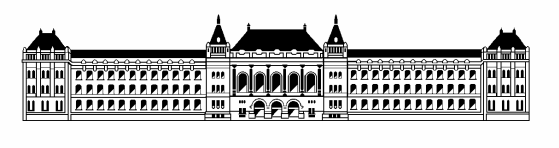

BUDAPESTI UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH PHD SCHOOL

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

Theses

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1. Introduction

One of the main areas of organic chemical research nowadays is the asymmetric catalysis with the aim of synthesizing optically pure compounds. The topic is of great importance as it is a basic requirement of today's chemical industry to prepare biologically active compounds (i.e. medicines, pesticides, cosmetics) in enantiopure form. One of the most attractive approaches of catalytic asymmetric syntheses is the application of enantioselective catalysts. The generally applied technique for catalytic asymmetric syntheses is the performance of the reactions under phase transfer conditions. This method has a great advantage due to the reaction's operational simplicity and environmental concerns.

In most cases monosaccharide-based chiral crown ethers can be considered as suitable phase transfer catalysts. However the nature of these macrocycles especially with reference to their chirality makes them capable of generating asymmetric induction in some reactions. It is also worth noting that carbohydrates are easily available and non-toxic, natural starting materials. Over the past few decades numerous carbohydrate-based macrocycles have been synthesized and examined particularly with regards to their complexing ability. Later it established that the compounds were able to differentiate between enantiomers therefore they became capable for the separation of the enantiomers and generation of the asymmetric induction. Up to now only a limited number of carbohydrate-based crown ethers proved to be effective phase transfer catalysts in asymmetric reactions. [1]

Over the past three decades macrocycles incorporating monosaccharide unit have been synthesized and examined at the Department of Organic Chemistry and Technology at the Budapest Technical University. Some compounds have been explored to function as effective enantioselective catalysts in some phase transfer reactions in which chiral products could be formed and the mechanism of the reaction could be affected by a metal cation as well. Hopefully our results may be of industrial importance.

[1] Jarosz, S.; Listkowski, A. *Curr. Org. Chem.* **2006**, *10* , 643

2. The aim of the research

Joining to the research referred to above, my aim of the present work was the synthesis and study of new monosaccharide-based crown ethers in order to find molecules that are able to generate asymmetric induction in specific reactions when applied as phase transfer catalysts. In addition to the description of results, the theoretical explanation and also the studied structure-activity relationships of the catalysts were planned to be studied.

3. Experimental methods

Conventional methods of organic preparative chemistry were used in syntheses, crystallization, and column chromatography in order to purify the crude products. Compounds were identified by IR, NMR and MS spectroscopy in addition to the elemental analyses. Enantiomeric excess (ee) was mainly determined by ^{1}H NMR spectroscopy applying a chiral shift reagent although in some cases the measurement was carried out by the use of chiral HPLC. Verification of the absolute configuration was obtained by CD spectroscopy.

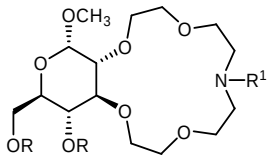
4. Results

My research work consists of three main parts. First different monosaccharide-based chiral crown ethers have been synthesized in multi-steps partially on the basis of methods as well as elaborated in our research group and described in chemical literature. In the second part of my dissertation the application of the above mentioned molecules as chiral phase transfer catalysts in asymmetric reactions of CH-acid compounds (2-nitropropane, substituted and unsubstituted malonic esters) as well as in the enantioselective epoxidation of chalcone and chalcone derivatives is reported. Finally molecular modeling calculations providing theoretical explanation to the obtained experimental data are presented.

