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A chemoenzymatic asymmetric synthesis of the hydroxy acid segment of schulzeines B and C

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ABSTRACT

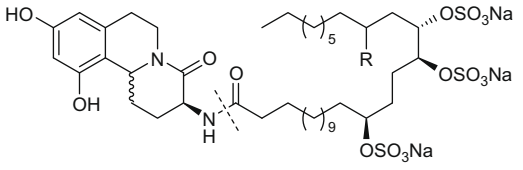
A chemoenzymatic asymmetric synthesis of the title compound was developed by a building-block approach. The key steps of the synthesis were (i) an enantioselective lipase-catalyzed acylation of a secondary alcohol, (ii) an efficient diastereoselective addition of an alkyl-lithium reagent to a glyceraldehyde derivative, (iii) conversion of an epoxide to a one-carbon homologated allylic alcohol via a sulphorane addition, and (iv) a cross metathesis between two chiral allylic alcohols and subsequent functionalization to obtain the ethyl ester of the hydroxy acid unit of the schulzeines.

1. Introduction

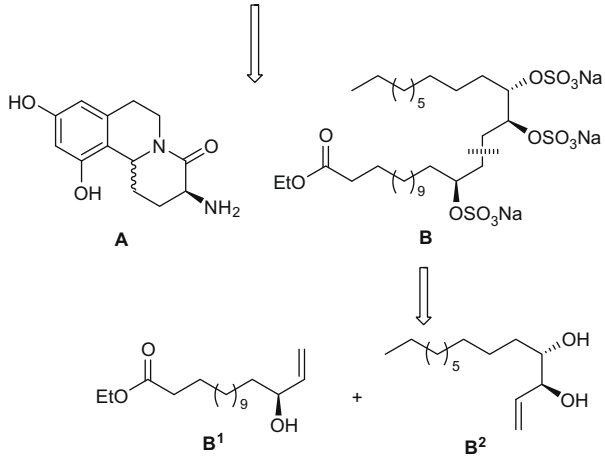
The tetrahydroisoquinoline alkaloids, designated as schulzeines A–C **1**–**3** were isolated by a bioassay-guided screening of the hydrophilic extract of the marine sponge *Penares schulzei* and found to inhibit yeast α-glucosidase with IC_{50} values of 48–170 nM and viral neuraminidase ($IC_{50} \sim \mu M$).[1] The constitution and the relative stereochemistry of the schluzeines were elucidated by chemical degradation and extensive 2D-NMR studies, and the absolute configuration by application of the Mosher method. The schulzeines encompass the 9,11-tetrahydroisoquinoline unit and are characterized by a fused δ-lactam ring **A** and a C_{28} sulfated fatty acid side chain **B** linked via an amide bond (Scheme 1).[2] Schulzeines B and C differ in the stereochemistry at the C-11b of the tetrahydroisoquinoline moiety, while schulzeine A possesses an additional methyl substitution at C-20 of the fatty acid chain. More recently, the stereochemistry of this stereogenic center in schulzeine A has been revised.[3]

Glycosidase inhibitors have become the subject of intense scrutiny because of their profound effect on glycoprotein processing, oligosaccharide metabolism, and cell–cell and cell–virus recognition processes.[4] The α-glucosidase inhibitors are potential therapeutics for the treatment of viral diseases, cancer, and diabetes.[5] Their intriguing bioactivity combined with the unique structure of the schulzeines aroused several synthetic efforts toward these targets.[6] Notably, all the reported syntheses of the tricyclic isoquinoline core began with glutamic acid derivatives, while the fatty acid segment has been synthesized using Sharpless' asymmetric dihydroxylation as the key step.

Our interest in the schulzeines was sparked by their biological activity, especially as potential anti-tumor and immunomodulatory agents.[7] Although the pharmacophore of the schluzeines has



1: schulzeine A: R = Me, (11b*R*); **2** schulzeine B: R = H, (11b*S*);
3: schulzeine C: R = H, (11b*R*)



Scheme 1.

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not been identified so far, their O-sulfated fatty acid segment is structurally related to other glucosidase inhibitors, including penasulfate[8a] and the penarolides.[8b] Hence, we were interested in developing an efficient asymmetric synthesis of the common hydroxyalkyl ester unit **20** of the schulzeines B and C. Similar polyhydroxy acids and the macrolides derived from them are of wide occurrence in various natural sources, and several of these show impressive anti-cancer, antiviral, antifungal as well as vaccine adjuvant activities.[9] Herein, we report the asymmetric synthesis of **20** that can be easily converted to schulzeines B and C by amidation of the required isoquinoline core and a late stage trisulfation.

