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First asymmetric synthesis of the oxylipin, (6*S*,9*R*,10*S*)-6,9,10-trihydroxyoctadeca-7*E*-enoic acid

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ABSTRACT

A brief and facile synthesis of the title compound has been developed using cyclohexylideneglyceraldehyde as a chiral template. The key steps in the synthesis were: (i) two highly diastereoselective organometallic addition reactions to the aldehyde to furnish the required synthons with the appropriate stereogenic centers, and (ii) their cross metathesis to give the *E*-olefin geometry of the target compound.

1. Introduction

Araceae is one of the most dominant tropical families amongst herbs and vines, and many of the species are used as traditional remedies or food. The plant, *Dracontium loretense* Engl., which belongs to this family (subfamily Lasioideae), is widely distributed in the Peruvian Amazon, where it is known as 'jergón sacha'. There are various preparations of jergón sacha such as dried powder, tincture, alcoholic, and its aqueous-alcoholic extracts, which are popular amongst current Peruvian herbal medicines. The infusion of its corms is considered an immune-booster in Peruvian folk medicine. The combination of the extracts of *D. loretense* and *Uncaria tomentosa* is also used by AIDS patients to reinforce the immune system.[1a–c] Very recently, four novel oxylipins **1a–d** (Fig. 1) were isolated from the *n*-butanol extract of *D. loretense* corms and their structures were elucidated by extensive spectrocopy.[2] The absolute configurations of the three stereogenic carbinol centers of **1d** remain unresolved, although the relative stereochemistry of the C-9 and C-10 centers was ascertained by NMR spectrometry. The *n*-butanol extract and some of its fractions (10 μg/mL), as well as compound **1d** (10 μM), showed potential immunostimulatory effects as revealed by a ^{3}H-thymidine incorporation assay with human peripheral blood mononuclear cells (PBMCs). However, at a higher concentration, these were toxic to the cells. Amongst the constituent oxylipins of *D. loretense*, only compound **1d** exhibited proliferation activity on the OKT3-activated PBMCs, while its C-10 epimer **1c** was inactive.[2] This emphasized the crucial role of the C-10 stereochemistry for biological activity.

The primary motivation of the present work stems from our own interest in aliphatic polyhydroxy acids as immunomodulatory, anti-inflammatory, and anti-neoplastic agents.[3] In particular, the reported immunomodulatory activity of **1d** was very attractive because many such agents show impressive anti-ulcer, anti-inflammatory, and anti-neoplastic properties. Similar polyhydroxy acids and the macrolides derived from them are of wide occurrence in various natural sources and show diverse biological properties.[4a–c] These factors and the lack of any synthesis of **1d** prompted us to develop the first asymmetric synthesis of the (6*S*,9*R*,10*S*)-stereomer of compound **1d**.

2. Results and discussion

For the past several years, we have been involved in devising simple and efficient asymmetric syntheses of various bioactive target compounds. To this end, we have found the inexpensive and easily available aldehyde **2** to be a versatile chiral template for the synthesis of a diverse array of natural compounds.[5] The aldehyde **2** is amenable to various diastereoselective transformations using commonly available, inexpensive reagents.[6] Herein, a convergent strategy toward the synthesis of the C_{18} fatty acid **1d** was conceived using a cross metathesis reaction between the chiral building blocks, '**A**' and '**B**' that would also provide the desired 7*E*-olefin function of the target oxylipin (Fig. 1). Different versions of the olefin metathesis reaction have turned out to be promising strategies for the construction of C–C bonds.[7] We have also successfully utilized the cross metathesis of terminal alkenes to formulate efficient syntheses of three hydroxy fatty acids.[8a–c] It was envisaged that the building blocks, '**A**' and '**B**' can be constructed by carrying out diastereoselective additions of alkyl/allyl organometallic reagents to aldehyde **2**. This would provide the required stereogenic diol/carbinol moieties of the '**A**' and '**B**' units, while the cyclohexylidenedioxy group can be suitably functionalized to provide the terminal alkene functionality.

Very recently, we have found that the Ga-mediated crotylation of aldehyde **2** at room temperature in the ionic liquid, [bmim][Br] proceeded with excellent diastereoselectivity.[9] For the synthesis

