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Towards a synthesis of epothilone A: asymmetric synthesis of C(1)–C(6) and C(7)–C(15) fragments†

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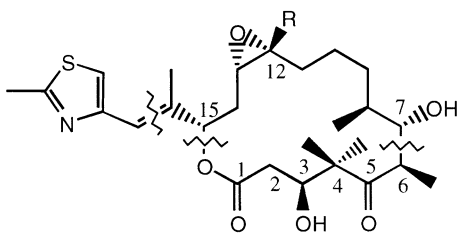
Abstract—The asymmetric synthesis of protected C(1)–C(6) and C(7)–C(15) fragments of epothilone A starting from 1,3-cyclohexanedione and methyl L-hydroxy propionate, respectively, is described.

1. Introduction

The isolation of a new group of macrocyclic natural products, the epothilones, has enabled research into structure–activity relationships (SAR) in the stabilization of microtubules to be conducted faster and more efficiently. Epothilones A **1** and B **2** were first isolated by Hofle's group from the myxobacteria *Sorangium Cellulosum*.[1] Due to their very interesting biological activities and novel structure, these biological analogues of taxol immediately attracted much attention from chemists and biologists and several groups have reported their approaches to the epothilones.[2] Herein, we report our preliminary results for epothilone A synthesis.



1 **Epothilone A:** R=H

2 **Epothilone B:** R=CH_3

The objective of the present exercise is to synthesize the fragments essential for biological activity as detailed in several SAR studies[3] and stitch them in a combinatorial fashion towards pseudonatural products.[4]

The retrosynthetic analysis of epothilone A indicated that appropriately protected forms of the three fragments **3**, **4** and **5** would be key intermediates (based on the literature)[5] (Scheme 1). Herein, we wish to report the asymmetric synthesis of C(1)–C(6) and C(7)–C(15) fragments starting from 1,3-cyclohexanedione and methyl 3-hydroxy-2-methyl-(2*R*)-propionate, respectively.

2. Results and discussion

2.1. Synthesis of the C(1)–C(6) fragment

3-Methoxy-2-cyclohexenone **7** was treated with ethylmagnesium bromide followed by acidic workup to give the enone **8**. Alkylation of the ethyl cyclohexenone **8** using potassium *tert*-butoxide and methyl iodide in THF yielded **9**, which was reduced with oxazaborolidine (Corey's reagent)[6] to furnish the chiral alcohol **10** with 92% e.e. On acetylation the alcohol **10** gave **11**, which on treatment with SeO_2 furnished the allylic hydroxy compound **12**. Dihydroxylation of **12** with osmium tetroxide then afforded the triol **13**. Aldehyde **14** was obtained by sodium periodate cleavage of triol **13**, which was further oxidized to give the required fragment **3** (Scheme 2).

2.2. Synthesis of the C(7)–C(15) fragment

After completion of the synthesis of the C(1)–C(6) fragment, attempts were then directed towards the synthesis of the C(7)–C(15) epothilone fragment, **4**, whose

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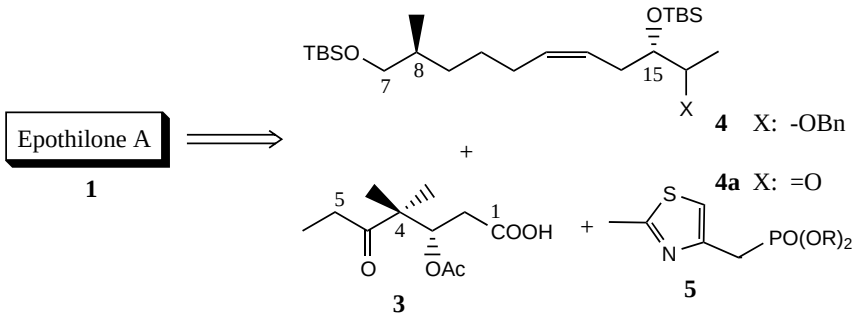
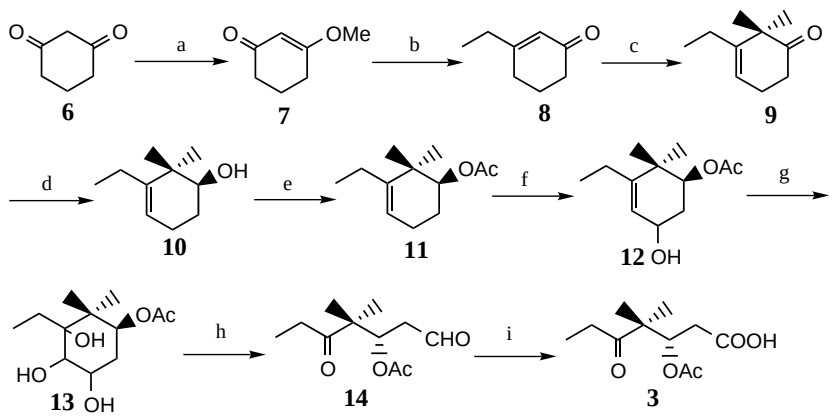


Scheme 1.

