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GUANIDINE ANALOGS OF A DEOXYSUGAR

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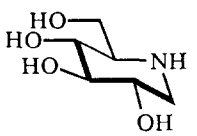
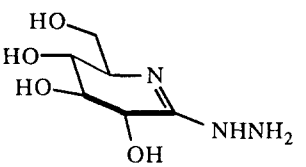
Abstract: Asymmetric syntheses of guanidine **3** and N-aminoguanidine **4** are described from (-)-epoxy alcohol **5**. Compounds **3** and **4**, which resemble D-glucose and D-mannose, were designed as generic hexopyranose substitutes and represent new templates for assembling glycomimetic structures.

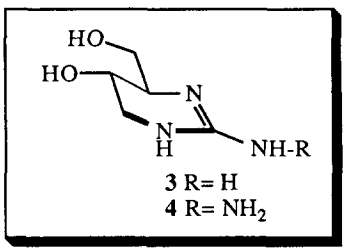
A key objective in the emerging field of *glycobiology*[1] has been the development of specific glycomimetics, i.e. carbon or heteroanalogs of sugars which mimic the structure and properties of carbohydrates. Such research has produced many linkage and configuration-specific inhibitors of glycosidases[2,3] such as the polyhydroxylated piperidines (e.g. **1**)[4,5] and amidrazones (e.g. **2**)[6,7] which disrupt the biosynthesis of N-linked glycoproteins and glycolipids that play prominent roles in immune recognition phenomena and cellular adhesion.[8-11] A major challenge for synthetic chemists is to devise non-carbohydrate templates (i.e. saccharide 'look-alikes') with which to assemble bioactive mono- and oligosaccharide analogs.



1



2

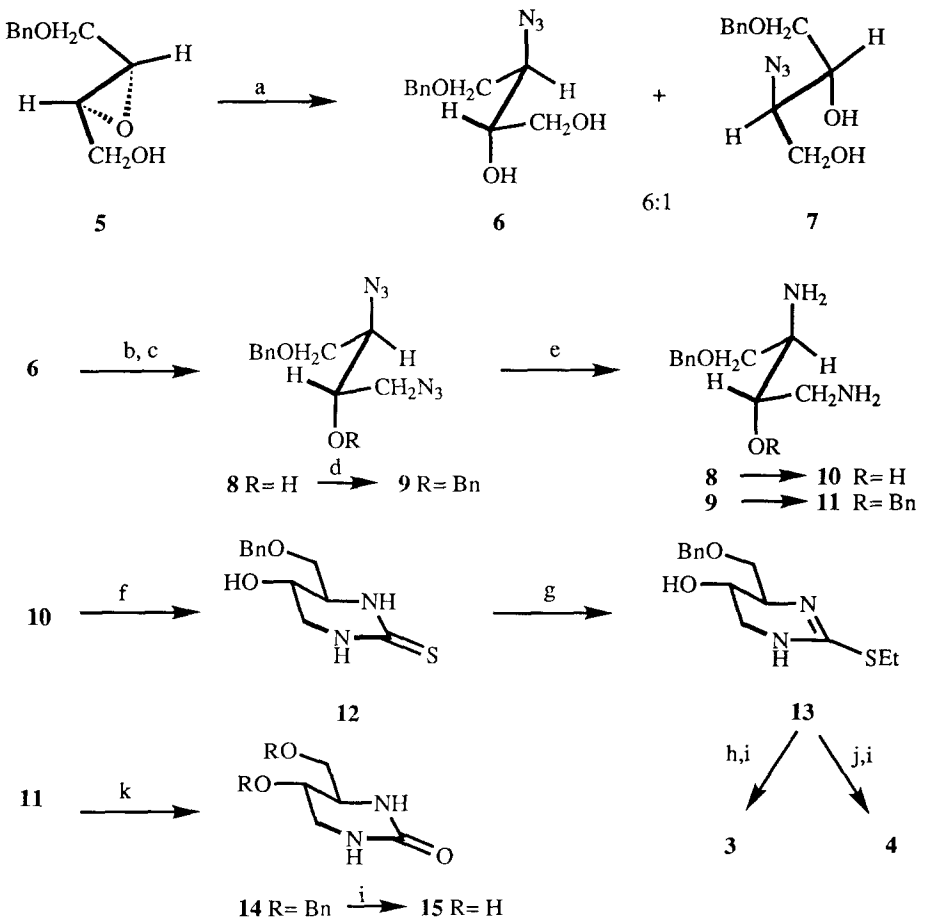


3 R= H
4 R= NH_2

We and others[12-14] have continued to explore related families of structures in designing new glycomimetic compounds for research and medicine. Here we describe an enantioselective route to guanidine **3** and N-aminoguanidine **4**, whose molecular frameworks bear close spatial relationships to a typical hexose.

