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# Dynamic combinatorial libraries of macrocycles derived from phthalic aldehydes and α,ω-diamines

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ABSTRACT

Dynamic combinatorial chemistry methodology was used to obtain eleven new polyazamacrocycles derived from isophthalic and terephthalic aldehyde and α,ω-diamines. Simple templates, such as alkali metal salts, were found to amplify large macrocycles: 45-membered [3+3]hexaazacrown and 60-membered [4+4]octaazacrown. Parent imine libraries were converted into corresponding secondary libraries of amines using a fast reduction protocol. Methyl carbamate protection of amine group allowed convenient isolation of polyazamacrocycles in very good yields.



## 1. Introduction

Toward the end of the past Millennium, two groups of supramolecular chemists: those of Sanders[1] and Lehn[2] turned their attention to dynamic combinatorial chemistry (DCC). DCC is a field that exploits self-assembly for the generation of libraries of chemical compounds through constant interchange between the components of the library; possible due to the use of reversible reactions.[3,4] This makes it possible to solve two problems of great importance for supramolecular chemistry: to design and then to synthesize guest-selective receptors.[5–7] Addition of a specific guest molecule (a template) results in the thermodynamic favourability of the best binding member of a library and increases its contribution in the library composition. By stabilizing the formed receptor, the process of its creation is enhanced. Among reversible processes useful for DCC, the reaction of carbonyl compounds with amines seems to be one of the most interesting due to the great importance of aza-macrocyclic receptors. Most of the published imine macrocycles were formed upon crystallization in the form of complexes, and their solution behavior under thermodynamic control was not previously investigated.[8,9] However, some synthetic problems were recently solved using the DCC strategy.[10–17]

In this context, it seemed to be attractive to study in detail the formation and dynamic behavior of imine macrocycles. As a convenient model, reactions of phthalic aldehydes and α,ω-diamines were chosen. The set of substrates chosen to study the formation and dynamic behavior of such libraries is presented in Fig. 1. The reactions of isophthalic and terephthalic aldehydes and their derivatives with polyazadiamines or polythiadiamines leading to macrocyclic Schiff bases were studied previously, due to their ability to complex various transition metal ions.[8,9,18] Macrocyclizations of polyoxadiamines were reported for 2,6-diformyl-4-chlorophenol by the Vigato group.[19] Ugras et al.[20] described the macrocyclic ligand derived from terephthalic aldehyde (**2**) and 1,8-diamino-3,6-dioxaoctane (**B**) showing some antibacterial and antifungal activity. In 1955, Kraessig[21] presented dibenzotetraaza-crown derived from terephthalic aldehyde (**2**) and 1,5-diamino-3-oxapentane (**A**). This macrocycle and its copper complexes were recently studied in details by Delgado et al.[22]

The general scheme for the creation of cyclic imines library (limited to [1+1], [2+2], and [3+3] macrocycles) is presented in

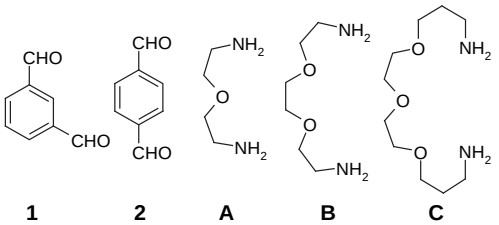


**Fig. 1.** Building blocks for imine libraries.

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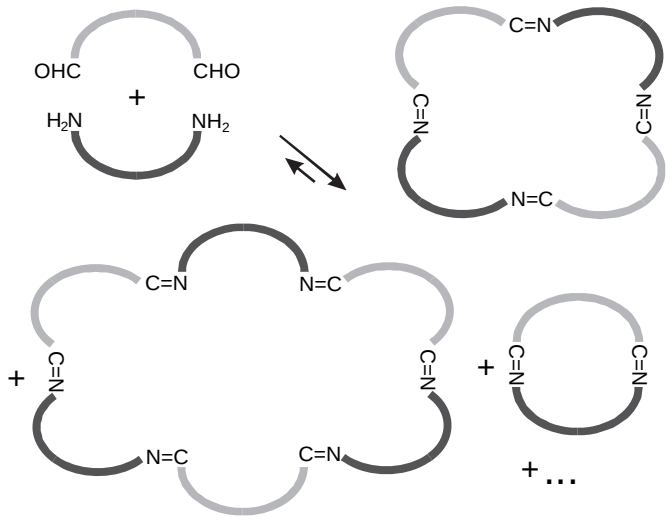
Scheme 1. To minimize the space required to draw all the macrocycles obtained during the project, we proposed, instead of common numbering, a self-explanatory naming system in which the first part stays for the macrocycle type: '**im**' for a polyimine, '**am**' for the corresponding polyamine, '**cb**' for a carbamate derivative; the second part: [**1**+**1**], [**2**+**2**], etc. represents the multiplicity of the macrocycle; the last part indicates the substrates used: **1** and **2** for isophthalic and terephthalic aldehyde, respectively, and **A** or **B** or **C** for the amine used. For example, **im**[**2**+**2**]-**1B** (Scheme 2) will represents the [2+2] macrocyclic imine derived from the library, made from isophthalic aldehyde (**1**) and 1,8-diamino-3,6-dioxaoctane (**B**).




