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An enantioselective synthesis of the core unit of the non-nucleoside reverse transcriptase inhibitor taurospongin A

Arun K. Ghosh* and Hui Lei

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607, USA

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Abstract—An enantioselective formal synthesis of taurospongin A has been achieved. The key steps involve chelation-controlled reductions of β-ketosulfoxide and β-hydroxy ketone intermediates and Sharpless asymmetric epoxidation to construct the tertiary alcohol stereoselectively.

1. Introduction

Combination therapy consisting of both nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors has become a standard treatment for HIV infection.[1] Because of numerous limitations of current chemotherapies, the design and discovery of novel, structurally diverse, agents is very important.[2] Taurospongin A (Fig. 1), a unique fatty acid derivative isolated from the Okinawan marine sponge *Hippospongia* sp. has very interesting biological properties:[3] it inhibits DNA polymerase β and HIV reverse transcriptase with K_i values of 1.7 and 1.3 μM, respectively. The initial structure elucidation and determination of the absolute stereochemistry of taurospongin were carried out through degradation studies.[3] The structural features of taurospongin A coupled with its potent reverse transcriptase inhibitory properties stimulated our interest in its synthesis and thus far, the only synthesis of (+)-taurospongin A has been reported by Lebel and Jacobsen.[4] Herein, we report a stereocontrolled synthesis of the C_1–C_{10} fragment **2** which contains all three stereocenters of taurospongin A. Segment **2** is an intermediate of the previous synthesis of (+)-taurospongin A.[4] A highly stereoselective chelation-controlled reduction of an optically active β-ketosulfoxide followed by diastereoselective reduction of the resulting β-hydroxy ketone efficiently constructed the *syn*-1,3-diol functionality of compound **3**. Sharpless epoxidation was then used to efficiently install the stereochemistry of the C_3 tertiary alcohol fragment of taurospongin. The key coupling step leading to the synthesis of **2** was accomplished by opening epoxide **3** with the alkynyllithium derived from **4**.

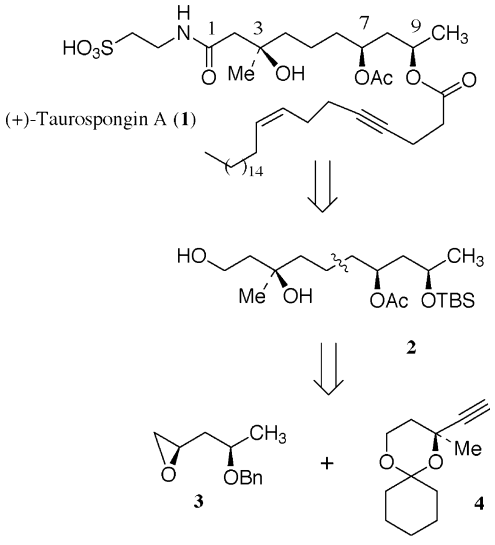

Figure 1.

2. Results and discussion

The preparation of enantiomerically pure epoxide **3** is illustrated in Scheme 1. The known[5] ketal **5** was prepared in multigram quantities by heating methyl acetoacetate and ethylene glycol in dry benzene for 3 h in the presence of a catalytic amount of *p*-TsOH with azeotropic removal of water. Treatment of **5** with the

