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READY AVAILABLE CHIRAL AZAPYRIDINOMACROCYCLES *N*-OXIDES; FIRST RESULTS AS LEWIS BASE CATALYSTS IN ASYMMETRIC ALLYLATION OF *p*-NITROBENZALDEHYDE

Maité Sylla-Iyarreta Veitía,* Mounia Joudat, Mathieu Wagner, Annie Falguières, Alain Guy, and Clotilde Ferroud*

Laboratory of Chemical and Pharmaceutical Transformations, ERL 3193 CNRS, ESPCI ParisTech, Cnam, 2 rue Conté 75003 Paris, France. Email: maite.sylla@cnam.fr, clotilde.ferroud@cnam.fr

Abstract – We report here the straightforward synthesis of the first series of enantiomerically pure azapyridinomacrocycles *N*-oxides containing a cyclohexyl chiral moiety. These compounds were readily obtained in good overall yields by a convergent synthesis using natural amino acids as starting building blocks and macrocyclisation as the key step. This method is rapid, efficient and suitable for the introduction of various substituents at the macrocyclic skeleton. Finally, the compounds were tested as organocatalysts for the enantioselective allylation of *p*-nitrobenzaldehyde with allyltrichlorosilane.

INTRODUCTION

During the last few years, pyridine-based *N*-oxides have emerged as highly versatile compounds, since they possess notable nucleophilicity and basicity properties which allow them to function as Lewis base catalysts and as ligand for metal complexes. In each case, an oxygen atom serves as a basic/ligating site.[1-4] In asymmetric synthesis, chiral pyridine-based *N*-oxides have been widely used in various catalytic processes including the asymmetric allylation of aldehydes,[5-11] the reduction of ketones,[12] the asymmetric cyclopropanation,[13] the enantioselective ring opening of meso-epoxides,[14,15] or the Strecker reaction.[16]

Since several years, our laboratory is interested in the synthesis of azapyridinomacrocycles.[17-21] These polyamine ligands are recognized for their capacity to chelate metallic cations, particularly those of the lanthanide family. Under their complexed form, these structures are involved in a wide field of applications such as diagnostic area as contrast agents in Magnetic Resonance Imaging (MRI). Until now,

the use of chiral macrocyclic derivatives as catalysts in enantioselective reactions is based exclusively on their ability to form stable complexes with metal cations. However, such polyazamacrocycles might lead to covalent catalysis suggesting that they could be used as organocatalysts.

Considering all the above and taking into account the experience of our laboratory, we have undertaken the preparation of two series of chiral azapyridinomacrocycles from natural and easily available amino acids featuring a pyridine *N*-oxide fragment as the key structural element (Figure 1). Their first application as chiral organocatalysts in the asymmetric allylation of *p*-nitrobenzaldehyde with allyltrichorosilane has been studied.

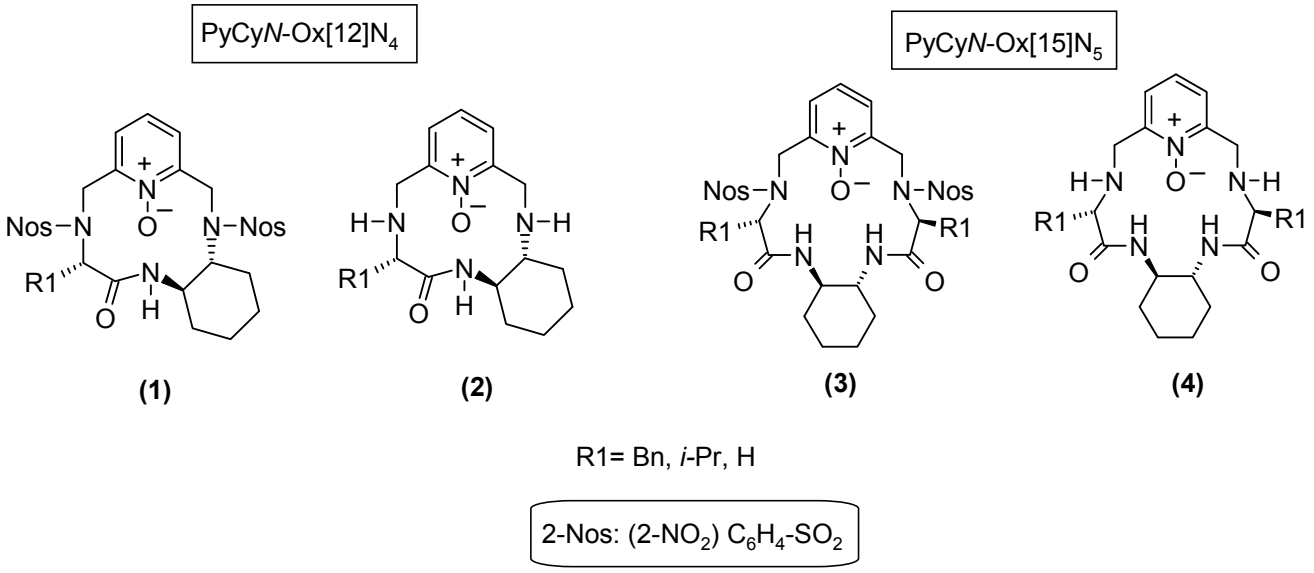


Figure 1. Series of azapyridinomacrocycles *N*-oxides

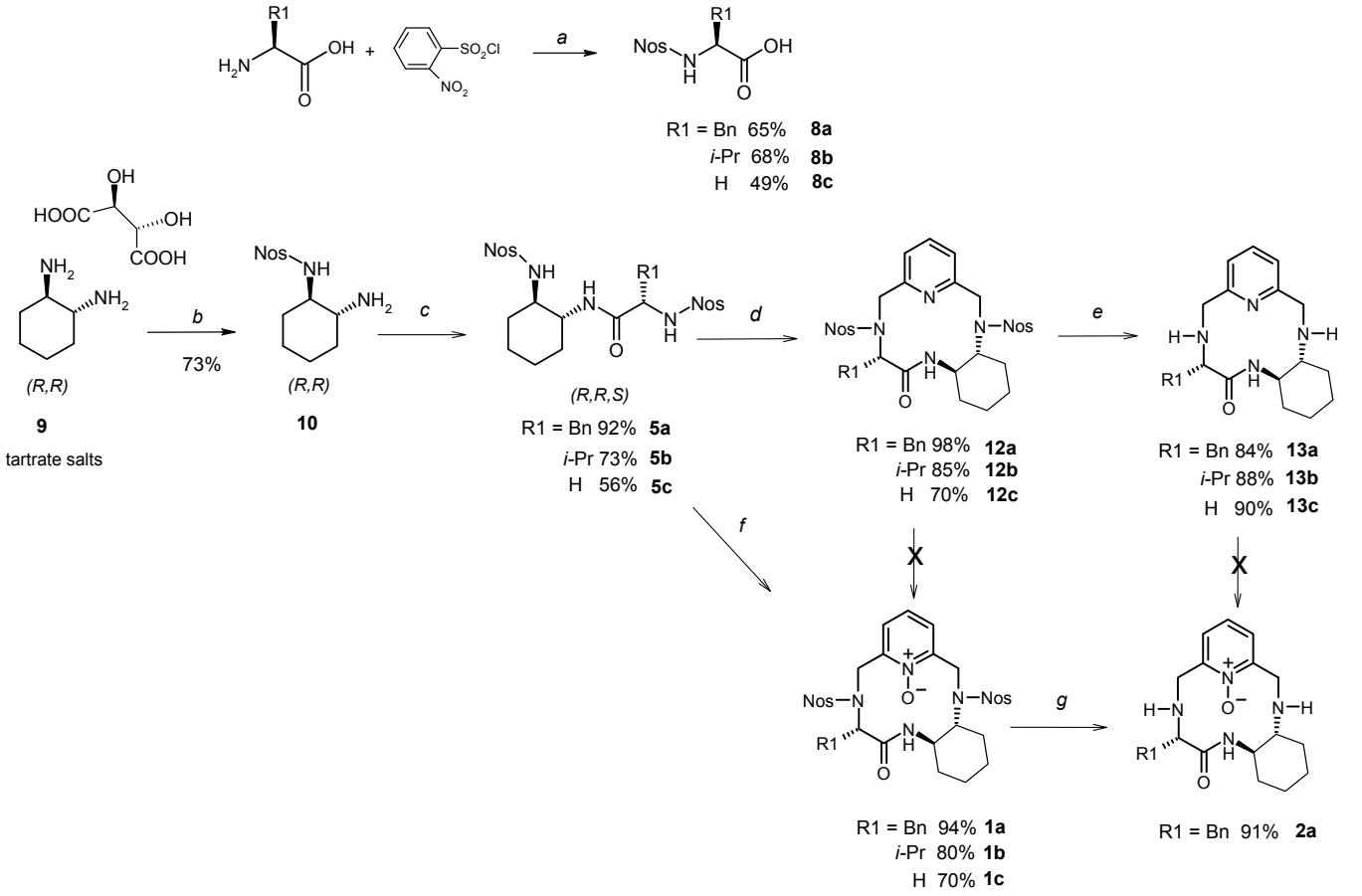
RESULTS AND DISCUSSION

Synthesis of azapiridinomacrocycles *N*-oxides

In the preparation of azapyridinomacrocycles *N*-oxides, two synthetic strategies could be considered. The first strategy concerns the oxidation of the polyazamacrocycles at the end of the synthesis. The second strategy results from the condensation of the corresponding polyamine moieties (**5**) and (**6**), with 2,6-bis(chloromethyl)pyridine *N*-oxide (**7**), previously prepared from the 2,6-bis(chloromethyl)pyridine.

To prepare the *N*-protected amino acids (**8**), the corresponding *L*-amino acids were reacted with one equivalent of 2-nitrobenzenesulfonylchloride in water at 60-70 °C for 17 h in presence of NaOH. The corresponding *N*-nosyl amino acids (**8a-c**) were isolated in 65, 68 and 49% yields respectively. The chiral pool, *trans*-1,2-(*R,R)*-diammoniumcyclohexane salt (**9**), was obtained from the racemic *trans*-1,2-diaminocyclohexane by a conventional resolution method using the *L*-tartaric acid. This method

reported in 2003 by Schanz and co-workers allows the isolation of both enantiomers in their enantiopure forms (ee> 99.8%) as chemically inert bis-ammonium salts during the same separation process.[22] The racemic *trans*-1,2-diaminocyclohexane was treated with 0.5 equiv of *L*-tartaric acid in a mixture of water and acetic acid to afford, after cooling to 5 °C, the selective precipitation of *trans*-1,2-*(R,R)*-diammonium cyclohexane as tartrate salt (**9**), with a yield of 45% and an enantiomeric purity of 99.9% (Scheme 1).



Scheme 1. Synthesis of azapyridinomacrocycles *N*-oxides, PyCy*N*-Ox[12]N_4. Reagents and conditions: (a) NaOH (2.1 equiv), H_2O, 60-70 °C, 17 h; (b) (i) NaOH, TEA (1.3 equiv), CH_2Cl_2, 0 °C, 10 min; (ii) $ArSO_2Cl$ (1.7 equiv), 0 °C to rt, 3 h; (c) (i) *N*-nosyl amino acid (8) (1.05 equiv), DMAP (1.05 equiv), anhydrous THF, 0 °C, 10 min; (ii) EDCI (1.05 equiv), rt, 17 h; (d) (i) K_2CO_3 (4 equiv), DMF, 90 °C; (ii) 2,6-bis(bromomethyl)pyridine (11) (1.2 equiv), DMF, reflux, 1-2 h; (e) PhSH (2.5 or 3 equiv), K_2CO_3 (4 equiv), DMF, rt, 2-5 h; (f) (i) K_2CO_3 (4 equiv), MeCN, reflux, 5 min then KI (2.2 equiv); (ii) 2,6-bis(chloromethyl)pyridine *N*-oxide (7) (1.1 equiv), MeCN, reflux, 3-5 h; (g) mercaptoethanol (11.2 equiv), DBU (4.5 equiv), MeCN, rt, 2 h.

The chiral amidodisulfonamide blocks (**5**) could be obtained from the commercially available racemic *trans*-diaminocyclohexane and natural amino acids by peptide coupling. We applied the Fukuyama's 2-nitrobenzenesulfonamide strategy[23,24] to control the selective regiofunctionalization of the polyamine

framework. The nosyl group is compatible with many chemical functions, stable in acidic (HCl 10 equiv, MeOH, 60 °C) and basic (NaOH, 10 equiv, MeOH, 60 °C) conditions and its cleavage is achieved under mild reaction conditions. The nosyl group is used both for *N*-protection and to increase acidity of the remaining N-H bond allowing the use of weak bases during the macrocyclization step. In addition, the bulky nature of this group takes part of the arrangement of the transition state required for intramolecular cyclization, thus avoiding intermolecular oligomerization process. Consequently the use of the 2-nitrobenzenesulfonamide group, in a protection-activation strategy of polyamines is very useful for an efficient synthesis of azamacrocycles compounds (Scheme 1).

Ng and co-workers in 2001[25] reported the efficient synthesis of several mono-*N*-sulfonyl diaminocyclohexane derivatives from tartrate salts (**9**) using a ratio 1.5/1 : diamine/sulfonyl chloride in presence of triethylamine. Using this protocol slightly modified, 1.7 equiv of 2-nitrobenzenesulfonyl chloride was reacted with the tartrate salts (**9**), in dichloromethane at 0 °C, then at room temperature in the presence of NaOH and triethylamine. The mono *N*-sulfonylated compound (**10**) was afforded after crystallization with 73% yield. The condensation of the compounds (**8**) and (**10**) was achieved by a peptide coupling reaction. The (*R*,*R*)-mono-*N*-sulfonylated cyclohexanediamine (**10**) was reacted with a stoichiometric amount of the corresponding *N*-nosyl amino acids (**8**) in THF employing EDCI/DMAP as activating agent. After stirring overnight at room temperature and then purification by flash chromatography on silica gel, the corresponding chiral amidodisulfonamide blocks (**5a-c**) were isolated in 92, 73 and 56% yields respectively (Scheme 2).