**Scheme 1.**

## 2. Results and discussion

### 2.1. Analysis of the parent imine libraries

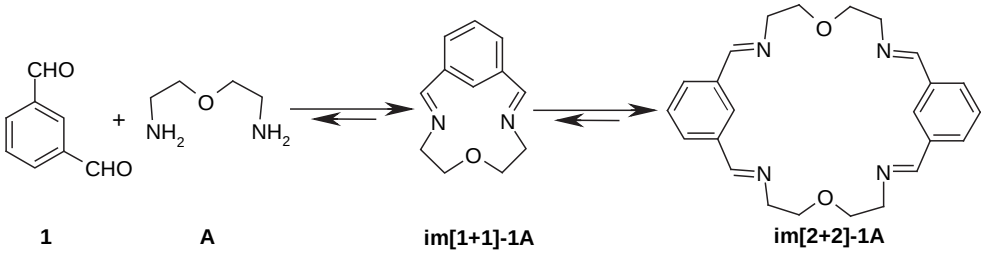
In the first attempt, like many others,[23–25] we chose ESI-MS as a method for qualitative determination of the composition of created imine libraries (as shown in Scheme 1) and estimation of the equilibration time. For example, in the reaction of isophthalic aldehyde (**1**) and diamine **A**, only macrocyclic product **im**[**2**+**2**]-**1A** is formed (Scheme 2). According to ESI-MS analyses, at the beginning, the product **im**[**1**+**1**]-**1A** was formed and later it was totally converted into the **im**[**2**+**2**]-**1A** macrocycle. The equilibrium of the reaction was established within 48 h. Similarly, aldehyde **1** and diamine **B** gave just one macrocycle, **im**[**2**+**2**]-**1B**. No linear products were observed in the library.

The problems with the ESI-MS approach appear as soon as the composition of non-templated multi-membered libraries is studied. The difficulties only deepen while examining the templated libraries, which are exemplified by reaction between aldehyde **1** and diamine **C** shown in Scheme 3 and summarized in Table 1. The ESI-MS results do not follow the composition of 'real' libraries (as analyzed by HPLC and on the basis of isolation of the pure compounds according to the protocol presented in Scheme 4 and discussed in the text later). According to ESI-MS, the non-templated library consisted mostly of the smallest [**1**+**1**]-**1C** macrocycle (75%), while HPLC revealed that, in reality, its concentration did not exceed 17% and that [**2**+**2**]-**1C** predominated (59%). Furthermore, [**3**+**3**]-**1C** was completely invisible by ESI-MS, while it comprises for one quarter of the library. It is well known that compounds of different structure have different sensitivities to ESI-MS, however, this method suggested positive templation in libraries, which finally appeared to be completely insensitive toward particular templates (TMACl, NaCl). Another issue was that ESI-MS results were strongly hardware-dependent, however, we were unable to set up and calibrate the equipment to avoid showing false templation results. These results finally excluded the use of ESI-MS, even for qualitative analysis. Taking all those considerations into account, we chose another method to determine the library composition.

### 2.2. Analysis of the secondary libraries of amines and carbamates

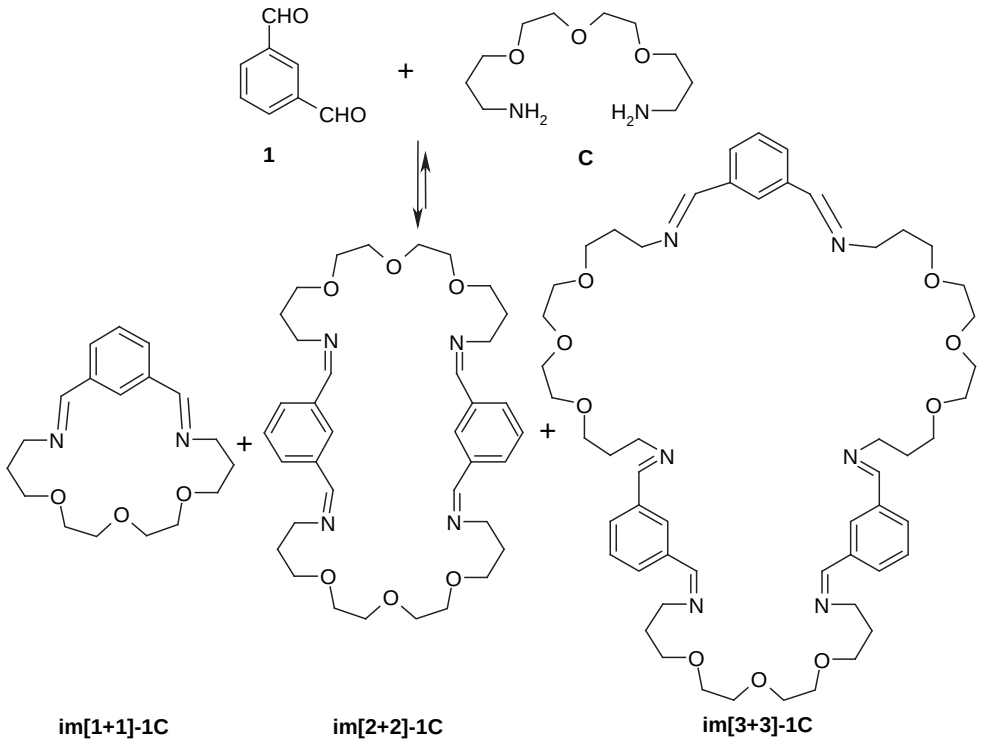
Since no other method than mass spectrometry allow for resolution of imine mixtures,[26] the parent imine libraries were 'frozen' by reducing them with $NaBH_4$ according to the previously reported protocol[27] that, for furan-based imines, allowed for full conversion in less than 1 min. To simplify the isolation and purification of the obtained products, the resulting secondary libraries of macrocyclic amines were then converted into methyl carbamates (Scheme 4). Such mixtures were also found to be easily resolved by HPLC for most aldehyde/amine combinations.

