Macrotricyclic Steroid Receptors by Pd^0-Catalyzed Cross-Coupling Reactions: Dissolution of Cholesterol in Aqueous Solution and Investigations of the Principles Governing Selective Molecular Recognition of Steroidal Substrates

by **Thomas Marti, Blake R. Peterson, Andreas Fürer, Tiziana Mordasini-Denti, Jürgen Zarske, Bernhard Jaun,** and **François Diederich***

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

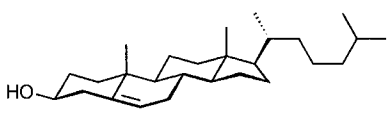
and **Volker Gramlich**

Laboratorium für Kristallographie, Eidgenössische Technische Hochschule, ETH-Zentrum, Sonneggstrasse 5, CH-8092 Zürich

Three double-decker cyclophane receptors, (±)-**2**, (±)-**3**, and (±)-**4** with 11–13-Å deep hydrophobic cavities were prepared and their steroid-binding properties investigated in aqueous and methanolic solutions. Pd^0-Catalyzed cross-coupling reactions were key steps in the construction of these novel macrotricyclic structures. In the synthesis of D_2-symmetrical (±)-**2**, the double-decker precursor (±)-**7** was obtained in 14% yield by fourfold *Stille* coupling of equimolar amounts of bis(tributylstannyl)acetylene with dibromocyclophane **5** (*Scheme 1*). For the preparation of the macrotricyclic precursor (±)-**15** of D_2-symmetrical (±)-**3**, diiodocylophane **12** was dialkynylated with $Me_3SiC{\equiv}CH$ to give **13** using the *Sonogashira* cross-coupling reaction; subsequent alkyne deprotection yielded the diethynylated cyclophane **14**, which was transformed in 42% yield into (±)-**15** by *Glaser-Hay* macrocyclization (*Scheme 2*). The synthesis of the C_2-symmetrical conical receptor (±)-**4** was achieved *via* the macrotricyclic precursor (±)-**25**, which was prepared in 20% yield by the *Hiyama* cross-coupling reaction between the diiodo[6.1.6.1]paracyclophane **19** and the larger, dialkynylated cyclophane **17** (*Scheme 4*). Solid cholesterol was efficiently dissolved in water through complexation by (±)-**2** and (±)-**3**, and the association constants of the formed 1:1 inclusion complexes were determined by solid-liquid extraction as $K_a = 1.1 \times 10^6$ and 1.5×10^5 $l\,mol^{-1}$, respectively (295 K) (*Table 1*). The steroid-binding properties of the three receptors were analyzed in detail by ^{1}H-NMR binding titrations in CD_3OD. Observed steroid-binding selectivities between the two structurally closely related cylindrical receptors (±)-**2** and (±)-**3** (*Table 2*) were explained by differences in cavity width and depth, which were revealed by computer modeling (*Fig. 4*). Receptor (±)-**2**, with two ethynediyl tethers linking the two cyclophanes, possesses a shallower cavity and, therefore, is specific for flatter steroids with a C(5)=C(6) bond, such as cholesterol. In contrast, receptor (±)-**3**, constructed with longer buta-1,3-diynediyl linkers, has a deeper and wider hydrophobic cavity and prefers fully saturated steroids with an aliphatic side chain, such as 5α-cholestane (*Fig. 7*). In the 1:1 inclusion complexes formed by the conical receptor (±)-**4** (*Table 3*), testosterone or progesterone penetrate the binding site from the wider cavity side, and their flat *A* ring becomes incorporated into the narrower [6.1.6.1]paracyclophane moiety. In contrast, cholesterol penetrates (±)-**4** with its hydrophobic side chain from the wider rim of the binding side. This way, the side chain is included into the narrower cavity section shaped by the smaller [6.1.6.1]paracyclophane, while the *A* ring protrudes with the OH group at C(3) into the solvent on the wider cavity side (*Fig. 8*). The molecular-recognition studies with the synthetic receptors (±)-**2**, (±)-**3**, and (±)-**4** complement the X-ray investigations on biological steroid complexes in enhancing the understanding of the principles governing selective molecular recognition of steroids.

1. Introduction. – Steroids are ubiquitous in eukaryotic organisms and display a great variety of different functions [1]. The most frequent steroid is the highly lipophilic

cholesterol (**1**), which is metabolized to the bile acids in the liver and also serves as starting material for the synthesis of steroid hormones. It influences the fluidity of cell membranes [2] and is involved in the regulation of gene transcription [3]. Cholesterol is delivered either exogenously by way of food uptake or is synthesized endogenously in the endoplasmic reticulum [2][4]. Transport of the highly H_2O-insoluble cholesterol or its esters is mediated by supramolecular transport systems consisting of very-low-density (VLDL), low-density (LDL), and high-density (HDL) lipoproteins [4][5]. Cholesterol is a major component of atherosclerotic plaque deposits in atherosclerosis, one of the most frequent causes of death in industrialized countries where diet is rich in the steroid. The other members of the steroid family adopt equally important biological functions [6].



Cholesterol (**1**)

At the heart of these biological processes lies the molecular recognition of the various steroids. In the 1990ies, high-resolution structural information on complexes of steroids with proteins, enzymes, and antibodies became available; these X-ray crystal structural data have recently been reviewed [7][1]). The X-ray analyses revealed a prominent role of aromatic amino-acid side chains (tryptophan (Trp), tyrosine (Tyr), phenylalanine (Phe)) in shaping the steroid-binding pockets, in particular, in antibody complexes. Thus, the structure of the complex between progesterone and the monoclonal anti-progesterone antibody DB3 [8h,i] showed that the steroid lies between two cofacial tryptophan residues which form a 'steroid sandwich'. In the case of apo-3α-hydroxysteroid dehydrogenase [9], the 11-Å deep hydrophobic steroid-binding cavity is aligned by only one aliphatic (leucine (Leu)) and five aromatic amino-acid residues (2 Tyr, 2 Phe, 1 Trp), confirming once more the importance of aromatic residues in steroid complexation [8c,d].

