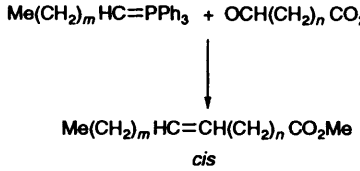
Synthesis of Very Long Chain Fatty Acid Methyl Esters

Marcel R. Kling,[a] Christopher J. Easton*[,a] and Alf Poulos[b]
[a] *Department of Organic Chemistry, University of Adelaide, GPO Box 498, Adelaide, South Australia 5001*
[b] *Department of Chemical Pathology, Adelaide Children's Hospital, North Adelaide, South Australia 5006*

Phosphoranes, produced by treating alkyltriphenylphosphonium bromides with lithium hexamethyldisilazide, reacted with ω-oxo esters to give modest yields of the corresponding methyl *cis*-alkenoates. By an alternative method, treatment of ω-iodo esters with the complexes formed from reactions of alkylcopper(I) and Grignard reagents gave methyl alkanoates, *cis*-alkenoates, and methylene-interrupted *cis,cis*-alka-dienoates and *cis,cis,cis*-trienoates. The stereochemical integrity of the esters was determined by ^{13}C NMR spectroscopy.

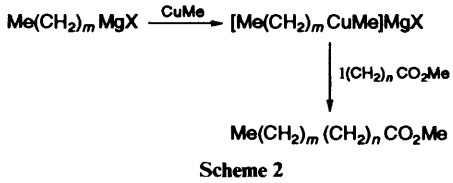
Fatty acids with chain lengths of > 22 carbons (very long chain fatty acids, VLCFA) have been found in a wide variety of species.[1,2] The degree of unsaturation of these compounds varies, depending on the source, but alkenoic VLCFA generally have the *cis*-stereochemistry and the more unsaturated analogues usually comprise methylene-interrupted all-*cis*-polyenes. Ready access to the VLCFA would greatly facilitate studies of their biochemical reactions but, since they generally occur only in trace amounts as components of complex mixtures, isolation of sufficient quantities from natural sources is impractical. Consequently, synthesis appears to be a more viable alternative method to obtain these compounds.

Many of the procedures that have been reported for the synthesis of the shorter chain fatty acids are potentially suitable for the synthesis of VLCFA. In this regard, the Wittig reaction of ω-oxo esters with phosphoranes, to produce *cis*-alkenoates (Scheme 1),[3,4] has been applied in the synthesis of methyl (*Z*)-



Scheme 1

hexacos-9-enoate.[4] Alternatively, fatty acid esters, including ethyl heptacosanoate, have been obtained from reactions between ω-iodo esters and complexes formed from methylcopper(I) and Grignard reagents (Scheme 2).[5] To the best of

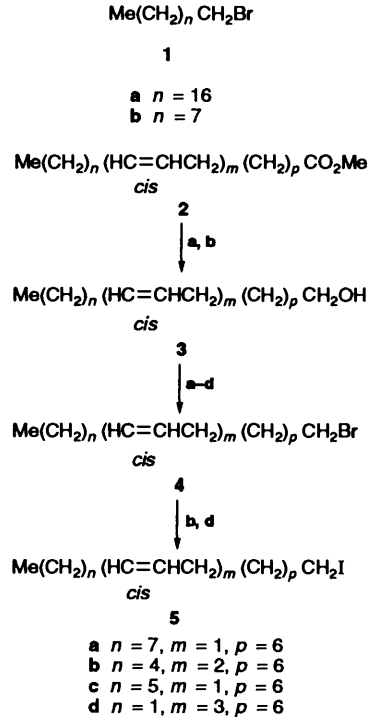


Scheme 2

our knowledge there has been no report of the synthesis of unsaturated VLCFA esters using this method. In order to obtain VLCFA and study their biochemical reactions, we have now examined and compared the general applicability of the two approaches to the synthesis of VLCFA methyl esters, including alkenoates and more highly unsaturated analogues.

Results and Discussion

The alkyl bromides **1a** and **1b**, the esters **2a** and **2b**, the alcohols **3c** and **3d**, and the acids **6a**, **6b** and **8d**, used in this study, were available commercially. The alkenyl bromides **4a–d** were

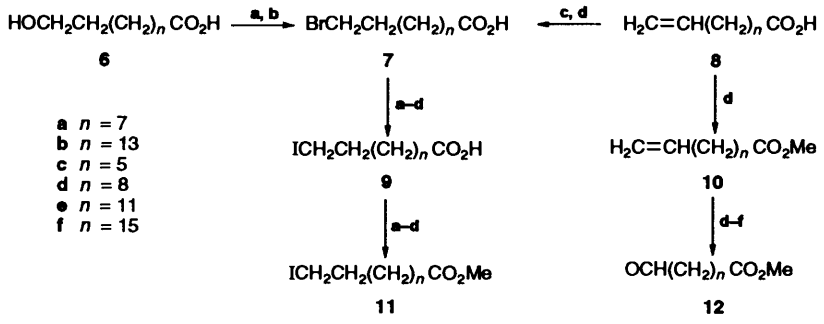


Scheme 3

prepared as shown in Scheme 3, by treatment of the corresponding alcohols **3a–d** with triphenylphosphine/carbon tetrabromide.[6] The alcohols **3a** and **3b** were prepared by reduction of the corresponding esters **2a** and **2b** with lithium aluminium hydride. Treatment of the bromides **4b** and **4d** with sodium iodide in acetone gave the corresponding iodides **5b** and **5d** (Scheme 3).

The ω-iodo esters **11a–d** were obtained as shown in Scheme 4. Treatment of the hydroxy acids **6a** and **6b** with hydrogen bromide in acetic acid gave the corresponding bromides **7a** and **7b**. The unsaturated acids **8c** and **8d** reacted with hydrogen bromide in light petroleum, in the presence of azoisobutyronitrile, to give the bromides **7c** and **7d**, respectively. The acid **8c** was obtained by oxidation of oct-7-en-1-ol.[7] The bromides **7a–d** reacted with sodium iodide in acetone to give the corresponding iodides **9a–d**, which were converted into the respective ω-iodo esters **11a–d** through reaction with methanol that had been pretreated with thionyl chloride.

The ω-oxo esters **12d–f** were obtained by treatment of the corresponding unsaturated esters **10d–f** with ozone,[8] followed by dimethyl sulfide (Scheme 4). The unsaturated ester **10d** was



Scheme 4

prepared by treatment of the acid **8d** with methanol that had been pretreated with thionyl chloride, whereas the unsaturated esters **10e** and **10f** were obtained through cuprate-mediated coupling reactions of the iodo esters **11a** and **11d** with but-3-enyl bromide and hept-6-enyl bromide, respectively.[5] Thus, the Grignard reagents obtained by treatment of but-3-enyl bromide and hept-6-enyl bromide with magnesium, were added to preformed methylcopper(I), to form the corresponding mixed dialkylcuprates, which reacted with the iodo esters **11a** and **11d**, respectively, to give the corresponding coupled products **10e** and **10f**. The yields of the esters **10e** and **10f** depended on the scale of the reactions. Good yields were obtained when reactions were performed on a 10 mmol scale or greater, otherwise the major reaction products were methyl undecanoate and methyl dodecanoate, formed by methyl group transfer to the respective iodo esters **11a** and **11d**. In any event, the ester **10e** was contaminated with a substantial amount of methyl undecanoate. Owing to the closely similar chromatographic behaviour of the unsaturated ester **10e** and methyl undecanoate, they were not separated and the mixture was used without further purification.

