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A Convergent Synthesis of α-*C*-1,3-Mannobioside *via* SmI_2-promoted *C*-Glycosylation

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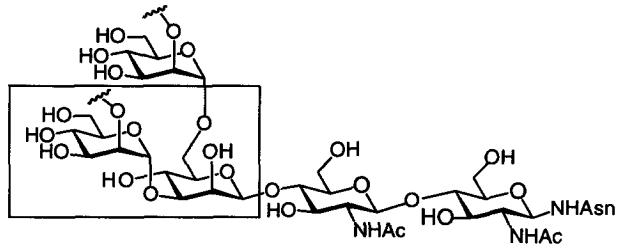
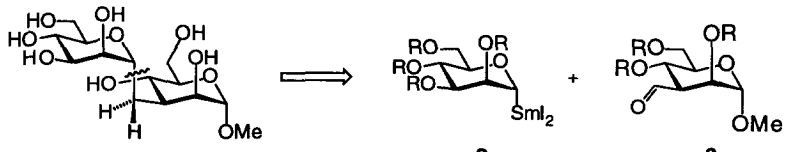
Abstract: The *C*-disaccharide of α-1,3-mannobioside has been synthesized *via* the direct coupling of a mannosyl pyridyl sulfone and a *C*-formyl branched sugar with the one electron reducing agent, SmI_2. The sterically hindered alcohol obtained in this coupling was successfully removed employing our previously described deoxygenating conditions. © 1999 Elsevier Science Ltd. All rights reserved.

Modified oligosaccharides in which the glycosidic oxygens are replaced with methylene groups (*C*-glycosides) have become important tools for the study of carbohydrate-protein interactions.[1] Because such compounds are resistant to metabolic processes they may likewise serve as stable analogues of carbohydrate-based drugs.[2] It is therefore important that an easy route to such analogues be available. Of the many approaches devised for the synthesis of *C*-oligosaccharides,[3] perhaps the most direct route involves the coupling of intact monosaccharide units,[4] a strategy which parallels the well known methods for *O*-glycoside synthesis. We have previously demonstrated the utility of this approach to the synthesis of two *C*-disaccharides[5] *via* the coupling of *in situ* generated glycosyl samarium reagents[6] with *C*-formyl-branched sugars. In this paper, we wish to report the synthesis of a *C*-glycoside analogue of α-1,3-mannobioside **1** which represents an important constituent of the asparagine-linked oligosaccharides (Figure 1). This synthesis has the potential of being adapted to a *C*-branched trisaccharide as well.



