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Stereoconvergent synthesis of C_1–C_{17} and C_{18}–C_{25} fragments of bafilomycin A_1 ☆

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Abstract

The effective syntheses of the enantiomerically pure C1–C17 **2** and C18–C25 **3** fragments as promising synthetic intermediates of bafilomycin A_1, **1** have been achieved.

Keywords: Bafilomycin A_1; Intermediates; Bicyclic precursor; Aldol; Vinyl stannane; Vinyl iodide; Evans-aldol

1. Introduction

Bafilomycin A_1 **1**, is a 16-membered macrolide, first isolated from a culture of *Streptomyces griseus* sp. by Werner et al. in 1983.[1] It is a potent vacuolar H^+-ATPase (V-ATPases) inhibitor.[2] The V-ATPases are known to participate in bone resorption and inhibitors of such enzymes may potentially be used for the treatment of osteoporosis.[3] Furthermore, this compound displayed broad antibacterial, antifungal,[4] and immunosuppressive activities.[5] Bafilomycin A_1 contains an acid and base-sensitive six-membered hemiketal that participates in a hydrogen-bond network with the C_9, C_{17} the hydroxyl group and the carbonyl of the 16-membered lactone that is responsible for biological activity. In light of its interesting chemical structure and profile of biological activity, bafilomycin A_1 has been an attractive target for synthesis. Consequently, four total syntheses[6] and several partial contributions[7] of bafilomycin A_1 have been reported by various research groups so far.

2. Results and discussion

The retrosynthesis, we envisaged for the synthesis of bafilomycin A_1 is shown in Scheme 1. The macrolactone can be opened and then disconnected between C_{11} and C_{12} via a Stille-coupling reaction. As part of our interest in the synthesis of bioactive natural products,[8] herein we report the synthesis of the C_1–C_{11}, C_{12}–C_{17}, and C_{18}–C_{25} fragments of bafilomycin A_1, and also the coupling of C_1–C_{11} fragment with the C_{12}–C_{17} fragment.

2.1. Synthesis of the C_1–C_{11} fragment **4**

The synthesis of the C_1–C_{11} fragment **4** started with a known triol[8a,b] **6** (Scheme 2). The 1,3-diol group in **6** was protected as an acetonide employing 2,2-dimethoxy propane and PPTS in CH_2Cl_2, and the free primary hydroxyl group was tosylated under standard conditions to yield the tosylate **9**. The tosyl compound **9** was treated with lithium acetylide–ethylenediamine complex in DMSO to give the acetylenic compound and the acetonide group was deprotected to yield the diol **10**. Oxidation of the primary alcohol in **10** with IBX furnished aldehyde **11**. When the secondary hydroxyl group in compound **11** was acetylated using Ac_2O, Et_3N in the presence of DMAP,

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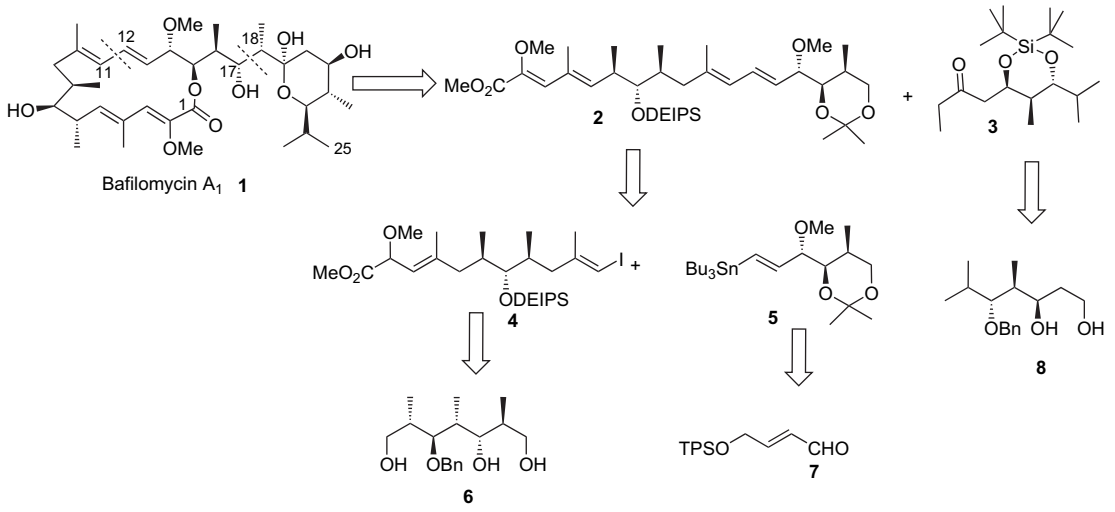
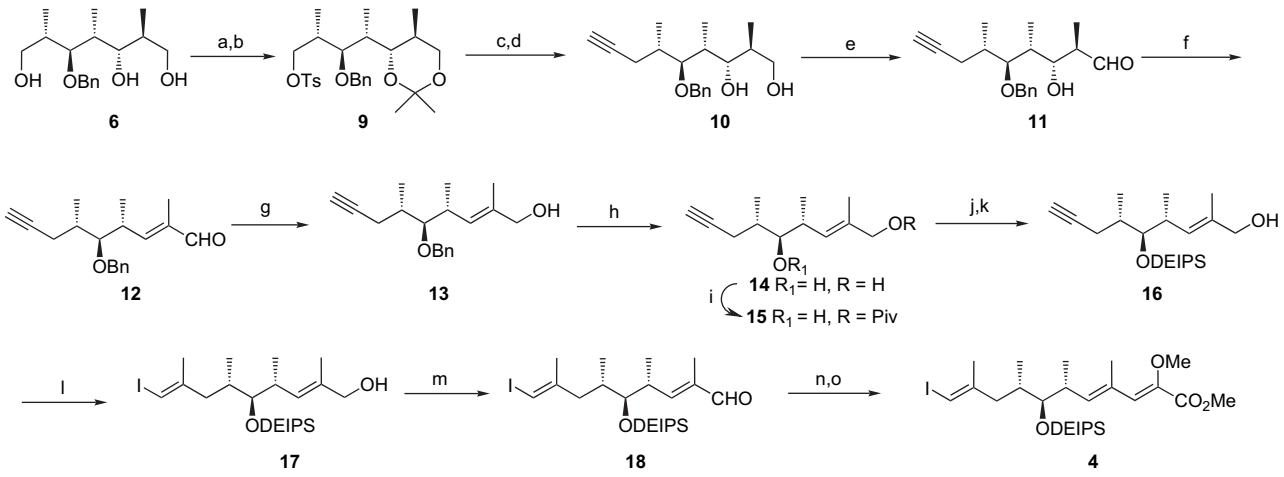


Scheme 1. Retrosynthetic analysis of bafilomycin A_1.



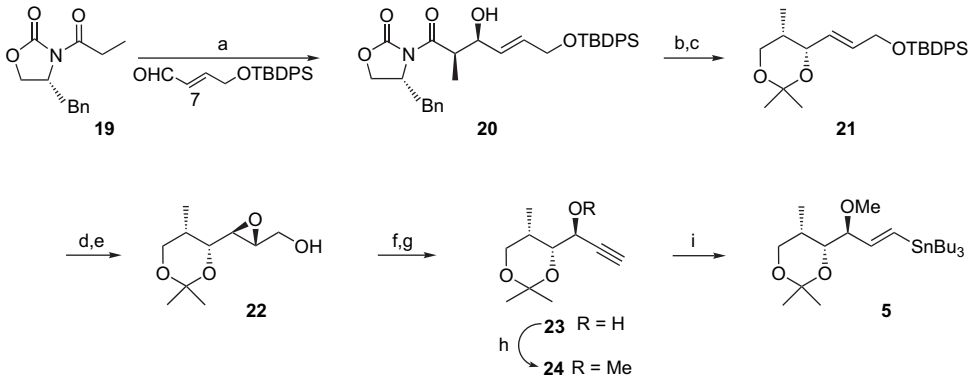
Scheme 2. Reagents and conditions: (a) 2,2 DMP, PPTS, CH_2Cl_2, 0 °C to rt, 3 h, 88%. (b) TsCl, NEt_3, DMAP, CH_2Cl_2, 96%. (c) LiC≡CH, $H_2N(CH_2)_2NH_2$, DMSO, rt, 1 h, 80%. (d) PPTS, MeOH, 3 h, 84%. (e) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 3 h, 62%. (f) Et_3N, Ac_2O, DMAP, CH_2Cl_2, 0 °C to rt, 85%. (g) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 92%. (h) Li, liq NH_3, THF, 2 min, 88%. (i) PvCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, 94%. (j) DEIPSCl, imidazole, DMF, rt, overnight, 85%. (k) K_2CO_3, MeOH, rt, overnight, 85%. (l) Cp_2ZrCl_2, Me_3Al, rt, 10 h then I_2, THF, −25 °C, 1 h, 82%. (m) MnO_2, CH_2Cl_2, rt, 1 h, 96%. (n) $CH_2(OMe)$-CO_2Me, LHMDS, THF, −78 °C, 94%. (o) $MeSO_2Cl$, Et_3N, DBU, CH_2Cl_2, 0 °C to rt, 80%.

β-elimination took place to give the unsaturated aldehyde **12**. The reduction of aldehyde functionality gave the corresponding alcohol **13** in 92% yield. Treatment of alkyne **13** with Li in liq NH_3 resulted the debenzylated product **14** in 88% yield. Compound **14** was selectively converted into mono pivalylated compound **15**. The free secondary hydroxyl group in compound **15** was silylated using diethylisopropylsilylchloride (DEIPSCl),[9] imidazole in DMF and the subsequent removal of the pivaloyl group furnished **16**. Negishi's methyl zirconation[10] of compound **16** led to the formation of compound **17**.

