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Chiral macrocyclic polyethers incorporating a tetraoxaspiro[5.5]undecane or trioxa-azaspiro[5.5]undecane moiety

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Abstract

New macrocyclic polyethers possessing chirality due to a spiro ring junction are prepared from 2,8-dihydroxymethylated (+)-1,4,7,10-tetraoxaspiro[5.5]undecane **1** and (+)-1,4,7-trioxa-10-azaspiro[5.5]undecane **2**, both (*E,E*). *N*-Functionalization of compounds derived from **2** is also examined. The complexing properties of representative ligands **3**, **4**, **5** measured by spectrophotometry in THF, for alkaline and alkaline-earth cations, indicate that these spheric positively-charged species are weakly associated.

1. Introduction

We previously reported the enantioselective synthesis of 2- and 8- functionalized 1,4,7,10-tetraoxaspiro[5.5]undecane **1**[1] and 1,4,7-trioxa-10-azaspiro[5.5]undecane **2**.[2] These novel spirane systems had structures with dianomeric axial oxygens and equatorial CH_2OH substituents,[3] i.e. with *E,E* stereochemistry. D-α,β-Isopropylidene glycerol or (*S*)-Solketal, a commercially available three-carbon precursor, was used as starting material (Scheme 1).

The proposed synthetic scheme allowed further developments, in particular towards macrocyclic systems, if appropriate cyclizations were carried out. To begin with, we studied macrocycles constructed with ethylenoxy units. Since the pioneering work of Pedersen,[4] much attention has been focused on

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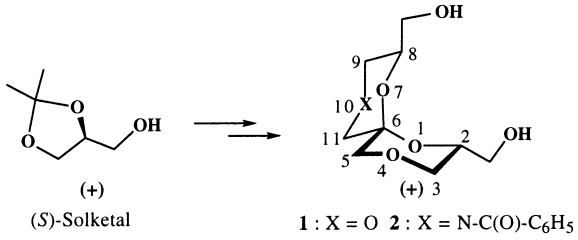


Scheme 1.

crown ethers and analogues, mainly for the design of new complexing agents for various positively-charged species.[5] In this context, crown-like structures have been used for chiral recognition of asymmetric species and many supporting skeletons for such chiral receptors have been studied.[6] However, to our knowledge no spirane system has ever been proposed for this purpose. Recent work describes spiroketal based polyethers,[7] but the structural approach is different, the cyclization being carried out from the racemic 3,5-diaxial diol of 1,7-dioxaspiro[5.5]undecane.

Use of spiroacetal **1** as a starting material would give cyclic structures with C_2 symmetry and a specific chirality due to the spiro ring junction. Also, introduction of a nitrogen atom in position 10 of **2** would afford unsymmetrical ligands that could be further functionalized.

The work reported here mainly concerns the synthesis of macrocycles, and a first example of *N*-functionalization is described. For this type of multidentate ligand, it can be predicted that preorganization of the cavity is not conducive to the efficient complexation of spheric cations, judging from the abundant previous work[8] in this field. To estimate the complexing properties for IA and IIA cations, we examined the fully oxygenated ligands **3**, **4**, **5**, by spectrophotometric measurements with metal picrates in THF.

We investigated the ability of these enantiopure macrocycles to selectively bind enantiomers of chiral molecules such as protonated amines. Results obtained by electrospray mass spectrometry, and including bicyclic analogues, will be the subject of a forthcoming paper.

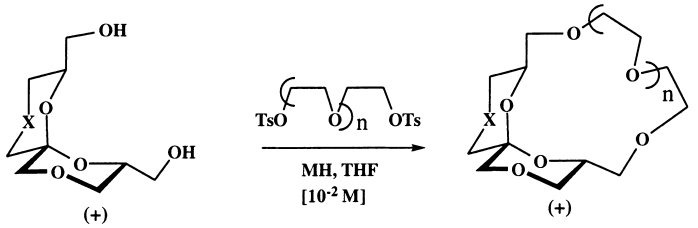
2. Results and discussion

2.1. Synthesis of cyclic polyethers

Macrocyclization was envisaged by 1:1 condensation between two bifunctional systems (Scheme 2). After examination of various experimental parameters such as temperature, reaction time, alcoholate formation, order of mixing, and solvents, the reaction was finally carried out by treatment of diol precursors **1** or **2** with hydride (4 equiv.) in THF followed by slow addition of ditosylate in THF in precisely set conditions (see Experimental section).

Also, to minimize side reactions such as polycondensations, and to increase yields, two factors were explored: (i) the choice of the alkaline hydride, (ii) the best conditions of concentration in the mean dilution domain 10^{-2}–10^{-3} mol/L.

Concentration experiments with NaH for compounds **4** and **7** led us to adopt the working domain of 10^{-2} mol/L. Alkaline hydrides can induce a template effect through the cation implicated in the alcoholate formation. Although the experiment was not carried out systematically for all the compounds, yields shown in Table 1 indicated that NaH was preferable for the smaller ring formation (n=1, 2), whereas KH afforded the better yield for n=3. The low-to-fair yields obtained are in the range generally observed for this type of reaction.



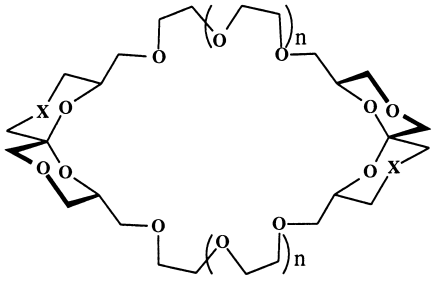
X = O **3** : n = 1, **4** : n = 2, **5** : n = 3
X = N-C(O)-C_6H_5 **6** : n = 1, **7** : n = 2, **8** : n = 3

Scheme 2.

Table 1
Cyclization yields with hydrides (monomers)

X = O	**3** (n = 1)	**4** (n = 2)	**5** (n = 3)
LiH	0%	-	-
NaH	36%	55%	15%
KH	17%	28%	27%
X = N-C(O)-C_6H_5	**6** (n = 1)	**7** (n = 2)	**8** (n = 3)
NaH	6%	26%	-
KH	-	-	28%

With smaller rings (*n*=1 and 2), dimers **9**–**12** depicted in Scheme 3 were additionally obtained in small amounts (Table 2).



X = O **9** : n = 1, **10** : n = 2
X = N-C(O)-C_6H_5 **11** : n = 1, **12** : n = 2

Scheme 3.

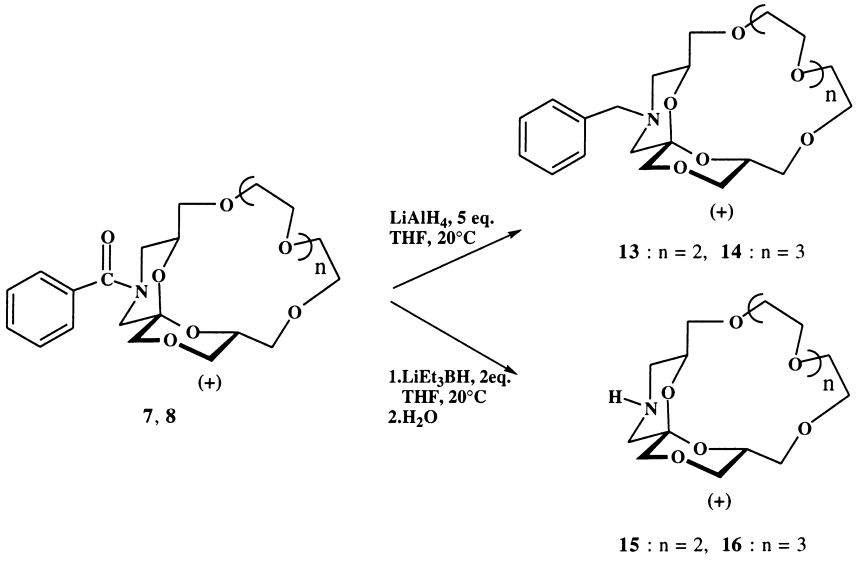
In this case, the 2+2 condensation gave macrocycles with higher symmetry than the corresponding monomers, i.e. D_2 symmetry for X=O and C_2 symmetry for X=N–C(O)–C_6H_5 (*cis* and *trans* isomers formed were not separated).