* Corresponding author. E-mail: arunghos@uic.edu

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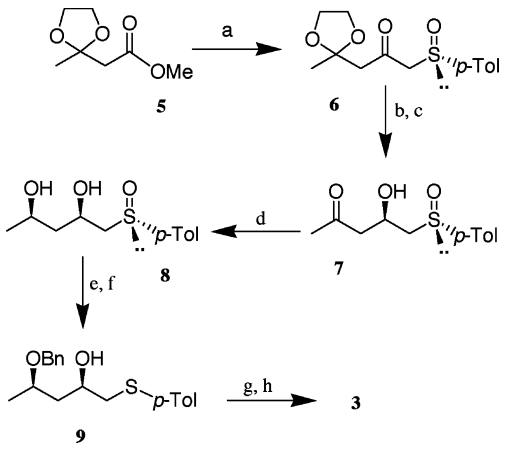
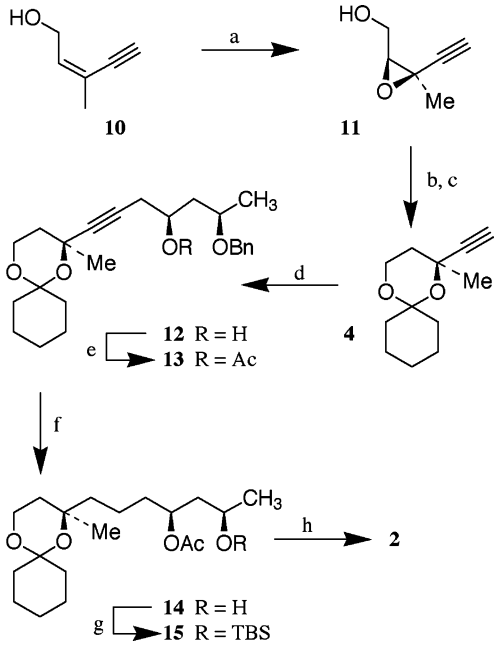


Scheme 1. *Reagents, conditions (and yields)*: (a) LDA, (*S*)-methyl-*p*-tolylsulfoxide, THF, 30 min (65%); (b) DIBAL, −78°C, THF, 30 min; (c) oxalic acid, THF/H_2O, 15 h (84%, two steps); (d) Et_2BOMe, $NABH_4$, THF/MeOH, 6 h, then H_2O_2, 10 h (92%); (e) $PhCH(OMe)_2$, *p*-TsOH·H_2O, CH_2Cl_2, 30 min; (f) DIBAL, 0–23°C, 6 h (74%, two steps); (g) Me_3OBF_4, CH_2Cl_2; (h) K_2CO_3, H_2O (70%, two steps).



Scheme 2. *Reagents, conditions (and yields)*: (a) $Ti(O^iPr)_4$, (+)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −30°C, 30 h (61%); (b) LAH, ether, 0°C, 1 h; (c) cyclohexanone dimethyl ketal, *p*-TsOH·H_2O (cat.), CH_2Cl_2, 23°C, 3 h (71%, two steps); (d) *n*BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, then **3**, 2 h (87%); (e) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 3 h (94%); (f) 10% Pd–C, H_2, EtOAc, 6 h (96%); (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 30 min (95%); (h) PPTS (cat.), MeOH, 15 min (95%).

(*S*)-methyl-*p*-tolylsulfoxide anion furnished the optically active β-ketosulfoxide **6** in 65% yield after chromatography.[6] DIBAL reduction of **6** in THF at −78°C as reported by Solladie et al.[7] then afforded the corresponding β-hydroxysulfoxide diastereoselectively. The ^1H and ^{13}C NMR analysis of the resulting β-hydroxysulfoxide revealed that the reduction occurred with excellent diastereoselectivity (>96% de). Removal of the ketal by exposure to oxalic acid in a mixture of THF and water furnished β-hydroxy ketone **7** in 84% yield in two steps. For *syn*-selective reduction of **7**, we examined the chelation-controlled reduction protocol developed by Prasad and co-workers[8] utilizing diethylmethoxyborane and sodium borohydride at −78°C.[9] This provided the *syn*-1,3-diol derivative **8** as a single diastereomer (by ^1H and ^{13}C NMR analysis) in 92% isolated yield. Treatment of **8** with benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TsOH·H_2O afforded the corresponding benzylidene acetal. Reduction of the resulting acetal with DIBAL effected regioselective reduction of the acetal as well as reduction of the sulfoxide moiety to the sulfide. Benzyl ether **9** was isolated in 74% yield for two steps. The β-hydroxysulfide functionality of **9** was converted to the corresponding oxirane **3** in a one pot, two-step sequence consisting of alkylation of **9** by exposure to trimethyloxoniumtetrafluoroborate in CH_2Cl_2 followed by treatment of the resulting mixture with aqueous potassium carbonate, providing **3** in 70% yield after chromatography.[10]

