

Synthesis and determination of pK_a values of new enantiopure pyridino- and piperidino-18-crown-6 ethers

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Abstract

This paper reports the preparation of eight new enantiopure amide type crown ethers and their optically active precursors. Chiral diamines were transformed to amide type pyridino-crown ethers reacting them with pyridine dicarbonyl dichlorides by high dilution technique. Two of the new pyridino-crown ethers were reduced to their piperidino analogues. A preliminary study for the potential application of nanofiltration in the purification and recovery of crown ethers is presented. According to the pK_a measurements these eight new macrocycles are potential organocatalysts (for instance in Michael addition reactions) thanks to their acidic and basic moieties and chiral skeletons, respectively.

Keywords: Chiral crown ethers, pyridino-18-crown-6 ligands, macrocycles, organocatalysis, high dilution technique, pK_a measurements

Introduction

Catalytic transformation provides the best „atom economy”, because the stoichiometric introduction and removal of (chiral) auxiliaries can be avoided, or at least minimized.¹ Development of specific bifunctional organocatalysts has been an active and fruitful area of investigation in the past few decades.² The strategy of bifunctional asymmetric catalysis

encompasses synergistic activation of a nucleophile and an electrophile by two or more reactive centers through the combination of a Lewis acid and Lewis base working in concert. Such approach results in high reaction rates and excellent stereoselectivities.³ Hydrogen bonding plays a crucial role in this catalysis. Hydrogen bonding to an electrophile decreases the electron density of this species, activating it toward nucleophilic attack. Recently chemists have begun to appreciate the tremendous potential offered by hydrogen bonding as a tool for electrophile activation in synthetic catalytic systems. In particular, chiral hydrogen-bond donors have emerged as a broadly applicable class of catalysts for enantioselective synthesis.

An amide unit, the key functional group of peptides, plays an important role in catalyst design and modification. Based on the understanding of different asymmetric catalytic reaction mechanisms, the creation of amide structure-based bifunctional organocatalysts was realized by rational arrangement of hydrogen-bond networks. Numerous asymmetric reactions, such as aldol, Mannich, Michael, Henry, amination, Biginelli, cyanosilylation and aza-Morita–Baylis–Hillman reactions, have been carried out successfully by these catalysts.⁴

In a pioneer investigation, Jørgensen and coworkers studied Diels–Alder reactions⁵ and Claisen rearrangements⁶ by computational methods. According to their model, two water molecules simultaneously establish H-bonds to the carbonyl oxygen of the substrate for optimal transition state stabilization. The concept of explicit double H-bonding activation was no longer restricted to one type of reaction or catalyst, but became a generally applicable principle.⁷ The simultaneous donation of two hydrogen bonds (for instance by two amide groups, or a urea or thiourea unit) has proven to be a highly successful strategy for electrophile activation. Such interactions benefit from increased strength and directionality compared to a single hydrogen bond. Organocatalysts containing double hydrogen bond moieties are capable of directing the assembly of molecules with similar control as covalent bonds.⁸

Results and Discussion

In the present study organocatalysts with the above mentioned double H-bonding activation by two amide groups and a chiral crown ether scaffold were prepared. Crown compounds including azacrown ones were shown to exhibit important applications such as selective ion separation and detection, biological applications and catalysis.⁹

Of particular interest are the crown ethers containing amide groups due to the altered binding properties of the macroring toward carbonyl compounds. Moreover, the number of ether oxygens, amide groups, ring size, lipophilic groups as well as other structural features control the selectivity toward different functional groups. The present paper describes the synthesis of six new C₂-symmetric chiral pyridino-18-crown-6 macrocycles [(*S,S*)-**1**–(*S,S*)-**6**, see Figure 1] with two amide functional groups incorporated into the macroring.

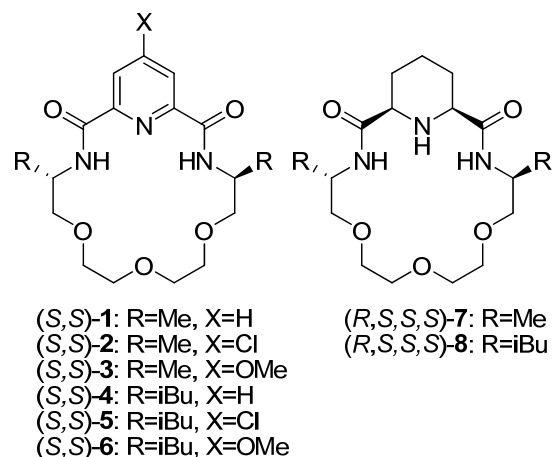


Figure 1. Schematics of new, enantiopure, amide type pyridino- [(*S,S*)-**1**–(*S,S*)-**6**] and piperidino- [(*R,S,S,S*)-**7**, (*R,S,S,S*)-**8**] 18-crown-6 ethers.

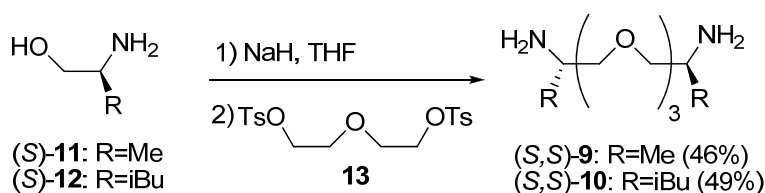
Furthermore, these amide type pyridino-18-crown-6 ethers were also converted into the members of a new class of crown ethers, the piperidino-18-crown-6 ethers [(*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**]. To the best of our knowledge these are the first aza-18-crown-6 ethers in which a nitrogen atom is in a piperidine ring. The simultaneous presence of a chiral crown ether and a piperidine ring in a macrocycle could diversify and increase the potential of biological activity. In addition, the macroring of the crown ethers containing a piperidine subunit confers a rigid conformation which can increase the selectivity of the catalytic reaction. Developments in aminocatalysis,^{10,11} which involve reactions catalyzed by secondary and primary amines *via* enamine and iminium ion intermediates, have been particularly exciting.

Purification of crown ethers after the macrocyclization and their recovery after catalytic applications can be difficult. Hence, a preliminary filtration study using nanofiltration was carried out to obtain rejection values for the prepared compounds. Organic solvent nanofiltration (OSN) is an emerging green technology that allows size-exclusion based separation of solutes between 50 and 2000 g·mol⁻¹ in organic media simply by applying a pressure gradient.^{12, 13} The new generation of OSN membranes can withstand aggressive solvents and exhibit high flux while completely rejecting relatively small solutes such as crown ethers which are at the lower end of the nanofiltration range.¹⁴⁻¹⁶ OSN was suggested for the separation of Williamson etherification reaction mixtures^{17,18} and homogeneous catalyst recovery.¹⁹ Schaepertoens *et al.* recently proposed a three-stage membrane cascade for the purification of dibenzo-18-crown-6 ether and *in situ* solvent recycle.²⁰ This article presents a preliminary study of the potential of OSN in the purification and recovery of pyridino- and piperidino-crown ether based catalyts.

Synthesis

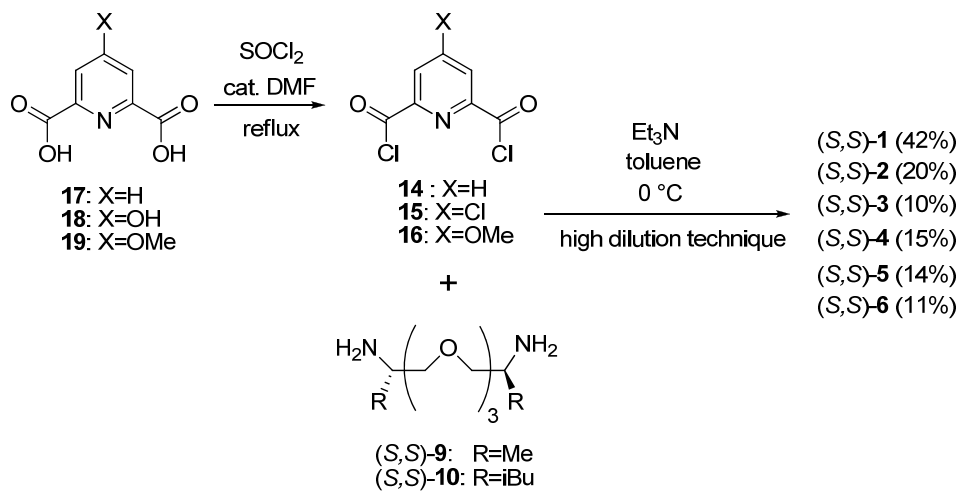
Chiral precursors [(*S,S*)-**9** and (*S,S*)-**10**] of the amide type pyridino-crown ethers (*S,S*)-**1**–(*S,S*)-**6** were prepared from the corresponding amino alcohols (*S,S*)-**11** and (*S,S*)-**12**²¹, respectively. The

hydroxyl groups of the amino alcohols were deprotonated using sodium hydride in THF, and the alkoxides were reacted with the reported²² diethylene glycol ditosylate **13** (see Scheme 1).



