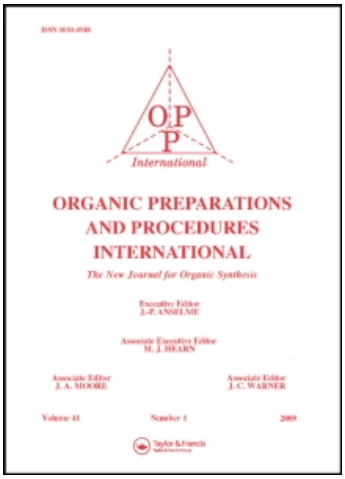

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AN IMPROVED SYNTHESIS OF ±18 METHYL EICOSANOIC ACID

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AN IMPROVED SYNTHESIS OF ±18 METHYL EICOSANOIC ACID

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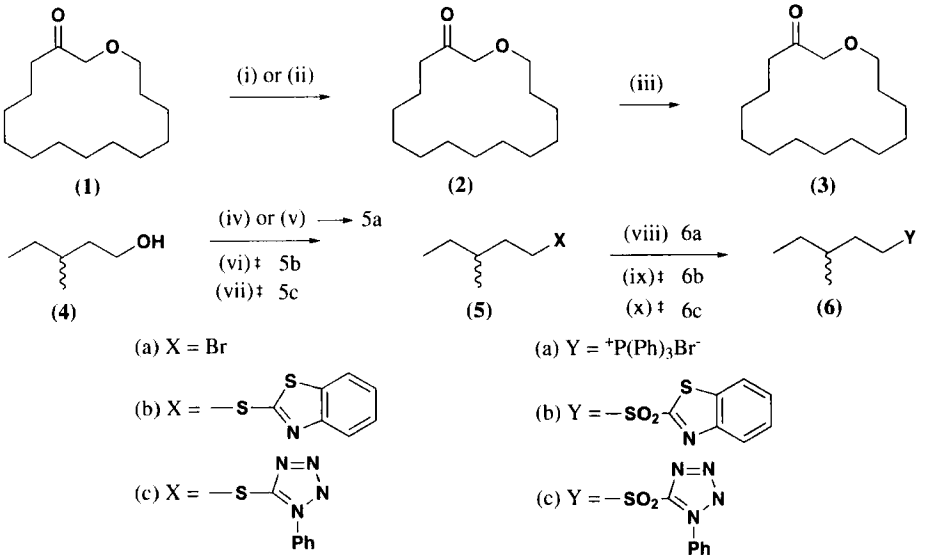
±18-Methyl eicosanoic acid (18MEA) has attracted attention as an additive to hair cosmetic compositions because of its ability to impart desirable conditioning effects. We required gram quantities of 18MEA for related studies and surveyed the literature for convenient preparative methods. The earliest description[1] of the synthesis of 18MEA reacts cyclopentadecanone with the Grignard reagent derived from ±3-methyl bromopentane to afford the corresponding tertiary alcohol. The latter was oxidised in low yield by chromium trioxide to afford the corresponding keto acid which was subsequently reduced by an undisclosed Wolff Kishner procedure to afford the product in 8% overall yield.

A more recent preparative description has been reported in the patent literature.[2] This approach described the preparation of ±2-methylbutyltriphenylphosphonium bromide in 42% yield from ±1-bromo-2-methylbutane, the latter being available by the bromination of commercially available ±2-methyl-1-butanol. In this approach the Wittig salt was condensed with methyl 15-formylpentadecanoate to afford the corresponding unsaturated ester. The latter was hydrogenated at a pressure of 100 atmospheres at 100° to afford 18MEA in an overall yield of 5%. Despite using modern procedures, the patent description was unsuitable for our purpose as it required an unavailable starting material methyl 16-hydroxyhexadecanoate, for the synthesis of the aldehydic precursor. Moreover the choice of pyridinium chlorochromate to oxidise the latter was environmentally unattractive and the hydrogenation conditions were not well suited for scale-up. In the present report, we describe a modified approach which employs inexpensive starting materials, which circumvents the use of heavy metal oxidants and which affords good yields of the desired product under mild conditions.

