

SOME ASPECTS OF REGIO-, STEREO-, AND CHEMOSELECTIVE REACTIONS IN CARBOHYDRATE CHEMISTRY

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Abstract- Selective transformations in carbohydrate chemistry will be illustrated with examples chosen from three distinct areas:

1. Phase transfer reactions are useful in obtaining partially substituted carbohydrate intermediates. The substitution patterns frequently are quite different to those obtained in homogeneous phase.
2. Various reagent systems have been developed for the conversion of hydroxy compounds to chlorodeoxy, bromodeoxy and deoxyiodo compounds as well as to olefinic derivatives. A number of partial substitutions have been achieved starting from unsubstituted hexopyranosides providing easy access to some compounds of biological significance.
3. Benzylidene acetals, phenyl substituted derivatives of these and also 2-propenylidene acetals may be reductively cleaved in the presence of proton or Lewis acids to give partially substituted derivatives useful as intermediates in various synthetic work. The regioselectivity may be manipulated by change in reagent or solvent.

INTRODUCTION

In the present lecture I shall give a survey of work that we have been carrying out during the last five years on some carbohydrate reactions that have useful regio-, stereo- and chemoselectivity. In general, simple models have been used, but a lot of this has since been extended into making more complicated molecules of biological significance. Examples will be given of this, as well as of some newer developments in the field. The survey will consist of three parts. The first of these will deal with phase transfer promoted reactions, the second with triphenylphosphine - imidazole mediated conversions of hydroxy compounds to deoxyhalogeno compounds, and the third topic is regioselectivity in the reductive opening of acetals to give partially protected ethers.

In the last few years there has been a rapidly expanding interest in the use of carbohydrates as starting materials for the synthesis of chiral natural products. In the pharmaceutical industry there has been a growing emphasis on the marketing of chiral and pharmacologically active products rather than of racemic mixtures in which often only one enantiomer has the desired activity. New methodology which contributes to the arsenal of available techniques for obtaining key intermediates is therefore of interest.

PARTIAL SUBSTITUTION BY PHASE TRANSFER

In monosubstitution of diols, using either a limited amount of reagent or limited reaction time, disubstituted as well as monosubstituted products are obtained. Indeed, if the relative reaction velocity of one or both the monosubstituted products is significantly higher than that of the starting material, the reaction mixture may contain mainly disubstituted product and starting material (1). In a base catalysed phase transfer process (2-4), (fig. 1), the substitution occurs in the organic phase. Provided that there is a significant difference in the distribution coefficients between the two phases for starting material on the one hand and monosubstituted products on the other, a reaction mixture rich in monosubstituted product may be obtained.

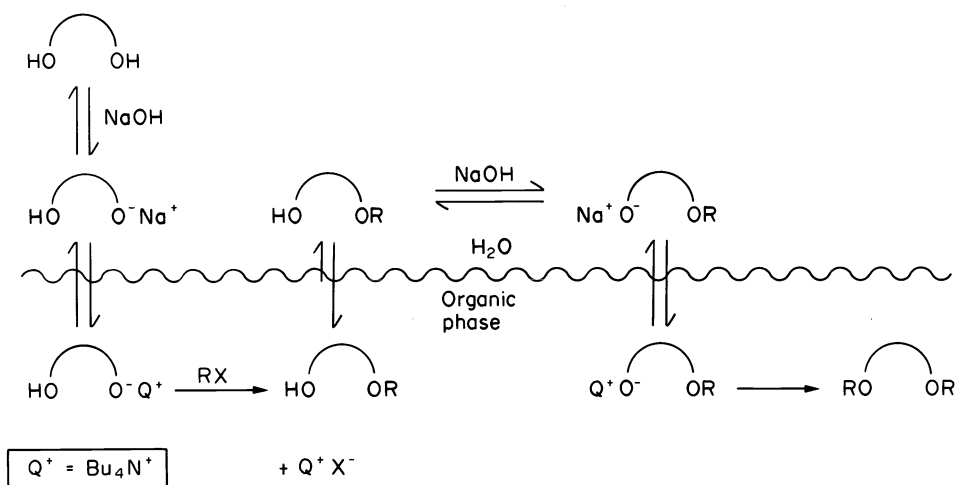


Fig. 1

A number of examples demonstrating this for partial benzylations (5) and tosylations (6) are shown in figs. 2 and 3.

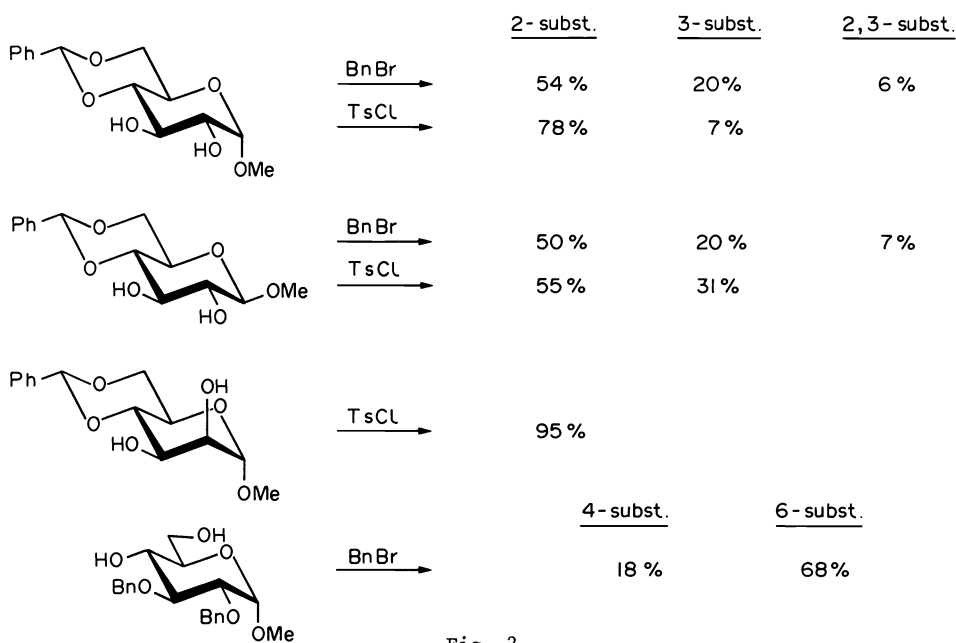


Fig. 2

In hexopyranosides, clear preferences are shown for 2-substitution (more acidic hydroxyl) and 6-substitution (primary hydroxyl).

