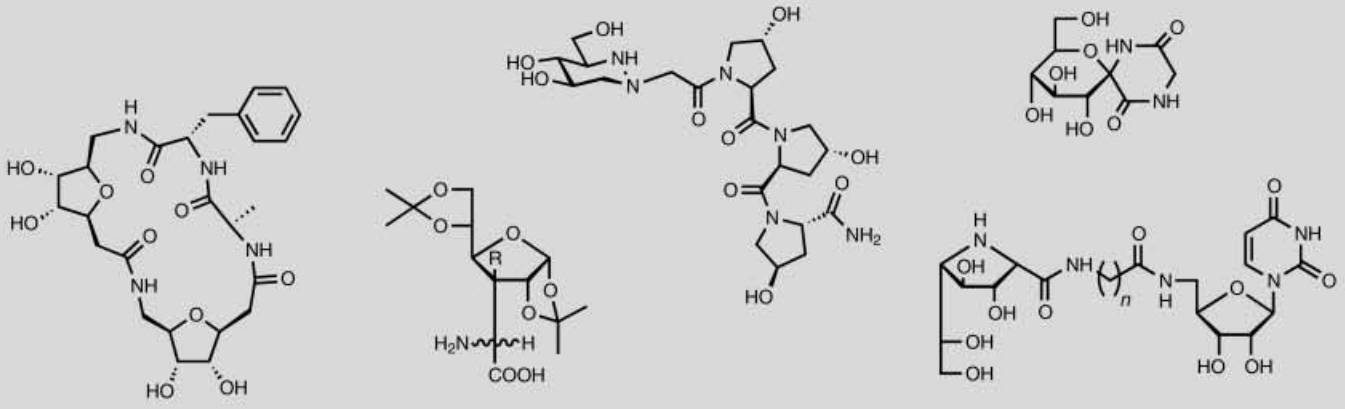
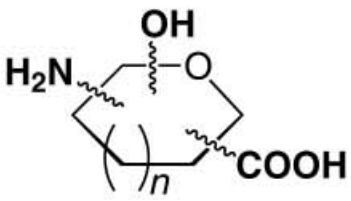
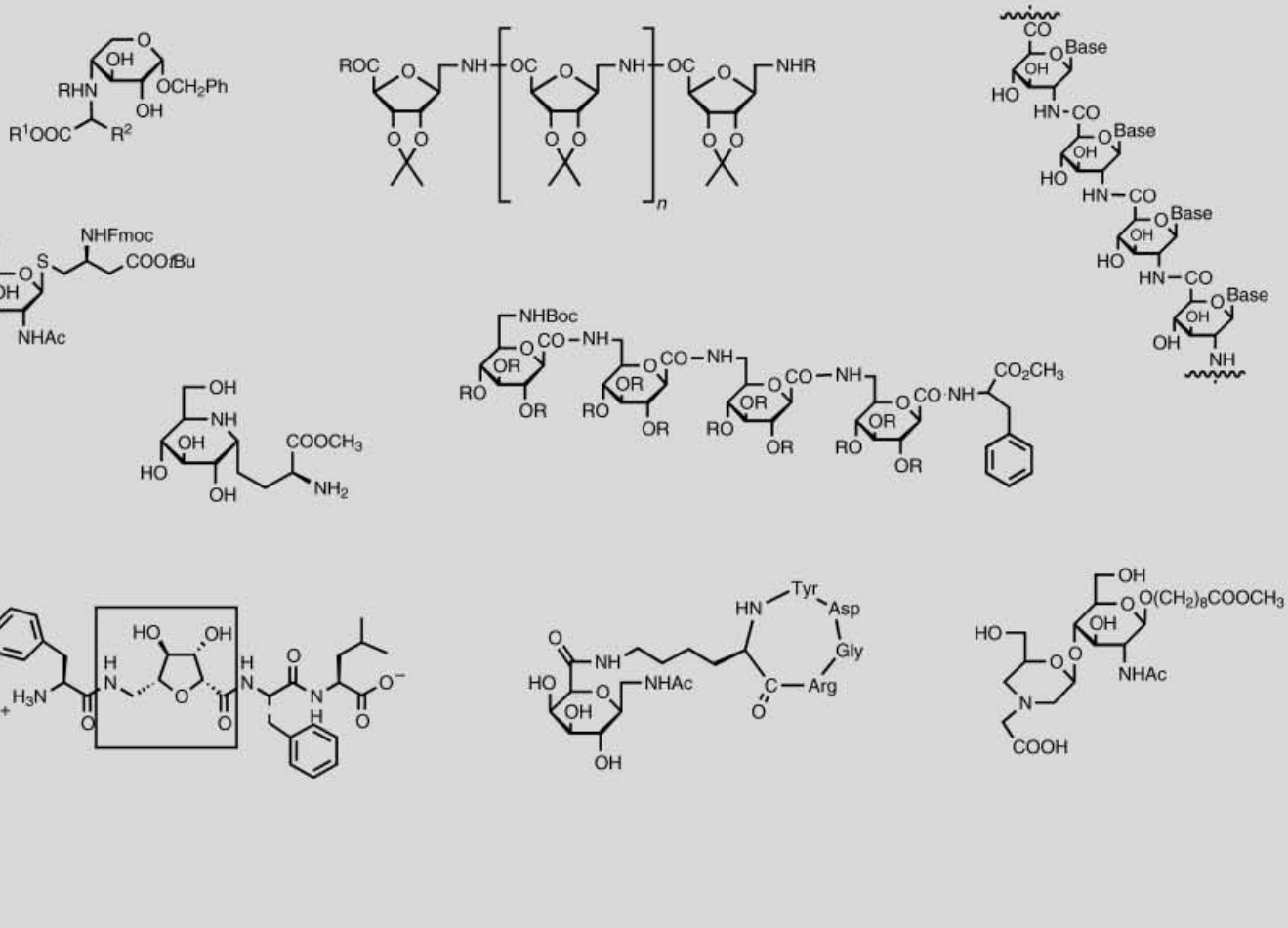


sugar–amino acid hybrids



glycomimetics
peptidomimetics
biopolymers
combinatorial chemistry



Glycosamino Acids: Building Blocks for Combinatorial Synthesis—Implications for Drug Discovery

Frank Schweizer*

The unique functions of carbohydrates, including energy storage, transport, modulation of protein function, intercellular adhesion, signal transduction, malignant transformation, and viral and bacterial cell–surface recognition, underlie a significant pharmaceutical potential. The development of combinatorial carbohydrate libraries in this important arena has been slow, in contrast to the rapid development of combinatorial synthesis in the area of small-molecule libraries and biopolymers. This is largely as a result of the inherent difficulties presented by this class of polyfunctional compounds. Nevertheless, strategies to cope with these problems have been devised over the past seven years, and combinatorial carbohydrate libraries have appeared. The incorporation of an amino acid moiety into the carbohydrate scaffold generates glycosamino acids, which are attractive building blocks for the preparation of carbohydrate-based libraries because of the well-established automated peptide synthesis. Derivatization as well as homo- and heterooligomerization of glycosamino acids can be used to create novel structures with unique properties. Glycosamino acids are hybrid structures of carbohydrates and amino acids which can be utilized to generate potential glycomimetics and peptidomimetics. The incorporation of glycosamino acids into peptides allows the engineering of carbohydrate-binding sites into synthetic polypeptides, which may also influence the pharmacokinetic and dynamic properties of the peptides. Furthermore, sugar–amino acid hybrids offer a tremendous structural and functional diversity, which is largely unexplored and requires combinatorial strategies for efficient exploitation. This article provides an overview of previous work on glycosamino acids and discusses their use in combinatorial synthesis and drug discovery.

Keywords: combinatorial chemistry · glycoconjugates · glycomimetics · peptidomimetics · sugar amino acids

1. Introduction

Amino acids and carbohydrates are two major building blocks used to generate diversity in nature. The ability of amino acids (α,β,...) to form secondary structures in proteins and polypeptides forms the basis of three-dimensional molecular architecture. Carbohydrates present in nucleotides, glycopeptides, and glycolipids communicate with their inter- and intracellular environment through a multitude of molecular interactions. Many of these recognition phenomena are involved in events such as metastasis, infection, and inflammation and have become the subject of intensive medical research. Glycosamino acids (GAAs) are molecules that combine the structural features of simple amino acids (amino and carboxylic acid functions) with those of simple carbohydrates (cyclic polyols, which may contain additional acetamido or amino functions).[1] The resulting hybrid is a highly substituted polyfunctionalized building block, which can be used for the synthesis of compound libraries by means of combinatorial synthesis.

Amino acid building blocks have been widely used for the synthesis of polyamide and small-molecule libraries.[2] In contrast to amino acids, GAAs are (poly)hydroxylated amino acids in which additional derivatization of the polyol can lead to increased diversity. GAAs can be derivatized and oligomerized into compound libraries through well-established automated peptide protocols. This approach is particularly attractive in the preparation of glycomimetic libraries, since oligosaccharide library synthesis has not yet reached the same level of automation as peptide synthesis. On the other hand, the engineering of an amino acid moiety into the sugar skeleton enables the GAA to be incorporated into short peptide sequences, thus opening the door to novel peptidomimetics. Additional hydroxy derivatization of the polyol

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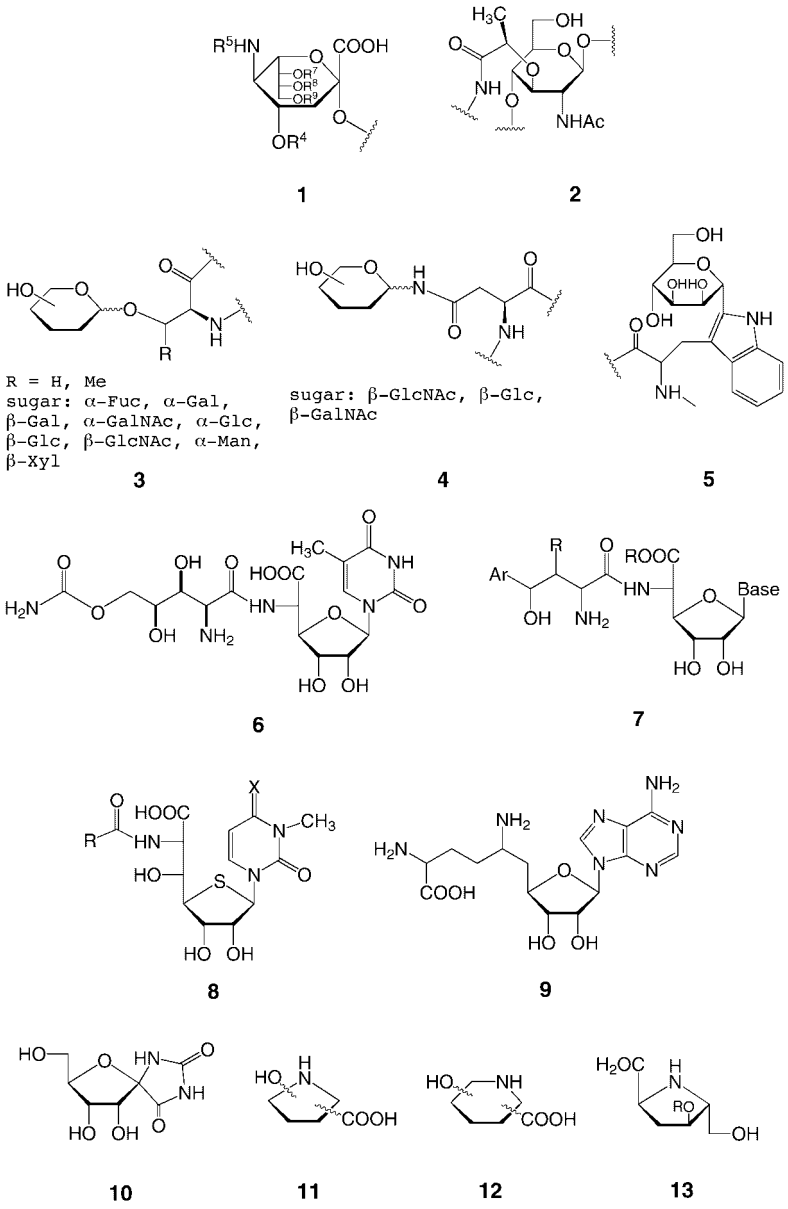
could increase the lipophilicity of the GAAs and render them likely to permeate cell membranes. Finally, the rich stereochemistry and the high degree of functionalization of GAAs allows them to be used as multivalent scaffolds or platforms for projecting pharmacophore groups. This article presents an overview of previous work on GAAs and discusses their use as building blocks for combinatorial synthesis as well as their implications for drug discovery. A referenced index of approximately 280 previously synthesized GAA structures is provided in Table 1 and Tables 1 – 19 in the Supporting Information.

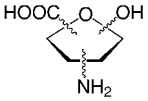
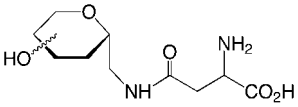
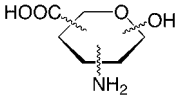
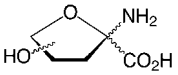
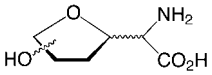
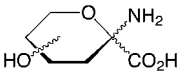
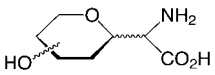
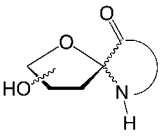
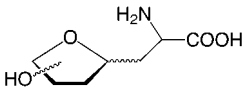
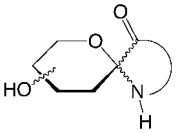
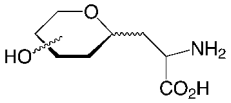
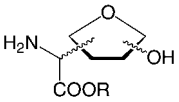
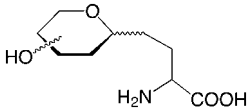
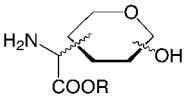
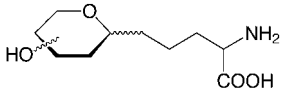
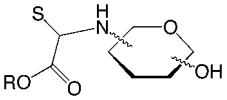
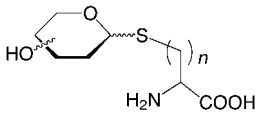
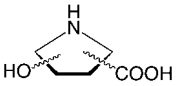
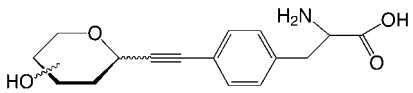
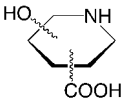
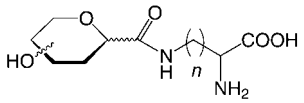


2. Natural Occurrence

GAAs and their derivatives occur in nature in various forms. For example, the δ-GAA sialic acid (**1**) is found in all living organisms, with the exception of certain bacteria. Many inter- and intracellular molecular recognition events depend on sialic acid residues. In the course of an infection, bacteria and viruses recognize sialic-acid-containing structures on the cell surface as adhesion receptors. So far, over 40 different naturally occurring sialic acids have been identified which are partially O- and N-substituted (O-methyl, -sulfate, -acetyl, -phosphate, N-glycolyl, or free amine). Muramic acid (**2**; 2-amino-2-deoxy-3-*O*-D-lactyl-D-glucose) occurs in bacterial polysaccharides and, in the form of UDP-*N*-acetylmuramyl pentapeptide, is involved in the synthesis of the peptidoglycan. Modified muramyl peptides have been the subject of intensive research over the last 25 years owing to their involvement in the synthesis of the bacterial cell wall.[3] GAAs **3** and **4** are components of O- and N-linked glycoproteins and glycopeptides. Other naturally occurring GAAs linked to proteins are cystine-linked glycoproteins[4, 5] and the recently identified C-linked mannopyranosyl-L-tryptophan **5**.[6, 7] The GAA-based peptidyl nucleoside antibiotic polyoxin (**6**) mimics UDP-*N*-acetylglucosamine, a substrate of chitin synthase, which catalyzes the final step in the biosynthesis of chitin, an essential component of fungal cell walls.[8] Other peptidyl nucleoside antibiotics include the nikkomycins **7**,[8] the albomycins **8**,[8, 9] and sinefungin (**9**).[8] The α,α-disubstituted hydantoin derivative

Frank Schweizer obtained his diploma from the Albert-Ludwigs University in Freiburg, Germany, in 1993 before enrolling for graduate studies at the University of Alberta in Edmonton, Canada. In 1998 he obtained his PhD on carbohydrate mimetics under the supervision of Professor O. Hindsgaul. In the same year he received a fellowship awarded to foreign researchers by the Japanese Society for the Promotion of Science (JSPS) to conduct research at the Noguchi Institute in Tokyo. Recently, he returned from Japan and rejoined the group of Professor O. Hindsgaul at the University of Alberta as a research associate. His research interests include combinatorial carbohydrate chemistry, sugar – amino acid hybrids, carbohydrate-based antibiotics, and sugar nucleotide synthesis.

