Quinones. Part 3.† Synthesis of Quinone Derivatives having Ethylenic and Acetylenic Bonds: Specific Inhibitors of the Formation of Leukotrienes and 5-Hydroxyicosa-6,8,11,14-tetraenoic Acid (5-HETE)

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A new series of quinone derivatives with alkenyl and alkynyl groups in the side chain has been synthesised. A ready and novel synthetic method for the preparation of quinone derivatives *via* application of a 4-hydroxybutylation reaction discovered in our laboratory has been developed. Oxidative demethylation of the hydroquinone dimethyl ethers (5), (9), and (10) with cerium(IV) ammonium nitrate selectively leads to the formation of the desired quinone derivatives (11)—(13) in good yield, in spite of the presence of double or triple bonds, hydroxy groups in the side chains, and/or four methoxy groups on the same phenyl ring. Inhibitory effects of these quinone derivatives on the formation of leukotrienes [LTC_4, LTD_4, LTB_4, and (5*S*,12*S*)- and (5*S*,12*R*)-6-*trans*-LTB_4] and 5-hydroxyicosa-6,8,11,14-tetraenoic acid (5-HETE) in rat basophilic leukaemia (RBL-1) cells were evaluated. It was found that quinone derivatives such as 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone (AA-861) (12d) proved to be potent and specific inhibitors of leukotrienes and 5-HETE formation from arachidonic acid.

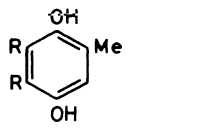
Quinone and (masked) hydroquinone compounds with polyprenylated side chains are widely distributed [1] in animals and plants. There are but few articles [2] concerned with the introduction of different kinds of side chains other than polyprenylated ones into quinone nuclei. In our previous articles [3] we referred to the pharmacological and physiological diversity of the naturally occurring quinone and (masked) hydroquinone compounds and there are an increasing number of interesting reports [4] concerned with such functions as immune response, cell activation, platelet activity, improvement of heart function, *etc.* We were recently the first to show [5] that quinone compounds have a strong inhibitory action on the generation of the slow reacting substance of anaphylaxis (SRS-A) in the lung fragments of actively sensitised guinea pigs and that they are potent specific inhibitors of 5-lipoxygenase from rat leukocytes which catalyse the production of 5-hydroperoxyicosa-6,8,11,14-tetraenoic acid (5-HPETE) from arachidonic acid.

Our continuing studies on quinone derivatives have been based on the assumption that quinones might play a significant role in living cells as antioxidants and scavengers or inhibitors of the generation of active oxygen species of such noxious intermediates as hydroperoxides and peroxides of polyunsaturated fatty acids and phospholipids. The present study focused on the synthesis of more potent inhibitors of the generation of SRS-A, which consists of leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4) as the principal active constituents, initiated by the 5-lipoxygenase pathway of arachidonic acid.[6]

We report here the synthesis of 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone (AA-861) (12d) and its analogues.

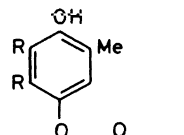
Synthesis of a new series of quinone derivatives in the present study started with the discovery of a ready 4-hydroxybutylation reaction of hydroquinone derivatives. Treatment of the hydroquinones (1a—c) with 1.1 equiv. of 2,3-dihydrofuran in the presence of D-camphor-10-sulphonic acid as catalyst at room temperature smoothly gave the corresponding hydroquinone monotetrahydrofuryl ethers (2a—c) as the main reaction products. After the addition of greater amounts of the acid catalyst, the monoethers were directly converted, by warming to 60 °C, into the corresponding 2-tetrahydrofuryl hydroquinones (3a—c) in excellent yield. Methylation of (3a—c) with methyl iodide gave the hydroquinone dimethyl ethers (3d—f) which were hydrogenolysed with 5% palladium–carbon in the presence of perchloric acid to give the 4-hydroxybutyl compounds (4a—c) in high yield, as the key intermediates for a new series of quinone derivatives.

Elongation of the butyl groups in (4a—c) with alkynyl groups was carried out by coupling reactions of the two types



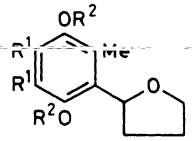
(1)

	R
a;	Me
b;	OMe
c;	—CH:CHCH:CH—



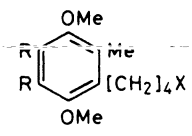
(2)

	R
a;	Me
b;	OMe
c;	—CH:CHCH:CH—



(3)

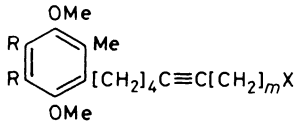
	R^1	R^2
a;	Me	H
b;	OMe	H
c;	—CH:CHCH:CH—	H
d;	Me	Me
e;	OMe	Me
f;	—CH:CHCH:CH—	Me



(4)

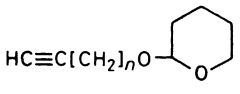
	R	X
a;	Me	OH
b;	OMe	OH
c;	—CH:CHCH:CH—	OH
d;	Me	I
e;	OMe	I
f;	—CH:CHCH:CH—	I

† Part 2 is reference 3*b*.



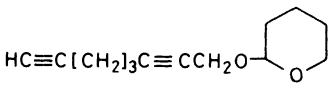
(5)

	(R)	m	X
a;	Me	1	OH
b;	OMe	1	OH
c;	Me	3	OH
d;	OMe	3	OH
e;	—CH:CHCH:CH—	3	OH
f;	Me	1	I
g;	OMe	1	I
h;	Me	3	I
i;	OMe	3	I
j;	—CH:CHCH:CH—	3	I

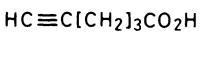


(6)

	n
a;	1
b;	2
c;	3



(7)



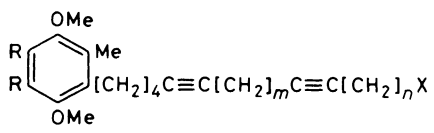
(8)

of iodo compound (4d—f) and (5f—j) with the acetylenic compounds (6)—(8). Conversion of (4a—c) into the corresponding iodides (4d—f) as one type of coupling partner was performed by mesylation [7,*] and iodination of the 4-hydroxybutyl groups. Coupling between (4d—f) and the acetylenes (6a or c) in the presence of sodium amide,[8] followed by acid hydrolysis of the resulting tetrahydropyranyl ethers, gave the corresponding alcohols (5a—e) in good yield. Another type of iodo derivative (5f—j) for the repetitive coupling reaction was also prepared from the alcohols (5a—e) in the same manner as described above.

The diyne compounds (9a—j) were synthesised either by the same coupling process as with the iodo compounds (4d—f) and (5h—j) using the acetylenic compounds (6a or c) and (7) as described above, or by the coupling reaction of the iodo compounds (5f, g) with the Grignard reagents [9] of the acetylenic compounds (6a—c) and (8). Partial hydrogenation of the diynes (9d, g—j) with Lindlar catalyst led to the formation of the *cis* dienes (10a—e) in good yield.