The iodo ester **11f** was prepared from the alkene **10f**, by treatment with hydrogen bromide in light petroleum, in the presence of azoisobutyronitrile, to give the bromide **13**, followed by treatment with sodium iodide in acetone.

$BrCH_2CH_2(CH_2)_{15}CO_2Me$

13

$CH_3(CH_2)_n(HC{=}CHCH_2)_m(CH_2)_p CO_2Me$
cis

14

a $n = 16, m = 1, p = 7$
b $n = 7, m = 1, p = 14$
c $n = 7, m = 1, p = 10$
d $n = 17, m = 0, p = 10$
e $n = 7, m = 1, p = 22$
f $n = 5, m = 1, p = 24$
g $n = 4, m = 2, p = 22$
h $n = 4, m = 2, p = 14$
i $n = 1, m = 3, p = 22$

Our examination of the use of the Wittig method in the synthesis of fatty acid methyl esters involved reactions of the phosphoranes, generated from the alkyl bromides **1a** and **1b**, with the ω-oxo esters **12d–f**. The bromides **1a** and **1b** were treated with triphenylphosphine in acetonitrile to produce the corresponding phosphonium salts. The salt derived from the bromide **1a** was obtained as colourless crystals that were stable in air and easily handled. By contrast, the salt of the bromide **1b** was a moisture- and air-sensitive glass. These salts were treated with lithium hexamethyldisilazide to generate the corresponding phosphoranes. The phosphorane derived from the bromide **1a** reacted with the oxo ester **12d** to give the VLCFA ester **14a** (67%) while treatment of the phosphorane derived from the bromide **1b** with the oxo esters **12f** and **12e** gave the esters **14b** (13%) and **14c** (12%) respectively.

The isomeric purity of the esters **14a–c** was determined using ^{13}C NMR spectroscopy (Table 2). It has been reported[9] that allylic carbons of straight chain *cis*-alkenes give rise to NMR signals in the range δ 27.22–27.39, while those of the corresponding *trans*-alkenes appear in the range δ 32.64–32.69. Consistent with that report, the ^{13}C NMR spectrum of methyl (*Z*)-heptadec-10-enoate was found to have signals at δ 27.1(4) and 27.1(7) due to the allylic carbon resonances, whereas the spectrum of methyl (*E*)-heptadec-10-enoate contained a single signal at δ 32.6 attributable to both allylic carbons. The spectrum of the ester **14a** showed peaks at δ 27.1(7) and 27.1(9), due to carbons C-9 and C-12, confirming the *cis*-stereochemistry, and no peaks were observed near δ 32.6 to indicate the presence of any of the corresponding *trans*-isomer. Similarly, in the case of the ester **14b**, a peak at δ 27.1(7) in the ^{13}C NMR spectrum, due to the allylic carbons C-16 and C-19, verified the *cis*-stereochemistry, and no peak was observed near δ 32.6. The spectrum of the ester **14c** contained all the resonances expected for the *cis*-isomer, including a signal at δ 27.2(4), attributable to carbons C-12 and C-15. In addition, there was a signal of relatively low intensity at δ 32.6(2), indicating that the ester **14c** was contaminated with *ca.* 5% of the corresponding *trans*-isomer. The signal arising from carbons C-13 and C-14 of the *cis*-ester **14c** appeared at δ 129.8(9), while the corresponding signal of the *trans*-isomer was characteristically downfield[9] at δ 130.3(5).

The modest yields of the esters **14b** and **14c**, and the lack of stereocontrol in the synthesis of the latter, illustrate limitations of the Wittig method in the synthesis of monoenoic acid esters. The method was found to be even less suitable for the synthesis of more highly unsaturated VLCFA esters, where complex isomeric mixtures always formed.

By contrast, copper-mediated reactions of ω-iodo esters with Grignard derivatives of alkyl and alkenyl bromides proved to be more generally applicable to the synthesis of a range of fatty acid methyl esters, of varying carbon chain length, degree of unsaturation, and series. Accordingly, the mixed dialkylcuprate obtained by treatment of the Grignard derivative of the bromide **1a** with methylcopper(I), reacted with the iodo ester **11d** to give the saturated ester, methyl nonacosanoate **14d** (23%). Similar reactions of the bromides **4a** and **4c** with the iodo esters **11b** and **11f**, respectively, gave the corresponding methyl alkenoates **14e** (13%) and **14f** (10%). The stereochemical integrity of the esters **14e** and **14f** was determined using ^{13}C NMR spectroscopy (Table 2). The spectrum of the ester **14e** showed a signal at δ 27.1(9), due to the allylic carbons C-24 and C-27, while that of the ester **14f** contained a resonance at δ 27.2(1), due to the allylic carbons C-26 and C-29. Neither spectrum showed a signal near δ 32.6, to indicate the presence of the corresponding *trans*-isomer. The mono-unsaturated esters **14b** and **14c** were also obtained using this method, in yields of 14 and 18%, respectively, and with complete stereochemical control within the limits of detection using ^{13}C NMR

Table 1 ^{1}H NMR spectral data of the esters **14**

Ester	Me/*J*	$(CH_2)_n$	C(3)H_2	Allylic	CH_2CO/*J*	Doubly allylic/*J*	OMe	Vinylic/*J*
a	0.88, t, 6.5	1.25, m	1.61, m	2.01, m	2.30, t, 7.5	—	3.67, s	5.34, t, 5.3
b	0.88, t, 6.5	1.25, m	1.62, m	2.01, m	2.30, t, 7.4	—	3.66, s	5.34, t, 4.7
c	0.88, t, 6.5	1.27, m	1.62, m	2.01, m	2.30, t, 7.5	—	3.66, s.	5.35, t, 4.6
d	0.88, t, 6.4	1.25, m	1.60, m	—	2.30, t, 7.5	—	3.67, s	—
e	0.88, t, 6.5	1.25, m	1.60, m	2.01, m	2.30, t, 7.5	—	3.67, s	5.35, t, 4.6
f	0.88, t, 6.2	1.25, m	1.60, m	2.01, m	2.30, t, 7.5	—	3.67, s	5.25, t, 4.6
g	0.89, t, 6.5	1.25, m	1.62, m	2.05, m	2.30, t, 7.5	2.77, t, 5.9	3.66, s	5.35, m
h	0.89, t, 6.6	1.25, m	1.62, m	2.05, m	2.30, t, 7.5	2.78, t, 5.9	3.67, s	5.36, m
i	0.98, t, 7.5	1.25, m	1.62, m	2.06, m	2.30, t, 7.5	2.81, t, 5.6	3.67, s	5.37, m

