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2,6,9-Trioxabicyclo[3.3.1]nona-3,7-dienes and 2,4,6,8-Tetraoxaadamantanes: Novel Chiral Spacer Units in Macrocyclic Polyethers

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The unusual chiral heterocyclic systems, trioxabicyclo[3.3.1]nona-3,7-dienes ("bridged bisdioxines"), are incorporated as novel spacer molecules into macrocyclic polyether ring systems of various sizes (8, 9 as well as 11–15) by cyclocondensation reaction of the bisacid chloride 4b or bisesters 6,7 and 10, with several ethylene glycols. The 2:2 macrocycles 12–14 are obtained in approximately 50:50 mixtures of diastereomers. These conclusions are mainly based on HPLC data presented in Table I as well as X-ray analyses of (1*R*,5*R*)-8c (space group Pbca, $a = 10.163(3)$ Å, $b = 18.999(4)$ Å, $c = 36.187(10)$ Å, $V = 6987(3)$ Å^3, $Z = 8$, $d_{calc} = 1.218\,g\,cm^{-3}$, 6974 reflections, $R = 0.0553$), *meso*/*rac*-11 (space group $P\bar{1}$, $a = 10.472(5)$ Å, $b = 16.390(5)$ Å, $c = 17.211(5)$ Å, $\alpha = 98.69(2)°$, $\beta = 93.04(2)°$, $\gamma = 98.52(2)°$, $V = 2879.3(18)$ Å^3, $Z = 2$, $d_{calc} = 1.173\,g\,cm^{-3}$, 11,162 reflections, $R = 0.0945$) and *meso*-12 (space group $P2_1/c$, $a = 9.927(2)$, $b = 18.166(3)$, $c = 17.820(3)$ Å, $\beta = 96.590(10)°$, $V = 3192.3(10)$ Å^3, $Z = 4$, $D_c = 1.109\,g\,cm^{-3}$, 3490 reflections, $R = 0.0646$). The 1:1 macrocycles 8b,c are also formed by intramolecular transesterification of the open-chain bisesters 7b,c and their formation is favored by the use of metal ions as templates. The bridged bisdioxine moieties in 8b and 12 are converted into the corresponding chiral tetraoxaadamantane spacers to afford macrocycles 16 and 17. Preliminary metal ion complexation studies with selected species (8c, 11–14) were also performed.

Keywords: Tetraoxaadamantanes; Novel chiral spacer units; Macrocyclic polyethers; HPLC; Bridged bisdioxines; X-ray

INTRODUCTION

Neat dipivaloylketene **1**, generated in quantitative yield by preparative flash vacuum pyrolysis (FVP) [1], dimerizes in an unusual [2 + 4] cycloaddition reaction to afford the extraordinarily stable α-oxoketene **2** [2], which can be converted into either mono- or bifunctionalized trioxabicyclo[3.3.1]nonadienes **3** and **4** ("bridged bisdioxines"), by addition of nucleophiles [3,4]. Hydrolysis of **2**, conversion to the bisacid chloride **4b**, and reaction with ethanol affords the bisester **4c** [3,4]. These molecules are readily converted to bifunctionalized 2,4,6,8-tetraoxaadamantanes **5** by acidic hydrolysis (Scheme 1) [5]. The mechanisms leading to compounds **3**–**5** are discussed in detail in Ref. [4]. Both the concavely shaped bridged bisdioxines **3** and **4** and the ball shaped tetraoxaadamantanes **5** exhibit axial chirality [6], as established by ^{1}H NMR measurements using chiral shift reagents [3–5].

The rigid molecular geometries ascertain dihedral angles between the two acid functionalities in **4** and **5** of ca. 120° according to X-ray crystallography [3–5]. This value agrees very well with the geometry of, e.g. isophthaloyl dichloride [7–11], 2,6-pyridine dicarbonyl dichloride [12,13] or even 1,3-adamantane dicarbonyl dichloride [14]. From this point of view,

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TABLE I Summary of the HPLC results

Macrocycle	Yield* Major fraction	Yield* Minor fraction	Diastereomeric ratio† RS:RR(SS)
11	36%	14%‡	~1:2
12	25%	4%‡	~1:1
13	32%¶ RS + RR(SS)		~1:1
8b	38%		
14	14%¶ RS + RR(SS)		~1:1
8c	32%		

*Isolated yields by flash chromatography. †From HPLC-data. ‡By separation of enriched diastereomers by flash-chromatography and preparative TLC. ¶Mixture of diastereomers.

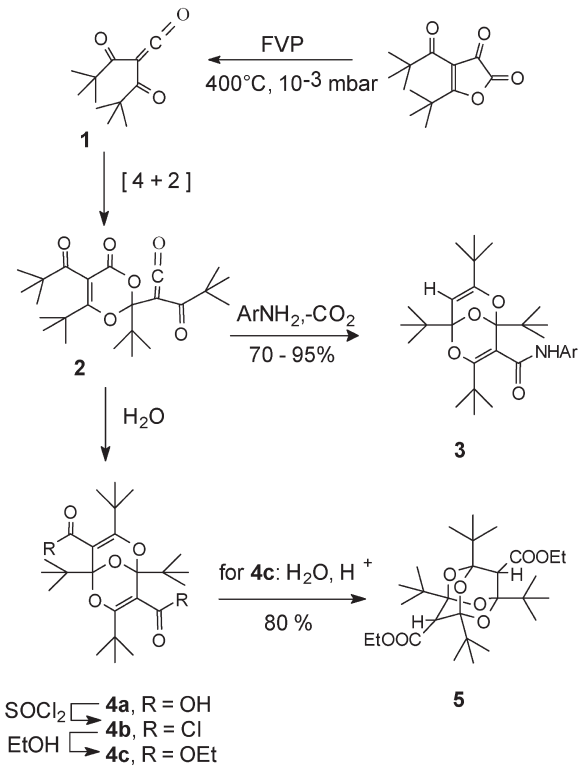
bridged bisdioxine and the tetraoxaadamantane moieties should be able to replace the commonly used isophthaloyl, pyridyl and adamantyl spacers in numerous macrocycles. Their properties with respect to possible host–guest interactions will be related to the high lipophilicities due to the *t*-butyl groups. Several examples of replacement of isophthaloyl dichloride by **4b** in macrocyclic synthesis [7–11] can be envisaged. Bridged calixarenes [12,13] should be available from replacing 2,6-pyridinedicarbonyl dichloride, and the 2,4,6,8-tetraoxadamantane spacer could be incorporated into cyclodepsipeptides [14], which are well known regulators of ion transport through membranes, e.g. valinomycin, which is responsible for the selective transport of potassium ions through biological membranes [15].

Here, we report the incorporation of the rare heterocyclic scaffolds present in **4** and **5**, as novel spacer units in macrocyclic ring systems of the crown ether type. This was achieved by esterification with ethylene glycols of variable length, thus generating macrocycles of different size and uncommon stereochemical features and thereby adding a new facet to the widely scattered family of macrocyclic polyethers [16–21].