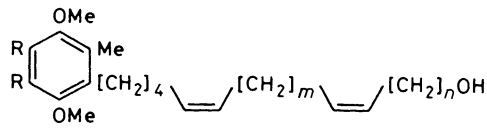
Recently, P. Jacob *et al.*[10] and L. Syper *et al.*[11] reported a new method of oxidative demethylation of hydroquinone dimethyl ethers with cerium(IV) ammonium nitrate in the presence of pyridinecarboxylic acids or their derivatives. We reported quite recently [3b] that this method is very useful and selective for the synthesis of various benzo- and naphthoquinones from hydroquinone dimethyl ethers. It is generally a fast reaction which also proceeds at low temperatures (0—2 °C). Selectivity in the oxidative demethylation is illustrated by the fact that a variety of substituents such as allyl, hydroxypropargyl, and methoxy are not affected under the

* Mesyl = methanesulphonyl.



(9)

	R	m	n	X
a;	Me	1	1	OH
b;	Me	1	2	OH
c;	Me	1	3	OH
d;	Me	3	1	OH
e;	Me	1	3	CO_2H
f;	OMe	1	1	OH
g;	OMe	1	3	OH
h;	OMe	3	1	OH
i;	OMe	3	3	OH
j;	—CH:CHCH:CH—	3	1	OH



(10)

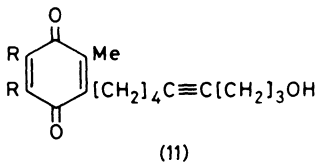
	R	m	n
a;	Me	3	1
b;	OMe	1	3
c;	OMe	3	1
d;	OMe	3	3
e;	—CH:CHCH:CH—	3	1

reaction conditions. The results of the oxidative demethylation of the hydroquinone dimethyl ethers (5c—e), (9a—j), and (10a—e) to the quinone derivatives (11a—c), (12a—j), and (13b, d—g) are listed in Table 5. It was found that the best yields of quinones derived from the 1,2,3,4-tetramethoxyphenyl derivatives (5b and d), (9f—i), and (10b—d) were obtained with cerium(IV) ammonium nitrate when pyridine-2,6-dicarboxylic acid was used as ligand, while the use of cerium(IV) ammonium nitrate alone was found to be superior to any combination of methods for the oxidative demethylation of the 1,4-dimethoxy-2,3,5-trimethylphenyl and 1,4-dimethoxy-2-methylnaphthyl derivatives (5a, c, and e), (9a—e, j), and (10a and e).

In addition, the quinone derivatives (13a, c, and d) with a penta-1,4-diene linkage were also prepared by Lindlar reduction of the corresponding penta-1,4-diyne compounds (12a, f, and g), followed by oxidation of the resulting hydroquinones with iron(III) chloride.

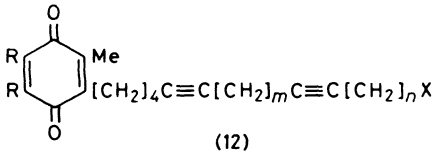
In general, a compound having either a penta-1,4-diyne or a penta-1,4-diene linkage is vulnerable to aerial oxidation but the linkages in the present quinone derivatives (12a—c, e—g) and (13a, c, and d) are fairly stable in comparison with those in the hydroquinone dimethyl ethers (9a—c, e—g) and (10b). This indicates that the quinone moiety may play the role of an intramolecular radical scavenger. Because of the chemical instability of the diene and diyne moieties, the hydroquinone dimethyl ethers (9a—c, e—g) and (10b) should be immediately converted into the corresponding quinone derivatives (12a—c, e—g) and (13a, c, and d).

The quinone derivatives synthesised above were tested for inhibitory effects on the formation of leukotrienes [LTC_4,



(11)

R	
a;	Me
b;	OMe
c;	—CH:CHCH:CH—



(12)

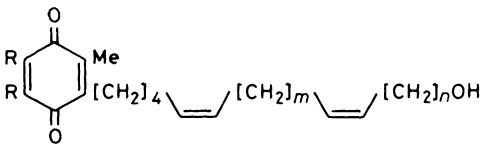
R		m	n	X
a;	Me	1	1	OH
b;	Me	1	2	OH
c;	Me	1	3	OH
d;	Me	3	1	OH
e;	Me	1	3	CO_2H
f;	OMe	1	1	OH
g;	OMe	1	3	OH
h;	OMe	3	1	OH
i;	OMe	3	3	OH
j;	—CH:CHCH:CH—	3	1	OH

LTD_4, LTB_4, and (5*S*,12*S*)- and (5*S*,12*R*)-6-*trans*-LTB_4] and 5-HETE in RBL-1 cells.[12] The effects * on the biosynthesis of the various metabolites of arachidonic acid were investigated using high-performance liquid chromatography (h.p.l.c.). The quinone derivatives were found to inhibit the biosyntheses of both leukotrienes and 5-HETE at concentrations of 10^{-6}M (68.5—83.6% inhibition) and to be much more potent inhibitors in comparison with the reference compounds icosa-5,8,11,14-tetraynoic acid (ETYA) [6c] and nordihydroguaiaretic acid (NDGA) [4,4′-(2,3-dimethyltetramethylene)dipyrocatechol] [6c] which are well known inhibitors of both cyclo-oxygenase and lipoxygenase. The biological and enzymatical results have been published elsewhere.[5]

Thus, quinone derivatives such as 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone (AA-861) (12d) might be an important drug for further studies on the specific inhibition of leukotrienes and 5-HETE, and the inflammatory response in human leukocytes. The results also indicate that the 5-lipoxygenase inhibitor might be of therapeutic value in the treatment of asthma. The biological and pharmacological studies are under investigation.

Experimental

Silica gel used for column chromatography was from Merck (Silica gel 60, 70—230 mesh). Tetrahydrofuran (THF), diisopropyl ether (IPE), and diethyl ether (Et_2O) were distilled from calcium hydride before use. M.p.s are uncorrected. ^{1}H N.m.r. spectra were recorded for $CDCl_3$ solutions with a Varian EM-390 and/or T-60 spectrometer using internal Me_4-Si (δ 0) as the standard. Solutions were dried over magnesium sulphate.



(13)

R		m	n
a;	Me	1	1
b;	Me	3	1
c;	OMe	1	1
d;	OMe	1	3
e;	OMe	3	1
f;	OMe	3	3
g;	—CH:CHCH:CH—	3	1

General Procedure for Preparation of the 2-Tetrahydrofurylhydroquinones (3a—c).—A mixture of a hydroquinone (1a—c) (0.20 mol) and 2,3-dihydrofuran (15.4 g, 0.22 mol) in toluene (300 ml) was stirred at room temperature. To the mixture was added D-camphor-10-sulphonic acid (0.23 g, 1 mmol). After 30 min, more acid catalyst (2.32 g, 10 mmol) was added to the reaction mixture which was then warmed to 60 °C and stirred for 2 h. When the reaction was complete, the product was isolated by the addition of water (300 ml). The organic layer was washed in turn with aqueous sodium hydrosulphite (disodium dithionite) and water, dried, and evaporated to dryness under reduced pressure. The residue was crystallised from IPE to give the *2-tetrahydrofurylhydroquinone* (3a—c). The data are listed in Table 1.

