Alkylated and bicyclic sugar amino acids : synthesis and applications

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8 Summary and Future Prospects

General summary

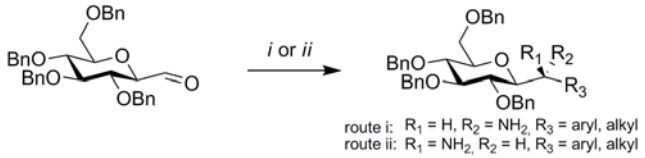
Sugar amino acids (SAAs), carbohydrate derivatives functionalized with an amine and a carboxylate, are the central class of molecules in this thesis. More specifically, this thesis encompasses different strategies aimed at the stereoselective synthesis of alkylated and bicyclic SAAs. The second part[1] of the thesis describes the application in a biological context of some of the SAAs and SAA core structures that are described in the first part.[2]

Chapter 1 describes the rationale behind the application of sugar amino acids from a stability (from a physiological point of view) and a structural (with respect to conformational influence on oligopeptide structures) perspective. An overview of a wide variety of structures applied as dipeptide isosteres is provided. Examples include linear dipeptide isosteres and peptide isosters developed around a cyclic core including carbacycles and heterocycles. A class of isosteres of the latter type that is described in detail are the SAAs. Several interesting examples of SAAs and their syntheses are described from a perspective focused on structure. Alkylated and byciclic SAAs are identified as targets of special interest.

A compendium of a large number of SAAs published to date is provided in **Chapter 2**. The structures, oxacycles only, are classified by ring size (3, 4, 5 or 6), the number of chemical bonds between the carboxylate and the amine (α, β, γ, δ, etc.) and the number of rings that constitute the central core (monocycle, bicycle).

The stereoselective introduction of peptide sidechains on pyranoid SAAs is the focus of **Chapter 3**. Two different strategies towards these alkylated species are evaluated (Scheme 1). The first involves the application of chiral nonracemic *tert*-butylsulfinamides, which provides, regardless of the stereochemistry of the sulfinamide, a product with *R* stereochemistry at the newly formed chiral centre. The second strategy, based on the direct addition of Grignard reagents onto the glucosyl aldehyde followed by Mitsunobu introduction of an azide with inversion, yields products with *S* stereochemistry. The latter strategy is applied in the synthesis of four SAAs having alanine (methyl), valine (isopropyl), leucine (isobutyl) and phenylglycine (phenyl) sidechains.

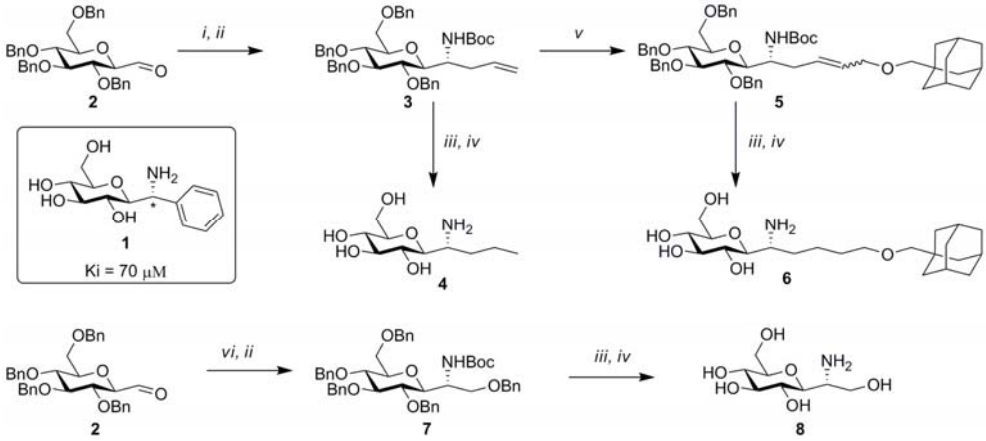
Scheme 1. Two stereoselective aminoalkylation strategies leading towards opposite stereochemistry.



