Stereoselective syntheses of (+)-rhopaloic acid A and (−)-*ent*- and (±)-*rac*-rhopaloic acid A

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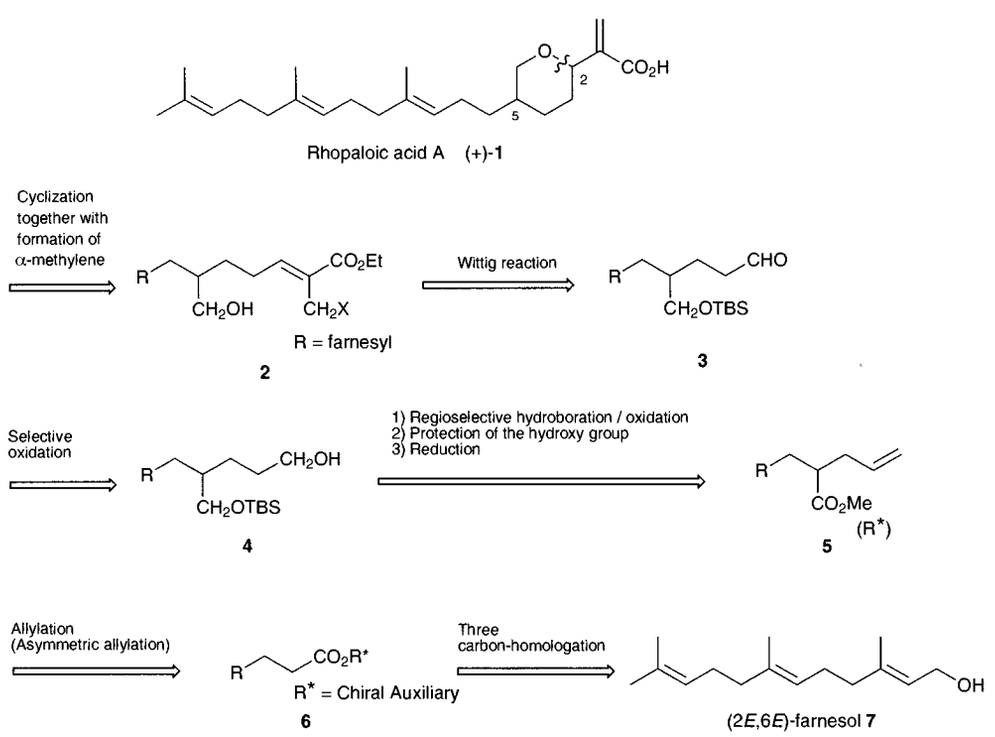
Rhopaloic acid A (+)-1 and the related compounds (−)-*ent*-1 and (±)-*rac*-1 have been stereoselectively synthesized. The synthetic strategy consists of successive homologation of (2*E*,6*E*)-farnesol 7 and cyclization to form a tetrahydropyran ring, together with final introduction of an α-methylene group on the carboxylic moiety. The cyclization is carried out by intramolecular hetero-Michael addition leading to 2,5-disubstituted tetrahydropyrans. The stereochemistry can be rationalized by invoking a model of a chair-like transition state. The asymmetric synthesis is achieved by way of the Evans' asymmetric alkylation procedure using (*S*)- or (*R*)-4-benzyloxazolidin-2-one as the chiral auxiliary. In the event, the configuration of natural rhopaloic acid A (+)-1 could be assigned as 2*R*,5*S* by comparison of the specific rotations of synthetic compounds with that of the natural product.

Introduction

(+)-Rhopaloic acid A (+)-**1**, which was isolated from a marine sponge, *Rhopaloeides* sp., inhibited gastrulation of starfish embryos and also exhibited potent cytotoxicities *in vitro* against human myeloid K-562 cells, human MOLT-4 leukemia cells and murine L1210 leukemia cells.[1] The structure was identified as (2β,5α,3*E*,7*E*)-(+)-α-[5-(4,8,12-trimethyltrideca-3,7,11-trienyl)tetrahydropyran-2-yl]-α-methyleneacetic acid. The interesting biological activity of this compound may be attributed to the structurally unique feature of its having a hydrophilic pyranylacrylic acid moiety connected to a hydrophobic isoprenoid entity.[2] Some sesterterpenes related to mamoalide having pyran and furanone rings as hydrophilic entities showed themselves to be potent inhibitors of phospholipase A_2.[2a] Some interesting phenomena concerned with the hydrophobic effect in DNA cleavage shown by alk(en)yl-di and tri-hydroxybenzenes have been discussed.[2b] With respect to the hydrophilic part, the acrylic acid moiety is also found in compounds such as conconadine[3a] and gerin,[3b] and the related 2-methylene-γ-lactone group in many bioactive natural products. Furthermore, a 2,5-disubstituted tetrahydropyran-2-ylacetic acid structure is novel in natural products. The potential of (+)-**1** and its analogues as biological probes as well as the interesting structural features provided the incentive for the synthetic undertaking described here. In this paper, the total syntheses of natural rhopaloic acid A (+)-**1**, non-natural enantiomeric rhopaloic acid A (−)-*ent*-**1**, and the racemic compound (±)-*rac*-**1** are described.[4]

Standard retrosynthetic manipulation of rhopaloic acid A **1** converts it into (2*E*,6*E*)-farnesol **7** (Scheme 1). Retrosynthetic cleavage of the indicated bond in **1** together with the double-bond migration furnishes the unsaturated ester **2** as a potential



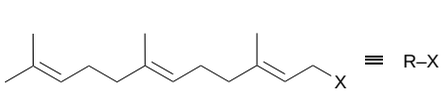
Scheme 1 Retrosynthesis of rhopaloic acid A (+)-**1**

precursor. The cyclization and α-methylene introduction is carried out simultaneously due to the high reactivity of the acrylate moiety to a variety of reagents. The predictable Wittig reaction of **3** leads to the formation of the α,β-unsaturated carboxylate derivative to give the intermediate **2**. Selective oxidation of the terminal alcohol would, after protection of the 4-hydroxymethyl function by a *tert*-butyldimethylsilyl (TBS) group, give **3**. The terminal hydroxy group could be formed by way of a regioselective hydroboration–oxidation procedure in the terminal olefin of **5**. Compound **5** could conceivably be formed in one step through a diastereoselective allylation by means of a chiral auxiliary. Compound **6** could be fashioned by way of three-carbon homologation steps from (2*E*,6*E*)-farnesol **7**.

Results and discussion

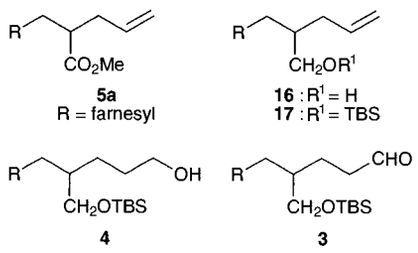
The two-carbon homologation exploited malonic esterification starting from **7**. Bromination of **7** with MsCl in CH_2Cl_2–LiBr in THF afforded (2*E*,6*E*)-farnesyl bromide (2*E*,6*E*)-**8** along with *ca*. 50% of (2*Z*,6*E*)-farnesyl bromide (2*Z*,6*E*)-**8**.[5a] Bromination of **7** with Me_2S–NBS in CH_2Cl_2 also gave a mixture of geometric isomers (2*E*,6*E*)-**8** and (2*Z*,6*E*)-**8** in which the ratio [(2*E*,6*E*)-**8**/(2*Z*,6*E*)-**8**] was 85 : 15.[5b] In the event, treatment of **7** with Ph_3P–CBr_4 in CH_2Cl_2 at 0 °C afforded **8** as an almost pure isomer of 2*E*,6*E* geometry which was contaminated by <5% of the (2*Z*,6*E*)-isomer.[6] The purity of the geometric isomer was determined by integration of the C-1 protons in the ^{1}H NMR spectrum. The bromide (2*E*,6*E*)-**8** was used for the following reaction without further purification. Reaction of **8** (1 equiv.) with dimethyl malonate (2 equiv.) and NaH (2 equiv.) gave dimethyl ester **9** in low to moderate yield (10–64%) along with the difarnesyl-substituted malonate ester **10** (7–37%) depending upon the reaction conditions. It is considered that deprotonation of **9** with an excess of dimethyl malonate anion generates another anion under the reaction conditions and that this would then be attacked by another molecule of **8** to give the difarnesyl-substituted malonate derivative **10**. Treatment of **8** (1 equiv.) with an excess of dimethyl malonate (5 equiv.) in the presence of NaH (1 equiv.) in THF gave **9** (78%, over two steps from 2*E*,6*E*-farnesol **7**).[7] Demethoxycarboxylation of **9** under neutral conditions (NaCl in moist DMF) afforded the methyl ester **11** (91%).

Reduction of **11** with $LiAlH_4$ afforded the alcohol **12** in quantitative yield. Treatment of **12** with Ph_3P–CBr_4 reagent gave the bromide **13** (92%).[6] Reaction of **13** with NaCN in DMF afforded the nitrile **14** (87%). Hydrolysis of **14** under basic conditions afforded the carboxylic acid **15** which upon esterification with MeI–K_2CO_3 gave the methyl ester **6a** (86%, over two steps).[8]



	X		X
7	OH : (2*E*,6*E*)-farnesol	**12**	CH_2CH_2OH
8	Br	**13**	CH_2CH_2Br
9	$CH(CO_2Me)_2$	**14**	CH_2CH_2CN
10	$CR(CO_2Me)_2$	**15**	$CH_2CH_2CO_2H$
11	CH_2CO_2Me	**6a**	$CH_2CH_2CO_2Me$

Allylation of the active methylene was utilized for the asymmetric three-carbon homologation, since it is possible to prepare the product of the desired configuration in a predictable manner by using chiral auxiliaries.[9] Treatment of **6a** with LDA followed by allyl bromide gave the allylated methyl ester **5a** (81%). Reduction of **5a** with $LiAlH_4$ afforded the alcohol **16** (88%). Protection of **16** with *tert*-butyldimethylsilyl chloride (TBSCl) gave **17** which upon hydroboration–oxidation with 9-BBN–H_2O_2 gave the primary alcohol **4** (69%, over two steps).



Swern oxidation of **4** afforded the aldehyde **3** in 80% yield, while with PCC and PDC it gave **3** in lower yields (48 and 36%, respectively).

