Convergent Synthesis of Passifloricin A via a Prins Cyclisation and Olefin Cross-Metathesis Approach

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Abstract: A stereoselective and convergent approach to the total synthesis of the natural product passifloricin A is illustrated using Prins cyclisation and metathesis reactions as key steps.

Key words: passifloricin A, Prins cyclisation, cross-metathesis, ring-closing metathesis, lithium aluminum hydride–lithium iodide

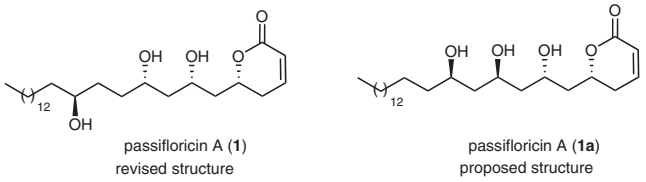


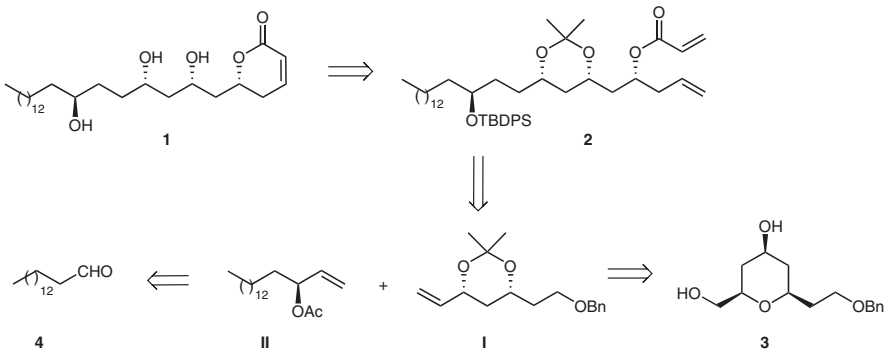
Figure 1

Passifloricin A (**1**), a 6-substituted α,β-unsubstituted δ-lactone (Figure 1), was isolated from *Passiflora foetida*,[1] a species from the family Passifloraceae which grows in tropical zones of America. It was found to show very interesting leishmanicidal[2] and antiprotozoal[3] activities. The relative configuration of passifloricin A has been established based purely on spectroscopic findings and the structure was proposed to be **1a** (Figure 1). Several syntheses[4] of the proposed structure **1a** of passifloricin A were reported; however, it was realised that the NMR data of the synthetic products did not match the data of the natural product and that they were different compounds. Quantum mechanical ^{13}C NMR GIAO chemical shift calculations,[5] as well as fluorous tagging en route,[6] also proved that the proposed structure was incorrect. The proposed structure **1a** was revised to structure **1** after the synthesis of several isomers[7] of the natural product and studies of their spectroscopic data. Later on, a linear synthesis of **1** appeared.[8]

We were attracted to passifloricin A (**1**) because of its interesting structure and important biological activities. The Prins cyclisation has emerged as a powerful synthetic tool for the construction of substituted tetrahydropyran rings of natural products.[9] In continuation of our interest in the Prins reaction[10] coupled with metathesis reactions and their exploration in the synthesis of molecules,[11] we now report a convergent synthesis of passifloricin A utilising Prins and metathesis reactions.

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecule **1** could be prepared through ring-closing metathesis of compound **2** which in turn could be made by a cross-metathesis reaction of two chiral allylic alcohol derivatives **I** and **II**. Compound **I** in turn could be obtained from tetrahydropyranol **3**, prepared by a Prins cyclisation reaction, whereas the chiral allylic acetate **II** could be obtained from the readily available aldehyde **4**.

The synthesis of fragment **I** (Scheme 2) began with the Prins cyclisation reaction of chiral homoallylic alcohol **5** with 3-(benzyloxy)propanal in the presence of trifluoroacetic acid, followed by hydrolysis of the resulting trifluoroacetate to afford the tetrahydropyranol **3** (enantiomer of **3**[11e]). The primary hydroxy group in compound **3** was selectively protected as its TBS ether **6**, and the secondary



Scheme 1 Retrosynthetic analysis for passifloricin A (**1**)

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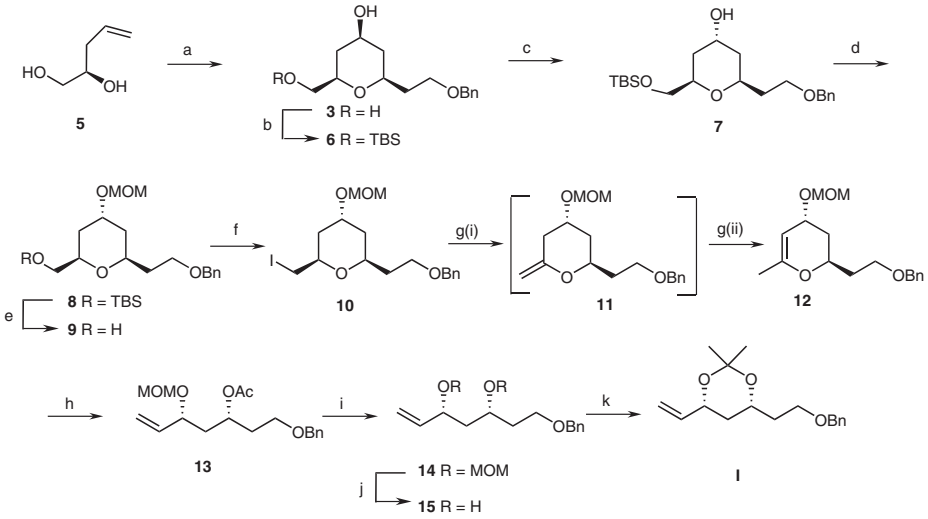


Scheme 2 *Reagents and conditions*: a) (i) 3-(benzyloxy)propanal, TFA, CH_2Cl_2, 3 h; (ii) K_2CO_3, MeOH, r.t., 0.5 h, 56% (over 2 steps); b) TBSCl, imidazole, CH_2Cl_2, 2 h, 92%; c) *p*-$O_2NC_6H_4CO_2H$, DEAD, Ph_3P, toluene, –78 to –20 °C, 1 h, then K_2CO_3, MeOH, r.t., 1 h, 75%; d) MOMCl, DIPEA, DMAP, CH_2Cl_2, r.t., 3 h, 92%; e) TBAF, THF, 0 °C, 8 h, 93%; f) I_2, Ph_3P, imidazole, MeCN–Et_2O, 0 °C, 2 h, 88%; g) (i) NaH, DMF, r.t., 6 h; (ii) silica gel rearrangement, 80%; h) (i) O_3, Ph_3P, CH_2Cl_2; (ii) $Ph_3P{=}CH_2$, *t*-BuOK, THF, –78 to 0 °C, 71% (over 2 steps); i) K_2CO_3, MeOH, r.t., 2 h, 95%; j) TFA, CH_2Cl_2, 25 °C, 2 h, 88%; k) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 2 h, 95%.