To assure that additional steps of reduction and carbamate functionalization did not alter the original ratio of macrocyclic members of a library, thus reflecting at least near-to-equilibrium




**Scheme 2.**

composition, further studies were carried out. The reduction step was found to take less than 1 min, as performed and measured using previously presented UV-methodology.[27] Kinetic measurements were undertaken for all aldehyde (**1**, **2**)—amine (**A**–**C**) pairs showing rapid conversion of imines to amines in all the cases and thus ensuring that the original ratios of macrocyclic compounds were maintained. For evaluation of the carbamate protection step, the reaction of **2** with **B** was chosen. Crude amine mixtures obtained from the reduction step were divided into two parts. The first half was used directly in a carbamate protection step, yielding 36% of **cb**[**2**+**2**]-**2B** and 9% of **cb**[**3**+**3**]-**2B**. From the second half, amines **am**[**2**+**2**]-**2B** and **am**[**3**+**3**]-**2B** were isolated and purified and then reacted with methyl chloroformate. The yields for the protected aminomacrocycles **cb**[**2**+**2**]-**2B** and **cb**[**3**+**3**]-**2B** were 36% and 10%, respectively (based on the initial amount of **2** and **B**), which basically means that the last step is quantitative. This entitled us to use the three-reaction sequence presented on Scheme 4 in all our studies and to assume that both the amine and carbamate mixtures fairly reflect the unbiased composition of the parent imine libraries.




**Scheme 3.**

**Table 1**
Comparison of ESI-MS and HPLC techniques used for determination of compositions of **1**+**C** libraries ([%][a])

| | [**1**+**1**]-**1C** | | [**2**+**2**]-**1C** | | [**3**+**3**]-**1C** | |
|---|---|---|---|---|---|---|
| | ESI-MS[b] | HPLC[c] | ESI-MS[b] | HPLC[c] | ESI-MS[b] | HPLC[c] |
| No template | 75 | 17[d] | 25 | 59[d] | — | 24[d] |
| TMACl | 4 | 17 | 96 | 59 | — | 24 |
| NaCl | 57 | 17 | 43 | 59 | — | 24 |

[a] Represents the ratio of the corresponding peak intensities to the sum of peaks intensities of all macrocycles.
[b] Measured for imines.
[c] Measured for corresponding carbamates (Scheme 4).
[d] Isolated yields of **cb**[**1**+**1**]-**1C**, **cb**[**2**+**2**]-**1C**, and **cb**[**3**+**3**]-**1C** were 7%, 25%, and 10%, respectively (Table 2).

## 2.3. Non-templated libraries

All the analyzed non-templated libraries show rather 'typical' compositions, in which mid-sized [2+2] macrocycles predominate (Table 2). The overall yields of macrocycles are good (36–71%), especially when we consider the relatively high reagent concentrations (50 mM) and the fact that imines were not 'trapped' and stabilized in a crystalline form. The [1+1] macrocycle was observed only in the reaction of isophthalic aldehyde (**1**) with the longest amine **C**. [3+3] Hexazacrowns, if present, accounted always only for a fraction of their smaller counterparts.

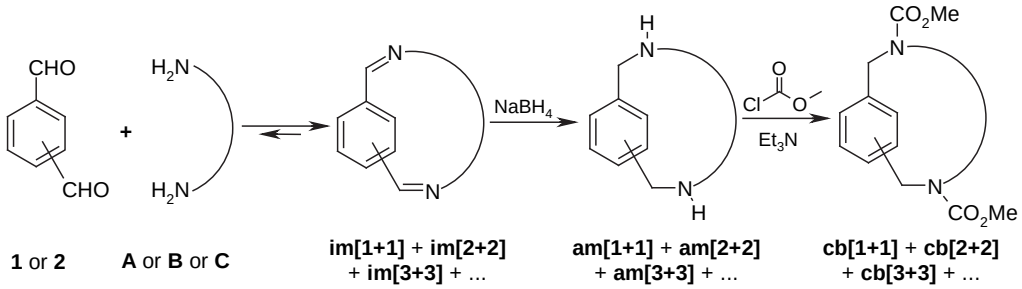
**Table 2**
Composition of non-templated libraries ([%], isolated yields)

| | Isophthalic aldehyde (**1**) | | | Terephthalic aldehyde (**2**) | | |
|---|---|---|---|---|---|---|
| | **cb**[**1**+**1**] | **cb**[**2**+**2**] | **cb**[**3**+**3**] | **cb**[**1**+**1**] | **cb**[**2**+**2**] | **cb**[**3**+**3**] |
| **A** | — | 71 | — | — | 45 | — |
| **B** | — | 47 | — | — | 36 | 9 |
| **C** | 7 | 25 | 10 | — | 29 | 9 |