Reagents and conditions: [**i**] (a) *R-tert*-butanesulfinamide, CH_2Cl_2, $Ti(OiPr)_4$ (b) RMgBr, Toluene (c) HCl, MeOH [**ii**] (a) RMgX, THF (b) HN_3, DEAD, PPh_3, toluene (c) PMe_3, dioxane, water.

An interesting application of the chemistry described in chapter 3 is presented in Scheme 2. In 1991, the group of Schmidt identified compound **1** as a micromolar inhibitor of β-glucosidase.[3,4] Interestingly, the epimer of compound **1** (at *) was found to be approximately a hundredfold less potent.

Scheme 2. Synthesis of possible β-glucosidase inhibitors **4**, **6** and **8**.



Reagents and conditions: [**i**] (a) *R-tert*-butanesulfinamide, CH_2Cl_2, $Ti(OiPr)_4$ (b) AllylMgBr, toluene (c) HCl, MeOH [**ii**] Boc_2O, CH_2Cl_2, DIPEA [**iii**] H_2, Pd/C, MeOH [**iv**] TFA [**v**] Grubbs' cat. II, (adamant-1-yl)methoxyprop-1-ene, CH_2Cl_2 [**vi**] (a) *R-tert*-butanesulfinamide, CH_2Cl_2, $Ti(OiPr)_4$ (b) $BnOCH_2MgBr$, toluene (c) HCl, MeOH.

Based on this information some interesting derivatives can be imagined which can be synthesized according to Scheme 2. Aldehyde **2** can be transformed into its corresponding *R*-sulfinamide and treated with allylmagnesium bromide. Cleavage of the auxiliary, followed by Boc protection of the free amine should yield intermediate **3**. Having this intermediate in hand, two options may be investigated. The first includes direct catalytic hydrogenation of compound **3** followed by TFA mediated removal of the Boc group. This is expected to lead to compound **4**, the *n*-propyl congener of compound **1** closely resembling the known inhibitor Zavesca.[5]

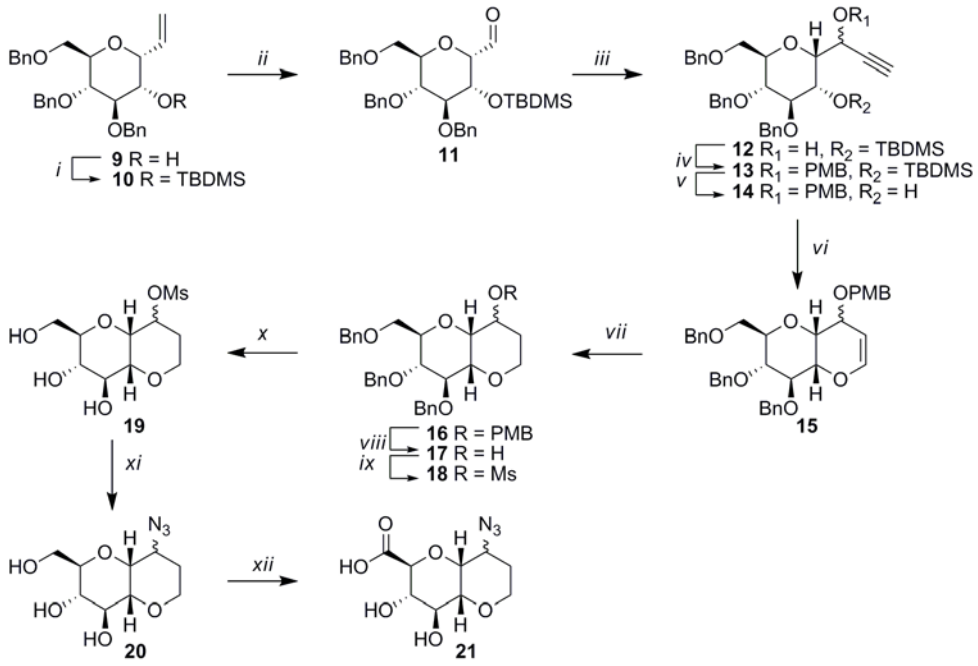
Alternatively, compound **3** can be subjected to cross metathesis with (adamant-1-yl)methoxyprop-1-ene. Catalytic reduction and TFA treatment should yield compound **6**, which is an analog of the known inhibitor *N*-(adamant-1-yl) methyloxypentyl-1-deoxynojirimycin.[6] According to similar conditions as descrived above, compound **8**, an analog of the known drug Miglitol,[7] might be generated. Another interesting possibility for the tuning of structures **4**, **6** and **8** is the introduction of functionalities at the free amine as described in chapter 6.

