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Stereoselective synthesis of C1–C9 and C9–C17 fragments of (+)-13-deoxytedanolide

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ABSTRACT

An efficient and highly stereoselective asymmetric synthesis of C1–C9 and C9–C17 fragments of (+)-13-deoxytedanolide have been achieved. Utilization of desymmetrization technique to prepare the triol with five stereogenic centers, regioselective Sharpless asymmetric dihydroxylation, Evans' aldol reaction, chiral methylation, and Wittig olefination are highlights of the synthesis.

1. Introduction

Tedanolide, an anti-tumor macrolide was isolated from a Caribbean sponge *Tedania ignis* in 1984 by Schmitz et al.[1] A closely related macrolide, 13-deoxytedanolide (**1**) was also isolated from *Mycale adhaerens* by Fusetani et al. in 1991.[2] While these two polyketides exhibited remarkable cytotoxicity at pico to nanomolar ranges, 13-deoxytedanolide was found highly cytotoxic with a reported IC_{50} of 94 pg/mL against P388 murine Leukemia cells.[2] Recently Fusetani et al. reported[3] that **1** bound to 60S large ribosomal subunit of the budding yeast *Saccharomyces cerevisiae*, inhibits polypeptide elongation. Although, many protein synthesis inhibitory natural products are known to bind to the prokaryotic large subunit, **1** is the first macrolide inhibitor that binds to the eukaryotic ribosome. Owing to the structural complexity and bioactivity, tedanolides have generated wide interest on their synthesis. Consequently, total syntheses[4,5] and several approaches toward their synthesis have been reported by various research groups.[6]

2. Results and discussion

In continuation of our efforts in the synthesis of marine natural products,[7] especially polypropionates, we report herein the stereoselective synthesis of C1–C9 and C9–C17 fragments of **1**. From the retrosynthetic strategy of **1** as shown in Scheme 1, we envisaged that **1** could be obtained by coupling the macrolactone **2** and side chain **3** via aldol reaction. The macrolactone **2** could be prepared by coupling the fragments **4** and **5** by cross-metathesis[8] and Yamaguchi macrolatonisation.[9] Carboxylic acid **4**, in turn could be derived from lactone **6** and alcohol **5** could be prepared from 1,5-pentanediol using Evans' aldol reaction, Wittig olefination, and Reformatsky reaction as key steps.

2.1. Synthesis of the C1–C9 fragment 4

The synthesis of C1–C9 fragment **4** was obtained by (Scheme 2) reductive opening of the lactone **6** with $LiAlH_4$ in dry THF, which furnished triol **7** with five chiral centers straight away.[7a,d] The triol **7** was converted to its corresponding acetonide derivative **8** (90% yield) by treating with 2,2-dimethoxypropane and PPTS in CH_2Cl_2. After protecting the primary –OH group of **8**, acetonide group was cleaved using *p*-TSA in methanol to afford **10** in 92% yield. Initial attempts to obtain monoprotected mesylate derivative ended up with low yield of the required compound. Silylation of **10** with TBDMSCl and imidazole in CH_2Cl_2 followed by treatment with MOMCl and DIPEA in CH_2Cl_2 afforded compound **12**, which was desilylated using TBAF in THF and mesylated with MsCl and Et_3N in CH_2Cl_2 to obtain **14** in high yield. Compound **14** was heated with NaI in DMF followed by treatment with DBU to obtain olefin **15**.[10] Initial efforts to generate the triol **17** by

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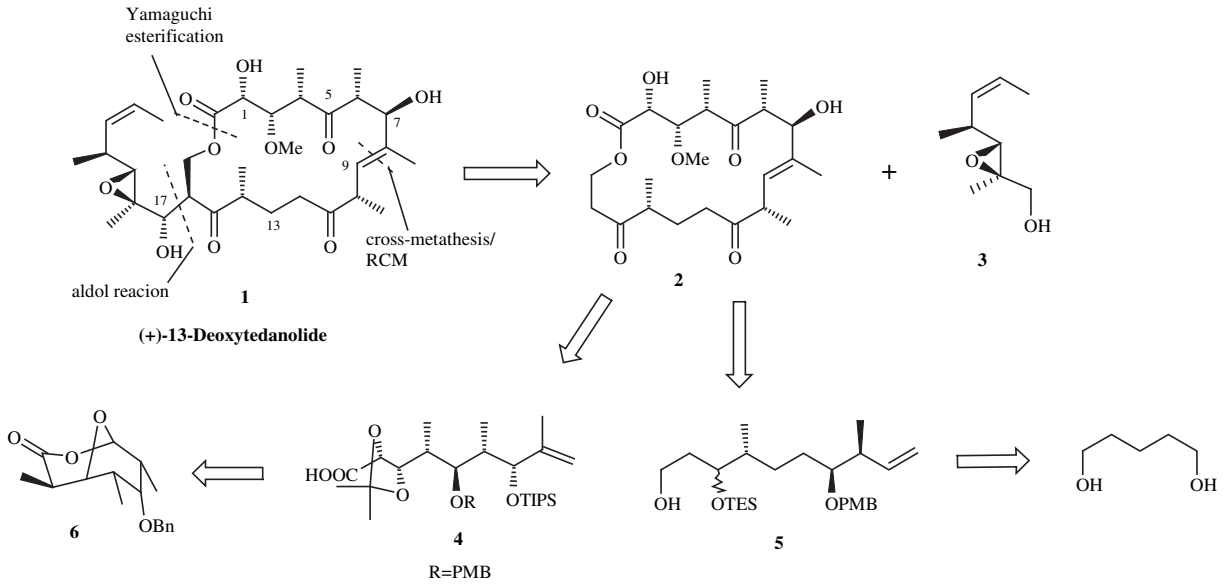


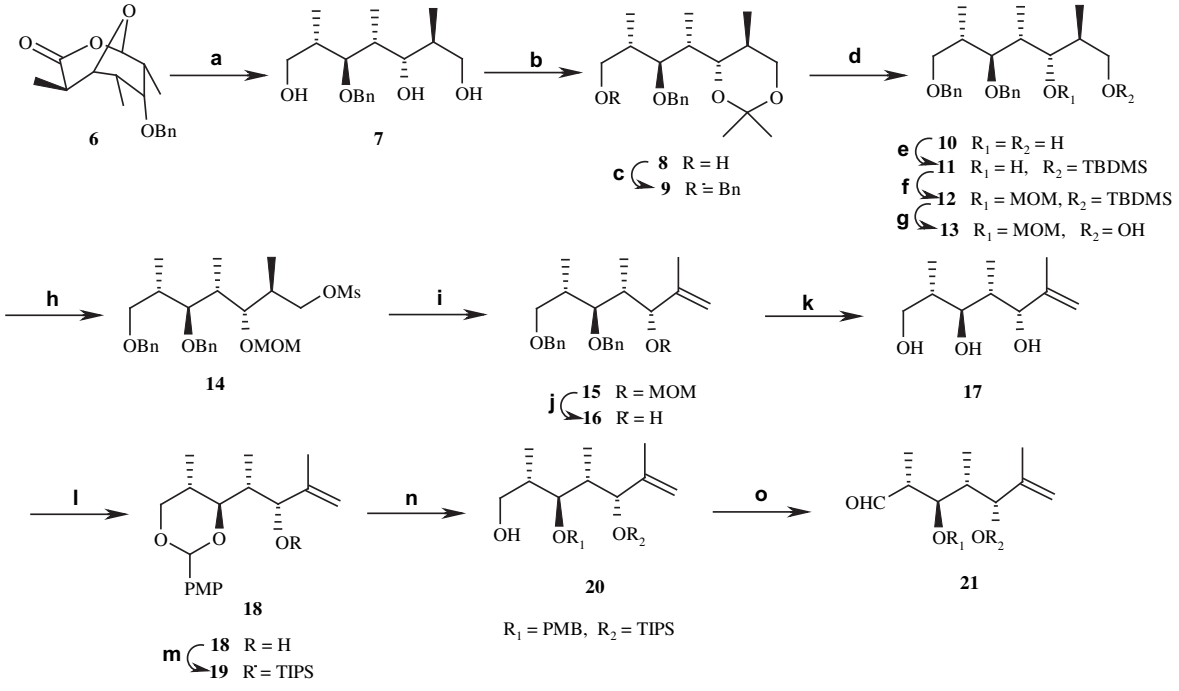
Scheme 1. Retrosynthetic analysis of (+)-13-deoxytedanolide **1**.

deprotection of triply benzylated system and MOM protected compound **14** lead to migration of the double bond, therefore, it was considered necessary to have allylic hydroxy group free. Hence prior to debenzylation, **15** was treated with phosphomolybdic acid (adsorbed on silica gel) under solvent-free conditions to obtain **16** in 95% yield.

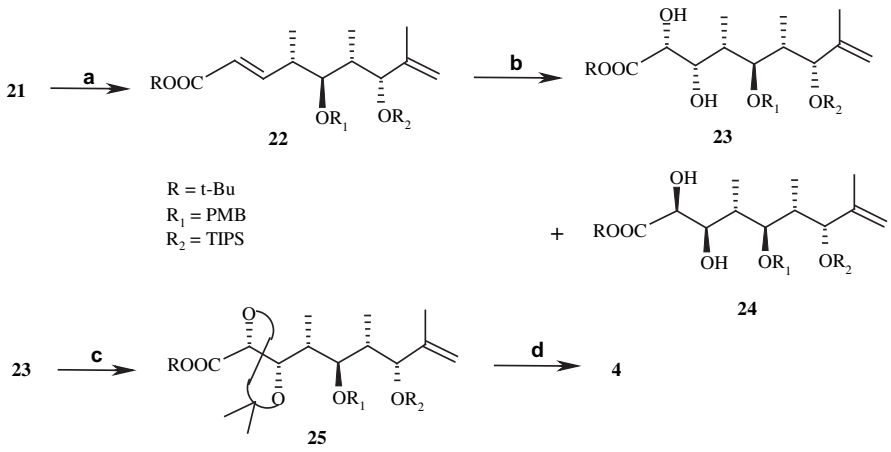
Debenzylation of **16** under Birch reduction[11] conditions gave the corresponding triol in 90% yield. The crude triol **17** was converted to PMB acetal using *p*-methoxybenzyldimethyl acetal and catalytic CSA in CH_2Cl_2. Silylation of **18** with TIPSOTf and DIPEA in CH_2Cl_2 gave compound **19**, which on reduction with DIBAL-H[12] in CH_2Cl_2 followed by Swern oxidation[13] of the alcohol **20** followed by Wittig olefination[14] of the corresponding aldehyde **21** with stabilized ylide $Ph_3P{=}CHCOO^tBu$ in benzene under reflux gave *trans*-α,β-unsaturated ester **22**. Compound **22** on Sharpless asymmetric dihydroxylation[15] (Scheme 3) with AD-mix-α (2.0 mol% based on OsO_4) gave C2,C3-*syn* diols (**23**/**24**=9.5/0.5, separated on silica gel column).[16] Acetonide protection of compound **23** and saponification by $LiOH{\cdot}H_2O$ in THF/MeOH/H_2O (4/1/2) completed the synthesis of C1–C9 fragment **4** of (+)-13-deoxytedanolide (Scheme 3).

