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Synthesis of the Aglycones of Poriolide and Isoporiolide, New Biphenyl-type Flavanones

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A key point of the synthesis of aglycones (**12** and **33**) derived from poriolide (**1**) and isoporiolide (**2**), the toxic constituents of *Leucothoe keiskei*, is the construction of the unsymmetric biphenyl compounds, this point was effected by application of the rearrangement reaction of suitable phenyltropone derivatives to biphenyl compounds.

Poriolide (**1**) and Isoporiolide (**2**) are the toxic constituents of *Leucothoe keiskei* Miq. (Ericaceae). Degradative and spectral investigations have shown in our previous paper[2] that these natural products belong to a new type of macrocyclic flavonoid glycoside having a biphenyl structure. The unique skeletal structure led us to select the aglycones of these glycosides as a goal for total synthesis. A key point of the synthesis of the aglycones is the construction of the unsymmetrical biphenyl compounds. Although, for the synthetic purpose, the Ullmann synthesis,[3] a method for the decomposition of a benzenediazonium salt in phenol,[4] photochemical synthesis[5] and some other reactions are available, these require well-selected reaction conditions and still give by-products. Application of the rearrangement reaction of phenyltropone derivatives to the corresponding biphenyl compounds reported in our recent paper[6] is the most efficient and convergent method for the synthesis of the key intermediates, unsymmetrical biphenyls.

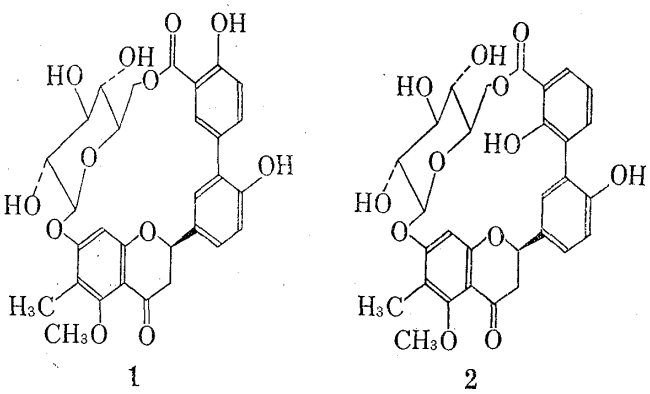

Chart 1

In order to obtain a 2,3′,4′,5-tetrasubstituted biphenyl for the synthesis of the biphenyl moiety of poriolide, a biphenyl (**4**) was prepared from 2-(4-methoxy-3-methylphenyl)tropone (**3**) by such a rearrangement reaction. The phenyltropone (**3**), prepared from the suitable Grignard reagent and 2-methoxytropone, was treated with magic methyl in methylene chloride to give the tropylium salt, which was rearranged in 65% yield to the biphenyl derivative (**4**) on reaction with dicarboethoxy methylenedimethylsulfurane. The biphenyl derivative (**4**) was oxidized with potassium permanganate followed by methylation to a methyl biphenylcarboxylate (**5**) in 71% yield. Conversion of the carbomethoxy function of **5** to the aldehyde group of **7** was quantitatively achieved by manganese dioxide oxidation of the reduction

1) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
2) A. Ogiso, A. Sato, I, Kashida, and H. Kuwano, *Chem. Pharm. Bull.* (Tokyo), **22**, 135 (1974).
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product (**6**). The methyl group of **7** was oxidized with lead tetraacetate in glacial acetic acid to an acetate (**8a**) in 50% yield, which was easily hydrolyzed to an alcohol (**8b**) in 66% yield. Condensation of **8b** with an acetophenone derivative (**9a**)[7] to a biphenyl-type flavanone (**10**) was carried out by an usual manner using potassium hydroxide in ethanol in 24% yield. To identify the synthetic flavanone with the natural aglycone derived from poriolide,[2] the carbinol function of **10** must be changed into the carbomethoxy group. The benzylalcohol (**10**) was readily oxidized with Sarett reagent to an aldehyde (**11**) in 92% yield. Although several attempts to oxidize the aldehyde (**11**) with silver salts to the desired acid failed owing to the instability of the flavanone in the alkaline medium, treatment with manganese dioxide-sodium cyanide in methanol[8] gave the ester (**12**) in 20% yield. Spectral data of **12** were superimposable to those of the aglycone ester derived from poriolide.