Common core structure of asparagine linked oligosaccharides



Methyl α-*C*-1,3-Mannobioside **1** **2** **3**

Figure 1

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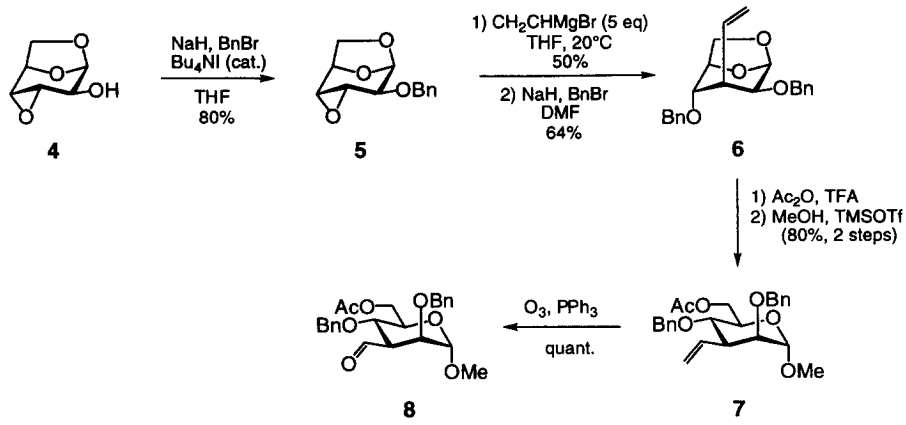
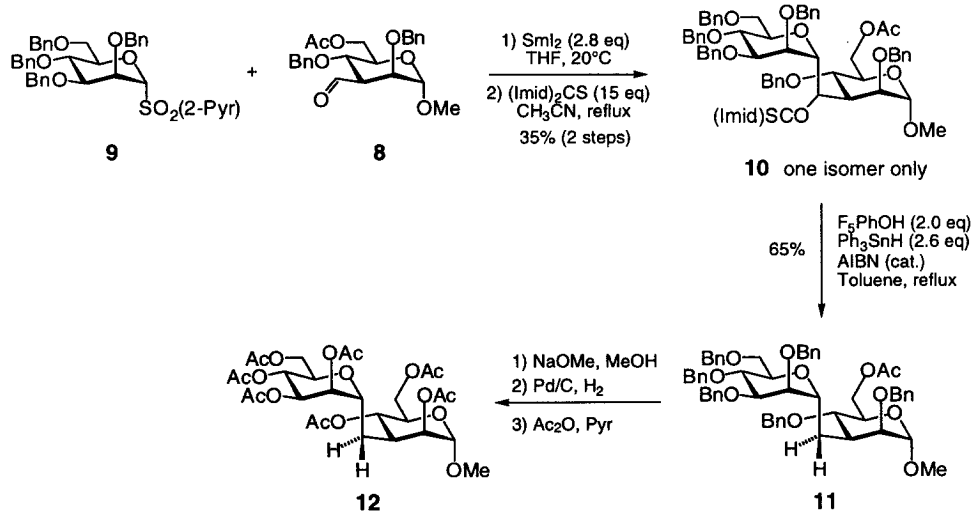


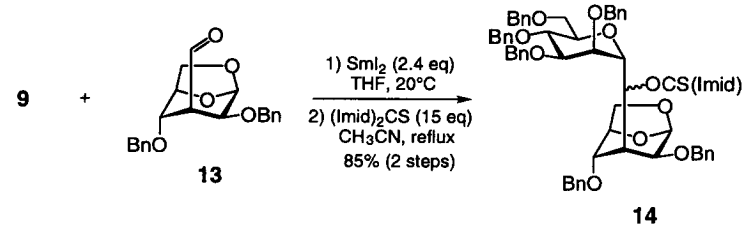
Scheme 1

The synthetic approach followed is outlined in Figure 1 involving the condensation of the anomeric samarium species **2**, easily obtained *via* the reductive samariation of the corresponding pyridyl sulfone,[6] with aldehyde **3**. For the synthesis of **3**, initial attempts to prepare this compound directly from mannose were futile, where introduction of an sp^2 carbon *via* S_N2 substitution at the C3 position led mainly to products of elimination. On the other hand, epoxide **4**, being easily accessible from D-glucose,[7] represented a potential candidate for the selective introduction of a functional group at C3 while possessing the correct stereochemistry at C2 and C4 (Scheme 1). Hence, the C2-alcohol in **4** was protected as its benzyl ether, after which epoxide **5** was opened in a regioselective manner with vinyl magnesium bromide to provide the C3,C4-diaxial product in 50% yield along with approx. 10% of the corresponding bromide at C3.[8] After a benzylation step to give **6**, acetolysis and *O*-glycosylation with methanol then afforded the methyl mannoside derivative **7** in 80% yield for two steps. Ozonolysis proceeded smoothly and quantitatively to give aldehyde **8**.



