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Formal synthesis of furanodictine B from D-glucose

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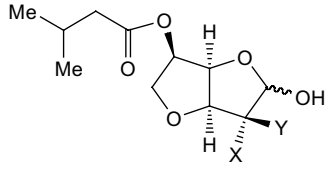
Abstract—An efficient formal synthesis of furanodictine B **1b** is described starting from D-glucose. The synthetic protocol is based on deriving the bicyclic intermediate **2** from D-glucose by a modified method and its further manipulations to obtain the advanced intermediate **8**. Methanolysis of compound **2** to the 2-hydroxy derivative **3** followed by its conversion to the corresponding 2-*O*-triflate **4** is described. Inversion of configuration at C(2) of compound **4** by nucleophilic displacement with NaN_3 gives the azido derivative **5**. Straightforward reactions of azide derivative **5** to the corresponding amine **6**, *N*-acetyl derivative **7** and to the required template **8** are described. Conversion of **8** to the natural product **1b** has previously been reported.

1. Introduction

Isolation of biologically active substances from natural sources with the potential for development as new drugs continues to be explored. In this pursuit, Oshima and co-workers have explored secondary metabolites produced by cellular slime moulds for their pharmacological activities[1–4] and isolated two novel aminosugar analogues, furanodictine A **1a** and B **1b**[5] from the methanolic extract of the multicellular fruit body of *Dictyostelium discoideum* and shown that they exhibited neuronal differentiation activity[6] (Fig. 1). Compounds **1a** and **1b** are the first examples of amino sugars with a 3,6-anhydrohexofuranose carbon skeleton. The absolute configurations of **1a** and **1b** were established as (2*R*,3*R*,4*S*,5*R*), and (2*S*,3*R*,4*S*,5*R*) by total synthesis from *N*-acetyl-D-glucosamine and *N*-acetyl-D-mannosamine, respectively.[5] A second synthetic route to prepare **1a** and **1b** was reported starting from D-arabinose.[7] Synthesis of the bicyclic bis-tetrahydrofurofuran structures, such as those present in **1a** and **1b**, has been the subject of our interest[8] as they constitute an integral part of several other natural products.[9] In spite of the above reported methods, there is still a need to prepare large quantities of such pharmacophore containing compounds from easily available raw materials by simple methods. Accordingly, a synthetic strategy starting from easily available raw material D-glucose was designed and executed.



1a) Furanodictine A (X=NHAc, Y=H)

1b) Furanodictine B (X=H, Y=NHAc)

Figure 1.

2. Results and discussion

The retrosynthetic analysis of **1b** has indicated that the absolute configurations at C(4), C(5) and C(6) are the same as those present in D-glucose at C(3), C(4) and C(5), respectively. The stereocentre at C(3) of **1b** can be derived by nucleophilic inversion (S_N2) of configuration at C(2) of D-glucose by azide. The bicyclic 3,6-anhydro sugar **3** can be constructed through the intramolecular cyclization of the C(3) hydroxyl group with C(6) by a simple protocol developed earlier by us (Fig. 2). Execution of the retrosynthetic plan is summarized in Scheme 1.

D-Glucose was converted to the 3,6-anhydro sugar derivative **2** by reaction of 1,2-*O*-isopropylidene glucofuranose with diethylcarbonate/NaH/THF by the modified method earlier described by us for the synthesis of bicyclo nucleosides (Scheme 1).[8]