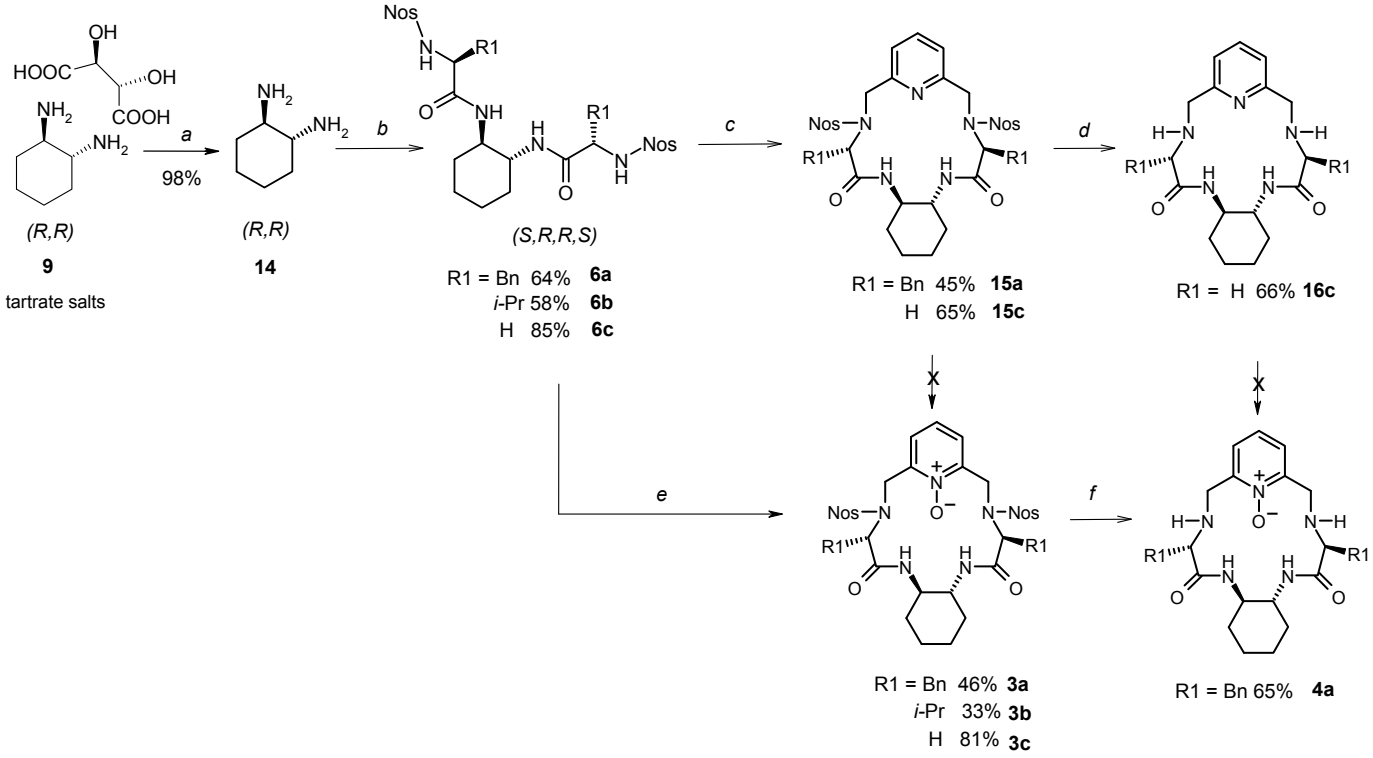
In the macrocyclisation step the corresponding polyamine moieties (**5**) were reacted with the 2,6-bis(bromomethyl)pyridine (**11**) according to the procedure based on a Richman-Atkins cyclization reaction.[26] In order to minimize the amounts of competitive adducts such as cyclic [2+2] or uncyclized [2+1] adducts, the optimization of the macrocyclisation conditions was carried out. A slow addition of a slight excess of 2,6-bis(bromomethyl)pyridine (**11**) to a warmed DMF solution (90 °C) of amidodisulfonamides (**5**) in the presence of an excess of K_2CO_3 (4 equiv), gave in less than two hours the desired macrocycles (**12a-c**) isolated after chromatography in 70 to 98% yields. It is to be noticed that the crude forms were pure enough to be used in the next step without prior purification (Scheme 1).

The cleavage of the 2-nitrobenzenesulfonamide framework to give the corresponding diamino-compounds (**13a-c**) was carried out following a conventional method[23,24] by treatment with thiophenol with potassium carbonate in DMF at room temperature. In such conditions, the desulfonylated macrocycles (**13a-c**) were isolated with yields of 84 to 90% (Scheme 2). The purification proceeded by a simple work-up involving an acid-basic extraction. In the last step, classical methods of *N*-oxidation were used (H_2O_2 30%/acetic acid, *m*-CPBA) to oxidize the compounds (**12**) and (**13**). Unfortunately, the *N*-oxidation of the pyridine moiety of the azapyridinomacrocycles never occured.

Considering the unsatisfying results obtained in the *N*-oxidation step of the first strategy, a convergent synthesis was carried out. The 2,6-bis(chloromethyl)pyridine *N*-oxide (**7**) was previously prepared by oxidation of the 2,6-bis(chloromethyl)pyridine following a simple procedure reported by Gan and co-workers.[27] and was obtained pure enough to be used in the next step without any further purification (91% yield). After optimization of macrocyclisation conditions, the best results were obtained when 2,6-bis(chloromethyl)pyridine *N*-oxide (**7**) was reacted with the corresponding polyamine moieties (**5**) in the presence of potassium carbonate and potassium iodide in refluxing MeCN. The desired nosylated azapyridinomacrocycle *N*-oxides PyCy*N*-Ox[12]N_4 (**1a-c**) were satisfactory afforded after purification by flash column chromatography on silica gel in 94, 80 and 70% yields respectively. The desulfonylated macrocycles (**2a**) was prepared following the same procedure described above but using 2-mercaptoethanol instead of thiophenol. This compound was isolated with yields of 91% (Scheme 2).

The same approach was envisaged to prepare the 15 membered azapyridinomacrocycles *N*-oxides, PyCy*N*-Ox[15]N_5 (**3**) and (**4**). The intermediate *N*-nosyl-tetraamine derivatives (**6**) were synthesized by a double peptide coupling between the 1,2-(*R,R*)-diaminocyclohexane (**14**) with 2 equiv of the corresponding *N*-nosyl amino acids (**8**) in THF. The 1,2-(*R,R*)-diaminocyclohexane (**14**) was obtained by releasing the corresponding tartrate salt (**9**) in the presence of 4 equiv of NaOH with a yield of 98%. After peptide coupling, the corresponding polyamine blocks (**6a-c**) were isolated in 64, 58 and 85% yields respectively (Scheme 2).

In the macrocyclisation step, the K_2CO_3 was substituted by the Cs_2CO_3, widely used for the templated construction of large rings, due to the "cesium effect".[33] Cesium allows an optimal preorganization of the two reactive species, thus promoting the macrocyclization compared to polymerization reaction. Consequently, 2,6-bis(bromomethyl)pyridine (**11**) was reacted with the corresponding polyamine moieties (**6**) in the presence of Cs_2CO_3 in DMF at 90 °C. The desired nosylated azapyridinomacrocycles PyCy[15]N_5 (**15a**) and (**15c**) were afforded after purification by flash column chromatography on silica gel in 45 and 65% yields respectively. The cleavage of the 2-nitrobenzenesulfonamide framework was carried out using the standard conditions described above (PhSH/K_2CO_3/DMF). The corresponding macrocycle (**16c**) was isolated in 66% yield. Once more, the *N*-oxidation of the pyridine moiety failed.



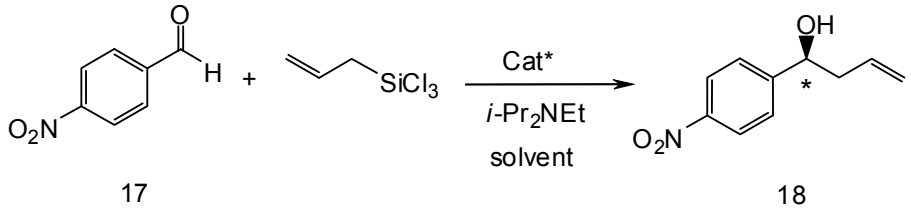
Scheme 2. Synthesis of azapyridinomacrocycles *N*-oxides, PyCy*N*-Ox[15]N_5. Reagents and conditions: (a) NaOH (4 equiv), H_2O/CH_2Cl_2, 25 min, rt; (b) (i) *N*-nosyl amino acid (8) (2.1 equiv), DMAP (2.1 equiv), anhydrous THF, 0 °C, 10 min; (ii) EDCI (1.05 equiv), rt, 17 h; (c) (i) Cs_2CO_3 (4 equiv), DMF, reflux; (ii) 2,6-bis(bromomethyl)pyridine (11) (1.2 equiv) DMF, reflux, 4 h; (d) PhSH (2.5 equiv), K_2CO_3 (4 equiv), DMF, rt, 5 h; (e) (i) K_2CO_3 (4 equiv), MeCN, reflux, 5 min. then KI (2.2 equiv); (ii) 2,6-bis(chloromethyl)pyridine *N*-oxide (7) (1.1 equiv), MeCN, reflux, 3-5 h; (f) mercaptoethanol (11.2 equiv), DBU (4.5 equiv), MeCN, rt, 2 h.

The second strategy was envisaged involving the macrocyclisation step by the condensation of the polyamine moieties (**6**) with the 2,6-bis(chloromethyl)pyridine *N*-oxide (**7**) using the same reaction conditions described above for the 12 membered azapyridinomacrocycles. The desired nosylated azapyridinomacrocycles *N*-oxides PyCy*N*-Ox[15]N_5 (**3a-c**) were satisfactory afforded after purification by flash column chromatography on silica gel in 46, 33, 81% yields respectively. The cleavage of 2-nitrobenzenesulfonamide moiety to afford the corresponding deprotected macrocycle (**4a**) was achieved according to the previously described method by reaction with mercaptoethanol in MeCN in presence of DBU at room temperature. In such conditions, the desulfonylated macrocycle PyCy*N*-Ox[15]N_5 (**4a**) was isolated in 65% yield (Scheme 2).

Asymmetric allylation of *p*-nitrobenzaldehyde

The application of the azapyridinomacrocycles *N*-oxides synthesized as chiral organocatalysts in the

asymmetric allylation of *p*-nitrobenzaldehyde with allyltrichorosilane (Scheme 3) was investigated and the main results (yields and ees determined by HPLC) are reported in Table 1. Addition of allyltrichorosilane to *p*-nitrobenzaldehyde was carried out in the presence of PyCy*N*-Ox[12]N_4 (**1**) and (**2**) or PyCy*N*-Ox[15]N_5 (**3**) and (**4**) derivatives as organocatalysts (20 mol%) and DIPEA. Different parameters were studied, such as the solvent, the amount of additives and the temperature.



17 18

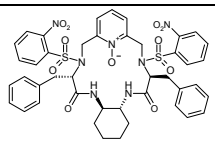
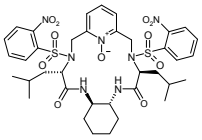
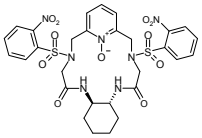
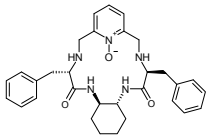
Cat* = PyCy*N*-Ox[12]N_4 or PyCy*N*-Ox[15]N_5

Scheme 3

In several studies, it has been clearly noticed that aldehydes with an electron-donating group at the para-position of benzaldehyde exhibit a negative impact on the enantioselectivity whereas the substrate bearing an electron-withdrawing group at the para-position resulted in a dramatic increase in both reactivity and enantioselectivity.[6,28,29] Considering these observations we decided to use the *p*-nitrobenzaldehyde as model in order to compare our results with those reported in the literature.

The first results showed that azapyridinomacrocycles *N*-oxides 12-membered PyCy*N*-Ox[12]N_4 (**1**) and (**2**) are unsuccessful catalysts (48% of conversion rate and 12% of ee). No significant differences were observed between the different functionalized 12 membered macrocycles and marginal improvements of the conversion rate were observed when dichloromethane or THF were used as solvents. Furthermore, disappointing results were also obtained for the denosylated macrocycle PyCy*N*-Ox[12]N_4 (**2a**). Therefore, we turned our attention to 15-membered macrocycles PyCy*N*-Ox[15]N_5 (**3**) and (**4**) as potentially more efficient catalysts. The results reported in Table 1 suggested a dramatic effect of the size of the cavity in the catalytic process. The results obtained with the denosylated macrocycle PyCy*N*-Ox[15]N_5 (**4a**), suggested that the nucleophilicity of the *N*-oxide moiety of (**3a**) is significantly reduced due to the electron-withdrawing effect of the nosyl group decreasing the conversion rate (compare entry 1 with 6).

