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Synthesis of an advanced intermediate enroute to thiomarinol antibiotics

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ABSTRACT

A stereoselective synthesis of the C1-C14 fragment of thiomarinols is disclosed. The key steps include the stereoselective preparation of an allylic sulfide via a chloro sulfide by 1,2-asymmetric induction, ring-closing metathesis reaction, Kirmse-Doyle reaction for the preparation of a γ,δ-unsaturated ester, Nozaki-Hiyama-Kishi coupling and Julia-Kocienski olefination reaction. Substrate controlled asymmetric induction has been advantageously employed for the creation of stereogenic centers. Noyori transfer hydrogenation and asymmetric hydrogenation reactions have been utilized for the creation of carbinol stereocenters.

1. Introduction

Thiomarinols A, B, E and H (Fig. 1) rare natural products, isolated from the marine bacterium *Pseudoalteromonas sp.* SANK73390,[1–3] possess a pyrrothine moiety linked through an amide to marinolic acids that are related to clinically potent antibiotic pseudomonic acid A.[4,6] Thiomarinol H, possessing an anhydroornithine moiety was isolated from *Alteromonas* sp.[5] The thiomarinols display potent activity against Gram-positive and Gram-negative bacteria including MRSA strain (MIC <0.01 μgmL^{-1}). Thiomarinols A, B, E and H differ structurally from pseudomonic acid by the presence of a C4-hydroxyl, a shorter C1-alkoxy chain and an *E*-alkene instead of the C10-C11 epoxide and is more potent possessing wider spectrum of activity.

Thiomarinols like pseudomonic acid A inhibit the bacterial isoleucinyl tRNA synthetase enzyme responsible for loading the amino acid isoleucine onto its associated tRNA required for ribosomal protein synthesis. The impressive bioactivity and intriguing structure with five contiguous stereocenters (C4-C8) have attracted considerable attention from synthetic and medicinal chemists.[7] Herein, we describe a stereoselective route to the advanced intermediate **6**, constituting the C1-C14 subunit of thiomarinols by application of an α-chloro sulfide for the stereoselective preparation of an allylic sulfide, ring-closing metathesis reaction and Kirmse-Doyle rearrangement as the crucial steps.

2. Results and discussion

The retrosynthesis is depicted in Scheme 1. Thiomarinol can be obtained from the unsaturated acid **6** and alcohol **7**. The acid **6** can be obtained from the reaction of a suitable nucleophile derived from the iodo alkene **9** with aldehyde **8**. Aldehyde **8** can be derived from aldehyde **10** by Julia-Kocienski olefination with sulfone **11**. Aldehyde **10** was envisaged to be obtained from the unsaturated ester **12** which in turn can be traced to allyl sulfide **13**. Sulfide **13** can readily be obtained from chloro diol **14**.

The synthesis began with the chloro diol **14** (>95 ee), obtained by hydrolytic kinetic resolution of epichlorohydrin,[8] which on treatment with thiophenol in the presence of DBU furnished the diol sulfide **15**. Selective mono protection of the primary hydroxyl as its silyl ether **16** followed by allylation of the secondary hydroxyl furnished compound **17**. Reaction of **17** with *N*-chlorosuccinimide yielded α-chloro sulfide **18** which without isolation was treated with vinylzinc bromide to afford allylic sulfide **19** (>95 dr).[9] Ring-closing metathesis using Grubbs' II generation catalyst[10] **20**, furnished sulfide **13**, Scheme 2.

Syringe pump addition of ethyl diazoacetate to the solution of sulfide **13** in the presence of catalytic rhodium acetate resulted

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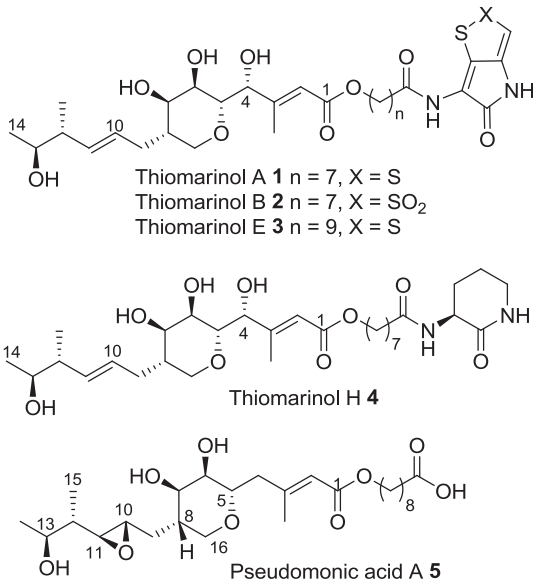


Fig. 1. Structures of thiomarinols and pseudomonic acid A.

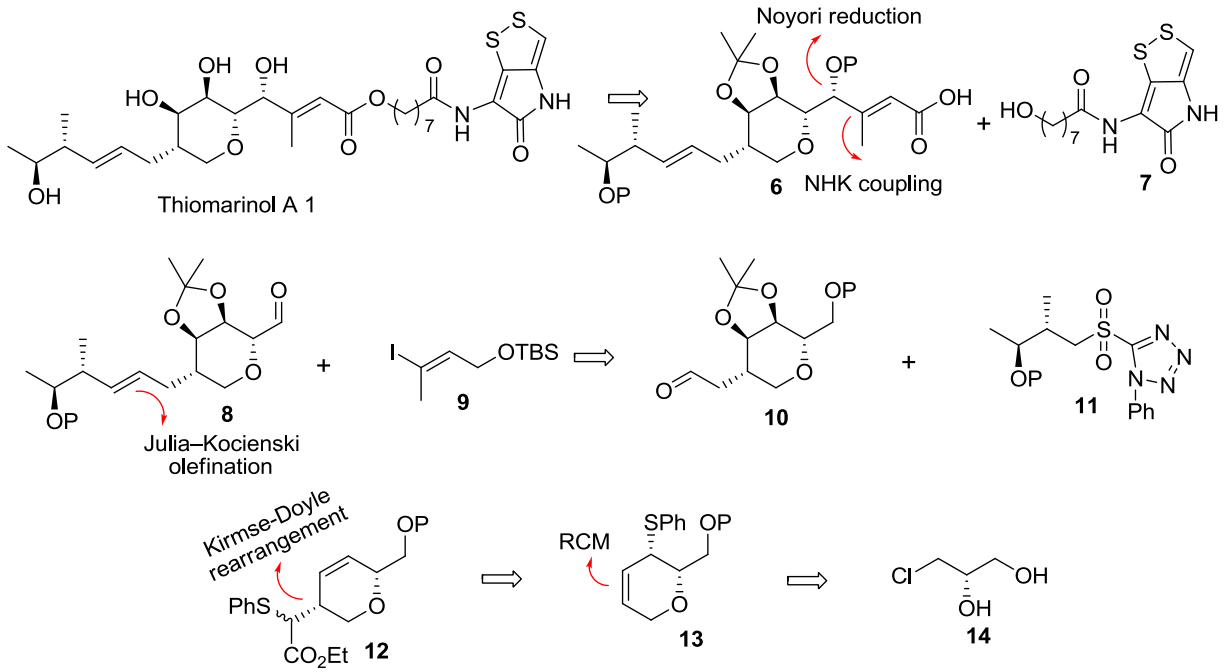
sequentially in ylide formation and Kirmse-Doyle rearrangement[11] to afford an inseparable epimeric mixture of esters **12**. Catalytic dihydroxylation employing the Upjohn process[12] led to substrate-controlled stereoselective introduction of the hydroxyl groups with concomitant oxidation of the sulfide to furnish epimeric sulfones **21**. Protection of the diol as the acetonide **22** followed by reductive desulfonylation[13] using Na-Hg yielded methyl ester **23** via transesterification. Partial reduction of the ester using DIBAL-H yielded aldehyde **10**, Scheme 3.

The sulfone partner for Julia olefination was readily prepared from ethyl acetoacetate **24**. BINAP-Ru(II)-catalyzed Noyori asymmetric hydrogenation[14] furnished β-hydroxy ester **25** (93:7 er).[15] The enantiomeric excess was determined from its mandelate ester derivative. Frater-Seebach alkylation[16] of the dianion derived from **25** with MeI afforded the ester **26** (95:5 dr). Protection of the hydroxy group as its MOM-ether **27** followed by reduction of the ester with LAH afforded alcohol **28**. Treatment with *N*-phenyltetrazole thiol **29** under Mitsunobu conditions[17] cleanly afforded sulfide **30** that was oxidized using *m*CPBA to furnish sulfone **11**, Scheme 4.