Table 2
Yields of dimer formation

X = O	**9** (n = 1)	**10** (n = 2)
	22% (NaH)	2% (KH)
X = N-C(O)-C_6H_5	**11** (n = 1)	**12** (n = 2)
	12% (NaH)	7% (KH)

2.2. *Reduction of amides* ***7***, ***8***

We previously showed[2] that an amide function in position 10 is necessary to obtain the spiroketal compound **2**. Replacement by an amine that could be protonated during the acidic intramolecular ketalization resulted in an incomplete cyclization of the ketodiol precursor. However, reduction of the carbonyl group or complete amine deprotection of the tertiary amide was achieved in the subsequent steps. It was controlled using hindered hydrides and appropriate experimental conditions. $LiAlH_4$ afforded the benzylamine while use of $LiEt_3BH$ and subsequent hydrolysis of the tetrahedral intermediate gave the free amine (Scheme 4). Yields ranged from 80% to 87%.



Scheme 4.

2.3. N-*Functionalization*

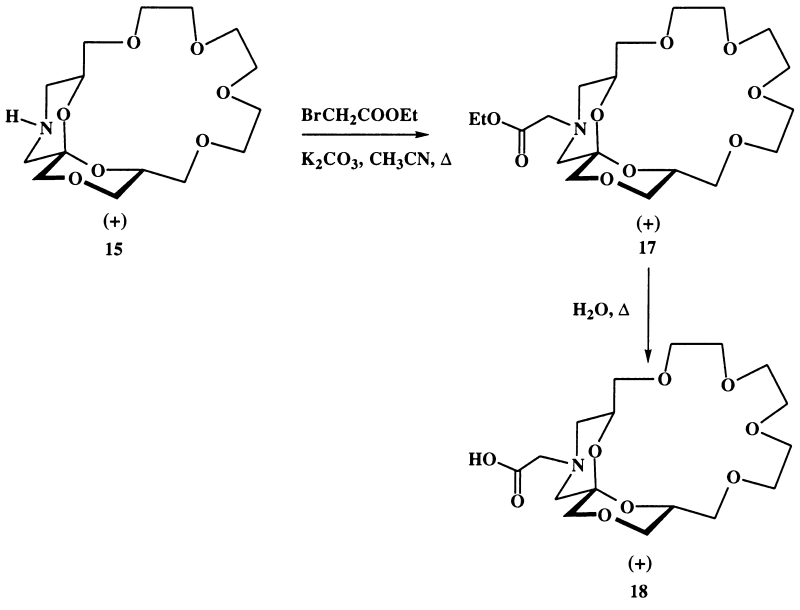
Reactivity of the chiral amines obtained was explored in compound **15** (Scheme 5).

For this first investigation, we studied the attachment of a carboxylic arm to help stabilize positively-charged species entering the cavity. Monoalkylation to give **17** was carried out with 86% yield; interestingly, excess bromo-ester induced quaternary ammonium salt formation. Further saponification with KOH in methanol afforded the potassium salt from which recovery of the free carboxylic acid proved difficult, probably because of the specific stability of the salt. Finally, the procedure described for similar lariat-ethers[9] by refluxing in distilled water yielded acid **18** (yield 91%).

2.4. *Complexation of IA and IIA cations in THF*

For this first investigation, ligands **3**, **4** and **5** available in sufficient quantity were considered as representative of the structural group studied, without considering *N*-functionalized macrocycles.

Of the various methods used for the determination of complexing properties, UV–visible spectrophotometry in tetrahydrofuran (THF) using alkaline or alkaline-earth picrates as spectroscopic probes[10] was chosen, because it is well suited for the study of associations with low stability. Additionally, it showed



Scheme 5.

Table 3
Association constants (log β_{11}) for ligand **5** (in THF)

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
log β_{11}	<2	2.07	3.24	2.85	2.79	<2	<2	<2	2.48
* σ_β		0.02	0.01	0.01	0.01				0.02
$<\lvert r \rvert>$		$1.1\ 10^{-3}$	$2.0\ 10^{-3}$	$2.0\ 10^{-3}$	$1.6\ 10^{-3}$				$2.2\ 10^{-3}$
σ_ρ		$1.4\ 10^{-3}$	$3.1\ 10^{-3}$	$3.0\ 10^{-3}$	$1.9\ 10^{-3}$				$3.0\ 10^{-3}$
$< r >$		10^{-4}	$-4.0\ 10^{-4}$	-8.10^{-4}	3.10^{-4}				$6.4\ 10^{-4}$

(* see experimental part)

a high sensitivity without consuming too much material. Details for measurements and mathematical treatments of results using the STAR program[11] are given in the Experimental section.

The following complexes between ligand (L) and metal (M) were assumed: ML, ML_2 and M_2L for the statistical treatment of results, but the figures obtained for stoichiometry 1:1 (ML), corresponding to the β_{11} stability constants, proved satisfactory and it was not necessary to consider higher molecular associations.

$$M + L \overset{\beta_{11}}{\rightleftharpoons} ML$$

In these experimental conditions, ligands **3** and **4** displayed no measurable complexing properties. Macrocycle **5** with one additive ethylenoxy unit gave the results in Table 3. Some complexing properties for alkaline cations were noted, with a selectivity for K^+.

In the same experimental conditions, 18-crown-6 used as reference ligand gave for K^+: log β_{11}=5.14. There is thus a factor of 1.9 in stability between ligand **5** and 18-crown-6, which is not surprising as the preorganization of the cavity is severely disturbed by the spiroketal moiety. Thus the distribution of the oxygens, which are donor centres in the macrocycle, and also the helical structure induced by the spirane ring junction affect the complexing properties of the crown-like system.

The selectivity order of **5** for the alkaline series is closely related to the one obtained (in methanol)

for 18-crown-6 (K^+>Rb^+>Cs^+>Na^+>Li^+) and different from that of 21-crown-7 (Cs^+>Rb^+>K^+»Na^+).[5c] This observation is in favour of a six coordinating sphere including the five oxygens of the ethylenoxy units and one oxygen of the spiroketal function in the complex formation. This is very likely since the simultaneous participation of both oxygens O(1) and O(7) should be excluded due to their staggered position relatively to the polyether bridge.

If a bicyclic system is attached in place of the simple oligoethylenoxy chain to give cryptant-like molecules, stabilities associated to the cations are increased, but, as observed here for a monocycle, distortions are induced in the bicycle by the helical conformation of the spirane part. The characterization of this effect will be reported in a forthcoming paper.

3. Conclusion

We have synthesized 16 new chiral crown ethers incorporating a tetraoxaspiro[5.5]undecane or trioxa-azaspiro[5.5]undecane framework in their structure, in a single step, using 1+1 condensations between chiral precursors **1** or **2** and di-*p*-tosylate of oligoethylene glycols. Three of the prepared monomers presented a C_2 symmetry (**3**–**5**) and nine no symmetry (**6**–**8**, **13**–**18**). Interestingly, four dimers corresponding to a 2+2 condensation were isolated, showing respectively D_2 (**9**, **10**) and C_2 (**11**, **12**) symmetries. *N*-Functionalization of the interesting chiral amines **15**, **16** proved straightforward. This approach should therefore afford numerous models for the design of new receptors for various molecular or ionic species.

4. Experimental section

4.1. General

Commercial Merck $60F_{254}$ silica gel plates were used for thin layer chromatography. Purification of compounds was carried out by column chromatography using Geduran SI60 40–60 mm silica gel (Merck) for the flash method and 60 0.063–0.200 mm silica gel (Merck) or neutral 90 aluminium oxide (Merck) for a normal column. All solvents were distilled before use. Optical rotations were measured for the sodium D line (589 nm) at 25°C with a Jasco DJP-370 polarimeter (*c* in g/mL). Infrared (IR) spectra were obtained using a Perkin–Elmer 881 spectrometer, and bands are expressed in frequency units (ν cm^{-1}).

