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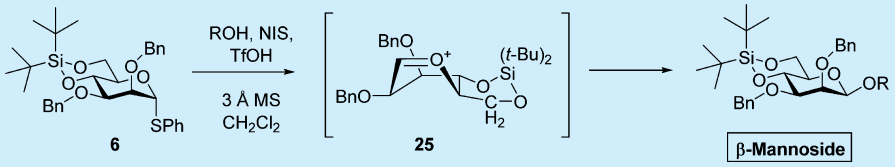
β-Selective Mannosylation with a 4,6-Silylene-Tethered Thiomannosyl Donor

Mads Heuckendorff, Jesper Bendix, Christian M. Pedersen,* and Mikael Bols*

Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen Ø, Denmark

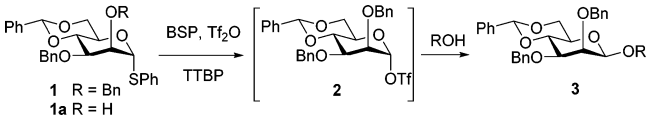
Supporting Information



ABSTRACT: Mannosylations using the new conformationally restricted donor phenyl 2,3-di-*O*-benzyl-4,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-mannopyranoside (**6**) have been found to be β-selective with a variety of activation conditions. The simplest activation conditions were NIS/TfOH, in which case it is proposed that the β-mannoside is formed from β-selective glycosylation of the oxocarbenium ion **25** in a $B_{2,5}$ conformation.

It has long been recognized that the synthesis of β-mannosides is one of the most challenging and difficult glycosylations in carbohydrate chemistry.[1] Although many protocols for β-mannoside synthesis have been reported, there is little doubt that the most direct and general procedure is the one developed by Crich et al. a decade ago (Scheme 1).[2] In this

Scheme 1. Crich's Method for β-Mannoside Synthesis



method, tethering the 4- and 6-OH groups of the mannosyl donor is important, and this is commonly done with 4,6-*O*-benzylidene acetal protection.[3] The details of activation are also important, with a preactivation procedure at low temperature, of a sulfoxide or thioglycoside, being required in order to form an α-mannosyl triflate that reacts with inversion to produces the β-mannoside.[4] Subsequently, several modifications have been reported,[5] but none of these appear to be as general or as well understood.

As a part of our ongoing research in glycosylation with conformationally restricted donors, where we have employed the di-*tert*-butylsilylene (DTBS)[6] group, we became curious whether a 4,6-*O*-silylene group could be used in a Crich-type β-mannosylation.[7] We were intrigued by the reactivity differences observed between silylene and benzylidene donors,[6f] and since the β-selectivity is believed to be caused by the deactivating influence of the benzylidene group, we considered that substitution might influence the selectivity.

Hence, we decided to investigate a 4,6-silylene-protected mannosyl donor in detail. The mannosyl donor **6** was synthesized in two straightforward steps from the thiomannoside **4** in yields (Figure 1) comparable with the synthesis of the

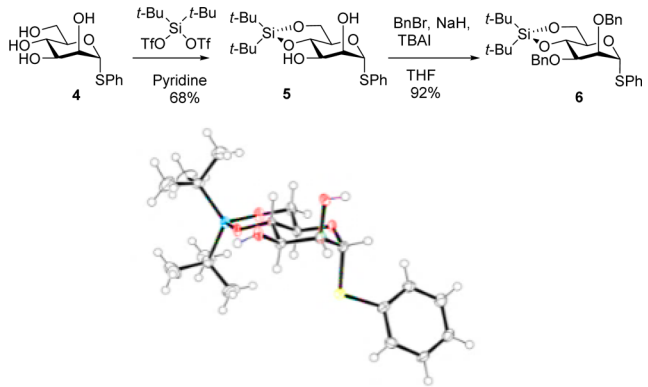


Figure 1. Synthesis of **6** and crystal structure of **5** (below).

widely used benzylidene analogue. Though crystallization of **6** was unsuccessful, an X-ray structure of the crystalline intermediate **5** could be obtained (Figure 1). The crystal structure revealed that the diol adopted an almost perfect $^4C_1$ conformation, but the silylene acetal is flattened out[6a] to an approximate envelope conformation with C5 out of the plane to avoid steric conflicts between the *tert*-butyl groups in the DTBS protective group. This is in contrast to the conformation of the benzylidene ring in a mannosyl donor **1**, which is a perfect chair. The conformational change is due to the longer bonds (1.65 Å vs ca. 1.44 Å in a benzylidene protected mannoside[8]) between O−Si and O−C, respectively.

