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SYNTHESIS OF THE LEUKOTRIENE ANTAGONIST ABLUKAST

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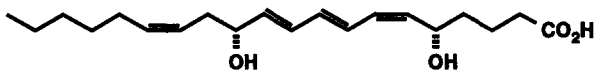
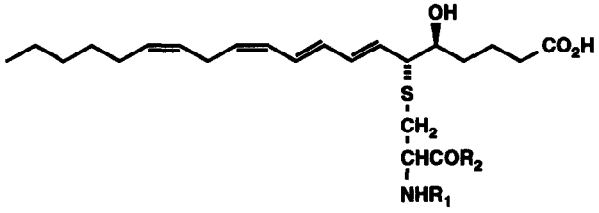
Abstract: An efficient synthesis of the leukotriene antagonist ablukast (**5**) has been achieved starting from 2,4-dihydroxyacetophenone. The latter, on a Claisen condensation with ethyl oxalate, followed by hydrogenation, gave the chromane ester **7**, which was subjected to a Fries rearrangement ($AcOH/BF_3.OEt_2$) and the product, after transesterification with methanol, was alkylated with 5-bromo-1-pentanyl acetate to afford the acetate **9**. A novel methanolysis of **9** with methanol in the presence of tetra-n-butylammonium hydroxide followed by mesylation of the derived alcohol furnished the mesylate **10**. Alkylation of the acetophenone derivative **16** with **10** using K_2CO_3 in the presence of tris(3,6-dioxaheptyl)amine and saponification gave **5**.

The leukotrienes (e.g., **1-4**) are eicosanoids derived from arachidonic acid via the Δ^5-lipoxygenase pathway.[1] Because they are implicated as mediators of a variety of pathophysiological conditions, including asthma, respiratory distress syndrome, allergic rhinitis, psoriasis, rheumatoid arthritis, inflammatory bowel disease (IBD) and gout, there is a sustained effort to find specific and selective antagonists and biosynthetic inhibitors of these metabolites.[2]

Extensive structure-activity studies in these laboratories have identified ablukast (Ulpax®, **5**), a 3,4-dihydro-2H-1-benzopyran-2-carboxylic acid linked to a hydroxyacetophenone via a 5-carbon tether, as a potent LTD_4 antagonist, which also inhibits LTB_4-induced bronchoconstriction in a guinea pig model.[3] Interestingly, the enantiomers of **5** were equipotent when administered intraveneously in a guinea pig LTD_4-induced bronchoconstriction model, whereas the (S)-enantiomer was found to be 15 times more potent than the (R)-enantiomer when the administration was by the aerosol route.[3] Ablukast is also of interest as a possible treatment for IBD, a family of chronic diseases associated with inflammation of the gastrointestinal tract, chronic diarrhea, and abdominal pain, in which LTB_4 has been implicated as a mediator.[4]



1, LTB_4

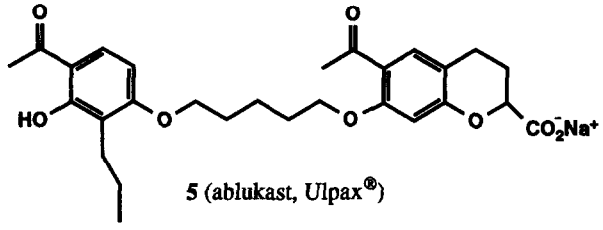


2, LTC_4: R_1=$COCH_2CH_2CHCO_2H$(Glu, E)
NH_2

$R_2 = NHCH_2CO_2H$ (Gly, G)

