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SYNTHESES OF ANACARDIC ACIDS AND GINKGOIC ACID

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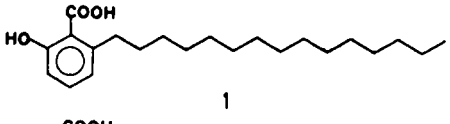
Abstract: Syntheses of two anacardic acids [6-pentadecyl- and 6-(10'-pentadecenyl)salicylic acid], inhibitors of prostaglandin synthetase and of the growth of certain insects, and ginkgoic acid via directive metallation is reported.

According to the information provided by the "Bwana Mganga," or local medicine man,[1] the hot water extract of the root of Ozoroa mucronata (Anacardiaceae) is drunk to elicit spontaneous abortion. It is also used to cure gonorrhea, diarrhea, intestine parasites and stomach trouble.[2] One of the authors (I. K.) found that the methylene chloride soluble portion of the methanol extract of the root inhibits prostaglandin synthetase activity.[3] The structures of the bioactive compounds were shown to be anacardic acids 1 and 2 by means of spectroscopic analysis.[3] Anacardic acid 1 is also found in cashew nut (Anacardium occidentale) shell oil.[4] The structurally related ginkgoic acid 3 occurs in Ginkgo biloba.[4]



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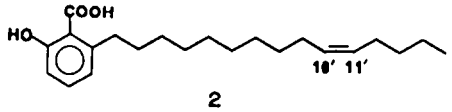

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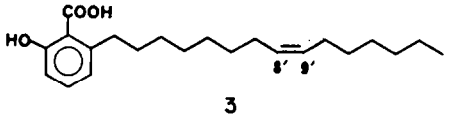
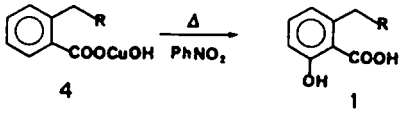


3

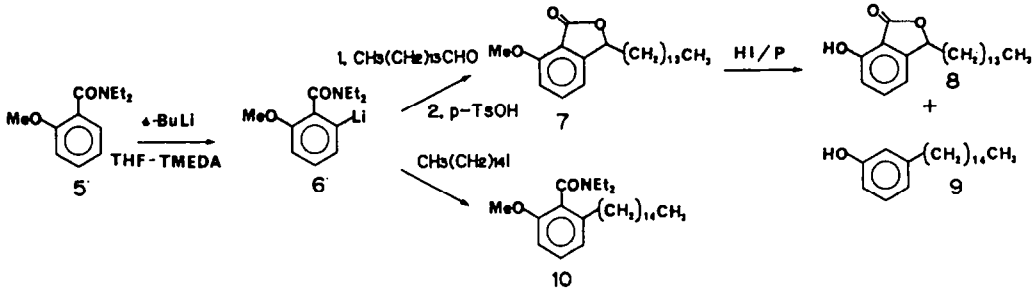
Although the three have relatively simple structures, available methods for the synthesis of 6-alkylsalicylic acids with long alkyl side chain were insufficient. For example, the thermal rearrangement of the basic copper salt of 2-alkylbenzoic acid 4 resulted in a very low yield of salicylic acid 1.[5]



4 1

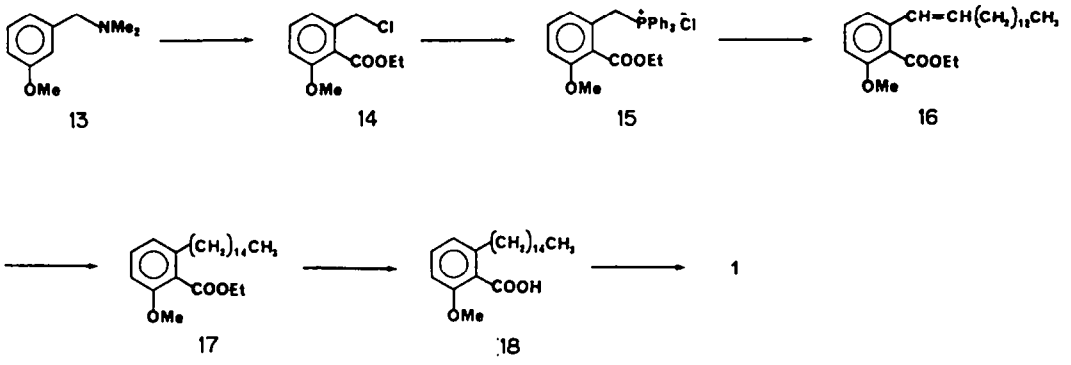
Herein we report a convenient method for the preparation of 6-alkylsalicylic acids. Our attempt for introducing a side chain into benzene nucleus relies on the well-documented directive metallation[6] followed by trapping with electrophiles.

Lithiation of 2-methoxy-N,N-diethylbenzamide 5 was effected with sec-butyllithium in THF and tetramethylethylenediamine (TMEDA) at -78 °C using the Snieckus conditions.[7] The lithio derivative 6 was then treated with pentadecanal. The crude product was heated with p-toluenesulfonic acid in toluene to give 3-alkylphthalide 7 in 37% yield after chromatographic purification. In accordance with the earlier work,[5] many attempts towards hydrogenolysis of this phthalide in the hope of formation of 6-alkylsalicylic acid failed (Et_3SiH/CF_3COOH,[8] H_2/Pd-C, Zn-Cu/AcOH[9]). Classical reduction using hydriodic acid and red phosphorus gave the demethoxy compound 8 and 3-pentadecylphenol 9. Direct alkylation of the lithio derivative 6 with 1-iodopentadecene gave 2-methoxy-6-pentadecyl-N,N-diethylbenzamide 10 in 47% yield. However, this benzamide proved remarkably resistant to alkaline or acidic hydrolysis due to severe steric hindrance.



