Towards complex sugar mimetics: the design, synthesis, and properties

1. Research Project Objectives *(scientific problem aimed to be solved by the proposed project, project's research hypotheses)*

The main goal of this project is to develop a general and convenient route to sugar mimics from simple monosaccharides and to check the structure/activity relationship (SAR)

We plan to elaborate a general methodology, which allows for a stereocontrolled preparation of ***different*** types of sugar mimetics: iminosugars and carbasugars from simple monosaccharides. Iminosugars are inhibitors of glycosidases and have potent activity; several such derivatives have found an application in a clinical treatment. Although the methodology of the preparation of sugar mimetics from sugars is well documented, we will explore new approaches and will give new insights into the subject, by establishing non-expensive routes from environmental friendly starting materials, namely hexoses and pentoses. The general concept of our project is shown in **Figure 1**.

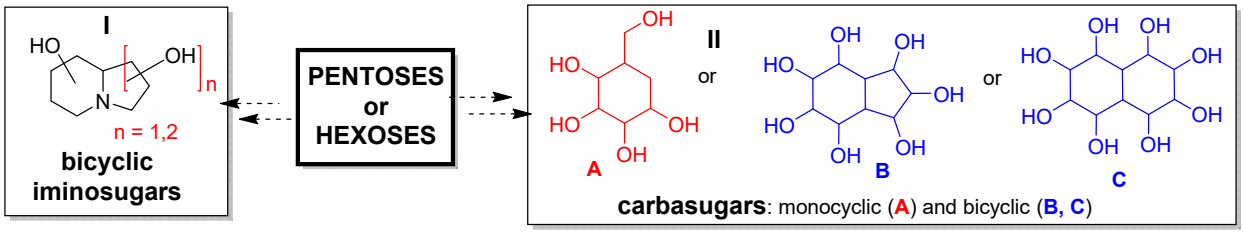


Figure 1. Simple monosaccharides in the synthesis of different types of sugar mimetics

The efforts will be put on the stereoselective preparation of imino sugars (**I** in **Fig. 1**). We have already proposed several useful routes, alternative to the previously described, which allow preparing different imino sugars either 'natural' *i.e.* existing in Nature or 'unnatural'. According to our methodology, a number of stereoisomeric 'natural' and 'unnatural' alkaloids can be prepared.

The synthesis will be oriented on such mimetics, which are capable to inhibit the enzymes. The potential enzymatic activity of the synthesized molecules can be examined using scoring and similarity functions by comparing molecular level properties of biomimetics with either already known effective inhibitors or saccharides. A range of properties can be obtained by using a straightforward Density Functional Theory (DFT) calculations, whereas an insight into interaction with actual glucosidases can be obtained by using classical molecular dynamics. This problem will be discussed in the next chapter.

Carbasugars having similar to iminosugars bioactivity, are usually monocyclic (*vide* **IIA**, **Fig. 1**); bi-cyclic analogs (**IIB** and **IIC**; **Fig. 1**) are less known. However, these derivatives may-be regarded as 'normal' carba-sugars with the rigid structure. This fact may have a significant impact on their biological activity. For example, to fit into the enzyme pocket, the sugar (iminosugar, carbasugar) should adopt not favored conformation **D** (**Fig. 2**). The preferred conformation, however, is just '*opposite*' (**E**, **Fig. 2**), but the required one can be fixed in a specifically designed bicyclic carbasugar skeleton (**F**, **Fig .2**). Thus, we plan the synthesis of various bicyclic derivatives differing in the configuration and the size of the rings (**G**, in **Fig. 2**).

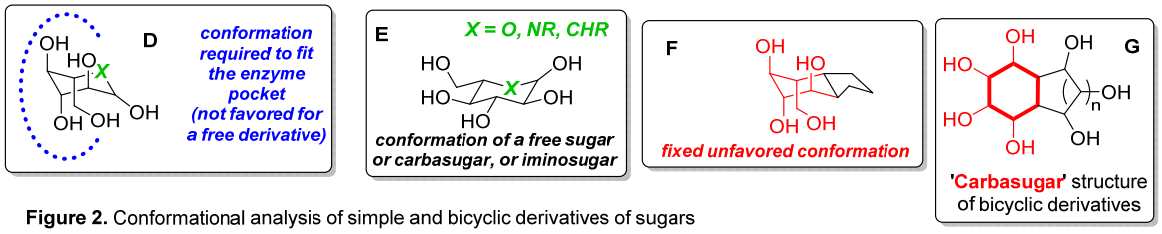


Figure 2. Conformational analysis of simple and bicyclic derivatives of sugars

We have proposed a general, useful methodology for the preparation of bicyclic carbasugars (**II**) from sugar allyltins (see next chapter). We plan now to exclude toxic organostannanes and to apply another tin-free

methodology leading to specific bicyclic carbasugars, structure of which will be selected based on the theoretical calculations.

2. Significance of the project *(state of the art, justification for tackling specific scientific problems by the proposed project, pioneering nature of the project, the impact of the project results on the development of the research field and scientific discipline).*

The targets proposed in this project belong to the class of compounds regarded as glycomimetics. Such derivatives are recognized by appropriate enzymes but, since they are not metabolized, they block their active center(s).[1] The most known group of sugar mimetics – possessing potent biological activity – are undoubtedly iminosugars, *i.e.* compounds closely related to sugars, with the endocyclic oxygen atom replaced by a nitrogen atom.[2,3] Representatives of this class: miglitol and miglustat have found an application in a clinical use; they are active forms of medicinal drugs: Glyset™ and Zavesca™. Both representatives are analogs of deoxynojirimycin (DNJ), probably the most recognized imino sugar (**Fig. 3**).

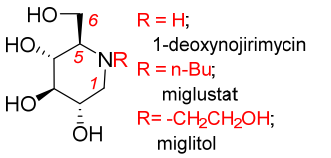


Figure 3. Examples of iminosugars

When the oxygen atom in the sugar ring is replaced with the CH_2 group (or other substituted carbon moiety), another class of compounds – carbasugars – is obtained (**Fig. 4**).[4] The representative derivatives from this group also possess interesting biological activities similar to imino sugars.