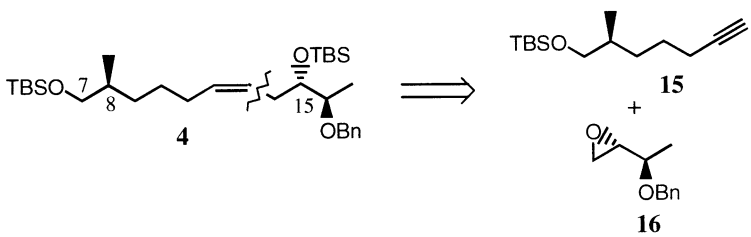


Scheme 2. *Reagents and conditions*: (a) $CH(OCH_3)_3$, MeOH, PTSA (cat.) benzene, reflux, 80 min, 92%; (b) EtMgBr, THF, H^+, 0°C, 2 h, 86%; (c) (i) ^{t}BuOK, MeI, THF, −78°C, 5 h, 80%; (d) (*S*)-diphenylprolinol, BH_3·DMS, THF, 45°C, 17 h, 81%; (e) Py., Ac_2O, CH_2Cl_2, rt, 11 h, 90%; (f) SeO_2, TBHP, CH_2Cl_2, rt, 5 h, 60%; (g) OsO_4, NMO, acetone/H_2O (8:2), rt, 16 h, 86%; (h) $NaIO_4$, SiO_2, CH_2Cl_2/H_2O (9:1), rt, 4 h, 77%; (i) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, rt, 4 h, 76%.

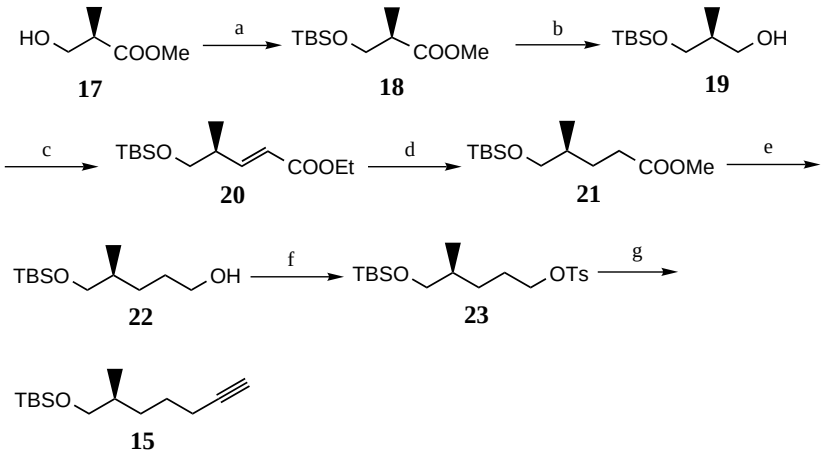
retrosynthetic analysis is shown in Scheme 3. This disconnection approach revealed two intermediates viz., acetylene **15** and epoxide **16**.

The synthesis of the acetylene **15** started from commercially available methyl-3-hydroxy-2-methyl-(2*R*)-propionate **17**. The free hydroxyl group was protected as its TBS ether to give **18**. The ester **18** was reduced with DIBAL-H to furnish the alcohol **19**, which was oxidized to aldehyde by PDC. The aldehyde thus obtained was subjected to stabilised-ylide Wittig olefination with carboethoxymethylenetriphenylphosphorane to give the α,β-unsaturated ester **20**. The double bond of **20** was reduced with Mg in methanol to yield the ester **21**.[7] The ester **21** was reduced to alcohol **22** using LiCl–$NaBH_4$,[8] followed by tosylation to give the compound **23**, which upon alkylation with lithium acetylide furnished the required acetylene **15** (Scheme 4).

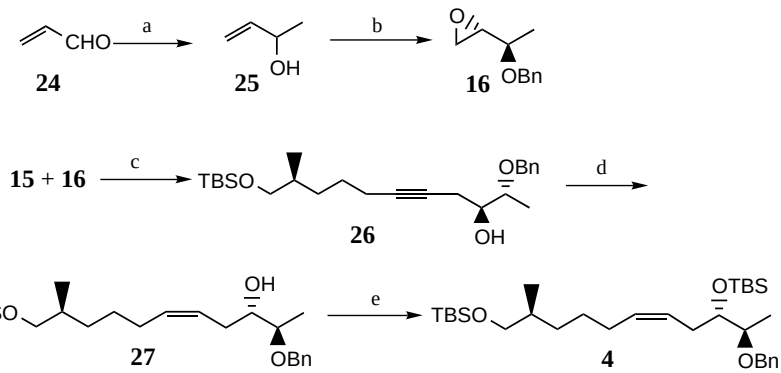
The chiral epoxide **16** was prepared from acrolein **24**, which was treated with methyl magnesium iodide to produce the alcohol **25**. Alcohol **25** was subjected to Sharpless asymmetric epoxidation [(−)-DIPT, $Ti(^iPrO)_4$] and subsequent protection of the alcohol as benzyl ether furnished the epoxide **16**. The epoxide **16** was ring-opened with acetylide **15**, using the Yamaguchi method[9] to afford the propargyl alcohol **26**, which was subjected to partial hydrogenation with Lindlar's catalyst to yield the *cis*-olefin **27**. Protection of the free hydroxyl group of **27** as its *tert*-butyldimethylsilyl ether furnished the desired fragment **4** (Scheme 5).



Scheme 3.



Scheme 4. (a) Imidazole, TBDMSCl, CH_2Cl_2, 0°C, 6 h, 92%; (b) DIBAL-H, CH_2Cl_2, 0°C–rt, 2 h, 78%; (c) (i) PDC, CH_2Cl_2, rt, 15 min, 97%, (ii) PPh_3=CHCOOEt, benzene, rt, 12 h, 82% (two steps); (d) Mg/MeOH, rt, 4 h, 82%; (e) LiCl–$NaBH_4$, EtOH/THF (1:1), rt, 12 h, 92%; (f) Et_3N, TsCl, CH_2Cl_2, rt, 10 h, 85%; (g) Li, liq. NH_3, acetylene (gas), DMSO, –20°C–rt, 3 h, 73%.



