Synthesis of 5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-benzo[*b*]furancarbaldehyde, a Novel Adenosine A_1 Receptor Ligand from the Root of *Salvia miltiorrhiza*

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A novel adenosine A_1 receptor ligand, 5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-benzo[*b*]furancarbaldehyde (**1**), is a constituent of the roots of *Salvia miltiorrhiza*. Through biomimetic considerations, methyl ferulate was used as starting material for an eight-step synthesis of **1**.

The dried roots of *Salvia miltiorrhiza* Bunge (Labiatae) (Chinese name "danshen") are used as a traditionally important Chinese herb in the treatment of cardiovascular disease. The aqueous extracts of this herb have been used widely in the People's Republic of China and Taiwan to treat acute myocardial infarction and angina pectoris.[1−3] More than 25 orange-red crystalline pigments, known as the tanshinones, have been isolated from this herb, and many of these show physiological activity.[4−13] Recently, Lin *et al*. have reported that several tanshinones show cytotoxicity and inhibition of platelet aggregation.[14−18] A new compound, 5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-benzo[*b*]furancarbaldehyde (**1**), was shown to have exceedingly high potency (IC_{50} 17 nM) in inhibiting [^{3}H]-phenylisopropyladenosine binding to the adenosine A_1 receptor of bovine cerebral cortex membranes.[19] The structure elucidation and an initial total synthesis of this new compound were carried out by Yang *et al*. in 1991.[20] The next year, this same group reported the synthesis of this novel adenosine A_1 receptor ligand and several of its derivatives.[21] Vanillin and 3-methoxy-4-hydroxyacetophenone were utilized as starting materials for the synthesis of compound **1**, involving thirteen steps altogether.[21]

In the present work, a key feature is the conventional coupling reaction from two monolignols based on free radical chemistry as part of a convenient route for the synthesis of **1**. In our previous reports for the oxidative coupling of two monolignols to lignan, we have utilized ferric ion,[22] sensitized photooxygenation,[23,24] and acidic chromium trioxide.[25] The former two methods proceed by radical coupling, and the last method via chromate coupling. The oxidation of methyl ferulate (**2**) in Me_2CO solution with aqueous ferric chloride yielded two products, dihydrobenzofuran (**3**) (34%) and aryldihydronaphthalene **4** (30%).[25] If the oxidizing conditions employed silver oxide in C_6H_6 and Me_2CO,[26] compound **3** (50%) was the only product (Scheme 1). Compound **3** was first protected with an acetyl group (Ac_2O, pyridine) to give compound **5**, which was then oxidized by dichlorodicyanobenzoquinone (DDQ) in dry C_6H_6 to afford a benzofuran (**6**). Hydrogenation of **6** with 10% Pd−C in MeOH in the presence of *p*-toluenesulfonic acid furnished compound **7** with simultaneous deacetylation. The product was reprotected with a benzyl group to yield compound **8**. After treatment with diisobutyl aluminum hydride in dry THF, compound **8** afforded diol **9**. Selective oxidation to the furancarbaldehyde was achieved with MnO_2 in EtOAc, and produced monoaldehyde **10** from diol **9**. Finally, deprotection of **10** with $TiCl_4$ in dichloromethane provided the target molecule **1** as a yellowish solid (mp 77−77.5 °C), which gave identical spectral data to literature values.[20,21] Our synthetic method of compound **1** is more advantageous, when compared to that of Wong *et al*.[21] for the following reasons. The total yield was improved from 5.3% to 14.9%, and the total synthetic steps were reduced from thirteen to eight. In addition, we directly synthesized the benzofuran skeleton in one step instead of seven steps, so this is a more convenient route for the synthesis of compound **1**.

Experimental Section

General Experimental Procedures. Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 IR spectrometer. ^{1}H-NMR spectra were run on Bruker AM-300 and AM-200 spectrometers. EIMS were obtained on a JEOL-JMS-100 spectrometer.