2.2. Synthesis of the C9–C17 fragment 5

The synthesis of C9–C17 fragment **5** started with benzylation of 1,5-pentanediol by NaH and BnBr in THF. Swern oxidation of the alcohol **26** followed by further oxidation with aq $NaClO_2$, H_2O_2 in CH_3CN resulted in the formation of corresponding carboxylic acid[17] **27** (73% over two steps). Auxiliary **42** was coupled to carboxylic acid

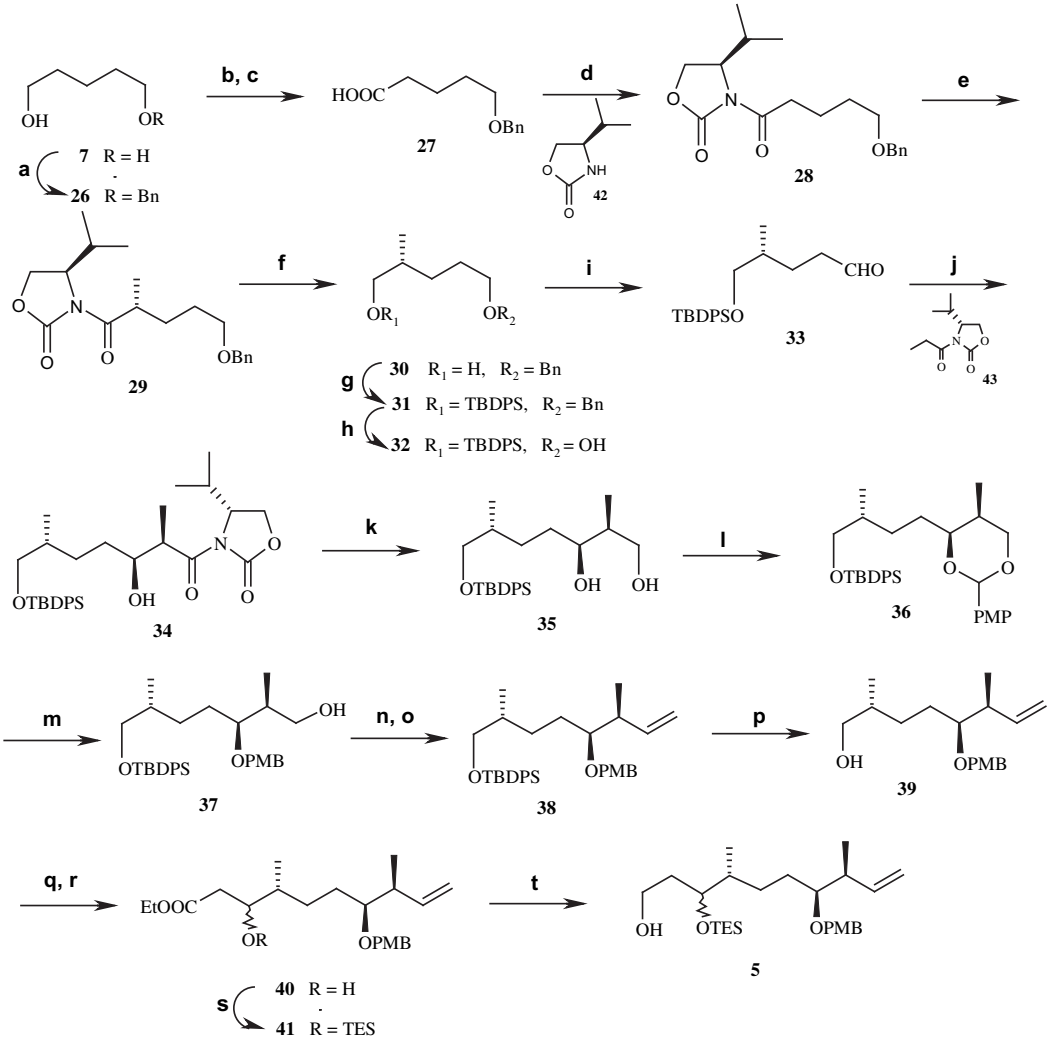


Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 4 h, 90%; (b) 2,2-DMP, PPTS, DCM, rt, 5 h, 90%; (c) NaH, BnBr, dry THF, 0 °C to rt, 5 h, 95%; (d) MeOH, PPTS, rt, overnight, 84%; (e) TBDMSCl, imidazole, DCM, rt, 2 h, 92%; (f) MOMCl, DIPEA, DCM, 0 °C to rt, 6 h, 90%; (g) TBAF, dry THF, rt, 2 h, 92%; (h) MsCl, Et_3N, dry DCM, 0 °C to rt, 1 h, 93%; (i) NaI, dry DMF, 50 °C, 5 h then DBU, 80 °C, 3 h, 88%; (j) PMA/SiO_2, Solvent-free, rt, 15 min, 91%; (k) Li metal, liq. NH_3, −45 °C, 10 min; (l) PMB dimethylacetal, CSA cat., DCM, rt, 2 h, after two steps 85%; (m) TIPSOTf, DIPEA, DCM, 0 °C to rt, 2 h, 95%; (n) DIBAL-H, DCM, 0 °C, 1 h, 93%; (o) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C, 96%.



Scheme 3. Reagents and conditions: (a) $Ph_3P{\equiv}CHCOO^tBu$, benzene, reflux, 2 h, 87%; (b) AD-mix-α, *t*-BuOH–H_2O (1/1), $MeSO_2NH_2$, rt, 24 h, (**23**/**24**=9.5/0.5) 90%; (c) 2,2-DMP, *p*-TSA cat., DCM, rt, 5 h, 93%; (d) LiOH·H_2O, THF/MeOH/H_2O (4/1/2), rt, 18 h, 88%.

27 under standard conditions to form the *N*-acylated oxazolidinone[18] **28**, which was methylated using NaHMDS and CH_3I in THF. Compound **29** on treatment with $NaBH_4$ in ethanol and silylation of the resulting alcohol **30** with TBDPSCl and imidazole, followed by debenzylation using 10% Pd/C under H_2 gas pressure, afforded the alcohol **32** in high yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) NaH, BnBr, dry THF, 0 °C to rt, 3 h, 80%; (b) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C; (c) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, H_2O_2, acetonitrile, 0 °C to rt, 6 h, after two steps 73%; (d) (i) **42**, *n*-BuLi, dry THF, −78 °C, (ii) pivaloyl chloride, Et_3N, dry THF, 0 °C to rt, 2 h, 85%; (e) NaHMDS, dry THF, −78 °C, MeI, 2 h, 81%; (f) $NaBH_4$, EtOH, 0 °C, 15 min, 85%; (g) TBDPSCl, imidazole, DCM, rt, 4 h, 95%; (h) H_2, 10% Pd/C, EtOAc, rt, 2 h, 95%; (i) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C; (j) **43**, Bu_2BOTf, DIPEA, DCM, −78 °C to rt, after two steps 82%; (k) $NaBH_4$, EtOH, 0 °C, 15 min, 85%; (l) PMB dimethylacetal, CSA cat., DCM, rt, 2 h, 87%; (m) DIBAL-H, dry DCM, 0 °C, 1 h, 90%; (n) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C; (o) Ph_3PCH_3Br, NaHMDS, dry THF, 0 °C, 1 h, after two steps 76%; (p) TBAF, dry THF, rt, 4 h, 92%; (q) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C to rt; (r) $BrCH_2COOEt$, Zn–Cu couple, dry THF, reflux, 1 h, after two steps 70%; (s) TESOTf, DIPEA, dry DCM, rt, 1 h; 93%; (t) DIBAL-H, dry DCM, 0 °C, 1 h, 92%.

Swern oxidation of **32** followed by Evans aldol reaction[19a,b] employing *N*-acylated oxazolidinone **43** provided aldol adduct **34** with desired chirality and the stereochemical outcome was conceived as reported on similar substrate.[19c] Reduction of **34** with $NaBH_4$ in EtOH gave **35**, which was protected as its *p*-methoxybenzyl acetal derivative **36**. Reduction of PMB acetal **36** with DIBAL-H in CH_2Cl_2 afforded the primary alcohol **37**, which on Swern oxidation followed by Wittig olefination with nonstabilized ylide $Ph_3P{=}CH_2$ gave **38** in 90% yield.[20] Desilylation and Swern oxidation followed by Reformatsky reaction[21] using $BrCH_2COOEt$ and Zn/Cu couple in refluxing THF afforded the β-hydroxy ester **40** in 70% yield over two steps. Compound **40** was protected as its silyl ether using TESOTf and DIPEA in CH_2Cl_2 followed by treatment with DIBAL-H in CH_2Cl_2 and completed the synthesis of C9–C17 fragment **5**.

3. Conclusion

In summary, we have demonstrated a highly stereoselective syntheses of C1–C9 and C9–C17 fragments of (+)-13-deoxytedanolide. Studies toward completing the total synthesis of **1** by coupling the two fragments and introduction of the side chain **3** is now under progress.

4. Experimental

4.1. General

Commercial reagents were used without further purification and all the solvents were purified by standard techniques. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Air sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. Infrared spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Perkin–Elmer Model 343 polarimeter preparing the samples in $CHCl_3$. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200, Bruker 300, Varian 400, and 500 NMR spectrophotometers. Chemical shifts (δ) are quoted in parts per million and are referred to tetramethylsilane (TMS) as internal standard. Coupling constants (J) are quoted in Hertz. Column chromatographic separations were carried out on silica gel (60–120 or 100–200 mesh) using ethyl acetate and hexane as eluents. ESI HRMS were recorded on 'High Resolution QSTAR XL hybrid MS/MS system, Applied Biosystems' under Electron Spray Ionization conditions by preparing the sample solutions in MeOH.

