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

József Kupai, Péter Kisszékelyi, Eszter Rojik, Gergő Dargó, László Hegedűs, Dóra Bezzegh, Péter Maszler, Luca Szabó, Tamás Németh, György Tibor Balogh, and Péter Huszthy*

a Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, PO Box 91, H-1521 Budapest, Hungary
b MTA–BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8., H-1111 Budapest, Hungary
c Compound Profiling Laboratory, Chemical Works of Gedeon Richter Plc., PO Box 27, H-1475 Budapest, Hungary
E-mail: huszthy@mail.bme.hu

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.592

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 pKₐ 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, pKₐ 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. Development of specific bifunctional organocatalysts has been an active and fruitful area of investigation in the past few decades. 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. 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.

In a pioneer investigation, Jørgensen and coworkers studied Diels–Alder reactions and Claisen rearrangements 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. 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.

**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. 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.
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)-7, (R,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 mixtures17,18 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 catalysts.

**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)-1221, respectively. The
hydroxyl groups of the amino alcohols were deprotonated using sodium hydride in THF, and the alkoxides were reacted with the reported 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)] 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. 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 reported\(^{32}\) 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 \textit{cis}-piperidine product\(^{32}\) 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 \textit{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.

\textbf{pK}_a \textbf{Measurements}

Hydrogen bonding interactions play a key role in noncovalent organocatalysis,\(^{33-35}\) thus determination of \(pK_a\) 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 review\(^4\) the \(pK_a\) 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 \(pK_a\) 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.\textsuperscript{38}

We should also note that the $p_K_a$ 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.\textsuperscript{39} For the tested chiral hydrogen bond donor catalysts ($p_K_a = 13-21$) a structure-activity enantioselectivity relationship was established.\textsuperscript{39}

Due to the above mentioned significance of the $p_K_a$ 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 ($p_K_a = \sim 12-14$ in aqueous media) to form strong hydrogen bonds.

![Figure 2. $p_K_{a,1}$, $p_K_{a,2}$ and $p_K_{a,3}$ values of amide type pyridino-crown ethers ($S,S$)-1–($S,S$)-6.](image)

![Table 1. Measured and predicted $p_K_a$ values of pyridino-crown ethers ($S,S$)-1–($S,S$)-6](image)

| Substituents | $p_K_{a,1}$ measured | $p_K_{a,1}$ Predicted\* | $p_K_{a,2}$ measured | $p_K_{a,2}$ Predicted\* | $p_K_{a,3}$ measured | $p_K_{a,3}$ Predicted\* |
|-------------|----------------------|------------------------|----------------------|------------------------|----------------------|------------------------|
| ($S,S$)-1   | 13.0±0.2             | 14.0                   | 15.0                 | 0.5±0.0                | -7.5                 |
| ($S,S$)-2   | 12.9±0.2             | 13.6                   | 14.6                 | 0.8±0.0                | -8.5                 |
| ($S,S$)-3   | 12.8±0.1             | 13.6                   | 14.3                 | 1.2±0.1                | -1.3                 |
| ($S,S$)-4   | 13.0±0.3             | 14.0                   | 15.0                 | 0.6±0.2                | -7.3                 |
| ($S,S$)-5   | 12.9±0.1             | 13.6                   | 14.6                 | 0.9±0.2                | -8.3                 |
| ($S,S$)-6   | 13.2±0.2             | 13.6                   | 14.3                 | 0.6±0.1                | -1.3                 |

\* $p_K_a$ values were predicted by MarvinSketch v.15.10.12.

Deviations of the $p_K_a$ values of amide groups (see Table 1) show that they were determined near by the upper limit of the measurement ($p_K_a \sim 13$), 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\textsubscript{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\textsubscript{a} ~ 1), has a large (up to 9 units) error, therefore in this case NMR titrations, the overlapping indicator method\textsuperscript{40} 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\textsubscript{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\textsubscript{a} ~ 4.4) than that of the pyridino-crown ethers (pK\textsubscript{a} ~ 0.5). The pK\textsubscript{a} values of the amide groups of piperidino-crown ethers could not be measured (they were outside the pK\textsubscript{a} region of 2-12).

