# Alkylated and bicyclic sugar amino acids : synthesis and applications

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# 1 General Introduction and Outline

## On Peptide Isosteres in General and Sugar Amino Acids in Particular

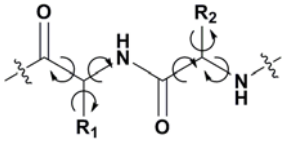
### General Introduction

Polypeptides are important naturally occurring polymers that are second only to polysaccharides, in abundance and diversity. Most natural polypeptides consist of unbranched linear chains composed of α-amino acids. With a limited palette of twenty common amino acids polymers can be generated with an almost unlimited variety in both structure and function.

Though it appears that nature has optimized amino acids as structural elements, there are a few drawbacks to the use of oligopeptides as therapeutical agents. The first and most obvious one is their stability. The interconnecting amide bond is at a first glance robust since it can only be cleaved by prolonged exposure to highly acidic conditions at elevated temperature. Nature however has found several ways to cleave this sturdy bond in a mild but effective fashion by means of proteolytic enzymes.

Oligopeptides often adopt flexible structures, which might be an undesirable aspect when applied as a drug, since the tertiary structure[1] of a molecule often plays a significant role in the binding of the drug to its target and thereby its activity. Although the peptide bond itself usually adopts the *s*-trans configuration, the flexibility of peptides stems from the rotational freedom of the remaining linkages. The rotational angles of a simple dipeptide are depicted in Figure 1.

**Figure 1.** Rotational flexibility of a dipeptide bond in an *s*-trans configuration.



## Replacing the peptide bond

The application of peptide isosteres with the objective to increase the metabolic stability of oligopeptides and to reduce their conformational flexibility has emerged over the last decade as an attractive strategy in the search of peptide based bioactive molecules. Peptide isosteres are not composed of alpha amino acids but have structures and properties resembling those of "common" peptides. Most applied are dipeptide isosteres, which are designed to replace two amino acids and are functionalized with an amine and a carboxylate functionality.

A first class of peptide isosteres is characterized by the replacement of peptidic bond with a different moiety of similar dimensions. Common examples include sulfonamides, alkenes and ether structures. An overview of these peptide isosteres is presented in Table 1.

**Table 1**: An overview of some frequently applied linear dipeptide isosteres

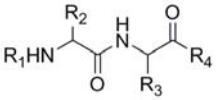
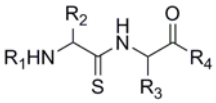
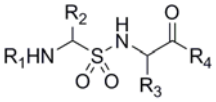
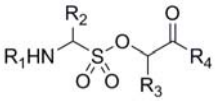
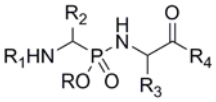
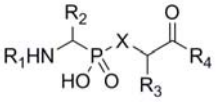
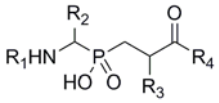
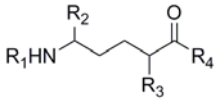
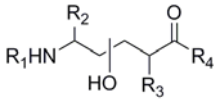
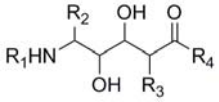
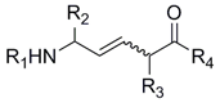
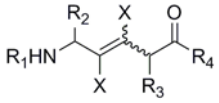
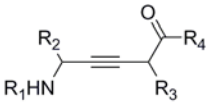
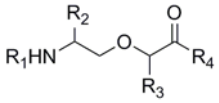
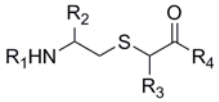
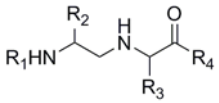
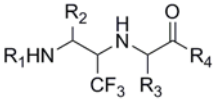
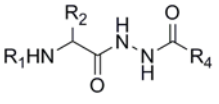
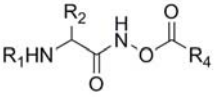
| Isostere | Structure | Literature examples |
|---|---|---|
| amide |  | Parent structure |
| thioamide |  | [2] |
| sulfonamide |  | [3] |
| sulfonate |  | [3c] |
| phoshonamide |  | [4] |
| phosphonate<br>phosphothioate |  | X = O,S [4b] |

**Table 1.** (*continued*)

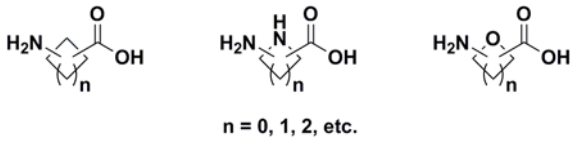
| | | |
|---|---|---|
| phosphinate |  | 3c |
| alkane |  | 5 |
| hydroxyethylene |  | β-OH[6]<br>γ-OH[7] |
| dihydroxyethylene |  | 8 |
| alkene |  | 9 |
| (di)haloalkene |  | 10 |
| alkyne |  | 11 |
| methyleneoxy |  | 12 |
| methylenemercapto |  | 13 |
| methyleneamino |  | 14 |
| trifuoroethylamino |  | 15 |
| hydrazide |  | 16 |
| amideoxy |  | 17 |

The degree of flexibility of these dipeptide isosteres can be much higher than that of the parent dipeptide such as in the alkane bridged species that displays two additional rotational angles or lower such as in the alkyne based compounds which effectively lose one rotational angle.

## Peptide isosters built around a cyclic core

A second class of peptide isosteres are cyclic molecules decorated with an amine and a carboxylic acid function. These ring structures can be aromatic, but usually, completely or partly saturated rings are applied. Common examples include carbacycles,[18] azacycles[19] and oxacycles, having various ring sizes (Figure 2).