*4.1.1. (2S,3R,4S,5S,6R)-5-(Benzyloxy)-2,4,6-trimethylheptane-1,3,7-triol (**7**).* To a stirred suspension of $LiAlH_4$ (4.9 g, 129.2 mmol) in dry THF (150 mL) at 0 °C was added dropwise a solution of lactone **6** (15 g, 51.7 mmol) in dry THF (30 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. Reaction mixture was cooled to 0 °C and quenched with dropwise addition of saturated aqueous NH_4Cl. The precipitate formed was filtered and washed with ethyl acetate (2×100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and the crude was purified by silica gel flash chromatography (3/2, EtOAc/hexane) to get **7** (12.75 g, 85%) as a colorless syrup; R_f=0.40 (3/2 EtOAc/hexane); $[\alpha]_D^{27.2}$ −3.1 (*c* 1.35, $CHCl_3$); IR (neat): 3508, 1462, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H, ArH), 4.63–4.72 (q, 2H, J=7.5 Hz, benzylic CH_2), 3.72–3.91 (m, 2H, OCH_2), 3.50–3.69 (m, 4H, 2×OCH, OCH_2), 3.39 (br s, OH), 1.76–2.08 (m, 3H, 3×CH), 1.57 (br s, OH) 1.12 (d, 3H, J=7.5 Hz, CH_3), 0.96 (d, 3H, J=7.5 Hz, CH_3), 0.73 (d, 3H, J=7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.3, 127.7, 127.5, 87.3, 75.9, 75.7, 68.1, 64.2, 37.5, 37.1, 35.3, 14.4, 12.9, 10.9; ESI HRMS: m/z calcd for $C_{17}H_{28}O_4Na$ $[M+Na]^+$ 319.1837, found 319.1833.

*4.1.2. (2R,3S,4R)-3-(Benzyloxy)-2-methyl-4-[(4R,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-1-ol (**8**).* To a solution of **7** (10.5 g, 35.5 mmol) in dry DCM (100 mL), 2,2-dimethoxypropane (6.5 mL, 53.2 mmol) and PPTS (0.42 g, 1.77 mmol) were added. The mixture was stirred at ambient temperature for 5 h. Saturated aqueous solution of sodium bicarbonate was added to the reaction mixture. The aqueous layer was extracted with DCM (2×100 mL) and the combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude product, which on purification by column chromatography on silica gel gave acetonide **8** as a white solid; (10.7 g, 90%), R_f=0.60 (1/1 EtOAc/hexane); mp: 96–97 °C; $[\alpha]_D^{25}$ +116.5 (*c* 0.5, $CHCl_3$); IR (neat): 3479, 2923, 1617, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.23 (m, 5H, ArH), 4.74–4.55 (ABq, 2H, J=11.7, 27.4 Hz, benzylic CH_2), 3.92–3.79 (m, 1H), 3.65 (dd, J=10.9, 4.7 Hz, 1H), 3.59–3.39 (m, 3H), 2.64 (dd, J=7.8, 2.3 Hz, 1H) 2.07–1.76 (m, 3H, 3×CH), 1.34 (s, 6H, 2×CH_3), 1.21 (d, 3H, J=7.0 Hz, CH_3), 0.87 (d, 3H, J=7.0 Hz, CH_3), 0.73 (d, 3H, J=7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.5, 127.7, 127.3, 98.0, 85.6, 75.4, 73.8, 66.2, 64.3, 87.5, 36.3, 30.3, 29.8, 19.8, 16.5, 12.5, 9.9; ESI HRMS: m/z calcd for $C_{20}H_{32}O_4Na$ $[M+Na]^+$ 359.2198, found 359.2205.

*4.1.3. (4R,5S)-4-[(1R,2S,3R)-2,4-Di(benzyloxy)-1,3-dimethylbutyl]-2,2,5-trimethyl-1,3-dioxane (**9**).* To a stirred suspension of NaH (60% suspension in mineral oil) (1.57 g, 32.7 mmol) in THF (80 mL) was added a solution of alcohol **8** (10.0 g, 29.7 mmol) in dry THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. It was cooled to 0–5 °C and benzyl bromide (3.5 mL, 32.7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0–5 °C and water was added slowly to dissolve the solids. The temperature was raised to 25 °C and the reaction mixture was extracted with diethyl ether (3×100 mL). The combined organic extract was washed with saturated NH_4Cl, water, brine, dried over Na_2SO_4, evaporated under reduced pressure, and purification by column chromatography on silica gel afforded **9** as a colorless oil (12.0 g, 95%), R_f=0.80 (1/4 EtOAc/hexane); $[\alpha]_D^{25}$ +77.93 (*c* 0.5, $CHCl_3$); IR (neat): 1456, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.18 (m, 10H, ArH), 4.60 (ABq, J=11.7 Hz, 2H, benzylic CH_2), 4.46 (s, 2H, benzylic CH_2), 3.83 (dd, J=10.4, 1.5 Hz, 1H, CH), 3.68–3.59 (m, 2H, CH_2), 3.44 (d, J=11.1 Hz, 1H, CH), 3.39–3.33 (m, 2H, CH_2), 2.1 (m, 1H, CH), 2.02–1.74 (m, 2H, 2×CH), 1.38 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.12 (d, J=7.0 Hz, 3H, CH_3), 0.87 (d, J=7.0 Hz, 3H, CH_3), 0.66 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 138.8, 128.2, 127.3, 127.1, 126.7, 97.9, 83.1, 74.7, 73.4, 72.9, 71.8, 66.2, 36.9, 36, 30.3, 29.8, 19.4, 16.6, 12.4, 9.8; ESI HRMS: m/z calcd for $C_{27}H_{38}O_4Na$ $[M+Na]^+$ 449.2667, found 449.2681.

*4.1.4. (2S,3R,4S,5S,6R)-5,7-Di(benzyloxy)-2,4,6-trimethylheptane-1,3-diol (**10**).* PPTS (0.31 g, 1.29 mmol) was added to a stirring solution of **9** (11.0 g, 25.8 mmol) in methanol (100 mL) at room temperature. After stirring overnight, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. Methanol was removed and the aqueous layer was extracted with DCM (3×50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The filtrate was evaporated under reduced pressure and the crude was purified by column chromatography on silica gel to afford **10** as an oily liquid (8.36 g, 84%). R_f=0.40 (1/1 EtOAc/hexane); $[\alpha]_D^{25}$ −58.05 (*c* 0.6, $CHCl_3$); IR (neat): 3431, 1456, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.22 (m, 10H, ArH), 4.60 (ABq, J=10.9 Hz, 2H, benzylic CH2), 4.47 (s, 2H, benzylic CH_2), 3.96 (br s, 1H, OH), 3.8 (d, J=9.8 Hz, 1H, CH), 3.68 (dd, J=8.7, 4.1 Hz, 1H, CH), 3.63–3.50 (m, 3H, CH_2, CH), 3.44 (dd, J=9.0, 3.0 Hz, 1H, CH),

2.1 (m, 1H, CH), 1.92–1.75 (m, 2H, CH_2), 1.12 (d, J=7.5 Hz, 3H, CH_3), 1.0 (d, J=6.8 Hz, 3H, CH_3), 0.73 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.5, 128.3, 127.9, 127.7, 127.6, 87.3, 76, 73.2, 72.2, 69.2, 37.2, 36.8, 34.7, 14.9, 13.3, 11.7; ESI HRMS: m/z calcd for $C_{24}H_{34}O_4Na$ $[M+Na]^+$ 409.2354, found 409.2362.

*4.1.5. (2S,3R,4S,5S,6R)-5,7-Di(benzyloxy)-1-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2,4,6-trimethylheptan-3-ol (**11**).* To a stirring solution of **10** (8 g, 20.7 mmol) in DCM (80 mL), imidazole (2.81 g, 41.4 mmol) and *tert*-butyldimethylsilylchloride (3.42 g, 22.77 mmol) were added. The reaction mixture was stirred for 2 h at room temperature and quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with DCM (3×50 mL), the combined layer was washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel column to give **11** (9.5 g, 92%) as a colorless oil. R_f=0.80 (1/4 EtOAc/hexane); $[\alpha]_D^{25}$ +3.53 (*c* 0.5, $CHCl_3$); IR (neat): 3431, 1456, 1063 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.18 (m, 10H, ArH), 4.60 (ABq, J=10.9 Hz, 2H, benzylic CH_2), 4.46 (s, 2H, benzylic CH_2), 3.76–3.63 (m, 3H, CH, CH_2), 3.62–3.47 (m, 3H, CH, CH_2), 2.10 (m, 1H, CH), 1.84 (m, 1H, CH), 1.70 (m, 1H, CH), 1.42 (br s, 1H, OH), 1.03 (d, J=7.2 Hz, 3H, CH_3), 1.0 (d, J=6.8, Hz, 3H, CH_3), 0.88 (s, 9H, 3×CH_3, *tert*-butyl/Si), 0.76 (d, J=6.8 Hz, 3H, CH_3), 0.04 (s, 6H, 2×$SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 136.8, 128.3, 128.1, 127.5, 127.3, 86.2, 76.0, 73.1, 72.7, 72.1, 67.1, 38.3, 36.4, 35.6, 25.9, 18.27, 15.5, 13.0, 10.7, −5.5; IR (neat): 3497, 1459, 1083 cm^{-1}; ESI HRMS: m/z calcd for $C_{30}H_{48}O_4NaSi$ $[M+Na]^+$ 523.3219, found 523.3241.

*4.1.6. tert-Butyl[(2S,3R,4R,5S,6R)-5,7-di(benzyloxy)-3-(methoxymethoxy)-2,4,6-trimethylheptyl]oxydimethylsilane (**12**).* Diisopropylethylamine (6.2 g, 36 mmol) and methoxymethyl chloride (MOMCl) (1.7 mL, 21.6 mmol) were added to a stirred solution of **11** (9.0 g, 18 mmol) in DCM (50 mL) at 0 °C under nitrogen atmosphere. After stirring for 6 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM (3×50 mL). The extracted organic layer was washed with saturated aqueous NH_4Cl, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel column to give **12** (8.8 g, 90%) as colorless oil; R_f=0.60 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +38.47 (*c* 0.45, $CHCl_3$); IR (neat): 1459, 1092, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.16 (m, 10H, ArH), 4.72–4.53 (m, 4H, benzylic 2×CH_2), 4.46 (s, 2H, CH_2, MOM), 3.71 (d, J=9.0 Hz, 1H, CH), 3.64–3.50 (m, 3H, CH, CH_2), 3.48–3.38 (m, 2H, CH_2), 3.34 (s, 3H, CH_3, MOM), 2.18 (m, 1H, CH), 1.86 (m, 1H, CH), 1.72 (m, 1H, CH), 1.14 (d, J=6.8, Hz, 3H, CH_3), 0.9–0.8 (m, 15H, 3×CH_3, *tert*-butyl, 2×CH_3), 0.01 (s, 6H, 2×CH_3, TBDMS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 128.2, 128.1, 127.4, 127.3, 127.1, 98.4, 84.0, 81.0, 74.3, 73.0, 72.3, 64.9, 55.4, 39.1, 38.0, 36.0, 29.7, 25.9, 16.4, 14.6, 10.9, −5.4; ESI HRMS: m/z calcd for $C_{32}H_{52}O_5NaSi$ $[M+Na]^+$ 567.3481, found 567.3480.

