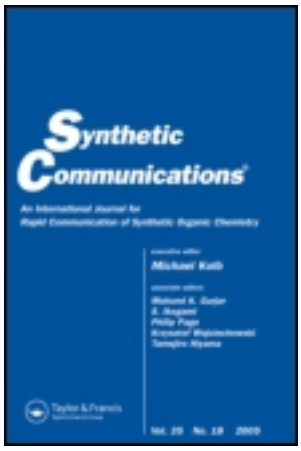


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Studies on Flavans. III. The Total Synthesis of (±)-7,4′-Dihydroxy-3′-methoxyflavan, (±)-7,3′-Dihydroxy-4′-methoxyflavan, and (±)-7,4′-Dihydroxyflavan

Jijun Xue [a], Xianshu Zhang [a], Xuesong Chen [a], Yingpeng Zhang [a] & Ying Li [a]

[a] National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu, People's Republic of China

Version of record first published: 15 Aug 2006.

To cite this article: Jijun Xue, Xianshu Zhang, Xuesong Chen, Yingpeng Zhang & Ying Li (2003): Studies on Flavans. III. The Total Synthesis of (±)-7,4′-Dihydroxy-3′-methoxyflavan, (±)-7,3′-Dihydroxy-4′-methoxyflavan, and (±)-7,4′-Dihydroxyflavan, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:20, 3527-3536

To link to this article: http://dx.doi.org/10.1081/SCC-120024733

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 20, pp. 3527–3536, 2003

Studies on Flavans. III. The Total Synthesis of (±)-7,4′-Dihydroxy-3′-methoxyflavan, (±)-7,3′-Dihydroxy-4′-methoxyflavan, and (±)-7,4′-Dihydroxyflavan

Jijun Xue, Xianshu Zhang, Xuesong Chen, Yingpeng Zhang, and Ying Li*

National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu, People's Republic of China

ABSTRACT

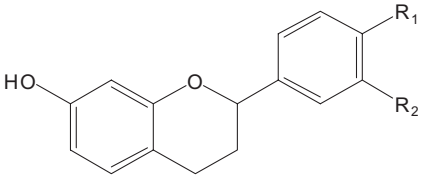
The first total synthesis of (±)-7,3′-dihydroxy-4′-methoxyflavan (**1**) and (±)-7,4′-dihydroxy-3′-methoxyflavan (**2**), along with the synthesis of (±)-7,4′-dihydroxyflavan (**3**), three naturally occurring flavans, were described. The key step is the cyclization of 1,3-diaryl-1-propanol by $BF_3{\cdot}Et_2O$.

Key Words: Synthesis; Flavans.

*Correspondence: Ying Li, National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, 298 Tianshui Road, Lanzhou, Gansu, 730000, People's Republic of China; E-mail: liying@lzu.edu.cn.

DOI: 10.1081/SCC-120024733 0039-7911 (Print); 1532-2432 (Online)