Studies with small synthetic receptors should ideally complement the biological investigations with large protein receptors and supramolecular transporting assemblies in enhancing the insight into steroid-recognition processes, and such reasoning led to the construction of the macrotricyclic steroid receptors described in this paper[2]). A profound molecular-level understanding of the principles governing steroid complexation and transport could open new perspectives for biomedical research and potentially lead to new therapeutic approaches. Established therapies against high serum cholesterol levels are bile-acid sequestration by synthetic polymers such as cholestyramin and inhibition of the enzymes HMG-CoA reductase or squalene cyclase, which are required for endogenous cholesterol synthesis [4][5d]. New approaches based on detailed molecular-recognition insights could allow the development of selective artificial receptors and solubilizing agents for cholesterol or compounds altering cholesterol absorption [11] and transport.

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[1]) For X-ray structures which describe both the structures of the free and complexed steroid receptors, see [8].

[2]) For preliminary communications on parts of this work, see [10].

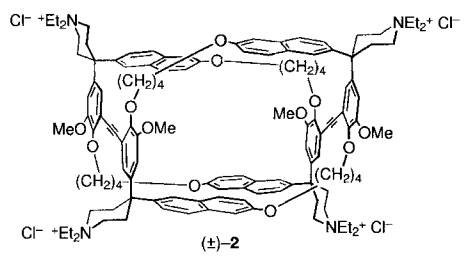
Investigations into selective binding mechanisms of steroid hormones could contribute to the rational development of methods to interfere with the signal induction and transcriptional machinery involving the steroid hormone receptor family [12]. Tightly binding receptors with slow exchange kinetics [13] could be used as hormone deposits and slow-release systems.

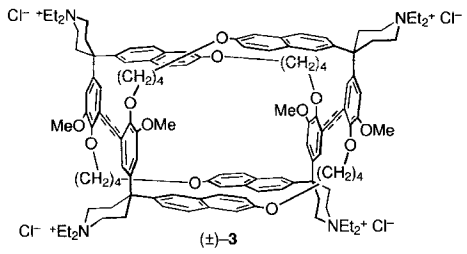
Despite these fascinating perspectives, supramolecular steroid chemistry is only in its infancy. The large number and diversity of steroids requires a profound understanding of their molecular-recognition principles in order to discriminate between derivatives with quite similar structures yet very different biological properties. For many years, the natural cyclodextrins and modified derivatives [14][15] have been the only nonproteinogenic receptors for steroids, and their potential for steroid solubilization, transport, and stabilization has been extensively investigated [7]. However, the stoichiometry of the formed inclusion complexes varies strongly, and the binding selectivity for specific steroids often is low; furthermore, cyclodextrins are known to complex an enormous range of other non-steroidal substrates. Very recently, *Breslow* and *Zhang* reported the synthesis of an efficient and selective cholesterol-binding bis-cyclodextrin receptor [16].

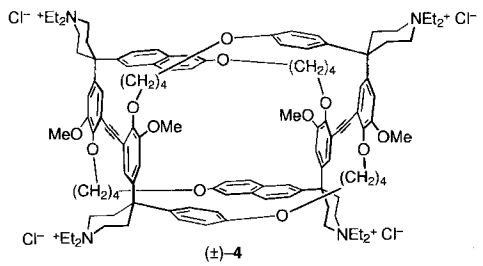
The first artificial host for steroids was reported in 1985 by *Koga* and coworkers [17]. Since then, a very limited number of novel synthetic steroid receptors have appeared in the literature [7]. Except for some steroid-recognizing polymers obtained by molecular imprinting [18], so far all artificial receptors have been based on cyclophanes [19] or calixarenes [20], which provide binding sites aligned with aromatic rings [21] in analogy to the steroid-recognition sites in the natural receptors. A few macrocycles were shown to recognize polar steroids by means of multiple H-bonding in both apolar solvents and in the solid state [22], while the others [10][17][23–25] bind in aqueous or alcoholic solutions, taking advantage of hydrophobic desolvation and dispersion forces as main attractive host-guest interactions.

Here, we describe the synthesis of the macrotricyclic steroid receptors (±)-**2**, (±)-**3**, and (±)-**4** with spacious hydrophobic binding cavities, which form stable complexes with steroids in aqueous and alcoholic solutions. The cylindrical compounds (±)-**2** and (±)-**3** were the first artificial complexing agents reported to efficiently dissolve solid cholesterol in aqueous solution [10]. They are composed of two identically sized cyclophanes shaped by two (naphthyl)(phenyl)methane units and bridged by two ethynediyl or buta-1,3-diynediyl linkers, respectively. Receptor (±)-**4** is cone-shaped and contains the cyclophane moiety of (±)-**2** (and (±)-**3** bridged by ethynediyl fragments to a second, smaller [6.1.6.1]paracyclophane made from two diphenylmethane spacers. Systematic ^{1}H-NMR investigations of the inclusion complexation of a variety of steroidal substrates by (±)-**2**, (±)-**3**, and (±)-**4** in CD_3OD now provide detailed insight into the principles governing the molecular recognition of steroids.

2. Results and Discussion. – 2.1. *Synthesis of the Receptors.* 2.1.1. *Synthesis of (±)-***2**. The key step in the synthesis of (±)-**2** was the Pd^0-catalyzed *Stille* cross-coupling of equimolar amounts of bis(tributylstannyl)acetylene and dibromocyclophane **5** or diiodocyclophane **6**, which can be prepared in multigram quantities in six steps starting from 2-bromo-6-ethoxynaphthalene [24a]. It is well-established that the Pd^0-catalyzed *Stille* coupling of stannylacetylenes with aryl halides provides arylalkynes in good-to-excellent