*4.1.7. (2S,3R,4R,5S,6R)-5,7-Di(benzyloxy)-3-(methoxymethoxy)-2,4,6-trimethylheptan-1-ol (**13**).* 1.0 M solution of TBAF in THF (18.7 mL, 18.7 mmol) was added to a stirred solution of **12** (8.5 g, 15.6 mmol) in THF (68 mL) at room temperature. The solution was stirred for 4 h and quenched with water (50 mL). The reaction mixture was extracted with EtOAc (3×60 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to obtain **13** (6.1 g, 92%). R_f=0.70 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ −29.37 (*c* 0.4, $CHCl_3$); IR (neat): 3447, 1455, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.19 (m, 10H, ArH), 4.64–4.48 (m, 4H, benzylic 2×CH_2), 4.46 (s, 2H, CH_2, MOM), 3.75–3.62 (m, 2H, CH_2), 3.56 (dd, J=8.7, 4.9 Hz, 1H, CH), 3.47(dd, J=8.7, 6.4 Hz, 1H, CH), 3.37–3.32 (m, 2H, CH_2), 3.35 (s, 3H, CH_3, MOM), 2.68 (br s, 1H, OH), 2.15 (m, 1H, CH), 1.89 (m, 1H, CH), 1.75 (m, 1H, CH), 1.1 (d, J=7.5, Hz, 3H, CH_3), 0.95 (d, J=6.8, Hz, 3H, CH_3), 0.88 (d, J=7.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 128.2, 127.4, 127.3, 98.3, 84.7, 81.6, 74.4, 73, 72.2, 65.3, 55.8, 38.8, 37.6, 36.2, 15.7, 14.5, 11.7; ESI HRMS: m/z calcd for $C_{26}H_{38}O_5Na$ $[M+Na]^+$ 453.2616, found 453.2624.

*4.1.8. (2S,3R,4R,5S,6R)-5,7-Di(benzyloxy)-3-(methoxymethoxy)-2,4,6-trimethylheptyl methanesulfonate (**14**).* To a stirred solution of **13** (5.8 g, 13.5 mmol) in dry DCM (50 mL), triethylamine (9.4 mL, 67.5 mmol) was added at room temperature. Methane sulfonyl chloride (1.2 mL, 16.2 mmol) was added at 0 °C and stirred at 25 °C for 1 h, quenched with water, and extracted with DCM (3×50 mL). The combined organic layer was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel chromatography to give **14** (6.3 g, 93%); R_f=0.75 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ +16.38 (*c* 0.7, $CHCl_3$); IR (neat): 1456, 1355, 1175, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.19 (m, 10H, ArH), 4.61–4.48 (m, 4H, benzylic 2×CH_2), 4.46 (s, 2H, CH_2, MOM), 4.20 (dd, J=9.4, 3.7 Hz, 1H, CH), 4.12 (dd, J=9.0, 5.6 Hz, 1H, CH), 3.67 (d, J=7.9 Hz, 1H, CH), 3.58 (dd, J=9.0, 5.6 Hz, 1H, CH), 3.45–3.39 (m, 2H, CH_2), 3.34 (s, 3H, CH_3, MOM), 2.85 (s, 3H, CH_3, mesyl), 2.18 (m, 1H, CH), 1.99 (m, 1H, CH), 1.89 (m, 1H, CH), 1.12 (d, J=6.8 Hz, 3H, CH_3), 0.95 (d, J=7.5, Hz, 3H, CH_3), 0.90 (d, J=6.8, Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.2, 127.4, 127.2, 98.3, 84.1, 80.4, 74.2, 73.1, 72.4, 72.2, 55.7, 37.9, 36.9, 36.0, 16.1, 14.3, 11.1; ESI HRMS: m/z calcd for $C_{27}H_{40}O_7NaS$ $[M+Na]^+$ 531.2392, found 531.2411.

*4.1.9. (3S,4R,5S,6R)-5,7-Di(benzyloxy)-3-(methoxymethoxy)-2,4,6-trimethyl-1-heptene (**15**).* A mixture of **14** (6 g, 11.8 mmol) and NaI (8.85 g, 59 mmol) in DMF (60 mL) was heated at 50 °C for 5 h. The mixture was cooled to room temperature, DBU (2.1 mL, 14.2 mmol) was added and the reaction mixture was heated at 80 °C for 3 h. The mixture was cooled to room temperature and poured into chilled water and extracted with diethyl ether (3×100 mL). The combined organic extract was washed with water, saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography to give **15** (4.3 g, 88%) as a colorless liquid. R_f=0.55 (0.5/9.5 EtOAc/hexane); $[\alpha]_D^{25}$ +122.53 (*c* 0.25, $CHCl_3$); IR (neat): 1633, 1454, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.22 (m, 10H, ArH), 4.93 (s, 1H, olefinic), 4.92 (s, 1H, olefinic), 4. 66 (ABq, J=11.3 Hz, 2H, benzylic CH_2), 4.50 (d, J=6.4 Hz, 2H, benzylic CH_2), 4.45 (s, 2H, CH_2, MOM), 4.17 (d, J=3.7 Hz, 1H, CH), 3.62 (dd, J=9.0, 4.5 Hz, 1H, CH), 3.40 (d, J=7.5 Hz, 1H, CH), 3.36 (m, 1H, CH), 3.37 (s, 3H, CH_3, MOM), 2.12 (m, 1H, CH), 1.93 (m, 1H, CH), 1.62 (s, 3H, CH_3), 1.12 (d, J=7.2 Hz, 3H, CH_3), 0.91 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 139.1, 138.7, 128.2, 127.3, 127.2, 113.2, 94.6, 83.2, 80.2, 73.6, 73, 72.3, 55.8, 38.5, 35.9, 18.8, 16.6, 10.4; ESI HRMS: m/z calcd for $C_{26}H_{36}O_4Na$ $[M+Na]^+$ 435.2511, found 435.2532.

*4.1.10. (3S,4S,5S,6R)-5,7-Di(benzyloxy)-2,4,6-trimethyl-1-hepten-3-ol (**16**).* Compound **15** (3.8 g, 9.2 mmol) was mixed with phosphomolybdic acid (0.08 g, 0.045 mmol, adsorbed on 7.2 g of silica gel) and stirred vigorously at room temperature. After stirring for 30 min, DCM (50 mL) was added to the mixture and filtered-off the catalyst. The filtered cake was washed with DCM (2×20 mL) and the combined filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give **16** (3.0 g, 91%) as a colorless viscous liquid. R_f=0.65 (1/4 EtOAc/hexane); $[\alpha]_D^{28}$ +3.2 (*c* 0.6, $CHCl_3$); IR (neat): 3439, 1494, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 10H, ArH), 5.0 (s, 1H, olefinic), 4.88 (s, 1H, olefinic), 4.59 (ABq, J=11.3 Hz, 2H, benzylic CH_2), 4.48 (s, 2H, benzylic CH_2), 4.36 (br s, 1H, OH), 3.66 (dd, J=9.0, 4.5 Hz, 1H, CH),3.58 (dd, J=9.0, 3.0 Hz, 1H, CH), 3.50 (dd, J=9.0, 3.7 Hz, 1H, CH), 3.40 (s, 1H, CH), 2.16 (m, 1H, CH), 1.92 (m, 1H, CH), 1.64 (s, 3H, CH_3), 1.06 (d, J=6.8 Hz, 3H, CH_3), 0.95 (d, J=7.5 Hz, 3H,

CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.05, 138.4, 138.0, 128.4, 128.3, 128.1, 127.7, 127.5, 127.3, 110.1, 84.9, 74.8, 73.1, 72.7, 71.8, 36.8, 35.7, 18.03, 14.4, 10.9; ESI HRMS: *m*/*z* calcd for $C_{24}H_{32}O_3Na$ $[M+Na]^+$ 391.2249, found 391.2288.

*4.1.11. (3S,4S)-4-[(4S,5R)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-2-methyl-1-penten-3-ol (**18**).* To the blue solution, prepared by addition of lithium metal (1.0 g, 152 mmol) to liquid NH_3 (100 mL), was added a solution of **16** (2.8 g, 7.6 mmol) in dry THF (5 mL) at −40 °C. The reaction mixture was stirred for 10 min and quenched by addition of NH_4Cl (8.1 g, 152 mmol). After removal of NH_3 by a stream of N_2, ethyl acetate (50 mL) was added, stirred vigorously, and filtered-off the solids. The filtrate was concentrated under reduced pressure and the residue (compound **17**) was used for the next step without further purification.

Compound **17** (1.4 g, 7.4 mmol), camphorsulfonic acid (0.085 g), and *p*-anisaldehyde dimethylacetal (2 mL, 11.1 mmol) in DCM (15 mL) were stirred for 2 h at room temperature. Triethylamine (4 mL) was added and the reaction mixture stirred for further 10 min. Solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography to give **18** (1.9 g, 85%) as a white semi-solid. R_f=0.55 (1/4 EtOAc/hexane); $[\alpha]_D^{26}$ +88.33 (*c* 0.3, $CHCl_3$); IR (neat): 3349, 1637, 1453, 1261 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, *J*=8.9 Hz, 2H, ArH), 6.83 (d, *J*=8.5 Hz, 2H, ArH), 5.34 (s, 1H, PMP), 5.07 (s, 1H, olefinic), 4.88 (s, 1H, olefinic), 4.43 (br s, 1H, OH), 4.14 (dd, *J*=11.2, 4.6 Hz, 1H, CH), 3.79 (s, 3H, CH_3, OCH_3), 3.57 (dd, *J*=10.0, 1.5, 1H), 3.47 (m, 2H, CH_2), 2.29 (m, 1H, CH), 2.0 (m, 1H, CH), 1.67 (s, 3H, CH_3), 0.98 (d, *J*=7.0 Hz, 3H, CH_3), 0.82(d, *J*=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 151.7, 127.1, 124.3, 113.8, 110.7, 102.1, 87.1, 79.8, 72.8, 55.5, 33.4, 31.0, 20.1, 12.4, 10.5; ESI HRMS: *m*/*z* calcd for $C_{18}H_{26}O_4Na$ $[M+Na]^+$ 329.1728, found 329.1760.