The modified Wittig–Horner–Emmons reactions of **3** with $(EtO)_2P(O)C(=CH_2)CO_2Et$ in the presence of $NaSCHMe_2$ furnished the α,β-unsaturated ester **18** (Scheme 2),[10] the ratio of geometric products varying with the reaction conditions. The reaction mixture when stirred at 0 °C for 3 h, gave a mixture of (*Z*)- and (*E*)-**18** (59%; *Z*/*E* 1.3 : 1.0), whilst a reaction conducted at 25 °C for 17 h afforded the thermodynamically controlled product (*Z*)-**18** as a single isomer in 53% yield.

The geometric assignment for (*Z*)-**18** was determined by comparison of its ^{1}H NMR chemical shifts for the vinyl proton. The triplet signal at δ 6.81 assigned to the 3-vinyl proton of the major isomer was observed at lower magnetic field than that (δ 5.97) of the minor one. On the other hand, 4-H methylene protons at δ 2.47 of the minor isomer appeared at lower magnetic field than those (δ 2.26) of the major one. According to the magnetic anisotropy of the ester group, the geometry of the major product was assigned as *Z* and that of the minor one as *E*, respectively. Furthermore, the geometry of the double bond at the C-2 position of **18** was confirmed with dif-NOE: when 3-H at δ 5.97 of the *E*-isomer was irradiated, the intensity of the 2-CH_2-S signal at δ 3.39 was enhanced by 8.2%.

Treatment of **18** with TBAF failed to give the pyran derivative **20**, only the deprotected product **19** (87%) being obtained instead. Although **19** was treated with NaH, the ring closed product **20** was not obtained (Scheme 2).

Treatment of (*E*)-**18** with the methylating reagent MeI–$AgBF_4$ followed by desilylation with TBAF afforded exclusively the *trans*-ethyl pyranylacrylate derivative **21** (31%; *cis*/*trans*, 6 : 94). Reaction of (*Z*)-**18** with the same reagents gave also *trans*-**21** with high stereoselectivity (37%; *cis*/*trans*, 5 : 95). Results for the intramolecular hetero-Michael addition of **18** are summarized in Table 1. The cyclizations were found to be kinetically controlled and irreversible. Recently, similar hetero-Michael addition studies of γ-oxygenated-α,β-unsaturated esters have been reported, the reaction also being found to be kinetically controlled.[11]

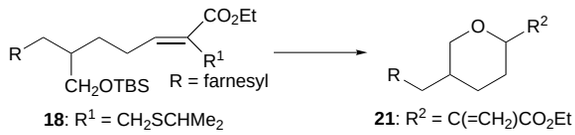
Assignment of 6-ax-H at δ 3.16 in the ^{1}H NMR spectrum of **21** was determined from the following coupling constants: $J_{5,6\text{-ax}}$ 11.2 and $J_{5,6\text{-eq}}$ 3.9 Hz. The relative stereochemistry of *trans*-**21** was confirmed by intensity enhancement of 2-H at δ 4.12 by 10.9% upon irradiation of the 6-ax-H at δ 3.16 through dif-NOE measurements.

The stereochemistry was rationalized by invoking a model of a chair-like transition state **I** in which the long-chain alkyl group is located in the equatorial mode and the stereochemical course of the approach of the α,β-unsaturated ester is controlled by 1,3-diaxial-repulsion between the acrylate moiety and protons (Fig. 1).[12]

Hydrolysis of *trans*-**21** with aqueous KOH afforded the racemic (±)-*rac*-**1** (34%), in which the geometry between C-2 and C-5 was retained under the reaction conditions. The stereochemistry of *trans*-(±)-**1** was assigned on the basis of the same considerations as those for **21**: $J_{5,6\text{-ax}}$ 11.2 and $J_{5,6\text{-eq}}$ 3.9 Hz; when 6-ax-H at δ 3.16 was irradiated, an intensity enhancement of 2-H at δ 4.12 by 6.9% was observed.

Synthesis of the optically active rhopaloic acid A (+)-**1** and

Table 1 Stereoselectivity in the intramolecular hetero-Michael addition of **18**



18: $R^1 = CH_2SCHMe_2$ **21**: $R^2 = C(=CH_2)CO_2Et$

Starting material	Reagents and conditions	Major product	Yield (%)	Ratio (*cis*/*trans*)
(2*E*)-**18**	i, MeI (3 equiv.), $AgBF_4$ (1.3 equiv.), 25 °C, 2 h; ii, TBAF (4.4 equiv.), 25 °C, 11 h	*rac*-**21**	31	6/94
(2*Z*)-**18**	i, MeI (4 equiv.), $AgBF_4$ (1.2 equiv.), 25 °C, 2 h; ii, TBAF (3 equiv.), 25 °C, 11 h	*rac*-**21**	37	5/95
(2*Z*,6*R*)-**18**	i, MeI (2 equiv.), $AgBF_4$ (1.1 equiv.), 25 °C, 5 h; ii, TBAF (5.6 equiv.), 25 °C, 13 h	(2*S*,5*R*)-**21**	36	4/96
(2*Z*,6*S*)-**18**	i, MeI (excess), $AgBF_4$ (3.8 equiv.), 25 °C, 5 h; ii, TBAF (13 equiv.), 0 °C, 6 h then 25 °C, 15 h	(2*R*,5*S*)-**21**	33	2/98

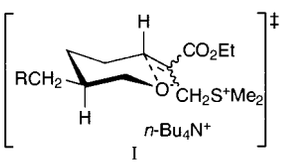


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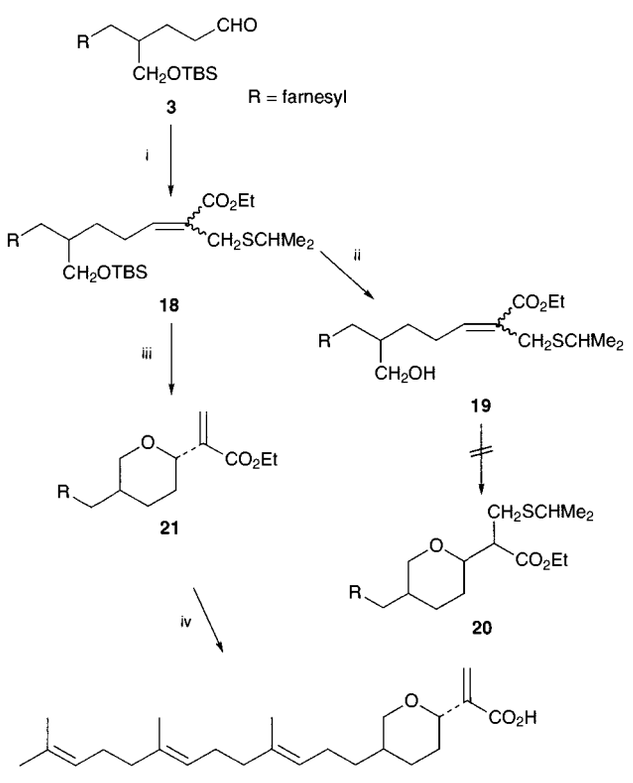
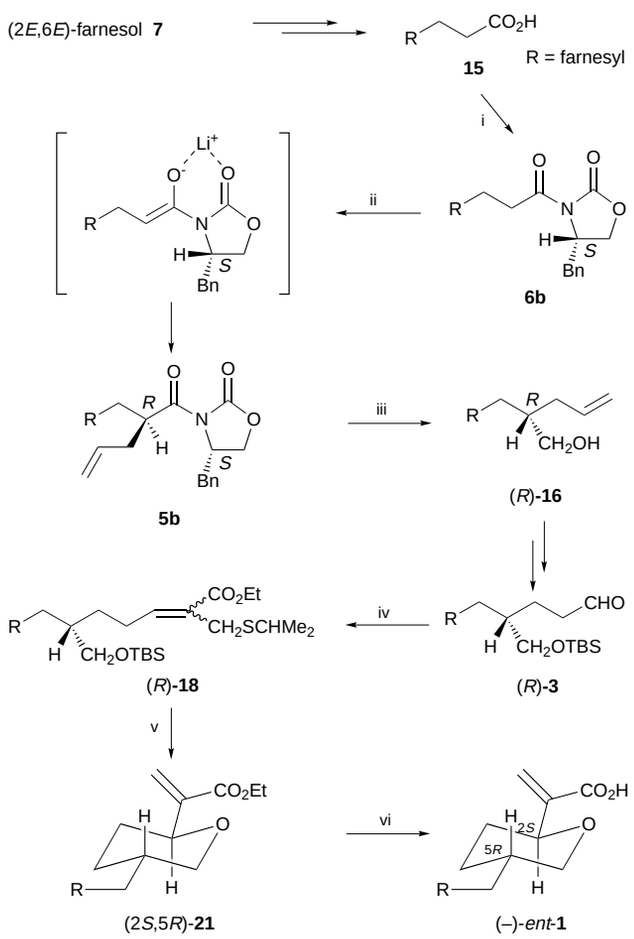
Fig. 1 Possible transition state model in the hetero-Michael addition



Scheme 2 *Reagents and conditions* (*and yields*): i, NaH, Me_2CHSH, $(EtO)_2P(O)C(=CH_2)CO_2Et$, THF, 0 °C, 10 min, then **3**, 0 °C, 3 h [59% (*E*: 26%, *Z*: 33%)]; ii, $Bu_4N^+F^-$, THF, room temp., 2 days (87%); iii, MeI, $AgBF_4$, CH_2Cl_2, 25 °C, 5 h, then $Bu_4N^+F^-$, THF, 25 °C, 20 h (32%); iv, aq. KOH, reflux, 22 h (34%)

(−)-*ent*-**1** was carried out by way of the Evans' asymmetric alkylation.[13] The auxiliary moiety, (*S*)-4-benzyloxazolidin-2-one, was attached to **15** (87%) to give **6b** (see Scheme 3). The lithium enolate of **6b** was treated with allyl bromide at −20 to −10 °C to give **5b** as a pure diastereoisomer (61% yield, 99% de). The optical purity was determined by converting the alcohol (*R*)-**16** into its benzoate (*R*)-**22** and analysing this on a chiral column.



