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SYNTHESIS OF AMINO- AND BRANCHED CHAIN MONO- AND OLIGOSACCHARIDES *

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Abstract - A report is given on the further development of the 1,3-dithiane method for the synthesis of branched chain carbohydrates. In connection with efforts towards glycoside synthesis of branched chain sugars, dihydrostreptosyl streptidine and dihydrostreptosyl-2-deoxystreptamine have been prepared. A critical survey on the problem of α-glycoside synthesis in general and in the amino sugar series is given. Based on syntheses with 2-azido-sugars, a novel α-glycoside synthesis for 2-amino sugar has been developed. Starting with the α-glycosyl bromides of 2-azido sugar, inversion to ß-glycosyl chlorides can be effected, which again by catalysis with silver perchlorate give high yields of α-glycoside. Thus all possible glycoside linkages could be realized in syntheses of disaccharides. An extention of this versatile method to the synthesis of tri - and oligosaccharides could be demonstrated.

INTRODUCTION

By observing trends and developments in the field of organic chemistry interesting markers can be distinguished. Some 20 - 25 years ago there started a phase of organic chemistry mainly devoted to theory and mechanistical studies. This development has been very fruitful and led to a far better understanding of many reaction sequences. On the other hand, however, this has demonstrated the limits implied in a theoretical approach. Consequently, it could have been expected, possibly as a sort of counter reaction to this, that a more practical development mainly devoted to synthesis strengthened considerably.

During the last 5 years an increasing number of most distinguished scientists have been attracted by these problems. During this time we have experienced a trend in the improvement of synthetic methods which most likely will provide us with remarkable results. The following demands are expected of improved methods:

(a) mild reaction conditions at low temperatures,
(b) high stereoselectivity,
(c) fast reactions and high yields.

These demands are of particular importance to carbohydrate chemistry which deals with most delicate polyfunctional compounds. As a consequence, carbohydrate chemistry is fully involved in this general trend and expects significant improvements by new methods.

In the present lecture I would like to present a contribution to the present problem of developing novel methods. To begin with, further developments in the preparation of branched chain monosaccharides will be discussed. Then the oligosaccharide synthesis of α-glycosidically linked branched chain sugars will be dealt with, and in the central part

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* This lecture is dedicated to Prof. Burckhard Helferich, Bonn, one of the pioneers in the field of glycoside synthesis, on the occasion of his 90th birthday.

an extended discussion of the synthesis of α-glycosides in amino sugar oligosaccharides will follow. Obviously, in this particular field there is a strong need for further selective reactions.

SYNTHESIS OF BRANCHED CHAIN SUGARS

Starting-point for our research was a new and simple synthesis of streptose, which we described some years ago (Fig. 1),(Ref. 1). A nucleophilic addition of the 1,3-dithiane anion to the ketose, and subsequent desulfuration and hydrolysis of the adduct yields free streptose. The nucleophilic reaction of suitably blocked ketoses with carbanionic species represents a well known and important preparation for branched chain sugars. The particular value of this method is due to the easy introduction of a functionalized side chain, which is a difficult task otherwise. Meanwhile several other carbanions have been proposed for the same purpose but we believe the dithiane method proved a success. According to these and related procedures we synthesized the aldgarose of aldgamycine (Ref. 2 and 3) and the γ-octose of the quinocycline complex (Ref. 4) meanwhile. In this connection I will not further discuss these syntheses but rather improvements of the dithiane procedure.

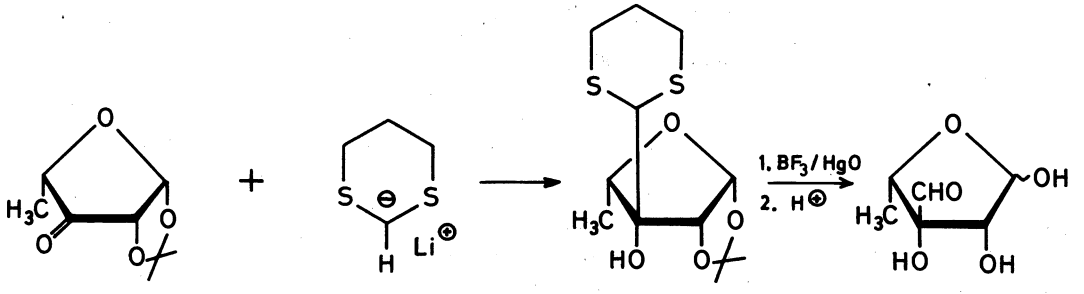


Figure 1

The nucleophilic 1,2-addition to ketoses yields branched chain sugars with a hydroxyl group at the branching point exclusively. However, compounds without such a hydroxyl group are of particular interest and rather more difficult to obtain. For this purpose there opens up a way by reductive elimination of the hydroxyl group at the branching point as shown in Fig. 2. The acetyl branched sugar normally prepared by the dithiane procedure is converted to its benzoate. This is liable to a radically induced reduction with tri-n-butyltin hydride to yield the deoxy branched sugar (Ref. 5). There is inversion of configuration observed with this reaction, and the best results are obtained with acetyl branched sugars. It should be pointed out that in this case the deoxygenation procedure of Barton (6) cannot be applied because the tertiary hydroxyl groups cannot be converted to the necessary xanthogenate ester.

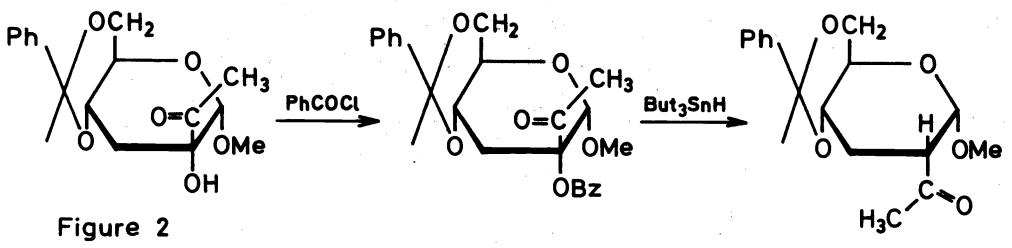


Figure 2

Another way to deoxy branched sugars would result with pyranoside enones if instead of a 1,2-addition to the carbonyl group there could be a successfully controlled 1,4-addition to the olefin. As shown in Fig. 3 this was indeed effected. In the presence of copper(I) chloride alkyl Grignards like vinylmagnesiumbromide yield the 1,4-adduct (Ref. 7). In

this case the reactive species obviously is an organo-copper. Using 1,3-dithiane anions a controlled 1,4-addition in the presence of copper catalysts could only be effected in some distinct cases (Ref. 7 and 8).

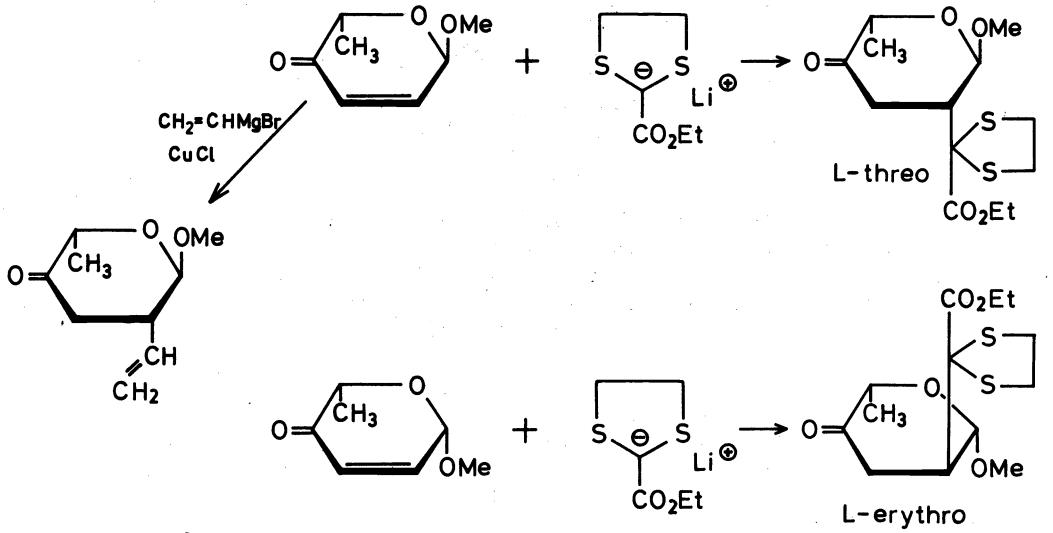


Figure 3

The reagent of choice is the anion of 2-carbethoxy-1,3-dithiane (Ref. 7 and 8) described by Schlessinger (9). It is more stable, can be easily prepared by metallation even with lithium piperidide, and adds to pyranoside enones in a 1,4-addition exclusively (Fig. 3) with enhanced stereoselectivity (Ref. 10). The new side chain adds to the molecule always in "trans" manner to the anomeric methoxyl group. Consequently, with the α-glycosidic enone the one and with the ß-glycosidic enone the other isomer with inverted stereochemistry at C-2 can be synthesized. Here is such a case where a reaction proceeds at -20° C within 60 min with high stereoselectivity and good yields!

