Synthesis of *rac*-hippospongic acid A and revision of the structure

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rac-Hippospongic acid A of the reported structure **1** and the revised structure **2** were synthesized. The synthetic strategy of these compounds consists of homologation of (2*E*,6*E*,10*E*)-geranylgeraniol and (2*E*,6*E*)-farnesol, respectively, Wadsworth–Emmons reaction, and cyclization to form the tetrahydropyran ring bearing an α-methylene group on the carboxylic moiety. Spectral comparisons of the synthetic compounds **1**, **2** and the natural product suggested that hippospongic acid A bears the structure of **2**.

Introduction

Among the wide variety of recently isolated biologically active marine metabolites is a unique group of compounds consisting of a long chain hydrophobic moiety and a hydrophilic part, such as curacin A,[1] luffariolides A–E,[2] rhopaloic acid A,[3] amphimic acid A and B,[4] and (+)-hippospongic acid A,[5] *etc.* (+)-Hippospongic acid A, which was isolated from the marine sponge *Hippospongia* sp., has been reported to bear a novel triterpenoid structure (**1**) and to inhibit gastrulation of starfish embryos (Fig. 1). Biosynthetic consideration of **1** leads to the assumption that its formation is by tail to tail condensation of geranylgeranyl diphosphate (C_{20}) with geranyl diphosphate (C_{10}).[6] Further, this compound shares structurally common features with rhopaloic acid A which has been shown to exhibit potent cytotoxicity *in vitro* against human myeloid K-562 cells, human MOLT-4 leukemia cells and murine L1210 leukemia cells in addition to the bioactivity towards starfish embryos.[3] The interesting biological activity of these compounds may be attributed to the structurally unique feature of having a hydrophilic pyranylacrylic acid moiety connected to a hydrophobic linear isoprenoid part.

These unique structural and biological properties prompted us to undertake a synthetic investigation of **1**, which would establish a basis for future examinations of the structure–bioactivity relationship of hippospongic acid A and its analogs. Upon synthesis of **1** it was found that the reported structure did not match that of the natural product. Along with the synthesis of **1** we report the synthesis of **2**, which we conclude bears the correct structure of the natural product.

Results and discussion

We envisioned that the protocol utilized for the synthesis of rhopaloic acid A could be applied for the synthesis of **1** and **2**.[7] The synthetic strategy consists of successive homologations of (2*E*,6*E*,10*E*)-geranylgeraniol and (2*E*,6*E*)-farnesol, respectively, and cyclization to form the tetrahydropyran rings with concomitant introduction of an α-methylene group;[8] the flip in position of the methyl group of the side chain in **2** could be accommodated by an ortho Claisen rearrangement.

Synthesis of 1 bearing the reported structure

The two carbon homologation exploited malonic esterification starting from (2*E*,6*E*,10*E*)-geranylgeraniol (**3**). Treatment of **3** with PPh_3–CBr_4 at 25 °C afforded geranylgeranyl bromide. Treatment of the bromide with dimethyl malonate in the presence of NaH gave the alkyl malonate **5** in 76% yield over two steps. Demethoxycarbonylation of **5** under neutral conditions (NaCl in moist DMF) afforded the monomethyl ester **6**. Reduction of **6** with $LiAlH_4$ in Et_2O at −20 °C gave **7** in 94% yield. Oxidation of the alcohol **7** (94%) with PCC in the presence of Florisil gave the aldehyde **8** in 68% yield.

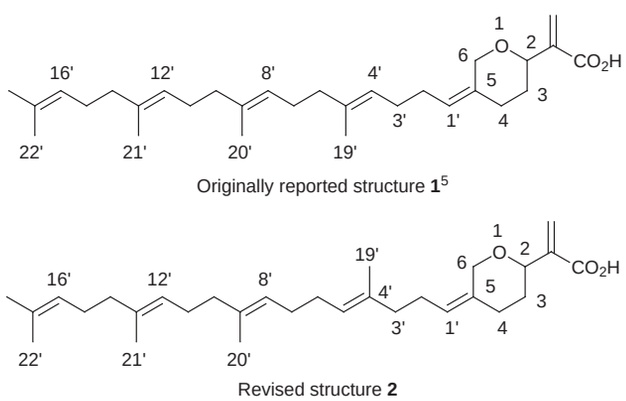
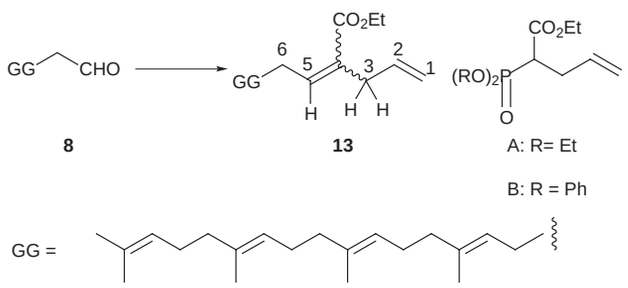


Fig. 1 Structures of hippospongic acid A.

In order to obtain the desired product (*Z*)-**13**, reaction conditions were examined in the Wadsworth–Emmons reaction of **8** (Table 1). The best results were when **8** was treated with $(EtO)_2P(O)CH(CH_2CH{=}CH_2)CO_2Et$ in the presence of NaH in THF at 0 °C; **13** was obtained as a mixture of geometric isomers (*Z*:*E* = 3:1) in 95% yield. The major isomer was assigned (*Z*)-**13** by comparison of ^{1}H NMR chemical shifts of the vinyl proton of the two isomers on the basis of the magnetic anisotropy of the ester group. The triplet signal at δ 6.84 assigned to the 5-vinyl proton of the minor isomer was observed at lower magnetic field than that (δ 5.90) of the major one, while 6-H methylene protons at δ 2.49 of the major isomer appeared at lower magnetic field than those (δ 2.21) of the minor one. Furthermore, difference ^{1}H NMR NOE experiments showed that irradiation of the vinylic 5-H (δ 5.90) of the major isomer resulted in enhancement of the intensity of the allyl-H signal (δ 2.99) by 4.1%. Separation of the mixture by column chromatography on silica gel (hexane–EtOAc, 99:1) afforded a pure sample of *Z*-isomer (*Z*)-**13**. Reduction of (*Z*)-**13** with $LiAlH_4$ in Et_2O at −20 °C selectively gave the desired compound **14** in quantitative yield. Protection of **14** with *tert*-

Table 1 Stereoselectivity in Wadsworth–Emmons reaction



Entry	Reagent and conditions	Solvent	Yield (%)	Ratio (Z:E)
1	A, NaH, 0 to 25 °C	THF	95	3.0:1.0
2	A, NaH, 0 to 25 °C	Et_2O	73	1.0:1.0
3	A, NaH, 0 to 25 °C	DMF	73	2.0:1.0
4	A, NaH, −78 to 25 °C	THF	70	0.8:1.0
5	A, Triton B, 0 to 25 °C	THF	81	0.7:1.0
6	A, *t*-BuOK, 0 to 25 °C	THF	67	0.8:1.0
8	B, NaH, −78 to 25 °C	THF	81	0.7:1.0
9	B, *t*-BuOK, −78 to 25 °C	THF	21	0.2:1.0

butyldimethylsilyl chloride followed by hydroboration with 9-BBN gave the primary alcohol **19** (62%, over two steps). Pyridinium chlorochromate oxidation of **19** afforded aldehyde **20** in 83% yield.

A modified Wadsworth–Emmons reaction of **20** with $(EtO)_2P(O)C(=CH_2)CO_2Me$ previously treated with $NaSCHMe_2$ gave **21** as a mixture of geometric isomers at the 2 position [(2Z)-**21**:(2E)-**21** = 1.7:1.0] in 94% yield. The geometry of the newly formed double bond was determined with difference ^{1}H NMR NOE experiments; when the vinylic 3-H (δ 5.99) of the minor isomer was irradiated, the intensity of the thiomethyl-H signal (δ 3.37) was enhanced by 4.0%. Exposure of **21** to methylation reagent MeI–$AgBF_4$ followed by desilylation with Bu_4NF afforded the methyl pyranylacrylate derivative **25** in 69% yield.[7,8] Hydrolysis of **25** with aq. LiOH afforded *rac*-**1** in 40% yield. A comparison of the spectra of synthetic *rac*-**1** with that of the natural product, however, showed some discrepancies, implying that the reported structure was not correct. The peaks at C3′, C4′, C5′ and C7′ (δ 25.7, 28.2, 125.0 and 134.3) are slightly different from that of the synthetic **1** (δ 26.6, 27.3, 123.5 and 135.8). Therefore, under the assumption that the originally reported assignment of the 19′ methyl group was wrong, we undertook the synthesis of isomeric compound **2**, which is more plausible from a biosynthetic viewpoint.

Synthesis of 2 bearing the revised structure

Compound **2** was synthesized from (2E,6E)-farnesol (**4**). Homologation of farnesol *via* the malonate derivative **9** by a procedure similar to that described for **3** gave the monomethyl ester **10** in 64% yield over three steps. Reduction of **10** with $LiAlH_4$ followed by Swern oxidation of the resulting alcohol **11** afforded the aldehyde **12** in 74% yield over two steps (Fig. 2). Treatment of aldehyde **12** with 2-propenyllithium at −78 to 25 °C gave **27** in 72% yield. Heating a mixture of **27** with 6 equiv. of triethyl orthoacetate in the presence of 0.06 equiv. propionic acid gave the ethyl ester **28** *via* Claisen rearrangement with high stereoselectivity (85%; E:Z = 96:4).[9] The major isomer was assigned (*E*)-**28** on the grounds of the NOE effect observed between H-3 (δ 2.29) and H-5 (δ 5.17) in the NOESY spectrum (Scheme 2). Reduction of **28** with $LiAlH_4$ followed by Swern oxidation of the resulting alcohol **29** afforded the aldehyde **30** in 77% yield over two steps.