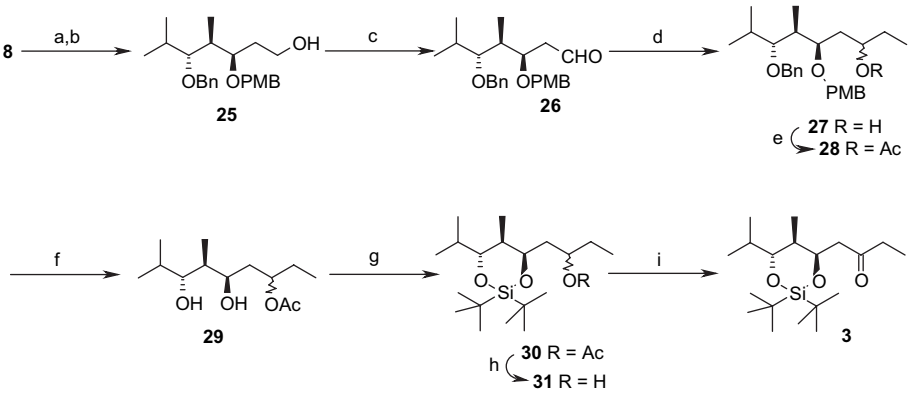
Oxidation of the allylic alcohol **17** with MnO_2 gave the corresponding α,β-unsaturated aldehyde **18**. The aldol condensation of **18** with lithium 2-methoxyacetate, followed by mesylation of the resulting alcohol and β-elimination furnished the C1−C11 fragment **4** of bafilomycin A_1 **1**, which was found to be identical with the compound reported by Hanessian et al.[6g]

2.2. Synthesis of the C_{12}−C_{17} fragment 5

Our synthesis of vinyl stannane intermediate **5** was developed on the basis of Evans asymmetric aldol reaction. Thus, asymmetric aldol reaction of oxazolidene **19** with the aldehyde[11] **7** using dibutylboronetriflate and triethylamine provided *syn*-aldol product **20** in 82% yield as single diastereoisomer (Scheme 3). After reduction with $LiBH_4$, the diol was converted to the corresponding acetonide **21** in 98% overall yield for two steps. Desilylation with TBAF in THF and then exposure of the resulting alcohol to Sharpless epoxidation afforded diastereomeric epoxy alcohols in 78% yield with 8:2 ratio, and were easily separated on silica gel column chromotography. The required major epoxy alcohol **22**, on treatment with Ph_3P/CCl_4, followed by a base induced double elimination with Li/liq NH_3 a protocol developed by our group[12]



Scheme 3. Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C to −78 °C then **7**, 1 h, 89%. (b) $LiBH_4$, Et_2O, H_2O, 0 °C, 1 h, 98%. (c) 2,2 DMP, PPTS, CH_2Cl_2, 0 °C, 1 h, 96%. (d) TBAF, THF, 0 °C to rt, 2 h, 95%. (e) $Ti(O^iPr)_4$, (−)DIPT, TBHP, CH_2Cl_2, −20 °C, 24 h, 78%. (f) TPP, CCl_4, reflux, 1.5 h, 90%. (g) Li, liq NH_3, $Fe(NO)_3$, −78 °C, 2 h, 82%. (h) NaH, MeI, THF, 0 °C to rt, 1 h, 98%. (i) $Pd(PPh_3)_4$, Bu_3SnH, CH_2Cl_2, 0 °C to rt, 0.5 h, 78%.

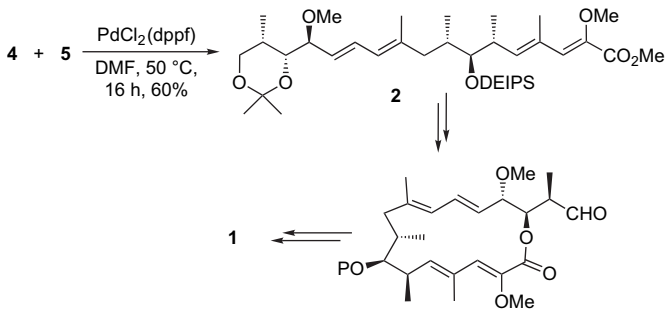


Scheme 4. Reagents and conditions: (a) PPTS, $PMP(OMe)_2$, CH_2Cl_2, rt, 1 h, 96%. (b) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 85%. (c) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 3 h, 83%. (d) Mg/EtBr, THF, 2 h, 90%. (e) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 94%. (f) 5% Pd/C, EtOAc, rt, 1 h, 90%. (g) $(t\text{-}Bu)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 85%. (h) NaOMe, THF, 1 h, 90%. (i) DMP, CH_2Cl_2, $NaHCO_3$, 0 °C to rt, 1 h, 88%.

afforded propargylic alcohol **23**. The hydroxyl group in **23** was protected as its methyl ether **24**. Finally, treatment of **24** with tributyltin hydride in the presence of a catalytic quantity of bistriphenylphosphine palladium(II) chloride[13] led to the desired vinyl stannane C_{12}–C_{17} subunit **5** (Scheme 3). The spectral properties (^{1}H, IR, mass HRMS) and specific rotation $[\alpha]_D^{25}$ +16.5 (*c* 1.10, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25}$ +16.4 (*c* 1.01, $CHCl_3$)} of vinyl stannane **5** proved to be identical with the reported compound.[6d]

2.3. Synthesis of the C_{18}–C_{25} fragment 3

The synthesis of the intermediate **3** starts with the known diol **8**, which was reported by us.[14] The diol **8**, upon reaction with *p*-methoxy benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid (PPTS) resulted the protected compound, which on subsequent regioselective reductive ring-opening reaction with DIBAL-H in CH_2Cl_2 produced the free primary alcohol **25** (Scheme 4), which on oxidation with IBX then furnished the aldehyde **26**. The ethylenic alcohol was easily obtained by reaction of **26** with EtMgBr in THF and the resulting alcohol **27** was converted into the acetyl derivative **28**. Hydrogenolysis of the benzyl and PMB ethers using Pd/C in EtOAc gave a diol **29** in 90% yield. The diol **29** then was protected with a di-*tert*-butylsilyl group,[15] followed by deacetylation of **30** afforded free hydroxyl compound **31**. Oxidation of **31** using Dess–Martin periodinane afforded the desired C_{18}–C_{25} fragment **3** as a white solid, mp 40–41 °C {lit.[6d] mp 40.0–40.5 °C}. The spectral properties (^{1}H, ^{13}C NMR, mass, IR, HRMS) and specific rotation $[\alpha]_D^{25}$ +84.8 (*c* 0.9, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25}$ +85.2 (*c* 0.89, $CHCl_3$)} of ethylketo **3** are identical with reported compound.[6d]



Scheme 5.

2.4. Coupling of fragments **4** and **5** to obtain **2**

The cross-coupling reaction between the vinyl iodide **4** corresponding to the C_1–C_{11} fragment of **1** and the vinyl tributyltin **5** corresponding to the C_{12}–C_{17} fragment of **1** by Stille[16] method using a catalytic amount of $PdCl_2$(dppf)[17] in DMF at 50 °C for 16 h afforded the desired *E*,*E*-diene **2** in 60% yield (Scheme 5), which has been converted to **1** by coupling with **3**.[6d]

3. Conclusion

Thus we have demonstrated the formal synthesis of bafilomycin A_1 **1** by preparing two important intermediates, viz. C_1–C_{17} fragment **2** and C_{18}–C_{25} fragment **3**, which have been utilized for synthesis of bafilomycin A_1 **1**.[6d]

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as internal standard. Coupling constants (*J*) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh). Mass spectra were obtained on Finnegan MAT 1020B or micro mass VG 70-70H spectrometers operating at 70 eV using a direct inlet system.

4.1.1. (2*S*,3*S*,4*S*)-3-(Benzyloxy)-2-methyl-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]entan-1-ol

To a solution of triol **6**[8] (5.5 g, 16.4 mmol) in dry dichloromethane (40 mL), 2,2-dimethoxy propane (14.8 mL, 114.6 mmol) and PPTS (2.2 g, 14.1 mmol) were added. The mixture was stirred at ambient temperature for 3 h. Sodium bicarbonate was added to neutralize PPTS and filtered. Removal of solvent and purification by silica gel column chromatography (20% EtOAc in hexane as eluent) afforded the mono acetonide (5.42 g, 88%) as a white solid, R_f=0.60 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ +32.77 (*c* 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73 (d, 3H, *J*=6.8 Hz, CH_3), 0.87 (d, 3H, *J*=6.8 Hz, CH_3), 1.21 (d, 3H, *J*=6.8 Hz, CH_3), 1.34 (s, 6H, 2×CH_3), 1.78–2.05 (m, 3H, 3×CH), 2.63 (dd, 1H, *J*=3.0, 8.3 Hz, CH), 3.42–3.59 (m, 3H, CH and CH_2), 3.62 (dd, 1H, *J*=5.3, 12.1 Hz, CH), 3.80–3.90 (m, 2H, CH_2), 4.64 (ABq, 2H, *J*=11.3, 27.2 Hz, benzylic CH_2), 7.22–7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.5, 127.6, 127.0, 98.0, 85.6, 75.4, 73.4, 66.2, 64.3, 87.5, 36.3, 30.3, 29.8, 19.5, 16.4, 12.5, 9.8; IR (neat): 3478, 2921, 1617, 1031 cm^{-1}; FABMS: 337 $[M+H]^+$; HRMS (ESIMS): *m/z* calcd for $C_{20}H_{32}O_4Na$ $[M+Na]^+$ 359.2198, found 359.2193.

4.1.2. (2*S*,3*S*,4*S*)-3-(Benzyloxy)-2-methyl-4-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]pentyl 4-methyl-1-benzenesulfonate (**9**)

To a stirred solution of alcohol (5 g, 14.88 mmol) in dry triethylamine (6.25 mL, 44.64 mmol) at 0 °C was added *p*-toluenesulfonylchloride (3.12 g, 16.4 mmol). After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with water (30 mL) and the resultant mixture was then extracted with ethyl acetate (50 mL×3). The extracts were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 12% EtOAc in hexane as eluent) gave tosyl compound **9** (7 g, 96%) as a colorless viscous liquid, R_f=0.72 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ +35.6 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68 (d, 3H, *J*=6.8 Hz, CH_3), 0.83 (d, 3H, *J*=6.8 Hz, CH_3), 1.05 (d, 3H, *J*=6.8 Hz, CH_3), 1.31 (d, 6H, *J*=6.8 Hz, 2×CH_3), 1.74–1.88 (m, 2H, 2×CH), 2.12–2.24 (m, 1H, CH), 2.45 (s, 3H, ArCH_3), 3.33 (dd, 1H, *J*=1.5, 9.8 Hz, CH), 3.42 (t, 1H, *J*=11.3 Hz, CH), 3.62 (dd, 1H, *J*=5.3, 11.3 Hz, CH), 3.74 (dd, 1H, *J*=1.5, 10.6 Hz, CH), 3.87 (dd, 1H, *J*=7.5, 9.8 Hz, CH), 4.23 (dd, 1H, *J*=5.3, 9.8 Hz, CH), 4.55 (s, 2H, benzylic CH_2), 7.14–7.32 (m, 7H, ArH), 7.77 (d, 2H, *J*=8.3 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.2, 138.5, 132.9, 129.4, 127.9, 127.5, 126.9, 126.4, 97.6, 82.5, 74.6, 72.9, 71.6, 65.7, 36.7, 35.1, 29.9, 29.5, 21.1, 19.1, 15.8, 12.0, 9.3; IR (neat): 2972, 2852, 1626, 1359, 1174 cm^{-1}; ESIMS: 513.1 $[M+Na]^+$; HRMS (ESIMS) *m/z* calcd for $C_{27}H_{38}O_4SNa$ $[M+Na]^+$ 513.2286, found 513.2287.

