Carbohydrate-Based Mimetics in Drug Design: Sugar Amino Acids and Carbohydrate Scaffolds†

Sibylle A. W. Gruner,‡,§ Elsa Locardi,‡ Elisabeth Lohof,‡ and Horst Kessler*,‡,§

Institut für Organische Chemie und Biochemie, Technische Universität München, Lichtenbergstrasse 4, D-85747 Garching, Germany, and Novaspin Biotech GmbH, Mühlfeldweg 46, D-85748 Garching, Germany

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I. Introduction

A. Concept

Among the major classes of biomolecules, carbohydrates allow almost unlimited structural variations. The molecular diversity of carbohydrates offers a valuable tool for drug discovery in the areas of biologically important oligosaccharides, glycoconjugates, and molecular scaffolds by investigating their structural and functional impact. The modifications such as those of the naturally occurring O-/N-glycosidic bonds remain of interest to increase the enzymatic stability, as well as to facilitate the assembly of large, diverse oligomer carbohydrate or peptidomimetic libraries by solid-phase techniques.

The high density of functional groups per unit mass and the choice of stereochemical linkages at the anomeric carbon has always challenged synthetic chemists toward a multitude of approaches to this rich class of compounds. Monosaccharides also provide rigid molecular systems (privileged structures) which can be used as molecular templates to display pharmacophoric groups in well defined spatial orientations. To generate chemically diverse carbohydrate building blocks more suitable for use in combinatorial organic synthesis, at least one amine and one carboxylic acid functional group was incorporated into the sugar ring.

Naturally Occurring Sugar Amino Acids. Sugar amino acids can be found in nature largely as construction elements.[1−4] The most prominent and abundant example is sialic acid often located peripherically on glycoproteins. This family of natural SAAs consists of *N*- and *O*-acyl derivatives of neuraminic acid **1** (Figure 1). The main substituents on nitrogen are the N-acetyl and N-glycosyl groups. Glycosaminuronic acids, **2**−**5**, are usually found in form of derivatives, such as 2-acetamido-2-deoxy-glucuronic acid, found in bacterial cell walls[5] and 2-acetamido-2-deoxygalacturonic acid as one component of bacterial Vi antigen of *Escherichia coli*.[6] Derivatives of glucosaminuronic acid were also detected in the cancomycin family of antibiotics similar to vancomycin.[7]

Interestingly, natural SAAs can be found in nucleoside antibiotics (for a review, see ref 8). Two different 3-amino-3-deoxy uronic acids, derivatives of 3-amino-3-deoxy-D-gulopyranuronic acid and 3-amino-3,4-dideoxy-D-xylohexopyranuronic acid, were found in ezomycin A.[8,9] 4-Amino-4-deoxy-glucuronic acid **5**, can be found in gougerotin,[10−14] a antibiotic from *Streptomyces* bacteria, as the carbohydrate residue of the nucleoside.

The naturally occurring furanoid SAA (+)-hydantocidin **7** (Figure 1), which represents a spiro-

† Dedicated to Professor Lutz F. Tietze in occasion of his 60th birthday.

* To whom correspondence should be addressed. Fax: (+49) 89-289 13210. E-mail: kessler@ch.tum.de.
‡ Institut für Organische Chemie und Biochemie.
§ Novaspin Biotech GmbH.

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Elisabeth Lohof was born in Miltenberg, Germany. She received her Diplom degree in Chemistry from the Technical University of Munich in 1993. She continued her graduate studies at the Technical University of Munich with Professor Horst Kessler working on the synthesis and NMR structural studies of sugar amino acid derivatives in their incorporation into peptides and received her Ph.D. degree in Chemistry in 1998.

Elsa Locardi was born in Venice, Italy, in 1971. She received her *Laurea* in Chemistry in 1996 from the University of Padova, in the group of Professor Stefano Mammi. Her studies have primarily focused on the conformational analysis of peptides using NMR and molecular modeling techniques. She has continued her biophysical research under the supervision of Professor Murray Goodman at the University of California at San Diego, CA, until 1999. She is currently working in the laboratory of Professor Horst Kessler toward her Ph.D. degree at the Technische Universität München, Germany. Her research involves the synthesis and structural determination of oligomers from sugar amino acids and mannose-based peptidomimetics.

hydanthion derivative,[15−17] exhibits herbicidal activity.

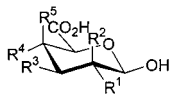
Siastatin B **8** (Figure 1) is among the class of SAAs, in which the nitrogen is located within the pyranoid ring structure. This inhibitor for both β-glucuronidase and *N*-acetylneuraminidase was isolated from a *Streptomyces* culture.[18]

B. Notes on Nomenclature

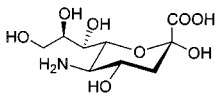
We use the term "sugar amino acid", SAA, as a functional, succinct classification term, although a plethora of terms have been proposed in the literature for compounds derived from SAAs. These include saccharide-peptide hybrids, glycosamino acids and glycotides,[19] peptidosaccharides,[20] saccharopeptides,[21−23] amide-linked carbohydrates, tetrahydrofuran-(pyran) amino acids,[24−26] and carbopeptoids,[27−30] although the latter compounds most often do not have a peptoid functionality (IUPAC definition). The term saccharopeptides has also been used to describe oligosaccharides in which the glycosidic linkage has been replaced by an amide bond.[31,32] Some publications use the term "sugar amino acids" for glycosylated amino acids,[33,34] for a disaccharide based on an amino- and carboxyl cyclopropyl-carbohydrate derivative,[35] or in one case even for conjugates based

Horst Kessler was born in Suhl (Thuringia) Germany in 1940. He studied chemistry in Leipzig and Tübingen, where he received his Ph.D. degree with Eugen Müller in 1966 and his habilitation in 1969. He was appointed full professor for organic chemistry at the J. W. von Goethe Universität in Frankfurt in 1971. In 1989, he moved to the Technische Universität München. Prof. Kessler is the recipient of the Otto Bayer award (1986), the Max Bergmann medal for peptide chemistry (1988), the Emil Fischer medal (1997), and the Max-Planck-Forschungspreis (2001). Since 1996, he has been a member of the "Bayerische Academie der Wissenschaft". Guest professorships lead him to Halifax, Tokyo, Madison, Haifa, and Austin. His current interests are in the area of bioorganic and medicinal chemistry, with specific focus on the study of biological recognition phenomena and on conformationally oriented design of biologically active molecules, such as carbohydrates, peptidomimetics, and peptides. Another field of interest is the development and application of new NMR techniques to peptides, proteins and nucleic acis as well as their complexes.

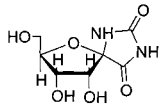
Sibylle Gruner was born in 1972 in Munich, Germany. She started to study chemistry in 1993 at the Universität Karlsruhe, and continued her education at the Ecole Européenne de Chimie, Polymères et Matériaux de Strasbourg, France. During her master thesis with Prof. D. Seebach at the ETH Zurich, she worked on the synthesis and structural investigations of β-peptides. After receiving her degree in chemistry in 1998, she joined the research group of Prof. H. Kessler at the Technische Universität München. Her doctoral studies focus on carbohydrate-based mimetics in drug design, with special emphasis on sugar amino acids as structural templates, and key residues of bioactive peptidomimetics as well as on secondary structure investigations of sugar amino acid oligomers. In 2001, she joined Novaspin Biotech GmbH. She was the recipient of a Helmut Bredereck Lecture award at the GDCh Jahrestagung 2001.



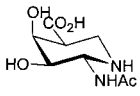
Glycosaminuronic acids		R^1	R^2	R^3	R^4	R^5
glucosaminuronic acid	**2**	NH_2	H	OH	OH	H
galactosaminuronic acid	**3**	NH_2	H	OH	H	OH
mannosaminuronic acid	**4**	H	NH_2	OH	OH	H
4-amino-4-deoxy-glucuronic acid	**5**	OH	H	OH	NH_2	H



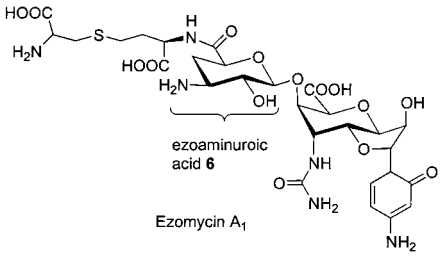
Neuraminic acid **1**



Hydantocidin **7**



Siastatin B **8**



ezoaminuroic acid **6**

Ezomycin A_1

Figure 1. Naturally occurring sugar amino acids.

on the Michael addition of C-terminally protected amino acids to 2,3-dideoxy-hex-2-enopyranos-4-uloses.[36]

In some cases the SAAs are linked to each other, and in other cases to amino acids. In this review we use the term SAA for compounds with two immediate linkages of the amino and carboxy functionalities to the carbohydrate frame (Figure 2). Further elongations with one connectivity, that is a carbon chain, are considered glycosylated amino acids or glycopeptides and are included in other extensive reviews.[34,37−39]

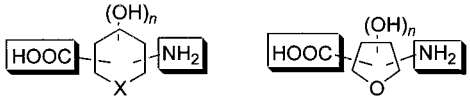


Figure 2. Sugar amino acids as structural scaffolds, as carbohydrate mimetics, and as peptide mimetics.

C. Scope of This Review

The scope of this survey is to review the synthesis of SAAs, their incorporation in peptidic or saccharidic structures, and their potential use in medicinal chemistry. Besides their immediate intrinsic different pharmacological properties, SAAs can be used as building blocks for the preparation of modified analogues of biologically active peptides and/or oligosaccharides. The difference in ring size allows modification of the conformations of the peptides and carbohydrates.

On the other hand, SAAs can be used as starting compounds for different oligomers. They are potential pharmaceutical compounds and are valuable for the synthesis of natural products or analogues and also as building blocks in drug design and drug research.

II. Synthesis of Individual SAA Building Blocks

The synthesis of sugar amino acids is easily accomplished in a few steps starting from commercially available or easily accessible monosaccharides, i.e., glucose, glucosamine, diacetone glucose, galactose, etc. The amino functionality of the SAA can be introduced as an azide, cyanide or nitromethane equivalent, followed by subsequent reduction. The carboxylic function is introduced directly as CO_2, or as a hydrolyzable cyanide, by a Wittig reaction and subsequent oxidation or by selective oxidation of a primary alcohol.

A. Furanoid SAAs

1. α-SAAs

Several derivatives with an α-amino acid moiety at the anomeric position of the sugar were synthesized by Fleet et al., including glucose,[40] rhamnose,[41] galactose,[42] and mannose[29] (Figure 3) derivatives. The various routes developed by Fleet's group and Dondoni's group have recently been summarized in ref 34.

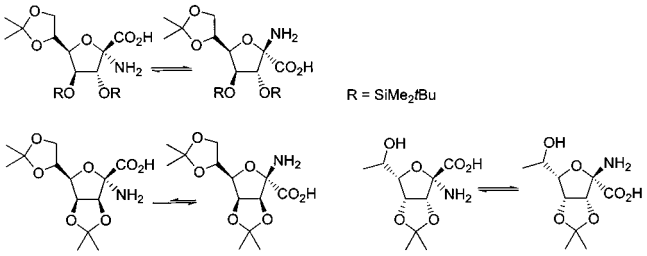


Figure 3. Some of Fleet's α-SAAs.

Fleet's azide precursors and N-protected SAAs are stable against epimerization; however, all free SAAs (also the pyranoid derivatives) and their respective esters equilibrate to a mixture of α- and β-anomers in solution.

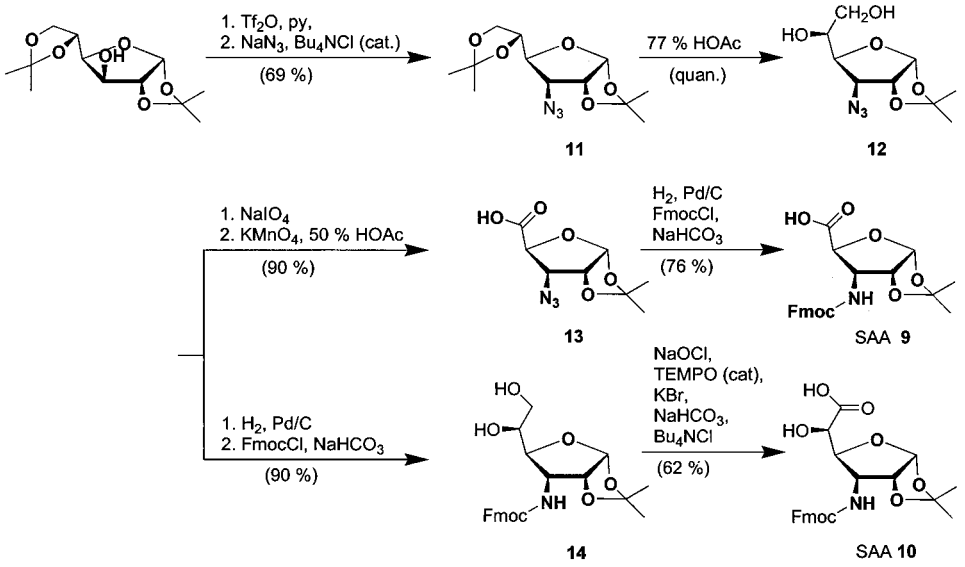
This class of SAAs has also been employed as precursors to five- and six-membered spiroheterocyclic derivatives of carbohydrates such as the rhamnose functionality, required for enhanced activity analogues of hydantocidin.[41−43] The naturally occurring (+)-hydantocidin **7**[15−17] (see Figure 1) exhibits herbicidal activity. Those spirodiketopiperazine derivatives are considered as potential inhibitors of carbohydrate processing enzymes and thus might be useful in elucidating the biosynthesis of the cell walls of mycobacteria.

2. β- and γ-SAAs

We recently reported the synthesis of the β-SAAs SAA **9** and SAA **10** as turn mimetics.[44−46] They were synthesized as shown in Scheme 1 in good overall yield of 47% for SAA **9** and 39% for SAA **10**.[44−47] Azides **11** and **12** have already been described by several groups.[19,48−52] **12** was used by Teraji as a precursor for the total synthesis of chryscandin, an antifungal antibiotic.[52] By addition of catalytic amounts of Bu_4NCl, the yields of the azide intermediate **11** were improved to 70% (instead of 48%).[44,45]

Azidolysis is followed by quantitative deprotection of the exocyclic hydroxyl groups using acetic acid

Scheme 1. Synthesis of Fmoc-Protected SAAs 9 and 10



yielding **12**.[51] Reduction of the azide and Fmoc-protection is achieved simultaneously in a one-pot reaction yielding about 70% of the Fmoc-protected amine.

