SYNTHESIS AND BIOLOGICAL ACTIVITY OF ARTHROGRAPHOL AND RELATED COMPOUNDS

Muneharu Miyake,[a] Yoshiaki Hanaoka,[a] and Yasuo Fujimoto[a]*

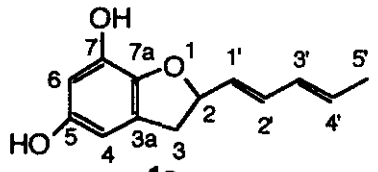
Yoshio Sato, [b]Naoki Taketomo,[b] Itsuro Yokota,[b] and Yoshihiro Yoshiyama[b]

a College of Pharmacy, Nihon University, Narashinodai 7-7-1, Funabashi, Chiba 274, Japan

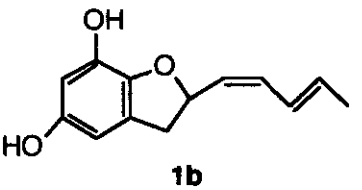
b Meiji Institute of Health Science, Meiji Milk Products Co., Ltd., Naruda 540 Odawara, Kanagawa 250, Japan

Abstract - (±)- Arthrographol (**1a**) and related compounds were synthesized and their inhibitory activities against 5-lipoxygenase were investigated. The 1'(Z)-isomer (**1b**) of arthrographol was found to be three times active than arthrographol itself.

Arthrographol (**1a**) was isolated as an antibiotic and a chitin synthase inhibitor from the metabolites of *Arthrographis pinicola*[1] and *Aspergillus oryzae*.[2] Recently, arthrographol was found to be a potent inhibitor[3] of 5-lipoxygenase which is the first enzyme in the course of the biological transformation of arachidonic acid to leukotrienes causing inflammation and allergy. We describe here syntheses of (±)-arthrographol[4] (**1a**) and its isomers (**1b and 2**) and their inhibitory activities against 5-lipoxygenase.



1a



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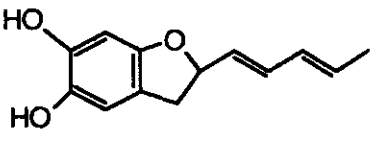

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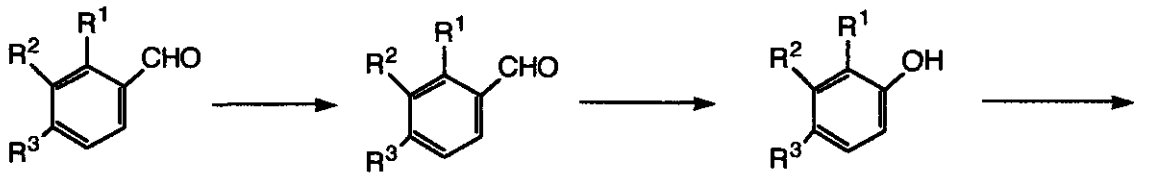
Figure 1

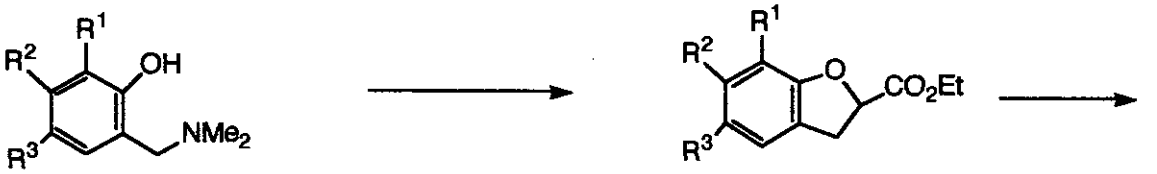
Treatment of 3,4-dihydroxybenzaldehyde (**3**) with benzyl bromide gave a dibenzyl derivative (**5**) in high yield (97.4 %). Baeyer-Villiger oxidation of **5** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded 3,4-dibenzyloxyphenol (**7**, 82 %) which was converted into a Mannich base (**9**, 72 %) by the action of dimethylamine - formaldehyde.



