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Enantioselective syntheses of (−)-pinellic acid, α- and β-dimorphecolic acid

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Abstract—An efficient enantioselective convergent approach for the synthesis of (−)-pinellic acid **1**, α- and β-dimorphecolic acid (**2** and **3**) from 1,9-nonane diol is described. The synthetic strategy features Sharpless asymmetric hydroxylation, Sonogashira coupling and Birch reduction.

1. Introduction

Influenza is an infectious disease that infects birds and mammals (primarily in the upper airways and lungs in mammals) and is caused by an RNA virus of the *Orthomyxoviridae* family (the influenza viruses). The most common and characteristic symptoms of influenza in humans are fever, pharyngitis, myalgia, severe headache, coughing, and malaise. Flu rapidly spreads around the world in seasonal epidemics,[1] killing millions of people in pandemic years, and hundreds of thousands in nonpandemic years.

Kampo medicine, 'Sho-seiryu-to' was found to possess potent adjuvant activity by oral administration on nasal influenza infection and nasal influenza vaccination.[2] (−)-Pinellic acid **1** (9*S*,12*S*,13*S*-trihydroxy-10*E*-octadecenoic acid, Fig. 1) was isolated from the tubers of *Pinellia ternata*, one of the eight component herbs of the Kampo formula, Sho-seiryu-to (SST).[3] Pinellic acid is a novel and potentially useful oral adjuvant when used in conjunction with intranasal inoculation of influenza HA vaccines.[3a] Pinellic acid showed no haemolytic activity.[3a] Among the series of pinellic acid isomers, the (9*S*,12*S*,13*S*)-compound, which is a natural product, exhibited the most potent adjuvant activity.[4]

Unsaturated hydroxy fatty acids (**2**–**5**) play an important role in biological systems and were isolated from both animals and plants. β-Dimorphecolic acid (**2**) is a unique hydroxydienoid fatty acid, which was first isolated from the seed oil of *Dimorphotheca aurantiaca*.[5] It was also isolated from *Osteospermum aurantiaca*[5] and *Osteospermum ecklonis*.[6] However, its diene congener α-dimorphecolic acid **3** was isolated from the plant *Glechoma hederacea* L. Labiatae[7] (commonly known as '*lierre terrestre*', 'ground ivy' or 'creeping Charlie'), which has been demonstrated to be a calcium specific ionophore,[8] an inhibitor of acetylcholine esterase (ACE)[9] and aromatase,[10] as well as being implicated in the pathogenesis of familial Mediterranean fever.[11] In addition, it can competitively inhibit enzyme activity stimulated by PGE_1 and PGD_2. This fatty acid has been previously isolated from *Tragopogon porrifolius* L. Compositae[12] and *Xeranthemum annuurn* Asso Compositae.[13] It has also been found in rice plants infected with blast disease[14] and in bovine heart mitochondria.[8] This fatty acid contains structural features that are not typically found in plant fatty acids, including a C-9 hydroxyl group and C10–C12 conjugated double bonds, which possess a wealth of biological properties.[15] Owing to their lipid nature, long-chain fatty acids play a vital role in maintaining cellular properties,[16] and consequently can elicit a variety of biological responses. Little is known about the biological properties of β-dimorphecolic acid.

In the interest of evaluating the biological and pharmacological properties of these compounds, it was necessary to obtain sufficient quantities by chemical synthesis. Ōmura et al. reported the first synthesis of (−)-pinellic acid **1** and determined its absolute configuration by synthesizing all its isomers via regioselective Sharpless asymmetric dihydroxylation and stereoselective reduction,[17a,b] followed by another recent synthesis by Sabitha et al. via Sharpless asymmetric epoxidation.[17c] Rama Rao and co-workers[18a] accomplished the first total synthesis of racemic dimorphecolic acid and coriolic acid **4** from tetrahydrofurfuryl chloride. Subsequently Takeda and co-workers[18b] also synthesized racemic dimorphecolic acid by using Grignard

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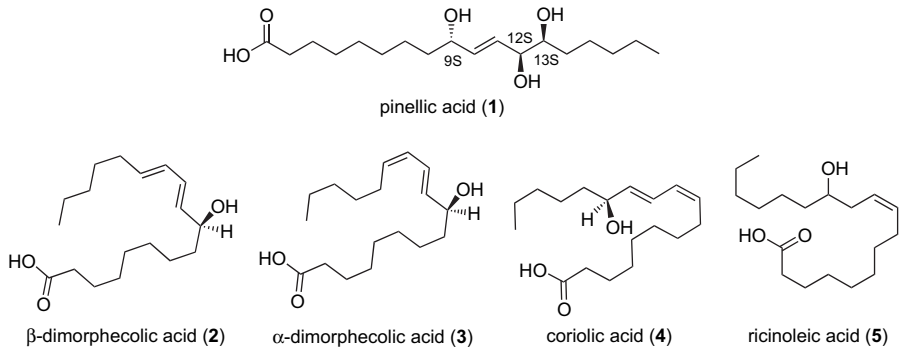


Figure 1.

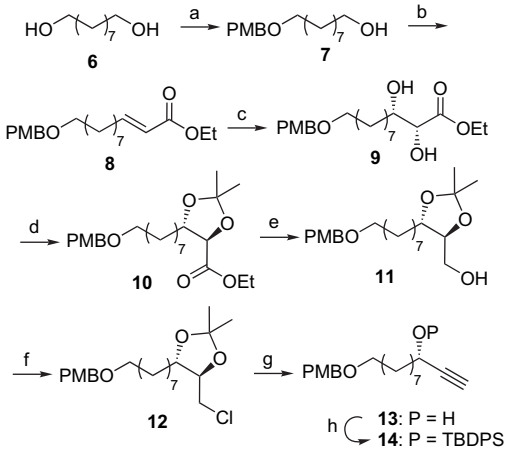
reactions. While Sato and co-workers[19a] accomplished stereospecific synthesis of α-dimorphecolic acid by employing Cu^{I}–Pd^{0} coupling as a key step, the enantioselective synthesis of β-dimorphecolic acid **2** was reported by Ley and Meek[19b] by utilizing a π-allyltricarbonyliron lactone complex to control the formation of all the stereochemical features of the natural product. As a part of our research programme aimed at developing enantioselective synthesis of naturally occurring lactones[20] and amino alcohols,[21] we have accomplished the stereoselective total synthesis of (−)-pinellic acid **1**, α- and β-dimorphecolic acid (**2** and **3**) starting from the commercially available starting material 1,9-nonane diol employing the Sharpless asymmetric dihydroxylation as the source of chirality.

