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**Synthesis of monosaccharide-based crown ethers and their application in
asymmetric reactions**

PhD Theses

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1. Introduction

Asymmetric catalysis, which has the aim to synthesize enantiopure compounds, is one of the main fields of research in modern organic chemistry. Importance of the topic can be seen in the demands towards the chemical industry. Drugs, pesticides and cosmetics come to public utilization in optically pure form. The most modern and most economical method for preparation of enantiopure components is enantioselective synthesis with presence of chiral catalysts. Reactions carried out under phase transfer conditions are special types of asymmetric catalysis, which have the advantage that mild conditions can be applied.

Monosaccharide-based chiral crown ethers are mostly good phase transfer catalysts, and they can generate asymmetric induction in certain reactions. Their further advantage is that carbohydrates are cheap, easily accessible natural components. So far, a number of various monosaccharide-based crown macrocycles have been synthesized, and mainly their complex forming abilities were investigated. These compounds are able to differentiate enantiomers, accordingly they are applicable for separation of antipodes and production of asymmetric induction. Until now only a few researchers managed to achieve significant enantiomeric excess in asymmetric reactions using carbohydrate-based crown ethers [8], or separate antipodes using stationary phase containing chiral crown ethers [9].

Monosaccharide-based chiral crown compounds synthesized at the Department of Organic Chemistry and Technology (BUTE) were investigated, and some of them proved to be efficient enantioselective catalyst in certain reactions, which induce formation of new stereogenic center. A metal cation has always a role in these reactions. The results can be significant in terms of practical applications.

2. Objectives

The aim of the research project was to prepare new monosaccharide-based crown ethers and their application in reactions as chiral phase transfer catalysts. I wanted to investigate the correlation between structure and effect, and define the optimal conditions for enantioselectivity. I also looked for new model reactions, in which our carbohydrate-based crown ethers generate asymmetric induction.

3. Experimental methods

Conventional methods of organic preparative chemistry have been used in syntheses, crystallization, distillation, preparative TLC and column chromatography in order to purify the products. Compounds have been identified by NMR (including DEPT, COSY, HMQC, HMBC and H2BC techniques), MS spectroscopy and additionally by elemental analyses. Enantiomeric excess has been determined by ^1H NMR spectroscopy applying (+)-Eu(hfc)₃ as a chiral shift reagent although in some cases the measurement was carried out by chiral HPLC. Determination of absolute configuration was based on X-ray diffraction measurements.

4. Summary of results

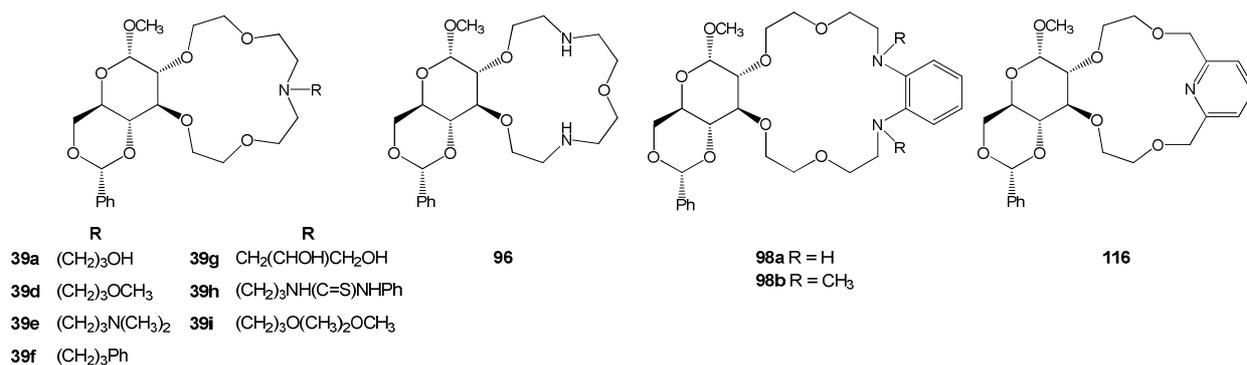
My research work consists of two main parts. First, different monosaccharide-based chiral crown ethers have been synthesized in several steps, partially on the basis of methods described in chemical literature, partially using techniques elaborated in our group. In addition the newly prepared crown ethers have been tested in some model reactions (Darzens-condensation, Michael-addition, epoxidation) as chiral phase transfer catalysts. In context of previously mentioned examinations a number of new chiral compounds have been synthesized.