Mannosylation of a series of acceptors (Figure 2) that previously had been glycosylated with **1** was carried out with **6** using the Crich preactivation procedure (Table 1).[9] In this, an activation reaction is performed between **6** and the reagents

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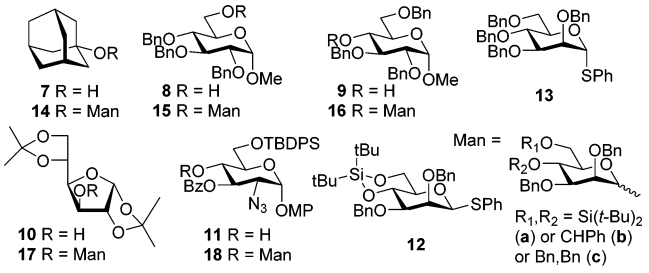


Figure 2. Acceptor alcohols **7**−**11**, mannosyl donors **12** and **13** and products **14**−**18**.

(BSP, Tf_2O, TTBP), which converts the thioglycoside into a leaving group and forms the α-triflate. Upon subsequent addition of the alcohol substitution with inversion occurs. In our experiments with this protocol (Table 1) preactivation times of 5 or 30 min were attemped with no notable difference in the results. As is evident from Table 1, the donor **6** gave the β-mannosides with high selectivity and yield, and these results are essentially similar to those reported previously in the literature with **1** (Table 1, columns 7−8). Activation using the modified protocol reported by the Leiden group[10] was also successful (Table 1, entry 2).

When acceptors with a 4-OH group were used, the stereoselectivity dropped (entries 4 and 6), particularly with acceptor **11**. As a control, glycosylation with stereoisomeric thioglycoside **12** (prepared as outlined in Figure 1 but from the β-analogue of **4**) was performed (Table 1, entry 7) with no significant difference from the results obtained with **6** (entry 1). All of these experiments are consistent with the mechanistic scheme proposed by Crich (Scheme 1) wherein the α-triflate intermediate is formed during the preactivation period and then converted mainly to the β-mannoside when the acceptor is added.[11]

When carrying out the glycosylation of **7** with **6** using NIS/TfOH in CH_2Cl_2 at −78 °C followed by slow heating to 0 °C (Table 2, entry 1) we saw, to our surprise, that the β-glycoside (yield: 99%, selectivity: 6:1, separation not possible) was obtained. Repeating this reaction with other acceptors (entries 2−5) also gave good to excellent yield and β-selectivity. Starting and running the reaction at 25 °C did not change the yield or selectivity significantly (entry 6), which means that the NIS/TfOH protocol is the easiest protocol to make a β-mannoside using **6**.

The silylene-protected donor **6** was found to be somewhat more reactive than the benzylidene analogue **1**. When the reaction of **6** with **7** was initiated at −78 °C a color change, indicating the beginning of the reaction, occurred at −20 °C. This activation temperature is between that of **1** and the perbenzylated donor **13**.

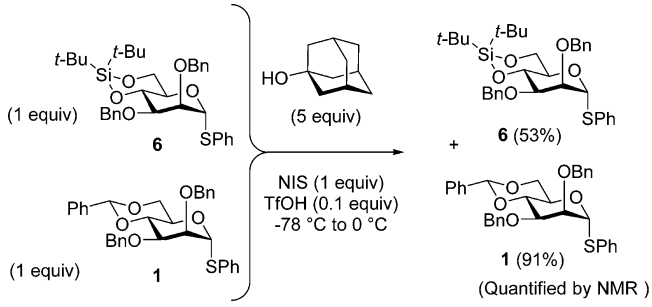
Table 2. Results of Reaction of Mannosyl Donors with Acceptor Alcohols Using NIS and Various Acid Catalysts in CH_2Cl_2[a]

entry	donor	acceptor	main product	acid	temp (°C)	yield (%)	β/α
1	**6**	**7**	**14a**	A	−78 → 0	99	6/1
2	**6**	**8**	**15a**	A	−78 → 0	88	9/1
3	**6**	**9**	**16a**	A	−78 → 0	67	3/1
4	**6**	**10**	**17a**	A	−78 → 0	73	10/1
5	**6**	**11**	**18a**	A	−78 → 0	78	2/1
6	**6**	**7**	**14a**	A	25	80	4/1
7	**6**	**7**	**14a**	C	−78 → 0	88	1/10
8	**6**	**7**	**14a**	D	−78 → 0	82	6/1
9	**6**	**7**	**14a**	B	25	86	5/1
10	**12**	**7**	**14a**	A	−78 → 0	99	6/1
11	**13**	**7**	**14c**	A	−78 → 0	87	1/1

[a]Key: (A) TfOH (catalytic); (B) $AgClO_4$/*t*-BuBr; (C) TMSOTf (1.1 equiv); (D) TMSOTf (0.1 equiv).

