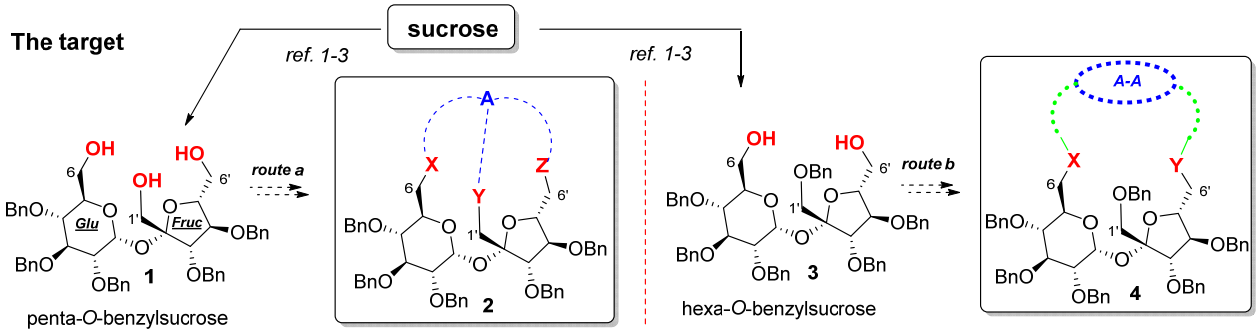
Synthesis and properties of cryptands with sucrose scaffold

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 connected with the synthesis of cryptands with sucrose scaffold, which will be based mostly on penta-*O*-benzylsucrose (**1**). The connection of all terminal positions (C6,C6',C1') *via* linkers should allow the preparation of cryptand of type **2**. Construction of cryptands based on hexa-*O*-benzylsucrose (**3**) might also be possible by an insertion of the proper macrocycle onto **3**. Both ways are drawn schematically in Scheme 1.

The syntheses of the key-substrates, which will be used in the preparation of the above molecules, *i.e.* triol **1** and diol **3**, were elaborated for the first time in our laboratory[1,2,3]



Scheme 1. The proposed plan for the synthesis of cryptands **2** and **4**

Triol **1** will be converted into cryptand **2** by an activation of all terminal positions (C1',C6,C6') either (***a***) directly or (***b***) indirectly, followed by cyclization. First methodology (***a***) will convert the hydroxyl groups at the C1',C6,C6' positions into *eg.* mesylates (or other good leaving groups); the second one (***b***) will require elongation of the position(s) with a linker. It should be possible to elongate either position ***separately*** with a ***different*** linker or to place the same linker on all three terminals. It should be pointed out, that we have elaborated the convenient method for the ***selective protection*** of either terminal position; for more detail see **chapter 3: work plan**.

An alternative method of the synthesis of cryptands will be based on diol **3**. After activation and/or elongation of the terminal positions, another macrocycle (***A-A*** in Scheme 1; it can be *eg.* ***di-aza-crown-6***) could be introduced. Since we have the methods for the ***selective*** protection of either '*glucose*' or '*fructose*' end (***Glu*** or ***Fruc***), different linkers can be put at both sucrose '*ends*'.

Since, as already mentioned, we have the convenient methodology for the differentiation of all terminal hydroxyl groups in triol **1** as well as in diol **3** (see our reviews in *ref.* 1-3) it will be possible to introduce the linkers not only of different size but also differing in heteroatom (X,Y,Z = O, NR, or eventually sulfur). Some of these 'elongated' sucroses are already prepared in our laboratory.

This will allow for the preparation of a variety of structurally different cryptands with the same chiral core – sucrose. The syntheses of more complex derivatives will be discussed in the next sections.

The cryptands prepared within this project – schematically depicted as **2** and **4** – will be used for the complexation of chiral ammonium salts. We expect that such compounds might have interesting complexing properties. This assumption is based on our observation of the complexation of chiral guests by crown and aza-crown analogs with sucrose scaffold (described in our review papers: *ref.* 1-3).

The structure of cryptands, being more rigid than the aza-crown derivatives, should allow for a better differentiation of enantiomers. Moreover, the access of chiral guest(s) is possible from one side only, which should enhance the complexing properties of the host molecule: sucrose crtyptand.

The geometry of sucrose cryptands - the new, not known yet class of compounds - will be investigated. Even more interesting will be determination of the precise structure of the complexes with such receptors. The most obvious way to establish the geometry of either cryptands or their complexes seems to be the X-ray methodology. However, based on our previous observations concerning the sucrose crown and aza-crown analogs, this might be a serious problem. Although we have prepared a large family of the aza-crown receptors,[1-3] the structure of only one of them could be solved by X-Ray.[4]

Thus, the *in silico* methods will be used to establish the structure of the macrocycles and/or complexes.