4.1. Synthesis of crown ethers

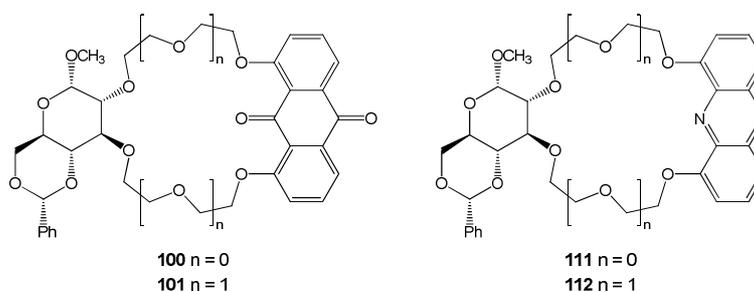
Five kinds of monosaccharides have been used for the syntheses of the crown ethers resulting in 24 new chiral macrocycles.

Monoaza-15-crown-5 type chiral lariat ethers were synthesized in five steps from the appropriately protected D-glucopyranoside. The nitrogen atoms of these macrocycles have various type of substituents having different properties (**39a-i**).

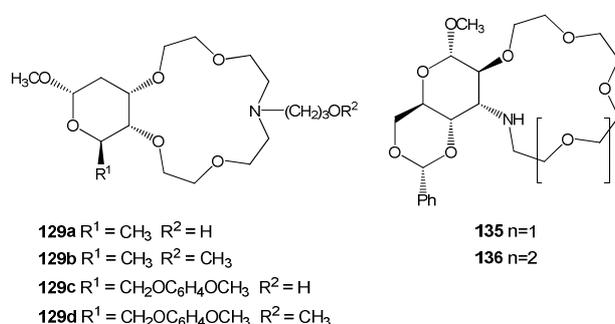
Diaza crown ethers having 15- and 18-membered ring have been synthesized (**96**, **98a-b**), which contained secondary and tertiary amino groups. The catalytic nature of these compounds probably differ from the monoaza macrocycles. Synthesis of **116** containing a pyridin ring has been reproduced with enhanced yield using alternative procedure.



Glucose-based crown ethers having fluorescent group in the macro-ring have also been synthesized during the work. These macrocycles containing 9,10-anthraquinone (**100**, **101**) or acridine unit (**111**, **112**) could be used to distinguish between enantiomers applying spectroscopic methods (experiments are in progress).



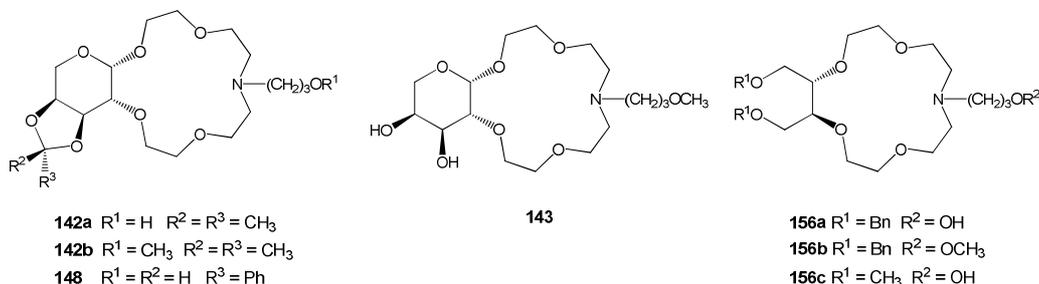
D-Glucose could be transformed into other monosaccharides by using methods of carbohydrate chemistry. These derivatives have been utilized in preparation of new crown compounds. The 2-deoxyribohexopyranosides have been synthesized in five / six steps from the appropriately protected D-glucose as starting material. These ribohexopyranoside derivatives have been used to prepare monoaza-15-crown-5 type lariat ethers (**129a-d**).



Macrocycles having nitrogen atom bounded directly to the monosaccharide unit have been prepared using D-glucose derivatives as starting materials. The key step of the synthesis

was a ring-opening reaction between ethanol-amine and an anhydromannoside compound. This transformation was carried out by full regio- and stereoselectivity, and the product has been used to form altropyranoside-based crown ethers (**135**, **136**).

