

## Anhydro sugars, valuable intermediates in carbohydrate syntheses

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**Abstract:** The versatility of the epoxyhydroxy functionality in pyranoses is demonstrated giving access to sugar amino acids and peptides, aminodeoxy, halodeoxy, branched-chain, cyclopropanated and aziridino sugars.

### INTRODUCTION

Anhydro sugars are stable intermediates with unique properties of the oxirane ring to serve, both, as a protecting group and readily accessible reaction sites which have led to their extensive exploitation in carbohydrate syntheses. Besides, they have the advantage of the ease of removal of the protection after the desired synthetic strategy has been accomplished. During the last decade, a series of communications have appeared from our laboratory making frequent use of epoxy sugars as versatile chiral synthons in the synthesis of amino sugars, sugar amino acids and peptides, cyclopropanated and branched-chain pyranosides, halodeoxy sugars and sugar esters, chiral  $\gamma$ -butyrolactones, dihydrofurans or polyfunctionalized tetrahydrofurans, many of which are of potential biochemical interest (1-28).

### RESULTS AND DISCUSSION

#### Syntheses involving displacements of the triflyl group in 2,3-anhydro sugars

Trifluoromethanesulfonic acid esters are important intermediates in modern synthetic as well as mechanistic organic chemistry. Particularly the trifluoromethanesulfonates, commonly referred to as triflates, have shown excellent leaving group properties and serve in numerous transformations (29). Triflate derivatives have also been used in carbohydrate chemistry (30), and we have carried out a series of reactions involving displacement of the triflate group from C-4 of 2,3-anhydro sugars by a wide variety of nucleophiles. The displacement reactions at this position are not only favoured by the neighbouring oxirane ring (31), but also by the favourable geometry (2). The sugar triflates are prepared from corresponding anhydro sugars by treating them with 1.1 equivalent triflic anhydride in pyridine at low temperature.

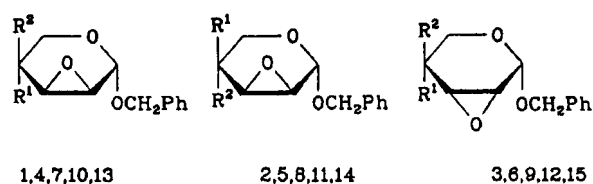
#### Aminodeoxy sugars

Although several types of reactions have been useful in obtaining aminodeoxy sugars, displacement processes generally have been most effective (32). Many displacement reactions, however, suffer from severe limitations (32-34) including competing elimination reactions and the inability to effect displacement in certain situations, particularly if the leaving group is attached to a secondary carbon atom. We have now determined that many of these limiting factors can be overcome by using the triflyl group which permits facile introduction of azido and amino functions at, both, primary and secondary positions. Thus, the 4-azido-4-deoxy sugars **4-6** are prepared by slow warming the solution of the triflates **1-3** in DMF with an excess of sodium azide from -40 °C to room temperature (2) (Scheme 1). The compounds **5** and **6** were previously prepared as described in reference (1) through the displacement of the tosyl group from C-4 by sodium azide in DMF at 50 °C. The yields were, however, lower than those obtained from triflates. A comparative study of the leaving group capability of the triflyl and tosyl groups is made by monitoring the reaction with the help high performance liquid chromatography. The

reaction with triflates takes 90 min for completion, while that with the corresponding tosylates only goes to 70% completion after 48 h, revealing the excellent leaving group property of the triflate group. Selective hydrogenation of the azido group with platinum oxide in methanol cleanly affords the aminodeoxy sugars 7-9 respectively (2) (Scheme 1).