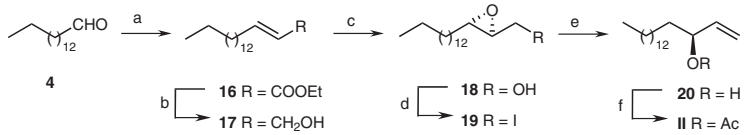
hydroxy group was inverted under standard Mitsunobu conditions[12] to afford **7**, which was expected to give the required *syn*-1,3-diol system after elaboration. Protection of the secondary alcohol in compound **7** as the methoxymethyl ether **8**, followed by removal of the silyl group, provided primary alcohol **9** in good yield. Treatment of alcohol **9** with iodine in the presence of triphenylphosphane and imidazole in acetonitrile–diethyl ether gave the corresponding iodo compound **10**. Elimination of hydrogen iodide[13] from **10**, using sodium hydride in *N*,*N*-dimethylformamide, provided enolic exocyclic alkene **11**, which on column chromatography using silica gel gave rearranged product **12**.

Compound **12** was subjected to ozonolysis to give the corresponding acetoxy aldehyde, which without purification was treated with methylene(triphenyl)phosphorane to furnish alkene **13**.[14] Hydrolysis of the acetate and removal of the MOM group resulted in diol **15**, which was protected as the acetonide, using 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate, to provide the desired chiral benzyl ether fragment **I**.

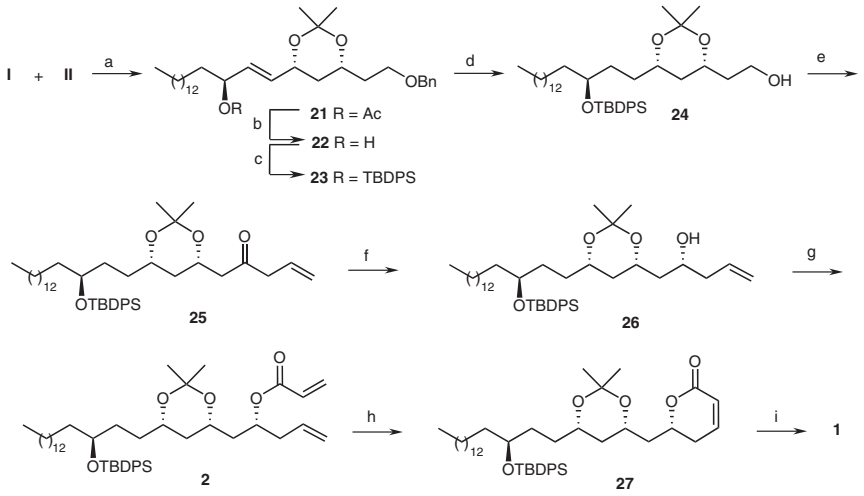
The synthesis of fragment **II** (Scheme 3) began from the commercially available aldehyde **4** by subjecting it to a Wittig reaction using ethyl (triphenylphosphoranylidene)acetate to give the α,β-unsaturated ester **16**, which was reduced using diisobutylaluminum hydride to give the corresponding allylic alcohol **17** in 92% yield. Epoxidation of the allylic alcohol **17** was achieved under Sharpless conditions using (+)-diethyl tartrate to give chiral epoxy alcohol **18**, which was converted into the corresponding epoxy iodide **19** using iodine, triphenylphosphane and imidazole in acetonitrile–diethyl ether in 90% isolated yield. The iodo compound **19** on refluxing in ethanol with zinc yielded the allylic alcohol **20**, from which the corresponding allylic acetate **II** was prepared, by treatment with acetic anhydride in the presence of triethylamine and 4-(dimethylamino)pyridine, to facilitate the cross-metathesis reaction as shown in Scheme 4.

After several trial reactions of the cross-metathesis reaction between two fragments with different protecting groups, we succeeded in obtaining high yields using allylic alcohol derivatives **I** and **II**, as shown in Scheme 4.

Accordingly, the chiral benzyl ether **I** was subjected to a cross-metathesis reaction with the allylic acetate **II** in the presence of Grubbs II catalyst in refluxing dichloromethane to furnish the desired cross-coupled product **21** (78%, based on conversion of **I**) along with trace amounts of homodimerised product (detected by MS). After hydrolysis of the acetate group, the secondary hydroxy group was protected as the TBDPS ether **23**, which was followed by catalytic hydrogenation using palladium on



Scheme 3 *Reagents and conditions*: a) $Ph_3P{=}CHCO_2Et$, benzene, r.t., 1 h, 95%; b) DIBAL-H, CH_2Cl_2, –15 °C to r.t., 2 h, 92%; c) *t*-BuOOH, 4 Å MS, Ti(O*i*-Pr)$_4$, (+)-DET, CH_2Cl_2, –20 ºC, 10 h, 92%; d) I_2, Ph_3P, imidazole, MeCN–Et_2O, 0 °C, 1.5 h, 90%; e) Zn, EtOH, reflux, 2 h, 95%; f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 96%.



Scheme 4 *Reagents and conditions*: a) 4 mol% Grubbs II catalyst, CH_2Cl_2, 40 °C, 10 h, 78%; b) K_2CO_3, MeOH, r.t., 1 h, 95%; c) TBDPSCl, imidazole, CH_2Cl_2, 4 h, 90%; d) H_2, Pd/C, EtOAc, r.t., 95%; e) (i) DMP, CH_2Cl_2, r.t., 1 h; (ii) allyl bromide, Zn, THF, 0 °C to r.t., 4 h, 88% (over 2 steps); (iii) DMP, CH_2Cl_2, r.t., 1.5 h, 85%; f) LAH–LiI (1:1), Et_2O, –100 to 0 °C, 1 h, 86%; g) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 1 h, 92%; h) Grubbs II catalyst, CH_2Cl_2, 40 °C, 3 h, 75%; i) 5 N aq HCl, THF, r.t., 8 h, 92%.

carbon in ethyl acetate to give the primary alcohol **24** in 95% yield.