The Wadsworth–Emmons reaction of **30** with $(EtO)_2P(O)CH(CH_2CH{=}CH_2)CO_2Et$ in the presence of NaH gave **16** as a mixture of geometric isomers (Z:E 1.3:1.0) in 91% yield. The double bond geometry was determined by analogy of the

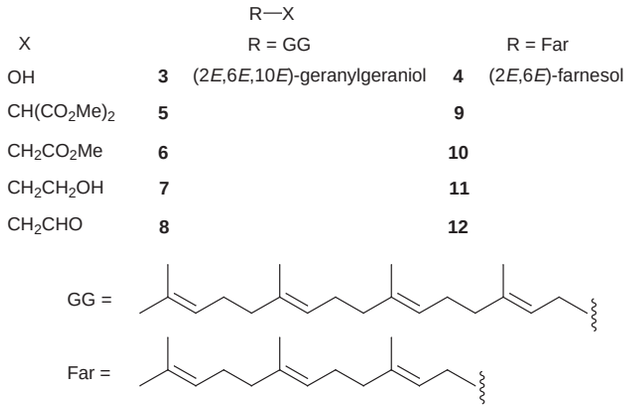


Fig. 2 Compounds of **3**–**8** and **9**–**12**.

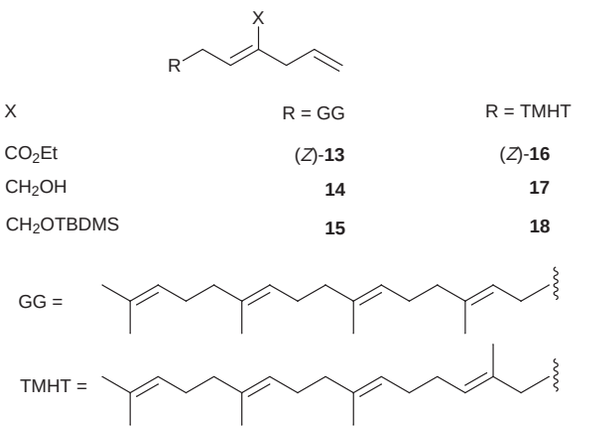


Fig. 3 Compounds of (*Z*)-**13**–**15** and (*Z*)-**16**–**18**.

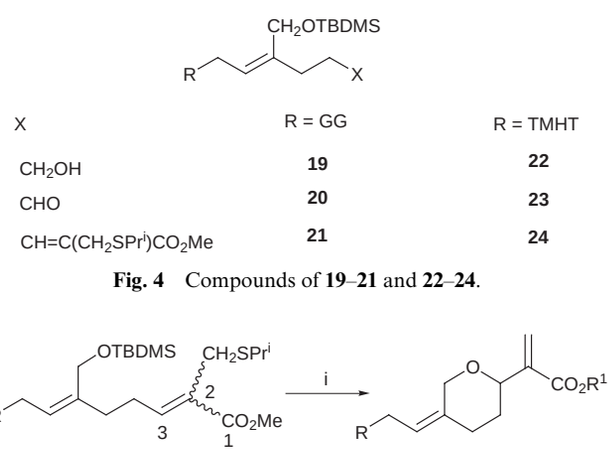
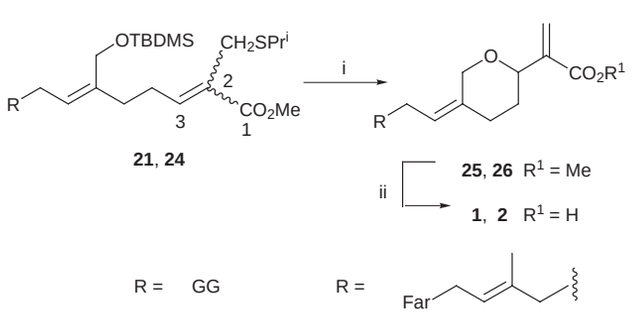


Fig. 4 Compounds of **19**–**21** and **22**–**24**.

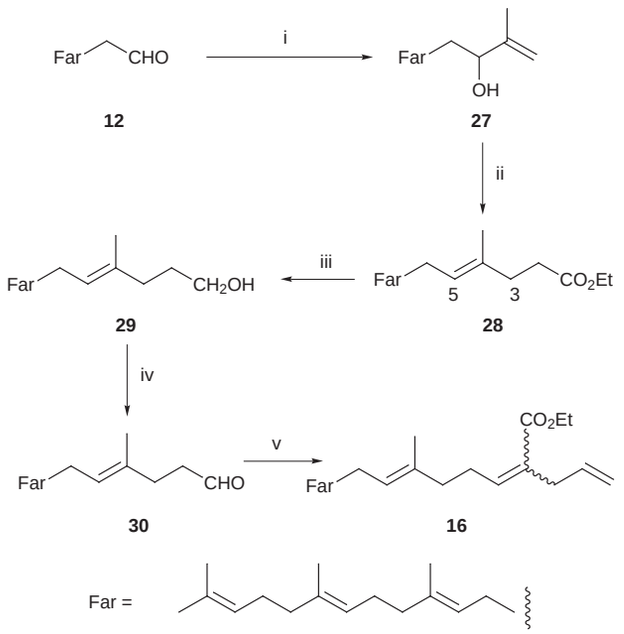


Scheme 1 Formation of pyranylacrylate moiety and hydrolysis.

spectra of **13** and **16**. Separation of the mixture of **16** on silica gel afforded pure (*Z*)-**16** (52%) along with (*E*)-**16** (39%).

Application of the procedures from (*Z*)-**13** to **1** (*vide supra*) to (*Z*)-**16** gave the carboxylic acid **2** by way of cyclization of **24** followed by hydrolysis of **26** (Fig. 3 and 4, Scheme 1).

The ^{1}H and ^{13}C NMR and mass spectra of the synthetic carboxylic acid **2** were nearly identical with those recorded for natural hippospongic acid A. The only notable difference was the ^{13}C chemical shift of the acrylic acid moiety which could be attributed to differences in the state of hydrogen bonding.



Scheme 2 *Reagents and conditions*: i, 2-bromopropene (1.9 equiv.), *t*-BuLi (3.8 equiv.), Et_2O, −78 to 25 °C, 8 h, 72%; ii, $CH_3C(OCH_3)_3$ (6 equiv.), propionic acid (0.06 equiv.), 138 °C, 1 h, 85%; iii, $LiAlH_4$ (1.1 equiv.), Et_2O, −20 to 25 °C, 6 h, 96%; iv, $(COCl)_2$ (1.1 equiv.), DMSO (1.3 equiv.), Et_3N (2.8 equiv.), −40 to 25 °C, 6 h, 80%; v, NaH (1.5 equiv.), $(EtO)_2P(O)CH(CH_2CH{=}CH_2)CO_2Et$ (1.5 equiv.), THF, 0 to 25 °C, 8 h, 91%.

In conclusion, the total synthesis of *rac*-hippospongic acid A has been achieved, leading to a revision of the reported structure of the natural product.

Experimental

All reactions were carried out under N_2. THF was distilled after refluxing over Na–benzophenone prior to use. CH_2Cl_2 was distilled over CaH_2 before use. Silica gel $60F_{254}$ was used for preparative thin layer chromatography (PTLC). NMR spectra were recorded on a JNM-LA500 instrument, and ^1H and ^{13}C NMR spectra were observed in $CDCl_3$ solutions with TMS as the internal reference. IR spectra were recorded on a JASCO IRA-1H instrument and MS spectra were recorded on a JEOL JMS-SX102A instrument under electron ionization (EI) conditions (70 eV). The primary alcohol **11** was prepared by the method previously described.[7]

Methyl (4*E*,8*E*,12*E*)-2-methoxycarbonyl-5,9,13,17-tetramethyloctadeca-4,8,12,16-tetraenoate 5

To a solution of (2*E*,6*E*,10*E*)-geranylgeraniol **2** (3.1 g, 11 mmol) and Ph_3P (3.3 g, 13 mmol) in CH_2Cl_2 (30 ml) was added CBr_4 (4.6 g, 14 mmol) at 25 °C in one portion. After stirring at the same temperature for 2 h, the mixture was quenched with aqueous $NaHCO_3$ and the organic layer was washed with water and brine, and concentrated. Hexane was added to the crude product and the soluble portion was filtered. The filtrate was concentrated to afford the bromide as a pale yellow oil. The crude bromide was used for the next reaction without further purification.