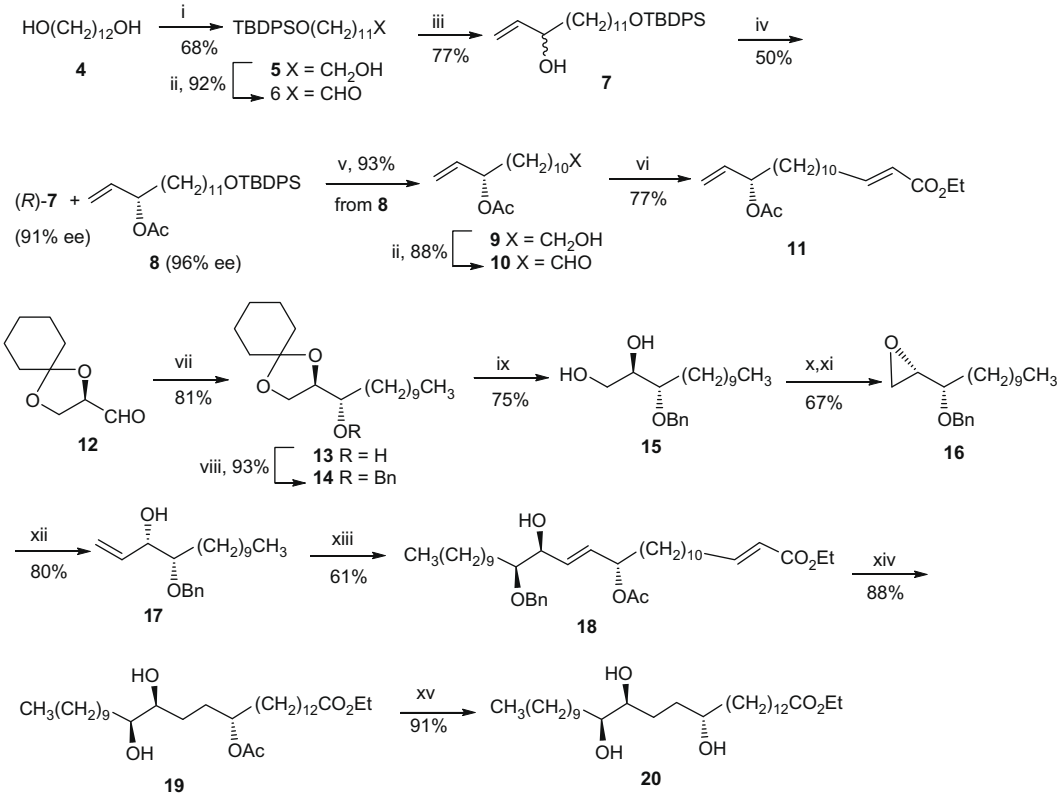
2. Results and discussion

For the past several years, we have been interested in formulating the simple and efficient asymmetric synthesis of various bioactive target compounds, which remains a challenging area, despite impressive progress in organic synthesis.[10a–c] To this end, we have extensively used inexpensive and easily accessible (*R*)-cyclohexylideneglyceraldehyde **12** as a versatile chiral template[11a–h] and/or employed biocatalytic routes[12a–d] for the asymmetric syntheses of a diverse array of natural compounds. A chemoenzymatic approach, combining these methodologies may often provide easy access to the target compounds, as is illustrated in this paper for the syntheses of the title compound.

Different versions of the olefin metathesis reaction have turned out to be a promising strategy for the construction of C–C bonds.[13] Recently we have successfully utilized cross metathesis of terminal alkenes to formulate the efficient syntheses of two hydroxy fatty acids.[14] Hence, a convergent strategy toward the C_{28} fatty acid ester **20** was conceived using a similar cross metathesis reaction between the building blocks $\mathbf{B^1}$ and $\mathbf{B^2}$. We envisaged that the required building blocks could be individually synthesized by a biocatalytic route, and using the aldehyde **12**, respectively.

As per the synthetic plan (Scheme 2), the commercially available diol **4** was monoprotected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of 4-dimethylaminopyridine (DMAP) to furnish compound **5**, which on oxidation with pyridinium chlorochromate (PCC) afforded the aldehyde **6**. Its reaction with vinylmagnesium bromide afforded the allylic alcohol **7**. For its resolution, a lipase-catalyzed *trans*-acetylation appeared promising. Lipases are widely used in asymmetric organic synthesis since they do not require any cofactor, operate on a wide range of substrates, retain good catalytic activity in different media, display good stereoselectivity, and are commercially available in free as well as immobilized forms.[15a–c] We were particularly interested in the lipase preparation, Novozyme 435® that is inexpensive, robust and effective in resolving racemic carbinol and amines.[15d] Although the above-mentioned lipase is generally effective in resolving linear secondary alcohols, the enantioselectivity is known to be governed by the reaction conditions such as solvent used and/or the acyl donor.[16a–c] In our recent work, we also observed that Novozyme 435® is very effective in resolving alcohols, possessing methyl[14a] or vinyl groups[14b] adjacent to the carbinol functionality.