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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, economic and societal impact).*

Supramolecular chemistry is the field of chemistry dealing with non-covalent host-guest' interactions.[5,6] Enantioselective complexation of chiral cations is one of the main problems of supramolecular chemistry.[6,7] Chiral crown ethers (or their aza-analogs) are used also as stationary phases in chromatographical separation of enantiomers.[8]

Synthesis of macrocyclic receptors, being able to complex enantioselectively chiral cations, is typically initiated from the cheap and readilly available chiral platforms, from which sugars – because of their availability and the structural diversity – are undoubtedly the most convenient.[9]

Sucrose is the most abundant di-saccharide occurring in Nature, produced in the scale 160 millions of tons each year. Most of this amount is consumed by the food market; however, few percent (which means couple of mln of ton) remains, and such huge overproduction should be utilized in other way. No wonder that many scientific groups, mostly in industry but also at the universities, are trying to convert sucrose into various – not nutritive – products such as biopolymers, biofuel, or fine chemicals. The importance of the studies on sucrose may be illustrated by the fact that the name '*sucrochemistry*'- by the analogy with '*petrochemistry*' - was coined to the chemistry and application of sucrose in different fields.[1]

The projects carried out in our laboratory are directed to the synthesis of macrocyclic derivatives with sucrose scaffold (*eg.* **5**-**7**), and especially to the receptors able to complex chiral guests[10,11,12,13,14,15] (**8**-**10**; Fig. 1). For example, receptor **8** was able to differentiate α-phenylethylammonium cations with moderate association constants and moderate enantioselectivity (K_a ~1.2 x 10^3 M^{-1} for the *S*-isomer and 0.8 x 10^3 M^{-1} for the *R*-isomer). However, the analog **9** distinguished the *S*-isomer with 100% enantioselectivity.[13] On the other hand, association constants of the complexes of the esters of amino acids - in the form of their hydrochlorides - with **10** were high (~10^4 M^{-1}) but this receptor showed no enantioselectivity.[14]

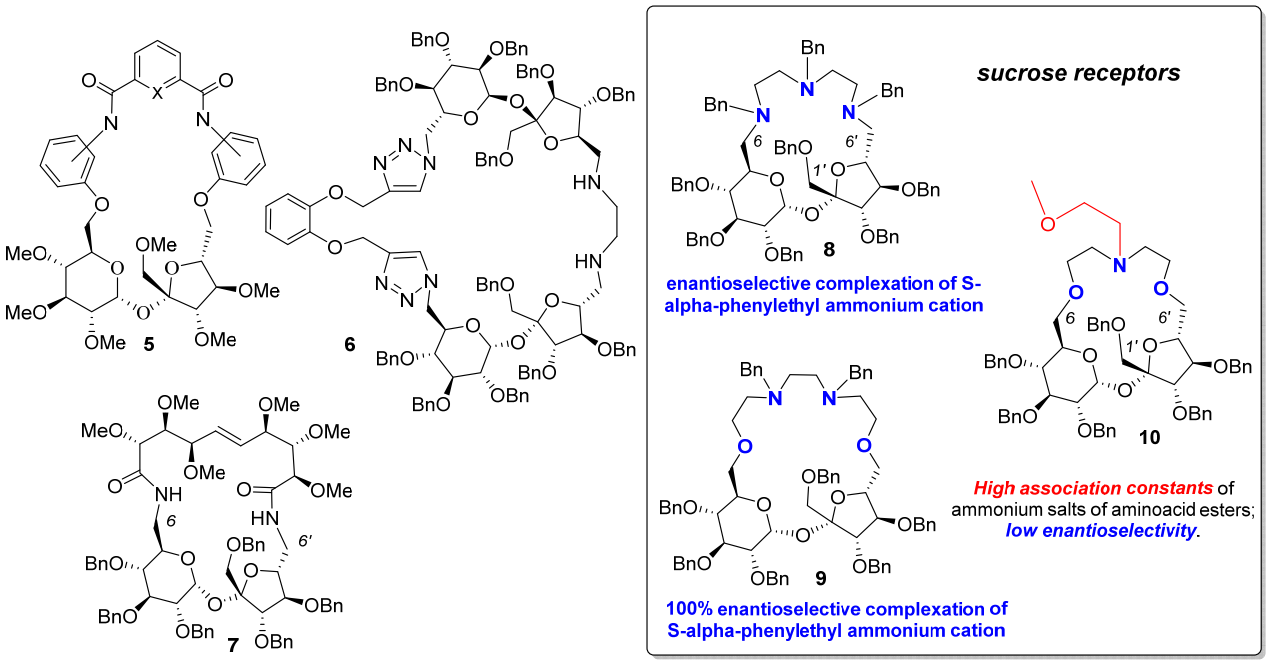
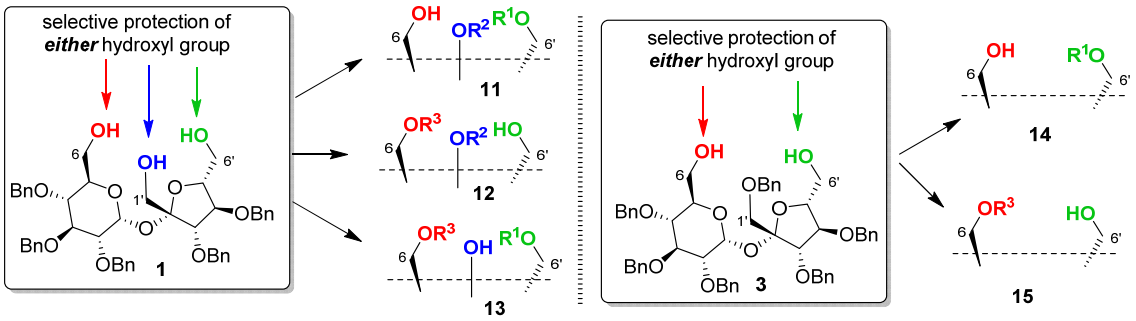