Treatment of sulfone[18] **11** with KHMDS followed by addition of aldehyde **10** and stirring while gradually allowing it to attain rt overnight furnished alkene **31** (*E*:*Z* = 88:12). Deprotection of the silyl ether using TBAF afforded alcohol **32**. It is to be noted that alcohol **32** has been employed as the key intermediate in the synthesis of pseudomonic acid.[19] Selective oxidation of the primary alcohol using $PhI(OAc)_2$ and TEMPO[20] yielded aldehyde **8** which was subjected to NHK coupling[21] with iodo alkene **9**[22] to furnish an inseparable mixture of allylic alcohols **33** (dr 45:55). Oxidation of the epimeric alcohols to the ketone **34** using Dess-Martin periodinane[23] followed by stereoselective reduction using Noyori's catalyst[24] afforded alcohol **36** (dr 92:8). Protection of the secondary alcohol as the TBS ether **37** followed by selective removal of the primary TBS ether afforded alcohol **38**. Oxidation using $PhI(OAc)_2$ and TEMPO in aq acetonitrile[25] furnished the advanced intermediate **6**, corresponding to the C1-C14 subunit of thiomarinol, Scheme 5.

3. Conclusions

In conclusion, a stereoselective route to the advanced intermediate of thiomarinol antibiotics is described. The key steps include the preparation of an allylic sulfide by reaction of vinylzinc bromide with chloro sulfide, ring-closing metathesis reaction, Kirmse-Doyle rearrangement, Julia-kocienski olefination and Nozaki-Hiyama-Kishi coupling for the successful introduction of the C4-hydroxyl group. Also Noyori transfer hydrogenation and asymmetric hydrogenation reactions have been used to introduce carbinol



Scheme 1. Retrosynthetic Disconnection of Thiomarinol.

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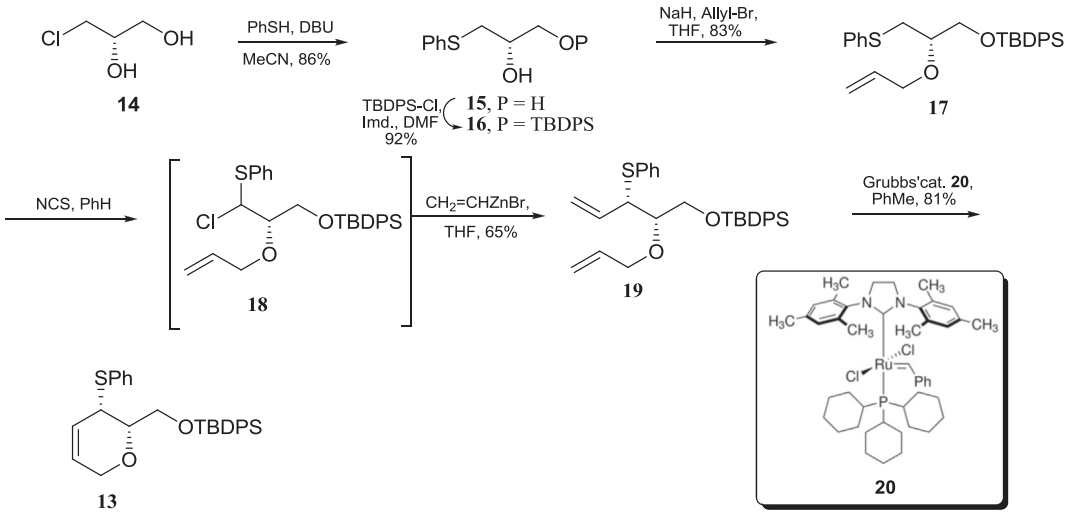
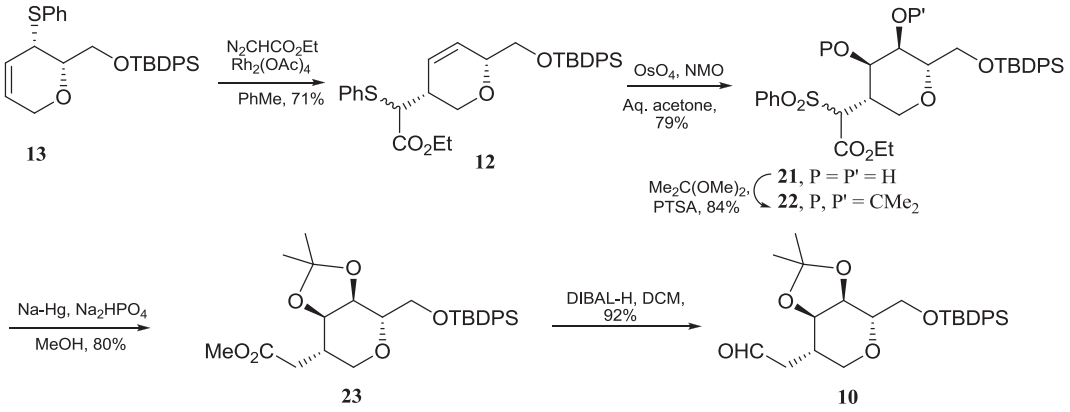
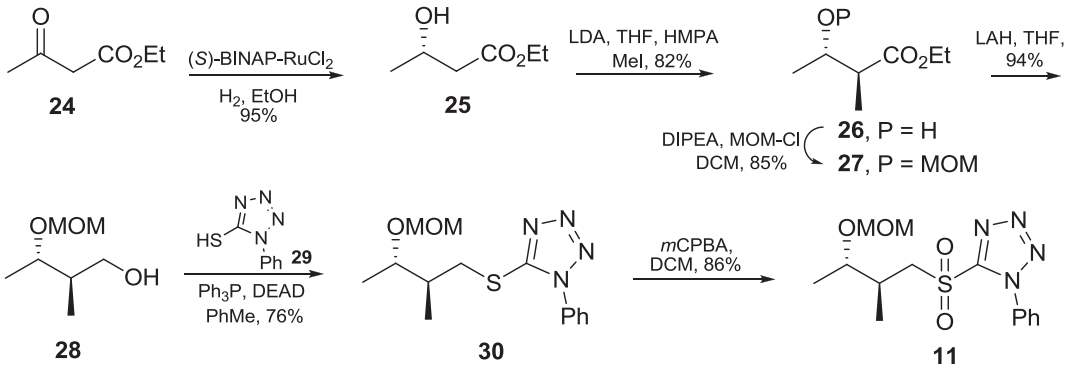


Scheme 2. Synthesis of allylic Sulfide **13**.



Scheme 3. Synthesis of Aldehyde **10**.



Scheme 4. Synthesis of Sulfone **11**.

stereocenter stereoselectively. The utility of chloro sulfides in C-C bond formation and introduction of stereogenic centers is elegantly demonstrated.

4. Experimental

Dry reactions were performed under an inert atmosphere using argon or nitrogen. All glassware apparatus used for reactions were thoroughly oven-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and toluene from CaH_2; MeOH from Mg cake; $CHCl_3$ from P_2O_5; acetone from $KMnO_4$ and K_2CO_3. 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 are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded neat or in KBr (as mentioned) and reported in wavenumbers

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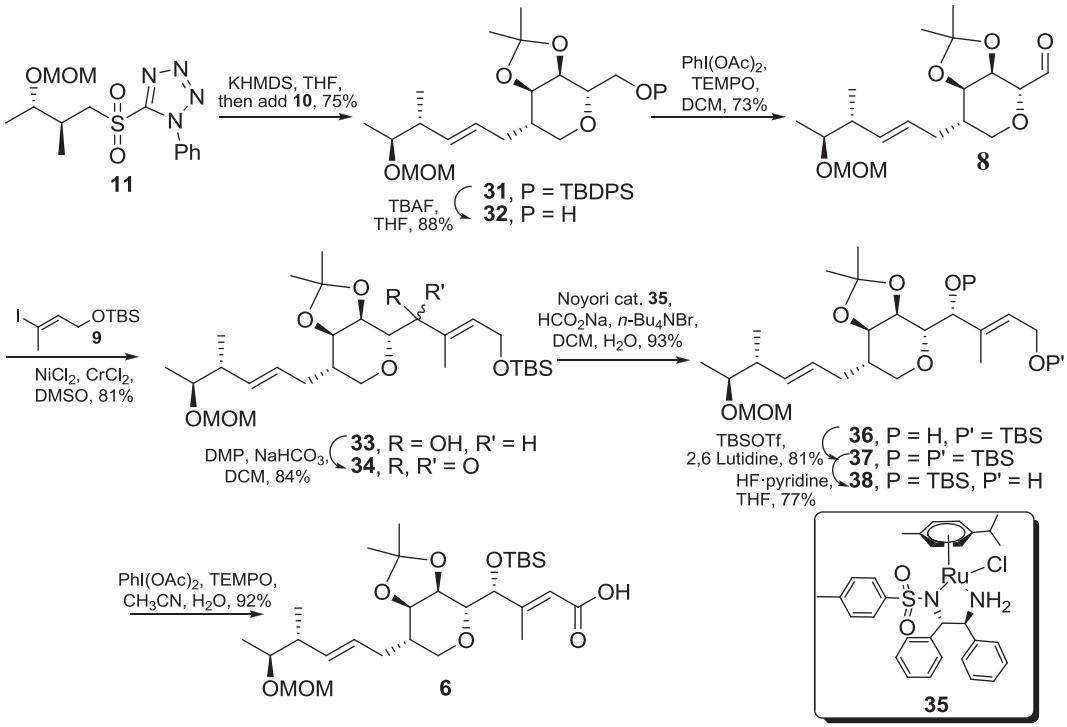

Scheme 5. Synthesis of advanced intermediate **6**.