Scheme 1. Preparation of new methyl- [(*S,S*)-**9**] and isobutyl-substituted [(*S,S*)-**10**] diamines from *L*-alaninol [(*S*)-**11**] and *L*-leucinol [(*S*)-**12**].

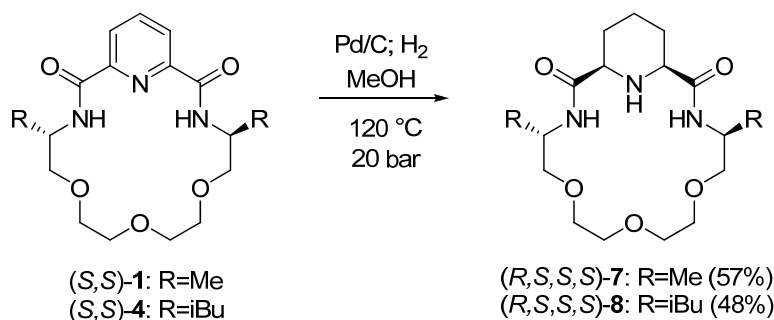
The macrocyclization reaction was carried out with pyridino-2,6-dicarbonyl dichlorides (**14**–**16**) [prepared *in situ* from the corresponding dicarboxylic acids (**17**^{23, 24}, **18**^{25, 26} and **19**²⁵⁻²⁸)] and chiral diamines [(*S,S*)-**9**, (*S,S*)-**10**] and resulted in new amide type pyridino-crown ethers [(*S,S*)-**1**–(*S,S*)-**6**, see Scheme 2]. These reactions used the high dilution technique.²⁹⁻³¹ This method involves dropping the two reactants into a reaction vessel at the same time and speed from two different dropping funnels into a large volume of solvent. Due to the slow (ca. 0.01 mL min⁻¹) and simultaneous addition of the bifunctional reactants in low concentration (ca. 1-10 mM) the probability of intermolecular collisions between the reacting partners is dramatically reduced and the formation of oligomers suppressed. At the same time, an intramolecular reaction does not require interactions between molecules and therefore high dilution does not affect the efficiency of cyclization. The inconvenience of this method (small amounts of product and large volumes of solvent), plus its low efficiency for the preparation of medium-ring systems, made it mandatory to develop alternate routes based upon selectively facilitating the intramolecular reaction. The formation of higher macrocycles (for example dimers, trimers etc.) was not investigated.



Scheme 2. Preparation of enantiopure amide type pyridino-18-crown-6 ethers (*S,S*)-**1**–(*S,S*)-**6**.

Our aim was to prepare amide type piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8** in order to obtain higher basicity. It is reported³² that pyridine-2,6-dicarboxylic acid (**17**, Scheme 2) was converted into the corresponding piperidine derivative in water by catalytic hydrogenation using 10% Pd/C at 50 °C with hydrogen under atmospheric pressure. In the case of the reduction of pyridino-crown ether diamides (*S,S*)-**1** and (*S,S*)-**4**, for reasons of solubility the reaction was carried out in methanol instead of water. Working at atmospheric pressure, this hydrogenation did not result in the desired piperidino-crown ether derivatives (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**. In our case the reduction required a higher temperature (120 °C) and pressure (20 bar), as well as a longer reaction time (24 h) (Scheme 3).

The above-mentioned reduction of pyridinedicarboxylic acid **17** gave the *cis*-piperidine product³² and considering the mechanism of the hydrogenation reaction, it can be presumed that in the case of piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8** the piperidine ring will also attach *cis*.



Scheme 3. Synthesis of enantiopure piperidino-18-crown-6 ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8** by catalytic hydrogenation of pyridino-18-crown-6 ethers (*S,S*)-**1** and (*S,S*)-**4**.

The eight new bifunctional amide type crown ethers (*S,S*)-**1**–(*R,S,S,S*)-**8** are potential organocatalysts. Their testing in asymmetric reactions is in progress and results will be published as soon as the work on it is finished.

p*K*_a Measurements

Hydrogen bonding interactions play a key role in noncovalent organocatalysis,³³⁻³⁵ thus determination of p*K*_a values facilitate the understanding of catalytic activity and catalyst design. However, the equilibrium values have their limitations for a kinetic property such as transition state stabilization.³⁶ According to a recent review⁴ the p*K*_a values of H-bond donor species in small-molecule catalysis are in the range of 6-28 in DMSO.

One of the most important families of the amide type catalysts, the proline amide derivatives with strong electron withdrawing groups, were found to exhibit much higher catalytic activity and enantioselectivity than the corresponding chiral amides with electron donating groups.³⁷ The p*K*_a values of the potential proline amide organocatalysts are in the range of 11-23 in DMSO.

As it is known that a more acidic amide leads to the formation of a stronger hydrogen bond, increasing the acidity of amides should provide an effective strategy to improve the catalytic activity of amide type catalysis. Furthermore, the stronger hydrogen bonding can also be helpful for stereocontrol, leading to a better enantioselectivity.³⁸

We should also note that the p_sK_a values of another type of organocatalysts, the bifunctional dialkyl amino and cinchona-derived thioureas, were recently determined in DMSO and correlated with their relative activity in some Michael addition reactions.³⁹ For the tested chiral hydrogen bond donor catalysts ($p_sK_a = 13-21$) a structure-activity enantioselectivity relationship was established.³⁹

Due to the above mentioned significance of the pK_a values of the organocatalysts, the acidity and basicity of our new crown ether type potential bifunctional organocatalysts were measured. The proton dissociation constants of the amide groups of pyridino-crown ethers (*S,S*)-1–(*S,S*)-6 were determined by UV-spectrophotometric titrations using the D-PAS technique. As can be seen in Figure 2 and Table 1, the amide groups are acidic enough ($pK_a = \sim 12-14$ in aqueous media) to form strong hydrogen bonds.

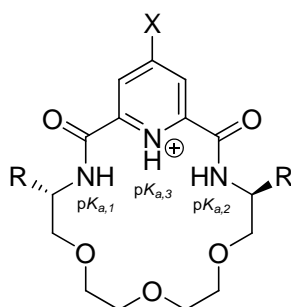


Figure 2. $pK_{a,1}$, $pK_{a,2}$ and $pK_{a,3}$ values of amide type pyridino-crown ethers (*S,S*)-1–(*S,S*)-6.

Table 1. Measured and predicted pK_a values of pyridino-crown ethers (*S,S*)-1–(*S,S*)-6

Substituents	$pK_{a,1}$		$pK_{a,2}$	$pK_{a,3}$	
	measured	Predicted*	Predicted*	measured	Predicted*
(<i>S,S</i>)-1 R=Me, X=H	13.0±0.2	14.0	15.0	0.5±0.0	-7.5
(<i>S,S</i>)-2 R=Me, X=Cl	12.9±0.2	13.6	14.6	0.8±0.0	-8.5
(<i>S,S</i>)-3 R=Me, X=OMe	12.8±0.1	13.6	14.3	1.2±0.1	-1.3
(<i>S,S</i>)-4 R=iBu, X=H	13.0±0.3	14.0	15.0	0.6±0.2	-7.3
(<i>S,S</i>)-5 R=iBu, X=Cl	12.9±0.1	13.6	14.6	0.9±0.2	-8.3
(<i>S,S</i>)-6 R=iBu, X=OMe	13.2±0.2	13.6	14.3	0.6±0.1	-1.3

* pK_a values were predicted by MarvinSketch v.15.10.12.

