Budapest University of Technology and Economics
Department of Organic Chemical Technology

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

PhD. Thesis

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1. Introduction

Chemistry, owing to the appearance of the supramolecular chemistry, has gone through huge development during the last decades. The supramolecular chemistry deals with the supramolecula which is an association of two or more stable particles, cohered by not covalent but so-called secondary forces. This field can be examined well through crown ethers. If we make these macrocyclic molecules chiral by building monosaccharide into the ether then they have not only property of complex forming property but also they are showing two interesting features: on one hand they recognize enantiomers i.e. they are able to make difference between sides of enatiotop and therefore these compounds are suitable for separation of raceme mixture. On the other hand participating in enantiomer selective reactions they are able to make asymmetric induction so the product of the reaction is not raceme mixture but any of the enantiomers (antipodes) in excess (in best case the pure enantiomer).

All this give the currency of the project, since nowadays important demand opposite both chemical industry and pesticide industry, is that biologically active compounds comes to public utilization in pure enantiomer form. The most modern (and most economical) method for preparation is the enantiomer selective synthesis with chirally auxiliary products or chirally catalyst in presence.

Theoretically chiral crown ethers made up of carbohydrates are hiding serious potentiality in them. Practically slight part of the big number of synthesized molecules was effective. That is why we aimed to prepare new carbohydrate-base crown ethers which are active phase-transfer catalysts in enantioselective reactions as well as we planned to extend its field of application and searched new model reactions for our catalysts.

2. Summary of results

The paper consists of two bigger parts. In the first part I am reviewing synthesis of new carbohydrate-based crown-ethers as well as presenting examination for complex formation. In the second part I am presenting the application of the compounds above in few enantiomer selective phase-transfer reactions.

2.1 Synthesis and complex forming ability

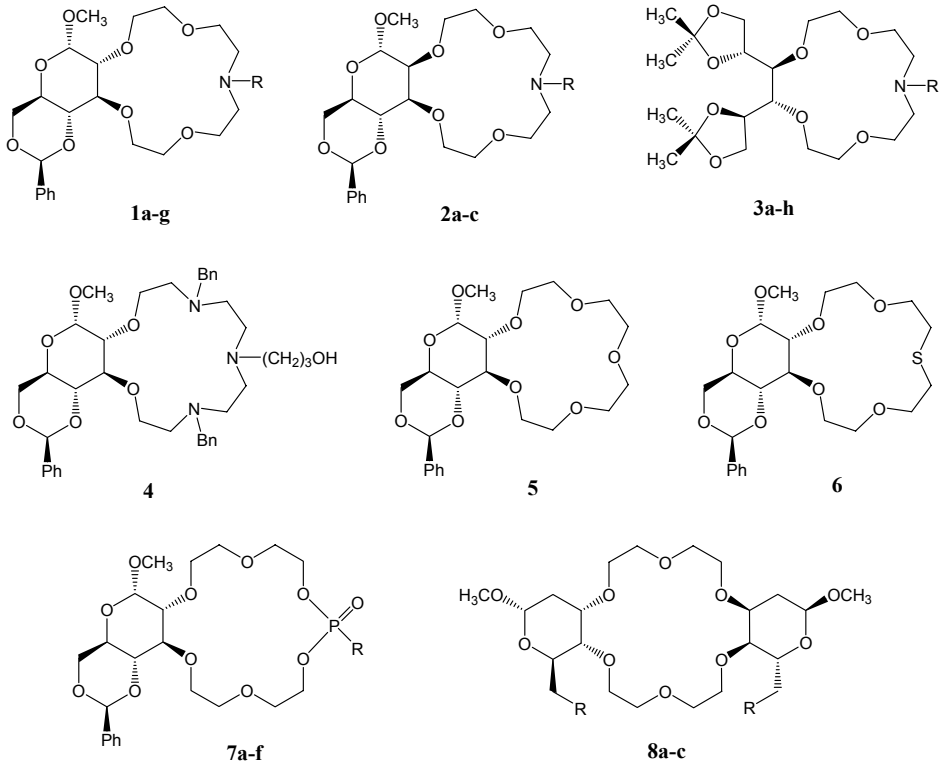


Figure 1.

