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A Novel Application of "Benzotriazole" Methodology : Reactions of Polyhydroxylated bis-(benzotriazolyl) piperidines with Mono- and Bidentate Nucleophiles.

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Abstract: A variety of 2,6 substituted trihydroxy piperidines **4** was synthesized with stereocontrol from the corresponding 2,6 bis-(Benzotriazolyl) trihydroxy piperidine **9**, which in turn was prepared from 1,2-O-isopropylidene-D-glucofuranose **5** employing a simple, two step chemical manipulation. These products are potential glycosidase inhibitors and can be transformed to other useful chiral products.

Many naturally occurring and designed polyhydroxylated piperidines (Aza Sugars, Fig. 1), exhibit specific and potent inhibitory activity against *glycosidases*, and are therefore pharmacologically important as potential drugs for treating viral infections including HIV, cancer, and diabetes.[1]

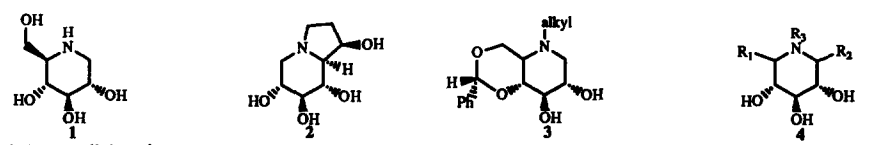


FIGURE 1

A number of syntheses of the above class of compounds has been reported,[2] which involve many steps and also extensive protection and deprotection and are limited as to the type of substitution at 2 and 6 position. Since the interest in this class of compounds continues unabated, refined methods for their preparation are still of considerable value.

We wish to report a mild, inexpensive, and, efficient way to synthesize a variety of polyhydroxylated piperidines from readily available sugars, employing the benzotriazole methodology developed and recently reviewed by Katritzky and coworkers.[3] Included in their work is the synthesis of 1,2,6-trisubstituted piperidines[4] obtained from the reaction of pentanedial, a primary amine, and two equivalents of benzotriazole, and finally displacement of the pseudohalogenic benzotriazole group with H^- or Grignard reagents. A novel and useful extension of this chemistry would be the use of polyhydroxylated, carbohydrate derived dialdehydes.

Accordingly, we have evaluated such a possibility, including the use of new types of nucleophile, and our results leading to compounds of general structure **4** are described here.

1,2-O-isopropylidene-D-glucofuranose **5** was transformed to the meso dialdehyde **7** by oxidation ($NaIO_4$) followed by hydrolysis (aqueous Dowex^R H^+). Treatment of **7** with 2 eq. benzotriazole and benzyl amine provided the bis-(benzotriazolyl) trihydroxy compound **9** as a mixture of anomers.[5]

The chemistry of displacing the benzotriazole moiety with nucleophiles without the need for hydroxyl protection was explored. Towards this end compound **9** was treated with excess of nucleophile in THF/DMSO.[6] In the event, an efficient reaction ensued in each case and the products were readily obtained in pure form by silica gel flash chromatography and/or fractional crystallization.

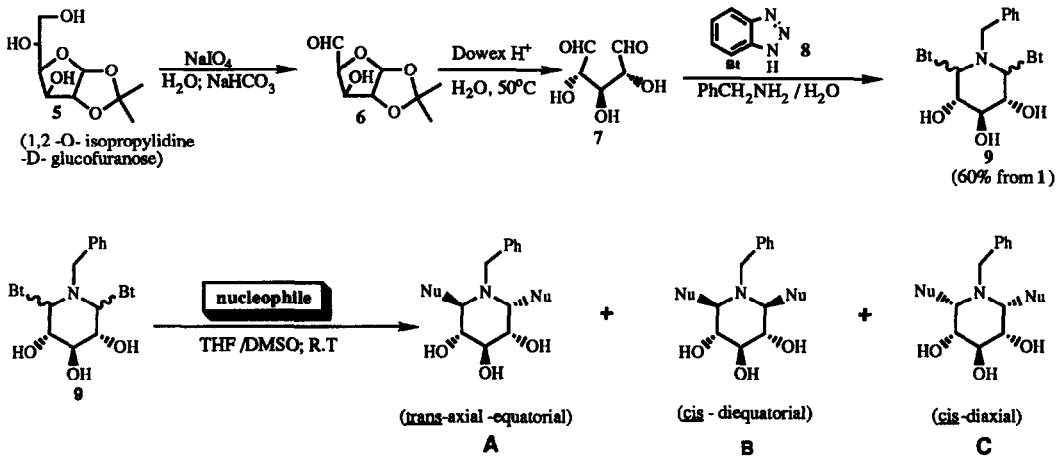
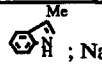


