A Novel Synthesis of Flavanones from 2-Hydroxybenzoic Acids

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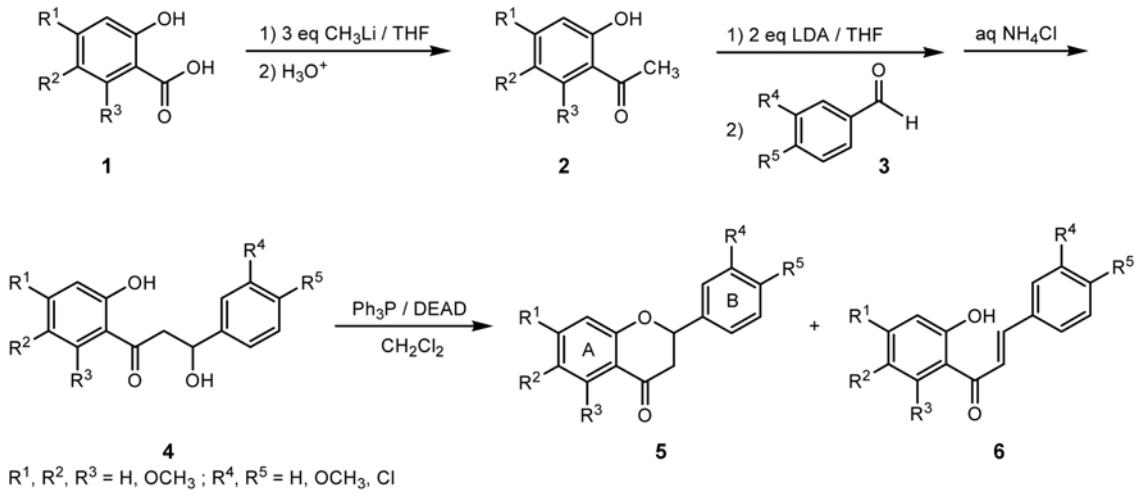
The flavanones are mainly distributed in citrus fruits and have attracted considerable attention because they possess antioxidant effect, potent inhibition of cancer cell proliferation, and cytotoxic activity.[1] The most frequently employed method for preparing flavanones involves the oxidative cyclization of 2'-hydroxychalcones.[2] The treatment of 2'-hydroxychalcones with Co(salpr) in methanol under oxygen,[3] $K_3Fe(CN)_6$ using phase transfer catalysis,[4] and photochemical irradiation[5] gives flavanones, but the yields are mostly low to moderate. 2'-Hydroxychalcones are also converted to flavanones by the treatment with acidic reagents[6] such as H_2SO_4 in methanol,[6a] KF-celite in methanol,[6b] CF_3COOH,[6c] and polyphosphoric acid[6d] or basic reagents[7] such as pyridine,[7a] KOH in methanol,[7b] and DBU in microwave irradiation,[7c] but most procedures are performed at high temperatures. Alternatively flavanones are prepared by the cyclization of 3-bromo-1-phenylprop-2-ynyl aryl ethers in the presence of $Hg(OCOCF_3)_2$ after $NaBH_4$ workup[8] or the dehydration/cyclization of 3-hydroxy-1-*o*-hydroxyphenyl-3-phenylpropan-1-ones derived from isoxazoles,[9] but the former fails to furnish the methoxy substituted flavanones and the latter proceeds in four steps.

However, there are no reports on the preparation of flavanones by the cyclodehydration of 1-(2'-hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ols which are prepared from 2'-hydroxyacetophenones and benzaldehydes. This synthetic strategy can avoid the undesirable reaction such as the partial cyclization of 2'-hydroxychalcones to flavanones during the synthesis.[10] Although 1-(2'-hydroxyphenyl)-1-oxo-propan-3-ols, prepared from 2'-hydroxyacetophenones and aldehydes or ketones with LDA, cyclize with acidic reagents[11] such as HCl in methanol[11a] and H_2SO_4 in HOAc[11b] or HMPT[12] to give the corresponding chroman-4-ones, all these methods work only at high temperatures and furthermore there are no reports on the preparation of flavanones with 2-substituted phenyl groups. In this paper we report that flavanones can be efficiently synthesized *via* 1-(2'-hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ols from the starting 2-hydroxybenzoic acids in three steps.