2. Results and discussion

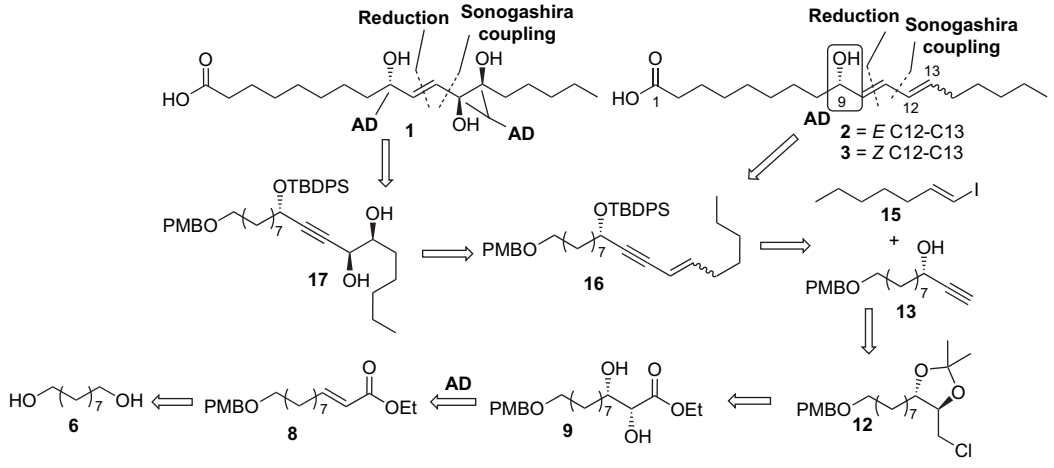
Our retrosynthetic strategy for the synthesis of (−)-pinellic acid **1**, α- and β-dimorphecolic acid (**2** and **3**) is outlined in Scheme 1. We envisioned that the 12*S*,13*S* *syn*-diol **17** could be prepared from 1,3-enyne **16**, which in turn would be prepared by Sonogashira coupling[22] of chiral propargylic alcohol **13** with vinyl iodide **15**. Chiral propargylic alcohol **13** could be prepared from 1,9-nonane diol **6**, through base induced elimination of chloro compound **12**. In this strategy, the 9*S* hydroxy group could be installed through Sharpless asymmetric dihydroxylation[23] of an olefin **8**, which in turn would be prepared from 1,9-nonane diol **6**.

2.1. Synthesis of chiral propargylic alcohol

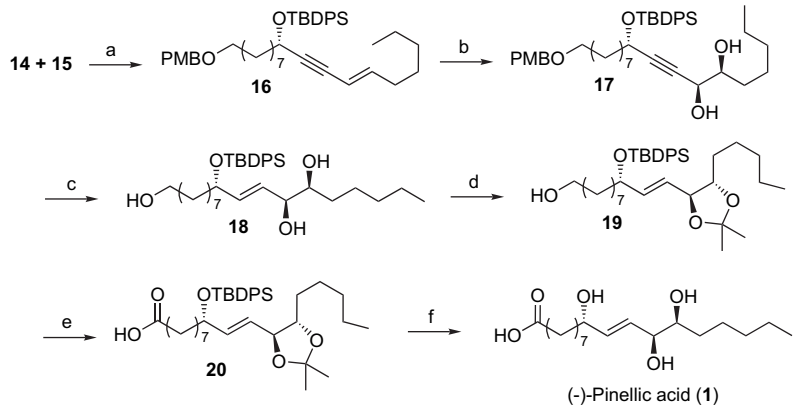
The synthesis of (−)-pinellic acid **1**, α- and β-dimorphecolic acid (**2** and **3**) started from commercially available 1,9-nonane diol **6** as illustrated in Schemes 2 and 3. Thus, selective



Scheme 2. Reagents and conditions: (a) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 95%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M solution in toluene), *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 94%; (e) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 95%; (f) *N*-chlorosuccinimide, PPh_3, CH_2Cl_2, 0 °C to rt, 3 h, 89%; (g) *n*-BuLi, HMPA, THF, −42 °C to rt, 30 min, 82%; (h) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, overnight, 98%.



Scheme 1. Retrosynthetic analysis of (−)-pinellic acid (**1**), α- and β-dimorphecolic acid (**2** and **3**).



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 6 h, 86%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M solution in toluene), *t*-BuOH/H_2O 1:1, 0 °C, 24 h, 91%; (c) Na/liq NH_3, THF, −40 °C, 90%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 92%; (e) (i) IBX, EtOAc, reflux, 5 h; (ii) $NaClO_2$, DMSO, NaH_2PO_4, rt, overnight, 81%; (f) HCl (cat.), MeOH, rt, overnight, 78%.

mono protection of **6** with *p*-methoxybenzyl bromide in the presence of NaH gave the monoprotected diol **7** in 95% yield, which was oxidized to the corresponding aldehyde under Swern conditions,[24] and subsequently treated with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene at reflux to furnish the *trans*-olefin **8** in 91% yield. Olefin **8** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under asymmetric dihydroxylation (AD) conditions[23] to give the diol **9** in 96% yield with 99% ee. Treatment of diol **9** with 2,2-dimethoxypropane in the presence of *p*-TSA gave compound **10**, which on reduction with DIBAL-H furnished the alcohol **11** in excellent yield. The alcohol **11** was converted to chloride **12** in 89% yield. Propargylic alcohol **13** was obtained by treatment of **12** with *n*-BuLi in the presence of HMPA[25] in 82% yield. The free hydroxy group of **13** was protected with TBDPSCl to furnish compound **14**.

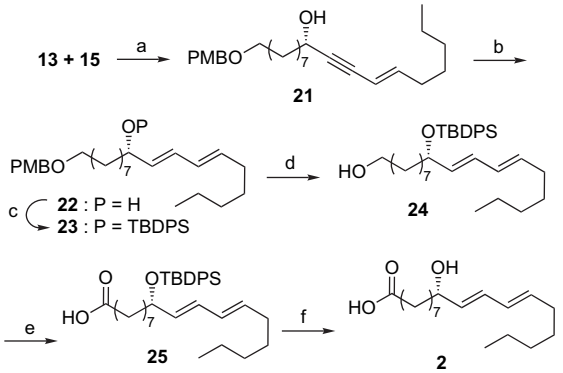
2.2. Synthesis of (−)-pinellic acid (1)

Having completed the synthesis of chiral propargylic alcohol **14**, our next aim was to prepare enyne **16** through Sonogashira coupling[22] and carry out subsequent transformations in order to get the target molecule **1**. Towards this, the coupling of **14** with *trans*-vinyl iodide **15**[26] using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished the 1,3-enyne product **16** in excellent yield (Scheme 3). Asymmetric dihydroxylation[23] of 1,3-enyne **16** under standard conditions gave the acetylenic diol **17** in good yield with high diastereomeric excess (de >96%) as judged by ^1H and ^{13}C NMR spectral analysis. Reduction of alkyne **17** to the (*E*)-alkene and concomitant removal of the PMB group proceeded smoothly under Birch conditions using Na/liq NH_3[27] to afford **18** in 90% yield. Diol **18** was protected as its isopropylidene derivative **19** in the presence of 2,2-dimethoxypropane and a substoichiometric amount of *p*-TSA in good yield.