![Figure 3. pK\textsubscript{a},1, pK\textsubscript{a},2 and pK\textsubscript{a},3 values of piperidino-crown ethers (R,S,S,S)-7 and (R,S,S,S)-8, respectively.](image)

**Table 2.** Measured and predicted pK\textsubscript{a} values of piperidino-crown ethers (R,S,S,S)-7 and (R,S,S,S)-8, respectively

| Substitutes | pK\textsubscript{a},1 | pK\textsubscript{a},2 | pK\textsubscript{a},3 |
|-------------|---------------------|---------------------|---------------------|
| (R,S,S,S)-7 | measured | predicted* | measured | predicted* |
| R=Me       | 13.0                | 13.5                | 4.42±0.00           | 7.5 |
| (R,S,S,S)-8 | R=iBu n.a.         | 12.7                | 13.3                | 4.38±0.02           | 7.5 |

*pK\textsubscript{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.\textsuperscript{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 (pKa ~13.0, see Figure 2 and Table 1) and that of the pyridine derivative 20 (pKa = 13.1, see Figure 4 and Table 3). The pyridine (20) and piperidine [(R,S)-21] diamides have more basic nitrogens (pKa ~ 0.7 for 20, and pKa ~ 6.3 for (R,S)-21) than those of the crown ethers (pKa ~ 0.5 for (S,S)-1 and (S,S)-4, and pKa ~ 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 pKa values of the basic nitrogens decreased to 1-2 units.

Figure 4. pKa,1, pKa,2 and pKa,3 values of the amide type pyridine (20) and piperidine [(R,S)-21] diamides.

Table 3. Measured and predicted pKa values of diamides 20 and (R,S)-21, respectively

|          | pKa,1  | pKa,2  | pKa,3  | Predicted | Predicted* |
|----------|--------|--------|--------|-----------|------------|
| Measured |        |        |        |           |            |
| 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        |

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

The pKa values of our new potential organocatalysts were measured in water. The amide groups have pKa 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 pKa values of our amides, we compared the pKa values in water and in DMSO. The pKa 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                  | $pK_a,1$ (DMSO) | $pK_a,1$ (water) |
|-----------------------|-----------------|-----------------|
| Barbituric acid       | 8.40            | 3.40            |
| $\text{F}_3\text{COSO}_2\text{NH}_2$ | 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$^b$       |

$^a$Extrapolated with Yashuda–Shedlovsky method in DMSO-H$_2$O; $^b$Data from the literature.$^{43,44}$

We can conclude that the amide groups of new pyridino- and piperidino-crown ethers have such $pK_a$ 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.$^{46}$
on our preliminary nanofiltration results, we plan to enhance the membrane processing of crown ethers via cascade approach and hybrid processes.

![Graph A](image1)

**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 13C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for 1H and at 75 MHz for 13C spectra) and it is indicated in each individual case. Mass spectra were recorded on CAMAG TLC-MS Interface (HPLC pump: Shimadzu LC-20AD Prominance 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 (Elementanalyze 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 patent^4^ 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.\textsuperscript{48} The $pK_a$ values were calculated by Refinement Pro\textsuperscript{TM} 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 $t = 25.0 \pm 0.5 \, ^\circ C$. All
$pK_a$ values were measured in 6 or 9 replicates.

Membranes were fabricated based on the recent developments by Valtcheva \textit{et al.}\textsuperscript{49,50}
Polybenzimidazole membrane (22 wt\%) crosslinked with $\alpha,\alpha'$-dibromo-$p$-xylene was used for
the rejection studies of the crown ethers. Solutes were dissolved in toluene (0.1 g $L^{-1}$) and loaded
onto 58 cm$^2$ membrane disc. The nanofiltration was carried out in cross-flow configuration with
recirculation (100 L $h^{-1}$) 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:

\begin{align}
F &= \frac{V_P}{A_m} \times \frac{1}{t} \\
R &= 1 - \frac{c_{P,x}}{c_{R,x}}
\end{align}

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 $x$.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure6.png}
\caption{Schematic diagram of the nanofiltration process comprising of a stirred feed tank, high
pressure pump, crossflow membrane cell, pressure gauge and back pressure regulator.}
\end{figure}
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.

(2S,2'S)-(+-)-1,1′-[2,2′-Oxybis(ethane-2,1-diyl)bis(oxy)]dipropane-2-amine (S,S)-9. Rf: 0.16 (silica gel TLC, CH3CN-MeOH-Et3N 1:1:0.1); [α]D25 = +18 (c 2.79, CHCl3); IR (neat) νmax 3358, 3289, 3186, 2958, 2865, 1654, 1590, 1452, 1374, 1350, 1297, 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 µL, 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′-(2S,2'S)-1,1′-[2,2′-oxybis(ethane-2,1-diyl)bis(oxy)]bis(propane-2,1-diyl)diacetamide are the following: Rf: 0.81 (SiO2 VRK, CH3CN-MeOH-Et3N 1:1:0.1); [α]D25 = –37 (c 1.76, CHCl3); IR (neat) νmax 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.