Figure 1. Examples of macrocyclic derivatives with sucrose scaffold prepared in our laboratory

Synthesis of cryptands with sucrose scaffold – unknown class of such receptors – is the next step in the application of this di-saccharide for the creation of '*fine chemicals*'. Preparation of sucrose cryptands will be a challenge in the chemistry of sucrose and - we hope - also in supramolecular chemistry. Taking into account our previous results on the selective complexation of chiral guests by the analogs of aza-crown ethers with sucrose scaffold (*e.g.* compounds **8**-**10** in Fig. 1), one might expect that sucrose cryptands, having much more rigid structure, should possess better complexing properties. As is reported, cryptands have much higher affinity towards ammonium cations than the corresponding aza-crown analogs.[16] Although cryptands with sugar scaffold are known for a long time - one of the first examples was reported in 1983[17] - the synthesis of such derivatives based on di-saccharides is rather uncommon.[18]

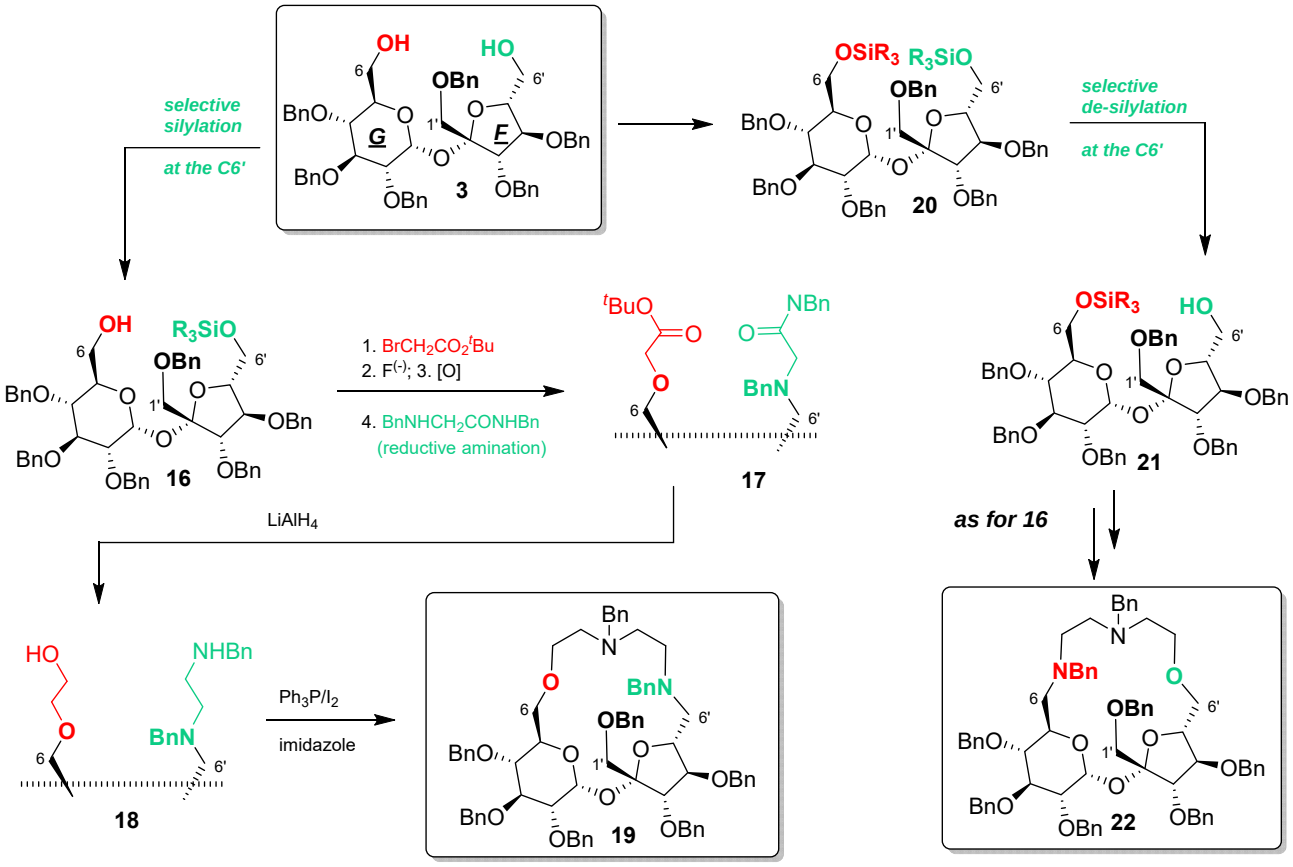
Synthesis and properties of cryptands with sucrose scaffold