In the Figure 1. **1-3** monoaza-15-crown-5 compounds were prepared from the properly protected monosaccharide with a three-step reaction elaborated at the department. The latter three-step reaction is exemplified in the Figure 2. through the example of glucose-based crown-ethers. These compounds are containing different substituents on the nitrogen atom of the ring. Crown ethers containing mannose and mannit were prepared from the properly protected monosaccharide according to synthesis in the Figure 2.

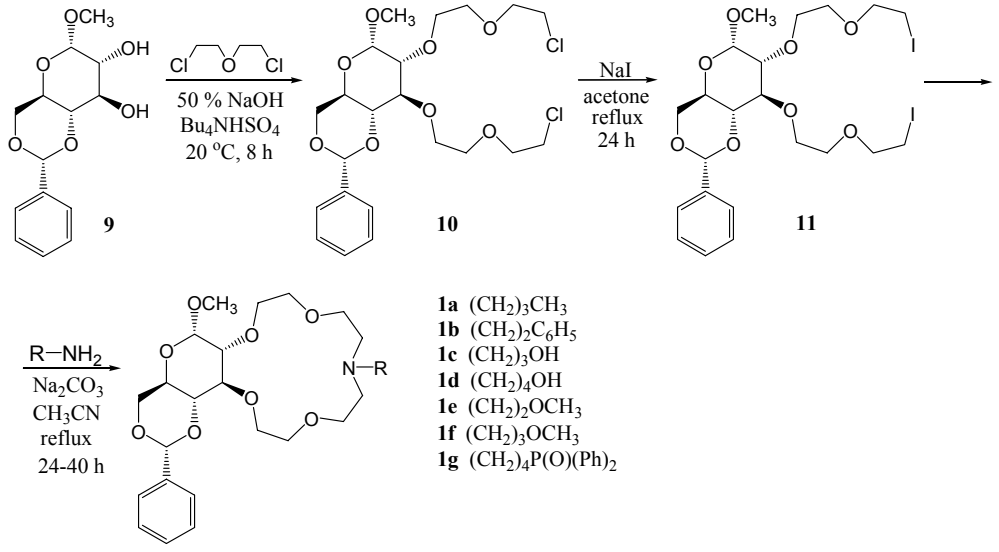


Figure 2.

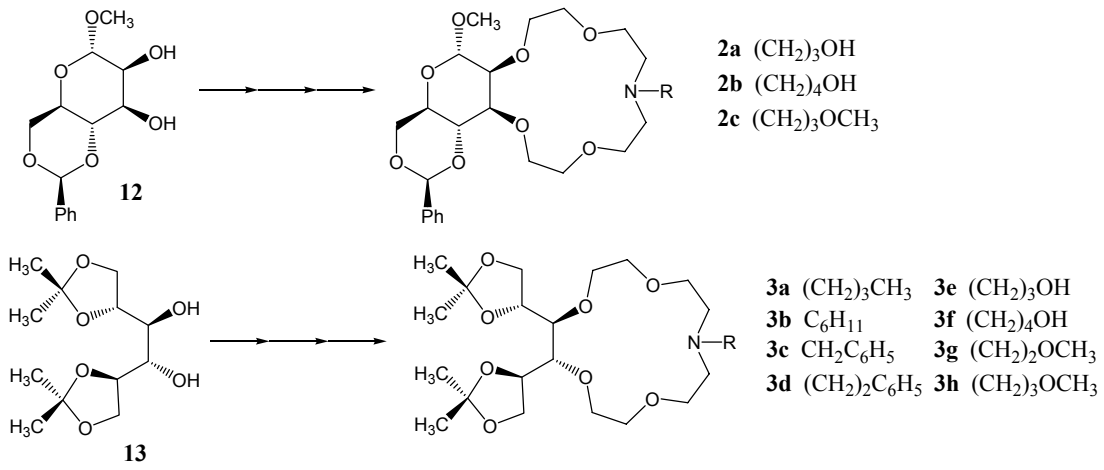


Figure 3.

The glucose-based derivative not substituted on the nitrogen was prepared from the bischloro compound (**10**) with two-step reaction. First one was a ring closure with tosyl-amide then we removed the tosyl-group with Na-amalgam (Figure 4). We synthesized the macrocyclic compounds unsubstituted and containing mannose as well as mannit derivative in an analogous way.