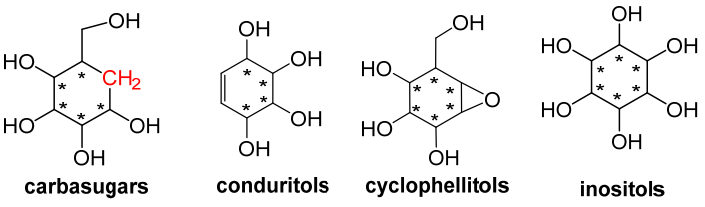


Figure 4. Carbocyclic polyhydroxylated derivatives with strong biological activity

Other compounds closely related to sugars, with the fully carbocyclic structure, represent the family of conduritol,[5] cyclophellitol,[6] and inositol[7] (**Fig. 4**); all of them possess significant biological activity.

The synthesis of such mono-carbocyclic derivatives is quite well explored; however, the carbo-bicyclic analogs are less known. They strongly resemble natural inhibitors of glycosidases[8] (**Fig. 5**); no wonder, therefore, that some of these compounds disclose interesting biological activity. They are, at the same time, the analogs of bicyclic imino sugars and the analogs of 'normal' (*i.e.* monocyclic) carbasugars with rigid structure.

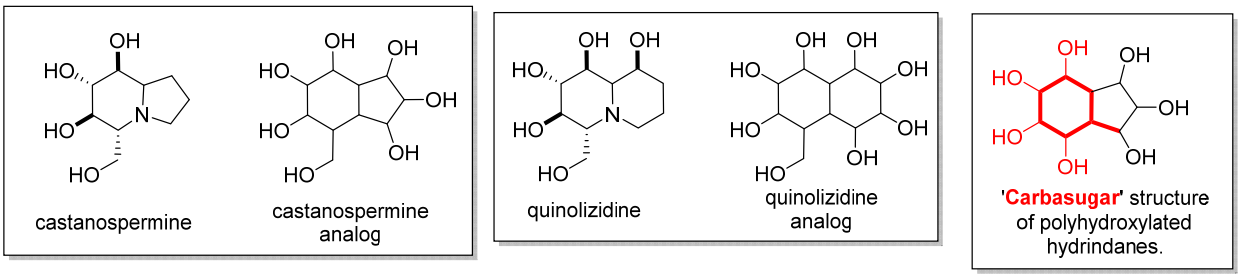
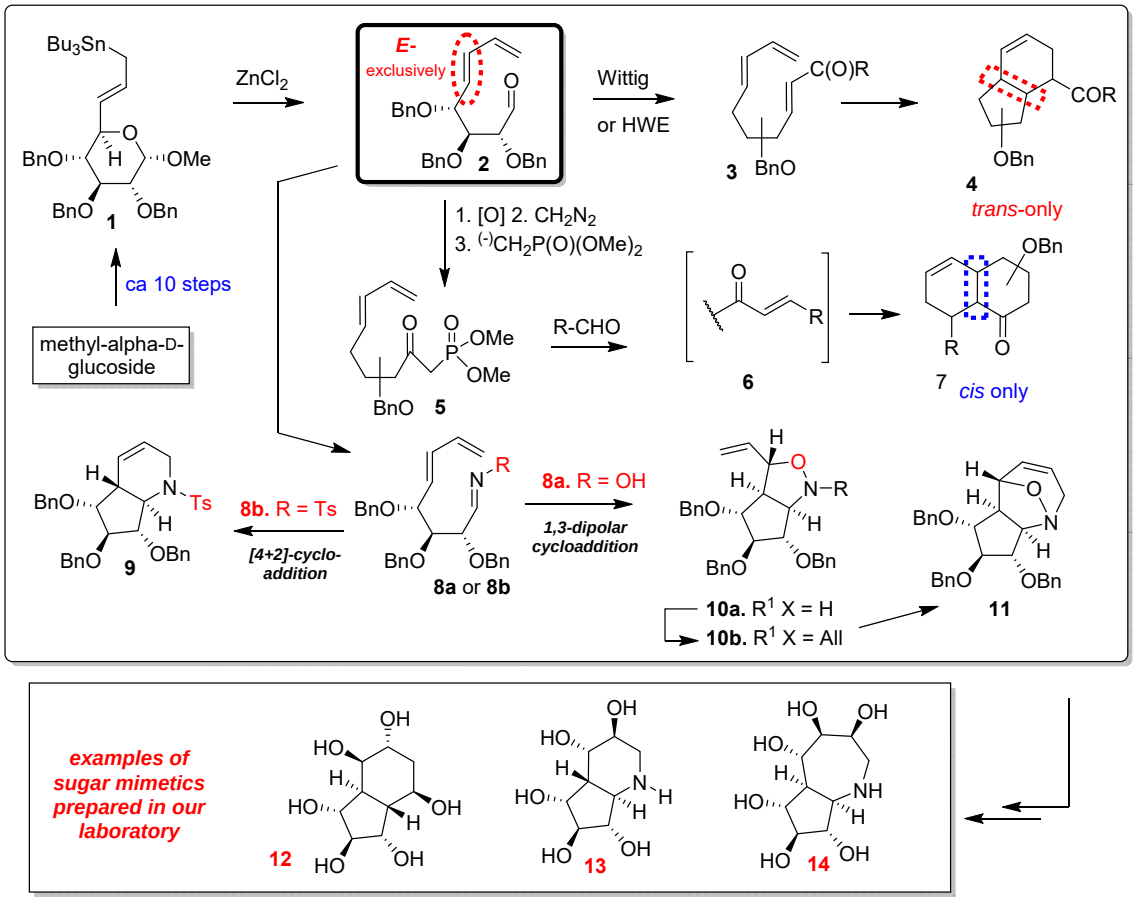


Figure 5. The similarity of the polyhydroxylated carbobicyclic derivatives to bicyclic iminosugars.