TABLE 1

Nucleophile (Reagent)	Prdct.	Yield[6] %	Ratio A : B : C	δ values for N-benzyl methylenes A	B	C
H^- ($NaBH_4$)	**10**	70	-------		3.47 singlet	
$C_2H_5^-$ (C_2H_5MgBr)	**11**	60	**3 : 1 : 1**	3.54, 3.80 (d, J = 14)	3.7 singlet	3.94 singlet
CN^- (NaCN)	**12**	70	**8 : 2 : 0**	3.54, 4.26 (d, J = 13.4)	4.08 singlet	---
CH_3S^- ($NaSCH_3$)	**13**	60	**7.5: 2: 0.5**	3.68, 4.73 (d, J = 13.9)	4.13 singlet	4.02 singlet
 ; NaH	**14**	65	**10 : 0 : 0**	3.9-4.1 (ABq)[9]		
 ; NaH	**15**	60	**0 : 1 : 9**	--	3.83 singlet [10]	3.62 singlet

The stereochemical outcome of the displacement reaction depended on the size of the nucleophile and usually resulted in the formation of *trans* isomer. In the case of *cis* substitution two isomers are possible; the diequatorial product was almost exclusively favored. The exception to this rule was the case of a bidentate nucleophile, exemplified by indolocarbazole,[8] where the *cis* diaxial isomer **15C** was predominant.[10]

^{1}H NMR spectra[7] of the *trans* and *cis* isomers were quite distinct with respect to the N-CH_2Ph signals.[11] They are nonequivalent in the *trans* isomers and appeared as AB systems (J = ~14 Hz). In the symmetrical *cis* products singlets were observed with significant chemical shift differences between the two possible isomers. This observation made the determination of isomer distribution in the product mixture by ^{1}H NMR analysis quite simple.

In summary, we have described a simple efficient route to novel aza sugar derivatives, one attractive feature of this methodology being the predictability and ease of determination of the stereochemistry. The 2,6-dicyano product **12** is also potentially useful for further modification leading to unsymmetrically substituted products and other chiral products.[12,13] Indole example **14** could be regarded as a simple example for synthesis of azasugar nucleosides. Indolocarbazole derived product **15** gives intermediates related to aza analogs of PKC inhibitor staurosporine; we will report elsewhere on our studies of compounds of this type.

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5. Compound **9** was prepared without purifying the intermediates: $NaIO_4$ (6.0 g, 0.028 mol) was added in portions over 10 min. to a solution of **5** (5.5 g, 0.025 mol) and $NaHCO_3$ (1.25 g) in water (100 mL). After stirring for 1 h the precipitated white solid was filtered off and the product was extracted from the filtrate with EtOAc. The organics were dried ($MgSO_4$), and concentrated to provide the aldehyde **6**. ^{1}H NMR showed it to be a mixture of aldehyde and it's hydrated form. The crude aldehyde was redissolved in water (60 mL) and treated with cation excahnge resin DOWEX^R (50W) H^+ (8g) at 60°C for 2 h (monitored by TLC). The resin was removed by filteration and the filterate containing the dialdehyde **7** was added to a solution of benzotriazole (5.95 g, 0.05 mol) and benzylamine (2.6 g, 0.025 mol) in water (200 mL). The reaction mixture immediately turned cloudy followed by formation of a gummy solid after 6 h. The product was extracted into 200 mL EtOAc washed with 4 X 50 mL water and dried ($MgSO_4$). Reduction of the volume to 50 mL under reduced pressure resulted in crystallization of **9**. The product was collected by filteration as a white solid; additional product crystallized from the mother liquor upon standing overnight. The combined yield was 7.2 g (60%). m.pt. = 109-111°C; Anal. Calcd for $C_{24}H_{23}N_7O_3.H_2O$. Calcd: C, 60.60; H, 5.26; N, 20.60. Found: C, 60.81; H, 5.19; N, 20.46. ^{1}H NMR analysis showed it to be stereo and regio isomeric mixture. FAB-MS: m/z = 458 $(M+1)^+$, m/z = 339 $(M-118\ (benzotriazole))^+$.
6. THF was employed as the solvent to synthesize compounds **10** and **11** and the remaining compounds were synthesized using DMSO as the solvent Typical procedure: To a DMSO / THF solution containing 4 equivalents of the nucleophile was added bis-benzotriazole **9**. After stirring for 6 h, the reaction was quenched

with aqueous ammonium chloride, diluted with EtOAc and washed in sequence with water, and aqueous sodium carbonate (to remove benzotriazole). The organics were dried ($MgSO_4$) and concentrated. The isomers were isolated by fractional crystallization/silica gel flash chromatography. Yields are unoptimized.