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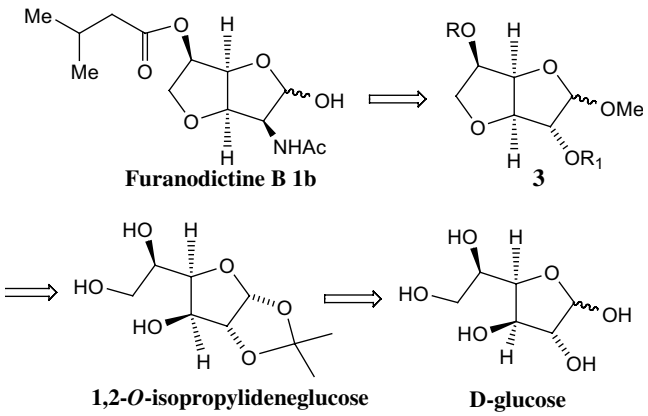
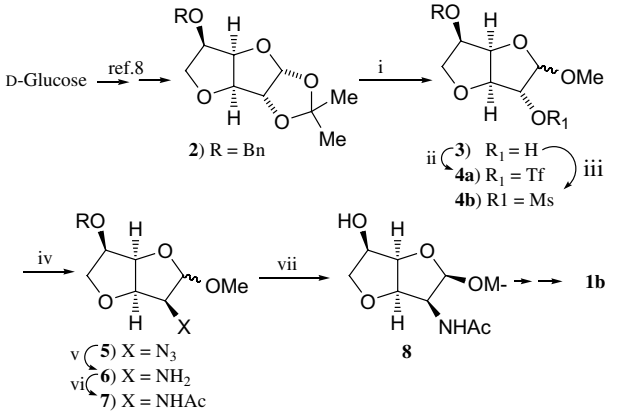


Figure 2.



Scheme 1. Reagents and conditions: (i) IR120-H^+, MeOH, reflux, 2 h, 85%; (ii) Tf_2O, pyridine, 0 °C to rt, 1 h, 87%; (iii) MsCl, Et_3N, 0 °C; (iv) NaN_3, DMF, 60 °C, 6 h, 87%; (v) Ph_3P, THF–CH_2Cl_2, rt, 3 h, 81%; (vi) Ac_2O, pyridine, CH_2Cl_2, rt, 2 h, 95%; (vii) $Pd(OH)_2/C/H_2$, MeOH, 1 atm, 2 h, 95%.

The bicyclic compound **2** on methanolysis catalyzed by ion exchange resin gave the 2-hydroxy derivative **3** in 85% yield as a diastereomeric mixture (anomeric ratio $\alpha/\beta = 2{:}3$). Compound **3**, on reaction with triflic anhydride/pyridine gave the corresponding 2-*O*-triflate derivative **4a**, which on nucleophilic displacement (S_N2) reaction with NaN_3/DMF/60 °C smoothly afforded the azido derivative **5**. A similar nucleophilic displacement reaction of the 2-*O*-mesylate derivative **4b** with NaN_3/DMF/80 °C was unsuccessful. Reduction of the azido derivative **5** was achieved with $Ph_3P/H_2O/CH_2Cl_2$ to afford amine **6** contaminated with phosphorus by-products. Compound **6** was purified as the hydrochloride salt. Compound **6** was acetylated (Ac_2O/Py) to give compound **7** (mp 94–97 °C), which was subjected to hydrogenolysis [$Pd(OH)_2/C/H_2$/1 atm/MeOH] to isolate the required methyl 3,6-anhydro-*N*-acetylamino-β-D-mannofuranoside **8** as a crystalline solid (mp 174–175 °C). Compound **8** was characterized by ^{1}H NMR (300 MHz, $CDCl_3$) spectrum from the appearance of H-1 at δ 4.97 as a doublet ($J = 2.3$ Hz), methoxy group at δ 3.36 and acetyl group at δ 2.01. ^{1}H NMR data of compound **8** was in agreement with that reported in the literature.[5] Compound **8** exhibited a specific rotation of $[\alpha]_D^{25} = +148$ (*c* 0.8, MeOH) and mass of M^+ 218, which is in agreement with the structure. The advanced intermediate **8** was obtained in 13.2% overall yield from D-glucose. Conversion of compound **8** to the natural product **1b** has been reported earlier[5] there by completing the formal synthesis of **1b**.

3. Conclusion

In conclusion, a simple and efficient route for the formal total synthesis of furanodictine B **1b** has been developed starting from D-glucose. The synthetic protocol developed offers advantages to synthesize the analogues required for the development of new drugs.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance (300 MHz) and Varian Gemini (200 MHz) instruments with tetramethyl silane as the internal standard for solutions in $CDCl_3$. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a JASCO DIP-370 polarimeter. Melting points were determined by using Fischer–John's melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer 1310 spectrometer.