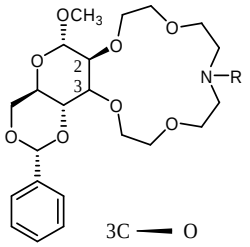
4. 1. Synthesis of crown ethers

First compounds of similar structure namely monoaza-15-crown-5 lariat ethers incorporating gluco-, manno- and altropyranoside units were synthesized (Scheme 1, com-

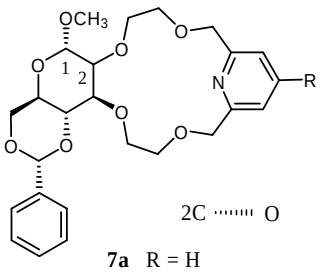
pounds **1**, **2** and **3**). Applying the appropriate protected monosaccharides as starting materials, these derivatives were obtained in three steps. The method referred to above is shown in more details on Scheme 2, where the altropyranoside-based crown ethers **3** will be represented. In each compound glycosidic hydroxyl group of the sugar moiety was protected in the form of methyl glucoside while the C(4) and C(6) hydroxyl groups as benzylidene acetal, respectively. The substituents (of different lipophylity) on the nitrogen atoms of the macrocycles were varied in order to examine their effects in various reactions.



1a R – R = CH–Ph, $R^1 = (CH_2)_3OH$
1b R – R = CH–Ph, $R^1 = (CH_2)_3OCH_3$
4a R – R = CH-(1)-Naph, $R^1 = (CH_2)_3OH$
4b R – R = CH-(1)-Naph, $R^1 = (CH_2)_3OCH_3$
5a R – R = $C(CH_3)_2$, $R^1 = (CH_2)_3OH$
5b R – R = $C(CH_3)_2$, $R^1 = (CH_2)_3OCH_3$
6a R = H, $R^1 = (CH_2)_3OH$
6b R = H, $R^1 = (CH_2)_3OCH_3$

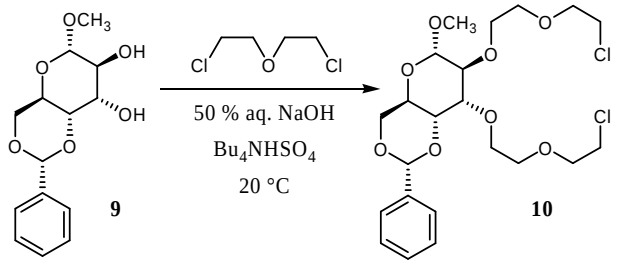


3C — O
2a R = $(CH_2)_3$-OH
2b R = $(CH_2)_3$-OCH_3
3C ····· O
3a R = $(CH_2)_3$-OH
3b R = $(CH_2)_3$-OCH_3
3c R = H



2C ····· O
7a R = H
7b R = OCH_3
7c R = $OCH_2CH{=}CH_2$
2C — O
8 R = H

Scheme 1



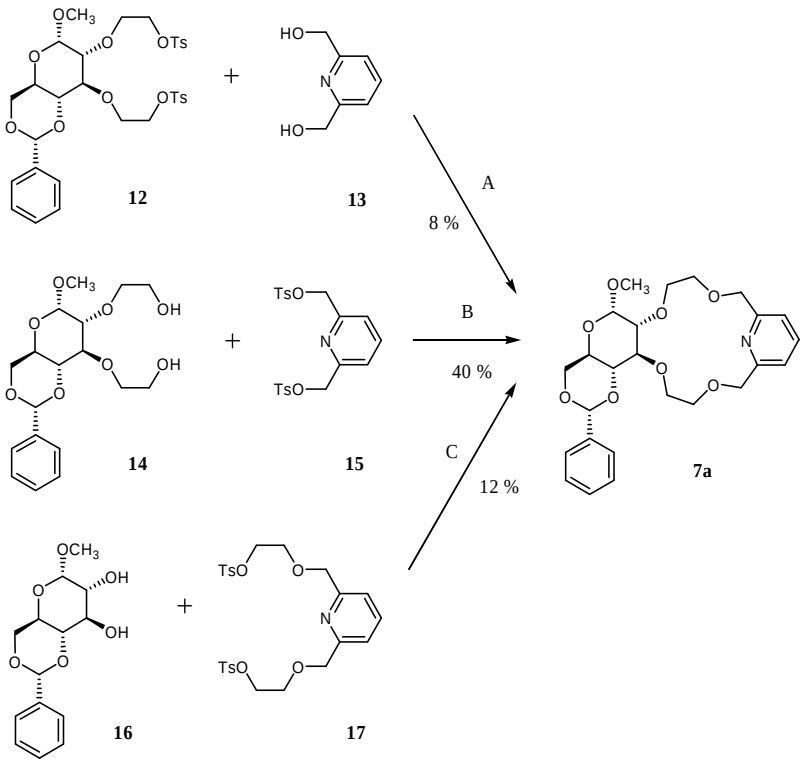
50 % aq. NaOH
Bu_4NHSO_4
20 °C
9
10
NaI
acetone
reflux
24 h
11
$R{-}NH_2$
Na_2CO_3
CH_3CN
reflux
24-48 h