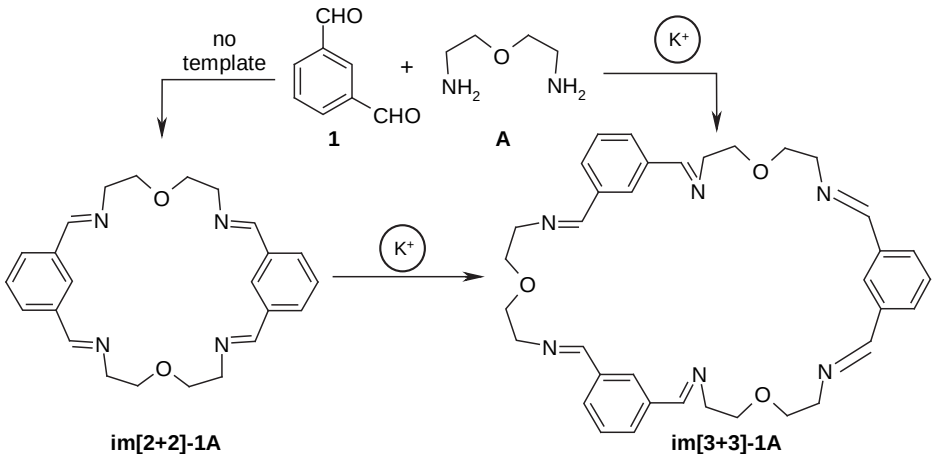
## 2.4. Behavior of libraries toward cationic templates

In the next step of our studies, templates were included in all previously performed reactions. As templates, alkali metal ($Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$), transition and heavy metals ($Pb^{2+}$, $Cu^{2+}$, $Zn^{2+}$, $Ni^{2+}$), and simple organic cations (tetramethylammonium and choline) were used.

For the reaction of isophthalic aldehyde **1** and amine **A**, potassium was found to be a potent and selective template. While, in the non-templated library, the [**2**+**2**]-**1A** macrocycle was the only product (71%), addition of 2 equiv of potassium perchlorate completely changed the outcome of the reaction (Scheme 5). [**2**+**2**]-**1A**




**Scheme 4.**




**Scheme 5.**

vanished and 36-membered macro-ring [**3**+**3**]-**1A** became the only product (45%). To confirm the thermodynamic background of the process, the template was added to a preequilibrated library containing **im**[**2**+**2**]-**1A**. Similarly to the situation, where the template is added simultaneously with the substrates, 48 h after addition of $KClO_4$, [**3**+**3**]-**1A** was found to be the only macrocyclic library member. **Im**[**3**+**3**]-**1A** may be considered potassium selective since, in our studies, no other cation supported its formation.

The potassium cation was also able to produce higher-order macrocycles in the **1**+**B** library. For this pair of reagents, HPLC of crude reaction mixtures was used to evaluate the template effects, since the HPLC results were found to reflect the library composition quite accurately (see Tables 2 and 3). In the absence of any template, 30-membered **im**[**2**+**2**]-**1B** was the only macrocyclic product. When potassium salts were used as templates, larger ones, i.e., [**3**+**3**]-**1B** and [**4**+**4**]-**1B** appeared, the latter one being a rare 60-membered ring (Fig. 2). The appearance of such a large macrocycle suggests very strong interaction with the template, since the presence of eight labile imine bonds in one molecule makes it inherently very unstable. To find out possible influence of the anionic counterion on the [**4**+**4**]-**1B**, we tested two other MeOH-soluble salts ($KPF_6$, KSCN). They both supported the formation of [**3**+**3**] and [**4**+**4**] macrocycles, although to lesser extent than potassium perchlorate. This behavior is unclear, but may result from different dissociation constants and solvation patterns of all three salts. Decreasing the amount of template to 1 equiv led to a drop in concentration of the largest macrocycle, while leaving the **im**[**3**+**3**]-**1B** intact. Increase in $KClO_4$ concentration (to 5 equiv) did not alter the library composition. Templation with 2 equiv of $KClO_4$ was found to be optimal and allowed the isolation of macrocycles **cb**[**3**+**3**]-**1B** and **cb**[**4**+**4**]-**1B** in 17% and 14% yield, respectively, which has to be considered as 'very high' with respect to their size. According to HPLC, $Na^+$ can amplify [**3**+**3**]-**1B** content up to 25%, $Li^+$, $Rb^+$, and $Cs^+$ were found to be inactive (Table 3).

Similar studies were performed for other cations, those that have any influence on the studied reaction are presented in Table 3. In most of the reactions, the yield of [**2**+**2**]-**1B** did not change, meaning that the bigger macrocycles are probably formed from linear precursors, leaving [**2**+**2**]-**1B** intact. In general—transition metals, ammonium, and alkylammonium salts template [**4**+**4**]-**1B** selectively over [**3**+**3**]-**1B**. The results obtained for transition metals suggest competitive binding of the amine **B** by a cation, since significant amounts of 1,3-benzenedimethanol (**diol**) are observed, although the amount of **im**[**2**+**2**]-**1B** does not decrease in any case except for $ZnCl_2$.

In the non-templated reaction of isophthalic aldehyde (**1**) with amine **C**, three macrocycles differing in size were stable enough to be observed, but none of the templates studied was able to alter their distribution significantly. Similarly, we have not found any template selective toward any library formed using terephthalic aldehyde (**2**) and amines **A**–**C**.