3, LTD_4: R_1 = H, $R_2 = NHCH_2CO_2H$

4, LTE_4: R_1 = H, R_2 = OH

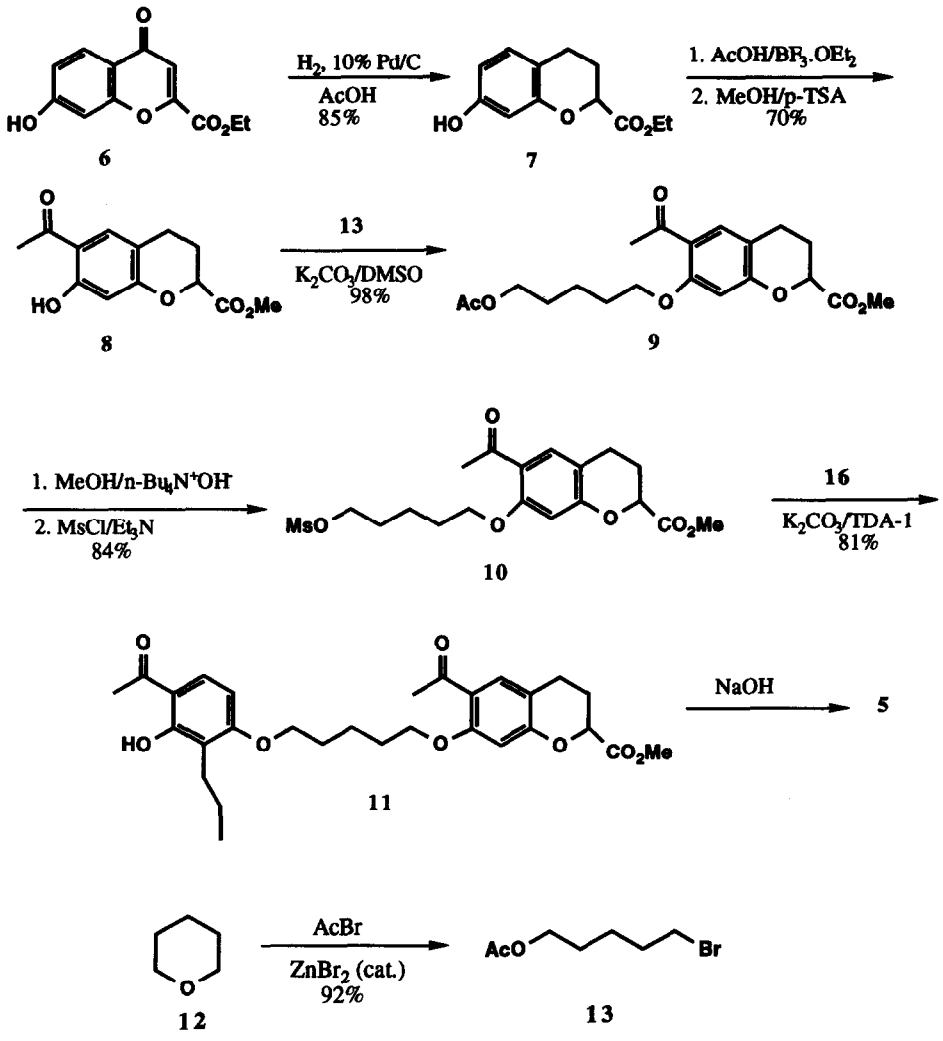


5 (ablukast, Ulpax®)

In support of a clinical program that required large quantities of racemic ablukast (**5**), as its sodium salt, an efficient and practical synthesis of this compound became necessary. Herein we describe a synthesis of **5**, starting from 2,4-dihydroxyacetophenone (**14**), which involves a phase transfer-mediated, regiospecific alkylation of the acetophenone **16** with the mesylate **10**, and provides the drug substance with a purity >99.7% without the need for chromatography at any stage of the synthesis (see **Schemes I and II**).

Using a slight modification of a procedure reported by Appleton et al., **6** was obtained by a Claisen condensation of 2,4-dihydroxyacetophenone with diethyl oxalate.[5] Hydrogenation of **6** in acetic acid in the presence of 10% Pd/C resulted in removal of the double bond and of the carbonyl group to give **7** in 85% yield. Conversion of **7** into **8** was accomplished by a Fries rearrangement, using acetic acid in the presence of BF_3. OEt_2, followed by transesterification with methanol. By this procedure, the desired 6-acetyl regioisomer **8** crystallized directly from the reaction mixture. A straightforward alkylation of **8** with 5-bromo-1-pentanyl acetate (**13**)[6] in the presence of K_2CO_3 afforded **9** in 98% yield. 5-Bromo-1-pentanyl acetate (**13**) was prepared in 92% yield by the zinc bromide-catalyzed opening of tetrahydropyran with acetyl bromide.