3a R = $(CH_2)_3$-OH
3b R = $(CH_2)_3$-OCH_3

Scheme 2

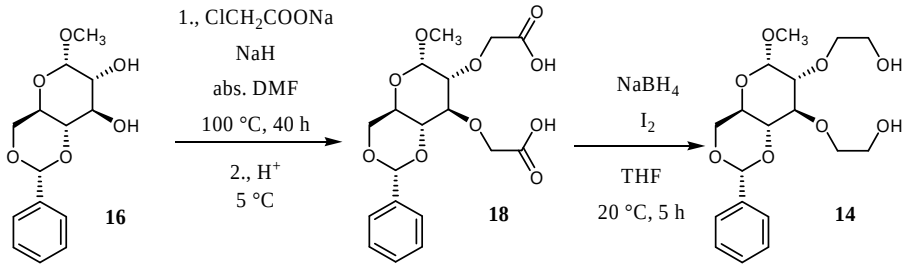
Afterwards the 4,6-*O*-protecting groups were altered in the case of the glucose-based crown ethers in order to synthesize 4,6-*O*-1-napthylmethylene, 4,6-*O*-isopropylidene and lariat ethers with free hydroxyl groups in positions 4 and 6 (Scheme 1 **1**, **4-6** compounds) along with 4,6-*O*-benzylidene acetal. The compound bearing 1-napthylmethylene protecting group was prepared by the reaction of methyl-α-D-glucopyranoside and 1-napthaldehyde-dimethyl acetal in DMF in the presence of camphoresulfonic acid as catalyst. Following the establishment of the required protecting groups the preparation of macrocycle **4** and **5** was accomplished in three steps as described earlier.

Finally the glucopyranoside- and mannopyranoside-based crown ethers incorporating a pyridine ring were synthesized. The macrocycles were obtained in 5 to 10 steps based on methods described in chemical literature for similar compounds, however new ideas were also considered. The synthesis of crown ether **7a** incorporating unsubstituted pyridine ring was attempted by applying three different ring closure reactions. Amongst them method B proved to be favored (Scheme 3). It is worth mentioning that beside of the template effect the tendency for elimination may be responsible for the yield of the ring closure reactions. The complexing ability of the reagents in the intramolecular ring closure reactions was investigated by FAB-MS spectroscopy.



Scheme 3

The synthesis of the “half-crown” diol **14** was accomplished by a new, reliable and reproducible method, in which sugar diacid **18** originated from the *O*-alkylation of compound **16** carried out with sodium chloroacetate, was reduced (Scheme 4). The method described as above was successfully applied in the synthesis of the mannose analogue as well.

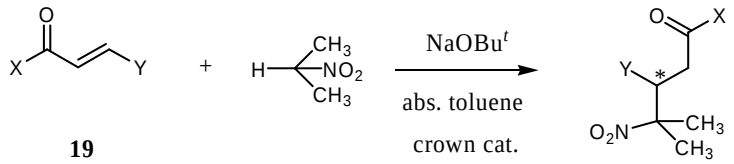


Scheme 4

The alkali metal picrate extracting ability of some carbohydrate-based crown ethers was measured and compared in dichloromethane-water system by which the phase transfer ability could be well characterized. It has been found that the substituents on the nitrogen atom had tremendous influence on the extracting ability and selectivity. Additional mass spectroscopy investigations confirmed that the glucose-based crown ethers had stronger complexing ability than mannose-based analogues of similar structure, which was explained by the difference in the configuration of the macrocycles. Later this difference yielded dissimilar results in enantioselective syntheses.