**Figure 2.** General structures of carbacycles, azacycles and oxacycles.



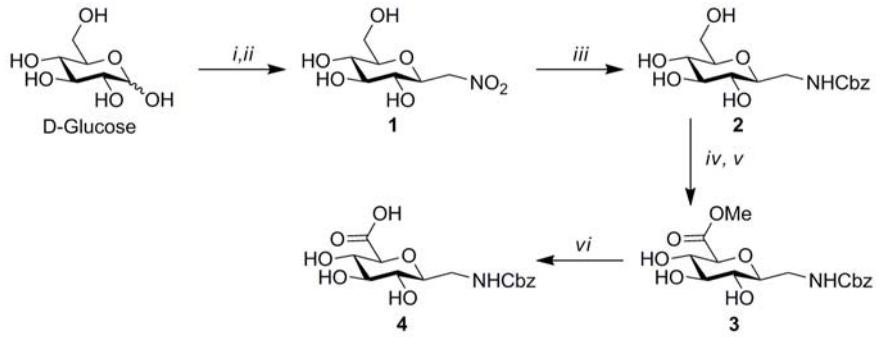

The azacycles are often based on an alkaloid core, thereby allowing isosteres with a bicyclic structure.[20] Azacyclic isosteres that deserve special mentioning are those based on a triazole ring formed by a copper catalyzed azide-alkyne cycloaddition (colloquially know as the click reaction).[21]

## Oxacyclic peptide analogs: Sugar amino acids

The starting compounds of choice for the generation of oxacyclic amino acids are monosaccharides. In fact, oxacyclic amino acids are usually called sugar amino acids (SAAs).[22] The use of sugars as building blocks for the synthesis of amino acids has many benefits. First, sugars are, generally, inexpensive chemicals. Second, sugars have limited conformational freedom, a feature that is often sought after. Last, sugars are chiral molecules bearing hydroxyl functions, that can be modified at will. An elaborate overview of most of the SAAs published so far is given in Chapter 2.

The first synthesis of a sugar amino acid was reported by the group of Kessler.[23] Pyranoid sugar amino acid H-Gum-OH (**4**) was synthesized from D-Glucose in 6 steps according to Scheme 1.

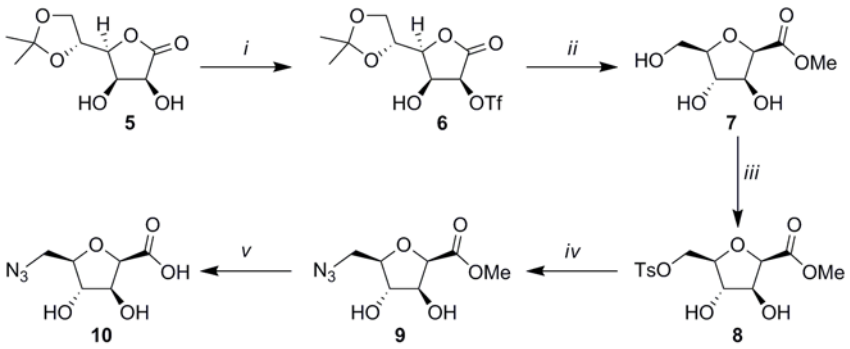
**Scheme 1**. Synthesis of H-Gum-OH (**4**) by the group of Kessler.




Reagents and conditions: [**i**] $MeNO_2$, NaOMe [**ii**] HCl, $H_2O$, ΔT, 36% over two steps [**iii**] first $H_2$, Pd/C, MeOH then CbzCl, $NaHCO_3$, 98.5% [**iv**] $O_2$, Pt/C, $H_2O$ [**v**] MeOH, DCC, DMAP, 35% two steps [**vi**] NaOH, MeOH, $H_2O$, quantitative.

D-Glucose was nitromethylated by a Henry reaction on the glucose aldehyde followed by an acid catalyzed elimination and conjugate addition of the 5-OH onto the nitrovinyl.[24] Catalytic reduction of the nitro group followed by CBz protection gave glucoside **2**. The carbinol was oxidized using oxygen gas and platinum and the free acid was methylated to facilitate isolation and purification. The SAA **4** was obtained upon basic hydrolysis of the methyl ester.

**Scheme 2**. Synthesis of Furanoid SAA **10** by the group of Fleet.




Reagents and conditions: [**i**] $Tf_2O$, pyridine, $CH_2Cl_2$ [**ii**] 1% HCl in MeOH 84% two steps [**iii**] TsCl, pyridine [**iv**] $NaN_3$, DMF 72% two steps [**v**] NaOH, dioxane, quantitative.

