

Recent advances in glycosylation reactions

Pierre Sinay

Ecole Normale Supérieure, Laboratoire de Chimie, 24, Rue Lhomond 75231 Paris, France

Abstract - Several novel solutions to the efficient and selective preparation of glycosides are presented. Commercial tris(4-bromophenyl)ammonium hexachloroantimonate, a one-electron transfer homogeneous reagent, nicely activates in acetonitrile various ethyl or phenyl *S*-glycosides having either participating or non-participating substituents at C-2 to give β -*O*-glycosides in good yield. In a variation on the theme, phenyl *S*-glycosides react with alcohols under mild electrochemical conditions to give the corresponding *O*-glycosides. Azidoxanthates, prepared via a two-step sequence from various galactals, are efficient galactosyl donors for the stereoselective synthesis of protected precursors of biologically important galactosamine-containing oligosaccharides. We have also discovered that anomeric enol-ethers, or the corresponding carbonates, are remarkably efficient glycosyl donors. Finally, a "non-orthodox" strategy based on the idocyclization of appropriate acyclic enol-ethers resulted in a novel approach to KDO-containing disaccharides. This last synthesis critically benefited from the use of the Tebbe reagent for the preparation of the key starting enol ethers.

INTRODUCTION

Simple, efficient and selective preparation of oligosaccharides is a central problem in carbohydrate chemistry. The historical publication of Koenigs and Knorr, in 1901, first introduced glycosyl halides as glycosyl donors (ref. 1), and launched a method which -- through a vast series of variations -- has been by and large the essential one for a very long period of time (ref. 2, 3). The introduction of the orthoester procedure was probably the first important attempt to find an alternative to the Koenigs-Knorr method (ref. 4). This reaction has been refined over the years, mainly by the Russian School (ref. 5, 6). A subtle understanding of the chemical properties of the halogeno sugars resulted in 1975 in the development by Lemieux *et al.* (ref. 7, 8) of the halide-catalyzed glycosylation reaction which has been successfully applied to the synthesis of several blood group antigenic determinants. A limitation of this variation on the theme was the lack of reactivity with many "sugar alcohols" with weak reacting capacities, typically methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (ref. 9) which has become, over recent years, a standard for evaluating the "road holding" of any novel glycosylation strategy.

In 1978 we disclosed the imidate procedure (ref. 10), a novel alternative to the Koenigs-Knorr reaction. The disadvantage of our original procedure -- a rather laborious synthesis of the glycosyl donor from a halogeno sugar -- was circumvented by R. R. Schmidt *et al.* (ref. 11) and the imidate glycosylation reaction is now of much more use in the field. It is important to stress that the much higher reactivity of trichloroacetimidates compared to acetimidates may be detrimental to the α -selectivity. Indeed, the mild acetimidate glycosylation reaction is highly selective, a distinct advantage which should be kept in mind when dealing with sufficiently reactive acceptors. This research has probably contributed to moving further and further away from the time-resistant "paradigm" introduced by Koenigs and Knorr at the turn of the century.

With the availability of efficient glycosyl donors paving at last the avenue to higher oligosaccharides of biological relevance, a practical difficulty soon emerged: in order to keep manipulation of complex oligosaccharide fragments to a minimum, and to fully explicit convenient synthesis, it appeared important to build blocks which could be directly transferred to an acceptor upon activation. Thioglycosides are now attracting considerable attention in this respect (ref. 12). They are stable under a variety of chemical transformations and can be activated by thiophilic reagents.

Recent results obtained in the author's laboratory in the field of glycosylation are now being analyzed in this lecture which can be divided into four main topics.

- 1) Activation of thioglycosides with either TBPA⁺, a one-electron transfer homogeneous reagent, or via anodic oxidation (heterogeneous one-electron transfer).
- 2) Use of anomeric *S*-xanthates of 2-azido-2-deoxy-D-galactopyranosyl derivatives as efficient glycosyl donors.
- 3) Synthesis and use of anomeric enol-ethers, or the corresponding carbonates, as novel glycosyl donors.
- 4) Development of "non-orthodox" strategies for the synthesis of KDO- containing disaccharides.

I. THE "ONE-ELECTRON TRANSFER" APPROACH TO GLYCOSIDES

I.1 Glycosylation using a one-electron transfer homogeneous reagent: a novel and efficient synthesis of β -linked disaccharides

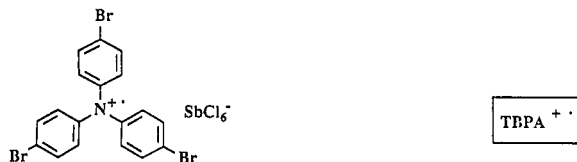
The hereto reported activations of thioglycosides can be divided into three categories.

1. Formation of a reactive sulfonium intermediate through a two-electron process taking advantage of the well-known affinity of sulfide groups for soft electrophiles. A variety of logical reagents have been described (ref. 13). Our attention was drawn by the recent development of NOBF_4 (ref. 14), as this reagent was used by Musker (ref. 15) as a typical one-electron oxidizing agent of peculiar thioethers in acetonitrile.

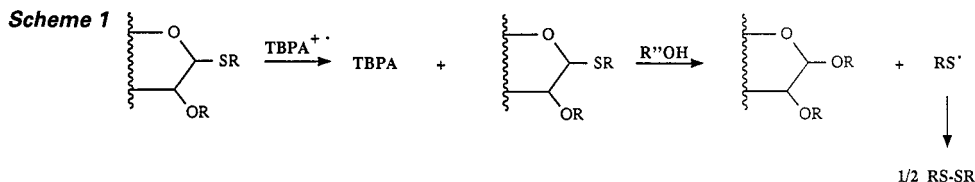
2. Oxidation of thioglycosides to either anomeric sulfoxides or sulfones, which have been used in glycosylation reactions (ref. 16, 17).

3. Use of heavy metal salts (soft acids) (ref. 18). It is interesting to note that $\text{Cu}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in acetonitrile was also reported by Musker (ref. 19) as a one-electron oxidizing agent of peculiar thioethers.