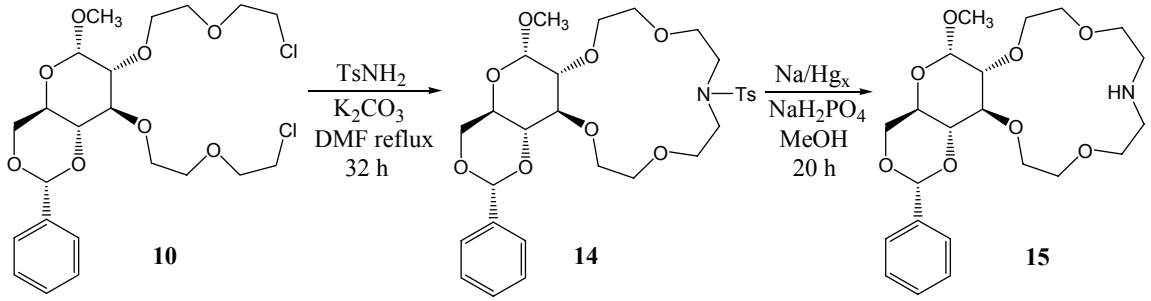


Figure 4.

Besides macrocycles mentioned above we synthesized type of triaza-15-crown-5 made up of glucose (**4**), 15-crown-5 containing only oxygen as well as monotia-15-crown-5. Starting from the properly protected glucose we obtained monophospha-17-crown-7, in the Figure 5. with 5-step synthesis which are containing different kinds of functional groups on the phosphor of the ring such as: phosphoric acid (**7a**), phosphoramide (**7b-d**), phosphorester (**7e-f**).

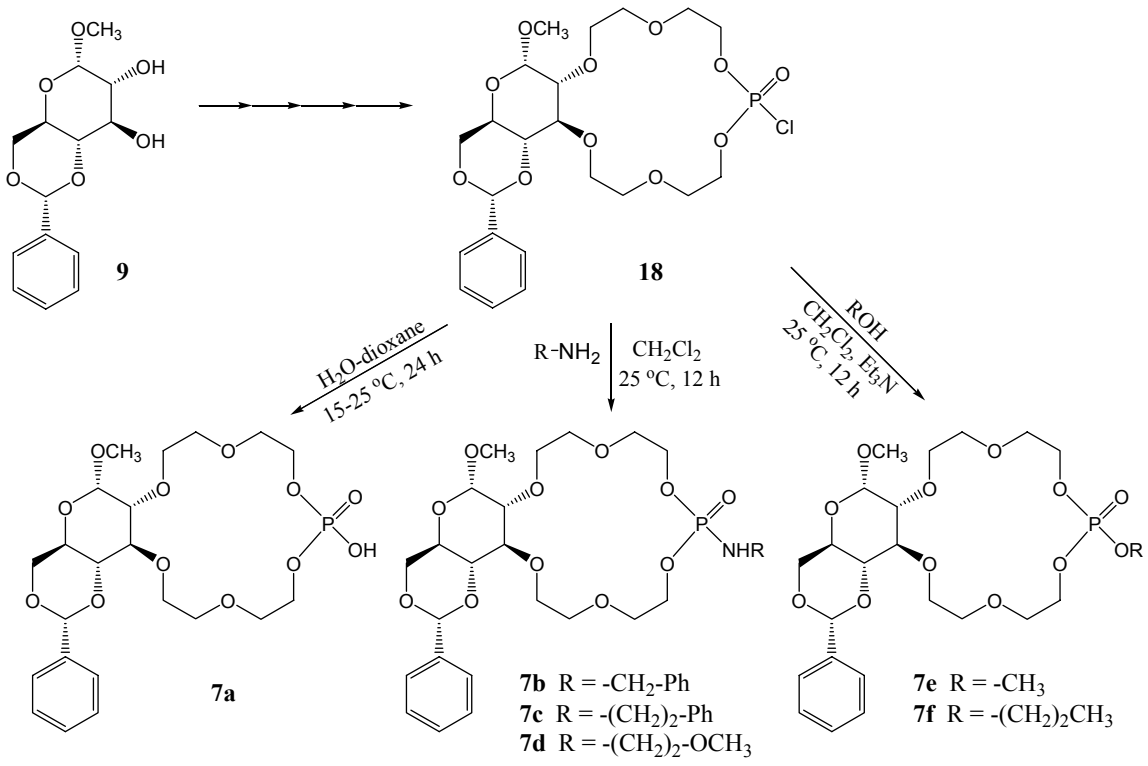


Figure 5.