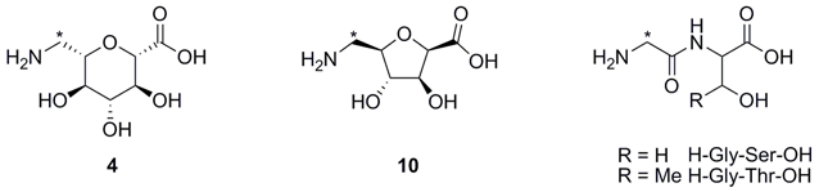
Shortly thereafter, the group of Fleet published the synthesis of furanoid SAA **10** (Scheme 2).[25] The synthesis commenced with D-γ-mannolactone monoacetonide (**5**). Selective triflation of the 2-OH and subsequent acid catalyzed cycloisomerization gave C-glycoside **7**. Selective tosylation of the carbinol in compound **7** followed by treatment with sodium azide gave compound **9**. The synthesis was completed by basic hydrolysis

of the methyl ester to give product **10** in quantitative yield with the amine conveniently masked as an azide.[26]

## Alkylated SAA's : the introduction of (peptide) sidechains

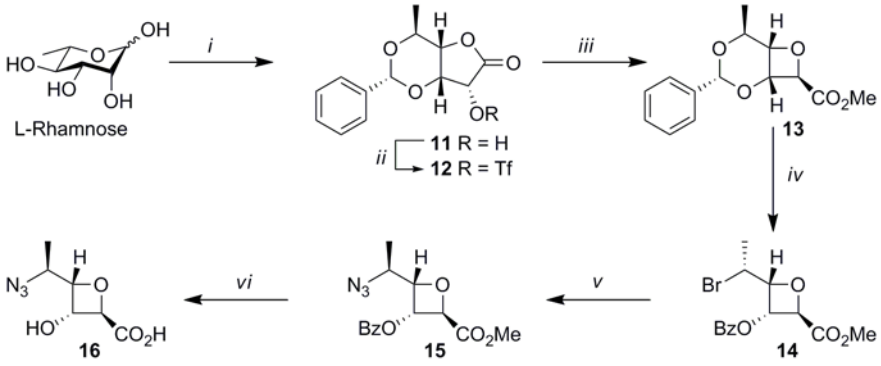
Both of SAAs **4** and **10** are unsubstituted at the carbon atom that is bound to the amine. (*, Figure 3) Having no side chain functionality at that position these SAAs can be considered isosteres of H-Gly-Ser-OH, or H-Gly-Thr-OH.

**Figure 3**. SAAs **4** and **10** as isosters of H-Gly-Ser-OH or H-Gly-Thr-OH.




In order to be able to mimic dipeptides other than H-Gly-X-OH, it is necessary to install an additional functionality at the carbon connected to the amine (marked with an asterisk). One approach to obtain functionalized dipeptide isosteres comprises the application of starting compounds in which the required functionality is already incorporated. This is exemplified with the synthesis of SAA **16** from L-rhamnose by the group of Fleet.[27]

**Scheme 3**. Synthesis of Furanoid SAA **16** by the group of Fleet.

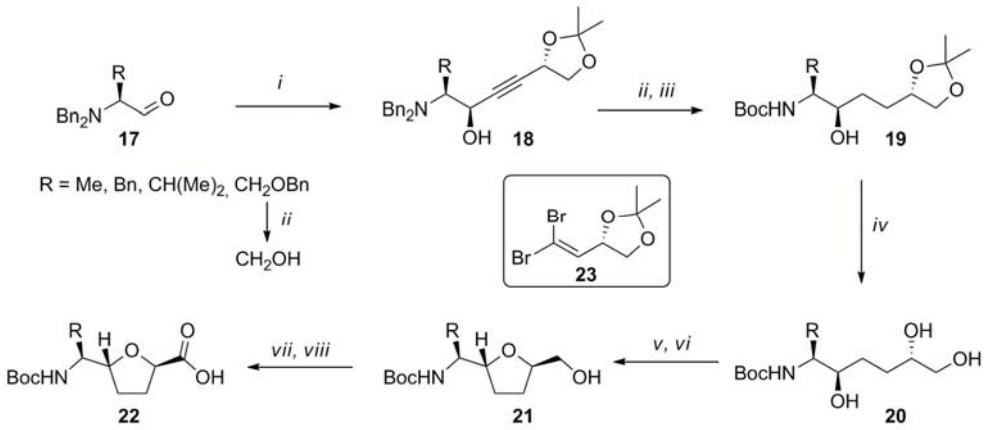



Reagents and conditions: [**i**] $Br_2$, $BaCO_3$, $H_2O$ then PhCHO, conc. HCl, 72% over two steps [**ii**] $Tf_2O$, pyridine, THF [**iii**] $K_2CO_3$, MeOH, MeCN, 89% over two steps [**iv**] NBS, $BaCO_3$, $CCl_4$, 86% [**v**] $NaN_3$, DMSO, 65% [**vi**] NaOH, $H_2O$, THF quantitative.

In the first step L-rhamnose was oxidized to a γ-lactone with barium carbonate and elemental bromine and concomitantly protected with a benzylidene. Triflation of the free hydroxyl and base catalyzed cycloisomerization provided oxetane **13**. Treatment of this oxetane under Hanessian-Hullar conditions[28] provided bromide **14** which was reacted with full inversion of stereochemistry with sodium azide to give compound **15**. Cleavage of both esters under basic conditions provided SAA**16**, a H-LAla-DSer-OH isoster.

