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The Chemistry of Natural Products

Second edition

Edited by

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Preface

The first edition of this book appeared in 1984 and covered the literature until the end of 1982 (one chapter dealt with much of 1983). The present volume is based on the literature published since then until approximately mid-1992. As before, it attempts to highlight the most important advances in all the main areas of natural products research, focusing on structure, chemistry, synthesis, and this time, where appropriate, biosynthesis. Each chapter is necessarily selective but the scope is extended by frequent citation of recent reviews.

R.H.T.

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1 Carbohydrates

K.J. HALE and A.C. RICHARDSON

1.1 Introduction

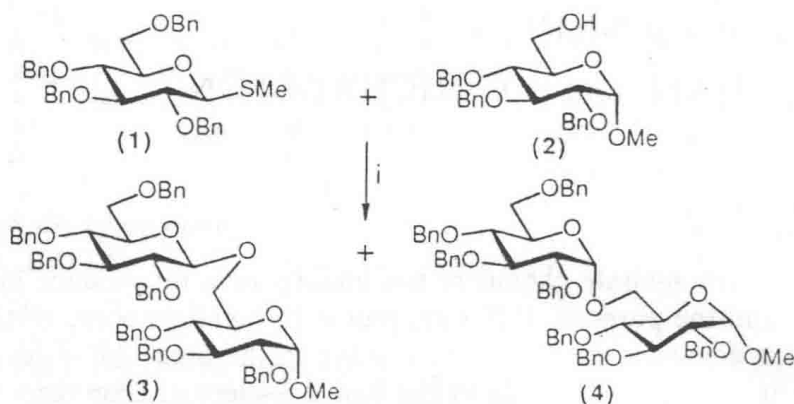
Synthetic carbohydrate chemistry has undergone a renaissance in the last decade, and the purpose of this chapter is to highlight some of the more significant advances that have taken place in the area. All aspects of the subject are reviewed annually in the Royal Society of Chemistry publication *Specialist Periodical Reports: Carbohydrate Chemistry*.

1.2 Recent developments in *O*-glycosidation methodology

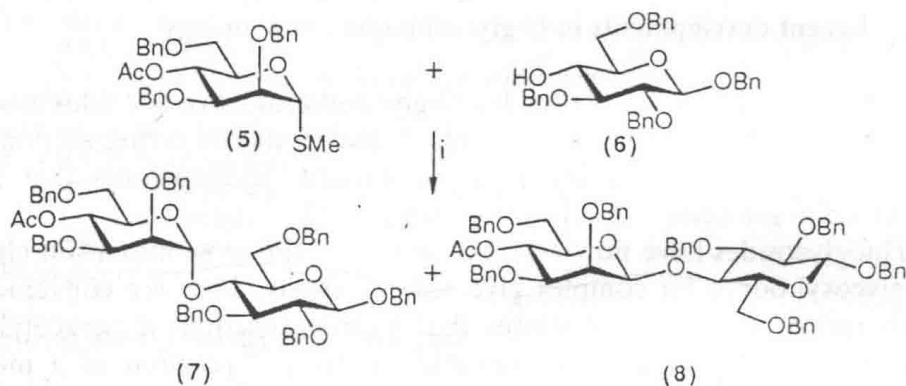
The historical methods¹⁻¹² used for *O*-glycosidation have been discussed in some detail in a series of monographs,¹³ and in the following sections we will emphasise some of the more significant developments that have occurred in glycosidation technology since 1982.

Thioglycosides have now emerged as one of the most important classes of glycosyl donor for complex glycoside synthesis. They are conveniently prepared by a number of routes that include reaction of peracetylated sugars with a thiol and a Lewis acid catalyst;¹⁴ reaction of a methyl glycoside with a thioalkylsilane and a Lewis acid;¹⁵⁻¹⁶ treatment of a suitably protected sugar hemiacetal with a phosphine and an alkyl disulphide,¹⁷ or by Mitsunobu reaction of a lactol with a thiol nucleophile.¹⁷ The main advantage of thioglycosides as glycosyl donors lies in their ability to withstand a wide variety of chemical transformations, and subsequently to undergo glycosylation with an acceptor alcohol, after having been converted into a reactive sulphonium intermediate by complexation with a soft thiophilic reagent. A wide variety of thiophilic electrophiles and metal ions are available for this purpose, all of which operate under mild conditions that do not disrupt acid- and base-sensitive functionality that may be present in the reactants. By judicious choice of reagent, reaction solvent, and substituent at C(2), thioglycoside donors can be conveniently converted into either 1,2-*cis*- or 1,2-*trans*-glycosides with fair to good levels of stereocontrol.