The ω-cyclopentadecalactone (**1**) was chosen as a starting point in our synthesis as it was commercially available in kilogram quantities. Using similar conditions to those outlined in the patent description, treatment of **1** with methoxide afforded the requisite hydroxy ester (**2**) in 71% yield. This yield was improved by adopting the *p*-toluenesulfonic acid catalysed method of Mori *et al.*[3] which afforded **2** almost quantitatively. In order to obtain the carboxaldehyde (**3**) we examined the pyridinium chlorochromate mediated oxidation of **2** under the conditions suggested in the patent descrip-

tion. However we found that the aldehyde isolated by that procedure often required extended purification by column chromatography. Moreover we observed that, despite very little change in the ^{1}H NMR spectrum, the melting point of the product prepared and chromatographed in this manner increased to 65°, well above the reported literature value[3]. In order to identify a more reliable route to **3** we evaluated the oxidation of **2** under Swern conditions.[4] Using the present procedure multi-gram batches (>20g) of **3** were available in yields above 70% (Scheme 1). In an attempt to obviate the need for chromatography we also examined the tetravalent chromium dioxide based oxidant Magtrieve™ which is reported[5] to be a mild, selective, recoverable oxidant suitable for a variety of alcohols. The combination of the simple procedure (refluxing in dichloromethane or chloroform) and the facile work-up (removal of the catalyst either by filtration or magnetic separation) added to its attractiveness. However in both solvents the oxidation of **2** was incomplete after 24h at reflux and the formation of other compounds was observed by ^{1}H NMR. Accordingly we reverted to the Swern procedure *vide supra.*



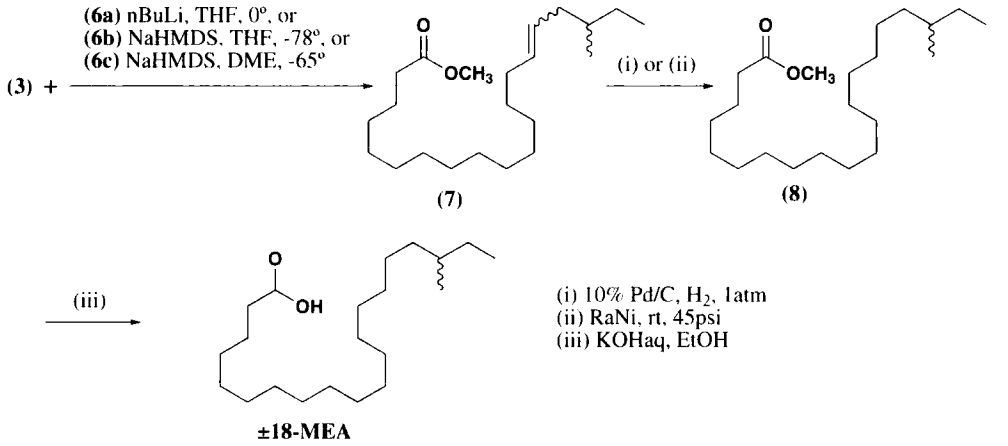
(i) $NaOCH_3$ / MeOH / Δ; (ii) p-TosH / MeOH / Δ; (iii) $(COCl)_2$, DMSO, TEA, -10°;
(iv) H_2SO_4 / HBr (aq); (v) NBS, PPh_3, DCM; (vi) DEAD, PPh_3, 2-mercaptobenzothiazole;
(vii) DEAD, PPh_3, Phenyl-1-*H*- tetrazole-5-thiol; (viii) PPh_3 toluene, $(n\text{-}Bu)_4NI$, Δ; (ix) *m*-CPBA, DCM;
(x) monoperoxyphthalic acid magnesium salt monohydrate

Scheme 1

With a reliable procedure for the aldehydic fragment in hand, we examined procedures to provide the other coupling partner. Again following the patent approach we converted ±3-methyl-1-pentanol (**4**) into the corresponding alkyl bromide (**5a**) by refluxing the alcohol in a mixture of hydrobromic and sulfuric acids. Distillation afforded **5a** in 75% yield. In an attempt to improve this we investigated the *N*-bromosuccinimide mediated procedure of Fuganti and co-workers[6] but found the yields to be lower.