In 2005, Chakraborty *et al.*[29] published a method to generate a range of substituted furanoid SAAs starting from building blocks derived from protected amino aldehydes that were prepared from common alpha amino acids. (Scheme 4)

**Scheme 4**. Synthesis of furanoid SAA dipeptide isosters by the group of Chakraborty *et al.*

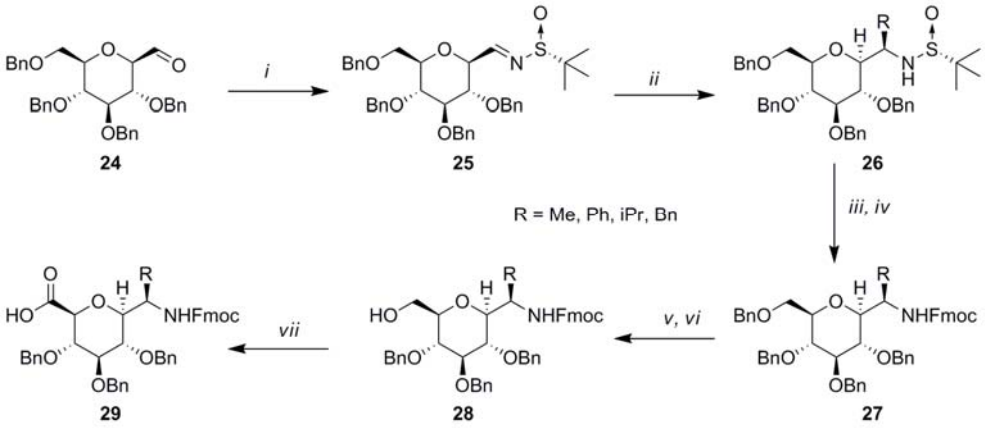



Reagents and conditions: [**i**] **23**, n-BuLi, THF 78-93% [**ii**] $H_2$, $Pd(OH)_2$ MeOH [**iii**] $Boc_2O$, $Et_3N$, MeOH 85-92% two steps [**iv**] CSA, MeOH, 85-92% [**v**] TrisCl, pyridine, $CH_2Cl_2$ [**vi**] $K_2CO_3$, MeOH 72-88% two steps [**vii**] $SO_3$-py., $Et_3N$, DMSO, $CH_2Cl_2$ [**viii**] $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH 84-88% two steps.

The aminoaldehyde of choice was reacted with an acetylide, formed from dibromide **23** under Corey-Fuchs[30] conditions, to generate compound **18**. Catalytic reduction followed by Boc protection gave intermediate **19**. Removal of the acetonide gave triol (or tetraol when R = $CH_2OH$ / $CH_2OBn$) **20** that was cyclized via selective sulfonylation and epoxide formation. The acid was generated though a sequential Parikh-Doering[31] and Pinnick[32] oxidation.

In 2004, Raunkjær *et al.*[33] employed a strategy using chiral nonracemic sulfinimides[34] to generate pyranoid dipeptide isosters. The stereochemistry at the carbon attached to the amine qualifies these isosteres as H-D-Xaa-Ser/Thr-OH mimics (Scheme 5).

**Scheme 5**. Synthesis of pyranoid SAA dipeptide isosters by Raunkjær *et al*..




Reagents and conditions: [**i**] (*R*)-*tert*-butylsulfinamide, anhydrous $CuSO_4$, $CH_2Cl_2$, rt, 24 h, 70% [**ii**] RMgX, $PhCH_3$ -78 °C [**iii**] HCl/MeOH, rt [**iv**] Fmoc-OSu, DiPEA, $CH_2Cl_2$, 1,4-dioxane, rt. 50-70% over three steps [**v**] $ZnCl_2$, AcOH, $Ac_2O$, rt. [**vi**] HCl/MeOH, rt. [**vii**] TEMPO, BAIB, $CH_2Cl_2/H_2O$, rt 64-74% over three steps.

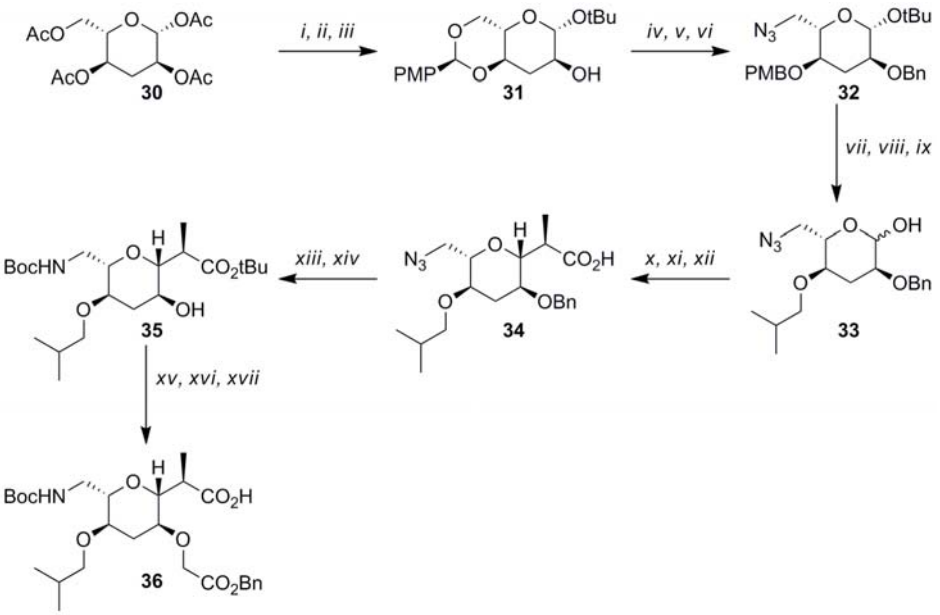
Formyl tetra-*O*-benzyl-β-*C*-D-glucopyranoside **24** was condensed with chiral nonracemic *R*-tert-butylsulfinamide. The thus generated sulfinimine **25** was reacted with a range of Grignard reagents to generate diastereoselectively sulfinamine **26**. Acidic cleavage of the sulfinamide followed by Fmoc protection of the free amine yielded carbamate **27**. Selective deprotection of the primary benzyl ether using a two step protocol yielded alcohol **28** that was oxidized to SAA **29** using the TEMPO/BAIB reagent system.

