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SYNTHESIS OF *C*-RING HYDROXYLATED NEOFLAVONOIDS BY LIGAND COUPLING REACTIONS

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Abstract: Reaction of 4-trifluoromethanesulfonyloxycoumarin derivatives with benzyloxyphenylboronic acid derivatives under modified Suzuki reaction conditions afforded the corresponding neoflavones. Selective debenzylation took place in high yields when the palladium-catalysed hydrogenolysis was performed in the presence of acetic acid.

Neoflavonoids of the 4-arylcoumarin type have the largest distribution of the neoflavonoids. They are found in the *Guttiferae, Rubiaceae, Leguminosae, Passifloraceae,* and recently in the *Compositae*. Two main approaches have been devised for the synthesis of neoflavonoids: the von Pechmann synthesis and the ligand coupling reaction of the two aromatic units.[1] Ligand coupling reactions can

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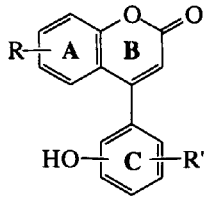
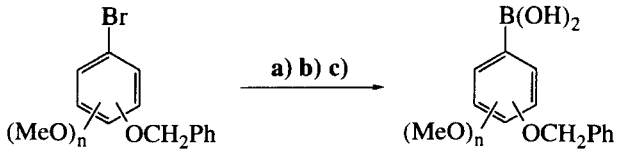
be performed either with main group heteroatomic derivative reagents[2] or by transition metal catalyzed oxidative addition-reductive elimination reactions.[3] We have reported two reactions allowing the ligand coupling synthesis of neoflavonoids: the C-4 arylation of 3-hydroxycoumarins with aryllead triacetates[4] and the C-4 arylation of 4-activated coumarins.[5] In this latter approach, 4-arylcoumarins can be easily obtained by the reaction of 4-trifluoromethanesulfonyloxycoumarins with arylboronic acids in the presence of a palladium catalyst, such as $Pd(PPh_3)_4$, and copper(I) iodide as a co-catalyst. Only simple substrates and reagents, not suitable for further elaboration, have been reported. However, the natural 4-arylcoumarins show a varied pattern of nuclear substitution and can be classified into three structural types: (*a*) compounds with hydroxyl or methoxyl substituents in ring A, (*b*) compounds with C- or O-isoprenoid substituents and cyclic variants in ring A, (*c*) compounds with hydroxyl and methoxyl functions in rings A and C. We have now extended this copper co-catalyzed modification of the Suzuki arylation reaction to prepare protected *C*-ring hydroxylated 4-arylcoumarins in good to high yields, which lead after chemoselective deprotection to *C*-ring hydroxylated 4-arylcoumarins.



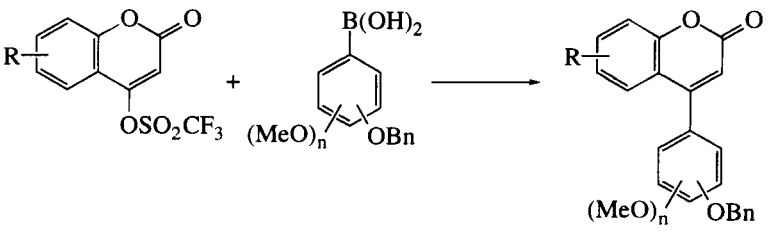
Among the various protecting groups suitable for our sequence of reactions, we selected the benzyl protecting group because of their stability under a variety of conditions, low cost and ease of formation.[6] Different benzyl derivatives of hydroxymethoxyphenyl boronic acids were selectively obtained by metallation of

the appropriate benzyloxyaryl bromides with butyllithium followed by reaction with triisopropylborate. After hydrolysis, the boronic acids are in general a mixture of boronic acid and of their boroxin. Therefore, the dried boronic acids containing the boroxin were not fully characterized, but used directly in the arylation reactions.



a) *n*-BuLi / THF / -78°C / 0.5 h **b)** (*i*-PrO)$_3$B, (1.2 equiv.) / -78°C / 2 h
c) H_2O / HCl / ether

