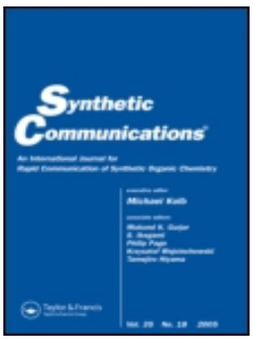

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SYNTHESIS OF AN UNNATURAL ANACARDIC ACID ANALOGUE

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ABSTRACT

The unnatural **E** isomer of anacardic acid **7** has been synthesized employing the following key steps: Swern oxidation of a diastereoisomeric mixture of β-hydroxyphosphine oxides **13a/b** to the corresponding ketone **14** followed by stereospecific reduction to the pure threo isomer **13b** which upon treatment with sodium hydride underwent trans elimination to afford the **E** ester **15**.

Naturally occurring anacardic acids **1–4** are derivatives of 6-pentadecenyl salicylic acid in which the C-15 side chain is either saturated viz. **1**, has a **Z** double bond at C-8 viz., **2**, has a Z, Z diene at C-8 and C-11 viz., **3**, or has a triene arrangement viz., **4**.[1]

The spectrum of biological activity of the anacardic acids **1–4** ranges from antibacterial[2] to antitumor[3] to a strong molluscicidal activity being associated with the degree of unsaturation of the C-15 side chain.[4] It has been demonstrated that the role the length of the side chain plays in biological

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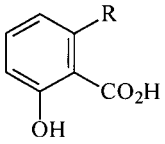


1 R = $(CH_2)_{14}CH_3$
2 R = Z $(CH_2)_7CH{=}CH(CH_2)_5CH_3$
3 R = Z,Z $(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_2CH_3$
4 R = Z,Z $(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$
5 R = $(CH_2)_{11}CH_3$
6 R = Z $(CH_2)_9CH{=}CH(CH_2)_3CH_3$
7 R = E $(CH_2)_7CH{=}CH(CH_2)_5CH_3$

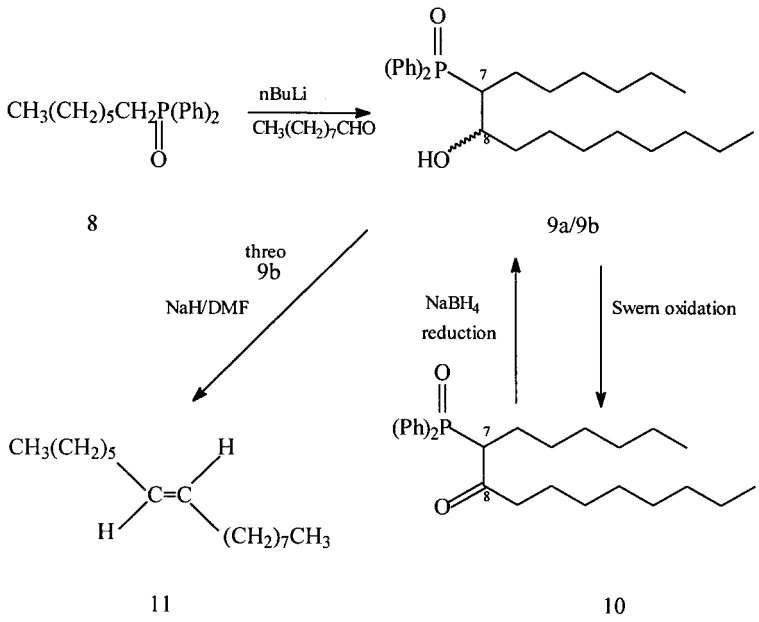
activity is very important with the saturated C-12 analogue **5** being more active against *Pseudonomous acnes* than the most active anacardic acid **4**.[5]

To our knowledge the only unsaturated anacardic acids synthesized are **2** and **6** both having the **Z** geometry in the olefin bond.[6,7] Thus one may assume that for the C-15 series of anacardic acids, the **Z** geometry of the double bond is necessary for biological activity. However, in order to validate this assumption it would be necessary to synthesize at least one alternative geometric isomer for comparative evaluations. This paper describes the synthesis of the **E** analogue **7** of the natural **Z** anacardic acid **2**.