We have elaborated a convenient route to polyhydroxylated, carbobicyclic derivatives,[9] as well as rare imino-sugars,[10] from sugar allyltins. The methodology is exemplified by the transformations of D-glucose as shown in **Scheme 1**. Readily available methyl α-D-glucoside was converted into organometallic derivative **1**; this was the first synthesis of sugar allyltin compounds reported in the literature.[11] We found, that a controlled fragmentation of sugar allyltins induced with a mild Lewis acid (preferably $ZnCl_2$) provided the corresponding dienoaldehydes (*e.g.* **2**) with the *E*-configuration across the internal double bond, regardless of the geometry of starting allyltin.[12] These observations opened a convenient route to a variety of bicyclic derivatives, such as *e.g.* **12-14**.

Dienoaldehyde **2** was converted into triene **3** by reaction with the corresponding phosphorane (Wittig reaction) or phosphonate (HWE reaction). Cyclization of **3** – induced with a Lewis acid or high pressure – afforded

hydrindane skeleton **4** with the *trans*-ring junction, which resulted from the *endo*-transition state of the Diels-Alder cyclization. Selectivity of this [4+2] cycloaddition was dependent on the configuration of the starting dienoaldehyde (derived from D-glucose, D-mannose, or D-galactose).[9]



Scheme 1. Application of sugar allyltins in the preparation of sugar mimics: carbo- and hetero-cyclic derivatives

Alternatively, **2** was converted into phosphonate **5** which – by reaction with aldehydes – underwent a conversion into triene **6** and finally into decalin **7** with the *cis*-ring junction.[13]

Dienoaldehyde **2** served also as a convenient precursor of rare imino sugars. It was thus converted into an oxime (**8a**) which underwent – instead of the expected hetero Diels-Alder process – the 1,3-dipolar cycloadditon to **10a**. Allylation of the nitrogen atom (→ **10b**) followed by the *RCM* reaction afforded **11**, finally converted into iminosugar **14**.[10] On the other hand, reaction of **2** with tosyl amine afforded **8b**, which underwent the hetero Diels-Alder reaction providing the expected product **9**. Functionalization of all these intermediates yielded the polyhydroxylated bicyclic derivatives such as *e.g.* **12-14**. None of the prepared compounds showed any significant activity towards glycosidases.[9,10]

Our tin-methodology towards sugar mimetics presented in Scheme 1 has several disadvantages. First, it is not environmentally friendly; organic stannanes are toxic, thus application of them in pharmacy, even as starting materials, is not allowed. Second, the synthesis is long and tedious, which resulted mostly from a multistep conversion of starting glycosides into allyltin derivatives (such as **1**). Moreover, we are able to obtain only *trans*-decalin and *cis*-perhydroindane systems, which is a consequence of the stereochemistry of the intramolecular Diels-Alder reactions of intermediate trienes (**3** → **4-*trans*** and **6** → **7-*cis***).

Preparation of the alternative bicyclic derivatives: *trans*-decalins and *cis*-perhydroindanes required another solution(s). ***First***, most obvious possibility, lays in changing the geometry of the reacting molecules. The elaboration of the convenient procedure for the preparation of dienes with the *Z*-configuration across the internal

double bond is, therefore, needed. The access to such dienes would open a convenient route to bicyclic derivatives with different geometry at the ring junction (**Fig. 6**).

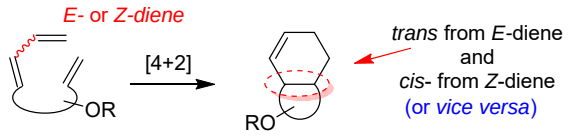
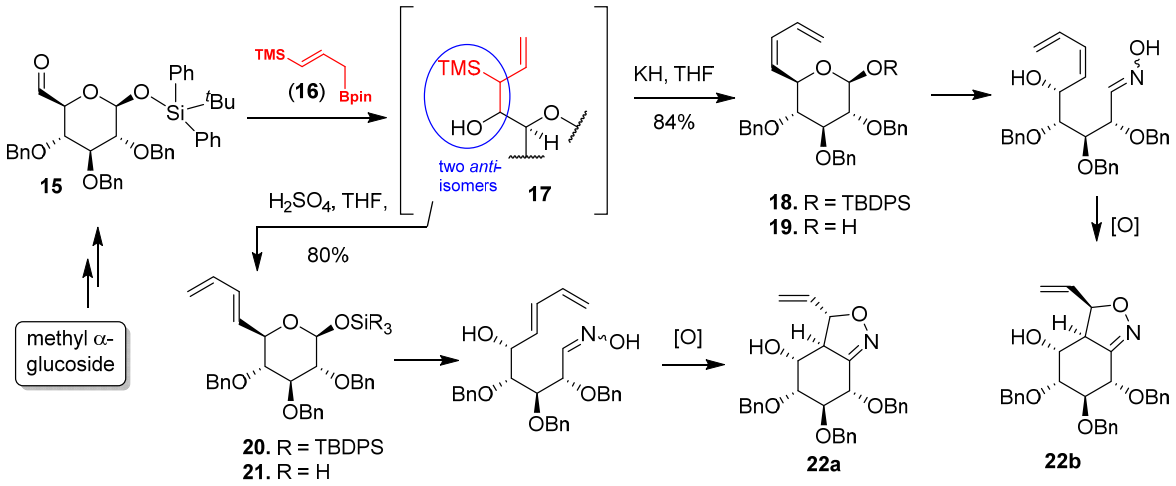


Figure 6. Synthesis of different steroisomers of bicyclic targets

Recently we have proposed a method allowing the preparation of the *Z*-dienes, which may-be used as precursors of the trienes shown in Fig. 6 (this aspect will be discussed in the section: **work plan**).

