Methods for Anomeric Carbon-Linked and Fused Sugar Amino Acid Synthesis: The Gateway to Artificial Glycopeptides

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I. Introduction

Quite common sugar amino acids are natural products in which the carboxylate and amino groups are directly linked to two different carbon atoms of a pyranose or furanose ring. Typically, the sialic acids with *N*-acetylneuraminic acid (Neu5Ac or NANA), the most diffuse member of the family, constitute a large class of biologically important compounds that are present in animal and vegetable organisms.[1,2] However, increasing attention has been recently turned to unnatural sugar amino acids in which the entire α-amino acid group $CH(NH_2)CO_2H$ (glycinyl moiety) is connected either directly or through an all-carbon tether to the anomeric carbon atom of the sugar unit. The tether can be a saturated or an unsaturated carbon chain or part of an aromatic ring. Among these compounds there is a special interest in isosteres (*C*-glycans) of glycosyl L-serine and L-threonine (*O*-glycans) and glycosyl L-asparagine (*N*-glycans), the most common components of native glycopeptides[3] (Figure 1). Given the key role of oligosaccharides in glycoprotein biological activity such as intercellular trafficking and receptor binding and signaling on one side[4] and the enzymatic degradation via the hydrolysis of the *O*- or *N*-glycosidic bonds on the other side, the incorporation of *C*-glycosyl amino acids in glycopeptides may serve in preparing chemically and metabolically resistant analogues that display inhibitor activity toward *O*- or *N*-glycosidases.[5] The final goal of these synthetic efforts is the development of glycopeptide-based drugs with improved pharmacokinetic properties. While *O*-glycosyl tyrosine moieties are less widely spread in natural glycopeptides, the carbon-linked analogues possessing a methylene group instead of the phenolic oxygen enter in the same category of these *C*-glycosyl amino acids. A similar isosteric modification can be considered for glycopeptide antibiotics such as vancomycin whose disaccharide moiety is installed by an *O*-glycosidic linkage formed with the *p*-hydroxy group of 3,4,5-trihydroxyphenylalanine residue.[6] Thus, section II will cover synthetic methods of *C*-glycosyl amino acids as defined above.[7] While most compounds are only synthetic, a few natural products featuring a *C*-glycosidic linkage to tryptophan will be described also.

A second and rather special class of sugar amino acids is constituted by *N*-glycosides of 2-ulosonic acids whose syntheses are reviewed in section III. These compounds can be considered as fused sugar glycines since the amino acid group is sharing its central carbon atom with a furanose or pyranose ring (Figure 2). These novel unnatural materials are quite attractive components for incorporation into peptide chains or for peptide library synthesis with a set of new amino acids with highly hydroxylated components. The synthetic utility of anomeric sugar glycines stems also from their transformation into spiro derivatives, particularly spirohydantoin analogues of the natural product (+)-hydantocidin, a spirohydantoin of D-ribose.[8a,b] Since the potent biological activity of hydantocidin as a nontoxic herbicide and plant growth regulator is due to its ability to inhibit[8c] the purine biosynthesis at the site of adenylosuccinate synthetase, structurally related analogues may equally play some role in carbohydrate-based biological processes.

For the above premises, this review will not deal with synthetic approaches to carbon-linked sugar amino acids in which the glycinyl moiety is linked to a carbon atom other than the anomeric one.[9] The majority of these nonanomeric derivatives constitute the nucleoside part of natural peptidyl antibiotics such as polyoxin and nikkomycin. The synthesis of these carbon-linked amino acids has been appropriately described in the context of the total synthesis of the relevant natural products.[10,11]

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Alessandro Dondoni has been Professor of Organic Chemistry at the University of Ferrara since 1975. His research interests include the design of new reagents and the developments of stereoselective synthetic methods. Recent work has been focused on the preparation of natural product-like compounds, particularly small peptide and glycoconjugate analogues. He started a new program on glycosylated calixarenes and calixarene-containing polymers. In 1999 he obtained the Avogadro-Minakata Lectureship Award of the Chemical Society of Japan and the Ziegler–Natta Lectureship Award of the German Chemical Society. In the same year he was awarded the Lincei National Academy prize in Chemistry sponsored by the Italian Minister of Cultural Heritage and Activities.

Alberto Marra graduated in Pharmaceutical Sciences from the University of Pisa in 1985 and obtained his Ph.D. degree in Organic Chemistry from the University Paris VI in 1989 under the supervision of Professor P. Sinaÿ. He spent one more year in Paris at the Ecole Normale Supérieure as Researcher of the French National Research Council. He was a postdoctoral Research Associate at the University of Zurich with Professor A. Vasella (1991) and then moved to the University of Ferrara where he joined the group of Professor A. Dondoni. He was appointed to a lectureship in organic chemistry at the Faculty of Engineering from 1992 to 1998 and was promoted to the position of Associate Professor in 1998 at the same university. As in the early activity, his present research interest centers on carbohydrate chemistry. Recent work also deals with the synthesis and properties of calixarene derivatives.

II. C-Glycosyl Amino Acids

A. *C*-Glycosyl Glycines

These compounds exhibit a single carbon−carbon bond holding the glycinyl group to the anomeric carbon atom of the sugar moiety. The first report on the synthesis of these sugar amino acids goes back to the late 1940s. The synthesis of glucosyl and lactosyl glycines was reported by condensation of the corresponding peracetylated bromosugars with sodium *N*-formylamino diethyl malonate, CH(O)-

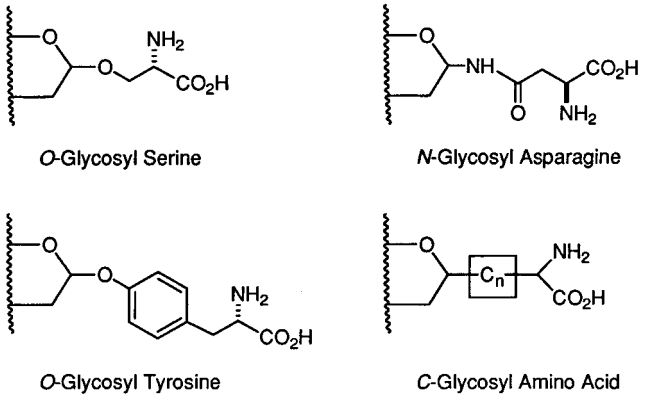


Figure 1. Natural and unnatural glycosyl amino acids.

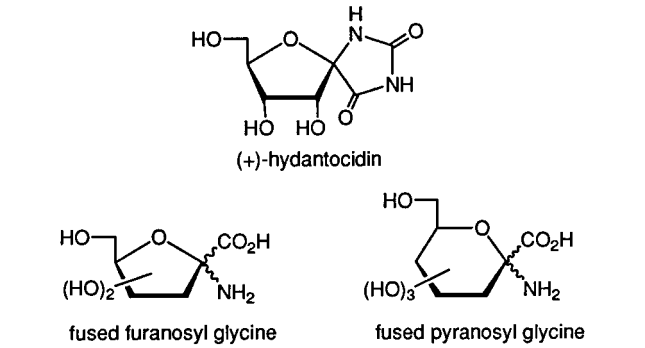
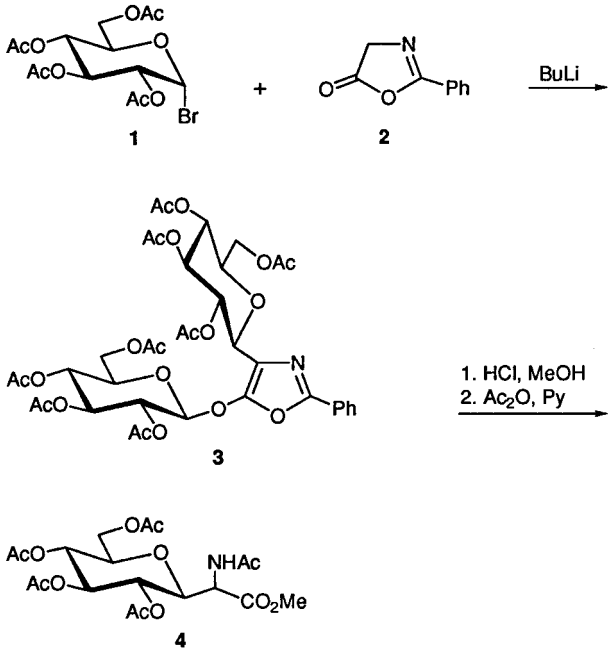


Figure 2. (+)-Hydantocidin and fused glycosyl glycines.

$NHCNa(CO_2Et)_2$, followed by saponification and decarboxylation.[12] However, later attempts to repeat these reactions failed in other laboratories.[13] Hence, the first well-documented synthesis of a *C*-glycosyl glycine is that reported[14] by Rosenthal and Brink in 1975 by coupling the peracetylated bromoglucose **1** with the anion derived from the oxazolinone **2** (Scheme 1). Although isolated in very low yield from

Scheme 1

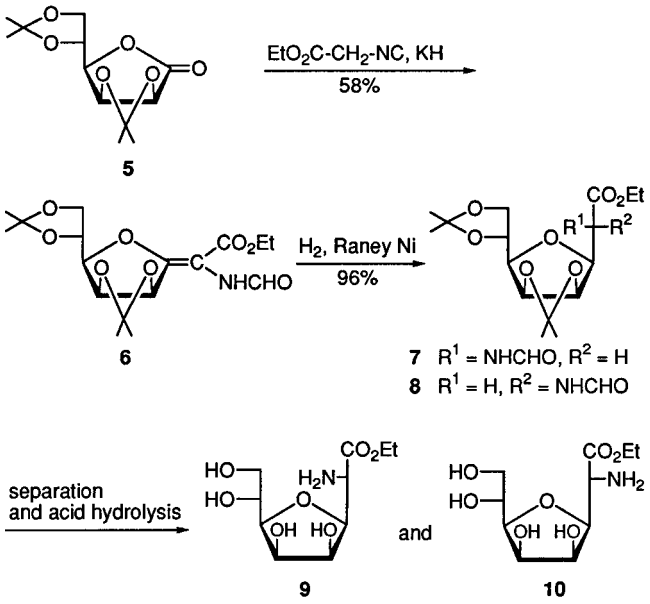


the rather complex reaction mixture, the bis-glycosylated oxazole **3** was transformed into methyl (*R*,*S*)-

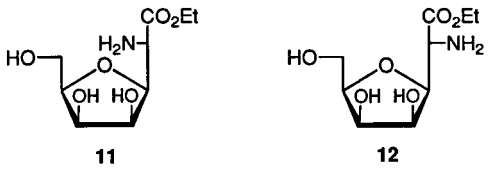
2-(β-D-glucopyranosyl)glycinate **4** by acid hydrolysis in methanol. The β-linkage in the *C*-glycoside **4** was proved by NMR analysis.

In the same period the synthesis of various *C*-glycofuranosyl glycines was carried out[15] with the aim of preparing C-1 regioisomers of the sugar amino acid moiety (C-4 linked) of *C*-nucleosides, particularly polyoxins. Typically, the addition of potassium ethyl isocyanoacetate to the D-mannono-1,4-lactone **5** (Scheme 2) afforded the exocyclic enol ether **6** as the

Scheme 2

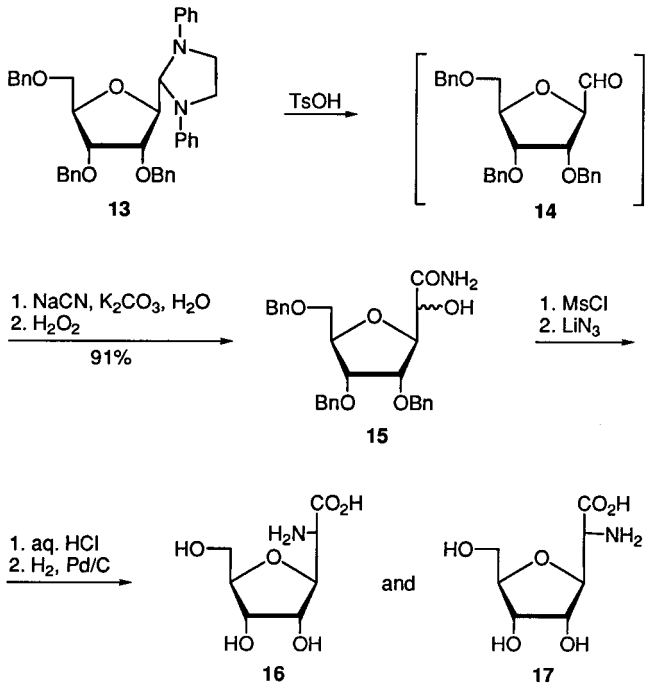


main product, which upon reduction by catalytic hydrogenation gave a mixture of *N*-formyl L-glycinate **7** (90%) and the D-isomer **8** (6%). Separation of these compounds by chromatography and acid hydrolysis afforded the free 2-(β-D-mannofuranosyl)-L-glycine **9** and the corresponding D-amino acid **10**. The shortening of the C-6 side chain by one carbon atom in the octonates **7** and **8** followed by the same acid hydrolysis as above gave the corresponding 2-(β-D-lyxofuranosyl)-L- and D-glycines **11** and **12**. The β-configuration at the anomeric carbon of the sugar glycines **9**−**12** was assigned by chemical and physical (Cotton effect) methods.



In another approach, Robins and Parker[16] used a Strecker-type reaction for the synthesis of 2-(β-D-ribofuranosyl)-L- and D-glycines **16** and **17** (Scheme 3). Unmasking of the formyl *C*-glycoside **14** by acid-catalyzed hydrolysis of 2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1,3-diphenylimidazolidine **13** followed by in situ treatment with sodium cyanide/potassium carbonate and then hydrogen peroxide gave the α-hydroxy amide **15** (90%) as a mixture of diastereomers in about a 1:1 ratio. The individual diastereomers were separated as 2-*O*-mesyl derivatives that

Scheme 3



in turn served as substrates for the introduction of the amino group via the corresponding azides. Key steps in this transformation were (a) the stereospecific S_N2 reaction of the 2-*O*-mesyl derivative with lithium azide, (b) the hydrolysis of the amide function in hot hydrochloric acid/dioxane solution (quantitative), and (c) the Pd-catalyzed hydrogenolysis of the azido function and benzyl protecting groups. The L- and D-amino acid configuration of sugar glycines **16** and **17** was assigned from ORD and CD curves obtained from their solutions in 6 N hydrochloric acid. Positive effects were obtained for the L-isomer **16**, as in general observed for L-amino acids, whereas the D-isomer showed negative values. The synthesis of D-ribofuranosyl glycines was aimed at preparing polyhydroxylated analogues of the natural product antibiotic (+)-furanomycin, which was assigned early as structure **18** (Figure 3) with a relative *cis* orientation of the methyl and glycinyl substituents.[17] However, various chemical syntheses[18] including one from the Robins and Parker laboratory[19] and the X-ray analysis of the *N*-acetyl derivative[20] demonstrated the *trans* disposition of the substituents as shown in structure **19**.

Quite critic in respect to earlier syntheses of *C*-glycosyl glycines, Lieberknecht and co-workers[21] investigated the model reaction of protected D-ribofuranoses **20a**−**c** with the glycine-derived phosphonate **21** (Scheme 4). The base-induced Wittig−Horner olefination followed by the intramolecular Michael-type addition afforded mixtures of β-D-ribofuranosyl L- and D-glycine epimers. A partial stereocontrol of the Wittig−Michael sequence was achieved starting from the *O*-silyl derivative **20b** (R = $SiMe_2t$-Bu), which under optimized conditions (*t*-BuOK, CH_2Cl_2, from −70 °C to room temperature) gave isomers **22b** and **23b** in a 83:17 ratio (92% overall yield). The choice of suitable conditions appeared quite critical in order to obtain a satisfactory stereocontrol since

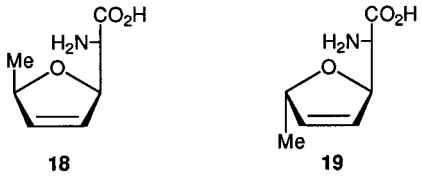
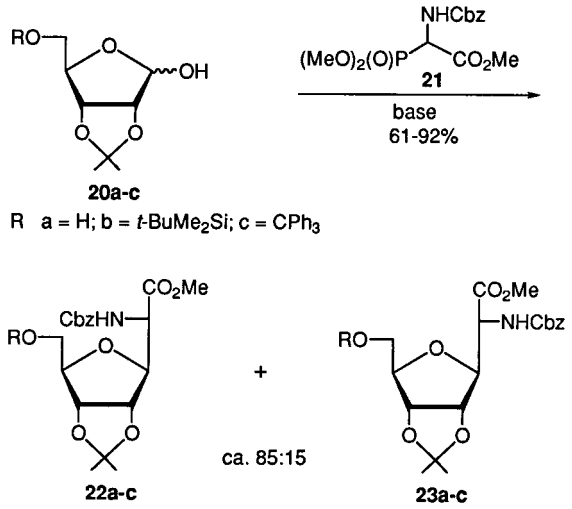


Figure 3. Structure **18** and revised structure **19** of (+)-furanomycin.

Scheme 4

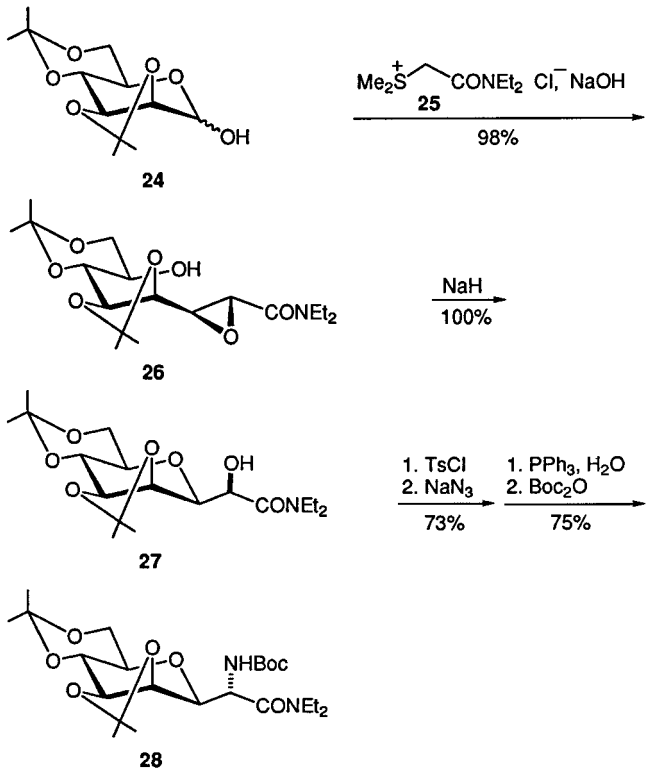


α-linked isomers were formed by changing the base and the protective group R in the D-ribofuranose **20**. Hence, while the extension of this approach to other glycofuranosides can be foreseen, the stereochemical outcome in each synthesis can be quite variable and hardly predictable.