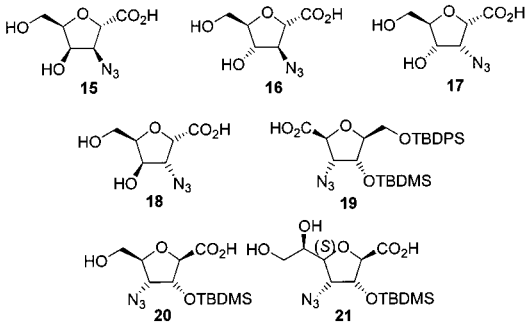
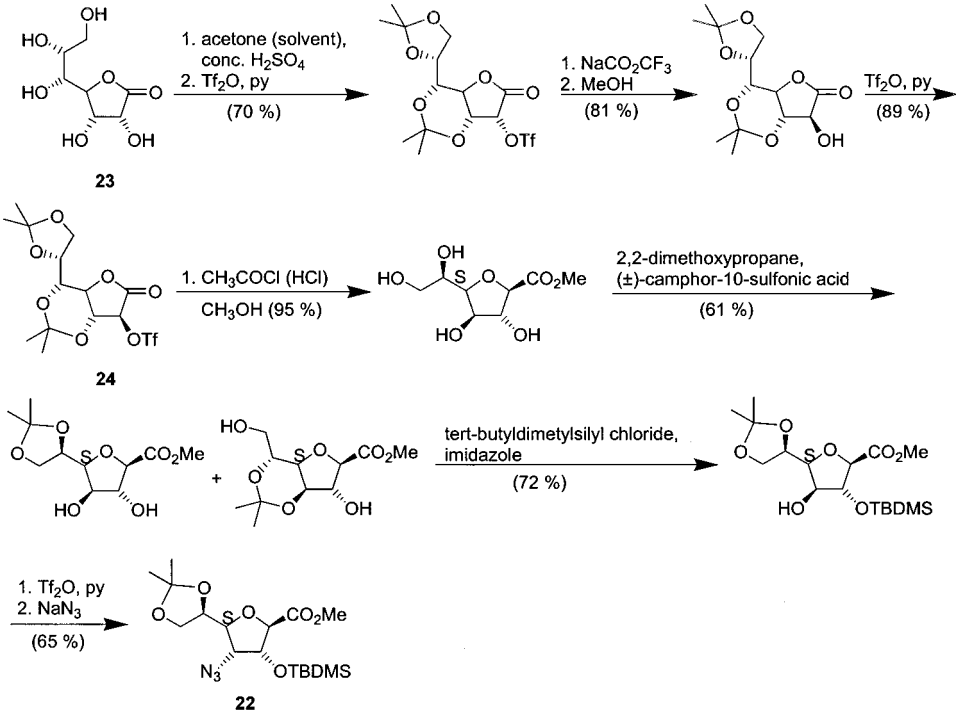


Figure 4. Some of Fleet's large collection of azides, used as β- and γ-SAA precursors.

Fleet et al. published the synthesis of several azide precursors to β- and γ-SAAs shown in Figure 4.[53,54]

They synthesized the β-SAA precursor **19** and the γ-SAA precursors **20** and **21** via **22**, which was obtained by the route described in Scheme 2.[54−58] Key step of the synthesis of **22** was the hydrolysis of the side-chain acetonide of **24** and methanolysis of the lactone with intramolecular displacement of the triflate at C-2 by 5-OH.[55,58] Side-chain hydrolysis of the acetonide of **22** afforded the γ-SAA precursor **21**, subsequent periodate cleavage, followed by immediate cyanoborohydride reduction of the resulting aldehyde in acetic acid yielded the γ-SAA precursor **20**. Overall yields for **20** and **21**, starting from D-*glycero*-D-*gulo*-heptono-1,4-lactone **23**, were 10 and 13%, respectively. Sodium borohydride reduction of the ester function in **22**, followed by a series of protection

Scheme 2. Synthesis of Protected γ-SAA Precursor 22



deprotection steps and subsequent oxidation of the diol moiety with sodium periodate in the presence of catalytic amounts of ruthenium(III) chloride, led to the β-SAA precursor **19** in an overall yield starting from **23** of about 3%.

3. δ-SAAs

As dipeptide isosteres for the incorporation into peptide based drugs Le Merrer and co-workers synthesized **25** and **28** (Figure 5).[59] The benzylated

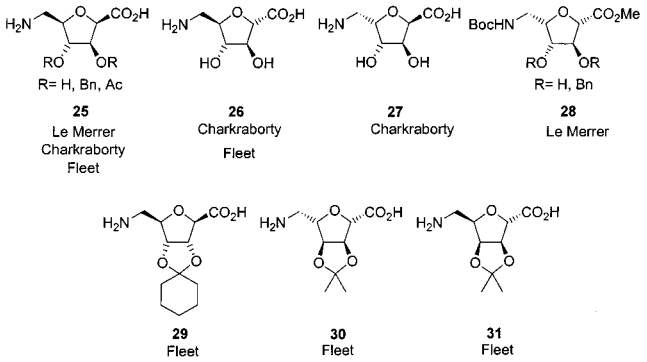
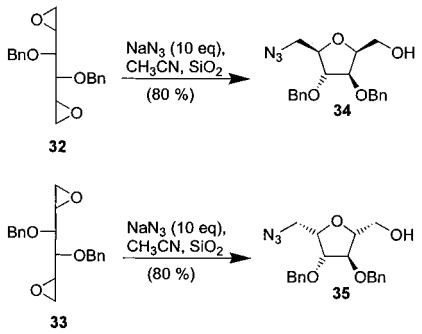


Figure 5. Some of Le Merrer's, Fleet's, and Charkraborty's furanoid δ-SAAs.

derivatives were designed as mimics for hydrophobic amino acids, and the unprotected SAAs as mimics for hydrophilic amino acids (see also section IV).

Key step of their synthesis was the one-pot silica gel assisted azidolysis followed by *O*-ring closure of the bis-epoxides **32** and **33** (Scheme 3) to yield **34** and

Scheme 3. Key Step of Le Merrer's Synthesis of 25 and 28

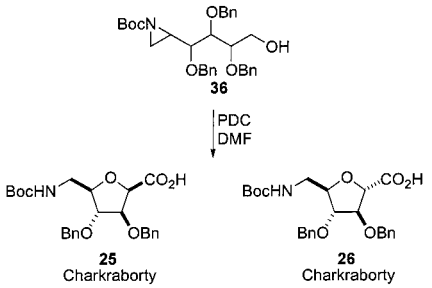


35 respectively. $Na_2Cr_2O_7$ oxidation of the primary hydroxyl group, treatment with an excess of diazomethane, followed by an one pot conversion of the respective azidoesters by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate, yielded the N-Boc protected, fully benzylated SAA methylesters of **25** and **28**.

SAA **25** was also synthesized by Chakraborty's and Fleet's groups, using different reaction pathways.[60−63]

Further, to the use as dipeptide isosteres Chakraborty et al. synthesized several δ-SAAs (Figure 5).[60,61] The key step of their synthesis of SAA **25** and SAA **26** followed a different reaction path, in which an intramolecular 5-*exo* opening of the terminal aziridine ring (Scheme 4) of the hexose-derived substrate **36** (with the respective stereochemistry) by the γ-benzyloxy oxygen with concomitant debenzylation

Scheme 4. Synthesis of 25 and 26 Starting from 36[a]



[a] The stereochemistry of **36** determines if the synthesis results in **25** or **26**.[61]

occurred during pyridinium dichromate (PDC) oxidation of the primary hydroxyl group with complete stereocontrol.

At about the same time, Fleet et al. synthesized a wide range of different δ-SAAs including also **25**, to study the influence of the SAA's stereochemistry and of the hydroxyl protecting groups on the secondary structure of their linear homooligomers.[62−68] A few representative examples are shown in Figure 5.

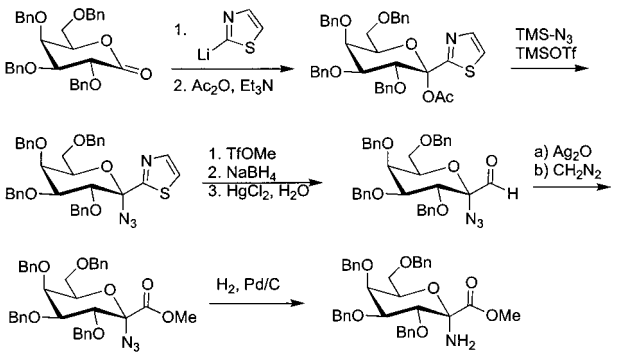
B. Pyranoid SAAs

The most obvious approach for the synthesis of sugar amino acids is the oxidation of amino sugars for example glucosamine. Thus, Heyns and Paulsen described the first synthesis of a sugar amino acid, glucosaminuronic acid, in 1955 by catalytic oxidation of the primary hydroxyl group,[69] in an effort to elucidate the structure of bacterial cell wall components and to synthesize analogues. The synthesis was later improved by Weidmann and Zimmerman.[70] The oxidation of the amino sugar was also used by Paulsen et al. in the early synthesis of D-galactosaminuronic acid to confirm the structure of isolated components of bacterial Vi antigen.[6]

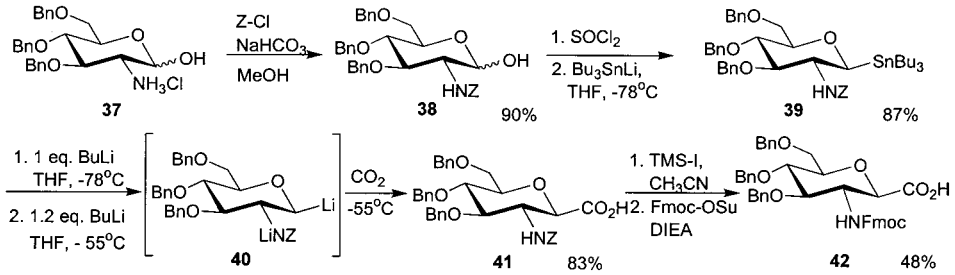
1. α-SAAs

Dondoni and co-workers developed an elegant method for the synthesis of α-SAAs. Because of the special reactivity of the anomeric center, it was possible to introduce a thiazole as a formyl group equivalent to the sugar lactone. After hydrolysis of the thiazole, the aldehyde can be oxidized under mild conditions with Ag_2O to a carboxyl group (Scheme 5).[71,72]

Scheme 5. Dondoni's Synthesis of α-SAAs Using the Thiazoles as a Formyl Equivalent[71,72]



Scheme 6. Synthesis of Fmoc-SAA(Bn)$_3$−OH 42



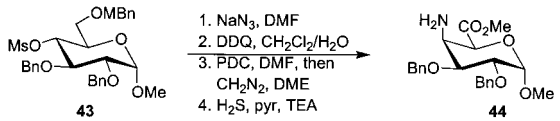
Preparation and structure determination of α-SAAs via corresponding hydantoin derivatives has been presented by Koos et al.[73] Starting from methyl 6-deoxy-2,3-*O*-isopropylidene-α-l-*lyxo*-hexopyranosid-4-ulose, hydantoin derivatives were synthesized under various reaction conditions. Selective acid hydrolysis of the isopropylidene group followed by basic hydrolysis of the hydantoin ring gave the desired products.

2. β-SAAs

For the synthesis of Fmoc-SAA(Bn)$_3$−OH **42** (Scheme 6) we followed the procedure developed earlier in our group for the stereoselective *C*-glycosidation of 2-acetamido-2-deoxy-D-glucose achieved by the use of the configurationally stable dianion.[74−77] Starting from D-glucosamine, the partially benzylated sugar **37** was obtained in two steps according to a procedure of Fletcher and Inch.[78] The amino function was subsequently protected by Z-Cl to obtain **38** in 90% yield. Chlorination of the anomeric hydroxyl group provided the α-chloro compound, which was treated with tributyltin lithium to afford **39** in 79% yield.[74−77] The generation of the glycosyl dianion **40** was accomplished in two separate temperature steps: first, deprotonation of the urethane nitrogen at −78 °C using 1 equiv of BuLi; second, transmetalation at −55 °C using 1.2 equiv of BuLi. The dianion **40** turned the solution to a deep red color and was subsequently trapped by carbon dioxide to afford **41** in 83% yield. For the application in solid-phase peptide synthesis, **41** was transformed into the Fmoc-derivative **42**. TFA/thioanisole[79] or catalytic hydrogenolysis on Pd/C[80] were not selective for removal of the Z group in **41**. The best result for cleaving the Z-group was obtained by using trimethylsilyl iodide in CH_3CN.[81] However, the C^7-*O*-benzyl ether of **41** was cleaved to some extent. While the amount of side product was temperature independent, the yield was optimized by varying the reaction time. The crude reaction mixture was treated with Fmoc-ONSu[82] to afford **42** in 48% yield.

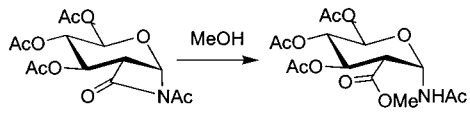
Vogel and Gries described the synthesis of a 4-amino-4-deoxy-D-galacturonic acid derivative in six steps from methyl 2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-D-glucopyranoside **43** (Scheme 7).[83] Treatment of **43** with methanesulfonyl chloride and subsequent substitution of the resulting 4-*O*-methanesulfonyl group with sodium azide gave under inversion at *C*-4 the 4-azido-D-galacto derivative. After deprotection at O-6, the carboxyl group was introduced by Corey oxidation and esterified with diazomethane. Conversion of the azidodeoxygalacturonate derivative to the target compound **44** was achieved by reduction with H_2S in pyridine.