Table 2 ^{13}C NMR spectral data of the esters **14**

Ester	ω1	ω2	C-3	Doubly allylic	Allylic	$(CH_2)_n$	ω3	C-2	OMe	Vinylic	C-1
a	14.1	22.7	24.9	—	27.1(7), 27.1(9)	29.1–29.8	31.9	34.1	51.4	129.8, 129.9	174.3
b	14.1	22.7	24.9	—	27.1(7)	29.1–29.8	31.9	34.1	51.4	129.8	174.3
c	14.1	22.7	25.0	—	27.2(4)	29.1–29.8	32.0	34.1	51.4	129.9	174.4
e	14.2	22.7	24.9	—	27.1(9)	29.1–29.8	31.9	34.1	51.5	129.9	174.4
f	14.1	22.7	25.0	—	27.2(1)	29.0–29.7	31.8	34.1	51.4	129.9	174.3
g	14.0	22.6	25.0	25.6(1)	27.2(2)	29.1–29.7	31.5	34.1	51.4	127.9, 130.1	174.3
h	14.1	22.6	24.9	25.6(0)	27.1(8), 27.2(2)	29.1–29.7	31.5	34.1	51.5	127.9, 130.2	174.4
i	14.3	—[a]	25.0	25.5(2), 25.6(0)	20.5(5), 27.2(5)	29.2–29.7	—[a]	34.1	51.4	127.6, 128.2, 130.4	174.3

[a] Carbons ω2 and ω3 are allylic and vinylic, respectively, in the ester **14i**.

spectroscopy, through reactions of the bromide **4a** with the iodo ester **11c** and methyl 4-iodobutyrate.

The procedure was extended to the synthesis of alkadienoates and trienoates. Reaction of the bromide **4b** with the iodo ester **11b** gave the ester **14g** (22%), while analogous reactions of the bromides **4b** and **4d** with the iodo-esters **11c** and **11b**, respectively, gave the corresponding coupled products **14h** and **14i**.

As described above for the synthesis of the esters **10e** and **10f**, the copper-mediated reactions to give the esters **14b–i** were accompanied by methyl group transfer to the iodo esters **11b**, **11c**, **11f** and methyl 4-iodobutyrate. As particular examples, methyl nonanoate and methyl heptadecanoate were isolated in yields of 58 and 43%, respectively, from the reactions to form the esters **14b** and **14e**. Although the experience with the reactions to give the esters **10e** and **10f** indicated that this type of side reaction would be less significant with reactions carried out on a larger scale, the scale of synthesis of the esters **14b–i** is restricted by the cost of, and limited access to, the starting materials.

Fortunately, the esters **14b–g** were easily separable by chromatography from the products of methyl group transfer reactions, but the esters **14h** and **14i** were contaminated with methyl nonanoate and methyl heptadecanoate, respectively, which could not be separated in this way. Instead, (*Z,Z*)-octadeca-9,12-dienyl- and (*Z,Z,Z*)-octadeca-9,12,15-trienylcopper(I) were used in place of methylcopper(I), to prevent methyl group transfer reactions, in order to obtain uncontaminated samples of the esters **14h** and **14i**, respectively. Thus, the iodide **5b** was treated with *tert*-butyllithium and cuprous iodide to give (*Z,Z*)-octadeca-9,12-dienylcopper(I), which reacted with the Grignard reagent derived from the bromide **4b** to give the corresponding dialkylcopper(I) complex. Reaction of this complex with the iodo ester **11c** gave the pure ester **14h** (12%). A similar procedure using the iodide **5d**, the bromide **4d**, and the iodo ester **11b**, gave the trienoate **14i** (10%).

^{13}C NMR spectroscopy was used to confirm the stereochemistry of the esters **14g–i** (Table 2). The spectrum of the dienoate **14g** showed signals at δ 27.2(2) and 25.6(1), characteristic of the allylic carbons and the doubly allylic carbon, respectively, in a methylene-interrupted *cis*, *cis*-diene.[9] In a similar fashion, the spectrum of the ester **14h** contained signals at δ 27.1(8) and 27.2(2), attributable to the allylic carbons C-16 and C-22, and at δ 25.6(0) for the doubly allylic carbon C-19, while the spectrum of the trienoate **14i** included resonances at δ 25.5(2) and 25.6(0) for the doubly allylic carbons C-27 and C-30, and at δ 20.5(5) and 27.2(5) for carbons C-33 and C-24, respectively. The chemical shift of C-33 is affected by the proximity of that carbon to the end of the carbon chain and is consistent with values reported for fatty acids of the $n-3$ series, to which the ester **14i** belongs.

Based on the above results, copper-mediated coupling reactions of ω-iodo esters with Grignard reagents, derived from alkyl and alkenyl bromides, are more generally suitable than the reactions of ω-oxo esters with phosphoranes, for the synthesis of VLCFA esters. Nevertheless, compounds of this type are accessible using either approach, and from a range of starting materials, as used in this study.

Experimental

General.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. B.p.s are quoted as the block temperature required for distillation. IR spectra were recorded as liquid films or as solutions in chloroform, on a Hitachi 270-30 spectrometer. ^{1}H NMR spectra were recorded in chloroform, unless otherwise stated, using Me_4Si as internal standard, on either a Varian T-60, a Bruker CXP-300, or a Bruker ACP-300 spectrometer. ^{13}C NMR spectra were recorded in chloroform using Me_4Si as internal standard, on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. NMR spectral data of the esters (**14a–i**) are listed in Tables 1 (^{1}H) and 2 (^{13}C). *J*-Values are given in Hz. Electron impact (EI) mass spectra were recorded on an AEI MS-30 double focussing spectrometer, operating at 70 eV. Elemental analyses were performed by Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada, or by Chemical and Microanalytical Services Pty. Ltd., North Essendon, Victoria, Australia.

All solvents were purified and dried using standard methods. Light petroleum refers to the fraction with b.p. 66–68 °C. Ether

refers to diethyl ether. Flash-column chromatography[10] was performed on Merck Kieselgel 60 (230–400 mesh ASTM).

1-Bromooctadecane **1a**, 1-bromononane **1b**, methyl (*Z,Z*)-octadeca-9,12-dienoate **2b**, 10-hydroxydecanoic acid **6a**, 16-hydroxyhexadecanoic acid **6b**, undec-10-enoic acid **8d**, and but-3-enyl bromide were purchased from Aldrich Chemical Co. Methyl (*Z*)-octadec-9-enoate **2a** was purchased from Koch-Light Laboratories. (*Z*)-Hexadec-9-en-1-ol **3c** and (*Z,Z,Z*)-octadeca-9,12,15-trien-1-ol **3d** were obtained from Nu-Chek-Prep, Inc., Elysian, Minnesota, USA.

(*Z*)-*Octadec-9-en-1-ol* **3a**.—A solution of the ester **2a** (3.0 g, 10.1 mmol) in ether (20 cm^3) was added slowly to a stirred suspension of lithium aluminium hydride (0.77 g, 20.3 mmol) in ether (20 cm^3). After the vigorous reaction had subsided, the mixture was heated at reflux for 3 h and then cooled and poured into saturated aqueous ammonium chloride (100 cm^3) and water (20 cm^3). The layers that formed were separated and the aqueous layer was extracted with ether (3 × 20 cm^3). The organic layer and the ether extracts were combined and the mixture was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil distilled to give the title alcohol **3a** as a colourless oil (2.1 g, 78%), b.p. 200 °C/0.03 mmHg (block) (lit.,[11] b.p. 177–183 °C/3 mmHg); $\delta_H(CCl_4)$ 0.89 (m, 3 H, CH_3), 1.33 (m, 24 H, CH_2), 1.52 (br s, 1 H, OH), 2.00 (m, 4 H, allylic), 3.53 (t, *J* 6.0, 2 H, CH_2OH) and 5.29 (t, *J* 4.5, 2 H, vinylic).