Scheme 5. (a) MeMgI, THF, rt, 1 h, 76%; (b) (i) (–)-DIPT, Ti(^{i}PrO)$_4$, TBHP, 4 Å MS, CH_2Cl_2, –20°C, 14 h, 50%, (ii) NaH, BnBr, THF, 0°C, 6 h, 78%; (c) ^{n}BuLi, $BF_3{\cdot}Et_2O$, THF, –78°C, 30 min, 75%; (d) Pd–$BaSO_4/H_2$, EtOH, rt, 20 min, 95%; (e) imidazole, TBDMSCl, CH_2Cl_2, 0°C–rt, 6 h, 88%.

3. Conclusion

In conclusion, the asymmetric synthesis of two important synthetic precursors of epothilone A, the C(1)–C(6) and C(7)–C(15) fragments, was achieved from commercially available starting materials.

4. Experimental

Crude products were purified by column chromatography on silica gel of 60–120 mesh. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Varian Gemini-200, AV-300 MHz spectrometer and chemical shifts are reported in ppm unless otherwise stated. Mass spectra were recorded on VG micromass-7070H (70 eV). HPLC analysis was performed on a Schimadzu liquid chromatography LC-6A, equipped with a SCE-6A, system controller, SPD-6A, fixed wavelength UV monitor as detector and chromatograpac C-R4A data processor as integrator. The column was 4.6×250 mm, chiral cell OD column (Dia cell). The optical rotations were recorded using a Jasco Dip 360 digital polarimeter. Infrared spectra were obtained neat and only the most significant absorptions in cm^{-1} are indicated. All solvents used were purified by a known procedure. All reactions were carried out under an atmosphere of nitrogen using dry glassware.

4.1. 3-Methoxy-2-cyclohexen-1-one 7

A mixture of cyclohexane-1,3-dione **6** (5 g, 51.02 mmol), *p*-toluenesulfonic acid (0.21 mg), methanol (17 mL) and trimethyl orthoformate (5.2 mL) was heated under reflux in benzene (85 mL) for 80 min. The cooled reaction mixture was washed with a 10% aq. NaOH solution (2×20 mL), brine (20 mL), dried and evaporated in vacuo. Purified by distillation (bp = 52–53°C, 0.7 mmHg) to give **7** in 92% yield (5.9 g). IR (neat): ν 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.32 (s, 1H, –CO–**CH**=), 3.69 (s, 3H, –O**CH**$_3$), 2.45–2.23 (m, 4H, –CO–**CH**$_2$–, =CH–**CH**$_2$–), 2.06–1.89 (m, 2H, –CH_2–**CH**$_2$–CH_2–); EIMS (m/z): 126 (M^+).

4.2. 3-Ethyl-2-cyclohexen-1-one 8

The Grignard reagent was prepared from magnesium (2.37 g, 98.94 mmol), ethyl bromide (10.68 g, 22.1 mL,

98.94 mmol) and dry THF (75 mL). To this a solution of 3-methoxy-2-cyclohexen-1-one **7** (5.66 g, 44.97 mmol) in dry THF (15 mL) was added and the mixture was stirred for 2 h. After the Grignard complex was decomposed with dilute sulfuric acid, the mixture was extracted with ether. The ether solution was washed with dilute $NaHCO_3$, water and dried over Na_2SO_4. After evaporation of volatiles, the crude product was purified by silica gel column chromatography to give **8** in 86% yield (4.8 g). IR (neat): ν 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.79 (s, 1H, =**CH**–CO–), 2.39–2.1 (m, 6H, –**CH**$_2$–**CH**$_2$–**CH**$_2$–), 1.96 (q, $J=12.8$, 6 Hz, 2H, CH_3–**CH**$_2$–), 1.06 (t, $J=6.8$ Hz, 3H, **CH**$_3$–CH_2–); EIMS (m/z): 124 (M^+).

4.3. 3-Ethyl-2,2-dimethyl-3-cyclohexen-1-one 9

To a solution of 3-ethyl-2-cyclohexen-1-one **8** (4.66 g, 37.63 mmol) in dry THF (75 mL) was added potassium *tert*-butoxide (12.63 g, 112.9 mmol) at −78°C under a nitrogen atmosphere. After 15 min, methyl iodide (11.66 mL, 188.2 mmol) was slowly added to the reaction mixture at the same temperature. After 5 h, the reaction mixture was cooled to room temperature and extracted with ether (2×50 mL). The extracts were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and the volatiles were evaporated on a rotary evaporator. The crude product was purified by column chromatography to give **9** in 80% yield (4.57 g). IR (neat): ν 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.79 (m, 1H, =**CH**–CH_2), 2.41–2.19 (m, 4H, CH_3–**CH**$_2$–, =CH–**CH**$_2$–), 1.86 (t, $J=6.89$ Hz, 2H, –CH_2–**CH**$_2$–CO–), 1.24–1.10 (m, 9H, **CH**$_3$–CH_2–, 2×**CH**$_3$); EIMS (m/z): 152 (M^+); HRMS: calcd 152.2354; found: 152.2356.