The synthesis of compound **4** was carried out utilizing Pattenden's protocol as shown in Scheme 2.[11] The (*Z*)-enynol **10** was prepared in multi-gram quantities using the method described in the literature.[12] Sharpless asymmetric epoxidation[13] of **10** with (+)-DET provided epoxide **11** enantioselectively. The enantiomeric purity of **11** (98% ee, $[\alpha]_D^{20} = -16.5$ (*c* 0.85, $CHCl_3$) was determined by formation of the Mosher ester and ^{19}F NMR analysis.[14] Reduction of the epoxide with LAH in ether at 0°C afforded the corresponding 1,3-diol which was treated with cyclohexanone dimethyl ketal in the presence of a catalytic amount of *p*-TsOH·H_2O to provide ketal **4** in 71% yield from **11**.

Treatment of alkyne **4** with *n*BuLi in THF at −78°C for 20 min provided the alkynyl anion which was reacted with epoxide **3** in the presence of $BF_3{\cdot}OEt_2$ at −78°C for 2 h to furnish alcohol **12** in 87% yield. Acetylation of the alcohol with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP afforded acetate **13** in 94% yield. Hydrogenation of **13** over 10% Pd–C in ethyl acetate effected saturation of the triple bond as well as removal of the benzyl group to afford alcohol **14**. It was converted to TBS ether **15** by reaction with TBSOTf in the presence of 2,6-lutidine at 0°C for 30 min. Exposure of **15** to PPTS in methanol at 23°C for 15 min removed the cyclohexylidene ketal and provided diol **2** which has been converted previously to (+)-taurospongin by Lebel and Jacobsen.[4] Spectral data (^1H and ^{13}C NMR) for synthetic **2** ($[\alpha]_D^{23} = -3.8$ (*c* 1.58, $CHCl_3$), lit. $[\alpha]_D^{23} = -2.5$ (*c* 1.73, $CHCl_3$) are in full agreement with those reported in the literature.[4]

3. Conclusion

In conclusion, an enantioselective formal synthesis of (+)-taurospongin A has been accomplished utilizing chelation-controlled reduction and Sharpless asymmetric epoxidation as the key steps. The present synthesis will provide further access to structural variants of taurospongin A for important structure–activity studies.

4. Experimental

All moisture sensitive reactions were carried out under argon or nitrogen atmosphere. Anhydrous solvents were obtained as follows: tetrahydrofuran and diethyl ether, distilled from sodium and benzophenone; dichloromethane, distilled from CaH_2; triethylamine, distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240–400 mesh silica gel under low pressure of 5–10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (400 MHz), Avance 500 (500 MHz) and Varian 300 (300 MHz) spectrometers.

4.1. (*S*)-4,4-(Ethylenedioxy)-1-(*p*-tolylsulfinyl)pentan-2-one, 6

To a stirred solution of LDA [prepared from iPr$_2$NH (2.2 mL, 15.4 mmol) and nBuLi (8.1 mL, 13.0 mmol)] in THF at 0°C was added (*S*)-methyl-*p*-tolylsulfoxide (Aldrich, 0.91 g, 5.9 mmol) in THF (5 mL). The resulting mixture was stirred for 30 min at 0°C and added to a solution of methyl ester **5** (0.98 g, 6.1 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 30 min and quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (50% EtOAc in hexanes) to provide the title compound (1.08 g, 65% yield) as a colorless oil. $[\alpha]_D^{23} = -153$ (*c* 0.81, $CHCl_3$); IR (film): 2981, 2893, 1710, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 2.33 (s, 3H), 2.74 (ABq, 2H, $J = 13.2$, $\Delta\nu = 28.6$ Hz), 3.84–3.91 (m, 6H), 7.25 (d, 2H, $J = 7.8$ Hz), 7.47 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 24.2, 52.9, 64.2, 64.3, 68.6, 107.2, 123.8, 129.7, 139.5, 141.7, 198.9