Oxidation of the primary alcohol in **19** to the corresponding aldehyde using IBX[28] and further oxidation using $NaClO_2$ in DMSO under buffered conditions[29] furnished the acid **20**. Finally, the acetonide and TBDPS groups were deprotected under acidic conditions (catalytic HCl in MeOH) to afford the target molecule **1** in 78% overall yield from **19**. The physical and spectroscopic data of **1** were identical with those reported.[17]

2.3. Synthesis of β-dimorphecolic acid (2)

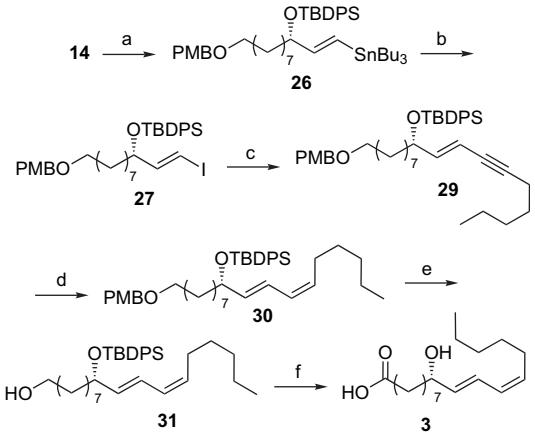
After completion of the synthesis of (−)-pinellic acid **1**, we then further proceeded with the synthesis of β-dimorphecolic acid **2** from 1,3-enyne product **21** (Scheme 4). Thus, coupling of **13** with *trans*-vinyl iodide **15** using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished the 1,3-enyne product **21** in 86% yield. Reduction of **21** proceeded smoothly with the required (*E*)-geometry of the alkene using LAH in refluxing THF to afford **22** in good yield. The free hydroxy group of **22** was protected with TBDPSCl followed by deprotection of the PMB group with DDQ[30] to furnish compound **24** in good yield. Oxidation of the primary alcohol in **24** to the corresponding aldehyde using Swern conditions[24] and further oxidation using $NaClO_2$ in DMSO under buffer conditions[29] afforded the acid **25**. Finally, the TBDPS group was deprotected using TBAF to afford the target molecule **2** in 89% yield. The physical and spectroscopic data of **2** were identical with those reported.[18,19,31]



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 8 h, 86%; (b) LAH, THF, 0 °C to rt, 83%; (c) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, overnight, 96%; (d) DDQ, CH_2Cl_2/H_2O (9:1), 89%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C; (ii) $NaClO_2$, DMSO, H_2O, NaH_2PO_4, rt, 1.5 h; (f) TBAF, THF, rt, overnight, 89%.

2.4. Synthesis of α-dimorphecolic acid

To achieve the synthesis of α-dimorphecolic acid, chiral propargylic alcohol **14** was converted into (*E*)-vinyl iodide through a vinyl stannane (Scheme 5). Thus, acetylene **14** was readily converted into (*E*)-vinyl stannane **26** by reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene in 99% yield. Tributyltin was then replaced with iodide by using I_2 in CH_2Cl_2[32] to afford the corresponding iodo compound **27** in excellent yield. The Sonogashira coupling[22] of **27** with commercially available 1-heptyne **28** was successfully carried out using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **29** in good yield. The partial hydrogenation of the triple bond in **29** proved to be challenging. Irrespective of whether substoichiometric quantities or several molar equivalents of quinoline were present, the mixture of **30** and over hydrogenated product was formed. The use of 1-octene as a co-solvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene =10:1:1)[33] furnished the diene **30** as a single product. The subsequent deprotection of the *p*-methoxybenzyl group with DDQ[30] furnished the alcohol **31** in 94% yield. Oxidation of the resulting alcohol to the corresponding aldehyde using Swern conditions[24] and further oxidation using sodium chlorite in DMSO under buffer conditions[29] afforded the acid. Finally, the TBDPS group was deprotected using TBAF to afford the target molecule **3** in good yield. The physical and spectroscopic data of **3** were identical with those reported.[18]



Scheme 5. Reagents and conditions: (a) $(n\text{-Bu})_3SnH$, AIBN, C_6H_6, reflux, 4 h, 99%; (b) I_2, CH_2Cl_2, 30 min, 96%; (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 1-heptyne (**28**), 6 h, 89%; (d) H_2, Lindlar's catalyst, EtOAc/pyridine/1-octene (10:1:1), 6 h, 95%; (e) DDQ, CH_2Cl_2/H_2O (9:1), 94%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C, 95%; (ii) $NaClO_2$, DMSO, H_2O, NaH_2PO_4, rt, 1.5 h, 86%.

3. Conclusions

In conclusion, efficient total syntheses of (−)-pinellic acid **1**, α- and β-dimorphecolic acid (**2** and **3**) with high enantioselectivity have been developed in which all the stereocentres were established by Sharpless asymmetric dihydroxylation. Notable features of this approach include Sonogashira coupling, reduction to establish the *trans*- and *cis*-olefin geometry. Further application of this methodology to the syntheses of related compounds for structure–activity relationship studies is currently underway in our laboratory.

4. Experimental

4.1. General methods

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded at 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100–200 and 230–400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Enantiomeric excess was determined using chiral HPLC.

4.1.1. 9-(4-Methoxybenzyloxy)nonan-1-ol (7). To a solution of 1,9-nonane diol **4** (8.0 g, 49.92 mmol) in dry DMF (200 mL) was added sodium hydride (50%, 2.64 g, 77.70 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (10.04 g, 49.92 mmol) and tetra *n*-butylammonium iodide (1.84 g, 4.99 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3× 100 mL). The combined organic layers were washed with water (3×100 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **7** (13.31 g, 95%) as a colourless oil. IR ($CHCl_3$): ν=3400, 2937, 2863, 1612, 1513, 1248, 1174, 1097 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.27–1.42 (m, 10H), 1.52–1.64 (m, 4H), 3.49 (t, J=5.0 Hz, 2H), 3.62 (t, J=5.0 Hz, 2H), 3.81 (s, 3H), 4.48 (s, 2H), 6.88 (d, J=10.0 Hz, 2H), 7.26 (d, J=10.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 26.1, 27.8, 28.9, 29.1, 29.6, 55.1, 62.2, 69.9, 72.5, 113.8, 129.2, 130.4, 159.2. Anal. Calcd for $C_{17}H_{28}O_3$ (280.40): C, 72.82; H, 10.06%. Found: C, 72.99; H, 9.87%.

4.1.2. (*E*)-Ethyl 11-(4-methoxybenzyloxy)undec-2-enoate (8). To a solution of oxalyl chloride (4.75 g, 37.44 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added dropwise dry DMSO (5.85 g, 5.3 mL, 74.89 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **7** (7.0 g, 24.96 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (10.10 g, 13.9 mL, 99.85 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (150 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of Celite. The filtrate was concentrated to give the aldehyde (9.86 g, 95%) as pale yellow oil, which was used as such for the next step without purification.

To a solution of (ethoxycarbonylmethylene)triphenyl-phosphorane (10.5 g, 30.17 mmol) in dry benzene (150 mL)

was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 4 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **8** (7.92 g, 91%) as a pale yellow liquid. IR ($CHCl_3$): ν=2956, 2858, 1724, 1654, 1038, 1300, 1204, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.30–1.37 (m, 11H), 1.48–1.68 (m, 4H), 2.28 (q, J=7.0 Hz, 2H), 3.48 (t, J=6.0 Hz, 2H), 3.85 (s, 3H), 4.25 (q, J=8.0 Hz, 2H), 4.48 (s, 2H), 5.90 (d, J=15.0 Hz, 1H), 6.91 (d, J=8.0 Hz, 2H), 6.98 (dt, J=15.0, 10.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 26.0, 27.8, 28.9, 29.1, 29.6, 32.0, 54.9, 59.9, 69.9, 72.3, 113.5, 121.1, 128.9, 130.6, 149.1, 158.9, 166.5. Anal. Calcd for $C_{21}H_{32}O_4$ (348.48): C, 72.38; H, 9.26%. Found: C, 72.52; H, 9.11%.