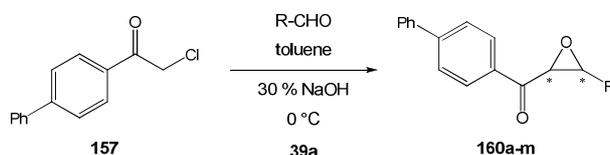
The crown compounds presented above contain carbohydrates consisting of six carbon atoms. In addition, L-arabinose has also been applied as starting material for preparation of macrocycles. Crown ethers having isopropylidene-acetal on the arabinopyranoside unit have been synthesized (**142a-b**). An unprotected crown compound (**143**) has been obtained by removal of the acetal group in compound **142b**. It was not possible to form directly 3,4-*O*-benzylidene-L-arabinopyranoside, therefore crown ether **148** has been synthesized by an indirect method.



L-Threitol-based macrocycles have been produced using diethyl-tartrate as starting material. These compounds containing 1,4-di-*O*-benzyl- or 1,4-di-*O*-methyl-substituted threitol unit (**156a-c**) are more flexible than the crown ethers containing acetal protecting group.

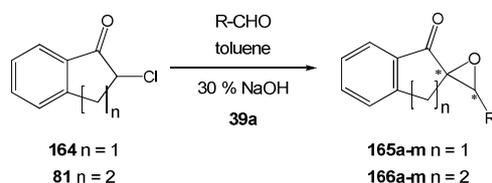
4.2. Enantioselective syntheses

The prepared macrocycles have been tested in asymmetric syntheses as chiral phase transfer catalysts. Only the successful reactions are mentioned in the dissertation, in which significant enantioselectivity has been obtained. The most effective chiral crown ether proved to be the glucose-based monoaza-15-crown-5 lariat ether **39a**. In most cases, this derivative has been used in the asymmetric reactions as a catalyst.

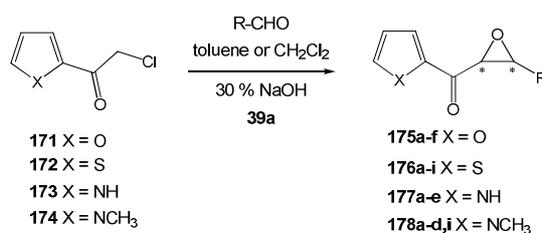


The reaction of 4-phenyl- α -chloroacetophenone (**157**) and aromatic aldehydes have been studied. The *trans*-epoxyketones **160a-m** were obtained in optical yields of 40-96 %. Use of substituted benzaldehydes led to lower ee values that were dependent on the substitution pattern of the phenyl ring (40-84 %). There was a tendency observed in case of nitro-substitution and methyl-substitution, that the farther the substituent of benzaldehyde is placed from the reaction center, the more considerable the extent of the asymmetric induction is. The pure levorotatory enantiomer of epoxyketone **160b** (R = 2-Cl-C₆H₄) was subjected to single crystal X-ray analysis. According to this, the absolute configuration is 2*R*,3*S*.

Cyclic α -chloroketones (**164** and **81**) were readily prepared from 1-indanone (**161**) and 1-tetralone (**162**) using selective monochlorination method. The Darzens-reactions of these compounds also have been studied in the presence of catalyst **39a**.



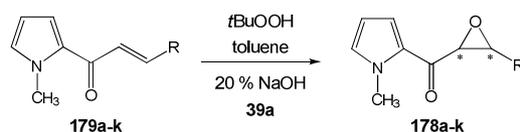
Products (**165a-m**) formed in the reaction of 2-chloro-1-indanone (**164**) were obtained in 0-85 % ee. With an exception, the substituted derivatives were formed in lower ee values than using benzaldehyde. We wished to investigate, if the ring size of the cyclic chloro-ketone has an impact on the enantioselectivity. The results of the reactions applying 2-chloro-1-tetralone (**81**) were quite different. Epoxyketones **166a-m** were obtained in variable optical yield (32-75 % ee), and in case of substitution on the aromatic ring lower ee values were measured. Repeated recrystallization of products **166d** (R = 4-Cl-C₆H₄) and **166m** (R = naphthalene-2-yl) led to pure enantiomers whose absolute configuration was determined by single crystal X-ray crystallography. In both cases the configuration of the stereogenic centers was found to be 2*R*,3'*S*.



