

Conformationally Biased Selective Alkylation of *trans*-Cyclohexane-1,2-bis(sulfonamide) Assisted by Solvent-Tuned Protecting Groups: Applications to the Synthesis of a Large Optically Active Polyazamacrocyclic

Carmen Peña,^[a] Ignacio Alfonso,^[b] and Vicente Gotor^{*[a]}

Dedicated to the memory of Professor Marcial Moreno-Mañas

Keywords: Protecting groups / Alkylation / Sulfonamides / Conformation analysis / Azamacrocycles

The selective alkylation of (*R,R*)-cyclohexane-1,2-bis(sulfonamide) with trityl bromoalkyl ethers has been studied in detail. The major formation of either mono- or dialkylated compounds clearly depends on the right combination of protecting groups and the reaction solvent. An exhaustive study suggests that this effect can be reasonably explained by the conformational preferences of the monoalkylated compounds, which also depend on the reaction medium, solvophobic effects and weak intramolecular interactions. Structural analysis by NOE measurements showed the presence of

folded conformations in solution for all the tested examples. Monte Carlo conformational searches supported this proposal, showing a very good correlation between the fraction of folded species and the selectivity towards monoalkylation. Finally, tuning of the reaction conditions, leading to either extended or folded conformations of the monoalkylated synthetic intermediates, was exploited for the efficient synthesis of a large optically active polyazamacrocyclic.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

Introduction

Conformational preferences play an essential role in chemistry^[1] and biology.^[2] The three-dimensional disposition of different residues, for instance, is the key factor in the folding of biological macromolecules and, therefore, in the active form of proteins and enzymes.^[3] Usually the spontaneous rearrangement into a given conformation is promoted by the cooperative action of weak interactions which work very distinctly depending on the environment.^[4] Thus, for instance, hydrophobic and hydrogen-bonding interactions are essential for understanding the stability of the DNA double helix,^[5] the formation of some peptidic motifs like α -helices^[6] and β -sheets^[7] or even the existence of lipid bilayers in cell membranes.^[8] Surprisingly, this interpretation has not commonly been used to explain chemical reactivity^[9] even though conformational preferences could be critical to the properties of a molecule. On the other hand, following our studies devoted to the syntheses of new optically active cyclic^[10] and linear^[11] polyamines and their subsequent applications to chiral anion molecular recognition,^[10c,12] we focused our efforts on the development of

new synthetic methodologies for the mono- or dialkylation of nonracemic *trans*-cyclohexane-1,2-bis(sulfonamide) **1**. During this ongoing research we found unexpected results for the above-mentioned reaction.^[13] Although the monoalkylation or monoprotection of cyclohexane-1,2-diamine is not an easy task,^[14] here we report an easily tunable methodology for obtaining mono- or dialkylated bis(sulfonamide)s in high yields and selectivity depending on the reaction conditions. We also decided to study this process in depth in order to understand the factors affecting it and to try to explain the observed behavior, which could be related to the existence of either folded or extended conformations of the monoalkylated intermediate. The possibility of obtaining monoalkylated derivatives is of great synthetic importance as it would enable the preparation of unsymmetrically substituted chiral ligands and synthons.^[15] Related to this and as an illustration of the potential utility of our results, we applied the rationale of our synthetic methodology to the preparation of a new enantiopure large polyazamacrocyclic.

Results and Discussion

Selective Alkylation Reaction

In a preliminary communication,^[13] we reported the effect of solvent polarity on the reaction of bis(sulfonamide)

[a] Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo,

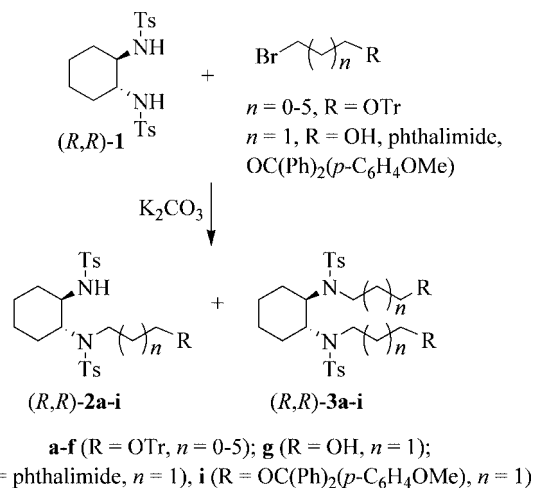
C/ Julián Clavería, s/n, 33071, Oviedo, Spain

[b] Departamento de Química Inorgánica y Orgánica, ESTCE, Universidad Jaime I,

Avd. Sos Baynat, s/n, 12071 Castellón, Spain

E-mail: vgs@fq.uniovi.es

1 with different trityl bromoalkyl ethers (Scheme 1). We found interesting trends in the alkylation of **1** with an excess of the electrophile and by using potassium carbonate as a base. The product distribution between the mono- and dialkylated final compounds depends dramatically on the reaction conditions and, more precisely, on the solvent polarity. Results shown in Table 1 highlight this trend. When the process was carried out in dry acetonitrile, a very common solvent for nucleophilic substitution, the reaction practically stopped after the monoalkylation step (Table 1, entries 1–5). These results could initially be explained by the steric hindrance between the Ts and Tr protecting groups. Accordingly, for $n = 0$, alkylation occurred with only low yields, the rest of the bis(sulfonamide) being recovered unreacted (ca. 50%). We extended the study to trityl bromoalkyl ethers with different numbers of methylenes ($n = 1$ –5). Surprisingly, for all the examples tested, the reaction was also highly selective ($\geq 85\%$) towards the formation of the monoalkylated products, showing smooth variations in yield with increasing lengths of the alkyl chain. These unexpected results suggest that the trityl protecting group is able to prevent reaction on a remote NH center of the molecule up to 12 bonds apart, which is quite remarkable considering the length of the aliphatic spacer between the nitrogen atoms and the Tr group. Regarding the selectivity of the process, dependence on the aliphatic methylenic length is rather intriguing. Thus, if we compare the results of entries 1–3, we find that the selectivity towards the monoalkylated compound increases with increasing length of the alkylating agent. The expected effect should be the reverse if we just consider the steric hindrance between the Tr and Ts groups. In addition, although the selectivity is complete for $n = 2, 3$, it drops slightly for $n = 4$ and is partially recovered for $n = 5$. This irregular behavior cannot be explained by simple consideration of the steric interactions between the Ts and Tr groups as this effect would gradually be attenuated when increasing the number of methylenic groups in the electrophile.



Scheme 1. Alkylation of bis(sulfonamide) (*R,R*)-**1**.

More interestingly, when the reaction was carried out in dry toluene, a solvent expected to be less suitable for S_N2

Table 1. Selective alkylation of bis(sulfonamide) (*R,R*)-**1**.

Entry	<i>n</i>	R	Solvent	Yields 2 ^[a]	Yields 3 ^[a]	Selectivity ^[b] 2/3
1	0	OCPh ₃	CH ₃ CN	2a (20)	3a (4)	27:5:[68] ^[c]
2	1	OCPh ₃	CH ₃ CN	2b (70)	3b (11)	86:14
3	2	OCPh ₃	CH ₃ CN	2c (80)	–	100:0
4	3	OCPh ₃	CH ₃ CN	2d (75)	–	100:0
5	4	OCPh ₃	CH ₃ CN	2e (67)	3e (12)	85:15
6	5	OCPh ₃	CH ₃ CN	2f (75)	3f (5)	94:6
7	0	OCPh ₃	PhCH ₃	–	3a (80)	0:100
8	1	OCPh ₃	PhCH ₃	–	3b (72)	0:100
9	2	OCPh ₃	PhCH ₃	–	3c (77)	0:100
10	3	OCPh ₃	PhCH ₃	–	3d (79)	0:100
11	4	OCPh ₃	PhCH ₃	–	3e (80)	0:100
12	5	OCPh ₃	PhCH ₃	–	3f (82)	0:100
13	1	OH	CH ₃ CN	2g (21)	3g (50)	30:70
14	1	OH	PhCH ₃	2g (60)	3g (30)	67:33
15	1	Phthalimide	CH ₃ CN	2h (44)	3h (28)	61:39
16	1	OCPh ₂ [–] (<i>p</i> -MeOC ₆ H ₄)	CH ₃ CN	2i (66)	3i (22)	75:25

[a] Isolated yields [%] after flash chromatography are given in parentheses. [b] Calculated from the isolated yields. [c] Value in brackets corresponds to the percentage of recovered starting material (50%).

processes, the corresponding dialkylated compound was exclusively obtained in very good isolated yields and total chemoselectivity (entries 7–12 in Table 1). The yield obtained is especially shocking for the shortest electrophile (entry 7), demonstrating the large effect of the reaction medium on the accessibility of the free NH group of the monoalkylated intermediate, even for the example in which the Ts and Tr groups are closest. However, the steric hindrance in the dialkylated derivatives is evidenced from the broad signals displayed in the ¹H NMR spectra, which suggest the presence of dynamic conformational processes on the NMR timescale. Thus, for the shortest derivative (*R,R*)-**3a**, the presence of different conformers in solution was observed by the splitting of the signals of the proton nuclei in the proximity of the sulfonamide groups, which showed typical coalescence behavior ($n = 0$, $T_{\text{coal}} = 323$ K, 500 MHz, CDCl₃).^[16]

As we were intrigued by the effect of the Tr group in different solvents, we have proposed a reasonable explanation for these results. Considering the flexibility of aliphatic linear chains and by comparing data gathered in Table 1, we ruled out steric repulsion as the only source of this behavior. We then suspected that the conformation of the monoalkylated sulfonamide (*R,R*)-**2** could play an important role in the reactivity of the second NH group. With the alkyl chain in an extended conformation (I in Figure 1), the Tr group would be far away from the second sulfonamide. However, in a folded conformation (II), the aromatic rings of the Ts and Tr groups would be close to each other. With the bulky Tr group, this arrangement would protect the free NH group in **2** from reaction with a second electrophile. Thus, the steric effect of the trityl protecting group would be operative exclusively through a folded conformation of the monoalkylated intermediate. Besides, this conforma-

tional equilibrium is expected to be highly dependent on the polarity of the medium. Polar solvents (such as acetonitrile) would favor folded conformers due to solvophobic effects, while hydrophobic environments (such as toluene) would stabilize the extended form. This equilibrium based on the polarity of the solvent used leads to a reasonable explanation of our results.

