Notes

Studies on Flavans. 1. Facile Synthesis of (±)-7-Hydroxy-3′,4′-methylenedioxyflavan and (±)-4′-Hydroxy-7-methoxyflavan by a BF_3·Et_2O-Mediated Pyran Cyclization

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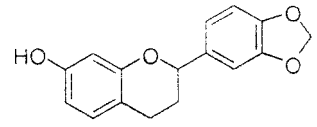
A facile approach for the synthesis of flavans was developed by employing a BF_3·Et_2O-catalyzed pyran cyclization in an aprotic polar solvent as a key step, by which concise total syntheses of (±)-7-hydroxy-3′,4′-methylenedioxyflavan (**1**) and (±)-4′-hydroxy-7-methoxyflavan (**2**), two naturally occurring flavans, were achieved.

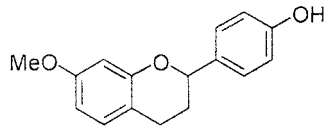
Naturally occurring flavans, characterized by the presence of a benzopyran core, exist widely in the plant kingdom and exhibit many important biological and pharmacological activities.[1−9] Considerable studies on the synthesis of flavan have been carried out, and a number of synthetic methods have been developed[9−24] over the past decades for the purposes of structural determination and/or analogue preparation for further biological studies. Among them, reductive deoxygenation of the flavanone and *protic acid*-catalyzed cyclization to form the benzopyran ring are common approaches, yet these approaches typically suffer from poor yields and harsh reaction conditions. For example, a large excess of a hydride reducing agent, i.e., $NaBH_4$,[10] $Na(CN)BH_4$,[11] or $LiAlH_4$[12] is always required for the completion of reductive deoxygenation of the fully assembled flavanones. In some cases, the strong reducing conditions (i.e., $LiAlH_4$−$AlCl_3$) result in the cleavage of the benzopyran ring.[12] The reaction conditions for the cyclization of corresponding carbinol or styrene derivatives of chalcones by exposure to *protic acids*, i.e., HCl,[12] HOAc,[13] or H_3PO_4[17] to form the benzopyran ring are quite harsh for some acid-labile protecting groups (such as methoxymethyl, MOM) that may be necessary for further derivatization. Thus, an efficient, general, and direct synthetic method from readily accessible chalcones is desirable.

In continuation of our ongoing program on the studies of flavanoids, we report herein a facile synthetic approach (Scheme 1) based on the Lewis acid (BF_3·Et_2O)-mediated benzopyran formation in an *aprotic* polar solvent, as illustrated in the total synthesis of the two naturally occurring flavans, (±)-7-hydroxy-3′,4′-methylenedioxyflavan (**1**) and (±)-4′-hydroxy-7-methoxyflavan (**2**).

(±)-7-Hydroxy-3′,4′-methylenedioxyflavan (**1**) and its 7-glucoside were first isolated[25] from the native American medicinal herb *Zephyranthes flava*, which has been used traditionally for the treatment of diabetes, ear and chest ailments, and some viral infections. (±)-4′-Hydroxy-7-methoxyflavan (**2**) was first identified[26] as a chemical component of *Stypandra grandis* and later characterized as one of the antifeedant compounds in *Lycoris raliata*.[26]



1



2

Its structure was confirmed[27] by hydrogenation of the corresponding flavylium salt formed by condensation of the appropriately substituted benzaldehyde and acetophenone under acidic conditions.Hydrogenation of chalcone **3**[28] using Raney Ni (W-2 type) in ethanol as the catalyst afforded benzylic alcohol **5** (93%), the key precursor for benzopyran cyclization. Treatment of **5** with boron trifluoride etherate (0.5 equiv)[29] dropwise in anhydrous 1,4-dioxane at room temperature for ca. 20 min[30] was followed by extractive workup with ether to produce the desired cyclization product **7** in 57% yield. Ferreira and co-workers reported[31,32] that reduced *retro*-chalcones can undergo a similar simultaneous deprotection−cyclization in methanolic aqueous hydrochloric acid (3 M) to afford the corresponding catechin derivatives presumably via an incipient C-1 carbocation species. It is noteworthy that the methoxymethoxy (MOM) group, usually labile to acid, was left intact under this condition. Dioxane is the most favorable solvent tested so far for the cyclization, while other solvents such as THF, ether, or methylene chloride resulted in poor yield of the desired product. The title compound **1** was obtained as its racemate by mild acidic hydrolysis (3 N HCl in methanol) in 93% yield. The synthetic product has identical melting point (115−117 °C) and spectroscopic properties as those reported for the natural product.[25]

