Bis-Heteronucleophilic Michael Addition to Divinyl Sulfone: A New Efficient Access to Macrocycles

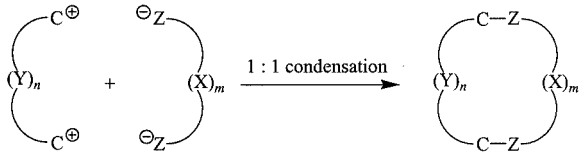
Marie-Laure Teyssot,[a] Martine Fayolle,[a] Christian Philouze,[b] and Claude Dupuy*[a]

Keywords: Michael addition / Synthetic methods / Macrocycles / Cryptands / Sulfones

The Michael addition of bis(nitrogen or sulfur) nucleophiles to divinyl sulfone provides the corresponding macrocyclic adducts in good yields. The structures of some new macrocyclic sulfones are established by X-ray crystallographic analysis and NMR spectroscopy. The subsequent cleavage of benzyl or tosyl groups yields the unprotected macrocyclic sulfones.

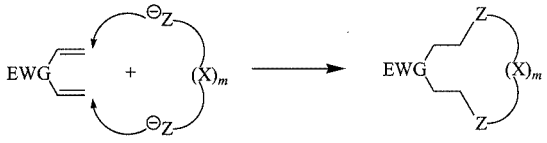
Introduction

Syntheses of macrocyclic compounds which contain nine or more atoms in the ring, including at least three heteroatoms, have been known for a long time.[1−5] The condensation of two bifunctional fragments is the most usual strategy for the construction of the macrocyclic system. Nearly all the syntheses using this approach link nucleophilic heteroatoms (Z = N, O, S) with electrophilic carbon atoms (Scheme 1).



Scheme 1. Construction of a macrocyclic compound from two fragments

The electrophilic centre is a primary carbon atom bearing a good leaving group such as iodide, sulfonate or a carboxylic function. In the course of our studies of new access to macrocyclic compounds,[6] we planned the preparation of macrocycles by bis-heteronucleophilic addition to bis-Michael acceptors (Scheme 2; EWG = electron-withdrawing group).



Scheme 2. A new strategy to obtain macrocycles from bis-Michael acceptors

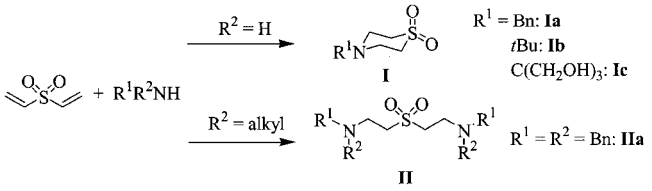
Conjugate addition is an important bond-forming strategy applied in organic synthesis.[7] The heteronucleophilic addition to bis-Michael acceptors[8] and the intramolecular Michael reaction[9] have been used to obtain cyclic compounds, usually five- or six-membered rings. Some diaza- and oxaazacyclooctenes or -cyclononenes were also prepared from 2,3-bis(phenylsulfonyl)-1,3-butadiene by addition of various nucleophiles.[10] More recently, Pietrusiewicz et al. have presented the synthesis of macrocyclic systems containing phosphorus and sulfur, based on a double conjugate addition of dithiolates to vinylphosphane oxides and sulfides as Michael acceptors.[11]

Results and Discussion

In this paper we report our results on the bis-heteronucleophilic Michael addition to divinyl sulfone (EWG = SO_2). The two vinyl groups of this commercially available compound are well known to be activated toward heteronucleophilic additions including reactions with amines,[12−21] alcohols,[20,22] thiols,[20,22−24] phosphanes[25] and sodium peroxide.[26] With primary amines, the usual product is the thiomorpholine 1,1-dioxide derivative. Vinyl sulfones have become generally accepted as useful intermediates in organic synthesis.[27−29] They serve efficiently as both Michael acceptors and as 2π partners in cycloaddition reactions.

[a] Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité (LEDSS 4), UMR CNRS 5616, Université J. Fourier, B. P. 53, 38041 Grenoble Cedex 9, France
Fax: (internat.) + 33-4/76514927
E-mail: Claude.Dupuy@ujf-grenoble.fr
[b] Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité (Service de crystallographie), UMR CNRS 5616, Université J. Fourier,
B. P. 53, 38041 Grenoble Cedex 9, France

First with a nitrogen atom as the nucleophile, we tried to find the optimal experimental conditions for the intermolecular addition of primary and secondary benzylamines (Scheme 3).



Scheme 3. Aza-Michael addition of various amines to divinyl sulfone

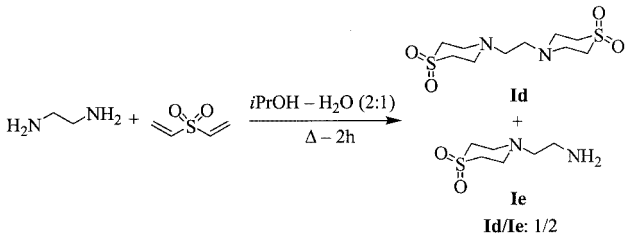
The best results were obtained with protic solvents such as methanol, propan-2-ol or a water/propan-2-ol mixture after 2 h of reflux (Table 1). This can be explained by an easier and faster proton transfer on the enolate-type structure formed after the addition.[30] We chose propan-2-ol instead of methanol because, in some cases, we observed the formation of a methanol addition product. This side reaction has been confirmed by refluxing divinyl sulfone in methanol in the presence of triethylamine: 37% of the methanol adduct are detected after 3 h.

Table 1. Intermolecular additions of benzylamine and dibenzylamine to divinyl sulfone

Solvent[a]	$BnNH_2$ (**Ia**)		Bn_2NH (**IIa**)	
	Room temp.	Reflux	Room temp.	Reflux
MeOH	100	100	84	85
*i*PrOH	77	100	88	89
*i*PrOH/H_2O (2:1)	98	100	93	93
Toluene	58	30[b]	61	59
CH_2Cl_2	48	33[b]	84	85

[a] Reflux time: 2 h; yield of isolated compound. [b] With monoadduct.

The primary amines give exclusively the cyclic adduct even when they are neopentylic like in *tert*-butylamine (**Ib**; 90%; *i*PrOH) and in aminotris(hydroxymethyl)methane (**Ic**; 94%; *i*PrOH). In order to confirm these results with the same conditions as for macrocyclization, we added ethylenediamine to divinyl sulfone. This reaction afforded only six-membered rings as shown in Scheme 7. Only compound **Id** has been isolated but the presence of **Ie** was proved by mass, IR, ^1H and ^{13}C NMR spectra of the crude



Scheme 4. Aza-Michael addition of ethylenediamine to divinyl sulfone

reaction mixture (Scheme 4). The ratio of the two compounds has been calculated on the basis of integration in the ^1H NMR spectrum. After the first addition of the primary amine, the resulting secondary amine undergoes a six-membered ring closure which is faster than a second addition of a primary amine. This 6-*endo*-trig cyclization is favored according to Baldwin's rules.[31]

Since primary amines provide only the thiomorpholine 1,1-dioxide derivatives, it can be concluded that we need to add secondary amines in order to favor the bis(aza-Michael) addition to divinyl sulfone (Scheme 2). That is why we used various bis-secondary amines **1**−**8** and bis(sulfonamides) **9**−**11** (Figure 1). This diversity will allow the preparation of macrocycles with different sizes.

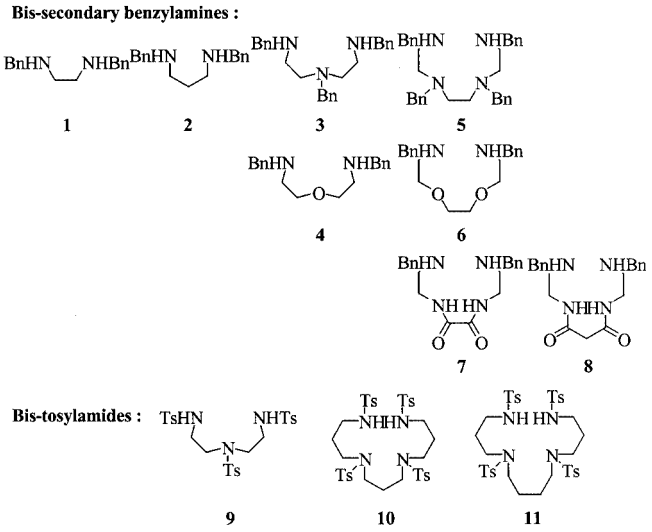
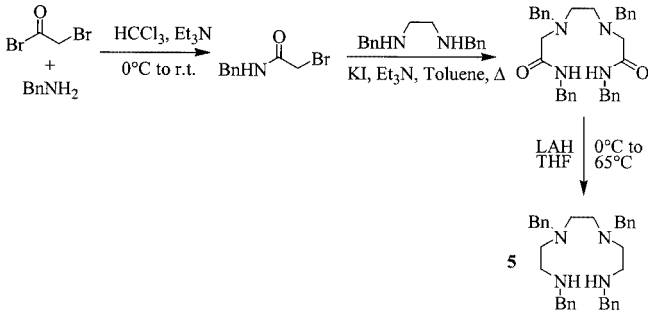


Figure 1. Utilized bis-secondary amines and tosylamides

N,*N*′-Dibenzylethylenediamine (**1**) is a commercially available product. The monoalkylation of a primary polyamine is not easy. It often requires an excess of a reactant. In order to use a simple way to obtain compounds **2** and **6**, we chose the reductive amination of benzaldehyde with the corresponding polyamine in the presence of sodium triacetoxyborohydride,[32] which appeared to give good yields of monoalkylation.