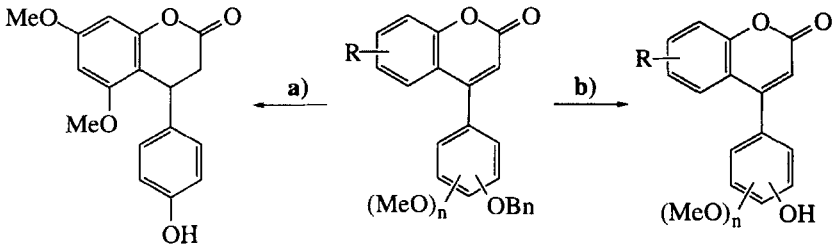
The required 4-trifluoromethanesulfonyloxycoumarins are easily prepared through reaction of the appropriate 4-hydroxycoumarins with trifluoromethanesulfonic anhydride in the presence of triethylamine in CH_2Cl_2 at 0°C.[5] Use of the benzyl-protected arylboronic acids in the Suzuki-type coupling reaction led under mild reaction conditions to high yields of the protected hydroxycoumarin derivatives (76-94% yields). The presence of a 5-methoxy substituent did not interfere with the overall yield.



Reaction conditions: $Pd(PPh_3)_4$ (0.05 equiv.), CuI (1 equiv.), Na_2CO_3 (7 equiv.), C_6H_6-EtOH, 76-94%

Numerous methods of selective deprotection of the benzyloxy groups are available. With our substrates, Lewis acid catalyzed reactions as well as oxidative

methods were unsuccessful for the removal of the benzyl groups. In the presence of the easily reduced pyranone system, palladium-catalyzed hydrogenation required carefully controlled conditions to lead to the phenolic compounds in good yields. The outcome of the catalytic hydrogenolysis of the benzyl-protected neoflavonoids appeared to be critically dependent upon the reaction conditions. Indeed, when the reaction was attempted with a 10% molar ratio of Pd/C to substrate in ethanol as the solvent, no reaction occurred even after 48 hours.



a) H_2 / Pd-C 10% / EtOH / 1atm / 15 h , 86%
b) H_2 / Pd-C 10% / THF-AcOH / 1atm / 40 h, 72-96%

It was only with a 80% molar ratio that the reaction went to completion, but it afforded only the overreduced 4-aryl-3,4-dihydro-2*H*-1-benzopyran-2-one in high yield (> 80%). However, the selective debenzylation was controlled by performing the palladium-catalyzed hydrogenation with a 10% molar ratio of Pd/C catalyst in THF in the presence of a small amount of acetic acid. In this way, various 4-(hydroxyphenyl)- and 4-(hydroxymethoxyphenyl)-coumarins were obtained in good to high yields (72-96%). It is worth underlining the remarkable influence of the pH on the outcome of these reductions. Indeed, Sajiki and Hirota have recently reported the completely reversed chemoselectivity when the reaction is performed in the presence of a nitrogen-containing base.[7] In their case, chemoselective reduction of styrene or cinnamic acid derivatives was obtained, the benzyloxy group remaining unaffected. In contrast, only the benzyloxy group

was hydrogenolysed in our system when the reaction was performed in the presence of acetic acid, and the 3,4-double bond remained intact.

Conclusion

The copper (I) iodide co-catalyzed Suzuki arylation reaction is compatible with benzyloxy protected phenol derivatives. It affords good yields of neoflavone derivatives. The selective debenzylation can be efficiently performed under acidic reaction conditions. Therefore, this methodology gives an easy and selective access to hydroxy containing neoflavonoids, and is a sequence which should be suitable for the synthesis of various combinations of *A*- and/or *C*-ring hydroxy containing neoflavone structures.

Experimental

For the general procedures, see previous papers.[5]

Preparation of Arylboronic Acids

The arylboronic acids were prepared by reaction of the appropriate aryllithium on triisopropylborate following the procedure of Thompson and Gaudino.[8]

4-Benzyloxyphenyl boronic acid: 89% from benzyl(4-bromophenyl)ether,[9] m.p. 189-194 °C; δ_H (270 MHz, DMSO-d_6) 7.78 (2H, d, *J* 8.61, 2-H and 6-H), 7.36-7.48 (5H, m, Bn-H), 6.99 (2H, d, *J* 8.61, 3-H, 5-H) and 5.10 (2H, s, CH_2).