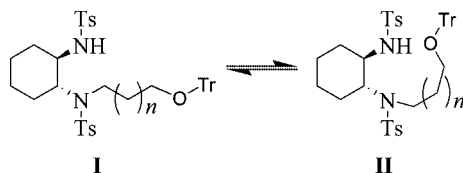
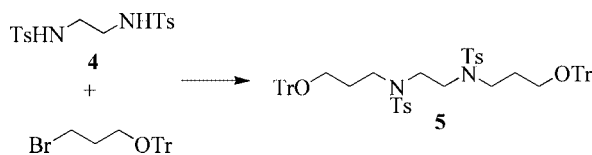


Figure 1. Proposed conformational equilibrium of the monoalkylated intermediate.

Some additional experiments were performed to obtain more information about the variables affecting this reaction and to try to validate our proposal. First of all, the use of more reactive carbonates (such as Cs_2CO_3)^[17] had a slight effect on the reaction kinetics but not on the product distributions, ruling out any ion-pairing effect on the selectivity. Other sulfonamide-based protecting groups such as nitrobenzenesulfonyl (Ns) or trimethylsilyl ethanesulfonyl (SES) were also examined, but the corresponding cyclohexane derivatives and the subsequent synthetic intermediates exhibited many solubility and stability problems. In order to check the effect of the conformational flexibility on this process, we also carried out the reaction using ethylenebis(sulfonamide) **4** instead of the *trans*-cyclohexane moiety. The cyclohexane-1,2-diamine structure is expected to preorganize in a folded conformation whereas the ethylenediamine motif would increase the conformational freedom. Accordingly, when using ethylenebis(sulfonamide) **4** the reaction in acetonitrile led to the exclusive formation of the dialkylated derivative **5** in very good yields (ca. 80%, Scheme 2). These results support the importance of the geometrical restrictions of the cyclohexane structure, with the system pre-folding in solution.



Scheme 2.

Substitution of the Tr protecting group was also investigated for one of the derivatives ($n = 1$). As the simplest change, we carried out the reaction with the free bromo alcohol both in acetonitrile and in toluene (entries 13 and 14 in Table 1). Although the chemoselectivity drops, a trend was observed that is the reverse of the one displayed by the highly nonpolar tritylated derivative. Thus, a small preference for the formation of the dialkylated compound was observed in acetonitrile, while the monoalkylated derivative was slightly preferred in toluene. Using the above-men-

tioned rationale, the folded conformations of the monoalkylated compound would be favorable in this case in a more hydrophobic solvent, while solvation of the OH group in acetonitrile would favor extended structures. Another very useful electrophile for the synthesis of polyamines,^[18] *N*-(3-bromopropyl)phthalimide, was also assayed, leading to lower selectivity towards monoalkylation than was observed with Tr (entries 2 and 15), in good accordance with its intermediate polarity. A final example, which supports the need for the highly hydrophobic nature of the Tr group, was obtained by using the slightly more polar *p*-methoxyphenyldiphenylmethyl-protected 3-bromopropanol (entry 16). Although the steric requirements of this group are very similar to those of Tr, the selectivity towards the monoalkylated derivative was slightly lower, which is in agreement with its more efficient solvation in acetonitrile.

Additional experimental evidence for the existence of folded conformations of the monoalkylated *O*-trityl derivatives was obtained from 1D and 2D NOESY experiments.^[19] For instance, we obtained weak but measurable NOE effects with (*R,R*)-**2e** between the *ortho* proton of the Ts group of the alkylated sulfonamide and the methyl protons of the Ts group of the nonalkylated one (Figure 2). In addition, this methyl group also shows NOE contacts with the *ortho* protons of the Tr group. This would set the three protecting groups at a distance of less than 5 Å,^[20] supporting the existence of folded conformations of (*R,R*)-**2e** and

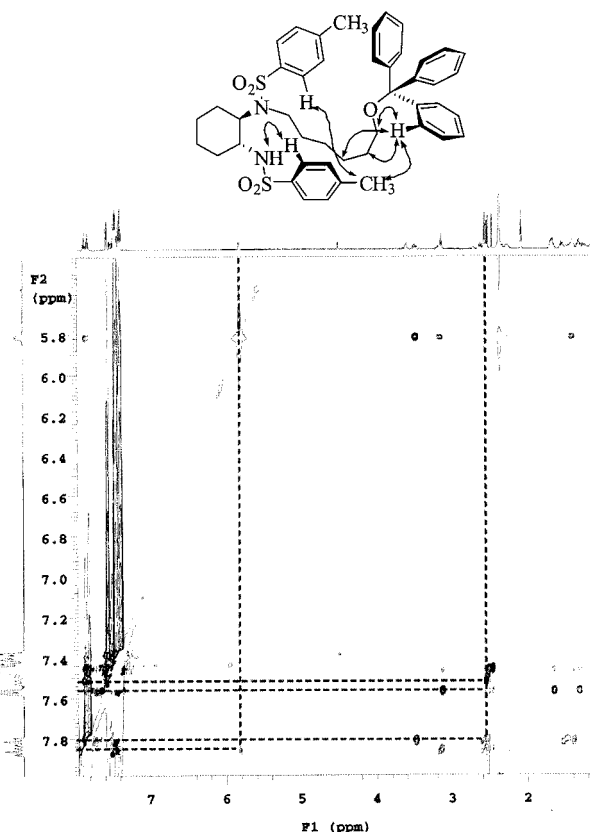


Figure 2. Selected NOE effects observed in the NOESY spectrum of (*R,R*)-**2e** (CD_3CN , 500 MHz).

also suggesting a *syn* disposition of the two Ts groups. The overall effect would be a large steric hindrance around the nonalkylated NH group. Similar results were obtained with all the monoalkylated derivatives of the series.

With all this experimental evidence we have shown that there is a synergistic effect between the preorganized conformation in solution, the bulky and hydrophobic Tr protecting group and the polarity of the solvent which ultimately determines the selectivity of the alkylation process. Under suitable reaction conditions the free NH group of the monosubstituted intermediates can be protected. Thus, the Tr residue of the alkylating agent can act as a protecting group in acetonitrile, but its shielding effect can be eliminated by simply changing the polarity of the medium. This is an interesting example of solvophobic effects, with a terminal group preventing the reaction at a remote center of the molecule. From a synthetic point of view, this effect is of interest because of the possibility of selectively obtaining mono- or dialkylated bis(sulfonamide)s by simply changing the solvent, in the same manner as a conventional protection/deprotection strategy. Concomitantly, suitable control of the sequential alkylation reaction would allow unsymmetrical substitution of the bis(sulfonamide) core. These possibilities have been exploited in the efficient synthesis of a large D_4 symmetrical optically active polyazamacrocyclic.

Conformational Analysis by Molecular Modeling

As the explanation for the observed results seems to rely on the conformational preferences of the corresponding monoalkylated intermediates, we have also tried to support our proposal by molecular modeling studies. In order to obtain a global picture of the systems under study, as they are supposed to be quite flexible, we subjected compounds **2a–f** to Monte Carlo conformational searches without constraints. Two different force fields were used (MMFF and MMFFaq). Although many local energy minima were obtained, as expected in open-chain derivatives, some interesting trends can be extracted. First of all, the *trans*-cyclohexane moiety tends to retain the chair conformation, setting the two sulfonamide groups in an equatorial disposition, which is in agreement with the NMR spectroscopic data. A representative example is shown in Figure 3 for the most flexible compound (**2f**, $n = 5$). Superimposition of the lowest-energy conformers within a 1 kcal/mol energy range clearly shows how the cyclohexane moiety retains its conformation while the other parts of the molecule are sensibly more flexible. Interestingly, the structure tends to locate aromatic rings from all the protecting groups (Tr and both Ts) in an averaged spatial proximity. Thus, many conformers were obtained showing close contacts between the aromatic rings either in a face-to-face or edge-to-face fashion.^[21] These noncovalent weak interactions force the aliphatic alkyl chain to fold back over the Ts groups and even the Ts groups to fold towards each other in a *syn* disposition. This disposition is in good agreement with the NOE data.

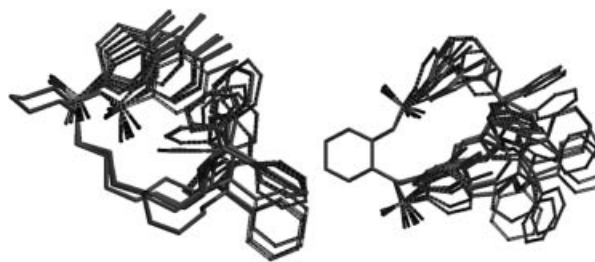


Figure 3. Side and upper views of superimposed conformations of **2f** within an energy gap of 1 kcal/mol. Hydrogen atoms have been omitted for clarity.