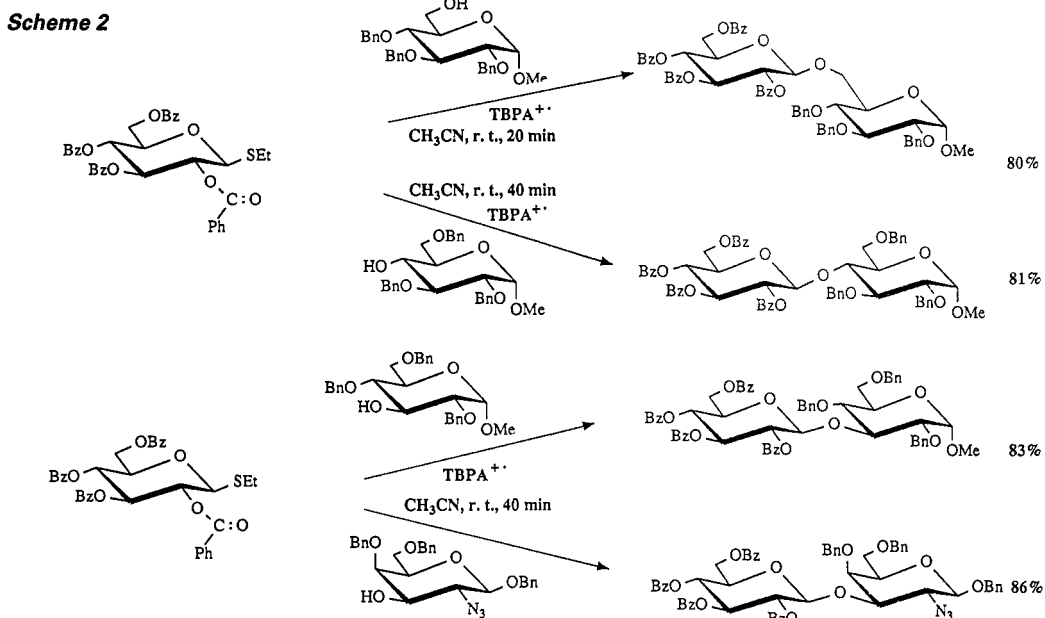
We thus anticipated that tris(4-bromophenyl)ammoniumyl hexachloroantimonate ($\text{TBPA}^{+\cdot}$), a stable commercial crystalline radical cation used as a one-electron transfer reagent, might be a suitable promoter for homogeneous electron transfer from sulfur in acetonitrile.



The formed radical cation $\text{GlySR}^{+\cdot}$ might well undergo a cleavage to give a thiyl radical (RS^\cdot) and a cation Gly^+ which is stabilized by the neighboring oxygen atom. *This would constitute the principle of a conceptually novel glycosylation reaction* (Scheme 1). Radical cation $\text{TBPA}^{+\cdot}$ was used relevantly for the cleavage of the dithioacetal protecting group (ref. 20).

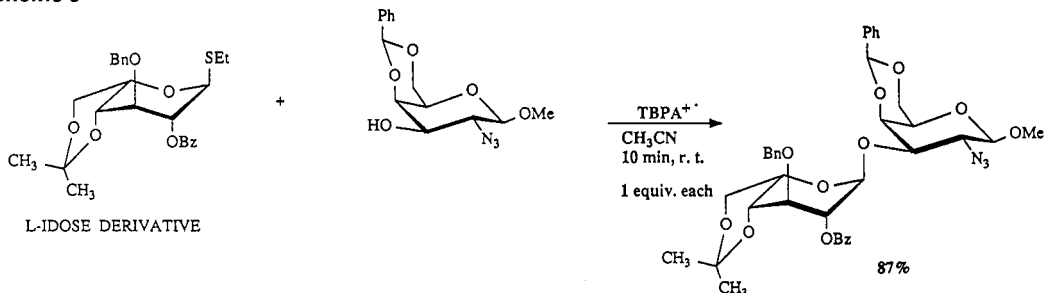


Indeed this idea worked extremely well. First we explored glycosyl donors having participating substituents at C-2. Condensation of ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- β -D-glucopyranoside with various "sugar alcohols" in acetonitrile at room temperature gave the corresponding disaccharides in good yield (Scheme 2).



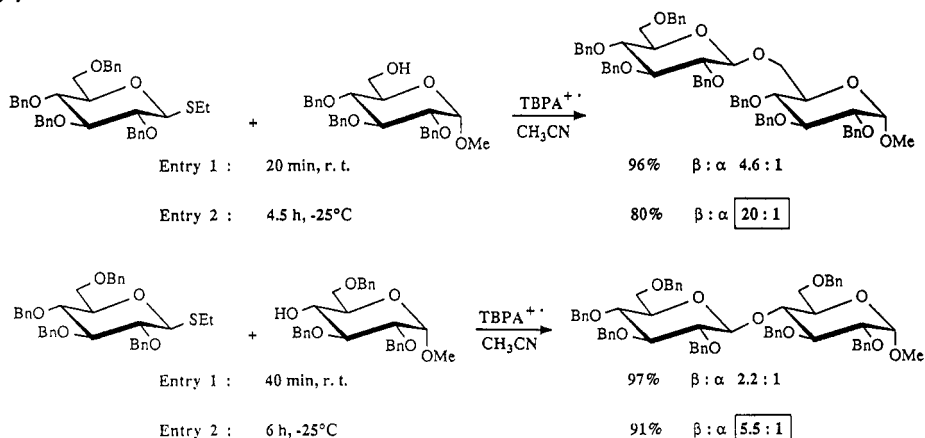
TBPA⁺⁺ exhibits in acetonitrile a typical dark blue color which disappears when the reaction is completed. The tris(4-bromophenyl)amine can be isolated (90%) from the reaction mixture and can be reused after one-electron oxidation to TBPA⁺⁺ (ref. 21). This reaction is compatible with acetals -- isopropylidene and benzylidene -- and azido groups (Scheme 3). Glycosylation with non-participating substituents at C-2 was next investigated.

