# Stereoselective Synthesis of β-Mannopyranosides via the Temporary Silicon Connection Method

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Increasing interest in the synthesis of biologically significant carbohydrate glycosides and conjugates has led to the development of ever more selective methods for the control of stereochemistry at the anomeric center. The stereospecific formation of *β-mannopyranosides* has proved particularly difficult to achieve, however, in spite of considerable effort, because the vicinal cis (axial) β-hydroxyl group blocks access to the β-face.[1] The presence of the β-mannopyranoside entity, inter alia, in the core region of N-linked glycoproteins (cf. Figure 1) warrants significant attention toward its construction.

A general solution to this type of problem was introduced in 1983, with the demonstration that a carbon substituent could be introduced, regio- and stereospecifically, in many ring systems by using the *temporary* attachment of the desired substituent to a stereochemistry-controlling hydroxyl within the ring system.[2] Internal transfer of the substituent by cyclization cis to the controlling hydroxyl then allowed completion of the process by removal of the temporary connector. Possible choices for the latter are limited. We made use of a temporary acetal link in a prostaglandin synthesis[3] and a temporary silyl ether connection in a method for the controlled introduction of methyl groups.[4] In these particular examples, the tethered entities were cyclized by free-radical processes.

In the carbohydrate area, the temporary connection method was first applied in the acetal version to the stereospecific synthesis of C-glycosides.[5] We, in turn, explored the temporary silyl ether version for the same purpose[6] and found it especially significant that the approach was successful even for the synthesis of a *β-C-mannopyranoside*, thus obtained free from its α-isomer (cf. **1** → **2**, Figure 2).

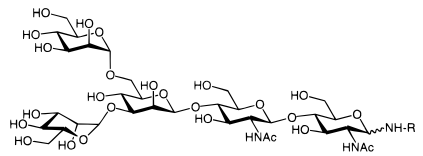

**Figure 1.** Core pentasaccharide of N-linked glycoproteins.

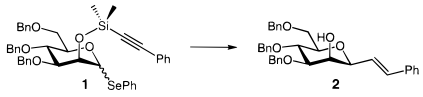

**Figure 2.**

So far as the synthesis of typical β-mannopyranosides, the first applications of the temporary tethering concept were carried out, independently, by Hindsgaul[7] and us,[8] using respectively mixed acetals and silyl ether connectors. More recently, Ito and Ogawa demonstrated the efficient use of *p*-methoxybenzylidene acetals.[9]

We now report our further exploration of the temporary silyl ether route to β-mannopyranosides. As we had done previously, we used the sulfoxide departing group method of Kahne[10] to attempt the formation of a variety of β-mannopyranoside-linked disaccharides. In our initial sequence, we performed the required thiophenyl to phenyl sulfoxide oxidation *after* initial formation of the mixed silaketal. This was satisfactory when β-mannoside formation involved connection of the second sugar via its *primary* alcohol, but we found it, in general, much more efficient to use the *preformed* mannose sulfoxide **3**,[11] because we discovered that the *mixed* silaketals **4** could be produced simply by the interaction of an equimolar mixture of the mannose sulfoxide **3** and the sugar to be tethered with 1 equiv of dimethyldichlorosilane, thus avoiding isolation of the sensitive chlorodimethylsilyl ether intermediate (Scheme 1).[12]

Activation of the tethered species **4** was then carried out with triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine, keeping the temperature at −100 °C during addition of the anhydride to ensure complete stereoselectivity. Upon warming these solutions to room temperature, the tethered species from glucose derivatives **5**,[6] **6**,[13] and **7**[14] produced the desired disaccharides **11**, **12**, and **13**, free from their α-mannoside anomers,[15] in 92, 65, and 82% yields, respectively.[16]

These results were encouraging, because they showed that the temporary silicon connection was able to give the desired

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(1) For a survey of the chemical synthesis of β-mannopyranosides, see: (a) Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1969**, *39*, 2474. (b) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 211, 225. (c) Paulsen, H.; Kutschker, W.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102, 3233. (d) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121. (e) Garegg, P. J.; Ossowski, P. *Acta Chem. Scand.* **1983**, *B37*, 229. (f) Rathmore, H.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 1945. (g) Gunther, W.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1050. (h) Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623. (i) Brunckova, J.; Crich, D.; Yao, Q. *Tetrahedron Lett.* **1994**, *35*, 6619. (j) Liu, K. C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892. (k) Lichtenthaler, F. W.; Schneider Adams, Th.; Immel, S. *J. Org. Chem.* **1994**, *59*, 6735.