The most important and original achievement of our group in the field of sucrose chemistry is undoubtedly the preparation of macrocyclic derivatives with sucrose scaffold able to differentiate chiral ammonium cations. As already mentioned, the key-compounds in such syntheses, penta- and hexa-*O*-benzyl-sucroses (**1** and **3** respectively), were prepared for the first time in our laboratory.[1-3] We have also elaborated the convenient methodology for the differentiation of all terminal hydroxyl groups in triol **1** and diol **3** which allows for an easy preparation of derivatives **11**-**15** shown in Scheme 2.



Scheme 2. Differentiation of the terminal hydroxyl groups in diol **1** and triol **3** elaborated in our laboratory (*ref. 1-3*)

The examples presented in Scheme 3 illustrate the preparation of specifically blocked sucroses and their application in the synthesis of macrocyclic receptors.



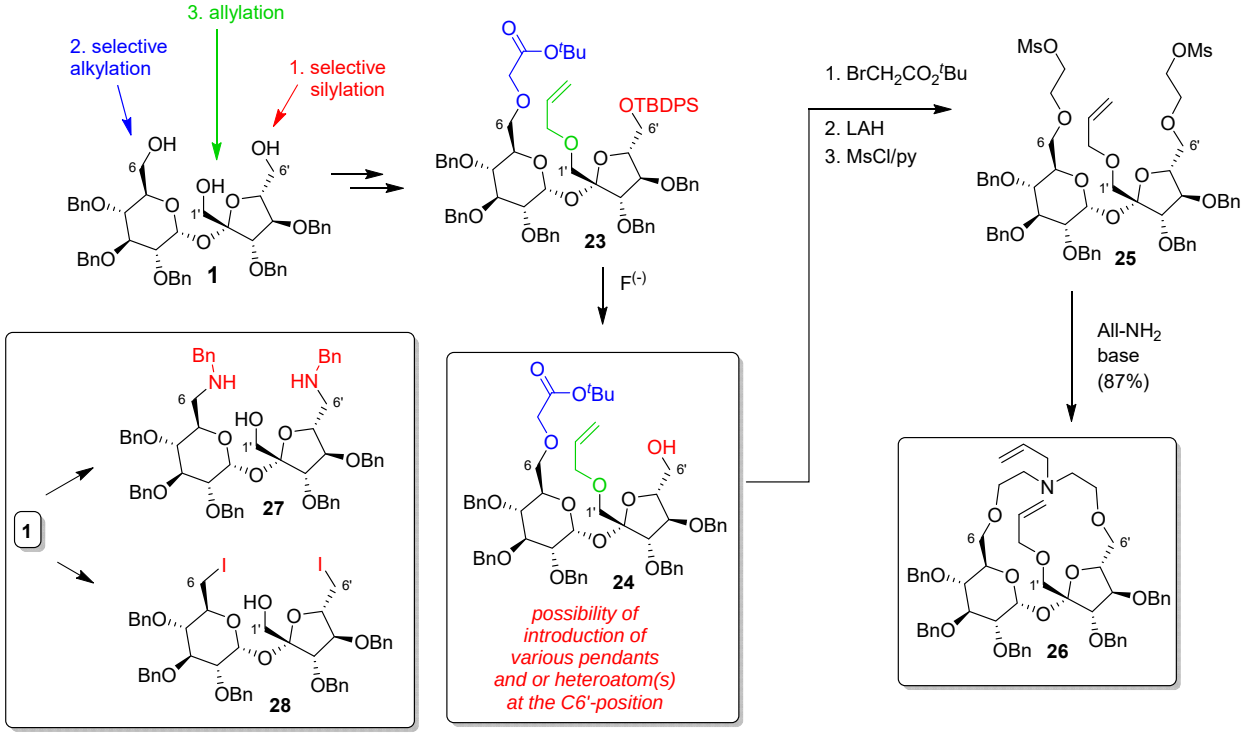
Scheme 3. Synthesis of unsymmetrical receptors with sucrose scaffold from the same prepcursor - diol **3**

