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The First Total Synthesis of (±)-3′, 7-Dihydroxy-4′-methoxyflavan

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Abstract: The first total synthesis of (±)-3′, 7-dihydroxy-4′-methoxyflavan, a naturally occurring flavan, was described. The key step is the cyclization of 1, 3-diaryl-1-propanol by $BF_3 \cdot Et_2O$.

Keywords: (±)-3′, 7-Dihydroxy-4′-methoxyflavan, total synthesis.

Naturally occurring flavans, a branch of flavanoids, exist widely in the plant kingdom and exhibit many important biological and pharmacological activities[1]. In previous work, we have reported a convenient and efficient synthetic method based on the Lewis acid ($BF_3 \cdot Et_2O$)-mediated benzopyran formation in an aprotic polar solvent[2,3]. In order to support the practicability of this method, herein we wish to describe the first total synthesis of (±)-3′, 7-dihydroxy-4′-methoxyflavan **1**.

(-)-3′, 7-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[4]. As we know, the total synthesis of **1** has not been reported yet.

3, 4-Dihydroxybenzaldehyde **2** with dimethyl sulfate in the presence of potassium carbonate in acetone under reflux produced isovanilin **3**, along with the 3, 4-O-dimethylated product. **3** was converted into benzaldehyde **4** by the treatment with methoxymethyl chloride and potassium carbonate in acetone under reflux. **4** with CH_3MgI in THF gave the alcohol **5**, which was converted into acetophenone **6** by the oxidation of PCC in CH_2Cl_2. Condensation of **6** with 2,4-dimethoxymethoxybenzaldehyde **7** proceeded in a solution of KOH (20.0 eq.) in absolute methanol gave the corresponding chalcone **8**. And **8** was reduced in ethanol under catalysis of Pd-C (5%) to afford 1, 3-diaryl-1-propanol **9**. Cyclization of **9** by $BF_3 \cdot Et_2O$ in 1, 4-dioxane at room temperature gave **10**. The target compound (±)-3′, 7-dihydroxy-4′-methoxyflavan **1** was obtained by deprotecting **10** with 3 mol/L HCl in methanol under reflux. The spectral data of synthetic **1**[5] are identical with those of natural product[4]. Thus, a general and facile approach for the synthesis of flavan has been proved to be practical based on the cyclization of 1, 3-diaryl-1-propanol by $BF_3 \cdot Et_2O$ as the key step.

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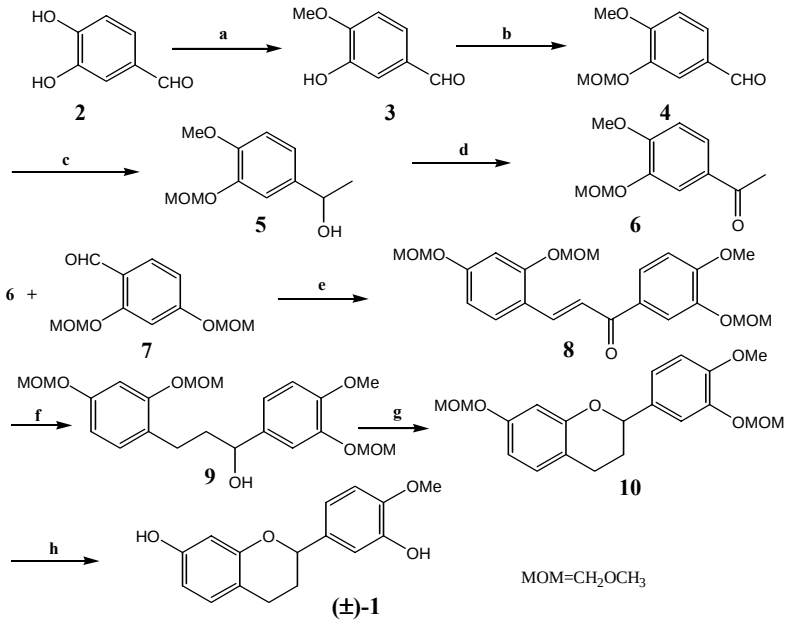

Reagents and conditions: a. $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux, 2 h, 65%; b. MOMCl, K_2CO_3, acetone, reflux, 2 h, 88%; c. CH_3MgI, THF, -10-0°C, 1 h, 76%; d. PCC, CH_2Cl_2, r. t., 1.5 h, 85%; e. KOH (20.0 eq.), absolute CH_3OH, r. t., 16 h, 85%; f. H_2, Pd-C (5%), r. t., 10 h, 99%; g. $BF_3 \cdot Et_2O$, 1, 4-dioxane, r. t., 20 min, 90%; h. 3 mol/l HCl, CH_3OH, reflux, 30 min, 80%.

Referrences and Notes

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5. The data of (±)-**1**: m. p. 151-152°C. ^{1}H NMR (δ): 2.0-2.2 (m, 2H, 3-H), 2.6-2.8 (m, 2H, 4-H), 3.81 (s, 3H, OCH_3), 4.86 (dd, 1H, J=3.0 Hz, 9.6Hz, 2-H), 6.31 (d, 1H, J=2.0 Hz, H-8), 6.33 (d, 1H, J=2.0 Hz, H-6), 6.77 (d, 1H, J=8.4 Hz, H-5′), 6.84 (d, 1H, J=8.4 Hz, H-5, 6′), 6.92 (d, 1H, J=1.6 Hz, H-2′). IR ν_{max}^{KBr} (cm^{-1}): 3396, 2977, 2925, 1595, 1509, 1459. Ms (*m/z*): [M^+] 272 (37.2), 162 (17.9), 150 (100), 137 (49.9), 123 (22.4), 104 (42.7).

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