(2S,2'S)-(+-)-1,1′-[2,2′-Oxybis(ethane-2,1-diyl)bis(oxy)]bis(4-methylpentane-2-amine) (S,S)-10. Rf: 0.18 (silica gel TLC, CH3CN-MeOH- Et3N 1:1:0.1); [α]D25 = +4 (c 2.59, CHCl3); IR (neat) νmax 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,
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 µL, 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 \(N,N'-(2S,2'S)-1,1'-(2,2'-oxybis(ethane-2,1-diyl))bis(oxy))bis(4-methylpentane-2,1-diyl)diacetamide\) are the following: 

- \(R_f\): 0.63 (SiO\(_2\) VRK, CH\(_3\)CN-MeOH-Et\(_3\)N 1:1:0.1); 
- \(\alpha_{D}^{25}\) = –33 (c 0.31, CHCl\(_3\)); 
- IR (neat) \(\nu_{\text{max}}\) 3466, 3430, 3275, 3078, 2955, 2928, 2868, 1743, 1647, 1550, 1468, 1373, 1297, 1261, 1104, 1037, 951, 802, 608, 600 cm\(^{-1}\); 
- \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (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 D\(_2\)O, amide protons disappeared); 
- \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) (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 C\(_{20}\)H\(_{40}\)N\(_2\)O\(_5\): 388.3, found (M+H\(^{+}\)) 389.3; 
- Anal. calcd for C\(_{20}\)H\(_{40}\)N\(_2\)O\(_5\): 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 SOCl\(_2\) 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 (3×200 mL). The combined organic phase was dried over MgSO\(_4\), 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 \[(S,S)-1–(S,S)-6\].

\((4S,14S)-(−)-4,14-Dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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 alumina 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; Rf: 0.58 (alumina TLC, EtOH-toluene 1:20); [α]D25 = -65 (c 1.03, CHCl3); IR (KBr) νmax 3419, 2962, 2922, 2853, 1659, 1643, 1583, 1570, 1447, 1423, 1410, 1377, 1363, 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.

(4S,14S)-(−)-19-Chloro-4,14-dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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. Rf: 0.45 (alumina TLC, EtOH-toluene 1:20); [α]D25 = -22 (c 1.12, CHCl3); IR (neat) νmax 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.

(4S,14S)-(−)-19-Methoxy-4,14-dimethyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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; Rf: 0.50 (alumina TLC, EtOH-toluene 1:100); [α]D25 = -52 (c 0.97 CHCl3); IR (KBr) νmax 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); 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, 70.53, 72.40, 73.95, 125.59, 147.63, 150.82, 161.96; MS calcd for C18H27N3O6: 381.2, found (M+H)⁺: 382.2; Anal. Calcd for C18H27N3O6: C, 56.68; H, 7.17; N, 11.02. Found: C, 56.65; H, 7.17; N, 10.94.
(4S,14S)-(−)-4,14-Diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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. Rf: 0.55 (alumina TLC, EtOH-toluene 1:20); [α]D^25 = −132 (c 1.54, CHCl3); IR (neat) νmax 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.

(4S,14S)-(−)-19-Chloro-4,14-diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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. Rf: 0.60 (alumina TLC, EtOH-toluene 1:20); [α]D^25 = −35 (c 0.93, CHCl3); IR (neat) νmax 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 groups), 1.50-1.56 (m, 2H), 1.60-1.65 (m, 2H), 1.71-1.77 (m, 2H), 3.43-3.71 (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.