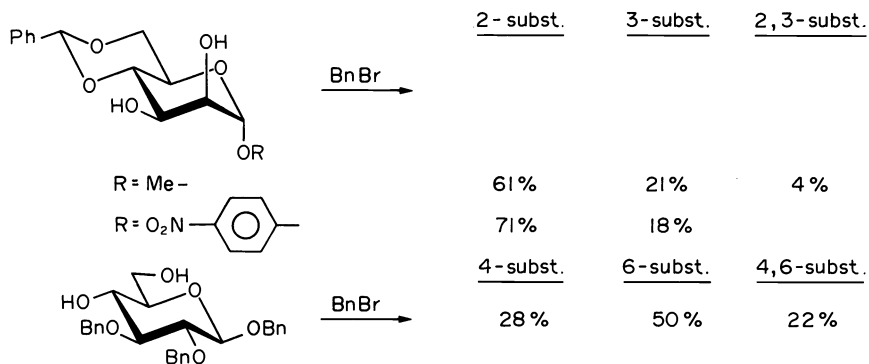
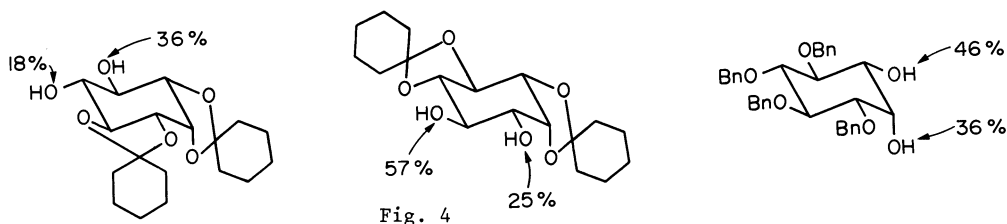


Fig. 3

Similar observations have subsequently been reported by other groups. Some examples from the inositol series, however, (fig. 4) indicate that the results not always are obviously predictable (7). In particular, the last example shows low preference for alkylation of an equatorial hydroxyl group over that of an axial one.



It would be useful if this technique could be extended into partial acylations. The total system is, however, strongly basic and the products are subject to deacylation as well as to acyl migration, rendering the whole system unpredictable and generally not very useful using liquid/liquid transfer processes. Box and coworkers (8), however, have reported that liquid/solid systems may be useful in this context. The results shown in fig. 5 bear this out. As with the alkylations and tosylations, substitution at the 2-position is preferred. This result is opposite to that obtained by partial benzoylation using a limited amount of benzoyl chloride in pyridine (9).

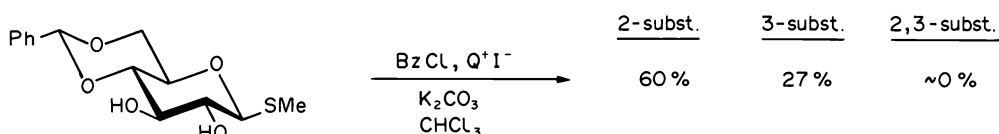
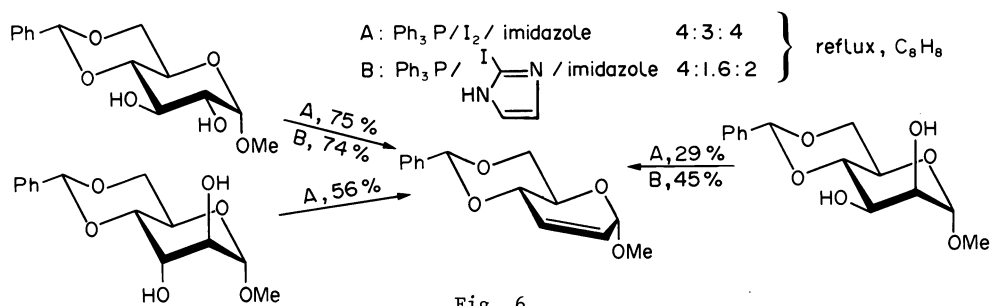


Fig. 5

OLEFINATIONS

The conversion of vicinal diols into olefins has attracted considerable attention. The reason for this is that this opens the way to a host of structural modifications. Some of these are: the synthesis of modified nucleosides and aminoglycoside antibiotics, of vicinal dideoxy sugars, and of structural manipulation via allylic substitution sequences to name but a few. The classical approach to this problem is the Tipson-Cohen procedure in which a vicinal ditosylate is heated with zinc dust and sodium iodide in dimethyl formamide (10). Other methods include the Corey-Winter procedure in which a cyclic thiocarbonate is refluxed with trialkyl phosphite (11). In a pyranose ring, this normally requires cis orientation of the original hydroxyl groups. So does the Hanessian procedure, in which a cis-diol is converted into a 1-dimethylamino(methylene) acetal in which the nitrogen atom then is quaternized by treatment with iodomethane and the product heated to give the olefin (12). The method that I am about to describe here has the advantage of consisting of one single reaction step. Also, since it works best for trans-1,2-diols it nicely complements the Corey-Winter and the Hanessian procedures. Two similar reagent systems have been developed. The first is triphenylphosphine/iodine/imidazole, named System A in the following illustrations. The second one is triphenylphosphine/triiodoimidazole/imidazole, named System B. The reaction is carried out in refluxing toluene and the reaction medium is biphasic. The early results obtained are summarised in figures 6 and 7 (13,14). Clearly, the best yields are obtained with trans hydroxyl groups. Also these reactions are useful for obtaining olefins in one step from the diols. The chemoselectivity of the procedure is illustrated by its compatibility with acetalic, benzylic and carboxylic ester groups.



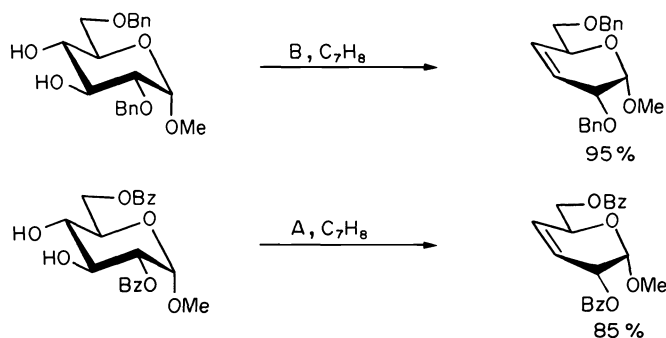


Fig. 7

Mechanistic studies have not been carried out, however, a plausible scheme which accounts for the products formed is shown in fig 8. This process bears an obvious relationship to the classical Arbuzov reaction. Therefore, using the same type of reagent, starting from a monoalcohol, it should be possible to make deoxyhalogeno derivatives of carbohydrates.