Scheme 3 *Reagents and conditions* (*and yields*): i, Et_3N, PivCl, THF, then *N*-lithiooxazolidin-2-one, THF, −78 °C, 15 h (87%); ii, LDA, THF, −78 °C, 30 min, then allyl bromide, −20 to −10 °C, 6 h (61%); iii, $LiAlH_4$, THF, 0 °C, 15 h (87%); iv, NaH, Me_2CHSH, $(EtO)_2P(O)(=CH_2)CO_2Et$, THF, 0 °C, 10 min, then (*R*)-**3**, 25 °C, 17 h (54%) (only *Z*-isomer); v, MeI, $AgBF_4$, CH_2Cl_2, 5 h then $Bu_4N^+F^-$, THF, 25 °C, 13 h (36%); vi, aq. KOH, reflux, 22 h (56%)

Considerations of the chelation model of the enolate intermediate predicted that the stereochemistry at the C-2 position of **5b** would have the *R*-configuration.[9,13] Following removal of the chiral auxiliary by $LiAlH_4$ reduction (87%) and protection (74%) of the alcohol (*R*)-**16** with a *tert*-butyldimethylsilyl group, the silyl ether (*R*)-**17** was subjected to regioselective

hydroboration with 9-BBN reagent followed by oxidation with H_2O_2 to give (*R*)-**4** (92%). Swern oxidation of (*R*)-**4** afforded (*R*)-**3** in 80% yield. The modified Wittig–Horner–Emmons type reaction of (*R*)-**3** afforded the α,β-unsaturated ester (2*Z*,6*R*)-**18** (54%) which was cyclized to (2*S*,5*R*)-**21** as a mixture of *cis*- and *trans*-isomers (36%; *cis*/*trans* 4:96). The geometric isomers were separated into a pure sample by HPLC. Hydrolysis of *trans*-(2*S*,5*R*)-**21** gave the optically pure *trans*-(2*S*,5*R*)-*ent*-**1** in 6% overall yield from (*R*)-**16**. The specific rotation of *ent*-**1** was $[a]_D^{25}$ −37.6 (*c* 0.315, $CHCl_3$). This synthetic compound was identical (^1H and ^{13}C NMR and IR spectroscopy) with an authentic sample isolated from the marine sponge, *Rhopaloeides* sp.[1] However, the specific rotation of the natural and synthetic samples was of opposite sign and of equal magnitude, indicating that the synthetic material is the enantiomorph of the natural product.

The asymmetric synthesis of the natural product (+)-**1** was accomplished by the same route as the preparation of (−)-**1**. Allylation of **6c** attached (*R*)-4-benzyloxazolidin-2-one as the chiral auxiliary by the same synthetic route to give **5c** (82%) in which the configuration at the C-2 position was expected to be *S*. The diastereoselectivity was evaluated by a chiral HPLC of the subsequent benzoate derivative (*S*)-**22**. Reduction of **5c** with $LiBH_4$ gave (*S*)-**16** as the optically pure sample (60% yield, 99% ee) along with (*R*)-4-benzyloxazolidin-2-one (recovered in 76%). Successive conversions of **5c** afforded the product which had specific rotation of the same sign as natural rhopaloic acid A (+)-**1** of which the configuration was determined to be 2*R*,5*S* on the basis of the above considerations.

On the basis of the stereochemistry in the asymmetric synthesis of (+)-**1** and (−)-**1**, the configuration of the natural rhopaloic acid A is assigned as 2*R* and 5*S*, respectively, $[a]_D^{25}$ +40 (*c* 0.47, $CHCl_3$).[1]

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 JEOL GSX-270 instrument and ^1H and ^{13}C NMR spectra were observed in $CDCl_3$ solution with $SiMe_4$ as the internal reference. IR spectra were recorded on a JASCO IRA-1H instrument and MS spectra were recorded on a JEOL SX-102A instrument under electron ionization (EI) conditions. The EI data were obtained by using 70 eV electrons. Optical rotations, recorded on a JASCO DIP-370 polarimeter, are given as 10^{-1} deg cm^2 g^{-1}.

Methyl (4*E*,8*E*)-2-methoxycarbonyl-5,9,13-trimethyltetradeca-4,8,12-trienoate 9

To a solution of (2*E*,6*E*)-farnesol **7** (30.8 g, 0.14 mol) and Ph_3P (43.6 g, 0.17 mol) in CH_2Cl_2 (150 ml), was added CBr_4 (63.9 g, 0.19 mol) at 0 °C in one portion. After being stirred at the same temperature for 6 h, the mixture was quenched with aqueous $NaHCO_3$ and the organic layer was separated, 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 **8** (51.0 g) as a pale yellow oil. The product **8** was more than 95% pure (2*E*,6*E*)-isomer in which there was a small amount of the (2*Z*,6*E*)-isomer as an impurity. The bromide **8** was used for the next reaction without further purification. For (2*E*,6*E*)-**8**: δ_H(270 MHz, $CDCl_3$) 1.60 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.73 (s, 3 H, vinyl-CH_3), 1.95–2.20 (m, 8 H, 4-H, 5-H, 8-H, 9-H), 4.02 (d, *J* 8.3, 2 H, 1-H), 5.05–5.15 (m, 2 H, 6-H, 10-H) and 5.54 (t, *J* 8.3, 1 H, 2-H); a doublet signal at δ 4.10 (d, *J* 8.3, 2 H, 1-H) was assigned to the proton at C-1 for the (2*Z*,6*E*)-**8** isomer (<5%).

To a mixture of NaH [60% oil suspension; 184 mmol, 7.35 g washed with hexane] in THF (120 ml), was added dimethyl malonate (100 ml, 0.88 mol) in THF (200 ml) at 0 °C and the mixture was stirred for 3 h at 25 °C. To the solution, was added **8** in THF (100 ml) over a 1 h period. After being stirred for 10 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 ($MgSO_4$), filtered and evaporated. The resulting residue was purified by bulb-to-bulb distillation (200–210 °C/1 Torr) to give **9** as a pale yellow oil (36.4 g, 78% yield from **7**). An analytical sample of **9** was obtained by column chromatographic separation on silica gel (EtOAc–hexane, 1:5) (Found: C, 71.38; H, 9.31. $C_{20}H_{32}O_4$ requires C, 71.39; H, 9.59%); R_F 0.41: ν_{max}(neat)/cm^{-1} 2900, 1720, 1420, 1320, 1200 and 1140; δ_H(270 MHz, $CDCl_3$) 1.57 (s, 3 H, vinyl-CH_3), 1.58 (s, 3 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.66 (s, 3 H, vinyl-CH_3), 1.93–2.10 (m, 8 H, 6-H, 7-H, 10-H, 11-H), 2.61 (t, *J* 7.3, 2 H, 3-H), 3.36 (t, *J* 7.3, 1 H, 2-H), 3.71 [s, 6 H, CO_2CH_3 (×2)] and 5.03–5.12 (m, 3 H, 4-H, 8-H, 12-H); δ_C(68 MHz, $CDCl_3$) 15.9, 16.0, 17.6, 25.6, 26.5, 26.7, 27.5, 39.6 (×2), 51.8, 52.3 (×2), 119.3, 123.8, 124.3, 131.2, 135.7, 138.7 and 169.5 (×2); *m*/*z* (EI) 336.2336 (M^+, 32%. $C_{20}H_{32}O_4$ requires 336.2301) and 69 (100).

(6*E*,10*E*,15*E*,19*E*)-13,13-Di(methoxycarbonyl)-2,6,10,16,20,24-hexamethylpentacosa-2,6,10,15,19,23-hexaene 10

To a mixture of NaH [60% oil suspension; 281 mmol, 11.2 g, washed with hexane] in THF (600 ml), was added dimethyl malonate (26.0 ml, 228 mmol) in THF (600 ml) at 0 °C and the mixture was stirred for 3 h at 25 °C. To the solution, was added **8** (32.9 g, 115 mmol) in THF (150 ml) over a 1 h period. After being stirred for 18 h at room temperature, the mixture was quenched with aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography (silica gel, EtOAc–hexane, 1:5) to afford, respectively, **9** (4.82 g, 12%) and **10** (7.76 g, 12%) as pale yellow oils. An analytical sample of **10** was obtained by column chromatography separation on silica gel (EtOAc–hexane, 1:5) R_F 0.44; ν_{max}(neat)/cm^{-1} 2900, 2850, 1720, 1430, 1370, 1200, 1170 and 900; δ_H(270 MHz, $CDCl_3$) 1.58 (s, 15 H, vinyl-CH_3), 1.68 (s, 9 H, vinyl-CH_3), 1.93–2.14 (m, 16 H, 4-H, 5-H, 8-H, 9-H, 17-H, 18-H, 21-H, 22-H), 2.60 (d, *J* 7.3, 4 H, 12-H, 14-H), 3.69 [s, 6 H, CO_2CH_3 (×2)], 5.00 (t, *J* 7.3, 2 H, 11-H, 15-H) and 5.05–5.18 (m, 4 H, 3-H, 7-H, 19-H, 23-H) [Found (HRMS): M^+, 540.4183. $C_{35}H_{56}O_4$ requires *M*, 540.4179].

Methyl (4*E*,8*E*)-5,9,13-trimethyltetradeca-4,8,12-trienoate 11

A mixture of **9** (36.4 g, 0.11 mol), NaCl (15.3 g, 0.26 mol) and water (3.9 ml, 0.22 mol) in DMF (100 ml) was heated at reflux for 20 h. The mixture was cooled, poured into water and extracted with Et_2O. The combined extracts were dried ($MgSO_4$), filtered and concentrated. Purification of the residue by bulb-to-bulb distillation (175–180 °C/1 Torr) afforded **11** as a pale yellow oil (27.6 g, 91%); R_F 0.55 (silica gel, EtOAc–hexane, 1:5); ν_{max}(neat)/cm^{-1} 2900, 1740, 1440, 1360, 1200 and 1160; δ_H(270 MHz, $CDCl_3$) 1.59 (s, 6 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.93–2.11 (m, 8 H, 6-H, 7-H, 10-H, 11-H), 2.30–2.35 (m, 4 H, 2-H, 3-H), 3.66 (s, 3 H, CO_2CH_3) and 5.04–5.14 (m, 3 H, 4-H, 8-H, 12-H); δ_C(68 MHz, $CDCl_3$) 15.8, 17.5, 23.4, 25.5, 26.4, 26.6, 34.1, 39.5, 39.6, 51.2, 67.8, 122.2, 123.9, 124.3, 131.0, 134.9, 136.6 and 173.7 [Found (HRMS): M^+, 278.2246. $C_{18}H_{30}O_2$ requires *M*, 278.2246].

