A Phosphine mediated synthesis of 1,4-oxazepine and 1,5-oxazocine based sugar hybrids from deoxysugar azides.

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Synthesis of deoxy sugar azides:

6-O-\(p\)-Toluenesulfonyl-3-deoxy-1,2-O-isopropylidened\(\alpha\)-D-glucofuranose (B). To the solution of A\(^1\) (3.0 g, 13.6 mmol) in pyridine (20 mL), \(p\)-toluenesulfonyl chloride (3.8 g, 20.4 mmol) was added in portions at 0 °C and reaction mixture allowed to stir for overnight at room temperature. Reaction mixture was diluted with ice water and neutralized with 1N HCl to pH 6 followed by extraction with dichloromethane (3X30 mL), combined organic layer washed with brine and dried over anhydrous sodium sulfate. After evaporation of solvent followed by purification using silica gel chromatography to furnish B, (2.3g); Yield 45%; \([\alpha]^{24.4}_{D} = -1^\circ\) (c 0.5, CH\(_3\)OH); IR (thin film): 671, 760, 929, 1035, 1216, 1421, 1520, 1730, 2403, 3021 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.26 (s, 3H, acetonide C\(\text{H}_3\)), 1.43 (s, 3H, acetonide C\(\text{H}_3\)), 1.74 (ddd, \(J = 17.6, 10, 4.4\) Hz, 1H, deoxyglucofuranose H-3), 2.00 (ddd, \(J = 26.4, 13.2, 4.4\) Hz, 1H, deoxyglucofuranose H-3), 2.41 (s, 3H, \(p\)-Ph\(\text{CH}_3\)), 2.84 (br s, 1H, deoxyglucofuranose C-5, O\(\text{H}\)), 3.91-3.95 (m, 2H, deoxyglucofuranose H-4 and Ts\(\text{OCH}_2\)), 4.09 (m, 2H, deoxyglucofuranose H-4 and Ts\(\text{OCH}_2\)), 4.68 (t, \(J = 4.4\) Hz, 1H, deoxyglucofuranose H-5), 5.26 (s, 1H, deoxyglucofuranose H-2), 5.71 (d, \(J = 3.6\) Hz, 1H, deoxyglucofuranose H-1), 7.32 (d, \(J = 8.0\) Hz, 2H, \(p\)-CH\(_3\)Ph\(H\)), 7.75 (d, \(J = 8.0\) Hz, 2H, \(p\)-CH\(_3\)Ph\(H\)); \(^{13}\)C NMR (100.6 MHz,
CDCl₃) δ 145.1, 132.4, 130.0 (2C), 128.0 (2C), 111.4 (acetonide C(Me)₂), 105.4 (glucofuranose C-1), 80.4 (glucofuranose C-2), 77.6 (glucofuranose C-4), 71.2 (glucofuranose C-5), 70.2 (glucofuranose CH₂N₃), 34.2 (glucofuranose C-3), 26.7 [C(CH₃)₂], 26.1 [C(CH₃)₂], 21.6 (p-CH₃Ph).

6-Azido-3,6-di-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (12). To a solution of B (2.3 g, 6.14 mmol) in DMF (20 mL), sodium azide (2.13 g, 30.7 mmol) was added and reaction mixture allowed to stir for 18 hours at 90 °C. Reaction mixture was diluted with ice water and extraction with dichloromethane (3X30 mL), combined organic layer washed with brine and dried over anhydrous sodium sulfate. After evaporation of solvent to furnish 12, (1.2g); Yield 80%; [α]₂⁴⁺.６ D = -13° (c 0.5, CH₃OH); IR (thin film): 669, 758, 931, 1215, 1524, 2105, 2401, 3019 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.31(s, 3H, acetonide CH₃), 1.50 (s, 3H, acetonide CH₃), 1.85 (ddd, J = 15.6, 10.8, 4.8 Hz, 1H, deoxyglucofuranose H-3), 2.01 (dd, J = 13.2, 4.4 Hz, 1H, deoxyglucofuranose H-3), 2.30 (d, J = 2.8 Hz, 1H, deoxyglucofuranose H-3), 3.36 (ddd, J = 21.6, 12.8, 4.0 Hz, 2H, N₃CH₂), 3.96-3.99 (m, 1H, deoxyglucofuranose H-5), 4.17 (ddd, J = 15.2, 9.6, 5.2 Hz, 1H, deoxyglucofuranose H-4), 4.76 (t, J = 3.6 Hz, 1 Hz, deoxyglucofuranose H-2), 5.80 (d, J = 3.6 Hz, 1H, deoxyglucofuranose H-1); ¹³C NMR (100.6 MHz, CDCl₃) δ 111.5 (acetonide C(Me)₂), 105.3 (C-1), 80.6 (C-2), 78.6 (C-4), 70.9 (C-5), 53.3 (CH₂N₃), 33.3 (C-3), 26.8 [C(CH₃)₂], 26.1 [C(CH₃)₂].