Table 1. Index of previously synthesized A_0 – A_5 GAAs.

GAA structure	GAA type[a]	Table[b]	Number of examples	GAA structure	GAA type[a]	Table[b]	Number of examples
	A_0	1	38		A_1	10	1
	A_0	2	21		A_2	11	13
	A_1	3	14		A_2	12	3
	A_1	4	7		A_2	13	15
	A_1	5	2		A_2	14	6
	A_1	5	13		A_3	15	17
	A_1	6	17		A_3	16	11
	A_1	7	11		A_4	17	27
	A_1	8	7		A_5	18	9
	A_1	9	14		A_5	19	25
	A_1	10	10				

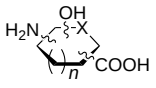
[a] see Schema 1. [b] Tables 1 – 19, which contain approximately 280 GAA-based structures, can be found in the Supporting Information.

10[10] also contains a GAA substructure. Hydantoin derivative **10** shows potent selective antiherbal activity with no toxicity to microorganisms and animals. Replacement of the endocyclic oxygen atom in the pyranose with a nitrogen atom leads to azasugar-based GAAs found in hydroxylated prolines **11**, pipecolic acids **12**, and the antibacterial bulgecine (**13**).[11] Hydroxylated prolines have been shown to influence secondary structures in peptides significantly.[12] Other antibiotics with a GAA moiety include chryscandin,[13] amipurimycin,[14] miharamycin,[15] gougerotin,[16] blasticidin,[17] bagougeramine,[18] and aezomycin,[19] as well as the glycopeptide antibiotics A40926a, b.[20]

3. Classification of GAAs

GAAs may be classified into five groups, depending on the position of the amino acid moiety on the cyclic polyol (Scheme 1). The amino acid moiety may either be incorporated directly into a sugar-derived 5- or 6-membered ring, as in the sugar amino acids (SAAs) (**A_0** type), or tethered to the sugar ring, as in structures **A_1** – **A_4** (Scheme 1). The A_1 GAAs or the double-substituted A_2 GAAs are formed by linking the amino acid moiety adjacent to the endocyclic heteroatom. In the branched A_3 and A_4 GAAs, the amino acid moiety is linked further away from the endocyclic heteroatom. Finally,

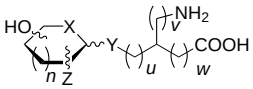
amino acid moiety is incorporated into the regular sugar frame



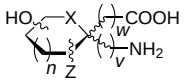
A_0

(sugar amino acid (SAA))

amino acid moiety is tethered to the carbohydrate adjacent to heteroatom X

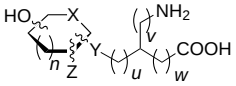


A_1 (glycosyl amino acid)

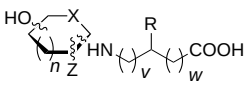


A_2 (double substituted glycosyl amino acid)

amino acid moiety is tethered to the carbohydrate not adjacent to heteroatom X

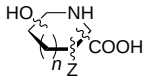


A_3



A_4

azasugar-based GAA

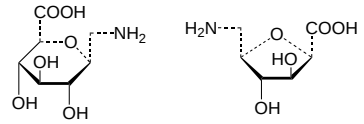


A_5

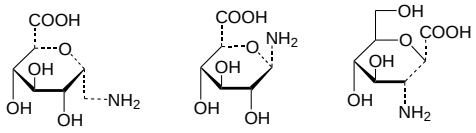
(azasugar acid (ASA))

Scheme 1. Classification of GAAs according to the position of the amino acid moiety on the monosaccharide scaffold. X = O, S, P…; n = 0, 1, 2…; Y = CH, CH_2, S, O, NHCO, CONH, NR; u = 0,1,2…; v = 0,1,2…; w = 0,1,2…, Z = NHAc, OH, H.

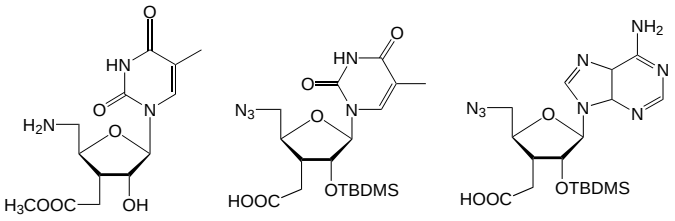
substitution of the endocyclic oxygen atom by a nitrogen atom provides azasugar-based A_5 GAAs, referred to herein as azasugar acid (ASA) (Scheme 1). Substitution of the endocyclic oxygen by other heteroatoms (S, P, Se…) can also be envisaged.



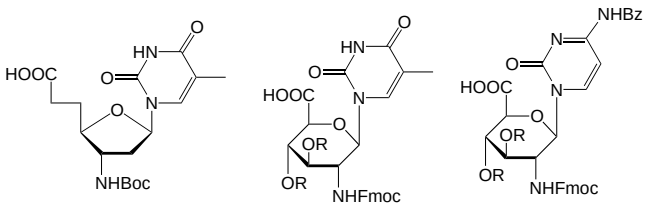
14 **15**



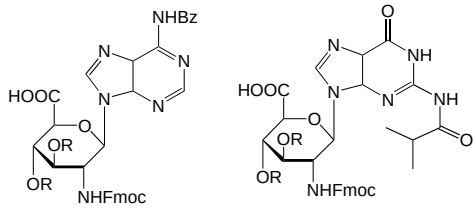
16 **17** **18**



19 (T) **20** (T) **21** (A)



22 (T) **23** (T) **24** (C)



25 (A) **26** (G)

Scheme 2. A_0 GAAs used in the synthesis of peptidomimetics and antisense oligonucleotides (Fmoc = 9-fluorenylmethoxycarbonyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl).

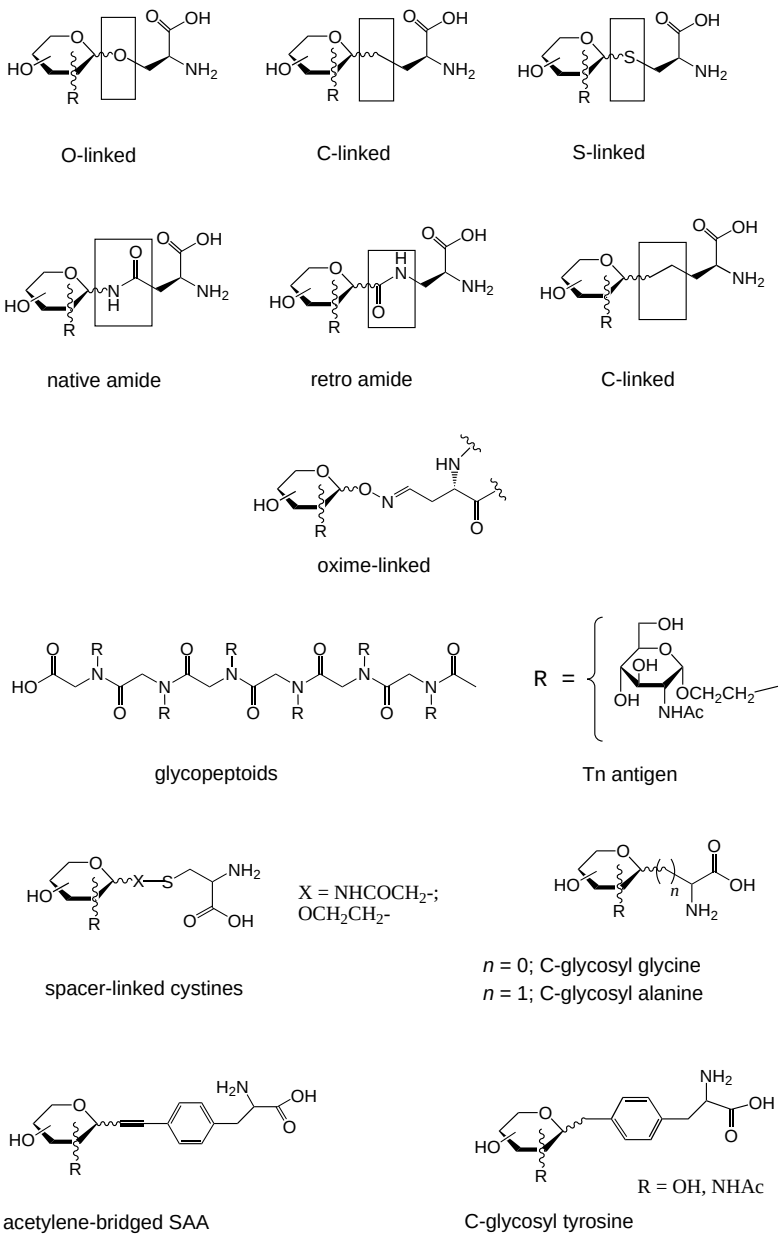
3.1. A_0 Sugar Amino Acids

The incorporation of a carboxylic acid and an amino function into a cyclic carbohydrate skeleton results in conformationally restricted SAAs. The rigidity can be used to generate secondary structures, provided that the SAAs are oligomerized or incorporated into short peptides. The SAAs **14**, **15**, and **16** have been studied as dipeptide isosteres (Scheme 2).[21–24] Similarly, the SAAs **17** and **18** have been shown to mimic β- and γ-turns when incorporated into short peptide sequences.[21] The C3-branched SAA ester **19**[25] and the derivatives **20**–**22**[26, 27] have been prepared as building blocks for the synthesis of furanoside-based antisense oligonucleotides. The pyranoside-based oligonucleotide analogues **23**–**26**[28] have been prepared and oligomerized into glucopyranosyl nucleic amides (GNA).[29] A list of references for SAAs (A_0-type) is provided in Table 1.

3.2. A_1 GAAs

Oligosaccharides attached to polypeptides can modulate protein folding, intra- and intercellular trafficking, receptor binding and signaling,[30, 31] enhance the thermal stability of proteins,[32] and protect them against proteolytic degradation.[33, 34] Carbohydrates attach to proteins through three major types of linkage: a) N-glycoside linkage between the reducing terminal sugar and the amide group of asparagine

(Scheme 3), b) O-glycoside linkage between the sugar and a hydroxy group of an amino acid, most commonly serine and threonine, but also 5-hydroxylysine, 4-hydroxyproline, and tyrosine are known,[35] c) ethanolamine phosphate linkage between the C-terminal residue of the protein and an oligosaccharide attached to phosphatidylinositol (GPI anchor). Other naturally occurring linkages include the S-glycoside linkage to cystine[4, 5] and C-glycoside linkage to tryptophan (Scheme 3).[6, 7] However, O- and N-linked glycopeptides are metabolically unstable towards glycosidases, an inherent limitation of these materials as potential drugs. Mimics of the naturally occurring glycopeptide linkages have been prepared to overcome these drawbacks.[36] For example, the exocyclic oxygen atom in the O-Ser(Thr) linkage has been replaced by a methylene unit[37–47] or by sulfur.[48–52] N-linked glycopeptides may be mimicked by retro amides,[53, 54] glycopeptoids,[55] and C-linked glycopeptides in which the amide group has been replaced by an ethylene isostere (Scheme 3).[56–59] GAAs with an oxime linkage between the sugar and the peptide have been prepared by chemoselective ligation.[60] Glycopeptoids (N-substituted oligoglycines)[55, 61] and various spacer linked cystines[62] are also known. Other potential glycopeptide mimetics are the C-glycosylglycines and C-glycosylalanines (Scheme 3). Both types of SAAs differ from the native O-linked SAA in that the amino acid side chain is shorter by one or two carbon atoms. A short and versatile synthesis of α-C-glycosylalanines in the fucose, mannose, galactose, and glucose series by means of an asymmetric Strecker synthesis was described recently.[63] Acetylene-bridged GAAs[64] and C-glycosyltyrosines[65] have also been synthesized and incorporated into C-glycopeptides (Scheme 3). The acetylene bridge is less polar than the natural ether or amide linkage of O- or N-glycopeptides and thus it has been postulated that membrane transport properties are improved. Furthermore, the rigid tether should make the saccharide moieties less flexible, which may result in smaller entropy losses during binding.[64, 66] Despite a multitude of synthetic glycopeptide mimetics (Table 1), only a few reports are found in which their bioactivity has been evaluated. For example, an oxime-linked version of the 19 amino acid glycopeptide, drosocin, which has a single site of O-linked glycosylation, was similar to the native molecule in bacteriostatic activity.[67] Nevertheless, replacement of the native sugar linkage may result in reduced bioactivity. Studies on model glycoproteins have revealed that the monosaccharide units most proximal to the peptide backbone can profoundly influence local peptide structure.[68]



Scheme 3. GAAs for the synthesis of natural and non-natural glycopeptides.

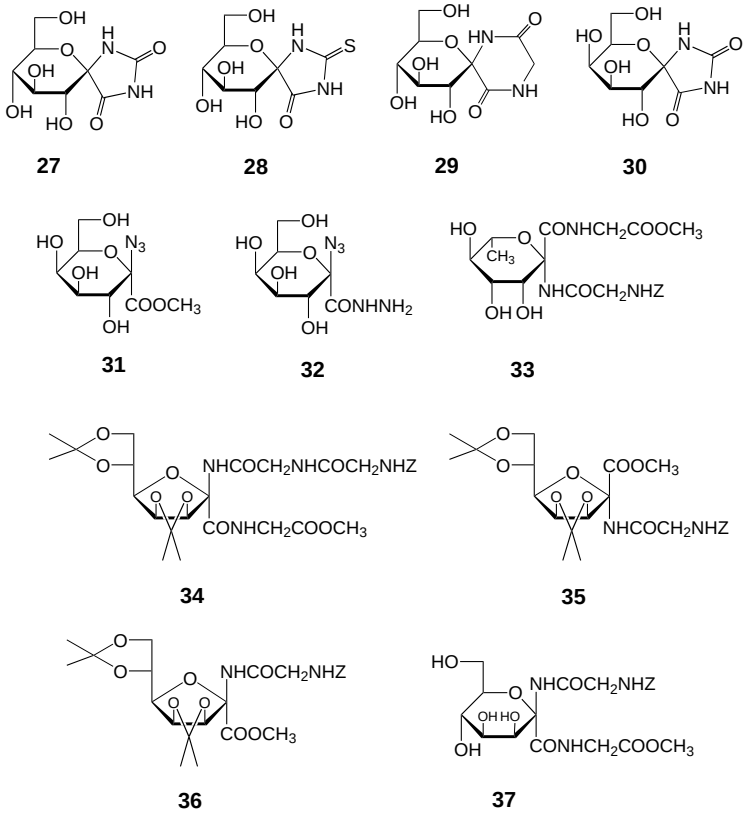
3.3. A_2 GAAs

Double substituted A_2 GAAs have been found as components of natural products and as inhibitors of glycogen phosphorylase. For example, the naturally occurring spiroribofuranose hydantoin **10** shows strong herbicidal activity, with no toxicity to microorganisms or animals.[10] Stereoisomers and deoxy analogues of **10** (except for the 5-epimer) are not biologically active,[10, 69–76] but spirothiohydantoin analogues of **10** maintained herbicidal activity.[77] The mode of action of the hydantoin is not completely understood, although a mechanism that accounts for the herbicidal activity has been suggested.[173] Other disubstituted spirosugar α-amino acids, such

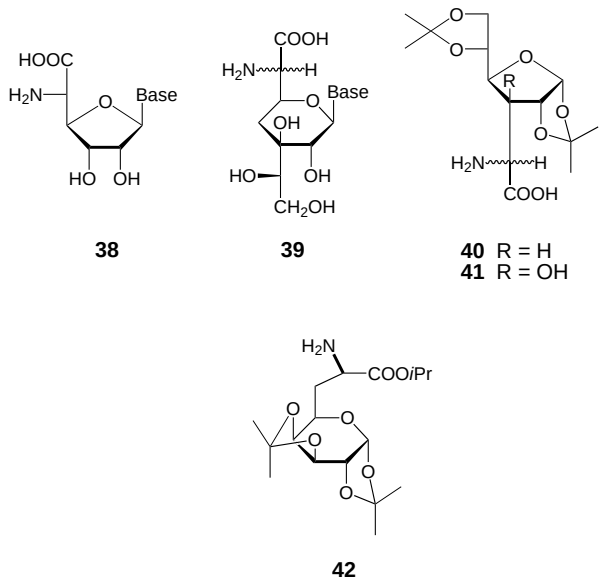
as **27**,[78] **28**,[79] and **29**[80] are efficient specific inhibitors of muscle and liver glycogen phosphorylase (GP), a major regulatory enzyme of blood sugar levels (Scheme 4). Inhibition of this enzyme can provide a means for controlling blood glucose levels and may lead to new therapeutic agents for the treatment of diabetes.[81] Interestingly, compound **29** does not inhibit a wide range of glycosidases, which indicates a specific inhibition of GP.[80] In contrast, the galactohydantoin **30** does not inhibit a variety of enzymes, including glycogen phosphorylases, galactosidases, and glucosyl- and galactosyl transferases.[82] Similarly, compounds **31** and **32** showed no inhibitory effect against a variety of transferases and galactosidases.[82] Several di-, tri-, and tetrapeptides with GAA derivatives of rhamnopyranose **33**,[83] mannofuranose **34**–**36**,[84–86] and mannopyranose **37**[84] have been synthesized (Scheme 4). These compounds may find use as novel N-linked glycoprotein analogues or as α,α-disubstituted amino acids with the ability to control the secondary structure of short peptides and for the introduction of carbohydrate-recognition sites in synthetic peptides.[86] No data on the bioactivity of these short peptides has been reported so far. A list of A_2 GAAs and their derivatives is given in Table 1.