Following an analogous sequence as described above, starting from the chalcone **4**, compound **2** was synthesized as a racemic mixture in an overall yield of 74%. The synthetic (±)-**2** has the same melting point (143−145 °C) and spectral properties as the natural product.[26,27]

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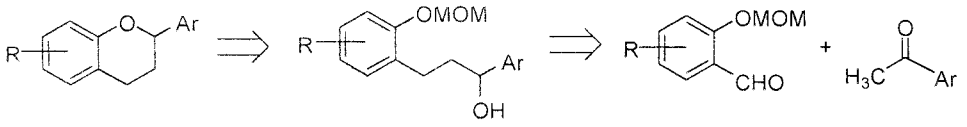
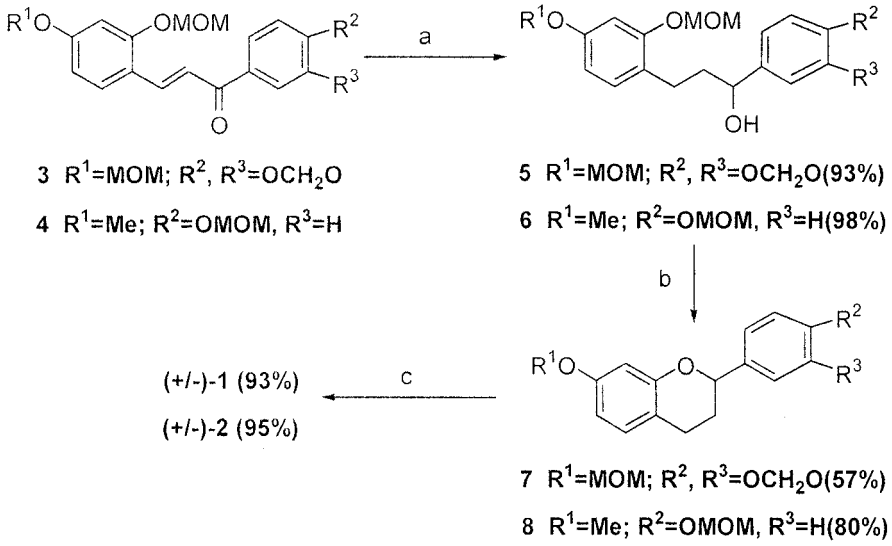
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) H_2/Raney Ni(W-2), EtOH, 22 °C; (b) $BF_3{\cdot}Et_2O$, 1,4-dioxane, 23 °C, 0.5 h; (c) 3 N HCl, MeOH, reflux.

The approach described herein is facile, short, and applicable to various flavan derivatives. $BF_3{\cdot}Et_2O$ was used as a unique Lewis acid to catalyze the pyran cyclization in an *aprotic* media, without affecting the acid-labile functional group such as MOM.

Experimental Section

General Experimental Procedures. IR spectra were obtained on a FT-170 SX spectrometer. ^{1}H NMR spectra were obtained on a Bruker AM-400 or AC-80 instrument in $CDCl_3$ solution, and chemical shifts were recorded in ppm (δ) units using TMS as an internal standard. MS were measured on a ZAB-HS spectrometer by direct inlet at 70 eV.