3: R^1 = H; R^2, R^3 = OH
4: R^1, R^3 = OH; R^2 = H

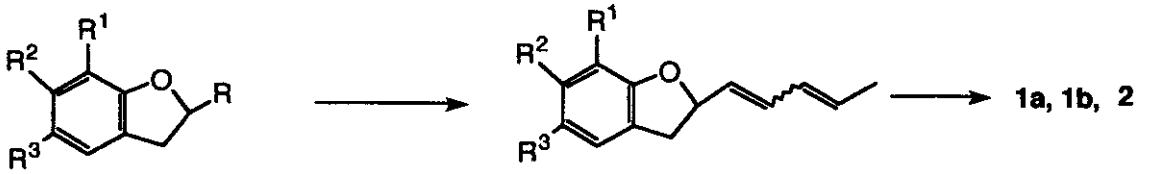
5: R^1 = H; R^2, R^3 = OBn
6: R^1, R^3 = OMOM; R^2 = H

7: R^1 = H; R^2, R^3 = OBn
8: R^1, R^3 = OMOM; R^2 = H



9: R^1 = H; R^2, R^3 = OBn
10: R^1, R^3 = OMOM; R^2 = H

11: R^1 = H; R^2, R^3 = OBn
12: R^1, R^3 = OMOM; R^2 = H
13: R^1, R^3 = OH; R^2 = H
14: R^1, R^3 = OEE; R^2 = H



15: R^1 = H; R^2, R^3 = OBn; R = CH_2OH
16: R^1 = H; R^2, R^3 = OBn; R = CHO
17: R^1, R^3 = OEE; R^2 = H; R = CH_2OH
18: R^1, R^3 = OEE; R^2 = H; R = CHO

19a: R^1 = H; R^2, R^3 = OBn (1'*E*, 3'*E*)
19b: R^1 = H; R^2, R^3 = OBn (1'*Z*, 3'*E*)
20a: R^1, R^3 = OEE; R^2 = H (1'*E*, 3'*E*)
20b: R^1, R^3 = OEE; R^2 = H (1'*Z*, 3'*E*)

Scheme 1

Reaction of **9** with ethoxycarbonylmethyldimethylsulfonium bromide[5] in the presence of potassium carbonate gave a dihydrobenzofuran derivative (**11**, 59.3 %). Reduction of **11** with lithium aluminum hydride gave an alcohol (**15**, 94.3 %) which was subjected to Moffat's oxidation to produce an aldehyde (**16**, 61.8 %). Wittig reaction of **16** with triphenylphosphonium *E*-butene ylide led to the formation of a mixture of 1'(*E*), 3'(*E*)- (**19a**) and 1'(*Z*), 3'(*E*)-diene (**19b**, 70.6 %) in a ratio of 1 : 1 on the inspection of its ^{1}H-nmr spectrum. Althogh the reason is not clear, all trans-isomer was obtained as a sole product after cleavage of benzyl groups of the mixture (**19a** and **19b**) with Me_2S-BF_3·Et_2O. During this deprotection procedure, considerable amounts of the products might be decomposed (~30 % yield). Therefore, we employed more readily removable protective group than benzyl one in the synthesis of arthrographol. Protection of the hydroxyl groups of 2,4-dihydroxybenzaldehyde (**4**) was performed by the action of methoxymethyl chloride (MOM-Cl) - *N*,*N*-diisopropylethylamine and then the resulting methoxymethyl derivative (**6**) was converted into a dihydrobenzofuran derivative (**12**) according to the similar procedures used in the synthesis of **11**. Removal of methoxymethyl groups of **12** followed by reprotection of the resulting hydroxyl groups with ethyl vinyl ether / pyridinium *p*-toluenesulfonate (PPTS) yielded an ethoxyethyl derivative (**14**).[6] Compound (**14**) was transformed into a mixture of 1'(*E*), 3'(*E*)- (**20a**) and 1'(*Z*), 3'(*E*)-diene (**20b**) (49.4 %, **20a** : **20b** = 1 : 9)[7] by a series of similar reactions used in the synthesis of **19**. Deprotection of the mixture (**20a** and **20b**) with MeOH-H_2O-AcOH (50 : 50 : 1) gave a mixture of (±)-arthrographol (**1a**) and its isomer (**1b**) which was separated by high performance liquid chromatography (hplc). Treatment of the mixture (**1a** and **1b**) with diphenyl disulfide[8] gave (±)-arthrographol (**1a**). The ^{1}H-nmr (400 MHz) and mass spectra of synthetic arthrographol were identical with those of natural arthrographol. While synthetic arthrographol and its isomer (**2**) showed similar inhibitory effect against 5-lipoxygenase to that of natural (-)-arthrographol (IC_{50} = 2.0 μg/ml), 1'(*Z*), 3'(*E*)-isomer **2** (IC_{50} = 0.7 μg/ml) was found to be three times active than arthrographol itself.