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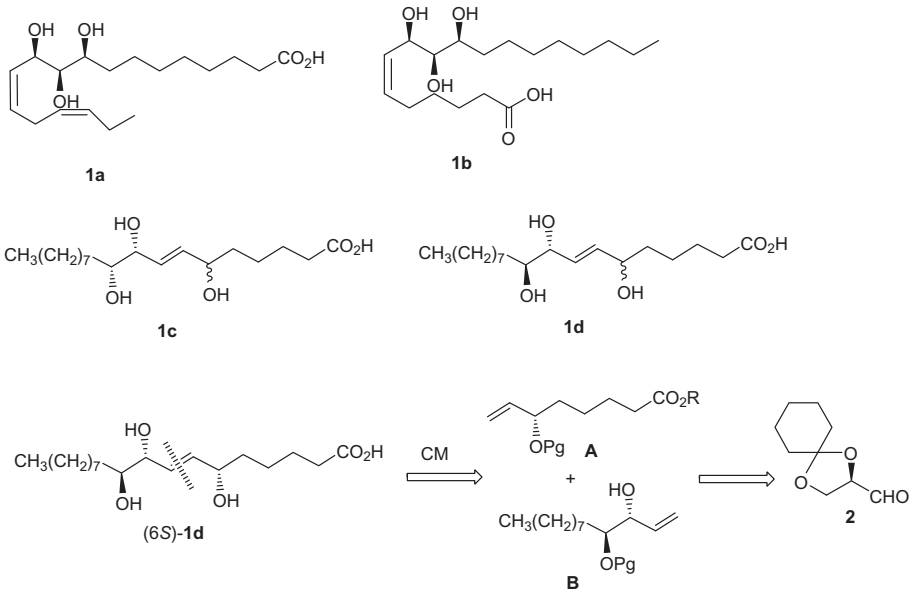


Figure 1.

(Scheme 1) of the '**A**' unit, a similar protocol was employed using allyl bromide. This furnished the homoallylic alcohol **3** almost exclusively (*anti*/*syn* = 95:5). The pure *anti*-isomer was easily separated by column chromatography. This was silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of 4-dimethylaminopyridine (DMAP) to furnish **4**. The alkene function of **4** was regioselectively hydroborated with BH_3–Me_2S (BMS) and the resultant product oxidized with H_2O_2 to afford alcohol **5**. This upon oxidation with pyridinium chlorochromate (PCC) afforded the aldehyde **6**. Its base-catalyzed Horner–Emmons reaction with triethyl phosphonoacetate produced the conjugated ester **7**. Although inconsequential to the present synthesis, the 2*E*-geometry of the ester **7** can be easily confirmed from the ^{1}H NMR spectrum. Catalytic hydrogenation of **7** gave the ester **8**, which upon treatment with aqueous trifluoroacetic acid (TFA) furnished the diol ester **9**. Its reaction with excess *p*-toluenesulphonyl chloride (*p*-TsCl) in the presence of pyridine furnished the ditosylate, which on heating with NaI and Zn-dust in DMF afforded the alkene ester **10** in an unusually clean manner.

As per our synthetic plan, the synthesis of the other building block **15** (**B** equivalent) required two key steps. For the synthesis of the chiral diol segment of compound **15**, we resorted to our own methodology of alkyl lithium addition to aldehyde **2**.[5d] The cyclohexylidenedioxy moiety of the resultant product was then converted to the one-carbon homologated allylic alcohol using sulfur-ylide chemistry. Despite its tremendous potential, the latter reaction has not been utilized extensively in organic synthesis. Thus, aldehyde **2** was reacted with $CH_3(CH_2)_7Li$ to furnish the *anti*-triol derivative **11** almost exclusively (dr = 95:5). In contrast, using the corresponding Grignard reagent produced a 29:71 mixture of *syn*/*anti* isomers. The *anti*-compound **11**[10] could be easily isolated as a pure enantiomer by column chromatography. The *anti*-stereochemistry of **11** was confirmed from the ^{1}H NMR resonances of the carbinol protons that appeared at δ 3.70–3.78 (1H) and δ 3.86–3.97 (m, 3H). For the corresponding *syn*-isomer, these appear as 1:1:2 multiplets at δ 3.46–3.48, δ 3.68–3.72 and δ 3.94–4.02.[10] Silylation of alcohol **11** with TBDPSCl/DMAP in CH_2Cl_2 produced compound **12**, which upon treatment with aqueous TFA furnished diol **13**. Its reaction with *p*-TsCl/pyridine proceeded regioselectively at the primary carbinol function to furnish the corresponding monotosylate. This was converted to epoxide **14** by treatment with K_2CO_3 in MeOH. The reaction of the sulphorane, generated by the base (*n*-BuLi)-catalyzed deprotonation of trimethylsulphonium iodide (Me_3SI) with epoxide **14** proceeded regioselectively at the C-1 position to afford allylic alcohol **15**.

