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Synthesis of *bis*(1,3-Dihydroxy-*iso*propyl)amine by Reductive Amination of Dihydroxyacetone: Open Chain Equivalent of DMDP and a Potential AB_4 Dendritic Monomer

David A. Scott,[a] Thomas M. Krülle,[a,c] Malcolm Finn,[a] Robert J. Nash,[b] Ana L. Winters,[b] Naoki Asano,[c] Terry D. Butters[d] and George W. J. Fleet[a*]

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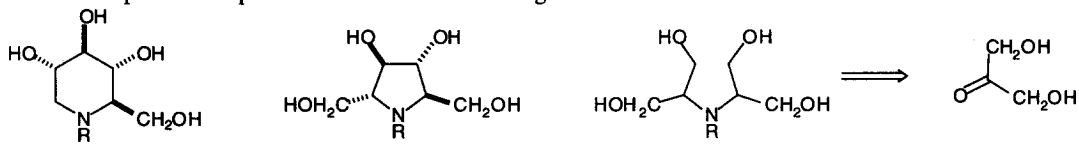
[a]Dyson Perrins Laboratory, Oxford Centre for Molecular Sciences, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK.
[b]Institute of Grassland and Environmental Research, Plas Gogerddan, Aberystwyth, Dyfed, SY23 3EB, UK.
[c]Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa 920-11, Japan.
[d]Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QY, UK.
[e]British Biotech Pharmaceuticals Ltd., Watlington Road, Oxford OX4 5LY, UK.

Abstract: Reductive amination of dihydroxyacetone by ammonium salts with sodium cyanoborohydride gives *bis*(1,3-dihydroxy-*iso*propyl)amine [BDI] in good yield and high purity. BDI and its diacetonide are hindered nucleophiles but may be further reductively alkylated to form *N*-alkyl derivatives. BDI is an open chain equivalent of DMDP [2,5-dideoxy-2,5-imino-D-mannitol] but neither BDI nor its *N*-alkyl derivatives show inhibition of any glycosidase or transferase assayed. BDI may provide an example of an AB_4 dendritic monomer.

This paper reports the efficient synthesis of *bis*(1,3-dihydroxy-*iso*propyl)amine [BDI] **5** and its *N*-butyl derivative **6**, in which the key step is reductive amination of dihydroxyacetone under conditions where two units of dihydroxyacetone are condensed. Deoxynojirimycin (DNJ) **1** and DMDP **3** are members of an extensive family of naturally occurring and synthetic nitrogen analogues of monosaccharides with a range of biological activities, the best known of which is their specific inhibition of glycosidases; for example, both DNJ and DMDP - widely distributed in plants - are potent inhibitors of various α-glucosidases.[1]



1: R = H
2: R = *n*-butyl

3: R = H
4: R = *n*-butyl

5: R = H
6: R = *n*-butyl

dihydroxyacetone

N-Alkylation of these amines changes their biological activities and the *N*-butyl derivatives **2** and **4** show antiviral properties,[2] probably by modifying *N*-linked glycoprotein processing by inhibition of glucosidases. Additionally such modifications may increase lipid solubility, and thus intracellular bioavailability. Enzymes other than hydrolases are affected. *N*-ButylDNJ **2** and *N*-butylDMDP **4** inhibited UDP-glucose-ceramide transferase,[3] a key enzyme involved in the biosynthesis of glycosphingolipids; inhibition of this biosynthetic pathway may provide a strategy for the treatment of a number of genetic storage diseases arising from the enzyme deficiencies, including Tay-Sachs and Gauchers diseases.[4] In a search for a compound which is specific for the transferase, a large number of *N*-alkylated analogues of various azafuranose and azapyranose sugars have been evaluated. The structure activity relationship of such materials is not easy to rationalise; inhibition of UDP-glucose-ceramide transferase is not dependent on UDP-glucose concentration, so it appears that the inhibitors mimic ceramide rather than the sugar. There are 10 stereoisomers of DMDP but hydrogenolytic cleavage of the C3-C4 bond would give rise to BDI **5** with no stereogenic centres. Some less symmetrical acyclic analogues of DNJ have been shown to be moderate inhibitors of glucosidases.[5,6] *N*-Butyl BDI **6** was prepared in the hope that it might, as a ceramide analogue, inhibit the transferase significantly.

