Highly Regio and Stereoselective One Pot Synthesis of Carbohydrate Based Butyrolactones

Syed Khalid Yousuf, Debaraj Mukherjee*, Mallikharjunrao L, Subhash Chandra Taneja

Bioorganic Chemistry Section, Indian Institute of Integrative Medicine (CSIR), Canal Road,
Jammu Tawi, India-180001

dmukherjee@iiim.res.in

Supporting Information

Section A: General Information	3
Section B: Experimental Procedures and spectral analysis	3-9
Section C: ^1H NMR, ^{13}C NMR, and 2D Spectras	10-25

Section A: General Information

^1H and ^{13}C NMR spectra were recorded on 200 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). MS were recorded on LC Mass spectrometer. Silica gel coated aluminium plates were used for TLC. Elemental analyses were performed on Elementar. Reagents and solvents used were mostly of LR grade.

Section B: General procedure for the reaction of 1,2 and 2, 3-glycals 1: To a solution of Glycal (1,2 & 2,3) (1.8mmol) in acetic anhydride, acetic acid (20ml) (16:4v/v) at 60°C under sonication was added KOAc (15mmol, 1.4 g) followed by the addition of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (3.7 mmol, 991mg). The reaction mixture was kept under the same conditions until the black colour had disappeared. The completion of the reaction was monitored through TLC. The reaction mixture was cooled and the cold mixture was added to sufficient volume of water. The product was extracted with ethyl acetate, washed with sodium bicarbonate, dried and subjected to column chromatography to yield the corresponding product.

Reaction of Tri-O-benzyl D-glucal and optimisation of reaction conditions.

Table 1: Standardisation of reaction conditions

S. NO.	Reagents	reaction condition	Conversion/Yield%
1	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH,	60°C , 6hrs	0/0
2	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Toluene	60°C , 6hrs	0/0
	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Benzene	60°C , 6hrs	0/0
2	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Ac_2O	60°C , 6hrs	70/35
	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Ac_2O , KOAc	60°C , 6hrs	70/45
4	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Ac_2O ,	Sonication at 60°C , 6hrs	80/45
5	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, AcOH, Ac_2O , KOAc	Sonication at 60°C , 6hrs	100/78

Spectral analysis of compounds:

2a

Prepared by the general procedure **1** using 1.8 mmol (748mg) of glycal **1a** and purified on silica gel (EtOAc/PE: 18/82) to obtain the product **2a** (665mg, 78%) as oily liquid: $[\alpha]_D^{20} = +21.3$ (*c* 0.1, CHCl₃); **¹H NMR (500MHz, CDCl₃) of 2a:** δ 7.1–7.3 (m, 15H, CHPh), 5.85 (d, *J* = 4.95 Hz, 1H, H-1), 4.8 (d, *J* = 11.5Hz, 1H, CH₂–Ph), 4.7 (d, *J* = 11.5 Hz, 1H, CH₂–Ph), 4.52–4.64 (m, 4 x CH₂Ph), 3.81–3.77 (m, 3H), 3.71–3.68 (m, 1H), 3.47–3.50 (m, 1H), 2.40 (dd, *J* = 15.5, 7.5Hz, 1H, 7'-H), 2.54 (dd, *J* = 15.5, 4.5Hz, 1H, 7-H), 2.60 (m, 1H, 2'-H). **¹³C NMR (50MHz, CDCl₃) of 2a:** δ 172.9 (-CO), 138.1, 138.0, 137.9 (3 x C-CH₂O), 128.5, 128.46, 128.4, 128.0, 127.8, 127.7 (6 x CH), 101.1 (C-1), 79.3, 74.1, 73.9 (C-3, C-4, C-5), 68.9(C-6), 40.5 (C-2), 33.9 (C-7). ESI MS (*m/z*): 497 [M+Na]. Anal. Cal. for C₂₉H₃₀O₆: C, 73.40, H, 6.37; Found: C, 73.25, H, 6.24.