7. All new compounds were characterized by ^{1}H-NMR,^{13}C-NMR, MS, and combustion analysis and/or high resolution MS. **Selected Spectroscopic Data**: Compound **10:** m.pt. = 155-157°C; FAB-MS m/z =224 $(M+1)^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.78 (2x1H, ABX system, dd, J = 8, 8 Hz), 2.78 (2x1H ABX system, m), 2.86 (1H, m, collapsed to t after D_2O exch., J = 6 Hz), 3.26 (2 H, br. m, sharpens after D_2O exch.), 3.47 (2H, S), 4.68 (2H, J = 4 Hz, D_2O exch.), 4.74 (1H, d, J = 4 Hz, D_2O exch.), 7.2-7.4 (m, 5H). Compound **11A**: FABHRMS m/e 280.1911 ($M+H^+$, $C_{16}H_{26}NO_3$ requires 280.1913); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.73 (3H, t, J = 7.4Hz), 0.9 (3H, t, J = 7.4 Hz), 1.4 (2H, m), 1.87 (2H, m), 2.48 (2H, m), 3.18 (3H, m), 3.54 (1H, d, J = 14 Hz), 3.8 (1H, d, J = 14 Hz), 4.46 (1H, d, J = 2 Hz, D_2O exch.), 4.58 (2H, overlapping doublets, disappear after D_2O exch.) Compound **11B**: FABHRMS m/e: 280.1919 ($M+H^+$, $C_{16}H_{23}NO_3$ requires 280.1913); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.79 (6H, t, J = 6 Hz), 1.5 (2H, m), 1.73 (2H, m), 2.27 (2H, m), 2.93 (1H, m, collapses to t after D_2O exch., J = 9 Hz), 3.12 (2H, m), 3.7 (2H, s), 4.56 (2H, d, J = 6 Hz, D_2O exch.), 4.66 (1H, d, J = 4 Hz, D_2O exch.), 7.2-7.4 (5H, m). Compound **11C**: CI^+/CH_4 MS m/z = 280 $(M+1)^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.82 (6H, t, J = 6 Hz), 1.4 (2H, m), 1.62 (2H, m), 2.66 (2H, br. m), 3.5 (3H, br. s, sharpens after D_2O exch.), 3.94 (2H, s), 4.56 (2H, s, D_2O exch.), 4.71 (1H, s, D_2O exch.), 7.25-7.4 (5H, m). Compound **12A:** mpt. = 178-180°C; Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.54; H, 5.49; N, 15.38. Found: C, 60.86; H, 5.40; N, 14.92.; FABHRMS m/e: 274.1190 ($M+H^+$, $C_{14}H_{15}N_3O_3$ requires 274.1192); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.23 (1H, m, collapses to dd after D_2O exch., J = 8.5, 8.5 Hz), 3.34 (1H, m, collapses to dd after D_2O exch. J = 8.5, 5 Hz) 3.49 (2H, overlapping dd), 3.54 (1H, d, J = 13.43 Hz), 3.74 (1H, d, J = 5 Hz), 4.26 (1H, d, J = 13.43 Hz), 5.53 (1H, d, J = 5 Hz, D_2O exch.), 5.74 (1H, d, J = 4 Hz, D_2O exch.), 6.11 (1H, d, J = 6.5 Hz, D_2O exch.), 7.3-7.45 (5H, m). Compound **12B**: mpt. =183-185°C; FABHRMS m/e : 274.1185 (M+H+, $C_{14}H_{15}N_3O_3$ requires 274.1192); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.24 (1H, m, collapses to dd after D_2O exch. J = 6.3, 6.4 Hz), 3.61 (4H, m, overlapping dd), 4.08 (2H, s), 5.48 (1H, d, J = 4Hz, D_2O exch.), 5.8 (2H, d, J = 6 Hz, D_2O exch.) 7.3-7.45 (5H, m). Compound **15B**: CI^+/CH_4 MS m/z = 476 $(M+1)^+$;^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.81 (3H, br. m, sharpens after D_2O exch.), 3.83 (2H, s), 4.7 (1H, d, J = 2 Hz, D_2O exch.), 5.62 (2H, d, J = 4Hz, D_2O exch.), 5.76 (2H, d, J = 2.5 Hz), 7.1-7.5 (11H, m), 7.92 (2H, s), 8.18 (2H, d, J = 8 Hz). Compound **15C**: CI^+/CH_4 MS m/z = 476 $(M+1)^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.24 (1H, m, collapses to dd J = 9.9, 9.9 Hz after D_2O exch.), 3.62 (2H, s), 4.01 (2H, m, collapses to dd J = 9.9, 4.5 Hz after D_2O exch.), 4.78 (1H, d, J = 4 Hz, D_2O exch.), 5.26 (2H, d, J = 4 Hz., D_2O exch.), 5.92 (2H, d, J = 4.5 Hz.), 7.1-7.6 (11H, m), 7.94 (2H, s), 8.2 (2H, d, J = 8Hz).
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9. Signals overlap with hydroxyl bearing methine protons.
10. The hydroxyl groups are equatorially disposed with the exception of **15B**, where the *cis* diaxial nature of the indolocarbazole aza sugar forces the hydroxyls to assume axial orientation.
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