Supporting Information

Use of a Sonogashira-Acetylide Coupling Strategy for the Synthesis of the Aromatic Spiroketal Skeleton of γ-Rubromycin

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General Methods. All reagents were used as supplied. Solvents were purified by the methods given in *Purification of Laboratory Chemicals* by D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 2nd Edition, Pergammon Press, 1980. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE DRX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) or a Bruker AVANCE 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer at ambient temperatures. Flash chromatography was performed using Scharlau 60 (40-60 μm mesh) silica gel. Melting points in degrees Celsius (°C) were determined on an Electrothermal® melting point apparatus and are uncorrected. Accurate mass measurements were recorded on a VG-70SE mass spectrometer.

Typical Procedure for the Acetylide Addition Step:

1-(3-Methoxy-2-methoxymethoxyphenyl)-4-(2-methoxymethoxyphenyl)but-3-yn-2-ol (**31) -** To a solution of ethynyl-2-(methoxymethoxy)benzene **16** (242.7 mg, 1.5 mmol) in THF (3 mL) at –78 °C was added *n*-butyllithium (0.6 mL of 2.5 M solution in hexanes, 1.6 mmol) dropwise. The solution was kept at –78 °C for 35 min then a solution of aldehyde **14** (265 mg, 1.3 mmol) in THF (2.5 mL) was added dropwise. After 1 h, the reaction mixture was warmed slowly to room temperature and left to stir for 2.5 h. Water

(5 mL) was added and the mixture extracted with ethyl acetate (4 x 8 mL). The organic extracts were combined, washed with brine (5 mL), dried over magnesium sulphate and concentrated at reduced pressure. Purification by flash column chromatography using hexane-ethyl acetate (70:30) afforded alcohol **31** (239 mg, 61%) as a pale yellow oil. (Found: M^+, 372.1569, $C_{21}H_{24}O_6$ requires 372.1573); ν_{max} (film)/cm^{-1} 3433 (br, s, OH), 3070 (C-H, aromatic), 2937, 2837(s, CH), 2229 (C≡C), 1597, 1585 (ArC=C), 1488 (OCH_2O), 1079, 1049 (C-O), 754 (ArC-H); δ_H (300 MHz, $CDCl_3$) 2.86 (1H, s, broad, O*H*), 3.21 (1H, dd, *J* 5.5, 13.6 Hz, H-1_A), 3.29 (1H, dd, *J* 8.0, 13.6 Hz, H-1_B), 3.51 (3H, s, OCH_2OCH_3), 3.64 (3H, s, OCH_2OCH_3), 3.87 (3H, s, OMe), 4.90-4.94 (1H, m, H-2), 5.13 (1H, d, *J* 10.9 Hz, OCH_AH_BO), 5.15 (1H, d, *J* 10.8 Hz, OCH_AH_BO), 5.22 (2H, s, OCH_2O), 6.84 (1H, dd, *J* 1.7, 7.8 Hz, H-4′), 6.94 (1H, ddd, *J* 1.1, 7.6, 7.6 Hz, H-5″), 6.97 (1H, dd, *J* 1.7, 7.8 Hz, H-6′), 7.05 (1H, t, *J* 7.8 Hz, H-5′), 7.07-7.11 (1H, m, H-3″), 7.22-7.29 (1H, m, H-4″), 7.38 (1H, dd, *J* 1.7, 7.6 Hz, H-6″); δ_C (75 MHz, $CDCl_3$) 38.7 (CH_2, C-1), 55.7 (CH_3, OMe), 56.2 (CH_3, OCH_2OCH_3), 57.4 (CH_3, OCH_2OCH_3), 63.2 (CH, C-2), 81.0 (quat., C-4), 94.2 (quat., C-3), 94.9 (CH_2, OCH_2O), 99.1 (CH_2, OCH_2O), 111.0 (CH, C-4′), 113.4 (quat., C-1″), 115.2 (CH, C-3″), 121.7 (CH, C-5″), 123.1 (CH, C-6′), 124.2 (CH, C-5′), 129.5 (CH, C-4″), 131.3 (quat., C-1′), 133.6 (CH, C-6″), 145.1 (quat., C-3′), 152.0 (quat., C-2′), 157.7 (quat., C-2″); *m/z* (EI, %) 372 (M^+, 0.1), 354 (0.1), 342 (3.6), 327 (1.1), 310 (9), 277 (9), 266 (8), 205 (8), 150 (11), 137 (18), 45 (100).

Typical Procedure for the Spiroketalization Step:

7-Methoxy-3*H*-spiro[1-benzofuran-2,2′-chromane] (8) – A solution of ketone **11** (62 mg, 0.17 mmol) in dichloromethane (2 mL) containing 4Å molecular sieves was treated with bromotrimethylsilane (260 mg, 1.7 mmol) at –40 °C under nitrogen and the mixture stirred for 1 h. The reaction mixture was warmed to 0 °C and stirred for 7 h then warmed to room temperature and stirred for a further 7 h. The reaction mixture was poured into water (2 mL) and extracted with ethyl acetate (4 x 2 mL). The combined organic extracts were washed with brine (5 mL), dried over magnesium sulphate and concentrated at reduced pressure to give a yellow solid. Purification by flash column chromatography using hexane-ethyl acetate (80:20) afforded the *title compound* **8** (38 mg, 86%) as a yellow solid, m.p. 117-118 °C. (Found: M^+, 268.1102, $C_{17}H_{16}O_3$ requires 268.1099); ν_{max}

(film)/cm^{-1} 3053 (CH, aromatic), 1584 (ArC=C), 1093 and 1049 (C-O); δ_H (300 MHz, $CDCl_3$) 2.13-2.24 (1H, m, H-3′$_A$), 2.37 (1H, ddd, *J* 3.3, 5.9, 13.4 Hz, H-3′$_B$), 2.82 (1H, ddd, *J* 3.3, 5.8, 16.7 Hz, H-4′$_A$), 3.30 (1H, d, *J* 16.4 Hz, H-3$_A$), 3.32 (1H, ddd, *J* 5.9, 12.0, 16.7 Hz, H-4′$_B$), 3.45 (1H, d, *J* 16.4 Hz, H-3$_B$), 3.81 (3H, s, OMe), 6.76-6.79 (2H, m, H-6, H-8′), 6.84-6.92 (3H, m, H-4, H-5, H-6′), 7.07-7.17 (2H, m, H-5′, H-7′); δ_C (75 MHz, $CDCl_3$) 22.0 (CH_2, C-4′), 30.5 (CH_2, C-3), 42.3 (CH_2, C-3′), 56.0 (CH_3, OMe), 109.6 (quat., C-2), 111.8 (CH, C-6), 117.0 (CH, C-8′), 117.1 (CH, C-6′), 121.0 (CH, C-5), 121.4 (quat., C-4′a), 121.7 (CH, C-4), 126.5 (quat., C-3a), 127.4 (CH, C-7′), 129.1 (CH, C-5′), 144.4 (quat., C-7a), 146.3 (quat., C-7), 152.3 (quat., C-8′a); *m/z* (EI, %) 268 (M^+, 41), 267 (9), 167 (3), 161 (100), 149 (12), 131 (12), 107 (21), 97 (10), 77 (8), 57 (26).