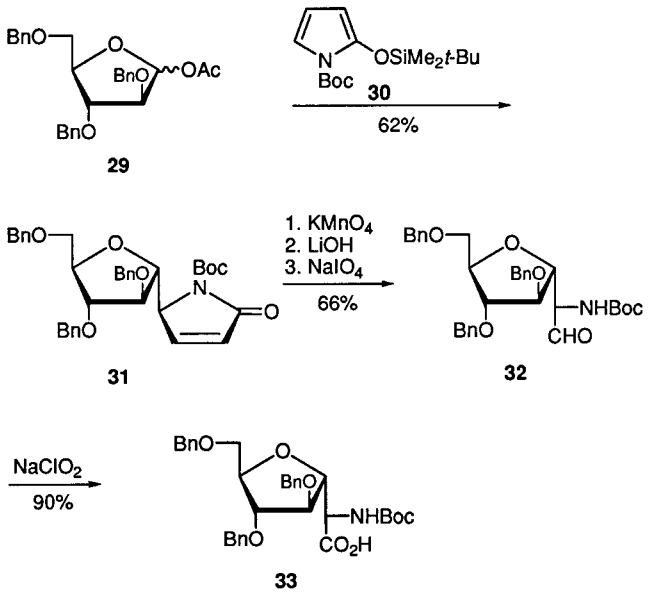
A stereoselective ylide-based approach has been reported recently by López-Herrera and co-workers.[22] In this method, the reaction of the highly rigidified D-mannopyranose derivative **24** with the amide-stabilized sulfur ylide, generated in situ from the corresponding sulfonium chloride **25** and 10% aqueous NaOH (Scheme 5), afforded the chiral epoxy amide **26** as a single product in 98% yield.[23] High stereoselectivity was achieved in the subsequent oxirane ring opening of **26** by NaH to give the *C*-mannopyranoside **27** in virtually quantitative yield. Finally, the transformation of **27** into the *N*-Boc α-amino amide **28** was carried out by replacement of the hydroxy group with the amino group via tosylation, substitution with NaN_3, and reduction. Unfortunately attempts to convert **28** to the free β-D-mannopyranosyl L-glycine were unsuccessful due to the difficult removal of the protective groups.

The siloxypyrrole-based method developed by Casiraghi and Rassu and their co-workers is quite promising.[24] The trityl perchlorate-promoted *C*-glycosylation of *N*-Boc 2-(*tert*-butyldimethylsiloxy)pyrrole **30** with the arabinofuranose acetate **29** (Scheme 6) gave the α-linked sugar lactam **31** as the major diastereomer (62% isolated yield). This compound was converted into the α-D-arabinofuranosyl D-glycine **33** via the α-amino aldehyde **32**. The cleavage of the pyrrolinone ring to the formyl group involved a three-step reaction sequence (dihydroxylation of the carbon−carbon double bond, base opening of the

Scheme 5



Scheme 6



lactone ring, and oxidative fission of the diol), which was carried out in a single flask without isolation of intermediates. Hence, the configuration at the carbon center of the glycinyl group appeared to have been established in the *C*-glycosidation step. A stereochemical model was provided, justifying the assigned stereochemistry to adduct **31**. This model essentially involves the *endo*-type approach of the siloxypyrrole to the less hindered face opposite to the 2-OBn group of the sugar oxycarbenium ion generated from **29** by the Lewis acid. Unfortunately, the study of a single model reaction does not permit one to draw extensive conclusions on the stereochemical outcome nor the generality of the method.

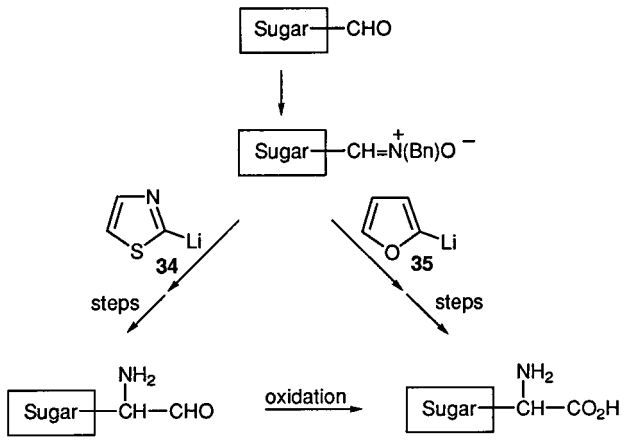
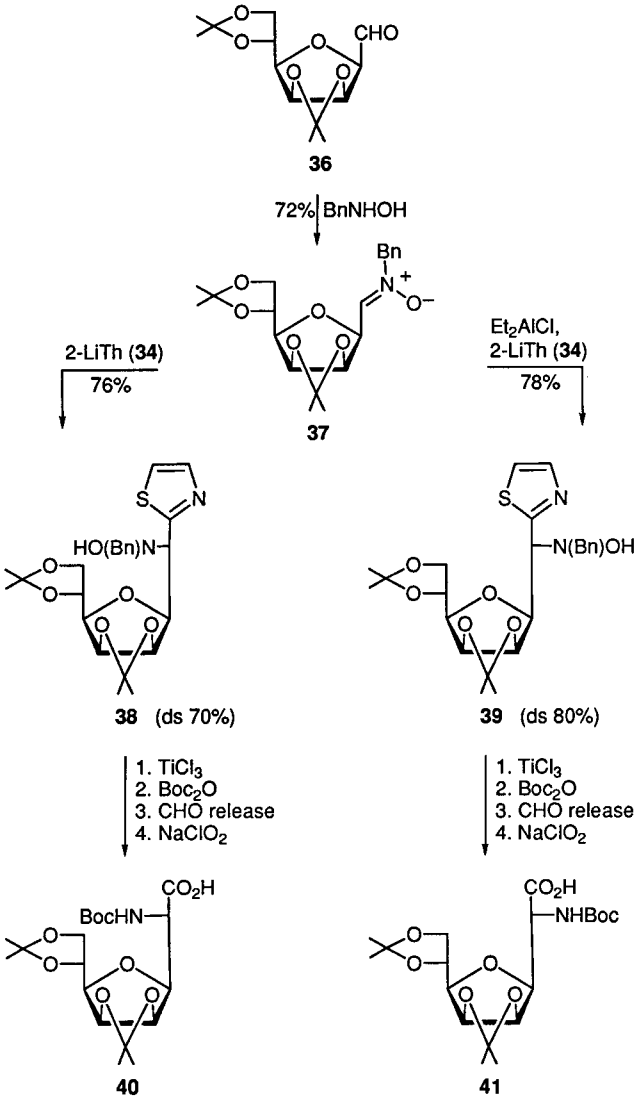


Figure 4. Nitrone approach to *C*-glycosyl glycines.

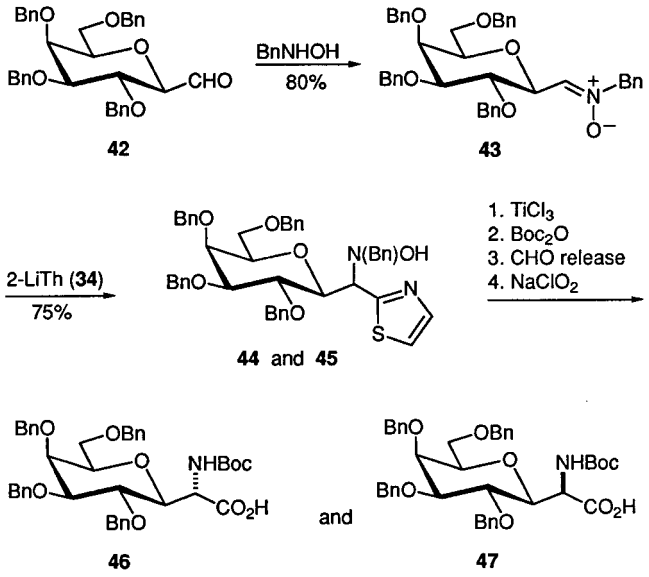
A recent approach in which the problem of the stereochemistry at the anomeric center of the sugar moiety is overcome was described by Dondoni and co-workers.[25] The key step consisted of the construction of the glycinyl moiety via addition of a suitable *C*-nucleophile (2-lithiothiazole **34** or 2-lithiofuran **35**) to the nitrone group linked in a stereochemically well-defined manner to the anomeric carbon of the sugar moiety. Specifically, the nitrone group served as the precursor of the amino group and the thiazole[26] or furan[27] ring as the precursor of the carboxylate function (Figure 4). Various *N*-benzyl nitrones of sugars were readily available by condensation of formyl *C*-glycosides with *N*-benzylhydroxylamine.[28] These compounds were configurationally stable, easily storable for months without appreciable decomposition. Hence, in this approach it was only necessary to control the stereochemistry at the central carbon atom of the glycinyl moiety under construction in order to obtain either the L- or D-α-amino acid. As shown in the example reported in Scheme 7, this issue has been addressed and the problem elegantly solved. The addition of 2-lithiothiazole **34** to the *N*-benzyl nitrone **37** derived from formyl *C*-mannofuranoside diacetonide **36** showed opposite diastereoselectivity depending on whether the addition of the nucleophile occurred to the free nitrone or its precomplexed form with diethylaluminum chloride (Et_2AlCl) (Scheme 7). Under the former conditions, the main product was the *N*-benzyl-hydroxylamine **38** with the *S*-configuration at the newly formed stereocenter whereas under the latter conditions the main product was the *R*-configured epimer **39**. The structure of **39** was established by X-ray crystallography. Suitable elaboration of the hydroxylamines **38** and **39**, i.e., the reduction of the *N*-benzylhydroxylamino group to amino group and the conversion of the thiazole ring to formyl and oxidation, afforded the pair of β-D-mannofuranosyl glycines as L- (compound **40**) and D-isomer (compound **41**).

The same nitrone-based approach was employed[25] for the preparation of epimeric β-D-galactopyranosyl glycines **46** and **47** starting from the galactoside nitrone **43** (Scheme 8). However, the addition of 2-lithiothiazole **34** to either free **43** or its precomplexed derivative with Et_2AlCl afforded mixtures of *N*-benzylhydroxylamines **44** and **45** in a similar ratio

Scheme 7



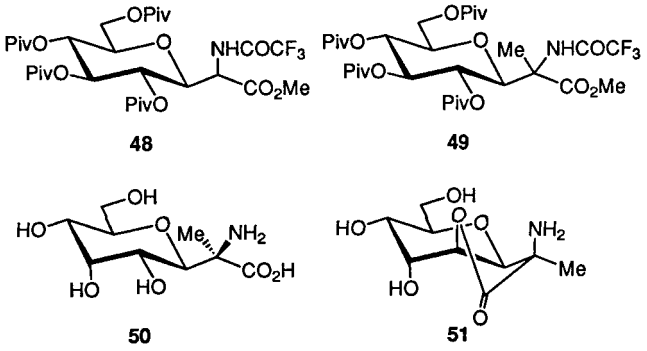
Scheme 8



(3:1). The assignment of the structure of these compounds was based on a CD study of the corresponding *N*-Boc amines. According to earlier observations on similar compounds, the *R*- and *S*-isomers

were characterized by the positive and negative Cotton effect, respectively. The lack of a full stereocontrol as observed in the addition of 2-lithiothiazole **34** to **43** may be a limitation on the use of this nitrone-based approach to *C*-glycosyl glycines. A more extensive investigation by the use of other nitrones of readily available formyl *C*-glycosides[29] will establish the scope of this sugar amino acid synthesis. In the meantime, it was observed[25] that the glycinyl group with tunable *R*- or *S*-configuration can be efficiently introduced at the nonanomeric center of various furanoses and pyranoses via the above complexed and noncomplexed nitrone addition strategy.

In closing this section, another scarcely exploited approach has to be mentioned. The β-D-glucopyranosyl glycine methyl ester **48** was prepared as a mixture of *R*- and *S*-epimers by *C*-glycosylation of the *O*-alkyl, *O*-silyl ketene acetal derived from *N*-trifluoroacetyl glycine alkyl ester.[30] Quite interestingly, β-D-*C*-glucopyranosyl alanine **49**, a quaternary α-amino acid, was prepared also by the same route starting from the ketene acetal derived from a *N*-trifluoroacetyl alaninate. Another paper has appeared[31] dealing with the stereoselective synthesis of the quaternary *C*-glycosyl amino acid β-D-*C*-allosyl alanine **50**, while the altrosyl isomer **51** was obtained in the form of the corresponding lactone.

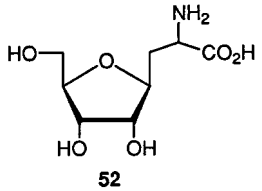


48 **49** **50** **51**

B. *C*-Glycosyl Alanines

Unlike the above quaternary α-amino acids **49**−**51**, the compounds reviewed in this section are glycosyl-substituted alanines at the methyl group of the amino acid. Therefore, the bridge holding the glycinyl and carbohydrate moieties is constituted by one carbon atom.

The synthesis of epimeric 3-(β-D-ribofuranosyl)-alanine **52** was accomplished by Rosenthal and Brink starting from a β-linked formyl *C*-riboside.[32] The

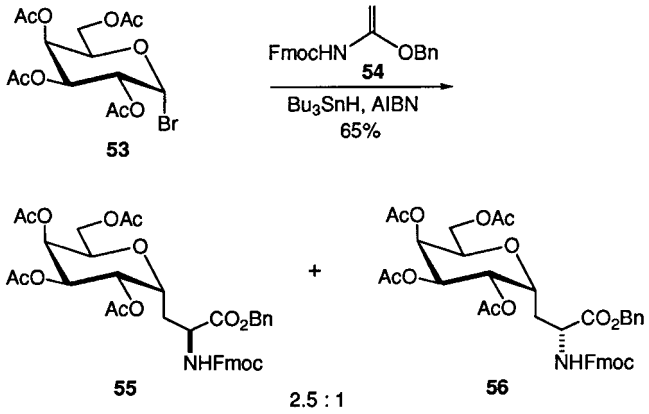


52

installation of the amino acid-bearing carbon chain was achieved by coupling the sugar aldehyde with 2-phenyloxazolin-5-one followed by cleavage of the heterocyclic ring with methanol and reduction of the resulting enoate. Unfortunately, the latter reaction was unselective and gave a mixture of epimeric α-amino acids. On the other hand, the β-linkage at the anomeric carbon of the starting sugar aldehyde was preserved in the final products.

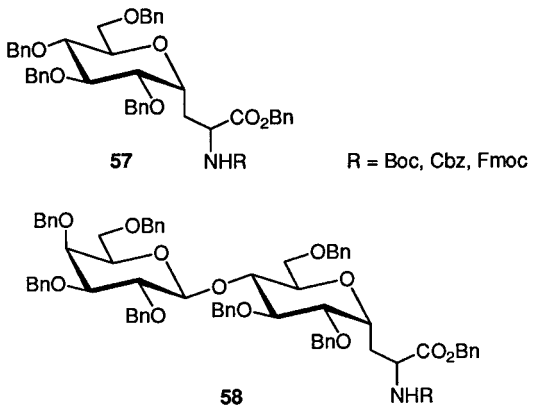
More recently a small library of *C*-glycopeptides containing α-linked D-galactosyl-, D-glucosyl-, and D-lactosyl (*R*)- and (*S*)-alanine units has been reported by Kessler and co-workers.[33] Moreover, the same research group described the synthesis of a *C*-glycosylated nonapeptide incorporating an α-configured *C*-galactosyl alanine.[34] The nonapeptide was regarded as an analogue of the nonglycosylated LH−RH agonist buserelin, and its bioactivity as a fertility drug was determined. The synthesis of the core *C*-glycosyl alanines was based on the tin−hydride-promoted free-radical addition of glycosyl bromides to urethane-protected dehydroalanine derivatives. Typically the Bu_3SnH/AIBN-promoted coupling between the peracetylated α-D-galactopyranosyl bromide **53** and the *N*-Fmoc dehydroalaninate **54** afforded a mixture of α-D-galactosyl (*S*)- and (*R*)-alanine epimers **55** and **56** in a 2.5:1 ratio and 65% overall yield (Scheme 9). Similar yields and ratios of

Scheme 9



53 **55** **56**

the α-amino acid epimers were registered in the other cases that have been reported[33] (compounds **57** and **58**). Hence, while the carbon−carbon bond-forming



57

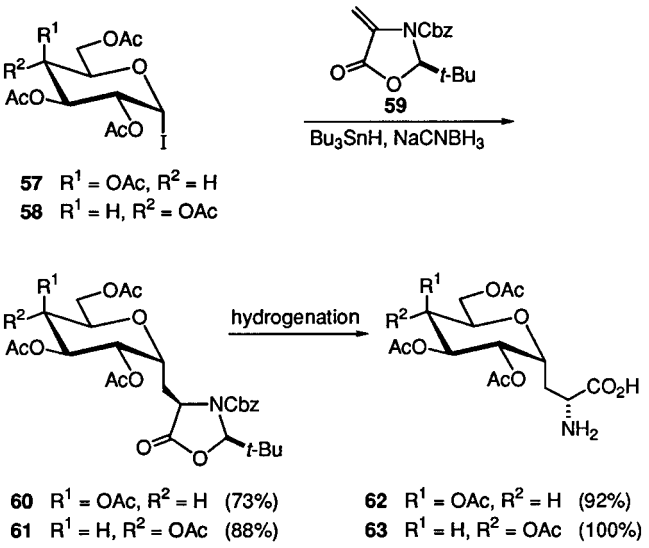
58

step gave essentially the α-configured *C*-glycoside, the hydrogen-atom transfer to the C-2 of the amino acid moiety was poorly stereoselective and led to mixtures of isomers. Even the use of chiral dehy-

droalanine derivatives by incorporation into dipeptide and tripeptide systems did not improve the stereoselectivity of the latter step. Nevertheless, the gram-scale separation of the epimers by chromatography demonstrated the preparative scope of this method.

