An Improved Synthesis of the Anti-Picornavirus Flavone 3-O-Methylquercetin

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Summary

Two optimised procedures to synthesise 3-*O*-methylquercetin (**1**), an important antivirally active flavone, are presented: one is based on an Allan-Robinson condensation, the other one on a modified phase transfer catalysed Baker-Venkataraman transformation.

Introduction

In the last decade, several 3-methoxyflavones isolated from different *Euphorbia* sp., were found to be highly active against a wide range of human picornaviruses, such as poliomyelitis-, coxsackie-, and rhinoviruses[1–3]. In this series, 3-*O*-methylquercetin (**1**) (3-*O*-MQ; 3′,4′,5,7-tetrahydroxy-3-methoxyflavone) was chosen as a natural prototype with promising properties. Its antiviral activity was not only very pronounced in infected tissue culture cells, but the effect was also very stable. When administered intraperitoneally to mice, **1** protected the animals against lethal infections of coxsackie B_4, but no signs of toxicity or death were observed in uninfected control mice that were treated with five times the level of **1** used to treat infected mice[1].

The attractive mechanism of action[4–7], the pronounced and broad antiviral activity and the lack of resistance induction make 3-*O*-MQ (**1**) a good antiviral candidate against picornaviruses. In order to study in detail its toxicity and bioavailability in animals it is necessary to obtain **1** in sufficiently large amounts. This prompted us to pursue an efficient and high yield synthetic route for this compound.

Although 3-*O*-MQ (**1**) has been synthesised earlier [8–11], only low to moderate yields could be obtained. In this note an optimised synthesis of the starting materials and two high yield methods for the synthesis of **1** are given. In method A, **1** is synthesised via an Allan-Robinson reaction, in method B via a modified phase transfer catalysed Baker-Venkataraman transformation. Both methods are described in detail and compared with each other.

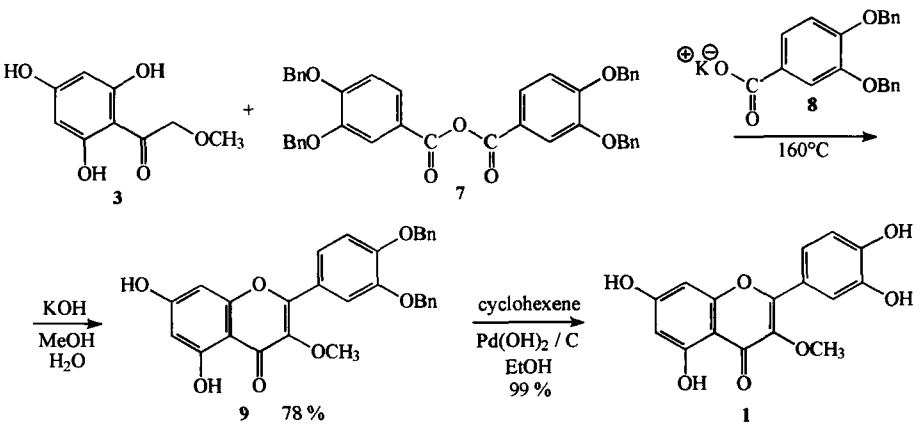
Results and Discussion

Starting materials

2′,4′,6′-Trihydroxy-2-methoxyacetophenone (**3**) was synthesised by a Houben-Hoesch reaction[12,13] from phloroglucinol (**2**) and methoxyacetonitrile. Oxidation of 3,4-dibenzyloxybenzaldehyde (**4**) with potassium permanganate in acetone-water (10:1) gives 3,4-dibenzyloxybenzoic acid (**5**). For the synthesis of 3,4-dibenzyloxybenzoyl chloride (**6**) from **5**, thionyl chloride was used in the presence of a catalytic amount of *N,N*-dimethylformamide[14], resulting in a considerably higher yield (98%) than that reported by Pacheco (67%)[8]. 3,4-Dibenzyloxybenzoic anhydride (**7**) was synthesised from **5** and **6** in an ether-pyridine mixture[8].