True to our expectation, the alcohol **7** could be efficiently resolved using inexpensive vinyl acetate, both as the acyl donor, and solvent to obtain the (*S*)-acetate **8** (96% ee) and (*R*)-**7** (91% ee) at ~50% conversion (5.5 h). For determining the % ees of the products, a part of the acetate (*S*)-**8** was hydrolyzed with KOH/



Scheme 2. Reagents and conditions: (i) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 °C/8 h (68%), (ii) PCC/NaOAc/CH_2Cl_2/25 °C/3 h (**6**: 92%; **10**: 88%), (iii) CH_2=CHMgBr/THF/25 °C/6 h (77%), (iv) vinyl acetate/Novozyme 435/25 °C/26 h (50%), (v) Bu_4NF/THF/0–25 °C/3 h (93%), (vi) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0 °C to 25 °C/18 h (77%), (vii) $CH_3(CH_2)_9Li$/THF/−78 °C/3 h (81%), (viii) NaH/THF/BnBr/Bu_4NI/Δ/4 h (93%), (ix) aqueous 2 M HCl/25 °C/6 h (75%), (x) TMSCl/EtOAc/−20 °C/20 min; MsCl/Et_3N/−20 °C/30 min; aqueous 2 M HCl/25 °C/1 h (79%), (xi) K_2CO_3/MeOH/25 °C/3 h (84%), (xii) Me_3SI/BuLi/THF/−40 °C/1 h, −40 °C/3 h then 25 °C/12 h (80%), (xiii) **11**/Grubbs' 2nd generation catalyst/CH_2Cl_2/25 °C/22 h (61% based on **17**), (xiv) H_2/10% Pd–C/EtOH/25 °C (88%), (xv) Amberlyst 15®/EtOH/25 °C/18 h (91%).

MeOH to furnish the alcohol (*S*)-**7**. The % ees of the enantiomeric alcohols (*R*)- and (*S*)-**7** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters, prepared using (*R*)-α-methoxytrifluoromethyl phenylacetyl (MTPA) chloride.[17] The acetate (*S*)-**8** was desilylated with Bu_4NF to furnish the primary alcohol **9**, which was used for the synthesis of the building block **11** (**B**[1] equivalent). For assigning the configuration of **8**, a part of the alcohol **9** was mesylated and subsequently reduced with $LiAlH_4$ to furnish (*S*)-tetradec-1-en-3-ol. Comparison of its specific rotation with the reported value established its configuration.[18] For the synthesis of the intermediate **11**, the alcohol **9** was oxidized with PCC to furnish the aldehyde **10**. This on Wittig–Horner reaction with triethyl phosphonoacetate furnished the conjugated ester **11**. The *E*-geometry of the olefin function was ascertained from the ^1H NMR spectrum.

For the other building block **17** (**B**[2] equivalent), following our own methodology, the known aldehyde **12** was reacted with $CH_3(CH_2)_9Li$ to furnish the *anti*-triol derivative **13** almost exclusively (dr: = 96:4). Use of the corresponding Grignard reagent produced a 22:78 mixture of *syn*/*anti* triol derivatives. The *anti*-compound **13**[19] could be easily obtained in stereochemically pure form by column chromatography. The *anti*-stereochemistry of **13** was confirmed from the ^1H NMR resonances of the carbinol protons that appeared at δ 3.63 (t, 1H) and δ 3.87–3.97 (m, 3H). For the corresponding *syn*-isomer, these appear at δ 3.46–3.48, δ 3.68–72 and δ 3.94–4.02 as 1:1:2 multiplets.[19] Benzylation of **13** with benzyl bromide (BnBr) and Bu_4NI in the presence of NaH as the base produced compound **14**. This on treatment with aqueous HCl furnished the diol **15**. Its reaction with trimethylsilyl chloride (TMSCl) in the presence of Et_3N in EtOAc followed by mesylation of the resultant product with mesyl chloride (MsCl), and subsequent desilylation with HCl furnished the C-2 mesylated intermediate. After isolation, this was treated with K_2CO_3 to furnish the (2*S*,3*S*)-epoxide **16**. This was reacted with the sulphorane, generated by a base (*n*-BuLi)-catalyzed deprotonation of trimethylsulfonium iodide (Me_3SI) to afford the allylic alcohol **17**.