Diol **3** was ***selectively silylated*** at the C6'-position (→ **16**) which allowed to introduce the appropriate pendant at the alternative C6-position ('*glucose end*') by reaction with *tert*-butyl bromoacete. Deprotection of the C6'-position and standard transformations performed at the liberated '*fructrose end*' provided compound **17**. Reduction of both: ester and amide functions with $LiAlH_4$ afforded aminoalcohol **18**, which underwent cyclization under the Garegg-Samuelsson conditions to give the first 'unsymmetrical' receptor **19**.

Alternatively, double silylation of **3** afforded compound **20** which could be ***highly regioselectively de-protected*** at the '*fructose end*' to yield alcohol **21**. The same sequence of reactions (as for **16**) gave another regioisomeric receptor **22**.[19]

Penta-*O*-benzylsucrose (**1**) seems to be a convenient starting material for the preparation of cryptands, since it offers a possibility for ***connecting all terminal positions*** via linkers. Preliminary study to achieve this goal is shown in Scheme 4.

Triol **1** was selectively silylated at the C6'-hydroxyl group and then selectively alkylated – with *tert*-butyl bromoacetate – at the '*glucose end*' (6-OH). The remaining hydroxyl function at the C1'-position was allylated which led to compound **23** in good yield. Removal of the silyl block from the C6' provided alcohol **24**. The hydroxyl group was alkylated with the same group (*tert*-butyl bromoacetate) and the resulting product was converted in a few well-defined steps into di-mesylate **25**. Reaction of this compound with allyl amine provided macrocycle **26**; the cyclization step proceeded with an excellent yield.[20,21] We have elaborated also a convenient synthesis of other precursors such as **27** and **28**,[20,21] which may be used for the preparation of cryptands.



Scheme 4. Synthesis of macrocyclic deriative **26** and precursors: **24**, **27**, and **28** from (**1**)

Alcohol **24**, an intermediate in the synthesis of macrocycle **26**, offers more opportunity for the preparation of a family of sucrose cryptands. The '*fructose end*' (C6') can be elongated by various units which should make possible preparing cryptands with different structures. Moreover, the hydroxyl group can-be replaced with *e.g.* nitrogen functionality, thus expanding the family of sucrose cryptands.

In this project, we propose the synthesis of cryptands with sucrose scaffold, the unknown yet class of compounds. We expect, based on our previous results concerning sucrose aza-crown analogs, that sucrose cryptands should have interesting complexing properties towards chiral ammonium cations. We might also expect good enantioselectivity even in complexation of amino acids (in the form of their ammonium salts).

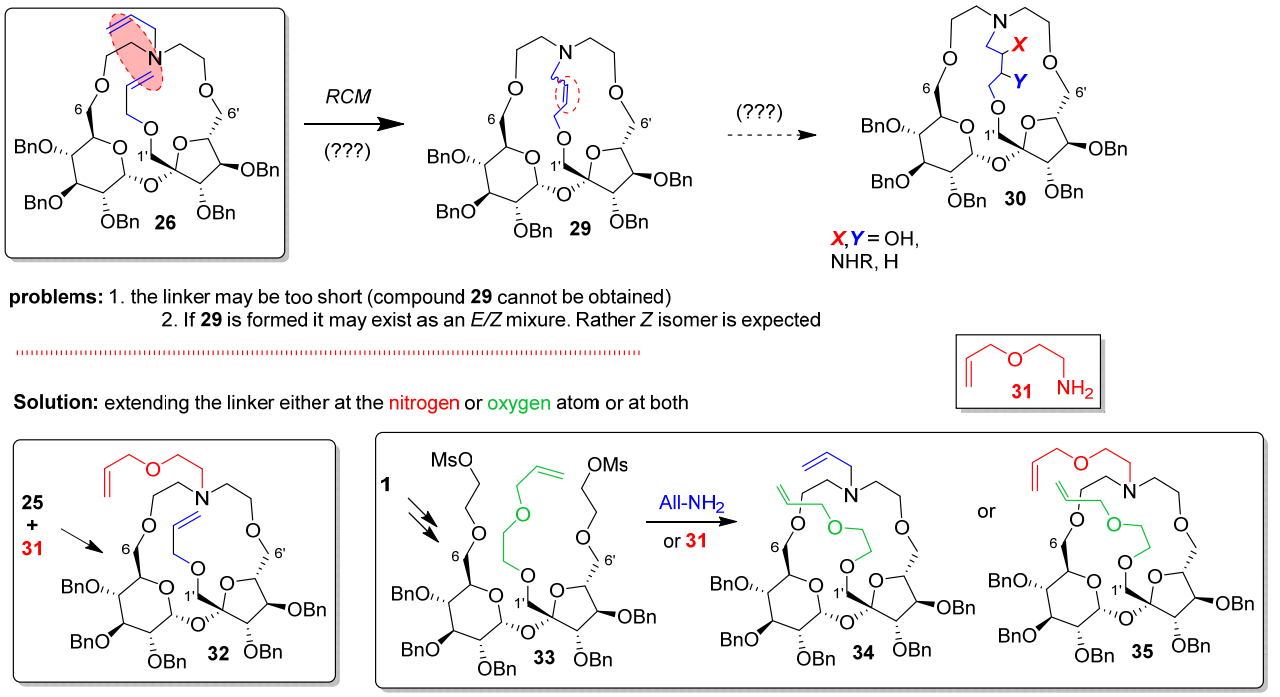
3. Work plan *(outline of the work plan, critical paths, state of preliminary and initial research indicating feasibility of research objectives)*