Method A

Our first method for the synthesis of 3-*O*-MQ (**1**) is based on the Allan-Robinson strategy[15] (Scheme 1). 3′,4′-Di-*O*-benzyl-3-*O*-methylquercetin (**9**) is synthesised by an Allan-Robinson condensation. In this reaction 2′,4′,6′-trihydroxy-2-methoxyacetophenone (**3**) and 3,4-dibenzyloxybenzoic anhydride (**7**) are heated under reduced pressure, in the presence of potassium 3,4-dibenzyloxybenzoate (**8**) as an alkaline catalyst. A strongly increased yield (30%→78%) is obtained by modifying the alkaline solvolysis and the purifi-



Scheme 1: Allan-Robinson condensation.

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cation of the reaction mixture described in the literature[8]. During the solvolysis with KOH in methanol a considerable amount of methyl 3,4-dibenzyloxybenzoate is formed, which is laborious to separate from the flavone **9**. By adding a small amount of water to the solvolysis mixture only potassium 3,4-dibenzyloxybenzoate is formed. The flavone **9** can now easily be purified by washing with a $NaHCO_3$-solution and recrystallisation from ethanol.

For the synthesis of 3-*O*-MQ (**1**), the benzyl groups are removed by catalytic transfer hydrogenolysis, using cyclohexene and $Pd(OH)_2$ in ethanol[16]. TLC analysis revealed completion of the debenzylation within 1 minute. This method, giving almost 100% yield, is far superior to the standard debenzylation methods used in flavonoid chemistry such as acid hydrolysis with HCl in acetic acid[8], hydrogenolysis with $H_2/Pd/C$[17], or BBr_3 in CH_2Cl_2[18]. In our case, all these methods give side-products and result in lower yields (70–90%) of 3-*O*-MQ (**1**).

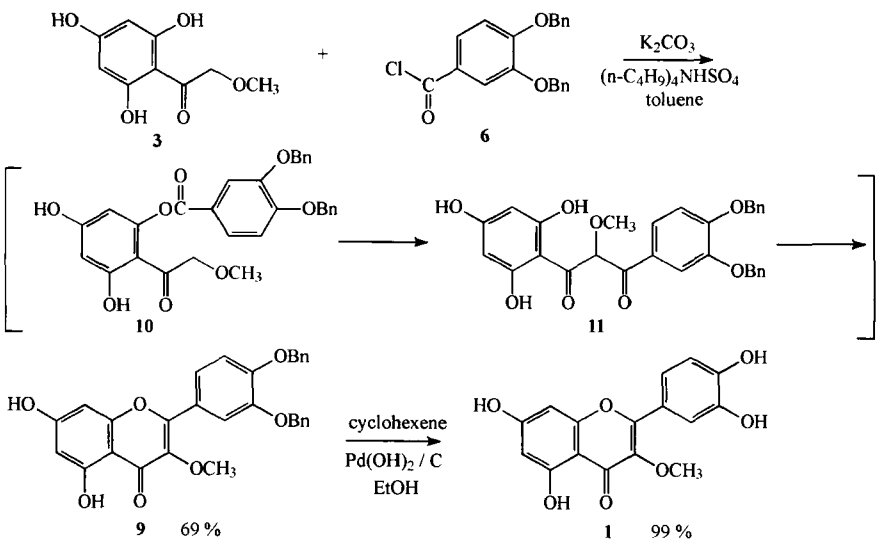
The overall yield of our method A is 78%, which is considerably higher than the yields given in the literature. Pacheco[8] mentions 30% for the Allan-Robinson condensation and gives no yield for the acidic debenzylation step. Kuhn and Löw[9] using benzoylated instead of benzylated anhydride **7**, obtain free 3-*O*-MQ (**1**) immediately from the Allan-Robinson condensation in 28% yield.

Method B

The Baker-Venkataraman method normally consists of three distinct steps: benzoylation of the acetophenone **3**, base-catalysed rearrangement of the benzoylated acetophenone **10** to the 1,3-diketone **11**, and cyclodehydration to the flavone **9**. In our method B these three reaction steps are executed all at once.