Scheme 2

The coupling between aldehyde **8** and tetrabenzylmannosyl pyridyl sulfone **9**[6d] (1.7 eq) was effected by treating a THF solution of the two monosaccharides with SmI_2 (Scheme 2). An immediate reaction ensued leading to an inseparable mixture of products which was subsequently subjected to 15 eq. of thiocarbonyldiimidazole in hot acetonitrile. As was earlier observed in the synthesis of methyl α-1,2-mannobioside,[5c] the secondary alcohol of the furnished *C*-disaccharide proved resistant to functionalization, and only through the slow evaporation of the acetonitrile at 81°C was the thiocarbonylimidazole derivative **10** secured in a 35% yield for the two steps. Only a *C*-disaccharide as its α-anomer was obtained in agreement with our earlier studies in the Barbier-type couplings of mannosyl pyridyl sulfones with aldehydes.[6a,c,d] It is also interesting to note the stereospecificity of this reaction producing exclusively one isomer at the exocyclic stereogenic center. The coupling yield was nevertheless modest and surely reflects the highly crowded environment of the aldehyde group in **8**. This was also experienced in the coupling of **9** with the aldehyde **13** obtained from the oxidative cleavage of the 1,6-anhydro derivative **6** as shown in Scheme 3, where a 38% yield of the *C*-dimer **14** (2.7:1 mixture) was furnished after the same two steps.



Scheme 3

Finally, the deoxygenation step was successfully achieved employing our recently described protocol for the reduction of sterically hindered secondary alcohols.[5c] Hence, refluxing a toluene solution of **10** with pentafluorophenol, triphenyltin hydride and AIBN for 30 min. led to the isolation of the 1,3-linked *C*-disaccharide **11** in a 65% yield after chromatographic separation. Removal of the protecting groups using conventional techniques and peracetylation then afforded the heptaacetate **12** as a colorless syrup.[9] In the ^1H NMR spectrum of **12**, it is interesting to note the deviation of the non-reducing sugar from the normal $^4C_1$ conformation. This was unexpected in comparison to the normal ring conformation observed for the heptaacetate of methyl α-1,2-mannobioside, and clearly illustrates that for **12** there is greater steric interactions between the two monosaccharide units.

In summary, we have prepared a novel *C*-disaccharide using the direct coupling approach promoted by SmI_2. Future work will focus on the selective introduction of a formyl group at the C6 position of **11**, such that access to a branched *C*-trisaccharide may be possible.

Acknowledgements

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References and Notes

1. a) A. Wei, K. M. Boy, Y. Kishi, *J. Am. Chem. Soc.* **1995**, *117*, 9432; b) J.-F. Espinosa, F.J. Cañada, J.L. Asensio, H. Dietrich, M. Martín-Lomas, R.R. Schmidt, J. Jiménez-Barbero, *Angew. Chem.* **1996**, *108*, 323; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 303; b) J.-F. Espinosa, F.J. Cañada, J.L. Asensio, M. Martin-Pastor, H. Dietrich, M. Martin-Lomas, R.R. Schmidt, J. Jiménez-Barbero, *J. Am. Chem. Soc.* **1996**, *118*, 10862; c) J.-F. Espinosa, E. Montero, A. Vian, J.L. Garcia, H. Dietrich, M. Martín-Lomas, R.R. Schmidt, A. Imberty, J. Cañada, J. Jiménez-Barbero, *J. Am. Chem. Soc.* **1998**, *120*, 1309; d) R. Ravishankar, A. Surolia, M. Vijayan, S. Lim, Y. Kishi, *J. Am. Chem. Soc.* **1998**, *120*, 11297.

2. For example, a) A. Helmboldt, J.-M. Mallet, M. Petitou, P. Sinaÿ, *Bull. Soc. Chim. Fr.* **1997**, *134*, 1057; b) A. Helmboldt, M. Petitou, J.-M. Mallet, J.-P. Hérault, J.-C. Lormeau, P.A. Driguez, J.-M. Herbert, P. Sinaÿ, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1507; c) M. Petitou, J.-P. Hérault, J.-C. Lormeau,A. Helmboldt, J.-M. Mallet, P. Sinaÿ, , J.-M. Herbert, *Bioorg. Med. Chem.* **1998**, *6*, 1509.

3. a) M.H.D. Postema, *C-Glycoside Synthesis*; CRC Press, Boca Raton, FL, **1995**; b) D.E. Levy, C. Tang, *The Chemistry of C-Glycosides*; Pergamon Press, Exeter, **1995**; c) G. Casiraghi, F. Zanardi, G. Rassu, P. Spanu, *Chem. Rev.* **1995**, *95*, 1677.

