Pure & Appl. Chem., Vol. 61, No. 7, pp. 1217–1234 1989.
Printed in Great Britain.

Recent synthetic studies in nitrogen-containing and deoxygenated sugars

Hans H. Baer

Department of Chemistry, University of Ottawa, Ottawa, Ont., K1N9B4, Canada

Abstract - Selected methodological aspects of synthesis and structural modification of monosaccharides, aminocyclitols, and trehalose-type disaccharides are presented. The survey is divided into sections concerning the use of palladium-mediated synthetic reactions, the application of iron-carbonyl reagents, deoxygenation and other reductive processes with boron-containing reagents, amination of unsaturated carbohydrates, the use of carbohydrate trifluoromethanesulfonates, and new chemistry of nitro sugars.

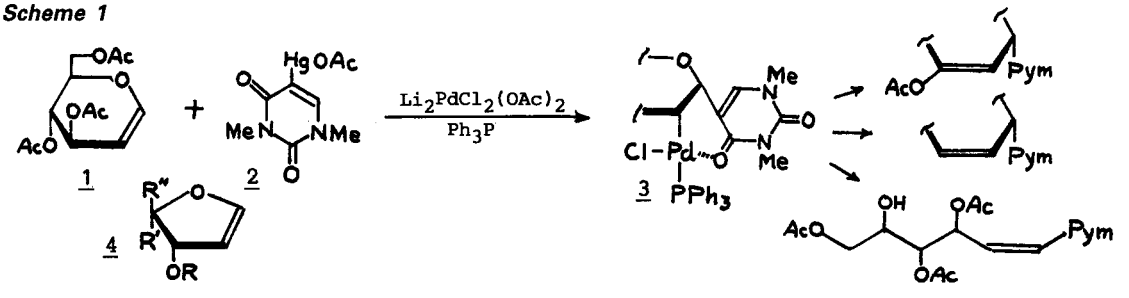
INTRODUCTION

The current development of general organic and medicinal chemistry is deriving much benefit from the expertise of carbohydrate specialists, be it in elucidation and synthesis of complex, carbohydrate-containing natural products of biological or medical significance, or be it through the design of sugar-based synthons that provide novel modes of synthetic access to chiral organic molecules. Conversely, carbohydrate chemistry has in recent times been greatly stimulated by the advent of many elegant new procedures and efficient reagents primarily developed in sister branches of organic chemistry. However, the successful application of a given, new preparative method to synthesis or functional modification of such polyfunctional, often sensitive, and stereochemically multifaceted molecules as carbohydrates in general and oligosaccharides in particular is usually not a trivial matter. Much patient experimentation is normally required to establish suitable reaction conditions appropriate to the peculiarities of sugar substrates; to check compatibility of a new reagent that is to effect a desired transformation, with other functionalities present in the molecule; to determine influences of configuration and conformation on the course of reaction; and to tackle problems of product separation and purification, which in carbohydrates may differ considerably from those encountered elsewhere. Such challenges have been and are being met successfully in countless cases, and as a result, modern synthetic carbohydrate chemistry has become a most exciting and diversified field. Some examples of recent methodological progress will be given in this paper.

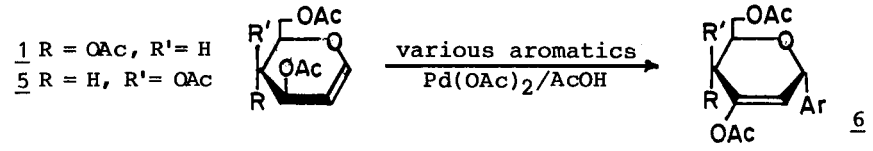
1 PALLADIUM-MEDIATED SYNTHESES

One area from which carbohydrate synthesis has received much fertilization in recent years is organometallic chemistry, particularly the field of transition metal-assisted reactions. Beginning with the early 1980's the potential of palladium-catalyzed transformations in carbohydrates (other than the long-established use of that metal in catalytic hydrogenation) was simultaneously and independently recognized in at least four laboratories (refs. 1-4). Much of the work was centered on the regio- and stereo-controlled formation of C-glycosidic and C-nucleosidic linkages, with unsaturated sugar derivatives as substrates. Thus, Daves and coworkers (ref. 2) found that a heterocyclic (or aryl) organopalladium species, formed by transmetallation from the corresponding organomercurial (e.g., 2), underwent regio- and stereospecific cis addition to 3,4,6-tri-O-acetyl-D-glucal (1), to give a single, isolable adduct(3) whose controlled depalladation led to a variety of(pyranosidic and open-chain) C-nucleosides and aryl C-glycosides. Use of furanoid glycals (4) gave analogous, furanosidic C-nucleosides wherein the anomeric configuration was specifically determined by the relative steric bulks of substituents on the two respective faces of the molecules 4 (Scheme 1).

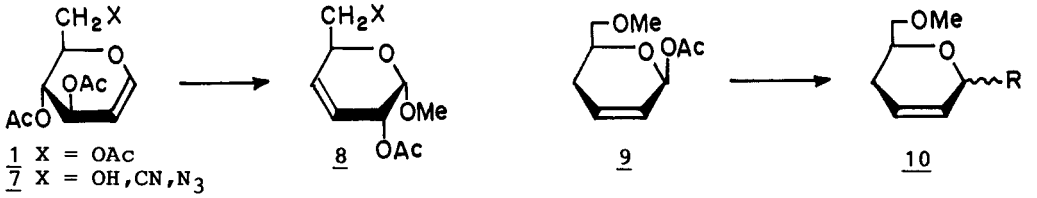
Scheme 1



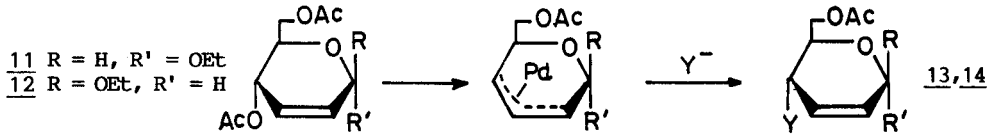
Arylpalladium intermediates, to be added across enol ether double bonds,need not be generated from mercurials but can be formed in situ from aromatic compounds directly, by the action of palladium acetate in the presence of acetic acid. This approach was used by Czernecki and coworkers (ref. 3), who obtained good yields of aryl C-glycosides (6) with benzene and a range of its methoxy derivatives, both from glucal 1 and isomeric galactal 5. These studies have been extended recently to include reactions of several other organometallic compounds with halo sugars, 1,2-anhydro sugars, lactones, and 1-ene-3-ones (both pyranoid and furanoid), affording C-glycosides in high yields.



An interesting methoxypalladation coupled with an allylic rearrangement has been described by Dunkerton and her coworkers (ref. 4a). Triacetylglucal 1 and derivatives (7) having the AcO-6 group replaced by OH, CN, or N_3 (but not by H or NHAc) reacted with methanol and palladium chloride, followed by sodium cyanoborohydride, to give methyl 2-O-acetyl-3,4-dideoxy-3-enopyranosides (8). C-Glycosides of type 10 were obtained from 2-enose 1-acetates of type 9 as well as from analogous 1-thio acetates by reaction with carbanions in presence of tetrakis(triphenylphosphine)palladium(0); interestingly, stabilized carbanions (e.g., acetamidomalonates) reacted with net retention of configuration at C-1, whereas nonstabilized carbanions (arylzinc and vinylzinc chlorides) gave net inversion (ref. 4b-d).



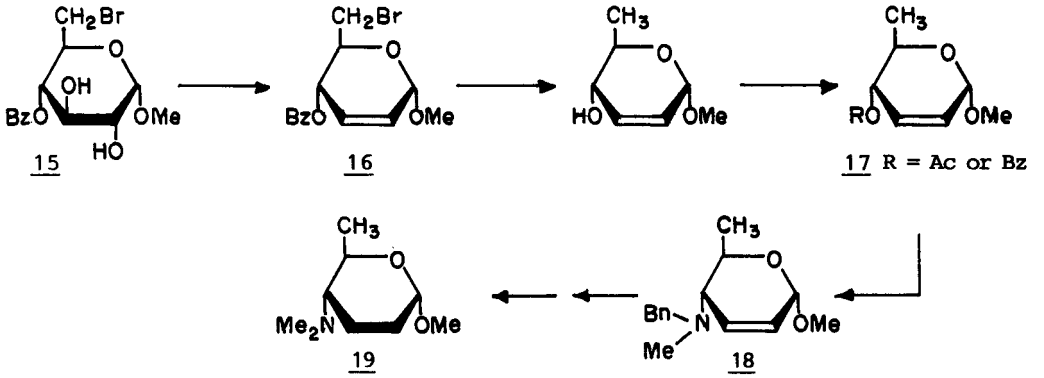
The first reports on allylic substitution in unsaturated sugar acetates, catalyzed by tetrakis(triphenylphosphine)palladium(0), were made by Baer and Hanna (ref. 1a,b). Originally described in 1970 (ref. 5) and then most thoroughly investigated and fruitfully applied by Trost (ref. 6), the method has proved efficient for the preparation of pyranosides aminated or alkylated in position 4. Thus, the anomeric ethyl 2-enopyranoside 4,6-diacetates 11 and 12, both of which are separately accessible without problems from triacetylglucal 1, each reacted with the Pd° complex present in catalytic quantity, under departure of acetate ion from C-4 and formation of a palladium π-allyl complex on the β face of the molecule. Displacement of the metal by a nucleophile (amine or carbanion) entering from the opposite direction gave substitution products with net retention of configuration. Regioselectivity was very high in favor of 4-substitution, presumably owing to a polarizing effect of the anomeric center on the π-allyl-Pd complex. Thus, diethylamine, piperidine, cyclohexylmethylamine, benzylmethylamine, sodio dimethyl and diethyl malonates, and sodio methyl (phenylsulfonyl)acetate gave products 13 and 14 exclusively or in strong preponderance, with isolated yields in the 60-90% range. The primary amine, benzylamine, also gave 13 (Y = NHBn) but in lower yield due to complicating, partial reaction with the AcO-6 group.



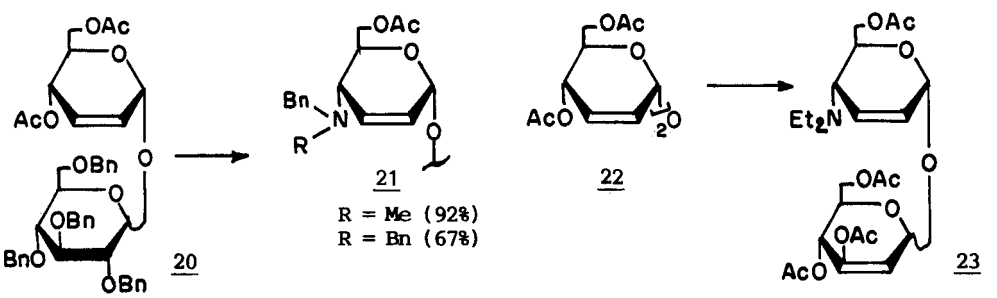
Dibenzylamine provided a curious exception in that it produced, with 11, a 3:7 mixture of the expected 13 (Y = NBn_2) and the α-D-threo-2-dibenzylamine-3-enoside isomer; with 12 it reacted even more abnormally, giving an aminated product of glycoside ring opening.

Practical use was made of the allylic amination in an efficient synthesis (ref. 1c) of the amino sugar D-forosamine, a constituent of the spiramycin group of macrolide antibiotics. The key steps preparatory to amination involved synthesis of the 6-bromo-2-enoside 16 from the known D-glucose derivative 15 by action of triiodoimidazole according to Garegg and Samuelsson (ref. 7), reductive debromination of 16 (accompanied by debenzoylation) with lithium triethylborohydride, and reacylation of the allylic alcohol (Scheme 2). The acetate 17 (or the corresponding benzoate) was subjected to palladium-catalyzed substitution using benzylmethylamine, to furnish 18 in 80% yield. Simultaneous N-debenzylation and alkene saturation by catalytic hydrogenation, followed by N-methylation, then provided methyl α-D-forosaminide (19).

Scheme 2



Limited studies have been undertaken regarding possible applications of the method to amino disaccharide synthesis, with focus on trehalose-type compounds. Several aminated analogs of α,α-trehalose (α-D-glucopyranosyl α-D-glucopyranoside), including the 4-amino-4-deoxy derivative, occur in Nature as fungal metabolites showing modest antibiotic activity, and the chemical synthesis of these natural products and of configurational variants is therefore of some interest. Whereas the blocked, monounsaturated trehalose analog **20** was readily aminated at C-4 by benzylmethylamine or dibenzylamine to give **21**, reactions of the symmetrical diene **22** with these amines were attended by problems which have not yet been overcome. With diethylamine, **22** gave the monosubstitution product **23** only, in modest yield. Clearly, further study is required to render the method useful in the disaccharide field (Baer, Hanna, and Gan, unpublished results).