4.1.3. (2*R*,3*S*)-Ethyl 11-(4-methoxybenzyloxy)-2,3-dihydroxyundecanoate (9). To a mixture of $K_3Fe(CN)_6$ (17.01 g, 51.65 mmol), K_2CO_3 (7.14 g, 51.65 mmol) and $(DHQ)_2PHAL$ (134 mg, 1 mol %), in *t*-BuOH/H_2O (1:1, 175 mL) cooled at 0 °C was added OsO_4 (0.70 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methanesulfonamide (1.64 g, 17.22 mmol). After being stirred for 5 min at 0 °C, the olefin **8** (6.0 g, 17.22 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **9** (6.32 g, 96%) as a colourless syrupy liquid. The enantiomeric purity of the diol **9** was estimated to be >99% by chiral HPLC analysis (Chiralcel OD, petroleum ether/*i*-PrOH (96:4), 1 mL/min, 240 nm). $[\alpha]_D^{25}$ −6.7 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): ν=3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.25–1.36 (m, 13H), 1.50–1.74 (m, 4H), 2.51 (br s, 2H), 3.46 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.90 (d, J=6.6 Hz, 1H), 4.06–4.16 (m, 1H), 4.32 (q, J=7.0 Hz, 2H), 4.46 (s, 2H), 6.93 (d, J=8.5 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 25.5, 26.0, 29.2, 29.3, 29.5, 33.5, 55.0, 61.6, 70.0, 72.3, 73.0, 73.1, 113.6, 128.9, 130.7, 158.9, 173.4. Anal. Calcd for $C_{21}H_{34}O_6$ (382.50): C, 65.94; H, 8.96%. Found: C, 66.09; H, 8.81%.

4.1.4. (4*S*,5*S*)-Ethyl 5-(8-(4-methoxybenzyloxy)octyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (10). To a solution of the diol **9** (5.0 g, 13.07 mmol), *p*-TSA (100 mg) in CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (2.0 g, 19.61 mmol) and the reaction mixture stirred overnight at room temperature. Solid $NaHCO_3$ (1 g) was added and the mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and the filtrate concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent gave **10** (5.19 g, 94%) as a colourless liquid. $[\alpha]_D^{25}$ −23.1 (*c* 1.7, $CHCl_3$); IR (neat): ν=2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.29–1.40 (m, 13H), 1.46 (s, 3H), 1.49 (s, 3H), 1.56–1.63 (m, 2H), 1.66–1.80 (m, 2H), 3.45 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 4.11–4.14 (m, 2H), 4.25 (q, J=7.32 Hz, 2H), 4.45 (s, 2H), 6.91 (d, J=8.8 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.8, 25.4, 25.6, 25.9, 29.2, 29.3, 29.6, 54.8, 60.9, 69.3, 72.3, 78.7, 110.5, 113.5, 128.8, 130.3, 158.9, 172.5. Anal. Calcd for $C_{24}H_{38}O_6$ (422.56): C, 68.22; H, 9.06%. Found: C, 68.01; H, 9.21%.

4.1.5. ((4*S*,5*S*)-5-(8-(4-Methoxybenzyloxy)octyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (11). To a solution of **10** (5.0 g, 11.83 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added dropwise DIBAL-H (17.7 mL, 17.74 mmol, 1.0 M solution in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 °C and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **11** (4.28 g, 95%) as a colourless oil. $[\alpha]_D^{25}$ −13.05 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): ν=3440, 2938, 2860, 1361, 1204, 1126, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.28–1.40 (m, 10H), 1.41 (s, 3H), 1.42 (s, 3H), 1.51–1.63 (m, 4H), 2.18 (s, 1H), 3.46–3.54 (m, 2H), 3.61 (dd, J=7.5, 4.4 Hz, 1H), 3.76 (m, 2H), 3.81 (s, 3H), 3.90 (dt, J=7.6, 4.0 Hz, 1H), 4.44 (s, 2H), 6.89 (d, J=8.7 Hz, 2H), 7.25 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 25.4, 25.9, 26.9, 27.2, 29.3, 29.4, 29.7, 55.2, 62.1, 69.7, 72.4, 76.7, 81.6, 108.4, 113.7, 129.1, 130.5, 159.1. Anal. Calcd for $C_{22}H_{36}O_5$ (380.52): C, 69.44; H, 9.54%. Found: C, 69.62; H, 9.33%.

4.1.6. (4*S*,5*R*)-4-(8-(4-Methoxybenzyloxy)octyl)-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (12). To a solution of alcohol **11** (5.0 g, 13.14 mmol) and Ph_3P (4.14 g, 15.77 mmol) in dry CH_2Cl_2 (50 mL) was added NCS (2.11 g, 15.77 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature, and stirred for 2 h. The mixture was diluted with 100 mL of hexane and passed through a pad of Celite under suction to remove the precipitate of Ph_3PO. The filtrate was concentrated, and resulting residue was dissolved in 100 mL of hexane and passed through a pad of Celite to remove the precipitate of Ph_3PO again. Evaporation of solvent gave **12** (4.67 g, 89%) as a colourless oil. $[\alpha]_D^{25}$ −5.6 (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ=1.29 (br s, 10H), 1.40 (s, 3H), 1.41 (s, 3H), 1.52–1.61 (m, 4H), 3.42 (t, J=6.6 Hz, 2H), 3.57 (d, J=4.7 Hz, 2H), 3.79 (s, 3H), 3.84–3.88 (m, 2H), 4.42 (s, 2H), 6.88 (d, J=8.6 Hz, 2H), 7.23 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.8, 26.1, 27.0, 27.5, 29.3, 29.5, 29.7, 33.5, 44.4, 55.2, 70.2, 72.5, 79.4, 80.3, 109.1, 113.8, 129.1, 130.9, 159.1. Anal. Calcd for $C_{22}H_{35}ClO_4$ (398.96): C, 66.23; H, 8.84; Cl, 8.89%. Found: C, 66.45; H, 8.66; Cl, 8.92%.

4.1.7. (*S*)-11-(4-Methoxybenzyloxy)undec-1-yn-3-ol (13). To a solution of HMPA (11.43 g, 70.18 mmol) in dry THF (20 mL) was added *n*-BuLi (70.20 mL, 70.18 mmol, 1.0 M solution in hexane) at −42 °C under N_2. After 10 min, a solution of chloride **12** (4.0 g, 10.03 mmol) in THF (10 mL) was added dropwise over 5 min. The reaction mixture was warmed to room temperature and stirred for another 0.5 h. Saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with EtOAc (3× 30 mL), and combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column

chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **13** (2.50 g, 82%) as a colourless oil. $[\alpha]_D^{25}$ −1.75 (*c* 0.76, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ=1.33–1.51 (m, 10H), 1.59–1.79 (m, 4H), 1.86 (br s, 1H), 2.48 (d, *J*=2.0 Hz, 1H), 3.46 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 4.39 (dd, *J*=6.6, 1.8 Hz, 1H), 4.46 (s, 2H), 6.93 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=24.8, 25.9, 28.9, 29.1, 29.2, 29.4, 37.4, 55.0, 61.7, 69.9, 72.2, 72.4, 85.1, 113.5, 129.1, 130.4, 158.8. Anal. Calcd for $C_{19}H_{28}O_3$ (304.42): C, 74.96; H, 9.27%. Found: C, 74.81; H, 9.39%.