(2) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

(3) Stork, G.; Sher, P. M.; Chen, H. L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

(4) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826.

(5) (a) De Mesmaeker, A.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1988**, *29*, 6585. (b) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57. (c) De Mesmaeker, A.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 6307. (d) De Mesmaeker, A.; Hoffmann, P.; Winkler, T.; Waldner, A. *Synlett* **1990**, 201. (e) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T.; Hug, P.; Winkler, T. *Synlett* **1990**, 687. (f) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Hug, P.; Winkler, T. *Synlett* **1992**, 285. (g) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Winkler, T. *Synlett* **1994**, 330.

(6) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. See also: (a) Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661. (b) Xin, Y. C.; Mallet, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1993**, 864. (c) Chenede, A.; Perry, E.; Rekai, E. D.; Sinaÿ, P. *Synlett* **1994**, 420.

(7) (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *112*, 9376. (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 795. (c) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447.

(8) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. See also: (a) Bols, M. *Tetrahedron* **1993**, *49*, 10049. (b) Bols, M. *Acta Chem. Scand.* **1993**, *47*, 829.

(9) (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765. (b) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680.

(10) (a) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (b) Hamilton-Andreotti, A.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 3352. (c) Ragahvan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (d) Yan, L.; Taylor, C. M.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6853.

(11) Only one sulfoxide diastereomer was produced (in 89% yield) by oxidation of the corresponding sulfide with *m*-CPBA. See ref 7 for the synthesis of the sulfide precursor to **3**.

(12) For example, a mixture of 1 equiv of imidazole, 0.5 equiv each of DMAP, mannose sulfoxide **3**, and β-methyl glucoside **6** (THF at −78 °C), treated with 0.5 equiv of dichlorodimethylsilane, gave 84% of the corresponding tethered species (cf. **4**). Addition of 2 equiv of triflic anhydride to the above in ether−methylene chloride (−100 °C) then gave **12** (65%, after flash chromatography). See supporting information for more details. The success of this procedure derives from the slower silylation of the 2-hydroxyl derivative of mannose sulfoxide **3** than of the free hydroxyl of the glucose derivative in the cases we have examined. The exact reason is not firmly established.

(13) Methyl glucoside **6** was prepared from 3,4,6-tribenzylglucal using the method of: Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(14) Koto, S.; Morishima, R.; Kawahara, K.; Ishikawa, K.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 631.

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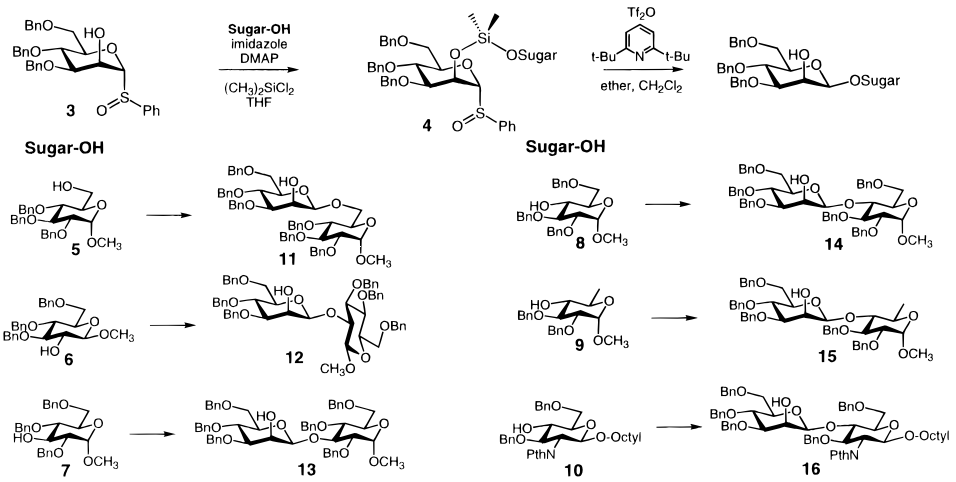
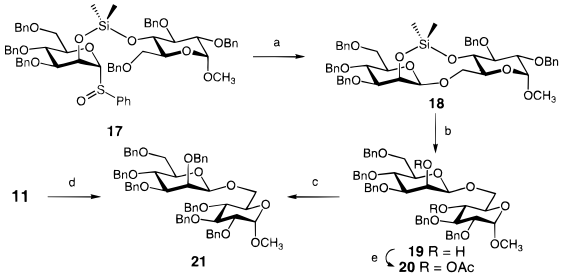
**Scheme 1**