4.2. Methyl 3,6-anhydro-5-*O*-benzyl-D-glucofuranoside 3

To a solution of compound **2** (4.0 g, 13.66 mmol) in methanol was added IR120-H+ (2.0 g) and refluxed for 2 h. When TLC revealed the absence of starting material, the solution was decanted from the resin, concentrated and purified by column chromatography to afford the title compound **3** (3.12 g, 85%) as a syrup; $[\alpha]_D^{25} = +143$ (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm, *J* Hz) (diastereomeric mixture): 7.40–7.20 (m, 5H, Ar-H); 5.05 (d, 0.3H, 2.1, H-1); 4.90 (s, 0.7H, 2.1, H-1); 4.82–3.60 (m, 7H, H2–H6, $PhCH_2$); 3.45, 3.40 (2s, OMe). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.38; H, 6.65.

4.3. Methyl 3,6-anhydro-5-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-glucofuranoside 4a

To a solution of compound **3** (3.0 g, 11.1 mmol) in CH_2Cl_2 was added pyridine (2.6 mL, 33.5 mmol) and triflic anhydride (2 mL, 11.9 mmol) at 0 °C after which it was stirred at room temperature for 1 h. When TLC revealed no starting material, the solution was diluted with dichloromethane (200 mL), washed with dil HCl (2 × 50 mL), water (2 × 80 mL), brine solution (2 × 50 mL) and then dried over Na_2SO_4. Removal of the solvent gave the title compound **4a** (3.8 g, 87%) as a syrup; $[\alpha]_D^{25} = +160$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm, *J* Hz) (diastereomeric mixture): 7.40–7.20 (m, 5H, Ar-H); 5.21 (d, 0.3H, H-1); 5.14 (s, 0.7H, H-1); 5.04 (s, 0.7H, H-2);

4.95–4.50 (m, 4.7H, H-1,3,4,5, $PhCH_2$); 4.10–3.60 (m, 2H, H-6,6); 3.48, 3.43 (2s, OMe). Anal. Calcd for $C_{15}H_{17}F_3O_7S$: C, 45.23; H, 4.30. Found: C, 45.34; H, 4.45.

4.4. Methyl 3,6-anhydro-5-*O*-benzyl-2-*O*-methanesulfonyl-D-glucofuranoside 4b

To a solution of compound **3** (25 g, 9.2 mmol) in CH_2Cl_2 was added triethylamine (38 mL, 27.3 mmol) and methanesulfonyl chloride (11 mL, 13.7 mmol) at 0 °C and stirred at room temperature for 1 h. When TLC revealed no starting material, the solution was diluted with dichloromethane (150 mL), washed with water (2 × 50 mL), $NaHCO_3$ solution (2.2 g in 100 mL water), brine solution (50 mL) and then dried over Na_2SO_4. Removal of solvent gave the title compound **4b** (3.6 g, 90% yield) as a syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm, *J* Hz) (diastereomeric mixture): 7.38–7.20 (m, 5H, Ar-H); 5.31 (s, 0.3H, H-1); 5.31–5.11 (m, 1.3H, H-1,2); 4.90–4.50 (m, 4.7H, H-1,3,4,5, $PhCH_2$); 4.10–3.60 (m, 2H, H-6,6); 3.48, 3.43 (2s, OMe); 3.08, 3.03 (2s, SO_2Me). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.38; H, 6.65.

4.5. Methyl 3,6-anhydro-2-azido-5-*O*-benzyl-2-deoxy-D-mannofuranoside 5

To a solution of compound **4a** (3.7 g, 9.25 mmol) in DMF was added NaN_3 (1.8 g, 27.8 mmol) and heated to 60 °C for 3 h. When TLC revealed the absence of starting material, the reaction mixture was diluted with water and extracted into ether. The ether layer was washed with water, dried over Na_2SO_4 and concentrated to gave the title compound **5** (2.3 g, 87%) as a syrup; $[\alpha]_D^{25} = +93$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm, *J* Hz) (diastereomeric mixture): 7.4–7.30 (m, 5H, Ar-H); 4.91 (d, 1H); 4.85–4.65 (m, 2H); 4.10–3.55 (m, 4H); 3.48–3.41 (2s, OMe). IR: 2130 cm^{-1} ($CHCl_3$). Anal. Calcd for $C_{14}H_{17}O_4N_3$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.98; H, 5.79; N, 14.29.