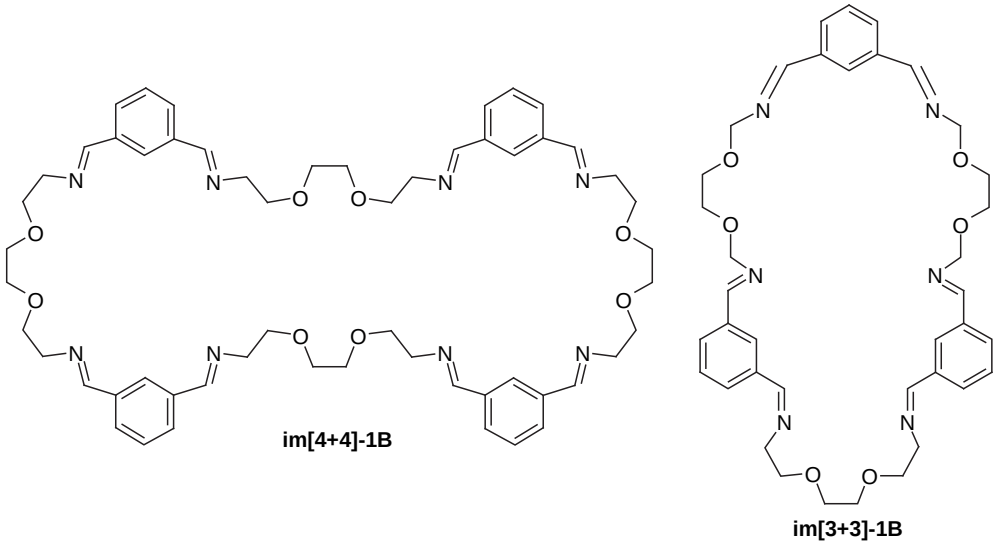



**Fig. 2.** 60-membered and 45-membered macrocycles amplified by potassium salts in **1**+**B** library.

**Table 3**
Composition of templated **1**+**B** libraries ([%][a])

| | Amount of template (equiv) | **Diol**[b] | **cb[2+2]-1B** | **cb[3+3]-1B** | **cb[4+4]-1B** |
|---|---|---|---|---|---|
| No template | — | 7 | 48 | — | — |
| $KPF_6$ | 2 | 7 | 45 | 8 | 8 |
| KSCN | 2 | 12 | 45 | 8 | 9 |
| $KClO_4$ | 1 | 8 | 45 | 15 | 2 |
| $KClO_4$ | 2 | 9 | 44 | 17 | 14 |
| $KClO_4$ | 5 | 8 | 45 | 17 | 15 |
| $NaClO_4$ | 2 | 2 | 47 | 25 | 12 |
| TMACl | 2 | 14 | 48 | — | 16 |
| Choline chloride | 2 | 17 | 50 | 6 | 15 |
| $NH_4ClO_4$ | 2 | 6 | 40 | — | 16 |
| $PbCl_2$ | 2 | 40 | 45 | — | 10 |
| $Cu(OAc)_2$ | 2 | 40 | 46 | — | 4 |
| $ZnCl_2$ | 2 | 40 | 35 | — | 6 |

[a] Measured for corresponding carbamates using HPLC; represents % of the corresponding peak in respect to the whole chromatogram.
[b] 1,3-Benzenedimethanol (product of reduction of dialdehyde **1**).

## 3. Conclusions

We presented eleven new, varying in size, macrocycles obtained using the 'all in solution' approach of dynamic combinatorial chemistry. The proposed methodology involves very fast (less than 1 min) reduction of imines to amines. This assures 'transcription' of the equilibrium concentrations of macrocyclic imines into the resulting secondary library of amines and thus allows unbiased templation. Furthermore, we found that carbamate protection of amines greatly improves isolation of final compounds, while HPLC allows for easy and robust screening and then optimization of conditions enhancing the desired macrocycles. Using this approach, we have synthesized two large and rare macrocycles of 45- and 60-membered ring in very good yields (with respect to their size).

## 4. Experimental

### 4.1. General

NMR spectra were recorded with Varian Unity Plus 200 MHz spectrometer for solutions in $CDCl_3$ using $Me_4Si$ as internal standard. Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Reactions were monitored by TLC (silica gel 60 $F_{254}$, 0.2 mm, Merck), visualization was effected with UV. Column chromatography was performed on silica gel (Merck, 230–400 mesh). HPLC were performed using LaChrom Merck HPLC equipped with Metachem (Varian) Polaris C-18A column (5 μm, 250×4.6 mm) and C-18 Phenomenex precolumn; DAD detection: (190–400 nm), integration of the signal at 198 nm; isocratic elution, 1.5 ml/min of water: acetonitrile (50:50).

Due to cis/trans isomerism of carbamates most of the signals in $^1$H NMR spectra were broadened and in $^{13}$C NMR spectra some signals were multiplied.

### 4.2. General procedure for the synthesis of azacoronands

*Parent imine library creation*. To 0.1 M solution of a phthalic aldehyde (in 20 ml of dry MeOH), 0.1 M solution of amine (in 20 ml of dry MeOH) was added. In templated experiments, this was followed by immediate addition of a template. The reaction mixture was stirred at room temperature for 2 days in a closed vessel.