General Procedure for Preparation of the 2-Tetrahydrofurylhydroquinone Dimethyl Ethers (3d—f).—A stirred solution of a 2-tetrahydrofurylhydroquinone (3a—c) (0.10 mol) in dimethylformamide (200 ml) was cooled to 5 °C under nitrogen. To the solution was added sodium hydride (60% oil dispersion; 8.8 g, 0.22 mol, after removal of the oil by washing with hexane) under the same conditions. After 10 min methyl iodide (35.5 g, 0.25 mol) was added to the mixture during 15 min and the solution was stirred for another 15 min. When the reaction was complete, ice–water (250 ml) and IPE (500 ml) were added to the reaction mixture and the product was extracted with IPE. The extract was washed with water, dried, and evaporated under reduced pressure. The residue was distilled to give the *hydroquinone dimethyl ether* (3d—f). The data are listed in Table 1.

General Procedure for Preparation of the 4-Hydroxybutyl Compounds (4a—c).—A mixture of a hydroquinone dimethyl ether (3d—f) (0.10 mol), acetic acid (375 ml), and 70% perchloric acid (0.75 ml) was hydrogenated over 5% palladium–charcoal (2.5 g) at 70 °C under atmospheric pressure for 1.5 h. When the reaction was complete, the catalyst was removed by filtration. To the filtrate was added water (25 ml) and the solution was evaporated under reduced pressure. To the residue was added IPE (300 ml) and saturated aqueous sodium hydrogencarbonate (250 ml) and the organic phase was separated. After removal of the solvent under reduced pressure, the residue was dissolved in a mixture of methanol (250 ml) and 10% aqueous sodium hydroxide (60 ml). The solution was stirred for 30 min at room temperature. After the hydrolysis was complete, the methanol was evaporated

* The results will be published elsewhere.

Table 1. Data for the 2-tetrahydrofurylhydroquinones (3a—c) and their dimethyl ethers (3d—f)

Compd.	Yield (%)	Formula M.p. or b.p.	% Found (Required) C	H	^{1}H N.m.r. δ
(3a)	90	$C_{13}H_{18}O_3$ M.p. 104—105 °C	70.2 (70.2)	8.2 (8.1)	1.7—2.4 (4 H, m, 2 CH_2), 2.11 (3 H, s, Me), 2.14 (6 H, s, 2 Me), 3.7—4.3 (2 H, m, CH_2O), 4.16 (1 H, s, OH), 5.10 (1 H, m, =CH-O), and 8.87 (1 H, s, OH)
(3b)	82	$C_{13}H_{18}O_5$ M.p. 77—78 °C	61.3 (61.4)	7.1 (7.1)	1.7—2.4 (4 H, m, 2 CH_2), 2.08 (3 H, s, Me), 3.7—4.3 (2 H, m, CH_2), 3.87 (3 H, s, OMe), 3.92 (3 H, s, OMe), 5.07 (1 H, m, =CH-O), 5.39 (1 H, s, OH), and 8.56 (1 H, s, OH)
(3c)	88	$C_{15}H_{16}O_3$ M.p. 129—130 °C	73.8 (73.7)	6.5 (6.6)	1.7—2.5 (4 H, m, 2 CH_2), 2.22 (3 H, s, Me), 3.8—4.4 (2 H, m, CH_2), 4.67 (1 H, s, OH), 5.19 (1 H, m, =CH-O), 7.3—7.5 (2 H, m, ArH), 7.8—8.0 (1 H, m, ArH), 8.1—8.3 (1 H, m, ArH), and 9.53 (1 H, s, OH)
(3d)	98	$C_{15}H_{22}O_3$ B.p. 130—140 °C (1.0 mmHg)	71.8 (71.9)	8.8 (8.8)	1.9—2.3 (4 H, m, 2 CH_2), 2.16 (6 H, s, 2 Me), 2.29 (3 H, s, Me), 3.60 (3 H, s, OMe), 3.64 (3 H, s, OMe), 3.7—4.3 (2 H, m, CH_2), and 5.23 (1 H, m, =CH-O)
(3e)	98	$C_{15}H_{22}O_5$ B.p. 130—138 °C (0.2 mmHg)	63.7 (63.8)	7.6 (7.8)	1.9—2.3 (4 H, m, 2 CH_2), 2.23 (3 H, s, Me), 3.7—4.3 (2 H, m, CH_2), 3.74 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.88 (3 H, s, OMe), and 5.19 (1 H, m, =CH-O)
(3f)	97	$C_{17}H_{20}O_3$ B.p. 156—158 °C (0.2 mmHg)	75.1 (74.9)	7.5 (7.5)	1.9—2.3 (4 H, m, 2 CH_2), 2.46 (3 H, s, Me), 3.7—4.3 (2 H, m, CH_2), 3.81 (3 H, s, OMe), 3.87 (3 H, s, OMe), 5.48 (1 H, m, =CH-O), 7.3—7.6 (2 H, m, ArH), and 7.9—8.2 (2 H, m, ArH)

under reduced pressure. The product, isolated in the usual manner, gave the *4-hydroxybutyl compound* (4a—c). The data are listed in Table 2.

General Procedure for Preparation of the Iodo Compounds (4d—f) *and* (5f—j).—A stirred mixture of a hydroxy compound (4a—c) or (5a—e) (10 mmol) and triethylamine (2.1 g, 15 mmol) was dissolved in methylene dichloride (25 ml) at −5 °C. To the solution was then added dropwise a solution of methanesulphonyl chloride (1.43 g, 12 mmol) in the same solvent during 30 min and the mixture was stirred for another 30 min under the same conditions. After the reaction was complete, ice-water (25 ml) and cold 10% hydrochloric acid (25 ml) were added to the mixture. The organic layer was separated and washed with saturated aqueous sodium hydrogencarbonate and then saturated, aqueous sodium chloride, dried, and concentrated under reduced pressure. The residue was dissolved in acetone (30 ml), to which was added sodium iodide (3.0 g). The mixture was warmed at 50 °C for 2 h. When the reaction was complete, the acetone was evaporated under reduced pressure. The product was extracted with IPE. The extract was washed in turn with 5% aqueous sodium hydrogensulphite and saturated aqueous sodium chloride, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel, with hexane–IPE (3 : 1—2 : 1) as eluant to give the *iodo compound* (4d—f) or (5f—j). The data are listed in Table 2.

Preparation of the Acetylenic Compounds (5a—e) *and* (9a—j).—*Method A.* A solution of the tetrahydropyranyl ether of propargyl alcohol, (6a) (16.8 g, 0.12 mol), in Et_2O (15 ml) was added dropwise to a suspension of sodium amide [freshly prepared from sodium (2.88 g) in the presence of iron(III) nitrate (50 mg)] in liquid ammonia (300 ml) under argon at between −50 and −40 °C during 20 min. The mixture was then stirred for a further 40 min under the same conditions. A solution of the iodo compound (4e) (39.4 g, 0.10 mol) in Et_2O (40 ml) was then added dropwise to the above mixture at between −50 and −40 °C during 40 min, and the reaction mixture was then stirred for a further 1 h under the same conditions. When the reaction was complete, ammonium chloride (6.7 g) was added to the reaction mixture. Ammonia was evaporated off under reduced pressure and the product was isolated by the addition of IPE (300 ml) and Et_2O (300 ml). The extract was worked up in the usual manner. The resulting product was dissolved in methanol (200 ml) to which was added toluene-*p*-sulphonic acid (0.95 g) and the solution was heated at 70 °C for 0.5 h. When the reaction was complete, saturated aqueous sodium hydrogencarbonate (50 ml) was added and the methanol was evaporated under reduced pressure. The residue, worked up in the usual way, was chromatographed on silica gel using IPE–ethyl acetate (49 : 1) as eluant to give 1-(*7-hydroxyhept-5-ynyl*)-2,3,4,5-*tetramethoxy*-6-*methylbenzene* * (5b) (27.4 g).

