FULL PAPER

Stereoselective Synthesis of (+)-Petromyroxol

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The stereoselective total synthesis of (+)-petromyroxol, isolated from the water conditioned with the larval sea lamprey has been accomplished by employing the cross-metathesis, tandem *Sharpless* asymmetric dihydroxylation/S_N2 cyclization, and regioselective ring opening of epoxide as the key steps.

Keywords: Petromyroxol, Cross-metathesis, Tandem dihydroxylation/S_N2 cyclization.

Introduction

The *Annonaceous acetogenins* exhibit a broad spectrum of biological activities, such as antitumor, antihelmic, antimalarial, antimicrobial, antiprotozoal, pesticidal, and immunosuppressant properties.[1]) Indeed, tetrahydrofuran is a core structure of acetogenins and many biologically active natural products [2] including lignans [3], polyether ionophores [4], and macrolides.[2]) Therefore, numerous strategies have been reported for the synthesis of tetrahydrofuran scaffolds.[3]) In particular, (+)- and (−)-petromyroxols (**1** and **2**) are the representative examples of acetogenin family of natural products, which were isolated recently by *Li et al.* from the water conditioned with larval sea lamprey (*Fig.*) [8]. Of these enantiomers, (+)-petromyroxol shows a strong olfactory activity.

Following our interest on total synthesis of biologically active molecules [9], we herein report a stereoselective total synthesis of (+)-petromyroxol (**1**) employing the cost-effective and readily available D-mannitol as a starting material. According to our strategy, the target molecule (**1**) could be obtained from intermediate **3**, whereas **3** could be synthesized by regioselective ring opening of epoxide **4**, which in turn could be prepared from a key intermediate **5** through sequential deprotection followed by protection and elimination protocols. Tetrahydrofuran ring **6** could be prepared by *Sharpless* asymmetric dihydroxylation of olefin **7** followed by S_N2 cyclization. The internal olefin **7** could be constructed through a cross-metathesis of homoallylic alcohol (**8**) and 5-hexen-1-ol (**9**). The homoallylic alcohol **8** could easily be prepared by *Barbier* allylation of aldehyde (**10**), which could in turn be obtained from D-mannitol using a known procedure (*Scheme 1*) [10].

Results and Discussions

As illustrated in *Scheme 1*, our strategy began from a commercially available D-mannitol. Initially, D-mannitol was converted into (*R*)-glyceraldehyde-1,2-cyclohexylidene (**10**) using a known procedure [10]. Treatment of aldehyde **10** with allyl bromide in the presence of Zn metal in aqueous media under *Luche* conditions [11] gave the *anti*-homoallylic alcohol **8** in a highly diastereoselective manner (*syn*/*anti* 5:95). The cross-metathesis of one equiv. of homoallylic alcohol **8** and two equiv. of 5-hexene-1-ol [12] (**9**) under Ar atmosphere in anhydrous CH_2Cl_2 in the presence of 5 mol-% second generation *Grubbs*' catalyst under reflux conditions gave the olefin **7** with excellent stereoselectivity (*E*/*Z* ratio of 85:15) as observed by ^{1}H-NMR spectroscopy. Selective protection of primary alcohol **7** as its TBDPS ether **11** followed by protection of secondary alcohol using $MeSO_2Cl$, Et_3N, and DMAP (cat.) in CH_2Cl_2 gave the mesylate **12**. The mesylate plays a dual role as a protecting group and a leaving group at later stage. Now the stage was set to the synthesis of *trans*-substituted tetrahydrofuran **6** through a sequential *Sharpless* asymmetric dihydroxylation and S_N2 cyclization following *Marshall*'s protocol [13]. The mesylate **12** was then subjected to *Sharpless* asymmetric dihydroxylation to yield the tetrahydrofuranol. The one-pot asymmetric dihydroxylation of **12** by AD-mix-α, followed by S_N2 cyclization led to the inversion of configuration at reacting centre with diastereomeric ratio of 9:1. Protection of the secondary

[1]) For recent reviews of *A. acetogenins*, see [1].

[2]) For previous reviews on tetrahydrofuran synthesis, see [5].

[3]) Representative acetogenins total syntheses, see [6]; previous syntheses of (+)-petromyroxol, see [7].