Oxidation of the resulting alcohol **24** with Dess–Martin periodinane (DMP) in dichloromethane afforded the aldehyde, which on further treatment with allyl bromide and zinc in tetrahydrofuran gave carbinol as a diastereomeric mixture which, without characterisation, was subjected to oxidation to give ketone **25**. Ketone **25** was further subjected to a *syn*-stereoselective 1,3-asymmetric reduction using lithium aluminum hydride–lithium iodide[15] in diethyl ether at –100 °C to provide the desired homoallylic alcohol **26** in 86% yield (*syn*/*anti* = 95:5). The homoallylic alcohol **26** was esterified with acryloyl chloride to provide the diene **2**. The ring-closing metathesis reaction in refluxing dichloromethane using Grubbs II catalyst furnished the lactone **27**, which on treatment with 5 N hydrochloric acid in tetrahydrofuran gave the target molecule, passifloricin A (**1**), in 92% yield. The spectroscopic data and optical rotation values for the synthetic material are in agreement with those reported for the natural product.[7]

In conclusion, the total synthesis of passifloricin A has been achieved in a stereocontrolled manner by the creation of chiral centres via Prins cyclisation, lithium aluminum hydride–lithium iodide reduction and Sharpless asymmetric epoxidation reactions.

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF and EtOAc. All reactions were monitored by TLC (silica gel coated plates, visualisation under UV light). *n*-Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Büchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini), Bruker UXNMR FT-300 MHz (Avance) and Inova FT-400 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR spectra were recorded neat or as KBr pellets on a Thermo-Nicolet Nexus 670 FT-IR spectrophotometer. Mass spectra were recorded under EI conditions at 70 eV on LC/MSD (Agilent Technologies) spectrometers. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F254 silica gel plates.

(2*R*,4*S*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-(hydroxymethyl)tetrahydro-2*H*-4-pyranol (3)

TFA (37.5 mL, 490.1 mmol) was added slowly to a soln of homoallylic alcohol **5** (2.5 g, 24.5 mmol) and 3-(benzyloxy)propanal (12.0 g, 73.5 mmol) in CH_2Cl_2 (90 mL) at r.t. under N_2 atmosphere. The reaction mixture was stirred for 3 h and then sat. $NaHCO_3$ soln (200 mL) was added and the pH was adjusted to >7 by the addition of Et_3N. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 70 mL); the organic layers were combined and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (40 mL) and the solution was stirred with K_2CO_3 (6.77 g) for 30 min. The MeOH was then removed under reduced pressure and H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (EtOAc–hexane, 8:2) yielded **3** (3.65 g, 56%) as a gummy liquid.

$[\alpha]_D^{25}$ +13.1 (*c* 0.05, $CHCl_3$).

IR (neat): 3410, 2922, 2854, 1736, 1453, 1368, 1244, 1096, 1029, 742, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H), 4.47 (ABq, *J* = 12.5, 14.7 Hz, 2 H), 4.02–3.66 (m, 1 H), 3.66–3.30 (m, 6 H), 1.98–1.59 (m, 3 H), 1.57–1.30 (m, including two OH, 3 H), 1.28–1.06 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.3, 127.6, 75.9, 72.8, 72.7, 67.5, 66.5, 65.5, 40.9, 36.6, 35.9.

LC–MS: *m*/*z* = 289 $[M + Na]^+$.

(2*R*,4*S*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-([(*tert*-butyl)dimethylsilyl]oxymethyl)tetrahydro-2*H*-4-pyranol (6)

To a stirred soln of diol **3** (3.5 g, 13.1 mmol) in anhyd CH_2Cl_2 (25 mL), imidazole (1.78 g, 26.2 mmol) was added at 0 °C and the mixture was stirred for 15 min. Then, TBSCl (1.97 g, 13.1 mmol) was

added at 0 °C and the mixture was stirred for 2 h. After completion of the reaction as indicated by TLC, the reaction mixture was directly concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 3:7) to yield the pure product **6** (4.6 g, 92%) as a colourless liquid.

$[\alpha]_D^{25}$ +15.4 (*c* 1.0, $CHCl_3$).

IR (neat): 3403, 2926, 2859, 1451, 1367, 1096, 1028, 744 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 5 H), 4.46 (s, 2 H), 3.80–3.72 (m, 1 H), 3.67–3.43 (m, 5 H), 3.38–3.30 (m, 1 H), 2.0–1.86 (m, 2 H), 1.83–1.69 (m, 2 H), 1.41 (br s, 1 H), 1.17–1.04 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 128.2, 127.5, 127.4, 76.1, 72.9, 72.4, 68.0, 66.5, 66.2, 41.2, 37.7, 36.0, 25.8, –5.2.

LC–MS: *m*/*z* = 403 $[M + Na]^+$.

(2*R*,4*R*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-([(*tert*-butyl)dimethylsilyl]oxymethyl)tetrahydro-2*H*-4-pyranol (7)

To a stirred soln of alcohol **6** (4.5 g, 11.8 mmol) in toluene (30 mL) was added Ph_3P (6.2 g, 23.6 mmol) and *p*-nitrobenzoic acid (3.95 g, 23.6 mmol). The mixture was brought to –78 °C and DEAD (6.1 mL, 35.4 mmol) was slowly added. The mixture was slowly brought to –20 °C and stirred for 1 h. Then, the mixture was concentrated under reduced pressure. To the residue, MeOH (30 mL) and K_2CO_3 (2.76 g, 20 mmol) were added and the mixture was stirred for 1 h. Then, the reaction mixture was filtered through a plug of Celite® and washed with EtOAc. The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 3:7) to yield the pure product **7** (3.37 g, 75%) as a colourless liquid.

$[\alpha]_D^{25}$ +9.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3435, 2928, 2859, 1462, 1117, 1074, 837, 777 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5 H), 4.47 (s, 2 H), 4.24–4.20 (m, 1 H), 3.95–3.86 (m, 1 H), 3.81–3.73 (m, 1 H), 3.62–3.43 (m, 4 H), 1.77–1.57 (m, 4 H), 1.51–1.40 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.6, 128.3, 127.6, 127.4, 72.9, 72.2, 68.5, 66.8, 66.6, 64.4, 36.4, 35.1, 26.0, 18.4, –5.1.

LC–MS: *m*/*z* = 403 $[M + Na]^+$.

([(2*R*,4*R*,6*R*)-6-[2-(Benzyloxy)ethyl]-4-(methoxymethoxy)tetrahydro-2*H*-2-pyranyl]methoxy)(*tert*-butyl)dimethylsilane (8)

To a soln of alcohol **7** (3.2 g, 8.4 mmol) in anhyd CH_2Cl_2 (30 mL) at 0 °C were added DIPEA (9.7 mL, 56.6 mmol), DMAP (cat.) and MOMCl (1.4 mL, 16.8 mmol) successively and the mixture was stirred at r.t. for 3 h. The reaction was quenched by adding H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed with brine (15 mL), dried (Na_2SO_4, 2 g) and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc–hexane, 2:8) to afford the MOM ether **8** (3.28 g, 92%) as a colourless liquid.