In order to compare trends depending on the methylenic spacer length (n) the conformations within an energy gap of 3 kcal/mol were considered and grouped into two families. The first one contains the geometries with a completely extended (all-*anti*) arrangement of the methylenic spacer $[-\text{TsN}-\text{CH}_2-(\text{CH}_2)_n-\text{CH}_2-\text{O}-]$ and the second those with at least one *gauche* torsion angle in that moiety which are regarded as being folded. The numbers of total and folded conformers for each compound determined using two different force fields are shown in Table 2. Accordingly, we calculated the fraction of folded conformers, considering the computed relative energies and following a Boltzmann distribution. If we plot the fraction of folded conformers obtained by Monte Carlo simulations versus the length of the alkylating agent (n), a correlation with the monoalkylation selectivity can be found (Figure 4). The larger is the fraction of folded species, the higher is the selectivity of the monoalkylation reaction. Actually, the deviation from the observed trend found experimentally for $n = 4$ is reflected in this simple analysis (Figure 4). Modeling suggests that the flexibility of the chain with $n = 4$ is less than for other values of n (either shorter or longer) and therefore protects NH less efficiently. Thus, the source of the observed selectivity seems to be closely related to the conformational preferences of the monoalkylated compound towards folded conformers. As previously anticipated, the folded conformers of **2a–f** would set the aromatic rings of the protecting groups preventing the second nucleophilic NH center from a subsequent reaction to give the dialkylated species **3a–f**.^[22]

Table 2. Number of total and folded conformations obtained by Monte Carlo searches of **2a–f**.

Compound (n)	MMFF conformers $\Delta E \leq 3$ kcal/mol		MMFFaq conformers $\Delta E \leq 3$ kcal/mol	
	Total	Folded	Total	Folded
2a (0)	6	2	11	4
2b (1)	13	9	13	9
2c (2)	12	12	22	21
2d (3)	5	5	11	11
2e (4)	15	11	17	14
2f (5)	21	19	22	22

In addition, some differences are observed when comparing the nonpolar (MMFF) and polar (MMFFaq) environments within the force fields used for the calculations. Al-

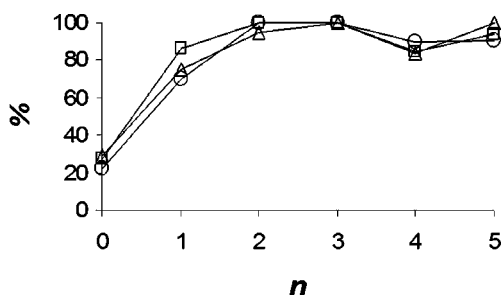


Figure 4. Plots of monoalkylation selectivity (squares) and fraction of folded conformations obtained by Monte Carlo searches (MMFF in circles and MMFFaq in triangles) versus the length of the alkyl chain (n in Scheme 1).

though the fraction of folded species is very similar, greater flexibility (larger number of conformations) is found as the polarity of the medium increases. This can be interpreted as an effect of stabilization of some conformers in polar environments, which are not energetically accessible in the absence of the compensatory effects of the solvent. More interestingly, when comparing the global minima obtained with and without the considered solvent, we found that the minima derived from MMFFaq calculations present a more hindered NH group than the one in the absence of solvent effects. Figure 5 shows the CPK representation of a selected example ($n = 4$). This structure presents a more compact geometry than that of the minimum in vacuo, again supporting our proposal. Note also that these folded structures exhibited interatomic distances that are compatible with the observed NOEs. In addition, we found very similar situations with the other compounds of the series.

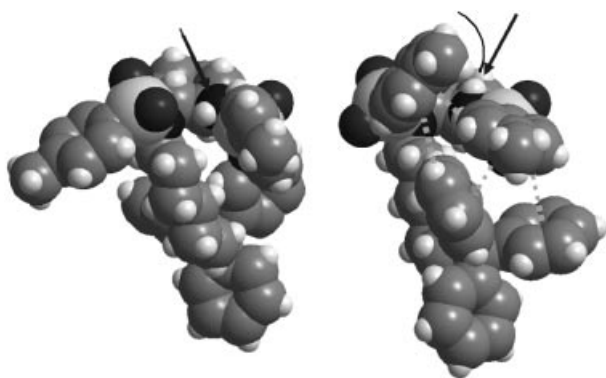


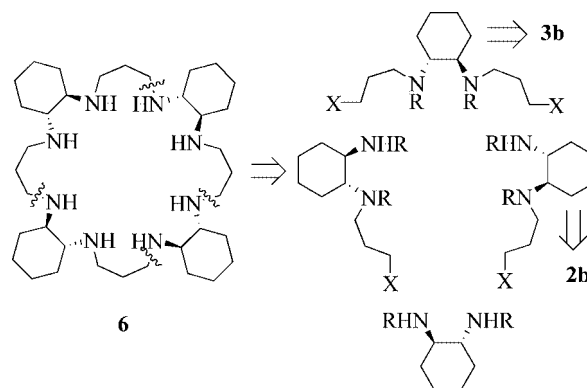
Figure 5. Global minima obtained for **2e** with MMFF (left) and MMFFaq (right) force fields. An arrow points to the nonalkylated NH and possible aryl-aryl interactions are highlighted with dashed lines.

Consequently, the overall effect of a polar solvent would be to fold the structure in a more compact and hindered conformation, preventing the second alkylation reaction. On the other hand, in the presence of a hydrophobic and aromatic solvent, the aromatic rings of the protecting groups of the monoalkylated intermediate would be efficiently solvated, the bulkiness of the Tr group being ineffective. Under these circumstances, the system behaves as

a flexible extended nonhindered molecule, leading to the efficient dialkylation reaction, as with the linear ethylene-bis(sulfonamide) **4**.

Synthesis of a Large Optically Active Polyazamacrocycle

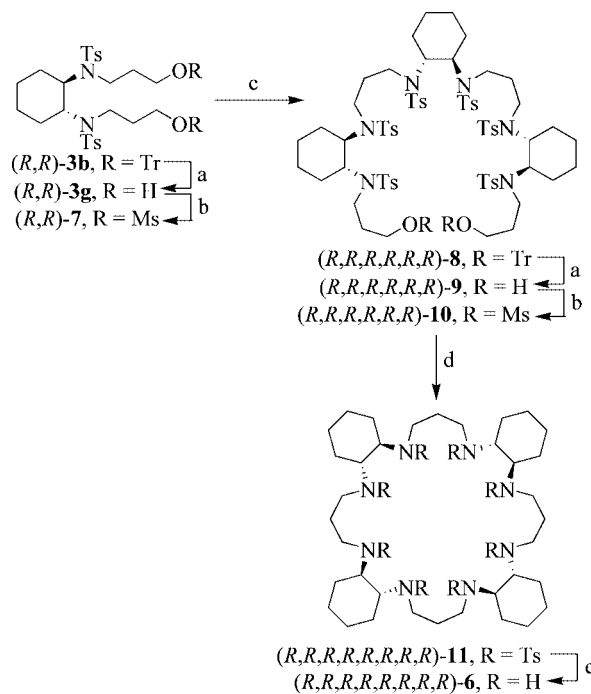
Considering the results obtained and with the aim of showing the synthetic applicability of this selective alkylation process, we envisioned the synthesis of an optically active 28-membered polyazamacrocycle, (*R,R,R,R,R,R,R,R*)-**6** (Scheme 3). Related compounds have been efficiently used for the enantioselective molecular recognition of chiral anions of biological relevance in aqueous solution.^[10c,12] The structure of the proposed receptor would contain eight chiral centers in a D_4 symmetrical arrangement and also eight secondary amino groups which would cause it to display a large positive charge density in aqueous solution close to physiological pH. To prepare this compound, a possible retrosynthetic analysis would be as shown in Scheme 3, which requires the preparation of both the monoalkylated (*R,R*)-**2b** and dialkylated (*R,R*)-**3b** derivatives of bis(sulfonamide) (*R,R*)-**1**. In addition, consecutive coupling between them has to be planned carefully using the rationale described in the previous sections. This retrosynthetic scheme exemplifies the power and practicality of the methodology demonstrated in this paper.



Scheme 3. Retrosynthetic analysis of macrocycle (*R,R,R,R,R,R,R,R*)-**6** (R: protecting group, X: leaving group).

The conventional deprotection of Tr groups in (*R,R*)-**3b** followed by mesylation of alcohol groups in (*R,R*)-**3g** afforded the doubly electrophilic compound (*R,R*)-**7** in 60% overall isolated yield (Scheme 4). Double nucleophilic coupling of (*R,R*)-**7** with two equivalents of (*R,R*)-**2b** led to compound (*R,R,R,R,R,R,R,R*)-**8**, also in 60% yield after chromatographic purification. According to our proposal, this process has to be performed in toluene, which favors the highly solvated extended conformations of (*R,R*)-**2b**, allowing the second alkylation to proceed. Note that in the synthetic sequence of (*R,R*)-**1** to (*R,R*)-**2b** and then to (*R,R,R,R,R,R,R,R*)-**8**, the two sulfonamide groups of the starting material have been selectively and consecutively alkylated by simply changing the solvent of the reaction, avoiding standard protection/deprotection steps. This is a very clear illustration