A method quite efficiently exploiting the chirality of an alanine derivative as a building block adapted for the *C*-glycosidation reaction has been reported in a preliminary form.[35] The L-alanine was converted into a chiral methyleneoxazolidinone, such as the (*R*)-enantiomer **59** shown in Scheme 10. The Bu_3SnH/$NaCNBH_3$-promoted radical additions of the peracetylated iodosugars **57** (D-*galacto*) and **58** (D-*gluco*) to **59** gave the corresponding α-linked *C*-glycosides **60** (73%) and **61** (88%) as single diastereomers. Subsequent hydrogenolysis of these compounds proceeded almost quantitatively to give the α-D-galactosyl D-alanine **62** and the α-D-glucosyl isomer **63**. Evidently in both cases the addition of **59** occurred exclusively to the α-face of the glycosyl radical and the hydrogen-atom transfer to the intermediate oxazolidinoyl radical occurred with high stereoselectivity as well in an *anti* manner to the *tert*-butyl group.[36] Hence, the original configuration of the L-alanine appeared to have been inverted in the resulting *C*-glycosyl amino acids.

Scheme 10

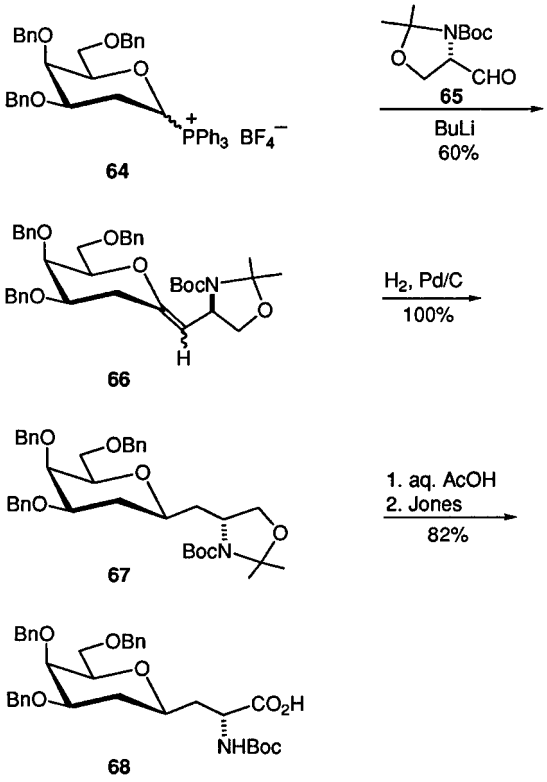


57 R^1 = OAc, R^2 = H
58 R^1 = H, R^2 = OAc

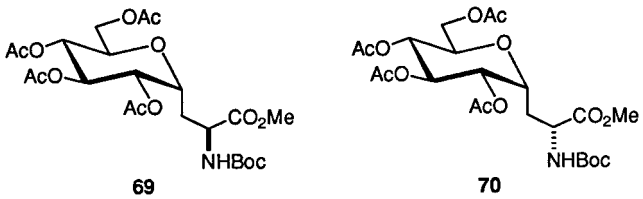
60 R^1 = OAc, R^2 = H (73%)
61 R^1 = H, R^2 = OAc (88%)
62 R^1 = OAc, R^2 = H (92%)
63 R^1 = H, R^2 = OAc (100%)

Also, Lieberknecht and Bravo and their co-workers intended to develop a synthetic approach exploiting the configuration already in place of the amino group in an amino acid-derived reagent.[37] To this aim, the L-serine-derived aldehyde **65** was considered as the reagent of choice[38] for introducing a β-amino alcohol unit at the sugar anomeric carbon atom via Wittig reaction with the ylide derived from 2-deoxy-galactosyl phosphonium fluoroborate **64** (Scheme 11). Hence, the generation of the ylide from **64** using BuLi and coupling with **65** afforded the exocyclic enol ether **66** as a mixture of *E*/*Z* isomers in a 1:1 ratio and 60% overall yield. Quite rewardingly, the hydrogenation of the above mixture of products turned out to occur quantitatively with a very good level of stereoselectivity to give the β-linked *C*-glycoside **67** as a single product. The two-step cleavage of the *N*-Boc oxazolidine ring of this compound afforded the target 2-deoxy-D-galactopyranosyl D-alanine **68**. While the preparation of the L-isomer can be carried by using the enantiomer of **65**, the synthesis of other compounds featuring different carbohydrate moieties is conditioned by the availability of isomers of the sugar phosphonium salt **64**.

Scheme 11

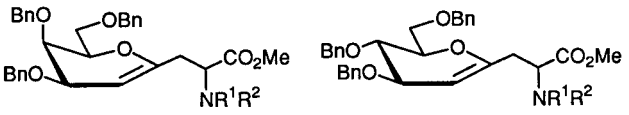


A nonstereoselective route to 3-(α-D-glucopyranosyl)-L-alanine **69** and the D-isomer **70** has been reported starting from an allyl *C*-glucoside.[39] The method is essentially centered on the Sharpless asymmetric dihydroxylation of the allyl chain followed by oxidation of the primary hydroxyl group and substitution of the secondary hydroxyl group with the amino function via the azido derivative. Thus, access to the two epimeric α-amino acids **69** and **70** was made possible by the low stereoselectivity of the Sharpless dihydroxylation step.



69 **70**

A new entry to *C*-glycosyl amino acids has been recently reported[40] via Claisen−Ireland [3,3]-sigmatropic rearrangement of *exo*-methylene glycals whose hydroxy group at C-2 was esterified with glycine. However, the rearrangement of galactose- and glucose-derived glycals gave the corresponding *C*-glycosides **71** and **72** as mixtures of epimers at the carbon atom of the glycinyl moiety.

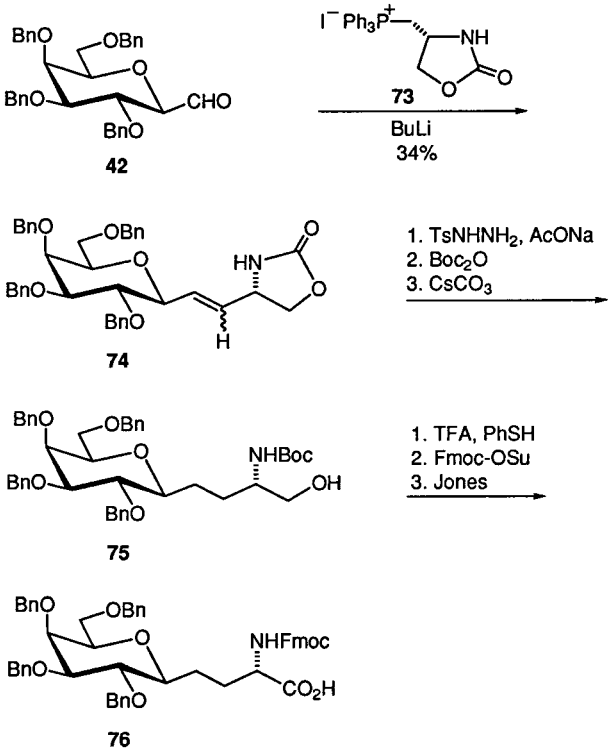


71a R^1 = H, R^2 = Boc **72a** R^1 = H, R^2 = Boc
71b R^1, R^2 = Phth **72b** R^1, R^2 = Phth

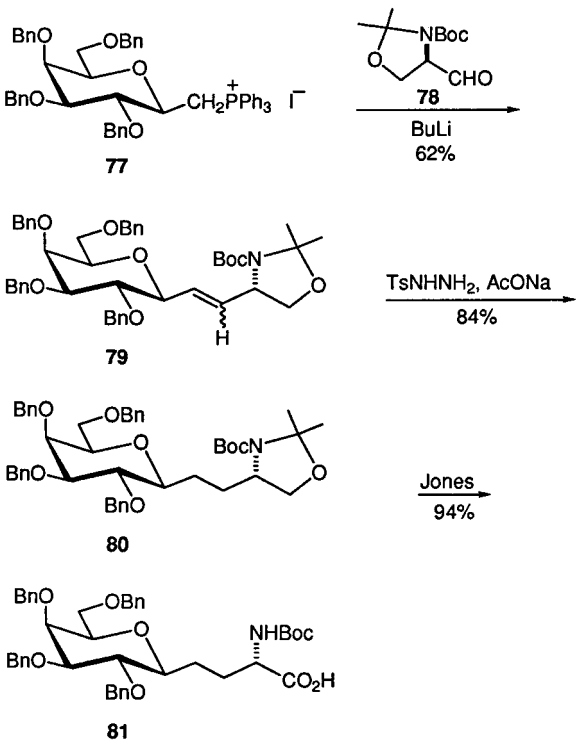
C. *C*-Analogues of Glycosyl Serines

In these compounds the carbohydrate and glycinyl moieties are connected through a two-carbon-atom bridge. These amino acids are commonly referred to as carbon-linked analogues of glycosyl serines or even more simply *C*-glycosyl serines, because they can be considered formally derived from *O*-glycosyl serines (Figure 1) by replacement of the anomeric *O*-glycosidic linkage with a carbon−carbon bond. The widespread occurrence of *O*-glycosyl serine and threonine units in natural glycopeptides is promoting a great deal of synthetic work toward their *C*-analogues for reasons that have been succinctly outlined in the Introduction section of this review. However, the interest for this class of amino acids is quite recent and parallels the increasing importance of glycobiology, the science "dealing with the role of carbohydrates in biological events".[4a] Being well aware from various treatises in the field[41] on the importance of carbohydrate attachment in biopolymers, in the early 1990s Petrus and BeMiller attempted a synthetic approach to the methylene isostere of β-D-xylopyranosyl L-serine by a nitroaldol condensation of the sugar nitromethane with formaldehyde.[42] The first synthesis of the target amino acid was not completed, while the assignment of the stereochemistry of intermediates was postponed to an X-ray structure determination. The synthesis of a β-linked *C*-galactosyl L-serine **76** was reported in 1992 by Bednarski and co-workers (Scheme 12), and the compound was used in two different biological studies.[43] In the first study[43a] the glycosyl α-amino acid was incorporated by solid-phase synthesis into a 17-amino acid α-helical peptide. This peptidomimetic synthesis owed its impetus to the desire to evaluate the effect of such an isosteric substitution on the conformation of the peptide backbone and on the biological properties. The objective of the second study[43b] was the use of the same amino acid for the construction of a long-chain alkyl amide (tetradecyl) as a galactosphingolipid mimic. The biological aim was to discover new inhibitors of the HIV-1 infection in CD4-negative cells. The key step in the reaction sequence leading to **76** and shown in Scheme 12 involved the coupling of sugar and amino acid chiral building blocks with a firmly established configuration at the anomeric carbon atom and at the carbon bearing the amino group. Accordingly, a Wittig-type reaction was carried out using the configurationally stable β-linked formyl *C*-galactoside **42** and the ylide derived from the oxazolidinone-based phosphonium salt **73**, a known β-alanyl anion equivalent.[44] The resulting olefin **74** (*E*- and *Z*-isomers, 34% overall yield) was reduced with in situ generated imide, and the oxazolidinone ring was cleaved to the amino alcohol **75**. The oxidation step with the Jones reagent (CrO_3/H_2SO_4) and exchange of the amino protecting groups from *N*-Boc to *N*-Fmoc for Fmoc-based automated peptide synthesis were routine and gave the target product **76**. However, while the transformation of **74** into **76** involved high-yield reactions, the Wittig-type coupling between **42** and **73** occurred in rather low yield (34%) and was hardly reproducible in our hands. This serious drawback led us to develop an alternative *C*-galactosyl serine isostere synthesis. In our method[45] the reaction partners in the Wittig-type reaction were the ylide derived from the D-galactosylmethyl phosphonium salt **77** and the amino aldehyde[38] **78** (Scheme 13).

Scheme 12



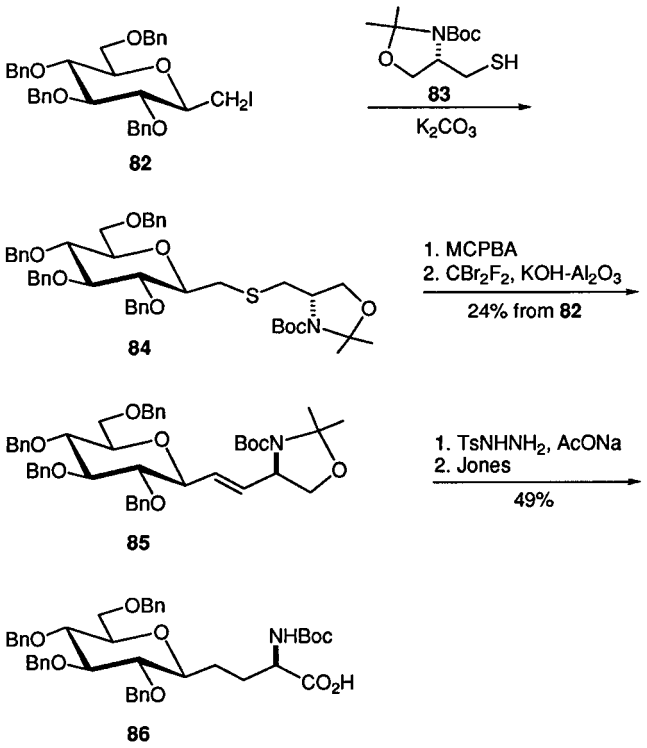
Scheme 13



This reaction afforded the olefin **79** as a mixture of *Z*- and *E*-isomer (7:1 ratio) in 62% isolated yield. This mixture was reduced with diimide, and the resulting *C*-galactoside **80** was transformed into *C*-galactosyl *N*-Boc L-serine **81** using the Jones reagent. Suitable conditions were described to perform the hydrolysis−oxidation of the oxazolidine ring to carboxylic acid in a single step.

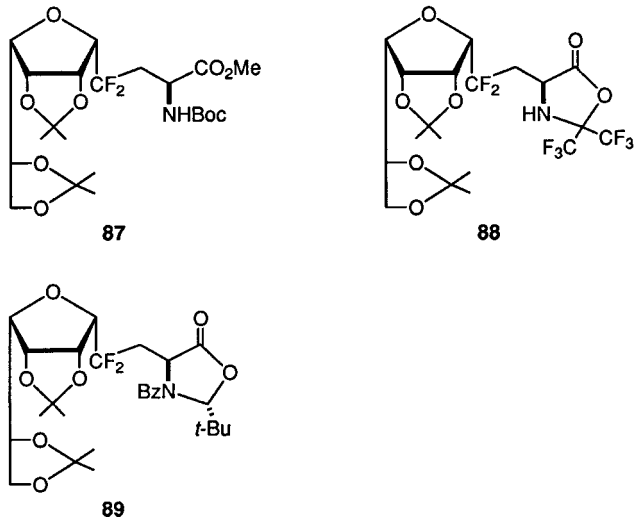
The coupling between the iodomethyl *C*-glucoside **82** and the chiral thiol **83** (Scheme 14) was the key

Scheme 14



step in another approach centered on the use of a *C*-glycoside and an alanine equivalent.[46] The oxidation of the resulting sulfide **84** and subsequent extrusion of SO_2 by Ramberg−Bäcklund rearrangement served to build up the carbon bridge between the two chiral moieties in the form of the *E*-alkene **85**. The latter was readily transformed into the *C*-glucosyl D-serine **86** by the same reaction sequence described in Scheme 13 for the conversion of **79** to **81** (diimide reduction and Jones oxidation). The L-isomer of **86**, the methylene isostere of the *O*-glycoside which is present in natural glycopeptides, should be accessible by the same route starting from the enantiomer of **83**. The synthesis of this compound by another approach will be described below in this section.

Free-radical coupling reactions between *gem*-difluoro-substituted sugar derivatives (*gem*-difluoroenol ether and its selenophenol adduct) and suitable alanine-derived reagents were used for the preparation of α-linked *gem*-difluoromethylene isosteres **87**−**89** of furanosyl L-serine.[47] The formation of radical intermediates either at the anomeric carbon or at the exocyclic α-position led to mixtures of α- and *β*-anomers. Consequently, low yields were registered for compounds **87** (14%) and **88** (30%), while compound



89 was isolated in higher yield (72%) but accompanied by 20% of the diastereoisomer at the amino acid center. The synthesis of analogues of **88** and **89** bearing shorter carbon chains at the nonreducing end of the furanose ring was also described. No characteristics of the products which have been prepared were provided in this communication.

Given the evident advantages associated with the use of masked α-amino acid building blocks, the homoalanine equivalent reagents **90**−**92** (Figure 5)

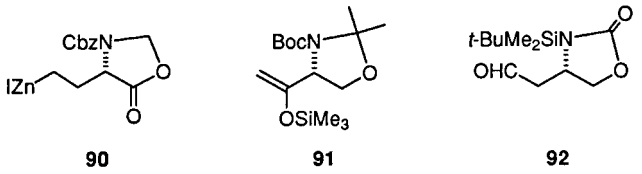
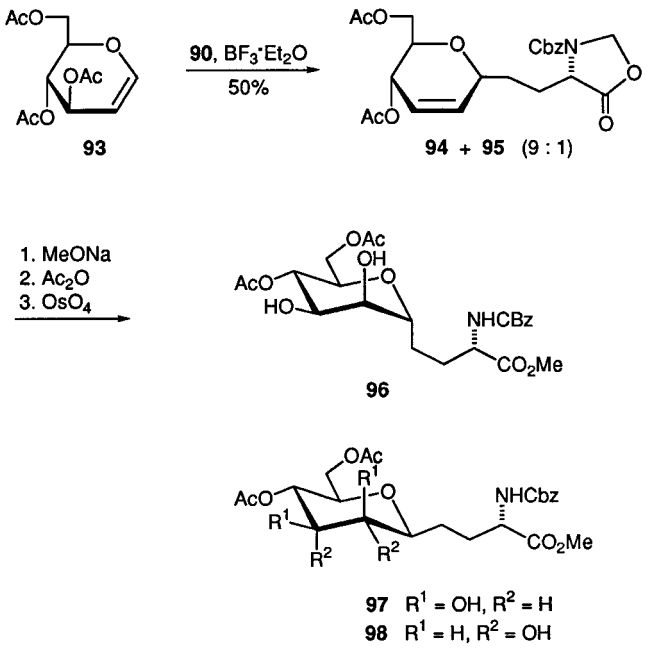


Figure 5. Homoalanine equivalent reagents.