$[\alpha]_D^{25}$ +12.6 (*c* 1.0, $CHCl_3$).

IR (neat): 2928, 2858, 1464, 1104, 1040, 838, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 5 H), 4.63 (s, 2 H), 4.48 (s, 2 H), 4.04–3.98 (m, 1 H), 3.91–3.80 (m, 1 H), 3.77–3.67 (m, 1 H), 3.62–3.42 (m, 4 H), 3.33 (s, 3 H), 1.82–1.62 (m, 3 H), 1.43–1.30 (m, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 128.2, 127.5, 127.3, 94.8, 72.9, 72.8, 69.8, 69.1, 66.8, 66.7, 55.2, 36.8, 36.5, 32.9, 26.0, 18.5, –5.0.

LC–MS: *m*/*z* = 447 $[M + Na]^+$.

[(2*R*,4*R*,6*R*)-6-[2-(Benzyloxy)ethyl]-4-(methoxymethoxy)tetrahydro-2*H*-2-pyranyl]methanol (9)

To a stirred soln of compound **8** (3.0 g, 7.07 mmol) in anhyd THF (15 mL), TBAF (1 M in THF; 7.1 mL, 7.1 mmol) was added slowly at 0 °C. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 3:7) to yield the pure product **9** (2.04 g, 93%) as a colourless liquid.

$[\alpha]_D^{25}$ +8.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3455, 2923, 2876, 1102, 1037, 740 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5 H), 4.63 (s, 2 H), 4.48 (ABq, *J* = 12.0, 4.5 Hz, 2 H), 4.05–3.99 (m, 1 H), 3.96–3.77 (m, 2 H), 3.60–3.47 (m, 3 H), 3.44–3.34 (m, 1 H), 3.33 (s, 3 H), 1.83–1.58 (m, 4 H), 1.51–1.29 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.5, 127.4, 94.8, 72.9, 72.5, 69.4, 69.2, 66.5, 66.0, 55.2, 36.4, 36.3, 32.0.

LC–MS: *m*/*z* = 333 $[M + Na]^+$.

(2*R*,4*R*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-(iodomethyl)-4-(methoxymethoxy)tetrahydro-2*H*-pyran (10)

To a soln of primary alcohol **9** (1.9 g, 6.1 mmol) in anhyd MeCN–Et_2O (1:1; 20 mL) were added imidazole (1.04 g, 15.2 mmol), Ph_3P (3.9 g, 15.2 mmol) and I_2 (2.32 g, 9.15 mmol) at 0 °C. The mixture was allowed to warm to r.t. and was stirred for 2 h. The reaction was quenched with sat. aq Na_2SO_3 (8 mL). The resultant mixture was diluted with EtOAc (20 mL), washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc–hexane, 1:9) gave iodide **10** (2.26 g, 88%) as a colourless, clear liquid.

$[\alpha]_D^{25}$ +2.2 (*c* 1.0, $CHCl_3$).

IR (neat): 2945, 2856, 1450, 1364, 1144, 1098, 1037, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 4.63 (s, 2 H), 4.49 (s, 2 H), 3.77–3.60 (m, 2 H), 3.59–3.48 (m, 2 H), 3.38–3.27 (m, 1 H), 3.33 (s, 3 H), 3.13 (d, *J* = 6.0 Hz, 2 H), 2.21–2.14 (m, 1 H), 1.94–1.84 (m, 1 H), 1.82–1.72 (m, 2 H), 1.26–1.09 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 128.2, 127.6, 127.4, 94.4, 74.9, 72.9, 72.6, 72.4, 66.3, 55.2, 38.1, 36.0, 8.7.

LC–MS: *m*/*z* = 443 $[M + Na]^+$.

(2*R*,4*R*)-2-[2-(Benzyloxy)ethyl]-4-(methoxymethoxy)-6-methyl-3,4-dihydro-2*H*-pyran (12)

To a soln of iodide **10** (2.2 g, 5.23 mmol) in DMF (100 mL) at 0 °C was added 60% NaH in oil (1.04 g, 26.15 mmol). After being stirred at r.t. for 6 h, the reaction mixture was quenched with H_2O (10 mL) at 0 °C. The resultant mixture was diluted with EtOAc (50 mL), washed with H_2O (25 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc–hexane, 2:8) gave exocyclic enol ether **11** which on column chromatography provided the rearranged product **12** (1.22 g, 80%) as a colourless, clear liquid.

$[\alpha]_D^{25}$ +24.6 (*c* 1.0, $CHCl_3$).

IR (neat): 2960, 2832, 1622, 1510, 1428, 1389, 1102, 745 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H), 4.72 (s, 1 H), 4.61 (s, 2 H), 4.53 (s, 2 H), 4.28 (m, 1 H), 3.61–3.51 (m, 2 H), 3.43–3.29 (m, 1 H), 3.36 (s, 3 H), 2.12–1.9 (m, 1 H), 1.9–1.2 (br m, 6 H).

LC–MS: *m*/*z* = 315 $[M + Na]^+$.

(1*R*,3*R*)-1-[2-(Benzyloxy)ethyl]-3-(methoxymethoxy)-4-pentenyl Acetate (13)

Ozone was bubbled through a soln of **12** (1.2 g, 4.1 mmol) in CH_2Cl_2 (12 mL) at –78 °C until no unreacted starting material was observed on TLC. The reaction mixture was purged with N_2 to re-

move the excess ozone and cooled to 0 °C. Ph_3P (2.1 g, 8.2 mmol) was added and the mixture was stirred for 2 h and then concentrated under reduced pressure. After hexane (20 mL) was added, the mixture was filtered through a Celite® pad and the residue was washed with hexane. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude aldehyde was subjected to the next reaction without further purification. To the ylide generated from methylene(triphenyl)phosphorane (4.9 g, 11.9 mmol) and *t*-BuOK (2.2 g, 20.5 mmol) in anhyd THF (30 mL), a soln of the aldehyde in anhyd THF (12 mL) was added at 0 °C. The mixture was stirred for 2 h at that same temperature. After completion of the reaction, the reaction mixture was quenched with sat. NH_4Cl soln (25 mL) and extracted with EtOAc (2 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc–hexane, 2:8) afforded **13** (0.94 g, 71%, over 2 steps) as a colourless oil.

$[\alpha]_D^{25}$ +8.7 (*c* 1.0, $CHCl_3$).