(*Z,Z*)-*Octadeca-9,12-dien-1-ol* **3b**. This compound, prepared from the ester **2b** as described for the synthesis of the alcohol **3a**, was obtained as a colourless oil (1.47 g, 81%), b.p. 230 °C/0.03 mmHg (block) (lit.,[12] b.p. 148–150 °C/1 mmHg); δ_H 0.86 (m, 3 H, CH_3), 1.47 (m, 18 H, CH_2), 2.08 (br s, 1 H, OH), 2.30 (m, 4 H, allylic), 2.75 (m, 2 H, doubly-allylic), 3.62 (t, *J* 6.0, 2 H, CH_2OH) and 5.35 (m, 4 H, vinylic).

(*Z*)-*Octadec-9-enyl Bromide* **4a**.—Carbon tetrabromide (1.45 g, 4.37 mmol) was added in small portions to a solution of the alcohol **3a** (1.17 g, 4.37 mmol) and triphenylphosphine (1.16 g, 4.42 mmol) in dichloromethane (8 cm^3), cooled in ice.[6] The mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residual solid was extracted with light petroleum and the extracts were concentrated under reduced pressure. Chromatography of the residual oil, with light petroleum as eluent, gave the title bromide **4a** as a colourless oil (1.32 g, 91%); $\delta_H(CCl_4)$ 0.88 (m, 3 H, CH_3), 1.65 (m, 28 H, CH_2), 3.31 (t, *J* 6.5, 2 H, CH_2Br) and 5.24 (t, *J* 4.5, 2 H, vinylic). The spectral properties of the bromide **4a** are consistent with those reported previously.[13]

(*Z,Z*)-*Octadeca-9,12-dienyl bromide* **4b**. This compound, prepared from the alcohol **3b** as described for the synthesis of the bromide **4a**, was obtained as a colourless oil (1.60 g, 95%); $\delta_H(CCl_4)$ 0.90 (m, 3 H, CH_3), 1.67 (m, 22 H, CH_2), 2.72 (m, 2 H, doubly allylic), 3.34 (t, *J* 6.5, 2 H, CH_2Br) and 5.29 (m, 4 H, vinylic); ν_{max}/cm^{-1} 3008, 2924, 2852, 1466, 724 and 660; *m/z* (EI) 330 (M^+), 328 (M^+), 137, 123, 109 and 95.

(*Z*)-*Hexadec-9-enyl bromide* **4c**. This compound, prepared from the alcohol **3c** as described for the synthesis of the bromide **4a**, was obtained as a colourless oil (1.27 g, 94%); $\delta_H(CCl_4)$ 0.89 (m, 3 H, CH_3), 1.65 (m, 24 H, CH_2), 3.32 (t, *J* 6.5, 2 H, CH_2Br) and 5.25 (t, *J* 4.5, 2 H, vinylic); ν_{max}/cm^{-1} 3000, 2924, 2848, 1650, 1466, 725 and 658; *m/z* (EI) 304 (M^+), 302 (M^+), 150, 148, 111, 97, 83, 69 and 55.

(*Z,Z,Z*)-*Octadeca-9,12,15-trienyl bromide* **4d**. This compound, prepared from the alcohol **3d** as described for the synthesis of the bromide **4a**, was obtained as a colourless oil (1.31 g, 92%); $\delta_H(CDCl_3)$ 0.97 (t, *J* 7.5, 3 H, CH_3), 1.68 (m, 16 H, CH_2), 2.73 (m, 4 H, doubly allylic), 3.30 (t, *J* 6.5, 2 H, CH_2Br) and 5.26 (m, 6 H, vinylic); ν_{max}/cm^{-1} 3008, 2924, 2852, 1650, 1464, 720 and 658; *m/z* (EI) 328 (M^+), 326 (M^+), 272, 270, 135, 121, 108, 95, 93, 79 and 67.

(*Z,Z*)-*Octadeca-9,12-dienyl Iodide* **5b**.—A solution of the bromide **4b** (0.50 g, 1.52 mmol) and sodium iodide (0.57 g, 3.80 mmol) in acetone (10 cm^3) was heated at reflux for 16 h and then cooled to room temperature and poured onto water (200 cm^3). The mixture was extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were washed with 10% aqueous sodium thiosulfate (30 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residual oil, with light petroleum as eluent, gave the title iodide **5b** (0.45 g, 78%); $\delta_H(CCl_4)$ 0.90 (m, 3 H, CH_3), 1.67 (m, 22 H, CH_2), 2.71 (m, 2 H, doubly allylic), 3.12 (t, *J* 6.5, 2 H, CH_2I) and 5.25 (m, 4 H, vinylic); ν_{max}/cm^{-1} 3004, 2924, 2848, 1650, 1464 and 722; *m/z* (EI) 376 (M^+), 196, 156, 110, 95, 81, 67, 55 and 41; *m/z* (EI) 376.162 (M^+) [Calc. for $C_{18}H_{33}I$ (M^+); *m/z* 376.163].

(*Z,Z,Z*)-*Octadeca-9,12,15-trienyl iodide* **5d**. This compound was prepared from the bromide **4d** as described above for the synthesis of the iodide **5b** (0.40 g, 70%); δ_H 0.98 (t, *J* 7.5, 3 H, CH_3), 1.75 (m, 16 H, CH_2), 2.75 (m, 4 H, doubly allylic), 3.12 (t, *J* 6.5, 2 H, CH_2I) and 5.29 (m, 6 H, vinylic); ν_{max}/cm^{-1} 3008, 2924, 2848, 1650, 1464 and 718; *m/z* (EI) 374 (M^+), 345, 317, 183, 155, 136, 121, 109, 107, 94, 91, 79 and 55; *m/z* (EI) 374.146 (M^+) [Calc. for $C_{18}H_{31}I$ (M^+) *m/z* 374.147].

10-*Bromodecanoic Acid* **7a**.—A suspension of the hydroxy acid **6a** (5.03 g, 26.8 mmol) in a solution of 33% hydrogen bromide in acetic acid (70 cm^3) was stirred at room temperature for 16 h and then heated at 100 °C for 4 h. It was then cooled and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (40 cm^3) and the resultant solution was washed with water (2 × 20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure, to give a solid which recrystallized from light petroleum to give the title bromo acid **7a** as a colourless solid (5.06 g, 75%), m.p. 36.5 °C (lit.,[14] m.p. 37–38 °C); $\delta_H(CCl_4)$ 1.85 (m, 16 H, CH_2), 3.34 (*t*, *J* 6.5, 2 H, CH_2Br) and 11.77 (br s, 1 H, CO_2H).

16-*Bromohexadecanoic acid* **7b**. This compound, prepared from the hydroxy acid **6b** as described for the synthesis of the bromo acid **7a**, was obtained as a colourless solid (2.69 g, 87%), m.p. 68–69 °C (lit.,[15] m.p. 70–70.5 °C); δ_H 1.60 (m, 26 H, CH_2), 2.37 (m, 2 H, CH_2CO), 3.43 (t, *J* 6.5, 2 H, CH_2Br) and 10.50 (br s, 1 H, CO_2H).