*4.1.12. Triisopropyl[((1S)-1-(1R)-1-[(4S,5R)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]ethyl-2-methyl-2-propenyl)oxy]silane (**19**).* To a solution of **18** (1.0 g, 3.25 mmol) in CH_2C1_2 (20 mL) were added DIPEA (1.1 mL, 6.5 mmol) and the triisopropylsilyl triflate (1.1 mL, 4.2 mmol) at 0 °C under nitrogen. After 5 min, the cooling bath was removed and the mixture stirred for 2 h at room temperature. Water (50 mL) was added and the aqueous layer extracted with DCM (3×30 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4), evaporated in vacuo, and the residue was purified by column chromatography on silica gel to give **19** (1.51 g, 95%) as a colorless liquid. R_f=0.70 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +28.0 (*c* 0.13, $CHCl_3$); IR (neat): 1614, 1461, 1247, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J*=8.4 Hz, 1H, ArH), 7.24 (d, *J*=8.4 Hz, 1H, ArH), 6.81 (d, *J*=8.8 Hz, 1H, ArH), 6.78 (d, *J*=8.8 Hz, 1H, ArH), 5.31 (s, 1H, PMP), 4.92 (s, 1H, olefinic), 4.90 (s, 1H, olefinic), 4.42 (d, *J*=6.6 Hz, 1H, CH), 4.11–3.95 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.36 (m, 1H, CH), 2.78 (dd, *J*=14.3, 6.9 Hz, 1H, CH), 2.01 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.13–0.89 (m, 24H, 3×HC(CH_3)$_2$, CH_3), 0.79 (d, *J*=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 143.8, 132.0, 127.2, 114.2, 113.4, 101.0, 81.5, 79.3, 73.2, 55.5, 41.0, 35.6, 17.6, 16.0, 15.2, 12.3, 11.8; ESI HRMS: *m*/*z* calcd for $C_{27}H_{46}O_4NaSi$ $[M+Na]^+$ 485.7313, found 485.7309.

*4.1.13. (2R,3S,4R,5S)-3-[(4-Methoxybenzyl)oxy]-2,4,6-trimethyl-5-[(1,1,1-triisopropyl silyl)oxy]-6-hepten-1-ol (**20**).* A 20% solution of DIBAL-H in toluene (4.6 mL, 9.0 mmol) was added dropwise to a stirring solution of **19** (1.0 g, 2.16 mmol) in DCM (50 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous potassium sodium tartrate solution (40 mL). The reaction mixture was diluted with DCM (60 mL) and vigorously stirred for 30 min. The aqueous layer was extracted with DCM (3×30 mL). The combined organic layer was dried over Na_2SO_4, concentrated in vacuo. The residue was purified by column chromatography on silica gel to give **20** (0.932 g, 93%) as a colorless oil. R_f=0.60 (1/4 EtOAc/hexane); $[\alpha]_D^{28}$ +2.6 (*c* 1.5, $CHCl_3$); IR (neat): 3448, 1613, 1460, 1248, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J*=8.7 Hz, 2H, ArH), 6.82 (d, *J*=8.5 Hz, 2H, ArH), 4.89 (s, 1H, olefinic), 4.87 (s, 1H, olefinic), 4.48 (ABq, *J*=10.6 Hz, 2H, benzylic CH_2), 4.23 (d, *J*=6.8 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.75 (d, *J*=11.7 Hz, 1H, CH), 3.49 (m, 1H, CH), 3.34 (t, *J*=4.3 Hz, 1H, CH), 2.60 (m, 1H, CH), 2.01 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.12–0.12 (m, 27H, 3×HC(CH_3)$_2$, 2×CH_3); ESI HRMS: *m*/*z* calcd for $C_{27}H_{48}O_4NaSi$ $[M+Na]^+$ 487.3219, found 487.3231.

*4.1.14. tert-Butyl(2E,4R,5S,6R,7S)-5-[(4-methoxybenzyl)oxy]-4,6,8-trimethyl-7-[(1,1,1-triisopropylsilyl)oxy]-2,8-nonadienoate (**22**).* A solution of dimethyl sulfoxide (DMSO) (0.4 mL, 5.9 mmol) in DCM (20 mL) was added to a stirring solution of $(COCl)_2$ (0.4 mL, 5.4 mmol) in DCM (20 mL) at −78 °C. After 20 min, a solution of **20** (1.25 g, 2.69 mmol) in DCM (20 mL) was added at the same temperature. The mixture was stirred for 20 min at −78 °C and triethylamine (2.0 mL, 13.4 mmol) was added at the same temperature. Dry ice bath was removed and stirring was continued at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with DCM (2×50 mL). The organic extract was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and the crude product was used for the next step without further purification.

(*tert*-Butoxycarbonylmethylene) triphenyl phosphorane (1.21 g, 3.22 mmol) was added to a stirring solution of the above aldehyde in benzene (50 mL) at room temperature under N_2. After refluxing for 2 h, the reaction mixture was diluted with *n*-hexane (100 mL) and filtered through a Celite pad. The filtrate was evaporated in vacuo and the residue was chromatographed on silica gel column to obtain the *trans*-α,β-unsaturated ester **22** (1.325 g, with 87% yield) as a colorless liquid. R_f=0.75 (1/4 EtOAc/hexane); $[\alpha]_D^{25}$ +26.0 (*c* 0.12, $CHCl_3$); IR (neat, cm^{-1}): 1713, 1648, 1614, 1460, 1248, 1144; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.3 Hz, 2H, ArH), 7.17 (dd, *J*=15.8, 8.3 Hz, 1H, conjugated olefinic β), 6.98 (d, *J*=8.3 Hz, 2H, ArH), 5.83 (d, *J*=15.8 Hz, 1H, conjugated olefinic α), 5.08 (s, 1H, olefinic), 5.01 (s, 1H, olefinic), 4.63 (AB q, *J*=11.3 Hz, 2H, benzylic CH_2), 4.44 (d, *J*=5.3 Hz, 1H, CH), 3.96 (s, 3H, OCH_3), 3.44 (dd, *J*=6.0, 2.2 Hz, 1H, CH), 2.79 (m, 1H, CH), 2.05 (m, 1H, CH), 1.85 (s, 3H, CH_3), 1.65 (s, 9H, t-butyl), 1.28 (d, *J*=6.8 Hz, 3H, CH_3), 1.22 (m, 21H, 3×HC(CH_3)$_2$), 1.07 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 158.9, 150.7, 146.8, 128.7, 128.0, 122.2, 113.6, 112.2, 83.1, 79.9, 72.1, 67.4, 55.2, 40.4, 38.5, 28.2, 18.3, 12.9, 10.5; ESI HRMS: *m*/*z* calcd for $C_{33}H_{56}O_5NaSi$ $[M+Na]^+$ 583.3794, found 583.3808.

*4.1.15. tert-Butyl(2S,3R,4R,5R,6S,7S)-2,3-dihydroxy-5-[(4-methoxybenzyl)oxy]-4,6,8-trimethyl-7-[(1,1,1-triisopropylsilyl)methyl]-8-nonenoate (**23**).* $CH_3SO_2NH_2$ (0.11 g, 1.16 mmol) was added to a stirring solution of AD-mix-α (8.5 g) in a mixture of *t*-BuOH and H_2O (1/1, 20 mL) at room temperature. After 5 min, solution of **22** (0.65 g, 1.16 mmol) in *t*-BuOH (1.0 mL) was added at 0 °C and stirring was continued for 28 h at room temperature. The reaction mixture was quenched with Na_2SO_3 (8.0 g) at 0 °C and extracted with EtOAc (3×50 mL). The combined organic layer was washed with saturated aqueous NH_4Cl, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column to afford two diastereomers **23** and **24** in the ratio (9.5/0.5) with overall yield (0.62 g, 90%) as a colorless liquids. R_f=0.65 (3/7 EtOAc/hexane); **23**: $[\alpha]_D^{28}$ +21.0 (*c* 0.17, $CHCl_3$); IR (neat): 3452, 1743, 1604, 1460, 1248, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J*=8.7 Hz, 2H, ArH), 6.84 (d, *J*=8.7 Hz, 2H, ArH), 4.96 (s, 1H, olefinic), 4.92 (s, 1H, olefinic), 4.53 (AB q, *J*=10.6 Hz, 2H, benzylic CH_2), 4.35 (d, *J*=6.0 Hz, 1H, CH), 4.03 (m, 2H, 2×CH), 3.81 (s, 3H, OCH_3), 3.49 (m, 1H, CH), 3.01 (br s, 1H), 2.11–1.94 (m, 2H, 2×CH), 1.76 (s, 3H, CH_3), 1.50 (s, 9H, *tert*-butyl), 1.13 (d, *J*=7.2 Hz, 3H, CH_3),

1.09 (m, 21H, 3×HC(CH_3)$_2$), 1.02 (d, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 159.6, 147.0, 128.9, 114.0, 113.0, 84.9, 82.4, 77.5, 73.4, 72.9, 72.5, 55.2, 40.6, 37.5, 27.9, 18.3, 18.2, 13.5, 12.9, 10.5; ESI HRMS: m/z calcd for $C_{33}H_{58}O_7NaSi$ $[M+Na]^+$ 617.3849, found 617.3871.

*4.1.16. tert-Butyl(4R,5R)-5-(1S,2S,3R,4S)-2-[(4-methoxybenzyl)oxy]-1,3,5-trimethyl-4-[(1,1,1-triisopropylsilyl)oxy]-5-hexenyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**25**).* To a solution of **23** (0.3 g, 0.5 mmol) in dry DCM (10 mL) 2,2-demethoxy propane (1.0 mL, 0.75 mmol) and *p*-TSA (50 mg) were added. The mixture was stirred at ambient temperature for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column to afford the acetonide **25** (0.29 g, 93%) as a colorless liquid. R_f=0.70 (1/4 EtOAc/hexane); $[\alpha]_D^{25}$ +5.0 (*c* 0.25, $CHCl_3$); IR (neat): 1721, 1617, 1460, 1249, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J=8.7 Hz, 2H, ArH), 6.80 (d, J=8.7 Hz, 2H, ArH), 4.91 (s, 1H, olefinic), 4.83 (s, 1H, olefinic), 4.61–4.33 (m, 3H, CH, benzylic CH_2), 4.08 (d, J=6.8 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.78 (m, 1H, CH), 3.47 (dd, J=7.9, 2.3 Hz, 1H, CH), 2.09–1.78 (m, 2H, 2×CH), 1.67 (s, 3H, CH_3), 1.46–1.33 (m, 18H, 6×CH_3), 1.09–1.01 (m, 21H, 3×HC(CH_3)$_2$), 0.96 (d, J=7.2 Hz, 3H, CH_3); ESI HRMS: m/z calcd for $C_{36}H_{62}O_7NaSi$ $[M+Na]^+$ 657.4162, found 657.4165.