IR (neat): 2926, 2887, 1735, 1641, 1240, 1096, 1029, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 5 H), 5.70–5.53 (m, 1 H), 5.27–5.05 (m, 3 H), 4.66–4.60 (m, 1 H), 4.49–4.42 (m, 3 H), 4.01 (q, *J* = 6.7 Hz, 1 H), 3.52–3.41 (m, 2 H), 3.32 (s, 3 H), 1.97 (s, 3 H), 1.96–1.82 (m, 3 H), 1.81–1.65 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 138.2, 137.4, 128.3, 127.7, 127.5, 118.1, 93.6, 74.4, 73.0, 69.1, 66.5, 55.5, 40.0, 34.4, 21.2.

LC–MS: *m*/*z* = 345 $[M + Na]^+$.

(3*R*,5*R*)-1-(Benzyloxy)-5-(methoxymethoxy)-6-hepten-3-ol (14)

Compound **13** (1.5 g, 4.6 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (1.27 g, 9.2 mmol) was added. The mixture was stirred at r.t. for 2 h, then filtered through a plug of Celite® and concentrated under reduced pressure. Flash chromatography (EtOAc–hexane, 3:7) of the residue afforded **14** (1.23 g, 95%) as a colourless liquid.

$[\alpha]_D^{25}$ +5.8 (*c* 1.0, $CHCl_3$).

IR (neat): 3345, 2944, 2863, 1630, 1445, 1132, 1045, 740 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 5 H), 5.87–5.79 (m, 1 H), 5.21–5.02 (m, 2 H), 4.72–4.6 (m, 2 H), 4.49 (s, 2 H), 4.39–4.2 (m, 1 H), 3.92–3.86 (m, 1 H), 3.52–3.49 (m, 2 H), 3.35 (s, 3 H), 2.9 (br s, 1 H), 1.9–1.6 (m, 4 H).

LC–MS: *m*/*z* = 303 $[M + Na]^+$.

(3*R*,5*R*)-7-(Benzyloxy)-1-heptene-3,5-diol (15)

Compound **14** (1.1 g, 3.92 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (1.19 mL, 15.6 mmol) was added dropwise at 25 °C. The reaction mixture was stirred at that same temperature for 2 h, then was quenched with sat. $NaHCO_3$ soln (8 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (8 mL) and concentrated under reduced pressure. The residue was subjected to column chromatography (EtOAc–hexane, 6:4) to afford the pure diol **15** (0.81 g, 88%) as a colourless, gummy oil.

IR (neat): 3399, 2929, 2863, 1642, 1445, 1090, 995, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 5.89–5.75 (m, 1 H), 5.23 (td, *J* = 17.3, 1.5 Hz, 1 H), 5.04 (td, *J* = 10.5, 1.5 Hz, 1 H), 4.50 (s, 2 H), 4.38–4.29 (m, 1 H), 4.16–4.0 (m, 1 H), 3.76–3.58 (m, 2 H), 3.57–3.38 (br s, 1 H), 1.91–1.53 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7, 140.5, 128.3, 127.7, 127.6, 114.1, 73.2, 73.0, 71.5, 68.4, 43.0, 36.8.

LC–MS: *m*/*z* = 237 $[M + H]^+$.

(4*R*,6*R*)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-6-vinyl-1,3-dioxane (I)

To a stirred soln of diol **15** (0.82 g, 3.3 mmol) in anhyd CH_2Cl_2 (8 mL) was added 2,2-dimethoxypropane (15 mL) and a catalytic amount of PPTS, and the mixture was stirred at r.t. for 2 h. Et_3N (1 mL) was added to the mixture which was then stirred for 10 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 2:8) to yield compound **I** (0.91 g, 95%) as a colourless liquid.

$[\alpha]_D^{25}$ +11.3 (*c* 1.0, $CHCl_3$).

IR (neat): 2990, 2860, 1647, 1375, 1200, 1102, 739, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H), 5.83–5.69 (m, 1 H), 5.19 (td, *J* = 17.3, 1.5 Hz, 1 H), 5.06 (td, *J* = 10.5, 1.5 Hz, 1 H), 4.47 (ABq, *J* = 12.0, 2.0 Hz, 2 H), 4.36–4.25 (m, 1 H), 4.11–3.97 (m, 1 H), 3.61–3.45 (m, 2 H), 1.79–1.63 (m, 2 H), 1.54–1.20 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 138.5, 128.3, 127.6, 127.5, 118.2, 98.5, 72.9, 70.1, 66.0, 65.6, 36.4, 30.1, 19.7.

LC–MS: *m*/*z* = 299 $[M + Na]^+$.

Ethyl (*E*)-2-Heptadecenoate (16)

To aldehyde **4** (5 g, 22.1 mmol) was added benzene (50 mL) followed by the two-carbon Wittig ylide (9.2 g, 26.5 mmol) and the mixture was stirred at r.t. for 1 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with brine (15 mL) and H_2O (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude compound was eluted on a silica gel column (EtOAc–hexane, 1:9) to afford the pure ester **16** (6.2 g, 95%) as a colourless solid.

IR (KBr): 2925, 2854, 1723, 1654, 1179, 1043, 719 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 6.97–6.84 (m, 1 H), 5.81–5.72 (m, 1 H), 4.16 (q, *J* = 14.3 Hz, 2 H), 2.19 (dq, *J* = 1.5, 8.3 Hz, 2 H), 1.52–1.38 (m, 2 H), 1.36–1.16 (m, 25 H), 0.88 (t, *J* = 7.5 Hz, 3 H).

LC–MS: *m*/*z* = 319 $[M + Na]^+$.

(*E*)-2-Heptadecen-1-ol (17)

To a soln of ester **16** (4.5 g, 15.1 mmol) in anhyd CH_2Cl_2 (50 mL) cooled to –15 °C, 1 M DIBAL-H in CH_2Cl_2 (31.9 mL, 31.9 mmol) was added dropwise and the mixture was stirred at that temperature for 2 h. The reaction mixture was then quenched by the slow addition of anhyd MeOH (10 mL) and was brought to r.t. Sat. aq sodium potassium tartrate (30 mL) was added to the mixture which was stirred until two layers separated. The solvent was evaporated under reduced pressure and the remaining aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc–hexane, 2:8) afforded pure **17** (3.55 g, 92%) as a colourless solid.

IR (KBr): 3417, 2919, 2852, 1636, 1459, 756 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.69–5.56 (m, 2 H), 4.04 (d, *J* = 4.5 Hz, 2 H), 2.06–2.00 (m, 2 H), 1.45–1.20 (m, 24 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.5, 128.7, 63.8, 32.1, 31.8, 29.6 (several overlapped peaks), 29.4, 29.3, 29.1, 27.4, 14.0.

LC–MS: *m*/*z* = 277 $[M + Na]^+$.