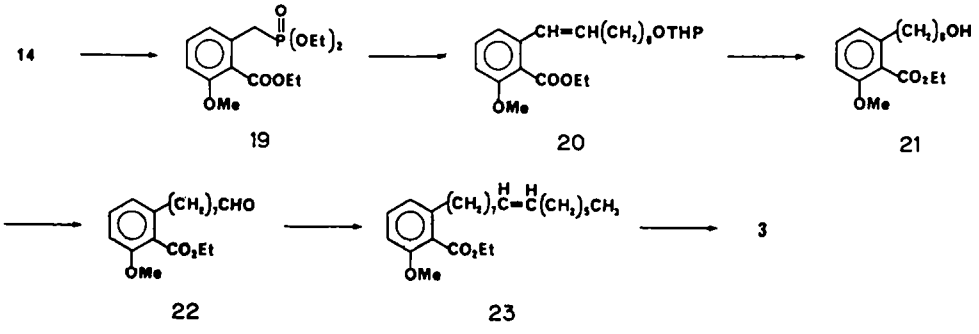
In view of the great difficulty in obtaining 6-alkylsalicylic acid by direct alkylation, we carried out another approach. The next approach was based on the observation that the treatment of N,N-dimethylaminomethylbenzene 11 with n-butyl lithium followed by quenching with ethyl chloroformate gave ethyl 2-chloromethylbenzoate 12.[10]

Lithiation of 3-methoxy-N,N-dimethylbenzylamine 13 with n-butyllithium in THF at 0 °C followed by quenching with a large excess of ethyl chloroformate gave 6-chloromethylsalicylate in 67% yield. We then employed the Wittig reaction to extend the side chain at the C-6 position of 14. The phosphonium salt 15 was treated with lithium bis(trimethylsilyl)amide at -78 °C and quenched with tetradecanal to give 1:3 mixture of cis and trans olefins 16 in 50% yield.[11]



Reduction of the double bond of 16 was fairly difficult. It was finally effected using 5% platiunm on carbon as the catalyst to give 17. Prolonged alkaline hydrolysis in refluxing aqueous DMSO[12] gave the salicylic acid 18 in good yield. The final demethylation with boron tribromide gave the salicylic acid 1, which was identical with natural anacardic acid (mp, TLC, IR and NMR). Although this method is not straightforward, anacardic acid was obtained in 17% overall yield from 13.

Ginkgoic acid was prepared by using a similar method. The Horner-Emmons olefination[13] of the carbanion of the phosphonate 19 with ω-tetrahydropyranyloxyheptanal[14] in a mixture of THF and HMPA at -20 °C gave a 1:3 mixture of cis and trans olefins 20 in 77% yield. Hydrolysis of the THP ether followed by hydrogenation of the double bond as before led to the saturated alcohol 21 in 97% yield. Oxidation of the alcohol 21 by Swern's procedure[15] afforded the aldehyde 22 in 78% yield. The latter was subjected to the Wittig reaction in THF at room temperature to give the cis olefin 23 in 77% yield (cis:trans=98:2). The signal in the ^{13}C NMR spectrum at 27.3 ppm was assigned to the two allylic carbons of C-7' and C-10', indicating that the double bond of 23 is cis.[16] The protecting groups were removed by successive treatment with sodium hydroxide in aqueous DMSO and with sodium ethanethiolate in DMF,[17] to give the salicylic acid 3 in an overall yield of 29% from 14. The direct comparison of synthetic 3 with natural ginkgoic acid proved the two to be identical (mp, TLC, GLC, IR, NMR and MS).[18]



A more direct method for the preparation of 6-alkenylsalicylic acid was the alkylation of 6-(phenylsulfonylmethyl)salicylate 29, which was obtained from the chloride 14 and benzenesulfinic acid sodium salt in DMF.[19] We applied this method for the synthesis of anacardic acid ($C_{15:1}$)[20] 2. The necessary alkenyl bromide 28 was prepared according to the following scheme.

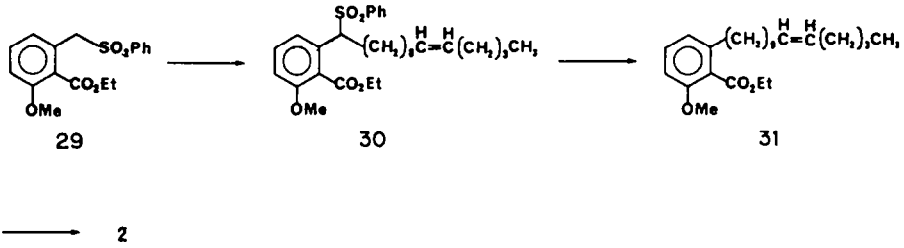
$$HO(CH_2)_9OH \longrightarrow THPO(CH_2)_9OH \longrightarrow THPO(CH_2)_8CHO \longrightarrow$$

24 25 26

$$THPO(CH_2)_8\overset{Z}{C}H{=}CH(CH_2)_3CH_3 \longrightarrow Br(CH_2)_8\overset{Z}{C}H{=}CH(CH_2)_3CH_3$$