Scheme I



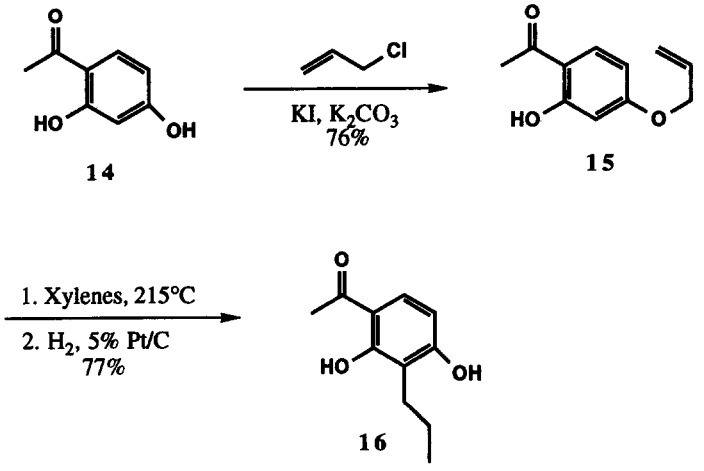
TDA-1 = $N(CH_2CH_2OCH_2CH_2OCH_3)_3$

In order to effect coupling with the acetophenone moiety **16**, it was necessary to replace the acetate group in **9** with a suitable leaving group. This required removal of the acetate group without concomitant hydrolysis of the methyl ester. Methanolysis with NaOMe-MeOH was an obvious choice for this

transformation, but, under a variety of conditions, some hydrolysis of the methyl ester invariably accompanied the removal of the acetate group during work-up of the reaction mixture. After an extensive study using methanol in the presence of a variety of acids (e.g., $BF_3.OEt_2$, p-TSA, Dowex cation exchange resin, anhyd. HCl), and KCN, the methanolysis was achieved with n-$Bu_4N^+OH^-$ in methanol to give the hydroxy ester, which, without purification, was mesylated (MsCl/Et_3N) to afford the crystalline mesylate **10** in 84% yield from **9**. To the best of our knowledge this is the first use of a tetraalkylammonium hydroxide in the alcoholysis of esters. Triton B (benzyltrimethylammonium hydroxide) was also effective in this transformation. The seemingly trivial alkylation of the acetophenone **16** with **10** to give **11** required an in-depth investigation and was eventually accomplished in 81% yield (99.7% pure material) using K_2CO_3 as base in the presence of the solid-liquid phase transfer catalyst tris(3,6-dioxaheptyl)amine (TDA-1)[7] and toluene as solvent. Careful saponification of **11** gave the crystalline sodium salt **5** with a purity >99.7% (HPLC analysis), suitable for clinical use.

The synthesis of the acetophenone moiety **16** followed established protocol.[3,5] A regiospecific allylation of 2,4-dihydroxyacetophenone (**14**) with allyl chloride gave the allyl ether **15** in 76% yield, which was subjected to a Claisen rearrangement at 215°C followed by hydrogenation to give crystalline **16** in 77% yield.

Scheme II



Experimental

General. Unless otherwise indicated, IR and NMR spectra were determined in $CHCl_3$ and $CDCl_3$, respectively. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.4 MHz, respectively. Assignments of the ^{13}C NMR are based on chemical shifts (δ), off-resonance, and DEPT spectra and are tentative. Coupling constants (J) are given in Hz. Thin layer chromatoplates (silica gel G) were purchased from Merck (Darmstadt); spots were visible under short-wavelength UV light or made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates.

Ethyl 7-Hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate (6). A solution of 109.8 g (0.75 mol) of diethyl oxalate and 65 g (0.427 mol) of 2',4'-dihydroxyacetophenone (Aldrich) in 100 mL of EtOH was added slowly under Ar, with cooling, to a stirred solution of NaOEt (from 40 g of Na and 550 mL of EtOH). The mixture was stirred at 50°C for 3 h, cooled to room temperature, and poured into a separatory funnel containing 500 mL of 2N HCl. It was extracted with CH_2Cl_2 (2 x 500 mL), washed with 500 mL of satd. $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a red oil, which was dissolved in 250 mL of EtOH and 10 mL of conc. HCl. The mixture was boiled under reflux for 1 h, cooled to ca. 10°C, and the product was collected by filtration. It was washed with some EtOH followed by hexane to give 86.0 g (86% yield) of **6**: mp 218-223°C. Crystallization of a portion from hot AcOH gave an analytical sample: mp 221-223°C (lit.[5] mp 224-225°C); UV (EtOH) 209 (ε=28,000), 238 (18,600), 311 (ε=8,380) nm; IR (KBr) 3108, 1743, 1643 cm^{-1}; ^1H NMR ($CDCl_3$ + d_6-DMSO) δ 1.42 (3H, t, J=7), 4.45 (2H, q, J=7), 6.95 (1H, d, J=8), 6.98 (1H, s), 6.99 (1H, s), 8.00 (1H, d, J=8), 10.36 (1H, s, OH); MS ***m/z*** 234 (M^+, 100). Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.24; H, 4.37.