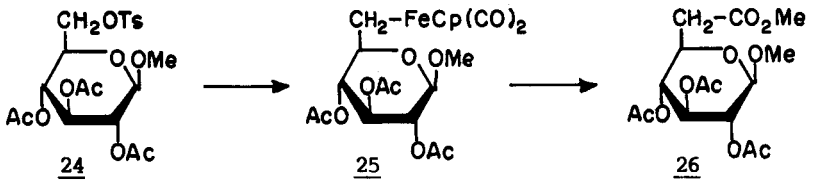


2 APPLICATION OF IRONCARBONYL REAGENTS

Rosenthal (ref. 9) was the first to realize the great potential of transition metal-carbonyl complexes as synthetic aids of considerable promise in carbohydrate chemistry. He and his coworkers studied extensively the use of cobalt carbonyls in the "oxo reaction", i.e., the hydroformylation or hydro(hydroxymethyl)ation of alkenes and oxiranes as applied to sugar derivatives. Among the numerous transformations elaborated were chain-lengthening processes at the nonreducing terminal of aldose derivatives (ref. 10). However, the processes needed to be performed in an autoclave under high pressure and required elevated temperatures or extended reaction times. These disadvantages may be circumvented by use of more-reactive ironcarbonyl reagents. Thus, Baer and Hanna (ref. 11) effected chain elongation at C-6 of aldohexoses by means of sodium dicarbonyl-η^5-cyclopentadienyliron (NaFp) in tetrahydrofuran solution under mild conditions. The Fp^- anion, an extremely powerful nucleophile (ref. 12), displaces halide or p-toluenesulfonate ion at room temperature from a suitable substrate, to form a stable, σ-bonded alkyliron complex; subsequent oxidation by bromine (or iodine, or cupric or ferric salts) brings about carbonyl insertion to give a cationic acyliron complex, which is rapidly attacked by added methanol to produce a carboxylic ester (equation 1; ref. 13).

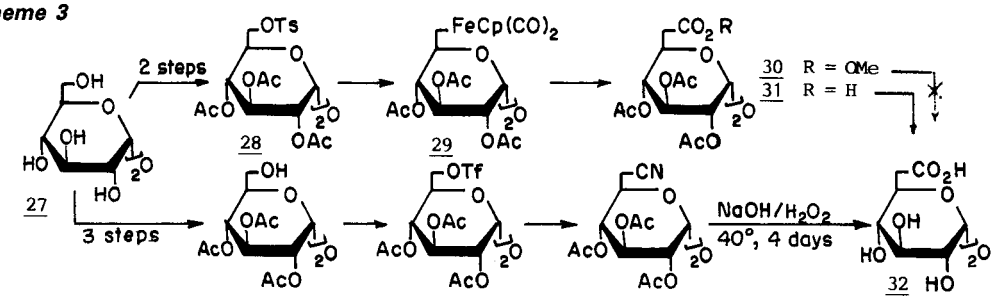
$$RX + Na^+[FeCp(CO)_2]^- \longrightarrow R\text{-}FeCp(CO)_2 + NaX \xrightarrow{-e^-} ([R\text{-}FeCp(CO)_2]^+) \rightarrow [R\text{-}CO\text{-}FeCpCO]^+ \rightarrow RCO_2Me \quad (1)$$

With methyl 2,3,4-tri-O-acetyl-6-O-tosyl-β-D-glucopyranoside (**24**) as the sugar substrate, the method gave an 80% yield of the 6-deoxyheptosiduronic ester **26**; the iron intermediate **25** could be isolated and characterized analytically, although isolation was not necessary. Several methyl 6-bromo-6-deoxy-α- and -β-D- glucopyranosides (and a 6-deoxy-6-iodo-α-D-mannopyranoside) carrying O-acetyl, O-benzoyl, O-methyl, or free hydroxyl groups on the sugar ring gave the corresponding methyl (methyl 6-deoxyheptopyranosid)uronates in yields of 70-90% (ref. 11).

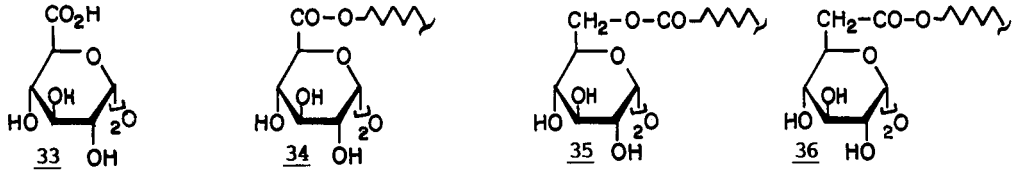


The method has also been employed for homologation of α,α-trehalose (27, Scheme 3). From its hexa-O-acetyl 6,6'-ditosylate 28 was obtained via 29 the bis-6-deoxyheptosiduronic dimethyl ester 30. In connection with a project to be mentioned below, the corresponding free diacid 32 was required, but attempts at saponification of 30 under a variety of mild alkaline conditions failed, evidently because of an extreme proneness of such a β-alkoxy ester to suffer degradation of the disaccharidic structure through β-elimination of ring oxygen. However, substitution of water for methanol in the oxidative carbonyl insertion – solvolysis reaction of 29 furnished the acetylated dicarboxylic acid 31, which was saponified to 32 without any problem. An alternative synthesis of 32 from 27 was achieved by standard transformations (see Scheme 3), but comparison of the two routes indicates the ironcarbonyl approach to be shorter and more elegant (Baer, Breton, and Shen; unpublished work).

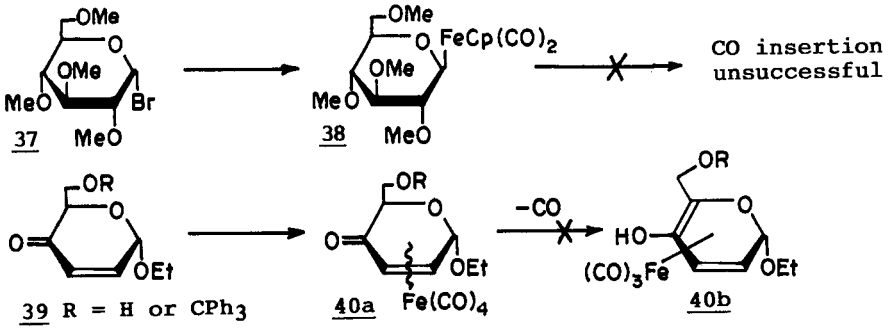
Scheme 3



The previously unknown bis-deoxyheptosiduronic acid 32 represents a homolog of "trehalosuronic acid" 33, obtained (ref. 14) by catalytic oxidation of 27. The latter acid has been esterified with long-chain lipid alcohols to provide molecules dubbed "mirror pseudo cord factors" (34) because of their reverse regiochemical arrangement of the ester bonds compared to those present in the natural, mycobacterial cord factor (α,α-trehalose 6,6'-dimycolate, 35); such structures may serve as useful probes in the study of mycobacterial biochemistry (ref. 14). Esterification of 32 with fatty alcohols (eventually including those derivable from mycolic acid) should lead to "mirror" structures (36) that mirror the bacterial product 35 more closely than does 34. Attempts to reach these targets are in progress in this laboratory.

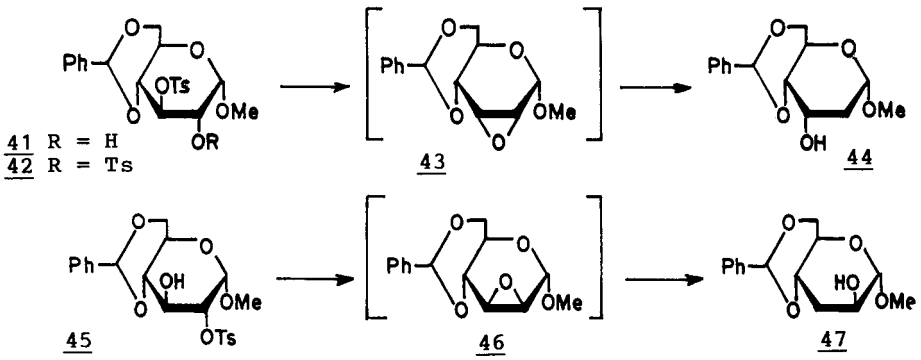


The aforementioned reagent, NaFp, reacted with per-O-methyl-α-D-glucopyranosyl bromide (37) to give a stable, crystalline glucopyranosyliron complex (38) which, however, could not be induced to undergo oxidative carbonyl insertion by use of cupric ion as the oxidant (ref. 15). Another reagent, namely diironnonacarbonyl, formed with glycosidic enones (39) separable mixtures of diastereomeric complexes (40a); unfortunately it was not possible to prepare dienol complexes such as 40b, which might have been amenable to Friedel-Crafts acylation at C-2 (ref. 16).



3 SELECTED REACTIONS WITH BORON-CONTAINING REDUCTANTS

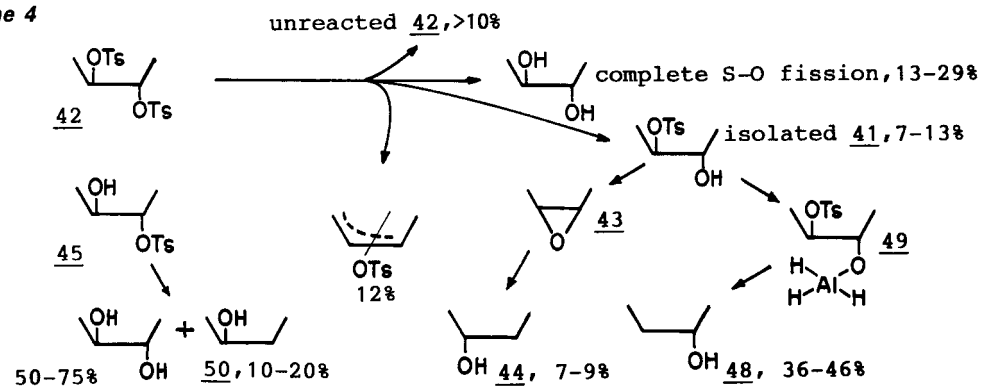
In recent years, lithium triethylborohydride (Super Hydride, LTBH; see ref. 17) has enjoyed growing popularity among organic chemists as an extremely efficient reductant, acting similar to, but more powerfully than, the familiar lithium aluminum hydride (LAH). The latter is well-known to act on sugar sulfonic esters to cause either C-O fission (desulfonyloxylation) or S-O fission (desulfonylation), normally depending on whether the sulfonate is a primary or a secondary one, respectively. (Exceptions to this rule are known, however.) A first report (ref. 18) on the use of LTBH in carbohydrate chemistry seemed to suggest an analogous behavior of that reagent towards certain sugar tosylates: Whereas a primary tosylate was efficiently desulfonyloxylated, deoxygenation in two examples of secondary ones did not succeed. However, we subsequently found in detailed investigations (ref. 19) that secondary tosylates of glycosides can be smoothly desulfonyloxylated with LTBH, to give excellent yields of deoxyglycosides, provided certain structural prerequisites are fulfilled. Thus, methyl 4,6-O-benzylidene-3-O-tosyl-α-D-glucopyranoside (**41**) was converted by excess LTBH in refluxing tetrahydrofuran into the 2-deoxy-α-D-*ribo*-hexopyranoside **44**, isolated in 96% yield after a reaction time of 30 min. The reaction was shown to proceed via intermediary epoxide **43**, which was isolable when the process was interrupted before completion. The 2,3-ditosylate **42** also furnished **44**, evidently by way of initial S-O fission at position 2. Only traces of the parent 2,3-diol resulting from twofold S-O cleavage were formed. Similarly, the 2-monotosylate **45** gave, via isolable epoxide intermediate **46**, the 3-deoxy-α-D-*arabino*-hexopyranoside **47** in 90% yield, accompanied by a somewhat increased proportion (5%) of diol that reflected a greater susceptibility, to attack at sulfur, for the 2-O-tosyl group than the 3-O-tosyl group.



The β-anomers of **41**, **42**, and **45** were deoxygenated in the same way, giving similarly high yields of 2- and 3-deoxyglycosides, except that their epoxy intermediates (the anomers of **43** and **46**) underwent reductive ring opening less regioselectively, generating mixtures of products from normal, diaxial opening and products of anti-Fürst-Plattner opening. The intermediacy of epoxides in all of these facile deoxygenations was supported, apart from actual isolation as mentioned, by the fact that 3-O-methyl-2-O-tosyl and 2-O-methyl-3-O-tosyl analogs suffered, respectively, exclusive S-O fission (at O-2) or very slow and incomplete deoxygenation (at C-3) by direct S_N2 displacement (ref. 19).