27 28

Partial protection of 1,9-nonanediol with 1 equivalent of dihydropyran and pyridinium p-toluenesulfonate[21] gave the monoalcohol 25 in 60% yield. Oxidation of 25 by Swern's procedure[15] gave the aldehyde 26 in 92% yield. The Wittig olefination of 26 with pentylidenetriphenylphosphorane gave the olefin 27 in 72% yield. Hydrolysis of the THP ether followed by tosylation and bromination gave the bromide 28 in 57% yield from 27. Treatment of the sulfone 29 with LDA at -68 °C resulted in a brown enolate within 10 minutes. Quenching the enolate with the bromide 28 gave the alkylated product 30 in 64% yield. The benzenesulfonyl group was removed by reduction of 30 with 5% sodium amalgam[22] to give the ester 31 in 88% yield. The two protecting groups were removed by the same method as already mentioned to give anacardic acid ($C_{15:1}$) 2 in 62% yield. The comparison of synthetic 2 with the natural anacardic acid ($C_{15:1}$) proved the two to be identical (IR, NMR and MS).



29 30 31

$\longrightarrow$ 2

In conclusion, we have found a more versatile pathway for construction of poly-unsaturated 6-alkenylsalicylic acids. Further efforts are being directed towards their syntheses.

EXPERIMENTAL

All b. ps and m. ps were uncorrected. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Triethylamine, tetramethylethylenediamine and DMF were distilled from CaH_2. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (69F-254). UV-light or 7% phosphomolybdic acid in ethanol followed by heating was used as developing agent. E. Merck silica gel (60, particle size 0.040-0.063 mm) and Fuji silica gel (KC-2, 100-200 mesh) were used for column chromatography. IR spectra were recorded on a Nippon Bunko A-100 IR spectrometer. High-resolution electron-impact mass spectra were obtained on a JEOL LMS-HX 100 spectrometer. 60 MHz and 200 MHz ^1H NMR spectra were recorded on Hitachi R-600 and JEOL FX-200 spectrometers, respectively. Elemental analyses were performed by Mr. Goda, Osaka City University.

3-Methoxy-N,N-dimethylbenzylamine 13. A mixture of m-anisic acid (5 g, 33 mmol) and thiony chloride (7 mL, 100 mmol) was stirred at room temperature for 1 h. After removal of the excess reagent, the residue was diluted with methylene chloride (CH_2Cl_2) and 14 mL of 50% dimethylamine was added. The mixture was stirred for 1 h at room temperature and then poured into water and extracted with CH_2Cl_2. The organic layer was washed with 1 M HCl and brine, and dried ($MgSO_4$), and evaporated to give 5.257 g of a benzamide (89%) as a clear oil, b.p. 126-127 °C/ 0.4 Torr.

To a suspension of lithium aluminum hydride (1.78 g, 46.9 mmol) in 30 mL of dry THF was added a solution of the benzamide (7.657 g, 42.7 mmol) in 30 mL of THF at 0 °C. The mixture was stirred at room temperature for 30 min and then heated under reflux for 2 h. The mixture was

treated with by successive dropwise addition of 2 mL of 5% NaOH solution. The resulting precipitates were filtered and washed with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Distillation gave 13 (6.323 g, 90%) as a pale yellow oil, b.p. 43-49 °C/0.12 Torr. IR(neat); 2830, 1605, 1275, 1155, 1050, 785 and 695 cm^{-1}. ^1H NMR (60 MHz, CCl_4); 2.16 (s, 6H), 3.32 (s, 3H), 3.75 (s, 3H) and 6.55-7.25 ppm (m, 4H). MS; m/z 165 (M^+), 122 and 58 (base peak). Calcd. for $C_{10}H_{15}NO$: 165.1154. Found: 165.1133.

Ethyl 6-chloromethyl-2-methoxybenzoate 14 . To a stirred solution of 13 (1.5 g, 9.1 mmol) in 25 mL of dry THF was added n-butyllithium (1.6 M hexane solution, 8 mL, 12.8 mmol) under argon atmosphere at 0 °C. After the solution had been stirred at room temperature for 1 h, ethyl chloroformate (5 mL, 52.3 mmol) was added at -78 °C and the mixture was stirred at the same temperature for 1 h and was allowed to stand at room temperature overnight. The mixture was quenched with water, extracted with CH_2Cl_2 and the extract was concentrated to yield an oil. Distillation gave pure 14 (1.407 g, 68%) as a pale yellow oil, b.p. 105-112 °C/0.55 Torr. IR(neat); 1720, 1580, 1265 and 725 cm^{-1}. ^1H NMR (60 MHz, CCl_4); 1.37 (t, 3H, J=7 Hz), 3.82 (s, 3H), 4.34 (q, 2H, J=7 Hz), 4.52 (s, 2H) and 6.73-7.43 ppm (m, 3H). MS; m/z 230, 228 (M^+), 185, 184, 183, 182 (base peak), 163, 148 and 105. Calcd. for $C_{11}H_{13}ClO_3$: 228.0576. Found: 228.0536.

2-Ethoxycarbonyl-3-methoxybenzyltriphenylphosphonium chloride 15 . A solution of 14 (0.84 g, 3.7 mmol) and triphenylphosphine (0.923 g, 3.7 mmol) in 6 mL of dry acetonitrile was refluxed for 3 days. The solvent was removed and the residue was triturated with dry ether, filtered and evaporated under vacuum to afford 15 (1.758 g, 98%) as a white powder, m.p. 200-206 °C. IR(Nujol); 1720, 740 and 690 cm^{-1}.