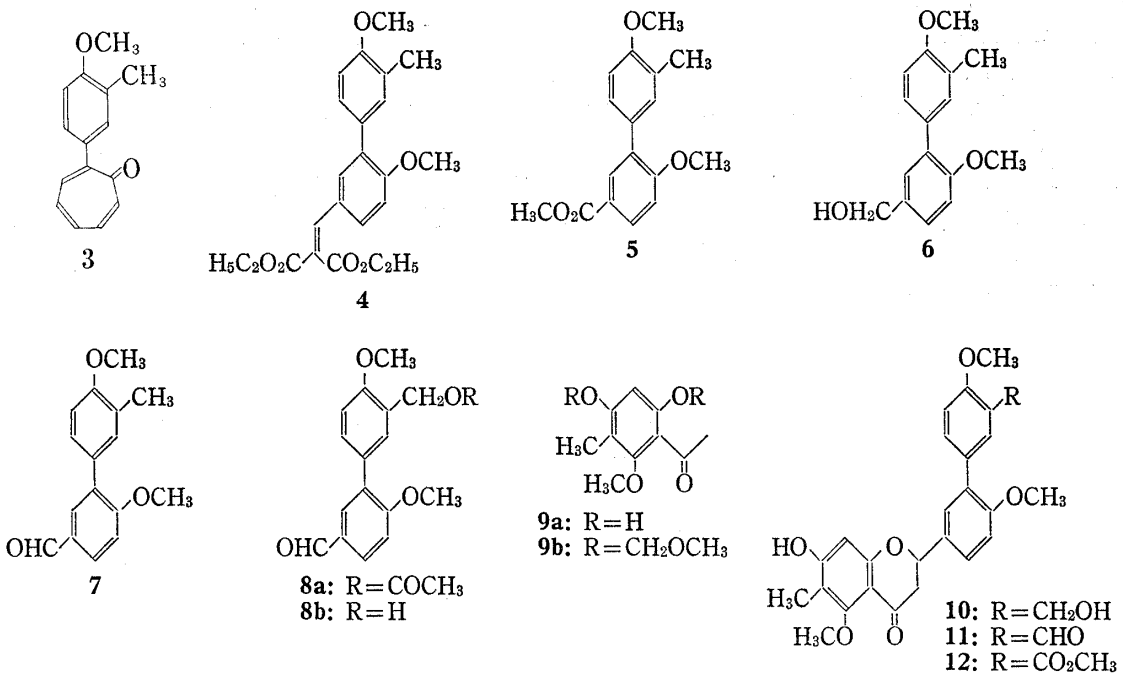

Chart 2

Since the final oxidation step was not satisfactory in the above synthetic sequence, an alternative successful synthesis was effected through intermediates originally bearing a carboxyl group. The phenyltropone (**13**), prepared by treatment of 5-bromo-*o*-anisic acid with *n*-butyllithium followed by addition of 2-chlorotropone, was converted into the biphenylcarboxylate (**14**) in 62% yield by the same reactions as the step **3** to **4**. The saponified product (**15**) was decarboxylated at 215° under reduced pressure (0.05 mmHg) and methylated to the diester (**16**) in 60% yield. On oxidation with osmium tetroxide-sodium periodate, the double bond in **16** cleaved to form the aldehyde (**17**). Aldol condensation of the aldehyde (**17**) with an acetophenone derivative (**9b**) by the action of sodium hydride and subsequent removal of the protective methoxymethyl groups gave the corresponding chalcone, which was successfully cyclized to the target substance (**12**) on standing in aqueous pyridine solution.[9]

Since the biphenyl moiety in the structure of isoporiolide (**2**) has a 2,2′,3,5′-substitution pattern, at first we chose the biphenyl derivative (**19**) prepared from 3-bromo-2-methoxytoluene in 34% yield *via* a phenyltropone (**18**). Oxidation of **19** with potassium permanganate followed by methylation gave a biphenylcarboxylate (**20**) in 30% yield, which was quantita-

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8) E.J. Corey, N.W. Gilman, and B.E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
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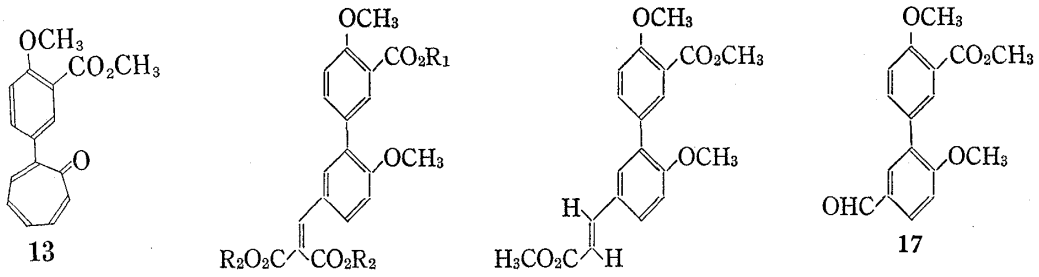

Chart 3

tively brominated with N-bromosuccinimide, and then the bromide (**21**) was oxidized under Kornblum conditions to an aldehyde (**22**) in 45%. The acetal derivative (**23**) was reduced with lithium aluminum hydride to an alcohol (**24**), which was treated with acid to remove the acetal function. The aldehyde group was oxidized with silver oxide to a carboxylic acid (**25**), which was methylated and oxidized with Sarett reagent to an aldehyde (**26**). The aldehyde (**26**) was reduced with sodium borohydride to the alcohol (**27**) identical with an alkaline degradation product of isoporiolide (**2**). Therefore, this completely determines the positions of substituents in the biphenyl moiety, which comprises the only difference between poriolide and isoporiolide.

