New Chiral Catalysts Containing *N,O*-Heterocycles Derived from Chiral Amino Alcohols

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Dedicated to Ernest L. Eliel with our greatest consideration and respect

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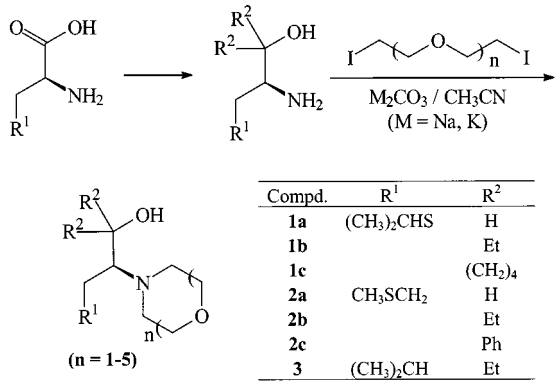
The enantioselectivity exerted by a new series of chiral catalysts containing *N,O*-heterocycles of different sizes has been checked in the addition of diethylzinc to benzaldehyde, which was used as a model reaction. The catalysts were derived from natural amino acids, following a relatively simple procedure, and in several cases excellent *ee* values were obtained. The results were complementary since *ee*'s ranged from 98% (*R*) to 94% (*S*) excesses of the final 1-phenylpropan-1-ol. Molecular mechanics calculations suggested that the production of the *R* alcohol may be explained by a mechanism similar to that described by Noyori, in which $ZnEt_2$ interacts solely with the N–C–C–OH fragment, whereas the formation of the *S* enantiomer needed the direct participation of the lateral chain of the parent amino acid and the *N,O*-heterocycle.

Introduction

Chiral β-amino alcohols are common motifs in the design of catalysts for asymmetric synthesis as they are, in general, readily accessible in an enantiomerically pure form in a few steps from natural precursors, i.e. α-amino acids.[1] Thus, for example, the stereoselective preparation of secondary alcohols by addition of dialkylzinc reagents to aldehydes, catalyzed by chiral β-amino alcohols[2] has been extensively investigated by the German laboratory.[3] On the other hand, chiral β-amino alcohols are also the key entry point to the synthesis of chiral azacrown ethers which have been used by the Spanish laboratory to catalyze asymmetric Michael-type additions.[4] Bringing together both areas of expertise, we are now working on the design of new, optically active catalysts based on *N,O*-heterocycles of different ring sizes. In a previous communication[5] we reported the excellent enantioselection induced by some of the catalysts **1b,c** (Scheme 1), derived from (*R*)-cysteine, in the addition of diethylzinc to benzaldehyde which we used as a model reaction. In the present paper we give a full account of our attempts at understanding the role played by the side chain R^1 of the parent amino acid and the influence of the size of the *N,O*-heterocycle. We hereby extend our results to a new series derived from (*S*)-methionine (**2a–c**) and (*S*)-leucine (**3**; Scheme 1) and try, for the first time, to rationalize the observed enantioselection by molecular mechanics calculations.



Compd.	R^1	R^2
1a	$(CH_3)_2CHS$	H
1b		Et
1c		$(CH_2)_4$
2a	CH_3SCH_2	H
2b		Et
2c		Ph
3	$(CH_3)_2CH$	Et

Scheme 1

Results and Discussion

Synthesis and NMR Spectroscopic Data

The synthesis of the amino alcohols **1a–c**, **2a–c** and **3** was accomplished in a four- or five-step sequence from (*R*)-cysteine, (*S*)-methionine and (*S*)-leucine, respectively, according to procedures described in the literature.[6] In the case of compounds **1** (Scheme 1), the thiol group was first transformed into its *i*Pr-thioether before converting the acid group into its ethyl ester. Treatment of the latter with the appropriate Grignard reagent or hydride afforded the desired amino alcohols[7] which, upon treatment with the appropriate diiodopolyethylendioxa derivative in the presence of M_2CO_3 (M = Na, K), gave the *N,O*-heterocycles depicted in Scheme 1 in *ca.* 50% average overall yield.[8]

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The NMR spectra of the compounds in Scheme 1 showed relatively large chemical shift differences between the different diasterotopic protons [see for example the case of **3** (n = 3) depicted in Figure 1]. This suggests highly conformational-biased structures in which intramolecular hydrogen bonding between the OH group and the N atom should play a decisive role (see Figure 1).[9] Moreover, some compounds displayed broad and/or split signals at room temperature indicating the existence of hindered rotation around the bond between the stereogenic center and the N atom (C*−N). For instance, compounds **3** with the larger heterocycles (n = 3 to 5; Scheme 1) showed two broad signals ($\Delta\delta$ = 600−650 Hz) at room temp. in the ^{13}C NMR spectrum for the heterocyclic C−N−C fragment and coalescence occurred at 50−60°C in $CDCl_3$, thus giving a value for $\Delta G^{\neq}$ close to 24 kcal·mol^{-1}. In the case of **3** bearing the morpholine ring (n = 1) or the small "9-crown-3" (n = 2), their ^{13}C NMR spectra at room temp. were slightly above or at coalescence, respectively, indicating that the barrier to rotation of the C*−N bond is lower when the ring is smaller (ca. 14 kcal/mol). On the other hand, the NMR spectra of the methionine derivatives (**2**) at room temp. were, in general, much narrower implying that the barrier to rotation is the lowest in the series. This should be due, as expected, to the inferior bulkiness of R^1 in **2** (Scheme 1).

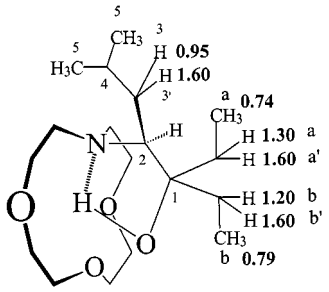


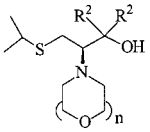
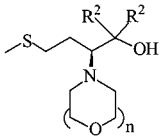
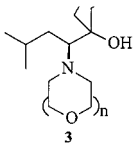
Figure 1. Some relevant ^1H NMR chemical shifts for compound **3** (n = 3) (cf. Scheme 1) and expected mayor conformer of the fragment N−C−C−OH

Diethylzinc Addition

The enantioselective addition of diethylzinc to C=O bonds has been checked with benzaldehyde in the presence of the optically active catalysts **1**−**3**. In a typical procedure,[10] the reaction was carried out at 22°C for 48 h with a catalyst concentration of 5 mol-% relative to benzaldehyde. Chemical yields ranged from moderate to good. Table 1 summarizes the obtained results, which have been gathered in Figure 2 to facilitate the discussion.

It can be seen that the presence of R^2 substituents is essential for our catalysts to induce a reasonable degree of enantioselection. Hence, when R^2 = H as in compounds **1a** and **2a** (solid circles and triangles in Figure 2), *ee* values were always very small (Table 1). On the other hand, with bulkier R^2 groups higher *ee* values were obtained. This is especially evident along series **2** where the highest enantioselectivities were obtained when R^2 = Ph (Table 1; entries

Table 1. Enantiomeric excesses and chemical yields of the diethylzinc addition to benzaldehyde catalyzed by chiral compounds **1**−**3**

Catalyst	entry	Compd. (n)	% e.e (conf.)[a]	yield
 **1** **a**: R^2 = H **b**: R^2 = Et **c**: R^2 = -$(CH_2)_4$-	1	**1a** (1)	26 (*R*)	65
	2	**1b** (1)	92 (*R*)	84
	3	**1c** (1)	71 (*R*)	81
	4	**1a** (2)	7 (*R*)	68
	5	**1b** (2)	48 (*R*)	83
	6	**1c** (2)	70 (*R*)	85
	7	**1a** (3)	3 (*S*)	59
	8	**1b** (3)	5 (*S*)	79
	9	**1c** (3)	11 (*S*)	82
	10	**1a** (4)	9 (*R*)	44
	11	**1b** (4)	33 (*R*)	78
	12	**1c** (4)	38 (*R*)	82
	13	**1a** (5)	12 (*R*)	54
	14	**1b** (5)	36 (*R*)	76
	15	**1c** (5)	31 (*R*)	75
 **2** **a**: R^2 = H **b**: R^2 = Et **c**: R^2 = Ph	16	**2a** (1)	8 (*R*)	47
	17	**2b** (1)	83 (*R*)	79
	18	**2c** (1)	53 (*R*)	85
	19	**2a** (2)	14 (*R*)	68
	20	**2b** (2)	63 (*S*)	76
	21	**2c** (2)	94 (*S*)	81
	22	**2a** (3)	1 (*S*)	62
	23	**2b** (3)	39 (*S*)	79
	24	**2c** (3)	93 (*S*)	89
	25	**2a** (4)	4 (*R*)	59
	26	**2b** (4)	31 (*S*)	73
	27	**2c** (4)	91 (*S*)	94
	28	**2a** (5)	1 (*S*)	56
	29	**2b** (5)	35 (*S*)	70
	30	**2c** (5)	72 (*S*)	85
 **3**	31	**3** (1)	98 (*R*)	76
	32	**3** (2)	72 (*R*)	76
	33	**3** (3)	16 (*R*)	80
	34	**3** (4)	50 (*R*)	73
	35	**3** (5)	33 (*R*)	70

[a] Product configuration as determined by chiral GC analysis (SGE Cydec-B, chiral) and comparison with authentic samples

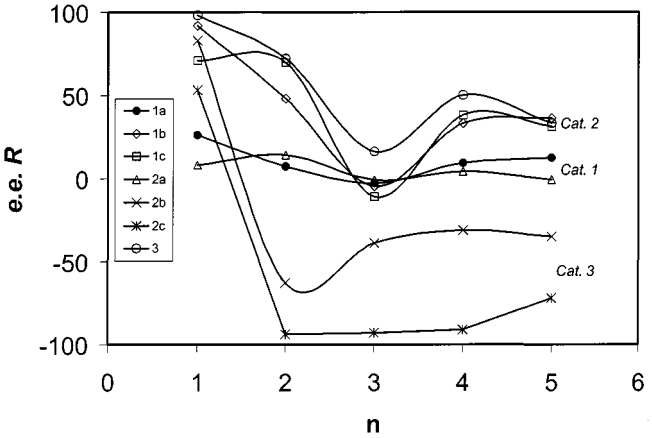
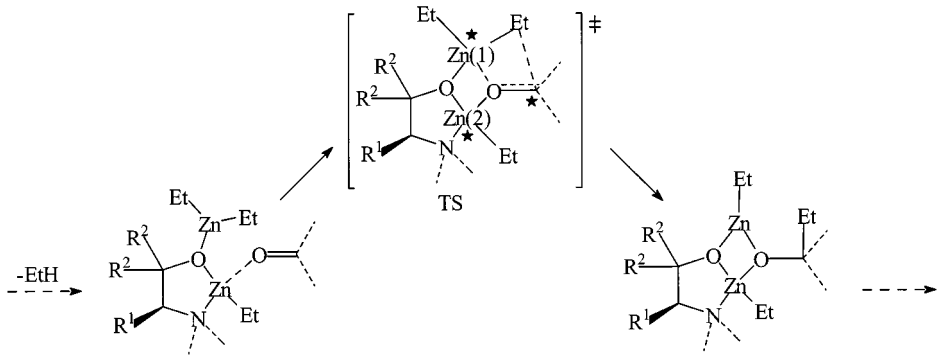