4.4. (1*S*)-3-Ethyl-2,2-dimethyl-3-cyclohexen-1-ol 10

To a solution of $BH_3{\cdot}Me_2S$ (9.6 mL of 2 M solution in toluene, 19.2 mmol) was added a solution of (*S*)-diphenyl prolinol (0.373 g, 1.5 mmol) in THF (12 mL) and the reaction mixture was stirred at 45°C for 16 h under nitrogen. To the resulting turbid solution of oxazaborolidine, a solution of 3-ethyl-2,2-dimethyl-3-cyclohexen-1-one **9** (4.5 g, 29.6 mmol) in anhydrous THF (20 mL) was added dropwise over a period of 30–40 min. After completion of the addition, the reaction mixture was continued to stir at the same temperature for 15 min. It was then cooled to room temperature and cautiously quenched with MeOH (6 mL). The solvent was evaporated and the residue was dissolved in ether. The ether phase was washed with 1 M HCl followed by brine and dried over anhydrous Na_2SO_4. The residue obtained after removal of ether was purified by column chromatography to afford the alcohol **10** (3.69 g, 81% yield). The optical purity was determined by a chiral HPLC column (Schimadzu liquid chromatography LC-6A) as benzoate and found to be 92% e.e. IR (neat): ν 3622 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.38 (broad s, 1H, =**CH**–CH_2–), 3.68 (broad s, 1H, –CH_2–CH (OH)–), 2.05–1.86 (m, 4H, CH_3–**CH**$_2$, –CH=**CH**$_2$–), 1.60–1.20 (m, 2H, =CH–**CH**$_2$–CH_2–), 1.07–0.94 (m, 3H, **CH**$_3$–CH_2–), 0.90 and 0.88 (2×s, 2×3H, 2×–**CH**$_3$); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 122.1, 96.2, 74.6, 38.9, 32.8, 29.7, 26.2, 26, 21.8, and 12.2; EIMS (m/z): 154 (M^+); HRMS: calcd 154.2516; found: 154.2530; $[\alpha]_D=-15.9$ (c 1, $CHCl_3$).

4.5. (1*S*)-3-Ethyl-2,2-dimethyl-3-cyclohexenyl acetate 11

To a solution of alcohol **10** (4 g, 25.9 mmol) in dry CH_2Cl_2 (60 mL) containing dry pyridine (2.3 mL, 28.57 mmol) was added a solution of acetic anhydride (3.17 g, 31.16 mmol) in CH_2Cl_2 (8 mL) at 0°C under nitrogen. The reaction mixture was stirred for 10 h at room temperature then washed with a saturated $CuSO_4$ solution (2×40 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the acetate **11** (4.58 g, 90%). IR (neat): ν 3624, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.3 (broad s, 1H, =**CH**–), 4.95 (broad s, 1H, –**CH**(OAc)–), 2.1–1.9 (s and m, 7H, **CH**$_3$–CO–, CH_3–**CH**$_2$, –CH=**CH**$_2$–), 1.61–1.3 (m, 2H, =CH–CH_2–**CH**$_2$–), 1.1–0.95 (m, 3H, CH_3–CH_2–), 0.9 (s, 6H, 2×–**CH**$_3$); EIMS (m/z): 196 (M^+); $[\alpha]_D=-24.7$ (c 0.5, $CHCl_3$).

4.6. (1*S*)-3-Ethyl-5-hydroxy-2,2-dimethyl-3-cyclohexenyl acetate 12

A solution of acetate **11** (3 g, 15.3 mmol) in CH_2Cl_2 (60 mL) was stirred at 35°C with SeO_2 (0.849 g, 7.6 mmol) and dry *tert*-butylhydroperoxide (6.887 g, 76.5 mmol). The reaction mixture was extracted with CH_2Cl_2 (50 mL), extracts were washed with 10% aq. KOH (2×25 mL), and the organic phase was dried and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to afford the allylic hydroxyl compound **12** (1.94 g, 60%). IR (neat): ν 3624, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.26–5.2 (m, 1H, =**CH**–), 5.16–5.09 (m, 1H, –**CH**(OAc)–), 4.25–4.1 (broad m, 1H, =CH–**CH**(OH)–), 2.25–2.1 (m, 2H, CH_3–**CH**$_2$), 2.06 (s, 3H, **CH**$_3$–CO–), 1.51–1.36 (m, 2H, CH(OH)–**CH**$_2$–), 1.04 (t, $J=7.0$ Hz, 3H, **CH**$_3$–CH_2–), 0.98, 089 (2×s, 6H, 2×–**CH**$_3$); EIMS (m/z): 212 (M^+); HRMS: calcd 212.2870; found: 212.2867; $[\alpha]_D=-12.62$ (c 0.8, $CHCl_3$).

4.7. (1*S*)-3-Ethyl-3,4,5-trihydroxy-2,2-dimethylcyclohexyl acetate 13

To a solution of **12** (1 g, 4.68 mmol) in acetone/water (16:4) was added a catalytic amount of OsO_4 (0.05 mL, 0.02 M solution). After 15 min, *N*-methyl morpholine oxide (0.828 g, 6.12 mmol) was added and the mixture was stirred overnight at ambient temperature. After the reaction was completed, the solvent was removed and a sat. sodium metabisulfite solution (15 mL) was added to the residue. The resulting mixture was stirred for 30 min. The reaction mixture was extracted with ethyl acetate (2×25 mL) and the extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford the triol **13** (1 g, 86%). IR (neat): ν 3624, 3612, 1738 cm^{-1}; ^1H NMR (D_2O exchange, 200 MHz): δ

4.99–4.84 (m, 1H, –**CH**(OAc)–), 4.4–4.24 (m, 1H, –**CH**(OH)–CH(OH)–), 4.18–4.0 (m, 1H, –**CH**(OH)–CH_2–), 2.07 (s, 3H, –CO–**CH_3**), 1.36–1.16 (m, 4H, CH_3–**CH_2**–, –**CH_2**–CH(OAc)–), 1.1–0.8 (m, 9H, **CH_3**–CH_2–, 2×**CH_3**); EIMS (*m*/*z*): 246 (M^+); $[\alpha]_D = -6.0$ (*c* 1, $CHCl_3$).