To further investigate the reactivity difference between **1** and **6**, a competition experiment was performed with 1 equiv of each donor, 1 equiv of promoter, and 5 equiv of acceptor **7** (Scheme 2). This experiment showed mainly the conversion of

Scheme 2. Competition Experiment between the Benzylidene-Tethered Donor 1 and the Silylene-Tethered 6



6, confirming that the silylene donor is the more reactive; i.e., the oxocarbenium intermediate more stabilized. On the other hand, an attempt to couple **6** to the donor/acceptor alcohol **1a** failed, which indicates that the reactivity difference between the silylene and benzylidene donor is minor.[12]

From a mechanistic point of view, the β-selectivity observed with NIS/TfOH is surprising as the acceptor is present during activation, which normally would be supposed to result in α-mannoside formation.[2] Ambiguous results are found in the literature regarding the use NIS/triflate in β-mannosylations.[13] For example, You et al. obtained β/α ratios between 3/1 to 7/1 with various sugar acceptors when activating an ethylthio

Table 1. Results of Reaction of 6 with Acceptor Alcohols Using the Crich Protocol (BSP, TTBP, Tf_2O, CH_2Cl_2, −60 °C)

entry	acceptor	product	yield (%)	β/α	J_{CH}, β/α	yield with **1** (%)	β/α with **1** (%)
1	**7**	**14a**	99	9/1	153/167	88[9a]	>9/1[9a]
2[a]	**7**	**14a**	75	9/1		96[10]	>9:1[10]
3	**8**	**15a**	79	9/1	156/164		
4	**9**	**16a**	61	5/1	156/171	90[9b]	10/1[9b]
5	**10**	**17a**	96	9/1	154/172	77[9]	>9:1[9]
6	**11**	**18a**	99	2/1	156/170		
7[b]	**7**	**14a**	99	6/1			

[a]The Leiden protocol (Ph_2O, TTBP, Tf_2O, CH_2Cl_2, −78 °C) was used. [b]The donor **12** was used rather than **6**.

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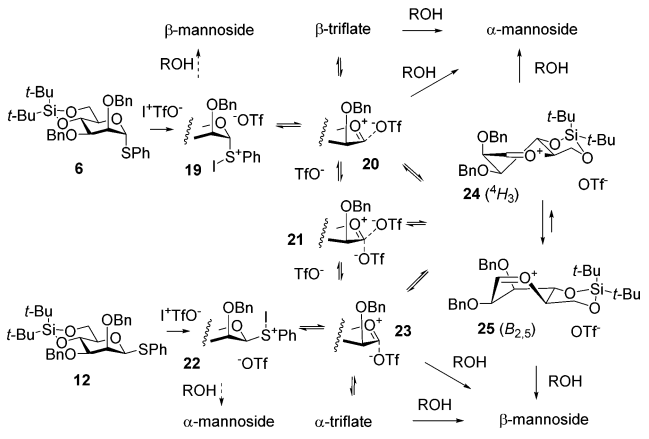
analogue of **1** with NIS and catalytic TfOH at 0 °C.[14] On the other hand, the reaction of **1** and **7** with NIS and TMSOTf (1.1 equiv) at 0 °C was reported to give a disappointing 1/1 β/α ratio.[3] For this reason, we also tried TMSOTf. When activation was performed with 1.1 equiv (Table 2, entry 7) we observed α-selectivity (β/α = 1/10), but when catalytic TMSOTf was used, β-selectivity returned (entry 8, β/α = 6/1). However, this discrepancy was found to be due to anomerization. When an NMR tube with β-mannoside **14a** in chloroform was treated with TMSOTf, complete anomerization from β to α was observed in 15 min. We therefore conclude that, in the silylene case, the main kinetic product of NIS/TMSOTf glycosylation is the β-mannoside. It is also noteworthy that triflate is not necessary in order to obtain β-selectivity. Activation of **6** under triflate-free conditions using $AgClO_4$ also gave mainly β-mannoside (entry 9).[15]

A reaction with the β-analogue of **6**, i.e., **12**, and the acceptor **7** was also performed (Table 2, entry 10), and this gave exactly the same results as when using **6**: yield of 99% and a β/α ratio of 6:1. This precludes a mechanism of direct S_N2-substitution of an iodoniumsulfide by the acceptor alcohol as was proposed in the ethylthio benzylidenemannoside case[14] since that would result in different product ratios from **6** and **12**. Reaction of perbenzylated donor **13** with **7** gave, as expected, no selectivity (entry 11) and confirms the importance of the 4,6-tethering group for obtaining the β-selectivity.