Deviations of the pK_a values of amide groups (see Table 1) show that they were determined near by the upper limit of the measurement ($pK_a \sim 13$), and therefore extrapolation methods were

used. However, since these values are not thermodynamic data, the tendency of the measured and predicted values is the same. As can be seen, the alkyl groups at the chiral centers have no significant effect on the pK_a value; they probably have a role in the enantioselectivity of the catalysts.

There was no significant difference between the measured and the predicted acidities of the amide groups. Unfortunately, the estimation of the basicity of the pyridine nitrogen, near the lower limit of measurement ($pK_a \sim 1$), has a large (up to 9 units) error, therefore in this case NMR titrations, the overlapping indicator method⁴⁰ and other prediction methods should be used to give more reliable data.

Since piperidine is more basic than pyridine, pyridino-crown ethers were reduced to obtain potential bifunctional organocatalysts bearing a more basic NH group. As the piperidino-crown ethers do not have a chromophore unit, the pK_a values were determined by potentiometric titrations. According to our measurements (see Figures 2–3, and Tables 1–2), the piperidino-crown ethers have a more basic nitrogen atom ($pK_a \sim 4.4$) than that of the pyridino-crown ethers ($pK_a \sim 0.5$). The pK_a values of the amide groups of piperidino-crown ethers could not be measured (they were outside the pK_a region of 2-12).

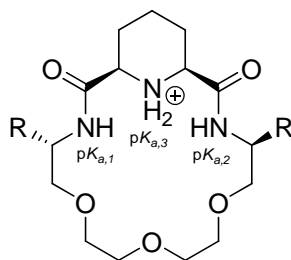


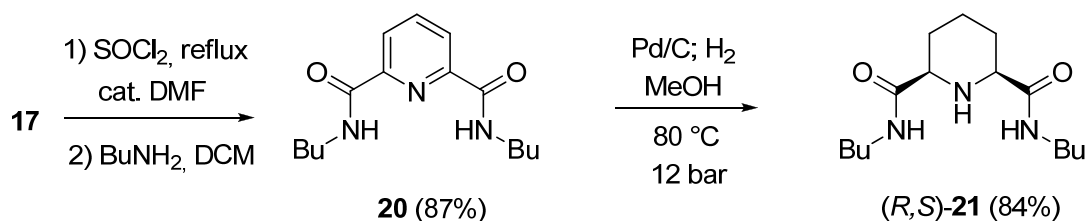
Figure 3. $pK_{a,1}$, $pK_{a,2}$ and $pK_{a,3}$ values of piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**, respectively.

Table 2. Measured and predicted pK_a values of piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**, respectively

Substitutes	$pK_{a,1}$		$pK_{a,2}$	$pK_{a,3}$	
	measured	predicted*	predicted*	measured	predicted*
(<i>R,S,S,S</i>)- 7 R=Me	n.a.	13.0	13.5	4.42±0.00	7.5
(<i>R,S,S,S</i>)- 8 R=iBu	n.a.	12.7	13.3	4.38±0.02	7.5

* pK_a values were also predicted by MarvinSketch v.15.10.12.

In order to study the influence of the macroring on the acidity and basicity, we prepared diamide **20** from pyridine-2,6-dicarboxylic acid (**17**) using a modified procedure.⁴¹ The catalytic reduction of pyridine derivative **20** gave piperidinedicarboxamide (*R,S*)-**21** (see Scheme 4).



Scheme 4. Synthesis of pyridinedicarboxamide **20** and piperidinedicarboxamide **(R,S)-21**.

There was no significant difference between the acidity of the pyridino-crown ethers **(S,S)-1** and **(S,S)-4** ($\text{p}K_{\text{a}} \sim 13.0$, see Figure 2 and Table 1) and that of the pyridine derivative **20** ($\text{p}K_{\text{a}} = 13.1$, see Figure 4 and Table 3). The pyridine (**20**) and piperidine [**(R,S)-21**] diamides have more basic nitrogens ($\text{p}K_{\text{a}} \sim 0.7$ for **20**, and $\text{p}K_{\text{a}} \sim 6.3$ for **(R,S)-21**) than those of the crown ethers ($\text{p}K_{\text{a}} \sim 0.5$ for **(S,S)-1** and **(S,S)-4**, and $\text{p}K_{\text{a}} \sim 4.4$ for **(R,S,S,S)-7** and **(R,S,S,S)-8**, respectively). In the case of the diamides **20** and **(R,S)-21**, the error for the prediction of the $\text{p}K_{\text{a}}$ values of the basic nitrogens decreased to 1-2 units.

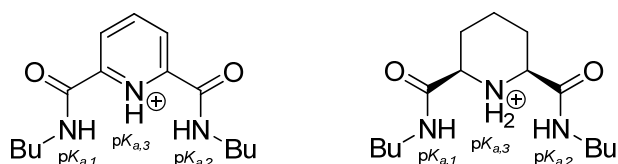


Figure 4. $\text{p}K_{\text{a},1}$, $\text{p}K_{\text{a},2}$ and $\text{p}K_{\text{a},3}$ values of the amide type pyridine (**20**) and piperidine [**(R,S)-21**] diamides.

Table 3. Measured and predicted $\text{p}K_{\text{a}}$ values of diamides **20** and **(R,S)-21**, respectively

	$\text{p}K_{\text{a},1}$		$\text{p}K_{\text{a},2}$	$\text{p}K_{\text{a},3}$	
	measure	predicted*	predicted*	measured	predicted*
20	13.1±0.3	13.9	14.9	0.7±0.1	-7.5
(R,S)-21	n.a	15.4	15.9	6.33±0.01	7.5

* $\text{p}K_{\text{a}}$ values were also predicted by MarvinSketch v.15.10.12.

The $\text{p}K_{\text{a}}$ values of our new potential organocatalysts were measured in water. The amide groups have $\text{p}K_{\text{a}}$ values in the range of 12.8-13.2 (see Table 1). As we mentioned earlier, the acidity of most of the published hydrogen bond catalysts were determined in DMSO. In order to evaluate the aqueous $\text{p}K_{\text{a}}$ values of our amides, we compared the $\text{p}K_{\text{a}}$ values in water and in DMSO. The $\text{p}K_{\text{a}}$ values of some compounds with hydrogen bond donor functional groups were determined in both solvents.⁴² We also measured three of them (see Table 4) using a co-solvent method.

Table 4. pK_a values of compounds with hydrogen bond donor functional groups in DMSO and in water

Acid	$p_sK_{a,1}$ (DMSO) Bordwell ⁴²	$pK_{a,1}$ (water) measured
Barbituric acid	8.40	3.40
F ₃ CSO ₂ NH ₂	9.70 (9.7 ^a)	6.26
PhCOOH	11.10	4.19
Phthalimide	13.40	8.30 ^b
Diphenylthiourea	13.40	11.24
Succinimide	14.60 (14.6 ^a)	9.40
PhSO ₂ NH ₂	16.10	9.83
CH ₃ SO ₂ NH ₂	17.50 (17.9 ^a)	10.70
Diphenylurea	19.60	12.59
CH ₃ CONH ₂	25.5	15.10 ^b

^aExtrapolated with Yashuda–Shedlovsky method in DMSO-H₂O; ^bData from the literature.^{43,44}

We can conclude that the amide groups of new pyridino- and piperidino-crown ethers have such p_sK_a values (lower than 28) that they are good candidates for bifunctional organocatalysts with wide applications.