In the final sequence of reactions, alcohol **15** was subjected to a cross-metathesis reaction with ester **10** in the presence of Grubbs' 2nd generation catalyst to furnish the desired alcohol **16** (63%, based on **10**) along with the unreacted substrates **10** and **15**. The homo-dimerized product of **10** was also obtained in 10–12% yields. We used alcohol **15** in excess, as its dimerized product would produce a highly polar product, which can be easily separated from alcohol **16**. Generally, increasing the steric bulk via the addition of a hydroxyl protection reduces the cross-metathesis reactivity of the alkenols.[7f] Hence we used directly the unprotected alcohol **15** for the metathesis. Desilylation of the compound **16** with Bu_4NF afforded the ester **17**, which on alkaline hydrolysis furnished the title acid **1d**.

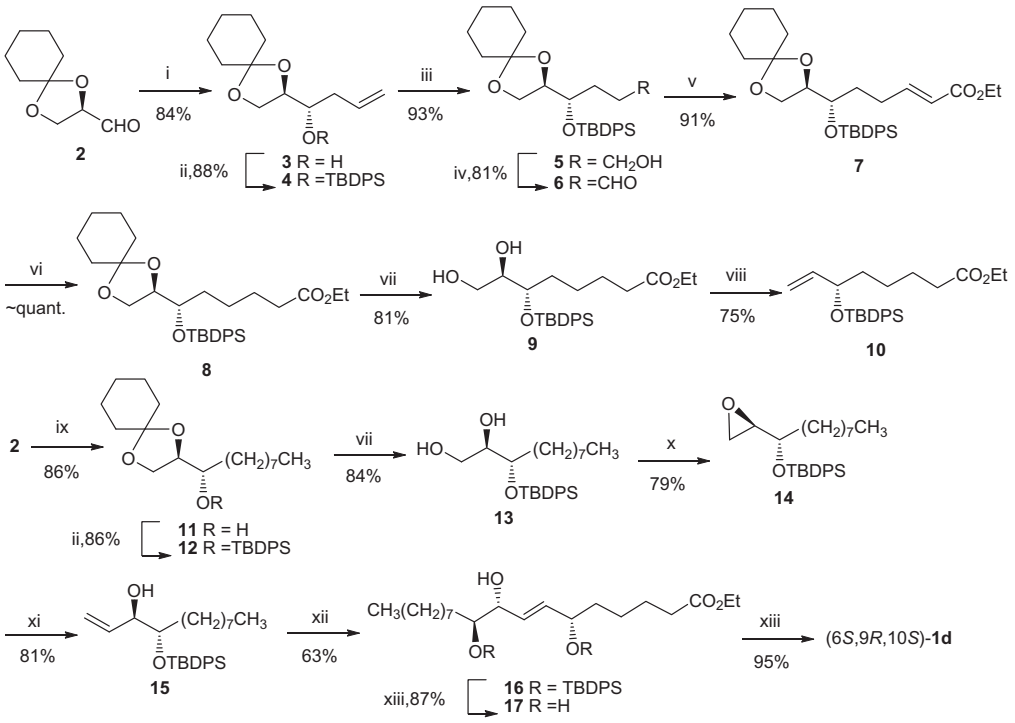
3. Experimental

3.1. General experimental details

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 ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker AC-200 spectrometer in $CDCl_3$. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

3.1.1. (2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-cyclohexylidenedioxyhex-5-ene 4

To a stirred and cooled (−30 °C) solution of the mixture of **3** (1.48 g, 6.95 mmol), imidazole (0.80 g, 11.80 mmol) and DMAP (catalytic) in CH_2Cl_2 (25 mL) was dropwise added TBDPSCl (2.86 g, 10.4 mmol) in CH_2Cl_2 (10 mL). After stirring the mixture for 10 h at room temperature, it was poured into ice-cold water (25 mL). The organic layer was separated and the aqueous portion



Scheme 1. Reagents and conditions: (i) Allyl bromide/Ga/[bmim][Br]/4 h; (ii) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 °C/10 h; (iii) BMS/THF/0 °C/3 h; aqueous NaOH/H_2O_2/0–25 °C/15 h; (iv) PCC/NaOAc/CH_2Cl_2/0 °C/3 h; (v) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0–25 °C/18 h; (vi) H_2/10% Pd-C/EtOH/25 °C/22 h; (vii) aqueous 80% TFA/CH_2Cl_2/0 °C/3 h/25 °C/18–24 h; (viii) PTSCl/pyridine/0–25 °C/24 h (89%); Zn/DMF/80 °C/4 h; (ix) $CH_3(CH_2)_7Li$/THF/−78 °C to 25 °C/3 h; (x) PTSCl/pyridine/0 °C/18 h; K_2CO_3/MeOH/25 °C/3 h; (xi) Me_3SI/BuLi/THF/−40 °C/4 h/25 °C/12 h; (xii) **10**/Grubbs' 2nd generation catalyst (5 mol %)/CH_2Cl_2/25 °C/22 h; (xii) Bu_4NF/THF/0 °C/3 h; (xiii) aqueous-ethanolic KOH/25 °C/4 h.