Scheme 3



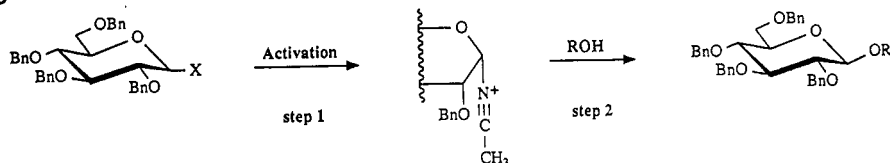
Ethyl or phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside react with primary or secondary "sugar alcohols" in acetonitrile at room temperature to give selectively β -*O*-glycosides in excellent yields (Scheme 4).

Scheme 4



The β -selectivity consistently observed in acetonitrile is due to the stereoselective kinetic formation (ref. 22) of a reactive α -nitrilium intermediate acting as the glycosylating species (ref. 23) (Scheme 5). We assume that step 1 is rate-determining and that step 2 determines the steric outcome of the reaction with the $\beta : \alpha$ selectivity being higher at low temperature. An excellent β -selectivity was observed (ref. 24) at -78°C in propionitrile (m.p. -103°C) when step 1 was sufficiently fast.

Scheme 5

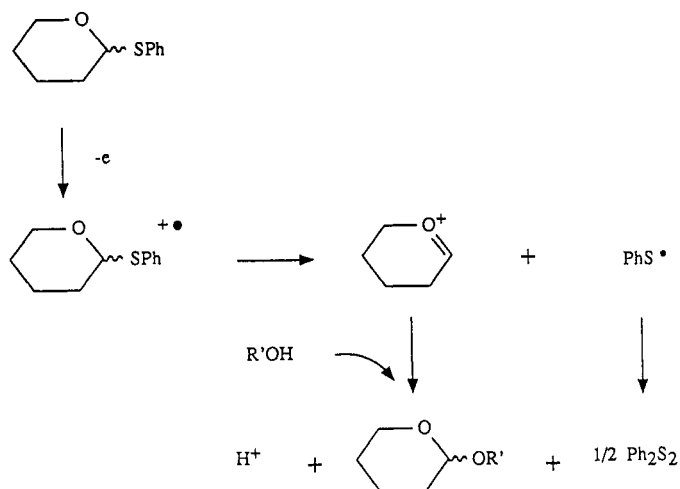


1.2 Electrochemical glycosylation using phenyl *S*-glycosides

It is known (ref. 25) that alkyl phenyl sulfides (Ph-S-R) are easily oxidized anodically to provide a radical cation (Ph-S-R)⁺⁺. We discovered (ref. 26) that electro-oxidative generation of the reactive oxycarbenium species (Scheme 6) from a phenyl *S*-glycoside resulted in an efficient and economical glycosylation.

The electrolyses were carried out in acetonitrile at room temperature in an undivided cell with LiBF₄ as the supporting electrolyte. The electrolyses were performed at a constant current (50 mA) until complete disappearance of the phenyl *S*-glucoside. The reaction was developed both with phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranoside and with phenyl 2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranoside (Scheme 7). One can also take advantage of *in situ* electrochemical regeneration of the triarylamine radical cation for which only catalytic amounts of the neutral triarylamine are necessary.

Scheme 6

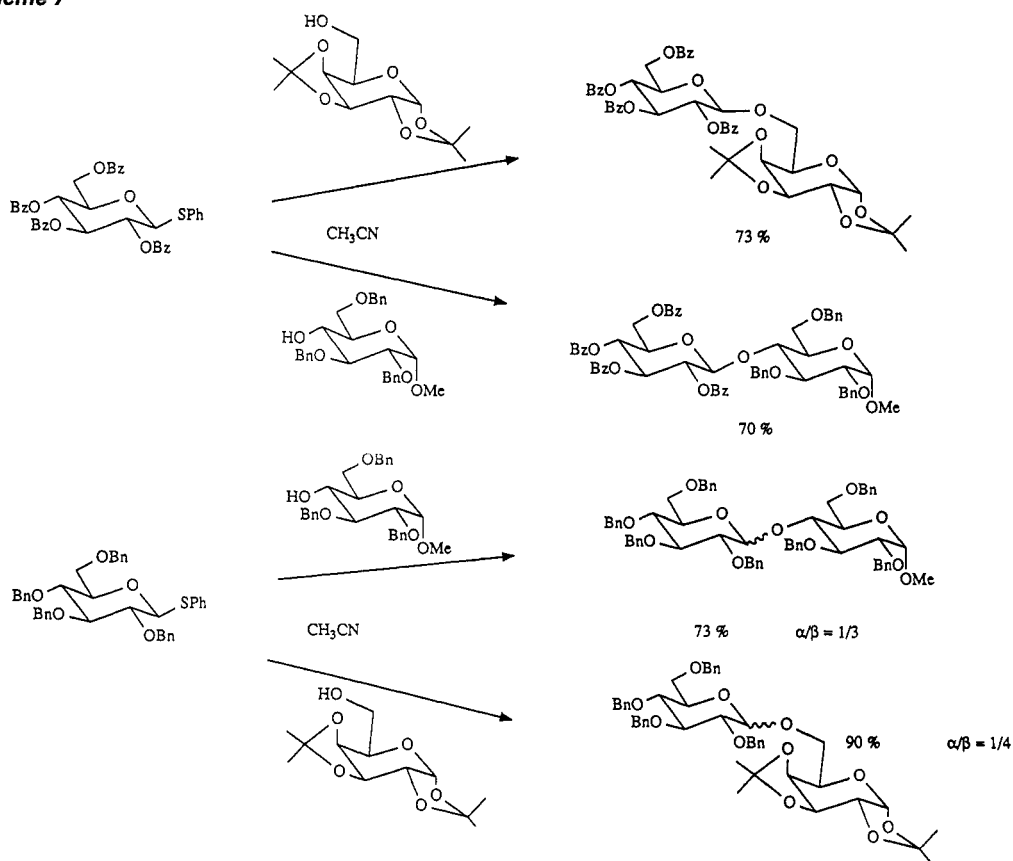


The yields are in the 70-90% range. By comparison to a previous report (ref. 27) based on the use of aryl *O*-glycosides, the present electrochemical glycosylation has the advantage of requiring easily available starting materials and lower oxidation potentials. The latter fact makes this procedure particularly attractive with respect to compatibility with various protecting groups.