 DOI: 10.1002/hlca.201600064

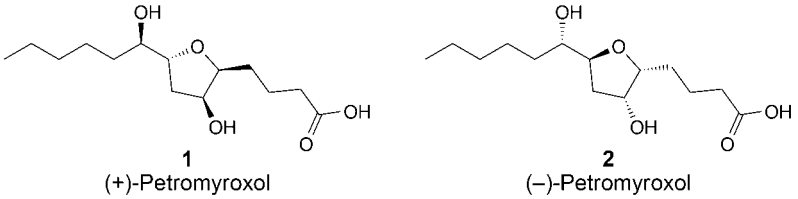
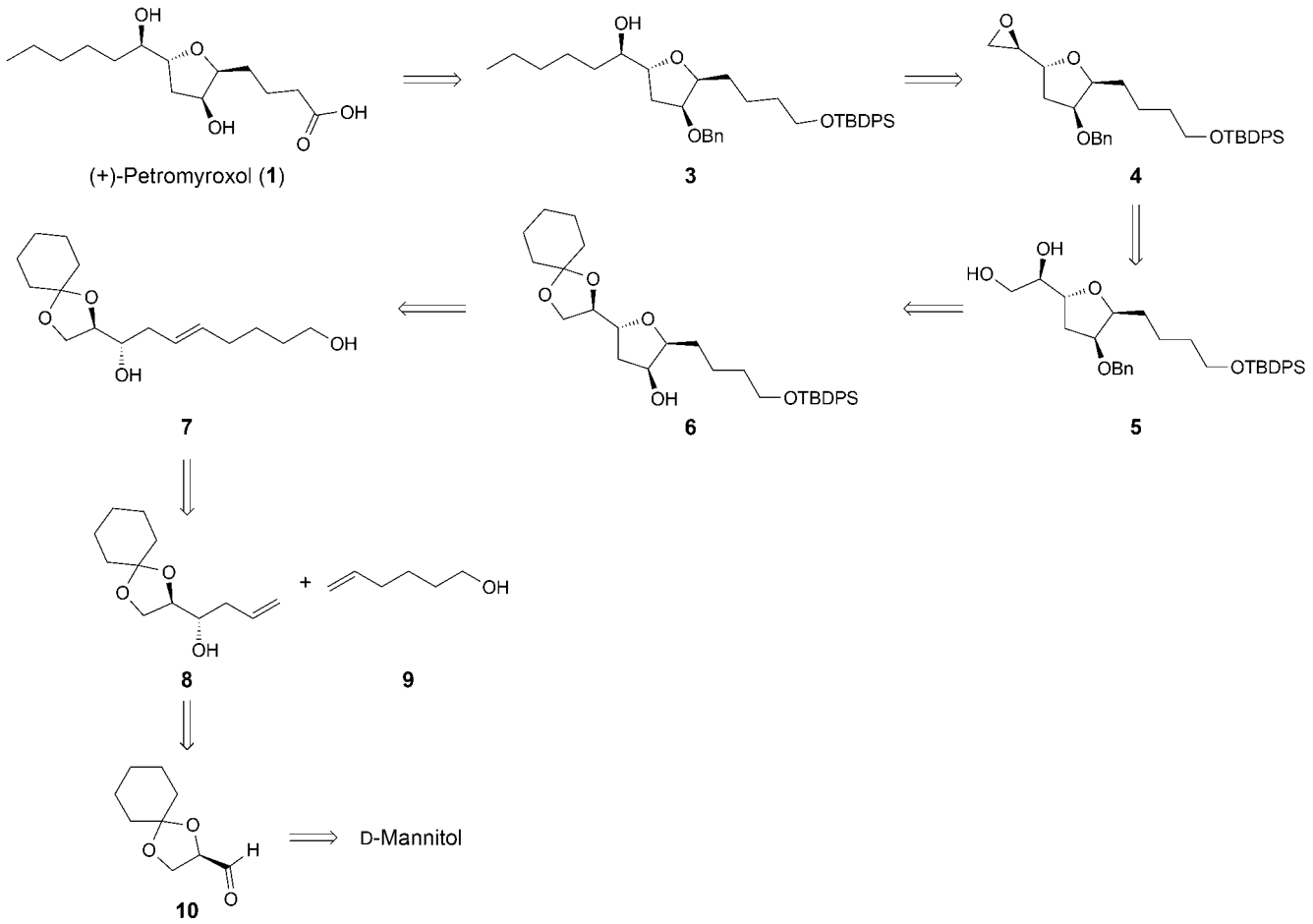


Figure. Chemical structure of (+)- and (−)-petromyroxol.

Scheme 1. Retrosynthetic analysis of (+)-petromyroxol (**1**).