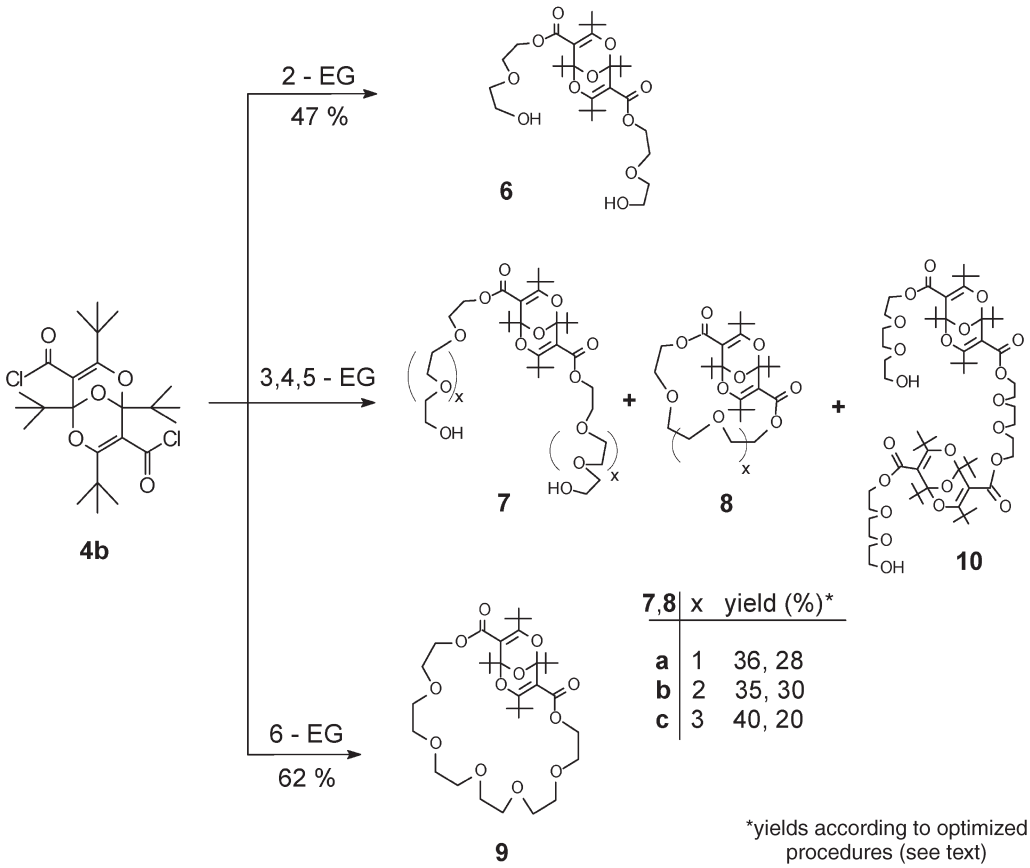
RESULTS AND DISCUSSION

The reaction of bisacid chloride **4b** with ethylene glycols of variable chain lengths (di– to hexaethylene glycol) afforded the bisesters **6** and **7**, as well as the corresponding macrocycles **8** and **9** depending on the reaction conditions (Scheme 2). Thus, the reaction mixture from **4b** and triethylene glycol too afforded the open-chain 2:3 product **10**. Macrocyclization via formation of lactones is a well known and commonly used methodology [22–24]. Utilizing the Ruggli–Ziegler dilution principle [25], equimolar mixtures of **4b** and tri-, tetra-, or pentaethylene glycols (3,4,5-EG) yielded the macrocycles **8** in yields of 20–30% as the main reaction products. Since the diethylene glycol chain (2-EG) is too short to allow cyclization, the open-chain bisester **6** was the only product isolated. Triethylene glycol (3-EG) cyclized with **4b** to afford the very narrow macrocycle **8a** in 28% yield, obviously the steric hindrance due to the bulky *t*-butyl groups is not as severe as one would expect from the corresponding molecular model. On the other hand, with hexaethylene glycol (6-EG) the macrocycle **9** was formed predominantly (62% yield); no further product could be isolated from the reaction mixture under any of the conditions employed. Due to the longer chain of the glycol, intramolecular cyclization to **9** is strongly favored over the formation of the open-chain bisester.

The structural and conformational determination of macrocycles **8** and **9** is based on detailed ^{1}H- and ^{13}C NMR measurements using NOE, HMBC [26], and HMQC [27,28] experiments. The presence of the bridged bisdioxine units in **8** and **9** was unambiguously established by comparing their ^{13}C NMR data (see "Experimental Section") with those of several analogues reported earlier [4]. From the three-dimensional molecular model of **8b** derived from NOE and HMBC-experiments, it became clear that, under normal conditions in solution, the molecule avoids an accurate all-syn (crown-ether like) arrangement of the ring oxygens. A similar situation was found in the crystal. Structure analysis of **8c** confirmed that the compound is a racemate of the enantiomers (1*R*,5*R*)-**8c** and (1*S*,5*S*)-**8c** related by the



SCHEME 1



7,8	x	yield (%)*
a	1	36, 28
b	2	35, 30
c	3	40, 20

SCHEME 2

centers of symmetry in the centrosymmetric space-group (Fig. 1). The bonding distances, angles and torsion angles in the 2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene moiety agree well with those observed in 2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarbaldehyde [29] and *N*-phenyl-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4-carboxamide [4].

Due to the *tert*-butyl groups in positions 3 and 7 of the bicyclic sub-units, the pentaethylene glycol chain in **8c** exhibits a stretched rather than convoluted conformation. Only the portion most distant to the bicyclic sub-unit (C87–C90) is coiled.

In order to shift the reaction outcome toward the open-chain bisesters **7**, required as starting materials for the synthesis of the larger macrocycles **11**–**14** (Scheme 3) an excess of the ethylene glycol was used (glycol : **4b** = 4 : 1). Under these conditions the open chain bisesters **7** were obtained in yields of 35–40%, while the amount of **6** (45%) remained essentially unchanged. Here, it is important to note that, under any reaction conditions employed, intensive use of dry flash chromatography [31,32] was essential for the work up of the crude reaction mixtures in order to separate and purify the target molecules (bisesters **6**, **7** or macrocycles **8**, **9**). In particular, it is highly important to obtain the bisesters **6** and **7** free from any excess of glycol in order to avoid problems in isolating and purifying the desired macrocyclic systems **11**–**14**. The open-chain bisesters **6** and **7** also bind water strongly in a 1:1 molar ratio, persisting after drying on the vacuum line at 10^{-3} mbar, and, in some cases, also contain minor amounts of ethyl acetate used as a chromatography eluant (see "Experimental Section").

When the pure bisesters **6** and **7** are reacted with **4b** the new macrocycles **11**–**14** were obtained in low to moderate yields (Scheme 3 and Table I). These compounds were separated and purified by flash chromatography. In the cases of **7b** and **7c**, the expected products **13** and **14** were formed together with macrocycles **8b** and **8c**, with only one bisdioxine spacer in the macrocycle. In an effort to enhance the yield of the target molecules **13** and **14**, and to avoid the formation of **8b,c**, some template experiments [33–36] were performed. When adding metal salts with different cationic radii ($RhCl_3$, NaSCN and KSCN) to the reaction of **4b** and **7b,c** the formation of the unwanted 1:1 macrocycles **8b,c** was favored in each case (increase of yields from ca. 35 to 55%).

The size of macrocycles **11** and **12** was established by X-ray analyses (see below). In order to determine the structures of **13** and **14**, in particular, to confirm the presence of a 2:2 product (two bridged bisdioxines connected through two tetra- or pentaethylene glycol chains), mass

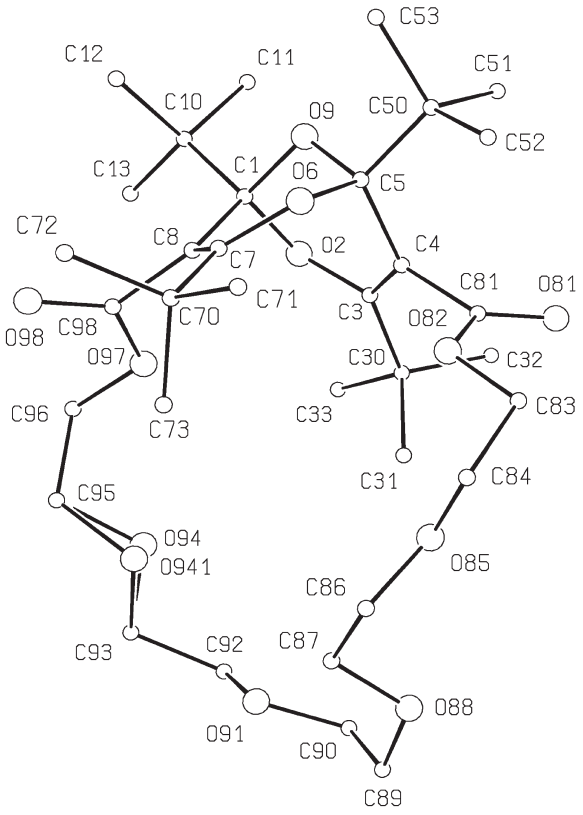


FIGURE 1 ORTEP [30] plot of (1*R*,5*R*)-**8c** showing the atomic numbering scheme. The atoms are drawn with arbitrary radii; the hydrogen atoms are omitted.

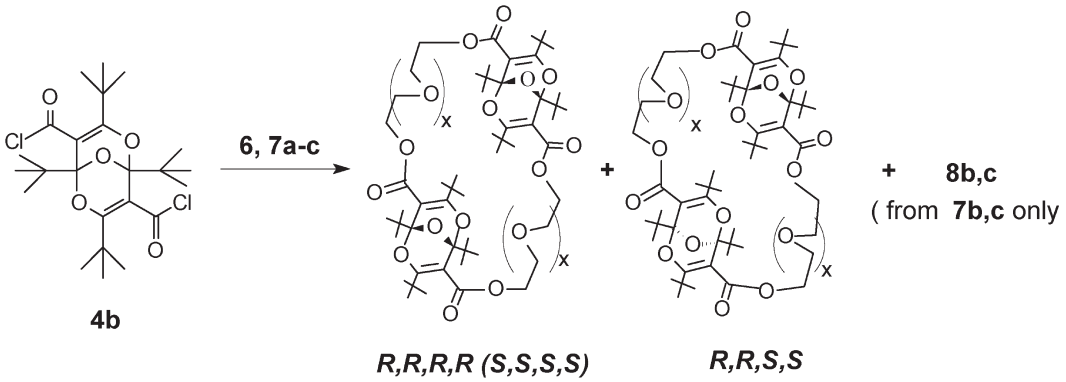
spectrometry played an important role since NMR spectroscopy does not allow to distinguish between 1:1, 2:2 or even 3:3 (see **15**) products. The mass spectra were recorded in the FAB mode (matrix: *m*-nitrobenzyl alcohol) and revealed the presence of $m/z = 1194.0$ $[M + H]^+$ for **13** and 1281.5 $[M + H]^+$ and 1303.5 $[M + Na]^+$ for **14**.

The structural elucidation of **10** as a 2:3 product is based on its elemental analysis, a FAB mass spectrum (glycerine matrix; $m/z = 1257.2$ $[M + H]^+$) as well as ^1H- and ^{13}C NMR spectra, verifying the presence of two bisdioxine units together with three triethylene glycol chains from the ratio of CH_2-protons to *t*-butyl groups.