Moreover, this procedure excluded the use of toxic organostannanes and was applicable also for the selective preparation of the *E*-dienes as shown in **Scheme 2**.[14]

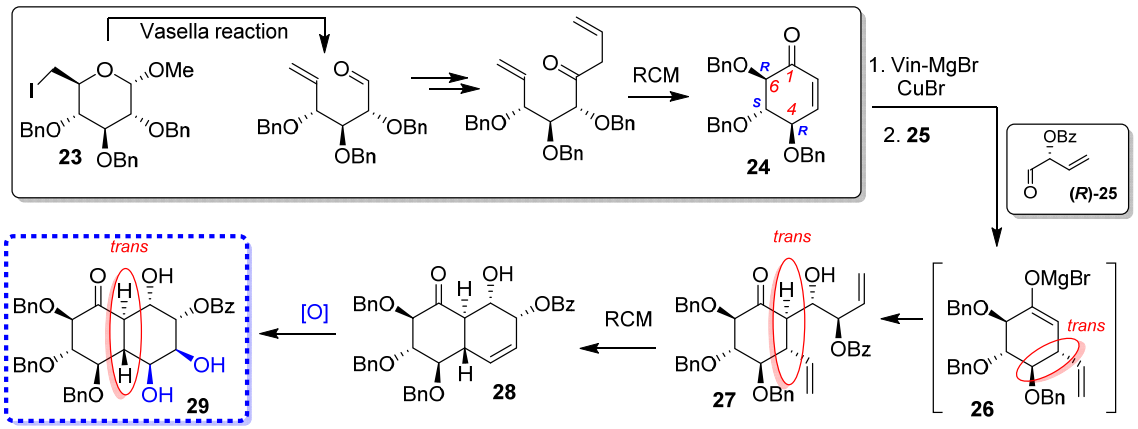


Scheme 2. Stereoselective preparation of sugar dienes from *the same* precursor and their futher conversion into isoxazolines

Methyl α-D-glucoside was converted in a few, well-defined steps into the protected derivative **15**. Its reaction with pinacol (*E*)-1-(trimethylsilyl)-1-propene-3-boronate (**16**) provided adduct **17** as a mixture of two isomers with the relative *anti*-configuration. Treatment of **17** with potassium hydride gave diene **18** with the *Z*-configuration across the internal double bond, while treatment with sulfuric acid furnished the *E*-diene **20**. Both isomers were deprotected at the anomeric center affording hemiacetals **19** and **21** respectively, which were converted into oxazolines **22a** and **22**b as shown in Scheme 2.[14]

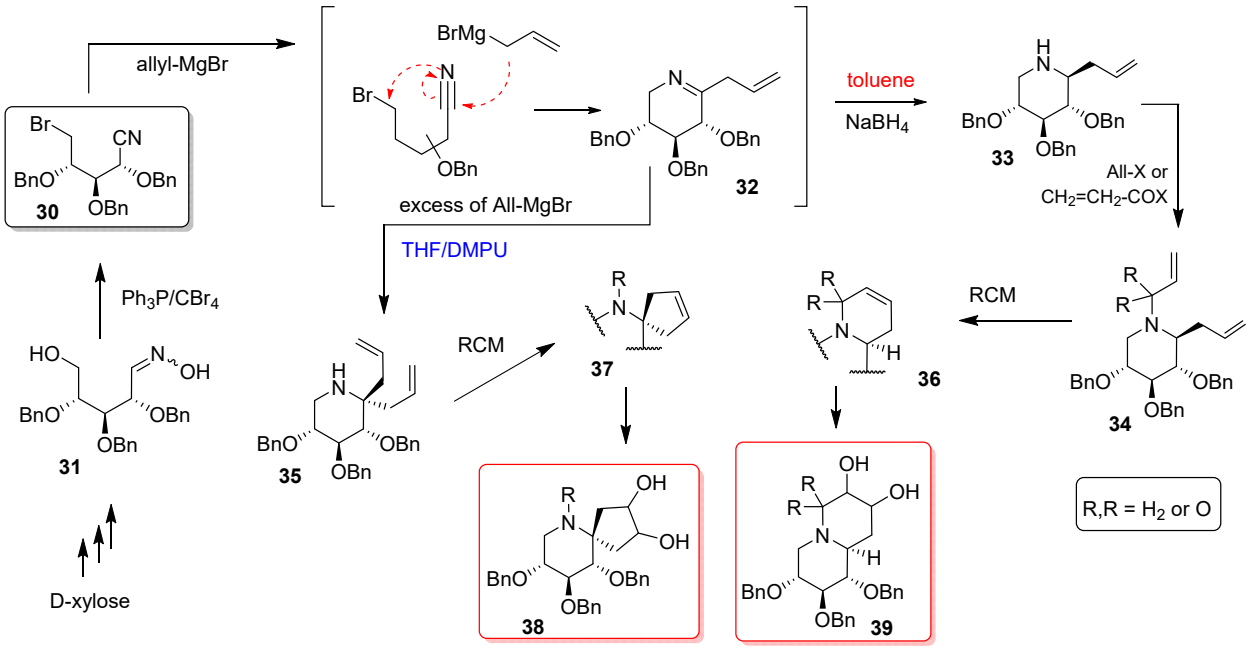
Second approach, quite different to the cyclization route proposed in Fig. 6, was based on a concept in which the *trans*-relation between the substituents was built ***before*** cyclization.[15] The synthesis of *trans*-decalins was initiated from cyclohexenone **24**, readily prepared from 6-iodoglucoside **23** according to the methodology shown in Scheme 3.