(cm^{-1}). Mass spectral data were obtained using MS (EI) ESI and 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, 400, or 500 MHz and ^{13}C NMR spectra at 75, 100, or 125 MHz in $CDCl_3$ with the residual solvent signal as an internal standard unless mentioned otherwise; 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.

4.1. Experimental procedures

4.1.1. (S)-3-Chloro-1,2-propanediol **14**

To a solution of (*S,S*)-Jacobsen's catalyst (242 mg, 400 μmol, 0.005 equiv) in CH_2Cl_2 (6 mL) was added AcOH (250 μL) and the mixture stirred in air for 30 min. The crude catalyst residue obtained after concentration was dissolved in (±)-epichlorohydrin (6.25 mL, 80.0 mmol). The solution was cooled to 0 °C and treated with THF (2 mL) and H_2O (760 μL, 44.0 mmol). After 12 h at 4 °C, the residual epoxide was removed in vacuo at 20 °C. The residue was diluted with hexanes:EtOAc (5:3, 100 mL) and H_2O (30 mL) and the resulting mixture was filtered to remove solid catalyst. The layers were separated and the organic layer was washed with H_2O (2 × 30 mL). The combined aqueous layers were concentrated to yield (*S*)-3-chloro-1,2-propanediol (ee >95%, 3.57 g, 32.3 mmol) in 43% yield. TLC: R_f = 0.2 (ethyl acetate:hexanes, 4:6); ^1H NMR (300 MHz, $CDCl_3$): δ 5.41–4.41 (bs, *OH*), 3.99–3.82 (m, 1H), 3.81–3.49 (m, 4H). MS (ESI): 133 $[M+Na]^+$.

4.1.2. (S)-3-(Phenylthio)propane-1,2-diol (**15**)

To a solution of PhSH (21.5 mL, 210 mmol) in anhydrous CH_3CN (300 mL) was added DBU (33.2 mL, 220 mmol) slowly via syringe at 0 °C and the reaction mixture was stirred for 10 min. A solution of (*S*)-(+)-3-chloro-1,2-propanediol (22 g, 200 mmol) in anhydrous CH_3CN (100 mL) was added to the above reaction mixture at the same temperature and allowed to warm to room temperature. After 6 h, CH_3CN was evaporated under reduced pressure and the residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure to afford a crude product. Purification by the flash column chromatography using 30% EtOAc/hexane (v/v) as the eluent afforded diol **15** (31.6 g, 171.7 mmol) in 86% yield. TLC: R_f = 0.2 (ethyl acetate:hexanes, 4:6); $[\alpha]^{20}_D$: +20.7° (*c* 1, MeOH); IR (neat): 3338, 2919, 1646, 1437, 1100, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.19 (m, 5H), 3.85–3.72 (m, 2H), 3.59 (dd, *J* = 11.3, 6.0 Hz, 1H), 3.12 (dd, *J* = 13.6, 3.8 Hz, 1H), 3.00 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.83–2.60 (bs, 1H), 2.21–1.90 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 130.1, 129.1, 126.8, 69.9, 65.1, 37.7; MS (ESI): 207 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_9H_{12}O_2SNa$: 207.0450, found 207.0453.

4.1.3. (S)-1-((tert-Butyldiphenylsilyl)oxy)-3-(phenylthio)propan-2-ol (**16**)

To a solution of diol **15** (29.4 g, 160 mmol) in DMF (200 mL) was added imidazole (21.8 g, 320 mmol) followed by TBDPS-Cl (41 mL, 156.8 mmol) at 0 °C and the stirring was continued for 4 h at room temperature. The reaction was quenched by adding cold H_2O (120 mL) and diluted with dichloromethane (200 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 4% EtOAc/hexane (v/v) as the eluent afforded compound **16** (62.2 g, 147.4 mmol) in 92% yield. TLC: R_f = 0.4 (ethyl acetate:-hexanes, 1:9); $[\alpha]^{20}_D$: +37.7° (*c* 1, $CHCl_3$); IR (neat): 3448, 2930,

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2859, 1428, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.48–7.31 (m, 8H), 7.30–7.14 (m, 3H), 3.88–3.77 (m, 1H), 3.76–3.69 (m, 2H), 3.15 (dd, J = 13.6, 6.0 Hz, 1H), 3.03 (dd, J = 13.6, 6.8 Hz, 1H), 2.65 (d, J = 3.0 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 134.8, 132.9, 129.9, 129.5, 129.0, 127.8, 126.2, 70.2, 66.1, 37.2, 27.0, 19.3; MS (ESI): 461 $[M+Na+O]^+$; HRMS (ESI): *m/z* Calcd. for $C_{25}H_{30}O_3SSiNa$: 461.1577, found 461.1588. Note: The sulfide was oxidised to the sulfoxide during analysis.

4.1.4. (S)-(2-(Allyloxy)-3-(phenylthio)propoxy)(tert-butyl) diphenylsilane (**17**)

To a suspension of NaH (60% Nujol, 6.8 g, 169 mmol) in anhydrous THF (280 mL) cooled to 0 °C, maintained under N_2 atmosphere, was added a solution of compound **16** (54.8 g, 130 mmol) in anhydrous THF (120 mL) dropwise. The reaction mixture was stirred at room temperature for 30 min, during which time a large amount of opaque white solid had formed. The reaction mixture was recooled to 0 °C and allyl bromide (16.9 mL, 195 mmol) was added dropwise and the stirring continued for 8 h at room temperature. The reaction was quenched by adding ice pieces and the mixture was diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with H_2O (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 2.5% EtOAc/hexane (v/v) as the eluent to afford compound **17** as a colourless oil (50 g, 108.2 mmol) in 83% yield. TLC: R_f = 0.6 (ethyl acetate:hexanes, 1:9); $[\alpha]^{20}_D$: +2.7° (*c* 1, $CHCl_3$); IR (neat): 2930, 2857, 1737, 1427, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77–7.60 (m, 4H), 7.51–7.31 (m, 8H), 7.30–7.11 (m, 3H), 5.92–5.75 (m, 1H), 5.24–5.06 (m, 2H), 4.09–3.92 (m, 2H), 3.84–3.67 (m, 2H), 3.64–3.52 (m, 1H), 3.28 (dd, J = 13.6, 5.3 Hz, 1H), 3.05 (dd, J = 13.6, 6.8 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8, 135.6, 134.8, 133.3, 133.2, 129.7, 129.0, 128.8, 127.7, 125.8, 117.0, 78.3, 71.4, 64.5, 35.4, 26.8, 19.2; MS (ESI): 501 $[M+Na+O]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{34}O_3SSiNa$: 501.1890, found 501.1884. Note: The sulfide was oxidised to the sulfoxide during analysis.