To a mixture of NaH (60% in mineral oil, 0.64 g, 16 mmol, washed with hexane) in THF (10 ml) was added dimethyl malonate (2.1 ml, 18 mmol) in THF (2 ml) at 0 °C for 30 min. To the solution was added the bromide in THF (2 ml) over a 15 min period. After stirring for 12 h at room temperature, the mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the dimethyl ester **5** as a pale yellow oil (3.3 g, 76%); R_f (EtOAc–hexane, 1:9) 0.45; ν_{max}(neat)/cm^{-1} 2950, 2920, 2850, 1740, 1440, 1340 and 1150; δ_H (500 MHz; $CDCl_3$) 5.14–5.05 (m, 4 H, 4-H, 8-H, 12-H, 16-H), 3.72 (s, 6 H, CO_2CH_3), 3.37 (t, *J* 7.6, 1 H, 2-H), 2.61 (t, *J* 7.6, 2 H, 3-H), 2.11–2.02 (m, 6 H, 7-H, 11-H, 15-H), 2.02–1.94 (m, 6 H, 6-H, 10–H, 14-H), 1.68 (s, 3 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3) and 1.60 (s, 9 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$) 169.5(×2), 138.7, 135.0, 134.8, 131.1, 124.3, 124.1, 123.8, 119.3, 52.2(×2), 51.8, 39.6(×3), 27.5, 26.6(×2), 26.5, 25.6, 17.6 and 15.9(×3) [Found (HRMS): M^+, 404.2928. $C_{25}H_{40}O_4$ requires *M*, 404.2927].

Methyl (4*E*,8*E*,12*E*)-5,9,13,17-tetramethyloctadeca-4,8,12,16-tetraenoate 6

A mixture of **5** (3.6 g, 9.0 mmol), NaCl (0.50 g, 9.0 mmol) and water (0.3 ml, 18 mmol) in DMF (10 ml) was heated at reflux for 15 h. The mixture was cooled, poured into NH_4Cl aq. and extracted with Et_2O. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the methyl ester **6** as a pale yellow oil (2.6 g, 82%); R_f (EtOAc–hexane, 1:9) 0.55; ν_{max}(neat)/cm^{-1} 2970, 2920, 2850, 1740, 1440, 1380, 1250 and 1170; δ_H (500 MHz; $CDCl_3$) 5.14–5.06 (m, 4 H, 4-H, 8-H, 12-H, 16-H), 3.66 (s, 3 H, CO_2CH_3), 2.33 (m, 4 H, 2-H, 3-H), 2.12–2.02 (m, 6 H, 7-H, 11-H, 15-H), 2.02–1.94 (m, 6 H, 6-H, 10–H, 14-H), 1.68 (s, 3 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.60 (s, 9 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$) 173.7, 136.6, 135.0, 134.8, 131.1, 124.4, 124.2, 124.0, 122.2, 51.3, 39.7(×3), 34.2, 26.7, 26.6, 26.5, 25.6, 23.5, 17.6 and 15.9(×3) (Found: C, 79.67; H, 11.22. $C_{23}H_{38}O_2$ requires C, 79.71; H, 11.05%).

(4*E*,8*E*,12*E*)-5,9,13,17-Tetramethyloctadeca-4,8,12,16-tetraen-1-ol 7

To a solution of **6** (2.5 g, 7.1 mmol) in Et_2O (10 ml) at −20 °C was added $LiAlH_4$ (0.27 g, 7.1 mmol). After stirring for 6 h at 25 °C, Et_2O and water were added into the reaction mixture. The resulting mixture was filtered with suction and the residue was washed with Et_2O. The filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the alcohol **7** as a colourless oil (2.1 g, 94%); R_f (EtOAc–hexane, 1:9) 0.25; ν_{max}(neat)/cm^{-1} 3340, 2920, 1670, 1450, 1380 and 1150; δ_H (500 MHz; $CDCl_3$) 5.15–5.05 (m, 4 H, 4-H, 8-H, 12-H, 16-H), 3.60 (t, *J* 6.4, 2 H, CH_2OH), 2.25 (br s, 1 H, CH_2OH), 2.11–2.02 (m, 8 H, 3-H, 7-H, 11-H, 15-H), 2.02–1.94 (m, 8 H, 2-H, 6-H, 10–H, 14-H), 1.67 (s, 3 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3) and 1.58 (s, 9 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$) 135.6, 134.8, 134.7, 131.0, 124.3, 124.2, 124.1, 123.7, 62.4, 39.6(×3), 32.6, 26.7, 26.5(×2), 25.5, 24.7, 17.5 and 15.9(×3) [Found (HRMS): M^+, 318.2919. $C_{22}H_{38}O$ requires *M*, 318.2923].

(4*E*,8*E*,12*E*)-5,9,13,17-Tetramethyloctadeca-4,8,12,16-tetraen-1-al 8

To a mixture of pyridinium chlorochromate (1.3 g, 5.8 mmol) and Florisil (1.3 g) suspended in CH_2Cl_2 (10 ml) was added **7** (1.4 g, 4.5 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 12 h at 25 °C. The solid mixture of Florisil and chromium salts was removed by filtration and the filtrate was concentrated *in vacuo*. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the aldehyde **8** as a colourless oil (1.5 g, 68%); R_f (EtOAc–hexane, 1:9) 0.60; ν_{max}(neat)/cm^{-1} 2970, 2920, 2850, 2720, 1730, 1670, 1450, 1380 and 1150; δ_H (500 MHz; $CDCl_3$) 9.76 (t, *J* 2.0, 1 H, CHO), 5.13–5.07 (m, 4 H, 4-H, 8-H, 12-H, 16-H), 2.46 (td, *J* 7.3, 1.96, 2 H, 2-H), 2.33 (q, *J* 7.3, 2 H, 3-H), 2.10–2.02 (m, 6 H, 7-H, 11-H, 15-H), 2.02–1.94 (m, 6 H, 6-H, 10-H, 14-H), 1.68 (s, 3 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3) and 1.59 (s, 9 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$)

202.5, 136.8, 135.1, 134.9, 131.2, 124.4, 124.2, 123.9, 122.0, 43.9, 39.7(×2), 39.6, 26.7, 26.6, 26.5, 25.6, 20.8, 17.6 and 16.0(×3) (Found: C, 83.32; H, 11.54. $C_{22}H_{36}O$ requires C, 83.48; H, 11.46%).

(4*Z*,8*E*,12*E*,16*E*)-and (4*E*,8*E*,12*E*,16*E*)-4-Ethoxycarbonyl-9,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene (*Z*)- and (*E*)-13

To a suspension of NaH (60% in mineral oil, 0.15 g, 3.7 mmol, washed with hexane) in THF (50 ml) was added $(EtO)_2$-P(O)CH($CH_2CH{=}CH_2$)CO_2Et (0.99 g, 3.7 mmol) in THF (10 ml) at 0 °C . After the mixture had been stirred for 30 min at 0 °C, **8** (0.97 g, 3.1 mmol) in THF (10 ml) was added to it and stirring was continued for 6 h at 25 °C. The reaction mixture was then poured into aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 1:99) gave (*Z*)-**13** (0.75 g, 57%) and (*E*)-**13** (0.49 g, 37%) as colourless oils. For (*Z*)-**13**, R_f(EtOAc–hexane, 1:9) 0.73; ν_{max}(neat)/cm^{-1} 2980, 2920, 2860, 1720, 1640, 1450, 1380 and 1210; δ_H (500 MHz; $CDCl_3$) 5.90 (tt, *J* 7.3, 1.2, 1 H, 5-H), 5.81 (ddt, *J* 20.1, 9.8, 6.7, 1 H, 2-H), 5.11 (m, 4 H, 8-H, 12-H, 16-H, 20-H), 5.05 (dtd, *J* 20.1, 3.4, 1.5, 1 H, 1-H), 5.02 (dtd, *J* 9.8, 2.8, 1.5, 1 H, 1-H), 4.20 (q, *J* 7.3, 2 H, OC*H*$_2$CH$_3$), 2.99 (dddd, *J* 6.7, 3.4, 2.8, 1.2, 2 H, 3-H), 2.49 (q, *J* 7.3, 2 H, 6-H), 2.15–2.02 (m, 8 H, 7-H, 11-H, 15-H, 19-H), 1.99 (m, 6 H, 10-H, 14-H, 18-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.29 (t, *J* 7.3, 3 H, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 167.7, 142.4, 136.1, 135.9, 134.9(×2), 131.2, 130.3, 124.4, 124.2(×2), 123.4, 116.0, 60.1, 39.7(×3), 38.4, 29.8, 27.7, 26.8, 26.6(×2), 25.7, 17.6, 16.1, 16.0(×2) and 14.2 (Found: C, 81.77; H, 10.82. $C_{29}H_{46}O_2$ requires C, 81.63; H, 10.87%). For (*E*)-**13**, R_f (EtOAc–hexane, 1:9) 0.63; ν_{max}(neat)/cm^{-1} 2980, 2920, 2860, 1720, 1640, 1450, 1380 and 1210; δ_H (500 MHz; $CDCl_3$) 6.84 (t, *J* 7.3, 1 H, 5-H), 5.80 (ddt, *J* 17.1, 10.1, 6.1, 1 H, 2-H), 5.15–5.07 (m, 4 H, 8-H, 12-H, 16-H, 20-H), 5.01 (dtd, *J* 17.1, 3.4, 1.5, 1 H, 1-H), 5.02 (dtd, *J* 10.1, 3.4, 1.5, 1 H, 1-H), 4.18 (q, *J* 7.3, 2 H, OC*H*$_2$CH$_3$), 3.07 (dt, *J* 6.1, 3.4, 2 H, 3-H), 2.21 (dt, *J* 7.3, 6.4, 2 H, 6-H), 2.15–2.02 (m, 8 H, 7-H, 11-H, 15-H, 19-H), 2.01–1.96 (m, 6 H, 10-H, 14-H, 18-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.28 (t, *J* 7.3, 3 H, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 167.5, 143.3, 136.3, 135.5, 135.0, 134.8, 131.2, 130.0, 124.4, 124.2, 124.1, 123.0, 114.9, 60.4, 39.6(×3), 30.8, 28.9, 27.0, 26.7, 26.6(×2), 25.6, 17.6, 16.0(×3) and 14.2 [Found (HRMS): M$^+$, 426.4399. $C_{29}H_{46}O_2$ requires *M*, 426.4398].