In the last sequence of reactions, the alcohol **17** was subjected to a cross-metathesis reaction with the allylic acetate **11** in the presence of Grubbs' 2nd generation catalyst to furnish the desired alcohol **18** (61%, based on conversion of **17**) along with the unreacted alcohols **11** and **17**. The homo-dimerized products of **11** and **17** were obtained in trace amounts. We used the alcohol **17** in excess in view of its easy availability and also the fact that its dimerized product (if any) would produce a highly polar product, which can be separated easily from the alcohol **18**. Generally, increasing steric bulk through the addition of hydroxyl protection reduces the cross-metathesis reactivity of the alkenols.[13f] Hence we used the unprotected alcohol **17** directly for the metathesis. The ^1H NMR resonances of the newly generated olefinic protons and that at the C-2 position appeared together as complex multiplets, precluding the assignment of the geometry of the newly generated olefin function. However, this was not important for the present synthesis. Catalytic hydrogenation of **18** gave the acetoxy ester **19**, which was converted to the target hydroxy ester **20** by an acid (Amberlyst 15®)-catalyzed *trans*-esterification with ethanol.

3. Experimental

3.1. General experimental details

The chemicals (Fluka and Lancaster) were used as received. Other reagents were of AR grade. All anhydrous reactions were carried out under an Ar atmosphere, using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrometer. The ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker AC-200 spectrometer. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

3.2. 12-*tert*-Butyldiphenylsilyloxydodecan-1-ol 5

A mixture of **4** (7.0 g, 34.65 mmol), TBDPSCl (10.0 g, 36.42 mmol), imidazole (2.82 g, 41.48 mmol), and DMAP (cat.) in CH_2Cl_2 (50 mL) was stirred at room temperature for 8 h. The mixture was poured into H_2O (50 mL), the organic layer separated and the aqueous portion extracted with $CHCl_3$ (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), aqueous 10% HCl (1 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–15% EtOAc/hexane) of the residue furnished **5**. Yield: 10.37 g (68%); colorless oil; IR: 3348, 3071, 3049 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.17–1.40 (m, 16H), 1.44 (br s, 1H), 1.53–1.65 (m, 4H), 3.58–3.67 (m, 4H), 7.25–7.41 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR: δ 19.2, 25.7, 26.8, 29.4, 29.6, 32.6, 32.7, 63.1, 63.9, 127.5, 129.4, 134.1, 135.5. Anal. Calcd for $C_{28}H_{44}O_2Si$: C, 76.30; H, 10.06. Found: C, 76.14; H, 9.88.

3.3. 12-*tert*-Butyldiphenylsilyloxydodecanal 6

To a cooled (0 °C) and stirred suspension of PCC (4.71 g, 21.83 mmol) and NaOAc (10 mol %) in CH_2Cl_2 (30 mL) was added the alcohol **5** (6.4 g, 14.55 mmol) in one portion. After stirring for 3 h, the reaction mixture was diluted with Et_2O (30 mL) and the supernatant passed through a pad of silica gel (2″ × 1″). Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) furnished pure **6**. Yield: 5.86 g (92%); colorless oil; IR: 2712, 1726 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.25–1.42 (m, 14H), 1.44–1.62 (m, 4H), 2.37–2.45 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 7.34–7.42 (m, 6H), 7.64–7.69 (m, 4H), 9.75 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR: δ 19.2, 22.1, 25.7, 26.9, 29.1, 29.4, 29.5, 32.6, 43.9, 64.0, 127.5, 129.5, 134.1, 135.6, 203.0. Anal. Calcd for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65. Found: C, 76.48; H, 9.81.

3.4. (±)-14-*tert*-Butyldiphenylsilyloxytetradec-1-en-3-ol 7

To a stirred solution of **6** (5.60 g, 12.78 mmol) in THF (25 mL) was slowly added $CH_2{=}CHMgBr$ (36.5 mL, 25.57 mmol, 0.7 M in THF), and the mixture stirred for 6 h. The reaction was quenched with aqueous 10% NH_4Cl, the mixture filtered and concentrated in vacuo. The residue was dissolved in Et_2O (30 mL), the organic layer washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal in vacuo and column chromatography (silica gel, 0–10% Et_2O/hexane) of the residue afforded (±)-**7**. Yield: 4.59 g (77%); colorless oil; IR: 3357, 997 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.26–1.42 (m, 16H), 1.45–1.60 (m, 5H), 3.64 (t, *J* = 6.4 Hz, 2H), 4.07–4.17 (m, 1H), 5.06–5.26 (m, 2H), 5.78–5.98 (m, 1H), 7.31–7.44 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR: δ 19.2, 25.3, 25.7, 26.8, 29.4, 29.6, 32.6, 37.0, 64.0, 73.3, 114.5, 127.5, 129.4, 134.1, 135.5, 141.3. Anal. Calcd for $C_{30}H_{46}O_2Si$: C, 77.19; H, 9.93. Found: C, 77.34; H, 9.78.

