δ 6.30–5.00 (m, 5 H), 4.35–3.85 (m, 1 H); UV max (basic EtOH) 247 nm (ε 9800), 326 (19800); mass spectrum (Me_3Si derivative), m/e 406.2546 (calcd for $C_{23}H_{38}O_4Si$, M^+, 406.2539), 316, 279, 262, 225, 196, 164, 143, 133, 119, 99, 73. Anal. ($C_{20}H_{30}O_4$) C, H.

B. Via Direct Lactonization of PGE_2 (38). A mixture of PGE_2 (**38**; 352 mg, 1 mmol), 393 mg (1.5 mmol) of triphenylphosphine, and 330 mg (1.5 mmol) of 2,2'-dipyridyl disulfide in 5 mL of dry, oxygen-free xylene was stirred under nitrogen at room temperature for 18 h. The reaction mixture was then diluted with 250 mL of xylene and heated at reflux for 2 h. Following removal of the xylene at reduced pressure (rotovac/vacuum pump), the residue was partitioned between brine and EtOAc. The EtOAc extracts were washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Chromatographic purification of the crude product (70 g of silica gel, 40% EtOAc/hexane, 6.5-mL fractions) afforded 176 mg of crystalline PGE_2 1,15-lactone (**37**; fractions 89–130; 53% of theory). Recrystallization from EtOAc/hexane yielded lactone **37** with mp 72–74 °C, identical spectrally and by TLC with the material obtained in part A immediately above.

Utilizing procedures analogous to those described in this experiment, we synthesized the following PGE 1,15-lactones.

PGE_1 1,15-lactone (43): via procedure A (oxidation of **39**), 70% yield; via direct lactonization of PGE_1, 54%. In each case, the chromatographically pure product (from silica gel, 50% EtOAc/hexane) was recrystallized from ether/hexane and exhibited mp 89–90 °C; R_f 0.67 (20% acetone/CH_2Cl_2); IR (mull) 3390, 3320, 1745, 1720, 1335, 1255, 1235, 1195, 1180, 1160, 1100, 1075, 980 cm^{-1}; NMR ($CDCl_3$) δ 6.1–5.85 (m, 2 H), 5.45–5.05 (m, 1 H), 4.40–3.85 (m, 1 H); UV max (basic EtOH) 242 nm (ε 9200), 270 (8150), 324 (19750); mass spectrum (Me_3Si derivative), m/e 408.2694 (calcd for $C_{23}H_{40}O_4Si$, M^+, 408.2696), 393, 390, 380, 375, 365, 364, 318, 264, 150, 99. Anal. ($C_{20}H_{32}O_4$) C, H.

17-Phenyl-18,19,20-trinor-PGE_2 1,15-lactone (44): via procedure B (direct lactonization); xylene solvent; 2.5 h reflux; chromatographic purification on silica gel (80% ether/hexane); 37% yield. Recrystallization of the chromatographically pure product from ether/hexane gave clean lactone **44**: mp 81–83 °C; R_f 0.57 (70% EtOAc/hexane), 0.66 (20% acetone/CH_2Cl_2); IR (mull) 3400, 1725, 1605, 1500, 1330, 1240, 1160, 1145, 1085, 1045, 975, 745, 725, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.10 (m, 5 H), 6.30–5.00 (m, 5 H), 4.30–2.80 (m, 1 H); UV max (basic EtOH) 243 nm (ε 9750), 320 (18800); mass spectrum (Me_3Si derivative), m/e 440.2351 (calcd for $C_{26}H_{36}O_4Si$, M^+, 440.2383), 350, 313, 296, 259, 241, 205, 184, 169, 143, 133, 117, 105, 91, 73. Anal. ($C_{23}H_{28}O_4$) C, H.

PGA_2 1,15-Lactone (45). A solution of 350 mg of PGE_2 1,15-lactone (**37**) in 10 mL of dry pyridine was treated with 4 mL of acetic anhydride, and the clear reaction mixture was allowed to stand at 25 °C for 3 h. The reaction mixture was then cooled to 0 °C, treated dropwise over 15 min with 20 mL of CH_3OH, and allowed to stand in a melting ice bath over 2 h. After an additional 18 h at 25 °C, the mixture was poured into ice, ether, water, and 70 mL of 2 N aqueous $KHSO_4$ and extracted thoroughly with ether. The extracts were washed with water, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. Chromatographic purification of the crude product (100 g of silica gel, 15% EtOAc/hexane, 8-mL fractions) afforded 120 mg of crystalline PGA_2 1,15-lactone (**45**) (fractions 82–108; 36% yield). The analytical sample was obtained by recrystallization from ether/hexane: mp 60.0–61.5 °C; R_f 0.76 (70% EtOAc/hexane), 0.85 (20% acetone/CH_2Cl_2); IR (mull) 3010, 1715, 1705, 1580, 1355, 1345, 1325, 1245, 1170, 1145, 1140, 1035, 970 cm^{-1}; NMR ($CDCl_3$) δ 7.35–7.20 (m, 1 H, C-11), 6.25–5.00 (m, 6 H, C-5, C-6, C-10, C-13, C-14, C-15), 3.2–2.9 (m, 1 H, C-12); UV max (neutral EtOH) 215 nm (ε 9350); UV max (basic EtOH) 240 nm (ε 9650), 255 sh (8300), 267 sh (7650), 325 (19750); mass spectrum, m/e 316.2074 (calcd for $C_{20}H_{28}O_3$, M^+, 316.2038), 298, 288, 259, 229, 198. Anal. ($C_{20}H_{28}O_3$) C, H.

PGB_2 1,15-Lactone (47).[28] PGB_2 was converted to the 1,15-lactone by the direct lactonization procedure (B) described earlier for the PGEs (xylene, reflux 16 h). Chromatographic purification of the crude product (100 g of silica gel, 60% ether/hexane, 20-mL fractions) yielded 200 mg of lactone **47**, a viscous, pale yellow oil (fractions 14–20; 63% yield): R_f 0.37 (ether/hexane, 1:1); IR (neat) 1715, 1640, 1595, 1370, 1240, 1160, 980, 940, 760 cm^{-1}; NMR ($CDCl_3$) δ 6.80–5.97 (m, 2 H), 5.70–5.07 (m, 3 H); UV max (neutral EtOH) 277 nm (ε 16800); mass spectrum, m/e 316.2021 (calcd for $C_{20}H_{28}O_3$, M^+, 316.2038), 298, 288, 269, 217.