8-*Bromooctanoic Acid* **7c**.—Hydrogen bromide gas was passed through a solution of oct-7-enoic acid **8c** (2.46 g, 17.3 mmol) and azoisobutyronitrile (*ca.* 20 mg) in light petroleum (25 cm^3), for 15 min whilst the mixture was illuminated with a 300 W UV lamp. The mixture was irradiated for a further 15 min and then cooled to −10 °C. The resulting precipitate was filtered off and recrystallized from light petroleum to give the title bromide **7c** as colourless crystals (2.66 g, 69%), m.p. 33–36 °C (lit.,[14] m.p. 36–37 °C); δ_H 1.85 (m, 12 H, CH_2), 3.41 (t, *J* 6.5, 2 H, CH_2Br) and 10.42 (br s, 1 H, CO_2H).

11-*Bromoundecanoic acid* **7d**. This compound, prepared from undec-10-enoic acid **8d** as described for the synthesis of the bromo acid **7c**, was obtained as colourless crystals (19.25 g, 67%), m.p. 44–47 °C (lit.,[16] m.p. 49–50 °C); δ_H 1.65 (m, 16 H, CH_2), 2.37 (m, 2 H, CH_2CO), 3.44 (t, *J* 6.5, 2 H, CH_2Br) and 10.40 (br s, 1 H, CO_2H).

10-*Iododecanoic acid* **9a**. This compound, prepared from the bromo acid **7a** as described for the synthesis of the iodide **5b** and recrystallized from light petroleum, was obtained as colourless crystals (5.36 g, 90%), m.p. 49–50 °C (lit.,[14] m.p. 49–50 °C); $\delta_H(CCl_4)$ 1.60 (m, 14 H, CH_2), 2.30 (m, 2 H, CH_2CO), 3.13 (t, *J* 6.5, 2 H, CH_2I) and 11.71 (br s, 1 H, CO_2H).

16-*Iodohexadecanoic acid* **9b**. This compound, prepared from the bromo acid **7b** as described for the synthesis of the iodide **9a**, was obtained as colourless crystals (5.18 g, 90%), m.p. 71–73 °C (lit.,[17] m.p. 76 °C); δ_H 1.60 (m, 26 H, CH_2), 2.37 (m, 2 H,

CH_2CO), 3.21 (t, *J* 6.5, 2 H, CH_2I) and 11.30 (br s, 1 H, CO_2H).

8-*Iodooctanoic acid* **9c**. This compound, prepared from the bromo acid **7c** as described for the synthesis of the iodo acid **9a**, was obtained as colourless crystals (2.51 g, 83%), m.p. 42.5–44 °C; δ_H 1.85 (m, 12 H, CH_2), 3.18 (t, *J* 6.5, 2 H, CH_2I) and 9.05 (br s, 1 H, CO_2H); ν_{max}/cm^{-1} 3450–2400, 2932, 2856 and 1710; *m/z* (EI) 270 (M^+), 252, 143, 125, 97, 83 and 55.

11-*Iodoundecanoic acid* **9d**. This compound prepared from the bromo acid **7d** (10.0 g, 38 mmol) as described for the synthesis of the iodide **9a**, was obtained as colourless crystals (8.88 g, 75%), m.p. 64.5–65 °C (lit.,[14] m.p. 64–65 °C); δ_H 1.70 (m, 16 H, CH_2), 2.32 (m, 2 H, CH_2CO), 3.15 (t, *J* 6.5, 2 H, CH_2I) and 11.83 (br s, 1 H, CO_2H).

Methyl Undec-10-*enoate* **10d**.—Undec-10-enoic acid **8d** (3.02 g, 16.4 mmol) was added to methanol (200 cm^3) that had been pretreated with thionyl chloride (1.0 cm^3), and the mixture was stirred at room temperature for 4 h. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (50 cm^3). The resultant solution was washed with saturated aqueous sodium hydrogen carbonate (50 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil distilled to give the title ester **10d** as a colourless oil (2.60 g, 80%), b.p. 130 °C/0.05 mmHg (block) (lit.,[18] b.p. 248 °C); δ_H 1.80 (m, 16 H, CH_2), 3.70 (s, 3 H, OCH_3), 5.00 (m, 2 H, ω1-vinylic) and 5.85 (ddt, *J* 16.5, 9.0, 6.5, 1 H, ω2-vinylic).

Methyl 10-*iododecanoate* **11a**. This compound, prepared from the iodo acid **9a** as described for the synthesis of the ester **10d**, was obtained as a colourless oil (1.12 g, 89%), b.p. 140 °C/0.03 mmHg (block) (lit.,[19] b.p. 139–141 °C/0.15 mmHg); δ_H 1.60 (m, 14 H, CH_2), 2.31 (m, 2 H, CH_2CO), 3.18 (t, *J* 6.5, 2 H, CH_2I) and 3.67 (s, 3 H, OCH_3).

Methyl 16-*iodohexadecanoate* **11b**. This compound, prepared from the iodo acid **9b** as described for the synthesis of the ester **10d**, was obtained as colourless crystals after recrystallization from methanol (4.38 g, 84%), m.p. 37.5–38 °C; δ_H 1.62 (m, 26 H, CH_2), 2.31 (m, 2 H, CH_2CO), 3.22 (t, *J* 6.5, 2 H, CH_2I) and 3.70 (s, 3 H, OCH_3); ν_{max}/cm^{-1} 2928, 2852, 1730 and 1174; *m/z* (EI) 396 (M^+), 364, 259, 226 and 208.

Methyl 8-*iodooctanoate* **11c**. This compound, prepared from the iodo acid **9c** as described for the synthesis of the ester **10d**, was obtained as a colourless oil (2.22 g, 88%), b.p. 150 °C/0.2 mmHg (block); $\delta_H(CCl_4)$ 1.80 (m, 12 H, CH_2), 3.15 (t, *J* 6.5, 2 H, CH_2I) and 3.64 (s, 3 H, OCH_3); ν_{max}/cm^{-1} 2928, 2852, 1738, 1436 and 1174; *m/z* (EI) 285 ($M^+ + 1$), 253, 183, 169, 157, 125, 97 and 83.

Methyl 11-*iodoundecanoate* **11d**. This compound, prepared from the iodo acid **9d** as described for the synthesis of the ester **10d**, was obtained as a colourless oil (4.59 g, 95%), b.p. 180 °C/0.04 mmHg (block) (lit.,[5] b.p. 98–102 °C/0.15 mmHg), which solidified with time, m.p. 24–25 °C; δ_H 1.60 (m, 16 H, CH_2), 2.32 (m, 2 H, CH_2CO), 3.20 (t, *J* 6.5, 2 H, CH_2I) and 3.69 (s, 3 H, OCH_3).