4.1.8. ((*S*)-11-(4-Methoxybenzyloxy)undec-1-yn-3-yloxy) (*tert*-butyl)diphenylsilane (14). A stirred solution of compound **13** (3.0 g, 9.85 mmol) and imidazole (1.0 g, 14.78 mmol) in dry CH_2Cl_2 (30 mL) was treated under argon with TBDPSCl (3.0 g, 10.84 mmol) at 0 °C and the reaction mixture was stirred overnight at the same temperature. The reaction mixture was quenched by addition of aqueous NH_4Cl (30 mL) and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave the compound **14** (5.24 g, 98%) as a colourless syrupy liquid. $[\alpha]_D^{25}$ −22.3 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): ν=3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.10 (s, 9H), 1.24 (br s, 10H), 1.53–1.72 (m, 4H), 2.33 (d, *J*= 2.0 Hz, 1H), 3.44 (t, *J*=6.6 Hz, 3H), 3.82 (s, 2H), 3.35 (ddd, *J*=6.1, 1.9 Hz, 1H), 4.45 (s, 2H), 6.92 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37–7.45 (m, 6H), 7.64–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.2, 24.3, 24.5, 26.1, 26.5, 26.8, 28.9, 29.25, 29.28, 29.65, 37.2, 38.1, 55.0, 63.6, 69.2, 70.0, 72.4, 85.0, 113.6, 117.0, 127.3, 127.5, 129.1, 129.4, 129.56, 129.65, 129.7, 130.7, 133.9, 134.7, 135.7, 135.9, 159.0. Anal. Calcd for $C_{35}H_{46}O_3Si$ (542.82): C, 77.44; H, 8.54%. Found: C, 77.51; H, 8.45%.

4.1.9. (*E*)-1-Iodohept-1-ene (15). Anhydrous $CrCl_2$ (22.09 g, 179.71 mmol) is suspended in THF (150 mL) under argon atmosphere. A solution of hexanaldehyde (3.0 g, 29.95 mmol) and iodoform (23.58 g, 59.90 mmol) in THF (30 mL) is added dropwise to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture is poured into water (100 mL) and extracted with ether (3×100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **15** (5.90 g, 88%) with *E*/*Z*=95:5 selectivity as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ=0.92 (t, *J*=7.1 Hz, 3H), 1.26–1.43 (m, 6H), 1.62 (q, *J*=7.4 Hz, 1H), 2.00–2.18 (m, 1H), 6.01 (d, *J*=15.4 Hz, 1H), 6.44–6.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 22.9, 28.5, 32.1, 34.4, 141.2, 82.1. Anal. Calcd for $C_7H_{13}I$ (224.08): C, 37.52; H, 5.85; I, 56.63%. Found: C, 37.81; H, 5.72; I, 56.56%.

4.1.10. ((*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-12-en-10-yn-9-yloxy) (*tert*-butyl)diphenylsilane (16). To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (181 mg, 0.257 mmol), CuI (147 mg, 0.77 mmol) in Et_3N (2 mL) were added solutions of (*E*)-1-iodohept-1-ene **15** (982 mg, 4.38 mmol) in Et_3N (2 mL) and acetylene **14** (1.2 g, 3.94 mmol) in Et_3N (2 mL) under argon. After 6 h, the reaction mixture was filtered through Celite and filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **16** (1.36 g, 86%) as a pale yellow oil. $[\alpha]_D^{25}$ 3.5 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$): ν=2952, 2854, 1615, 1514, 1232, 1132, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.91 (t, *J*= 6.4 Hz, 3H), 1.09 (s, 9H), 1.22–1.43 (m, 16H), 1.56–1.72 (m, 4H), 2.06 (q, *J*=7.0 Hz, 2H), 3.44 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.44 (s, 2H), 4.47–4.54 (m, 1H), 5.38 (dd, *J*= 15.8, 1.6 Hz, 1H), 5.76–5.97 (m, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 7.36–7.43 (m, 6H), 7.68–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 19.3, 22.4, 24.9, 26.1, 27.0, 28.4, 29.2, 29.4, 29.8, 31.2, 32.9, 38.4, 55.2, 64.4, 70.2, 72.5, 83.7, 89.2, 109.1, 113.7, 134.8, 135.9, 136.1, 144.0, 159.1. Anal. Calcd for $C_{42}H_{58}O_3Si$ (638.99): C, 78.94; H, 9.15; Si, 4.40%. Found: C, 78.76; H, 9.33; Si, 4.58%.

4.1.11. (6*S*,7*S*,10*S*)-10-(*tert*-Butyldiphenylsilyloxy)-18-(4-methoxybenzyloxy)octadec-8-yne-6,7-diol (17). To a mixture of $K_3Fe(CN)_6$ (1.55 g, 4.69 mmol), K_2CO_3 (649 mg, 4.69 mmol) and $(DHQ)_2PHAL$ (12 mg, 1 mol %), in *t*-BuOH/H_2O (1:1, 20 mL) cooled at 0 °C was added OsO_4 (0.06 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methanesulfonamide (149 mg, 1.56 mmol). After being stirred for 5 min at 0 °C, the olefin **16** (1.0 g, 1.56 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **17** (941 mg, 91%) as a colourless syrupy liquid. $[\alpha]_D^{25}$ +8.8 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J*= 6.8 Hz, 3H), 1.07 (s, 9H), 1.27 (br s, 18H), 1.57–1.73 (m, 4H), 2.34 (br s, 2H), 3.29–3.34 (m, 2H), 3.81 (s, 3H), 3.90 (t, *J*=7.3 Hz, 2H), 4.23–4.34 (m, 1H), 4.45 (s, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 7.35–7.49 (m, 6H), 7.69–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 13.9, 19.1, 22.5, 24.8, 25.1, 26.1, 26.8, 29.0, 29.3, 29.4, 29.7, 31.7, 32.1, 38.2, 55.2, 63.7, 65.9, 70.1, 72.4, 74.5, 83.2, 87.7, 113.7, 127.3, 127.6, 129.2, 129.6, 129.8, 130.7, 133.4, 134.1, 135.8, 135.9, 159.1. Anal. Calcd for $C_{42}H_{60}O_5Si$ (673.01): C, 74.95; H, 8.99; Si, 4.17%. Found: C, 75.10; H, 8.80; Si, 4.09%.

4.1.12. (9*S*,12*S*,13*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-octadec-10-ene-1,12,13-triol (18). To the blue solution prepared by addition of lithium metal (334 mg, 48.18 mmol) to liquid NH_3 (5 mL) was added a solution of **17** (450 mg, 0.668 mmol) in dry THF (5 mL) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by addition of 2.68 g (50.14 mmol) of NH_4Cl. After removal of NH_3 by a stream of N_2, the mixture was diluted with 50 mL of $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:6) as eluent gave the triol **18** (333 mg, 90%) as a colourless syrupy liquid. $[\alpha]_D^{25}$ 9.3 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3376, 1644, 1367, 1310, 1178, 1128, 1045, 980, 721 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ=0.87 (t, J=6.3 Hz, 3H), 1.04 (s, 9H), 1.4 (br s, 18H), 1.51–1.72 (m, 4H), 2.35 (br s, 2H), 3.38–3.48 (m, 1H), 3.61 (t, J=6.6 Hz, 2H), 3.94 (t, J=5.9 Hz, 1H), 4.08 (q, J=6.6 Hz, 1H), 5.67 (dd, J=15.5, 5.9 Hz, 1H), 5.86 (dd, J=15.5, 5.6 Hz, 1H), 7.36–7.43 (m, 6H), 7.66–7.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 22.6, 25.0, 26.1, 26.9, 28.1, 27.0, 28.1, 28.9, 29.1, 29.2, 31.8, 32.8, 32.9, 55.1, 64.1, 72.1, 74.6, 75.3, 127.5, 134.0, 134.8, 135.8, 136.1, 137.8. Anal. Calcd for $C_{34}H_{54}O_4Si$ (554.88): C, 73.60; H, 9.81; Si, 5.06%. Found: C, 73.8; H, 9.64; Si, 5.33%.