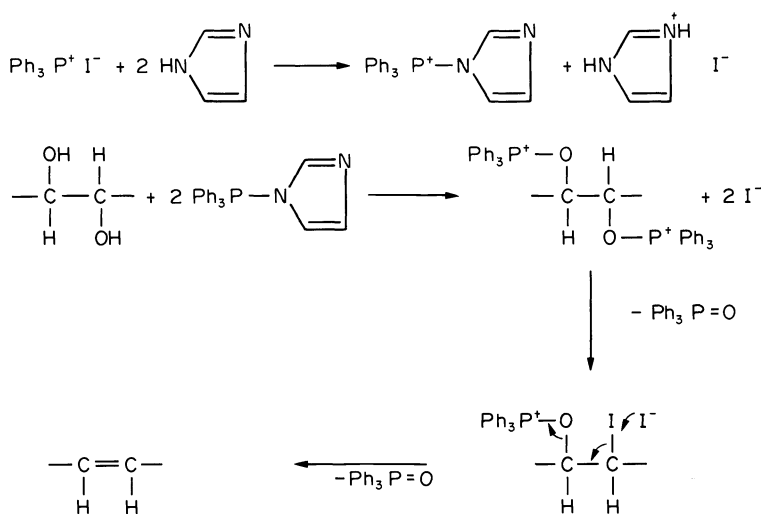


Fig. 8

IODINATIONS

Deoxyiodo sugars are of biological interest. One example of this is their use in X-ray urology. They are also useful intermediates in the synthesis of deoxysugars and in other contexts as synthetic intermediates. In the last few years considerable progress has been made in the synthesis of deoxyhalogeno sugars. Tetrahalomethanes together with triphenylphosphine has been shown to give substitution at C-6 in hexopyranosides (15-17). The synthesis of various chlorodeoxy sugars have been described by Jones, Szarek and co-workers (18). Various reagents have been developed based on triphenyl phosphite (19-22). Kunz and Schmidt (22) have treated betaines generated from the reaction of alcohols with triphenyl phosphine and diethyl azodicarboxylate (Mitsunobu reaction, 23) with iodomethane to obtain deoxyiodo compounds. The use of triflate as a leaving group together with halide as nucleophile has been described by Binkley and coworkers (24). Hanessian and coworkers have described the use of imidazolylsulfonates which upon treatment with the appropriate nucleophile yields azido and deoxyhalogeno sugars (25). These, together with the various systems described here (26-30) allow for a wide choice in synthetic chemistry. However, our triphenylphosphine/halogen/imidazole reagents have the added attraction of allowing for partial substitution in polyhydroxy systems, in addition to the capability of performing some particularly tricky substitutions at highly unreactive positions.

A plausible mechanistic rationale for the results obtained in halogenations is shown in fig 9.

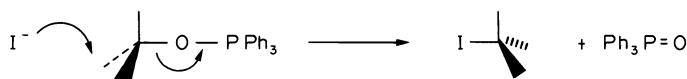


Fig. 9

This takes into account the fact that inversion is observed on secondary carbons. Figure 10 summarises results obtained in exchange of hydroxyl by iodine in monohydroxylic protected carbohydrate derivatives using the two reagent systems described above, differing in that A contains iodine and B instead contains triiodoimidazole. The reaction medium is toluene at reflux temperature. Nucleophilic substitution at the 2-position of hexopyranosides normally is difficult due to the proximity to the anomeric centre. Nevertheless, reasonable yields are obtained in the examples shown.

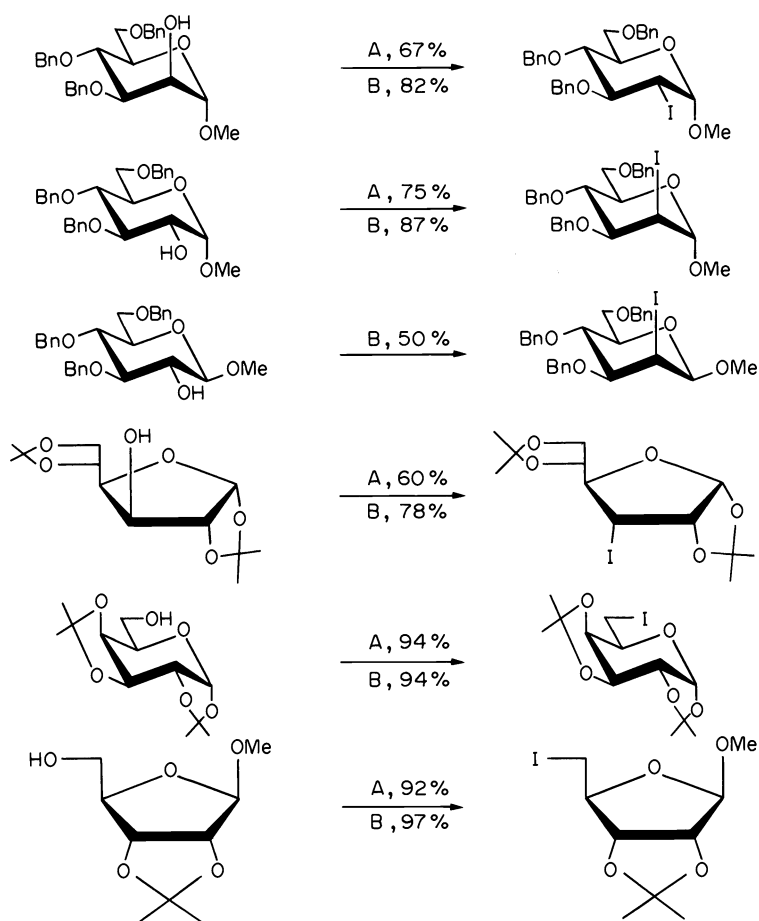


Fig. 10

These reactions were then extended to partial substitution in unprotected hexopyranosides (fig 11). In these more recent examples we have left the biphasic, refluxing toluene system and use a monophasic system which is superior for these particular reactions. The regioselectivity for 6-substitution is of course expected. In methyl α -D-glucopyranoside subsequent substitution occurs at C-4.