(4*Z*,8*E*,12*E*,16*E*)-4-Hydroxymethyl-9,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene 14

To a solution of (*Z*)-**13** (1.7 g, 4.0 mmol) in Et_2O (10 ml) at −20 °C was added $LiAlH_4$ (0.15 g, 4.0 mmol). After stirring for 6 h at 25 °C, Et_2O and water were added into the reaction mixture. The resulting mixture was filtered with suction and the residue was washed with Et_2O. The filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the alcohol **14** as a colourless oil (1.5 g, 99%); R_f (EtOAc–hexane, 1:9) 0.25; ν_{max}(neat)/cm^{-1} 3340, 2920, 2850, 1670, 1640, 1440 and 1380; δ_H (500 MHz; $CDCl_3$) 5.83 (ddt, *J* 17.1, 10.1, 1.0, 1 H, 2-H), 5.35 (t, *J* 7.3, 1 H, 5-H), 5.17–5.06 (m, 5 H, 1-H, 8-H, 12-H, 16-H, 20-H), 5.04 (dtd, *J* 10.1, 2.1, 1.2, 1 H, 1-H), 4.12 (s, 2 H, C*H*$_2$OH), 2.87 (m, 2 H, 3-H), 2.17–2.02 (m, 10 H, 6-H, 7-H, 11-H, 15-H, 19-H), 2.02–1.94 (m, 6 H, 10-H, 14-H, 18-H), 1.68 (s, 3 H, vinyl-CH_3) and 1.60 (s, 12 H, vinyl-CH_3), the hydroxy proton was not observed due to broadening of the signal; δ_C (125 MHz; $CDCl_3$) 137.0, 136.9, 136.0, 135.0, 134.9, 131.2, 129.5, 124.4, 124.2(×2), 123.6, 116.0, 60.2, 39.7(×4), 28.1, 27.9, 26.8, 26.6(×2), 25.7, 17.6, 16.1 and 16.0(×2) [Found (HRMS): M$^+$, 384.3383. $C_{27}H_{44}O$ requires *M*, 384. 3392].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-9,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene 15

To a mixture of **14** (1.1 g, 2.8 mmol) and imidazole (0.38 g, 5.6 mmol) in DMF (4 ml) was added *tert*-butyldimethylsilyl chloride (0.55 g, 3.7 mmol). The reaction mixture was stirred for 12 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water and saturated NaCl, dried with anhydrous $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 2:98) to give **15** as a colourless oil (1.2 g, 84%); R_f (EtOAc–hexane, 1:9) 0.9; ν_{max}(neat)/cm^{-1} 2960, 2930, 2860, 1640, 1460, 1450, 1250 and 1080; δ_H (500 MHz; $CDCl_3$) 5.82 (ddt, *J* 17.1, 10.1, 7.0, 1 H, 2-H), 5.26 (t, *J* 7.3, 1 H, 5-H), 5.16–5.08 (m, 4 H, 8-H, 12-H, 16-H, 20-H), 5.05 (dtd, *J* 17.1, 1.9, 1.5, 1 H, 1-H), 5.01 (dtd, *J* 10.1, 2.1, 1.5, 1 H, 1-H), 4.16 (s, 2 H, CH_2OSi), 2.85, (m, 2 H, 3-H), 2.13–2.02 (m, 10 H, 6-H, 7-H, 11-H, 15-H, 19-H), 2.02–1.95 (m, 6 H, 10-H, 14-H, 18-H), 1.68 (s, 3 H, vinyl-CH_3), 1.61 (s, 12 H, vinyl-CH_3), 0.91 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 137.3, 137.1, 135.5, 134.9, 134.8, 131.2, 127.2, 124.4, 124.3(×2), 123.8, 115.5, 60.2, 39.7(×3), 38.7, 28.3, 27.8, 26.7(×3), 25.9(×3), 25.7, 18.3, 17.6, 16.0(×3) and −5.3(×2) [Found (HRMS): M$^+$, 498.4286. $C_{33}H_{58}OSi$ requires *M*, 498.4257].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-9,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaen-1-ol 19

To a solution of **15** (1.2 g, 2.4 mmol) in THF (4 ml) was added 9-BBN (0.5 M in THF) (7.1 ml, 3.6 mmol) at 0 °C and the mixture was stirred for 15 h at 0–25 °C. The solution was cooled to 0 °C and water was added. A solution of NaOH (0.48 g, 12 mmol) in water (4 ml) and 30% aqueous H_2O_2 (1.4 g, 12 mmol) were added to the reaction mixture at 0 °C and the resulting mixture was stirred at 0–25 °C. After stirring for 3 h, water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 5:95) to give **12** as a colourless oil (0.91 g, 74%); R_f (EtOAc–hexane, 1:9) 0.3; ν_{max}(neat)/cm^{-1} 3360, 2930, 2860, 1450, 1380 and 1250; δ_H (500 MHz; $CDCl_3$) 5.28 (t, *J* 6.7, 1 H, 5-H), 5.14–5.07 (m, 4 H, 8-H, 12-H, 16-H, 20-H), 4.18 (s, 2 H, CH_2OSi), 2.17 (t, *J* 7.3, 2 H, C*H*$_2$OH), 2.11–2.01 (m, 10 H, 6-H, 7-H, 11-H, 15-H, 19-H), 2.01–1.95 (m, 8 H, 3-H, 10-H, 14-H, 18-H), 1.91–1.84 (m, 2 H, 2-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 0.90 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$), the hydroxy proton was not observed due to broadening of the signal; δ_C (125 MHz; $CDCl_3$) 137.9, 135.6, 135.0, 134.9, 131.2, 127.1, 124.4, 124.2(×2), 123.8, 62.6, 60.7, 39.7(×3), 31.3, 30.7, 28.3, 27.8, 27.2, 26.7(×2), 25.9(×3), 25.7, 18.3, 17.6, 16.1, 16.0(×2) and −5.3(×2) [Found (HRMS): M$^+$, 516.4366. $C_{33}H_{60}O_2Si$ requires *M*, 516.4363].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-9,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaen-1-al 20

To a mixture of pyridinium chlorochromate (0.48 g, 2.2 mmol) and Florisil (0.48 g) suspended in CH_2Cl_2 (20 ml) was added **19** (0.84 g, 1.6 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 3 h at 25 °C. The solid mixture of Florisil and chromium salts was removed by filtration and the filtrate was concentrated *in vacuo*. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the aldehyde **20** as a colourless oil (0.69 g, 83%); R_f (EtOAc–hexane, 1:9) 0.60; ν_{max}(neat)/cm^{-1} 2960, 2930, 2860, 1730, 1470, 1440, 1380 and 1250; δ_H (500 MHz; $CDCl_3$) 9.57 (t, *J* 1.8, 1 H, CHO), 5.24 (t, *J* 7.0, 1 H, 5-H), 5.14–5.07 (m, 4 H, 8-H, 12-H, 16-H, 20-H), 4.18 (s, 2 H,

CH_2OSi), 2.56 (td, *J* 7.3, 1.8, 2 H, 2-H), 2.44 (t, *J* 7.3, 2 H, 3-H), 2.11–2.02 (m, 10 H, 6-H, 7-H, 11-H, 15-H, 19-H), 2.02–1.94 (m, 6 H, 10-H, 14-H, 18-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$) and 0.06 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 202.8, 137.9, 135.6, 135.0, 134.9, 131.2, 127.1, 124.4, 124.2(×2), 123.6, 60.5, 42.6, 39.7(×3), 28.2, 27.7, 27.2, 26.7(×3), 25.9(×3), 25.7, 18.3, 17.7, 16.0(×3) and −5.4(×2) (Found: C, 76.95; H, 11.63. $C_{33}H_{58}O_2Si$ requires C, 76.98; H, 11.35%).

Methyl (2*Z*,6*Z*,10*E*,14*E*,18*E*)- and (2*E*,6*Z*,10*E*,14*E*,18*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-11,15,19,23-tetramethyltetracosa-2,6,10,14,18,22-hexaenoate (2*Z*)- and (2*E*)-21