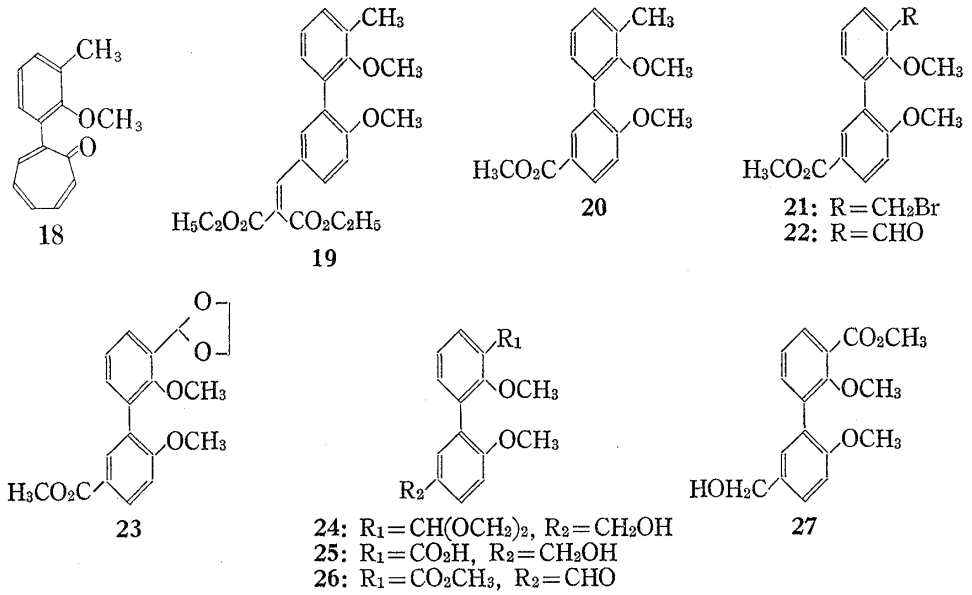

Chart 4

The above route for the synthesis of the appropriate biphenylaldehyde (**26**) is tedious and not efficient for a total synthesis. As we mentioned in the previous paper, 3-substituted-2-alkoxybiphenyls can be prepared as the predominant rearrangement products accompanied by 5-substituted-2-alkoxybiphenyls when relatively reactive ylides such as *p*-bromobenzoylmethylenedimethylsulfurane are used. A series of operations starting from a phenyltropone (**28**) led to the formation of the desired biphenyl (**29**) in 40% yield along with the isomer (**30**). The structural assignment of the biphenyl (**29**) and its isomer (**30**) was effected by comparison of the nuclear magnetic resonance spectra of the both compounds. The methoxyl methyl protons at the 2-position of **29** resonate at δ 3.46 while those of the 2-position of **30** appear at δ 3.74. As several examples are shown in the report,[6] the isomer whose methoxyl methyl resonance appears in higher field is easily assigned to the structure **29**. On oxidation with

potassium permanganate followed by methylation, **29** was converted into the biphenylcarboxylate (**31**) in 72% yield. Transformation of the aromatic methyl group of **31** to the formyl group of **32** was carried out in 44% yield by the procedure of N-bromosuccinimide bromination followed by Kornblum oxidation. The aglycone (**33**) obtained from **32** and **9b** in 20% yield under the same reaction conditions as in the case of the aglycone (**12**) was identified with the natural one by spectral methods.

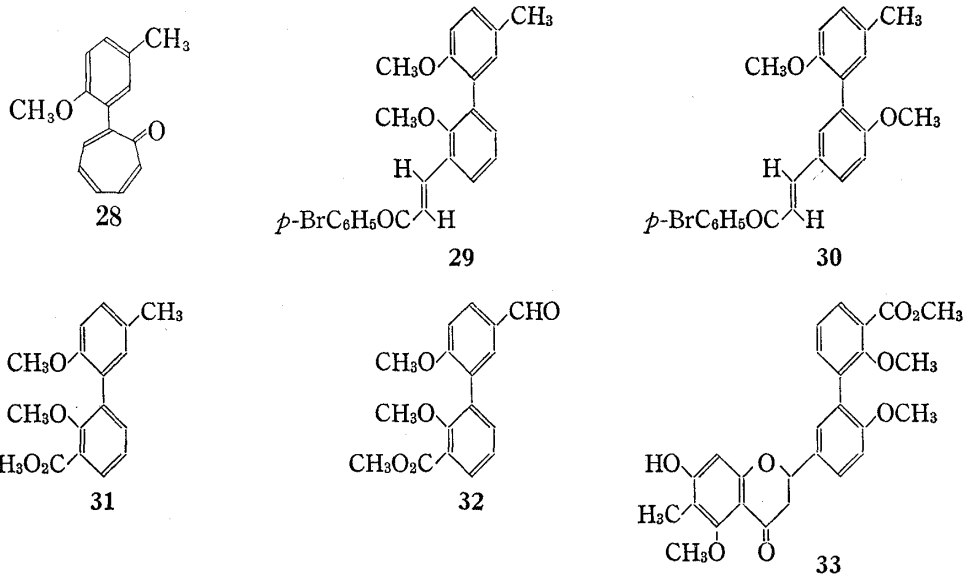

Chart 5

Experimental

The melting points were determined in capillary tubes and uncorrected. The ultraviolet (UV) spectra were measured in 95% ethanol using a Beckman DK-2A spectrophotometer. Infrared (IR) spectra were determined on a JASCO IR-A2 spectrophotometer. The nuclear magnetic resonance (NMR) spectra were determined with Varian A-60 and HA-100 spectrometer using tetramethylsilane as an internal reference in deuterochloroform except otherwise mentioned. Preparative thin-layer chromatography was carried out by using Silica gel F_{254} plates.

2-(4-Methoxy-3-methylphenyl)tropone (3)——To a Grignard reagent prepared from 48 g of 5-bromo-2-methoxytoluene and 5.4 g of magnesium in 100 ml of dry ether was added a solution of 20 g of 2-methoxytropone in 70 ml of dry benzene under nitrogen atmosphere. After stirring for 2 hr at room temperature, the reaction mixture was treated with 5% sulfuric acid. The organic layer was washed with water, dried and evaporated to give 55 g of a red oil which was distilled to remove the low-boiling point materials. The residual oil was treated with hydrogen chloride in 1 liter of dry benzene to form an oily precipitate. The salt separated was decomposed by addition of water and extracted with ether. The extract was chromatographed on silica gel (1 kg), and the benzene eluent was distilled to give 33 g of yellow oil, bp 155—157° (0.04 mmHg). IR $\nu_{max}^{Liq.}$ cm^{-1}: 1620, 1600, 1575, 1490. UV λ_{max} nm (ε): 230 (23400), 360 (7100). NMR δ: 2.25 (3H, s), 3.86 (3H, s), 6.7—7.5 (8H). *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.40; H, 6.26.