There is a significant difference between the TBPA^{•+} mediation and the electrochemical oxidation. In the TBPA^{•+} mediated process, there is probably initial formation of a complex or an adduct with the thioglycoside so that an inner-sphere mechanism is postulated. In the alternative electrochemical process, one electron is abstracted from the sulfur atom by an outer-sphere mechanism.

We believe that such mild mechanisms of activation are particularly suitable for a unique modulation of the reactivity of thioglycosides, a feature which is of critical importance for the development of block synthesis of complex oligosaccharides.

Scheme 7

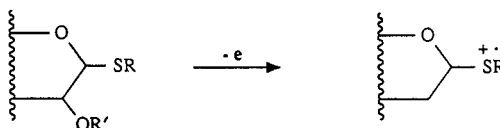


II. THE USE OF ANOMERIC S-XANTHATES OF 2-AZIDO-2-DEOXY-D-GALACTOPYRANOSYL DERIVATIVES AS EFFICIENT GLYCOSYL DONORS

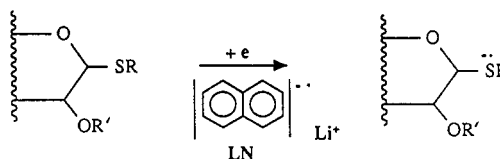
In the first part of this lecture, we used the property of sulfur, compared with oxygen, to undergo a one-electron oxidation resulting in a reactive sulfur-centered radical cation. Sulfur may also undergo a one-electron reduction with lithium naphthalenide (LN) (Scheme 8).

Scheme 8

OXIDATION

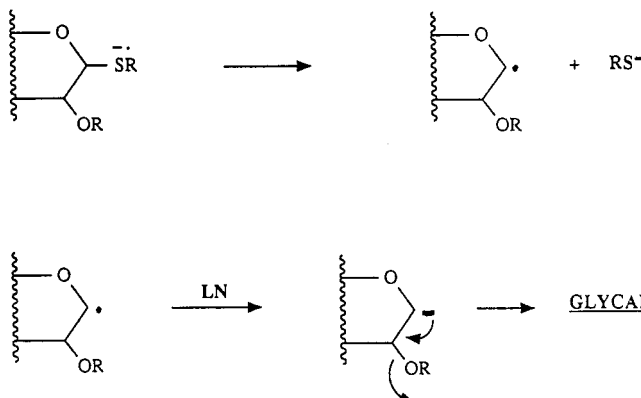


REDUCTION



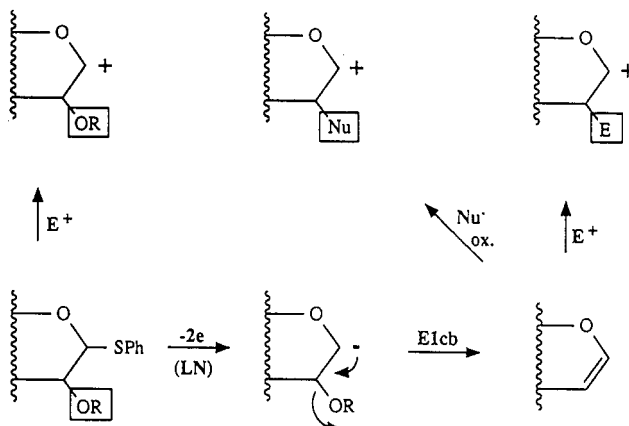
The generated radical anion is cleaved to an anomeric radical which is again reduced with LN to give an unstable C-1 anion.

Scheme 9



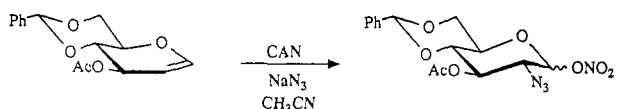
This is followed by fast elimination of the 2-*O*-substituted group. This novel approach allows an easy preparation of a variety of pyranoid glycal derivatives from phenyl thioglycosides (ref. 28). A glycal may now react with either an electrophile E^+ (typically I^+ or $PhSe^+$) or a nucleophile in the presence of a one-electron oxidant (azidonitration reaction) (ref. 29) to give new glycosylating species.

Scheme 10



This demonstrates clearly the versatility of the anomeric carbon-sulfur bond (Scheme 10). With a variety of glycols on hand, we studied their azidonitration and found that the reaction was highly stereoselective in the case of rigid glucals and galactals (Scheme 11).