Scheme 7. 4-Amino-4-deoxy-d-galacturonic Acid Derivative



Activation of 2-*C*:1-*N* carbonyl-2-deoxyglycopyranosylamines toward opening of the β-lactam ring at the carbonyl carbon has been applied by Mostowicz et al. (Scheme 8) to synthesize *N*-acylglucosylamines with α-D-configuration which are not easily accessible in other ways.[84]

Scheme 8. Synthesis of 2-Deoxy-2-C-acyloyl Compounds

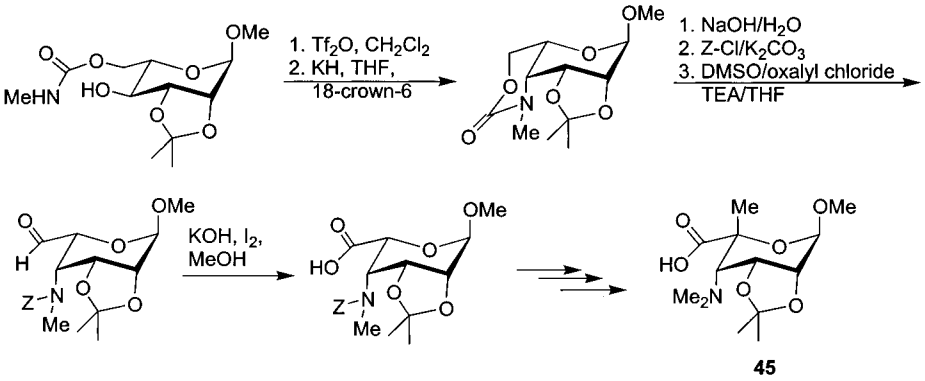


An example, in which the direct oxidation of the primary alcohol failed, because of the delicate functional group assembly, is the synthesis of SAA **45** as part of the enediyne toxin C-1027Chr (Scheme 9).[85] This compound showed a promising toxicity against certain cell lines. Intriguingly, the amino functionality was introduced intramolecularly by an internal substitution of the triflate group by the nitrogen carbamate.

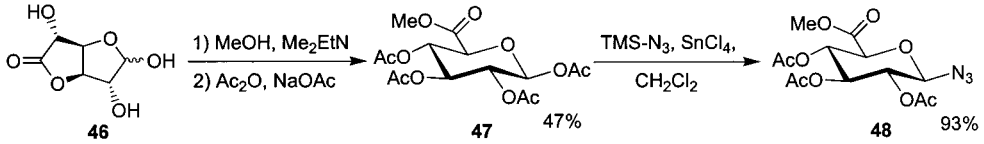
3. γ-SAAs

Azide **48** has been described by Nitta et al.,[86] who prepared it from the unstable 2,3,4,6-tetra-*O*-acetyl-1-bromo-glucopyranoside (obtained from α/β pentaacetylglucopyranoside) using NaN_3/DMF and by Györgydeak et al.[87] We have improved the overall yield following the route outlined in Scheme 10.[88] Glucuronolactone **46** was converted to the methyl-ester with methanol via base catalysis and then acetylated by a mixture of acetanhydride and sodium acetate.[89] Crystallization allowed separation of the β-acetate **47** from the α-anomer. Other acetylation methods, i.e., acetanhydride/pyridine or acetanhydride/perchloric acid also provide the acetylated glucuronolactone along with the α-acetate. The azide **48** was obtained from **47** using tin tetrachloride and trimethylsilyl azide[90] in an overall yield of 93%. Catalytic reduction (H_2/Pd) at low temperature provided the free amine quantitatively.

Scheme 9. SAA 45 Was Synthesized as a Building Block for C-1027Chr[85]



Scheme 10. Synthesis of Azide 48

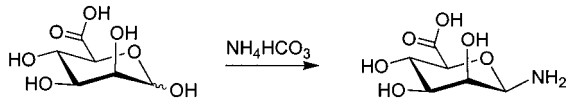


Later TEMPO catalyzed oxidation was used, starting from the 1-azido-1-deoxyglucopyranose. Methylation with MeI and acetylation facilitated isolation of **48**.[91,92]

The mannuronic acid analogue was synthesized by amination of mannuronic acid with NH_3,[93] although no further application is mentioned.[94] This method is certainly useful for the amination of the anomeric hydroxyl group. Yet it is rarely used in the synthesis of glycoconjugates.

A simple and convenient preparative method of *N*-acetylglucosamine C-glycosides, with high stereoselectivity, was reported by Kim et al.[95] The β-isomer of the C-glycoside ethyl 2-acetamino-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl acetate was prepared in two steps (Scheme 12) by reaction of 2-acetamino-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride with potassium diethylmalonate and 18-crown-6, followed by decarboxylation in refluxing DMSO and NaCl solution.

Scheme 11. Synthesis of Amino-mannuronic Acid[93,94,227]



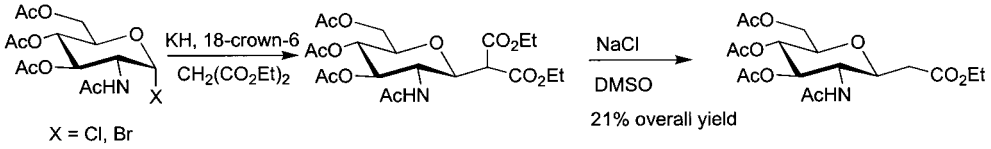
Hedenetz and co-workers described the synthesis of 2,3-diacetamido-2,3-dideoxy-D-mannuronic acid derivatives, which is reported in Scheme 13.[96]

Ezoaminuroic acid is a SAA, which is part of the nucleoside antibiotic ezomycin A.[8] In one of the more recent syntheses of this SAA, the primary hydroxyl group was oxidized after the assembly of the disaccharidic nucleoside employing Widlanski conditions.[97,98]

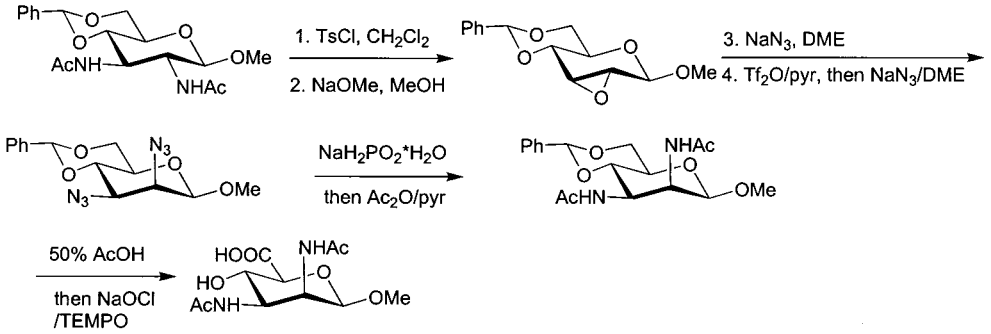
4. δ- and ϵ-SAAs

In 1994 we reported the first example of a sugar amino acid (Gum = glucosyl-uronic acid-methylamine SAA **88**) as a new type of peptidomimetic.[99] The β configurated Gum can be prepared as the Fmoc-

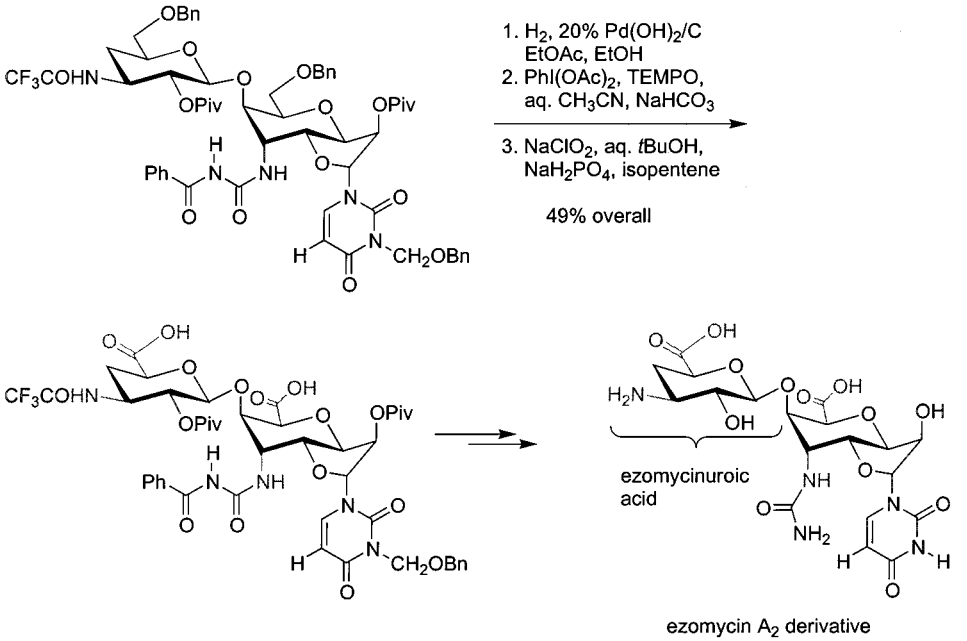
Scheme 12. Synthesis of C-Glycoside of *N*-Acetylglucosamine



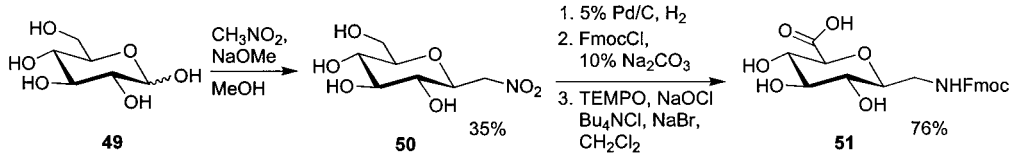
Scheme 13. 2,3-Diacetamido-2,3-dideoxy-d-mannuronic Acid as Bacterial Cell Wall Component *Bacillus stearothermophilus* PV72



Scheme 14. Synthesis of the SAA Ezomycinuroic Acid in a Ezomycin A Derivative



Scheme 15. Synthesis of Fmoc-SAA-OH 51



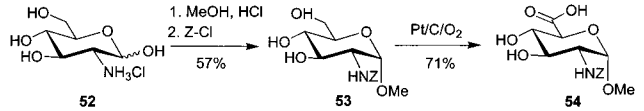
derivative **51** for SPPS or as Z-SAA-OMe for solution phase synthesis. Synthesis of **51** is reported in Scheme 15. The CH_2NH_2 equivalent is introduced as CH_3NO_2 via nucleophilic aldol reaction. The linear condensation product is cyclized by acid-catalyzed intramolecular ring closure to yield β-D-glucopyranosylnitromethane, which because of its polarity is isolated using basic ion-exchange resin. The nitro compound is reduced with hydrogen, using 10% Pd/C under pressure and subsequent protection with Fmoc-Cl. The primary hydroxyl group is selectively oxidized by TEMPO catalyzed sodium hypochlorite oxidation.[91,100]

Starting from glucosamine, the α-anomeric, Z-protected SAA **54** is synthesized in an overall yield of 37% as described by Heyns and Paulsen (Scheme 16).[69] The amino function was protected using Z-Cl in 91% yield. The α-methyl glucoside is obtained via the classical acid catalyzed Fischer glycosylation[101] using methanol. Subsequently the primary hydroxyl group was oxidized using 10% Pt/C and oxygen.

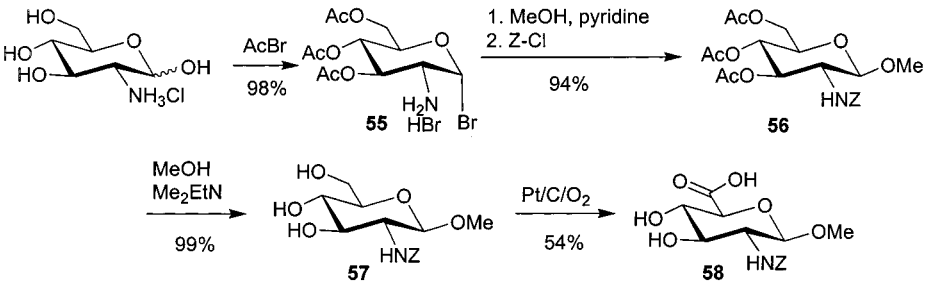
The β-anomer **58** is prepared from glucosamine in 49% yield. (Scheme 17).[102,103] The β-methyl glucoside is obtained *via* treatment of bromide **55** with methanol in pyridine and followed by Z-protection. Deacetylation of **56** by methanolysis and subsequent selective oxidation of the primary alcohol with $Pt/C/O_2$, afforded **58**, which can be employed in standard solution phase peptide synthesis. Since both derivatives—**54** and **58**—are *O*-glycosides, prolonged exposure to acidic conditions, like TFA, leads to degradation.[104−106]

The oxidation of the primary hydroxyl group can also be facilitated by oxidation with ruthenium(iii)-chloride and sodium periodate. The other hydroxyl groups had to be protected during this procedure. Subsequent transformations to obtain the muramic

Scheme 16. Synthesis of Z-SAA-OH 54



Scheme 17. Synthesis of Z-SAA-OH 58



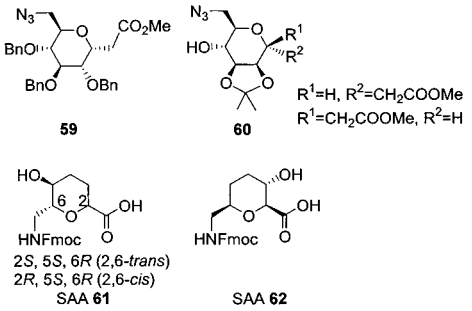


Figure 6. SAA precursors **59** and **60** and SAA building blocks **61** and **62**.

acid congener could be performed in a straightforward fashion.[107]

A library of SAA precursors (three pyranoid and nine furanoid analogues), protected as azido esters, was presented by Lansbury and co-workers[19] as building blocks for combinatorial synthesis. In each case, the amino group was incorporated by displacement of a sulfonate ester with an azide nucleophile. In the case of the pyranoid rings, the carboxyl group was introduced, using an oxidative cleavage of a C-allyl glycosides. SAA precursor **59** (Figure 6) was prepared from 1,6-β-D-anydroglucose in six steps, the key step being a stereospecific C-allylation at the anomeric center. SAA precursor **60** was prepared from peracetylated mannose. The allyl glycoside was generated as an anomeric mixture.

van Boom and co-workers reported the synthesis of partially deoxygenated gluconic amino acids from fully acetylated D-glucal. When incorporated into polypeptide sequences, SAA **61**[108] showed activity against the protein farnesyl transferase (see section V, part D) and SAA **62**[109] stabilized a β-hairpin structure present in the native form. The first step in the synthesis of both building blocks is a Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal with TMS−CN using catalytic $BF_3 \cdot OEt_2$ which gave a mixture of the anomeric cyanides. In SAA **61**, the amine group was introduced via a regioselective substitution of the primary alcohol with phthalimide under Mitsunobu conditions, the carboxyl group via hydrolyzation of a cyanide. Hydrogenolysis of the cyanide group afforded the amine, and oxidation of the primary alcohol via Swern to the aldehyde and successive sodium chlorite oxidation to the acid afforded SAA **62**.