1,4-Addition of vinylmagnesium bromide to **24** afforded intermediate **26** which – upon treatment with unsaturated aldehyde **(*R*)-25** – provided adduct **27** with the *trans*-relation between both newly introduced substituents. The 6-membered ring was constructed in the *RCM* reaction; the resulting endocyclic olefin **28** was *cis*-dihydroxylated to afford the fully hydroxylated *trans*-decalin **29**.[15]



Scheme 3. Syntheis of highly oxygenated *trans*-decalins from D-glucose

We have proposed also a useful route to iminosugars excluding toxic organotin intermediates. The general idea, shown in **Scheme 4**, is based on a cascade addition of Grignard reagents to halonitriles and subsequent spontaneous cyclization.[16] Addition of allylmagnesium bromide to bromonitrile **30** – readily obtained from the corresponding oxime **31** – afforded cyclic intermediate **32**, which was reduced either to piperidine **33** or reacted with another equivalent of All-MgBr to **35**. The selectivity (mono *versus* double allylation) depended on the polarity of the solvent used. After introduction of the second unsaturated unit to **33**, the resulting derivative **34** was cyclized under the *RCM* conditions to afford bicyclic derivative **36**.

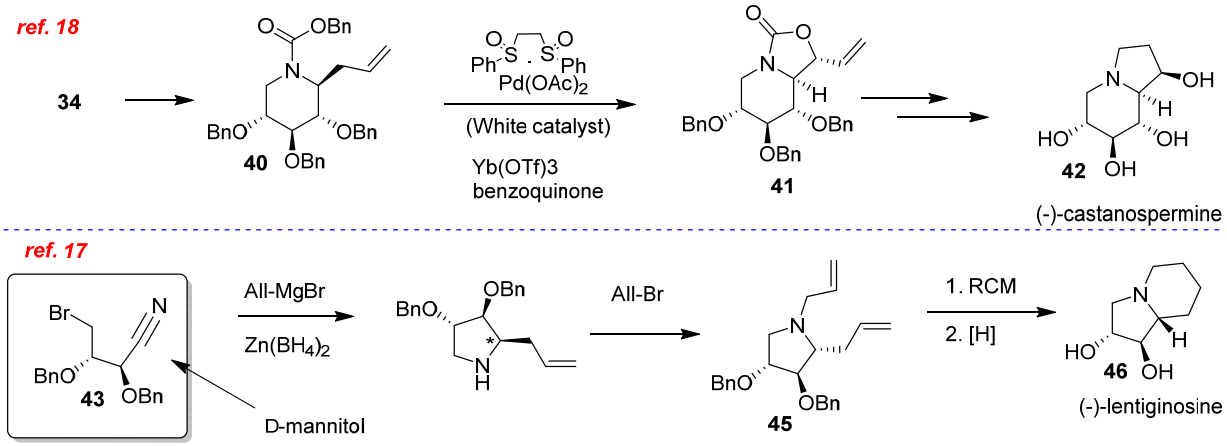


Scheme 4. Preparation of iminosugars from sugar-derived ω-bromonitriles (ref. 16)

Cyclization of **35** in the presence of the Grubbs' catalyst gave the spiro-derivative **37**. Compounds **36** and **37** were di-hydroxylated providing the corresponding iminosugars **38** and **39**.[16]

The methodology presented in **Scheme 4** was further extended to several other sugar-derived ω–bromonitriles.[17] The intermediates obtained in these transformations were used to prepare selected imino sugars: unnatural (-)-castanospermine (**42**) from **34**[18] and (-)-lentiginosine (**46**) from bromonitrile **47**[17] (**Scheme 5**).

The advantage of this methodology lays in the fact that the sugar-derived bromonitriles are readily available from different monosaccharides. It means that the starting materials with various length (C4-C7) and different configurations can be prepared as desired.



Scheme 5. Synthesis of alkaloids from strating materials prepared according to the cascade methodology

3. Work plan *(outline of the work plan, critical paths, state of preliminary and initial research indicating feasibility of research objectives)*

As shown in **point 2: significance of the project**, we have quite good experience in the preparation of various polyhydroxylated bicyclic derivatives: imino- or carbasugars. To some extent, we are also able to play with the configuration (*trans* or *cis*) at the ring junction in such compounds. However, more basic research should be performed in order to elaborate a general methodology which would allow preparinge the desired, biologically active compound(s).

Second point is that our synthetic efforts should be directed to such derivatives, which are supposed to have biological activity. Since iminosugars and carbasugars are active inhibitors of glycosidases, and several of them are already used in pharmacy, one can expect also the activity of compounds prepared within this project. This is, however, difficult problem. It is know, that even small difference in the structure of the molecule may change completely the biological properties. The other, also important aspect, results from the toxicity of such molecules; many iminosugars are highly toxic.[19]

The structure of biologically active mimetics may-be proposed based on *in silico* study (see ***3-I***)

The most important part of the project will be the synthesis of sugar mimetics. We will elaborate the general route(s) which should allow preparing the targets with the structure predicted (proposed) from the *in silico* study.

The properties of the synthesized derivatives will be verified – in an external service – on selected enzymes and eventually cell lines in specialized institutions such as Institute of Biochemistry and Biophysics, PAS (IBB, PAS), and the National Institute of Public Health - National Institute of Hygiene (NIPH-NIH). The results obtained will help to find out the structure activity relationship (SAR).

The work plan of this project will be, therefore, divided into two main parts: 1) the *in silico* study to predict and propose the structures of potentially active mimetics and 2) elaboration of the general route(s) to sugar mimetics and the synthesis of the predicted by *in silico* study derivatives.

3-I. The* in-silico *study towards sugar mimetics

By inhibiting the glycoside hydrolase enzyme action (α-glucosidases), the complex carbohydrates are not metabolized into simple monosaccharides (*e.g.*, glucose). The inhibiting effect of glycomimetic molecules depends on the degree of similarity to reagents and products of glucosidases. We propose to rank synthesized inhibitors based on their similarity to molecularly similar glucoside inhibitors that are already in commercial use. We will consider a range of molecular level properties to derive the similarity and scoring functions including solvation energies, polarizabilities, hydrophobicity and charge distribution obtained on a Density Functional Theory level. Our approach follow the principle of the structure-activity relationship (SAR) - similar molecules should exhibit similar activity, here α-glucosidases inhibition.