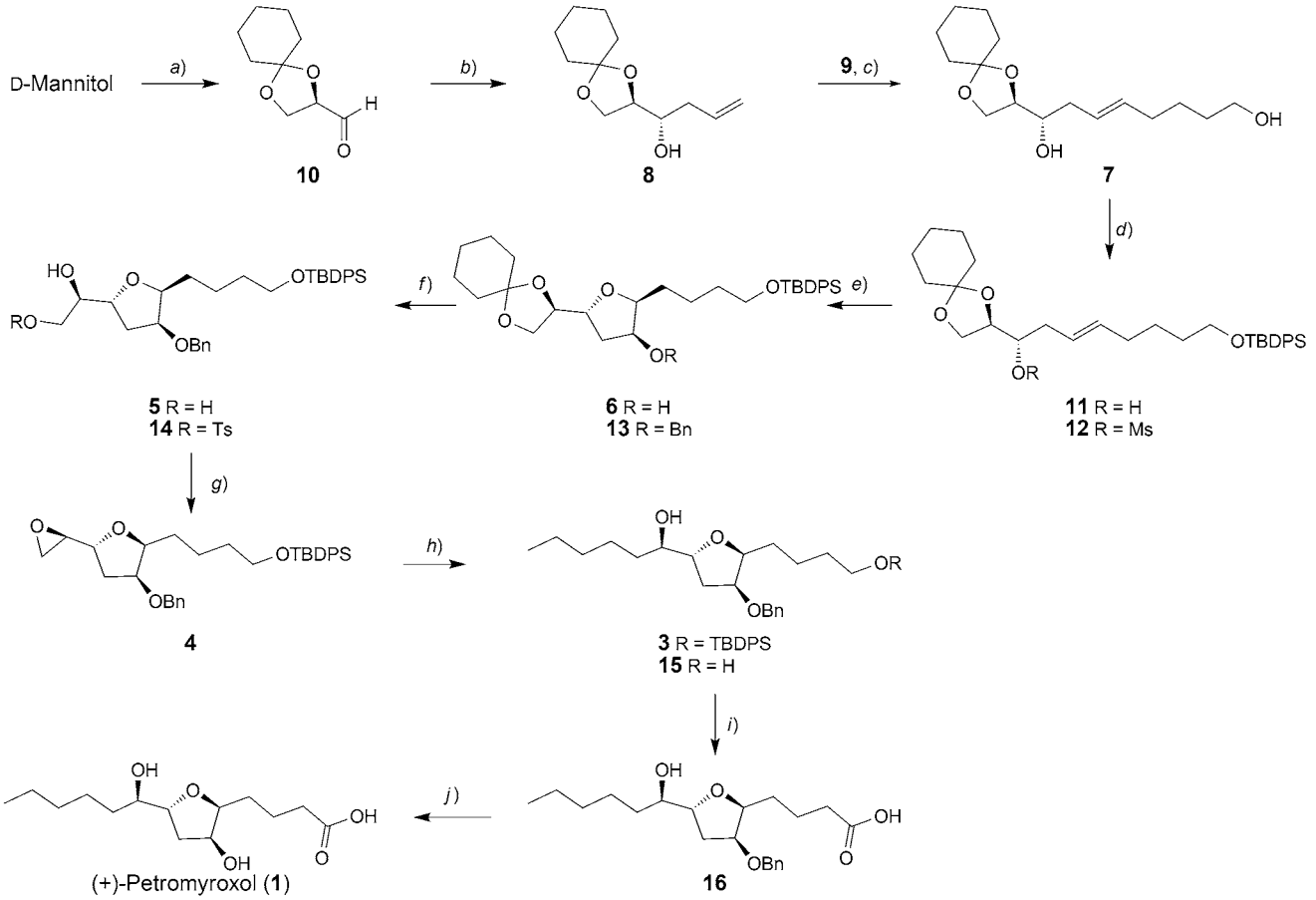


alcohol **6** using benzyl bromide in the presence of NaH gave the benzyl ether **13**. Cleavage of the cyclohexylidene group **13** under acidic conditions (80% aq. TFA) gave the diol, and subsequent tosylation of **5** using Bu_2SnO, *p*-TsCl, and Et_3N [14] afforded the tosylate **14**, which was then treated with base to give the epoxide **4**. Selective ring opening of the epoxide with a cuprate derived from BuMgBr gave the secondary alcohol **3**. Deprotection of TBDPS ether **3** with TBAF gave the primary alcohol **15**, which was then subjected to TEMPO/BAIB oxidation in CH_3CN:H_2O to afford the acid **16** in 80% yield [15]. Finally, the deprotection of benzyl group using Pd/C under H_2 atmosphere in EtOH afforded the target molecule (**1**) in 86% yield. The spectral data (^{1}H- and ^{13}C-NMR and HR-MS) of petromyroxol (**1**) was identical in all respects with those collected for the natural compound [8].

Conclusions

In conclusion, we have accomplished the total synthesis of (+)-petromyroxol in 14 steps with 8.1% overall yield. The required stereochemistry at C(5) and C(8) in (+)-petromyroxol was successfully established from readily available D-mannitol. The key reactions involved in this approach are *Grubbs* cross-metathesis, tandem *Sharpless* asymmetric dihydroxylation/S_N2 cyclization, and regioselective ring opening of epoxide.

