Synthesis of Some Aromatic Prostaglandin Analogues. Part 1

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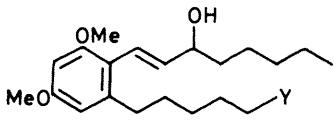
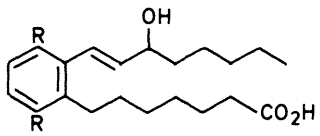
7-[2-(3-Hydroxyoct-1-enyl)-3,5-dimethoxyphenyl]heptanoic acid (4) has been prepared in six steps from 3,5-dimethoxybenzaldehyde.

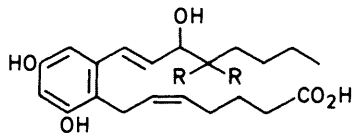
Analogues of prostaglandins in which the cyclopentane ring has been replaced by a phenyl group have some distinct advantages as potential drugs. Most of the stereochemical problems and problems of long-term storage associated with prostaglandins are avoided, hence any potential drugs of this sort will be cheaper to produce and easier to formulate. The current interest in this type of compound is demonstrated by the recently reported preparations of compounds (1),[1] (2),[2] and (3).[3] This paper describes the preparation of the prostaglandin analogue 7-[2-(3-hydroxyoct-1-enyl)-3,5-dimethoxyphenyl]heptanoic acid (4) by an economical and highly flexible route capable of producing any required analogue in multigram quantities.



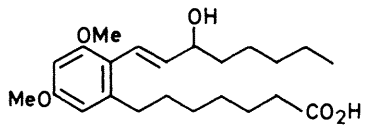
(1) Y = CO_2H, CH_2OR



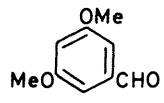
(2) R = H, OAlkyl



(3) R = H, Me



(4)

