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Further Studies in α-*C*-Mannosylation Promoted by Samarium Diiodide

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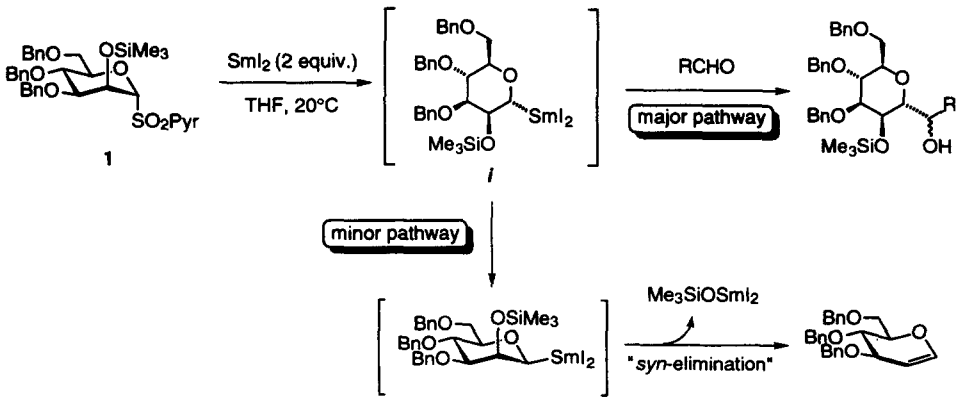
Abstract: Mannosyl pyridylsulfones with varying C2-OH protecting groups were reacted with cyclohexanone in the presence of SmI_2. With $SiMe_2tBu$ and Bn, high yields of an α-*C*-mannoside were obtained. In the former case no β-elimination was observed. The relative configuration of the major diastereomer obtained upon coupling with aldehydes was determined.

In a recent publication, we described an exceptionally mild and stereospecific approach to α-*C*-mannosides via the reductive samariation of pyridylsulfone **1** and its immediate coupling to carbonyl substrates under Barbier conditions.[1,2] The anomeric organosamarium intermediate ***i*** displayed remarkable stability to β-elimination, a property which completely deviates from results obtained with the corresponding lithium derivative[3-5] and which is explained in part by the requirement of a *syn*-orientation of the C1-Sm and C2-$OSiMe_3$ bonds for effective elimination (*syn*-elimination mechanism).[1] In some of our ongoing synthetic work on *C*-glycosides it became necessary to identify another more stable C2-OH protecting group required in subsequent transformations of the formed *C*-glycoside. In this communication, we show the importance of the C2-OH protecting group with respect to the efficiency and stereoselectivity of the *C*-mannoside formed and assign the relative configuration, previously not determined,[1] of the stereomers obtained upon coupling of the mannosyl pyridylsulfones with aldehydes.



A series of mannosyl pyridylsulfones **2-8** with varying C2-OH protecting groups was prepared starting from the previously described 2-pyridyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**9**) either by initial protection of **9** followed by sulfide to sulfone oxidation, or by reversing the order.[6] The sulfones were then

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subjected to 2 equivalents of samarium diiodide in the presence of a carbonyl substrate at 20°C, to measure the efficiency of the coupling reaction, the stereoselectivity obtained at the anomeric center, and the percentage of