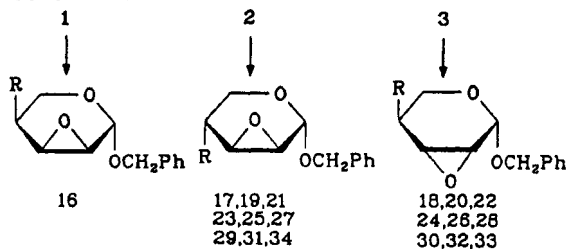
Our next strategy was to introduce the amino function directly at C-4 without the intervening azide. Attempts to displace the triflyl group by sodamide in HMPA proved futile, as the strongly basic nature of the attacking nucleophile gives rise to undesirable side reactions like  $\beta$ -elimination and attack on the oxirane ring. The triflyl group in 1-3 can, however, be displaced by  $\text{NH}_3 / \text{CHCl}_3$  at 50 °C after 5 h, resulting in the aminodeoxy sugars 7-9 (5). The scope of the reaction is further demonstrated by employing 1,2:3,4-di-*O*-isopropylidene-6-*O*-triflyl- $\alpha$ -D-galactopyranose, 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl- $\alpha$ -D-allofuranose and 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl- $\alpha$ -D-glucufuranose for which the substitution is known to be difficult (35,36). In each case, the corresponding aminodeoxy sugar is obtained in good yield. The triflyl groups at C-4 of 2,3-anhydro sugars are further activated for displacement due to the neighbouring oxirane ring and the favourable molecular geometry, allowing facile displacement by passing gaseous ammonia into acetonic solutions of 1-3 at -10 °C for 1 h, resulting in improved yields of the amines 7-9 (5,6). The one step procedure is therefore markedly superior to traditional methods employing intermediate azidodeoxy sugars, particularly for the introduction of amino groups in the presence of highly reduction-sensitive functionalities (Scheme 1).

Scheme 1.



	R <sup>1</sup>	R <sup>2</sup>
1-3	OSO <sub>2</sub> CF <sub>3</sub>	H
4-6	H	N <sub>3</sub>
7-9	H	NH <sub>2</sub>
10-12	H	<i>p</i> -NHC <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
13-15	H	<i>p</i> -NHC <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> CCH <sub>3</sub>

Scheme 2.



16-18:	R = NH-CH(COOCH <sub>2</sub> Ph)-CH <sub>3</sub>
19-20:	R = NH-CH(COOMe)-CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
21-22:	R = NH-CH(COOCH <sub>2</sub> Ph)-(CH <sub>2</sub> ) <sub>4</sub> NH-COOCH <sub>2</sub> Ph
23-24:	R = NH-CH(COOMe)-CH <sub>3</sub>
25-26:	R = NH-CH(COOMe)-CH <sub>2</sub> -CH <sub>2</sub> -S-CH <sub>3</sub>
27-28:	R = NH-CH(COOCH <sub>2</sub> Ph)-CH <sub>2</sub> -CH <sub>2</sub> -COOCH <sub>2</sub> Ph
29-30:	R = NH-CH(COOMe)-CH <sub>2</sub> Ph
31-32:	R = N-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CHCOOMe
33:	R = OH
34:	R = NH-CH(CH <sub>2</sub> Ph)-CO-NH-CH <sub>2</sub> -COOCH <sub>2</sub> Ph

The foregoing strategy is also applied to comparatively weaker aromatic amines consisting of *tert*-butyl-*p*-aminobenzoate and its methyl ester analogue. The former constitutes the essential part of highly effective folic acid which influences the formation of blood and is used with vitamin B<sub>12</sub> against pernicious anaemia (37). The free amino functions of both of these were utilized to cause smooth displacement of the triflyl group in 1-3 obtaining the amino sugars 10-15. The reactions were carried out in acetonitrile at room temperature in the presence of equimolar amounts of collidine. A detailed pharmacological screening of the compounds 10-15 is presently under way and one of these (11) has already shown some antiviral activity.

#### Sugar amino acids and sugar peptides

From the high selectivity observed during the foregoing reactions it appears that substitution of the triflyl group in partially blocked sugar triflates by the free amino function of suitably protected naturally occurring amino acids should perform the desired C-N coupling between two important groups of natural products, resulting in novel syntheses of a new class of pharmacologically interesting compounds. Representatives of different classes of amino acids are used to demonstrate the scope of the reaction. These include methyl esters of *L*-alanine, *L*-phenylalanine, *L*-leucine, *L*-proline or *L*-methionine along with the dibenzyl ester of *L*-glutamic acid and benzyl esters of *N*<sup>ε</sup>-(benzyloxycarbonyl)-*L*-lysine and *L*-alanine. All of these are respectively used to displace the triflyl group in 1-3 (Scheme 2). The reactions can be carried out in DMF or acetonitrile by slowly warming from -20 °C to room temperature followed by stirring for further 5 h. Besides the target compounds 16-32 (Scheme 2) which were in

major concentration, formation of two other minor products is observed in each case. One of these was isolated pure and identified as benzyl 2,3-anhydro- $\alpha$ -D-lyxopyranoside from reactions with **2** and its  $\beta$ -L-isomer **33** from the reaction of **3**. The origin of these compounds can be explained through the competing nucleophilic displacement of the triflyl group by the moisture present in DMF or atmosphere. The same strategy can be applied for the syntheses of sugar peptides. This has been demonstrated by us using L-phenylalanyl-glycine benzyl ester to displace the triflyl group in **2** and obtain the sugar peptides **34** (**7**) (Scheme 2).