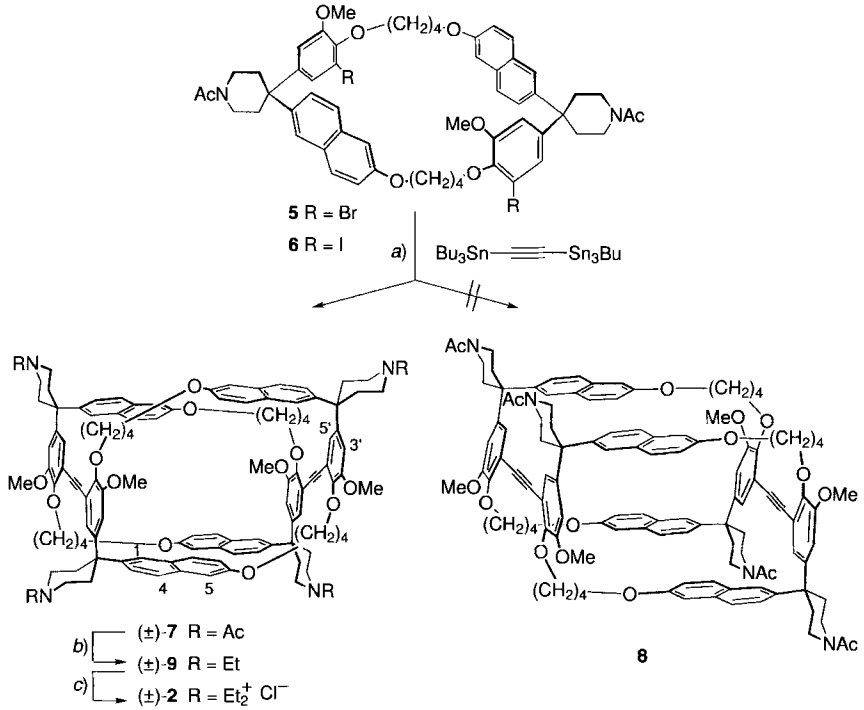


yields [26]. The use of this reaction in cyclizations, however, is limited to a few cases [27]. Gratifyingly, addition of commercially available bis(tributylstannyl)acetylene to 1 equiv. of **5** in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ in *N,N*-dimethylformamide (DMF) resulted in the selective formation of the chiral, D_2-symmetrical macrotricycle (±)-**7** in 14% yield (*Scheme 1*) and none of the possible achiral, C_{2h}-symmetrical isomer **8** was formed. Reduction of (±)-**7** with $LiAlH_4$ to tetramine (±)-**9**, followed by quaternization with EtI and ion-exchange chromatography (Cl^-), afforded the H_2O soluble receptor (±)-**2**.

The formation of only one of two possible diastereoisomers in the *Stille* macrocyclization was indicated by the observation of only a single spot by thin layer chromatography (TLC (SiO_2; CH_2Cl_2/MeOH 20:1): R_f 0.15) as well as by the presence of only one set of resonances in the ^1H- and ^{13}C-NMR spectra. Two-dimensional NMR spectroscopic studies with tetramine (±)-**9** demonstrated that the chiral D_2-symmetrical isomer (±)-**7** was formed exclusively. First, unambiguous ^1H assignments were made with the help of COSY spectra. Subsequently, ROESY spectroscopy [28] provided evidence of intramolecular aliphatic-aromatic $^1H\{^1H\}$ nuclear *Overhauser* effects (NOEs) which are only possible in the D_2-symmetrical compound (*Fig. 1*). In addition to the NMR evidence, molecular-dynamics (MD) simulations with MacroModel [29] using the AMBER* force field [30] and the GB/SA solvation model for $CHCl_3$ [31] showed the D_2-isomer (±)-**7** to be more stable by 6 kcal mol^{-1} than the C_{2h}-isomer **8**, which would explain the exclusive formation of (±)-**7**.

2.1.2. *Synthesis of Receptor (±)-**3***. To increase the depth of the steroid-binding cavity, the macrotricyclic receptor (±)-**3** with two buta-1,3-diynediyl linkers bridging the two cyclophane moieties was prepared starting from the (naphthyl)(phenyl)methane derivative **10** [24a] (*Scheme 2*). Electrophilic *ortho*-iodination of **10** with ICl in the presence of NEt_3 afforded iodide **11** in 64% yield. Subsequent macrocyclization (Cs_2CO_3,

Scheme 1. *Synthesis of Receptor (±)-2*



a) $[Pd(PPh_3)_4]$, 2,6-di(*tert*-butyl)-*p*-cresol, DMF, 110°, pressure bottle, 2 d, 14% (from **5**). *b*) $LiAlH_4$, Et_2O, r.t., 16 h, 59%. *c*) EtI, $CHCl_3$, 20°, 4 d, then *Dowex* resin (Cl^-; H_2O/MeOH 1:1), 78%.

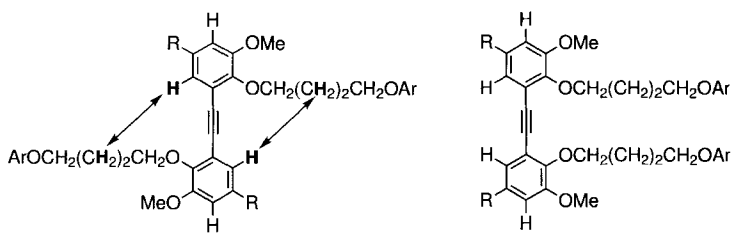
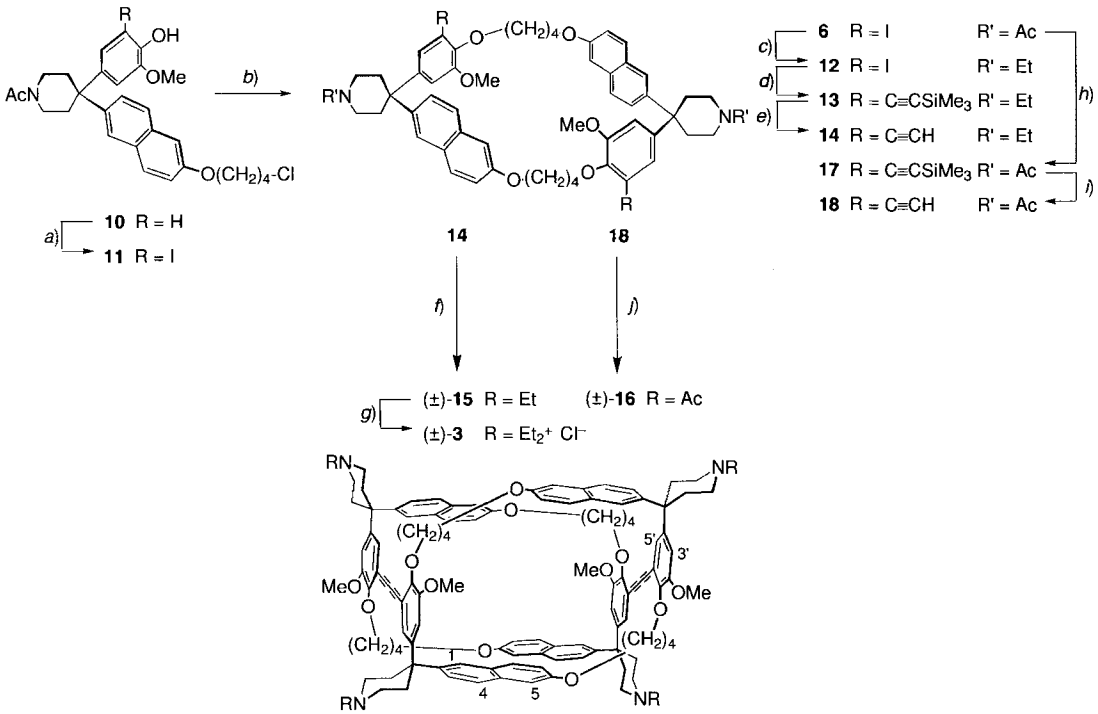