Mass spectra were obtained either from our own Hewlett Packard 5989B spectrometer (EI), or a ZAB-SEQ spectrometer (EI or FAB^+ for exact mass determination) at the Centre d'Analyse du CNRS, Solaize, France. NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C on a Bruker AC 400 spectrometer, using $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts δ are reported in ppm, and coupling constants *J* in Hz. The assignments of carbons labelled with superscripts *, ‡, § are uncertain and could be interchanged. The presence of two rotamers linked to the amide function gave broadened ^1H spectra, with poor resolution, for compounds **6**, **7**, **8**, **11** and **12**.

UV spectra were run with a Uvikon 941 spectrometer. THF (spectrograde) was dried by distillation in the presence of potassium metal, under nitrogen and with benzophenone ketyl as indicator, just before use in spectrophotometric measurements. Metal picrates were prepared in deionized water by neutralizing picric acid with the corresponding metal carbonates. The salts were recrystallized successively from deionized water and from ethanol, washed with ether and finally dried under vacuum.

4.2. Procedure for the macrocyclization reaction

A dry two-necked round bottom flask fitted with a condenser was cooled in an ice bath under argon. The alkaline hydride (NaH or KH) (9.09 mmol, 4 equiv.) suspended in a mineral oil was carefully washed three times with dry hexane (stored on sodium) and lastly with freshly distilled anhydrous THF; it was then placed in the flask. A few millilitres of anhydrous THF were added to the hydride. A solution (2.27 mmol in 100 ml anhydrous THF) of the spiroacetal **1** {$[\alpha]_D^{25}$ +3 (*c* 0.03; MeOH)} or **2** {$[\alpha]_D^{25}$+35 (*c* 0.04; $CHCl_3$)} prepared by methods already described[1,2] was then added. The mixture was gently heated (30–40°C) for 1.5 h, with magnetic stirring, until complete formation of the alcoholate. It was then warmed up to THF reflux and a solution of the oligoethyleneglycol di-*p*-tosylate (10.0 mmol, 1.1 equiv.) in anhydrous THF (100 mL) was added slowly with an automatic syringe at a moderate rate (15 mL/h). Reflux was continued under argon for five days.

After cooling, the mixture was diluted in water (100 mL) with caution to avoid splashing. The solvent was evaporated and the mixture extracted with ethyl acetate. After separation, the organic phase was washed with water and the aqueous phase extracted with chloroform. The combined organic phases were dried on $MgSO_4$ and evaporated. The residual mixture was purified by column chromatography (eluents are indicated for each compound).

4.3. (2R,6S,8R)-13,16,19-Trioxacyclo[$9^{2,8}$]-1,4,7,10-tetraoxaspiro[5,5]undecane (E,E) **3**

Eluent for column chromatography: gradient from AcOEt to AcOEt:MeOH, 90:10. Yield 36% (with 22% of dimer **9**, see below). Colourless oil. $[\alpha]_D^{25}$ +4 (*c* 0.026; $CHCl_3$). IR (film) ν_{max}: 1150–1050 (C–O–C). ^{1}HNMR δ: 3.22 (2H, d, H-5a, H-11a, $J_{5a\text{-}5e}$=11.5); 3.32 (2H, *p*t, H-3a, H-9a, $J_{3a\text{-}3e}$=11.1, $J_{3a\text{-}2}$=11.1); 3.43 (2H, dd, H-12B, H-20B, $J_{12B\text{-}12A}$=10.3, $J_{12B\text{-}2}$=6.4); 3.58 (2H, d, H-5e, H-11e, $J_{5e\text{-}5a}$=11.2); 3.59 (2H, dd, H-12A, H-20A, $J_{12A\text{-}12B}$=10.3, $J_{12A\text{-}2}$=4.6); 3.60–3.73 (8H, m, 2H-14, 2H-15, 2H-17, 2H-18); 3.90 (2H, dd, H-3e, H-9e, $J_{3e\text{-}3a}$=11.1, $J_{3e\text{-}2}$=2.6); 4.24 (2H, dddd, H-2, H-8, $J_{2\text{-}3a}$=11.1, $J_{2\text{-}3e}$=2.7, $J_{2\text{-}12A}$=4.6, $J_{2\text{-}12B}$=6.4). ^{13}C NMR δ: 67.1 (C-2, C-8); 68.5 (C-3, C-9); 68.6 (C-5, C-11); 70.7 (C-14, C-18)*; 71.0 (C-12, C-20); 71.2 (C-15, C-17)*; 91.7 (C-6). MS (EI) *m*/*z* (%): 290 (22, $M^{+\cdot}$); 272 [5, $(M-H_20)^{+\cdot}$]; 260 [4, $(M-CH_2O)^{+\cdot}$]; 217 (3); 202 (4); 158 (6); 145 (4); 131 (12); 115 (6); 101 (20); 87 (63, $C_4H_7O_2^+$); 71 (55); 57 (75); 45 (100, $C_2H_5O^+$). Exact mass found: 290.1365; $C_{13}H_{22}O_7$ requires 290.1365.

4.4. (2R,6S,8R)-13,16,19,22-Tetraoxacyclo[$12^{2,8}$]-1,4,7,10-tetraoxaspiro[5,5]undecane (E,E) **4**

Eluent for column chromatography: gradient from AcOEt to AcOEt:MeOH, 95:5. Yield 55% (with 2% of dimer **10**, see below). Colourless oil. $[\alpha]_D^{25}$ +29 (*c* 0.036; $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1150–1050 (C–O–C). ^{1}H NMR δ: 3.22 (2H, d, H-5a, H-11a, $J_{5a\text{-}5e}$=11.5); 3.23 (2H, *p*t, H-3a, H-9a, $J_{3a\text{-}3e}$=11.0, $J_{3a\text{-}2}$=11.0); 3.47 [4H, 2H-12, 2H-23, ABX system, AB part, δB=3.44 (2H, H-12B, H-23B, $J_{12B\text{-}12A}$=11.1, $J_{12B\text{-}2}$=5.2); δA=3.50 (2H, H-12A, H-23A, $J_{12A\text{-}12B}$=11.1, $J_{12A\text{-}2}$=6.5)]; 3.54 (2H, d, H-5e, H-11e, $J_{5e\text{-}5a}$=11.5); 3.59–3.72 (12H, m, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21); 3.84 (2H, dd, H-3e, H-9e, $J_{3e\text{-}3a}$=11.3, $J_{3e\text{-}2}$=2.7); 4.39 (2H, X part, dddd, H-2, H-8, $J_{2\text{-}3a}$=11.0, $J_{2\text{-}3e}$=2.7, $J_{2\text{-}12A}$=6.5, $J_{2\text{-}12B}$=5.2). ^{13}C NMR δ: 67.9 (C-2, C-3, C-8, C-9); 68.4 (C-5, C-11); 70.5 (C-15, C-20); 70.7 (C-17, C-18); 70.8 (C-12, C-23); 71.4 (C-14, C-21); 91.7 (C-6). MS (EI) *m*/*z* (%): 334 (10, $M^{+\cdot}$); 304 (1); 274 (4); 247 [3, $(M-C_4H_7O_2)^+$]; 203 (4); 181 (4); 131 (20); 119 (8); 103 (20); 87 (54, $C_4H_7O_2^+$); 71 (50, $C_4H_7O^+$); 55 (66); 45 (100, $C_2H_5O^+$); 43 (68); 28 (100). Exact mass found: 334.1624; $C_{15}H_{26}O_8$ requires 334.1627.