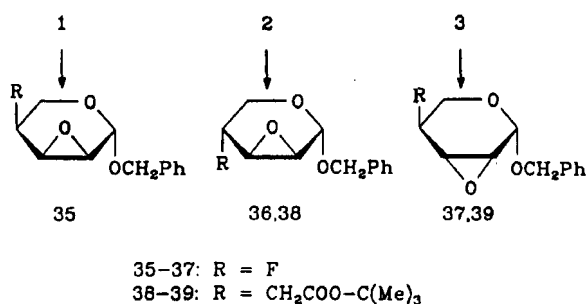
### Fluorodeoxy sugars

Fluorinated carbohydrates have recently gained importance due to possible applications in the insecticide and herbicide areas besides acting as inhibitors of certain enzymes (**38**). These are also distributed in nature in combined forms as essential parts of some highly effective antibiotics (**39**). The displacement reactions generally have to be carried out under forcing conditions of temperature and concentration and require strict control of the acidity of reactions to prevent elimination. A reaction which overcomes these limiting factors is the displacement of triflyl groups by fluoride ions in the neighbourhood of the oxirane ring in **1-3** (Scheme 3). Each of these was treated with tetrabutylammonium fluoride at room temperature in benzene instead of acetonitrile, whereby an appreciable decrease in reaction time along with a substantial increase in product yields was achieved. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds **35-37** show interesting additional couplings with fluorine which are markedly dependent on their structures and conformations (**40**) (Scheme 3).

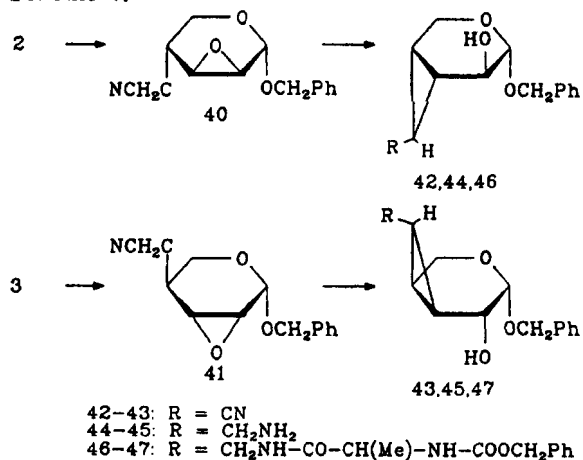
### Branched-chain sugars

The displacement of the triflyl group with carbanions provides an approach to branched-chain sugars bearing functionalities for subsequent elaboration to compounds of biological interest. The lithium enolate of tert-butyl acetate (**41,42**) reacts smoothly with the triflates **2** and **3** in a mixture of THF and DMSO at  $-110^\circ\text{C}$  to afford the branched-chain sugar derivatives **38** and **39** respectively (Scheme 3). Further elaboration of these compounds is in progress.

Scheme 3.



Scheme 4.



### Syntheses involving displacement and cleavage of the epoxide ring

Cyclopropanated sugars, aziridino sugars and free 3- and 4-amino acid deoxyaldopyranoses are achieved through initial displacement of the triflyl group in **1-3** by different nucleophiles, followed either by internal oxirane ring cleavage by the trans-oriented nucleophile thus introduced or by external epoxide cleavage by various reagents under acidic conditions.

### Cyclopropanated sugars

If **2** and **3** are treated with the lithium salt of acetonitrile (**43**) in the presence of an additional equivalent of lithium diisopropylamide (LDA), the cyclopropanated sugar derivatives **42** and **43** are obtained, respectively (Scheme 4). Although a number of 2,3-cyclopropanated sugars have been described in the literature (**44-47**), to our knowledge these are the first examples of 3,4-cyclopropanated pyranosides. Apparently, the initially formed cyanomethyl derivatives **40** and **41** (Scheme 4) are further alkylated by