A cyclocondensation reaction of **10** with the bisacid chloride **4b** leads to the formation of the 3:3 product **15** (13% yield) as a highly viscous oil which solidifies after intensive chromatographic separation and purification. Macrocycle **15** represents the largest cycle of the whole series. This compound should exist as a complex mixture of diastereomers, which was not investigated further. The size of the molecule was verified from the FAB mass spectrum (m/z 1657.9 $[M + 1]^+$); the ^1H NMR spectrum exhibited CH_2 and $C(CH_3)_3$ protons in a 1:1 ratio (Scheme 4).

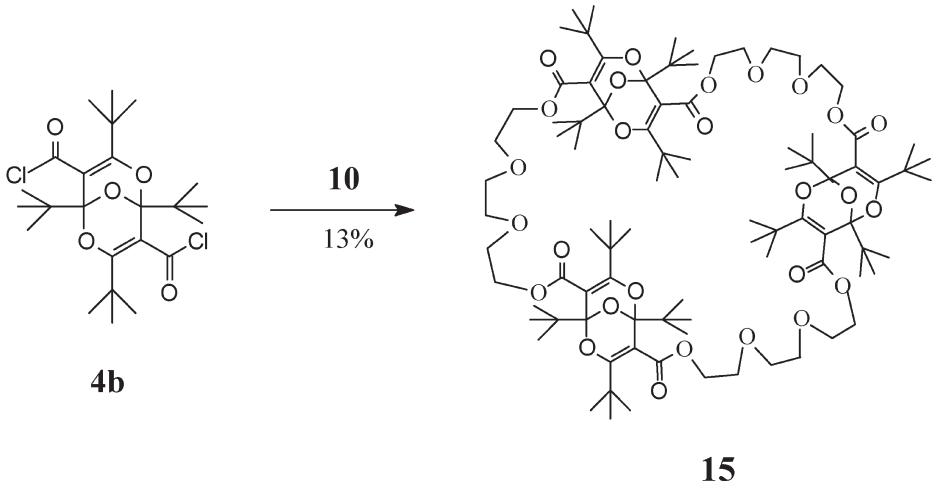
Macrocycle **15** strongly retains ethyl acetate in ca.1:1 molar ratio as evidenced by the ^1H NMR spectrum and elemental analysis.

The experimental findings during synthesis of Compounds **11**–**14** merit further discussion: due to the axial chirality of the bisdioxine skeleton [3–6],



	Ratio of Diastereomers *racem* : *meso*	overall yields
11, x = 1	~ 2 : 1	50 %
12, x = 2	~ 1 : 1	29 %
13, x = 3	~ 1 : 1	32 %
14, x = 4	~ 1 : 1	14 %

SCHEME 3



SCHEME 4

the macrocyclic systems **11**–**14** having *two* bridged bisdioxine spacers each should be present as mixtures of diastereomers (*RR*, *SS* = *meso* and *bis*-*R*,*R*/*bis*-*S*,*S* = *rac*) as a consequence of cyclocondensation reactions of *rac*–bisesters **6** and **7** with *rac*–bisacid chloride **4b** (Scheme 3).

During attempts to separate the single diastereomers chromatographically, a somewhat different picture was found depending on the length of the ethylene glycol chains connecting the two bridged bisdioxine spacers:

In case of macrocycle **11**, the mixture of the two diastereomers was first purified with the aid of flash chromatography. In addition, preparative TLC allowed the separation into two fractions of different amounts (major fraction 36%; minor fraction 14%), the major one being slightly enriched in one diastereomer (*vide infra*). Crystals suitable for X-ray analysis were grown from this fraction (Fig. 2). Furthermore, in the ^{1}H NMR spectrum at 360 MHz a very narrow doubling of the signals of the *t*-butyl groups was observed, while in the ^{13}C NMR spectrum some signals of the trioxabicyclo[3.3.1]nonadiene ring appeared twice.

The crystal structure analysis of **11** showed that the majority of the compound is a racemate of the enantiomers (*bis*-1*R*,5*R*)-**11** (Fig. 2) and (*bis*-1*S*,5*S*)-**11** (39.7% each) related by the center of symmetry. The remainder of the molecules (20.5%) exhibit the diastereomeric *meso*-form (1*R*,5*R*,1*S*,5*S*)-**11** (Fig. 3). The bonding distances, angles and torsion angles in the 2,6,9-trioxabicyclo(3.3.1)nona-3,7-diene structural fragments again agree well with those observed in structural analogues [4,29]. Due to the *tert*-butyl groups at the positions 3 and 7 of the bicyclic subunits, the molecules of **11** exhibit stretched rather than convoluted conformations.

From the reaction of **4b** and bisester **7a**, a mixture of diastereomers of the new macrocycle **12** was obtained. This product again could be separated into two layers (amounts 25 and 4%, respectively) following the same chromatographic procedure as described for **11**. Crystals suitable for X-ray analysis were obtained from the main fraction, and the X-ray data made evident the exclusive presence of the *R*,*R*,*S*,*S*-(*meso*)-diastereomer in the crystal (Fig. 4). The molecules are located around an inversion center. The two *tert*-butyl groups at positions 3 and 7 of the bicyclic sub-units are disordered over two orientations mutually twisted around the C3–C30 and the C7–C70 bonds by ca. 60°. The other two *tert*-butyl groups attached to C1 and C5 are fully ordered.

Cyclocondensation reaction of the bisesters **7b,c** with bisacid chloride **4b** resulted in the formation of mixtures of diastereomers **13** and **14** in overall yields of 32 (**13**) and 18% (**14**). Unlike the situations for **11** and **12**, it was not possible to separate them further chromatographically. Instead, the macrocycles **8b** and **8c**, containing only one bisdioxine subunit, were obtained as byproducts (38 and 32%, respectively). Since the starting materials **7b,c** had been carefully freed from any excess of tetra- or pentaethylene glycol, an intramolecular transesterification [37–40] must have occurred, probably initiated and/or catalyzed by hydrogen chloride liberated from the cyclocondensation reaction with **4b**. The simultaneously formed ethylene glycols (4,5-EG) then compete with the bisesters **7b,c** for the bisacid chloride **4b** (Scheme 5). The smaller strain within the larger ring systems of **8b,c** strongly favors their formation over that of **8a**.

In order to further establish these divergent findings during preparation of the 2:2 compounds **11**–**14**, HPLC-measurements with chiral stationary phases (CSP III, Chiralpak AD, Chiralcel ODH, SS-Ulmo [41]) were performed. A summary of these experiments is given in Table I (for details see "Experimental Section"). In principle, these experiments confirm that compounds **12**–**14** exist as approximately equimolar mixtures of diastereomers

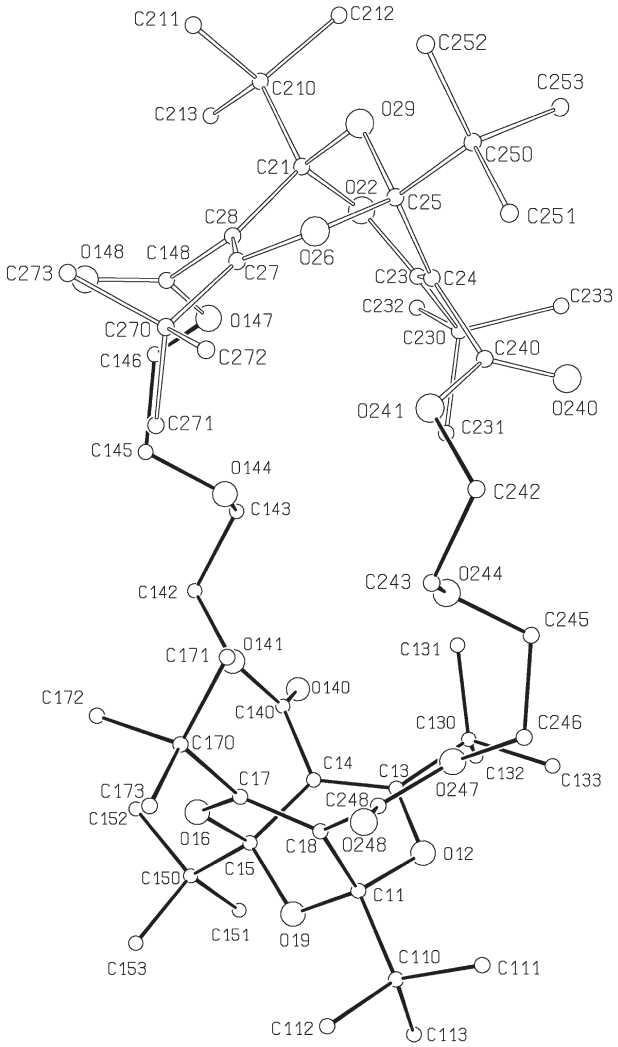


FIGURE 2 ORTEP [30] plot of (*bis*-1*R*,5*R*)-**11** showing the atomic numbering scheme. The atoms of the upper part of the molecule drawn with open bonds have site occupation factors of 0.795(3). The atoms are drawn with arbitrary radii; the hydrogen atoms are omitted.