4-Benzyloxy-3-methoxyphenyl boronic acid: 91% from 4-benzyloxy-3-methoxybromobenzene,[10] m.p. 198-203°C; δ_H (270 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 5.07 (2H, s, CH_2), 6.95 (1H, d, *J* 8.1, 4-H) and 7.22-7.40 (7H, m, 2-H, 6-H and Bn-H).

3-Benzyloxy-4-methoxyphenyl boronic acid: 92% from 4-methoxy-3-benzyloxybromobenzene,[10] m.p. 134-138°C; δ_H (270 MHz, $CDCl_3$) 3.96 (3H, s,

4-OCH_3), 5.14 (2H, s, CH_2), 6.98 (1H, d, *J* 8.8, 5-H) and 7.53 (7H, m, 2-H, 6-H, Bn-H).

Coupling of 4-trifluoromethanesulfonyloxycoumarins with arylboronic acids

General procedure - A mixture of 4-trifluoromethanesulfonyloxycoumarin (1 equiv.), tetrakis(triphenylphosphane)palladium (0) (0.04 equiv.), copper (I) iodide (1.1 equiv.), sodium carbonate (7 equiv.) and dry benzene (10 mL) was stirred for 30 minutes under N_2 and a solution of the arylboronic acid (3 equiv.) in dry ethanol (3 mL) was added. The reaction was heated under reflux for 20 h, cooled and hydrogen peroxide (1 mL of an aqueous 30 % w/v solution) was added to oxidise the unreacted boronic acid. The mixture was diluted with chloroform (40 mL), washed with water (3 x 40 mL), saturated aqueous sodium bicarbonate solution (3 x 40 mL) and the aqueous layers were re-extracted with chloroform (3 x 40 mL). The combined organic layers were dried ($MgSO_4$), and then concentrated to dryness under reduced pressure. The residue was purified by preparative layer chromatography (PLC) to afford the product.

4'-Benzyloxy-4-phenyl-2*H*-1-benzopyran-2-one: PLC eluant: CH_2Cl_2; yield 84% as needles from ethanol/water, m.p. 139-141°C; ν_{max} (KBr)/cm^{-1} 1709, 1603, 1244 and 1018; δ_H (270 MHz, $CDCl_3$) 5.14 (2H, s, CH_2), 6.35 (1H, s, 3-H), 7.12 (2H, d, *J* 8.8, 3'-H and 5'-H), 7.26-7.21 (1H, m, 6-H) and 7.35-7.58 (10H, m, 8-H, 7-H, 5-H, 2'-H, 6'-H and Bn-H); δ_C (67.80 MHz, $CDCl_3$) 70.20 (CH_2), 114.63 (C-3), 115.22 (C-3' and C-5'), 117.40 (C-8), 119.11 (C-10), 124.17 (C-6), 127.08 (C-5), 127.68 (C-2" and C-6"), 128.35 (C-1'), 128.26 (C-4"), 128.77 (C-3" and C-5"), 130.05 (C-2' and C-6'), 131.91 (C-7), 136.45 (C-1"), 154.22 (C-9), 155.39 (C-4), 160.05 (C-2) and 161.09 (C-4'); *m/z* 329 (M+1, 4), 328 (M^+, 7), 152 (5), 91 (100), 77 (4), 65 (11) and 28 (6) (Found: C, 80.10; H, 4.95. $C_{22}H_{16}O_3$ requires: C, 80.39; H, 4.91%).

4'-Benzyloxy-5-methoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: CH_2Cl_2; yield 84% as needles from ethanol/water, m.p. 160-162°C; ν_{max} (KBr)/cm^{-1} 1708, 1599, 1478, 1090 and 799; δ_H (270 MHz, $CDCl_3$) 3.49 (3H, s, 5-OCH_3), 5.13 (2H, s, CH_2), 6.16 (1H, s, 3-H), 6.68 (1H, dd, *J* 0.9 and 8.3, 6-H), 6.99 (2H, d, *J* 8.8, 3'-H and 5'-H), 7.03 (1H, dd, *J* 0.9 and 8.3, 8-H), 7.22 (2H, d, *J* 8.8 2'-H and 6'-H) and 7.31-7.49 (6H, m, 7-H and Bn-H); δ_C (67.80 MHz, $CDCl_3$) 55.63 (5-OMe), 70.10 (CH_2), 106.69 (C-8), 109.10 (C-10), 110.04 (C-6), 113.79 (C-3), 115.88 (C-3' and C-5'), 127.60 (C-2" and C-6"), 128.16 (C-4"), 128.28 (C-1'), 128.73 (C-3" and C-5"), 128.73 (C-2' and C-6'), 132.29 (C-7), 136.78 (C-1"), 155.16 (C-9), 155.52 (C-4), 157.39 (C-5), 158.81 (C-2) and 160.68 (C-4'); *m/z* 359 (M+1, 2), 358 (M^+, 7), 91 (100), 65 (10) and 28 (10) (Found: C, 76.67; H, 5.02. $C_{23}H_{18}O_4$ requires: C, 77.01; H, 5.06%).