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

To a suspension of $LiAlH_4$ (4.38 g, 115 mmol) in THF (100 ml) at 0 °C, was added a solution of **11** (27.6 g, 99 mmol) in THF (100 ml) portionwise. After being stirred for 1 h at 25 °C, Et_2O and water were added to the reaction mixture at 0 °C. The

resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the resulting oil by bulb-to-bulb distillation (180–190 °C/1 Torr) afforded **12** as a pale yellow oil (22.5 g, 91%). An analytical sample of **12** was obtained by PTLC on silica gel (EtOAc–hexane, 1:5) R_F 0.25 (Found: C, 81.40; H, 12.13. $C_{17}H_{30}O$ requires C, 81.54; H, 12.07%); ν_{max}(neat)/cm^{-1} 3300, 2900, 2850, 1440, 1380 and 1140; δ_H(270 MHz, $CDCl_3$) 1.60 (s, 6 H, vinyl-CH_3), 1.61 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.94–2.20 (m, 12 H, 2-H, 3-H, 6-H, 7-H, 10-H, 11-H), 3.62 (t, *J* 6.6, 2 H, 1-H) and 5.04–5.18 (m, 3 H, 4-H, 8-H, 12-H); the hydroxy and proton was not observed due to the broadening of the signal; δ_C(68 MHz, $CDCl_3$) 15.9 (×2), 17.6, 24.2, 25.6, 26.5, 26.7, 32.6, 39.6 (×2), 62.5, 123.7, 124.1, 124.3, 131.1, 134.9 and 135.6; *m*/*z* (EI) 250.2299 (M^+, 17%. $C_{17}H_{30}O$ requires 250.2297) and 69 (100).

(4*E*,8*E*)-5,9,13-Trimethyltetradeca-4,8,12-trienyl bromide 13

To a solution of **12** (22.5 g, 90 mmol) in CH_2Cl_2 (100 ml) at 0 °C, was added a mixture of Ph_3P (28.8 g, 0.11 mol) and CBr_4 (45.0 g, 0.14 mol) in one portion. The reaction mixture was stirred for 1 h at 0 °C and then quenched with water. The resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was triturated with hexane after which the hexane solution was concentrated to leave a yellow oil. Bulb-to-bulb distillation of this (170–180 °C/1 Torr) afforded **13** as a pale yellow oil (25.8 g, 92%). The oil was purified by column chromatography on silica gel (hexane) R_F 0.44; ν_{max}(neat)/cm^{-1} 2900, 1430, 1380, 1360, 1260 and 700; δ_H(270 MHz, $CDCl_3$) 1.60 (s, 6 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.84–1.93 (m, 2 H, 2-H), 1.97–2.19 (m, 10 H, 3-H, 6-H, 7-H, 10-H, 11-H), 3.39 (t, *J* 6.6, 2 H, 1-H) and 5.04–5.15 (m, 3 H, 4-H, 8-H, 12-H); δ_C(68 MHz, $CDCl_3$) 16.0, 16.1, 17.6, 25.6, 26.3, 26.4, 26.7, 32.8, 33.4, 39.7 (×2), 122.4, 124.0, 124.3, 131.9, 135.0 and 136.7 [Found (HRMS): M^+, 312.1476. $C_{17}H_{29}{}^{79}Br$ requires *M*, 312.1453].

(5*E*,9*E*)-6,10,14-Trimethylpentadeca-5,9,13-trienenitrile 14

A sample of sodium cyanide (5.60 g, 0.11 mol) was added to a solution of **13** (22.2 g, 71 mmol) in DMF (100 ml) and the reaction mixture was stirred for 1 h at room temperature. The mixture was poured into water and extracted with Et_2O. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The resulting oil was separated by bulb-to-bulb distillation (180–190 °C/1 Torr) to give **14** as a pale yellow oil (15.9 g, 87%). An analytical sample of **14** was obtained by column chromatographic separation on silica gel (EtOAc–hexane, 1:5) (Found: C, 83.28; H, 11.37; N, 5.32. $C_{18}H_{29}N$ requires C, 83.33; H, 11.27; N, 5.40%); R_F 0.59; ν_{max}(CH_2Cl_2)/cm^{-1} 2900, 2850, 2250, 1425 and 1370; δ_H(270 MHz, $CDCl_3$) 1.59 (s, 6 H, vinyl-CH_3), 1.62 (s, 3 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.68–1.72 (m, 2 H, 3-H), 1.93–2.20 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.31 (t, *J* 7.1, 2 H, 2-H) and 5.03–5.14 (m, 3 H, 5-H, 9-H, 13-H); δ_C(68 MHz, $CDCl_3$) 15.9, 16.0, 16.2, 17.6, 25.4, 25.6, 26.4, 26.5, 26.6, 39.6 (×2), 119.7, 121.7, 123.8, 124.2, 131.1, 135.0 and 137.6; *m*/*z* (EI) 259.2283 (M^+, 7%. $C_{20}H_{29}N$ requires 259.2300) and 69 (100).

(5*E*,9*E*)-6,10,14-Trimethylpentadeca-5,9,13-trienoic acid 15

A mixture of **14** (15.9 g, 0.061 mol) in EtOH (100 ml) and KOH (36.7 g, 0.66 mol) in water (100 ml) was heated at reflux for 30 h. Evaporation of the reaction mixture under reduced pressure left a residue which was extracted with CH_2Cl_2. The aqueous layer was acidified with conc. HCl and extracted with Et_2O. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The resulting oil was separated by column chromatography on silica gel (EtOAc–hexane, 1:5) to give **15** (R_F 0.23) as a pale yellow oil (14.9 g, 88%); ν_{max}(CH_2Cl_2)/cm^{-1} 2900, 1700, 1420, 1380 and 1220; δ_H(270 MHz, $CDCl_3$) 1.61 (s, 9 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.69–1.71 (m, 2 H, 3-H), 1.94–2.18 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.36 (t, *J* 7.6, 2 H, 2-H), 5.06–5.17 (m, 3 H, 5-H, 9-H, 13-H) and 10.00–11.00 (br s, 1 H); δ_C(68 MHz, $CDCl_3$) 16.0 (×2), 17.6, 24.7, 25.6, 26.5, 26.7, 27.1, 33.4, 39.7 (×2), 123.1, 124.1, 124.4, 131.2, 135.0, 136.3 and 180.4 [Found (HRMS): M^+, 278.2254. $C_{18}H_{30}O_2$ requires *M*, 278.2246].

Methyl (5*E*,9*E*)-6,10,14-trimethylpentadeca-5,9,13-trienoate 6a

To a mixture of **15** (8.19 g, 29 mmol) and K_2CO_3 (12.2 g, 88 mmol) in DMF (30 ml) was added MeI (6.0 ml, 96 mmol) and the resulting solution was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with Et_2O. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The oily product was separated with bulb-to-bulb distillation (160–170 °C/1 Torr) to give **6a** as a pale yellow oil (8.40 g, 98%). An analytical sample of **6a** was obtained by column chromatographic separation on silica gel (EtOAc–hexane, 1:5) R_F 0.53; ν_{max}(neat)/cm^{-1} 2900, 2850, 1730, 1420, 1360 and 1160; δ_H(270 MHz, $CDCl_3$) 1.60 (s, 6 H, vinyl-CH_3), 1.62–1.67 (m, 2 H, 3-H), 1.68 (s, 6 H, vinyl-CH_3), 1.94–2.19 (m, 10 H, 4-H, 7-H, 8-H, 11-H, 12-H), 2.30 (t, *J* 7.6, 2 H, 2-H), 3.66 (s, 3 H, CO_2CH_3) and 5.06–5.17 (m, 3 H, 5-H, 9-H, 13-H) [Found (HRMS): M^+, 292.2442. $C_{19}H_{32}O_2$ requires *M*, 292.2402].

(4*S*,5′*E*,9′*E*)-3-(1′-Oxo-6′,10′,14′-trimethylpentadeca-5′,9′,13′-trienyl)-4-benzyloxazolidin-2-one 6b

To a solution of **15** (3.15 g, 11 mmol) and Et_3N (1.6 ml, 12 mmol) in THF (20 ml), was added pivaloyl chloride (1.4 ml, 11 mmol) at 0 °C to give the anhydride. The reaction mixture was stirred at 0 °C for 30 min. Alternatively, to a solution of (*S*)-4-benzyloxazolidin-2-one (2.0 g, 11 mmol) in THF (30 ml) in another flask, was added a solution of BuLi (1.6 M in hexane solution; 7.9 ml, 12.6 mmol) at −78 °C for 30 min to give *N*-lithio-(*S*)-4-benzyloxazolidin-2-one. The reaction mixture was allowed to warm to ambient temperature and then added to a suspension of the above anhydride at −78 °C. After 15 h, the reaction mixture was poured into aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue was separated by column chromatography on silica gel (EtOAc–hexane, 1:5) to give **6b** (R_F 0.36) as a colourless oil (4.27 g, 87%) (Found: C, 76.66; H, 9.16; N, 3.18. $C_{28}H_{39}NO_3$ requires C, 76.85; H, 8.98; N, 3.20%); $[\alpha]_D^{25}$ +35.3 (*c* 0.61, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2900, 2850, 1760, 1670, 1420, 1360, 1340, 1240 and 1180; δ_H(270 MHz, $CDCl_3$) 1.61 (s, 6 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.70–1.81 (m, 2 H, 3′-H), 1.95–2.15 (m, 10 H, 4′-H, 7′-H, 8′-H, 11′-H, 12′-H), 2.77 (dd, *J* 13.2, 9.8, 1 H, benzyl-H), 2.85–3.05 (m, 2 H, 2′-H), 3.31 (dd, *J* 13.2, 2.9, 1 H, benzyl-H), 4.15–4.25 (m, 2 H, 5-H), 4.64–4.74 (m, 1 H, 4-H), 5.05–5.25 (m, 3 H, 5′-H, 9′-H, 13′-H), 7.15–7.25 (m, 2 H, ArH) and 7.25–7.45 (m, 3 H, ArH); δ_C(68 MHz, $CDCl_3$) 15.9, 16.0, 17.6, 24.3, 25.6, 26.6, 26.7, 27.2, 35.0, 37.9, 39.7 (×2), 55.1, 66.0, 123.3, 124.1, 124.3, 127.2, 128.9 (×2), 129.4 (×2), 131.1, 134.9, 135.3, 136.1, 153.3 and 173.3; *m*/*z* (EI) 437.2932 (M^+, 15%. $C_{28}H_{39}NO_3$ requires 437.2930) and 69 (100).