Purification and catalyst recovery via nanofiltration

In order to increase the yield of crown ethers by more effective separation of the starting materials and the products, preliminary studies were carried out applying the OSN method. The experimental rejections obtained for the crown ethers and their precursors in toluene at 20 bar are presented as a function of compound molecular weight in Figure 5A. The flux obtained was 62 L.m⁻².h⁻¹. Rejection of pyridino-crown ethers (*S,S*)-**1** and (*S,S*)-**4** is between 97% and 100%, while the rejection of precursors falls between 16% and 33% except for diisobutyl substituted diamine (*S,S*)-**10**, which showed 80% rejection. Nanofiltration processes are usually operated in diafiltration mode, which means that fresh solvent is continuously added to the feed in order to push the small compounds through the membrane and keep the concentration of the products constant. Based on the experimentally obtained rejection values, Figure 5B shows the simulated concentration profile of the compounds during diafiltration.

These results confirm that nanofiltration can be used for the separation of most of the precursors from the crown ethers, except diisobutyl substituted diamine (*S,S*)-**10**. Nonetheless, the insufficient rejection of crown ethers leads to significant product loss as the nanofiltration proceeds. Recently, Kim *et al.* have proposed an efficient purification methodology employing a two-stage cascade configuration, which addresses this inherent limitation of membrane processes.⁴⁵ Furthermore, a stand-alone downstream unit operation OSN can be synergistically combined with another separation process to achieve better performance.⁴⁶ Based

on our preliminary nanofiltration results, we plan to enhance the membrane processing of crown ethers *via* cascade approach and hybrid processes.

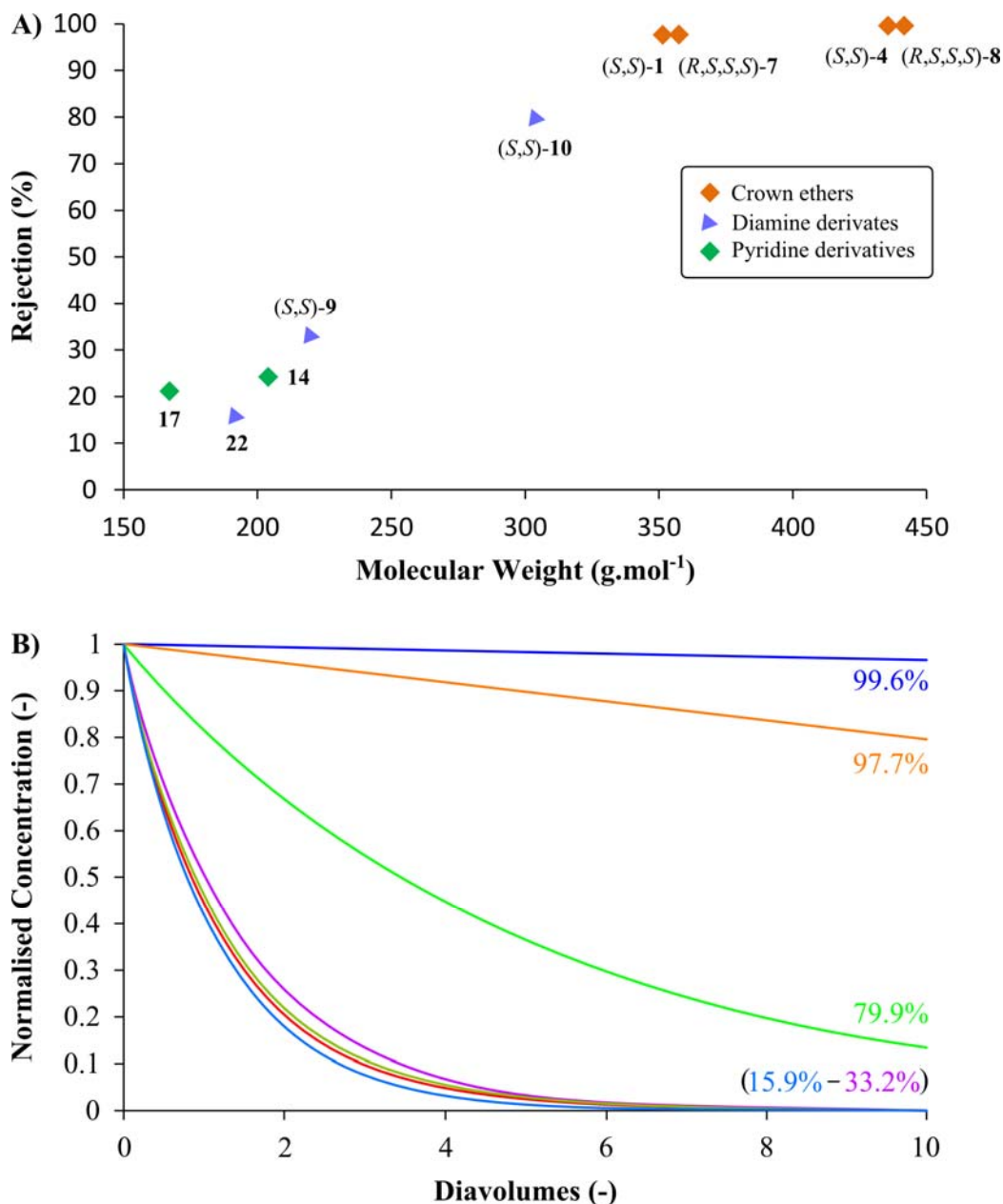


Figure 5. **A)** Rejection of crown ethers and their precursors in toluene at 20 bar. **B)** Simulated concentration profile of the compounds where the numbers on the plot indicate the rejection values. (Green: pyridinedicarboxylic acid **17**, pyridinedicarbonyl dichloride **14**; blue: chiral diamines (S,S)-**9** and (S,S)-**10**, and their unsubstituted analogue tetraethylene glycol-diamine **22**; orange: crown ethers (S,S)-**1**, (S,S)-**4**, (R,S,S,S)-**7** and (R,S,S,S)-**8**). For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

Conclusions

We can conclude that new dimethyl- and diisobutyl-substituted enantiopure pyridino-18-crown-6 ether derivatives (*S,S*)-**1**–(*S,S*)-**6** can be prepared from the corresponding enantiopure chiral diamines (*S,S*)-**9** and (*S,S*)-**10**, respectively, and pyridinediacid dichlorides **14**–**16** in toluene by macrocyclization using high dilution technique. Pyridino-crown ethers (*S,S*)-**1** and (*S,S*)-**4**, can be converted to piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**, respectively by catalytic hydrogenation. The pK_a measurements of pyridino- and piperidino-crown ethers suggest that they are good candidates for bifunctional organocatalysts.

The feasibility of nanofiltration for crown ether catalyst purification and recovery was also demonstrated for the first time. The application of the new organocatalysts as well as their purification and recovery using two-stage membrane cascades will be reported as soon as the work on them is finished.

Experimental Section

General. Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter which was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded in $CDCl_3$ either on a Bruker DRX-500 Avance spectrometer (at 500 MHz for 1H and at 125 MHz for ^{13}C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for 1H and at 75 MHz for ^{13}C spectra) and it is indicated in each individual case. Mass spectra were recorded on CAMAG TLC-MS Interface (HPLC pump: Shimadzu LC-20AD Prominence SQ MS: Shimadzu LCMS-2020 MS settings: Detector Voltage: 1.10 kV, m/z : 105-1000, Scan speed: 1075 u/sec, DL temperature: 250 °C, Nebulizing Gas Flow: 1.5 L/min, Drying Gas Flow: 15 L/min. eluent: acetonitrile:0.1 v/v% formic acid 95:5, 1.500 mL/min). Elemental analyses were performed on a Vario EL III instrument (Elementanalyse Corp., Germany) in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. The 10% Pd/C (Selcat Q) catalyst was manufactured in accordance with a patent⁴⁷ of Szilor Fine Chemicals (Budapest, Hungary). The dispersion of the catalyst, determined by H_2 -, O_2 - and CO -chemisorption measurements, is $D = 0.50$. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminium oxide (neutral, activated, Brockman I) and silica gel 60 (70-230 mesh, Merck) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Evaporations were carried out under reduced pressure unless otherwise stated.