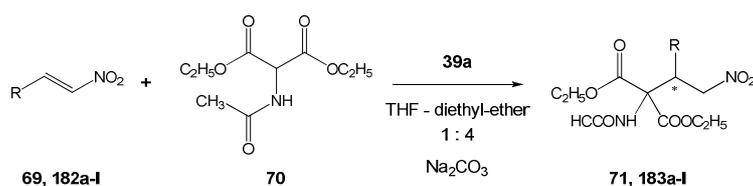
Some heteroaromatic chloromethyl ketones (containing furan, thiophene and pyrrole ring) (**171-174**) have also been synthesized and their Darzens-condensation with various

aromatic aldehydes have been investigated. *Trans*-epoxyketones **175a-f** formed with negative optical rotation values were obtained in variable ee values (24-70 %) applying 2-(chloroacetyl)furan (**171**). The use of substituted benzaldehydes led to higher optical yields than utilizing benzaldehyde. Effect of the substituents was the opposite in the Darzens-condensation of compound **172**. The reaction of substituted benzaldehydes with 2-(chloroacetyl)thiophene (**172**) provided lower ee values of 51-68 %. It is an exception and is interesting that using piperonal gave the best enantioselectivity (**176i**, R = 3,4-methylenedioxy-C₆H₄, 86 % ee). Moreover, after completion of the reaction, nearly half of the product precipitated from the mixture as a pure enantiomer. Absolute configurations of compound **176f** (R = 2-H₃C-C₆H₄) and **176i** (R = 3,4-methylenedioxy-C₆H₄) were determined, in both cases the configuration found to be 2*R*,3*S*.

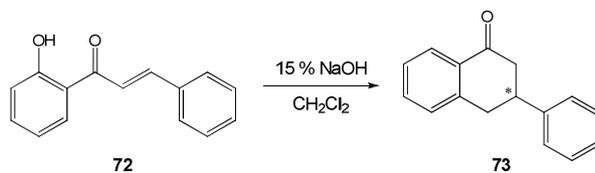
Analogous reactions of aromatic aldehydes with 2-(chloroacetyl)pyrrole (**173**) were carried out under similar conditions, but the yields and enantioselectivities were low. The best result has been achieved with naphthalene-1-carbaldehyde, and the product obtained in 51 % ee (**177c**, R = naphthalene-1-yl) could be purified by repeated crystallization to afford suitable crystals. The absolute configuration found to be 2*R*,3*S*. Applying compound **174**, that contains an *N*-methylpyrrole unit, enantioselectivities were less than 20 %. Epoxyketones having *N*-methylpyrrole moiety have been synthesized in better optical yields using an alternative method.



In the first step, the corresponding α,β -unsaturated ketones (**179a-k**) were produced, then oxidized in a liquid-liquid system with *tert*-butyl hydroperoxide. Epoxidation of the α,β -enones gave the products (**178a-k**) much better yields and ee values (51-88 % ee), while duration of the reactions increased significantly.



The Michael-addition of diethyl acetamidomalonate (**70**) to aromatic nitrovinyl compounds (**69**, **182a-l**) has also been studied in the presence of **39a**. Conditions of the solid-liquid phase have been optimized, and the products have been obtained in 0-99 % ee. Three of the adducts (**71**, R = C₆H₅, **183c**, R = 4-Cl-C₆H₄, **183d**, R = 4-O₂N-C₆H₄) were generated in excellent optical purity (97-99 % ee).



The newly synthesized crown ethers generated asymmetric induction in some cases, but they failed to achieve the effect of catalyst **39a**. Significant enantioselectivity was only generated in the synthesis of flavanone (**73**) from 2'-hydroxychalcone (**72**) by the **156b** threitol-based crown ether (66 % ee). This is remarkable, because as far as we know, in case of this ring-closure reaction, there has not been achieved more than a few percent ee value before.

5. Theses

1. D-Glucose-, D-ribose-, D-altrose-, L-arabinose- and L-threitol-based chiral crown ethers have been synthesized in several steps and applied as phase transfer catalysts in asymmetric reactions. Glucose-based macrocycles containing fluorescent groups are especially novel compounds according to the literature. The latter crown components have not been prepared for phase transfer catalysis, and their ability of enantiomer recognition has not yet been proven.