A powerful activator of thiomethylglycosides is the combination of benzeneselenenyl triflate and 4Å molecular sieves in dry toluene. It permits rapid glycosidation even at -40°C,¹⁸ and leads to almost exclusive formation of 1,2-*trans*-glycosides when an acyl or amido group is located at C(2)



Scheme 1 *i*, PhSeOTf, PhMe, -40°C , 0.5 h (91%, $\beta/\alpha = 88:12$).



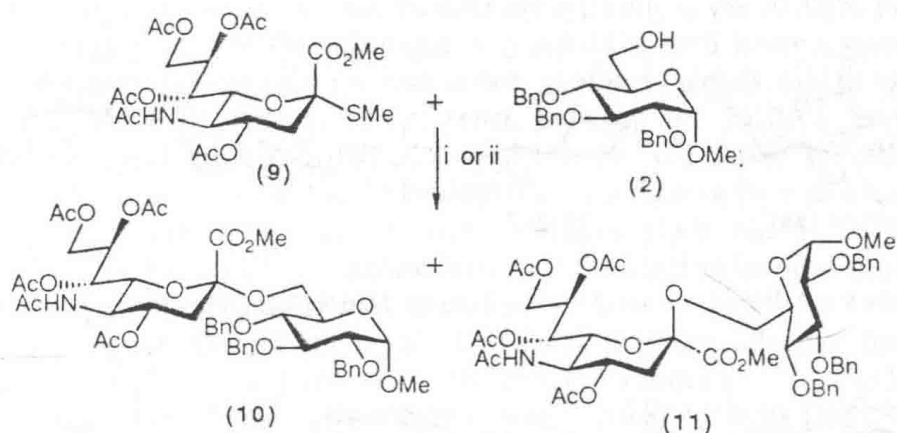
Scheme 2 *i*, PhSeOTf, PhMe, -40°C , 0.5 h (99%, $\alpha/\beta = 84:16$).

of the donor. In the case of thioglucoside (1) and thiomannoside (5), with non-participatory groups at C(2), the 1,2-*trans* products are again predominant (Schemes 1 and 2).

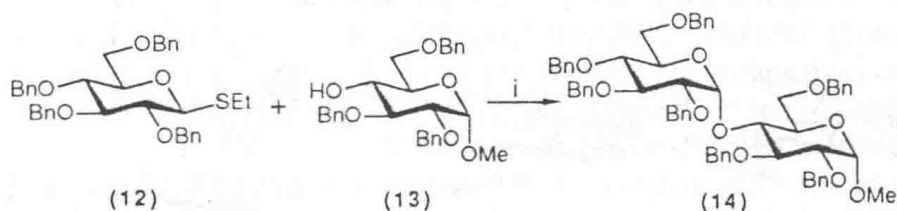
Benzeneselenenyl triflate is an especially valuable promoter for the preparation of synthetically challenging sialic acid oligosaccharides from thiomethylglycosides. In the system shown in Scheme 3, either the α - or β -linked isomers could be obtained as major products depending on whether 1,2-dichloroethane or acetonitrile was used as reaction solvent.¹⁸

Other good thioglycoside activators, for the formation of 1,2-*trans* glycosidic bonds to donors with participatory groups at C(2), are *N*-bromosuccinimide,¹⁶ methyl triflate,¹⁹ and dimethyl(methylthio)sulphonium triflate (DMTST).²⁰

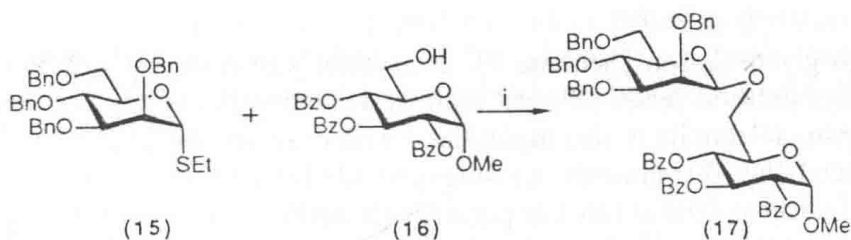
The synthesis of 1,2-*cis*-glycosides from 1-thioalkylglycoside donors is usually less successful and is best accomplished when there is a non-participatory group at C(2) of the donor, and when methyl sulphenyl bromide is employed as the promoter.²¹ However, even this regimen gives only modest 1,2-*cis* selectivity with 1-thioalkylglucosides (Scheme 4) and 1-thioalkylmannosides (Scheme 5).