III. Carbohydrates and SAAs as Scaffolds

Carbohydrates represent an attractive source of readily available, stereochemically defined scaffolds as they contain well-defined and readily convertible substituents with a rigid pyran ring or the more flexible furan ring.[110−113] The functional pharmacophoric groups can thus be presented in a distinct arrangement.

The genesis of carbohydrate privileged structures was first described by Hirschmann and co-workers.[114] A somatostatin agonist was discovered which contained a deoxyglucose nucleus carrying the key amino acid side chains of a cyclic hexapeptide agonist (Figure 7).[110] Successively, a NK-1 receptor antagonist was identified by modification of the deoxyglucose-based somatostatin agonist.[115,116]

The tetrasubstituted xylofuranose **63** was synthesized by Papageorgiou et al. as a potential nonpeptide mimic of somatostatin (Figure 8).[117] The scaffold was designed based on molecular dynamics simulations and the results from Hirschmann et al.[110] The biological activity of the mixture of the α and β anomers in a ratio of 2:3 revealed a promising $IC_{50} = 16$ μm. They did show a similar conformational behavior as the Hirschmann scaffolds.

A number of carbohydrate-based structures have been designed and synthesized by Nicolaou et al.[118] as potential mimics of the potent peptidic antagonist of $\alpha_v\beta_3$ and $\alpha_v\beta_5$, the cyclic pentapeptide RGDfV[169,189−193] (Figure 9).[118] The biological activity of the derivatives was rather low, which indicates that for this receptor the two amide bonds in the lower part of the cyclic peptide are indeed essential for activity.

A focused combinatorial library of mimetics of the RGD sequence based on sugar scaffolds has been rationally constructed by Moitessier et al. with a particular emphasis on the stereoselectivity of the library (Figure 10).[119,120] In this case a modest biological activity was observed for the $\alpha_{IIb}\beta_3$ antagonists (as low as $IC_{50} = 20$ μm).[119] For the $\alpha v\beta 3$ antagonists only the percentage of inhibition of cell adhesion on vitronectin substratum was reported.[120]

In search of nonpeptidic endothelin antagonists, Diguarher et al. synthesized a series of derivatives, such as compound **64**, based on the highly active endothelin antagonist BQ123 (Figure 11).[121]

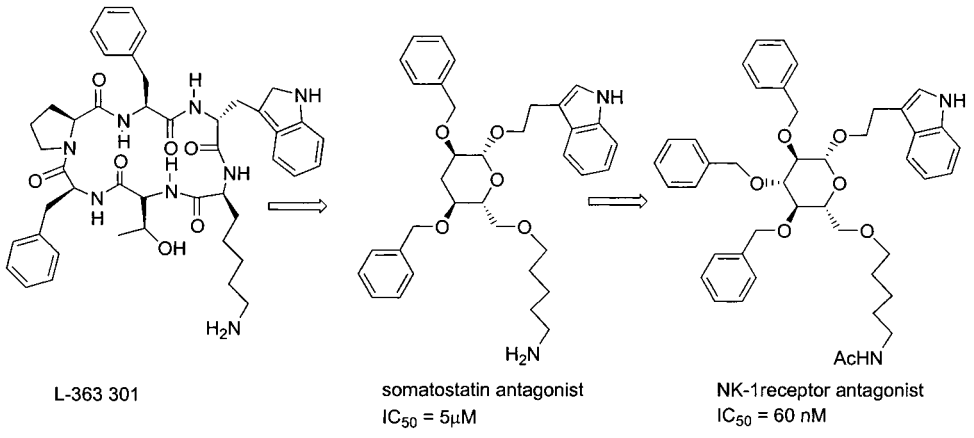


Figure 7. Glucose-based scaffold for the cyclic hexapeptide.

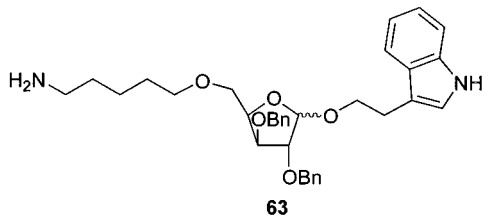


Figure 8. Somatostatin scaffold based on xylose by Papageorgiou et al.[117]

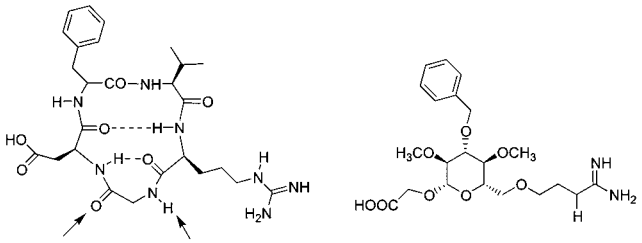


Figure 9. Scaffold based on glucose by K. C. Nicolaou et al.[118] and the cyclic pentapeptide with the bioactive RGD sequence[169,189−193] and the essential two amide bonds.

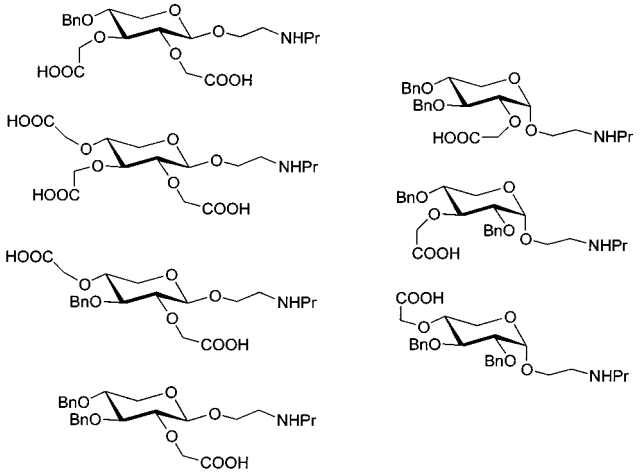


Figure 10. $\alpha_{IIb}\beta_3$ (left)[119] and $\alpha_v\beta_3$ (right)[120] antagonists based on xylose.

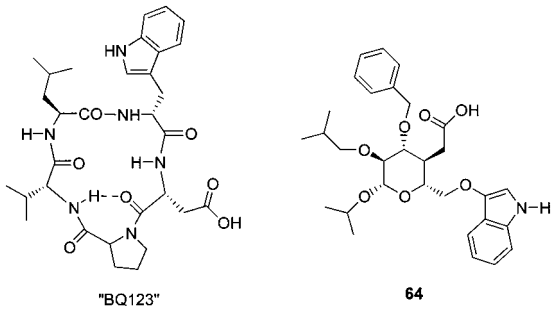


Figure 11. Glucose scaffold based on the cyclic pentapeptide endothelin antagonist BQ 123.[121]

Although the side-chain orientations of these compounds were close to those of the cyclic peptide, these derivatives did not show any significant binding to the endothelin receptors. This also indicates that some of the amide linkages in the peptidic backbone might be essential for receptor binding.

Inspired by the work of Hirschmann and Nicolaou, Amstrong and co-workers prepared a D-glucose scaffold of hapalosin (Figure 12), a cyclic depsipeptide

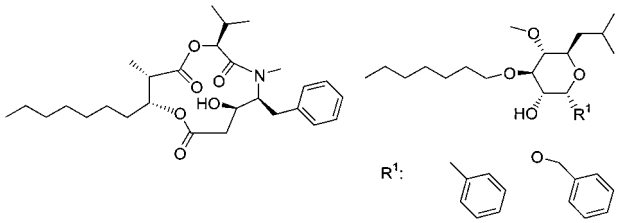


Figure 12. Glucose (and allose) scaffolds based on hapalosin by R. Armstrong.[122]

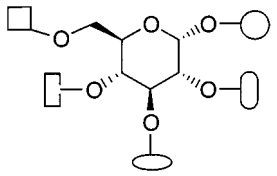


Figure 13. Combinatorial synthesis with carbohydrate scaffolds.[112]

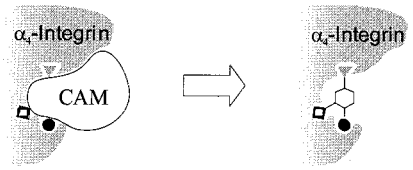


Figure 14. Rational design of $\alpha4\beta1$ and $\alpha4\beta7$ integrin antagonists.

which inhibits the P-glycoprotein, P-gp.[122] This transmembrane protein effects the removal of a broad spectrum of structurally diverse compounds from within the cell and therefore may play an important role in the phenomena of multiple drug resistance, which is a major problem in cancer therapy.

Unfortunately, like many other scaffold mimetics, this compound did not produce any activity, although these derivatives also contribute to the setting of the framework of structure−activity relationships.

Kunz et al. were able to synthesize large substance libraries of carbohydrates based on solid-phase chemistry, which allowed the defined functionalization of hydroxyl groups.[112] Although no biological activities were given, this approach represents a promising access to new lead structures. A similar diversity has been described by Wong et al.[122] More complex oligosaccharides structures can be synthesized using for example the Ugi reaction as utilized by Lockhoff.[123]

Recently, we published the design, synthesis and biological evaluation of β-D-mannose based nonpeptidic mimetics of the vascular cell adhesion molecule-1 (VCAM-1) and of the mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which are the natural ligands of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptors.[124]

Similar recognition motifs were identified for these ligands: Ile-Asp-Ser- Pro (IDSP) in VCAM-1 and Leu-Asp-Thr (LDT) in MAdCAM-1. By the "spatial screening" procedure a cyclic hexapeptide with high selectivity for cell attachment via the $\alpha_4\beta_7$ integrin was developed.[125] This lead structure was used to develop a library of substituted monosaccharides (Figure 15). One sugar-based derivative showed inhibitory activity toward integrin $\alpha_4\beta_1$-mediated binding of Jurkat cell to VCAM-1.

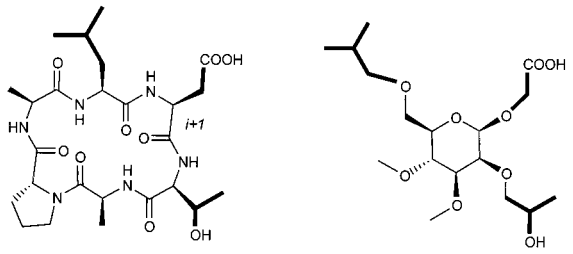


Figure 15. Design of a library of sugar-based peptidomimetics. In the peptide, the pharmacophoric LDT-motif is localized within a β turn with the aspartic acid in the $i+1$ position. The carbohydrate scaffold presents the essential pharmacophoric groups in the same relative orientation as the lead peptide.[124]

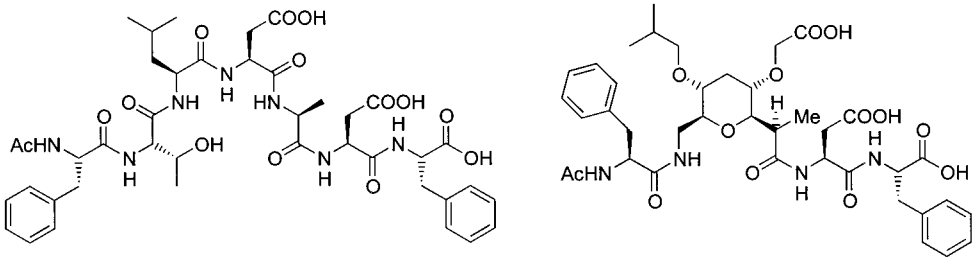
Sugar amino acids in particular are also ideal peptidomimetic scaffolds, as they may function as structural pharmacophores depending on their substituents in addition to the imperative amino and carboxyl function.[99] Smith et al. reported the design of an inhibitor of mammalian ribonucleotide reductase (mRR) **66** based on the bound conformation of the heptapeptide N−AcFTLDADF using a pyranoid SAA scaffold (Figure 16).[126] This SAA was employed to mimic a β-turn present in the peptidic precursor and to carry, via ether linkage, the pharmacophores and Leu and Asp side chains, present in the $i+1$ and $i+2$ positions of the turn, respectively. A Wittig reaction at the nonprotected anomeric hydroxyl group using ethyl(triphenylphosphoranylidene)acetate followed by cyclization via intramolecular Michael addition afforded the Ala mimicking group attached to the sugar ring via C-glycosidic linkage. The amine group was introduced by activation of the primary hydroxyl and azide formation. The tetrahydropyran-based mimetic **66** was found to inhibit mRR, though considerably less well than *N*-AcFTLDADF (K_i of 400−500 μM for **66** vs K_i of 15−20 μM for **65**).

To investigate the potential of carbohydrates for the design and synthesis of universal pharmacophore mapping libraries, two monosaccharide scaffolds **67** and **68** were prepared by Sofia et al.[127] Three sites of diversification were incorporated to provide the minimal requirements for pharmacophoric chiral molecular recognition: the carboxylic acid moiety, an Fmoc-protected amine, and a hydroxyl group.

Chemical diversity was introduced at the three sites using the solid-phase synthetic approach for **67** reported in Scheme 19. The first diversification step was introduced by anchoring the building blocks to the resin at the C-termini via a prelinked diversity element. Carbamate formation at the free hydroxyl group followed by amide formation at the deprotected amine yielded the desired resin-linked trifunctionalized scaffolds.