4.8. (5*S*)-5-Acetoxy-7-formyl-4,4-dimethyl-3-heptanone 14

To a stirred solution of triol **13** (0.3 g, 1.219 mmol) in CH_2Cl_2:H_2O (9:1) was added $NaIO_4$ (0.782 g, 3.6 mmol) and SiO_2 (0.3 g) at room temperature. After 4 h, the reaction mixture was filtered through a sintered funnel and extracted with DCM (2×15 mL). The combined organic layer was washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, and the solvent was evaporated by rotary evaporator, and the residue was purified by column chromatography to afford aldehyde **14** (0.2 g, 77%). IR (neat): *v* 1740, 1724, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.74 (s, 1H, –**CHO**), 5.18 (dd, $J=9$, 3 Hz, 1H, –**CH**(OAc)–), 2.48 (q, $J=8.8$ Hz, 2H, CH_3–**CH_2**–CO–), 2.06 (s, 3H, –CO–CH_3), 1.98–1.78 (m, 2H, –**CH_2**–CHO), 1.22 (broad s, 9H, **CH_3**–CH_2–, 2×**CH_3**); EIMS (*m*/*z*): 214 (M^+); $[\alpha]_D = -2.5$ (*c* 2, $CHCl_3$).

4.9. (3*S*)-3-Acetoxy-4,4-dimethyl-5-oxoheptanoic acid 3

A mixture of aldehyde **14** (0.15 g, 0.7 mmol), ^{t}BuOH (10 mL), isobutylene (5 mL in 5 mL THF), H_2O (1 mL), sodium hypochlorite $NaClO_2$ (0.19 g, 2.1 mmol) and sodium dihydrogenphosphate (NaH_2PO_4) (0.126 g, 1.05 mmol) was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography to produce the pure keto acid **3** (0.12 g, 76%). IR (neat): *v* 3350, 1722, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 10.9–10.68 (broad m, –COOH), 5.2 (dd, $J=8$, 2.3 Hz, 1H, –**CH**(OAc)–), 2.66–2.44 (m 2H, CH_3–**CH_2**–CO–), 2.15–1.78 (s and m, 5H, –CO–**CH_3**, –**CH_2**–COOH), 1.4–1.04 (m, 9H, **CH_3**–CH_2–, 2×**CH_3**); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 198.6, 176.8, 163.4, 73.5, 52.2, 39.4, 29.7, 25.8, 20.8, 20.5 and 18.2; EIMS (*m*/*z*): 230 (M^+); HRMS: calcd 214.2608; found: 214.2603; $[\alpha]_D = +12.4$ (*c* 1, $CHCl_3$).

4.10. Methyl-(2*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpropanoate 18

To a stirred solution of **17** (5 g, 42.4 mmol) and imidazole (4.32 g, 63.6 mmol) in CH_2Cl_2 (125 mL) was added TBDMS-Cl (6.35 g, 42.4 mmol) portion wise at 0°C. The reaction mixture was stirred at the same temperature for 6 h and then quenched with water. CH_2Cl_2 layer was separated and the aq. layer was extracted with additional CH_2Cl_2 (2×30 mL). The combined CH_2Cl_2 layer was washed with water, brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography to give **18** (9 g, 92%). IR (neat): *v* 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.82–3.54 (s and dd (unresolved), 5H, TBSO-**CH_2**–, –**OCH_3**), 2.7–2.52 (m, 1H, –CH_2–**CH**(CH_3)–CO–), 1.12 (d, $J=6.8$ Hz, 3H, CH_3–**CH**–), 0.88 (s, 9H, (**CH_3**)$_3$C–Si–), 0.2 (s, 6H, (**CH_3**)$_2$Si–); EIMS (*m*/*z*): 232 (M^+); $[\alpha]_D = +17.7$ (*c* 1.7, $CHCl_3$).

4.11. (2*S*)-3-*tert*-Butyldimethylsilyloxy-2-methylpropanol 19

To a stirred solution of **18** (5 g, 21.6 mmol) in dry CH_2Cl_2 (75 mL) at −10°C was added DIBAL-H (7.65 g, 53.9 mmol, 2 M solution in hexane) under nitrogen. The reaction mixture was stirred at 0°C for 30 min and allowed to warm to room temperature and further stirred for an additional 2 h. After the excess DIBAL-H was decomposed with methanol (3 mL), the mixture was poured into a sodium potassium tartrate solution (10 g in 100 mL water) with vigorous stirring until the layers were separated. The aqueous layer was extracted with ether (2×60 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to afford **19** as a colorless viscous oil (3.43 g, 78%). IR (neat): *v* 3538 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.78–3.48 (m, 4H, TBSO–**CH_2**–, –**CH_2**–OH), 2.0–1.8 (m, 1H, –CH_2–**CH**(CH_3)–CH_2–), 0.95 (s, 9H, (**CH_3**)$_3$C–Si–), 0.83 (d, $J=7.0$ Hz, CH_3–**CH**–), 0.4 (s, 6H, (CH_3)$_2$Si–); EIMS (*m*/*z*): 204 (M^+); $[\alpha]_D = +20.6$ (*c* 0.8, $CHCl_3$).

4.12. Ethyl (4*S*)-(*E*)-5-*tert*-butyldimethylsilyloxy-4-methyl-2-pentenoate 20

Chromium trioxide (5.88 g, 58.8 mmol) was added to a stirred solution of dry pyridine (9.29 g, 117.6 mmol) in dry CH_2Cl_2 (80 mL). The solution was stirred for 15 min at room temperature and then treated with a solution of alcohol **19** (4 g, 19.6 mmol) in CH_2Cl_2 (10 mL). After stirring for an additional 15 min at room temperature, the solution was decanted from the mixture and the residue was filtered through a silica gel pad, eluting with ether (100 mL). The filtrate was concentrated on a rotary evaporator to give the aldehyde (3.86 g, 97%).