of the synthetic applicability of the studied reaction. Again, a deprotection/mesylation sequence led to the conversion of (R,R,R,R,R,R) -**8** into (R,R,R,R,R,R) -**10** with similar yields to those obtained in the conversion of (R,R) -**3b** to (R,R) -**7**. Cyclization of (R,R,R,R,R,R) -**10** with (R,R) -**1**, promoted by Cs_2CO_3 in acetonitrile, yielded the octatosylated macrocycle (R,R,R,R,R,R,R,R) -**11** in a very good yield (74%). Although NMR spectra with very broad signals were obtained for (R,R,R,R,R,R,R,R) -**11**, consistent with reduced conformational flexibility, its cyclic structure was clearly demonstrated by ESI-TOF mass spectrometry, which exhibited peaks corresponding to $[\mathbf{11} \cdot \text{Na}_2]^{2+}$ and $[\mathbf{11} \cdot \text{Na}_2 + \text{H}_2\text{O}]^{2+}$ at $m/z = 947$ and 956 , respectively. This cyclization process also led to a small amount of open-chain oligomers (ca. 12%) which were detected in the crude ^1H NMR and ESI-MS spectra and were readily separated from the cyclic compound by flash chromatography. Interestingly, when the reaction was performed in toluene, a mixture of open-chain oligomers was observed in both the ^1H NMR and ESI-MS spectra with no traces of the macrocycle being detected. These results suggest that our interpretation of the solvent effect is applicable not only to the alkylation of (R,R) -**1** but to the general behavior of conformationally preorganized compounds. Besides, we realized that our rationale is in very good agreement with the explanation proposed to account for the success of the Richman–Atkins procedure for the synthesis of polyazamacrocycles.^[23] As initially described in the seminal paper on this reaction, the best combination seems to be bulky hydrophobic protecting groups in very polar solvents. This situation would increase the fraction of folded species of the open-chain intermediate, entropically favoring the cyclization towards the final product. Finally, detosylation of (R,R,R,R,R,R,R,R) -**11** with aqueous HBr in the presence of PhOH yielded the free macrocycle, which can be easily converted into the octahydrochloride salt by conventional basic/acidic extraction procedures (85% yield from **11**). In this case, after cleavage of the bulky Ts protecting groups, clean ^1H and ^{13}C NMR spectra were obtained for (R,R,R,R,R,R,R,R) -**6** which exhibited signals compatible with a clear D_4 symmetry in solution. This observation implies that no epimerization



Scheme 4. Synthesis of macrocycle (R,R,R,R,R,R,R,R) -**6**. Reagents and conditions: a) TFA in CH_2Cl_2 :MeOH; b) MsCl/ NEt_3 in CH_2Cl_2 [60%, two steps from (R,R) -**3b**]; c) (R,R) -**2b**, Cs_2CO_3 , NBu_4Cl cat., PhCH_3 (60%); d) (R,R) -**1**, Cs_2CO_3 , CH_3CN , (74%); e) HBr (aq.), PhOH, then NaOH with CH_2Cl_2 extraction and then HCl (85%).

drochloride salt by conventional basic/acidic extraction procedures (85% yield from **11**). In this case, after cleavage of the bulky Ts protecting groups, clean ^1H and ^{13}C NMR spectra were obtained for (R,R,R,R,R,R,R,R) -**6** which exhibited signals compatible with a clear D_4 symmetry in solution. This observation implies that no epimerization

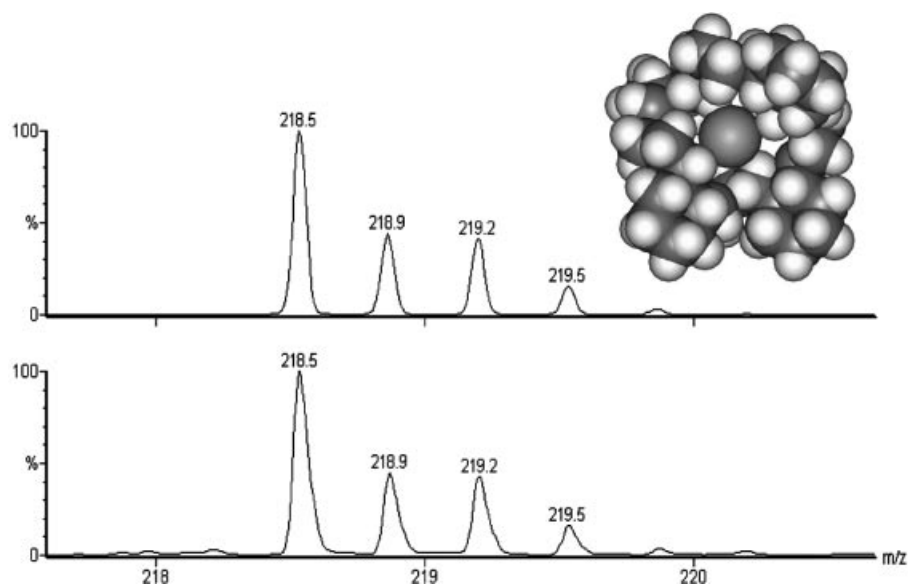


Figure 6. Experimental (lower trace) and simulated (upper trace) ESI-TOF spectra of an aqueous solution of the octahydrochloride of (R,R,R,R,R,R,R,R) -**6**, showing the base peak assigned to the $[\mathbf{6} \cdot 4\text{H}^+ + \text{Cl}]^{3+}$ species. A molecular model (Monte Carlo simulation with MMFFaq minimizations) is also shown in CPK representation.

process happened during our synthetic procedure as a change in the configuration of any chiral center of (*R,R,R,R,R,R,R,R*)-**6** would lead to a diastereomeric mixture with lower symmetry which would be clearly detectable in the NMR spectra by a larger number of anisochronic nuclei.

The potential applications of this macrocycle in anion recognition are evidenced in the ESI-TOF spectrum of an aqueous solution of the octahydrochloride of (*R,R,R,R,R,R,R,R*)-**6**, for which the base peak corresponds to the $[6\cdot 4H^+ + Cl^-]^{3+}$ species (Figure 6).^[24] Full isotopic analysis of accurate ESI-TOF experiments confirmed the assignment, suggesting that the main species in aqueous solution is the tetraprotonated chloride supramolecular complex, in good agreement with the expected basicity of **6**, its quaternary symmetry and very large cavity. Moreover, molecular modeling studies suggest that the chloride anion fits well inside the tetraprotonated macrocyclic cavity (see inset in Figure 6). Experiments towards applications of this receptor in chiral anion recognition are underway in our laboratories and will be reported in due course.

Conclusions

The selective alkylation of cyclohexane-1,2-bis(sulfonamide) has been studied in detail. The results obtained in solvents of different polarity have been efficiently correlated with the conformational preferences of the corresponding monoalkylated intermediates. Reactions carried out with different derivatives, NMR experiments and molecular modeling are in agreement with the presence of folded conformations in polar environments, in which the steric effect of the terminal Tr group prevents subsequent reaction of the nonalkylated sulfonamide. In more solvating media, more extended conformers prevail and this protection effect no longer exists, leading to the final dialkylated compound. Thus, by simply changing the solvent of the reaction, we can obtain either the mono- or dialkylated derivatives. Finally, this rationale has been used for the efficient synthesis of an enantiopure optically active large polyazamacrocycle.

Experimental Section

General: Reagents were purchased from Aldrich, Acros or Fluka and used without further purification. Solvents were purified by distillation with the appropriate drying agent. Specific rotations were measured with a Perkin–Elmer 241 apparatus. Mass spectra were performed with a HP-MS 1100 (ESI) or a MAT 95 (EI) spectrometer. NMR experiments were performed with a Bruker AC-300, a Bruker AC-300 DPX or a Varian UNITY 500 spectrometer. Molecular modeling calculations were performed using Spartan 04 software.^[25] To obtain the energy minima, the conformer distribution calculation option available in Spartan 04 was used. With this option, an exhaustive Monte Carlo search without constraints was performed for every structure. The torsion angles were randomly varied and the structures obtained fully optimized using either the MMFF or MMFFaq force fields in separate runs. Thus, 100 energy minima (for every run) within an energy gap of 10 kcal/mol were generated. These structures were analyzed and ordered according to the relative energy, with the repeated geometries being eliminated.

General Procedure for the Monoalkylation Reaction: In a flask under nitrogen, (*R,R*)-**1** (2 mmol, 0.844 g) and anhydrous K_2CO_3 (2.76 g, 20 mmol) were suspended in dry CH_3CN (12 mL) and the mixture heated to 70 °C for half an hour. Then, the corresponding electrophile (8 mmol) was added dropwise and the obtained mixture stirred at 70 °C for 2 days (TLC: AcOEt/hexane, 3:2). After that, the reaction was cooled to room temperature, acidified with 3 N HCl (15 mL) and extracted with CH_2Cl_2 . The combined organic layers were dried with Na_2SO_4 and the solvents evaporated to dryness. The final product was isolated by flash chromatography using the appropriate solvent mixture.

Compound (*R,R*)-2a: Yield 283 mg, 20%; white solid, m.p. 204–207 °C. $[α]_D^{20} = -15.8$ ($c = 0.41$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.31$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.71$ –1.74 (m, 8 H), 2.22–2.35 (m, 1 H), 2.40 (s, 3 H), 2.65–2.97 (m, 3 H), 3.13–3.34 (m, 2 H), 5.40 (d, $J = 5.4$ Hz, 1 H), 7.14 (d, $J = 8.1$ Hz, 2 H), 7.25–7.59 (m, 19 H), 7.82 (d, $J = 8.3$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 21.5 (CH_3), 23.9 (CH_2), 25.2 (CH_2), 30.8 (CH_2), 35.1 (CH_2), 41.7 (CH_2), 53.3 (CH), 59.7 (CH), 62.1 (CH_2), 86.5 (C), 126.6 (CH), 127.0 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 129.6 (CH), 129.6 (CH), 137.8 (C), 138.0 (C), 143.2 (C), 143.3 (C), 143.7 (C) ppm. MS (ESI): m/z (%) = 731.4 (40) $[M + Na]^+$. $C_{41}H_{44}N_2O_5S_2$ (708.4): C 69.46, H 6.26, N 3.95; found C 69.40, H 6.14, N 3.80.