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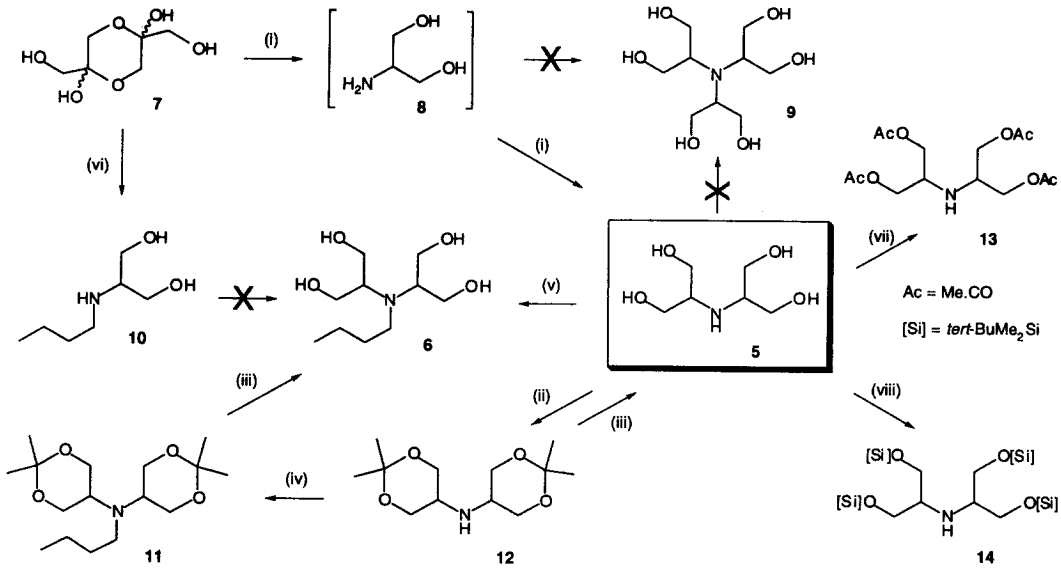

Scheme: (i) NH_4Cl or NH_4F, $NaBH_3CN$, MeOH, AcOH (ii) Me_2CO, $Me_2C(OMe)_2$, DMF, conc. H_2SO_4 (iii) CF_3COOH:H_2O, 1:1 (iv) $Me(CH_2)_2CHO$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$ (v) $Me(CH_2)_2CHO$, H_2, Pd black , H_2O (vi) $Me(CH_2)_2CH_2NH_2$, H_2, Pd black, H_2O (vii) excess Ac_2O, pyridine (viii) *tert*-$BuMe_2SiCl$ (6 equiv.), imidazole, DMF

BDI **5** may be efficiently prepared by the reductive amination of ammonium salts and dihydroxyacetone **7** [as the dimer] by sodium cyanoborohydride [see below for a representative procedure].[7] The reductive amination takes place sequentially but there is a greater predisposition for the first product **8** to undergo a second reductive amination step than for its initial formation. The monomeric reductive amination product **8** is distinct from BDI **5** in ^1H NMR. In the presence of 6 equivalents of ammonium ions to one equivalent of **7**, the ratio of BDI **5** to serinol **8** formed was approximately 1.8 to 1 as judged by ^1H NMR. GCMS analysis of the trimethylsilyl derivatives of mixtures of serinol **8** and BDI **5** allowed quantitative analysis of the proportions of the two products formed in these reductions;[8] no trace of **8** was found when dihydroxyacetone **7** was used in a two-fold molar excess to the ammonium salt. No conditions have yet been found which result in a third reductive amination, potentially to give **9**; no trace of this trimeric product was detected by GCMS or otherwise. The only basic product formed in the reaction is BDI **5**, which can thus readily be obtained in a pure form by ion exchange chromatography in 85-90% yields based on the ammonium salt, potentially on a large scale.