Figure 2. Plot of *ee* values *vs.* ring size for the compounds of Table 1

19 to 30). It is noteworthy that all morpholine derivatives (cf. Figure 2; n = 1) gave (*R*)-1-phenylpropan-1-ol, regardless of the nature of the R^1 group, and in some instances with excellent *ee* values (see, for example, entries 2 and 31). In these cases, calculations (vide infra) supported a reaction pathway similar to that proposed by Noyori, where neither the morpholine ring nor the R^1 chain play a direct role in the induced enantioselection. However, it was observed that



Scheme 2. Crucial steps in dialkylzinc addition mechanism

an increase of ring size diminished the degree of *R* enantioselection and in some cases caused the *S* alcohol to be in excess (see, for example, entries 8, 9 and 19−30). With this in mind, Figure 2 clearly shows that our catalysts may be grouped into three different categories, of which that containing **1a** and **2a**, both exerting very low *ee*'s, has already been mentioned. The second category, containing **1b** (diamonds), **1c** (squares) and **3** (circles), displayed a very similar evolution of induced *ee* values as a function of ring size. Taking into account that these catalysts only differ in the sulfur atom (cf. Scheme 1), Figure 2 suggests a negligible influence of this heteroatom on the reaction products of compounds **1**. Besides, the minimum enantioselection was attained for n = 3, i.e. for the 12-crown-4. Considering the known affinity of Zn^{2+} for macrocycles of four heteroatoms,[11] this fact suggests a possible competition of the metal for chelation to two different sites: the N−C−C−OH fragment, as in the mechanism proposed by Noyori (see below), and the *N,O*-heterocycle. Our results suggest that these chelation patterns lead to different stereochemical outcomes. In the third and last category (Figure 2), one may group together compounds **2b** (crosses) and **2c** (stars). They induced an almost constant production of (*S*)-1-phenylpropan-1-ol for n = 2 to 5, which was remarkably high in the case of **2c**.

A cross comparison between the second and third categories is instructive concerning the role of sulfur, which was considered negligible in the case of catalysts **1**. For instance, **1b** and **2b** (n = 2) produced very different *ee* values (**1b**, 48% *R*; **2b**, 63% *S*; entries 5 and 20) even though they are quite alike except for the position and substitution of the sulfur atom. The only plausible explanation for this difference is that participation of the S atom cannot be definitely ruled out in the course of the reaction, provided this heteroatom is sterically unhindered as in **2b**. However, the influence of sulfur should also be influenced by the size of the *N,O*-heterocycle since, as we have already commented, when n = 1 (Figure 2) all compounds (except **2a** which did not induce any significant *ee*) displayed a similar reactivity regardless of the presence or absence of sulfur. The rigidity of the morpholine ring, relative to its larger counterparts, may favor a Noyori-type mechanism, which would appear to satisfactorily explain the enantioselection observed for n = 1 (see calculations section). Work is in progress to find an alternative model to Noyori's which could take into account the various effects exerted by the S atom of the R^1 chain, and the *N,O*-heterocycle.

Calculations

The mechanism of the addition of dialkylzinc reagents to aldehydes promoted by chiral amino alcohols is relatively well documented by Noyori.[12][13] Scheme 2 depicts the crucial steps of the catalytic cycle.

Taking into account the two possible pro-*R* and pro-*S* situations for ethyl transfer, and that the two Zn atoms are stereogenic in the transition state (TS; Scheme 2), one must consider eight possible diastereomeric TS's for ethyl addition from Et_2Zn to benzaldehyde when catalyzed by the compounds of Scheme 1. Molecular mechanics calculations of these eight TS's were performed with the HyperChem program and MM+, which is based on Allinger's MMP2.[14] In order to obtain reliable parameters for the bonds of the bimetallic core of the dinuclear complex we adjusted their values and atom types (Figure 3 and Table 2) by reproducing the structures of the model transtion states calculated by Noyori by ab initio methods.[11]

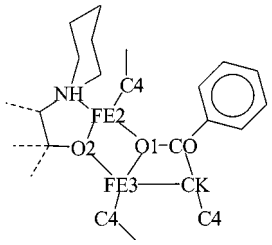


Figure 3. Atom types for MM+ calculation

The RMS fit between our calculated structures by MM+ and Noyori's ab initio was better than 0.96. We found that for all calculated diastereomeric transition-state complexes, the most stable conformer was predicted to have: (i) an axial arrangement of the morpholine Zn−N bond (ca. 2 Å), therefore leaving the shorter bond with the stereogenic carbon equatorial; (ii) a pseudoequatorial arrangement of the R^1 chain which is thus assumed to play only *an indirect role* in the asymmetric induction. Additionally, the different ethyl and phenyl groups in the molecule were conformationally searched to reach the lowest energy minima.

Table 2. Final parameters and chosen atom types for Hyperchem calculations (see text)

T1	T2	KS	L0	L1	DIPOLE
nh	fe2	5.000	2.143	0.000	0.000
o2	fe2	5.000	1.950	0.000	0.000
o2	fe3	5.000	1.920	0.000	0.000
o1	fe2	2.500	2.050	0.000	0.000
o1	fe3	2.500	2.530	0.000	0.000
c4	fe2	5.000	1.970	0.000	0.000
c4	fe3	5.000	1.980	0.000	0.000
ck	co	2.500	2.250	0.000	0.000
fe3	ck	2.500	2.160	0.000	0.000

T1	T2	T3	KS	TYPE1	TYPE2	TYPE3
o2	fe2	nh	0.400	80.300	80.300	80.300
fe2	o2	fe3	0.300	113.100	113.100	113.100
o2	fe2	o1	1.000	82.950	82.950	82.950
o2	fe3	o1	0.500	71.000	71.000	71.000
o2	fe2	c4	0.500	141.200	141.200	141.200
o1	fe2	c4	0.100	121.400	121.400	121.400
o2	fe3	c4	0.100	131.300	131.300	131.300
o1	fe3	c4	0.100	122.600	122.600	122.600
fe2	o2	c4	2.000	116.000	116.000	116.000
fe3	o2	c4	0.500	120.500	120.500	120.500
fe2	nh	c4	0.100	98.600	98.600	98.600
nh	fe2	c4	0.050	117.400	117.400	117.400
fe2	c4	fe2	0.100	120.000	120.000	120.000
fe2	c4	c4	0.100	109.500	109.500	109.500
fe3	c4	c4	0.100	109.500	109.500	109.500
fe2	o1	co	0.100	133.900	133.900	133.900
fe3	o1	co	0.500	80.800	80.800	80.800
fe2	o1	fe3	0.500	88.000	88.000	88.000
fe2	o2	fe3	0.500	112.400	112.400	112.400
fe3	ck	co	0.100	73.700	73.700	73.700
fe3	ck	h	0.100	128.900	128.900	128.900
fe3	ck	c4	999.000	109.500	109.500	109.500
c4	ck	co	999.000	180.000	180.000	180.000
o1	co	ck	0.500	114.400	114.400	114.400
o2	fe3	ck	0.400	102.800	102.800	102.800
c4	fe3	ck	2.000	126.000	126.000	126.000
ck	co	h	0.300	86.600	86.600	86.600
co	ck	h	0.100	109.500	109.500	109.500
fe2	nh	hb	0.500	112.900	112.900	112.900
ck	fe3	o1	0.200	79.000	79.000	79.000
fe2	c4	h	1.000	112.800	112.800	112.800
fe3	c4	h	1.000	112.800	112.800	112.800
nh	fe2	o1	0.500	103.100	103.100	103.100
h	ck	h	0.050	105.400	0.000	0.000
c4	c4	fe2	0.450	109.500	109.500	109.500
c4	c4	fe3	0.450	109.500	109.500	109.500
c4	fe3	c4	2.000	126.000	126.000	126.000

Table 3 shows the predicted relative energies of the various transition states calculated.

It can be seen that in all calculated morpholine TS′s the lowest energy corresponded to situations where the configuration at both metallic stereocenters resulted *S*. Furthermore, Table 3 shows that the calculated lowest energy TS′s were predicted to lead to (*R*)-1-phenylpropan-1-ol, in excellent agreement with our experimental results. This fact gives additional support to Noyori′s mechanism, at least in the case of our morpholine derivatives.

Table 3. MM+ relative energies (kcal/mol) of the eight possible diastereomeric transition states for ethyl transfer from Et_2Zn to benzaldehyde catalyzed by selected compounds **1b**, **2a** and **2c**

Zn(1),Zn(2)[a]	**1b** (n=1)	**2a** (n=1)	**2c** (n=1)	**2c** (n=2)
RR→(R)	3.6	0.6	2.3	2.5
RR→(S)	16.1	10.2	11.2	7.1
RS→(R)	6.6	5.0	5.7	1.7
RS→(S)	5.7	3.1	4.9	8.2
SR→(R)	3.4	1.7	4.1	3.4
SR→(S)	0.5	0.4	2.6	0.7
SS→(R)	**0.0**	**0.0**	**0.0**	**0.0**
SS→(S)	6.8	7.0	8.4	11.2

[a] Respective configuration of metal atoms. The configuration following the arrow indicates the stereochemistry of the final alcohol.

An inspection of all calculated TS′s shows that their librational motion should be severely restricted (and hence the induced enantioselection increased) by a critical cascade of interactions among the R^2 substituents (Et or Ph) and the ethyl groups bonded to Zn. This is in qualitative agreement with our experimental observation that catalyst **2a** (Table 1; entry 16), without R^2 substituents, gave the poorest *ee* value in the morpholine series. However, Table 3 also shows that, quantitatively speaking, these calculations have to be considered with a degree of caution. The energy difference (kcal/mol) between the lowest TS and the next lowest one leading to the *S* alcohol was in the order (n = 1) **2c** (2.6) > **1b** (0.5) > **2a** (0.4). This is in very crude agreement with the observed induced *ee* values (53%, 92% and 8% for entries 18, 2 and 16 in Table 1, respectively).

Finally, we have calculated for one example, **2c** (n = 2), the influence of the ring size. The last column in Table 3 shows that the predicted energy difference between TS′s leading to *R* and *S* alcohols is greatly reduced in the case of **2c**, from 2.6 kcal/mol for n = 1 to 0.7 kcal/mol for n = 2. However, the TS leading to the *R* alcohol is still the lowest in energy, contrary to the experimental results in which the *S* alcohol was produced in 94% *ee* (Table 1, entry 21). This suggests that one should invoke additional factors, other than simply steric ones, to explain the production of the *S* alcohol for **2b−c** when the ring is larger than morpholine.

Conclusions

The catalysts described in this paper produced excellent *ee* values for the addition of diethylzinc to benzaldehyde and gave complementary results concerning enantioselection of the final alcohol since *ee*′s ranged from 98% to 94% of *R* and *S* excesses, respectively. We have explained the production of the *R* alcohol by a mechanism similar to that described by Noyori, in which $ZnEt_2$ interacts solely with the N−C*−C−OH fragment, leaving the lateral chain of the parent amino acid (R^1) and the *N,O*-heterocycle to play an indirect role in the induced enantioselection. However, our results have shown that the direct participation of R^1 (provided it contained an unhindered thioether function) and the *N,O*-heterocycle (if it was sufficiently large) reversed the stereochemical outcome of the reaction by a mechanism which is still unclear.