*4.1.17. (4R,5R)-5-(1S,2R,3R,4S)-2-[(4-Methoxybenzyl)oxy]-1,3,5-trimethyl-4-[(1,1,1-triisopropylsilyl)oxy]-5-hexenyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (**4**).* A solution of lithium hydroxide (0.09 g, 2.14 mmol in 10 mL of water) was added to a solution of **25** (0.14 g, 0.22 mmol) in THF/MeOH (4/1, 25 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate (30 mL) and 2 N HCl (3.0 mL) was added to adjust the pH of the reaction mixture to 5. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **4** (0.11 g, 88%) as a colorless viscous liquid. R_f=0.45 (2/3 EtOAc/hexane); $[\alpha]_D^{25}$ −5.0 (*c* 0.19, $CHCl_3$); IR (neat): 3449, 1719, 1617, 1460, 1250, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, J=8.5 Hz, 2H, ArH), 6.78 (d, J=8.5 Hz, 2H, ArH), 4.91 (s, 1H, olefinic), 4.87 (s, 1H, olefinic), 4.51–4.43 (m, 3H, CH, benzylic CH_2), 4.30 (d, J=7.7 Hz, 1H, CH), 4.13 (d, J=7.7 Hz, 1H, CH), 3.77 (s, 3H), 3.26 (dd, J=7.2, 3.0 Hz, 1H, CH), 2.19 (m, 1H, CH), 2.01 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.25 (s, 6H, 2×CH_3), 1.10–1.01 (m, 24H, 3×HC(CH_3)$_2$, CH_3), 0.98 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 160.1, 143.3, 128.9, 126.34, 113.8, 107.4, 104.1, 82.3, 80.37, 77.8, 72.8, 68.0, 55.2, 40.0, 36.2, 26.8, 18.3, 18.2, 12.8, 12.0, 11.37; ESI HRMS: m/z calcd for $C_{32}H_{54}O_7NaSi$ $[M+Na]^+$ 601.3536, found 601.3543.

*4.1.18. 5-(Benzyloxy)-1-pentanol (**26**).* A solution of 1,5-pentanediol (10 g, 96.15 mmol) in THF (10 mL) was added to a flask containing NaH (60% suspension in mineral oil, 5.5 g, 115.38 mmol) in THF (90 mL) at room temperature. The mixture was stirred at room temperature for 30 min and cooled to 0 °C. Benzyl bromide (11.5 mL, 96.15 mmol) was added slowly dropwise and the mixture was stirred for 3 h at room temperature. Water was added slowly to quench the reaction and extracted with ether (3×100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel to provide **26** (14.9 g, 80%) as a colorless oil. R_f=0.40 (1/1 EtOAc/hexane); IR (neat): 3381, 1453, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 5H, ArH), 4.47 (s, 2H, benzylic), 3.60 (t, J=6.5 Hz, 2H, CH_2), 3.44 (t, J=6.5 Hz, 2H, CH_2), 1.79–1.29 (m, 6H, 3×CH_2); ESI MS: 195 $[M^+ +1]$.

*4.1.19. 5-(Benzyloxy)pentanoic acid (**27**).* A solution of dimethyl sulfoxide (DMSO) (11.2 mL, 158.7 mmol) in DCM (30 mL) was added to a stirring solution of $(COCl)_2$ (10 mL, 114.3 mmol) in DCM (30 mL) at −78 °C. After 20 min, a solution of **26** (14.0 g, 72.16 mmol) in DCM (140 mL) was added at the same temperature. The reaction mixture was stirred for 20 min and triethylamine (50 mL, 360.8 mmol) was added at −78 °C. Dry ice bath was removed and the stirring was continued at room temperature for 30 min. Saturated aqueous NH_4Cl (60 mL) was added to quench the reaction mixture and extracted with DCM (3×100 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, concentrated in vacuo, and used in the next step without purification.

A solution of $NaClO_2$ (80% assay) (12.25 g, 108.2 mmol) in water (112 mL) was added to a solution of above aldehyde in acetonitrile (70 mL), $NaH_2PO_4 \cdot 2H_2O$ (2.25 g, 14.4 mmol), and 35% H_2O_2 (7.7 mL, 79.37 mmol). The reaction mixture was stirred at room temperature for 6 h, cooled to 0–5 °C and Na_2SO_3 was added to quench the unreacted $NaClO_2$ and H_2O_2 at 0 °C. The reaction mixture was acidified with 10% aqueous HCl and extracted with DCM (3×50 mL). The combined organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by silica gel flash chromatography to provide the carboxylic acid **27** (7.8 g, 73%) as a colorless viscous oil. R_f=0.35 (1/1 EtOAc/hexane); IR (neat): 3032, 1709, 1452 cm^{-1}; IR (neat): 3032, 1709, 1452 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (br s, 1H, COOH), 7.25 (m, 5H, ArH), 4.46 (s, 2H, benzylic CH_2), 3.45 (t, J=6.0 Hz, 2H, CH_2), 2.36 (t, J=6.8 Hz, 2H, CH_2), 1.78–1.60 (m, 4H, 2×CH_2); ESI HRMS: m/z calcd for $C_{12}H_{16}O_3Na$ $[M+Na]$ 231.0997, found 231.1005.

*4.1.20. (4R)-3-[5-(Benzyloxy)pentanoyl]-4-isopropyl-1,3-oxazolan-2-one (**28**).* A solution of *n*-BuLi in hexane (2.5 M, 23.0 mL, 57.6 mmol) was added dropwise to a stirring solution of **42** (6.2 g, 48 mmol) in anhydrous THF (100 mL) at −78 °C. The mixture was stirred at this temperature for 30 min. Acid **27** (12 g, 57.69 mmol) was taken in THF (120 mL) in a separate flask and cooled to 0 °C. Triethylamine (11.36 mL, 81.6 mmol) and pivaloyl chloride (7.52 mL, 62.4 mmol) were slowly added and after stirring for 30 min at 0 °C, the lithio-(4*R*)-4-isopropyl-2-oxazolidinone was added to this mixed anhydride. The mixture was warmed to room temperature over a period of 2 h. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc (3×50 mL). The organic layer was washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and brine. The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to provide **28** (15.5 g, 85%) as a colorless oil. R_f=0.55 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ −39.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H, ArH), 4.47 (s, 2H, CH_2), 4.36 (m, 1H, CH), 4.23–4.13 (m, 2H, CH_2), 3.48 (t, J=6.0 Hz, 2H), 3.03–2.81 (m, 2H, CH_2), 2.36 (m, 1H, CH), 1.81–1.62 (m, 4H, 2×CH_2), 0.92 (d, J=7.2 Hz, 3H, CH_3), 0.87 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 153.9, 138.4, 128.2, 127.4, 127.3, 72.7, 69.8, 63.2, 58.2, 35.0, 28.9, 28.2, 21.0, 17.7, 14.5; IR (neat): 1780, 1701, 1456 cm^{-1}; ESI HRMS: m/z calcd for $C_{18}H_{25}NO_4Na$ $[M+Na]$ 342.1681, found 342.1684.

*4.1.21. (4R)-3-[(2S)-5-(Benzyloxy)-2-methylpentanoyl]-4-isopropyl-1,3-oxazolan-2-one (**29**).* The solution of **28** (10.0 g, 31.3 mmol) in THF (50 mL) was cooled to −78 °C and 1 M solution of NaHMDS (34.5 mL, 34.48 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h and iodomethane (9.75 mL, 156.5 mmol) was added in to the reaction mixture. After stirring for 30 min, the

solution was allowed to warm to room temperature. The mixture was quenched with aqueous NH_4Cl solution and extracted with ether (3×50 mL). The organic extract was washed with saturated NH_4Cl solution, saturated $NaHCO_3$, brine, dried over (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography on silica gel column to obtain **29** (8.4 g, 81%) as a colorless oil. R_f=0.60 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ −46.0 (*c* 0.25, $CHCl_3$); IR (neat): 1778, 1699, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 5H, ArH), 4.45 (s, 2H, CH_2), 4.35 (m, *J*=3.7 Hz, 1H, CH), 4.16–4.04 (m, 2H, CH_2), 3.49–3.39 (m, 2H, CH_2), 2.34 (m, 1H, CH), 1.80 (m, 1H, CH), 1.67–1.35 (m, 4H, 2×CH_2), 1.2 (d, *J*=6.8 Hz, 3H, CH_3), 0.91 (d, *J*=6.8 Hz, 3H, CH_3), 0.87 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 153.5, 138.5, 129.4, 128.2, 127.4, 127.3, 72.7, 70.1, 63.0, 58.2, 37.4, 29.6, 28.3, 27.2, 17.8, 17.7, 14.5; ESI HRMS: Calculated *m*/*z* for $C_{19}H_{27}NO_4Na$ [M+Na] 356.1837, found 356.1842.

*4.1.22. (2S)-5-(Benzyloxy)-2-methylpentan-1-ol (**30**).* To a solution of **29** (7.0 g, 21 mmol) in EtOH (70 mL), $NaBH_4$ (1.59 g, 42 mmol) was added at 0 °C and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated NH_4Cl solution. EtOH was removed and the aqueous layer extracted with EtOAc (3×50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography on silica gel column to give **30** (3.7 g, 85%) as a colorless oil. R_f=0.45 (1/1 EtOAc/hexane); $[\alpha]_D^{26}$ +31.0 (*c* 0.1, $CHCl_3$); IR (neat): 3449, 1457, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 5H, ArH), 4.47 (s, 2H, CH_2), 3.48–3.36 (m, 4H, 2×CH_2), 1.73–1.42 (m, 5H, 2×CH_2 and CH), 0.91 (d, *J*=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 72.9, 70.6, 67.9, 35.5, 29.5, 27.0, 16.5; ESI HRMS: *m*/*z* calcd for $C_{13}H_{20}O_2Na$ [M+Na] 231.1360, found 231.1362.