1-(3′,4′-Methylenedioxyphenyl)-3-(2′,4′-dimethoxymethoxyphenyl)propanol (5) and 1-(4′-Methoxymethoxyphenyl)-3-[(2′-methoxymethoxy-4′-methoxy)phenyl]propanol (6). A solution of **3** (400 mg, 1.1 mmol) and W-2 type Raney-Ni (100 mg) in EtOH (6 mL) was kept for 24 h under 2 atm pressure of hydrogen. The reaction mixture was filtered and evaporated under reduced pressure to give an oily residue that was purified by flash column chromatography on silica gel (petroleum ether−EtOAc, 8:1) to yield **5** (377 mg, 93%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98(2H, m, 2-H), 2.65(2H, t, J = 7.2 Hz, 3-H), 3.46 and 3.47(6H, s, OCH_3), 4.55(1H, dd, J = 8.0, 5.6 Hz, 1-CH), 5.14 and 5.17(4H, s, OCH_2O), 5.93(2H, s, OCH_2O), 6.64(1H, dd, J = 8.4, 2.4 Hz, ArH), 6.77(4H, m, ArH), 7.03(1H, d, J = 8.4 Hz, ArH); IR (KBr) 1015, 1247 cm^{-1}; EIMS m/z [M]$^+$ 376(38), 314(50), 269(54), 148-(31), 135(14), 84(44), 45(100).

Alcohol 6 was prepared in an analogous manner by hydrogenation of the corresponding chalcone **4** and was obtained as a colorless liquid in 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01(2H, m, 2-H), 2.67(2H, m, 3-H), 3.47, 3.48 and 3.78 (9H, s, OCH_3), 4.60(1H, dd, J = 8.1, 5.2 Hz, 1-CH), 5.17, 5.18(4H, s, OCH_2O), 6.51(1H, dd, J = 8.0, 2.4 Hz, ArH), 6.70-(1H, d, J = 2.4 Hz, ArH), 7.01(2H, d, J = 8.4 Hz, ArH), 7.06-(2H, d, J = 8.4 Hz, ArH), 7.29(1H, d, J = 8.4 Hz, ArH); IR (KBr) 3425, 1076 cm^{-1}; EIMS m/z [M]$^+$ 362(16), 317(5), 300-(34), 267(7), 255(13), 239(8), 181(9), 167(9), 164(8), 151(9), 137-(31), 121(6), 91(4), 45(100).

7-Methoxymethoxy-3′,4′-methylenedioxyflavan (7) and 7-Methoxy-4′-methoxymethoxyflavan (8). To a well-stirred solution of **5** (50 mg, 0.13 mmol) in 1,4-dioxane (5 mL) was added dropwise a solution of $BF_3{\cdot}Et_2O$ (0.05 mL, 0.06 mmol) in 10 mL of 1,4-dioxane at ambient tempature. The resulting mixture was stirred for 20 min at room temperature, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with ether. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether−EtOAc, 16:1) to yield **7** (24 mg, 57%), as a pale yellow solid (mp 47−48 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10(2H, m, 3-H), 2.71−2.94(2H, m, 4-H), 3.47(3H, s, OCH_3), 4.94(1H, dd, J = 10.2, 2.2 Hz, 2-H), 5.13(2H, s, 7-OCH_2O), 5.97-(2H, s, 3′,4′-OCH_2O), 6.58(1H, d, J = 2.5 Hz, ArH), 6.61(1H, dd, J = 8.4, 2.5 Hz, ArH), 6.81(1H, d, J = 8 Hz, ArH), 6.88-(1H, dd, J = 8.0, 1.2 Hz, ArH), 6.93(1H, d, J = 1.2 Hz, ArH), 6.98(1H, d, J = 8 Hz, ArH); IR (KBr) 2896, 1619, 1583 cm^{-1}; EIMS m/z [M]$^+$ 314(53), 283(59), 269(23), 253(3), 239(4), 148-(100), 135(32), 45(86).

Flavan 8 was prepared in an analogous manner from **6** and was obtained as an amorphous solid in 80% yield (mp 24−25 °C): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11(2H, m, 3-H), 2.82-(2H, m, 4-H), 3.48, 3.75(6H, s, OCH_3), 4.98(1H, dd, J = 10.1, 2.3 Hz, 2-H), 5.18(2H, s, 4′-OCH_2O), 6.46(1H, d, J = 2.3 Hz, ArH), 6.48(1H, d, J = 2.3 Hz, ArH), 6.98(1H, d, J = 8.1 Hz, ArH), 7.05(2H, m, ArH), 7.34(2H, dd, J = 8.5, 2.4 Hz, ArH); IR (KBr) 2929, 1618, 1583, 1507 cm^{-1}; EIMS m/z [M]$^+$ 300-(41), 285(31), 134(63), 45(100).

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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