PGD_2 1,15-Lactone (51). Full details of the synthesis and spectral characterization of lactone **51** are found in ref 16.

Acknowledgment. The authors are grateful to D. R. Morton and N. A. Nelson for their synthesis of lactones **12** and **47**, respectively, to J. M. Baldwin, A. D. Forbes, M. J. Sutton, and D. C. Beuving for their skilled technical assistance, to C. F. Lawson and the Prostaglandin Screening Laboratories for the rat blood pressure and gerbil colon data cited in Table III, and to L. Baczynskyj and P. A. Meulman for their aid in spectral interpretation.

Registry No. **9**, 551-11-1; **10**, 55314-48-2; **10**·2Me_3Si, 85720-23-6; **11**, 62411-08-9; **11** (acid), 35700-23-3; **11**·2Me_3Si, 85720-24-7; **12**, 85720-13-4; **12** (acid), 39746-23-1; **12**·2Me_3Si, 85720-25-8; **13**, 85761-26-8; **13** (acid), 57773-66-7; **13**·2Me_3Si, 85720-26-9; **14**, 62443-67-8; **14** (acid), 62411-10-3; **14**·2Me_3Si, 85720-27-0; **16**, 62410-77-9; **18**, 62410-85-9; **19**, 62410-86-0; **20**, 62410-87-1; **21**, 62410-84-8; **21**·2Me_3Si, 65627-26-1; **22**, 85720-14-5; **23**, 85720-15-6; 15(*R*)-**24**, 85720-16-7; **25**, 35700-22-2; **26**, 85720-17-8; **27**, 85720-18-9; **28**, 85720-19-0; **29**, 85720-20-3; **30**, 85720-21-4; **31**, 80029-28-3; **31**·2Me_3Si, 85720-28-1; **32**, 42161-63-7; **32** (pyridinethiol ester), 85720-22-5; **34**, 55314-49-3; **34**·2Me_3Si, 62410-21-3; **35**, 62410-94-0; **36**, 62410-95-1; **37**, 62410-93-9; **38**, 363-24-6; **39**, 62411-18-1; **39** (acid), 745-62-0; **39**·2Me_3Si, 85720-29-2; **40**, 62411-21-6; **41**, 62411-17-0; **41** (acid), 51705-19-2; **41**·2Me_3Si, 64775-50-4; **42**, 62411-15-8; **42** (acid), 38344-08-0; **42**·2Me_3Si, 85720-30-5; **43**, 62411-20-5; **43**·Me_3Si, 85720-31-6; **44**, 62411-16-9; **44** (acid), 38315-43-4; **44**·Me_3Si, 85720-32-7; **45**, 62443-66-7; **47**, 62410-97-3; **47** (acid), 13367-85-6; **51**, 62410-98-4; 2,2'-dipyridyl disulfide, 2127-03-9; PGD_2, 41598-07-6.

Synthesis of Three Potential Inhibitors of Leukotriene Biosynthesis[1]

Jürg R. Pfister*,† and D. V. Krishna Murthy‡

Institute of Organic Chemistry and Institute of Biological Sciences, Syntex Research, Palo Alto, California 94304.
Received May 10, 1982

The syntheses of 7,7-dimethyl- (1), 10,10-dimethyl- (2), and 5,6-benzoarachidonic acid (3), potential substrate analogue inhibitors of leukotriene biosynthesis, are described. Two of these compounds (1 and 2) apparently stimulated, while 3 inhibited, the activity of lipoxygenase from intact human polymorphonuclear leukocytes in vitro when stimulated with Ca^{2+} and calcium ionophore A23187 in the presence of BSA and arachidonic acid.

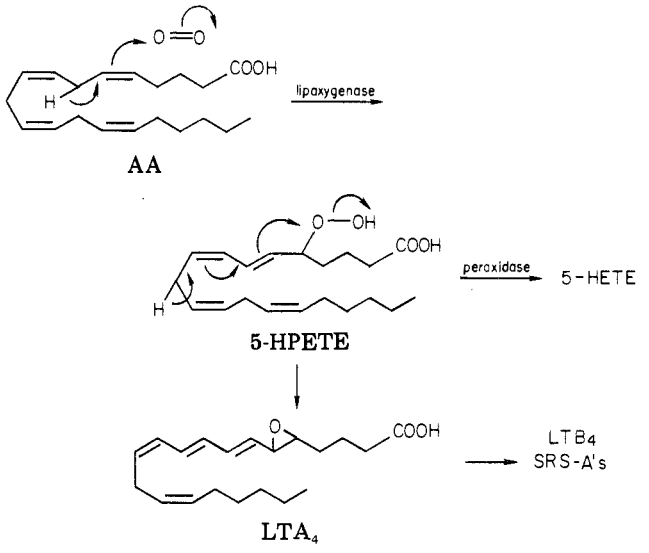
Metabolism of arachidonic acid (AA) by lipoxygenase leads to the formation of a variety of products, among which the chemotactic factor LTB_4 and the spasmogenic slow-reacting substances of anaphylaxis (SRS-A's) are of particular biological importance. Consequently, specific

† Institute of Organic Chemistry.
‡ Institute of Biological Sciences.

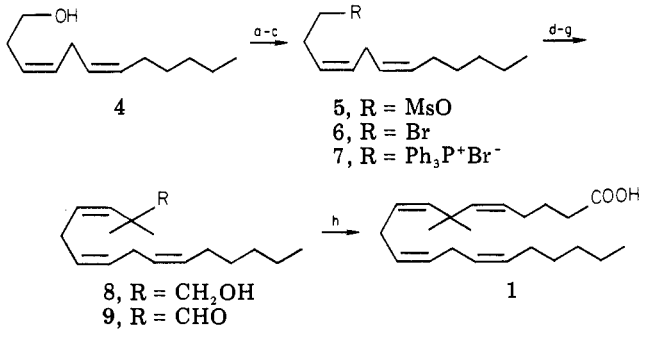
(1) Contribution no. 623 from the Institute of Organic Chemistry.