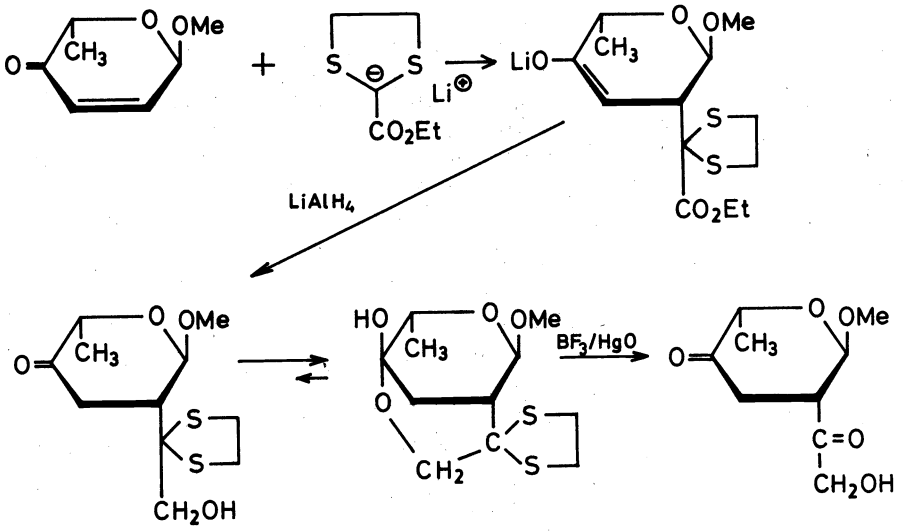
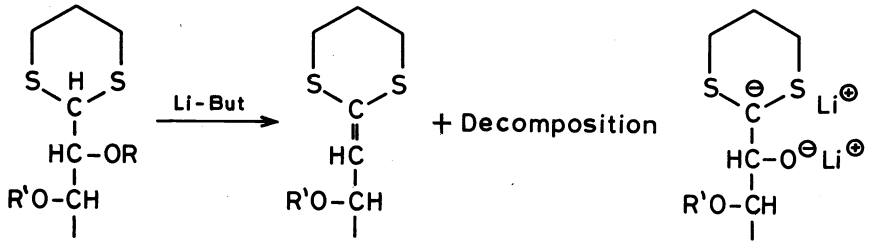


Figure 4

With the final product of the L-threo form the carbethoxy group in the side chain should be reduced to a hydroxymethyl group without an attack at the 4-keto group. This complex problem could be solved as shown in Fig. 4 (Ref. 8 and 10). In the reaction of enone and anion a lithium enolate is formed as intermediate, which is present in solution as such. By the direct reduction of the solution with lithium aluminium hydride there occurs only a reduction in the side chain, whereas the keto group remains blocked as enolate. After hydrolytic work-up the reduced ketone is obtained which cyclizes to a ketal. After desulfuration the wanted open diulose (Fig. 4, bottom right) is obtained. This particular compound was prepared because it shows the structure given by Asai (11) for pillarose of pillaromycine. Meanwhile it could be demonstrated by X-ray structure analysis performed by Fraser-Reid et al. (Ref. 12) that this formula is wrong. I will refer to the right structure later on.

There was a need to make use of the dithiane method to introduce further functionalized side chains, particularly those carrying a hydroxyl function next to the mercaptal group. However, by metallation studies with butyllithium applied to mercaptals of the type shown in Fig. 5 elimination to the olefin and subsequent decomposition is observed.



R= Alkyl, Acyl, Acetal

Figure 5

Again this problem can be solved using compounds with a free hydroxyl group next to the mercaptal group. In metallation with 2 moles of butyllithium a dianion is obtained (Fig. 5, right side), the reaction of which with carbonyl groups works essentially as with the normal monoanion.

Two examples for such a reaction are shown in Fig. 6. Reaction of the galacto-6-aldehyde in the center with the dianion to the left yields a chain extension of two carbon atoms (Ref. 13). Furthermore starting with the mercaptal of 3,4-isopropyliden-D-erythrose a dianion can be obtained. Again this reacts with the former galacto compound to yield a

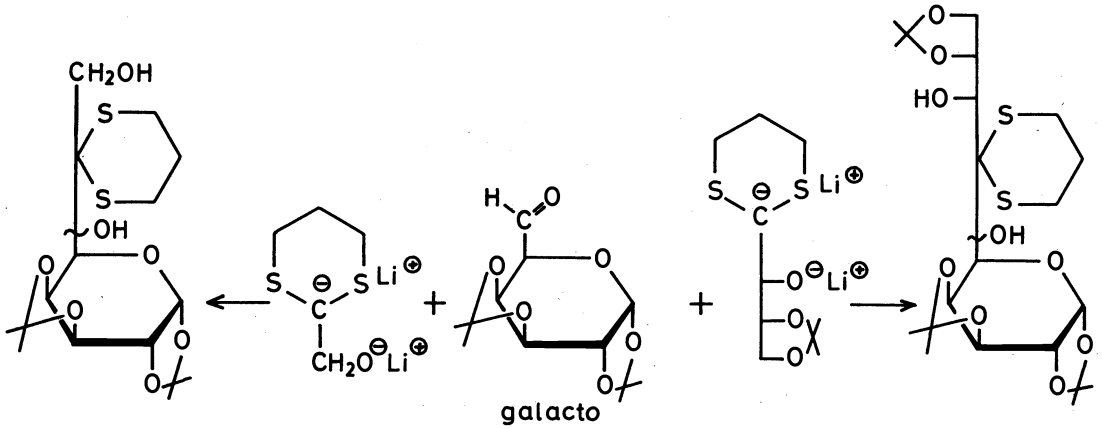


Figure 6

sugar with nine carbon atoms (Fig. 6, right side), (Ref. 13). Obviously here we have a novel procedure by which long-chain carbohydrates can be obtained easily.

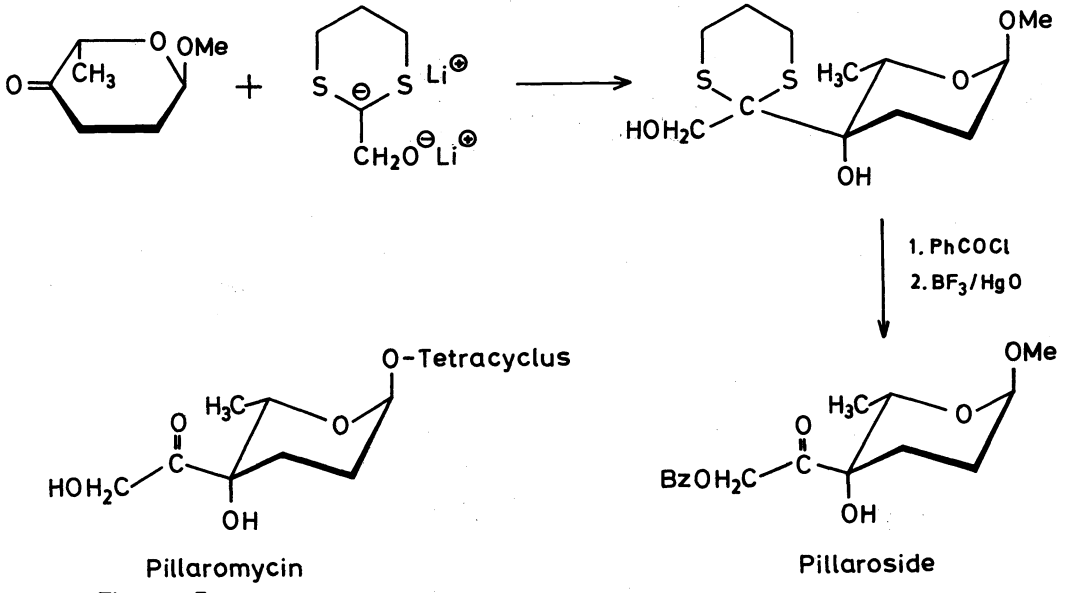


Figure 7

Using a dianion, as shown in Fig. 7, we find a simple synthesis of the compound which now shows the correct structure of pillarose. Nucleophilic addition of this dianion can be effected to the 2,3-dideoxy-4-ulose by which the dithiane sugar with the equatorial side chain is obtained with preponderant stereoselectivity (Ref. 14). Subsequent benzoylation and desulfuration yields a pillaroside, analytical data of which are in convincing agreement with the best characterized corresponding derivative of natural pillarose (Ref. 14). Fig. 7 (bottom left) shows the corrected structure given by Fraser-Reid (12) to pillaromycine.

GLYCOSIDE SYNTHESES WITH BRANCHED CHAIN SUGARS

In the following we will look upon oligosaccharide syntheses using branched chain sugars. Of particular interest are glycoside syntheses of streptose (Fig. 8). In our synthesis of streptose we obtain the dithiane derivative easily, and consequently it seemed to be favourable to keep this easily removable blocking group and perform glycoside syntheses with halides of the dithiane sugar itself. Both these halides shown in Fig. 8 proved to be applicable for this purpose. In the presence of a 2,3-carbonate group reaction with alcohols yields ß-L-glycosides stereoselectively. Apparently in this case we have a S_N2-reaction predominantly (Ref. 15). However, the same compound blocked with a 2,3-isopropylidene group gives rise to the formation of the α-L-glycosides in glycoside synthesis. The reason for the enhanced formation of the α-L-glycoside in the presence of an acetal group cannot be explained simply, and it does not appear to be sensible to discuss some kind of neighbouring group participation. Anyway, with these two compounds there are suitable means to prepare either α- or ß-glycosides stereoselectively (Ref. 15).