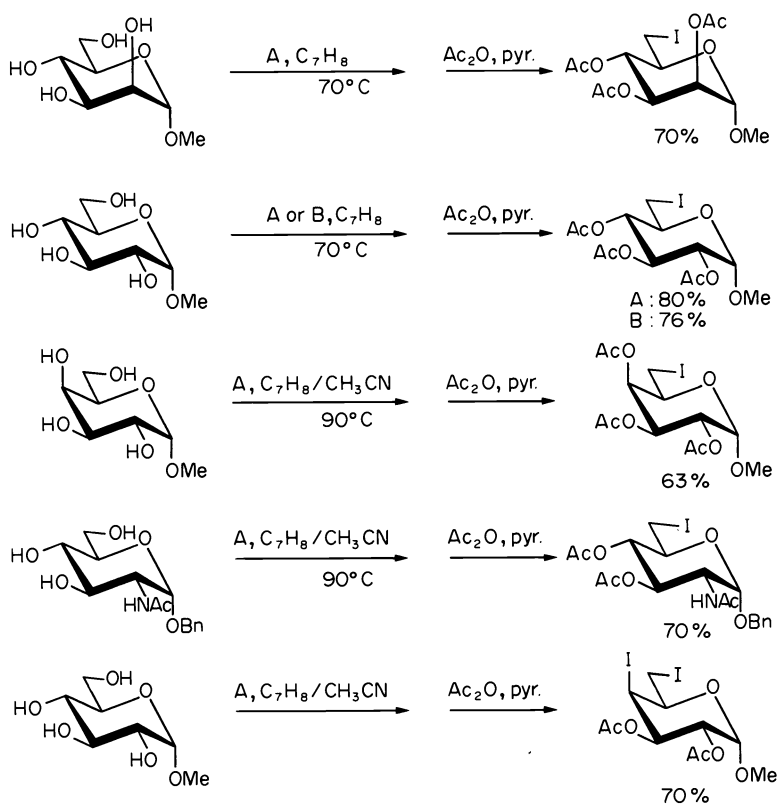


Fig. 11

We have extended these reactions into a particularly facile synthesis of an intermediate for the synthesis of purpurosamine, a constituent of the gentamicin C_{1a} aminoglycoside antibiotic as well as of the modified antibiotic 3',4'-dideoxykanamycin B (Dibekacin). In an initial attempt, benzyl 2-acetamido-2-deoxy- α -D-glucopyranoside was treated with triphenylphosphine/triiodoimidazole in toluene-acetonitrile to give the 3,4-olefinic 6-deoxyiodo product (fig. 12). This was converted into the azide as shown. Much better yields were obtained starting instead with the carbobenzoxy derivative of the aminoglycoside which upon treatment with reagent A in toluene-acetonitrile gave an 82% yield of the purpurosamine precursor (31).

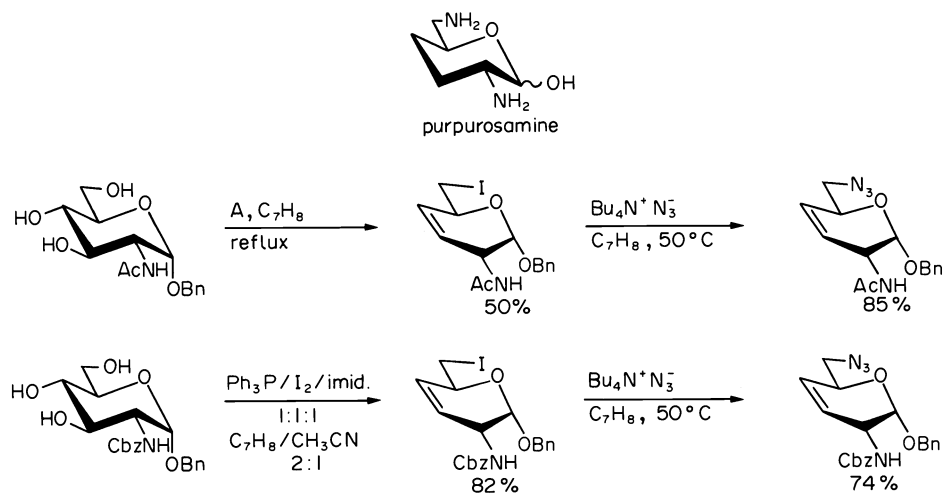


Fig. 12

Deoxyhalogeno sugars are useful intermediates for making deoxy sugars. Figure 13 shows a recent application. The 3-*O*- α -abequosyl- α -*D*-mannopyranosyl group contains the immunodominant fragment of the *Salmonella* serogroup B polysaccharide. In the context of studying relations between functionality, conformation and immunology in studies of binding between *Salmonella* oligosaccharides and antibodies, we needed the 6-deoxymannose analog of this disaccharide. In the synthesis shown we proceeded from an intermediate easily accessible from previous work. The 6-position in the mannosyl residue was preferentially iodinated in high yield to give the required 6-deoxy precursor (32).

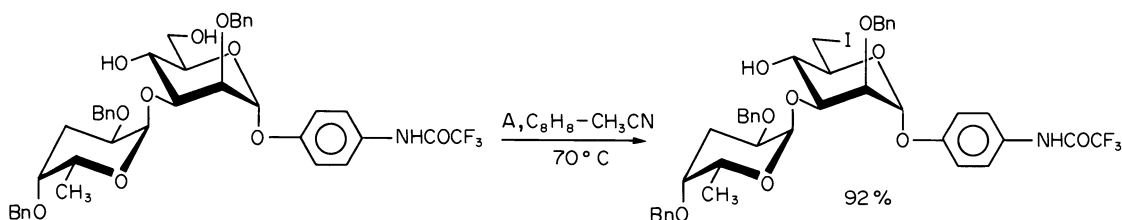


Fig. 13

BROMINATIONS

In order to extend the findings for conversion of hydroxy groups into deoxyiodo groups, we treated various hexopyranosides with triphenyl phosphine, tribromimidazole, and imidazole in toluene at reflux temperature (29). This is a biphasic system with regard to reagents, corresponding to system B earlier on. Results are outlined in fig. 14.

