A Convenient Route to Alkaloid Lipids: Application for the Synthesis of a *Leptophylline A* Analogue

Sofia D. Koulocheri,[a] Emmanuel N. Pitsinos,[b] Serkos A. Haroutounian*[a]

[a] Chemistry Laboratory, Agricultural University of Athens, Iera Odos 75, Athens 11855, Greece
Fax +30(1)5294265; E-mail: sehar@aua.gr

[b] Laboratory of Organic and Bioorganic Chemistry, Institute of Physical Chemistry, NCSR "Demokritos", P.O. Box 60228, Athens 15310, Greece

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Abstract: A synthetic route for efficient access to alkaloid lipids, using the chiral 2,3,6-trisubstituted piperidine acetaldehyde **9** as an intermediate, is reported. The utility of the synthetic route was demonstrated in the asymmetric synthesis of an unnatural analogue of *Cassia leptophylla* alkaloid lipid, *leptophyllin A*, in 16 steps and 15% overall yield starting from D-glucal.

Key words: piperidines, alkaloids, asymmetric synthesis

Alkaloid lipids are natural compounds isolated from the leaves, stems and roots of various *Prosopis*, and *Cassia* species.[1] Their structural framework consists of a polar head group (a 2,6-disubstituted-3-piperidinol) and a lipid tail group (Figure 1, compounds **1**–**7**). Besides their unique structural features, these compounds and their synthetic analogues were also found to possess a wide range of antibiotic, anesthetic and CNS stimulating properties.[2] Consequently, they have attracted increasing scientific interest.[3] Intense research activity directed towards the efficient and stereoselective synthesis of these compounds and their derivatives has been initiated, producing a large number of biologically active compounds.[4]

Recently, bioassay-guided fractionation of a bioactive leaf extract of the Brazilian legume *Cassia leptophylla*[5] led to the isolation and structure elucidation of three new alkaloid lipids named *leptophylline B* (**5**), *leptophylline A* (**6**), and *3-acetylleptophylline* (**7**). These new structures represent the first example of alkaloid lipids that display significant anticancer activity[5] and differ from other *Prosopis* and *Cassia* alkaloid lipids in the length and unusual dihydroxy functionality of their aliphatic side chains.

As part of our ongoing studies on the asymmetric synthesis of biologically interesting piperidine alkaloid derivatives,[6] these intriguing molecules have attracted our attention. Aiming to develop a general synthetic route for the preparation of such compounds, our retrosynthetic strategy envisioned the use of the chiral 2,6-disubstituted-piperidin-3-ol **9** as a key intermediate (Scheme 1). This molecule has the desired all *cis*-configuration and an acetaldehyde functionality on carbon atom C-6 that allows for the facile attachment of various lipid side chains. Furthermore, this compound is easily obtained by diastereoselective transformation of the corresponding 6-hydroxy-2*S*-hydroxymethyl-dihydropyridone **10**, which can be prepared efficiently from the readily available D-glucal according to our recently reported synthetic route.[7]

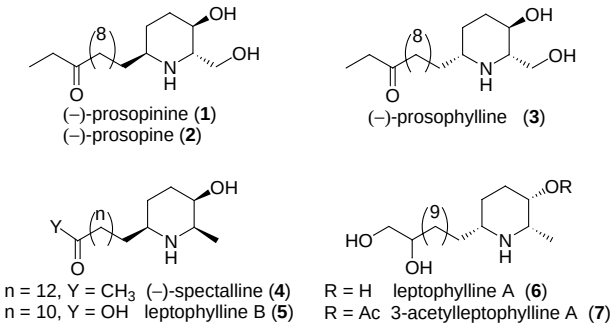
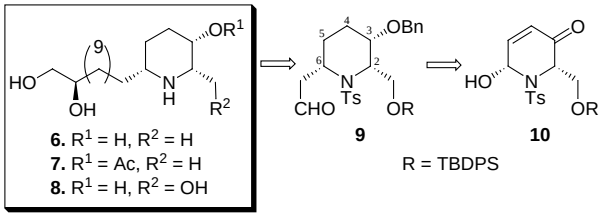
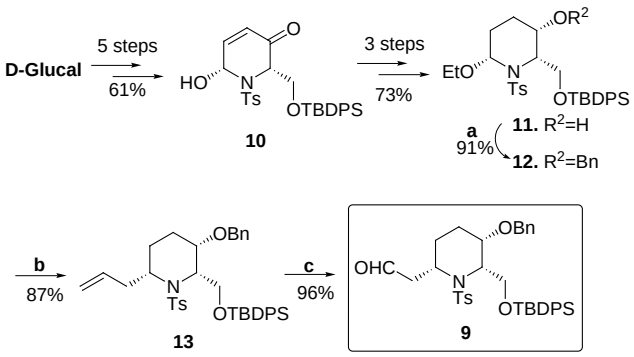


Figure 1



Scheme 1



Scheme 2 *Reagents and conditions*: (a) NaH, BnBr, Bu_4NI, THF; (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C; (c) i. $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_2$, $CH_3SO_2NH_2$, *t*-BuOH−H_2O (1:1), ii. $NaIO_4$, H_2O−EtOH (1:1).