Table 1. Allylation of *p*-nitrobenzaldehyde with allyltrichlorosilane catalyzed by 15-membered azapyridinomacrocycles *N*-oxides[a]

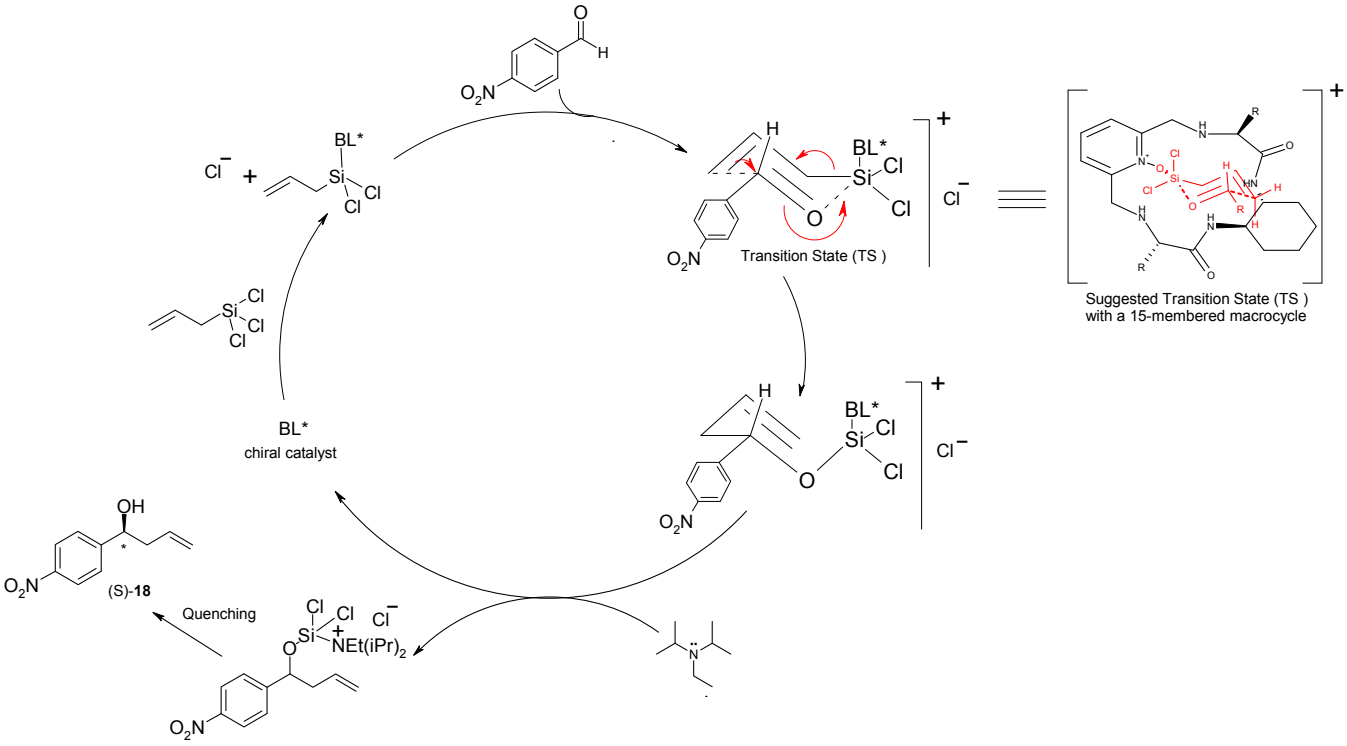
Entry	Catalyst	#	Temp/°C	Time/h	Yield (%)[b]	ee (%) [c]	Configuration of 18[d]
1		**3a**	20	72	28	10	(S)-(–)
2		**3b**	20	72	48	2	(R)-(+)
3		**3b**	0	72	27	3	(R)-(+)
4		**3c**	20	48	60	5	(R)-(+)
5		**3c**	0	48	42	6	(R)-(+)
6		**4a**	20	24	83	13	(S)-(–)
7		**4a**	0	24	72	8	(S)-(–)
8		**4a**	-30	24	58	14	(S)-(–)
9		**4a**	-38	24	43	40	(S)-(–)
10[e]		**4a**	-38	24	65	5	(S)-(–)

[a] The reaction was carried out in MeCN at 0.15 mmol scale with 2.4 equiv of allyltrichorosilane in the presence of the corresponding catalyst (20 mol%) and DIPEA (3 equiv). [b] Conversion was determined by HPLC. [c] Established by chiral HPLC. [d] Established from the optical rotation (measured in $CHCl_3$) and HPLC retention times by comparison with the literature data.[31,32] [e] 6 equiv of DIPEA were used.

A dramatic improvement in the reaction rate and asymmetric conversion was observed with the 15-membered macrocycle PyCy*N*-Ox[15]N_5 **(4a)**, 83% at 20 °C in MeCN. However, the asymmetric induction was rather low in this case: 13% ee. To amend this flaw, we explored the effect of the temperature and the solvent. Thus, the allylation reaction using PyCy*N*-Ox[15]N_5 **(4a)** as catalyst was carried out at 0 °C, -30 °C and -38 °C. Decreasing the temperature from 20 °C to - 30 °C induces a lower conversion rate, without any significant increase of the enantioselectivity (entries 6, 7 and 8). The best results were obtained at -38 °C (40% ee) (entry 9). We used these conditions to investigate a possible solvent effect. In dichloromethane, the reaction was slower and rather less enantioselective than in MeCN, whereas practically no reaction was observed in THF. We checked the influence of the DIPEA as additive. In the absence of DIPEA, the reaction was slower and less selective. An increase in the amount of DIPEA (6 equiv instead 3 equiv) led to higher conversion rates but surprisingly decrease the enantiomeric excess (compare entry 9 with 10). Hence, the combination of PyCy*N*-Ox[15]N_5 **(4a)** as catalyst in MeCN

appears to be a well-balanced choice, characterized by acceptable conversion rates, enantioselectivities and catalyst loading (20 mol %).

A proposed mechanism for the asymmetric allylation and a hypothesized transition state are outlined in Scheme 4. It has been suggested that the *N*-oxide binds to the silicon atom to generate a penta coordinate cationic siliconium which activates as Lewis acid the carbonyl of the aldehyde. The nucleophilic attack on the carbonyl group takes place at the γ position of allyl group via a six-membered cyclic chair like transition structure to give the corresponding homoallylalcohol. It may be reasonable to suppose that the diisopropylethylamine promotes the dissociation of catalyst from silicon atom in the compound by ligand exchange to regenerate the catalyst and as a result allow assisting the reaction turnover. Thus, we consider a similar mechanism to that proposed by Malkov in the case of terpene-derived bipyridine *N,N'*-dioxides.[6] We can state that the reaction proceeds via a closed chair like transition structure highly crowded organized around the silicon. This commonly accepted arrangement provides an enantiocontrol in the allylation of aromatic aldehydes.[9,30,31]



Scheme 4. Proposed mechanism and transition state in catalysed allylation

It is noteworthy that the size of the cavity plays an important role in catalytic process. In our case it may be supposed that the transition state should be accommodate inside of the macrocycle skeleton. The more flexible skeleton of 15-membered macrocycles could explain the higher conversion yields and

stereoselectivities observed in comparison with the 12-membered more conformationally restricted macrocycles. This space disposition of the transition state would also allow additional interactions between the silicon and the nitrogen atoms of the macrocyclic structure, generating a cationic complex (TS). Moreover, in the silicon chelation, the *N*-oxide moiety of the desulfonylated macrocycles is more accessible than in the sulfonylated compounds. This could explain why the compound (**4a**) is a more efficient catalyst.

In summary, eight chiral azapyridinomacrocycles *N*-oxides have been easily synthesized, from inexpensive starting materials. The optimization of the reaction conditions allowed us to obtain a first serie of 12-membered chiral azapyridinomacrocycles *N*-oxides PyCy*N*-Ox[12]N_4 (**1**) and (**2**) with 40% to 78% overall yields and a second one of 15-membered PyCy*N*-Ox[15]N_5 (**3**) and (**4**) with 20% to 68% overall yields. The macrocycles were tested as potential catalyts in the enantioselective allylation of *p*-nitrobenzaldehyde with trichloroallylsilane and resulted in good conversion above 80% and promising enantioselectivity (40% ee) for PyCy*N*-Ox[15]N_5 (**4a**). Further studies are in progress to explore this trend using larger macrocycles and to assess these original ligands in other enantioselective organocatalyzed reactions.

EXPERIMENTAL

Chemicals

All reagents were obtained from commercial sources unless otherwise noted, and used as received. Room temperature refers to ambient room temperature (18-25 °C). Heated experiments were conducted using thermostatically controlled oil baths. All reactions were monitored by analytical thin layer chromatography (TLC) performed on aluminium sheets precoated silica gel plates (60 F_{254}, Merck). TLC plates were visualized using UV (254 nm) and ninhydrine sprays or in an iodine chamber as appropriate. Frontal retention values R_f have been mentioned when necessary. Flash column chromatography was carried out routinely using silica gel 60 (particle size 0.040-0.063 mm, Merck).

Physical measurements

The structure of the products prepared by different methods was checked by comparison of their NMR, IR and MS data and by the TLC behaviour. ^{1}H and ^{13}C-NMR spectra were acquired on a Bruker BioSpin GmbH spectrometer 400 MHz, at room temperature. Chemical shifts are reported in δ units, parts per million (ppm). Coupling constants (*J*) are measured in hertz (Hz). Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; ddd, doublet of a doublet of doublets, m, multiplet; br, broad; *eq*., equatorial; *ax*., axial. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. For the assignments of the NMR signals, we use the

convention presented in Figure 2. GC analyses were performed with an Agilent 6890N instrument equipped with a 15 m x 0.25 mm HP-5MS column and an Agilent 5973N MS detector-column temperature gradient 60-180 °C for 2,6-Bis(chloromethyl)pyridine *N*-oxide. Infrared spectra were recorded from a thin film between KBr plates or as a KBr disc with a Nicolet FT-IR Avatar 320 spectrometer. Melting points (Mp) were determined on a Leica VMHB system Kofler apparatus. High-resolution mass spectra (HRMS) analyses have been done on samples whose purity was checked by HPLC and/or ^{1}H NMR. Ionizations by electrospray (ESI-HRMS) were acquired on a Thermo Scientific LTQ Orbitrap mass spectrometer. Low-resolution mass spectra (LRMS) resulting from ionization by electronic impact (EI-LRMS) were acquired on an Agilent 5973 Network MSD mass spectrometer; ionizations by electrospray (ESI-LRMS) were performed on a Waters Micromass ZQ2000 (mass) spectrometer and on a Waters LCT-Premier XE mass spectrometer TOF type. The samples were prepared in MeOH or MeCN and the analyses were performed in MeOH/HCOOH 0.05%. The cone voltage (CV) was indicated and the *m/z* resulting from fragmentation processes are indicated, and sometimes assigned; the corresponding ionic abundances were reported in percentage relative to the more abundance. Specific rotations were determined on a Perkin Elmer 241 polarimeter with an error of $<\pm 0.1$ and $[\alpha]_D$ values are given in 10^{-1} dg cm^2 g^{-1}; concentration (c) is in g/100 mL. The HPLC analyses were performed using different columns. The chemical purity of macrocycles was determined using a reverse phase column Hypersil ODS C18, 150 mm x 4.6 mm, 5 μm. The HPLC analyses for the catalytic study were carried out with a normal phase column (Hypersil, 150 mm x 4.6 mm, 5 μm) in an isocratic system of elution using a Photodiode Array Detector (PDA) Waters 996 (220 nm - 350 nm). The retention times R_t are expressed in minutes in the decimal system. Enantiomeric excess was determined by chiral HPLC analyses using a chiral normal stationary phase (Column ADH chiralpak, 250 mm x 4.6 mm, 5 μm). Allylation reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware, twice evacuated and filled with inert gas. All solvents for the reactions were of reagent grade. The DIPEA was distilled from sodium hydroxide and the allyltrichlorosilane was used as purchased. The monitoring of the allylation reactions was carried out by HPLC. The conversions have been calculated using the response factor between the *p*-nitrobenzaldehyde and its corresponding homoallylic alcohol.

CAUTION: 2,6-Bis(chloromethyl)pyridine and its solutions should be handled in a well ventilated hood. Skin and eye contact must be carefully avoided since the compound is an aggressive irritant. The compound has a small vapor pressure at 23 °C and it can cause bronchial irritation as well. Moreover in the preparation of its corresponding *N*-oxide the safety measures during the work-up should be taken because of the formation of explosive compounds. All *N*-oxides could induce irritation, so care should be exercised when preparing and handling these compounds.

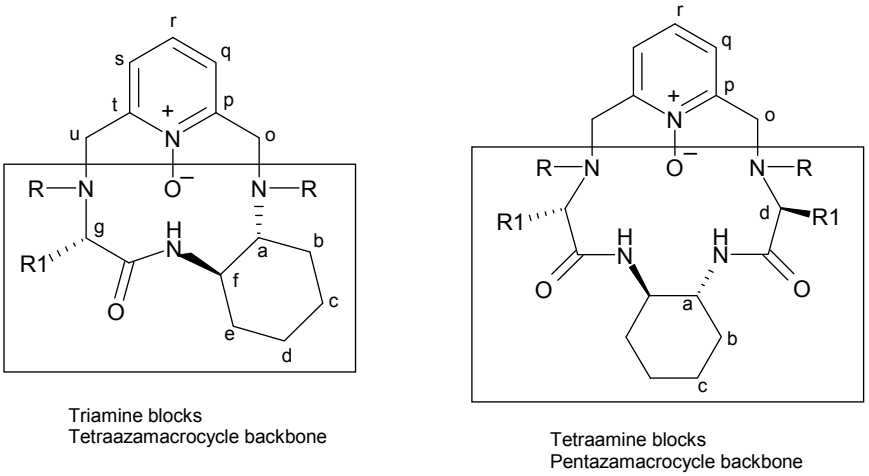


Figure 2. Convention adopted to assign signals of ^{1}H and ^{13}C-NMR spectra

Bis(chloromethyl)pyridine *N*-oxide (7)

To a solution of 2,6-bis(chloromethyl)pyridine (6.0 g, 34.3 mmol) in acetic acid (38 mL) was added 35% aq. H_2O_2 (15.2 mL, 15 equiv). The solution was stirred and heated at 70 °C for 5 h (monitoring by TLC) and the resulting mixture was evaporated *in vacuo* (30 – 35 °C). The white residue obtained was dissolved in CH_2Cl_2 (50 mL) and extracted with aqueous solution of $NaHCO_3$–Na_2CO_3 (1:1) (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated leaving 2,6-bis(chloromethyl)pyridine *N*-oxide **7** as a white solid which was used in the next step without any further purification. Yield: 5.9 g (91%). R_f = 0.6, SiO_2, (cyclohexane/EtOAc 3:7); GC (method 60): R_t = 10.7; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.84 (s, 2H, H_o); 7.33 (t, 1H, ^{3}J = 7.9 Hz , H_r); 7.61 (d, 2H, ^{3}J = 7.9 Hz, H_q); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.81 (C_o); 124.84 (C_q); 125.04 (C_r); 147.42 (C_p); *m/z* (EI): 175 (100), 140 (70); IR (KBr): ν 3019, 2964, 1259 cm^{-1}