4'-Benzyloxy-7-methoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: $CHCl_3$-CH_3OH 99:1; yield 84% as plates from ethanol/water, m.p. 192-195°C; ν_{max} (KBr)/cm^{-1} 1729, 1614, 1216 and 819; δ_H (270 MHz, $CDCl_3$) 3.86 (3H, s, 7-OCH_3), 5.13 (2H, s, CH_2), 6.23 (1H, s, 3-H), 6.65 (1H, dd, *J* 8.8 and 2.4, 6-H), 6.77 (1H, d, *J* 2.4, 8-H), 6.85 (1H, d, *J* 8.8, 5-H), 7.0 (2H, d, *J* 8.8, 3'-H and 5'-H), 7.16 (2H, d, J 8.6 Hz, 2'-H and 6'-H) and 7.35-7.44 (5H, m, Bn-H); δ_C (67.80 MHz, $CDCl_3$) 55.80 (7-OMe), 70.14 (CH_2), 10.29 (C-8), 111.91 (C-6), 114.74 (C-3), 114.92 (C-3' and C-5'), 121.04 (C-10), 128.08 (C-1'), 128.20 (C-5), 128.79 (C-2" and C-6"), 128.90 (C-4"), 129.34 (C-3" and C-5"), 130.81 (C-2' and C-6'), 136.74 (C-1"), 151.44 (C-9), 154.16 (C-4), 158.83 (C-2), 161.05 (C-4') and 161.71 (C-7); *m/z* 358 (M^+, 7), 91 (100), 65 (10) and 28 (50) (Found: C, 77.30; H, 5.06. $C_{23}H_{18}O_4$ requires: C, 77.01; H, 5.06%).

4'-Benzyloxy-5,7-dimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant:

CH_2Cl_2; yield 83% as needles from ethanol/water, m.p. 169-171°C; lit.,[11] m.p. 168-169°C.

4'-Benzyloxy-7,8-dimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: $CHCl_3$-CH_3OH 99:1; yield 91% as needles from ethanol-water, m.p. 138-140°C; ν_{max} (KBr)/cm^{-1} 1725, 1599, 1241, 1100 and 802; δ_H (270 MHz, $CDCl_3$) 3.94 (3H, s, 7-OCH_3), 4.01 (3H, s, 8-OCH_3), 5.14 (2H, s, CH_2), 6.19 (1H, s, 3-H), 6.83 (1H, d, *J* 8.9, 6-H), 7.10 (2H, d, *J* 8.9, 3'-H and 5'-H), 7.25 (1H, d, *J* 8.9, 5-H) and 7.35-7.48 (7H, m, 2'-H, 6'-H and Bn-H); δ_C (67.80 MHz, $CDCl_3$) 56.36 (7-OMe), 61.54 (8-OMe), 70.16 (CH_2), 107.91 (C-3), 111.83 (C-6), 113.90 (C-10), 115.10 (C-3' and C-5'), 122.19 (C-5), 128.17 (C-2" and C-6"), 128.71 (C-1'), 128.90 (C-4"), 129.39 (C-3" and C-5"), 130.59 (C-2' and C-6'), 131.69 (C-8), 136.43 (C-1"), 148.40 (C-9), 155.39 (C-4), 155.55 (C-7), 159.93 (C-2) and 160.77 (C-4'); *m/z* 389 (M+1, 1), 388 (M^+, 6), 300 (4), 257 (7), 91 (67), 32 (39) and 28 (100) (Found: C, 74.14; H, 5.23. $C_{24}H_{20}O_5$ requires: C, 74.21; H, 5.18%).