The compounds (5a) and (5c—e) were prepared by the same method as described above from the corresponding materials. The data are listed in Table 3.

Method B. To a stirred suspension of sodium amide (1.01 g, 26 mmol) in THF (15 ml) was added dropwise a solution of 8-(tetrahydropyran-2-yloxy)octa-1,6-diyne [13] (7) (4.12 g, 20.0 mmol) in THF (10 ml) at room temperature under nitrogen during 30 min. After the addition of the reagent, the reaction mixture was brought to 50 °C, stirred for 1.5 h, and then cooled to −5 °C. After the addition of hexamethylphosphosphoramide (5 ml) to the reaction mixture, a solution of 1-(4-iodobutyl)-2,3,4,5-tetramethoxy-6-methylbenzene (4e) (6.30 g, 16.0 mmol) in THF (15 ml) was added dropwise during 30 min to the stirred mixture. The reaction mixture was then brought to room temperature. After 1 h, ammonium chloride (1.4 g) and water (20 ml) were added to decompose the excess of reagents. The THF was evaporated under reduced pressure. The product obtained in the usual way was dissolved in methanol (40 ml). Toluene-*p*-sulphonic acid (0.19 g) was then added to the solution, which was then heated at 70 °C for 30 min. After being cooled the reaction mixture was treated with sodium hydrogencarbonate (0.20 g) and the solvent was evaporated under reduced pressure. The residue, worked up in the usual way, was chromatographed on silica gel with IPE as eluant to give 1-(12-*hydroxydodeca*-5,10-*diynyl*)-2,3,4,5-*tetramethoxy*-6-*methylbenzene* † (9h) (4.30 g).

* 7-(2,3,4,5-Tetramethoxy-6-methylphenyl)hept-2-yn-1-ol.

† 12-(2,3,4,5-Tetramethoxy-6-methylphenyl)dodeca-2,7-diyn-1-ol.

Table 2. Data for the 4-hydroxybutyl compounds (4a—c) and iodo compounds (4d—f) and (5f—j)

Compd.	Yield (%)	Formula M.p. or b.p. [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(4a)	90	$C_{15}H_{24}O_3$ M.p. 88—89 °C	71.5 (71.3)	9.5 (9.5)	1.4—1.7 (5 H, m, 2 CH_2 and OH), 2.15 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.61 (2 H, m, CH_2), 3.61 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 3.65 (2 H, t, CH_2O)
(4b)	90	$C_{15}H_{24}O_5$ B.p. 142—152 °C (0.2 mmHg)	63.4 (63.3)	8.5 (8.5)	1.4—1.8 (total 5 H, m, 2 CH_2 and OH), 2.16 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.67 (2 H, t, CH_2O), 3.76 (3 H, s, OMe), 3.80 (3 H, s, Me), and 3.88 (6 H, s, 2 Me)
(4c)	89	$C_{17}H_{22}O_3$ M.p. 56—57 °C	74.5 (74.4)	8.1 (8.1)	1.5—1.8 (5 H, m, 2 CH_2 and OH), 2.39 (3 H, s, Me), 2.81 (2 H, m, CH_2), 3.67 (2 H, t, CH_2), 3.84 (3 H, s, Me), 3.87 (3 H, s, OMe), 7.3—7.5 (2 H, m, ArH), 7.9—8.1 (2 H, m, ArH)
(4d)	94	$C_{15}H_{23}IO_2$	49.8 (49.7)	6.4 (6.4)	1.4—1.7 (2 H, m, CH_2), 1.91 (2 H, m, CH_2), 2.16 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.61 (2 H, m, CH_2), 3.20 (2 H, t, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe)
(4e)	94	$C_{15}H_{23}IO_4$	45.8 (45.7)	5.8 (5.9)	1.4—1.7 (2 H, m, CH_2), 1.90 (2 H, m, CH_2), 2.15 (3 H, s, Me), 2.59 (2 H, m, CH_2), 3.20 (2 H, t, CH_2), 3.76 (3 H, s, OMe), 3.80 (3 H, s, OMe), and 3.87 (6 H, s, 2 OMe)
(4f)	95	$C_{17}H_{21}IO_2$ M.p. 68—69 °C	53.2 (53.1)	5.6 (5.5)	1.5—2.2 (4 H, m, CH_2), 2.40 (3 H, s, Me), 2.82 (2 H, m, CH_2), 3.23 (2 H, t, CH_2O), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 7.3—7.5 (2 H, m, ArH), and 7.8—8.1 (2 H, m, ArH)
(5f)	90	$C_{18}H_{25}IO_2$	54.1 (54.0)	6.4 (6.3)	1.5—1.7 (4 H, m, 2 CH_2), 2.1—2.3 (2 H, m, CH_2), 2.16 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 3.66 (2 H, t, CH_2)
(5g)	90	$C_{18}H_{25}IO_4$	50.0 (50.0)	5.7 (5.8)	1.4—1.8 (4 H, m, CH_2), 2.20 (3 H, s, Me), 2.2—2.4 (2 H, m, CH_2), 2.61 (2 H, m, CH_2), 3.75 (2 H, t, CH_2), 3.83 (3 H, s, OMe), 3.88 (3 H, s, OMe), and 3.95 (6 H, s, 2 OMe)
(5h)	94	$C_{20}H_{29}IO_2$	56.0 (56.1)	6.7 (6.7)	1.4—1.7 (4 H, m, 2 CH_2), 1.93 (2 H, m, CH_2), 2.0—2.4 (4 H, m, 2 CH_2), 2.16 (6 H, s, 2 OMe), 2.21 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.27 (2 H, t, CH_2), 3.63 (3 H, s, OMe), and 3.65 (3 H, s, OMe)
(5i)	93	$C_{20}H_{29}IO_4$	52.3 (52.2)	6.4 (6.3)	1.4—1.8 (6 H, m, 3 CH_2), 1.9—2.4 (4 H, m, 2 CH_2), 2.19 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.29 (2 H, t, CH_2), 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), and 3.92 (6 H, s, 2 OMe)
(5j)	95	$C_{22}H_{27}IO_2$	58.8 (58.7)	6.0 (6.0)	1.5—2.3 (10 H, m, 5 CH_2), 2.40 (3 H, s, Me), 2.80 (2 H, m, CH_2), 3.27 (2 H, t, CH_2), 3.85 (3 H, s, OMe), 3.88 (3 H, s, OMe), 7.3—7.5 (2 H, m, ArH), and 7.8—8.1 (2 H, m, ArH)

[a] Those compounds for which a m.p. or b.p. is not given were oils.

The compounds (5c—e) and (9d, and h–j) were prepared by the same method as described above from the corresponding materials. The data are listed in Table 3.

