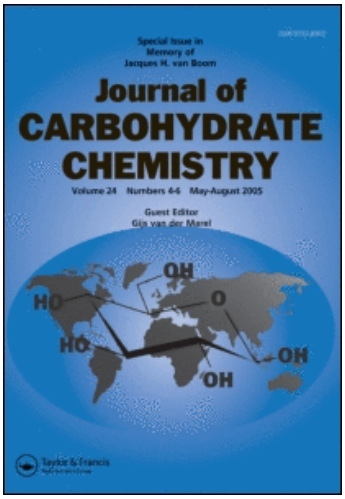

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Synthesis of Two D-Glucosamine Derived 3,4-Epoxides as Potential Scaffolds for Combinatorial Chemistry

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Key Words: D-Glucosamine; 3,4-epoxide; Amino; Regioselective *O*-tosylation; Opening.

Combinatorial chemistry allows the synthesis of libraries of compounds by combination of building blocks or by combinatorial elaboration of a central scaffold.[1,2] Carbohydrates hold great promise as scaffolds due to their high degree of functionalization, relative conformational rigidity, commercial availability of many stereoisomeric forms, and their well-described chemistry. Hirschmann, Nicolaou, Smith, and their coworkers pioneered the use of carbohydrates as scaffolds in their design and synthesis of β-D-glucose derived non-peptide peptidomimetics of the peptide hormone

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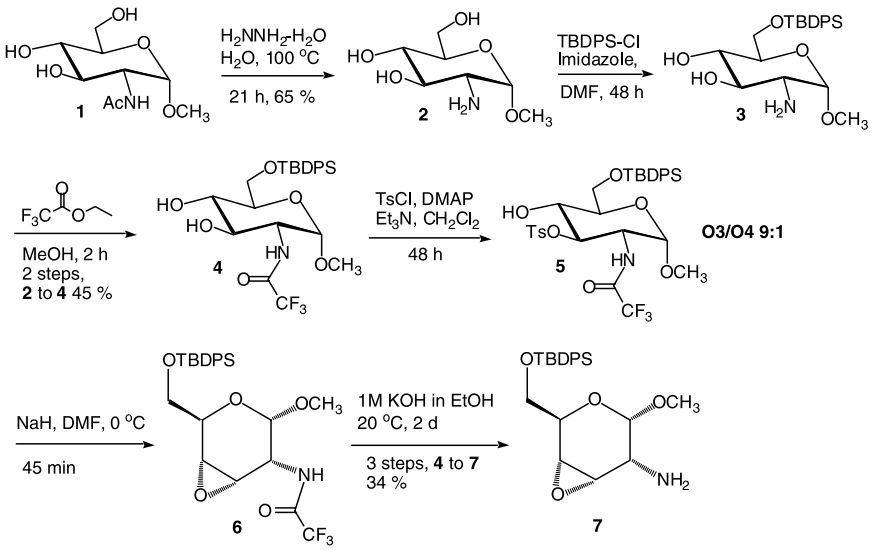
somatostatin (SRIF).[3,4] However, only relatively few examples on the application of carbohydrates as scaffolds in combinatorial chemistry have been described.[5–11] For example, Brill et al. anchored a 1,6-anhydro-β-D-glucopyranoside (levoglucosan) derived epoxide to a solid support and introduced diversity by opening of the support-bound 2,3-epoxide.[9] Hirschmann et al. employed the opening of a D-glucose derived 1,2-epoxide with a thiol in one of the initial steps towards the synthesis of a library of D-glucose derived compounds.[10]

We reasoned that introduction of all substituents by *O*-acylation or carbamoylation would give final products with too high a degree of conformational freedom. To introduce substituents directly on the carbohydrate ring and to keep protecting group manipulations on the resin-bound carbohydrate scaffold to a minimum, we decided to prepare a scaffold in which diversity would be introduced by opening of an epoxide. Also, it was a requirement that the scaffold should contain nitrogen, as amines are found in many pharmacologically relevant molecules, *e.g.*, CNS active compounds. We chose inexpensive D-glucosamine as starting material, to prepare a 3,4-epoxide, and to block the C-1 as the methyl glycoside (Scheme 1). Both solution and solid-phase strategies were envisioned; for the solid-phase strategy, the amine could serve as a convenient point for anchoring to a solid support through a Backbone Amide Linker (BAL).[12,13] Here we present the synthesis of two new D-glucosamine derived amino epoxides and preliminary studies on opening of one of the epoxides in solution.

First, methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, **1**, easily accessible by Fischer glycosylation, was *N*-deacetylated by treatment with hydrazine to give known methyl 2-amino-2-deoxy-α-D-glucopyranoside **2** (Scheme 1). The *N*-acetyl group served well here as it was stable to Fischer glycosylation conditions; however, it had to be exchanged with a more labile *N*-trifluoroacetyl group to allow final deprotection



Scheme 1. Synthesis of amino epoxide **7**.

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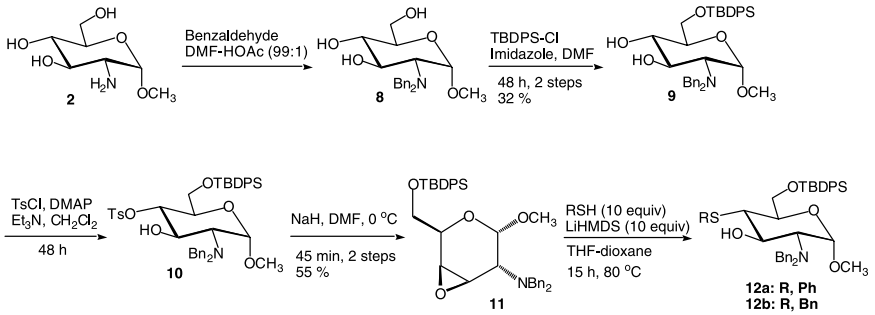

Scheme 2. Synthesis of amino protected epoxide **11** and opening with thiols.

under milder conditions. Initial experiments had shown that Fischer glycosylation of 2-trifluoroacetamido-D-glucopyranose resulted in only low yields of the desired methyl glucoside, probably due to cleavage of the *N*-trifluoroacetyl moiety. Treatment of triol amine **2** with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) in *N*,*N*-dimethylformamide (DMF) in the presence of imidazole selectively protected O-6 to give diol amine **3**, which was chemoselectively *N*-trifluoroacetylated by reaction with ethyl trifluoroacetate in MeOH to give **4** in 45% for the two steps. Treatment of diol **4** with tosyl chloride in CH_2Cl_2 in the presence of *N*,*N*-dimethylaminopyridine (DMAP) and Et_3N provided monotosylate **5** in a high yield with a remarkable O3/O4 ratio of 9:1. This was essential, as tosylation at O-3 or O-4 give different epoxides in the next step. In the key step, the epoxide was smoothly established by treatment of tosylate **5** with sodium hydride in DMF[14] to give **6**. Hovewer, control of the reaction time was essential, as the maximal yield was obtained after a 45 min reaction. Substituting sodium hydride in DMF for 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at reflux or with potassium *tert*-butoxide in DMF both resulted in reduced yields. In the final step, the *N*-trifluoroacetyl group was removed to give target amino epoxide **7**.[a] However, treatment with 1M aq sodium hydroxide also partly removed the TBDPS protecting group, *without* affecting the epoxide. The three steps (**4**→**7**) proceeded in an overall yield of 34% yield (Scheme 1).

For solution studies, we required an epoxide derivative with the amine protected. Reductive amination of starting amine **2** with benzaldehyde in DMF-HOAc (99:1) in the presence of $NaBH_3CN$ provided the *N*,*N*-dibenzylated derivative **8** (Scheme 2) (*N,N*-Dibenzyl protected glucosamine donors have been prepared by *N*-alkylation with benzyl bromide: see Ref. [15]). Previous studies on reductive alkylation of amino acids had shown that whereas DMF as solvent promoted dialkylation, MeOH preferably gave the monoalkylated product.[16] The following transformations to **9**, **10**, and **11** were achieved with procedures similar to those for synthesis of epoxide **7**. Interestingly,

[a]Selected ^{1}H chemical shifts, δ, in ppm (coupling constants in Hz to the following ^{1}H) for **7**: H-1, 4.58 (4.9); H-2, 3.14 (2.2); H-3, 3.31 (4.7); H-4, 3.45 (0.6); H-5, 3.92 (4.7); H-6 3.88 (m).