Ethyl (R,S)-3,4-Dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate (7). A solution of 80 g (0.34 mol) of **6** in 60 mL of AcOH and 275 mL of THF was hydrogenated over 4.0 g of 10% Pd on charcoal at 45°C and 65 psi. After hydrogen absorption ceased, the catalyst was removed by filtration and the solvents were evaporated under reduced pressure, co-distilling with toluene to remove residual acetic acid. Crystallization from CCl_4 gave 65 g (85%) of **7**: mp 80-82°C (lit.[3] mp 81-82.5°C).

Ethyl (R,S)-3,4-Dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate (8). A stirred mixture of 65 g (0.293 mol) of **7** in 650 mL of AcOH, 1.5 mL of Ac_2O, and 65 mL of $BF_3.OEt_2$ was heated at reflux for 18 h and evaporated. To the residue was added 700 mL of H_2O, and the mixture was stirred at room temperature for 1.0 h. The product was collected by filtration and washed with hexane. It was then dissolved in 900 mL of MeOH, treated with 6.6 g of p-toluenesulfonic acid, boiled under reflux for 18 h, and cooled to 0°C. The product was collected by filtration to give 52 g (70% yield) of **8**: mp 140-142°C (lit.[3] mp 135-137°C): UV (EtOH) 215 (ε=22,590), 219 (ε=22,150), 237 (ε=11,000), 276 (ε=14,420), 325 (ε=5,952) nm; IR 1725, 1642 cm^{-1}; ^1H NMR δ 2.24 (2 H, m), 2.52 (3 H, s), 2.75 (2 H, m), 3.77 (3 H, s), 4.80 (1 H, t, J=7), 6.46 (1 H, s), 7.39 (1 H, s); ^{13}C NMR δ 22.19 (CH_2), 24.21 (CH_2), 26.19 (CH_3), 52.46 (CH_3), 73.92 (CH), 104.44 (d, ArCH), 112.88 (s, ArC), 114.52 (s, ArC), 132.13 (d, ArCH), 159.86 (s, ArC), 162.76 (s, ArC), 170.52 (C=O, ester), 202.59 (C=O, ketone); MS ***m/z*** 250 (M^+, 80). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.09; H, 5.68.

Methyl (R,S)-6-Acetyl-3,4-dihydro-7-[(5-acetoxypentyl)oxy]-2H-1-benzopyran-2-carboxylate (9). A 1-L, 3-necked, round-bottomed flask equipped with a mechanical stirrer and an Ar bubbler was charged with 37.5 g (0.179 moles) of 5-bromo-1-pentanyl acetate (**13**), 350 mL of anhyd. DMSO, 40.7 g (0.163 mol) of **8**, and 51.0 g (0.369 mol) of anhyd. powdered K_2CO_3. The mixture was stirred at room temperature for 18 h, poured into 1.0 L of H_2O and extracted into EtOAc (2 x 1 L). The extract was washed with 1 L of brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in 200 mL of Et_2O, cooled to 5°C and, with stirring, diluted with petroleum ether (bp 35-60°C). The product was collected by filtration, washed with a little 1:1 Et_2O-petroleum ether (bp 40-60°C) and dried to give 60.0 g (97%) of **9**: mp 51-53°C, UV (EtOH) 312 (ε=7,200), 268 (ε=11,200), 230 (ε=16,900), 216 (ε=19,000) nm; IR 1745, 1732, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (2 H, t), 1.69 (2 H, t), 1.86 (2 H, t), 2.03 (3 H, s, OAc), 2.20 (2 H, m), 2.56 (3 H, s, Ac), 2.72 (2 H, m, $ArCH_2$), 3.78 (3 H, s, OMe), 4.02 (2 H, t, J=6.4, $ArOCH_2$), 4.07 (2 H, t, J=6.3, $AcOCH_2$), 4.80 (1 H, dd, J=4.2), 6.47 (1H, s), 7.56 (1H, s); ^{13}C NMR δ 20.97 (CH_3), 22.21 (CH_2), 22.78 (CH_2), 24.53 (CH_2), 28.29 (CH_2), 28.77 (CH_2), 32.12 (CH_3), 52.54 (CH_3), 64.23 (CH_2), 68.3 (CH_2), 74.13 (CH), 100.53 (CH), 113.38 (s, ArC), 121.31 (s, ArC), 132.21 (ArCH), 158.03 (s, ArC), 158.85 (s, ArC), 170.84 (C=O, ester), 171.13 (C=O, ester), 197.85 (C=O, ketone); MS ***m/z*** 378 (M^+, 20), 363 (M^+-CH_3, 15), 319 (M^+-OAc, 12), 303 (M^+-Me-AcOH, 25). Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.49; H, 7.16.