In the first step, we will calibrate the similarity function by considering monosacharides - products of glucosidase action - with inhibitors of proven efficacy (*e.g.*, swainsonine, castanospermine). In the second step, we will rank the synthesized biomimetics by their similarity to the monosaccharides and pharmacologically effective inhibitors used in the calibration step.

Finally, the interactions between the few top-ranked sugar mimetics, with a range of glycoside hydrolase enzymes, will be examined using molecular dynamics simulations. In **Fig. 7**, an example of molecular dynamics simulations from a preliminary study in our team of an important human glycosidase[20] (one of enzymes that will be used in our inhibitor ranking procedure) is shown.

An actual enzymatic efficiency of the theoretically most promising biomimetics will be further tested experimentally.

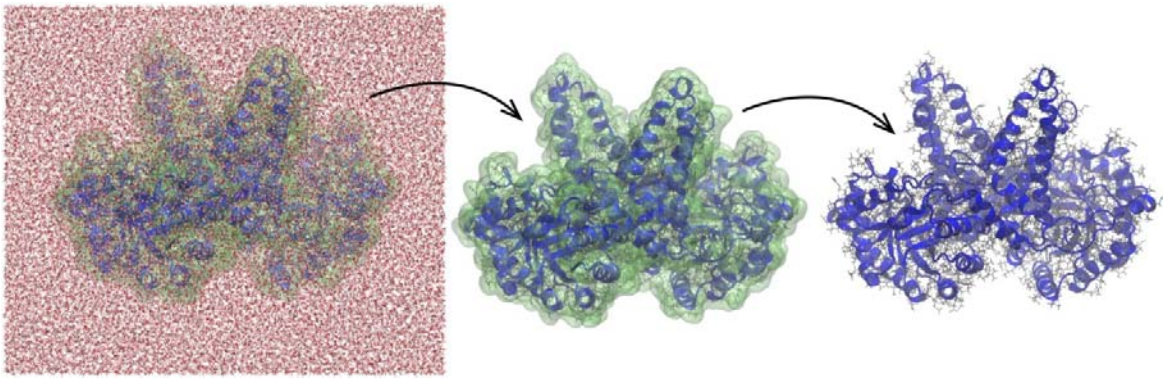
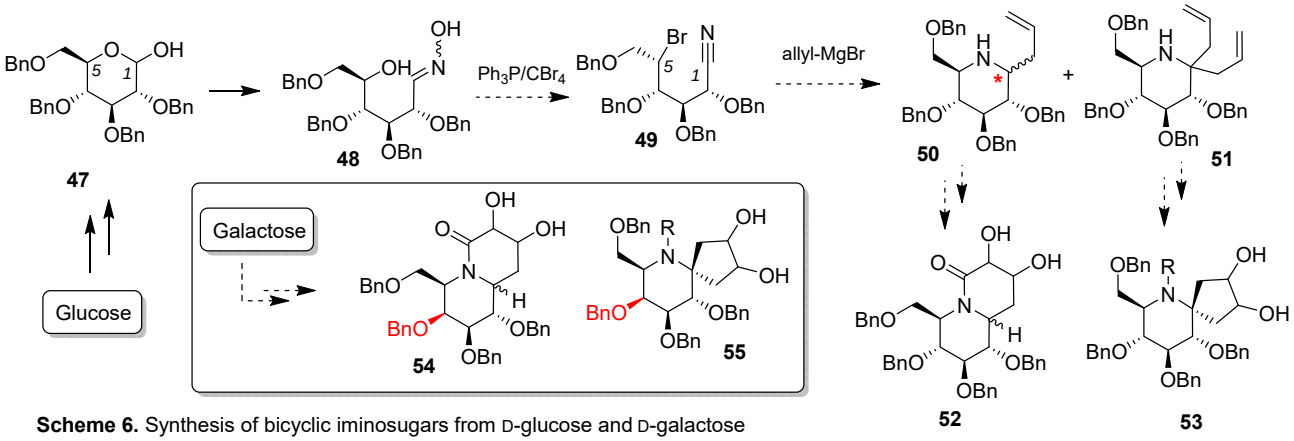


Figure 7. Snapshots from the molecular dynamics simulations of human O-GlcNAcase in water – (an example of glucosidase that attract enormous research interest in the area of enzyme-inhibiting therapies, see ref. 20 for details).

3-II. Stereoselective synthesis of sugar mimetics

In this chapter, the development of the general useful methodology towards sugar mimetics will be proposed. The approach to iminosugars and carbasugars will be presented separately.

3-II-1. Synthesis of iminosugars having different configuration/substitution pattern than previously prepared. These mimetics will be prepared from simple and readily available monosaccharides as shown in **Scheme 6**. We expect that they can be prepared using the methodology (depicted in Scheme 4) described by us recently.



Scheme 6. Synthesis of bicyclic iminosugars from D-glucose and D-galactose

Protected glucose derivative **47** will be converted into oxime **48** and further into ω-bromonitrile **49** (with the inversion of the configuration at the C-5). Reaction of this compound with All-MgBr should afford either mono- or di-substituted derivative (**50** and **51**; both with the inversion at the C-5) analogously to our original procedure shown in Scheme 4.