Oxidative Coupling of Methyl Ferulate (2) with Ferric Chloride or Silver Oxide. $FeCl_3$•6 H_2O (14 g) in H_2O (150 mL) was slowly added to the solution of **2** (9 g) in Me_2CO (150 mL) over 3 h at 0 °C. After being stirred at −10 °C for 48 h, the reaction mixture was warmed to room temperature, and stirred for 24 h. The solvent was evaporated under reduced pressure at room temperature, and the aqueous residue extracted by EtOAc (3 × 200 mL). The combined organic layer was washed with H_2O and brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a residue. The residue was purified by Si gel column chromatography to give **3** [(3.05 g, 34%, EtOAc−hexane, 1:4): mp 163−164 °C; IR (dry film) ν max 3423, 3030, 1734, 1705, 1628, 1599, 1517, 1491, 1272, 1170, 1032, 982 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.80, 3.83, 3.87, 3.91 (3H each, s), 4.34 (1H, d, J = 8.1 Hz, H-3), 5.66 (1H, s, ArOH), 6.10 (1H, d, J = 8.1 Hz, H-2), 6.32 (1H, d, J = 15.9 Hz, H-9), 6.90 (3H, s, H-2′, H-5′, H-6′), 7.02 (1H, s, H-6), 7.19 (1H, s, H-4), 7.64 (1H, d, J = 15.9 Hz, H-8); EIMS (70 eV) m/z [M]$^+$ 414 (100), 382 (63), 350

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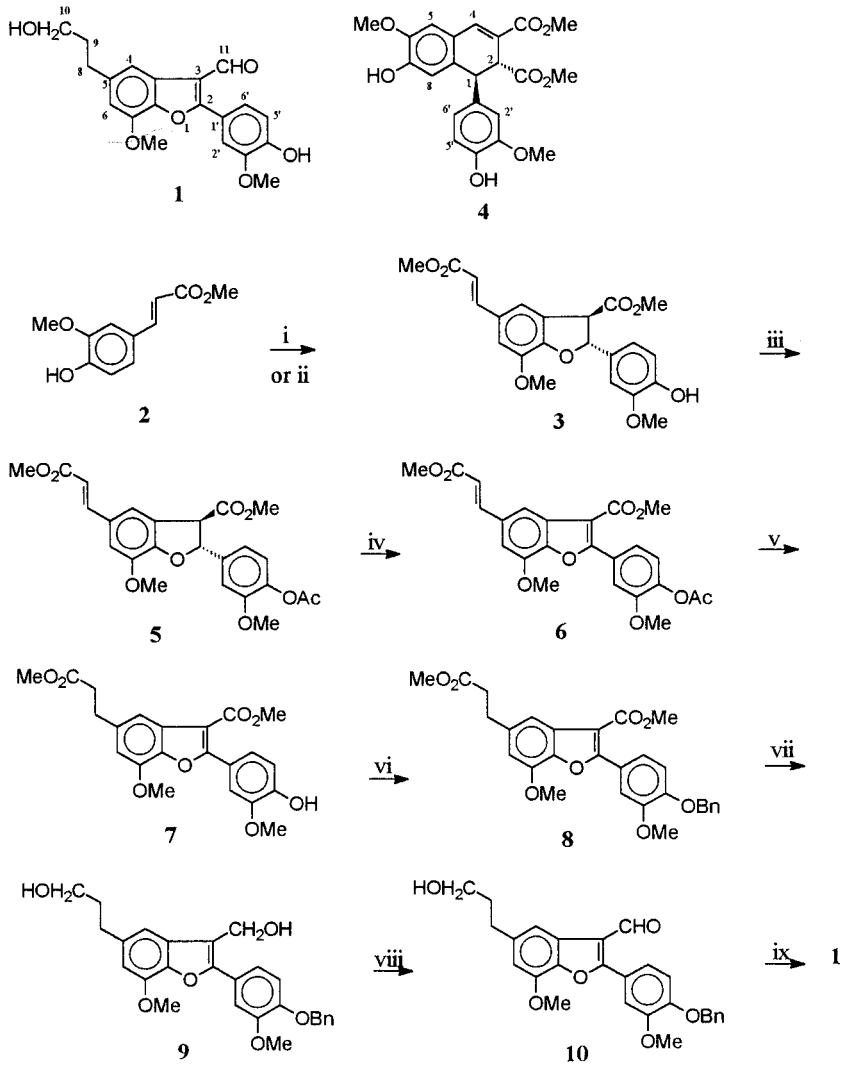
Scheme 1. Synthesis of **1**[a]