4'-Benzyloxy-3'-methoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: CH_2Cl_2; yield 76% as needles from ethanol-water, m.p. 185-187°C; ν_{max} (KBr)/cm^{-1} 1730, 1608, 1460, 1147, 1011 and 749; δ_H (270 MHz, $CDCl_3$) 3.92 (3H, s, 3'-OCH_3), 5.24 (2H, s, CH_2), 6.36 (1H, s, 3-H) and 6.95-7.61 (12H, m, 5-H, 6-H, 7-H, 8-H, 2'-H, 5'-H, 6'-H and Bn-H); δ_C (67.80 MHz, $CDCl_3$) 56.28 (3'-OMe), 71.01 (CH_2), 112.01 (C-2'), 113.59 (C-5'), 114.76 (C-3), 117.76 (C-8), 119.11 (C-10), 121.32 (C-6'), 124.19 (C-6), 127.65 (C-5), 127.87 (C-2" and C-6"), 128.69 (C-4" and C-1'), 129.33 (C-3" and C-5"), 131.91 (C-7), 136.64 (C-1"), 149.48 (C-3'), 149.74 (C-4'), 154.26 (C-9), 155.46 (C-4) and 160.99 (C-2); *m/z* 358 (M^+, 4), 91 (100), 65 (7) and 28 (9) (Found: C, 76.83; H, 5.16. $C_{23}H_{18}O_4$ requires: C, 77.01; H, 5.06%).

4'-Benzyloxy-3',5,7-trimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: $CHCl_3$-C_2H_5OH 99:1; yield 94% as an amorphous powder from ethanol-water, m.p. 155-157°C; lit.,[11] m.p. 157-158°C.

3'-Benzyloxy-4',5,7-trimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: PLC eluant: $CHCl_3$; 91% as needles from chloroform/methanol, m.p. 100-102°C; ν_{max} (KBr)/cm^{-1} 1723, 1592, 1512, 1226 and 1109; δ_H (270 MHz, $CDCl_3$) 3.22 (3H, s, 5-OCH_3), 3.84 (3H, s, 4'-OCH_3), 3.94 (3H, s, 7-OCH_3), 5.12 (2H, s, CH_2), 5.94 (1H, s, 3-H), 6.18 (1H, d, *J* 2.4, 6-H), 6.48 (1H, d, *J* 2.4, 8-H), 6.85 (1H, m, 2'-H, 6'-H), 6.87 (1H, d, *J* 8.2, 5'-H) and 7.26-7.45 (5H, m, Bn-H); δ_C (67.80 MHz, $CDCl_3$) 55.3 (5-OMe), 55.8 (7-OMe), 56.1 (4'-OMe), 71 (CH_2), 93.31 (C-8), 95.66 (C-6), 103.5 (C-10), 110.6 (C-2'), 112.4 (C-5'), 113.8 (C-3), 120 (C-6'), 127.7 (C-2" and C-6"), 128.1 (C-4"), 128.5 (C-3" and C-5"), 132.3 (C-1'), 137 (C-1"), 146.6 (C-3'), 149.7 (C-4'), 155.3 (C-4), 157 (C-9), 158.1 (C-5), 160.9 (C-2) and 163.2 (C-7); *m/z* 418 (M^+, 3), 328 (6), 91 (100) and 28 (14) (Found: C, 71.46; H, 5.43. $C_{25}H_{22}O_6$ requires: C, 71.69; H, 5.29%).