4. 2. Enantioselective syntheses

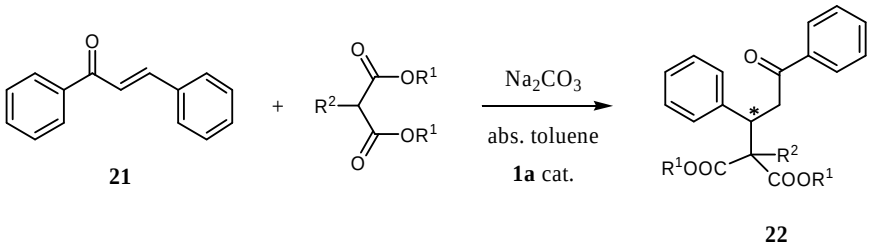
The newly prepared compounds were used as chiral phase transfer catalysts in two-phase model reactions, in which good and outstanding results were achieved. Significant enantioselectivity was obtained in Michael additions (Scheme 5 and 6) of CH-acid compounds (2-nitropropane, different types of malonic esters) with some α,β-enones (chalcones, chalcone analogues etc.) as well as in the epoxidation of chalcone and chalcone derivatives with *tert*-butyl-hydroperoxide (Scheme 7).



19 **20**

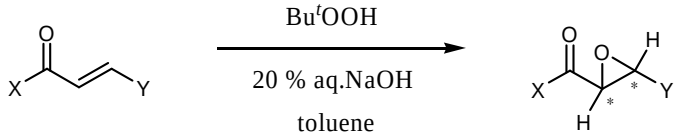
X és Y = Ph, Ar, R

Scheme 5



21 **22**

Scheme 6



19 **23**

Scheme 7

Therefore these reactions were studied in detail.

Structure-activity relationships were concluded from the basis of the experiments. It could be seen that the type and protecting group of the monosaccharide in line with the side chain of the crown ether played a significant role in the enantioselectivity. In case of Michael additions and epoxidations the best asymmetric induction was achieved by the glucose-based macrocycle with 4,6-*O*-benzylidene and 1-napthylmethylene protecting group, while considering the side chain, the hydroxpropyl substituent on the nitrogen atom turned out to be optimal. Applying different types of crown ether catalysts, ee values of 8-92 % and 9-94 % were measured in the reaction of 2-nitropropane with chalcone and epoxidation of chalcone, respectively. It was proved that the 4,6-O-protecting group made the molecule rigid while in the lack of it the enantioselectivity was dramatically decreased. It is worth noting that apart from some exceptions the mannose-based crown ethers promoted the formation of the opposite enantiomer in contrast with glucose-based analogues. For example, while (*R*) Michael adduct and (2*R*,3*S*) epoxy ketone were obtained in the presence of glucose-based catalysts (except for **7**, **8**), the mannose-based macrocycles used as catalyst favored the formation of (*S*) and (2*S*,3*R*) antipodes, respectively. The crown ethers incorporating pyridine unit was found to be moderately effective catalysts (in Michael addition 67-80 %, in epoxidations 25-54 % ee values). In all investigated cases “methylation” of the hydroxypropyl side chain led to lower asymmetric induction. Replacement of the hydroxyl group in the side chain to methoxy

groups (while increasing the lipophylity) generated lower asymmetric induction. Since the macrocycle incorporating glucopyranoside moiety proved to be the most efficient, further experiments were carried out with crown ether **1a**.

The yields and the enantioselectivities in Michael additions are significantly affected by the nature of the substituents of X and Y. In case of substituted chalcones and chalcone analogues lower enantioselectivity was observed in comparison to the values occurred in the case of unsubstituted chalcones (13-58 % and 15-77 % ee, respectively).

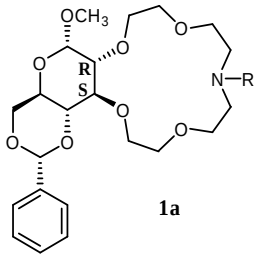
Moderate enantioselectivity was achieved in the additions of malonic esters to chalcone, i. e. in the case of diethyl malonate employing Na_2CO_3 as the base in a solid-liquid two-phase system (8-44 % ee).

Applying substituted chalcones in epoxidation quite different ee values were obtained depending on the characteristics of the substituents (14-99 % ee). Electronic effects were found to be dominated at the Y group of the substituted chalcones.

