Tetrahedron Letters, Vol. 33, No. 41, pp. 6053-6056, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

"ACTIVE" AND "LATENT" THIOGLYCOSYL DONORS IN OLIGOSACCHARIDE SYNTHESIS. APPLICATION TO THE SYNTHESIS OF α-SIALOSIDES

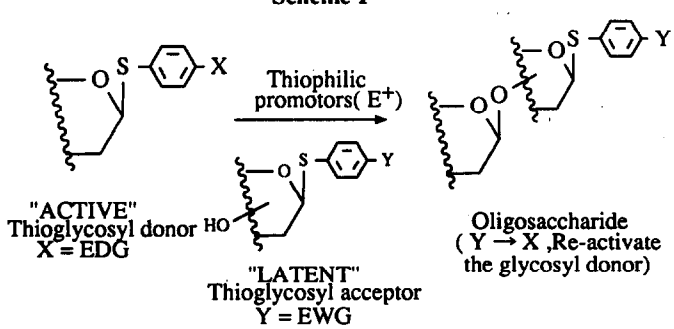
René Roy*, Fredrik O. Andersson, and Marie Letellier
Department of Chemistry, University of Ottawa
Ontario, Canada K1N 6N5

Summary: The use of a new "active" and "latent" thioglycosyl donor strategy in glycoside synthesis is described using arylthio α-sialosides of different reactivities.

Cell surface carbohydrates, and sialic acid (**1**, N-acetylneuraminic acid) in particular, constitute efficient receptors for hormones, toxins, bacteria and viruses.[1,2] Therefore, numerous efforts in the field of carbohydrate chemistry have been devoted to the syntheses of oligosaccharide sequences capable of acting as cell adhesion inhibitors or as antigens from which specific antibodies can be triggered. Contemporary activities in oligosaccharide syntheses have culminated in the design of powerful glycosylation methods.[3,4] Remarkable recent contributions to oligosaccharide syntheses rely on the concept of "armed" and "disarmed" glycosyl donors such as *n*-pentenyl-[5], thio-glycosides[6] and glycals.[7] More recently, Mehta and Pinto[8] reported an alternative strategy possessing added flexibilities.

In the latter approach, the higher reactivity of phenylselenoglycosides over thioglycosides was demonstrated, thus introducing the concept of selectivity in glycoside activations. Our new concept, illustrated in Scheme 1, also relies on selective activation. However, it differs from the previous one by the use of single aryl thioglycosides, the reactivity of which being predetermined by the choice of the substituents on the arylthio moieties. Access to a wide variety of thiophilic promoters, coupled to the controllable modulation of the sulfur nucleophilicities, allows the introduction of the concept of "active" and "latent" thioglycosyl donors. The "latent" thioglycosyl derivatives, possessing one free hydroxyl group and corresponding to "temporary inactive" species, serve as glycosyl acceptors. Then their reactivities can be "turned on" by transforming their electron withdrawing (EWG) thioaryl substituents into electron donating groups (EDG), thus "reactivating" the sulfur atoms toward electrophilic promotors usually employed in glycosylation reactions. Alternatively, the "active" thioglycosyl donors should already possess EDG substituents on their aryl moieties.

Scheme 1



The required α-thiosialosyl donors (**3-6**) were prepared under stereocontrolled inversion of configuration at the anomeric center using recently described phase transfer catalyzed conditions from β-acetochloroneuraminic acid **2**.[9] Then, the validity of the strategy was first demonstrated using the known 1,2-di-0-tetradecyl-sn-glycerol (**8**)[10] as model primary hydroxyl group-containing glycosyl acceptor. For comparison purposes, the β-chloride **2**[11] and the methylthio-α-sialoside **3**[9] were used in the glycosylation reactions. Thus, β-chloride **2** ($HgBr_2/HgCN_2$) and thioglycoside **3** using dimethyl(methylthio)sulfonium triflate (DMTST)[12] as promoter reacted with acceptor **8** in dichloromethane to provide an anomeric mixture (60:40) of the known sialosides **10-11**[9,13] in 62 and 82% yield respectively (Table I). The reaction of **3** with **8** was much faster than the reaction using the β-chloride **2**.