$\beta$-mannoside attachment of glucose derivatives, in reasonable yields, not only via the primary 6-hydroxyl but also via the secondary 2- or 3-hydroxyls. The remaining secondary 4-hydroxyl of glucose is considerably more hindered, but because it is involved in a number of biologically important $\beta$-mannoside polysaccharides, we gave that case particularly thorough attention. The tethered species, **17**, was made in the usual way from **8**,[17] in essentially quantitative yield, but triflic anhydride treatment produced the desired 4-*O*-glucosyl $\beta$-mannoside **14**[1k,18] in only 12% yield. The major product (82%) retained the dimethylsilyl connector, although it had lost the phenyl sulfoxide and one of the benzyl groups.[19] After much chemical and spectroscopic study,[20] the structure of this unusual product was determined to be **18**, a conclusion which was confirmed by showing the identity of the product of desilylation and benzylation of **18** with the product of benzylation of **11** (Scheme 2). The surprising loss of the O-benzyl group from the tethered glucose moiety actually took place at ca. −20 °C, a temperature lower than that necessary to complete the usual disaccharide formation (e.g., **6** → **12**).

**Scheme 2**[a]



[a] (a) $Tf_2O$, 2,6-di-*tert*-butylpyridine, $CH_2Cl_2$, $Et_2O$, −100 °C to room temperature, 2.5 h, 82%. (b) TBAF, THF, room temperature, 1 h, 98%. (c) $Ac_2O$, DMAP, pyridine, 15 h, 89%. (d) NaH, BnBr, DMF, 0 °C to room temperature, 16 h.

Whatever its cause in the particular case of **8** (conformational and/or electronic effects?), the problem was apparently not a necessary corollary of attempted connection at the 4-hydroxyl of glucose. For example, the tethered 6-*deoxy* species corresponding to **9**[21] did lead to the $\beta$-mannoside **15** in 48% yield. Even more biologically relevant (cf. Figure 1), the tethered intermediate from 2-deoxy-2-phthalimidoglucose derivative **10**[7] led to the hoped-for disaccharide **16**[18] in a serviceable 54% yield.[22] It seems clear that the temporary silicon connection may prove useful in the construction of $\beta$-mannopyranoside units.

**Acknowledgment.** We thank the National Science Foundation and the National Institutes of Health for their support of this work.

**Supporting Information Available:** Typical experimental procedure and $^1$H-NMR spectra for mannosides **12**, **13**, **15**, **18**, and **19** (and their silaketal precursors), as well as the $^1$H−$^1$H COSY-45 and $^1$H−$^1$H ROESY spectra used to establish **12**, **13**, **15**, and **20** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) The presence of NOEs between the hydrogen at the anomeric center of the mannose substituent and its corresponding $C_3$ and $C_5$ hydrogens strongly supports the $\beta$-stereochemistry of mannosides **12**, **13**, and **15**. An additional NOE between the anomeric hydrogen and the proximal hydrogen on the glucosidic moiety provided further support for the assigned connectivity.

(16) Yields for both steps of the method as well as the overall recovery of disaccharide are tabulated below:

| substrate | tethering | glycosylation | overall |
|---|---|---|---|
| **5** | 89% | 92% | 82% |
| **6** | 84% | 65% | 55% |
| **7** | 88% | 82% | 72% |
| **8** | 98% | 12%* | 12% |
| **9** | 60% | 48% | 29% |
| **10** | 78% | 54%* | 42% |

*The remaining material underwent 6-*O*-debenzylation (i.e., to **18**).

(17) Garegg, P. J.; Iversen, I.; Oscarson, S. *Carbohydr. Res.* **1976**, *50*, C12.

(18) The $^1$H NMR spectra of this product matched that reported by Hindsgaul (see ref 7c).

(19) Triflation of **17** produced 12% of **14**, 82% of **18**, and 4% of the α-anomer of **18**. Changing the protecting groups about the mannose substituent (i.e., methyl instead of benzyl ethers) did not alter the outcome of this process.

(20) A combination of $^1$H−$^1$H COSY-45 and $^1$H−$^1$H ROESY spectra on bis-acetate **20** establishes the position of linkage (i.e., the presence of an NOE between the mannosidic anomeric hydrogen and the $C_6$ hydrogens of the glucosidic moiety) and stereochemistry (i.e., detection of NOEs between the $C_3$, $C_5$, and anomeric hydrogens within the mannose substituent).

(21) Stevens, C. L.; Blumbergs, P.; Otterbach, D. H. *J. Org. Chem.* **1966**, *31*, 2817.

(22) Glycosylation of the silaketal from **10** was accompanied by production of 41% of its 6-*O*-debenzylated product.