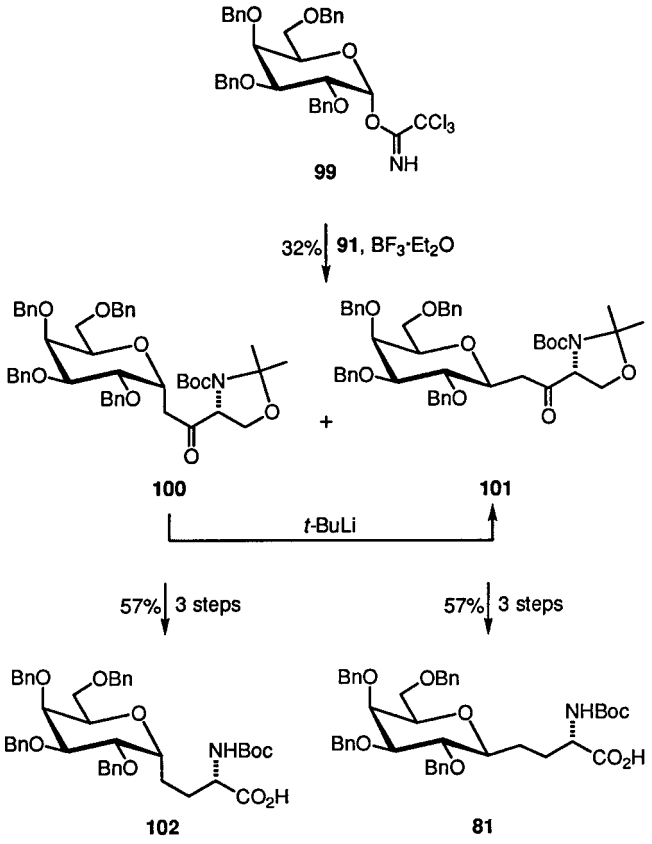
were also devised[48−50] as building blocks in new synthetic approaches via stereoselective *C*-glycosidation reactions. Compounds **90** and **91** represent nucleophilic reagents, i.e., potential *γ*-homoalanyl anions, whereas **92** is an electrophilic radical or cation equivalent. Accordingly, the in situ generated zinc reagent **90** of Dorgan and Jackson[48] reacted regioselectivity at C-1 of the tri-*O*-acetyl-D-glucal **93** in the presence of boron trifluoride etherate to give the α-adduct **94** and the *β*-isomer **95** in a 9:1 ratio and 50% overall yield (Scheme 15). The mixture of these *C*-glycosides was transformed into the α- and *β*-D-mannopyranose L-serine methylene isosteres **96** and **97** and into the *β*-D-allopyranose derivative **98** via a reaction sequence involving the unmasking of the glycinyl moiety from the oxazolidinone ring, reacetylation of the deprotected hydroxy groups, and the *cis*-hydroxylation of the double bond. Inappropriately, in this communication the characteristics of the final amino acids were not described.

A new approach to *C*-glycosyl serines was described by us[49] with the use of the silyl enol ether **91**. This new reagent can be prepared in multigram scale in five steps starting from commercially available methyl L-threoninate. The Lewis-acid-promoted coupling of **91** with the electrophilic sugar galactopyranosyl trichloroacetimidate **99** (Scheme 16) occurred with

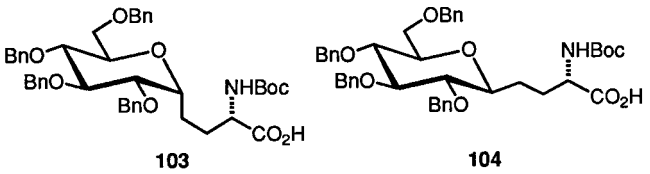
Scheme 15



Scheme 16

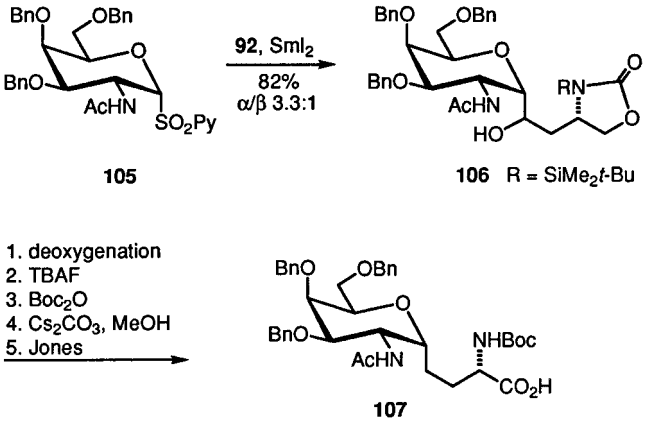


high α/β selectivity (19:1), while the yield of the isolated α-linked *C*-glycoside **100** could not be improved above 32%. However, a large amount of the most expensive reagent, the silyl enol ether **91**, was recovered configurationally unaltered in the form of its precursor acetyl oxazolidine. The presence of the carbonyl group in the side chain of **100** allowed the base-promoted transformation into the thermodynamically more stable β-linked anomer **101**. Then from each isolated and pure *C*-galactoside **100** or **101** the corresponding D-galactopyranose-CH_2-L-serine **102** or **81** was obtained by the removal of the carbonyl oxygen (reduction and then Barton−McCombie deoxygenation) and the one-pot oxidative cleavage (Jones reagent) of the heterocyclic ring. By the same reaction sequence, the α- and β-linked D-glucopyranose pair **103** and **104** was also prepared, thus providing an additional demonstration of the viability of this method to α- and β-linked *C*-analogues of glycosyl serines starting from a single carbohydrate precursor. It is worth noting that the L-amino acid **104** is the epimer of compound **86** shown in Scheme 14.



The use of the aldehyde **92** was described in a report from the laboratories of Beau and Skrydstrup.[50] The work was targeted to the synthesis of a hydrolytically stable methylene isostere of 2-acetamido-2-deoxy-α-D-galactopyranosyl L-serine, a tumor-associated antigen. Also, reagent **92** was reported to be a stable and storable product that can be prepared in few steps from L-aspartic acid. Following parallel work in the authors laboratories on the synthesis of *C*-glycosides via coupling of anomeric samarium derivatives of sugars with electrophiles,[51] the *C*-glycosylation was performed by reductive samariation (SmI_2) of the galactosyl pyridyl sulfone **105** in the presence of the aldehyde **92** (Scheme 17). The

Scheme 17

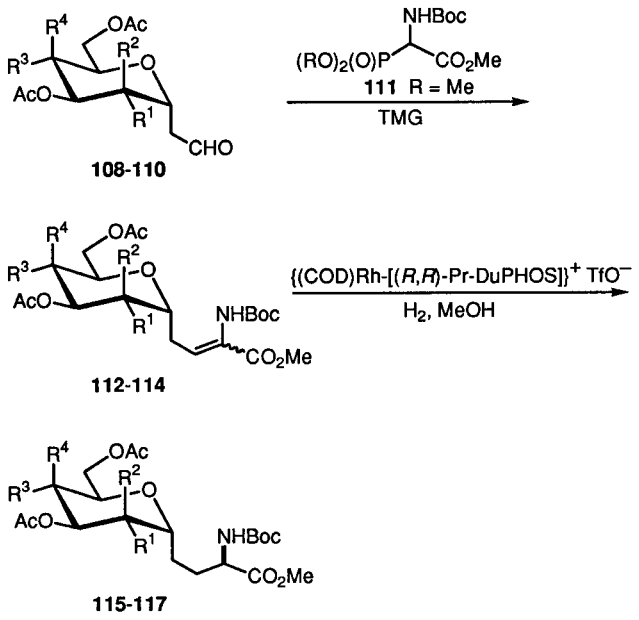


anionic *C*-glycosylation proceeded with satisfactory α-selectivity (α: β = 3.3:1) to give the *C*-glycoside **106** in good isolated yield. This successful coupling demonstrated the tolerance of the samariation-based glycosidation with the presence of an acidic NH proton in the glycosyl donor. Also, in this case the transformation of **106** into the amino acid **107** was routine[52] via deoxygenation and conversion of the oxazolidinone ring into the *N*-Boc glycinyl group.

Other methods have been reported not exploiting the chirality of natural amino acids. For instance, the groups of Toone[53] and Schmidt[54] developed similar methods that were based on the use of the glycine-

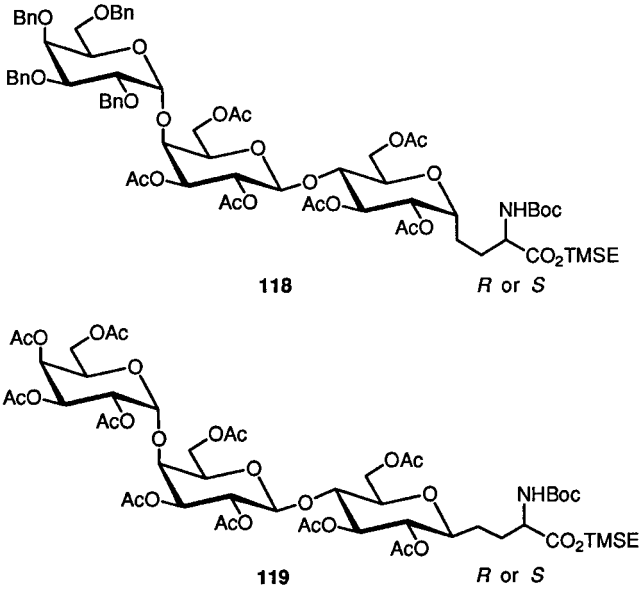
derived dimethyl or diethyl phosphonate **111**, analogues of reagent **21**, which was earlier employed for the synthesis of *C*-glycosyl *N*-Cbz-glycines (see Scheme 4). These methods involved the Wittig−Horner olefination of *C*-linked sugar aldehydes with the phosphonate to give *C*-linked enamide esters that in turn were transformed to amino acids by reduction of the carbon−carbon double bond. Hence, a good level of stereocontrol in the later step was crucial for the assessment of the configuration at the central carbon atom of the glycinyl moiety. This issue was elegantly addressed by Toone and co-workers[53] by an asymmetric catalytic hydrogenation using DuPHOS−Rh^+ catalysts. In particular, the *E*/*Z* mixtures of α-linked enamide esters of glucose **112**, galactose **113**, and mannose **114** (Scheme 18) were transformed into the

Scheme 18

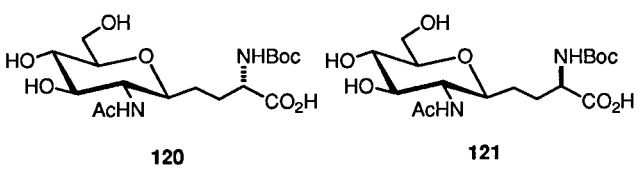


Compound	R^1	R^2	R^3	R^4	yield % enamide	de % amino acid
108, 112, 115 (gluco)	OAc	H	OAc	H	79	>95
109, 113, 116 (galacto)	OAc	H	H	OAc	85	77
110, 114, 117 (manno)	H	OAc	OAc	H	88	>95

corresponding *C*-glycosyl D-serine methylene isosteres **115**−**117** using the rhodium catalyst with *R*,*R*-*n*-Pr ligand. Some significant results (yields and diastereomeric excess, de) are reported in Scheme 18. Both D- and L-amino acids were accessible by changing the DuPHOS ligand since *R*,*R*-*n*-Pr and *R*,*R*-Et ligands gave products with *R* configuration while the *S*,*S*-Me ligand gave the *S*-isomer. In support to the versatility of this method, it was claimed that the β-linked anomers of glucose, galactose, and mannose serine isosteres had been prepared with results that paralleled those obtained with the α-anomers in terms of yield and diastereoselectivity. Moreover, a further development of the methodology appeared in a quite recent publication of the same group[55] dealing with the synthesis of *C*-glycosyl serine analogues (Galα1 → 4Galβ1 → 4Glcβ-CH_2−Ser) of the P^k trisaccharide that binds the shiga toxin and shiga-like toxins, the bacterial toxins responsible of various diseases such as haemorrhagic colitis. Hence, the final goal was the preparation of stable glycopeptides that may inhibit the shiga-like toxin's recognition by the P^k trisaccharide receptor domain. Asymmetric catalytic hydrogenation of the enamide ester α- and β-linked to the trisaccharide Gal-Gal-Glc using DuPHOS−Rh^+ with different ligands allowed one to prepare the α- and β-*C*-glycosides **118** and **119** in the D- and L-serine series. Since the carboxyl group was protected as the (trimethylsilyl)ethyl (TMSE) ester, these compounds are appropriate precursors of free glycosyl amino acids for solid-phase glycopeptide synthesis.



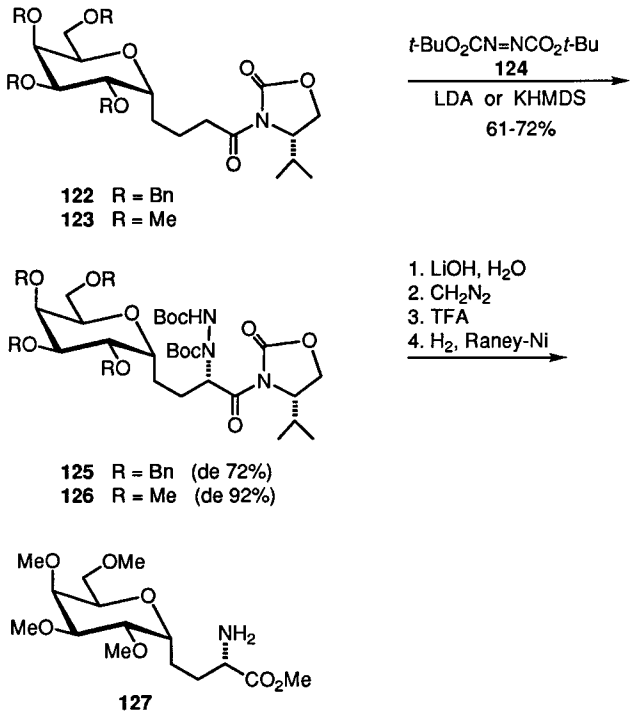
The method of Schmidt[54] did not involve the asymmetric hydrogenation of the enamide esters and therefore led to mixtures of *R*- and *S*-configured amino acids in nearly equal amounts. By this method, the *C*-glycosyl analogues **120** and **121** of 2-acetamido-2-deoxy-β-D-glucopyranosyl L-serine and D-serine were simultaneously yet nonstereoselectively prepared. The use of chiral hydrogenation catalysts that would lead to either **120** or **121** selectively did not work well, presumably because of the presence of the acetamido group in the sugar moiety. *N*-Acetylglucosamine (GlcNAc) and *N*-acetylgalactosamine (GalNAc) residues are largely diffuse in natural peptides in the form of *O*-glycosyl serine and threonine derivatives. Although the specific functions of these *O*-glycosidic linkages is not fully understood, the access to glycopeptides carrying GlcNAc and GalNAc residues linked by a hydrolytically stable bond is of great interest.[5a,7]



The de novo construction of the glycinyl moiety was considered in other synthetic routes to *C*-glycosyl

serines. The key step in a recent approach involved the electrophilic amination of *C*-glycosyl oxazolidinone enolates using a dialkyl azodicarboxylic ester derivative.[56] As illustrated in Scheme 19, the addition

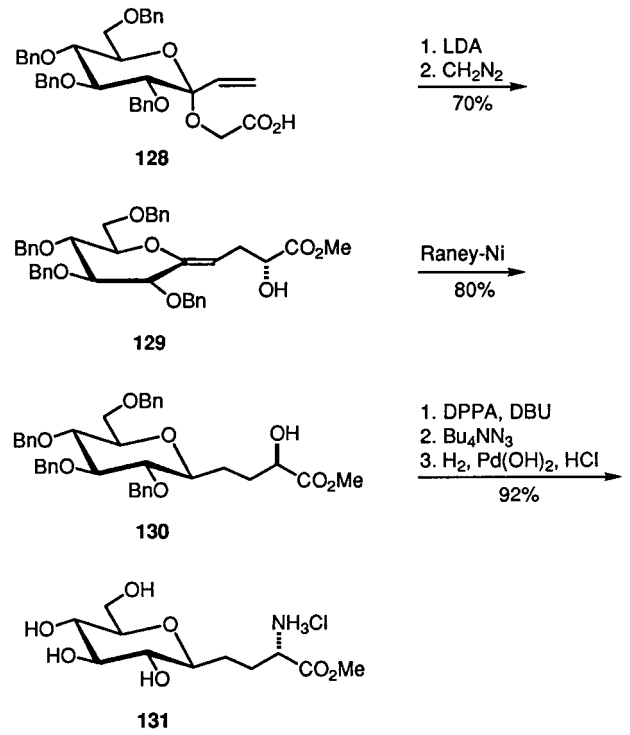
Scheme 19



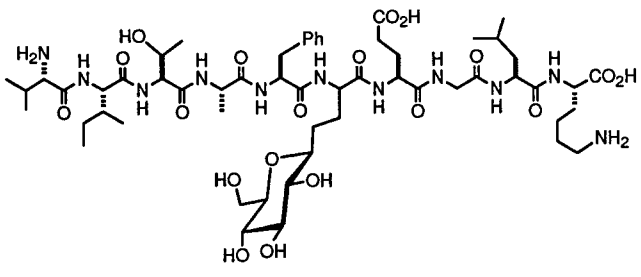
of di-*tert*-butyl azodicarboxylate **124** (DBAD) to the potassium or lithium enolate derived from the α-linked *C*-glycosides **122** and **123** afforded the corresponding hydrazides **125** (de 72%) and **126** (de 92%) as major adducts in mixtures of diastereoisomers. The isolation of pure compounds **125** and **126** was not described. Nevertheless, the four-step transformation of **126** into the glycosyl amino acid **127** was reported. Using the *β*-anomer of **122**, the corresponding hydrazide was obtained by the same method in a rewarding much higher selectivity (de 98%) than compound **125**.

The anionic [2,3]-Wittig rearrangement of the ethanoyl D-vinylketoglucoside **128** (Scheme 20) was the initial step of another approach to a *β*-linked *C*-glucosyl L-serine derivative.[57] This sigmatropic pericyclic process took place with very high internal asymmetric induction with respect to both the geometry of the double bond (*Z*) and the configuration (*R*) at the newly formed stereocenter. After esterification, the substituted exocyclic enol ether **129** was isolated as a single product that upon hydrogenation with Raney-Ni gave the *β*-linked *C*-glycoside **130** in very good yield. This compound was transformed into the target amino acid **131** in a routine manner via substitution of the hydroxy group with the azido group and reduction. This method still remains documented by a single example. The stereochemical outcome of the sigmatropic rearrangement in compounds bearing different sugar moieties may vary considerably in each case. However, the above synthetic work was accompanied by an interesting application carried out by the same research groups.