[(2*S*,3*S*)-3-Tetradecyl-2-oxiranyl]methanol (18)

To a suspension of powdered, activated 4 Å molecular sieves (0.2 g) in anhyd CH_2Cl_2 (15 mL), $Ti(O\textit{i}\text{-}Pr)_4$ (0.69 mL, 2.3 mmol) and (+)-DET (0.4 mL, 2.3 mmol) were added sequentially at –20 °C and the mixture was stirred for 30 min. Allylic alcohol **17** (3 g, 11.8 mmol) in anhyd CH_2Cl_2 (20 mL) was added and stirring was con-

tinued for another 30 min at that same temperature. Then, 5 M *t*-BuOOH in toluene (4.7 mL, 23.6 mmol) was added and, after being stirred for another 10 h at that same temperature, the reaction mixture was quenched by the addition of H_2O (10 mL). The mixture was allowed to remain at r.t. with stirring for 30 min. After recooling to 0 °C, aq NaOH soln (30% w/v, 10 mL, saturated with brine) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 3:7) to afford pure **18** (2.93 g, 92%) as a colourless solid.

$[\alpha]_D^{25}$ –8.9 (*c* 1.0, $CHCl_3$).

IR (KBr): 3285, 2919, 2847, 1461, 1021, 721 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.95–3.83 (m, 1 H), 3.66–3.55 (m, 1 H), 2.97–2.85 (m, 2 H), 1.77 (br s, 1 H), 1.64–1.40 (m, 4 H), 1.36–1.18 (m, 22 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.7, 58.4, 55.9, 31.8, 31.5, 29.6 (several overlapped peaks), 29.5, 29.3, 25.9, 22.6, 14.0.

LC–MS: *m*/*z* = 293 $[M + Na]^+$.

(2*R*,3*S*)-2-(Iodomethyl)-3-tetradecyloxirane (19)

To a soln of epoxy alcohol **18** (2.5 g, 9.2 mmol) in anhyd MeCN–Et_2O (1:1; 25 mL) were added imidazole (1.32 g, 19.4 mmol), Ph_3P (5.3 g, 20.3 mmol) and I_2 (3.2 g, 12.9 mmol) at 0 °C. The mixture was allowed to warm to r.t. and was stirred for 1.5 h. The reaction was quenched with sat. aq $Na_2S_2O_3$ (25 mL). The resultant mixture was diluted with EtOAc (30 mL), washed with H_2O (20 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc–hexane, 1:9) gave iodide **19** (3.16 g, 90%) as a colourless solid.

$[\alpha]_D^{25}$ +4.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 2916, 2849, 1467, 1170, 882, 718 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.30–3.24 (m, 1 H), 2.96–2.90 (m, 2 H), 2.74–2.70 (m, 1 H), 1.59–1.40 (m, 4 H), 1.33–1.22 (m, 22 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.5, 58.2, 31.9, 31.6, 29.6 (several overlapped peaks), 29.3, 25.8, 22.6, 14.1, 5.0.

LC–MS: *m*/*z* = 403 $[M + Na]^+$.

(*S*)-1-Heptadecen-3-ol (20)

To a soln of iodide **19** (3 g, 7.8 mmol) in EtOH (20 mL), commercial Zn dust (10.3 g, 157.7 mmol) was added. The mixture was refluxed for 2 h and then cooled to 25 °C. NH_4Cl (4.0 g) was added and the mixture was filtered through a plug of Celite®. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc–hexane, 2:8) gave allylic alcohol **20** (1.90 g, 95%) as a colourless solid.

$[\alpha]_D^{25}$ +3.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3350, 2922, 2852, 1468, 922, 718 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.88–5.79 (m, 1 H), 5.20 (d, *J* = 17.3 Hz, 1 H), 5.08 (d, *J* = 12.8 Hz, 1 H), 4.10–4.04 (m, 1 H), 1.78 (br s, 1 H), 1.56–1.43 (m, 2 H), 1.36–1.19 (m, 24 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 114.9, 36.8, 31.9, 29.6, 29.5 (several overlapped peaks), 29.3, 25.3, 22.6, 14.1.

LC–MS: *m*/*z* = 277 $[M + Na]^+$.

(*S*)-1-Tetradecyl-2-propenyl Acetate (II)

To allylic alcohol **20** (1.5 g, 5.9 mmol) dissolved in CH_2Cl_2 (10 mL) was added Et_3N (2.4 mL, 17.7 mmol), Ac_2O (1.1 mL, 11.8 mmol) and DMAP (cat.) at 0 °C, and the mixture was stirred at r.t. for 2 h. The mixture was diluted with CH_2Cl_2 (4 mL), washed with H_2O (8 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 1:9) to obtain **II** (1.67 g, 96%) as a colourless liquid.

$[\alpha]_D^{25}$ –5.5 (*c* 1.0, $CHCl_3$).

IR (neat): 2925, 2854, 1741, 1461, 1237, 719 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82–5.68 (m, 1 H), 5.27–5.11 (m, 3 H), 2.05 (s, 3 H), 1.69–1.43 (m, 2 H), 1.36–1.19 (m, 24 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 136.6, 116.4, 74.8, 34.1, 31.9, 29.6 (several overlapped peaks), 29.3, 25.0, 22.6, 21.2, 14.0.

LC–MS: *m*/*z* = 319 $[M + Na]^+$.

(1*S*,2*E*)-3-((4*R*,6*R*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl)-1-tetradecyl-2-propenyl Acetate (21)

A mixture of compound **I** (1.2 g, 4.3 mmol), compound **II** (1.5 g, 5.2 mmol) and Grubbs II catalyst (5 mol%) in CH_2Cl_2 (10 mL) was stirred at 40 °C for 10 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc–hexane, 2:8) to give pure **21** (1.84 g, 78%) as a gummy liquid.

$[\alpha]_D^{25}$ –11.9 (*c* 1.0, $CHCl_3$).

IR (neat): 2925, 2854, 1737, 1458, 1372, 1238, 1099, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 5.67–5.51 (m, 2 H), 5.23–5.13 (dd, *J* = 6.0, 12.8 Hz, 1 H), 4.48 (ABq, *J* = 12.0, 14.2 Hz, 2 H), 4.35–4.25 (m, 1 H), 4.09–3.95 (m, 1 H), 3.61–3.44 (m, 2 H), 2.03 (s, 3 H), 1.80–1.07 (br m, 30 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 138.4, 133.0, 128.9, 128.3, 127.6, 127.5, 98.6, 73.9, 72.9, 69.0, 66.0, 65.7, 37.0, 36.4, 34.2, 31.8, 30.1, 29.6 (several overlapped peaks), 29.3, 25.0, 22.6, 21.2, 19.7, 14.0.

LC–MS: *m*/*z* = 567 $[M + Na]^+$.