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The synthesis of compound **9** was accomplished as depicted in Scheme 2. Enantioselective transformation of D-glucal to the trisubstituted piperidine **11** was achieved by an 8-step synthetic sequence in high yield, via the intermediate 6-hydroxy-2*S*-hydroxymethyl-dihydropyridone **10**.[7] Protection of the hydroxyl group and reaction with allyltrimethylsilane in the presence of a catalytic amount of titanium tetrachloride at −78 °C resulted in the exclusive formation of the all *cis*-diastereomer of 6-allyl-piperidine **13**. The diastereoselectivity of this transformation can be rationalised, assuming an *N*-acyliminum ion intermediate (Figure 2).[8] The strong $A^{(1,2)}$ strain between the *tert*-butyldiphenyl-silyloxymethyl group on carbon atom C-2 and the *N*-tosyl group favors conformer **II** over conformer **I**. Exclusive formation of the 2,6-*cis*-isomer was revealed by HPLC and ^{1}H NMR analysis and could be attributed to the stereoelectronically preferred axial attack by the silane nucleophile on **II**.[8]

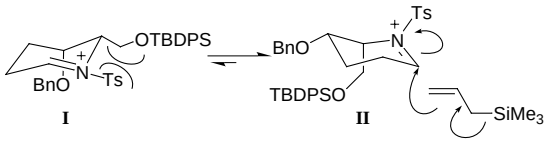


Figure 2

The stereochemistry of carbon atom C-6 in aldehyde **9** was assigned on the basis of 2D COSY and NOESY NMR spectroscopic studies. The aldehyde **9** was obtained in excellent yield after dihydroxylation and subsequent periodate cleavage of olefin **13**. Thus, the strong NOE correlation among the CH_2 protons of acetaldehyde, H-5_{eq} and the methylenic protons of the silyloxymethyl group are indicative of the α-axial orientation of the acetaldehyde moiety at carbon atom C-6 (Figure 3). Furthermore, the small coupling constants observed between H-6 and the two protons H-5 are consistent with the β-equatorial orientation of H-6, reinforcing the previous assignment.

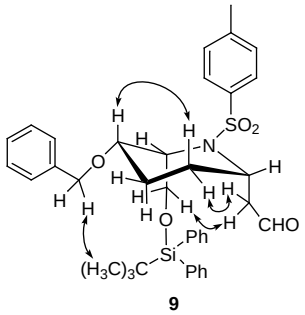
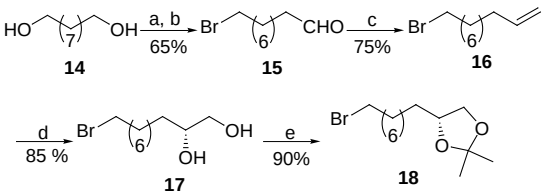


Figure 3

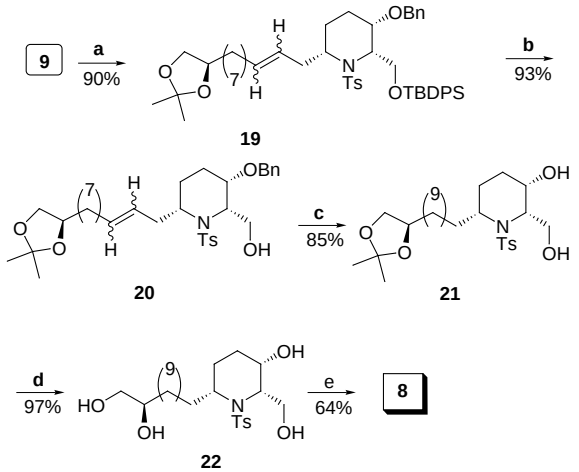
The all *cis* aldehyde **9** was envisioned to be the key intermediate for the preparation of a broad variety of natural and unnatural alkaloid lipids.[9] To demonstrate the synthetic utility and versatility of this aldehyde, we targeted the novel chimeric alkaloid lipid analog **8** (Scheme 1). This compound would combine in a single molecule, the aliphatic side of *leptophylline A* with the polar head group of *Prosopis* alkaloids. To this end, the chiral aliphatic substrate **18** was derived from the readily available 1,9-nonandiol, according to the reaction sequence outlined in Scheme 3. The 1,9-nonandiol **14** was transformed to the corresponding bromoalcohol and oxidized to aldehyde **15**. Subsequent Wittig olefination afforded the bromo-alkene **16**. Asymmetric dihydroxylation and subsequent acetalization provided the desired substrate **18** in very good chemical yield (85%) with 80% ee.