The above aldehyde (3.86 g, 19.1 mmol) was immediately dissolved in benzene (70 mL), and the solution treated with carboethoxymethylenetriphenylphosphorane (6.33 g, 18.14 mmol). The reaction mixture was stirred overnight at room temperature. After concentration, the residue was purified by column chromatography to afford compound **20** as a viscous liquid (4.26 g, 82%). IR (neat): *v* 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.9 (dd, $J=14.4$, 5.8 Hz, 1H, EtOOC–**CH**=CH–), 5.8 (d, $J=17.3$ Hz, 1H, EtOOC–CH=**CH**–), 4.2 (q, $J=15.6$, 7.8 Hz, 2H, CH_3–**CH_2**O–CO–), 3.6–3.44 (m, 2H, TBSO–**CH_2**–) 2.48–2.42 (m, 1H, –CH_2–**CH**(CH_3)–), 1.26 (t, $J=3.8$ Hz, 3H, **CH_3**–CH_2O–CO–), 1.05 (d, $J=4.3$ Hz, 3H, –CH(**CH_3**)–), 0.9 (s, 9H, (**CH_3**)$_3$C–Si–), 0.4 (s, 6H, (**CH_3**)$_2$Si–); EIMS (*m*/*z*): 272 (M^+); HRMS: calcd 272.4577; found: 272.4574; $[\alpha]_D = +12.8$ (*c* 1.3, $CHCl_3$).

4.13. (4*S*)-Methyl-5-*tert*-butyldimethylsilyloxy-4-methylpentanoate 21

To a stirred solution of the ester **20** (3 g, 11 mmol) in dry methanol (60 mL) was added magnesium turnings (0.795 g, 33.1 mmol) and the mixture was stirred for 4 h at room temperature under nitrogen. The reaction mixture was taken into water (30 mL) to which dilute acetic acid was added and the resulting mixture was stirred vigorously to give a clear solution. The mixture was treated with an NH_4OH solution to adjust the pH to 8.5 and extracted with ether (75 mL). The total extracts were washed with water (20 mL), a saturated $NaHCO_3$ solution (20 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to give the crude oily compound. Purification by column chromatography afforded the pure methyl ester **21** (2.35 g, 82%). IR (neat): ν 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.64 (s, 3H, –COO**CH**$_3$), 3.22 (d, 2H, TBSO–**CH**$_2$–CH(CH$_3$)–), 2.4–2.22 (m, 2H, –CH$_2$–**CH**$_2$–COOCH$_3$), 1.83–1.52 (m, 2H, –CH(CH$_3$)–**CH**$_2$–CH$_2$–), 1.4–1.12 (m, 1H, –**CH**(CH$_3$)–), 0.98–0.82 (m, 12H, –CH(**CH**$_3$)–, (**CH**$_3$)$_3$C–Si–), 0.2 (s, 6H, (**CH**$_3$)$_2$Si–); EIMS (m/z): 260 (M^+); $[\alpha]_D = +11.6$ (c 1.1, $CHCl_3$).

4.14. (4*S*)-5-*tert*-Butyldimethylsilyloxy-4-methylpentan-1-ol 22

To a cooled solution of $NaBH_4$ (0.877 g, 23.07 mmol) and LiCl (0.98 g, 23.07 mmol) in EtOH (20 mL), a solution of the ester **21** (2 g, 7.69 mmol) in THF (20 mL) was added dropwise over 30 min at 0°C. The reaction mixture was stirred at room temperature for 12 h. The mixture was filtered and the filtrate was evaporated in vacuo. The crude residue was dissolved in ethyl acetate and treated with saturated NH_4Cl, the solvent was then evaporated. Purification by column chromatography afforded the alcohol **23** (0.82 g, 92%). IR (neat): ν 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.62–3.54 (m, 2H, –CH$_2$–**CH**$_2$–OH), 3.46–3.34 (m, 2H, TBSO–**CH**$_2$–CH(CH$_3$)–), 1.64–1.40 (m, 4H, –**CH**$_2$–**CH**$_2$–CH$_2$OH), 1.2–1.08 (m, 1H, –**CH**(CH$_3$)–), 0.94–0.82 (m, 12H, –CH(**CH**$_3$)–, (**CH**$_3$)$_3$C–Si–), 0.2 (s, 6H, (**CH**$_3$)$_2$Si–); EIMS (m/z): 232 (M^+); $[\alpha]_D = +9.8$ (c 1, $CHCl_3$).

4.15. (4*S*)-5-*tert*-Butyldimethylsilyloxy-4-methylpentyl-4-methyl-1-benzenesulfonate 23

To a solution of compound **22** (1.6 g, 6.9 mmol) in dry CH_2Cl_2 (30 mL) containing dry Et_3N (0.58 g, 10.34 mmol) was added *p*-toluene sulfonyl chloride (1.31 g, 6.89 mmol) in CH_2Cl_2 (5 mL) at 0°C under nitrogen. The reaction mixture was stirred for 10 h at room temperature, then washed with water (15 mL) and extracted with CH_2Cl_2 (25 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the tosylate **23** (2.28 g, 85%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.78 (d, $J = 7.8$ Hz, 2H, **Ar**–), 7.32 (d, $J = 7.8$ Hz, 2H, Ar–), 3.98 (t, $J = 6.8$ Hz, 2H, –CH$_2$–**CH**$_2$–OTs), 3.36 (d, $J = 5.4$ Hz, 2H, TBSO–**CH**$_2$–CH(CH$_3$)–), 2.46 (s, 3H, Ar–**CH**$_3$) 1.79–1.32 (m, 4H, –**CH**$_2$–**CH**$_2$–CH$_2$OTs), 1.1–1.02 (m, 1H, –**CH**(CH$_3$)–), 0.94–0.78 (m, 12H, –CH(**CH**$_3$)–, (**CH**$_3$)$_3$C–Si–), 0.2 (s, 6H, (**CH**$_3$)$_2$Si–); EIMS (m/z): 386 (M^+); $[\alpha]_D = +6.6$ (c 0.6, $CHCl_3$).