At the outset it was realized that the synthetic protocol had to ensure that the **E** isomer was to be formed without any contamination from the **Z** isomer to avoid any ambiguities in the biological evaluations. Modifications to the Wittig olefin synthesis have favoured **E** olefins with stabilized ylides and **Z** olefins with non-stabilized ylides but are not exclusively so.[8] We decided to focus on the modified Horner-Wittig protocol that was reported to provide almost exclusively the **E** olefin.[9,10]

In an attempt to verify the methodology chosen, we embarked on the synthesis of **E** 7-hexadecene **11**. Thus, condensation between heptyl bromide and triphenylphosphine in boiling acetonitrile followed by heating of the product with aqueous sodium hydroxide,[11] afforded the phosphine oxide **8** in 94% yield. Treatment of the phosphine oxide **8** with 1 equivalent of *n*-butyllithium followed by quenching with nonal afforded the alcohols **9a** and **9b** in 70% yield as a mixture of *erythro* **9a** and *threo* **9b** isomers in the ratio of 4 : 1 based upon the signal intensities of the carbinol C-8 in the ^{13}C-n.m.r. spectrum at 70.04 and 72.70 ppm respectively.[7] Since conversion of this mixture into an olefin would result in the incorrect **Z** geometry from the *erytho* isomer **9a**, the ratio of 9a : 9b was altered as shown in Scheme 1.

Swern oxidation[12] of the diastereoisomeric mixture of alcohols **9a/9b** afforded the ketone **10** in 76% yield. This was followed by stereoselective reduction with sodium borohydride reported to favour threo selectivity[13] to afford the alcohols **9a/9b** in 80% yield and in this instance the ratio of *erythro* **9a** to *threo* **9b** diastereoisomer was reversed and found by



Scheme 1.

^{13}C-n.m.r. spectroscopy to be 1 : 5 as evidenced by the relative intensities of the C-8 signals at 70.04 and 72.7 ppm.[7] Finally, treatment of this mixture of **9a/9b** with 2 equivalents of sodium hydride in dimethyl formamide at 50°C[14] afforded the hexadecene **11** in 76% yield. The ratio of **E : Z** isomers was 5 : 1 as demonstrated by the relative peak heights for C-6 and C-9 for the **E** isomer at 32.6 ppm compared to the signal at 27.2 ppm for the **Z** isomer in the ^{13}C-n.m.r. spectrum.[7] Although, in our hands, this protocol did not provide the **E** isomer exclusively, we decided to employ it for our synthesis of the **E** anacardic acid **7**.

Treatment of phosphine oxide **8** with 1 equivalent of *n*-butyllithium at 0°C followed by quenching with aldehyde **12**[6] afforded the β-hydroxy phosphine oxides **13a** and **13b** in 76% yield. This diastereoisomeric mixture was oxidized by Swern methodology as before to yield the ketone **14** in 83% yield. In the infrared spectrum of **14**, two carbonyl stretching frequencies were observed viz., 1728 cm^{-1} for the ester and 1713 cm^{-1} for the ketone group while a strong band at 1190 cm^{-1} was assigned to the P=O group. Diagnostic peaks in the ^{1}H-n.m.r. spectrum are a two proton triplet at 2.40 ppm ($J = 7.0$ Hz) for 7′-H, and a doublet of doublet of doublets at

3.56 ppm with coupling of 12.8 Hz between 9′-H and 10′-Ha, further coupling of 11.6 Hz between 9′-H and 10′-Hb and finally coupling of 3.0 Hz between 9′-H and P which is assigned to 9′-H.