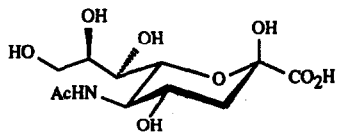
When the above glycosylation reactions were repeated with the "active" arylthio-α-sialosyl donors **4** and **5** under the same conditions (CH_2Cl_2, room temperature) the yields were similar and the stereoselectivity was only marginally reduced (entry 3,4, Table I). The reaction was faster for the more reactive donor **5** compared to **4**. Changing the solvent from CH_2Cl_2 to a 1:1 mixture of CH_3CN:CH_2Cl_2 had two beneficial effects. The reaction time was further reduced and the α-stereoselectivity was slightly increased (entries 4 and 5).[14] Moreover, as anticipated, treatment of the "latent" (unreactive) 4-nitrophenylthio-α-sialosyl donor **6** with **8** under the above conditions (entry 6) gave no detectable formation of the corresponding sialosides **10-11**. However, transformation of the "latent" donor **6** into the "active" form **7** (i: $SnCl_2$, EtOH, reflux, 30 min., ii: Ac_2O, pyridine, 98% yield) and glycosylation of **8** as above (entry 7) provided the sialosides **10-11** in 30 min. (70% yield) with a slightly better α-stereoselectivity.

To further demonstrate the usefulness of the crystalline "active" thiosialosyl donor **5** in disaccharide synthesis, **5** was treated with the galactosyl acceptor **9** in a 2:1 mixture of CH_3CN:CH_2Cl_2 and N-iodosuccinimide-triflic acid as promotor[6,15] (-15°C, 2h.) to provide the known[16] disaccharides **12-13** (2.6:1, α/β) mixture in 89% yield after silica gel chromatography. Correspondingly, the "latent" sialosyl donor **6** was found inert under these conditions.

TABLE I. Glycosylation reactions of **2** - **7** with **8**.

Entry	Donor[a]	Solvent[b]	Time (h)	Yield (%)[c]	**10:11**[d] α/β
1	**2**	CH_2Cl_2(A)	48	62	60:40
2	**3**	A	1	82	60:40
3	**4**	A	24	81	55:45
4	**5**	A	8	80	50:50
5	**5**	B	0.5	73	70:30
6	**6**	B	NR	-	-
7	**7**	B	0.5	81	75:25

[a] Donor:acceptor:DMTST (1.5:1:3). [b] Reactions at room temperature. B: CH_3CN : CH_2Cl_2 (1 : 1 mixture).
[c] Isolated yields. Products were fully characterized and agreed with literature data[9,13]. [d] By ^1H NMR spectroscopy.



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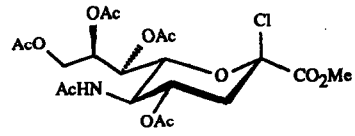

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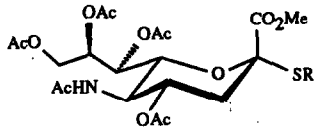
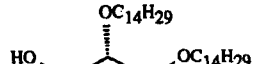


3 R = Me
4 R = Ph
5 R = p-MeO-Ph
6 R = p-NO_2-Ph
7 R = p-NHAc-Ph



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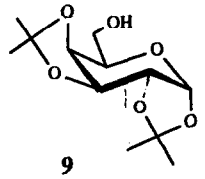

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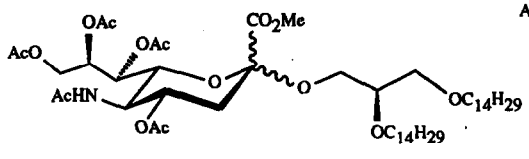
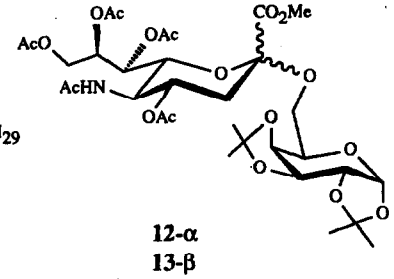


10-α
11-β



12-α
13-β

The new strategy described above compared well with other sialylation methodologies.[14,17,18] However, recent report by Lönn and Stenvall[18] has reported better α-stereoselectivities from sialosyl xanthate, which is also obtainable in high yield under PTC conditions.[19] Works are in progress to activate selectively the xanthate in the presence of thioglycosides.

In conclusion, preliminary results confirmed the concept of using "active" and "latent" thioglycosyl donors in glycoside synthesis. The concept has been successfully applied to glucosides and N-acetylglucosaminides.[20] The methodology is complementary to the "armed" and "disarmed" strategy[5,7] and should add other controllable variables in blockwise oligosaccharide syntheses.

ACKNOWLEDGEMENT

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC). We are indebted to MECT Corporation (Japan) for a generous supply of sialic acid.

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(Received in USA 18 June 1992; accepted 15 July 1992)