***N*-(2-Aminocyclohexyl)-2-nitrobenzene-1-sulfonamide (10)**

To a solution of (±) *trans*-1,2-diaminocyclohexane diammonium tartrate salts **9** (12.5 g, 47 mmol, 1 equiv) in 75 mL of 2 M NaOH was added CH_2Cl_2 (460 mL) and triethylamine (8.75 mL, 61.1 mmol, 1.3 equiv). The reaction mixture was cooled at 0 °C for 10 min, then a solution of 2-nitrobenzenesulfonyl chloride (6 g, 27 mmol, 1.7 equiv) in CH_2Cl_2 (312 mL) was added dropwise. After 30 min of stirring at 0 °C, the reaction mixture was stirred at room temperature for 3 h (monitoring by TLC, cyclohexane/ EtOAc, 5:5). Then 50 mL of water were added and the organic phase was recovered and washed with a solution of 1M HCl (100 mL, pH 1). The aqueous phase was then extracted with CH_2Cl_2 (2 x 100 mL) and basified with sodium hydrogen carbonate until pH 8. The aqueous phase was back-extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and

concentrated under reduced pressure. The yellow solid was recrystallized in CH_2Cl_2 to afford the expected product **10** as yellow crystals. Yield: 8 g (99%). R_f = 0.3, SiO_2, (cyclohexane/EtOAc, 3:7); Mp 131-130 °C, $[\alpha]_D^{25}$ -218.76 ± 0.1 (*c* 4, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.92-1.25 (m, 4H, $H_{eax.}$, $H_{dax.}$, $H_{cax.}$, $H_{bax.}$), 1.49-1.70 (m, 3H, $H_{eeq.}$, $H_{deq.}$, $H_{ceq.}$), 1.75-1.85 (m, 1H, $H_{beq.}$), 2.33-2.46 (m, 1H, H_f), 2.70-2.81 (m, 1H, H_a), 7.81-7.86 (m, 2H, CHar), 7.91-7.93 (m, 1H, $CHarCSO_2$), 8.08-8.13 (m, 1H, $CHarCNO_2$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 24.2 (C_c or C_d), 24.5 (C_d or C_c), 32.21 (C_e), 33.8 (C_b), 53.6 (C_f), 60.3 (C_a), 124.1 ($CHarCNO_2$), 129.9 ($CHarCSO_2$), 132.4 (CHar), 133.8 (CHar), 133.8 ($C_{quat}SO_2$), 147.3 ($C_{quat}NO_2$); *m/z* (ESI+, CV 25): 300.2 M^++H^+ (100), IR (KBr): ν 3455, 2927, 2861, 1656, 1543, 1364 ($\nu_{as}SO_2$), 1160 (ν_sSO_2) cm^{-1}.

General procedure for the preparation of polyamines blocks (5) intermediates of PyCy[12]N_4

To a solution of *N*-(2-aminocyclohexyl)-2-nitrobenzene-1-sulfonamide **10** (1 equiv) in anhydrous THF was added the corresponding *N*-nosyl amino acid **8** (1.05 equiv) and the DMAP (1.05 equiv). The reaction mixture was cooled at 0 °C for 10 min, then EDCI (1.05 equiv) was added. At the end of the addition, the mixture was stirred at room temperature for 17 h (monitoring by TLC). The reaction mixture was taken up in CH_2Cl_2 and the organic phase was washed with a solution of 1M HCl aqueous and then with a saturated aqueous solution of sodium hydrogen carbonate. The layers were separated and the organic phase was recovered, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to afford the corresponding polyamine moieties. Yields: **5a**, 92%; **5b**, 73%; **5c** 56%.

(*S*)-2-(2-Nitrophenylsulfonamido)-*N*-((1*R*,2*R*)-2-(2-nitrophenylsulfonamido)cyclohexyl)-3-phenyl-propanamide (5a)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane mononosylated **10** (776 mg, 2.6 mmol) in anhydrous THF (26 mL) was added the *N*-nosylphenylalanine **8a** (1 g, 2.85 mmol) and the DMAP (345 mg, 2.85 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (546 mg, 2.85 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 17 h (monitoring by TLC, cyclohexane/EtOAc 5:5). After workup the crude was purified by flash chromatography on silica gel to afford the expected compound **5a** as a yellowish solid. Yield: 1.5 g (92%). R_f = 0.2, SiO_2, (CH_2Cl_2/MeOH 99:1); Mp 97-99 °C, $[\alpha]_D^{25}$ -6.04 ± 0.1 (*c* 4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17-1.40 (m, 4H, $H_{eax.}$, $H_{dax.}$, $H_{cax.}$, $H_{bax.}$), 1.62-1.75 (m, 2H, $H_{ceq.}$, $H_{deq.}$), 1.75-1.83 (m, 1H, $H_{beq.}$), 1.99-2.06 (m, 1H, $H_{eeq.}$), 2.84-2.88 (dd of AB, 1H, ^2J = 14.5 Hz, $^3J_{CH2benzyl-Hg}$ = 8 Hz, CH_2benzyl), 3.07-3.12 (dd of AB, 1H, ^2J = 14.5 Hz, $^3J_{CH2benzyl-Hg}$ = 4.5 Hz, CH_2benzyl), 3.12-3.18 (m, 1H, H_a), 3.63-3.69 (m, 1H, H_f), 4.06-4.10 (m, 1H, H_g), 5.97 (m, 2H, 2NH), 6.56 (d, 1H, $^3J_{NH-Hf}$ = 8 Hz, NH), 6.95 (m, 5H, CHarbenzyl), 7.55-7-68 (m, 5H, CHar), 7.77-7.82 (m, 2H, CHar), 8.07-8.1 (m,1H, CHar);

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.3 (C_d or C_c), 24.7 (C_c or C_d), 32.1 (C_e), 33.1 (C_b), 38.6 (CHar), 52.9 (C_a), 58.3 (C_f), 60.3 (C_g), 125.2 and 125.9 ($CHarCNO_2$), 126.9 (CHar), 128.5 (2 CHar), 129.0 (2 CHar), 130.5 and 130.9 ($CHarCSO_2$), 132.6 ($C_{quat\ benzyl}$), 132.9 (CHar), 133.2(CHar), 133.50 (CHar), 133.56 (CHar), 134.9 and 135.7 ($C_{quat}SO_2$), 147.0 and 147.7 ($C_{quat}NO_2$), 170.7 (C=O); m/z (ESI+, CV 65): 654.2 M^++23 (100).

(*R*)-3-Methyl-2-(2-nitrophenylsulfonamido)-*N*-((1*R*,2*R*)-2-(2-nitrophenylsulfonamido)cyclohexyl)-butanamide (5b)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane mononosylated **10** (1.5 g, 5 mmol) in anhydrous THF (50 mL) was added the *N*-nosylvaline **8b** (1.7 g, 5.5 mmol) and the DMAP (671 mg, 5.5 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (1.05 g, 5.5 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 8 h (monitoring by TLC, cyclohexane/EtOAc 3:7). After workup the crude was purified by flash chromatography on silica gel to afford the expected compound **5b** as a yellowish solid. Yield: 2.13 g (73%). R_f = 0.5, SiO_2, (cyclohexane/EtOAc 4:6); Mp 102-103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78 (d, 3H, ^3J = 7 Hz, CH_3); 0.84 (d, 3H, ^3J = 7 Hz, CH_3); 0.85-0.99 (m, 4H, $H_{eax.}$, $H_{dax.}$, $H_{cax.}$, $H_{bax.}$); 1.50-1.63 (m, 2H, $H_{eeq.}$, $H_{deq.}$); 1.90-1.96 (m, 1H, $H_{beq.}$); 2.21-2.23 (m, 1H, $CH(CH_3)_2$); 3.02-3.15 (m, 1H, H_a); 3.43-3.54 (m, 1H, H_f); 3.72-3.75 (dd, 1H, $^3J_{g\text{-}CH(CH3)2}$ = 4.5 Hz and $^3J_{g\text{-}NH}$ = 7.5 Hz, H_g); 5.39 (d, 1H, $^3J_{NH\text{-}Ha}$ = 8.3 Hz, NH), 6.07 (d,1H, $^3J_{NH\text{-}Hg}$ = 7.5 Hz, NH); 6.51 (d, 1H, $^3J_{NH\text{-}Hf}$ = 7.5 Hz, NH); 7.64-7.73 (m, 4H, CHar); 7.76-7.84 (m, 2H, CHar); 8.01-8.1 (m, 2H, CHar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.0 (CH_3), 19.3 (CH_3), 24.0 (C_d or C_c), 24.6 (C_c or C_d), 31.1 ($CH(CH_3)_2$), 32.2 (C_e or C_b), 32.8 (C_b or C_e), 53.2 (C_a), 57.6 (C_f), 64.4 (C_g), 125.41 ($CHarCNO_2$), 124.48 (CHar), 130.4 and 131.0 ($CHarCSO_2$), 133.1 (CHar), 133.30 ($C_{quat}SO_2$), 133.33 (CHar), 133.7 (CHar), 133.8 (CHar), 134.8 ($C_{quat}SO_2$), 147.74 and 147.76 ($C_{quat}NO_2$), 170.3 (C=O); *m/z* (ESI+, CV 65): 606.2 M^++23 (100), HRMS: calcd. for $C_{23}H_{29}N_5O_9S_2$ $[M+Na]^+$ (606.12989); found (606.13010).

2-(2-Nitrophenylsulfonylamino)-*N*-[(1*R*,2*R*)-2-(2-nitrophenylsulfonylamino)cyclohexyl]acetamide (5c)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane mononosylated **10** (2 g, 6.7 mmol) in anhydrous THF (67 mL) was added the *N*-nosylglycine **8c** (1.8 g, 7.02 mmol) and the DMAP (860 mg, 7.02 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (1.3 g, 7.02 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 8 h (monitoring by TLC, cyclohexane/EtOAc 3:7). After workup previously described the crude was purified by flash chromatography on silica gel to afford the expected compound **5c** as a yellowish solid. Yield: 1.04 g (56%). R_f = 0.2, SiO_2, (cyclohexane/EtOAc 3:7); Mp 90-92 °C; The analytical data (^{1}H NMR and ^{13}C

NMR) are in accordance with those of the literature;[21] IR (KBr): ν 3369, 2934, 2860, 1671, 1541, 1362 ($\nu_{as}SO_2$), 1167 (ν_sSO_2) cm^{-1}, HRMS: calcd. for $C_{20}H_{23}N_5O_9S_2$ $[M+Na]^+$ (564.08294); found (564.08328).

General procedure for the preparation of the polyamines blocks (6) intermediates of PyCy[15]N_5

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane **14** (1 equiv) in anhydrous THF was added the corresponding *N*-nosyl amino acid **8** (2.1 equiv) and the DMAP (2.1 equiv). The reaction mixture was cooled at 0 °C for 10 min, then EDCI (2.1 equiv) was added. At the end of the addition, the mixture was stirred at room temperature for 17 h (monitoring by TLC). The reaction mixture was taken up in CH_2Cl_2 and the organic phase was washed with a solution of 1M HCl and then with a saturated aqueous solution of sodium hydrogen carbonate. The layers were separated and the organic phase was recovered, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to afford the corresponding polyamine moieties. Yields: **6a**, 64%; **6b**, 58%; **6c** 85%.

(2*S*,2'*S*)-*N*,*N*'-((1*R*,2*R*)-Cyclohexan-1,2-diyl)bis(2-(2-nitrophenylsulfonamido)-3-phenylpropanamide (6a)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane **14** (1.3 g, 11.84 mmol) in anhydrous THF (115 mL) was added the *N*-nosylphenylalanine **8a** (8.7 g, 24.86 mmol) and the DMAP (3.04 g, 24.9 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (7.8 g, 24.9 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 17 h (monitoring by TLC, cyclohexane/EtOAc 6:4). The reaction mixture was taken up in CH_2Cl_2 (80 mL) and the organic phase was washed firstly with a solution of 1M HCl (20 mL), then with a saturated aqueous solution of sodium hydrogen carbonate (30 mL). The layers were separated and the organic phase was recovered, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to afford the expected compound **6a** as a whitish solid. Yield: 5.8 g (64%). R_f = 0.4, SiO_2, (cyclohexane/EtOAc, 3:7); Mp 115-118 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01-1.29 (m, 4H, $H_{cax.}$, $H_{bax.}$); 1.52-1.69 (m, 2H, $H_{ceq.}$); 1.85-1.95 (m, 2H, $H_{beq.}$); 2.80 (dd, 2H, $^3J_{CH2benzyl-Hd}$ = 9.8 Hz, ^2J = 14.1 Hz, CH_2benzyl); 3.23 (dd, 2H, $^3J^3_{CH2benzyl-Hd}$ = 5 Hz, ^2J = 14.1 Hz, CH_2benzyl); 3.54-3.66 (m, 2H, H_a); 4.05-4.10 (m, 2H, H_d); 6.77-7.00 (m, 12H, 10CHar, 2NH); 7.43-7.73 (m, 8H, 6CHar, 2NH); 7.84-7.90 (m, 2H, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.61 (C_c), 30.84 (C_b), 38.19 ($C_{CH2benzyl}$), 51.66 (C_a), 59.58 (C_d), 124.24 ($CHarCSO_2$), 126.16 ($CHarCNO_2$), 127.63 (CHar), 129.01 (CHar), 132.23 (CHar), 133.08 (CHar), 133.24 ($C_{quat}SO_2$), 136.47 ($C_{quatbenzyl}$), 146.81 ($C_{quat}NO_2$), 170.05 (C=O); *m/z* (ESI+, CV 65): 801.4 M^++23 (100), 817.3 M^++39 (45); HRMS: calcd. for $C_{36}H_{38}N_6O_{10}S_2$ $[M+Na]^+$ (801.19830); found (801.19959); IR (KBr): ν 3304, 3095, 2942, 1656, 1540, 1353 ($\nu_{as}SO_2$), 1166 (ν_sSO_2) cm^{-1}.