*4.5. (2*R,*6*S,*8*R*)-13,16,19,22,25-Pentaoxacyclo[15*^{2,8}*]-1,4,7,10-tetraoxaspiro[5,5]undecane (*E,E*) **5***

Eluent for column chromatography same as for **4**. Yield 27%. Colourless oil. $[\alpha]_D^{25}$ +15 (*c* 0.015; $CHCl_3$). IR (film) ν_{max}: 1150–1050 (C–O–C). ^{1}H NMR δ: 3.25 (2H, H-5a, H-11a, $J_{5a\text{-}5e}$=11.5); 3.29 (2H, *p*t, H-3a, H-9a, $J_{3a\text{-}3e}$=11.0, $J_{3a\text{-}2}$=11.0); 3.42 (2H, H-12B, H-26B, dd, $J_{12B\text{-}12A}$=10.3, $J_{12B\text{-}2}$=5.1); 3.56 (2H, H-12A, H-26A, dd, $J_{12A\text{-}12B}$=10.3, $J_{12A\text{-}2}$=6.4); 3.61 (2H, d, H-5e, H-11e, $J_{5e\text{-}5a}$=11.7); 3.63–3.72 (16H, m, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, 2H-23, 2H-24); 3.87 (2H, dd, H-3e, H-9e, $J_{3e\text{-}3a}$=11.4, $J_{3e\text{-}2}$=2.6); 4.36 (2H, dddd, H-2, H-8, $J_{2\text{-}3a}$=11.0, $J_{2\text{-}3e}$=2.6, $J_{2\text{-}12A}$=6.4, $J_{2\text{-}12B}$=5.1). ^{13}C NMR δ: 67.7 (C-2, C-8); 68.1 (C-3, C-9); 68.5 (C-5, C-11); 70.4 (C-14, C-24)*; 70.5 (C-15, C-23)*; 70.7 (C-12, C-26); 70.9 (C-17, C-21)*; 71.0 (C-18, C-20)*; 91.8 (C-6). MS (EI) *m*/*z* (%): 378 (100, $M^{+\cdot}$); 360 (15); 347 (9); 334 (6); 322 (26); 304 (24); 289 (5); 260 (23); 247 (9); 241 (3); 217 (33); 203 (17); 173 (18); 158 (10); 133 (28); 101 (45); 87 (44); 71 (43); 55 (47); 45 (97); 29 (53). Exact mass found: 378.1890; $C_{17}H_{30}O_9$ requires 378.1890.

*4.6. (2*R,*6*S,*8*S*)*-N-*Benzoyl-13,16,19-trioxacyclo[9*^{2,8}*]-1,4,7-trioxa-10-azaspiro[5,5]undecane (*E,E*) **6***

Eluent for column chromatography same as for **4**. Yield 6% (with 2% of dimer **11**, see below). Colourless oil. $[\alpha]_D^{25}$ +47 (*c* 0.05; $CHCl_3$). IR (film) ν_{max}: 1640 (C=O amide); 1240 (C–O–C); 1150–1050 (C–O–C). ^{1}H NMR δ: 2.60–4.75 (22H, unresolved massif); 7.40 (5H, Ar–H). ^{13}C NMR δ: 43.6 (C-9); 51.1 (C-11); 67.4 and 67.7 (C2, C8); 67.3–71.6 (C-3, C-5, C-12, C-14, C-15, C-17, C-18, C-20); 92.0 (C-6); 127.3, 127.6, 127.8, 128.2, 128.3, 129.4 (Ar–CH); 135.2 (Ar–C); 170.4 (C=O). MS (EI) *m*/*z* (%): 394 (7, MH^+); 393 (30, $M^{+\cdot}$); 375 [2, $(M-C_3H_5O)^{+\cdot}$]; 336 (1); 320 (10); 278 (16); 262 (33); 235 (6); 205 (8); 190 (5); 175 (10); 161 (20); 146 (6); 131 (4); 105 (100, Ph–CO^+); 77 (24, Ph^+); 57 (10); 45 (10, $C_2H_5O^+$). Exact mass found: 393.1783; $C_{20}H_{27}NO_7$ requires 393.1787.

*4.7. (2*R,*6*S,*8*S*)*-N-*Benzoyl-13,16,19,22-tetraoxacyclo[12*^{2,8}*]-1,4,7-trioxa-10-azaspiro[5,5]undecane (*E,E*) **7***

Eluent for column chromatography same as for **4**. Yield 26% (with 7% of dimer **12**, see below). Colourless oil. $[\alpha]_D^{25}$ +40 (*c* 0.04; $CHCl_3$). IR (film) ν_{max}: 1640 (C=O amide); 1150–1050 (C–O–C). ^{1}H NMR δ: 2.60–4.75 (17H, unresolved massif); 7.40 (5H, Ar–H). ^{13}C NMR δ: 43.6 and 45.7 (C-9); 49.5 and 51.1 (C-11); 67.3–72.0 (C-2, C-3, C-5, C-8, C-12, C-14, C-15, C-17, C-18, C-20, C-21, C-23); 91.9 and 92.5 (C-6); 127.3, 128.3, 129.7, 129.8 (Ar–CH); 135.1 and 135.3 (Ar–C); 171.0 and 171.2 (C=O). MS (EI) *m*/*z* (%): 437 (30, $M^{+\cdot}$); 407 (1); 364 (9); 322 (14); 306 [28, $(M-C_8H_{15}O_4)^+$]; 278 (21); 262 (36); 249 (6); 235 (13); 219 (6); 205 (16); 190 (9); 175 (15); 161 (29); 146 (6); 131 (6); 105 (100, Ph–CO^+); 77 (40, Ph^+); 57 (19); 45 (25). Exact mass found: 437.2037; $C_{22}H_{31}NO_8$ requires 437.2049.

*4.8. (2*R,*6*S,*8*S*)*-N-*Benzoyl-13,16,19,22,25-pentaoxacyclo[15*^{2,8}*]-1,4,7-trioxa-10-azaspiro[5,5]-undecane (*E,E*) **8***

Eluent for column chromatography same as for **4**. Yield 28%. Colourless oil. $[\alpha]_D^{25}$ +50 (*c* 0.05; $CHCl_3$). IR (film) ν_{max}: 1640 (C=O amide); 1240 (C–O–C); 1150–1050 (C–O–C). ^{1}H NMR δ: 2.60–4.75 (30H, unresolved massif); 7.40 (5H, Ar–H). ^{13}C NMR δ: 43.7 and 45.3 (C-9); 49.3 and 51.2 (C-11); 67.3–71.6 (C-2, C-3, C-5, C-8, C-12, C-14, C-15, C-17, C-18, C-20, C-21, C-23, C-24, C-26); 92.0 and 92.5 (C-6); 127.3, 127.5, 128.4, 128.7, 129.2, 129.7 (Ar–CH); 135.4 (Ar–C); 171.4 (C=O). MS (EI) *m*/*z* (%): 481 (14, $M^{+\cdot}$); 438 [1, $M-C_2H_3O)^+$]; 408(3); 394 [1, $(M-C_4H_7O_2)^+$]; 350

[10, $(M-C_6H_{11}O_3)^+$]; 306 [18, $(M-C_8H_{15}O_4)^+$]; 278 (9); 262 (16); 262 (36); 235 (8); 205 (9); 160 (17); 131 (3); 105 (100, Ph–CO^+); 77 (20, Ph^+); 57 (10); 45 (17, $C_2H_5O^+$). Exact mass found: 481.2318; $C_{24}H_{35}NO_9$ requires 481.2312.