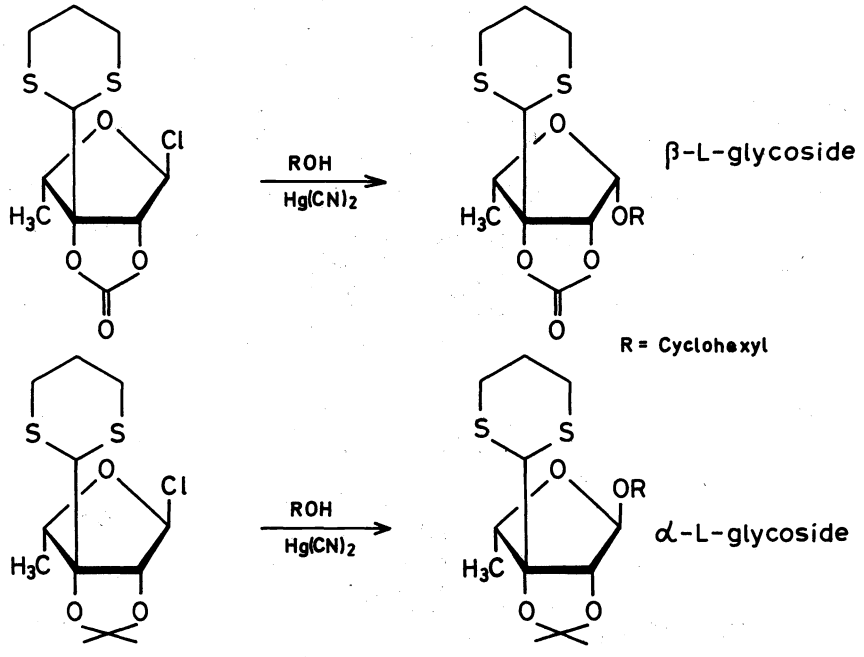


Figure 8

As shown in Fig. 9, heptaacetylstreptidine was used as aglycon. It is a homogenous chiral compound with a free hydroxyl group at C-4, obtained by selective hydrolysis from streptomycine (Ref. 16). Unfortunately, this compound showed but little reactivity, and has to be counted among the least reactive although selectively blocked saccharide units. Nevertheless, reaction to a pseudodisaccharide with an α-glycosidic linkage could be performed (Ref. 16). However, there occur some problems with the deblocking of this compound because the isopropylidene group shows increased stability towards acid hydrolysis. Thus during removal of this group the newly formed glycosidic linkage is broken.

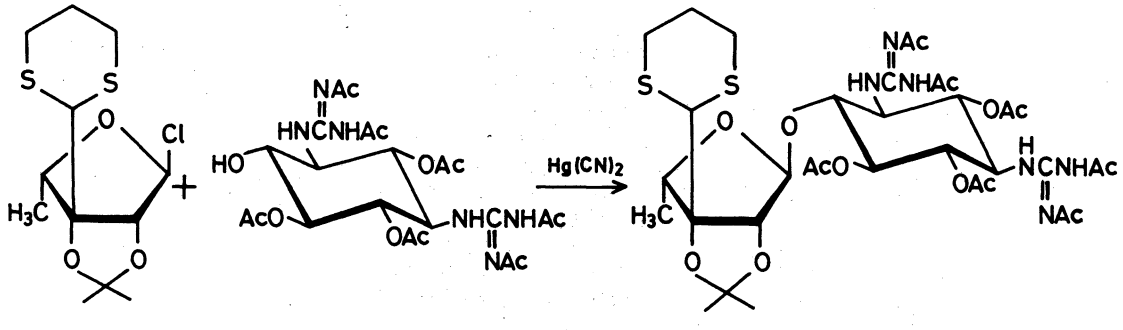


Figure 9

In order to overcome these problems the synthesis was modified as shown in Fig. 10. Again the halide prepared from 2,3-benzylidene-dithiane streptose yields α-glycosides predominantly. Thus the corresponding streptosyl chloride and the selectively blocked streptidine derivative form the pseudodisaccharide (top right), (Ref. 16). With this compound deblocking procedures could be performed. First by desulfuration the dithiane ring is removed, then hydrogenolysis eliminates the benzylidene group and

similarly reduces the aldehydo group of streptose to a hydroxymethyl group. By subsequent removal of the acetyl groups the free dihydrostreptosyl streptidine (Fig. 10, bottom right) can be obtained (Ref. 16).

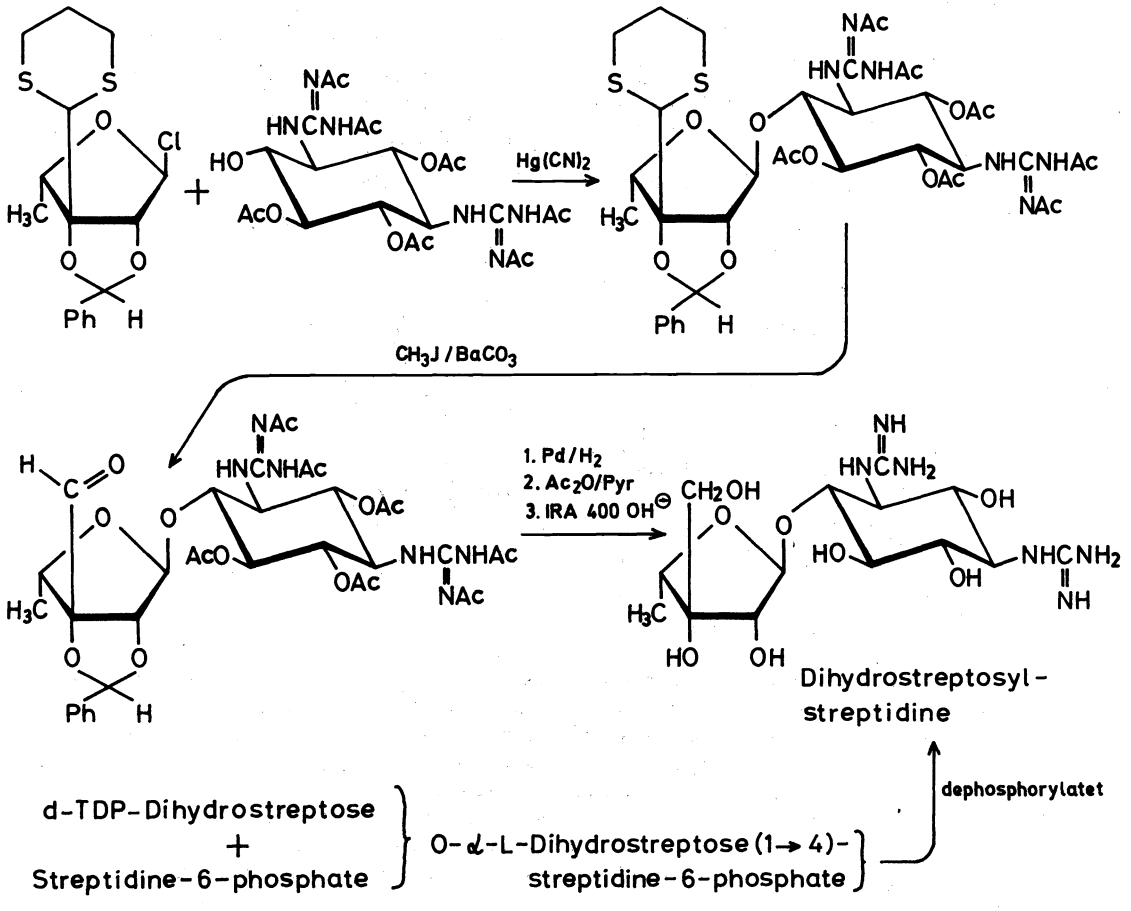


Figure 10

It should be pointed out that this pseudodisaccharide unit cannot be obtained by partial hydrolysis of streptomycine. In partial hydrolysis of streptomycine always the labile glycosidic linkage of the furanoid streptose is broken primarily. On the other hand just this pseudodisaccharide unit seems to be of decisive importance in the biosynthesis of streptomycine because it seemed to be formed as a partial unit in primary steps. Meanwhile Grisebach (17) succeeded to demonstrate the enzymatical linkage of d-TDP-dihydrostreptose with streptidine-6-phosphate (Fig. 10, bottom). By dephosphorylation of dihydrostreptosyl streptidine-6-phosphate a compound was obtained, all properties of which were identical with those of synthetical dihydrostreptosyl streptidine (Ref. 17). Thereby a central step in the streptomycine biosynthesis was put on a sound basis.

Furthermore, a glycoside synthesis could also be performed with streptose and 2-deoxystreptamine (Fig. 11), (Ref. 18). In this case it proved to be more favourable to make use of the streptosyl bromide. As aglycon the selectively protected 2-deoxystreptamine derivative prepared by Umezawa (19) was chosen which is considerably more reactive than the streptidine derivative discussed before. It is, however, a racemate, and consequently the glycoside synthesis yields the diastereomeric mixture of two pseudodisaccharides (Ref. 18). Following reaction to the diacetate and subsequent desulfuration the diastereomers can be separated. They can be further deblocked by hydrogenolysis of the benzylidene groups and removal of the carboethoxy groups with barium hydroxide.

Thus both free dihydrostreptosyl-2-deoxystreptamines with either α-glycosidic 4-O- or 6-O-linkage are available.