Methyl (R,S)-6-Acetyl-3,4-dihydro-7-[5-[(methylsulfonyl)oxy]pentyloxy]-2H-1-benzopyran-2-carboxylate (10). A solution of 72.08 g (0.19 mol) of **9** in 1.4 L of MeOH was treated with 38 mL of a 1.0 molar solution of tetrabutylammonium hydroxide and the mixture was stirred at room temperature for 3.0 h, 3.0 mL of AcOH was added and the solution was evaporated at 35°C. The residue was dissolved in 400 mL of EtOAc and the solution was washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated to give 60.45 g (94% yield) of the intermediate hydroxy ester (an analytical sample may be obtained by crystallization from 70% EtOAc in hexane, mp 58-61°C). A stirred solution of 60.25 g of the hydroxyester in 700 mL of EtOAc was cooled to 5°C and treated with 75.5 mL (3 equivalents) of Et_3N and 32.6 mL (2.35 equivalents) of methanesulfonyl chloride. The mixture was stirred at 6°C for 2.0 h, transferred to a separatory funnel and washed sequentially with water, 2N HCl, and brine. Concentration of the EtOAc to ca. 300 mL and dilution with 250 mL of hexane led to crystallization (0°C, 18 h). The product was collected by filtration and washed with some cold hexane - EtOAc (1:1) to give 66 g (84% yield from **9**) of **10**: mp 73-76°C; UV (EtOH) 313 (ε=6,980), 268 (ε=16,050); IR 1750, 1662, 1359, 1172, 1152 cm^{-1}; ^1H NMR δ 1.61 (2 H, m), 1.85 (4 H, m), 2.20 (2 H, m), 2.58 (3 H, s), 2.72 (2 H, m), 2.95 (3 H, s), 3.80 (3 H, s), 3.99 (2 H, t, J=6.2), 4.26 (2 H, t, J=6.2), 4.75 (1 H, dd, J=4.4, 4.0), 6.46 (1 H, s), 7.54 (1 H, s); ^{13}C NMR 22.23 (t, CH_2), 22.39 (t, CH_2), 24.55 (t, CH_2), 28.63 (t, CH_2), 28.87 (t, CH_2), 32.19 (q, CH_3), 37.31 (q, CH_3), 52.57 (q, CH_3), 68.19 (t, CH_2), 69.80 (t, CH_2), 74.04 (d, CH), 100.50 (d, CH), 113.44 (s, ArC), 121.20 (s, ArC), 132.12 (d, ArCH), 158.03 (s, ArC), 158.69 (s, ArC), 170.75 (C=O, ester), 197.64 (C=O, ketone); MS ***m/z*** 414 (M^+, 18). Anal. Calcd for $C_{19}H_{28}O_8S$: C, 55.06; H, 6.32. Found: C, 55.24; H, 6.47.

Methyl (R,S)-6-Acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate (11). A mixture of 66.13 g (0.159 mol) of mesylate **10**, 30.99 g (0.159 mol) of **16**, 33.07 g (0.239 mol) of pulverized K_2CO_3, 5.16 g (15.9 mmol) of tris(3,6-dioxaheptyl)amine