2,4′-Dimethoxy-3′-methyl-5-(β,β-dicarboethoxyvinyl)biphenyl (4)——A solution of 32 g of the phenyltropone (3) and 17 g of methyl fluorosulfonate in 120 ml of dry methylene chloride was kept at room temperature overnight under nitrogen atmosphere to give 42.9 g of a tropylium salt as orange needles. To a suspension of the salt in 600 ml of dry methylene chloride was added a solution of 28.2 g of dicarboethoxymethylenedimethylsulfurane in 200 ml of dry methylene chloride. After standing overnight, the reaction mixture was washed with water, dried and evaporated to give the desired compound (4), which was recrystallized from isopropyl ether affording 33 g of colorless needles, mp 88—90°. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1710, 1625, 1600, 1510, 1490. UV λ_{max} nm (ε): 282 (25200), 305 (sh. 21500). NMR δ: 1.30 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=7.0 Hz), 4.33 (2H, q, J=7.0 Hz), 4.38 (2H, q, J=7.0 Hz), 2.28 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 6.8—7.6 (6H), 7.75 (1H, s). *Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.38; H, 6.62.

Methyl 4′,6-Dimethoxy-3′-methyl-3-biphenylcarboxylate (5)——A solution of 1.0 g of the diester (4) and 1.46 g of potassium permanganate in 25 ml of 50% aqueous pyridine was heated at 50—60° for 1 hr.

After filtration, the solution was acidified with 10% hydrochloric acid to give a crystalline precipitate, which was recrystallized from methanol affording 400 mg of needles, mp 226—227°. A solution of the carboxylic acid in 20 ml of methanol containing 3% of hydrogen chloride was refluxed for 1 hr. The reaction mixture was evaporated and the residual oil was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give the ester (**5**), which was recrystallized from *n*-hexane–acetone to form 400 mg of colorless prisms, mp 86—87°. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1600, 1580, 1500, 1250. UV λ_{max} nm (ε): 250 (32500), 285 (sh. 13900). NMR δ: 2.29 (3H, s), 3.87 (6H, s), 3.91 (3H, s), 6.8—8.2 (6H). *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.69; H, 6.30.

5-Hydroxymethyl-2,4′-dimethoxy-3′-methylbiphenyl (6)——To a solution of 1.2 g of lithium aluminum hydride in 150 ml of dry tetrahydrofuran was added a solution of 11.0 g of the methylester (**5**) in 50 ml of dry tetrahydrofuran. After stirring for 2 hr at room temperature, the reaction mixture was treated with 5 ml of water to decompose the excess reagent. The filtrate was evaporated and dissolved in ethyl acetate. Working up of the ethyl acetate layer as usual gave the alcohol (**6**), which was recrystallized from *n*-hexane–isopropyl ether affording 9.0 g of colorless prisms, mp 56—57°. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1610, 1510. NMR δ: 2.00 (1H, s), 2.27 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 4.68 (2H, s), 6.8—7.5 (6H). *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.28; H, 7.09.

5-Formyl-2,4′-dimethyl-3′-methylbiphenoxy (7)——A mixture of 500 mg of the alcohol (**6**) and 870 mg of manganese dioxide in 30 ml of dry benzene was refluxed for 2 hr. The reaction mixture was filtered and evaporated to give the aldehyde (**7**), which was recrystallized from isopropyl ether to form 470 mg of colorless needles, mp 71.5—72.5°. IR ν_{max}^{Nujol} cm^{-1}: 1685, 1610, 1590, 1515, 1490. UV λ_{max} nm (ε): 262 (32200), 280 (sh. 20300). NMR δ: 2.28 (3H, s), 3.90 (6H, s), 6.8—8.0 (6H), 9.98 (1H, s). *Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25. Found: C, 75.14; H, 6.34.

3′-Acetoxymethyl-5-formyl-2,4′-dimethoxybiphenyl (8a)——To a solution of 6.0 g of the aldehyde (**7**) in 70 ml of glacial acetic acid was gradually added 28 g of lead tetraacetate during 10 hr keeping at 80°. After removal of the solvent, the reaction mixture was extracted with ethyl acetate and treated with water. The ethyl acetate layer was filtered and worked up as usual to give 8.0 g of an orange oil, which was chromatographed on silica gel (200 g) to give the acetate (**8a**). Recrystallization from *n*-hexane–acetone gave 3.5 g of colorless needles, mp 109—110°. NMR δ: 2.10 (3H, s), 3.91 (6H, s), 9.94 (1H, s).

5-Formyl-3′-hydroxymethyl-2,4′-dimethoxybiphenyl (8b)——A solution of 2.8 g of the acetate (**8a**) in 10 ml of dioxane containing 5 ml of 10% sodium hydroxide solution was stirred for 2 hr at room temperature. The reaction mixture was evaporated and the residue was dissolved in ethyl acetate. The solution was worked up as usual to afford the alcohol (**8b**), which was recrystallized from acetone–benzene yielding 2.1 g of needles, mp 97—98°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1690, 1600, 1580, 1500. UV λ_{max} nm (ε): 262 (23300), 280 (sh. 18300). NMR δ: 2.38 (1H, s), 3.90 (6H, s), 4.76 (2H, s), 6.8—8.0 (6H), 9.96 (1H, s). *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.77; H, 5.89.