(4*R*,5′*E*,9′*E*)-3-(1′-Oxo-6′,10′,14′-trimethylpentadeca-5′,9′,13′-trienyl)-4-benzyloxazolidin-2-one 6c

The reaction conditions for the preparation of **6b** were followed using **15** (2.6 g, 9.3 mmol), pivaloyl chloride (1.4 ml, 11 mmol), Et_3N (1.6 ml, 11 mmol), (*R*)-4-benzyloxazolidin-2-one (1.8 g, 10 mmol) and a 1.6 M solution of BuLi in hexane (6.4 ml, 10 mmol). Column chromatographic separation (silica gel, EtOAc–hexane, 1:5) of the crude product afforded **6c** (R_F 0.33) as a colourless oil (3.9 g, 95%); $[\alpha]_D^{25}$ −35.5 (*c* 3.9, $CHCl_3$).

(7*E*,11*E*)-4-Methoxycarbonyl-8,12,16-trimethylheptadeca-1,7,11,15-tetraene 5a

To a solution of Pr^i_2NH (1.4 ml, 10 mmol) in THF (10 ml), was added 1.63 M BuLi (4.9 ml, 8.0 mmol) over 5 min at −78 °C. After the mixture had been stirred at 0 °C for 30 min, it was cooled to −78 °C. Compound **6a** (1.94 g, 6.7 mmol) was then added to the mixture at −78 °C followed by a sample of allyl bromide (2.9 ml, 33.5 mmol), added at the same temperature. The cooling bath was removed and the mixture was stirred overnight at room temperature. The mixture was then poured into ice-cooled aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by bulb-to-bulb distillation (175–185 °C/1 Torr) to give **5a** as a pale yellow oil (1.78 g, 81%). An analytical sample of **5a** was obtained by column chromatographic separation on silica gel (EtOAc–hexane, 1:5) R_F 0.67; ν_{max}(neat)/cm^{-1} 2900, 2850, 1730, 1420, 1360 and 1150; δ_H(270 MHz, $CDCl_3$) 1.45–1.60 (m, 2 H, 5-H), 1.56 (s, 6 H, vinyl-CH_3), 1.65 (s, 6 H, vinyl-CH_3), 1.92–2.13 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.13–2.49 (m, 3 H, 3-H, 4-H), 3.63 (s, 3 H, CO_2CH_3), 4.93–5.20 (m, 5 H, 1-H, 7-H, 11-H, 15-H) and 5.62–5.82 (m, 1 H, 2-H) [Found (HRMS): M$^+$, 332.2708. $C_{22}H_{36}O_2$ requires *M*, 332.2715].

(4*S*,2′*R*,5′*E*,9′*E*)-3-(1′-Oxo-2′-prop-2″-enyl-6′,10′,14′-trimethylpentadeca-5′,9′,13′-trienyl)-4-benzyloxazolidin-2-one 5b

To a solution of Pr^i_2NH (2.6 ml, 20 mmol) in THF (12 ml), was added a solution of BuLi (1.6 M hexane solution; 9.7 ml, 16 mmol) at −78 °C. The mixture was allowed to warm to 0 °C, at which temperature it was stirred for 30 min before being cooled again to −78 °C. To the cooled solution, was added a solution of **6b** (6.05 g, 14 mmol) in THF (12 ml) at −78 °C for 30 min. To the mixture, was added a sample of allyl bromide (6.0 ml, 69 mmol) at the same temperature. The reaction mixture was stirred at −20 to −10 °C for 6 h and then poured into ice-cooled aqueous NH_4Cl. The resulting mixture was extracted with Et_2O and the combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was separated by column chromatography on silica gel (EtOAc–hexane, 1:5) to give **5b** (R_F 0.52) as a colourless oil (3.79 g, 61%) (Found: C, 77.75; H, 9.10; N, 2.81. $C_{31}H_{43}O_3N$ requires C, 77.95; H, 9.07; N, 2.93%); $[a]_D^{25}$ +44.1 (*c* 3.9, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2900, 1770, 1680, 1430, 1370, 1340, 1230, 1200, 1090 and 900; δ_H(270 MHz, $CDCl_3$) 1.58 (s, 3 H, vinyl-CH_3), 1.59 (s, 6 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.74–1.87 (m, 2 H, 3′-H), 1.93–2.11 (m, 10 H, 4′-H, 7′-H, 8′-H, 11′-H, 12′-H), 2.28–2.38 (m, 1 H, 1″-H), 2.42–2.53 (m, 1 H, 1″-H), 2.66 (dd, *J* 13.2, 10.0, 1 H, benzyl-H), 3.30 (dd, *J* 13.2, 3.4, 1 H, benzyl-H), 3.88–3.97 (m, 1 H, 2′-H), 4.08–4.20 (m, 2 H, 5-H), 4.62–4.73 (m, 1 H, 4-H), 5.02–5.14 (m, 5 H, 3″-H, 5′-H, 9′-H, 13′-H), 5.76–5.91 (m, 1 H, 2″-H) and 7.21–7.36 (m, 5 H, ArH); δ_C(68 MHz, $CDCl_3$) 16.0 (×2), 17.6, 25.6, 25.7, 26.6, 26.7, 31.4, 36.9, 38.1, 39.7 (×2), 41.9, 55.5, 65.8, 117.1, 123.5, 124.1, 124.4, 127.2, 128.9 (×2), 129.4 (×2), 131.2, 135.0, 135.2, 135.4, 135.8, 153.0 and 175.9; *m*/*z* (EI) 477.3266 (M$^+$, 6%. $C_{31}H_{43}NO_3$ requires 477.3243) and 69 (100).

(4*R*,2′*S*,5′*E*,9′*E*)-3-(1′-Oxo-2′-prop-2″-enyl-6′,10′,14′-trimethylpentadeca-5′,9′,13′-trienyl)-4-benzyloxazolidin-2-one 5c

The reaction conditions for preparation of (+)-**5b** were followed using **6c** (3.8 g, 8.78 mmol), Pr^i_2NH (1.7 ml, 12 mmol), a 1.6 M solution of BuLi in hexane (6.3 ml, 10 mmol) and allyl bromide (3.2 ml, 37 mmol). Column chromatographic separation on silica gel (EtOAc–hexane, 1:5) of the crude product afforded **5c** (R_F 0.55) as a colourless oil (3.2 g, 76%); $[a]_D^{25}$ −45.6 (*c* 1.4, $CHCl_3$).

(7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethylheptadeca-1,7,11,15-tetraene 16

To a suspension of $LiAlH_4$ (1.96 g, 51. 8 mmol) in THF (50 ml), was added a solution of **5a** (11.0 g, 33.2 mmol) in THF (50 ml) at 0 °C and the mixture was stirred at the same temperature. After 3 h, water (1 ml) was carefully added to the mixture at 0 °C followed by concentrated aqueous NaOH (1 ml), carefully added. The resulting precipitate was filtered off and thoroughly washed. The filtrate was diluted with water and the resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by bulb-to-bulb distillation (190–200 °C/1 Torr) to give **16** as a pale yellow oil (8.89 g, 88%); ν_{max}(neat)/cm^{-1} 3500, 2900, 2850, 1440, 1380, 1030, 990 and 910; δ_H(270 MHz, $CDCl_3$) 1.25–1.46 (m, 2 H, 5-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.60–1.65 (m, 1 H, 4-H), 1.93–2.15 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.13 (t, *J* 6.8, 2 H, 3-H), 3.54 (d, *J* 5.9, 1 H, CH_2OH), 3.55 (d, *J* 5.4, 1 H, CH_2OH), 4.99–5.14 (m, 5 H, 1-H, 7-H, 11-H, 15-H) and 5.75–5.90 (m, 1 H, 2-H); the hydroxy proton was not observed because of broadening of the signal; δ_C(68 MHz, $CDCl_3$) 15.9, 17.6, 25.1, 25.2, 25.6, 26.5, 26.7, 30.7, 30.9, 35.6, 39.7, 39.9, 65.3, 116.1, 124.1, 124.3 (×2), 131.2, 134.9, 135.2 and 137.0 [Found (HRMS): M$^+$, 304.2799. $C_{21}H_{36}O$ requires *M*, 304.2766].

(4*R*,7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethylheptadeca-1,7,11,15-tetraene (*R*)-16

By a method similar to that used in the preparation of **16**, (*R*)-**16** (bp 190–200 °C/1 Torr; 3.66 g, 87%) was obtained from **5b** (6.15 g, 13 mmol) and $LiAlH_4$ (1.08 g, 29 mmol). The product was further purified by column chromatography on silica gel (EtOAc–hexane, 1:5) R_F 0.15; $[a]_D^{25}$ −4.8 (*c* 2.0, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-Hydroxymethyl-8,12,16-trimethylheptadeca-1,7,11,15-tetraene (*S*)-16

To a solution of **5c** (2.4 g, 8.0 mmol) in dry MeOH (1.1 ml) at 0 °C, was slowly added a solution of $LiBH_4$ (520 mg, 24 mmol) in THF (19 ml). The reaction mixture was stirred at 0 °C for 3 h and then quenched with aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated. Column chromatographic separation of the crude product (silica gel, EtOAc–hexane, 1:5) gave (*R*)-4-benzyloxazolidin-2-one as white crystals (860 mg, 76%) and (*S*)-**16** (R_F 0.15) as a colourless oil (973 mg, 60%); $[a]_D^{25}$ +4.5 (*c* 3.4, $CHCl_3$).