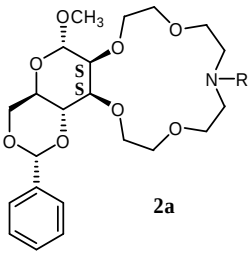
4. 3. Molecular modeling calculations

Molecular modeling calculations were carried out in the Department of Inorganic and Analytical Chemistry with kind help of Dr. Dóra K. Menyhárd, the aim of which was to explore the reaction mechanism of chalcone epoxidation. It was demonstrated that the configuration of the sugar unit anellated the crown system in the catalysts had crucial influence on the enantioselectivity (Scheme 8).

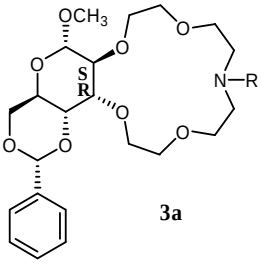
Catalysts



1a



2a



3a

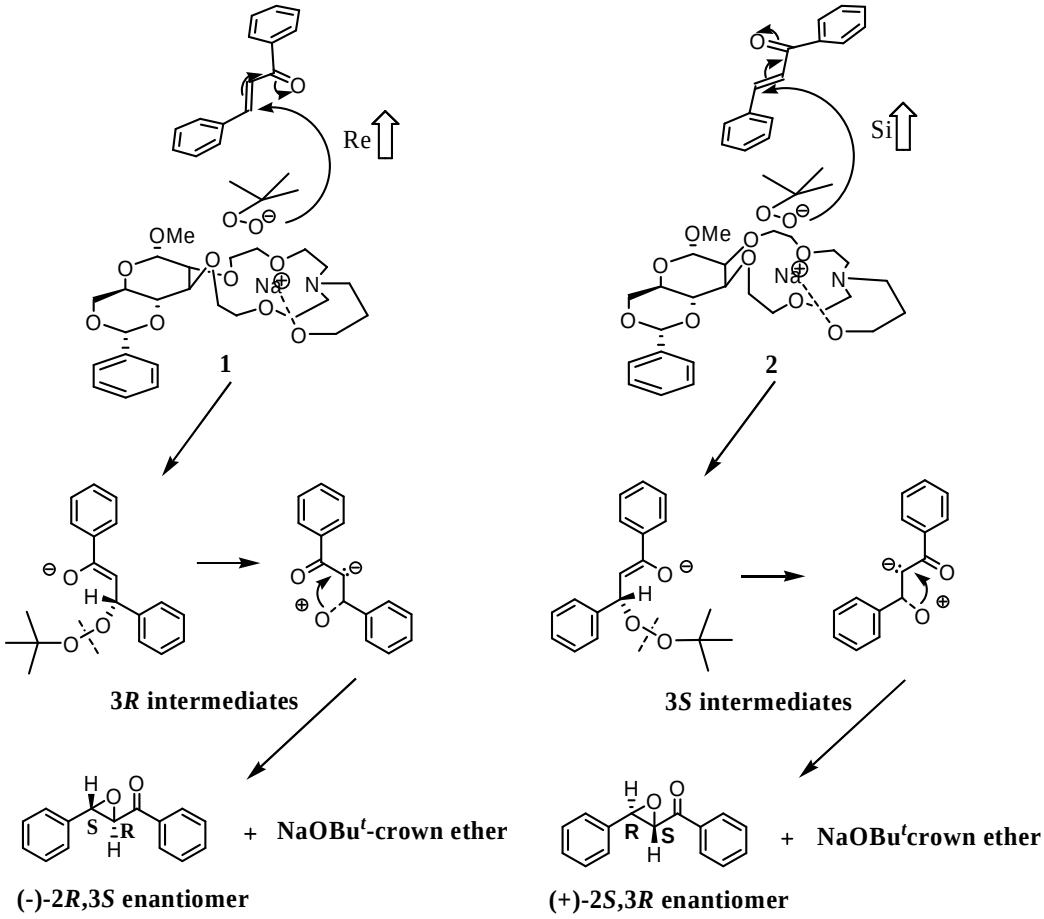
R = $CH_2CH_2CH_2OH$

Preferred enantiomer	(-)-(2*R*,3*S*)	(+)-(2*S*,3*R*)	racemate
Ee (%)	94	82	3

Scheme 8

Based on the results of calculations we gave an explanation for the influence became dominating through the presence of the lariat ether substituent which selected the energetic ordering of the respective chiral transition states through their H-bonding capabilities. It was also found that in the studied systems the conformation of the azacrown

ethers was determined by the presence or absence of the central cation rather than by the approach of the reaction partner. It can be stated that the molecular modeling calculations completely proved our experimental results. Furthermore we successfully demonstrated the possible reason for outstanding asymmetric induction of the glucopyranoside-based crown ethers (and the inefficiency of the compound containing altropyranoside moiety). Additionally we wished to get an answer as to how the configuration of the epoxy ketone products was afforded in case of different crown ethers (Scheme 9).