(1*E*,3*S*)-1-((4*R*,6*R*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl)-1-heptadecen-3-ol (22)

Compound **21** (1.0 g, 1.8 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (0.5 g, 3.6 mmol) was added. After the mixture was stirred at r.t. for 1 h, it was filtered through a plug of Celite®. Removal of the solvent under reduced pressure followed by flash chromatography (EtOAc–hexane, 3:7) of the residue afforded alcohol **22** (0.87 g, 95%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +10.1 (*c* 1.5, $CHCl_3$).

IR (neat): 3422, 2922, 2852, 1462, 1378, 1103, 738 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 5.72–5.54 (m, 2 H), 4.47 (ABq, *J* = 2.2, 12.0 Hz, 2 H), 4.35–4.25 (m, 1 H), 4.10–3.96 (m, 2 H), 3.60–3.44 (m, 2 H), 1.79–1.62 (m, 2 H), 1.55–1.22 (br m, 28 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 134.2, 131.0, 128.3, 127.6, 127.5, 98.7, 73.0, 72.2, 69.3, 66.0, 65.7, 37.0, 36.5, 31.9, 30.2, 29.6 (several overlapped peaks), 29.5, 29.3, 25.4, 22.7, 19.8, 14.1.

LC–MS: *m*/*z* = 525 $[M + Na]^+$.

([(1*S*,2*E*)-3-((4*R*,6*R*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl)-1-tetradecyl-2-propenyl]oxy)(*tert*-butyl)diphenylsilane (23)

To a stirred soln of compound **22** (0.8 g, 1.59 mmol) in anhyd CH_2Cl_2 (10 mL), imidazole (0.21 g, 3.1 mmol) was added at 0 °C, and the mixture was stirred for 15 min. Then, TBDPSCl (0.45 mL, 1.75 mmol) was added at 0 °C and the mixture was stirred for 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was directly concentrated under reduced pressure and the residue was column chromatographed (EtOAc–hexane, 2:8) to yield the pure product **23** (1.06 g, 90%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +18.4 (*c* 1.0, $CHCl_3$).

IR (neat): 2982, 2846, 1472, 1110, 1034, 728 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.54 (m, 4 H), 7.42–7.17 (m, 11 H), 5.53 (dd, *J* = 7.9, 15.2 Hz, 1 H), 5.16 (dd, *J* = 5.8, 15.2 Hz, 1 H), 4.47 (ABq, *J* = 2.6, 12.2 Hz, 2 H), 4.18–4.01 (m, 2 H), 4.0–3.85 (m, 1 H), 3.59–3.39 (m, 2 H), 1.75–1.57 (m, 2 H), 1.53–1.11 (br s, 28 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.04 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

LC–MS: *m*/*z* = 763 $[M + Na]^+$.

2-((4*R*,6*S*)-6-[(3*S*)-3-([(*tert*-Butyl)diphenylsilyl]oxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (24)

To a stirred soln of **23** (0.9 g, 1.21 mmol) in EtOAc (15 mL) was added 10% Pd/C (0.2 g) and the mixture was stirred under H_2 atmosphere for 12 h. The mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 3:7) to obtain **24** (0.754 g, 95%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +4.2 (*c* 1.0, $CHCl_3$).

IR (neat): 3423, 2926, 2855, 1463, 1108, 1054, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.59 (m, 4 H), 7.45–7.27 (m, 6 H), 4.06–3.9 (m, 1 H), 3.78–3.56 (m, 4 H), 2.39–2.21 (br s, 1 H), 1.71–1.56 (m, 2 H), 1.44–1.08 (br m, 32 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 1.04 (s, 9 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.9, 134.7, 129.4, 127.4, 98.4, 77.4, 73.1, 69.1, 60.8, 38.1, 36.6, 36.3, 32.0, 31.7, 30.3, 29.7 (several overlapped peaks), 29.4, 27.2, 24.9, 22.7, 19.5, 14.2.

LC–MS: *m*/*z* = 654 $[M + 1]^+$.

1-((4*S*,6*S*)-6-[(3*S*)-3-([(*tert*-Butyl)diphenylsilyl]oxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl)-4-penten-2-one (25)

To a soln of DMP (0.68 g, 1.6 mmol) in CH_2Cl_2 (8 mL) at r.t. was added a soln of alcohol **24** (0.7 g, 1.07 mmol) in CH_2Cl_2 (6 mL). After being stirred for 1 h, the mixture was diluted with Et_2O (10 mL) and washed once with 10% $Na_2S_2O_3$–sat. aq $NaHCO_3$ soln (1:1; 5 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed once with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was directly used for the next reaction. To a stirred soln of this aldehyde (0.6 g, 0.91 mmol) in THF (10 mL) at 0 °C was added activated Zn (0.120 g, 1.82 mmol) and dropwise allyl bromide (0.15 mL, 1.82 mmol). After being stirred at r.t. for 4 h, the reaction mixture was quenched with sat. NH_4Cl soln (5 mL), and the product was extracted into EtOAc (2 × 10 mL). The combined organic phases were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried (Na_2SO_4) and concentrated, and the crude product was purified by column chromatography (EtOAc–hexane, 3:7) to obtain a diastereomeric mixture of secondary alcohol (0.65 g, 88%) as a pale yellow liquid. This alcohol was used for the next reaction without any further characterisation. To a soln of DMP (0.437 g, 1.29 mmol) in CH_2Cl_2 (8 mL) at r.t. was added a soln of the above alcohol (0.6 g, 0.86 mmol) in CH_2Cl_2 (6 mL). After being stirred for 1 h, the mixture was diluted with Et_2O (10 mL) and washed once with 10% $Na_2S_2O_3$–sat. aq $NaHCO_3$ soln (1:1; 5 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed once with brine (4 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 2:8) to yield ketone **25** (0.508 g, 85%) as a light yellow liquid.

$[\alpha]_D^{25}$ +12.1 (*c* 1.0, $CHCl_3$).

IR (neat): 2926, 2855, 1718, 1462, 1108, 1056, 703, 610 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.56 (m, 6 H), 7.44–7.26 (m, 4 H), 5.98–5.77 (m, 1 H), 5.20–4.99 (m, 2 H), 4.29–4.10 (m, 1 H), 3.75–3.55 (m, 2 H), 3.15 (d, *J* = 6.9 Hz, 2 H), 2.62 (dd, *J* = 6.6, 16.0 Hz, 1 H), 2.34 (dd, *J* = 6.8, 16.0 Hz, 1 H), 1.45–1.08 (br m, 32 H), 1.36 (s, 3 H), 1.29 (s, 3 H), 1.04 (s, 9 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.8, 135.9, 135.8, 134.7, 129.3, 127.3, 118.9, 73.0, 69.0, 65.6, 48.8, 48.7, 38.7, 36.6, 36.2, 31.9, 30.1, 29.7 (several overlapped peaks), 29.5, 29.3, 27.0, 23.7, 22.7, 19.4, 14.1.