IV. Carbohydrate Mimetics

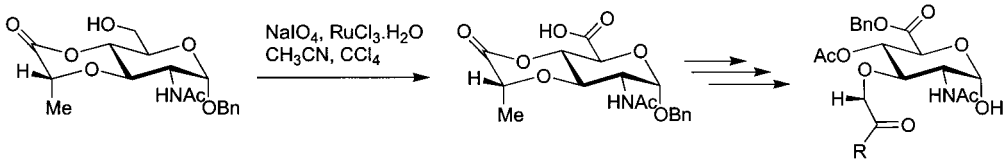
SAAs have also been concentrated on the use of SAA analogues as biopolymer building blocks to mimic oligo- and polysaccharide structures via amide bond linkages.[128,129] In fact, the assembly of synthetic



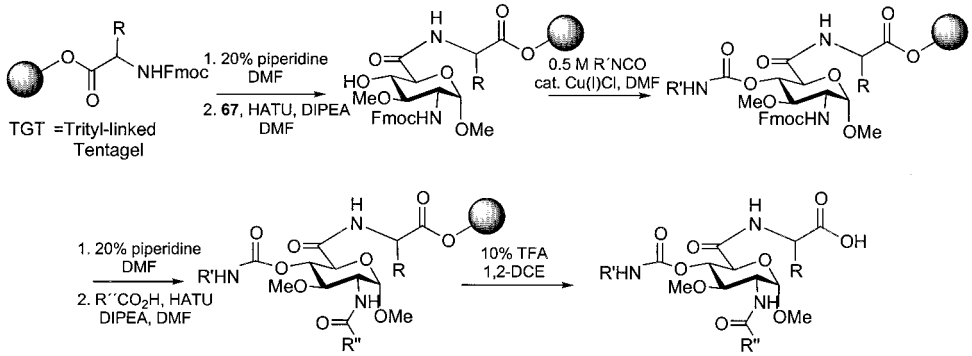
65 66

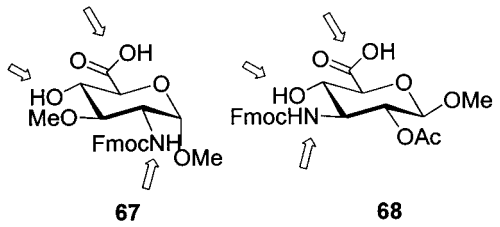
Figure 16. Carbohydrate-derived inhibitor **66** of mammalian ribonucleotide reductase.[126]

Scheme 18. Synthesis of a SAA as an analogue of *N*-acetyl Muramic Acid (R = NH_2, OMe)



Scheme 19. Strategy Employed for the Synthesis of the Resin-Linked Trifunctionalized Scaffolds





67 68

Figure 17. Carbohydrate-based scaffolds for pharmacophore mapping.[127,224,225]

polysaccharide libraries in solution or on solid-phase is difficult despite the recent progresses using chemical and enzymatic techniques.[130,131] Taking advantage of the well-established chemistry of peptides many homooligomers from SAAs and hybrid sequences containing natural amino acids (AAs), carbohydrates, and SAAs have been synthesized. These resultant oligomers represent useful drug candidates, since they may overcome the problems associated with oligosaccharide and peptide libraries such as the susceptibility toward glycosidases due to the altered peptide backbone and their resistance to many proteases due to their resemblance to carbohydrates.

A. Linear Oligomers

The first oligomers were synthesized in solution by Fuchs and Lehmann, although they did only characterize the individual products by mass spectroscopy.[132−135] The first dimers were synthesized from D-glucosaminuronic acid and D-mannosaminuronic acid by coupling with DCC by Tsuchida et al. in 1976.[136]

More recently, oligomers were synthesized both in solution[21,28,137] and on solid phase[138,139] and have been proposed to mimic oligosaccharide[27] and oligonucleotide (so-called GNA, glucopyranosyl nucleic amide) (Figure 18)[104,105] backbone structures via amide bond linkages. The aim of GNA development was to improve the properties of the presently most useful class of antisense agents, the phosphorothioates. Hence, to find more stable agents, less toxic and binders more selective than the phosphorothioates were used. After the discovery, that PNA is a selective binder of DNA and RNA, the idea of replacing the phosphodiester linkages with amide bonds was advisable. Following this idea, Goodnow et al.[104,105] presented oligomers of Gum as novel antisense agents with the nucleobases attached via N-glycosidic linkage at the anomeric center. The binding properties to DNA and RNA sequences were established by

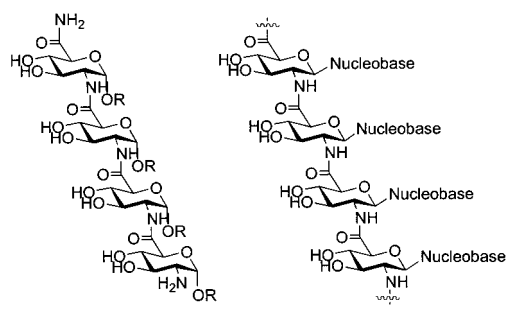


Figure 18. Oligomers of Gum; R = Me,[23] R = Bn[138] and with nucleobases.[104,105]

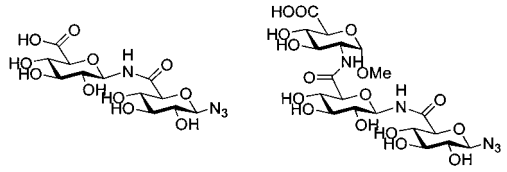


Figure 19. Oligomers by P. Fügedi's group.[140,141]

measurement of melting temperatures and related thermodynamic constants. The GNAs showed similar selectivity and binding affinities as DNA and RNA.

Wessel and co-workers, who first introduced in 1995 the synthesis of amide-linked oligomers in solution (Figure 18), used a [2+2] block synthesis.[21] In their synthetic protocol, the benzyloxycarbonyl (Z) group was employed as amine protecting group, and carboxylic acids were protected as *tert*-butyl ester. The two monomer building blocks were coupled via mixed anhydrides, and the obtained dimer after *tert*-butyl deprotection was activated via 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT). No protection of the hydroxyl groups was needed.

Fügedi et al. presented[22,23,140,141] several oligomers, which were evaluated in glycosidase inhibitor assays (Figure 19) with moderate activities.

McDevitt and Lansbury applied the 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) method in solution.[19] The amino function was protected as an azide. Successively, amide coupling was carried out efficiently via the benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) and diisopropylethylamine (DIPEA) procedure[28] using *tert*-butoxycarbonyl (Boc) chemistry or via EDC/1-hydroxybenzotriazole (HOBt)-catalyzed condensation.[142] A solid-phase approach was developed in 1995 by Müller et al.[138] using benzhydrylamine polystyrene resin functionalized with an amide linker. The N-protection was achieved with fluoren-9-ylmethoxycarbonyl (Fmoc) group. The free carboxyl group was activated in situ with *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU) in the presence of DIPEA as base without need of hydroxyl protection. Other coupling reagents implemented on solid-phase were *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[105] or BOP[139] in *N*-methylpyrrolidone (NMP) or in *N*,*N*-dimethylformamide (DMF) as solvents.

In the field of carbohydrate mimetics, sialic acid analogues have received particular attention. Sabesan[20] reported the peptide linked sialoside **69** mimicking an α-D-NeuAc(2 → 6)β-D-Gal unit which is found in numerous glycoproteins and glycolipids and is also a receptor ligand for influenza virus hemagglutinin and substrate for neuraminidase. The inhibitory activity of this mimetic was not reported.

Gervay et al. described the synthesis in solution of amino acid conjugates to *N*-acetylneuraminic acid[143,144] and later on amide-linked dimeric sequences.[3,145] Oligomer **70** (Figure 21) was synthesized using solid-phase techniques, and the structures were analyzed in solution to determine whether they adopted the same solution conformation as their glycosyl-linked cognate.[139] Although the conformational preferences of these structure were not com-

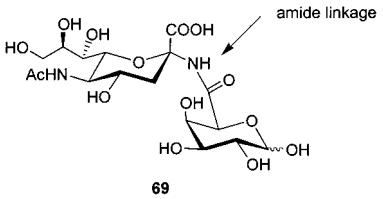


Figure 20. SAA-galactose conjugate **69** with an amide linkage replacing the natural ether linkage.[20]

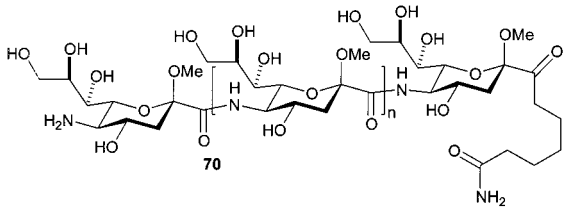


Figure 21. Amide-linked sialooligomers by Gervay et al. $n = 0-6$.[139,143]

pletely resolved and were dependent on the chain-length, amide proton NH/ND exchange rates determined by NMR and circular dichroism spectra can be interpreted as an evidence for a preferred secondary structure.

SAA oligomers were sulfated as reported by the Ichikawa group (Figure 22) to mimic and replace natural sulfated polysaccharides such as dextran sulfate and heparin, well-known inhibitors of HIV replication, to overcome the poor absorption, instability, and anticoagulant activity of their precursors. A sulfated tetrameric analogue linked via the *C*-1 β-carboxylate and the *C*-2 amino groups fully blocked syncytium formation caused by HIV infection to CD4 cell at 50 μM concentration,[28] and the sulfated β-1,6 amide-linked analogue showed micromolar activity in the protection of MT2 cells from HIV infection.[137]

Hybrid molecules with alternating SAAs and β-amino acids were also designed (Figure 23).[146] The objective was to create another class of nonnatural peptide or carbohydrate molecules and screen them in an in vitro assay system involving highly metastatic tumor cell lines. An inhibitory activity toward cell adhesion (Chemotaxis) and invasion was observed with an $IC_{50} = 10$ μM.

The work of van Boom et al. introduced a new aspect to the synthesis of SAA oligomers. For the first time glycosylated SAAs or disaccharide SAAs were used to assemble the branched oligosaccharide mimetic **71** as a mimetic of the phytoalexin elicitor branched α-methyl heptaglucoside **72** (Figure 24). In **71**, four amide bonds replace the β-1,6-acetal linkages of the pentasaccharide backbone of **72**.[142] The building blocks for oligomer **71** were readily accessible by glycal chemistry. The lack of phytoalexin-elicitor activity shown by the β-1,6-glucuronosylamide oligomer was attributed to the reduced flexibility of the amide bond with respect to native acetal bond or to a different molecular structure and hydrogen-bonding potential.

With the aim of designing artificial glycoclusters with specific functions, Nishimura and co-workers[106] reported the synthesis of poly(SAAs) **73** able to self-assemble to form stable monomolecular layers. Polymerization of 1-*O*-dodecyl-Gum**,** derived from the readily available D-glucofuranurono-6,3-lactone, was accomplished using diphenylphosphoryl azide (DPPA).

B. Cyclic Oligomers

Recently, mixed cyclic oligomers containing SAAs have been proposed by van Boom et al.[147] and by us as potential molecules for host−guest chemistry.[148,149] 2D NMR data suggests preferred secondary conformations for oligomers **74**[147] and **75**.[148,149]

The parallel solid-phase synthesis of cyclic sugar amino acid/amino acid hybrid molecules containing furanoid SAAs was carried out by van Boom et al.[147] using Boc *N*-protection strategy and BOP/DIPEA as coupling reagents. The first amino acid was anchored on an oxime resin in order to employ acid catalyzed cyclization and cleavage from the resin.

We also studied the structural implications that cyclization caused on the helical linear oligomer **82** containing SAA **9** alternatively coupled with β-alanine, via circular dichroism and NMR (see next section, VA).[46,47]

In recent work, we introduced cyclic homooligomers of SAAs as novel cyclodextrin-like artificial receptors.[150] This idea was based upon the assumption that a cyclic array of carbohydrate moieties and amino acid functional groups may lead to exquisite specificity of recognition and catalysis.

By exploiting standard solid and solution phase coupling procedures linear and cyclic homooligomers containing Gum were synthesized.[150] High yields and very short coupling times for the oligomerization and cyclization of sequences containing 2, 3, 4, and 6 units were achieved. The conformational preferences in aqueous solution of the cyclic derivatives and their applications as potential host molecules were described. Taking into consideration the trans config-

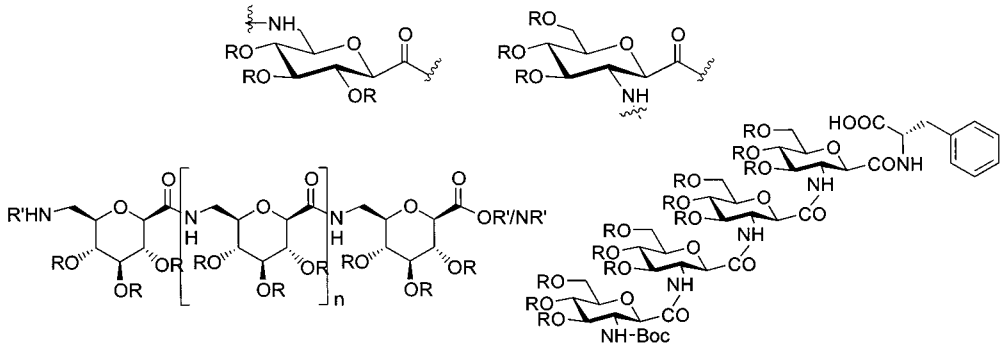


Figure 22. SAA oligomer building blocks and general structures of the oligomers by Ichikawa et al. (R = H, SO_3Na).[28,137]

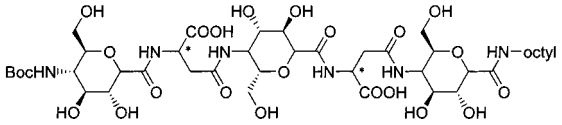


Figure 23. SAA-amino acid conjugates by Ichikawa et al.[146]

uration of the amide bonds and the $^4C_1$ conformation of the pyranoid ring, confirmed via coupling constants and ROE data, two low energy structures were found for the SAA unit which differ in the relative orientation (syn or anti) of the C−H^5 and C═O bonds. Stereoviews of the all-syn and all-anti conformations of the cyclic trimer are depicted in Figure 27. The molecular structure of the cyclic oligomers in the all-syn conformation generates a hydrophilic exterior surface and a nonpolar interior cavity which resemble the cyclodextrin molecular shape. Indeed, the complexation of the cyclic hexamer with two model guest molecules (*p*-nitrophenol, benzoic acid) was proved from titration studies using NMR spectroscopic parameters: chemical shifts, longitudinal relaxations (T_1) and diffusion coefficients. All of them showed different values for host and guest molecules measured independently and in the presence of each other.