Method C. A stirred solution of 1-(7-iodohept-5-ynyl)-2,5-dimethoxy-3,4,6-trimethylbenzene (5f) (4.00 g, 10 mmol) in THF (10 ml) was added dropwise during 20 min to a THF solution of the Grignard reagent freshly prepared by the reaction of the tetrahydropyranyl ether (6a) (1.56 g, 11 mmol) with ethyl magnesium bromide (11 mmol) and copper(I) bromide (30 mg) under argon. The reaction mixture was stirred for 2 h at 50 °C. When the reaction was complete, aqueous ammonium chloride was added to the reaction mixture. The THF was evaporated under reduced pressure. To the residue, worked up in the usual way, was added methanol (50 ml) and toluene-*p*-sulphonic acid (0.1 g). The mixture was then heated at 70 °C for 30 min. After being cooled the reaction mixture was treated with saturated aqueous sodium hydrogencarbonate (20 ml) and then the methanol was evaporated under reduced pressure. The product, obtained in the usual manner, was chromatographed on silica gel with IPE as eluant to give 1-(10-*hydroxydeca*-5,8-*diynyl*)-2,5-*dimethoxy*-3,4,6-*trimethylbenzene* * (9a) (2.44 g).

The compounds (9b, c, and e—g) were prepared by the same method as described above from the corresponding materials. The data are listed in Table 3.

Preparation of the Dienes (10a—e).—A solution of compound (9h) (0.97 g, 2.5 mmol) in ethyl acetate (20 ml) was hydrogenated in the presence of quinoline (14 μl) and Lindlar catalyst (0.10 g) at room temperature. When two equivalents of hydrogen had been absorbed, the reaction was stopped. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel with IPE as eluant to give 1-[12-*hydroxydodeca*-5(*Z*),10(*Z*)-*dienyl*]-2,3,4,5-*tetramethoxy*-6-*methylbenzene* † (10c) (0.90 g). Data for the other compounds, (10a, b, d, and e), prepared by the same method as described above from the corresponding materials (9d, and g—j) are listed in Table 4.

Preparation of the Quinone Derivatives (11a—c), (12a—j), *and* (13a—g).—*Method A.* A stirred solution of compound (9h) (0.50 g, 1.29 mmol) and pyridine-2,6-dicarboxylic acid (0.65 g, 3.87 mmol) in a mixture of acetonitrile (4 ml) and water (2 ml) was cooled to 0—2 °C and treated dropwise with a cold solution of cerium(IV) ammonium nitrate (2.12 g) in 50% aqueous acetonitrile (5 ml) during 15 min; the mixture was stirred for a further 15 min, after which time the resulting precipitate was filtered off. The product, obtained in the usual way, was chromatographed on silica gel with IPE–ethyl acetate (95 : 5) as eluant to give 2-(12-*hydroxydodeca*-5,10-*diynyl*)-5,6-*dimethoxy*-3-*methyl*-1,4-*benzoquinone* (12h) (0.42 g).

The compounds (11b), (12f, g, and i), and (13d—f) were

* 10-(2,5-Dimethoxy-3,4,6-trimethylphenyl)deca-2,5-diyn-1-ol.

† 12-(2,3,4,5-Tetramethoxy-6-methylphenyl)dodeca-2(*Z*),7(*Z*)-dien-1-ol.

Table 3. Data for the acetylenic compounds (5a—e) and (9a—j)

Compd.	Method [Starting materials]	Yield (%)	Formula M.p. [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(5a)	A [(4d) + (6a)]	75	$C_{18}H_{26}O_3$ M.p. 65—66 °C	74.5 (74.4)	9.1 (9.0)	1.5—1.7 (4 H, m, 2 CH_2), 1.77 (1 H, s, OH), 2.1—2.3 (2 H, m, CH_2), 2.16 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 4.19 (2 H, t, CH_2)
(5b)	A [(4e) + (6a)]	85	$C_{18}H_{26}O_5$	67.0 (67.1)	8.2 (8.2)	1.4—1.7 (4 H, m, 2 CH_2), 1.81 (1 H, s, OH), 2.16 (3 H, s, Me), 2.26 (2 H, m, CH_2), 2.57 (2 H, m, CH_2), 3.76 (6 H, s, 2 OMe), 3.87 (6 H, s, 2 OMe), 4.22 (2 H, t, CH_2)
(5c)	A [(4d) + (6c)] B [(4d) + (6c)]	71 72	$C_{20}H_{30}O_3$	75.3 (75.4)	9.5 (9.5)	1.5—1.8 (total, 7 H, m, 3 CH_2 and OH), 2.1—2.3 (4 H, m, 2 CH_2), 2.16 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 3.71 (2 H, t, CH_2)
(5d)	A [(4e) + (6c)] B [(4e) + (6c)]	84 72	$C_{20}H_{30}O_5$	68.5 (68.5)	8.4 (8.6)	1.4—1.8 (total 7 H, m, 3 CH_2 and OH), 2.1—2.3 (4 H, m, CH_2), 2.16 (3 H, s, Me), 2.56 (2 H, m, CH_2), 3.71 (2 H, t, Me), 8.76 (3 H, s, OMe), 3.80 (3 H, s, OMe), and 3.88 (6 H, s, 2 OMe)
(5e)	A [(4f) + (6c)] B [(4f) + (6c)]	51 81	$C_{22}H_{28}O_3$	77.5 (77.6)	8.4 (8.3)	1.5—1.8 (total 7 H, m, 3 CH_2 and OH), 2.1—2.4 (4 H, m, 2 CH_2), 2.39 (3 H, s, Me), 2.79 (2 H, m, CH_2), 3.69 (2 H, t, CH_2), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), 7.3—7.5 (2 H, m, ArH), and 7.9—8.1 (2 H, m, ArH)
(9a)	C [(5f) + (6a)]	74	$C_{21}H_{28}O_3$	76.7 (76.8)	8.5 (8.6)	1.5—1.7 (5 H, m, 2 CH_2 and OH), 2.1—2.3 (2 H, m, CH_2), 2.16 (6 H, s, 2 Me), 2.23 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.13 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 4.20 (2 H, t, CH_2)
(9b)	C [(5f) + (6b)]	56	$C_{22}H_{30}O_3$	77.3 (77.2)	8.9 (8.8)	1.5—1.7 (4 H, m, 2 CH_2), 1.92 (1 H, s, OH), 2.1—2.3 (2 H, m, CH_2), 2.16 (6 H, s, 2 Me), 2.21 (3 H, s, Me), 2.41 (2 H, m, CH_2), 2.60 (2 H, m, CH_2), 3.09 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 3.66 (2 H, t, CH_2)
(9c)	C [(5f) + (6c)]	65	$C_{23}H_{32}O_3$	77.4 (77.5)	9.0 (9.2)	1.5—2.0 (total 7 H, m, 3 CH_2 and OH), 2.1—2.3 (4 H, m, 2 CH_2), 2.16 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.60 (2 H, m, CH_2), 3.07 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 3.70 (2 H, t, CH_2)
(9d)	A [(5h) + (6a)] B [(4d) + (7)]	21 73	$C_{23}H_{32}O_3$	77.6 (77.5)	9.1 (9.0)	1.4—1.8 (total 7 H, m, 3 CH_2 and OH), 2.1—2.4 (6 H, m, 3 CH_2), 2.15 (6 H, s, 2 Me), 2.21 (3 H, s, Me), 2.61 (2 H, m, CH_2), 3.64 (3 H, s, OMe), 3.66 (3 H, s, Me), and 4.23 (2 H, t, CH_2)
(9e)	C [(5f) + (8)]	62	$C_{24}H_{32}O_4$	75.0 (74.8)	8.4 (8.3)	1.5—1.9 (6 H, m, 3 CH_2), 2.1—2.3 (4 H, m, 2 CH_2), 2.15 (6 H, s, 2 Me), 2.20 (3 H, s, Me), 2.46 (2 H, m, CH_2), 2.60 (2 H, m, CH_2), 3.07 (2 H, t, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), and 11.2 (1 H, s, CO_2H)
(9f)	C [(5g) + (6a)]	37	$C_{21}H_{28}O_5$	69.8 (70.0)	7.8 (7.8)	1.4—1.8 (4 H, m, 2 CH_2), 1.94 (1 H, s, OH), 2.1—2.3 (2 H, m, CH_2), 2.16 (3 H, s, Me), 2.57 (2 H, m, CH_2), 3.14 (2 H, m, CH_2), 3.76 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.87 (6 H, s, 2 OMe), and 4.22 (2 H, t, CH_2)
(9g)	C [(5g) + (6c)]	62	$C_{23}H_{32}O_5$	71.2 (71.1)	8.2 (8.3)	1.4—1.9 (total 7 H, m, 3 CH_2 and OH), 2.1—2.4 (4 H, m, 2 CH_2), 2.16 (3 H, s, Me), 2.57 (2 H, m, CH_2), 3.06 (2 H, m, CH_2), 3.70 (2 H, t, CH_2), 3.76 (3 H, s, OMe), 3.80 (3 H, s, Me), and 3.87 (6 H, s, 2 OMe)
(9h)	A [(5i) + (6a)] B [(4e) + (7)]	57 75	$C_{23}H_{32}O_5$	71.1 (71.1)	8.2 (8.3)	1.4—1.8 (total 7 H, m, 3 CH_2 and OH), 2.1—2.4 (6 H, m, 3 CH_2), 2.17 (3 H, s, Me), 2.67 (2 H, m, CH_2), 3.76 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.88 (6 H, s, 2 OMe), and 4.20 (2 H, t, CH_2)