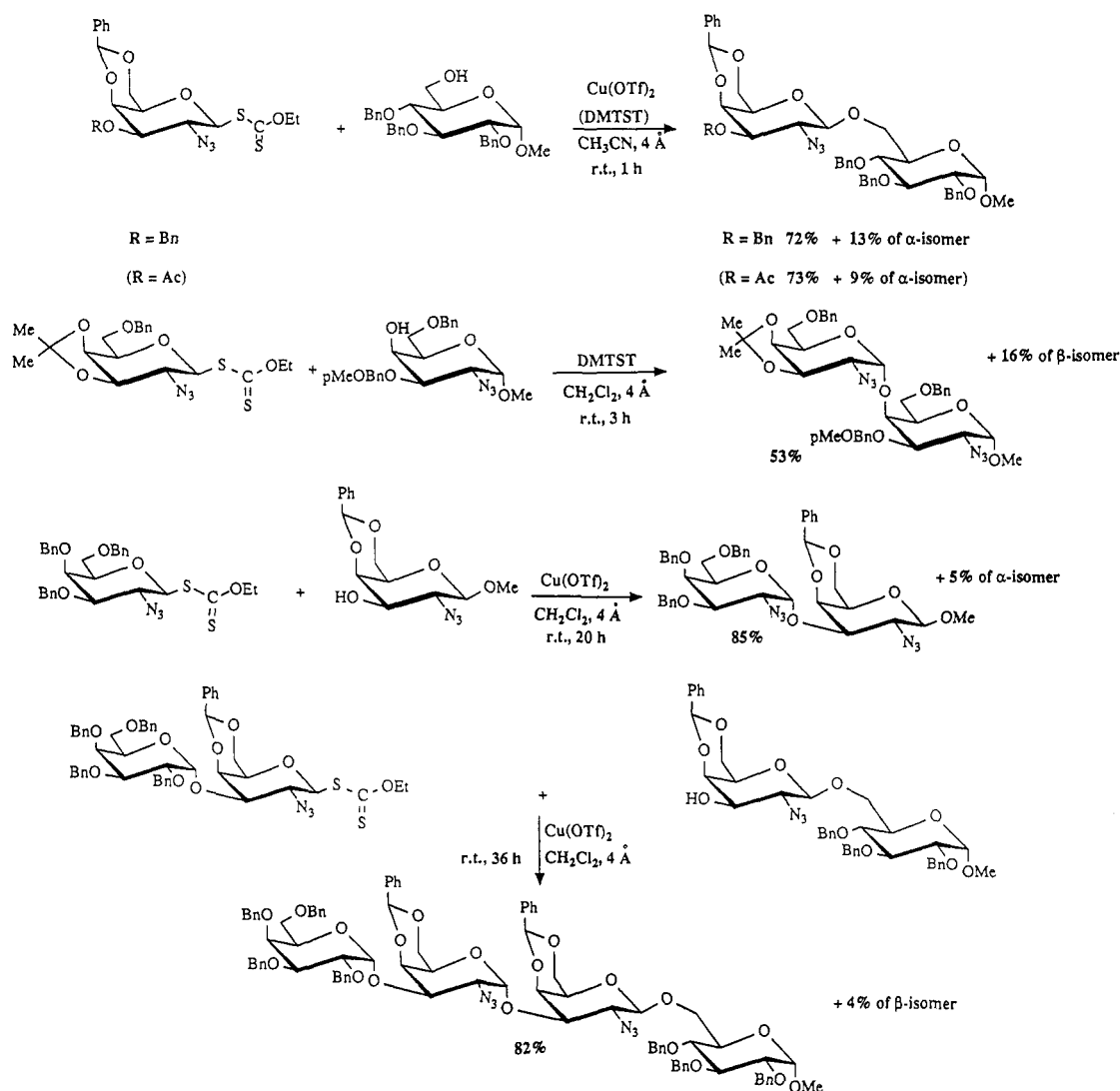
Scheme 11



GLUCO : MANNO RATIO OF 19 : 1!

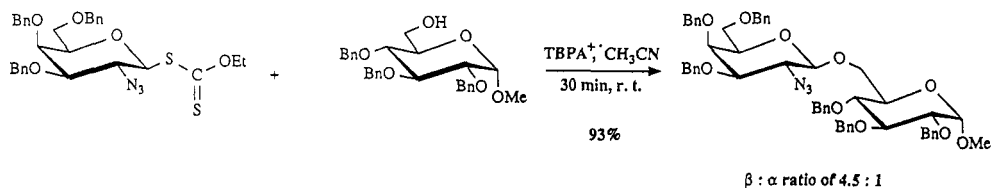
We noticed that direct displacement of an anomeric nitrate with a thiolate ion resulted in denitration so that the thioglycoside derivatives of 2-azido-2-deoxy-D-galactopyranose have to be prepared indirectly by a more circuitous route (ref. 30, 31). However, we found that direct displacement (ref. 32) with commercially available *O*-ethyl *S*-potassium dithiocarbonate in acetonitrile proceeded in almost quantitative yields. We discovered next that anomeric *S*-xanthates are efficient glycosyl donors, a fact which is apparent from the selected examples presented in Scheme 12 (ref. 32). Good yields were obtained using either DMTST or copper(II) triflate as promoters and operating at room temperature. The reaction time was about 2 h, except in the case of the combination dichloromethane/Cu(OTf)₂ (~24 h).

Scheme 12



We also found that TBPA⁺ nicely activated the anomeric *S*-xanthate (Scheme 13) in acetonitrile.

Scheme 13



We believe that the previously described strategy is going to be very useful for the practical stereoselective synthesis of biologically important galactosamine-containing oligosaccharides. It benefits from a combination of sequential advantages: *i*) the convenient and high-yielding synthesis of variously protected pyranoid glycols from phenyl *S*-glycosides, *ii*) the highly selective azidonitration of conformationally rigid glycols, *iii*) the efficient S_N2 displacement of anomeric nitrates by *O*-ethyl *S*-potassium dithiocarbonate, *iv*) the properties of anomeric *S*-xanthates to be activated by a variety of procedures.

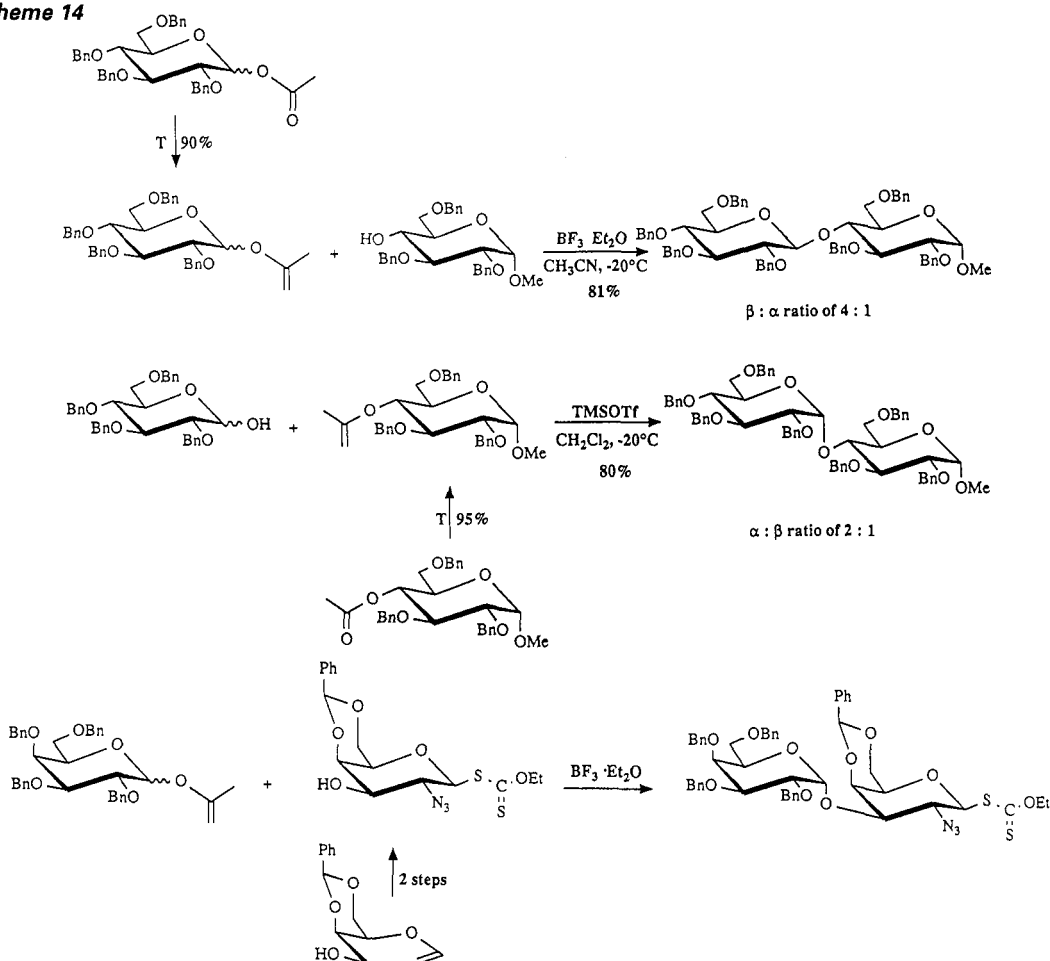
III. SYNTHESIS AND USE OF CARBOHYDRATE ENOL-ETHERS AND RELATED DERIVATIVES IN THE FIELD OF GLYCOSYLATION