*4.1.23. [(2S)-5-(Benzyloxy)-2-methylpentyl]oxy(tert-butyl)diphenylsilane (**31**).* To a solution of **30** (3.0 g, 14.4 mmol) in DCM (50 mL), imidazole (1.95 g mL, 28.8 mmol) and TBDPSCl (4.35 g, 15.84 mmol) were added sequentially at room temperature. After being stirred for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with DCM (3×50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography on silica gel gave compound **31** (6.1 g, 95%) as a colorless liquid. R_f=0.75 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +22.0 (*c* 0.17, $CHCl_3$); IR (neat): 1463, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J*=7.5 Hz, 4H, ArH), 7.38–7.19 (m, 11H, ArH), 4.45 (s, 2H, benzylic CH_2), 3.53–3.36 (m, 4H, 2×CH_2), 1.71–1.44 (m, 4H, 2×CH_2), 1.20 (m, 1H, CH), 1.04 (s, 9H, *tert*-butyl), 0.93 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.6, 134.0, 132.7, 129.4, 128.3, 127.5, 127.4, 76.5, 72.8, 68.6, 35.6, 29.6, 26.8, 26.2, 19.3, 16.8; ESI HRMS: *m*/*z* calcd for $C_{29}H_{38}O_2NaSi$ [M+Na] 469.2538, found 469.2551.

*4.1.24. (4S)-5-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-4-methylpentan-1-ol (**32**).* To a solution of **31** (5.0 g, 11.2 mmol) in EtOAc (25 mL), 10% Pd/C (0.595 g, 0.56 mmol in terms of Pd) was added and the reaction mixture was hydrogenated for 2 h. Palladium was filtered through Celite bed and the filter cake washed with EtOAc (10 mL). The combined organic solvent was concentrated in vacuo. The residue was purified by chromatography on silica gel column to afford **32** (3.79 g, 95%) as a colorless oil. R_f=0.60 (2/3 EtOAc/hexane); $[\alpha]_D^{26}$ +8.1 (*c* 0.5, $CHCl_3$); IR (neat): 3418, 1466, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J*=7.5 Hz, 4H, ArH), 7.42–7.30 (m, 6H, ArH), 3.60–3.41 (m, 4H, 2×CH_2), 1.71–1.40 (m, 4H, 2×CH_2), 1.17 (m, 1H, CH), 1.05 (s, 9H, *tert*-butyl), 0.93 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.0, 132.1, 128.6, 128.1, 72.8, 61.2, 33.8, 29.8, 27.1, 25.8, 19.5, 16.6; ESI HRMS: *m*/*z* calcd for $C_{22}H_{32}O_2NaSi$ [M+Na] 379.2069, found 379.2077.

*4.1.25. (4S)-3-((2R,3S,6S)-7-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-3-hydroxy-2,6-dimethylheptanoyl)-4-isopropyl-1,3-oxazolan-2-one (**34**).* A solution of dimethyl sulfoxide (DMSO) (1.3 mL, 18.5 mmol) in DCM (15 mL) was added to a stirring solution of $(COCl)_2$ (1.47 mL, 16.84 mmol) in DCM (15 mL) at −78 °C. After 20 min, a solution of **32** (3.0 g, 8.42 mmol) in DCM (30 mL) was added at the same temperature. After stirring the mixture for 20 min, triethylamine (5.86 mL, 42.1 mmol) was added at −78 °C. The reaction was brought to room temperature and stirring was continued for 30 min at the same temperature. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with DCM (3×50 mL). The organic extract was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and the crude product was used in the next step without further purification.

To the auxiliary **43** (1.48 g, 8 mmol) in DCM (15 mL) under nitrogen, was added Bu_2BOTf (8.4 mL, 8.42 mmol) followed by DIPEA (1.72 mL, 10.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. The solution of aldehyde in DCM (15 mL) was added and stirred for 30 min at −78 °C. The reaction mixture was stirred for 2 h further at room temperature. The boron–aldolate complex was quenched with pH 7 phosphate buffer (15 mL) followed by addition of 30% H_2O_2–MeOH (1/1, 30 mL) at 0 °C and stirred for 1 h. The reaction mixture was extracted with ether (3×40 mL) and the combined organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by silica gel column chromatography gave pure Evan's aldol adduct **34** (3.7 g, 82%) as a colorless liquid. R_f=0.55 (2/3 EtOAc/hexane); $[\alpha]_D^{26}$ −15.0 (*c* 0.25, $CHCl_3$); IR (neat): 3447, 1782, 1696, 1109 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.67–7.58 (m, 4H, ArH), 7.40–7.30 (m, 6H, ArH), 4.41 (m, 1H, CH), 4.30–4.14 (m, 2H, CH_2), 3.83 (br s, 1H, OH), 3.66 (m, 1H, CH), 3.42 (m, 2H, CH_2), 2.86 (m, 1H, CH), 2.33 (m, 1H, CH), 1.76–1.28 (m, 4H, 2×CH_2), 1.24 (m, 1H, CH), 1.20 (d, *J*=7.0 Hz, 3H, CH_3), 1.05 (s, 9H, *tert*-butyl), 0.94 (d, *J*=6.6 Hz, 3H, CH_3), 0.93 (d, *J*=7.3 Hz, 3H, CH_3), 0.89 (d, *J*=7.3 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.9, 153.4, 135.5, 133.9, 129.4, 127.5, 71.5, 68.6, 63.2, 58.1, 41.8, 35.7, 31.0, 29.4, 28.2, 26.8, 19.2, 17.8, 16.8, 10.5; ESI HRMS: *m*/*z* calcd for $C_{31}H_{45}NO_5NaSi$ [M+Na] 562.2964, found 562.2973.

*4.1.26. (2S,3S,6S)-7-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-2,6-dimethylheptane-1,3-diol (**35**).* Compound **34** (3.0 g, 5.5 mmol) was reduced to **35** (2.3 g, 85%) by following the procedure as enumerated in 4.1.22. R_f=0.40 (6/4 EtOAc/hexane); $[\alpha]_D^{25}$ +10.0 (*c* 0.24, $CHCl_3$); IR (neat): 3436, 1464, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ [ppm] 7.62 (d, *J*=7.5 Hz, 4H, ArH), 7.42–7.29 (m, 6H, ArH), 3.78–3.59 (m, 3H, CH_2 and CH), 3.54–3.40 (m, 2H, CH_2), 1.77–1.50 (m, 3H, CH_2 and CH), 1.40 (m, 1H, CH), 1.09 (m, 2H, CH_2), 1.05 (s, 9H, *tert*-butyl), 0.94 (d, *J*=6.8 Hz, 3H, CH_3), 0.88 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] 135.6, 133.9, 129.5, 127.5, 75.0, 68.6, 67.3, 38.8, 35.7, 31.4, 29.6, 26.8, 19.2, 16.9, 9.9; ESI HRMS: *m*/*z* calcd for $C_{25}H_{38}O_3NaSi$ [M+Na] 437.2487, found 437.2505.

*4.1.27. tert-Butyl((2S)-4-[(4S,5S)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-2-methylbutyloxy)diphenylsilane (**36**).* Compound **35** (2.0 g, 4.8 mmol), camphorsulfonic acid (0.056 g, 0.24 mmol), and *p*-anisaldehyde dimethylacetal (1.05 mL, 5.76 mmol) in DCM (20 mL) were stirred for 2 h at room temperature. Triethylamine (2.0 mL) was added and the solution was stirred for additional 10 min, the solvent was removed and the residue was purified by silica gel flash column chromatography to obtain **36** (2.2 g, 87%) as a white semi-solid. R_f=0.30 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +5.0 (*c* 0.22, $CHCl_3$); IR (neat): 1462, 1247, 1110, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J*=6.0 Hz, 4H, ArH), 7.42–7.28 (m, 8H, ArH), 6.8 (d,

J=9.0 Hz, 2H, ArH), 5.37 (s, 1H, benzylic), 4.04–3.91 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.77 (m, 1H, CH), 3.46 (m, 2H, CH_2), 1.70–1.31 (m, 6H, 2×CH_2 and 2×CH), 1.13 (d, J=6.8 Hz, 3H, CH_3), 1.05 (s, 9H, *tert*-butyl), 0.92 (d, J=6.0 Hz, 3H, CH_3); ESI HRMS: m/z calcd for $C_{33}H_{44}O_4NaSi$ [M+Na] 555.2906, found 555.2930.

*4.1.28. (2S,3S,6S)-7-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-3-[(4-methoxybenzyl)oxy]-2,6-dimethylheptan-1-ol (**37**).* Compound **37** (0.9 g, 90%) was prepared from compound **36** (1.0 g, 1.87 mmol) as a colorless oil by the procedure as described in 4.1.13. The product was purified by silica gel chromatography. R_f=0.55 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ +19.0 (c 0.25, $CHCl_3$); IR (neat): 3446, 1465, 1247, 1109, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.67–7.58 (m, 4H, ArH), 7.41–7.12 (m, 7H, ArH), 6.81 (m, 3H, ArH), 4.43 (s, 2H, benzylic CH_2), 3.78 (d, J=4.4 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.50–3.34 (m, 3H, CH_2, and CH), 1.98 (br s, 1H, OH), 1.71–1.38 (m, 3H, CH_2, and CH), 1.37–1.20 (m, 3H, CH_2, and CH), 1.05 (s, 9H, *tert*-butyl), 0.93 (d, J=6.2 Hz, 3H, CH_3), 0.83 (d, J=7.0 Hz, 3H, CH_3); ESI HRMS: m/z calcd for $C_{33}H_{46}O_4NaSi$ [M+Na] 534.8073, found 557.8079.

*4.1.29. tert-Butyl((2S,5S,6S)-5-[(4-methoxybenzyl)oxy]-2,6-dimethyl-7-octenyloxy) diphenylsilane (**38**).* A solution of dimethyl sulfoxide (DMSO) (0.2 mL, 2.88 mmol) in CH_2Cl_2 (3 mL) was added to a stirring solution of $(COCl)_2$ (0.23 mL, 2.62 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After 20 min, a solution of **37** (0.7 g, 1.31 mmol) in CH_2Cl_2 (5 mL) was added at the same temperature. After stirring the reaction mixture for 20 min, triethylamine (0.9 mL, 6.55 mmol) was added at −78 °C. The reaction was brought to room temperature and stirring was continued for 30 min. Saturated aqueous NH_4Cl (30 mL) was added, and the mixture was extracted with DCM (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo proceeded to the next step without purification.