An SAA that takes peptide mimicry to the extreme was published by Smith *et al.* in 1998 (compound **36**, Scheme 6).[35] Even though there is no substituent next to the amine qualifying it as a H-Gly isoster, the carbohydrate core bears the sidechains of three different amino acids thus making it a true peptide mimetic.

β-3-Deoxy-L-glucose-tetraacetate **30** was converted to its *tert*-butyl glycoside under Koenigs Knorr conditions, deacetylated and protected with an anisylidene. Benzylation of the remaining free hydroxyl, regioselective opening of the anisylidene and introduction of the azide via the primary mesylate gave compound **32**. Selective cleavage of the paramethoxybenzyl ether, followed by alkylation with isobutylbromide and acidic hydrolysis of the *tert*-butyl group yield anomeric mixture **33**. A Wittig/conjugate addition reaction followed by saponification of the ester gave compound **34** alongside a minor amount of its methyl epimer. Transformation of the carboxylate into a *tert*-butyl ester and the azide into a Boc protected amine, via catalytic hydrogenation, yielded compound **35**. Allylation of the remaining free hydroxyl

followed by oxidative degradation to a glycolate ether, benzylation of the free carboxylate and acidic removal of the *tert*-butylester yielded SAA **36**.

**Scheme 6**. Synthesis of pyranoid SAA **36** that is a fourfold peptide isostere by Smith *et al.*.



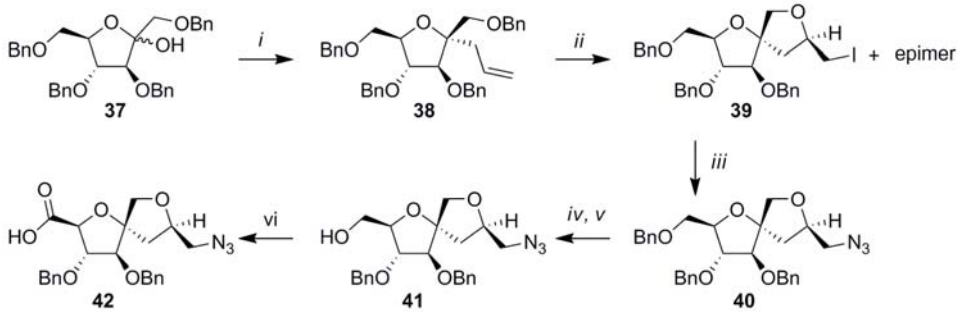

Reagents and conditions: [**i**] HBr, $Ac_2O$, t-BuOH, 45% [**ii**] NaOMe, MeOH [**iii**] $PMPCH(OMe)_2$, PPTS 61% over two steps [**iv**] BnBr, NaH, TBAI, THF 93% [**v**] DIBAL, $CH_2Cl_2$ [**vi**] first MsCl, $Et_3N$, DMAP, $CH_2Cl_2$ then $NaN_3$, DMF, Δ, 72% two steps [**vii**] DDQ, $CH_2Cl_2$, $H_2O$, 74% [**viii**] NaH, $Me_2CHCH_2Br$, TBAI, THF 86% [**ix**] 70% aq. AcOH 72% [**x**] $Ph_3P{=}C(Me)CO_2Et$, MeCN, Δ 76% [**xi**] NaOMe, MeOH [**xii**] LiOH•$H_2O$, MeOH/$H_2O$ 66% [**xiii**] (*t*-BuO)$_2CHNMe_2$, PhMe, 80% [**xiv**] $H_2$, Pd/C, $Boc_2O$, AcOEt, 73% [**xv**] AllylBr, NaH, THF, TBAI, 84% [**xvi**] $RuO_2$, $NaIO_4$, BnBr, $K_2CO_3$, 72% [**xvii**] TFA, anisole, $Boc_2O$, 95%.

## Bicyclic sugar amino acids

Bicyclic SAAs have a sidechain functionality that is part of a ring moiety. The sidechain is used to annulate a second ring onto the parent oxacycle. Bicyclic SAA's are, in literature, relatively rare to date with most examples limited to H-Gly- mimicing peptide analogs. An interesting synthesis of a bicyclic SAA was published by Cipolla *et al.* in 2002 (Scheme 7).[36]

Tetrabenzyl-D-fructose **37** was allylated with allyltrimethylsilane and a catalytic amount of Lewis acid. Allyl derivative **38** was submitted to a iodo-etherification to obtain two epimeric spiro compounds (**39**). The epimers were separated and successively treated with $NaN_3$, debenzylated at the primary position and oxidized to the bicyclic SAA using Jones' reagent[37] (intermediates for only one epimer are depicted).