The synthesis of four isomeric pyranopyran ε-sugar amino acids is described in **Chapter 4**. A cobalt mediated acidic epimerization allows for the generation of both the cis- and trans fused pyranopyran system. A synthetic route involving, among others, a Petasis reaction, ring-closing metathesis and a TEMPO mediated oxidation provided the SAAs. One of the four SAAs generated is demonstrated to be suitable for solid phase peptide chemistry by the synthesis of a heterotetrameric peptide.

One of the drawbacks of the four synthesized SAAs presented in chapter 4 is that they are no true dipeptide isosters (δ-SAAs). In Scheme 3, a possible synthesis of the the δ-congener of the SAAs in chapter 4 is described.

Known vinylglucoside **9**[8] is projected to be protected as a silyl ether. Ozonolysis of the olefin followed by addition of sodium acetylide to the thus formed aldehyde should yield intermediate **12**. Protection of the free hydroxyl as the *p*-methoxybenzyl ether followed by desilylation, is expected to yield intermediate **14** which may be a suitable substrate for cyclization towards enolether under the influence of $W(CO)_6$ and light.[9] Platinum mediated hydrogenation normally reduces the enol ether to an ether while leaving all the benzylic protecting groups intact. Compound **19** may be obtained by selective removal of the *p*-methoxybenzyl group, mesylation and palladium mediated catalytic reduction. Substitution of the mesylate with sodium azide and TEMPO mediated oxidation would give SAA **21**. The configuration at the δ-position can be *R*, *S* or a mixture of the two. Based on the findings described in chapter 4, separation of the epimers should occur as early on in the synthesis as possible.

Scheme 3. Synthesis of pyranopyran δ-SAA **21**.



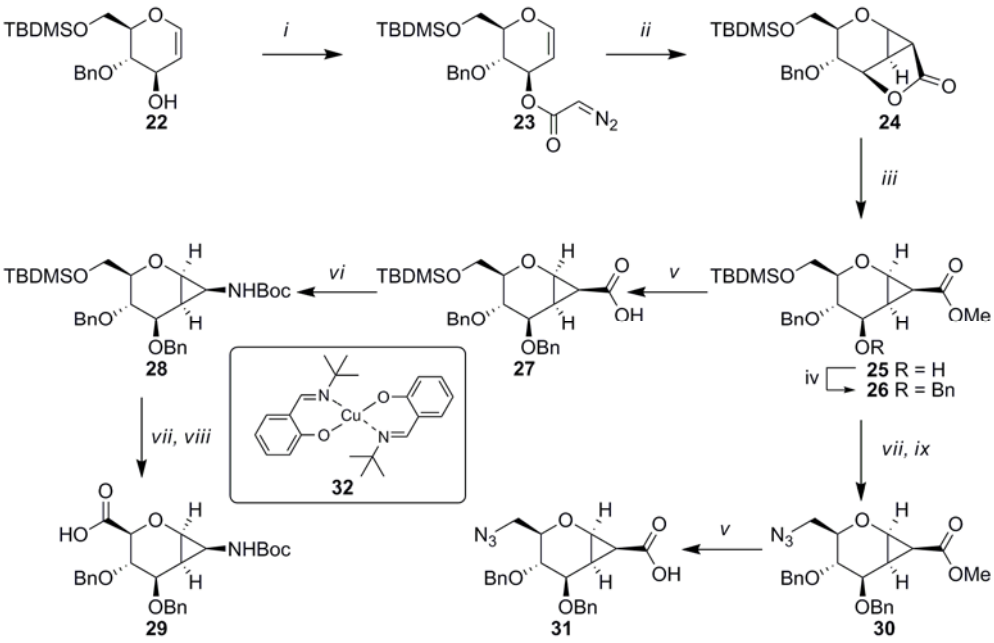
Reagents and conditions: [**i**] TBDMSCl, imidazole, pyridine [**ii**] O_3, CH_2Cl_2, MeOH, Me_2S, -78°C [**iii**] sodium acetylide, THF, 0°C [**iv**] PMBCl, NaH, DMF [**v**] TBAF, THF [**vi**] $W(CO)_6$, DABCO, THF, *hv* [**vii**] Pt/C, H_2, MeOH [**viii**] CAN, CH_2Cl_2, water [**ix**] MsCl, CH_2Cl_2, triethylamine [**x**] Pd/C, H_2, MeOH [**xi**] NaN_3, 15-crown-5, DMF, Δ [**xii**] TEMPO, NaOCl, KBr, $NaHCO_3$, MeCN, water.