O-tosylation of **9** occurred regioselectively at O-4 in contrast to the 3-*O*-tosylation found in **4**. Treatment of 4-*O*-tosylate **10** with sodium hydride in DMF, as above for **6**, formed the expected stereoisomeric epoxide **11** (Scheme 2).[b] Attempted hydrogenolytic debenzylation also gave rise to several byproducts, probably due to destruction of the epoxide.

The control of regioselectivity in *O*-tosylation by the 2-amino protecting group is noteworthy. Glycosylation of O-3 in *N*-Phth protected acceptors has been reported to be difficult.[17,18] *N*,*N*-dibenzyl, but not *N*-trifluoroacetyl, now appears to have an analogous steric influence. This proved fortunate for the present application as it gave access to the two different stereoisomeric forms of the epoxide.

In preliminary studies on the opening of the epoxides, *N*,*N*-dibenzylated epoxide **11** was reacted in solution with thiophenol in THF-dioxane in the presence of LiHMDS (Scheme 2).[9] The 4-deoxy-4-thiophenyl D-*gluco* configured derivative **12a** was obtained in 68% isolated yield. Benzyl mercaptan opened epoxide **11** in a similar manner to give **12b** in 31%. The reduced yield was probably due to loss during work-up. The *gluco* configuration was easily established by analysis of ^{1}H NMR ^3J coupling constants (for both **12a** and **b**: $^3J_{2,3}$ 10.2 Hz; $^3J_{3,4}$ 10.7 Hz);[c] the position of the thioether was evident from the chemical shift of H-4 (**12a** 3.00 ppm; **12b** 2.57 ppm).[d]

In conclusion, two stereoisomeric D-glucosamine derived 3,4-epoxides with TBDPS protection at O-6 were synthesized in 5 and 6 steps, respectively, from methyl 2-acetamido-α-D-glucopyranoside. The stereochemical orientation of the epoxide was controlled through amino protecting group directed regioselective *O*-tosylation prior to epoxide formation. Solution experiments showed that the *N*,*N*-protected epoxide was opened to give the D-*gluco* configured product with a 4-thiophenyl moiety. These epoxides are potential scaffolds for combinatorial chemistry applications.

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[b]Selected ^{1}H chemical shifts, δ, in ppm (coupling constants in Hz to the following ^{1}H) (δ, *J*) for **11**: H-1 4.47 (4.3 Hz); H-2 2.97 (4.5); H-3 and H-4 3.29-3.34; H-5 3.94 (t, 7.1 Hz); H-6a 3.74 (dd, 6.3 Hz, 10.5 Hz); H-6b 3.65 (3.9 Hz, 9.9 Hz).

[c]Selected ^{1}H chemical shifts, δ, in ppm (coupling constants in Hz to the following ^{1}H) (δ, *J*) for **12a**: H-1 4.76 (3.0 Hz); H-2 2.84 (10.2 Hz); H-3 4.13 (10.7); H-4 3.00 (11.1 Hz); H-5 3.70; H-6a 3.97 (11.1 Hz, 1.7 Hz); J-6b 3.86 (5.1Hz).

[d]Selected ^{1}H chemical shifts, δ, in ppm (coupling constants in Hz to the following ^{1}H) (δ, *J*) for **12b**: H-1 4.73 (3.0 Hz); H-2 2.75 (10.2 Hz); H-3 4.10 (10.7); H-4 2.57 (10.7 Hz); H-5 3.64; H-6a 3.96 (11.3 Hz, 1.7 Hz); J-6b 3.81 (5.5 Hz).