While compound **3** was easily synthesized by a two-step sequence from diethylenetriamine by benzoylation followed by reduction with a global yield of 58%, this method did not succeed for triethylenetetraamine. Thus, *N*,*N*′,*N*″,*N*‴-tetrabenzyltriethylenetetraamine (**5**) was obtained with an overall yield of 20% using a three-step sequence[33] (Scheme 5).

Diamine **4** was obtained in good yield according to a previously published method.[34] The reaction of *N*-benzylethylenediamine with diethyl oxalate[35] and diethyl malonate[36] provided the bis(amidobenzylamines) **7** and **8**, respectively. Standard tosylation methods gave the tosylated compounds **9**, **10** and **11** from the corresponding amines.[37]



Scheme 5. Synthesis of *N*,*N*′,*N*′′,*N*′′′-tetrabenzyltriethylenetetraamine (**5**)

Aza-Michael additions of bis-secondary benzylamines on divinyl sulfone were carried out under the optimal experimental conditions for intermolecular addition, i.e. in a refluxing water/propan-2-ol (1:2) mixture. Reaction times were determined by monitoring the disappearance of divinyl sulfone by ^{1}H NMR spectroscopy. These reactions afford new *S*,*S*-dioxothiaaza or *S*,*S*-dioxooxathiaaza macrocycles **1a**−**8a** generally with high yields (Figure 2). They vary in size from nine- to sixteen-membered rings and include diverse heteroatoms. Compounds **7a** and **8a** are of particular interest because they could be selectively deprotected and therefore substituted by different groups in order to change their properties.

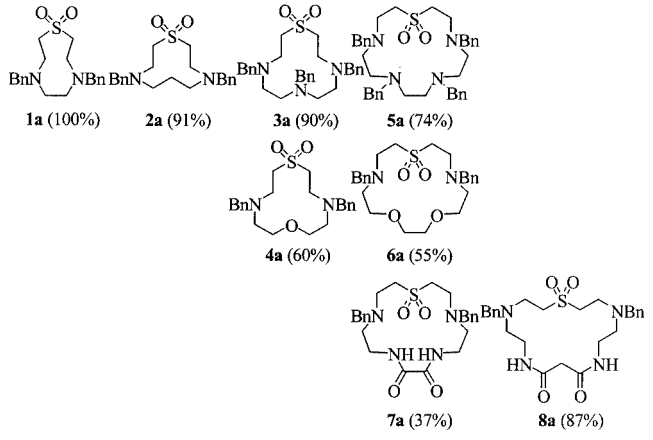
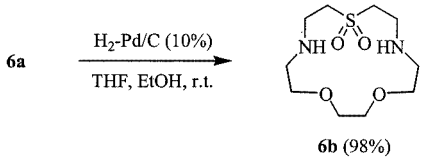


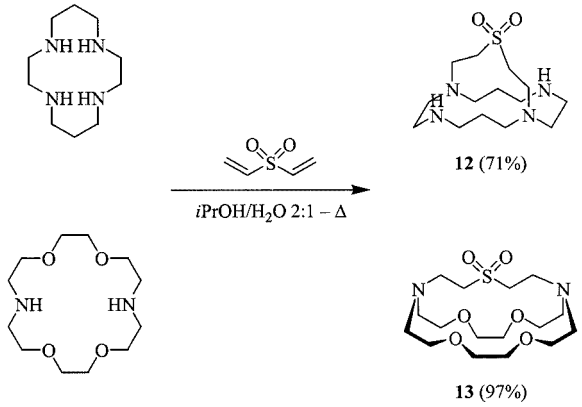
Figure 2. New *S*,*S*-dioxothia macrocycles from divinyl sulfone and bis-secondary amines

Benzyl groups can be easily removed by hydrogenolysis, for example 1,4-dioxa-10-thia-7,13-diazacyclopentadecane 10,10-dioxide (**6b**) was obtained in 98% yield (Scheme 6).



Scheme 6. Cleavage of benzyl groups in an *S*,*S*-dioxothia macrocycle

The two cryptands **12** and **13** were also prepared by the same method from commercially available cyclam (1,4,7,10-tetraazacyclotetradecane) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, respectively (Scheme 7).



Scheme 7. Cryptands from commercially available macrocycles

Concerning the aza-addition of tosylated polyamines, we used the same standard conditions as for the macrocyclic formation by bis-nucleophilic substitution, potassium carbonate as base in refluxing acetonitrile. By this method, we managed to obtain three new polyaza macrocyclic sulfones **9a**, **10a** and **11a** with excellent yields (Figure 3). With macrocycle **11a**, removal of the tosyl groups was achieved in an 87% yield using the HBr/AcOH/PhOH system[38] (Scheme 8).

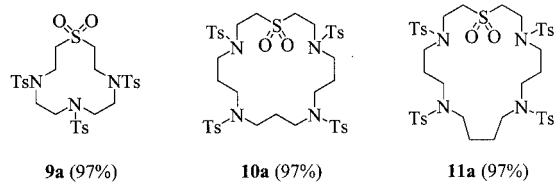
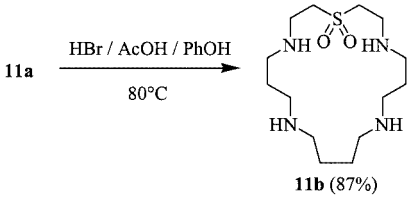


Figure 3. New *S*,*S*-dioxothia macrocycles from divinyl sulfone and bis(sulfonamides)



Scheme 8. Cleavage of tosyl groups

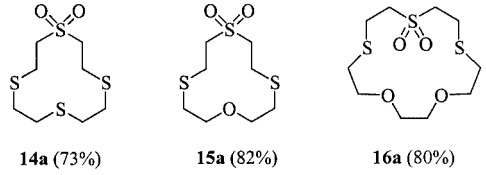


Figure 4. New thia and oxathia macrocyclic sulfones from divinyl sulfone and bis(thiols)

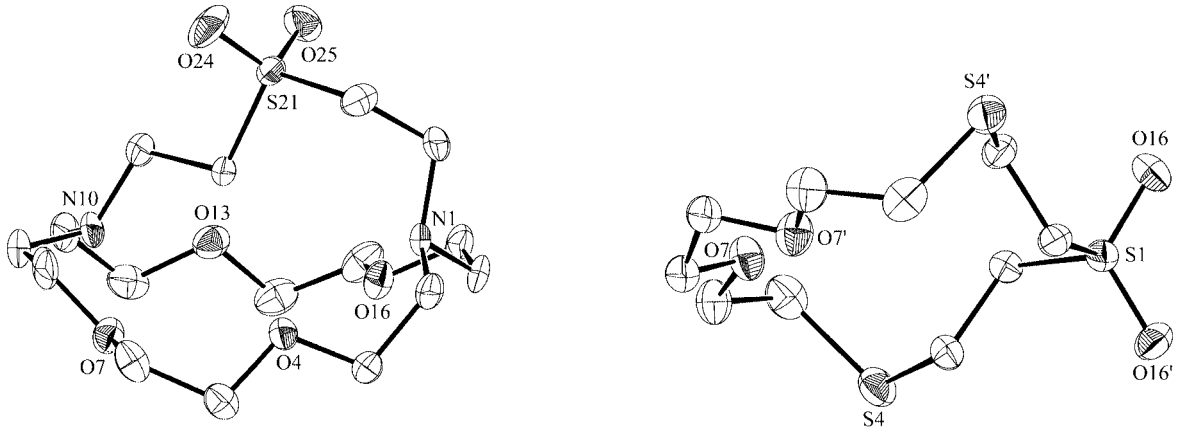


Figure 5. ORTEP drawings of the crystal structures of compounds **13** and **16a**

Previous studies have shown that thiols, in the presence of a base, react with divinyl sulfone to give the monoadduct[23] and/or the diadduct[20] according to experimental conditions. As for amines, we first tried to add phenylmethanethiol to divinyl sulfone in the presence of triethylamine[39] in a water/propan-2-ol mixture (pH = 8−9). This reaction afforded 98% of the diadduct. We applied these experimental conditions to the following commercially available thiols: bis(2-mercaptoethyl) sulfide (**14**), bis(2-mercaptoethyl) ether (**15**) and 4,7-dioxa-1,10-dithiadecane (**16**). As expected, the thia or oxathia macrocyclic sulfones **14a**, **15a** and **16a** were obtained in good yields (Figure 4).