2. L-Arabinose-based monoaza-15-crown-5 lariat ethers have been formed. Synthesis of compound **148** having 3,4-*O*-benzylidene group was carried out in an indirect way. L-Arabinose-based macrocycles had medium effect as enantioselective catalysts. The best results among these components have been obtained using crown ether **148** [3].

3. Main intermediers of ribose-based crown ethers have been synthesized applying a new method. The appropriate monosaccharides containing epoxy or acetal group have been

converted using regio- and stereoselective reactions. Selective protection of primary hydroxyl group has been carried out using Mitsunobu-reaction. Crown ether (**129c**) prepared from the latter compound induced good enantioselectivity in a Michael-addition (80 % ee) [5].

New altropiranoside-based macrocycles have been synthesized from a compound, that has been formed from in the ring-opening reaction of 2,3-anhydro-mannopyranoside derivative with ethanolamine. This reaction was regio- and stereoselective [5].

4. 1,4-Di-*O*-benzyl- and 1,4-di-*O*-methyl-L-threitol-based chiral crown ethers have been prepared using diethyl-tartrate as starting material. These compounds generated significant asymmetric induction in some model reactions. Intramolecular ring-closure of 2'-hydroxychalcone has been carried out in good ee value (66 % ee) in the presence of **156b** threitol-based catalyst. This is remarkable because as far as we know, this type of synthesis of flavanone has not been achieved enantioselectively.

5. The fact has been identified that among the crown ethers synthesized up to now the **39a** D-glucose-based monoaza-15-crown-5 lariat ether having a 3-hydroxypropyl substituent on the nitrogen is the most effective enantioselective catalyst in the liquid-liquid phase Darzens-condensations. In the reaction of 4-phenyl- α -chloroacetophenone with aromatic aldehydes *trans*-epoxyketones were obtained in optical yields of 40-96 %. Use of substituted benzaldehydes led to lower ee values than applying benzaldehyde (96 %) [1,4].

In the reactions of aromatic aldehydes with 2-chloro-1-indanone enantioselectivities were up to 85 %. In case of applying 2-chloro-1-tetralone containing larger ring, the best optical purity was 75 %. Use of substituted benzaldehydes provided lower ee values (except in two cases) [4].

In the Michael-addition of diethyl acetamidomalonate to aromatic nitrovinyl compounds catalyst **39a** generated asymmetric induction up to 99 % ee [1].

6. The glucose-based crown ether **39a** induced a greater extent of asymmetric induction in Darzens-condensation of heteroaromatic chloromethyl ketones (containing furan, thiophene and pyrrole ring) with various aromatic aldehydes. Epoxyketones formed with negative optical rotation values were obtained in variable ee values (24-70 %) applying 2-(chloroacetyl)furan. The use of substituted benzaldehydes led to higher optical yields than utilizing benzaldehyde. Effect of the substituents was the opposite in the Darzens-condensation of 2-(chloroacetyl)thiophene. The reaction of substituted benzaldehydes with

this compound provided lower ee values of 51-68 %. The catalyst **39a** proved to be barely effective in Darzens-condensations of 2-(chloroacetyl)pyrrole and *N*-methyl-2-(chloroacetyl)pyrrole [1,2].

7. Epoxiketones containing *N*-methylpyrrole ring have been synthesized in liquid-liquid epoxidation using catalyst **39a** in optical yield of 51-88 % [2].

6. Possibilities of application

This work contributes to enhance the knowledge connected to monosaccharide-based chiral crown ethers. Methods and opportunities of application could aid the development of the subject area and the better understanding of the mechanism of the investigated reactions. Syntheses could supply the further researches. Crown ethers containing fluorescent groups can be suitable for spectroscopic discrimination of ions or enantiomers.

Synthesis of enantiopure materials under phase transfer conditions is both economically and environmentally significant. Those model reactions are especially interesting, in which chiral epoxiketones were formed, because these compounds are biologically active and are potential sources of intermediers in pharmaceutical industry. The Darzens-condensation carried out under phase transfer conditions may be suitable for application in large scale. Synthesis of the chiral flavanone utilizing 2'-hydroxychalcone can be useful for practical application.