(TDA-1, Aldrich)[7] in 900 mL of toluene was stirred under Ar at reflux for 6 h and then at rt overnight. The mixture was poured into 300 mL of H_2O, and the organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated to give 84.3 g of **11**. Crystallization from MeOH (0°C, 18 h) gave 66 g (81% yield) of **11**: mp 77-80°C; UV (EtOH) 217 (ε=32,600), 230 (ε=25,100), 277 (ε=22,600), 316 (sh, ε=11,600) nm; IR 1752, 1660, 1613 cm^{-1}; ^1H NMR δ 0.92 (3 H, t, J=7.3) 1.5-2.3 (10 H, m), 2.52 (3 H, s, Ac), 2.55 (3 H, s, Ac), 2.70 (4 H, m), 3.80 (3 H, s, OMe), 4.05 (4H, q. J=5.6, 2 x CH_2O), 4.75 (1H, dd, J=4.8, 4.7), 6.4 (1H, d, J=9), 6.48 (1H, s), 7.51 (1H, d, J=9), 7.57 (1H, s); ^{13}C δ 14.40 (q, CH_3), 22.08 (t, CH_2), 22.33 (t, CH_2), 23.10 (t, CH_2), 24.48 (t, CH_2), 24.53 (t, CH_2), 24.60 (t, CH_2) 26.36 (q, CH_3), 29.03 (t, CH_2), 67.96 (t, CH_2), 68.43 (t, CH_2), 74.10 (d, CH), 100.55 (d, ArCH), 102.70 (d, ArCH), 130.14 (d, ArCH), 132.20 (d, CH), 158.08 (s, ArC), 158.85 (s, ArC), 162.04 (s, ArC), 162.87 (s, ArC), 170.80 (C=O, ester), 197.65 (C=O, ketone), 202.91 (C=O, ketone); MS ***m/z*** 512 (M^+, 5). Anal. Calcd for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 67.89; H, 7.21.

(R,S)-6-Acetyl-7[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-2H-H-benzopyran-2-carboxylic Acid Sodium Salt (Ablukast, 5). A stirred solution of 55.82 g (0.109 mol) of **11** in 725 mL of MeOH was treated with 4.45 g (0.111 mol) of NaOH in 20 mL of H_2O and the mixture was stirred at reflux for 1.25 h. It was cooled, concentrated to a volume of ca. 360 mL, diluted with 310 mL of Et_2O, and left at 0°C overnight. The product was collected by filtration, dried in vacuo to give 45.76 g of **5** as the monohydrate. A further 12.27 g of product was obtained from the mother liquor to give a total yield of 99%. UV (EtOH) 217 (31,900), 232 (ε=22,600), 281 (ε=26,500), 316 (sh, ε=13,900) nm; IR (KBr) 3420, 1662, 1610 cm^{-1}; ^1H NMR (D_2O) δ 0.70 (3H, t, J=7), 1.72 (2 H, br s), 1.40 (2 H, br s), 1.59 (3 H, br s), 1.95 (2 H, br d), 2.20 (3 H, s), 2.25 (3 H, s), 2.30 (2 H, br s), 2.54 (2 H, br s), 3.70-3.90 (4 H, br d), 4.40 (1 H, br s), 6.21 (1 H, d, J=7), 6.25 (1 H, s), 7.25 (1 H, d, J=7), 7.32 (1 H, s). Anal. Calcd for $C_{28}H_{35}O_9Na$: C, 62.44; H, 6.55; Na, 4.77. Found: C, 62.25; H, 6.55; Na, 4.55.

The free acid may be obtained by acidification with 2N HCl, mp 114-116°C (lit.[3] mp 113-115°C): ^1H NMR δ 0.90 (3 H, t, J=7), 1.52 (2 H, m), 1.69 (2 H, m), 1.88 (4 H, m), 2.22 (2 H, m), 2.54 (3 H, s), 2.58 (3 H, s), 2.72 (2 H, m), 4.03 (4 H, br s), 4.77 (1 H, dd, J=4.5), 6.45 (1 H, d, J=9), 6.48 (1 H, s), 7.55 (1 H, d, J=9) 7.58 (1 H, s), 8.20 (1 H, br s). Anal. Calcd for $C_{28}H_{36}O_9$: C, 65.11; H, 6.97. Found: C, 65.02; H, 6.87.