extracted with $CHCl_3$ (2 × 15 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by purification of the residue by column chromatography (silica gel, 0–5% EtOAc/hexane) afforded pure **4**. Yield: 2.75 g (88%); colorless oil; $[\alpha]_D^{24} = +16.8$ (*c* 1.13, $CHCl_3$); IR: 3070, 1639 cm^{-1}; ^1H NMR: δ 1.07 (s, 9H), 1.38–1.44 (m, 2H), 1.50–1.64 (m, 8H), 2.12–2.21 (m, 2H), 3.68–3.79 (m, 1H), 3.89–3.96 (m, 2H), 4.04–4.09 (m, 1H), 4.87–4.99 (m, 2H), 5.74–5.78 (m, 1H), 7.36–7.44 (m, 6H), 7.67–7.76 (m, 4H); ^{13}C NMR: δ 19.3, 23.8, 23.9, 25.2, 26.9, 34.8, 36.1, 38.7, 65.8, 73.1, 77.3, 109.2, 117.4, 127.4, 127.5, 129.6, 129.7, 133.5, 133.8, 133.9, 135.9. Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.48; H, 8.36.

3.1.2. (4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhexan-1-ol 5

To a stirred and cooled (0 °C) solution of **4** (3.52 g, 7.82 mmol) in THF (20 mL) was added BMS (0.52 mL, 5.2 mmol), and the mixture stirred for 3 h at the same temperature. Aqueous 3 M NaOH (3.13 mL) was then added, followed by H_2O_2 (30%, 3.13 mL) at 0 °C. After stirring for 3 h at 0 °C and 12 h at room temperature, the mixture was extracted with EtOAc (3 × 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: 3.39 g (93%); colorless oil; $[\alpha]_D^{25} = +3.4$ (*c* 1.13, $CHCl_3$); IR: 3433 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.32–1.39 (m, 2H), 1.41–1.52 (m, 13H), 3.39 (t, *J* = 6.2 Hz, 2H), 3.64–3.72 (m, 1H), 3.78–3.83 (m, 1H), 3.92–4.13 (m, 2H) 7.32–7.47 (m, 6H), 7.64–7.77 (m, 4H); ^{13}C NMR: δ 19.4, 23.8, 23.9, 25.1, 26.9, 27.2, 30.2, 34.8, 36.1, 60.4, 62.7, 66.8, 73.6, 109.5, 127.5, 129.7, 133.5, 133.9, 135.8, 135.9. Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60. Found: C, 71.64; H, 8.78.

3.1.3. (4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhexanal 6

To a cooled (0 °C) and stirred suspension of PCC (1.90 g, 8.82 mmol) and NaOAc (10 mol %) in CH_2Cl_2 (20 mL) was added alcohol **5** (2.70 g, 5.77 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: 2.19 g (81%); colorless oil; $[\alpha]_D^{24} = +7.7$ (*c* 1.24, $CHCl_3$); IR: 2714, 1729 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.32–1.36 (m, 2H), 1.45–1.52 (m, 8H), 1.81–1.88 (m, 2H), 2.25–2.54 (m, 2H), 3.48–3.62 (m, 1H), 3.67–3.77 (m, 1H), 3.88–4.00 (m, 2H), 7.34–7.43 (m, 6H), 7.62–7.68 (m, 4H), 9.14 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR: δ 19.4, 23.8, 25.1, 26.3, 26.9, 34.7, 36.1, 38.8, 67.2, 73.3, 77.6, 109.7, 127.7, 129.8, 133.3, 133.5, 135.9, 202.2. Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21. Found: C, 72.21; H, 8.18.

3.1.4. Ethyl (6*S*,7*R*)-6-*tert*-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoct-2*E*-enoate 7

To a stirred suspension of pentane-washed NaH (0.444 g, 9.24 mmol, 50% suspension in oil) in THF (20 mL) was added triethyl phosphonoacetate (1.85 mL, 9.24 mmol) in THF (5 mL). After 15 min, when the solution became clear, the mixture was cooled to 0 °C, and the aldehyde **6** (2.15 g, 4.61 mmol) in THF (5 mL) was dropwise added into it. After stirring at room temperature for 18 h, the mixture was poured into ice-water and extracted with Et_2O (3 × 20 mL). The ether layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), dried, and concentrated in vacuo to give a residue, which upon column chromatography (silica gel, 0–10% Et_2O/hexane) furnished pure **7**. Yield: 2.25 g (91%); colorless oil; $[\alpha]_D^{24} = +12.7$ (*c* 1.07, $CHCl_3$); IR: 1716, 997 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.33–1.37 (m, 2H), 1.45–1.59 (m, 8H), 1.65–1.76 (m, 2H), 2.12–2.21 (m, 2H),

