Supplementary Data

Effective synthesis of 1β-acyl glucuronides by selective acylation

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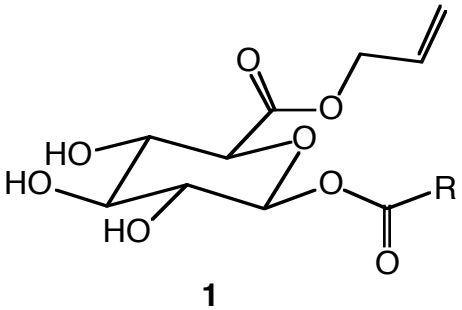
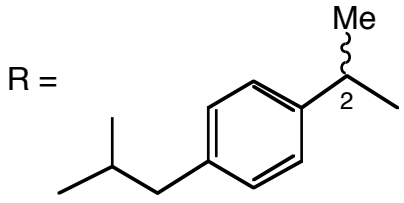
Typical Acylation Procedure: 4-Bromobenzoic Acid 1β-*O*-Acyl Glucuronide, Allyl Ester: (Compound **9** in MS): 4-Bromobenzoic acid **8** (0.101 g,0.5 mmol), allyl glucuronate **7** (0.117 g, 0.5 mmol) and HATU (0.190 g, 0.5 mmol) were stirred in dry acetonitrile (5 mL) with N-methyl morpholine (0.110 mL, 0.101 g, 2 eq.) under nitrogen at 20°C. The reaction was monitored by TLC (10% EtOH-CH_2Cl_2, Merck Kieselgel analytical plates) and after 2 h it was quenched by addition of Amberlyst A-15 (H^+, 2 eq.). After evaporation at <30°C (Buchi rotavapor) the residue was chromatographed on Merck 938 S silica, eluting with 7% EtOH-CH_2Cl_2. Appropriate fractions were pooled and evaporated, eventually under high vacuum, to afford the title compound as a foam (0.108 g, 52%), with spectroscopic data as reported by H. Juteau, Y. Gareau and M. Labelle, *Tetrahedron Lett.*, 1997, **38**, 1481 (see also below).

Characterisation

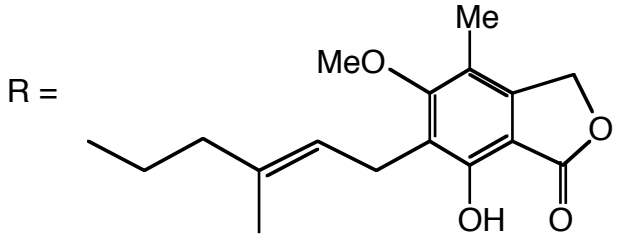
Of the compounds described in this paper, the following **allyl esters** are new, and are fully characterised as given below:



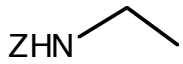
1



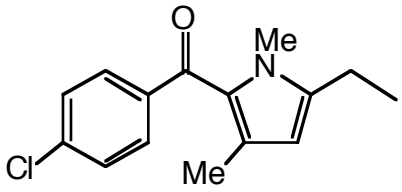
1a



1b

R = 

1c

R = 

1d

1a (**2S**)**- Ibuprofen acyl glucuronide, allyl ester**: Found: C, 62.6; H, 7.1; m/z 445.1826. $C_{22}H_{30}O_8$ requires C, 62.6 ; H, 7.1%; $C_{22}H_{30}O_8Na$ requires m/z 445.1838; ν_{max}./cm^{-1} (Nujol) 3200-3600 (br), 3538, 1744, 1720 (sh), and1515; δ_H [400MHz, $(CD_3)_2CO$]: 0.90 (6 H, d, J = 6.6 Hz, $(CH_3)_2$CH), 1.46 (3 H, d, J = 7.2 Hz, CH_3CHAr), 1.86 (1 H, m, $(CH_3)_2CH$), 2.46 (2 H, d, J = 7.2 Hz, CHCH_2Ar), 3.45, 3.63 and 3.83 (4 H, 3 m, 2'-H + 3'-H + 4'-H + ArCHCH$_3$), 4.03 (1 H, d ,J = 9.4 Hz, 5'-H), 4.64 (2 H, m, OCH_2CH=CH$_2$), 5.19 and 5.34 (2 H, 2 m, OCH$_2$CH=CH_2),5.62 (1 H, d, J = 8.2 Hz, 1'-H), 5.92 (1 H, m, OCH$_2CH$=CH$_2$), 7.13 and 7.26 (4 H, approx. dd, ArH); δ_C [100MHz, $(CD_3)_2CO$]: 19.56, 23.07, 31.13, 45.92, 45.95, 66.45, 72.95, 73.82, 77.52, 77.54, 95.91, 118.63, 118.76, 128.63, 130.50, 133.45, 138.97, 141.60, 169.11 and 174.14; Mass spec. (ES+ve mode): m/z 445 (MNa+, 100%), 867 (weak, 2MNa$^+$).