0022-2623/83/1826-1099$01.50/0

Scheme I



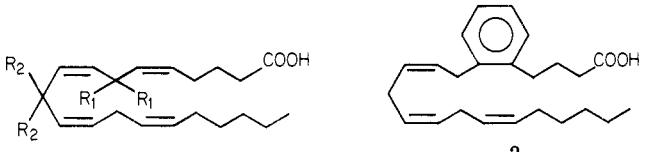
Scheme II[a]



[a] Reagents: a = MsCl, Et_3N; b = LiBr; c = PPh_3; d = BuLi; e = 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]-propanal; f = *p*-TsOH, MeOH; g = Me_2SO, $(COCl)_2$; h = $Ph_3P{=}CH(CH_2)_3COO^-Na^+$.

inhibitors of lipoxygenase might be of value in the treatment of inflammatory processes and asthma.[2]

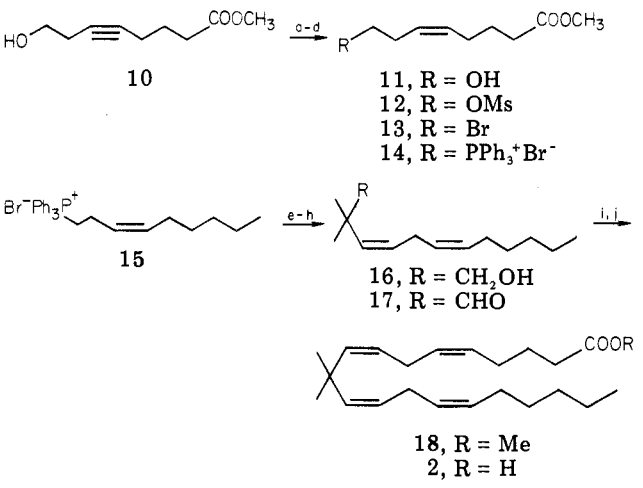
We describe herein synthetic routes to 7,7-Me_2-AA (**1**),



10,10-Me_2-AA (**2**), and 5,6-benzo-AA (**3**), which were chosen as potentially attractive candidates for the study of the inhibition of leukotriene and SRS-A biosynthesis, with which they could interfere at two specific points in the proposed chain of events[3] (see Scheme I). Compounds **1** and **3** might block the formation of 5-HPETE from AA (a double-bond shift from the 5,6- to the 6,7-position is unlikely because C-7 in **1** is tetrasubstituted; this same shift would involve deconjugation of the benzene ring in **3**), whereas **2** might inhibit the conversion of 5-HPETE to LTA_4 (no abstractable hydrogens at C-10). These structural modifications were hoped to prevent these compounds from serving as alternate substrates for lipoxygenase.

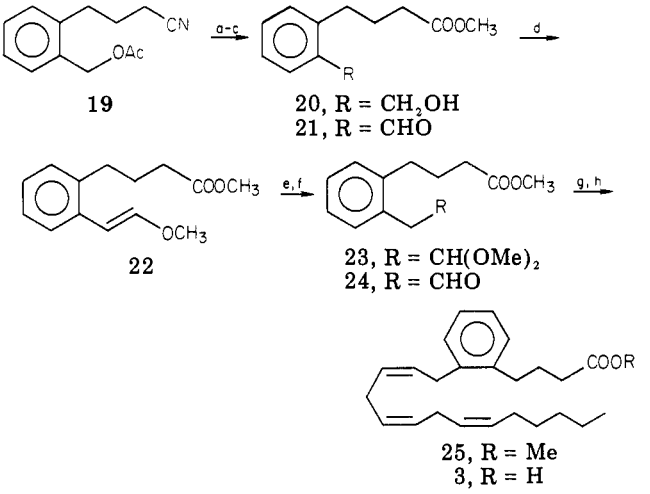
(2) P. Borgeat and P. Sirois, *J. Med. Chem.*, **24**, 121 (1981).
(3) P. Borgeat and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 2148 (1979).

Scheme III[a]



[a] Reagents: a = H_2, Lindlar; b = MsCl, Et_3N; c = LiBr; d = PPh_3; e = BuLi; f = 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal; g = *p*-TsOH, MeOH; h = CrO_3, pyridine; i = 14, BuLi; j = LiOH.

Scheme IV[a]



[a] Reagents: a = KOH; b = Li_2CO_3, MeI; c = PDC, DMF; d = $MeOCH{=}PPh_3$; e = *p*-TsOH, MeOH; f = H_2SO_4, THF; g = 7, BuLi; h = LiOH.

Chemistry. The preparation of 7,7-Me_2-AA (**1**) was carried out as outlined in Scheme II. 3(*Z*),6(*Z*)-Dodecadien-1-ol[4] (**4**) was converted via the mesylate **5** into the bromide **6**. Quaternization with Ph_3P provided the phosphonium salt **7**, which was deprotonated (BuLi–THF), and the resulting ylide was reacted with 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal[5] to give, after deprotection, the dimethylcarbinol **8**. Oxidation of **8** with oxalyl chloride–Me_2SO[6] yielded the tertiary aldehyde **9**, which was reacted with the ylide salt derived from 5-(triphenylphosphonio)valeric acid and dimsyl sodium in Me_2SO[7] to furnish 7,7-dimethylarachidonic acid (**1**).

For the synthesis of 10,10-Me_2-AA (**2**, Scheme III), a synthon containing carbons 1 through 8 was first prepared. Thus, catalytic reduction of methyl 8-hydroxy-5-octynoate[8]

(4) A. Tai, F. Matsumara, and H. Coppel, *J. Insect Physiol.*, **17**, 181 (1971).
(5) H. Marschall, K. Tantau, and P. Weyerstahl, *Chem. Ber.*, **107**, 887 (1974).
(6) A. Mancuso, S. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
(7) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5657 (1969).