[a] Key: (i) $FeCl_3$•6 H_2O, Me_2CO/H_2O, −10 °C; (ii) Ag_2O, $Me_2COC_6H_6$, room temperature; (iii) Ac_2O, pyridine, room temperature; (iv) DDQ, dry C_6H_6, reflux; (v) 10% Pd-C, H_2, TsOH•H_2O, MeOH, room temperature; (vi) BnBr, K_2CO_3, 2-butanone, reflux; (vii) DIBAL, dry THF, −5 °C; (viii) MnO_2, EtOAc, room temperature; (ix) $TiCl_4$, CH_2Cl_2, room temperature.

(67)]; and **4** [(2.67 g, 30%, EtOAc−hexane, 3:7); mp 215−216 °C; IR (dry film) ν max 3405, 3030, 1720, 1694, 1630, 1600, 1508, 1268, 1080, 1033, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.60, 3.73, 3.76, 3.88 (3H each, s), 3.95 (1H, d, J = 3.0 Hz, H-2), 4.52 (1H, d, J = 3.0 Hz, H-1), 5.52, 5.85 (1H each, s, ArOH), 6.38 (1H, dd, J = 1.7, 8.1 Hz, H-6′), 6.60 (1H, d, J = 1.7 Hz, H-2′), 6.68 (1H, s, H-8), 6.69 (1H, d, J = 8.1 Hz, H-5′), 6.81 (1H, s, H-5), 7.64 (1H, s, H-4); EIMS (70 eV) m/z $[M]^+$ 414 (22), 354 (100), 323 (47), 291 (12), 177 (10), 162 (12), 105 (9), 59 (20)]. According the conditions used by Maeda *et al.*, only product **3** (50%) was obtained by oxidizing with Ag_2O in C_6H_6−Me_2CO.[26]

Acetylation of 3. A mixture of **3** (730 mg) and Ac_2O (2 mL) in pyridine (2 mL) was stirred at room temperature overnight. The reaction mixture was poured onto crushed ice and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with 3 N HCl, saturated aqueous $NaHCO_3$, and brine, and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure produced **5** (768 mg, 95%): mp 135−137 °C; IR (dry film) ν max 3030, 2947, 2839, 1759, 1735, 1707, 1628, 1603, 1493, 1430, 1367, 1272, 1033, 1170, 1095, 982, 899, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34, 3.83, 3.86, 3.89, 3.96 (3H each, s), 6.22, 4.41 (1H each, d, J = 8.1 Hz, H-2, H-3), 7.68, 6.37 (1H each, d, J = 15.9 Hz, H-8, H-9), 7.04−7.08 (4H, m, H-6, H-2′, H-5′, H-6′), 7.24 (1H, s, H-4); EIMS (70 eV) m/z $[M]^+$ 456 (93), 414 (53), 382 (100), 350 (71), 235 (8), 205 (6), 196 (6), 137 (15), 43 (6).