3.4. A_3 and A_4 GAAs

Non-anomeric linking of the amino acid moiety to the carbohydrate portion provides A_3 and A_4 GAAs. These GAAs are found in a variety of antibiotics (Scheme 5). The C-glycofuranosyl α-amino acid **38**[87–91] has attracted much attention because of its presence in the polyoxin and nikkomycin antibiotics, and the C-glycopyranosyl α-amino acid **39**[92–94] is a component of the nucleoside antibiotic ampurimycin. Analogues of the polyoxin-based GAA were synthesized by Rosenthal et al.[95–97] For example, compounds **40** and **41** bear the amino acid moiety at C3, instead of at C4 as is the case in polyoxin. Unfortunately, no biological data have been provided for these amino acids. The glycopyranosyl α-amino acid **42** has recently been prepared and incorporated into a short peptide sequence.[89] It has been suggested that the incorporation of these non-natural glycopyranosyl α-amino acids into native peptides may lead to enhanced resistance against enzymatic degradation and induction of conformational restraint on the peptide.[89] Linking the sugar moiety through the amino function of the amino acid provides aminodeoxy sugars with an incorporated amino acid moiety (A_4 GAAs). A list of previously synthesized C-branched sugar amino acids (A_3 and A_4 GAAs) is provided in Tables 1.



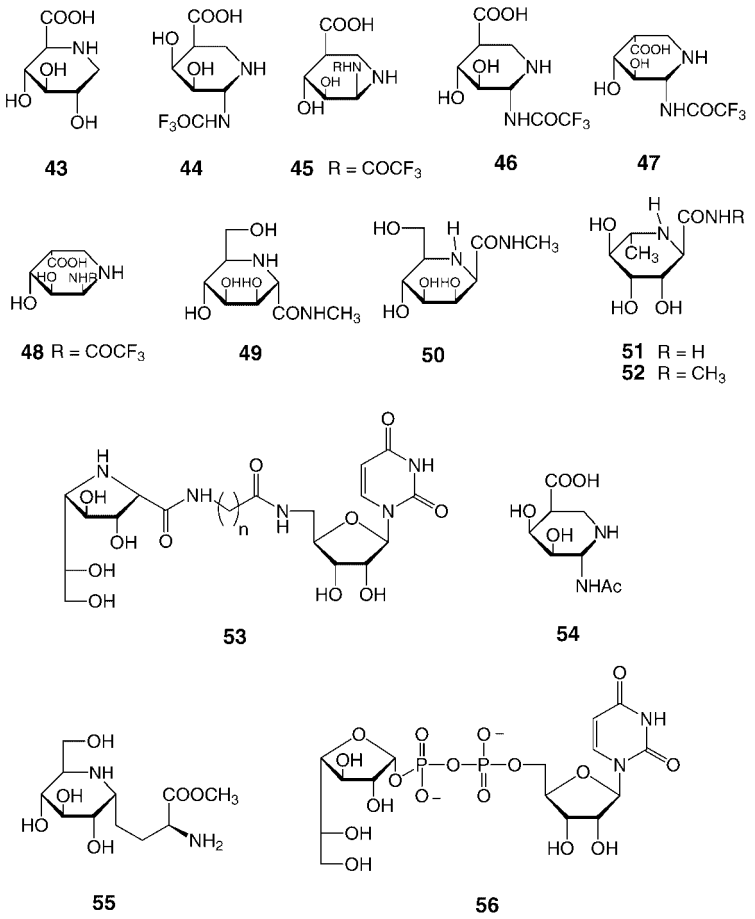
Scheme 4. A_2 GAAs and derivatives with the incorporated anomeric center of a carbohydrate.



Scheme 5. A_3 GAAs: the amino acid moiety forms the part of a branched carbohydrate structure.

3.5. Azasugar Acids (A_5 Type)

Replacement of the endocyclic oxygen atom by a nitrogen atom leads to a different class of GAAs, referred to herein as azasugar acids ASAs (Scheme 6). Azasugars have been intensively studied as glycosidase inhibitors, and several potent azasugar-based glycosidase inhibitors have been discovered.[98] The ASAs **43**,[99] **44**, **45**, and **46** belong to the uronic acid family and are potent inhibitors of



Scheme 6. Azasugar acid (ASA): GAAs in which the endocyclic oxygen atom has been substituted by an amino function.

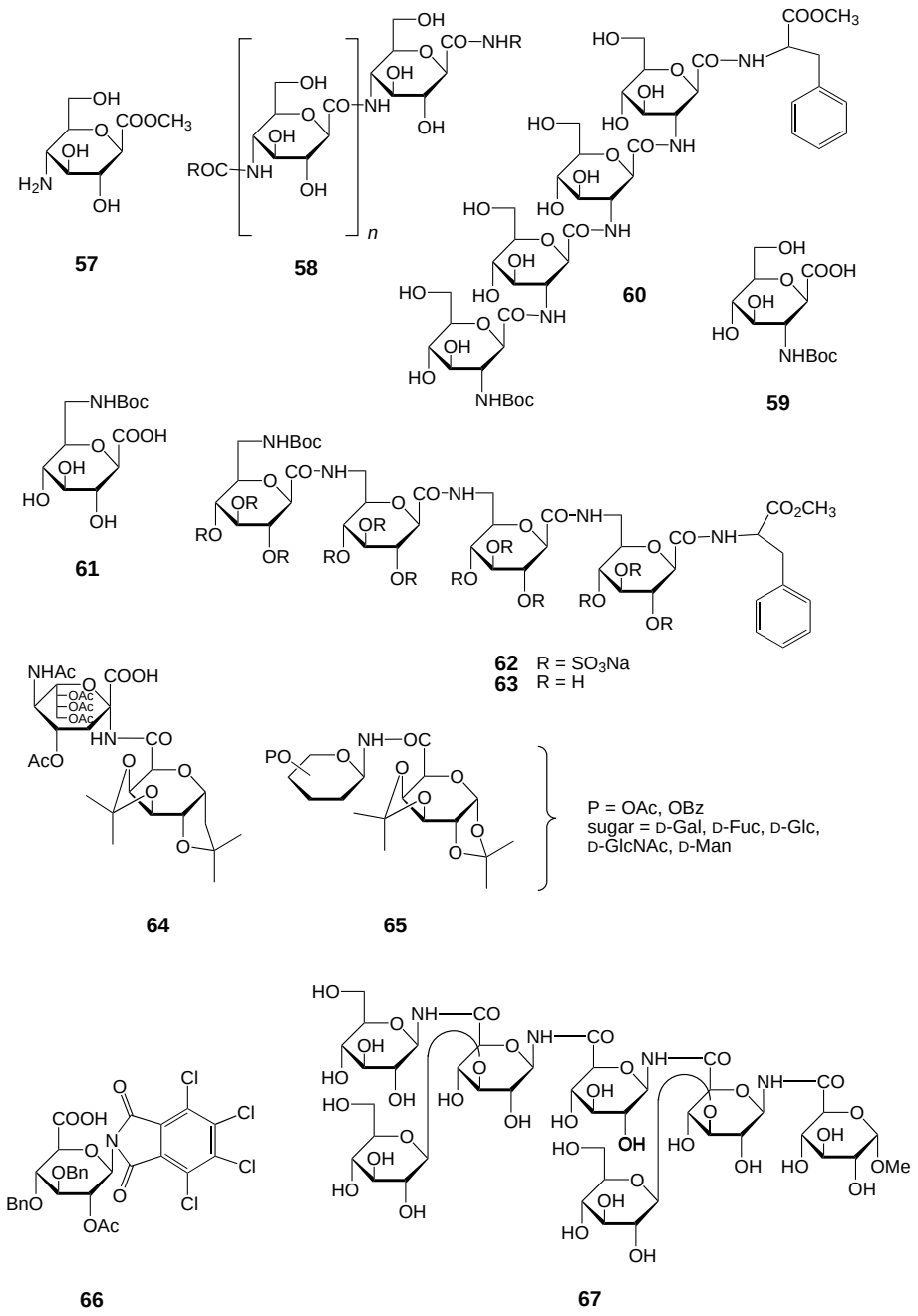
glucuronidases.[100] In contrast the amino acid **47** is a weak glucuronidase inhibitor, and the amine **48** does not inhibit glucuronidase from bovine liver.[100] Rather surprising is the behavior of the mannose-based azasugar amides **49** and **50**, which are potent inhibitors of two β-*N*-acetylglucosaminidases (human placenta and bovine liver), but do not show any inhibition of α-*N*-acetylgalactosaminidase from chicken liver.[101] The L-rhamnopyranose-derived amides **51** and **52** are potent inhibitors of naringinase (L-rhamnosidase) and also inhibit the biosynthesis of thymidine diphosphate-L-rhamnose from thymidine diphosphate-D-glucose.[102] This may lead to novel carbohydrate-based chemotherapeutic agents for the treatment of mycobacterial infection, since rhamnopyranose occurs in the disaccharide linker between the arabinogalactan polysaccharide and the peptidoglycan regions of the cell wall of *Mycobacterium tuberculosis*. An alternative approach to interfere with the cell wall synthesis of *Mycobacterium tuberculosis* may be the inhibition of Gal*f* transferases. In vitro studies have shown that uridine 5′-diphosphogalactofuranose **56** is the donor for the galactosyltransferases involved in the biosynthesis of the cell wall of *Mycobacterium tuberculosis*. The activated glycosyl donor has been mimicked successfully with various glycosyltransferases[103] and may provide a new strategy to cope with mycobacterial infections. For example, the ASA conjugate **53**, which contains an amino acid linker between the nucleoside and iminogalactofuranose components, has been suggested as a potential mimic of the natural donor.[104] Furthermore, replacement of the labile phosphodiester bonds with amides should increase the stability and cell permeability of these compounds. Another very interesting ASA is the neuraminidase inhibitor siastatin B (**54**),[105] which shows inhibitory effects against various neuraminidases, β-glucuronidase, and *N*-acetyl-β-D-glucosaminidase. Recently, nojirimycinyl C-(L)-serine (**55**), a combination of a C-GAA and the well-known glucosidase inhibitor nojirimycin, was prepared.[106] This compound might be a promising building block to elucidate the biological function of protein glycosylation as a result of its metabolic stability and inhibitory activity against glycosidases. A list of synthetic A_5 GAAs is given in Table 1.

4. Use of GAAs in Combinatorial Synthesis

Monosaccharide building blocks with incorporated amino and carboxylic acid functional groups (GAAs) have been proposed by McDevitt and Lansbury[1] as versatile building blocks for combinatorial synthesis. In particular, the well-established chemistry of amide formation is a very attractive strategy to prepare compound libraries of GAA oligomers (glycotides). Synthetic glycotides were proposed as drug candidates because they would not be susceptible to glycosidases and may not be recognized by proteases as a result of the altered backbone relative to the natural substrate.[1] Functional group modifications of the polyol moiety could increase the lipophilicity of the molecules and render them more likely to permeate cell membranes.[1] Besides their use in peptide coupling reactions, GAAs may also be useful building blocks for other chemical transformations that are compatible with combinatorial strategies, including reductive aminations[107] and multicomponent reactions.[108]

4.1. Oligosaccharide Mimetics—Homooligomerization of A_0 GAAs

SAAs in which the amino, carboxylic acid, and polyol functions are directly incorporated into a sugar ring have been used as oligosaccharide mimetics (Scheme 7). Lehmann and Fuchs developed polysaccharide analogues in which the glycoside linkages were replaced by amide bonds.[109] The amine **57** was exposed to methanolic NaOMe to afford polycondensed amide-linked oligomers **58**.[110] The water-soluble condensation products were not further characterized, but could be readily saponified with sodium hydroxide, presumably as a result of the participation of the 7-OH group of the sugar oligomer. Later, Nicolaou et al.[111] termed these analogues carbopeptoids because of their hybrid character between carbohydrate and peptide. The difficulties associated with the synthesis of oligosaccharide libraries, for example,