Scheme 20



The azido ester precursor of **131** was employed, after saponification, for the preparation of the *C*-linked glycosyl decapeptide **132** by solid-phase peptide synthesis.[58] Unfortunately, epimerization at the α-carbon bearing the azido group occurred during the hydrolysis of the methyl ester. Nevertheless, the mixture of the *C*-glycosyl azido acid epimers was reacted with a solid-phase linked tetrapeptide by TBTU/NEM activation.[59] Then the azido group was reduced to the amino group using racemic 1,4-dithiothreithol, and the synthesis of the decapeptide was completed by the Fmoc-based standard method. Studies on the activity of **132** in T-cell stimulation were announced.



132

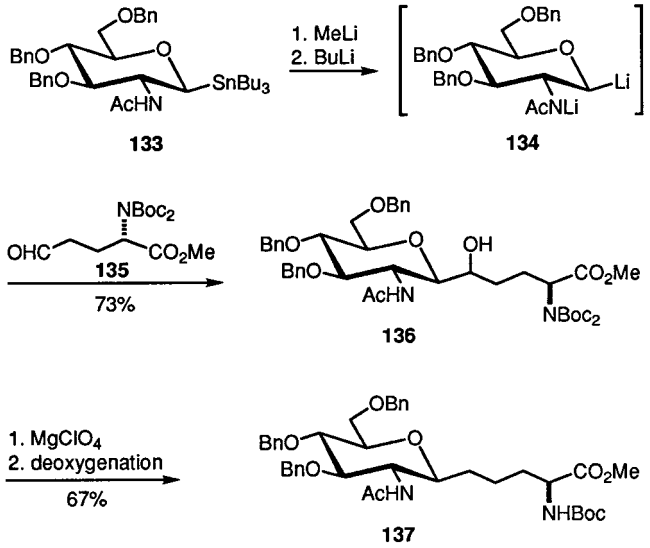
D. *C*-Analogues of Glycosyl Asparagines

A three-carbon atom bridge holds the carbohydrate and glycinyl moieties of this family of C-glycosyl amino acids. These compounds can be considered as the analogues of *N*-glycosyl asparagine (Figure 1) wherein the anomeric amidic bond has been substituted by a carbon−carbon bond. Hence, usable quantities of these amino acids with suitable protections of the amino and hydroxy groups are needed for the synthesis of modified glycopeptides.

The first synthesis of a C-glycosyl asparagine was reported three years ago by Kessler and co-workers.[60]

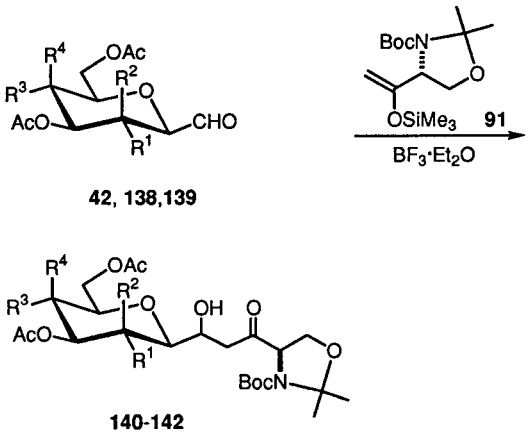
The target product was the ethylene isostere of N^4-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine, a quite diffuse amino acid in natural peptides. The key step in the synthesis relied on the stereocontrolled coupling of dilithio *N*-acetylglucosamine **134** with the five-carbon-atom aldehyde **135** derived from glutamic acid (Scheme 21). The exclusive formation of the β-D-linked C-glycoside **136** (73%) as a 1:1 mixture of diastereomers was expected on the basis of earlier work by the same research group on *C*-glycosidation reactions with anomeric carbanions.[61] The transformation of **136** into the target amino acid **137** was straightforward as it required only the removal of the Boc-protecting group and the Barton–McCombie dehydroxylation.

Scheme 21



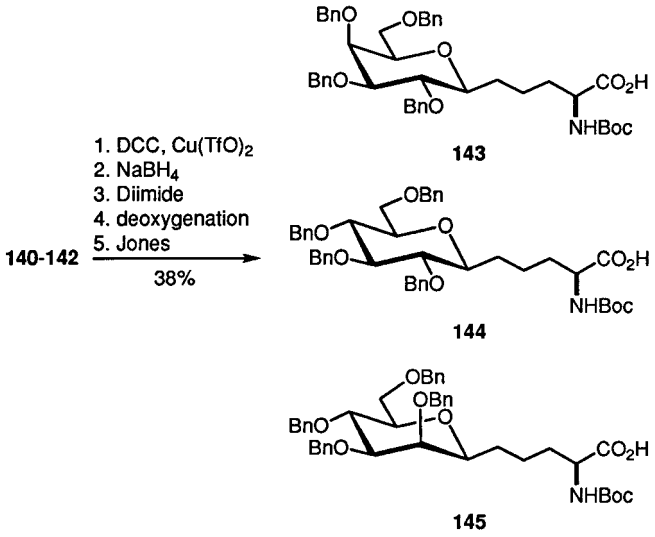
The scope of the method of Kessler remains to be established since only the above example has been reported so far. A limitation can be foreseen for the synthesis of compounds carrying a protected hydroxy group at C-2 of the sugar moiety because the metalation at C-1 is very likely accompanied by extensive 1,2-elimination.[61] On the other hand, the presence of an unprotected 2-hydroxy group in the sugar component and generation of a glycosyl dianion in order to prevent the β-elimination would lead to the presence of two free hydroxy groups in the resulting coupling product, making the selective removal of the one in the side chain quite problematic. An alternative approach was developed in our laboratory[49b,62] to overcome this potential limitation. The method was centered on the Mukaiyama-type aldol condensation between formyl *C*-glycosides and the threonine derived silyl enol ether **91** shown in Figure 5. Also, this method followed the leading concept of exploiting the existing configuration at the anomeric carbon atom of a sugar building block and at the carbon atom carrying the amino group in an amino acid equivalent. The scope of this approach was demonstrated by the synthesis of three β-linked C-glycosyl L-asparagines (D-*galacto*, **143**; D-*gluco*, **144**; D-*manno*, **145**) starting from the formyl *C*-glycosides **42**, **138**, and **139** (Scheme 22). The Lewis-acid-promoted (BF_3·OEt_2) condensation of these aldehydes with the silyl enol ether **91** gave the corresponding aldols **140**–**142** in fairly good yields. Subsequently, these compounds were transformed into the amino acids **143**–**145** via complete deoxygenation[63] and Jones oxidative cleavage of the oxazolidine ring (Scheme 23).

Scheme 22



Aldehyde	R^1	R^2	R^3	R^4	Hydroxyketone (yield)
42 (galacto)	OBn	H	H	OBn	**140** (78%)
138 (gluco)	OBn	H	OBn	H	**141** (70%)
139 (manno)	H	OBn	OBn	H	**142** (71%)

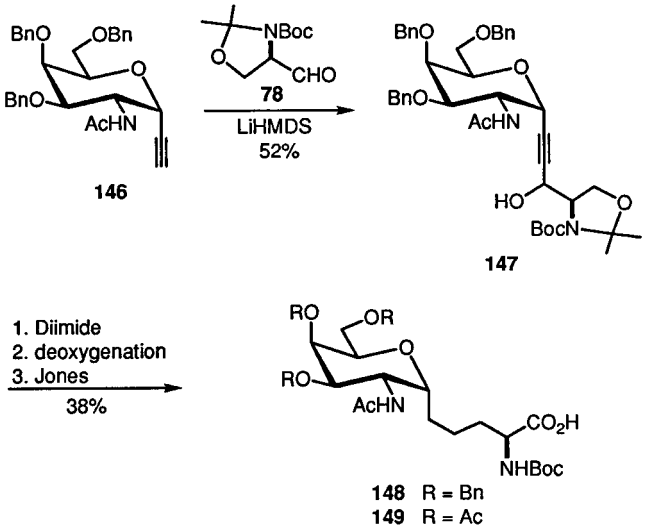
Scheme 23



Various β- and α-linked formyl *C*-glycosides were available[29] for the extension of the scope of the method described above. However, most α-D-linked (axial) isomers were unstable due to their tendency to isomerize to β-isomers particularly under basic conditions. Therefore, the method appeared to be more versatile for the synthesis of β-linked *C*-glycosyl amino acids and rather limited for the α-isomers.[49b] A quite versatile approach that allowed an entry to the α- and β-anomer pairs of various *C*-glycosyl asparagines was developed by the Dondoni group.[64] The coupling of configurationally stable anomeric sugar acetylenes[65] with the chiral amino aldehyde **78** constituted the key carbon–carbon bond-forming reaction for the construction of the five-carbon-atom chain at the anomeric center of the selected sugar.

The method is illustrated in Schemes 24 and 25 with

Scheme 24



the syntheses of the *C*-analogues of α-D- and *β*-D-linked GalNAc L-asparagines. Two identical reaction sequences were followed. Succinctly, the sugar acetylene (**146** or **150**) was first metalated (LiHMDS) and then reacted with the protected D-serinal **78**. The resulting propargylic alcohol (**147**, 52%, or **151**, 75%) was reduced (diimide) and deoxygenated (Barton–McCombie), and the oxazolidine ring was oxidatively cleaved (Jones) to the glycinyl moiety to give the target α-amino acid (**148** or **152**). It was demonstrated that these orthogonally protected *C*-glycosylated amino acids can be transformed in suitable building blocks for solid-phase peptide synthesis. For

Scheme 25

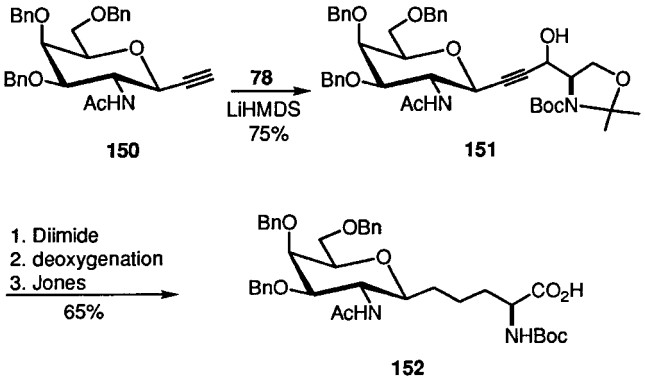
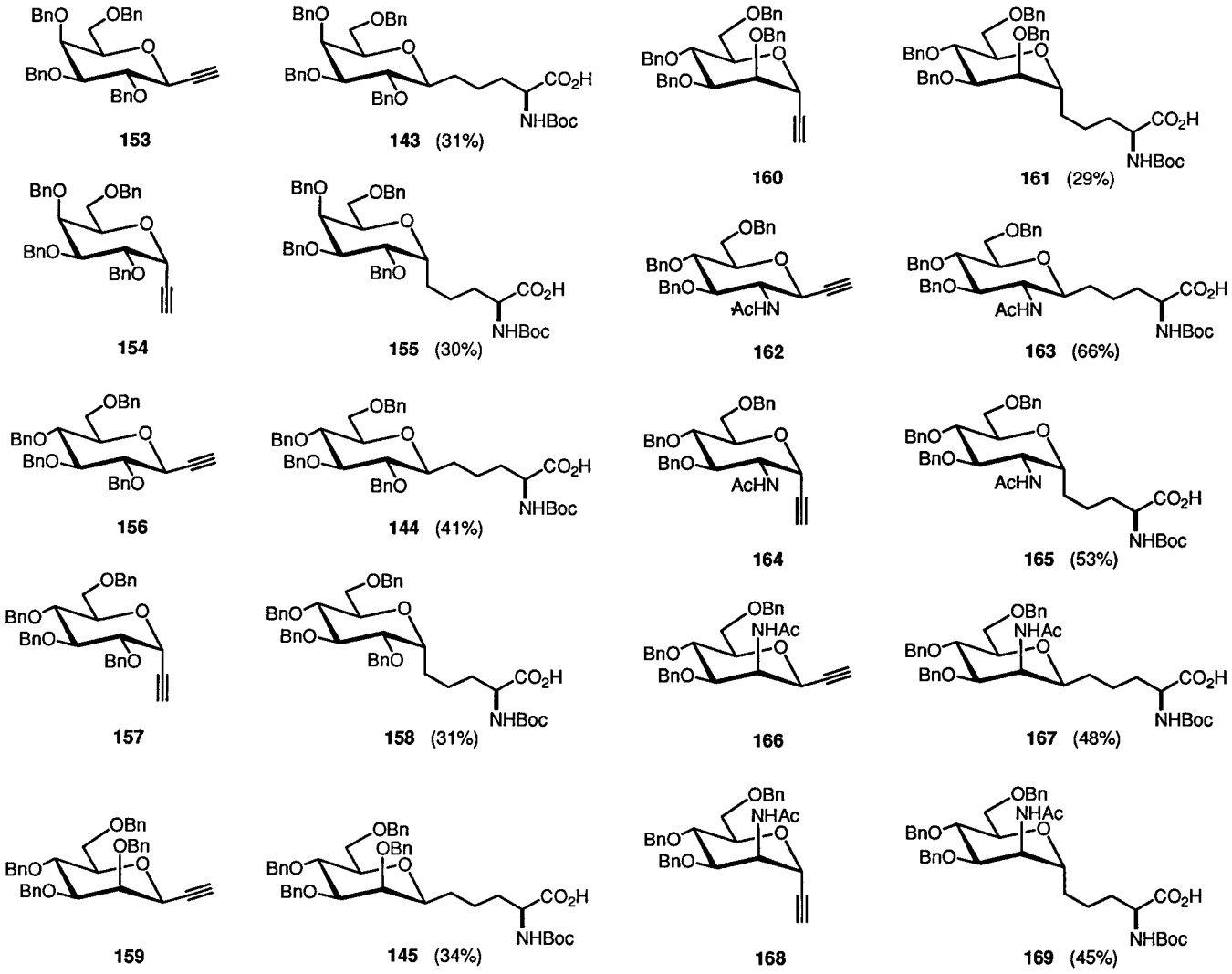


Table 1. Other Ethylene Isosteres of Glycosyl Asparagines and Their Sugar Acetylene Precursors

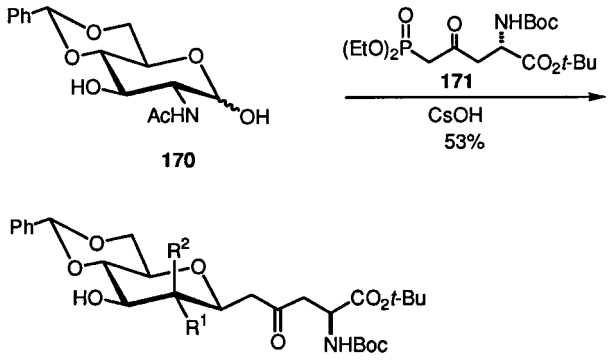


example, **148** was transformed into the peracetylated sugar derivative **149** via debenzylation by hydrogenation and acetylation. Other compounds that have been prepared are shown in Table 1. Compounds **143**−**145** proved to be identical by NMR analysis and optical rotation values to the products obtained by another route in the same laboratory (see Schemes 22 and 23).

Other approaches to these amino acids have been reported. Arya and co-workers described[56a] the synthesis of a potential precursor to the α-linked galactose derivative **155** shown in Table 1. The method involved the electrophilic amination of a suitable *C*-glycoside as described in Scheme 19 for the synthesis of a *C*-analogue of serine. Taylor and co-workers[46] prepared the *C*-glucosyl asparagine **144** (see Table 1) by the hydroboration−Suzuki coupling of an *exo*-glycal with an oxazolidine-substituted vinyl iodide.

All compounds presented above can be considered as ethylene isosteres of natural glycosyl asparagines. A new type of *C*-glycosyl asparagine isostere which has been described in a recent communication[66] is represented by **172** and **173** (Scheme 26). These

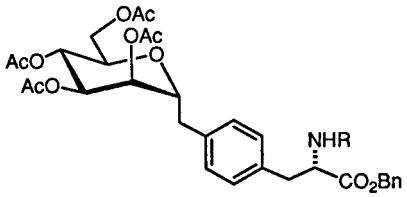
Scheme 26



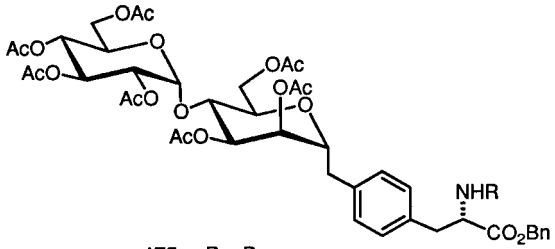
compounds feature only the substitution of the NH of the amide group by a CH_2. The key step for the assembly of the carbohydrate and amino acid moieties involved a Horner−Emmons−Wadsworth olefination and Michael addition sequence between the protected *N*-acetylglucosamine **170** and the aspartic acid-derived *β*-ketophosphonate **171**. The coupling product was obtained in satisfactory yield (53%) under suitable conditions (CsOH in MeOH, room temperature). Nonetheless, the reaction afforded a 1:1 mixture of *C*-glycoside isomers that after separation by chromatography was characterized as the GlcNAc derivative **172** and the ManNAc isomer **173**. Since the glucose derivative **172** is the most important target for biological studies, conditions have been explored to isomerize the mannose derivative **173** by base-catalyzed (*t*-BuOLi) retro-Michael reaction.

E. *C*-Analogues of Glycosyl Tyrosines

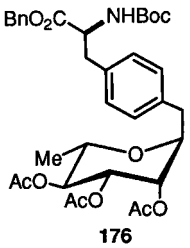
There is only one very recent paper by Gallagher and co-workers dealing with the synthesis of these compounds, shortly called *C*-glycosyl tyrosines, featuring a methylene group instead of the phenolic oxygen of tyrosine[67] (see Figure 1). Four structurally distinct compounds have been prepared that differ for the glycosyl moiety. These include D-mannose in **174**, the disaccharide Glcα1→4Man in **175**, L-rhamnose in **176**, and an unsaturated 2,3-dideoxyfuranose in **177**.