Dehydrogenation of 5 with Dichlorodicyanobenzoquinone. DDQ (1.5 g) was added to a solution of **5** (768 mg) in dry C_6H_6 (30 mL) under Ar. The reaction mixture was refluxed for 60 h, then filtered. Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on Si gel to produce **6** (516 mg, 67%, EtOAc−hexane, 4:6): mp 154−155 °C; IR (dry film) ν max 3030, 2945, 2840, 1758, 1706, 1629, 1599, 1498, 1433, 1366, 1306, 1263, 1044, 1171, 1091, 979, 909, 883, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33, 3.82, 3.91, 3.94, 4.03 (3H each, s), 7.79, 6.44 (1H each, d, J = 16.0 Hz, H-8, H-9), 7.78, 7.01 (1H each, d, J = 1.3 Hz, H-4, H-6), 7.13 (1H, d, J = 8.3 Hz, H-5′), 7.65 (1H, dd, J = 2.0, 8.3 Hz, H-6′), 7.81 (1H, d, J = 2.0 Hz, H-2′); EIMS (70 eV) m/z $[M]^+$ 454 (20), 413 (20), 412 (100), 349 (11), 43 (17).

Hydrogenation and Deprotection of 6. Compound **6** (75 mg), 10% Pd-C (10 mg), and TsOH•H_2O (10 mg) in MeOH (6 mL) solution were reacted under H_2 with stirring for 8 h. After being filtered and neutral-

ized by saturated aqueous $NaHCO_3$ (20 mL), the reaction mixture was evaporated to give a residue. The aqueous solution of the residue was extracted by EtOAc (3 × 50 mL), and then the combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on Si gel to yield **7** (57.3 mg, 84%, EtOAc−hexane, 4:6): mp 121−122 °C; IR (dry film) ν max 3414, 3030, 2945, 2841, 1740, 1704, 1596, 1507, 1476, 1437, 1366, 1271, 1046, 1174, 1092, 886, 861, 824, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04, 2.68 (2H each, t, J = 7.8 Hz, H-8, H-9), 3.67, 3.90, 3.94, 3.98 (3H each, s), 5.99 (1H, s, ArOH), 7.40, 6.67 (1H each, d, J = 1.1 Hz, H-4, H-6), 6.97 (1H, d, J = 8.3 Hz, H-5′), 7.59 (1H, dd, J = 1.7 and 8.3 Hz, H-6′), 7.67 (1H, d, J = 1.7 Hz, H-2′); EIMS (70 eV) m/z $[M]^+$ 414 (100), 383 (8), 354 (9), 341 (15), 323 (26).

Benzylation of 7. A mixture of **7** (49 mg), DMSO (0.15 mL), K_2CO_3 (100 mg), and benzyl bromide (0.5 mL) in 2-butanone (10 mL) was refluxed under Ar for 6 h. H_2O (30 mL) was added to the reaction mixture, and then the aqueous solution was extracted by EtOAc (3 × 50 mL), the organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on Si gel to yield **8** (46 mg, 77%, Me_2CO−hexane, 1:4): mp 168−169 °C; IR (dry film) ν max 3030, 2942, 1735, 1706, 1595, 1507, 1476, 1437, 1377, 1262, 1047, 1172, 1093, 887, 856, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04, 2.68 (2H each, t, J = 7.7 Hz, H-8, H-9), 3.67, 3.90, 3.95, 3.98 (3H, each, s), 5.20 (2H, s, ArOCH_2Ph), 6.67 (1H, d, J = 1.2 Hz, H-6), 6.93 (1H, d, J = 8.4 Hz, H-5′), 7.28−7.44 (6H, m, phenyl protons, H-4), 7.57 (1H, dd, J = 2.1 and 8.4 Hz, H-6′), 7.67 (1H, d, J = 2.1 Hz, H-2′); EIMS (70 eV) m/z $[M]^+$ 504 (60), 470 (8), 413 (100), 380 (8), 321 (33), 250 (8), 153 (7), 91 (75), 65 (18), 57 (8), 43 (20).