Methyltriphenylphosphonium bromide (1.4 g, 3.93 mmol) in THF (20 mL) at 0 °C was treated with sodium bis-(trimethylsilyl)amide (2.6 mL, 1 M in THF, 2.62 mmol), and the resulting solution was stirred at 0 °C for 30 min. The aldehyde in THF (5.0 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×25 mL). The combined ether fractions were washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to afford compound **38** (0.53 g, 76%) as a colorless liquid. R_f=0.75 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +5.0 (c 0.25, $CHCl_3$); IR (neat): 1618, 1461, 1247, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.62 (d, J=6.0 Hz, 4H, ArH), 7.43–7.29 (m, 6H, ArH), 7.18 (d, J=8.3 Hz, 2H, ArH), 6.8 (d, J=8.3 Hz, 2H, ArH), 5.76 (m, 1H, olefinic CH), 4.98 (m, 2H, olefinic CH_2), 4.40 (s, 2H, benzylic CH_2), 3.77 (s, 3H, OCH_3), 3.51–3.36 (m, 2H, CH_2), 3.16 (m, 1H, CH), 2.42 (m, 1H, allylic CH), 1.59 (m, 2H, CH_2), 1.46–1.33 (m, 3H, CH_2 and CH), 1.04 (s, 9H, *t*-butyl), 0.99 (d, J=6.8 Hz, 3H, CH_3), 0.91 (d, J=5.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 140.9, 135.5, 134.0, 129.4, 129.2, 127.5, 114.3, 114.1, 113.6, 82.8, 71.3, 68.7, 55.2, 40.7, 35.8, 29.3, 28.9, 28.3, 27.9, 26.8, 19.3, 16.9, 15.5; ESI HRMS: m/z calcd for $C_{34}H_{46}O_3NaSi$ [M+Na] 553.3113, found 553.3116.

*4.1.30. (2R,5S,6S)-5-[(4-Methoxybenzyl)oxy]-2,6-dimethyl-7-octen-1-ol (**39**).* To a solution of **38** (0.6 g, 1.13 mmol) in dry THF (20 mL), TBAF (1.5 mL, 1 M in THF, 1.5 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. It was quenched with saturated aqueous NH_4Cl solution (30 mL), extracted with EtOAC (3×25 mL), and the combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography to obtain **39** (0.202 g, 92%) as a colorless liquid. R_f=0.55 (4/7 EtOAc/hexane); $[\alpha]_D^{25}$ +3.1 (c 0.5, $CHCl_3$); IR (neat): 3439, 1615, 1460, 1247, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20(d, J=8.4 Hz, 2H, ArH), 6.81 (d, J=8.8 Hz, 2H, ArH), 5.78 (m, 1H, olefinic CH), 5.05–4.96 (m, 2H, olefinic CH_2), 4.43 (m, 2H, benzylic CH_2), 3.79 (s, 3H, OCH_3), 3.47–3.55 (m, 2H, CH_2), 3.19 (m, 1H, CH), 2.46 (m, 1H, allylic CH), 1.64–1.22 (m, 5H, 2×CH_2, and CH), 1.02 (dd, J=6.8, 3.6 Hz, 3H, CH_3), 0.90 (dd, J=6.6, 2.8 Hz, 3H, CH_3); ESI HRMS: m/z calcd for $C_{18}H_{28}O_3Na$ [M+Na] 315.4164, found 315.4161.

*4.1.31. Ethyl(4S,7S,8S)-3-hydroxy-7-[(4-methoxybenzyl)oxy]-4,8-dimethyl-9-decenoate (**40**).* A solution of dimethyl sulfoxide (DMSO) (0.6 mL, 9.0 mmol) in DCM (5.0 mL) was added to a stirring solution of $(COCl)_2$ (0.7 mL, 8.2 mmol) in DCM (5.0 mL) at −78 °C. After 20 min, a solution of **39** (1.20 g, 4.1 mmol) in DCM (20 mL) was added at the same temperature. After stirring the mixture for 20 min at −78 °C, triethylamine (30 mL, 21.5 mmol) was added. The reaction mixture was brought to room temperature and stirring was continued for 30 min. Saturated aqueous NH_4Cl (25 mL) solution was added to quench the reaction, extracted with DCM (3×50 mL). The organic layer was washed with water, brine, and dried over Na_2SO_4, concentrated in vacuo, and proceeded to next step without purification.

To a warm (60 °C) mixture of acetic acid (20 mL) and cupric acetate dihydrate (0.082 g, 0.41 mmol) was added zinc dust (1.57 g, 24.6 mmol) while stirring the reaction mixture vigorously, over a period of 2 min. Instantaneously, a reddish black solid (zinc/copper couple) was formed with an exothermic reaction. The reaction was cooled to room temperature and acetic acid was decanted. The solid was washed with acetic acid (2×20 mL) followed by ether (3×50 mL) and the wet Zn/Cu couple was used for the reaction immediately.

To the Zn/Cu couple in THF (20 mL), the solution of aldehyde and 2-bromoethyl acetate (0.5 mL 4.5 mmol) in THF (10 mL) was added under N_2 atmosphere at room temperature. The reaction mixture was refluxed gently for 1 h, allowed to cool to room temperature. After quenching the reaction mixture with saturated aqueous NH_4Cl (10 mL), it was filtered on Celite. The Celite cake was washed with diethyl ether (20 mL) and the filtrate was dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel to afford the β-hydroxyl ester (diastereomeric mixture) **40** (1.09 g, 70% after two steps) as a colorless oil. R_f=0.65 (3/7 EtOAc/hexane); $[\alpha]_D^{25}$ +15.7 (c 0.5, $CHCl_3$); IR (neat): 3451, 1730, 1613, 1460, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, J=8.4 Hz, 2H, ArH), 6.81 (d, J=8.4 Hz, 2H, ArH), 5.79 (m, 1H, olefinic CH), 5.0 (m, 2H, olefinic CH_2), 4.43 (s, 2H, benzylic CH_2), 4.15 (q, J=7.0 Hz, 2H, ethyl CH_2), 3.87 (m, 1H, CH), 3.79 (s, 3H, OCH_3), 3.18 (m, 1H, CH), 2.53–2.21 (m, 3H, CH_2, and allylic CH), 1.69–1.34 (m, 5H, 2×CH_2, and CH), 1.28 (t, J=7.0 Hz, 3H, CH_3), 1.02 (dd, J=6.6, 1.8 Hz, 3H, CH_3), 0.88 (d, J=5.9 Hz, 3H, CH_3); ESI HRMS: m/z calcd for $C_{22}H_{34}O_5Na$ [M+Na] 401.2303, found 401.2291.

*4.1.32. Ethyl(4S,7S,8S)-7-[(4-methoxybenzyl)oxy]-4,8-dimethyl-3-[(1,1,1-triethylsilyl) oxy]-9-decenoate (**41**).* To a solution of **40** (0.44 g, 1.12 mmol) in DCM (20 mL) were added DIPEA (0.56 mL, 3.36 mmol) and the triethylsilyltriflate (0.24 mL, 13.6 mmol) at 0 °C under nitrogen. After 5 min the cooling bath was removed and the mixture stirred for 1 h at room temperature. Water was added to quench the reaction and separated the layers. The aqueous layer was extracted with DCM (2×30 mL) and the combined organic layers were dried (Na_2SO_4), evaporated, and purified by chromatography on silica gel column to get **41** (0.532 g, 93%) as a colorless liquid. R_f=0.65 (1/9 EtOAc/hexane); $[\alpha]_D^{25}$ +19.2 (c 0.12, $CHCl_3$); IR (neat): 1730, 1613, 1460, 1247, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J=8.3 Hz, 2H, ArH), 6.80 (d, J=8.6 Hz, 2H, ArH), 5.78 (m, 1H, olefinic CH), 5.0 (m, 2H, olefinic CH_2), 4.41 (s, 2H, benzylic CH_2), 4.09 (m, 3H, CH_2 and CH), 3.79 (s, 3H, OCH_3), 3.17 (m,

1H, CH), 2.52–2.24 (m, 3H, CH_2, and allylic CH), 1.60–1.32 (m, 2H, CH_2), 1.26 (m, 6H, CH_3, CH_2, and CH), 1.02 (dd, J=6.8, 3.8 Hz, 3H, CH_3), 0.93 (t, J=7.9 Hz, 9H, 3×CH_3), 0.89–0.80 (m, 3H, CH_3), 0.56 (q, J=7.9 Hz, 6H, 3×CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 146.8, 138.3, 130.9, 128.3, 113.7, 113.5, 83.09, 71.5, 67.6, 60.3, 55.2, 40.8, 40.3, 34.3, 30.1, 29.6, 16.3, 15.6, 14.1, 6.8, 4.9; ESI HRMS: m/z calcd for $C_{28}H_{48}O_5NaSi$ [M+Na] 515.3168, found 515.3161.

*4.1.33. (4S,7S,8S)-7-[(4-Methoxybenzyl)oxy]-4,8-dimethyl-3-[(1,1,1-triethylsilyl)oxy]-9-decen-1-ol (**5**).* Compound **41** (0.25 g, 0.5 mmol) in DCM (20 mL), under N_2 atmosphere, was cooled to 0 °C, and diisobutylaluminum hydride (20% solution in toluene, 1.7 mL, 2.1 mmol) was slowly added over 10 min. After addition was complete, stirring was continued for 1 h at 0 °C. The reaction mixture was carefully quenched with methanol (10 mL). Saturated aqueous solution of potassium sodium tartrate solution (20 mL) and ethyl acetate (20 mL) was added. The mixture was stirred vigorously for 1 h to get the clear separation of organic and aqueous layers. Separated the layers and the aqueous layer was extensively extracted with ethyl acetate (3×50 mL). The combined organic layers were dried (Na_2SO_4) evaporated to dryness and purified by flash chromatography on silica gel to obtain **5** (0.21 g, 92%) as a colorless liquid. R_f=0.55 (5/8 EtOAc/hexane); $[\alpha]_D^{25}$ +28.0 (c 0.1, $CHCl_3$); IR (neat): 3448, 1613, 1462, 1247, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J=8.3 Hz, 2H, ArH), 6.80 (dd, J=8.6, 2.2 Hz, 2H, ArH), 5.79 (m, 1H, olefinic CH), 5.0 (m, 2H, olefinic CH_2), 4.51–4.34 (m, 2H, benzylic CH_2), 3.79 (s, 3H, OCH_3), 3.75–3.64 (m, 3H, CH_2, and CH), 3.16 (m, 1H, CH), 2.43 (m, 1H, allylic CH), 1.71–1.44 (m, 3H, CH_2, and CH), 1.34–1.20 (m, 4H, 2×CH_2), 1.05–0.79 (m, 15H, 3×CH_3), 0.60 (q, J=7.9 Hz, 6H, 3×CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 136.2, 128.6, 129.8, 115.0, 113.3, 80.2, 74.3, 71.5, 65.2, 54.1, 44.7, 39.9, 31.3, 29.8, 16.3, 13.2, 8.7, 4.4; ESI HRMS: m/z calcd for $C_{26}H_{46}O_4NaSi$ [M+Na] 473.3063, found 473.3066.

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