(*2S,2S'*)-*N,N'*-((1*R*,2*R*)-Cyclohexan-1,2-diyl)bis(3-methyl-2-(2-nitrophenylsulfonamido)butanamide) (6b)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane **14** (0.8 g, 7.34 mmol) in anhydrous THF (75 mL) was added the *N*-nosylvaline **8b** (4.6 g, 15.4 mmol) and the DMAP (1.88 g, 15.4 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (2.95 g, 15.4 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 18 h (monitoring by TLC, cyclohexane/EtOAc 3:7). The reaction mixture was taken up in CH_2Cl_2 (50 mL) and the organic phase was washed with a solution of 1M HCl (12 mL) and then with a saturated solution of sodium hydrogen carbonate (19 mL). The layers were separated and the organic phase was recovered, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to afford the expected compound **6b** as a whitish solid. Yield: 2.9 g (58%). R_f = 0.6, SiO_2, (CH_2Cl_2/MeOH (95:5); Mp 111-113 °C; $[\alpha]_D^{24}$ + 61.1 ± 0.1 (c 4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.77 (d, 6H, ^3J = 6.8 Hz, CH_3), 0.80 (d, 1H ^3J = 6.8 Hz, CH_3), 1.12-1.19 (m, 4H, H_b, $H_{cax.}$), 1.55-1.67 (m, 2H, $H_{ceq.}$), 1.91-1.98 (m, 2H, $H_{beq.}$), 2.08-2.17 (m, 2H, $CH(CH_3)_2$), 3.48-3.57 (m, 2H, H_a), 3.69-3.75 (dd, 1H, $^3J_{Hd\text{-}NH}$ = 7.6 Hz, $^3J_{Hd\text{-}CH(CH3)2}$ = 4.8 Hz, H_d), 6.28 (d, 2H, $^3J_{NH\text{-}Hd}$ = 7.3 Hz, NH), 6.85 (d, 2H, $^3J_{NH\text{-}Ha}$ = 6.3 Hz, NH), 7.65-7.73 (m, 4H, CHar), 7.78-7.85 (m, 2H, $CHarCSO_2$), 7.99-8.06 (m, 2H, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.2 (CH_3), 19.1 (CH_3), 24.3 (C_c), 30.1 ($CH(CH_3)_2$), 31.8 (C_b), 54.1 (C_a), 63.2 (C_d), 125.4 ($CHarCNO_2$), 130.6 ($CHarCSO_2$), 132.9 (CHar), 133.8 (CHar), 147.74 ($C_{quat}NO_2$); *m/z* (ESI+, CV 45): 683.4 M^++ H (30), 705.4 M^++23 (100), 721.4 M^++39 (33); HRMS: calcd. for $C_{28}H_{38}N_6O_{10}S_2$ $[M+Na]^+$ (705.19830); found (705.19830).

(*2S,2S'*)-*N,N'*-((1*R*,2*R*)-Cyclohexan-1,2-diyl)bis(3-methyl-2-(2-nitrophenylsulfonamido) acetic (6c)

To a solution of *trans*-(*R,R*)-1,2-diaminocyclohexane **14** (1.28 g, 11.2 mmol) in anhydrous THF (122 mL) was added the *N*-nosylglycine **8c** (6.11 g, 23.5 mmol) and the DMAP (2.87 g, 23.5 mmol). The reaction mixture was cooled at 0 °C for 10 min, and then EDCI (4.5 mg, 23.5 mmol) was added. At the end of the addition, the mixture was stirred at room temperature for 17 h (monitoring by TLC, EtOAc). The reaction mixture was taken up in CH_2Cl_2 (76 mL) and the organic phase was washed with a solution of 1M HCl (19 mL) and then with a saturated aqueous solution of sodium hydrogen carbonate (28 mL). The layers were separated and the organic phase was recovered, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to afford the expected compound **6c** as a yellowish solid. Yield: 5.7 g (85%). R_f = 0.2, SiO_2, (AcOEt); Mp 105-106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13-1.35 (m, 4H, $H_{cax.}$, $H_{bax.}$), 1.61-1.72 (m, 2H, $H_{ceq.}$), 1.82-1.92 (m, 2H, $H_{beq.}$), 3.59-3.72 (m, 6H, H_a, H_d), 6.41 (s br, 2H, $CHarCNO_2$), 6.65 (d, 2H, $^3J_{NH\text{-}Ha}$ = 6.8 Hz, NH), 7.63-7.70 (m, 4H, CHar), 7.76-7.96 (m, 2H, CHar), 7.99-8.11 (m, 2H, $CHarCSO_2$); ^{13}C NMR

($CDCl_3$, 100 MHz): δ = 24.6 (C_c), 31.9 (C_b), 46.2 (C_d), 53.6 (C_a), 125.5 (CHar), 131.2 ($CHarCSO_2$), 132.9 (CHar), 133.0 (CHar), 133.9 ($C_{quat}SO_2$), 147.9 ($C_{quat}NO_2$), 168.5 (C=O); *m/z* (ESI+, CV (85): 621.2 M^++ 23 (100), 622.2 M^++23+H (25); HRMS: calcd. for $C_{22}H_{26}N_6O_{10}S_2$ $[M+Na]^+$ (621.10440); found (621.10463).

General procedure for the preparation of disulfonylated macrocycles PyCy[12]N_4 (12)

To a solution of the polyamine moiety **5** (1 equiv) in DMF (or MeCN) was added anhydrous potassium carbonate (4 equiv). The mixture was stirred at reflux during 30 min Then, a solution of 2,6-bis(bromomethyl)pyridine **11** (1.2 equiv) in DMF (or MeCN) was added dropwise over 30 min while stirring at reflux and the heating was maintained for 1-2 h (monitoring by TLC, ethylacetate). The crude mixture was concentrated and the residue was taken up in CH_2Cl_2/H_2O (4:1 v/v). The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding macrocycles **12**, Yields: **12a**, 98%; **12b**, 85%, **12c** 70%.

(4*R*,9*R*,12*S*)-12-Benzyl-3,13-bis(2-nitrobenzenesulfonyl)-3,10,13,19-tetraazatricycle[13,3,1,0]nonadeca-1(19), 15,17-trien 11-one (12a)

This compound was prepared according to the general procedure previously described. A solution of the polyamine moiety **5a** (1.1g, 1.74 mmol) in DMF (118 mL) and anhydrous potassium carbonate (965 mg, 7.0 mmol) was stirred at reflux for 30 min. A solution of 2,6-bis(bromomethyl)pyridine **11** (550 mg, 2.1 mmol) in anhydrous DMF (50 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 3 h. After workup, the crude residue was purified by flash column chromatography on silica gel (AcOEt/*c*Hex, 75/25). The macrocycle **12a** was obtained as a yellow solid. Yield: 1.25 g (98%). R_f = 0.23, SiO_2, (AcOEt/*c*Hex, 50/50); Mp 234 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85-1.16 (m, 4H, $H_{bax.}$, $H_{cax.}$, $H_{dax.}$, $H_{eax.}$); 1.30-1.62 (m, 3H, $H_{beq.}$, $H_{ceq.}$, $H_{deq.}$); 1.88-2.01 (m, 1H, $H_{eeq.}$); 2.66-2.70 (dd, 1H, ^3J = 5.0 Hz, ^2J = 13.3 Hz, $H_{CH2benzyl}$); 2.90-3.03 (m, 1H, H_f); 3.34-3.40 (dd, 1H, ^3J = 9.1 Hz; ^2J = 13.3 Hz, $H_{CH2benzyl}$); 3.70-3.77 (m, 1H, H_a); 4.12 (d of AB, 1H, ^2J = 16.6 Hz, H_u); 4.60-4.64 (m, 1H, H_g); 4.65 (d of AB, 1H, ^2J = 17.1 Hz, H_o); 4.80 (d of AB, 1H, ^2J = 16.1 Hz, H_u); 4.98 (d of AB, 1H, ^2J = 17.1 Hz, H_o); 6,85-7.06 (m, 7H, 5CHar, H_s, H_r); 7.22 (d, 1H, $^3J_{NH\text{-}Hf}$ = 4.5 Hz, NH); 7.32-7.61 (m, 7H, H_r, $CHarCHCNO_2$, $CHarCHCSO_2$, $CHarCSO_2$); 7.80 (d, 1H, ^3J = 7.5 Hz, $CHarCNO_2$); 7.86-7.88 (dd, 1H, ^3J = 8.0 Hz, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9 and 25.6 (C_c or C_d); 29.6 (C_b); 33.2 (C_e); 35.5 (CH_2benzyl); 48.1 and 49.0 (C_o or C_u); 52.1 (C_f); 59.5 (C_a); 61.4 (C_g); 120.0 and 120.5 (C_q or C_s); 124.3 and 124.4 ($CHarCSO_2$); 126.4 (CHar); 128.1 and 128.5 (CHar); 129.5 (2 CHar); 131.1 and 131.5 ($CHarCNO_2$); 131.6 and 131.8 ($CHarCHCNO_2$); 133.2 and 133.5 ($CHarCHCSO_2$); 133.6 and 133.9 ($C_{quat}SO_2$); 136.6

(C_r); 136.9 (C_{quat} benzyl); 147.9 (2 $C_{quat}NO_2$); 155.7 and 156.2 (C_p or C_t); 168.3 (C=O); *m/z* (ESI+, CV 60): 735.4 $[M+H]^+$ (100) , 757.4 $[M+Na]^+$ (9).

(4*R*,9*R*,12*S*)-12-Isopropyl-3,13-bis(2-nitrobenzenesulfonyl)-3,10,13,19-tetraazatricyclo[13,3,1,0]-nonadeca-1(19), 15,17-trien 11-one (12b)

This compound was prepared according to the general procedure previously described. A solution of the polyamine moiety **5b** (1.2 g, 2 mmol) in MeCN (140 mL) and anhydrous potassium carbonate (1.11 g, 8.0 mmol) was stirred at reflux for 30 min. A solution of 2,6-bis(bromomethyl)pyridine **11** (655 mg, 2.47 mmol) in anhydrous MeCN (60 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 2 h. After workup, the crude residue was purified by flash column chromatography on silica gel (AcOEt/*c*Hex, 50/50). The macrocycle **12b** was obtained as a yellow solid. Yield: 1.16 g (85%). R_f = 0.43, SiO_2, (AcOEt/*c*Hex, 60/40); Mp 249 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.53 (d, 3H, ^3J = 6.8 Hz, CH_3); 0.84 (d, 3H, ^3J = 6.2 Hz, CH_3); 1.07-1.22 (m, 2H, H_{cax}, $H_{dax.}$); 1.31-1.71 (m, 6H, $H_{bax.}$, $H_{eax.}$, $H_{beq.}$, $H_{ceq.}$, $H_{deq.}$, $H_{eeq.}$); 2.08 (m, 1H, H_f); 2.36-2.51 (m, 1H, $CH(CH_3)_2$), 2.91-3.04 (m, 1H, H_g); 3.9-4.05 (m, 1H, H_a); 4.16 (d of AB, 1H, ^2J = 16.3 Hz, H_o); 4.45 (d of AB, 1H, ^2J = 17.3 Hz, H_u); 4.92 (d of AB, 1H, ^2J = 16.3 Hz, H_o); 5.07 (d of AB, 1H, ^2J = 17.1 Hz, H_u); 6.99 (d, 1H, ^3J = 7.5 Hz, H_s or H_q); 7.04 (d, 1H, ^3J = 7.8 Hz, H_q or H_s); 7.37-7.69 (m, 8H, CHar, NH); 7.96-8.02 (m, 2H, H_{16}, $H_{16'}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =18.4 and 20.1 (CH_3); 24.1 (C_c); 25.2 (C_d); 26.9 ($CH(CH_3)_2$); 29.7 (C_b); 33.7 (C_e); 48.2 and 49.1 (C_o or C_u); 52.0 (C_f); 59.5 (C_a); 65.4 (C_g); 119.8 and 120.2 (C_q or C_s); 124.1 and 124.6 ($CHarCSO_2$); 130.9 and 131.5 ($CHarCNO_2$); 131.6 (2 $CHarCHCNO_2$); 133.3 and 133.4 ($CHarCHCSO_2$); 134.0 and 135.1 ($C_{quat}SO_2$); 136.6 (C_r); 147.7 and 148.1 ($C_{quat}NO_2$); 155.2 and 156.6 (C_p or C_t); 168.9 (C=O); *m/z* (ESI+, TOF): 687.1 $[M+H]^+$ (100), 709.1 $[M+Na]^+$ (100).

(4*R*,9*R*)-3,13-Bis(2-nitrobenzenesulfonyl)-3,10,13,19-tetraazatricyclo[13,3,1,0]nonadeca-1(19),-15,17-trien 11-one (12c)

This compound was prepared according to the general procedure previously described. A solution of the polyamine moiety **5c** (7 g, 12.9 mmol) in DMF (850 mL) and anhydrous potassium carbonate (7.17 g, 51.7 mmol) was stirred at reflux for 30 min. A solution of 2,6-bis(bromomethyl)pyridine **11** (5.8 g, 15.48 mmol) in anhydrous DMF (430 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 1 h. After workup, the crude residue was purified by flash column chromatography on silica gel (AcOEt). The macrocycle **12c** was obtained as a yellow solid. Yield: 5.8 g (70%). R_f = 0.45, SiO_2, (AcOEt); Mp 239 °C; The analytical data (^{1}H NMR, ^{13}C NMR, HPLC, and HRMS) are in accordance with those of the literature.[21]

Preparation of disulfonated macrocycles PyCy[15]N_5 (15)

To a solution of the polyamine moiety **6** (1 equiv) in DMF was added cesium carbonate (4 equiv). The

mixture was stirred at 90 °C during 30 min. Then, a solution of 2,6-bis(bromomethyl)pyridine **11** (1.2 equiv) in DMF (or MeCN) was added dropwise over 30 min while stirring at reflux and the heating was maintained until completion of the reaction. The crude mixture was then concentrated and the residue was taken up in CH_2Cl_2/H_2O (1:1 v/v). The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc) to afford the corresponding macrocycles **15**.