Ethyl 2-methoxy-6-(1-pentadecyl)benzoate 16 . To a suspension of the phosphonium salt 15 (1 g, 2.03 mmol) in 10 mL of dry THF was added dropwise lithium bis(trimethylsilyl)amide (1 M hexane solution, 2.5 mL, 2.4 mmol) at -78 °C under argon atmosphere. After the solution had been stirred at -78 °C for 30 min, a solution of tetradecanal (0.517 g, 2.4 mmol) in 5 mL of THF was added dropwise and then allowed to warm to room temperature overnight. After removal of the solvent, the residue was diluted with hexane and the resulting precipitates were filtered. The filtrate was concentrated and chromatographed on silica gel (95:5 then 1:1 hexane-AcOEt as eluent) to afford 16 (0.39 g, 50%) as a yellow oil. GLC; OV-101 (3%), 1.1 m column, 180-230 °C, t 18.7 (cis) and 22.8 min (trans), (cis:trans=1.1:1). IR(neat); 1720, 1570, 1260, 1105 and 1065 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.98 (t, 3H, J=7 Hz), 1.26 (m, 22H), 1.35, 1.38 (pair of t, 3H, J=7 Hz), 2.15 (m, 2H), 3.82, 3.83 (pair of s, 3H), 4.35, 4.40 (pair of q, 2H, J=7 Hz), 5.71 (cis, dt, J=11.5, 7.4 Hz), 6.20 (trans, dt, J=15.8, 6.8 Hz), 6.32 (d, J=15.8 Hz), 6.35 (d, J=11.5 Hz), 6.76 (dd, J=8.5, 1.5 Hz), 7.09 (d, J=8.5 Hz), 6.80 (d, J=8 Hz), 6.85 (d, J=8 Hz), 7.26 (t, J=8.5 Hz) and 7.28 ppm (t, J=8 Hz). MS; m/z 388 (M^+), 359, 342, 205 and 174 (base peak). Calcd. for $C_{25}H_{40}O_3$: 388.2977. Found: 388.2983.

Ethyl 2-methoxy-6-pentadecylbenzoate 17 . A mixture of the olefin 16 (0.394 g, 1.01 mmol) and 5% Pt-C (0.12 g) in 6 mL of ethyl acetate was shaken for 2 h under hydrogen atmosphere. The catalyst was filtered through a short column of silica gel and the filtrate was concentrated. The crude oil was purified by flash chromatography (SiO_2, 9:1 hexane-ether as eluent) to afford 0.242 g (61%) of 17 as colorless needles, m.p. 40.5-41.5 °C (sublimation). IR($CHCl_3$); 3020, 2930, 2860, 1720, 1585, 1470, 1270, 1110, 1075 and 720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.88 (t, 3H, J=7 Hz), 1.27 (m, 22H), 1.38 (t, 3H, J=7 Hz), 1.56 (m, 2H), 2.54 (m, 2H), 3.81 (s, 3H), 4.38 (q, 2H, J=7 Hz), 6.74 (d, 1H, J=8 Hz), 7.78 (d, 1H, J=8 Hz) and 7.24 ppm (t, 1H, J=8 Hz). MS; m/z 390 (M^+), 345, 194 and 161 (base peak). Calcd. for $C_{25}H_{42}O_3$: 390.3134. Found: 390.3136.

2-Methoxy-6-pentadecylbenzoic acid 18 . A solution of 17 (0.17 g, 0.44 mmol) and 1 mL of 20% NaOH solution in 1 mL of DMSO was heated at 120 °C for 15 h. The mixture was acidified with 1 M HCl and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give 18 as colorless needles (0.146g, 93%), m.p. 77.5-78.5 °C (from ether-hexane). IR ($CHCl_3$); 3500-2300, 3020, 2940, 2860, 1705, 1590, 1470, 1270, 1080, 935 and 720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.88 (t, 3H, J=8 Hz), 1.25 (m, 22H), 1.58 (m, 2H), 2.73 (m, 2H), 3.89 (s, 3H), 6.79 (d, 1H, J=8 Hz) and 7.30 ppm (t, 1H, J=8 Hz). Anal. calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56; O, 13.24. Found: C, 76.03; H, 10.49; O, 13.48.

6-Pentadecylsalicylic acid 1 . To a solution of 18 (0.098 g, 0.27 mmol) in 5 mL of dry CH_2Cl_2 was added boron tribromide (1 M solution in CH_2Cl_2, 0.6 mL) dropwise at -40°C under argon atmosphere. After stirring for 2 h at room temperature the mixture was poured into ice-water and was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 1 as colorless needles (0.81 g, 86%), m.p. 90.2-91.5 °C (from hexane). IR($CHCl_3$); 3030, 2920, 2870, 1645, 1600, 1445, 1205, 780 and 710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.87 (t, 3H, J=7.2 Hz), 1.23 (m, 22H), 1.58 (m, 2H), 2.96 (m, 2H), 6.75 (d, 1H, J=8.2 Hz), 6.85 (d, 1H, J=8.2 Hz), 7.34 (t, 1H, J=8.2 Hz) and 10.99 ppm (br, 1H). Anal. calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.57; H, 10.31; O, 14.12.

7-Tetrahydropyranyloxyheptanal. To a mixture of 1,7-heptanediol (3.0 g, 22.7 mmol) and p-toluenesulfonic acid (0.04 g, 0.25 mmol) in 15 mL of dry CH_2Cl_2 was added a solution of dihydropyran (2.48 mL, 27.2 mmol) in 15 mL of dry CH_2Cl_2. After stirring for 1.5 h the mixture was washed with sat. $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated to give a THP ether as a yellow oil (5.478 g).