4.1.13. (*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-11-((4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)undec-10-en-1-ol (19). Compound **19** was prepared following the procedure described for compound **10** in 92% yield as a colourless liquid. $[\alpha]_D^{25}$ 16.1 (*c* 0.57, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.90 (t, J=6.3 Hz, 3H), 1.07 (s, 9H), 1.19–1.39 (br s, 18H), 1.41 (s, 3H), 1.45 (s, 3H), 1.54–1.73 (m, 4H), 2.31 (br s, 1H), 3.64 (t, J=6.6 Hz, 2H), 4.09 (q, J=6.6 Hz, 1H), 4.14–4.20 (m, 2H), 5.65 (dd, J=15.5, 7.1 Hz, 1H), 5.85 (dd, J=15.5, 5.7 Hz, 1H), 7.36–7.43 (m, 6H), 7.69–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 19.3, 22.5, 24.9, 26.1, 26.9, 28.3, 29.2, 29.4, 29.7, 31.2, 31.9, 32.6, 64.1, 71.7, 80.1, 81.9, 108.6, 127.4, 134.0, 134.8, 135.8, 136.1, 137.8. Anal. Calcd for $C_{37}H_{58}O_4Si$ (594.94): C, 74.70; H, 9.83; Si, 4.72%. Found: C, 75.01; H, 9.65; Si, 4.87%.

4.1.14. (*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-11-((4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)undec-10-enoic acid (20). To a solution of **19** (212 mg, 0.356 mmol) in EtOAc (5 mL) in 25 mL R.B. flask was added IBX (299 mg, 1.069 mmol) in one portion and the reaction mixture was refluxed for 5 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give the crude aldehyde, which was used in the next step without further purification.

A solution of 79% $NaClO_2$ (48 mg, 0.53 mmol) in 1.0 mL of water was added dropwise to a stirred solution of the above crude aldehyde (210 mg, 0.354 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (84 mg, 0.71 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated to give the acid **20** (81%, 174 mg) as a yellowish liquid. $[\alpha]_D^{25}$ −9.3 (*c* 0.43, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.89 (3H, t, J=6.3 Hz), 1.07 (s, 9H), 1.19–1.39 (br s, 16H), 1.41 (s, 3H), 1.45 (s, 3H), 1.50–1.62 (m, 4H), 2.26 (t, 2H, J=7.6 Hz), 3.41 (m, 1H), 4.12–4.16 (m, 2H), 5.66 (dd, 1H, J=15.6, 5.2 Hz), 5.71 (dd, 1H, J=15.6, 5.1 Hz), 7.36–7.43 (m, 6H), 7.69–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=177.6, 137.8, 136.1, 135.8, 134.8, 131.3, 134.0, 127.4, 108.6, 82.1, 80.3, 71.7, 38.8, 32.6, 31.9, 31.2, 29.7, 29.4, 29.2, 28.3, 26.9, 26.1, 24.9, 22.5, 19.3, 14.0. Anal. Calcd for $C_{37}H_{56}O_5Si$ (608.92): C, 72.98; H, 9.27%. Found: C, 73.10; H, 9.38%.

4.1.15. (9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecenoic acid [(−)-pinellic acid 1]. To a stirred solution of compound **20** (66 mg, 0.108 mmol) in MeOH was added a catalytic amount of concd HCl at room temperature and the reaction mixture stirred overnight at the same temperature. The mixture was filtered through a Celite pad and washed with MeOH and concentrated. The crude product was redissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using $CHCl_3$/MeOH (10:1) furnished the target compound pinellic acid (−)-1 (28 mg, 78%) as a white solid. R_f=0.24 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1). Mp: 104–106 °C (lit.[17a] mp: 104–106 °C); $[\alpha]_D^{25}$ −7.9 (*c* 0.30, MeOH) (lit.[17a] $[\alpha]_D^{25}$ −8.1 (*c* 0.32, MeOH)); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, J=6.3 Hz, 3H), 1.45–1.25 (m, 16H), 1.50–1.62 (m, 4H), 2.27 (t, J=7.6 Hz, 2H), 3.41 (m, 1H), 3.91 (dd, J=5.5, 5.0 Hz, 1H), 4.05 (m, 1H), 5.65 (dd, J=15.6, 5.2 Hz, 1H), 5.72 (dd, J=15.6, 5.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=177.6, 136.6, 131.2, 76.4, 75.8, 73.0, 38.3, 35.1, 33.6, 33.2, 30.5, 30.4, 30.1, 26.6, 26.5, 26.1, 23.7, 13.9.

4.1.16. (*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-12-en-10-yn-9-ol (21). To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (276 mg, 0.39 mmol), CuI (225 mg, 1.18 mmol) in Et_3N (2 mL) were added solutions of (*E*)-1-iodohept-1-ene **15** (1.50 g, 6.70 mmol) in Et_3N (2 mL) and acetylene **13** (1.2 g, 3.94 mmol) in Et_3N (2 mL) under argon. After 8 h, the reaction mixture was filtered through Celite and the filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **21** (1.36 g, 86%) as a pale yellow oil. $[\alpha]_D^{25}$ 1.75 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): ν=3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, J=6.7 Hz, 3H), 1.20–1.52 (m, 16H), 1.53–1.75 (m, 4H), 2.01–2.20 (m, 2H), 3.44 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 4.12–4.26 (m, 1H), 4.44 (s, 2H), 5.52 (dd, J=15.9, 1.64 Hz, 1H), 6.07–6.26 (m, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.29 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 22.5, 25.4, 25.6, 25.7, 28.3, 29.2, 29.4, 29.7, 31.2, 32.9, 38.4, 55.2, 64.4, 70.2, 72.5, 83.7, 89.2, 109.1, 113.7, 129.1, 130.9, 144.4, 159.1. Anal. Calcd for $C_{26}H_{40}O_3$ (400.59): C, 77.95; H, 10.06%. Found: C, 78.21; H, 10.11%.

4.1.17. (*S*,10*E*,12*E*)-1-(4-Methoxybenzyloxy)-octadeca-10,12-dien-9-ol (22). To a suspension of lithium aluminium hydride (61 mg, 1.62 mmol) in THF (40 mL) was added a solution of **21** (650 mg, 1.62 mmol) in THF (40 mL) at 0 °C. The mixture was warmed to room temperature and was stirred for 10 min. The mixture was refluxed for 1 h and then cooled to 0 °C. The reaction was quenched with saturated aqueous potassium sodium tartrate solution. After the suspension was stirred vigorously, the aqueous layer was extracted with ether. The ethereal extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **22** (542 mg, 83%) as a pale yellow oil. $[\alpha]_D^{25}$ 3.1 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν=3400, 2938, 2863, 1612, 1513, 1457, 1216, 1054, 990; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, J=6.7 Hz, 3H), 1.20–1.50 (m, 16H), 1.53–1.76 (m, 4H), 2.08 (q, J=6.8 Hz, 2H), 3.44 (t, J=6.6 Hz, 2H), 3.80 (s, 3H), 4.05–4.24 (m, 1H), 4.45 (s, 2H), 5.53 (dd, J=15.9, 6.5 Hz, 1H), 5.71 (m, 1H), 6.01 (dd, J=15.1, 6.6 Hz, 1H), 6.15 (dd, J=15.2, 10.5 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.29 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.8, 22.5, 25.4, 25.7, 28.9,

29.3, 29.4, 29.5, 31.4, 32.6, 32.8, 37.3, 55.0, 72.9, 73.1, 113.5, 129.1, 129.5, 130.1, 131.0, 133.6, 135.8, 158.8. Anal. Calcd for $C_{26}H_{42}O_3$ (400.59); C, 77.56; H, 10.51%. Found: C, 77.62; H, 10.33%.