This is the major isomer isolated by chromatography and is assigned the same (**2S**)-configuration as the parent drug. The minor isomer, assigned as (**2R**)-, is distinguished by δ_H [400MHz, $(CD_3)_2CO$]: 0.89 (6 H, d, J = 6.6 Hz, $(CH_3)_2$CH),1.48 (3 H, d, J = 7.2 Hz, CH_3CHAr), 1.85 (1 H, m, $(CH_3)_2CH$), 2.46 (2 H, d, J = 7.2 Hz, CHCH_2Ar), 3.42, 3.56 and 3,67 (3 H, 3 m, 2'-H + 3'-H + 4'-H), 3.82 (1 H, q, J = 7.2 Hz, ArCHCH$_3$),4.05 (1 H, d, J = 9.4 Hz, 5'-H), 4.67 (2 H, m, OCH_2CH=CH$_2$), 5.21 and 5.41 (2 H, 2 m, OCH$_2$CH=CH_2), 5.58 (1 H, d, J = 8.1 Hz, 1'-H), 5.94 (1 H, m, OCH$_2CH$=CH$_2$), 7.13 and 7.27 (4 H, approx. dd, ArH). Found: m/z 445.1823; $C_{22}H_{30}O_8Na$ requires m/z 445.1838.

1b: **Mycophenolic acid acyl glucuronide, allyl ester**: Found: C, 57.9 ; H,5.9 ; $C_{26}H_{32}O_{12}$ requires C, 58.2; H, 6.0% ; ν_{max}./cm^{-1} (Nujol) 3400 (v br), 1750 (sh), 1732, 1710 (sh) and 1621; δ_H [400MHz, $(CD_3)_2CO$]: 1.68 (3 H, s, CH$_3$C=C), 2.03 (3 H, s, CH$_3$Ar), 2.16, 2.33 (4 H, 2 t, COCH$_2$CH$_2$), 3.20-3.50 (5 H, m, 2'-H + 3'-H + 4'-H+ CH$_2$Ar), 3.66 (3 H, s, CH$_3$O), 3.87 (1 H, d, J = 9.5 Hz, 5'-H), 4.51 (2 H, m, OCH_2CH=CH$_2$), 5.10, 5.25 (2 H, approx. 2 d, CH$_2$CH=CH_2), 5.17 (3 H, m, ArCH_2O + C=CHCH$_2$Ar), 5.40 (1 H, d, J = 8.1 Hz, 1'-H) and 5.85 (1 H, m, CH$_2CH$=CH$_2$); δ_C [100MHz, $(CD_3)_2CO$]: 11.86, 15.99, 16.64,

23.60, 33.73, 35.20, 61.79, 66.50, 70.91, 72.97, 73.82, 77.40, 95.51, 107.67, 118.07, 118.76, 123.00, 124.48, 133.42, 134.87, 146.43, 154.45, 164.70, 169.19, 172.53 and 173.22; m/z (ES+ve mode): 559 (MNa^+, 100%) and 575 (MK^+, 5%). Found: m/z, 559.1797. $C_{26}H_{32}O_{12}Na$ requires MNa^+, 559.1791.

1c: **Benzyloxycarbonylglycine acyl glucuronide, allyl ester**: Found: C, 53.7; H, 5.6 ; N, 3.2; m/z 448.1234. $C_{19}H_{23}NO_{10}$ requires C, 53.6; H,5.4; N, 3.3 %; $C_{19}H_{23}NO_{10}Na$ requires m/z 448.1220; ν_{max}./cm^{-1} (Nujol) 3200-3600 (br), 1760 (sh), 1732, 1700 (sh) and 1531; δ_H [400MHz, $(CD_3)_2CO$]: 3.46, 3.61 and 3.68 (3 H, 3 m, 2'H + 3'-H + 4'-H), 3.95-4.05 (2 H, m, $NHCH_2CO$), 4.08 (1 H, d, J = 9.5 Hz, 5'-H), 4.67 (2 H, m, $OCH_2CH=CH_2$), 5.25 and 5.41 (2 H, 2 m, $OCH_2CH=CH_2$),5.63 (1 H, d, J = 8.1 Hz, 1'-H), 5.90-6.00 (1 H, m, $OCH_2CH=CH_2$),6.81 (1 H, br t, $NHCH_2$) and 7.30-7.40 (5 H, m, ArH); δ_C [100MHz, $(CD_3)_2CO$]: 43.42, 55.43, 65.45, 66.63, 67.39, 72.94, 73.87, 77.27, 77.53, 96.14, 118.90, 129.13, 129.65, 133.42, 157.92, 169.09 and 170.20; m/z (ES+ve mode): 448 (MNa^+, 100%).