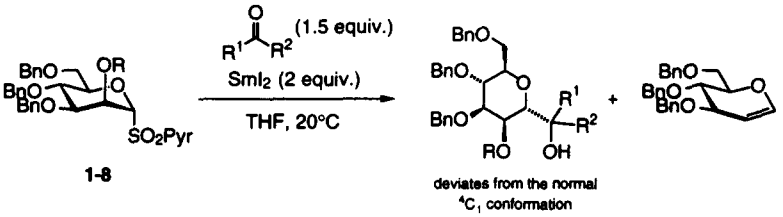
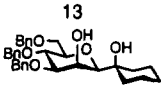
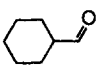
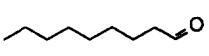
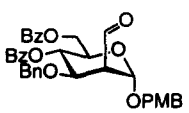
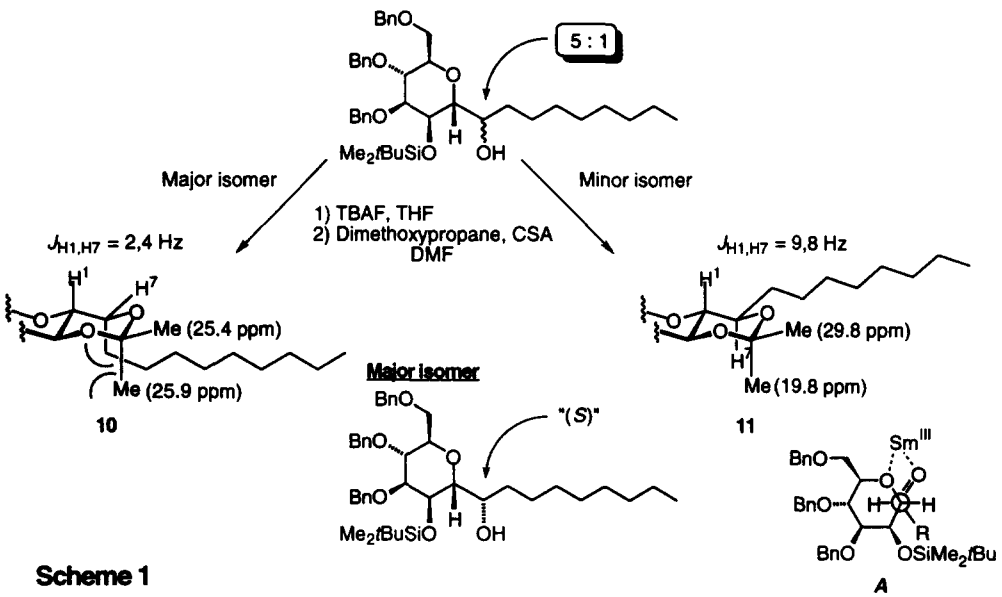


Table 1: SmI_2-promoted *C*-Glycosylations with Pyridylsulfones **1-8**[a]

Entry	R		Carbonyl comp.	*C*-glycoside (isolated yields %)[b]	Glucal (isolated yields %)[b]
1	$SiMe_3$	1		86[c]	1
2	$SiMe_3$	1		77 (13:2)[c,d]	7
3	Bn	2		81	6
4	MEM	3		45	25
5	THP	4		56	21
6		5		0	62
7		6		0	99
8	H	7		13  (20)	18
9	$SiMe_2tBu$	8		80	0
10	$SiMe_2tBu$	8		84 (4:1)[d]	0
11	$SiMe_2tBu$	8		71 (5:1)[d]	0
12	$SiMe_2tBu$	8		85 (1:0)[d]	0

[a]See ref. 1 for experimental details. [b]Based on isolated, chromatographically pure material.
[c]Results taken from ref. 1. [d]Figures in brackets refers to the diastereofacial selectivity

β-elimination. The results are depicted in Table 1. As with the previous results in which the $SiMe_3$ protecting group was used (entries 1 and 2), the benzyl protecting group (entry 3) led to good coupling yields with low β-elimination (6%). Somewhat surprising were the results obtained with the MEM and THP groups (entries 4 and 5) which displayed high anomeric selectivity but only low coupling yields with substantially increased production of tribenzylglucal. The carbonate and carbamate derivatives **5** and **6** (entries 6 and 7) led to essentially no formation of the α-*C*-mannoside which parallels previous results observed with the C2-acetate. Also surprising was the non-selective coupling of the pyridylsulfone **7** with a free C2-OH group which afforded an approximately 2:3 mixture of α,β-*C*-glycosides in 33% yield (entry 8).[7] On the other hand, the use of a sterically more bulky silicon-protecting group, such as $SiMe_2tBu$, furnished good coupling yields with cyclohexanone and various aldehydes (**8**, entries 9-12), different from all previous cases in that *no elimination product could be detected in the reaction mixture*.[8] This result conforms well with our previously proposed hypothesis that a *syn*-relationship between the C1-Sm and C2-OR bonds is required for β-elimination. The greater bulkiness of the $SiMe_2tBu$ group favors completely the preferential conformational change displayed by the anomeric organosamarium such that only a *trans*-relationship between the two vicinal substituents is maintained.[1]