3.58–3.66 (m, 1H), 3.70–3.76 (m, 1H), 3.90–4.05 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 5.66 (d, J = 16.0 Hz, 1H), 6.71–6.79 (m, 1H), 7.32–7.43 (m, 6H), 7.62–7.68 (m, 4H); ^{13}C NMR: δ 14.2, 19.3, 23.7, 23.8, 25.0, 26.9, 32.1, 34.7, 36.0, 59.9, 67.0, 73.5, 77.4, 109.5, 121.1, 127.5, 129.7, 133.3, 133.6, 135.7, 135.8, 148.7, 166.5. Anal. Calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26. Found: C, 71.44; H, 8.48.

3.1.5. Ethyl (6*S*,7*R*)-6-*tert*-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoctanoate 8

A mixture of **7** (1.3 g, 2.42 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 furnished pure **8**. Yield: 1.25 g (~quant.); colorless oil; $[\alpha]_D^{24} = +7.7$ (c 1.06, $CHCl_3$); IR: 1735 cm^{-1}; ^{1}H NMR: δ 1.04 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.20–1.48 (m, 8H), 1.50–1.60 (m, 8H), 2.07–2.15 (m, 2H), 3.63–3.78 (m, 2H), 3.89–3.97 (m, 2H), 4.08 (q, J = 7.2 Hz, 2H), 7.32–7.42 (m, 6H), 7.63–7.70 (m, 4H); ^{13}C NMR: δ 14.1, 19.3, 23.6, 23.7, 23.8, 24.8, 25.1, 26.9, 33.6, 34.1, 34.7, 36.0, 60.0, 66.5, 73.5, 77.5, 109.3, 127.5, 129.6, 133.5, 134.0, 135.8, 173.5. Anal. Calcd for $C_{32}H_{46}O_5Si$: C, 71.33; H, 8.61. Found: C, 71.34; H, 8.47.

3.1.6. Ethyl (6*S*,7*R*)-6-*tert*-butyldiphenylsilyloxy-7,8-dihydroxyoctanoate 9

A mixture of **8** (1.20 g, 2.23 mmol) in CH_2Cl_2 (15 mL) and aqueous 80% TFA (8 mL) was stirred at 0 °C for 3 h and then at 25 °C until completion of the reaction (TLC, 24 h). Most of the solvent was removed in vacuo. The residue was 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), aqueous 10% $NaHCO_3$ (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 **9**. Yield: 0.830 g (81%); colorless oil; $[\alpha]_D^{25} = +26.5$ (c 1.08, $CHCl_3$); IR: 3455, 1731 cm^{-1}; ^{1}H NMR: δ 1.06 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.32–1.43 (m, 6H), 2.04–2.12 (m, 2H), 2.43 (br s, 2H), 3.63–3.72 (m, 3H), 3.80–3.84 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 7.36–7.47 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR: δ 14.2, 19.4, 24.7, 27.0, 29.7, 32.5, 33.9, 60.2, 63.1, 73.4, 75.1, 127.6, 127.8, 129.9, 133.0, 133.5, 135.8, 173.6. Anal. Calcd for $C_{26}H_{38}O_5Si$: C, 68.08; H, 8.35. Found: C, 67.86; H, 8.53.

3.1.7. Ethyl (6*S*)-6-*tert*-butyldiphenylsilyloxyoct-7-enoate 10

To a cooled (0 °C) and stirred solution of **9** (0.820 g, 1.79 mmol) in pyridine (8 mL) was added p-TsCl (0.750 g, 3.94 mmol). The reaction mixture was brought to room temperature and stirred for 24 h. It was then poured onto ice-cold water (30 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed successively with H_2O (2 × 10 mL), aqueous 2 M HCl (2 × 10 mL), 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 gave the pure ditosylate as a mixture of rotamers. Yield: 1.22 g (89%); colorless oil; $[\alpha]_D^{24} = +20.9$ (c 1.03, $CHCl_3$); IR: 1370, 1177 cm^{-1}; ^{1}H NMR: δ 1.00 (m, 9H), 1.23–1.51 (m, 7H), 1.60–1.80 and 1.90–2.10 (m, 2H), 2.45 (s, 6H), 3.80–3.88 (m, 1H), 4.03–4.28 (m, 3H), 4.34–4.43 (m, 1H), 4.56–4.70 (m, 1H), 7.30–7.48 (m, 8H), 7.50–7.69 (m, 10H); ^{13}C NMR: δ 14.2, 19.3, 21.7, 24.3, 26.8, 33.5, 33.8, 60.2, 67.0, 73.7, 80.8, 127.5, 127.7, 127.9, 128.1, 129.9, 130.0, 135.7, 136.1, 144.9, 145.1, 172.7.