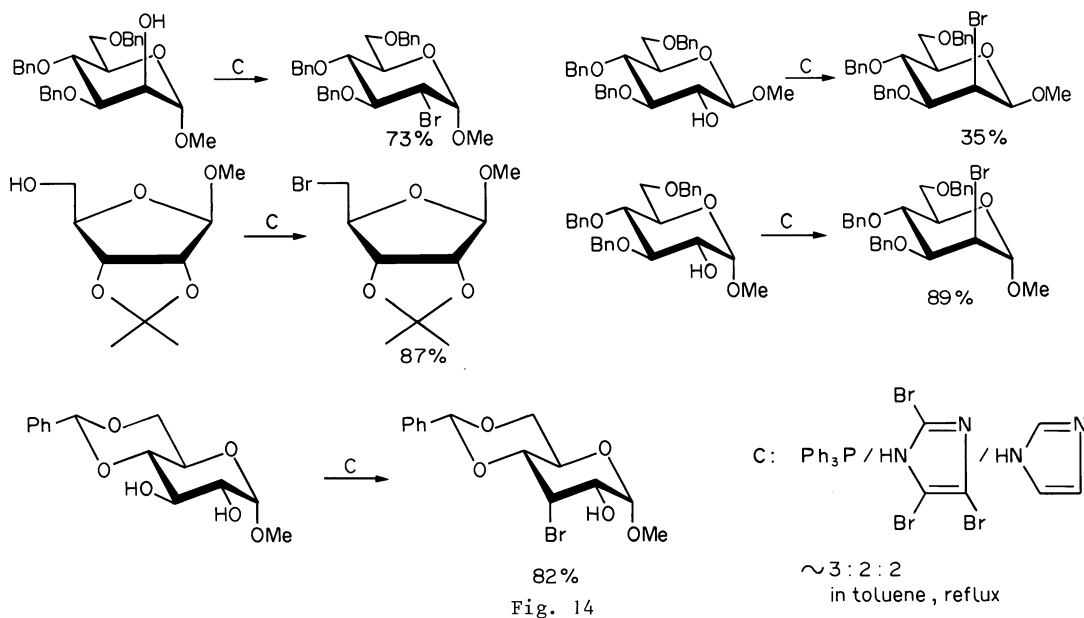


Fig. 14

It will be seen that except for the notoriously difficult axial substitution on the 2-position of 3,4,6-substituted methyl β -*D*-glucoside, substitutions of monohydroxylic compounds proceed in good yields. Configurational inversion at chiral centres are observed throughout. For polyhydroxy compounds, dibrominations may be obtained (fig. 15). Thus methyl α -*D*-mannopyranoside yields the 4,6-dibromo-4,6-dideoxy compound, which would be expected from Jones' and Szarek's previous work on chlorinations using sulfonyl chloride in pyridine. It is therefore surprising that the corresponding glucopyranoside yields the 3,6-dibromo compound shown. The 3,6-dideoxyhexopyranoside, obtained from this dibromo compound by hydrogenation is methyl α -paratose. Paratose is the immunodominant hexose in the *Salmonella* A group lipopolysaccharide and this constitutes a particularly facile synthesis of this rare sugar.

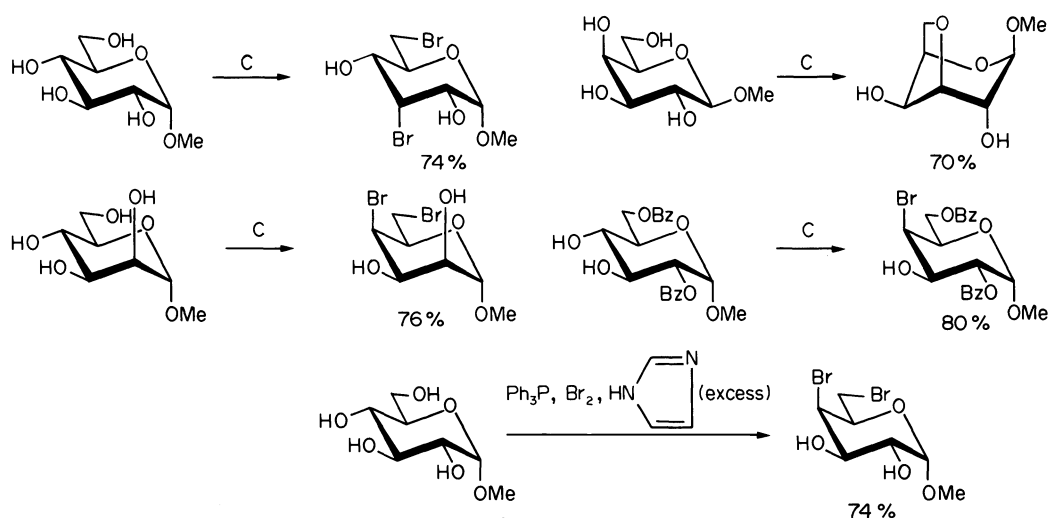


Fig. 15

We suggest that the intermediate responsible for the formation of the 3,6-dibromo compound is a six-membered cyclic dioxaphosphorane involving O-2 and O-4 with the hexoside in the 1C_4 conformation. This would leave only positions 3 and 6 open to substitution. Changing the reaction conditions by using a large excess of imidazole and bromine rather than tribromoimidazole, on the other hand, gives methyl 4,6-dibromo-4,6-dideoxy- α -D-galactopyranoside, presumably due to breakdown of the phosphorane (in equilibrium with the corresponding zwitterionic phosphonium compounds) by the excess imidazole and "normal" substitution at the 4,6-positions. Also, blocking the 2-position as in the example with methyl 2,6-di-O-benzoyl- α -D-glucopyranoside, leads to bromination in the 4-position. Methyl α -D-mannopyranoside may be seen as capable of forming a five-membered dioxaphosphorane bridging O-2 and O-3. It certainly cannot form a 2,4-linked dioxaphosphorane. Consequently, formation of the 4,6-bromo-4,6-dideoxy compound seems quite reasonable. Treatment of methyl β -D-galactopyranoside under these conditions disappointingly yields only the 3,6-anhydro compound. Some recent results are shown in fig. 16 (33). The partial bromination of p -methoxybenzyl 2-phthalimido- β -D-glucopyranoside yields first the 6-substituted compound and then the disubstituted ones, 4,6-substitution predominating. The reaction may be monitored to give predominantly the mono- or di-substituted products.

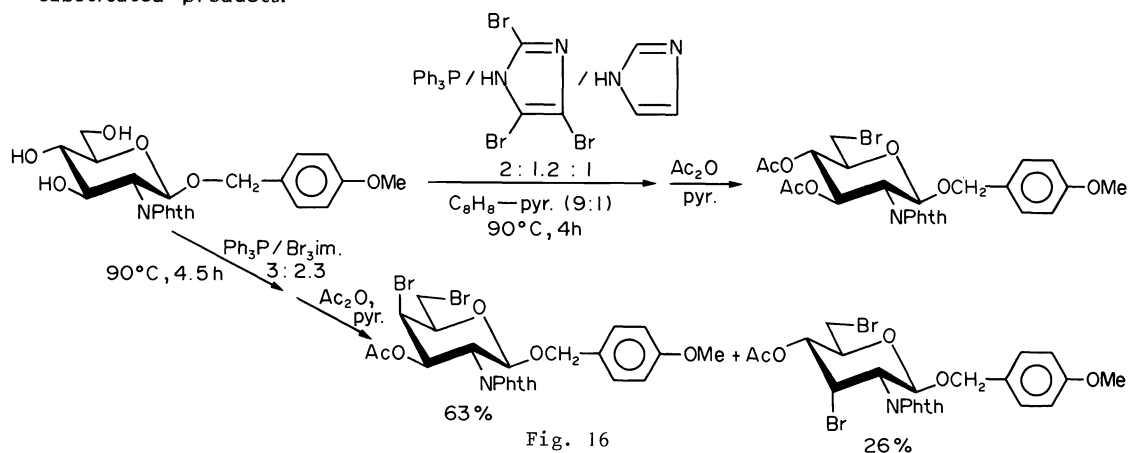
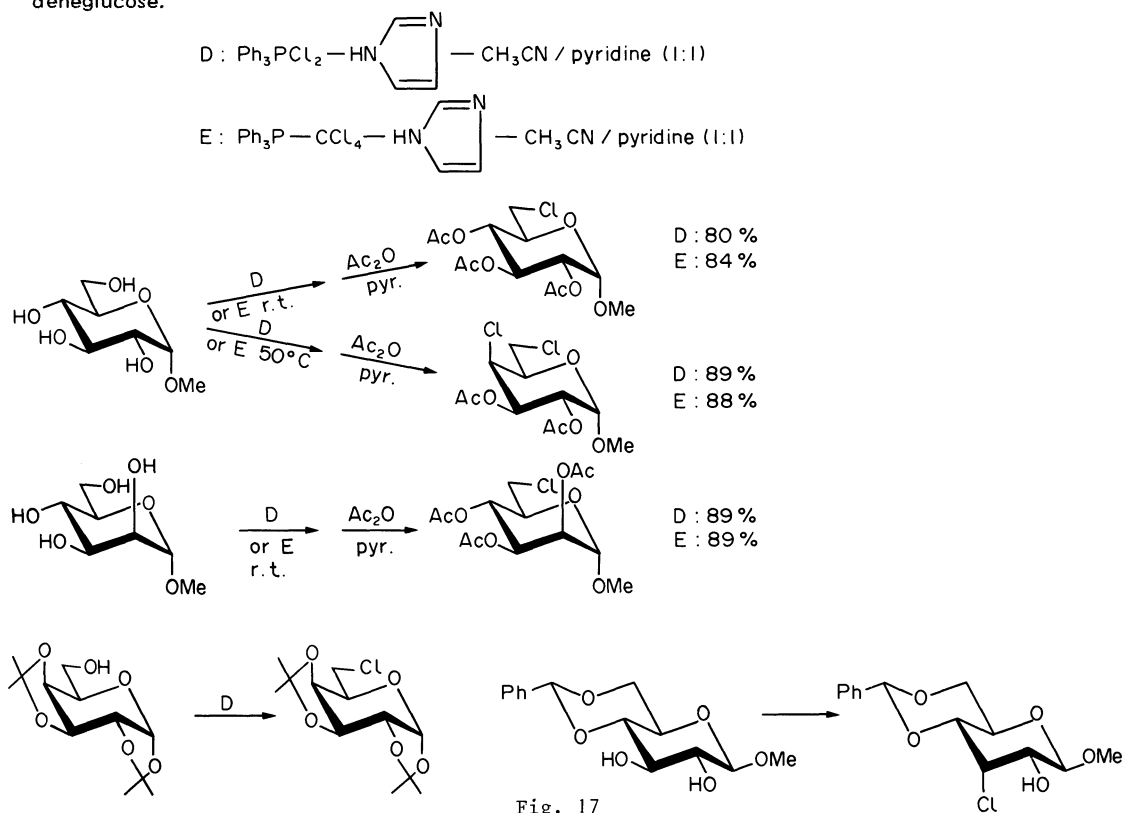