The study of crown and aza-crown ether analogs with sucrose scaffold was successful; we have demonstrated that such receptors have good affinity towards ammonium cations and display very high enantioselectivity for *S*-α-phenylethylammonium cation. In this project, we plan to prepare more demanding sucrose macrocycles such as cryptands.

The study will start from compound **26**, which was recently prepared in our laboratory. The ring closing metathesis reaction (*RCM*)[22] should provide compound **29**, which may-be formed as a mixture of the *E* and *Z* isomers, although the *Z*-isomer should predominate for steric reasons. Functionalization of the double bond in **29**

(*cis*- or *trans*-dihydroxylation, aminohydroxylation) will provide **30**. The expectation of the positive results in the *RCM* process performed on sucrose substrate is reasonable, since we have recently reported the successful application of this method as a key-step in the synthesis of macrocycle **7** shown in Fig. 1.[13]

Of course, the eventual linker - resulting from the *RCM* coupling of two allyl moieties present in **26** - may be too short and compound **29** might not be formed. It should be possible, however, to introduce the elongated units at the terminal positions as shown in Scheme 5.



Scheme 5. Possible preparation of sucrose cryptands by the *RCM* reaction

Compound **32** could-be obtained by a reaction of **25** with a 'homologated' amine **31** according to the method already successfully applied for the preparation of di-allyl derivative **26**. Alternatively, triol **1** may-be converted, instead of **25** (with the allyl block at the C1'), into a homologated derivative **33**. Cyclization of **33** with allyl amine should provide macrocycle **34**, while the same reaction with **31** should afford **35**.

The *RCM* reaction of either one of the reported three compounds should allow obtaining the corresponding cryptands. Since the steric hindrance in those derivatives is smaller than in the (hypothetical) derivative **30**, we can expect the formation of both geometrical isomers. Functionalization of them (as proposed for **29**) would allow the preparation of a larger family of sucrose cryptands.