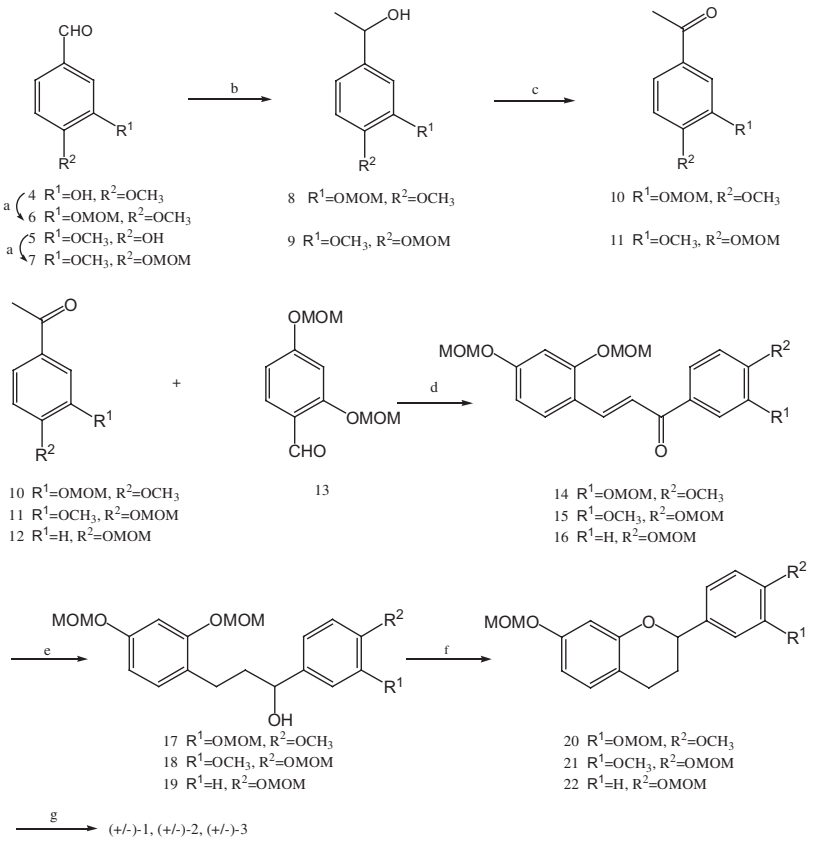
Naturally occurring flavans, a branch of flavanoids, exist widely in the plant kingdom and exhibit many important biological and pharmacological activities.[1–3] There are many approaches to the synthesis of flavans, but they are commonly in poor yield and in intense conditions.[4–7] The lack of a general and efficient method for the formation of benzopyran presents a major challenge for the total synthesis of this class of natural products. In previous work,[8,9] we have reported a convenient and efficient synthetic method[8] based on the Lewis acid ($BF_3 \cdot Et_2O$)-mediated benzopyran formation in an aprotic polar solvent and two naturally occurring flavans has been synthesized.[9] In order to support the practicability of this method and develop it, in continuation of our studies, this method was used for synthesizing other flavans. Herein we report its development and three naturally occurring products were synthesized by this method, they are (±)-7,3′-dihydroxy-4′-methoxyflavan (**1**), (±)-7,4′-dihydroxy-3′-methoxyflavan (**2**) and (±)-7,4′-dihydroxyflavan (**3**) (Sch. 1). As well as we know, the total synthesis of **1** and **2** have not been reported yet.



(+/-)-**1** R_1=OMe, R_2=OH
(+/-)-**2** R_1=OH, R_2=OMe
(+/-)-**3** R_1=OH, R_2=H

Scheme 1.

The synthetic route is following (Sch. 2). 7,3′-Dihydroxy-4′-methoxyflavan (**1**) was firstly isolated from *Dracaena cinnabari* by Mohamed Masaoud et al. in 1994. *Dracaena cinnabari*, which is called dragon's blood, has been known for a long time in folk medicine as an astringent in diarrhoea and dysentery, as well as an antiseptic, haemostatic and antiulcer remedy.[10] The synthesis of **1** was commenced from isovanilin (**4**), which was readily prepared from selective methylation of 4-OH of 3,4-dihydroxybenzaldehyde with dimethyl sulfate and K_2CO_3 in dry acetone under reflux. Methoxymethylation of **4** with MOMCl and K_2CO_3 in acetone was followed by Grignard reaction of **6** with CH_3MgI in ethyl ether, which gave 1-(3-methoxymethoxy-4-methoxyphenyl) ethanol (**8**).



Scheme 2. Reagents and conditions: (a) CH_3OCH_2Cl, K_2CO_3, acetone, reflux; (b) CH_3MgI, THF, reflux; (c) PCC, CH_2Cl_2, r. t.; (d) KOH, CH_3OH (abs.), r. t.; (e) H_2/Pd-C (5%), EtOH, r. t.; (f) $BF_3{\cdot}Et_2O$, 1, 4-dioxane, r. t.; (g) 3M HCl, CH_3OH.

Oxidation of **8** by PCC in methylene dichloride yielded 3′-methoxymethoxy-4′-methoxyacetophenone (**10**). This is a new approach to 3′-methoxymethoxy-4′-methoxyactophenone, from which 3′-hydroxy-4′-methoxyacetophenone could be obtained in one step. **13** was readily prepared from 2,4-dihydroxybenzaldehyde by methoxymethylation method previously reported by us.[9] Condensation of **10** and **13** proceeded in a solution of KOH (20.0 equiv.) in absolute methanol gave chalcone **14**. In opposition to the condensation in KOH-EtOH-H_2O reported by us in previous work,[9] this condensation has higher yield, more simple result

and its product is easier to purify. The key precursor for the formation of benzopyran, alcohol **17** comes from reduction of **14** with H_2/Pd-C. **17** was treated with $BF_3{\cdot}Et_2O$ in 1,4-dioxane at room temperature to give flavan **20**, which is the key step. The condition is very gentle and the yield is satisfying. Deprotection of methoxymethyl group of **20** by treatment with 3M HCl in CH_3OH led to the first target product (±)-**1**.