Scheme 3 Reagents and conditions: (a) HBr, $PhCH_3$; (b) PCC, CH_2Cl_2; (c) CH_3PPh_3Br, *n*-BuLi, THF; (d) $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, $K_2OsO_2(OH)_2$, K_2CO_3, *t*-BuOH−H_2O (1:1); (e) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, acetone.

Introduction of the aliphatic side chain onto the piperidine ring was performed via Wittig reaction of aldehyde **9** with the enantiomerically enriched triphenylphosphonium ylide. This ylide was derived from bromide **18**, furnishing the corresponding alkene **19**, which was purified by chromatography and selective crystallization.

Subsequent sequential removal of the silyl protective group, catalytic hydrogenation-hydrogenolysis and cleavage of the acetonide and tosyl protective groups provided the desired synthetic alkaloid lipid **8** in 16 steps and 15% overall yield (from D-Glucal).



Scheme 4 Reagents and conditions: (a) PPh_3, **18**, *n*-BuLi; (b) TBAF, THF; (c) H_2, Pd/C, MeOH; (d) HCl, EtOH; (e) Na, naphthalene, DME.

In conclusion, we have described the efficient and stereoselective preparation of the all *cis*-aldehyde **9**, a useful and versatile intermediate for the synthesis of alkaloid lipids. In addition, the convenient preparation of a novel alkaloid

lipid analog, incorporating in a single molecule the aliphatic tail chain of *leptophylline A* and the polar head group of a *Prosopis* alkaloid, is presented. The described approach is highly convergent and is generally applicable since the side chain at carbon atom C-6 can be easily modified to provide access to a broad variety of natural and synthetic alkaloid lipids of structural and biological importance.

All reactions were carried out under an argon atmosphere unless otherwise noted. Solvents were distilled prior to use. THF was distilled from sodium-benzophenone, and CH_2Cl_2 was distilled over CaH_2 immediately prior to use. Starting materials and reagents were purchased from Aldrich (analytical reagent grades) and used without further purification. The (2*S*,3*S*,6*R*)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-ethoxy-1-tosylpiperidin-3-ol (**11**) ($[\alpha]_D^{22}$ = +60.4 (*c* 0.90, MeOH); mp 111–112 °C) was prepared according to literature procedure.[7] Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna 750, series II spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AM-250 or DRX-400 spectrometers (250 MHz and 400 MHz, respectively) using TMS as internal standard. Optical rotations were measured with a Perkin−Elmer 241 polarimeter at ambient temperature. Elemental analyses were provided by the University of Illinois microanalytical service laboratory. HPLC separations were performed using a Hewlett Packard 1100 series instrument with a variable wavelength UV detector and coupled to HP Chem-Station utilizing the manufacturer's 5.01 software package. TLC was conducted on Merck glass plates coated with silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM).

(2*S*, 3*S*, 6*R*)-3-Benzyloxy-2-(*tert*-butyl-diphenyl-silyloxymethyl)-6-ethoxy-1-tosyl piperidine (12)

To an ice-cold stirred soln of compound **11** (2.5 g, 4.4 mmol) in anhyd THF (7 mL), NaH was added in small quantities (126 mg, 5.28 mmol). The reaction mixture was allowed to reach r.t. and stirred for 30 min. A catalytic amount of Bu_4NI (80 mg, 0.22 mmol) was added followed by addition of BnBr (0.74 mL, 6.61 mmol). After stirring for 2 h, the reaction was quenched with sat. aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a yellowish slurry which was purified by chromatography (EtOAc−hexane, 1:4; R_f = 0.55) to provide **12** in pure white crystalline form. Yield: 2.1 g (91%).

$[\alpha]_D^{22}$ = +59.06 (*c* 1.06, EtOAc); mp 75–77 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.1 Hz, 3 H, C<u>H</u>$_3$CH$_2$O), 1.09 (s, 9 H, C-CH$_3$), 1.15–1.27 (m, 1 H, H-4), 1.41–1.51 (m, 1 H, H-4), 1.66–1.83 (m, 2 H, H-5), 2.34 (s, 3 H, ArCH$_3$), 2.91–3.00 (m, 1 H, H-3), 3.42 (dq, *J* = 9.5, 7.1 Hz, 1 H, OC<u>H</u>HCH$_3$), 3.90 (dq, *J* = 9.5, 7.1 Hz, 1 H, OCH<u>H</u>CH$_3$), 3.96 (dd, *J* = 11.2, 5.0 Hz, 1 H, C<u>H</u>HOTBDPS), 4.01 (d, *J* = 12.2 Hz, 1 H, C<u>H</u>HPh), 4.06–4.16 (dd, *J* = 11.2, 10.1 Hz, 1 H, CH<u>H</u>OTBDPS), 4.21 (d, *J* = 12.2 Hz, 1 H, CH<u>H</u>Ph), 4.35 (m, 1 H, H-2), 5.07 (d, *J* = 3.3 Hz, 1 H, H-6), 7.03 (dd, *J* = 7.5, 1.6 Hz, 2 H, ArH), 7.10 (d, *J* = 8.3 Hz, 2 H, ArH), 7.21–7.28 (m, 3 H, ArH), 7.34–7.43 (m, 6 H, ArH), 7.56 (d, *J* = 7.9 Hz, 2 H, ArH), 7.70 (dd, *J* = 7.5, 1.6 Hz, 2 H, ArH), 7.82 (dd, *J* = 7.5, 1.6 Hz, 2 H, ArH).