3.5. (*S*)-3-Acetoxy-14-*tert*-butyldiphenylsilyloxytetradec-1-ene 8

A mixture of (±)-**7** (2.0 g, 4.29 mmol), vinyl acetate (5 mL) and Novozyme 435® (0.250 g) was agitated on an orbital shaker at 110 rpm for 5.5 h. The reaction mixture was filtered, and the solution was concentrated in vacuo to give a residue, which on column chromatography (silica gel, 0–10% EtOAc/hexane) gave pure (*R*)-**7** and (*S*)-**8**. (*R*)-**7**: Yield: 0.780 g (39%); colorless oil; $[\alpha]_D^{22} = -3.0$ (*c* 1.07, $CHCl_3$); (*S*)-**8**: Yield: 0.960 g (44%); colorless oil; $[\alpha]_D^{22} = -4.4$ (*c* 1.11, $CHCl_3$); IR: 1740, 1033, 930 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.15–1.42 (m, 16H), 1.43–1.65 (m, 4H), 2.04 (s, 3H), 3.65

(t, J = 6.4 Hz, 2H), 5.12–5.26 (m, 3H), 5.69–5.80 (m, 1H), 7.31–7.46 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR: δ 19.2, 21.2, 25.1, 25.8, 26.9, 29.4, 29.6, 32.6, 34.2, 64.0, 74.8, 116.5, 127.6, 129.5, 134.1, 135.6, 136.7, 170.2. Anal. Calcd for $C_{32}H_{48}O_3Si$: C, 75.54; H, 9.51. Found: C, 75.39; H, 9.37.

3.6. (*S*)-12-Acetoxytetradec-13-en-1-ol 9

To a cooled (0 °C) and stirred solution of **8** (0.950 g, 1.87 mmol) in THF (5 mL) was added Bu_4NF (1.87 mL, 1 M in THF, 1.87 mmol). The reaction mixture was brought to room temperature and stirred until the reaction was complete (cf. TLC, 3 h). The mixture was poured into ice cold water (15 mL) and extracted with EtOAc (2 × 10 mL). The organic extract was washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by column chromatography of the residue (silica gel, 0–15% EtOAc/hexane) furnished **9**. Yield: 0.470 g (93%); colorless oil; $[\alpha]_D^{22} = -6.1$ (c 1.08, $CHCl_3$); IR: 3421, 1738 cm^{-1}; ^{1}H NMR: δ 1.22–1.39 (m, 16H), 1.52–1.61 (m, 4H), 2.05 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 5.16–5.25 (m, 3H), 5.68–5.84 (m, 1H); ^{13}C NMR**:** δ 21.2, 25.0, 25.7, 29.3, 29.4, 32.6, 34.1, 62.9, 74.8, 116.4, 136.5, 170.4. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.88; H, 11.07.

3.7. (*S*)-12-Acetoxytetradecan-13-enal 10

As described for **6**, oxidation of the alcohol **9** (0.800 g, 2.96 mmol) with PCC (0.958 g, 4.44 mmol) and NaOAc (10 mol %) in CH_2Cl_2 (25 mL), followed by work up gave **10**. Yield: 0.700 g (88%); colorless oil; $[\alpha]_D^{22} = -4.6$ (c 1.04, $CHCl_3$); IR: 2716, 1737 cm^{-1}; ^{1}H NMR: δ 1.19–1.32 (m, 14H), 1.56–1.65 (m, 4H), 2.02 (s, 3H), 2.36–2.41 (m, 2H), 5.09–5.21 (m, 3H), 5.67–5.78 (m, 1H), 9.72 (t, J = 1.5 Hz, 1H); ^{13}C NMR**:** δ 21.1, 21.9, 24.9, 29.0, 29.2, 29.3, 34.0, 43.8, 74.7, 116.4, 136.5, 170.3, 202.1. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.68; H, 10.67.