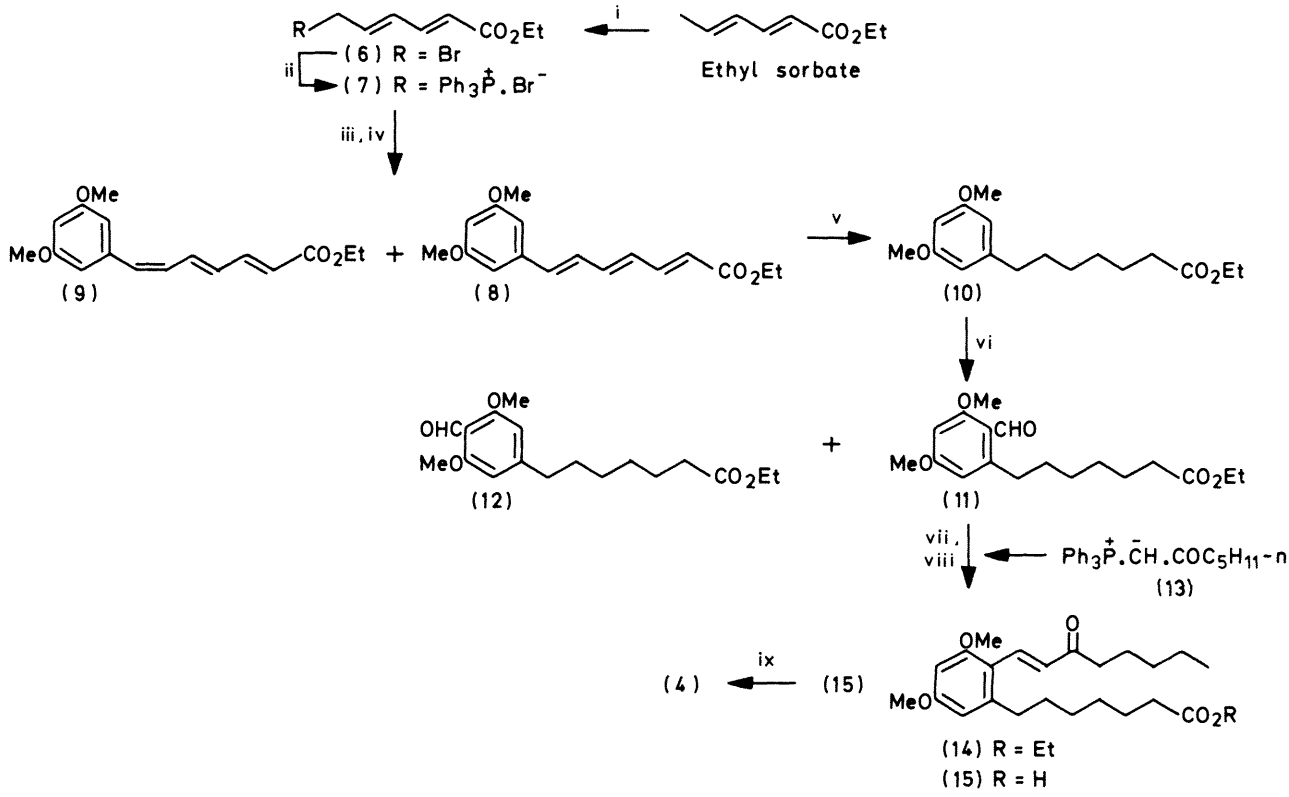


(5)

Esterification of 3,5-dimethoxybenzoic acid, followed by lithium aluminium hydride reduction [4] and oxidation with chromium trioxide–pyridine [5] or pyridinium chlorochromate [6] gave 3,5-dimethoxybenzaldehyde (5) in high yield and this preparation could be carried out on a large scale. The aldehyde was to be coupled with the phosphorane derived from ethyl 6-bromosorbate (6) but we found this bromo ester to be not readily accessible by literature routes.[7] However, treatment of ethyl sorbate with *N*-bromosuccinimide (NBS) in chlorobenzene under reflux [8] gave the required bromo ester (6) in 80% purity after a single distillation. Reaction of this crude mixture with triphenylphosphine [9] gave the phosphonium salt (7) in 25% overall yield. Later work showed that the corresponding methyl ester analogue of (7) could be prepared in this way in a higher overall yield than previously reported [10] and in a purer state than compound (7). Treatment of (7) with aqueous base generated the corresponding ylide which was coupled with 3,5-dimethoxybenzaldehyde (5) to give crystalline ethyl 7-(3,5-dimethoxyphenyl)hepta-2*E*,4*E*,6*E*-trienoate (8) (34%) and its 2*E*,4*E*,6*Z*-isomer (9) (64%). These stereochemical assignments are not based directly on the n.m.r. spectra of (8) and (9) which are highly complex, but on comparison with the spectra of ethyl 3-(3,5-dimethoxyphenyl)prop-2*E*-enoate and ethyl 5-(3,5-dimethoxyphenyl)penta-2*E*,4*E*-dienoate. Each of these compounds displays a doublet–triplet pattern for the aromatic protons and, of the heptadienoate isomers prepared, only (8) shows a similar pattern.