Scheme 2. Synthesis of (+)-petromyroxol (**1**).



a) According to [11]. *b*) Zn, allyl bromide, THF, sat. NH_4Cl soln. (cat.), 6 h, 0 °C, 90%. *c*) **9**, *Grubbs*' second generation catalyst, CH_2Cl_2, 40 °C, 6 h, 85%. *d*) 1. TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 2 h, 90%; 2. MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h, 87%. *e*) 1. AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 6 h, 78%, 0 °C to r.t.; 2. NaH, BnBr, DMF, 0 °C, 6 h, 87%. *f*) 80% TFA, 0 °C, 3 h, 75%. *g*) 1. Bu_2SnO, Et_3N, TsCl, 0 °C to rt, 3 h, 90%; 2. MeONa, MeOH, 0 °C to r.t., 2 h, 76%. *h*) 1. C_4H_9Br, Mg, THF, 30 °C, then CuI, 3 h, 73%; 2. TBAF, THF, 0 °C to r.t., 2 h, 78%. *i*) TEMPO, BAIB, MeCN/H_2O (4:1), 0 °C to r.t., 2 h, 80%. *j*) 10% Pd/C, H_2, EtOH, r.t., 4 h, 86%.

V. V. B. R. thank *CSIR* for the award of fellowships.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/hlca.201600064.

Experimental Part

General

Reagents and solvents were obtained from commercial sources and dried before use. All the reactions are performed in oven dried glassware under an inert atmosphere of N_2. The reactions were monitored by thin-layer chromatography using UV light as a visualizing agent and/or by exposure to I_2 vapors and/or by spraying with *p*-anisaldehyde/H_2SO_4 reagent followed by heating at *ca.* 60 °C. Column chromatographic separations (CC) were carried out over a silica gel (SiO_2; 60 – 120 mesh) and flash chromatographic separations were carried out using 230 – 400 mesh SiO_2 using a mixture of AcOEt/hexane as eluent. Optical rotations: *Digipol-781 M6U* Polarimeter. NMR Spectra: in $CDCl_3$ on *Bruker Avance 500* NMR instrument operating at 500 MHz (^{1}H-NMR) and 150 MHz (^{13}C-NMR). Chemical shifts (δ) are quoted in parts per million (ppm) and are internally referenced (0.0 ppm for TMS for ^{1}H-NMR and 77.0 ppm for ^{13}C-NMR). Coupling constants (*J*) are quoted in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: *s* = *singlet*, *d* = *doublet*, *dd* = *doublet* of *doublet*s, *t* = *triplet*, *q* = *quartet*, *m* = *multiplet*, and br. = broad. Mass spectra were recorded on *Micromass VG-7070H* for EI and *VG Autospec M* for FAB-MS.

(1*S*,3*E*)-1-[(2*R*)-1,4-Dioxaspiro[4.5]decan-2-yl]oct-3-ene-1,8-diol (**7**). A soln. of homoallylic alcohol **8** (2.4 g, 8.4 mmol) and olefin **9** (1.4 g, 16.9 mmol) in dry CH_2Cl_2 (12 ml) was transferred to a flame-dried 10 ml two neck

round-bottom flask equipped with a condenser and a magnetic stirring bar under Ar at 45 °C. A soln. of the second generation *Grubbs*' catalyst (5 mol-%) in dry CH_2Cl_2 (1 ml) was injected *via* syringe. The mixture was stirred for 12 h at 45 °C, cooled to r.t., and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the alcohol **7** as viscous oil with 76% yield. $[\alpha]_D^{25}$ = +17.2 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 5.62 – 5.51 (*m*, 1 H); 5.50 – 5.40 (*m*, 1 H); 4.05 – 3.96 (*m*, 2 H); 3.95 – 3.87 (*m*, 1 H); 3.76 – 3.68 (*m*, 1 H); 3.67 – 3.60 (*m*, 2 H); 2.37 – 2.21 (*m*, 2 H); 2.20 – 2.02 (*m*, 3 H); 1.70 – 1.52 (*m*, 10 H); 1.51 – 1.33 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 134.1; 125.4; 109.5; 77.6; 71.1; 64.8; 62.6; 36.3; 36.1; 34.8; 32.2; 32.1; 25.3; 25.0; 23.9; 23.7. HR-ESI-MS: 307.1873 ([*M* + Na]$^+$, $C_{16}H_{28}NaO_4^+$; calc. for 307.1885).