Reduction of 8. Diisobutyl aluminum hydride (1 M in hexane) (1 mL) was added to a solution of **8** (44 mg) in dry THF (6 mL) at −5 °C under Ar. The reaction mixture was stirred for 4 h at −5 °C and 4 h at room temperature and then was quenched with wet THF at −5 °C. To this mixture was added 10% H_2SO_4 (20 mL), and the reaction mixture was stirred for 30 min. THF was evaporated under reduced pressure and the aqueous layer of the reaction mixture was extracted by EtOAc (3 × 50 mL). Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on Si gel to yield **9** (35 mg, 90%, EtOAc−hexane, 4:6); mp 130−131 °C; IR (dry film) ν max 3381, 3030, 2926, 2805, 1595, 1507, 1457, 1372, 1260, 1019, 1050, 900, 830, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.90 (2H, m, H-9), 2.74 (2H, t, J = 7.7 Hz, H-8), 3.64 (2H, t, J = 6.3 Hz, H-10), 3.93, 3.97 (3H each, s), 4.82 (2H, s, H-11), 5.17 (2H, s, ArOCH_2Ph), 7.05, 6.62 (1H each, br s, H-4, H-6), 6.92 (1H, d, J = 8.4 Hz, H-5′), 7.28−7.44 (7H, m, phenyl protons, H-2′, H-6′); EIMS (70 eV) m/z $[M]^+$ 448 (50), 357 (100), 341 (11), 325 (5), 314 (10), 311 (15), 285 (6), 264 (14), 222 (5), 166 (6), 91 (48).

Oxidation of 9 with Manganese Dioxide. Fresh MnO_2 (200 mg) was added to the solution of **9** (17.3 mg) in EtOAc (2 mL). The reaction mixture was stirred at room temperature for 20 min and filtered to afford **10** (14.8 mg, 85%): mp 112−113 °C; IR (dry film) ν max 3432, 3030, 2927, 2853, 2780, 1657, 1595, 1507, 1476, 1437, 1261, 1029, 1057, 898, 856, 804, 737, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (2H, m, H-9), 2.81 (2H, t, J = 7.5 Hz, H-8), 3.69 (2H, t, J = 6.4 Hz, H-10), 3.96, 4.00 (3H each, s), 5.25 (2H, s, ArOCH_2Ph), 6.73 (1H, br s, H-6), 7.00 (1H, d, J = 8.3 Hz, H-5′), 7.30−7.45 (7H, m, phenyl protons, H-4, H-6′), 7.64 (1H, br s, H-2′), 10.26 (1H, s, CHO); EIMS (70 eV) m/z $[M]^+$ 446 (57), 445 (10), 355 (100), 281 (14), 91 (91), 65 (12), 55 (9).

Deprotection of 10 with Titanium Tetrachloride. $TiCl_4$ (0.15 mL) was added to a solution of **10** (6.3 mg) in CH_2Cl_2 (1 mL) at room temperature under Ar. The reaction mixture was stirred for 20 min, then quenched with ice at room temperature. Next, 3 N HCl (0.5 mL) was added, and the reaction mixture was stirred for 30 min. H_2O (30 mL) was then added, the reaction mixture extracted by EtOAc (3 × 50 mL), and the organic layer washed with saturated aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on Si gel to yield product **1** (4.8 mg, 94%, EtOAc−hexane, 1:1); mp 77−77.5 °C; IR (dry film) ν max 3398, 3030, 2926, 2853, 2780, 1652, 1595, 1507, 1476, 1437, 1271, 1050, 1030, 900, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (2H, m, H-9), 2.81 (2H, t, J = 7.3 Hz, H-8), 3.70 (2H, t, J = 6.5 Hz, H-10), 3.98, 4.00 (3H each, s), 6.00 (1H, br s, ArOH), 7.36, 6.73 (1H each, d, J = 1.4 Hz, H-4, H-6), 7.05 (1H, d, J = 8.0 Hz, H-5′), 7.38 (1H, d, J = 8.0 Hz, H-6′), 7.64 (1H, s, H-2′), 10.26 (1H, s, CHO); EIMS (70 eV) m/z $[M]^+$ 356 (95), 326 (30), 312 (100), 283 (31), 268 (28), 241 (27), 181 (31), 165 (37), 152 (37), 139 (32), 57 (32), 43 (40).