Table 3 (*continued*)

Compd.	Method [Starting materials]	Yield (%)	Formula M.p. [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(9i)	B [(5i) + (6c)]	81	$C_{25}H_{36}O_5$	72.0 (72.1)	8.8 (8.7)	1.4—1.9 (total 9 H, 4 CH_2 and OH), 2.1—2.4 (8 H, m, 4 CH_2), 2.16 (3 H, s, Me), 2.56 (2 H, m, CH_2), 3.73 (2 H, t, CH_2), 3.76 (3 H, s, OMe), 3.80 (3 H, s, OMe), and 3.88 (6 H, s, 2 OMe)
(9j)	B [(5j) + (6a)]	50	$C_{25}H_{30}O_3$	79.4 (79.3)	7.9 (8.0)	1.5—1.8 (total 7 H, m, 3 CH_2 and OH), 2.1—2.4 (6 H, m, 3 CH_2), 2.41 (3 H, s, Me), 2.80 (2 H, m, CH_2), 3.85 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.20 (2 H, t, CH_2), 7.3—7.5 (2 H, m, ArH), and 7.9—8.1 (2 H, m, ArH)

[a] Compounds (5b—e) and (9a—j) were oils.

Table 4. Data for the dienes (10a—e)

Compd.	Yield (%)	Formula [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(10a)	92	$C_{23}H_{36}O_3$	76.7 (76.6)	10.0 (10.1)	1.2—1.6 (total 7 H, m, 3 CH_2 and OH), 1.9—2.2 (6 H, m, 3 CH_2), 2.16 (6 H, m, 3 CH_2), 2.19 (3 H, s, Me), 2.58 (2 H, m, CH_2), 3.62 (3 H, s, OMe), 3.64 (3 H, s, OMe), 4.0—4.2 (2 H, m, CH_2), and 5.3—5.6 (4 H, m, 2 CH=CH)
(10b)	72	$C_{23}H_{36}O_3$	78.5 (70.4)	9.1 (9.2)	1.3—1.9 (total 7 H, m, 3 CH_2 and OH), 1.9—2.3 (4 H, m, 2 CH_2), 2.19 (3 H, s, Me), 2.62 (2 H, m, CH_2), 2.84 (2 H, m, CH_2), 3.71 (2 H, t, CH_2), 3.85 (3 H, s, Me), 3.89 (3 H, s, OMe), 3.98 (6 H, s, 2 OMe), and 5.4—5.6 (4 H, m, 2 CH=CH)
(10c)	92	$C_{23}H_{36}O_5$	70.3 (70.4)	9.2 (9.2)	1.2—1.7 (total 7 H, m, 3 CH_2 and OH), 1.9—2.3 (6 H, m, 3 CH_2), 2.14 (3 H, s, Me), 2.55 (2 H, m, CH_2), 3.76 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.87 (6 H, s, 2 OMe), 4.0—4.2 (2 H, m, CH_2), and 5.3—5.6 (4 H, m, 2 CH=CH)
(10d)	93	$C_{25}H_{40}O_5$	71.4 (71.4)	9.5 (9.6)	1.3—1.8 (total 9 H, m, 4 CH_2 and OH), 1.9—2.3 (8 H, m, 4 CH_2), 2.21 (3 H, s, Me), 2.62 (2 H, m, CH_2), 3.72 (2 H, t, CH_2), 3.85 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.99 (6 H, s, 2 OMe), and 5.4—5.6 (4 H, m, 2 CH=CH)
(10e)	93	$C_{25}H_{34}O_3$	78.6 (78.5)	8.8 (9.0)	1.2—1.7 (total 7 H, m, 3 CH_2 and OH), 1.9—2.3 (6 H, m, 3 CH_2), 2.39 (3 H, s, Me), 2.79 (2 H, m, CH_2), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.0—4.2 (2 H, t, CH_2), 5.3—5.6 (4 H, m, 2 CH=CH), 7.3—7.5 (2 H, m, ArH), and 7.9—8.1 (2 H, m, ArH)

[a] Compounds (10a—e) were oils.

prepared by the same method as described above from the corresponding materials (5d), (9f—i), and (10b—d). The data are listed in Table 5.

Method B. A solution of compound (9d) (3.56 g, 10 mmol) in a mixture of acetonitrile (25 ml) and water (15 ml) was cooled to 0—2 °C and treated dropwise with a cold solution of cerium(IV) ammonium nitrate (16.4 g) in 50% aqueous acetonitrile (35 ml) during 20 min. The mixture was stirred for a further 20 min under the same conditions. The product, obtained in the usual manner, was chromatographed on silica gel with IPE as eluant to give 2-(12-*hydroxydodeca*-5,10-*diynyl*)-3,5,6-*trimethyl*-1,4-*benzoquinone* (AA-861) (12d) (2.97 g).