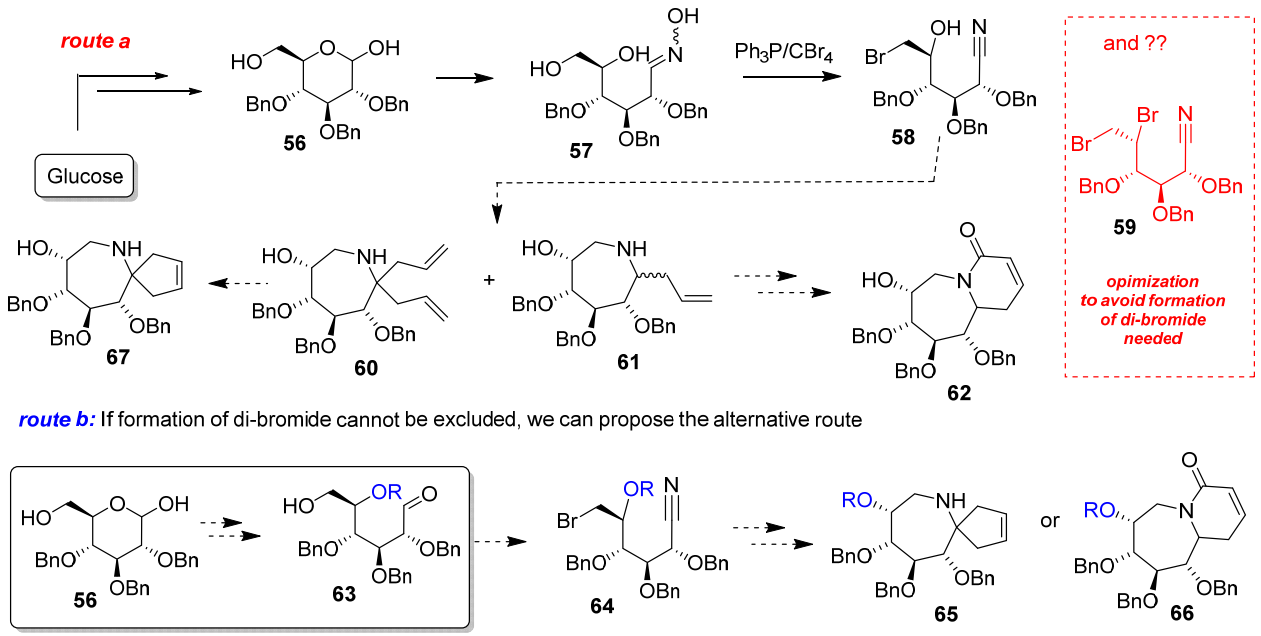
The following problems should be solved: 1) stereochemical outcome of the process leading to **50** and 2) how to direct the reaction to either mono- or di-substituted derivative (**50** vs **51**).

Implementation of the above methodology to other sugars (*i.e.* galactose) should provide another set of bicyclic iminosugars differing in the configuration of the six-membered ring (**54** and/or **55**).

3.II-2. Synthesis of iminosugars with 7-membered ring

The same methodology will be applied for the preparation of bicyclic or monocyclic iminosugars with larger rings. The model synthesis will be initiated from glucose-derived oxime **57** as shown in **Scheme 7**, which – upon treatment with Ph_3P/CBr_4 – should afford bromonitrile **58** with the free OH at the C-5 position (Scheme 7).

We can rather expect the selective reaction of the primary hydroxyl group with the Appel reagent (Ph_3P/CBr_4) than the bromination of both available positions (C5 and C6). However, if dibromide **59** will be formed, we have the alternative solution (***route b*** in Scheme 7). This approach will require selective protection/deprotection strategy (well known in sugar chemistry) to prepare derivative **63** with only primary hydroxyl group free. For the preparation of this compound, a similar methodology which allowed the efficient synthesis of **15** (see Scheme 2) will be used.



Scheme 7. Preparation of the 7-membered iminosugars from D-glucose

Further reactions [such as those shown in Schemes 6 and 7 (route a)] would provide the expected iminosugars (*e.g.* **65** and **67**).

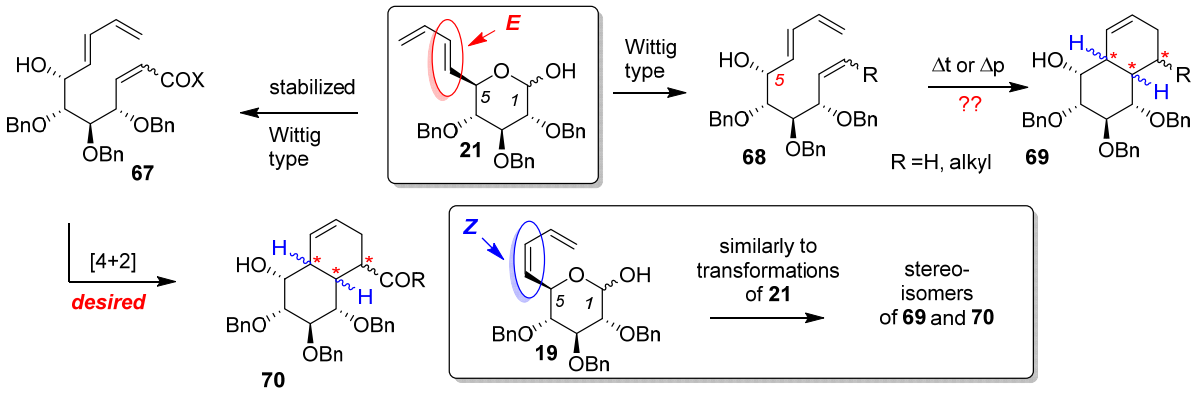
The examples shown in Schemes 6 and 7 would be selected to test our synthetic route(s). We can use different sugars as starting material and change/modify the strategy in order to prepare compounds of biological interest.

The desired structure of such – interesting from biological point of view – compounds will be indicated by the *ab initio* study (see chapter 3-I)

3-II-1. Stereoselective syntheses of carbasugars

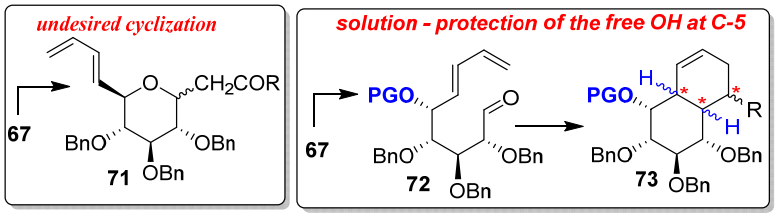
As shown in Scheme 2, we have proposed an efficient and highly stereoselective route to sugar dienes with the *E*- or *Z*-geometry across the internal double bond (**19** and **21**).[14] These intermediates were already used for the synthesis of hetero-bicyclic derivatives (**22a** and **22b**) *via* an oxime intermediate. We plan to use them for the

preparation of bicyclic carbasugars as shown in Scheme 8. The idea is exemplified by the reaction of the *E*-diene **21** (**Scheme 8**).