Compound (*R,R*)-2b: Yield 1.01 g, 70%; white solid, m.p. 191–196 °C. $R_f = 0.31$ (CH_2Cl_2). $[α]_D^{20} = -31.2$ ($c = 0.95$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ –1.81 (m, 10 H), 2.20 (s, 3 H), 2.44 (s, 3 H), 2.50–2.86 (m, 3 H), 2.89–3.18 (m, 2 H), 3.24–3.48 (m, 1 H), 5.63 (d, $J = 4.6$ Hz, 1 H), 7.12–7.49 (m, 19 H), 7.68 (d, $J = 8.3$ Hz, 2 H), 7.80 (d, $J = 8.3$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 21.5 (CH_3), 24.1 (CH_2), 25.4 (CH_2), 30.4 (CH_2), 30.9 (CH_2), 35.3 (CH_2), 40.5 (CH_2), 54.1 (CH), 60.1 (CH), 60.9 (CH_2), 86.5 (C), 126.8 (CH), 127.1 (CH), 127.2 (CH), 127.8 (CH), 128.6 (CH), 129.6 (CH), 129.8 (CH), 137.9 (C), 138.2 (C), 142.9 (C), 143.5 (C), 143.9 (C) ppm. MS (ESI): m/z (%) = 745.2 (100) $[M + Na]^+$, 503.1 (70) $[M + Na - Tr]^+$. $C_{42}H_{46}N_2O_5S_2$ (722.4): C 69.78, H 6.41, N 3.87; found C 69.65, H 6.53, N 3.54.

Compound (*R,R*)-2c: Yield 1.18 g, 80%; white solid, m.p. 233–235 °C. $[α]_D^{20} = -37.9$ ($c = 0.43$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.42$ (1.1% AcOEt/ CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ –1.86 (m, 12 H), 2.34 (s, 3 H), 2.39 (s, 3 H), 2.74–3.08 (m, 2 H), 3.19–3.43 (m, 4 H), 5.71 (d, $J = 4.2$ Hz, 1 H), 7.08–7.53 (m, 19 H), 7.77 (d, $J = 7.9$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 21.5 (CH_3), 24.0 (CH_2), 25.3 (CH_2), 26.5 (CH_2), 27.0 (CH_2), 30.5 (CH_2), 35.4 (CH_2), 42.5 (CH_2), 53.8 (CH), 59.8 (CH), 62.1 (CH_2), 86.3 (C), 126.7 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 128.5 (CH), 129.5 (CH), 129.8 (CH), 137.9 (C), 138.0 (C), 142.8 (C), 143.4 (C), 144.1 (C) ppm. MS (ESI): m/z (%) = 581.3 (100) $[M - Ts]^+$. $C_{43}H_{48}N_2O_5S_2$ (736.4): C 70.08, H 6.56, N 3.80; found C 70.23, 6.66, N 3.58.

Compound (*R,R*)-2d: Yield 1.13 g, 75%; white solid, m.p. 160–162 °C. $[α]_D^{20} = -26.7$ ($c = 0.39$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.31$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ –1.74 (m, 14 H), 2.34 (s, 3 H), 2.41 (s, 3 H), 2.79–3.10 (m, 4 H), 3.19–3.39 (m, 2 H), 5.63 (d, $J = 4.2$ Hz, 1 H), 7.08–7.49 (m, 19 H), 7.62 (d, $J = 8.3$ Hz, 2 H), 7.80 (d, $J = 8.3$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 23.8 (CH_2), 24.0 (CH_2), 25.3 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 30.6 (CH_2), 35.2 (CH_2), 42.8 (CH_2), 54.0 (CH), 59.8 (CH), 63.2 (CH_2), 86.2 (C), 126.7 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 129.5 (CH), 129.7 (CH), 137.8 (C), 138.1 (C), 142.9 (C),

143.4 (C), 144.2 (C), 146.8 (C) ppm. MS (ESI): m/z (%) = 773.2 (40) $[M + Na]^+$, 509.2 (100) $[M - Tr]^+$. $C_{44}H_{50}N_2O_5S_2$ (750.4): C 70.37, H 6.71, N 3.73; found C 70.30, H 6.85, N 3.62.

Compound (R,R)-2c: Yield 1.04 g, 67%; white solid, m.p. 91–94 °C. $[a]_D^{20} = -35.2$ ($c = 0.62$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.25$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ – 1.91 (m, 16 H), 2.36 (s, 3 H), 2.42 (s, 3 H), 2.93–3.24 (m, 4 H), 3.27–3.46 (m, 2 H), 5.71 (d, $J = 4.6$ Hz, 1 H), 7.14–7.63 (m, 19 H), 7.67 (d, $J = 8.5$ Hz, 2 H), 7.83 (d, $J = 8.2$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$ (CH_3), 24.2 (CH_2), 25.5 (CH_2), 25.7 (CH_2), 27.0 (CH_2), 30.1 (CH_2), 30.7 (CH_2), 35.4 (CH_2), 43.0 (CH_2), 54.2 (CH), 60.0 (CH), 63.5 (CH_2), 87.2 (C), 126.9 (CH), 127.0 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH), 129.7 (CH), 129.9 (CH), 138.8 (C), 139.0 (C), 143.9 (C), 144.4 (C), 145.3 (C) ppm. MS (ESI): m/z (%) = 787.2 (100) $[M + Na]^+$. $C_{45}H_{52}N_2O_5S_2$ (764.4): C 70.65, H 6.85, N 3.66; found C 70.54, H 6.80, N 3.36.

Compound (R,R)-2f: Yield 1.17 g, 75%; white solid, m.p. 52–54 °C. $[a]_D^{20} = -30.3$ ($c = 0.60$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.30$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.76$ – 1.91 (m, 18 H), 2.40 (s, 6 H), 2.91–3.17 (m, 4 H), 3.26–3.43 (m, 2 H), 5.75 (d, $J = 4.1$ Hz, 1 H), 7.12–7.56 (m, 19 H), 7.68 (d, $J = 8.3$ Hz, 2 H), 7.83 (d, $J = 8.1$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.2$ (CH_3), 23.8 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 26.7 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 35.0 (CH_2), 42.7 (CH_2), 53.8 (CH), 59.6 (CH), 63.2 (CH_2), 86.0 (C), 126.5 (CH), 126.6 (CH), 126.9 (CH), 127.1 (CH), 127.4 (CH), 128.4 (CH), 129.4 (CH), 129.4 (C), 129.6 (C), 137.6 (C), 137.8 (C), 142.7 (C), 143.2 (C), 144.1 (C) ppm. MS (ESI): m/z (%) = 801.3 (45) $[M + Na]^+$, 559.2 (100) $[M + Na - Tr]^+$. $C_{46}H_{54}N_2O_5S_2$ (778.4): C 70.92, H 6.99, N 3.60; found C 70.73, H 7.15, N 3.50.

Compound (R,R)-2h: Yield 536 mg, 44%; white solid, m.p. 79–81 °C. $[a]_D^{20} = -45.3$ ($c = 0.49$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 1712\text{ cm}^{-1}$. $R_f = 0.11$ (CH_2Cl_2 :AcOEt, 90:5). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ – 1.37 (m, 6 H), 1.37–2.03 (m, 3 H), 2.18–2.34 (m, 1 H), 2.41 (s, 3 H), 2.42 (s, 3 H), 2.48–2.81 (m, 2 H), 2.88–3.19 (m, 1 H), 3.19–3.56 (m, 3 H), 5.56 (d, $J = 4.4$ Hz, 1 H), 7.30 (d, $J = 8.6$ Hz, 4 H), 7.63 (d, $J = 8.1$ Hz, 2 H), 7.70–7.91 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 23.9 (CH_2), 25.2 (CH_2), 29.0 (CH_2), 30.5 (CH_2), 35.2 (CH_2), 35.3 (CH_2), 40.4 (CH_2), 53.9 (CH), 59.9 (CH), 60.3 (CH_2), 127.1 (CH), 129.6 (CH), 129.8 (CH), 131.7 (C), 134.0 (CH), 137.32 (C), 137.9 (C), 143.1 (C), 143.6 (C), 168.0 (C) ppm. MS (ESI): m/z (%) = 632.1 (100) $[M + Na]^+$. $C_{31}H_{35}N_3O_6S_2$ (609.1): C 61.06, H 5.79, N 6.89; found C 61.36, H 5.99, N 6.80.

Compound (R,R)-2i: Yield 993 mg, 66%; white solid, m.p. 82–86 °C. $[a]_D^{20} = -45.4$ ($c = 0.83$, AcOEt). IR (KBr): $\tilde{\nu} = 3070\text{ cm}^{-1}$. $R_f = 0.15$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ – 1.52 (m, 6 H), 1.52–1.82 (m, 4 H), 2.19 (s, 3 H), 2.42 (s, 3 H), 2.48–2.65 (m, 1 H), 2.65–2.85 (m, 2 H), 2.85–3.16 (m, 2 H), 3.31–3.46 (m, 1 H), 3.81 (s, 3 H), 5.69 (d, $J = 4.4$ Hz, NH), 6.9 (d, $J = 8.9$ Hz, 2 H), 7.10–7.55 (m, 16 H), 7.68 (d, $J = 8.3$ Hz, 2 H), 7.8 (d, $J = 8.1$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$ (CH_3), 21.3 (CH_3), 23.9 (CH_2), 25.1 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 35.0 (CH_2), 40.3 (CH_2), 55.0 (CH), 59.9 (CH), 60.5 (CH_2), 86.0 (C), 112.9 (CH), 126.6 (CH), 126.7 (CH), 127.6 (CH), 127.5 (CH), 128.1 (CH), 129.4 (CH), 127.7 (CH), 130.0 (CH), 135.4 (C), 137.6 (C), 137.4 (C), 142.8 (C), 143.3 (C), 142.2 (C), 144.3 (C), 158.4 (C) ppm. MS (ESI): m/z (%) = 997.7 (60) $[M + Na]^+$, 776.32 (100) $[M + 1 + Na]^+$. $C_{43}H_{48}N_2O_6S_2$ (752.3): C 68.59, H 6.43, N 3.72; found C 68.42, H 6.65, N 3.50.