We also synthesized two types of macrocyclic compounds made of ribo-hexapiranozid (**8a-c**), last three steps of this synthesis can be seen in the Figure 6.

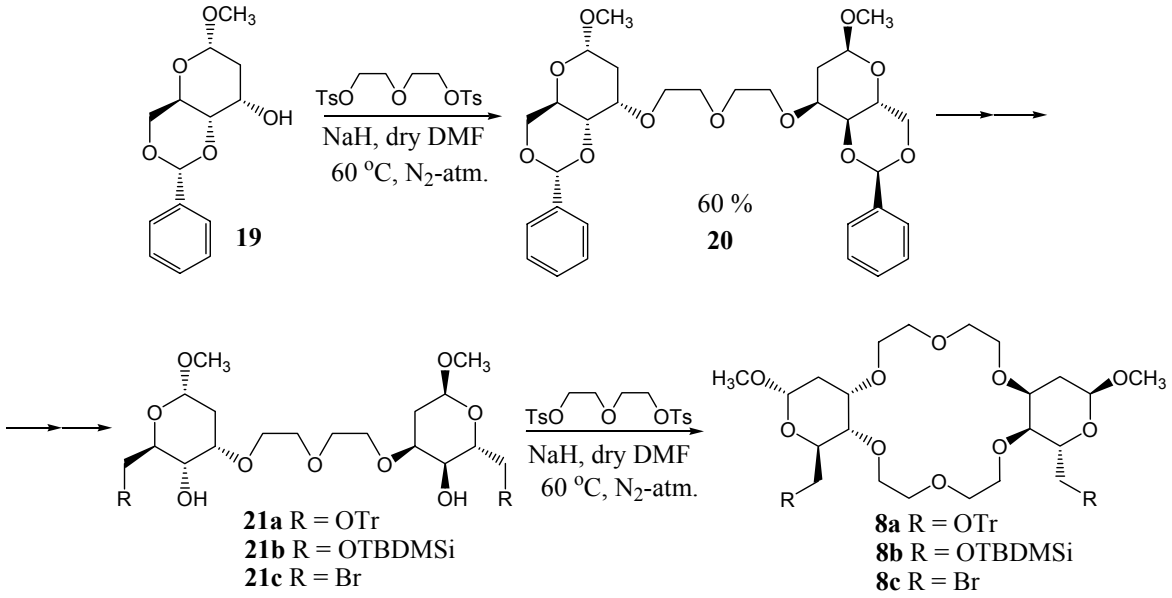


Figure 6.

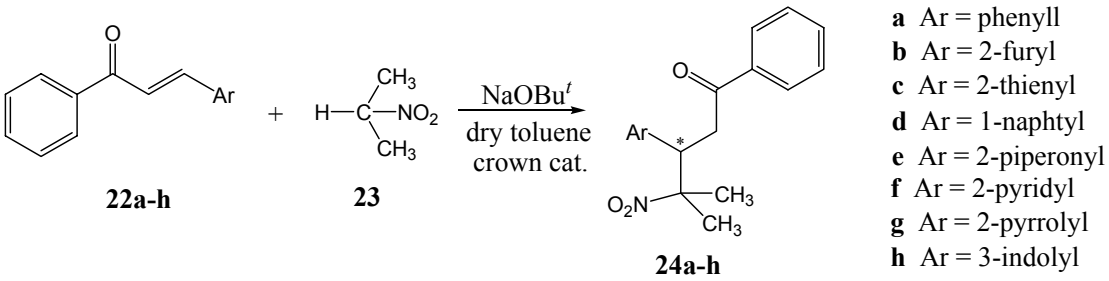
To describe the tendency of complex forming, we examined the picrate-salt's extracting ability, applying lithium, sodium, potassium, rubidium, cesium, and ammonium-picrates in dichloromethane - water mixture.

It was experienced that length of the side-arm and the heteroatom at the end of the chain have strong effect on the feature of the lariat ether. In general the tendency of the complex forming decreases in the case of lariat-ethers (**1-3**) (to unsubstituted compounds **15-17**) but the ion selectivity increases. Those macrocycles containing sulphur (**5**) showed the least extracting ability but this molecule has the most considerable ion-selectivity (prefers lithium). The best result was returned with not substituted glucose-based derivative **15** which showed 97 -100 % of extracting ability in case of 6 picrate salts.