Experimental Section

General: ^{1}H NMR: Bruker AC 300 (300 MHz), Bruker DRX 500 (500 MHz), δ = 0 (tetramethylsilane) and 7.24 ($CHCl_3$). Characterization of signal multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet bm = broad multiplet. − ^{13}C NMR: Bruker AC 300 (75 MHz), Bruker DRX 500 (125 MHz), δ = 77.0 ($CDCl_3$). Assignments of the signals in the ^{13}C NMR spectrum were supported by measurements applying DEPT, HMQC and COSY 45 techniques. High resolution mass and FAB spectra were recorded on a VG Autospec spectrometer. Optical rotation was measured on a Perkin−Elmer M-50 polarimeter. Amino alcohols and polyethylenoxadiiodo derivatives were prepared as previously described.[6,4] Starting amino acids were provided by Degussa AG and the diethylzinc from Witco GmbH.

General Procedure for Preparation of *N,O*-Heterocycles: To a refluxed suspension of 1 equiv. of ca. 1×10^{-3} M amino alcohol and 4−5 equiv. of sodium or potassium carbonate in dry acetonitrile, 1 equiv. of the corresponding polyethylendioxadiiodo (ca. $7 \cdot \times 10^{-2}$ M in dry acetonitrile) was added in small portions during a time span of several hours. The reaction mixture was refluxed for several days and its progress was checked by TLC. The mixture was allowed to cool to room temperature and the salts filtered off. The filtrate was concentrated at reduced pressure and then washed with 50−150 mL of water and extracted with dichloromethane (4 × 100 mL). The organic layer was dried over sodium sulfate and the solvent evaporated at reduced pressure. The remaining oil was chromatographed on silica gel with the eluent indicated in each case.

General Procedure for Diethylzinc Addition: A solution of diethylzinc (1.1 M in toluene, 10 mmol) was added to a solution of the respective amount of catalyst **1−3** (5 mol-% relative to benzaldehyde) in dry toluene at −20°C under an argon atmosphere. The mixture was allowed to reach room temperature and then treated with 10 mmol of benzaldehyde in dry toluene. The resulting yellow mixture was stirred for 16 h at room temperature. The reaction was quenched with 2 N hydrochloric acid, the organic layer separated and the aqueous layer extracted with diethyl ether. The combined organic layers were extracted with sodium hydrogen sulfite solution, sodium hydrogen carbonate solution and water, before drying (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue distilled under vacuum to afford 1-phenyl-1-propanol. The enantiomeric excess was determined by GC analysis (SGE Cydec-B, chiral) and the absolute configuration was detected by chiral GC analysis by comparison with authentic samples. The obtained results are gathered in Table 1.

(*R*)-3-Isopropylthio-2-morpholin-4′-yl-propan-1-ol {1a (n = 1)}: This compound was prepared following the general procedure described above from (*R*)-cysteinol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with *n*-hexane/ethyl acetate (2:8, + 3% triethylamine); R_f = 0.28 − Yield: 0.93 g (53%) colorless oil. − $[\alpha]_D^{20}$ = +35.1 (*c* = 1.19, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3400−3200 cm^{-1} (OH). − ^{1}H NMR ($CDCl_3$): δ = 1.23 {d, *J* = 6.67 Hz, 3 H, $CH(CH_3)_2$}, 1.27 {d, *J* = 6.65 Hz, 3 H, $CH(CH_3)_2$}, 2.32 (dd, *J* = 10.14 Hz, *J* = 13.68 Hz, 1 H, CH_2S), 2.49 {m, 2 H, CH_2S, $CH(CH_3)_2$}, 2.70−2.92 (m, 5 H, 3-H_2, 5-H_2, CH_2OH), 3.37 (dd, *J* = 9.52 Hz, *J* = 10.91 Hz, 1 H, CH_2OH), 3.4−3.76 (m, 5 H, CHN, 2-H_2, 6-H_2). − ^{13}C NMR ($CDCl_3$): δ = 23.11, 23.15 {$CH(CH_3)_2$}, 26.55 (CH_2S), 35.60 {$CH(CH_3)_2$}, 48.49 (C-3, C-5), 59.95 (CH_2OH), 65.07 (CHN), 67.24 (C-2, C-6). − MS (CI, *i*-butane); *m*/*z* (%): 220 (100) [MH^+]. − $C_{10}H_{21}NO_2S$ (219.3): calcd. C 54.76, H 9.65, N 6.38, S 14.62; found C 54.60, H 9.53, N 6.59, S 14.26.

(*R*)-2-(1′,4′-Dioxa-7′-azacyclononan-7′-yl)-3-isopropylthiopropan-1-ol, {1a (n = 2)}: This compound was prepared following the general procedure described above from (*R*)-cysteinol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with *n*-hexane/ethyl acetate (2:8); R_f = 0.23. − Yield: 0.57 g (27%) colorless oil. − $[\alpha]_D^{20}$ = +42.8 (*c* = 1.19, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3600−3300 cm^{-1} (OH), 1200 (C−O−C). − ^{1}H NMR ($CDCl_3$): δ = 1.24 {d, *J* = 6.68 Hz, 3 H, $CH(CH_3)_2$}, 1.26 {d, *J* = 6.72 Hz, 3 H, $CH(CH_3)_2$}, 2.39 (dd, *J* = 8.44 Hz, *J* = 12.61 Hz, 1 H, CH_2S), 2.73 (dd, *J* = 5.55 Hz, *J* = 12.10 Hz, 1 H, CH_2S), 2.78−2.96 (m, 6 H, $CH(CH_3)_2$, CH_2OH, 6-H_2, 8-H_2), 3.30 (m, 1 H, CH_2OH), 3.56−3.78 (m, 9 H, 2-H_2, 3-H_2, 5-H_2, 9-H_2, CHN). − ^{13}C NMR ($CDCl_3$): δ = 23.22 {$CH(CH_3)_2$}, 28.20 (CH_2S), 35.60 {$CH(CH_3)_2$}, 51.69 (C-5, C-8), 61.65, 63.74 (CH_2OH, CHN), 73.21, 73.94 (C-2, C-3, C-5, C-9). − MS (CI, *i*-butane); *m*/*z* (%): 264 (100) [MH^+]. − $C_{12}H_{25}NO_3S$ (263.4): calcd. C 54.72, H 9.57, N 5.32, S 12.17; found C 54.61, H 9.60, N 5.33, S 12.23.

(*R*)-3-Isopropylthio-2-(1′,4′,7′-trioxa-10′-azacyclododecan-10′-yl)-propan-1-ol, {1a (n = 3)}: This compound was prepared following the general procedure described above from (*R*)-cysteinol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with *n*-hexane/triethylamine (3:2); R_f = 0.30. − Yield: 1.18 g (48%) slightly yellow oil. − $[\alpha]_D^{20}$ = +56.4 (*c* = 1.19, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3550−3150 cm^{-1} (OH), 1130 (C−O−C). − ^{1}H NMR ($CDCl_3$): δ = 1.23 {d, *J* = 6.6 Hz, 6 H, $CH(CH_3)_2$}, 2.30 (dd, *J* = 7.89 Hz, *J* = 12.59 Hz, 1 H, CH_2S), 2.63−2.95 (m, 7 H, CH_2S, $CH(CH_3)_2$, CH_2OH, 9-H_2, 11-H_2), 3.26 (m, 1 H, CH_2OH), 3.45−3.70 (m, 13 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 12-H_2), 4.27 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 23.24 {$CH(CH_3)_2$}, 27.98 (CH_2S), 35.61 {$CH(CH_3)_2$}, 50.42 (C-9, C-11), 61.35, 61.67 (CHN, CH_2OH), 69.07, 69.99, 70.43 (C-2, C-3, C-5, C-6, C-8, C-12). − MS (CI, *i*-butane); *m*/*z* (%): 308 (100) [MH^+]. − $C_{14}H_{29}NO_4S$ (307.5): calcd. C 54.69, H 9.51, N 4.56, S 10.43; found C 54.60, H 9.21, N 4.55, S 10.54.

(*R*)-3-Isopropylthio-2-(1′,4′,7′,10′-tetraoxa-13′-azacyclopentadecan-13′-yl)-propan-1-ol, {1a (n = 4)}: This compound was prepared following the general procedure described above from (*R*)-cysteinol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxapentadecane. Column chromatography with *n*-hexane/ethyl acetate (3:7, + 3% triethylamine); R_f = 0.19. − Yield: 0.91 g (29%) colorless oil. − $[\alpha]_D^{20}$ = +39.0 (*c* = 1.0, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3500−3200 cm^{-1} (OH). − ^{1}H NMR ($CDCl_3$): δ = 1.24 {d, *J* = 6.81 Hz, 3 H, $CH(CH_3)_2$}, 1.26 {d, *J* = 6.62 Hz, 3 H, $CH(CH_3)_2$}, 2.32 (dd, *J* = 8.31 Hz, *J* = 12.70 Hz, 1 H, CH_2S), 2.66 (dd, *J* = 5.24 Hz, *J* = 12.30 Hz, 1 H, CH_2S), 2.74−3.03 {m, 6 H, CH_2OH, 12-H_2, 14-H_2, $CH(CH_3)_2$}, 3.28 (m, 1 H, CH_2OH), 3.51−3.70 (m, 17 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 15-H_2). − ^{13}C NMR ($CDCl_3$): δ = 23.27 {$CH(CH_3)_2$}, 27.63 (CH_2S), 35.57 {$CH(CH_3)_2$}, 51.03 (C-12, C-14), 61.63 (CH_2OH), 63.12 (CHN), 70.03, 70.33, 70.42, 70.87 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-15). − MS (CI, *i*-butane); *m*/*z* (%): 352 (100) [MH^+]. − $C_{16}H_{33}NO_5S$ (351.5): calcd. C 54.67, H 9.46, N 3.98, S 9.12; found C 54.40, H 9.32, N 3.89, S 8.99.

(*R*)-3-Isopropylthio-2-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclooctadecan-16′-yl)-propan-1-ol, {1a (n = 5)}: This compound was prepared following the general procedure described above from (*R*)-cysteinol, potassium carbonate and 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with ethyl acetate/*n*-hexane/triethylamine (8:1:1); R_f = 0.40. − Yield: 0.52 g (17%)

slightly yellow oil. − $[\alpha]_D^{20}$ = +34.7 (*c* = 1.11, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3400−3100 cm^{-1} (OH). − ^1H NMR ($CDCl_3$): δ = 1.22 {d, *J* = 6.61 Hz, 3 H, CH(CH_3)$_2$}, 1.24 {d, *J* = 6.63 Hz, 3 H, CH(CH_3)$_2$}, 2.28 (dd, *J* = 8.54 Hz, *J* = 12.75 Hz, 1 H, CH_2S), 2.63−2.99 {m, 7 H, CH_2S, CH_2OH, 15-H_2, 17-H_2, C*H*(CH_3)$_2$}, 3.27 (m, 1 H, CH_2OH), 3.45−3.73 (m, 21 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 12-H_2, 13-H_2, 17-H_2). − ^{13}C NMR ($CDCl_3$): δ = 23.27, 23.38 {CH(*C*H_3)$_2$}, 27.42 (CH_2S), 35.57 {*C*H(CH_3)$_2$}, 50.43 (C-15, C-17), 61.48 (CH_2OH), 62.82 (CHN), 70.40, 70.57, 70.86 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-13, C-17). − MS (CI, *i*-butane); *m*/*z* (%): 396 (100) [MH^+]. − $C_{18}H_{37}NO_6S$ (395.6): calcd. C 54.66, H 9.43, N 3.54, S 8.11; found C 54.70, H 9.82, N 3.50, S 8.07.