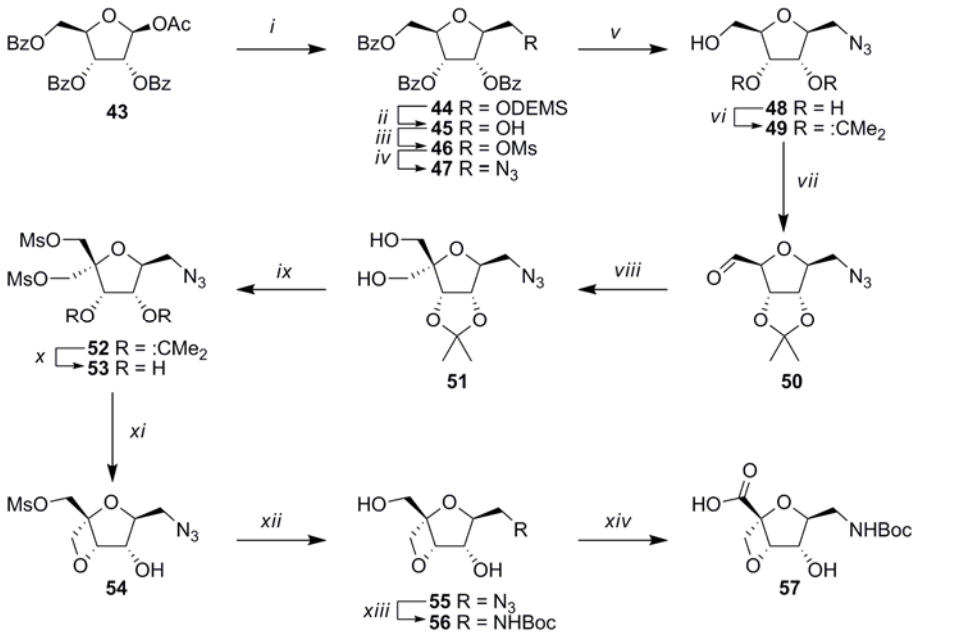
**Scheme 7**. Synthesis of the bicyclic spiro SAA **42** by the group of Nicotra.



Reagents and conditions: [**i**] AllylTMS, $BF_3$•$OEt_2$ 98% [**ii**] $I_2$, THF 98% (39 : epimer in a 3:2 ratio) [**iii**] $NaN_3$, $Bu_4NI$, DMF 76-81% [**iv**] $Ac_2O$/TFA (4:1 v/v) 86-93% [**v**] NaOMe, MeOH 82-87% [**vi**] $CrO_3$, $H_2SO_4$, acetone/$H_2O$ 70-82%.

A sugar amino acid based on a 2,6-dioxabicyclo[3.2.0]heptane core was published by Van Well *et al.* in 2003.[38] Key features include a cobalt catalyzed silyloxymethylation and a tandem aldol/Canizzaro hydroxymethylation (Scheme 8).

**Scheme 8**. Synthesis of SAA **57** by Van Well *et al.*.



Reagents and conditions: [**i**] $Co_2(CO)_8$, DEMS, CO, $CH_2Cl_2$ 30°C 75% [**ii**] AcOH/$H_2O$/THF, 3/1/6 v/v/v, 95% [**iii**] MsCl, pyridine, 93% [**iv**] $NaN_3$, DMF, Δ, 96% [**v**] KOtBu, MeOH, quant. [**vi**] 2,2-dimethoxypropane, pTsOH, acetone 87% [**vii**] Dess-Martin periodinane, $CH_2Cl_2$, 0°C [**viii**] $H_2CO$, 2M NaOH (*aq.*), dioxane, 0°C then $NaBH_4$, 52% [**ix**] MsCl, pyridine, 92% [**x**] 4M HCl (aq.) 89% [**xi**] 1M NaOH (*aq.*), dioxane, 25°C, 89% [**xii**] 1M NaOH (aq.), dioxane, 80°C, 81% [**xiii**] Boc-ON, $Me_3P$, THF, 70% [**xiv**] TEMPO, KBr, NaOCl, aq. $NaHCO_3$, aq. NaCl, $H_2O$, 0°C 70%.

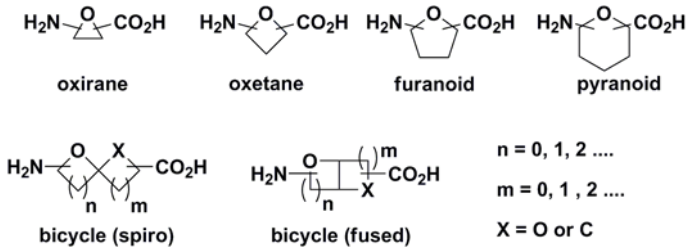
Ribose derivative **43** was silyloxymethylated at the anomeric center using the conditions developed by Chatanai *et al.*[39] The silyl ether was cleaved and an azide was introduced at the primary position via the mesylate. All benzoate esters were removed and an 1,2-acetonide was introduced to obtain derivative **49**. Oxidation of the carbinol to a carbaldehyde followed by a tandem aldol-Canizzaro reaction yielded diol **51**. Mesylation of the two free hydroxyls followed by removal of the acetonide allowed the intramolecular formation of oxetane **54** under basic conditions. Removal of the remaining mesylate using NaOH at elevated temperature followed by transformation of the azide into a Boc protected amine yielded amino alcohol **56** which was oxidized using TEMPO to obtain SAA **57**.

## Aim and Outline of this thesis

The work described in this thesis was aimed at the development of alkylated and bicyclic SAAs and the evaluation of the structures generated within a biological context.

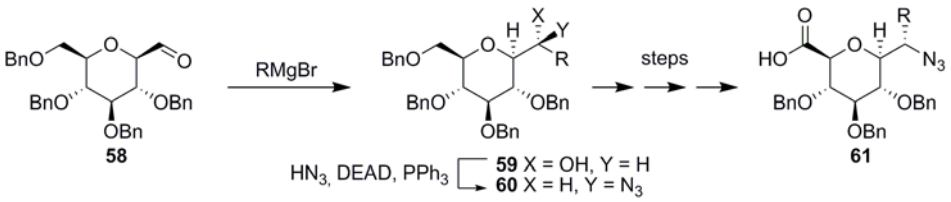
In **Chapter 2** an overview is given of the sugar amino acids that have appeared in literature (Figure 4). The chapter deals with monocyclic SAAs of ring sizes ranging from three to six: oxiranes, oxetanes, tetrahydrofurans and tetrahydropyrans. At the end of the chapter the limited number known of bicyclic SAAs are displayed. Linear carbohydrate derived amino acids as well as amino acid heterocycles possessing ring heteroatoms other than oxygen are omitted.