All pK_a determinations were carried out in an aqueous medium. The proton-dissociation constants were determined by both the UV-spectrophotometric titrations using the D-PAS

technique and, in the absence of a chromophore, by potentiometric titration using the pH-metric method (Sirius Analytical Instruments Ltd., Forest Row, UK) attached to a Sirius T3 instrument.⁴⁸ The pK_a values were calculated by Refinement ProTM software. Spectrophotometry can be applied to pK_a measurement provided that the compound has a chromophore in proximity to the ionisation centre, and the absorbance changes sufficiently as a function of pH. The absorbancies in the spectral region of 260-300 nm were used in the analysis. All measurements were performed in solutions of 0.15 M KCl under nitrogen atmosphere, at $t = 25.0 \pm 0.5$ °C. All pK_a values were measured in 6 or 9 replicates.

Membranes were fabricated based on the recent developments by Valtcheva *et al.*^{49,50} Polybenzimidazole membrane (22 wt%) crosslinked with α,α' -dibromo-*p*-xylene was used for the rejection studies of the crown ethers. Solutes were dissolved in toluene ($0.1 \text{ g}\cdot\text{L}^{-1}$) and loaded onto 58 cm^2 membrane disc. The nanofiltration was carried out in cross-flow configuration with recirculation ($100 \text{ L}\cdot\text{h}^{-1}$) at 20 bar (see Figure 6). Permeate flux was measured and permeate and retentate samples were taken at steady state after approximately 2 days of continuous operation. Permeate fluxes (F) and rejections (R) were calculated as given in Equation 1 and Equation 2, respectively:

$$F = V_P \cdot A_m^{-1} \cdot t^{-1} \quad (1)$$

$$R_x = 1 - c_{P,x} \cdot c_{R,x}^{-1} \quad (2)$$

where F is the permeate flux, V_P is the volume of permeate, A_m is the membrane area, t is the time, R_x is the rejection of compound x , $c_{P,x}$ is the permeate concentration of compound x , and $c_{R,x}$ is the retentate concentration of compound x .

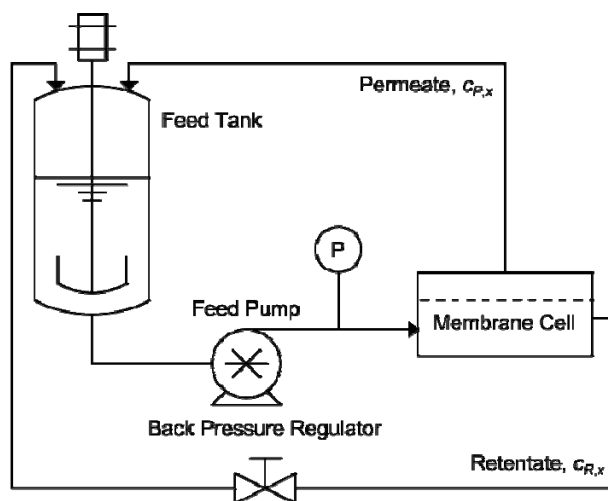


Figure 6. Schematic diagram of the nanofiltration process comprising of a stirred feed tank, high pressure pump, crossflow membrane cell, pressure gauge and back pressure regulator.

General procedure for preparation of the enantiopure diamines (*S,S*)-9 and (*S,S*)-10, respectively. Enantiopure amino alcohol (*S*)-11 or (*S*)-12 (0.05 mol), in dry THF (120 mL) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil; 5.20 g, 0.13 mol) in dry THF (120 mL) at 0 °C under Ar. The reaction mixture was stirred at rt for 2 h, treated with diethylene glycol bis-*p*-toluenesulphonate (**13**, 12.43 g, 0.03 mol) dissolved in dry THF (120 mL), and stirred at rt for a further 72 h. The reaction mixture was treated with water (480 mL) and the volatile components were removed by evaporation. The pH of the residue was adjusted to 1 with 10 M HCl, and shaken with ethyl acetate (3 × 50 mL). The aqueous phase was evaporated and the product was isolated from the dihydrochloride salt by ion-exchange chromatography [Amberlite resin IRA-402 (OH), ethanol] to give diamines (*S,S*)-9 (3.04 g, 46%) and (*S,S*)-10 (4.48 g, 49%), respectively as oily products. Physical and spectroscopic data of the products follow.

(2*S*,2'*S*)-(+)-1,1'-[2,2'-Oxybis(ethane-2,1-diyl)bis(oxy)]dipropane-2-amine (*S,S*)-9. R_f : 0.16 (silica gel TLC, CH₃CN-MeOH-Et₃N 1:1:0.1); $[\alpha]_D^{25} = +18$ (c 2.79, CHCl₃); IR (neat) ν_{\max} 3358, 3289, 3186, 2958, 2865, 1654, 1590, 1452, 1374, 1350, 1297, 1248, 1100, 997, 878, 828, 659, 586, 530 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 0.98 (d, 6H, J 7 Hz), 3.07-3.19 (m, 4H), 3.35-3.38 (m, 2H), 3.54-3.61 (m, 8H), 7.30 (d, 2H, shaking with D₂O, amino protons disappeared); ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 19.44, 45.98, 70.32, 70.39, 78.02; MS calcd for C₁₀H₂₄N₂O₃: 220.2, found (M+H)⁺: 221.2; Anal. calcd for C₁₀H₂₄N₂O₃: C, 54.52; H, 10.98; N, 12.72. Found: C, 54.47; H, 11.03; N, 12.61.

In order to prove the existence of the amino groups, a sample (23.1 mg 0.105 mmol) of diamine (*S,S*)-9 was converted to its bisacetamide derivative by reacting it with acetic anhydride (24 μ L, 0.254 mmol) in DCM (1 mL) at rt for 10 min. The volatile components were evaporated and the crude product (28.1 mg, 88%) was dried in a desiccator in the presence of KOH pellets for overnight. Physical and spectroscopic data of *N,N'*-(2*S*,2'*S*)-1,1'-[2,2'-oxybis(ethane-2,1-diyl)bis(oxy)]bis(propane-2,1-diyl)diacetamide are the following: R_f : 0.81 (SiO₂ VRK, CH₃CN-MeOH-Et₃N 1:1:0.1); $[\alpha]_D^{25} = -37$ (c 1.76, CHCl₃); IR (neat) ν_{\max} 3297, 3076, 2973, 2869, 1735, 1652, 1550, 1494, 1457, 1375, 1286, 1262, 1222, 1118, 1043, 976, 719, 604, 559, 539 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.18 (d, 6H, J 7 Hz), 1.97 (s, 6H), 3.43-3.49 (m, 4H), 3.62-3.65 (m, 8H), 4.11-4.17 (m, 2H), 6.16 (br s., 2H, shaking with D₂O, amide protons disappeared); ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 17.55, 23.29, 44.84, 70.42, 70.52, 74.00, 169.61; MS calcd for C₁₄H₂₅N₂O₅: 304.2, found (M+H)⁺: 305.2; Anal. calcd for C₁₄H₂₅N₂O₅: C, 55.24; H, 9.27; N, 9.20. Found: C, 55.11; H, 9.41; N, 9.14.

(2*S*,2'*S*)-(+)-1,1'-[2,2'-Oxybis(ethane-2,1-diyl)bis(oxy)]bis(4-methylpentane-2-amine) (*S,S*)-10. R_f : 0.18 (silica gel TLC, CH₃CN-MeOH-Et₃N 1:1:0.1); $[\alpha]_D^{25} = +4$ (c 2.59, CHCl₃); IR (neat) ν_{\max} 3360, 3283, 2953, 2868, 1578, 1467, 1383, 1366, 1297, 1261, 1107, 943, 922, 878, 809, 614, 524, 486 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 0.85 (d, 6H, J 7 Hz), 0.87 (d, 6H, J 7 Hz), 1.09-1.19 (m, 4H), 1.61-1.74 (m, 2H), 2.95-3.03 (m, 2H), 3.38-3.61 (m, 12H), 7.27 (d, 4H, shaking with D₂O, amino protons disappeared); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 21.95,

23.35, 24.50, 43.03, 48.31, 70.42, 70.47; MS calcd for C₁₆H₃₆N₂O₃: 304.3, found (M+H)⁺: 305.3; Anal. calcd for C₁₆H₃₆N₂O₃: C, 63.12; H, 11.92; N, 9.20. Found: C, 63.09; H, 11.94; N, 9.19.