4.1.5. (((2S,3S)-2-(Allyloxy)-3-(phenylthio)pent-4-en-1-yl)oxy)(tert butyl)diphenylsilane (**19**)

To a solution of vinylmagnesium bromide (1 M in THF, 30 mL, 30 mmol) cooled to −10 °C was added $ZnBr_2$ (1.5 M in THF, 20 mL, 30 mmol) dropwise and the mixture was stirring for 1 h at room temperature. While transmetalation was in progress, the chloro sulfide intermediate **18** was prepared by addition of *N*-chlorosuccinimide (2.9 g, 22 mmol) to a solution of the sulphide **17** (9.3 g, 20 mmol) in anhydrous benzene (200 mL) at ambient temperature and stirred for a period of 15 min. The resulting chloro sulfide solution in benzene (200 mL) was added to the vinylzinc bromide reagent and stirring continued at ambient temperature for 7 h. The reaction was quenched by the addition of aqueous saturated ammonium chloride solution (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography on silica gel using 2.5% EtOAc/hexane (v/v) as the eluent afforded diene **19** (6.4 g, 13.1 mmol) in 65% yield. TLC: R_f = 0.6 (ethyl acetate:hexanes, 1:9); $[\alpha]^{20}_D$: +15.8° (*c* 1.4, $CHCl_3$); IR (neat): 2931, 2858, 1732, 1428, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.63 (m, 4H), 7.47–7.33 (m, 8H), 7.28–7.16 (m, 3H), 5.93–5.81 (m, 2H), 5.25–5.10 (m, 2H), 5.02–4.95 (m, 2H), 4.11 (dd, J = 12.4, 4.8 Hz, 1H), 4.06–3.93 (m, 3H), 3.79 (dd, J = 10.5, 4.8 Hz, 1H), 3.66–3.61 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 135.6, 135.6, 134.9, 133.3, 133.2, 132.2, 129.7, 128.6, 127.7, 126.6, 116.9, 116.4, 81.5, 72.0, 63.6, 54.9, 26.9, 19.3; MS (ESI): 511 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{30}H_{36}O_2SSiNa$: 511.2098, found 511.2113.

4.1.6. tert-Butyldiphenyl(((2S,3S)-3-(phenylthio)-3,6-dihydro-2H-pyran-2-yl)methoxy)silane (**13**)

The solution of diene **19** (2.4 g, 5 mmol) in anhydrous toluene (10 mL) was degassed by bubbling N_2 for 15 min. Grubbs 2nd generation catalyst (124 mg, 0.15 mmol, 3 mol%) was added and the reaction mixture was refluxed for 8 h and then allowed to attain ambient temperature. Toluene was removed under reduced pressure. The crude reaction mixture was purified via flash column chromatography on silica gel using 3% EtOAc/hexane (v/v) as the eluent to afford sulfide **13** as a colourless oil (1.86 g, 4.04 mmol) in 81% yield. TLC: R_f = 0.4 (ethyl acetate:hexanes, 1:9); $[\alpha]^{20}_D$: −117° (*c* 0.9, $CHCl_3$); IR (neat): 2932, 2857, 1472, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.59 (m, 4H), 7.47–7.31 (m, 8H), 7.23–7.15 (m, 3H), 6.06–5.95 (m, 1H), 5.77–5.68 (m, 1H), 4.16–4.08 (m, 2H), 4.02–3.95 (m, 1H), 3.95–3.85 (m, 2H), 3.77–3.71 (m, 1H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.0, 133.1, 129.6, 128.5, 127.7, 127.5, 126.9, 126.1, 77.4, 66.1, 64.8, 45.4, 27.0, 19.3; MS (ESI): 499 $[M+Na+O]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{32}O_3SSiNa$: 499.1734, found 499.1732. Note: The sulfide was oxidised to the sulfoxide during analysis.

4.1.7. (R)-Ethyl 2-((3R,6R)-6-(((tert-butyldiphenylsilyl)oxy) methyl)-3,6-dihydro-2H-pyran-3-yl)-2-(phenylthio)acetate and (S)-Ethyl 2-((3R,6R)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-3,6-dihydro-2H-pyran-3-yl)-2-(phenylthio)acetate (**12**)

A magnetically stirred mixture of allylic sulfide 13 (4.2 g, 9 mmol), rhodium acetate (79.5 mg, 0.18 mmol, 2 mol%) in anhydrous toluene (15 mL) was heated at 90 °C under nitrogen atmosphere. Ethyl diazoacetate (1.9 mL, 18 mmol) in toluene (4 mL) was added dropwise to the above mixture via a syringe pump during 3 h. The solution was refluxed for another 4 h and cooled to room temperature. The catalyst was removed by partitioning between toluene and aqueous 10% HCl solution (12 mL). The organic layer was separated and washed with H_2O (15 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography on silica gel using 3% EtOAc/hexane (v/v) as the eluent afforded compound 12 (3.5 g, 6.4 mmol) in 71% yield. TLC: R_f = 0.2 (ethyl acetate:hexanes, 1:9); IR (neat): 2931, 2859, 1728, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.64 (m, 2H), 7.47–7.38 (m, 8H), 7.27–7.24 (m, 3H), 6.27–6.22 (m, 1H), 5.93–5.89 (m, 1H), 4.24–4.18 (m, 1H), 4.11–4.08 (m, 2H), 3.78–3.71 (m, 4H), 3.66–3.60 (m, 1H), 2.56–2.49 (m, 1H), 1.16–1.12 (m, 3H), 1.08–1.05 (s, 9H); MS (ESI): 569 $[M+Na]^+$. Note:- The spectrum is of the product along with inseparable impurities formed during the reaction.

4.1.8. (R)-Ethyl- 2-((3S,4R,5R,6S)-6-(((tert-butyldiphenylsilyl)oxy) methyl)-4,5-dihydroxytetrahydro-2H-pyran-3-yl)-2-(phenylsulfonyl)acetate and (S)-Ethyl 2-((3S,4R,5R,6S)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-4,5-dihydroxytetrahydro-2H-pyran-3-yl)-2-(phenylsulfonyl)acetate (**21**)

To a solution of dihydropyran 12 (6.6 g, 12 mmol) in acetone:-water (9:1, 48 mL), *N*-methylmorpholine *N*-oxide (4.2 g, 36 mmol) and osmium tetroxide (0.04 M in Toluene, 6 mL, 0.24 mmol) were added and the mixture stirred at ambient temperature overnight. The reaction was quenched with aq saturated sodium sulphite (50 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers ware washed with H_2O (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude

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residue via flash column chromatography on silica gel using 30% EtOAc/hexane (v/v) as the eluent afforded diol 21 (5.8 g, 9.5 mmol) in 79% yield. TLC: $R_f = 0.2$ (ethyl acetate:hexanes, 4:6); IR (neat): 3447, 2924, 2854, 1612, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92–7.84 (m, 2H), 7.74–7.62 (m, 5H), 7.60–7.49 (m, 2H), 7.48–7.35 (m, 6H), 4.69–4.64 (m, 0.5H), 4.48–4.35 (m, 1H), 4.33–4.24 (m, 0.5H), 4.17–3.86 (m, 4H), 3.85–3.74 (m, 2.5H), 3.67–3.56 (m, 1H), 3.40–3.32 (m, 0.5H), 2.82–2.71 (m, 1H), 1.10–1.05 (m, 9H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 165.5*, 137.6, 137.5*, 135.6, 135.6*, 135.5, 134.4*, 134.3, 132.8, 132.7*, 132.5, 130.0, 129.9*, 129.3, 129.0*, 127.9, 127.8, 75.6, 75.0*, 70.2, 68.9*, 68.1, 68.0*, 67.2, 66.2*, 65.4, 64.8*, 63.3, 62.4*, 62.3, 62.2*, 40.4, 40.0*, 26.9, 26.8*, 19.2, 19.1*, 13.7, 13.5*; MS (ESI): 635 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{32}H_{40}O_8SSiNa$: 635.2105, found 635.2108. Note:- The ^{13}C signals for one of the epimeric alcohol is denoted by an asterisk mark.

4.1.9. (R)-Ethyl 2-((3aR,4S,7S,7aR)-4-(((tert-butyldiphenylsilyl)oxy) methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl)-2-(phenylsulfonyl)acetate and (S)-Ethyl 2-((3aR,4S,7S,7aR)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl)-2-(phenylsulfonyl)acetate (**22**)

To a stirred suspension of diol 21 (4.9 g, 8 mmol) and anhydrous Na_2SO_4 (1.3 g, 9 mmol) in EtOAc (16 mL) was added 2,2-dimethoxypropane (16 mL) and a few crystals of *p*-toluenesulfonic acid monohydrate. After 4 h of stirring at room temperature, the solution was diluted with EtOAc (20 mL) and anhydrous Na_2SO_4 was removed via filtration. The resulting solution was washed with aq saturated $NaHCO_3$ (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent afforded compound 22 (4.4 g, 6.7 mmol) in 84% yield. TLC: $R_f = 0.5$ (ethyl acetate:hexanes, 2:8); IR (neat): 2930, 1737, 1145, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94–7.84 (m, 2H), 7.74–7.63 (m, 5H), 7.60–7.50 (m, 2H), 7.46–7.31 (m, 6H), 4.71–4.65 (m, 0.5H), 4.35–4.29 (m, 1H), 4.25–4.05 (m, 2H), 4.01–3.80 (m, 4H), 3.76–3.66 (m, 1H), 3.65–3.57 (m, 0.5H), 3.53–3.37 (m, 1H), 2.97–2.79 (m, 1H), 1.63–1.43 (m, 6H), 1.00–0.97 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 165.2*, 137.7, 137.7*, 135.7, 135.6*, 134.3, 134.3*, 133.4, 133.4*, 133.4, 129.6, 129.6*, 129.3, 129.1*, 127.6, 127.6, 127.6*, 109.2, 108.9*, 79.2, 78.7*, 72.9, 72.8*, 70.6, 70.5*, 69.7, 69.6*, 64.5, 64.2*, 63.6, 62.3, 62.2*, 37.0, 36.9*, 28.0, 26.9, 26.8*, 26.5, 26.4*, 19.3, 19.3*, 13.7, 13.6*; MS (ESI): 675 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{35}H_{44}O_8SSiNa$: 675.2418, found 675.2421. Note:- The ^{13}C signals for one of the epimeric alcohol is denoted by an asterisk mark.