(1*S*,3*E*)-8-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-[(2*R*)-1,4-dioxaspiro[4.5]decan-2-yl]oct-3-en-1-ol (**11**). To a stirred and cooled (0 °C) soln. of alcohol **7** (2 g, 7.04 mmol) and imidazole (0.71 g, 10.56 mmol) in CH_2Cl_2 (20 ml) was added TBDPSCl (2.12 g, 7.75 mmol) in CH_2Cl_2 (15 ml). After stirring the mixture for 2 h at r.t., it was poured into ice-cold water. The org. layer was separated and the aq. portion was extracted with CH_2Cl_2. The combined org. extracts were washed with H_2O followed by brine soln. and dried (Na_2SO_4). Removal of the solvent *in vacuo* followed by purification of the residue by CC afforded the pure compound **11** . Yield: 3.3 g (90%). $[\alpha]_D^{25}$ = +13.6 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.69 – 7.64 (*dd*, *J* = 5.1, 2.5, 4 H); 7.50 – 7.32 (*m*, 6 H); 5.57 – 5.47 (*m*, 1 H); 5.46 – 5.35 (*m*, 1 H); 4.04 – 3.95 (*m*, 2 H); 3.95 – 3.87 (*m*, 1 H); 3.76 – 3.69 (*m*, 1 H); 3.69 – 3.61 (*m*, 2 H); 2.33 – 1.95 (*m*, 5 H); 1.67 – 1.52 (*m*, 10 H); 1.50 – 1.30 (*m*, 4 H); 1.05 (*m*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 135.5; 134.4; 133.9; 129.4; 127.5; 125.1; 109.5; 77.6; 70.7; 64.8; 63.6; 36.4; 36.2; 34.8; 32.2; 32.0; 26.8; 25.5; 25.1; 23.9; 23.7; 19.2. HR-ESI-MS: 545.3047 ([*M* + Na]$^+$, $C_{32}H_{46}NaO_4Si^+$; calc. 545.3063).

(1*S*,3*E*)-8-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-[(2*R*)-1,4-dioxaspiro[4.5]decan-2-yl]oct-3-en-1-yl Methanesulfonate (**12**). To a soln. of compound **11** (2.8 g, 5.36 mmol) in dry CH_2Cl_2 were added NEt_3 (1.19 ml, 8.57 mmol) and DMAP (cat.) at 0 °C. To this mixture was added mesyl chloride (0.8 ml, 7.51 mmol) slowly with vigorous stirring for 2 h at r.t. The reaction was quenched with cold H_2O at 0 °C. The two phases were separated and the aq. phase was extracted with CH_2Cl_2. The combined org. layers were washed with H_2O, brine soln., dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product which up on chromatography provided the product **12** as a colorless liquid with 87% yield. $[\alpha]_D^{25}$ = +8.2 (*c* = 0.12, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.71– 7.63 (*dd*, *J* = 5.1, 2.5, 4 H); 7.45 – 7.35 (*m*, 6 H); 5.68 – 5.50 (*m*, 1 H); 5.45 – 5.32 (*m*, 1 H); 4.81 – 4.70 (*m*, 1 H); 4.21 – 4.14 (*m*, 1 H); 4.05 – 3.99 (*m*, 1 H); 3.91 (*dp*, *J* = 9.9, 6.6, 1 H); 3.65 (*td*, *J* = 6.3, 2.3, 2 H); 3.03 – 2.99 (*m*, 3 H); 2.49 – 2.38 (*m*, 2 H); 2.01 (*dd*, *J* = 9.0, 6.8, 2 H); 1.67 – 1.51 (*m*, 12 H); 1.48 – 1.34 (*m*, 4 H); 1.08 – 1.01 (*m*, 9 H).^{13}C-NMR (125 MHz, $CDCl_3$): 135.5; 134.0; 129.5; 127.6; 123.1; 110.2; 81.2; 75.3; 64.8; 63.7; 38.7; 36.0; 35.2; 34.7; 32.2; 32.0; 26.8; 25.4; 25.0; 23.9; 23.7; 19.2 HR-ESI-MS: 600.3010 ([*M*]$^+$, $C_{33}H_{48}O_6SSi^+$; calc. 600.2941).

(6*S*)-3,6-Anhydro-6-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-1,2-*O*-cyclohexane-1,1-diyl-4-deoxy-D-*arabino*-hexitol (**6**). To a stirred soln. of mesylate **12** (1.5 g, 2.5 mmol) in ^{t}BuOH/H_2O (1:1, 12 ml) were added AD-mix-α (3.5 g, 1.4 g mmol^{-1}) and methanesulfonamide (0.34 g, 3.76 mmol) at 0 °C and the mixture was allowed to stir for 14 h at 0 °C and stirred for another 4 h at r.t. The reaction was quenched with Na_2SO_3 soln. and stirred for 1 h at r.t. until it became colorless. AcOEt was used for extraction and the org. layer was washed with brine soln., dried (Na_2SO_4), and concentrated under reduced pressure to give the crude product which was purified by SiO_2 CC to furnish the compound **6** as colorless oil (1 g, 78%). $[\alpha]_D^{25}$ = +12.1 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.71 – 7.61 (*m*, 4 H); 7.53 – 7.29 (*m*, 6 H); 4.23 (*s*, 1 H); 4.21 – 4.15 (*m*, 1 H); 4.09 – 4.04 (*m*, 1 H); 4.02 – 3.97 (*m*, 1 H); 3.82 (*m*, 1 H); 3.79 (*t*, *J* = 7.8, 1 H); 3.67 (*t*, *J* = 6.4, 1 H); 2.10 – 1.91 (*m*, 2 H); 1.75 – 1.48 (*m*, 15 H); 1.46 – 1.37 (*m*, 2 H); 1.04 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 135.5; 134.0; 129.5; 127.6; 110.0; 83.2; 77.9; 76.5; 72.7; 65.4; 63.6; 37.5; 35.7; 35.3; 32.5; 28.5; 26.8; 25.2; 24.0; 23.9; 22.4; 19.2. HR-ESI-MS: 561.2993 ([*M* + Na]$^+$, $C_{32}H_{46}NaO_5Si^+$; calc. 561.3012).