General Procedure for the Dialkylation Reaction: The reaction was carried out following the procedure used for monoalkylation but

in dry toluene. A catalytic amount of tetrabutylammonium chloride was also added to increase the solubility of the inorganic salt in toluene.

Compound (R,R)-3a: Yield 1.59 g, 80%; white solid, m.p. 100–104 °C. $[a]_D^{20} = -9.0$ ($c = 0.47$, AcOEt). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.63$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.79$ – 1.80 (m, 8 H), 2.40 (s, 6 H), 2.72–3.31 (m, 4 H), 3.32–3.67 (m, 3 H), 3.74–4.30 (m, 3 H), 6.80–8.17 (m, 38 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 25.0 (CH_2), 31.8 (CH_2), 43.3 (CH_2), 57.5 (CH), 62.6 (CH_2), 86.8 (C), 126.8 (CH), 127.1 (CH), 127.6 (CH), 128.5 (CH), 129.4 (CH), 138.7 (C), 142.7 (C), 143.9 (C) ppm. MS (ESI): m/z (%) = 1017.2 (100) $[M + Na]^+$. $C_{62}H_{62}N_2O_6S_2$ (994.4): C 74.73, H 6.48, N 2.60; found C 74.63, H 6.45, N 2.65.

Compound (R,R)-3b: Yield 1.47 g, 72%; white solid, m.p. 253–256 °C. $[a]_D^{20} = -33.2$ ($c = 0.25$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.63$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ – 1.42 (m, 2 H), 1.42–2.02 (m, 8 H), 2.02–2.24 (m, 2 H), 2.40 (s, 6 H), 2.84–3.53 (m, 8 H), 3.54–4.20 (m, 2 H), 6.90–7.61 (m, 34 H), 7.65–7.97 (d, $J = 8.1$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 25.3 (CH_2), 30.6 (CH_2), 31.8 (CH_2), 42.0 (CH_2), 58.4 (CH), 61.4 (CH_2), 86.3 (C), 126.8 (CH), 127.3 (CH), 127.6 (CH), 128.5 (CH), 129.4 (CH), 138.5 (C), 142.7 (C), 144.1 (C) ppm. MS (ESI): m/z (%) = 1023.3 (100) $[M + 1]^+$. $C_{64}H_{66}N_2O_6S_2$ (1022.7): C 75.11, H 6.50, N 2.74; found C 75.31, H 6.20, N 2.54.

Compound (R,R)-3c: Yield 1.62 g, 77%; white solid, m.p. 73–76 °C. $[a]_D^{20} = -11.8$ ($c = 0.58$, AcOEt). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.63$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.09$ – 2.08 (m, 16 H), 2.36 (s, 6 H), 2.88–3.38 (m, 8 H), 3.87–4.13 (m, 2 H), 6.95–7.59 (m, 34 H), 7.59–7.78 (d, $J = 7.9$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 25.3 (CH_2), 26.8 (CH_2), 27.7 (CH_2), 32.2 (CH_2), 44.3 (CH_2), 58.3 (CH), 62.8 (CH_2), 86.1 (C), 126.6 (CH), 127.2 (CH), 127.5 (CH), 128.5 (CH), 129.3 (CH), 139.0 (C), 142.7 (C), 144.1 (C), 144.2 (C) ppm. MS (ESI): m/z (%) = 1073.3 (90) $[M + 1 + Na]^+$. $C_{66}H_{70}N_2O_6S_2$ (1050.4): C 75.40, H 6.71, N 2.66; found C 75.55, H 6.54, N 2.64.

Compound (R,R)-3d: Yield 1.70 g, 79%; white solid, m.p. 71–75 °C. $[a]_D^{20} = -14.24$ ($c = 0.50$, AcOEt). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.63$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$ – 1.98 (m, 20 H), 2.42 (s, 6 H), 2.86–3.33 (m, 8 H), 3.87–4.17 (m, 2 H), 7.10–7.69 (m, 34 H), 7.80 (d, $J = 8.1$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 24.2 (CH_2), 25.3 (CH_2), 29.5 (CH_2), 29.9 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 58.4 (CH), 63.4 (CH_2), 86.1 (C), 126.7 (CH), 127.2 (CH), 127.5 (CH), 128.5 (CH), 129.4 (CH), 129.3 (CH), 138.9 (C), 142.8 (C), 142.8 (C), 144.3 (C) ppm. MS (ESI): m/z (%) = 1101.3 (20) $[M + Na]^+$. $C_{68}H_{74}N_2O_6S_2$ (1078.4): C 75.66, H 6.91, N 2.60; found C 75.60, H 6.80, N 2.60.

Compound (R,R)-3e: Yield 1.77 g, 80%; white solid, m.p. 74–77 °C. $[a]_D^{20} = -15.9$ ($c = 0.80$, AcOEt). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.63$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ – 1.96 (m, 24 H), 2.42 (s, 6 H), 2.82–3.28 (m, 8 H), 3.80–4.14 (m, 2 H), 7.07–7.63 (m, 34 H), 7.81 (d, $J = 7.9$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (CH_3), 25.4 (CH_2), 25.8 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 29.9 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 58.4 (CH), 63.4 (CH_2), 85.1 (C), 126.7 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 129.4 (CH), 138.9 (C), 142.8 (C), 144.4 (C) ppm. MS (ESI): m/z (%) = 1129.3 (40) $[M + Na]^+$. $C_{70}H_{78}N_2O_6S_2$ (1106.4): C 75.91, H 7.10, N 2.53; found C 75.74, H 7.05, N 2.64.

Compound (R,R)-3f: Yield 1.86 g, 82%; white solid, m.p. 57–60 °C. $[a]_D^{20} = -18.6$ ($c = 0.60$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3058\text{ cm}^{-1}$. $R_f = 0.52$ (CH_2Cl_2). 1H NMR (300 MHz, $CDCl_3$): $\delta = 0.65$ – 2.00 (m, 28 H), 2.41 (s, 6 H), 2.72–3.64 (m, 8 H), 3.73–4.06 (m, 2 H), 6.89–8.03

(m, 38 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.3 (CH_3), 25.4 (CH_2), 26.1 (CH_2), 27.4 (CH_2), 29.0 (CH_2), 29.9 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 58.4 (CH), 63.5 (CH_2), 86.2 (C), 126.7 (CH), 127.3 (CH), 127.6 (CH), 128.6 (CH), 129.4 (CH), 138.9 (C), 142.8 (C), 144.4 (C) ppm. MS (ESI): m/z (%) = 979.6 (100) $[\text{M} - \text{Ts}]^+$. $\text{C}_{72}\text{H}_{82}\text{N}_2\text{O}_6\text{S}_2$ (1134.6): C 76.15, H 7.28, N 2.47; found C 76.05, H 7.35, N 2.23.

Compound (R,R)-3h: Yield 446 mg, 28%; white solid, m.p. 83–85 °C. $[\alpha]_D^{20}$ = –45.87 (c = 0.92, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1711 cm^{-1} . R_f = 0.13 ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 90:5). ^1H NMR (300 MHz, CDCl_3): δ = 1.02–1.45 (m, 4 H), 1.47–1.78 (m, 5 H), 1.86–2.23 (m, 3 H), 2.37 (s, 6 H), 2.85–3.34 (m, 3 H), 3.41–3.69 (m, 4 H), 3.69–3.99 (m, 3 H), 7.21 (d, J = 8.1 Hz, 4 H), 7.63 (d, J = 8.0 Hz, 2 H), 7.66–7.96 (m, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.4 (CH_3), 25.3 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 36.0 (CH_2), 41.9 (CH_2), 58.5 (CH), 123.1 (CH), 127.3 (CH), 129.6 (CH), 132.1 (C), 133.7 (CH), 138.0 (C), 143.1 (C), 168.3 (C) ppm. MS (ESI): m/z (%) = 819.0 (100) $[\text{M} + \text{Na}]^+$. $\text{C}_{42}\text{H}_{44}\text{N}_4\text{O}_8\text{S}_2$ (796.3): C 63.30, H 5.56, N 7.03; found C 63.15, H 5.64, N 7.15.

Compound (R,R)-3i: Yield 476 mg, 22%; white solid, m.p. 85–87 °C. $[\alpha]_D^{20}$ = –28.36 (c = 0.46, AcOEt). IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1} . R_f = 0.35 (CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): δ = 1.09–2.26 (m, 12 H), 2.41 (s, 6 H), 2.83–3.48 (m, 8 H), 3.79 (s, 6 H), 3.94–4.11 (m, 2 H), 6.90 (d, J = 8.8 Hz, 4 H), 7.03–7.56 (m, 28 H), 7.78 (d, J = 8.1 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.4 (CH_3), 25.3 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 42.0 (CH_2), 55.1 (CH), 61.2 (CH_2), 86.0 (C), 112.8 (CH_3), 126.6 (CH), 127.3 (CH), 127.6 (CH), 128.3 (CH), 129.4 (CH), 130.2 (CH), 135.7 (C), 138.5 (C), 142.7 (C), 144.5 (C), 144.7 (C), 158.3 (C) ppm. MS (ESI): m/z (%) = 1105.03 (20) $[\text{M} + \text{Na}]^+$. $\text{C}_{66}\text{H}_{70}\text{N}_2\text{O}_8\text{S}_2$ (1082.4): C 73.17, H 6.51, N 2.59; found C 73.02, H 6.70, N 2.38.