Scheme 1

In the case of sulfone **8**, its coupling with aldehydes afforded a mixture of stereoisomers at the newly formed exocyclic stereocenter with a selectivity of 4 to 1 or greater. In order to assign the relative stereochemistry of the two isomers we profited from the previous work of Rychnovsky for the stereochemical determination of 1,3-diols by ^{13}C NMR analysis.[9] The chromatographically separable *C*-glycosides of entry 11 in Table 1 were hence individually desilylated and transformed to their corresponding isopropylidenes **10** and **11** (Scheme 1).[10] The ^{13}C NMR spectrum of the major isomer **10** showing acetonide methyl resonances at 25.4 and 25.9 ppm suggests that the dioxolane ring occupies a skew boat conformation due to a significant 1,3-diaxial interaction in the chair. This situation can only occur if the major isomer has the (*S*)-configuration at the exocyclic stereocenter C7. On the other hand, methyl peaks of the minor isomer **11** observed at 19.8 and 29.8 ppm clearly indicate a chair conformation with an equatorially-oriented octyl group. A large ^3J

coupling constant between H1 and H7 of 9.8 Hz was also noted in the ^1H NMR spectrum of **11**. These results are in agreement with the minor isomer possessing the (*R*)-configuration at C7. This work therefore clarifies the stereochemical outcome of the coupling reactions involving mannosyl anomeric Sm(III) compounds with aldehydes as observed by us[1,2] and others.[11] The diastereoselectivity may be explained by considering the cyclic transition structure *A*. The R group of the aldehyde is *anti* to the endocyclic oxygen which avoids sterical interactions with the sugar ring.[5b]

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5. In the *gluco*-case, deprotonation of the C2-OH prior to lithiation can lead to a stable anomeric lithium species at low temperature: a) Wittmann, V.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1091-1093; b) Lesimple, P.; Beau, J.-M. *Bioorg. Med. Chem.* **1994**, *2*, 1319-1330.
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7. The significant formation of glucal observed for entries 4 and 5, Table 1, could be the result of an internal six-membered ring chelate involving the anomeric Sm^{III} metal ion which facilitates elimination. This is probably the case for entries 6 and 7 as well. Internal coordination through a four-membered ring chelate with a C2-alkoxide may explain the preference for β-*C*-mannoside formation in entry 8.
8. *Typical procedure:* A 0.1 M THF solution of SmI_2 (2.2 equiv.) was added quickly to a well degassed solution of pyridylsulfone **8** (1 equiv.) and the carbonyl substrate (1.5 equiv.) in THF (5 ml / mmol of **8**). The reaction mixture was treated with saturated NH_4Cl, extracted twice with CH_2Cl_2, and the organic phase was dried and evaporated to dryness. The crude product was purified by flash chromatography.
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10. Selected ^1H NMR (250 MHz, $CDCl_3$) data for **10**: δ 4.20 (1H, dd, *J* = 7.0, 7.0 Hz, H5), 4.09 (1H, d, *J* = 5.5 Hz, H2), 4.09 (1H, dd, *J* = 5.5, 2.9 Hz, H1), 3.99 (1H, ddd, *J* = 10.3, 5.6, 2.9 Hz, H7), 3.92 (1H, d, *J* = 3.9 Hz, H3), 3.83 (1H, dd, *J* = 9.9, 7.0 Hz, H6a), 3.69 (1H, dd, *J* = 9.9, 7.0 Hz, H6b), 3.66 (1H, d, *J* = 3.9 Hz, H6b), 1.45 (3H, s, CH_3), 1.38 (3H, s, CH_3).
    Selected ^1H NMR (250 MHz, $CDCl_3$) data for **11**: δ 4.19 (1H, dd, *J* = 7.2, 6.8 Hz, H5), 4.10 (1H, dd, *J* = 9.8, 2.8 Hz, H2), 3.90 (1H, dd, *J* = 10.0, 6.8 Hz, H6a), 3.83 (1H, dd, *J* = 2.8, 2.8 Hz, H3), 3.77 (1H, m, H7), 3.72 (1H, dd, *J* = 10.0, 7.2 Hz, H6b), 3.66 (1H, d, *J* = 2.8 Hz, H4), 3.55 (1H, dd, *J* = 9.8, 9.8 Hz, H1), 1.54 (3H, s, CH_3), 1.45 (3H, s, CH_3).
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