(6*S*)-3,6-Anhydro-5-*O*-benzyl-6-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-1,2-*O*-cyclohexane-1,1-diyl-4-deoxy-D-*arabino*-hexitol (**13**). To a suspension of NaH (0.1 g, 2.6 mmol) in DMF (25 ml), a soln. of **6** (1.2 g, 2.2 mmol) in DMF (10 ml) was added at 0 °C. After the mixture was stirred at r.t. for 1 h, BnBr (0.3 ml, 2.6 mmol) was added dropwise to the mixture. The resulting mixture was stirred for 4 h at r.t. The reaction was then quenched with ice cooled H_2O, diluted with Et_2O, and washed with H_2O and brine. The org. layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 CC to give **13** (1.38 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ = −9.8 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.71 – 7.61 (*m*, 4 H); 7.46 – 7.22 (*m*, 11 H); 4.61 (*d*, *J* = 12.0, 1 H); 4.41 (*d*, *J* = 12.0, 1 H); 4.29 – 4.17 (*m*, 1 H); 4.00 – 3.92 (*m*, 1 H); 3.90 – 3.80 (*m*, 1 H); 3.74 – 3.69 (*m*, 2 H); 3.65 (*t*, *J* = 6.4, 2 H); 3.56 – 3.49 (*m*, 1 H); 2.57 (*s*, 1 H); 2.25 – 1.90 (*m*, 2 H); 1.77 – 1.53 (*m*, 4 H); 1.04 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.2; 135.5; 134.0; 129.5; 128.3; 127.6; 127.3; 110.1; 83.3; 79.2; 78.8; 72.5; 71.2; 65.0; 63.8; 33.6; 32.7; 28.8; 26.8; 22.6; 19.2. HR-ESI-MS: 651.3480 ([*M* + Na]$^+$, $C_{39}H_{52}NaO_5Si^+$; calc. 651.3482).

(6*S*)-3,6-Anhydro-5-*O*-benzyl-6-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-4-deoxy-D-*arabino*-hexitol (**5**). Compound **13** (1.0 g, 1.86 mmol) was mixed with 80% aq. TFA (8 ml) and stirred for 2.5 h at 0 °C, and diluted with CH_2Cl_2 and H_2O. The org. layer was separated and the aq. layer was extracted with CH_2Cl_2, and the combined

org. layers were washed successively with aq. 20% $NaHCO_3$, H_2O, and brine soln. and dried (Na_2SO_4). Removal of the solvent *in vacuo* followed by purification using CC furnished the pure compound **5** with yield 75% as a thick liquid. $[\alpha]_D^{25}$ = +4.2 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.71 – 7.61 (*m*, 4 H); 7.46 – 7.22 (*m*, 11 H); 4.61 (*d*, *J* = 12.0, 1 H); 4.41 (*d*, *J* = 12.0, 1 H); 4.29 – 4.17 (*m*, 1 H); 4.00 – 3.92 (*m*, 1 H); 3.90 – 3.80 (*m*, 1 H); 3.74 – 3.69 (*m*, 2 H); 3.65 (*t*, *J* = 6.4, 2 H); 3.56 – 3.49 (*m*, 1 H); 2.57 (*s*, 1 H); 2.25 – 1.90 (*m*, 2 H); 1.77 – 1.53 (*m*, 4 H); 1.49 – 1.20 (*m*, 3 H); 1.04 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.2; 135.5; 134.0; 129.5; 128.3; 127.6; 127.5; 83.3; 79.2; 78.8; 72.5; 71.2; 65.0; 63.8; 33.6; 32.7; 28.8; 26.9; 22.6; 19.2. HR-ESI-MS: 571.2837 ($[M + Na]^+$, $C_{33}H_{44}NaO_5Si^+$; calc. 571.2856).