7-Hydroxy-4′,5-dimethoxy-6-methyl-3′-(3-hydroxymethyl-4-methoxyphenyl)dihydroflavone (10)——A solution of 181 mg of the acetophenone (**9a**) and 254 mg of the hydroxyaldehyde (**8b**) in 30% aqueous ethanol containing 1.4 g of potassium hydroxide was kept at room temperature overnight under nitrogen atmosphere. The reaction mixture was diluted with water, after standing for 30 min, the mixture was washed with ethyl acetate and water layer was acidified with conc. hydrochloric acid. The ethyl acetate extract was chromatographed on silica gel to separate 39 mg of the chalcone and 119 mg of the dihydroflavone (**10**), which was recrystallized from acetone–benzene yielding 101 mg of colorless needles, mp 212—214°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1660, 1600, 1595, 1510, 1490. UV λ_{max} nm (ε): 283 (25300). NMR δ: 2.39 (3H, s), 2.94 (1H, dd, J= 3.5, 16.5 Hz), 3.24 (1H, dd, J=12.5, 16.5 Hz), 3.64 (3H, s), 3.70 (3H, s), 4.04 (3H, s), 5.16 (2H, s), 5.41 (1H, dd, J=3.5, 12.5 Hz), 6.65 (1H, s), 6.9—8.2 (6H). *Anal.* Calcd. for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82. Found: C, 69.40; H, 5.98.

7-Hydroxy-4′,5-dimethoxy-6-methyl-3′-(3-formyl-4-methoxyphenyl)dihydroflavone (11)——To the Sarett reagent prepared from 670 mg of chromium trioxide and 7 ml of pyridine was added a solution of 400 mg of the benzylalcohol (**10**) in 10 ml of pyridine under ice-cooling. After standing overnight, the reaction mixture was diluted with ethyl acetate and resulting precipitate was filtered. The organic layer was washed with dil. hydrochloric acid, satd. aqueous sodium bicarbonate solution and water successively. Evaporation of the solvent and recrystallization from methanol gave 370 mg of the aldehyde (**11**), mp 225—227°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1680, 1620, 1600, 1570. UV λ_{max} nm (ε): 284 (19700), 324 (8300). NMR δ (C_5D_5N): 2.38 (3H, s), 2.92 (1H, dd, J=3.5, 16.5 Hz), 3.23 (1H, dd, J=12.5, 16.5 Hz), 3.65 (3H, s), 3.76 (3H, s), 4.03 (3H, s), 6.67 (1H, s), 6.8—8.3 (6H), 10.66 (1H, s). *Anal.* Calcd. for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found: C, 69.68; H, 5.40.

7-Hydroxy-4′,5-dimethoxy-6-methyl-3′-(3-carbomethoxy-4-methoxyphenyl)dihydroflavone (12)——A mixture of 100 mg of the aldehyde (**11**) and 1.39 g of manganese dioxide and 820 mg of sodium cyanide in 480 mg of glacial acetic acid in 30 ml of methanol and 10 ml of tetrahydrofuran was stirred for 24 hr at room temperature. The filtrate was evaporated and dissolved in ethyl acetate, the solution was worked up as usual and the products was purified by a preparative thin-layer chromatography developing with benzene–ethyl acetate (2: 1). Recrystallization of the desired compound (**12**) from *n*-hexane–acetone gave 21 mg of needles, mp 212—213°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3240, 1720, 1670, 1615, 1495. UV λ_{max} nm (ε): 284 (23900). NMR

δ (C_5D_5N): 2.39 (3H, s), 2.95 (1H, dd, J=3.5, 16.4 Hz), 3.25 (1H, dd, J=12.4, 16.4 Hz), 3.66 (3H, s), 3.77 (3H, s), 3.83 (3H, s), 4.04 (3H, s), 5.55 (1H, dd, J=3.5, 12.4 Hz). *Anal.* Calcd. for $C_{27}H_{26}O_8$: C, 67.77; H, 5.48. Found: C, 67.66; H, 5.43.

To a solution of 31 mg of the acetophenone (**9b**) and 35 mg of the aldehyde (**17**) in 2 ml of dry benzene was added 8 mg of 50% sodium hydride and the mixture was refluxed for 4 hr. The reaction mixture was poured into ice-water and the organic layer was dried and evaporated to dryness. The resulting oil was dissolved into 5 ml of 10% aqueous methanol containing few drops of conc. hydrochloric acid and heated under reflux for 3 hr. After removal of the solvent, the residue was dissolved into 5 ml of 20% aqueous pyridine and kept at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with 10% hydrochloric acid, dried and evaporated to yield 40 mg of a red oil. The oil was subjected to a preparative thin-layer chromatography. Developing with benzene–ethyl acetate (2: 1) gave 8 mg of the desired dihydroflavone (**12**), which was recrystallized from *n*-hexane–acetone to yield 5 mg of colorless needles, mp 212—213°.

Methyl 3-Troponyl-6-methoxybenzoate (**13**)——To a solution of 11.5 g of 5-bromo-*o*-anisic acid in 100 ml of dry tetrahydrofuran was added 100 ml of 15% butyllithium in *n*-hexane at −50°. After 30 min, a suspension of 7 g of 2-chlorotropone in 50 ml of dry tetrahydrofuran was added to the reaction mixture at −50° and stirring was continued for 1 hr. The reaction mixture was poured into water and extracted with chloroform. The water layer was acidified with hydrochloric acid and extracted with chloroform. The troponylbenzoic acid obtained from the chloroform extract was methylated with diazomethane and the product was purified by a preparative thin-layer chromatography to give 2.1 g of the methyl ester (**13**), which was recrystallized from isopropyl ether giving the analytical sample, mp 97°. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1605, 1585. NMR δ: 3.90 (3H, s), 3.95 (3H, s), 6.9—7.5 (6H), 7.77 (1H, dd, J=9.0 and 2.0 Hz), 8.00 (1H, d, J=2.0 Hz). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.07; H, 5.14.

