Supporting Information

for

A simple and effective preparation of quercetin pentamethyl ether from quercetin

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Experimental procedures, $^1$H and $^{13}$C NMR assignments of methylated products 3, 4 and 5 and references
General

Reaction with MeI/K₂CO₃/DMF (run 1 in Table 1)

Reaction with MeI/K₂CO₃/acetone (run 2 in Table 1)

Reaction with Me₂SO₄/K₂CO₃/acetone (run 3 in Table 1)

Reaction with MeI/NaH/DMF (run 4 in Table 1)

Reaction with Me₂SO₄/10% NaOH/CH₂Cl₂/Bn(Et)₃NCl (run 1 in Table 2)

Reaction with Me₂SO₄/NaOH/DMSO (run 3 in Table 2)

Reaction with MeI/KOH/DMSO

¹H and ¹³C NMR assignments of quercetin trimethyl ether [5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,7-dimethoxy-4H-1-benzopyran-4-one] (3)

¹H and ¹³C NMR assignments of quercetin tetramethyl ether [5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4H-1-benzopyran-4-one] (4)

¹H and ¹³C NMR assignments of 6-methylquercetin pentamethyl ether [2-(3,4-dimethoxyphenyl)-3,5,7-trimethoxy-6-methyl-4H-1-benzopyran-4-one] (5)

References
Melting points were determined with a melting point hot-stage instrument and are uncorrected. ESI mass spectra were obtained using a time-of-flight mass spectrometer.

$^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively, in CDCl$_3$. Chemical shifts were calibrated with internal tetramethylsilane or with the solvent peak for the $^1$H and $^{13}$C NMR spectra. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br = broad. For preparative TLC PLC Silica gel 60 F$_{254}$ (1 or 2 mm) was used. Reaction mixture was extracted with ethyl acetate (EtOAc), and organic solutions obtained were washed with H$_2$O followed by brine and evaporated under reduced pressure after drying over MgSO$_4$, unless otherwise noted.

**Reaction with Mel/K$_2$CO$_3$/DMF (run 1 in Table 1)**  According to the reported conditions [1] a suspension of quercetin (2) (0.146 g, $4.8 \times 10^{-4}$ mol), K$_2$CO$_3$ (0.418 g, $30 \times 10^{-4}$ mol), and Mel (0.5 g, $35 \times 10^{-4}$ mol) in DMF (1.3 mL) was stirred at 35 °C for 24 h. After quenched with H$_2$O and acidified with 20% H$_2$SO$_4$ (pH ca 5) the mixture was extracted. Purification of the residue (0.157 g) by preparative TLC (CHCl$_3$) afforded quercetin tetramethyl ether 4 (Rf = 0.30-0.56, 0.084 g, 49%), quercetin trimethyl ether 3 (Rf = 0.12–0.24, 0.036 g, 22%), and quercetin pentamethyl ether 1 (Rf = 0.02–0.12, 0.039 g, 21%).

**Reaction with Mel/K$_2$CO$_3$/acetone (run 2 in Table 1)**  According to the reported conditions [2] a suspension of 2 (0.156 g, $5.2 \times 10^{-4}$ mol), K$_2$CO$_3$ (0.218 g, $15.8 \times 10^{-4}$ mol), and Mel (0.5 g, $35 \times 10^{-4}$ mol) in acetone (2.5 mL) was stirred under reflux for 24 h. After quenched with H$_2$O and acidified with 20% H$_2$SO$_4$ (pH ca 5) the mixture was centrifuged. The insoluble residue was washed with H$_2$O followed by acetone to recover 2 (0.134 g, 86%).

**Reaction with Me$_2$SO$_4$/K$_2$CO$_3$/acetone (run 3 in Table 1)**  According to the reported conditions [3] a suspension of 2 (0.151 g, $5.0 \times 10^{-4}$ mol), K$_2$CO$_3$ (2.3 g, $166 \times 10^{-4}$ mol), and Me$_2$SO$_4$ (0.6 mL, $63 \times 10^{-4}$ mol) in acetone (23 mL) was refluxed for 23 h under stirring. After addition of acetone the insoluble material was filtered off and washed with acetone. The
filtrate and the washings were combined and evaporated to give 1 (0.166 g, 89%), which was recrystallized from acetone.

**Reaction with Mel/NaH/DMF (run 4 in Table 1)** According to the reported conditions [4] a mixture of 2 (0.149 g, 4.9 × 10⁻⁴ mol), NaH (0.052 g, 22 × 10⁻⁴ mol), and Mel (0.5 mL, 80 × 10⁻⁴ mol) in DMF (10 mL) was stirred at rt for 21 h. After quenched with H₂O the mixture was extracted. Purification of the residue (0.166 g) by preparative TLC (CHCl₃ : EtOAc = 8 : 1, v/v) afforded 3 (Rf = 0.34–0.65, 0.068 g, 39%) as a main product.

**Reaction with Me₂SO₄/10% NaOH/CH₂Cl₂/Bn(Et)₃NCl (run 1 in Table 2)** A mixture of 2 (0.50 g, 1.65 × 10⁻³ mol), Bn(Et)₃NCl (0.04 g, 0.18 × 10⁻³ mol), and Me₂SO₄ (0.94 mL, 9.9 × 10⁻³ mol) in CH₂Cl₂ (5 mL) and 10% NaOH aq solution (4 mL) was stirred at rt for 5 h. After quenched with H₂O and acidified with 20% H₂SO₄ (pH ca 5) the mixture was extracted. Purification of the residue (0.597 g) by preparative TLC (CHCl₃) afforded 4 (Rf = 0.12–0.24, 0.274 g, 46%) and 1 (Rf = 0.02–0.12, 0.193 g, 31%).