2b

Prepared by the general procedure **1** using 1.8 mmol (489mg) of glycal **1b** and purified on silica gel (EtOAc/PE: 24/76) to obtain the product **2b** (415mg, 70%) as oily liquid: $[\alpha]_D^{20} = +61$ (*c* 0.1, CHCl₃); **¹H NMR (500MHz, CDCl₃) of 2b:** δ 5.9 (δ, *J* = 4.88Hz, 1H, H-1), 5.08–5.03 (m, 2H, H-3, H-4), 4.38 (d, *J* = 4.77 Hz, 12.4 Hz, 1H, H-6a), 4.17 (dd, *J* = 2, 36 Hz, 12.3 Hz, 1H, H-6b), 4.07 (ddd, *J* = 2.3 Hz, 2.91 Hz, 4.65 Hz, 1H, H-5), 2.80–2.68 (m, 3H, H-2, H1'a, H1'b), 2.08 (s, 3H, COCH₃), 2.06 (s, 3H, COCH₃), 2.05 (s, 3H, COCH₃). **¹³C NMR (50MHz, CDCl₃) of 2b:** δ 171.5 (CO lactone), 170.3, 169.8, 169.3 (2 x -OCOCH₃), 100.2

(C-1), 71.7, 70.1, 67.6 (C-3, C-4, C-5), 62.0 (C-6), 39.9 (C-2), 34.2 (C-7), 20.6, 20.5, 20.4 (3 x -OCOCH₃). ESI MS (m/z): 353 [M+Na]. Anal. Cal. for C₁₄H₁₈O₉: C, 50.91, H, 5.49; Found: C, 50.69, H, 5.60.

2c

Prepared by the general procedure **1** using 1.8 mmol (489mg) of glycal **1c** and purified on silica gel (EtOAc/PE: 24/76) to obtain the product **2c** (415mg, 70%) as oily liquid: $[\alpha]_D^{20} = +53$ (c 0.1, CHCl₃); ¹H NMR (500MHz, CDCl₃) of **2c**: δ 5.93 (d, *J* = 4.20 Hz, 1H, H-1), 5.35-5.35 (m, 1H, H-4), 4.82 (dd, *J* = 2.80 Hz, 12.25 Hz, 1H, H-3), 4.29-4.07 (m, 1H, H-5), 2.78-2.75 (m, 1H, H-2), 2.42 (d, *J* = 4.2 Hz, 1H, H1'a), 2.22 (d, *J* = 4.2 Hz, 1H, H1'b), 2.08 (s, 3H, COCH₃), 2.06 (s, 3H, COCH₃), 2.05 (s, 3H, COCH₃). ¹³C NMR (50MHz, CDCl₃) of **2c**: δ 171.6 (CO lactone), 170.0, 169.7, 169.1 (2 x -OCOCH₃), 101.1 (C-1), 68.9, 68.5, 61.6 (C-3, C-4, C-5), 64.8 (C-6), 35.4 (C-7), 34.2 (C-2), 20.7, 20.68, 20.61 (3 x -OCOCH₃). ESI MS(m/z): 353 [M+Na]. Anal. Cal. For C₁₄H₁₈O₉: C, 50.91, H, 5.49; Found: C, 50.70, H, 5.61.

2d

Prepared by the general procedure **1** using 1.8 mmol (824mg) of glycal **1d** and purified on silica gel (EtOAc/PE: 17/83) to obtain the product **2d** (696mg, 75%) as oily liquid: $[\alpha]_D^{20} = +46$ (c 0.1, CHCl₃); ¹H NMR (500MHz, CDCl₃) of **2d**: δ 8.04-7.35 (m, 15 x CHPh, 15H), 6.12 (d, *J* = 4.65 Hz, 1H, H-1), 5.92 (d, *J* = 2.71 Hz, 1H, H-4), 5.31 (dd, *J* = 2.88 Hz, 10.5