Anal. Calcd for $C_{38}H_{47}NO_5SSi$ (657.9): C, 69.37; H, 7.20; N, 2.13. Found: C, 69.22; H, 7.10; N, 2.22.

(2*S*, 3*S*, 6*R*)-6-Allyl-3-benzyloxy-2-(*tert*-butyl-diphenyl-silyloxymethyl)-1-tosyl piperidine (13)

To a stirred soln of $TiCl_4$ (45 μL, 0.41 mmol) in anhyd CH_2Cl_2 (1 mL) at –78 °C, a soln of **12** (256 mg, 0.39 mmol) and allyltrimethylsilane (0.12 mL, 0.75 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise over a 5 min period. The soln was allowed to gradually warm to 0 °C and stirred for a total period of 90 min. Then the reaction was quenched with H_2O (2 mL) and the aq layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc−hexane, 1:4; R_f = 0.57) to give **13** as white crystals. Yield: 222 mg (87%).

$[\alpha]_D^{22}$ = +20 (*c* 0.5, EtOAc); mp 90–92 °C.

IR: 1640 cm^{-1} (CH=CH$_2$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H, CCH$_3$), 1.14–1.29 (m, 1 H, H-5), 1.45–1.62 (m, 3 H, H-4, H-5), 2.20–2.25 (m, 1 H, C<u>H</u>HCH=CH$_2$), 2.37 (s, 3 H, ArCH$_3$), 2.43 (dt, *J* = 13.6, 5.3 Hz, 1 H, CH<u>H</u>CH=CH$_2$), 3.25 (ddd, *J* = 11.5, 5.3 Hz, 1 H, H-3), 3.73–3.82 (m, 1 H, H-6), 3.83 (dd, *J* = 11.2, 7.9 Hz, 1 H, C<u>H</u>HOTBDPS), 4.00 (dd, *J* = 11.2, 5.3 Hz, 1 H, CH<u>H</u>OTBDPS), 4.31 (d, *J* = 11.8 Hz, 1 H, C<u>H</u>HPh), 4.43 (d, *J* = 11.8 Hz, 1 H, CH<u>H</u>Ph), 4.62 (dt, *J* = 7.9, 5.3 Hz, 1 H, H-2), 4.87 (d, *J* = 17.1 Hz, 1 H, CHCH=C<u>H</u>H), 4.94 (d, *J* = 10.1 Hz, 1 H, CHCH=CH<u>H</u>), 5.60–5.75 (m, 1 H, CHC<u>H</u>=CH$_2$), 7.09–7.18 (m, 3 H, ArH), 7.27–7.32 (m, 4 H, ArH), 7.34–7.45 (m, 6 H, ArH), 7.65 (d, *J* = 7,9 Hz, 2 H, ArH), 7.72 (dd, *J* = 7.9, 1.3 Hz, 2 H, ArH), 7.78 (dd, *J* = 7.9, 1.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{39}H_{47}NO_4SSi$ (653.95): C, 71.63; H,7.24; N, 2.14. Found: C, 71.50; H, 7.31; N, 2.11.

(2*S*, 3*S*, 6*R*)-[5-Benzyloxy-6-(*tert*-butyl-diphenyl-silyloxymethyl)-1-tosylpiperidin-2-yl]-acetaldehyde (9)

A soln of $K_3Fe(CN)_6$ (181 mg, 0.549 mmol) and K_2CO_3 (75 mg, 0.549 mmol) in *t*-BuOH–H_2O (1:1, 1.6 mL) was stirred for 15 min. Then, $K_2OsO_2(OH)_2$ (0.66 mg, 0.0018 mmol) was added and stirring was continued for additional 15 min. The mixture was cooled to 0 °C and $CH_3SO_2NH_2$ (32 mg, 0.336 mmol) and 6-allyl-piperidine **13** (120 mg, 0.183 mmol) were added at once. The heterogeneous slurry was allowed to reach r.t. and stirred vigorously for 1 h. The reaction was quenched by addition of Na_2SO_3 (70 mg, 0.55 mmol) and stirred for an additional 30 min. Then the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oil obtained was purified by chromatography (EtOAc−hexanes, 1:2) and the resulting dihydroxy intermediate was dissolved in THF–H_2O (1:1, 5 mL). $NaIO_4$ (39 mg, 0.183 mmol) was added and after stirring for 30 min the reaction mixture was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc−hexane, 1:4, R_f = 0.22) to furnish aldehyde **9** as white crystals. Yield: 115 mg (96%).