To a solution of oxalyl chloride (0.25 mL, 2.8 mmol) in 15 mL of dry CH_2Cl_2 at -50 °C was added a solution of DMSO (0.41 mL, 5.8 mmol) in 15 mL of dry CH_2Cl_2. After the mixture had been stirred for 5 min, a solution of the THP ether (0.5 g, 2.3 mmol) in 9 mL of CH_2Cl_2 was added within 5 min, and stirring was continued for an additional 15 min. Triethylamine (0.95 mL, 12 mmol) was added and the mixture was stirred for 5 min and then allowed to warm to room temperature. Water was then added and the aqueous phase was extracted with CH_2Cl_2. Combined extracts were then washed with brine, dried and concentrated. The residue was purified by chromatography (SiO_2, 95:5 then 6:1 hexane-AcOEt as eluent) to give 7-tetrahydro-pyranyloxyheptanal (0.286 g, 64% from heptanediol) as a colorless oil. IR(neat); 2700, 1720, 1200, 1120, 1030, 905, 865 and 810 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$); 1.46-1.64 (m, 14H), 2.45 (dt, 2H, J=6, 2 Hz), 3.22-4.09 (m, 4H), 4.58 (br,

1H), 9.81 (t, 1H, J=2 Hz). MS; m/z 213 (M^+-1), 196, 184, 101, 95, 85 (base peak), 69 and 56. Calcd. for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1569.

P-(2-Ethoxycarbonyl-3-methoxybenzyl)-O,O-diethylphosphonate 19. A mixture of the benzoate 14 (1.3 g, 5.68mmol) and triethylphosphite (0.99 mL, 5.68 mmol) was refluxed for 3 h. The excess reagent was removed under reduced pressure to afford the phosphonate 19 (1.87 g, 100%) as a yellow oil. The product was used without further purification. IR(neat); 1720, 1600, 1585, 1470, 1260, 1030, 780 and 735 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$); 1.25 (t, 3H, J=7.5 Hz), 3.09 (s, 1H), 3.47 (s, 1H), 3.85 (s, 3H), 4.22 (q, 2H, J=7.5 Hz), 4.44 (q, 2H, J=7.5 Hz), 6.82-7.82 ppm (m, 3H). MS; m/z 330 (M^+), 284 (base peak), 228, 165 and 148. Calcd. for $C_{15}H_{23}O_6P$: 330.1233. Found: 330.12 33.

Ethyl 2-methoxy-6-(8-tetrahydropyranyloxy-1-octenyl)benzoate 20. To a solution of the phosphonate 19 (1.78 g, 5.39 mmol) and 2 mL of HMPA in 15 mL of dry THF at -60 °C was added a solution of potassium t-butoxide (1.21 g, 10.8 mmol) in 7 mL of dry THF under argon atmosphere. The mixture was stirred for 30 min at that temperature, and the solution of 7-tetrahydropyranyloxyheptanal (0.49 g, 2.29 mmol) in 6 mL of dry THF was added. After the mixture had been stirred for 5 min at -20 °C, it was allowed to warm to room temperature and stirred overnight, quenched with sat. NH_4Cl solution and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 9:1 hexane-AcOEt as eluent) to afford olefin 20 (0.688 g, 77%) as a pale yellow oil. IR(neat); 1725, 1650, 1595, 1575, 1465, 1270, 1110, 1070, 1030, 970 and 735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 1.36-1.93 (m, 14H), 1.37 (t, 3H, J=7 Hz), 2.18 (q, 2H, J=6 Hz), 3.39 (dt, 1H, J=10, 7 Hz), 3.49 (m, 1H), 3.74 (dt, 1H, J=10, 7 Hz), 3.81 (s, 3H), 3.85 (m, 1H), 4.41 (q, 2H, J=7 Hz), 4.57 (m, 1H), 6.21 (dt, 1H, J=15.8, 6 Hz), 6.33 (d, 1H, J=15.8 Hz), 6.77 (d, 1H, J=8.2 Hz), 7.11 (d, 1H, J=8.2 Hz) and 7.27 ppm (t, 1H, J=8.2 Hz). MS; m/z 390 (M^+), 344, 306, 260 (base peak), 187, 174 and 85. Calcd. for $C_{23}H_{34}O_5$: 390.2407. Found: 390.2423.

Ethyl 6-(8-hydroxyoctyl)-2-methoxybenzoate 21. A mixture of the THP ether 20 (0.52g, 1.33 mmol) and p-toluenesulfonic acid (0.062 g, 0.326 mmol) in 10 mL of 95% methanol was stirred for 2 h at room temperature. Anhydrous K_2CO_3 (0.048 g) was added to the mixture and filtered. After removal of the solvent crude product was purified by column chromatography (SiO_2, 3:1 hexane-AcOEt as eluent) to afford ethyl 2-methoxy-6-(8-hydroxy-1-octenyl)benzoate as a pale yellow oil (0.388 g, 95%). GLC; SE 30 (3%), 1.1 m column, 100-230 °C, t_r 27.5 (cis), 29.8 min (trans), (trans:cis=1:3). IR(neat); 3380, 1720, 1645, 1595, 1575, 1470, 1265, 1110, 1065, 960 and 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 1.37 (t, 3H, J=7 Hz), 1.2-1.8 (m, 8H), 1.64 (br, 1H), 2.19 (q, 2H, J=7 Hz), 3.63 (t, 2H, J=7 Hz), 3.81 (s, 3H), 4.41 (q, 2H, J=7 Hz), 6.20 (dt, 1H, J=15.6, 7 Hz), 6.34 (d, 1H, J=15.6 Hz), 6.78 (d, 1H, J=8.2 Hz), 7.10 (d, 1H, J=8.2 Hz) and 7.28 ppm (t, 1H, J=8.2 Hz). MS; m/z 306 (M^+), 260, 205, 187 (base peak), 174, 161, 147, 132 and 81.