C. Glucosidase Inhibitors

Sugar mimics in which the ring oxygen has been replaced by nitrogen have gained considerable interest as inhibitors of glycosidase, enzymes which are involved in numerous biological processes.

The nitrogen substitution renders the compounds metabolically inert but does not prevent their recognition by glycosidases and other carbohydrate-recognizing proteins. They inhibit glycosidases by mimicking the pyranosyl and furanosyl moiety of the corresponding substrates. The realization that amino-sugar glycosidase inhibitors might have enormous therapeutic potential in many disease or protective mechanisms by altering the glycosylation or catabolism of glycoproteins, or by blocking the recognition of specific sugars, has led to a tremendous interest and demand of these compounds. Thus, glycosidase inhibitors are potential antiviral, anticancer, and antidiabetic drugs. As the extraction and isolation of naturally occurring glycosidase inhibitors from often rather scarce sources is both time-consuming and costly, many natural products and analogues have been synthesized. (For extensive reviews on imino sugars and on glucosidase inhibitors, see Fleet's, Dwek's, and Bols' reviews in this issue.)

Many of them, may be considered as SAAs, like the examples shown in Figure 28. The analogue **76** of deoxymannonojirimycin was isolated from *Lonchocapus seciceus*, and has been shown to be a potent and specific inhibitor for both a glucoprotein-processing mannosidase and a bovine α-L-fucoside.[151] (2*S*,3*R*,-4*R*,5*S*)-3,4,5-trihydroxypipecolic acid **77** was isolated from *Raphia racemosa*[152] as a glucuronidase and iduronidase inhibitor.[153] Siastatin B (**8**) is a potent neuraminidase inhibitor, and was first isolated in 1974 from *Clostridium perfringens*,[18] its absolute configuration was proven by total synthesis.[154] The inhibitory activity of those isolated natural SAAs, sparked extensive research in that field and many synthetic derivatives were synthesized.[155,156] Using **76** as a lead structure, Ichikawa et al. developed the potent (K_i = 79 nM) β-glucuronidase inhibitor **81**.[157]

Of the many ring nitrogen containing glycosidase inhibitors, most are synthesized by reductive cyclic amination. The hydrogenation of pyridine ring is seriously hampered by the lack of crucial stereoselective hydrogenation.

V. Carbohydrate-Based Peptidomimetics

A. Mixed Linear and Cyclic Carbohydrate-Based Peptidomimetics

In recent work, we synthesized SAA **9** or SAA **10** containing, mixed linear and cyclic oligomers **82**−**84** (Figure 29a).[46,47] β-Ala and GABA were used as amino acid counterparts, because they represent likewise to SAA **9** and SAA **10** β- and γ-amino acids respectively, and they are completely unsubstituted, thus secondary structure results exclusively from the SAA incorporated.

The linear SAA oligomers **82** and **83** were synthesized on the solid-phase using Fmoc-strategy. The large number of 24 unambiguous interresidue NOE contacts (out of a total of 76 NOEs) for oligomer **82**, obtained from extensive NMR studies in CH_3CN, were used in subsequent simulated annealing and MD calculations, to elucidate a 12/10/12-helical structure of oligomer **82** in CH_3CN (Figure 29b), thus indicating that SAA **9** very strongly induces secondary structure.[46] A characteristic CD curve for oligomer **82** is observed up to 75 °C in both CH_3CN and

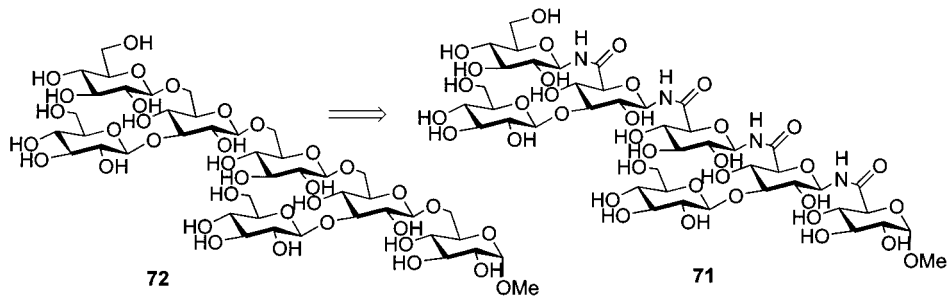


Figure 24. Structures of the 3^2,3^4-di-β-D-glucopyranosylgentiopentaoside **72** exhibiting phytoalexin-elicitor activity and the SAA-oligomer **71**.[142]

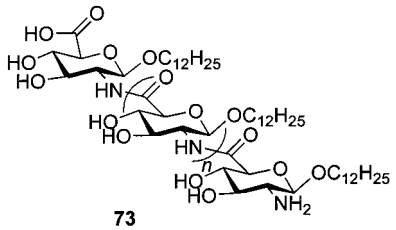


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Figure 25. Poly(SAAs) able to self-assemble.

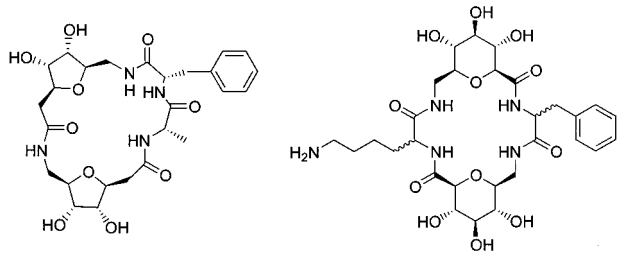

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Figure 26. Mixed cyclic oligomers **74**[147] and **75**.[149]

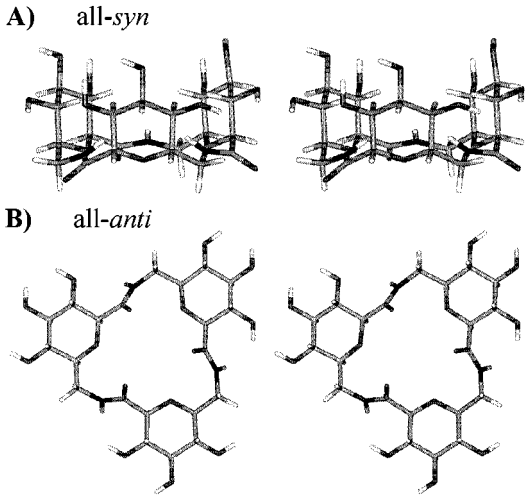
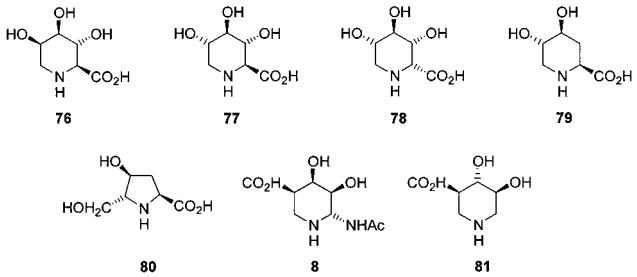


Figure 27. Stereoviews of the all-syn and all-anti conformations of the cyclic trimer.



76 77 78 79 80 8 81

Figure 28. Some of the SAA, which are glucosidase inhibitors; their names and references: **76** (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid,[151] **77** (2*S*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid,[152,153,156] **78** (2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid,[156] **79** (2*S*,4*S*,5*S*)-3,4-dihydroxypipecolic acid,[156] **80** bulgencinine,[156] **8** siastatin B,[18,154] **81** (3*S*,4*R*,5*R*)-4,5-dihydroxy-3-piperidinecarboxylic acid.[157]

CH_3CN/H_2O, even though **82** contains β-Ala, which is known to destabilize helices. In DMSO, however, the data suggests several averaged secondary structures.[46]

83 does not seem to form a stable conformation in solution. The cyclic SAA containing oligomer *cyclo*-[-SAA **9**-β-Ala-]$_3$ **84** exhibits a C_3 symmetric conformation on the NMR chemical shift time scale. However, it is not yet apparent if this a consequence of rapidely interconverting conformations of lower symmetry or if the preferred conformation is indeed a C_3 symmetric conformation.

B. Linear Carbohydrate-Based Peptidomimetic Homooligomers

For the peracetylated tetramers of **25** (Figure 5) as well as for the SAAs **29** and **30,** Fleet et al. observed a repeating β-turn like bond structure by a combination of solution NMR and IR techniques.[30,63,67,158] All of the oligomers adopt a repeating 10-membered hydrogen-bonded ring structure. These results show that protecting groups and substitution patterns of the hydroxyl groups in the sugar ring do not significantly influence the secondary structure of their homooligomers.

On the basis of their solution NMR studies, Fleet et al. propose a left-handed helical structure for the octamer of **31** (Figure 5).[63,65,159]

The tetramer of **26** shows no secondary structure.[63] The NMR signals are not dispersed. For all three amide protons the same chemical shift is observed, while for the oligomers above with defined secondary structures dispersed chemical shifts were observed. Chakraborty and co-workers investigated several protected and unprotected oligomers of **26**. The unprotected octamer shows a strong positive band in its CD spectra in MeOH and TFE, which might hint at a possible presence of a distinct secondary structure. However, the ^{1}H NMR spectra in various polar solvents did not show dispersed chemical shifts for the amide protons.[160]

C. Turn Mimetics and Model Peptides

Since proteins tend to exert their biological activity through only small regions of their folded surfaces, their functions could in principle be reproduced in much smaller designer molecules that retain these crucial surfaces. There are many options for modifications, such as introduction of constraints, cyclization, and/or replacement of the peptidic backbone or part of it, carbohydrate in general and SAA in particular provide just that.

SAAs can adopt robust secondary turn or helical structures and thus may allow one to mimic helices or sheets. They can be used as substitutes for single amino acids or as dipeptide isosters. If used as replacement of hydrophobic residues, the sugar can also be functionalized with hydrophobic side chains (e.g., they may be benzylated), however, if hydrophilic residues are replaced, or if solubility should be improved, the sugar hydroxyl groups are unprotected or functionalized with hydrophilic residues.

We explored the conformational influence of a large number of SAAs on the peptide backbone by incorporation of SAA **85**−**92**, SAA **9**, and SAA **10**, respectively, into several different model peptides as well as in biologically active peptides.[1,2,44−47,88,161] The cyclic and linear peptides were investigated by NMR spectroscopy, distance geometry, and subsequent MD calculations to determine the potential of the turn-

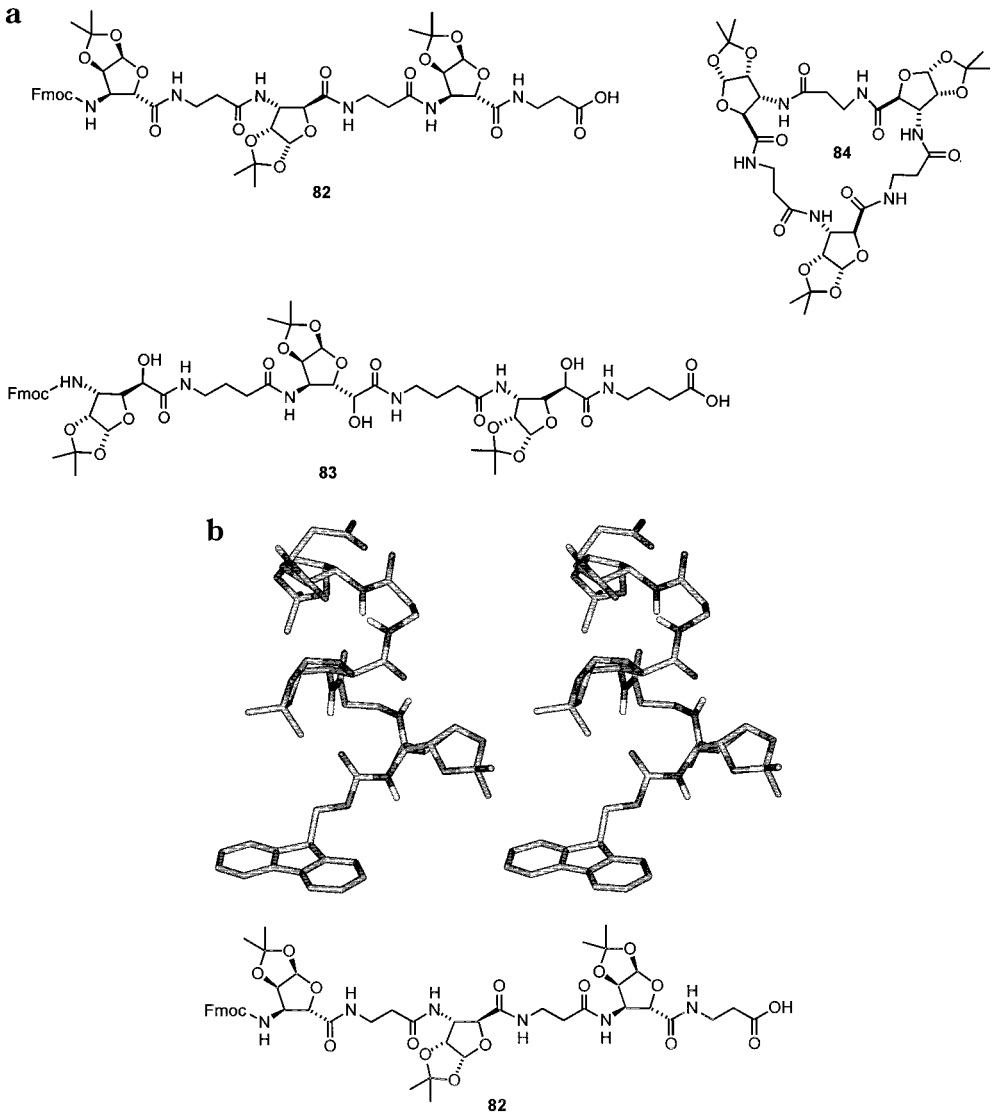


Figure 29. (a) Mixed linear oligomers **82** and **83** as well as cyclic oligomer **84** of β- and γ-SAA **9** and **10**. (b) Stereoview of the average structure of mixed linear oligomer **82**, as deduced by a 150 picosecond restrained molecular dynamics simulation in an explicit, all-atom CH_3CN solvent box. The side view of the formed right-handed 12/10/12-helix of **82**, consisting of a central 10-membered and two terminal 12-membered H-bonded rings, and with C:O and N−H bonds pointing alternatively up and down along the axis of the helix are shown. All four H-bonds formed are depicted.

inducing and stabilizing potential of SAAs as both local and global constraints. As can be seen in Figure 30 the SAAs do adopt defined turn arrangements in cyclic peptides.