4'-Hydroxy-5,7-dimethoxy-4-phenyl-3,4-dihydro-*2H*-1-benzopyran-2-one: To 4'-benzyloxy-5,7-dimethoxy-4-phenyl-*2H*-1-benzopyran-2-one (0.040 g, 0.11 mmol) in dry ethanol (10 mL) was added 10% palladium on carbon (0.030 g). The mixture was stirred under an hydrogen atmosphere at atmospheric pressure for 14 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Recrystallisation of the residue from methanol gave 4'-hydroxy-5,7-dimethoxy-4-phenyl-3,4-dihydro-*2H*-1-benzopyran-2-one (0.025 g, 86%) as needles, m.p. 206-208°C; ν_{max} (KBr)/cm^{-1} 3386, 1742, 1594, 1503, 1143 and 834; δ_H (270 MHz, CD_3COCD_3) 2.95 (1H, t, *J* 6, 4-H), 3.76 (3H, s, 5-OCH_3), 3.82 (3H, s, 7-OCH_3), 4.49 (2H, d, *J* 6, 3-H), 6.31 (1H, d, *J* 2.4, 6-H), 6.39 (1H, d, *J* 2.4 8-H), 6.71 (2H, d, *J* 8.6, 3'-H and 5'-H), 6.91 (2H, d, *J* 8.6, 2'-H and 6'-H)

and 8.30 (1H, br. s, 4'-OH); δ_C (67.80 MHz, CD_3COCD_3): 34.38 (C-3), 37.98 (C-4), 55.86 (5-OMe), 56.18 (7-OMe), 94.64 (C-8), 95.47 (C-6), 107.35 (C-10), 116.19 (C-3' and C-5'), 128.56 (C-2' and C-6'), 133.66 (C-1'), 154.11 (C-9), 157.15 (C-4'), 158.37 (C-5), 161.62 (C-2) and 167.89 (C-7); *m/z* 301 (M+1, 6), 300 (M^+, 44), 285 (3), 272 (20), 259 (100), 241 (1), 207 (20), 181 (27), 153 (74), 115 (21), 107 (60), 69 (30) and 28 (34) (Found: C, 67.75; H, 5.43. $C_{17}H_{16}O_5$ requires: C, 67.99; H, 5.37%).

General procedure for removal of the benzyl group: The substrate to be reduced was dissolved in a mixture of dry THF (10 mL) and acetic acid (0.25 mL). 10 % Palladium (Pd) on carbon (25% equiv. of weight of substrate) was added and the mixture shaken under an hydrogen atmosphere at atmospheric pressure for the required time using a Parr low pressure hydrogenator. The reaction mixture was then filtered and the solvent distilled. The residue was purified by PLC (eluant: $CHCl_3$-CH_3OH 99:1) to yield the product.

4'-Hydroxy-5,7-dimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: yield 80% as needles from methanol, m.p. 210-213°C; lit.,[12] m.p. 214-215°C.

4'-Hydroxy-7,8-dimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: yield 96% as needles from methanol, m.p. 212-215°C; ν_{max} (KBr)/cm^{-1} 3421, 1690, 1601, 1373, 1100, 811; δ_H (270 MHz, CD_3COCD_3) 3.92 (3H, s, 7-OCH_3), 3.96 (3H, s, 8-OCH_3), 6.11 (1H, s, 3-H), 6.99 (3H, d, *J* 8.8, 3'-H, 5'-H and 6-H), 7.35 (2H, d, *J* 8.8, 5-H), 7.37 (2H, d, *J* 8.8, 2'-H and 6'-H) and 7.91 (1H, br s, ex. D_2O, 4'-OH); δ_C (67.80 MHz, CD_3COCD_3) 56.52 (7-OMe), 61.12 (8-OMe), 108.79 (C-3), 111.62 (C-6), 114.25 (C-10), 116.23 (C-3' and C-5'), 122.85 (C-5), 128.32 (C-2' and C-6'), 130.56 (C-1'), 138.60 (C-8), 148.20 (C-9), 155.50 (C-4), 155.80 (C-7), 159.43 (C-4') and 160.53 (C-2); *m/z* 299 (M+1, 9), 298 (M^+, 57), 283 (9), 270

(15), 255 (28), 227 (5), 212 (6), 199 (12), 184 (10), 171 (17), 155 (14), 128 (11), 69 (15) and 28 (100) (Found: C, 68.14; H, 4.73. $C_{17}H_{14}O_5$ requires: C, 68.45; H, 4.73%).

4'-Hydroxy-3',5,7-trimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: yield 78% as plates from ether, m.p. 172-173°C; lit.,[12] m.p. 173-174°C).

3'-Hydroxy-4',5,7-trimethoxy-4-phenyl-*2H*-1-benzopyran-2-one: yield 72% as plates from ethanol, m.p. 153-155°C; lit.,[12] m.p. 153-154°C).

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