Hydrogenation of the mixture of trienoates (8) and (9) gave ethyl 7-(3,5-dimethoxyphenyl)heptanoate (10). An alternative route to this system, more convenient on a large scale (>1 mol), entailed Wolff–Kishner reduction and re-methylation of 6-(3,5-dimethoxybenzoyl)hexanoic acid [11] which afforded the methyl ester analogue of (10). Vilsmeier formylation of (10) gave two aldehydes in the ratio 4.5 : 1, both of which exhibited singlets for the methoxy protons in the n.m.r. spectrum. Addition of a europium shift reagent to each n.m.r. solution caused the methoxy signal of the major isomer only to split into two, and hence this isomer was assigned the unsymmetrical 2-formyl structure (11). Further proof was provided by the observation that the 7-H_2 protons in compound (11) were shifted downfield by 0.3 p.p.m. relative to the corresponding protons in compound (12), clearly a deshielding effect by the adjacent formyl group. Wittig reaction of (11) with 2-oxoheptylidenetriphenylphosphorane (13) gave the enone (14), almost exclusively as the *E*-isomer. The phosphorane was prepared in 44% overall yield by brominating heptan-2-one by the method of Gaudry and Marquet,[12] treating the crude bromo ketone with triphenylphosphine, and converting the resulting phosphonium salt into the ylide (13) with a two-phase system of aqueous sodium hydroxide and dichloromethane—a considerable improvement over previously reported procedures.[13] The enone-ester (14) was hydrolysed to 7-[3,5-dimethoxy-2-(3-oxo-oct-1-enyl)phenyl]heptanoic acid (15) which in turn was reduced to the desired allylic alcohol (4) with potassium borohydride in a citrate buffer.[14] Care had to be exercised in the preparation of compound (4) as it was quite heat-labile (>60 °C). These reactions are shown in the Scheme.

This general method of synthesis has several major advantages over that described by Galantay [1] for the preparation of the one-carbon homologue (1). The Sandoz route is lengthier and requires selective oxidation of a benzylic alcohol by the expensive dichlorodicyanoquinone, followed three steps later by a chromic acid oxidation of a terminal alcohol to introduce the carboxylic acid group. This gives a product of poor quality as evidenced by their quoted melting point of 38 °C for 6-[3,5-dimethoxy-2-(3-oxo-oct-1-enyl)phenyl]-hexanoic acid. Material prepared by our method from 6-(3,5-dimethoxyphenyl)hexanoic acid melted at 65—67 °C.



Scheme. *Reagents and conditions:* i, NBS; ii, PPh_3; iii, NaOH; iv, (5); v, H_2, Pd–C; vi, $POCl_3$–$HCONMe_2$; vii, toluene, heat; viii, NaOH; ix, KBH_4

Interestingly, compounds (4) and (15) were potent depressors of serum cholesterol and serum triglyceride levels, but displayed no biological activity that could be regarded as typical of the prostaglandins.

Experimental

Light petroleum refers to the fraction boiling between 60 and 80 °C. Organic solutions were dried over anhydrous magnesium sulphate and solvents were dried, where necessary, by passage through a column of basic alumina. Unless otherwise stated n.m.r., i.r., and u.v. spectra were recorded in solution in deuteriochloroform, bromoform, and ethanol, respectively.

5-Methoxycarbonylpenta-2E,4E-dienyltriphenylphosphonium Bromide and the Corresponding Ethyl Ester (7).—Methyl sorbate * (445 g, 3.53 mol) and NBS (654 g, 3.67 mol) in dry chlorobenzene (3 l) were slowly heated to 100 °C and benzoyl peroxide (39 g, 0.16 mol) was then cautiously added in portions. After the addition the reaction mixture was heated under reflux for 1.5 h, cooled, and the chlorobenzene was removed by evaporation under reduced pressure. The residual paste was triturated with diethyl ether, filtered, and the ethereal solution was washed with 5% aqueous sodium hydroxide until the washings were colourless, and was then dried and the ether was evaporated off. Fractional distillation of the resulting oil gave methyl 6-bromohexa-2*E*,4*E*-dienoate (400 g, 70%), b.p. 89—94 °C at 0.1 mmHg (lit.,[10a] 75 °C at 1 mmHg). From this, the title compound was prepared by the method of Weedon *et al.*,[10b] m.p. 189.8 °C (dichloromethane–ethyl acetate) (lit.,[10b] 188 °C).

A similar bromination of ethyl sorbate gave ethyl 6-bromo-2*E*,4*E*-hexadienoate (6) (38%) of *ca.* 80% purity, b.p. 108—130 °C at 2 mmHg (lit.,[7] 87—89 °C at 0.4 mmHg), from which was prepared 5-ethoxycarbonylpenta-2*E*,4*E*-dienyltriphenylphosphonium bromide (7) (60%), m.p. 168.1 °C (lit.,[9] 175—177 °C).