4.1.10. Methyl 2-((3aR,4S,7S,7aR)-4-(((tert-butyldiphenylsilyl)oxy) methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl) acetate (**23**)

Sodium amalgam (6%, 3.06 g, 13.7 mmol) was added in four equal portions during 15 min to a stirred, ice-cooled mixture of the sulfone 22 (2.5 g, 4.57 mmol), anhydrous disodium orthophosphate (1.94 g, 13.7 mmol) in anhydrous methanol (40 mL). The resulting mixture was stirred further for a period of 1 h with continued cooling and then allowed to warm to ambient temperature and stirred for 2 h. Methanol was evaporated and crude residue was partitioned between ether (50 mL) and water (50 mL). The ether layer was separated and washed with water (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent afforded ester 23 (1.81 g, 3.64 mmol) in 80% yield. TLC: $R_f = 0.3$ (ethyl acetate:hexanes, 2:8); $[\alpha]^{20}_D$: −9.8° (*c* 2.84, $CHCl_3$); IR (neat): 2958, 2931, 1738, 1087, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.64 (m, 4H), 7.46–7.32 (m, 6H), 4.13–4.08 (m, 1H), 4.04–3.97 (m, 1H), 3.91–3.84 (dd, $J = 11.3$, 2.3 Hz, 1H), 3.82–3.64 (m, 6H), 3.43–3.35 (m, 1H), 2.66–2.40 (m, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 135.7, 135.7, 133.6, 133.6, 129.6, 127.6, 127.5, 108.9, 79.0, 75.3, 69.9, 65.9, 64.5, 51.7, 34.8, 33.9, 28.2, 26.9, 26.4, 19.3; MS (ESI): 521 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{38}O_6NaSi$: 521.2330, found 521.2345.

4.1.11. 2-((3aR,4S,7S,7aR)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl) acetaldehyde (**10**)

To a solution of ester 23 (1.75 g, 3.5 mmol) in anhydrous CH_2Cl_2 (25 mL) cooled to −78 °C, maintained under nitrogen atmosphere was added DIBAL-H (1.2 M in Toluene, 2.9 mL, 3.5 mmol) dropwise during 15 min and the mixture stirred further for a period of 15 min. The reaction mixture was quenched using an aqueous saturated solution of sodium potassium tartrate (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by the flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford aldehyde 10 (1.5 g, 3.21 mmol) in 92% yield. TLC: $R_f = 0.4$ (ethyl acetate:hexanes, 3:7); $[\alpha]^{20}_D$: −14.2° (*c* 1, $CHCl_3$); IR (neat): 2930, 2859, 1729, 1109, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.74–7.65 (m, 4H), 7.46–7.32 (m, 6H), 4.09–3.97 (m, 2H), 3.89 (dd, $J = 11.3$, 2.3 Hz, 1H), 3.83–3.69 (m, 2H), 3.64 (dd, $J = 12.1$, 1.5 Hz, 1H), 3.43–3.35 (m, 1H), 2.78 (dd, $J = 16.6$, 6.8 Hz, 1H), 2.68–2.50 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 135.6, 133.4, 129.5, 127.5, 108.9, 78.8, 75.3, 69.7, 65.9, 64.3, 44.5, 31.4, 28.1, 26.8, 26.3, 19.2; MS (ESI): 491 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{27}H_{36}O_5SiNa$: 491.2224, found: 491.2226.

4.1.12. tert-Butyl(((3aR,4S,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)methoxy) diphenylsilane (**31**)

The solution of sulfone 11 (1.3 g, 3.84 mmol) in anhydrous THF (40 mL) cooled to −78 °C was treated dropwise with potassium bis(trimethylsilyl)amide (0.5 M in Toluene, 9.2 mL, 4.6 mmol) under argon. The resulting yellow solution was stirred at −78 °C for 0.5 h. The solution of aldehyde 10 (1.5 g, 3.2 mmol) in anhydrous THF (20 mL) was slowly introduced via syringe. The reaction mixture was stirred at −78 °C for 1.5 h and then allowed to warm to ambient temperature and stirred overnight. The cloudy white reaction mixture was quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford compound 31 (*E*:*Z* = 88:12) as a colorless oil (1.4 g, 2.4 mmol) in 75% yield. TLC: $R_f = 0.5$ (ethyl acetate:hexanes, 2:8); $[\alpha]^{20}_D$: −3.5° (*c* 0.7, $CHCl_3$); IR (neat): 2960, 2929, 1735, 1384, 1035, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.67 (m, 4H), 7.44–7.34 (m, 6H), 5.51–5.38 (m, 2H), 4.68 (d, $J = 6.9$ Hz, 1H), 4.61 (d, $J = 6.9$ Hz, 1H), 4.19–4.08 (m, 1H), 4.01 (dd, $J = 8.9$, 5.0 Hz, 1H), 3.88 (dd, $J = 11.3$, 2.1 Hz, 1H), 3.76 (dd, $J = 11.3$, 5.3 Hz, 1H), 3.72–3.68 (m, 2H), 3.63–3.56 (m, 1H), 3.39–3.33 (m, 4H), 2.37–2.15 (m, 3H), 2.01–1.94 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.10 (d, $J = 6.4$ Hz, 3H), 1.07 (s, 9H), 1.01 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 135.7, 135.1, 133.7, 133.7, 129.5, 127.8, 127.5, 127.5, 108.5, 95.1, 78.9, 76.6, 75.5, 69.8, 65.7, 64.5, 55.3, 42.2,

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36.8, 33.7, 28.3, 26.8, 26.4, 19.3, 17.0, 15.8; MS (ESI): 605 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{34}H_{50}O_6NaSi$: 605.3269, found: 605.3283.

4.1.13. ((3aR,4S,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)methanol (**32**)

To a solution of compound 31 (1.0 g, 1.72 mmol) in THF (8 mL) was added TBAF (1 M in THF, 1.72 mL, 1.72 mmol). The reaction was stirred at room temperature for 3 h and then quenched with saturated NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using 30% EtOAc/hexane (v/v) as the eluent to afford compound 32 as a colorless oil (0.52 g, 1.51 mmol) in 88% yield. TLC: $R_f = 0.3$ (ethyl acetate:hexanes, 3:7); $[\alpha]^{20}_D$: −6.5° (*c* 1, $CHCl_3$); IR (neat): 3416, 2927, 1731, 1342, 1059, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.52–5.38 (m, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.17–4.11 (m, 1H), 3.87 (dd, *J* = 9.2, 5.0 Hz, 1H), 3.84–3.77 (m, 1H), 3.74 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.71–3.65 (m, 1H), 3.62–3.52 (m, 2H), 3.39–3.31 (m, 4H), 2.35–2.12 (m, 3H), 2.07–1.94 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.2, 127.5, 108.7, 95.1, 78.4, 76.5, 75.2, 70.0, 66.0, 63.2, 55.3, 42.2, 36.6, 33.8, 28.2, 26.2, 17.0, 15.8; MS (ESI): 367 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{18}H_{32}O_6Na$: 367.2091, found: 367.2093.