4.1.18. ((*S*,10*E*,12*E*)-1-(4-Methoxybenzyloxy)-octadeca-10,12-dien-9-yloxy) (*tert*-butyl)diphenylsilane (23). Compound **23** was prepared following the procedure described for compound **14** in 96% yield as a colourless liquid. $[\alpha]_D^{25}$ +19.5 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): ν=2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.04 (s, 9H), 1.19–1.50 (m, 16H), 1.53–1.81 (m, 4H), 2.07 (q, *J*=7.0 Hz, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.10 (q, *J*=6.8 Hz, 1H), 4.44 (s, 2H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (m, 1H), 6.01 (dd, *J*=15.1, 6.8 Hz, 1H), 6.16 (dd, *J*=15.2, 10.5 Hz, 1H), 6.89 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H), 7.36–7.46 (m, 6H), 7.64–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 19.2, 22.5, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 54.9, 64.3, 70.3, 72.5, 113.8, 127.5, 127.6, 127.7, 129.1, 129.4, 129.5, 129.6, 130.1, 131.1, 133.4, 134.0, 135.7, 135.9, 159.0. Anal. Calcd for $C_{42}H_{60}O_3Si$ (641.01): C, 78.70; H, 9.43; Si, 4.38%. Found: C, 78.88; H, 9.29; Si, 4.51%.

4.1.19. (*S*,10*E*,12*E*)-9-(*tert*-Butyldiphenylsilyloxy)-octadeca-10,12-dien-1-ol (24). To a stirring solution of PMB ether **22** (380 mg, 0.59 mmol) in CH_2Cl_2/H_2O (10 mL/0.5 mL, 20:1) was added DDQ (161 mg, 0.71 mmol). The resulting mixture was stirred for 45 min at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was then filtered through a pad of Celite and washed with 50% EtOAc/hexane (20 mL). The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **24** (275 mg, 89%) as a colourless oil. $[\alpha]_D^{25}$ +6.28 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν=3400, 2928, 2855, 1659, 1589, 1464, 1427, 1389, 1216, 1112, 986 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.04 (s, 9H), 1.19–1.50 (m, 16H), 1.53–1.81 (m, 4H), 2.08 (q, *J*=7.0 Hz, 2H), 3.64 (t, *J*=6.6 Hz, 2H), 4.12 (q, *J*=6.6 Hz, 1H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (dt, *J*=15.2, 7.1 Hz, 1H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 6.16 (dd, *J*=15.2, 10.4 Hz, 1H), 7.36–7.45 (m, 6H), 7.66–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 19.2, 22.5, 25.6, 25.8, 26.9, 28.8, 29.5, 29.7, 31.5, 32.6, 32.7, 37.4, 64.1, 73.1, 127.6, 129.4, 129.5, 131.1, 133.6, 134.3, 135.7. Anal. Calcd for $C_{34}H_{52}O_2Si$ (520.86): C, 78.40; H, 10.06; Si, 5.39%. Found: C, 78.61; H, 9.87; Si, 5.52%.

4.1.20. (9*S*,10*E*,12*Z*)-9-Hydroxy-10,12-octadecadienoic acid [β-dimorphecolic acid] (2). To a solution of oxalyl chloride (76 mg, 0.05 mL, 0.60 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added dropwise dry DMSO (94 mg, 0.095 mL, 1.90 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **24** (210 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (0.163 g, 0.22 mL, 1.61 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×25 mL) and combined organic layers were washed with water (3×20 mL), brine (20 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde (302 mg) as pale yellow syrup, which was used as such for the next step without further purification.

A solution of 79% $NaClO_2$ (68 mg, 0. 60 mmol) in 1.0 mL of water was added dropwise to a stirred solution of crude aldehyde (209 mg, 0.40 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (97 mg, 0.81 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated to give the crude product **25**, which was used as such for the next step without further purification.

The above crude acid **25** (215 mg, 0.40 mmol) was dissolved in THF (5 mL), followed by the dropwise addition of TBAF (0.80 mL, 1 M solution in THF, 0.80 mmol). The reaction mixture was stirred at room temperature overnight and then quenched by addition of water, and the aqueous layer was extracted with EtOAc (3×30 mL) and combined EtOAc extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave β-dimorphecolic acid (**2**) (82 mg, 69% yield over three steps) as a cream-coloured solid. Mp 38–40 °C (lit.[19] 39–40 °C); $[\alpha]_D^{25}$ +15.1 (*c* 0.8, in MeOH) [lit.[19] $[\alpha]_D^{25}$ +15.4 (*c* 5.0, in MeOH)]; IR (KBr): ν=3422, 2924, 2869, 1712, 1459, 1321, 1211, 986 cm^{-1}; ^1H NMR (200 MHz, CD_3OD): δ=0.89 (t, *J*=6.8 Hz, 3H), 1.19–1.51 (m, 16H), 1.53–1.81 (m, 4H), 2.06 (q, *J*=7.0 Hz, 2H), 2.24 (t, *J*=7.5 Hz, 2H), 4.02 (q, *J*=6.6 Hz, 1H), 5.51 (dd, *J*=15.1, 6.5 Hz, 1H), 5.66 (m, 1H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 6.14 (dd, *J*=15.1, 10.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 22.5, 24.9, 25.3, 28.9, 29.1, 29.3, 29.7, 31.4, 32.6, 34.1, 37.2, 72.8, 129.4, 131.0, 133.5, 135.6, 178.5.

4.1.21. ((*S*,*E*)-11-(4-Methoxybenzyloxy)-1-(tributyl-stannyl)undec-1-en-3-yloxy) (*tert*-butyl)diphenylsilane (26). To a stirred solution of **14** (1.80 g, 3.32 mmol) in benzene (30 mL) were added *n*-Bu_3SnH (1.1 mL, 3.98 mmol) and AIBN (catalytic) at room temperature under N_2. The reaction mixture was gently refluxed with stirring for 4 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **26** (2.74 g, 99%) as yellowish oil. $[\alpha]_D^{25}$ −9.8 (*c* 0.64, $CHCl_3$); IR ($CHCl_3$): ν=3004, 2957, 2928, 2853, 1612, 1513, 1464, 1378, 1247, 1173, 1036 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.88–0.93 (m, 9H), 1.10 (s, 9H), 1.24 (br s, 10H), 1.26–1.31 (m, 10H), 1.42–1.74 (m, 12H), 3.44 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 4.12 (q, *J*=6.6 Hz, 1H), 4.45 (s, 2H), 5.95 (dd, *J*=19.0, 5.1 Hz, 1H), 6.36 (d, *J*=19.0 Hz, 1H), 6.92 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37–7.45 (m, 6H), 7.64–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=8.9, 9.4, 10.2, 10.6, 11.2, 13.5, 19.3, 24.2, 24.5, 26.1, 26.4, 26.9, 28.9, 29.3, 29.3, 29.7, 37.2,

38.1, 55.2, 61.8, 69.9, 72.3, 113.6, 117.0, 127.2, 127.3, 127.4, 129.2, 129.5, 129.56, 129.65, 129.7, 130.8, 133.9, 134.5, 134.9, 135.7, 135.9, 144.9, 159.1. Anal. Calcd for $C_{47}H_{74}O_3SiSn$ (833.88): C, 67.70; H, 8.94; Si, 3.37%. Found: C, 67.59; H, 9.21; Si, 3.62%.