*4.9. (1*S,*5*R,*15*R,*19*S,*23*R,*33*R*)-3,7,10,13,17,21,25,28,31,35,37,38,39,40-Tetradecaoxatetracyclo[36,1^{1,5},1^{15,19},1^{19,23},1^{1,33}]tetracontane (*E,E*),(*E,E*)* ***9***

This compound was isolated simultaneously with compound **3** in the purification step of the reaction mixture. Yield 22%. Colourless oil. $[\alpha]_D^{25}$ −4 (*c* 0.025; $CHCl_3$). IR (film) ν_{max}: 1150–1050 (C–O–C). ^{1}H NMR δ: 3.21 (4H, d, H-2a, H-18a, H-20a, H-36a, $J_{2a\text{-}2e}$=11.5); 3.34 (4H, *p*t, H-4a, H-16a, H-22a, H-34a, $J_{4a\text{-}4e}$=11.1, $J_{4a\text{-}5}$=11.1); 3.44 (4H, dd, H-6B, H-14B, H-24B, H-32B, $J_{6B\text{-}6A}$=10.4, $J_{6B\text{-}5}$=6.1); 3.57 (4H, d, H-2e, H-18e, H-20e, H-36e, $J_{2e\text{-}2a}$=11.5); 3.58-3.68 (20H, m, H-6A, 2H-8, 2H-9, 2H-11, 2H-12, H-14A, H-24A, 2H-26, 2H-27, 2H-29, 2H-30, H-32A); 3.88 (4H, dd, H-4e, H-16e, H-22e, H-34e, $J_{4e\text{-}4a}$=11.5, $J_{4e\text{-}5}$=2.6); 4.17 (4H, m, H-5, H-15, H-23, H-33). ^{13}C NMR δ: 67.1 (C-5, C-15, C-23, C-33); 68.4 (C-4, C-16, C-22, C-34); 68.6 (C-2, C-18, C-20, C-36); 70.6 (C-8, C-12, C-26, C-30)*; 71.0 (C-6, C-14, C-24, C-32); 71.1 (C-9, C-11, C-27, C-29)*; 91.7 (C-1, C-19). MS (EI) *m*/*z* (%): 580 (10, $M^{+\cdot}$); 562 (3); 548 (2); 368 (4); 331 (15); 302 (3); 289 (4); 256 (22); 231 (11); 217 (12); 203 (18); 189 (4); 173 (9); 145 (16); 131 (27); 111 (30); 99 (27); 87 (73, $C_4H_7O_2^+$); 71 (69, $C_4H_7O^+$); 57 (88); 45 (100, $C_2H_5O^+$). Exact mass found: 580.2731; $C_{26}H_{44}O_{14}$ requires 580.2731.

*4.10. (1*S,*5*R,*18*R,*22*S,*26*R,*39*R*)-3,7,10,13,16,20,24,28,31,34,37,41,43,44,45,46-Hexadecaoxatetracyclo[42,1^{1,5},1^{18,22},1^{22,26},1^{1,39}]hexatetracontane (*E,E*),(*E,E*)* ***10***

This compound was isolated simultaneously with compound **4** in the purification step of the reaction mixture. Yield 2%. Colourless oil. $[\alpha]_D^{25}$ 0 (*c* 0.05; $CHCl_3$). IR (film) ν_{max}: 1050–1150 (C–O–C). ^{1}H NMR δ: 3.26 (4H, d, H-2a, H-21a, H-23a, H-42a, $J_{2a\text{-}2e}$=11.6); 3.37 (4H, *p*t, H-4a, H-19a, H-25a, H-40a, $J_{4a\text{-}4e}$=11.1, $J_{4a\text{-}5}$=11.1); 3.44 (4H, H-6B, H-17B, H-27B, H-38B, dd, $J_{6B\text{-}6A}$=10.4, $J_{6B\text{-}5}$=6.0); 3.59 (4H, d, H-2e, H-21e, H-23e, H-42e, $J_{2e\text{-}2a}$=11.6); 3.61 (4H, H-6A, H-17A, H-27A, H-38A, dd, $J_{6A\text{-}6B}$=10.4, $J_{6A\text{-}5}$=5.6); 3.62–3.69 (24H, m, 2H-8, 2H-9, 2H-11, 2H-12, 2H-14, 2H-15, 2H-29, 2H-30, 2H-32, 2H-33, 2H-35, 2H-36); 3.89 (4H, dd, H-4e, H-19e, H-25e, H-40e, $J_{4e\text{-}4a}$=11.1, $J_{4e\text{-}5}$=2.6); 4.22 (4H, dddd, H-5, H-18, H-26, H-39, $J_{5\text{-}4a}$=11.1, $J_{5\text{-}4e}$=2.6, $J_{5\text{-}6A}$=5.6, $J_{5\text{-}6B}$=6.0). ^{13}C NMR δ: 67.2 (C-5, C-18, C-26, C-39); 68.4 (C-4, C-19, C-25, C-40); 68.6 (C-2, C-21, C-23, C-42); 70.6 (C-8, C-15, C-29, C-36)*; 70.7 (C-9, C-14, C-30, C-35)*; 71.0 (C-6, C-17, C-27, C-38); 71.2 (C-11, C-12, C-32, C-33)*; 91.7 (C-1, C-22). Exact mass found (FAB$^+$): 669.3337 (MH^+); $C_{30}H_{52}O_{16}$ requires 669.3333 (MH^+).

*4.11. (1*S,*5*R,*15*S,*19*S,*23*R,*33*S*)-N,N′-Benzoyl-3,7,10,13,21,25,28,31,37,38,39,40-dodecaoxa-17,35-diazatetracyclo[36,1^{1,5},1^{15,19},1^{19,23},1^{1,33}]tetracontane (*E,E*),(*E,E*)* ***11***

This compound was isolated simultaneously with compound **6** in the purification step of the reaction mixture. Yield 12%. Colourless oil. $[\alpha]_D^{25}$ +54 (*c* 0.05; $CHCl_3$). IR (film) ν_{max}: 1640 (C=O amide); 1150–1050 (C–O–C). ^{1}H NMR δ: 2.60–4.75 (44H, unresolved massif); 7.40 (10H, Ar–H). ^{13}C NMR δ: 43.9 and 45.4 (C-16, C-34); 51.4 and 52.9 (C-18, C-36); 67.7 and 68.2 (C-5, C-15, C-23, C-33); 68.8 and 71.9 (C-2, C-4, C-6, C-8, C-9, C-11, C-12, C-14, C-20, C-22, C-24, C-26, C-27, C-29, C-30, C-32); 92.1 (C-1, C-19); 127.4, 127.6, 128.4, 128.9, 129.8, 131.0 (Ar–CH); 135.5 (Ar–C); 171.4 (2 C=O). MS (EI) *m*/*z* (%): 786 (30, $M^{+\cdot}$); 768 (7); 713 (2); 681 [16, $(M-PhCO)^+$]; 647 (3); 611 [3, $(M-C_8H_{15}O_4)^+$]; 567 [5, $(M-C_{10}H_{19}O_5)^+$]; 495 (5); 434 (7); 394 (3); 357 (3); 320 (8); 278 (7); 262 (12); 205 (5); 160 (14);

105 (100, $PhCO^+$); 77 (23, Ph^+); 57 (7); 45 (11). Exact mass found: 786.3578; $C_{40}H_{54}N_2O_{14}$ requires 786.3575.

*4.12. (1*S,*5*R,*18*S,*22*S,*26*R,*39*S*)*-N,N′-Benzoyl-3,7,10,13,16,24,28,31,34,37,43,44,45,46-tetradecaoxa-20,41-diazatetracyclo[42,1^{1,5},1^{18,22},1^{22,26},1^{1,39}]hexatetracontane (*E,E*),(*E,E*) **12**

This compound was isolated simultaneously with compound **7** in the purification step of the reaction mixture. Yield 7%. Colourless oil $[\alpha]_D^{25}$ +32 (*c* 0.036; $CHCl_3$). IR (film) ν_{max}: 1640 (C=O amide); 1150–1050 (C–O–C). ^{1}H NMR δ: 2.65–4.75 (52H, unresolved massif); 7.40 (10H, Ar–H). ^{13}C NMR δ: 43.9 and 45.4 (C-19, C-40); 51.4 and 52.9 (C-21, C-42); 67.7–68.2 (C-5, C-18, C-26, C-39); 68.8–71.9 (C-2, C-4, C-6, C-8, C-9, C-11, C-12, C-14, C-15, C-17, C-23, C-25, C-27, C-29, C-30, C-32, C-33, C-35, C-36, C-38); 92.1 (C-1, C-22); 127.4, 127.6, 128.4, 128.9, 129.8, 131.0 (Ar–CH); 135.5 (Ar–C); 171.4 (2 C=O). MS (EI) *m*/*z* (%): 875 (1, MH^+); 569 (13); 551 (4); 526 (1); 496 (4); 464 (4); 438 (8); 410 (5); 394 (14); 350 (15); 322 (8); 306 (18); 278 (10); 262 (17); 249 (8); 235 (8); 219 (4); 205 (9); 190 (7); 175 (13); 161 (25); 131 (4); 105 (100, Ph–CO^+); 77 (14, Ph^+); 57 (8). Exact mass found (FAB^+): 875.4170 (MH^+); $C_{44}H_{62}N_2O_{16}$ requires 875.4177 (MH^+).