Hz, 1H, H-3), 4.44 (dd, $J = 5.1$ Hz, 11.03 Hz, 2H, H6a, H6b), 4.12 (dd, $J = 7.12$ Hz, 14.2 Hz, 1H, H-5), 3.07 (ddd, $J = 4.8$ Hz, 4.4 Hz, 10.8 Hz, 1H, H-2), 2.80 (dd, $J = 6.84$ Hz, 17.6 Hz, 1H, H1'a), 2.73 (d, $J = 17.6$ Hz, 1H, H1'b). **^{13}C NMR (50MHz, CDCl_3) of 2d:** δ 171.6 (CO lactone), 165.9, 165.6, 165.2 (3 x CO-Ph), 133.7, 133.6, 133.2, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.6, 128.45, 128.42, 128.3, (15 x CH-Ar , 3 x C-Ar), 101.2 (C-1), 70.3, 70.0, 65.8 (C-3, C-4, C-5), 60.4 (C-6), 34.7 (C-7), 31.5 (C-1). ESI MS (m/z): 539 [M+Na]. Anal. Cal. for $\text{C}_{29}\text{H}_{24}\text{O}_9$: C, 67.44, H, 4.69; Found: C, 67.32, H, 4.57.

2e

Prepared by the general procedure **1** using 1.8 mmol (878mg) of glycol **1e** and purified on silica gel (EtOAc/PE: 4/96) to obtain the product **2e** (716mg, 73%) as oily liquid: $[\alpha]_{\text{D}}^{20} = +10$ (c 0.1, CHCl_3); **^1H NMR (500MHz, CDCl_3) of 2e:** δ 5.85 (d, $J = 6.71$ Hz, 1H, H-1), 3.83-3.81 (m, 2H, H-3, H-5), 3.7 (dd, $J = 4.88$ Hz, 9.88 Hz, 1H, H-4), 3.48 (dd, $J = 9.07$ Hz, 18.18 Hz, 1H, H1'a/b), 2.72-2.66 (m, 1H, H-2), 2.48 (dd, $J = 10.7$ Hz, 18.18 Hz, 1H, H1'b/a), 0.85 (s, 3H, C- CH_3), 0.84 (s, 3H, C- CH_3), 0.83 (s, 3H, C- CH_3), 0.82 (s, 3H, C- CH_3), 0.81 (s, 3H, C- CH_3), 0.80 (s, 3H, C- CH_3), 0.79 (s, 3H, C- CH_3), 0.78 (s, 3H, C- CH_3), 0.04 (s, Si- CH_3), 0.03 (s, Si- CH_3), 0.021 (s, Si- CH_3), 0.02 (s, Si- CH_3), -0.0065 (s, Si- CH_3), -0.0078 (s, Si- CH_3), **^{13}C NMR (50MHz, CDCl_3) of 2e:** δ 175.5 (CO-lactone), 99.4 (C-1), 75.6, 69.8, 69.5 (C-3, C-4, C-5), 62.9 (C-6), 38.9 (C-7), 29.9 (C-2), 26.0, 25.9, 25.8, 25.7, 25.6, 25.5, 25.4, 24.3, 25.2, 18.3, 17.8, 17.7, -4.2, -4.4, -4.5, -4.8, -5.1, -5.2. ESI MS (m/z): 569 [M+Na]. Anal. Cal. for $\text{C}_{26}\text{H}_{54}\text{O}_6\text{Si}_3$: C, 57.09, H, 9.95; Found: C, 57.11, H, 9.84.