4.1.3. (4*S*,5*S*)-4-[(1*S*,2*S*,3*S*)-2-(Benzyloxy)-1,3-dimethyl-5-hexynyl]-2,2,5-trimethyl-1,3-dioxane

To a stirred solution of **9** (4 g, 8.16 mmol) in dry dimethyl sulfoxide (34.5 mL) was added lithium acetylide ethylenediamine complex (90%, 4.18 g, 40.8 mmol) at 0 °C in one portion. After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) under ice cooling, and the resultant mixture was then extracted with ether (25 mL×3). The extracts were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 8% EtOAc in hexane as eluent) gave alkyne compound (2.25 g, 80%) as a color oil, R_f=0.80 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ +22.67 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.70 (d, 3H, *J*=6.8 Hz, CH_3), 0.88 (d, 3H, *J*=7.5 Hz, CH_3), 1.20 (d, 3H, *J*=6.8 Hz, CH_3), 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.02 (m, 1H, CH), 1.75–1.92 (m, 3H, CH and CH_2), 2.13 (td, 1H, *J*=2.3, 9.8 Hz, CH), 2.32 (dt, 1H, *J*=3.0, 6.0 Hz, CH), 3.33 (dd, 1H, *J*=1.5, 9.1 Hz, CH), 3.44 (t, 1H, *J*=11.3 Hz, CH), 3.63 (dd, 1H, *J*=4.5, 11.3 Hz, CH), 3.82 (dd, 1H, *J*=1.5, 10.6 Hz, CH), 4.61 (ABq, 2H, *J*=11.3, 15.9 Hz, benzylic CH_2), 7.19–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.2, 128.2, 127.2, 126.6, 97.9, 96.2, 83.3, 75.0, 73.4, 69.0, 66.1, 36.9, 35.4, 30.4, 30.0, 19.6, 19.3, 18.6, 12.6, 9.9; IR (neat): 2924, 2854, 1641, 1364, 1007, 995 cm^{-1}; FABMS: 345 $[M+H]^+$; HRMS (ESIMS): *m/z* calcd for $C_{22}H_{32}O_3Na$ $[M+Na]^+$ 367.2249, found 367.2249.

*4.1.4. (2S,3S,4R,5S,6S)-5-(Benzyloxy)-2,4,6-trimethyl-8-nonyne-1,3-diol (**10**)*

To a stirred solution of acetonide (2.2 g, 6.4 mmol) in MeOH (10 mL) at 0 °C was added pyridinium *p*-toluenesulfonate (1.6 g, 6.4 mmol). After the reaction mixture was stirred at 25 °C for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) under ice cooling, and the resultant mixture was then extracted with ether (30 mL×3). The extracts were washed with saturated aqueous NaCl (12 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 50% EtOAc in hexane as eluent) gave **10** (1.71 g, 84%) as colorless oil, R_f=0.35 (1:1 EtOAc and hexane). $[\alpha]_D^{30}$ −22.58 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75 (d, 3H, *J*=6.8 Hz, CH_3), 1.03 (d, 3H, *J*=6.8 Hz, CH_3), 1.19 (d, 3H, *J*=6.8 Hz, CH_3), 1.50 (br s, OH), 1.71 (s, 3H, CH_3), 1.74–1.96 (m, 2H, CH_2), 2.00 (t, 1H, *J*=3.0 Hz, acetylene), 2.07–2.33 (m, 1H, CH), 2.36 (dt, 1H, *J*=3.0, 6.0, 16.6 Hz, CH), 2.54 (ddd, 1H, *J*=3.0, 6.0, 16.6 Hz, CH), 3.38–3.65 (m, 1H, CH), 3.76–3.99 (m, 2H, CH_2), 4.71 (s, 2H, benzylic CH_2), 7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.5, 128.0, 127.7, 88.8, 82.3, 76.7, 76.5, 70.5, 68.9, 37.3, 34.9, 34.8, 22.4, 16.2, 13.2, 11.6; IR (KBr): 3413, 3345, 2927, 2865, 1644, 1239, 995 cm^{-1}; FABMS 305 $[M+H]^+$; HRMS (ESIMS) *m/z* calcd for $C_{19}H_{28}O_3Na$ $[M+Na]^+$ 327.1936, found 327.1940.

*4.1.5. (2R,3R,4R,5S,6S)-5-(Benzyloxy)-3-hydroxy-2,4,6-trimethyl-8-nonynal (**11**)*

To a stirred solution of IBX (2.07 g, 7.4 mmol) in 4 mL dry DMSO was added diol **10** (1.5 g, 4.93 mmol) in 15 mL dry CH_2Cl_2 at 0 °C. The resulting reaction mixture stirred at 25 °C for 3 h. Solid was filtered and washed with diethyl ether. The filtrate was extracted with ether, washed with water and brine, and dried over anhydrous Na_2SO_4, the ether layer was concentrated under reduced pressure and the crude product was subjected to column chromatography (SiO_2, 15% EtOAc in hexane as eluent) to give aldehyde **11** (1.01 g, 62%) as a colorless liquid, R_f=0.58 (1:1 EtOAc and hexane). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.73 (d, 3H, *J*=6.8 Hz, CH_3), 1.04 (d, 3H, *J*=6.8 Hz, CH_3), 1.17 (d, 3H, *J*=7.2 Hz, CH_3), 1.56 (br s, OH), 1.79–1.06 (m, 3H, CH_2 and CH), 1.96 (t, 1H, *J*=3.0 Hz, acetylene), 2.56 (m, 1H, CH), 2.59 (dd, 1H, *J*=5.9, 15.4 Hz, CH), 3.44 (m, 1H, CH), 3.91 (dd, 1H, *J*=3.4, 5.9 Hz, CH), 4.68 (s, 2H, benzylic CH_2), 7.32 (m, 5H, ArH), 9.77 (s, 1H, CHO); IR (neat): 3453, 2928, 2846, 1698, 1641, 995 cm^{-1}; LC–MS: 325.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1779, found 325.1608.

*4.1.6. (E,4R,5S,6S)-5-(Benzyloxy)-2,4,6-trimethyl-2-nonen-8-ynal (**12**)*

To an ice-cold solution of **11** (1 g, 3.3 mmol) in dry CH_2Cl_2 (11.2 mL) and triethylamine (1.4 mL, 6.82 mmol) was added dropwise acetic anhydride (0.37 mL, 3.97 mmol) and catalytic amount of DMAP with stirring. After the reaction mixture was stirred at 25 °C for 14 h, the mixture was poured into ice-cooled water (13 mL) and the resultant mixture was then extracted with ether (3×10 mL). The extracts were washed with saturated aqueous NaCl (13 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 13% EtOAc in hexane as eluent) gave **12** (0.8 g, 85%) as a colorless oil, R_f=0.62 (1:1 EtOAc and hexane). $[\alpha]_D^{30}$ −41.24 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.99 (d, 3H, *J*=7.0 Hz, CH_3), 1.09 (d, 3H, *J*=7.0 Hz, CH_3), 1.76 (s, 3H, CH_3), 1.95 (t, 1H, *J*=2.3 Hz, acetylene), 2.28 (dt, 1H, *J*=3.1, 7.0, 17.1 Hz, CH), 2.44 (ddd, 1H, *J*=2.3, 6.2, 17.1 Hz, CH), 3.01 (tt, 1H, *J*=3.1, 7.0 Hz, CH), 3.38 (dd, 1H, *J*=3.1, 7.0 Hz, CH), 4.54 (ABq, 2H, *J*=11.7, 23.3 Hz, benzylic CH_2), 6.59 (d, 1H, *J*=10.1 Hz, olefin), 7.32 (m, 5H, ArH), 9.38 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.7, 155.7, 146.2, 138.7, 128.4, 128.3, 127.7, 127.5, 85.5, 82.5, 75.5, 70.2, 36.3, 22.2, 17.6, 16.1, 9.3; IR (neat): 2954, 2861, 1685, 1641, 989 cm^{-1}; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{24}O_2$ $[M]^+$ 284.3971, found 284.3968.

*4.1.7. (E,4R,5S,6S)-5-(Benzyloxy)-2,4,6-trimethyl-2-nonen-8-yn-1-ol (**13**)*

Sodiumborohydride (180 mg, 5.3 mmol) was added portion wise to the stirred cold solution of unsaturated aldehyde **12** (1 g, 3.5 mmol) in 5 mL MeOH. After the reaction mixture was stirred at 25 °C for 1 h, MeOH was evaporated and the resulted residue was quenched with water and extracted with ethyl acetate (3×10 mL), combined extracts were washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 40% EtOAc in hexane as eluent) gave **13** (0.925 g, 92%) as colorless viscous liquid, R_f=0.50 (1:1 EtOAc and hexane). $[\alpha]_D^{30}$ −14.21 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01 (d, 3H, *J*=7.0 Hz), 1.09 (d, 3H, *J*=7.0 Hz, CH_3), 1.27 (q, 1H, *J*=7.8, 9.3 Hz, CH), 1.42 (br s, OH), 1.68 (s, 3H, CH_3), 1.81 (m, 1H, CH), 1.92 (t, 1H, *J*=2.3 Hz, acetylene), 2.34 (m, 1H, CH), 2.72 (m, 1H, CH), 3.22 (dd, 1H, *J*=3.9, 8.6 Hz, CH), 3.97 (s, 2H, CH_2), 4.64 (q, 2H, *J*=10.9, 13.3 Hz, benzylic CH_2), 5.49 (d, 1H, *J*=9.4 Hz, olefin), 7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 134.6, 128.3, 127.6, 127.5, 86.6, 83.3, 75.4, 69.7, 69.0, 35.8, 34.9, 22.0, 18.7, 16.4, 13.8; IR (neat): 3423, 2927, 2859, 1639, 995 cm^{-1}; FABMS: 269 (M−18); HRMS (ESIMS): *m/z* calcd for $C_{19}H_{26}O_2Na$ $[M+Na]^+$ 309.3983, found 309.3667.