4.2. (2*R*,S_S)-2-Hydroxy-1-(*p*-tolylsulfinyl)pentan-4-one, 7

To a stirred solution of **6** (660 mg, 2.33 mmol) in THF (30 mL) at −78°C was added DIBAL (4.67 mL 1 M solution in hexane, 4.67 mmol) dropwise. The resulting mixture was stirred for 30 min and quenched with methanol and warmed to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc and 10% aqueous potassium sodium tartrate solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to provide crude β-keto-α-hydroxysulfoxide. An analytical sample was prepared after column chromatography over silica gel (25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.86 (dd, 1H, $J = 14.5$, 3.8 Hz), 1.91 (dd, 1H, $J = 14.5$, 7.9 Hz), 2.41 (s, 3H), 2.79 (dd, 1H, $J = 13.0$, 3.0 Hz), 2.86 (dd, 1H, $J = 13.0$, 9.5 Hz), 3.89–4.00 (m, 5H), 4.46–4.54 (m, 1H), 7.33 (d, 2H, $J = 8.4$ Hz), 7.55 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.1, 44.5, 63.0, 64.3, 64.5, 109.6, 123.9, 129.9, 140.7, 141.4.

To a stirred solution of the above alcohol in THF (5 mL) and H_2O (10 mL) was added oxalic acid (581.1 mg, 4.6 mmol). The resulting mixture was stirred at room temperature for 15 h and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was washed with ether to provide β-hydroxy ketosulfoxide **7** as a white solid (406 mg, 84% two steps). Mp 105°C; $[\alpha]_D^{23} = -305$ (*c* 0.34, $CHCl_3$); IR (film): 3379, 2921, 1710, 1084 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.28 (s, 3H), 2.51–2.67 (m, 2H), 2.71–2.89 (m, 2H), 4.53–4.60 (m, 1H), 4.76 (br, 1H), 7.20 (d, 2H, $J = 7.8$ Hz), 7.44 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 30.4, 49.4, 62.3, 63.0, 123.6, 129.7, 139.7, 141.2, 207.1

4.3. (2*R*,4*S*,S_S)-2,4-Dihydroxy-1-(*p*-tolylsulfinyl)pentane, 8

To a stirred solution of **7** (257 mg, 1.1 mmol) in THF (20 mL) and methanol (4 mL) was added diethylmethoxyborane (0.17 mL, 1.3 mmol). After stirring for 15 min at room temperature, the reaction mixture was cooled to −78°C and sodium borohydride (57 mg, 1.5 mmol) was added. The reaction mixture was stirred at −78°C for additional 6 h and 50% aqueous H_2O_2 (0.5 mL) was added. The mixture was warmed to room temperature and diluted with EtOAc and H_2O. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, Na_2SO_3, brine, dried over Na_2SO_4 and evaporated under reduced pressure. The resulting white solid (236 mg, 92% yield) was sufficiently pure to be used for next step reaction without further purification. Mp 122°C; $[\alpha]_D^{23} = -291$ (*c* 1.01, $CHCl_3$); IR (film): 3370, 2966, 2922, 1066, 1028, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 3H, $J = 6.2$ Hz), 1.48 (dt, 1H, $J = 14.2$, 3.0 Hz), 1.64 (dt, 1H, $J = 14.2$, 9.5 Hz), 2.35 (s, 3H), 2.74 (dd, 1H, $J = 13.2$, 2.3 Hz), 2.87 (dd, 1H, $J = 13.2$, 9.9 Hz), 3.99–4.03 (m, 1H), 4.21 (s, 1H), 4.38–4.44 (m, 1H), 5.30 (d, 1H, $J = 3.0$ Hz), 7.27 (d, 2H, $J = 8.2$ Hz), 7.48 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 23.8, 44.4, 64.4, 66.3, 67.5, 123.9, 130.0, 139.8, 141.6; HRMS (EI) m/z calcd for $C_{12}H_{18}O_3NaS$ (M^++Na): 265.0874; found: 265.0874.