Fig. 1. *Aromatic-aliphatic* $^1H\{^1H\}$ *nuclear* Overhauser *effects (NOEs) observed by ROESY spectroscopy of (±)-***9** *support the* D_2*-symmetrical structure.* Irradiation at the frequency of the aromatic signal leads to approximately equal NOE enhancements for the two CH_2 groups shown in bold. The alternative C_{2h}-symmetrical isomer cannot exhibit the observed NOE enhancements. Shown are only the fragments of the two isomers that are relevant for the NOE discussion.

refluxing MeCN) gave the diiodocyclophane **6** in good yield (48%). Diisobutylaluminum hydride (DIBAL-H) was used in the reduction of the tertiary amide groups to give **12** (82%), and double *Sonogashira* cross-coupling reaction [32] with $Me_3SiC{\equiv}CH$ (10 equiv.) provided the bis(silylethynylated) macrocycle **13** (92%). Alkyne-deprotection

with K_2CO_3 in MeOH/THF [33] produced **14** which was subsequently subjected to *Glaser-Hay* macrocyclization [34] furnishing as a single macrotricyclic product the racemic D_2-symmetrical (±)-**15** in a remarkably high yield of 42%. Subsequent quaternization with EtI followed by ion-exchange (Cl^-) afforded (±)-**3** in 88% yield. By a similar route, in which the tertiary amide functions in **6** were not reduced prior to the *Glaser-Hay* coupling, the macrotricyclic tetrakis(tertiary amide) (±)-**16** was obtained *via* the diethynylcyclophanes **17** and **18**. Compound (±)-**16** proved to be very useful in the assignment of the receptor symmetry. The buta-1,3-diynediyl fragments in (±)-**16** were found to be very sensitive to reduction, and the use of reducing agents such as $LiAlH_4$, $Li(MeO)_3AlH$, or $NaBH_4/TiCl_4$ [35] to transform tetramide (±)-**16** into tetramine (±)-**15** resulted in partial reduction of the buta-1,3-diynediyl moieties to mixtures of (*Z*)- and (*E*)-olefins; in addition, other unidentified side reactions occurred. The best yield of (±)-**15** obtained in the reduction of (±)-**16** with $LiAlH_4$ was only 8%. Attempted cleavage of the amide groups in (±)-**16** with KOH in 2-methoxyethanol [36] followed by *Eschweiler-Clarke* reductive methylation (HCOOH, HCHO) [36] was also not successful, again presumably due to the instability of the buta-1,3-diynediyl linkers under these conditions.

Scheme 2. *Synthesis of Receptor* (±)-**3**

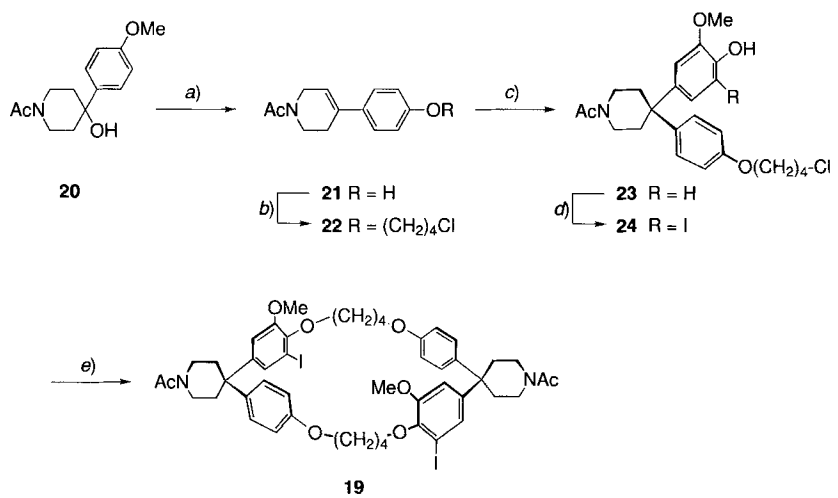


a) ICl, NEt_3 CH_2Cl_2, 0°, 3.5 h, 64%. *b*) Cs_2CO_3, MeCN, Δ, 3 d, 48%. *c*) DIBAL-H, CH_2Cl_2, 0°, 1 h, 82%. *d*) $Me_3SiC{\equiv}CH$, $[PdCl_2(PPh_3)_2]$, CuI (cat.), $NHEt_2$, 100°, pressure bottle, 18 h, 92%. *e*) K_2CO_3, MeOH/THF 1:1, r.t., 3 h, 94%. *f*) CH_2Cl_2, CuCl, *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA), air, r.t., 16 h, 42%. *g*) EtI, $CHCl_3$, r.t., 4 d, then *Dowex* resin (Cl^-, H_2O/MeOH 1:1), 88%. *h*) $Me_3SiC{\equiv}CH$, $[PdCl_2(PPh_3)_2]$, CuI, $NHEt_2$, Δ, 18 h. *i*) K_2CO_3, THF/MeOH 1:1, r.t., 3.5 h. *j*) CuCl, TMEDA, CH_2Cl_2/acetone 1:1, air, r.t., 16 h, 19% over three steps.

The formation of only one diastereoisomer, (±)-**15** or (±)-**16**, respectively, in the *Glaser-Hay* macrocyclizations was established by TLC and by the presence of only one set of resonances in the corresponding ^{13}C- and ^{1}H-NMR spectra. None of the alternative, achiral C_{2h}-symmetrical isomer was isolated. The D_2-symmetry of the macrotricycles was established unambiguously by the enantiomeric resolution of (±)-**16** on a chiral stationary high performance liquid chromatography (HPLC) phase ((*S,S*)-*Whelk-O1* column, CH_2Cl_2/MeOH 20:1). On-line polarimetric detection showed that (−)-**16** had a shorter retention time than (+)-**16**. MD Simulations as described in *Sect. 2.1.1* indicated that D_2-symmetrical (±)-**15** was by 4 kcal mol^{-1} more stable than the corresponding C_{2h}-isomer.