REFERENCES

1. Terret, N.K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998.
2. Bunin, B.A. *The Combinatorial Index*; Academic Press: San Diego, 1998.
3. Hirschmann, R.; Nicolaou, K.C.; Pietranico, S.; Salvino, J.; Leahy, E.M.; Sprengeler, P.A.; Furst, G.; Smith, A.B.; Strader, C.D.; Cascieri, M.A.; Candelore, M.R.; Donaldson, C.; Vale, W.; Maechler, L. Nonpeptidal peptidomimetics with a β-D-glucose scaffolding. A partial somatostatin agonist bearing a close structural relationship to a potent, selective substance P antagonist. J. Am. Chem. Soc. **1992**, *114*, 9217–9218.
4. Hirschmann, R.; Nicolaou, K.C.; Pietranico, S.; Leahy, E.M.; Salvino, J.; Arison, B.; Cichy, M.A.; Spoors, P.G.; Shakespeare, W.C.; Sprengeler, P.A.; Hamley, P.; Smith, A.B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R.M.; Cascieri, M.R.; Strader, C.D. The versatile steroid nucleus: design and synthesis of a peptidomimetic employing this novel scaffold. J. Am. Chem. Soc. **1993**, *115*, 12550–12568.
5. Sofia, M.J.; Hunter, R.; Chan, T.Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. Carbohydrate-based small-molecule scaffolds for the construction of universal pharmacophore mapping libraries. J. Org. Chem. **1998**, *63*, 2802–2803.
6. Silva, D.J.; Sofia, M.J. Novel carbohydrate scaffolds. Assembly of a uridine-mannose scaffold based on tunicamycin. Tetrahedron Lett. **2000**, *41*, 855–858.
7. Kallus, C.; Opatz, T.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. Combinatorial solid-phase synthesis using D-galactose as a chiral five-dimensional diversity scaffold. Tetrahedron Lett. **1999**, *40*, 7783–7786.
8. Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. Carbohydrates as multifunctional chiral scaffolds in combinatorial synthesis. Angew. Chem. Int. Ed. **1998**, *37*, 2503–2505.
9. Brill, W.K.-D.; De Mesmaeker, A.; Wendeborn, S. Solid-phase synthesis of levoglucosan derivatives. Synlett **1998**, 1085–1090.
10. Hirschmann, R.; Decry, L.; Smith, A.B. Development of an efficient, regio- and stereoselective route to libraries based on the β-D-glucose scaffold. J. Org. Chem. **2000**, *65*, 8307–8316.
11. Sofia, M.J.; Silva, D.J. Recent developments in solid- and solution-phase methods for generating carbohydrate libraries. Curr. Opin. Drug Discov. Dev. **1999**, *2*, 365–376.
12. Tolborg, J.F.; Jensen, K.J. Solid-phase oligosaccharide synthesis with tris(alkoxy)benzyl amine (BAL) safety-catch anchoring. Chem. Commun. **2000**, 147–148.
13. Petersen, L.; Jensen, K.J. DISAL glycosyl donors for efficient glycosylations under acidic conditions: application to solid-phase oligosaccharide synthesis. J. Chem. Soc., Perkin Trans. 1 **2001**, 2175–2182.
14. Suami, T.; Tadano, K.; Iimura, Y.; Tanabe, H. Direct conversion of D-glucosamine into D-gulosamine. Carbohydr. Res. **1985**, *135*, 319–323.
15. Jiao, H.; Hindsgaul, O. The 2-*N,N*-dibenzylamino group as a participating group in the synthesis of β-glycosides. Angew. Chem. Int. Ed. **1999**, *38*, 346–348.
16. Jensen, K.J.; Alsina, F.; Songster, M.F.; Vagner, J.; Albericio, F.; Barany, G. Backbone amide linker (BAL) strategy for solid-phase synthesis of *C*-terminal-modified and cyclic peptides. J. Am. Chem. Soc. **1997**, *120*, 5441–5452.

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17. Ellervik, U.; Magnusson, G. A high yielding chemical synthesis of sialyl Lewis x tetrasaccharide and Lewis x trisaccharide; examples of regio- and stereodifferentiated glycosylations. J. Org. Chem. **1998**, *63*, 9314–9322.
18. Zhu, T.; Boons, G.-J. A novel and efficient synthesis of a dimeric Le^x oligosaccharide on polymeric support. J. Am. Chem. Soc. **2000**, *122*, 10222–10223.

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