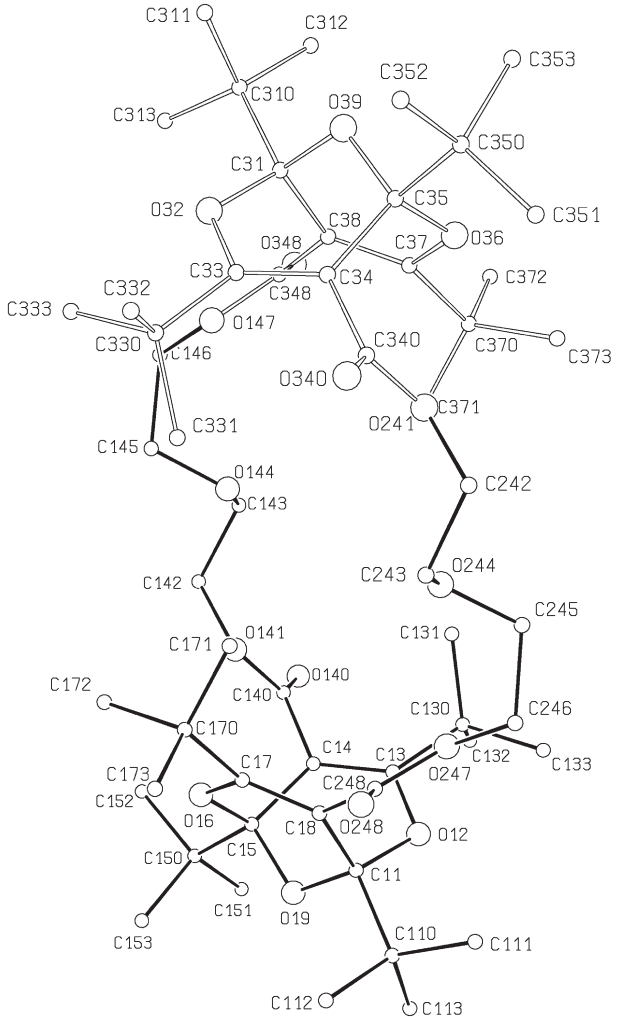


FIGURE 3 ORTEP [30] plot of (1*R*,5*R*,1*S*,5*S*)-**11** showing the atomic numbering scheme. The atoms of the upper part of the molecule drawn with open bonds have site occupation factors of 0.205(3). The atoms are drawn with arbitrary radii; the hydrogen atoms are omitted.

(*rac*-and *meso*-molecules), although in case of **12** a chromatographic separation into two fractions was feasible. With **11**, a slight predominance of the pair of enantiomers (*bis*-1*R*,5*R*/*bis*-1*S*,5*S*-**11**) is observed. This could either be attributed to some degree of diastereoselectivity coming from slightly different sterical hindrance of the bulky *t*-butyl groups in both diastereomers bearing the shortest ethylene glycol chain (2-EG), or to slightly different physical properties (solubility) of both diastereomers during the various chromatographic procedures applied.

2,4,6,8-Tetraoxaadamantanes

A convenient *de novo* synthesis of functionalized 2,4,6,8-tetraoxaadamantanes was achieved by simple acid hydration of the corresponding trioxabicyclononadienes (bridged bisdioxines) [5]. In order to enhance the assortment of potential host molecules, this chemical conversion was also applied to macrocycles of type **8** and **11**–**14**. As an example, the desired annelated tetraoxaadamantane **16** was obtained in 60% yield by acidic hydration of **8b** (Scheme 6).

The ^{1}H- and ^{13}C NMR data compared with those of other tetraoxaadamantanes confirm the presence of the adamantane skeleton [5]. The C–H signal at $\delta = 2.96$ ppm and the quarternary, acetal type ring carbons at 99.5 and 101.6 ppm are particularly characteristic. Macrocycle **16** exhibits axial chirality as established by ^{1}H NMR studies. Using Eu(hfc)$_3$ as a chiral shift reagent, a splitting of signals was observed (ratio 1:1): the *tert*-butyl groups at δ 0.96 and 1.14 ppm were shifted downfield to δ 1.40, 1.46 and 1.87, 1.91 ppm, respectively, whereas the C–H signal moved into the crowded CH_2-region.

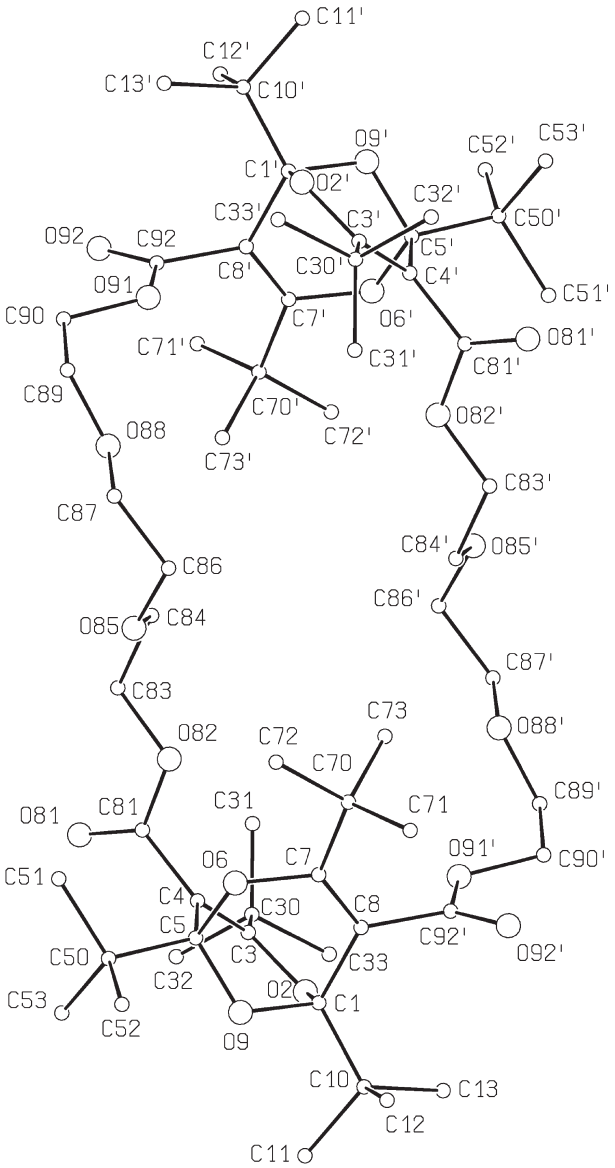
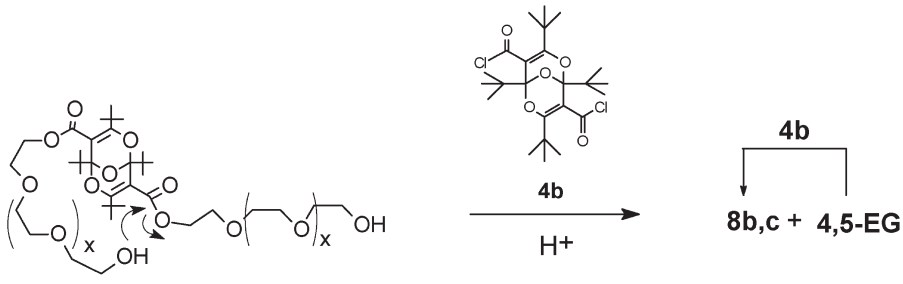


FIGURE 4 ORTEP [30] plot of 1*R*,5*R*,1*S*,5*S*-**12** showing the atomic numbering scheme. Only the more prominently occupied *tert*-butyl groups attached to C3 and C7 with site occupation factors of 0.842(7) and 0.765(8) for the atoms C30–33 and C70–C73, respectively, are plotted. The atoms are drawn with arbitrary radii; the hydrogen atoms are omitted.