The preceding part of this lecture dealt with the glycosylating properties of the anomeric carbon-sulfur bond. We would now like to introduce various novel and conceptually different strategies.

III.1 Anomeric enol-ethers: a novel class of glycosyl donors

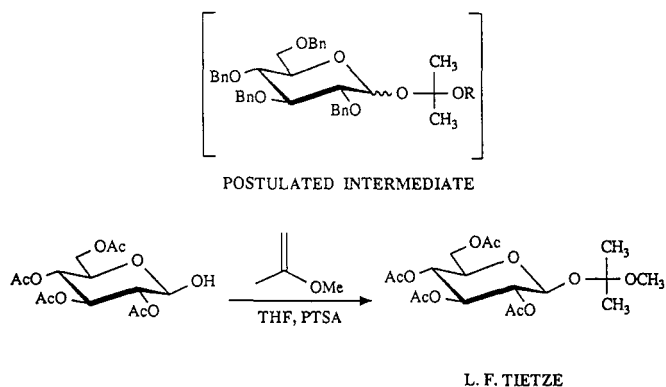
Treatment of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with a freshly prepared (ref. 33) solution of Tebbe's reagent (ref. 34) in toluene gave an entry to anomeric enol ethers (ref. 35) which proved to be efficient glycosyl donors under the mediation of various electrophiles.

Scheme 14



In an alternative strategy, a "disarmed" acceptor was "armed" by a two-step sequence (acetylation, Tebbe methylation) so that glycosylation with tetra-*O*-benzylglucose was possible (Scheme 14). The common postulated intermediate to these two novel glycosylation reactions (Scheme 15) is similar to a recently prepared acetal glycoside (ref. 36).

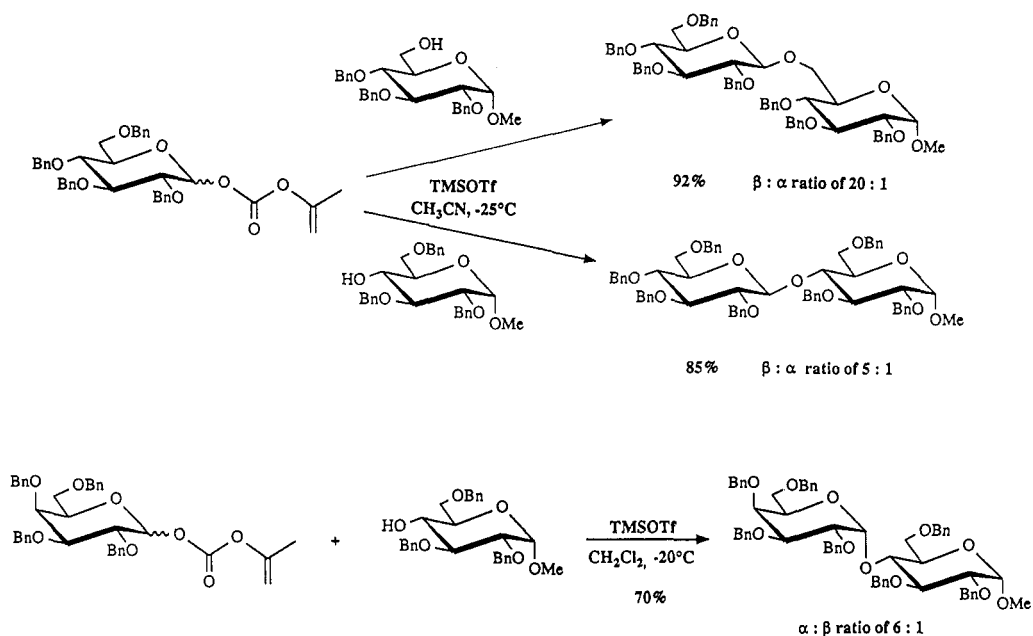
Scheme 15



III.2 Isopropenyl glycosyl carbonates: another class of efficient glycosyl donors

Isopropenyloxycarbonylchloride is a commercial reagent. We anticipated that straightforward reaction with hemiacetals would provide an anomeric carbonate having a reactivity comparable to that of the corresponding enol-ethers and much higher than that of regular anomeric carbonates (ref. 37). This was the case leading to a novel glycosylation reaction (Scheme 16).