Methyl 2′,4-Dimethoxy-5′-(β,β-dicarboethoxyvinyl)-3-biphenylcarboxylate (**14**)——A mixture of 1.5 g of the phenyltropone (**13**) and 0.75 ml of methyl fluorosulfonate in 45 ml of dry methylene chloride was stirred overnight at room temperature. To the mixture was added 1.5 g of dicarboethoxymethylenedimethylsulfurane. After stirring for 5 hr at room temperature, the reaction mixture was poured into water and extracted with chloroform. The product obtained from the chloroform extract was purified by a dry-column chromatography by using silica gel to give 0.87 g of the biphenyl (**14**) and 0.65 g of the starting phenyltropone recovered. IR ν_{max}^{Liq} cm^{-1}: 1730, 1600, 1590. NMR δ: 1.28 (3H, t, J=7.0 Hz), 1.32 (3H, t, J=7.0 Hz), 3.87 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 4.30 (2H, q, J=7.0 Hz), 4.34 (2H, q, J=7.0 Hz), 6.9—7.1 (2H), 7.3—8.1 (4H), 7.70 (1H, s). *Anal.* Calcd. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 64.83; H, 5.72.

Methyl 2′4-Dimethoxy-5′-(β-carbomethoxyvinyl)-3-biphenylcarboxylate (**16**)——A solution of 10 g of the biphenyl (**14**) in 100 ml of ethanol and 100 ml of 10% potassium hydroxide solution was refluxed overnight. The reaction mixture was acidified with conc. hydrochloric acid giving 5.5 g of the crystalline biphenyltricarboxylic acid (**15**), mp 206°. From the ethyl acetate extract of the mother liquor, 3.0 g of the acid (**15**) was obtained. Heating of 200 mg of the biphenyltricarboxylic acid (**15**) at 215° under the reduced pressure (0.05 mmHg) for 10 min gave a decarboxylated product, which was esterified with diazomethane and separated by a preparative thin-layer chromatography to yield 110 mg of the diester (**16**). IR ν_{max}^{Liq} cm^{-1}: 1720, 1640, 1600. NMR δ: 3.78 (3H, s), 3.83 (3H, s), 3.92 (3H, s), 3.95 (3H, s), 6.37 (1H, d, J=17 Hz), 6.8—7.1 (2H), 7.4—8.1 (4H), 7.67 (1H, d, J=17 Hz). *Anal.* Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.31; H, 5.72.

Methyl 5′-Formyl-2′,5-dimethoxy-3-biphenylcarboxylate (**17**)——To a suspension of 110 mg of the diester (**16**) in 5 ml of dioxane–water (3: 1) was added a solution of 54 mg of osmium tetroxide in 10 ml of dioxane–water (3: 1) and 200 mg of sodium periodate successively. The mixture was stirred overnight at room temperature and extracted with chloroform. The chloroform extract was washed with aqueous sodium thiosulfate solution and separated by a preparative thin-layer chromatography giving 80 mg of the aldehyde (**17**), mp 98—99° (recrystallized from isopropyl ether). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1680, 1600, 1570. NMR δ: 3.92 (6H, s), 3.96 (3H, s), 6.9—7.2 (2H), 7.5—8.1 (4H), 9.97 (1H, s). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.96; H, 5.22.

2-(2-Methoxy-3-methylphenyl)tropone (**18**)——To a solution of the Grignard reagent prepared from 1.05 g of magnesium and 8.75 g of 3-bromo-2-methoxytoluene in 10 ml of dry ether, was added a solution of 4.46 g of 2-methoxytropone in 10 ml of dry benzene. After 2 hr, 5% sulfuric acid was added to the reaction mixture and separated organic layer was dried and evaporated. The residual oil was distilled to remove the low-boiling point materials and chromatographed on silica gel (300 g). The eluent with benzene–ethyl acetate (5: 1) was recrystallized from isopropyl ether to give 1.4 g of yellow prisms, mp 101—103°. IR ν_{max}^{Nujol} cm^{-1}: 1630, 1580, 1520. UV λ_{max} nm (ε): 315 (26500). NMR δ: 2.3 (3H, s), 3.58 (3H, s), 6.95—7.35 (8H). *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.69; H, 6.28.

2,2′-Dimethoxy-3′-methyl-5-(β,β-dicarboethoxyvinyl)biphenyl (**19**)——To a solution of 7.72 g of the phenyltropone (**18**) in 70 ml of dry methylene chloride was added a solution of 3.38 g of methyl fluorosulfonate in 3 ml of dry methylene chloride at room temperature and the mixture was stirred overnight. To a suspension of the resulting crystalline salt in 20 ml of dry methylene chloride was added a solution of 9.75 g of dicarboethoxydimethylsulfurane in 10 ml of dry methylene chloride under ice-cooling. After stirring

for 2.5 hr at room temperature, the reaction mixture was washed with water, dried and evaporated to give 20 g of a brown oil, which was chromatographed on silica gel (600 g). The eluent with benzene–ethyl acetate (10: 1) was recrystallized from isopropyl ether yielding 4.3 g of the biphenyl (**19**) as pale yellow prisms, mp 91°. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1710, 1600, 1500. UV λ_{max} nm (ε): 283 (20900), 305 (sh. 18700). NMR δ (CCl_4): 1.24 (3H, t, J=7.0 Hz), 1.29 (3H, t, J=7.0 Hz), 2.28 (3H, s), 4.25 (4H, q, J=7.0 Hz), 3.33 (3H, s), 3.78 (3H, s), 6.8—7.6 (7H). *Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.00; H, 6.46.