We examined a classic Baker-Venkataraman synthesis[10,19,20], usually employed for 3-unsubstituted flavones, but this reaction resulted only in very low yields. Also a phase transfer catalysed Baker-Venkataraman transformation[21,22] was unsuccessful due to an increased hydrolysis of the acid chloride. Therefore we modified the reported procedure[22] by using solid potassium carbonate as the base in a solution of acetophenone **3**, 3,4-dibenzyloxybenzoyl chloride (**6**) and the phase transfer catalyst tetrabutylammonium hydrogen sulphate in toluene (Scheme 2). This reaction gives immediately the 3′,4′-di-*O*-benzyl-3-*O*-methylquercetin (**9**), partially benzoylated at C_7. The compounds **10** and **11** are not isolated. The partially benzoylated product is refluxed in a 5% K_2CO_3-solution giving the free flavone **9** in a reasonable yield (69%). The benzylated B-ring is now deprotected by catalytic transfer hydrogenolysis as in method A.

Although the modified phase transfer catalysed Baker-Venkataraman transformation has a lower yield (69%) than the Allan-Robinson reaction (78%), it has an important advantage. Method B needs less than 30% of the amount of acid **5**, needed in method A, since the synthesis of anhydride **7** (60%) can be avoided and since only half of the anhydride molecule is used in the Allan-Robinson condensation reaction.



Scheme 2: Modified phase transfer catalysed Baker-Venkataraman transformation.

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Experimental

Melting points were determined on a Tottoli apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 400 Spectrometer, IR spectra on a Perkin Elmer 580 apparatus and DCI mass spectra on a Ribermag R10-10B quadrupole mass spectrometer. Ammonia (0.1 mm Hg) was used as reagent gas. CC was performed on Kieselgel 60 (Merck), 0.040–0.063 mm (230–400 mesh).

2′,4′,6′-Trihydroxy-2-methoxyacetophenone (**3**)

Anhydrous phloroglucinol (**2**)(6.3 g, 50 mmol) was dissolved in dry ether (60 ml). Anhydrous $ZnCl_2$ (1.8 g, 13 mmol) and methoxyacetonitrile (3.7 ml, 50 mmol) were added. The flask was placed in an ice-bath. Anhydrous HCl gas was bubbled through the solution for 2 h under stirring. The ketimine hydrochloride which precipitated from the solution was filtered off, washed twice with a small amount of dry ether, dissolved in water and refluxed for 30 min. After cooling a pink crystalline product precipitated which was recrystallised from water. Yield: 80%. mp 192–194 °C (ref.[23] 192 °C).– 1H-NMR (CD_3COCD_3) δ: 5.92 (s, 2H, $H_{3',5'}$), 4.64 (s, 2H, -CH_2-), 3.40 (s, 3H, -OCH_3).– ^{13}C-NMR (CD_3COCD_3) δ: 202.32 (C_1), 165.77 ($C_{4'}$), 165.16 ($C_{2',6'}$), 105.76 ($C_{1'}$), 95.78($C_{3',5'}$), 78.23 (-CH_2-), 59.16 (-OCH_3).– DCI-MS (NH_3): *m/z* = 153 ($[ArCO]^+$), *m/z* = 199 ($[MH]^+$), *m/z* = 216 ($[MNH_4]^+$).

3,4-Dibenzyloxybenzoic acid (**5**)