(4S,14S)-(−)-19-Methoxy-4,14-diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),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 1:160 mixture as an eluent to yield (S,S)-6 (75.0 mg, 11%) as a yellowish brown oil. Rf: 0.52 (alumina...
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 (Selca 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:

Rf: 0.43 (alumina TLC, EtOH-toluene 1:20); [α]D25 = –16 (c 0.83, CHCl3); IR (neat) \(\nu_{\text{max}}\) 3424, 3083, 2962, 2854, 2677, 1727, 1673, 1650, 1632, 1574, 1530, 1468, 1450, 1439, 1412, 1397, 1365, 1333, 1262, 1200, 1103, 972, 889, 842, 800, 762, 738, 693, 661, 639, 580, 530, 460, 456 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl3) \(\delta\) (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), 3.61-3.91 (m, 10H), 3.95 (s, 3H), 4.33-4.37 (m, 2H), 7.86 (s, 2H), 8.25 (d, 2H, \(J=10\) Hz, shaking with D\(_2\)O, amide protons shifted to 8.53 ppm); \(^13\)C NMR (75.5 MHz, CDCl3) \(\delta\) (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 C\(_{24}\)H\(_{39}\)N\(_3\)O\(_6\): 465.3, found (M\(^+\))\(^+\): 466.3; Anal. calcd for C\(_{24}\)H\(_{39}\)N\(_3\)O\(_6\): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.90; H, 8.46; N, 9.00.

(1R,4S,14S,17S)-(–)-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; Rf: 0.43 (alumina TLC, EtOH-toluene 1:20); [α]D25 = –24 (c 1.17, CHCl3); IR (KBr) \(\nu_{\text{max}}\) 3376, 3341, 3235, 2962, 2863, 1666, 1620, 1556, 1510, 1454, 1384, 1370, 1303, 1274, 1261, 1195, 1107, 1056, 921, 800 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) \(\delta\) (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); 7.07 (br s, 2H, shaking with D\(_2\)O, amide protons shifted to 7.30 ppm); \(^13\)C NMR (75.5 MHz, CDCl3) \(\delta\) (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 C\(_{17}\)H\(_{31}\)N\(_3\)O\(_5\): 357.2, found (M\(^+\))\(^+\): 358.2; Anal. calcd for C\(_{17}\)H\(_{31}\)N\(_3\)O\(_5\): C, 57.12; H, 8.74; N, 11.76. Found: C, 57.05; H, 8.88; N, 11.72.

(1R,4S,14S,17S)-(–)-4,14-Diisobutyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosane-2,16-dione (R,S,S,S)-8: Rf: 0.45 (alumina TLC, EtOH-toluene 1:20); [α]D25 = –40 (c 1.02, CHCl3); IR (neat) \(\nu_{\text{max}}\) 3390, 3341, 3270, 2952, 2925, 2867, 1649, 1522, 1469, 1453, 1385, 1366, 1349, 1333, 1310, 1246, 1200, 1116, 1028, 950, 920, 881, 816, 729, 645, 549, 503, 477 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) \(\delta\) (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\(_2\)O, 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 C₂₅H₄₃N₃O₅: 441.3, found (M+H)⁺: 442.3; Anal. calcd for C₂₅H₄₃N₃O₅: 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; Rf: 0.39 (silica gel TLC, MeOH-toluene 1:4); IR (KBr) νmax 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.

(2R,6S)-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; Rf: 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) νmax 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, 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.
C_{15}H_{29}N_{3}O_{2}: 283.2, found (M+H)^{+}: 284.2; Anal. calcd for C_{15}H_{29}N_{3}O_{2}: C, 63.57; H, 10.31; N, 14.83. Found: C, 63.46; H, 10.35; N, 14.80.

Acknowledgements

The financial support of the Hungarian Scientific Research Fund/National Research, Development and Innovation Office, Hungary (OTKA/NKFIH Nos. K 112289 and PD 108462) and the New Széchenyi Development Plan (TÁMOP-4.2.1/B-09/1/KMR-2010-0002) are gratefully acknowledged.