Scheme 3 i, PhSeOTf , $(\text{ClCH}_2)_2$, -23°C , 0.5 h (63%, $\alpha/\beta = 16:84$); ii, PhSeOTf , MeCN , -35°C , 0.5 h (78%, $\alpha/\beta = 82:18$).



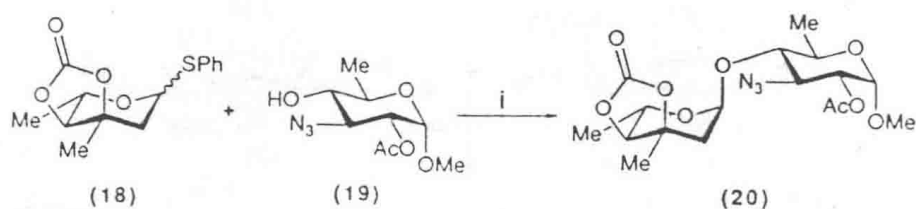
Scheme 4 i, MeSBr , CH_2Cl_2 , RT, 15 h (57%, $\alpha/\beta = 2.1:1$).



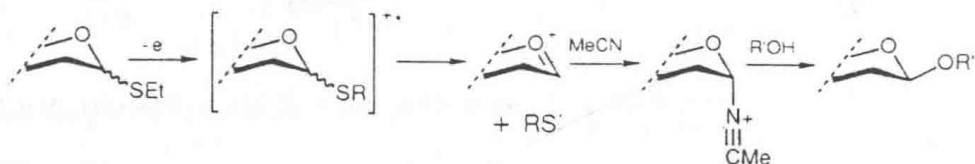
Scheme 5 i, MeSBr , CH_2Cl_2 , RT, 15 h (84%, $\beta/\alpha = 2.4:1$).

For many years the preparation of 2-deoxy-glycosides from 2-deoxy-glycosyl bromides was fraught with difficulties due to the extreme lability of this class of glycosyl donor. The added stability, ease of preparation, and excellent reactivity of 2-deoxy-thioalkylglycoside donors now makes these an ideal choice for the preparation of 2-deoxy- α -glucosides (Scheme 6).¹⁶

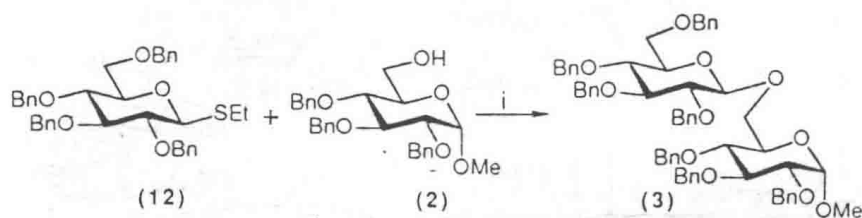
Sinay has reported a novel method for activating thioalkylglycosides that involves treatment with a one-electron transfer reagent such as tris(4-bromophenyl)ammonium hexachloroantimonate (TBPA^+).¹³ This generates a thioglycosyl radical cation which breaks down into a thiyl radical (which dimerises to a disulphide) and a stabilised glycosyl cation which can



Scheme 6 *i*, *N*-Bromosuccinimide, 4Å mol. sieves, MeCN (72%, $\alpha/\beta = 9:1$).