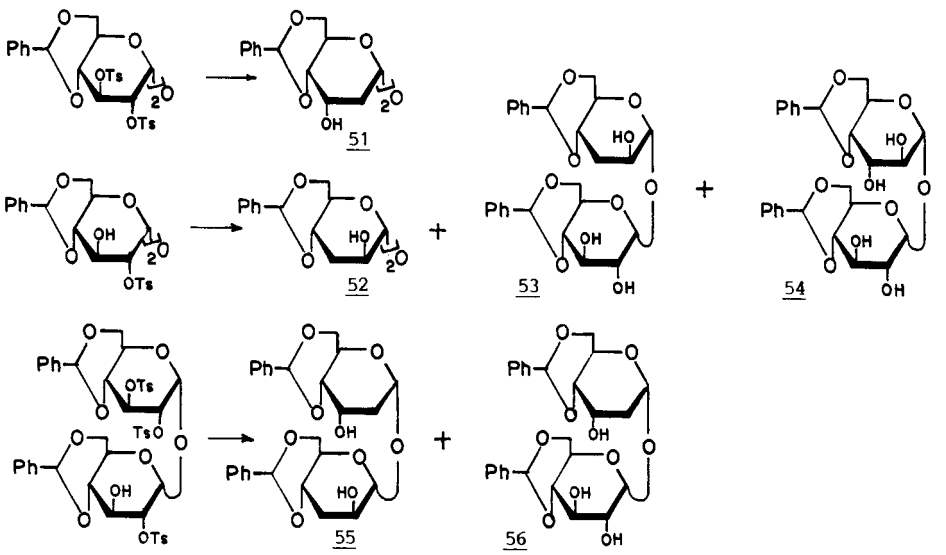
It is interesting to compare the action of LTBH on **41**, **42**, and **45** just outlined with that of LAH in dioxane at 100°. The results of previous studies (ref. 20), largely confirmed by reinvestigations of our own (ref. 19), are surveyed in Scheme 4. The reaction of LAH is rather sluggish, and characterized by a great deal of S-O fission, especially in **45**. Reductive desulfonyloxylation, to the extent that it does take place, proceeds from **41** (or from **42** via **41**) only in small measure through the epoxide **43** to give 2-deoxyglycoside **44** (7-9%); the chief product of deoxygenation (36-46%) is the 3-deoxy-α-D-*ribo*-hexopyranoside **48** (not formed with LTBH), which evidently arises by internal hydride transfer in intermediary hydridoaluminate **49**. The same mechanism operating in **45** accounts for the production (in low yield because of predominant S-O fission) of the 2-deoxy-D-*arabino* isomer **50**, likewise not formed with LTBH.

Scheme 4



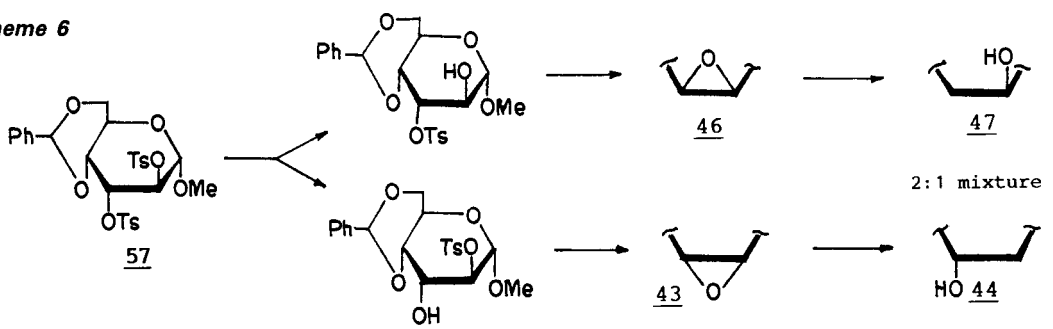
Application of the LTBH method to various tosylates of 4,6;4',6'-di-O-benzylidene-α,α-trehalose proceeded in full analogy to the application in monosaccharidic α-glycosides just discussed, albeit with lower yields (ref. 21). As depicted in Scheme 5, it permitted the preparation of the previously known, symmetrical dideoxy disaccharides 51 and 52, and of the hitherto unknown, unsymmetrical, mono- and di-deoxy sugars 53, 55, and 56. The new, unsymmetrical analog of trehalose having the α-D-altro,α-D-gluco configuration (54) arose as a minor product from an incomplete reduction, by way of hydrolysis of an intermediary epoxide. The formation of 53, 54, and 56 again points to a relatively easy S-O fission taking place in the 2-tosyloxy group.

Scheme 5



Preferred S-O fission at position 2 was also evident in the behavior of the α-D-altroside 2,3-ditosylate 57, although this compound was desulfonylated to a considerable extent at O-3, too, in contrast to its gluco isomer 42. As a result, the action of LTBH (1h at 66°) produced a 2:1 mixture of 47 and 44, isolated in 94% yield (Scheme 6; ref. 22). For comparison, reaction of LAH at 100° was incomplete after 18h and formed 47 and 44 in a 5:1 ratio (72%), together with 11% of parent 2,3-diol, which indicated an increased tendency for S-O fission in the latter reagent (ref. 23).

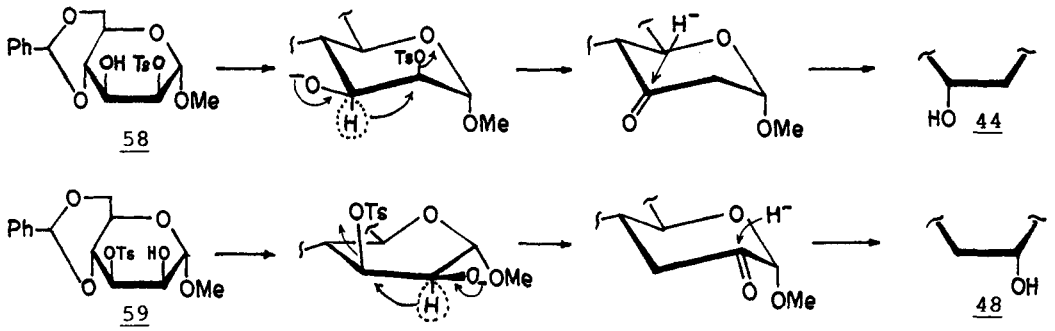
Scheme 6



In the α-D-manno isomers 58 and 59 (Scheme 7) the 2,3-functionalities are cis oriented, which forecloses the formation of epoxides and their successor products by basic reagents. Nevertheless, both isomers reacted readily (0.5-1.5h) with LTBH at 66°, giving good yields of deoxyglycosides. From the 2-tosylate 58 was obtained the 2-deoxyglycoside 44, whereas the 3-tosylate 59 gave the 3-deoxyglycoside 48 in a yield (77%) higher than that obtainable by the action of LAH upon 42 (cf. Scheme 4). These results (ref. 22) are explained by the occurrence of desulfonyloxylation via hydride shifts as shown in Scheme 7. Similar shifts were encountered in reactions of ribonucleoside monotosylates with LTBH (ref. 24).

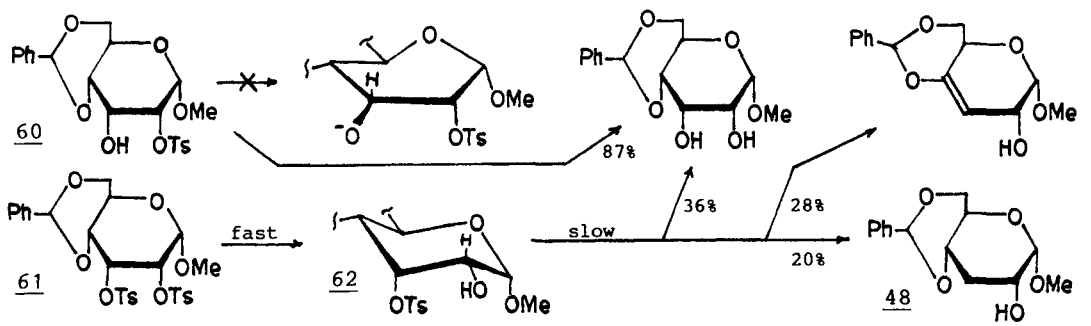
In contrast with the foregoing cases, the 2-tosylate 60 of α-D-allo configuration suffered exclusive O-desulfonylation to produce 2,3-diol, isolated in 87% yield. Apparently the twist conformation conducive to a 3→2 hydride shift is difficult to attain for this molecule (see Scheme 8). Rather more unexpected was the behavior of the 3-O-tosyl regioisomer 62. Rapidly engendered from the 2,3-ditosylate 61 by LTBH, its further reaction proved unusually slow, even though a facile 2→3 hydride shift might have been predicted to occur. Large proportions of diol and of the product of 3,4-elimination of p-toluenesulfonic acid were formed, and the 20% of (expected) 3-deoxyglycoside 48 that did arise in a 24-h reaction owed its formation

Scheme 7



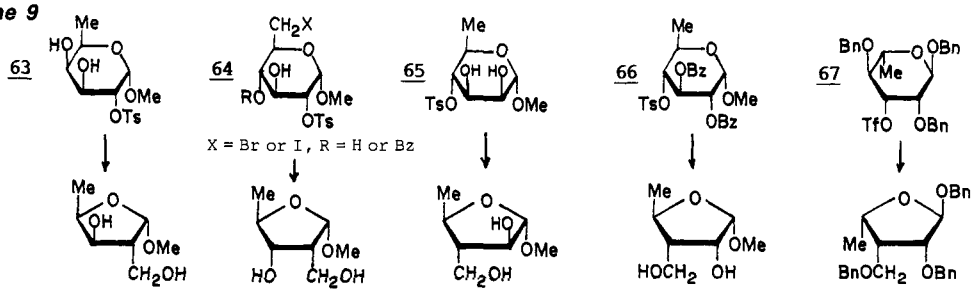
only in part by hydride shift; part of it arose by direct S_N2 displacement. A ratio of about 7:3 for the two parallel modes of formation of **48** was indicated by the distribution of incorporated deuterium when lithium triethylborodeuteride was used (ref. 22).

Scheme 8



In all of the LTBH-induced desulfonyloxylations discussed thus far, the pyranoside ring was conformationally constrained by a trans-fused 4,6-acetal ring. When the unconstrained hexopyranosides **63-66** were subjected to the same reaction conditions, we were surprised to find ring contraction occurring as an exclusive or predominant event, to give the deoxygenated, C-hydroxymethyl-branched pentofuranosides shown in Scheme 9. This was remarkable because each of the starting 2- or 4-tosylates possessed a free (or potentially free) hydroxyl group trans vicinally situated to the ester group and might therefore have been anticipated to yield deoxyhexopyranosides by way of intermediary epoxides (ref. 25). Furthermore, methyl 4,6-O-benzylidene-α-D-galactopyranoside 2,3-ditosylate, which differs from its gluco isomer **42** by having a conformationally more flexible structure with cis-fused acetal ring, underwent both modes of reaction. After initial mono-O-desulfonylation with little regiochemical discrimination, the resultant 2-monotosylate followed the epoxide path to produce a 3-deoxy-α-D-lyxo-hexopyranoside whilst the resultant 3-monotosylate incurred ring contraction (ref. 25).

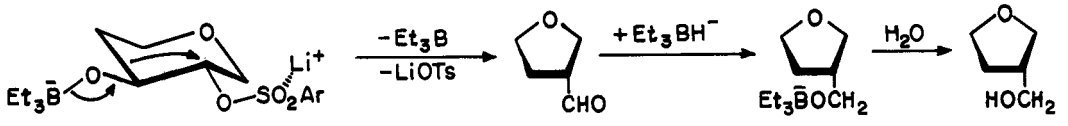
Scheme 9



The mechanism of LTBH-induced ring contraction is not yet fully understood. A formally related precedent concerns the fully benzylated hexopyranoside 3-triflate **67**, which reacted with LTBH as shown in Scheme 9 (ref. 26). However, the tosylates **63-66** all contain a free or potentially free adjacent hydroxyl group as already pointed out, and stable blockage was found to prevent rearrangement (ref. 27). Epoxides initially engendered might have been postulated as intermediates in the ring contraction, for epoxide — carbonyl rearrangements (including instances with alkyl migration) are known and are, relevantly, catalyzed by lithium salts (ref. 28). However, this possibility was dismissed by the demonstration (ref. 29) that at least two such epoxides (that were prepared independently) were reduced by LTBH in "normal" fashion, without any indication of rearrangement. It may therefore reasonably be assumed that alkoxytriethylboronates, which are formed instantly from alcohols with LTBH, initiate the ring contraction

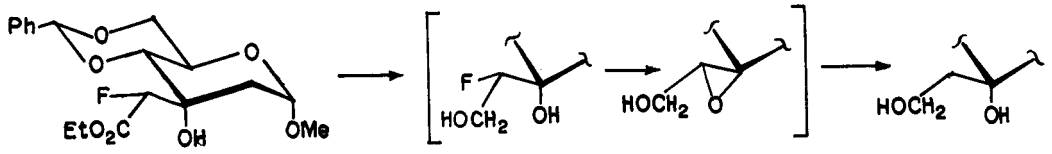
as suggested in Scheme 10. It is to be noted that lithium ion must in some way be implicated in the mechanism, presumably through its coordinating ability, for sodium triethylborohydride, or indeed LTBH in the presence of lithium-sequestering crown ether, do not induce ring contraction but cause normal deoxygenation via the epoxide path. Likewise, the alkyl groups on boron seem to be of influence, for lithium tri-s-butylborohydride (L-Selectride) also reacts without effecting ring contraction (ref. 27).

Scheme 10



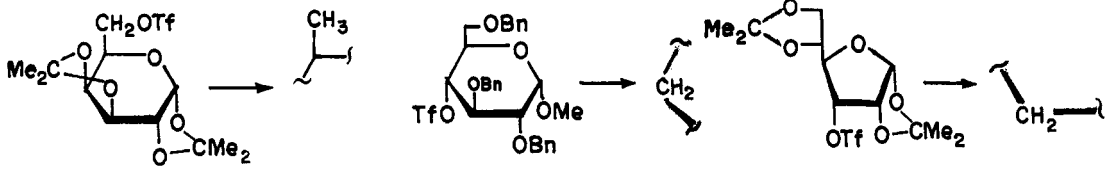
Lithium triethylborohydride is also able to effect defluorination (ref. 30). An example is given in Scheme 11.The authors assume that the ethyl ester group in the carbohydrate shown is first reduced; it is noteworthy that in the intermediary diol so produced it is the tertiary and not the primary carbinol which displaces fluoride, forming an epoxide from which the final product then emerges.