4.4. (2*R*,4*S*)-4-Benzyloxy-2-hydroxy-1-(mercapto-*p*-tolyl)pentane, 9

To a stirred solution of **8** (191 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) was added benzaldehyde dimethyl acetal (0.24 mL, 1.6 mmol) and *p*-TsOH·H_2O (15 mg, 0.1 mmol). The resulting mixture was stirred for 1 h and quenched with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (50% EtOAc in hexanes) to provide the corresponding benzylidene acetal. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, 3H, $J=6.2$ Hz), 1.48 (dt, 1H, $J=13.0$, 11.1 Hz), 1.65 (dt, 1H, $J=13.0$, 2.4 Hz), 2.41 (s, 3H), 2.85–2.94 (m, 2H), 4.01–4.01 (m, 1H), 4.50–4.55 (m, 1H), 5.67 (s, 1H), 7.31–7.56 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 21.9, 38.5, 64.9, 70.9, 73.2, 101.0, 124.2, 126.5, 128.6, 129.2, 130.4, 138.5, 141.5, 141.9.

The above benzylidene acetal was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. DIBAL (7.9 mL, 1 M solution in hexane, 7.9 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred for an additional 6 h. The reaction mixture was quenched with 1N HCl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (30% EtOAc in hexanes) to provide **9** as a colorless oil (176 mg, 74%). $[\alpha]_D^{23}=-36.5$ (*c* 0.46, $CHCl_3$); IR (film): 3421, 2921, 1641 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J=6.1$ Hz), 1.73–1.84 (m, 2H), 2.35 (s, 3H), 2.93 (dd, 1H, $J=13.4$, 5.9 Hz), 3.00 (dd, 1H, $J=13.4$, 6.6 Hz), 3.78–3.82 (m, 1H), 3.90–3.93 (m, 1H), 4.40 (d, 1H, $J=11.4$ Hz), 4.64 (d, 1H, $J=11.4$ Hz), 7.09 (d, 2H, $J=7.9$ Hz), 7.28–7.34 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 21.4, 42.0, 42.9, 70.0, 70.7, 75.6, 128.2, 128.9, 130.1, 130.3, 130.5, 132.6, 136.7, 138.4; HRMS (EI) *m*/*z* calcd for $C_{19}H_{24}O_2NaS$ (M^++Na): 339.1395; found: 339.1406.

4.5. (2*R*,4*S*)-4-Benzyloxy-1,2-epoxypentane, 3

To a stirred solution of **9** (54 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) was added trimethyloxonium tetrafluoroborate (32 mg, 0.22 mmol) and the resulting mixture was stirred for 2 h at room temperature. An aqueous solution of K_2CO_3 (50 mg in 2 mL H_2O) was added and stirring was continued for 30 h. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexanes) to provided **3** as a colorless oil (24 mg, 70% for two steps). $[\alpha]_D^{23}=-20.1$ (*c* 0.69, $CHCl_3$); IR (film): 2918, 2854, 1452, 1064 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (d, 3H, $J=6.2$ Hz), 1.69 (dt, 1H, $J=14.2$, 5.5 Hz), 1.87 (dt, 1H, $J=14.2$, 6.2 Hz), 2.48 (dd, 1H, $J=5.0$, 2.7 Hz), 2.75 (t, 1H, $J=4.7$ Hz), 3.05 (m, 1H), 3.74 (m, 1H), 4.48 (d, 1H, $J=11.7$ Hz), 4.60 (d, 1H, $J=11.7$ Hz), 7.32–7.35 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0, 39.7, 47.2, 50.0, 70.7, 73.0, 127.9, 127.9, 128.7, 139.1; HRMS (EI) *m*/*z* calcd for $C_{12}H_{16}O_2Na$ (M^++Na): 215.1048; found: 215.1050.