EXPERIMENTAL

Melting points were determined using a Yanagimoto Melting point Apparatus Yanaco MP and are uncorrected. ^{1}H- and ^{13}C-nmr were recorded on a JEOL JNM-GSX 400 spectrometer in $CDCl_3$ containing tetramethylsilane as an internal standard unless otherwise stated. Masss spectra were taken on a HITACHI M-2000 double-focusing spectrometer. High performance liquid chromatography (hplc) was run on a Waters 600E system instrument.

3,4-Dibenzyloxybenzaldehyde (5) A mixture of 3, 4-dihydroxybenzaldehyde (**3**) (20 g, 145 mmol), K_2CO_3 (40 g, 290 mmol) and benzyl bromide (49.6 g, 290 mmol) in acetone (300 ml) was stirred at 80 °C for 6 h. After filtration of the reaction mixture, the filtrate was poured into Et_2O. The organic layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, crude material was recrystallized from AcOEt-hexane to give **5** as pale yellow needles (44 g, 97.4 %). mp 84 - 85 °C (lit.,[9] mp 90 - 92 °C).

2,4-Dimethoxymethyloxybenzaldehyde (6) A solution of 2, 4-dihydroxybenzaldehyde (**4**) (20 g, 145 mmol), MOM-Cl (35 g, 435 mmol) and *N*,*N*-diisopropylethylamine (56.2 g, 435 mmol) in THF (180 ml) was stirred under ice-cooling for 1 h, and then the stirring was continued at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt and washed with brine. The AcOEt layer was dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by column chromatography on silica gel eluted with hexane-AcOEt (5 : 1) to afford **6** (30.3 g, 92.4 %) as a colorless oil. EIms m /z: 226 $(M)^+$(100), 181 $(M\text{-}C_2H_5O)^+$(52). ^{1}H-Nmr δ: 3.49, 3.53 (3H, each, s), 5.22, 5.29 (2H, each, s), 6.75 (1H, dd, J=2.2, 8.8 Hz), 6.83 (1H, d, J=2.2 Hz), 7.81 (1H, d, J= 8.8 Hz), 10.35 (1H, s, CHO). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.54; H, 6.28.

3,4-Dibenzyloxyphenol (7) A solution of **5** (18 g, 56.5 mmol) and *m*-CPBA (15 g, 60.9 mmol) in AcOEt (200 ml) was stirred at room temperature overnight, and then AcOEt (300 ml) was added. The mixture was washed with satd. $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in THF (50 ml) and then 15 % NaOH (50 ml) was added. The mixture was stirred at room temperature for 30 min. The resultant solution was acidified with 15 % HCl to pH 2 at 0 °C and extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, crude product was collected by precipitation from $CHCl_3$ - hexane. Purification of the crude product by column chromatography on silica gel eluted with hexane-AcOEt (2:1) afforded **7** (14.2 g, 82.0 %) as pale yellow fine needles. mp 99 - 100 °C (AcOEt - hexane) (lit.,[10] mp 110.5 - 111.5°C).

2,4-Dimethoxymethyloxyphenol (8) Compound (**6**) was treated as mentioned above to afford **8** (79.2 %, a colorless oil). EIms m/z: 214 $(M)^+$(70), 45 $(C_2H_5O)^+$(100); HRms: found, m/z 214.0862 $(M)^+$; calcd for $C_{13}H_{21}NO_5$, 214.0832. ^{1}H-Nmr δ: 3.48, 3.52 (3H, each, s), 5.09, 5.18 (2H, each, s), 5.64 (1H, br s, OH), 6.65 (1H, dd, J=2.9, 8.8 Hz), 6.83 (1H, d, J=2.9 Hz), 6.85 (1H, d, J= 8.8 Hz).