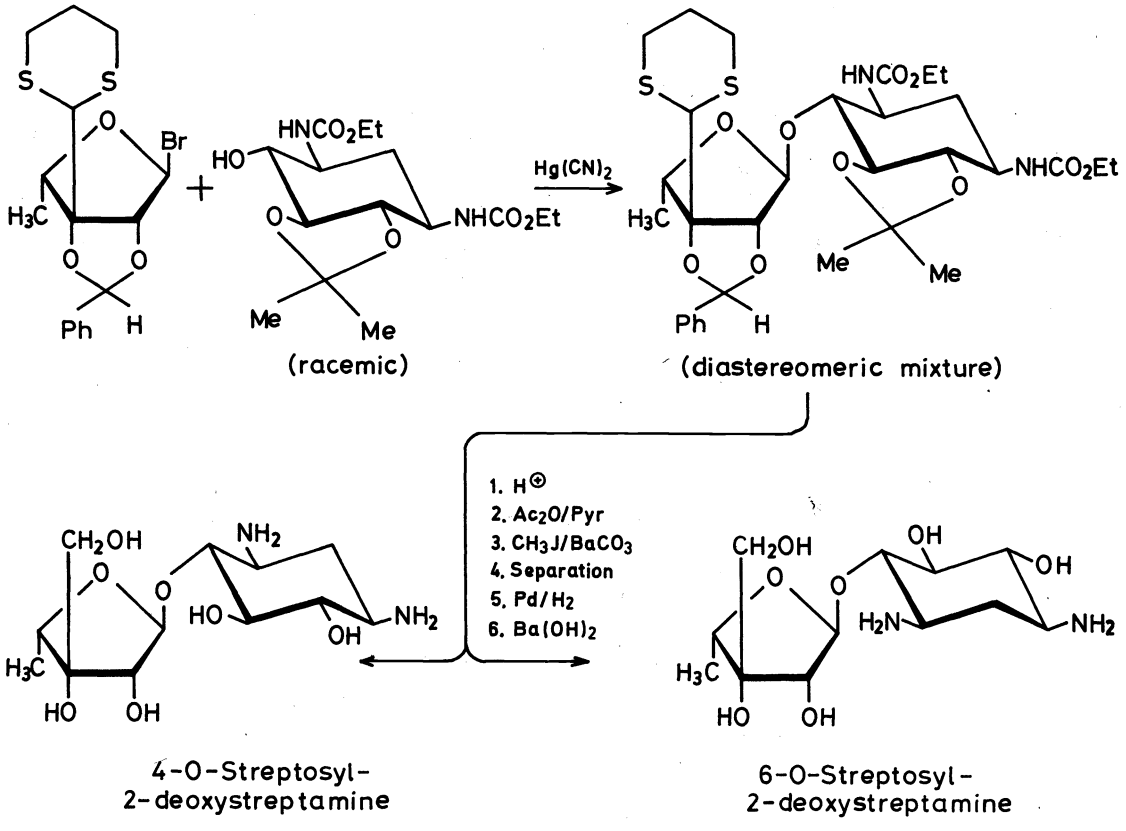


Figure 11

Considering these results it seems to be favourable for glycoside syntheses in furanoid systems to make use of a 2,3-acetal protection. By applying careful conditions these rather reactive halides can be obtained. A further extension to different furanoid systems seems to be promising.

SYNTHESIS OF α-GLYCOSIDES OF AMINO SUGAR OLIGOSACCHARIDES

The central meaning of α-glycoside synthesis particularly in the field of oligosaccharide antibiotics could be noted destinctly from the above elucidations. I would like now to concentrate further on the field of α-glycoside synthesis but beforehand intend to give some general comments to this question.

In general an important assumption for the α-glycoside synthesis is a substituent attached to C-2 which does not exhibit neighbouring group activities. To this a vast fundus of material is available and generally well known. A considerable amount of research has been done, according to which in such substituted normal sugars or aminosugars by application of certain salts like e.g. mercury (II) cyanide according to Helferich (20) or special bases and solvents a rather high amount of α-glycosides could be obtained. These reactions are very useful, however, very often they are rather closely connected to the individual substrate applied, and a further generalization can seldom be adopted. I tend here to underline only those methods which can be used in a general application, and which proved to be valid on a broad experimental basis.

The generally applicable procedures of α-glycoside synthesis start with the supposition that the generally unstable ß-glycosyl halide should react largely under S_N2 related conditions with inversion of configuration (Fig. 12). Two methods proved to be valid to control this difficult problem.

In the first method according to Lemieux (21), (Fig. 12) tetraethylammonium halide, that means halide anions, are added in the reaction of an α-glycosyl halide with the aglycone. Thus, as also could be shown by Fletcher (22), a reaction with the halide under inversion and formation of the ß-glycosyl halide occurs (Fig. 12, top). This reaction is reversible and the starting halide can be formed back again. If the energy profiles in the reaction coordinates are of the kind, that the ß-glycosyl halide reacts fast, but the α-glycosyl halide rather slowly with the alcohol to form a glycoside, then an enhanced amount of α-glycoside is expected, even though the proportion of ß-glycosyl halide is low in the reaction mixture. Quite often the energy profiles have the required form and consequently this method proved applicable as a "one-pot-procedure" for the α-glycoside synthesis. An example given by Lemieux (23) shows Fig. 12 (middle) in which two galacto units have reacted to form an α1→3-linked disaccharide.

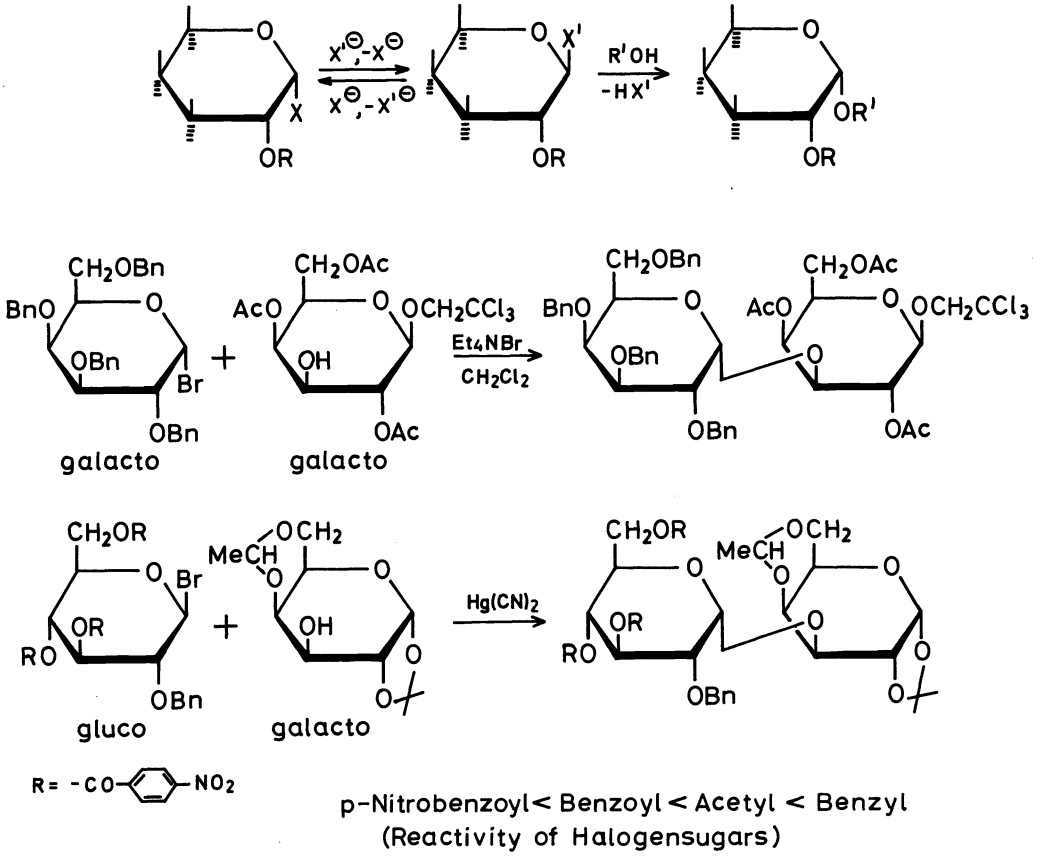


Figure 12

The reactivities or stabilities respectively of the anomeric halosugars, which are the basis for the energy profiles, are of considerable importance in this method. As could be demonstrated by Fletcher (22), there are means by which the reactivities of halosugars can be varied selectively using different substituents, e.g. there is observed an increase in reactivity in the series p-nitrobenzoyl, benzoyl, acetyl, and benzyl (Fig. 12, bottom). That means the p-nitrobenzoates are most, the benzylethers least stable. This is the reason that in several cases ß-glycosylbromides of p-nitrobenzoates could be isolated. In glycoside synthesis these will give high yields of α-glycosides. An example is given

by Flowers (23) in the condensation of the gluco- and the galacto-compound to an $\alpha 1 \rightarrow 3$-linked disaccharide (Fig. 12, bottom).