4.6. Methyl 2-amino-3,6-anhydro-5-*O*-benzyl-2-deoxy mannofuranoside 6

To a solution of compound **5** (2.2 g, 7.5 mmol) in THF/CH_2Cl_2 (20 mL/5 mL) was added triphenylphosphine (4.4 g, 16.8 mmol), two drops of water and stirred for 2 h. When TLC revealed no starting material, the reaction mixture was concentrated, dissolved in CH_2Cl_2 (100 mL) and treated with 10% aq HCl (50 mL) solution. The acidic aqueous phase was separated, washed with CH_2Cl_2 (50 mL), neutralized with 5% aq NaOH and extracted into CH_2Cl_2, washed with water, dried over Na_2SO_4 and concentrated to give the title compound **6** (1.6 g, 81% yield) as a syrup; ^{1}H NMR data (300 MHz, $CDCl_3$) δ (ppm, *J* Hz) (diastereomeric mixture): 7.20–7.40 (m, 5H, Ar-H); 4.25–4.80 (2d, 1H, 12); 4.74–4.65 (2s, 1H); 4.66–4.70 (t, 1H, 11.2); 4.57–4.60 (2s, 1H); 4.40–4.46 (t, 1H, 11.2); 4.02–4.08 (dd, 1H, 9.1, 5.2); 3.9–3.96 (dd, 1H, 9.1, 5.2); 3.68–3.74 (t, 1H, 24); 3.45 (s, OMe); 3.25–3.28 (t, 1H, 16.4). Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.54; H, 7.15; N, 5.29.

4.7. Methyl 2-acetamido-3,6-anhydro-5-*O*-benzyl-2-deoxy mannofuranoside 7

To a solution of compound **6** (1.4 g, 5.2 mmol) in CH_2Cl_2 (5 mL) and pyridine (1.2 mL, 15.2 mmol) was added acetic anhydride (8 mL, 7.8 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. When TLC revealed the absence of starting material the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% aq $CuSO_4$ (2 × 50 mL), water (50 mL), dried over Na_2SO_4, concentrated and purified using column chromatography to give the title compound **7** (1.54 g, 95%) as a solid. Mp 94–97 °C; $[\alpha]_D^{25} = +143$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CDCl) δ (ppm, *J* Hz) (diastereomeric mixture): 7.20–7.30 (m, 5H, Ar-H); 4.90 (d, 1H, 1.8); 4.72–4.70 (2s, 1H); 4.65 (d, 2H, 6.2); 4.52–4.50 (2s, 1H); 4.18–4.28, 4.0–4.10 (2dd, 2H, 8.9, 5.2); 3.90 (d, 2H, 3.2); 3.20–3.30 (2s, OMe); 2.10– 1.80 (2s, OAc). Anal. Calcd for $C_{16}H_{21}O_5N$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.75; H, 6.97; N, 4.53.

4.8. Methyl 2-acetamido-3,6-anhydro-2-deoxy-β-D-mannofuranoside 8

To a solution of compound **7** (1.1 g, 3.5 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ (100 mg) and stirred under hydrogen atmosphere (1 atm). When TLC revealed the absence of starting material, the catalyst was filtered off and washed with MeOH. The combined filtrates were concentrated and purified by column chromatography to give the title compound **8** (0.71 g, 95%) as a colourless solid. Mp 174–175 °C, $[\alpha]_D^{25} = +142$ (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm, *J* Hz): 6.30 (br s, 1H, NH); 4.97 (d, 1-H, 2.3, H-1); 4.64–4.78 (m, 2H, H-2,3); 4.17–4.27 (m, 2H, H-4,5); 3.81–3.92 (m, 2H, H-6,6); 3.36 (OMe). FAB MS (*m/z*) 218 (M^+). Anal. Calcd for $C_9H_{15}O_5N$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.89; H, 6.99; N, 6.37.

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