In order to prove the existence of the amino groups, a sample (21.5 mg 0.07 mmol) of diamine (*S,S*)-**10** was converted to its bisacetamide derivative reacting it with acetic anhydride (17 μ L, 0.17 mmol) in DCM (1 mL) at rt for 10 min. The volatile components were evaporated and the crude product (23.0 mg, 84%) was dried in a desiccator in the presence of KOH pellets for overnight. Physical and spectroscopic data of *N,N'*-(**2*S*,2'*S***)-**1,1'**-(**2,2'**-oxybis(ethane-2,1-diyl)bis(oxy))bis(4-methylpentane-2,1-diyl)diacetamide are the following: R_f: 0.63 (SiO₂ VRK, CH₃CN-MeOH-Et₃N 1:1:0.1); [α]_D²⁵ = -33 (*c* 0.31, CHCl₃); IR (neat) ν_{\max} 3466, 3430, 3275, 3078, 2955, 2928, 2868, 1743, 1647, 1550, 1468, 1373, 1297, 1261, 1104, 1037, 951, 802, 608, 600 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 0.90 (d, 12H, *J* 7 Hz), 1.31-1.46 (m, 4H), 1.56-1.65 (m, 2H), 1.97 (s, 6H) 3.43-3.52 (m, 4H), 3.57-3.64 (m, 8H), 4.09-4.18 (m, 2H), 5.94 (d, 2H, shaking with D₂O, amide protons disappeared); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 22.55 and 23.22 (diastereotopic methyl groups), 23.63, 25.12, 41.09, 47.43, 70.71, 70.85, 73.46, 169.90; MS calcd for C₂₀H₄₀N₂O₅: 388.3, found (M+H)⁺: 389.3; Anal. calcd for C₂₀H₄₀N₂O₅: C, 61.82; H, 10.38; N, 7.21. Found: C, 61.73; H, 10.47; N, 7.14.

General procedure for the preparation of the enantiopure, amide type pyridino-crown ethers (*S,S*)-1**–(*S,S*)-**6**.** To a pyridinedicarboxylic acid **17** or **18** or **19** (2.08 mmol) was first added a catalytic amount of pure DMF (two drops) followed by dropwise addition of thionyl chloride (5.16 mL, 8.46 g, 70.75 mmol), and the resulting mixture was stirred at reflux temperature under Ar for 6 h. The volatile components were evaporated and the traces of SOCl₂ were removed by repeated distillation of toluene from the mixture. The crude product was used in the next step without further purification.

Mixtures of diamine (*S,S*)-**9** or (*S,S*)-**10** (2.08 mmol) and triethylamine (0.78 mL, 5.62 mmol) in pure and dry toluene (390 mL) and the above prepared pyridine-2,6-dicarbonyl dichloride **14** or **15** or **16** (2.08 mmol) in pure and dry toluene (390 mL) were added simultaneously over a 5 h period to vigorously stirred pure and dry toluene (120 mL) at 0 °C. After the addition, the reaction mixture was stirred at rt for 30 hours and then filtered. The volatile components were evaporated, the residue was taken up in DCM (200 mL), and the solution was shaken with water (200 mL). The aqueous layer was extracted with DCM (3 \times 200 mL). The combined organic phase was dried over MgSO₄, filtered and the solvent was evaporated. The crude product was purified as described below for each compound to result in the optically active pyridino-crown ethers [(*S,S*)-**1**–(*S,S*)-**6**].

(4*S*,14*S*)-(–)-4,14-Dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(2*T*),17,19-triene-2,16-dione (*S,S*)-1**.** Crown ether (*S,S*)-**1** was prepared as described above in the General procedure starting from pyridine-2,6-dicarboxylic acid (**17**) (347.8 mg, 2.08 mmol), thionyl chloride (5.16 mL, 70.75 mmol), chiral diamine (*S,S*)-**9** (458.5 mg, 2.08 mmol) and triethylamine (0.78 mL, 5.62 mmol) using toluene (900 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:80 mixture as an eluent to

yield (*S,S*)-**1** (307.1 mg, 42%) as white crystals. Mp: 165-167 °C; R_f : 0.58 (alumina TLC, EtOH-toluene 1:20); $[\alpha]_D^{25} = -65$ (*c* 1.03, CHCl₃); IR (KBr) ν_{\max} 3419, 2962, 2922, 2853, 1659, 1643, 1583, 1570, 1537, 1447, 1423, 1410, 1377, 1363, 1356, 1346, 1261, 1103, 1018, 801 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.32 (d, 6H, *J* 7 Hz), 3.49-3.51 (m, 2H), 3.62-3.66 (m, 8H), 3.86-3.90 (m, 2H), 4.32-4.35 (m, 2H), 7.94 (t, 1H, *J* 8 Hz), 8.25 (d, 2H, *J* 8 Hz), 8.29 (d, 2H, *J* 8 Hz, shaking with D₂O amide protons shifted to 8.56 ppm); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 18.00, 45.65, 70.38, 72.29, 74.02, 125.10, 138.69, 149.23, 162.97; MS calcd for C₁₇H₂₅N₃O₅: 351.2, found (M+H)⁺: 352.2; Anal. calcd for C₁₇H₂₅N₃O₅: C, 58.11; H, 7.17; N, 11.96. Found: C, 58.07; H, 7.19; N, 11.94.

(4*S*,14*S*)-(-)-19-Chloro-4,14-dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicoso-1(2*I*),17,19-triene-2,16-dione (*S,S*)-2**.** Crown ether (*S,S*)-**2** was prepared as described above in the General procedure starting from chelidamic acid (**18**) (358.9 mg, 1.96 mmol), thionyl chloride (4.86 mL, 66.67 mmol), chiral diamine (*S,S*)-**9** (432.0 mg, 1.96 mmol), triethylamine (0.74 mL, 5.30 mmol) using toluene (850 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:80 mixture as an eluent to yield (*S,S*)-**2** (151.2 mg, 20%) as pale yellow oil. R_f : 0.45 (alumina TLC, EtOH-toluene 1:20); $[\alpha]_D^{25} = -22$ (*c* 1.12, CHCl₃); IR (neat) ν_{\max} 3421, 3078, 2873, 2345, 1670, 1646, 1578, 1517, 1474, 1450, 1358, 1258, 1168, 1132, 1103, 1002, 893, 853, 800, 782, 749, 666, 607, 528, 485 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.36 (d, 6H, *J* 7 Hz); 3.66-3.72 (m, 10H); 3.91-3.95 (m, 2H); 4.35-4.40 (m, 2H); 8.16 (d, 2H, *J* 9 Hz, shaking with D₂O, amide protons shifted to 8.53 ppm); 8.34 (s, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 18.12, 45.95, 70.53, 72.40, 73.95, 125.59, 147.63, 150.82, 161.96; MS calcd for C₁₇H₂₄ClN₃O₅: 385.1, found (M+H)⁺: 386.1; Anal. calcd for C₁₇H₂₄ClN₃O₅: C, 52.92; H, 6.27; Cl, 9.19; N, 10.89. Found: C, 52.74; H, 6.34; Cl, 9.12; N, 10.70.