2. 2. Asymmetric synthesis

Several of our compounds made asymmetric induction when we applied them as chiral phase-transfer catalyst. In most efficient reactions some CH acid compound is the reagent from which reactive anion was formed by base with adequate pK_a in the course of reaction, all this happens in presence of catalytic amount of chiral crown ether. If we add the salt of base as solid to the reaction mixture which is prepared in apolar solvent, the salt go into the solvent as rate as the crown compound forms complex with it and brings the salt of the base in solvent this way (solid-liquid phase transfer process). After that the CH acid compound can lose proton and react with the other reagent but each process requires chiral environment. This process can lead to asymmetric induction when some of the enantiomers forms in excess instead of racemic mixture.

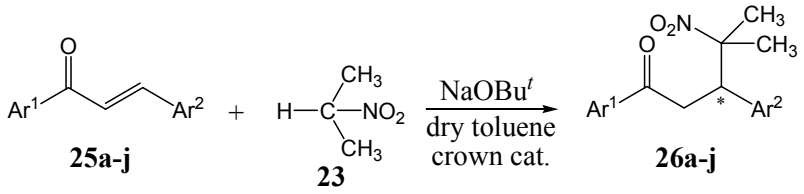
I am presenting in my dissertation three different kinds of reactions in which I was able to reach 90 % enantiomer excess in some case.



22a-h **23** **24a-h**

a Ar = phenyll
b Ar = 2-furyl
c Ar = 2-thienyl
d Ar = 1-naphtyl
e Ar = 2-piperonyl
f Ar = 2-pyridyl
g Ar = 2-pyrrolyl
h Ar = 3-indolyl

Figure 7.



Compound	Ar^1	Ar^2
a	4-Cl-Ph	Ph
b	4-CH_3-Ph	Ph
c	4-CH_3O-Ph	Ph
d	Ph	4-CH_3-Ph
e	Ph	4-NO_2-Ph
f	Ph	4-$N(CH_3)_2$-Ph
g	Ph	3,4-di-CH_3O-Ph
h	4-Cl-Ph	4-Cl-Ph
i	4-F-Ph	2-Cl-Ph
j	4-NO_2-Ph	4-CH_3O-Ph

Figure 8.

The Figure 7. and 8. shows the Michael addition in which the monoaza-15-crown-5 (**1-3**) containing one carbohydrate unit was found the most effective in solid-liquid mixture (NaOBu^t, toluol).

We have found that ratio of the chiral induction and the yield depend on the type of carbohydrate and its substituents as well as the side-arm on the nitrogen atom of the crown-ring. In the raction of 2-nitropropane with chalcone we reached the best result with the glucose-based macrocycle containing 2-metoxietil group substituent. This catalyst gave the (+)-(*R*)-antipode of adduct's (**24a**), while the mannose-based crown-ether with 3-hidroxypropyl side-arm (**2b**) we obtained (-)-(*S*) product with 97 % in excess. In the reactions of chalcone derivates containing different substituents on the aromatic ring (8.figure) in each case we experienced less (to the unsubstituted chalcone) enantiomer excess (**26 a-j**, 16-72% ee.) i.e. the substitutes worsened the asymmetric induction. It didn't bring better result when we exchanged the aromatic ring for other type of aromatic or heteroaromatic compounds because we were able to approach the results which have been resulted with chalcone (**22a**) only 2 times (**24b**, 80% ee., **1g** with macrocycle; **24f**, with crown-ether 81% ee.).

Examining the substituents on the nitrogen of the crown ring we found that benzyl-, 2 phenyl -ethyl-, and cyclohexyl groups effects less active catalysts (10-47% ee.). The best enantiomer selectivity have been resulted with those lariat ethers that have certain length of side-arm

(optimally possessing 3-carbon chain) and hetero atom at the end of the chain (OH, OCH_3, P=O) (87-97% ee.).