(*R*)-3-Ethyl-1-isopropylthio-2-morpholin-4-yl-pentan-3-ol {1b (n = 1)}: This compound was prepared following the general procedure described above from (*R*)-2-amino-3-ethyl-1-isopropylthiopentan-3-ol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with ethyl acetate/*n*-hexane (4:6); R_f = 0.49. − Yield: 1.34 g (49%) colorless oil. − $[\alpha]_D^{20}$ = −45.14 (*c* = 0.88, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3600−3200 cm^{-1} (OH). − ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.32 Hz, 3 H, CH_2CH_3), 0.89 (t, *J* = 7.47 Hz, 3 H, CH_2CH_3), 1.26 {d, *J* = 6.63 Hz, 3 H, CH(CH_3)$_2$}, 1.29 {d, *J* = 6.68 Hz, 3 H, CH(CH_3)$_2$}, 1.32−1.46 (2m, 4 H, CH_2CH$_3$), 2.61, 2.77, 3.02 (3m, 7 H, C*H*(CH$_3$)$_2$, CH_2S, 3-H_2, 5-H_2), 3.58−3.71 (m, 5 H, H 2, 2-H_2, 6-H_2). − ^{13}C NMR ($CDCl_3$): δ = 7.62, 7.67 (CH_2CH_3), 23.21, 23.30 {CH(*C*H_3)$_2$}, 27.42, 27.52 (*C*H_2CH$_3$), 28.84 (CH_2S), 35.98 {*C*H(CH$_3$)$_2$}, 52.23 (C-3, C-5), 67.75 (C-2, C-6), 68.98 (CHN), 75.40 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 276 (100) [MH^+]. − $C_{14}H_{29}NO_2S$ (275.5): calcd. C 61.05, H 10.61, N 5.08, S 11.64; found C 61.66, H 10.23, N 4.98, S 11.97.

(*R*)-2-(1′,4′-Dioxa-7′-azacyclononan-7′-yl)-3-ethyl-1-isopropylthiopropan-1-ol, {1b (n = 2)}: This compound was prepared following the general procedure described above from (*R*)-2-amino-3-ethyl-1-isopropylthiopentan-3-ol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with ethyl acetate/*n*-hexane (9:1, + 1% triethylamine); R_f = 0.28. − Yield: 0.45 g (14%) colorless oil. − $[\alpha]_D^{20}$ = −10.8 (*c* = 1.09, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3500−3300 cm^{-1} (OH), 1200 (C−O−C). − ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.27 Hz, 3 H, CH_2CH_3), 0.92 (t, *J* = 7.48 Hz, 3 H, CH_2CH_3), 1.27 {d, *J* = 6.69 Hz, 3 H, CH(CH_3)$_2$}, 1.30 {d, *J* = 6.70 Hz, 3 H, CH(CH_3)$_2$}, 1.24−1.39 (m, 4 H, CH_2CH$_3$), 2.64 (m, 1 H, CH_2S), 2.77−3.14 (m, 6 H, CH_2S, C*H*(CH$_3$)$_2$, 6-H_2, 8-H_2), 3.55−3.92 (m, 9 H, CHN, 2-H_2, 3-H_2, 5-H_2, 9-H_2), 4.06 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 7.68 (CH_2CH_3), 23.29, 23.37 {CH(*C*H_3)$_2$}, 28.07 (CH_2S), 28.94 (*C*H_2CH$_3$), 35.86 {*C*H(CH$_3$)$_2$}, 68.73 (CHN), 73.98 (C-2, C-3, C-5, C-9), 74.46 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 320 (100) [MH^+]. − $C_{16}H_{33}NO_3S$ (319.5): calcd. C 60.15, H 10.41, N 4.38, S 10.04; found C 59.99, H 10.38, N 4.37, S 10.10.

(*R*)-3-Ethyl-1-isopropylthio-2-(1′,4′,7′-trioxa-10′-azacyclododecan-10′-yl)-pentan-3-ol, {1b (n = 3)}: This compound was prepared following the general procedure described above from (*R*)-2-amino-3-ethyl-1-isopropylthiopentan-3-ol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with ethyl acetate/*n*-hexane (7:3); R_f = 0.41. − Yield: 0.87 g (24%) colorless oil. − $[\alpha]_D^{20}$ = −15.1 (*c* = 0.97, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3500−3000 cm^{-1} (OH), 1080 (C−O−C). − ^1H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 7.15 Hz, 3 H, CH_2CH_3), 0.89 (t, *J* = 7.14 Hz, 3 H, CH_2CH_3), 1.27 {d, *J* = 6.2 Hz, 3 H, CH(CH_3)$_2$}, 1.28 {d, *J* = 6.2 Hz, 3 H, CH(CH_3)$_2$}, 1.53−1.75 (m, 4 H, 2 × CH_2CH$_3$), 2.69 (dd, *J* = 3.3 Hz, *J* = 12.7 Hz, 1 H, CH_2S), 2.76 (dd, *J* = 3.3 Hz, *J* = 11.54 Hz, 1 H, CH_2S), 2.82−2.98 {m, 6 H, CHN, 9-H_2, 11-H_2, C*H*(CH$_3$)$_2$}, 3.39−3.67 (m, 12 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 12-H_2), 4.25 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 7.65, 7.75 (CH_2CH_3), 23.34, 23.44 {CH(*C*H_3)$_2$}, 27.47, 27.64 (*C*H_2CH$_3$), 29.78 (CH_2S), 35.89 {*C*H(CH$_3$)$_2$}, 65.89 (CHN), 70.12 (C-2, C-3, C-5, C-6, C-8, C-12), 75.43 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 364 (100) [MH^+]. − $C_{18}H_{37}NO_4S$ (363.6): calcd. C 59.47, H 10.26, N 3.85, S 8.82; found C 59.62, H 10.48, N 3.74, S 8.69.

(*R*)-3-Etyl-1-isopropylthio-2-(1′,4′,7′,10′-tetraoxa-13′-azacyclopentadecan-13′-yl)-pentan-3-ol, {1b (n = 4)}: This compound was prepared following the general procedure described above from (*R*)-2-amino-3-ethyl-1-isopropylthiopentan-3-ol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxapentadecane. Column chromatography with ethyl acetate/*n*-hexane (7:3, + 1% triethylamine); R_f = 0.26. − Yield: 1.31 g (32%) colorless oil. − $[\alpha]_D^{20}$ = −16.89 (*c* = 0.74, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3600−3100 cm^{-1} (OH), 1150 (C−O−C). − ^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 7.47 Hz, 3 H, CH_2CH_3), 0.88 (t, *J* = 7.31 Hz, 3 H, CH_2CH_3), 1.27 {d, *J* = 6.68 Hz, 3 H, CH(CH_3)$_2$}, 1.28 {d, *J* = 6.65 Hz, 3 H, CH(CH_3)$_2$}, 1.54−1.77 (m, 4 H, CH_2CH$_3$), 2.68−3.05 (m, 7 H, CH_2S, C*H*(CH$_3$)$_2$, 12-H_2, 14-H_2), 3.45−3.71 (m, 17 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 15-H_2), 4.12 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 7.68, 7.76 (CH_2CH_3), 23.36, 23.45 {CH(*C*H_3)$_2$}, 27.42, 27.52 (*C*H_2CH$_3$), 29.31 (CH_2S), 35.95 {*C*H(CH$_3$)$_2$}, 68.14 (CHN), 70.10, 70.73, 71.18 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-15), 75.76 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 408 (100) [MH^+]. − $C_{20}H_{41}NO_5S$ (407.6): calcd. C 58.93, H 10.14, N 3.43, S 7.87; found C 58.73, H 10.19, N 3.26, S 7.41.

(*R*)-3-Ethyl-1-isopropylthio-2-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclooctadecan-16′-yl)-pentan-3-ol {1b (n = 5)}: This compound was prepared following the general procedure described above from (*R*)-2-amino-3-ethyl-1-isopropylthiopentan-3-ol, potassium carbonate and 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with ethyl acetate/*n*-hexane 8:2, + 3% triethylamine; R_f = 0.14. − Yield: 1.11 g (31%) colorless oil. − $[\alpha]_D^{20}$ = −24.0 (*c* = 1.24, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3500−3300 cm^{-1} (OH), 1100 (C−O−C). − ^1H NMR ($CDCl_3$): δ = 0.84 (t, *J* = 7.51 Hz, 3 H, CH_2CH_3), 0.87 (t, *J* = 7.46 Hz, 3 H, CH_2CH_3), 1.25 {d, *J* = 6.61 Hz, 3 H, CH(CH_3)$_2$}, 1.28 {d, *J* = 6.74 Hz, 3 H, CH(CH_3)$_2$}, 1.37−1.74 (m, 4 H, CH_2CH$_3$), 2.65−3.02 {m, 7 H, CH_2S, 15-H_2, 17-H_2, C*H*(CH$_3$)$_2$}, 3.64 (m, 21 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 12-H_2, 14-H_2, 18-H_2). − ^{13}C NMR ($CDCl_3$): δ = 7.66 (CH_2CH_3), 23.30, 23.39 {CH(*C*H_3)$_2$}, 27.45, 27.79 (*C*H_2CH$_3$), 29.05 (CH_2S), 35.94 {*C*H(CH$_3$)$_2$}, 54.63 (C-15, C-17), 65.93 (CHN), 70.37, 70.71, 70.96 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-14, C-18), 75.58 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 452 (100) [MH^+]. − $C_{22}H_{45}NO_6S$ (451.7): calcd. C 58.50, H 10.04, N 3.10, S 7.10; found C 58.42, H 10.13, N 3.09, S 7.05.

(*R*)-1-[(2′-Isopropylthio-1′-morpholin-4′′-yl)ethyl]-cyclopentan-1-ol, {1c (n = 1)}: This compound was prepared following the general procedure described above from (*R*)-1′-amino-1-ethyl-2′-isopropylthiocyclopentan-1-ol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with ethyl acetate/*n*-hexane 4:6; R_f = 0.49. − Yield: 1.10 g (50%) colorless oil. − $[\alpha]_D^{20}$ = −36.8 (*c* = 1.04, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3400−3000 cm^{-1} (OH). − ^1H NMR ($CDCl_3$): δ = 1.25 {d, *J* = 6.66 Hz, 3 H, CH(CH_3)$_2$}, 1.34 {d, *J* = 6.65 Hz, 3 H, CH(CH_3)$_2$}, 1.34−1.84 (m, 8 H, cyclopentyl-CH_2), 2.36 (dd, *J* = 2.22 Hz, *J* = 12.06 Hz, 1 H, CH_2S), 2.65−3.01 (m, 6 H, C*H*(CH$_3$)$_2$, CH_2S, 3-H_2, 5-H_2), 2.72

(dd, J = 2.45 Hz, J = 9.21 Hz, 1 H, CHN), 3.66 (m, 4 H, 2-H_2, 6-H_2). − ^{13}C NMR ($CDCl_3$): δ = 23.16, 23.27 {CH(CH_3)$_2$}, 23.50, 24.84, 36.01, 36.09 (cyclopentyl-CH_2), 27.14 (CH_2S), 38.65 {CH(CH$_3$)$_2$}, 50.94 (C-3, C-5), 67.66 (C-2, C-6), 70.21 (CHN), 82.05 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 274 (100) [MH$^+$]. − $C_{14}H_{27}NO_2S$ (273.4): calcd. C 61.50, H 9.95, N 5.12, S 11.73; found C 61.67, H 9.90, N 5.11, S 11.83.