1d: **Zomepirac acyl glucuronide, allyl ester**: Found: C,56.3 ; H,5.1 ; N, 2.8; m/z, 530.1219. $C_{24}H_{26}ClNO_9$ requires C, 56.7; H, 5.1; N, 2.8 %; $C_{24}H_{26}ClNO_9Na$ requires m/z 530.1194; ν_{max}./cm^{-1} (Nujol) 3200-3600 (br), 1770, 1750 (sh), 1726, 1613, 1580 and 1550 (sh); δ_H [400MHz, $(CD_3)_2CO$]: 3.46, 3.59 and 3.67 (3 H, 3 m, 2'H + 3'-H + 4'-H),3.72 (3 H, s, CH3 on pyrrole ring), 3.91 (3 H, s, NCH_3), 4.06 (1 H, d, J = 9.5 Hz, 5'-H), 4.68 (2 H, m, $OCH_2CH=CH_2$), 5.23 and 5.38 (2 H, 2 m, $OCH_2CH=CH_2$),5.65 (1 H, d, J = 8.1 Hz, 1'-H), 5.90-6.00 (1 H, m, $OCH_2CH=CH_2$), 6.03 (1 H, s, pyrrole-3-H), 7.55 and 7.69 (4 H, approx. dd, ArH); δ_C [100MHz, $(CD_3)_2CO$]: 14.87, 33.24, 33.87, 66.55, 72.99, 73.88, 77.56, 77.66, 96.28, 113.74, 118.79, 129.26, 129.85, 130.87, 131.87, 133.48, 134.36, 138.33, 141.22, 169.23, 169.60 and 186.94; m/z (ES+ve mode): 530 (MNa^+, 100%).

The other acyl glucuronide allyl esters (viz. of acids **8**, **10**, **11** and **12** in our MS) were reported by H. Juteau, Y. Gareau and M. Labelle, *Tetrahedron Lett*., 1997, **38**, 1481. For these derivatives we give proton NMR and mass spectrometric data:

4-Bromobenzoic acid acyl glucuronide, allyl ester: Found: m/z 438.9992 and 440.9966. $C_{16}H_{17}{}^{79}BrO_8Na$ and $C_{16}H_{17}{}^{81}BrO_8Na$ require 439.0004 and 440.9984

respectively. δ_H [400MHz, $(CD_3)_2CO$]: 3.63 (2 H, m) and 3.72 (1 H, m, 2'H + 3'-H + 4'-H), 4.11 (1 H, d, J = 9.5 Hz, 5'-H), 4.63 (2 H, m, O*CH*$_2$CH=CH$_2$), 5.18 and 5.35 (2 H, 2 m, OCH$_2$CH=*CH*$_2$),5.81 (1 H, d, J = 7.8 Hz, 1'-H), 5.91 (1 H, m, OCH$_2$*CH*=CH$_2$), 7.67 and 8.00 (4 H, approx. dd, ArH); m/z (ES+ve mode): 439, 441 (MNa^+ for ^{79}Br, ^{81}Br respectively).

2-Bromobenzoic acid acyl glucuronide, allyl ester: Found: m/z 439.0022 and 441.0002. $C_{16}H_{17}{}^{79}BrO_8Na$ and $C_{16}H_{17}{}^{81}BrO_8Na$ require 439.0004 and 440.9984 respectively. δ_H [200MHz, $(CD_3)_2CO$]: 3.50-3.80 (3 H, 3 m, 2'H + 3'-H + 4'-H), 4.17 (1 H, d, J = 9.4 Hz, 5'-H), 4.66 (2 H, m, O*CH*$_2$CH=CH$_2$), 5.21 and 5.37 (2 H, 2 m, OCH$_2$CH=*CH*$_2$), 5.83 (1 H, d, J = 7.8 Hz, 1'-H), 5.85-6.05 (1 H, m, OCH$_2$*CH*=CH$_2$), 7.50-7.60(2 H, m, ArH), 7.75-7.80 and 7.95-8.05 (2 H, 2 m, ArH); m/z (ES+ve mode): 439, 441 (MNa^+ for ^{79}Br, ^{81}Br respectively), also weak 445, 447 (MK^+).