The Michael addition is reversible. The retro-Michael reaction can occur mainly in the presence of a base. For example, this reaction is used to cleave products prepared on sulfonyl resins.[40] It is noteworthy that, in our case, no retro-reaction was observed even in the presence of butyllithium when we performed α-alkylation experiments or by refluxing the cyclic Michael adduct **Ia** overnight in a propan-2-ol/20% aqueous NaOH mixture. Furthermore, these macrocyclic sulfones remain unchanged on silica gel, although this technique has been used to generate conjugate systems,[41] or in acidic media like for the cleavage of tosyl groups (Scheme 8).

All the new macrocycles were characterized by NMR spectroscopy (^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC) and for some of them (**2a**, **9a**, **13**, **16a**), the isolated crystals were suitable for crystal structure analysis.[42] The structures obtained for cryptand **13** and macrocycle **16a** are presented in Figure 5.

Conclusion

In summary, a facile synthesis of macrocyclic sulfones has been reported. The aza- or thia-Michael addition to divinyl sulfone opens up an efficient approach to a great variety of macrocycles. Their complexation ability is under investigation. We also expand this strategy to other bis-Michael acceptors such as divinyl ketone or aryl(vinyl)-phosphane oxides.[43]

Experimental Section

General Remarks: All chemicals were used as purchased unless otherwise noted. Tetrahydrofuran was distilled under argon from sodium/benzophenone ketyl. Acetonitrile and toluene were dried with 4-Å molecular sieves prior to use. Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60F_{254} aluminum sheets and spots were visualized using a UV lamp (254 nm), iodide and/or a phosphomolybdic acid solution (5% in ethanol). Liquid column chromatography and flash column chromatography were performed using Merck silica gel 60 (0.06−0.2 mm) and Merck silica gel 60 (0.04−0.06 mm), respectively. Melting points were determined in open capillaries using a Büchi 530 apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet Impact 400 FT spectrometer as films on KBr plates for liquids and as KBr discs for solids. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 (^{1}H: 300 MHz; ^{13}C: 75.47 MHz) and a Varian 500 (^{1}H: 500 MHz; ^{13}C: 125.76 MHz). Chemical shifts δ are given in ppm relative to TMS in $CDCl_3$ as solvent or relative to the solvent chemical shift for others. Coupling constants *J* are given in Hz. The following abbreviations are used: s singlet, d doublet, dd doublet of doublet, t triplet, q quadruplet, quin quintuplet, m multiplet and ps pseudo. Mass spectra were obtained with a ThermoFinnigan PolarisQ spectrometer with an ionic trap as detector. Elemental analyses were determined by the Service Central d'Analyse du CNRS (Vernaison, France).

Starting Materials: Divinyl sulfone (DVS), *N*,*N*′-dibenzylethylenediamine, *N*-benzylethylenediamine, 1,3-diaminopropane, diethylenetriamine, diethyl oxalate, diethyl malonate, benzylamine, dibenzylamine, *tert*-butylamine, tris(aminomethyl)aminomethane, ethylenediamine, bis(2-mercaptoethyl) sulfide (**14**), bis(2-mercaptoethyl) ether (**15**) and 4,7-dioxa-1,10-dithiadecane (**16**) are commercial. 1,7-Dibenzyl-4-oxa-1,7-diazaheptane (**4**), 1,4,7-tritosyl-1,4,7-triazaheptane (**9**), 1,5,9,13-tetratosyl-1,5,9,13-tetraazatridecane (**10**), 1,5,10,14-tetratosyl-1,5,10,14-tetraazatetradecane (**11**) and *N*-benzyl-2-bromoacetamide were prepared according to literature procedures.

1,5-Dibenzyl-1,5-diazapentane (2): Benzaldehyde (2.12 g, 20 mmol) and sodium triacetoxyborohydride (5.93 g, 28 mmol) in acetonitrile (50 mL) were added successively to a stirred solution of 1,3-diaminopropane (741 mg, 10 mmol) in dry acetonitrile (50 mL), under Ar. The reaction mixture was stirred at room temperature

for 20 h. Excess hydride was then neutralized by addition of 1 M aqueous NaOH solution until the white solid disappeared. The aqueous phase was extracted with ethyl acetate (3 × 50 mL), the combined organic phases were dried with anhydrous sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 100:0:0 to 89:10:1) to afford diamine **2** as a pale yellow oil (1.66 g, 6.5 mmol, 65%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (quint, ^3J = 6.6 Hz, 2 H), 2.73 (t, ^3J = 6.6 Hz, 4 H), 3.15 (br. s, 2 H), 3.78 (s, 4 H), 7.24−7.31 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 29.3, 48.0, 53.8, 127.0, 128.1, 128.4, 139.7 ppm. IR: ν̃ = 3286 (NH), 3081, 3028 (CHAr), 2928, 2807 (CH), 1455, 1121, 741, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 108 (4) $[BnNH_2 + H]^+$, 120 (7) $[BnNHCH_2]^+$, 255 (100) $[M + H]^+$. $C_{17}H_{22}N_2$ (254.4) + 1/2 H_2O: calcd. C 77.52, H 8.80, N 10.64; found C 77.61, H 8.70, N 10.53.

1,4,7-Tribenzoyl-1,4,7-triazaheptane: A mixture of triethylamine (3.34 g, 33 mmol) and diethylenetriamine (1.03 g, 10 mmol) in toluene (20 mL) was added dropwise to a cold solution (0 °C) of benzoyl chloride (4.22 g, 30 mmol) in dry toluene (40 mL) under Ar. At the end of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated and the residue taken up with $CHCl_3$ (100 mL), washed successively with 3 M hydrochloric acid solution (50 mL), 2 M sodium hydroxide solution (40 mL), water (40 mL) and brine (40 mL). The organic phase was dried with anhydrous Na_2SO_4 and reduced to dryness. The crude product was then crystallized in ethyl acetate to afford a white solid (3.01 g, 7.25 mmol, 73%). M.p. 126−127 °C. ^1H NMR (300 MHz, CD_3OD): δ = 3.52 (br. t, 2 H), 3.63 (br. t, 2 H), 3.80 (br. t, 2 H), 3.91 (br. t, 2 H), 7.24−7.88 (m, 15 H), 7.54 (br. s, 2 H) ppm. ^{13}C NMR (75.47 MHz, CD_3OD): δ = 39.3, 39.5, 46.3, 50.4, 128.1, 128.7, 130.0, 131.0, 133.2, 135.6, 136.0, 137.8, 170.4, 171.0, 175.5 ppm. IR: ν̃ = 3323 (NH), 3065, 3012 (CHAr), 2951 (CH), 1630 (CO), 1538 (NH), 1417, 1296, 1242, 1182, 794, 696 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 104 (19) $[PhCO]^+$, 416 (100) $[M + H]^+$. $C_{25}H_{25}N_3O_3$ (415.5): calcd. C 72.27, H 6.06, N 10.11; found C 72.01, H 5.94, N 10.11.

1,4,7-Tribenzyl-1,4,7-triazaheptane (3): Lithium aluminum hydride (3.4 g, 89 mmol) was added in small portions to a stirred, cold (0 °C) suspension of 1,4,7-tribenzoyl-1,4,7-triazaheptane (3.1 g, 7.47 mmol) in anhydrous tetrahydrofuran (100 mL) under Ar. The temperature was maintained at 0 °C until gas emission had ceased. The reaction mixture was then allowed to warm to room temperature and refluxed overnight. The excess hydride was neutralized by adding successively water (3.4 mL), 15% aqueous sodium hydroxide solution (3.4 mL) and water (10.2 mL). The precipitate was filtered off and the filtrate reduced to dryness under reduced pressure. The residue was taken up in chloroform (100 mL) and washed with brine (50 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated. The crude product was then purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 100:0:0 to 88:10:2) yielding **3** (2.2 g, 5.9 mmol, 79%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (br. s, 2 H), 2.57−2.69 (m, 8 H), 3.53 (s, 2 H), 3.67 (s, 4 H), 7.20−7.27 (m, 15 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 46.7, 53.6, 53.9, 59.2, 126.7, 126.8, 128.0, 128.1, 128.2, 128.7, 139.4, 140.2 ppm. IR: 3309 (NH), 3050, 3035 (CHA_r), 2936, 2807 (CH), 1500, 1463, 749, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 91 (16) $[Bn]^+$, 193 (14) $[M - 2\,Bn + 2\,H]^+$, 269 (26) $[M - BnNH_2]^+$, 281 (14) $[M - PhCH_3]^+$, 374 (100) $[M + H]^+$, 391 (6) $[M + NH_4]^+$. $C_{25}H_{31}N_3$ (373.5): calcd. C 80.39, H 8.37, N 11.25; found C 79.82, H 8.23, N 11.20.