The synthesis of a new type of bicyclic SAAs, namely cyclopropanopyrans, is described in **Chapter 5**. A suitably protected glucal is cyclopropanated with ethyl diazoacetate under the influence of Rh_2OAc_4. From one key intermediate two sugar amino acids were synthesized. A δ-SAA is synthesized using amongst others a Curtius rearrangement[10] and a Jones oxidation.[11] An ε-SAA was obtained via more direct route employing a Mitsunobu introduction of an azide functionality. Both SAAs are tertamerized in solution demonstrating their applicability in peptide chemistry.

The SAAs outlined in chapter 5 have little or no turn inducing configurations. An adaptation of the syntheses described in chapter 5 that would provide SAAs that have strong turn inducing behavior is depicted in Scheme 4. Glucal **22** is diazoacetylated using the chloride of glycolic acid tosylhydrazone. Under the influence of catalyst **32**, an intramolecular cyclopropanation is carried out yielding lactone **24**.[12] The intramolecular nature of the reaction only allows the formation of an endo-cis (with respect to the benzylether at C3) configuration. Opening of the lactone under Zemplén[13] conditions and benzylation of the free hydroxyl could provide

cyclopropanopyran **26**. A four step reaction sequence involving a Curtius rearrangement and a Jones oxidation is expected to provide δ-SAA **29**. A shorter three step sequence should lead to SAA **31**.

Scheme 4. Synthesis of pyranopyran δ-SAA **21**.



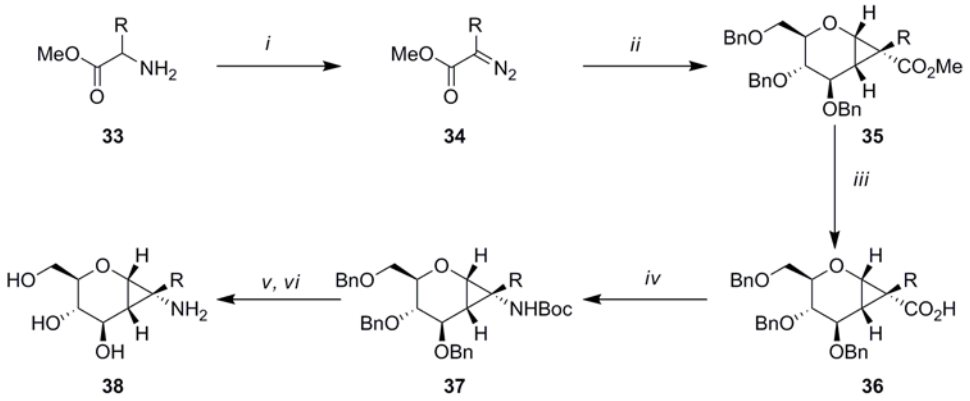
Reagents and conditions: [**i**] first ClCOCH=NHNHTs, Me_2NPh, CH_2Cl_2, DMF then Et_3N [**ii**] **32**, toluene, Δ [**iii**] NaOMe, MeOH [**iv**] BnBr, NaH, DMF [**v**] LiOH, MeOH, dioxane, water [**vi**] DPPA, Et_3N, tBuOH, molecular sieves, Δ [**vii**] TBAF, THF [**viii**] H_2CrO_4, acetone, water [**ix**] HN_3, DEAD, PPh_3, toluene.