(3*S*,7*R*,12*R*,16*S*)-4,15-Dibenzyl-3,16-bis(2-nitrobenzenesulfonyl)-3,6,13,16,22-pentaazatricyclo-[16.3.1.0^{7,12}]docosa-1(21),18(22),19-trien-5,14-dione (15a)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **6a** (100 mg, 0.14 mmol) and anhydrous cesium carbonate (189 mg, 0.58 mmol) in anhydrous DMF (9 mL) was stirred at 90 °C for several minutes. A solution of 2,6-bis(bromomethyl)-pyridine **11** (44 mg, 0.17 mmol) in anhydrous DMF (4.5 mL) was added dropwise and the mixture was heated for 24 h. After the work-up, the crude residue was purified by flash column chromatography on silica gel (EtOAc and then EtOAc/MeOH 95:5) to afford the expected compound **15a** as a yellow solid. Yield: 50 mg (45%). R_f = 0.80, SiO_2, (CH_2Cl_2/MeOH 95:5); Mp 170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99-1.11 (m, 4H, $H_{bax.}$, $H_{cax.}$); 1.35-1.62 (m, 2H, $H_{ceq.}$); 1.80-1.85 (m, 2H, $H_{beq.}$); 2.93-3.18 (m, 2H, CH_2benzyl); 3.55-3.59 (m, 2H, H_a); 3.63-3.69 (m, 2H, CH_2benzyl); 4.40-4.44 (m, 2H, H_d); 4.46 (d of AB, 2H, ^2J = 15.1 Hz, H_o); 4.92 (d of AB, ^2J = 15.6 Hz, H_o); 6.86-6.89 (m, 2H, H_q); 6.95-6.98 (m, 10 H, CHar); 7.37-7.39 (m, 2H, CHar), 7.49-7.69 (m, 5H, H_r, $CHarCSO_2$, CHar); 7.89-7.90 (m, 2H, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 4.3 (C_c); 31.3 (C_b); 33.6 (CH_2benzyl); 50.2 (C_o); 61.2 (C_d); 64. 2(C_a); 123.8 ($CHarCSO_2$); 124.7 (CHar); 126.4 (C_q); 128.3 (CHar); 129.1 (CHar); 131.8 ($CHarCNO_2$); 131.9 ($CHarCHNO_2$); 132.3 ($CHarCHCSO_2$); 133.8 ($C_{quat}SO_2$); 137.1 (C_{quat} benzyl); 148.0 ($C_{quat}NO_2$); 156.2 (C_p); 169.2 (2C=O); *m/z* (ESI+, CV 63): 882.4 $[M+H]^+$ (100).

(7*R*,12*R*)-3,16-Bis-(2-nitrobenzenesulfonyl)-3,6,13,16,22-pentaazatricyclo[16.3.1.0^{7,12}]docosa-1(21), 18(22),19-trien-5,14-dione (15c)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **6c** (712 mg, 1.2 mmol) and anhydrous cesium carbonate (1.54 g, 4.76 mmol) in anhydrous DMF (80 mL) was stirred at 90 °C for several minutes. A solution of 2,6-bis(bromomethyl)-pyridine **11** (378 mg, 1.43 mmol) in anhydrous DMF (40 mL) was added dropwise and the mixture was heated for 6 h. After the work-up, the crude residue was purified by flash column chromatography on silica gel (EtOAc/*c*Hex 1:1) to afford the expected compound **15c** as a yellow solid. Yield: 542 mg (65%). R_f = 0.19, SiO_2, (EtOAc/*c*Hex 1:1); Mp 158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01-1.20 (m, 4H, $H_{bax.}$,

$H_{cax.}$); 1.56-1.58 (m, 2H, $H_{ceq.}$); 1.81-184 (m, 2H, $H_{beq.}$); 2.82-3.30 (m, 2H, H_a); 3.89 (d of AB, 2H, ^2J = 17.1 Hz, H_d); 4.21 (d of AB, 2H, ^2J = 17.1 Hz, H_d); 4.28 (d of AB, 2H, ^2J = 14.1 Hz, H_o); 4.56 (d of AB, 2H, ^2J = 14.5 Hz, H_o); 6.38 (d, 2H, ^3J = 6.5 Hz, NH); 7.25 (d, 2H, ^3J = 8 Hz, H_q); 7.54-7.66 (m, 7H, CHar, $CHarCHCNO_2$, $CHarCHCSO_2$, H_r); 8.12-8.32 (m, 2H, $CHarHCSO_2$); 8.42 (m, 2H, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.4 (C_c); 31.7 (C_b); 50.6 (C_d); 53.9 (C_a); 54.0 (C_o); 123.5 (C_q); 124.4 ($CHarCSO_2$); 131.1 ($CHarCNO_2$); 132.1 ($CHarCHCSO_2$); 132.5 ($C_{quat}\,CSO_2$); 134.0 ($CHarCHCSO_2$); 138.2 (C_q); 148.2 ($C_{quat}\,CNO_2$); 154.4 (C_p); 168.1 (C=O); *m/z* (ESI+, CV 63) : 703.2 $[M+H]^+$ (100).

General procedure for the preparation of desulfonylated macrocycles PyCy[12]N_4 (13) and PyCy[15]N_5 (16)

To a solution of the corresponding nosylated macrocycle (1 equiv) in anhydrous MeCN (or DMF) were added thiophenol (2.5 equiv) and anhydrous K_2CO_3 (4 equiv). The resulting mixture was stirred at room temperature (monitoring by TLC). The crude mixture was then concentrated and the residue was taken up in a mixture of 2M HCl/CH_2Cl_2 (1:1). The aqueous layer was then extracted with CH_2Cl_2 and basified by addition of pellets of NaOH. After extraction with CH_2Cl_2, the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to afford the corresponding denosylated macrocycles **13** and **16**.

(4*R*,9*R*)-12-Benzyl-3,10,13,19-tetraazatricyclo[13.3.1.0*4,9*]nonadeca-1(19),15,17-trien-11-one (13a)

This compound was prepared according to the general procedure previously described. To a solution of the corresponding nosylated macrocycle **12a** (0.7 g, 0.95 mmol) in DMF (10 mL) were added thiophenol (0.29 mL, 2.88 mmol) and anhydrous K_2CO_3 (0.395 g, 3.81 mmol). The resulting mixture was stirred at room temperature for 2 h. After workup, the expected compound **13a** was obtained as a white solid. Yield: 290 mg (84%). R_f = 0.1, SiO_2, (CH_2Cl_2/MeOH, NH_4OH 95:5:0.5); Mp 220 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ =0.59-0.72 (m, 1H, $H_{eax.}$); 0.96-1.37 (m, 3H, $H_{cax.}$, $H_{dax.}$, $H_{bax.}$); 1.52-1.61 (m, 1H, $H_{ceq.}$ or $H_{deq.}$); 1.61-1.71 (m, 1H, $H_{deq.}$ or $H_{ceq.}$); 1.86-1.95 (m, 1H, $H_{eeq.}$); 1.98-2.07 (m, 2H, H_1, $H_{beq.}$); 2.65 (sl, 2H, NH); 2.88-2.95 (m, 1H, CH_2benzyl); 2.99-3.09 (m, 2H, CH_2benzyl, H_g); 3.29-3.40 (m, 2H, H_a, H_f); 3.68 (d of AB, 1H, ^2J = 16.1 Hz, H_o); 3,79 (d of AB, 1H, ^2J = 16.3 Hz, H_u); 4.02 (d of AB, 1H, ^2J = 16.1 Hz, H_o); 4.22 (d of AB, 1H, ^2J = 16.3 Hz, H_u); 6.91-6.99 (m, 2H, H_s, H_p); 7.17-7.28 (m, 6H, CHar , NHCO); 7.51 (t, 1H, ^3J = ^3J = 7.6 Hz, H_r); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.7 (C_c or C_d); 24.9 (C_d or C_c); 31.9 (C_e); 33.8 (C_b); 41.5 (CH_2benzyl); 51.5 (C_o); 52.7 (C_f); 54.7 (C_u); 62.6 (C_a); 66.2 (C_g); 120.0 (C_s or C_q); 120.7 (C_q or C_s); 126.4 (CHar); 128.4 (CHar); 129.2 (CHar); 136.7 (C_r); 138.8 (C_{quat} benzyl); 159.6 (C_t or C_p); 159.8 (C_p or C_t); 175.2 (C=O); $[\alpha]_D^{25}$ +29,84 ± 0.1 (*c* 2, $CHCl_3$); IR (KBr; cm^{-1}): 3430; 3289; 2923; 2849; 1635; 1575; 1419; *m/z* (ES+): 403.2 $[M+K]^+$; 387.2 $[M+Na]^+$; 365.3 $[M+H]^+$, 729.48 $[2M+H]^+$; GC/MS: 50 °C (1 min); 180 °C à 300 °C (20 °C/min); 300 °C (1 min); R_t =11,53 min *m/z*: 364 $[M]^+$ (8), 273

$[M\text{-}CH_2C_6H_5]^+$ (20), 245 $[M\text{-}CH_2C_6H_5CHNH]^+$ (100), 133 (62), 106 (52), 91 $[C_7H_7]^+$ (22), 78 $[C_6H_6]^+$ (16).

(4*R*,9*R*,12*S*)-12-*Iso*-propyl-3,10,13,19-tetraazatricyclo[13,3,1,$0^{4,9}$]nonadeca-1(19),15,17-trien-11-one (13b)

This compound was prepared according to the general procedure previously described. To a solution of the corresponding nosylated macrocycle **12b** (0.4 g, 0.58 mmol) in DMF (6 mL) were added thiophenol (0.178 mL, 1.74 mmol, 3 equiv) and anhydrous K_2CO_3 (0.323 g, 2.33 mmol). The resulting mixture was stirred at room temperature for 4 h. After workup, the expected compound **13b** was obtained as a white solid. Yield: 160 mg (88%). R_f = 0.55, Al_2O_3, (CH_2Cl_2/MeOH, 95:5); Mp 249 °C; GC (method 180): R_t = 8.5; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85 (d, 3H, ^3J = 6.8 Hz, H_{10} or $3H_{11}$); 0.90-0.97 (m, 1H, (H_3 or H_4)$_{ax.}$); 1.02 (d, 3H, ^3J = 6.5Hz, H_{11} or H_{10}); 1.04-1.29 (m, 2H, (H_4 or H_3, H_5)$_{ax.}$); 1.30-1.45 (m, 1H, $H_{2ax.}$); 1.55-1.75 (m, 1H, $H_{4\ eq.}$); 1.78-1.90 (m, 2H, $H_{5eq.}$, H_1); 1.91-2.00 (m, 2H, H_9, $H_{2eq.}$); 2.24-2.37 (m, 1H, H_8); 3.42-3.57 (m,1H, H_6); 3.67 (AB, 1H, $^2J_{H19'\text{-}H19}$ = 15.8 Hz, $H_{19'}$); 3.78 (AB, 1H, $^2J_{H13'\text{-}H13}$ = 16.3 Hz, $H_{13'}$); 3.99 (AB, 1H, $^2J_{H19\text{-}H19'}$ = 15.8 Hz, H_{19}); 4.27 (AB, 1H, $^2J_{H13\text{-}H13'}$ = 16.3 Hz, H_{13}); 5.77-5.97 (m, 1H, NH_{21}) 6.96 (d, 1H, ^3J = 7.3 Hz, H_{15} ou H_{17}); 6.97 (d, 1H, ^3J = 7.5 Hz, H_{17} ou H_{15}); 7.42-7.63 (t, 1H, $^3J_{H16\text{-}15} = {}^3J_{H16\text{-}17}$ = 7.5 Hz, H_{16}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =19.1 (C_{10} or C_{11}); 19.3 (C_{11} or C_{12}); 24.6 (C_4 or C_3); 24.7 (C_3 or C_4); 32.7 (C_2 or C_5); 32.9 (C_9); 51.1 (C_{19} and C_{13}); 51.2 (C_6); 62.9 (C_1); 70.3 (C_8); 120.5 (C_{17} ou C_{15}); 120.6 (C_{15} ou C_{17}); 136.6 (C_{16}); 160.4 (C_{14} et C_{18}); 175.9 (C_7); *m/z* 316 $[M]^+$ (13), 245 (82), 107 (100).

(4*R*,9*R*,12*S*)-12-*Iso*-propyl-3,10,13,19-tetraazatricyclo[13,3,1,$0^{4,9}$]nonadeca-1(19),15,17-trien-11-one (13c)

This compound was prepared according to the general procedure previously described. To a solution of the corresponding nosylated macrocycle **12c** (1 g, 1.55 mmol) in DMF (15 mL) were added thiophenol (0.395 mL, 3.87 mmol) and anhydrous K_2CO_3 (0.86 g, 6.2 mmol). The resulting mixture was stirred at room temperature for 5 h. After workup, the expected compound **13c** was obtained as a white solid. Yield: 382 mg (90%). R_f = 0.48, Al_2O_3, (CH_2Cl_2/MeOH, 95:5); Mp 113 °C; The analytical data (^{1}H NMR, ^{13}C NMR and HRMS) are in accordance with those of the literature.[21]

(7*R*,12*R*)-3,6,13,16,22-Pentaazatricyclo[16.3.1.$0^{7,12}$]docosa-1(21),18(22),19-trien-5,14-dione (16c)

This compound was prepared according to the general procedure previously described. To a solution of the corresponding nosylated macrocycle **15c** (0.3 g, 0.43 mmol) in DMF (4.3 mL) were added thiophenol (0.138 mL, 1.28 mmol, 3 equiv) and anhydrous K_2CO_3 (0.238 g, 1.72 mmol). The resulting mixture was stirred at room temperature for 4 h. After workup, the expected compound **16c** was obtained as yellow pale cristals. Yield: 90 mg (66%). R_f = 0.46, Al_2O_3, (CH_2Cl_2/MeOH, 95:5); Mp 132 °C; ^{1}H NMR ($CDCl_3$,

400 MHz): δ = 0.93-1.16 (m, 4H, $H_{bax.}$, $H_{cax.}$); 1.45-1.74 (m, 2H, $H_{ceq.}$); 1.80-1.94 (m, 2H, $H_{beq.}$); 3.10-3.42 (m, 2H, H_a); 3.43-3.52 (m, 2H, H_d); 3.90-4.27 (m, 2H, H_d); 4.27-4.57 (m, 2H, H_o); 4.71-4.99 (m, 2H, H_o); 7.24 (d, 2H, ^3J = 8.0Hz, H_q); 7.76 (t, 1H, ^3J = 7.8 Hz, H_r). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.4 (C_c); 31.5 (C_b); 49.3 (C_d); 50.5 (C_o); 52.2 (C_a); 122.0 (C_q); 138.5 (C_r); 152.9 (C_p); 162.5 (C=O); *m/z* (ESI+, CV 63): 332.18 $[M+H]^+$ (100).