*4.1.8. (E,4R,5S,6S)-2,4,6-Trimethyl-2-nonen-8-yne-1,5-diol (**14**)*

Lithium metal (51 mg, 7.3 mmol) was added to a stirred solution of freshly distilled ammonia (10 mL) and compound **13** (0.7 g, 2.4 mmol) in dry THF (5 mL) in a 100 mL two neck round bottom flask fitted with a cold finger condenser at −33 °C. The reaction mixture was then stirred for another 2 min at −33 °C and quenched by the addition of solid ammonium chloride and the ammonia was then allowed to evaporate. The residue left was partitioned between water and ether and the aqueous phase extracted with ether (3×30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 60% EtOAc in hexane as eluent) to afford the pure **14**

(0.422 mg, 88%) as a clear colorless liquid, R_f=0.30. $[\alpha]_D^{25}$ +5.73 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.01 (d, 3H, *J*=6.6 Hz, CH_3), 1.02 (d, 3H, *J*=7.3 Hz, CH_3), 1.41 (br s, 1H, OH), 1.69 (s, 3H, CH_3), 1.67–1.69 (m, 2H, CH_2), 1.88 (t, 1H, *J*=2.2 Hz, acetylene), 2.21–2.37 (m, 2H, 2×CH), 2.62 (m, 2H, 2×CH), 3.27 (t, 1H, *J*=5.9 Hz, CH), 4.00 (s, 2H, CH_2), 5.37 (d, 1H, *J*=9.5 Hz, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.8, 126.2, 83.5, 78.7, 69.3, 68.2, 35.2, 34.8, 20.9, 18.0, 16.6, 14.0; IR (neat): 3403, 3350, 2924, 2854, 1641, 995 cm^{-1}; LC–MS: 219.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1360, found 219.1365.

*4.1.9. (E,4R,5S,6S)-5-Hydroxy-2,4,6-trimethyl-2-nonen-8-ynyl pivalate (**15**)*

To an ice-cold solution of **14** (0.4 g, 2.04 mmol) in dry CH_2Cl_2 (11.2 mL) were added dropwise triethylamine (0.85 mL, 6.12 mmol) and pivaloyl chloride (0.38 mL, 3.06 mmol) with stirring. After the reaction mixture was stirred at 25 °C for 4 h, the mixture was poured into ice-cooled water (13 mL), and the resultant mixture was then extracted with ether (10 mL×3). The extracts were washed with saturated aqueous NaCl (13 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 25% EtOAc in hexane as eluent) gave **15** (0.53 g, 94%) as a colorless viscous liquid, R_f=0.65 (1:2 EtOAc and hexane). $[\alpha]_D^{25}$ +10.90 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.02 (d, 6H, *J*=6.2 Hz, 2×CH_3), 1.21 (S, 9H, *tert*-butyl), 1.68 (s, 3H, CH_3), 1.69–1.79 (m, 2H, CH_2), 1.88 (t, 1H, *J*=2.3 Hz, acetylene), 2.20–2.37 (m, 2H, 2×CH), 2.61 (m, 1H, CH), 3.27 (dd, 1H, *J*=5.5, 7.0 Hz, CH), 3.38 (br s, OH), 4.45 (ABq, 2H, *J*=12.5, 23.4 Hz, CH_2), 5.41 (d, 1H, *J*=8.6 Hz, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 184.7, 131.7, 129.6, 83.4, 78.5, 69.8, 69.3, 38.8, 35.3, 35.2, 26.9, 20.9, 17.6, 16.7, 14.1; IR (neat): 3504, 3308, 2967, 1725, 1284, 992 cm^{-1}; LC–MS: 303 $[M+Na]^+$ 321 $[M+K]^+$; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{24}O_2Na$ $[M+Na]^+$ 280.4051, found 280.4047.

4.1.10. (E,4R,5S,6S)-5-[(1,1-Diethyl-1-isopropylsilyl)oxy]-2,4,6-trimethyl-2-nonen-8-ynyl pivalate

To a stirred solution of **15** (0.5 g, 1.78 mmol) in dry DMF (2 mL) and imidazole (730 mg, 10.7 mmol) was added dropwise diethylisopropylsilylchloride (0.58 mL, 3.57 mmol) at 0 °C. After the reaction mixture was stirred at 25 °C for 12 h, the mixture was poured into ice-cooled water (9 mL), and the resultant mixture was then extracted with ether (7 mL×3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 8% EtOAc in hexane as eluent) gave protected compound (0.69 g, 85%) as a colorless liquid, R_f=0.55 (1:4 EtOAc and hexane). $[\alpha]_D^{30}$ −0.20 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.63 −0.72 (m, 4H, 2×CH_2), 0.94–1.08 (m, 21H, 7×CH_3), 1.23 (s, 3H, CH_3), 1.73–1.86 (m, 1H, CH), 1.89 (t, 1H, *J*=2.3 Hz, acetylene), 2.13 (ddd, 1H, *J*=3.0, 8.3 Hz, CH), 2.28 (ddd, 1H, *J*=2.3, 5.3 Hz, CH), 2.61 (m, 1H, CH), 3.61 (dd, 1H, *J*=3.0, 5.3 Hz, CH), 4.44 (s, 2H, CH_2), 5.56 (d, 1H, *J*=9.8 Hz, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.2, 130.6, 129.1, 83.7, 79.2, 69.7, 69.2, 38.8, 37.5, 35.7, 27.2, 21.9, 18.5, 17.7, 17.6, 16.4, 14.0, 13.5, 7.4, 7.3, 4.5; IR (neat): 3448, 2960, 1731, 1459, 1033 cm^{-1}; LC–MS: 431.2 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{24}H_{44}O_3SiNa$ $[M+Na]^+$ 431.2957, found 431.2952.

4.1.11. (E,4R,5S,6S)-5-[(1,1-Diethyl-1-isopropylsilyl)oxy]-2,4,6-trimethyl-2-nonen-8-yn-1-ol

To the solution of pivalate (0.7 g, 1.71 mmol) in 4 mL MeOH was added K_2CO_3 (171 mg, 1.71 mmol). The reaction mixture was stirred at room temperature for overnight. The resultant mixture was filtered and washed with MeOH. The combined filtrate and washings were concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 25% EtOAc in hexane as eluent) gave free alcohol **16** (0.47 g, 85%) as a colorless liquid, R_f=0.68 (1:1 EtOAc and hexane). $[\alpha]_D^{30}$ +3.68 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.63–0.73 (m, 4H, 2×CH_2), 0.92–1.09 (m, 18H, 6×CH_3), 1.25 (br s, OH), 1.67 (s, 3H, CH_3), 1.71–1.82 (m, 1H, CH), 2.10 (t, 1H, *J*=2.5 Hz, acetylene), 2.22–2.34 (m, 1H, CH), 2.58 (m, 1H, CH), 3.56 (dd, 1H, *J*=3.4, 5.8 Hz, CH), 3.96 (s, 2H, CH_2), 5.47 (d, 1H, *J*= 9.4 Hz, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.8, 128.6, 83.7, 79.4, 69.2, 69.1, 37.4, 35.7, 22.0, 18.6, 17.6, 16.6, 13.8, 13.5, 7.4, 4.5; IR (KBr): 3441, 2945, 2878, 1452, 1248, 723 cm^{-1}; LC–MS: 347 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{36}O_2SiNa$ $[M+Na]^+$ 347.2382, found 347.2376.

*4.1.12. (2E,4R,5S,6S,8E)-5-[(1,1-Diethyl-1-isopropylsilyl)oxy]-9-iodo-2,4,6,8-tetramethyl-2,8-nonadien-1-ol (**17**)*

To a stirred solution of Cp_2ZrCl_2 (0.9 g, 3.08 mmol) in dry 1,2-dichloroethane (10 mL) was added dropwise 2 M Me_3Al/*n*-hexane (2.31 mL, 4.62 mmol). After 0.5 h at 25 °C, a solution of **16** (0.5 g, 1.54 mmol) in dry 1,2-dichloroethane (2 mL) was added to the reaction mixture. After 13 h, to the reaction mixture at −30 °C was added slowly a solution of I_2 (3.92 g, 15.4 mmol) in dry THF (18 mL), and the resultant mixture was stirred at −30 °C for 1.5 h. The reaction mixture was warmed to 0 °C, and ice-cooled saturated aqueous K_2CO_3 (40 mL) was added. The resultant mixture was extracted with ether (3×30 mL). The extracts were washed with saturated aqueous $Na_2S_2O_3$ (2×30 mL) and saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 12% EtOAc in hexane as eluent) gave vinyliodo **17** (0.59 g, 82%) as a pale yellow viscous liquid, R_f=0.52 (3:7 EtOAc and hexane). $[\alpha]_D^{30}$ −8.82 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.65 (q, 4H, *J*=7.4, 14.8 Hz, 2×CH_2), 0.78 (d, 3H, *J*=6.7 Hz, CH_3), 0.92–1.09 (m, 17H, 5×CH_3 and CH_2), 1.26 (m, 1H, CH), 1.67 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.97 (m, 1H, CH), 2.42 (dd, 1H, *J*=3.7, 13.3 Hz, CH), 2.58 (m, 1H, CH), 3.43 (t, 1H, *J*=4.5 Hz, CH), 3.97 (s, 2H, CH_2), 5.48 (d, 1H, *J*=8.9 Hz, olefin), 5.83 (s, 1H, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.0, 133.4, 129.1, 80.4, 75.1, 69.2, 42.9, 35.9, 35.6, 23.6, 18.9, 17.6, 16.1, 13.8, 13.5, 7.3, 4.5; IR (neat): 3437, 2958, 1453, 1248, 1097, 724 cm^{-1}; ESIMS: 489.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{20}H_{39}O_2SiINa$ $[M+Na]^+$ 489.1661, found 489.1657.