$[\alpha]_D^{22}$ = +30 (*c* 0.3, EtOAc); mp 159–161 °C.

IR: 1724 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H, CCH$_3$), 1.17–1.33 (m, 1 H, H-5$_{ax}$), 1.34–1.45 (m, 1 H, H-5$_{eq}$), 1.47–1.78 (m, 2 H, H-4), 2.34 (s, 3 H, ArCH$_3$), 2.68 (dd, *J* = 17.8, 9.5 Hz, 1 H, C<u>H</u>HCHO), 2.91 (dd, *J* = 17.8, 4.1 Hz, 1 H, CH<u>H</u>CHO), 3.24 (m, 1 H, H-3), 3.82 (dd, *J* = 11.2, 9.5 Hz, 1 H, C<u>H</u>HOTBDPS), 3.97 (dd, *J* = 11.2, 5.4 Hz, 1 H, CH<u>H</u>OTBDPS), 4.24 (d, *J* = 12.0 Hz, 1 H, C<u>H</u>HPh), 4.29–4.39 (m, 1 H, H-6), 4.35 (d, *J* = 12.0 Hz, 1 H, CH<u>H</u>Ph), 4.57 (dt, *J* = 9.4, 5.4 Hz, 1 H, H-2), 7.07–7.14 (m, 2 H, ArH), 7.15 (d, *J* = 8.3 Hz, 2 H, ArH), 7.26–7.33 (m, 3 H, ArH), 7.35–7.48 (m, 6 H, ArH), 7.60 (d, *J* = 8.3 Hz, 2 H, ArH), 7.73 (dd, *J* = 9.5, 5.4 Hz, 2 H, ArH), 7.78 (dd, *J* = 9.5, 5.4 Hz, 2 H, ArH), 9.64 (s, 1 H, CHO).

Anal. Calcd for $C_{38}H_{45}NO_5SSi$ (655.9): C, 69.58; H, 6.92; N, 2.14. Found: C, 69.38; H, 7.01; N, 2.10.

9-Bromo-nonanal (15)

A soln of 1,9-nonandiol (8 g, 50 mmol) and 48% HBr (6 mL) in benzene (100 mL) was refluxed for 24 h in a Dean Stark apparatus. The resulting soln was washed successively with NaOH (6 N, 50 mL), HCl (10%, 50 mL) and H_2O (2 × 150 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to a colorless oil which was purified by chromatography (Et_2O–hexane, 1:4) to yield **15** (7.8 g). The latter was dissolved in CH_2Cl_2 (75 mL) and PCC (16.2 g, 75 mmol) was added. After 30 min of stirring, the supernated was decanted and filtered through a short pad of silica gel. The insoluble residue remaining in the reaction vessel was washed several times with Et_2O and the combined washings were passed through the same silica gel pad. The combined filtrates were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was further purified by flash chromatography (EtOAc–hexane, 1:9; R_f = 0.58). Yield: 7.18 g (65%).

IR (KBr): 1720 cm^{-1} (C=O), 2923, 2855, 1462 (CH_2).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.23–1.45 (m, 8 H, CH_2), 1.51–1.71 (m, 2 H, $C\underline{H}_2CH_2CHO$), 1.84 (dt, *J* = 13.4, 6.7 Hz, 2 H, $C\underline{H}_2CH_2Br$), 2.42 (td, *J* = 7.5, 2.0 Hz, 2 H, $C\underline{H}_2CHO$) 3.40 (t, *J* = 6.7 Hz, 2 H, $CH_2C\underline{H}_2Br$), 9.8 (t, *J* = 2.0 Hz, 1 H, CHO).

Anal. Calcd for $C_9H_{17}BrO$ (221.13): C, 48.88; H, 7.55. Found: C, 49.05; H, 7.61.

10-Bromo-dec-1-ene (16)

To a suspension of methyltriphenylphosphonium bromide (14.3 g, 40 mmol) in anhyd THF (50 mL), *n*-BuLi (1.6 M in hexane, 21.9 mL, 35 mmol) was added. The resulting orange colored mixture was stirred for 1 h, cooled to –78 °C and a soln of aldehyde **15** (5 g, 22.6 mmol) in THF (10 mL) was added. The reaction was allowed to reach r.t. and stirred for an additional 1 h. The mixture was extracted with EtOAc (2 × 60 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting colorless oil was purified by chromatography (EtOAc–hexane, 5:95; R_f = 0.7) to afford alkene **16** as a colorless oil. Yield: 3.7 g (75%).