With the view to carrying out a Wittig condensation we reacted **5a** with triphenyl phosphine in refluxing benzene. The reaction appeared to have slowed after 3 days and the phosphonium salt **(6a)** was isolated in 23% yield. To accelerate this, the reaction was carried out in refluxing toluene containing a catalytic amount of tetra-*n*-butylammonium iodide, after 10 days the requisite salt could be obtained in 64% yield.

Treatment of **6a** with *n*-butyllithium at 0° gave the corresponding ylide which was reacted *in situ* with **3** in THF to give the alkene **(7)** in 28% yield. (Scheme 2). Given the lengthy reaction time required to access **6a** and low yield of the coupling reaction we investigated other condensation protocols.



Scheme 2

Julia and co-workers reported[7] that the anions generated by the treatment of substituted benzothiazolylsulfones could react with carbonyl compounds to yield intermediates which underwent rearrangement and a subsequent extrusion of sulfur dioxide to afford the corresponding alkenes. This so called "Julia coupling" technique has been used to advantage by other workers who have examined the role of the base in the determination of the *E/Z* ratio[8] and described procedural improvements[9] to the technique. Accordingly we set about preparing the requisite sulfone in order to assess its suitability in our system.

Under standard Mitsunobu conditions we could conveniently convert 20g batches of alcohol **4** into the corresponding sulfide **(5b)** in 89% yield by reacting it with diethyl azodicarboxylate (DEAD), triphenyl phosphine and 2-mercaptobenzothiazole. In order to accomplish the oxidation of **5b** to the sulfone **(6b)** we firstly examined oxone™ as it was inexpensive and had been used[10] to effect clean oxidations of a variety of sulphide substrates. Employing the so described[10] aqueous methanolic solvent system, no oxidation of **5b** was observed, however further investigation of other solvent mixtures was not undertaken. Instead we employed *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane according to the method of Kocienksi[9] and could obtain **6b** in 83% yield.

Adopting the "one-pot" coupling techniques prescribed by Kocienksi[9] and using the preferred base of Charette *et al*[8] *ie.* sodium hexamethyldisilazide, (NaHMDS), **6b** and **3** could be coupled in THF to give **7** in 30% yield. To gauge the value of a stepwise approach, **6b** was treated with (NaHMDS) at –78° for 1 hour prior to the addition of **3**. Under these conditions the yield of **7** was 6%, suggesting that the intermediate carbanion of **6b** was unstable and either decomposed or participated in self condensation reactions. Addressing the issue of carbanion stability and solvent, Kocienski, in a later publication[11] reported that sulfones derived from 1-phenyl-1*H*-tetrazol-5-thiol generally gave higher yields than condensations carried out with the 2-mercaptobenzothiazole analogues. Moreover he found that conducting the reactions in DME also offered some potential for an improvement in yield. Accordingly we prepared the corresponding sulfide **5c** in 83% yield in 0.25 mole batches. Using similar oxidation methods, although treatment of **5c** with *m*CPBA gave the sulfone **6c** in high yield, chromatography was necessary to separate significant amounts of an unidentified *m*CPBA-derived by-product. In order to circumvent this, we examined magnesium monperphthalate, an oxidant used by others[12] as an alternative to peracids. This procedure afford almost pure **6c** in >95% yield. Treatment of a mixture of **6c** and **3** with NaHMDS in DME at -65° improved the coupling yield to 58%. To reproduce the conditions used by Kocienski[11], the reaction was repeated at -55°. Under these conditions however the reaction was not as clean, albeit the yield of **7** remaining essentially the same.

To determine if the high temperatures and pressures employed in the patent disclosure were necessary, we examined the milder hydrogenation system of Matsuda[3]. Under those conditions the hydrogenation of a 15-triacontenoate was carried out in ethyl acetate at room temperature by stirring the alkene under one atmosphere of hydrogen in the presence of 10% palladium on carbon. Employing these conditions to the reduction of carefully purified **7** afforded a good yield of the saturated ester (**8**). However unless all traces of impurity were removed the reductions were sluggish and unpredictable. Presuming catalyst poisoning by sulfur containing by-product was responsible, Raney nickel mediated hydrogenation was investigated. Using a 50% aqueous slurry of nickel, the hydrogenations were complete after several hours under 45psi of hydrogen yielding **8** in 96%. The lower limit of the required hydrogen pressure was not however determined.