(*R*)-1-[2′-Isopropylthio-1′-(1′′,4′′-dioxa-7′′-azacyclononan-7′′-yl)-ethyl]-cyclopentan-1-ol, {1c (n = 2)}: This compound was prepared following the general procedure described above from (*R*)-1′-amino-1-ethyl-2′-isopropylthiocyclopentan-1-ol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with ethyl acetate/*n*-hexane 7:3, + 1% triethylamine; R_f = 0.48. − Yield: 0.61 g (24%) slightly yellow oil. − IR (NaCl): ṽ = 3300−3000 cm^{-1} (OH). − ^{1}H NMR ($CDCl_3$): δ = 1.20 {d, J = 6.64 Hz, 3 H, CH(CH_3)$_2$}, 1.23 {d, J = 6.86 Hz, 3 H, CH(CH_3)$_2$}, 1.33−1.87 (m, 8 H, cyclopentyl-CH_2), 2.54−2.94 {m, 8 H, CHN, 2′-H_2, 6-H_2, 8-H_2, CH(CH$_3$)$_2$}, 3.55−3.87 (m, 8 H, 2-H_2, 3-H_2, 5-H_2, 9-H_2), 4.60 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 23.32 {CH(CH_3)$_2$}, 24.78, 35.60, 36.00 (cyclopentyl-CH_2), 28.92 (CH_2S), 39.14 {CH(CH$_3$)$_2$}, 54.50 (C-6, C-8), 69.65 (CHN), 73.88, 73.94 (C-2, C-3, C-5, C-9), 82.17 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 318 (100) [MH$^+$]. − $C_{16}H_{31}NO_3S$ (317.5): calcd. C 60.53, H 9.84, N 4.41, S 10.10; found C 60.58, H 9.93, N 4.53, S 10.42.

(*R*)-1-[(2′-Isopropylthio-1′-(1′′,4′′,7′′-trioxa-10′′-azacyclo-dodecan-10′′-yl)ethyl]-cyclopentan-1-ol, {1c (n = 3)}: This compound was prepared following the general procedure described above from (*R*)-1′-amino-1-ethyl-2′-isopropylthiocyclopentan-1-ol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with ethyl acetate/*n*-hexane 7:3; R_f = 0.20. − Yield: 1.01 g (28%) yellow oil. − $[\alpha]_D^{20}$ = −13.4 (*c* = 1.55, dichloromethane). − IR (NaCl): ṽ = 3500−3100 cm^{-1} (OH), 1180 (C−O−C). − ^{1}H NMR ($CDCl_3$): δ = 1.26 {d, J = 6.62 Hz, 3 H, CH(CH_3)$_2$}, 1.29 {d, J = 6.73 Hz, 3 H, CH(CH_3)$_2$}, 1.37−1.86 (m, 8 H, cyclopentyl−CH_2), 2.63 (dd, J = 2.2 Hz, J = 11.5 Hz, 1 H, CH_2S), 2.80−2.96 (m, 7 H, CH_2S, CH(CH$_3$)$_2$, CHN, 9-H_2, 11-H_2), 3.42−3.77 (m, 12 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 12-H_2), 4.60 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 23.27, 23.37 {CH(CH_3)$_2$}, 23.47, 24.89, 35.29, 35.97 (cyclopentyl-CH_2), 29.54 {CH(CH$_3$)$_2$}, 39.32 (CH_2S), 53.25 (C-9, C-11), 67.68 (CHN), 69.79, 70.16, 70.36 (C-2, C3, C-5, C-6, C-8, C-12), 82.82 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 362 (100) [MH$^+$]. − $C_{18}H_{35}NO_4S$ (361.5): calcd. C 59.81, H 9.76, N 3.87, S 8.87; found C 59.80, H 9.92, N 3.75, S 8.97.

(*R*)-1-[(2′-Isopropylthio-1′-(1′′,4′′,7′′,10′′-tetraoxa-13′′-azacyclo-pentadecan-13′′-yl)ethyl]-cyclopentan-1-ol, {1c (n = 4)}: This compound was prepared following the general procedure described above from (*R*)-1′-amino-1-ethyl-2′-isopropylthiocyclopentan-1-ol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxapentadecane. Column chromatography with ethyl acetate/*n*-hexane 7:3, + 1% triethylamine; R_f = 0.30. − Yield: 1.22 g (38%) colorless oil. − $[\alpha]_D^{20}$ = −15.4 (*c* = 0.81, dichloromethane). − IR (NaCl): ṽ = 3600−3200 cm^{-1} (OH), 1050 (C−O−C). − ^{1}H NMR ($CDCl_3$): δ = 1.18 {d, J = 6.66 Hz, 3 H, CH(CH_3)$_2$}, 1.22 {d, J = 6.72 Hz, 3 H, CH(CH_3)$_2$}, 1.30−1.84 (m, 8 H, cyclopentyl-CH_2), 2.60 (dd, J = 3.21 Hz, J = 12.33 Hz, 1 H, CH_2S), 2.72 (dd, J = 3.26 Hz, J = 10.43 Hz, 1 H, CH_2S), 2.76−2.93 (m, 5 H, CH(CH$_3$)$_2$, 12-H_2, 14-H_2), 3.42−3.77 (m, 17 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 15-H_2), 4.38 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 23.30 {CH(CH_3)$_2$}, 23.35, 24.54, 35.69, 35.86 (cyclopentyl-CH_2), 29.19 {CH(CH$_3$)$_2$}, 39.18 (CH_2S), 54.32 (C-12, C-14), 68.71 (CHN), 69.97, 70.52, 70.89, 71.23 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-15), 83.40 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 406 (100) [MH$^+$]. − $C_{20}H_{39}NO_5S$ (405.6): calcd. C 59.23, H 9.69, N 3.45, S 7.91; found C 59.00, H 9.61, N 3.44, S 8.01.

(*R*)-1-[(2′-Isopropylthio-1′-(1′′,4′′,7′′,10′′,13′′-pentaoxa-16′′-aza-cyclooctadecan-16′′-yl)ethyl]-cyclopentanol, {1c (n = 5)}: This compound was prepared following the general procedure described above from (*R*)-1′-amino-1-ethyl-2′-isopropylthiocyclopentan-1-ol, potassium carbonate and 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with ethyl acetate/*n*-hexane 8:2, + 2% triethylamine; R_f = 0.26. − Yield: 1.26 g (35%) colorless oil. − $[\alpha]_D^{20}$ = −13.8 (*c* = 1.28, dichloromethane). − IR (NaCl): ṽ = 3500−3200 cm^{-1} (OH), 1150 (C−O−C). − ^{1}H NMR ($CDCl_3$): δ = 1.23 {d, J = 6.70 Hz, 3 H, CH(CH_3)$_2$}, 1.27 {d, J = 6.68 Hz, 3 H, CH(CH_3)$_2$}, 1.33−1.88 (m, 8 H, cyclopentyl-CH_2), 2.65 (dd, J = 4.10 Hz, J = 11.92 Hz, 1 H, CH_2S), 2.76−2.97 (m, 6 H, CH_2S, CH(CH$_3$)$_2$, 15-H_2, 17-H_2), 3.46−3.70 (m, 21 H, CHN, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 12-H_2, 14-H_2, 18-H_2), 4.39 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 23.32 {CH(CH_3)$_2$}, 23.34, 24.43, 35.77, 35.90 (cyclopentyl-CH_2), 29.09 {CH(CH$_3$)$_2$}, 39.12 (CH_2S), 53.72 (C-15, C-17), 68.34 (CHN), 70.38, 70.56, 70.70, 70.93 (C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-14, C-18), 83.55 (COH). − MS (CI, *i*-butane); *m*/*z* (%): 450 (100) [MH$^+$]. − $C_{22}H_{43}NO_6S$ (449.7): calcd. C 58.77, H 9.64, N 3.12, S 7.13; found C 58.05, H 10.01, N 3.26, S 7.45.

(*S*)-4-Methylthio-2-morpholin-4-yl-butan-1-ol, {2a (n = 1)}: This compound was prepared following the general procedure described above from (*S*)-methioninol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with *n*-hexane/triethylamine 5:5, R_f = 0.38. − Yield: 1.35 g (66%). − $[\alpha]_D^{20}$ = +38.2 (c = 1.03, dichloromethane). − IR (NaCl): ṽ (cm^{-1}) = 3410 (b, O−H), 2930, 2900, 2840 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.40−1.53 (m, 1 H, SCH$_2$CH_2), 1.88−1.96 (m, 1 H, SCH$_2$CH_2), 2.11 (s, 3 H, SCH_3), 2.40−2.58, 2.61−2.82 (2 m, 4 H + 3 H, SCH_2CH$_2$, NCH, 3-H_2, 5-H_2), 3.11 (br, 1 H, OH), 3.33−3.41 (m, 1 H, CH_2OH), 3.55 (dd, ^{3}J = 5.0, 10.7 Hz, 1 H, CH_2OH), 3.64−3.77 (m, 4 H, 2-H_2, 6-H_2). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.4 (SCH_3), 25.1 (SCH$_2$$CH_2$), 31.7 (S$CH_2CH_2$), 48.5 (2 C, C-3, C-5), 60.0 (CH_2OH), 64.2 (NCH), 67.4 (2 C, C-2, C-6). − MS (CI, *i*butane); *m*/*z* (%): 206 (100) [MH$^+$], 158 (119) [MH$^+$ − MeSH]. − $C_9H_{19}NO_2S$ (205.3): calcd. C 52.65, H 9.33, N 6.82, S 15.62; found C 52.81, H 9.28, N 6.87, S 15.51.

(*S*)-4-Methylthio-2-(1,4-dioxa-7-azacyclonon-7′-yl)-butan-1-ol, {2a (n = 2)}: This compound was prepared following the general procedure described above from (*S*)-methioninol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with ethyl acetate/*n*-hexane/triethylamine 2:6:2, R_f = 0.42. − Yield: 0.61 g (26%). − $[\alpha]_D^{20}$ = +30.2 (*c* = 0.95, dichloromethane). − IR (NaCl): ṽ (cm^{-1}) = 3420 (b, O−H), 2910, 2850 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.47−1.60 (m, 1 H, SCH$_2$CH_2), 1.75−187 (m, 1 H, SCH$_2$CH_2), 2.10 (s, 3 H, SCH_3), 2.42−2.56, 2.69−2.79, 2.85−2.97 (3 m, 2 H + 2 H + 3 H, SCH_2CH$_2$, NCH, 6-H_2, 8-H_2), 3.24−3.33, 3.50−3.56, 3.64−3.83 (3 m, 1 H + 1 H + 8 H, CH_2OH, 2-H_2, 3-H_2, 5-H_2, 9-H_2). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.6 (SCH_3), 27.2 (SCH$_2$$CH_2$), 31.5 (S$CH_2CH_2$), 51.8 (2 C, C-6, C-8), 62.0 (CH_2OH), 63.1 (NCH), 73.6, 73.9 (4 C, C-2, C-3, C-5, 9-C). − MS (CI, *i*butane); *m*/*z* (%): 250 (100) [MH$^+$], 202 (10) [MH$^+$ − MeSH]. − $C_{11}H_{23}NO_3S$ (249.4): calcd. C 52.98, H 9.30, N 5.62, S 12.86; found C 52.74, H 9.19, N 5.53, S 12.81.