Scheme 11



The higher reactivity of trifluoromethanesulfonates, as compared to tosylates, is reflected in the fact that a number of (fully blocked) primary as well as secondary sugar triflates have been reductively desulfonyloxylated in high yield by sodium borohydride in acetonitrile solution at room temperature, although reaction times of 48-95h were required (ref. 31). Examples are presented in Scheme 12. By use of sodium borodeuteride it was demonstrated that these reactions involved S_N2 displacements, and it is recalled from preceding paragraphs that such displacement is not a facile process in tosylates, even with the much more powerful nucleophile, LTBH. Contrary to the action of LTBH on the triflate **67** (Scheme 9), sodium borohydride caused no ring contraction in those cases where structural features would have permitted it, e.g., in methyl 2,3,6-tri-O-benzyl-4-O-triflyl-α-D-glucopyranoside (Scheme 12), which is structurally related both to **66** (with respect to configuration and sulfonate position) and to **67** (with respect to benzyl ether blocking).

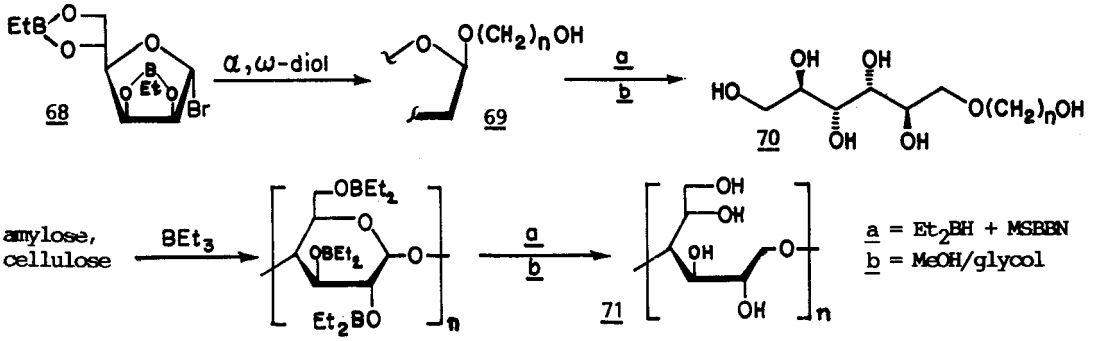
Scheme 12



Most interesting and synthetically useful investigations concerning the application of a number of other boron-containing reductants in carbohydrate chemistry have been reported by Garegg and his coworkers (refs. 32,36,38). Thus, sodium cyanoborohydride in the presence of hydrogen chloride was shown to effect reductive opening of cyclic acetals, whereby, for example, hexopyranoside 4,6-O-benzylideneacetals regioselectively afford 6-benzyl ethers in 80-95% yield (ref. 32). The process is complementary to the method extensively studied by Gorin and by Lipták and Nánási (for a review, see ref. 33), which uses LAH in the presence of aluminum chloride and generates 4-benzyl ethers from such acetals. For dioxolane-type benzylidene rings (2,3- or 3,4-fused), the regioselectivity of Garegg's method is governed by the disposition (endo or exo) of the phenyl substituent, in the same sense as pertains to the LAH method (see refs. 34,35). On the other hand, trimethylamine-borane complex in the presence of aluminum chloride was found to open and reduce 4,6-benzylidene acetals regioselectively in one or the other direction, depending upon the solvent employed (ref. 36). The procedures were also used for cleavage of 4-methoxybenzylidene acetals (ref. 37); from 4,6-acetals, cyanoborohydride preferentially produces 6-ethers in the presence of trifluoroacetic acid, but 4-ethers in the presence of trimethylsilyl chloride. Finally, sodium dicyanoborohydride or 4-methylmorpholine-borane can be employed in acid hydrolysis of glycosides to give alditols (ref. 38).

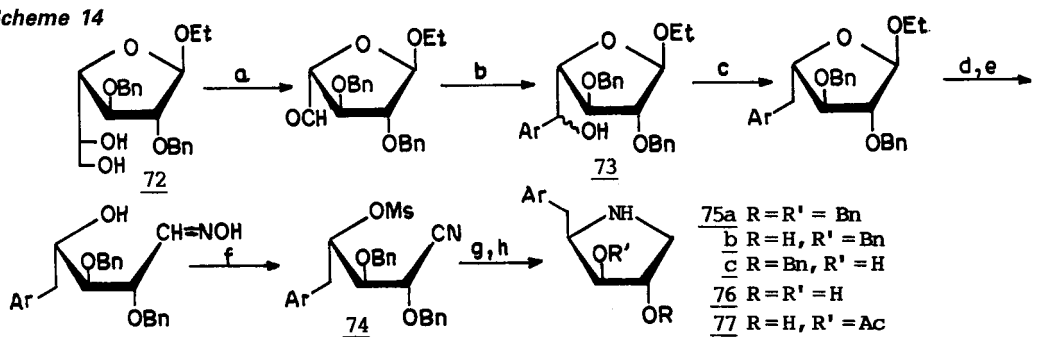
Köster and Dahlhoff (ref. 39) have elaborated an elegant method of converting glycosides into alditol 1-ethers. Thus, the ethylborinate-protected mannofuranosyl bromide **68** (Scheme 13) was glycosylated with α,ω-glycols. Treatment of the glycosides **69** with diethylborane in the presence of 9-mesyloxy-9-borabicyclo[3.3.1]nonane at 120° resulted in reductive ring opening, and subsequent deborylation with methanol and ethylene glycol gave the alditol 1-ethers **70**. Application of the method to amylose and cellulose (first protected as per-diethylboronates by action of triethylborane) furnished poly-1,4-glucitol (**71**).

Scheme 13



Borane-tetrahydrofuran complex is known to reduce nitriles to amines (ref. 40), and this was utilized in the course of a new synthesis of the antifungal antibiotic (-)-anisomycin (ref.41). The synthesis started from D-galactose which in five high-yielding steps was converted into the partially blocked furanoside 72 (ref. 42), and then proceeded as outlined in Scheme 14. Reduction of the benzylic alcohols 73 by ionic deoxygenation using triethylsilane in the presence of trifluoroacetic acid was precedented by a similar deoxygenation in a previous anisomycin synthesis, which departed from D-glucose (ref. 43). Three further steps led to the nitrile-mesylate 74 as indicated. The nitrile reacted readily with borane-tetrahydrofuran under reduction to the amine stage and concomitant ring closure by internal S_N2 displacement, to establish the heterocyclic ring system 75. It is noteworthy that the procedure entailed partial benzyl ether cleavage, for the (isolable) main product, the dibenzyl ether 75a, was accompanied in the reaction mixture by appreciable proportions of monoethers 75b and 75c. This was of little consequence in the present case, as complete debenzylation, subsequently achieved by transfer hydrogenation over palladium, was to follow in any event. The key step of ring closure (74 → 75) was also achievable with LAH, although in lower yield; the latter reagent had been employed in the reductive cyclization of a structural analog of 74, performed during an alternative synthesis of anisomycin starting from D-ribose (ref. 44). Deacetylanisomycin (76), obtained by the described route in 18-20% overall yield from readily accessible 72, can be selectively acetylated to the antibiotic (77) by an efficient procedure (ref. 45).

Scheme 14



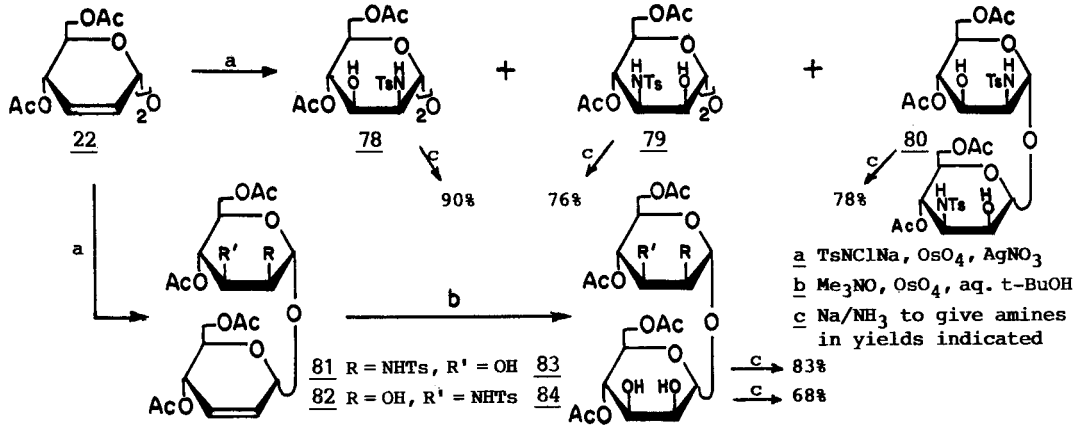
a $NaIO_4$; b p-$MeOC_6H_4MgBr$; c Et_3SiH/H^+; d H^+/H_2O; e H_2NOH; f MsCl/Py; g BH_3-THF; h Pd/HCO_2H

4 SELECTED METHODS FOR SUGAR AMINATION

Many classical, general methods for the synthesis of amino sugars exist and are widely used. They include the Fischer-Kiliani cyanohydrin reaction as applied to glycosylamines (especially in conjunction with the controlled hydrogenation of α-aminonitriles elaborated by R. Kuhn), the opening of epoxides and the replacement of sulfonic esters by nitrogen nucleophiles, and the nitroalkane methodology, which are probably the most versatile among the procedures. Intramolecular rearrangements (Amadori; Heyns) of glycosylamines, and hydrogenation of carbohydrate derivatives containing carbon-nitrogen multiple bonds (e.g, nitriles, phenylhydrazones, or oximes) have been used on many occasions (ref. 46). The reductive amination of keto derivatives by sodium cyanoborohydride and ammonium acetate mechanistically belongs to the last-mentioned category; its application to a disaccharidic diketone has recently been studied (ref. 47). Reactions of glycals with nitrosyl chloride or dinitrogen tetraoxide (ref. 48), and with sodium azide-ceric ammonium nitrate (ref. 49) have opened important avenues to 2-amino sugars. Monosaccharidic enosides have been cis-oxyaminated by osmium tetraoxide catalysis (ref. 50). The palladium-assisted amination of enosides has already been outlined in Section 1. Some recent developments in the field of sugar amination will be discussed in the paragraphs that follow. Moreover, Section 5 will, in part, bear on amino sugar synthesis from a different perspective.

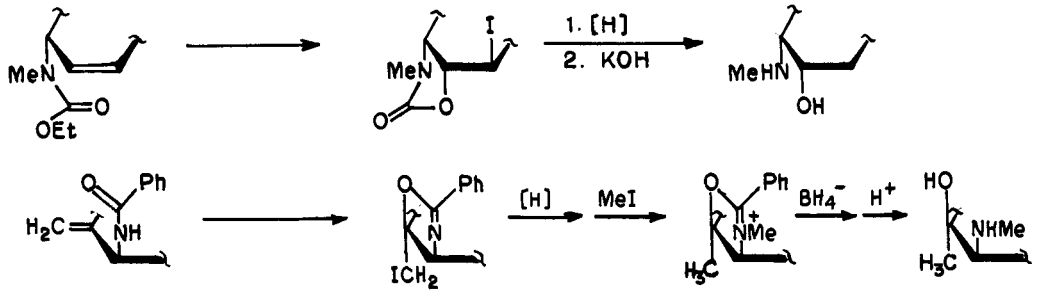
The procedures of osmylation for introduction of cis-amino alcohol and cis-diol groupings into unsaturated sugars have been applied to oligosaccharide modification for the first time (refs. 51,52). Thus, the symmetrical, dienic trehalose derivative **22**, synthesized from glucal **1**, was bis-oxyaminated with chloramine T (Scheme 15). The substituents entered stereospecifically on the β-faces of both rings, but regioselectivity was only modest, as was also the case in monosaccharidic analogs (cf. ref. 50), and the three regioisomeric bistosylamides **78-80** were obtained in yields of 18, 10, and 37%, respectively, together with small proportions of monooxyaminated products **81** and **82**. N-Detosylation and O-deacetylation of **78-80**, individually, gave high yields of the 2,2'-diamino-2,2'-dideoxy, 2,3'-diamino-2,3'-dideoxy, and 3,3'-diamino-3,3'-dideoxy derivatives of α-D-mannopyranosyl α-D-mannopyranoside (ref. 51). When a limited proportion of chloramine-T was used, the osmylation of **22** yielded each of the two monotosylamides (**81**, **82**) in acceptable amounts (18-20%). Hydroxylation of the remaining double bond, also under osmium catalysis, with trimethylamine N-oxide or N-methylmorpholine N-oxide as oxidants, then gave the diols **83** and **84**, from which the corresponding, free 2-amino-2-deoxy and 3-amino-3-deoxy-α-D-mannopyranosyl α-D-mannopyranosides were elaborated in high yields (ref. 52). As already briefly stated in Section 1, such aminated analogs of α,α-trehalose are of considerable interest in view of the natural occurrence of aminotrehaloses as antibiotics. Further synthetic approaches will be outlined in a subsequent paragraph.