7,4′-Dihydroxy-3′-methoxyflavan (**2**) was isolated firstly[11] in 1980 from *Iryanthera elliptica Duke*, a slender tree which occurs in the Brazilian region of the Amazon. In 1996,[12] it was isolated from the monocotyledon *Mariscus psilostachys C. B. Clarke* by Eliane G. again. This small herb belongs to the Cyperaceae and its distributed throughout tropical Africa. Although no uses for *M. psilostachys* are directly reported in the traditional pharmacopoea of Zimbabwe, it is well known[12] that other species of the same genus are commonly used by West Africa healers to treat different affections (gonorrhoes, Infected wounds, etc.). **2** was synthesized in analogue manner from vanillin (**5**) and **13** as the starting materials through the steps of protection of phenolic hydroxyl, Grignard reaction, oxidation, condensation, reduction, cyclization, and deprotection. In the key step, if $BF_3{\cdot}Et_2O$, not the solution of $BF_3{\cdot}Et_2O$ in 1,4-dioxane, was added directly to the solution of **18** in 1,4-dioxane, the MOM protective group would be removed and monoMOM-protecting flavan formed. But it is not clear which MOM was removed. In order to make sure of the result of the key step, the solution of $BF_3{\cdot}Et_2O$ in 1,4-dioxane was added dropwise very slowly to the substrate so that the MOM groups were kept. After deprotecting the MOM group of **21** with 3 M HCl in MeOH, another target, the flavan (±)-**2** was formed.

7,4′-Dihydroxyflavan (**3**) is a phytoalexin. In 1980,[13] David T. Coxon et al. found that it could be isolated from the lesions of inoculation of *Narcisses pseudonarcisses L.* bulb, but it was absent from fresh or frozen and thawed healthy tissues. The synthesis of **3** was started from **13** and **12**, which were condensated in KOH alcoholic solution to yield chalcone **16**. Hydrogenation of **16** using Pd-C (5%) as the catalyst in ethanol afforded propanol **19**, which was treated with $BF_3{\cdot}Et_2O$ to give flavan **22**. Demethxoymethylation of **22** with 3 M HCl in methanol under reflux led to the target (±)-**3**.

EXPERIMENTAL

General Experimental Procedures

Melting points were measured on a Kofler hot stage and are uncorrected. For column chromatography, 100–200 mesh silica gel was used.

Infrared spectra were obtained on a FT-170SX spectrometer. ^{1}H NMR spectra were recorded on DRX-200 instrument in $CDCl_3$. Chemical shifts were reported in ppm units with TMS as the internal standard. EIMS were measured on a HP-5988A spectrometer by direct inlet at 70 eV.

1-(4-Methoxy-3-methoxymethoxyphenyl) ethanol (8). A mixture of Mg (58 mg, 2.4 mmol) and CH_3I (0.15 mL, 2,4 mmol) in dry ethyl ether (10 mL) was heated to reflux for 30 min. Then it was cooled to 0°C, stirred and a solution of **6** (392 mg, 2.0 mmol) in dry ether (5 mL) was added dropwise to it. And after it was refluxed for 30 min, the mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (v/v, 4:1) to give **8** (322 mg, 76% yield) as a colorless oil. IR (KBr) ν 3391, 2968, 1593, 1511, 1441, 1131, 809 cm^{-1}. ^{1}H NMR δ 2.67 (3H, d, $J = 6.0$ Hz, CH_3), 3.67, 4.00 (3H each, s, CH_3O), 4.94 (1H, q, $J = 6.0$ Hz, 1-H), 5.34 (2H, s, OCH_2O), 6.94 (1H, d, $J = 8.0$ Hz, 5′-H). 7.30 (1H, dd, $J = 8.0$, 2.0 Hz, 6′-H), 7.03 (1H, d, $J = 2.0$ Hz, 2′-H). EIMS m/z $[M]^+$ 212 (1.8), 198 (2.7), 168 (12.4), 150 (2.5), 125 (16.2), 77 (10.9), 45 (100).