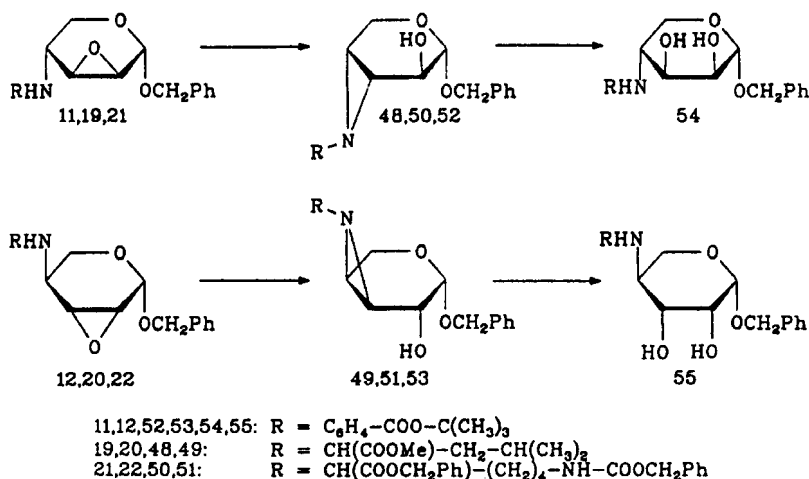
the trans-oriented oxirane ring. In fact, all attempts to isolate **40** and **41** by performing the reaction with one equivalent of LDA, also yield **42** and **43**. Thus, the transfer of a proton from **40** and **41** to the unreacted acetonitrile anion is significantly faster than the reaction of the latter with the triflate. The functionalized cyclopropanated sugars offer an excellent opportunity for appending biologically important peptides to sugars. In order to elaborate these compounds along this line, we reduced the nitrile group of **42** and **43** with lithium aluminium hydride to the corresponding aminomethyl derivatives **44** and **45** in excellent yields (Scheme 4). The resulting amino functions were coupled with benzylcarbonyl-L-alanine to afford the amides **46** and **47** respectively (Scheme 4). The success of this reaction provides an approach towards attaching a peptide chain at this position (14).

### Aziridino sugars

Aziridino sugars are important because of their biological activities. Furthermore, they are key intermediates for the introduction of a second amino functionality and a large variety of nucleophiles by way of trans-diaxial cleavage of epimine rings (48).

During the coupling of the sugars and amino acids (see above), the formation of a minor product is observed in the majority of the reactions. These are, however, formed in extremely low concentration and could only be isolated pure from the coupling reaction of the methyl ester of L-leucine and the benzyl ester of N'-benzyloxycarbonyl-L-lysine, respectively and characterized as aziridino sugars **48-51** (Scheme 5). Their formation can be rationalized by a classical intramolecular isomerization of an  $\alpha$ -imino oxirane into an  $\alpha$ -hydroxy epimine. The isomerization is jointly mediated by the trans-oriented secondary amino function and the solvent medium. Thus, in **31** and **32**, where the nitrogen is tertiary, no isomerization is observed. Moreover, more isomerization is observed in protic solvents, particularly ethanol and methanol. It is further demonstrated by us that the aziridino sugars can be obtained as major compounds by treating an  $\alpha$ -imino oxirane with  $\text{BF}_3$  in ether and trimethylsilylazide. Thus, the amino sugars **11** and **12** can cleanly be converted into the corresponding aziridino sugars **52** and **53** (Scheme 5). The coordination of  $\text{BF}_3$  with the oxirane oxygen activates C-3 towards back-side attack of the imino group, followed by hydrolysis of the intermediate  $\text{BF}_3$  adduct to provide the target compounds in a single step. The reactions of both, **11** and **12**, also lead consistently to the amino sugars **54** and **55** (Scheme 5). Their formation can be explained by trans-diaxial cleavage of the epimine ring by the moisture present

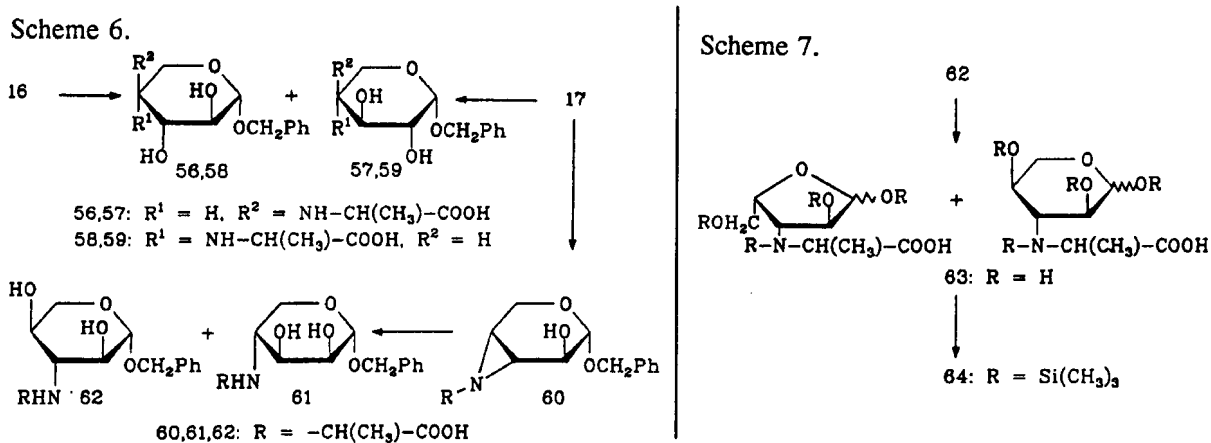
Scheme 5.