*4.1.13. (2E,4R,5S,6S,8E)-5-[(1,1-Diethyl-1-isopropylsilyl)oxy]-9-iodo-2,4,6,8-tetramethyl-2,8-nonadienal (**18**)*

To a solution of **17** (0.5 g, 1.07 mmol) in dry CH_2Cl_2 (15 mL) was added MnO_2 (2.82 g, 32.1 mmol). After the reaction mixture was stirred at 25 °C for 2 h, the mixture was filtered through Celite, and the filtered cake was washed with CH_2Cl_2. The filtrate and washings were combined and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 10% EtOAc in hexane as eluent) gave **18** (0.48 g, 96%) as a colorless gummy liquid, R_f=0.45 (3:7 EtOAc and hexane). $[\alpha]_D^{30}$ −1.17 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.67 (q, 4H, *J*=7.5, 15.9 Hz, 2×CH_2), 0.76 (d, 3H, *J*=6.8 Hz, CH_3), 0.92−1.12 (m, 16H, 5×CH_3 and CH), 1.26 (m, 1H, CH), 1.75 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.98 (dd, 1H, *J*=9.8, 12.8 Hz, CH), 2.36 (dd, 1H, *J*=3.8, 12.8 Hz, CH), 2.86 (tt, 1H, *J*=2.3, 6.8 Hz, CH), 3.57 (m, 1H, CH), 5.86 (s, 1H, olefin), 6.65 (d, 1H, *J*=9.1 Hz, olefin), 9.38 (s, 1H, CHO); IR (neat): 2956, 2878, 1694, 1460, 1284, 1094, 720 cm^{-1}; ESIMS: 487.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{20}H_{37}O_2SiINa$ $[M+Na]^+$ 487.1505, found 487.1487.

*4.1.14. Methyl(2Z,4E,6R,7S,8S,10E)-7-[(1,1-diethyl-1-isopropylsilyl)oxy]-11-iodo-2-methoxy-4,6,8,10-tetramethyl-2,4,10-undecatrienoate (**4**)*

To a stirred solution of methyl methoxy acetate (217 mg. 2.15 mmol) in THF (3 mL) at −78 °C was added LiHMDS (1 M in THF 1.3 mL, 1.29 mmol). The mixture was stirred at −78 °C for 0.5 h before a solution of the **18** (200 mg, 0.43 mmol) in THF (2 mL) was added. The mixture was then stirred at −78 °C for 2 h, after which TLC indicated no aldehyde remained. The mixture was quenched with dilute aqueous ammonium chloride solution and extracted with ether (3×15 mL). The combined ether extracts were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue afforded the γ-hydroxy ester (223 mg, 94%). The mixture was used for the next step.

To solution of the γ-hydroxy ester (200 mg, 0.36 mmol) in dry CH_2Cl_2 (4 mL) were added MsCl (82.5 mg, 0.72 mmol) and triethylamine (109 mg, 1.08 mmol). The mixture was stirred at room temperature for 3 h before DBU (109 mg, 0.72 mmol) was added. The mixture was stirred for another 2 h and then quenched with aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (3×15 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (SiO_2, 20% EtOAc in hexane as eluent) of the residue afforded the γ-hydroxy ester **4** (184 mg, 80%) as a pale yellow viscous liquid, R_f=0.60 (3:7 EtOAc and hexane). $[\alpha]_D^{30}$ +21.67 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.64 (q, 4H, *J*=7.6, 15.8 Hz, 2×CH_2), 0.76 (d, 3H, *J*=6.8 Hz, CH_3), 0.94−1.08 (m, 16H, 5×CH_3 and CH), 1.65−1.82 (m, 2H, CH_2), 1.79 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.41 (dd, 1H, *J*=3.8, 12.8 Hz, CH), 2.68 (m, 1H, CH), 3.46 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 3.79 (s, 3H, CO_2CH_3), 5.83 (s, 1H, olefin), 5.90 (d, 1H, *J*=9.1 Hz, olefin), 6.51 (s, 1H, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 146.8, 142.8, 141.7, 130.0, 129.9, 80.2, 75.3, 60.2, 51.9, 43.2, 36.5, 36.0, 23.6, 18.6, 17.6, 15.7, 14.8, 13.5, 7.4, 7.3, 4.5, 4.4; IR (neat): 3435, 2955, 1721, 1452, 1248, 720 cm^{-1}; LC−MS: 573.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{24}H_{43}O_4SiINa$ $[M+Na]^+$ 573.1873, found 573.1871.

*4.1.15. (4R)-4-Benzyl-3-((2R,3S,4E)-6-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-3-hydroxy-2-methyl-4-hexenoyl)-1,3-oxazolan-2-one (**20**)*

Di-*n*-butylboryltrifluoromethanesulfonate (17 mL, 1 M in CH_2Cl_2, 16.97 mmol) was added to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **19** (3.96 g, 15.4 mmol) in 35 mL of CH_2Cl_2 at such a rate as to maintain the internal temperature below +3 °C. Triethylamine (2.7 mL, 18.5 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to −78 °C and aldehyde **7** (5 g, 15.4 mmol) in 15 mL CH_2Cl_2 was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 15 mL aqueous phosphate buffer solution of pH 7.0 and 50 mL of MeOH (internal temperature below +10 °C). A solution of 30 mL of MeOH and 15 mL of 30% aqueous H_2O_2 was added carefully (internal temperature below +10 °C), and the resulting yellow solution was stirred at 0 °C for 1 h. The reaction mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of saturated brine. The organic solution was dried over anhydrous Na_2SO_4 and purified by flash column chromatography (SiO_2, 50% EtOAc in hexane as eluent) to give *syn*-aldol adduct **20** as a colorless oil (7.6 g, 89%, >95:5 diastereoselectively), R_f=0.42 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ −33.61 (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 (s, 9H, *tert*-butyl), 1.22 (d, 3H, *J*=6.8 Hz, CH_3), 2.73 (dd, 1H, *J*=9.8, 13.6 Hz, PhCH), 3.27 (dd, 1H, *J*=3.0, 13.6 Hz, PhCH), 3.80 (m, 1H, CH), 4.13 (d, 2H, *J*=5.3 Hz, CH_2), 4.22 (d, 2H, *J*=3.8 Hz, CH_2), 4.47 (t, 1H, *J*=3.8 Hz, CH), 4.62 (m, 1H, CH), 5.72 (dd, 1H, *J*=5.3, 15.1 Hz, olefin), 5.85 (dt, 1H, *J*=3.8, 15.8 Hz, olefin), 7.15−7.43 (m, 11H, ArH), 7.64 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.6, 153.0, 135.4, 134.9, 133.5, 131.1, 129.6, 129.3, 129.0, 128.7, 127.6, 127.3, 71.9, 66.1, 63.6, 55.1, 42.7, 37.7, 26.7, 19.1, 11.0; IR (neat): 3449, 2931, 2856, 1780, 1696, 1384, 1029 cm^{-1}; LC−MS: 580.2 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{33}H_{39}O_5SiNa$ $[M+Na]^+$ 580.2495, found 580.2498.

4.1.16. (2S,3S,4E)-6-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-2-methyl-4-hexene-1,3-diol

To a stirred solution of **20** (7 g, 12.56 mmol) in Et_2O (50 mL) at 0 °C, $LiBH_4$ (0.414 g, 5.5 mmol) was added in one portion. After the addition was complete, the reaction was allowed to stir for 1 h at 0 °C. After reaction was completed, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate (3×30 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (SiO_2, 70% EtOAc in hexane as eluent) yielded diol (4.73 g, 98%) as colorless oil, R_f=0.20 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ −0.58 (*c* 1.6, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.86 (d, 3H, J=7.3 Hz, CH_3), 1.07 (s, 9H, *tert*-butyl) 1.92 (m, 1H, CH) 3.63 (m, 2H, CH_2), 3.64 (d, 1H J=1.5 Hz, CH), 4.18–4.33 (m, 3H, CH_2 and CH), 5.79 (m, 2H, olefinic), 7.28–7.43 (m, 6H, ArH), 7.58–7.70 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 133.7, 130.7, 130.0, 129.7, 127.7, 75.3, 66.2, 63.9, 39.9, 26.8, 19.2, 11.3; IR (neat): 3412, 3069, 2856, 1638, 1029, 701 cm^{-1}; LC–MS: 407.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{23}H_{32}O_3SiNa$ $[M+Na]^+$ 407.2018, found 407.2020.

4.1.17. tert-Butyl(diphenyl)((E)-3-[(4S,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl]-2-propenyloxy)silane (**21**)

To a solution of diol (3 g, 7.8 mmol) in dry CH_2Cl_2 (40 mL), 2,2-dimethoxy propane (12 mL) and PPTS (1 g) was added. The mixture was stirred at ambient temperature for 3 h. Sodium bicarbonate was added to neutralize PPTS and filtered. Removal of solvent and purification by silica gel column chromatography (SiO_2, 20% EtOAc in hexane as eluent) afforded the mono acetonide **21** (3.18 g, 96%) as a colorless liquid, R_f=0.55 (1:2 EtOAc and hexane). $[\alpha]_D^{25}$ +13.99 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05 (d, 3H, J=7.3 Hz, CH_3), 1.07 (s, 9H, *tert*-butyl), 1.41 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.59 (dd, 1H, J=1.5, 11.0 Hz, CH), 4.12 (dd, 1H, J=2.9, 11.8 Hz, CH), 4.21 (d, 2H, J=2.2 Hz, CH_2), 4.52 (t, 1H, J=2.2 Hz, CH), 5.71 (m, 2H, olefin), 7.29–7.44 (m, 6H, ArH), 7.61–7.72 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 133.7, 130.0, 129.6, 128.9, 127.6, 98.7, 71.9, 66.4, 63.9, 33.0, 29.7, 26.8, 19.3, 19.2, 11.1; IR (neat): 3443, 2933, 2859, 1634, 1377, 705 cm^{-1}; LC–MS: 447.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{26}H_{36}O_3SiNa$ $[M+Na]^+$ 447.2331, found 447.2330.