4.16. (6*S*)-7-*tert*-Butyldimethylsilyloxy-6-methyl-1-heptyne 15

In a two necked round bottomed flask fitted with a condenser, a KOH guard tube and a septum, liq. NH_3 (40 mL) was collected and small pieces of freshly cut lithium (0.181 g, 25.9 mmol) were introduced to the reaction mixture with stirring until the blue color persisted for 10 min. Acetylene gas was bubbled into the reaction mixture for 45 min at −20°C, then a solution of the tosylate **23** (2 g, 5.18 mmol) in dry DMSO was added slowly and the reaction mixture was stirred for 2 h at 0°C. The reaction was quenched with solid NH_4Cl. Ammonia was allowed to escape and crushed ice was added to the reaction mixture, which was then extracted with ether (2×50 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography to give **15** (0.9 g, 73%). ^1H NMR ($CDCl_3$, 200 MHz): δ 3.46–3.32 (m, 2H, TBSO–**CH**$_2$–CH(CH$_3$)–), 2.22–2.1 (m, 2H, –**CH**$_2$–C≡) 1.9–1.82 (m, 1H,–C≡**CH**), 1.7–1.4 (m, 4H, –**CH**$_2$–**CH**$_2$–CH$_2$–C≡), 1.22–1.1 (m, 1H, –**CH**(CH$_3$)–), 0.96–0.82 (m, 12H, –CH(**CH**$_3$)–, (**CH**$_3$)$_3$C–Si–), 0.2 (s, 6H, (**CH**$_3$)$_2$Si–); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 84.3, 68.2, 68.0, 35.4, 32.3, 29.6, 25.9, 25.9, 18.7, 18.3 and 16.6; EIMS (m/z): 240 (M^+); HRMS: calcd 240.4577; found: 240.4579; $[\alpha]_D = +5.2$ (c 0.5, $CHCl_3$).

4.17. 3-Butene-2-ol 25

Magnesium (1.92 g, 80.35 mmol) was taken in dry ether (60 mL) and methyl iodide (11.4 g, 80.35 mmol) was added dropwise slowly to the mixture in ether (10 mL) under nitrogen. After all the magnesium was dissolved, acrolein **24** (3 g, 53.57 mmol) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with ether (2×20 mL). The organic layer was dried over Na_2SO_4, and evaporation of ether (without vacuum) resulted in the alcohol **25** (2.1 g, 70%). IR (neat): ν 3622 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.96–5.72 (m, 1H, CH$_2$=**CH**–), 5.06 (dd, $J = 26.9$, 16.8 Hz, 2H, **CH**$_2$=CH–), 4.22 (p, 1H, =CH–**CH**(OH)–CH$_3$), 1.2 (d, $J = 6.3$ Hz, 3H, –CH(OH)–**CH**$_3$).

4.18. (1*R*,2*S*)-2-(1-Benzyloxyethyl)oxirane 16

To a stirred suspension of activated powdered 4 Å molecular sieves (1 g) in dry CH_2Cl_2 (50 mL) were added (–)-diisopropyl tartrate (DIPT) (5.84 g, 24.9 mmol), Ti(^{i}PrO)$_4$ (5.9 g, 20.8 mmol) and the allyl alcohol **25** (1.5 g, 20.8 mmol) at −20°C under nitrogen. Then *tert*-butyl hydroperoxide (TBHP) (1.12 g, 12.5 mmol) was added and the homogenous reaction mixture was maintained at −20°C (in a freezer) overnight. The cold reaction mixture was poured into a precooled (−20°C) solution containing acetone (20 mL) and water (10 mL). The resulting mixture was stirred and allowed

to warm to room temperature; stirring was continued until filtration gives a clear solution. The filtrate was concentrated and the crude was purified by column chromatography to afford the epoxy alcohol. IR (neat): ν 3620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.72–3.64 (m, 1H, –**CH**(OH)–), 3.54–3.46 (m, 1H, CH_2–O–**CH**(CH–)–)), 2.88 (d, $J=1$ Hz, 3H, –**CH_2**–O–**CH**(CH–)–), 1.26 (d, $J=2.6$ Hz, 3H, –CH(OH)–**CH_3**); $[\alpha]_D=-16.4$ (c 1, MeOH).

To a suspension of sodium hydride (0.27 g, 11.36 mmol, 60% in paraffin oil) in dry THF (25 mL) was added the epoxy alcohol (0.5 g, 5.68 mmol) at 0°C under a nitrogen atmosphere. After stirring for 30 min, benzyl bromide (0.97 g, 5.68 mmol) was slowly added at 0°C and the mixture was stirred for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice-cold water (15 mL), extracted with ether (2×20 mL), washed with brine (15 mL), dried over Na_2SO_4 and evaporated in vacuo. Silica gel column chromatography afforded **16** (0.78 g, 78%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.38–7.18 (m, 5H, Ph-), 4.66–4.34 (m, 2H, Ph**CH_2**O–), 3.46–3.14 (m, 4H, –**CH_2**–O–**CH**(**CH**OBn)–), 1.34–1.2 (m, 3H, –CH(OBn)–**CH_3**); EIMS (m/z): 178 (M^+); HRMS: calcd 178.2296; found: 178.2299; $[\alpha]_D=+4.5$ (c 1.56, EtOH).

