.3, 13.2, -4.1, -4.8; HRMS (ESI), calcd for C20H24O3SiNa [M+N]+ 373.2169; found 373.2170.

(2S,3R)-3-{(tert-Butyldimethylsiloxyl)-2-methylpent-4-en-1-ol (25). To a solution of compound 24 (1.5 g, 4.27 mmol) in CH2Cl2 (15 mL) 0 °C was added DDQ (1.16 g, 5.13 mmol) and aqueous pH 7.0 buffer (5 mL). After stirring for 45 minutes, the reaction temperature was quenched by the addition of saturated aqueous NaHCO3 (10 mL) solution. The mixture was diluted with CH2Cl2 (15 mL), the layers were separated, and the aqueous layer was extracted with CH2Cl2 (3×10 mL). The combined organic layer was washed with brine, dried over Na2SO4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc 19:3 v/v) to furnished a pale yellow liquid 25 (918 mg, 93%); [Rf 0.5, EtOAc/hexane 1:9 v/v]; [α]D25 +7.26 (c 1.0, CHCl3); IR (CH2Cl2) ν: 3458, 2929, 2858, 1462, 1250 cm−1; 1H NMR (400 MHz, CDCl3) δ: 5.83 (ddd, J 17.1, 10.4, 6.7 Hz, 1H), 5.23-5.11 (m, 2H), 4.07 (t, J 8.0 Hz, 1H), 3.73 (d, J 10.9 Hz, 1H), 3.61-3.54 (m, 1H), 2.72 (brs, 1H), 1.76-1.67 (m, 1H), 0.94 (d, J 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); 13C NMR (100 MHz, CDCl3) δ: 140.3, 115.7, 79.6, 66.0, 40.8, 26.0, 18.2, 14.3, -3.9, -4.8; HRMS (ESI), calcd for C12H26O2SiNa [M+N]+ 253.1594; found 253.1597.
(ZR,3R)-3-(tert-Butyldimethylsilyloxy)-2-methylpent-4-enoic acid (12). To a solution of alcohol 25 (900 mg, 3.90 mmol) in DCM:H₂O (2:1) (12) mL was added TEMPO (121 mg, 0.78 mmol) and bis(acetoxy)iodobenzene (BAIB) (2.76 g, 8.59 mmol) sequentially. The resulting mixture was stirred at room temperature for 24 hours and quenched by addition of saturated solution of Na₂S₂O₃. The mixture was diluted with EtOAc (15 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Silica gel column chromatography (hexane/EtOAc, 4:1 v/v) of the residue afforded acid 12 (830 mg, 87%) as a yellow solid. Mp 77-78 °C; [Rf 0.5, EtOAc/hexane 3:7 v/v]; [α]D²⁵ -12.5 (c 1.0, CHCl₃); IR (CH₂Cl₂) ν: 2929, 2857, 1719, 1461, 1252 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 5.75 (ddd, J 17.3, 10.4, 7.2 Hz, 1H), 5.21 (ddt, J 12.6, 10.5, 1.3 Hz, 2H), 4.25 (t, J 6.96 Hz, 1H), 2.59-2.55 (m, 1H), 1.13 (d, J 6.80 Hz, 3H), 0.91-0.84 (s, 9H), 0.075 (s, 3H), 0.049 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.2, 138.3, 117.3, 76.2, 46.7, 25.8, 18.2, 13.5, -4.1, -5.1; HRMS (ESI), calcd for C₁₂H₂₄O₃SiNa [M+Na]⁺ 267.1387; found 267.1395.

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Supplementary Material

Electronic supplementary information (ESI) available: copies of ¹H and ¹³C NMR spectra of compounds 11, 13, 16-20, 21-25, and HPLC data of compound 13. This material can be found via the “Supplementary Content” section of this article’s webpage.

References


24. HPLC: Chiralcel OD-H (250 * 45 mm), EtOH:PE (0:99) v/v, flow rate 1.0 mL/Min, λmax 220nm, tR = 10.83; tR = 12.05, tR= 13.55 and tR = 14.91; >99 % ee, anti:syn, 98.2.


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