Table I. Effects of 1-3 on Lipoxygenase Activity in Intact Human PMNs[a]

no.	% effect (±SD)[b] at 1 × 10^{-4} M on formation of 5-HETE	% effect (±SD)[b] at 1 × 10^{-4} M on formation of LTB_4
1	+29 (±13)[c]	+19 (±10)
2	+60 (±10)	+40 (±10)
3	−94 (±3)	−91 (±2)

[a] See Experimental Section for methods. [b] Values from four determinations. [c] A plus sign denotes apparent stimulation; a minus sign denotes inhibition.

(10) over Lindlar catalyst, followed by sequential treatment of the resulting cis-olefinic alcohol 11 with MsCl–Et_3N and LiBr, and quaternization with Ph_3P gave the 8-(triphenylphosphonio)-5(*Z*)-octenoate 14. The remainder of the carbon chain was then built up by Wittig reaction of the known phosphonium salt 15[9] with 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal,[5] removal of the THP group (to give 16), and oxidation with Collins reagent[10] to provide aldehyde 17. Treatment of the latter with the ylide derived from 14 gave the methyl ester of 10,10-Me_2-AA (18), which was converted into the desired free acid 2 by hydrolysis with LiOH.

For the synthesis of the 5,6-benzo analogue 3 (Scheme IV), the acetoxy nitrile 19[11] was saponified with KOH, and the resulting crude hydroxy acid was esterified to form the hydroxy ester 20, which was oxidized to the aldehyde 21 utilizing pyridinium dichromate in DMF.[12] Wittig reaction of 21 with the ylide derived from $MeOCH_2PPh_3^+Cl^-$ and dimsyl sodium in Me_2SO[13] afforded the enol ether 22 as an ca. 1:1 *E*/*Z* mixture. Hydrolysis of 22 was best effected in two stages consisting of conversion into the dimethyl acetal 23 (*p*-TsOH–MeOH), followed by treatment with 2% H_2SO_4 in THF. The resulting phenylacetaldehyde 24, on reaction with the ylide prepared from phosphonium salt 7, provided the methyl ester of 5,6-benzo-AA (25), which was hydrolyzed with LiOH to afford 5,6-benzoarachidonic acid (3) itself.

Results and Conclusions

The three target compounds were examined in vitro as inhibitors of 5-lipoxygenase and cyclooxygenase[14] from intact human polymorphonuclear leukocytes (PMNs) at a concentration of 10^{-4} M using [1-^{14}C]arachidonic acid (AA) as the substrate (see Experimental Section). Compounds 1 and 2 appeared to stimulate the 5-lipoxygenase activity (e.g., the formation of both 5-HETE and LTB_4; Table I). On the other hand, although an earlier experiment with compound 3 also suggested an apparent stimulation of the 5-lipoxygenase activity, further testing in several experiments revealed that the compound inhibited the formation of 5-HETE and LTB_4 by greater than 90% at 10^{-4} M. Under the same conditions, the known lipoxygenase inhibitor BW 755C[15] totally inhibited the formation of the above two compounds (IC_{50} for BW 755C in several experiments ranged from 1.1 × 10^{-5} to 4 × 10^{-5} M).

The apparent stimulation of lipoxygenase activity seen with compounds 1 and 2 in intact human PMNs (stimulated by Ca^{2+} and A23187 in the presence of BSA) could be rationalized in two ways. It is possible that the test compounds might compete with the substrate AA for binding to BSA and, hence, increase the availability of the AA, thus leading to increased formation of the enzymatic products 5-HETE and LTB_4. Secondly, it is conceivable that the compounds might bind to a site adjacent to the binding site of the substrate, which might result in a conformational change at the substrate binding site, leading to increased substrate affinity and, therefore, increased product formation. The apparent stimulation of the 12-lipoxygenase activity in platelets by some acetylenic eicosanoids has been reported;[16] however, no explanation for these findings was offered. In addition, it was found that the IC_{50} values for these eicosanoid inhibitors of 12-lipoxygenase using the high-speed supernatants of platelet lysates were several orders of magnitude less than the IC_{50} values for inhibiting the same enzyme using intact washed platelets.

Although other investigators have used cell-free 5-lipoxygenase preparations from rat RBL-1 cells to test lipoxygenase inhibitors, including eicosanoid analogues,[17] we felt that it would be more appropriate to utilize intact human PMNs, since we are seeking agents that might ultimately prove clinically useful.

Experimental Section

Melting points (uncorrected) were obtained on a Mel-Temp apparatus, infrared spectra were obtained on a Perkin-Elmer 237 grating instrument, ^{1}H NMR spectra were obtained on a Varian EM 390 or Bruker WM 300, ^{13}C NMR were obtained on a Bruker WH 90, and mass spectra were obtained on a Varian MAT instrument. Combustion analyses were obtained from Syntex Analytical Research or Atlantic Microlab. Centrifugally accelerated chromatography was performed on a Chromatotron Model 7924 (Harrison Research, Palo Alto, CA). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl; hexamethylphosphoric triamide (HMPA) was vacuum distilled from calcium hydride. Dry dichloromethane was obtained by distillation from phosphorous pentoxide.

1-Bromo-3(*Z*),6(*Z*)-dodecadiene (6). To a stirred solution of 15.0 g (81.5 mmol) of 3(*Z*),6(*Z*)-dodecadien-1-ol[4] (4) and 17.0 mL (0.12 mol) of Et_3N in 200 mL of dry CH_2Cl_2, cooled to 0 °C, was added dropwise over 15 min a solution of 7.6 mL (97.5 mmol) of MsCl in 30 mL of CH_2Cl_2. After stirring at 0 °C for 2 h, the reaction was quenched with H_2O. The organic phase was separated, washed with 2 N HCl and brine, and dried over $MgSO_4$. Filtration and rotary evaporation gave the crude mesylate 5, which was refluxed with 9.25 g (106 mmol) of LiBr in 250 mL of acetone for 3 h. The reaction mixture was cooled and filtered, the filtrate was evaporated, and the residue was distributed between Et_2O and H_2O. The dried ($MgSO_4$) organic phase was evaporated, and the residue was vacuum distilled to afford 17.7 g (88.6%) of 6, bp 75–77 °C (0.5 mm). Anal. ($C_{12}H_{21}Br$) C, H.