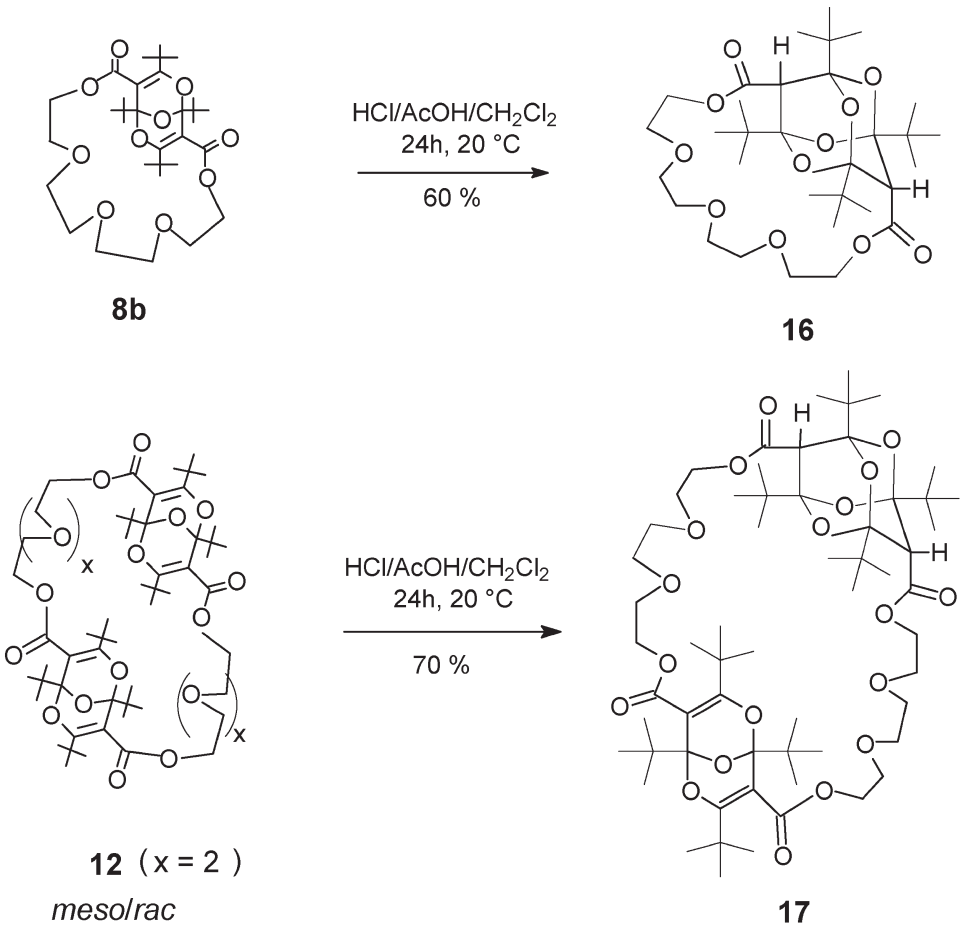
When **12** was treated with AcOH/HCl under various reaction conditions (change of reaction time or concentration of reactants, or use of gaseous HCl) the only product isolated was the macrocycle **17** (70% yield) in which only *one* bisdioxine unit is converted into the tetraoxaadamantyl moiety. The size of the new ring system was confirmed by mass spectrometry ($m/z = 1123.5$). The structure was derived from elemental analysis and ^{1}H- and ^{13}C NMR spectra: two signals with slightly different intensities for the C–Hs at C-9 and C-10 of the adamantyl subunit at 2.94 and 3.04 ppm, indicate the presence of rotamers as previously observed for the diethyl tetraoxaadamantane dicarboxylate [5]. Characteristic ^{13}C NMR data are assigned for the adamantyl (172.0, C = O; 101.1, 100.1, quarternary sp^3-ring carbons; 47.5, C-9/C-10), and the bridged bisdioxine subunit (169.5, C = O; 163.2, C-3/C-7; 102.4, C-4/C-8; 98.2, C-1/C-5).

Metal Ion Binding Properties—Preliminary Results

The macrocycles **8c**, **11**–**14** were selected and checked for their binding properties towards hard and soft metal cations employing liquid–liquid extraction experiments [42]. Aqueous solutions of the metal salts (1.10^{-4} M) and picric acid (5.10^{-3} M) were extracted with chloroform solutions of the corresponding ligands (1.10^{-3} M). The determination of the concentration of the metal ions in both layers was carried out by radiotracer technique [43]. In order to obtain an overview on the extraction properties of the macrocyclic systems **8c**–**14**, Na^+, Cs^+, Ca^{++}, Sr^{++}, Ba^{++}, Ag^+, Zn^{++} and Hg^{++} were employed as metal ions. Compared to the extraction power of simple crown ethers [42] the extractabilities were found rather low in all examples investigated. Compound **12** shows the highest extractability of 0.1–0.2% for Sr^{++} and Ba^{++}, whereas **13** and **14** extract 1% of Hg^{++} from chloride solution. These results obviously are due to the introduction of the sterically crowded bisdioxine spacer as well as



SCHEME 5



SCHEME 6

a rather high flexibility of the whole macrocycle, which leads to an unfavorable arrangement of the oxygen donor atoms in the molecules. Currently our investigations on the one hand focus on application of organic guest molecules instead of metal ions utilizing the higher lipophilicity coming from the *t*-butyl groups, and on the other hand, to make the new macrocycles more rigid by introducing, e.g. aromatic ring systems into the polyether chain.

CONCLUSION

Bisacid chloride **4b** exhibits axial chirality and is readily inserted as an uncommon sub-unit into several macrocyclic ring systems of the hemi-crown ether type by cyclocondensation reactions with various ethylene glycols. In this way 1:1 (**8**, **9**), 2:2 (**11**–**14**) macrocycles and a large 3:3 ring (**15**) are accessible in acceptable yields, considering the extensive use of dry flash chromatography as well as preparative TLC required for separation and purification of the products. Macrocycles **11**–**14** are generated as diastereomeric mixtures, evidenced by HPLC measurements on chiral stationary phases. In case of **11** and **12** chromatographic separation and enrichment of one diastereomer could be achieved occasionally, moreover, **11** also turned out to exhibit a slight overall predominance of the *rac*-form. Remarkably, the bridged bisdioxine units can in principle be converted "in chain" into the tetraoxaadamantane skeletons by acid hydration without any hydrolytic cleavage of the ester functionalities, as demonstrated by conversion of the 1:1 macrocycle **8b** into **16** and of the 2:2 macrocycle **12** into **17**. Selected examples of those new macrocyclic systems indicate rather low extraction rates with several metal ions.

EXPERIMENTAL SECTION

General

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 360 and 200 MHz; ^{13}C NMR spectra at 90 and 50 MHz, respectively, in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in ppm (δ) relative to TMS. IR spectra were determined as potassium bromide pellets. Mass spectral data were obtained either in the FAB mode employing nitrobenzylic alcohol or glycerine matrices, or in

the CI mode (for **9** and **17**). Dry flash column chromatography was performed using silica gel (5–40 μm, Merck 60H). Analytical thin-layer chromatography was done on precoated silicagel aluminum plates containing a fluorescent indicator (GF-254 Merck) or by spraying with vanilline/sulfurous acid and warming up.

Materials

Dipivaloylmethane and oxalyl dichloride were purchased from Aldrich Chemicals and used without further purification, bisacid chloride **4b** was prepared according to the literature [4]. 2,3,4,5,6-Ethylene glycols are commercially available and were dried over molecular sieves (4 Å). The stationary phase (silica gel 60H, Merck) and all solvents used as eluants in dry flash chromatography (DFC) were purchased in high p.a. quality (evaporation residue $<0.0003\%$).

Reaction of Bisacid Chloride 4b with Ethylene Glycols. General Procedures

(A) Targets Bisesters 6 and 7

Bisacid chloride **4b** (480 mg, 1.01 mmol), dissolved in dichloromethane (10 ml), was added dropwise to a solution of the corresponding ethylene glycol (4 mmol) in dichloromethane (10 ml) during 30 min. The reaction mixture was stirred at rt for 12–48 h, then evaporated, and the oily residue was dissolved in a minimum amount of the solvent mixtures used as eluant during the subsequent separation and purification by dry flash chromatography. The combined fractions of the specific bisesters were evaporated and remaining solvents removed by lyophilisation on the vacuum line (10^{-2}–10^{-3} mbar). In subsequent cyclocondensation reactions of **4b** to produce the corresponding macrocycles **11**–**14**, the bisesters **6** and **7** have to be completely free of any unreacted ethylene glycol. This is controlled by TLC with the aid of the spray reagent vanilline/sulfurous acid/heat. In case ethylene glycols are still present, the DFC procedure has to be repeated.

4,8-Bis(7-hydroxy-1-oxo-2,5-dioxaheptyl)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (6). Forty seven percent; oil; eluant petroleum ether (40–60°C)/ethyl acetate 4:1; $R_f = 0.30$; IR (KBr) 3400 (b, OH), 3020–2800 (CH), 1720 (C = O), 1620 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 18H) 1.22 (s, 18H), 2.32 (bs, 2H), 3.51–3.78 (m, 12H), 4.00–4.13 (m, 2H), 4.31–4.45 (m, 2H). Anal. Calcd for $C_{32}H_{54}O_{11}$: C, 62.50; H, 8.86. Found: C, 62.60; H, 8.97.

4,8-Bis(10-hydroxy-1-oxo-2,5,8-trioxadecanyl)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]-nona-3,7-diene (7a). Thirty six percent; oil; eluant petroleum ether (40–60°C)/ethyl acetate/methanol = 2:2:0.2; $R_f = 0.21$; IR(KBr) 3450 (b,OH), 3040–2780 (CH), 1720 (C = O), 1620 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 18H), 1.20 (s, 18H), 2.60 (s, 2H), 3.52–3.78 (m, 20H), 4.1(m, 2H),4.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.7, 28.7 ($C(CH_3)_3$), 37.5, 39.5 ($C(CH_3)_3$), 61.7, 63.7, 68.6, 70.3, 70.5, 72.6 (CH_2), 98.1 (C-1/C-5), 102.4 (C-4/C-8), 162.9 (C-3/C-7), 169.2 (C = O); MS (FAB, glyc) m/z 703.5 ($M + H^+$). Anal. Calcd for $C_{36}H_{62}O_{13}\cdot H_2O$: C, 59.97; H, 8.95. Found: C, 59.59; H, 8.81.