*Ethyl 7-(3,5-Dimethoxyphenyl)hepta-*2E,4E,6-E- *and* -Z-*trienoate* (8) *and* (9).—The phosphonium salt (7) (72 g, 0.15 mol) was dissolved in a mixture of toluene (1 l) and water (3.5 l), 10% aqueous sodium hydroxide (80 ml, 0.2 mol) was added, and the mixture was vigorously shaken. The toluene layer was separated, combined with a further toluene extract of the aqueous layer, dried, and filtered. 3,5-Dimethoxybenzaldehyde (5) (16.6 g, 0.1 mol) was added to the resulting solution and the reaction mixture was heated under reflux for 2 h. After evaporation of the toluene the residue was crystallised from acetone–light petroleum (to remove triphenylphosphine oxide) and the mother-liquors were evaporated and crystallised from methanol to give the E,E,E-*isomer of the title compound* (8) (10.0 g, 34%) as yellow needles, m.p. 88.7 °C (Found: C, 70.6; H, 7.05. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%); $\nu_{max.}$ 1 699 (CO_2Et), 1 629, 1 606, 1 590, and 1 580 cm^{-1} (aromatic + C=C); τ (60 MHz) † 2.20—3.40 (m, 3-, 4-, 5-, 6-, and 7-H), 3.42 (d, *J* 3 Hz, 2′- and 6′-H), 3.60 (t, *J* 3 Hz, 4′-H), 4.12 (d, *J* 14 Hz, 2-H), 5.80 (q, *J* 7 Hz, CH_2CH_3), 6.21 (s, 2 × OCH_3), and 8.72 (t, *J* 7 Hz, CH_2CH_3); $\lambda_{max.}$ 255 (ε 7 100) and 342.5 nm (44 700).

The mother-liquors from the crystallisation were evaporated and chromatographed on silica [light petroleum–ethyl acetate (4 : 1)] to give the E,E,Z-*isomer of the title compound* (9) (18.60 g, 64%) as a yellow oil (Found: C, 70.75; H, 6.75%); $\nu_{max.}$ 1 699 (CO_2Et), 1 621, 1 607, and 1 590 cm^{-1} (C=C and aromatic); τ (60 MHz) 2.35—3.85 (m, 3-, 4-, 5-, 6-, and 7-H), 3.58 (s, 2′-, 4′-, and 6′-H), 4.10 (d, *J* 16 Hz, 2-H), 5.81 (q, *J*

* Methyl hexa-2*E*,4*E*-dienoate.

† In the n.m.r. assignments primed numbers are used for the phenyl protons and [for compounds (4), (14), and (15)] doubly primed numbers for the oct-1-enyl chain.

7 Hz, CH_2CH_3), 6.21 (s, 2 × OCH_3), and 8.71 (t, *J* 7 Hz, CH_2CH_3); $\lambda_{max.}$ 262 (ε 7 300) and 342 nm (32 300).

Ethyl 7-(3,5-*Dimethoxyphenyl*)*heptanoate* (10).—A mixture of the ethyl 7-(3,5-dimethoxyphenyl)hepta-2,4,6-trienoates (8) and (9) (86 g, 0.30 mol) was dissolved in ethanol (500 ml) and the solution was hydrogenated over 5% palladium–carbon (5 g) at atmospheric pressure. When the uptake of hydrogen had ceased the reaction mixture was filtered through kieselguhr and the filtrate was evaporated to give the *title compound* (10) (87 g, 99%) as an oil (Found: C, 69.7; H, 9.0. $C_{17}H_{26}O_4$ requires C, 69.35; H, 8.9%); $\nu_{max.}$ 1 722 cm^{-1} (CO_2Et); τ 60 MHz) 3.70 (s, 2′-, 4′-, and 6′-H), 5.91 (q, *J* 7 Hz, CH_2CH_3), 6.26 (s, 2 × OCH_3), 7.47 (t, *J* 6 Hz, 7-H_2), 7.75 (t, *J* 6 Hz, 2-H_2), 8.00—8.80 (m, 3-, 4-, 5-, and 6-H_2), and 8.79 (t, *J* 7 Hz, CH_2CH_3); $\lambda_{max.}$ 221.5 (ε 7 800), 273.5 (1 500), and 280 nm (1 500).