The conversion of **8** to 18MEA was carried out under standard hydrolysis conditions to provide the target compound in 85% yield after recrystallization. Applying the present approach 18MEA is available in an overall yield of 27%.

EXPERIMENTAL SECTION

Silica gel (230-400 mesh) was purchased from Merck. Melting points were taken on a Reichert-Jung hot stage melting point apparatus and are reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on an AC250 Bruker spectrometer using $CDCl_3$ unless otherwise stated. Microanalyses were performed on a Carlo Erba EA-1108 CHNS-O by Campbell Microanalytical Laboartory, University of Otago, New Zealand. Mass spectra, were recorded on a JMS-DX303 mass spectrometer.

Methyl 15-Hydroxypentadecanoate (2).- A mixture of ω-cyclopentadecalactone (22.7 g, 0.093 mol) and *p*-toluenesulfonic acid monohydrate (0.60 g, 0.003 mol) in methanol (700 mL) was heated at reflux for 24h. The mixture was poured into water (800 mL) and extracted with chloroform (3 x 800 mL). The organic extracts were washed with sat. aq. $NaHCO_3$ (2 x 800 mL), brine (2 x 800 mL), dried ($MgSO_4$), filtered and reduced to dryness to afford **2** as a white solid (25.3 g, 99% yield), mp. 50-51°, *lit.*[3] 49°.

Methyl 14-Formylbutadecanoate (3).- A solution of anhydrous DMSO (24.4 mL, 0.34 mol) in anhydrous DCM (35 mL) was added dropwise to a solution of oxalyl chloride (14.3 mL, 0.17 mol) in dry DCM (170 mL) at -60°. After stirring at this temperature for 5 min the mixture was warmed to -10° and the hydroxy ester **2** (19.5 g, 0.072 mol) in DCM (70 mL) added over 10 min. After stirring for a further 15 min at -10°, triethylamine (50.2 mL, 0.36 mol) in DCM (50 mL) was added and stirring continued for an additional 5 min. Water (500 mL) was added and the aqueous phase extracted with DCM (3 x 400 mL). The organic extracts were washed with water (3 x 400 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude solid was purified by column chromatography on silica gel (eluant: pet. spirits (bp 40-60°) / ethyl acetate (4:1)) to afford **3** (15.0 g, 77% yield), mp. 30-31°, *lit.*[3] 27-29°. The purity of the **3** prepared in this fashion was estimated by ^1H NMR and was typically 70%. The material was normally used immediately or stored under nitrogen at 0°. Repeated chromatography of **3** led to slow decomposition of the product. ^1H NMR (200 MHz): δ 9.76 (t, *J*=1.9Hz, 1H, CHO), 3.66 (s, 3H, CH_3), 2.41 (dt, *J*=7.3, 1.8Hz, 2H, CH_2CHO), 2.29 (t, *J*=7.5Hz, 2H, CH_2CO_2), 1.7-1.2 (m, 22H, $(CH_2)_{11}$); ^{13}C NMR (50 MHz): δ 202.9, 174.3, 51.4, 43.9, 34.1, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 22.1.

±1-Bromo-3-methylpentane (5a).- A solution of ±3-methyl-1-pentanol (5.1 g, 0.05 mol), conc. H_2SO_4 (2.8 g) and aq. HBr (8.6 g, 48%w/w) was stirred at reflux for 3 days. The mixture was poured onto ice/water (100 mL), neutralised with aq. $NaHCO_3$ (10% w/w) and extracted with diethyl ether (3 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude oil was distilled under house vacuum to afford **5a**[6] (6.4 g, 78% yield).