2'-Hydroxyacetophenones **2** were readily prepared by the treatment of 2-hydroxybenzoic acids **1** with 3 equiv of CH_3Li in THF in 74-93% yields according to our previous method.[13] 1-(2'-Hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ols **4**, precursors of flavanones **5**, were prepared by the treatment of the lithium dianions of **2** with benzaldehydes **3** (Scheme 1). To a yellowish solution of the lithium dianions, generated from **2** and 2 equiv of LDA in THF for 1.5 h at −20 °C, were added **3** at −78 °C. After being stirred for 1 h at −78 °C, the mixture was quenched with sat. NH_4Cl solution. The condensed residue after usual workup was purified by silica gel chromatography using 20% EtOAc/*n*-hexane to afford **4** in 81-94% yields without the formation of the corresponding 2'-hydroxychalcones **6**.

With **4** in hand, the cyclodehydration of **4** to **5** was studied



Scheme 1

Table 1. Preparation of Flavanones from 2-Hydroxybenzoic Acids

Flavanones **5**	R^1	R^2	R^3	R^4	R^5	Isolated yields, %[a]
a	H	H	H	H	H	64
b	H	H	H	H	Cl	60
c	H	H	H	H	OCH_3	64
d	H	H	H	OCH_3	OCH_3	56
e	OCH_3	H	H	H	H	63
f	OCH_3	H	H	H	Cl	70
g	OCH_3	H	H	H	OCH_3	68
h	H	OCH_3	H	H	H	69
i	H	OCH_3	H	H	Cl	59
j	H	OCH_3	H	H	OCH_3	61
k	H	H	OCH_3	H	H	51
l	H	H	OCH_3	H	OCH_3	55

[a]Overall yields of three steps from the starting 2-hydroxybenzoic acids.

using 1-(2'-hydroxyphenyl)-1-oxo-propan-3-(4'-methoxyphenyl)-3-ol **4c** as a model substrate. Initially the cyclodehydration was attempted by treating **4c** with $Ph_3P/CCl_4/Et_3N$[14] in CH_3CN or DMF/$(COCl)_2/Et_3N$ (Vilsmeier reagent)[15] in CH_2Cl_2. Under these reaction conditions, to our disappointment, desired 4'-methoxyflavanone **5c** was obtained as a minor product with chalcone **6c** as a major product in 82% and 80% yield, respectively, in a ratio of 1:4 and 1:3, respectively, detected by ^{1}H NMR integration. The cyclodehydration of **4c** was next examined with Ph_3P/diethyl azodicarboxylate (DEAD)[16] varying solvents. The treatment of **4c** with Ph_3P/DEAD in CH_2Cl_2, THF, CH_3CN at 0 °C gave **5c** and **6c** with a ratio of 13:1, 6:1, and 1.5:1, respectively, in 99%, 98%, and 94% yield, respectively. Thus, the cyclodehydration of **4** was carried out by the slow addition of DEAD to a mixture solution of **4** and Ph_3P in CH_2Cl_2 at 0 °C. After completion of the reaction, the condensed residue was subjected to a short pathway silica gel chromatography using 30% EtOAc/*n*-hexane to eliminate Ph_3P=O and diethyl 1,2-hydrazinedicarboxylate. The successive recrystallization of the condensed mixture in *n*-hexane gave pure **5** in 76-89% yields.

As shown in Table 1, various flavanones were synthesized in high overall yields (51-70%) from the starting **1**. The reaction worked well both for the methoxy substituent (**5e**-**5j**) on the A-ring and the chloro (**5b**, **5f**, **5i**) or methoxy substituent (**5c**, **5d**, **5g**, **5j**) on the B-ring of **5** regardless of the kind and the position of substituents under the present reaction conditions. Furthermore, the ortho substituted methoxy group (**5k**, **5l**) of A-ring didn't influence the cyclodehydration of **4**. Thus, the present method provides (i) a novel synthesis of **5** from β-hydroxy ketone intermediates **4** (ii) the avoidance of isomerization between 2'-hydroxychalcones and flavanones (iii) the high yield of **5**.