The core structure presented in chapter 5 is employed for the development of a potential glycosidase inhibitor as described in **Chapter 6**. A protected cyclopropanopyranylamine was synthesized via a rhodium acetate mediated cyclopropanation of tri-*O*-benzyl-glucal, saponification of the ester moiety and concomitant Curtius rearrangement. This amine was alkylated or acylated leading to five compounds that were evaluated on their inhibitory activity of GBA1, GBA2 and lysosomal α-glycosidase.

The introduction of an additional alkyl chain onto the cyclopropane might be an interesting expansion of the compounds described in chapter 6. Diazo esters can easily be generated from esters of common α-amino acids.[14] Application of these diazoesters in the cyclopropanation of tri-O-benzyl-glucal is expected to predominantly lead to cyclopropanopyrans with the stereochemistry as depicted in compound **35** (Scheme 5). The size of the sidechain of the diazo ester can have a profound effect on the selectivity

of the cyclopropanation since the bulkiest substituent is expected to adapt the *exo*-orientation in the product. Saponification of the ester moiety, Curtius rearrangement and deprotection should lead to compounds of general structure **38**.

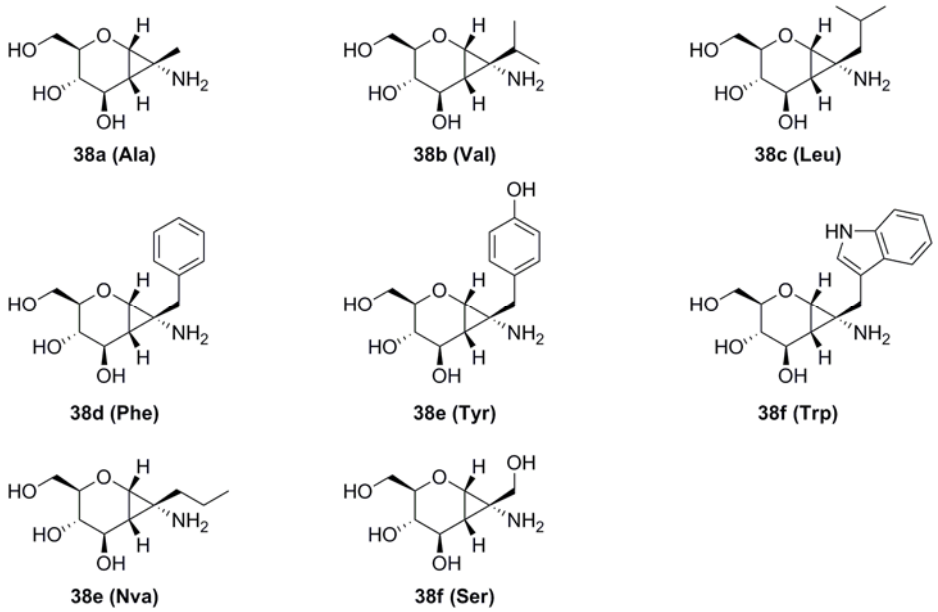
Scheme 5. Synthesis of C-alkylated cyclopropanopyranylamines.



Reagents and conditions: [**i**] HOAc, isoamylnitrite, $CHCl_3$ [**ii**] Rh_2OAc_2, 3,4,6-tri-O-benzylglucal, CH_2Cl_2 [**iii**] LiOH, dioxane, methanol, water [**iv**] DPPA, TEA, tBuOH, molecular sieves, Δ [**v**] Pd/C, H_2, MeOH [**vi**] TFA, CH_2Cl_2.