(6*S*)-1,2:3,6-Dianhydro-5-*O*-benzyl-6-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-4-deoxy-D-*arabino*-hexitol *via* **(6*S*)-3,6-Anhydro-5-*O*-benzyl-6-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-4-deoxy-1-*O*-[(4-methylphenyl)sulfonyl]-D-*arabino*-hexitol** (**14**). To a soln. of diol **5** (0.85 g, 1.55 mmol) in dry CH_2Cl_2 (30 ml) were added Bu_2SnO (15 mol-%) and Et_3N (0.3 ml, 2.33 mmol) at 0 °C. The mixture was allowed to stir for 30 min at 0 °C, and TsCl (0.35 g, 1.86 mmol) was added. After 2.5 h, the reaction was quenched with cold H_2O at 0 °C. The two phases were separated and the aq. phase was extracted with CH_2Cl_2. The combined org. layers were washed with H_2O, brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product, which was purified by SiO_2 CC to afford the tosylate **14** as colorless oil (0.8 g, 90%). To a stirred soln. of the above tosylate **14** in dry MeOH (14 ml) was added a soln. of MeONa (3 mmol) in MeOH (2 ml) at 0 °C, and the mixture was stirred for 1 h at the same temp. and then for 2 h at r.t. The mixture was quenched with H_2O and extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4), concentrated under reduced pressure, and purified by SiO_2 chromatography to afford the epoxide **4**. $[\alpha]_D^{25}$ = +16.7 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.71 – 7.62 (*m*, 4 H); 7.51 – 7.18 (*m*, 11 H); 4.60 (*d*, *J* = 12.1, 1 H); 4.42 (*d*, *J* = 12.0, 1 H); 4.20 – 4.08 (*m*, 1 H); 4.01 – 3.94 (*m*, 1 H); 3.87 – 3.79 (*m*, 1 H); 3.64 (*t*, *J* = 6.5, 2 H); 3.03 – 2.95 (*m*, 1 H); 2.82 – 2.74 (*m*, 2 H); 2.31 – 2.21 (*m*, 1 H); 2.01 – 1.89 (*m*, 1 H); 1.72 – 1.53 (*m*, 4 H); 1.52 – 1.22 (*m*, 3 H); 1.04 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.3; 135.5; 134.1; 129.5; 128.3; 127.6; 127.4; 83.0; 79.2; 75.4; 71.2; 63.9; 54.3; 44.7; 34.5; 32.7; 28.8; 26.9; 22.6; 19.2. HR-ESI-MS: 531.2916 ($[M + H]^+$, $C_{33}H_{43}O_4Si^+$; calc. 531.2925).

(1*R*)-1-[(2*R*,4*S*,5*S*)-4-(Benzyloxy)-5-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)oxolan-2-yl]hexan-1-ol (**3**). To a stirred soln. of epoxide **4** (0.55 g, 1.21 mmol) in 5 ml of THF was added a catalytic of CuI under Ar atmosphere. The mixture was cooled to −30 °C, and a soln. of 1.8 ml (1.35 mol) of BuMgBr was added slowly under vigorous stirring. The mixture was allowed to warm to r.t. After stirring for 1.5 h, the reaction was quenched with a sat. NH_4Cl and extracted with AcOEt. The combined org. extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford the compound **3** with 73% yield as a clear liquid. $[\alpha]_D^{25}$ = +6.8 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.77 – 7.61 (*m*, 4 H); 7.46 – 7.35 (*m*, 6 H); 7.35 – 7.25 (*m*, 5 H); 4.62 (*d*, *J* = 12.0, 1 H); 4.42 (*d*, *J* = 12.0, 1 H); 4.06 – 3.93 (*m*, 2 H); 3.84 – 3.78 (*m*, 1 H); 3.71 – 3.63 (*m*, 2 H); 3.42 – 3.35 (*m*, 1 H); 2.27 (*d*, *J* = 4.7, 1 H); 2.18 – 2.12 (*m*, 1 H); 1.80 – 1.65 (*m*, 2 H); 1.65 – 1.57 (*m*, 3 H); 1.56 – 1.23 (*m*, 10 H); 1.05 (*d*, J = 2.3, 9 H); 0.94 – 0.87 (*m*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.3; 135.5; 134.1; 129.5; 128.3; 127.6; 127.5; 82.2; 80.2; 79.7; 74.0; 71.1; 63.9; 34.0; 33.5; 32.7; 31.9; 28.8; 26.9; 25.3; 22.6; 19.2; 14.1. HR-ESI-MS: 588.3520 ($[M]^+$, $C_{37}H_{52}O_4Si^+$; calc. 588.3635).