A mixture of the above compound (1.22 g, 1.59 mmol), NaI (1.43 g, 9.53 mmol) and Zn-dust (0.650 g, 10.0 mmol) in DMF (10 mL) was heated at 90 °C for 8 h (TLC). The mixture was brought to room temperature, poured in H_2O (30 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed successively with 10% aqueous $Na_2S_2O_3$ (1 × 10 mL), H_2O (3 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–10% Et_2O/hexane) of the residue gave pure **10**. Yield: 0.565 g (84%); colorless oil; $[\alpha]_D^{24} = +21.3$ (c 1.01, $CHCl_3$); IR: 1735, 997 cm^{-1}; ^{1}H NMR: δ 1.05 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.39–1.58 (m, 6H), 2.16 (t, J = 7.0 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 4.92–5.01 (m, 3H), 5.70–5.80 (m, 1H), 7.33–7.38 (m, 6H), 7.61–7.68 (m, 4H); ^{13}C NMR: δ 14.2, 19.3, 23.9, 24.8, 26.9, 34.2, 37.0, 60.1, 74.3, 114.3, 127.3, 127.4, 129.4, 129.5, 134.1, 134.3, 135.8, 135.9, 140.6, 173.6. Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54. Found: C, 73.78; H, 8.71.

3.1.8. (2*R*,3*S*)-1,2-Cyclohexylidenedioxyundecan-3-ol 11

To a cooled (−78 °C) and stirred solution of $C_8H_{17}Li$ [prepared from 1-bromooctane (11.60 g, 60.0 mmol) and Li (0.890 g, 127.1 mmol)] in THF (80 mL) was added **2** (5.10 g, 30.0 mmol) in THF (20 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 upon column chromatography (silica gel, 0–15% EtOAc/hexane) furnished **11**. Yield: 7.32 g (86%); colorless oil; $[\alpha]_D^{24} = +12.6$ (c 1.02, $CHCl_3$), {lit.[10] $[\alpha]_D^{24} = +6.2$ (c 1.15, $CHC1_3$)}; IR: 3457 cm^{-1}; ^{1}H NMR: δ 0.86 (t, J = 6.4 Hz, 3H), 1.17–1.43 (m containing a s at δ 1.21, 16H), 1.56–1.79 (m, 8H), 1.94 (br s, 1H), 3.70–3.78 (m, 1H), 3.86–3.97 (m, 3H); ^{13}C NMR: δ 13.9, 22.5, 23.7, 23.9, 25.0, 25.7, 29.1, 29.4, 29.5, 31.7, 32.5, 34.8, 36.0, 63.9, 70.5, 78.2, 109.3. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.94; H, 11.50.

3.1.9. (2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-cyclohexylidenedioxyundecane 12

As described earlier, silylation of **11** (2.87 g, 10.10 mmol) with TBDPSCl (3.53 g, 12.85 mmol), imidazole (0.87 g, 12.85 mmol) and DMAP (catalytic) in CH_2Cl_2 (40 mL), followed by work up and column chromatography (silica gel, 0–5% EtOAc/hexane) afforded pure **12**. Yield: 4.54 (86%); colorless oil; $[\alpha]_D^{24} = +15.5$ (c 1.06, $CHCl_3$); IR: 3072, 3050 cm^{-1}; ^{1}H NMR: δ 0.89 (t, J = 6.4 Hz, 3H), 1.14–1.38 (m containing a s at δ 1.06, 25H), 1.48–1.72 (m, 8H), 3.66–3.75 (m, 2H), 3.80–3.87 (m, 1H), 3.93–4.10 (m, 1H), 7.34–7.47 (m, 6H), 7.67–7.75 (m, 4H); ^{13}C NMR: δ 14.1, 19.4, 22.6, 23.8, 23.9, 24.2, 25.2, 26.9, 29.1, 29.3, 29.6, 31.8, 34.1, 34.8, 36.1, 66.4, 73.7, 77.7, 109.3, 127.4, 129.5, 133.8, 134.3, 135.8, 135.9. Anal. Calcd for $C_{33}H_{50}O_3Si$: C, 75.81; H, 9.64. Found: C, 75.74; H, 9.48.