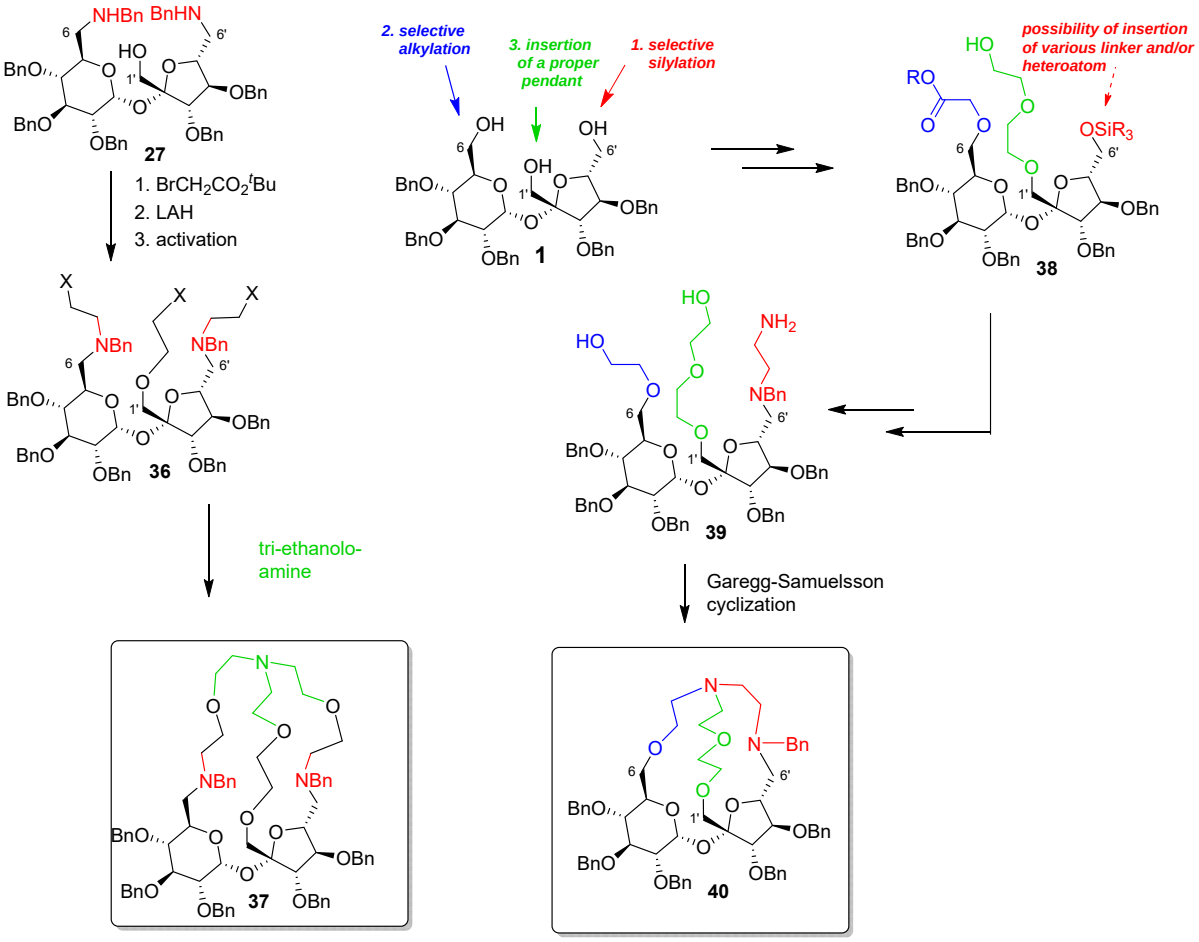
Another sequence of reactions - shown in Scheme 6 - would be also applied in the preparation of cryptands. It will be initiated from compounds already presented above. In Scheme 6, *only the selected examples* are shown to illustrate our approach.

Di-amine **27** can be alkylated at all three terminal positions with *e.g. tert*-butyl bromoacetate. Further standard transformations (depicted in Scheme 6) should provide derivative **36** ready for cyclization. Its treatment with tri-ethanolo-amine would furnish cryptand **37**.

Compound **38,** which is the homologated analog of **23** already described in Scheme 4, could be used for the preparation of a family of cryptands with different heteroatoms at the C6 and C6' positions. The appropriate pendant (several different units might be placed at this position) could be introduced at the C6' and then the intermediate could be converted into *e.g.* **39**, which might cyclize under the Gregg-Samuelsson conditions to provide the corresponding cryptand **40** (Scheme 6).

The important problem will be now to study the complexation of chiral amines by the obtained macrocycles. The measurement of the association constants will be performed (after determination of the stoichiometry of the complex by the Job's method) mostly by the NMR technique (NMR titration). We will also assign the corresponding constants using the microcalorimetric and/or spectrophotometric measurements. In the beginning, we will study the complexation of α-phenylethyl amine.

Synthesis and properties of cryptands with sucrose scaffold



Scheme 6. Possible routes to sucrose cryptands from triol **1** and its derivatives

One may consider also the possibility of application of the above cryptands as catalysts in enantioselective model reactions, such as: aldol reaction of 1,4-addition of nucleophiles to α,β-unsaturated ketones. This is, however, not main goal of the project.

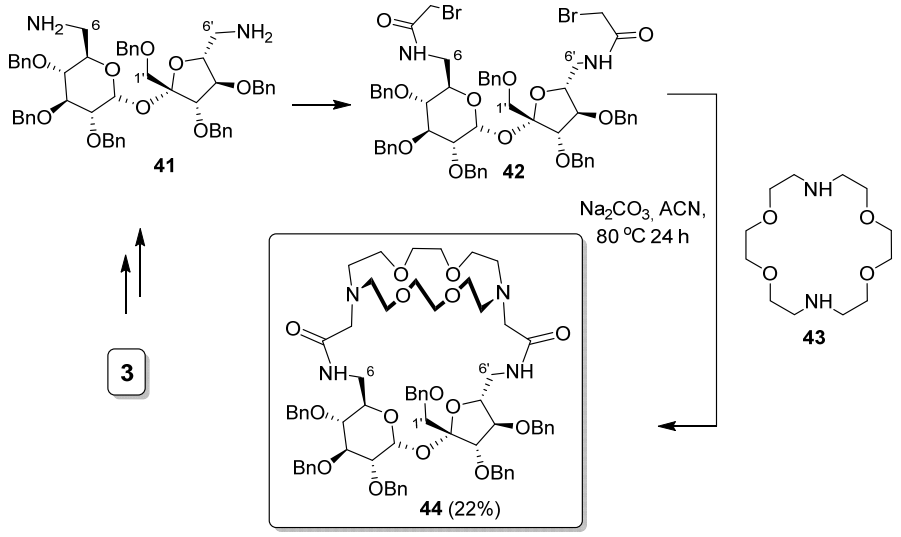
In case of obtaining the receptors (or better complexes) as crystalline compounds, their geometry will be assigned by the X-Ray analysis. This can be, however, a serious problem, since up to date only one structure of the sucrose aza-crown receptor was solved by this method.