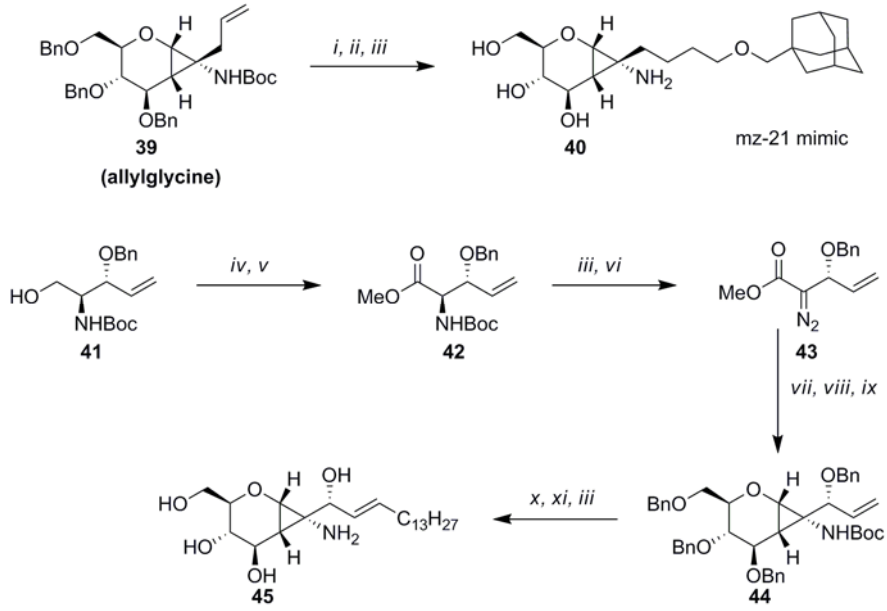
Some potentially interesting examples for R are given in Figure 1 below. For each of the compounds, the amino acid used to generate the diazoester is given in parentheses.

Figure 1. Some potentially interesting C-alkylated cyclopropanopyranylamines.



Two additional potentially interesting alkylated cyclopropanopyran compounds are depicted in Scheme 6. Compound **40** should be accessible from compound **39** according to a three step protocol involving a cross-metathesis reaction. The alkyl chain of compound **45** mimics sphingosine and might be generated from known pentenol **41**. Oxidation of the carbinol and concomitant methylation of the carboxylate is expected to yield amino ester **42**. Formation of intermediate **44** could be possible via the formation of the diazoester and cyclopropanation under the conditions described above. The synthesis would be completed through a three step protocol (cross metathesis, Birch reduction and TFA treatment) yielding compound **45**.

Scheme 6. Two special cases of *C*-alkylated cyclopropanopyranylamines.



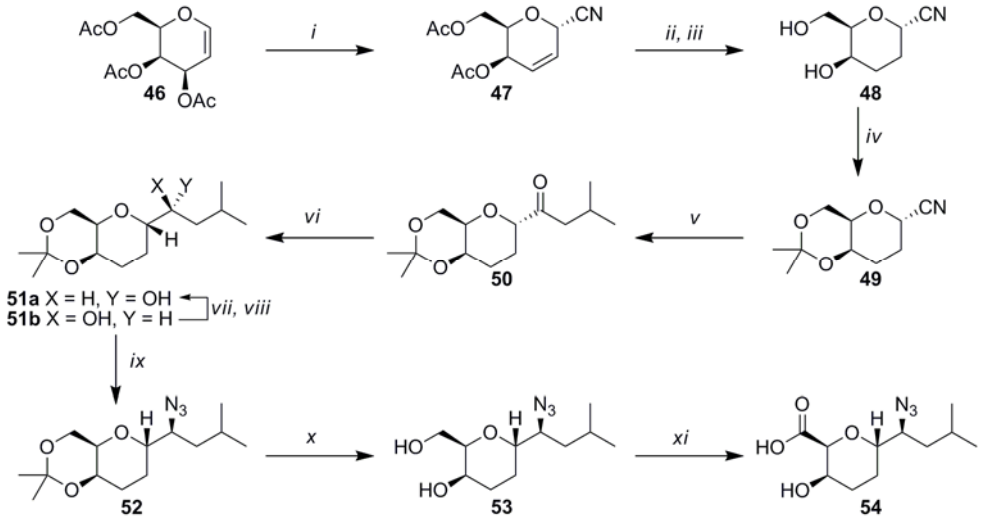
Reagents and conditions: [**i**] Grubbs' cat. II, (adamant-1-yl)methoxyprop-1-ene, CH_2Cl_2 [**ii**] Pd/C, H_2, MeOH [**iii**] TFA [**iv**] TEMPO, BAIB, CH_2Cl_2, water [**v**] TMS-CH_2N_2, toluene, methanol [**vi**] HOAc, isoamylnitrite, $CHCl_3$ [**vii**] Rh_2OAc_2, 3,4,6-tri-*O*-benzylglucal, CH_2Cl_2 [**viii**] LiOH, dioxane [**ix**] DPPA, TEA, *t*-BuOH, molecular sieves, Δ [**x**] Grubbs' cat. II, pentadec-1-ene, CH_2Cl_2 [**xi**] Na, NH_3, -50°C.