2. 2. 2. *Darzens condensation between α-chloro-acetophenone and aromatic aldehydes*

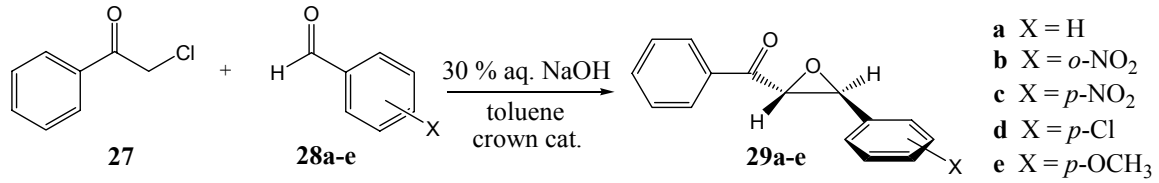
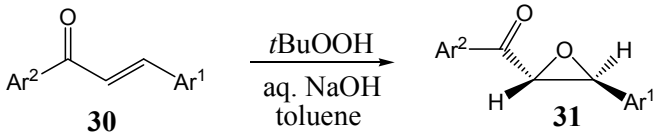


Figure 9.

This reaction was carried out in liquid-liquid mixture (NaOH-toluol) and always gave trans isomers. It turned out to be the most effective catalyst are the lariat-ethers made up from glucose-based monoaza-15-crown. As concerning the structure of the catalyst we revealed few correlations, for instance hydroxyl end-group of the side-arm chain has crucial role since if blocked as ether worsen the catalytic effect. Length of the side-arm on the nitrogen is also influential factor: optimal if it contains 3 carbons. The reaction takes place with larger enantioselectivity at lower degree. The best result was obtained by glucose-based macrocycle containing 3-hidroxypropyl substitutions at -20 ^oC so we got enantiomer (-)-(2*R*, 3*S*) of epoxi-ketone (**29a**) 72% in excess (Figure 9.).

2. 2. 3. Epoxidation of the double-bond in chalcone and substituted chalcones



	Ar^1	Ar^2		Ar^1	Ar^2
a	Ph	Ph	**h**	4-NO_2-Ph	Ph
b	Ph	4-CH_3-Ph	**i**	4-OCH_3-Ph	4-NO_2-Ph
c	Ph	4-OCH_3-Ph	**j**	4-Cl-Ph	4-Cl-Ph
d	Ph	4-Cl-Ph	**k**	4-F-Ph	2-Cl-Ph
e	Ph	2,4-di-Cl-Ph	**l**	4-CH_3-Ph	4-CH_3-Ph
f	Ph	2,4-di-Cl-Ph	**m**	4-CH_3-Ph	2,4-di-Cl-Ph
g	4-CH_3-Ph	Ph			

Figure 10.

Epoxidation of the chalcone and its substituted derivatives was accomplished in liquid-liquid phase mixture (20 % NaOH - toluol) with terc-butyl peroxide, at 6 ^{o}C (Figure 10). We obtained trans epoxy ketone in all cases. We examined the effect of the side-arm and the monosaccharide unit. The best result have been given with glucose-based catalyst containing of 3-hydroxypropyl substituent (**1c**) so 2*R*,3*S* enantiomer arose 92% in excess. We obtained 2*S*,3*R* antipode 80% in excess with crown-ethers containing the same substituted mannose. In case of substituted chalcones we reached better enantioselectivity with derivatives containing methyl- (**31b**, Ar^1 = H, Ar^2 = 4-CH_3-Ph), as well as methoxy group (**31c**, Ar^1 = H, Ar^2 = 4-OCH_3-Ph) so we obtained 71-81 % ee, at room temperature.

3. The results' magnificence and application

In the course of our project we were examining methods for synthesizing chiral crown-ethers made up from carbohydrates and possible application areas. We showed few relates amongst construction of macrocyclic molecules, features of complex forming property and the asymmetric induction causing by them. These rules can be omnified.

The enantioselective method meets both today's strict environmental and economical requirements. We succeeded in finding effective catalyst for certain reactions. The enantiomer excess (72-97%) reached are good reason for trying in practical important reactions. Besides that lariat-ethers could be used whether themselves or stuck to solid carrier (after further research) as enantioselective electrode or column charge in HPLC.

Publications recited in the PhD. Paper

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[B5]. Bakó, T.; Bakó, P.; Keglevich, Gy.; Báthori, N.; Czugler, M.; Tatai, J.; Novák, T.; Parlagh, Gy.; Tőke, L. Enantioselective Michael reaction of 2-nitropropane to chalcone analogues catalysed by chiral azacrown ethers based on α-D-glucose and D-mannitol *Tetrahedron: Asymmetry* **2003**, *14*, 1917.

[B6]. 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.

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