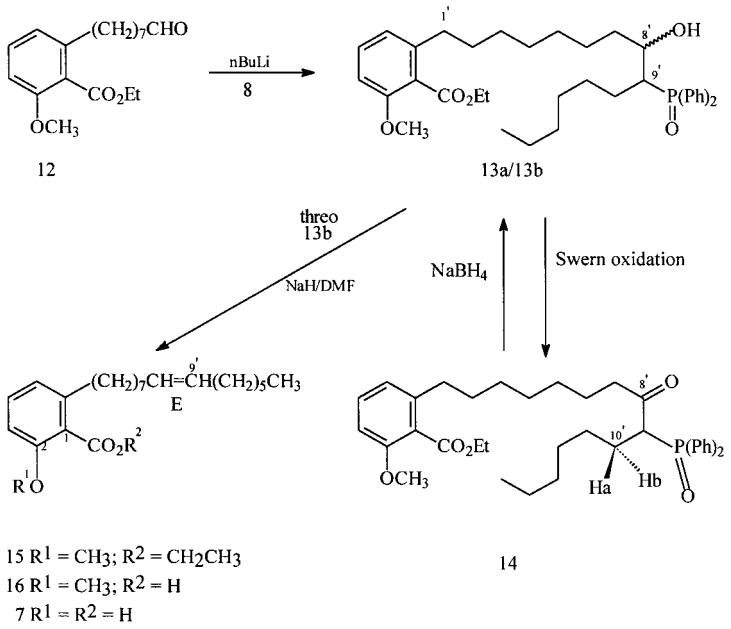
Reduction of ketone **14** with sodium borohydride in boiling ethyl alcohol as described earlier afforded exclusively the pure *threo* isomer **13b**[10] in 80% yield. A strong absorption band at 3358 cm^{-1} in the infrared spectrum confirmed the presence of the hydroxy group while absorptions at 1726 and 1164 cm^{-1} are assigned to the ester and P=O groups respectively. Unfortunately the 8′- and 9′-H's appeared as an overlapping multiplet at 2.25 ppm which precluded an ambiguous assignment. However the ^{13}C-n.m.r. spectrum demonstrated clearly that only the *threo* isomer **13b** was formed since there was only a signal at 72.6 ppm and none in the region of 70 ppm.[7]

Treatment of the *threo* β-hydroxyphenylphosphine oxide **13b** with **2** equivalents of sodium hydride in dimethylformamide at 50°C produced a single isomer (by GC) in 65% of the **E**-olefin **15**. Assigment of the **E** geometry is based on the following: there is a strong out-of-plane vibration at 966 cm^{-1} in the infrared spectrum[15] while in the ^{13}C-n.m.r. spectrum there was only a signal at 32.6 ppm for 7′- and 10′-C and no peak at $\approx$27 ppm.[7] Again, there was a lack of clarity in the ^{1}H-n.m.r spectrum due to the 8′- and 9′-H's appearing as an overlapping multiplet at 5.37 ppm. Hydrolysis of ester **15** was achieved by treatment with aqueous sodium hydroxide (20%) in boiling dimethylsulphoxide to afford the corresponding acid **16** in 86% yield. As expected the ^{13}C-n.m.r. spectrum showed the 7′- and 10′-C's as a signal at 32.6 ppm. Finally, treatment of acid **16** with sodium ethane thiolate in dimethyl formamide under reflux[16] dimethylated the molecule to produce the **E**-anacardic acid **7** in 73% yield (see Scheme 2).

Thus the first synthesis of the unnatural anacardic acid **7** has been achieved in six steps and an overall yield of 21% starting from the known aldehyde **12**. Currently evaluations are being undertaken on a comparative basis with the known anacardic acid **2** to establish the role of the geometry of the 8′-9′ double bond in the C-15 side chain.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini-200 MHz spectrometer at ambient temperature in deuterochloroform using the residual chloroform as an internal reference. IR spectra were recorded on a Perkin-Elmer FT-IR 1000 PC spectrometer as either thin films or for Nujol mulls. Mass spectra were recorded on a VG Micromass 16F mass spectrometer at 70 eV or on a Finigan MAT GCQ. Elemental



Scheme 2.

analyses were performed on a Heraeus CHN-RAPID analyzer, or on a NA 1500, CARLO ERBA instrument. Melting points are quoted uncorrected and were recorded on a Fischer–John apparatus.

All reactions were monitored by thin layer chromatography (t.l.c.) carried out on silica gel GF254 (0.25 mm) plates. Column chromatography refers to dry-packed columns using Merck Kieselgel 60(70–230 mesh).

Solvents for chromatography were distilled before use. Tetrahydrofuran (THF) was dried immediately before use. Methylene chloride was distilled from P_2O_5. Triethylamine and DMF were stored over 3A molecular sieves. The phrase "residue obtained upon work-up" refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

Heptyldiphenylphosphine Oxide 8

Heptylbromide (0.57 ml, 3.7 mmol) and triphenylphosphine (0.92 g, 3.7 mmol) in acetonitrile (6 ml) were heated under gentle reflux for 72 h.