General procedure for the preparation of disulfonated macrocycles PyCy*N*-Ox[12]N_4 (1) and PyCy*N*-Ox[15]N_5 (3)

A suspension of the polyamine moiety **5** or **6** (1 equiv) and anhydrous potassium carbonate (4 equiv) in anhydrous MeCN was stirred at reflux for several minutes. Then potassium iodide (2.2 equiv) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (1.1 equiv) in anhydrous MeCN was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 3-5 h (monitoring by TLC, Et_2O). The crude mixture was concentrated and the residue was taken up in CH_2Cl_2/H_2O (3:1 v/v, 30 mL). The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated at 40 °C. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding macrocycles **1** and **3**, Yields: **1a**, 94%; **1b**, 80%, **1c**, 70% and **3a**, 46%; **3b**, 33%, **3c**, 81%

(4*R*,9*R*,12*S*)-12-benzyl-3,13-bis(2-nitrobenzenesulfonyl)-19-oxy-3,10,13,19-tetraazatricycle[13,3,1,0]-nonadeca-1(19), 15,17-trien 11-one (1a)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **5** (958 mg, 1.52 mmol) and anhydrous potassium carbonate (830 mg, 6.08 mmol) in anhydrous MeCN (100 mL) was stirred at reflux for several minutes. Then potassium iodide (548 mg) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (320 mg, 1.67 mmol) in anhydrous MeCN (25 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 3 h (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **1a** was obtained as a yellow solid. Yield: 885 mg (94%). R_f = 0.2, SiO_2, (CH_2Cl_2/MeOH/NH_3, 95:4:1); Mp 194 °C; $[\alpha]_D^{24}$ -66.6 ± 0.1 (c 1.0, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.76 (m, 1H, $H_{eax.}$), 0.95 (m, 2H, $H_{cax.}$, $H_{dax.}$), 1.01 (m, 1H, $H_{bax.}$), 1.40 (m, 1H, $H_{deq.}$), 1.49 (m, 1H, $H_{ceq.}$), 1.75 (m, 1H, $H_{beq.}$), 1.94 (m, 1H, $H_{eeq.}$), 2.57 (m, 2H, $H_{CH2benzyl}$, H_f), 3.42 (dd, 1H, ^2J = 15.2 Hz, ^3J = 8.7 Hz, $H_{CH2benzyl}$), 3.59 (m, 1H, H_a), 4.32 (d, 1H, ^2J = 15.4 Hz, H_o), 4.42 (m, 1H, H_g), 4.46 (d, 1H, ^2J = 14.5 Hz, H_u), 5.08 (d 1H, ^2J = 15.4 Hz, H_o), 5.14 (1H, d, ^2J = 14.5 Hz, H_u), 6.90 (m, 2H, CHar), 6.84 (d, 1H, $^3J_{NH\text{-}Hf}$ = 3.9 Hz, NH), 7.02 (m, 3H, CHar), 7.21 (t, 1H, $^3J_{r\text{-}s}$ = 7.8 Hz, H_r), 7.74 (d, 2H, $^3J_{s\text{-}r}$ = 7.8 Hz, H_s, H_q), 7.77 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.4 Hz, $CHarCHCNO_2$), 7.84 (ddd, 1H, ^3J = 7.6 Hz, ^4J = 0.9 Hz, $CHarCHCSO_2$), 7.85

(dd, 1H, ^3J = 7.6 Hz, ^4J = 1.52 Hz, $CHarCHCNO_2$), 7.88 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz, $CHarCHCSO_2$), 7.91 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.4 Hz, $CHarCSO_2$), 7.96 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.5 Hz, $CHarCSO_2$), 8.13 (dd, 1H, ^3J = 7.9 Hz, ^4J = 0.9 Hz, $CHarCHNO_2$), 8.20 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz, $CHarCHNO_2$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.46 (C_d), 24.75 (C_c), 28.40 (C_b), 32.79 (C_e), 33.64 ($C_{CH2benzyl}$), 43.81 (C_o), 45.10 (C_u), 53.86 (C_f), 57.94 (C_a), 59.46 (C_g), 122.66 (C_r), 124.23 and 124.95 ($CHarCSO_2$), 125.76 (CHar), 127.42 (C_s or C_q), 127.57 (CHar), 128.75 (CHar), 129.01 (C_s or C_q), 131.52 and 131.70 ($CHCNO_2$), 132.14 (CHar), 132.46 (CHar), 134.23 (CHar)*, the signal of C=O and quaternary carbons were not distinguished*; *m/z* (ESI+, CV= 97): 773.3, M^++23 (100); 774.3, M^++23 +H^+, (40); HRMS: calcd. for $C_{34}H_{34}N_6O_{10}S_2Na$ $[M+Na]^+$ (773.16700); found (773.16663); HPLC purity: 97%, Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MeCN/H_2O 8:2, 0.7 mL min^{-1}, λ= 220 nm, R_t = 5.17 min.

(4*R*,9*R*,12*S*)-12-Isopropyl-3,13-bis(2-nitrobenzenesulfonyl)-19-oxy-3,10,13,19-tetraazatricyclo[13,3,1,0] nonadeca-1(19), 15,17-trien 11-one (1b)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **5b** (397 mg, 0.68 mmol) and anhydrous potassium carbonate (376 mg, 2.78 mmol) in anhydrous MeCN (45 mL) was stirred at reflux for several minutes. Then potassium iodide (247 mg) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (143 mg, 0.74 mmol) in anhydrous MeCN (20 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 4 h 30 (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **1b** was obtained as a whitish solid. Yield: 384 mg (80%). R_f = 0.2, SiO_2, (CH_2Cl_2/MeOH, 97:3); Mp 204 °C; $[\alpha]_D^{24}$ -19.8 ± 0.1 (c 1.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.50-1.55 (m, 13H, $2CH_3$, H_c, H_d, H_e, $CH(CH_3)_2$, 2.00-2.10 (m, 2H, H_b), 2.35-2.55 (m, 2H, H_g), 4.00-4.25 (m, 2H, H_o or H_u), 5.20-5.45 (m, 2H, H_u or H_o), 7.00-7.40 and 7.60-7.85 (2m, 11H, CHAr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.72 ($2CH_3$), 24.50 (C_c or C_d), 25.88 (C_d or C_c), 26.53 ($CH(CH_3)_2$), 29.84 (C_p), 34.20 (C_b), 45.47 (C_o or C_u), 47.14 (C_u or C_o), 54.49 (C_g), 125.44, 126.9, 128.37, 129.18, 132.03, 133.33, 133.60 (CHar), 135.31 ($2C_{quat}SO_2$), 145.12 ($2C_{quat}NO_2$), 148.12 (C_t and C_p), *Uncertain assignement for aromatic carbones, the signal of C=O was not distinguished*; *m/z* (ESI+, CV= 81): 725.3, M^++23 (100); 741.3, M^++39 (56); HRMS: calcd. for $C_{30}H_{34}N_6O_{10}S_2Na$ $[M+Na]^+$ (725.16700); found (725.16728); HPLC purity: 95% on a Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MeCN/H_2O 8:2, 0.7 mL min^{-1}, λ= 220 nm, R_t = 5.08 min.

(4*R*,9*R*)-3,13-Bis(2-Nitrobenzenesulfonyl)-19-oxy-3,10,13,19-tetraazatricyclo[13,3,1,0]nonadeca-1(19),15,17-trien 11-one (1c)

This compound was prepared according to the general procedure previously described. A suspension of

the polyamine moiety **5c** (408 mg, 0.76 mmol) and anhydrous potassium carbonate (415 mg, 3.01 mmol) in anhydrous MeCN (25 mL) was stirred at reflux for several minutes. Then potassium iodide (278 mg) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (160 mg, 0.84 mmol) in anhydrous MeCN (50 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 3 h (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **1c** was obtained as a yellow solid. Yield: 344 mg (70%). R_f = 0.2, SiO_2, (CH_2Cl_2/MeOH, 97:3); Mp 202 °C; $[\alpha]_D^{24}$ -80.1 ± 0.1 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (m, 2H, $H_{eax.}$, $H_{dax.}$), 1.10 (m, 1H, $H_{bax.}$), 1.38 (m, 1H, $H_{cax.}$), 1.52 (m, 1H, $H_{dax.}$), 1.62 (m, 1H, $H_{ceq.}$), 1.67 (m, 1H, $H_{beq.}$), 2.20 (m, 1H, $H_{eeq.}$), 2.72 (m, 1H, H_f), 3.47 (m, 1H, H_a), 4.07 (d, 1H, ^2J = 15.7 Hz, H_g), 4.23 (d, 1H, ^2J = 15.8 Hz, H_o), 4.29 (d, 1H, ^2J = 15.7 Hz, H_g), 4.44 (d, 1H, ^2J = 13.9 Hz, H_u), 5.22 (d, 1H, ^2J = 13.9 Hz, H_u), 5.45 (d 1H, ^2J = 15.8 Hz, H_o), 7.02 (d, 1H, $^3J_{NH\text{-}Hf}$ = 3.9 Hz, NH), 7.21 (t, 1H, $^3J_{Hr\text{-}Hs}$ = 7.7 Hz, H_r), 7.28 (ddd, 1H, 2 ^3J = 7.8 Hz, ^4J = 2.1 Hz, CHarCHCNO$_2$), 7.65 (ddd, 1H, 2 ^3J =7.7 Hz, ^4J = 1.9 Hz, CHarCHCSO$_2$), 7.69-7.80 (m, 6H, H_s, H_{19}, H_q, 4 CHar), 8.15-8.23 (m, 2H, 2 CHar); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.98 (C_d), 25.95 (C_c), 28.91 (C_b), 44.72, (C_u), 45.38 (C_o), 51.37 (C_g), 54.64 (C_f), 59.79 (C_a), 124.55 (C_q), 125.30 (C_s), 125.56 (C_r), 127.44 (CHar), 129.75 (CHar), 131.29 (CHar), 132.06 (CHar), 132.21 (CHar), 132.58 (CHar), 133.37 (CHar), 133.58 (CHar), 133.92 (C_p), 134.23 (C_t), 144.85 and 146.72 ($C_{quat}SO_2$), 148.00 and 148.26 ($C_{quat}NO_2$), 168.39 (C=O); *m/z* (ESI+, CV= 73): 683.2, M^++23 (100); 684.2, M^++23 +H^+, (30); HRMS: calcd. for $C_{27}H_{28}N_6O_{10}S_2Na$ $[M+Na]^+$ (683.12005); found (683.11969); HPLC purity: 82%, Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MECN/H_2O 8:2, 0.7 mL min^{-1}, λ= 220 nm, R_t = 4.45 min.

(4*S*,7*R*,12*R*,15*S*)-4,15-Dibenzyl-3,16-bis(2-nitrobenzenesulfonyl)-2-oxy-3,6,13,16,22-pentaazatricyclo-[16,3,1,0]docosa-1(21), 18(22),19-trien-5,14-dione (3a)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **6a** (1.04 g, 1.34 mmol) and anhydrous potassium carbonate (741 mg, 5.36 mmol) in anhydrous MeCN (88 mL) was stirred at reflux for several minutes. Then potassium iodide (489 mg) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (283 mg, 1.47 mmol) in anhydrous MeCN (44 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 5 h (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **3a** was obtained as a yellowish solid. Yield: 550 mg (46%). R_f = 0.8, SiO_2, (cyclohexane/ EtOAc, 9:1); Mp 169-171 °C; $[\alpha]_D^{24}$ +106.2 ± 0.1 (c 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (m, 2H, $H_{bax.}$), 1.10 (m, 2H, $H_{cax.}$), 1.56 (m, 2H, $H_{ceq.}$), 1.92 (m, 2H, $H_{beq.}$), 2.89 (m, 2H, $CH_{2benzyl}$), 2.90 (m, 2H, H_a), 3.46 (s br, 2H, $CH_{2benzyl}$), 4.63 (s br, 2H, H_d), 4.69 (d, 2H, 2^2J = 15.2 Hz, H_o), 5.00 (d, 2H, ^2J = 15.2 Hz, H_o), 6.44 (s br, 2H, NH), 7.06 (sbr, 10H, CHar), 7.20 (t, 1H, $^3J_{r\text{-}q}$ = 7.8 Hz, H_r), 7.50 (m, 2H,

CHar), 7.58 (m, 2H, CHar), 7.59 (d, 2H, $^3J_{Hr-Hq}$ = 7.8 Hz, $2H_q$), 7.69 (dd, 2H, ^3J = 7.8 Hz, $CHarCSO_2$), 8.00 (s br, 2H, $CHarCNO_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 21.35 (C_c), 31.84 (C_b), 34.06 (CH_2benzyl), 43.74 (C_o), 54.03 (C_a), 62.25 (C_d), 123.91 (C_r), 125.46 ($CHarCSO_2$), 126.30 (CHar), 128.22 (CHar), 128.93 ($2C_q$), 129.42 (Ar), 131.97 (CHar), 132.87 ($CHarCNO_2$), 133.52 (CHar), 137.22 (C_{quat} benzyl), 145.71 ($2C_p$), 147.51 ($C_{quat}SO_2$, $C_{quat}NO_2$), 168.54 (2C=O); *m/z* (ESI+, CV= 85): 920.6, M^++23 (100); 921.6.2, M^++23 +H^+, (60); HRMS: calcd. for $C_{43}H_{43}N_7O_{11}S_2Na$ $[M+Na]^+$ (920.23542); found (920.23504); HPLC purity: 96%, Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MeCN/H_2O 8:2, 0.7 mL min^{-1}, λ = 220 nm, R_t = 6.88 min.