3.8. Ethyl (*S*)-14-acetoxyhexadeca-2*E*,15-dienoate 11

To a cooled (0 °C) and stirred suspension of pentane-washed NaH (0.140 g, 2.91 mmol, 50% suspension in oil) in THF (5 mL) was added triethyl phosphonoacetate (0.652 g, 2.91 mmol) in THF (5 mL). After 15 min, when the solution became clear, the aldehyde **10** (0.650 g, 2.42 mmol) in THF (5 mL) was injected into it. After stirring at room temperature for 18 h, the mixture was poured into ice-water and extracted with Et_2O (3 × 10 mL). The ether layer was washed with water (2 × 10 mL) and brine (1 × 5 mL), dried, and concentrated in vacuo to give a residue, which on column chromatography (silica gel, 0–10% Et_2O/hexane) furnished pure **11**. Yield: 0.630 g (77%); colorless oil; $[\alpha]_D^{22} = -5.4$ (c 1.03, $CHCl_3$); IR: 1739, 1722, 982 cm^{-1}; ^{1}H NMR: δ 1.05–1.31 (m, 17H), 1.42–1.61 (m, 4H), 2.05 (s, 3H), 2.12–2.22 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 5.11–5.25 (m, 3H), 5.63–5.84 (m containing a d at δ 5.79, J = 15.8 Hz, 2H), 6.88–7.02 (m, 1H); ^{13}C NMR: δ 14.2, 21.2, 24.9, 27.9, 29.0, 29.3, 29.4, 32.0, 34.1, 60.0, 74.8, 116.4, 121.1, 136.5, 149.4, 166.7, 170.3. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 71.16; H, 10.16.

3.9. (2*R*,3*S*)-l,2-Cyclohexylidenedioxytridecan-3-ol 13

To a cooled (−78 °C) and stirred solution of 1-decyl-Li [prepared from 1-bromodecane (15.60 g, 70.59 mmol) and Li (1.1 g, 155.29 mmol)] in THF (70 mL) was added **12** (6.0 g, 35.29 mmol) in THF (30 mL). After stirring the mixture for 3 h at −78 °C, it was gradually brought to room temperature and treated with aqueous saturated NH_4Cl, the supernatant was decanted and the residue washed with Et_2O (2 × 20 mL). The combined organic extracts were washed with aqueous saturated NH_4Cl (1 × 10 mL), dried and concentrated in vacuo to give a residue, which on column chromatography (silica gel, 0–15% EtOAc/hexane) furnished **13**. Yield: 8.90 g (81%); colorless oil; $[\alpha]_D^{22} = +5.1$ (c 1.14, $CHCl_3$), {lit.[19] $[\alpha]_D^{22} = +4.2$ (c 0.83, $CHCl_3$)}; IR: 3418 cm^{-1}; ^{1}H NMR: δ 0.86 (dist. t, J = 6.8 Hz, 3H), 1.20–1.40 (m, 20H), 1.56–1.62 (m, 8H), 1.94 (br s, 1H), 3.63 (t, J = 6.4 Hz, 1H), 3.87–3.97 (m, 3H); ^{13}C NMR: δ 13.9, 22.4, 23.5, 23.7, 24.9, 25.5, 29.1, 29.4, 31.7, 32.4, 34.6, 35.9, 63.9, 70.4, 78.1, 109.2. Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.17; H, 11.47.

3.10. (2*R*,3*S*)-3-Benzyloxy-l,2-cyclohexylidenedioxytridecane 14

To a stirred suspension of NaH (1.44 g, 50% suspension in oil, 29.97 mmol) in THF (30 mL) was added **13** (8.5 g, 27.24 mmol)) in THF (30 mL) under Ar. After the evolution of H_2 had subsided, the mixture was refluxed for 1 h, brought to room temperature, Bu_4NI (10 mol %) and BnBr (5.59 g, 32.69 mmol) in THF (30 mL) was added dropwise. The mixture was refluxed until consumption of **13** (cf. TLC, ~4 h), brought to room temperature, and treated with ice-cold H_2O (30 mL). The organic layer was separated, the aqueous portion extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–10% EtOAc/hexane) of the residue furnished **14**. Yield: 10.19 g (93%); colorless oil; $[\alpha]_D^{22} = +5.0$ (c 1.16, $CHCl_3$); IR: 3060, 1644 cm^{-1}; ^{1}H NMR: δ 0.87 (dist. t, J = 6.4 Hz, 3H), 1.15–1.39 (m, 20H), 1.51–1.61 (m, 8H), 3.48–3.56 (m, 1H), 3.86–3.90 (m, 1H), 3.95–4.04 (m, 2H), 4.51–4.73 (m, 2H), 7.29–7.34 (m, 5H); ^{13}C NMR: δ 14.1, 22.7, 23.8, 24.0, 25.0, 25.2, 29.3, 29.6, 29.7, 31.4, 31.9, 34.9, 36.2, 65.8, 72.9, 77.6, 79.0, 109.4, 127.5, 127.8, 128.3, 138.7. Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.71; H, 10.47.