1-(3-Methoxy-4-methoxymethoxyphenyl) ethanol (9) was prepared from **7** in analogue manner in 70% yield. IR (KBr) ν 3406, 2968, 1594, 1513, 1463, 1157, 818 cm^{-1}. ^{1}H NMR δ 1.42 (3H, d, $J = 6.4$ Hz, CH_3), 3.46, 3.83 (3H each, s, CH_3O), 4.78 (1H, q, $J = 6.4$ Hz, 1-H), 5.15 (2H, s, OCH_2O), 6.80 (1H, dd, $J = 2.0$, 8.2 Hz, 5′-H), 6.92 (1H, d, $J = 2.0$ Hz, 2′-H), 7.04 (1H, d, $J = 8.2$ Hz, 6′-H). EIMS m/z $[M]^+$ 212 (9.3), 167 (7.6), 150 (9.9), 135 (11.6), 121 (16.4), 93 (8.4), 45 (100).

3-Methoxymethoxy-4-methoxyacetophenone (10). To a mixture of PCC (1.60 g, 7.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise the solution of **8** (1.06 g, 5 mmol) in CH_2Cl_2 (5 mL). After stirred for 1.5 h at room temperature, the mixture was filtered with a short silica gel column. The filtrate was concentrated and the residue was purified with silica gel column chromatography eluting with petroleum ether-EtOAc (v/v, 8:1) to give **10** (890 mg, 85% yield) as a colorless oil. IR (KBr) ν 2957, 1675, 1595, 1511, 1429, 1152, 812 cm^{-1}. ^{1}H NMR δ 2.53 (3H, s, CH_3CO), 3.48, 3.93 (3H each, s, OCH_3), 5.31 (2H, s, OCH_2O), 6.89 (1H, d, $J = 8.4$ Hz, 5-H), 7.61 (1H, dd, $J = 2.0$, 8.4 Hz, 6-H), 7.72 (1H, d, $J = 2.0$ Hz, 2-H). EIMS m/z $[M]^+$ 210 (16.9), 180 (7.8), 119 (5.5), 91 (4.6), 45 (100).

3-Methoxy-4-methoxymethoxyacetophenone (11) was prepared by oxidation of **9** in the same way in 85% yield as a pale yellow oil. IR (KBr) ν 2958, 1676, 1592, 1509, 1463, 1139, 814 cm^{-1}. ^{1}H NMR δ 2.52

(3H, s, CH_3CO), 3.47, 3.89 (3H each, s, CH_3O), 5.26 (2H, s, OCH_2O), 7.13 (1H, d, $J = 8.8$ Hz, 6-H), 7.49 (1H, dd, $J = 2.0$, 8.8 Hz, 5-H), 7.50 (1H, d, $J = 2.0$ Hz, 2-H). EIMS m/z $[M]^+$ 210 (7.3), 180 (3.7), 165 (5.0), 149 (1.2), 137 (1.1), 91 (2.7), 45 (100).

2,3′,4-Trimethoxymethoxy-4′-methoxychalcone (14). A well-stirred solution of **10** (420 mg, 2 mmol) and KOH (2.24 g, 40 mmol) in absolute CH_3OH (10 mL) was cooled by ice-bath. Then **13** (452 mg, 2 mmol) in CH_3OH (6 mL) was added dropwise. Stirred for 16 h at room temperature, the solution was poured into 20 mL ice-water, acidified to pH = 2 and extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with petroleum ether-EtOAc (v/v, 4:1) to give a yellow oil **14** (3.56 g, 85% yield). IR (KBr) ν 2922, 1653, 1598, 1505, 1432, 1260, 1154, 996, 923, 807 cm^{-1}. ^1H NMR δ 3.37, 3.41, 3.43, 3.82 (3H each, s, CH_3O), 5.08, 5.16, 5.20 (2H each, s, OCH_2O), 6.63 (1H, dd, $J = 2.0$, 8.6 Hz, 5-H), 6.76 (1H, d, $J = 2.0$ Hz, 3-H), 6.85 (1H, d, $J = 8.6$ Hz, 6-H), 7.50 (1H, d, $J = 15.4$ Hz, H_β), 7.52 (1H, d, $J = 9.0$ Hz, 6′-H), 7.65 (1H, dd, $J = 2.4$, 9.0 Hz, 5′-H), 7.80 (1H, d, $J = 2.4$ Hz, 2′-H), 8.04 (1H, d, $J = 15.4$ Hz, H_α). EIMS m/z $[M]^+$ 418 (0.2), 373 (3.5), 357 (13.9), 313 (1.8), 283 (0.7), 195 (42.5), 151 (6.7), 45 (100).