(7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-1,7,11,15-tetraene 17

To a mixture of **16** (1.58 g, 5.20 mmol) and imidazole (671 mg, 9.86 mmol) in DMF (7 ml), was added *tert*-butyldimethylsilyl chloride (1.14 g, 7.55 mmol). The reaction mixture was stirred for 3 h and then quenched with aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water and aqueous NaCl, dried ($MgSO_4$) and concentrated. The crude product was purified with column chromatography (silica gel, hexane) to give **17** (R_F 0.83) as a pale yellow oil (1.89 g, 87%) (Found: C, 77.46; H, 11.88. $C_{27}H_{50}OSi$ requires C, 77.43; H, 12.03%); ν_{max}(neat)/cm^{-1} 2900, 2850, 1440, 1380, 1250, 1090, 900, 830 and 770; δ_H(270 MHz, $CDCl_3$) 0.03 (s, 6 H, CH_3-Si), 0.89 [s, 9 H, $(CH_3)_3$C-Si], 1.25–1.44 (m, 2 H, 5-H), 1.50–1.59 (m, 1 H, 4-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95–2.17 (m, 12 H, 3-H, 6-H, 9-H, 10-H, 13-H, 14-H), 3.48 (d, *J* 5.9, 1 H, CH_2OSi), 3.49 (d, *J* 5.4, 1 H, CH_2OSi), 4.95–5.05 (m, 2 H, 1-H), 5.08–5.15 (m, 3 H, 7-H, 11-H, 15-H) and 5.70–5.85 (m, 1 H, 2-H); δ_C(68 MHz, $CDCl_3$) −5.4 (×2), 16.0, 17.7, 18.3, 25.3 (×2), 25.7, 25.9 (×3), 26.6, 26.8, 29.7, 30.6, 35.5, 39.7, 40.0, 64.9, 115.7, 124.3, 124.4, 124.7, 131.2, 134.9 (×2) and 137.4; *m*/*z*

(EI) 418.3666 (M^+, 14%. $C_{27}H_{50}OSi$ requires 418.3631) and 69 (100).

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-1,7,11,15-tetraene (*R*)-17

By a method similar to that used in the preparation of **17**, (*R*)-**17** (1.08 g, 74%) was obtained from (*R*)-**16** (1.07 g, 3.5 mmol), *tert*-butyldimethylsilyl chloride (637 mg, 4.23 mmol) and imidazole (532 mg, 7.8 mmol). The crude product was separated by column chromatography on silica gel (hexane) to give *tert*-butyldimethylsilyl ether (*R*)-**17** as a pale yellow oil. An analytical sample of (*R*)-**17** was obtained by PTLC on silica gel (hexane) (R_F 0.83); $[\alpha]_D^{25}$ +2.6 (*c* 3.0, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-1,7,11,15-tetraene (*S*)-17

The reaction conditions for the preparation of (*R*)-**17** were followed using (*S*)-**16** (356 mg, 1.17 mmol), TBSCl (212 mg, 1.40 mmol) and imidazole (223 mg, 3.28 mmol). Column chromatographic separation (silica gel, hexane) of the crude product afforded (*S*)-**17** (R_F 0.83) as a colourless oil (289 mg, 59%); $[\alpha]_D^{25}$ −4.7 (*c* 2.98, $CHCl_3$).

(7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-ol 4

To a solution of **17** (1.89 g, 4.52 mmol) in THF (5 ml), was added 9-BBN (0.5 M in THF; 13.6 ml, 6.8 mmol) at 0 °C and the mixture was stirred overnight at 0 °C–ambient temperature. The solution was cooled at 0 °C and diluted with water. A solution of NaOH (631 mg, 15.8 mmol) in water (3 ml) and 30% aqueous H_2O_2 (1.65 g, 14.6 mmol) were added to the reaction mixture at 0 °C which was then stirred at 0 °C–ambient temperature. After storage overnight, the mixture was diluted with water and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 1:5) to give **4** (R_F 0.28) as a pale yellow oil (1.55 g, 79%) (Found: C, 74.39; H, 12.08; $C_{27}H_{52}O_2Si$ requires C, 74.24; H, 12.00%); ν_{max}(neat)/cm^{-1} 3300, 2880, 1440, 1380, 1250, 1060, 830 and 770; δ_H(270 MHz, $CDCl_3$) 0.04 (s, 6 H, CH_3-Si), 0.89 [s, 9 H, $(CH_3)_3$C-Si], 1.23–1.52 (m, 7 H, 2-H, 3-H, 4-H, 5-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95–2.15 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 3.50 (t, *J* 5.4, 2 H, 1-H), 3.62 (t, *J* 6.8, 1 H, CH_2OSi), 3.64 (t, *J* 6.8, 1 H, CH_2OSi) and 5.07–5.14 (m, 3 H, 7-H, 11-H, 15-H); the hydroxy proton was not observed because of broadening of the signal; δ_C(68 MHz, $CDCl_3$) −5.5 (×2), 15.9, 17.6, 18.3, 22.1, 25.3 (×2), 25.6, 25.9 (×3), 26.4 (×2), 28.1, 32.2, 39.7, 39.9, 41.9, 63.3, 65.4, 124.2, 124.4, 124.7, 131.1, 134.8 and 134.9; *m*/*z* (EI) 436.3771 (M^+, 18%. $C_{27}H_{52}O_2Si$ requires 436.3737) and 69 (100).

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-ol (*R*)-4

By a method similar to that used in the preparation of **4**, (*R*)-**4** was obtained from (*R*)-**17** (1.38 g, 3.3 mmol), 9-BBN (0.5 M in THF solution; 7.2 ml, 3.6 mmol), NaOH (389 mg, 9.73 mmol) and 30% aqueous H_2O_2 (692 mg, 6.1 mmol). The resulting oily product was separated by column chromatography (silica gel, EtOAc–hexane, 1:5) to give the alcohol (*R*)-**4** as a pale yellow oil [1.0 g, 69%; 92% yield based on the recovery of (*R*)-**17**] and the starting material (*R*)-**17** (364 mg) was recovered. An analytical sample of (*R*)-**4** was obtained by PTLC on silica gel (EtOAc–hexane, 1:5) (R_F 0.28); $[\alpha]_D^{25}$ +8.8 (*c* 0.3, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-ol (*S*)-4

The reaction conditions for preparation of (*R*)-**4** were followed using (*S*)-**17** (289 mg, 0.69 mmol), a 0.5 M solution of 9-BBN in THF (1.5 ml, 0.75 mmol), NaOH (110 mg, 2.75 mmol) and 30% aqueous H_2O_2 (204 mg, 1.8 mmol). Column chromatographic separation (silica gel, EtOAc–hexane, 1:5) of the crude product afforded (*S*)-**4** (R_F 0.28) as a colourless oil (78.9 mg, 26%); $[\alpha]_D^{25}$ −4.8 (*c* 1.47, $CHCl_3$).

(7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-al 3

To a solution of $(COCl)_2$ (0.38 ml, 4.36 mmol) in CH_2Cl_2 (50 ml), was added a solution of DMSO (0.63 ml, 8.88 mmol) in CH_2Cl_2 (10 ml) at −60 °C. After 15 min, **4** (1.92 g, 4.40 mmol) was added to the mixture at −60 °C. The mixture was then stirred for 30 min after which a sample of Et_3N (3.1 ml, 22.2 mmol) was added to it and stirring continued at −60 to −10 °C for 5 h. After this the mixture was quenched with sat. aqueous NH_4Cl and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to give the crude product. Purification of this by column chromatography (silica gel, EtOAc–hexane, 1:5) afforded **3** (1.52 g, 80%), R_F 0.65, as a pale yellow oil together with recovered **4** (228 mg, 12%). For **3** (Found: C, 74.36; H, 11.80. $C_{27}H_{50}O_2Si$ requires C, 74.59; H, 11.59%); ν_{max}(neat)/cm^{-1} 2900, 1720, 1440, 1380, 1250, 1080, 830 and 770; δ_H(270 MHz, $CDCl_3$) 0.04 (s, 6 H, CH_3-Si), 0.89 [s, 9 H, $(CH_3)_3$C-Si], 1.23–1.44 (m, 3 H, 4-H, 5-H), 1.45–1.55 (m, 2 H, 3-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.94–2.12 (m, 10 H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.45 (td, *J* 7.7, 1.7, 2 H, 2-H), 3.47 (dd, *J* 10.0, 5.6, 1 H, CH_2OSi), 3.55 (dd, *J* 10.0, 4.6, 1 H, CH_2OSi), 5.05–5.14 (m, 3 H, 7-H, 11-H, 15-H) and 9.76 (t, *J* 1.7, 1 H, 1-H); δ_C(68 MHz, $CDCl_3$) −5.5 (×2), 16.0, 17.7, 18.2, 23.6, 25.3 (×2), 25.7, 25.9 (×3), 26.6, 26.7, 31.0, 39.5, 39.7 (×2), 41.5, 64.9, 124.2, 124.3, 124.4, 131.2, 134.9, 135.1 and 202.9; *m*/*z* (EI) 434.3542 (M^+, 16%. $C_{27}H_{50}O_2Si$ requires 434.3580) and 69 (100).

(4*R*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-al (*R*)-3

By a method similar to that used in the preparation of **3**, (*R*)-**3** was obtained from (*R*)-**4** (1.92 g, 4.40 mmol), $(COCl)_2$ (0.38 ml, 4.36 mmol), DMSO (0.63 ml, 8.9 mmol) and Et_3N (3.1 ml, 22.2 mmol). The crude product was separated by column chromatography (silica gel, EtOAc–hexane, 1:5) to afford the aldehyde (*R*)-**3** as a pale yellow oil [1.52 g, 80%, 91% yield based on the recovery of (*R*)-**4**] together with recovered (*R*)-**4** (228 mg, 12%). An analytical sample of (*R*)-**3** was obtained by PTLC on silica gel (EtOAc–hexane, 1:5) R_F 0.65; $[\alpha]_D^{25}$ +7.7 (*c* 3.7, $CHCl_3$).

(4*S*,7*E*,11*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-al (*S*)-3

The reaction conditions for preparation of (*R*)-**3** were followed using (*S*)-**17** (116 mg, 0.27 mmol), DMSO (0.1 ml, 1.4 mmol), $(COCl)_2$ (0.05 ml, 0.6 mmol) and Et_3N (0.20 ml, 1.4 mmol). PTLC (silica gel, EtOAc–hexane, 1:5) of the crude product afforded (*S*)-**3**, R_F 0.65, as a colourless oil (50.8 mg, 44%); $[\alpha]_D^{25}$ −4.7 (*c* 2.98, $CHCl_3$).