The nitrogen in BDI **5** is not very nucleophilic. The major product isolated from acetylation of **5** by acetic anhydride is the tetraacetate ester **13** (60% yield), resulting from acylation of the alcohols rather than of the amine; the carbonyl stretch at 1740 cm^{-1} and a highly symmetrical ^{13}C NMR spectrum [δ_C ($CDCl_3$) 20.7 (q, CH_3), 53.5 (t, NCH_2), 63.9 (t, OCH_2), 170.7 (s, C=O)] provide strong support for **13** as the structure of the acetylated compound. Reaction of **5** with TBDMS chloride in the presence of imidazole gave the symmetrical tetrasilyl ether **14**, m.p. 35-37°C, in 78% yield. All the alcohol functions in BDI **5** were protected as the diacetonide **12** by treatment with acetone and dimethoxypropane in DMF in the presence of an acid catalyst [procedure given at the end of the paper]; **12** provides a suitable derivative of **5** for elaboration by nucleophilic attack by the amine function.

Thus reductive alkylation of the diacetonide **12** with *n*-butyraldehyde by sodium triacetoxyborohydride in dichloroethane[9] gave the *N*-butyl derivative **11**[10] in 79% yield. Removal of the acetonide protecting groups in **11** by aqueous trifluoroacetic acid gave the *N*-butyltetraol **6**[11] as a potential ceramide mimic in quantitative yield. Alternatively, *N*-butylBDI **6** may be obtained in 81% yield by direct reductive alkylation of unprotected BDI **5** by hydrogenation in the presence of palladium black. An attempt to prepare **6** by reductive amination of butylamine with dihydroxyacetone under a wide variety of conditions only led to the isolation of **10**, the product formed from one equivalent of dihydroxyacetone with one equivalent of the primary amine.

The open chain DMDP analogues BDI **5** and **6** were tested at a concentration of 1 mM against a number of glycosidases but there was no significant inhibition of any hydrolase.[12] *N*-ButylBDI **6** was also assayed for potential inhibition of UDP-glucosyl ceramide transferase but again no effect on the enzyme was observed.[13] Derivatives of BDI **5** are not likely to be of interest in specific enzyme inhibition. Branched symmetrical small molecules have found application as monomers in dendrimer construction.[14] Dendritic building blocks are classified as AB_n compounds, where n represents the degree of branching. For nearly all dendritic compounds, n = 2 or 3; a more highly branched monomer would allow more units of the required peripheral functionality to be achieved in relatively few generations. BDI **5** is a very rare example of an AB_4 monomer[15] and may provide the opportunity for the development of very highly branched structures with a large array of primary hydroxyl groups. The polyhydroxylated head unit of BDI **5** has been incorporated into a range of *N*-alkylated derivatives which show potential as novel non-ionic surfactants.[16,17]

bis(1,3-Dihydroxy-isopropyl)amine [BDI] 5

Sodium cyanoborohydride (10.0 g, 159 mmol, 3 eq) was added to a solution of dihydroxyacetone dimer (28.67g, 159 mmol, 3 eq) and ammonium chloride (2.84 g, 53 mmol, 1 eq) in methanol (400 ml) and acetic acid (40 ml). After stirring for 20 hours, aqueous hydrochloric acid (2 M, 100 ml) was added, and after stirring for 4 hours the reaction was concentrated *in vacuo*, dissolved in methanol (100 ml), filtered and concentrated once more. The viscous residue was dissolved in water and applied to an ion-exchange column (Amberlite, IR120, H^+), which was eluted first with water, and then a solution of aqueous ammonia (1 M). The solvent was removed to give *BDI 5*, a hygroscopic oil, (7.49g, 85%), δ_H (200 MHz, D_2O): 2.85 (2 H, quint, J = 5.5 Hz, NCH), 3.53 (4 H, dd, J = 5.5 Hz, J = 11.5 Hz, 4 OCH), 3.61 (4 H, dd, J = 5.5 Hz, J = 11.5 Hz, 4 OCH); δ_C (50 MHz, D_2O): 58.1 (d, 2 NCH), 61.8 (t, 4 OCH_2).