Compound 5: This compound was obtained in acetonitrile following the procedure used for the monoalkylation reaction. Yield 1.55 g, 80%; white solid, m.p. 181–183 °C. R_f = 0.63 (CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): δ = 1.78–2.01 (m, 4 H), 2.43 (s, 6 H), 3.01–3.45 (m, 12 H), 7.07–7.91 (m, 38 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.4 (CH_3), 29.3 (CH_2), 47.3 (CH_2), 48.2 (CH_2), 60.7 (CH_2), 86.5 (C), 126.9 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 129.6 (CH), 135.8 (C), 143.3 (C), 144.0 (C) ppm. MS (ESI): m/z (%) = 992.2 (20) $[\text{M} + \text{Na}]^+$. $\text{C}_{60}\text{H}_{60}\text{N}_2\text{O}_6\text{S}_2$ (968.4): C 74.35, H 6.24, N 2.89; found C 74.50, H 6.40, N 2.75.

General Procedure for Tr Deprotection: The corresponding dinitrilylated compound (0.62 mmol, 1.2 g) was dissolved in dry CH_2Cl_2 (20 mL) then MeOH (12 mL) and trifluoroacetic acid (3.71 mmol, 0.275 mL) were added. The reaction mixture was stirred until the starting material had disappeared (TLC monitoring). The crude was evaporated and the final product purified by flash chromatography.

Compound (R,R)-3g showed the correct spectroscopic and analytical data.^[10d]

Compound (R,R,R,R,R)-9: Yield 562 mg, 62%; white solid, m.p. 123–125 °C. $[\alpha]_D^{20}$ = –1.50 (c = 0.55, CHCl_3). R_f = 0.12 ($\text{AcOEt}/\text{hexane}$, 2:1). ^1H NMR (300 MHz, CDCl_3): δ = 0.83–1.63 (m, 22 H), 1.83–2.17 (m, 10 H), 2.32 (s, 18 H), 2.45–2.70 (m, 2 H), 2.70–3.27 (m, 11 H), 3.63–3.96 (m, 9 H), 6.89–7.38 (m, 12 H), 7.38–7.98 (m, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.3 (CH_3), 24.7 (CH_2), 25.0 (CH_2), 29.8 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 33.3 (CH_2), 40.8 (CH_2), 40.6 ($2\times\text{CH}_2$), 58.3 (CH), 58.6 (CH), 59.3 (CH), 60.2 ($2\times\text{CH}_2$), 127.1 (CH), 129.2 (CH), 129.3 (CH), 137.5 (C), 137.8 (C), 138.4 (C), 142.5 (C), 142.8 (C) ppm. MS (ESI): m/z (%) = 1484.7 (20) $[\text{M} + \text{Na}]^+$. $\text{C}_{72}\text{H}_{98}\text{N}_4\text{O}_{14}\text{S}_6$ (1462.6): C 59.07, H 6.75, N 5.74; found C 59.24, H 6.90, N 5.52.

General Procedure for the Mesylation Reaction: Mesyl chloride (0.105 mL, 1.35 mmol) was added dropwise to a solution of the corresponding diol (0.4 mmol, 0.584 g) in dry CH_2Cl_2 (5 mL) and dry Et_3N (0.2 mL, 1.43 mmol) at 0 °C. Once the starting diol had been consumed (TLC monitoring) the solvent was evaporated and the product purified by flash chromatography.

Compound (R,R)-7 showed the correct spectroscopic and analytical data, as described previously.^[10d]

Compound (R,R,R,R,R)-10: Yield 557 mg, 86%; white solid, m.p. 133–135 °C. $[\alpha]_D^{20}$ = –15.29 (c = 0.49, CHCl_3). R_f = 0.31 ($\text{AcOEt}/\text{hexane}$, 1:1). ^1H NMR (300 MHz, CDCl_3): δ = 0.70–1.68 (m, 27 H), 1.84–2.11 (m, 3 H), 2.11–2.55 (m, 20 H), 2.66–3.34 (m, 15 H), 3.56–4.44 (m, 10 H), 6.89–7.46 (m, 12 H), 7.46–7.95 (m, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.3 (CH_3), 24.7 (CH_2), 24.9 (CH_2), 25.1 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 36.9 (CH_3), 40.8 (CH_2), 41.5 (CH_2), 58.3 (CH), 58.6 (CH), 59.3 (CH), 60.1 (CH_2), 69.0 ($2\times\text{CH}_2$), 127.2 (CH), 129.4 (CH), 129.5 (CH), 129.6 (CH), 137.5 (C), 137.6 (C), 138.5 (C), 142.7 (C), 143.0 (C), 143.2 (C) ppm. MS (ESI): m/z (%) = 1639.2 (20) $[\text{M} + \text{H}_2\text{O}]^+$. $\text{C}_{74}\text{H}_{102}\text{N}_6\text{O}_{18}\text{S}_8$ (1618.5): C 54.86, H 6.35, N 5.19; found C 54.55, H 6.20, N 5.05.

Coupling of (R,R)-7 with Two Equivalents of (R,R)-2b: Synthesis of (R,R,R,R,R)-8: In a flask maintained under nitrogen, (R,R)-2b (2.4 mmol, 1.73 g), Cs_2CO_3 (11.8 mmol, 3.85 g) and a catalytic amount of tetrabutylammonium chloride were suspended in dry toluene (72 mL). The mixture was stirred and heated at 70 °C for half an hour and after that (R,R)-7 (1.2 mmol, 0.83 g) dissolved in toluene (3 mL) was added dropwise. The reaction was stirred at 70 °C for 5 days, the solvent was evaporated and the product isolated after chromatographic purification using 2.5% ethyl acetate in CH_2Cl_2 as eluent to yield compound (R,R,R,R,R)-8. Yield 1.40 g, 60%; white solid, m.p. 208–211 °C. $[\alpha]_D^{20}$ = +26.8 (c = 0.46, AcOEt). R_f = 0.88 (CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): δ = 0.90–1.93 (m, 28 H), 1.93–2.25 (m, 4 H), 2.44 (m, 18 H), 2.80–3.41 (m, 16 H), 3.68–4.15 (m, 6 H), 6.91–7.55 (m, 42 H), 7.55–7.95 (m, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.4 (CH_3), 25.0 ($2\times\text{CH}_2$), 25.4 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 41.8 ($2\times\text{CH}_2$), 58.1 (CH), 58.4 (CH), 58.9 (CH), 61.4 ($2\times\text{CH}_2$), 86.3 (C), 126.8 (CH), 127.3 (CH), 127.6 (CH), 128.6 (CH), 129.4 (CH), 138.3 (C), 138.6 (C), 138.9 (C), 142.7 (C), 144.1 (C) ppm. MS (ESI): m/z (%) = 997.7 (20) $[\text{M} + 2\text{Na}]^+$, 1969.7 (10) $[\text{M} + \text{Na}]^+$. $\text{C}_{110}\text{H}_{126}\text{N}_6\text{O}_{14}\text{S}_6$ (1946.8): C 67.80, H 6.52, N 4.31; found C 67.60, H 6.42, N 4.20.

Cyclization Reaction: Synthesis of (R,R,R,R,R)-11: In a flask maintained under nitrogen, (R,R)-1 (0.215 mmol, 0.09 g) was dissolved in dry acetonitrile (7 mL) and CS_2CO_3 (2.1 mmol, 0.7 g) was added and the mixture heated at 70 °C for half an hour. Then a solution of (R,R,R,R,R)-10 (0.215 mmol, 0.314 g) in acetonitrile was added dropwise and the resulting mixture stirred at 70 °C for 5 days. After this time, the solvent was evaporated and the macrocyclic tosylated polyamine (R,R,R,R,R)-11 was purified by flash chromatography using 7% ethyl acetate in dichloromethane as eluent. Yield 294 mg, 74%; white solid, m.p. 210–212 °C. $[\alpha]_D^{20}$ = –9.3 (c = 0.48, CHCl_3). R_f = 0.14 ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 7:1). ^1H NMR (300 MHz, CDCl_3): δ = 0.99–1.74 (m, 32 H), 1.80–2.22 (m, 8 H), 2.29–2.45 (m, 21 H), 2.79–3.30 (m, 16 H), 3.76–4.08 (m, 8 H), 7.08–7.45 (m, 16 H), 7.58–8.00 (m, 16 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.3 (CH_3), 25.0 (CH_2), 30.7 (CH_2), 41.7 (CH_2), 58.3 (CH), 127.3 (CH), 129.4 (CH), 138.7 (C), 142.6 (C) ppm. MS (ESI-TOF): calcd. for $\text{C}_{92}\text{H}_{122}\text{N}_8\text{O}_{17}\text{S}_8\text{Na}_2^{2+}$ ($[\text{M} + 2\text{Na} + \text{H}_2\text{O}]^{2+}$, 100%): 956.3244; found 952.3236; calcd. for

C₉₂H₁₂₀N₈O₁₆S₈Na₂²⁺ ([M + 2Na]²⁺, 10%): 947.3191; found 947.3217.