Methyl 2′,6-Dimethoxy-3′-methyl-3-biphenylcarboxylate (**20**)——To a solution of 12 g of the diester (**19**) in 120 ml of pyridine was added a solution of 9.8 g of potassium permanganate in 100 ml of water under ice-cooling and the mixture was stirred for 5 hr at room temperature. After filtration, the reaction mixture was acidified with hydrochloric acid. Resulting precipitate was dried and dissolved in abs. methanol containing 3% of hydrogen chloride. The solution was refluxed for 30 min and evaporated to give the ester (**20**), which was recrystallized from isopropyl ether affording 3.3 g of colorless needles, mp 95—96°. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1600, 1500. UV λ_{max} nm (ε): 237 (41800), 258 (29700). NMR δ: 2.35 (3H, s), 3.40 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 6.8—8.3 (6H).

Methyl 3′-Bromomethyl-2′,6-dimethoxy-3-biphenylcarboxylate (**21**)——A solution of 1.9 g of the ester (**20**), 1.4 g of NBS and a catalytic amount of dibenzoyl peroxide in 40 ml of carbon tetrachloride was refluxed for 30 min. After filtration, evaporation of the solvent and recrystallization from *n*-hexane–ether gave 2.3 g of the bromide (**21**) as colorless needles, mp 108—109°. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1600, 1500. UV λ_{max} nm (ε): 230 (26500), 260 (sh, 13500). NMR δ: 3.48 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 4.65 (2H, s), 7.0—8.3 (6H).

Methyl 3′-Formyl-2′,6-dimethoxy-3-biphenylcarboxylate (**22**)——A mixture of 2.29 g of the bromide (**21**) and 6.86 g of sodium bicarbonate in 46 ml of dimethyl sulfoxide was heated at 110° for 30 min under nitrogen atmosphere. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was worked up as usual and purified by a dry-column chromatography using silica gel (180 g) eluting with benzene–ethyl acetate (9: 1). The resulting aldehyde (**22**) was recrystallized from isopropyl ether gave 830 mg of colorless needles, mp 95°. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1695, 1590, 1500. UV λ_{max} nm (ε): 234 (22000), 252 (sh, 15800). NMR δ: 3.53 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 7.0—8.2 (6H), 10.44 (1H, s). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.14; H, 5.33.

Methyl 3′-Ethylenedioxymethyl-2′,6-dimethoxy-3-biphenylcarboxylate (**23**)——A solution of 770 mg of the aldehyde (**22**), 0.4 ml of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid in 6.2 ml of ethylene glycol was heated at 100° for 2 hr. The reaction mixture was poured into satd. aqueous sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate layer was worked up as usual and the product was recrystallized from isopropyl ether to yield 730 mg of the acetal (**23**), mp 103—105°. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1590, 1500. UV λ_{max} nm (ε): 285 (3800). NMR δ (CCl_4): 3.38 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 4.03 (4H, m), 6.10 (1H, s), 6.8—8.2 (6H). *Anal.* Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.84. Found: C, 66.41; H, 5.84.

Methyl 5′-Hydroxymethyl-2,2′-dimethoxy-3-biphenylcarboxylate (**27**)——To a solution of 145 mg of lithium aluminum hydride in 10 ml of dry ether was added a solution of 690 mg of the acetal (**23**) in 7 ml of dry tetrahydrofuran and the mixture was stirred for 1 hr at room temperature. After addition of ethyl acetate to decompose excess reagent, the organic layer was worked up as usual to give 530 mg of an oil. The oil was dissolved in 65% of aqueous methanol containing two drops of conc. hydrochloric acid and boiled for 30 min. To the solution of 500 mg of resulting oil in 20 ml of ethanol was added a solution of 90 mg of silver nitrate in 1 ml of water and 4 ml of 0.5N sodium hydroxide, and the mixture was stirred overnight at room temperature. After filtration, the reaction mixture was acidified with conc. hydrochloric acid and extracted with ethyl acetate. The oily product obtained from the ethyl acetate extract was dissolved in 20 ml of 3% hydrogen chloride–methanol and refluxed for 2 hr. The ethyl acetate extract of the products was chromatographed on silica gel (15 g) and eluted with benzene–ethyl acetate (1: 1) to yield 150 mg of the benzyl alcohol (**27**). IR ν_{max}^{Liq} cm^{-1}: 3450, 1720, 1610, 1590, 1500. UV λ_{max} nm (ε): 287 (5200). NMR δ [$(CD_3)_2CO$]: 3.46 (3H, s), 3.74 (3H, s), 3.86 (3H, s), 4.04 (1H, t, J=6.0 Hz), 4.58 (2H, d, J=6.0 Hz), 7.0—7.7 (6H). *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.29; H, 6.24.

2-(2-Methoxy-5-methylphenyl)tropone (**28**)——To the Grignard reagent prepared from 10 g of 2-bromo-4-methylanisole and 1.2 g of magnesium in 100 ml of dry ether was added a solution of 6.2 g of 2-methoxytropone in 30 ml of dry ether. After stirring for 1 hr at room temperature, the reaction mixture was poured into water and extracted with ether. The products obtained from the ether extract was separated by a dry-column chromatography using silica gel (700 g) and recrystallized from isopropyl ether to yield 3.24 g of the phenyltropone (**28**), mp 89—90°. IR ν_{max}^{Nujol} cm^{-1}: 1630, 1578. NMR δ: 2.30 (3H, s), 3.72 (3H, s), 6.8—7.4 (8H). *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.61; H, 6.20.