Triphenylphosphonium Salt 7. A solution of 8.3 g (33.9 mmol) of 6 and 11.5 g (43.9 mmol) of Ph_3P in 120 mL of MeCN was refluxed under N_2 for 48 h. The solvent was removed in vacuo,

(8) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976).
(9) J. Rokach, Y. Girard, Y. Guindon, J. G. Atkinson, M. Larue, R. N. Young, P. Masson, and G. Holme, *Tetrahedron Lett.*, 1485 (1980).
(10) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(11) U.S. Patent 3 984 469 (1976).
(12) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).
(13) S. Danishefsky, K. Nagasawa, and N. Wang, *J. Org. Chem.*, **40**, 1989 (1975).
(14) Recent experiments in our laboratory have shown that little or no cyclooxygenase products (e.g., PGE_2, $PGF_{2\alpha}$, and TXB_2) are formed from human PMNs when stimulated by Ca^{2+} and calcium ionophore A23187.
(15) G. A. Higgs, R. J. Flower, and J. R. Vane, *Biochem. Pharmacol.*, **28**, 1959 (1979).
(16) F. F. Sun, J. C. McGuire, D. R. Morton, J. E. Pike, H. Sprecher, and W. H. Kunau, *Prostaglandins*, **21**, 333 (1981).
(17) (a) E. J. Corey and H. Park, *J. Am. Chem. Soc.*, **104**, 1750 (1982). (b) D. Sok, C. Han, J. Pai, and C. J. Sih, *Biochem. Biophys. Res. Commun.*, **107**, 101 (1982). (c) B. A. Jakschik, D. M. DiSantis, S. K. Sankarappa, and H. Sprecher, "Leukotrienes and Other Lipoxygenase Products", Raven Press, New York, 1982, pp 127–135.

and the oily residue was stirred under reflux for 2 h with 100 mL of Et_2O. After the solution cooled, the Et_2O was decanted, and this procedure was repeated. The residue was then stirred at room temperature for 24 h with an additional 100 mL of Et_2O, during which time fine microcrystals of **7** formed. Isolation of this salt was carried out by suction filtration in a glove box under dry N_2, washing with dry Et_2O, and drying in a vacuum desiccator over P_2O_5 at 0.05 mm for 20 h to give 18 g (91%) of **7**, mp 53–55 °C. This very hygroscopic material was stored and handled only in an inert atmosphere. Anal. ($C_{30}H_{36}BrP$) C, H.

2,2-Dimethyl-3(*Z*),6(*Z*),9(*Z*)-pentadecatrien-1-ol (8). To a solution of 14.8 g (29.2 mmol) of **7** in THF (300 mL) cooled to −78 °C was added slowly by syringe a 1.6 M solution of BuLi in hexane (18.25 mL, 29.2 mmol). After 20 min, 30 mL of HMPA was added, followed 5 min later by a solution of 5.43 g (29.2 mmol) of 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal[5] in 25 mL of THF. After stirring at −78 °C for 30 min and at ambient temperature for 2 h, the reaction was quenched by the addition of H_2O. Most of the THF was removed by rotary evaporation, and the residue was extracted with Et_2O. The dried ($MgSO_4$) organic phase was filtered and evaporated, and the residue was stirred with 500 mg of *p*-TsOH in 100 mL of MeOH at room temperature for 6 h. After dilution with H_2O and extraction (Et_2O), the crude trienol **8** was purified by column chromatography with 20% AcOEt in hexane as the eluant to afford 5.46 g (76%) of **8** as a colorless oil: NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.14 (s, 6), 1.30 (m, 6), 2.06 (m, 2), 2.81 (t, 2, J = 7 Hz), 3.42 (s, 2), 5.25–5.45 (m, 6). Anal. ($C_{17}H_{30}O$) C, H.

2,2-Dimethyl-3(*Z*),6(*Z*),9(*Z*)-pentadecatrien-1-al (9). To a stirred solution of 1.7 mL (19.5 mmol) of oxalyl chloride in 30 mL of dry CH_2Cl_2, cooled to −60 °C, was slowly added a solution of 2.8 mL (39.5 mmol) of Me_2SO in 10 mL of CH_2Cl_2. After the solution was stirred at −60 °C for 20 min, a solution of 3.5 g (13.16 mmol) of **8** in 10 mL of CH_2Cl_2 was added, followed 5 min later by 9.8 mL (70.44 mmol) of Et_3N. The reaction mixture was allowed to warm to room temperature over 2 h and then quenched with H_2O. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with H_2O, 2 N HCl, and again H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed (5% Et_2O in hexane), and the uniform fractions were distilled in a Kugelrohr: yield 3.28 g (94.5%) of **9**; bp 100–105 °C (0.1 mm); IR (film) 1730 cm^{-1}. Anal. ($C_{17}H_{28}O$) C, H.

7,7-Dimethylarachidonic Acid (1). A solution of 2.34 g (5.28 mmol) of 5-(triphenylphosphonio)valeryl bromide in 25 mL of Me_2SO was treated at room temperature with 5.0 mL (10 mmol) of a 2 M dimsyl sodium solution in Me_2SO.[7] After 30 min, the dark red solution was diluted with 20 mL of THF and cooled to 10 °C. Aldehyde **9** (930 mg, 3.52 mmol), dissolved in 5 mL of THF, was then added, and the reaction mixture was stirred at 10 °C for 15 min. Quenching with dilute AcOH and extraction with Et_2O gave a crude product, which was purified on silica gel (hexane–AcOEt–AcOH, 85:15:1) to give 990 mg (85%) of **1**: bp 125–130 °C (0.03 mm); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.19 (s, 6), 1.24–1.42 (m, 6), 1.66 (m, 2), 2.0–2.17 (m, 4), 2.34 (t, 2, J = 7 Hz), 2.75–2.88 (m, 4), 5.11–5.20 (m, 2), 5.30–5.47 (m, 4), 5.50–5.61 (m, 2); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.60, 24.53, 25.79, 27.27, 27.72, 28.69, 29.37, 31.26, 31.44, 31.57, 33.73, 36.64, 127.7, 128.1, 128.3, 128.5, 130.4, 139.5, 140.2, 179.9. Anal. ($C_{22}H_{36}O_2$) C, H.