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References and Notes

(1) Chang, H. M.; Choang, T. F.; Chui, K. Y.; Hon, P. M.; Lee, C. M.; Mak, T. C. W.; Wong, H. N. C. *J. Chem. Res. (S)* **1990, 114**−**115.**
(2) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537−3543.
(3) Chen, W. Z. *Acta Pharm. Sin.* **1984**, *19*, 876−880.
(4) Takiura, K.; Koizumi, K. *Chem. Pharm. Bull.* **1962**, *10*, 134−140.
(5) Kakisawa, H.; Hayashi, T.; Okazaki, I.; Ohashi, M. *Tetrahedron Lett.* **1968**, 3231−3234.
(6) Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670−1675.
(7) Luo, H. W.; Wu, B. J.; Wu, M. Y.; Yong, Z. G.; Jan, Y. *Acta Pharm. Sin.* **1985**, *20*, 542−544.
(8) Luo, H. W.; Chen, S.; Lee, J.; Snyder, J. K. *Phytochemistry* **1988**, *27*, 290−292.
(9) Feng, B. S.; Li, S. R. *Acta Pharm. Sin.* **1980**, *15*, 489−494.
(10) Hayashi, T.; Handa, T.; Ohashi, M.; Kakisawa, H.; Hsu, H. Y.; Chen, Y. P. *J. Chem. Soc., Chem. Commun.* **1971**, 541−542.
(11) Baillie, A. C.; Thomson, R. H. *J. Chem. Soc.* (*C*), **1968**, 48−52.
(12) Fang, C. N.; Chang, P. L.; Hsu, T. P. *Acta Chim. Sin.* **1976**, *34*, 197−209.
(13) Lee, A. R.; Wu, W. L.; Chang, W. L.; Lin, H. C.; King, M. L. *J. Nat. Prod.* **1987**, *50*, 157−160.
(14) Lin, H. C.; Chang, W. L. *Chin. Pharm. J.* **1991**, *43*, 11−17.
(15) Lin, H. C.; Chang, W. L.; Chen, G. L. *Chin. Pharm. J.* **1991**, *43*, 501−504.
(16) Lin, H. C.; Chang, W. L. *Chin. Pharm. J.* **1993**, *45*, 21−27.
(17) Lin, H. C.; Chang, W. L. *Chin. Pharm. J.* **1993**, *45*, 85−87.
(18) Lin, H. C.; Chang, W. L. *Chin. Pharm. J.* **1993**, *45*, 615−618.
(19) Cheung, W. T.; Shi, M. M.; Young, J. D.; Lee, C. M. *Biochem. Pharmacol.* **1987**, *36*, 2183−2186.

(20) Yang, Z.; Hon, P. M.; Chui, K. Y.; Xu, Z. L.; Chang, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M. *Tetrahedron Lett*. **1991**, *33*, 2061−2064.
(21) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem*. **1992**, *57*, 7248−7257.
(22) Kuo, Y. H.; Lin, S. T. *Experientia* **1983**, *39*, 991−993.
(23) Kuo, Y. H.; Kuo, P. C.; Lin, S. T. *Proc. Natl. Sci. Counc., Repub. China, Part B: Life Sci*. **1983**, *7*, 28−34.
(24) Kuo, Y. H.; Chen, L. H.; Wang, L. M. *Chem. Pharm. Bull*. **1991**, *39*, 2196−2200.
(25) Kuo, Y. H.; Lin, S. T. *Chem. Pharm. Bull*. **1993**, *41*, 1507−1512.
(26) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull*. **1994**, *42*, 2500−2505.

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