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EFFICIENT SIALYLATION WITH PHOSPHITE AS LEAVING GROUP

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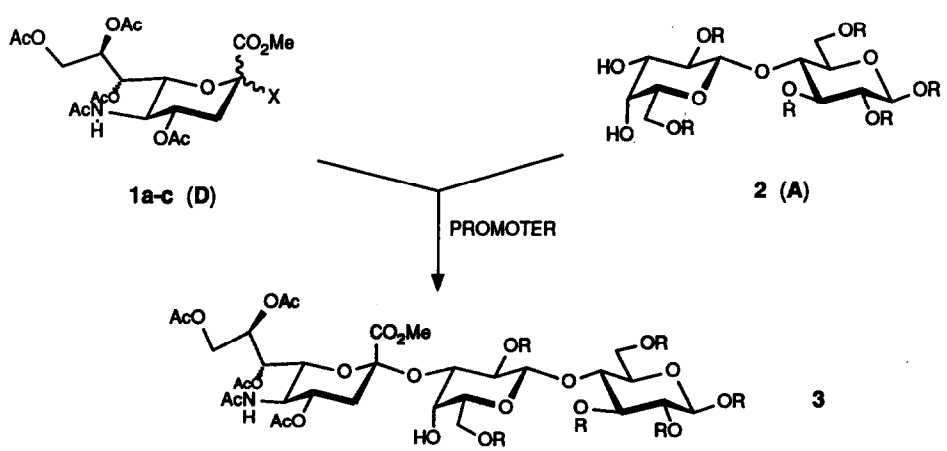
Abstract: The search for an acid labile leaving group attached to the anomeric position of O-protected N-acetyl-neuraminic acid led to phosphite derivative **1c** which provided in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate the desired high glycosyl donor properties. Thus, with methanol and mono- and disaccharides **2**, **4**, **6**, and **8** as acceptors in acetonitrile as solvent α-glycosides **3**, **5**, **7**, and **9**, respectively, were obtained in good yields.

Improvements in sialylation of sugars both in terms of yields and ease of performance of the reaction is a major task in the synthesis of complex gangliosides[1]. Halogenoses of O,N-acylated neuraminic acid esters activated by silver or mercury salts gave (particularly with secondary hydroxy groups) only modest yields of the desired α-products[1,2]. Therefore, neighboring group assistance with the help of auxiliary groups in 3-position of the neuraminic acid moiety were introduced[3,4]; however, the generation of the required starting materials and the removal of the auxiliary groups limit the application of this approach.

Scheme 1



Recently, thioglycosides of neuraminic acid derivatives [prepared via halogenoses with sulfides[5] or via 2-O-acyl protected derivatives with methyl trimethylsilyl sulfide and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as promoter[6], respectively] have been proposed as sialyl group donors[5,6]; the requirement of at least equimolar amounts of thiophilic reagents [N-iodosuccinimide (NIS)[6,7], DMTST[5], methylsulfenyl bromide[8], silver triflate[8]) constitutes a disadvantage in this approach.

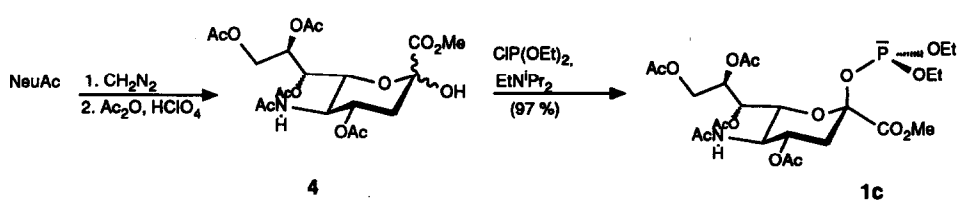
The nitrile effect in O-glycosylation reactions[9] which favors under kinetically controlled conditions the equatorial glycoside (α-product in neuraminic acid) applied to thio group activated neuraminic acid derivatives **1a,b** led to improved α-selectivities[6-8]; however, the performance of the reaction and the yields remained generally unsatisfactory as exhibited in our experiments with the typical acceptor **2**[10] (Table 1) providing known trisaccharide **3**[11], useful in the synthesis of the glycosphingolipids of the *ganglio* series[12].