(*S*)-4-Methylthio-2-(1′,4′,7′-trioxa-10′-azacyclododec-10′-yl)-butan-1-ol, {2a (n = 3)}: This compound was prepared following the general procedure described above from (*S*)-methioninol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatog-

raphy with ethyl acetate/*n*-hexane/triethylamine (2:6:2), R_f = 0.39. − Yield: 1.89 g (64%). − $[\alpha]_D^{20}$ = +60.1 (*c* = 1.00, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3410 (b, O−H) cm^{-1}, 2930, 2870 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 1.30−1.53 (m, 1 H, SCH_2CH_2), 1.67−1.81 (m, 1 H, SCH_2CH_2), 2.10 (s, 3 H, SCH_3), 2.38−2.55, 2.60−2.70, 2.75−2.94 (3 m, 2 H + 2 H + 3 H, SCH_2CH_2, NC*H*, 9-H_2, 11-H_2), 3.24−3.33, 3.40−3.50, 3.51−3.76 (3 m, 1 H + 3 H + 10 H, CH_2OH, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 12-H_2), 4.27 (br, 1 H, O*H*). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.3 (SCH_3), 26.9 (SCH_2CH_2), 31.7 (SCH_2CH_2), 50.5 (2 C, C-9, C-11), 60.6 (N*C*H), 61.9 (CH_2OH), 69.2, 70.0, 70.4 (6 C, C-2, C-3, C-5, C-6, C-8, C-12). − MS (CI, *i*butane); *m*/*z* (%): 294 (100) [MH^+], 246 (8) [MH^+ − MeSH]. − $C_{13}H_{27}NO_4S$ (293.4): calcd. C 53.21, H 9.27, N 4.77, S 10.93; found C 53.18, H 9.21, N 4.72, S 10.89.

(*S*)-4-Methylthio-2-(1′,4′,7′,10′-tetraoxa-13′-azacyclopentadec-13′-yl)-butan-1-ol, {2a (n = 4)}: This compound was prepared following the general procedure described above from (*S*)-methioninol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane. Column chromatography with ethyl acetate/*n*-hexane/triethylamine 3:4:3, R_f = 0.38. − Yield: 1.02 g (30%). − $[\alpha]_D^{20}$ = +39.1 (*c* = 1.00, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3340 (b, O−H) cm^{-1}, 2920, 2870 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 1.40−1.53 (m, 1 H, SCH_2CH_2), 1.71−1.84 (m, 1 H, SCH_2CH_2), 2.10 (s, 3 H, SCH_3), 2.40−2.55, 2.64−2.74, 2.79−2.96 (3 m, 2 H + 2 H + 3 H, 12-H_2, 14-H_2, SCH_2CH_2, NC*H*), 3.23−3.31, 3.41−3.56, 3.57−3.74 (3 m, 1 H + 3 H + 14 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 15-H_2, CH_2OH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.5 (SCH_3), 26.6 (SCH_2CH_2), 31.8 (SCH_2CH_2), 51.1, 61.8 (3 C, C-12, C-14, CH_2OH), 62.4 (N*C*H), 70.0, 70.4, 70.9 (8 C, C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-15). − MS (CI, *i*butane); *m*/*z* (%): 338 (100) [MH^+], 290 (9) [MH^+ − MeSH]. − $C_{15}H_{31}NO_5S$ (337.5): calcd. C 53.39, H 9.26, N 4.15, S 9.50; found C 53.47, H 9.31, N 4.11, S 9.39.

(*S*)-4-Methylthio-2-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclooctadec-16′-yl)-butan-1-ol, {2a (n = 5)}: This compound was prepared following the general procedure described above from (*S*)-methioninol, potassium carbonate and 1,17 diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with *n*-hexane/diisopropylamine (4:6), R_f = 0.20. − Yield: 0.84 g (22%). − $[\alpha]_D^{20}$ = +37.7 (*c* = 1.00, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3320 (b, O−H) cm^{-1}, 2910, 2870 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 1.38−1.52 (m, 1 H, SCH_2CH_2), 1.72−1.88 (m, 1 H, SCH_2CH_2), 2.10 (SCH_3), 2.40−2.55, 2.62−2.74, 2.78−2.96 (3 m, 2 H + 2 H + 3 H, 15-H_2, 17-H_2, SCH_2CH_2, NC*H*), 3.22−3.32, 3.40−3.75 (2 m, 1 H + 21 H, 2-H_2, 3-H_2, 5-H_5, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 12-H_2, 14-H_2, 18-H_2, CH_2OH). − ^{13}C NMR ($CDCl_3$): δ = 15.4 (SCH_3), 26.4 (SCH_2CH_2), 31.7 (SCH_2CH_2), 50.5, 61.7, 62.0 (4 C, C-15, C-17, CH_2OH, N*C*H), 70.4, 70.5, 70.8 (10 C, C-2, C-3, C-5, C-6, C-8. C-9, C-11, C-12, C-14, C-18). − MS (CI, *i*butane); *m*/*z* (%): 382 (100) [MH^+], 334 (7) [MH^+ − MeSH]. − $C_{17}H_{35}NO_6S$ (381.5): calcd. C 53.52, H 9.25, N 3.67, S 8.40; found C 53.45, H 9.34, N 3.71, S 8.32.

(*S*)-3-Ethyl-6-methylthio-4-morpholin-4-yl-hexan-3-ol, {2b (n = 1)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diethylmethioninol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with *n*-hexane/triethylamine (8:2), R_f = 0.55 and ethyl acetate/*n*-hexane/triethylamine 2:7.5:0.5, R_f = 0.51. − Yield: 1.24 g (47%). − $[\alpha]_D^{20}$ = −26.2 (*c* = 1.01, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3460 (b, O−H) cm^{-1}, 2960, 2910, 2880, 2850 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 0.85 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 0.86 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.22−1.43, 1.54−1.78, 1.85−2.01 (3 m, 3 H + 2 H + 1 H, SCH_2CH_2, CH_2CH_3, CH_2CH_3), 2.09 (s, 3 H, SCH_3), 2.43−2.55 (m, 1 H, SCH_2CH_2), 2.56−2.75 (m, 4 H, SCH_2CH_2, NC*H*, 3-H_2), 2.81−2.91 (m, 2 H, 5-H_2), 3.48 (br, 1 H, O*H*), 3.61−3.70 (m, 4 H, 2-H_2, 6-H_2). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 7.5 (CH_2CH_3), 7.6 (CH_2CH_3), 15.5 (SCH_3), 25.9, 27.2, 28.9 (3 C, CH_2CH_3, CH_2CH_3, SCH_2CH_2), 33.8 (SCH_2CH_2), 52.6 (2 C, C-3, C-5), 67.7 (2 C, C-2, C-6), 68.3 (N*C*H), 75.1 (Et_2COH). − MS (CI, *i*butane); *m*/*z* (%): 262 (100) [MH^+], 244 (18) [MH^+ − H_2O]. − $C_{13}H_{27}NO_2S$ (261.4): calcd. C 59.73, H 10.41, N 5.36, S 12.26; found C 59.75, H 10.36, N 5.21, S 12.14.

(*S*)-3-Ethyl-6-methylthio-4-(1,4-dioxa-7-azacyclonon-7′-yl)-hexan-3-ol, {2b (n = 2)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diethylmethioninol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with *n*-hexane/triethylamine (8:2), R_f = 0.34 and ethyl acetate/*n*-hexane/triethylamine (3:6:1), R_f = 0.49. − Yield: 1.13 g (37%). − $[\alpha]_D^{20}$ = −61.2 (*c* = 1.25, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3450 (b, O−H) cm^{-1}, 2960, 2910, 2860 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 0.68−0.86 (m, 6 H, CH_2CH_3, CH_2CH_3), 1.08−1.46 (m, 4 H, CH_2CH_3, CH_2CH_3) 1.73−1.85 (m, 1 H, SCH_2CH_2), 2.00−2.17 (m, 1 H, SCH_2CH_2), 2.08 (s, 3 H, SCH_3), 2.49−2.66, 2.73−2.87 (2 m, 3 H + 2 H, SCH_2CH_2, 6-H_2, 8-H), 3.17−3.46 (m, 5 H, 8-H, 5-H_2, 9-H_2), 3.50−3.65 (m, 6 H, NC*H*, O*H*, 2-H_2, 3-H2). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 7.3 (CH_2CH_3), 7.7 (CH_2CH_3), 15.8 (SCH_3), 17.3, (SCH_2CH_2), 24.5 (CH_2CH_3), 28.2 (CH_2CH_3), 33.3 (SCH_2CH_2), 51.7, 58.9 (2 C, C-6, C-8), 69.5, 70.2, 70.3, 70.5 (4 C, C-2, C-3, C-5, C-9), 70.4 (N*C*H), 73.1 (Et_2COH). − MS (CI, *i*butane); *m*/*z* (%): 306 (100) [MH^+]. − $C_{15}H_{31}NO_3S$ (305.5): calcd. C 58.98, H 10.23, N 4.59, S 10.50; found C 58.79, H 10.14, N 4.51, S 10.35.

(*S*)-3-Ethyl-6-methylthio-4-(1′,4′,7′-trioxa-10′-azacyclododec-10′-yl)-hexan-3-ol, {2b (n = 3)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diethylmethioninol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with *n*-hexane/toluene/triethylamine 5:4:1, R_f = 0.27 and toluene/triethylamine 8:2, R_f = 0.63. − Yield: 0.95 g (27%). − $[\alpha]_D^{20}$ = −46.1 (*c* = 0.98, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3450 (b, O−H) cm^{-1}, 2990, 2970, 2890 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 0.75−0.88 (m, 6 H, CH_2CH_3, CH_2CH_3), 1.15−1.52 (m, 4 H, CH_2CH_3, CH_2CH_3), 1.78−1.91 (m, 1 H, SCH_2CH_2), 2.09−2.23 (m, 1 H, SCH_2CH_2), 2.14 (s, 3 H, SCH_3), 2.55−2.66, 2.67−2.78, 2.82−2.93 (3 m, 1 H + 2 H + 2 H, SCH_2CH_2, NC*H*, 9-H_2), 3.24−3.50, 3.55−3.70 (2 m, 4 H + 10 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 11-H_2, 12-H_2). − ^{13}C NMR ($CDCl_3$): δ = 7.4 (CH_2CH_3), 7.8 (CH_2CH_3), 16.0 (SCH_3), 17.4, 24.6, 28.3 (3 C, CH_2CH_3, CH_2CH_3, SCH_2CH_2), 33.4 (SCH_2CH_2), 51.8, 58.8 (2 C, C-9, C-11), 69.6, 70.3, 70.4, 70.5, 70.6 (7 C, C-2, C-3, C-5, C-6, C-8, C-12, N*C*H), 73.4 (Et_2COH). − MS (CI, *i*butane); *m*/*z* (%): 350 (100) [MH^+]. − $C_{17}H_{35}NO_4S$ (349.5): calcd. C 58.42, H 10.09, N 4.01, S 9.17; found C 58.49, H 10.13, N 4.09, S 9.11.