LC–MS: *m*/*z* = 714 $[M + Na]^+$.

(2*R*)-1-((4*R*,6*S*)-6-[(3*S*)-3-([(*tert*-Butyl)diphenylsilyl]oxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl)-4-penten-2-ol (26)

To a soln of ketone **25** (0.4 g, 0.57 mmol) in anhyd Et_2O (10 mL) at r.t. under N_2 was added LiI (0.232 g, 1.7 mmol) and the mixture was stirred at –40 °C for 30 min. The resulting mixture was then cooled to –100 °C, LAH (0.06 mg, 1.59 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was then allowed to reach 0 °C, diluted with Et_2O (10 mL) and quenched by the dropwise addition of sat. aq Na_2SO_4 (10 mL). The solid material was collected by filtration and washed thoroughly with hot EtOAc several times. The combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 3:7) to afford alcohol **26** (0.34 g, 86%) as a light yellow, gummy liquid.

$[\alpha]_D^{25}$ +6.4 (*c* 1.0, $CHCl_3$).

IR (neat): 3452, 2926, 2855, 1378, 1107, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.61 (m, 4 H), 7.46–7.29 (m, 6 H), 5.94–5.75 (m, 1 H), 5.18–5.05 (td, *J* = 11.1, 5.2 Hz, 2 H), 4.20–3.98 (m, 1 H), 3.97–3.78 (m, 1 H), 3.77–3.52 (m, 2 H), 2.32–2.15 (m, 2 H), 1.64–1.52 (m, 2 H), 1.45–1.10 (br m, 32 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.1, 135.8, 133.9, 129.3, 127.4, 119.4, 98.2, 77.6, 72.2, 70.3, 58.2, 38.2, 36.2, 35.4, 32.3, 30.6, 29.7 (several overlapped peaks), 29.3, 27.0, 24.5, 22.4, 20.2, 14.5.

LC–MS: *m*/*z* = 693 $[M^+]$.

(1*R*)-1-[((4*S*,6*S*)-6-[(3*S*)-3-([(*tert*-Butyl)diphenylsilyl]oxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl)methyl]-3-butenyl Acrylate (2)

Acryloyl chloride (0.02 mL, 0.31 mmol) was added dropwise under N_2 to a soln of alcohol **26** (0.18 g, 0.25 mmol), Et_3N (0.1 mL, 0.64 mmol) and DMAP (cat.) in anhyd CH_2Cl_2 (5 mL) at 0 °C. The mixture was allowed to reach r.t. and stirred for 1 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with brine (3 mL) and extracted with CH_2Cl_2 (2 × 3 mL). The organic phases were washed with 1 M aq HCl (2 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 2:8) to give the pure acrylate **2** (0.178 g, 92%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +11.8 (*c* 1.0, $CHCl_3$).

IR (neat): 2883, 1726, 1644, 1488, 1143, 1092, 734 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.59 (m, 4 H), 7.45–7.28 (m, 6 H), 6.42 (dd, *J* = 16.4, 1.4 Hz, 1 H), 6.10 (dd, *J* = 16.4, 8.2 Hz, 1 H), 5.90–5.72 (m, 2 H), 5.12–5.02 (m, 3 H), 3.95–3.79 (m, 1 H), 3.80–3.56 (m, 2 H), 2.45–2.29 (m, 2 H), 1.49–1.09 (m, 34 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.03 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

LC–MS: *m*/*z* = 770 $[M + Na]^+$.

(6*R*)-6-[((4*S*,6*S*)-6-[(3*S*)-3-([(*tert*-Butyl)diphenylsilyl]oxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl)methyl]-5,6-dihydro-2*H*-2-pyranone (27)

Grubbs II catalyst (8 mg, 5 mol%) dissolved in CH_2Cl_2 (10 mL) was added to a soln of acrylic ester **2** (0.14 g, 0.18 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 40 °C for 3 h by which time all of the starting material was consumed (TLC). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc–hexane, 4:6) to obtain **27** (0.101 g, 75%) as a colourless, gummy liquid.

$[\alpha]_D^{25}$ +0.9 (*c* 1.0, $CHCl_3$).

IR (neat): 2926, 2855, 1729, 1462, 1380, 1107, 1054, 707 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.60 (m, 4 H), 7.43–7.30 (m, 6 H), 6.94–6.83 (m, 1 H), 6.03 (td, *J* = 10.0, 1.7 Hz, 1 H), 4.72–4.50 (m, 1 H), 4.20–3.96 (m, 1 H), 3.82–3.52 (m, 2 H), 2.50–2.18 (m, 2 H), 1.55–1.08 (m, 34 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 145.2, 136.0, 134.7, 129.4, 127.4, 121.3, 98.5, 74.7, 72.9, 69.0, 64.5, 42.1, 40.8, 37.0, 36.1, 31.8, 30.1, 29.6 (several overlapped peaks), 29.3, 24.8, 19.9, 14.0.

LC–MS: *m*/*z* = 736 $[M + NH_4]^+$.

Passifloricin A (1)

To a soln of compound **27** (0.08 g, 0.11 mmol) in THF (4 mL) was added 5 N aq HCl (2 mL), and the mixture was stirred at r.t. for 8 h. After completion of the reaction, the reaction mixture was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with H_2O (5 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography to afford compound **1** (0.045 g, 92%) as a colourless solid; mp 102–105 °C (Lit.[7] mp 103–106 °C).

$[\alpha]_D^{25}$ +34.3 (*c* 1.0, $CHCl_3$) {Lit.[7] $[\alpha]_D^{25}$ +33.3 (c 0.8, $CHCl_3$)}.

IR (KBr): 3325, 2917, 1707, 1530, 1251, 1027, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95–6.87 (m, 1 H), 6.03 (d, *J* = 9.8 Hz, 1 H), 4.75–4.63 (m, 1 H), 4.21–4.10 (m, 1 H), 4.02–3.91 (m, 1 H), 3.72–3.61 (m, 1 H), 2.46–2.40 (m, 1 H), 2.10–1.99 (m, 1 H), 1.83–1.37 (m, 8 H), 1.34–1.20 (m, 28 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 145.1, 121.1, 76.2, 72.4, 71.6, 69.6, 42.5, 42.4, 37.4, 34.2, 32.5, 32.0, 29.7 (several overlapped peaks), 29.4, 29.2, 25.7, 22.5, 14.0.

LC–MS: *m*/*z* = 463 $[M + Na]^+$.

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