4.1.14. (3aR,4R,7S,7aR)-7-((4R,5S,E)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-carbaldehyde (**8**)

To a solution of alcohol 32 (0.76 g, 2.2 mmol) in anhydrous CH_2Cl_2 (11 mL) cooled to 0 °C was added BAIB (0.85 g, 2.64 mmol), TEMPO (40 mg, 0.22 mmol) under nitrogen atmosphere and stirred at 0 °C until complete consumption of starting material occurred (ca. 4 h). The reaction mixture was passed through a short pad of Celite, the volatiles were removed under reduced pressure to afford the crude aldehyde which was purified by flash column chromatography using 25% EtOAc/hexane (v/v) as the eluent to afford aldehyde 8 (0.55 g, 1.6 mmol) in 73% yield. TLC: $R_f = 0.2$ (ethyl acetate:hexanes, 3:7); $[\alpha]^{20}_D$: −12.5° (*c* 1, $CHCl_3$); IR (neat): 2960, 2938, 1735, 1325, 1065, 835 cm $^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): δ 9.73 (s, 1H), 5.53–5.37 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.20–4.11 (m, 2H), 3.94 (d, *J* = 7.6 Hz, 1H), 3.80 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.66 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.62–3.55 (m, 1H), 3.36 (s, 3H), 2.34–2.25 (m, 1H), 2.24–2.12 (m, 2H), 2.05–1.96 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 135.5, 127.1, 109.4, 95.0, 77.3, 76.5, 75.2, 70.8, 66.3, 55.3, 42.1, 36.5, 33.3, 28.2, 26.1, 17.1, 15.8; MS (ESI): 365 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{18}H_{30}O_6Na$: 365.1935, found 365.1937.

4.1.15. (R,E)-4-((tert-Butyldimethylsilyl)oxy)-1-((3aR,4S,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-methylbut-2-en-1-ol and (S,E)-4-((tert-Butyldimethylsilyl)oxy)-1-((3aR,4S,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-methylbut-2-en-1-ol (**33**)

To a stirred suspension of $NiCl_2$ (7.3 mg, 0.05 mmol) and $CrCl_2$ (0.84 g, 6.8 mmol) in degassed DMSO (25 mL) under an argon atmosphere was added a solution of the aldehyde 8 (0.29 g, 0.85 mmol) and iodo alkene 9 (2.12 g, 6.8 mmol) in degassed DMSO (8 mL). The mixture was stirred for 19 h, diluted with an aq saturated NH_4Cl solution (60 mL) and extracted with EtOAc (3 × 60 mL). The combined extracts were washed with H_2O (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 30% EtOAc/hexane (v/v) as the eluent to provide allylic alcohol 33(dr 45:55) as an epimeric mixture (0.36 g, 0.69 mmol) in 81% yield. TLC: $R_f = 0.4$ (ethyl acetate:hexanes, 4:6); IR (neat): 3416, 2927, 2832, 1731, 1384, 1059, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.67–5.59 (m, 1H), 5.51–5.35 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.26 (d, *J* = 5.8 Hz, 2H), 4.14–4.10 (m, 1.5H), 4.05–3.98 (m, 1H), 3.96–3.92 (m, 0.5H), 3.74–3.63 (m, 2H), 3.62–3.55 (m, 1H), 3.42 (dd, *J* = 8.9, 5.2 Hz, 0.5H), 3.38–3.32 (m, 3.5H), 2.64–2.55 (bs, 0.5*OH*), 2.48–2.43 (bs, 0.5*OH*), 2.34–2.25 (m, 1H), 2.21–2.12 (m, 2H), 2.00–1.94 (m, 1H), 1.63 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.3, 135.2*, 134.9*, 134.2, 128.1, 127.6*, 127.5, 108.7, 108.5*, 95.1, 78.6, 78.5*, 77.4, 76.5, 75.4, 75.3*, 70.8, 70.6*, 66.2, 65.9*, 60.1, 60.0*, 55.4, 42.2, 36.7, 33.8, 33.7*, 28.2, 26.3, 26.0, 18.3, 17.0, 15.8, 13.0*, 12.9, −5.1, −5.2; MS (ESI): 551 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{52}O_7SiNa$: 551.3375, found 551.3381. Note:- The ^{13}C signals for one of the epimeric alcohol is denoted by an asterisk mark.

4.1.16. (E)-4-((tert-Butyldimethylsilyl)oxy)-1-((3aR,4R,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-methylbut-2-en-1-one (**34**)

To a stirred solution of alcohol 33 (0.264 g, 0.5 mmol) in anhydrous dichloromethane (4 mL) was added solid $NaHCO_3$ (0.17 g, 2 mmol) followed by the Dess–Martin periodinane (0.28 g, 0.65 mmol). After stirring for 30 min, the reaction mixture was filtered through a pad of Celite. To the organic layer, aqueous saturated $Na_2S_2O_3$ solution (6 mL) and aqueous saturated $NaHCO_3$ solution (5 mL) were added and the biphasic mixture was stirred until both the layers had cleared. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed with brine (8 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide ketone 34 as a clear colorless oil (0.22 g, 0.42 mmol) in 84% yield which was taken ahead to the next step without any further purification. TLC: $R_f = 0.3$ (ethyl acetate:hexanes, 3:7); IR (neat): 3447, 2924, 2874, 1654, 1515, 1301, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (tq, *J* = 5.1, 1.0 Hz, 1H), 5.53–5.30 (m, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 7.3 Hz, 1H), 4.45 (dd, *J* = 5.1, 1.0 Hz, 2H), 4.36 (dd, *J* = 7.0, 5.1 Hz, 1H), 4.20–4.17 (m, 1H), 3.79 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.62–3.51 (m, 2H), 3.36 (s, 3H), 2.34–1.95 (m, 4H), 1.76 (s, 3H), 1.56 (s, 3H), 1.36 (s, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); MS (ESI): 549 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{50}O_7SiNa$: 549.3218, found 549.3234.

4.1.17. (R,E)-4-((tert-Butyldimethylsilyl)oxy)-1-((3aR,4S,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-methylbut-2-en-1-ol (**36**)

To a solution of ketone 34 (100 mg, 0.19 mmol) in mixture of CH_2Cl_2 and H_2O (1:1, 10 mL) at 25 °C were added HCO_2Na (0.13 g, 1.9 mmol), *n*-Bu_4NBr (18 mg, 0.06 mmol) and cat. RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (2.5 mg, 0.004 mmol) and the biphasic mixture was stirred vigorously at 25 °C for 24 h. The mixture was then diluted with H_2O (8 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide alcohol 36 (dr 92:8) as a clear

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colorless oil (93 mg, 0.176 mmol) in 93% yield which was used without any further purification. TLC: $R_f = 0.4$ (ethyl acetate:hexanes, 4:6); $[\alpha]^{20}_D$: +0.7° (*c* 0.9, $CHCl_3$); IR (neat): 3448, 2931, 2854, 1728, 1427, 1384, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.64 (t, *J* = 5.8 Hz, 1H), 5.61–5.35 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.26 (d, *J* = 5.8 Hz, 2H), 4.14–4.10 (m, 2H), 4.02 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.73–3.63 (m, 2H), 3.62–3.56 (m, 1H), 3.42 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.36 (s, 3H), 2.59 (d, *J* = 3.2 Hz, 1*OH*), 2.34–2.25 (m, 1H), 2.21–2.11 (m, 2H), 2.20–1.93 (m, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.2, 134.2, 128.2, 127.6, 108.7, 95.1, 78.6, 77.4, 76.5, 75.4, 70.9, 66.2, 60.0, 55.4, 42.2, 36.7, 33.8, 28.2, 26.3, 26.0, 18.3, 17.0, 15.8, 12.9, −5.1, −5.2; MS (ESI): 551 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{52}O_7SiNa$: 551.3375, found 551.3382.

4.1.18. (R,E)-5-((3aR,4R,7S,7aR)-7-((4R,5S,E)-5-(Methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2,2,3,3,6,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodec-6-ene (**37**)

To a stirred solution of allylic alcohol 36 (44 mg, 0.083 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C were added 2,6 lutidine (22 μL, 0.19 mmol) followed by TBSOTf (20 μL, 0.09 mmol) and the reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was then quenched with aqueous saturated NH_4Cl solution (1 mL) and the biphasic mixture was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 20% EtOAc/hexane (v/v) as the eluent afforded compound 37 with dr 45:55 (43 mg, 0.067 mmol) in 81% yield. TLC: $R_f = 0.6$ (ethyl acetate:hexanes, 4:6); $[\alpha]^{20}_D$: +1.1° (*c* 1, $CHCl_3$); IR (neat): 2930, 2858, 1732, 1412, 1357, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.56 (tq, *J* = 6.1, 1.2 Hz, 1H), 5.46–5.35 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.23 (d, *J* = 5.9 Hz, 2H), 4.15–4.08 (m, 2H), 4.05–4.02 (m, 1H), 3.63 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.60–3.56 (m, 1H), 3.54 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.46 (dd, *J* = 7.6, 3.5 Hz, 1H), 3.36 (s, 3H), 2.34–2.24 (m, 1H), 2.20–2.07 (m, 2H), 1.93–1.85 (m, 1H), 1.62 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 9H), 0.02 (S, 3 h); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.2, 135.0, 127.8, 127.2, 108.1, 95.1, 80.1, 77.7, 76.6, 75.6, 69.8, 65.4, 60.0, 55.3, 42.2, 37.1, 33.3, 28.3, 26.5, 25.9, 18.3, 16.9, 15.7, 13.1, −4.7, −4.9, −5.15, −5.2; MS (ESI): 665 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{34}H_{66}O_7Si_2Na$: 665.4239, found 665.4261.

