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Highly Stereoselective Synthesis of Primary, Secondary, and Tertiary α-*S*-Sialosides under Lewis Acidic Conditions

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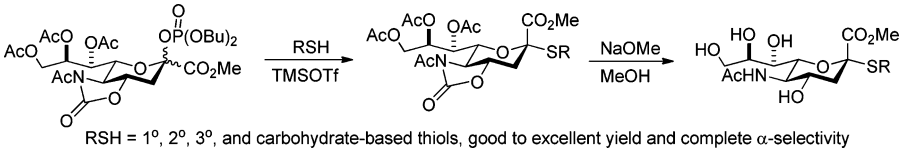
ABSTRACT



RSH = 1°, 2°, 3°, and carbohydrate-based thiols, good to excellent yield and complete α-selectivity

***N*-Acetyl 4-*O*,5-*N*-oxazolidinone protected sialyl phosphates of either anomeric configuration are excellent donors for the formation of α-*S*-sialosides at −78 °C in dichloromethane with primary, secondary, and tertiary thiols including galactose 3-, 4-, and 6-thiols. The reactions, which proceed under typical Lewis acid promoted glycosylation conditions, are highly α-selective and do not suffer from competing elimination of the phosphate.**

Thioglycosides, including the thiosialosides, have been widely exploited as nonhydrolyzable mimics of *O*-glycosides for use in the study of glycosidase enzymes for which they are both potential inhibitors and stable substrate analogs that facilitate crystallographic studies.[1] The stereoselective synthesis of the α-*O*-sialosides has been a notoriously difficult problem in carbohydrate chemistry,[2] to which we and others recently introduced a practical stereoselective solution based on the use of 4-*O*-5-*N*-oxazolidinone protected sialyl donors[3] and their *N*-acetyl counterparts.[4] More recently, we extended this chemistry to encompass the highly stereoselective synthesis of the α-*C*-sialosides using allyltributylstannane and trimethylsilyl enol ethers as nucleophiles.[5] We now show that these same

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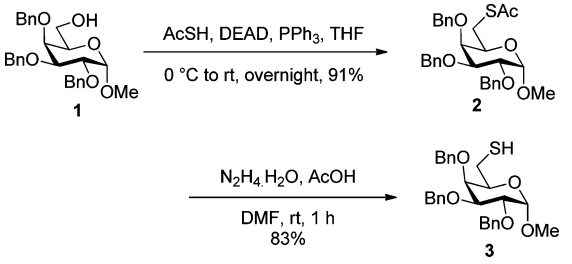
donors are applicable to the highly stereoselective synthesis of the α-*S*-sialosides for which surprisingly few syntheses by sialylation of thiols have been reported,[1g,6] with the more common approach being alkylation of 2-mercapto sialic acid derivatives.[1e–g,7] Interestingly, the few syntheses of α-*S*-sialosides that have been reported by the sialylation of thiols made use of alkali metal thiolates with which to displace chloride from the anomeric position of a *β*-sialyl chloride, conditions which are limited in functional group compatibility and require the isolation of a single diastereomerically pure sialyl chloride.[1g,i,6] Indeed, other authors have described problems arising from elimination reactions of the sialyl chloride under these conditions.[7g]

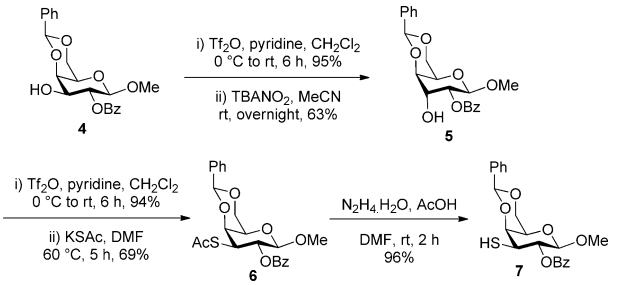
To test the applicability of the *N*-acetyl oxazolidinone-protected sialyl donors for the formation of α-*S*-sialosides, we prepared three deoxy mercapto sugars as acceptors by standard methods. Thus, the galactose 6-thiol **3** was obtained by the Mitsunobu reaction on the corresponding alcohol **1**,[8] via the thioacetate **2**, employing thioacetic acid as a nucleophile (Scheme 1).[9]