4,5-Dibenzyloxy-2-dimethylaminomethylphenol (9) To a mixture of **7** (11.0 g, 35.9 mmol), 50 % Me_2NH (31.6 g, 0.36 mol) and H_2O (50 ml) in THF (50 ml), a solution of 37 % HCHO (29.1 g, 0.36 mol) in H_2O (50 ml) was added slowly at room temperature. The mixture was stirred for 2 h and allowed to stand overnight. The reaction mixture was extracted with AcOEt and the combined extract was washed with brine, dried over $MgSO_4$. The organic solvent was evaporated in *vacuo* to leave an oil which was purified by silica gel column chromatography eluted with $CHCl_3$-MeOH (10 : 1) to afford **9** (9.39 g, 72.0 %) as a yellow-orange powder. Recrystallization from hexane gave colorless fine needles. mp 58 - 59 °C. EIms m /z: 363 $(M)^+$(1.9), 91 $(M\text{-}C_7H_7)^+$ (100). ^{1}H-Nmr δ: 2.29 (6H, s, $N(CH_3)_2$), 3.50 (2H, s), 5.02 (2H, s), 5.10 (2H, s), 6.51 (1H, s), 6.57 (1H, s), 7.28-7.45 (10 H, s). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.14; H, 6.93; N, 3.93.

4,6-Dimethoxymethyloxy-2-dimethylaminomethylphenol (10) Compound (**8**) was coverted into a Mannich base (**10**) according to the procedure mentioned above. (91.1 %, a reddish oil). EIms m /z: 271 $(M)^+$(95), 226 $(M\text{-}C_2H_5O)^+$(99); HRms: found, m/z 271.1383(M^+); calcd for $C_{13}H_{21}NO_5$, 271.1418. ^{1}H-Nmr δ: 2.33 (6H, s, $(CH_3)_2N$), 3.48, 3.53 (3H, each, s), 3.60 (2H, s, CH_2N), 5.07, 5.21 (2H, each, s), 6.40 (1H, d, J=2.9 Hz), 6.81 (1H, d, J=2.9 Hz), 7.27 (1H, s, OH).

5,6-Dibenzyloxy-2-ethoxycarbonyl-2,3-dihydrobenzofuran (11) A mixture of ethoxycarbonylmethyldimethylsulfonium bromide (2.06 g, 9 mmol) and K_2CO_3 (1.24 g, 9 mmol) in DMF (10 ml) was stirred at room temperature for 5 h and then compound (**9**) (1.09 g, 3 mmol) was added to the mixture. The reaction mixture was stirred at 60 - 70 °C for 4 h. After cooling, the mixture was filterd and the filtrate was diluted with AcOEt. The AcOEt solution was washed with brine, dried over $MgSO_4$ and then the solvent was evaporated *in vacuo* to leave an oil which was purified by silica gel column chromatography eluted with haxane-AcOEt (5 : 1) to afford a pale yellow oil. The product crystallized upon the addition of hexane was collected by filtration to give **11** (0.72 g, 59.3 %) as colorless fine needles. mp 68 - 69 °C. EIms m /z: 404 $(M)^+$(6.9), 91 $(M\text{-}C_7H_7)^+$(100). ^{1}H-Nmr δ: 1.30 (3H, t, J=7.0 Hz), 3.26 (1H, dd, J=7.0, 15.4 Hz), 3.44 (1H, dd, J=10.6, 15.7 Hz), 4.25 (2H, q, J=7.0 Hz), 5.04 (2H, s), 5.10 (2H, s), 5.11-5.16 (1H, m), 5.59 (1H, s), 6.79 (1H, s), 7.28-7.44 (10 H, m). Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.47; H, 6.01.