This resulted in a SAA construction kit for predetermined constrained local conformations in synthetic peptides containing a series of SAAs (Figure 31).[1,2] These units offer possibilities as mimetic structures for both amino acids and dipeptide isosters.

SAAs **87**−**91** induce β-turns independent of the substitution pattern of the sugar ring while SAA **92** mimics a γ-turn.

The first noncyclic, peptidic β-hairpin structure containing a SAA was recently reported by van Boom et al. They used SAA **62** to stabilize a β-turn in the polypeptide chain AcKKYTVSI−SAA **62**−KKITVSI.[162]

It was proven by CD and NMR spectroscopy that the peptide adopts a β-hairpin structure in 50% aqueous methanol (Figure 32). However, the peptide remains unfolded in water.

D. Biologically Active Peptides Containing SAA Building Blocks

After verifying the conformational influence of the SAAs in cyclic peptides as compared to the backbone of model peptides we, as well as several other groups, focused our attention on the synthesis, conformational and biological evaluation relative to biologically active peptides. SAAs were used as turn mimetics and local constraints,[1,2,4,44,45,59−61,88,99,108,161] but also to improve pharmacokinetics,[161,163] to introduce a radioactive label for imaging[164] or to glycosylate a peptide.[165] The opioid, integrin, and somatostatin receptors were some of the pharmacologically interesting targets, which were chosen to investigate. We selected two structurally cyclic peptides, such as the "Veber-Hirschmann" peptide *cyclo*(-Phe-Pro-Phe-D-Trp-Lys-Thr-) **97**[166,167] and our *cyclo*(-Arg-Gly-Asp-D-Phe-Val-) peptide[168] as well as linear LH−RH analogues as a platform to determine the pharmacological

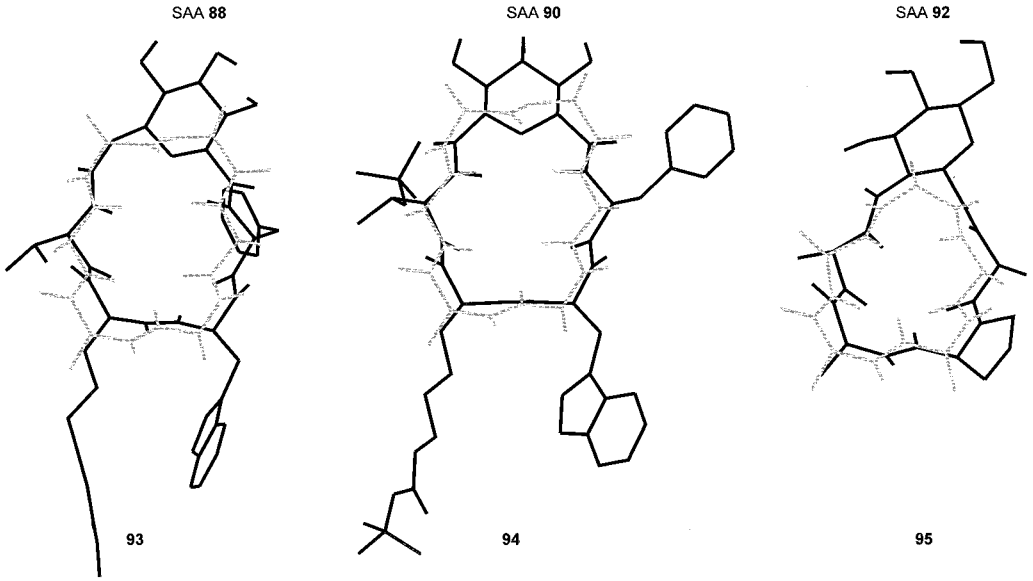
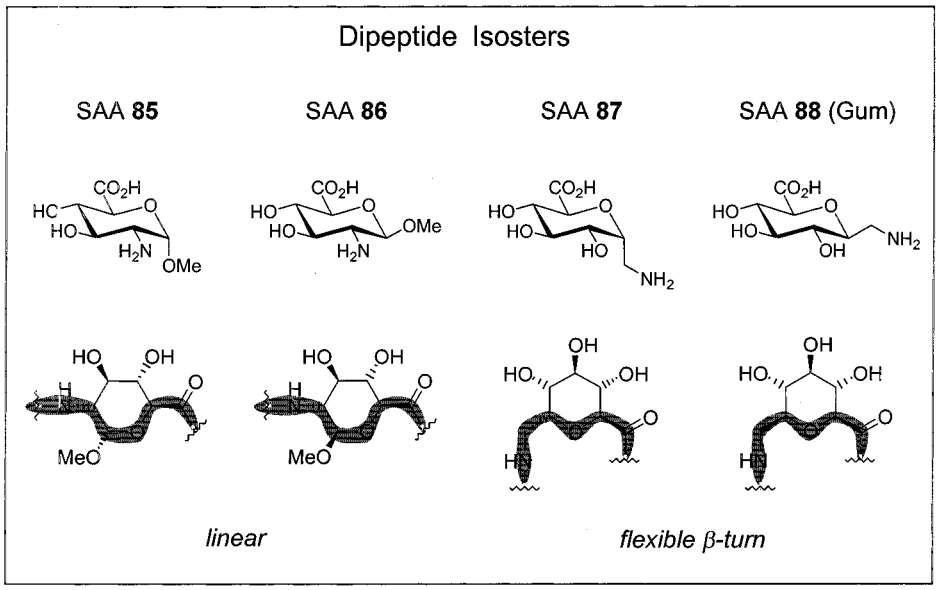


Figure 30. Superposition of **93** (black) and an idealized βII′/βII′-turn arrangement (gray); superposition of **94** (black) and an idealized βII′/βII′-turn arrangement (gray); superposition of **95** (black) and an idealized βII′/γ-turn arrangement (gray).



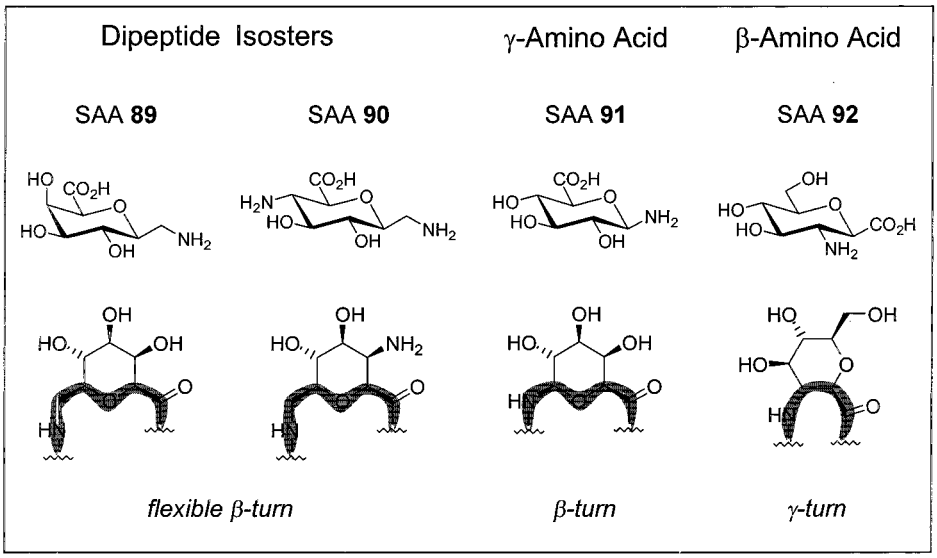


Figure 31. Extended SAA construction kit.

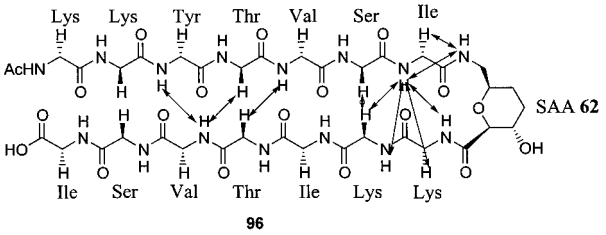


Figure 32. Relevant long range and turn region NOEs of **96**.[162]

potential of SAA scaffolds. Soon other groups started using SAAs in various biologically active peptides.

1. Somatostatin Analogues

Somatostatin is a 14-residue cyclic peptide hormone formed in the hypothalamus. Like its precursor, somatostatin-28, it plays an important role in a large number of physiological actions. For instance it inhibits the release of growth hormone (GH),[169,170] and plays a role in the inhibition of insulin secretion.[171,172] It was shown that somatostatin analogues inhibit tumor cell growth and induce apoptosis.[173,174]

The first SAA introduced into a bioactive peptide was glucosyluronic acid methylamine (Gum) **88**.[88,99] We introduced it as a dipeptide isoster into a cyclic hexapeptide of the "minimal" somatostatin sequence[166,175] *cyclo*[SAA **88**-Phe-D-Trp-Lys-Thr-]. By various NMR techniques and subsequent distance geometry calculations and molecular dynamic simulation, it was shown that SAA **88** induces a β-turn[88] (Figure 30).

The growth hormone release was inhibited with an IC_{50} value in the submicromolar range.

More recently, it was demonstrated that the new SAA **9** containing cyclic somatostatin analogues **98** and **99** exhibit strong antiproliferative and apoptotic activity against multidrug-resistant hepatoma carcinoma.[44,45] This is of special interest, since resistance to chemotherapy has become a major problem in cancer therapy.

The peptides were assembled on solid phase. Standard Fmoc-protocol was employed,[176] using HATU and HOAt as coupling reagents as well as 2,4,6-collidine as base.[177,178] Cyclization was performed in solution with DPPA under standard conditions.[179] Antitumor activity of the compounds **98**−**101** was tested on drug sensitive and multi-drug resistant various carcinoma cell lines.[180−182] A big aromatic residue in the Thr^{10} position seems to be essential for high antiproliferative and apoptotic activity. The IC_{50} values of 75 and 47 μm of compound **98** and of 31 and of 25 μm of compound **99** for drug sensitive and multidrug-resistant hepatoma cancer cell lines, respectively, make them promising lead compounds for potential chemotherapeutic drugs against multidrug-resistant hepatoma carcinoma. Preliminary results have shown that activity can be even more improved, by replacement of the D-Trp with L-benzothienylalanine (Bta) resulting in compound **100** or D-Bta compound **101**. Those compounds were more active than TT232: *cyclo*[2,6]-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH_2 **102**,[173] the only other compound so far known that shows apoptotic and antiproliferative activity against multidrug-resistant carcinoma cell lines. By introducing our new SAA **9** into the peptide backbone, pharmacokinetic properties can easily be improved as well as bioavailability, and enzymatic-stability of the compounds will most likely be enhanced.

2. SAAs in Enkephalin Analogs

To explore the effect of the dipeptide isosters SAA **85** and SAA **88** on the conformation of linear peptides

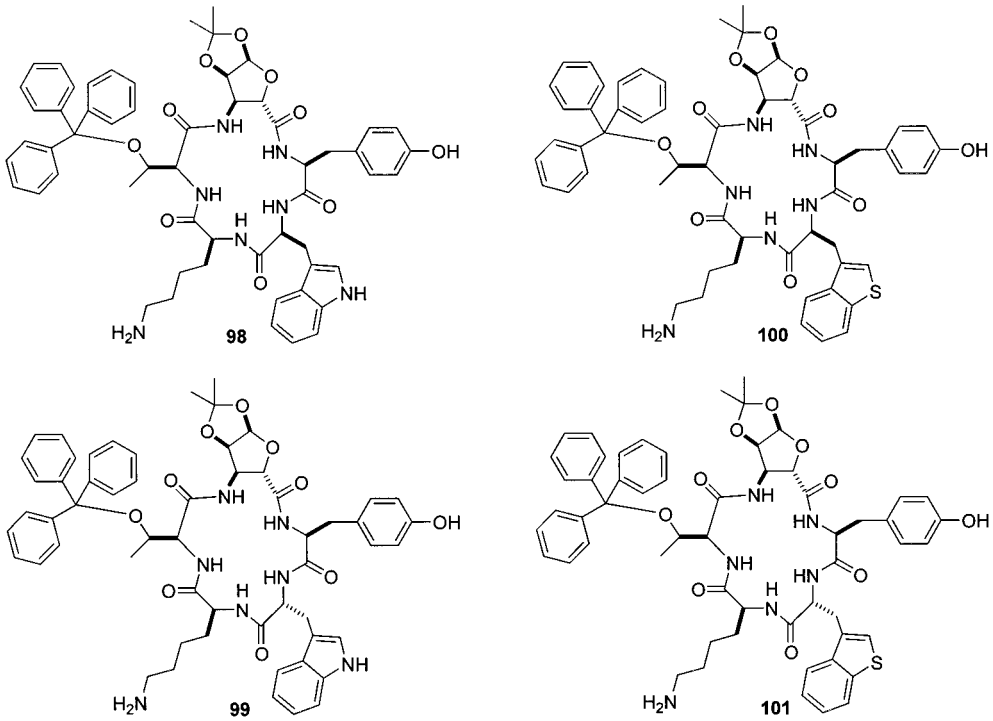


Figure 33. SAA **9** containing compounds **98**, **99**, **100**, and **101** with antiproliverative and apoptotic activity in the low μm range.