Methyl 7-(3,5-*Dimethoxyphenyl*)*heptanoate*.—6-(3,5-Dimethoxybenzoyl)hexanoic acid [11] (12 g, 48 mmol), potassium hydroxide (7.75 g, 138 mmol), and hydrazine hydrate (8.0 ml, 165 mmol) in ethylene glycol (100 ml) were heated under reflux for 0.75 h and the solvent and excess of reagent were then distilled off up to a vapour temperature of 200 °C. The residual product was then heated under reflux for 4 h. After being cooled to ambient temperature the reaction mixture was diluted with water (1 l) and this aqueous solution was washed twice with diethyl ether, acidified to pH 1, and extracted twice with ethyl acetate. The latter extracts were combined, washed in turn with water and brine, dried, and evaporated to give a red, viscous oil. This oil, methyl iodide (12 ml, 193 mmol), and anhydrous potassium carbonate (18 g, 130 mmol) in acetone (130 ml) were heated under reflux for 18 h, cooled, filtered, and the filtrate was evaporated under reduced pressure. Chromatography [silica; light petroleum–ethyl acetate (4 : 1)] gave the *title compound* (10.6 g, 88%) as an oil (Found: C, 68.5; H, 8.35. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.65%); $\nu_{max.}$ 1 730 cm^{-1} (CO_2Me); τ (100 MHz) 3.76 (s, 2′-, 4′-, and 6′-H), 6.21 (s, 2 × OCH_3), 6.36 (s, CO_2CH_3), 7.50 (t, *J* 7 Hz, 7-H_2), 7.78 (t, *J* 7 Hz, 2-H_2), and 8.10—8.96 (m, 3-, 4-, 5-, and 6-H_2); $\lambda_{max.}$ 221.5 (ε 8 200), 273 (1 500), and 282 nm (1 500).

Ethyl 7-(2-*Formyl*-3,5-*dimethoxyphenyl*)*heptanoate* (11) *and Ethyl* 7-(4-*Formyl*-3,5-*dimethoxyphenyl*)*heptanoate* (12).—A solution of dimethylformamide (31 ml, 0.4 mol) in dry dichloromethane (300 ml) was stirred and cooled to 0 °C and phosphorus oxide trichloride (37 ml, 40 mmol) was added dropwise. After 10 min a solution of ethyl 7-(3,5-dimethoxyphenyl)heptanoate (10) (58.8 g, 20 mmol) in dry dichloromethane (200 ml) was added and the reaction mixture was set aside at room temperature for 93 h before cautiously being poured into saturated aqueous sodium hydrogen carbonate (2.5 l). The organic layer was separated, combined with three further CH_2Cl_2 extracts of the aqueous layer, washed with water, dried, and the solvent was removed under reduced pressure. The residue was chromatographed [silica; light petroleum–ethyl acetate (3 : 1)] to give *ethyl* 7-(2-*formyl*-3,5-*dimethoxyphenyl*)*heptanoate* (11) (39.20 g, 61%), m.p. 51 °C (from ethyl acetate–light petroleum) (Found: C, 67.1; H, 8.2; $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.1%); $\nu_{max.}$ 1 722 (CO_2Et) and 1 673 cm^{-1} (CHO); τ (60 MHz) −0.40 (s, CHO), 3.70 (s, 4′- and 6′-H), 5.91 (q, *J* 7 Hz, CH_2CH_3), 6.18 (s, 2 × OCH_3), 7.08 (t, *J* 7 Hz, 7-H_2), 7.71 (*t*, *J* 7 Hz, 2-H_2), 8.00—8.80 (m, 3-, 4-, 5-, and 6-H_2), and 8.80 (t, *J* 7 Hz, CH_2CH_3); $\lambda_{max.}$ 232 (ε 15 200), 233.5 (15 400), 277.5 (13 900), and 312.5 nm (18 100), followed by *ethyl* 7-(4-*formyl*-3,5-*dimethoxyphenyl*)*heptanoate* (12) (8.8 g, 14%), m.p. 40.5 °C (from ethyl acetate–light petroleum) (Found: C, 67.2; H, 8.3%); $\nu_{max.}$ 1 724 (CO_2Et) and 1 680 cm^{-1} (CHO); τ (60 MHz) −0.42 (s, CHO), 3.62 (s, 2′- and 6′-H), 5.89 (q, *J* 7 Hz, CH_2CH_3), 6.12 (s, 2 × OCH_3), 7.40 (t, *J* 7 Hz, 7-H_2), 7.71 (t, *J* 7 Hz, 2-H_2), 8.00—8.80 (m, 3-, 4-, 5-, and 6-H_2), and 8.77 (t, *J* 7 Hz, CH_2CH_3); $\lambda_{max.}$ 279 (ε 15 100) and 323.5 nm (3 900).