A mixture of 3,4-dibenzyloxybenzaldehyde (**4**)(10.0 g, 32 mmol), $KMnO_4$ (7.4 g, 47 mmol), acetone (800 ml) and H_2O (80 ml), was refluxed with stirring for 6.5 h. The brown mixture was evaporated to dryness under reduced pressure and the residue was treated with a 1% Na_2CO_3-solution (1600 ml). This mixture was warmed and filtered on a steam filter. The brown residue was washed with warm water (600 ml). The filtrate and wash fractions were combined and acidified with a 5M HCl solution. The white precipitate

was filtered off, washed with water, dried in vacuo and recrystallised from ethanol. Yield: 93%. mp 183–184 °C (ref.[8] 185 °C).– ^{1}H-NMR ($CDCl_3$) δ: 7.63 (dd, *J* = 8.54 Hz 2.14 Hz, 1H, H_6), 7.61 (d, *J* = 2.14 Hz, 1H, H_2), 7.37 (m, 4H, $H_{2',2'',6',6''}$), 7.29 (m, 4H, $H_{3',3'',5',5''}$), 7.25 (m, 2H, $H_{4',4''}$), 6.87 (d, *J* = 8.55 Hz, 1H, H_5), 5.16 (s, 2H, -OCH_2''-), 5.12 (s, 2H, -OCH_2'-).– ^{13}C-NMR (DMSO-d_6) δ: 166.94 (C=O), 152.14 (C_4), 147.69 (C_3), 137.03 ($C_{1'}$), 136.73 ($C_{1''}$), 128.38 ($C_{3',3'',5',5''}$), 127.77 ($C_{4',4''}$), 127.41 ($C_{2',2'',6',6''}$), 123.57 ($C_{1,6}$), 114.92 (C_2), 113.27 (C_5), 70.20 (-O*C*H$_2$'-), 70.02 (-O*C*H$_2$''-).– DCI-MS (NH_3): *m/z* = 352 ([MNH_4]$^+$).– IR (C=O): 1685 cm^{-1}.

3,4-Dibenzyloxybenzoyl chloride (**6**)

3,4-Dibenzyloxybenzoic acid (**5**) (17.0 g, 51 mmol) was dissolved in thionyl chloride (200 ml). DMF (2.1 ml, 28 mmol) was added and the solution was stirred and refluxed for 6 h. The solvent was removed under reduced pressure and the reaction product was dried in vacuo. Yield: 98%. mp 91–93 °C (ref.[8] 96 °C).– ^{1}H-NMR ($CDCl_3$) δ: 7.68 (dd, *J* = 8.54 Hz 2.13 Hz, 1H, H_6), 7.56 (d, *J* = 2.14 Hz, 1H, H_2), 7.37 (m, 4H, $H_{2',2'',6',6''}$), 7.30 (m, 4H, $H_{3',3'',5',5''}$), 7.26 (m, 2H, $H_{4',4''}$), 6.89 (d, *J* = 8.55 Hz, 1H, H_5), 5.19 (s, 2H, -OCH_2''-), 5.12 (s, 2H, -OCH_2'-).– ^{13}C-NMR (DMSO-d_6) δ: 166.88 (*C*=O), 152.14 (C_4), 147.69 (C_3), 137.03 ($C_{1'}$), 136.73 ($C1''$), 128.38 ($C_{3',3'',5',5''}$), 127.77 ($C_{4',4''}$), 127.41 ($C_{2',2'',6',6''}$), 123.51 (C_1), 123.39 (C_6), 114.80 (C_2), 113.21 (C_5), 70.14 (-O*C*H$_2$'-), 69.96 (-O*C*H$_2$''-).– DCI-MS (NH_3): *m/z* = 317 ([ArCO]$^+$), *m/z* = 370,372 ([MNH_4]$^+$).– IR (C=O): 1742 cm^{-1}.

3,4-Dibenzyloxybenzoic anhydride (**7**)