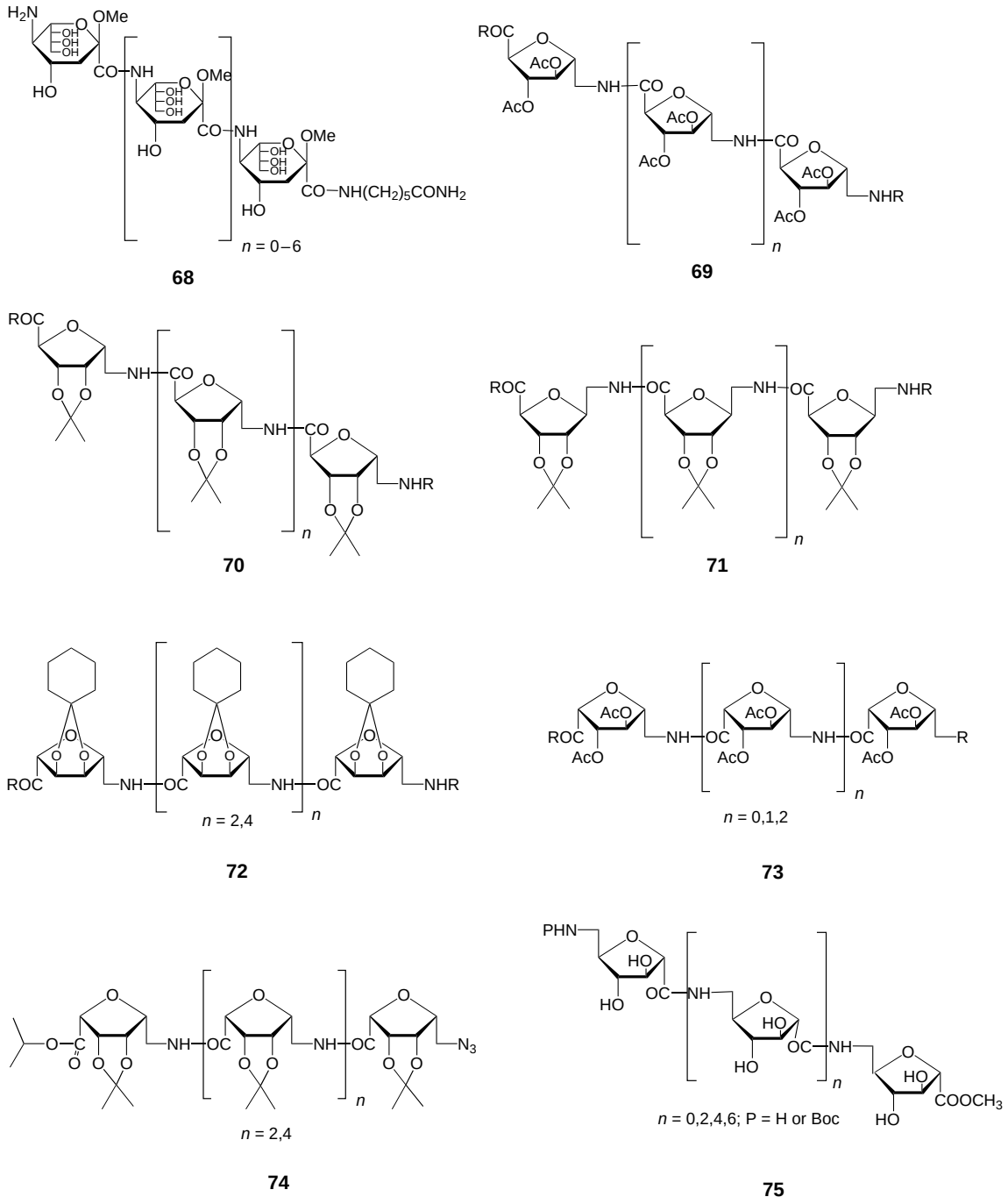


Scheme 7. A_0 GAAs used in the synthesis of oligosaccharide mimetics.

stereocontrol of the newly formed glycoside bond (α or β), efficiency of the glycosylation reaction, and the susceptibility towards lysis by glycosidases, were expected to be overcome through the replacement of the glycoside linkage by peptide bonds. The first characterized carbopeptoids were synthesized by Ichikawa et al. by using D-glucosamine-derived SAA building block **59** as a key building block. Elongation of **59** afforded the tetramer **60**, which after O-sulfation showed a strong inhibitory potency against HIV infection of CD4 cells.[113] Similarly, oligomerization of the Boc-protected SAA **61** followed by sulfation and deprotection gave the $\beta(1\rightarrow6)$-linked carbopeptoid **62**, which strongly inhibited the HIV infection of MT2 cells.[112] Interestingly, the nonsulfated analogue **63** did not show any measurable inhibitory effect in the same assay. Sabesan[114] prepared several amide-linked sugar dimers **64** and **65** in which the nitrogen atom of the peptide bond is connected to the anomeric carbon atom (Scheme 7). He suggested that this type of amide linkage might be sterically more compatible with that of a glycoside oxygen atom, but no biological data were provided. Similarly, the sugar amino acid **66** was used in the synthesis of the carbopeptoid **67**, an analogue of the naturally occurring phytoalexin elicitor (Scheme 7). Unfortunately, the heptamer **67** was not biologically active.[115]

Analogously to amino acids, sugar–amino acid hybrids induce secondary structures by oligomerization (Scheme 8).[116–124] Gervay and co-workers synthesized dimeric to octameric $(1\rightarrow5)$-linked sialooligomers **68** in solution[118] and in the solid phase.[119] Circular dichroism (CD) and NH/ND exchange rates were used to show that oligomers of constrained carbohydrate-derived amino acids form stable secondary structures in water. Fleet and co-workers investigated the ability of several 5-aminomethyltetrahydrofuran-2-carboxylate oligomers to form secondary structures (Scheme 8).[116, 117, 120–125] The tetrameric *trans* SAAs **69** and **70** did not form strong intramolecular hydrogen bonds in chloroform, whereas octameric **70** showed a strong intramolecular hydrogen bonding pattern reminiscent of a left-handed α-helix.[120] The tetrameric *cis* SAAs **71**–**73** form secondary structures in solution ($CDCl_3$) similar to a repeating β-turn. Tetramer **72**, which has the opposite configuration of **71** and an isopropylidene rather than a cyclohexylidene protecting group, had a very similar ^{1}H NMR spectrum, which indicates that the different ketal protecting group has very little effect on the conformation in solution.[120, 124] Recently, the synthesis of tetrameric **72** was extended to the octamer; the structure of this compound in a solution of chloroform was again suggested to be a repeating β-turn.[124] Interestingly, the unprotected tetramer **72** dissolved in methanol exhibited similar secondary structures to those of protected tetramer **72** in chloroform.[124] The known oligomers **74**[123] and **75**[126] do not form well-defined secondary structures.

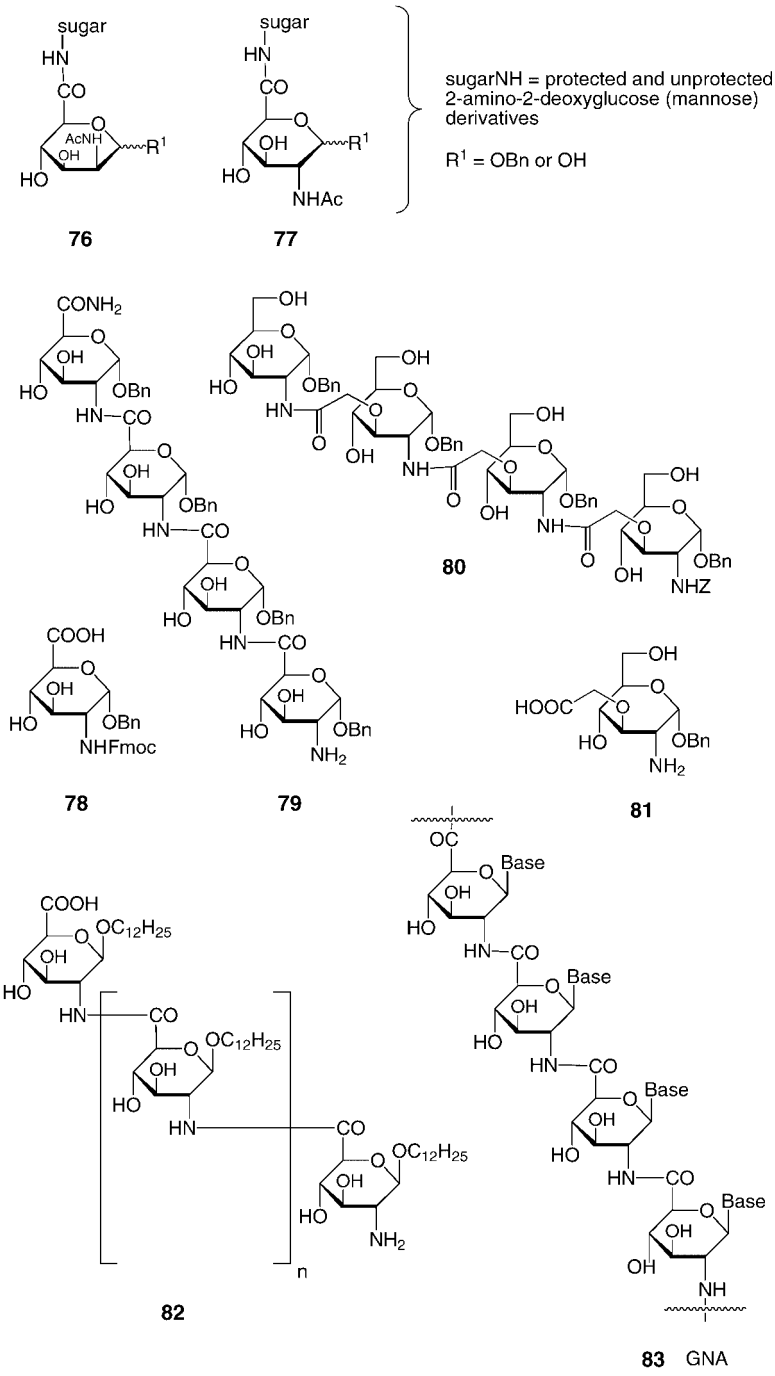
SAA oligomers in which the anomeric carbon atom is not part of the linkage region have also been prepared



Scheme 8. Homooligomerization of A_0 GAAs. Some oligomers induce secondary structures in organic solvents.

(Scheme 9). Yoshimura et al reported the first synthesis of (2→6) amido-linked disaccharides **76** and **77** by using 2-acetamido-2-deoxy-D-glucuronic and 2-acetamido-2-deoxy-D-manuronic acid, respectively.[127] Wessel and co-workers subsequently oligomerized the Fmoc-protected 2-amino-2-deoxy-D-glucuronic acid **78** to the tetramer **79** in the solid phase.[128] The same group also synthesized the tetramer **80**, which has normuramic acid (**81**) as a building block.[129] The polymerization of 1-*O*-dodecyl-2-amino-2-deoxy-β-D-glucopyranosiduronic acid afforded polymeric SAA **82**, which forms closely packed monolayers upon spreading of a dilute DMSO/$CHCl_3$ solution on a pure water surface.[130]

SAAs have also been used to prepare compounds with potential antisense properties. The replacement of the phosphodiester backbone in DNA and RNA by an achiral peptide bond has been actively pursued. In particular, the low membrane permeability (negative charge density) and the high susceptibility to nucleolytic cleavage of the phosphodiesters might be improved with neutral amide linkages. Recently, ribose-derived SAA nucleotides have appeared and have been used as monomers for oligomerization. Fujii and co-workers prepared the 2-deoxyribose building block **22**(T) (Scheme 2), which underwent solid-phase oligomerization to the 10-mer level.[174] Robbins et al. synthesized the nucleo-



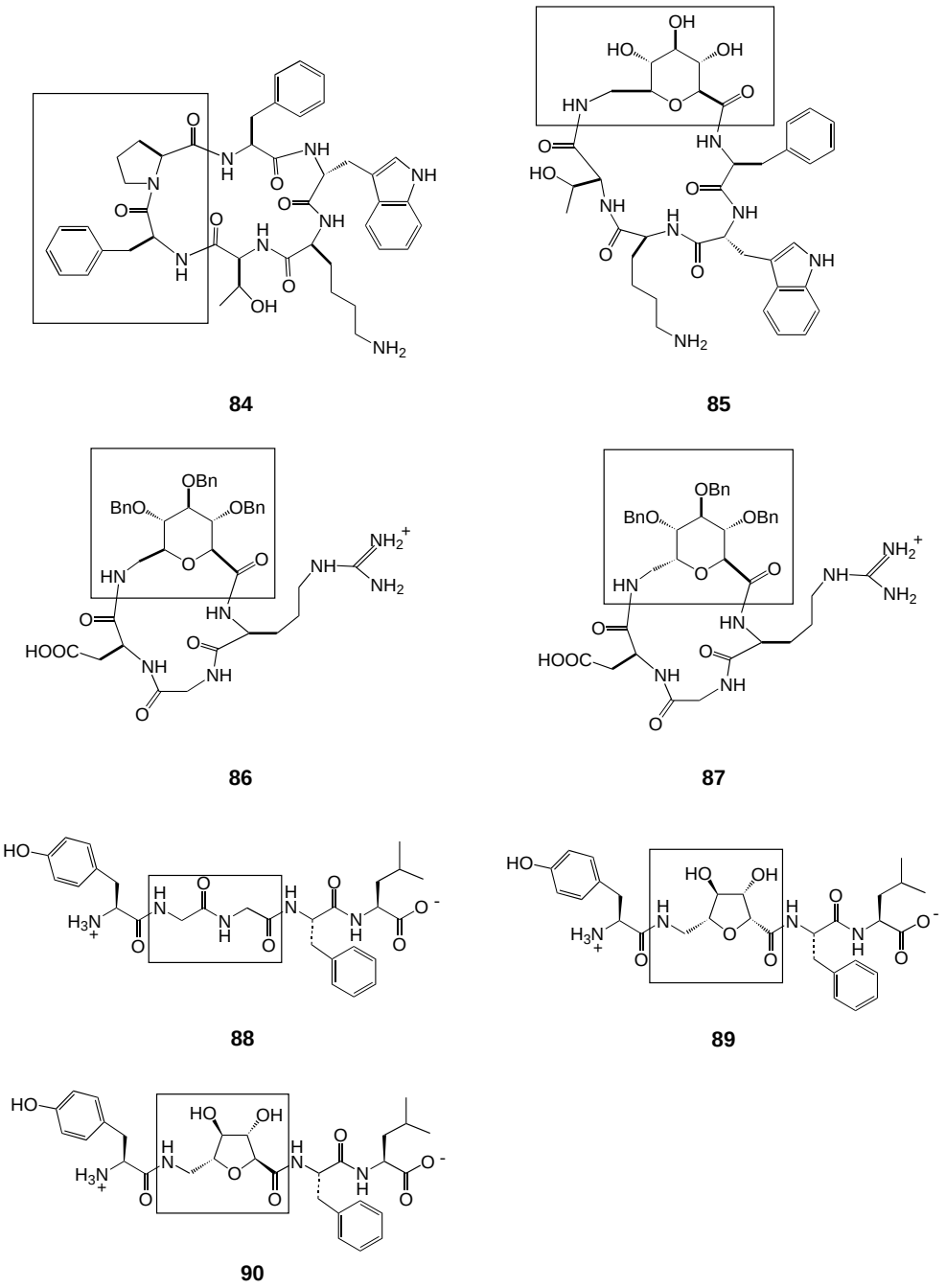
Scheme 9. Amide-linked A_0 GAA oligomers in which the anomeric (pseudo-anomeric) center is not involved in the linkage (Z = benzyloxycarbonyl, Bn = benzyl).

sides **19**(T), **20**(T), and **21**(A) and investigated their oligomerization.[131, 132] Pyranoside-based SAAs were investigated as potential building blocks for new antisense agents by Goodnow et al.[28] The four glucosamine-based oligonucleotide analogues **23**(T), **24**(C), **25**(A), and **26**(G) (Scheme 2) were synthesized[28] and incorporated into glucopyranosyl nucleic amides (GNA) **83**[29] (Scheme 9) to afford the homopyrimidine sequence (H–TCTTCCTCTCTCT–Lys–NH_2) and a decameric oligomer (H–TCACTAGATG–Lys–NH_2). The binding affinities and selectivities of these oligomers to DNA and RNA targets were determined by measuring duplex formation and melting temperatures. The results demonstrated that GNAs are able to mimic some binding properties of DNA and RNA. In all cases the calculated changes in entropy for GNA/DNA and GNA/RNA melting transitions, compared to those for the corresponding DNA/DNA and DNA/RNA were consistent with the idea that GNA oligomer conformation is already organized and requires little reorganization.