4.19. (2*R*,3*S*,10*S*)-2-Benzyloxy-11-*tert*-butyldimethylsilyloxy-10-methyl-5-undecyn-3-ol 26

Under a nitrogen atmosphere, a solution of *n*-butyl lithium in hexane (1.4 M solution, 2 mL, 2.5 mmol,) was added to a dry THF solution (20 mL) of the acetylene **15** (0.4 g, 1.7 mmol) at −78°C and the mixture was stirred for 10 min. Boron trifluoride etherate (0.2 mL) was added to the above solution and stirring was continued for 10 min at −78°C and a THF solution of the epoxide **16** (0.296 g, 1.7 mmol) was added. After stirring for 30 min at −78°C, the reaction mixture was quenched with aqueous ammonium chloride. The organic layers were extracted with ethyl acetate (2×20 mL) and dried over Na_2SO_4. After removal of the solvents, and purification by silica gel column chromatography, the propargylic alcohol **26** was obtained (0.52 g, 75%). IR (neat): ν 3628 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.36–7.26 (m, 5H, Ph–), 4.7–4.42 (m, 2H, Ph**CH_2**O–), 3.76–3.3 (m, 4H, TBSO–**CH_2**–, –CH(OH)–**CH**(OBn)–), 2.46–2.34 (m, 2H, =C–**CH_2**–CH(OH)–), 2.18–2.08 (m, 2H, –CH_2–**CH_2**–C=), 1.56–1.4 (m, 4H, –**CH_2**–**CH_2**–CH_2–), 1.3–1.18 (m, 4H, –**CH**(CH_3), –CH(OBn)–**CH_3**), 0.96–0.82 (m, 12H, (**CH_3**)$_3$C–Si–, –CH(**CH_3**)–), 0.2 (s, 6H, (**CH_3**)$_2$Si–); EIMS (m/z): 418 (M^+); $[\alpha]_D=+7.9$ (c 1, $CHCl_3$).

4.20. (1*R*,2*S*,9*S*)-(4*Z*)-1-[2,10-Di(*tert*-butyldimethylsilyloxy)-1,9-dimethyl-4-decynyloxymethyl]benzene 27

To a mixture of **26** (0.5 g, 1.19 mmol) and 5% Pd–$BaSO_4$ (0.01 g) in methanol (8 mL) was added a 1 M solution of quinoline in methanol (0.1 mL) and the mixture was subjected to hydrogenation at atmospheric pressure (using balloon). After 20 min the catalyst was filtered, the solvent was evaporated and the residue was filtered through a short column of silica gel to give **27** (0.47 g, 95%). IR (neat): ν 3632 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.25 (m, 5H, **Ph**–), 5.46–5.4 (m, 2H, –CH_2–**CH**=**CH**=CH_2–), 4.62 (d, $J=12$ Hz, 2H, Ph**CH_2**O–), 3.46–3.25 (m, 4H, TBSO–**CH_2**–, –**CH**(OH)–**CH**(OBn)–), 1.5–1.2 (m, 9H, –(CH_3)**CH**–**CH_2**–**CH_2**–**CH_2**–CH=CH–**CH_2**–), 1.15 (d, $J=4.8$ Hz, 3H, –(OBn)CH–**CH_3**), 0.94–0.76 (m, 12H, (**CH_3**)$_3$C–Si–, –CH(**CH_3**)–), 0.2 (s, 6H, (**CH_3**)$_2$Si–); EIMS (m/z): 420 (M^+); $[\alpha]_D=+14.8$ (c 1.6, $CHCl_3$).

4.21. (1*R*,2*S*,9*S*)-(4*Z*)-1-[2,10-Di(*tert*-butyldimethylsilyloxy)-1,9-dimethyl-4-decenyloxymethyl]benzene 4

To a stirred solution of **27** (0.4 g, 0.95 mmol) and imidazole (0.085 g, 1.42 mmol) was added TBDMS-Cl (0.157 g, 1.04 mmol) portionwise at 0°C. The reaction mixture was stirred at the same temperature for 6 h and then quenched with water. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (2×30 mL). The combined CH_2Cl_2 layer was washed with water, brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography to afford **4** (0.44 g, 88%). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.38–7.24 (m, 5H, **Ph**–), 5.45–5.38 (2H, –CH_2–**CH**=**CH**=CH_2–), 4.62 (d, $J=13.3$ Hz, 2H, PhCH_2O–), 3.47–3.25 (m, 4H, TBSO–**CH_2**–, –**CH**(OH)–**CH**(OBn)–), 1.48–1.24 (m, 9H, –(CH_3)**CH**–**CH_2**–**CH_2**–**CH_2**–CH=CH–**CH_2**–), 1.05 (d, $J=5.5$ Hz, 3H, –(OBn)CH–**CH_3**), 0.94–0.88 (2×s, 21H, 2×(**CH_3**)$_3$C–Si–, –CH(**CH_3**)–), 0.1–0.15 (2×s, 12H, 2×(**CH_3**)$_2$Si–); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 139.2, 128.3, 127.6, 127.4, 76.6, 74, 71, 32.2, 31.1, 26.2, 26.1, 25.7, 22.8, 18.3, 17, 14.3, 13.9, −4.2, −4.4, −5.1; FABMS: m/z 534 (M^+); HRMS: calcd 536.9672; found: 536.9668; $[\alpha]_D=+9.8$ (c 0.8, $CHCl_3$).

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