4.1.18. (E)-3-[(4S,5S)-2,2,5-Trimethyl-1,3-dioxan-4-yl]-2-propen-1-ol

To a stirred solution of **21** compound (3 g, 7.0 mmol) in THF (15 mL) and was added TBAF (8.5 mL (1 M in THF), 8.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 40% EtOAc in hexane as eluent) on silica gel to give the allyl alcohol (1.25 g, 95%) as a colorless liquid, R_f=0.55 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ +10.25 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, 3H, J=6.6 Hz, CH_3), 1.41 (d, 6H, J=10.7 Hz, 2×CH_3), 3.56 (d, 2H, J=11.6 Hz, CH_2), 4.13 (d, 2H, J=4.1 Hz, CH_2), 4.07 (d, 1H, J=2.5 Hz, CH), 4.44–4.55 (m, 1H, CH), 5.61 (dd, 1H, J=5.0, 15.7 Hz, olefin), 5.83 (dt, 1H, J=5.0, 15.7 Hz, olefin); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 130.5, 130.4, 98.7, 71.8, 66.3, 32.8, 30.8, 29.6, 19.1, 11.0; IR (neat): 3443, 2933, 2859, 1634, 1377, 705 cm^{-1}; LC–MS: 209.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 209.1153, found 209.1145.

4.1.19. (2R,3S)-3-[(4R,5S)-2,2,5-Trimethyl-1,3-dioxan-4-yl]oxiran-2-ylmethanol (**22**)

Dry CH_2Cl_2 of 10 mL was added to 4Å activated molecular sieves powder and the suspension mixture was cooled to −20 °C. D-(+) DET (0.302 g, 1.3 mmol) in dry DCM (2 mL) and Ti(O^iPr)$_4$ (0.4 mL, 1.3 mmol) were added subsequently with stirring and the resulting mixture was stirred for 30 min at −20 °C, allyl alcohol (1.2 g, 6.5 mmol) in dry CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred for another 30 min at −20 °C. TBHP (3.3 M in toluene, 6 mL, 19.4 mmol) was then added and the reaction mixture was stirred at the same temperature for 24 h. It was then warmed to 0 °C, quenched with 2 mL of water and stirred for 1 h at room temperature. Aqueous NaOH solution (30%) saturated with NaCl (6 mL) was then added and the reaction mixture was stirred vigorously for another 30 min at room temperature. The resulting mixture was washed well with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (SiO_2, 60% EtOAc in hexane as eluent) to afford compound **22** (1.0 g, 78%) as a colorless viscous liquid, R_f=0.55 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ −18.45 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (d, 3H, J=6.8 Hz, CH_3), 1.36 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.60–1.71 (m, 1H, CH), 2.14–2.43 (br s, OH), 2.92 (dd, 1H, J=2.3, 5.3 Hz, CH), 3.12–3.17 (m, 1H, CH), 3.56 (dd, 1H, J=1.5, 11.3 Hz), 3.62 (dd, 1H, J=4.5, 12.8 Hz, CH), 3.84–3.93 (m, 2H, CH_2), 4.07 (dd, 1H, J=3.0, 11.3 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.8, 70.0, 66.1, 61.1, 56.8, 55.6, 30.2, 29.3, 18.8, 11.3; IR (neat): 3414, 1616, 1381, 1219, 1009, 772 cm^{-1}; FABMS: 203 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{10}H_{18}O_4Na$ $[M+Na]^+$ 225.1102, found 225.1105.

4.1.20. (4R,5S)-4-[(2S,3S)-3-(Chloromethyl)oxiran-2-yl]-2,2,5-trimethyl-1,3-dioxane

To a stirred solution of compound **22** (0.7 g, 3.46 mmol) in 8 mL dry CCl_4 were added triphenylphosphine (1.45 g, 5.2 mmol) and $NaHCO_3$ (0.29 g, 3.46 mmol). The resulting mixture was vigorously refluxed for 2 h. Solids were filtered and washed with ether. The solvent was removed under reduced pressure and purified by silica gel column chromatography (SiO_2, 25% EtOAc in hexane as eluent) to afford chloro compound (0.69 g, 90%), as a colorless viscous liquid, R_f=0.65 (2:3 EtOAc and hexane). $[\alpha]_D^{25}$ −21.83 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (d, 3H, J=6.8 Hz, CH_3), 1.40 (d, 6H, J=9.8 Hz, 2×CH_3), 1.61–1.73 (m, 1H, CH), 2.87 (dd, 1H, J=1.5, 4.5 Hz, CH), 3.28 (td, 1H, J=1.5, 6.0 Hz, CH), 3.50–3.69 (m, 3H, CH and CH_2), 3.89–3.94 (m, 1H, CH), 4.10 (dd, 1H, J=3.02, 11.3 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.7, 69.5, 66.0, 58.4, 55.3, 44.2, 30.1, 29.2, 18.7, 11.2; ESIMS: 243.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{10}H_{17}O_3ClNa$ $[M+Na]^+$ 243.0763, found 243.0775.

4.1.21. (1S)-1-[(4R,5S)-2,2,5-Trimethyl-1,3-dioxan-4-yl]-2-propyn-1-ol (**23**)

To freshly distilled ammonia (10 mL) in 100 mL two neck round bottom flask fitted with a cold finger condenser was added catalytic amount of ferric nitrate followed by the piecewise addition of lithium metal (0.2 g, 30 mmol) at −33 °C and the resulting gray colored suspension was stirred for 30 min. To this reaction mixture compound, chloro compound was added

(0.65 g, 3.0 mmol) in dry THF (4 mL) over a period of 5 min. The reaction mixture was then stirred for 1 h at −33 °C and quenched by the addition of solid ammonium chloride (0.4 g) and the ammonia was then allowed to evaporate. The reaction mixture was extracted with water (2×10 mL) and ethyl acetate (2×10 mL). The combined organic layers were washed once with water and brine solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified on column chromatography (SiO_2, 45% EtOAc in hexane as eluent) to afford the pure compound **23** (445 mg, 82%) as a clear colorless liquid, R_f=0.50 (2:3 EtOAc and hexane). $[\alpha]_D^{25}$ −3.73 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, 3H, *J*=6.8 Hz, CH_3), 1.42 (d, 6H, *J*=14.4 Hz, 2×CH_3), 1.75−1.88 (m, 1H, CH), 2.38 (d, 1H, *J*=1.9 Hz, acetylene), 3.58 (dd, 1H, *J*=1.3, 11.7 Hz, CH), 3.99 (dd, 1H, *J*=2.5, 7.7 Hz, CH), 4.07 (dd, 1H, *J*=2.6, 11.5 Hz, CH), 4.25 (d, 1H, *J*=7.5 Hz, CH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 99.1, 82.8, 73.8, 66.8, 62.5, 29.4, 29.1, 24.8, 18.9, 11.0; IR (neat): 3451, 2925, 2364, 1461, 1031, 767 cm^{-1}; LC−MS: 207 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{10}H_{16}O_3Na$ $[M+Na]^+$ 207.0997, found 207.1002.

*4.1.22. (4R,5S)-4-[(1S)-1-Methoxy-2-propynyl]-2,2,5-trimethyl-1,3-dioxane (**24**)*

To a stirred suspension of freshly activated sodium hydride (187 mg, 8.15 mmol) in dry THF (3 mL) at 0 °C, alcohol **23** (0.5 g, 2.7 mmol) in dry THF (3 mL) was added dropwise. After stirring for 30 min, MeI (0.25 mL, 4.0 mmol) was added. After completion of the reaction (1 h), the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo, purification by silica gel column chromatography (SiO_2, 30% EtOAc in hexane as eluent) afforded **24** (524 mg, 98% yield) as colorless oil, R_f=0.65 (2:3 EtOAc and hexane). $[\alpha]_D^{25}$ −3.83 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (d, 3H, *J*=6.8 Hz, CH_3), 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.66−1.76 (m, 1H, CH), 2.32 (d, 1H, *J*=1.9 Hz, acetylene), 3.41 (s, 3H, OCH_3), 3.56 (dd, 1H, *J*=1.51, 11.5 Hz, CH), 3.74 (dd, 1H, *J*=1.9, 8.9 Hz, CH), 3.99 (dd, 1H, *J*=2.5, 8.9 Hz, CH), 4.06 (dd, 1H, *J*=2.8, 11.5 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 99.0, 81.3, 74.1, 73.2, 71.0, 66.6, 56.6, 29.5, 29.2, 18.9, 10.5; IR (neat): 3451, 2922, 2362, 1638, 1462, 1021, 771 cm^{-1}; LC−MS: 221 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1153, found 221.1156.

*4.1.23. Methyl(1S,2E)-3-(1,1,1-tributylstannyl)-1-[(4R,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl]-2-propenyl ether (**5**)*

To a solution of alkyne **24** (0.5 g, 2.5 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added $Pd(PPh_3)_2Cl_2$ (356 mg, 0.5 mmol) and Bu_3SnH (0.2 mL, 7.5 mmol) was the added dropwise and the mixture was stirred at 0 °C for 1 h, TLC indicated that all the starting materials reacted. The mixture was concentrated in vacuo and the residue was subjected to column chromatography (SiO_2, 5% EtOAc in hexane as eluent) to give product **5**[6d] (0.9 g, 78%) as a colorless oil, R_f=0.90 (1:10 EtOAc and hexane). $[\alpha]_D^{25}$ +16.5 (*c* 1.10, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25}$ +16.4 (*c* 1.01, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.75−0.96 (m, 15H, 3×CH_3 and 3×CH_2), 1.07 (d, 3H, *J*=6.8 Hz, CH_3), 1.20−1.40 (m, 12H, 2×CH_3 and 3×CH_2), 1.40−1.56 (m, 6H, 3×CH_2), 1.72 (m, 1H, CH), 3.25 (s, 3H, OCH_3), 3.35 (dd, 1H, *J*=2.3, 9.1 Hz, CH), 3.56 (d, 1H, *J*=12.8 Hz, CH), 3.74 (dd, 1H, *J*=2.3, 9.1 Hz, CH), 4.04 (dd, 1H, *J*=3.0, 11.3 Hz, CH), 5.74 (d, 1H, *J*=6.0, 18.9 Hz, olefin), 6.14 (d, 1H, *J*=18.9 Hz, olefin); ESIMS: 513.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{23}H_{46}O_3SnNa$ $[M+Na]^+$ 513.2366, found 513.2357.