**Figure 4.** Overview of the structures of the SAAs described in chapter 2



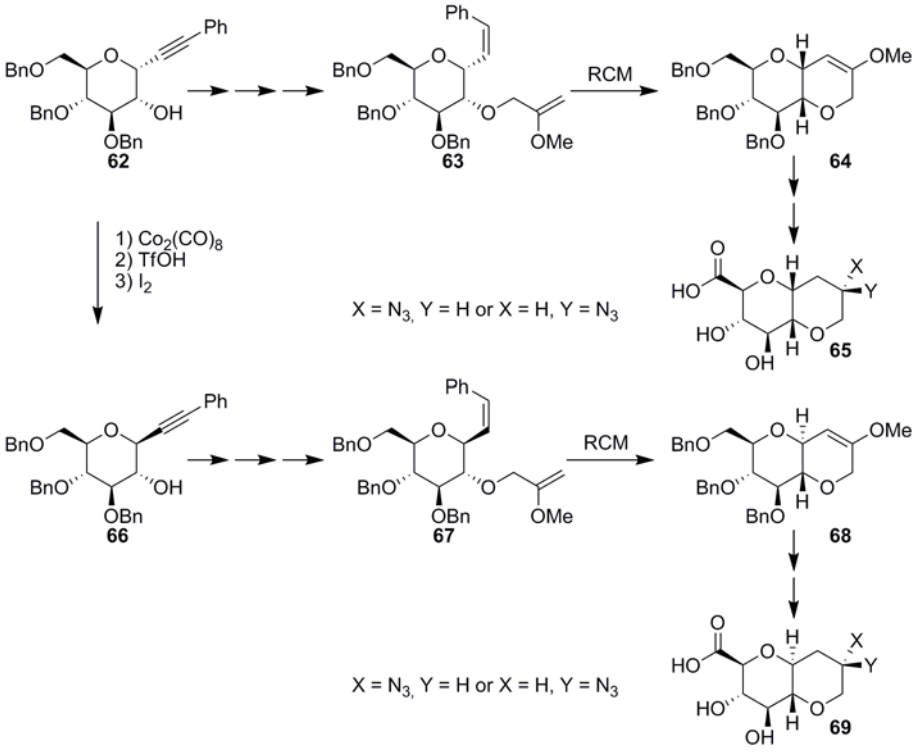

The synthesis of H-L-Xaa-L-Ser/Thr-OH mimetics from C-formyl tetra-*O*-benzyl-β-D-glucopyranoside is described in **Chapter 3**. Key feature of the synthesis is the stereoselective addition of Grignard reagents onto the aforementioned aldehyde (**58**) to afford a secondary alcohol that is substituted by an azide with inversion under Mitsunobu conditions (Scheme 9).

**Scheme 9**. Overview of the SAA syntheses described in chapter 3.



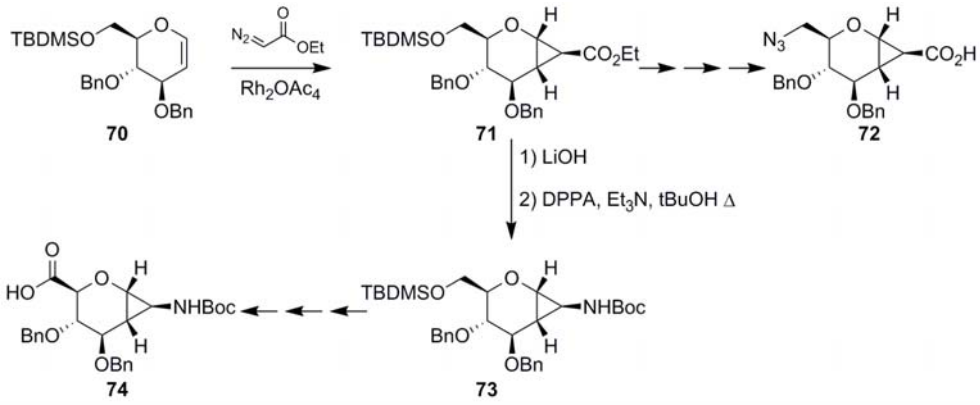

**Chapter 4** deals with the synthesis of pyranopyran SAAs (Scheme 10). The syntheses employed a single alkynyl glucoside (**62**) that was transformed into four different bicyclic SAAs. Some of the transformations used in the synthetic route deserve special attention including a cobalt complex mediated isomerization of acetylenic species **62** and a Petasis/RCM based strategy towards the generation of the second cycle of the pyranopyran yielding intermediates **64** and **66** respectively. One of the thus formed SAAs (**69**) was applied in the synthesis of a heterotetrameric chain.