To a suspension of NaH (60% in mineral oil, 42 mg, 1.0 mmol, washed with hexane) in THF (5 ml) was added propane-2-thiol (0.010 ml, 1.1 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Me$ (0.23 g, 1.0 mmol) in THF (1 ml) at 0 °C . After the mixture had been stirred for 15 min at 0 °C, **20** (0.54 g, 1.0 mmol) in THF (1 ml) was added to it and stirring was continued for 12 h at 25 °C. The reaction mixture was then poured into aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated. Preparative TLC (silica gel, hexane–EtOAc, 98 : 2) of the crude product gave (2*Z*)-**21** (0.46 g, 59%) and (2*E*)-**21** (0.24 g, 35%) as colourless oils. For (2*Z*)-**21**, R_f (EtOAc–hexane, 1 : 9) 0.68; ν_{max}(neat)/cm^{-1} 2930, 2860, 1720, 1640, 1440, 1280, 1190 and 1070; δ_H (500 MHz; $CDCl_3$) 6.82 (t, *J* 7.6, 1 H, 3-H), 5.26 (t, *J* 6.7, 1 H, 7-H), 5.14–5.08 (m, 4 H, 10-H, 14-H, 18-H, 22-H), 4.18 (s, 2 H, CH_2OSi), 3.75 (s, 3 H, CO_2CH_3), 3.46 (s, 2 H, CH_2S), 2.92 (septet, *J* 6.7, 1 H, $SCH(CH_3)_2$), 2.39 (dt, *J* 7.6, 7.3, 2 H, 4-H), 2.24 (t, *J* 7.3, 2 H, 5-H), 2.09–2.02 (m, 10 H, 8-H, 9-H, 13-H, 17-H, 21-H), 2.01–1.95 (m, 6 H, 12-H, 16-H, 20-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 1.28 (d, *J* 6.7, 6 H, $SCH(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 167.5, 144.7, 137.4, 135.6, 135.0, 134.9, 131.2, 129.3, 127.1, 124.4, 124.2(×2), 123.7, 60.4, 51.8, 39.7(×3), 35.5, 33.5, 28.3, 27.8(×2), 26.8, 26.7(×2), 26.3, 25.9(×3), 25.7, 23.4(×2), 18.3, 17.7, 16.1, 16.0(×2) and −5.3(×2) [Found (HRMS): M$^+$ 658.4866. $C_{40}H_{70}O_3SiS$ requires *M*, 658.4815]. For (2*E*)-**21**, R_f (EtOAc–hexane, 1 : 9) 0.78; ν_{max}(neat)/cm^{-1} 2930, 2860, 1720, 1650, 1440, 1250, 1200, 1070; δ_H (500 MHz; $CDCl_3$) 5.99 (t, *J* 7.3, 1 H, 3-H), 5.24 (t, *J* 7.3, 1 H, 7-H), 5.14–5.08 (m, 4 H, 10-H, 14-H, 18-H, 22-H), 4.16 (s, 2 H, CH_2OSi), 3.76 (s, 3 H, CO_2CH_3), 3.37 (s, 2 H, CH_2S), 2.82 (septet, *J* 6.7, 1 H, $SCH(CH_3)_2$), 2.60 (td, *J* 7.6, 7.3, 2 H, 4-H), 2.21 (t, *J* 7.6, 2 H, 5-H), 2.09–2.02 (m, 6 H, 12-H, 16-H, 20-H), 2.01–1.95 (m, 10 H, 8-H, 9-H, 13-H, 17-H, 21-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 1.23 (d, *J* 6.7, 6 H, $SCH(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$) and 0.06 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 167.3, 144.4, 137.6, 135.6, 135.0, 134.9, 131.2, 128.7, 126.9, 124.4, 124.2(×2), 123.8, 60.3, 51.4, 39.7(×3), 34.4, 34.1, 34.0, 28.4, 28.1, 27.8, 26.8, 26.7(×2), 25.9(×3), 25.7, 23.2(×2), 18.3, 17.6, 16.1, 16.0(×2) and −5.3(×2) [Found (HRMS) M$^+$ 658.4859. $C_{40}H_{70}O_3SiS$ requires *M*, 658.4815].

Methyl (5*Z*,4′*E*,8′*E*,12′*E*)-2-methylene-2-[5-(5′,9′,13′,17′-tetramethyloctadeca-4′,8′,12′,16′-tetraenylidene)tetrahydropyran-2-yl]acetate 25

To a mixture of **21** (22 mg, 0.033 mmol) and $AgBF_4$ (20 mg, 0.10 mmol) in CH_2Cl_2 (1 ml) was added MeI (0.021 ml, 0.33 mmol). The reaction mixture was stirred for 30 min at 25 °C and then filtered. After the filtrate was evaporated, the residue was diluted with THF (4 ml) and treated with a 1.0 M solution of TBAF in THF (0.10 ml, 0.10 mmol). After stirring for 1 h at 25 °C, the reaction was quenched with aqueous NH_4Cl and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and evaporated. Preparative TLC (silica gel, hexane–EtOAc, 98 : 2) of the crude product gave **25** (11 mg, 0.023 mmol) as a colourless oil in 69% yield; R_f (EtOAc–hexane, 1 : 9) 0.75; ν_{max}(neat)/cm^{-1} 2920, 2850, 1720, 1630, 1440, 1380, 1290, 1190, 1150 and 1080; δ_H (500 MHz; $CDCl_3$) 6.25 (d, *J* 0.9, 1 H, α-methylene), 5.90 (d, *J* 0.9, 1 H, α-methylene), 5.23 (t, *J* 6.4, 1 H, 1′-H), 5.16–5.07 (m, 4 H, 4′-H, 8′-H, 12′-H, 16′-H), 4.70 (d, *J* 12.5, 1 H, 6-H), 4.33 (d, *J* 11.0, 1 H, 2-H), 3.90 (d, *J* 12.5, 1 H, 6-H), 3.77 (s, 3 H, CO_2CH_3), 2.38 (br t, *J* 12.5, 1 H, 4-H), 2.32 (br t, *J* 12.2, 1 H, 4-H), 2.13-2.01 (m, 11 H, 3-H, 2′-H, 3′-H, 7′-H, 11′-H, 15′-H), 2.01–1.94 (m, 6 H, 6′-H, 10′-H, 14′-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.36 (dddd, *J* 12.8, 12.5, 11.0, 4.6, 1 H, 3-H); δ_C (125 MHz; $CDCl_3$) 166.4, 141.6, 135.7, 135.0, 134.9, 133.1, 131.2, 124.5(×2), 124.4, 124.2(×2), 123.6, 75.4, 67.1, 51.8, 39.7(×3), 33.9, 33.1, 28.2, 27.3, 26.8, 26.7, 25.7(×2), 17.7, 16.1 and 16.0(×2) [Found (HRMS) M$^+$ 468.3585. $C_{31}H_{48}O_3$ requires *M*, 468.3603].

(5*Z*,4′*E*,8′*E*,12′*E*)-2-Methylene-2-[5-(5′,9′,13′,17′-tetramethyloctadeca-4′,8′,12′,16′-tetraenylidene)tetrahydropyran-2-yl]-acetic acid 1

To a solution of **25** (18 mg, 0.037 mmol) in THF (0.2 ml) was added $LiOH·H_2O$ (16 mg, 0.37 mmol) in H_2O (0.15 ml) at 0 °C. After the reaction mixture was stirred for 24 h at 25 °C, it was acidified with 1 M HCl and diluted with Et_2O; the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous Na_2SO_4, and evaporated. Column chromatography (6 wt% water–silica gel, hexane–EtOAc, 8 : 2) of the crude product gave *rac*-**1** (6.8 mg, 0.015 mmol) as a colourless oil in 40% yield; R_f (EtOAc–hexane, 3 : 7) 0.40; ν_{max}(neat)/cm^{-1} 2920, 2850, 1700, 1630, 1440, 1380, 1290, 1160 and 1082; δ_H (500 MHz; $CDCl_3$) 6.39 (s, 1 H, α-methylene), 5.96 (s, 1 H, α-methylene), 5.26 (t, *J* 6.7, 1 H, 1′-H), 5.15–5.07 (m, 4 H, 4′-H, 8′-H, 12′-H, 16′-H), 4.72 (d, *J* 12.8, 1 H, 6-H), 4.32 (d, *J* 11.0, 1 H, 2-H), 3.90 (d *J* 12.8, 1 H, 6-H), 2.38 (br t, *J* 13.4, 1 H, 4-H), 2.35 (br t, *J* 13.1, 1 H, 4-H), 2.15–2.02 (m, 11 H, 3-H, 2′-H, 3′-H, 7′-H, 11′-H, 15′-H), 2.02–1.95 (m, 6 H, 6′-H, 10′-H, 14′-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.44 (dddd, *J* 12.5, 11.0, 7.3, 5.2, 1 H, 3-H); the carboxylic proton was not observed because of broadening of the signal; δ_C (125 MHz; $CDCl_3$) 169.7, 140.6, 135.8, 135.0, 134.9, 132.6, 131.2, 127.1, 125.0, 124.4, 124.2(×2), 123.5, 75.7, 67.1, 39.7(×3), 33.7, 32.9, 28.2, 27.3, 26.8, 26.7, 26.6, 25.7, 17.7, 16.1 and 16.0(×2) [Found (HRMS): M$^+$, 454.3458. $C_{30}H_{46}O_3$ requires *M*, 454.3447].

(4*E*,8*E*)-5,9,13-Trimethyltetradeca-4,8,12-trien-1-al 12

To a solution of $(COCl)_2$ (1.0 ml, 12 mmol) in CH_2Cl_2 (40 ml) was added a solution of DMSO (1.5 ml, 21 mmol) in CH_2Cl_2 (5 ml) at −40 °C. After 10 min, **11** (2.6 g, 11 mmol) was added to the mixture at −40 °C and the resulting solution was stirred for 30 min. Et_3N (7.4 ml, 53 mmol) was added to the reaction mixture and the mixture was stirred at −40 to 25 °C. The reaction mixture was stirred for 8 h and then quenched with aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and brine, and then dried with $MgSO_4$. Removal of solvent gave the crude product. Purification with column chromatography (silica gel, EtOAc–hexane, 5 : 95) gave **12** (2.1 g, 79%) as a pale yellow oil; R_f (EtOAc–hexane, 1 : 9) 0.60; ν_{max}(neat)/cm^{-1} 2970, 2930, 2860, 2720, 1730, 1670, 1650, 1450, 1380 and 1240; δ_H (500 MHz; $CDCl_3$) 9.76 (t, *J* 1.8, 1 H, CHO), 5.13–5.06 (m, 3 H, 4-H, 8-H, 12-H), 2.46 (t, *J* 7.3, 2 H, 2-H), 2.33 (td, *J* 7.3, 7.0, 2 H, 3-H), 2.11–2.02 (m, 4 H, 7-H, 11-H), 2.02–1.93 (m, 4 H, 6-H, 10-H), 1.68 (s, 3 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.60 (s, 3 H, vinyl-CH_3) and 1.59 (s, 3 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$) 202.6, 136.9, 135.1, 131.3, 124.4, 124.0, 122.0,

44.0, 39.7, 39.6, 26.7, 26.5, 25.7, 20.8, 17.6 and 16.0(×2) [Found (HRMS): M^+, 248.2145. $C_{17}H_{28}O$ requires *M*, 248.2140].