*Reduction step*. The reaction mixture was cooled down to 5 °C using ice-water bath, and 2.2 equiv of $NaBH_4$ was added. When evolution of hydrogen ceased, 5% HCl was added slowly to the mixture to reach pH=2. The mixture was concentrated under vacuum to remove MeOH, than diluted with water and washed with ethyl acetate. The aqueous phase was alkalized with aqueous ammonia to pH=10 and extracted with methylene chloride. The organic phase was washed with brine and dried over magnesium sulfate. Solvents were removed under vacuum giving the crude mixture of macrocyclic amines.

In the case of the reaction of **2** and **B** macrocyclic amines **am[2+2]-2B** and **am[3+3]-2B** were isolated and purified by silica gel column chromatography, using $MeOH/NH_{3(25\%\,aq)}$ (98:2) as an eluent.

*Carbamate protection step*. The crude amine mixture was dissolved in MeOH and to this solution trietylamine (2.2 equiv, based on initial amount of aldehyde/amine used for creation of the library) was added followed by dropwise addition of methyl chloroformate (2.2 equiv). The resulting mixture was stirred at room temperature for 24 h, then solvents were evaporated under vacuum and the resulting mixture was separated by silica gel column chromatography, using $CH_2Cl_2$/MeOH (98:2) as an eluent.

*4.2.1. Macrocycle **cb[2+2]-1A***. Yield: 71% (non-templated reaction). Colorless solid. Mp 140–141 °C. $R_f$: 0.60 (95:5 $CHCl_3$/MeOH). $^1$H NMR($CDCl_3$): δ 3.32–3.53 (m, $NCH_2CH_2O$, 16H), 3.75 (s, $OCH_3$, 12H), 4.63 (s, Ar–$CH_2$, 8H), 7.03–7.36 (m, Ar–*H*, 8H). $^{13}$C NMR ($CDCl_3$): δ 46.38+47.19 ($NCH_2CH_2O$), 51.96+52.13 (Ar–*C*), 53.01 ($OCH_3$), 71.10 ($NCH_2CH_2O$), 125.44+126.27+129.45 ($Ar_{C-H}$) 138.36 ($Ar_{ipso}$), 157.09+157.29 (*C*=O). HRMS (ESI) *m*/*z* calculated 667.2955 for $C_{32}H_{44}N_4O_{10}Na$ obtained 667.2950.

*4.2.2. Macrocycle **cb[3+3]-1A***. Yield: 45% ($KClO_4$ templated reaction). Pale yellow oil. $R_f$: 0.48 (95:5 $CHCl_3$/MeOH). $^1$H NMR ($CDCl_3$): δ 3.30–3.49 (m, $NCH_2CH_2O$, 24H), 3.71 (s, $OCH_3$, 18H), 4.51 (s, Ar–$CH_2$, 12H), 7.04–7.29 (m, Ar–*H*, 12H). $^{13}$C NMR ($CDCl_3$): δ 46.87+45.95 ($NCH_2CH_2O$), 51.41 (Ar–*C*), 52.78 ($OCH_3$), 69.64 ($NCH_2CH_2O$), 125.77+126.52+128.88 ($Ar_{C-H}$) 138.33 ($Ar_{ipso}$) 156.93 (*C*=O). HRMS (ESI) *m*/*z* calculated 989.4484 for $C_{48}H_{66}N_6O_{15}Na$ obtained 989.4449.

*4.2.3. Macrocycle **cb[2+2]-1B***. Yield: 48% (non-templated reaction); 46% ($KClO_4$ templated reaction). Pale yellow oil. $R_f$: 0.50 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=5.23min. $^1$H NMR ($CDCl_3$): δ 3.50+3.31–3.59 (s+m, $OCH_2CH_2O$+$NCH_2CH_2O$, 24H), 3.72 (s, $OCH_3$, 12H), 4.53 (s, Ar–$CH_2$, 8H), 7.01–7.28 (m, Ar–*H*, 8H). $^{13}$C NMR ($CDCl_3$): δ 46.01+46.90 ($NCH_2CH_2O$), 51.48+51.58 (Ar–*C*), 52.97 ($OCH_3$), 69.28+70.63 ($CH_2OCH_2$), 126.04+126.92+129.08 ($Ar_{C-H}$) 138.47 ($Ar_{ipso}$) 157.44 (*C*=O). HRMS (ESI) *m*/*z* calculated 755.3479 for $C_{36}H_{52}N_4O_{12}Na$ obtained 755.3499.

*4.2.4. Macrocycle **cb[3+3]-1B***. Yield: 17% ($KClO_4$ templated reaction). Pale yellow oil. $R_f$: 0.38 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=7.16min. $^1$H NMR ($CDCl_3$): δ 3.51+3.34–3.58 (s+m, $OCH_2$-$CH_2O$+$NCH_2CH_2O$, 36H), 3.71 (s, $OCH_3$, 18H), 4.53 (s, Ar–$CH_2$, 12H), 7.05–7.27 (m, Ar–*H*, 12H). $^{13}$C NMR ($CDCl_3$): δ 45.96+46.78 ($NCH_2CH_2O$), 51.44 (Ar–*C*), 52.95 ($OCH_3$), 69.77+70.62 ($CH_2OCH_2$), 126.18+126.83+128.98 ($Ar_{C-H}$), 138.51 ($Ar_{ipso}$), 157.12+157.35 (*C*=O). HRMS (ESI) *m*/*z* calculated 1121.5270 for $C_{54}H_{78}N_6O_{18}Na$ obtained 1121.5242.