**Reaction with Me₂SO₄/NaOH/DMSO (run 3 in Table 2)** To a stirred suspension of powdered NaOH (0.22 g, 5.5 × 10⁻³ mol) in DMSO (1 mL) was slowly added 2 (0.20 g, 6.7 × 10⁻⁴ mol) followed by Me₂SO₄ (0.6 mL, 6.3 × 10⁻³ mol) at rt and the resulting mixture was stirred at rt for 2 h. After quenched with H₂O (10 mL) the insoluble material was filtered and washed with H₂O (to pH ca 7) to give 1 (0.17 g, 66%).

**Reaction with Mel/KOH/DMSO** To a stirred suspension of powdered KOH (0.83 g, 14.8 × 10⁻³ mol) in DMSO (4 mL) was slowly added 2 (0.51 g, 1.67 × 10⁻³ mol) followed by Mel (0.9 mL, 14.5 × 10⁻³ mol) at rt and the resulting suspension was stirred at rt for 1.5 h. After quenched with H₂O and acidified with 20% H₂SO₄ (pH ca 5) the mixture was extracted. The organic solutions were washed with 5% NaHCO₃ aq, H₂O and brine. Trituration of the residue (0.492 g) obtained with acetone afforded 1 (0.394 g) as off-white powder. Purification of the mother liquor by preparative TLC (CHCl₃/EtOAc = 5:1, v/v) afforded 5 (Rf = 0.34–0.48, 0.007 g, 1%) and an additional 1 (Rf = 0.14–0.28, 0.024 g; total 0.418 g, 67%).
On 5: mp 158–160 °C; ESI–MS: m/z 387.1435 (calcd. for C_{21}H_{28}O_{7}: 387.1438). Anal. Calcd for C_{21}H_{28}O_{7}: C, 65.28; H, 5.74; Found: C, 65.25; H, 6.02.

\textbf{1^H and 13^C NMR assignments of quercetin trimethyl ether}

\textbf{[5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,7-dimethoxy-4H-1-benzopyran-4-one]} (3)

\textit{^1H NMR} (DMSO-\textit{d}_6) \delta 3.81 (3H, s, OMe), 3.867 (3H, s, OMe), 3.873 (3H, s, OMe), 6.37 (1H, d, J = 2.0 Hz, 6- or 8-H), 6.72 (1H, d, J = 2.0 Hz, 6- or 8-H), 7.11 (1H, d, J = 9.2 Hz, 5'-H), 7.58 (1H, dd, J = 9.2, 2.2 Hz, 6'-H), 7.59 (1H, d, J = 2.2 Hz, 2'-H), 9.44 (1H, s, OH), 12.65 (1H, s, OH); \textit{^13C NMR} (DMSO-\textit{d}_6) \delta 55.7, 56.1, 59.7, 92.3, 97.8, 105.2, 111.9, 115.1, 120.4, 122.2, 138.2, 146.4, 150.3, 155.6, 156.3, 160.9, 165.2, 178.1.

\textbf{1^H and 13^C NMR assignments of quercetin tetramethyl ether}

\textbf{[5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4H-1-benzopyran-4-one]} (4)

\textit{^1H NMR} \delta 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 3.97 (3H, s, OMe), 3.98 (3H, s, OMe), 6.35 (1H, d, J = 2.4 Hz, 6- or 8-H), 6.44 (1H, d, J = 2.4 Hz, 6- or 8-H), 6.99 (1H, d, J = 8.4 Hz, 5'-H), 7.69 (1H, d, J = 2.4 Hz, 6'-H), 7.73 (1H, dd, J = 8.4, 2.4 Hz, 6'-H), 12.57-12.62 (1H, br, OH); \textit{^13C NMR} \delta 56.0, 56.1, 56.2, 60.3, 92.4, 98.0, 106.2, 111.0, 111.5, 122.3, 123.1, 139.1, 148.9, 151.5, 156.0, 156.9, 162.2, 165.6, 178.9.

\textbf{1^H and 13^C NMR assignments of 6-methylquercetin pentamethyl ether}

\textbf{[2-(3,4-dimethoxyphenyl)-3,5,7-trimethoxy-6-methyl-4H-1-benzopyran-4-one]} (5)

\textit{^1H NMR} \delta 2.18 (3H, s, CMe), 3.86 (3H, s, 3-OMe), 3.90 (3H, s, 5-OMe), 3.93 (3H, s, 7-OMe), 3.97 (3H, s, 3'-OMe), 3.97 (3H, s, 4'-OMe), 6.69 (1H, s, 8-H), 6.98 (1H, d, J = 8.8 Hz, 5'-H), 7.70-7.73 (2H, m, 2'- and 6'-H); \textit{^13C NMR} \delta 8.1 (CMe), 55.9 (7-OMe), 56.0 (3'- or 4'-OMe), 59.9 (3'- or 4'-OMe), 61.5 (5-OMe), 94.6 (C8), 110.7 (C5'), 111.2 (C2'), 112.4 (C4a), 118.1 (C6), 121.6 (C6'), 123.4 (C1'), 141.0 (C3), 148.6 (C3'), 150.8 (C4'), 153.0 (C2), 156.4 (C8a), 157.5 (C5), 162.2 (C7), 173.4 (C4).
References