A mixture of the above alcohol (0.1 g, 0.33 mmol) and 5% Pt-C (0.036 g) in 3 mL of ethyl acetate was shaken under hydrogen atmosphere. The catalyst was filtered through a short column of silica gel and the filtrate was concentrated to give 21 (0.102 g, 100%) as a pale yellow oil. IR(neat); 3380, 1725, 1600, 1585, 1470, 1440, 1270, 1110, 1085, 1020, 795 and 750 cm^{-1}. ^1H NMR (200 MHZ, $CDCl_3$); 1.24-1.44 (m, 8H), 1.38 (t, 3H, J=7 Hz), 1.57 (m, 4H), 1.73 (br s, 1H), 2.57 (t, 2H, J=7.4 Hz), 3.67 (t, 2H, J=7 Hz), 3.83 (s, 3H), 4.41 (q, 2H, J=7 Hz), 6.77 (d, 1H, J=8.2 Hz), 6.82 (d, 1H, J=8.2 Hz) and 7.27 ppm (t, 1H, J=8.2 Hz). MS; m/z 308 (M^+), 262 and 161 (base peak). Calcd. for $C_{18}H_{28}O_4$:308.1988. Found: 308.1982.

Ethyl 6-(7-formylheptyl)-2-methoxybenzoate 22. To a solution of oxalyl chloride (0.14 mL, 1.63 mmol) in 3 mL of dry CH_2Cl_2 at -78 °C was added a solution of DMSO (0.24 mL, 3.4 mmol) in 3 mL of dry CH_2Cl_2. After the mixture had been stirred for 5 min, a solution of the alcohol 21 (0.398 g, 1.26 mmol) in 3 mL of CH_2Cl_2 was added within 5 min. Triethylamine (0.55 mL, 9.35 mmol) was added and the mixture was stirred for 5 min and then allowed to warm to room temperature. Water was then added and the aqueous phase was extracted with CH_2Cl_2. Combined extracts were washed with 1 M HCl, sat $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 9:1 hexane-AcOEt as eluent) to give 22 as a colorless oil (0.302 g, 78%). IR(neat); 2720, 1725, 1600, 1585, 1470, 1270, 1110, 1075, 1020, 795and 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 1.31 (br s, 6H), 1.37 (t, 3H, J=7 Hz), 1.60 (m, 4H), 2.41 (dt, 2H, J=2.2, 7.2 Hz), 2.56 (t, 2H, J=7.2 Hz), 3.81 (s, 3H), 4.20 (q, 2H, J=7 Hz), 6.77 (d, 1H, J=8.2 Hz) and 7.27 ppm (t, 1H, J=8.2 Hz). MS; m/z 306 (M^+), 261, 233, 196, 175, 161 (base peak), 148 and 121. Calcd. for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1821.

Ethyl 2-methoxy-6-(8-pentadecyl)benzoate 23. To a suspension of heptyltriphenylphosphonium bromide (1.15 g, 2.61 mmol) in 15mL of dry THF was added dropwise n-butyllithium (1.1 M hexane solution, 1.75 mL, 2.03 mmol) at 0 °C under argon atmosphere. After the solution had been stirred at 0 °C for 30 min, a solution of 22 (0.4 g, 0.65 mmol) in 8 mL of THF was added at -30 °C and the mixture was stirred for an additional 40 min and then allowed to warm to room temperature. The mixture was quenched with water and MeOH and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 2:1 hexane-benzene as eluent) to afford 23 as a pale yellow oil (0.196 g, 77%). GLC; SE 30 (3%), 1.1 m column, 150-230 °C, t_r 25.0 min (cis only). IR(neat); 1725, 1600, 1585, 1470, 1435, 1265, 1105, 1075, 800, 745 and 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.88 (t, 3H, J=6.8 Hz), 1.27 (m, 16H), 1.37 (t, 3H, J=7 Hz), 1.58 (m, 2H), 2.00 (m, 4H), 2.55 (t, 2H, J=7.8 Hz), 3.81 (s, 3H), 4.20 (q, 2H, J=7 Hz), 5.35 (m, 2H), 6.75 (d, 1H, J=8 Hz), 6.82 (d, 1H, J=8 Hz) and 7.26 ppm (t, 1H, J=8 Hz). ^{13}C NMR (50.2 MHz, $CDCl_3$); 14.07, 22.66, 29.02, 29.26, 29.37, 29.55, 29.55, 29.67, 29.78, 31.24, 31.83, 33.46, 55.89, 61.03, 108.56, 121.53, 129.82, 129.94, 130.05, 141.27, 156.33 and 168.39 ppm. MS; m/z 388 (M^+), 343, 194, 175, 161 (base peak), 148, 121 and 55. Calcd. for $C_{25}H_{40}O_3$: 388.2977. Found: 388.2988.