4,8-Bis(13-hydroxy-1-oxo-2,5,8,11-tetraoxatridecanyl)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (7b). Thirty five percent; oil; eluant ethyl acetate/hexane/methanol = 9:2:1; $R_f = 0.33$; IR(KBr) 3480-3400 (OH), 2980–2780 (CH), 1718 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18H), 1.25 (s, 18H), 2.60 (s, 2H), 3.54–3.72 (m, 28H), 4.13 (m, 2H), 4.28 (m, 2H). Anal. Calcd for $C_{40}H_{70}O_{15}\cdot H_2O$: C, 59.37; H, 8.97. Found: C, 59.05; H, 8.93.

4,8-Bis(16-hydroxy-1-oxo-2,5,8,11,13-pentaoxahexadecanyl)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (7c). Forty percent; oil; eluant ethyl acetate/hexane/methanol = 9.5 : 2 : 1; $R_f = 0.23$; IR (KBr) 3420–3320 (OH), 2920–2860 (CH), 1720 (C = O), 1620 (C = C); ^1H NMR ($CDCl_3$) δ 1.02 (s, 18H), 1.98 (s, 18H), 2.75 (s, 2H), 3.55–3.69 (m, 36H), 4.09 (m, 2H), 4.20 (m, 2H). Anal. Calcd for $C_{44}H_{78}O_{17}\cdot H_2O$: C, 58.89; H, 8.99. Found: C, 58.46; H, 8.77.

(B) Synthesis of Macrocycles 8 and 9

A solution of the corresponding ethylene glycol (0.32 mmol) in dichloromethane (5 ml) was added slowly dropwise to a stirred solution of freshly prepared **4b** (0.3 mmol), dissolved in dichloromethane (5 ml). The reaction mixture remained for 12–48 h at rt. After evaporation the oily residue was dissolved in a minimum amount of the solvents applied as eluants during DFC procedure. The combined fractions were evaporated and the solid residue was crystallized from proper solvents.

4,8-(1,12-Dioxo-2,5,8,11-tetraoxadodecano)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]-nona-3,7-diene (8a). Twenty eight percent; mp 230–232°C (ethyl acetate/hexane); eluant petroleum ether/ethyl acetate = 4:1, $R_f = 0.36$; IR(KBr) 3020–2840 (CH), 1730, 1720 (C = O), 1620 (C = C); ^1H NMR ($CDCl_3$) δ 1.10 (s, 18H), 1.22 (s, 18H), 3.42–3.67 (m, 8H), 3.78–3.92 (m, 2H), 4.48–4.62 (m, 2H); MS (FAB, NOBA) m/z 553 ($M + H^+$). Anal. Calcd for $C_{30}H_{48}O_9$: C, 65.18; H, 8.76. Found: C, 65.52; H, 9.00.

4,8-(1,15-Dioxo-2,5,8,11,14-pentaoxapentadecano)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo [3.3.1]nona-3,7-diene (8b). Sixty two percent; mp 195–197°C (acetonitrile); eluant petroleum ether/ethyl acetate = 5:1, $R_f = 0.20$; IR (KBr) 3040–2840 (CH), 1720 (C = O), 1625 (C = C) cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.06 (s,18H), 1.25 (s, 18H), 3.50–3.72 (m, 12H), 3.78–3.90 (m, 2H), 4.50–4.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.7 ($C(CH_3)_3$), 37.4, 39.4 ($C(CH_3)_3$), 64.1, 68.4, 70.5, 71.1 (CH_2), 98.2 (C-1, C-5), 102.3 (C-4, C-8), 163.3 (C-3, C-7), 170.0 (C = O); MS (EI) m/z (rel intensity) 596 (M^+, 20), 511 (30), 427 (100). Anal. Calcd for $C_{32}H_{52}O_{10}$: C, 64.39; H, 8.79. Found: C, 64.60; H, 8.89.

4,8-(1,18-Dioxo-2,5,8,11,14,17-hexaoxaoctadecano)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (8c). Thirty two percent; mp 135°C (ethyl acetate/hexane); eluant hexane/ethyl acetate = 6:3.5, $R_f = 0.33$; IR(KBr) 2960–2860 (CH), 1715 (C = O), 1615 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.21 (s, 18H), 3.5–3.7 (m, 16H), 3.85 (m, 2H), 4.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.8 ($C(CH_3)_3$), 37.5, 39.5 ($C(CH_3)_3$), 64.5, 68.7, 71.7, 77.1 (CH_2), 98.0 (C-1, C-5), 102.5 (C-4, C-8), 163.0 (C-3, C-7), 169.9 (C = O). MS (FAB, NOBA) m/z 641.2 ($M + H^+$). Anal. Calcd for $C_{34}H_{56}O_{11}$: C, 63.71; H, 8.81. Found: C, 63.95; H, 8.74.

4,8-(1,21-Dioxo-2,5,8,11,14,17,20-heptaoxauncosano)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (9). Sixty two percent; mp 40°C; eluant hexane/ethyl acetate = 3:2, $R_f = 0.15$; IR(KBr) 2960–2840 (CH), 1720 (C = O), 1620 (C = C); ^1H NMR ($CDCl_3$) δ 1.02 (s, 18H), 1.21 (s, 18H), 3.58–3.72 (m, 20H), 3.9–4.10 (m, 2H), 4.32–4.49 (m, 2H); MS (CI) 685.5 ($M + H^+$) Anal. Calcd for $C_{36}H_{60}O_{12}$: C, 63.12; H, 8.84. Found: C, 63.12; H, 8.99.

1,12-Bis[8-(10-hydroxy-1-oxo-2,5,8-trioxadecyl)-1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dien-4-yl]-1,12-dioxo-2,5,8,11-tetraoxadodecane (10). During work-up of the crude reaction mixture obtained from reacting **4b** with triethylene glycol following protocol A, **10** was isolated besides **7a** by DFC applying the same eluants (ethyl acetate/petroleum ether (40–60°C)/methanol = 2 : 2 : 0.1) but having a different R_f-value (0.12). 21%; oil; IR(KBr): 3450 (OH), 3040–2700 (CH), 1720 (C = O), 1620 (C = C); ^1H NMR ($CDCl_3$) δ 1.05 (s, 36H), 1.21 (s, 36H), 1.60 (b, 2H), 3.55–3.78 (m, 28H), 4.14–4.38 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 24.7, 28.7 ($C(CH_3)_3$), 37.6, 39.5 ($C(CH_3)_3$), 61.6, 63.72, 63.75, 68.6, 70.4, 70.6, 72.6 (CH_2), 98.1 (C-1/C-5), 102.5 (C-4, C-8), 162.9 (C-3, C-7), 169.2 (C = O). MS (FAB, glyc) m/z 1257.2 ($M + H^+$). Anal. Calcd for $C_{66}H_{110}O_{22}$: C, 63.13; H, 8.83. Found: C, 62.64; H, 8.83.

Bis-(1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,9-dioxo-2,5,8-trioxanonane) (11, *mixture of diastereomers*). A solution of **6** (0.5 mmol) in dichloromethane (5 ml) was added drop by drop during 2 h to bisacid chloride **4b** (0.5 mmol), dissolved in dichloromethane (5 ml), with stirring at rt. After 12 h, the reaction mixture was evaporated to dryness and the colorless residue was purified first by DFC to remove several impurities. Then the crude main product again was separated with the aid of preparative TLC into two fractions (major fraction: $R_f = 0.32$, yield 35%; minor fraction: $R_f = 0.23$; 14% yield). The eluant in both cases is hexane/ethyl acetate = 9.5:0.5. *Major fraction*: mp 203°C; IR (KBr) 3020–2840 (CH), 1720 (C = O), 1615 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0, 1.02 (diastereomers, 36 H), 1.2, 1.22 (diastereomers, 36H), 3.63 (m, 8H), 4.0 (m, 4H), 4.25 (m, 4H); ^{13}C NMR ($CDCl_3$, signal doubling is due to diastereomerism) δ 24.7, 28.7 ($C(CH_3)_3$), 37.5, 39.5 ($C(CH_3)_3$), 63.5, 68.2/68.6 (CH_2), 98.2 (C-1/C-5); 102.2/102.3 (C-4/C-8), 163.7/163.9 (C-3/C-7), 169.5/169.7 (C = O); MS (FAB, NOBA) $m/z = 1017.6$ ($M + H^+$). Anal. Calcd for $C_{56}H_{88}O_{16}$: C, 66.10; H, 8.72. Found: C, 66.17; H, 8.66. *Minor fraction*: mp 197°C; IR (KBr), MS and NMR spectra are virtually identical with those of the major fraction. Anal. Calcd for $C_{56}H_{88}O_{16}$: C, 66.10; H, 8.72. Found: C, 65.93; H, 8.51. From the major fraction crystals were grown suitable for X-ray analysis.