Chapter 7 describes the application of several of the SAAs presented in earlier chapters this thesis as building blocks in the synthesis of a panel of nine, epoxomicin[15] based, potential proteasome inhibitors. Competition experiments with known proteasome inhibitor MV-151[16] however revealed little to no inhibitory activity for any of the compounds synthesized.

An interesting sugar amino acid that could be introduced in the epoxomicin sequence is described below. The synthesis commences with the known Ferrier rearrangement of

tri-*O*-acetyl-D-galactal **46** yielding dihydropyran **47**.[17] Deacetylation under acidic conditions followed by careful hydrogenation should yield compound **48**. Protection of the 1,3-diol with an acetonide followed by a Grignard reaction onto the nitrile is expected to yield ketone **50**. Azide **52** would be accessible by reduction of the ketone, followed by a Mitsunobu introduction of the azide. In the case of the formation of an undesired diastereoisomer of the secondary alcohol, epimerization can be carried out via the *p*-nitrobenzoate under Mitsunobu conditions. SAA **54** might be obtained after deprotection of the 1,3-diol followed by selective oxidation of the primary hydroxyl using TEMPO reagent.

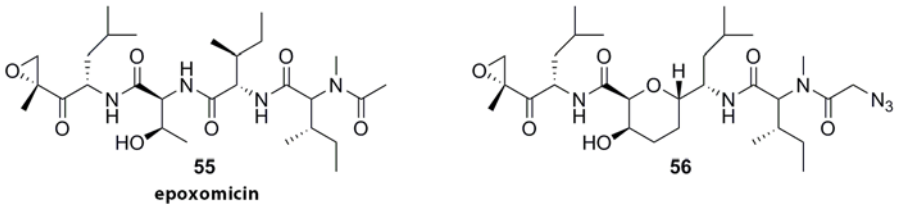
Scheme 7. Proposed synthesis of SAA **54**.



Reagents and conditions: [**i**] TMSCN, BF_3•OEt_2, $ClCH_2CH_2Cl$ [**ii**] MeOH, Amberlite IR120 H^+, Δ. [**iii**] Pd/C, H_2, MeOH [**iv**] dimethoxypropane, CSA, acetone [**v**] First, iBuMgBr, Et_2O, Δ then sat. aq. NH_4Cl [**vi**] $NaBH_4$, MeOH [**vii**] *p*-nitrobenzoic acid, PPh_3, DEAD, toluene [**viii**] NaOMe, MeOH [**ix**] HN_3, PPh_3, DEAD, toluene [**x**] CSA, CH_2Cl_2, water [**xi**] TEMPO, BAIB, CH_2Cl_2, water.

Attachment of both the warhead and the azido tail according to the methods described in chapter 7 would give epoxomicin analog **56** (Figure 2).

Figure 2. Epoxomicin and epoxomicin analog **56**.



References

(1) Chapters 6 and 7.

(2) Chapters 3, 4 and 5.

(3) Schmidt, R. R.; Dietrich, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1328-1329.

(4) The β-glucosidase applied to evaluate the inhibitory activity of compound **1** was cellobiase from sweet almonds.

(5) Registered trademark of Actelion Pharmaceuticals. Synonyms include *N*-butyl-deoxynorjirimycin and Miglustat.

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(7) Miglitol is also known as *N*-(2-hydroxyethyl)-deoxynorjirimycin.

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