2,3-Dihydro-5,7-dimethoxymethyloxy-2-ethoxycarbonylbenzofuran (12) Compound **10** was converted into a dihydrobenzofuran (**12**) according to the procedure mentioned above. (57.5 %, a pale yellow oil). EIms m /z: 312 $(M)^+$(88); HRms: found, m/z 312.1188(M^+); calcd for $C_{15}H_{20}O_7$,

312.1196. ^{1}H-Nmr δ: 1.30 (3H, t, J=7.0 Hz) 3.34 (1H, dd, J=6.2, 16.1 Hz, H-3), 3.47, 3.51(3H, each, s), 3.52 (1H, dd, J=10.6, 16.1 Hz, H-3), 4.25 (2H, q, J=7.0 Hz), 5.20 (1H, dd, J=6.2, 10.6 Hz, H-2), 5.07, 5.21 (2H, each, s), 6.60 (1H, d, J=2.9 Hz), 6.71 (1H, d, J=2.9 Hz).

2,3-Dihydro-5,7-dihydroxy-2-ethoxycarbonylbenzofuran (13) A solution of **12** (7.42 g, 23.8 mmol) and 12 N HCl / MeOH (3 ml) in THF (25 ml) was stirred under ice-cooling for 5 h. The reaction mixture was diluted with AcOEt and the organic layer was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave a reddish oil which was purified by silica gel column chromatography eluted with hexne-AcOEt (1 : 1) to afford white crystals. Recrystallization from AcOEt-hexane gave **13** (3.08 g, 57.7%) as colorless prisms. mp 175 - 176 °C. EIms: m /z: 224 $(M)^+$(83), 151$(M-CO_2Et)^+$(100); HRms: found, m/z 224.0734$(M)^+$; calcd for $C_{11}H_{12}O_5$, 224.0676. ^{1}H-Nmr (acetone-d_6) δ: 1.26 (3H, t, J=7.0 Hz) 3.25 (1H, dd, J=6.7, 15.7 Hz, H-3), 3.48 (1H, dd, J=10.3, 15.7 Hz, H-3), 4.20 (2H, q, J=7.0 Hz), 5.14 (1H, dd, J=6.7, 10.3 Hz, H-2), 6.21 (1H, d, J=2.2 Hz), 6.24 (1H, d, J=2.2 Hz), 7.74, 8.00 (1H, each, s, OH).

5,7-Bis(1-ethoxyethyloxy)-2-ethoxycarbonyl-2,3-dihydrobenzofuran (14) A solution of ethyl vinyl ether (12.6 ml, 13.38 mmol) in CH_2Cl_2 (10 ml), **13** (3.0 g, 13.38 mmol) in THF (20 ml) and PPTS (251 mg, 1 mmol) was stirred at room temperature for 0.5 h. The mixture was diluted with AcOEt and the organic layer was washed with satd. $NaHCO_3$ and dried over $MgSO_4$. The organic solvent was evaporated *in vacuo* to leave a yellow oil which was purified by silica gel column chromatography eluted with hexane-AcOEt (4 : 1) to afford **14** (4.61 g, 93.5%) as a colorless oil. EIms m/z: 368 $(M)^+$(0.9), 224 $(M-C_4H_8O \times 2)^+$(100); HRms: found, m/z 368.1795$(M)^+$; calcd for $C_{19}H_{28}O_7$, 368.1820. ^{1}H-Nmr (acetone-d_6) d: 1.15-1.18 (m, CH_3 x 5), 3.32 (1H, dd, J=6.2, 16.1 Hz, H-3), 3.51-3.66 (3H,m), 3.76-3.91 (2H, m), 5.16-5.22 (2H, m), 5.49 (1H, m, H-2), 6.56 (1H, br s), 6.63-6.67 (1H, m).

5,6-Dibenzyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran (15) Compound (**11**) (1.93 g, 4.77 mmol) in THF (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1 g, 26.4 mmol) in THF (10 ml) under ice-cooling. After 0.5 h, H_2O (1 ml), 15 % NaOH (1 ml), and H_2O (3 ml) was added slowly in that order under stirring, and then $MgSO_4$ was added and stirring was continued for 0.5 h at room temperature. The mixture was filterd and the filtrate was evaporated *in vacuo* to give **15** (1.63 g, 94.3 %) as a colorless oil, which crystallized upon cooling as white crystals, was used in the next step without further purification. mp 145 - 146 °C. EIms m /z: 362 $(M)^+$(15), 91 $(M-C_7H_7)^+$(100). ^{1}H-Nmr δ: 1.86 (1H, t, J=5.9 Hz, OH), 2.90 (1H, dd, J=7.7, 15.4 Hz), 3.14 (1H, dd, J=9.5, 15.4 Hz), 3.68-

3.74 (1H, m), 3.78-3.83 (1H, m), 4.85-4.88 (1H, m), 5.04 (2H, s), 5.10 (2H, s), 6.48 ((1H, s), 6.80 (1H, s), 7.27-7.44 (10H, m). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.23; H, 6.12. Found: C, 76.09; H, 6.13.