Table 1 Application of Different Methodologies to the Synthesis of Sialyl-lactoside **3** from Donors **1a-c** and Acceptor **2**

REFERENCE TO METHODOLOGY	DONOR	X	RATIO D:A [eq]	SOLVENT	TEMP. [°C]	PROMOTER SYSTEM [eq]	YIELD [%]
P. SINAY, A. MARRA	1a	SC(S)OEt	1 : 2	CH_3CN	- 15	DMTST (2 eq)	26 (α)
- R.R. SCHMIDT, A. TOEPFER	1a	SC(S)OEt	1 : 1.5	CH_3CN	- 30	NIS (1 eq), TfOH (0.2 eq)	25 (α)
- H. LOENN, AL.	1a	SC(S)OEt	2 : 1	CH_3CN/CH_2Cl_2	- 60	AgOTf (2 eq), MeSBr (2 eq)	25-30 (α)
A. HASEGAWA, Al.	1b	SMe	1.6 : 1	CH_3CN	- 40	NIS (2.0 eq), TfOH (0.2 eq)	45-50 (α)
THIS PAPER	1c	$OP(OEt)_2$	1 : 1.5	CH_3CN	- 40	TMSOTf (0.1 eq)	50-55 (α)

Obviously, with nitriles as solvent just a simple acid sensitive leaving group is required; it can be activated by catalytic amounts of acid (for instance, TMSOTf) when the leaving group, due to appropriate choice, does not consume the catalyst. Consideration of several leaving groups led to phosphate[13] and phosphite moieties and their derivatives which can be directly attached to the anomeric hydroxy group of readily available neuraminic acid derivative **4** (two steps from neuraminic acid)[14] as displayed, for instance, in the quantitative formation of β-configurated diethyl phosphite **1c**[15,16]. As expected, a solution of donor **1c** and acceptor **2** provided in the presence of catalytic amounts of TMSOTf the desired α-sialylated trisaccharide **3** in respectable yields (Table 1), thus exhibiting the ease of the performance and the efficiency of this methodology.

Scheme 2

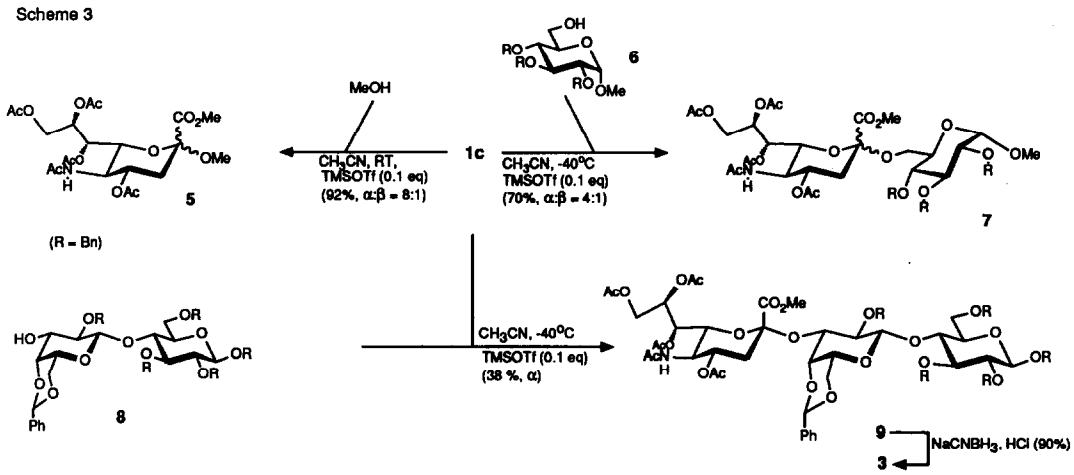


4 **1c**

Further examples with methanol, 6-O-unprotected glucose derivative **6**[17], and 3b-O-unprotected lactose derivative **8**[7] as acceptors afforded the desired glycosides **5**[14], **7**[18] and **9**[7], respectively, in high yields and α-selectivities.

Particularly worth mentioning is the result with acceptor **8** because full O-protection next to the 3-O-position of a galactose derivative led generally to very low sialylation yields. For structural proof, product **9** was converted with $NaCNBH_3$/HCl into known trisaccharide **3**[7]. The structures of compounds **3**, **5**, and **7** were assigned by comparison with literature data [11,14,18].

Scheme 3



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