bis(1,3-Dihydroxy-isopropyl)amine [BDI] Diacetonide 12

Acetone (30 ml), 2,2-dimethoxypropane (10 ml) and concentrated sulfuric acid (1 ml) were added to a solution of BDI **5** (1.71 g, 10.35 mmol) in DMF (10 ml) at room temperature. An initially formed precipitate gradually dissolved. The reaction mixture was stirred for 4 h, after which solid sodium bicarbonate (5 g) was added until the pH had risen to 7. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The aqueous layer was extracted with ethyl acetate (2 x 50ml), and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated to give *BDI diacetonide 12* (1.89 g, 74%), sufficiently pure for further elaboration. A sample of **12** was crystallised from hexane/ether, m. p. 65°C; δ_H (200 MHz, $CDCl_3$) 1.42 (12 H, s, 2 $C(C\underline{H}_3)_2$), 2.74 (2 H, m, J = 4.0 Hz, J = 6.7 Hz, 2 NCH), 3.63 (4 H, dd, J = 6.7 Hz, J_{gem} = 11.5 Hz, 4 OCH), 3.86 (4 H, dd, J = 4.0 Hz, J_{gem} = 11.5 Hz, 4 OCH); δ_H (500 MHz, acetone-d_6): 1.30, 1.34 (12 H, 2 s, 2 $C(\underline{C}H_3)_2$), 2.72 (2 H, m, 2 NCH), 3.51 (4 H, dd, J = 7.8 Hz, J_{gem} = 11.6 Hz, 4 OCH), 3.86 (4 H, dd, J = 4.8 Hz, J_{gem} = 11.6 Hz, 4 OCH); δ_C (50 MHz, acetone-d_6): 21.9, 26.1 (2 q, 2 $C(\underline{C}H_3)_2$), 49.5 (d, 2 CHN), 65.1 (t, 4 CH_2), 98.0 (s, 2 $\underline{C}(CH_3)_2$).

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7. Satisfactory spectroscopic data, together with CHN analysis or HRMS, has been obtained for all new compounds reported in this paper.

8. The silylated derivatives were prepared with a mixture of trimethylchlorosilane-hexamethyldisilazane-pyridine (1:3:9). GCMS was carried out using BPX5 capillary column (25m x 0.22 mm i.d.) and a temperature programme running from 180-250°C at 10° / minute. The detector was an EI Perkin Elmer Q-MASS 910 operating at 70eV. **5** had a retention time of 4.2 min and **8** had a retention time of 2.3 min.

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10. Selected data for the *N*-butyl diacetonide **11**: oil, δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, $CH_2C\underline{H}_3$), 1.27, 1.33 (4 H, 2 m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.37, 1.43 (12 H, 2 s, 2 $C(C\underline{H}_3)_2$), 2.67 (2 H, t, J = 6.9 Hz, NCH_2), 3.05 (2 H, quint, J = 7.8 Hz, 2 NCH), 3.73 (8 H, app. d, J = 7.8 Hz, 4 OCH_2); δ_C (100 MHz, DEPT, $CDCl_3$) 14.0 (q, $CH_2\underline{C}H_3$), 20.0 (t, $\underline{C}H_2CH_3$), 20.5, 27.2 (2 q, 2 $C(\underline{C}H_3)_2$), 33.2 (t, $NCH_2\underline{C}H_2$), 46.9 (t, NCH_2), 52.1 (d, CH), 62.5 (t, OCH_2), 97.8 (s, $\underline{C}(CH_3)_2$).

11. Selected data for *N*-butylBDI **6**: δ_H (200 MHz, D_2O) 0.83 (3 H, t, $CH_2C\underline{H}_3$), 1.09 – 1.43 (4 H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 2.68 (2 H, t, J = 7.1 Hz, NCH_2), 3.00 (2 H, quint, J = 6.9 Hz, 2 NCH), 3.50 (8 H, app. d, J = 6.9 Hz, 4 OCH_2); δ_C (50 MHz, D_2O) 14.1, (q, $CH_2\underline{C}H_3$), 20.4 (t, $\underline{C}H_2CH_3$), 32.7 (t, $NCH_2\underline{C}H_2$), 45.2 (t, NCH_2), 60.6 (t, OCH_2), 61.3 (d, CH).

12. The glycosidases assayed include α-glucosidase (yeast), β-glucosidase (almond), α-mannosidase (Jack bean), α-galactosidase (human, bovine, and *Aspergillus niger*), β-galactosidase (green coffee bean) β-N-acetylglucosaminidase (bovine kidney), naringinase (*Penicillium decumbens*) and α-L-fucosidase (bovine epididymis). Substrates were 3.5 mM p-nitrophenylglycosides and assays conducted as previously described in Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R. C.; Cairns, A. J.; Fleet, G. W. J. *Phytochemistry* **1997**, *46*, 255.

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