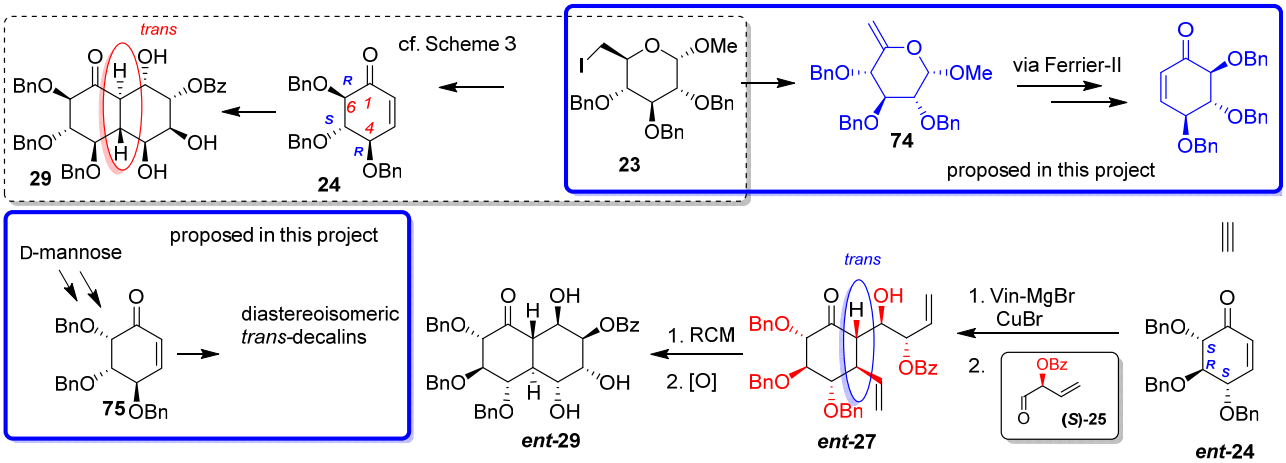
Scheme 8. Preparation of bicyclic carbasugars from sugar dienes of precisely defined geometry

Reaction of **21** with the Wittig (or Wittig type) reagent should afford triene **68**, cyclization of which would provide decalin **69**. Reaction of **21** with the stabilized Wittig reagent will give another triene **67**. Such triene should undergo the [4+2] cyclization to **70**. Of course, there is a risk of an undesired cyclization to *C*-glycoside **71** (**Scheme 9**). In this case, the protection of the hydroxyl group at the C-5 is required. This protection/deprotection strategy, commonly applied in sugar chemistry, would add, however, several steps to our synthesis.



Scheme 9. The alternative preparation of bicyclic carbasugars from sugar dienes

In Scheme 3 we presented the methodology of the synthesis of highly oxygenated *trans*-decalins from 4(R),5(S),6(R)-cyclohex-en-1-one (**24**). Applying ***the same*** methodology it will be possible to prepare the enantiomer of *trans*-decalin shown in Scheme 3. This concept is presented in **Scheme 10**.



Scheme 10. Syntheis of highly oxygenated *trans*-decalins from D-glucose: already accomplished (**29**) and planned in this project

Starting from the same precursor **23** it is possible to prepare the enantiomer of compound **24** applied by us in the synthesis of e.g. decalin **29** (cf. Scheme 3). This can be done by so-called Ferrier-II rearrangement (and subsequent standard transformations) of olefin **74** prepared from **23**.[21] Simple repetition of the synthesis from Scheme 3, changing only the reacting aldehyde from ***R*-26** to ***S*-26** will give the enantiomer of decalin **29** (***ent*-29**).

Of course, this synthesis does not bring anything new (it must give the same result) but the compound: ***ent*-29** may be interesting because of the biological properties (which might be eventually predicted by an *in silico* study).

There are also other possibilities: application of other sugars (*e.g.* D-mannose) as a starting material and reaction of such prepared cyclohexenones (e.g. **75**) with other unsaturated aldehydes, which can give an access to bicyclic derivatives with different configuration and eventually different rings.

4. Research Methodology *(underlying scientific methodology, data reduction and treatment schemes, type and degree of access to the equipment to be used in the proposed research)*

The syntheses of all targets will be performed at the Institute of Organic Chemistry, PAS. The Institute has all necessary equipment to realize these tasks. The compounds will be characterized mostly using the equipment present in our Institute. We have one of the best NMR, MS, CD, and elemental analysis laboratories in Poland.

We have also the equipment to perform the organic synthesis under very high pressure (up to 12 000 atm.) which should be very useful for conducting the cyclizations. We have noticed that high pressure not only highly accelerates the rate of the cyclization but also improves significantly stereoselectivity of the process.

The *in silico* study will be done in our Institute and at the Institute of Physical Chemistry, PAS which has devoted computational clusters – fully capable of delivering the accompanying molecular modeling, inhibitor SAR scoring calculations. The IPC, PAS has two clusters tailored for the DFT calculations (64 cores Intel Xeon 2.6GHz) and classical MD simulations (128 cores, Intel Xeon 3.6GHz with Nvidia Tesla GPU graphic cards), respectively.

The biological activity studies will be performed in the Institute of Biochemistry and Biophysics, PAS (IBB, PAS) and National Institute of Public Health - National Institute of Hygiene (NIPH-NIH) (external services).

The results obtained within this project will be published in top scientific journals and presented on the international and national conferences (*e.g.* Eurocarb, International Carbohydrate Symposium, Symposia on Organic Syntheses, Meetings of the Polish Chemical Society).

5. Literature references

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