2.1.3. *Synthesis of Receptor (±)-***4**. In the cone-shaped double-decker cyclophane (±)-**4**, two differently sized macrocycles, a smaller and a larger one, are bridged by ethynediyl linkers. Therefore, the fourfold *Stille* cross-coupling reaction as in the synthesis of (±)-**2** (*Scheme 1*) could no longer be applied to the construction of the macrotricyclic scaffold. A direct coupling between two different dihalogenated macrocycles and 2 equiv. of bis(tributylstannyl)acetylene would produce three macrotricyclic products, two cylindrical ones made from identically sized macrocycles and the desired conical one formed from two differently sized macrocycles. Hence, another macrocyclization approach was pursued. The smaller cyclization component, diiodocyclophane **19**, was synthesized by a methodology similar to that applied to the preparation of **6** (*Scheme 2*) [24a][37]. The synthesis started from the tertiary alcohol **20**, which was obtained by *Grignard* reaction of 4-bromoanisol with 1-acetylpiperidin-4-one, and yielded **19** *via* the sequence **20** → **21** → **22** → **23** → **24** → **19** (*Scheme 3*). Whereas the macrocyclization of **24** (c = 4.2 mM) under standard conditions (Cs_2CO_3, refluxing MeCN) afforded **19** in yields of only 15–20%, the addition of *p*-xylene ($c \approx$ 0.95M) as a template [38] resulted in a greatly improved yield of 43%.

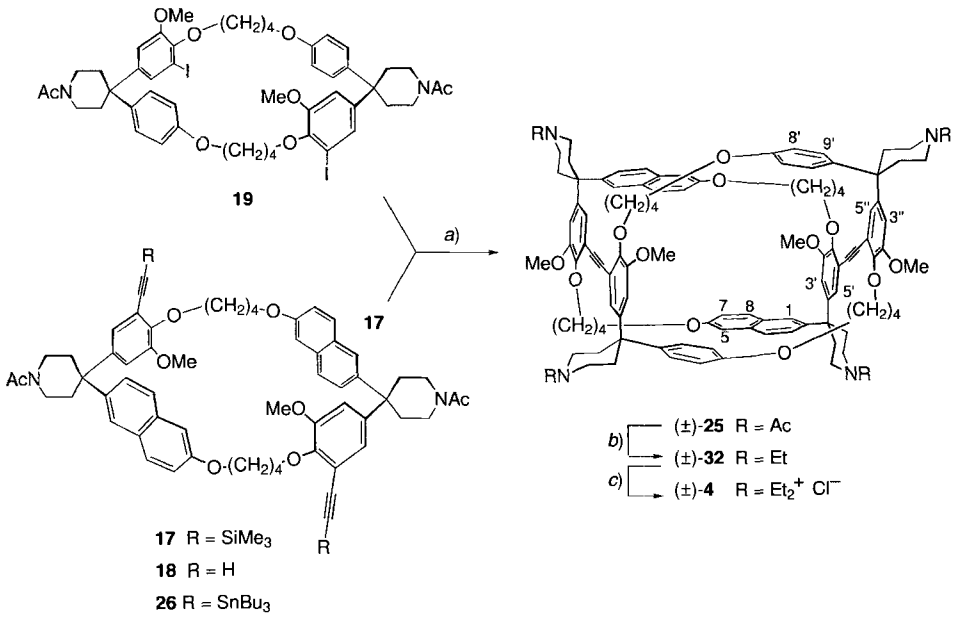
Scheme 3. *Synthesis of Diiodocyclophane* **19**



a) BBr_3, CH_2Cl_2, Δ, 3 h, 98%. *b*) $Cl(CH_2)_4Cl$, K_2CO_3, MeCN, Δ, 28 h, 74%. *c*) Guaiacol, $BF_3 \cdot OEt_2$, CH_2Cl_2, r.t., 9 d, 68%. *d*) ICl, NEt_3, CH_2Cl_2, 0°, 2 h, 63%. *e*) Cs_2CO_3, MeCN/*p*-xylene 7.5:1, Δ, 3 d, 43%.

The construction of the macrotricyclic scaffold was initially attempted using the *Sonogashira* cross-coupling reaction between cyclophanes **18** and **19** under high dilution conditions. The desired product, C_2-symmetrical (±)-**25**, however, could not be detected by either TLC or fast-atom-bombardment (FAB) mass spectrometry. To generate a more reactive alkyne derivative, the formation of the bis(tributylstannylated) cyclophane **26** (*Scheme 4*) for subsequent *Stille* cross-coupling with **19** was attempted. This methodology was first tested in a suitable model reaction, the synthesis of diarylalkyne **27** by cross-coupling two components **28** and **29**, which mimic the electronic properties of the fragments in cyclophanes **19** and **26** involved in the projected *Stille* coupling (*Scheme 5*).

Scheme 4. *Synthesis of Receptor (±)-4 from* **19** *and* **17**

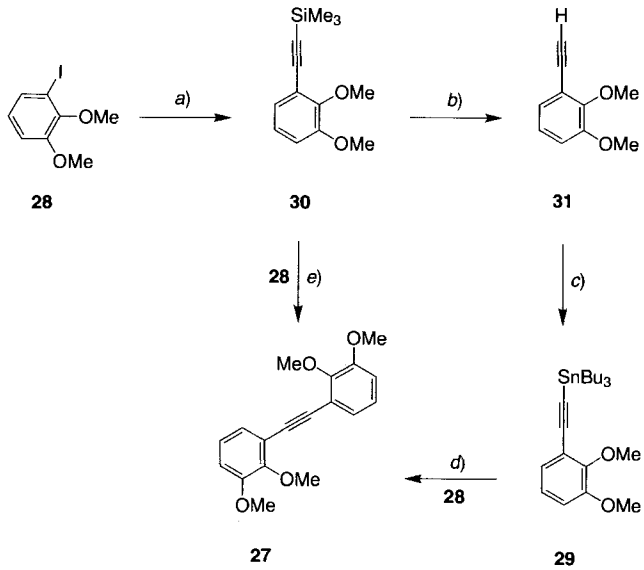


a) TAS-F, $[Pd(PPh_3)_4]$, THF, −78° → reflux, 24 h, 20%. *b*) $LiAlH_4$, Et_2O, r.t., 24 h, 65%. *c*) EtI, $CHCl_3$, r.t., 5 d, then *Dowex* resin (Cl^-; H_2O/MeOH 1:1), 70%.

