Supplementary Data

Effective synthesis of 1β-acyl glucuronides by selective acylation

Jennifer A. Perrie, John R. Harding, David W. Holt, Atholl Johnston, Paul Meath, and Andrew V. Stachulski

Typical Acylation Procedure: 4-Bromobenzoic Acid 1β-0-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-CH₂Cl₂, 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-CH₂Cl₂. 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:
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%; \nu_{\text{max}}/\text{cm}^{-1} (Nujol) 3200-3600 (br), 3538, 1744, 1720 (sh), and 1515; \delta_H [400MHz, (CD_3)_2CO]: 0.90 (6 H, d, J = 6.6 Hz, (CH_3)_2CH), 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_2CH=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); \delta_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 \delta_H [400MHz, (CD_3)_2CO]: 0.89 (6 H, d, J = 6.6 Hz, (CH_3)_2CH), 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_2CH=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%; \nu_{\text{max}}/\text{cm}^{-1} (Nujol) 3400 (v br), 1750 (sh), 1732, 1710 (sh) and 1621; \delta_H [400MHz, (CD_3)_2CO]: 1.68 (3 H, s, CH_3C=C), 2.03 (3 H, s, CH_3Ar), 2.16, 2.33 (4 H, 2 t, COCH_2CH_2), 3.20-3.50 (5 H, m, 2’-H + 3’-H + 4’-H+ CH_2Ar), 3.66 (3 H, s, CH_3O), 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_2CH=CH_2), 5.17 (3 H, m, ArCH_2O + C=CHCH_2Ar), 5.40 (1 H, d, J = 8.1 Hz, 1’-H) and 5.85 (1 H, m, CH_2CH=CH_2); \delta_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})_{2}CO]: 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_{2}CO), 4.08 (1 H, d, J = 9.5 Hz, 5'-H), 4.67 (2 H, m, OCH_{2}CH=CH_{2}), 5.25 and 5.41 (2 H, 2 m, OCH_{2}CH=CH_{2}),5.63 (1 H, d, J = 8.1 Hz, 1'-H), 5.90-6.00 (1 H, m, OCH_{2}CH=CH_{2}),6.81 (1 H, br t, NHCH_{2}) and 7.30-7.40 ( 5 H, m, ArH); δ_{C} [100MHz, (CD_{3})_{2}CO]: 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_{9}Na 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})_{2}CO]: 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_{2}CH=CH_{2}), 5.23 and 5.38 (2 H, 2 m, OCH_{2}CH=CH_{2}),5.65 (1 H, d, J = 8.1 Hz, 1'-H), 5.90-6.00 (1 H, m, OCH_{2}CH=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})_{2}CO]: 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}BrO_{8}Na and C_{16}H_{17}BrO_{8}Na require 439.0004 and 440.9984
respectively. δH [400MHz, (CD3)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, OCH2CH=CH2), 5.18 and 5.35 (2 H, 2 m, OCH2CH=CH2), 5.81 (1 H, d, J = 7.8 Hz, 1’-H), 5.91 (1 H, m, OCH2CH=CH2), 7.67 and 8.00 (4 H, approx. dd, ArH); m/z (ES+ve mode): 439, 441 (MNa+ for 79Br, 81Br respectively).

2-Bromobenzoic acid acyl glucuronide, allyl ester: Found: m/z 439.0022 and 441.0002. C16H1779BrO8Na and C16H1781BrO8Na require 439.0004 and 440.9984 respectively. δH [200MHz, (CD3)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, OCH2CH=CH2), 5.21 and 5.37 (2 H, 2 m, OCH2CH=CH2), 5.83 (1 H, d, J = 7.8 Hz, 1’-H), 5.85-6.05 (1 H, m, OCH2CH=CH2), 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 79Br, 81Br respectively), also weak 445, 447 (Mk+).

Phenylacetic acid acyl glucuronide, allyl ester: Found: m/z 375.1073. C17H20O8Na requires m/z 375.1056; δH [400MHz, (CD3)2CO]: 3.46, 3.58 and 3.68 (3 H, 3 m, 2’H + 3’-H + 4’-H), 3.76 (2 H, s, ArCH2CO), 4.04 (1 H, d, J = 9.6 Hz, 5’-H), 4.65 (2 H, m, OCH2CH=CH2), 5.21 and 5.37 (2 H, 2 m, OCH2CH=CH2), 5.61 (1 H, d, J = 8.1 Hz, 1’-H), 5.90-6.00 (1 H, m, OCH2CH=CH2) 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. C18H22O9Na requires m/z 405.1162; δH [400MHz, (CD3)2CO]: 3.41 (3 H, s, CH3O), 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, OCH2CH=CH2), 4.92 [1 H, s, ArCH(OMe)], 5.19 and 5.35 (2 H, 2 m, OCH2CH=CH2), 5.61 (1 H, d, J = 8.0 Hz, 1’-H), 5.92 (1 H, m, OCH2CH=CH2), 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: δH [400MHz, (CD3)2CO]: 3.38 (3 H, s, CH3O), 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, OCH2CH=CH2), 4.91 [1 H, s, ArCH(OMe)], 5.16 and 5.31 (2 H, 2 m, OCH2CH=CH2), 5.56 (1 H, d, J = 8.0 Hz, 1’-H), 5.88 (1 H, m, OCH2CH=CH2), 7.30-7.40 and 7.45-7.50 (4 H, 2 m, ArH).
Acyl glucuronides, free carboxylic acids: (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$_3$)$_2$CO]: 3.28, 3.46, 3.57 (3 H, 3 m, 2’H + 3’-H + 4’-H), 3.77 (2 H, s, ArCH$_2$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$_3$)$_2$CO]: 1.81 (3 H, s, CH$_3$C=C), 2.15 (3 H, s, ArCH$_3$), 2.30, 2.51 (4 H, 2m, COCH$_2$CH$_2$), 3.38 (2 H, d, J = 6.9 Hz, ArCH$_2$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$_3$O), 5.27 (1 H, t, J = 6.25 Hz, C=CH.CH$_2$), 5.30 (2 H, s, ArCH$_2$O) 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