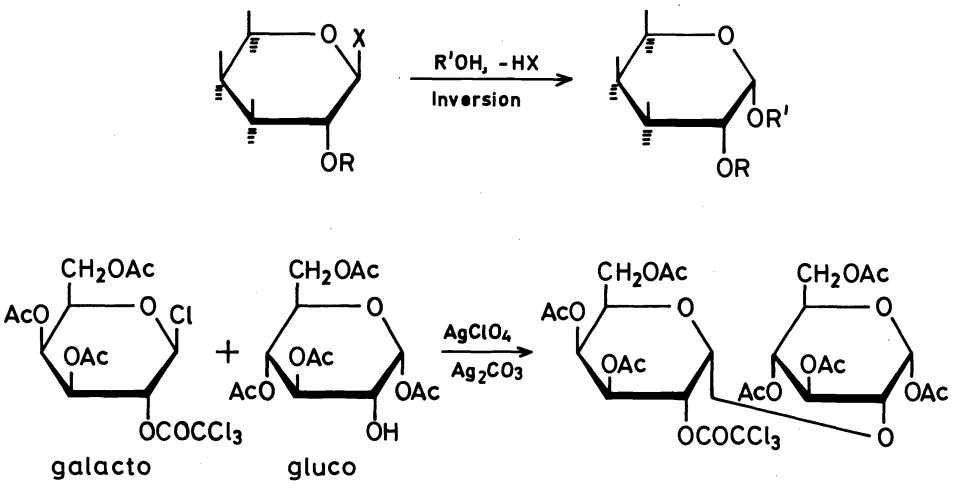


Figure 13

The second method based on the work of Wolfrom (25), Igarashi (26), and mainly Helferich (27), (Fig. 13) recommends the isolation of the ß-glycosyl halide which then again is reacted with the alcohol under mild reaction conditions with inversion of configuration (Fig. 13, top). Separation of ß-glycosyl halides can be effected by exactly controlled inversion of the α-glycosyl halides using tetraethylammonium halide. The further reaction of the ß-glycosyl halides obtained is performed in the presence of silver carbonate and catalytical amounts of silver perchlorate, and under rather mild conditions in fast reactions high amounts of α-glycosides can be obtained. As an example the reaction described by Helferich (27) between a galacto- and a gluco-compound is shown, which gives the $\alpha 1 \rightarrow 2$-linked disaccharide (Fig. 13). According to our opinion this method may be looked upon as the most efficient at the moment.

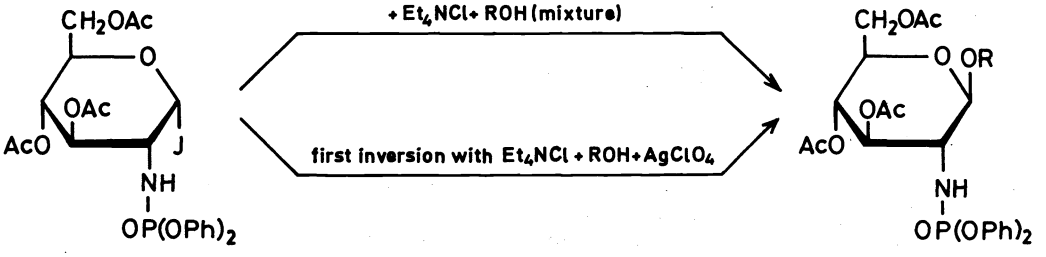


Figure 14

There remains the question whether or to what extent either of these methods could be applied to amino sugars. To begin with there opens up a problem because as to our knowledge there has not been described a suitable ß-glycosyl halide in amino sugars which would be necessary for the α-glycoside synthesis. A suitable amino sugar halide with which the halide inversion could be tested is the α-glycosyl iodide prepared by us recently (Ref. 28) and shown in Fig. 14. In reaction of this halide with tetraethylammonium halide and alcohols ß-glycosides are obtained exclusively. A controlled inversion with tetraethylammonium chloride could not be realized. Obviously partly formed ß-glycosyl chloride must invert very fast back to the α-glycosyl chloride, thus finally the ß-glycosides could be detected as the single products. These results

demonstrate clearly that neither of both the efficient methods can be applied in the field of amino sugars.

The single way the "nitrosoglycal" procedure of Lemieux and Nagabhusan (29) is based on a different type of reaction (Fig. 15). According to this the addition of saccharide units to nitroso halides or nitroso glycales yields oximinoglycosides with predominating α-glycosidic linkages. As an example, the synthesis of D,D-streptobiosamine (Fig. 15)

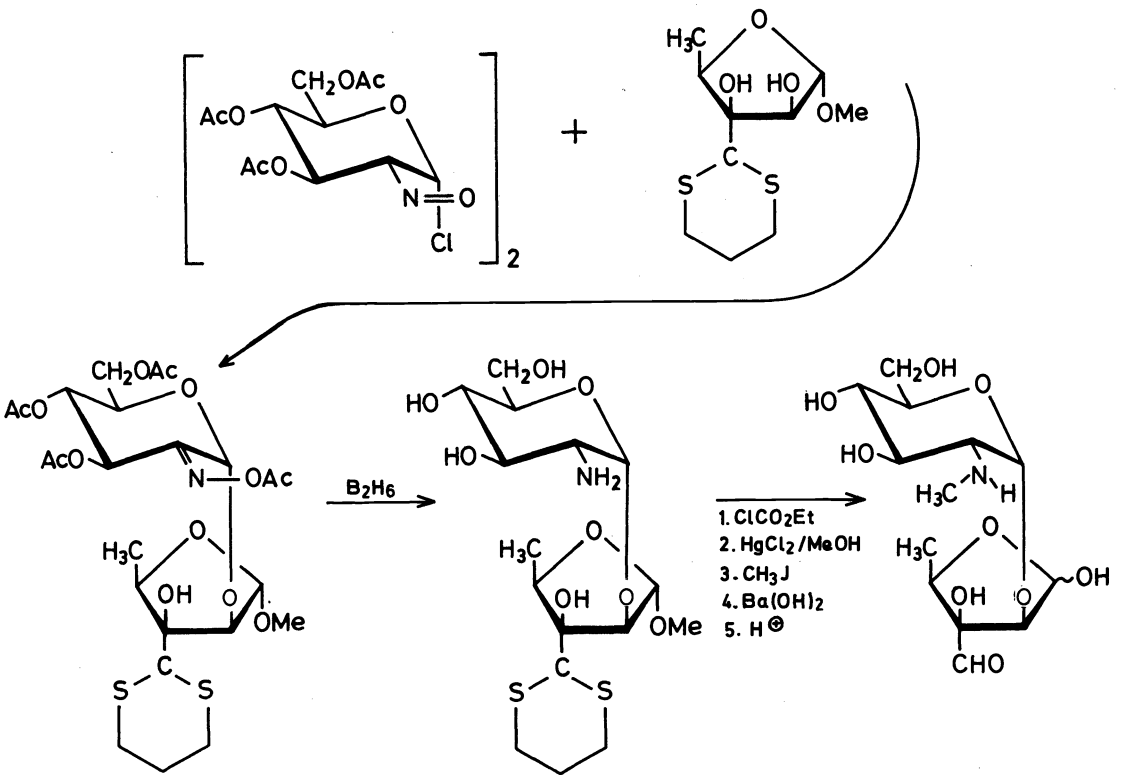


Figure 15

is shown which we carried out in connection with studies in streptomycine syntheses (Ref. 30). Similarly, the natural L,L-isomer can be obtained. The dimeric nitroso compound and the protected dithianestreptose yield an $\alpha 1 \rightarrow 2$-linked oximinodisaccharide. A selective reduction towards the amino sugar with gluco configuration could be performed using diborane. By a sequence of blocking and deblocking steps the N-methyl group could be introduced, and thus finally the free streptobiosamine obtained. The advantage of this method is based on the simple availability of the starting material, a glycal. However, there are several problems connected with the selective reduction of the oximino to the amino compound. In addition to this with certain aglycons and in the pentose series the selectivity of the addition step with formation of the α-glycoside is restricted.

Because a direct α-glycoside synthesis of amino sugars starting with their ß-glycosyl halides does not operate, as discussed before, we investigated the properties of 2-azido-sugars. An azido group does not exhibit any neighbouring group effects, and can be easily hydrogenated to an amino group. 2-Azido-sugars are supposed to be obtained only sluggishly, because a nucleophilic substitution at C-2 is particularly difficult, which can be understood following Hough and Richardson (31) because of strong polar rejection.