Scheme 15



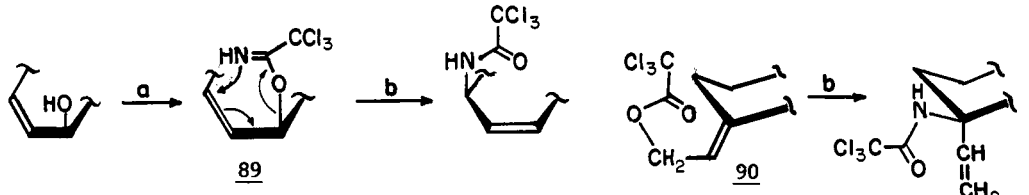
An elegant new method for establishing cis amino-hydroxy functionality in sugars was devised by Fraser-Reid and coworkers (ref. 53). It is the iodonium ion-induced cyclization of allylic urthanes or amides, exemplified in Scheme 16. This strategy requires, first, the provision of an allylic amine by one of several available methods. The ethyl urethane (e.g., **85**) or benzamide (e.g., **87**) obtainable therefrom undergoes iodolactonization under the influence of iodonium biscollidine perchlorate, to give a cyclic carbamate (**86**) or oxazoline (**88**), respectively, thus establishing the desired structural feature of a cis amino alcohol in blocked form. The incorporated iodine is reductively removed, best with tributylstannane, and hydrolysis of the nitrogen heterocycle then gives the amino sugar. A short synthesis of the glycosteroidal amino sugar holacosamine (ref. 53b) is representative of the methodology. In the case of oxazoline intermediates (e.g. **88**), hydrolysis is preceded by quaternization of the nitrogen and borohydride reduction of the oxazolinium double bond. It is to be noted that use of such exocyclic alkenes as **87** permits the stereospecific generation of a tertiary carbinol function. Syntheses of the C-methyl branched sugars garosamine (ref. 53a) and 3-epi-sibirosamine (ref. 53c) took advantage of this novel approach.

Scheme 16



Another novel route to amino sugars, reported by Dyong, Weigand, and Thiem (ref. 54), consists of thermal rearrangement of allylic trichloroacetimidates as sketched in Scheme 17. The imidates are prepared from the corresponding alcohols by reaction with trichloroacetonitrile and potassium hydride; endocyclic (**89**) as well as exocyclic (**90**) structures may be utilized.

Scheme 17



89 90

a Cl_3CCN, KH, -10°; b 165°, in o-$C_6H_4Cl_2$

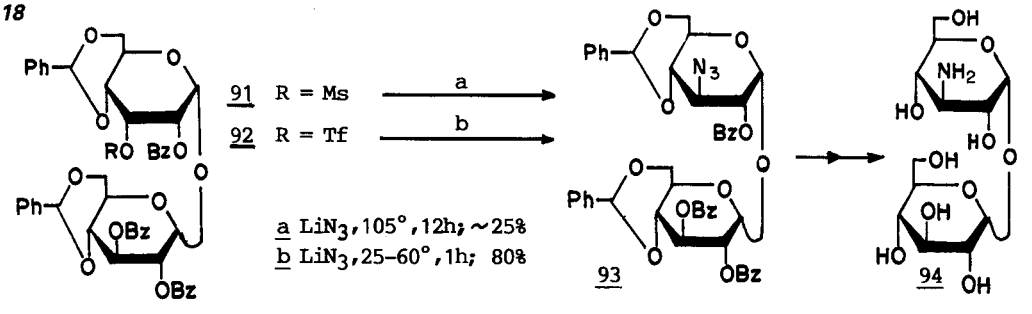
5 USES OF TRIFLUOROMETHANESULFONATES

During the past decade, ever-increasing use has been made in synthetic organic chemistry of the superb leaving group for nucleophilic displacements, the trifluoromethanesulfonic (triflic) ester function (ref. 55). First introduced in carbohydrate synthesis by Perlin in 1974 (ref.56), triflation of sugars and utilization of triflates has since gained enormous popularity (ref.57). Certain aspects of the behavior of triflates in comparison to that of tosylates have already been touched upon in Section 2, and some recent studied are to be delineated in the paragraphs that follow.

Modification of disaccharides

In our own work we first came to appreciate the superiority of the triflate group over the mesylate group in the synthesis of 3-amino-3-deoxy-α,α-trehalose (94), the key step of which is portrayed in Scheme 18. Whereas azide displacement in the mesylate 91 was very sluggish and gave a mediocre yield of the desired compound 93, accompanied by an undesired elimination product (the 3-deoxy-3-enoside), the triflate 92 reacted almost instantaneously at room temperature and was completely displaced after brief warming, to give an 80% yield of 93 without observable elimination (ref. 58). The amino disaccharide 94 has incidentally been reported (ref. 59), soon after, to occur in nature as a metabolite of Norcardiopsis trehalosei and to exhibit antibiotic activity.

Scheme 18



91 R = Ms a
92 R = Tf b

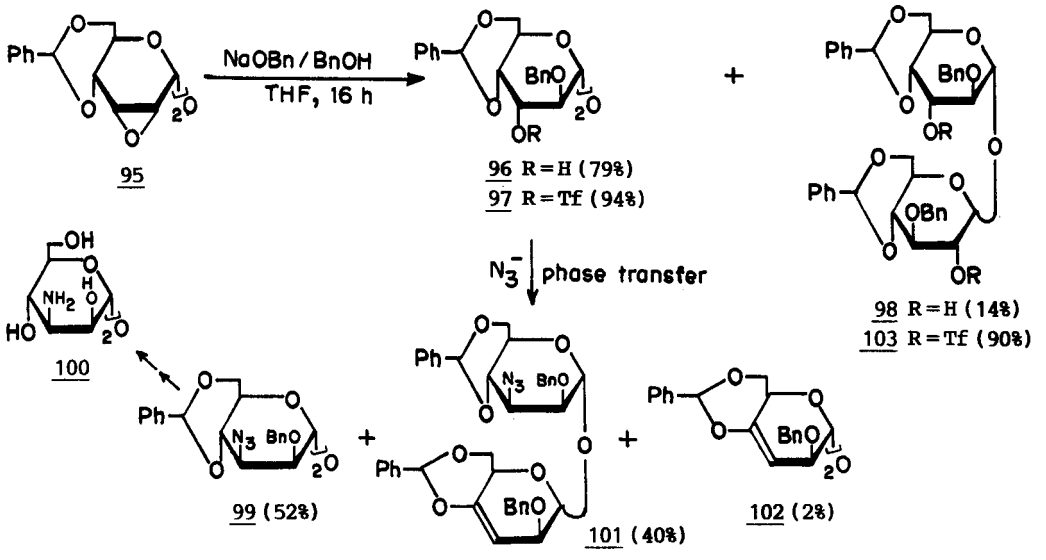
a LiN_3, 105°, 12h; ~25%
b LiN_3, 25-60°, 1h; 80%

93 94

3-Amino-3-deoxy-α-D-mannopyranosyl 3-amino-3-deoxy-α-D-mannopyranoside (100) had previously been obtained by nitromethane cyclization methodology (ref. 60), and more recently by the osmylation procedure (see Scheme 15), but yields were low and a more practical access to this sugar was desirable. Therefore, triflate displacement in the disaccharidic 3,3'-ditriflate 97 having the α-D-altro, α-D-altro configuration was investigated. Compound 97 was readily prepared from the known diepoxide 95 (obtainable from trehalose in 3 steps) via the diol 96 (see Scheme 19), but considerable difficulties were encountered in displacement with azide ion. S_N2 attack evidently was impeded by the axial benzyloxy groups at C-2 and C-2', and a great deal of competing 3,4-elimination took place under all of the many reaction conditions tried. Indeed, elimination giving mainly 101 (plus small proportions of 102) predominated in most trials, although some of the desired diazide 99 was usually formed also. Nevertheless, by patient experimentation it eventually became possible to establish phase transfer conditions for azide displacement that furnished 99 in 52% yield. Final conversion of 99 into the target diamine 100 (2 steps) presented no problems, so that a 5-step synthesis of the latter from readily accessible 95 was accomplished with >20% overall yield (ref. 61).

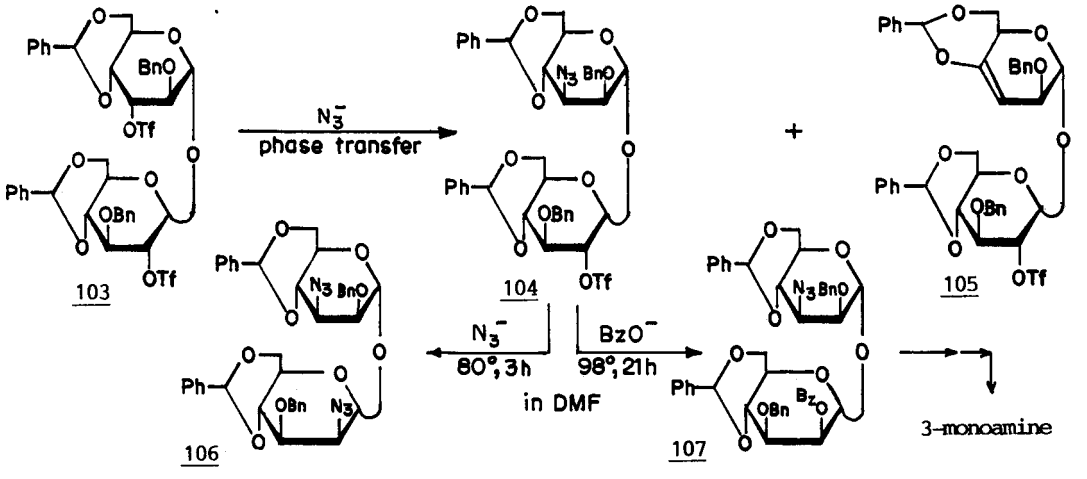
The unsymmetrical α-D-altro, α-D-gluco 3,2'-diol 98 arose as a by-product (14%) in the preparation of 96 from 95 by partial anti-Fuerst-Plattner ring opening. The operations could be conveniently performed on a large scale, and 98 could thus be prepared in preparatively useful quantities; its ditriflate 103 was put to good use as shown in Scheme 20 (ref. 62). It turned out that the 3-triflyloxy group (in the altro moiety) was selectively displaced by azide under phase transfer conditions, to give the 3-azido-2'-triflate 104 (55%), together with the unsaturated 2'-triflate 105 (22%) and only 8% of the diazide 106. However, under homogeneous conditions in N,N-dimethylformamide at 80-100°, the 2'-ester in 104 was displaced readily; use of sodium azide led to the unsymmetrical diazide 106, whereas use of sodium benzoate gave the

Scheme 19



3-azido-2'-benzoate 107. Compound 106 constitutes a potential precursor for the 2,3'-diamine that was alternatively obtained by oxyamination (cf. Section 4, Scheme 15). Conversion of 107 by standard procedures into the corresponding 3-monoamine was performed (ref. 62) to complement the osmylation route (ref. 52).

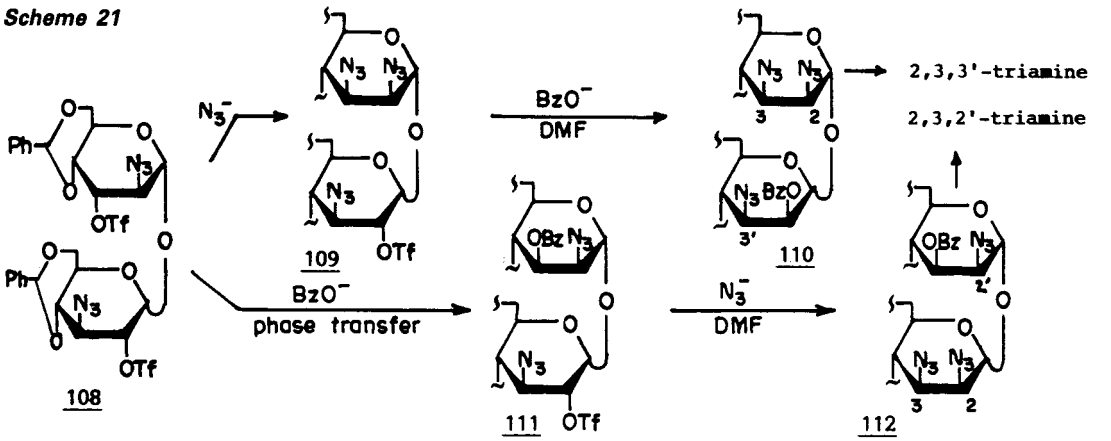
Scheme 20



Similar regioselective displacements were achieved in the unsymmetrical 2,3'-diazido-3,2'-di-triflate 108 (Scheme 21). It was found (ref. 63) that such discriminating displacements may also succeed under mild homogeneous conditions, namely, with tetramethylguanidinium azide in benzene-dichloromethane; the 2,3,3'-triazido-2'-triflate 109 was so obtained in 68% yield with only 15% of disubstitution product and 8% of elimination product. Subsequent displacement of the 2'-triflic ester with benzoate in DMF at 100° furnished the 2,3,3'-triazido-2'-benzoate 110 (90% yield) which was converted into the corresponding 2,3,3'-triamino disaccharide. Reversal of the sequence, i.e., regioselective monosubstitution in 108 by benzoate, followed by more-forcing azide substitution, gave high yields of 111 and the 2,3,2'triazido-3'-benzoate 112 , regioisomeric with 110. Standard manipulations afforded the free 2,3,2'-triamino disaccharide from 112. The symmetrical 2,3,2',3'-tetraamino sugar was also prepared in the course of these studies.