Bis-(1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,12-dioxo-2,5,8,11-tetraoxadodecane) (12, *mixture of diastereomers*). Bisester **7a** (0.67 mmol), dissolved in dichloromethane (6.5 ml), was added slowly dropwise to a solution of **4b** (0.73 mmol) in dichloromethane (6.5 ml) during 2 h at rt with stirring. After 48 h the solvent was removed *in vacuo* and the crude residue triturated with ethylacetate to afford a colorless solid (**12**, 0.125 g, 20%). The ethyl acetate filtrate was evaporated and the solid obtained separated by DFC (eluant hexane/ethylacetate = 8:1) to afford a product which by preparative TLC finally was again separated into two fractions. The main compound ($R_f = 0.44$), isolated from the *major fraction*, was identical to the product obtained directly from the reaction mixture (see above) thus enhancing its overall yield to 25% and, as made evident from HPLC (see "Results and Discussion" section), was a nearly 1:1 mixture of diastereomers. From that fraction crystals suitable for X-ray analysis were grown. The compound of the *minor fraction* ($R_f = 0.56$, yield 4%) was an enriched *rac*-**12** (see HPLC). *Major fraction*: mp 205–207°C; IR(KBr) 3020–2840 (CH), 1720 (C = O), 1620 (C = C); ^1H NMR ($CDCl_3$) δ 1.02 (s, 36H), 1.21 (s, 36H), 3.47–3.58 (m, 8H), 3.62–3.72 (m, 8H), 3.92–4.06 (m, 4H), 4.30–4.48 (m, 4H); ^{13}C NMR ($CDCl)_3$ δ 24.7, 28.8 ($C(CH_3)_3$), 37.5, 39.5 ($C(CH_3)_3$), 63.8, 68.8, 70.4 (CH_2), 98.2 (C-1/C-5), 102.4 (C-4/C-8), 163.2 (C-3/C-7), 169.5 (C = O); MS (FAB, gly) m/z 1105.6 ($M + H^+$). Anal. Calcd for $C_{60}H_{96}O_{18}$: C, 65.18; H, 8.76. Found: C, 65.68; H, 9.07. *Minor fraction*: mp 197–199°C; IR (KBr) identical with the *major fraction*; ^1H and ^{13}C NMR spectra are also identical within the average accuracy of chemical shift values in general; MS (FAB, gly) m/z 1105.6 ($M + H^+$).

Bis-(1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-dien-4,8-diyl)-di(1,15-dioxo-2,5,8,11,14-pentaoxapentadecane) (13, *mixture of diastereomers*). The compound **7b** (0.35 mmol), dissolved in dichloromethane (3.5 ml) were added dropwise during 2 h to a solution of **4b** (0.35 mmol) in dichloromethane (3.5 ml) with stirring at rt. After 24 h the solvent was evaporated and the crude residue was separated chromatographically by DFC (eluant hexane/ethyl acetate = 8:2). The chromatographic procedure had to be repeated twice to get pure fractions of **13** as well as the 1:1-cyclus **8b**. 2:2 macrocycle **13**: $R_f = 0.19$, yield 32%; mp. 146°C; IR (KBr) 3020–2880 (CH), 1715 (C = O), 1620 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 36H), 1.20 (s, 36H), 3.55-3.70 (m, 24H), 4.05 (m, 4H), 4.30 (M, 4H); MS (FAB, NOBA) m/z 1194.0 ($M + H^+$). Anal. Calcd for $C_{64}H_{104}O_{20}$: C, 64.39; H, 8.76. Found: C, 64,32; H, 8.62. Macrocycle **8b** (see above) was isolated in 38% yield ($R_f = 0.31$).

Bis-(1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-dien-4,8-diyl)-di(1,18-dioxo-2,5,8,11,17-hexaoxahexadecane) (14, *mixture of diastereomers*). Bisester **7c** (0.70 mmol), dissolved in dichloromethane (7 ml) was added drop by drop during 2 h to a stirred solution of **4b** (1.0 mmol) in dichloromethane (7 ml) with additional stirring at rt for 48 h. Then the reaction mixture was evaporated and the crude residue subjected to DFC (eluant hexane/ethyl acetate = 6:3.5). Macrocycle **14**: $R_{f=}$0.23; yield 18%; mp 104°C; IR (KBr) 3020–2900 (CH), 1715 (C = O), 1620 (C = C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 36H), 1.21 (s, 36H); 3.55–3.70 (m, 32H), 4.05 (m, 4H), 4.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8 ($C(CH_3)_3$), 37.5, 39.5 ($C(CH_3)_3$), 63.8, 68.7, 70.6 (CH_2), 98.2 (C-1/C-5), 102.5 (C-4/C-8), 163.0 (C-3/C-7); 169.3 (C = O). MS (FAB, NOBA) m/z 1281.5 ($M + H^+$), 1303.5 ($M + Na^+$). Anal. Calcd for $C_{68}H_{112}O_{22}$: C, 63.71; H, 8.81. Found: C, 63.31; H, 8.81. Macrocycle **8c:** yield 32% ($R_f = 0.35$).

Tris-(1,3,5,7-tetra-*tert*-butyl-2,6,8-trioxabicyclo[3.3.1]nona-3,7-dien-4,8-diyl)-tri(1,12-dioxo-2,5,8,11-tetraoxadodecane) (15). 2:3 educt **10** (0.20 mmol), dissolved in dichloromethane (1.5 ml) was added slowly to a solution of bisacid chloride **4b** (0.25 mmol) in dichloromethane (1.5 ml) during 3 h with stirring. After 48 h the solvent was removed and the crude residue (five compounds on TLC) was separated by DFC (silicagel 60H, 40 g, eluant hexane/ethyl acetate = 8:2); $R_f = 0.30$, yield 13%; mp 130–131°C; ^1H NMR δ 1.06 (s, 54H), 1.23 (sb, 54H), 2.02 (s, 3H), 3.55–3.75 (m, 24H), 4.12 (m, 8H), 4.28 (m, 6H); MS(FAB, NOBA) m/z 1657.9 ($M + H^+$). Anal. Calcd for $C_{90}H_{144}O_{27}\cdot C_4H_8O_2$ (ethyl acetate): C, 64.64; H, 8.78. Found: C, 63.99; H, 8.84.

9,10-(1,15-Dioxo-2,5,8,11,14-pentaoxapentadecano)-1,3,5,7-tetra-*tert*-butyl-2,4,6,8-tetraoxaadamantane (16). Aequous hydrochloric acid (150 mg, 37%) was added to a solution of macrocycle **8b** (150 mg, 0.251 mmol) in a mixture of dichloromethane/acetic acid (1.5 ml/1.5 ml) at rt. In addition, a gentle stream of gaseous hydrogen chloride was run into the reaction mixture for 30 s. After stirring for 1 d, the dichloromethane was allowed to escape at rt thus releasing a colorless solid, which could be recrystallized from acetonitrile to give pure **16** (95 mg, 60%). Mp 251–253°C; IR(KBr) 3040–2820 (CH), 1715 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 18H), 2.96 (s, 2H), 3.38–3.68 (m, 12H), 3.68–3.82 (m, 2H), 4.52–4.70 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.0, 25.47 ($C(CH_3)_3$, 40.37, 40.77 ($C(CH_3)_3$), 46.60 (d, $J_{CH} = 110$ Hz, C-9/C-10), 63.07, 66.90, 70.72, 71.64 (CH_2), 99.53, 101.60 (C-1, C-3, C-5, C-7), 171.93 (C = O). Anal. Calcd for $C_{32}H_{54}O_{11}$: C, 62.51; H, 8.85. Found: C, 62.81; H, 8.87.

1,12,1′,12′-(1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-(1,3,5,7-tetra-*tert*-butyl-2,4,6,8-tetraoxaadamantane-9,10-diyl)-di(1,12-dioxo-2,5,8,11-tetraoxadodecane) (17). *Rac/meso*-**12** (80 mg, 0.072 mmol) were dissolved in a mixture of dichloromethane (1.0 ml) and acetic acid (1.0 ml). Aequous HCl (0.1 ml, 37%) was added with stirring and the reaction mixture remained standing for 2 d. Then the dichloromethane was allowed to escape at rt and **17** started to precipitate. After 3d the solid residue was treated with acetonitrile and isolated by suction to afford the pure product (55 mg, 71%); mp 198–200°C; ^1H NMR ($CDCl_3$) δ 0.95–1.25 (m, 72H), 2.94 (s, 1H), 3.04 (s, 1H), 3.46–3.68 (m, 16H), 3.95 (m, 4H), 4.40 (m, 4H); ^{13}C NMR ($CDCl_3$)$_3$ δ 24.6, 24.8, 25.2, 28.7 ($C(CH_3)_3$), 37.5, 39.5, 40.4, 43.8 ($C(CH_3)_3$), 47.5 (CH), 63.8, 68.1, 68.8, 70.38 (CH_2), 98.19 (C-1/C-5), 102.45 (C-4/C-8), 100.1, 101.1 (C-1/C-3/C-5/C-7, adamantyl), 163.2 (C-3/C-7), 168.4, 169.48, 171.85 (C = O); MS (CI) m/z (rel. intensities) 1123.5 ($M + H^+$, 10), 1105.5 (100). Anal. Calcd for $C_{60}H_{98}O_{19}$: C, 64.13; H, 8.80. Found: C, 64.21, H, 8.88.