The residue obtained after removal of the solvent under vacuum was treated with water (20 ml) and a 45% (w/v) aqueous sodium hydroxide solution (20 ml) followed by heating under reflux for 30 min. The cooled solution was extracted with dichloromethane to afford the phosphine oxide **8** (0.90 g; 94%) as a white solid, m.p. 58–59°C (from hexane). ν_{max} 1180 and 1118 cm^{-1}; δ_H 0.84 (3H, t, $J = 6.8$ Hz, 7-H), 1.20–1.40 (8H, m, 3-, 4-, 5- and 6-H), 1.60 (2H, m, 2-H), 2.24 (2H, m, 1-H), and 7.41–7.70 (10H, m, Ph_2P). (Found: C, 75.7; H, 8.4%; M^+ 300. Calc. for $C_{19}H_{25}PO$: C, 75.9; H, 8.4%; M^+ 300).

7-Diphenylphosphinoylhexadecan-8-ol 9a and 9b

To a stirred solution of phosphine oxide **8** (2.0 g; 6.65 mmol) in tetrahydrofuran (THF) (10 ml) at 0°C was added *n*-butyllithium (6.0 ml of a 1.43 M solution) and stirring was continued for 30 min. The red solution was then cooled to −78°C and nonyl aldehyde (0.93 g; 6.65 mmol) in THF (5 ml) was added dropwise. The pale yellow solution was allowed to warm to 25°C over 2 h and then quenched with water (50 ml). The THF was removed under reduced pressure and brine (20 ml) was added and the aqueous solution exhaustively extracted with methylene dichloride. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (1 : 4) initially and later hexane–ethylacetate–acetic acid (7 : 3 : 1) as eluent to afford a mixture of *erythro* **9a** and *threo* **9b** alcohols (2.0 g; 70%) as white crystals, m.p. 80–81°C (from hexane). ν_{max} 3338 and 1158 cm^{-1}; δ_H 0.78 and 0.86 (each 3H, t, $J = 6.8$ Hz, 16- and 1-H), 1.04–1.85 (25H, m, 2- to 6-H and 9- to 15-H and 8-OH), 4.00 (1H, m, 7-H), 4.20 (1H, m, 8-H), and 7.45–7.83 (10H, M, Ph_2P). δ_C due to the numerous overlapping peaks, only two vital signals are quoted here viz. 70.04 and 72.70 in the ratio of 4 : 1. (Found: C, 76.1; H, 10.4%; M^+ 442. Calc. for $C_{28}H_{43}PO$: C, 75.9; H, 9.8%; M^+ 442).

7-Diphenylphosphinohexadecan-8-one 10

To a solution of oxalyl chloride (1.8 ml; 20.9 mmol) in dichloromethane (50 ml) at −50°C was added dropwise dimethylsulphoxide (3.5 ml; 45.5 mmol) under nitrogen. Stirring was continued for 10 min at this temperature and then the alcohol mixture of **9a/9b** (8.4 g; 19 mmol) in dichloromethane (25 ml) was added dropwise over 5 min. After stirring and additional 20 min at this temperature, triethylamine (9.5 ml; 68 mmol) was added over 5 min and the resultant mixture allowed to warm to 25°C over 1 h. Water (100 ml) was added and the aqueous mixture was extracted with

dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (2 : 3) as eluent to afford ketone **10** (6.35 g; 76%) as white crystals, m.p. 67–68°C (from hexane). ν_{max} 1705 and 1180 cm^{-1}; δ_H 0.80 and 0.85 (each 3H, t, $J = 6.8$ Hz, 1- and 16-H), 0.95–1.40 (22H, m, 2- to 6-H and 10- to 15-H), 2.42 (2H, m, 9-H), 3.54 (1H, dt, $J = 11.5$ and 3.0 Hz, 7-H), and 7.44–7.83 (10H, m, Ph_2P). δ_C 13.9, 14.0, 22.4, 22.6, 23.0, 28.6, 28.8 (×2), 29.0, 29.3, 31.3, 31.7, 43.8, 56.5, 57.7, 128.6, 128.7, 128.8, 128.9, 130.3, 131.2, 131.4, 131.5, 132.1, 132.2 (×2), 132.4, and 207.8. (Found: C, 76.1; H, 9.1% M^+ 440. Calc. for $C_{28}H_{41}PO_2$: C, 76.3; 9.3% M 440).