(6*E*,10*E*)-3-Hydroxy-2,7,11,15-tetramethylhexadeca-1,6,10,14-tetraene 27

To a solution of 2-bromopropene (1.3 ml, 15 mmol) in Et_2O (30 ml) was added a 1.7 M of solution *t*-BuLi in pentane (18 ml, 30 mmol) at −78 °C followed by stirring for 15 min. To the solution of 2-lithiopropene formed was added **12** (1.9 g, 7.7 mmol) in Et_2O (10 ml) at −78 °C. After stirring for 8 h at room temperature, the mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the alcohol **27** as a colourless oil (1.6 g, 72%); R_f (EtOAc–hexane, 1:9) 0.28; ν_{max}(neat)/cm^{-1} 3370, 2970, 2930, 2860, 2360, 1650, 1450 and 1380; δ_H (500 MHz; $CDCl_3$) 5.20–5.07 (m, 3 H, 6-H, 10-H, 14-H), 4.94 (s, 1 H, 1-H), 4.83 (s, 1 H, 1-H), 4.06 (t, *J* 6.7, 1 H, 3-H), 2.13–1.92 (m, 12 H, 4-H, 5-H, 8-H, 9-H, 12-H, 13-H), 1.72 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3) and 1.60 (s, 6 H, vinyl-CH_3), the hydroxy proton was not observed because of broadening of the signal; δ_C (125 MHz; $CDCl_3$) 147.5, 135.8, 135.0, 131.2, 124.4, 124.1, 123.8, 110.9, 75.6, 39.7(×2), 35.0, 26.7, 26.6, 25.7, 24.1, 17.6(×2) and 16.0(×2) (Found: C, 82.72; H, 11.90. $C_{20}H_{34}O$ requires C, 82.70; H, 11.80%).

Ethyl (4*E*,8*E*,12*E*)-4,9,13,17-tetramethyloctadeca-4,8,12,16-tetraenoate 28

The alcohol **27** (1.6 g, 5.4 mmol) was heated with triethyl orthoacetate (5.2 g, 32 mmol) and propionic acid (24 mg, 0.32 mmol) at 138 °C for 1 h. The mixture was quenched with aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the ethyl ester **28** as a colourless oil (1.6 g, 85%); R_f (EtOAc–hexane, 1:9) 0.7; ν_{max}(neat)/cm^{-1} 2980, 2920, 2860, 1740, 1670, 1450 and 1380; δ_H (500 MHz; $CDCl_3$) 5.17 (m, 1 H, 5-H), 5.15–5.07 (m, 3 H, 8-H, 12-H, 16-H), 4.12 (q, *J* 7.3, 2 H, OC*H*$_2$CH$_3$), 2.39 (t, *J* 8.3, 2 H, 2-H), 2.29 (t, *J* 8.3, 2 H, 3-H), 2.11–1.93 (m, 12 H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.24 (t, *J* 7.3, 3 H, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 173.5, 135.3, 134.9, 133.4, 131.2, 125.1, 124.4, 124.2, 124.1, 60.2, 39.7(×2), 34.7, 33.3, 28.2, 28.1, 26.8, 26.6, 25.7, 17.6, 16.0(×2), 15.9 and 14.2 (Found: C, 79.98; H, 11.04. $C_{24}H_{40}O_2Si$ requires C, 79.94; H, 11.18%).

(4*E*,8*E*,12*E*)-4,9,13,17-Tetramethyloctadeca-4,8,12,16-tetraen-1-ol 29

To a solution of **28** (1.6 g, 4.5 mmol) in Et_2O (30 ml) at −20 °C was added $LiAlH_4$ (0.19 g, 5.0 mmol). After being stirred for 6 h at 25 °C, Et_2O and water were added into the reaction mixture. The resulting mixture was filtered with suction and the residue was washed with Et_2O. The filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the alcohol **29** as a colourless oil (1.4 g, 96%); R_f (EtOAc–hexane, 1:9) 0.27; ν_{max}(neat)/cm^{-1} 3350, 2970, 2930, 2860, 1670, 1450 and 1390; δ_H (500 MHz; $CDCl_3$) 5.24–5.07 (m, 4 H, 5-H, 8-H, 12-H, 16-H), 3.63 (t, *J* 6.3, 2 H, C*H*$_2$OH), 2.16–1.91 (m, 16 H, 3-H, 4-H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H), 1.68 (s, 3 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3) and 1.60 (s, 9 H, vinyl-CH_3); the hydroxy proton was not observed because of broadening of the signal; δ_C (125 MHz; $CDCl_3$) 135.3, 134.9, 134.7, 131.2, 124.9, 124.4, 124.2, 124.1, 62.8, 39.7(×2), 36.0, 30.8, 28.2(×2), 26.8, 26.6, 25.7, 17.6, 16.0(×2) and 15.9 [Found (HRMS): M^+, 318.2951. $C_{22}H_{38}O$ requires *M*, 318.2923].

(4*E*,8*E*,12*E*)-4,9,13,17-Tetramethyloctadeca-4,8,12,16-tetraen-1-al 30

To a solution of $(COCl)_2$ (0.41 ml, 4.7 mmol) in CH_2Cl_2 (20 ml) was added a solution of DMSO (0.40 ml, 5.6 mmol) in CH_2Cl_2 (2 ml) at −40 °C. After 30 min, **29** (1.4 g, 4.3 mmol) was added to the mixture at −40 °C and stirred for 30 min. A sample of Et_3N (1.6 ml, 12 mmol) was added to the reaction mixture and the mixture was stirred at −60 to 25 °C. The reaction mixture was stirred for 6 h and quenched with aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and brine and then dried with anhydrous $MgSO_4$. Removal of solvent gave the crude product. Purification with column chromatography (silica gel, EtOAc–hexane, 5:95) afforded 1.1 g (80%) of **30** as a pale yellow oil; R_f (EtOAc–hexane, 1:9) 0.60; ν_{max}(neat)/cm^{-1} 2960, 2920, 2860, 2720, 1730, 1670, 1650, 1440 and 1380; δ_H (500 MHz; $CDCl_3$) 9.75 (t, *J* 1.8, 1 H, CHO), 5.21–5.07 (m, 4 H, 5-H, 8-H, 12-H, 16-H), 2.51 (td, *J* 7.6, 1.8, 2 H, 2-H), 2.32 (t, *J* 7.6, 2 H, 3-H), 2.16–1.95 (m, 12 H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H), 1.68 (s, 3 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3) and 1.60 (s, 9 H, vinyl-CH_3); δ_C (125 MHz; $CDCl_3$) 202.6, 135.4, 134.9, 133.0, 131.2, 125.5, 124.4, 124.2, 124.0, 42.2, 39.7(×2), 31.9, 28.2, 28.0, 26.8, 26.6, 25.7, 17.6, 16.1 and 16.0(×2) [Found (HRMS): M^+, 316.2785. $C_{22}H_{36}O$ requires *M*, 316.2766].

(4*Z*,8*E*,12*E*,16*E*)- and (4*E*,8*E*,12*E*,16*E*)-4-Ethoxycarbonyl-8,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene (*Z*)- and (*E*)-16