*4.13. (2*R,*6*S,*8*S*)*-N-Benzyl-13,16,19,22-tetraoxacyclo[12^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]undecane (E,E) **13**

To a suspension of $LiAlH_4$ (33 mg, 0.86 mmol, 5 equiv.) in dry THF (0.2 mL) was slowly added, at room temperature and under argon, a solution of benzamide **7** (75 mg, 0.17 mmol) in dry THF (2mL). The mixture was stirred for 2 h. The excess $LiAlH_4$ was then destroyed by Mihaïlovic's method.[12] After filtration the solvent was removed and the crude material purified by chromatography on silica gel. Eluent: gradient from AcOEt to AcOEt:MeOH, 95:5. Yield 87%. Colourless oil. $[\alpha]_D^{25}$ +35 (*c* 0.018; $CHCl_3$). IR (film) ν_{max}: 1150–1050 (C–O–C). ^{1}H NMR δ: 1.81 (1H, *p*t, H-9a, $J_{9a\text{-}9e}$=10.9, $J_{9a\text{-}8}$=10.9); 1.85 (1H, d, H-11a, $J_{11a\text{-}11e}$=11.3); 2.67 (1H, d, H-11e, $J_{11e\text{-}11a}$=11.3); 2.78 (1H, br d, H-9e, $J_{9e\text{-}9a}$=10.9, $J_{9e\text{-}8}$<1); 3.20 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.2, $J_{3a\text{-}2}$=11.2); 3.24 (1H, d, H-5a, $J_{5a\text{-}5e}$=11.4); 3.38–3.80 (19H, m, H-5e, 2H-12, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, 2H-23, NC*H*$_2$Ph); 3.83 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.2, $J_{3e\text{-}2}$=2.6); 4.27–4.42 (2H, m, H-2, H-8); 7.20–7.40 (5H, m, 5 Ar–H). ^{13}C NMR δ: 54.1 (C-9); 56.2 (C-11); 62.9 (N*C*H$_2$Ph); 67.8 (C8); 68.2 (C-3); 69.0 (C-2); 70.3 (C-5); 70.5 (C-14)*; 70.6 (C-15)*; 70.8 (C-20, C-21)*; 71.0 (C-23); 71.5 (C-17, C-18); 72.6 (C-12); 93.1 (C-6); 127.3 (C-4′); 128.6 (C-3′, C-5′); 129.4 (C-2′, C-6′); 136.8 (C-1′). MS (EI) *m*/*z* (%): 423 (26, $M^{+\cdot}$); 393 [6, $(M-CH_2O)^+$]; 332 [4, $(M-C_7H_7)^+$]; 292 [3, $(M-C_6H_{11}O_3)^+$]; 248 (7); 204 (5); 176 (12); 160 (67); 146 (8); 133 (12); 120 (28); 91 (100, $C_7H_7^+$); 73 (8); 57 (12); 45 (17). Exact mass found: 423.2242; $C_{22}H_{33}NO_7$ requires 423.2257.

*4.14. (2*R,*6*S,*8*S*)*-N-Benzyl-13,16,19,22,25-pentaoxacyclo[15^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]-undecane (E,E) **14**

This compound was prepared from benzamide **8** (60 mg, 0.125 mmol) and $LiAlH_4$ (24 mg, 0.625 mmol, 5 equiv.) following the procedure described for **13**. Eluent for column chromatograpy: gradient from AcOEt to MeOH. Yield 80%. Colourless oil. $[\alpha]_D^{25}$ +28 (*c* 0.01; $CHCl_3$). IR (film) ν_{max}: 1150–1050 (C–O–C). ^{1}H NMR δ: 1.87 (1H, *p*t, H-9a, $J_{9a\text{-}9e}$=13.9, $J_{9a\text{-}8}$=13.9); 1.90 (1H, d, H-11a, $J_{11a\text{-}11e}$=11.3); 2.72 (1H, d, H-11e, $J_{11e\text{-}11a}$=11.3); 2.83 (1H, br d, H-9e, $J_{9e\text{-}9a}$=13.9, $J_{9e\text{-}8}$<1); 3.28 (1H, d, H-5a, $J_{5a\text{-}5e}$=11.4); 3.29 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.0, $J_{3a\text{-}2}$=11.0); 3.42 (1H, dd, H-26B, $J_{26B\text{-}26A}$=10.7,

$J_{26B\text{-}8}$=4.7); 3.45 (1H, dd, H-12B, $J_{12B\text{-}12A}$=10.4, $J_{12B\text{-}2}$=5.5); 3.50–3.78 (21H, m, H-5e, H-12A, H-26A, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, 2H-23, 2H-24, NCH_2Ph); 3.88 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.2, $J_{3e\text{-}2}$=2.6); 4.25–4.37 (2H, m, H-2, H-8); 7.20–7.35 (5H, m, 5Ar–H). ^{13}C NMR δ: 54.1 (C-9); 56.1 (C-11); 62.8 (NCH_2Ph); 67.4 (C-8); 68.4 (C-3); 68.7 (C-2); 70.3 (C-5); 70.4 (C-14, C-15)*; 70.5 (C-17)*; 70.6 (C-18)*; 70.8 (C-12); 70.9 (C-20, C-21, C-23)*; 71.0 (C-24)*; 72.3 (C-26); 93.1 (C-6); 127.3 (C-4′); 128.3 (C-3′, C-5′); 129.3 (C-2′, C-6′); 136.9 (C-1′). MS (EI) *m*/*z* (%): 468 (3, MH^+); 437 [2, $(M-CH_2O)^+$]; 376 (1); 336 [1, $(M-C_6H_{11}O_3)^+$]; 292 [2, $(M-C_8H_{15}O_4)^+$]; 248 [3, $M-C_{10}H_{19}O_5)^+$]; 220 (3); 204 (4); 246 (3); 176 (5); 160 (32); 134 (7); 120 (13); 91 (100, $C_7H_7^+$); 57 (23).