Ethyl (2*E*,9*E*,13*E*)- and (2*Z*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-10,14,18-trimethylnonadeca-2,9,13,17-tetraenoate (*E*)- and (*Z*)-18

To a suspension of NaH (60% oil suspension; 0.32 mmol, 12.9 mg, washed with hexane) in THF (1 ml), was added at 0 °C propane-2-thiol (0.05 ml, 0.54 mmol) and $(EtO)_2P(O)$-$C(=CH_2)CO_2Et$ (93.3 mg, 0.32 mmol) in THF (1 ml). After the mixture had been stirred for 10 min at 0 °C, **3** (135 mg, 0.31 mmol) in THF (1 ml) was added to it and stirring continued for 3 h at the same temperature. After this the reaction mixture was diluted with aqueous NH_4Cl and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified with PTLC on silica gel

(EtOAc–hexane, 1:5, twice development) to give (*E*)-**18** (43.7 mg, 26%) and (*Z*)-**18** (60.9 mg, 33%) as a colourless oil. For (*E*)-**18** R_F 0.66; δ_H(270 MHz, $CDCl_3$) 0.03 (s, 6 H, CH_3-Si), 0.89 [s, 9 H, $(CH_3)_3$C-Si], 1.25 [d, *J* 6.8, 6 H, CH(CH_3)$_2$], 1.31 (t, *J* 7.2, 3 H, OCH_2CH_3), 1.18–1.37 (m, 4 H, 5-H, 7-H), 1.54–1.64 (m, 1 H, 6-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.95–2.15 (m, 10 H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.47 (dt, *J* 7.8, 7.3, 2 H, 4-H), 2.85 [septet, *J* 6.6, 1 H, C*H*(CH_3)$_2$], 3.39 (s, 2 H, CH_2-S), 3.47–3.53 (m, 2 H, CH_2OSi), 4.24 (q, *J* 7.2, 2 H, OCH_2CH_3), 5.05–5.21 (m, 3 H, 9-H, 13-H, 17-H) and 5.97 (t, *J* 7.3, 1 H, 3-H); δ_C(68 MHz, $CDCl_3$) −5.4 (×2), 14.3, 16.0, 17.7, 18.3, 23.2, 25.3 (×2), 25.7, 25.9 (×3), 26.6 (×2), 26.7, 26.8, 26.9, 30.7, 30.9, 34.2, 34.5, 39.7, 39.9, 60.4, 65.0, 124.2 (×2), 124.4, 124.6, 129.0, 131.2, 134.9, 143.3 and 166.9 [Found (HRMS): M^+, 592.4371. $C_{35}H_{64}O_3SiS$ requires *M*, 592.4345]. (*Z*)-**18**, R_F 0.74; ν_{max}(neat)/cm^{-1} 2900, 2850, 1700, 1435, 1360, 1240, 1080, 830 and 770; δ_H(270 MHz, $CDCl_3$) 0.04 (s, 6 H, $SiCH_3$), 0.89 [s, 9 H, SiC(CH_3)$_3$], 1.28 [d, *J* 6.8, 6 H, SCH(CH_3)$_2$], 1.30 (t, *J* 7.0, 3 H, OCH_2CH_3), 1.35–1.56 (m, 5 H, 5-H, 6-H, 7-H), 1.61 (s, 9 H, vinyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.93–2.12 (m, 10 H, 8-H, 11-H, 12-H, 16-H, 17-H), 2.26 (dt, *J* 7.3, 7.8, 2 H, 4-H), 2.95 [septet, *J* 6.8, 1 H, C*H*(CH_3)$_2$], 3.47 (s, 2 H, CH_2-S), 3.47–3.52 (m, 2 H, CH_2OSi), 4.21 (q, *J* 7.0, 2 H, OCH_2CH_3), 5.05–5.15 (m, 3 H, 9-H, 13-H, 17-H) and 6.81 (t, *J* 7.3, 1 H, 3-H); δ_C(68 MHz, $CDCl_3$) −5.4 (×2), 14.2, 16.0, 17.7, 18.3, 23.4, 25.3 (×2), 25.7, 25.9 (×3), 26.2, 26.4, 26.5, 26.7, 26.8, 30.3, 31.0, 34.8, 35.5, 39.7, 39.9, 60.7, 65.0, 124.3, 124.4, 124.5, 124.7, 131.2, 134.9, 135.0, 144.8 and 165.0 [Found (HRMS): M^+, 592.4378. $C_{35}H_{64}O_3SiS$ requires *M*, 592.4345].

Ethyl (2*Z*,6*R*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-10,14,18-trimethylnonadeca-2,9,13,17-tetraenoate (2*Z*,6*R*)-18

To a suspension of NaH (60% oil suspension; 3.74 mmol, 150 mg, washed with hexane) in THF (3 ml), were added propane-2-thiol (0.38 ml, 4.1 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Et$ (885 mg, 3.69 mmol) in THF (1 ml) at 0 °C. After the mixture had been stirred for 10 min at 0 °C, (*R*)-**3** (1.55 g, 3.57 mmol) in THF (3 ml) was added to it and stirring continued for 17 h at 25 °C. The reaction mixture was then poured into aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was separated by PTLC on silica gel (EtOAc–hexane, 1:10, developed twice) to give (2*Z*,6*R*)-**18** (silica gel, EtOAc–hexane, 1:5), R_F 0.74, as a colourless oil (1.17 g, 54%); $[a]_D^{25}$ +3.2 (*c* 0.18, $CHCl_3$).

Ethyl (2*E*,6*R*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-10,14,18-trimethylnonadeca-2,9,13,17-tetraenoate (2*E*,6*R*)-18

To a suspension of NaH (60% oil suspension; 1.98 mmol, 79.2 mg, washed with hexane) in THF (2 ml) at 0 °C, were added propane-2-thiol (0.2 ml, 1.95 mmol) and a solution of $(EtO)_2P(O)C(=CH_2)CO_2Et$ (480 mg, 2.00 mmol) in THF (1 ml). The mixture was stirred at 0 °C for 10 min, after which a solution of (*R*)-**3** (800 mg, 1.84 mmol) in THF (2 ml) was added to it and stirring continued at 0 °C for 3 h. The mixture was then diluted with aqueous NH_4Cl and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified with PTLC on silica gel (EtOAc–hexane, 1:10, developed twice) to give a mixture of (*Z*)- and (*E*)-**18** as a colourless oil (615 mg, 57%; *Z*/*E* 1:2.4): (2*E*,6*R*)-**18** R_F 0.66 (silica gel, EtOAc–hexane, 1:5).

Ethyl (2*Z*,6*S*,9*E*,13*E*)-6-(*tert*-butyldimethylsilyloxymethyl)-2-isopropylthiomethyl-10,14,18-trimethylnonadeca-2,9,13,17-tetraenoate (2*Z*,6*S*)-18

The reaction conditions for the preparation of (2*Z*,6*R*)-**18** were followed using (*S*)-**3** (50.8 mg, 0.12 mmol), NaH (60% oil suspension; 0.50 mmol, 19.9 mg, washed with hexane), propane-2-thiol (0.08 ml, 0.86 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Et$ (150 mg, 0.63 mmol). PTLC (silica gel, EtOAc–hexane, 1:10, developed twice) of the crude product afforded (2*Z*,6*S*)-**18**, R_F 0.74, as a colourless oil (17.4 mg, 25%); $[a]_D^{25}$ +1.6 (*c* 2.24, $CHCl_3$).

Ethyl (2*Z*)-6-hydroxymethyl-2-isopropylthiomethyl-10,14,18-trimethylnonadeca-2,9,13,17-tetraenoate 19

To a solution of (*Z*)-**18** (22.0 mg, 0.037 mmol) in THF (0.3 ml), was added a 1.0 M solution of TBAF in THF (0.1 ml, 0.1 mmol) and the reaction mixture was stirred at 25 °C for 2 days. Aqueous NH_4Cl was added to the reaction mixture after which the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by PTLC on silica gel (EtOAc–hexane, 1:5) to give **19** (R_F 0.22) as a colourless oil (15.5 mg, 87%); δ_H(270 MHz, $CDCl_3$) 1.25 [d, *J* 6.8, 6 H, SCH(CH_3)$_2$], 1.31 (t, *J* 7.1, 3 H, OCH_2CH_3), 1.24–1.56 (m, 5 H, 5-H, 6-H, 7-H), 1.61 (s, 6 H, vinyl-CH_3), 1.69 (s, 6 H, vinyl-CH_3), 1.93–2.12 (m, 10 H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.44–2.60 (m, 2 H, 4-H), 2.87 [septet, *J* 6.8, 1 H, SC*H*(CH_3)$_2$], 3.39 (s, 2 H, CH_2S), 3.50–3.70 (m, 2 H, CH_2OH), 4.24 (q, *J* 7.1, 2 H, OCH_2CH_3), 5.07–5.18 (m, 3 H, 9-H, 13-H, 17-H) and 6.03 (t, *J* 7.6, 1 H, 3-H); the hydroxy proton was not observed because of broadening of the signal [Found (HRMS): M^+, 478.3488. $C_{29}H_{50}O_3S$ requires *M*, 478.3497].