(1*R*)-1-[(2*R*,4*S*,5*S*)-4-(Benzyloxy)-5-(4-hydroxybutyl)oxolan-2-yl]hexan-1-ol (**15**). To a stirred soln. of **3** (0.5 g, 0.8 mmol) in THF (25 ml) was added TBAF (1.3 ml, 1.0M in THF, 1.2 mmol) slowly at 0 °C. After the mixture was maintained for 40 min at 0 °C, it was poured into H_2O and extracted with AcOEt. The combined org. phases were washed with H_2O and brine consecutively, dried (Na_2SO_4), and concentrated. The crude product was purified by SiO_2 chromatography to give **15** (0.26 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ = +12 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.37 – 7.26 (*m*, 5 H); 4.62 (*d*, *J* = 12.0, 1 H); 4.42 (*d*, *J* = 12.0, 1 H); 4.06 – 3.93 (*m*, 2 H); 3.84 – 3.78 (*m*, 1 H); 3.71 – 3.63 (*m*, 2 H); 3.42 – 3.35 (*m*, 1 H); 2.27 (*d*, *J* = 4.7, 1 H); 2.18 – 2.12 (*m*, 1 H); 1.80 – 1.65 (*m*, 2 H); 1.65 – 1.57 (*m*, 3 H); 1.56 – 1.23 (*m*, 10 H); 0.94 – 0.87 (*m*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.3; 128.3; 127.6; 127.5; 82.3; 80.2; 79.7; 74.0; 71.1; 63.9; 34.0; 33.5; 32.7; 31.8; 28.7; 25.3; 22.6; 14.2. HR-ESI-MS: 373.2452 ($[M + Na]^+$, $C_{21}H_{34}NaO_4^+$; calc. 373.2355).

4-{(2*S*,3*S*,5*R*)-3-(Benzyloxy)-5-[(1*R*)-1-hydroxyhexyl]oxolan-2-yl}butanoic Acid (**16**). The oily residue **15** was dissolved in CH_3CN and H_2O (4:1 *v*/*v*) mixture and then treated with a soln. of BAIB (2.5 equiv.) and TEMPO (0.1 equiv.). The mixture was stirred for 5 h and quenched with a sat. soln. of $Na_2S_2O_3$. The biphasic system was extracted several times with CH_2Cl_2 and the combined org. phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 CC the residue to furnish the pure compound **16** with 80% as a liquid. $[\alpha]_D^{25}$ = −8.2 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.39 – 7.16 (*m*, 5 H); 4.58 (*d*, *J* = 12.1, 1 H); 4.42 – 4.33 (*d*, *J* = 12.1, 1 H); 4.01– 3.93 (*m*, 2 H); 3.85 – 3.79 (*m*, 1 H); 3.38 – 3.32 (*m*, 1 H); 2.40 – 2.27 (*m*, 2 H); 2.15 – 2.07 (*m*, 1 H); 1.77 – 1.56 (*m*, 5 H); 1.52 – 1.17 (*m*, 9 H); 0.84 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.5; 138.2; 128.4; 127.7; 127.5; 81.9; 80.4; 79.7; 74.0; 71.1; 33.9; 33.9; 33.4; 31.9; 28.5; 25.3; 22.6; 21.6; 14.1. HR-ESI-MS: 387.2138 ($[M + Na]^+$, $C_{21}H_{32}NaO_5^+$; calc. 387.2147).

4-{(2*S*,3*S*,5*R*)-3-Hydroxy-5-[(1*R*)-1-hydroxyhexyl]oxolan-2-yl}butanoic Acid (**1**). A soln. of **16** (100 mg, 0.29 mmol)

in EtOH (3 ml) was treated with Pd/C (10 mol-%, 15 mg) and the reaction vessel was thoroughly evacuated by H_2. The suspension was vigorously stirred under H_2 (1 atm) for 10 h then carefully filtered through *Celite*, then washed with EtOH (2 × 20 ml), and concentrated *in vacuo*. The residue was purified by SiO_2 CC (SiO_2, 8% MeOH/CH_2Cl_2) to furnish the target molecule **1** in 86% as a liquid. $[\alpha]_D^{25}$ = +10.8 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.36 – 4.11 (*m*, 1 H); 3.99 (*ddd*, *J* = 9.0, 6.9, 6.5, 1 H); 3.82 – 3.56 (*m*, 1 H); 3.46 – 3.16 (*m*, 1 H); 2.44 – 2.22 (*m*, 2 H); 1.97 (*m*, 1 H); 1.89 – 1.74 (*m*, 1 H); 1.72 – 1.52 (*m*, 5 H); 1.51 – 1.39 (*m*, 3 H); 1.39 – 1.11 (*m*, 7 H); 0.82 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 177.7; 82.3; 80.5; 74.1; 73.2; 37.5; 33.6; 33.0; 31.8; 28.1; 25.2; 22.5; 21.2; 14.0. HR-ESI-MS: 297.1665 ([*M* + Na]$^+$, $C_{14}H_{26}NaO_5^+$; calc. 297.1678).

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Received March 10, 2016
Accepted May 11, 2016