2-Methoxy-6-(8-pentadecenyl)benzoic acid. A mixture of 23 (0.2 g, 0.51 mmol) and 2 mL of 20% NaOH in 2 mL of DMSO was refluxed for 24 h. After dilution with water, the mixture was extracted with ether. The aqueous phase was acidified with conc. HCl and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to afford the methoxy carboxylic acid

as a pale yellow oil (0.18 g, 97%). IR(neat); 3600-2400, 3020, 1705, 1605, 1590, 1475, 1290, 1275, 1085, 800 and 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.87 (t, 3H, J=7 Hz), 1.30 (m, 16H), 1.62 (m, 4H), 1.98 (m, 2H), 2.69 (t, 2H, J=8 Hz), 3.87 (s, 3H), 5.34 (m, 2H), 6.79 (d, 1H, J=8.2 Hz), 7.31 (t, 1H, J=8.2 Hz) and 10.11 ppm (br, 1H). MS; m/z 360 (M^+), 342, 215, 201, 189, 175, 166, 161 (base peak), 148, 91 and 55. Calcd. for $C_{23}H_{36}O_3$: 360.2664. Found: 360.2675.

2-Hydroxy-6-(8-pentadecenyl)bensoic acid (Ginkgoic acid) 3. To a suspension of NaH (0.011 g, 0.28mmol) in 1.5 mL of dry DMF at 0 °C was added ethanethiol (0.02 mL, 0.27 mmol) dropwise under argon atmosphere and the mixture was stirred for 30 min at room temperature. Then a solution of the methoxy carboxylic acid (0.032 g, 0.089 mmol) in 1 mL of DMF was added and the mixture was refluxed for 3 h. After removal of the solvent under reduced pressure the residue was acidified with 3 M HCl, extracted with ether. The extract was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography followed by distillation to give colorless needles (0.02 g, 67%), m.p. 45.3-48 °C (sublimation). IR($CHCl_3$); 3010, 2920, 2840, 1655, 1595, 1200, 1040, 925, 875, 845, 715 and 660 cm^{-1}. ^1H NMR (200 Mhz, $CDCl_3$); 0.88 (t, 3H, J=7 Hz), 1.25 (m, 16H), 1.51 (m, 2H), 1.93 (m, 4H), 2.89 (t, 2H, J=7 Hz), 5.25 (m, 2H), 6.66 (dd, 1H, J=7.8, 1.8 Hz), 6.77 (dd, 1H, J=8.4, 1.8 Hz), 7.26 (dd, 1H, J=7.8, 8.4 Hz), 9.4 (br, 1H) and 10.9 ppm (br, 1H). MS; m/z 346 (M^+), 328, 310, 202, 162, 152, 146, 134 and 108. Calcd. for $C_{22}H_{34}O_3$: 346.2508. Found: 346.2492.

9-Tetrahydropyranyloxynonal 26. The title compound was prepared by using the procedure for 7-tetrahydropyranyloxyheptanal. A pale yellow oil. IR(neat); 2725, 1725 and 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 1.10-1.90 (m, 18H), 2.20-2.60 (m, 2H), 3.15-4.10 (m, 4H), 4.54 (br s, 1H) and 9.77 ppm (t, 1H, J=2.4 Hz). MS; m/z 241 (M^+-1), 123, 101 and 85 (base peak). Calcd. for $C_{14}H_{26}O_3$: 242.1882. Found: 242.1896.

1-Tetrahydropyranyloxy-9-tetradecene 27. To a suspension of pentyltriphenylphosphonium iodide (4.47 g, 9.7 mmol) in 25 mL of dry THF was added dropwise a solution of potassium t-butoxide (0.94 g, 8.4 mmol) in 20 mL of THF at -25 °C under argon atmosphere. After the solution had been stirred at -20 °C for 2 h, a solution of 26 (1.569 g, 6.47 mmol) in 20 mL of THF was added at -13 °C. The mixture was allowed to warm to room temperature and stirred for 12 h, quenched with sat. NH_4Cl solution, extracted with hexane. After removal of the solvent, the residue was re-extracted with hexane and the extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 95:5 hexane-AcOEt as eluent) to afford the olefin 27 (1.373 g, 72%) a pale yellow oil. GLC; SE 30 (3%), 1.1 m column, 100-230 °C, t_r 25.6 min (cis only). ^1H NMR (200 MHz, $CDCl_3$); 0.84 (t, 3H, J=6 Hz), 1.05-1.78 (m, 22H), 1.78-2.30 (m, 4H), 3.10-4.10 (m, 4H), 4.52 (br, 1H) and 5.53 ppm (t, 2H, J=4.8 Hz). MS; m/z 296 (M^+), 278, 223, 194 and 85 (base peak). Calcd. for $C_{19}H_{36}O_2$: 296.2715. Found: 296.2711.