Phenylacetic acid acyl glucuronide, allyl ester: Found: m/z 375.1073. $C_{17}H_{20}O_8Na$ requires m/z 375.1056; δ_H [400MHz, $(CD_3)_2CO$]: 3.46, 3.58 and 3.68 (3 H, 3 m, 2'H + 3'-H + 4'-H), 3.76 (2 H, s, Ar*CH*$_2$CO),4.04 (1 H, d, J = 9.6 Hz, 5'-H), 4.65 (2 H, m, O*CH*$_2$CH=CH$_2$), 5.21 and 5.37 (2 H, 2 m, OCH$_2$CH=*CH*$_2$), 5.61 (1 H, d, J = 8.1 Hz, 1'-H), 5.90-6.00 (1 H, m, OCH$_2$*CH*=CH$_2$) and 7.25-7.35 (5 H, m, ArH); m/z (ES +ve mode): 375 (MNa^+, 100%).

(R)-O-Methyl mandelic acid acyl glucuronide, allyl ester: Found: m/z, 405.1154. $C_{18}H_{22}O_9Na$ requires m/z 405.1162; δ_H [400MHz, $(CD_3)_2CO$]: 3.41 (3 H, s, CH_3O), 3.43, 3.55 and 3.67 (3 H, 3 m, 2'H + 3'-H + 4'-H), 4.05 (1 H, d, J = 9.6 Hz, 5'-H), 4.65 (2 H, m, O*CH*$_2$CH=CH$_2$), 4.92 [1 H, s, Ar*CH*(OMe)], 5.19 and 5.35 (2 H, 2 m, OCH$_2$CH=*CH*$_2$),5.61 (1 H, d, J = 8.0 Hz, 1'-H), 5.92 (1 H, m, OCH$_2$*CH*=CH$_2$), 7.30-7.40 (2 H, m, ArH) and 7.50-7.55 (2 H, m, ArH); m/z (ES +ve mode): 405 (MNa^+, 100%) and 787 ($2MNa^+$, 12%).

This is the major isomer and is assigned the same (**R**)- stereochemistry as the parent acid. The minor isomer, assigned as the (**S**)- isomer, is distinguished by: δ_H [400MHz, $(CD_3)_2CO$]: 3.38 (3 H, s, CH_3O), 3.45, 3.58 and 3.64 (3 H, 3 m, 2'H + 3'-H + 4'-H), 4.01 (1 H, d, J = 9.6 Hz, 5'-H), 4.60 (2 H, m, O*CH*$_2$CH=CH$_2$), 4.91 [1 H, s, Ar*CH*(OMe)], 5.16 and 5.31 (2 H, 2 m, OCH$_2$CH=*CH*$_2$), 5.56 (1 H, d, J = 8.0 Hz, 1'-H), 5.88 (1 H, m, OCH$_2$*CH*=CH$_2$), 7.30-7.40 and 7.45-7.50 (4 H, 2 m, ArH).

<u>Acyl glucuronides, free carboxylic acids</u>: (made previously by other methods, see MS):

Phenylacetic acid acyl glucuronide (H. Juteau, Y. Gareau and M. Labelle, *Tetrahedron Lett*., 1997, **38**, 1481): Found: m/z 311.0764. $C_{14}H_{15}O_8$ requires $[M-H]^+$, 311.0767; δ_H [400MHz, $(CD_3)_2CO$]: 3.28, 3.46, 3.57 (3 H, 3 m, 2'H + 3'-H + 4'-H), 3.77 (2 H, s, Ar*CH*$_2$CO), 3.87 (1 H, d, J = 9.4 Hz, 5'-H), 5.54 (1 H, d, J = 8.1 Hz, 1'-H) and 7.20-7.35 (5 H, m, ArH); m/z (ES-ve mode) 311 ($[M-H]^+$, 100%).

Mycophenolic acid acyl glucuronide (M. Kittlemann, U. Rheinegger, A. Espigat, L. Oberer, R. Aichholz, E. Francotte and O. Ghisalba, *Adv. Synth. Catal.*, 2003, **345**, 825): δ_H [400MHz, $(CD_3)_2CO$]: 1.81 (3 H, s, CH_3C=C), 2.15 (3 H, s, $ArCH_3$), 2.30, 2.51 (4 H, 2m, $COCH_2CH_2$), 3.38 (2 H, d, J = 6.9 Hz, Ar*CH*$_2$CH), 3.43, 3.53 and 3.58 (3 H, 3m, 2'-H + 3'-H + 4'-H), 3.70 (1 H, d, J = 9.5 Hz, 5'-H), 3.78 (3 H, s, CH_3O), 5.27 (1 H, t, J = 6.25 Hz, C=*CH*.CH_2), 5.30 (2 H, s, $ArCH_2O$) and 5.45 (1 H, d, J = 8.1 Hz, 1'-H). Mass spec. (ES-ve mode): Found: m/z, 495.1514. $C_{23}H_{27}O_{12}$ requires $[M-H]^+$, 495.1503.

A. V. Stachulski 30/3/2005