(7*R*,9*R*)-3,16-Bis(2-nitrobenzenesulfonyl)-23-oxy-3,6,13,16,22-pentaazatricyclo[16,3,1,0]docosa-1(21), 18(22),19-triene-5,14-dione (3b)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **6b** (401 mg, 0.59 mmol) and anhydrous potassium carbonate (325 mg, 2.36 mmol) in anhydrous MeCN (35 mL) was stirred at reflux for several minutes. Then potassium iodide (215 mg) was added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (125 mg, 0.65 mmol) in anhydrous MeCN (15 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 6 h (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **3b** was obtained as a pale yellow solid. Yield: 207 mg (33%). R_f = 0.4, SiO_2, (CH_2Cl_2/MeOH, 95:5); Mp 194 °C with decomposition; $[\alpha]_D^{24}$ +106 ± 0.1 (c 1.3, CH_2Cl_2); ^1H NMR (DMSO-d_6, 400 MHz): δ = 1.0-1.1 (dbr, 6H, *J* = 6.4 Hz, $2CH_3$), 1.15-1.2 (m, 6H, $2CH_3$), 1.35-1.45 (m, 2H, H_c), 1.50-1.75 (m, 2H, H_b), 1.80-2.0 (m, 4H, H_c, H_b), 2.61-2.70 (m, 2H, $CH(CH_3)_2$), 3.85-4.00 (m, 2H, H_o), 4.05-4.25 (m, 2H, H_d), 4.30-4.40 (d, 2H, *J* = 10.2 Hz, H_a), 4.75-4.90 (d, 2H, *J* = 13.2 Hz, H_o), 6.99 (sb, 1H, NH), 7.45-7.55 (m, 2H, CHar), 7.60-7.70 (m, 2H, CHar), 7.91-8.0 (m, 1H, CHar), 8.01-8.20 (m, 6H, CHar), 8.40-8.65 (sb, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 18.93 (CH_3), 19.23 (CH_3), 24.55 (C_c), 33.70 (C_b), 39.7 ($CH(CH_3)_2$, 43.51 (C_o), 51.56 (C_a), 66.63 (C_d), 122.09, 124.27, 128.11, 129.25, 129.69, 131.67, 132.51 ($2C_q$, C_r, CHar), 133.38 ($C_{quat}SO_2$), 146.38 ($2C_p$), 147.19 ($C_{quat}NO_2$), 169.24 (*C=O*), 171.98 (C=O); *m/z* (ESI+): 824.3, M^++23 (100); 825.3, M^++23 +H^+, (45), CV 50; HRMS: calcd. for $C_{35}H_{43}N_7O_{11}S_2Na$ $[M+Na]^+$ (824.23542); found (824.23526); HPLC purity: 80%, Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MeCN/H_2O 8:2, 0.7 mL min^{-1}, λ = 220 nm, R_t = 5.72 min.

(7*R*,9*R*)-3,16-Bis(2-nitrobenzenesulfonyl)-23-oxy-3,6,13,16,22-pentaazatricyclo[16,3,1,0]docosa-1(21), 18(22),19-triene-5,14-dione (3c)

This compound was prepared according to the general procedure previously described. A suspension of the polyamine moiety **6c** (55 mg, 0.092 mmol) and anhydrous potassium carbonate (50 mg, 0.37 mmol) in anhydrous MeCN (6 mL) was stirred at reflux for several minutes. Then potassium iodide (33 mg) was

added at once. A solution of 2,6-bis(chloromethyl)pyridine *N*-oxide **7** (19 mg, 0.1 mmol) in anhydrous MeCN (3 mL) was added dropwise in the previous mixture while stirring at reflux and the heating was maintained for 6 h (monitoring by TLC, Et_2O). After the workup previously described the macrocycle **3c** was obtained as a yellow solid. Yield: 39 mg (81%). R_f = 0.2, SiO_2, (CH_2Cl_2/MeOH, 95:5); Mp 144 °C; $[\alpha]_D^{24}$ +52.9 ± 0.1 (c 1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.12 (m, 4H, $2H_{bax.}$, $2H_{cax.}$), 1.59 (m, 2H, $2H_{ceq.}$), 1.72 (m, 2H, $2H_{beq.}$), 3.33 (m, 2H, $2H_a$), 3.92 (d, 2H, ^2J = 18.0 Hz, H_d), 4.17 (d, 2H, ^2J = 18.0 Hz, H_d), 4.64 (s br, 4H, H_o), 7.38 (s br, 3H, $2H_q$, H_r), 7.66 (d, 2H, $^3J_{NH\text{-}Ha}$ = 7.3 Hz, NH), 7.78 (ddd, 2H, 2^3J = 7.7 Hz, ^4J = 1.4 Hz, CHarCHCNO$_2$), 7.92 (ddd, 2H, 2^3J = 7.7 Hz, ^4J = 1.4 Hz, CHarCHCSO$_2$), 8.02 (dd, 2H, ^3J = 6.8 Hz, ^4J = 1.4 Hz, CHarCSO$_2$), 8.40 (dd, 2H, ^3J = 7.7 Hz, ^4J = 1.4 Hz, CHarCNO$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 24.00 (C_c), 31.86 (C_b), 45.35 (C_o), 50.43 (C_d), 52.14 (C_a), 124.17 (CHarCSO$_2$), 125.21 ($2C_q$), 125.97 (C_r), 13016 (CHarCNO$_2$), 132.30 (CHar), 134.44 (CHar); *m/z* (ESI+, CV= 45): 740.2, M^++23 (100); 741.2, M^++23+H^+, (30); HRMS: calcd. for $C_{29}H_{31}N_7O_{11}S_2Na$ $[M+Na]^+$ (740.14152); found (740.14159); HPLC purity: 98%, Hypersil ODS C18, column, 250 mm, 4.6 mm, 5 μm, MeCN/H_2O 8:2, 0.7 mL min^{-1}, λ= 220 nm, R_t = 4.19 min.

General procedure for the preparation of desulfonylated macrocycles PyCy*N*-Ox[12]N_4 (2a) and PyCy*N*-Ox[15]N_5 (4a)

To a solution of the corresponding nosylated macrocycles **1a** or **3a** (1 equiv) in anhydrous MeCN were added mercaptoethanol (11.2 equiv) and DBU (4.5 equiv). The resulting mixture was stirred at room temperature for 2h (monitoring by TLC). The crude mixture was then concentrated and the residue was taken up in a mixture of MeCN:H_2O (1:1). The organic layers were separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding denosylated macrocycles **2a** and **4a**. Yields **2a**, 91%; and **4a**, 65%.

(4*R*,9*R*)-12-Benzyl-19-oxy-3,10,13,19-tetraaza-tricyclo[13.3.1.0*4,9*]nonadeca-1(19),15,17-trien-11-one (2a)

To a solution of the corresponding nosylated macrocycle **1a** (220 mg, 0.29 mmol, 1 equiv) in anhydrous MeCN (15 mL) were added mercaptoethanol (0.24 mL, 3.46 mmol, 11.2 equiv) and DBU (0.2 mL, 1.34 mmol, 4.5 equiv). The resulting mixture was stirred at room temperature for 2 h (monitoring by TLC, EtOAc). The crude mixture was then concentrated and the residue was taken up in a mixture of MeCN:H_2O (1:1) (40 mL). The organic layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2/ MeOH/NH_4OH 95:4:1) to afford the expected compound **2a** as a yellow solid. Yield: 100 mg (91%). R_f =

0.1, SiO_2, (CH_2Cl_2/MeOH, NH_4OH 95:4:1); Mp 86 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.29-0.39 (m, 1H, $H_{eax.}$), 1.00-1.3 (m, 4H, $H_{cax.}$, $H_{dax.}$, $H_{bax.}$, $H_{eeq.}$), 1.41-1.57 (m, 1H, $H_{beq.}$), 1.69-1.75 (m, 1H, $H_{ceq.}$), 1.77-1.90 (m, 1H, $H_{deq.}$), 2.10-2.60 (m, 2H, H_a, H_f), 2.61 (dd of ABX, 1H, J_{AB} = 12.9 Hz, J_{AX} = 9.8 Hz, CH_2benzyl), 3.44-3.50 (m of ABX, 1H, H_g), 3.68 (d of AB, 1H, $J_{Ho\text{-}NH}$ = 1.9 Hz, H_o), 7.72 (s br, 1H, H_u), 4.18 (d, 1H, J = 15.8 Hz, H_o), 4.89 (d, 1H, J = 14.6 Hz, H_u), 5.7 (s br, 1H, NH), 7.05-7.26 (m, 8H, H_s, H_r, H_q, CHar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.57 (C_b), 25.95 (C_c), 30.50 (C_d), 32.79 (C_e), 41.71 (CH_2benzyl), 44.97 (C_o or C_u), 45.22 (C_u or C_o), 56.23 (C_f), 58.82 (C_q), 63.69 (C_g), 124.71, 126.44, 126.82, 128.23, 128.35, 129.15, 129.43 (C_s, C_r, C_q, CHar), 137.50 (C_{quat} benzyl), 149.82 (C_t or C_p), 152.17 (C_p or C_t), 173.69 (C=O); *m/z* (ESI+, CV = 25): 381.3, M^++H (100); 382.3, M^++$2H^+$, (30); HRMS: calcd. for $C_{22}H_{29}N_4O_2$ $[M+H]^+$ (381.22850); found (381.22858).

(4*S*,7*R*,12*R*,15*S*)-4,15-Dibenzyl-22-oxy-3,6,13,16,22-pentaazatricyclo[16.3.1.0*7,12*]docosa-1(21), 18(22),19-triene-5,14-dione (4a)

To a solution of the corresponding nosylated macrocycle **3a** (260 mg, 0.29 mmol, 1 equiv) in anhydrous MeCN (10 mL) were added mercaptoethanol (0.24 mL, 3.16 mmol, 11.2 equiv) and DBU (0.2 mL, 1.34 mmol, 4.5 equiv). The resulting mixture was stirred at room temperature for 2 h (monitoring by TLC, cyclohexane/EtOAc, 5:5). The crude mixture was then concentrated and the residue was taken up in a mixture of MeCN:H_2O (1:1) (40mL). The organic layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc/NH_4OH 9:1) to afford the expected compound **4a** as a beige solid. Yield: 100 mg (65%). R_f = 0.1, SiO_2, (cyclohexane/EtOAc 9:1); Mp 68 °C, ^1H NMR ($CDCl_3$, 400 MHz)*: δ = 0.45-0.65 (m, 2H, $2H_{bax.}$), 0.8-1.0 (m, 2H, $2H_{cax.}$), 1.35-1.52 (m, 4H, $2H_{beq.}$, $2H_{ceq.}$), 2.70-2.81 (dd, 4H, J = 15.4 Hz, 2J = 6.9 Hz, CH_2benzyl), 2.82-2.90 (m, 2H, H_a), 3.20-3.31 (t, 2H, 2J = 7.5 Hz, H_g), 3.88-4.08 (m, 4H, H_o), 7.00-7.21 (m, 13H, $2H_q$, H_r, CHar).* The signals accounting for *NH* were not distinguished. ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 24.19 (C_c), 31.51 (C_b), 41.65 (CH_2benzyl), 47.39 (C_o), 53.63 (C_a), 64.19 (C_d), 124.73 (C_q), 124.92 (C_r), 126.49 (CHar), 128.35 (CHar), 129.26 (CHar), 137.92 (C_{quat} benzyl), 150.02 (C_p), 173.15 and 174.80 (C=O); *m/z* (ESI+): 528.4, M^++H (100); 529.5, M^++$2H^+$, (30); HRMS: calcd. for $C_{31}H_{38}N_5O_3$ $[M+H]^+$ (528.29692); found (528.29602).

General procedure for reaction of allyltrichlorosilane with *p*-nitrobenzaldehyde

Allyltrichorosilane (52 µL, 0.36 mmol, 2.4 equiv) was added to a solution of the catalyst (0.02 mmol), diisopropylethylamine (78.5 µL, 0.45 mmol, 3 equiv) and *p*-nitrobenzaldehyde (22.7 mg, 0.15 mmol, 1 equiv) in anhydrous MeCN (1 mL) under argon at 0 °C. The mixture was stirred at the corresponding temperature (monitoring by HPLC using a mini pre-column on silica gel; see Table **1** for the reaction

times and temperatures), and quenched with saturated aqueous solution of sodium hydrogen carbonate (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2) to afford the expected compound **18** as a brown solid.

(*S*)-(−)-1-(*p*-Nitrophenyl)-3-buten-1-ol (entry 9, Table 1)[31,32]

R_f = 0.5, SiO_2, (CH_2Cl_2/MeOH 98:2); $[\alpha]_D^{21}$ - 22 ± 0.1 (c 0.1, $CHCl_3$); The ^1H NMR data is in accordance with those of the literature. The conversion rate was determinate by HPLC (Hypersil, 150 mm x 4.6 mm, 5 μm) in an isocratic system of elution using a PDA detector Waters (n-heptane/CH_2Cl_2/MeOH 20:80:0.1), 0.8 mL min^{-1}, λ = 272 nm, $R_{t\ aldehyde}$ = 3.37 min, $R_{t\ alcohol}$ = 7.52 min. The enantiopurity was determined by chiral HPLC analyses (Column ADH chiralpak, 250 mm x 4.6 mm, 5 μm), using a PDA detector Waters (n-hexane/EtOH 94:6), using a UV detector, 0.4 mL min^{-1}, λ = 220 nm, R_R = 38.41 min and R_S = 40.40 min; enantiomeric excess was determined to +/- 0.25%. The absolute configuration was established by the comparison of their optical rotations (measured in $CHCl_3$) and HPLC retention times with the literature data.

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