To a suspension of NaH (60% in mineral oil, 0.43 g, 11 mmol, washed with hexane) in THF (22 ml), was added $(EtO)_2P(O)$-$CH(CH_2CH{=}CH_2)CO_2Et$ (2.8 g, 11 mmol) in THF (2 ml) at 0 °C. After the mixture had been stirred for 30 min at 0 °C, **30** (2.3 g, 7.2 mmol) in THF (2 ml) was added to it and stirring was continued for 2 h at 25 °C. The reaction mixture was then poured into aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 1:99) gave (*Z*)-**16** (1.6 g, 52%) and (*E*)-**16**, (1.2 g, 39%) as colourless oils. For (*Z*)-**16**, R_f (EtOAc–hexane, 1:9) 0.73; ν_{max}(neat)/cm^{-1} 2980, 2930, 2860, 1720, 1640, 1450 and 1380; δ_H (500 MHz; $CDCl_3$) 5.89 (t, *J* 7.3, 1 H, 5-H), 5.81 (ddt, *J* 17.1, 9.1, 7.0, 1 H, 2-H), 5.20–5.07 (m, 4 H, 9-H, 12-H, 16-H, 20-H), 5.04 (dtd, *J* 17.1, 3.4, 1.5, 1 H, 1-H), 5.01 (dtd, *J* 9.1, 2.7, 1.5, 1 H, 1-H), 4.20 (q, *J* 7.3, 2 H, OC*H*$_2$CH$_3$), 2.90 (m, 2 H, 3-H), 2.56 (q, *J* 7.3, 2 H, 6-H), 2.11–1.93 (m, 14 H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.29 (t, *J* 7.3, 3 H, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 167.7, 142.6, 136.2, 135.2, 134.9, 134.2, 131.2, 130.1, 125.1, 124.4, 124.3, 124.2, 116.0, 60.1, 39.7(×2), 39.2, 38.4, 28.3, 28.2, 26.8, 26.7, 25.7(×2), 17.7, 16.0(×2), 15.9 and 14.3 [Found (HRMS): M^+, 426.3488. $C_{29}H_{46}O_2$ requires *M*, 426.3498]. For (*E*)-**16**, R_f (EtOAc–hexane, 1:9) 0.63; ν_{max}(neat)/cm^{-1} 2980, 2930, 2860, 1720, 1640, 1450 and 1380; δ_H (500 MHz; $CDCl_3$) 6.83 (t, *J* 7.3, 1 H, 5-H), 5.81 (ddt, *J* 17.1, 10.1, 6.1, 1 H, 2-H), 5.20–5.07 (m, 4 H, 9-H, 12-H, 16-H, 20-H), 5.02 (dtd, *J* 17.1, 3.4, 1.5, 1 H, 1-H), 4.98 (dtd, *J* 10.1, 3.0, 1.5, 1 H, 1-H), 4.18 (q, *J* 7.3, 2 H, OC*H*$_2$CH$_3$), 3.07 (m, 2 H, 3-H), 2.28 (q, *J* 7.6, 2 H, 6-H), 2.11–1.93 (m, 14 H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.68 (s, 3 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3), 1.60 (s, 9 H, vinyl-CH_3) and 1.28 (t, *J* 7.3, 3 H, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 167.6, 143.4, 135.6, 135.2, 134.9, 133.9, 131.2, 130.0, 125.3, 124.4, 124.2, 124.1, 115.0, 60.4, 39.7(×2), 38.4, 30.9, 28.3, 28.2, 27.3, 26.8, 26.7, 25.7, 17.7, 16.0(×2), 15.9 and 14.2 (Found: C, 81.52; H, 11.03. $C_{29}H_{46}O_2$ requires C, 81.63; H, 10.87%).

(4*Z*,8*E*,12*E*,16*E*)-4-Hydroxymethyl-8,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene 17

To a solution of (*Z*)-**16** (1.5 g, 3.5 mmol) in Et_2O (10 ml) at −20 °C was added $LiAlH_4$ (0.13 g, 3.5 mmol). After being stirred for 2 h at 25 °C, Et_2O and water were added into the reaction mixture. The resulting mixture was filtered with suction and the residue was washed with Et_2O. The filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the alcohol **17** as a colourless oil (1.3 g, 99%); R_f (EtOAc–hexane, 1:9) 0.27; ν_{max}(neat)/cm^{-1} 3360, 2980, 2940, 2870, 1730, 1670, 1640, 1440 and 1380; δ_H (500 MHz; $CDCl_3$) 5.83 (ddt, *J* 17.1, 9.7, 6.7, 1 H, 2-H), 5.33 (t, *J* 7.3, 1 H, 5-H), 5.17–5.06 (m, 5 H, 1-H, 9-H, 12-H, 16-H, 20-H), 5.04 (dtd, *J* 9.7, 2.1, 1.0, 1 H, 1-H), 4.13 (s, 2 H, C*H*$_2$OH), 2.87 (m, 2 H, 3-H), 2.19 (q, *J* 7.3, 2 H, 6-H), 2.11–1.93 (m, 14 H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.68 (s, 3 H, vinyl-CH_3) and 1.60 (s, 12 H, vinyl-CH_3), the hydroxy proton was not observed because of broadening of the signal; δ_C (125 MHz; $CDCl_3$) 137.0, 136.7, 135.2, 134.9, 134.4, 131.2, 129.5, 125.0, 124.4, 124.2(×2), 116.0, 60.3, 39.8, 39.7(×2), 28.2(×2), 26.8, 26.7, 26.3, 25.7(×2), 17.7 and 16.0(×3) [Found (HRMS): M^+, 384.3385. $C_{27}H_{44}O$ requires *M*, 384. 3392].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-1,4,8,12,16,20-hexaene 18

To a mixture of **17** (1.3 g, 3.4 mmol) and imidazole (0.47 g, 6.9 mmol) in DMF (4 ml) was added *tert*-butyldimethylsilyl chloride (0.68 g, 4.5 mmol). The reaction mixture was stirred for 4 h at 25 °C and quenched with sat. NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water and aqueous NaCl, dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 2:98) to give **18** as a colourless oil (1.5 g, 85%); R_f (EtOAc–hexane, 1:9) 0.9; ν_{max}(neat)/cm^{-1} 2980, 2930, 2860, 1640, 1470, 1450, 1380 and 1250; δ_H (500 MHz; $CDCl_3$) 5.81 (ddt, *J* 17.4, 10.1, 3.0, 1 H, 2-H), 5.23 (t, *J* 7.3, 1 H, 5-H), 5.17–5.07 (m, 4 H, 9-H, 12-H, 16-H, 20-H), 5.03 (dtd, *J* 17.4, 3.4, 1.5, 1 H, 1-H), 5.00 (dtd, *J* 10.1, 2.1, 1.5, 1 H, 1-H), 4.14 (s, 2 H, CH_2OSi), 2.83 (m, 2 H, 3-H), 2.18–1.93 (m, 16 H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 6 H, vinyl-CH_3), 1.59 (s, 6 H, vinyl-CH_3), 0.92 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 137.1(×2), 135.1, 134.9, 134.6, 131.2, 127.2, 124.7, 124.4, 124.3(×2), 115.5, 60.3, 39.9, 39.8, 39.7, 38.7, 28.3, 28.2, 26.8, 26.7, 26.3, 26.0(×3), 25.7, 18.4, 17.7, 16.0(×3) and −5.3(×2) [Found (HRMS): M^+, 498.4245. $C_{33}H_{58}OSi$ requires *M*, 498.4257].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaen-1-ol 22

To a solution of **18** (0.46 g, 0.93 mmol) in THF (5 ml) was added 9-BBN (0.5 M in THF) (3.7 ml, 1.8 mmol) at 0 °C and the mixture was stirred for 12 h at 0–25 °C. The solution was cooled to 0 °C and water was added. A solution of NaOH (0.17 g, 4.3 mmol) in water (0.43 ml) and 30% aqueous H_2O_2 (0.43 g, 3.7 mmol) were added to the reaction mixture at 0 °C and the resulting mixture was stirred at 0–25 °C. After stirring for 12 h, water was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 5:95) to give **22** as a colourless oil (0.40 g, 83%); R_f (EtOAc–hexane, 1:9) 0.3; ν_{max}(neat)/cm^{-1} 3340, 2930, 2860, 1700, 1670, 1450, 1380 and 1250; δ_H (500 MHz; $CDCl_3$) 5.25 (t, *J* 7.0, 1 H, 5-H), 5.17–5.06 (m, 4 H, 9-H, 12-H, 16-H, 20-H), 4.17 (s, 2 H, CH_2OSi), 3.62 (t, *J* 6.1, 2 H, C*H*$_2$OH), 2.21–1.92 (m, 18 H, 3-H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.87 (m, 2 H, 2-H), 1.68 (s, 3 H, vinyl-CH_3), 1.59 (s, 12 H, vinyl-CH_3), 0.90 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); the hydroxy proton was not observed because of broadening of the signal; δ_C (125 MHz; $CDCl_3$) 137.7, 135.1, 134.9, 134.6, 131.2, 127.1, 124.7, 124.4, 124.2(×2), 62.5, 60.7, 39.8, 39.7(×2), 31.3, 30.8, 28.2, 27.2, 26.8, 26.6, 26.1, 25.9(×3), 25.6, 18.3, 17.6, 16.0(×2), 15.9 and −5.3(×2) [Found (HRMS): M^+, 516.4340. $C_{33}H_{60}O_2Si$ requires *M*, 516.4363].

(4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaen-1-al 23

To a mixture of pyridinium chlorochromate (0.18 g, 0.81 mmol) and Florisil (0.35 g) suspended in CH_2Cl_2 (10 ml) was added **22** (0.30 g, 0.58 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 3 h at 25 °C. The solid mixture of Florisil and chromium salts was removed by filtration and the filtrate was concentrated *in vacuo*. Purification by column chromatography (silica gel, EtOAc–hexane, 5:95) gave the aldehyde **23** as a colourless oil (0.21 g, 72%); R_f (EtOAc–hexane, 1:9) 0.60; ν_{max}(neat)/cm^{-1} 2930, 2860, 2710, 1730, 1670, 1440, 1390 and 1250; δ_H (500 MHz; $CDCl_3$) 9.74 (t, *J* 2.0, 1 H, CHO), 5.21 (t, *J* 7.3, 1 H, 5-H), 5.18–5.04 (m, 4 H, 9-H, 12-H, 16-H, 20-H), 4.17 (s, 2 H, CH_2OSi), 2.55 (td, *J* 7.3, 2.0, 2 H, 2-H), 2.43 (t, *J* 7.3, 2 H, 3-H), 2.17–1.88 (m, 16 H, 6-H, 7-H, 10-H, 11-H, 14-H, 15-H, 18-H, 19-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 0.90 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 202.8, 136.7, 135.2, 134.9, 134.4, 131.2, 127.1, 124.9, 124.4, 124.2(×2), 60.5, 42.6, 39.7(×3), 28.3, 28.2, 27.3, 26.8, 26.7, 26.1, 25.9(×3), 25.7, 18.3, 17.6, 16.0(×2), 15.9 and −5.4(×2) [Found (HRMS): M^+, 514.4210. $C_{33}H_{58}O_2Si$ requires *M*, 516.4206].