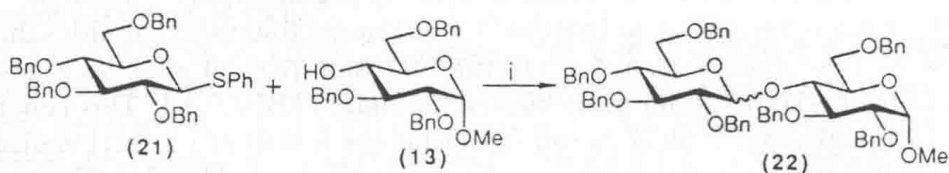
Scheme 7



Scheme 8 *i*, $(p\text{-BrC}_6\text{H}_4)_3\text{N}^+\text{SbCl}_6^-$, MeCN, -25°C , 4.5 h (80%, $\beta/\alpha = 20:1$).

undergo glycosylation (Scheme 7). If a participatory group is located at C(2), this method leads to formation of 1,2-*trans*-glycosides exclusively. Good *trans* selectivity is also maintained with ethyl or phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio- β -D-glucopyranosides provided the glycosylations are conducted in acetonitrile at low temperature (Scheme 8). The β selectivity that tends to be observed in glycosylations that are performed in nitrile solvents has been ascribed to formation of an α -nitrilium intermediate as the reactive glycosylating agent (Scheme 7).^{22,53}

Sinay has also found that phenylthioglycosyl radical cations can be generated electrochemically in acetonitrile, by performing electrolyses at 50 mA in an undivided cell with lithium tetrafluoroborate as a supporting



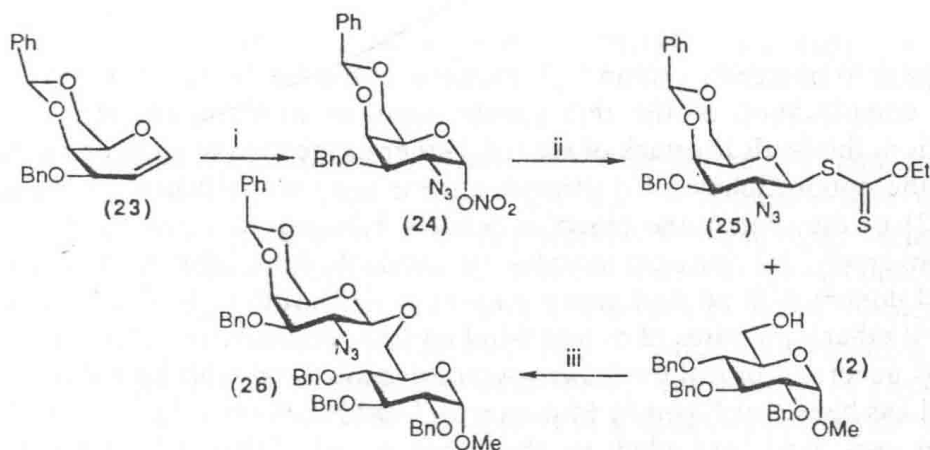
Scheme 9 *i*, Undivided electrolytic cell, LiBF₄, MeCN, 50 mA, RT, 15 h (73%, $\beta/\alpha = 3:1$).

electrolyte.²³ The yields of disaccharides are typically in the 70–90% range, and most importantly the technique is compatible with many commonly encountered protecting groups such as benzyl ethers, acetals, and benzoate esters (Scheme 9). The main difference between the TBPA⁺ and the electrochemical mediated oxidation processes is the mode of electron transfer from sulphur. In the TBPA⁺ process an inner-sphere mechanism is postulated whereby electron transfer takes place via a TBPA⁺–thioglycoside coordinated complex, while for the electrochemical protocol an outer-sphere mechanism may operate.

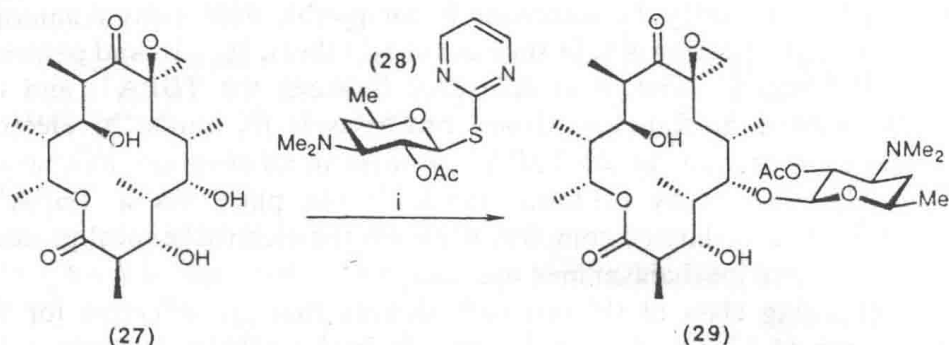
A promising class of thioglycoside donors that are effective for the preparation of 2-aminoglycosides is thioglycosyl xanthates (Scheme 10).²⁴ These undergo efficient glycosidation after activation with DMTST or copper (II) triflate, giving mainly 1,2-*cis*-pyranosides in dichloromethane, and 1,2-*trans*-pyranosides in acetonitrile.