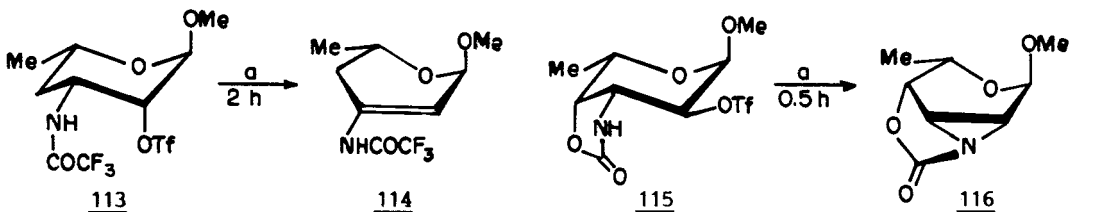
Although "classical" sulfonic esters (mesylates and tosylates) are generally known to be unreactive towards S_N2 displacement when situated at C-2 of pyranose rings, there were several prior examples for displacement of the highly nucleofugal triflate group from that position reported in the literature, and it would have been difficult to predict that a differential reactivity as here observed exists and can be used advantageously for regioselective functionalization.

Scheme 21



Rearrangement of hexopyranoside 2-triflates to 2,5-anhydro sugar derivatives

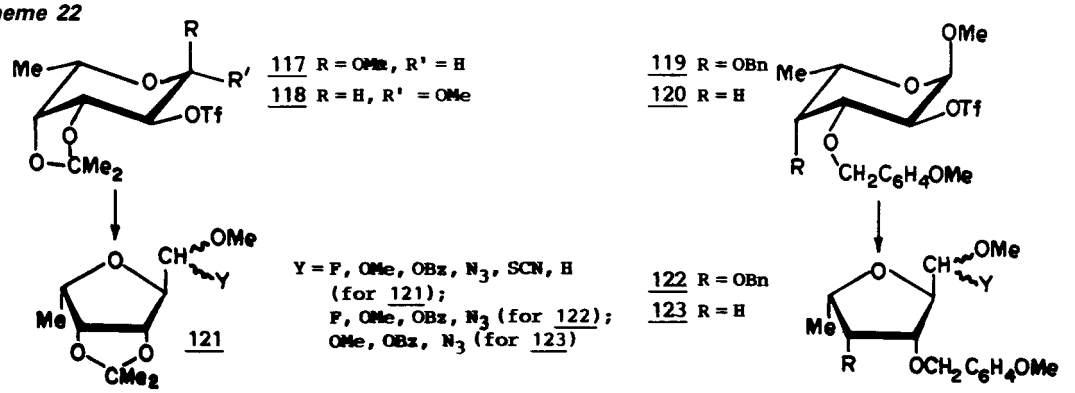
As was seen in the preceding subsection, competing elimination may interfere with S_N2 displacement in triflates when the molecular geometry is conducive to the former or adverse to the latter. In the particular studies just described, elimination problems surfaced mainly with respect to triflyloxy groups at C-3, and not with those at C-2. However, similar difficulties have frequently thwarted attempts at displacement of 2-triflates also, especially in the area of substitution by fluoride ion, notwithstanding the many successfully-performed 2-fluorinations and other substitutions. (For reviews of the pertinent literature, see refs. 64,65). A recent example of facile elimination, occurring to the exclusion of displacement, is the reaction 113→114, where approach of F^- to C-2 is unfavorable whilst the C-2,3 geometry is appropriate for elimination (ref.66). More surprising was the result of a reaction intended to provide a preparative precursor for hitherto unknown (R)-2-fluoro-L-daunosamine, which was to be used in anthracycline modification. When the cyclic carbamate 115 was treated with fluoride ion at low temperature, it was transformed with great ease into the highly strained, tricyclic system 116 (90% yield; unpublished observation by Y. Shu in this Laboratory).



a $Bu_4NF/MeCN$, −20→+20°

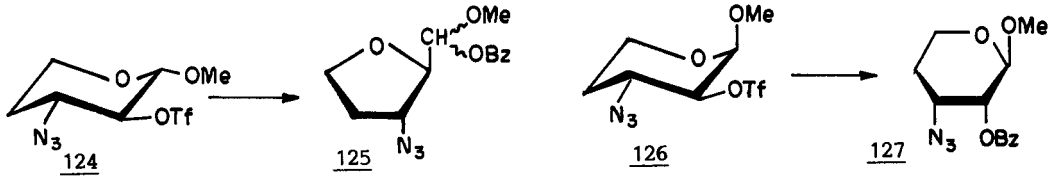
It was thereupon decided to attempt fluorination in the analogous cyclic ketal 117, with the idea of introducing a C-3 amino group later on; in this way the unforeseen complication met in 115 was to be circumvented. Compound 117 was synthesized, as were its anomer 118 and the monocyclic analogs 119 and 120 (ref. 65). All four triflates, however, underwent displacement accompnied by ring contraction when allowed to react, not only with the efficient (ref. 67) fluorinating agent hydrogen fluoride-triethylamine complex but also with a variety of other nucleophiles including methanol (in the presence of sodium bicarbonate), sodium benzoate, azide, thiocyanate, and borohydride (Scheme 22).

Scheme 22



The reactions proceeded smoothly at room temperature, and the 2,5-anhydro sugar derivatives 121-123 were isolated in high yields. The product were mixtures of 1-epimers (except of course when Y = OMe or H). No evidence was found for the formation of pyranosidic displacement products. The isolated fluoro ethers (121 and 122, Y = F) proved extremely labile and tended to decompose rapidly at normal temperature (with liberation of HF), but they were sufficiently stable for promptly enacted, spectroscopic characterization (ref. 65).

Rearrangement of the aldohexopyranose to the 2,5-anhydro-aldehydo-hexose structure by ring oxygen migration is a well-known event in reactions where a positive charge is generated at C-2, notably in nitrous acid deamination of 2-amino sugars (ref. 68). However, few such ring contractions had until recently been encountered in hexopyranoside 2-sulfonic esters. Thus, rearrangement had been observed in solvolysis of a 2-O-(p-nitrophenylsulfonyl)glucoside (ref. 69), and analogous ring sulfur migration had been demonstrated for methyl 5-thioribopyranoside 2-mesylates (ref. 70). More recently, certain α- and β-D-galactopyranoside 2-(N-imidazolylsulfonates) have been shown by David (ref. 71) to suffer the same rearrangement during nucleophilic substitution with tetrabutylammonium azide or benzoate; they included in fact close structural relatives of 117-119. As far as pyranoside 2-triflates are concerned, there seems to have been only an isolated instance of such an occurrence among the many recorded (refs.64, 65) displacements and eliminations: Methyl 3-azido-3,4-dideoxy-α-D,L-threo-pentopyranoside (124) gave, with sodium benzoate, the anhydro sugar 125 as the preponderant product; the β-anomer 126 reacted with normal displacement to give 127 (ref. 72).



However, contemporary with our investigations, ring contractions effected by azide ion were described by Fleet (ref. 73) for the 6-t-butyldiphenyloxy analogs of (D) 117 and 118, and also for the corresponding α-D-altro isomer. Hence the reaction type appears to be a fairly general alternative to simple displacements and eliminations that are more commonly seen in the chemistry of pyranoside 2-triflates. It remains to be rationalized why it takes place in some cases and not in others under comparable conditions. Leaving aside the 4-deoxy compounds 120 and 124, it is perhaps significant that rearrangement prevailed in the galacto series (cf. also ref. 71) and was observed in at least one altroside, but not (refs. 64,65) in the numerous glucoside, mannoside, idoside, and taloside 2-triflates thus far examined. Any explanation to be advanced must be consistent with these empirical facts.

A different kind of rearrangement has been observed in a number of reactions of 1,2-trans glycosides and thioglycosides. It also involves departure of a leaving group from C-2 with concomitant development of a transient positive charge, but a 1→2 shift of the anomeric group ensues, rather than migration of the ring oxygen atom. First observed in brominolysis of methyl 2-deoxy-2-iodo-α-D-mannopyranoside triacetate (ref. 74), the process has recently been shown to occur when 1,2-trans glycosides (or thioglycosides) that contain a free OH-2 group are treated with diethylaminosulfur trifluoride (ref. 75). An intermediary $Et_2N\text{-}SF_2\text{-}O$- ester is probably formed, and displaced with rearrangement to give 2-O-alkyl (or 2-thioalkyl)-glycopyranosyl fluorides. No evidence has been found for such anomeric-group migration to occur during displacement reactions of 118, 124, or related 1,2-trans 2-sulfonates (65, 71-73), and conversely, no ring oxygen migration seems to have been noticed in the studies just cited (ref. 75). It should be interesting to find out what are the determinant factors for occurrence of one or the other of the two types of rearrangement.

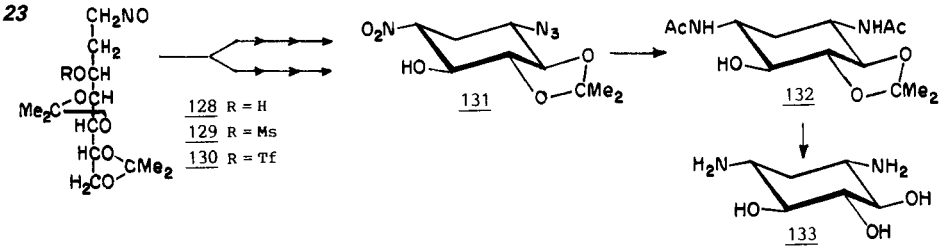
6 SOME NEW APPLICATIONS AND NEW REACTIONS OF NITRO SUGARS

Stereospecific approaches to aminocyclitols

The Fischer cyclization of 6-deoxy-6-nitrohexoses to give deoxynitroinositols (ref. 76) has over the past 20 years been variously modified and widely employed to gain access to a large variety of nitrogenous cyclitols (ref. 77). The methodology has now been used for a novel approach to the important constituent of aminocyclitol antibiotics, 2-deoxystreptamine (133), sketched in Scheme 23 (ref. 78). Synthesis starting from D-mannose provided, in 5 steps standard in nitro sugar chemistry, the 1,2-dideoxy-1-nitro-D-manno-heptitol diacetonide 128. Its mesylate 129 and triflate 130 were converted by two alternative routes into the azidonitro cyclitol 131. Both routes involved selective removal of the terminal isopropylidene group, periodate oxidation to give a blocked 6-nitro-aldehydo-hexose, and cyclization of the latter, with introduction of the azido group by sulfonate displacement either prior to these manipulations (in 130), or following the cyclization (of 129). Catalytic hydrogenation of 131 and

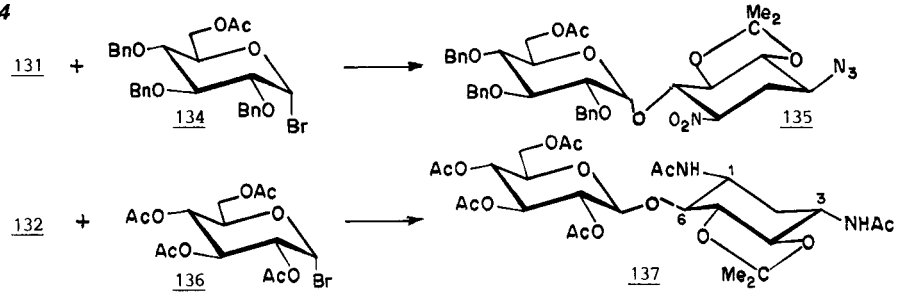
N-acetylation furnished 132, which was deprotected to give the target compound 133. The key feature of this synthesis of (achiral) 133 is that the target is approached through chiral precursors (131, 132) that may be used as stepping stones for stereospecific syntheses of unsymmetrically substituted, and therefore chiral, derivatives of the meso compound 133. In aminocyclitol antibiotics, 133 invariably is substituted unequally at O-4 and O-6, and sometimes at N-1 and N-3.