Experimental Section

Preparation of 1-(2'-hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ol 4a (General procedure). To a solution of 2'-hydroxyacetophenone (545 mg, 4.0 mmol) in THF (12 mL) was added lithium diisopropylamide (2.0 M, 4.2 mL, 8.4 mmol) at −20 °C under argon atmosphere and stirred for 1.5 h. The mixture was then cooled to −78 °C and a solution of benzaldehyde (425 mg, 4.0 mmol) in THF (8 mL) was added. After being stirred for 1 h at −78 °C, the mixture was quenched with sat. NH_4Cl (3 mL). After evaporation of THF, the mixture was poured into sat. NH_4Cl (30 mL) and the aqueous phase was extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 20% EtOAc/*n*-hexane to give **4a** (824 mg, 85%). M.p. 75-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.08 (s, 1H), 7.70 (dd, J_1 = 8.1 Hz, J_2 = 1.6 Hz, 1H), 7.28-7.52 (m, 6H), 7.00 (dd, J_1 = 8.4 Hz, J_2 = 0.9 Hz, 1H), 6.85-6.91 (m, 1H), 5.37 (dd, J_1 = 8.8 Hz, J_2 = 3.3 Hz, 1H), 3.46 (dd, J_1 = 17.6 Hz, J_2 = 8.8 Hz, 1H), 3.36 (dd, J_1 = 17.6 Hz, J_2 = 3.3 Hz, 1H), 3.22 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 163.0, 143.1, 137.3, 130.5, 129.1, 128.3, 126.1, 119.8, 119.5, 119.1, 70.3, 47.6; FT-IR (KBr) 3439 (O-H), 3032, 2907, 1637 (C=O), 1579, 1448, 1268, 1061, 754, 701 cm^{-1}; Ms *m/z* (%) 224 (M^+-18, 82), 223 (81), 147 (57), 120 (100), 104 (43), 92 (57), 77 (17).

Preparation of flavanone 5a (General procedure). To a mixture solution of **4a** (727 mg, 3.0 mmol) and triphenylphosphine (787 mg, 3.0 mmol) in methylene chloride (18 mL) was slowly added diethyl azodicarboxylate (40 wt % in toluene, 1.5 mL, 3.3 mmol) at 0 °C over 3 min. After being stirred for 10 min, the solvent of the resulting yellow mixture was evaporated *in vacuo*. The residue was subjected to a short pathway silica gel column chromatography using 30% EtOAc/*n*-hexane to give a mixture of flavanone and the corresponding chalcone in a ratio of 13:1 (639 mg, 95%). The mixture was recrystallized in *n*-hexane to give **5a** (579 mg, 86%) as a colorless solid. M.p. 74-75 °C (lit.[4] 76 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 7.36-7.55 (m, 6H), 7.04-7.09 (m, 2H), 5.49 (dd, J_1 = 13.2 Hz, J_2 = 3.0 Hz, 1H), 3.10 (dd, J_1 = 16.9 Hz, J_2 = 13.2 Hz, 1H), 2.90 (dd, J_1 = 16.9 Hz, J_2 = 3.0 Hz, 1H); FT-IR (KBr) 3035, 2962, 1688 (C=O), 1606, 1462, 1304, 1228, 1065, 760, 696 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 162.0, 139.1, 136.6, 129.3, 129.2, 127.5, 126.6, 122.0, 121.3, 118.5, 80.0, 45.1; Ms *m/z* (%) 224 (M^+, 100), 223 (93), 147 (54), 120 (83), 92 (44), 77 (11).

4'-Chloroflavanone (5b). M.p. 84-85 °C (lit.[17] 85 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H), 7.49-7.55 (m, 1H), 7.39-7.45 (m, 4H), 7.03-7.10 (m, 2H), 5.47 (dd, J_1 = 13.0 Hz, J_2 = 3.2 Hz, 1H), 3.04 (dd, J_1 = 16.8 Hz, J_2 = 13.0 Hz, 1H), 2.88 (dd, J_1 = 16.8 Hz, J_2 = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 161.3, 137.3, 136.3, 134.6, 129.1, 127.5, 127.1, 121.8, 120.9, 118.1, 78.8, 44.6; FT-IR (KBr) 3036, 2977, 1697 (C=O), 1602, 1471, 1152, 821 cm^{-1}; Ms *m/z* (%) 260 (M^++2, 33), 259 (42), 258 (M^+, 100), 257 (85), 147 (44), 120 (90), 92 (33).

4'-Methoxyflavanone (5c). M.p. 96-97 °C (lit.[4] 98 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J_1 = 8.3 Hz, J_2 = 1.7

Hz, 1H), 7.46-7.53 (m, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.02-7.07 (m, 2H), 6.96 (d, J = 8.7 Hz, 2H), 5.43 (dd, J_1 = 13.3 Hz, J_2 = 2.8 Hz, 1H), 3.83 (s, 3H), 3.11 (dd, J_1 = 16.8 Hz, J_2 = 13.3 Hz, 1H), 2.86 (dd, J_1 = 16.8 Hz, J_2 = 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 162.0, 160.4, 136.6, 131.2, 128.1, 127.4, 121.9, 121.3, 118.5, 114.6, 79.8, 55.8, 44.9; FT-IR (KBr) 3007, 2963, 1690 (C=O), 1614, 1463, 1252, 1028, 826 cm^{-1}; Ms *m/z* (%) 254 (M^+, 64), 253 (48), 147 (16), 134 (100), 121 (27), 92 (10).