2,4′,4-Trimethoxymethoxy-3′-methoxychalcone (15) was obtained by condensation of **13** and **11** in analogue manner in 85% yield as a yellow oil. IR (KBr) ν 2924, 1663, 1601, 1505, 1433, 1261, 1151, 1078, 808 cm^{-1}. ^1H NMR δ 3.24, 3.27, 3.28, 3.75 (3H each, s, OCH_3), 4.97, 5.06, 5.10 (2H each, s, OCH_2O), 6.52 (1H, dd, $J = 2.2$, 8.6 Hz, 5-H), 6.65 (1H, d, $J = 2.2$ Hz, 3-H), 7.00 (1H, d, $J = 8.6$ Hz, 6-H), 7.39 (1H, d, $J = 15.8$ Hz, H_β), 7.42 (1H, d, $J = 8.6$ Hz, 6′-H), 7.43 (1H, dd, $J = 2.0$, 8.6 Hz, 5′-H), 7.43 (1H, d, $J = 2.0$ Hz, 2′-H), 7.93 (1H, d, $J = 15.8$ Hz, H_α). EIMS m/z $[M]^+$ 418 (0.3), 357 (7.4), 195 (11.9), 45 (100).

2,4′,4-Trimethoxymethoxychalcone (16) was prepared in the same way from **13** and **12** in 90% yield as a yellow oil. IR (KBr) ν 2930, 1680, 1618, 1600, 1500, 1453, 1150, 1078, 810 cm^{-1}. ^1H NMR δ 3.44, 3.45, 3.50 (3H each, s, CH_3O), 5.16, 5.21, 5.23 (2H each, s, OCH_2O), 6.70 (1H, dd, $J = 2.4$, 8.6 Hz, 5-H), 6.82 (1H, d, $J = 2.4$ Hz, 3-H), 7.08 (2H, d, $J = 8.8$ Hz, 3′, 5′-H), 7.51 (1H, d, $J = 15.8$ Hz, H_β), 7.99 (1H, d, $J = 8.6$ Hz, 6-H), 8.10 (1H, d, $J = 15.8$ Hz, H_α), 7.58 (2H, d, $J = 8.8$ Hz, 2′, 6′-H). EIMS m/z $[M]^+$ 388 (0.4), 327 (12.8), 283 (1.5), 241 (1.4), 165 (36.6), 135 (13.1), 121 (1.7), 45 (100).

1-(4-Methoxy-3-methoxymethoxyphenyl)-3-(2,4-dimethoxymethoxyphenyl)-1-propanol (17). A well-stirred solution of **14** (418 mg, 1.0 mol) and Pd-C (5%) (40 mg) in EtOH (10 mL) was kept for 24 h at room temperature under 2 atm atmosphere of hydrogen. The reaction mixture

was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether-EtOAc (v/v, 4:1) to give **17** (418 mg, 99% yield) as a colorless gum. IR (KBr) ν 3430, 2962, 2929, 2822, 1610, 1444, 1153, 1127, 811, 736 cm^{-1}. ^1H NMR δ 1.88–2.09 (2H, m, 2-H), 2.61 (2H, t, $J = 7.4$Hz, 3-H), 3.45, 3.47, 3.50, 3.87 (3H each, s, CH_3O), 4.51 (2H, dd, $J = 2.6$, 7.8 Hz, 1-H), 5.13, 5.16, 5.20 (2H each, s, OCH_2O), 6.64 (1H, dd, $J = 2.4$, 8.4 Hz, 6′-H), 6.78 (1H, d, $J = 2.4$ Hz, 2′-H), 6.83 (1H, dd, $J = 1.8$, 8.2 Hz, 5″-H), 6.94 (1H, d, $J = 1.8$ Hz, 3″-H), 7.05 (1H, d, $J = 8.4$ Hz, 5′-H), 7.14 (1H, d, $J = 8.2$ Hz, 6″-H). EIMS m/z $[M]^+$ 422 (0.5), 197 (3.3), 181 (2.5), 167 (5.7), 151 (3.6), 137 (6.9), 105 (1.1), 91 (3.1), 45 (100).