References

1. Trost, B. M. Angew. Chem. Int. Ed. 1995, 34, 259. [http://dx.doi.org/10.1002/anie.199502591]
2. Zhao, Y.-L.; Wang, Y.; Luo, Y.-C.; Fu, X.-Z.; Xu, P.-F. Tetrahedron Lett. 2015, 56, 3703. [http://dx.doi.org/10.1016/j.tetlet.2015.02.134]
3. Liu, X.; Lin, L.; Feng, X. Chem. Commun. 2009, 6145. [http://dx.doi.org/10.1039/b913411e]
4. Doyle, A. G.; Jacobsen, E. N. Chem. Rev. 2007, 107, 5713. [http://dx.doi.org/10.1021/cr068373r]
5. Blake, J. F.; Jørgensen, W. L. J. Am. Chem. Soc. 1991, 113, 7430. [http://dx.doi.org/10.1021/ja00019a055]
6. Severance, D. L.; Jørgensen, W. L. J. Am. Chem. Soc. 1992, 114, 10966. [http://dx.doi.org/10.1021/ja00053a046]
7. Taylor, M. S.; Jacobsen. E. N Angew. Chem. Int. Ed. 2006, 45, 1520. [http://dx.doi.org/10.1002/anie.200503132]
8. Kelly, R.; Min, H. J. Am. Chem. Soc. 1994, 116, 7072. [http://dx.doi.org/10.1021/ja00095a009]
9. Behbehani, H.; Ibrahim, M. R.; Ibrahim, Y. A. Tetrahedron Lett. 2002, 43, 6421. [http://dx.doi.org/10.1016/S0040-4039(02)01379-5]
10. List, B. Synlett 2001, 1675. [http://dx.doi.org/10.1055/s-2001-18074]
11. List, B. Chem. Commun. 2006, 819. [http://dx.doi.org/10.1039/b514296m]
12. Szekely, G.; Jimenez-Solomon, M. F.; Marchetti, P.; Kim, J. F.; Livingston, A. G. Green Chem. 2014, 16, 4440. [http://dx.doi.org/10.1039/c4gc00701h]
13. Razali, M.; Kim, J. F.; Attfield, M.; Budd, P. M.; Drioli, E.; Lee, Y. M.; Szekely, G. Green Chem. 2015, 17, 5196.
14. Kim, J. F.; Szekely, G.; Schaepertoens, M.; Valtcheva, I. B.; Jimenez-Solomon, M. F.; Livingston, A.G. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2371.

http://dx.doi.org/10.1021/sc5004083

15. Burgal, J. S.; Peeva, L. G.; Kumbharkar, S.; Livingston, A. G. *J. Membr. Sci.* **2015**, *479*, 105.

http://dx.doi.org/10.1016/j.memsci.2014.12.035

16. Hermans, S.; Mariën, H.; Goethem, C. V.; Vankelecom, I. F. *Curr. Opin. Chem. Eng.* **2015**, *8*, 45.

http://dx.doi.org/10.1016/j.coche.2015.01.009

17. Szekely, G.; Schaepertoens, M.; Gaffney, P. R. J.; Livingston, A. G. *Chem. Eur. J.* **2014**, *20*, 10038.

http://dx.doi.org/10.1002/chem.201402186

18. Szekely, G.; Schaepertoens, M.; Gaffney, P. R. J.; Livingston, A. G. *Polym. Chem.* **2014**, *5*, 694.

http://dx.doi.org/10.1039/c3py01367g

19. Datta, A.; Ebert, K.; Plenio, H. *Organometallics* **2003**, *22*, 4685.

http://dx.doi.org/10.1021/om0303754

20. Schaepertoens, M.; Didaskalou, C.; Kim, J. F.; Livingston, A. G.; Szekely, G. *J. Membr. Sci.* **2016**, in press.

http://dx.doi.org/10.1016/j.memsci.2016.04.056

21. Rinaldi, P. L.; Wilk, M. *J. Org. Chem.* **1983**, *48*, 2141.

http://dx.doi.org/10.1021/jo00161a005

22. Bonger, K. M.; van den Berg, R. J. B. H. N.; Heitman, L. H.; Ijzerman, A. P.; Oosterom, J.; Timmers, C. M.; Overkleeft, H. S.; van der Marel, G. A. *Bioorg. Med. Chem.* **2007**, *15*, 4841.

http://dx.doi.org/10.1016/j.bmc.2007.04.065

23. Xiao, H.; Tao, X.; Wang, Y.; Qian, S.; Shi, G.; Li, H. *Tetrahedron Lett.* **2008**, *49*, 6819.

http://dx.doi.org/10.1016/j.tetlet.2005.08.024

24. Kupai, J.; Huszthy, P.; Katz, M.; Tóth, T. *Arkivoc* **2012**, (v), 134.

http://dx.doi.org/10.3998/ark.5550190.0013.513

25. Horváth, Gy.; Rusa, C; Köntös, Z.; Gerencsér, J.; Huszthy, P. *Synth. Commun.* **1999**, *29*, 3719.

http://dx.doi.org/10.1080/00397919908086011

26. Kupai, J.; Huszthy, P.; Székely, K.; Tóth, T.; Párkányi, L. *Arkivoc* **2011**, (ix), 77.

http://dx.doi.org/10.3998/ark.5550190.0012.906

27. Bradshaw, J. S.; Huszthy, P.; Wang, T.-M.; Zhu, C.-Y.; Nazarenko, A. Z.; Izatt, R. M. *Supramolecular Chem.* **1993**, *1*, 267.