4a

Prepared by the general procedure **1** using 1.8 mmol (459mg) of glycal **3a** and purified on silica gel (EtOAc/PE: 16/84) to obtain the product **4a** (405mg, 72%) as oily liquid: $[\alpha]_D^{20} = +22$ (c 0.1, CHCl₃); **¹H NMR (500MHz, CDCl₃) of 4a:** δ 5.81(d, $J_{H1,2} = 3.9$ Hz, 1H, H-1), 5.16 (dd, $J_{H3,4} = 3.2$ Hz, $J_{H4,5} = 8.45$ Hz, 1H, H-4), 4.30 (dd, $J = 4.89$ Hz, $J = 12.2$ Hz, 1H, H-6a), 4.22 (dd, $J = 2.73$ Hz, $J = 12.2$ Hz, 1H, H-6b), 4.19 (dd, $J_{H2,3} = 4.2$ Hz, $J_{H3,4} = 3.2$ Hz, 1H, H-3), 4.18-4.17 (m, 1H, H-5), 2.78 (dd, $J_{H1,2} = 3.9$ Hz, $J_{H2,3} = 4.2$ Hz, 1H, H-2), 2.15 (s, 3H, COCH₃), 2.10 (s, 3H, COCH₃). **¹³C NMR (50MHz, CDCl₃) of 4a:** δ 173.2 (CO lactone), 170.5(-OCOCH₃), 169.7 (-OCOCH₃), 169.4(-OCOCH₃), 97.7 (C-1), 70.0(C-5), 66.4 (C-4), 62.4(CH₂), 58.3(C-3), 40.4(C-2), 29.0(CH₂, lactone), 20.7(-OCOCH₃), 20.5(-OCOCH₃), 20.4(-OCOCH₃). ESI MS (m/z): 336 [M+Na]. Anal. Cal. for C₁₂H₁₅ N₃O₇: C, 46.01, H, 4.83, N, 13.41; Found: C, 46.12, H, 4.75, N, 13.49.

4b

Prepared by the general procedure **1** using 1.8 mmol (576mg) of glycal **3b** and purified on silica gel (EtOAc/PE: 15/85) to obtain the product **4b** (510mg, 75%) as oily liquid: $[\alpha]_D^{20} = +108$ (c 0.1, CHCl₃); **¹H NMR (500MHz, CDCl₃) of 4b:** δ 7.31-7.19 (m, 5H, CHPh), 4.97 (d, $J = 3.10$ Hz, 1H, H-1), 4.70 (t, $J = 9.58$ Hz, 19.28 Hz, 1H), 4.60 (d, $J = 1.87$ Hz, 1H), 4.42 (d,

$J = 1.87$ Hz, 1H), 4.24 (dd, $J = 4.70$ Hz, 12.16 Hz, 1H), 4.08-4.02 (m, 1H), 3.97 (dd, $J = 1.70$ Hz, 12.15 Hz, 1H), 3.84 (m, 1H), 2.21 (dd, $J = 5.20$ Hz, 13.19 Hz, 1H, CH₂), 1.6-1.7 (m, 3H, H-2, CH₂), 2.04 (s, 3H, COCH₃), 2.03 (s, COCH₃, 3H). ¹³C NMR (50MHz, CDCl₃) of **4b**: δ 172.1 (-CO lactone), 171.4, 170.8 (-CO, -OCOCH₃), 137.2 (C(q) Ar), 128.5, 128.4, 128.3, 127.93, 127.9 (5 x C, Ar), 97.1 (C-1), 73.3, 69.2, 68.0, 67.6, 63.3 (C-3, C-4, C-5, C-6, -CH₂-Ar), 37.9 (CH₂, lactone), 35.5 (C-2), 20.9 (-OCOCH₃), 20.8 (-OCOCH₃). ESI MS (m/z): 401 [M+Na]. Anal. Cal. for C₁₉H₂₂O₈: C, 60.31, H, 5.86; Found: C, 60.22, H, 5.76.