6-Azido-3,6-di-deoxy-1,2-O-isopropylidene-α-D-gulo-1,4-furanose (13).
To a solution of C² (3.40 g, 15.45 mmol) in pyridine (20 mL), p-toluenesulfonyl chloride (3.2 g, 16.9 mmol) was added in portions at 0 °C and reaction mixture allowed to stir for overnight at
room temperature. Reaction mixture was diluted with ice water and neutralized with 1N HCl to pH 6 followed by extraction with dichloromethane (3X30 mL), combined organic layer washed with brine and dried over anhydrous sodium sulfate. After evaporation of solvent to furnish crude tosylate D, (4.6 g). To the solution of crude D (4.6 g, 12.29 mmol) in DMF (30 mL), sodium azide (8.48 g, 122.9 mmol) was added and reaction mixture allowed stir for 18 hours at 90 °C. Reaction mixture was diluted with ice water and extraction with dichloromethane (3X30 mL), combined organic layer washed with brine and dried over anhydrous sodium sulfate followed by evaporation of solvent and purification on silica gel column chromatography in EtOAc: Hexane to furnish 13, (900 mg).

Yield 25% For two steps; [α]²⁴D = -31.2 (c 0.5, CH₃OH); IR (thin film): 669, 759, 923, 1215, 2106, 2401, 3019 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) δ 1.32(s, 3H, acetonide CH₃), 1.56 (s, 3H, acetonide CH₃), 2.05 (dd, J = 14.4, 2.0 Hz, 1H, deoxyglucofuranose H-3), 2.22-2.29 (m, 1H, deoxyglucofuranose H-3), 3.03 (dd, J = 2.8 Hz, 1H, deoxyglucofuranose C-5, OH), 3.30 (dd, J = 12.8, 6.0 Hz, 1H, N₃CH₂ H-6), 3.40 (dd, J = 12.8, 4.4 Hz, 1H, N₃CH₂), 3.90-3.96 (m, 1H, deoxyglucofuranose H-5), 4.21 (dd, J = 18, 9.2, 2.4 Hz, 1H, deoxyglucofuranose H-4), 4.77 (app. t, J = 5.2 Hz, 1H, deoxyglucofuranose H-2), 5.82 (d, J = 4.0 Hz, 1H, deoxyglucofuranose H-1); ¹³C NMR (100.6 MHz, CDCl₃) δ 112.7 (acetonide C(Me)₂), 106.3 (C-1), 81.5 (C-2), 80.6 (C-4), 72.1 (C-5), 53.2 (CH₃N₃), 33.4 3 (C-3), 27.0 (CH₃)₂, 25.9 (CH₃)₂).

**Methyl 6-Azido-6-deoxy-2,3-isopropylidine-α-D-mannopyranoside (20).** To a solution of Methyl 6-azido-6-deoxy-α-D-mannopyranoside³ E (2.0 g, 9.13 mmol) in acetone (20 mL), ρTSA (0.23 g, 1.80mmol) and 2,2’ dimethoxypropane (1.1 g, 1.09 mmol) was added at room temperature and reaction mixture allowed to stir for 18 hours at same temperature. Reaction mixture was evaporated to dryness diluted with ice water and saturated NaHCO₃ (10 mL)
followed by extraction with ethyl acetate (3X30 mL), combined organic layer washed with brine and dried over anhydrous sodium sulfate. After evaporation of solvent and purification using silica gel column chromatography to furnish 20 (1.8 g); Yield 78%; $[\alpha]_{D}^{24.6} = -8.8^\circ$ (c 0.5, CH$_3$OH); IR (thin film): 669, 758, 1215, 2105, 2401, 3019, 3436 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.36 (s, 3H, acetonide CH$_3$), 1.53 (3H, acetonide CH$_3$), 3.13 (bs, 1H, mannose C-4, OH), 3.44 (s, 3H, mannose OCH$_3$), 3.49-3.61 (m, 3H, N$_2$CH$_2$ and mannose H-4), 3.68-3.76 (m, 1H, mannose H-5 and H-3), 4.08-4.15 (m, 2H, mannose H-2 and H-3), 4.93 (s, 1H, mannose H-1); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 109.9 (acetonide C(Me)$_2$), 98.4 (mannose C-1), 78.5 (C-3), 75.6 (C-5), 70.2 (C-4), 69.4 (C-2), 55.3(OCH$_3$), 51.8 (CH$_2$N$_3$), 28.0 [C(CH$_3$)$_2$], 26.1 [C(CH$_3$)$_2$]; LCMS = 260.1 (M+1).

References:

Sample Name:
Data Collected on: DEER600-wm600
Archive directory:
Sample directory:
File Name: ADV-P-418-030
Pulse Sequence: Proton (2D-pul)
Subject: okc3
Data collected on: Apr 23 2010

Temp. 25.6 C / 298.1 K
Operator: wmr1
Relax. delay 1,300 sec
Pulse 45.0 degrees
Acq. time 1,700 sec
Wm/s 891.2 Hz
128 repetitions
CHANNEL 80, 399.900708 Hz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 65536
Total time 31 min

Sample Name:
Data Collected on: DEER600-wm600
Archive directory:
Sample directory:
File Name: ADV-P-418-030_LNC
Pulse Sequence: MRNO (2D-pul)
Subject: okc3
Data collected on: Apr 23 2010

Temp. 25.6 C / 298.1 K
Operator: wmr1
Relax. delay 1,000 sec
Pulse 45.0 degrees
Acq. time 1,260 sec
Wm/s 891.2 Hz
128 repetitions
CHANNEL 80, 399.900465 Hz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 15 hr, 55 min
S-23
S-24