±5-(3-Methylpentyl)-2-mercaptobenzothiazole (5b).- A solution of diethyl azodicarboxylate (DEAD) (17.3 mL, 0.11 mol) was added dropwise to a solution of triphenylphosphine (28.9 g, 0.11 mol), ±3-methyl-1-pentanol (10.2 g, 0.10 mol) and 2-mercaptobenzothiazole (18.4 g, 0.11 mol) in anhydrous THF (1200 mL) at 15° under N_2. The yellow solution was stirred at room temperature for 48h. The solvent was removed and the residue triturated with hexane / ethyl acetate (5:1). Insolubles were removed by filtration and the solvents concentrated. The procedure was repeated twice more. The resulting oil (29g) was purified by silica gel column chromatography (eluant: pet. spirits (bp 40-60°) / ethyl acetate (20:1) to afford **5b** as a pale yellow oil (22.3 g, 89% yield). ^1H NMR (200 MHz): δ 3.45-3.23 (m, 2H, CH_2-S), 1.91-1.11 (m, 5H), 0.97-0.87 (m, 6H, 2 x CH_3); ^{13}C NMR (50 MHz): δ 167.2, 153.2, 135.0, 125.9, 124.0, 121.3, 120.8, 35.7, 33.8, 31.5, 29.0, 18.7, 11.1; *Anal.* Calcd. for $C_{13}H_{17}NS_2$: C, 62.11; H, 6.82; N, 5.57. Found: C, 62.62; H, 6.94; N, 5.56; Acc. Mass (CI): Calcd. for $C_{13}H_{18}NS_2$: 252.0880, Found: 252.0866.

1-Phenyl-5-[thio-(±3'-methylpentyl)]-1*H*-tetrazole (5c).- A solution of DEAD (15.0 g, 0.086 mol) in anhydrous THF (25 mL) was added dropwise to a solution of ±3-methyl-1-pentanol (8.03 g, 0.078 mol), triphenylphosphine (22.6 g, 0.086 mol) and 1-phenyl-1*H*-tetrazole-5-thiol (15.4 g, 0.086 mol) in anhydrous THF (300 mL) under N_2 whilst maintaining the temperature below 15°. The yellow solution was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue shaken with hexane (100 mL). The resulting solid was collected and triturated with hexane (2 x 100 mL). The combined hexane extracts were concentrated *in vacuo* to afford a pale coloured oil. This was purified by column chromatography (eluant: pet. spirits (bp 40-60°) / ethyl acetate, 20:1) to afford **5c** (18.80 g, 83% yield). ^{1}H NMR (200 MHz): δ 7.55 (m, 5H, ArH), 3.51-3.27 (m, 2H, CH_2-S), 1.90-1.09 (m, 5H), 0.93-0.83 (m, 6H, 2 x CH_3); ^{13}C NMR (50 MHz): δ 154.3, 133.6, 130.0, 129.7, 123.8, 35.6, 33,7, 31.4, 29.0, 18.7, 11.1.

Anal. Calcd for $C_{13}H_{18}N_4S$: C, 59.51; H, 6.91; N, 21.35; S 12.22. Found: C, 59.84; H, 7.19; N, 21.16; S 12.49

±3-Methylpentyltriphenylphosphonium Bromide (6a).- A mixture of **5a** (2.3 g, 0.014 mol), triphenylphosphine (3.6 g, 0.014 mol) and *n*-tetrabutylammonium iodide (0.1 g, 0.27 mmol) in toluene (50 mL) was stirred at reflux for 10 days. The mixture was cooled and filtered to afford **6a** (6.9g, 74% yield), mp. 192-3° (*lit.*[13]185-7°). ^{1}H NMR (200 MHz): δ 7.88-7.64 (m, 15H, ArH), 3.76-3.61 (m, 2H, P-CH_2), 1.89-1.02 (m, 5H), 0.94 (d, *J*=6.4Hz, 3H, CH_3-CH), 0.77 (t, *J*=7.4Hz, 3H, CH_3-CH_2).