Methyl (2*Z*,6*Z*,10*E*,14*E*,18*E*)- and (2*E*,6*Z*,10*E*,14*E*,18*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-10,15,19,23-tetramethyltetracosa-2,6,10,14,18,22-hexanoate (2*Z*)- and (2*E*)-24

To a suspension of NaH (60% in mineral oil, 25 mg, 0.62 mmol, washed with hexane) in THF (1 ml) was added propane-2-thiol (0.056 ml, 0.62 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Me$ (0.14 g, 0.62 mmol) in THF (1 ml) at 0 °C. After the mixture had been stirred for 15 min at 0 °C, **23** (0.21 g, 0.42 mmol) in THF (1 ml) was added to it and stirring was continued for 3 h at 25 °C. The reaction mixture was then poured into aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated. Preparative TLC (silica gel, hexane–EtOAc, 98:2) of the crude product gave (2*Z*)-**24** (0.19 g, 70%) and (2*E*)-**24** (0.070 g, 24%) as colourless oils. For (2*Z*)-**24**, R_f (EtOAc–hexane, 1:9) 0.68; ν_{max}(neat)/cm^{-1} 2960, 2860, 1720, 1670, 1640, 1440 and 1250; δ_H (500 MHz; $CDCl_3$) 6.82 (t, *J* 7.3, 1 H, 3-H), 5.24 (t, *J* 7.3, 1 H, 7-H), 5.18–5.01 (m, 4 H, 11-H, 14-H, 18-H, 22-H), 4.17 (s, 2 H, CH_2OSi), 3.75 (s, 3 H, CO_2CH_3), 3.46 (s, 2 H, CH_2S), 2.91 (septet, *J* 6.7, 1 H, SC*H*$(CH_3)_2$), 2.38 (dt, *J* 7.6, 7.3, 2 H, 4-H), 2.23 (t, *J* 7.3, 2 H, 5-H), 2.15–1.83 (m, 16 H, 8-H, 9-H, 12-H, 13-H, 16-H, 17-H, 20-H, 21-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 1.28 (d, *J* 6.7, 6 H, SCH(C*H*$_3$)$_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$) and 0.07 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 167.5, 144.7, 137.3, 135.2, 134.9, 134.6, 131.2, 129.4, 127.1, 124.7, 124.4, 124.2(×2), 60.4, 51.8, 39.8, 39.7(×2), 35.5, 33.5, 28.3, 28.2, 27.8, 26.8, 26.7, 26.3, 26.2, 25.9(×3), 25.7, 23.4(×2), 18.3, 17.7, 16.0(×3) and −5.3(×2) (Found: C, 72.71; H, 10.75. $C_{40}H_{70}O_3SiS$ requires C, 72.89; H, 10.70%). For (2*E*)-**24**, R_f (EtOAc–hexane, 1:9) 0.78; ν_{max}(neat)/cm^{-1} 2960, 2930, 2860, 1730, 1670, 1640, 1440, 1380 and 1250; δ_H (500 MHz; $CDCl_3$) 5.99 (t, *J* 7.3, 1 H, 3-H), 5.21 (t, *J* 7.3, 1 H, 7-H,), 5.17–5.06 (m, 4 H, 11-H, 14-H, 18-H, 22-H), 4.15 (s, 2 H, CH_2OSi), 3.76 (s, 3 H, CO_2CH_3), 3.37 (s, 2 H, CH_2S), 2.82 (septet, *J* 6.7, 1 H, SC*H*$(CH_3)_2$), 2.59 (q, *J* 7.3, 2 H, 4-H), 2.20 (t, *J* 7.3, 2 H, 5-H), 2.15–1.89 (m, 16 H, 8-H, 9-H, 12-H, 13-H, 16-H, 17-H, 20-H,

21-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3), 1.24 (d, *J* 6.7, 6 H, SCH(CH_3)$_2$), 0.90 (s, 9 H, SiC(CH_3)$_3$), 0.06 (s, 6 H, $SiCH_3$); δ_C (125 MHz; $CDCl_3$) 167.3, 143.4, 137.5, 135.2, 134.9, 134.7, 131.2, 128.7, 126.9, 124.6, 124.4, 124.3, 124.2, 60.3, 51.4, 39.9, 39.7(×2), 34.4, 34.1, 34.0, 28.3, 28.2, 28.1, 26.8, 26.7, 26.3, 25.9(×3), 25.7, 23.2(×2), 18.3, 17.7, 16.0(×3) and −5.3(×2) [Found (HRMS): M^+, 658.4849. $C_{40}H_{70}O_3SiS$ requires *M*, 658.4815].

Methyl (5*Z*,4′*E*,8′*E*,12′*E*)-2-methylene-2-[5-(4′,9′,13′,17′-tetramethyloctadeca-4′,8′,12′,16′-tetraenylidene)tetrahydropyran-2-yl]acetate 26

To a mixture of **24** (100 mg, 0.15 mmol) and $AgBF_4$ (95 mg, 0.49 mmol) in CH_2Cl_2 (4 ml) was added MeI (0.094 ml, 1.5 mmol). The reaction mixture was stirred for 30 min at 25 °C and then filtered. After the filtrate was evaporated, the residue was diluted with THF (15 ml) and treated with a 1.0 M solution of TBAF in THF (0.48 ml, 0.48 mmol). After stirring for 2 h at 25 °C, the reaction was quenched with aqueous NH_4Cl, and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and evaporated. Preparative TLC (silica gel, hexane–EtOAc, 98:2) of the crude product gave **26** (22 mg, 31%) as a colourless oil: ν_{max}(neat)/cm^{-1} 2930, 2850, 1720, 1630, 1440, 1380 and 1280; δ_H (500 MHz; $CDCl_3$) 6.25 (s, 1 H, α-methylene), 5.90 (s, 1 H, α-methylene), 5.20 (t, *J* 6.4, 1 H, 1′-H), 5.16–5.07 (m, 4 H, 5′-H, 8′-H, 12′-H, 16′-H), 4.69 (d, *J* 12.8, 1 H, 6-H), 4.33 (d, *J* 10.4, 1 H, 2-H), 3.88 (d, *J* 12.8, 1 H, 6-H), 3.77 (s, 3 H, CO_2CH_3), 2.38 (br t, *J* 13.7, 1 H, 4-H), 2.32 (br t, *J* 12.8, 1 H, 4-H), 2.13–1.94 (m, 17 H, 3-H, 2′-H, 3′-H, 6′-H, 7′-H, 10′-H, 11′-H, 14′-H, 15′-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.36 (m, 1 H, 3-H); δ_C (125 MHz; $CDCl_3$) 166.4, 141.6, 135.2, 134.9, 134.4, 133.0, 131.2, 124.8, 124.6, 124.5, 124.4, 124.3, 124.2, 75.4, 67.1, 51.8, 39.8, 39.7(×2), 33.9, 33.1, 28.3, 28.2, 26.8, 26.7, 25.7(×2), 17.7, 16.1 and 16.0(×2) [Found (HRMS): M^+, 468.3608. $C_{31}H_{48}O_3$ requires *M*, 468.3603].

(5*Z*,4′*E*,8′*E*,12′*E*)-2-Methylene-2-[5-(4′,9′,13′,17′-tetramethyloctadeca-4′,8′,12′,16′-tetraenylidene)tetrahydropyran-2-yl]-acetic acid 2

To a solution of **26** (14 mg, 0.030 mmol) in THF (0.15 ml) was added LiOH·H_2O (13 mg, 0.31 mmol) in H_2O (0.15 ml) at 0 °C. After the reaction mixture was stirred for 24 h at 25 °C, it was acidified with 1 M HCl and diluted with Et_2O; the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried with anhydrous Na_2SO_4 and evaporated. Column chromatography (6 wt% water–silica gel, hexane–EtOAc, 8:2) of the crude product gave *rac*-**2** (11 mg, 0.024 mmol) as a colourless oil in 80% yield; R_f (EtOAc–hexane, 3:7) 0.40; ν_{max}(neat)/cm^{-1} 2930, 2860, 1700, 1630, 1450, 1380 and 1290; δ_H (500 MHz, $CDCl_3$) 6.37 (s, 1 H, α-methylene), 5.90 (s, 1 H, α-methylene), 5.24 (t, *J* 7.3, 1 H, 1′-H), 5.17–5.08 (m, 4 H, 5′-H, 8′-H, 12′-H, 16′-H), 4.72 (d, *J* 12.8, 1 H, 6-H), 4.32 (d, *J* 11.0, 1 H, 2-H), 3.91 (d, *J* 12.8, 1 H, 6-H), 2.39–2.34 (m, 2 H, 4-H), 2.15–1.95 (m, 17 H, 3-H, 2′-H, 3′-H, 6′-H, 7′-H, 10′-H, 11′-H, 14′-H, 15′-H), 1.68 (s, 3 H, vinyl-CH_3), 1.60 (s, 12 H, vinyl-CH_3) and 1.50 (m, 1 H); the carboxylic proton was not observed because of broadening of the signal; δ_C (125 MHz, $CDCl_3$) 169.8, 140.6, 135.2, 134.9, 134.4, 132.5, 131.2, 127.1, 125.0, 124.9, 124.4, 124.2(×2), 76.0, 67.1, 39.7(×3), 33.7, 32.9, 28.3, 28.2, 26.8, 26.7, 25.7(×2), 17.7, 16.1 and 16.0(×2) [Found (HRMS): M^+, 454.3419. $C_{30}H_{46}O_3$ requires *M*, 454.3447].

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