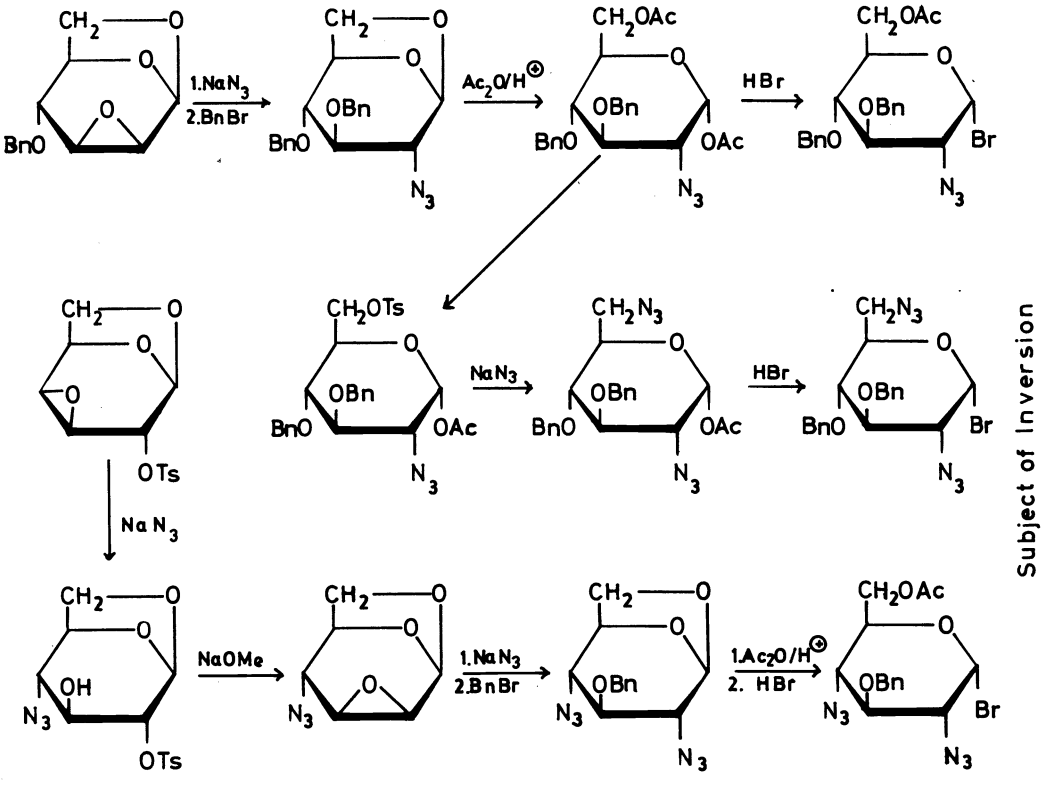


Figure 16

However, as shown in Fig. 16, there is an easy access to 2-azido-sugars, starting with the well known and straightforward to prepare epoxides of 1,6-anhydro-sugars. By opening the epoxide with sodium azide and subsequent acetolysis (Fig. 16, top) the wanted 2-azido-glucose can be obtained, the α-glycosyl bromide of which can be prepared by well known procedures (Ref. 32). Starting with the 2-azido-glucose derivative (Fig. 16, middle) a 2,6-diazido-gluco compound can be prepared similarly via the 6-tosylate and transformed to its halide (Ref. 33). A 2,4-diazido-gluco compound is available by a twofold epoxide opening according to the reaction sequence given in Fig. 16 at the bottom (Ref. 34). Here again following acetolysis the corresponding halide can be prepared in the similar manner (Ref. 33). Thus three α-halides of mono- and diazido sugars are available which can be used for inversion studies.

It turned out that an exactly controlled inversion of the three shown α-halides is possible (Ref. 35). The α-bromide and tetraethylammonium chloride yield the ß-chloride in acetonitril (Fig. 17). The reaction can be easily followed polarimetrically and is stopped at the maximum negative rotation by addition of toluene. The amount of ß-glycosyl chloride mostly exceeds 90 % in these cases. After separation of the ammonium salt the ß-glycosyl chloride obtained can be used directly for the oligosaccharide synthesis.

In Fig. 17 two reactions are shown with the ß-glycosyl chloride obtained by inversion (Ref. 35). The disaccharide synthesis is performed by adding the ß-chloride to the other saccharide component in dichlormethane in the presence of silver carbonate and catalytical amounts of silver perchlorate or collidine and silver perchlorate. Using these conditions the oligosaccharide synthesis is done at -5° C within 15 min. The yields with a high amount of α-glycosides are good. It is essential to exclude moisture totally. This is again a reaction which needs only very mild conditions, is fast and gives material in good yields and high stereoselectivity. We also tried other soluble silver salts, none

of which according to our experience proved to be of particular value compared with the above method.

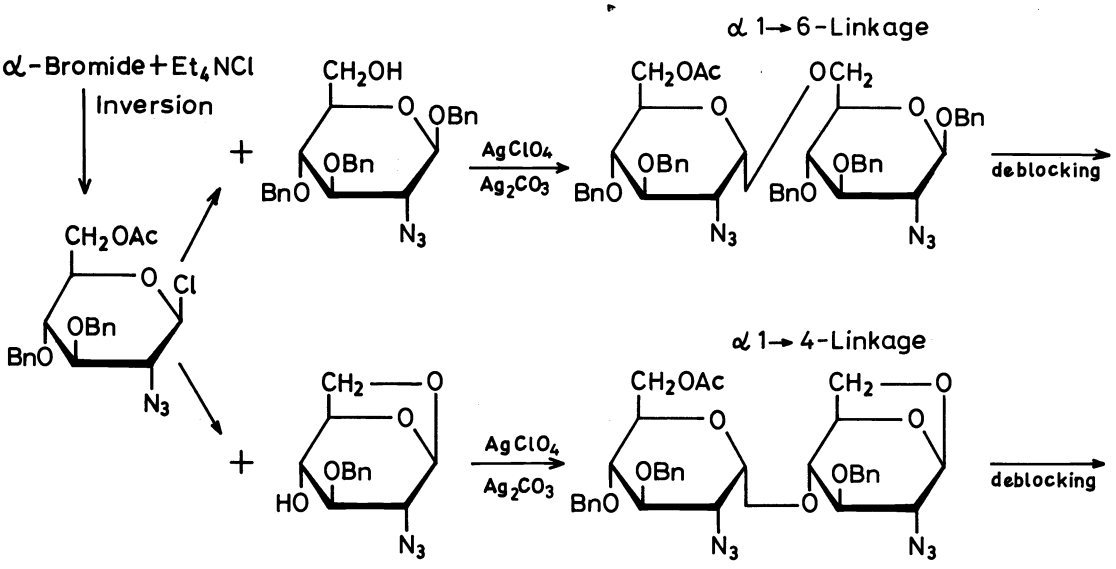


Figure 17

Thus by this reaction towards a 1→6-linked disaccharide with 85 % yield a product is obtained which contains the α-glycoside in 85 %. (Fig. 17, top), (Ref. 35). A 1→4-linked disaccharide (Fig. 17, bottom) can be isolated in 75 % yield. In this case the amount of the α-glycoside is 85 % again.

In Fig. 18 further syntheses of disaccharides are shown starting with the ß-chloride and saccharide compounds having less reactive hydroxyl groups. A 1→3-linked disaccharide can be obtained in 75 % yield (Fig. 18, top), 85 % of which consists of the α-glycoside (Ref. 35). Furthermore, it was possible to prepare a 1↔1-linked disaccharide (Fig. 18, bottom) in 45 % yield, with 85 % of the α,α-linked isomer (Ref. 33). These four

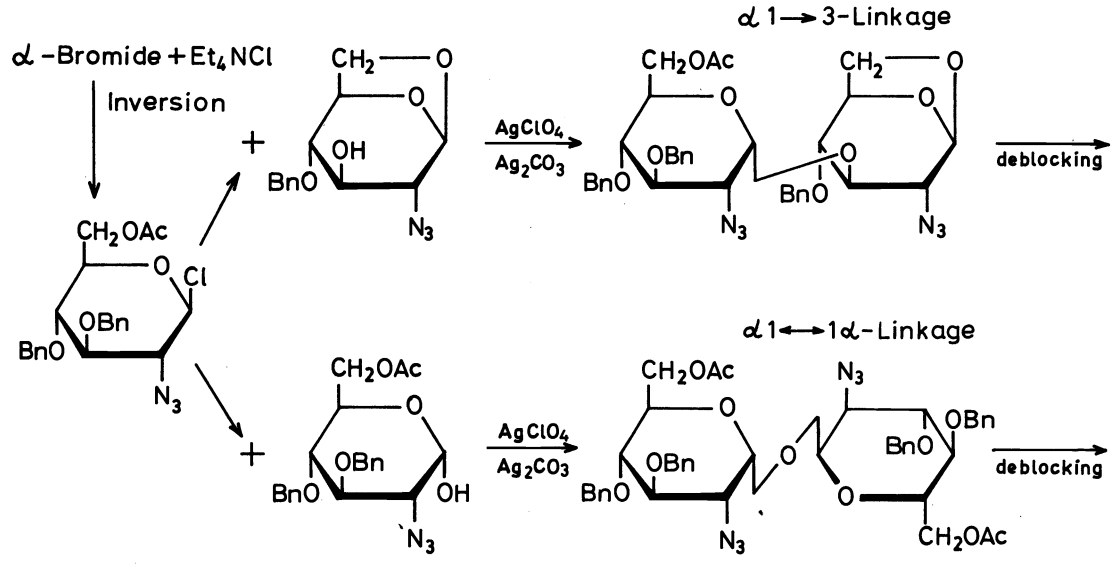


Figure 18

synthesized types of disaccharides contain two units of 2-azido-glucose. Consequently, their transfer to the corresponding amino sugar disaccharides is easily realized.