7-Diphenylphosphinoylhexadecan-8-ol 9a and 9b

To ketone **10** (470 mg; 1.07 mmol) in ethyl alcohol (20 ml) was added sodium borohydride (60 mg; 1.51 mmol) and the resulting mixture was stirred and heated under reflux for 3 h. Saturated ammonium chloride (15 ml) was added to the cooled solution and the ethyl alcohol was removed under reduced pressure. Brine (15 ml) was added to the residue followed by extraction with dichloromethane. The residue obtained upon work-up was chromatographed using hexane–ethyl acetate–acetic acid (7 : 3 : 1) as eluent to afford a mixture of *erythro* **9a** and *threo* **9b** alcohols (370 mg; 80%), as white crystals m.p. 115–116°C (from hexane). ν_{max} 3326 and 1164 cm^{-1}; δ_H 0.80 and 0.83 (each 3H, t, $J = 6.8$ Hz, 16- and 1-H), 1.10–1.65 (24H, m, 2- to 6-H and 9- to 15-H), 1.42 (1H, brs, 8-OH, D_2O exchangeable), 3.90 (1H, m, 7-H), 4.21 (1H, t, $J = 7.2$ Hz, 8-H), and 7.46–7.90 (10H, m, Ph_2P). δ_C 14.0, 14.1, 22.2, 26.6, 28.7, 29.1, 29.2, 29.3, 29.4, 31.2, 31.4, 31.8, 36.8, 42.2, 70.0, 72.7, 128.5, 127.7 (×2), 128.9, 129.0, 130.6, 130.8, 131.0, 131.1, 131.3 and 131.7 (×2). (Found: C, 76.0; H, 10.3%; M^+ 442. Calc. for $C_{28}H_{43}PO$: C, 75.9; H, 9.8%; M 442).

E 7-Hexadecene 11

Sodium hydride (91 mg; 55% dispersion in oil, 2.0 mmol) was added in one portion to a stirred solution of the alcohol **9a/9b** (*vide supra*) (460 mg, 1.04 mmol) in dimethyl formamide (25 ml) at 25°C. The clear solution was heated to 50°C for 30 min after which time a white precipitate formed. Water (30 ml) was added to the cooled mixture followed by brine (20 ml) and the resulting clear solution was extracted with ether and the residue obtained upon work up was chromatographed using ethyl acetate–hexane (1 : 9) as eluent to yield hexadecane **11** (117 mg; 76%) as a colourless oil

comprising an **E : Z** ratio of 5 : 1 ν_{max} 965 and 723 cm^{-1}; δ_H 0.87 (6H, t, $J = 6.8$ Hz, 7- and 16-H), 1.26 (20H, 2- to 5- and 10- to 15-H), 1.95 (4H, m, 6- and 9-H), and 5.38 (2H, m, 7- and 8-H). δ_C 14.1 (×2), 22.6, 22.7, 27.2, 28.8, 29.2, 29.3, 29.5, 29.6, 29.7, 31.8, 31.9, 32.6 (×2) and 130.5 (×2). (Found: C, 85.7; H, 14.4%; M^+ 224. Calc. for $C_{16}H_{32}$: C, 85.7, H, 14.2%, M 224).

Ethyl 6-(8′-Hydroxy-9′-diphenylphosphinopentadecyl)-2-methoxybenzoate 13a/13b

Applying the same synthetic protocol described for the synthesis of alcohols **9a/9b** but using aldehyde **12**[6] afforded a thick oil which was flash chromatographed using hexane–ethyl acetate–acetic acid (7 : 3 : 1) as eluent to yield a diastereoisomeric mixture of alcohols **13a/13b** in 76% yield as white crystals, m.p. 95–112°C. ν_{max} 3327, 1727 and 1165 cm^{-1}.