Scheme 1. Synthesis of a 6-Mercaptogalactopyranoside



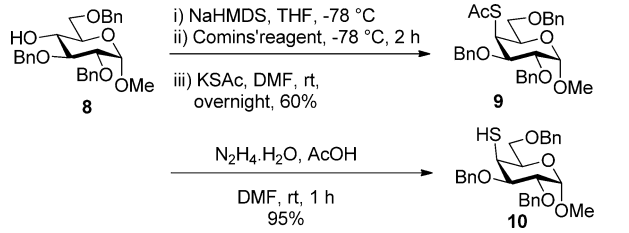
A galactose 3-thiol was obtained from the 4,6-*O*-benzylidene protected galactose 3-OH derivative **4**[10] by adaptation of the syntheses of related thiols described previously by the Schmidt[6b,c] and Bundle[1g] groups. Thus, triflation of **4** with triflic anhydride followed by displacement with tetrabutylammonium nitrite gave the gulose derivative **5**, from which the thiol **7** was obtained by a second inversion and subsequent hydrazinolysis of the intermediate thioacetate **6** (Scheme 2).

Scheme 2. Synthesis of a 3-Mercaptogalactopyranoside



Finally, to probe the effect of steric hindrance on glycosylation, we prepared the galactose 4-thiol derivative **10** from the glucose derivative **8**.[11] Triflation of **8** was best accomplished with Comins' reagent, *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulf donimide),[12] followed by displacement with potassium thioacetate giving the thioester **9**, from which **10** was obtained on exposure to hydrazine acetate (Scheme 3).

Scheme 3. Synthesis of a 4-Mercaptogalactopyranoside



Turning to the sialidation reaction, we elected to work with the sialyl phosphates introduced by the Wong group[4e] and prepared from the *N*-acetyl oxazolidinone protected sialyl thioglycosides[4a,b] in a single step. This choice was made to avoid potential complications arising from the reaction of thiophilic reagents, needed for thioglycoside activation, with the thiol nucleophiles. We note, however, based on previous work from our laboratory that the Kahne sulfoxide glycosylation method[13] is generally compatible with the use of thiols as nucleophiles and, thus, with the formation of thioglycosides.[14] Thus, as the *N*-acetyl oxazolidinone protecting system has very recently been shown to enable the isolation of stable sialyl sulfoxides for the first time,[4h] the sulfoxide method presents a potential but as yet untested alternative to the use of the sialyl phosphates.

Initial experiments were conducted with the α-configured donor **11α**[4e,5] in dichloromethane at −78 °C using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the

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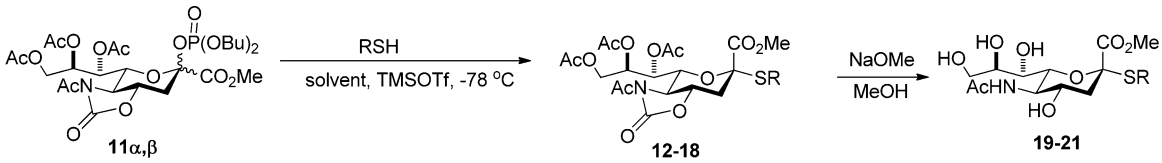
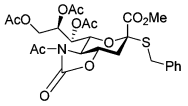
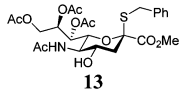
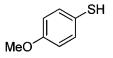
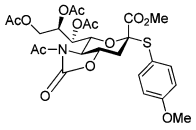
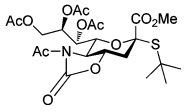
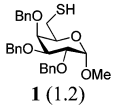
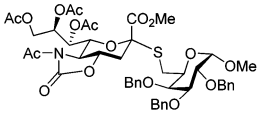
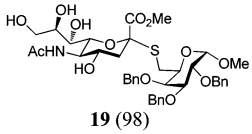
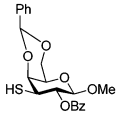
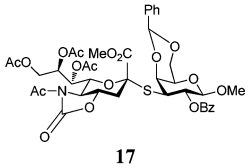
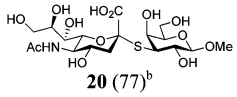
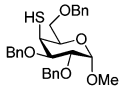
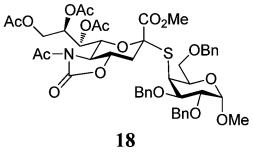
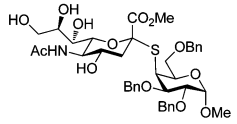
Table 1. Electrophilic *S*-Sialylation and Subsequent Oxazolidinone Cleavage