1,4,7,10-Tetrabenzyl-2,9-dioxo-1,4,7,10-tetraazadecane: Potassium iodide (0.664 g, 4 mmol), triethylamine (445 mg, 4.4 mmol) and *N*,*N*′-dibenzylethylenediamine (481 mg, 2 mmol) were added to a stirred solution of *N*-benzyl-2-bromoacetamide (912 mg, 4 mmol) in dry toluene (130 mL) under Ar. The reaction mixture was then refluxed overnight. After evaporation of the solvent, the residue was taken up in chloroform (100 mL) and washed successively with 1% aqueous hydrochloric acid solution (50 mL), water (50 mL) and saturated aqueous sodium hydrogen carbonate solution (50 mL). The organic phase was next dried with anhydrous Na_2SO_4 and reduced to dryness. Purification by column chromatography ($CHCl_3$/MeOH/NH_4OH, 99.5:0.5:0.05) afforded the diamide (900 mg, 1.68 mmol, 84%) as a white solid. M.p. 123−124 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 4 H), 3.06 (s, 4 H), 3.47 (s, 4 H), 4.35 (d, ^3J = 6.0 Hz, 4 H), 7.06 (br. s, 2 H), 7.16−7.28 (m, 20 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 43.0, 52.5, 58.1, 59.7, 127.5, 127.6, 128.6, 128.7, 128.9, 137.3, 138.3, 170.6 ppm. IR: ν̃ = 3377 (NH), 3080, 3020 (CHAr), 2936, 2845 (CH), 1683 (CO), 1531 (NH), 1463, 1212, 756 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 338 (11) $[M - 2\,BnO + 2\,H]^+$, 535 (100) $[M + H]^+$. $C_{34}H_{38}N_4O_2$ (534.7): calcd. C 76.37, H 7.16, N 10.48; found C 75.79, H 7.11, N 10.47.

1,4,7,10-Tetrabenzyl-1,4,7,10-tetraazadecane (5): $LiAlH_4$ (114 mg, 3 mmol) was added in small portions to a stirred solution of 1,4,7,10-tetrabenzyl-2,9-dioxo-1,4,7,10-tetraazadecane (535 mg, 1 mmol), in anhydrous THF (70 mL) under Ar at 0 °C. After the gas evolution had ceased, the reaction mixture was allowed to warm to room temperature and refluxed overnight. It was then cooled to 0 °C and water (0.1 mL), 15% aqueous NaOH (0.1 mL) and water (3 mL) were added successively. The grey precipitate was filtered off and the filtrate reduced to dryness. The residue was taken up in chloroform (60 mL) and washed with brine (40 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:0.1 to 89:10:1) yielding **5** (140 mg, 0.28 mmol, 28%) as a light brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 4 H), 2.57−2.67 (m, 8 H), 2.90 (br. s, 2 H), 3.48 (s, 4 H), 3.65 (s, 4 H), 7.18−7.26 (m, 20 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 46.4, 51.9, 53.4, 53.6, 59.0, 126.8, 126.9, 128.16, 128.2, 128.3, 128.8, 139.2, 139.7 ppm. IR: ν̃ = 3331 (NH), 3065, 3035 (CHAr), 2929, 2800 (CH), 1500, 1447, 749, 696 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) =108 (11) $[BnNH_2 + H]^+$, 120 (7) $[BnNHCH_2]^+$, 134 (15) $[BnNHCH_2CH_2]^+$, 148 (18) $[BnNHCH_2CH_2N]^+$, 241 (11) $[BnNHCH_2CH_2NHBn + H]^+$, 253 (20) $[BnNHCH_2CH_2NHBnCH_2]^+$, 267 (12) $[MeBnNCH_2CH_2NHBnCH_2]^+$, 507 (100) $[M + H]^+$. $C_{34}H_{42}N_4$ (506.7) + 1/2 H_2O: calcd. C 79.18, H 8.40, N 10.86; found C 79.27, H 8.44, N 11.03.

1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane (6): Benzaldehyde (212 mg, 2 mmol) was added at room temperature to a stirred solution of 4,7-dioxa-1,10-diazadecane (148 mg, 1 mmol) in dry acetonitrile (10 mL) under Ar. Sodium triacetoxyborohydride (593 mg, 2.8 mmol), suspended in dry acetonitrile (20 mL), was then added. After 20 h of stirring at room temperature, excess hydride was neutralized by adding 1 M aqueous sodium hydroxide solution (10 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (30 mL), dried with anhydrous Na_2SO_4 and the solvents evaporated. The residue was then purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 100:0:0 to 94.5:5:0.5) and yielded diamine **6** as a colorless oil (215 mg, 0.65 mmol, 65%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82 (br. s, 2 H), 2.79 (t, ^3J =

5.25 Hz, 4 H), 3.59 (m, 8 H), 3.79 (s, 4 H), 7.25−7.31 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.7, 53.8, 70.2, 70.6, 126.8, 128.1, 128.3, 140.3 ppm. IR: ṽ = 3323 (NH), 3096, 3065 (CHA_r), 2868 (CH), 1455, 1121, 748, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 329 (100) $[M + H]^+$. $C_{20}H_{28}N_2O_2$ (328.5): calcd. C 73.14, H 8.59, N 8.53; found C 72.86, H 8.82, N 8.53.

1,10-Dibenzyl-5,6-dioxo-1,4,7,10-tetraazadecane (7): Diethyl oxalate (1.46 g, 10 mmol) was added to a stirred solution of *N*-benzylethylenediamine (3.0 g, 20 mmol) in ethanol (50 mL) . The reaction mixture was stirred at room temperature overnight. The residue was crystallized in an MeOH/EtOH mixture and the white precipitate was filtered off. The filtrate was reduced to dryness and purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:0.1 to 89:10:1) affording **7** (2.61 g, 7.4 mmol, 74%) as a yellow solid. M.p. 67−68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (br. s, 2 H), 2.81 (t, ^3J = 6.0 Hz, 4 H), 3.41 (q, ^3J = 6.0 Hz, 4 H, ^3J = 5.9 Hz), 3.79 (s, 4 H), 7.23−7.28 (m, 10 H), 7.85 (br. t, 2 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 39.4, 47.6, 53.4, 127.0, 128.0, 128.4, 139.9, 160.0 ppm. IR: ṽ = 3316 (NH), 3096, 3065, 3035 (CHA_r), 2929, 2830 (CH), 1683 (CO), 1516, 1455, 1356, 1129, 1037, 741, 711 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 205 (8) $[M - BnNHCH_2CH_2NH]^+$, 222 (100) $[M - BnNHCH_2CH_2 + 2 H]^+$, 355 (10) $[M + H]^+$. $C_{20}H_{26}N_4O_2$ (354.5): calcd. C 67.77, H 7.39, N 15.81; found C 67.56, H 7.32, N 15.48.

1,11-Dibenzyl-5,7-dioxo-1,4,8,11-tetraazaundecane (8): Diethyl malonate (1.6 g, 10 mmol) was added to a stirred solution of *N*-benzylethylenediamine (3.0 g, 20 mmol) in chloroform (10 mL) and the reaction mixture was heated at 50 °C for 48 h. The resulting pink solution was then concentrated and the residue purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 94.5:5:0.5) to afford compound **8** (2.55 g, 6.9 mmol, 69%) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 (br. s, 2 H), 2.75 (t, ^3J = 5.9 Hz, 4 H), 3.14 (s, 2 H), 3.34 (td, 4 H, ^3J = 5.8, $^3J_{7-8}$ = 5.9 Hz), 3.76 (s, 4 H), 7.26−7.32 (m, 10 H), 7.40 (br. t, 2 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 39.2, 43.2, 47.8, 53.4, 127.1, 128.1, 128.4, 139.9, 167.5 ppm. IR: ṽ = 3294 (NH), 3088, 3020 (CHAr), 2937, 2845 (CH), 1660 (CO), 1562 (NH), 1462, 741, 711 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) =351 (20) $[M - OH]^+$, 369 (100) $[M + H]^+$. $C_{21}H_{28}N_4O_2$ (368.5): calcd. C 68.45, H 7.66, N 15.21; found C 68.69, H 7.67, N 15.10.

General Procedure for the Conjugate Addition of Heteronucleophiles to Divinyl Sulfone (DVS): DVS (0.02 M in propan-2-ol) was added dropwise to a stirred refluxing solution of the nucleophile (0.01 M in a propan-2-ol/water, 1:1). At the end of the addition, reflux was maintained for at least 1 h. Reaction advancement was monitored by the disappearance of the vinylic proton signal in the ^{1}H NMR spectrum. When this signal disappeared or when its intensity no longer evolved, the reaction mixture was reduced to dryness under reduced pressure. (a) In the case of dibenzylamine, ethylenediamine or phenylmethanethiol, the concentration of the nucleophile was 0.02 M. (b) When the nucleophile was sulfur the solution was brought to pH = 8−9 by adding a few drops of triethylamine. (c) For the conjugate addition of sulfonamides, the reaction was carried out in acetonitrile in the presence of potassium carbonate (1 equiv. by NH function) under Ar.