4.1.22. ((*S*,*E*)-11-(4-Methoxybenzyloxy)-1-iodoundec-1-en-3-yloxy) (*tert*-butyl)diphenylsilane (27). To a cooled (0 °C), stirred solution of **26** (1.60 g, 1.92 mmol) in CH_2Cl_2 (40 mL) was added iodine (973 mg, 3.84 mmol). After 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $Na_2S_2O_3$ and 10% KF solutions, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **27** (1.24 g, 96%) as a yellowish oil. $[\alpha]_D^{25}$ −6.1 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$): ν=2948, 2933, 2861, 1612, 1515, 1465, 1372, 1174, 1092, 948 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.10 (s, 9H), 1.24 (br s, 10H), 1.53–1.72 (m, 4H), 3.47 (t, *J*=6.1 Hz, 2H), 3.92 (s, 3H), 4.12 (q, *J*=6.6 Hz, 1H), 4.45 (s, 2H), 6.29 (m, 2H), 6.53 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37–7.45 (m, 6H), 7.64–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.2, 24.3, 24.5, 26.1, 26.5, 26.8, 28.9, 29.25, 29.28, 29.65, 37.2, 38.1, 55.0, 62.8, 70.1, 72.2, 114.0, 117.0, 127.2, 127.3, 127.4, 128.6, 129.5, 129.6, 129.7, 130.8, 133.9, 134.5, 134.9, 135.7, 135.9, 147.6, 161.4. Anal. Calcd for $C_{35}H_{47}IO_3Si$ (670.74): C, 62.67; H, 7.06; I, 18.92%. Found: C, 62.89; H, 6.96; I, 19.24%.

4.1.23. ((*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-10-en-12-yn-9-yloxy) (*tert*-butyl)diphenylsilane (29). Compound **29** was prepared following the procedure described for compound **21** in 89% yield as a pale yellow oil. $[\alpha]_D^{25}$ −15.4 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν=3004, 2957, 2928, 2853, 1612, 1513, 1464, 1378, 1247, 1173, 1036 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.04 (s, 9H), 1.20–1.52 (m, 16H), 1.53–1.81 (m, 4H), 2.08 (q, *J*=6.8 Hz, 2H), 3.49 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.14–4.28 (m, 1H), 4.44 (s, 2H), 5.72 (dd, *J*=15.9, 1.64 Hz, 1H), 6.03–6.24 (m, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H), 7.36–7.45 (m, 6H), 7.66–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 19.2, 22.6, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 55.1, 64.6, 71.3, 72.5, 81.8, 82.4, 113.8, 127.5, 127.6, 127.7, 129.0, 129.4, 129.6, 130.5, 132.5, 133.8, 134.0, 135.7, 135.9, 159.1. Anal. Calcd for $C_{42}H_{58}O_3Si$ (638.99): C, 78.94; H, 9.15; Si, 4.40%. Found: C, 79.22; H, 9.01; Si, 4.67%.

4.1.24. ((*S*,10*E*,12*Z*)-1-(4-Methoxybenzyloxy)-octadeca-10,12-dien-9-yloxy) (*tert*-butyl)diphenylsilane (30). To a solution of **29** (620 mg, 0.97 mmol) in 10 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (20 mg). The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **30** (590 mg, 95%) as a pale yellow oil. $[\alpha]_D^{25}$ +12.59 (*c* 0.43, $CHCl_3$); IR ($CHCl_3$): ν=3600, 1715, 985, 950 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.90 (t, *J*=6.8 Hz, 3H), 1.04 (s, 9H), 1.19–1.51 (m, 16H), 1.54–1.80 (m, 4H), 2.09 (q, *J*=7.1 Hz, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.12 (q, *J*=6.9 Hz, 1H), 4.41 (s, 2H), 5.49 (dt, *J*=11.0, 7.1 Hz, 1H), 5.64 (dd, *J*=15.0, 7.0 Hz, 1H), 6.01 (dd, *J*=11.0, 11.0 Hz, 1H), 6.51 (dd, *J*=15.1, 11.0 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 7.36–7.48 (m, 6H), 7.66–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 19.2, 22.5, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 54.9, 64.9, 70.5, 72.3, 113.8, 113.8, 126.1, 127.5, 127.6, 127.9, 129.1, 129.4, 129.5, 129.6, 130.1, 131.1, 133.4, 134.0, 135.7, 135.9, 159.0. Anal. Calcd for $C_{42}H_{60}O_3Si$ (641.01): C, 78.70; H, 9.43; Si, 4.38%. Found: C, 78.84; H, 9.28; Si, 4.41%.

4.1.25. (*S*,10*E*,12*Z*)-9-(*tert*-Butyldiphenylsilyloxy)-octadeca-10,12-dien-1-ol (31). Compound **31** was prepared following the procedure described for compound **25** in 94% yield as a colourless liquid. $[\alpha]_D^{25}$ +10.1 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$): ν=3400, 2928, 2855, 1659, 1589, 1464, 1427, 1389, 1216, 1112, 986, 950, 985 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.05 (s, 9H), 1.19–1.52 (m, 16H), 1.53–1.79 (m, 4H), 2.21 (q, *J*=7.0 Hz, 2H), 3.68 (t, *J*=6.6 Hz, 2H), 4.07 (q, *J*=7.1 Hz, 1H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (m, 2H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 7.36–7.45 (m, 6H), 7.66–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 19.2, 22.9, 25.7, 25.8, 26.9, 28.8, 29.5, 29.7, 31.4, 32.6, 32.7, 37.8, 64.4, 73.1, 126.3, 127.6, 127.9, 129.4, 129.5, 133.2, 134.1, 135.7. Anal. Calcd for $C_{34}H_{52}O_2Si$ (520.86): C, 78.40; H, 10.06; 6.14; Si, 5.39%. Found: C, 78.53; H, 10.28; Si, 5.58%.

4.1.26. α-Dimorphecolic acid (3). Compound **3** was prepared following the procedure described for compound **2** in 89% yield as a yellow syrup. $[\alpha]_D^{25}$ +11.4 (*c* 0.4, in MeOH); IR (KBr): ν=3600, 1715, 950, 985 cm^{-1}; ^1H NMR (200 MHz, CD_3OD): δ=0.90 (t, *J*=6.7 Hz, 3H), 1.19–1.50 (m, 16H), 1.52–1.79 (m, 4H), 2.20 (m, 2H), 2.36 (t, *J*=7.0 Hz, 2H), 4.17 (q, *J*=7.0 Hz, 1H), 5.47 (dt, *J*=11.0, 7.1 Hz, 1H), 5.66 (dd, *J*=15.0, 7.0 Hz, 1H), 5.98 (dd, *J*=11.0, 11.0 Hz, 1H), 6.51 (dd, *J*=15.1, 11.0 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD): δ=14.1, 22.5, 25.6, 25.8, 26.9, 28.8, 29.5, 29.7, 31.5, 32.6, 32.7, 37.4, 73.0, 126.2, 127.9, 133.2, 135.9, 178.6.

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