1-Bromo-9-tetradecene 28. A mixture of the THP ether 27 (1.373 g, 4.99 mmol) and p-toluenesulfonic acid (50 mg) in 20 mL of 95% methanol was stirred for 40 min at room temperature and then warmed at 50 °C for 2.5 h. Anhydrous K_2CO_3 was added until the pH of the solution became 8.0. The mixture was filtered and the filtrate was evaporated. The crude product was purified by column chromatography (SiO_2, 95:5 hexane-AcOEt as eluent) to afford 9-tetradecenol (0.781 g, 80%). The alcohol was dissolved in pyridine (6 mL) and p-toluenesulfonyl chloride (0.988 g, 5.18 mmol) was added to this solution at 0 °C and the mixture was allowed to stirr at room temperature for 12 h. After the solvent had been removed under reduced pressure, the mixture was dissolved in CH_2Cl_2 and the solution was washed successively with 1 M HCl solution, sat. $NaHCO_3$ solution, and brine and evaporated to give a tosylate (1.722 g). A mixture of this tosylate, anhydrous LiBr (0.837 g, 8 mmol) and 35 mL of acetone was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was partitioned between hexane and water. The organic layer was washed successively with aq. $NaHCO_3$ solution, brine, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (SiO_2, hexane as eluent) gave the bromide 28 (0.739 g, 57%) as a pale greenish yellow oil. GLC; SE 30 (3%), 1.1 m column, 100-230 °C, t_r 16.8 min (cis only). IR(neat); 3010, 1650 and 1480 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$); 0.89 (t, 3H, J=5.4 Hz), 1.05-1.64 (m, 16H), 1.65-2.30 (m, 4H), 3.40 (t, 2H, J=6.2 Hz) and 5.35 ppm (t, 2H, J=4 Hz). MS; m/z 276, 274 (M^+), 164, 162, 150, 148, 135, 125, 111, 97 (base peak) and 83. Calcd. for $C_{14}H_{27}Br$: 274.1296. Found: 274.1297.

Ethyl 2-methoxy-6-(1-phenylsulfonyl-10-pentadecenyl)benzoate 30. To a solution of 5.2 mmol of lithium diisopropylamide (from 0.9 mL of isopropylamine and 4 mL of 1.5 M n-butyllithium hexane solution) in 4 mL of dry THF, cooled to -70 °C under argon, was added a solution of the sulfone 29 (0.995 g, 2.42 mmol) in 17 mL of THF was added dropwise. After stirring for an additional 20 min, the bromide 28 (0.672 g, 2.44 mmol) in 15 mL of THF was added dropwise at -70 °C. Stirring was continued for an additional 20 min in the cold and 20 h at room temperature. After addition of water, the mixture was extracted with CH_2Cl_2, and the extract was washed successively with 1 M HCl, sat. $NaHCO_3$ solution, brine, dried and evaporated. The crude product was purified by chromatography (SiO_2, 95:5 then 4:1 hexane-AcOEt as eluent) to give 30 as a yellow oil (0.939 g, 64%). IR(neat); 3070, 3000, 1720, 1585, 1360, 1265, 1150, 1080 and 731 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.87 (t, 3H, J=4.2 Hz), 1.27 (t, 3H, J=7.2 Hz), 1.00-1.67 (m, 18H), 3.74 (s, 3H), 4.23 (q, 2H, J=7.8 Hz), 3.90-4.50 (m, 1H), 5.33 (t, 2H, J=4.8 Hz) and 6.75-7.78 ppm (m, 8H). MS; m/z 528 (M^+), 482, 387 (base peak) and 341. Calcd. for $C_{31}H_{44}O_5S$: 528.2891. Found: 528.2892.

Ethyl 2-methoxy-6-(10-pentadecenyl)benzoate 31. To a solution of 30 (0.667 g, 1.1 mmol) in 30 mL of ethanol was added 5% sodium amalgam (4 g) in portions with stirring. The mixture was heated 1.75 h at 80 °C, filtered and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 and the solution was successively washed with 1 M HCl, sat. $NaHCO_3$ solution, brine, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (SiO_2, benzene as eluent) to give 31 as a pale yellow oil (0.431 g, 84%). IR(neat); 3070, 3010, 1730, 1600, 1585 and 1270 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$); 0.88 (t, 3H, J=4.8 Hz), 1.05-1.74 (m, 18H), 1.35 (t, 3H, J=7.2 Hz), 1.76-2.20 (m, 4H), 2.34-2.75 (m, 2H), 3.79 (s, 3H), 4.39 (q, 2H, J=6 Hz), 5.33 (t, 2H, J=3.6 Hz) and 6.56-7.45 ppm (m, 3H). MS; m/z 388 (M^+, base peak), 343, 324, 194 and 160. Calcd. for $C_{25}H_{40}O_3$: 388.2977. Found: 388.2992.

2-Hydroxy-6-(10-pentadecenyl)benzoic acid 2. A solution of 31 (0.506 g, 1.09 mmol) and 4 mL of 20% NaOH solution in 4 mL of DMSO was heated at 125 °C for 3 days. The mixture was acidified with conc HCl and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give an acid as a pale yellow oil (0.419 g, 88%).

To a suspension of NaH (32 mg, 60% mineral oil dispersion, washed twice with anhydrous hexane) in 4 mL of DMF was added ethane-thiol (0.11 mL, 1.23 mmol) at 0 °C under argon. After stirring for 15 min at 0 °C, the above acid (0.179 g, 0.409 mmol) in 6 mL of DMF was added and the mixture was heated for 3 h at 140 °C. After the solvent and excess reagent were removed under reduced pressure, the residue was acidified with 2 M HCl and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (SiO_2, 95:5 benzene-AcOEt as eluent) to give 2 as colorless needles (0.169 g, 98%), m.p. 45.8-46.2 °C. ^{2}IR($CHCl_3$ solution); 3020, 2850, 1650, 1610, 1300 and 1040 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$); 0.85 (t, 3H, J=6.6 Hz), 1.04-1.44 (m, 16H), 1.44-1.64 (m, 2H), 1.82-2.08 (m, 4H), 2.88 (t, 2H, J=7 Hz), 5.28 (t, 2H, J=4.4 Hz), 6.64-6.84 (m, 2H) and 7.1-7.2 ppm (m, 1H). MS; m/z 346 (M^+, base peak), 328, 310, 161, 152 and 134. Calcd. for $C_{22}H_{34}O_3$: 346.2508. Found: 346.2502.

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