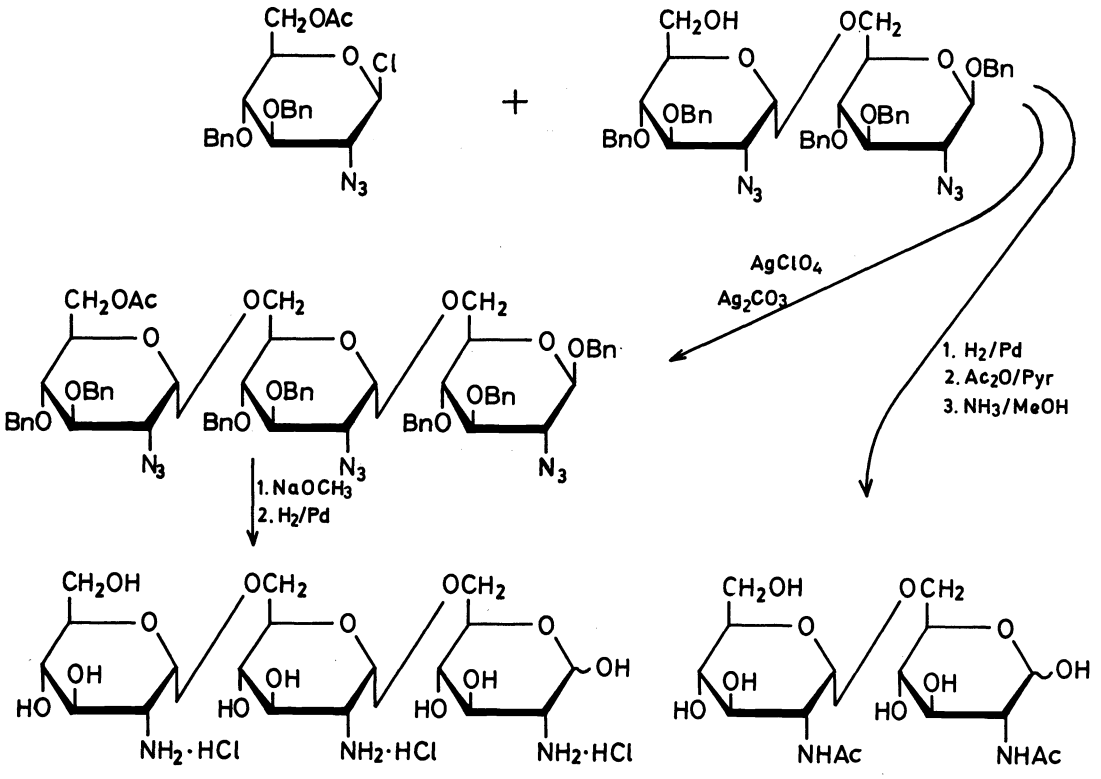


Figure 19

The eminent advantage of this disaccharide synthesis is due to the fact that, starting with a selectively protected 1,6-anhydro compound, selectively deblocked disaccharides can be constructed (Fig. 19). This is particularly important in cases where trisaccharides of special linkages have to be synthesized. E.g. in the $\alpha 1 \rightarrow 6$-linked disaccharide (Fig. 19, top) the 6-O-acetyl group can be removed easily. That means a further reaction with another ß-chloride unit towards a trisaccharide in the same yield and stereoselectivity is possible without difficulties (Ref. 36).

There are shown two examples for deblocking procedures in Fig. 19. By hydrogenation, acetylation, and hydrolysis the disaccharide derivative was transformed to the corresponding acetamido-sugar disaccharide (Ref. 36). The trihydrochloride of the amino sugar trisaccharide can be obtained by hydrogenation of the trisaccharide (Ref. 36).

The further synthesis to oligosaccharides can be continued correspondingly (Fig. 20). By reaction of the partially deblocked trisaccharide with the ß-halide a tetrasaccharide can be prepared (Ref. 36). Considering that all different glycoside linkages could be realized by this method, it is obvious that the most various possibilities open up to operate with selectively blocked units. It may be pointed out that structures and type of linkages in these oligosaccharides could be put on sound analytical basis by 270 MHz n.m.r. spectra.

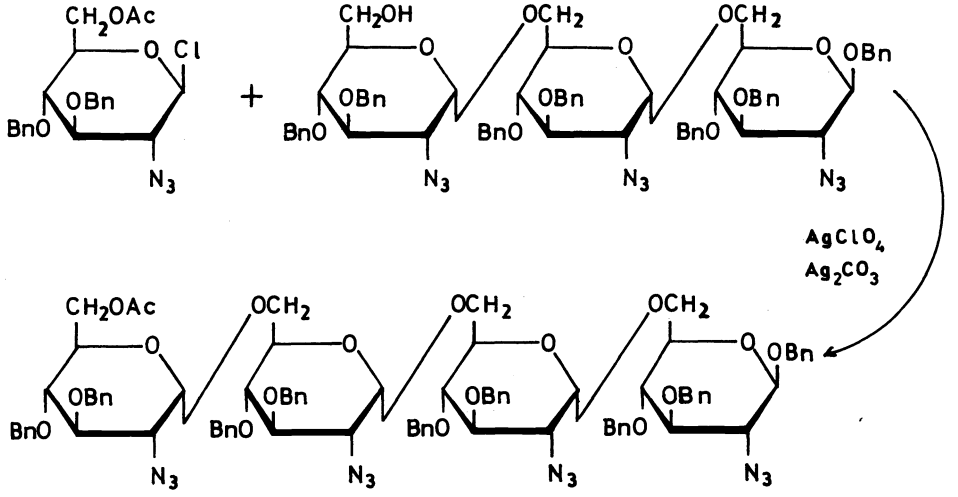


Figure 20

An example showing reactions with other saccharides is given by the synthesis of 1→1-linked disaccharides (Fig. 21) which usually involves some problems. The ß-halide reacts with these derivatives of glucose or mannose which have a free anomeric hydroxyl group to yield disaccharides with α,α-linkages (Ref. 33). The first disaccharide (Fig. 21, top) is a primary step to trehalosamine, the second the same to the corresponding manno-analog.

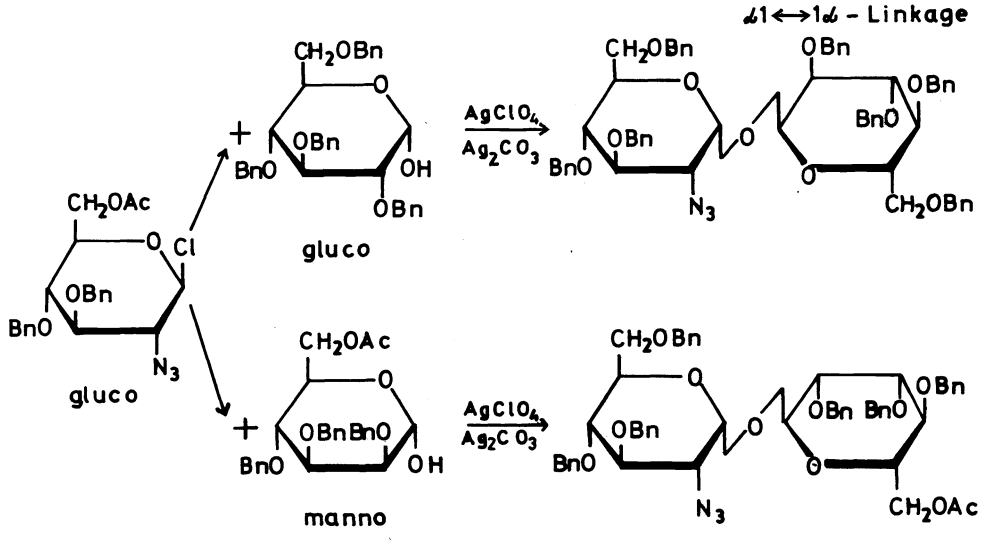


Figure 21

Let us now consider disaccharide syntheses with polyazido-sugars, which subsequently lead to the preparation of polyamino oligosaccharides (Fig. 22). Without problems the α-bromide of 2,4-diazido-glucose can be inverted to its ß-chloride (Fig. 22, top). Accordingly, this ß-chloride can be used for the synthesis of disaccharides under the same conditions as shown before. As depicted in Fig. 22, a 1→3-linked disaccharide is obtained in 70 % yield, 90 % of which is the α-anomer (Ref. 33). Following acetolysis of this derivative the disaccharide halide can be prepared which awaits further reactions.

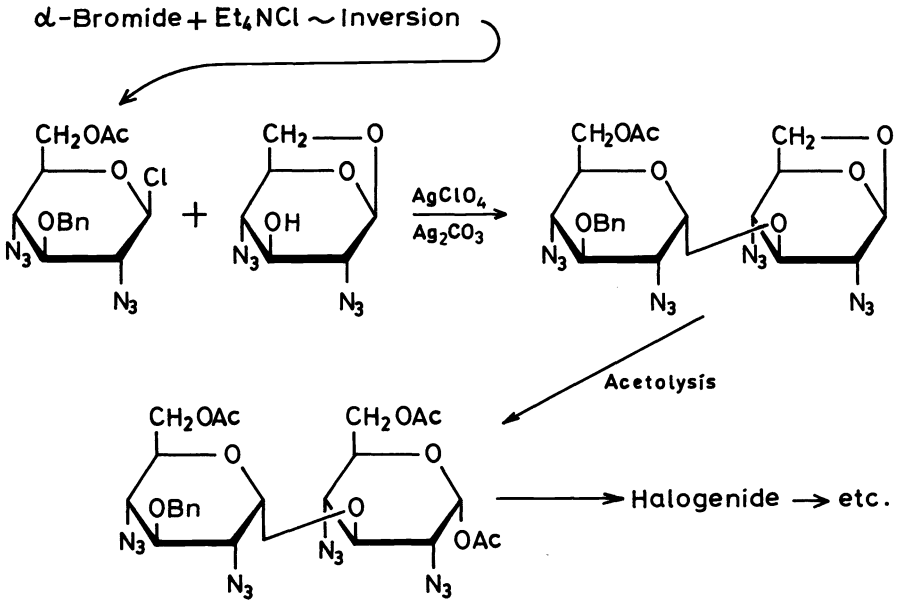


Figure 22

Similarly the α-bromide of 2,6-diazido-glucose can be inverted to the ß-glycosyl chloride (Fig. 23). The disaccharide synthesis with this second saccharide having a free hydroxyl group at C-3 gives the α1→3-linked compound which can be transformed as shown before (Ref. 33).