4.1.19. (R,E)-4-((tert-Butyldimethylsilyl)oxy)-4-((3aR,4R,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-3-methylbut-2-en-1-ol (**38**)

A solution of 37 (20 mg, 0.03 mmol) in anhydrous THF (1.5 mL) cooled to 0 °C was treated with a solution of HF-pyridine (ca ~70% HF, 0.2 mL). The reaction was stirred at the same temperature for a period of 3 h, at which time the reaction was diluted dropwise with aqueous saturated $NaHCO_3$ solution (1 mL) and warmed to room temperature with stirring. The reaction mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 30% EtOAc/hexane (v/v) as the eluent afforded compound 38 (12 mg, 0.023 mmol) in 77% yield. TLC: $R_f = 0.3$ (ethyl acetate:hexanes, 4:6); $[\alpha]^{20}_D$: +17° (*c* 2.3, $CHCl_3$); IR (neat): 3416, 2927, 2857, 1731,1487, 1335, 1059, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.83–5.69 (m, 1H), 5.47–5.36 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.26–4.16 (m, 3H), 4.12–4.06 (m, 2H), 3.67 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.61–3.56 (m, 2H), 3.41 (dd, *J* = 8.2, 3.1 Hz, 1H), 3.36 (s, 3H), 2.36–2.26 (m, 1H), 2.21–2.13 (m, 2H), 1.94–1.87 (m, 1H), 1.70 (s, 3H), 1.45 (s, 3H), 1.29 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.0, 135.2, 127.7, 124.4, 108.1, 95.2, 79.4, 77.0, 76.7, 75.5, 69.0, 65.3, 58.5, 55.3, 42.3, 36.8, 33.2, 28.3, 26.5, 25.9, 18.3, 17.0, 15.8, 13.8, −4.8; MS (ESI): 551 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{52}O_7SiNa$: 551.3375, found 551.3384.

4.1.20. (R,E)-4-((tert-Butyldimethylsilyl)oxy)-4-((3aR,4R,7S,7aR)-7-((4R,5S,E)-5-(methoxymethoxy)-4-methylhex-2-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-3-methylbut-2-enoic acid (**6**)

To a stirred solution of alcohol 38 (10 mg, 0.019 mmol) in a mixture of CH_3CN:H_2O (1:1, 3 mL) were added BAIB (177.5 mg, 0.57 mmol) and TEMPO (5.6 mg, 0.04 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred further for a period of 2 h. The reaction mixture was passed through a short pad of silica gel and the volatiles were removed under reduced pressure to afford the crude residue. The residue was dissolved in CH_2Cl_2 and the pH adjusted to 9 using saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was adjusted to pH = 3–4 using aqueous 1N HCl. The acid was extracted with CH_2Cl_2 (3 × 5 mL), the combined extracts were washed with brine (6 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford acid 6 (9 mg, 0.017 mmol) in 92% yield. TLC: $R_f = 0.2$ (ethyl acetate:hexanes, 6:4); $[\alpha]^{20}_D$: +29° (*c* 0.7, $CHCl_3$); IR (neat): 3447, 2927, 2857, 1691, 1617, 1315, 1059, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.05 (q, *J* = 1.2 Hz, 1H), 5.48–5.35 (m, 2H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.28–4.24 (m, 1H), 4.17 (dd, *J* = 8.3, 5.1 Hz, 1H), 4.09 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.69 (dd, *J* = 11.5, 2.7 Hz, 1H), 3.64–3.55 (m, 2H), 3.46 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.36 (s, 3H), 2.38–2.27 (m, 2H), 2.21–2.12 (m, 4H), 1.95–1.89 (m, 1H), 1.43 (s, 3H), 1.29 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); MS (ESI): 565 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{50}O_8SiNa$: 565.3167, found 565.3186.

4.1.21. (S)-Ethyl 3-hydroxybutanoate (**25**)

A 100-mL, parr hydrogenation vessel was charged with Ethyl acetoacetate (6.5 g, 50 mmol) and degassed Ethanol (70 mL). To this mixture was added the in situ prepared [(*S*)-2,2′ Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex (0.1 mol%, 43 mg, 0.05 mmol) in degassed Ethanol (5 mL) under an argon. The hydrogenation vessel was attached to a hydrogen source and hydrogenation was carried out at 50 psig H_2 and 80 °C for 8 h. After the reaction mixture was allowed to cool to room temperature, the stop valve was opened, excess hydrogen was carefully bled off, and the apparatus was disassembled. The resulting orange solution was poured into a 250 mL, round-bottomed flask, and the hydrogenation vessel was rinsed with dichloromethane (3 × 30 mL). The solvent was removed by a rotary evaporator, and the residue was distilled to give hydroxy ester 25 with er 93:7 (6.3 g, 47.5 mmol) in 95% yield (bp 72 °C, 12 mm Hg). TLC: $Rf = 0.3$ (ethyl acetate: hexane, 30:70); $[\alpha]^{25}D = +38°$ (*c* = 1.0, CHCl3); IR (neat) ν_{max}: 3449, 2979, 2938, 1732, 1377, 1188 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.18–4.10 (m, 3H), 2.94–2.68 (bs, *OH*), 2.43 (dd, *J* = 16.8, 4.0 Hz, 1H), 2.37 (dd, *J* = 16.8, 8.9 Hz, 1H), 1.27 (t, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 64.1, 60.5, 42.8, 22.3, 14.0; MS (ESI): 133 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_6H_{13}O_3$: 133.0859, found 133.0860.

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*4.1.22. (2S,3S)-Ethyl 3-hydroxy-2-methylbutanoate (**26**)*

n-BuLi (2.5 M in hexane, 37.8 mL, 94.5 mmol) was added dropwise to a solution of diisopropylamine (13.9 mL, 99 mmol) in anhydrous THF (100 mL) cooled to −78 °C. The resulting yellow solution was stirred at this temperature for 1 h before a solution of ethyl (*S*)-3-hydroxybutyrate **25** (5.9 g, 45 mmol) in anhydrous THF (32 mL) and anhydrous HMPA (15 mL) was slowly added via cannula. The mixture was allowed to warm to −40 °C and stirred for 20 min before it was recooled to −78 °C and iodomethane (3.5 mL, 56.3 mmol) was introduced and stirred for 1 h. The mixture was warmed to 0 °C and stirred further for a period of 2 h before the reaction was quenched with aq saturated NH_4Cl solution (12 mL). 1N HCl (10 mL) was then added to adjust the pH to 7. The layers were separated and the aq layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated and the residue was purified by flash column chromatography using 30% EtOAc/hexane (v/v) as the eluent to afford compound **26** (dr 95:5) as a colourless oil (5.4 g, 37 mmol) in 82% yield. TLC: $R_f = 0.3$ (ethyl acetate:hexane, 35:65); $[\alpha]^{20}_D$: +21.8° (*c* 1, $CHCl_3$), IR (neat): 3449, 2979, 2938, 1732, 1377, 1188 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.17 (q, *J* = 7.2 Hz, 2H), 3.91–3.83 (m, 1H), 2.74–2.68 (bs, *OH*), 2.43 (quintet, *J* = 7.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 69.2, 60.5, 46.8, 20.5, 14.1, 13.8; MS (ESI): 147 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_7H_{15}O_3$: 147.1016, found 147.1015.