Fig. 16

CHLORINATIONS

An obvious extension of this work is to make chlorodeoxy sugars. We found that trichloroimidazole is tedious to make. Dichloroimidazole which is easily made is quite unreactive in our type of reagent system. We have, however, developed two alternative reagents for the conversion of hydroxy functions into chlorodeoxy ones (30). The reagents developed are not as efficient as those for bromination and iodination, but still represent an advance compared to existing methodology with regard to substitution at secondary positions in pyranosides.

Examples are shown in fig. 17. Attempts at obtaining substitutions at position 2 in hexopyranosides have not been successful. Neither has substitution at C-3 in diisopropylidene-glucose.



REGIOSELECTIVE REDUCTIVE OPENING OF CYCLIC ACETALS

Reductive ring openings of cyclic benzylidene acetals were introduced to carbohydrate chemistry by Bhattacharjee and Gorin (34). It has been extensively explored by Nánási, Lipták and coworkers (35). A typical early result, showing the predominant regioselectivity for reactions with 4,6-acetals, (dioxane rings) as reported by these workers is shown in fig. 18. It will be seen that the regioselectivity differs for the two diastereoisomeric benzylidene acetals. The subject has been extensively reviewed by Gelas (36).

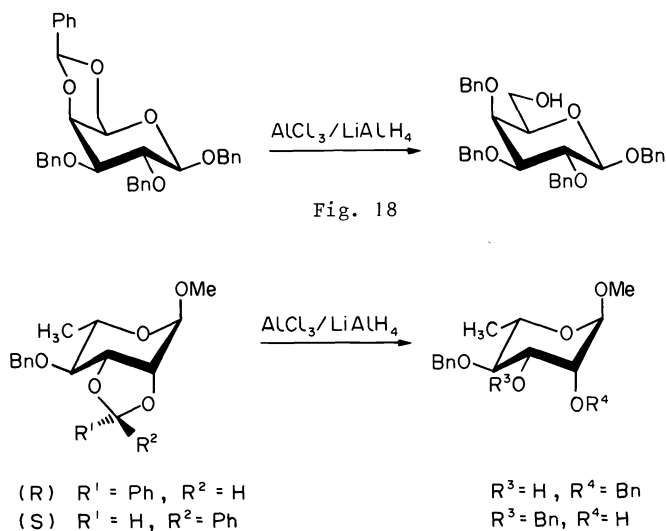
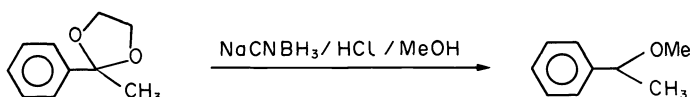


Fig. 19

We got into this after reading a report by Horne and Jordan that reduction as well as acetal exchange was observed upon treating the phenylethyldene acetal of ethylene glycol with sodium cyanoborohydride and hydrogen chloride in methanol (fig 20), (37).



Horne and Jordan. Tet. Lett 1978

Fig. 20

The transfer of this reaction into hexopyranoside chemistry yielded unexpected results (fig. 21), (38,39). The reaction conditions were: solution of the compound in tetrahydrofuran containing excess sodium cyanoborohydride and running in diethyl ether saturated with hydrogen chloride. The main product, obtained in good yield had the benzyl group in the 6-position and HO-4 was free.

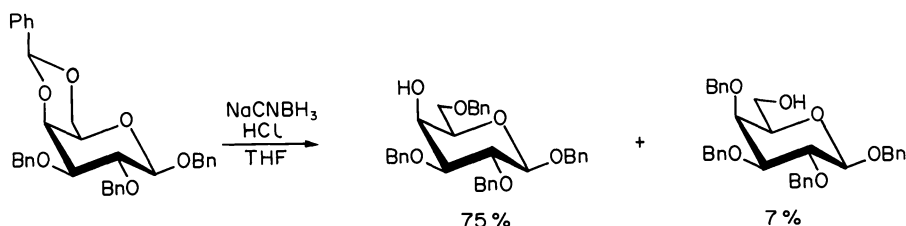


Fig. 21

This then would seem to complement the Nánási/Lipták regioselectivity and offer a choice in regioselectivity in these openings. We then tried reductive openings on the same dioxolane benzylidene acetals as these workers and obtained exactly the same regioselectivity (fig 22).