(*S*)-3-Ethyl-6-methylthio-4-(1′,4′,7′,10′-tetraoxa-13′-azacyclopentadec-13′-yl)-hexan-3-ol, {2b (n = 4)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diethylmethioninol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane. Column chromatography with *n*-hexane/toluene/triethylamine (4:4:2), R_f = 0.47. − Yield: 1.15 g (29%). − $[\alpha]_D^{20}$ = −40.7 (*c* = 1.00, dichloromethane). − IR (NaCl): $\tilde{\nu}$ = 3440 (b, O−H) cm^{-1}, 2980, 2930, 2880 (m, C−H). − ^1H NMR ($CDCl_3$): δ = 0.76−0.88 (m, 6 H, CH_2CH_3, CH_2CH_3), 1.16−1.53 (m, 4 H, CH_2CH_3, CH_2CH_3), 1.79−1.91 (m, 1 H, SCH_2CH_2), 2.08−2.22 (m, 1 H, SCH_2CH_2), 2.15 (s, 3 H, SCH_3), 2.56−2.65, 2.66−2.72, 2.81−2.92, (3 m, 1 H + 2 H + 2 H, SCH_2CH_2, NC*H*,

12-H_2), 3.23−3.50, 3.56−3.70 (2 m, 4 H + 14 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 14-H_2, 15-H_2). − ^{13}C NMR ($CDCl_3$): δ = 7.4 (CH_2CH_3), 7.8 (CH_2CH_3), 15.9 (S*C*H$_3$), 17.4, 24.6, 28.3 (3 C, *C*H$_2$CH$_3$, *C*H$_2$CH$_3$, SCH$_2$*C*H$_2$), 33.4 (S*C*H$_2$CH$_2$), 51.8, 58.8 (2 C, C-12, C-14), 69.5, 70.2, 70.4, 70.5 (9 C, C-2, C-3, C-5, C-6, C-8. C-9, C-11, C-15, N*C*H), 73.2 (Et$_2$*C*OH). − MS (CI, *i*butane); *m*/*z* (%): 394 (100) [MH$^+$]. − $C_{19}H_{39}NO_5S$ (393.6): calcd. C 57.98, H 9.99, N 3.56, S 8.15; found C 57.95, H 9.91, N 3.54, S 8.07.

(*S*)-3-Ethyl-6-methylthio-4-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclooctadec-16′-yl)-hexan-3-ol, {2b (n = 5)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diethylmethioninol, potassium carbonate and 1,17 diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with *n*-hexane/triethylamine/*i*propanol (8.5:1:0.5), R_f = 0.35. − Yield: 1.45 g (33%). − $[\alpha]_D^{20}$ = −36.5 (*c* = 1.01, dichloromethane). − IR (NaCl): ṽ = 3450 (b, O−H) cm^{-1}, 2980, 2940, 2870 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 0.75−0.88 (m, 6 H, CH_2CH_3, CH_2CH_3), 1.12−1.52 (m, 4 H, CH_2CH_3, CH_2CH_3), 1.78−1.90 (m, 1 H, SCH_2CH_2), 2.07−2.24 (m, 1 H, SCH_2CH_2), 2.14 (s, 3 H, S*C*H$_3$), 2.54−2.73, 2.78−2.92 (2 m, 3 H + 2 H, 15-H_2, N*C*H, S*C*H$_2$CH$_2$), 3.23−3.70 (m, 22 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 12-H_2, 14-H_2, 17-H_2, 18-H_2). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 7.3 (CH_2CH_3), 7.8 (CH_2CH_3), 15.9 (S*C*H$_3$), 17.4, 24.6, 28.3 (3 C, SCH_2CH_2, *C*H$_2$CH$_3$, *C*H$_2$CH$_3$), 33.4 (S*C*H$_2$CH$_2$), 51.8, 58.8 (2 C, C-15, C-17), 69.6, 70.2, 70.4, 70.5 (11 C, C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-14, C-18, N*C*H), 73.2 (*C*H$_2$OH). − MS (CI, *i*butane); *m*/*z* (%): 438 (100) [MH$^+$], 420 (3) [MH$^+$ − H_2O], 390 (2) [MH$^+$ − MeSH]. − $C_{21}H_{43}NO_6S$ (437.6): calcd. C 57.63, H 9.90, N 3.20, S 7.33; found C 57.55, H 9.81, N 3.14, S 7.19.

(*S*)-4-Methylthio-2-morpholin-4-yl-1,1-diphenylbutan-1-ol, {2c (n = 1)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diphenylmethioninol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography with *n*-hexane/triethylamine (8:2), R_f = 0.39; recrystallization from dichloromethane and *n*-hexane afforded colorless needles. Yield: 1.43 g (40%). M.p.: 113−114°C. − $[\alpha]_D^{20}$ = +4.3 (*c* = 1.00, dichloromethane). − IR (KBr): ṽ = 3340 (b, O−H) cm^{-1}, 3080, 3050, 3020 (w, ArC−H), 2950, 2910 (C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.80−2.05 (m, 2 H, SCH_2CH_2), 2.05 (s, 3 H, S*C*H$_3$), 2.38−2.74 (m, 6 H, S*C*H$_2$CH$_2$, 3-H_2, 5-H_2), 3.57−3.65 (m, 4 H, 2-H_2, 6-H_2), 3.69 (dd, ^{3}J = 2.4, 10.6 Hz, 1 H, N*C*H), 5.30 (br, 1 H, O*H*), 7.22−7.49 (m, 10 H, ArH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.6 (S*C*H$_3$), 27.3 (SCH_2CH_2), 33.2 (S*C*H$_2$CH$_2$), 52.1 (2 C, C-3, C-5), 67.8 (2 C, C-2, C-6), 70.2 (N*C*H), 78.6 (Ph$_2$*C*OH), 127.0, 127.3, 127.5, 128.1 (10 C, ArC), 144.1, 144.8 (2 C, q. ArC). − MS (CI, *i*butane); *m*/*z* (%): 358 (100) [MH$^+$], 340 (6) [MH$^+$ − H_2O], 310 (5) [MH$^+$ − MeSH]. − $C_{21}H_{27}NO_2S$ (357.5): calcd. C 70.55, H 7.61, N 3.92, S 8.97; found C 70.51, H 7.63, N 3.87, S 8.94.

(*S*)-4-Methylthio-2-(1,4-dioxa-7-azacyclonon-7′-yl)-1,1-diphenylbutan-1-ol, {2c (n = 2)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diphenylmethioninol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with *n*-hexane/triethylamine (8:2), R_f = 0.39. − Yield: 1.42 g (35%). − $[\alpha]_D^{20}$ = +15.8 (*c* = 1.01, dichloromethane). − IR (NaCl): ṽ = 3360 (b, O−H) cm^{-1}, 3080, 3050, 3020 (w, aromat. C−H), 2960, 2920, 2860 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.89−2.16 (m, 3 H, SCH_2CH_2, S*C*H$_2$CH$_2$) 2.15 (s, 3 H, S*C*H$_3$), 2.33−2.43 (m, 1 H, S*C*H$_2$CH$_2$), 2.65−2.73, 2.93−3.04, 3.18−3.25, 3.38−3.46 (4 m, 2 H + 1 H + 2 H + 3 H, 5-H_2, 6-H_2, 8-H_2, 9-H_2), 3.54−3.60, 3.62−3.69 (2 m, 2 H + 2 H, 2-H_2, 3-H_2), 4.29−4.37 (m, 1 H, N*C*H), 5.14 (br, 1 H, O*H*), 7.12−7.60 (m, 10 H, ArH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.9 (S*C*H$_3$), 19.6 (SCH_2CH_2), 33.3 (S*C*H$_2$CH$_2$), 51.5, 56.3 (2 C, C-6, C-8), 69.3, 70.0, 70.2, 70.5 (4 C, C-2, C-3, C5, C9), 72.3 (N*C*H), 75.5 (Ph$_2$*C*OH), 125.5, 125.7, 126.4, 126.5, 127.9, 128.0 (10 C, ArC), 144.1, 146.9 (2 C, q. ArC). − MS (CI, *i*butane); *m*/*z* (%): 402 (100) [MH$^+$]. − $C_{23}H_{31}NO_3S$ (401.6): calcd. C 68.79, H 7.78, N 3.49, S 7.98; found C 68.71, H 7.83, N 3.43, S 7.91.

(*S*)-4-Methylthio-1,1-diphenyl-2-(1′,4′,7′-trioxa-10′-azacyclododec-10′-yl)-butan-1-ol, {2c (n = 3)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diphenylmethioninol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with *n*-hexane/toluene/triethylamine 5:4:1, R_f = 0.46 and *n*-hexane/triethylamine (8:2), R_f = 0.33. −Yield: 0.95 g (21%). − $[\alpha]_D^{20}$ = +14.1 (*c* = 1.04, dichloromethane). − IR (NaCl): ṽ = 3360 (b, O−H) cm^{-1}, 3090, 3060, 3030 (w, ArC−H), 2960, 2920, 2870 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.88−2.14 (m, 2 H, SCH_2CH_2), 2.13 (s, 3 H, S*C*H$_3$), 2.30−2.39, 2.92−3.02 (2 m, 1 H + 1 H, S*C*H$_2$CH$_2$), 2.64−2.73, 3.15−3.23 (2 m, 2 H + 2 H, 9-H_2, 11-H_2), 3.37−3.45, 3.53−3.70 (2 m, 4 H + 8 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 12-H_2), 4.27−4.35 (m, 1 H, N*C*H), 5.10 (br, 1 H, O*H*), 7.11−7.58 (m, 10 H, ArH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.9 (S*C*H$_3$), 19.7 (SCH_2CH_2), 33.4 (S*C*H$_2$CH$_2$), 51.5, 56.3 (2 C, C-9, C-11), 69.4, 70.0, 70.3, 70.5, 72.4 (7 C, C-2, C-3, C-5, C-6, C-8, C-12, N*C*H), 75.5 (Ph$_2$*C*OH), 125.6, 125.8, 126.4, 126.5, 127.9, 128,0 (10 C, ArC), 144.1, 146.9 (2 C, q. ArC). − MS (CI, *i*butane); *m*/*z* (%): 446 (100) [MH$^+$], 428 (3) [MH$^+$ − H_2O]. − $C_{25}H_{35}NO_4S$ (445.6): calcd. C 67.38, H 7.92, N 3.14, S 7.19; found C 67.34, H 7.89, N 3.11, S 7.13.

(*S*)-4-Methylthio-1,1-diphenyl-2-(1′,4′,7′,10′-tetraoxa-13′-azacyclopentadec-13′-yl)-butan-1-ol, {2c (n = 4)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diphenylmethioninol, potassium carbonate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane. Column chromatography with *n*-hexane/toluene/triethylamine 5:4:1, R_f = 0.33 and *n*-hexane/triethylamine/acetone (8.5:1:0.5), R_f = 0.19. − Yield: 0.91 g (19%). − $[\alpha]_D^{20}$ = +14.4 (*c* = 1.03, dichloromethane). − IR (NaCl): ṽ = 3410 (b, O−H) cm^{-1}, 3010, 3040, 3070 (w, ArC−H), 2910, 2870 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.88−2.99, 2.01−2.15 (2 m, 1 H + 1 H, SCH_2CH_2), 2.13 (s, 3 H, S*C*H$_3$), 2.30−2.40, 2.92−3.02 (2 m, 1 H + 1 H, S*C*H$_2$CH$_2$), 2.66−2.72, 3.15−3.22 (2 m, 2 H + 2 H, 12-H_2, 14-H_2), 3.36−3.44, 3.53−3.69 (2 m, 4 H + 12 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 11-H_2, 15-H_2), 4.27−4.34 (m, 1 H, N*C*H), 7.09−7.56 (m, 10 H, ArH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 15.9 (S*C*H$_3$), 19.7 (SCH_2CH_2), 33.4 (S*C*H$_2$CH$_2$), 51.6, 56.4 (2 C, C-12, C-14), 69.4, 70.0, 70.3, 70.6 (8 C, C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-15), 72.4 (N*C*H), 75.6 (Ph$_2$*C*OH), 125.6, 125.8, 126.5, 128.0 (10 C, ArC), 144.2, 147.0 (2 C, q. ArC). − MS (CI, *i*butane); *m*/*z* (%): 490 (100) [MH$^+$]. − $C_{27}H_{39}NO_5S$ (489.7): calcd. C 66.23, H 8.03, N 2.86, S 6.55; found C 66.31, H 7.97, N 2.79, S 6.41.