Ethyl 6-(8′-Oxo-9′-diphenylphosphinoylpentadecyl)-2-methoxybenzoate 14

Applying the same Swern synthetic protocol as before, oxidation of the mixture of alcohols **13a/13b** afforded after chromatography using hexane–ethyl acetate–acetic acid as eluent, the ketone **14** in 83% yield as thick yellow oil. ν_{max} 1728, 1713 and 1190 cm^{-1}; δ_H 0.81 (3H, t, $J = 7.0$ Hz, 15′-H), 1.10–1.58 (20H, m, 2′- to 6′- and 10′- to 14′-H), 1.36 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 2.40 (2H, t, $J = 7.0$ Hz, 7′-H), 2.51 (2H, t, $J = 7.4$ Hz, 1′-H), 3.56 (1H, ddd, $J = 12.8$, 11.6 and 3.0 Hz, 9′-H), 3.80 (3H, s, OCH_3), 4.38 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 6.76 (1H, d, $J = 8.2$ Hz, 3-H), 6.81 (1H, d, $J = 8.2$ Hz, 5-H), 7.25 (1H, t, $J = 8.2$ Hz, 4-H), and 7.45–7.80 (10H, m, Ph_2P); δ_C 13.9, 14.3, 22.4 (×2), 23.0, 26.7, 28.6, 28.7 (×2), 28.8, 29.2, 29.3, 31.1, 31.3, 33.3, 43.8, 55.8, 56.5, 57.6, 61.1, 108.5, 121.5, 123.8, 128.6, 128.7, 128.8, 128.9, 130.2, 131.2, 131.4 (×2), 131.5, 132.2, 141.2, 156.3, 168.6 and 207.8. (Found: C, 73.4; H, 8.2%; M^+ 604. Calc. for $C_{37}H_{49}PO_5$: C, 73.4; H, 8.2%; M 604).

Threo Ethyl 6-(8′-Hydroxy-9′-diphenylphosphinoylpentadecyl)-2-methoxybenzoate 13b

Ketone **14** was reduced by sodium borohydride as described earlier to afford, after chromatography using hexane–ethyl acetate–acetic acid (7 : 3 : 1)

as eluent, pure *threo* alcohol **13b** in 80% yield, as white crystals, m.p. 130–131°C (from ethyl acetate–hexane). ν_{max} 3358, 1726 and 1164 cm^{-1}; δ_H 0.80 (3H, t, $J = 7.0$ Hz, 15′-H), 1.09–1.60 (23 H, m, 2′- to 7′-H, and 10′- to 14′-H, and 8′-OH), 1.36 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 2.10–2.40 (2H, m, 8′- and 9′-H), 2.45 (2H, t, $J = 8.0$ Hz, 1′-H), 3.80 (3H, s, OCH_3), 4.37 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 6.77 (1H, d, $J = 8.2$ Hz, 3-H), 6.80 (1H, d, $J = 8.2$ Hz, 5-H), 7.25 (1H, t, $J = 8.2$ Hz, 4-H), and 7.45–7.90 (10H, m, Ph_2P); δ_C 14.0, 14.3, 22.4 (×2), 26.2, 26.6, 28.5, 29.1, 29.3 (×2), 29.4, 31.2, 31.4, 33.4, 36.7, 42.0, 55.9, 61.1, 72.6, 108.5, 121.6, 123.2, 128.5, 128.7 (×3), 128.9, 130.0 (×2), 130.6, 130.8, 131.1, 131.3, 131.8, 141.3, 156.3, and 168.6. (Found: C, 73.1; H, 8.4%; M^+ 606. Calc. for $C_{37}H_{51}PO_5$: C, 73.2; H, 8.4%; M 606).

E Ethyl 2-Methoxy-6-(8′-pentadecenyl)benzoate 15

Treatment of the *threo* alcohol **13b** with 2 equivalents of sodium hydride as described earlier afforded, after chromatography using ethyl acetate–hexane (1 : 9) as eluent, the **E** olefin **15** in 65% yield as a clear oil and a single isomer as shown by GC-MS. ν_{max} 1731, 966 and 745 cm^{-1}; δ_H 0.87 (3H, t, $J = 7.0$ Hz, 15′-H), 1.27 (18H, m, 2′- to 6′-H and 11′- to 14′-H), 1.37 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.95 (4H, m, 7′- and 10′-H), 2.54 (2H, t, J 7.8 Hz, 1′-H), 3.81 (3H, s, OCH_3), 4.38 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 5.37 (2H, m, 8′- and 9′-H), 6.75 (1H, d, $J = 8.4$ Hz, 3-H), 6.80 (1H, d, $J = 8.4$ Hz, 5-H), and 7.25 (1H, t, $J = 8.4$ Hz, 4-H); δ_C 14.1, 14.3, 22.6, 28.8, 29.0, 29.3, 29.5, 29.6 (×2), 31.2, 31.7, 32.6 (×2), 33.4, 55.9, 61.1, 108.5, 121.6, 123.9, 130.2, 130.4, 130.5, 141.3, 156.3 and 168.6. (Found: C, 77.3; H, 10.3%; M^+ 388. Calc. for $C_{25}H_{40}O_3$: C, 77.2; H, 10.3%; M 388).