Scheme 9

5. Application and possible implementation

Besides the asymmetric phase transfer reactions represented as above the successful use of natural starting materials as catalysts gave definite evidence of the reason for existence of enantioselective reactions accomplished under mild reaction conditions.

Hopefully the results of our research and molecular modeling calculations will support the better understanding of these asymmetric syntheses in which chiral crown ethers are used as catalysts. In my synthetic work it was focused on those methods that are environmentally friendly and easy to use. Actually these concerns should serve as

key points for future studies. The starting materials of the chosen model reactions, i.e. the biologically active chalcone and its analogues are of practical importance in chemical industry. The applied methods (Michael addition and epoxidation) can be suitable for the syntheses of such intermediates and compounds that are considered to be biologically efficient. According to our expectations the synthesized macrocycles will also prove to be effective in other types of Michael reactions thus the number of compounds having asymmetric C-C bond can be increased and the method might be applied by the chemical industry. The asymmetric epoxidation of α,β-enones is especially of practical importance as the chiral epoxy ketone resulted from these reactions are widely used in the syntheses of some biologically active compounds.

6. Theses

I. Altogether 13 new chiral crown ethers have been synthesized of which the type of the monosaccharide (**1**-**3**) [1-3, 8], the protecting group on the C-4 and C-6 carbon atoms of the sugar unit and the substituents of the lariat side chain have been modified (**4**-**6**) [7]. New, easily applicable and reproducible method had been elaborated for the preparation of sugar-diol derivatives (i.e. **14**), by which it was possible to build pyridine ring into the macrocycle (**7**-**8**) [9]. Extracting ability and FAB-MS measurements proved that the complex forming ability of glucose-based macrocycles is much bigger in comparison to it's mannose-based analogues. The phenomenon can be explained by the glucose-based crown ether's structure close to the ideal "all gauche" configuration. Additionally it appeared that by the presence of the lariat side chain on the nitrogen atom, the extracting ability was decreased, however the selectivity was increased at the same time [5].

II. The synthesized chiral crown ethers were applied as phase transfer catalysts in the Michael addition of 2-nitropropane with chalcone as well as in the epoxidation of chalcone with *tert*-butyl-hydroperoxide that led to the conclusion that the type of the monosaccharide, along with the change of the protecting group and the substituents of the lariat side chain had high influence on the enantioselectivity [1-3, 6-9]. The glucose-based macrocycles with the presence of aromatic acetal ring proved to be optimal. Methylation of the hydroxyl group on the nitrogen atom of the lariat ether also resulted in reduced enantiomeric excess [7]. Those macrocycles with more rigid structure, which are incor-

porating a pyridine ring, did not increase the chiral discrimination; they proved to be only moderately effective catalysts [9].

III. Comparing the effects (stereochemistry of epoxy ketones and ee %) of similar glucose (**1a**), mannose (**2a**) and altrose-based (**3a**) macrocycles in the epoxidation of chalcone, the conclusion could be drawn that the configuration of the sugar unit anellated to the crown system in the catalysts had crucial influence on the asymmetric induction [1-3, 6-9]. In fact the above was demonstrated by the different energy and construction of the appropriately configurated intermedier's global minimum structures resulted from molecular modeling and quantum chemical calculations [8].

7. Articals and oral presentations

7. 1. Publications in the subject of the dissertation

[1] Bakó P., Bakó T., Mészáros A., Keglevich Gy., Szöllősy Á., Bodor S., **Makó A.**, Tőke L.: Phase-transfer catalysed asymmetric epoxidation of chalcones using chiral crown ethers derived from D-glucose and D-mannose
Synlett, **2004**, *(4)*, 643-646. IF: 2,738; Citations: 10.