Methyl Octadec-17-*enoate* **10f**.—By the method of Bergbreiter and Whitesides,[5] a solution of methyllithium in ether (1.2 mol dm^{-3}; 3.2 cm^3, 3.84 mmol) was added slowly to a suspension of cuprous iodide (0.867 g, 4.55 mmol) in tetrahydrofuran (4.5 cm^3), while the temperature was maintained between −60 and −78 °C. The resultant mixture was stirred at −78 °C for 1 h after which it was slowly allowed to warm to 0 °C, whereupon a bright yellow suspension formed. The mixture was immediately cooled to −78 °C and a solution of hept-6-enylmagnesium bromide [formed by the addition of 1-bromohept-6-ene[20] (1.61 g, 9.10 mmol) to magnesium (0.24 g, 9.87 mmol) in tetrahydrofuran (7 cm^3), under an atmosphere of nitrogen] was added, while the temperature was maintained below −60 °C. The mixture thus obtained was stirred at −78 °C for 1 h and then allowed to warm to 0–10 °C, whereupon a distinct purple colouration appeared. The mixture was then cooled to −78 °C and a solution of methyl 11-iodoundecanoate **11d** (1.44 g, 4.42 mmol) in tetrahydrofuran (15 cm^3) was added, while the temperature was maintained < −60 °C. That mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature whereupon it was stirred for 2 h, before being poured into saturated aqueous ammonium chloride (20 cm^3). The layers that formed were separated and the aqueous layer was extracted with ether (3 × 15 cm^3). The organic layer and the ether extracts were combined and the mixture was washed with brine (30 cm^3), dried ($MgSO_4$), and concentrated under pressure. Chromatography of the residual oil, with ether–light petroleum as eluent gave the title ester **10f** as colourless crystals (0.837 g, 74%), m.p. 24–26 °C; δ_H 1.31 (m, 26 H, CH_2), 2.22 (m, 4 H, CH_2CO and CH_2C=), 3.63 (s, 3 H, OCH_3), 4.98 (m, 2 H, ω1-vinylic), and 5.83 (ddt, *J* 16.5, 9.0, 6.5, 1 H, ω2-vinylic); ν_{max}/cm^{-1} 3076, 2924, 2848, 1742, 1642, 1466, 1438, 1176 and 910; *m/z* (EI) 296 (M^+), 265, 264, 222, 87 and 74.

For complete characterization, a sample of the ester **10f** was heated with dilute aqueous sodium hydroxide at reflux for 24 h,[5] to give octadec-17-enoic acid, m.p. 56–56.5 °C (lit.,[21] m.p. 55.5–56.1 °C), as colourless crystals from methanol.

Methyl 10-*Oxodecanoate* **12d**.—Ozone-containing oxygen was bubbled through a solution of the ester **10d** (1.0 g, 5.04 mmol) in chloroform (50 cm^3) for 5 h, while the mixture was maintained between −10 and −20 °C. Dimethyl sulfide (0.31 cm^3, 7.21 mmol) was then added to the mixture which was then stirred at room temperature for 16 h before concentration under reduced pressure. The residual oil was dissolved in dichloromethane (30 cm^3) and the solution was washed with water (2 × 20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the resultant oil, with ethyl acetate–light petroleum as eluent, gave the title ω-oxo ester **12d** as a colourless oil (0.49 g, 49%); δ_H 1.52 (m, 12 H, CH_2), 2.30 (m, 4 H, CH_2CO), 3.65 (s, 3 H, OCH_3) and 9.85 (t, *J* 1.8, 1 H, CHO). The spectral properties of the oxo ester **12d** are consistent with those reported previously.[22]

Methyl 13-*Oxotridecanoate* **12e**.—Treatment of the cuprate prepared from but-3-enyl bromide and the iodoester **11a**, as described for the synthesis of the ester **10f**, gave a 5:2 mixture of the unsaturated ester **10e** and methyl undecanoate as a colourless oil. The ester **10e** had δ_H 1.30 (s, 18 H, CH_2), 2.20 (m, 4 H, CH_2CO and CH_2C=), 3.65 (s, 3 H, OCH_3) 4.95 (m, 2 H, ω1-vinylic) and 5.83 (ddt, *J* 16.5, 9.0, 6.5, 1 H, ω2-vinylic). Methyl undecanoate had δ_H 0.87 (m, 3 H, CCH_3), 1.27 (m, 16 H, CH_2), 2.29 (m, 2 H, CH_2CO) and 3.66 (s, 3 H, OCH_3). A portion of the mixture was treated with ozone-containing oxygen followed by dimethyl sulfide, as described for the synthesis of the oxo ester **12d**, to give the title ω-oxo ester **12e** as a colourless oil (0.36 g, 68%); δ_H 1.85 (m, 22 H, CH_2), 3.67 (s, 3 H, OCH_3) and 9.85 (t, *J* 1.8, 1 H, CHO); ν_{max}/cm^{-1} 2924, 2852, 2716, 1740, 1466, 1438 and 1172; *m/z* (EI) 242 (M^+), 214, 211, 199, 167 and 54; *m/z* (EI) 242.187 (M^+) [Calc. for $C_{14}H_{26}O_3$ (M^+) *m/z* 242.188]. The spectral properties of the oxo ester **12e** are consistent with those reported previously.[23]

Methyl 17-*oxoheptadecanoate* **12f**. This compound, prepared from the unsaturated ester **10f** as described for the synthesis of the oxo ester **12d**, was obtained as a colourless solid (67%), m.p. 38–39.5 °C, after recrystallization from light petroleum; δ_H 1.55 (m, 26 H, CH_2), 2.33 (m, 4 H, CH_2CO), 3.65 (s, 3 H, OCH_3) and 9.83 (t, *J* 1.8, 1 H, CHO); ν_{max}/cm^{-1} 2928, 2852, 2728, 1724, 1409 and 1176; *m/z* (EI) 298 (M^+), 266, 254, 222, 122, 98 and 74; *m/z* (EI) 298.250 (M^+) [Calc. for $C_{18}H_{34}O_3$ (M^+); *m/z* 298.251].

Methyl 18-*bromooctadecanoate* **13**. This compound, prepared from the ester **10f** as described for the synthesis of the bromide **7c**, was obtained as colourless crystals (1.02 g, 66%), m.p. 36–37 °C (lit.,[24] m.p. 35–36 °C); δ_H 1.45 (m, 30 H, CH_2), 2.28 (m, 2 H, CH_2CO), 3.38 (t, *J* 6.5, 2 H, CH_2Br) and 3.65 (s, 3 H, OCH_3).

Methyl 18-*iodooctadecanoate* **11f**. This compound, prepared from the bromo ester **13** as described for the synthesis of the iodide **5b**, was obtained as colourless crystals after recrystallization from methanol (0.82 g, 73%), m.p. 44–44.5 °C; δ_H 1.55 (m, 30 H, CH_2), 2.28 (m, 2 H, CH_2CO), 3.22 (t, *J* 6.5, 2 H, CH_2I) and 3.71 (s, 3 H, OCH_3); ν_{max}/cm^{-1} 2924, 2852 and 1730; *m/z* (EI) 424 (M^+), 393, 293, 265, 247 and 155.

Octadecyltriphenylphosphonium Bromide.—A mixture of the bromide **1a** (2.05 g, 6.15 mmol), triphenylphosphine (3.78 g, 14.4 mmol) and acetonitrile (20 cm^3) was heated at reflux for 16 h. The resultant mixture was cooled and concentrated under reduced pressure to afford a colourless solid, which was washed several times with ethyl acetate and then recrystallized from dichloromethane–light petroleum to give the title salt as colourless crystals (1.98 g, 54%), m.p. 98–99.5 °C (lit.,[25] m.p. 99–100 °C).