(4*S*,14*S*)-(-)-19-Methoxy-4,14-dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicoso-1(2*I*),17,19-triene-2,16-dione (*S,S*)-3**.** Crown ether (*S,S*)-**3** was prepared as described above in the General procedure starting from methoxy-substituted carboxylic acid (**19**) (143.9 mg, 0.73 mmol), thionyl chloride (1.81 mL, 24.83 mmol), chiral diamine (*S,S*)-**9** (160.9 mg, 0.73 mmol), triethylamine (0.28 mL, 1.97 mmol) using toluene (320 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:140 mixture as an eluent to yield (*S,S*)-**3** (55.7 mg, 20%) as yellowish crystals. Mp: 129.5-131.5 °C; R_f : 0.50 (alumina TLC, EtOH-toluene 1:100); $[\alpha]_D^{25} = -52$ (*c* 0.97 CHCl₃); IR (KBr) ν_{\max} 3399, 3318, 2978, 2959, 2922, 2898, 1673, 1648, 1601, 1543, 1517, 1469, 1452, 1363, 1315, 1114, 1089, 1044, 1007, 884 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.38 (d, 6H, *J* 7 Hz); 3.55-3.57 (m, 2H); 3.67-3.74 (m, 8H); 3.90-3.95 (m, 2H); 3.96 (s, 3H); 4.35-4.41 (m, 2H); 7.86 (s, 2H); 8.35 (d, 2H, *J* 9 Hz, shaking with D₂O, amide protons shifted to 8.57 ppm); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 18.10, 45.87, 56.13, 70.55, 72.37, 74.20, 111.06, 151.40, 163.15, 168.39; MS calcd for C₁₈H₂₇N₃O₆: 381.2, found (M+H)⁺: 382.2; Anal. Calcd for C₁₈H₂₇N₃O₆: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.65; H, 7.17; N, 10.94.

(4*S*,14*S*)-(-)-4,14-Diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(2*I*),17,19-triene-2,16-dione (*S,S*)-4. Crown ether (*S,S*)-4 was prepared as described above in the General procedure starting from pyridine-2,6-dicarboxylic acid (**17**) (109.0 mg, 0.65 mmol), thionyl chloride (1.61 mL, 22.11 mmol), chiral diamine (*S,S*)-**10** (197.9 mg, 0.65 mmol), triethylamine (0.25 mL, 1.75 mmol) using toluene (290 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:160 mixture as an eluent to yield (*S,S*)-4 (42.6 mg, 15%) as a pale yellow oil. *R*_f: 0.55 (alumina TLC, EtOH-toluene 1:20); [α]_D²⁵ = -132 (*c* 1.54, CHCl₃); IR (neat) ν_{\max} 3407, 2954, 2925, 2868, 1671, 1568, 1518, 1469, 1444, 1385, 1366, 1356, 1337, 1260, 1247, 1168, 1111, 1031, 999, 962, 846, 805, 755, 734, 687, 668, 650, 620, 572, 562 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 0.96 (d, 6H, *J* 7 Hz, diastereotopic methyl groups), 0.99 (d, 6H, *J* 7 Hz, diastereotopic methyl groups), 1.52-1.57 (m, 2H), 1.60-1.66 (m, 2H), 1.69-1.75 (m, 2H), 3.62-3.70 (m, 10H), 3.94-3.98 (m, 2H), 4.35-4.38 (m, 4H), 8.00 (t, 1H, *J* 8 Hz), 8.25 (d, 2H, *J* 9 Hz, shaking with D₂O, amide protons shifted to 8.53 ppm), 8.34 (d, 2H, *J* 8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 22.78, 25.12, 41.28, 48.00, 70.36, 72.49, 72.80, 125.08, 138.71, 149.26, 162.98; MS calcd for C₂₃H₃₇N₃O₅: 435.3, found (M+H)⁺: 436.3; Anal. calcd for C₂₃H₃₇N₃O₅: C, 63.42; H, 8.56; N, 9.65. Found: C, 63.29; H, 8.63; N, 9.54.

(4*S*,14*S*)-(-)-19-Chloro-4,14-diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(2*I*),17,19-triene-2,16-dione (*S,S*)-5. Crown ether (*S,S*)-5 was prepared as described above in the General procedure starting from chelidamic acid (**18**) (161.1 mg, 0.88 mmol), thionyl chloride (2.17 mL, 29.93 mmol), chiral diamine (*S,S*)-**10** (197.9 mg, 0.88 mmol), triethylamine (0.33 mL, 2.38 mmol) using toluene (170 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:160 mixture as an eluent to yield (*S,S*)-5 (58.0 mg, 14%) as a pale yellow oil. *R*_f: 0.60 (alumina TLC, EtOH-toluene 1:20); [α]_D²⁵ = -35 (*c* 0.93, CHCl₃); IR (neat) ν_{\max} 3418, 2962, 2905, 2349, 1675, 1653, 1559, 1517, 1457, 1447, 1363, 1259, 1087, 1015, 865, 795, 702, 661 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ (ppm) 0.96 (d, 6H, *J* 7 Hz, diastereotopic methyl groups), 0.99 (d, 6H, *J* 7 Hz, diastereotopic methyl group), 1.50-1.56 (m, 2H), 1.60-1.65 (m, 2H), 1.71-1.77 (m, 2H), 3.63-3.71 (m, 10H), 3.89-3.92 (m, 2H), 4.32-4.37 (m, 2H), 8.30 (d, 2H *J* 9 Hz, shaking with D₂O, amide protons shifted to 8.53 ppm); 8.33 (s, 2H); ¹³C-NMR (75.5 MHz, CDCl₃) δ (ppm) 22.89, 22.98, 25.30, 41.26, 48.48, 70.54, 72.32, 73.00, 125.56, 147.64, 150.94, 162.21; MS calcd for C₂₃H₃₆ClN₃O₅: 469.2, found (M+H)⁺: 470.2; Anal. calcd for C₂₃H₃₆ClN₃O₅: C, 58.78; H, 7.72; Cl, 7.54; N, 8.94. Found: C, 58.66; H, 7.78; Cl, 7.53; N, 8.91.

(4*S*,14*S*)-(-)-19-Methoxy-4,14-diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(2*I*),17,19-triene-2,16-dione (*S,S*)-6. Crown ether (*S,S*)-6 was prepared as described above in the General procedure starting from methoxy-substituted carboxylic acid (**19**) (287.8 mg, 1.46 mmol), thionyl chloride (3.60 mL, 49.66 mmol), chiral diamine (*S,S*)-**10** (328.3 mg, 1.46 mmol), triethylamine (0.55 mL, 3.95 mmol) using toluene (280 mL). The crude product was purified by column chromatography on neutral aluminium oxide using EtOH-toluene 1:180 mixture as an eluent to yield (*S,S*)-6 (75.0 mg, 11%) as a yellowish brown oil. *R*_f: 0.52 (alumina

TLC, EtOH-toluene 1:20); $[\alpha]_D^{25} = -16$ (c 0.83, CHCl_3); IR (neat) ν_{max} 3424, 3083, 2962, 2926, 2854, 2677, 1727, 1673, 1650, 1632, 1602, 1574, 1530, 1468, 1450, 1439, 1412, 1397, 1365, 1333, 1262, 1200, 1103, 1031, 972, 889, 842, 800, 762, 738, 693, 661, 639, 580, 530, 460, 456 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ (ppm) 0.96 (d, 6H, J 7 Hz), 0.99 (d, 6H, J 7 Hz), 1.51-1.56 (m, 2H), 1.61-1.66 (m, 2H), 1.68-1.74 (m, 2H), 3.61-3.91 (m, 10H), 3.95 (s, 3H), 3.96-3.99 (m, 2H), 4.33-4.37 (m, 2H), 7.86 (s, 2H), 8.25 (d, 2H, J 10 Hz, shaking with D_2O , amide protons shifted to 8.53 ppm); ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 22.78, 25.11, 41.29, 48.02, 55.95, 70.39, 72.46, 72.83, 110.91, 151.26, 162.98, 168.25; MS calcd for $\text{C}_{24}\text{H}_{39}\text{N}_3\text{O}_6$: 465.3, found $(\text{M}+\text{H})^+$: 466.3; Anal. calcd for $\text{C}_{24}\text{H}_{39}\text{N}_3\text{O}_6$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.90; H, 8.46; N, 9.00.