4. For some examples of this approach, see ref. 3 and, a) G. Rubinstenn, J. Esnault, J.-M. Mallet, P. Sinaÿ, *Tetrahedron: Asymmetry* **1997**, *8*, 1327; 72; b) G. Rubinstenn, J.-M. Mallet, P. Sinaÿ, *Tetrahedron Lett.* **1998**, *39*, 3697; c) T. Skrydstrup, D. Mazéas, M. Elmouchir, G. Doisneau, J.-M. Beau, *Chem. Eur. J.* **1997**, *8*, 1342; d) A. Dondoni, A. Boscarato, H. Zuurmond, *Tetrahedron Lett.* **1996**, *37*, 7587; e) A. Dondoni, H. Zuurmond, A. Boscarato, *J. Org. Chem.* **1997**, *62*, 8114; f) A. Dondoni, M. Kleban, H. Zuurmond, A. Marra, *Tetrahedron Lett.* **1998**, *39*, 7991.

5. O. Jarreton, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1996**, 1661; b) L. Andersen, L.M. Mikkelsen, J.-M. Beau, T. Skrydstrup, *Synlett* **1998**, 1393; c) O. Jarreton, T. Skrydstrup, J.-F. Espinosa, J. Jiménez-Barbero, J.-M. Beau, *Chem. Eur. J.*, **1999**, *5*, 430.

6. a) D. Mazéas, T. Skrydstrup, J.-M. Beau, *Angew. Chem.* **1995**, *107*, 990; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 909; b) D. Urban, T. Skrydstrup, C. Riche, A. Chiaroni, J.-M. Beau, *J. Chem. Soc., Chem. Commun.* **1996**, 1883; c) O. Jarreton, T. Skrydstrup, J.-M. Beau,*Tetrahedron Lett.* **1997**, *36*, 303; d) T. Skrydstrup, O. Jarreton, D. Mazéas, D. Urban, J.-M. Beau, *Chem. Eur. J.*, **1998**, *4*, 655; e) D. Urban, T. Skrydstrup, J.-M. Beau, *J. Org. Chem.*, **1998**, *63*, 2507; f) D. Urban, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1998**, 955.

7. J. Dolezalová, T. Trnka, M. Cerny, *Collect. Czech. Chem. Commun.* **1982**, *47*, 2415.

8. T. Inghardt, T. Frejd, *Synthesis* **1990**, 285.

9. ^{1}H NMR (300 MHz, C_6D_6) data for *C*-disaccharide **12**: δ 5.58 (dd, *J* = 5.4, 3.3 Hz, 1 H, H3'), 5.44 (dd, *J* = 10.4, 10.4 Hz, 1 H, H4), 5.31 (dd, *J* = 7.2, 3.3 Hz, 1 H, H2'), 5.29 (broad s, 1 H, H2), 5.18 (dd, *J* = 5.4, 4.8 Hz, 1 H, H4'), 4.78 (dd, *J* = 11.4, 7.8 Hz, 1 H, H6a'), 4.72 (s, 1 H, H1), 4.44 (dd, *J* = 12.0, 5.1 Hz, 1 H, H6a), 4.22-4.12 (m, 2 H, H1', H6b), 4.06 (ddd, *J* = 7.8, 5.7, 2.5 Hz, 1 H, H5'), 3.99 (dd, *J* = 11.4, 3.5 Hz, 1 H, H6b'), 3.89 (m, 1 H, H5), 2.97 (s, 3 H, OCH_3), 2.58 (m, 1 H, H3), 1.86, 1.81, 1.72, 1.68, 1.63, 1.54, 1.50 (7 s, 21 H, 7 OAc), 1.40-1.24 (m, 2 H, H7a, H7b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.6, 170.5, 170.1, 169.7, 97.3, 72.3, 72.0, 71.7, 70.3, 69.0, 68.4, 68.1, 67.4, 63.0, 61.5, 55.1, 36.5, 27.7, 21.2, 20.9, 20.7; MS (EI): *m/z* 648 (M).