3',4'-Dimethoxyflavanone (5d). M.p. 123-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 7.46-7.53 (m, 1H), 6.97-7.07 (m, 4H), 6.90 (d, J = 7.9 Hz, 1H), 5.42 (dd, J_1 = 13.2 Hz, J_2 = 2.7 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.11 (dd, J_1 = 16.8 Hz, J_2 = 13.2 Hz, 1H), 2.87 (dd, J_1 = 16.8 Hz, J_2 = 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 161.6, 149.4, 149.3, 136.2, 131.2, 127.1, 121.6, 120.9, 118.8, 118.2, 111.1, 109.4, 79.6, 56.0 (overlapped O**C**H$_3$), 44.6; FT-IR (KBr) 3002, 2936, 1687 (C=O), 1607, 1464, 1266, 1141, 1027, 763 cm^{-1}; Ms *m/z* (%) 284 (M^+, 100), 283 (39), 253 (17), 164 (86), 151 (47), 121 (20).

7-Methoxyflavanone (5e). M.p. 89-90 °C (lit.[18] 90-91 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 1H), 7.38-7.50 (m, 5H), 6.62 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 2H), 5.47 (dd, J_1 = 13.2 Hz, J_2 = 3.0 Hz, 1H), 3.84 (s, 3H), 3.05 (dd, J_1 = 16.9 Hz, J_2 = 13.2 Hz, 1H), 2.83 (dd, J_1 = 16.9 Hz, J_2 = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 166.6, 163.9, 139.2, 129.3, 129.2, 126.6 (overlapped), 115.2, 110.7, 101.3, 80.4, 56.1, 44.7; FT-IR (KBr) 3014, 2970, 1679 (C=O), 1610, 1442, 1258, 1156, 746, 700 cm^{-1}; Ms *m/z* (%) 254 (M^+, 100), 253 (65), 177 (63), 150 (65), 122 (32), 77 (10).

4'-Chloro-7-methoxyflavanone (5f). M.p. 120-122 °C (lit.[17] 120-121 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 1H), 7.38-7.45 (m, 4H), 6.63 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 5.45 (dd, J_1 = 12.9 Hz, J_2 = 3.2 Hz, 1H), 3.84 (s, 3H), 2.99 (dd, J_1 = 16.8 Hz, J_2 = 12.9 Hz, 1H), 2.82 (dd, J_1 = 16.8 Hz, J_2 = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 166.6, 163.7, 137.7, 135.0, 129.4, 129.2, 127.9, 115.2, 110.8, 101.3, 79.6, 56.1, 44.6; FT-IR (KBr) 3021, 2967, 1682 (C=O), 1609, 1493, 1259, 1092, 828 cm^{-1}; Ms *m/z* (%) 290 (M^++2, 33), 289 (40), 288 (M^+, 100), 287 (64), 177 (63), 150 (84), 122 (42), 107 (22).

4',7-Dimethoxyflavanone (5g). M.p. 93-94 °C (lit.[18] 94-95 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 6.7 Hz, 2H), 6.96 (d, J = 6.7 Hz, 2H), 6.61 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 5.42 (dd, J_1 = 13.2 Hz, J_2 = 2.9 Hz, 1H), 3.83 (overlapped OC**H**$_3$, s, 6H), 3.06 (dd, J_1 = 16.9 Hz, J_2 = 13.2 Hz, 1H), 2.80 (dd, J_1 = 16.9 Hz, J_2 = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 166.6, 164.0, 160.4, 131.2, 129.1, 128.1, 115.2, 114.6, 110.6, 101.3, 80.2, 56.0, 55.8, 44.5; FT-IR (KBr) 3005, 2963, 1679 (C=O), 1610, 1444, 1257, 1159, 1027, 836 cm^{-1}; Ms *m/z* (%) 284 (M^+, 100), 283 (57), 177 (20), 134 (99), 121 (40), 91 (18).