3.11. (2*R*,3*S*)-3-Benzyloxytridecane-l,2-diol 15

A mixture of **14** (5.0 g, 12.44 mmol) and aqueous HCl (6 mL, 2 M) was stirred at 25 °C until completion of the reaction (cf. TLC, 6 h). Most of the solvent was removed in vacuo, the residue diluted with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed successively with H_2O (3 × 10 mL), 10% aqueous $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–5% MeOH–$CHCl_3$) of the residue gave pure **15**. Yield: 3.0 g (75%); colorless oil; $[\alpha]_D^{22} = +7.3$ (c 1.12, $CHCl_3$), (lit.[20] $[\alpha]_D = +6.4$ (c 1.07, CH_2Cl_2)); IR: 3398, 1620, 1063 cm^{-1}; ^{1}H NMR δ 0.87 (dist. t, J = 6.8 Hz, 3H), 1.21–1.59 (m, 18H), 2.72 (br s, 2H), 3.56–3.69 (m, 1H), 3.72–3.78 (m, 3H), 4.51–4.65 (m, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR: δ 14.0, 22.6, 25.2, 29.5, 29.7, 30.3, 31.8, 63.3, 72.5, 72.7, 80.8, 127.7, 127.8, 128.3, 138.1. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.35; H, 10.80.

3.12. (2*S*,3*S*)-3-Benzyloxy-l,2-epoxytridecane 16

To a cooled (−20 °C) and stirred solution of **15** (1.16 g, 3.60 mmol) and Et_3N (1.76 mL, 12.6 mmol) in EtOAc (12 mL) was added TMSCl (0.46 mL, 3.6 mmol). After stirring for 20 min, Et_3N (0.8 mL, 5.76 mmol) and MsCl (0.334 mL, 4.32 mmol) were added successively into the mixture. After stirring for another 30 min, the mixture was brought to 25 °C, aqueous 2 M aqueous HCl (7.0 mL) was added and stirring continued for 1 h. The organic layer was separated, the aqueous portion extracted with EtOAc (2 × 15 mL) and the combined organic extracts were washed successively with H_2O (3 × 10 mL), aqueous 2 M HCl (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal afforded the corresponding 1-hydroxy-2-mesylate. IR: 1456, 1350 cm^{-1}.

A mixture of the above compound (1.14 g, 2.83 mmol) and anhydrous K_2CO_3 (1.17 g, 8.48 mmol) in MeOH (20 mL), was stirred for 3 h at room temperature. The supernatant was decanted, the solid residue washed with EtOAc (20 mL) and the combined organic extracts concentrated in vacuo. The residue was taken in EtOAc (30 mL) washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. Column chromatography (silica gel, 0–5% EtOAc/hexane) of the residue gave pure **16**. Yield: 0.722 g (84%); colorless oil; $[\alpha]_D^{22} = -22.5$ (*c* 1.28, $CHCl_3$), (lit.[20] $[\alpha]_D = -17$ (*c* 1.16, CH_2Cl_2) for (2*R*,3*S*)-**16**); IR: 1254, 850 cm^{-1}; ^1H NMR: δ 0.87 (dist. t, *J* = 6.8 Hz, 3H), 1.26 (br s, 18H), 2.48–2.52 (dd, t, *J* = 1.8 Hz, 3.0 Hz, 1H), 2.79 (t, *J* = 3.0 Hz, 1H), 2.99–3.06 (m, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR: δ 14.1, 22.7, 25.5, 29.3, 29.5, 29.6, 31.9, 32.3, 43.1, 55.1, 71.6, 80.5, 127.4, 127.8, 128.3, 138.7. Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.75; H, 10.43.

3.13. (3*S*,4*S*)-4-Benzyloxytetradec-1-en-3-ol 17

To a cooled (−40 °C) and stirred suspension of Me_3SI (1.57 g, 7.73 mmol) in THF (20 mL) was added *n*-BuLi (4.31 mL, 1.5 M in hexane, 6.46 mmol). After stirring for 1 h, compound **16** (0.470 g, 1.55 mmol) in THF (5.0 mL) was injected into the mixture and stirring continued at −40 °C for 3 h and at room temperature for 12 h. H_2O (15 mL) was added to the mixture, the organic layer separated, and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (1 × 10 mL), and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–15% EtOAc/hexane) of the residue gave pure **17**. Yield: 0.393 g (80%); colorless oil; $[\alpha]_D^{22} = +3.1$ (*c* 0.980, $CHCl_3$); IR: 3444, 992, 922 cm^{-1}; ^1H NMR: δ 0.89 (dist. t, *J* = 6.4 Hz, 3H), 1.27 (br, s, 16H), 1.57–1.63 (m, 2H), 2.55 (br s, 1H), 3.32–3.39 (m, 1H), 4.08–4.17 (m, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 5.21–5.41 (m, 2H), 5.84–5.95 (m, 1H), 7.34–7.38 (m, 5H); ^{13}C NMR: δ 14.1, 22.7, 25.1, 29.4, 29.6, 29.7, 29.9, 30.4, 31.9, 72.6, 74.4, 82.3, 116.8, 127.8, 127.9, 128.5, 137.7. Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.05; H, 10.59.