3,4-Dibenzyloxybenzoic acid (**5**) (11.50 g, 34.4 mmol) and 3,4-dibenzyloxybenzoyl chloride (**6**)(12.13 g, 34.4 mmol) were dissolved in dry ether (800 ml). Anhydrous pyridine (25 ml) was added. The solution was stirred for 24 h at 0 °C. The reaction mixture was poured in ice water (2100 ml). The precipitated anhydride was filtered off and washed with cold solutions of 0.1M HCl, 0.1M Na_2CO_3 and water. The product was recrystallised from anhydrous ethyl acetate. Yield: 60%. mp 128 °C (ref.[8] 129 °C).– ^{1}H-NMR ($CDCl_3$) δ: 7.69 (dd, *J* = 8.55 Hz 2.14 Hz, 1H, H_6), 7.66 (d, *J* = 2.13 Hz, 1H, H_2), 7.45 (m, 4H, $H_{2',2'',6',6''}$), 7.37 (m, 4H, $H_{3',3'',5',5''}$), 7.32 (m, 2H, $H_{4',4''}$), 7.25 (d, *J* = 8.54 Hz, 1H, H_5), 5.24 (s, 2H, -OCH_2''-), 5.18 (s, 2H, -OCH_2'-).– ^{13}C-NMR ($CDCl_3$) δ: 162.10 (*C*=O), 153.91 (C_4), 148.06 (C_3), 136.73 ($C_{1'}$), 136.36 ($C_{1''}$), 128.38 ($C_{3',3'',5',5''}$), 127.96 ($C_{4',4''}$), 127.83 ($C_{2',2''',6',6''}$), 127.47 (C_1), 120.34 (C_6), 115.16 (C_2), 113.40 (C_5), 70.20 (-O*C*H$_2$'-, -O*C*H$_2$''-).– DCI-MS (NH_3): *m/z* = 651 ([MH]$^+$), *m/z* = 668 ([MNH_4]$^+$).– IR (C=O): 1754 cm^{-1} (asym), 1718 cm^{-1} (sym).

3',4'-Di-O-benzyl-3-O-methylquercetin (**9**)

Method A: A mixture of finely pulverised 2',4',6'-trihydroxy-2-methoxyacetophenone (**3**) (0.71 g, 3.6 mmol), 3,4-dibenzyloxybenzoic anhydride (**7**) (4.4 g, 6.8 mmol) and potassium 3,4-dibenzyloxybenzoate (**8**) (0.71 g, 1.9 mmol) was heated for 8 h at 160 °C under reduced pressure. The reaction mixture was dissolved in a mixture of MeOH (185 ml) and H_2O (20 ml). A solution of KOH (4.2 g) in MeOH (20 ml) and H_2O (4 ml) was added, and the resulting solution was refluxed for 30 min. Again 20 ml of water was added, and the mixture was further refluxed for 15 min. The solution was filtered and the precipitate was refluxed again with a KOH-H_2O-MeOH solution as before. The solution was filtered, the filtrates were combined and the solvent was removed under reduced pressure. The residue was dissolved in a 4% $NaHCO_3$-solution (700 ml). This solution was stirred and refluxed for 30 min. After cooling the solution was filtered and the residue was washed with a warm 4% $NaHCO_3$-solution and with warm water. After drying under reduced pressure the residue was recrystallised from anhydrous ethanol. (Purification can also be done by CC with CH_2Cl_2-MeOH (98:2), but is much more laborious.) Yield: 78% (the use of an equivalent amount of the anhydride results in a slightly lower yield). mp 184–185 °C (ref.[8] 180 °C).– ^{1}H-NMR (DMSO-d_6) δ: 7.72 (d, *J* = 2.13 Hz, 1H, $H_{2'}$), 7.65 (dd, *J* = 8.54 Hz 2.14 Hz, 1H, $H_{6'}$), 7.47 (m, 4H, $H_{2'',2''',6'',6'''}$), 7.42 (m, 4H, $H_{3'',3''',5'',5'''}$), 7.34 (m, 2H, $H_{4'',4'''}$), 7.24 (d, *J* = 8.85 Hz, 1H, $H_{5'}$), 6.46 (d, *J* = 1.99 Hz, 1H, H_8), 6.22 (d, *J* = 1.98 Hz, 1H, H_6), 5.26 (s, 2H, -OCH_2'''-), 5.24 (s, 2H, -OCH_2''), 3.71 (s, 3H, -OCH_3).– ^{13}C-NMR (DMSO-d_6) δ: 177.78 (C_4), 164.13 (C_7), 161.14 (C_5), 156.26 (C_9), 154.67 (C_2), 150.64 ($C_{4'}$), 147.64 ($C_{3'}$), 138.02 (C_3), 136.96 ($C_{1''}$), 136.66 ($C_{1'''}$), 128.33 ($C_{3'',3''',5'',5'''}$), 127.80 ($C_{4'',4'''}$), 127.46 ($C_{2'',2''',6'',6'''}$), 122.46 ($C_{1'}$), 122.13 ($C_{6'}$), 114.15 ($C_{5'}$), 113.70 ($C_{2'}$), 104.19 (C_{10}), 98.54 (C_6), 93.72 (C_8), 70.22 (-O*C*H$_2$''-), 69.90 (-O*C*H$_2$'''-), 59.59 (-O*C*H$_3$).– DCI-MS (NH_3): *m/z* = 497 ([MH]$^+$).