2-*Oxoheptylidenetriphenylphosphorane* (13).—Bromine (14 ml, 0.27 mol) was added dropwise to an ice-cold solution of heptan-2-one (35 g, 0.31 mol) in methanol (600 ml) and the solution was stirred at room temperature until it became colourless (1 h) before being recooled to 4 °C. Concentrated sulphuric acid (185 ml) was added cautiously whilst the temperature was kept below 20 °C, and the mixture was stirred for a further 3 h. Saturated aqueous sodium carbonate was then added until the reaction mixture was neutral, the volume was made up to 6 l with water, and the product was extracted with diethyl ether. The extract was washed in turn with water and brine, dried, and evaporated to an oil which was immediately added to a stirred solution of triphenylphosphine (65 g, 0.25 mol) in toluene (500 ml). After 18 h the resulting solid was filtered off and recrystallised from chloroform–ethyl acetate to give 2-oxoheptyltriphenylphosphonium bromide (61.42 g, 44% overall), m.p. 198 °C (lit.,[3] 198—199 °C). The phosphorane (13) was generated when required by partitioning the phosphonium salt between dichloromethane and 2M aqueous sodium hydroxide. The organic layer was then separated, dried, and evaporated, to give a quantitative yield of the *title compound* (13), m.p. 74 °C (lit.,[3] 73—74 °C).

Ethyl 7-[3,5-*Dimethoxy*-2-(3-*oxo*-*oct*-1-*enyl*)*phenyl*]*heptanoate* (14).—To the phosphorane (13) prepared from the phosphonium bromide (90 g, 0.2 mol) was added a solution of ethyl 7-(2-formyl-3,5-dimethoxyphenyl)heptanoate (11) (42 g, 0.13 mol) in toluene (250 ml), and the reaction mixture was heated under reflux for 5 d. The mixture was then diluted with ethyl acetate, washed in turn with 2M hydrochloric acid, water, and aqueous sodium hydrogen carbonate, dried, and the solvent was evaporated under reduced pressure. Chromatography [silica; light petroleum–ethyl acetate (3 : 1)] gave the *title compound* (14) (49.85 g, 91%) as a yellow oil (Found: C, 71.7; H, 9.2. $C_{25}H_{38}O_5$ requires C, 71.7; H, 9.15%); $\nu_{max.}$ 1 722 (CO_2Et), 1 673 (CO), and 1 645 cm^{-1} (C=C); τ (60 MHz) 2.28 (d, *J* 14 Hz, 1″-H), 3.10 (d, *J* 14 Hz, 2″-H), 3.68 (s, 4′- and 6′-H), 5.93 (q, *J* 7 Hz, OCH_2CH_3), 6.15 and 6.20 (each s, OCH_3), 7.30 and 7.41 (each t, *J* 7 Hz, together 7- and 4″-H_2), 7.74 (t, *J* 6 Hz, 2-H_2), 8.00—8.90 (m, 3-, 4-, 5-, 6-, 5″-, 6″-, and 7″-H_2), 8.79 (t, *J* 7 Hz, OCH_2CH_3), and 9.11 (t, *J* 5 Hz, 8″-H_3); $\lambda_{max.}$ 247.5 (ε 8 000), 315 (8 900), and 337 nm (10 200).