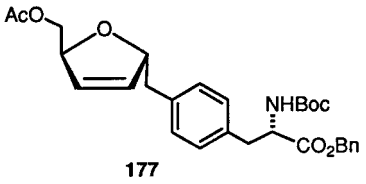
174a R = Boc
174b R = Fmoc



175a R = Boc
175b R = Fmoc



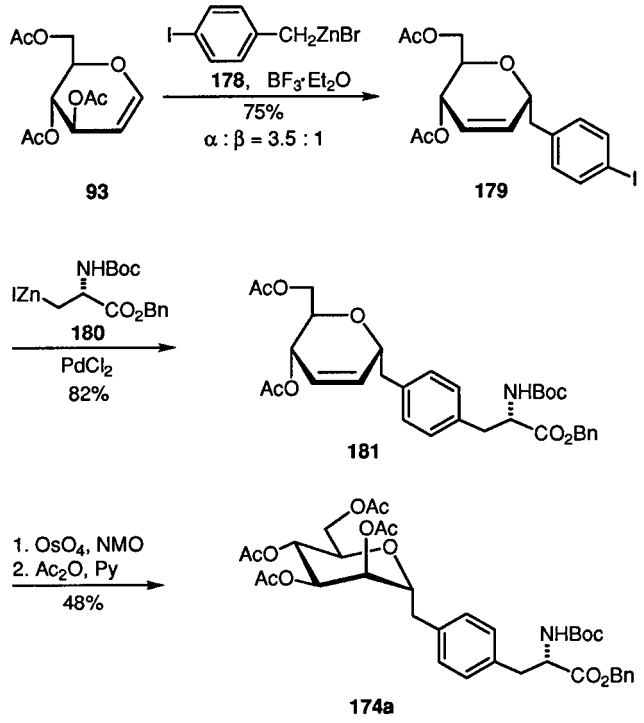
176



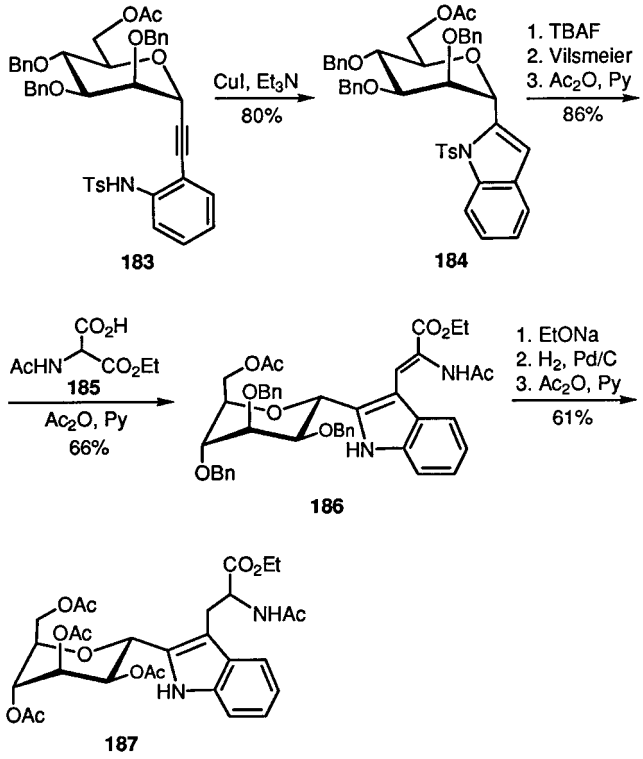
177

The synthesis of the *C*-mannosyl tyrosine **174a** exemplifies the main aspects of the reaction scheme that has been developed (Scheme 27). The method relied on two coupling reactions with organozinc reagents.[68] Hence, the *C*-glycosidic linkage was formed by the boron trifluoride etherate-promoted addition reaction of the 4-iodobenzyl bromide derived zinc reagent **178** with the D-glucal **93**, while the introduction of the glycinyl moiety on product **179** was carried out with the iodoalanine-derived zinc reagent **180** and Pd(0)-mediated catalysis. The osmium-mediated *cis*-dihydroxylation of the glycal **181** afforded the final sugar amino acid in 23% overall yield from **93**. The other compounds **175**, **176**, and **177** were prepared in a similar way with comparable yields. However, the glycosidation reaction occurred with low stereoselectivity as shown by the variable and modest α:*β* ratios ranging from 2 to 3.5:1 registered in three of the four cases examined. To demonstrate the utility of these orthogonally protected amino acids in solid-phase peptide synthesis, compounds **174a** and **175a** were transformed into the corresponding *N*-Fmoc derivatives **174b** and **175b** and two mannosyl-containing units were incorporated into a linear hexapeptide, which in turn was converted to a C_2-symmetric cyclic oligopeptide.

Scheme 27

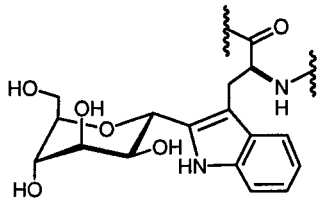


Scheme 28



F. *C*-Glycosyl Tryptophans

This section will be dealing with the only natural *C*-glycosyl amino acid that has been reported so far. In 1994 Vliegenthart and co-workers identified[69] the new glycoprotein structural motif **182** in human ribonuclease (RNase), wherein a mannose residue is connected to tryptophan by a *C*-glycosidic linkage. Subsequent fine studies by NMR spectroscopy[70] established the main structural features of the carbohydrate moiety (α-D-glycosidic bond and unusual $^1C_4$ conformation) and demonstrated that the *C*-mannopyranosyl tryptophan unit **182** was not an artificial product formed during the isolation procedures. More recently,[71] the same motif was found in recombinant human IL-12, implying that this post-translational modification might be widespread in various glycoproteins. The need for usable quantities of the free amino acid for biological studies stimulated the development of synthetic methods.

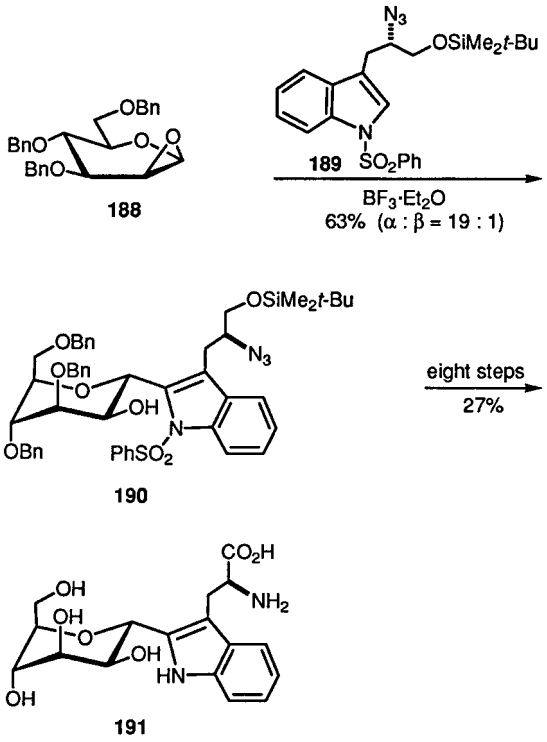


182

Isobe and co-workers described a synthetic approach involving an indolyl *C*-mannoside as intermediate and introduction of the alanyl side chain at C-3 position of the heterocycle[72] (Scheme 28). Hence, using the sugar acetylene chemistry developed in the Isobe laboratory,[73] the α-linked ethynyl *C*-mannoside **183** was first prepared from D-mannose acetate and the indole ring formed by CuI, Et_3N-promoted intramolecular cyclization. Several steps were required for the introduction of the amino acid side chain in **184** since the direct synthesis of **186** by the Yokoyama−Murakami methods[74] failed. Instead, compound **186** was prepared by formylation of **183** by the Vilsmeier reaction ($POCl_3$, DMF, KOH) and subsequent condensation with acetamide malonate monoethylester **185**. The hydrogenation of **186** and acetylation afforded the peracetylated α-*C*-mannopyranosyl tryptophan **187** as a mixture of diastereoisomers in nearly equal amounts.

A more stereoselective and concise synthesis of the same amino acid and incorporation into a peptide were described by Manabe and Ito.[75] Taking advantage of parallel studies on *C*-glycosylation of *N*-protected indoles via metalation at the C-2 position and coupling with 1,2-anhydro-D-mannose **188**, a convergent synthetic approach was developed starting from the indole derivative **189** (Scheme 29). The latter reagent that served as a precursor of the tryptophan moiety was readily prepared from commercially available L-tryptophanol. This secured an entry to a single and configurationally well-defined glycinyl moiety, an advantage that appeared quite evident also in other syntheses discussed in earlier sections. The coupling reaction of **188** and **189** afforded the α-linked *C*-glycoside **190** in satisfactory chemical yield (63%). The subsequent transformation of **190** to C^2-α-D-*C*-mannopyranosyl-L-tryptophan **191** was routine as it involved essentially two functional group transformations (oxidation of alcohol to carboxylic acid and reduction of the azido to amino group) and the removal of the protecting groups. The isolated compound **191** showed comparable ^1H and ^{13}C NMR spectra to those reported by the Vliegenthart group[70] for the mannosyl tryptophan unit characterized in the natural peptide **182**. The $^1C_4$ chair

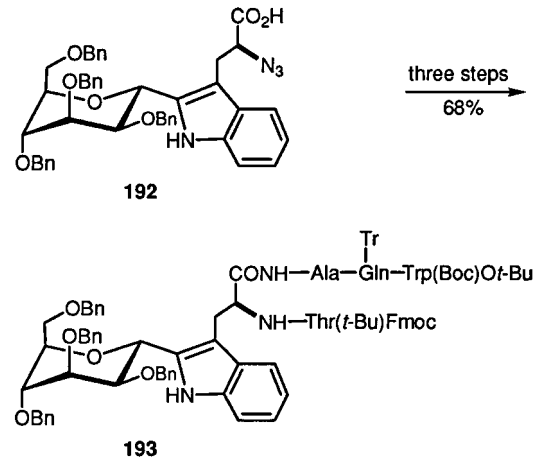
Scheme 29



conformation of the D-mannose moiety with the equatorially oriented L-tryptophan was thus confirmed.

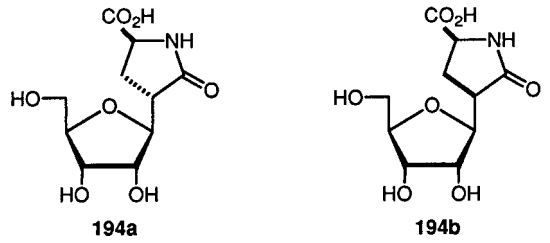
The transformation of the *C*-glycoside **190** into **191** involved the azido acid **192** as an intermediate. This orthogonally protected compound provided a formidable opportunity for the incorporation of the *C*-mannosyl tryptophan unit in the peptide **193** by the azido acid-based 'racemization-free' peptide synthesis (Scheme 30).

Scheme 30



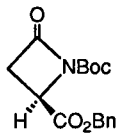
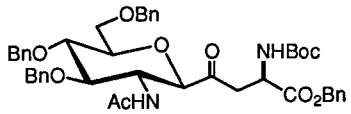
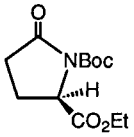
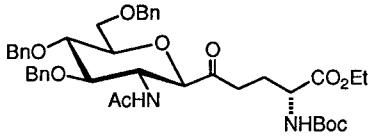
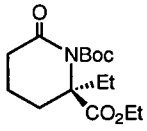
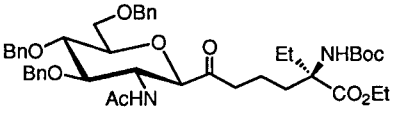
G. Miscellaneous

In addition to those described in the preceding sections, other types of C_n bridges can be found in anomeric *C*-glycosyl amino acids. The synthesis of *β*-D-ribosyl L-pyroglutamic acid derivatives **194a,b** was reported by Baldwin and co-workers[76] via the reaction of the Schollkopf's bis-lactim ether as glycine anion equivalent[77] with a protected D-ribosyl acrylate. However, these compounds were prepared for their use in biological studies regarding the biosynthetic origins of *C*-nucleosides.

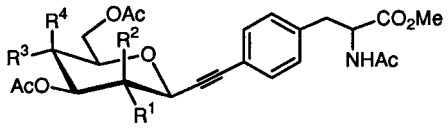


A straightforward entry to compounds **196**, **198**, and **200** (Table 2) whose carbonyl is a part of variable carbon bridges has been described by Westermann and co-workers.[78] This approach exploited the facile ring opening of *N*-Boc-protected lactams **195**, **197**, and **199** by the dilithio *N*-acetylglucosamine **134** generated from the *β*-linked stannyl derivative **133** as described earlier by Kessler[60] (see Scheme 21). The yields of isolated products were satisfactory but lower than in the Kessler approach. It is noteworthy that this method allowed the preparation of a quaternary glycosyl amino acid (compound **200**). This structural diversity may be advantageous in modified glycopeptide synthesis.

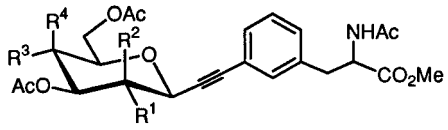
Table 2. *β*-Linked *C*-Glycosyl Amino Acids 196, 198, and 200 and Their Precursors 195, 197, and 199

Lactam	Product (yield)
 **195**	 **196** (32%)
 **197**	 **198** (42%)
 **199**	 **200** (38%)

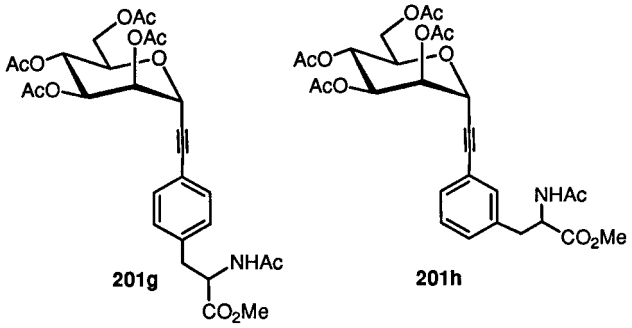
A more substantial modification of natural glycosyl amino acids can be found in the glycosylacetylene—phenylalanine derivatives **201** that have been described by Meldal and Vasella and co-workers.[79] The C_n bridge between the carbohydrate and the glycinyl moiety which is present in these compounds is constituted of an ethynediyl and a tolyl group. While the latter group served to anchor the amino acid moiety to the sugar acetylene via Pd chemistry, the rigid acetylene bridge was expected to confer some new chemical, structural, and biological properties to synthetic glycopeptides in which those amino acids were eventually incorporated.



201a (gluco) R^1,R^3 = OAc; R^2,R^4 = H
201b (galacto) R^1,R^4 = OAc; R^2,R^3 = H
201c (manno) R^1,R^4 = H; R^2,R^3 = OAc



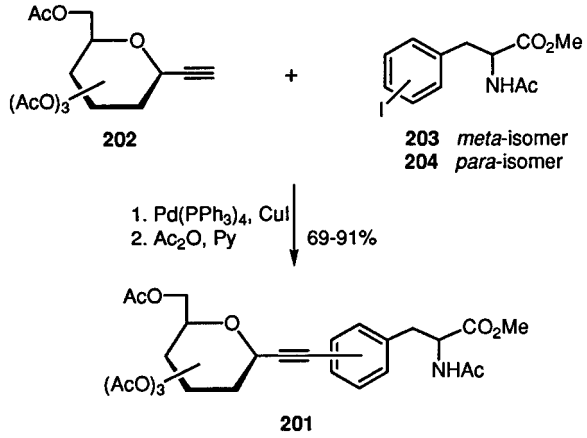
201d (gluco) R^1,R^3 = OAc; R^2,R^4 = H
201e (galacto) R^1,R^4 = OAc; R^2,R^3 = H
201f (manno) R^1,R^4 = H; R^2,R^3 = OAc



201g **201h**

Due to the final use of glycosyl amino acids as building blocks in glycopeptide mimic library synthesis, various compounds of the general type **201** were prepared by the $Pd(PPh_3)_4$/CuI-promoted coupling of hydroxy-protected (OAc) sugar acetylenes **202** with racemic 3- and 4-iodophenylalanine **203** and **204** in piperidine as a solvent (Scheme 31). This

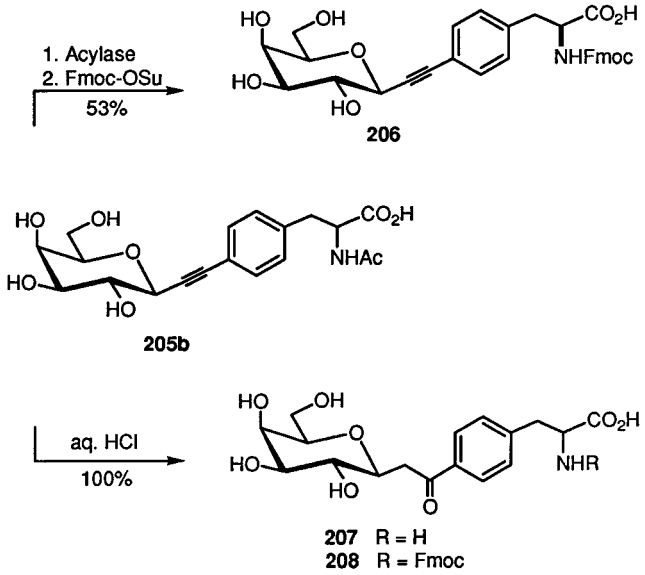
Scheme 31



202 **203** *meta*-isomer **204** *para*-isomer **201**

approach required optimized reaction conditions to obtain the coupling products in preparatively meaningful yields. Some problems arose from the partial deacetylation of the sugar moieties during the course of the coupling reactions. Nevertheless, the scope of this approach was documented by the synthesis of six compounds **201a**−**f** which display glucose, galactose, and mannose moieties β-D-linked through the acetylene bridge to the *meta* or *para* position of phenylalanine. Also, two compounds **201g** and **201h** having the amino acid group linked to the α-D-mannosylacetylene moiety were described. All compounds **201a**−**h** were converted into the corresponding *N*-acetylated amino acids by removal of the *O*-acetyl group with MeONa and saponification of the methyl ester. Since the iodinated phenylalanine reagents **203** and **204** are racemic compounds, each product **201** and the corresponding free amino acid was obtained as a mixture of diastereoisomers. However, stereoisomerically pure compounds were obtained by enzymatic deacylation of mixtures of *R,S*-stereoisomeric acetamides followed by Fmoc protection. For example, the epimeric galactosylacetylene−phenylalanine **205b** treated with the acylase I from *Aspergillus melleus* was selectively deacylated to the free L-amino acid, which in turn was transformed into the Fmoc derivative **206** (Scheme 32). Moreover, the