1-(3-Methoxy-4-methoxymethoxyphenyl)-3-(2,4-dimethoxymethoxyphenyl)-1-propanol (18) was prepared in analogue manner by hydrogenation of **15** in 99% yield as a colorless oil. IR (KBr) ν 2960, 1610, 1588, 1505, 1445, 1151, 1011, 811 cm^{-1}. ^1H NMR δ 1.88–2.09 (2H, m, 2-H), 2.67 (2H, t, $J = 8.0$ Hz, 3-H), 3.38, 3.44, 3.48, 3.85 (3H each, s, CH_3O), 4.57 (1H, dd, $J = 5.4$, 8.0 Hz, 1-H), 5.11, 5.14, 5.18 (2H each, s, OCH_2O), 6.63 (1H, dd, $J = 2.4$, 8.4 Hz, 6′-H), 6.77 (1H, d, $J = 2.4$ Hz, 2′-H), 6.81 (1H, dd, $J = 2.0$, 8.4 Hz, 5″-H), 6.93 (1H, d, $J = 2.0$ Hz, 3″-H), 7.03 (1H, d, $J = 8.4$ Hz, 5′-H), 7.07 (1H, d, $J = 8.4$ Hz, 6″-H). EIMS m/z $[M]^+$ 422 (0.4), 360 (3.4), 212 (3.3), 197 (1.8), 167 (3.9), 150 (1.5), 91 (2.4), 45 (100).

1-(4-Methoxymethoxyphenyl)-3-(2,4-dimethoxymethoxyphenyl)-1-propanol (19) was prepared by hydrogenation of **16** in 99% yield as a colorless oil. IR (KBr) ν 2925, 1610, 1506, 1447, 1402, 1152, 1114, 837. ^1H NMR δ 1.92–2.08 (2H, m, 2-H), 2.67 (2H, t, $J = 8.0$ Hz, 3-H), 3.46, 3.47, 3.48 (3H each, s, CH_3O), 4.59 (1H, dd, $J = 5.4$, 7.8 Hz, 1-H), 5.14, 5.15, 5.18 (2H each, s, OCH_2O), 6.65 (1H, dd, $J = 2.4$, 8.2 Hz, 5″-H), 6.79 (1H, d, $J = 2.4$ Hz, 3″-H), 7.02 (2H, d, $J = 8.6$ Hz, 3′, 5′-H), 7.03 (1H, d, $J = 8.2$ Hz, 6″-H), 7.28 (2H, d, $J = 8.6$ Hz, 2′, 6′-H). EIMS m/z $[M]^+$ 392 (35), 347 (15), 330 (75), 285 (35), 167 (54), 151 (22), 45 (100).

(±)-7,3′-Dimethoxymethoxy-4′-methoxyflavan (20). At room temperature, to a well-stirred solution of **17** (84 mg, 0.2 mmol) in dry 1,4-dioxane was added dropwise a solution of $BF_3 \cdot Et_2O$ (0.08 mL, 0.96 mmol) in dry 1,4-dioxane (10 mL). The resulting mixture was stirred for 30 min, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with ethyl ether. The organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (v/v, 16:1) to yield **20** (65 mg, 90% yield) as a colorless gum. IR (KBr) ν 2924, 1616, 1502, 1461, 1382, 1259, 1151, 906, 759 cm^{-1}. ^1H NMR δ 2.00–2.08 (2H, m,

3-H), 2.70–2.86 (2H, m, 4-H), 3.35, 3.45, 3.81 (3H each, s, OCH_3), 4.88 (1H, dd, $J=9.2$, 2.8 Hz, 2-H), 5.06, 5.17 (2H each, d, OCH_2O), 6.52 (1H, dd, $J=2.4$, 10.4 Hz, 6-H), 6.81 (1H, d, $J=2.4$ Hz, 8-H), 6.85 (1H, d, $J=2.0$ Hz, 2′-H), 6.91 (1H, d, $J=8.4$ Hz, 5-H), 6.97 (1H, d, $J=2.0$ Hz, 6′-H), 7.17 (1H, dd, $J=2.0$, 9.8 Hz, 5′-H). EIMS m/z $[M]^+$ 360 (2.7), 315 (1.9), 283 (1.1), 194 (3.4), 147 (3.0), 45 (100).