*4.15. (2*R,*6*S,*8*S*)-13,16,19,22-Tetraoxacyclo[12^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]undecane (*E,E*) **15***

To a solution of $LiEt_3BH$ in THF (1.37 mL, 1.37 mmol, 2 equiv., 1 M) was added dropwise under argon a solution of benzamide **7** (300 mg, 0.68 mmol) in dry THF (7 mL). The reaction mixture was stirred for 6 h at room temperature. The excess hydride was destroyed by addition of H_2O (0.25 mL, 13.7 mmol, 20 equiv.). The mixture was then heated at 60°C for 1 h in the presence of H_2O_2 (0.5 mL, 30 volumes) to oxidize the boroamine intermediate. The solvent was removed and the residue was dissolved in AcOEt. The organic layer was washed with saturated K_2CO_3 solution and dried on $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel with AcOEt:MeOH, 50:50 as eluent. Yield 86%. Colourless oil. $[\alpha]_D^{25}$ +28 (*c* 0.01; $CHCl_3$). IR (film) ν_{max}: 3400 (NH); 1100 (C–O–C). ^{1}H NMR δ: 1.85 (NH); 2.48 (1H, dd, H-9a, $J_{9a\text{-}9e}$=13.4, $J_{9a\text{-}8}$=11.4); 2.55 (1H, d, H-11a, $J_{11a\text{-}11e}$=13.5); 2.70 (1H, d, H-11e, $J_{11e\text{-}11a}$=13.5); 2.95 (1H, dd, H-9e, $J_{9e\text{-}9a}$=13.4, $J_{9e\text{-}8}$=2.4); 3.23 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.0, $J_{3a\text{-}2}$=11.0); 3.25 (1H, d, H-5a, $J_{5a\text{-}5e}$=11.6); 3.44 (1H, dd, H-23B, $J_{23B\text{-}23A}$=11.2, $J_{23B\text{-}8}$=5.0); 3.45 (1H, dd, H-12B, $J_{12B\text{-}12A}$=11.0, $J_{12B\text{-}2}$=5.0); 3.47 (1H, dd, H-12A, $J_{12A\text{-}12B}$=11.0, $J_{12A\text{-}2}$=4.5); 3.52 (1H, dd, H-23A, $J_{23A\text{-}23B}$=11.2, $J_{23A\text{-}8}$=7.0); 3.58-3.80 (13H, m, H-5e, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21); 3.87 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.0, $J_{3e\text{-}2}$=2.6); 4.15 (1H, dddd, H-8, $J_{8\text{-}9a}$=11.0, $J_{8\text{-}9e}$=2.5, $J_{8\text{-}23A}$=7.0, $J_{8\text{-}23B}$=5.0); 4.40 (1H, dddd, H-2, $J_{2\text{-}3a}$=11.0, $J_{2\text{-}3e}$=2.6, $J_{2\text{-}12A}$=4.5, $J_{2\text{-}12B}$=5.0). ^{13}C NMR δ: 47.2 (C-9); 49.4 (C-11); 67.7 (C-2); 68.0 (C-3); 69.4 (C-8); 69.9 (C-5); 70.4 (C-17)*; 70.5 (C-18)*; 70.7 (C-15)#; 70.8 (C-20)#; 71.2 (C-23); 71.5 (C-14)§; 71.6 (C-21)§; 72.4 (C-12); 91.6 (C-6). MS (EI) *m*/*z* (%): 333 (17, $M^{+\cdot}$); 303 (6); 246 [2, $(M-C_4H_7O_2)^+$]; 218 (1); 202 [4, $(M-C_6H_{11}O_3)^+$]; 188 (1); 172 (3); 158 (6); 144 (3); 128 (13); 114 (6); 100 (6); 87 (20); 70 (100); 70 (41); 57 (18); 45 (32). Exact mass found: 333.1787; $C_{15}H_{27}NO_7$ requires 333.1776.

*4.16. (2*R,*6*S,*8*S*)-13,16,19,22,25-Pentaoxacyclo[15^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]undecane (*E,E*) **16***

This compound was prepared from benzamide **8** (96 mg, 0.20 mmol) and $LiEt_3BH$ (0.4 mL, 0.4 mmol, 2 equiv., 1 M in THF) according to the procedure described for **15**. Reaction time: 1 h. Eluent for column chromatography: gradient from AcOEt:MeOH, 90:10 to pure MeOH. Yield 80%. Colourless oil. $[\alpha]_D^{25}$ +11 (*c* 0.05; $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3400 (NH); 1100 (C–O–C). ^{1}H NMR δ: 1.82 (1H, br s, NH); 2.41–2.58 (2H, m, H-9a, H-11a); 2.68 (1H, d, H-11e, $J_{11e\text{-}11a}$=13.4); 2.94 (1H, br d, H-9e, $J_{9e\text{-}9a}$=13.0, $J_{9e\text{-}8}$<1); 3.23 (1H, d, H-5a, $J_{5a\text{-}5e}$=11.6); 3.25 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.1, $J_{3a\text{-}2}$=11.1); 3.37 (1H, dd, H-26B, $J_{26B\text{-}26A}$=10.2, $J_{26B\text{-}8}$=5.0); 3.40 (1H, dd, H-12B, $J_{12B\text{-}12A}$=10.4, $J_{12B\text{-}2}$=4.9); 3.51 (1H, dd, H-26A, $J_{26A\text{-}26B}$=10.0, $J_{26A\text{-}8}$=8.1); 3.53 (1H, dd, H-12A, $J_{12A\text{-}12B}$=10.4, $J_{12A\text{-}2}$=8.2); 3.58 (1H, d, H-5e, $J_{5e\text{-}5a}$=11.6); 3.60–3.70 (16H, m, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, 2H-23, 2H-24); 3.83 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.1, $J_{3e\text{-}2}$=2.6); 4.07 (1H, m, H-8); 4.30 (1H, dddd, H-2, $J_{2\text{-}3a}$=11.1, $J_{2\text{-}3e}$=2.6, $J_{2\text{-}12A}$=8.2, $J_{2\text{-}12B}$=4.9). ^{13}C NMR δ: 47.3 (C-9); 49.3 (C-11); 67.3 (C-8); 68.0 (C-3); 68.8 (C-2); 69.8

(C-5); 70.8 (C-12); 70.4, 70.5, 70.6, 70.8, 70.9 (C-14, C-15, C-17, C-18, C-20, C-21, C-23, C-24); 72.1 (C-26); 91.5 (C-6). MS (EI) *m*/*z* (%): 377 (2, $M^{+\cdot}$); 347 (6); 304 (1); 246 (3); 202 (2); 158 (5); 132 (14); 114 (7); 87 (19); 70 (71); 45 (100). Exact mass found: 377.2049; $C_{17}H_{31}NO_8$ requires 377.2049.

*4.17. (2*R,*6*S,*8*S*)*-N-*Methyl(ethoxycarbonyl)-13,16,19,22-tetraoxacyclo[12^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]undecane (*E,E*)* ***17***

To a suspension of amine **15** (185 mg, 0.55 mmol) and anhydrous K_2CO_3 (230 mg, 1.66 mmol, 3 equiv.) in dry CH_3CN (9 mL) was added dropwise at room temperature and under argon, ethyl bromoacetate (184 mL, 278 mg, 1.66 mmol, 3 equiv.). The mixture was heated at 40–50°C for 6 h. The solvent was removed and the residue poured into water. After extraction with CH_2Cl_2, the organic layer was dried on $MgSO_4$ and evaporated. The crude material was purified by chromatography on silica-gel (eluent: gradient from AcOEt to AcOEt:MeOH, 95:5). Yield 86%. Brown oil. $[\alpha]_D^{25}$ +29 (*c* 0.036; $CHCl_3$). IR (film) ν_{max}: 1740 (C=O); 1100 (C–O–C). ^{1}H NMR δ: 1.26 (3H, t, 3H-28, $J_{28\text{-}27}$=7.1); 2.35 (1H, *p*t, H-9a, $J_{9a\text{-}9e}$=11.0, $J_{9a\text{-}8}$=11.0); 2.40 (1H, d, H-11a, $J_{11a\text{-}11e}$=11.3); 2.76 (1H, d, H-11e, $J_{11e\text{-}11a}$=11.3); 2.82 (1H, dd, H-9e, $J_{9e\text{-}9a}$=11.0, $J_{9e\text{-}8}$<1); 3.28 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.1, $J_{3a\text{-}2}$=11.1); 3.31 (1H, d, H-5a, $J_{5a\text{-}5e}$=11.5); 3.33 (2H, s, 2H-24); 3.46 (1H, dd, H-12A, $J_{12A\text{-}12B}$=10.9, $J_{12A\text{-}2}$=6.4); 3.50 (1H, dd, H-23A, $J_{23A\text{-}23B}$=11.4, $J_{23A\text{-}8}$=4.2); 3.54–3.83 (15H, m, H-5e, H-12B, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, H-23B); 3.93 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.1, $J_{3e\text{-}2}$=2.6); 4.16 (2H, q, 2H-27, $J_{27\text{-}28}$=7.1); 4.36 (1H, dddd, H-8, $J_{8\text{-}9a}$=11.0, $J_{8\text{-}9e}$<1, $J_{8\text{-}23A}$=5.2, $J_{8\text{-}23B}$=4.2); 4.42 (1H, dddd, H-2, $J_{2\text{-}3a}$=11.1, $J_{2\text{-}3e}$=2.6, $J_{2\text{-}12A}$=5.6, $J_{2\text{-}12B}$=6.4). ^{13}C NMR δ: 14.3 (C-28); 52.8 (C-9); 54.9 (C-11); 58.4 (C-24); 60.5 (C-27); 67.5 (C-2); 68.6 (C-3); 68.9 (C-8); 70.3 (C-5); 70.5, 70.7, 70.8, 70.9 (C-15, C-17, C-18, C-20); 71.2 (C-12); 71.4 (C-14)*; 71.6 (C-21)*; 72.3 (C-23); 93.1 (C-6); 170.1 (C-25). MS (EI) *m*/*z* (%): 419 (37, $M^{+\cdot}$); 373 (13); 346 (100); 316 (16); 156 (52); 130 (15); 116 (18); 100 (17); 87 (15); 73 (8); 57 (9); 45 (15). Exact mass found: 419.2138; $C_{19}H_{33}NO_9$ requires 419.2138.