in the solvent medium and in the atmosphere. These are, however, obtained in very meagre amounts. This is the first report of the use of trimethylsilyl azide as a dipolar aprotic solvent. It imparts a greater degree of control over undesirable side reactions like product hydrolysis and the participation of solvent medium in nucleophilic displacements which sometimes are encountered with DMF and acetonitrile, respectively. The conformations of the aziridino sugars **49**, **51**, and **53** are defined as  ${}^0\text{H}_1$  and those of **48**, **50** and **52** as  ${}^1\text{H}_2$  by  ${}^1\text{H}$  NMR spectroscopy at 400 MHz. It may be stated in this context that the predominant conformation in 2,3- and 3,4-anhydropentopyranosides is the one with the glycosidic group in axial position (49). The anomaly in the compounds **48**, **50** and **52** is probably due to the effect of steric and electrostatic repulsion between the axial benzyloxy group and the epimine ring nitrogen in the  ${}^0\text{H}_1$  conformation. The compounds **54** and **55** are shown to exist in the  $1\text{C}$  conformation by  ${}^1\text{H}$  NMR spectroscopic studies (7,9,10).

Free 3- and 4-amino acid deoxyaldopyranoses

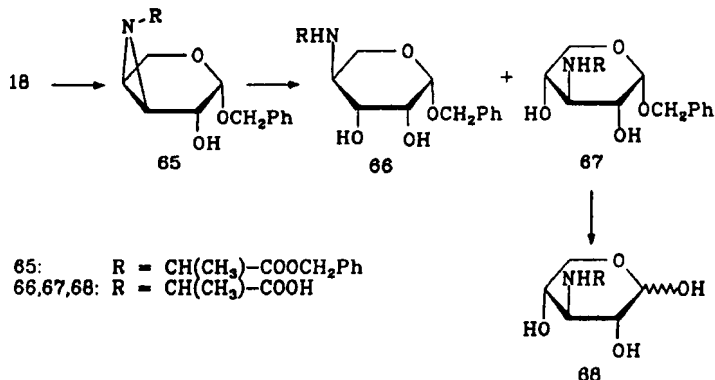
Hydrolysis of **16** with acetic acid and water (1:1) at 100 °C opens the oxirane ring diaxially; simultaneously, the ester group is hydrolyzed yielding compounds **56** and **57**, the former being the main product. A similar reaction with **17** provides **58** and **59** respectively. On the other hand, treatment of **17** with weak acids in protic solvents leads to the aziridino sugar **60**. A similar product is obtained in remarkable amount by chromatography of **17** over silica gel. The stable conformation of **17** is  ${}^{\circ}H_3$ , which changes into  ${}^5H_6$  during the reaction to generate an axial imino group in the neighbourhood of the oxirane ring, to promote the trans-diaxial cleavage of the latter. Acid hydrolysis of **60** under the same conditions was expected to afford **61** as major compound on the basis of trans-diaxial ring opening, but contrary to that, **62** is obtained as the main product of reaction. The stable conformation of **60** is  ${}^1H_6$  due to diaxial interaction between the anomeric benzyloxy group and the nitrogen of the epimine ring. However, in acetic acid the  ${}^{\circ}H_1$  form dominates due to the possibility of hydrogen bonding between the benzyloxy group and the proton attached to the nitrogen in acidic medium. Diaxial addition of water predominantly furnishes **62**, resulting in an overall migration of the amino acid residue from C-4 to C-3 (7,10, Scheme 6).