**Scheme 10**. Overview of the chemistry described in chapter 4.



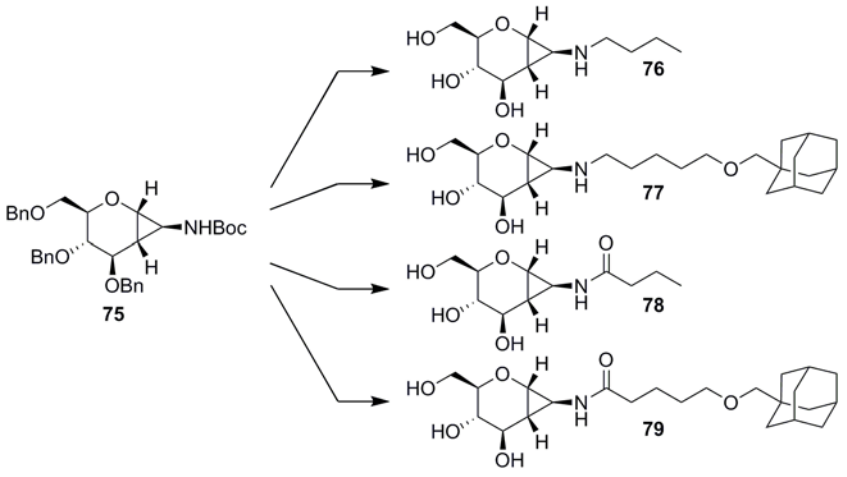
The synthesis of a more rigid and smaller bicyclic SAA is revealed in **Chapter 5**. Amongst others, a rhodium acetate catalyzed stereoselective cyclopropanation of a glycal (**70** → **71**) was used. Two highly rigid SAA's were oligomerized into two homotetramers.

**Scheme 11**. Synthesis of cyclopropanopyran SAAs described in chapter 5.



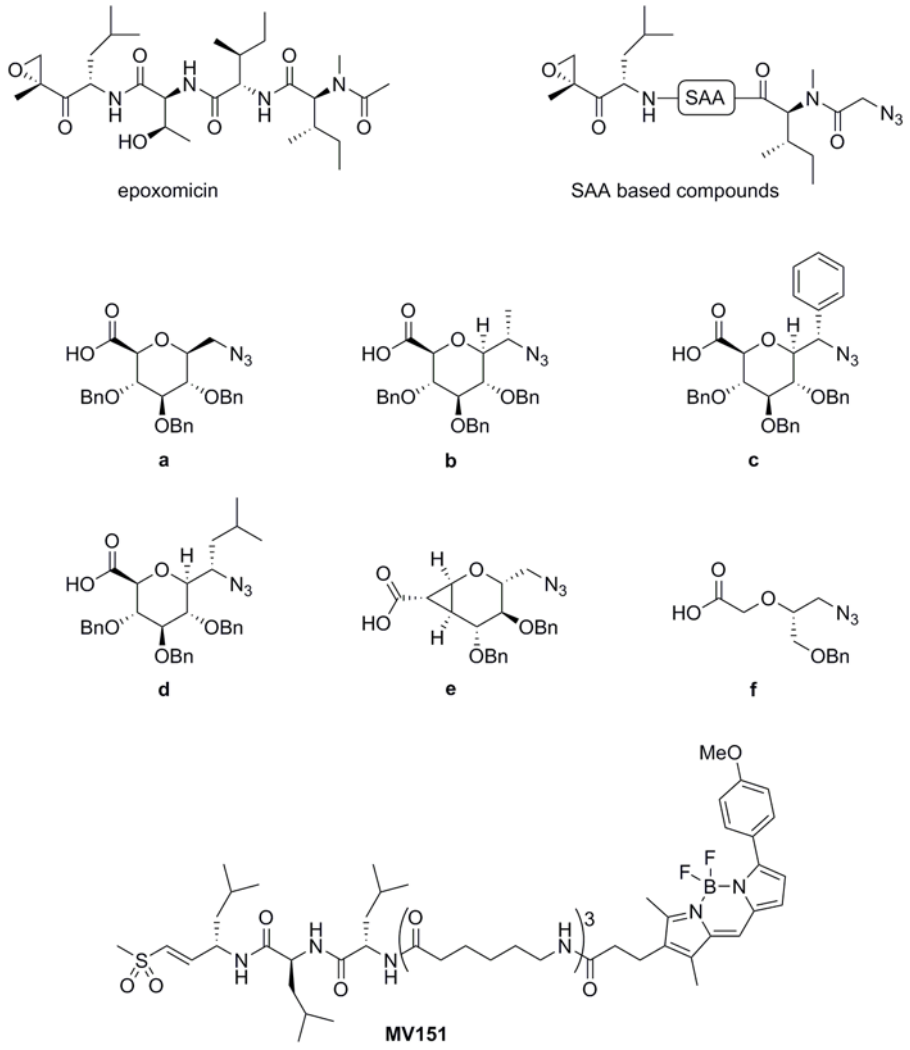

**Chapter 6** describes the application of the bicyclic core developed in chapter 5 to synthesize a small collection of aminoglycosides (**76**-**79**) that were tested for their inhibitory activity against a small panel of human lysosomal and non-lysosomal α- and β-glucosidases including ceramidase. The choice of alkyl and acyl chains was based on earlier published results on the inhibition of these enzymes.[40]

**Scheme 12**. Cyclopropanopyranylamines and amides to be evaluated as ceramidase inhibitors.



**Chapter 7** deals with the application of several SAAs described in this thesis as building blocks for potential proteasome inhibitors. A series of nine compounds was prepared and all are tested in a competition study with the known fluorescent proteasome inhibitor MV151.[41]

**Figure 5.** Overview of the SAAs applied in the synthesis of the epoxomicin analogs.




**Chapter 8** summarizes the work described in this thesis. Furthermore, general conclusions are given and future prospects are described.

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