*4.1.24. Methyl(2Z,4E,6R,7S,8S,10E,12E,14S)-7-[(1,1-diethyl-1-isopropylsilyl)oxy]-2,14-dimethoxy-4,6,8,10-tetramethyl-14-[(4R,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl]-2,4,10,12-tetradecatetraenoate (**2**)*

To a solution of **4** (0.10 g, 0.18 mmol) and **5**[6d] (0.095 g, 0.18 mmol) in dry DMF (3 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]palladium(II)chloride ($PdCl_2$(dppf)) (0.03 g, 0.04 mmol). After the reaction mixture was stirred at 50 °C for 15 h under nitrogen, ice-cold water (4 mL) was added, and the resultant mixture was then extracted with ether (3×5 mL). The extracts were washed with saturated aqueous NaCl (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 15% EtOAc in hexane as eluent) gave **2**[6d] (0.067 g, 60%) as a colorless viscous liquid, R_f=0.60 (3:7 EtOAc and hexane). $[\alpha]_D^{30}$ +32.12 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.65 (q, 4H, *J*=7.3, 15.3 Hz, 2×CH_2), 0.78 (d, 3H, *J*=5.9 Hz, CH_3), 0.82−1.14 (m, 14H, 4×CH_3 and 2×CH), 1.16−1.49 (m, 6H, 2×CH_2 and 2×CH), 1.33 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.64−1.87 (m, 2H, 2×CH), 1.74 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.28 (d, 1H, *J*=8.1 Hz, CH), 2.71 (m, 1H, CH), 3.25 (s, 3H, OCH_3), 3.32−3.37 (m, 3H, 3×CH), 3.65 (s, 3H, OCH_3), 3.75 (dd, 1H, *J*=2.2, 8.1 Hz, CH), 3.79 (s, 3H, CO_2CH_3), 4.06 (dd, 1H, *J*=2.2, 11.0 Hz, CH), 5.33 (dd, 1H, *J*=7.3, 14.7 Hz, CH), 5.81 (d, 1H, *J*=11.0 Hz, olefin), 5.97 (d, 1H, *J*=9.5 Hz, olefin), 6.37 (dd, 1H, *J*=11.0, 15.3 Hz, olefin), 6.52 (s, 1H, olefin); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 165.6, 142.5, 142.4, 137.8, 130.3, 129.6, 128.7, 125.9, 116.1, 98.7, 80.8, 80.3, 73.9, 67.0, 60.3, 56.2, 52.0, 43.9, 36.9, 35.5, 29.7, 29.5, 29.4, 18.9, 18.8, 17.6, 16.5, 15.5, 14.7, 13.4, 11.1, 7.4, 7.3, 4.5, 4.4; IR (neat): 3435, 2927, 1720, 1456, 1381, 1250, 1199, 1104, 1018, 716 cm^{-1}; LC−MS: 645.3 $[M+Na]^+$ and 681.1 $[M+K]^+$; HRMS (ESIMS): *m/z* calcd for $C_{35}H_{62}O_7SiNa$ $[M+Na]^+$ 645.4162, found 645.4147.

4.1.25. (4R)-4-[(1R,2R)-2-(Benzyloxy)-1,3-dimethylbutyl]-2-(4-methoxyphenyl)-1,3-dioxane

To a solution of diol **8**[14] (2.5 g, 9.39 mmol) in CH_2Cl_2 (5 mL) at ambient temperature were added *p*-methoxy benzaldehyde dimethyl acetal (6.4 mL, 0.37 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.05 g). The reaction mixture was stirred at ambient temperature for 1 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography (SiO_2, 25% EtOAc in hexane as eluent) to provide the desired product (3.46 g, 96%) as colorless oil, R_f=0.55 (2:3 EtOAc and hexane). $[\alpha]_D^{25}$ −92.15 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, 3H, *J*=6.8 Hz, CH_3), 0.94 (d, 3H,

J=6.8 Hz, CH_3), 1.06 (d, 3H, J=7.5 Hz, CH_3), 1.23 (dd, 1H, J=1.5, 12.8 Hz, CH), 1.58–1.71 (m, 1H, CH), 1.84–1.96 (m, 1H, CH), 1.97–2.15 (m, 1H, CH), 3.30–3.38 (dd, 1H, J=2.3, 9.8 Hz, CH), 3.80 (s, 3H, OCH_3) 3.87 (td, 1H, J=2.23, 12.1 Hz, CH), 4.13–4.26 (m, 2H, CH_2), 4.57 (ABq, 2H, J= 11.3, 24.9 Hz, benzylic CH_2), 5.29 (s, 1H, CH), 6.84 (d, 2H, J=9.1 Hz, ArH), 7.19–7.39 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 139.2, 131.8, 128.3, 127.5, 127.3, 127.4, 113.5, 100.8, 84.2, 75.9, 75.4, 67.3, 55.2, 40.8, 29.9, 28.5, 21.1, 14.9, 10.6; IR (KBr): 3854, 3415, 1618, 1219, 772 cm^{-1}; ESIMS: 407 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{24}H_{32}O_4Na$ $[M+Na]^+$ 407.2198, found 407.2202.

*4.1.26. (3R,4R,5R)-5-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]-4,6-dimethylheptan-1-ol (**25**)*

To a solution of acetonide (4.0 g, 10.41 mmol) in dry CH_2Cl_2 (50 ml) at 0 °C, a solution of DIBAL-H (9 mL, 1.4 M in toluene, 12.5 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was slowly allowed to warm to room temperature, stirred for 2 h for completion of the reaction, and was quenched by the addition of MeOH (1 mL), followed by saturated aqueous sodium potassium tartarate solution at 0 °C and stirred for 0.5 h. The aqueous layer was extracted with CH_2Cl_2 and washed with brine, and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude mixture on column chromatography (SiO_2, 40% EtOAc in hexane as eluent) afforded **25** (3.47 g, 85%) as colorless liquid, R_f=0.45 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ −31.39 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, 3H, J=6.8 Hz, CH_3), 0.92 (d, 3H, J=6.8 Hz, CH_3), 1.04 (d, 3H, J=6.8 Hz, CH_3), 1.43 (br s, OH) 1.58–1.81 (m, 2H, 2×CH), 1.83–2.01 (m, 2H, 2×CH), 3.23 (dd, 1H, J=3.0, 8.3 Hz, CH), 3.55–3.67 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.84 (td, 1H, J=6.8, 1.5 Hz, CH), 4.37 (dd, 1H, J=6.8, 11.3 Hz, CH), 4.49 (ABq, 2H, J=10.8, 19.2 Hz, benzylic CH_2), 4.52 (ABq, 2H, J=11.3, 18.1 Hz, benzylic CH_2), 6.79 (d, 2H, J=8.3 Hz, ArH), 7.17 (d, 2H, J=8.3 Hz, ArH), 7.20–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 137.2, 128.6, 128.3, 128.0, 113.6, 88.6, 75.2, 72.6, 72.1, 58.6, 55.4, 42.8, 33.9, 27.6, 17.4, 9.7; IR (KBr): 3414, 1617, 1353, 772 cm^{-1}; FABMS: 387 $[M+H]^+$; HRMS (ESIMS): *m/z* calcd for $C_{24}H_{34}O_4Na$ $[M+Na]^+$ 409.2722, found 409.2717.

*4.1.27. (3R,4R,5R)-5-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]-4,6-dimethylheptanal (**26**)*

To a stirred solution of IBX (5.36 g, 19.17 mmol) in 10 mL dry DMSO was added diol **25** (3.7 g, 9.58 mmol) in 15 mL dry CH_2Cl_2 at 0 °C. After completion of addition, the reaction mixture kept at room temperature for 3 h. After completion of reaction by TLC indication, the reaction mixture was filtered on a Celite using diethyl ether. The filtrate was washed with water and brine and dried over anhydrous Na_2SO_4. The ether layer was concentrated under reduced pressure and the crude product was subjected to column chromatography (SiO_2, 18% EtOAc in hexane as eluent) to give pure aldehyde **26** (3.05 g, 83%) as a viscous liquid, R_f=0.70 (3:7 EtOAc and hexane). $[\alpha]_D^{25}$ −47.34 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, 3H, J=3.8 Hz, CH_3), 0.93 (d, 3H, J=3.8 Hz, CH_3), 1.04 (d, 3H, J=7.5 Hz, CH_3), 1.62–1.75 (m, 1H, CH), 1.85–1.98 (m, 1H, CH), 2.55 (ddd, 1H, J=2.3, 6.0, 16.6 Hz, CH), 2.78 (ddd, 1H, J=2.3, 6.8, 16.6 Hz, CH), 3.27 (dd, 1H, J=3.0, 9.1 Hz, CH), 3.77 (s, 3H, OCH_3), 4.23–4.62 (m, 5H, 2×benzylic CH_2 and CH), 6.79 (d, 2H, J=8.3 Hz, ArH), 7.14 (d, 2H, J=8.3 Hz, ArH), 7.19–7.34 (m, 5H, ArH), 9.76 (t, 1H, J=2.3 Hz, CHO); IR (neat): 2953, 2856, 1683, 1352, 772 cm^{-1}; HRMS (ESIMS): *m/z* calcd for $C_{24}H_{32}O_4Na$ $[M+Na]^+$ 407.2198, found 407.2004.