Template Experiments

(a) Reaction of bisester **7b** with bisacid chloride **4b** in presence of potassium isothiocyanate: A solution of **7b** (155 mg, 0.196 mmol) and anhydrous KSCN (40 mg, 0.41 mmol) in acetonitrile (6 ml) was added during 1 h to bisacid chloride **4b** (100 mg, 0.21 mmol), dissolved in acetonitrile (3 ml) at 60°C. The suspension formed was then stirred at rt for 48 h, then the potassium salt was filtered off, the filtrate evaporated and the oily residue worked up by DFC (eluant hexane/ethyl acetate 80:20, silicagel Merck 60H (40 g)

The main fraction isolated afforded **8b** (70 mg, 56%).

(b) When this experiment was repeated applying sodium isothiocyanate again the 1:1 cyclus **8b** was formed preferably (33%, compared with 6% only of **13**).

(c) Reaction of bisester **7c** with bisacid chloride **4b** in presence of potassium isothiocyanate: A solution of bisester **7c** (360 mg, 0.41 mmol) and anhydrous KSCN (40 mg, 0.41 mmol) in acetonitrile (6 ml) was added dropwise during 1 h to bisacid chloride **4b** (220 mg, 0.463 mmol), dissolved in acetonitrile (6 ml) at 60°C. Then the reaction mixture remained standing at rt for 48 h and the work-up followed exactly the procedure given under (a) to finally give **8c** (80 mg, 16%) besides 2:2 cyclus **14** (20 mg, 4%).

HPLC Measurements

Compounds **11**–**14** have been dissolved in the proper mixture of solvents also applied as the corresponding mobile phase (hexane/2-propanol 98:2; 99.5:0.5; 99.75:0.25) in concentrations of 1.3–1.5 10^{-3} mol/l (injected volumes 10–25 µl); UV-detection at 254 and/or 215 nm. Columns: CSP III, [37–40] Chiralpak AD (Daicel Comp.), Chiralcel ODH (Daicel Comp.), *S*,*S*-Ulmo (Regis Technologies).

11, *Major fraction*: On Chiralpak AD splitting into three signals (*meso*-form and 2 enantiomers, retention time: 6.2, 6.9, 7.01 min), solvent hexane/2-propanol 98:2.

Minor fraction: On column CSP III separation into two signals (= two diastereomers), solvent hexane/2-propanol 98:2; $\alpha = 1.66$, on column Chiralcel ODH separation into 3 signals (2 of them broad), solvent hexane/isopropanol 99.5:0.5, α 1.06, 1.90. When the separated compounds of CSP III were each injected again (solvent hexane/2-propanol 99.5:0.5) signal 1 did not split any more (Chiralcel ODH, *S*,*S*-Ulmo), while signal 2 remained unchanged on *SS*-Ulmo, but splitted into two signals on Chiralcel ODH.

12, *Major fraction*: On CSP III one signal (retention time 4.39 min, solvent hexane/2-propanol 98:2), on Chiralcel ODH three signals (retention time: 18.56, 21.12, 27.32 min, solvent hexane/2-propanol 99.75:0.25).

Minor fraction: On CSP III again one signal (retention time 4.7 min, solvent hexane/2-propanol 98:2), on Chiralcel ODH three signals (retention time 9.17, 10.07 and 11.64 min, solvent hexane/2-propanol 99.5:0.5); ratio calculated from peak integration 4 (*racem*): 1 (*meso*).

13: On CSP III one signal (retention time 7.9 min, solvent hexane/2-propanol 98:2), on Chiralcel ODH splitting into two signals with shoulders (retention time 3.73, 4.93 min, solvent: hexane/2-propanol 98:2).

14: On CSP III one signal (retention time 16.2 min, solvent hexane/2-propanol 98:2), on Chiralcel ODH three peaks (broad, retention time 9.48, 10.05, 11.45 min, solvent hexane/2-propanol 98:2).

X-ray Structures[¶]

X-ray Diffraction Data of 8c

All the measurements were performed using graphite-monochromatized Mo-Kα radiation at 95 K: $C_{34}H_{56}O_{11}$, M_r 640.8, orthorhombic, space group Pbca, $a = 10.163(3)$ Å, $b = 18.999(4)$ Å, $c = 36.187(10)$ Å, $V = 6987(3)$ Å^3, $Z = 8$, $d_{calc} = 1.218$ g cm^{-3} $\mu = 0.090$ mm^{-1}. A total of 6974 reflections were collected ($2\Theta_{max} = 50°$), from which 6153 were unique ($R_{int} = 0.0260$), with 4365 having $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) [44] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [45]. One oxygen atom of the pentaethylene glycol chain is disordered over two sites with site occupation factors of 0.75(3) and 0.25(3) for O94 and O941, respectively. The non-hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms of the *t*-Bu groups were refined with common isotropic displacement parameters for the H-atoms of the same *t*-Bu group and idealized geometry with C–H distances of 0.98 Å, the H-atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H-atoms of the same C_2H_4 group and idealized geometry with C–H distances of 0.99 Å. For 425 parameters final *R* indices of $R = 0.0553$ and $wR^2 = 0.1300$ (GOF = 1.027) were obtained. The largest peak in a difference Fourier map was 0.243e Å^{-3}.

X-ray Diffraction Data of 11

All the measurements were performed using graphite-monochromatized Mo-Kα radiation at 95 K: $C_{56}H_{88}O_{16}$, M_r 1017.3, triclinic, space group $P\bar{1}$, $a = 10.472(5)$ Å, $b = 16.390(5)$ Å, $c = 17.211(5)$ Å, $\alpha = 98.69(2)°$, $\beta = 93.04(2)°$, $\gamma = 98.52(2)°$, $V = 2879.3(18)$ Å^3, $Z = 2$, $d_{calc} = 1.173$ g cm^{-3} $\mu = 0.085$ mm^{-1}. A total of 11,171 reflections were collected ($2\Theta_{max} = 50°$), from which 10,075 were

[¶]Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (International) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk] on quoting the deposition numbers CCDC-142882 (**8c**), 142883 (**11**) and 142884 (**12**).

unique ($R_{int} = 0.0219$), with 8146 having $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) [44] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [45]. In the asymmetric unit an (*R*,*R*)-molecule with atomic site occupation factors of 0.793(3) is superimposed by an (*R*,*S*)-molecule with site occupation factors of 0.207(3) whereby one of the two 1,3,5,7-tetra-*tert*-butyl-2,6,9-trioxabicyclo(3.3.1)nona-3,7-diene groups (atoms C11–C173) and the two diethylene glycol chains of the molecule were ordered. All equivalent bonds in the disordered part of the molecule were restrained (202 restraints) to have the same length (atoms C31–O348 compared to atoms C21–O248). The non-hydrogen atoms of the less occupied disordered group [atoms C31–O348 of the (*R*,*S*)-molecule] were refined with isotropic displacement parameters, all the other non-hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms of the *t*-Bu groups were refined with common isotropic displacement parameters for the H-atoms of the same *t*-Bu group and idealized geometry with C–H distances of 0.98 Å, the H-atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H-atoms of the same C_2H_4 group and idealized geometry with C–H distances of 0.99 Å. For 817 parameters final *R* indices of $R = 0.0869$ and $wR^2 = 0.230$ (GOF = 1.068) were obtained. The largest peak in a difference Fourier map was 0.700e Å^{-3}. The estimated error in the bond lengths ranges from 0.003 to 0.006 Å (mean value 0.0047 Å).

X-ray Diffraction Data of 12

All the measurements were performed using graphite-monochromatized Cu-Kα radiation at 293 K: $C_{60}H_{96}O_{18}$, M_r 1105.4, monoclinic, space group $P2_1/c$, $a = 9.927(2)$, $b = 18.166(3)$, $c = 17.820(3)$ Å, $\beta = 96.590(10)°$, $V = 3192.3(10)$ Å^3, $Z = 2$, $d_{calc} = 1.150$ g cm^{-3} $\mu = 0.685$ mm^{-1}. A total of 4555 reflections were collected ($2\Theta_{max} = 103°$), from which 3487 were unique ($R_{int} = 0.0552$), with 2696 having $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) [44] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [45]. Half a molecule is found per asymmetric unit. The non-hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms of the *t*-Bu groups were refined with common isotropic displacement parameters for the H-atoms of the same *t*-Bu group and idealized geometry with C–H distances of 0.96 Å, the H-atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H-atoms of the same C_2H_4 group and idealized geometry with C–H distances of 0.97 Å. For 410 parameters final *R* indices of $R = 0.0597$ and $wR^2 = 0.1716$ (GOF = 1.050) were obtained. The largest peak in a difference Fourier map was 0.264e Å^{-3}.

Extraction Studies

Extraction was performed at 24°C in micro centrifuge tubes (2 ml) by mechanically shaking of 0.5 ml of each of the organic and aqueous phases for 30 min, which was sufficient to reach the extraction equilibrium. All samples then were centrifuged and the concentration of metal ions in both layers was determined radiometrically [43] by measuring the gamma-radiation of Na-22, Cs-137, Sr-85, Ba-133, Ag-110m, Zn-65 and Hg-203 in a NaJ(Tl) scintillation counter (Cobra II, Canberra-Packard) and the beta-radiation of Ca-45 in a liquid scintillation counter (Tricarb 2500, Canberra-Packard).

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