5,6-Dibenzyloxy-2-formyl-2,3-dihydrobenzofuran (16) A solution of **15** (3.12 g, 8.61 mmol), *N*,*N* '-dicyclohexylcarbodiimide (7.10 g, 34.4 mmol) and 1M H_3PO_4/DMSO (4 ml) in DMSO (40 ml) was stirred at room temperature for 3 h. The reaction mixture was diluted with $CHCl_3$ (50 ml) and filterd. The filtrate was diluted with AcOEt (200 ml) and then washed with brine, dried over $MgSO_4$. The organic solvent was evaporated *in vacuo* to leave a pale yellow oil which was purified by silica gel column chromatography eluted with $CHCl_3$-AcOEt (9:1) to afford **16** (1.92 g, 61.8 %) as white crystals which was used in the next step without further purification. mp 44 - 45 °C. Elms m /z: 360 $(M)^+$(11), 91 $(M\text{-}C_7H_7)^+$(100); HRms: found, m/z 360.1333$(M)^+$; calcd for $C_{23}H_{20}O_4$, 360.1352.

5,7-Bis(1-ethoxyethyloxy)-2-hydroxymethyl-2,3-dihydrobenzofuran (17) Compound (**14**) was reduced with $LiAlH_4$ to give an alcohol (**17**) according to the procedure mentioned in the case of reduction of **11**. (90%, a colorless oil). Elms m /z: 326 $(M)^+$(1.4), 182 $(M\text{-}C_4H_8O \times 2)^+$(73); HRms: found, m/z 326.1730$(M)^+$; calcd for $C_{17}H_{24}O_6$, 326.1716. ^{1}H-Nmr δ: 1.17-1.24 (m, CH_3 x 2), 1.44-1.51 (m, CH_3 x 2), 3.01 (1H, m, H-3), 3.21 (1H, m, H-3), 3.51-3.85 (6H, m), 4.88-4.94 (1H, m), 5.20 (1H, dd, J=5.1, 10.2), 5.40-5.48 (1H, m), 6.56-6.86 (2H, m).

5,7-Bis(1-ethoxyethyloxy)-2-formyl-2,3-dihydrobenzofuran (18) A solution of $(COCl)_2$ (0.95 ml, 10.2 mmol) in CH_2Cl_2 (30 ml) and DMSO (1.59 ml, 20.4 mmol) in CH_2Cl_2 (20 ml) was stirred at -78 °C for 10 min and then **17** (3.03 g, 9.28 mmol) in CH_2Cl_2 (20 ml) was added to the stirred solution. After 1.5 h, TEA (6.5 ml, 46.4 mmol) was added and the stirring was continued for 15 min. The reaction mixture was allowed to warm up to room temperature in 1 h. Water (10 ml) was added to the mixture and then organic layer was washed with brine, dried over $MgSO_4$. The organic solvent was evaporated *in vacuo* to leave a yellow oil which was purified by silica gel column chromatography eluted with Et_2O to afford **18** (1.88 g, 62.4 %) as a pale yellow oil which was used in the next step without further purification. Elms m /z: 324 $(M)^+$(2.2), 18 $(M\text{-}C_4H_8O \times 2)^+$(100); HRms: found, m/z 324.1554$(M)^+$; calcd for $C_{17}H_{24}O_6$, 324.1560. ^{1}H-Nmr δ: 1.17-1.48 (m, CH_3 x 4), 2.98 (1H, m, H-3), 3.24 (1H, m, H-3), 3.21 (1H, m, H-3), 3.51-3.85 (6H, m), 4.88-4.94 (1H, m), 5.20 (1H, dd, J=5.1, 10.2), 9.86 (1H, br s, CHO).