Ethyl (3′*E*,7′*E*)-α-methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetate 21

To a solution of **18** (69.2 mg, 0.117 mmol) in CH_2Cl_2 (1 ml), were added MeI (0.2 ml, 3.21 mmol) and $AgBF_4$ (35.7 mg, 0.183 mmol). The reaction mixture was stirred for 22 h and then filtered. After the filtrate had been evaporated, the residue was diluted with THF (0.5 ml) and treated with a 1.0 M solution of TBAF in THF (0.5 ml, 0.5 mmol); the reaction mixture was then stirred for 20 h. After this, the reaction mixture was treated with aqueous NH_4Cl and the aqueous layer was separated and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by PTLC on silica gel (EtOAc–hexane, 1:5) to give a mixture of *cis*- and *trans*-**21** (14.9 mg, 32%; *cis*/*trans*, 6:94) as a colourless oil. For *trans*-**21**, R_F 0.63; ν_{max}(neat)/cm^{-1} 2900, 2850, 1705, 1435, 1370, 1280, 1250, 1170, 1140, 1080 and 1020; δ_H(270 MHz, $CDCl_3$) 0.87–1.35 (m, 4 H, 1′-H, 3-ax-H, 4-ax-H), 1.30 (t, *J* 7.3, 3 H, OCH_2CH_3), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.64–1.74 (m, 1 H, 5-H), 1.89–2.10 (m, 12 H, 3-eq-H, 4-eq-H, 2′-H, 5′-H, 6′-H, 9′-H, 10′-H), 3.16 (t, *J* 11.2, 1 H, 6-ax-H), 4.03 (ddd, *J* 11.2, 3.9, 1.5, 1 H, 6-eq-H), 4.12 (d, *J* 9.8, 1 H, 2-H), 4.22 (q, *J* 7.3, 2 H, OCH_2CH_3), 5.06–5.15 (m, 3 H, 3′-H, 7′-H, 11′-H), 5.88 (t, *J* 1.5, 1 H, α-methylene) and 6.23 (br s, 1 H, α-methylene); δ_C(68 MHz, $CDCl_3$) 14.2, 16.0, 17.7, 24.9, 25.7, 26.6, 26.8 (×2), 30.5, 32.3, 32.5, 35.3, 39.7 (×2), 60.6, 74.0, 75.5, 123.9, 124.2 (×2), 124.4, 131.2, 135.0, 135.3, 142.3 and 166.1 [Found (HRMS): M^+, 402.3151. $C_{26}H_{42}O_3$ requires *M*, 402.3134]. For *cis*-**21**, R_F 0.63; δ_H(270 MHz, $CDCl_3$) 1.14–1.76 (m, 5 H, 1′-H, 3-ax, 4-ax-H, 5-H), 1.29 (t, *J* 7.3, 3 H, OCH_2CH_3), 1.59 (s, 9 H, vinyl-CH_3), 1.67 (s, 3 H, vinyl-CH_3), 1.96–2.15 (m, 12 H, 3-eq-H, 4-eq-H, 2′-H, 5′-H, 6′-H, 9′-H, 10′-H), 3.64–3.70 (m, 2 H), 3.85–3.95 (m, 1 H), 4.22 (q, *J* 7.3, 2 H, OCH_2CH_3), 5.03–5.14 (m, 3 H, 3′-H, 7′-H, 11′-H), 5.88 (s, 1 H, α-methylene) and 6.23 (s, 1 H, α-methylene) [Found (HRMS): M^+, 402.3156. $C_{26}H_{42}O_3$ requires *M*, 402.3134].

Ethyl (2*S*,5*R*,3′*E*, 7′*E*)-α-methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetate (2*S*,5*R*)-21

By a method similar to that used in the preparation of **21**, (2*S*,5*R*)-**21** was obtained from (2*Z*,6*R*)-**18** (100.5 mg, 0.169

mmol), $AgBF_4$ (40.6 mg, 0.209 mmol), MeI (0.20 ml, 3.2 mmol) and TBAF (1.0 M TBAF in THF; 0.5 ml). The crude products were separated by PTLC (silica gel, EtOAc–hexane, 1:5) to give *trans*-(2*S*,5*R*)-**21**, R_F 0.75, as a colourless oil (24.8 mg, 36%; *cis*/*trans* = 4:96); $[\alpha]_D^{25}$ −46 (*c* 0.0436, $CHCl_3$).

Ethyl (2*R*,5*S*,3′*E*,7′*E*)-α-methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetate (2*R*,5*S*)-21

The reaction conditions for the preparation of **21** were followed using (2*Z*,6*S*)-**18** (17.4 mg, 0.029 mmol), MeI (0.4 ml, 6.4 mmol), $AgBF_4$ (21.8 mg, 0.112 mmol) and a 1.0 M solution of TBAF in THF (0.4 ml). Column chromatographic separation (silica gel, EtOAc–hexane, 1:5) of the crude product afforded *trans*-(2*R*,5*S*)-**21**, R_F 0.75, as a colourless oil (3.92 mg, 33%; *cis*/*trans* 2:98); $[\alpha]_D^{25}$ +43.1 (*c* 0.116, $CHCl_3$).

(2*S*,5*R*,3′*E*,7′*E*)-α-Methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetic acid; *ent*-rhopaloic acid A (2*S*,5*R*)-*ent*-1

To a solution of *trans*-(2*S*,5*R*)-**21** (6.04 mg, 0.015 mmol) in water (1 ml), was added KOH (113 mg, 2.0 mmol). The reaction mixture was refluxed for 22 h after which it was cooled to 25 °C, acidified with 1 M aqueous HCl and diluted with Et_2O; the aqueous layer was then separated and extracted with Et_2O. The combined organic layer and extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (6%-wt. water silica gel, EtOAc–hexane, 1:5) to give *trans*-(2*S*,5*R*)-*ent*-**1**, R_F 0.13, as a colourless oil (3.15 mg, 56%); $[\alpha]_D^{25}$ −37.6 (*c* 0.315, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3500–3000, 2900, 2850, 1680, 1620, 1430, 1370, 1280, 1160, 1140, 1080, 950 and 830; δ_H(270 MHz, $CDCl_3$) 0.85–1.23 (m, 4 H, 1′-H, 3-ax-H, 4-ax-H), 1.23–1.47 (m, 1 H, 5-ax-H), 1.60 (s, 9 H, vinyl-CH_3), 1.68 (s, 3 H, vinyl-CH_3), 1.90–2.10 (m, 12 H, 3-eq-H, 4-eq-H, 2′-H, 5′-H, 6′-H, 9′-H, 10′-H), 3.18 (t, *J* 11.2, 1 H, 6-ax-H), 4.07 (ddd, *J* 11.2, 3.9, 2.0, 1 H, 6-eq-H), 4.12 (d, *J* 12.2, 1 H, 2-ax-H), 5.05–5.15 (m, 3 H, 3′-H, 7′-H, 11′-H), 5.89 (s, 1 H, α-methylene), 6.36 (s, 1 H, α-methylene); the carboxy proton was not observed because of broadening of the signal; δ_C(125 MHz, $CDCl_3$) 16.0 (×2), 17.7, 24.9, 25.7, 26.6, 26.8, 30.2, 31.8, 32.4, 35.2, 39.7 (×2), 74.0, 76.3, 124.0, 124.1, 124.4, 126.7, 131.3, 135.0, 135.5, 140.7 and 168.6 [Found (HRMS): M^+, 374.2830. $C_{24}H_{38}O_3$ requires *M*, 374.2821].

(2*S,5*R**,3′*E*,7′*E*)-α-Methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetic acid; *rac*-rhopaloic acid A (2*S**,5*R**)-*rac*-1**

The reaction conditions for the preparation of (2*S*,5*R*)-*ent*-**1** were followed using a mixture of *cis*- and *trans*-**21** (*cis*/*trans* 6:94; 25.4 mg, 63.2 μmol) and KOH (113 mg, 2.0 mmol). Column chromatographic separation (6%-wt water silica gel, EtOAc–hexane, 1:5) afforded *rac*-**1** (R_F 0.13) as a colourless oil (*cis*/*trans* 8:92; 7.98 mg, 34%).

(2*R*,5*S*,3′*E*,7′*E*)-α-Methylene-5-(4′,8′,12′-trimethyltrideca-3′,7′,11′-trienyl)tetrahydropyran-2-ylacetic acid; rhopaloic acid A (+)-1

The reaction conditions for preparation of (2*S*,5*R*)-*ent*-**1** were followed using a mixture of *cis*- and *trans*-(2*R*,5*S*)-**21** (*trans* pure sample, 5.2 mg, 12.9 μmol) and KOH (56 mg, 1.0 mmol). Column chromatographic separation (6%-wt water silica gel, EtOAc–hexane, 1:5) afforded (+)-**1** (R_F 0.13) as a colourless oil (1.2 mg, 25%); $[\alpha]_D^{25}$ +39.0 (*c* 0.013, $CHCl_3$).

Determination of optical purity of 16: general method

(7*E*,11*E*)-4-(Benzoylhydroxymethyl)-8,12,16-trimethylheptadeca-1,7,11,15-tetraene (*R*)-22. To a solution of (*R*)-**16** (58.0 mg, 0.191 mmol) in CH_2Cl_2 (0.5 ml) at 0 °C, were added Et_3N (0.1 ml, 0.718 mmol) and benzoyl chloride (0.05 ml, 0.431 mmol). The reaction mixture was stirred at 25 °C for 18 h after which it was quenched with aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. PTLC (silica gel, EtOAc–hexane, 1:5) of the crude product afforded (*R*)-**22**, R_F 0.62, as a colourless oil (68 mg, 87%); $[\alpha]_D^{25}$ +5.4 (*c* 0.45, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2900, 2850, 1720, 1440, 1375, 1310, 1260, 1100 and 700; δ_H(270 MHz, $CDCl_3$) 1.43–1.52 (m, 2 H, 5-H), 1.57 (s, 9 H, vinyl-CH_3), 1.65 (s, 3 H, vinyl-CH_3), 1.86–2.13 (m, 11 H, 4-H, 6-H, 9-H, 10-H, 13-H, 14-H), 2.20 (t, *J* 6.8, 2 H, 3-H), 4.23 (d, *J* 5.9, 2 H, CH_2-OBz), 5.02–5.15 (m, 5 H, 1-H, 7-H, 11-H, 15-H), 5.72–5.87 (m, 1 H, 2-H), 7.37–7.43 (m, 2 H, ArH), 7.52–7.57 (m, 1 H, ArH) and 8.02–8.08 (m, 2 H, ArH); δ_C(68 MHz, $CDCl_3$) 16.0 (×2), 17.7, 25.2, 25.7, 26.6, 26.7, 31.0, 35.8, 37.0, 39.7 (×2), 67.0, 116.7, 124.0, 124.1, 124.4, 128.3 (×2), 129.5 (×2), 130.5, 131.2, 132.8, 135.0, 135.5, 136.1 and 166.6 [Found (HRMS): M^+, 408.3028. $C_{28}H_{40}O_2$ requires *M*, 408.3028].

The optical purity of (*R*)-**22** was determined by HPLC analysis (DAICEL CHIRALCEL-OD column, hexane–EtOAc, 400:1). The enantiomeric excess was 98% ee.

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