Scheme 16

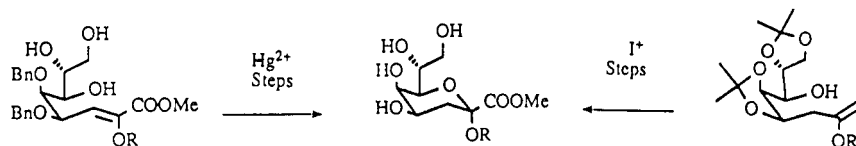


This scheme illustrates, once again, some features of the glycosylation reaction with glycosyl donors having a non-participating group on C-2. The use of anhydrous acetonitrile at low temperature gave a satisfactory $\beta : \alpha$ ratio which is consistently higher (20:1 or higher) with primary alcohols than with secondary alcohols (5:1 or higher). The best α -selectivity was observed in dichloromethane (or ether) with secondary alcohols and galactosyl donors.

IV. DEVELOPMENT OF "NON-ORTHODOX" STRATEGIES FOR THE SYNTHESIS OF KDO-CONTAINING DISACCHARIDES

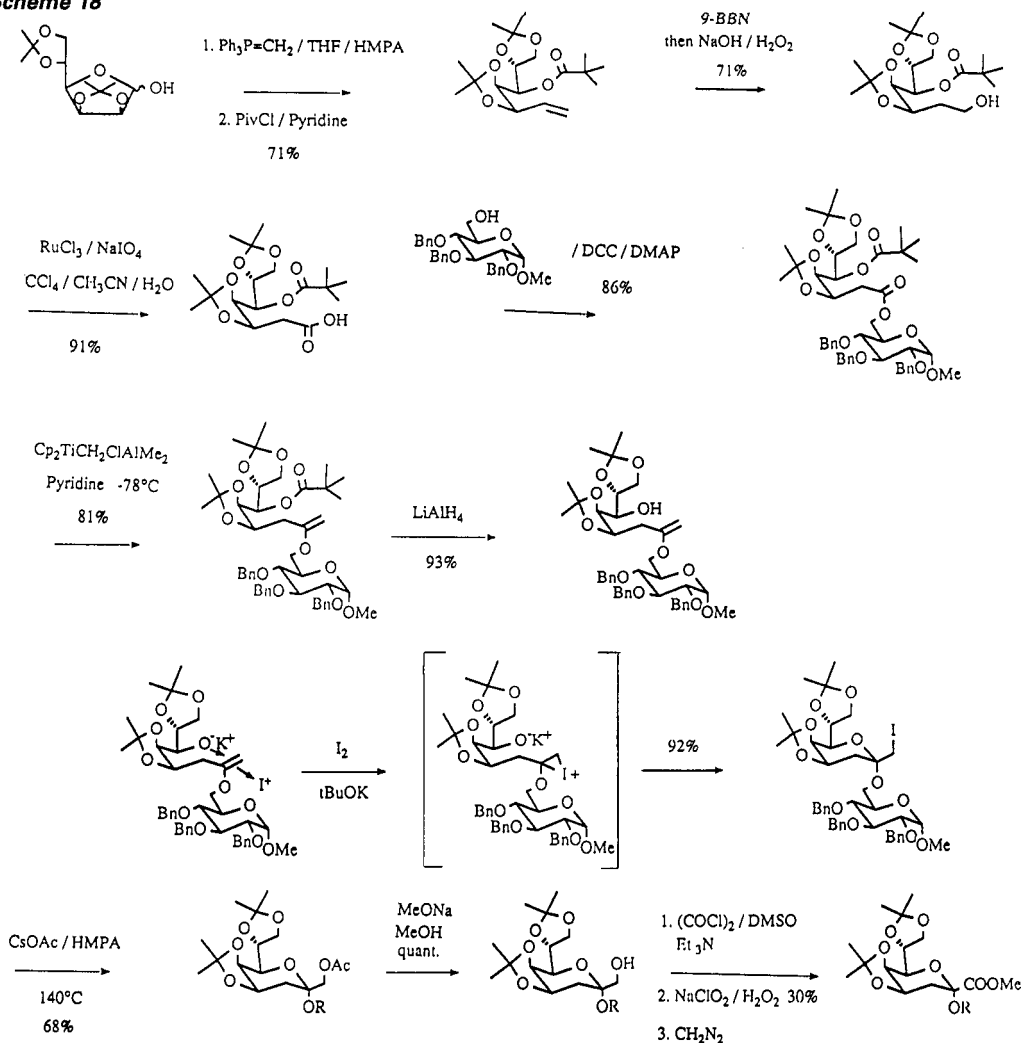
Some years ago we developed (ref. 38) a novel synthesis of KDO-containing disaccharides based on intramolecular oximercuriation-demercuration of an appropriate acyclic precursor. Another version of this reaction is now presented (Scheme 17) where the key step is a stereospecific intramolecular iodocyclization of a complex enol-ether (ref. 35, 39).

Scheme 17



This key enol-ether is formed by the reaction of Tebbe's reagent on the corresponding ester. The stereoselectivity of the cyclization may be rationalized in assuming a chair-like conformation for the transition state, where the OR group is pre-axial.

Scheme 18



The transformation of the CH_2I appendage into COOMe is achieved through a classical sequence.

Acknowledgement I am grateful to my co-workers A. Marra, J.-M. Mallet, A. Haudrechy, F. Gauffeny and A. Veyrières who developed the methodologies described here. The excellent technical assistance of J. Esnault is appreciated. The electrochemical glycosylation reaction was developed in collaboration with the group of Dr. C. Amatore (A. Jutand, G. Meyer). This research was supported by the Ecole Normale Supérieure and Centre National de la Recherche Scientifique (UA 1110).