11α,β 12-18 19-21

	donor	nucleophile (equiv)	TMSOTf (equiv)	product	CH_2Cl_2 % yield[a]	CH_2Cl_2 α:β	2:1 CH_2Cl_2:MeCN % yield[a]	2:1 CH_2Cl_2:MeCN α:β	hydrolysis (% yield)
1	11α	$PhCH_2SH$ (1)	1		45 (75 brsm) + 11α, 40	100:0	–		–
2	11α	$PhCH_2SH$ (1)	2	 **12**	18 (32 brsm) + 11α, 43	100:0	–		–
3	11α	$PhCH_2SH$ (2)	2		28 (52 brsm) + 11α, 46	100:0	–		–
4	11α	$PhCH_2SH$ (2)	1		80 (83 brsm) + 11α, 4	100:0	–		–
5	11α	$PhCH_2SH$ (5)	1	 **13**	78	0:100	–		–
6	11α	 (2)	1	 **14**	73	100:0	–		–
7	11α	 (2)	1	 **15**	89	100:0	–		–
8	11α	 **1** (1.2)	1	 **16**	56 (70 brsm) + 11α, 20	100:0	75 (94 brsm) + 11α, 20	100:0	 **19** (98)
9	11β		1		54 (70 brsm) + 11β, 23	100:0	55 (98 brsm) + 11β, 44	100:0	
10	11α	 **7** (1.2)	1	 **17**	50 (74 brsm) + 11α, 32	100:0	86%	100:0	 **20** (77)[b]
11	11β				39 (85 brsm) +11β, 54	100:0	50 (91 brsm) 11β, 45	100:0	
12	11α	 **10** (1.2)	1	 **18**	67 (92 brsm) + 11α, 27	100:0	62 (66 brsm) + 11α, 6	100:0	 **21** (79)
13	11β				60 (95 brsm) + 11β, 37	100:0	53 (67 brsm) + 21 11β, 21	100:0	

[a] brsm, based on recovered starting material. [b] An additional treatment with Dowex 50 was employed after the saponification resulting in cleavage of the benzylidene acetal.

promoter and benzyl mercaptan as the acceptor (Table 1). With 1 equiv of thiol and 1 equiv of promoter (Table 1, entry 1), a 45% yield of a single anomer of the product **12** was obtained together with 40% of recovered donor, corresponding to a 75% yield of the product based on recovered starting material. The anomeric stereochemistry of **12**, and of all other thioglycosides obtained subsequently, was assigned in the standard manner[15] following the measurement of the $^3J_{C,H}$ coupling constant between the carboxyl carbon or methoxy carbonyl and the axial proton at