4.6. (2*S*,3*R*)-3-Ethynyl-3-methyloxiranyl)methanol, 11

To a stirred suspension of powdered 4 Å molecular sieves (1.5 g) in CH_2Cl_2 (60 mL) cooled at −23°C were sequentially added (+)-DET (0.5 mL 2.8 mmol), Ti(O*i*Pr)$_4$ (0.69 mL, 2.3 mmol) and the resulting mixture was stirred for 20 min at −23°C. After this period, a solution of (*Z*)-3-methylpent-2-en-4-yn-1-ol **10** (1.5 g, 15.6 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise. After 20 min, TBHP (10.4 mL, 3.3 M solution in benzene, 34.4 mmol) was added and the resulting mixture was kept at −23°C for 30 h. After this period, 30% aqueous NaOH (20 mL) was added and the mixture was stirred at 0°C for 1 h. The resulting suspension was filtered through Celite. The filtrate was diluted with H_2O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (30% EtOAc in hexanes) to provide compound **11** as a colorless oil (1.07 g, 61%). $[\alpha]_D^{23}=-16.5$ (*c* 0.85 $CHCl_3$); IR (film): 3396, 2982, 2359, 1444, 1381, 1017 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 3H), 2.39 (s, 1H), 2.82 (br, 1H), 3.07 (dd, 1H, $J=6.3$, 4.8 Hz), 3.76 (dd, 1H, $J=12.3$, 6.3 Hz), 3.88 (dd, 1H, $J=12.3$, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 51.2, 61.9, 63.5, 72.9, 80.4; MS (ESI) *m*/*z* 135.0 (M^++Na).

4.7. (*S*)-3-Methyl-1,3-*O*-cyclohexylidenepent-4-yne, 4

To a stirred solution of epoxide **11** (0.96 g, 8.6 mmol) in ether (20 mL) at 0°C was added $LiAlH_4$ (812 mg, 21.4 mmol). After stirring at 0°C for one hour, the reaction was quenched with 10% aqueous potassium sodium tartrate solution. The layers were separated and the aqueous layer was saturated with NaCl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (45% EtOAc in hexanes) to provide the corresponding diol as a colorless oil (0.91 g, 93%). $[\alpha]_D^{23}=-6.0$ (*c* 1.0 $CHCl_3$); IR (film): 3344, 2980, 1417, 1373, 1133, 1094, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.76 (td, 1H, $J=14.4$, 3.9 Hz), 1.93 (ddd, 1H, $J=14.4$, 9.4, 4.8 Hz), 2.46 (s, 1H), 3.83 (td, 1H, $J=11.4$, 4.8 Hz), 4.18–4.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 43.0, 59.8, 68.1, 71.6, 86.7; MS (ESI) *m*/*z* 81.0, 137.1 (M^++Na).

To a stirred solution of the above diol (730 mg, 6.4 mmol) in CH_2Cl_2 (40 mL) was added cyclohexanone dimethyl ketal (2.14 mL, 14.0 mmol) and *p*-TsOH·H_2O (121.8 mg, 0.64 mmol). The resulting mixture was stirred for 3 h and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous

layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (5% EtOAc in hexanes) to provide compound **4** as a colorless oil (944 mg, 76%). $[\alpha]_D^{23}=+10.0$ (*c* 1.0 $CHCl_3$); IR (film): 3305, 2935, 1368, 1123, 1094, 948 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32–1.37 (m, 4H), 1.45 (s, 3H), 1.48–1.55 (m, 6H), 1.64 (td, 1H, $J=13.2$, 2.2 Hz), 1.82 (dt, 1H, $J=12.9$, 5.0 Hz), 2.37 (s, 1H), 3.77 (ddd, 1H, $J=12.0$, 5.1, 1.8 Hz), 4.24 (dt, 1H, $J=12.0$, 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 22.9, 25.6, 30.7, 32.4, 37.5, 39.6, 56.7, 65.4, 71.8, 88.2, 100.0; MS (ESI) *m*/*z* 233.1 (M^++K).