Methyl 8-Hydroxy-5(*Z*)-octenoate (11). Methyl 8-hydroxy-5-octynoate[8] (**10**; 5.3 g, 31.2 mmol) in THF (75 mL) containing Et_3N (1.5 mL) was hydrogenated at room temperature and 1 atm over 530 mg of Lindlar catalyst (Aldrich Chemical Co.). After 735 mL of H_2 (105% of theory) had been absorbed, the reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was chromatographed on silica gel (40% AcOEt in hexane), and the uniform fractions were distilled in a Kugelrohr at 90–110 °C (0.5 mm) to afford 4.3 g (80%) of **11**: IR (film) 3400, 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.70–2.6 (m, 9), 3.55 (m, 2), 3.66 (s, 3), 5.50 (m, 2); ^{13}C NMR ($CDCl_3$) δ 24.84, 26.66, 30.88, 33.42, 51.62, 62.22, 126.8, 131.5, 174.4. Anal. ($C_9H_{16}O_3$) C, H.

Methyl 8-Bromo-5(*Z*)-octenoate (13). This compound was prepared from **11** (4.8 g, 27.9 mmol) exactly as described for **6**. Silica gel chromatography (20% AcOEt in hexane) and Kugelrohr distillation at 110 °C (0.1 mm) provided 6.2 g (94.5%) of **13**: IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.80 (m, 8), 3.38 (t, 2, J = 7 Hz), 3.66 (s, 3), 5.48 (m, 2); ^{13}C NMR ($CDCl_3$) δ 24.64, 26.72, 30.82, 32.44, 33.42, 51.56, 127.2, 131.8, 174.1. Anal. ($C_9H_{15}BrO_2$) C, H.

Phosphonium Salt 14. A solution of 6.0 g (25.5 mmol) of **13** and 8.0 g (30.5 mmol) of Ph_3P in 60 mL of MeCN was refluxed under N_2 for 64 h. The reaction mixture was processed as described for **7** to furnish 11.3 g (89%) of **14**: mp 101–103 °C; IR (KBr) 1735, 1600 cm^{-1}. Anal. ($C_{27}H_{30}BrO_2P$) C, H.

2,2-Dimethyl-3(*Z*),6(*Z*)-dodecadien-1-ol (16). Ylide formation of **15**[9] (9.66 g, 19.4 mmol), reaction with 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal, and deprotection were performed as outlined for **8**. Chromatography on silica gel (20% AcOEt in hexane) afforded 3.9 g (93%) of pure **16**: IR (film) 3360 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.14 (s, 6), 1.32 (m, 6), 2.04 (q, 2, J = 7 Hz), 2.96 (t, 2, J = 7 Hz), 3.41 (s, 1), 5.21–5.47 (m, 4). Anal. ($C_{14}H_{26}O$) C, H.

2,2-Dimethyl-3(*Z*),6(*Z*)-dodecadien-1-al (17). To a solution of 21.6 mL (0.268 mol) of pyridine in 300 mL of dry CH_2Cl_2, cooled in an ice bath, was added 13.04 g (0.134 mol) of CrO_3 in portions. After the solution was stirred at ambient temperature for 30 min, 2.81 g (13.38 mmol) of **16**, dissolved in 15 mL of CH_2Cl_2 was added, and the reaction mixture was stirred at room temperature for 60 min. The dark solution was washed with dilute HCl, H_2O, aqueous Na_2SO_3, and again H_2O, dried, and evaporated to give 2.7 g of crude **17** as a yellow oil. Filtration through a short column of silica gel (2% Et_2O in hexane), followed by Kugelrohr distillation at 50–60 °C (0.02 mm), provided 2.3 g (80%) of **17**: IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.21 (s, 6), 1.30 (m, 6), 2.0 (q, 2, J = 7 Hz), 2.68 (t, 2, J = 7 Hz), 5.20–5.55 (m, 4), 9.52 (s, 1). Anal. ($C_{14}H_{24}O$) C, H.

Methyl 10,10-Dimethylarachidonate (18). A suspension of **14** (3.48 g, 7.0 mmol) in dry THF (90 mL) was cooled to −78 °C and treated dropwise with 1.6 M BuLi in hexane (4.37 mL, 7.0 mmol). After the solution was stirred for 20 min, 10 mL of HMPA was added, followed 5 min later by 1.3 g (6.25 mmol) of **17** in 10 mL of THF. The reaction mixture was stirred at −78 °C for 30 min and at ambient temperature for 2 h, quenched with dilute AcOH, concentrated on a rotary evaporator, and extracted with Et_2O. Column chromatography (5% Et_2O in hexane) afforded 1.42 g of **18** contaminated with starting aldehyde **17**, as well as 600 mg of a slightly more polar product. Pure **18** was obtained by centrifugally accelerated chromatography (1% Et_2O in hexane): yield 1.24 g (57%); bp 80–85 °C (0.01 mm); IR (film) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.21 (s, 6), 1.30 (m, 6), 1.70 (m, 2), 2.06 (m, 4), 2.3 (t, 2, J = 7 Hz), 2.81 (t, 4, J = 7 Hz), 3.67 (s, 3), 5.10–5.60 (m, 8); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.62, 24.96, 26.76, 27.39, 27.79, 27.83, 29.45, 31.34, 31.64, 33.61, 36.73, 51.47, 127.9, 128.02, 128.08, 128.3, 128.4, 128.9, 129.4, 130.5, 139.4, 139.5, 139.7, 139.8, 174.3. Anal. ($C_{23}H_{38}O_2$) C, H. The more polar product was identified as 5-butyl-14,14-dimethyl-9(*Z*),12(*Z*),15(*Z*),18(*Z*)-tetracosatetraen-5-ol: bp 160 °C (0.1 mm); IR (film) 3400 cm^{-1}; MS, m/e 412 ($M^+ - H_2O$), 373, 355, 179. Anal. ($C_{30}H_{54}O$) C, H.