Thus, the *in silico* methods will be applied to determine the geometry of cryptands and their complexes. For practical reasons the calculation will be performed for the methylated (and not benzylated) derivatives.

We will use the *in silico* calculations to determine the binding energy of the host-guest complexes. In the first stage, it will be necessary to optimize the method of calculation, which will consist in choosing the appropriate semi-empirical method and DFT functional, so the calculations will reflect well the experimental results. The search for the most stable conformation of the receptors and complexes will take place using the semi-empirical methods (PM6 and PM7). Optimized structures of complexes will be finally improved using the DFT method (*Density Functional Theory*). In case of the non-covalent interactions, good results are obtained using M05-2X functional,[23] but during the optimization of the calculation method, it is planned to use also other DFT functionals. The developed calculation methodology will allow for testing different combinations of the host-guest complexes using different variants of cryptands proposed in this project. To large extent, the data obtained in the calculations will direct the synthetic targets of this project.

All this information should allow us to design the synthesis of sucrose cryptands with better complexing properties towards ammonium cations.

Preliminary studies performed by us[20] already indicated, that hexa-*O*-benzylsucrose (**3**) could be also a convenient starting material for sucrose cryptand. It can be easily converted into amine **41** (we have already reported the synthesis of this compound) and, after reaction with bromoacetyl bromide, into di-amide **42**. Reaction of the latter with di-aza-18-crown-6 macrocycle **43** afforded cryptand **44** in acceptable yield.



Schemat 7. Synthesis of cryptand **44** with hexa-*O*-benzylsucrose (*preliminary unpublished results*)

The methodology presented in this project will allow for the preparation of a relatively large family of sucrose cryptands – the new, completely unknown class of compounds.

We will use the methods already applied with success in the preparation of sucrose crown and aza-crown analogs. Moreover, they were also tested successfully in the model synthesis of cryptands with sucrose scaffold. Thus the project, although quite innovative and thus with some degree of uncertainty, has a great chance for a positive realization.

Of course, we cannot propose now all the entire, detailed methodology to achieve our goal. During realization of this project, surely new trends and possibilities will arise. This should push our research to even more innovating fields covering sucrose receptors.

The compounds obtained within this project will be tested for complexation of chiral ammonium cations. We expect, based on the previous results concerning the aza-crown analogs with sucrose scaffold, that sucrose cryptands would distinguish the optical isomer with high enantioselectivity.

Selected cryptands prepared in this project will be de-protected. We have proven that deprotection of aza-crown derivatives based on hexa-*O*-benzylsucrose is possible under the standard conditions.[4]

The ‘free’ receptors will be tested for their complexing ability in such demanding solvent as water.

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 compounds will be performed at the Institute of Organic Chemistry, PAS. The Institute has all necessary equipment to realize all syntheses. 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. Part of the analytical characterization including *e.g.* X-ray measurements or calorimetric titration of the complexes will be performed in other institutions (Institute of Physical Chemistry, Warsaw University).

The structure of the receptors and complexes will be assigned by X-ray (if possible). This can be problematic since up to date ***only one*** structure of the sucrose aza-crown ether was solved by the X-Ray method; very few of such receptors were crystalline. The structure of sucrose cryptands and their complexes will be optimized *in silico*.

Our Institute has its own computing cluster that will be used for calculation purposes in this project. The calculations with the use of semi-empirical methods (PM6 and PM7) will be done using MOPAC quantum chemistry program. In contrast, DFT calculations will be performed using the Gaussian09 package considering the following functionals: M05-2X, M06-2X, MPWB1K, PBE1PBE, ωB97X-D. The appropriate functional will be chosen during the optimization of the calculation method. We shall use the 6-31+G(d) or 6-31+G(d,p) basis set for DFT calculations. Calculated binding energies will be corrected by using the counterpoise method in order to avoid the basis set superposition error (BSSE)

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, Meetings of the Polish Chemical Society).

5. Literature references

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