7. Articles and presentations

7.1. Publications in the subject of the dissertation

- [1] Bakó Péter, **Rapi Zsolt**, Keglevich György, Szabó Tamás, Sóti Péter, Vígh Tamás, Grün Alajos, Holczbauer Tamás: Asymmetric C-C bond formation via Darzens condensation and Michael addition using monosaccharide-based chiral crown ethers
Tetrahedron Letters **2011**, 52, 1473. [IF(2010): 2,618; cit.: 2]
- [2] **Rapi Zsolt**, Szabó Tamás, Keglevich György, Szöllősy Áron, Drahos László, Bakó Péter: Enantioselective synthesis of heteroaromatic epoxyketones under phase-transfer catalysis using D-glucose- and D-mannose-based crown ethers
Tetrahedron: Asymmetry **2011**, 22, 1189. [IF(2010): 2,484; cit.: 0]

- [3] Szabó Tamás, **Rapi Zsolt**, Keglevich György, Szöllősy Áron, Drahos László, Bakó Péter: Synthesis of L-arabinose-based crown ethers and their application as enantioselective phase transfer catalysts
Arkivoc **2012** (in press) [IF(2010): 1,096; cit.: 0]
- [4] **Rapi Zsolt**, Bakó Péter, Keglevich György, Szöllősy Áron, Drahos László, Botyánszki Adrienn, Holczbauer Tamás: Asymmetric phase transfer Darzens reactions catalyzed by D-glucose- and D-mannose-based chiral crown ethers
Tetrahedron: Asymmetry **2012**, 23, 489. [IF(2010): 2,484; cit.: 0]
- [5] **Rapi Zsolt**, Bakó Péter, Keglevich György, Szöllősy Áron, Drahos László, Hegedűs László: Synthesis of ribose and altrose based azacrown ethers and their application in an asymmetric Michael addition
Tetrahedron **2012** (submitted)

7.2. Publications connecting to the topic of the dissertation

- [6] Makó Attila, **Rapi Zsolt**, Drahos László, Szöllősy Áron, Keglevich György, Bakó Péter: Enantioselective Michael addition of 2-nitropropane to substituted chalcones and chalcone analogues catalyzed by chiral crown ethers incorporating an α -D-glucose and α -D-mannose unit
Letters in Organic Chemistry **2010**, 7, 424. [IF: 0,785; cit.: 1]
- [7] Makó Attila, **Rapi Zsolt**, Keglevich György, Szöllősy Áron, Drahos László, Hegedűs László, Bakó Péter: Asymmetric epoxidation of substituted chalcones and chalcone analogues catalyzed by α -D-glucose- and α -D-mannose-based crown ethers
Tetrahedron: Asymmetry **2010**, 21, 919. [IF: 2,484; cit.: 2]
- [8] Bakó Péter, Keglevich György, **Rapi Zsolt**: Asymmetric phase transfer reactions catalyzed by chiral crown ethers derived from monosaccharides
Letters in Organic Chemistry **2010**, 7, 645. [IF: 0,785; cit.: 2]
- [9] Bakó Péter, Keglevich György, **Rapi Zsolt**, Tőke László: The enantiomeric differentiation ability of chiral crown ethers based on carbohydrates
Current Organic Chemistry **2012**, 16, 297. [IF(2010): 2,92; cit.: 0]

7.3. Oral and poster presentations

1. **Rapi Zsolt**, Szöllősy Áron, Drahos László, Szabó Tamás, Vígh Tamás, Müller Judit, Bakó Péter: Monoszacharid alapú királis koronaéterekkel katalizált aszimmetrikus Darzens-kondenzációk (2009. október 26-29. XXXII. Kémiai Előadói Napok, Szeged)
2. **Rapi Zsolt**, Szöllősy Áron, Drahos László, Szabó Tamás, Vígh Tamás, Müller Judit, Bakó Péter: Heteroaromás klóracetil-vegyületek monoszacharid alapú királis koronaéterekkel katalizált aszimmetrikus Darzens kondenzációja (2010. február 4. Oláh György Doktori Iskola Konferenciája, Budapest; poster)
3. **Rapi Zsolt**, Vígh Tamás, Szabó Tamás, Sóti Péter, Bakó Péter: Monoszacharid alapú királis koronaéterek szintézise és alkalmazása enantioszelektív reakciókban (2011. február 3. Oláh György Doktori Iskola Konferenciája, Budapest)
4. **Rapi Zsolt**, Vígh Tamás, Szabó Tamás, Bakó Péter: Monoszacharid alapú királis koronaéterek (2011. szeptember 3. Szénhidrátkémiai Munkabizottság Ülése, Budapest)