10,10-Dimethylarachidonic Acid (2). A solution of 760 mg (2.2 mmol) of **18** and 760 mg (18.1 mmol) of $LiOH{\cdot}H_2O$ in THF–MeOH–H_2O (10 mL, 7:2:1) was stirred under N_2 at room temperature for 90 min. The reaction mixture was acidified (2% H_2SO_4) and extracted with Et_2O. Short-path distillation afforded 710 mg (97%) of **2**: bp 130–135 °C (0.03 mm); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 7 Hz), 1.21 (s, 6), 1.30 (m, 6), 1.71 (m, 2), 2.06 (m, 4), 2.37 (t, 2, J = 7 Hz), 2.82 (t, 4, J = 7 Hz), 5.10–5.60 (m, 8); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.58, 24.61, 26.60, 27.33, 27.75, 27.78, 29.38, 31.27, 31.57, 33.47, 36.59, 127.7, 127.8, 128.2, 128.5, 129.3, 130.2, 139.1, 139.4, 179.8. Anal. ($C_{22}H_{36}O_2$) C, H.

Methyl 4-[2-(Hydroxymethyl)phenyl]butanoate (20). A solution of **19**[11] (27.0 g, 124.7 mmol) and KOH (27 g, 0.48 mol) in EtOH–H_2O (270 mL, 1:1) was refluxed for 6 h under N_2. The cooled reaction mixture was concentrated in vacuo, acidified with 20% H_2SO_4, and extracted with Et_2O. The resulting crude hydroxy acid (26 g) was stirred with Li_2CO_3 (24.8 g, 0.335 mol) and MeI (20.9 mL, 0.335 mol) in DMF (220 mL) under N_2 at room temperature for 20 h. The reaction mixture was poured into excess 2 N HCl and extracted with ether. The organic phase was washed with H_2O, aqueous $NaHSO_3$, H_2O, aqueous $NaHCO_3$, and brine.

The dried extracts were evaporated, and the residue was chromatographed on silica gel (40% AcOEt in hexane) to provide 22.0 g (85%) of **20**: IR (film) 3420, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.73–2.88 (m, 6), 3.62 (s, 3), 4.68 (s, 2), 7.20 (m, 4). Anal. ($C_{12}H_{16}O_3$) C, H.

Methyl 4-(2-Formylphenyl)butanoate (21). To a solution of **20** (5.1 g, 24.5 mmol) in dry DMF (75 mL), cooled in an ice bath, was added 13.8 g (36.7 mmol) of pyridinium dichromate[12] in one portion. After the solution was stirred for 15 min, the ice bath was removed, and stirring was continued at ambient temperature for 75 min. The reaction mixture was diluted with 1 L of H_2O containing 20 g of Na_2SO_3 and extracted three times with Et_2O. The combined extracts were washed with H_2O, dilute HCl, H_2O, aqueous $NaHCO_3$, and brine. The dried solution was evaporated to leave 4.2 g (83%) of essentially pure **21**, which was short-path distilled at 100 °C (0.3 mm): IR (film) 1730, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (m, 2), 2.37 (m, 2), 3.04 (m, 2), 3.63 (s, 3), 7.20–7.90 (m, 4), 10.20 (s, 1). Anal. ($C_{12}H_{14}O_3$) C, H.

Enol Ether 22. A solution of 25.9 g (75.6 mmol) of $MeOCH_2PPh_3^+Cl^-$ in 60 mL of dry Me_2SO was treated at ambient temperature dropwise with a 2 M solution of dimsyl sodium in Me_2SO (37.8 mL, 75.6 mmol). After stirring for 15 min, a solution of **21** (4.0 g, 19.4 mmol) in 20 mL of Me_2SO was added to the ylide at 15 °C, and stirring at this temperature was continued for 15 min. The quenched (H_2O) reaction mixture was extracted with Et_2O, washed several times with H_2O, dried ($MgSO_4$), and evaporated. The residue, on chromatography (silica gel, 10% AcOEt in hexane), provided 4.0 g (88%) of **22** as an ca. 1:1 *E*/*Z* mixture: bp 90–100 °C (0.3 mm); IR (film) 1735, 1640 cm^{-1}; UV max (EtOH) 259 nm; NMR ($CDCl_3$, partial) δ 5.33 (d, J = 8 Hz), 6.13 (d, J = 8 Hz) [(*Z*)-enol ether]; 5.96 (d, J = 13 Hz), 6.83 (d, J = 13 Hz) [(*E*)-enol ether]. Anal. ($C_{14}H_{18}O_3$) C, H.

Phenylacetaldehyde 24. A solution of **22** (1.5 g, 6.41 mmol) in MeOH (30 mL) containing anhydrous *p*-TsOH (150 mg) was stirred in an oil bath at 55–60 °C for 6 h. The reaction mixture was concentrated in vacuo, diluted with H_2O, and extracted twice with Et_2O. The extracts were washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The filtered solution was evaporated, and the residue (ketal **23**) was refluxed for 2 h in THF–2% H_2SO_4 (30 mL, 9:1). After concentration to approximately one-third of the original volume, the reaction mixture was extracted with Et_2O, and the extract was washed with aqueous $NaHCO_3$ and brine. Evaporation of the dried solution left an oil, which was chromatographed on silica gel (20% AcOEt in hexane) to afford 1.0 g (71%) of aldehyde **24**: IR (film) 2720, 1725 cm^{-1} NMR ($CDCl_3$) δ 1.70–2.80 (m, 6), 3.67 (s, 3), 3.76 (d, 2, J = 3 Hz), 7.23 (m, 4), 9.72 (t, 1, J = 3 Hz). Anal. ($C_{13}H_{16}O_3$) C, H.