Scheme 23



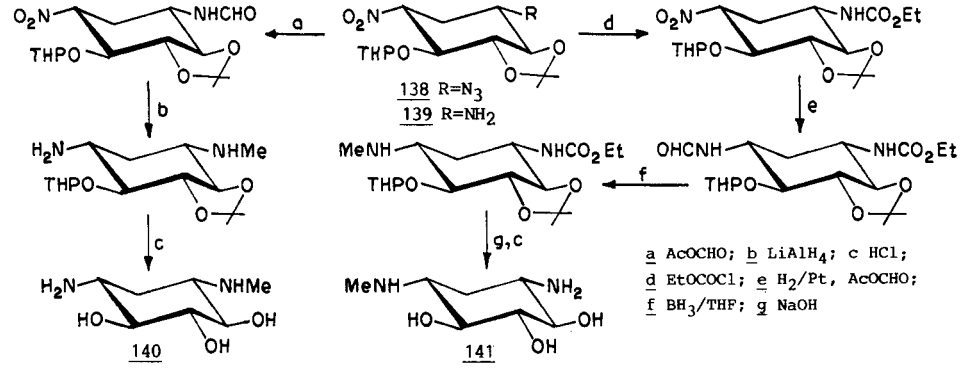
Examples of the utility of this approach are portrayed in Scheme 24 (H.H. Baer, J. Giziewicz, and T. Chen; unpublished). Condensation of **131** with the glycosyl donor 134 in the presence of mercuric cyanide and mercuric bromide furnished the α-glucoside 135, which can be elaborated to α-D-glucopyranosyl-(1→6)-2-deoxystreptamine, a component of kanamycins NK-1001 and -1012-1. That component had previously been made (ref. 79) by use of racemic deoxystreptamine derivaties, but yields were modest owing to unfavorable diastereoselectivities (2:1; 1:2). Similar condensation of 132 using the glycosyl donor 136 afforded the β-glucoside 137. Yields of 135 and 137 under conditions not yet optimized were ca. 50%. It may be anticipated that appropriate, temporary protection of OH-6 in 131 or 132, followed by deacetonation, will open the enantiotopic 4-position of deoxystreptamine for similar, stereospecific coupling.

Scheme 24



Furthermore, the two unequal nitrogen functions in 131 lend themselves to chemoselective and sequential operations so as to generate enantiospecifically such unequally N-substituted derivatives of 133 as for instance the enantiomeric hyosamines (140 and 141), components of the antibiotics hygromycin B and destomycin A, respectively. Thus, the tetrahydropyranyl derivative (138) of 131 was selectively reduced by transfer hydrogenation over palladium, and the resultant nitroamine 139 was converted into either one of the enantiomers 140 and 141 by the alternative N-monomethylation strategies shown in Scheme 25. The sequence leading to 141 makes use of the fact (ref. 80) that formamides are reduced readily by diborane-tetrahydrofuran complex, whereas carbamates are not so reduced (H.H. Baer and J. Giziewicz; unpublished).

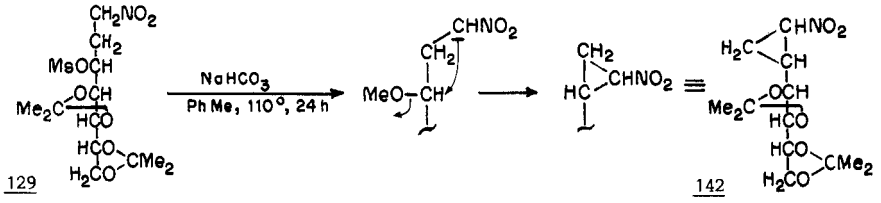
Scheme 25



Chemistry of a carbohydrate nitrocyclopropane and stereospecific synthesis of branched-chain systems

During our studies referred to earlier (see Scheme 23) it was found that azide displacement in the nitroalditol 3-mesylate 129 tends to give by-products resulting from internal attack of C-1 on C-3. These were identified as epimeric nitrocyclopropane derivatives, and their serendipitous discovery inaugurated a new field of investigation. A high-yielding (85%) syn-

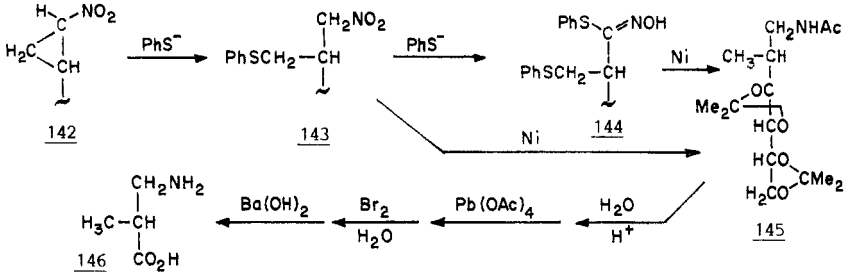
thesis of the nitrocyclopropano alditol 142 was achieved by treatment of 129 with solid sodium bicarbonate in refluxing toluene (ref. 81):



129 142

Compound 142 possesses in C-2 a stereospecifically engendered center of chain branching and is, therefore, an auspicious precursor for a variety of chiral, C-branched structures that may be difficult of access by other avenues. Indeed, nucleophilic opening of the nitrocyclopropane ring (Scheme 26) with sodium thiophenoxide gave the branched (phenylthio)methyl nitroalditol 143, isolable in yields of 30-40% (after reaction for 3-4 h in refluxing tetrahydrofuran), or in >90% yield (after reaction for 2.5 h in DMF at 60-70°). Prolonged action of thiophenoxide in tetrahydrofuran converted 143 into the phenyl thiohydroximate 144, in a process whose mechanism may be akin to the known formation of nitroacetaldoxime (methazonic acid) from two molecules of nitromethane under alkaline conditions. Compound 144 was obtained in 96% yield when the action of thiophenoxide upon 142 was allowed to take place in dioxane solution (4 h, 100°). Both 143 and 144 were desulfurized and reduced by Raney nickel, giving, after N-acetylation, the C-methyl-acetamidoalditol 145 (ref. 82). Deacetonation of 145 followed by oxidative degradation of the polyol chain by precedented procedures (ref. 83) concluded a stereospecific synthesis of (R)-3-amino-2-methylpropanoic acid (146), a biologically important product of thymine metabolism (ref. 84) not previously prepared in enantiospecific fashion.

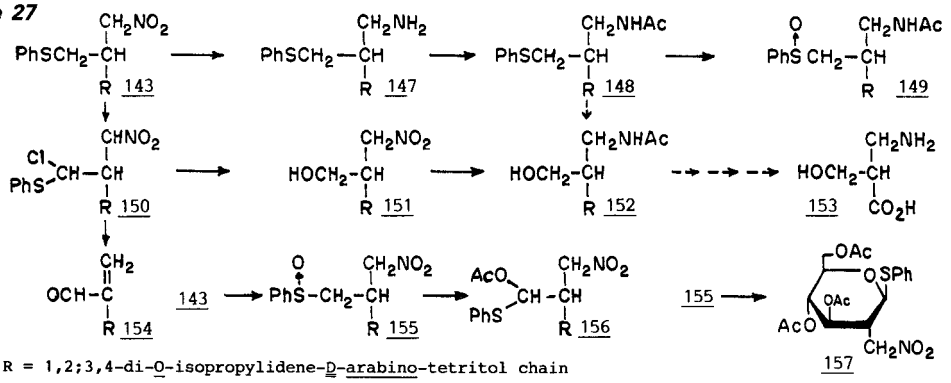
Scheme 26



142 143 144 145 146

Other interesting transformations of 143 are shown in Scheme 27 (unpublished work performed in collaboration with Prof. F. Santoyo Gonzalez, Granada). Thus, reduction by lithium aluminum hydride, acetylation, and m-chloroperoxybenzoic acid oxidation sequentially gave the amine 147, the acetamide 148, and the sulfoxide 149. It is presently under investigation whether 148 will give with cyanogen bromide (ref. 85) the alcohol 152, which should lend itself to degradation to the hitherto unknown, optically active , branched aminohydroxy acid 153. An alternative route to 152 and thence 153 consists of the following transformations. Treatment of 143 with N-chlorosuccinimide in carbon tetrachloride (ref. 86) led to the chlorosulfide 150, a highly reactive, 3:2 mixture of S-epimers. In aqueous acetone, 150 rapidly suffered hydrolysis and concomitant elimination of nitrous acid, giving the unsaturated aldehyde 154. However, hydrolysis in aqueous acetonitrile in the presence of sodium cyanoborohydride produced the nitroalcohol 151, which was hydrogenated catalytically to furnish 152 after N-acetylation. Furthermore, the nitro sulfoxide 155 was prepared by m-chloroperoxybenzoic acid oxidation of 143 (yield, 98%). When 155 was subjected to Pummerer reaction by treatment with trifluoroacetic anhydride, acetic anhydride, and collidine at room temperature (ref. 87), the expected acetoxy sulfide 156 was obtained in 42% yield. However, when the Pummerer reaction was performed with acetic anhydride in refluxing dichloromethane, in the presence of molecular sieve and a catalytic amount of p-toluenesulfonic acid, the surprising result was formation of 157,

Scheme 27



R = 1,2;3,4-di-O-isopropylidene-D-arabino-tetritol chain

143 147 148 149 150 151 152 153 154 155 156 157

phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-nitromethyl-1-thio-β-D-glucopyranoside, which was isolated in 48% yield. Evidently, complete deacetonation of the molecule occurred during the process, and the liberated, penultimate hydroxyl group engaged in cyclization with the aldehydic center generated by the Pummerer reaction. It should be most interesting to examine whether this transformation possesses generality. If so, it should be possible, for example, to convert D-glucose, via 6-deoxy-6-phenylthio-D-glucitol, into phenyl 1-thio-L-guloside, or similarly, D-galactose into phenyl 1-thio-L-galactoside. Other useful applications of this novel mode of thioglycoside formation could easily be conceived.

Acknowledgements

The research results from this Laboratory, reported or reviewed here, were obtained by the following dedicated and skilful coworkers: I. Arai, D.J. Astles, A.J. Bell, F. Bouchard, R.L. Breton, T. Chen, H.-c. Chin, Y. Gan, J. Giziewicz, H.R. Hanna, Z.S. Hanna, F. Hernández Mateo, M. Mekarska-Falicki, Nguyen C., B. Radatus, J. Rodwell, Y. Shen, L. Siemsen, Y. Shu, U. Williams, and M. Zamkanei. The collaboration of Dr. J. Defaye, C.N.R.S. Grenoble, France, and Dr. F. Santoyo González, University of Granada, Spain, in certain parts of the work is acknowledged. The research was financially supported by the Natural Sciences and Engineering Research Council of Canada, the United States Public Health Service, and (in part) by the Medical Research Council of Canada.