IR: 1645 cm^{-1} ($CH=CH_2$).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.45 (m, 8 H, CH_2), 1.84 (quint, *J* = 6.7 Hz, 2 H, $C\underline{H}_2CH_2Br$), 2.01–2.09 (m, 2 H, $C\underline{H}_2CH=CH_2$), 3.40 (t, *J* = 6.7 Hz, 2 H, $CH_2C\underline{H}_2Br$), 4.93 (ddt, *J*=10.1, 2.0, 1.0 Hz, 1 H, $CH_2CH=C\underline{H}H$), 4.99 (ddt, *J* = 17.1, 2.0, 1.0 Hz, 1 H, $CH_2CH=CH\underline{H}$), 5.80 (ddt, *J* = 17.1, 10.1, 6.7 Hz, 1 H, $CH_2C\underline{H}=CH_2$).

(2*R*)-10-Bromo-decane-1,2-diol (17)

To an ice-cold stirred soln of $(DHQD)_2$-PYR (16 mg, 1.83 mol%), $K_3Fe(CN)_6$ (1.81 g, 5.49 mmol), K_2CO_3 (0.75 g, 5.49 mmol) and $K_2OsO_2(OH)_2$ (6.6 mg, 0.018 mmol) in *t*-BuOH–H_2O (1:1, 15 mL), alkene **16** (0.40 g, 1.83 mmol) was added. The mixture was stirred at 0 °C for 10 h, quenched with Na_2SO_3 (70 mg, 0.55 mmol) and stirred for 30 min at r.t. The mixture was extracted with CH_2Cl_2 (30 mL) and the aq layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oil was purified by chromatography (EtOAc–hexane, 2:3; R_f 0.2) to furnish the dihydroxylation product **17** as a colorless oil. Yield: 394 mg (85%).

$[\alpha]_D^{22}$ = +10.7 (*c* 1.1, EtOH).

IR: 3391 cm^{-1} (OH).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.23–1.45 (m, 12 H, CH_2), 1.84 (quint, *J* = 6.7 Hz, 2 H, $C\underline{H}_2CH_2Br$), 3.40 (t, *J* = 6.7 Hz, 2 H, $CH_2C\underline{H}_2Br$), 3.76–3.79 (m, 1 H, $C\underline{H}OH$), 4.30–4.33 (m, 2 H, $C\underline{H}_2OH$).

Anal. Calcd for $C_{10}H_{21}BrO_2$ (253.18): C, 47.44; H, 8.36. Found: C, 47.57; H, 8.51.

The ratio of enantiomers was determined by reacting the diol **17** with *R*-(+)-MTPA and subsequent HPLC analysis [kromasil 100-5, C-18, H_2O–MeOH–CH_3CN gradient elution from 40:40:20→0:10:90, flow = 2 mL/min, UV detection at 254 nm]; R_t major 22.1 min (90%); and R_t minor 20.3 (of other enantiomer 10%).

(4*R*)-4-(8-Bromo-octyl)-2,2-dimethyl-[1,3]dioxolane (18)

To a stirred soln of 10-bromo-decane-1,2-diol (**17**) (400 mg, 1.36 mmol) and 2,2-dimethoxypropane (0.84 ml, 6.8 mmol) in anhyd acetone (2 mL), *p*-TsOH (5 mg, 0.02 mmol) was added. After stirring for 5 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc–hexane, 1:9; R_f = 0.64) to furnish **18** as colorless oil. Yield: 359 mg (90%).

$[\alpha]_D^{22}$ = +9.2 (*c* 0.9, EtOAc).

IR: 1320, 980 cm^{-1} (COC).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.23–1.45 (m, 12 H, CH_2), 1.34 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.83 (quint, *J* = 6.7 Hz, 2 H, $C\underline{H}_2CH_2Br$), 3.39 (t, *J* = 6.7 Hz, 2 H, $CH_2C\underline{H}_2Br$), 3.45–3.51 (m, 1 H, CHO), 4.03–4.07 (m, 2 H, CH_2O).

Anal. Calcd for $C_{13}H_{25}BrO_2$ (293.24): C, 47.44; H, 8.36. Found: C, 47.63; H, 8.23.

(2*S*, 3*S*, 6*S*, 4″*R*)-[3-Benzyloxy-2-(*tert*-butyl-diphenyl-silyloxymethyl)-6-[10′-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)-dec-2′-enyl]-1-tosylpiperidine (19)

A soln of 4-(8-bromo-octyl)-2,2-dimethyl-[1,3]dioxolane (**18**) (250 mg, 0.88 mmol) and Ph_3P (250 mg, 0.94 mmol) in anhyd CH_3CN (1 mL) was heated in a sealed tube for 24 h. The solvent was evaporated under reduced pressure and the resulting viscous liquid was washed several times with hexane and Et_2O to yield 0.86 g of triphenylphosphonium ylide as an amorphous solid (0.44 g, 90%). To an ice-cold suspension of Wittig reagent (250 mg, 0.45 mmol) in THF (3 mL), *n*-BuLi (1.6 M in hexane, 0.28 mL, 0.45 mmol) was added and the orange colored mixture was stirred at 0 ºC for an additional 30 min. To this mixture, an ice-cold soln of aldehyde **9** (148 mg, 0.23 mmol) in THF (1 mL) was cannulated. The reaction was allowed to reach r.t. and stirred for 1 h. After the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and Et_2O (15 mL), the organic phase was separated and the aq layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil which was purified by chromatography (EtOAc–hexane, 1:4; R_f = 0.41) to furnish **19** as a white solid which was recrystallized from Et_2O. Yield: 173 mg (90%).