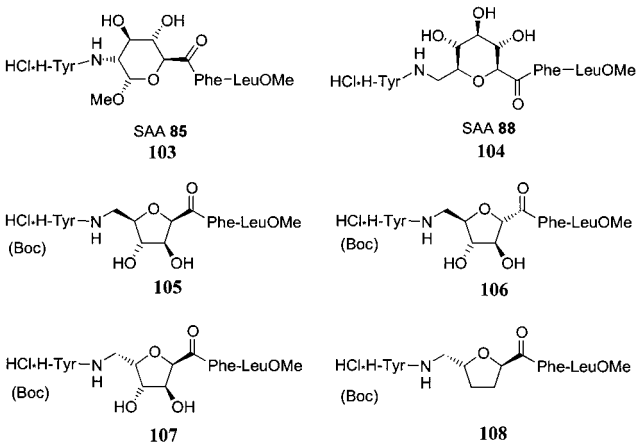


Figure 34. Leu-enkephalin analogues, in which Gly-Gly is replaced by various SAAs.[61,88,99]

by NMR spectroscopy, we synthesized the Leu-enkephalin analogues H-Tyr-SAA **85**−Phe-Leu-OMe (**103**) and H-Tyr-SAA **88**−Phe-Leu-OMe (**104**) (Figure 34).[88,99] The SAAs replace the Gly-Gly dipeptide of the natural sequence H-Tyr-Gly-Gly-Phe-Leu-OH, where Gly-Gly serves as a spacer in enkephalin between the messenger amino acid Tyr which is essential for the activity and the address sequence Phe-Leu responsible for the selectivity.[183,184]

Due to the functionality of the SAAs, these building blocks can be synthesized as Fmoc-derivatives and then be employed under standard SPPS[176] conditions using the Fmoc strategy and TBTU/HOBt[185] as a coupling reagent. The two enkephalin analogues **103** and **104** showed no biological activity in the guinea pig ileum assay (GPI).

However, when Chakraborty et al. incorporated their furanoid **25**, **26**, **27**, and dideoxy-**2**7 analogously into Leu-enkephalin, the analgesic activity of the resulting compounds **105**−**108** (Figure 34) was in the same range as that of Leu-enkephalin methyl ester.[60,61] The N-terminally Boc-protected analogues of **105**−**108** showed comparable activities as the unprotected ones. For synthesis of their peptidomimetic compounds they employed standard solution Boc strategy, using EDCI and HOBt as coupling agents.[186] Extensive CD and NMR studies, followed by constrained molecular dynamics simulations, revealed that the Boc-protected **105** and Boc-protected **107** have folded conformations composed of an unusual nine-membered pseudo β-turn-like structure with a strong intramolecular H-bond between LeuNH → sugarC3−OH. This turn moves the two aromatic rings of Tyr and Phe in close proximity, a prerequisite for biological activities of all opioid peptides. From analysis of the 3D structures of **105**−**108**, they concluded that a *cis*-β-hydroxycarboxyl moiety anchored on a five-membered ring was the essential structural motif, whose presence in some of these analogues was responsible for their folded conformations.

The group of Toth used SAA **91** (Figure 31) to "glycosylate" Leu- and Met-enkephalins via amide bond linkage to the C-terminal Leu or Met, respectively (Figure 35).[165]

They constructed the peptides **109**−**112** on solid phase, using Fmoc-strategy and HBTU/HOBt/DIEA

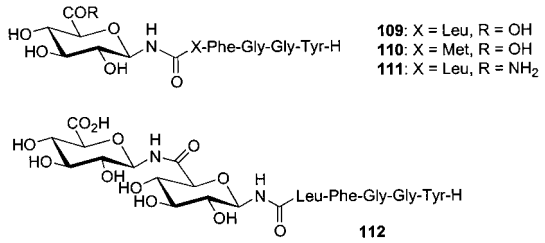


Figure 35. SAA "glycosylated" enkephalins.[165]

as coupling reagents. The peracetylated SAA **91** (Figure 31) azide precursor was reduced on resine by treatment with a mixture of triethylamine and propane-1,3-dithiol to generate the free amine in situ. They thereby used the azide as a amine protecting group instead of the Fmoc-protected SAA **91**. Pharmacological evaluation, using a GPI and mouse vas deferens (MVD) assay, revealed that **109** was three times more potent in the GPI assay and 40 times more potent in the MVD assay than Leu-enkephalinamide at inhibithing electrically stimulated muscle contractions.

3. Protein:Farnesyltransferase

Inhibition of protein:farnesyl transferase (PFT) should be effective to combate colon and pancreatic carcinomas.[187] Ras protein association with the plasma membrane is initiated by posttranslational farnesylation of the cysteine unit of the CAAX box (C, cysteine; A, any aliphatic amino acid; X, serine or methionine) in the pre-Ras protein by PFT, and that is essential for Ras function.[188] Continuous switching on phosphorylation cascade is caused by the activated GTP-bound state, in which oncogenic Ras proteins are locked. Van Boom et al. used SAA **61** and SAA **62** (Figure 6) as dipeptide isoster to replace AA. The resulting compounds **113** and **114** were both less active than for instance CAAX based inhibitors containing 4-aminobenzoic acid as AA. However both compounds show a distinct inhibitory effect—the "2,6-cis" isomer, the one containing SAA **61** is an about twice as active inhibitor as the "2,6-trans" isomer, containing SAA **62** (Figure 36).[108]

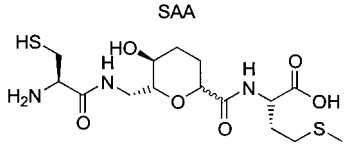


Figure 36. Structures and IC_{50} values PFT inhibitors **113** and **114** by van Boom et al.[108]

4. Integrin-Ligands

Integrins are located at the cell surface of a number of different cell types. They play a major role at cell−matrix interactions as well as at tumorgenesis. This invoked a pharmaceutical interest in $\alpha_v\beta_3$-antagonists, especially with regard to blocking the tumor-induced angiogenesis.[168,189−193] The recognition sequence of integrin ligands has been shown to be the

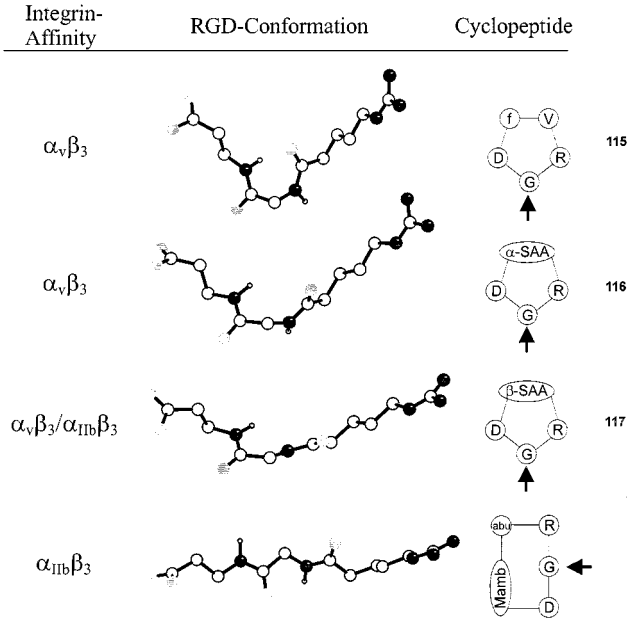


Figure 37. The RGD-conformations of the α-(**116**) and *β*-compounds (**117**) are compared to typical representatives of $\alpha_v\beta_3$- and $\alpha_{IIb}\beta_3$-antagonist structures, to the lead peptide *cyclo*(-RGDfV-) and the compound *cyclo*(-D-Abu-*N*MeArg-Gly-Asp-Mamb-) (Abu = A-aminobutyric acid, Mamb = *meta*-(aminomethyl)benzoic acid).[226] View along the pharmacophoric RGD-moiety is directed parallel to the ring plane of the cyclic peptide, as indicated by black arrows.

RGD-motif. We have used SAAs in that sequence as turn mimetic[161] to improve the pharmacokinetic properties of the compounds[161,163] and for tumor imaging to introduce the radio-nuclides.[164] The earliest attempts to modify cyclic RGD-peptides with carbohydrates impaired the biological activity of the RGD-compounds.[118,194] In more recent work[161] we chose as a lead structure for the derivatization of the RGD-motif the cyclic pentapeptide *cyclo*(-Arg-Gly-Asp-D-Phe-Val-) **115**, which binds selectively $\alpha_v\beta_3$-integrins.[168,189−193] In **115** the backbone conformation of the residues D-Phe-Val resembles a *β*II′-turn, thus forcing the RGD-sequence, which acts as pharmacophore, into a kinked, $\alpha_v\beta_3$-selective conformation. Fully benzylated Gum (both the α- and the *β*-anomer) has been shown to induce the type of turn necessary for the biological activity[1,2,88] and also had the aromatic functionality required for enhanced activity. Therefore we used both anomers to replace D-Phe-Val in **115** to give **116** and **117**, which exhibit a relatively high $\alpha_v\beta_3$ activity of IC_{50} = 150 nm (**116**) and 25 nm (**117**). However **117** showed also a high activity against the $\alpha_{IIb}\beta_3$-receptor (IC_{50} = 13.4 nm). The loss of selectivity of **117** compared to that of the α-SAA-peptide **116** can be explained by the higher flexibility of *β*-SAA-peptide **117**. Because of that flexibility, a kinked as well as a stretched conformation can be realized in solution. The compound is therefore able to re-adjust its conformation, matching the steric demands of both the $\alpha_{IIb}\beta_3$- and $\alpha_v\beta_3$-receptor pockets: high activity with a loss of selectivity is the consequence (Figure 37). This is confirmed by their NMR-based structural analysis and subsequent MD-simulations.

To improve pharmacokinetic properties, Val was substituted by Lys, which was glycosylated with different SAAs via an amide bond.[161,163,164] Activity and selectivity was sometimes even enhanced. Furthermore, via the amine function of the SAAs, ^{18}F-labeling is possible.[164,195] In in vivo studies, using $\alpha_v\beta_3$-positive and -negative murine and xenotransplanted human tumors receptor-specific binding of the radiolabeled **118** yielded high tumor:background ratios. First, imaging results using a small animal positron emission tomograph suggest **118** is suitable for noninvasive determination of the $\alpha_v\beta_3$ integrin status and therapy monitoring.

VI. Outlook and Conclusions

The syntheses and transformations and some of the pharmacological features of sugar amino acids have been reviewed, as they represent unique structures among carbohydrates and peptides. The examples presented demonstrate the wide range of their applicability. These range from structural to functional mimetics of natural products. SAA oligomers represent novel oligosaccharide structures with distinct

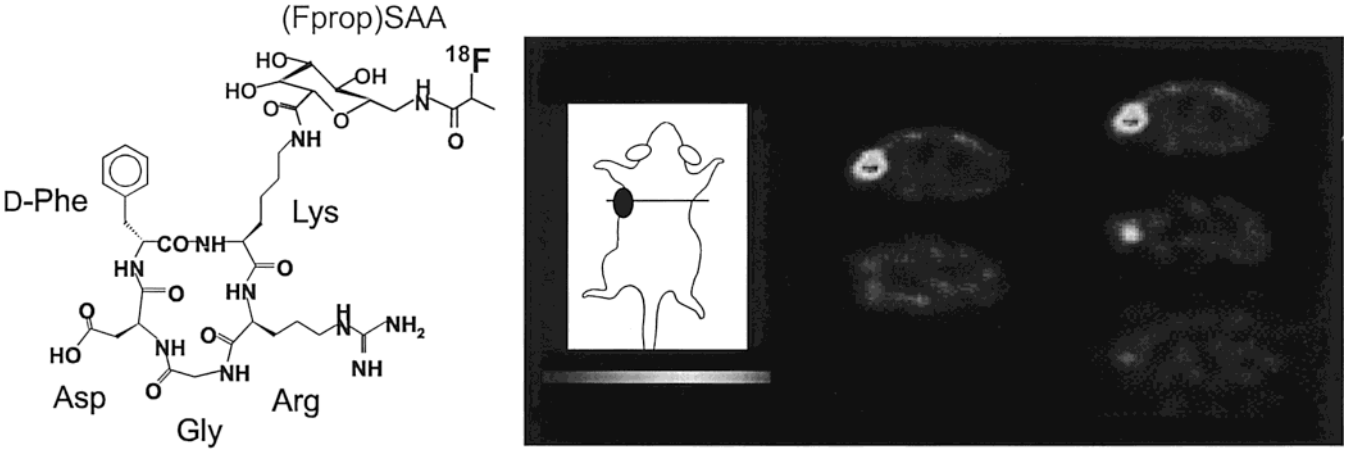


Figure 38. Structure of **118** and transaxial small animal PET images of nude mice bearing human melanoma xenografts, treated with **118**. Left side: location of images. Middle: $\alpha_v\beta_3$ positive tumor labeled with **118** (above) and $\alpha_v\beta_3$ negative tumor (below). Right side: **118** treated $\alpha_v\beta_3$ positive mice with increasing amounts of soluble RGD peptide.

secondary and tertiary structures that may help to contribute to the understanding of bio-(macro-)-molecular assemblies, similar to the peptidic foldamers intensively described by the groups of Gellman and Seebach.[196−223]

As for the inherent exquisite arrangement of functional groups in monosaccharides in general, this can be used as chiral templates for functional groups necessary for biological activity. The modern day small molecule design and synthesis of drugs also relies on scaffolds based on carbohydrates as these are powerful tools for the study of molecular recognition in structure−activity relationship studies. The mimetics are small in size, maintain solubility under physiological conditions and are amenable to detailed structural studies. SAA can be modified in this respect to influence the turn pattern and/or the pharmacophoric profile using turn inducing SAAs with the appropriate hydrophobic/hydrophilic substitution pattern.

The synthesis of the building blocks utilize standard carbohydrate chemistry, whereas the assembly of different conjugates results from both state-of-the-art peptide chemistry as well as carbohydrate chemistry. Thus the complexity of carbohydrates can be exploited to obtain larger numbers of compounds, as has been the primary objective of combinatorial chemistry in modern drug discovery, where much effort has been devoted to the development of procedures and/or methods that increase the efficiency of the drug discovery process. With modifications in and on the rings, the syntheses of further compounds may also be expected, and their utilization in combinatorial chemistry may also undergo fast progress.

As the scope of modern day synthesis evolves with new techniques and seemingly unlimited access to large amounts of compounds, the bottleneck for combinatorial chemistry and the synthesis of large libraries still remains with synthesis itself.

VII. Abbreviations

CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
DCC	dicyclohexylcarbodiimide
DIEA	diisopropylamine
DMF	dimethylformamide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Fmoc	9-fluorenyloxycarbonyl
HATU	*O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
NMP	*N*-methylpyrrolidone
SAA	sugar amino acid
TATU	*O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TBTU	*O*-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidioxyl radical
TFA	trifluoroacetic acid
THF	tetrahydrouran

VIII. References

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