(±)-7,4′-Dimethoxymethoxy-3′-methoxyflavan (21) was obtained by cyclization of **18** with Lewis acid $BF_3{\cdot}Et_2O$ in 10 min in 60% yield as a colorless gum. IR (KBr) ν 2932, 1618, 1503, 1463, 1151, 806 cm^{-1}. ^1H NMR δ 2.00–2.20 (2H, m, 3-H), 2.80–2.96 (2H, m, 4-H), 3.49, 3.53, 3.92 (3H each, s, CH_3O), 4.99 (1H, dd, $J=2.8$, 9.8 Hz, 2-H), 5.17, 5.27 (2H each, s, OCH_2O), 6.63 (1H, dd, $J=2.4$, 8.2 Hz, 6-H), 6.68 (1H, d, $J=2.4$ Hz, 8-H), 6.94 (1H, d, $J=2.2$ Hz, 2′-H), 7.01 (1H, d, $J=8.2$ Hz, 5-H), 7.02 (1H, dd, $J=2.2$, 8.2 Hz, 6′-H), 7.20 (1H, d, $J=8.2$ Hz, 5′-H). EIMS m/z $[M]^+$ 360 (7.2), 316 (2.8), 283 (3.2), 149 (9.8), 137 (8.2), 105 (8.0), 45 (100).

(±)-7,4′-Dimethoxymethoxyflavan (22) was obtained in analogue manner from **19** in 95% yield as a colorless oil. IR (KBr) ν 2925, 1624, 1507, 1152, 1109. ^1H NMR δ 2.03–2.18 (2H, m, 3-H), 2.77–2.94 (2H, m, 4-H), 3.48, 3.49 (3H each, s, OCH_3), 4.97 (1H, dd, $J=1.4$, 11.2 Hz, 2-H), 5.15, 5.20 (2H each, s, OCH_2O), 6.61 (1H, dd, $J=2.6$, 8.2 Hz, 6-H), 6.63 (1H, d, $J=8.2$ Hz, 5-H), 7.36 (2H, d, $J=8.8$ Hz, 2′, 6′-H), 7.10 (2H, d, $J=8.8$ Hz, 3′, 5′-H), 7.04 (1H, d, $J=2.6$ Hz, 8-H). EIMS m/z $[M]^+$ 330 (100), 285 (13.3), 269 (2.7), 253 (6.5), 165 (2.7), 139 (14.6), 91 (2.9), 77 (2.5).

(±)-7,3′-Dihydroxy-4′-methoxyflavan (1). To a well-stirred solution of **20** (72 mg, 0.2 mmol) in MeOH (5 mL) was added dropwise 3M HCl (1 mL). The solution was heated at reflux for 30 min, then H_2O (10 mL) was added, and the solution was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$. After filtered, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (v/v, 4:1) to give flavan **1** (43 mg, 80%) as a white solid. M.p. 151–152°C. IR (KBr) ν 3396, 2977, 2925, 1595, 1509, 1459, 1380, 1152, 1027, 803 cm^{-1}. ^1H NMR δ 2.0–2.2 (2H, m, 3-H), 2.6–2.8 (2H, m, 4-H), 3.81 (3H, s, OCH_3), 4.86 (1H, dd, $J=3.0$, 9.6 Hz, 2-H), 6.31 (1H, d, $J=2.0$ Hz, 8-H), 6.33 (1H, dd, $J=2.0$, 8.4 Hz, 6-H), 6.77 (1H, d, $J=8.4$ Hz, 5′-H), 6.84 (1H, d, $J=8.4$ Hz, 5-H), 6.85 (1H, dd, $J=1.6$, 8.4 Hz, 6′-H), 6.92 (1H, d, $J=1.6$ Hz, H-2′); EIMS m/z $[M]^+$ 272 (37.2), 162 (17.9), 150 (100), 137 (49.9), 123 (22.4), 104 (42.7).