*4.1.23. (2S,3S)-Ethyl 3-(methoxymethoxy)-2-methylbutanoate (**27**)*

To a stirred solution of compound **26** (5.1 g, 35 mmol) and TBAI (564 mg, 1.75 mmol) in anhydrous dichloromethane (70 mL) cooled to 0 °C was added dropwise *N,N*-diisopropylethylamine (9.2 mL, 52.5 mmol). The reaction mixture was stirred at 0 °C for 10 min and then MOM-Cl (3.2 mL, 42 mmol) was added and the mixture was stirred gradually allowing it to attain room temperature and stirred further for 4 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (70 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to furnish the crude product which was purified by flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give compound **27** as a colourless oil (5.7 g, 30 mmol) in 85% yield. TLC: $R_f = 0.4$ (ethyl acetate:hexane, 20:80); $[\alpha]^{20}_D$: +21.9° (*c* 1.0, $CHCl_3$); IR (neat): 2981, 2938, 1735, 1379, 1190, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.65–4.52 (m, 2H), 4.11 (q, *J* = 7.6 Hz, 2H), 3.93–3.82 (m, 1H), 3.31 (s, 3H), 2.62–2.59 (m, 1H), 1.27 (t, *J* = 7.6 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 95.4, 74.9, 60.3, 55.4, 45.9, 17.1, 14.2, 12.7; MS (ESI): 213 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_9H_{18}O_4Na$: 213.1097, found 213.1098.

*4.1.24. (2R,3S)-3-(Methoxymethoxy)-2-methylbutan-1-ol (**28**)*

To a suspension of LAH (2.3 g, 59.4 mmol) in anhydrous THF (50 mL) cooled to 0 °C was added a solution of **27** (5.1 g, 27 mmol) in anhydrous THF (20 mL) dropwise during 10 min. The reaction mixture was stirred for an additional 15 min at 0 °C and then allowed to warm to room temperature. After 3 h, the reaction mixture was diluted with ether (100 mL) and quenched with ice pieces. The resulting reaction mixture was filtered through a Celite pad. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product. Purification of the crude residue via flash column chromatography using 15% EtOAc/hexane (v/v) as the eluent afforded compound **28** as a colourless oil (3.76 g, 25.4 mmol) in 94% yield. TLC: $R_f = 0.2$ (ethyl acetate:hexane, 15:85); $[\alpha]^{20}_D$: +17.3° (*c* 1.3, $CHCl_3$); IR (neat): 3430, 2971, 2932, 2888, 1454, 1380, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.74 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 3.76–3.60 (m, 2H), 3.56 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.40 (s, 3H), 2.87–2.40 (bs, *OH*), 1.81–1.67 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 94.9, 77.2, 65.8, 55.5, 41.0, 17.7, 13.6; MS (ESI): 171 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_7H_{16}O_3Na$: 171.0992, found 171.0990.

*4.1.25. 5-(((2S,3S)-3-(Methoxymethoxy)-2-methylbutyl)thio)-1-phenyl-1H-tetrazole (**30**)*

To a solution of the mixture of alcohol **28** (3.4 g, 23 mmol) and triphenylphosphine (7.8 g, 29.9 mmol) in anhydrous toluene (38 mL) cooled to 0 °C was added 1-phenyltetrazole-5-thiol **29** (5.3 g, 29.9 mmol) followed by dropwise addition of DEAD (4.7 mL, 29.9 mmol). The reaction mixture was stirred gradually allowing it to warm to room temperature over a period of 20 min. The reaction mixture was quenched by adding aqueous saturated $NaHCO_3$ solution (22 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography using 8% EtOAc/hexane (v/v) as the eluent afforded compound **30** as a colourless oil (5.4 g, 17.5 mmol) in 76% yield. TLC: $R_f = 0.5$ (ethyl acetate:hexane, 20:80); $[\alpha]^{20}_D$: +28.2° (*c* 0.55, $CHCl_3$); IR (neat): 3065, 2971, 2930, 1499, 1385, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.65–7.44 (m, 5H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 3.72–3.60 (m, 2H), 3.40–3.20 (m, 4H), 2.17–2.00 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 133.7, 130.0, 129.7, 123.8, 95.2, 75.8, 55.5, 38.6, 36.6, 16.9, 15.2; MS (ESI): 309 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{14}H_{21}O_2N_4S$: 309.1380, found 309.1379.

*4.1.26. 5-(((2S,3S)-3-(Methoxymethoxy)-2-methylbutyl)sulfonyl)-1-phenyl-1H-tetrazole (**11**)*

To a solution of sulfide **30** (4.9 g, 16 mmol) in anhydrous CH_2Cl_2 (32 mL) cooled to −30 °C was added *m*CPBA (6.0 g, 35.2 mmol). The reaction mixture was stirred for 3 h at the same temperature and then quenched by the addition of saturated sodium sulfite (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (30 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography using 30% EtOAc/hexane (v/v) as the eluent afforded compound **11** as a colourless oil (4.7 g, 13.8 mmol) in 86% yield. TLC: $R_f = 0.3$ (ethyl acetate:hexane, 30:70); $[\alpha]^{20}_D$: +19.8° (*c* 0.75, $CHCl_3$); IR (neat): 3072, 2930, 1702, 1343, 1151, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2H), 7.61–7.52 (m, 3H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.52 (d, *J* = 6.9 Hz, 1H), 4.02 (dd, *J* = 14.7, 3.2 Hz, 1H), 3.66–3.57 (m, 1H), 3.52 (dd, *J* = 14.7, 9.2 Hz, 1H), 3.33 (s, 3H), 2.42–2.30 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 133.0, 131.3, 129.5, 125.1, 95.0, 75.7, 58.2, 55.6, 33.8, 17.1, 16.4; MS (ESI): 341 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{14}H_{21}O_4N_4S$: 7341.1278, found 341.1277.

*4.1.27. (S)-Mandelate ester of rac **25***

To a solution of racemic alcohol (33 mg, 0.25 mmol), obtained by treatment of ethyl acetoacetate with $NaBH_4$, in DCM (1.0 mL) was added (*S*)-(−)-α-methoxy phenylacetic acid (45.5 mg, 0.275 mmol), DMAP (5 mg, 15 mol%) and DCC (62.3 mg, 0.275 mmol) at 0 °C. The reaction mixture 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 the mandelate ester of the alcohol in 90% yield as mixture of diastereomer. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.40 (m, 4H), 7.39–7.30 (m, 6H), 5.40–5.26 (m, 2H), 4.74–4.71 (2s, 2H), 4.13–4.04 (m, 2H),

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3.96–3.77 (m, 2H), 3.42–3.39 (2s, 6H), 2.69–2.36 (m, 4H), 1.32–1.16 (m, 9H), 1.09 (t, $J = 6.8$ Hz, 3H).

4.1.28. *(S)-Mandelate ester of* ***25***

The ester was prepared as detailed above. TLC: R_f 0.3 (9:1 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.39 (m, 2H), 7.39–7.31 (m, 3H), 5.40–5.27 (m, 1H), 4.72 (s, 1H), 3.98–3.76 (m, 2H), 3.40 (s, 3 H), 2.55 (dd, $J = 15.9$, 8.3 Hz, 1H), 2.41 (dd, $J = 15.9$, 5.3 Hz, 1H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.09 (t, $J = 6.8$ Hz, 3H).

4.1.29. ***(E)-tert-Butyl((3-iodobut-2-en-1-yl)oxy)dimethylsilane (9)***

To a solution of Cp_2ZrCl_2 (321 mg, 1.1 mmol) in anhydrous THF (4 mL) cooled to 0 °C was added DIBAL-H (0.91 mL, 1.1 mmol) under nitrogen atmosphere. The resultant suspension was stirred for 30 min at 0 °C, followed by addition of a solution of (but-2-yn-1-yloxy)(*tert*-butyl)dimethylsilane (184 mg, 1.0 mmol) in anhydrous THF (1.0 mL). The mixture was warmed to room temperature and stirred until a homogeneous solution resulted (ca. 1 h) and then cooled to −78 °C, followed by addition of the solution of I_2 (330 mg, 1.3 mmol) in THF (3 mL). After 30 min at −78 °C, the reaction mixture was quenched with aq HCl (1N, 2 mL). The layers were separated and the aq layer extracted with ether (20 mL). The combined organic layers were washed successively with aq saturated $Na_2S_2O_3$ (10 mL), $NaHCO_3$ (10 mL), brine (20 mL), dried over $NaSO_4$, filtered and the solvent evaporated under reduced pressure to afford the crude product. Purification by the flash column chromatography using 4% EtOAc/hexane (v/v) as the eluent afforded compound **9** (274 mg, 0.88 mmol) in 88% yield. TLC: $R_f = 0.4$ (ethyl acetate:hexanes, 1:9); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (tq, $J = 6.5$, 1.5 Hz, 1H), 4.12 (d, $J = 6.4$ Hz, 2H), 2.41 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 95.9, 60.6, 28.1, 25.9, 18.3, −5.2. MS (ESI): 313 $[M+H]^+$.

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