The above experiments show that it is not plausible that glycosylations with NIS follow a mechanism involving formation and subsequent S_N2 substitution of an α-triflate (Scheme 3). Activation of thioglycosides with NIS/TfOH is

Scheme 3. Proposed Mechanism for the Glycosylation of 6 (or 1) Using NIS/TfOH



initiated by formation of catalytic amounts of I^+TfO^- or alternatively $IHNIS^+TfO^-$.[16] One of these intermediates reacts with the thioglycoside **6** or **12** resulting in an iodonium sulfide with a triflate counterion (**19** or **22**). This iodonium sulfide is not substituted directly by the acceptor alcohol (dashed arrows) since if it did **12** would give α-mannoside, which it does not (entry 10). Rather, it must collapse to a triflate or an oxocarbenium ion/triflate intimate ion pair (**20** or **23**). The most plausible stereochemistry of a triflate or triflate intimate ion pair is that the triflate is on the other side of the leaving group, i.e., inversion as it is known that halogenation of thioglycosides initially gives the inverted glycosyl halide.[17] From the intimate ion pairs a solvent-separated oxocarbenium ion triflate **24**/**25** can be formed, and through this intermediate the stereoisomeric triflates and intimate ion pairs should be in equilibrium. Another possible route from α- to β-triflate is through an ion triplet **21** as suggested in halide isomerizations.[18] However, an ion triplet requires the presence of triflate ions to form and can therefore not be expected to play a major role in reactions where only catalytic triflate is used. It is therefore clear that α-triflate will only be formed in the reaction of **6** with NIS and catalytic TfOH by isomerization through solvent-separated oxocarbenium ion triflate **24**/**25**. The oxocarbenium ion **24**/**25** is obviously much more reactive than any triflate and must react with the acceptor when formed. The conclusion of these considerations is that the preferential β-mannoside formation seen from both **6** and **12** in NIS-promoted glycosylations can only be a result of β-selective addition of the acceptor to the solvent-separated oxocarbenium ionpair **24**/**25**.

Normally, one would expect that this ion would adopt a $^4H_3$ conformation (**24**), a conformation that is likely to be attacked by an alcohol from the α-face.[19] However, the $^4H_3$ conformation is very unfavorable having equatorial OR groups in the 3 and 4 positions[20] and the 6-OR in the *tg* conformation.[21] The more electronically favorable axial rich $^3H_4$ conformation cannot be adopted due to the tethering influence of the 4,6-silylene group. We propose that the oxocarbenium ion adopts a $B_{2,5}$ conformation[22] **25** whereby the 3-OR group is moved to a more favorable pseudoaxial position.[23] Furthermore, the 2-H is axial, which allows hyperconjugative stabilization of the oxocarbenium ion.[24] The geometries of the two suggested conformations, **24** and **25**, were optimized using DFT calculations on truncated models, where the *tert*-butyl and benzyl groups were substituted by methyl groups (see the Supporting Information for details).The $B_{2,5}$ conformation was found to be energetically favored over the $^4H_3$, both in vacuum and in different solvents. The difference is, however, small (0.59 kcal/mol in CH_2Cl_2; 0.73 kcal/mol in MeCN) but supports the proposed mechanism in Scheme 3. Attack on **25** is highly β-selective due to an axial approach of the alcohol, which results in a $^1S_5$ conformation. This transfers into the low energy $^4C_1$ via a $^4H_5$ conformation, without significant staggering in the silylene ring. α-Attack on **25** leads to a more strained and unfavorable $^OS_2$ conformation. Axial (α) attack by an acceptor on the less favorable $^4H_3$ conformation **24** results directly in the low energy $^4C_1$ conformation, whereas a β-attack results in a less stable $^1S_3$ conformation. The observed selectivities can also be justified by studying the geometry-optimized models of **24** and **25**. Looking at the Newman projection along the C1−C2 axis, a β-attack on **25** results in an approach of the nucleophile in a staggered fashion, whereas an α-attack would result in eclipsing interactions between the nucleophile and the almost axial 2-H (Figure 3). In **24**, a β-attack would eclipse with the pseudoaxial 2-OBn and be highly disfavored, whereas an α-attack would be nearly staggered, since the 2-H is pseudoequatorial.

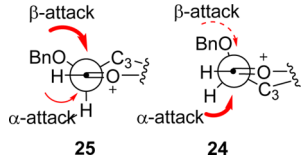


Figure 3. Newman projections of the nucleophilic attack on the two suggested oxocarbenium ion conformations **24** and **25**.

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In summary, we have found that **6** is a readily available glycosyl donor that can be used to produce β-mannosides using simple and popular NIS/TfOH activation with no preactivation or low-temperature chemistry necessary.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, competition experiments, NMR spectra, crystallographic data (CIF), and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cmp@chem.ku.dk.
*E-mail: bols@chem.ku.dk.

Notes

The authors declare no competing financial interest.

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