2,2′-Dimethoxy-5′-methyl-3-(β-*p*-bromobenzoylvinyl)biphenyl (**29**) **and 2,2′-Dimethoxy-5′-methyl-5-(β-*p*-bromobenzoylvinyl)biphenyl** (**30**)——A solution of 2.9 g of the phenyltropone (**28**) and 1.5 ml of methyl fluorosulfonate in 50 ml of dry methylene chloride was stirred overnight at room temperature. To the mixture was added 3.4 g of *p*-bromobenzoylmethylenedimethylsulfurane. After stirring for 5 hr, the reaction mixture was filtered to remove the precipitated crystalline mass, which was washed with chloroform. The combined chloroform layer was washed with water, dried and evaporated to give an oily residue. Se-

paration of the products by a dry-column chromatography using silica gel (500 g) gave the following substances in the order of the mobility; (**29**), 1.75 g, mp 115—116° (from isopropyl ether), (**30**), 0.7 g, mp 170—171° (from benzene–isopropyl ether), and the starting material. (**29**): IR ν_{max}^{Nujol} cm^{-1}: 1600, 1590, 1660. NMR δ: 2.33 (3H, s), 3.46 (3H, s), 3.75 (3H, s), 6.8—8.1 (11H), 8.18 (1H, d, J=16 Hz). *Anal.* Calcd. for $C_{24}H_{21}O_3Br$: C, 65.91; H, 4.84; Br, 18.27. Found: C, 65.88; H, 4.97; Br, 18.38. (**30**): IR ν_{max}^{Nujol} cm^{-1}: 1660, 1590, 1578. NMR δ (d_6-DMF): 2.33 (3H, s), 3.74 (3H, s), 3.83 (3H, s), 6.9—7.5 (4H), 7.6—8.3 (8H). *Anal.* Calcd. for $C_{24}H_{21}O_3Br$: C, 65.91; H, 4.84; Br, 18.27. Found: C, 65.81; H, 4.90; Br, 18.24.

Methyl 2,2′-Dimethoxy-5′-methyl-3-biphenylcarboxylate (**31**)——To a solution of 1.6 g of the biphenyl (**29**) in 20 ml of 50% aqueous pyridine was added a solution of 1.8 g of potassium permanganate in 20 ml of water under ice-cooling. After 1 hr, the reaction mixture was poured into aqueous sodium bicarbonate solution, filtered and acidified with dil. hydrochloric acid to afford a crystalline precipitate. The mother liquor was extracted with chloroform and the extract was worked up as usual to give additional crystals. The combined crystalline product was esterified with diazomethane and purified by a preparative thin-layer chromatography yielding 750 mg of the ester (**31**). IR ν_{max}^{Liq} cm^{-1}: 1720, 1610, 1590. NMR δ: 2.32 (3H, s), 3.52 (3H, s), 3.73 (3H, s), 3.92 (3H, s), 6.8—7.9 (6H). *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.05; H, 6.28.

Methyl 2,2′-Dimethoxy-5′-formyl-3-biphenylcarboxylate (**32**)——A solution of 500 ml of the ester (**31**), 350 mg of NBS and a catalytic amount of dibenzoyl peroxide in 10 ml of carbon tetrachloride was refluxed for 3 hr. The oily product obtained by an usual work-up was oxidized on heating with 4 ml of dimethyl sulfoxide and 1 g of sodium bicarbonate at 150° for 10 min. The reaction mixture was diluted with water and extracted with chloroform. Separation by a preparative thin-layer chromatography and recrystallization from isopropyl ether gave 250 mg of the aldehyde (**32**), mp 107—108.5°. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1690, 1600, 1590. NMR δ: 3.50 (3H, s), 3.87 (3H, s), 3.93 (3H, s), 7.13 (1H, d, J=7.5 Hz), 7.32 (1H, s), 7.3—7.6 (1H, m), 7.7—8.1 (2H), 7.93 (1H, d, J=7.5 Hz), 9.93 (1H, s). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.92; H, 5.33.

7-Hydroxy-4′,5-dimethoxy-6-methyl-3′-(3-carbomethoxy-2-methoxyphenyl)dihydroflavone (**33**)——A mixture of 42 mg of the aldehyde (**32**), 39 mg of the acetophenone (**9b**) and 10 mg of 50% sodium hydride in 2 ml of dry benzene was heated under reflux for 4 hr. The reaction mixture was poured into ice-water and the organic layer was washed with water and evaporated. A solution of the residual oil in 6 ml of 10% aqueous methanol containing one drop of conc. hydrochloric acid was refluxed for 3 hr. The ethyl acetate extract of the product was washed with water and evaporated giving an oil, which was dissolved in 5 ml of 10% aqueous pyridine. After standing overnight at room temperature, the solution was evaporated and extracted with ethyl acetate. Working up as usual and separation of the products by a preparative thin-layer chromatography gave 15 mg of the dihydroflavone (**33**), which was recrystallized from acetone yielding 10 mg of colorless needles, mp 201—203°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3280, 1725, 1680, 1610, 1510. UV λ_{max} nm (ε): 283 (24000). NMR δ [$(CD_3)_2CO$]: 2.03 (3H, s), 2.70 (1H, dd, J=3.0, 17.0 Hz), 3.01 (1H, dd, J=12.0, 17.0 Hz), 3.75 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 5.46 (1H, dd, J=3.0, 12.0 Hz), 6.32 (1H, s), 7.17 (1H, d, J=7.5 Hz), 7.20 (1H, t, J=8.5 Hz), 7.39 (1H, d, J=2.0 Hz), 7.45 (1H, dd, J=2.0, 8.5 Hz), 7.54 (1H, dd, J=2.0, 8.5 Hz), 7.70 (1H, dd, J=2.0, 7.5 Hz). *Anal.* Calcd. for $C_{27}H_{26}O_8$: C, 67.77; H, 5.48. Found: C, 67.91; H, 5.50.

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