3.1.10. (2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxyundecane-1,2-diol 13

As described earlier, compound **12** (2.87 g, 5.50 mmol) was deacetalized in CH_2Cl_2 (20 mL) with aqueous 80% TFA (8.0 mL). Usual work up and column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) afforded pure **13**. Yield: 2.0 g (84%); colorless oil; $[\alpha]_D^{24} = +21.0$ (c 1.04, $CHCl_3$); IR: 3398 cm^{-1}; ^{1}H NMR: δ 0.89 (t, J = 6.8 Hz, 3H), 1.09–1.35 (m containing a s at δ 1.10, 21H), 1.45–1.55 (br m, 4H), 3.65–3.72 (m, 3H), 3.78–3.89 (m, 1H), 7.35–7.49 (m, 6H), 7.68–7.75 (m, 4H); ^{13}C NMR: δ 14.1, 19.4, 22.6, 24.8, 27.0, 29.1, 29.2, 29.4, 31.7, 32.9, 63.1, 73.6, 75.5, 127.5, 127.7, 129.7, 129.8, 133.1, 133.7, 135.9. Anal. Calcd for $C_{27}H_{42}O_3Si$: C, 73.25; H, 9.56. Found: C, 73.14; H, 9.72.

3.1.11. (2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-epoxyundecane 14

To a cooled (0 °C) stirred solution of **13** (1.10 g, 2.49 mmol) in pyridine (8 mL) was added PTSCl (0.475 g, 2.49 mmol) in portions. After stirring for 18 h at the same temperature, the mixture was

poured into ice-water and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to furnish the monotosylate. Yield: 1.30 g (84%); colorless oil; $[\alpha]_D^{24} = +19.5$ (*c* 1.16, $CHCl_3$); IR: 3528, 1362, 1177 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.02 (s, 9H), 1.25–1.42 (m, 14H), 2.18 (br s, 1H), 2.45 (s, 3H), 3.75–3.87 (m, 2H), 3.98–4.04 (m, 1H), 4.21–4.27 (m, 1H), 7.31–7.45 (m, 8H), 7.61–7.66 (m, 4H), 7.78 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ 14.0, 19.3, 21.5, 22.5, 24.5, 26.9, 28.9, 29.2, 29.3, 31.7, 32.7, 71.3, 71.5, 74.2, 127.4, 127.6, 127.9, 129.8, 132.5, 132.9, 133.5, 135.7, 144.8.

A mixture of the above compound (1.20 g, 2.01 mmol) and anhydrous K_2CO_3 (0.63 g, 4.58 mmol) in MeOH (10 mL) was stirred for 3 h at room temperature. The supernatant was decanted, and 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 **14**. Yield: 0.770 g (90%); colorless oil; $[\alpha]_D^{24} = +20.2$ (*c* 1.14, $CHCl_3$); IR: 1110 cm^{-1}; ^1H NMR: δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 1.22–1.40 (m, 12H), 1.53–1.59 (m, 2H), 2.11–2.16 (m, 1H), 2.43–2.48 (m, 1H), 2.86–2.91 (m, 1H), 3.37–3.43 (m, 1H), 7.32–7.48 (m, 6H), 7.64–7.72 (m, 4H); ^{13}C NMR: δ 13.9, 19.2, 22.5, 24.1, 26.7, 29.0, 29.2, 29.5, 31.7, 35.2, 45.9, 54.1, 73.1, 127.3, 127.4, 129.4, 129.5, 133.6, 133.7, 135.7. Anal. Calcd for $C_{27}H_{40}O_2Si$: C, 76.36; H, 9.49. Found: C, 76.42; H, 9.27.

3.1.12. (3*R*,4*S*)-4-*tert*-Butyldiphenylsilyloxydodec-1-en-3-ol 15

To a cooled (−40 °C) and stirred suspension of Me_3SI (1.25 g, 6.13 mmol) in THF (20 mL) was added *n*-BuLi (3.0 mL, 1.5 M in hexane, 4.91 mmol). After stirring for 1 h, compound **14** (0.522 g, 1.23 mmol) in THF (5.0 mL) was injected into the mixture and stirring was continued at −40 °C for 3 h and at room temperature for 12 h. Next, H_2O (15 mL) was added to the mixture. The organic layer was 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 **15**. Yield: 0.436 g (81%); colorless oil; $[\alpha]_D^{24} = +16.5$ (*c* 1.08, $CHCl_3$); IR: 3475, 997, 925 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 1.14–1.39 (m, 14H), 1.96 (br s, 1H), 3.48–3.52 (m, 1H), 4.01–4.07 (m, 1H), 4.93–5.23 (m, 2H), 5.74–5.95 (m, 1H), 7.34–7.43 (m, 6H), 7.61–7.65 (m, 4H); ^{13}C NMR: δ 14.1, 19.3, 22.6, 25.4, 26.9, 29.1, 29.2, 29.4, 31.8, 31.9, 74.3, 77.9, 117.6, 127.4, 127.5, 127.6, 129.7, 129.8, 133.4, 133.6, 135.5, 135.7, 135.9, 136.4. Anal. Calcd for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65. Found: C, 76.84; H, 9.48.