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C3 in the sialic acid ring. Increasing the amount of TMSOTf employed led to a more complex reaction mixture and a lower yield, albeit with retention of the excellent stereoselectivity for the formation of **12** (Table 1, entry 2). The use of 2 equiv each of acceptor and promoter was also not beneficial (Table 1, entry 3). However, the employment of 2 equiv of thiol and 1 equiv of promoter gave a clean reaction mixture and an 80% yield of pure **12α** (Table 1, entry 4). Interestingly, an attempt to further improve the yield through the use of 5 equiv of thiol resulted in cleavage of the oxazolidinone ring and isolation of the β-thioglycoside **13** in high yield and selectivity (Table 1, entry 5). As careful monitoring of the reaction mixture by TLC and mass spectrometry revealed, cleavage of the oxazolidinone ring required the presence of both the promoter and an excess of thiol, allowing Lewis acid promoted removal of the oxazolidinone ring by the excess thiol subsequent to thioglycoside formation followed by equilibration of the anomeric stereochemistry. The essentially pure β-nature of the thioglycoside formed under these conditions is consistent with the very strong thermodynamic preference for the axial glycoside in the sialic acid series.[16] Equilibration of the anomeric stereochemistry is much more likely to occur on the more highly armed system following cleavage of the oxazolidinone ring. The use of 4-methoxythiophenol and of *tert*-butyl mercaptan as acceptors under the optimum conditions of 2 equiv of acceptor and 1 equiv of TMSOTf also gave excellent yields of the corresponding thiosialosides, **14** and **15**, respectively, both as single α-anomers (Table 1, entries 6 and 7).

With the focus turned toward the carbohydrate-based thiols **3**, **7**, and **10**, use of the galactose 6-thiol **3** as the acceptor resulted in the formation of the thioglycoside **16** in moderate to good yield and in the form of a single equatorial anomer (Table 1, entries 8 and 9). This result was independent of the configuration of the donor and applied both in neat dichloromethane as solvent and in a mixture of dichloromethane and acetonitrile, such as is common in other sialylation protocols. Directly comparable results were obtained with the galactose 3-thiol **7** (entries 10 and 11), again from both isomers of the donor.

Finally, the highly hindered galactose 4-thiol **10** was demonstrated to be a competent acceptor in this chemistry, giving the thioglycoside **18** in good yield as a single anomer from either stereoisomeric donor (Table 1, entries 12 and 13).[17] Deprotection of the thioglycosides **16**–**18** (Table 1, entries 8, 10, and 12) was achieved in the usual manner,[4] with clean removal of the oxazolidinone ring, by treatment with sodium methoxide in methanol.

The stereoselectivities observed in these reactions, with the exception of the example reported in Table 1, entry 5 discussed above, very strongly favor the α-anomer and more so than the already highly α-selective coupling to corresponding alcohols.[4] This is most consistent with an associative mechanism facilated by the use of the more powerful thiols as nucleophiles, which involves displacement of a covalent activated β-donor, possibly a sialyl triflate, with inversion of configuration. The alternative possibility of nucleophilic attack on a sialyl oxocarbenium ion is considered less likely on the grounds that the stereoselectivity of such systems diminishes with the use of more powerful nucleophiles and as the diffusion controlled limit is approached.[18] Although S_N2 processes are considered to be highly disfavored at tertiary centers, there is strong literature precedent, both stereochemical and kinetic, for the existence of such processes with good nucleophiles when one of the substituents is a carboxylate ester.[19] Finally, several clear demonstrations of associative glycosylation reactions have been reported in the recent literature.[20]

Overall, we demonstrate a practical method for the highly selective synthesis of α-*S*-sialosides that proceeds under typical glycosylation conditions and functions with either anomer of the donor. The reaction is applicable to primary, secondary, and tertiary thiols, whether simple or carbohydrate-based, and is somewhat immune to steric hindrance in the thiol. The type of competing elimination that plagues many sialylation methods, including *S*-sialidation with other donors, does not compete to any significant extent with the glycosylation reaction. As the thiosialosides have been reported to be excellent stable analogs for binding to a number of protein targets and for the inhibition of sialidase enzymes,[1d−f,h,i,7a,7d−7f,7h,21] we anticipate that this novel, practical chemistry will find application.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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