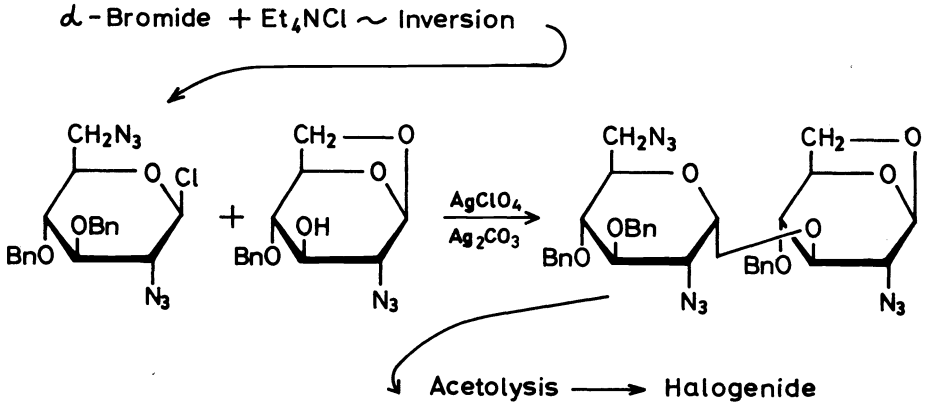


Figure 23

Most of the reactions discussed above have been performed using 2-azido-glucose derivatives which consequently lead to glycosides of glucosamine. However, in many glycoproteines and related compounds galactosamine predominates. This leads to the question whether the same procedure could be applied to galactosamine. A solution to this problem is even more important, because Lemieux's "nitrosoglycal procedure" meets with difficulties in the case of galacto derivatives (Ref. 21). The hydrogenation of the intermediate oximino-disaccharide predominantly yields the talo- and not the wanted galacto configuration.

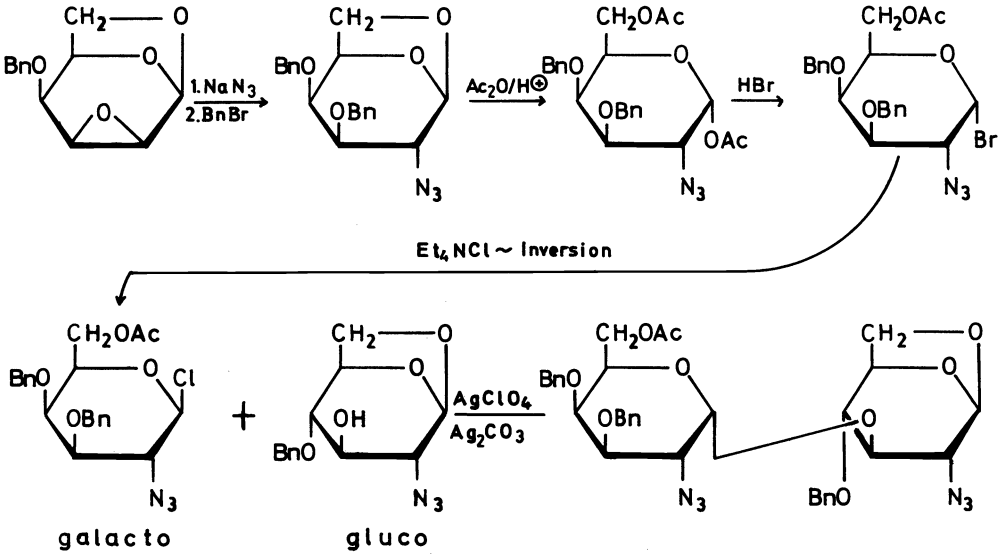


Figure 24

Application of the "azid procedure" needs a new synthesis of 2-azido-galactose, and thus galactosamine. As shown in Fig. 24, the preparation of 2-azido-galactose can be performed in the approved manner by opening the 1,6-2,3-dianhydro-talose with sodium azide (Ref. 37). By acetolysis the diacetate is obtained, which easily forms the wanted α-glycosyl bromide. Reaction with tetraethylammonium chloride leads to inversion to the ß-chloride, which can be used for disaccharide syntheses directly. Fig. 24 shows the preparation of a 1→3-linked disaccharide, which can be obtained in 70 % yield with 90 % of the α-linked isomer (Ref. 37). This reaction demonstrates a novel and easy access to α-glycosides of galactosamine.

I hope I could demonstrate a new effective α-glycoside synthesis in the field of amino sugars. The necessity for the development of multivalent useful units for oligosaccharides should be obvious. These together with an adequate application of protecting group chemistry will lead to selective oligosaccharide syntheses. At present we are engaged in further application of this method, and projects towards the synthesis of blood group substances and bacteria polysaccharides are proceeding in a promising way. On this subject I would like to report later on.

REFERENCES

1. H. Paulsen, V. Sinnwell and P. Stadler, Chem. Ber. 105, 1978-1988 (1972).
2. H. Paulsen and H. Redlich, Chem. Ber. 107, 2992-3012 (1974).
3. H. Paulsen, B. Sumfleth and H. Redlich, Chem. Ber. 109, 1362-1368 (1976).
4. H. Paulsen and V. Sinnwell, Angew. Chem. 88, 476-477 (1976); Angew. Chem. Int. Ed. Engl. 15, 438-439 (1976).
5. H. Redlich, H.J. Neumann and H. Paulsen, unpublished results.
6. D.H.R. Barton and S.W. McCombie, J.C.S. Perkin I 1975, 1574-1585.
7. H. Paulsen, W. Koebernick and H. Koebernick, Tetrahedron Lett. 1976, 2297-2300.
8. H. Paulsen and W. Koebernick, Carbohyd. Res. in press.
9. J.L. Herrmann, J.E. Richman and R.H. Schlessinger, Tetrahedron Lett. 1973, 2599-2606, 3267-3278.
10. H. Paulsen and W. Koebernick, Chem. Ber. in press.
11. M. Asai, Chem. Pharm. Bull. 18, 1699-1705, 1706-1712, 1713-1719, 1720-1723 (1970).
12. J.O. Pezzanite, J. Clardy, P.-Y. Lau, G. Wood, D.L. Walker and B. Fraser-Reid, J. Amer. Chem. Soc. 97, 6250-6251 (1975); D.L. Walker and B. Fraser-Reid, J. Amer-Chem. Soc. 97, 6251-6253 (1975).
13. H. Paulsen, K. Roden, V. Sinnwell and W. Koebernick, Angew. Chem. 88, 477 (1976); Angew. Chem. Int. Ed. Engl. 15, 439-440 (1976).
14. H. Paulsen, K. Roden, V. Sinnwell and W. Koebernick, Chem. Ber. in press.
15. H. Paulsen, P. Stadler and F. Tödter, Chem. Ber. in press.
16. H. Paulsen, P. Stadler, A. Banaszek and F. Tödter, Chem. Ber. in press.
17. B. Kniep and H. Grisebach, FEBS Letters 65, 44-47 (1976).
18. H. Paulsen, F. Tödter, A. Banaszek and P. Stadler, Chem. Ber. in press.
19. Y. Nishimura, T. Tsuchiya and S. Umezawa, Bull. Chem. Soc. Jap. 43, 2960-2965 (1970).
20. B. Helferich and J. Zirner, Chem. Ber. 95, 2604-2611 (1962).
21. R.U. Lemieux, K.B. Hendriks, R.V. Stick and K. James, J. Amer. Chem. Soc. 97, 4056-4062 (1975).
22. T. Ishikawa and H.G. Fletcher Jr., J. Org. Chem. 34, 563-571 (1969).
23. R.U. Lemieux and H. Driguez, J. Amer. Chem. Soc. 97, 4069-4075 (1975).
24. H.M. Flowers, Carbohyd. Res. 18, 211-218 (1971).
25. M.L. Wolfrom and D.R. Lineback, Methods in Carbohydrate Chemistry 2, 341 (1963).
26. K. Igarashi, J. Irisawa and T. Honma, Carbohydr. Res. 39, 341-349 (1975).
27. B. Helferich, W.M. Müller and S. Karbach, Liebigs Ann. Chem. 1974, 1514-1521.
28. H. Paulsen and H. Böttcher, unpublished results.
29. R.U. Lemieux, K. James and T.L. Nagabhushan, Can. J. Chem. 51, 42-47, 48-52 (1973).
30. H. Paulsen, P. Stadler and F. Tödter, Chem. Ber. in press.
31. Y. Ali, A.C. Richardson, C.F. Gibbs and L. Hough, Carbohyd. Res. 7, 255-271 (1968).
32. H. Paulsen, H. Koebernick, W. Stenzel and P. Köll, Tetrahedron Lett. 1975, 1493-1496.
33. H. Paulsen, O. Lockhoff, B. Schröder, B. Sumfleth and W. Stenzel, Tetrahedron Lett. 1976, 2301-2304.
34. H. Paulsen and H. Koebernick, Chem. Ber. 109, 104-111 (1976).
35. H. Paulsen and W. Stenzel, Angew. Chem. 87, 547-548 (1975); Angew. Chem. Int. Ed. Engl. 14, 558-559 (1975).
36. H. Paulsen and W. Stenzel, unpublished results.
37. H. Paulsen, Č. Kolář and W. Stenzel, Angew. Chem. 88, 478 (1976); Angew. Chem. Int. Ed. Engl. 15, 440-441 (1976).