Methyl 5,6-Benzoarachidonate (25). Wittig reaction of **24** (450 mg, 2.045 mmol) with the ylide derived from **7** (2.0 g, 3.93 mmol) as described previously gave, after centrifugally accelerated chromatography (5% AcOEt in hexane), 457 mg (71%) of **25**: IR (film) 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz), 1.30 (m, 6), 1.95 (m, 2), 2.06 (m, 2), 2.38 (t, 2, J = 7 Hz), 2.66 (m, 2), 2.83 (t, 2, J = 7 Hz), 2.94 (t, 2 J = 7 Hz), 3.42 (d, 2, J = 7 Hz), 3.67 (s, 3), 5.30–5.55 (m, 6), 7.15 (m, 4); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.59, 25.75, 25.94, 27.28, 29.36, 30.62, 31.57, 32.15, 33.78, 51.53, 126.4, 127.7, 129.8, 130.7, 138.8, 139.5, 174.0. Anal. ($C_{25}H_{36}O_2$) C, H.

5,6-Benzoarachidonic Acid (3). A solution of **25** (457 mg, 0.805 mmol) and $LiOH·H_2O$ (210 mg, 5.0 mmol) in 12.0 mL of THF–MeOH–H_2O (3:2:1) was stirred at room temperature under N_2 for 3 h. The acidified (2% H_2SO_4) reaction mixture was extracted with Et_2O, and the crude product was purified by centrifugally accelerated chromatography to provide 410 mg (93%) of **3**: IR (film) 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7 Hz), 1.29 (m, 6), 1.93 (m, 2), 2.05 (m, 2), 2.42 (m, 2), 2.68 (m, 2), 2.83 (t, 2, J = 7 Hz), 2.94 (t, 2, J = 7 Hz), 3.43 (m, 2), 5.30–5.50 (m, 6), 7.17 (m, 4); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.59, 25.62, 25.75, 27.28, 29.36, 30.62, 31.57, 32.02, 33.71, 126.5, 127.7, 128.6, 128.9, 129.4, 130.7, 138.8, 139.3, 179.8. Anal. ($C_{24}H_{34}O_2$) C, H.

Inhibition of Lipoxygenase Activity in Intact Human Polymorphonuclear Leukocytes (PMNs). Preparation of the Cells. The PMNs were prepared from 200–400 mL of heparinized blood of healthy donors not receiving any medication for at least 7 days. In general, PMNs were greater than 98% pure, and their viability was assessed by dye exclusion to be better than 95%. The cells were suspended in phosphate-buffer saline containing 1.0 mM $CaCl_2$ (pH 7.4) and bovine serum albumin (BSA, 0.2%) and used within 30 min. Since the cells appeared to remain more healthy and viable for much longer periods of time when BSA was included in the medium, particularly in the presence of AA and test substance at relatively high concentrations (1×10^{-4} M), BSA was routinely included in all assays.

Lipoxygenase Assay. Incubations were carried out at 37 °C for 5 min in a total volume of 0.2 mL. [1-^{14}C]Arachidonic acid (1×10^{-4} M, ca. 300 000 cpm) and calcium ionophore A23187 (in EtOH) were added to a suspension of cells (ca. 5×10^6) to initiate the reaction. Prior to the addition of arachidonic acid (AA), the test substance was added to the cells at appropriate concentrations and preincubated for 5 min. In general, stock solutions of test substances were prepared in EtOH and diluted with either incubation buffer or H_2O. The final concentration of EtOH in the incubations did not exceed 1%. Boiled enzyme blanks and controls not containing test compound were always included. The incubations were terminated by the addition of 3 volumes of MeOH, vortexed, and then kept on ice for 30 min. They were then centrifuged, supernatants were decanted, about 3 mL of H_2O was added, and the pH was brought to about 4.0 by the addition of HCl. This was extracted twice with 7 mL of Et_2O. The pooled extracts were washed with water, filtered through Whatman No. 1 filter paper, and evaporated to dryness. The residue was dissolved in 200 μL of MeOH, a small aliquot was counted for estimating recoveries, and a known volume (usually 100 μL) was applied to silica gel G plates and chromatographed (solvent system Et_2O–hexane–AcOH, 70:30:1). The lipoxygenase products (particularly 5-HETE and LTB_4; confirmed by cochromatography with authentic samples) were located by scanning in a Packard 7201 radiochromatogram scanner, scraped, suspended in Aquasol, and counted. The yields of products and percent inhibition were determined by calculating the percent radioactivity found in each zone as compared to the total radioactivity recovered from the plate.

Acknowledgment. The authors thank Dr. M. Maddox for the ^{13}C NMR spectra, J. Nelson for the 300-MHz proton spectra, and Myriam Kruseman-Aretz for biological experiments.

Registry No. 1, 85924-31-8; 2, 85924-32-9; 3, 85924-33-0; 4, 29125-78-8; 5, 85924-34-1; 6, 85924-35-2; 7, 83606-41-1; 8, 85924-36-3; 9, 85924-37-4; 10, 85924-38-5; 11, 83606-22-8; 12, 85924-39-6; 13, 85924-40-9; 14, 85924-41-0; 15, 85924-42-1; 16, 85924-43-2; 17, 85924-44-3; 18, 85924-45-4; 19, 85924-46-5; 20, 85924-47-6; 21, 85924-48-7; (*E*)-22, 85924-49-8; (*Z*)-22, 85924-50-1; 23, 85924-51-2; 24, 85924-52-3; 25, 85924-53-4; 2,2-dimethyl-3-[(tetrahydropyranyl)oxy]propanal, 52113-84-5; 5-(triphenylphosphonio)valeryl bromide, 85924-54-5; 5-butyl-14,14-dimethyl-9(*Z*),12(*Z*),15(*Z*),18(*Z*)-tetracosatetraen-5-ol, 85924-55-6; *O*-(hydroxymethyl)benzenebutanoic acid, 85924-56-7.