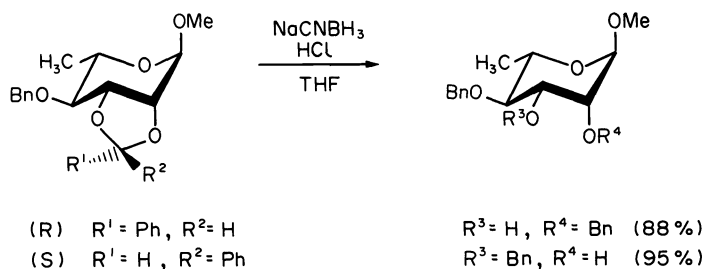


Fig. 22

Several examples of reductive ring openings of 4,6-O-benzylidene acetals are shown in fig. 23. The yields are high and the regioselectivity is independent on anomeric configuration and on configuration at O-4.

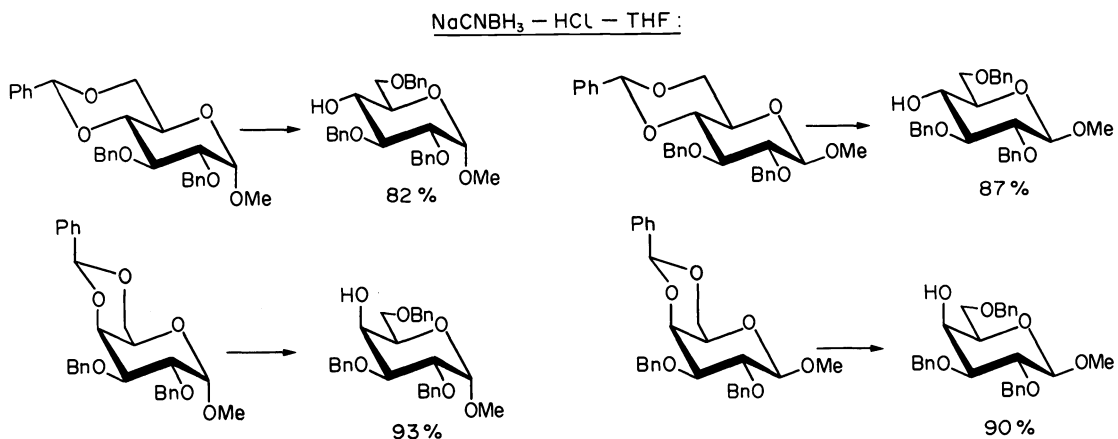
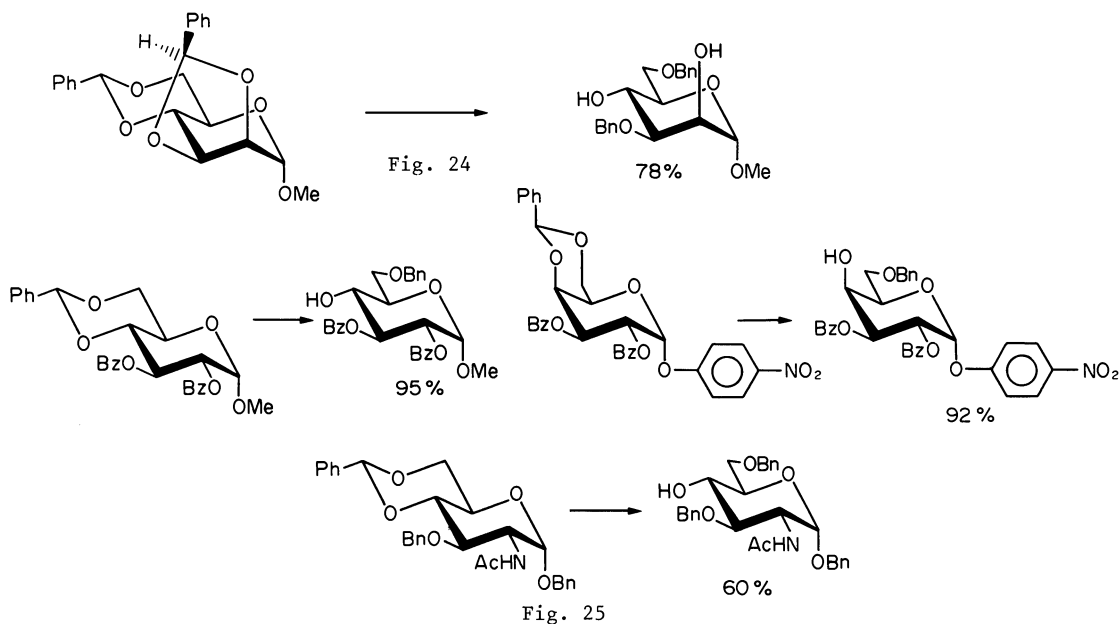


Fig. 23

The opening of a dibenzylidene acetal of methyl α -D-mannopyranoside is shown in fig. 24. These reductions are compatible with the presence of ester, acylamido as well as nitro groups (fig. 25).



They can be extended into allylic protection group chemistry (fig. 26), (40). The various 4,6-(2'-propenylidene) acetals shown were obtained by standard treatment of the pyranosides with acrolein dimethyl acetal in dimethyl formamide containing catalytic amounts of *p*-toluenesulfonic acid. This was followed by either benzylation or benzyloxylation and then reductive opening by sodium cyanoborohydride/hydrogen chloride in tetrahydrofuran as before. The regioselectivity is the same as before and also the compatibility with other protecting groups.