4-Benzylthiomorpholine 1,1-Dioxide (Ia): Benzylamine (107 mg, 1 mmol) was treated with DVS (118 mg, 1 mmol). The reaction was completed within 1 h and **Ia** was obtained pure and quantitatively (225 mg, 1 mmol) as a white solid. M.p. 77−78 °C (ref.[16] 74 °C).^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (ps t, 4 H), 3.05 (ps t, 4 H), 3.65 (s, 2 H), 7.26−7.34 (m, 5 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 50.5, 51.0, 61.4, 127.6, 128.5, 128.7, 137.2 ppm. IR: ṽ = 3058, 3005 (CHAr), 2950, 2830 (CH), 1272, 1136 (SO_2), 749, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 226 (100) $[M + H]^+$. $C_{11}H_{15}NO_2S$ (225.3): calcd. C 58.64, H 6.71, N 6.22, S 14.23; found C 58.31, H 6.65, N 6.28, S 14.11.

4-*tert*-Butylthiomorpholine 1,1-Dioxide (Ib): A solution of DVS (472 mg, 4 mmol) in *i*PrOH (6 mL) was added dropwise to a stirred refluxing solution of *tert*-butylamine (292 mg, 4 mmol). Reaction was completed within 1.5 h and a column chromatography purification ($CHCl_3$/MeOH, 100:0 to 98:2) afforded thiomorpholine **Ib** (728 mg, 3.8 mmol, 95%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 3.04 (m, 8 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 26.6, 44.5, 52.6, 54.6 ppm. IR: ṽ = 2982, 2875, 2830 (CH), 1334, 1303 (SO_2), 1265, 1128 (SO_2), 1045, 855, 718 cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 136 (26) $[M - t\text{Bu} + 2 H]^+$, 192 (100) $[M + H]^+$. $C_8H_{17}NO_2S$ (191.3): calcd. C 50.23, H 8.96, N 7.32, S 16.76; found C 50.56, H 9.06, N 7.28, S 16.73.

4-[Tris(hydroxymethyl)methyl]thiomorpholine 1,1-Dioxide (Ic): DVS (236 mg, 2 mmol) was added to a stirred solution of [tris(hydroxymethyl)amino]methane (242 mg, 2 mmol) in propan-2-ol. After refluxing the reaction mixture for 3 h, the crude product was crystallized from methanol and **Ic** was isolated as a white solid (450 mg, 1.88 mmol, 94%). M.p. 165 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ = 3.05−3.07 (m, 4 H), 3.22−3.24 (m, 4 H), 3.48 (d, ^3J = 5.0 Hz, 6 H), 4.40 (t, ^3J = 5.0 Hz, 3 H) ppm. ^{13}C NMR [75.47 MHz, $(CD_3)_2SO$]: δ = 45.9, 53.5, 61.5, 54.6 ppm. IR: ṽ = 3306 (OH), 2998, 2867 (CH), 1294, 1124 (SO_2) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 208 (10) $[M - CH_2OH]^+$, 240 (100) $[M + H]^+$. $C_8H_{17}NO_5S$ (239.3): calcd. C 40.15, H 7.16, N 5.85, found C 40.79, H 7.26, N 6.14.

1,2-Bis(1,1-dioxothiomorpholin-4-yl)ethane (Id): The reaction between DVS (118 mg, 1 mmol) and ethylenediamine (30 mg, 0.5 mmol) was completed within 1 h. Purification by flash column chromatography ($CHCl_3$/MeOH, 100:0 to 95:5) afforded **Id** (140 mg, 0.47 mmol, 95%) as a white solid. M.p. 215−216 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 2.69 (s, 4 H), 3.04−3.10 (m, 16 H) ppm. ^{13}C NMR (75.47 MHz, (CD_3OD): δ = 51.8, 51.95, 54.8 ppm. IR: ṽ = 2980, 2914, 2873 (CH), 1314, 1134 (SO_2), 1291, 1191, 1044, 963, 873, 734 cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 297 (100) $[M + H]^+$. $C_{10}H_{20}N_2O_4S_2$ (296.4): calcd. C 40.52, H 6.80, N 9.45, S 21.64; found C 40.68, H 6.89, N 9.46, S 21.59.

1,1,7,7-Tetrabenzyl-4-thia-1,7-diazaheptane 4,4-Dioxide (IIa): DVS (59 mg, 0.5 mmol) was added to dibenzylamine (197 mg, 1 mmol) and refluxed for 2 h. The residue was purified by flash column chromatography ($CHCl_3$) and **IIa** isolated as a white oil (237 mg, 0.46 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.89−2.97 (m, 8 H), 3.55 (s, 8 H), 7.23−7.31 (m, 20 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 46.6, 51.3, 58.5, 127.4, 128.4, 128.8, 138.3 ppm. IR: 3080, 3052, 3020 (CHAr), 2950, 2798 (CH), 1500, 1456, 1317, 1140 (SO_2), 700 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 91 (10) $[Bn]^+$, 316 (8) $[M - NBn_2]^+$, 332 (8) $[M - 2 Bn + 2 H]^+$, 513 (100) $[M + H]^+$. $C_{32}H_{36}N_2O_2S$ (512.7): calcd. C 74.96, H 7.08, N 5.46, S 6.25; found C 74.67, H 7.13, N 5.41, S 6.56.

4,7-Dibenzyl-1-thia-4,7-diazacyclononane 1,1-Dioxide (1a): DVS (59 mg, 0.5 mmol) and *N*,*N*′-dibenzylethylenediamine (120 mg, 0.5 mmol) were refluxed for 1 h. **1a** was isolated by flash column chromatography ($CHCl_3$) as a white solid (179 mg, 0.5 mmol, 100%). M.p. 107−108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25

(s, 4 H), 3.02 (t, ^3J = 5.45 Hz, 4 H), 3.68 (m, 8 H), 7.23−7.31 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 52.3, 55.0, 55.3, 63.4, 127.4, 128.4, 129.4, 138.3 ppm. IR: ṽ = 3096, 3073, 3012 (CHAr), 2921, 2822 (CH), 1272 (SO_2), 1219, 1136 (SO_2), 1113, 711, 680 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 359 (100) $[M + H]^+$. $C_{20}H_{26}N_2O_2S$ (358.5): calcd. C 67.01, H 7.31, N 7.81, S 8.94; found C 66.57, H 7.36, N 7.80, S 8.68.

4,8-Dibenzyl-1-thia-4,8-diazacyclodecane 1,1-Dioxide (2a): **2** (510 mg, 2 mmol) and DVS (236 mg, 2 mmol) were refluxed overnight and the macrocycle **2a** was isolated by column chromatography ($CHCl_3$/MeOH, 99.9:0.1) as translucent crystals (680 mg, 1.82 mmol, 91%). M.p. 143−144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (quint, 2 H, ^3J = 6.0 Hz), 2.49 (br. s, 4 H), 2.88 (br. s, 4 H), 3.24 (br. s, 4 H), 3.57 (s, 4 H), 7.22−7.32 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.4, 48.0, 50.2, 52.7, 59.9, 127.5, 128.4, 129.7, 137.2 ppm. IR: ṽ = 3063, 3028 (CHAr), 2976, 2920, 2802 (CH), 1500, 1450, 1282, 1128 (SO_2), 889, 748 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 109 (11) $[BnNH_4]^+$, 282 (13) $[M - Bn + H]^+$, 373 (100) $[M + H]^+$. $C_{21}H_{28}N_2O_2S$ (372.5): calcd. C 67.71, H 7.58, N 7.52, S 8.61; found C 67.71, H 7.59, N 7.60, S 8.65.

4,7,10-Tribenzyl-1-thia-4,7,10-triazacyclododecane 1,1-Dioxide (3a): Triamine **3** (374 mg, 1 mmol) was refluxed with DVS (118 mg, 1 mmol) overnight. **3a** was obtained after purification by column chromatography ($CHCl_3$/MeOH/NH_4OH, 99:0.5:0.05) as a pale yellow oil (440 mg, 0.9 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49−2.59 (m, 8 H), 3.08 (t, ^3J = 6.3 Hz, 4 H), 3.37 (t, ^3J = 6.3 Hz, 4 H), 3.44 (s, 2 H), 3.54 (s, 4 H), 7.22−7.29 (m, 15 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.7, 51.8, 52.1, 53.0, 58.8, 60.3, 127.1, 127.3, 128.2, 128.3, 129.2, 129.6, 138.1, 138.4 ppm. IR: ṽ = 3080, 3020 (CHAr), 2959, 2800 (CH), 1470, 1380, 1288, 1128 (SO_2), 741, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 91 (100) $[Bn]^+$, 492 (53) $[M + H]^+$. $C_{29}H_{37}N_3O_2S$ (491.7) + 3/2 H_2O: calcd. C 67.15, H 7.77, N 8.10, S 6.18; found C 66.97, H 7.21, N 7.95, S 6.23.