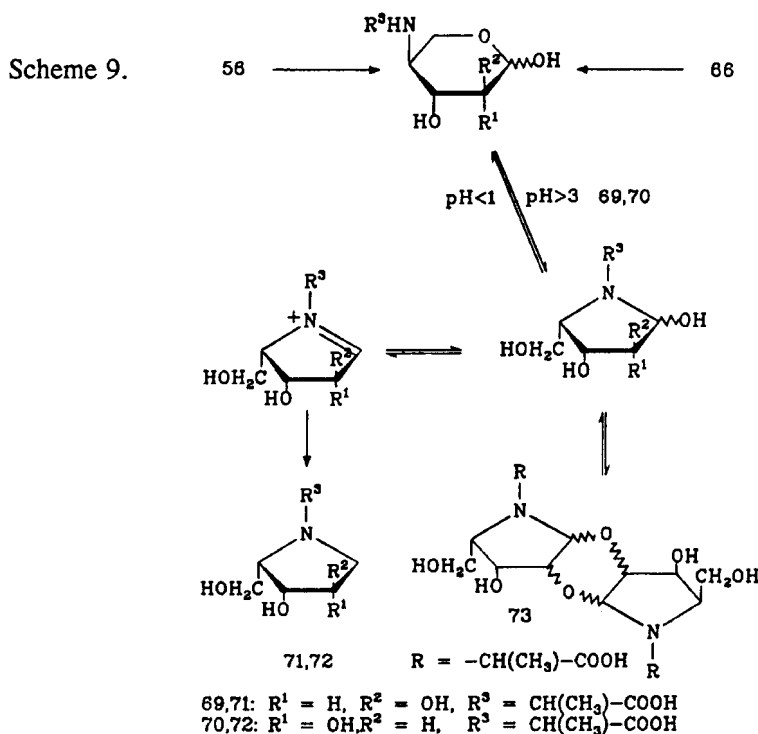


Hydrogenolysis of **62** over 10% palladium-charcoal in methanol yields an unstable hygroscopic product comprising of anomeric mixtures of furanoside and pyranoside forms (**63**). Silylation of **63** with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide and gas chromatography of the silylated product **64** shows four peaks of  $\alpha$ -,  $\beta$ - anomers of furanoside and pyranoside forms, respectively, in the intensity ratio of 1:1.2:11:12 (10, Scheme 7).

The acid hydrolysis of **18** proceeds much faster than that of **16**. Instead of the expected products **56** and **57**, which would result from a direct epoxide opening of **18**, the compound **66** is obtained as major product (35%) and **67** as minor product (6%). Their formation can be rationalized through the isomerization of **18** into its epimine **65** which prefers  ${}^{\circ}H_1$  conformation and the acidic epimine opening takes place trans-diaxially in accordance with the F $\ddot{u}$ rst and Plattner rule. Catalytic hydrogenation of **67** in water/methanol yields **68** quantitatively as a colourless solid, stable at - 20 °C. The  ${}^1H$  NMR of **68** shows only the signals of the two pyranose isomers (13, Scheme 8).

Scheme 8.





Catalytic hydrogenation of **56** respectively **66** under the same conditions as described for **67** results in the formation of 1-L-alanino-1,4-anhydro-1-deoxy-L-xylitol (**71**) and respectively its lyxitol isomer **72** instead of the expected **69** and **70** respectively (13,50,51). The latter are in fact observed as intermediates which further react to yield **71**, respectively **72**. Only under strong acidic conditions (dilute sulphuric acid) can the nucleophilicity of the nitrogen be sufficiently reduced to suppress the formation of five-membered rings. The free **69** and **70** can then be liberated by addition of a sufficient amount of barium hydroxide to precipitate all sulphate ions. Extensive  $^1\text{H}$  NMR investigations at different pH values prove that **69** and **70** prefer pyranose forms at acidic pH while the pyrrolidine and bis(pyrrolidine) (**73**) forms start to dominate at basic pH. Further studies are underway to investigate the biological properties of the described conjugates of sugars and amino acids, which so far have not been obtained from natural sources (13, Scheme 9).

### CONCLUDING REMARKS

The syntheses, surveyed in this article, demonstrate that epoxytriflate pyranoses are versatile synthons for numerous transformations of the starting carbohydrates into e.g. aminodeoxy, halodeoxy, cyclopropanated, branched-chain sugars or new classes of sugar amino acids and peptides. Due to preliminary studies, quite a few of these now accessible compounds seem to have effects on the immune systems or antibacterial activities and for some selected candidates potential drug development is in progress.

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