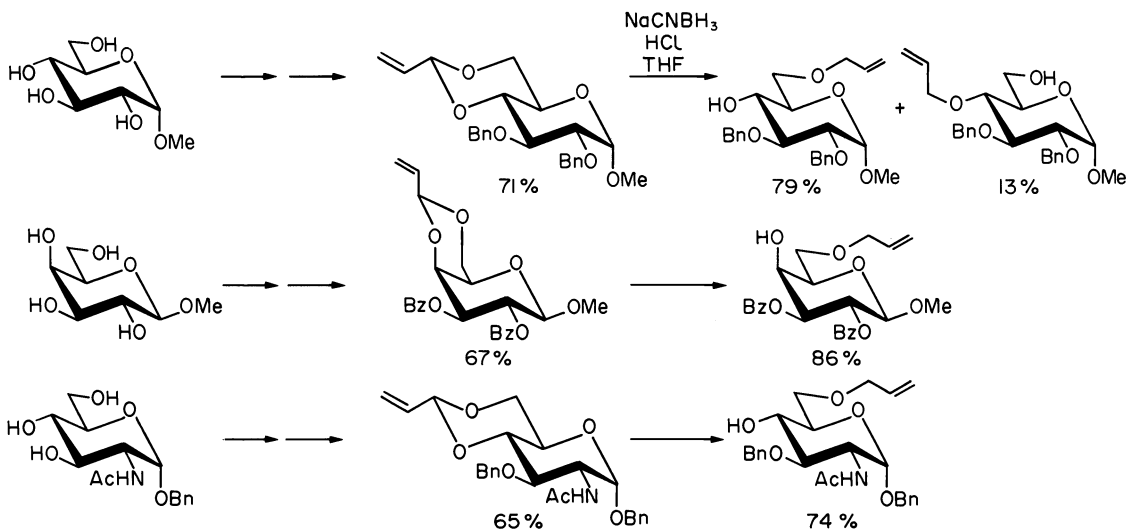
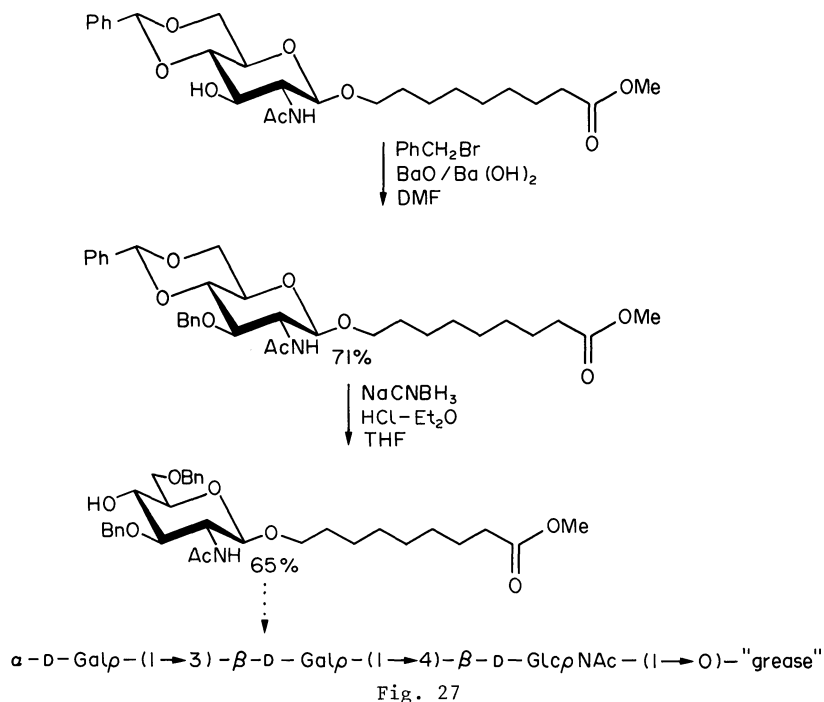
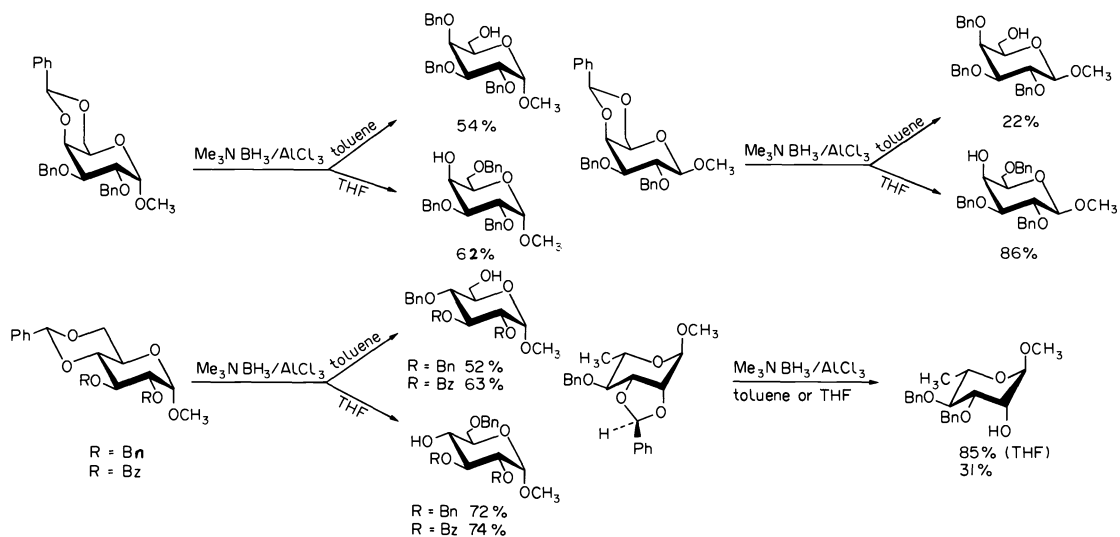


Fig. 26

These results are generally useful in protection group strategies. One example is shown in fig 27. For a synthesis of the trisaccharide glycoside shown, we needed a suitable "grease"-linked glucosamine intermediate with only HO-4 free. This was readily obtained by the route shown (41).



In further explorations of the possibilities in this field, we have found that in using borane-trimethylamine as reducing agent and aluminium chloride as the acid in this type of reaction, the regioselectivity in the opening of 4,6-benzylidene acetals may be controlled by the choice of solvent (42). The same compatibility with the presence of other protecting groups as that observed in our previous work was observed. Representative results are shown in fig 28.



Using tetrahydrofuran as the solvent, the benzyl group in the product is located at O-6 and HO-4 is free. Using toluene as solvent the opposite result is obtained. Again the regioselectivity of reductive opening of five-membered benzylidene rings is the same as that obtained in the original work by Nánási and Lipták and this is insensitive to solvent polarity. The regioselectivity in these examples was invariably high. The moderate yields in the examples using toluene as solvent represents degradation rather than low regioselectivity.

This particular reaction has been improved upon, by raising the ratio of reducing agent/Lewis acid and replacing toluene by dichloromethane (fig. 29), (43).

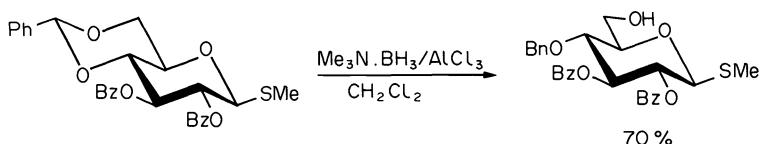


Fig. 29

In recent work by Samuelsson and coworkers in our laboratory, *p*-methoxybenzyl has emerged as a most interesting *O*-protecting group. It may be removed under mildly oxidative conditions such as treatment with ceric salts (44,45). Its compatibility with other protecting groups introduces a number of interesting possibilities in protecting group chemistry. An obvious extension of our acetal work is to use *p*-methoxybenzylidene acetals in the reductive systems described here, and obtaining partially *p*-methoxybenzyl ethers *via* short reaction schemes and with high regioselectivity. This work will be presented separately at this symposium. There are other obvious extensions. One of these is to use the borane-triethylamine/aluminium chloride reagent in toluene with 4,6-(2'-propenylidene acetals) of hexopyranosides and obtain allyl ethers with the allyl group at *O*-4 and *H**O*-6 free. Our systems are compatible with the presence of aromatic nitro groups. Another possibility might therefore be to extend this into the reductive opening of cyclic *o*-nitrobenzylidene acetals, thereby obtaining easy, regioselective routes to compounds containing photochemically removable protecting groups.

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