4,10-Dibenzyl-1-oxa-7-thia-4,10-diazacyclododecane 7,7-Dioxide (4a): DVS (118 mg, 1 mmol) was added to diamine **4** (284 mg, 1 mmol) and the reaction mixture was refluxed for 1 h. Purification by column chromatography (cyclohexane/ethyl acetate, 7:3; Et_3N 1%) yielded **4a** as a white solid (241 mg, 0.6 mmol, 60%). M.p. 73−74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (t, ^3J = 4.4 Hz, 4 H), 3.14 (ps t, 4 H, ^3J = 6.4, ^3J = 6.9 Hz), 3.29 (ps t, 4 H, ^3J = 6.4, ^3J = 6.9 Hz), 3.37 (t, ^3J = 4.4 Hz, 4 H), 3.69 (s, 4 H), 7.26−7.33 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 50.1, 51.3, 53.9, 61.3, 70.6, 127.3, 128.3, 129.0, 138.4 ppm. IR: ṽ = 3096, 3058, 3027 (CHAr), 2936, 2890 (CH), 1515, 1455, 1364, 1303 (SO_2), 1258, 1151 (SO_2), 1120 (C−O), 1113, 1060, 817, 741, 696 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 313 (11) $[M - Bn + 2 H]^+$, 403 (100) $[M + H]^+$. $C_{22}H_{30}N_2O_3S$ (402.6): calcd. C 65.64, H 7.51, N 6.96, S 7.97; found C 65.34, H 7.39, N 6.89, S 7.90.

4,7,10,13-Tetrabenzyl-1-thia-4,7,10,13-tetraazacyclopentadecane 1,1-Dioxide (5a): Reaction of tetraamine **5** (250 mg, 0.5 mmol) and DVS (59 mg, 0.5 mmol) was completed in 1.5 h. Column chromatography (cyclohexane/ethyl acetate, 7:3 to 5:5) yielded **5a** as a yellow oil (230 mg, 0.37 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61−2.64 (m, 12 H), 3.0 (t, ^3J = 6.7 Hz, 4 H), 3.22 (t, ^3J = 6.7 Hz, 4 H), 3.43 (s, 4 H), 3.54 (s, 4 H), 7.21−7.29 (m, 20 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.1, 52.1, 52.2, 52.25, 52.3, 59.3, 59.6, 126.9, 127.3, 128.1, 128.3, 129.0, 129.1, 138.1, 139.2 ppm. IR: ṽ = 3090, 3029 (CHAr), 2997, 2830 (CH), 1455, 1310, 1136 (SO_2), 1022, 741, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 625 (100) $[M + H]^+$. $C_{38}H_{48}N_4O_2S$ (624.9) + H_2O: calcd. C 70.99, H 7.84, N 8.71, S 4.99; found C 71.35, H 7.76, N 8.44, S 4.74.

7,13-Dibenzyl-1,4-dioxa-10-thia-7,13-diazacyclopentadecane 10,10-Dioxide (6a): Diamine **6** (328 mg, 1 mmol) and DVS (118 mg, 1 mmol) were refluxed overnight. After purification by column chromatography (cyclohexane/ethyl acetate, 5:5), macrocycle **6a** was isolated as a yellow oil (245 mg, 0.55 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (t, ^3J = 4.5 Hz, 4 H), 3.15−3.32 (m, 8 H), 3.51 (t, ^3J = 4.5 Hz, 4 H), 3.55 (s, 4 H), 3.66 (s, 4 H), 7.26−7.33 (m, 10 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.2, 52.1, 53.3, 60.0, 70.3, 70.5, 127.2, 128.3, 128.8, 138.6 ppm. IR: ṽ = 3088, 3020 (CHAr), 2929, 2853 (CH), 1455, 1371, 1288, 1121 (SO_2), 1068, 749, 711 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 447 (100) $[M + H]^+$. $C_{24}H_{34}N_2O_4S$ (446.6): calcd. C 64.54, H 7.67, N 6.27, S 7.18; found C 64.80, H 7.89, N 6.27, S 7.37.

1,4-Dioxa-10-thia-7,13-diazacyclopentadecane 10,10-Dioxide (6b): **6a** (154 mg, 0.35 mmol) in ethanol (10 mL) was added to a suspension of 10% Pd/C (30 mg) in THF (10 mL) and the reaction mixture was stirred for 2 d at room temperature under H_2. The solution was filtered through Celite and reduced to dryness. The residue was taken up in water (20 mL) and washed with diethyl ether (3 × 10 mL). Solvent evaporation afforded pure **6b** (90 mg, 0.34 mmol, 98%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76−2.80 (m, 6 H), 3.13 (t, ^3J = 5.5 Hz, 4 H), 3.40 (t, ^3J = 5.5 Hz, 4 H), 3.62 (s, 4 H), 3.63 (m, 4 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 43.7, 49.0, 54.4, 69.7, 70.2 ppm. IR: ṽ = 3362 (NH), 2952, 2830 (CH), 1668, 1455, 1409, 1288, 1120 (SO_2), 1030 cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 149 (4) $[(H_2NCH_2CH_2OCH_2)_2 + H]^+$, 267 (100) $[M + H]^+$. $C_{25}H_{34}N_4O_4S$ (266.4) + 1/2 H_2O: calcd. C 43.62, H 8.42, N 10.17; found C 43.70, H 8.23, N 10.00.

4,13-Dibenzyl-8,9-dioxo-1-thia-4,7,10,13-tetraazacyclopentadecane 1,1-Dioxide (7a): DVS (118 mg, 1 mmol) was added to compound **7** (354 mg, 1 mmol) and the reaction mixture was stirred at reflux overnight. Purification of the residue by column chromatography (CH_2Cl_2/MeOH, 99:1) afforded macrocycle **7a** (174 mg, 0.37 mmol, 37%) as a white solid. M.p. > 220 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66−2.69 (m, 4 H), 2.89 (s, 8 H), 3.28−3.34 (m, 4 H), 3.70 (s, 4 H), 7.25−7.36 (m, 10 H), 7.65 (br. t, 2 H, ^3J = 6.5 Hz) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 38.0, 48.1, 52.9, 53.5, 59.8, 127.7, 128.6, 129.3, 137.7, 160.6 ppm. IR: ṽ = 3290 (NH), 3077 (CHAr), 2979, 2922, 2832 (CH), 1649 (CO), 1543 (NH), 1453, 1338, 1136 (SO_2), 751, 710 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m*/*z* (%) = 473 (100) $[M + H]^+$. $C_{24}H_{32}N_4O_4S$ (472.6): calcd. C 60.99, H 6.82, N 11.86, S 6.78; found C 60.96, H 6.76, N 11.63, S 6.98.

4,14-Dibenzyl-8,10-dioxo-1-thia-4,7,11,14-tetraazacyclohexadecane 1,1-Dioxide (8a): Reaction of compound **8** (370 mg, 1 mmol) and DVS (118 mg, 1 mmol) was completed in 2 h. Purification by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:0.1 to 95:5:0.4) yielded macrocycle **8a** as a pale yellow oil (460 mg, 0.94 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (t, ^3J = 5.3 Hz, 4 H), 2.94 (ps t, 4 H), 3.05 (ps t, 4 H), 3.14 (s, 2 H), 3.36 (q, ^3J = 5.5 Hz, 4 H), 3.60 (s, 4 H), 7.22 (m, 10 H), 7.37−7.40 (m, 2 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 37.1, 44.4, 47.3, 52.3, 52.5, 58.7, 127.4, 128.4, 129.1, 137.5, 167.1 ppm. IR: ṽ = 3347 (NH), 3096, 3073, 3035 (CHAr), 2936, 2830 (CH), 1675 (CO), 1546 (NH), 1455, 1296, 1128 (SO_2), 1068, 923, 741 (CHAr) cm^{-1}. MS

(DCI, NH_3/isobutane): *m/z* (%) = 487 (100) $[M + H]^+$. $C_{25}H_{34}N_4O_4S$ (486.6) + 1/2 H_2O: calcd. C 60.58, H 7.12, N 11.30, S 6.47; found C 60.47, H 7.02, N 11.17, S 6.88.