*4.1.28. (5R,6R,7R)-7-(Benzyloxy)-5-[(4-methoxybenzyl)oxy]-6,8-dimethylnonan-3-ol (**27**)*

Freshly prepared EtMgBr (prepared in situ from 390 mg (15.62 mmol) of Mg and 1.42 g (15.62 mmol) of ethyl bromide in 10 mL of dry THF) was added dropwise to a stirred solution of aldehyde **26** (2 g, 5.2 mmol) in dry THF (10 mL) at 0 °C. After addition was completed, the reaction mixture was allowed to stir at room temperature for 2 h and then quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the compound from aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with water and brine solution and dried over Na_2SO_4. Concentration under reduced pressure and purification by column chromatography (SiO_2, 15% EtOAc in hexane as eluent) afforded **27** (1.93 g, 90%) as a colorless viscous liquid, R_f=0.60 (3:7 EtOAc and hexane). $[\alpha]_D^{25}$ −29.18 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83–0.98 (m, 9H, 3×CH_3), 0.99–1.08 (t, 3H, J= 6.8 Hz, CH_3), 1.33–1.63 (m, 2H, CH_2), 1.68–2.02 (m, 2H, CH_2), 2.57 (br s, OH), 3.13–3.28 (m, 1H, CH), 3.47–3.69 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.82–3.94 (m, 1H, CH), 4.33–4.60 (m, 5H, 2×benzylic CH_2 and CH), 6.75–6.83 (m, 2H, ArH), 7.16 (d, 2H, J=8.3 Hz, ArH), 7.12–7.34 (m, 5H, ArH); IR (KBr): 3414, 1617, 1353, 772 cm^{-1}; FABMS: 415 $[M+H]^+$; HRMS (ESIMS): *m/z* calcd for $C_{26}H_{38}O_4Na$ $[M+Na]^+$ 437.2667, found 437.2680.

*4.1.29. (3R,4R,5R)-5-(Benzyloxy)-1-ethyl-3-[(4-methoxybenzyl)oxy]-4,6-dimethylheptyl acetate (**28**)*

To a solution of **27** (1.5 g, 3.62 mmol), CH_2Cl_2 (8 mL), Et_3N (1.52 mL, 10.86 mmol) were added DMAP (0.5 equiv) and acetic anhydride (0.4 mL, 4.3 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 3 h, the reaction mixture was quenched with ice-cold water and the resultant mixture was then extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% EtOAc in hexane as eluent) to afford **28** (1.55 g, 94%) as colorless oil, R_f=0.68 (1:4 EtOAc and hexane). $[\alpha]_D^{25}$ −40.62 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, 3H, J=6.8 Hz, CH_3), 0.86–0.94 (m, 6H, 2×CH_3), 1.04 (d, 3H, J=6.8 Hz, CH_3), 1.05 (d, 3H, J=6.8 Hz, CH_3), 1.54–1.69 (m, 3H, 2×CH_2 and CH), 1.79 (s, 1/3×CH_3), 1.89 (s, 2/3×CH_3), 1.75–2.09 (m, 2H, CH_2), 3.24 (m, 1H, CH), 3.69–3.85 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 4.17–4.60 (m, 4H, 2×benzylic CH_2), 4.80 (m, 1/3H, CH), 4.93 (m, 2/3H, CH), 6.80 (d, 2H, J=8.3 Hz, ArH), 7.18–7.33 (m, 7H, ArH); IR (neat): 3450, 2964, 1734, 1243, 1067, 761 cm^{-1}; LC–MS: 479.2 $[M+Na]^+$;

HRMS (ESIMS): *m/z* calcd for $C_{28}H_{40}O_5Na$ $[M+Na]^+$: 479.2773, found: 479.2771.

4.1.30. (3R,4S,5R)-1-Ethyl-3,5-dihydroxy-4,6-dimethylheptyl acetate (29)

To a solution of compound **28** (1.2 g, 2.63 mmol) in dry EtOAc (10 mL) was added catalytic amount of Pd/C (10%) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 2 h. The reaction mixture was filtered off, washed with ethyl acetate, the filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (SiO_2, 40% EtOAc in hexane as eluent) to afford compound **29** (0.588 g, 90%) as a colorless liquid, R_f=0.58 (1:1 EtOAc and hexane). $[\alpha]_D^{25}$ +10.13 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.82–1.02 (m, 12H, 4×CH_3), 1.35–1.89 (m, 5H, 2×CH_2 and CH), 2.03 (s, 1/3×CH_3), 2.05 (s, 2/3×CH_3), 2.56 (m, 1/2H, OH), 2.96 (m, 1H, CH), 3.27 (q, 1H, *J*=6.8, 11.3 Hz, CH), 3.41 (br s, 1/2H, OH), 3.77 (dd, 1/2H, *J*=1.5, 11.3 Hz, CH), 3.99 (m, 1/2H, CH), 4.79–5.00 (m, 1H, CH); IR (neat): 3427, 2966, 1377, 1022, 609 cm^{-1}; ESIMS: 269.1 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{13}H_{26}O_4Na$ $[M+Na]^+$ 269.1728, found 269.1718.

4.1.31. 1-[(4R,5R,6R)-2,2-Di(tert-butyl)-6-isopropyl-5-methyl-1,3,2-dioxasilinan-4-yl]methylpropyl acetate (30)

To a solution of **29** (450 mg, 1.83 mmol) in dry DMF (3 mL) was added dropwise 2,6-lutidine (0.62 mL, 5.5 mmol, 98%) followed by *t*-$Bu_2Si(OTf)_2$ (0.4 mL, 2.2 mmol, 97%) at 0 °C. After stirred at 25 °C for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The resultant mixture was then extracted with Et_2O (3×10 mL). The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 6% EtOAc in hexane as eluent) to afford **30** (0.6 g, 85%) as colorless oil, R_f=0.62 (1:9 EtOAc and hexane). $[\alpha]_D^{25}$ +47.64 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.72 (t, 3H, *J*=7.8 Hz, CH_3), 0.85 (d, 3H, *J*=4.7 Hz, CH_3), 0.92 (td, 3H, *J*=3.12, 7.8 Hz, CH_3), 1.01 (s, 18H, 2×*tert*-butyl), 1.04 (d, 3H, *J*=7.8 Hz, CH_3), 1.46–1.93 (m, 5H, 2×CH_2 and CH), 2.03 (s, 3H, $OCOCH_3$), 2.17 (m, 1H, CH), 3.67 (dd, 1H, *J*=1.6, 9.4 Hz, CH), 4.02 (m, 1H, CH), 5.14 (m, 1H); IR (KBr): 3447, 2969, 2931, 2364, 1741, 1022 cm^{-1}; LC–MS: 409.3 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{21}H_{42}O_4SiNa$ $[M+Na]^+$ 409.2750, found 409.2739.

4.1.32. 1-[(4R,5R,6R)-2,2-Di(tert-butyl)-6-isopropyl-5-methyl-1,3,2-dioxasilinan-4-yl]-2-butanol (31)

To a solution of **30** (500 mg, 1.3 mmol) in dry MeOH (5 mL) was added 5 M NaOMe/MeOH (0.8 mL, 3.9 mmol) at 0 °C. After the reaction mixture was stirred at 25 °C for 2 h, the reaction mixture was quenched with ion-exchange resin IR-120B. The resultant mixture was filtered and the resin was washed with MeOH. The combined filtrate and washings were concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 12% EtOAc in hexane as eluent) gave **31** (0.4 g, 90%) as a colorless viscous liquid, R_f=0.55 (1:4 EtOAc and hexane). $[\alpha]_D^{25}$ +49.84 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.76 (d, 3H *J*=6.8 Hz, CH_3), 0.86 (d, 3H, *J*=6.8 Hz, CH_3), 0.95 (t, 3H, *J*=7.6 Hz, CH_3), 1.00 (d, 3H, *J*=6.8 Hz, CH_3), 1.03 (s, 18H, 2×*tert*-butyl), 1.55–1.36 (m, 3H, CH_2 and CH), 1.56–1.80 (m, 2H, CH_2), 2.15 (m, 1H, CH), 3.71 (dd, 1H, *J*=2.3, 9.1 Hz, CH), 3.73–3.81 (m, 1H, CH), 3.93 (br s, OH), 4.29 (ddd, 1H, *J*=1.5, 5.3 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 76.4, 73.6, 69.9, 38.9, 36.7, 30.5, 30.2, 27.5, 27.3, 21.6, 20.8, 20.1, 13.6, 13.1, 10.3; IR (KBr): 3471, 2965, 2364, 1463, 1041 cm^{-1}; LC–MS: 367.2 $[M+Na]^+$; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{40}O_3SiNa$ $[M+Na]^+$ 367.2644, found 367.2643.

4.1.33. 1-[(4R,5R,6R)-2,2-Di(tert-butyl)-6-isopropyl-5-methyl-1,3,2-dioxasilinan-4-yl]-2-butanone (3)

To a solution of alcohol **31** (0.35 g, 1.08 mmol) in CH_2Cl_2 (5 mL) were added dry pyridine (0.620 mL, 5.08 mmol) and Dess–Martin periodinane (0.863 g, 2.03 mmol) at 0 °C. After stirring for 2 h at 25 °C, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (10 mL) and the resultant mixture was then extracted with Et_2O (10 mL×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% EtOAc in hexane as eluent) to afford **3**[6d] (306 mg, 88%) as a white solid, R_f=0.80 (3:7 EtOAc and hexane). Mp: 40–41 °C {lit.[6d] mp: 40.0–40.5 °C}; $[\alpha]_D^{25}$ +84.8 (*c* 0.9, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25}$ +85.2 (*c* 0.89, $CHCl_3$)}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.72 (d, 3H, *J*=6.8 Hz, CH_3), 0.86 (d, 3H, *J*=6.8 Hz, CH_3), 0.97 (s, 9H, *tert*-butyl), 0.99 (s, 9H, *tert*-butyl), 1.00 (d, 3H, *J*=6.8 Hz, CH_3), 1.06 (t, 3H, *J*=7.6 Hz, CH_3), 1.72 (dseptet, 1H, *J*=6.8, 2.3 Hz, CH), 2.22 (m, 1H, CH), 2.35 (dd, 1H, *J*=14.3, 3.1 Hz, CH), 2.51 (dq, 1H, *J*=10.6, 7.5 Hz, CH_2), 2.54 (dq, 1H *J*=10.6, 7.5 Hz, CH_2), 2.69 (dd, 1H, *J*=14.3, 10.5 Hz, CH), 3.66 (dd, 1H, *J*=9.8, 2.2 Hz, CH), 4.60 (ddd, 1H, *J*=9.8, 6.0, 3.7 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.3, 76.5, 73.7, 45.4, 38.7, 36.1, 30.3, 27.4, 27.2, 21.6, 20.8, 20.0, 13.7, 13.1, 7.6; IR (neat): 2965, 2859, 1717, 1469, 1038, 825 cm^{-1}; LC–MS: 343.1 $[M+H]^+$; HRMS (ESIMS): *m/z* calcd for $C_{19}H_{38}O_3SiNa$ $[M+Na]^+$ 365.2487, found 365.2485.

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