$[\alpha]_D^{22}$ = +1.5 (*c* 0.55, hexane); mp = 78–80 °C.

IR: 1320, 980 cm^{-1} (COC).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H, CCH_3), 1.20–1.35 (m, 11 H, H-5, CH_2), 1.33 (s, 3 H, CCH_3), 1.38 (s, 3 H, CCH_3), 1.45–1.70 (m, 5 H, H-4, CH_2), 1.85–1.95 (m, 2 H, $CH_2C\underline{H}_2CH$), 2.34 (s, 3 H, $ArCH_3$), 2.37–2.43 (m, 2 H, $CHC\underline{H}_2CH$), 3.26–3.33 (m, 1 H, H-3), 3.48–3.54 (m, 1 H, OCH), 3.67–3.77 (m, 1 H, H-6), 3.88 (dd, *J* = 10.8, 8.3 Hz, 1 H, $C\underline{H}HOTBDPS$), 3.98–4.13 (m, 3 H, OCH_2, $CH\underline{H}OTBDPS$), 4.35 (d, *J* = 12.0 Hz, 1 H, $C\underline{H}HPh$), 4.47 (d, *J* = 12.0 Hz, 1 H, $CH\underline{H}Ph$), 4.72 (dt, *J* = 8.3, 5.7, 1 H, H-2), 5.28 (dt, *J* = 10.6, 6.8 Hz, 1 H, CH), 5.4 (dt, *J* = 10.6, 7.2 Hz, 1 H, CH), 7.10–7.20 (m, 4 H, ArH), 7.23–7.33 (m, 3 H, ArH), 7.33–7.49 (m, 6 H,

ArH), 7.65 (d, *J* = 8.3 Hz, 2 H, ArH), 7.73 (d, *J* = 6.5 Hz, 2 H, ArH), 7.78 (d, *J* = 6.5 Hz, 2 H, ArH).

Anal. Calcd for $C_{51}H_{69}NO_6SSi$ (852.25): C, 71.87; H, 8.16; N, 1.64. Found: C, 72.04; H, 8.31; N, 1.51.

(2*S*, 3*S*, 6*S*, 4″*R*)-{3-Benzyloxy-6-[10′-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)-dec-2′-enyl]-1-tosylpiperidin-2-yl}-methanol (20)

To a soln of olefin **19** (145 mg, 0.17 mmol) in THF (2 mL), TBAF (1.0 M soln in THF, 0.25 mL) was added. The mixture was stirred at 40 °C for 12 h, then the solvent was evaporated under reduced pressure to yield a yellowish slurry which was purified by chromatography (EtOAc–hexane, 3:2; R_f = 0.67) to give alcohol **20** as a colorless oil. Yield: 97 mg (93%)

$[\alpha]_D^{22}$ = +2.7 (*c* 0.7, EtOAc).

IR: 3445 cm^{-1} (OH), 1351, 980 (COC).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.35 (m, 11 H, H-5, CH_2), 1.33 (s, 3 H, CCH_3), 1.38 (s, 3 H, CCH_3), 1.45–1.70 (m, 5 H, H-4, CH_2), 1.98–2.11 (m, 2 H $CH_2C\underline{H}_2CH$), 2.33–2.42 (m, 2 H $CHC\underline{H}_2CH$), 2.43 (s, 3 H, $ArCH_3$), 2.62 (t, *J* = 7.0 Hz, 1 H, OH), 3.17–3.25 (m, 1 H, H-3), 3.47–3.55 (m, 1 H, OCH), 3.64–3.74 (m, 1 H, C<u>H</u>HOH), 3.98–4.14 (m, 4 H, H-6, OCH_2, CH<u>H</u>OH), 4.31 (dd, *J* = 13.1, 6.8 Hz, 1 H, H-2), 4.43 (d, *J* = 11.9 Hz, 1 H, C<u>H</u>HPh), 4.48 (d, *J* = 11.9 Hz, 1 H, CH<u>H</u>Ph), 5.38 (dt, *J* = 10.6, 6.8 Hz, 1 H, CH), 5.51 (dt, *J* = 10.6, 7.2 Hz, 1 H, CH), 7.23 (d, *J* = 8.3 Hz, 2 H, ArH), 7.25–7.30 (m, 2 H, ArH), 7.34–7.41 (m, 3 H, ArH), 7.63 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{35}H_{51}NO_6S$ (613.9): C, 68.48; H, 8.37; N, 2.28. Found: C, 68.38; H, 8.21; N, 2.25.