4.2. Oligomerization of SAAs with Other Amino Acids

The condensation of SAAs with amino acids provided conjugates, which were termed peptidosaccharides, saccharide-peptide hybrids, peptide-sugar hybrids, and saccharopeptides, and have important structural and biological features. One of the thrusts in this field is the use of SAA–amino acid conjugates as peptidomimetics. Kessler and co-workers were the first to demonstrate the potential of SAA as peptidomimetics.[21, 22] For example, the Pro–Phe dipeptide sequence in the somatostatin analogue cyclo-(Pro–Phe–D-Trp–Lys–Thr–Phe) **84** was replaced by the dipeptide isostere **14** (Scheme 2) to give the potent hexapeptide mimetic **85** (Scheme 10).[21] Furthermore, they incorporated the SAAs **14** and **16** into cyclic peptides that contained the RGD (Arg-Gly-Asp) motif. The cyclic pentapeptide cyclo-(-Arg–Gly–Asp–D-Phe–Val-) binds selectively to the $\alpha_v\beta_3$ receptor of the integrin family. Replacement of the two amino acids D-Phe–Val by the dipeptide isosteres **14** and **16** afforded the potent peptidomimetics **86** and **87** with high $\alpha_v\beta_3$ activity (IC_{50} = 25 nM for **86**) and 150 nM for **87**). Interestingly, the peptidomimetic **86**, which contains the flexible *cis* SAA, also exhibited a high affinity for the $\alpha_{IIb}\beta_3$ receptor (IC_{50} = 13.4 nM), which is absent in SAA-modified peptide **87** incorporating the *trans* SAA **16**.[24] This route opens the door to the development of novel receptor- and receptor-subtype-selective agents based on sugar platforms.[133–135] Chakraborty et al. incorporated the furanoid SAA **15** (Scheme 2) into Leu–enkephalin sequence **88**.[23] Replacement of the Gly–Gly sequence in the Leu–enkephalins by the isostere SAA **15** afforded the biologically active peptide **89**, which has an activity similar to that of Leu–enkephalin **88** (Scheme 10). Conformation analysis by means of CD, temperature coefficients of amide proton chemical shifts, and molecular dynamics revealed the presence of a nine-membered β-turnlike structure, absent in the saccharopeptide **90**, which contains a *trans* SAA.

The dimer **91** generated from sialic acid and glycine proved to be a moderate inhibitor of *Clostridial* sialidase (Scheme 11).[136] Conjugate **92**, which consists of an alternating sequence of SAA and β-amino acid residues (D- and L-



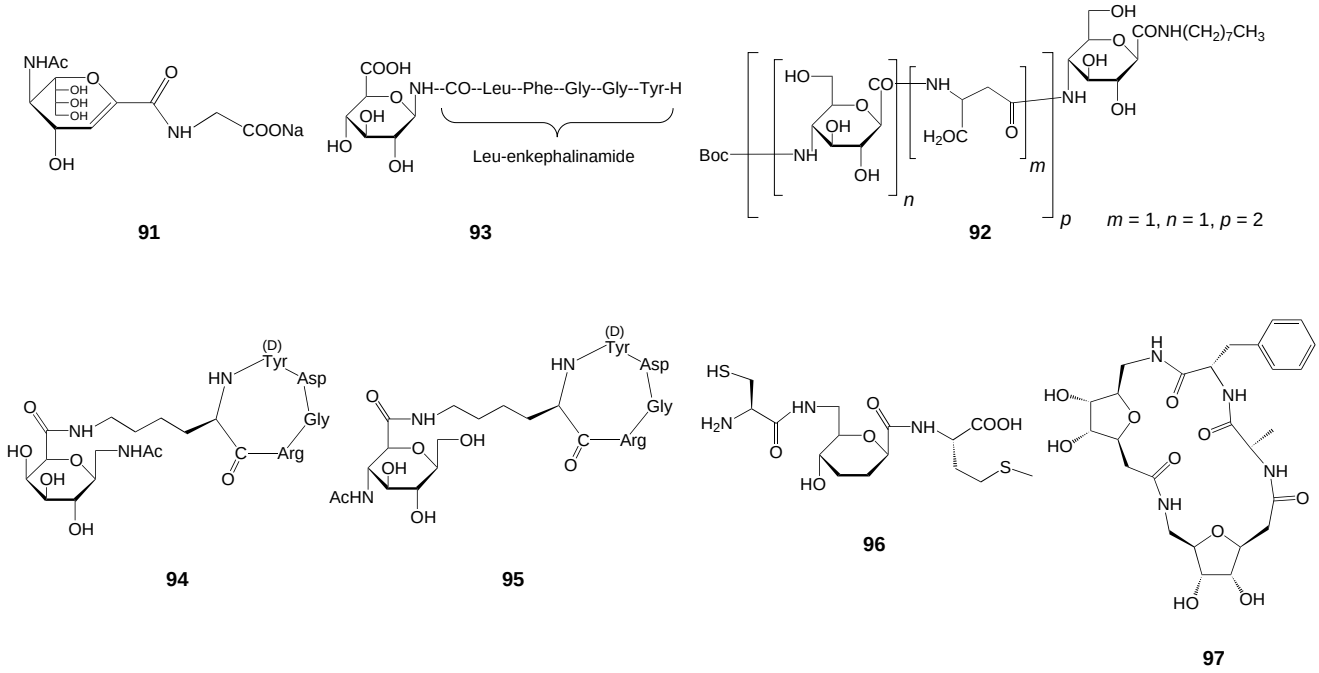
Scheme 10. A_0 GAA-based dipeptide isosteres which have been incorporated into short peptide sequences. The peptidomimetics **85**, **86**, **87**, and **89** are biologically active.

aspartic acid) was prepared by Ichikawa and co-workers. These hybrids are potent inhibitors of lung tumor cell invasion.[137] Incorporation of SAAs into the C-terminus of Leu– and Met–enkephalins produced selective and potent δ-opioid receptor agonists.[138] For example, pharmacological evaluation showed that glycopeptide **93**, which contains the Leu–enkephalinamide sequence, was 40 times more potent than Leu–enkephalinamide itself.[138] Recently, Kessler and co-workers demonstrated that the derivatization of the amino acid side chain in biologically active peptide compounds with SAAs influences activity and selectivity.[24] For example, peptide **94**, which is modified with a lysine side chain, showed the highest activity for the $\alpha_v\beta_5$ receptor ($IC_{50} = 24.7$ nM) in a series of RGD peptides.[24] Likewise, RGD peptide **95**, which is derivatized with a side chain, had a lower uptake in the liver than that of the nonglycosylated peptide. As a result, the initial blood concentrations were doubled.[24] SAA-based protein farnesyl transferase (PFT) inhibitors have also been reported.[139] For example, the saccharopeptide **96**, which contains a dipeptide isosteric sugar amino acid, inhibits bovine PFT ($IC_{50} = 214$ μM).

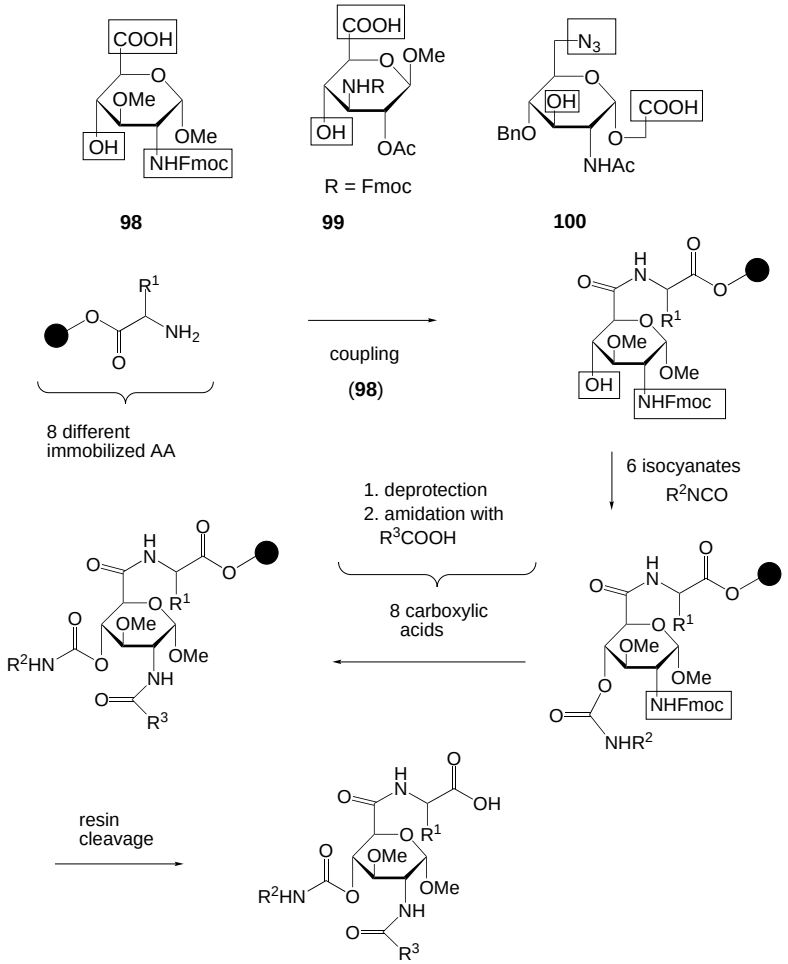
Recently, cyclic hybrids between sugar amino acids and amino acids were proposed as potential artificial receptors.[140] Van Boom and co-workers prepared several tetrameric hybrids in the solid phase and investigated their ability to form secondary structures. Hybrid **97** adopts a preferred conformation in water (Scheme 11). The coupling constant of the amide proton of alanine to its neighboring α proton is of the same order of magnitude as the coupling constants $J_{N\alpha}$ of a linear peptide that has an α-helical structure. It is anticipated that combinatorial exploitation of this solid-phase protocol may eventually lead to artificial receptor libraries based on sugar amino acid building blocks.

4.3. SAAs as Building Blocks for Sugar-Platform Libraries

Carbohydrates have the potential to be used as highly functionalized rigid scaffolds.[133–135, 141–144] In particular, the use of sugar-derived skeletons as nonpeptidomimetics of somatostatin (a cyclic tetradecapeptide)[134] demonstrated for the first time that sugars might be privileged platforms. Sofia et al.[145] elaborated on this idea and reported the synthesis of encoded trifunctionalized saccharide scaffolds termed "universal pharmacophore-mapping libraries". Two sugar building blocks **98** and **99**, which have a three-point attachment motif that consists of a carboxylic acid moiety, a free hydroxy group, and a protected amino group, were used for the construction of the library (Scheme 12). The free carboxylic acid was first treated with eight amino acids supported on trityl TentaGel resin, followed

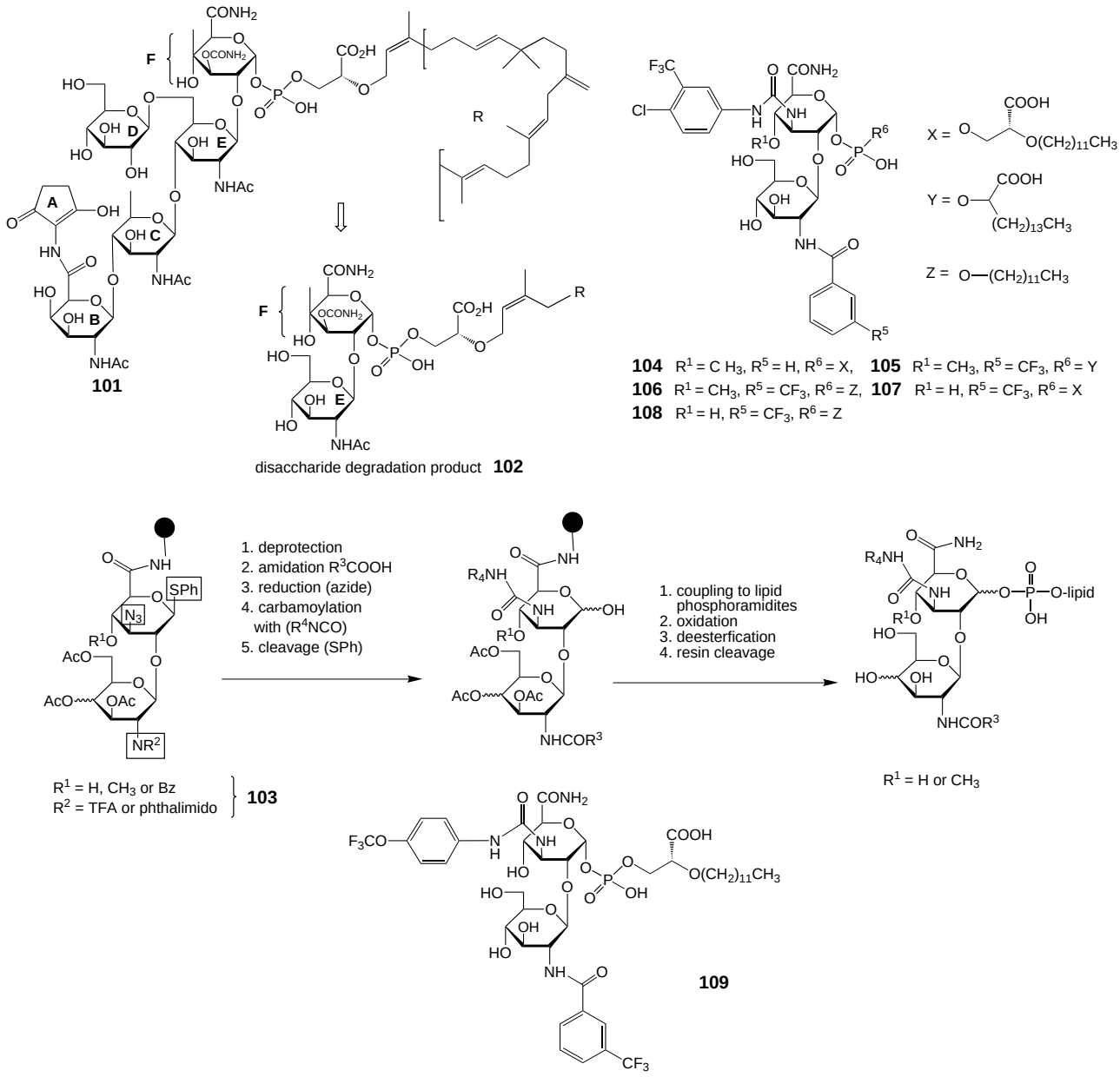


Scheme 11. GAAs linked to amino acids or peptides. Linking GAAs to oligopeptides influences the pharmacokinetic properties of biological active peptides (**93**–**95**). This approach can also be used to produce agents with anticancer- (**92**) and inhibitory potential (**96**), and may also find application in the synthesis of synthetic receptors (**97**).



Scheme 12. Synthesis of "universal pharmacophore libraries" based on a three-point attachment motif.[145, 146]

by carbamate formation at the free hydroxy site by using six isocyanates. Finally, the deprotected amino functional group was acylated with eight different carboxylic acids. Deacetylation (when necessary) and cleavage from the resin gave 16×48 sublibraries. Recently, a 12000-compound library was prepared by using **100** as a building block.[146] Sofia et al. also prepared a disaccharide library which mimics the transglycosylase inhibitor moenomycin A (Scheme 13).[147] Moenomycin A (**101**) is a pentasaccharide that contains a long lipid chain, which is attached to the reducing sugar F through a phosphoglycerate unit. Degradation studies, in conjunction with limited directed analogue synthesis, revealed that cell wall inhibitory activity was retained in disaccharide core structure **102**. Sofia et al. chose the supported disaccharide **103**, which is substituted with two protected amino functions and a thiophenylglycoside donor, to explore modifications at C1, C3, and C2′ (Scheme 12). Analogues in which the GlcNAc moiety was substituted by a GalNAc moiety were also investigated. Initially, the trifluoroacetate- or phthalimido-protected amino function at C2′ was deprotected and converted into the amide with a variety of activated carboxylic esters. After reduction of the azide and carbamoylation or amidation (not shown), the acetal groups were cleaved. The product

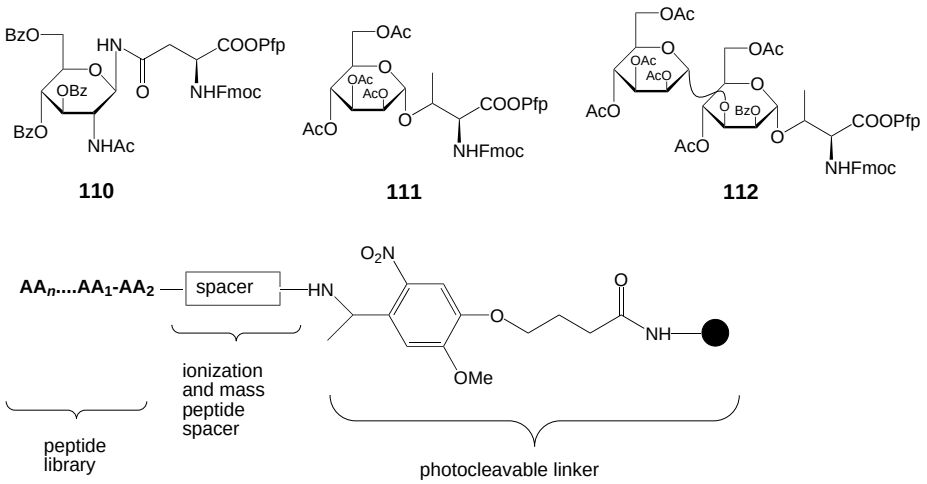


Scheme 13. Synthesis of a library of antibacterial disaccharides that mimic moenomycin A.[147]

was coupled to a variety of phosphoramidites, followed by oxidation, to give the desired phosphate intermediate. Finally, deprotection and cleavage from the resin afforded a 1300-membered disaccharide library, which was screened for both inhibition of bacterial cell wall biosynthesis and inhibition of bacterial growth. The results indicated that the replacement of the moenomycin glycerate lipid unit with either a 2-hydroxypropionic acid unit or a simple straight chain C12 lipid leads to compounds whose antibacterial activity is retained. In addition, all active disaccharides contained a substituted aromatic urea at C3. Interestingly, compounds **104**–**109** were effective against a strain of *E. faecium* that is naturally resistant to moenomycin. Furthermore, disaccharides **104**–**109** were shown to be as potent as the clinically used vancomycin as inhibitors of cell wall biosynthesis.