(±)-7,4′-Dihydroxy-3′-methoxyflavan (2) was obtained in analogue manner from **21** in 95% yield as a colorless oil. IR (KBr) ν 3397, 2978,

2929, 1731, 1622, 1596, 1510, 1380, 1271, 1112, 1046, 846 cm^{-1}. ^1H NMR δ 1.95–2.11 (2H, m, 3-H), 2.68–2.85 (2H, m, 4-H), 3.84 (3H, s, CH_3O), 4.88 (1H, dd, $J = 3.0$, 9.6 Hz, 2-H), 6.32 (1H, dd, $J = 2.4$, 8.8 Hz, 6-H), 6.33 (1H, d, $J = 2.4$ Hz, 8-H), 6.86 (1H, dd, $J = 2.0$, 8.8 Hz, 5′-H), 6.87 (2H, d, $J = 8.8$ Hz, 5-H), 6.88 (1H, dd, $J = 2.1$, 8.8 Hz, 6′-H), 7.19 (1H, d, $J = 2.0$ Hz, 2′-H). EIMS m/z $[M]^+$ 272 (36.8), 255 (3.6), 241 (3.4), 150 (100), 137 (45.7), 123 (38.1), 107 (19.1), 91 (16.1), 77 (14.2).

(±)-7, 4′-Dihydroxyflavan (3) was obtained in analogue manner from **22** in 95% yield as a colorless oil. IR (KBr) ν 2924, 1619, 1511, 1457, 1371, 1152, 1110, 839. ^1H NMR δ 1.97–2.07 (2H, m, 3-H), 2.57–2.82 (2H, m, 4-H), 4.87 (1H, dd, $J = 3.2$, 9.6 Hz, 2-H), 6.33 (1H, d, $J = 2.4$ Hz, 8-H), 6.34 (1H, dd, $J = 2.4$, 8.8 Hz, 6-H), 6.78 (2H, d, $J = 8.6$ Hz, 3′, 5′-H), 7.82 (1H, d, $J = 8.8$ Hz, 5-H), 7.18 (2H, d, $J = 8.6$ Hz, 2′, 6′-H). EIMS m/z $[M]^+$ 242 (100), 225 (6.8), 136 (7.0), 120 (23.5), 107 (5.8), 91 (3.5), 65 (2.7).

ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (20272020).

REFERENCES

1. Takasugi, M.; Kumagai, Y.; Nagao, S.S.; Shirato, A.; Takahashi, K. Chem. Lett. **1980**, *11*, 1459–1460.
2. Bauker, D.J.; Selway, J.W.T.; Batchelor, T.F.; Tisadale, M.; Caldwell, I.C.; Young, D.A.B. Nature **1981**, *292* (5821), 369–370.
3. Sini, K.S.S.; Ghosal, S. Phytochemistry **1984**, *23* (10), 2415–2421.
4. Sweeny, J.G.; Iacobucci, G.A. Tetrahedron **1977**, *33* (22), 2927–2932.
5. Bokadia, M.M.; Brown, B.R.; Cohera, D.; Roberts, A.; Somerfield, G.A. J. Chem. Soc. **1962**, (5), 1658–1666.
6. Jurd, L. Chem. Ind. (London) **1967**, (52), 2175–2176.
7. Ahluwalia, V.K.; Arora, K.K.; Mukherjee, K. Synthesis **1984**, (4), 346–348.
8. Hou, L.M.; Huang, C.S.; Cen, W. Chin. Chem. Lett. **1998**, *9*, 805–807.
9. Li, Y.; Yang, J.H.; Li, W.D.Z.; Hou, L.M.; Xue, J.J.; Li, Y.L. J. Nat. Prod. **2001**, *64* (2), 214–216.
10. Masaoud, M.; Ripperger, H.; Prozel, A. Phytochemistry **1995**, *38* (4), 745–749.

11. Raimundo, B.F.; Pedro, P.D.; Otto, R.G. Phytochemistry **1980**, *19* (3), 455–459.
12. Eliane, G.; Marc, M.; Sandor, A.; Steven, M.; Kurt, H. Phytochemistry **1996**, *43* (5), 1265–1269.
13. David, T.C.; Timothy, M.O.; John, W.M.; Alexander, E.A.P. Phytochemistry **1980**, *19* (5), 889–891.

Received in Japan March 1, 2003