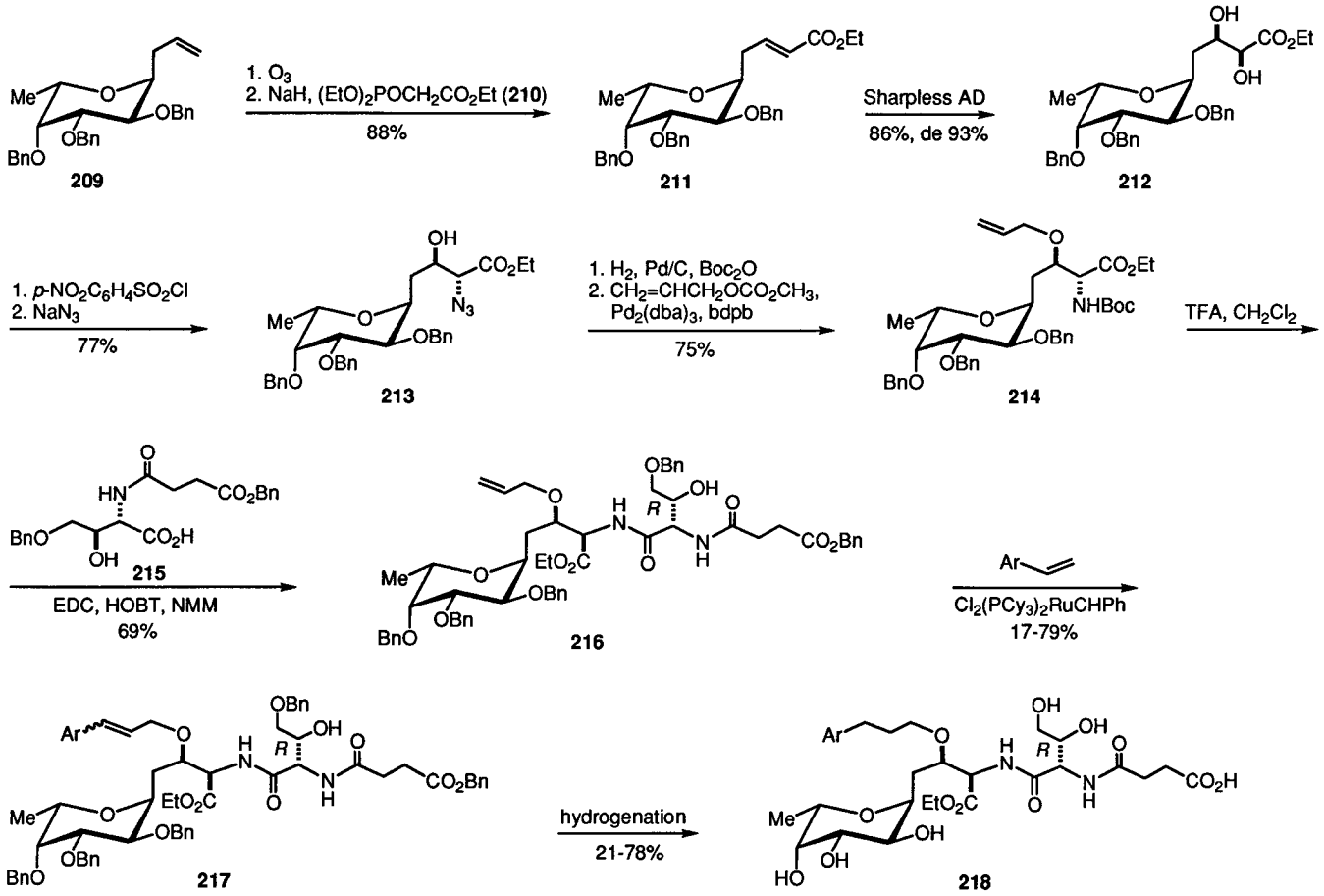
Scheme 32



chemical hydrolysis of the acetamide **205b** resulted in the formation of the oxo derivative **207** arising from the hydration of the ethynediyl group. This demonstrated that it should be possible to build up an oxomethylene bridge holding the carbohydrate moiety to phenylalanine and therefore prepare a class of *C*-glycosyl amino acids with a new molecular diversity. Compounds **206** and **208** were compatible with the conditions of Fmoc-based peptide synthesis and were used in the synthesis of *C*-linked glycopeptide T-cell antigens.

Another remarkable example of designed *C*-glycosyl amino acid and construction of biological active artificial glycopeptides has been recently provided by work carried out at Scripps and Novartis laboratories.[80] Targeting the synthesis of aryl-substituted *C*-glycopeptides containing fucosyl residues (*C*-fucopeptides) as sialyl Lewis X (SLe^x) mimetics, Wong and co-workers synthesized the *C*-fucosyl amino ester **214** (Scheme 33). On the basis of parallel studies on SLe^x mimetics, the *S*-configured *O*-allyl group was incorporated in the ethylene bridge holding the sugar and the glycinyl moiety with the aim of providing access to a wide variety of aryl ether derivatives via olefin metathesis with arylethylenes. In a typical

Scheme 33



target-oriented approach, the key *C*-glycosyl amino ester **214** was obtained in 40% yield by rather routine chemistry starting from the known allyl α-L-fucopyranoside **209**. The reaction sequence involved the chain elongation of **209** via ozonization and Wittig−Horner coupling with the phosphonate **210** to give the *E*-enoate **211**, then Sharpless AD reaction to the diol **212** followed by the selective displacement of one hydroxy group activated as *p*-nitrophenylsulfonyl (nosyl) derivative with NaN_3 to give the α-azido ester **213**, and finally the catalytic hydrogenation of the azido to amino group in the presence of Boc_2O and *O*-allylation to end up with the final product **214**. Removal of the *N*-Boc protective group from **214** and then coupling with the α-amino acid **215** under the standard conditions for peptide synthesis (activation by 1-hydroxybenzotriazole, HOBT; *N*-methylmorpholine, NMM; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, EDC) gave the mimetic precursor **216**, the template for the crossed metathesis reactions. Accordingly, the coupling of **216** with various aromatic olefins occurred readily in the presence of the Grubbs ruthenium catalyst $Cl_2(PCy_3)_2$-RuCHPh to give in most cases good yields (60−70%) of the metathesis products **217** as mixtures of *E* and *Z* isomers with great predominance of the former. This result is noteworthy because it demonstrates the potential of the still scarcely exploited crossed metathesis reaction of terminal olefins in complex molecules synthesis.[81] However, the final transformation of **217** into **218** by catalytic hydrogenation, i.e., reduction of the double bond and removal of the *O*-benzyl protective groups, required in some cases selective conditions to leave the more sensitive aromatic systems such anisyl, biphenyl, and naphthyl unaltered. Quite rewardingly, the synthesized *C*-fucopeptides **218** proved to act as actual SLe^x mimetics exhibiting up to 3 times higher binding affinity toward E-selectin and >1000 times more active toward P-selectin than SLe^x.

III. Fused Glycosyl Glycines

Dwek and Fleet summarized in a recent paper[82a] the philosophy that is behind the synthesis of this special class of quaternary α-amino acids in which the central carbon atom coincides with the anomeric carbon atom of a furanose or pyranose ring. These amino acid fragments as exemplified by the manno-

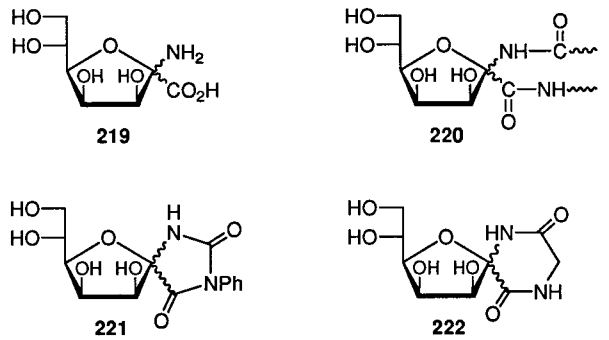


Figure 6. Fused anomeric mannofuranose glycine **219** and some derivatives: carbopeptoid **220**, spirohydantoin **221**, and spirodiketopiperazine **222**.

Table 3. Fused Glycosyl Glycines and Their Spirohydantoin and Spirodiketopiperazine Derivatives Prepared in the Fleet Laboratory

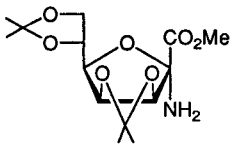
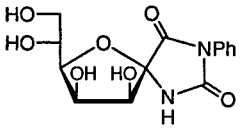
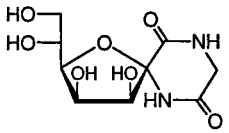
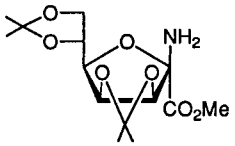
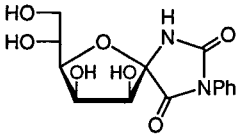
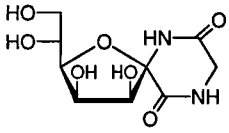
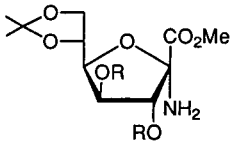
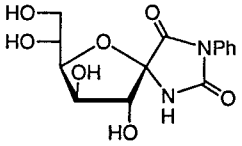
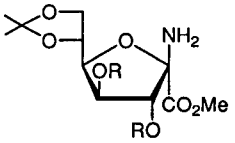
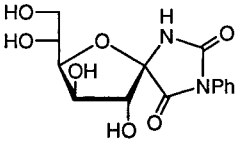
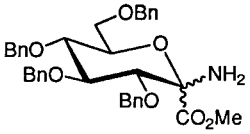
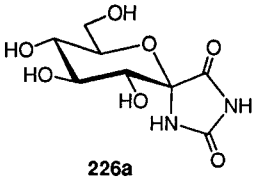
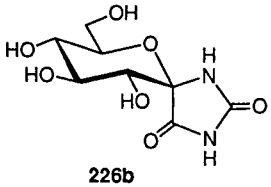
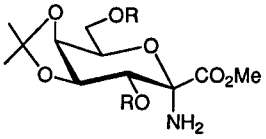
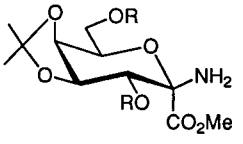
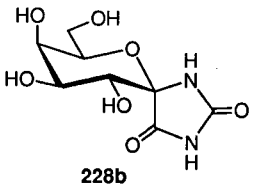
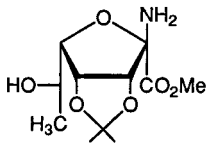
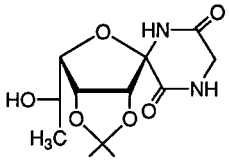
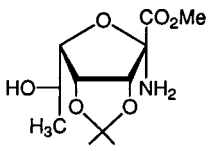
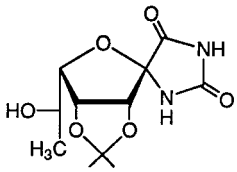
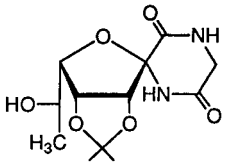
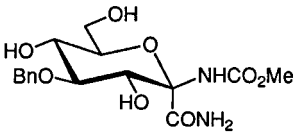
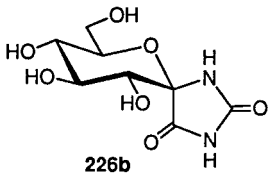
Sugar glycine	Spirohydantoin	Spirodiketopiperazine	Ref.
 **219a**	 **221a**	 **222a**	82
 **219b**	 **221b**	 **222b**	82
 **223a** R = $SiMe_2t$-Bu	 **224a**		85
 **223b** R = $SiMe_2t$-Bu	 **224b**		85
 **225**	 **226a**		86
	 **226b**		86
 **227a** R = $SiMe_2t$-Bu			88
 **227b** R = $SiMe_2t$-Bu	 **228b**		88

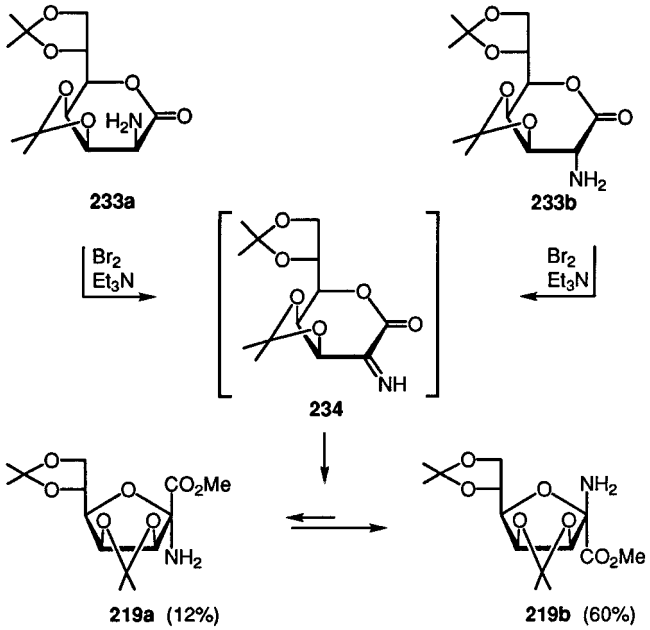
Table 3 (Continued)

Sugar glycine	Spirohydantoin	Spirodiketopiperazine	Ref.
 **229a**		 **230a**	89
 **229b**	 **231b**	 **230b**	89
 **232**	 **226b**		96

furanose **219** (Figure 6) constituted an attractive molecular diversity which was incorporated in peptide libraries **220**, thus giving rise to "materials (carbopeptoids) with the specific structural information of an individual carbohydrate recognition site". These amino acids have been regarded also as precursors to five- and six-membered spiroheterocycle derivatives of carbohydrates such as the spirohydantoin **221** and the spirodiketopiperazine **222**. These sugar spiranes have a natural counterpart in the potent herbicide (+)-hydantocidin,[8] the spirohydantoin of D-ribose (see Figure 2), and therefore were considered as potential inhibitors of carbohydrate processing enzymes.

The extensive synthetic work of Fleet and coworkers over the years furnished various anomeric furanosyl and pyranosyl glycines, most of which were transformed into spiro derivatives (Table 3). The key step in a first synthetic approach to fused furanosyl glycines involved the bromine-induced oxidative ring contraction of α-amino-δ-lactones[82] as exemplified in Scheme 34. Epimeric seven-carbon-atom α-amino-δ-lactones **233a** or **233b** upon treatment with bromine in methanol followed by addition of triethylamine were transformed into a mixture of slowly equilibrating D-mannofuranosyl glycinate **219a** (12%) and **219b** (60%). Also, an open-chain product was isolated in 17% yield. Since compounds **219a** and **219b** were obtained in the same ratio starting from either lactone **233a** or **233b**, it was suggested that the reactions proceeded through the common imine intermediate **234** that in turn underwent ring contraction via cleavage of the lactone bond and reclosure by bond formation of oxygen to carbon of the imine. Both epimeric amino esters **219a** and **219b** with the protected carbohydrate moiety were isolated and fully characterized, while the deprotected derivatives could

Scheme 34



not be obtained in pure form because of their rapid equilibration. The amino esters **219a** and **219b** were transformed[82] into the *N*-phenyl spirohydantoins **221a** and **221b** (Table 3) by reaction with phenylisocyanate and spontaneous intramolecular cyclization of the resulting ureas. In subsequent work the same compounds were also transformed into the corresponding spirodiketopiperazines **222a** and **222b** (Table 3) through their dipeptides with glycine.[82a,83] No anomeric equilibration of the diketopiperazine moiety was observed by acid treatments. On the other hand, equilibration experiments with potassium *tert*-butoxide in DMF showed that the β-anomer **222b** was more stable than the α-isomer **222a**. It was also

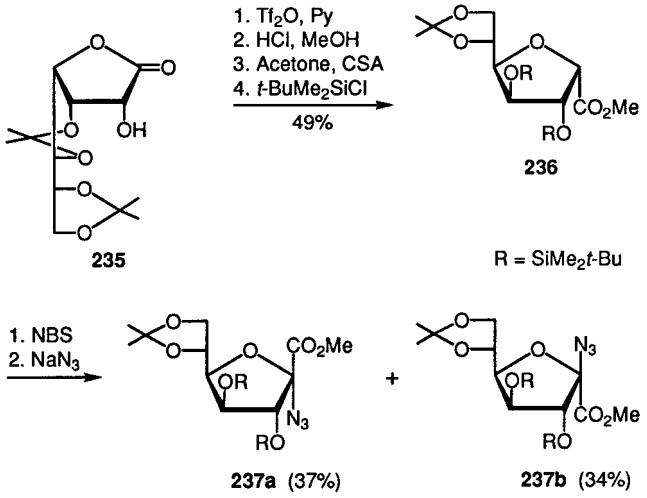
demonstrated that both the spiro derivatives of mannofuranose **221** and **222** do not interconvert into the corresponding mannopyranose forms. These experiments showed that mannofuranose structures containing an *N*-acylated α-amino acid moiety were configurationally stable under different conditions and therefore were suitable as building blocks for the generation of amide libraries at the anomeric positions of carbohydrates. Accordingly, the sugar glycinates **219a** and **219b** were incorporated into tri- and tetrapeptides.[84]

Other glycosyl glycines with both furanose and pyranose rings and their spiro derivatives (Table 3) were prepared in the Fleet laboratory via various synthetic routes. Since the above ring contraction method gave unsatisfactory results, another pathway was developed[85] for the synthesis of the epimeric glucofuranose derivatives **223a** and **223b**. The most laborious operation in this new route was the preparation of the azido esters **237a** and **237b** starting from the D-*glycero*-D-*gulo*-heptonolactone **235** (Scheme 35). This compound was transformed into the protected methyl 2,5-anhydro-heptonate **236**, which was subjected to the one-pot radical bromination (*N*-bromosuccinimide (NBS), benzoyl peroxide) and reaction with sodium azide. The latter key step was unselective as the azides **237a** and **237b** were obtained in about a 1:1 ratio and 71% overall yield. These compounds were individually isolated and transformed into the amino acids **223a** and **223b** via reduction of the azido function by hydrogenolysis. These anomeric amino esters underwent equilibration in solution, whereas their *N*-phenyl urea derivatives were stable. In fact, the ureas upon treatment with potassium *tert*-butoxide and removal of protecting groups afforded the corresponding anomeric spirohydantoins **224a** and **224b** (Table 3). The fused glucofuranosyl glycinates **223a** and **223b** did not isomerize to pyranose derivatives at least to an appreciable extent. Instead, the amino ester of glucopyranose **225** (Table 3) was prepared as a mixture of anomers by a similar route via azidation of a protected methyl 2,6-anhydro-heptonate and reduction of the azido group.[86] The individual amino esters, separated as urea derivatives, were transformed into the spirohydantoins **226a** and **226b** which represented the first examples of pyranose analogues of hydantocidin. Quite rewardingly, as predicted by molecular modeling, the β-isomer **226b** proved to be a potent inhibitor of glycogen phosphorylase (GPb) while the α-isomer **226a** had little effect on the enzyme. Also, a spirodiketopiperazine of glucopyranose was shown to be a specific inhibitor of phosphorylase.[87] This observation may allow the discovery of lead compounds for the development of drugs in an effort toward the treatment of diabetes. On the other hand, the D-galactopyranose spirohydantoin **228b** obtained from the glycinate **227b** (Table 3) caused no inhibition of the activity of a number of galactosyl transferases and galactosidases.[88] The equilibration of **227b** to the more stable isomer **227a** was observed on standing, but the latter could not be transformed into the corresponding spirohydantoin.