1,2-Dimethoxybenzene was *ortho*-lithiated [39] and quenched with I_2 to give **28** which was coupled to $Me_3SiC{\equiv}CH$ to provide **30** [40]. Attempts to directly replace the Me_3Si group in **30** by the Bu_3Sn group with subsequent *Stille* coupling to **28** in a one-pot reaction [41] were only partially successful: diarylalkyne **27** was obtained in yields up to 67%, but the reproducibility of the reaction turned out to be poor. Therefore, the more conventional method of deprotecting **30** to give **31** [40] followed by stannylation with $(Bu_3Sn)_2O$ [42] was applied to prepare **29** and subsequent *Stille* coupling afforded **27** in a reproducible overall yield of 57% (from **30**).

Although the *Stille* coupling was successful in the model reaction, it could not be applied to the cyclization of **19** and **26** to give the macrotricyclic system (±)-**25**. The conversion of terminal alkyne **18** to **26** in all runs afforded only partially stannylated cyclophane (^{1}H-NMR) which was impossible to purify, since the Bu_3Sn groups were

Scheme 5. *Pd^0-Catalyzed* Stille *Cross-Coupling in a Model Reaction*



a) $Me_3SiC{\equiv}CH$, $[PdCl_2(PPh_3)_2]$, CuI, $NHEt_2$, 90° (sealed tube), 6 h, 78%. *b*) K_2CO_3, MeOH/THF, r.t., 4 h, 92%. *c*) $(Bu_3Sn)_2O$, molecular sieves (4 Å), CH_2Cl_2, r.t., 3 h, 81%. *d*) $[Pd(PPh_3)_4]$, THF, 80° (sealed tube), 18 h, then HF · Py, r.t., 18 h, 77%. *e*) 1. $(Bu_3Sn)_2O$, Bu_4NF, molecular sieves (4 Å), THF, r.t., 18 h; 2. $[Pd(PPh_3)_4]$, 90°, 17 h; 3. HF · Py, r.t., 18 h, 67%.

completely lost upon chromatography on SiO_2. In contrast, model system **29** was perfectly stable to chromatography on this support. The origin of the reduced stability of the stannylated diethynylcyclophane is unknown.

The preparation of (±)-**25** was eventually achieved by the *Hiyama* cross-coupling reaction [43]. In this method, Me_3Si-protected alkynes are activated *in situ* by F^--mediated desilylation, thereby generating the nucleophilic species ready for the Pd^0-mediated cross-coupling. The reagent used for removal of the Me_3Si group is either Bu_4NF or TAS-F (*t*ris(dimethyl*a*mino)*s*ulfonium di*f*luorotrimethylsilicate); the latter can be purchased in anhydrous form and was, therefore, chosen for this work. By this method, cyclophanes **17** and **19** were coupled under high dilution to provide (±)-**25** in 20% yield. Of the two possible C_2-symmetrical diastereoisomeric pairs of enantiomers that can form in this macrocyclization, only the one which structurally resembles (±)-**7** (*Scheme 1*) was formed. The presence of only one racemate was evidenced by TLC analysis, ^1H- and ^{13}C-NMR spectroscopy, and analytical HPLC on the chiral stationary phase ((*S,S*)-*Whelk-O1* column; CH_2Cl_2/MeOH 20:1) which only gave two peaks for the two enantiomers. In a control run, HPLC on an achiral phase (SiO_2; CH_2Cl_2/MeOH 25:1) showed only one peak with t_R 9.60 min. MD Simulations predicted the isolated pair of enantiomers to be more stable by 7 kcal mol^{-1} than the other possible one.

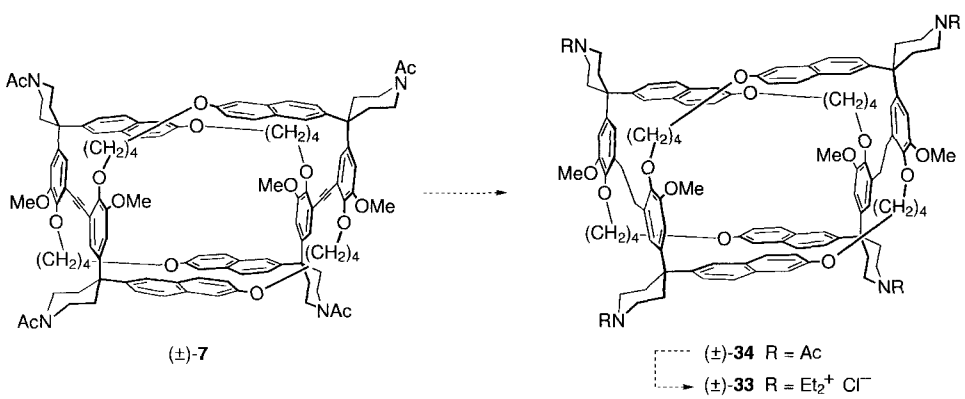
Further support for structure (±)-**25** was obtained after reduction with $LiAlH_4$ to (±)-**32**. For this tetramine, characteristic intramolecular NOEs such as those depicted in *Fig. 1* were measured by ROESY spectroscopy. Quaternization of (±)-**32** yielded, after ion exchange (Cl^-), the desired receptor (±)-**4**. In general, the double-decker cyclophane

tetrakis(acetamides) (±)-**7**, (±)-**16**, and (±)-**25** were difficult to characterize by ^{1}H-NMR at ambient temperature due to strong line broadening originating from both slow rotation of the doubly bridged aromatic rings in the macrotricyclic structures as well as from hindered rotation about the amide C–N bonds [44]. The most resolved ^{1}H-NMR spectra were usually obtained at the stage of the tetrakis(tertiary amines) (±)-**9**, (±)-**15**, and (±)-**32**; full assignment of all ^{1}H signals of the latter macrotricycle was obtained by ^{1}H{^{1}H} COSY and ROESY spectra recorded at 313 K.