The compounds (11a and c), (12a—c, e, and j), and (13b and g) were prepared by the same method as described above from the corresponding materials (5c and e), (9a—c, e, and j), and (10a and e). The data are listed in Table 5.

Method C. A solution of a quinone compound (12a, f, or g) (1.0 mmol) in ethyl acetate (10 ml) was hydrogenated in the presence of Lindlar catalyst (60 mg) and quinoline (10 μl) at room temperature. When 3 equiv. of hydrogen had been absorbed, the reaction was stopped. After removal of the catalyst the organic solution was washed in turn with 5% aqueous phosphoric acid (5 ml) and saturated aqueous sodium chloride (5 ml), and was then concentrated under reduced pressure. The residue was dissolved in THF (6 ml), to which was added 1M iron(III) chloride solution (2 ml). The reaction mixture was stirred for 30 min at room temperature. When the reaction was complete, the THF was evaporated under reduced pressure. The product, worked up in the usual manner, was chromatographed on silica gel with IPE–ethyl acetate (98 : 2) as eluant, to give the corresponding *quinone diene* (13a, c, or d). The data are listed in Table 5.

Reverse-phase High-performance Liquid Chromatographic Measurements of the Inhibition of Leukotrienes and 5-HETE in Rat Basophilic Leukaemia Cells (RBL-1).—RBL-1 cells grown in a Spinner culture were harvested. After centrifugation at 5 °C for 10 min at 400 g, cells were washed twice with a mast cell medium (MCM) with the composition NaCl (26.30 g), KCl (0.83 g), $Na_2HPO_4 \cdot 12H_2O$ (3.22 g), KH_2PO_4 (1.43 g), glucose (3.02 g), $CaCl_2$ (0.3 g), and water (3.0 l); pH 7.00, adjusted with 0.1M NaOH. Cells resuspended at 1×10^7 m^{-1}. Leukotrienes [LTC_4, LTD_4, LTB_4, (5*S*,12*S*)-, and (5*S*,12*R*)-6-*trans*-LTB_4] and 5-HETE were generated by the addition of arachidonic acid (50 μg ml^{-1}) and A-23187 (10 μg ml^{-1}) at

37 °C for 15 min. Duplicate samples of 10^7 RBL-1 cells each were preincubated at 37 °C for 5 min in a shaking water-bath and without quinone derivatives and/or reference compounds (from 10^{-4}M to 10^{-8}M), and then arachidonic acid (50 μg ml^{-1}) and A-23187 (10 μg ml^{-1}) were added and incubation was continued for a further 15 min. The reactions were stopped by the addition of 4 vol of ethanol containing 1,4-dimethoxy-3-(3-methoxypropyl)-2-methylnaphthalene (0.5 μg ml^{-1}) as internal standard. The mixtures were kept for 30 min. Cells were then precipitated by centrifugation at 400 g for 10

Table 5. Data for the quinone derivatives (11a—c), (12a—j), and (13a—g)

Compd.	Method	Yield (%)	Formula M.p. [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(11a)	B	90	$C_{18}H_{24}O_3$	75.3 (75.0)	8.3 (8.4)	1.4—1.9 (total 7 H, m, 3 CH_2 and OH), 2.00 (6 H, s, 2 Me), 2.02 (3 H, s, Me), 2.1—2.3 (4 H, m, 2 CH_2), 2.47 (2 H, m, CH_2), and 3.73 (2 H, t, CH_2)
(11b)	A	85	$C_{18}H_{24}O_5$	67.3 (67.5)	7.6 (7.5)	1.4—1.8 (total 7 H, m, 3 CH_2 and OH), 2.01 (3 H, s, Me), 2.1—2.3 (4 H, m, 2 CH_2), 2.46 (2 H, m, CH_2), 3.72 (2 H, t, CH_2), 3.97 (6 H, s, 2 OMe)
(11c)	B	91	$C_{20}H_{22}O_3$ M.p. 61—62 °C	77.2 (77.4)	7.1 (7.1)	1.4—1.8 (6 H, m, 3 CH_2), 1.83 (1 H, s, OH), 2.1—2.4 (4 H, m, 2 CH_2), 2.17 (3 H, s, Me), 2.63 (2 H, m, CH_2), 3.72 (2 H, t, CH_2), 7.5—7.8 (2 H, m, ArH), and 7.9—8.2 (2 H, m, ArH)
(12a)	B	77	$C_{19}H_{22}O_3$ M.p. 64—65 °C	74.8 (74.5)	7.3 (7.4)	1.4—1.7 (total 5 H, m, 2 CH_2 and OH), 1.99 (6 H, s, 2 Me), 2.02 (3 H, s, Me), 2.18 (2 H, m, CH_2), 2.47 (2 H, m, CH_2), 3.13 (2 H, m, CH_2), and 4.23 (2 H, t, CH_2)
(12b)	B	70	$C_{20}H_{24}O_3$	76.9 (76.9)	7.9 (7.7)	1.4—1.7 (total 5 H, m, 2 CH_2 and OH), 2.00 (6 H, s, 2 Me), 2.03 (3 H, s, Me), 2.1—2.3 (2 H, m, CH_2), 2.41 (2 H, m, CH_2), 2.48 (2 H, m, CH_2), 3.09 (2 H, m, CH_2), and 3.69 (2 H, t, CH_2)
(12c)	B	75	$C_{21}H_{26}O_3$	77.2 (77.3)	8.0 (8.0)	1.4—1.9 (total 7 H, m, 3 CH_2 and OH), 2.00 (6 H, m, 3 CH_2), 2.03 (3 H, s, Me), 2.1—2.3 (4 H, m, 2 CH_2), 2.48 (2 H, m, CH_2), 3.07 (2 H, m, CH_2), and 3.73 (2 H, t, CH_2)
(12d)	B	91	$C_{21}H_{26}O_3$ M.p. 55—56 °C	77.2 (77.3)	8.0 (8.0)	1.4—1.9 (total 7 H, m, 3 CH_2 and OH), 2.00 (6 H, s, 2 Me), 2.02 (3 H, s, Me), 2.1—2.3 (6 H, m, 3 CH_2), 2.47 (2 H, m, CH_2), and 4.21 (2 H, t, CH_2)
(12e)	B	64	$C_{22}H_{26}O_4$	74.6 (74.5)	7.5 (7.4)	1.4—1.9 (6 H, m, 3 CH_2), 1.99 (6 H, s, 2 Me), 2.02 (3 H, s, Me), 2.1—2.3 (4 H, m, 2 CH_2), 2.39 (2 H, m, CH_2), 2.47 (2 H, m, CH_2), 3.08 (2 H, t, CH_2), and 5.94 (1 H, s, CO_2H)
(12f)	A	76	$C_{19}H_{22}O_5$	69.2 (69.1)	6.8 (6.7)	1.4—1.7 (4 H, m, 2 CH_2), 1.97 (1 H, s, OH), 2.02 (3 H, s, Me), 2.02 (2 H, m, CH_2), 2.47 (2 H, m, CH_2), 3.13 (2 H, m, CH_2), 3.97 (6 H, s, 2 OMe), and 4.25 (2 H, t, CH_2)
(12g)	A	72	$C_{21}H_{26}O_5$	70.5 (70.4)	8.1 (7.3)	1.4—1.9 (total 7 H, m, 3 CH_2 and OH), 2.02 (3 H, s, Me), 2.1—2.4 (4 H, m, 2 CH_2), 2.47 (2 H, m, CH_2), 3.07 (2 H, m, CH_2), 3.72 (2 H, t, CH_2), and 3.97 (6 H, s, 2 OMe)
(12h)	A	91	$C_{21}H_{26}O_5$	70.4 (70.4)	7.4 (7.3)	1.4—1.8 (total 7 H, m, 3 CH_2 and OH), 2.03 (3 H, s, Me), 2.1—2.4 (6 H, m, 3 CH_2), 2.47 (2 H, m, CH_2), 3.97 (6 H, s, 2 OMe), and 4.22 (2 H, t, CH_2)
(12i)	A	83	$C_{23}H_{30}O_5$	71.3 (71.5)	7.9 (7.8)	1.4—1.8 (total 9 H, m, 4 CH_2 and OH), 2.01 (3 H, s, Me), 2.1—2.3 (8 H, m, 4 CH_2), 2.46 (2 H, m, CH_2), 3.72 (2 H, t, CH_2), and 3.96 (6 H, s, 2 OMe)
(12j)	B	90	$C_{23}H_{24}O_3$ M.p. 97—98 °C	79.1 (79.3)	6.8 (6.9)	1.5—1.8 (6 H, m, 3 CH_2), 1.81 (1 H, s, OH), 2.1—2.4 (6 H, m, 3 CH_2), 2.20 (3 H, s, Me), 2.64 (2 H, m, CH_2), 4.20 (2 H, t, CH_2), 7.6—7.8 (2 H, m, ArH), and 8.0—8.2 (2 H, m, ArH)
(13a)	C	80	$C_{19}H_{26}O_3$ M.p. 34—36 °C	75.6 (75.5)	8.8 (8.7)	1.3 (4 H, m, 2 CH_2), 1.8—2.2 (total 3 H, m, CH_2 and OH), 2.03 (9 H, s, 3 Me), 2.50 (2 H, m, CH_2), 2.84 (2 H, m, CH_2), 4.26 (2 H, t, CH_2), and 5.3—5.8 (4 H, m, 2 CH=CH)
(13b)	B	85	$C_{19}H_{30}O_3$	76.4 (76.3)	8.8 (9.1)	1.2—1.6 (total 7 H, m, 3 CH_2 and OH), 1.8—2.2 (6 H, s, 3 CH_2), 2.01 (9 H, s, 3 Me), 2.48 (2 H, m, CH_2), 4.0—4.2 (2 H, t, CH_2), and 5.3—5.6 (4 H, m, 2 CH=CH)
(13c)	C	84	$C_{19}H_{26}O_5$	68.2 (68.2)	7.7 (7.8)	1.3—1.6 (4 H, m, 2 CH_2), 1.65 (1 H, s, OH), 1.9—2.2 (2 H, m, CH_2), 2.00 (3 H, s, Me), 2.45 (2 H, m, CH_2), 2.82 (2 H, m, CH_2), 3.97 (6 H, s, 2 Me), 4.21 (2 H, t, CH_2), and 5.3—5.7 (4 H, m, 2 CH=CH)
(13d)	A C	72 83	$C_{21}H_{30}O_5$	69.7 (69.6)	8.5 (8.3)	1.3—1.8 (total 7 H, m, CH_2 and OH), 1.9—2.3 (4 H, m, 2 CH_2), 2.00 (3 H, s, Me), 2.46 (2 H, m, CH_2), 2.78 (2 H, m, CH_2), 3.64 (2 H, m, CH_2), 3.97 (6 H, s, 2 OMe), and 5.3—5.5 (4 H, m, 2 CH=CH)