Another series of thioglycoside donors that were originally introduced by Hanessian,²⁵ and later exploited by Woodward's coworkers in the erythromycin synthesis,¹⁷ are thiopyridyl and thiopyrimidinyl glycosides. These aglycones are transformed into reactive leaving groups by coordination with either mercury (II) salts,²⁵ silver triflate¹⁷ or methyl iodide.²⁶ These are then displaced by alcohols to form glycosides. The methodology is of particular value for the preparation of sensitive macrocyclic glycosides, as illustrated by an example in a recent route to oleandomycin developed by Tatsuta and coworkers (Scheme 11).²⁷

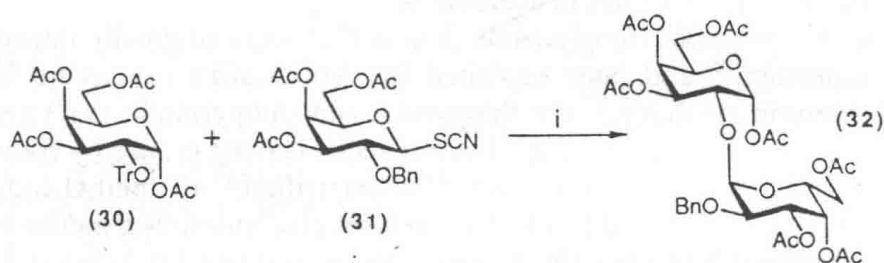
Kochetkov has reported an efficient, stereospecific, 1,2-*cis*-pyranoside synthesis that employs 1,2-*trans*-glycosyl thiocyanates as glycosyl donors and tritylated sugar derivatives as the glycosyl acceptors, with trityl perchlorate as the glycosidation catalyst (Scheme 12).²⁸ These reactions



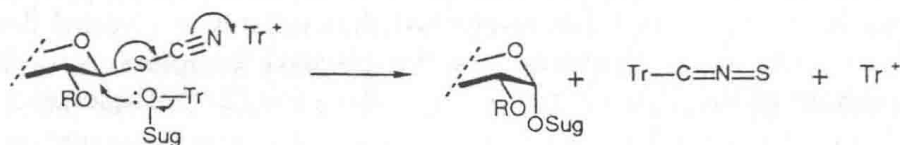
Scheme 10 i, NaN_3 , $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, MeCN, -20°C , 3 h (40%); ii, $\text{KS}(\text{CS})\text{OEt}$, EtOH, RT, 5 h (90%); iii, $\text{Cu}(\text{OTf})_2$, MeCN, RT (85%, $\beta/\alpha = 6:1$).



Scheme 11 i, AgOTf (6 equiv), (28) (5 equiv), 4Å mol. sieves, PhMe-CH₂Cl₂ (42%).



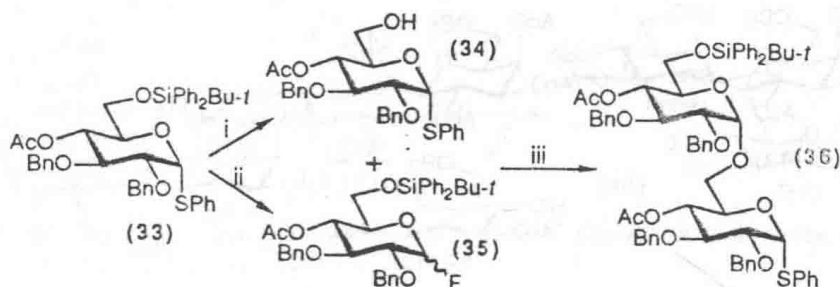
Scheme 12 i, Ph₃C⁺ClO₄⁻ (0.1 equiv), CH₂Cl₂, RT (59%).