5,6-Dibenzyloxy-2,3-dihydro-2-(1',3'-pentadienyl)benzofuran (19a and 19b) A mixture

of NaH (60 % in oil, 102 mg, 2.55 mmol), 2-butenyl triphenylphosphonium bromide (1.0 g, 2.55 mmol) in THF (10 ml) was stirred at room temperature. After 15 min, compound (**16**) (610 mg, 1.69 mmol) in THF (5 ml) was added and the stirring was continued for 5 h. Satd. NH_4Cl (10 ml) was added to the mixture and then it was extracted with AcOEt. The AcOEt solution was washed with brine, dried over $MgSO_4$. The organic solvent was evaporated *in vacuo* to leave a yellow oil which was purified by silica gel column chromatography eluted with haxane-AcOEt (9 : 1) to afford a mixture of the isomeric dienes (**19a**) and (**19b**) (475 mg, 70.6 %) as colorless crystals. mp 42 - 43 °C (mixture of **19a** and **19b**). EIms m /z: 398 $(M)^+$(6.0), 91 $(M\text{-}C_7H_7)^+$(100). Anal. Calcd for $C_{27}H_{26}O_3$: C, 81.38; H, 6.58. Found: C, 81.08; H, 6.58.

5,7-Bis(1-ethoxyethyloxy)-2,3-dihydro-2-(1',3'-pentadienyl)benzofuran (20a and 20b) Compound (**18**) was converted into a mixture of the isomeric dienes (**20a** : **20b** = 1 : 9) according to the procedure mentioned above. (49.4 %, a colorless oil). EIms m /z: 362 $(M)^+$(2.5), 218 $(M\text{-}C_4H_8O_2)^+$ (100); HRms: found, m/z 362.2076$(M)^+$; calcd for $C_{21}H_{30}O_5$, 362.2080.

5,7-Dihydroxy-2,3-dihydro-2-(1',3'-pentadienyl)benzofuran (Isomeric dienes (1a) and (1b)) The mixture of **20a** and **20b** (420 mg, 1.16 mmol) in MeOH (5 ml) and AcOH-MeOH-H_2O (1 : 50 : 50, 30 ml) was stirred at room temperature for 3 h. Satd. $NaHCO_3$ (50 ml) was added to the mixture and it was extracted with AcOEt (50 ml). The AcOEt solution was washed with brine, dried over $MgSO_4$. The organic solvent was evaporated in *vacuo* to leave a pale yellow oil which was purified by silica gel column chromatography eluted with haxane-AcOEt (3 : 1) to afford a mixture of the isomeric dienes (**1a**) and (**1b**) as colorless needles (230 mg, 90.9 %). mp 86 - 89 °C (CH_2Cl_2-hexane).

Isomerization to the 1'(*E*),3'(*E*)-Isomer (1a) The mixture of the dienes (**1a** and **1b**) (70 mg, 0.31 mmol) and diphenyl disulfide (13 mg, 0.06 mmol) in THF (5 ml) was heated under reflux for 16 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluted with hexane-AcOEt (3 : 1) to afford (*E*), (*E*)-**1a** as colorless needles (66 mg, 95.8 %). mp 114 - 116 °C (AcOEt-CH_2Cl_2-hexane) (lit.,[1] mp 124 - 126 °C).

Separation of 2,3-dihydro-5,7-dihydroxy-2-(1',3'-pentadienyl)benzofuran (1a and 1b) The mixture (**1a** and **1b**) was separated by hplc (Shodex-SIL-5E 10 x 250 mm, hexane-AcOEt = 3 : 1) to give **1a** (retention time: 16.3 min) and **1b** (retention time: 17.4 min).

5,7-Dihydroxy-2,3-dihydro-2-[(1'(*Z*),3'(*E*)-pentadienyl)]benzofuran (1b) Pale yellow oil. EIms m /z: 218 $(M)^+$(100), 163 $(M\text{-}C_4H_7)^+$(67), 138 $(M\text{-}C_6H_8)^+$(74); HRms: found, m/z 218.0948