Methyl (Z)-*Octacos*-10-*enoate* **14a**.—A solution of lithium hexamethyldisilazide, generated by the addition of butyllithium (1.5 mol dm^{-3} in hexane; 1.35 cm^3, 2.03 mmol) to hexamethyldisilazane (0.43 cm^3, 2.04 mmol) in tetrahydrofuran (1.6 cm^3) at 0 °C, was added to a suspension of octadecyltriphenylphosphonium bromide (1.20 g, 2.01 mmol) in tetrahydrofuran–hexamethylphosphoramide (4:1; 3 cm^3) cooled to 0 °C. The resultant orange solution was stirred for 10 min at 0 °C and then cooled to −78 °C when a solution of the oxo ester **12d** (0.20 g, 1.00 mmol) in tetrahydrofuran (3 cm^3) was added to it at that temperature. The mixture was subsequently allowed to warm to 0 °C and was stirred at that temperature for 1 h; it was then poured into saturated aqueous ammonium chloride (20 cm^3) and extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were washed with water (20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure to give an oil, which was chromatographed with ether–light petroleum as eluent, to give the title ester **14a** as colourless crystals after recrystallization from acetone (0.29 g, 67%), m.p. 36–37 °C; ν_{max}/cm^{-1} 2996, 2928, 2848, 1730, 1466, 1440 and 1176; *m/z* (EI) 437 ($M^+ + 1$), 436 (M^+), 405, 404, 362, 320, 228, 213, 199, 185, 171, 111, 97, 83, 69, 55, 43 and 41; *m/z* (EI) 436.426 (M^+) [Calc. for $C_{29}H_{56}O_2$ (M^+); *m/z* 436.428] (Found: C, 79.7; H, 13.2. Calc. for $C_{29}H_{56}O_2$: C, 79.8; H, 12.9%).

Nonyltriphenylphosphonium Bromide.—A mixture of the bromide **1b** (1.0 g, 4.83 mmol), triphenylphosphine (1.40 g, 5.34 mmol) and acetonitrile (4 cm^3) was heated at reflux for 36 h and then cooled and concentrated under reduced pressure to afford a colourless oil. This was washed several times with ether and then dried under reduced pressure to give the title salt as a hygroscopic, colourless glass. This material was used without characterization or purification.

Methyl (Z)-*hexacos*-17-*enoate* **14b**. This compound, prepared from the bromide **4a** and the ω-iodo ester **11c** as described for the synthesis of the ester **10f**, was obtained as a colourless oil (58 mg, 14%); ν_{max}/cm^{-1} 3004, 2924, 2852, 1744, 1650, 1468 and 1264; *m/z* (EI) 409 ($M^+ + 1$), 408 (M^+), 377, 376, 334, 292, 172, 143, 141, 129, 119, 117 87, 74, 55, 43 and 41; *m/z* (EI) 408.396 (M^+) [Calc. for $C_{27}H_{52}O_2$ (M^+) *m/z* 408.397] (Found: C, 79.1; H, 12.4. Calc. for $C_{27}H_{52}O_2$: C, 79.3; H, 12.8%).

The ester **14b** was also prepared from nonyltriphenylphosphonium bromide and the oxo ester **12f**, as described for the synthesis of the ester **14a**. After chromatography of the crude material, with ether–light petroleum as eluent, the product **14b** (16 mg, 13%) had physical and spectral properties identical with those described above.

Methyl (Z)-*docos*-13-*enoate* **14c**. This compound, prepared from the bromide **4a** and methyl 4-iodobutyrate, as described for the synthesis of the ester **10f**, was obtained as a colourless oil (18%); ν_{max}/cm^{-1} 3004, 2920, 2842, 1744, 1650, 1466 and 1170; *m/z* (EI) 353 ($M^+ + 1$), 352 (M^+), 321, 320, 278, 253, 236, 157, 125 and 97; *m/z* (EI) 352.336 (M^+) [Calc. for $C_{23}H_{44}O_2$ (M^+) *m/z* 352.334].

The ester **14c** was also prepared from nonyltriphenylphosphonium bromide and the oxo ester **12e**, as described for the synthesis of the ester **14a**. After chromatography of the crude material, with ether–light petroleum as eluent, the product **14c** (19 mg, 12%) contaminated with *ca.* 5% of the corresponding *trans*-isomer had physical and spectral properties similar to those described above. The ^{13}C NMR spectrum showed all the expected signals for the ester **14c**, with additional signals at δ 32.6(2) and 130.3(5) for the corresponding *trans*-isomer. The spectral properties of the ester **14c** are consistent with those reported.[26]

Methyl nonacosanoate **14d**. This compound, prepared from the bromide **1a** and the ω-iodo ester **11d** as described for the synthesis of the ester **10f**, was obtained as colourless crystals after recrystallization from light petroleum (0.11 g, 23%), m.p. 69–70 °C (lit.,[27] m.p. 68.8 °C); ν_{max}/cm^{-1} 2924, 2852, 1730, 1468 and 1194; *m/z* (EI) 452 (*M*$^+$), 420, 409, 395, 381, 367, 353, 199, 185, 143, 129, 87 and 74.

Methyl (Z)-*tetratriacont*-25-*enoate* **14e**. This compound, prepared from the bromide **4a** and the ω-iodo ester **11b** as described for the synthesis of the ester **10f**, was obtained as a colourless wax (63 mg, 13%), m.p. 45.5–46 °C; ν_{max}/cm^{-1} 3004, 2928, 2848, 1742, 1650, 1468 and 1172; *m/z* (EI) 521 ($M^+ + 1$), 520 (M^+), 489, 488, 446, 415, 97, 83, 74, 69, 57 and 55; *m/z* (EI) 520.519 (M^+) [Calc. for $C_{35}H_{68}O_2$ (M^+) *m/z* 520.522] (Found: C, 81.1; H, 13.7. Calc. for $C_{35}H_{68}O_2$: C, 80.7; H, 13.2%).

Methyl (Z)-*tetratriacont*-27-*enoate* **14f**. This compound, prepared from the bromide **4c** and the ω-iodo ester **11f** as described for the synthesis of the ester **10f**, was obtained as a colourless wax (35 mg, 10%), m.p. 46–47 °C; ν_{max}/cm^{-1} 3008, 2924, 2852, 1742, 1650, 1468, 1262, 1172, 1116 and 1014; *m/z* (EI) 521 ($M^+ + 1$), 520 (M^+), 489, 488, 446, 404, 143, 125, 111, 97, 83, 74, 69, 57, 55 and 43; *m/z* (EI) 520.520 (M^+) [Calc. for $C_{35}H_{68}O_2$ (M^+) *m/z* 520.522] (Found: C, 80.8; H, 13.7. Calc. for $C_{35}H_{68}O_2$: C, 80.7; H, 13.2%).

Methyl (Z,Z)-*tetratriaconta*-25,28-*dienoate* **14g**. This compound, prepared from the bromide **4b** and the ω-iodo ester **11b** as described for the synthesis of the ester **10f**, was obtained as a colourless wax (107 mg, 22%), m.p. 43–43.5 °C; ν_{max}/cm^{-1} 3008, 2924, 2848, 1742, 1650, 1468 and 1172; *m/z* (EI) 519 ($M^+ + 1$), 518 (M^+), 517, 487, 486, 284, 279, 253, 241, 227, 199, 185, 143, 129 and 87; *m/z* (EI) 518.504 (M^+) [Calc. for $C_{35}H_{66}O_2$ (M^+) *m/z* 518.506].