Table 5 (*continued*)

Compd.	Method	Yield (%)	Formula M.p. [a]	% Found (Required) C	H	^{1}H N.m.r. δ
(13e)	A	83	$C_{21}H_{30}O_5$	69.4 (69.6)	8.3 (8.3)	1.2—1.7 (total 7 H, m, 3 CH_2 and OH), 1.9—2.3 (6 H, m, 3 CH_2), 2.00 (3 H, s, Me), 2.44 (2 H, m, CH_2), 3.97 (6 H, s, 2 OMe), 4.0—4.2 (2 H, t, CH_2), and 5.3—5.6 (4 H, m, 2 CH=CH)
(13f)	A	85	$C_{23}H_{34}O_5$	70.8 (70.7)	8.8 (8.8)	1.5—1.8 (total 9 H, m, 4 CH_2 and OH), 1.9—2.2 (8 H, m, 4 CH_2), 2.00 (3 H, s, Me), 2.45 (2 H, m, CH_2), 3.65 (2 H, t, CH_2), 3.97 (6 H, s, 2 OMe), and 5.3—5.5 (4 H, m, 2 CH=CH)
(13g)	B	85	$C_{23}H_{28}O_3$	78.6 (78.4)	7.9 (8.0)	1.2—1.7 (total 7 H, m, 3 CH_2 and OH), 1.9—2.3 (6 H, m, 3 CH_2), 2.18 (3 H, s, Me), 2.63 (2 H, m, CH_2), 4.0—4.2 (2 H, t, CH_2), 5.3—5.6 (4 H, m, 2 CH=CH), 7.6—7.8 (2 H, m, ArH), and 8.0—8.2 (2 H, m, ArH)

[a] Those compounds for which a m.p. is not given were obtained as oils.

min. The supernatants were concentrated to small volume (*ca.* 100 μl) and were then made up to 1 ml by the addition of 70% aqueous methanol. The solutions were resolved by reverse-phase high-performance liquid chromatography (r.p.-h.p.l.c.) for identification and quantitative analysis of leukotrienes [14] and 5-HETE.[15] For characterisation of leukotrienes, r.p.-h.p.l.c. was carried out on a C_{18} (5 μm) TSK GEL LS-410 column (4 mm × 300 mm; Toyo Soda Manufacturing Co. Ltd., Tokyo) at a flow rate of 1 ml min^{-1} in an isocratic solvent system of acetonitrile–methanol–water–acetic acid [45 : 15 : 43 : 0.12 (v/v)] at pH 5.6, adjusted with ammonia. For characterisation of 5-HETE, the same column was used at the same flow rate in a solvent system of acetonitrile–methanol–water–acetic acid [150 : 50 : 110 : 0.3 (v/v)]. The optical densities (A_{280} for leukotrienes and A_{240} for 5-HETE) of the column effluent were continuously monitored with a multi-wavelength UV monitor, Hitachi 635M (Hitachi Tokyo) and A_{280} and A_{240} peaks were calculated with a SIC intelligent integrator model 7000A (System Instruments Corporation, Tokyo).

Acknowledgements

The authors thank Professor O. Hayaishi and Dr. S. Narumiya (Faculty of Medicine, Kyoto University, Kyoto, Japan) for their generous gift of RBL-1 cells, and also Drs. E. Ohmura, K. Morita, M. Nishikawa, and M. Fujino for their encouragement and valuable advice. We are much indebted to Dr. K. Tsukamoto and Mr. M. Koyama for their assistance in providing and maintaining the RBL-1 cells.

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Received 6th December 1982; *Paper* 2/2025