REFERENCES

1. H.H. Baer and Z.S. Hanna, (a) Carbohydr. Res. 78, c11-c14 (1980); (b) Can. J. Chem. 59, 889-906 (1981); (c) Carbohydr. Res. 94, 43-55 (1981).
2. I. Arai and G.D. Daves, Jr., J. Am. Chem. Soc. 103, 7683 (1981); U. Hacksell and G.D. Daves, Jr., J. Org. Chem. 48, 2870-2876 (1983); T.D. Lee and G.D. Daves, Jr., ibid. 48, 399-402 (1983); J.C. Cheng and G.D. Daves, Jr., XIIIth Internat. Carbohydr. Symp., Ithaca, N.Y. (1986), Abstr. A-16.
3. S. Czernecki and F. Gruy, Tetrahedron Lett. 437-440 (1981); S. Czernecki and V. Dechavanne, Can. J. Chem. 61, 533-540 (1983); S. Czernecki and V. Bellosta, 3rd Chem. Congr. North America, Toronto, Ont. (1988), Abstr. CARB-78.
4. (a) L.V. Dunkerton, K.T. Brady, and F. Mohamed, Tetrahedron Lett. 23, 599-602 (1982); (b) L.V. Dunkerton and A.J. Serino, J. Org. Chem. 47, 2812-2814 (1982); (c) L.V. Dunkerton, J.M. Euske, and A.J. Serino, XIIIth Internat. Carbohydr. Symp., Ithaca, N.Y. (1986), Abstr.A-22; (d) L.V. Dunkerton, N.K. Adair, and J.M. Euske, 3rd Chem. Congr. North America, Toronto, Ont. (1988), Abstr. CARB-17.
5. W.E. Walker, R.M. Manyk, K.E. Atkins, and M.L. Farmer, Tetrahedron Lett. 3817-3820 (1970); K.E. Atkins, W.E. Walker, and R.M. Manyk, ibid. 3821-3824 (1970); G. Hata, K. Takahashi, and A. Miyako, J. Chem. Soc., Chem. Commun. 1392-1393 (1970).
6. B.M. Trost, Tetrahedron 33, 2615-2649 (1977); R.F. Heck, Acc. Chem. Res. 12, 146-151(1979); J. Tsuji, Organic Synthesis with Palladium Compounds, Springer, New York (1980).
7. P.J. Garegg and B. Samuelsson, Synthesis, 813-814 (1979).
8. S. Umezawa, Adv. Carbohydr. Chem. Biochem. 30, 111-182 (1974); H. Naganawa, N. Usui, T. Takita, M. Hanada, K. Maeda, and H. Umezawa, J. Antibiot., Ser. A 27, 145-146 (1974); L.A. Dolak, T.M. Castle, and A.L. Laborde, J. Antibiot. 33, 690-694 (1980); T. Tsuno, C. Ikeda, K. Numata, K. Tomita, M. Konishi, and H. Kawaguchi, J. Antibiot. 39, 1001-1003 (1986).
9. A. Rosenthal, Adv. Carbohydr. Chem. 23, 59-114 (1968).
10. A. Rosenthal and G. Khan, Tetrahedron Lett. 477-480 (1967); A. Rosenthal and J.N.C. Whyte, Can. J. Chem. 46, 2239-2243 (1968).
11. H.H. Baer and H.R. Hanna, Carbohydr. Res. 102, 169-183 (1982).
12. R.E. Dessy, R.L. Pohl, and R.B. King, J. Am. Chem. Soc. 88, 5121-2124 (1966).
13. F.L. Bowden and L.H. Wood, in E.A. Koerner von Gustorf, F.-W. Grevels, and I. Fischer (Eds) The Organic Chemistry of Iron, Vol. 1, Academic Press, New York (1980), 345-396.
14. M.B. Goren and K.S. Jiang, Chem. Phys. Lipids 25, 209-224 (1979); Carbohydr. Res. 79, 225-234 (1980); A. Liav and M.B. Goren, ibid. 84, 171-174 (1980); A. Liav, B.C. Das, and M.B. Goren, ibid. 94, 230-235 (1981); I.D. Jenkins and M.B. Goren, Chem. Phys. Lipids 4, 225-235 (1986).
15. G.L. Trainor and B.E. Smart, J. Org. Chem. 48, 2447-2448 (1983).
16. B.M. Yunker and B. Fraser-Reid, J. Org. Chem. 44, 2742-2745 (1979).
17. H.C. Brown and S. Krishnamurthy, J. Am. Chem. Soc. 95, 1669-1671 (1973); Aldrichimica Acta 12, 3-11 (1979).
18. V. K. Srivastava and L.M. Lerner, Carbohydr. Res. 64, 263-265 (1978).
19. H.H. Baer and H.R. Hanna, Carbohydr. Res. 110, 19-41 (1982).
20. E. Vis and P. Karrer, Helv. Chim. Acta 37, 378-381 (1954); A. Zobácová, V. Heřmánková, and J. Jarý, Collect. Czech. Chem. Commun. 35, 327-333 (1970); S. Umezawa, T. Tsuchiya, and H. Hineno, Bull. Chem. Soc. Jpn. 43, 1212-1218 (1970).
21. H.H. Baer, M. Mekarska, and F. Bouchard, Carbohydr. Res. 136, 335-345 (1985).
22. H.H. Baer and M. Mekarska-Falicki, Can. J. Chem. 63, 3043-3052 (1985).
23. A. Zobácová, V. Heřmánková, and J. Jarý, Collect. Czech. Chem. Commun. 36, 1860-1866(1971).
24. F. Hansske and M.J. Robins, J. Am. Chem. Soc. 105, 6736-6734 (1983).
25. H.H. Baer, D.J. Astles, H.-c.Chin, and L. Siemsen, Can. J. Chem. 63, 432-439 (1985).
26. V. Pozsgay and A. Neszmélyi, Tetrahedron Lett. 211-214 (1980).
27. D.J. Astles, Ph.D. Thesis, University of Ottawa, Ottawa, Canada (1985).
28. B. Rickborn and R.M. Gerkin, J. Am. Chem. Soc.93, 1693-1700 (1971).
29. H.H. Baer and D.J. Astles, Carbohydr. Res. 126, 343-347 (1984).
30. S. Brandänge, O. Dahlman, and L. Mörch, J. Am. Chem. Soc. 103, 4452- (1981); S. Brandänge, O. Dahlman, and J. Ölund, Acta Chem. Scand. B 37, 141-145 (1983).
31. E.P. Barrette and L. Goodman, J. Org. Chem. 49, 176-178 (1984).
32. P.J. Garegg and H. Hultberg, Carbohydr. Res. 93, c10-c11 (1981); P.J. Garegg, H. Hultberg, and S. Wallin, ibid. 108, 97-101 (1982).
33. J. Gelas, Adv. Carbohydr. Chem. Biochem. 39, 71-156 (1981).
34. A. Lipták, Carbohydr. Res. 63, 69-75 (1978); Tetrahedron Lett. 3551-3554 (1976); A. Liptak, P. Fügedi, and P. Nánási, Carbohydr. Res. 51, c19-c21 (1976); 65, 209-217 (1978).

35. P. Rollin and P. Sinaÿ, C. R. Acad. Sci., Ser. C 284, 65-68 (1977).
36. M. Ek, P.J. Garegg, H. Hultberg, and S. Oscarson, J. Carbohydr. Chem. 2, 305-311 (1983); P.J. Garegg and S. Oscarson, Carbohydr. Res. 136, 207-213 (1985).
37. M. Kloosterman, T. Slaghek, J.P.G. Hermans, and J.H. van Boom, Rec. Trav. Chim. Pays-Bas 103, 335-341 (1984); R. Johansson, B. Samuelsson, J. Chem. Soc. PerkinTrans. 1, 2371-2374 (1984).
38. P.J. Garegg, B. Lindberg, P. Konradsson, and I. Kvarnström, 4th European Carbohydr. Symp., Darmstadt, FRG (1987), Abstr. C-24.
39. R. Köster, S. Penadés-Ullate, and W.V. Dahlhoff, Angew. Chem. 97, 508-510 (1985); W.V. Dahlhoff and A. Geisheimer, Z. Naturforsch. 40b, 141-149 (1985); W.V. Dahlhoff, XIIIth Internat. Carbohydr. Symp., Ithaca, N.Y. (1986), Abstr. A-17 and A-18; J. Imre, W.V. Dahlhoff, and R. Köster, ibid. Abstr. A-19.
40. H.C. Brown, P. Heim, and N.M. Yoon, J. Am. Chem. Soc. 92, 1637-1646 (1970).
41. H.H. Baer and M. Zamkanei, J. Org. Chem., in press (1988).
42. J. Thiem and H.-P. Wessel, Liebigs Ann. Chem. 2173-2184 (1983).
43. J.P.H. Verheyden, A.C. Richardson, R.S. Bhatt, B.D. Grant, W.L. Fitch, and J.C. Moffatt, Pure & Appl. Chem. 50, 1363-1383 (1978).
44. J.G. Buchanan, K.A. MacLean, R.H. Wightman, and H. Paulsen, J. Chem. Soc. Perkin Trans. 1 1463-1470 (1985).
45. D.P. Schumacher and S.S. Hall, J. Am. Chem. Soc. 104, 6076-6080 (1982).
46. D. Horton and J.D. Wander, in W. Pigman and D. Horton (Eds.), The Carbohydrates, Chemistry/Biochemistry, 2nd edit., Vol. IB, Academic Press, New York (1980) 643-760.
47. H.H. Baer and B. Radatus, Carbohydr. Res. 157, 65-81 (1986).
48. W.J. Serfontein, J.H. Jordaan, and J. White, Tetrahedron Lett. 1069-1072 (1964); R.U. Lemieux, T.L. Nagabhushan, and I.K. O'Neill, ibid. 1909-1912 (1964); Can. J. Chem. 46, 413-418 (1968); R.U. Lemieux and T.L. Nagabhushan, ibid. 46, 401-403 (1968).
49. R.U. Lemieux and R.M. Ratcliffe, Can. J. Chem. 57, 1244-1251 (1979).
50. K. Heyns and J. Feldmann, Tetrahedron Lett. 2789-2792 (1977); I. Dyong, G. Schulte, Q. Lam-Chi, and H. Friege, Carbohydr. Res. 68, 257-273 (1979); A. Banaszek and A. Zamojski, Pol. J. Chem. 53, 287-295 and 2029-2039 (1979).
51. H.H. Baer, L. Siemsen, J. Defaye, and K. Burak, Carbohydr. Res. 134, 49-61 (1984).
52. H.H. Baer and L. Siemsen, Carbohydr. Res. 146, 63-72 (1986).
53. (a) H.W. Pauls and B. Fraser-Reid, Can. J. Chem. 62, 1532-1538 (1984); (b) M. Georges, D. Mackay, and B. Fraser-Reid, ibid. 62, 1539-1543 (1984); (c) M. Georges, D. MacKay, and B. Fraser-Reid, Carbohydr. Res. 130, 115-124 (1984).
54. I. Dyong, J. Weigand, and J. Thiem, Liebigs Ann. Chem. 577-599 (1986).
55. P.J. Stang, M. Hanack, and L.R. Subramanian, Synthesis 85-126 (1982).
56. A. Maradufu and A.S. Perlin, Carbohydr. Res. 32, 261-277 (1974).
57. For an excellent review, see R.W. Binkley and M.G. Ambrose, J. Carbohydr. Chem. 3, 1-49 (1984); see also original research articles following in that issue.
58. H.H. Baer and A.J. Bell, Carbohydr. Res. 75, 175-184 (1979).
59. L.A. Dolak, T.M. Castle, and A.L. Laborde, J. Antibiot. 33, 690-694 (1980).
60. H.H. Baer and A.J. Bell, Can. J. Chem. 56, 2872-2878 (1978).
61. H.H. Baer, B. Radatus, and J. Defaye, Can. J. Chem. 63, 440-444 (1985).
62. H.H. Baer and B. Radatus, Carbohydr. Res. 144, 77-86 (1985).
63. H.H. Baer and B. Radatus, Carbohydr. Res. 146, 73-88 (1986).
64. R. Faghih, F. Cabrera Escribano, S. Castllo, J. Garcia, G. Lukacs, A. Olesker, and T.T. Tang, J. Org. Chem. 51, 4558-4564 (1986); B. Doboszewski, G.W. Hay, and W.A. Szarek, Can. J. Chem. 65, 412-419 (1987).
65. H.H. Baer, F. Hernández Mateo, and L. Siemsen, Carbohydr. Res., in press.
66. H.H. Baer and F. Hernández Mateo, Carbohydr. Res., in press.
67. D. Picq and D. Anker, Carbohydr. Res. 166, 309-313 (1987).
68. J. Defaye, Adv. Carbohydr. Chem. Biochem. 25, 181-228 (1970).
69. P.W. Austin, J.G. Buchanan, and R.M. Saunders, J. Chem. Soc. (C) 372-377 (1967).
70. N.A. Hughes and C.J. Wood, J. Chem. Soc. Perkin Trans. 1 695-700 (1986).
71. F.M. El Sayed Ahmed, S. David, and J.-M. Vatèle, Carbohydr. Res. 155, 19-31 (1986).
72. A. Grouiller, H. Bazin, and C. Gagnieu, Tetrahedron Lett. 23, 2559-2562 (1982).
73. G.W.J. Fleet and L.C. Seymour, Tetrahedron Lett. 28, 3015-3018 (1987).
74. R.U. Lemieux and B. Fraser-Reid, Can. J. Chem. 42, 539-546 (1964).
75. I.P. Street and S.G. Withers, Can. J. Chem. 64, 1400-1403 (1986); K.C. Nicolaou, T. Ladduwahetty, J.L. Randall, and A. Chucholowski, J. Am. Chem. Soc. 108, 2466-2467 (1986).
76. J.M. Grosheintz and H.O.L. Fischer, J. Am. Chem. Soc. 70, 1479-1484 (1948); H.H. Baer, Adv. Carbohydr. Chem. Biochem. 24, 67-138 (1969); F.W. Lichtenthaler, Newer Methods Preparative Org. Chem. 4, 155-195 (1968).
77. A. Hasegawa and H.Z. Sable, J. Org. Chem. 33, 1604-1612 (1968); T. Suami, S. Ogawa, N. Tanno, M. Suguro, and K.L. Rinehart, Jr., J. Am. Chem. Soc. 95, 8734-8737 (1973); S. Ogawa, K.L. Rinehart, Jr., G. Kimura, and R.P. Johnson, J. Org. Chem. 39, 812-821 (1974); J. Kovar and H.H. Baer, Can. J. Chem. 51, 1801-1811, 2836-2842, and 3373-3379 (1973); Carbohydr. Res. 39, 19-32 (1975); ibid. 45, 161-180 (1975); J. Yoshimura, M. Funabashi, and C.-G. Shiu, in K.L. Rinehart, Jr., and T. Suami (Eds.), Aminocyclitol Antibiotics, ACS Symposium Series 125, American Chemical Society, Washington (1980) 75-93.
78. H.H. Baer, I. Arai, B. Radatus, J. Rodwell, and Nguyen C., Can. J. Chem. 65, 1443-1451 (1987).
79. Y. Nishimura, T. Tsuchiya, and S. Umezawa, Bull. Chem. Soc. Jpn. 43, 2960-2965 (1970); R.U. Lemieux, T.L. Nagabhushan, K.J. Clemetson, and L.C.N. Tucker, Can. J. Chem. 51, 53-66, (1973).
80. H.C. Brown and P. Heim, J. Org. Chem. 38, 912-916 (1973).
81. B. Radatus, U. Williams, and H.H. Baer, Carbohydr. Res. 157, 242-250 (1986).
82. H.H. Baer, U. Williams, and B. Radatus, Carbohydr. Res. 174, 291-303 (1988).
83. M.L. Wolfrom, R.U. Lemieux, and S.M. Olin, J. Am. Chem. Soc. 71, 2870-2873 (1949).
84. D. Gani, P.B. Hitchcock, and D.W. Young, J. Chem. Soc. Perkin Trans. 1, 1363-1372 (1985).
85. E. Gross and B. Witkop, J. Am. Chem. Soc. 83, 1510-1511 (1961).
86. D.L. Tuleen and T.B. Stephens, J. Org. Chem. 34, 31-35 (1969).
87. R. Tanikaga, Y. Yabuki, N. Ono, and A. Kaji, Tetrahedron Lett. 26, 2257-2258 (1976).