Whereas matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry provided satisfactory characterization of the four-fold charged receptors (±)-**2** and (±)-**3**, this method, as well as FAB mass spectrometry, failed to detect the molecular ion of (±)-**4**. However, the molecular ion was readily observed by electrospray ionization (ESI) mass spectrometry [45] which is remarkable for a fourfold charged species of comparatively small size [46].

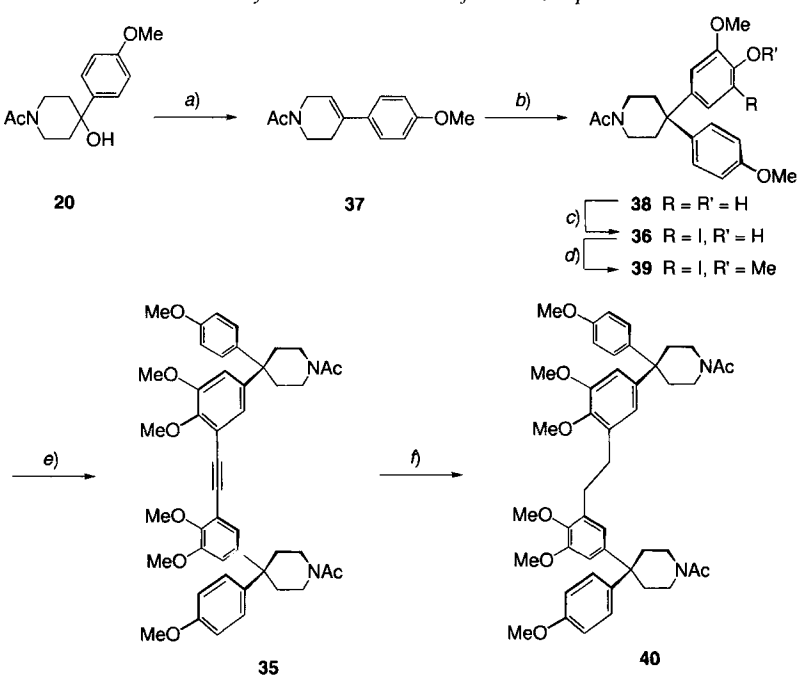
2.1.4. *Towards the Synthesis of a Double-Decker Receptor with Saturated Hydrocarbon Linkers between the two Cyclophanes: Development of a Model System.* We were interested in preparing receptor (±)-**33** with hydrocarbon bridges between the two cyclophane moieties by a synthetic sequence which involved the reduction of the ethynediyl linkers in (±)-**7** to give (±)-**34** as the key step (*Scheme 6*). The transformation of ethynediyl into ethanediyl linkers would reduce the degree of preorganization of the macrotricyclic receptor, which is usually associated in host-guest chemistry with reduced binding affinity and selectivity [47]. However, it could not be excluded in this specific case that the enhanced flexibility of the aliphatic bridges would rather lead to stronger binding by permitting the two cyclophane moieties to adopt a tighter fitting, more encapsulating geometry for steroids of complementary geometry. Since preliminary attempts to reduce the triple bonds in (±)-**7** indicated that this transformation was nontrivial, presumably due to the steric shielding of the acetylenic bridges by the appended cyclophanes, we explored this reduction in model compound **35**, which provides a steric and electronic environment around the triple bond similar to that in the double-decker cyclophane.

Scheme 6. *Targeted Synthesis of the Double-Decker Cyclophane Receptor (±)-33 with Saturated Hydrocarbon Linkers*



For the synthesis of **35** (*Scheme 7*), the iodo compound **36** was prepared from **20** *via* **37** and **38**, following a methodology similar to that applied to the formation of **24** (*Scheme 3*) [37]. Subsequent methylation to **39** and *Stille* cross-coupling with bis(tributylstannyl)acetylene afforded **35** in non-optimized procedures. The reduction of **35** to **40** proceeded smoothly and in high yield by catalytic hydrogenation (5 bar H_2) using either Pd/C [48] or PtO_2 [49] as the catalyst in MeOH. Several non-catalytic reduction methods were also tested [50]; however, they all failed to give **40**. Reduction of **35** with *in situ* generated diimide was unsuccessful [51] as was the conversion with $LiAlH_4/FeCl_2$ [52]. Unfortunately, application of the catalytic hydrogenation to the reduction of (±)-**7** was unsuccessful, even if the H_2 pressure was raised up to 70 bar. All other methods tried also failed to convert (±)-**7** into (±)-**34**. Clearly, the two rigidly fixed cyclophanes in the double-decker system sterically shield the C≡C bond effectively against attack by catalyst-bound H_2 or H-transfer from other reducing agents.

Scheme 7. *Synthesis and Reduction of Model Compound* **35**



20 **37** **35** **40**

a) TsOH, PhMe, Δ, 2 h, 87%. *b*) Guaiacol, $BF_3 \cdot OEt_2$, 85°, 2 h, 75%. *c*) ICl, NEt_3, CH_2Cl_2, 0°, 2 h, 47%. *d*) MeI, K_2CO_3, acetone, Δ, 3 h, 61%. *e*) $Bu_3SnC{\equiv}CSnBu_3$, $[Pd(PPh_3)_4]$, THF, 80°, 2 d, 27%. *f*) H_2 (5 bar), PtO_2, MeOH, 20°, 24 h, 80%.

Upon recrystallization from $CHCl_3/Et_2O$, crystals of **35** suitable for X-ray structural analysis were obtained. The monoclinic crystals ($P2_1/n$, $Z = 8$) contain 1 equiv. of $CHCl_3$ and 0.5 equiv. of H_2O, and show the molecules of **35** arranged in two very similar conformations, one of which is depicted in *Fig. 2*. The diarylacetylene moiety is nearly planar with dihedral angles C(18)–C(19)–C(19′)–C(18′) of 8.2° and 6.3°, respectively, in the two conformers. Computer simulations with MacroModel V.5.5 (1000-step Monte

Carlo (MC) simulations, AMBER* force field, GB/SA solvation model for $CHCl_3$) gave a dihedral angle of 9.4° for the lowest-energy structure but a different orientation of the other substituents on the aryl rings. The bond angles at the alkyne C-atoms in the two conformers are 173.4(5)° and 172.5(5)° (C(23)–C(23′)–C(19′)) and 176.4(5)° and 173.7(5)° (C(23′)–C(23)–C(19)), respectively.