Like their congener **2**, both **3** and **4** mimic a conformationally flattened hexopyranose, with **3** resembling guanidino-threose.[14] Additional sugar residues can be attached at the commonly substituted 1, 2, 4, and 6 positions on the ring. Moreover, by replacing the C2-hydroxyl group with nitrogen, both **3** and **4** can serve as a surrogate for either D-glucose or D-mannose, with electron density projected above and below the ring plane directly adjacent to the anomeric center. Like arginine residues which serve as key recognition and binding sites

SCHEME



(a) 1.2 equiv $Ti(iPrO)_4$, 2.4 equiv $TMSN_3$, benzene, 75°C, 15 min; (b) MsCl, Et_3N, CH_2Cl_2, 0°C, 3 h; (c) NaN_3, DMF, 60°C, 18 h; (d) 1 equiv each of $PhCH_2Br$ and NaH, DMF, rt, 18 h (e)10% Pd/C, H_2, CH_3OH, rt, 18 h; (f) 1,1'-thiocarbonyldiimidazole,CH_2Cl_2, rt, 16 h; (g) EtI, EtOH, rt, 2 d; (h) 2 equiv $NH_4^+ {}^-O_2CCH_2CH_3$ 130°C, 4 h; (i) Na-NH_3, -78°C to -33°C, 10 min; (j) NH_2NH_2, rt, 15 min; (k) 1,1'-carbonyldiimidazole, CH_2Cl_2, rt, 2 d.

for carboxylic acids,[15] structures **3** and **4** present bilateral N-C=N arrays for favorable H-bonding and electrostatic interactions with carboxylate functional groups. Finally, we note that **3** and **4** are locked in the hexopyranose form, in contrast to the pH-dependent structure of guanidino-threose (which exists as a mixture of mutarotating α and β-furanose anomers at neutral pH, but as a 6-membered cyclic guanidine at pH 11).

The synthesis began with the known[16] S,S-epoxide **5**, which reacted regioselectively with $Ti(OiPr)_2(N_3)_2$ (prepared *in situ*) to afford azido-1,2-diol **6** and azido-1,3-diol **7** in a 6:1 ratio (55-65% yield overall).[17,18] By careful flash column chromatography on SiO_2 using 1:1 hexane:ethyl acetate (EtOAc), pure **6** (R_f 0.47, EtOAc) could be obtained.[19] Selective mesylation of **6** (1.2 equiv MsCl, 0°C, 70%) followed by S_N2 displacement with NaN_3 cleanly furnished diazide **8** (quantitative yield).[20] Diazide **8** (R_f 0.52, 2:1 hexane:EtOAc) could be further O-benzylated using NaH and $PhCH_2Br$ to give ether **9** (R_f 0.68, 2:1 hexane:EtOAc). Heterogeneous catalytic reduction of **8** or **9** led to diamines **10** or **11**, respectively, in 80-90% yield.

Hydroxydiamine **10** (R_f 0.50, 7:3:1 CH_2Cl_2:CH_3OH:NH_4OH) was not converted cleanly to the corresponding urea using 1,1'-carbonyldiimidazole, forming instead a kinetically stable 2-oxazolidone. In an alternative approach, reaction of 1,1'-carbonyldiimidazole (1 equiv, CH_2Cl_2, rt, 12 h) with the di-O-benzyl diamine **11**[21] did succeed in producing **14** (R_f 0.58, 17:3:1 EtOAc:CH_3OH:H_2O) in 70% yield. This cyclic urea could be deprotected to **15** (R_f 0.50, 1:1 CH_2Cl_2:CH_3OH), using excess sodium in ammonia, but neither **14** nor **15** could be transformed directly or indirectly (via a uronium salt) to the desired guanidine **3**.

Ultimately, **10** did form thiourea **12** (40-50% yield; R_f 0.32, EtOAc) upon reaction with 1,1'-thiocarbonyldiimidazole. The corresponding S-ethylisothiourea **13**, prepared in 75% yield (R_f 0.29, 17:3:1 EtOAc:CH_3OH:H_2O), underwent smooth substitution either with ammonium propionate[22] or hydrazine, followed by dissolving metal reduction to remove the benzyl ether, thus affording **3** or **4**, respectively. Guanidine **3** was isolated as its acetate salt (50% yield; m.p. >165°C, d) after column chromatography using 5:1:2 CH_3CN:HOAc: H_2O.[23] Similar purification furnished N-aminoguanidine **4** as an amorphous acetate salt which was dissolved in 1M HCl and thus converted to the more crystalline hydrochloride salt (52% yield; m.p. 141-145°C).[24]

Pyranose mimics **3** and **4** are of particular interest as templates for the construction of novel glycomimetic oligomers for selectins and other adhesion receptors.[10,11]

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REFERENCES AND NOTES

1. Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992,** *2,* 199-210.
2. Elbein, A. D.; Molyneux, R. J. in *Alkaloids: Chemical and Biological Perspectives,* Pelletier, S. W., Ed., Wiley & Sons, New York, **1987,** 1-54.

3. Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990,** *48,* 319-384.
4. (a) Fellows, L. E. *Chem. Brit.* **1987,** *23,* 842-844; (b) Fellows, L. E. *New Scientist* **1989,** *123,* 45-46.
5. Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed.* **1981,** *20,* 744-761.
6. Y. T. Pan, G. P. Kaushal, G. Papandreou, B. Ganem, A. D. Elbein, *J. Biol. Chem.* **1992,** *267,* 8313-8318.
7. G. Papandreou, M. K. Tong, B. Ganem, *J. Am. Chem. Soc.* **1993,** *115,* 11682-11690.
8. Elbein, A. D. *Ann. Rev. Biochem.* **1987,** *56,* 497-534.
9. Sharon, N.; Lis, H. *Sci. Amer.* **1993,** *268(1),* 82-89.
10. Springer, T. A. *Cell* **1994,** *78,* 301-314.
11. (a) Springer, T. A. *Nature* **1990,** *346,* 425-434; (b) Cronstein, B. N.; Weissmann, G. *Arthritis Rheum.* **1993,** *36,* 147-157.
12. Knapp, S.; Choe, Y. H.; Reilly, E. *Tetrahedron Lett.* **1993,** *34,* 4443-4446.
13. Blériot, Y.; Genre-Grandpierre, A.; Tellier, C. *Tetrahedron Lett.* **1994,** *35,* 1867-1870.
14. Fotsch, C. H.; Wong, C.-H. *Tetrahedron Lett.* **1994,** *35,* 3481-3484.
15. Rebek, J. *Science* **1987,** *235,* 1478-1484.
16. Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982,** *47,* 1378-1380.
17. Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988,** *53,* 5185-5187.
18. Satisfactory ^{1}H, ^{13}C-NMR, IR and mass spectrometric data were obtained for all new compounds.
19. For **6**: $[\alpha]_D$ = -44° (c= 1.01, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24-7.45 (m, 5 H), 4.58 (s, 2 H), 3.51-3.81 (m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.2, 128.4, 127.8, 127.5, 73.4, 71.2, 69.8, 63.2, 61.9; IR (film) 3400, 3050, 2900, 2100, 1650, 1300, 1100 cm^{-1}.
20. For **8**: $[\alpha]_D$ = -49° (c= 1.34, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 7.22-7.33 (m, 5 H), 4.50 (dd, 2 H, J= 13.1, 12.0 Hz), 3.34-3.75 (m, 6 H); ^{13}C-NMR ($CDCl_3$) δ 137.0, 128.4, 127.6, 127.9, 73.4, 70.4, 69.5, 62.0, 53.6; IR (film) 3400, 3000, 2900, 2100, 1650, 1300, 1100 cm^{-1}.
21 For **11**: $[\alpha]_D$ = +77° (c= 0.31, CH_2Cl_2); R_f 0.24 in 20:1:4 CH_3CN:HOAc:H_2O; ^{1}H-NMR ($CDCl_3$) δ 7.24-7.35 (m, 10 H), 4.49-4.58 (m, 4 H), 3.50-3.60 (m, 2 H), 3.45 (m, 1 H), 3.35 (m, 1 H), 2.90 (m, 2 H), 1.57 (br. s, 4 H, NH); ^{13}C-NMR ($CDCl_3$) δ 138.2, 138.1, 128.4, 128.3, 127.7, 127.6, 127.5, 81.6, 73.2, 72.4, 72.1, 51.8, 41.3; IR (film) 3300, 3100, 2900, 1600, 1500, 1100 cm^{-1}.
22. Tarino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977,** *99,* 2818-2819.
23. For **3**: $[\alpha]_D$ = +29° (c= 0.38, CH_3OH); ^{1}H-NMR (D_2O) δ 3.99 (q, 1 H, J= 3.4 Hz), 3.44-3.52 (m, 2 H), 3.11-3.41 (m, 3 H); ^{13}C-NMR (D_2O) δ 153.7, 62.3, 60.5, 56.1, 42.3; IR (film) 3400, 1650, 1625, 1500 cm^{-1}.
24. For **4**: $[\alpha]_D$ = +93° (c= 0.08, CH_3OH); ^{1}H-NMR (D_2O) δ 4.03 (q, 1 H, J= 3.3 Hz), 3.35-3.53 (m, 3 H), 3.15-3.33 (m, 2 H); ^{13}C-NMR (D_2O) δ 154.8, 62.4, 60.9, 55.9, 42.0; IR (film) 3400, 1650, 1100 cm^{-1}; EIMS *m/z* 141 (M+1-H_2O, 24%), 128 (M+1-CH_2OH, 16%)

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