(*S*)-4-Methylthio-1,1-diphenyl-2-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclooctadec-16′-yl)-butan-1-ol, {2c (n = 5)}: This compound was prepared following the general procedure described above from (*S*)-α,α-diphenylmethioninol, potassium carbonate and 1,17 diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with *n*-hexane/triethylamine (7:3), R_f = 0.28 and cyclohexane/acetone/triethylamine (8:1.5:0.5), R_f = 0.20. − Yield: 1.12 g (21%). − $[\alpha]_D^{20}$ = +5.2 (*c* = 1.19, dichloromethane). − IR (NaCl): ṽ = 3380 (b, O−H) cm^{-1}, 3010, 3040, 3070 (w, ArC−H), 2870 (m, C−H). − ^{1}H NMR ($CDCl_3$): δ = 1.90−2.16 (m, 2 H, SCH_2CH_2), 2.14 (s, 3 H, S*C*H$_3$), 2.34−2.42 (m, 1 H, S*C*H$_2$CH$_2$), 2.65−2.72 (m, 2 H, 15-H_2), 2.96−3.05 (m, 1 H, S*C*H$_2$CH$_2$), 3.18−3.24 (m, 2 H, 17-H_2), 3.40−3.47, 3.55−3.68 (2 m, 4 H + 16 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2,

8-H_2, 9-H_2, 11-H_2, 12-H_2, 14-H_2, 18-H_2,), 4.32−4.40 (m, 1 H, NC*H*), 5.17 (br, 1 H, O*H*), 7.10−7.57 (m, 10 H, ArH). − ^{13}C NMR (DEPT, $CDCl_3$): δ = 16.0 (S*C*H_3), 19.7 (SCH_2*C*H_2), 33.4 (S*C*H_2CH$_2$), 51.6, 56.3 (2 C, C-15, C-17), 69.2, 70.0, 70.3, 70.6 (10 C, C-2, C-3, C-5, C-6, C-8, C-9, C-11, C-12, C-14, C-18), 72.6 (N*C*H), 75.7 (Ph_2*C*OH), 125.6, 125.8, 126.6, 128.0, 128.1 (10 C, ArC), 144.1, 146.7 (2 C, q. ArC). − MS (CI, *i*butane); *m/z* (%): 534 (100) [MH^+], 486 (14) [MH^+ − MeSH]. − $C_{29}H_{43}NO_6S$ (533.7): calcd. C 65.26, H 8.12, N 2.62, S 6.01; found C 65.31, H 8.17, N 2.64, S 5.93.

(*S*)-3-ethyl-6-methyl-4-(morpholin-4-yl)heptan-3-ol, {3 (n = 1)}: This compound was prepared following the general procedure described above from (*S*)-α,α- diethylleucinol, sodium carbonate and 1,5-diiodo-3-oxapentane. Column chromatography *n*-hexane/ethyl acetate (5:1); R_f = 0.6. − Yield 2.5 g (93%). − $[\alpha]_D^{20}$ = +8.2 (*c* = 1.25, CH_2Cl_2). − (For the sake of simplicity in the NMR spectroscopic data, the numbering indicated in Figure 1 was used) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, 13 H, 3-H, $CH_3^{a,b,5,5'}$), 1.28 and 1.65 (m, 6 H, CH_2^b, CH_2^a, 4-H, 3′-H), 2.55 (m 1 H, 2-H), 2.65 and 2.80 (m, 4 H, NCH_2), 3.65 (m, 4 H, OCH_2). − ^{13}C NMR (75 MHz $CDCl_3$): δ = 7.39 and 7.64 (CH_3^a, CH_3^b), 21.19 and 24.17 (CH_3^5, $CH_3^{5'}$), 26.43 (4-C), 26.94 and 28.87 (CH_2^a, CH_2^b), 35.69 (3-C), 52.53 (CH_2−N), 66.69 (2-C), 67.86 (CH_2−O), 74.77 (1-C). − MS (FAB+); *m/z* (%): 244 [M^+ + 1], 156 (100). − $C_{14}H_{29}NO_2$ (243.38): calcd C 69.09, H 12.01, N 5.75; found C 68.92, H 11.98, N 5.84.

(*S*)-3-ethyl-6-methyl-4-(1,4-dioxa-7-azacyclonon-7′-yl)heptan-3-ol, {3 (n = 2)}: This compound was prepared following the general procedure described above from (*S*)-α,α- diethylleucinol, sodium carbonate and 1,8-diiodo-3,6-dioxaoctane. Column chromatography with n-hexane/diethyl ether (1:3), R_f = 0.5. − Yield 0.4 g (16%). − $[\alpha]_D^{20}$ = −5.6 (*c* = 1.30, CH_2Cl_2). − (For the sake of simplicity in the NMR spectroscopic data, the numbering indicated in Figure 1 was used) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 13 H, 3-H, $CH_3^{a,b,5,5'}$), 1.20 and 1.67 (m, 6 H, CH_2^b, CH_2^a, 4-H, 3′-H), 2.70 (d, *J* = 14 Hz, 1 H, 2-H), 2.80−3.90 (bm, NCH_2, OCH_2). − ^{13}C NMR (75 MHz $CDCl_3$): δ = 7.39 and 7.57 (CH_3^a, CH_3^b), 21.66 and 24.39 (CH_3^5, $CH_3^{5'}$), 25.17 (4-C), 27.51 and 28.91 (CH_2^a, CH_2^b), 36.56 (3-C), 66.34 (2-C), 73.82 (1-C). − MS (FAB+); *m/z* (%): 288 [M^+ + 1], 200 (100). − $C_{16}H_{33}NO_3$ (287.24): calcd. C 66.86, H 11.57 N 4.87; found C 66.13, H 11.62, N 4.46.

(*S*)-3-ethyl-6-methyl-4-(1′,4′,7′-trioxa-10′-azacyclododec-10′-yl)-heptan-3-ol, {3 (n = 3)}: This compound was prepared following the general procedure described above from (*S*)-α,α- diethylleucinol, sodium carbonate and 1,11-diiodo-3,6,9-trioxaundecane. Column chromatography with n-hexane/diethyl ether (1:3); R_f = 0.4. − Yield 0.88 g (31%). − $[\alpha]_D^{20}$ = +6.6 (*c* = 1.09, CH_2Cl_2). − (For the sake of simplicity in the NMR data, the numbering indicated in Figure 1 was used) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 14 Hz, 3 H, CH_3^a), 0.79 (t, *J* = 14 Hz, 3 H, CH_3^b), 0.86 (d, *J* = 12 Hz, 6 H, CH_3^5, $CH_3^{5'}$), 0.94 (m, 1 H, 3-H), 1.11 (m, 1 H, H^a), 1.13 (m, 1 H, H^b), 1.58 (m, 4 H, 4-H, $H^{a'}$, 3-H, $H^{b'}$), 2.45 (br. s, 1 H, NCH_2), 2.68 (dd, *J* = 16, *J* = 4 Hz, 1 H, 2-H), 2.79 and 3.07 (br. s, 3 H, NCH_2), 3.50 (m, 12 H, OCH_2). − ^{13}C NMR (125 MHz $CDCl_3$): δ = 7.50 (CH_3^a, CH_3^b), 21.81 and 24.43 (CH_3^5, $CH_3^{5'}$), 25.23 (4-C), 27.40 (CH_2^a), 27.64 (CH_2^b), 39.91 (3-C), 50.25 and 58.35 (CH_2−N), 63.64 (2-C), 69.34, 69.59, 70.14, 70.60 (CH_2−O), 71.19 (1-C). − MS (FAB+); *m/z* (%): 332 [M^+ + 1], 244 (100). − $C_{18}H_{37}NO_4$ (331.25): calcd. C 65.22, H 11.25 N 4.23; found C 64.82, H 11.35, N 4.05.

(*S*)-3-ethyl-6-methyl-4-(1′,4′,7′,10′-tetraoxa-13′-azacyclo-pentadec-13′-yl)heptan-3-ol, {3 (n = 4)}: This compound was prepared following the general procedure described above from (*S*)-α,α- diethylleucinol, sodium carbonate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane. Column chromatography with *n*-hexane/diethyl ether (1:6); R_f = 0.3. − Yield 1.49 g (46%). − $[\alpha]_D^{20}$ = +2.6 (*c* = 1.09, CH_2Cl_2). − (For the sake of simplicity in the NMR spectroscopic data, the numbering indicated in Figure 1 was used) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 12 H, $CH_3^{a,b,5,5'}$), 1.00 (m, 1 H, 3-H), 1.25−1.75 (m, 6 H, CH_2^b, CH_2^a, 4-H, 3′-H), 2.70 (dd, *J* = 16, *J* = 4 Hz, 1 H, 2-H), 2.95 (br. s, 2 H, NCH_2) 3.60 (bm, 16 H, OCH_2). − ^{13}C NMR (75 MHz $CDCl_3$): δ = 7.45 and 7.50 (CH_3^a, CH_3^b), 21.76 and 24.36 (CH_3^5, $CH_3^{5'}$), 25.29 (4-C), 27.20 and 27.80 (CH_2^a, CH_2^b), 36.53 (3-C), 50.57 and 59.31 (CH_2−N), 64.33 (2-C), 69.98, 70.50, 71.23 (CH_2−O), 74.51 (1-C). − MS (FAB+); *m/z* (%): 376 [M^+ + 1], 288 (100). − $C_{20}H_{41}NO_5$ (375.54): calcd. C 63.96, H 11.00 N 3.73; found C 63.61, H 11.15, N 3.53.

(*S*)-3-ethyl-6-methyl-4-(1′,4′,7′,10′,13′-pentaoxa-16′-azacyclo-octadec-16′-yl)heptan-3-ol, {3 (n = 5)}: This compound was prepared following the general procedure described above from (*S*)-α,α- diethylleucinol, potassium carbonate and 1,17 diiodo-3,6,9,12,15-pentaoxaheptadecane. Column chromatography with dichloromethane/methanol (96:4); R_f = 0.3. − Yield 1.6 g (40%). − $[\alpha]_D^{20}$ = +11.3 (*c* = 1.01, CH_2Cl_2). − (For the sake of simplicity in the NMR spectroscopic data, the numbering indicated in Figure 1 was used) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (m, 13 H, $CH_3^{a,b,5,5'}$, 3-H), 1.25−1.80 (m, 6 H, CH_2^b, CH_2^a, 4-H, 3′-H), 2.70 (d, *J* = 16 Hz, 1 H, 2-H), 2.90 (br. s, 3 H, NCH_2) 3.50 (bm, 20 H, OCH_2). − ^{13}C NMR (75 MHz $CDCl_3$): δ = 7.22 and 7.38 (CH_3^a, CH_3^b), 21.54 and 24.19 (CH_3^5, $CH_3^{5'}$), 25.15 (4-C), 26.96 and 27.86 (CH_2^a, CH_2^b), 36.31 (3-C), 49.97 and 57.19 (CH_2−N), 63.33 (2-C), 69.32, 70.12, 70.30, 70.65, 71.06 (CH_2−O), 74.44 (1-C). − MS (FAB+); *m/z* (%): 420 [M^+ + 1], 332 (100). − $C_{22}H_{45}NO_6$ (419.60): calcd. C 62.97, H 10.81 N 3.34; found C 62.42, H 10.62, N 3.04.

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