3.1.13. Ethyl (6*S*,9*R*,10*S*)-6,10-di-*tert*-butyldiphenylsilyloxy-9-hydroxyoctadeca-7*E*-enoate 16

A mixture of **10** (0.097 g, 0.23 mmol), **15** (0.153 g, 0.35 mmol) and Grubbs' 2nd generation catalyst (5 mol %) in CH_2Cl_2 (5 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 **16**. Yield: 0.120 g (63% based on **10**); colorless oil; $[\alpha]_D^{25} = +16.3$ (*c* 1.02, $CHCl_3$); IR: 3583, 1736 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.19–1.44 (m containing a s at δ 1.12, 36H), 1.48–1.74 (m, 6H), 2.16 (t, *J* = 7.2 Hz, 2H), 3.41–3.48 (m, 1H), 4.01–4.14 (m containing a q at δ 4.07, *J* = 7.2 Hz, 4H), 5.68–5.72 (m, 2H), 7.35–7.41 (m, 12H), 7.61–7.68 (m, 8H); ^{13}C NMR: δ 14.1, 14.2, 19.3, 22.6, 23.9, 24.8, 25.5, 26.9, 29.2, 29.4, 31.8, 31.9, 34.2, 37.0, 60.1, 74.2, 74.4, 78.0, 114.3, 127.3, 127.4, 127.6, 129.4, 129.5, 129.7, 129.8, 133.4, 133.7, 134.1, 134.4, 135.5, 135.8, 135.9, 140.6, 173.6. Anal. Calcd for $C_{52}H_{74}O_5Si_2$: C, 74.77; H, 8.93. Found: C, 74.98; H, 9.09.

3.1.14. Ethyl (6*S*,9*R*,10*S*)-6,9,10-trihydroxyoctadeca-7*E*-enoate 17

To a cooled (0 °C) and stirred solution of **16** (0.300 g, 0.36 mmol) in THF (5 mL) was added Bu_4NF (0.57 mL, 1 M in THF, 0.57 mmol). The reaction mixture was brought to room temperature and stirred until the reaction was complete (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 **17**. Yield: 0.112 g (87%); colorless oil; $[\alpha]_D^{24} = +3.3$ (*c* 1.22, $CHCl_3$); IR: 3435, 1729 cm^{-1}; ^1H NMR: δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.26–1.39 (m, 14H), 1.42–1.54 (m, 6H), 2.25 (t, *J* = 7.0 Hz, 2H), 2.50 (br s, 1H), 2.71 (br s, 2H), 3.51–3.56 (m, 1H), 4.01–4.17 (m, 4H), 5.56–5.68 (m, 2H); ^{13}C NMR: δ 14.2, 18.9, 24.8, 26.2, 26.6, 31.2, 31.5, 34.2, 36.5, 37.2, 73.0, 74.2, 75.0, 78.3, 131.2, 137.1, 173.7. Anal. Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 67.26; H, 10.88.

3.1.15. (6*S*,9*R*,10*S*)-6,9,10-Trihydroxyoctadeca-7*E*-enoic acid 1d

A solution of **17** (0.1 g, 0.28 mmol) in aqueous-ethanolic KOH (2 M, 5 mL) was stirred at room temperature for 4 h. Most of the solvent was removed in vacuo. The residue was taken in $CHCl_3$ (10 mL), and the extract washed with water (2 × 5 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by preparative thin layer chromatography of the residue (silica gel, 5% MeOH/$CHCl_3$) furnished pure **1d**. Yield: 0.087 g (95%); semi-solid; $[\alpha]_D^{24} = +5.7$ (*c*, 0.831, $CHCl_3$), $[\alpha]_D^{24} = +6.3$ (*c* 0.980, MeOH) {lit.[2] $[\alpha]_D^{25} = -10.7$ (*c* 0.15, MeOH) for natural **1d**}; IR: 3630–3550, 3488, 1729 cm^{-1}; ^1H NMR (500 MHz): δ 0.86 (t, *J* = 6.2 Hz, 3H), 1.22–1.39 (m, 14H), 1.40–1.61 (m, 6H), 2.25 (t, *J* = 6.8 Hz, 2H), 1.83 (br s, 1H), 2.41 (br s, 2H), 3.52–3.55 (m, 1H), 4.04–4.10 (m, 2H), 5.56 (dd, *J* = 15.4, 5.4 Hz, 1H), 5.67 (dd, *J* = 15.4, 5.4 Hz, 1H); ^{13}C NMR: δ 14.2, 23.8, 26.4, 26.9, 30.7, 30.8, 31.2, 33.9, 34.2, 37.7, 73.2, 75.0, 76.8, 130.8, 137.0, 177.2.

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