4.8. (3*S*,7*S*,9*R*)-9-Benzyloxy-7-hydroxy-1,3-*O*-cyclohexylidene-3-methyldec-4-yne, 12

To a stirred solution of alkyne **4** (242 mg, 0.62 mmol) in THF (5 mL) cooled to −78°C was added *n*BuLi (0.82 mL, 1.6 M solution in hexane, 1.30 mmol) dropwise. After stirring for 20 min, $BF_3{\cdot}OEt_2$ (0.16 mL, 1.30 mmol) and (2*R*,4*S*)-4-benzyloxy-1,2-epoxypentane **3** (119 mg, 0.62 mmol) dissolved in THF (1 mL) were sequentially added. The reaction mixture was stirred at −78°C for 2 h and quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (15% EtOAc in hexanes) to provide **12** as a colorless oil (208 mg, 87%). $[\alpha]_D^{23}=-29.4$ (*c* 1.7 $CHCl_3$); IR (film): 3468, 2933, 2861, 1449, 1123, 1094, 945 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 1.06 (dd, 3H, $J=6.0$, 2.7 Hz), 1.44–1.58 (m, 4H), 1.63 (s, 3H), 1.68–1.97 (m, 10H), 2.37 (td, 1H, $J=16.4$, 7.6 Hz), 2.49 (ddd, 1H, $J=16.4$, 5.2, 1.4 Hz), 2.58 (br, 1H), 3.55–3.63 (m, 1H), 3.71–3.75 (m, 1H), 3.97–4.01 (m, 1H), 4.16 (dd, 1H, $J=11.7$, 2.2 Hz), 4.31–4.39 (m, 1H), 4.41 (d, 1H, $J=11.7$ Hz), 7.22–7.30 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6): δ 19.7, 23.3, 23.8, 26.4, 28.2, 31.7, 33.2, 38.5, 40.6, 43.5, 53.4, 57.2, 66.3, 70.4, 75.5, 81.1, 86.9, 99.8, 128.2, 128.4, 128.9, 138.8; MS (ESI) *m*/*z* 409.3 (M^++Na).

4.9. (3*S*,7*S*,9*R*)-7-Acetoxy-9-benzyloxy-1,3-*O*-cyclohexylidene-3-methyldec-4-yne, 13

To a stirred solution of alcohol **12** (122 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) were sequentially added triethylamine (0.12 mL, 0.93 mmol), acetic anhydride (74 mL, 0.78 mmol) and 4-dimethylaminopyridine (18.9 mg, 0.15 mmol). The reaction mixture was stirred for 3 h and quenched with aqueous saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (10% EtOAc in hexanes) to provide **13** as a colorless oil (125 mg, 94%). $[\alpha]_D^{23}=+13.9$ (*c* 1.8 $CHCl_3$); IR (film): 2932, 2360, 1739, 1372, 1195 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (dd, 3H, $J=6.1$, 1.1 Hz), 1.35–1.43 (m, 2H), 1.45 (s, 3H), 1.51–1.64 (m, 7H), 1.77–1.86 (m, 2H), 1.98 (s, 3H), 1.99–2.04 (m, 1H), 2.2 (br, 2H), 2.40 (dd, 1H, $J=16.9$, 5.3 Hz), 2.50 (ddd, 1H, $J=16.9$, 5.8, 3.5 Hz), 3.56–3.60 (m, 1H), 3.74–3.78 (m, 1H), 4.16–4.23 (m, 1H), 4.41 (d, 1H, $J=11.7$ Hz), 4.57 (d, 1H, $J=11.7$ Hz), 5.03–5.06 (m, 1H), 7.29–7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9, 21.5, 23.1, 23.5, 24.7, 26.0, 31.2, 33.0, 38.3, 40.2, 40.3, 57.4, 66.1, 70.0, 70.5, 72.1, 79.4, 86.8, 99.8, 127.9, 128.0, 128.7, 138.9, 170.7; MS (ESI) *m*/*z* 271.1, 451.3 (M^++Na).