7-[3,5-*Dimethoxy*-2-(3-*oxo*-*oct*-1-*enyl*)*phenyl*]*heptanoic Acid* (15).—The ester (14) (18.06 g, 43 mmol) was dissolved in methanol (350 ml), 2M aqueous sodium hydroxide (69.5 ml, 140 mmol) was added, and the reaction mixture was set aside at room temperature for 18 h before being diluted with water (3.5 l) and extracted with diethyl ether. The aqueous layer was then acidified to pH 2, extracted twice with ethyl acetate, and these latter extracts were combined, washed with brine, dried, and evaporated. Crystallisation of the solid residue (ethyl acetate–light petroleum) gave the *title compound* (15) (14.17 g, 84%) as a solid, m.p. 61 °C (Found: C, 70.9; H, 8.6. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%); $\nu_{max.}$ (Nujol) 3 700—3 200 (CO_2H), 1 709 (CO_2H), 1 687 and 1 679 (CO), and 1 584 cm^{-1} (C=C); τ (90 MHz) 1.30 (br s, CO_2H), 2.21 (d, *J* 16 Hz, 1″-H), 3.02 (d, *J* 16 Hz, 2″-H), 3.62 (s, 4′- and 6′-H), 6.15 and 6.18 (each s, OCH_3), 7.28 and 7.37 (each t, *J* 7 Hz, together 7- and 4″-H_2), 7.65 (t, *J* 7 Hz, 2-H_2), 8.00—8.90 (m, 3-, 4-, 5-, 6-, 5″-, 6″-, and 7″-H_2), and 9.10 (t, *J* 6 Hz, 8″-H_3); $\lambda_{max.}$ 248 (ε 10 200), 312 (14 300), and 337.5 nm (18 900).

7-[2-(3-*Hydroxyoct*-1-*enyl*)-3,5-*dimethoxyphenyl*]*heptanoic Acid* (4).—The acid (15) (0.98 g, 2.51 mmol) was reduced by the method of Miyano, Dorn, and Mueller [14] to give the *title compound* (4) (0.93 g, 94%) as a pale yellow gum (Found: C, 70.5; H, 9.2. $C_{23}H_{36}O_5$ requires C, 70.4; H, 9.25%); $\nu_{max.}$ 3 600 and 3 500 (free OH), 3 350—2 300 (H-bonded OH), 1 730 and 1 710 (monomeric and dimeric acid), and 1 606 cm^{-1} (C=C); τ (100 MHz) 3.32 (br s, CO_2H and OH), 3.45 (d, *J* 16 Hz, 1″-H), 3.62 (s, 4′- and 6′-H), 3.88 (dd, $J_{2'',1''}$ 16, $J_{2'',3''}$ 12 Hz, 2″-H), 5.67 (dt, $J_{3'',2''}$ 12, $J_{3'',4''}$ 6 Hz, 3″-H), 6.18 (s, 2 × OCH_3), 7.34 (t, *J* 7 Hz, 7-H), 7.67 (t, *J* 7 Hz, 2-H_2), 8.10—9.00 (m, 3-, 4-, 5-, 6-, 4″-, 5″-, 6″-, and 7″-H_2), and 9.11 (t, *J* 6 Hz, 8″-H_3); $\lambda_{max.}$ 262 (ε 11 400), 290 (5 000), 301 (4 200), and 330 nm (1 600).

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