4.4. Libraries from GAA derivatives of O- and N-linked Glycopeptides

Simple O-GAAs with protected[148–152] and unprotected sugar residues[153] as well as N-linked amino acids[148–152] have been used as building blocks to generate glycopeptides that can mimic oligosaccharide structures.[148–152] An impressive example is the synthesis of a 300000-membered ladder-encoded[154] glycopeptide library by Meldal and co-workers.[149] The Pfp-activated (Pfp = pentafluorophenyl) glycosyl amino esters **110**, **111**, and **112** and a variety of activated amino esters were used to generate a heptaglycopeptide library in the solid phase by using a photocleavable linker (Scheme 14). Each GAA was labeled with carboxylic acid tags to allow unambiguous identification of the glycan moiety. The glycopeptide sequence on the bead was decoded by photolytic

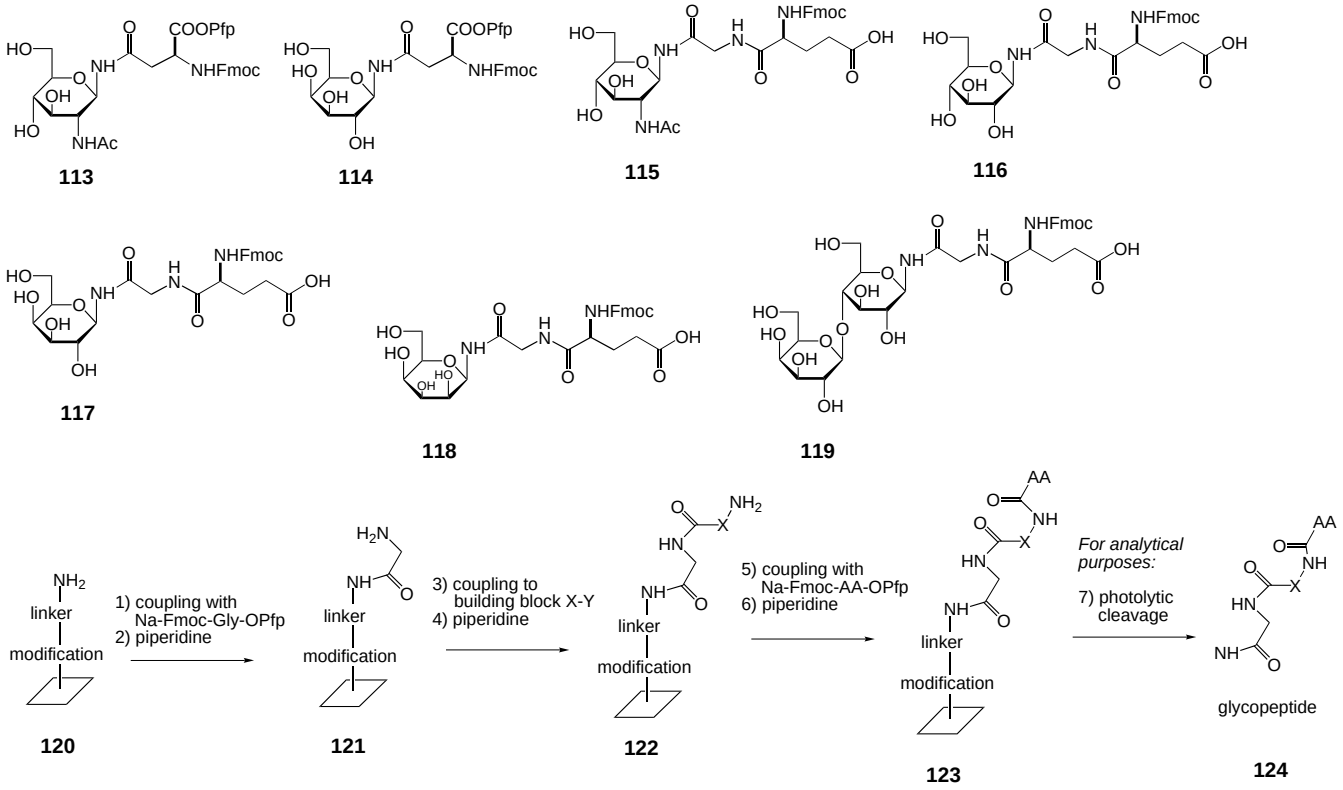


Scheme 14. GAA building blocks used in the synthesis of a 300000-membered glycopeptide library (Pfp = pentafluorophenyl).[149]

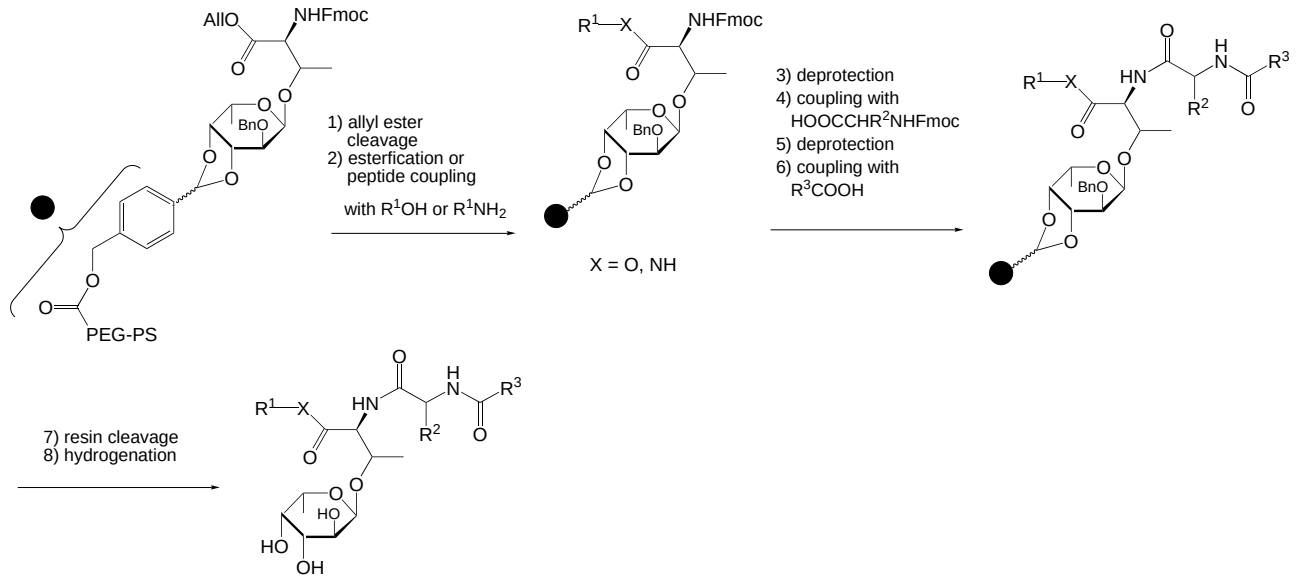
release and subsequent analysis of the resulting mass ladder of glycopeptide fragments by MALDI-TOF mass spectrometry. The synthesized library was screened "on bead" against the fluorescence-labeled lectin from *Lathyrus odoratus*, which shows a weak specificity for the α-methylglycosides of mannose, *N*-acetylglucosamine, and glucose. Interestingly, the most active compounds were glycopeptides that contain only one mannose residue.

Hummel and co-workers used the sugar-unprotected N-glycopeptide building blocks **113**–**119** for the synthesis of a glycopeptide library on a continuous surface (SPOT synthesis). SPOT synthesis on cellulose is a highly effective method for the rapid preparation of spatially addressable peptides (Scheme 15).[153] Initially, the cellulose membranes were modified by treatment with epibromohydrin and 4,7,10-tridecanediamine to provide homogeneous amino functionalization. For analytical purposes a Fmoc-protected photocleavable linker was coupled with the amine to provide, after reaction with piperidine, the immobilized amine **120**. Subsequently, the first amino acid N$^{\alpha}$-Fmoc-Gly-OPfp was coupled to the continuous surface. The remaining free amino functions were capped with a solution of acetic anhydride in methanol. In the second coupling step, the seven GAA building blocks **113**–**119** were coupled to the supported glycine, followed by deprotection. The coupling cycle was repeated with another amino acid. Highly pure tripeptides were obtained upon cleavage from the resin by means of UV irradiation (Scheme 15).

A library that consists of sialyl Lewis^{X} mimetics was reported by Wong and co-workers (Scheme 16).[152] Fucose, which contains the three hydroxy groups required for the recognition of sialyl Lewis^{X} by E-selectin, was retained as the only carbohydrate moiety, while the other three sugar residues were replaced with L-threonine and its derivatives. A fucosylated threonine amino acid residue was immobilized



Scheme 15. SPOT synthesis of an O-and N-linked glycopeptide library.[153]



Scheme 16. Synthesis of a library of sialyl Lewis^X mimetics (PEG = polyethyleneglycol, PS = polystyrene).[152]

on a carboxy-functionalized resin through an acid-sensitive *cis* 1,2-diol protecting and anchoring group. The allyl group was first cleaved, and the acid function was then derivatized as an ester or amide, followed by a conventional peptide coupling cycle and capping (Scheme 16). The deprotected and purified compounds were tested against E- and P-selectins and showed only moderate binding affinities.

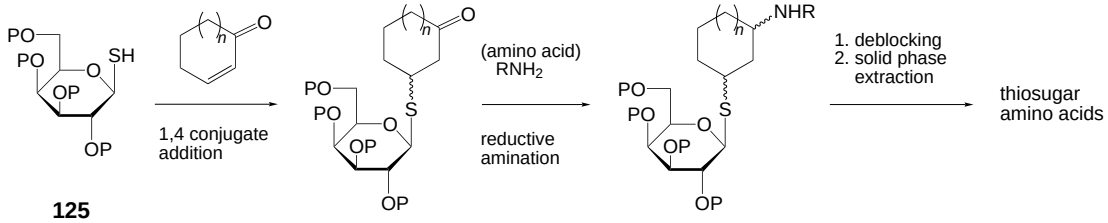
4.5. Library Synthesis by Using GAAs Not Derived from O- and N-linked Glycopeptides

Among the mimics of the naturally occurring glycopeptides, the S-GAA family has attracted considerable interest over the years. The driving force behind the synthesis of S-glycosides has been the production of glycomimetics with enhanced stability toward chemical and enzymatic degradation. Furthermore, the synthesis of S-glycosides is less complicated than the synthesis of C-glycosides. The first combinatorial approach towards S-GAA libraries (carbohybrids) was reported by Hindsgaul and co-workers (Scheme 17).[107] Hydrophobically tagged 1-thiogalactose derivative **125** underwent Michael reactions with five different Michael acceptors to yield diastereomeric adducts. In the second step, the ketone groups in the Michael adducts were reductively aminated with six different carboxy-protected amino acids. After deprotection, thirty (5×6) thiosugar amino acids were obtained as mixtures of four diastereomers each. The highlight of this approach is the use of fatty acid carbohydrate esters as hydrophobic tags, which permit the quantitative adsorption of the reaction products derived from the starting sugar onto reversed-phase C-18 resin. The excess organic reagents and by-products could be removed completely by washing with methanol, whereas the final purified product was eluted with hexane. One of the compounds of this library was found to be a competitive inhibitor of β-glactosidase from *E. coli*, with an inhibition constant of 1.7 μM. Since then, supported thiolates have been used in the solid-phase preparation of glycomimetics.[52, 155]

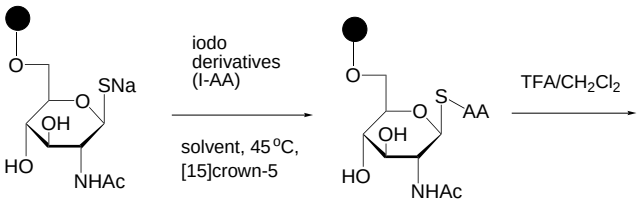
Hummel and Jobron described the synthesis of several unprotected S-GAA building blocks in the solid phase (Scheme 18).[52] The key step in their synthesis is the reaction of a supported sodium thiolate **126** with iodo derivatives of amino acids (I-AA) in the presence of [15]crown-5 as complexing agent. Resin cleavage with concomitant acid deprotection afforded various S-GAAs **127**, which can be used as building blocks in the combinatorial synthesis and solid-phase synthesis of S-glycopeptides.

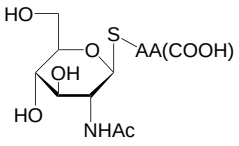
4.6. Combinatorial Approaches Towards Glycopeptides Derived from A_2 GAAs

There have been few reports of libraries that contain A_2 GAAs. One of the problems associated with sugar mimetics that incorporate an α-amino acid moiety at the

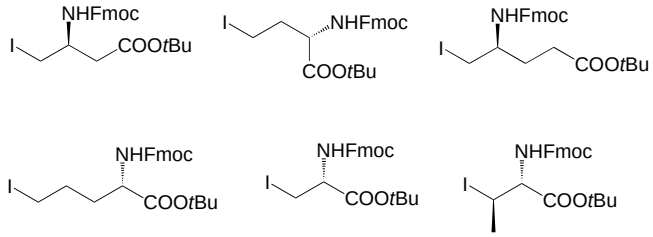


Scheme 17. Synthesis of a glycoside library of thiosugar amino acids (P = hydrophobic tag).[107]



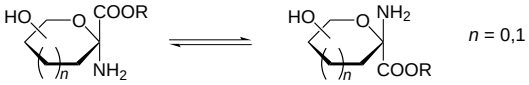


I-AA:



Scheme 18. Synthesis of S-glycosamino acid building blocks in the solid phase (TFA = trifluoroacetic acid, AA = amino acid).[52]

anomeric position is their tendency to equilibrate between two different stereoisomers (Scheme 19).[73, 74, 76, 82, 86] Acylation of the amine usually prevents this equilibration and the pure

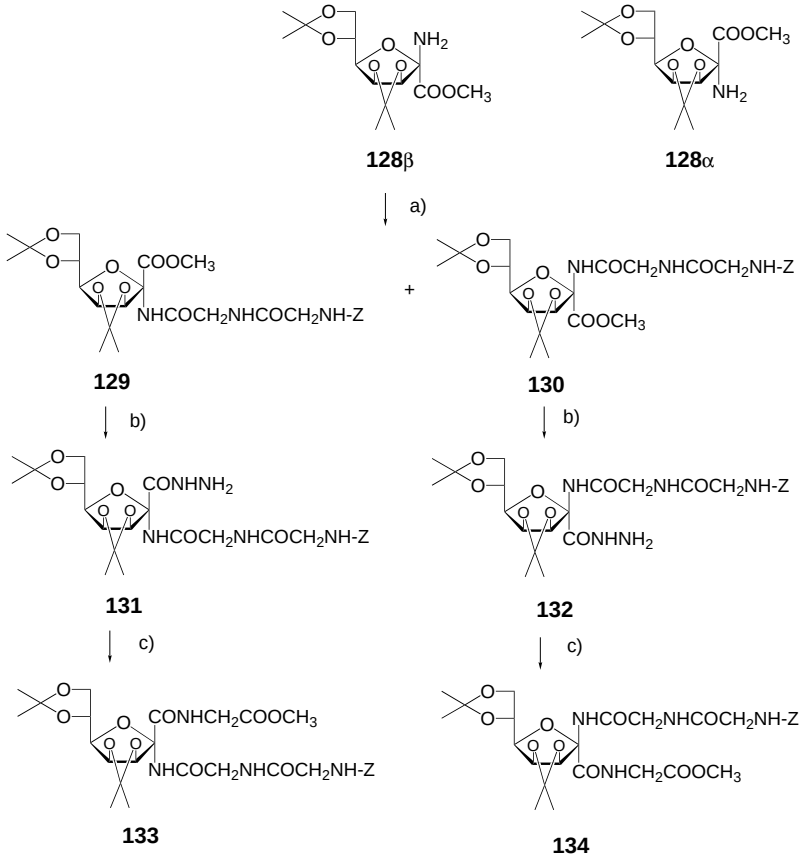


Scheme 19. Equilibration of an α-amino acid incorporated in the anomeric center of carbohydrates.