6-Methoxyflavanone (5h). M.p. 142-143 °C (lit.[18] 140-142 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.50 (m, 5H), 7.36 (d, J = 3.1 Hz, 1H), 7.13 (dd, J_1 = 9.0 Hz, J_2 = 3.1 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 5.44 (dd, J_1 = 13.3 Hz, J_2 = 3.0 Hz, 1H), 3.82 (s, 3H), 3.07 (dd, J_1 = 17.0 Hz, J_2 = 13.3 Hz, 1H), 2.88 (dd, J_1 = 17.0 Hz, J_2 = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 156.7, 154.6, 139.2, 129.2, 129.1, 126.5, 125.8, 121.2, 119.8, 107.7, 80.1, 56.2, 45.0; FT-IR (KBr) 3010, 2960, 1674 (C=O), 1616, 1461, 1226, 1034, 769, 696 cm^{-1}; Ms *m/z* (%) 254 (M^+, 29), 253 (18), 177 (16), 150 (100), 107 (18).

4'-Chloro-6-methoxyflavanone (5i). M.p. 114-115 °C (lit.[17] 115-116 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.44 (m, 4H), 7.35 (d, J = 3.2 Hz, 1H), 7.13 (dd, J_1 = 9.0 Hz, J_2 = 3.2 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 5.42 (dd, J_1 = 13.0 Hz, J_2 = 3.2 Hz, 1H), 3.82 (s, 3H), 3.02 (dd, J_1 = 16.9 Hz, J_2 = 13.0 Hz, 1H), 2.86 (dd, J_1 = 16.9 Hz, J_2 = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 156.4, 154.7, 137.8, 134.9, 129.4, 127.9, 125.9, 121.1, 119.8, 107.8, 79.3, 56.2, 44.9; FT-IR (KBr) 3013, 2951, 1686 (C=O), 1615, 1489, 1280, 1034, 825, 689 cm^{-1}; Ms *m/z* (%) 290 (M^++2, 19), 288 (M^+, 57), 177 (9), 150 (100), 135 (8), 107 (17).

4',6-Dimethoxyflavanone (5j). M.p. 158-159 °C (lit.[18] 159-160 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 3.2 Hz, 1H), 7.11 (dd, J_1 = 9.0 Hz, J_2 = 3.2 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 5.38 (dd, J_1 = 13.3 Hz, J_2 = 2.9 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.08 (d, J_1 = 16.9 Hz, J_2 = 13.3 Hz, 1H), 2.84 (dd, J_1 = 16.9 Hz, J_2 = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 159.9, 156.4, 154.2, 130.9, 127.7, 125.4, 120.7, 119.4, 114.2, 107.3, 79.5, 55.8, 55.4, 44.4; FT-IR (KBr) 3007, 2970, 1679 (C=O), 1613, 1487, 1250, 1029, 830 cm^{-1}; Ms *m/z* (%) 284 (M^+, 100), 283 (18), 150 (81), 134 (91), 107 (13).

5-Methoxyflavanone (5k). M.p. 146-147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.46 (m, 6H), 6.66 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.43 (dd, J_1 = 13.1 Hz, J_2 = 3.0 Hz, 1H), 3.93 (s, 3H), 3.07 (dd, J_1 = 16.4 Hz, J_2 = 13.1 Hz, 1H), 2.85 (dd, J_1 = 16.4 Hz, J_2 = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 163.2, 160.8, 138.7, 136.0, 128.8, 128.7, 126.1, 111.4, 110.2, 104.0, 78.9, 56.2, 46.0; FT-IR (KBr) 3020, 2976, 1675 (C=O), 1599, 1460, 1252, 1089, 750, 691 cm^{-1}; Ms *m/z* (%) 254 (M^+, 57), 253 (44), 177 (30), 150 (100), 122 (31), 107 (39).

4',5-Dimethoxyflavanone (5l). M.p. 104-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.42 (m, 3H), 6.95 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.38 (dd, J_1 = 13.1 Hz, J_2 = 2.8 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.09 (dd, J_1 = 16.4 Hz, J_2 = 13.1 Hz, 1H), 2.82 (dd, J_1 = 16.4 Hz, J_2 = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 163.3, 160.8, 159.9, 136.0, 130.7, 127.7, 114.1, 111.3, 110.2, 104.0, 78.7, 56.2, 55.4, 45.8; FT-IR (KBr) 3065, 2939, 1672 (C=O), 1603, 1468, 1253, 1027, 828 cm^{-1}; Ms *m/z* (%) 284 (M^+, 51), 283 (52), 150 (28), 134 (100), 121 (20), 107 (21).

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