Detosylation Procedure: Synthesis of (R,R,R,R,R,R)-6: In a flask, (R,R,R,R,R,R,R,R)-11 (0.1 mmol, 0.185 g), phenol (24.4 mg 0.259 mmol) and 48% aqueous HBr (2.6 mL) were mixed and heated at 110 °C for 8 days. Then the reaction solvent was extracted with CH₂Cl₂ and water and the organic layers discarded. The aqueous phase was basified with 1 N NaOH and extracted again with CH₂Cl₂ (3 × 15 mL). This organic fraction was dried and the solvent evaporated to dryness. The resulting product was dissolved in MeOH and acidified with concentrated HCl. The final title compound was thus isolated as the octahydrochloride salt by recrystallization. Yield 77 mg, 85%; pale yellow hygroscopic solid, decomposes without melting. [α]_D²⁰ = −60.8 (c = 0.37, H₂O). ¹H NMR (300 MHz, D₂O): δ = 1.00–1.25 (m, 8 H), 1.25–1.50 (m, 8 H), 1.50–1.70 (m, 8 H), 1.85–2.15 (m, 16 H), 3.00 (m, 8 H), 3.22 (m, 8 H), 3.35 (m, 8 H) ppm. ¹³C NMR (75 MHz, D₂O): δ = 21.5 (CH₂), 22.9 (CH₂), 25.4 (CH₂), 42.7 (CH₂), 57.6 (CH) ppm. MS (ESI-TOF): calcd. for C₃₆H₇₆ClN₈³⁺ ([M + 4H + Cl]³⁺, 100%): 218.5294; found 218.5275.

Acknowledgments

Financial support from the Spanish Ministerio de Educación y Ciencia (MEC, project CTQ-2004-04185) and the Principado de Asturias (IB05-04) is grateful acknowledged. I. A. also thanks MEC for personal financial support (Ramón y Cajal program).

- [1] See for instance: a) J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, 1949–1964 and references cited therein; b) S. Höger, *Angew. Chem. Int. Ed.* **2005**, *44*, 3806–3808; c) K.-Y. Yeung, I. Patterson, *Angew. Chem. Int. Ed.* **2002**, *41*, 4632–4653; d) R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2000**, *39*, 2054–2070.
- [2] V. N. Uversky, *Protein Sci.* **2002**, *11*, 739–756.
- [3] a) R. Gray, J. O. Trent, *Biochemistry* **2005**, *44*, 2469–2477; b) S. Jusuf, P. H. Axelsen, *Biochemistry* **2004**, *43*, 15446–15452; c) M. Jourdan, M. S. Searle, *Biochemistry* **2001**, *40*, 10317–10325.
- [4] a) N. Kurt, S. Cavagnero, *J. Am. Chem. Soc.* **2005**, *127*, 15690–15691 and references cited therein; b) K. A. Dill, *Biochemistry* **1990**, *29*, 7133–7155.
- [5] W. Saenger, *Principles of Nucleic Acid Structure* (Ed.: C. R. Cantor), Springer Verlag, New York, **1984**.
- [6] a) R. D. Gray, J. O. Trent, *Biochemistry* **2005**, *44*, 2469–2477; b) P. B. Harbury, P. S. Kim, T. Alber, *Nature* **1994**, *371*, 80–83; c) P. B. Harbury, T. Zhang, P. S. Kim, T. Alber, *Science* **1993**, *262*, 1401–1407.
- [7] a) M. F. Perutz, J. T. Finch, J. Berriman, A. Lesk, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5591–5595; b) B. C. F. Chu, L. E. Orgel, *Biochem. Biophys. Res. Commun.* **2001**, *283*, 351–355; c) Y. Trottier, Y. Lutz, G. Stevanin, G. Imbert, D. Devys, G. Cancel, F. Saudou, C. Weber, G. David, L. Tora, Y. Agid, A. Brice, J. L. Mandel, *Nature* **1995**, *378*, 403–406.
- [8] a) L. R. Pratt, A. Pohorille, *Chem. Rev.* **2002**, *102*, 2671–2691; b) R. W. Pastor, R. M. Venable, S. E. Feller, *Acc. Chem. Res.* **2002**, *35*, 438–446; c) Y. Okahata, *Acc. Chem. Res.* **1986**, *19*, 57–63.
- [9] a) M. T. Stone, J. M. Heemstra, J. S. Moore, *Acc. Chem. Res.* **2006**, *39*, 11–20; b) U. M. Lindström, F. Anderson, *Angew. Chem. Int. Ed.* **2006**, *45*, 548–551; c) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312–1317; d) I. Huc, *Eur. J. Org. Chem.* **2004**, 17–29; e) M. Inouye, M. Waki, H. Abe, *J. Am. Chem. Soc.* **2004**, *126*, 2022–2027; f) J. Becerril, M. Bolte, M. I. Burguete, F. Galindo, E. García-España, S. V. Luis, J. F. Miravet, *J. Am. Chem. Soc.* **2003**, *125*, 6677–6686; g) S. Otto, J. B. F. N. Engberts, *Org. Biomol. Chem.* **2003**, *1*, 2809–2820.
- [10] a) A. González-Álvarez, M. Rubio, I. Alfonso, V. Gotor, *Tetrahedron: Asymmetry* **2005**, *16*, 1361–1365; b) A. González-Álvarez, I. Alfonso, F. López-Ortiz, A. Aguirre, S. García-Granda, V. Gotor, *Eur. J. Org. Chem.* **2004**, 1117–1127; c) I. Alfonso, F. Rebolledo, V. Gotor, *Chem. Eur. J.* **2000**, *6*, 3331–3338; d) I. Alfonso, F. Rebolledo, V. Gotor, *Tetrahedron: Asymmetry* **1999**, *10*, 367–374; e) I. Alfonso, C. Astorga, F. Rebolledo, V. Gotor, *Tetrahedron: Asymmetry* **1999**, *10*, 2515–2522.
- [11] a) A. Luna, I. Alfonso, V. Gotor, *Org. Lett.* **2002**, *4*, 3627–3629; b) I. Alfonso, C. Astorga, F. Rebolledo, V. Gotor, *Chem. Commun.* **1996**, 2471–2472.
- [12] For examples from our group, see: a) A. González-Álvarez, I. Alfonso, P. Díaz, E. García-España, V. Gotor, *Chem. Commun.* **2006**, 1227–1229; b) I. Alfonso, B. Dietrich, F. Rebolledo, V. Gotor, J.-M. Lehn, *Helv. Chim. Acta* **2001**, *84*, 280–295; for some selected examples from other researchers, see: c) I. Stibor, P. Zlatuskova, *Top. Curr. Chem.* **2005**, *255*, 31–63; d) A. Ragusa, S. Rossi, J. M. Hayes, M. Stein, J. K. Kilburn, *Chem. Eur. J.* **2005**, *11*, 5674–5688; e) A. M. Piatek, Y. J. Bomble, S. L. Wiskur, E. V. Anslyn, *J. Am. Chem. Soc.* **2004**, *126*, 6072–6077; f) C. Miranda, F. Escartí, L. Lamarque, M. J. Yunta, P. Navarro, E. García-España, M.-L. Jimeno, *J. Am. Chem. Soc.* **2004**, *126*, 823–833; g) J. J. Lavigne, E. V. Anslyn, *Angew. Chem. Int. Ed.* **1999**, *38*, 3666–3669; h) J. L. Sessler, A. Andrievsky, V. Král, V. Lynch, *J. Am. Chem. Soc.* **1997**, *119*, 9385–9392.
- [13] C. Peña, I. Alfonso, N. H. Voelcker, V. Gotor, *Tetrahedron Lett.* **2005**, *46*, 2783–2787.
- [14] M. Kaik, J. Gawronsky, *Tetrahedron: Asymmetry* **2003**, *14*, 1559–1563.
- [15] For applications of unsymmetrically substituted ligands, see: a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071–3100.
- [16] a) J. E. W. Scheuermann, E. S. Bento, G. E. Hawkes, M. Watkinson, *Magn. Reson. Chem.* **2005**, *43*, 321–325; b) J. Sandström in *Dynamic NMR Spectroscopy*, Academic Press, London, **1982**.
- [17] B. K. Vriesema, J. Buter, R. M. Kellogg, *J. Org. Chem.* **1984**, *49*, 110–113.
- [18] a) J. A. Bender, N. A. Meanwell, T. Wang, *Tetrahedron* **2002**, *58*, 3111–3128; b) V. Kuksa, R. Buchan, P. K. T. Lin, *Synthesis* **2000**, 1189–1207; c) G. Karigiannis, D. Papaioannou, *Eur. J. Org. Chem.* **2000**, 1841–1863.
- [19] Several 1D and 2D NOESY experiments were performed on all the monoalkylated derivatives in different solvents and by using varied mixing times, giving similar results. As suggested by one referee, we have selected one example carried out in CD₃CN, although the ¹H NMR spectrum shows a complicated pattern due to the presence of a mixture of conformations in solution.
- [20] D. Neuhaus, M. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH, New York, **1989**.
- [21] For recent examples of aromatic interactions governing conformations, see: a) Y. Du, C. J. Creighton, Z. Yan, D. A. Gauthier, J. P. Dahl, B. Zhao, S. M. Belkowski, A. B. Reitz, *Bioorg. Med. Chem.* **2005**, *13*, 5936–5948; b) P. Bello, N. J. Heaton, A. Chana, J. Jiménez-Barbero, E. Riande, B. Herradón, *J. Phys. Org. Chem.* **2004**, *17*, 71–82.
- [22] One referee suggested that for the interpretation of our results, the Curtin–Hammett principle should be kept in mind, which states that usually it is not the stabilities of the conformers that determine the products, but rather their individual reaction rates. Thus, products are often formed entirely from less stable conformers. However, we tried to explain our experimental results by proposing a reasonable model, and considering the molecular mechanics analysis, our model reflects the trends observed experimentally. For a review on the Curtin–Hammett principle applied to conformation and reactivity, see: J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83–134.

- [23] J. E. Richman, T. J. Atkins, *J. Am. Chem. Soc.* **1974**, *96*, 2268–2270.
 [24] a) A. Di Tullio, S. Reale, F. De Angelis, *J. Mass Spectrom.* **2005**, *40*, 845–865; b) I. Alfonso, C. Astorga, V. Gotor, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *53*, 131–137.

[25] Spartan 04, Wavefunction Inc., Irvine, CA.

Received: March 16, 2006

Published Online: June 21, 2006