2-(±3-Methylpentyl)-sulfonylbenzothiazole (6b).- A solution of *m*-chloroperbenzoic acid (25 g, 0.14 mol) in anhydrous DCM (250 mL) was added to a stirred suspension of **5b** (10 g, 0.04 mol) and $NaHCO_3$ (16g, 0.20 mol) in DCM (250 mL). After 24h the mixture was poured into a 1:1 solution of sat. aqueous $Na_2S_2O_5$ / sat. aqueous $NaHCO_3$ (1000 mL). The organic phase was rewashed with additional sat. aq. $Na_2S_2O_5$ / sat. aq. $NaHCO_3$ (2 x 1000 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The pale orange residue (11.7 g) which remained was purified by column chromatography (silica gel, eluant: DCM / Pet. Spirits (2:1) to afford **6b** as a colourless oil (10.9 g, 97% yield). ^{1}H NMR (200 MHz): δ 8.16-8.11 (m, 1H, ArH), 7.96-7.92 (m, 1H, ArH), 7.56-7.50 (m, 2H, ArH), 3.50-3.40 (m, 2H, CH_2S), 1.92-1.00 (m, 5H, CH_2), 0.83-0.73 (m, 6H, 2 x CH_3); ^{13}C NMR (200 MHz): δ 165.7, 152.6, 136.6, 127.9, 127.5, 125.3, 122.2, 53.8, 33.3, 28.7, 28.1, 18.5, 11.0;

Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.10; H, 6.05; N, 4.94. Found: C, 55.40; H, 6.09; N, 5.01

Acc. Mass (CI): Calcd. for $C_{13}H_{18}NO_2S_2$: 284.0779. Found: 284.0748

1-Phenyl-5-[(±3'-methylpentyl)sulphonyl]-1*H*-tetrazole (6c).- Magnesium monoperphthalate hexahydrate (80% pure, 53.2 g, 0.086 mol) was added portionwise to **5c** (18.8 g, 0.072 mol) in ethanol (280 mL) at 0° and then stirred at room temperature overnight. Water (200 mL) was added and the mixture concentrated *in vacuo* to remove most of the ethanol. DCM (200 mL) was added and the aqueous phase extracted with more DCM (2 x 200 mL). The organic extracts were washed with aq. Na_2SO_3 soln. (3 x 200 mL), dried ($MgSO_4$), filtered and reduced to dryness leaving **6d** as a colourless oil (20.5 g, 97% yield). ^{1}H NMR (200 MHz): δ 7.55-7.68 (m, 5H, ArH), 3.72-3.65 (m, 2H, CH_2SO_2), 2.05-1.18, (m, 5H, $(CH_2)_2$, CH), 0.95 (2 x t, 6H, 2 x CH_3).

Anal. Calcd for $C_{13}H_{18}N_4O_2S$: C, 53.04; H, 6.16; N, 19.03; S 10.89. Found: C, 53.00; H, 6.35; N, 18.99; S 10.80

Methyl ±18-Methyl-15-*(E/Z)*-eicosenoate (7).- Sodium bis(trimethylsilyl)amide (74mL, 1M soln. in THF, 74.0 mmol) was added to a mixture of **6c** (18.1 g, 62.0 mmol) and the appropriate amount of **3** (based on a determination of its purity by ^{1}H NMR, 62.0 mmol) in anhydrous DME (400 mL) at -65°. During the addition the temperature of the mixture was adjusted between -65° and -55° in order to avoid freezing. The resulting yellow coloured solution was stirred at this temperature for 3h and then at room temperature for 17h. The solution was washed with aq. sat. NH_4Cl (500 mL) and the phases separated. The aqueous phase was re-extracted with diethyl ether (3 x 300 mL), and the combined organics washed with brine (2 × 500 mL), then water (500 mL). The organic fraction was dried ($MgSO_4$), filtered and reduced *in vacuo* to afford a yellow/orange coloured oil. The crude material was purified by column chromatography (eluant: $CHCl_3$/Pet. Spirits 30-40°, 1:1) to afford 2.18g (30% yield) of a mixture of the isomeric alkenes (**7**). ^{1}H NMR (200 MHz): δ 5.36 (m, 2H, CH=CH), 3.65, (s, 3H, CH_3O), 2.29 (t, *J*=7.4 Hz, 2H, α-CH_2), 2.1-1.9 (m, 2H, β-CH_2), 1.7-1.5 (m, 2H, γ-CH_2), 1.3-1.1 (bs, 25H), 0.9-0.8 (m, 6H, 2 x CH_3); ^{13}C NMR (50 MHz): δ 174.3, 131.6, 130.6, 128.8, 128.4, 75.3, 51.4, 39.7, 35.1, 34.9, 34.1, 32.6, 29.7, 29.64, 29.59, 29.50, 29.46, 29.34, 29.25, 29.2, 29.0, 27.3, 25.0, 19.1, 19.0, 11.6, 11.5.