4c

Prepared by the general procedure **1** using 1.8 mmol (489mg) of glycol **3c** and purified on silica gel (EtOAc/PE: 18/82) to obtain the product **4c** (427mg, 72%) as oily liquid: $[\alpha]_D^{20} = +78$ (c 0.1, CHCl₃); ¹H NMR (500MHz, CDCl₃) of **4c**: δ 5.32 (d, $J = 2.09$ Hz, 1H, H-1), 4.99-4.98 (m, 1H, H-4), 4.26-4.44 (m, 1H, H-6a/H-6b), 4.11-4.08 (m, 1H, H-6a/H-6b), 4.02-4.00 (m, 2H, H-3, H-5), 3.93-3.90 (m, 1H, CH(CH₃)₂), 2.91-2.86 (m, 1H, H-2), 2.61-2.58 (m, 2H, H1'a, H1'b), 2.09 (s, 3H, COCH₃), 2.07 (s, 3H, COCH₃). ¹³C NMR (50MHz, CDCl₃) of **4c**: 174.2 (-CO lactone), 170.0 (-OCOCH₃), 169.4 (-OCOCH₃), 94.7 (C-1), 69.2, 68.7, 65.5, 62.1, 61.6 (C-3, C-4, C-5, C-6, -OC), 41.7 (CH₂ lactone), 30.6 (C-2), 23.2, 23.0 (CH₃), 20.8, 20.7 (OCOCH₃). ESI MS (m/z): 353 [M+Na]. Anal. Cal. for C₁₅H₂₂O₈: C, 54.54, H, 6.71; Found: C, 54.44, H, 6.60.

4d

Prepared by the general procedure **1** using 1.8 mmol (604mg) of glycal **3e** and purified on silica gel (EtOAc/PE: 15/85) to obtain the product **4d** (460mg, 65%) as oily liquid: $[\alpha]_D^{20} = +62$ (c 0.1, CHCl₃); **¹H NMR (500MHz, CDCl₃) of 4d:** δ 7.29-7.26 (m, 2H, CHPh), 7.10-7.04 (m, 2H, CHPh), 5.65 (d, $J = 4.65$ Hz, 1H, H-1), 5.01 (t, $J = 3.29$ Hz, 6.55 Hz, 1H, H-4), 4.16-4.14 (m, 2H, H-6a, H-6b), 4.02-4.0 (m, 2H, H-3, H-5), 2.73-2.70 (m, 1H, H-2), 2.58 (dd, $J = 7.5$ Hz, 16.79 Hz, 1H, H-7a/H-7'b), 2.28 (s, 3H, ArCH₃), 2.04 (s, COCH₃), 1.99 (s, COCH₃). **¹³C NMR (50MHz, CDCl₃) of 4d:** δ 172.0 (-CO lactone), 170.0 (OCOCH₃), 169.9 (OCOCH₃), 139.0 (C (q), Ar), 134.8, 133.7, 130.3, 130.2 (4 x CH-Ar), 98.7 (C-1), 69.2, 67.4, 63.1, 62.5 (C-3, C-4, C-5, C-6), 38.3 (CH₂-lactone), 35.2 (C-2), 21.1 (CH₃-Ar), 20.9 (-OCOCH₃), 20.7(-OCOCH₃). ESI MS (m/z): 401 [M+Na]. Anal. Cal. for C₁₈H₂₀O₇: C, 56.83, H, 5.30; Found: C, 56.70, H, 5.19.

Copies of ^1H NMR, ^{13}C NMR along with ^1H - ^1H COSY, HMBC, and HSQC of some of the reference compounds

NMR at 500 MHz with CDCl₃ as solvent

¹³C NMR of compound 2a

^1H - ^1H COSY of compound 2a

NMR at 500 MHz with CDCl₃ as solvent

^1H - ^1H COSEY of compound 2b

NMR at 500 MHz with CDCl₃ as solvent

¹H NMR of compound 2c

¹³C NMR of compound 2c

NMR at 500 MHz with CDCl₃ as solvent

[illegible]

¹³C NMR of compound 2e

CC(C)(C)Si(C)(C)CO[C@H]1C[C@@H](OC(C)(C)C(C)(C)C(C)(C)C(C)(C)C)[C@H](OC(C)(C)C(C)(C)C(C)(C)C(C)(C)C)[C@@H](OC(=O)C)[C@H]1O

NMR at 500 MHz with CDCl₃ as solvent

¹³C NMR of compound 4a

NOSEY of compound 4a

HSQC of compound 4a

NMR at 500 MHz with CDCl₃ as solvent

¹H NMR of compound 4b

¹³C NMR of compound 4b

¹H-¹H COSY of compound 4b

hmbe od compound 4b

NMR at 500 MHz with CDCl₃ as solvent

NMR at 500 MHz with CDCl₃ as solvent