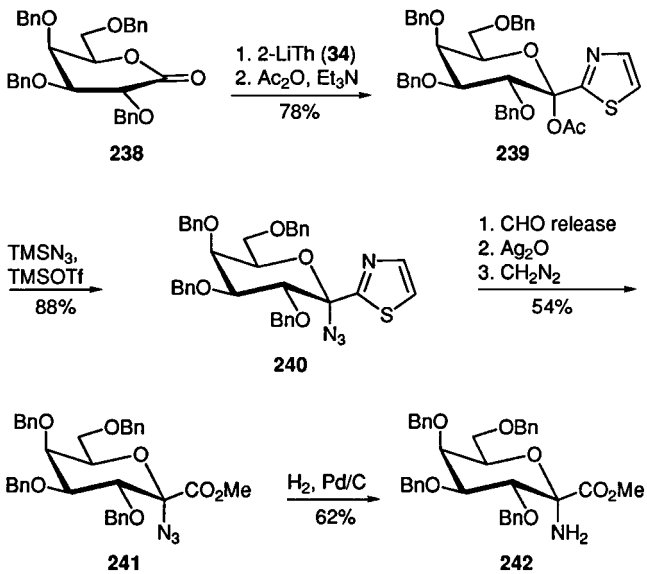
The synthetic sequence via azido ester was followed[89] for the preparation of the glycinates of L-rhamnofuranose **229b** and the corresponding spirohydantoin **231b** and spirodiketopiperazine **230b** (Table 3). The α-L-anomer glycinate **229a** was not isolated as an individual product but was postulated as an intermediate in the equilibration of **229b** upon treatment with Cbz-glycine activated by dicyclohexyl carbodiimide (DCC). In fact, the resulting amide was transformed into L-rhamnofuranose spirodiketopiperazine **230a**. These spiro derivatives of L-rhamnose were shown to interfere with mycobacterial cell growth and considered to provide a mechanism-based strategy for the chemotherapy of diseases such as tuberculosis and leprosy.

An alternative and simple route to anomeric glycosyl glycines through azido ester intermediates was developed by Dondoni and co-workers.[90] Our approach relied mainly on the thiazole-to-formyl synthetic equivalence, a concept that has been amply applied in numerous synthetic methods.[26] As exemplified in Scheme 36, the readily available D-galactonolactone **238** was transformed into the thiazolylketose acetate **239** by addition of 2-lithiothiazole **34** and

Scheme 35



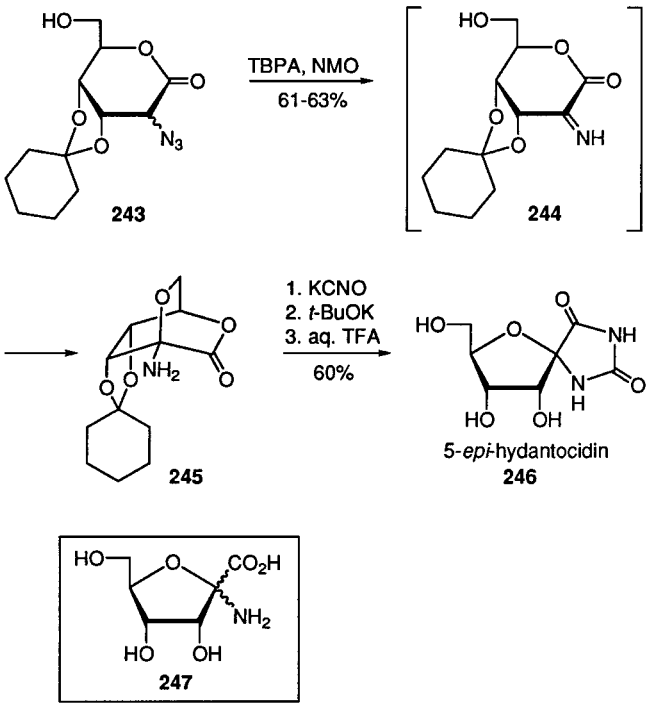
Scheme 36



acetylation.[91] The stereoselective *N*-glycosidation of **239** with trimethylsilyl azide ($TMSN_3$) in the presence of trimethylsilyl triflate (TMSOTf) afforded the α-D-azido galactopyranoside **240**. From this key intermediate, the azido ester **241** was liberated by the one-pot cleavage of the thiazole ring to the formyl group and subsequent oxidation of the latter to the carboxylate function. Finally, the reduction of the azido group of **241** by catalytic hydrogenation gave the fused galactopyranose glycine **242**, configurationally stable and fully characterized by NMR spectroscopy. The same reaction sequence was employed for the synthesis of the mannofuranose derivatives **219a** and **219b** (Table 3) via equilibration of the former. Given the availability of numerous sugar lactones, this method can be extended to the synthesis of other members of this class of amino acids.[92]

Fleet and co-workers developed[93] another method to synthesize spirohydantoins of carbohydrates[94] that involved a masked form of fused anomeric glycosyl glycines. This method can be considered as a variant of the bromine-induced oxidative ring contraction of α-amino-δ-lactones described in Scheme 34. In an earlier approach,[93] the epimeric α-azido-δ-lactone **243** (Scheme 37), prepared in six steps from D-ribose, was

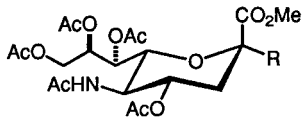
Scheme 37



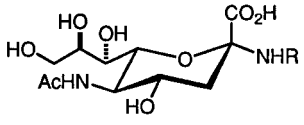
treated with a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of morpholine *N*-oxide (NMO). The only isolated product was the bicyclic compound **245** whose structure was established by single-crystal X-ray analysis. It was suggested that **245** was formed via intramolecular cyclization of the α-imino-lactone **244** as an intermediate. It was readily realized that compound **245** was a masked form of the fused D-ribose glycine **247** and could be transformed into a spirohydantoin. The transformation of **245** into the urea derivative by reaction with potassium cyanate followed by the potassium *tert*-butoxide-induced ring contraction and the removal of the cyclohexylidene group afforded the 5-*epi*-hydantocidin **246**. No epimerization at the spiro center of **246** took place during the removal of the protective group, while this isomer appeared to be more stable than the natural product. The same method through bicyclic amino lactones was employed for the preparation of spiro derivatives of L-rhamnopyranose[95] and various spirohydantoins of D-glucopyranose.[96] In this case the protected sugar glycine was isolated as the amide **232**, which was transformed into the spirohydantoin **226b** (Table 3).

The configurational instability of fused sugar glycines that is caused by their *O*,*N*-acetal character precluded in some cases the isolation of these compounds in stereochemically pure form. However, the work of the Fleet group demonstrated that *N*-acyl derivatives of these amino acids were configurationally stable. Somsák and Descotes and co-workers have been seeking a synthetic approach to *N*-acyl derivatives of anomeric sugar glycines not requiring the amino stage.[97] Sugar α-azido nitriles were considered as suitable starting materials since these compounds incorporated both the protected nitrogen and carbon functionalities at the anomeric carbon atom. However, while various α-azido nitriles were prepared and some of their reactions described, the transformation to *N*-acyl derivatives of anomeric sugar glycines was not carried out.

N-Glycosides of sialic acids have been regarded as being compounds stable against sialidases and therefore as potential inhibitors of these enzymes. Sialidases promote important biological processes in mammalian and bacterial organisms by the selective splitting only of the sialic *O*-ketosidic linkage.[1] The simple *N*-glycosides **250a** and **250b** of *N*-acetylneuraminic acid (Neu5Ac) described by Faillard and co-workers in 1992 can be considered as a special family of fused anomeric glycines.[98] The common precursor of these compounds was the azido α-D-sialoside **248** readily available from the reaction of the β-D-chloro Neu5Ac derivative and sodium azide under phase-transfer catalysis. The transformation of **248** to **250a**,**b** was routine via the quantitative reduction to **249** (H_2, Pd/C), acylation, and saponification. Neither the *N*-ketoside **250a** nor **250b** could be hydrolyzed by neuraminidase treatment.



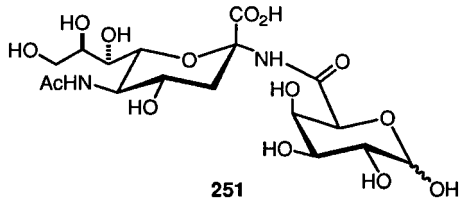
248 R = N_3
249 R = NH_2



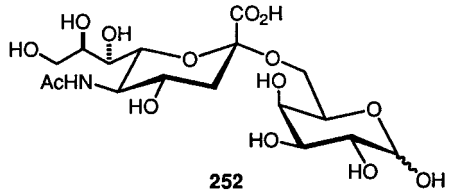
250a R = Ac
250b R = Bz

The interest for *N*-glycosides of Neu5Ac has continued in more recent years since these amino acids are regarded as building blocks for the preparation of peptide-linked sialosides. Of course, once again a great stimulus for the synthesis of these glycoconjugates came from their potential application in biological studies. Sabesan reported[99] on the synthesis of the amide **251**, a mimic of the Neu5Ac *O*-glycoside **252** that has been recognized a receptor ligand for influenza virus hemagglutinin and the neuramini-

dase. Hence, compound **251** as a potential influenza virus inhibitor was readily prepared by coupling the aforementioned fused sugar glycine **249** with D-galacturonic acid activated by 1,1′-carbonylbis(3-methylimidazolium triflate) followed by the removal of all protective groups. The conservation of the α-D-sialosidic (equatorial) linkage in compound **251** was



251



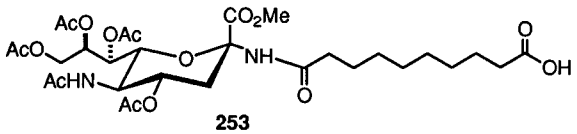
252

proved by NMR spectroscopy. This configuration is in agreement with the preferential equatorial orientation of the amide bond that was found in compounds prepared from various glycosylamines and the same D-galacturonic acid. Therefore, it was correctly pointed out that the peptidosaccharide mimics with axially oriented aglycone will be difficult to construct with stereochemical integrity.

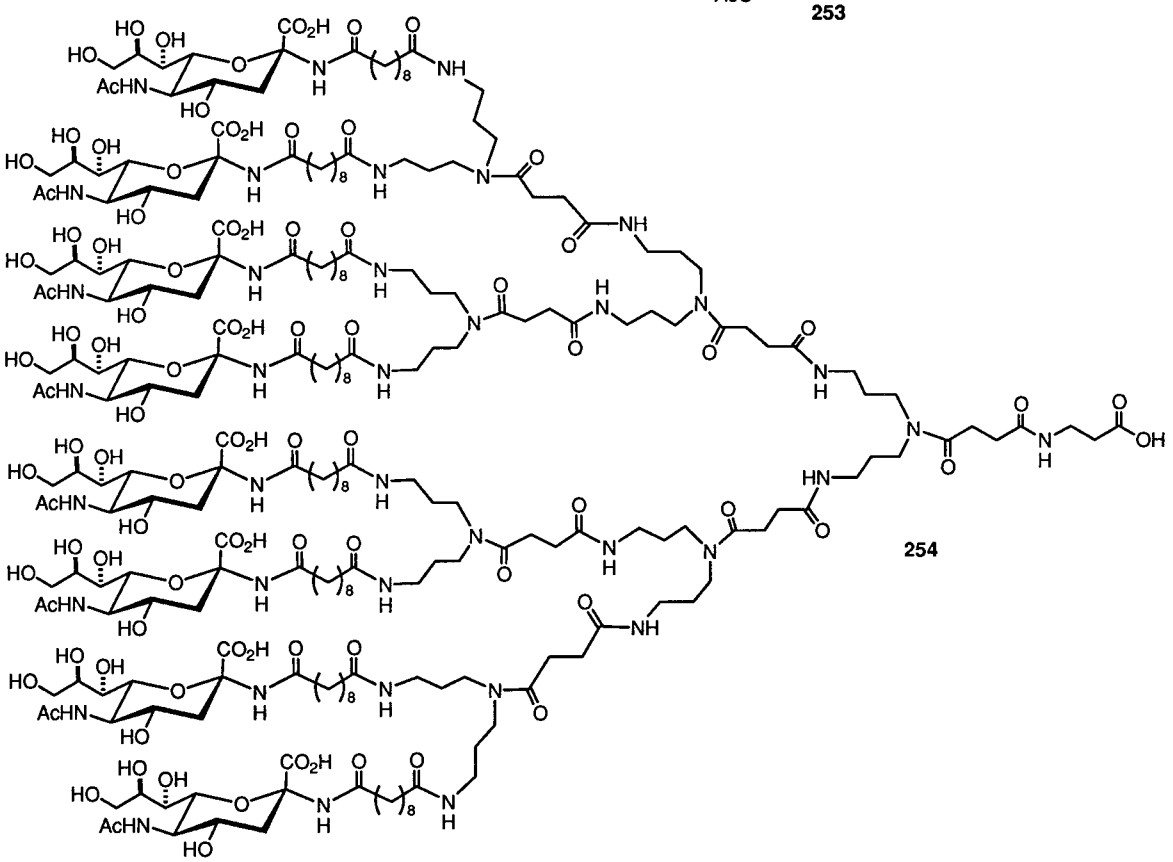
More complex *N*-glycoconjugates of neuraminic acid as the α-sialodendrimer **254** (Figure 7) have been prepared by Roy and Llinares[100] by solid-phase synthesis on a *N*,*N*-bis(3-aminopropyl)succinamic acid core. Also, in this synthesis the starting material was the anomeric azide **248**, which was readily transformed into the carboxylic acid **253** by reduction, acylation with $ClCO(CH_2)_8COCl$, and hydrolysis (53% overall yield). The introduction of the functionalized long spacer arm at the amino group of the intermediate **249** had the double action of minimizing anomerization and preparing a suitable building block for coupling with amine-terminated dendrimers. The sialodendrimer **254** free of all protective groups was isolated and fully characterized by NMR and MS analyses. Dendrimers unlike polymers are materials of a defined molecular composition. Therefore, the construction of well-tailored carbohydrate-containing macromolecules as exemplified by **254** is an interesting research area that is quite relevant to studies on cellular processes in which multiple noncovalent interactions between carbohydrate ligands and proteins should play a fundamental role.[101]

IV. Conclusions

Having solved over the last 30 years or so the majority of the problems associated with the stereo-



253



254

Figure 7. Sialodendrimer **254** and its precursor *N*-glycoside of neuraminic acid **253**.

controlled synthesis of natural *O*-oligosaccharides and *O*-glycoconjugates with a substantial beneficial effect on glycobiology,[102] in recent times organic chemists have been focusing more interest upon the development of synthetic procedures of unnatural carbon-linked analogues. Life science scientists such as biochemists, biologists, and medicinal chemists are posing a pressing need for the access to usable quantities of carbohydrate-based mimics of natural products. The use of these compounds extends over basic studies of biological processes and the development of new drugs against a variety of metabolic disorders. The invention of efficient synthetic methods that afford simple molecules as anomeric carbon-linked glycosyl amino acids is a part of this endeavor since these compounds are the basic building blocks for the construction of more complex molecular systems, mainly artificial glycopeptides. A carbon−carbon bond holding the carbohydrate moiety to the peptide chain not only may provide higher stability toward chemical and enzymatic degradation but also may affect the peptide conformation and folding with tremendous effects on molecular recognition and interactions.[103] Various synthetic approaches to *C*-glycosyl amino acids have been developed in relatively recent times. Preference has been given to the discovery of new methods, while their scope was not established. Hopefully the concise communications widely employed so far to announce a new synthetic approach or the synthesis of a few hitherto unreported products will be followed in short time by more extensive reports with full experimental details. Quite attractive methods are those in which the stereochemical problems are minimized by the use of suitable carbohydrate and amino acid reagents so that the configuration at the anomeric center of the sugar moiety and at the carbon atom of the glycinyl moiety is already established. Since various natural amino acids are readily available at a very low price, new reagents can be designed bearing a suitable functional group at one side of the carbon chain and the protected glycinyl moiety at the other side. Of course, methods based on the asymmetric synthesis of the α-amino acid chain by chiral external catalysis are also of great interest.

Since submission of this review, some new publications regarding the synthesis of *C*-glycosyl amino acids have appeared. In the following, these contributions are supplemented without claiming completeness (state as of June 2000).

In the framework of their ongoing research on the application of reductive samariation to the synthesis of unnatural peptides, Skrydstrup and co-workers reported in a preliminary form[104] the preparation of a single *C*-glycodipeptide by SmI_2-induced coupling (30% yield) of a *C*-glucosyl acetaldehyde derivative with a thiopyridyl-armed dipeptide. The reaction lacked stereoselectivity as the product resulted as a mixture of diastereoisomers. Roy and co-workers employed the olefin crossed metathesis as an approach to *C*-glycosyl amino acids.[105] The reported example illustrated the coupling of allyl tetra-*O*-benzyl-*β*-*C*-mannopyranoside with racemic *N*-Cbz allyl glycine benzyl ester to give a mixture of diastereomeric *E*- and *Z*-olefins. However, these products were not further elaborated. Very likely the lack of orthogonal protection of the functional groups prevented this final operation. Finally, Fuchss and Schmidt described the first example of a *C*-glycosyl amino acid in which the sugar moiety is an aza-sugar.[106] Indeed, the synthesis of *C*-nojirimycinyl L-serine was accomplished as previously reported[54] for the *C*-glycosyl serines **120** and **121**.

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