3',4'-Di-O-benzyl-3-O-methylquercetin (**9**)

Method B: 2',4',6'-Trihydroxy-2-methoxyacetophenone (**3**) (0.4 g, 2.0 mmol), finely powdered anhydrous K_2CO_3 (1.68 g, 12 mmol), tetrabutylammonium hydrogen sulphate (1.02 g, 3.0 mmol), 3,4-dibenzyloxybenzoyl chloride (**6**) (1.4 g, 4.0 mmol) and toluene (25 ml) were placed in a 100 ml three-necked round-bottom flask equipped with a condenser. The mixture was stirred at reflux temperature for 6 h under N_2. After cooling, the toluene was decanted and water (15 ml) was added to the remaining solid. The aqueous solution was extracted with CH_2Cl_2 (4×15 ml). The extract was washed with water (3×50 ml) and mixed with the toluene solution. The organic solvents were evaporated under reduced pressure to obtain a brown residue. The residue was dissolved in a 5% K_2CO_3-solution (20 ml), refluxed for 4 h and then saturated with solid CO_2. The semi-solid was collected, purified by CC with CH_2Cl_2-MeOH (98:2) and was recrystallised from anhydrous ethanol. Yield: 69%. (mp, ^{1}H-NMR, ^{13}C-NMR and DCI-MS (NH_3) as for method A).

3-O-Methylquercetin (**1**)

3',4'-Di-*O*-benzyl-3-*O*-methylquercetin (**9**) (0.22 g, 0.44 mmol) and $Pd(OH)_2$/C (0.23 g, 20% Pd) were suspended in ethanol (10 ml). Cyclohexene (5 ml) was added and the mixture was brought to reflux for half an hour. After cooling, the mixture was filtered off and the residue was washed with ethanol. The filtrate and washings were combined and evaporated to leave the 3-*O*-methylquercetin (**1**), which was recrystallised from ethanol-water. Yield: 99%. mp 274 °C (ref.[8] 275 °C).– ^{1}H-NMR (DMSO-d_6) δ: 7.53 (d, *J* = 2.24 Hz, 1H, $H_{2'}$), 7.23 (dd, *J* = 8.53 Hz 2.23 Hz, 1H, $H_{6'}$), 6.89 (d, *J* = 8.54 Hz, 1H, $H_{5'}$), 6.39 (d, *J* = 2.03 Hz, 1H, H_8), 6.17 (d, *J* = 2.03 Hz, 1H, H_6), 3.78 (s, 3H, -OCH_3).– ^{13}C-NMR (DMSO-d_6) δ: 177.85 (C_4), 164.14 (C_7), 161.28 (C_5), 156.34 (C_9), 155.61 (C_2), 148.67 ($C_{4'}$), 145.19 ($C_{3'}$), 137.70 (C_3), 120.89 ($C_{1'}$), 120.58 ($C_{6'}$), 115.77 ($C_{5'}$), 115.47 ($C_{2'}$), 104.20 (C_{10}), 98.53 (C_6), 93.60 (C_8), 59.66 (-O*C*H$_3$).– DCI-MS (NH_3): *m/z* = 317 ([MH]$^+$), *m/z* = 334 ([MNH_4]$^+$).

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