General procedure for hydrogenation of the enantiopure amide type pyridino-crown ethers (*S,S*)-1 and (*S,S*)-4. The hydrogenation reactions were carried out in a 80 mL stainless steel autoclave (Technoclave, Budapest, Hungary) equipped with a magnetic stirrer (stirring speed: 1100 rpm), at 20 bar hydrogen pressure and at 120 °C for 24 h. Typically, the reactor containing pyridino-crown ether (*S,S*)-1 and (*S,S*)-4 (1 mmol), 10% Pd/C (Selcat Q) catalyst (0.15 g) and MeOH (20 mL) was flushed with nitrogen and hydrogen, then charged with hydrogen to the specified pressure. After the hydrogenation was completed (24 h), the catalyst was filtered off and the solvent was removed. The residue was purified by column chromatography on silica gel using MeOH-acetonitrile 1:10 mixture as an eluent to yield (*R,S,S,S*)-7 (173.9 mg, 57%) as a white crystal or (*R,S,S,S*)-8 (146.0 mg, 48%) as a colourless oil. Physical and spectroscopic data of the products are the following:

(1*R*,4*S*,14*S*,17*S*)-(-)-4,14-Dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosane-2,16-dione (*R,S,S,S*)-7: Mp: 179-183 °C; R_f : 0.43 (alumina TLC, EtOH-toluene 1:20); $[\alpha]_D^{25} = -24$ (c 1.17, CHCl_3); IR (KBr) ν_{max} 3376, 3341, 3235, 2962, 2863, 1666, 1620, 1556, 1510, 1454, 1384, 1370, 1303, 1274, 1261, 1195, 1107, 1056, 921, 800 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 1.22 (d, 3H, J 6 Hz); 1.24 (d, 3H, J 6 Hz); 1.40-1.55 (m, 2H); 1.78-1.95 (m, 2H), 2.07-2.11 (m, 2H); 3.38-3.46 (m, 2H); 3.56-3.69 (m, 10H); 3.77-3.84 (m, 2H); 4.08-4.23 (m, 2H); 7.07 (br s., 2H, shaking with D_2O , amide protons shifted to 7.30 ppm); ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 17.82, 17.92, 24.20; 29.82, 30.06, 44.61, 45.09, 60.98, 61.21, 70.28, 70.45, 71.76, 71.87, 73.79, 73.97, 172.56, 172.77; MS calcd for $\text{C}_{17}\text{H}_{31}\text{N}_3\text{O}_5$: 357.2, found $(\text{M}+\text{H})^+$: 358.2; Anal. calcd for $\text{C}_{17}\text{H}_{31}\text{N}_3\text{O}_5$: C, 57.12; H, 8.74; N, 11.76. Found: C, 57.05; H, 8.88; N, 11.72.

(1*R*,4*S*,14*S*,17*S*)-(-)-4,14-Diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosane-2,16 dione (*R,S,S,S*)-8: R_f : 0.45 (alumina TLC, EtOH-toluene 1:20); $[\alpha]_D^{25} = -40$ (c 1.02, CHCl_3); IR (neat) ν_{max} 3390, 3305, 3270, 2952, 2925, 2867, 1649, 1522, 1469, 1453, 1385, 1366, 1349, 1333, 1300, 1246, 1200, 1116, 1028, 950, 920, 881, 816, 729, 645, 549, 503, 477 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 0.94 (d, 12H, J 6 Hz), 1.24-1.31 (m, 2H), 1.37-1.43 (m, 2H), 1.53-1.64 (m, 4H), 1.81-1.96 (m, 2H), 2.06-2.13 (m, 2H), 3.19-3.29 (m, 2H), 3.54-3.67 (m, 10H), 3.72-3.81 (m, 2H), 3.99-4.21 (m, 2H), 7.03-7.06 (d, 1H, shaking with D_2O , amide proton

disappeared), 7.11-7.14 (d, 1H, shaking with D₂O, amide proton disappeared); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 22.76, 22.84, 22.94, 23.01, 24.36, 25.27, 25.32, 29.82, 30.33, 40.71, 41.07, 46.86, 48.22, 61.17, 61.38, 70.51, 70.58, 71.73, 71.85, 72.69, 73.28, 172.94, 172.96; MS calcd for C₂₃H₄₃N₃O₅: 441.3, found (M+H)⁺: 442.3; Anal. calcd for C₂₃H₄₃N₃O₅: C, 62.56; H, 9.81; N, 9.52. Found: C, 62.49; H, 9.85; N, 9.48.

N²,N⁶-Dibutylpyridine-2,6-dicarboxamide (20). To pyridinedicarboxylic acid **17** (10.0 g, 59.8 mmol) was added first a catalytic amount of DMF (two drops) followed by thionyl chloride (43.4 mL, 71.1 g, 598 mmol), and the resulting mixture was stirred at reflux temperature under Ar for 2 h. The volatile components were evaporated and the traces of SOCl₂ were removed by repeated distillation of toluene from the mixture. The crude product was used in the next step without further purification. To this crude pyridine-2,6-dicarbonyl dichloride (**14**) DCM (20 mL) was added, and the resulting solution was treated with butylamine (59.1 mL, 43.74 g, 598 mmol) dissolved in pure and dry DCM (20 mL) at 0 °C. After the addition, the reaction mixture was stirred at rt for 22 hours, then filtered, and the residue washed with DCM (200 mL). The filtrate and washings were shaken with water (3×200 mL). The organic phase was dried over MgSO₄, filtered and the solvent was evaporated. The residue was recrystallized from CHCl₃-Et₂O to give dicarboxamide **20** (14.42 g, 87%) as white crystals. Mp: 159.1-159.3 °C; R_f: 0.39 (silica gel TLC, MeOH-toluene 1:4); IR (KBr) ν_{max} 3329, 3283, 2959, 2931, 2871, 1679, 1652, 1531, 1460, 1443, 1411, 1372, 1311, 1243, 1222, 1145, 850, 746, 677, 646 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 0.90 (t, 6H, *J* 8 Hz), 1.29-1.42 (m, 4H), 1.53-1.63 (m, 4H), 3.41-3.47 (m, 4H), 8.00 (t, 1H, *J* 8 Hz), 8.10 (br. s, 2H, shaking with D₂O amide protons shifted to 8.12 ppm), 8.34 (d, 2H, *J* 8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 13.92, 20.35, 31.95, 39.56, 125.04, 139.12, 149.17, 163.78; MS calcd for C₁₅H₂₃N₃O₂: 277.2, found (M+H)⁺: 278.2; Anal. calcd for C₁₅H₂₃N₃O₂: C, 64.95; H, 8.36; N, 15.15. Found: C, 64.84; H, 8.42; N, 15.13.

(2*R*,6*S*)-N²,N⁶-Dibutylpiperidine-2,6-dicarboxamide (*R,S*)-21. The hydrogenation was carried out in a 80 mL stainless steel autoclave (Technoclave, Budapest, Hungary) equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reactor containing pyridinedicarboxamide **20** (1.0 g, 3.6 mmol), 10% Pd/C (Selcat Q) catalyst (0.3 g) and MeOH (20 mL) was flushed with nitrogen and hydrogen, then charged with hydrogen to 12 bar at 80 °C. After the hydrogenation was completed (4 h), the catalyst was filtered off and the solvent was removed to yield piperidinedicarboxamide (*R,S*)-**21** (0.86 g, 84%) as white crystals. Mp: 132-133 °C; R_f: 0.31 (silica gel TLC, MeOH-toluene 1:4, spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating the dried plates); IR (KBr) ν_{max} 3300, 3103, 2957, 2930, 2861, 2799, 1646, 1563, 1467, 1455, 1437, 1365, 1325, 1263, 1240, 1152, 1140, 1116, 1140, 1116, 1093, 1081, 1053, 975, 938, 888, 872, 780, 743, 691, 551, 459 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 0.89 (t, 6H, *J* 7 Hz), 1.19-1.32 (m, 6H), 1.44-1.46 (m, 4H), 1.90-2.03 (m, 4H), 2.22 (br. s, 1H, shaking with D₂O piperidine NH proton shifted to 2.15 ppm), 3.18-3.22 (m, 6H), 6.62 (br. s, 2H, shaking with D₂O amide protons shifted to 6.56 ppm); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 13.85, 20.20, 24.24, 29.78, 31.79, 38.95, 60.42, 173.20; MS calcd for

C₁₅H₂₉N₃O₂: 283.2, found (M+H)⁺: 284.2; Anal. calcd for C₁₅H₂₉N₃O₂: C, 63.57; H, 10.31; N, 14.83. Found: C, 63.46; H, 10.35; N, 14.80.

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