*4.2.5. Macrocycle **cb[4+4]-1B***. Yield: 14% ($KClO_4$ templated reaction). Pale yellow oil. $R_f$: 0.29 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=9.52min. $^1$H NMR ($CDCl_3$): δ 3.52+3.35–3.55 (s+m, $OCH_2$-$CH_2O$+$NCH_2CH_2O$, 48H), 3.71 (s, $OCH_3$, 24H), 4.53 (s, Ar–$CH_2$, 16H), 7.05–7.28 (m, Ar–*H*, 16H). $^{13}$C NMR ($CDCl_3$): δ 45.95+46.75 (br s+br s, $NCH_2CH_2O$), 51.38 (Ar–*C*), 52.95 ($OCH_3$), 69.69+70.58 ($CH_2OCH_2$),

126.26+126.90+128.95 ($Ar_{C-H}$), 138.55 ($Ar_{ipso}$), 157.44 (br s, *C*=O). LRMS (ESI): *m*/*z* 1465.6 $[M+H]^+$.

*4.2.6. Macrocycle* ***cb*[*1*+*1*]-*1C***. Yield: 7% (non-templated reaction). Pale yellow oil. $R_f$: 0.64 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=3.85min. $^1H$ NMR ($CDCl_3$): $\delta$ 1.77 (br s, $CH_2CH_2CH_2$, 4H), 3.22–3.63 (m, O–$CH_2$+N–$CH_2$, 16H), 3.75 (s, $OCH_3$, 6H), 4.49 (s, Ar–$CH_2$, 4H), 7.08–7.27 (m, Ar–*H*, 4H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.12+28.77 ($CH_2CH_2CH_2$), 43.82+44.82 ($NCH_2CH_2O$), 51.19+51.46 (Ar–*C*), 52.85 ($OCH_3$), 68.35+70.53+71.04 ($CH_2OCH_2$), 126.59+127.48+129.30 ($Ar_{C-H}$), 138.60 ($Ar_{ipso}$). HRMS (ESI) *m*/*z* calculated 439.2444 for $C_{22}H_{35}N_2O_7$ obtained 439.2455.

*4.2.7. Macrocycle* ***cb*[*2*+*2*]-*1C***. Yield: 25% (non-templated reaction). Pale yellow oil. $R_f$: 0.45 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=7.32min. $^1H$ NMR ($CDCl_3$): $\delta$ 1.77 (br s, $CH_2CH_2CH_2$, 8H), 3.27–3.62 (m, O–$CH_2$+N–$CH_2$, 32H), 3.72 (s, $OCH_3$, 12H), 4.54 (s, Ar–$CH_2$, 8H), 7.07–7.29 (m, Ar–*H*, 8H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.16+28.57 ($CH_2CH_2CH_2$), 43.85+44.76 ($NCH_2CH_2O$), 50.72 (Ar–*C*), 52.85 ($OCH_3$), 68.67+70.34+70.74 ($CH_2OCH_2$), 126.21+126.90+128.97 ($Ar_{C-H}$), 138.58 ($Ar_{ipso}$), 157.50 (br s, *C*=O). HRMS (ESI) *m*/*z* calculated 877.4810 for $C_{44}H_{69}N_4O_{14}$ obtained 877.4852.

*4.2.8. Macrocycle* ***cb*[*3*+*3*]-*1C***. Yield: 10% (non-templated reaction). Pale yellow oil. $R_f$: 0.29 (95:5 $CHCl_3$/MeOH). $t_{R\ (HPLC)}$=15.53min. $^1H$ NMR ($CDCl_3$): $\delta$ 1.78 (br s, $CH_2CH_2CH_2$, 12H), 3.27–3.63 (m, O–$CH_2$+N–$CH_2$, 48H), 3.72 (s, $OCH_3$, 18H), 4.45 (s, Ar–$CH_2$, 12H), 7.10–7.30 (m, Ar–*H*, 12H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.25+28.54 ($CH_2CH_2CH_2$), 43.86+44.72 +44.74 ($NCH_2CH_2O$), 50.67 (Ar–*C*), 52.89 ($OCH_3$), 68.78+70.36+70.76 ($CH_2OCH_2$), 126.20+126.83+128.97 ($Ar_{C-H}$), 138.59 ($Ar_{ipso}$), 157.04+ 157.51 (*C*=O). LRMS (ESI): *m*/*z* 1315.6 $[M+H]^+$.

*4.2.9. Macrocycle* ***cb*[*2*+*2*]-*2A***. Yield: 45% (non-templated reaction). Colorless solid. Mp 131–135 °C. $R_f$: 0.64 (95:5 $CHCl_3$/MeOH). $^1H$ NMR ($CDCl_3$): $\delta$ 3.25–3.45 (m, $NCH_2CH_2O$, 16H), 3.71 (s, $OCH_3$, 12H), 4.43 (s, Ar–$CH_2$, 8H), 7.08 (br s, Ar–*H*, 8H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 46.93+47.86 ($NCH_2CH_2O$), 51.86 (Ar–*C*), 52.95 ($OCH_3$), 70.16 ($NCH_2CH_2O$), 127.26+128.06 ($Ar_{C-H}$) 137.24 ($Ar_{ipso}$), 157.28 (*C*=O). HRMS (ESI) *m*/*z* calculated 667.2955 for $C_{32}H_{44}N_4O_{10}Na$ obtained 667.2966.