3.14. Ethyl (14*S*,17*S*,18*S*)-14-acetoxy-17-hydroxy-18-benzyloxyoctacosa-2*E*,15*E*/*Z*-dienoate 18

A mixture of **11** (0.130 g, 0.38 mmol), **17** (0.180 g, 0.56 mmol) and Grubbs' 2nd generation catalyst (4 mol %) in CH_2Cl_2 (15 mL) was stirred for 22 h. After concentrating the mixture in vacuo, the residue was subjected to column chromatography (silica gel, 0–15% EtOAc/hexane) to give pure **18**. Yield: 0.146 g (61% based on conversion of **17**); colorless oil; $[\alpha]_D^{22} = -9.3$ (*c* 1.03, $CHCl_3$); IR: 3461, 1735, 1722, 972 cm^{-1}; ^1H NMR: δ 0.85 (dist. t, *J* = 6.2 Hz, 3H), 1.24–1.58 (m containing a s at δ 1.30, 39H), 2.03 (s, 3H), 2.15–2.24 (m, 3H), 3.27–3.35 (m, 1H), 4.07–4.28 (m, 4H), 4.47–4.65 (m, 2H), 5.22–5.25 (m, 1H), 5.70–5.83 (m, 2H), 6.98 (d, *J* = 16.2 Hz, 1H), 7.35–7.39 (m, 5H); ^{13}C NMR: δ 14.0, 21.2, 22.6, 24.9, 25.0, 27.9, 29.0, 29.3, 29.4, 29.5, 29.8, 30.3, 31.8, 32.1, 34.3, 60.0, 72.4, 73.2, 74.1, 82.3, 121.1, 127.7, 128.3, 130.5, 132.3, 138.1, 149.4, 166.7, 170.2. Anal. Calcd for $C_{39}H_{64}O_6$: C, 74.48; H, 10.26. Found: C, 74.72; H, 10.45.

3.15. Ethyl (14*S*,17*S*,18*S*)-14-acetoxy-17,18-dihydroxyoctacosanoate 19

A mixture of **18** (0.125 g, 0.20 mmol) and 10% Pd–C (0.05 g) in EtOH (10 mL) was magnetically stirred at 25 °C for 22 h under a positive pressure of H_2. The mixture was diluted with Et_2O (30 mL) and passed through a small pad of silica gel. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0–15% EtOAc/hexane) furnished pure **19**. Yield: 0.095 g (88%); colorless oil; $[\alpha]_D^{22} = +13.2$ (*c* 1.14, $CHCl_3$); IR: 3457, 1740, 1730 cm^{-1}; ^1H NMR: δ 0.86 (dist. t, *J* = 6.4 Hz, 3H), 1.23–1.60 (containing a s at δ 1.32, 47H), 2.03 (s, 3H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.69 (br s, 2H), 3.47–3.58 (m, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.28–4.36 (m, 1H); ^{13}C NMR: δ 14.1, 14.2, 21.3, 22.7, 25.0, 25.6, 26.0, 29.1, 29.2, 29.3, 29.6, 30.5, 31.9, 33.6, 34.1, 60.2, 74.3, 74.5, 74.7, 171.3, 174.0. Anal. Calcd for $C_{32}H_{62}O_6$: C, 70.80; H, 11.51. Found: C, 70.54; H, 11.72.

3.16. Ethyl (14*S*,17*S*,18*S*)-14,17-18-trihydroxyoctacosanoate 20

A mixture of **19** (0.09 g, 0.17 mmol) and Amberlyst 15® (0.05 g) in EtOH (5 mL) was magnetically stirred at 25 °C for 18 h. After filtering the mixture, it was concentrated in vacuo, and the residue subjected to preparative chromatography (silica gel, 15% EtOAc/hexane) to obtain pure **20**. Yield: 0.077 g (91%); colorless oil; $[\alpha]_D^{22} = -11.7$ (*c* 0.912, $CHCl_3$); IR: 3446, 1742 cm^{-1}; ^1H NMR: δ 0.87 (dist. t, *J* = 6.4 Hz, 3H), 1.27–1.56 (containing a s at δ 1.30, 47H), 2.32 (t, *J* = 6.8 Hz, 2H), 2.44 (br s, 2H), 2.82 (br s, 1H), 3.44–3.65 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR: δ 14.2, 21.2, 22.5, 25.0, 25.3, 25.5, 27.3, 27.7, 29.2, 29.3, 29.8, 30.2, 31.2, 31.9, 32.1, 34.4, 60.7, 72.4, 74.4, 74.7, 169.2. Anal. Calcd for $C_{30}H_{60}O_5$: C, 71.95; H, 12.08. Found: C, 70.54; H, 11.72.

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