REFERENCES

1. W. Koenigs and E. Knorr, *Ber.* 34, 957-962 (1901).
2. G. Wulff and G. Röhle, *Angew. Chem. Int. Ed. Engl.* 13, 157-216 (1974).
3. H. Paulsen, *Angew. Chem. Int. Ed. Engl.* 21, 155-224 (1982).
4. A.F. Bochkov and G.E. Zaikov, *Chemistry of the O-Glycosidic Bond: Formation and Cleavage* Pergamon Press, Oxford, 1979.
5. V.I. Betanelli, M.V. Ovchinnikov, L.V. Backinowsky and N.K. Kochetkov, *Carbohydr. Res.* 76, 252-256 (1979).
6. N.K. Kochetkov, *Tetrahedron* 43, 2389-2436 (1987).
7. R.U. Lemieux, K.B. Hendriks, R.V. Stick and K. James, *J. Am. Chem. Soc.* 77, 4056-4062 (1975).
8. R.U. Lemieux and H. Driguez, *J. Am. Chem. Soc.* 97, 4063-4069 (1975); *ibid* 97, 4069-4075; R.U. Lemieux, D.R. Bundle and D.A. Baker, *ibid.* 97, 4076-4083.
9. J.-M. Petit, J.-C. Jacquinet and P. Sinay, *Carbohydr. Res.* 82, 130-134 (1980).
10. P. Sinay, *Pure and Appl. Chem.* 50, 1437-1452 (1978).
11. R.R. Schmidt, *Angew. Chem. Int. Ed. Engl.* 25, 212-235 (1986).
12. P. Fügedi, P.J. Garegg, H. Lönn and T. Norberg, *Glycoconjugate J.* 4, 97-108 (1987).
13. K.C. Nicolaou, S.P. Seitz and D.P. Papahatjis, *J. Am. Chem. Soc.* 105, 2430-2434 (1983); H. Lönn, *Carbohydr. Res.* 139, 105-113 (1985); P. Fügedi and P.J. Garegg, *Carbohydr. Res.* 149, C9-C12 (1986); S. Sato, M. Mori, Y. Ito and T. Ogawa, *Carbohydr. Res.* 155, C6-C10 (1986); Y. Ito and T. Ogawa, *Tetrahedron Lett.* 4701-4704 (1987); H. Lönn, *Glycoconjugate J.* 4, 117-118 (1987); F. Dasgupta and P.J. Garegg, *Carbohydr. Res.* 177, C13-C17 (1988); Y. Ito and T. Ogawa, *Tetrahedron Lett.* 1061-1064 (1988); G.H. Veeneman and J.H. van Boom, *Tetrahedron Lett.* 275-278 (1990); G.H. Veeneman, S.H. van Leeuwen and J.H. van Boom, *Tetrahedron Lett.* 1331-1334 (1990); F. Dasgupta and P.J. Garegg, *Carbohydr. Res.* 202, 225-238 (1990); Y. Ito, T. Ogawa, M. Numata and M. Sugimoto, *Carbohydr. Res.* 202, 165-175 (1990); P. Konradsson, U.E. Udodong and B. Fraser-Reid, *Tetrahedron Lett.* 4313-4316 (1990).
14. V. Pozsgay and H. Jennings, *J. Org. Chem.* 52, 4635-4637 (1987).
15. W.K. Musker, T.L. Wolford and P. B. Roush, *J. Am. Chem. Soc.* 100, 6416-6421 (1978).
16. D. Kahne, S. Walker, Y. Cheng and D. Van Engen, *J. Am. Chem. Soc.* 111, 6881-6882 (1989).
17. D.S. Brown, S.V. Ley and S. Vile, *Tetrahedron Lett.* 4873-4876 (1988).
18. R.J. Ferrier, R.W. Hay and N. Vethaviasar, *Carbohydr. Res.* 27, 55-61 (1973); J.W. Van Cleve, *Carbohydr. Res.* 70, 161-164 (1979); T. Mukaiyama, T. Nakatsuka and S. Shoda, *Chem. Lett.* 487-490 (1979); S. Hanessian, C. Bacquet and N. Lehong, *Carbohydr. Res.* 80, C17-C22 (1980); P.J. Garegg, C. Henrichson and T. Norberg, *Carbohydr. Res.* 116, 162-165 (1983).
19. W.K. Musker and T.L. Wolford, *J. Am. Chem. Soc.* 98, 3055-3056 (1976).
20. M. Platen and E. Steckhan, *Chem. Ber.* 117, 1679-1694 (1984).
21. W. Schmidt and E. Steckhan, *Chem. Ber.* 113, 577-585 (1980).
22. A.J. Ratcliffe and B. Fraser-Reid, *J. Chem. Soc. Perkin Trans 1* 747-750 (1990).
23. J.-R. Pougny and P. Sinay, *Tetrahedron Lett.* 4073-4076 (1976).
24. S. Hashimoto, T. Honda and S. Ikegami, *J. Chem. Soc., Chem. Commun.* 685-687 (1989).
25. K. Uneyama and S. Torii, *Tetrahedron Lett.* 329-332 (1971).
26. C. Amatore, A. Jutand, J.-M. Mallet, G. Meyer and P. Sinay, *J. Chem. Soc., Chem. Commun.* 718-719 (1990).
27. R. Noyori and I. Kurimoto, *J. Org. Chem.* 51, 4320-4322 (1986).
28. A. Fernandez-Mayoralas, A. Marra, M. Trumtel, A. Veyrières and P. Sinay, *Carbohydr. Res.* 188, 81-95 (1989).
29. R.U. Lemieux and R.M. Ratcliffe, *Can. J. Chem.* 57, 1244-1251 (1979).
30. H. Paulsen, W. Rauwald and U. Weichert, *Justus Liebigs Ann. Chem.* 75-86 (1988).
31. M. Haraldsson, H. Lönn and T. Norberg, *Glycoconjugate J.* 4, 225-229 (1987).
32. A. Marra, L.K. Shi Shun, F. Gauffeny and P. Sinay, *Synlett*, 445-448 (1990).
33. T.S. Chou, S.-B. Huang and W.-H. Hsu, *J. Chinese Chem. Soc.* 30, 277-279 (1983).
34. F.N. Tebbe, G.W. Parshall and G.S. Reddy, *J. Am. Chem. Soc.* 100, 3611-3613 (1978).
35. A.G.M. Barrett, B.C.B. Bezuidenhout, A.F. Gasielki, A.R. Howell and M.A. Russell, *J. Am. Chem. Soc.* 111, 1392-1396 (1989).
36. L.F. Tietze and M. Löggers, *Justus Liebigs Ann. Chem.* 261-265 (1990).
37. M. Boursier and G. Descotes, *C. R. Acad. Sci., Ser. II* 308, 919-921 (1989).
38. F. Paquet and P. Sinay, *J. Am. Chem. Soc.* 106, 8313-8315 (1984).
39. A. Haudrechy and P. Sinay, *5th European Symp. on Carbohydr. (Eurocarb V) A-141*, Prague, August, 1989.