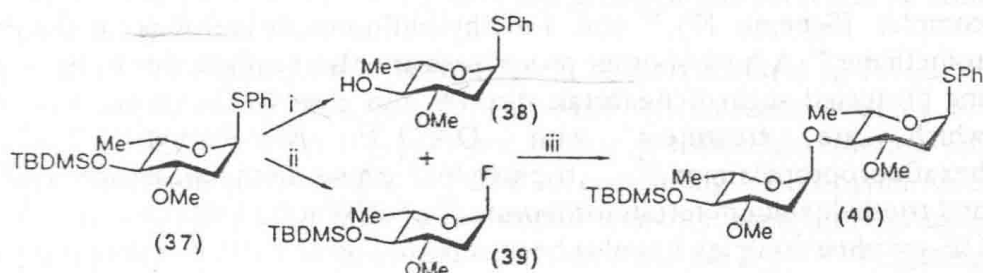
Scheme 13

appear to proceed by clean S_N2 inversion at the anomeric centre, initiated by complexation of the thiocyanate nitrogen with the triphenylmethyl cation; this leads to attack of the trityl ether oxygen at the anomeric carbon of the donor (Scheme 13). Provided there is a non-participatory group at C(2) of the donor, the reaction delivers 1,2-*cis*-pyranosides exclusively. Conversely, 1,2-*trans*-pyranosides are available from primary trityl ethers and donors with an acyl group present at C(2), although with secondary trityl ethers, mixtures of α- and β-linked disaccharides are obtained.

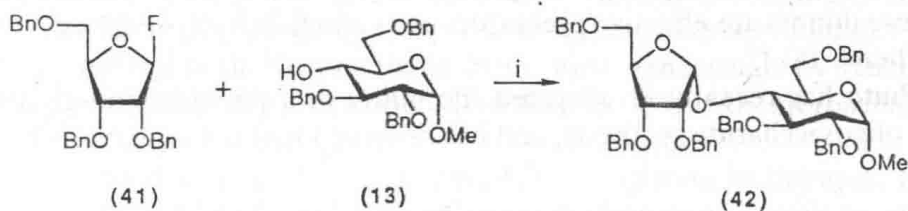
A general protocol for 1,2-*cis*-pyranoside synthesis with high stereocontrol has been developed by Mukaiyama²⁹ and Nicolaou^{30,31} (Scheme 14),³¹ that was later extended to the synthesis of 2-deoxyoligosaccharides (Scheme 15).³¹ It utilises 1-fluorosugars as glycosyl donors in the presence of an alcohol acceptor, tin (II) chloride, silver perchlorate, and 4Å molecular sieves. Other promoters used are tin (II) chloride–silver tri-



Scheme 14 i, $n\text{-Bu}_4\text{NF}$, THF, 0 to 25°C (98%); ii, Et_2NSF_3 , N -bromosuccinimide, CH_2Cl_2 , 0 to 25°C (90%, $\alpha/\beta = 1:1$); iii, SnCl_2 , AgClO_4 , Et_2O , 4Å mol. sieves, -15 to 25°C (80%, $\alpha/\beta = 15:1$).



Scheme 15 i, $n\text{-Bu}_4\text{NF}$, THF, 0 to 25°C (100%); ii, Et_2NSF_3 , NBS, CH_2Cl_2 , 0 to 25°C (80%); iii, SnCl_2 , AgClO_4 , Et_2O , 4Å mol. sieves, -15 to 25°C (65%).



Scheme 16 i, SnCl_2 , Ph_3CClO_4 , 4Å mol. sieves, Et_2O , -15°C (96%, $\alpha/\beta = 85:15$).

flate,³² silicon tetrafluoride,³³ boron trifluoride-etherate,³⁴ and triflic anhydride,³⁵ or for the relatively inaccessible 1,2-*cis*-ribofuranosides, trityl perchlorate, tin (II) chloride³⁶ and 4Å molecular sieves in ether (Scheme 16). For an excellent account of all the early chemistry of glycosyl fluorides the reader is referred to a review published by Micheel and Klemer in 1961,³⁷ and more recent discussions by Penglis,³⁸ Card³⁹ and Tsuchiya.⁴⁰

A large number of methods now exist for the preparation of glycosyl fluorides, one of which involves treatment of a thiophenylglycoside with N -bromosuccinimide and diethylaminosulphur trifluoride (DAST) (Schemes 14 and 15).³¹ Other reagents that convert thioalkylglycosides into glycosyl fluorides include N -bromosuccinimide and an HF-pyridine