http://dx.doi.org/10.1080/10610279308035170

28. Müller, S; Sanders, D. A.; Antonio, M. D.; Matsis, S.; Riou, J.-F.; Rodrigueza, R.; Balasubramaniana, S. *Org. Biomol. Chem.* **2012**, *10*, 6537.

http://dx.doi.org/10.1039/c2ob25830g
29. Kyba, E. P.; Hudson, C. W.; McPhaul, M. J.; John, A. M. J. Am. Chem. Soc. 1977, 99, 8053.  
   http://dx.doi.org/10.1021/ja00466a049
30. Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.;  
   Izatt, R. M. J. Org. Chem. 1992, 57, 5383.  
   http://dx.doi.org/10.1021/jo00046a020
31. Govender, T.; Hariprakasha, H. K.; Kruger, H. G.; Marchand, A. P. Tetrahedron: Asymmetry  
   2003, 14, 1553.  
   http://dx.doi.org/10.1016/s0957-4166(03)00272-6
32. Chênevert, R.; Dickman, M. Tetrahedron: Asymmetry 1992, 3, 1021.  
   http://dx.doi.org/10.1016/s0957-4166(00)86034-6
33. Etzenbach-Effers, K.; Berkessel, A. in Asymmetric Organocatalysis Vol. 291; List, B.; Ed.;  
   Springer-Verlag: Berlin, 2009, pp. 1-27.
34. Knowles, R. R.; Jacobsen, E. N. Proc. Natl. Acad. Sci. 2010, 107, 20678.  
   http://dx.doi.org/10.1073/pnas.1006402107
35. Kotke, M.; Schreiner, P. R. in Hydrogen Bonding in Organic Synthesis; Pihko, P., Ed.;  
   Wiley-VCH Verlag GmbH & Co. KGaA, 2009, pp. 141-351.
36. Jakab, G.; Tancon, C; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. Org. Lett. 2012, 14, 1724.  
   http://dx.doi.org/10.1021/ol300307c
37. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. J. Am.  
   Chem. Soc. 2005, 127, 9285.  
   http://dx.doi.org/10.1021/ja0510156
38. Li, Z.; Li, X.; Ni, X.; Cheng, J.-P. Org. Lett. 2015, 17, 1196.  
   http://dx.doi.org/10.1021/acs.orglett.5b00143
39. Li, X.; Deng, H.; Zhang, B.; Li, J. Y.; Zhang, L.; Luo, S. Z.; Cheng, J. P. Chem. Eur. J. 2010,  
   16, 450.  
   http://dx.doi.org/10.1002/chem.200902430
40. Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. J. Am. Chem. Soc. 1988, 110, 5903.  
   http://dx.doi.org/10.1021/ja00225a054
41. Cai, S.; Chen, C.; Shao, P.; Xi, C. Org. Lett. 2014, 16, 3142.  
   http://dx.doi.org/10.1021/ol501275r
42. Bordwell, F. G. Acc. Chem. Res. 1988, 21, 456.  
   http://dx.doi.org/10.1021/ar00156a004
43. March’s Advanced Organic Chemistry; Smith, M. B.; March, J., Eds.; Wiley-Interscience,  
   2007.
44. Huffman, L. M.; Stahl, S. S. J. Am. Chem. Soc. 2008, 130, 9196.  
   http://dx.doi.org/10.1021/ja802123p
45. Kim, J. F.; Szekely, G.; Valtcheva, I. B.; Livingston, A. G. Green Chem. 2014, 16, 133.  
   http://dx.doi.org/10.1039/c3gc41402g
46. Szekely, G.; Bandarra, J.; Heggie, W.; Sellergren, B.; Ferreira, F. C. Sep. Purif. Technol.  
   2012, 86, 79.
47. Máthé, T.; Tungler, A.; Petró, J. U.S. Patent 4,361,500, 1982.
48. Völgyi, G.; Ruiz, R.; Box, K.; Comer, J.; Bosch, E.; Takács-Novák, K. *Anal. Chim. Acta* **2007**, *583*, 418.
49. Valtcheva, I. B.; Kumbharkar, S. C.; Kim, J. F.; Bhole, Y.; Livingston, A. G. *J. Membr. Sci.* **2014**, *457*, 62.
50. Szekely, G.; Valtcheva, I. B.; Kim, J. F.; Livingston, A. G. *React. Funct. Polym.* **2015**, *86*, 215.