[2] Bakó T., Bakó P., Keglevich Gy., Bombicz P., Kubinyi M., Pál K., Bodor S., **Makó A.**, Tőke L.: Phase-transfer catalysed asymmetric epoxidation of chalcones using chiral crown ethers derived from D-glucose, D-galactose and D-mannitol
Tetrahedron:Asym. **2004**, *15*, 1589-1595. IF: 2,386; Citations: 20.

[3] Bakó P., **Makó A.**, Keglevich Gy., Kubinyi M., Pál K.: Synthesis of D-mannose-based azacrown ethers and their application in enantioselective reaction
Tetrahedron:Asym., **2005**, *16*, 1861-1871. IF: 2,429; Citations: 10.

[4] Huszthy P., Bakó P., **Makó A.**, Tőke L.: Királis koronaéterek
Magyar Kémiai Folyóirat, **2005**, *111 (2)*, 55-64. IF: -; I:-.

[5] Bakó P., **Makó A.**, Keglevich Gy., K. Menyhárd D., Sefcsik T., Fekete J.: Alkali metal- and Ammonium Picrate Extraction and Complex Forming Capabilities of D-Glucose and D-Mannose-based Lariat Ethers
J. Incl. Phenom. **2006**, *55*, 295-302. IF: 1,251; Citations: 2.

[6] Pál K., Kállay M., Kubinyi M., Bakó P., **Makó A.**: Circular dichroism spectra of trans chalcone
Tetrahedron:Asym., **2007**, *18*, 1521-1528. IF: 2,634; Citations: -.

[7] **Makó A.**, Szöllősy Á., Keglevich Gy., K. Menyhárd D., Bakó P. and Tőke L.: Synthesis of methyl-α-D-glucopyranoside-based azacrown ethers and their application in enantioselective reactions
Monatsh. Chem. **2008**, *139*, 525–535. IF: 1,426; Citations: 1.

[8] **Makó A.**, K. Menyhárd D., Bakó P., Keglevich Gy., Tőke L.: Theoretical study of the asymmetric phase-transfer mediated epoxidation of chalcone catalyzed by chiral crown ethers derived from monosaccharides
J. Mol. Struct. **2008**, *892*, 336–342. IF: 1,594; Citations: -.

[9] **Makó A.**, Bakó P., Szöllősy Á., Bakó T., Pelcz Cs., Keglevich P.: Synthesis of chiral pyridino-15-crown-5 type ligands containing α-D-hexapyranoside unit and their application in asymmetric synthesis
Arkivoc **2009**, (vii), 165-179. IF(2008): 1,253; Citations: -.

7. 2. Oral and poster presentation

1. **Makó A.**, Bakó P. és Bakó T. Kalkonok aszimmetrikus epoxidációja szénhidrátalapú koronaéterek jelenlétében
   XXVII. Kémiai Előadói Napok (MKE, Szeged, 2004. október 25-27.)
2. Pál K., Kubinyi M., **Makó A.**, Bakó P. Kalkon-epoxidok abszolút konfigurációjának meghatározása UV-Vis-CD-spektroszkópiával
   X. Nemzetközi Vegyészkonferencia (Kolozsvár, 2004. november 12-14.)
3. **Makó A.**, Bakó P., Szöllősy Á., Bodor S., K. Menyhárd D., Tőke L. D-glükózból felépülő királis koronaéterek szintézise és alkalmazása enantioszelektív katalizátorként
   MKE Vegyészkonferencia (Hajdúszoboszló, 2005. június 28-30. poster)
4. Pák K., Kubinyi M., Bakó P., **Makó A.** CD-Spectroskopy of chalcone epoxides obtained using chiral crown ether catalysts
   (VIII.th International Conference on Molecular Spectroskopy Ladek zdroj. Lower Silesia, Poland, 2005. szeptember 13-18. poster)
5. **Makó A.**, K. Menyhárd D., Bakó P. α-D-Glükóz- és α-D-mannóz-alapú azakorona éterek szintézise és alkalmazása kalkonok enantioszelektív epoxidációjában
   Oláh György Doktori Iskolájának IV. konferenciája (BME, Budapest, 2007. február 7.)