*4.2.10. Macrocycle* ***am*[*2*+*2*]-*2B***. $^1H$ NMR ($CDCl_3$): $\delta$ 1.98 (br s, *NH*, 4H), 3.00–3.50 (m, O–$CH_2$+N–$CH_2$, 24H), 3.60 (s, Ar–$CH_2$, 8H),7.00–7.10 (m, Ar–*H*, 8H). LRMS (ESI): *m*/*z* 501.4 $[M+H]^+$.

*4.2.11. Macrocycle* ***am*[*3*+*3*]-*2B***. $^1H$ NMR ($CDCl_3$): $\delta$ 1.99 (br s, *NH*, 4H), 3.00–3.50 (m, O–$CH_2$+N–$CH_2$, 24H), 3.62 (s, 8H, $CH_2N$), 7.01–7.11 (m, Ar–*H*, 8H). LRMS (ESI): *m*/*z* 751.6 $[M+H]^+$.

*4.2.12. Macrocycle* ***cb*[*2*+*2*]-*2B***. Yield: 36% (non-templated reaction). Colorless solid. Mp 118–122 °C. $R_f$: 0.66 (95:5 $CHCl_3$/MeOH). $^1H$ NMR ($CDCl_3$): $\delta$ 3.53+3.29–3.61 (s+m, $OCH_2CH_2O$+$NCH_2CH_2O$, 24H), 3.73 (s, $OCH_3$, 12H), 4.55 (s, Ar–$CH_2$, 8H), 7.08+7.14 (br s+br s, Ar–*H*, 8H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 45.72+46.52 ($NCH_2CH_2O$), 51.19+51.28 (Ar–*C*), 52.96 ($OCH_3$), 70.09+70.60 ($CH_2OCH_2$), 127.66+128.35 ($Ar_{C-H}$) 137.18 ($Ar_{ipso}$) 157.12+157.33 (*C*=O). HRMS (ESI) *m*/*z* calculated 755.3479 for $C_{36}H_{52}N_4O_{12}Na$ obtained 755.3470.

*4.2.13. Macrocycle* ***cb*[*3*+*3*]-*2B***. Yield: 9% (non-templated reaction). Pale yellow oil. $R_f$: 0.56 (95:5 $CHCl_3$/MeOH). $^1H$ NMR ($CDCl_3$): $\delta$ 3.52+3.46–3.59 (s+m, $OCH_2CH_2O$+$NCH_2CH_2O$, 36H), 3.71 (s, $OCH_3$, 18H), 4.53 (s, Ar–$CH_2$, 8H), 7.13+7.18 (br s+br s, Ar–*H*, 12H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 45.91+46.65 ($NCH_2CH_2O$), 51.19+51.28 (Ar–*C*), 52.94 ($OCH_3$), 69.87+70.64 ($CH_2OCH_2$), 127.60+128.28 ($Ar_{C-H}$) 137.21 ($Ar_{ipso}$) 157.13+157.31 (*C*=O). HRMS (ESI) *m*/*z* calculated 1121.5270 for $C_{54}H_{78}N_6O_{18}Na$ obtained 1121.5355.

*4.2.14. Macrocycle* ***cb*[*2*+*2*]-*2C***. Yield: 29% (non-templated reaction). Pale yellow oil. $R_f$: 0.63 (95:5 $CHCl_3$/MeOH). $^1H$ NMR ($CDCl_3$): $\delta$ 1.77 (br s, $CH_2CH_2CH_2$, 8H), 3.26–3.62 (m, O–$CH_2$+N–$CH_2$, 32H), 3.72 (s, $OCH_3$, 12H), 4.44 (s, Ar–$CH_2$, 8H), 7.16–7.19 (m, Ar–*H*, 8H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.13+28.57 ($CH_2CH_2CH_2$), 43.74+44.72 ($NCH_2CH_2O$), 50.52+50.70 (Ar–*C*), 52.84 ($OCH_3$), 68.62+70.34+70.77 ($CH_2OCH_2$), 127.65+128.31 ($Ar_{C-H}$), 137.32 ($Ar_{ipso}$), 157.54+157.59 (*C*=O). HRMS (ESI) *m*/*z* calculated 899.4630 for $C_{44}H_{68}N_4O_{14}Na$ obtained 899.4616.

*4.2.15. Macrocycle* ***cb*[*3*+*3*]-*2C***. Yield: 9% (non-templated reaction). Pale yellow oil. $R_f$: 0.44 (95:5 $CHCl_3$/MeOH). $^1H$ NMR ($CDCl_3$): $\delta$ 1.78 (br s, $CH_2CH_2CH_2$, 12H), 3.27–3.64 (m, O–$CH_2$+N–$CH_2$, 48H), 3.71 (s, $OCH_3$, 18H), 4.44 (s, Ar–$CH_2$, 12H), 7.16–7.19 (m, Ar–*H*, 12H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.13+28.51 ($CH_2CH_2CH_2$), 43.71+44.55 ($NCH_2CH_2O$), 50.36 (br s, Ar–*C*), 52.86 ($OCH_3$), 68.71+70.34+70.75 ($CH_2OCH_2$), 127.60+128.23 ($Ar_{C-H}$), 137.27 ($Ar_{ipso}$), 157.08+157.50 (*C*=O). LRMS (ESI): *m*/*z* 1315.6 $[M+H]^+$.

## Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.011.

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