*4.18. (2*R,*6*S,*8*S*)*-N-*Methylcarboxy-13,16,19,22-tetraoxacyclo[12^{2,8}]-1,4,7-trioxa-10-azaspiro[5,5]-undecane (*E,E*)* ***18***

A solution of ester **17** (47 mg, 0.112 mmol) in distilled H_2O (1 mL) was refluxed for 1 week. After complete hydrolysis of the ester, the crude solution was washed with $CHCl_3$. Evaporation of the aqueous phase afforded carboxylic acid **18**. Yield 91%. Brown oil. $[\alpha]_D^{25}$ +22 (*c* 0.04; H_2O). IR ($CHCl_3$) ν_{max}: 1740 and 1760 (COOH); 1160–1060 (C–O–C). ^{1}H NMR (D_20) δ: 2.84 (1H, *p*t, H-9a, $J_{9a\text{-}9e}$=11.3, $J_{9a\text{-}8}$=11.3); 2.86 (1H, d, H-11a, $J_{11a\text{-}11e}$=11.5); 3.22 (1H, *p*t, H-3a, $J_{3a\text{-}3e}$=11.3, $J_{3a\text{-}2}$=11.3); 3.30–3.63 (22H, m, 2H-5, H-9e, H-11e, 2H-12, 2H-14, 2H-15, 2H-17, 2H-18, 2H-20, 2H-21, 2H-23, 2H-24); 3.67 (1H, dd, H-3e, $J_{3e\text{-}3a}$=11.3, $J_{3e\text{-}2}$=2.6); 4.09 (1H, m, H-2); 4.26 (1H, m, H-8). ^{13}C NMR (D_20) δ: 53.3 (C-11); 55.0 (C-9); 59.6 (C-24); 67.2 (C-3); 67.3 (C-2); 68.7 (C-5); 69.6 (C-8); 70.1, 70.6, 70.7, 70.9, 71.1, 71.2, 71.9 (C-12, C-14, C-15, C-17, C-18, C-20, C-21, C-23); 93.3 (C-6); 169.9 (C-25). MS (EI) *m*/*z* (%): 391 (16, $M^{+\cdot}$); 373 (6); 346 [91, (M−COOH)]; 332 (4); 316 (18); 304 [9, $(M-C_4H_7O_2)^+$]; 302 (7); 274 (5); 260 [3, $(M-C_6H_{11}O_3)^+$]; 244 (4); 230 (3); 216 (6); 200 (4); 186 (4); 172 (6); 158 (5); 144 (10); 128 (100); 100 (29); 87 (40); 73 (22); 57 (42); 45 (68). Exact mass found: 391.1842; $C_{17}H_{29}NO_9$ requires 391.1839.

4.19. Complexation experiments

An approx. 5×10^{-5} molar ($C°_m$) solution of the relevant metal picrate was prepared in THF, 2 cm^3 of which was placed in the spectrometer cell. More of this solution was used to prepare a 10^{-2} M ($C°_L$) solution of the ligand. Using a microsyringe, amounts of this solution were incrementally added to the cell through a silicone septum inserted in its Teflon tap. In these conditions, the metal picrate concentration was kept constant at molarity $C°_m$, the ligand analytical concentration C_L being variable. The $C_L/C°_m$ ratio was progressively increased first in 0.1 unit steps, then beyond 1 in 1 unit steps and beyond 10 in 10 unit steps up to a value of 100. The pure solvent was used in the reference cell. Experiments were performed at 20°C.

The Uvikon 941 UV–visible spectrophotometer allows an accuracy better than 0.1 nm in wavelength and better than 2×10^{-3} unit in absorption. The spectrum of each solution was recorded from 300 to 450 nm in 0.2 nm steps at speed 200 nm min^{-1} and bandwidth 2 nm.

A first analysis of the data was performed using the Easy Plot software (location of the peaks, presence and location of the isobestic points, etc.) to suggest assumptions for further processing. Dissolved in THF, metal picrates occur only as contact ion pairs.[10] Coordination of the cation by the ligand could generate various sorts of separated ion pairs, formation of which will correspond to more or less pronounced bathochromic shifts. The spectral data, i.e. for each system absorption for 50 wavelengths distributed on both sides of the isobestic point for some 20 to 30 spectra, were processed using the STAR[11] program, which provides, for a given model (number and stoichiometry of the complexes formed), both the formation constants and the spectra of the species involved, by minimizing the sum ($\sum_\iota {r_i}^2$) of the square of the deviation of the calculated values from the experimental ones. Comparison of the values for the various statistical parameters (standard deviation σ_β, mean residual $\langle|r|\rangle$) and residual mean $\langle r\rangle$ and consideration of the expected experimental accuracy indicates the most satisfactory model. Equilibrium constants and associated statistical parameters are given in Table 3.

References

1. Lemaire, M.; Jeminet, G.; Gourcy, J.-G.; Dauphin, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2101–2108.
2. Lemaire, M.; Posada, F.; Gourcy, J.-G.; Jeminet, G. *Synthesis* **1995**, *6*, 627–629.
3. Lemaire, M.; Jeminet, G.; Cuer, A.; Gourcy, J.-G.; Dauphin, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1299–1302.
4. (a) Pedersen, C. J. *J. Am. Chem. Soc*. **1967**, *89*, 2495–2497. (b) Pedersen, C. J. *J. Am. Chem. Soc*. **1967**, *89*, 7017–7036. (c) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem., Int. Ed. Engl*. **1972**, *11*, 16–25.
5. (a) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev*. **1974**, *74*, 351–384. (b) Poonia, N. S.; Bajaj, A. V. *Chem. Rev*. **1979**, *79*, 389–445. (c) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev*. **1985**, *85*, 271–339.
6. (a) Stoddart, J. F. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds. Wiley-Interscience: New York, **1988**; Vol. 17, pp. 207–288. (b) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev*. **1997**, *97*, 3313–3361.
7. Brimble, M. A.; Johnston, A. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 265–269.
8. (a) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev*. **1991**, *91*, 1721–2085. (b) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res*. **1997**, *30*, 338–345.
9. Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc*. **1984**, *106*, 8240–8244.
10. Bourgoin, M.; Wong, K. H.; Hui, J. Y.; Smid, J. *J. Am. Chem. Soc*. **1975**, *97*, 3462–3467.
11. Beltran, J. L.; Codony, R.; Prat, M. D. *Anal. Chim. Acta* **1993**, *276*, 441–454.
12. Micovic, V. M.; Mihaïlovic, L. J. *J. Org. Chem*. **1953**, *18*, 1190–1200.