Anal. Calcd for $C_{22}H_{42}O_2$: C, 78.05; H, 12.50. Found: C, 78.33; H, 12.66

Methyl ±18-Methyleicosanoate (8) *via* Pd/Carbon Hydrogenation.- A suspension of 10% palladium on carbon (0.08 g, 5% w/w) and **7** (1.6 g, 4.8 mmol) in ethyl acetate (50 mL) was purged with hydrogen gas then shaken under atmospheric pressure for 26h. The mixture was filtered through glass filter paper to remove the catalyst and reduced to dryness to afford a pale yellow oil. The oil was purified by silica gel column chromatography (eluant: chloroform / Pet. Spirits bp.40-60°, 1:1) to afford **8** as a colourless oil (1.54g, 99% yield).

Methyl ±18-Methyleicosanoate (8) *via* Raney nickel Hydrogenation.- A suspension of Raney nickel catalyst (50% solution in H_2O, 1.52 g) and **7** (3.8 g, 11.2 mmol) in methanol (100 mL) was shaken under 45 psi of hydrogen gas at room temperature for 17h. The mixture was filtered and the catalyst rinsed with 5% water in ethanol and the filtrates reduced to dryness under reduced pressure. Ethanol (2 x 100 mL) was added and the mixture re-concentrated to a semi-solid product. This was passed down a short plug of silica eluting with a minimum amount of $CHCl_3$. Concentration of the eluant gave **8** as a colourless oil (3.63 g, 96% yield), bp 150° @ 0.1 mmHg (*lit.*[14] 194° @ 1.9mmHg. ^{1}H NMR (200MHz): δ 3.66 (s, 3H, CH_3O), 2.29 (t, *J*=7.5Hz, 2H, α-CH_2), 1.65-1.55 (m, 2H, β-CH_2), 1.24 (bs, 31H), 0.87-0.81 (m, 6H, 2 x CH_3); ^{13}C NMR (50 MHz): δ 174.3, 51.4, 36.6, 34.4, 34.1, 30.0, 29.7, 29.64, 29.59, 29.54, 29.49, 29.45, 29.40, 29.3, 29.2, 29.1, 27.1, 25.0, 19.2, 11.4.

Anal. Calcd for $C_{22}H_{44}O_2$: C, 77.58; H, 13.02. Found: C, 77.24, H, 13.06

±18-Methyleicosanoic acid (9).- A solution of **8** (3.7 g, 11 mmol) and 7% ethanolic KOH (50 mL, 60 mmol) was stirred at room temperature for 17h. The solution was treated with 2M H_2SO_4 (50 mL) and extracted into DCM (3 x 50 mL). The organic solution was washed with water (3 x 50 mL), dried

($MgSO_4$), filtered and reduced to dryness. The crude solid was recrystallised from methanol / water to yield **9** as colourless crystals (3.16 g, 88% yield), mp. 57-58° (*lit.*[2] 53°). ^1H NMR (200MHz): δ 2.35 (t, *J*=7.5Hz, 2H, CH_2CO), 1.70-1.55 (m, 2H, CH_2-C-CO), 1.40-1.05 (bs, 31H, 15 x CH_2, CH), 0.88-0.817 (m, 6H, 2 x CH_3); ^{13}C NMR (50 MHz): δ 180.0, 36.6, 34.4, 34.0, 30.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 27.1, 24.7, 19.2, 11.4; Acc. Mass (CI): Calcd ($C_{21}H_{43}O_2$) 327.3263, Found 327.3260.

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