E 2-Methoxy-6-(8′-pentadecenyl)benzoic Acid 16

A solution of the ester **15** (388 mg; 1 mmol) in dimethylsulphoxide (2.3 mol) was treated with aqueous sodium hydroxide (2.3 ml of a 5 M solution, 11.5 mmol) and heated at 110°C for 12 h under reflux. The cooled solution was acidified with 1 M HCl, diluted to 30 ml with water and extracted with ethyl acetate. The residue obtained upon work-up afforded the **E**-benzoic acid **16** (310 mg; 86%) as white crystals, m.p. 45–46°C (from hexane). ν_{max} 3258, 1715 and 966 cm^{-1}; δ_H 0.87 (3H, t, $J = 6.4$ Hz, 15′-H), 1.28 (16H, m, 3′- to 6′-H and 11′- to 14′-H), 1.60 (2H, m, 2′-H), 1.95 (4H, m, 7′- and 10′-H), 2.73 (2H, t, $J = 7.6$ Hz, 1′-H), 3.80 (3H, s, OCH_3), 5.36 (2H, m, 8′- and 9′-H), 6.81 (1H, d, $J = 8.4$ Hz, 3-H), 6.87

(1H, d, $J = 8.4$ Hz, 5-H), and 7.31 (1H, t, $J = 8.4$ Hz, 4-H); δ_C 14.1, 22.6, 28.8, 29.1, 29.3, 29.5, 29.6 (×2), 31.3, 32.6 (×2), 33.9, 56.2, 108.7, 121.4, 122.6, 130.4, 130.5, 131.2, 143.4, 156.8 and 170.8. (Found: C, 76.6; H, 10.2%; M^+ 360. Calc. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.2%; M 360).

E 6-(8′-Pentadecenyl)salicyclic Acid 7

To a stirred suspension of sodium hydride (18 mg; 55% dispersion in oil; 0.44 mmol) in dimethyl formamide (2 ml) at 0°C was added dropwise ethanethiol (0.03 ml; 0.42 mmol) under nitrogen. The mixture was stirred at 25°C for 30 min and then a solution of acid **16** (50 mg; 0.133 mmol) in dimethyl formamide (3 ml) was added and the resulting solution was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was acidified with 3 M HCl and extracted with ethyl acetate. The residue obtained upon work up was chromatographed using ethyl acetate–hexane (1 : 9) as eluent to afford the **E**-salicyclic acid **7** (35 mg; 73%) as white crystals, m.p. 68–69°C (from ethyl acetate–hexane). ν_{max} 3572–2540, 1661 and 966 cm^{-1}; δ_H 0.87 (3H, t, $J = 6.6$ Hz, 15′-H), 1.28 (16H, m, 3′- to 6′-H and 11′- to 14′-H), 1.60 (2H, m, 2′-H), 1.94 (4H, m, 7′- and 10′-H), 2.80–2.96 (2H, m, 1′-H), 5.37 (2H, m, 8′- and 9′-H), 6.77 (1H, d, $J = 8.2$ Hz, 3-H), 6.86 (1H, d, $J = 8.2$ Hz, 5-H) and 7.35 (1H, t, $J = 8.2$ Hz, 4-H). δ_C 14.1, 22.6, 28.2, 29.1, 29.3, 29.5, 29.6, 29.8, 31.3, 31.7, 32.6 (×2), 33.8, 97.5, 115.8, 122.4, 130.4 (×2), 135.2, 140.6, 163.8 and 174.2. (Found: C, 76.6; H, 9.6%; M^+ 346.2513. Calc. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.8%; M 346.2508).

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