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The Trityl Group as an Alternative in Mukaiyama's Glycosylation Reaction

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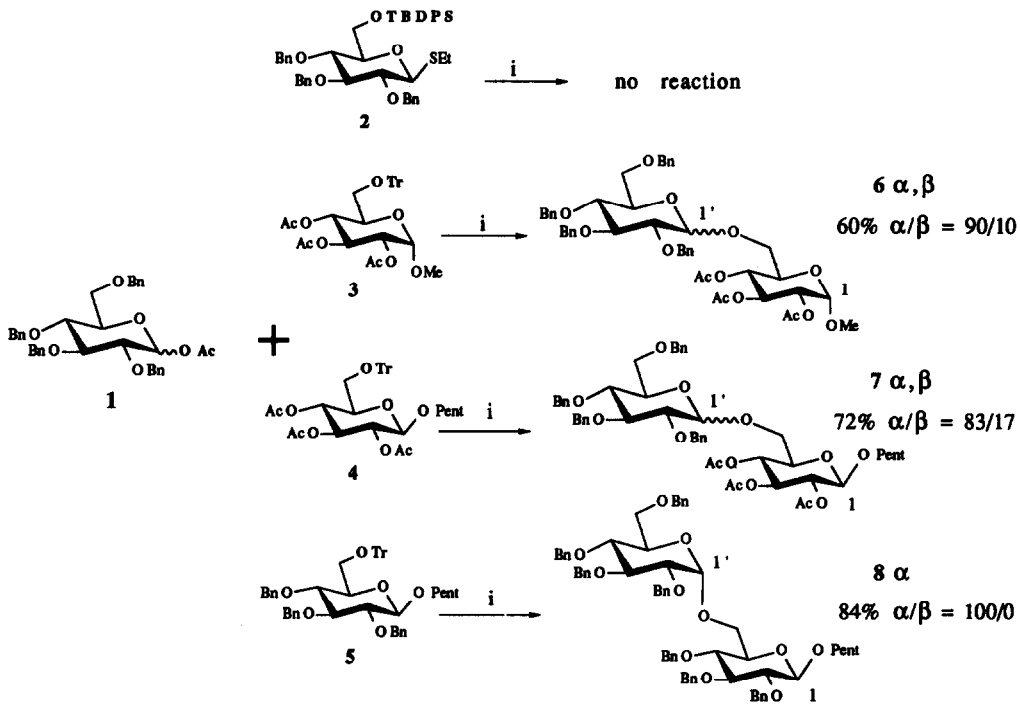
Abstract: The substitution of a trityl protecting group for TMS in the glycosylation method proposed by Mukaiyama makes it possible to use it in linear and cyclooligosaccharide with satisfying yields while the TMS glycosyl acceptor was unstable in the experimental conditions used and did not lead to any reaction product.

The glycosylation reaction of Mukaiyama involving activation of the anomeric position of the glycosyl donor by an acetate group and activation of the hydroxyl group of the glycosyl acceptor by a trimethylsilyl ether (TMS) is a very efficient method for stereoselective synthesis of 1,2-cis glycosidic linkages.[1] We were interested in this method to synthesize cyclic oligosaccharides in the isomaltose series (α-1,6 configuration). Unfortunately, in our case, lability of the TMS group prevent its utilisation in a large scope of experimental conditions.

To overcome this difficulty we have tried to replace the original TMS group by other protecting ethers known to be selective for the primary position and supposed to be also an activating substituent. We have chosen to check first trityl[2a] (Tr : Ph_3C-) and t-butyldiphenylsilyl (TBDPS)[3] ethers in a classical linear dimer synthesis. For the preparation of monomers **1** to **5**, standard methods have been used : acetylation,[2b] benzylation,[4] glycosidation with 4-penten-1-ol by the Koenigs-Knorr method.[5] As can be seen from the results given in Table 1, TBDPS has shown no reaction. On the contrary the trityl protecting group which has been used frequently to improve the nucleophilicity of hydroxyl groups in glycosylation reactions[6] gave good to very good yield of the desired dimers.[7] It must be underlined in addition that the stereoselectivity is also very satisfactory in favour of the required α configuration. In all cases only a small amount of deprotected glycosyl acceptors have been found beside the dimers.

This modification of the reaction of Mukaiyama has been applied to the synthesis of cyclic oligosaccharides in the isomaltose series.[8] In our opinion the proposed alternative to the original reaction of Mukaiyama is interesting from two points of view. First, the trityl group is very easily and selectively (in position 6) introduced. Second, it is no longer required to deprotect and silylate the hydroxyl group implicated in the glycosylation reaction. All reactions have been performed on millimolar scale. Silver perchlorate (monohydrate form) and tin(IV)tetrachloride are commercially available (Aldrich), they are used as such. Typical procedure for the glycosylation : to an etheral solution (3 mL) of $AgClO_4,H_2O$ (9 mg, 0.044 mmol) was added $SnCl_4$ (85 µL, 0.043 mmol) from a toluene solution (0.5 M). The mixture was stirred for 4h and the glycosyl donor **1** (252 mg, 0.432 mmol) and acceptor (0.52 mmol) were added simultaneously in etheral solution (3 mL). When the reaction was complete (TLC), it was diluted with methylene chloride, washed (saturated NaCl) and dried over sodium sulfate. The crude product was purified by column chromatography and HPLC.

Table 1. Glycosylation under Mukaiyama's conditions



i) $AgClO_4/SnCl_4$ (0.1 equiv.) ; glycosyl acceptor (1.2 equiv.) ; Et_2O ; 25°C.

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References and Notes

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7. ^1H and ^{13}C NMR δ(ppm), J (Hz) $CDCl_3$ at 400MHz

	6 α	**6 β**	**7 α**	**7 β**	**8 α**
δ(H-1)	4.45	4.43	4.78	4.87	4.42
$^3J_{1,2}$	7.89	7.79	3.75	3.67	7.74
δ(H-1')	4.80	4.40	4.91	4.43	5.08
$^3J_{1',2'}$	3.47	7.99	3,72	7.78	3.56
δ(C-1)	100.39	100.41	96.16	96.31	103.35
δ(C-1')	96.76	103.76	96.92	103.79	96.94

(FAB$^+$) ms : m/z **6** α,β : 895.2 $(M-H)^+$, 1029.2 $(M+Cs)^+$; **7** α,β : 841.2 $(M-H)^+$, 975.2 $(M+Cs)^+$; **8** α : 1039.4 $(M-H)^+$, 1173.3 $(M+Cs)^+$.

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