Methyl (Z,Z)-*Hexacosa*-17,20-*dienoate* **14h**.—A solution of *tert*-butyllithium in pentane (1.6 mol dm^{-3}; 1.0 cm^3, 1.60 mmol) was added to a solution of the iodide **5b** (0.30 g, 0.80 mmol) in ether (0.80 cm^3) at −78 °C, and the mixture was stirred at that temperature for 15 min. Cuprous iodide (0.15 g, 0.80 mmol) was then added to it and a black solid formed. Stirring was continued at −78 °C for 1 h, after which the temperature of the mixture was allowed to warm to 0 °C. The mixture was then cooled to −78 °C and a solution of the Grignard reagent generated from the bromide **4b** (0.32 g, 0.97 mmol) and magnesium (0.06 g, 2.47 mmol) in tetrahydrofuran (1.5 cm^3) was added to it at −78 °C and stirring was continued for 1 h. The resultant mixture was warmed to 0 °C, whereupon a black suspension formed, and then recooled to −78 °C and treated with a solution of the ω-iodo ester **11c** (0.41 g, 1.44 mmol) in

tetrahydrofuran (1 cm^3). That mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 3 h; it was then stirred at room temperature for a further 2 h. The mixture thus obtained was poured into aqueous ammonium chloride (20 cm^3). The layers that formed were separated and the aqueous layer was extracted with ether (3 × 10 cm^3). The organic layer and the ether extracts were combined, washed with brine (20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residual oil, with ether–light petroleum as eluent, gave the title ester **14h** (37 mg, 12%); ν_{max}/cm^{-1} 3008, 2928, 2852, 1742, 1650, 1466 and 1172; *m/z* (EI) 407 ($M^+ + 1$), 406 (M^+), 375, 374, 123, 109, 85, 81, 67, 55 and 41; *m/z* (EI) 406.380 (M^+) [Calc. for $C_{27}H_{50}O_2$ (M^+) *m/z* 406.381].

Methyl (Z,Z,Z)-*tetratriaconta*-25,28,31-*trienoate* **14i**. This compound prepared from the bromide **4d**, the iodide **5d**, and the ω-iodo ester **11b** as described for the synthesis of the ester **14h**, was obtained as a colourless wax (48 mg, 10%), m.p. 39–41 °C; ν_{max}/cm^{-1} 3008, 2924, 2848, 1742, 1650, 1466 and 1172; *m/z* (EI) 516 (M^+), 515, 284, 270, 253, 141, 227, 199, 185, 143 and 129; *m/z* (EI) 516.488 (M^+) [Calc. for $C_{35}H_{64}O_2$ (M^+) *m/z* 516.491] (Found: C, 81.2; H, 12.8. Calc. for $C_{35}H_{64}O_2$: C, 81.3; H, 12.5%).

Acknowledgements

This work was supported by the Adelaide Children's Hospital Research Trust and the University of Adelaide Research Scheme.

References

1 For a review see, T. Rezanka, *Progr. Lipid Res.*, 1989, **28**, 147.
2 For examples see, J. Templier, C. Largeau and E. Casadevall, *Phytochemistry*, 1987, **26**, 277; C. Litchfield, A. J. Greenberg, G. Noto and R. W. Morales, *Lipids*, 1976, **11**, 567; H. R. Schulten, N. Smmleit and H. H. Rump, *Chem. Phys. Lipids*, 1986, **41**, 209; M. I. Alvedano and H. Sprecher, *J. Biol. Chem.*, 1987, **262**, 1180; A. Poulos, P. Sharp, D. Johnson, I. White and A. Fellenberg, *Biochem. J.*, 1986, **240**, 891; A. Poulos, D. W. Johnson, K. Beckman, I. G. White and C. Easton, *Biochem. J.* 1987, **248**, 961; A. Poulos, P. Sharp, D. Johnson and C. Easton, *Biochem. J.*, 1988, **253**, 645.
3 C. Prakash, S. Saleh, B. J. Sweetman, D. F. Taber and I. A. Bair, *J. Labelled Compd. Radiopharm.*, 1989, **27**, 539; Y. Leblanc, B. J. Fitzsimmons, J. Adams, F. Perez and J. Rokach, *J. Org. Chem.*, 1986, **51**, 789; M. Labelle, J.-P. Falgueyret, D. Riendeau and J. Rokach, *Tetrahedron*, 1990, **46**, 6301.
4 L. D. Bergelson and M. M. Shemyakin, *Angew. Chem., Int. Ed. Eng.*, 1964, **3**, 250; L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, 1963, **19**, 149.
5 D. E. Bergbreiter and G. M. Whitesides, *J. Org. Chem.*, 1975, **40**, 779.
6 J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, 1968, **46**, 86.
7 H. Matsuda, A. Yamamoto, N. Iwamoto and S. Matsuda, *J. Org. Chem.*, 1978, **43**, 4567.
8 P. D. Gokhali, V. S. Dalavoy, A. S. C. Prakasa Rao, U. R. Nayak and S. Dev, *Synthesis*, 1974, 718.
9 F. D. Gunstone, M. R. Pollard, C. M. Scrimgeour and H. S. Vedanayagam, *Chem. Phys. Lipids*, 1977, **18**, 115.
10 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
11 E. E. Reid, F. O. Cockerille, J. D. Meyer, W. M. Cox and J. R. Ruhoff, *Org. Synth.*, Coll. Vol. II, 1943, 468.
12 O. Turpeinen, *J. Am. Chem. Soc.*, 1938, **60**, 56.
13 E. Ucciani and R. Piantoni, *Chem. Phys. Lipids*, 1968, **2**, 256.
14 F. L. M. Pattison, J. B. Stothers and R. G. Woolford, *J. Am. Chem. Soc.*, 1956, **78**, 2255.
15 P. Chuit and J. Hausser, *Helv. Chim. Acta*, 1929, **12**, 463.
16 M. S. Raasch, *J. Am. Chem. Soc.*, 1953, **75**, 2956.
17 J. Bougault, *Compt. Rend.*, 1910, **150**, 874.
18 G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1948, 658.
19 N. R. De Leu and H. C. Brown, *Synthesis*, 1976, 114.
20 P. Gaubert, R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1937, 1971.
21 W. F. Huber, *J. Am. Chem. Soc.*, 1951, **73**, 2730.
22 J.-H. Fuhrhop and M. Baccouche, *Justus Liebigs Ann. Chem.*, 1976, 2058.
23 K. M. Waugh and K. D. Berlin, *J. Org. Chem.*, 1984, **49**, 873.
24 U. Jensen-Korte and H.-J. Schafer, *Liebigs Ann. Chem.*, 1982, 1532.
25 T. Kauffmann, E. Rauch and J. Schulz, *Chem. Ber.*, 1973, **106**, 1612.
26 J. M. Bernassau and M. Fetizon, *Tetrahedron*, 1981, **37**, 2105.
27 F. Francis and S. H. Piper, *J. Am. Chem. Soc.*, 1939, **61**, 577.

Paper 2/05945B
Received 6th *November* 1992
Accepted 22nd *February* 1993