(2*S*, 3*S*, 6*R*, 4″*R*)-{6-[10′-(2″,2″-Dimethyl-[1″,3″]dioxolan-4″-yl)-decyl]-2-hydroxymethyl}-1-tosylpiperidin-3-ol (21)

Olefin **20** (62 mg, 0.1 mmol) was dissolved in MeOH (2 mL) and hydrogenated over 10% Pd/C (13 mg) under 1 bar pressure for 2 h. The mixture was filtered through celite and concentrated in vacuo to give a yellowish oil which was purified by chromatography (EtOAc–hexane, 3:2; R_f = 0.16) to furnish **21** as a colorless oil. Yield: 46 mg (85%).

$[\alpha]_D^{22}$ = +3.8 (*c* 0.65, EtOAc).

IR: 3450 cm^{-1} (OH), 1354, 982 (COC).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.76 (m, 22 H, H-5, H-4, CH_2), 1.35 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3), 2.42 (s, 3 H, $ArC\underline{H}_3$), 2.51 (s br, 1 H, OH), 2.61 (s br, 1 H, OH), 3.46–3.57 (m, 2 H, H-3, OCH), 3.72 (dd, 1 H, *J* = 10.6, 4.4 Hz, C<u>H</u>HOH), 3.89–3.99 (m, 1 H, H-6), 4.01–4.16 (m, 3 H, OCH_2, CH<u>H</u>OH), 4.16–4.25 (m, 1 H, H-2), 7.29 (d, *J* = 8.3 Hz, 2 H, ArH), 7.72 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{28}H_{47}NO_6S$ (525.7): C, 63.97; H, 9.01; N, 2.66. Found: C, 64.15; H, 8.88; N, 2.71.

(2*R*, 2′*R*, 5′*S*, 6′*S*)-12-(5′-Hydroxy-6′-hydroxymethyl-1′-tosylpiperidin-2′-yl)-dodecane-1,2-diol (22)

To a stirred soln of **21** (40 mg, 0.076 mmol) in MeOH (2 mL), *p*-TsOH (0.2 mg, 0.008 mmol) was added. After 1 h, the reaction was quenched with sat. aq $NaHCO_3$ and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc; R_f = 0.3) to furnish **22** as a colorless oil. Yield: 36 mg (97%).

$[\alpha]_D^{22}$ = +3.3 (*c* 0.3, EtOAc).

IR: 3448 cm^{-1} (OH).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.69 (m, 22 H, CH_2), 2.05 (s br, 1 H, OH), 2.22 (s br, 1 H, OH), 2.38 (s, 3 H, $ArCH_3$), 2.63 (s br, 1 H, OH), 2.85 (s br, 1 H, OH), 3.34–3.49 (m, 2 H, H-5′, C<u>H</u>OH), 3.58–3.72 (m, 3 H, C<u>H</u>HOH, $C\underline{H}_2OH$), 3.82–3.96 (m, 1 H, H-2′), 4.04–4.13 (m, 2 H, H-6′, CH<u>H</u>OH), 7.24 (d, *J* = 8.3 Hz, 2 H, ArH), 7.67 (d, *J* = 8.1 Hz, 2 H, ArH).

Anal. Calcd for $C_{25}H_{43}NO_6S$ (485.68): C, 61.82; H, 8.92; N, 2.88. Found: C, 62.11; H, 8.82; N, 2.71.

(2*R*, 2′*R*, 5′*S*, 6′*S*)-12-(5′-Hydroxy-6′-hydroxymethyl-piperidin-2′-yl)-dodecane-1,2-diol (8)

To a soln of naphthalene (50 mg, 0.39 mmol) in freshly distilled DME (2 mL), sodium (9 mg, 0.38 mmol) was added. The mixture was stirred at ambient temperature for 45 min (dark-green color), cooled to –78 °C and a soln of **22** (30 mg, 0.062 mmol) in DME (1 mL) was added. The reaction mixture was stirred at –78 °C for 30 min, quenched with brine (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc–MeOH, 10:1; R_f = 0.63) to furnish the desired product **8**. Yield: 16 mg (64%).

$[\alpha]_D^{22}$ = +4.7 (*c* 1.2, EtOAc).

IR: 3407 cm^{-1} (OH).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.15–1.69 (m, 22 H, CH_2), 2.07 (s br, 1 H, OH), 2.25 (s br, 1 H, OH), 2.63 (s br, 1 H, OH), 2.85 (s br, 1 H, OH), 3.15 (m, 2 H, H-2′, H-5′), 3.32–3.37 (m, 2 H, H-6′, CHOH), 3.55–3.72 (m, 4 H, $C\underline{H}_2OH$, $C\underline{H}_2OH$).

Anal. Calcd for $C_{18}H_{37}NO_4$ (331.49): C, 65.22; H, 11.25; N, 4.23. Found: C, 65.44; H, 11.38; N, 4.19.

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