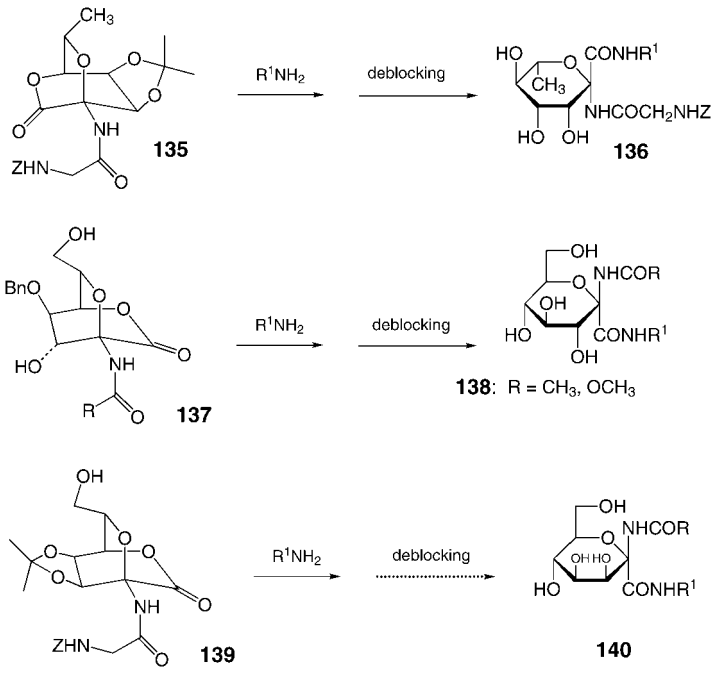
stereoisomers can be isolated.[82, 86] On the other hand, strongly basic conditions afford epimerized products.[74, 75, 86] Fleet and co-workers have studied the incorporation of the mannofuranose-based aminoester **128*α*** and **128*β*** into tri- and tetrapeptides (Scheme 20).[86] Coupling of **128*β*** with benzoyloxycarbonyl-protected Gly–Gly dipeptide afforded a mixture of tripeptides **129** and **130** in a ratio of 5:1. Extension of the tripeptide **129** at the C-terminus was effected by initial treatment with hydrazine hydrate and subsequent conversion into the acyl azide, followed by treatment with glycine methyl ester to give tetrapeptide **133**. Similar transformations of compound **130** gave the epimeric peptide **134**. Interestingly, no evidence of any epimerization at the anomeric center was found during any of the transformations after the initial acylation of the amino esters **128*β***. In contrast, separate treatment of **128*α*** and **128*β*** with phenylisocyanate afforded configurationally pure ureas. Presumably, the increased rate of urea formation relative to amide formation prevents equilibration of the amino esters **128*α*** and **128*β***. To synthesize epimer-free glycopeptides with incorporated anomeric α-amino acids, Fleet and co-workers treated bicyclic L-rhamnolactone **135**,[156] D-glucolactone **137**,[156] and D-mannolactone **139**[84] with primary amines to yield the tripeptides **136**, **138**, and **140**, respectively, after deprotection (Scheme 21). This approach, once implemented in a combinatorial strategy, may lead to novel glycopeptidomimetics.

4.7. Combinatorial Approaches Towards A_3 and A_4 GAAs

Branched A_3 GAAs are difficult to synthesize and have thus not been described often, and appear to have been incorporated only into short peptide sequences.[89] A_4 GAAs are formed by coupling an amino acid with a sugar scaffold through the amino function. Although no libraries with this building block have appeared so far, a few strategies with the potential for combinatorial application have been reported.[158–161] Among the possible A_4 structures, the 4-amino-4-deoxysugar skeleton, a potential antifungal and antibacterial

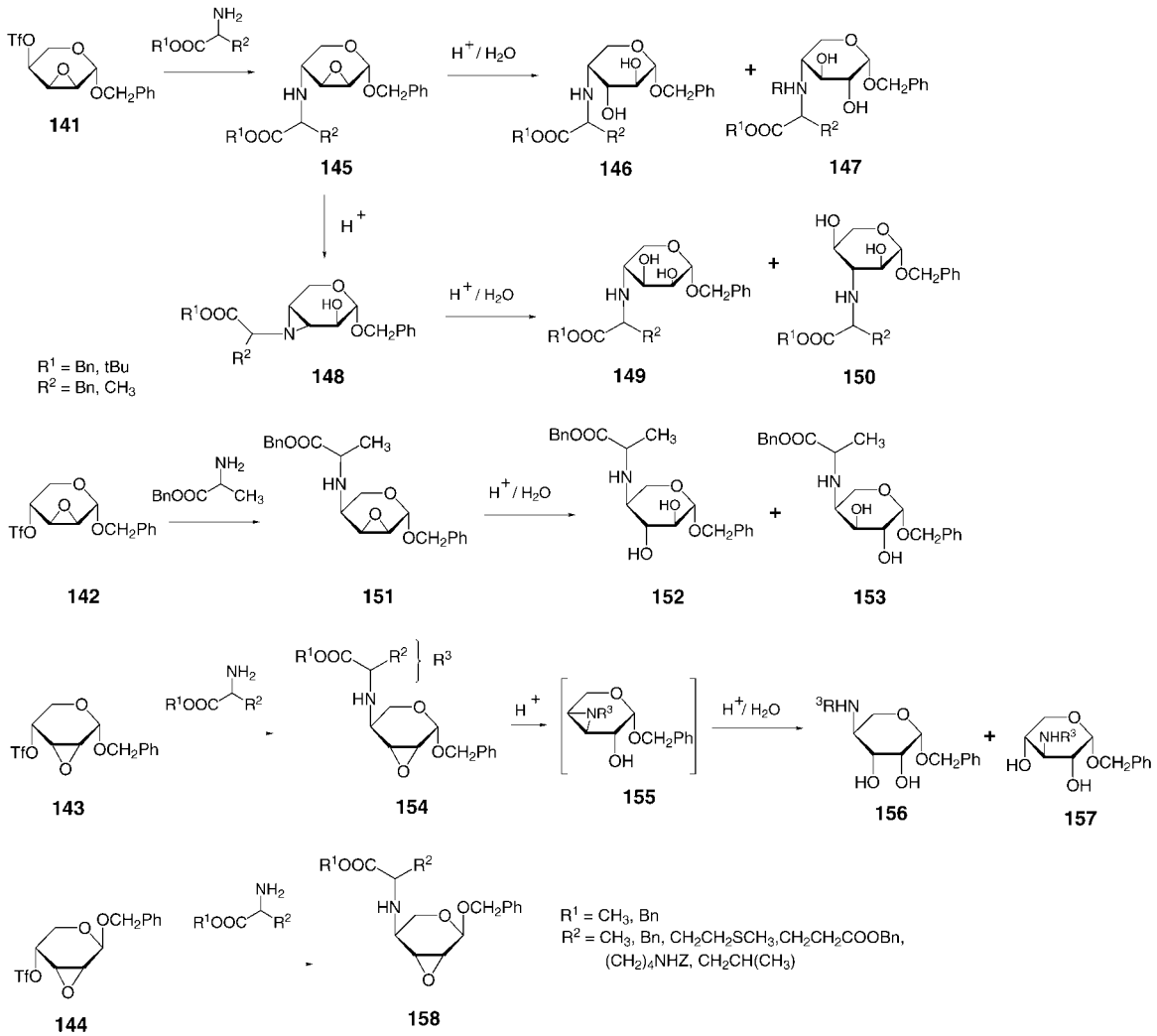


Scheme 20. Incorporation of an A_2 GAA into short peptides. Reagents and conditions: a) *Z*-$NHCH_2CONHCH_2COOH$, DCC, HOBt; b) NH_2NH_2, MeOH; c) *t*BuONO, HCl; then $Cl^-NH_3^+CH_2COOCH_3$, Et_3N (DCC = dicyclohexylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole).



Scheme 21. Lactone strategy to incorporate an A_2 GAA into short peptides (Z = benzyloxycarbonyl).

agent,[157] and the 2-amino-2-deoxysugar skeleton, a common building block in glycoconjugates such as peptidoglycans, mucopolysaccharides, bacterial lipopolysaccharides, antigens, and blood group substances, have attracted some interest.[158–161] Voelter and co-workers[158] investigated the substitution of the triflate group in 2,3-anhydro-4-*O*-trifluoromethanesulfonyl glycosides **141**–**144** by amino esters as a method to prepare sugar amino acid conjugates (Scheme 22). By using this strategy, it was possible to incorporate a variety of amino acid derivatives into the sugar scaffold. Treatment of triflate **141** with the free amine of alanine, phenylalanine, or *tert*-butyl 4-aminobenzoate provided epoxide **145**. Subsequent acid-catalyzed epoxide opening in an aqueous solution afforded diols **146** and **147**. Exposure of epoxide **145** to silica gel yielded aziridine **148** quantitatively which was converted into diols **149** and **150** by acid hydrolysis. Analogously, treatment of triflates **142**, **143**, and **144** with amino acid derivatives provided the corresponding sugar–amino acid conjugates **151**, **154**, and **158** in 60% average yield. Solvolysis of *trans*-amino epoxide **154** furnished diols **156** and **157**, presumably via aziridine intermediate **155**. Similarly, hydrolysis of **151** afforded GAA derivatives **152** and **153** (Scheme 22).

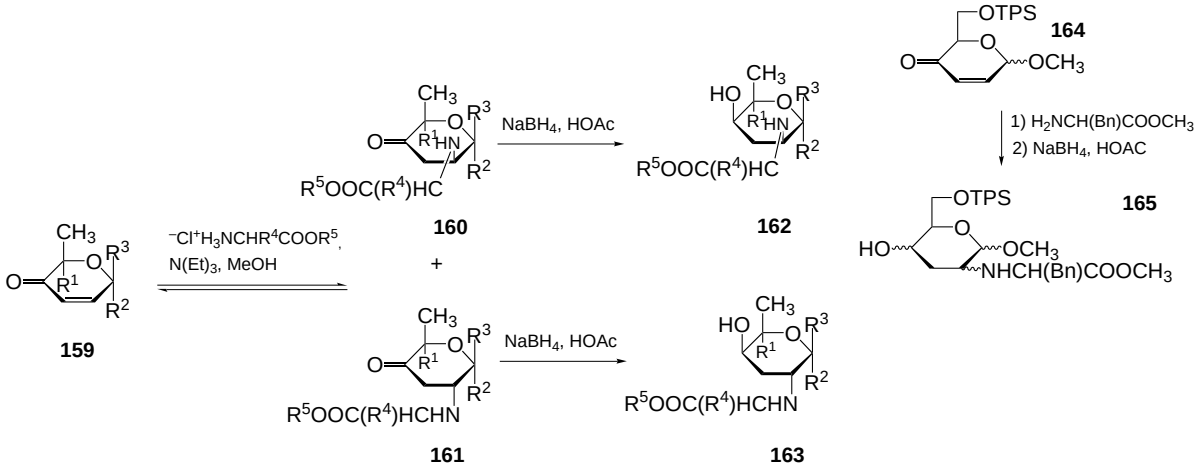


Scheme 22. Synthesis of A_4 GAAs by substitution of the triflate group (TfO) with amino acids (Bn = benzyl).

A Michael addition approach towards the synthesis of 2-amino-2,3-dideoxy-GAAs was described by Georgiadis and co-workers (Scheme 23).[159–161] The 2,3-dideoxy-hex-2-eno-pyranos-4-ulose **159** reacted with a variety of amino esters to yield the corresponding unstable Michael adducts **160** and **161**. Subsequent reduction of the ketone afforded the stable amino acid conjugates **162** and **163**. A similar reaction sequence on **164** provided the GAA **165**.

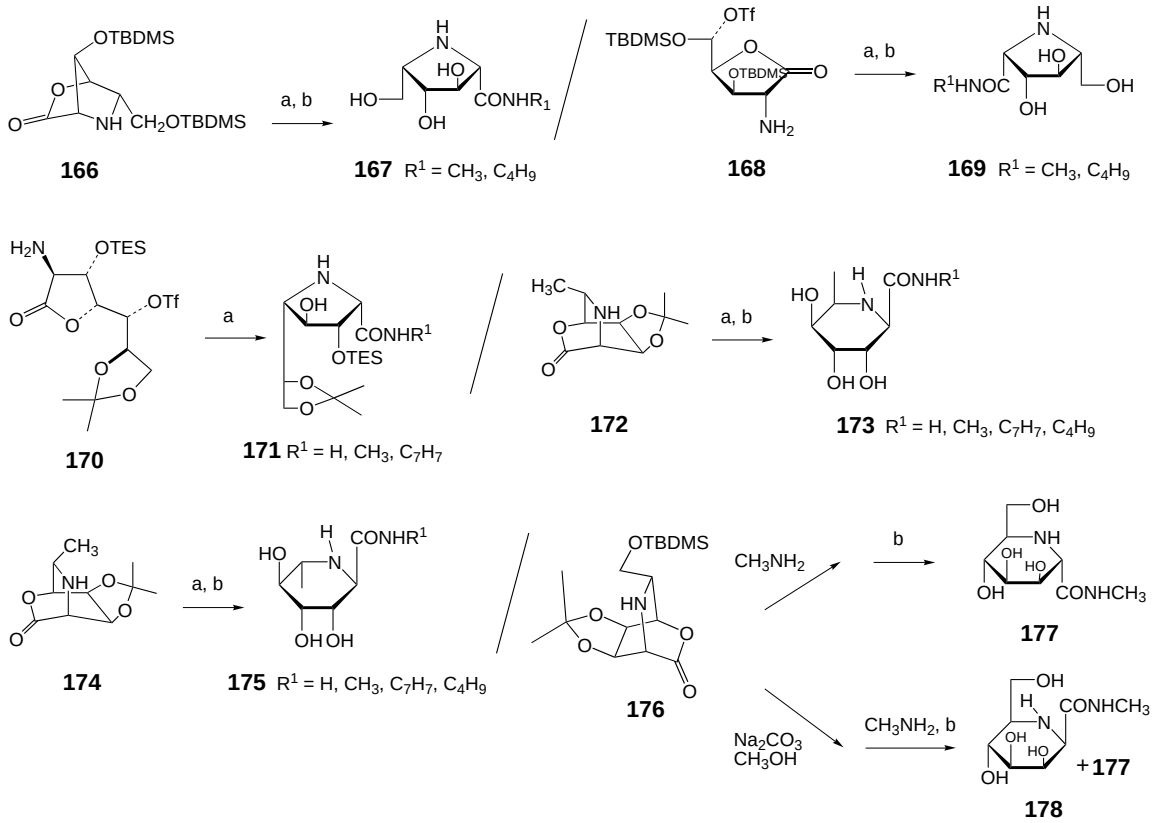
4.8. Access to Azasugar Acid Libraries

Among the azasugar amino acids, the proline derivatives and pipecolic acids have attracted considerable interest over the years as a result of their potential to induce secondary structures in peptides and their potential as glycosidase inhibitors. Fleet and co-workers reported a lactone strategy that can be used to incorporate proline and pipecolic acids into azasugar libraries (Scheme 24).[101, 102, 104, 162] Treatment of the lactones **166**, **168**, and **170** with primary amines and subsequent deprotection, if necessary, provided the corresponding hydroxyproline derivatives **167**,[162] **169**,[162] and **171**.[104] Similarly, the pipecolic acids **173**,[102] **175**,[102] **177**,[101] and **178**[101] were accessible from the bicyclic lactones **172**, **174**, and **176** (Scheme 24). Interestingly, the ASA-derivatives **177** and **178** showed strong competitive inhibition of β-*N*-acetylglucosaminidases from bovine liver and human placenta.[101]



159 **160** **161** **162** **163** **164** **165**

Scheme 23. Michael addition approach towards A_4 GAAs (TPS = triphenylsilyl). $R^1 = C_6H_5$ or $C_6H_4SO_2C_6H_5$; $R^2 = OCH_3$ or H; $R^3 = H$ or CH_3; $R^4 = H$ or CH_3 or Bn; $R^5 = CH_3$ or CH_2CH_3.