$(M)^+$; calcd for $C_{13}H_{14}O_3$, 218.0936. ^{1}H-Nmr δ: 1.82 (3H, br d, J=6.6 Hz, H-5'), 2.95 (1H, dd, J= 7.8, 15.4 Hz, H-3), 3.32 (1H, dd, J=8.8, 15.4 Hz, H-3) , 4.72, 5.16 (1H, each, br s, OH), 5.52 (1H, dd, J=9.5, 10.3 Hz, H-1'), 5.65 (1H, ddd, J=7.8, 8.8, 9.5 Hz, H-2), 5.86 (1H, dq, J=6.6, 14.7 Hz, H-4'), 6.20 (1H, t, J=10.3 Hz, H-2'), 6.26 (1H, d, J=2.2 Hz, H-4), 6.27 (1H, d, J=2.2 Hz, H-6), 6.39 (1H, dd, J=11.0, 14.7 Hz, H-3'). ^{13}C-Nmr δ: 18.4(C-5'), 37.8 (C-3), 79.8 (C-2), 102.6 (C-6), 103.6 (C-4), 126.1 (C-3'), 126.8 (C-1'), 128.1 (C-3a), 132.4 (C-2'), 133.3 (C-4'), 140.1 (C-7a or C-7), 140.3 (C-7 or C-7a), 150.4 (C-5).

5,6-Dihydroxy-2,3-dihydro-2-[(1'(*E*), 3'(*E*)-pentadienyl]benzofuran (2) The mixture of dienes (**19a** and **19b**) (950 mg, 2.38 mmol), Me_2S (9.5 ml, 129.4 mmol) and $BF_3 \cdot Et_2O$ (6 ml) in CH_2Cl_2 (8 ml) was stirred at -20 °C for 3 h. The mixture was allowed to warm up to room temperature in 1 h. Water (15 ml) was added to the mixture and it was extracted with AcOEt (15 ml). The AcOEt solution was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the soluvent gave a reddish oil which was purified by column chromatography on silica gel eluted with hexane-AcOEt (2 : 1) to afford a solid. Recrystallization from AcOEt-hexane gave **2** (162 mg, 31.2 %) as colorless needles. mp 129 - 130 °C. EIms m /z: 218 $(M)^+$ (100); HRms: found, m/z 218.0926(M^+); calcd for $C_{13}H_{14}O_3$, 218.0936. ^{1}H-Nmr (acetone-d_6) δ: 1.72 (3H, dd J=1.5, 6.6 Hz, H-5'), 2.80 (1H, dd, J=7.3, 15.4 Hz, H-3), 3.20 (1H, dd, J=9.5, 15.4 Hz, H-3), 5.09 (1H, m, H-2), 5.68-5.79 (2H, m, H-1' and H-4'), 6.08 (1H, br dd, 14.7, 10.3 Hz, H-3'), 6.27 (1H, dd, J=10.3, 15.4 Hz, H-2'), 6.26 (1H, s), 6.64 (1H, s), 7.20-7.70 (2H, 2 lump, OH). ^{13}C-Nmr δ: 18.1 (C-5'), 36.9 (C-3), 84.1 (C-2), 98.1 (C-4), 112.5 (C-7), 117.2 (C-3a), 131 (C-1' and C-3'), 131.7 (C-2'), 132.6 (C-4'), 139.4 (C-7a), 145.5 (C-5 or C-6), 153.8 (C-5 or C-6).

Method of 5-Lipoxygenase Inhibition Assay[11] Inhibition of 5-lipoxygenase was determined using crude enzyme prepared from rat basophilic leukemia (RBL-1) cells. Arachidonic acid (100 μM) conversion to 5-HETE with $CaCl_2$ (1mM), ATP (1 mM) and the enzyme solution in 0.1 M Tris-HCl buffer (pH 7.5) was measured by reversed phase hplc analysis. The inhibitory activity was calculated according to the measurement of converted 5-HETE with or without a test compound in the assay system.

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6. At first, we prepared methoxymethyl derivative of compound (**20**), however elimination of the methoxymethyl group under various conditions did not give satisfying results (~30 % yield). Thus we replaced the protecting group by ethoxyethyl group at this stage.
7. The low yield of this reaction might be due to the enolization of 2-formyldihydrobenzofurans (**16**) and (**18**) under reaction conditions. W. A. Ayer and P. A. Craw reported that 5,7-dimethoxy-2-formyldihydrobenzofuran was a mixture of the aldehyde form and its enol tautomer, see Ref. 4a.
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