5-Bromo-1-Pentanyl Acetate (13). A 2-L, 3-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser and an Ar bubbler, was charged with 430.7 g (5.00 moles) of tetrahydropyran, 399.6 g (3.25 moles) of acetyl bromide and 1.13 g (5.0 mmol) of zinc bromide. The mixture was stirred at reflux for 2.5 h, cooled to rt, and transferred to a separatory funnel with 1.0 L of hexane. The solution was washed with 250 mL of sat. $NaHCO_3$, H_2O (2 x 500 mL), 500 mL of brine, dried (Na_2SO_4), and evaporated to give 692 g of crude **13**. Distillation gave 625.6 g (92% yield) of **13**: bp 60-67°C/0.08 Torr.; IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR δ 1.50 (2 H, t, J=7), 1.66 (2 H, t, J=7), 1.86 (2 H, t, J=7), 2.06 (3 H, s), 3.42 (2 H, t, J=7, CH_2Br), 4.07 (2 H, t, J=7); MS ***m/z*** 148 (M^+-AcOH). Anal. Calcd for $C_7H_{13}BrO_2$: (C, 40.21; H, 6.27; Br, 38.22. Found: C, 39.82; H, 6.35; Br, 38.45.

1-[2-Hydroxy-4-(2-propenyloxy)phenyl]ethanone (15). A mixture of 100 g (0.657 mol) of 2',4'-dihydroxyacetophenone (Aldrich), 51 g (0.666 mol) of allyl chloride, 100 g (0.723 mol) of pulverized anhyd. K_2CO_3, and 20 g (0.12 mol) of KI in 400 mL of acetone was stirred at reflux for 24 h, cooled to rt, and filtered

through Celite. The filter cake was washed with 30 mL of acetone, and the combine filtrate and washing were evaporated. The residue was slurried with 250 mL of Et_2O and filtered. Evaporation and distillation of the residue gave 97 g (76% yield) of **15**: bp 115-120°C/0.2 (Torr.); UV (EtOH) 212 (ε=17,580), 229 (ε=9,700), 274 (ε=15,180), 313 (ε=6,900); IR 3025, 1630 cm^{-1}; ^1H NMR δ 2.54 (3 H, s), 4.55 (2 H, d, J=5), 5.30 (1 H, d, J=11), 5.40 (1 H, d, J=17), 6.00 (1 H, ddd, J=17,11,5), 6.40 (1 H, s), 6.43 (1 H, d, J=9), 7.62 (1 H, d, J=9), 12.72 (1 H, s, OH); ^{13}C NMR δ 26.18 (q, $\underline{C}H_3CO$), 68.98 (t, OCH_2), 101.74 (d, ArCH), 108.06 (d, ArCH), 114.01 (s, ArC), 118.35 (t, vinyl CH_2), 132.18 (d, vinyl CH), 165.04 (s, ArC), 165.17 (s, ArC), 205.59 (s, C=O); MS ***m/z*** 192 (M^+, 35). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H. 6.30.

1-[2,4-Dihydroxy-3-propylphenyl)ethanone (16). A solution of 50 g (0.26 mol) of **15** in 250 mL of xylenes was heated at 215°C in a glass-lined autoclave for 18 h, cooled to rt, and the product was collected by filtration. It was washed with hexane and dried to give 40 g (80% yield) of 1-[2,4-dihydroxy-3-(2-propenyl)phenyl]ethanone, mp 133-135°C. A solution of 35 g (0.182 mol) of this material in 300 mL of a 1:1 mixture of toluene and THF was hydrogenated over 3.5 g of 5% Pt on charcoal at ambient temperature and 30 psi until hydrogen absorption ceased. Removal of the catalyst by filtration and of the solvents by evaporation gave a tan-colored solid which was slurried with hexane to give 34 g (96% yield) of **16**: mp 123-125°C; UV (EtOH) 215 (ε=18,720, 231 (ε=9,210), 285 (ε=17,250), 320 (ε=5,600) nm; IR (KBr) 3580, 3342, 1623 cm^{-1}; ^1H NMR (d_6-DMSO) δ 0.88 (3 H, t, J=7), 1.47 (2 H, m), 2.50 (2 H, s, $ArCH_2$), 2.52 (3 H, s, CH_3CO), 6.45 (1 H, d, J=9), 7.63 (1 H, d, J=9), 10.45 (1 H, s, OH), 13.04 (1 H, s, OH); ^{13}C NMR ($CDCl_3$ + d_6-DMSO) δ 14.219 (q, CH_3), 21.83 (t, CH_2), 24.35 (t, CH_2), 26.00 (q, CH_3), 107.54 (d, ArCH), 113.0 (s, ArC), 116.16 (s, ArC), 129.85 (d, ArCH), 162.42 (s, ArC), 163.06 (s, ArC), 202.76 (s, C=O); MS ***m/z*** 194 (M^+, 47), 179 (M^+-Me, 35), 165 (M^+-Et, 100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.16; H, 7.24.

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