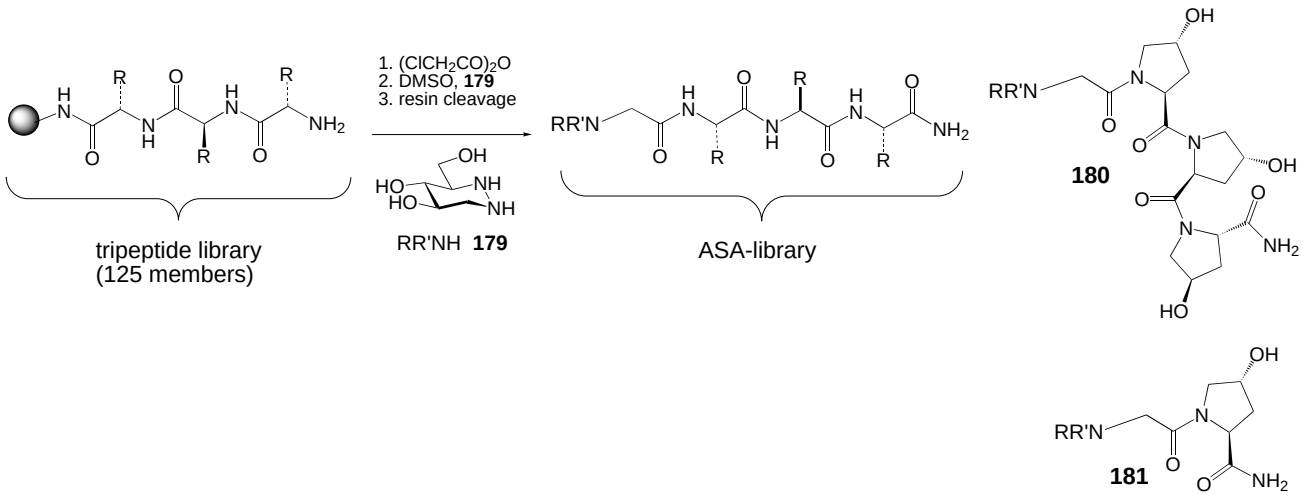


166 **167** $R^1 = CH_3, C_4H_9$ **168** **169** $R^1 = CH_3, C_4H_9$

170 **171** $R^1 = H, CH_3, C_7H_7$ **172** **173** $R^1 = H, CH_3, C_7H_7, C_4H_9$

174 **175** $R^1 = H, CH_3, C_7H_7, C_4H_9$ **176** **177** **178** +**177**

Scheme 24. Lactone strategy to prepare derivatives of A_5 GAAs (TBDMS = *tert*-butyldimethylsilyl). a) R^1NH_2, b) deblocking.

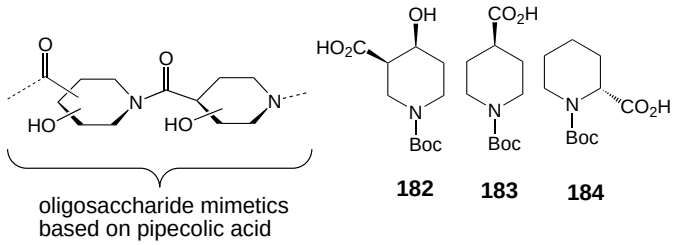


Scheme 25. Synthesis of an ASA library designed to interact with glycosidases.[163, 164]

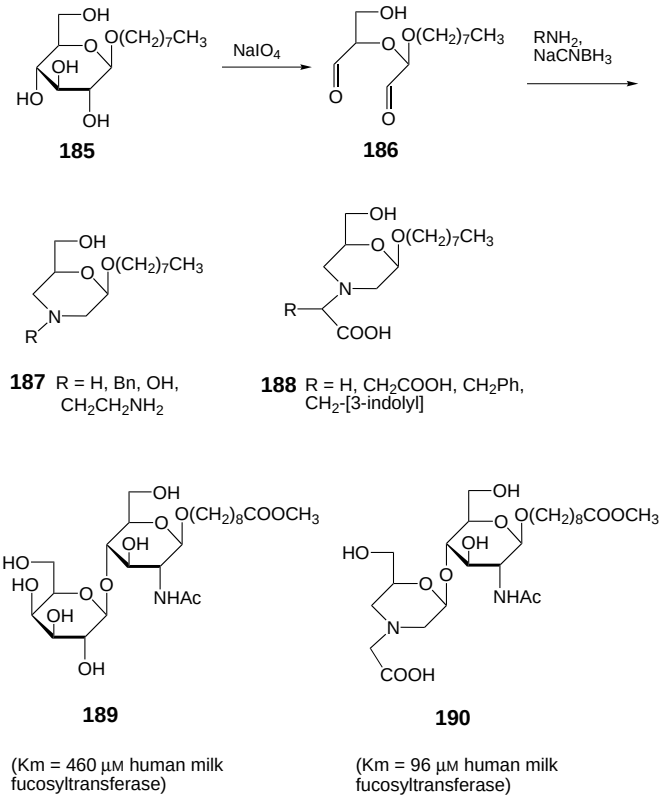
A library of azasugar glycosidase inhibitors was prepared recently by Bols and co-workers (Scheme 25).[163, 164] Initially, a tripeptide library that consisted of the L-amino acids of threonine, serine, 4-hydroxyproline, phenylalanine, and alanine was synthesized in the solid phase (4-methylbenzhydrylamine resin) by using the split-and-mix method. Subsequently, the resulting five sub-libraries of 25 peptides in each reactor were treated individually with chloroacetic anhydride followed by substitution with the azasugar azafagomine (**179**) and cleavage from the resin. Deconvolution of the most active sub-libraries yielded the potent inhibitor **180** for β-glucosidase from almonds ($K_i = 40$ μM). All the peptide positions of **180** have hydroxyproline substituents. Interestingly, this compound was 40 times more active than **181**, but still 60 times less active than the unmodified azafagomine, which indicates that the triproline residue contributed to binding. Most compounds in this library also inhibited glycogen phosphorylase.

A small 27-membered amide library of piperidine-based carbohydrate mimics were synthesized in the solid phase.[165] A split-and-mix synthesis with building blocks **182**, **183**, and **184** (Scheme 26) afforded 27 trimers, which where subsequently tested for activity against α-glucosidase (yeast), β-glucosidase (almonds), isomaltose (yeast), α-fucosidase (human placenta), β-mannosidase (snail), and β-galactosidase (*E. coli*). Unfortunately, none of the enzymes were inhibited significantly by the library compounds.

Hindsgaul and co-workers developed a short pathway to morpholine-based SAAs (Scheme 27).[166] Periodate oxidation of the octylglucoside **185** affords dialdehyde **186**, which can be purified easily by simple adsorption onto reverse-phase C-18 resins. Reductive amination of **186** with a variety of amines (benzylamine, hydroxylamine, unprotected amino acids) affords morpholine-based ASAs **187** and **188**. The reaction was extended to the *N*-acetyllactosamine derivative **189**, in which only the terminal Gal residue contains vicinal diols. Periodate oxidation followed by reductive amination with glycine gave the 3′-azadisaccharide derivative **190**. Interestingly, the disaccharide mimetic **190** was a better substrate than **189** for human milk fucosyltransferase (Scheme 27).



Scheme 26. Synthesis of a library of amides designed as oligosaccharide mimetics. The library is based on pipecolic acid building blocks.[165]



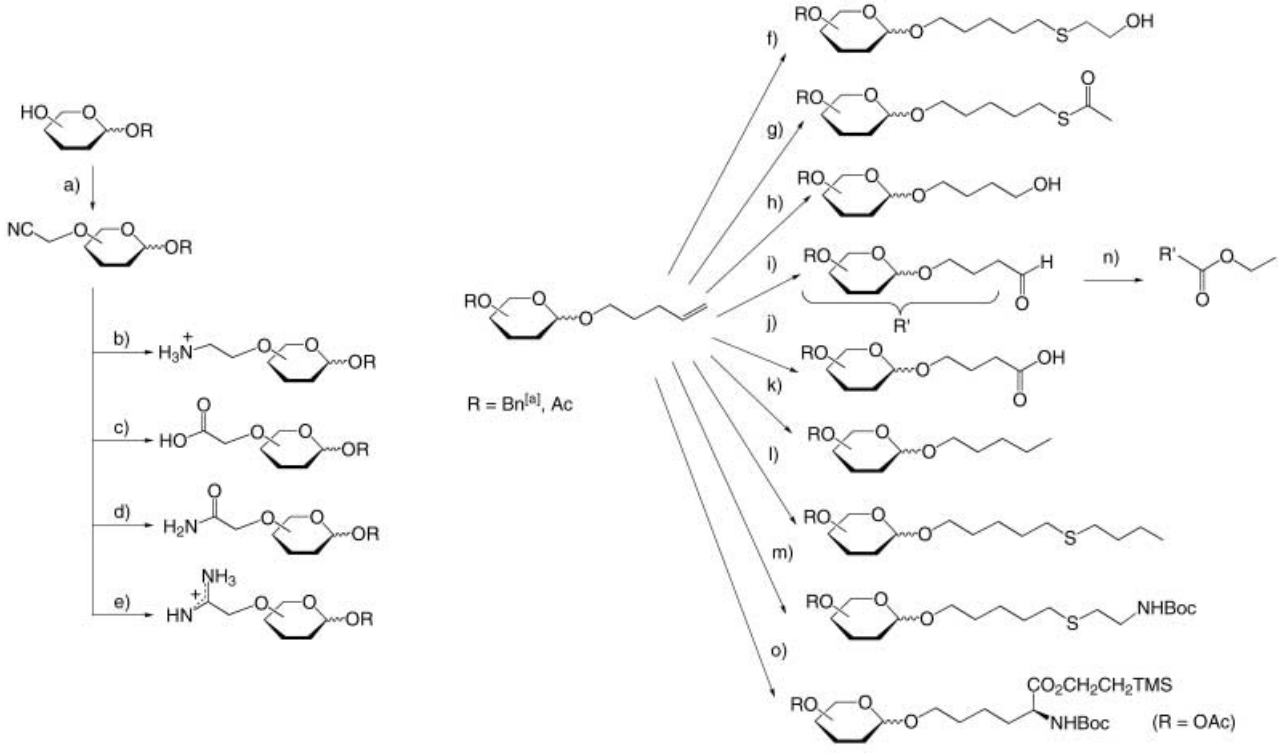
Scheme 27. Synthesis of morpholine-based GAAs.[166]

5. Synthetic Operations on the Polyol Platform Designed to Increase Functional Diversity of GAAs

Although carbohydrate scaffolds are highly functionalized building blocks, their functional diversity is limited to the presence of primary and secondary hydroxy groups. To increase the functional diversity of the sugar platform, easy, high-yielding transformations of the alcohol function into derivatives is required. So far, most of the previous work in this article has dealt with the conversion of alcohols into esters, ethers, carbamates, and carbonates. Furthermore, activation of the hydroxy group as activated esters has been used to incorporate amines, amino acids, azides,[167] and thiols[155] into the sugar scaffold by nucleophilic substitution. Nucleophilic displacement of activated primary hydroxy functions usually proceeds easily, whereas secondary hydroxy groups require more drastic conditions and therefore are subject to side reactions. Recently, hypervalent silicate intermediates were used as efficient nucleophilic azide or cyanide sources to undergo rapid and efficient azide displacement reactions with primary and secondary alkyl halides and sulfonates.[94] Alternatively, additional diversity may also be introduced through functionalized tethers.[168, 169] Hindsgaul and Malet[168] derivatized mono- and disaccharides with the O-cyanomethyl group, which is a versatile precursor for a variety of functional groups including carboxylic acids, amines, amides, and amidines (Scheme 28). O-pentenyl glycosides can also be easily converted into novel structures under mild conditions (Scheme 28).[169, 172] Similar conversions can also be envisaged with O-allyl ethers of sugars.[170, 171]

6. Summary and Outlook

GAAs are versatile building blocks for combinatorial synthesis (for examples, see Table 1 and relevant tables in the Supporting Information). Derivatization and oligomerization of the amino acid moiety has been used to generate simple glycomimetic libraries. Biological evaluation of these compounds has resulted in the discovery of potent inhibitors of carbohydrate–protein binding. Besides being sugarlike, GAAs are also potential peptidomimetics. SAA-based dipeptide isosteres have been incorporated into short peptide sequences, which were shown to be biologically active. Finally, the rich stereochemistry and high degree of functionalization of GAAs may result in their use as scaffolds for the construction of pharmacophore groups. Combinatorial derivatization of the polyol moiety of GAAs as esters, ethers, carbonates, or carbamates by orthogonal protection[141, 142] may lead to structures with new pharmacological properties. Because of the wide implications of peptides and carbohydrates in many diseases[31] and as building blocks for biopolymers, GAAs hold great promise for drug discovery and materials science.



Scheme 28. Ether- or glycoside-based tethers attached to the carbohydrate platform can be used to increase the functional diversity of the polyol scaffold.[168, 169, 172] Reagents and conditions: a) NaH, $BrCH_2CN$, CH_3CN; b) $BH_3 \cdot Me_2S$, THF, reflux; c) NaOH, MeOH, reflux; d) NaOMe/MeOH, 12 h, room temperature, then $NaHCO_3$; e) NaOMe/MeOH, 12 h, room temperature, then NH_4Cl; f) $HOCH_2CH_2SH$, AIBN, dioxane, Δ; g) CH_3COSH, AIBN, dioxane, Δ; h) O_3, CH_2Cl_2, $-78\,^{\circ}C$, then $BH_3 \cdot Me_2S$ or $NaBH_4$; i) O_3, CH_2Cl_2, $-78\,^{\circ}C$, then $BH_3 \cdot Me_2S$; j) $RuCl_3/NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$ (2:2:3); k) H_2, Wilkinson's catalyst, EtOAc; l) $CH_3(CH_2)_2CH_2SH$, AIBN, dioxane, Δ; m) $HSCH_2CH_2NHBoc$, AIBN, dioxane, Δ; n) NaH, $(EtO)_3P(O)CH_2COOEt$, THF, $0\,^{\circ}C$; o) 1. O_3, MeOH, CH_2Cl_2, pyridine, Me_2S; 2. tetramethylguanidine, THF, $-78\,^{\circ}C \rightarrow RT$, $P(OMe)_2(O)CH(NHBoc)CO_2CH_2CH_2TMS$; 3. (*S*,*S*)-Et-DuPHOS-Rh^+, THF, room temperature, H_2 (50 psi); [a] except for o). (AIBN = azobisisobutyronitrile, Et-DuPHOS = 2′,5′,2″,5″)-tetraethyl.

Abbreviations:

AA: amino acid
GAA: glycosamino acid
GNA: glyconucleic acid
SAA: sugar amino acid
Ur: uridine

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