4.10. (3*R*,7*S*,9*R*)-7-Acetoxy-1,3-*O*-cyclohexylidene-9-hydroxy-3-methyldecane, 14

A solution of **13** (90 mg, 0.21 mmol) in EtOAc (10 mL) containing Pd/C (18 mg) was put under a H_2 balloon. The solution was stirred for 6 h and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue oil was purified by column chromatography (35% EtOAc in hexanes) to provide the title compound as a colorless oil (68.9 mg, 96%). $[\alpha]_D^{23}=-5.3$ (*c* 1.5 $CHCl_3$); IR (film); 3454, 2934, 2859, 1735, 1246, 1107 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 1.18 (d, 3H, $J=6.0$ Hz), 1.24 (s, 3H), 1.32–1.77 (m, 18H), 1.71 (s, 3H), 1.93–1.98 (m, 2H), 3.51–3.59 (m, 1H), 3.65–3.88 (m, 2H), 5.22–5.28 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 19.2, 20.6, 23.2, 23.4, 25.8, 26.8, 30.0, 34.3, 35.1, 36.0, 38.6, 43.9, 44.1, 55.7, 65.2, 71.7, 72.1, 97.8, 170.1; MS (ESI) *m*/*z* 285.7, 365.2 (M^++Na).

4.11. (3*R*,7*S*,9*R*)-7-Acetoxy-9-*O*-*tert*-butyldimethylsilyl-1,3-*O*-cyclohexylidene-3-methyldecane, 15

To a stirred solution of **14** (64.5 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (33 mL, 0.29 mmol) and TBSOTf (50 mL, 0.23 mmol). The reaction mixture was stirred for 30 min and quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (10% EtOAc in hexanes) to provide compound **15** as a colorless oil (83 mg, 95%). $[\alpha]_D^{23}=-1.3$ (c 1.5, $CHCl_3$); IR (film): 2933, 2857, 1738, 1463, 1246, 1135, 1108 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 0.17 (s, 3H), 0.20 (s, 3H), 1.10 (s, 9H), 1.11 (d, 3H, $J=6.0$ Hz), 1.20 (s, 3H), 1.26–1.31 (m, 5H), 1.59–1.74 (m, 12H), 1.84 (s, 3H), 1.96–2.05 (m, 3H), 3.69–3.74 (m, 1H), 3.77–3.83 (m, 1H), 3.96–4.00 (m, 1H), 5.33–5.36 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ −5.3, −3.9, 14.5, 18.4, 19.6, 20.9, 23.6, 23.9, 26.2, 27.1, 30.3, 34.9, 35.7, 36.4, 39.1, 44.7, 45.2, 56.1, 66.4, 70.6, 72.1, 98.2, 170.0; MS (ESI) *m*/*z* 184.0, 341.1, 479.3 $(M+Na)^+$; HRMS (EI) *m*/*z* calcd for $C_{25}H_{48}O_5NaSi$ (M^++Na): 479.3161; found: 479.6164.

4.12. (3*R*,7*S*,9*R*)-7-Acetoxy-9-*O*-*tert*-butyldimethylsilyl-3-methyldecane-1,3-diol, 2

To a stirred solution of **15** (42 mg, 0.09 mmol) in MeOH (3 mL) was added PPTS (5.1 mg, 0.02 mmol). The reaction mixture was stirred for 15 min and

quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was purified by column chromatography (50% EtOAc in hexanes) to provide **2** as a colorless oil (33 mg, 95%). $[\alpha]_D^{23} = -3.8$ (c 1.58 $CHCl_3$); IR (film): 3380, 2955, 2930, 2860, 1740, 1460, 1375, 1250, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.15 (d, 3H, $J = 6.1$ Hz), 1.22 (s, 3H), 1.23–1.37 (m, 2H), 1.46–1.59 (m, 5H), 1.60–1.67 (m, 1H), 1.75–1.90 (m, 2H), 2.03 (s, 3H), 2.45 (s, 2H), 3.80–3.93 (m, 3H), 4.95–5.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.4, −3.9, 18.5, 20.9, 21.8, 23.8, 26.2, 27.1, 35.3, 41.8, 42.0, 44.7, 60.3, 66.0, 71.9, 74.0, 171.1; HRMS (EI) m/z calcd for $C_{19}H_{40}O_5NaSi$ (M^++Na): 399.2543; found: 399.2547.

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