4,7,10-Tritosyl-1-thia-4,7,10-triazacyclododecane 1,1-Dioxide (9a): DVS (118 mg, 1 mmol) was added to a mixture of tosylated amine **9** (524 mg, 1 mmol) and potassium carbonate (415 mg, 3 mmol). The reaction was completed in 3 h and after evaporation of the solvent, the residue was taken up in a saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with anhydrous Na_2SO_4 and the solvents evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 99:1:0.1) affording **9a** as a white solid (664 mg, 0.97 mmol, 97%). M.p. 155−158 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 2.42 (s, 6 H), 3.14 (m, 4 H), 3.43 (m, 4 H), 3.50 (m, 4 H), 3.75 (m, 4 H), 7.29−7.34 (m, 6 H), 7.47 (d, ^3J = 8.32 Hz, 2 H), 7.66 (d, ^3J = 8.32 Hz, 4 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.4, 44.6, 48.3, 50.8, 52.9, 127.4, 127.8, 129.8, 129.9, 131.4, 133.8, 144.4, 144.7 ppm. IR: ṽ = 3073 (CHAr), 2997, 2929 (CH), 1273, 1159 (SO_2), 749 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 91 (24) $[Bn]^+$, 156 (11) $[Ts + H]^+$, 174 (25) $[Ts + NH_4]^+$, 374 (11) $[M - 2\,Ts + H]^+$, 528 (14) $[M - Ts]^+$, 684 (66) $[M + H]^+$, 701 (100) $[M + NH_4]^+$, 741 (4) $[M + t\text{Bu}]^+$. $C_{29}H_{37}N_3O_8S_4$ (683.9): calcd. C 50.93, H 5.45, N 6.14, S 18.76; found C 50.56, H 5.40, N 6.08, S 18.84.

4,8,12,16-Tetratosyl-1-thia-4,8,12,16-tetraazacyclodecaoctane 1,1-Dioxide (10a): DVS (118 mg, 1 mmol) was added to a solution of **10** (804 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) and the reaction mixture was refluxed for 2 h. After evaporation of the solvent, the residue was taken up in $CHCl_3$ (30 mL) and water (20 mL), decanted and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried with anhydrous Na_2SO_4 and the solvents evaporated to dryness. Purification by column chromatography ($CHCl_3$/MeOH/NH_4OH, 99:1:0.1) afforded **10a** as a white solid (910 mg, 0.99 mmol, 99%). M.p. 179−180 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.94−2.06 (m, 6 H), 2.43 (s, 12 H), 3.08−3.21 (m, 12 H), 3.47−3.52 (m, 8 H), 7.31−7.37 (dd, 8 H, ^3J = 8.3 Hz), 7.65−7.71 (dd, 8 H, ^3J = 8.3 Hz) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.47, 21.52, 29.6, 30.4, 43.9, 47.7, 48.2, 48.9, 54.1, 127.1, 127.6, 129.8, 130.1, 133.5, 135.3, 143.6, 144.3 ppm. IR: ṽ = 3073, 3042 (CHAr), 2944, 2868 (CH), 1600, 1447, 1341, 1158 (SO_2), 1091, 953, 817, 741, 696 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 767 (27) $[M - Ts]^+$, 923 (35) $[M + H]^+$, 940 (100) $[M + NH_4]^+$. $C_{41}H_{54}N_4O_{10}S_6$ (923.2) + 2 H_2O: calcd. C 51.34, H 6.09, N 5.84, S 16.71; found C 51.44, H 5.79, N 5.90, S 16.73.

4,8,13,17-Tetratosyl-1-thia-4,8,13,17-tetraazacyclodecanonane 1,1-Dioxide (11a): DVS (118 mg, 1 mmol) was added to a solution of **11** (818 mg, 1 mmol) in the presence of potassium carbonate (276 mg, 2 mmol). Reflux continued for 20 h and the solvent was evaporated. The residue was dissolved in a mixture of $CHCl_3$ (30 mL) and water (20 mL) and the aqueous phase extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried with anhydrous Na_2SO_4 and the solvents evaporated to dryness. Column chromatography ($CHCl_3$/MeOH, 99.5:0.5) yielded macrocycle **11a** (887 mg, 0.95 mmol, 95%) as a white solid. M.p. 183−184 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (m, 4 H), 1.94−1.98 (m, 4 H), 2.43 (s, 12 H), 3.10−3.20 (m, 12 H), 3.50 (s, 8 H), 7.29−7.35 (dd, 8 H, ^3J = 8.3 Hz), 7.64−7.70 (dd, 8 H, ^3J = 8.3 Hz) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.49, 21.53, 26.7, 28.9, 42.7, 47.4, 48.6, 49.3, 54.0, 127.1, 127.5, 129.8, 130.1, 134.0, 135.7, 143.4, 144.2 ppm. IR: ṽ = 3044, 3012 (CHAr), 2930, 2873 (CH), 1608, 1477, 1346, 1159 (SO_2), 1085, 947, 808, 741, 703 (CHAr) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 781 (20) $[M - Ts]^+$, 937 (6) $[M + H]^+$, 954 (100) $[M + NH_4]^+$. $C_{42}H_{56}N_4O_{10}S_5$ (937.3): calcd. C 53.82, H 6.02, N 5.98, S 17.11; found C 53.51, H 5.91, N 5.88, S 16.72.

1-Thia-4,8,13,17-tetraazacyclodecanonane 1,1-Dioxide (11b): 11a (470 mg, 0.5 mmol) was added to a stirred solution of HBr (33% in AcOH) in the presence of phenol (900 mg, 9 mmol). The reaction mixture was stirred overnight at 80 °C. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 (100 mL) and water (50 mL). The aqueous phase was washed with CH_2Cl_2 and reduced to dryness. The resulting hydrobromide was dissolved in water (10 mL) and passed through Dowex 1 × 8 resin (basic form). The collected fractions were concentrated affording crude amine **11b** (130 mg, 0.41 mmol, 81%) as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (m, 4 H), 1.75 (quint, 4 H, ^3J = 6.7 Hz), 2.70−2.76 (m, 12 H), 3.17 (t, ^3J = 6.1 Hz, 4 H), 3.50 (t, ^3J = 6.1 Hz, 4 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.1, 26.6, 41.6, 46.1, 46.2, 47.8, 53.1 ppm. IR: ṽ = 3321 (NH), 2951, 2828 (CH), 1648, 1586, 1486, 1286, 1124 (SO_2) cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 321 (100) $[M + H]^+$. $C_{14}H_{32}N_4O_2S$ (320.5) + HBr: calcd. C 41.89, H 8.29, N 13.96, S 7.99; found C 42.24, H 8.91, N 13.73, S 7.90.

17-Thia-1,4,8,11-tetraazabicyclo[6.6.5]nonadecane 17,17-Dioxide (12): DVS (236 mg, 2 mmol) was added to a solution of cyclam (0.4 g, 2 mmol) and refluxed for 16 h. Purification by column chromatography ($CHCl_3$/MeOH/NH_4OH, 4:1:0.2) afforded cryptand **12** as a white solid (450 mg, 1.4 mmol, 71%). M.p. 118−120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (dd, ^1J = 2.7, ^3J = 15.6 Hz, 2 H), 1.92−2.06 (m, 4 H), 2.44−2.74 (m, 12 H), 2.95−3.02 (m, 4 H), 3.12−3.22 (m, 4 H), 3.32 (br. s, 2 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.2, 46.7, 48.5, 51.7, 53.2, 53.4, 58.6 ppm. IR: ṽ = 3283 (NH), 2974, 2898, 2822 (CH), 1470, 1303, 1151 (SO_2), 772 cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 319 (100) $[M + H]^+$. $C_{14}H_{30}N_4O_2$ (318.5) + H_2O: calcd. C 49.97, H 9.59, N 16.65, S 9.53; found C 49.90, H 9.26, N 16.65, S 9.48.

4,7,13,16-Tetraoxa-21-thia-1,10-diazabicyclo[8.8.5]nonadecane 21,21-Dioxide (13): After the addition of DVS (118 mg, 1 mmol) to diaza-18-crown-6 (264 mg, 1 mmol), reflux was maintained for 1 h. Cryptand **13** was isolated by column chromatography ($CHCl_3$/MeOH/NH_4OH, 94.5:5:0.5) as a white solid (370 mg, 0.97 mmol, 97%). M.p. 85−86 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.61−2.69 (m, 8 H), 2.98 (t, ^3J = 6.7 Hz, 4 H), 3.43 (t, ^3J = 6.7 Hz, 4 H), 3.51−3.56 (m, 8 H), 3.58−3.64 (m, 8 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.3, 54.4, 57.0, 69.1, 70.3 ppm. IR: ṽ = 2966, 2875, 2807 (CH), 1364, 1272, 1121 (SO_2), 741 cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 381 (100) $[M + H]^+$. $C_{16}H_{32}N_2O_6S$ (380.5): calcd. C 50.50, H 8.48, N 7.36, S 8.43; found C 50.47, H 8.50, N 7.21, S 8.77.

1,4,7,10-Tetrathiacyclododecane 1,1-Dioxide (14a): Bis(2-mercaptoethyl) sulfide (172 mg, 1 mmol) was refluxed with DVS (118 mg, 1 mmol) overnight. Purification of the residue by flash column chromatography ($CHCl_3$) afforded **14a** as a white solid (200 mg, 0.73 mmol, 73%). M.p. 198−199 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 8 H), 3.01 (ps t, 4 H, ^3J = 7.0, ^3J = 7.8 Hz), 3.45 (ps t, 4 H, ^3J = 7.0, ^3J = 7.8 Hz) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.6, 30.5, 30.6, 52.2 ppm. IR: ṽ = 3004, 2928 (CH), 1440, 1326 (SO_2), 1265, 1143 (SO_2), 1105, 961, 885, 843 cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 213 (12) $[M - CH_2CH_2S + H]^+$, 273 (15) $[M + H]^+$, 290 (100) $[M + NH_4]^+$. $C_8H_{16}O_2S_4$ (272.4): calcd. C 35.26, H 5.92, S 47.07; found C 35.14, H 5.75, S 46.77.

7-Oxa-1,4,10-trithiacyclododecane 1,1-Dioxide (15a): DVS (118 mg, 1 mmol) was added to bis(2-mercaptoethyl) ether (138 mg, 1 mmol) and the reaction mixture stirred overnight. The crude product was purified by flash column chromatography ($CHCl_3$) yielding **15a** as a white solid (210 mg, 0.82 mmol, 82%). M.p. 162−163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (t, ^3J = 4.7 Hz, 4 H), 3.11 (ps t, 4 H), 3.41 (ps t, 4 H), 3.80 (t, ^3J = 4.7 Hz, 4 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.7, 30.6, 51.2, 74.4 ppm. IR: $\tilde{\nu}$ = 2944, 2921, 2891, 2860 (CH), 1432, 1318 (SO_2), 1288, 1158 (SO_2), 1128 (C−O), 1037, 946, 824, 756 cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 257 (22) $[M + H]^+$, 274 (100) $[M + NH_4]^+$. $C_8H_{16}O_3S_3$ (256.4): calcd. C 37.47, H 6.29, S 37.52; found C 37.48, H 6.08, S 37.06.

7,10-Dioxa-1,4,13-trithiacyclopentadecane 1,1-Dioxide (16a): After addition of DVS (118 mg, 1 mmol) to a solution of 4,7-dioxa-1,10-dithiadecane (182 mg, 1 mmol), reflux was maintained for 1 d. The 1+1 cyclization product **16a** (239 mg, 0.8 mmol, 80%, crystals) and a small amount of the 2+2 product (15 mg, 0.03 mmol, 3%, white solid) were isolated by flash column chromatography ($CHCl_3$/MeOH, 98:2). M.p. 101−102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (t, ^3J = 4.9 Hz, 4 H), 3.07−3.11 (m, 4 H), 3.41−3.47 (m, 4 H), 3.64 (s, 4 H), 3.76 (t, ^3J = 4.9 Hz, 4 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.4, 32.2, 54.1, 70.6, 73.4 ppm. IR: $\tilde{\nu}$ = 2990, 2952, 2921, 2891 (CH), 1470, 1417, 1326 (SO_2), 1288, 1151 (SO_2), 1105 (C−O), 1037, 923, 847, 725 cm^{-1}. MS (DCI, NH_3/isobutane): *m/z* (%) = 301 (14) $[M + H]^+$, 318 (100) $[M + NH_4]^+$. $C_{10}H_{20}O_4S_3$ (300.5): calcd. C 39.97, H 6.71; found C 39.96, H 6.85.

Acknowledgments

Our work has been generously supported by the Centre National de la Recherche Scientifique (CNRS) and the University J. Fourier (UJF). Financial assistance from the Ministère de l'Education Nationale for a grant conceded to M.-L. T. is also gratefully acknowledged.

[1] Y. A. Zolotov, *Macrocyclic Compounds in Analytical Chemistry*, Wiley Interscience, New York, **1997**, p. 1−62.
[2] G. W. Gokel, *Crown Ethers and Cryptands* (Ed.: J. F. Stoddart), Cambridge, **1991**.
[3] M. Hiraoka, *Crown Ethers and Analogous Compounds*, Elsevier, Amsterdam, **1992**, p. 1−99.
[4] L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complex*, Cambridge University Press, Cambridge, **1989**, p. 21−50.
[5] D. Parker, *Macrocycle Synthesis* (Ed.: D. Parker), Oxford University Press, Oxford, **1996**.
[6] M. F. Sebban, P. Vottero, A. Alagui, C. Dupuy, *Tetrahedron Lett.* **2000**, *41*, 1019−1022.
[7] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Series, vol. 9 (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon Press, Oxford, **1992**.
[8] Bis-Michael acceptors are listed in: *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**.
[9] R. D. Little, M. R. Masjedizadeh, O. Wallquist, J. I. Mc Loughlin in *Organic Reactions*, vol. 47 (Ed.: L. A. Paquette), Wiley, New York, **1995**, p. 315−552.
[10] A. Padwa, B. H. Norman, *J. Org. Chem.* **1990**, *55*, 4801−4807.
[11] K. Zygo, W. Wieczorek, K. M. Pietrusiewicz, *14th International Conference on Phosphorus Chemistry*, Cincinnatti, **1998**.
[12] G. Gao, D. Yan, *Chem. Commun.* **2001**, 107−108.
[13] G. Hallas, R. Marsden, J. D. Heytworth, D. Mason, *J. Chem. Soc., Perkin Trans. 2* **1986**, 123−126.
[14] B. U. Minbaev, M. F. Shostakovskii, A. D. Kagarlistskii, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, *19*, 957−959.
[15] K. Nagarajan, V. P. Arya, T. George, V. Sudarsaman, R. K. Shah, A. N. Goud, S. J. Shenoy, V. Hakan, Y. S. Kulkarni, M. K. Rao, *Indian J. Chem.* **1982**, *21B*, 928−940.
[16] V. P. Arya, *Indian J. Chem.* **1975**, *13*, 1262−1266.
[17] B. A. Arbuzov, G. G. Batenko, A. B. Remizov, E. N. Klimovitskii, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1972**, *8*, 375−379.
[18] J. Maillard, M. Vincent, P. Delaunay, M. Rapin, Vo-Van-Tri, G. Remond, *Chim. Ther.* **1969**, *4*, 80−88.
[19] K. Yoda, T. Toda, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2519−2521.
[20] E. N. Prilezhaeva, E. S. Shapiro, *Dokl. Chem. (Engl. Transl.)* **1967**, 579−582.
[21] A. C. Bellaart, *Recl. Trav. Chim. Pays Bas* **1967**, *81*, 156−159.
[22] A. H. Ford-Moore, *J. Chem. Soc.* **1949**, 2433−2440.
[23] Lin Li, S. W. Tsai, A-L. Anderson, D. A. Keire, A. A. Ravbitschek, J. E. Shively, *Bioconjugate Chem.* **2002**, *13*, 110−115.
[24] R. M. Black, K. Brewster, R. J. Clarke, J. M. Harrison, *Phosphorus, Sulfur Silicon* **1992**, *71*, 49−58.
[25] Y. Nagao, H. Sakurai, *Chem. Lett.* **1976**, 379−380.
[26] H. Kropf, M. Ball, *Tetrahedron* **1972**, *28*, 1391−1401.
[27] N. S. Simpkins, *Tetrahedron* **1990**, *46*, 6951−6984.
[28] D. Enders, S. F. Müller, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **2000**, 879−892 and references cited therein.
[29] Y. Kuroki, R. Lett, *Tetrahedron Lett.* **1984**, *25*, 197−200.
[30] H. K. Oh, J. H. Yang, H. W. Lee, I. Lee, *J. Org. Chem.* **2000**, *65*, 5391−5395 and references cited therein.
[31] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, *18*, 734−736.
[32] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849−3862.
[33] M. A. Casadei, B. Di Rienzo, A. Inesi, F. M. Moracci, *J. Chem. Soc., Perkin Trans. 1* **1992**, 375−378.
[34] V. J. Gatto, K. A. Arnold, A. M. Viscariello, S. R. Miller, C. R. Morgan, G. W. Gokel, *J. Org. Chem.* **1986**, *51*, 5373−5384.
[35] H. A. O. Hill, K. A. Raspin, *J. Chem. Soc. A* **1968**, 3036−3039.
[36] G. Hervé, H. Bernard, L. Toupet, H. Handel, *Eur. J. Org. Chem.* **2000**, 33−35.
[37] A. Bencini, A. Bianchi, E. Garcia-España, M. Micheloni, P. Paoletti, *Inorg. Chem.* **1987**, *26*, 681−684.
[38] B. Dietrich, B. Dilworth, J.-M. Lehn, J.-P. Souchez, M. Cesario, J. Guilhem, C. Pascard, *Helv. Chim. Acta* **1996**, *79*, 569−587.
[39] S. Stewer, J. Podlech, *Eur. J. Org. Chem.* **2002**, 899−916.
[40] D. A. Goff, R. N. Zuckermann, *Tetrahedron Lett.* **1996**, *37*, 6247−6250.
[41] R. L. Snowden, M. Wüst, *Tetrahedron Lett.* **1986**, *27*, 699−702.
[42] CCDC-187096, -187418, -187503 and -187703 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[43] M.-L. Teyssot, Thesis, Université Grenoble I, France, to be published.

Received July 10, 2002
[O02377]