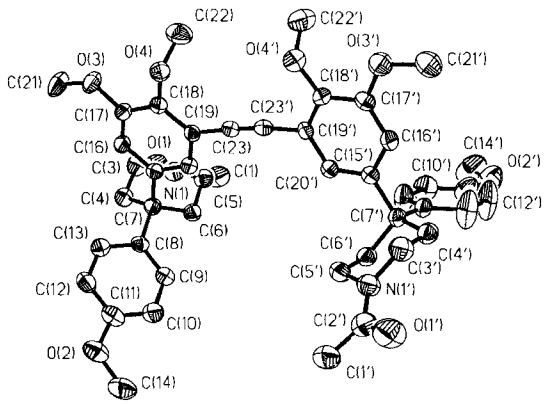


Fig. 2. *X-Ray crystal structure of* **35**. Only one of two very similar conformers in the crystal is shown. Incorporated solvent molecules are omitted. Thermal displacement ellipsoids are shown at the 50% probability level.

For a maximum space occupancy, molecules of **35** form a remarkable, tightly packed dimer motif in the crystal, demonstrating their high degree of self-complementarity (*Fig. 3*). Closer inspection of the packing revealed that formation of dimers occurred between different conformers only. Stabilization of each assembly is provided by four intermolecular aromatic edge-to-face contacts, with H–C(10), H–C(10′) of the *para*-disubstituted benzene rings in one conformer pointing toward the π-electron cloud of the tetrasubstituted benzene rings of the other one. These four contacts involve different inter-ring distances and angles. The most favorable contact occurs at a distance of 4.99 Å between ring centers and at an interplanar angle between the two rings of nearly 90°, thereby resembling closely to the most favorable edge-to-face contact seen in the X-ray crystal structures of orthorhombic benzene [53a–c] and the benzene inclusion complex of a [6.1.6.1]paracyclophane [53d]. The three other aromatic ring contacts occur at even shorter center-to-center distances (4.42, 4.57, and 4.65 Å, resp.) but at smaller interplanar angles (between 20° and 60°). A total of 76 short intermolecular contacts (≤ 4 Å) are found in the dimer, and calculation of the solvent-accessible surface area [54] revealed that 470 Å^2 (41% of the total area) of the surface of each conformer are buried in the dimer.

2.2. *Properties of Receptors (±)-***2** *and (±)-***3**. 2.2.1. *Solubility Properties and Receptor Dimensions*. The two cylindrical receptors are highly soluble in H_2O ((±)-**2**: 6 mg ml^{-1}, 3.0 mM; (±)-**3**: 4 mg ml^{-1}, 1.7 mM). They do not aggregate appreciably at concentrations below 2.5 mM ((±)-**2**) and 1.7 mM ((±)-**3**), as determined by ^{1}H-NMR dilution experiments. Thus, the additional hydrophobic surface from the longer buta-1,3-diynediyl linkers decreases somewhat the solubility and the critical aggregation concen-

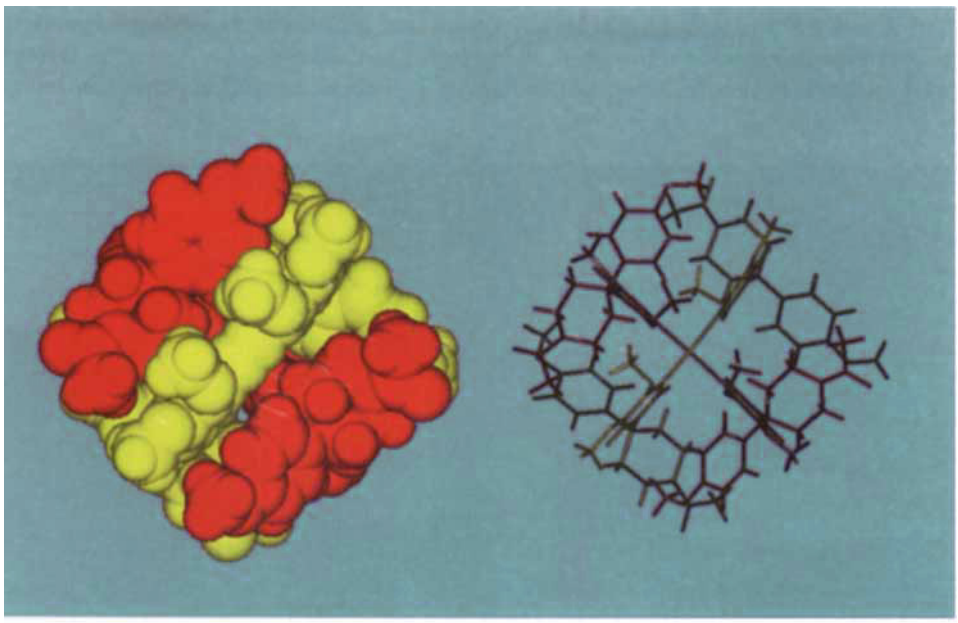


Fig. 3. *Dimer motif seen in the crystal packing of* **35**

tration (CAC) of (±)-**3** in comparison to (±)-**2**, with the smaller ethynediyl linkers. The overall relatively high CACs of both receptors are due, in part, to the presence of the four peripheral MeO substituents, which were shown previously to significantly increase the CAC values of other H_2O soluble cyclophanes [55]. At 298 K, the ^{1}H-NMR signals of the receptors in D_2O are somewhat broadened, but sharpen substantially upon heating to 330 K. We assign the signal broadening at the lower temperature to dynamic processes such as slow rotation of the doubly bridged naphthyl rings. Much sharpened resonances are observed in CD_3OD and reflect faster dynamic processes in this solvent.

By connecting two cyclophanes such as **5** with two ethynediyl bridges, the depth of the cavity binding site increases from *ca.* 5 Å (in **5**, *Scheme 1*) to *ca.* 11 Å in (±)-**2** (*Fig. 4*). With the larger buta-1,3-diynediyl spacers, the depth of the cavity in (±)-**3** is further increased to *ca.* 13 Å. Thus, binding sites are created which, both in terms of space and hydrophobicity, resemble those seen by X-ray crystallography in the complexes of steroid-binding proteins with steroids (see *Introduction*). Computer modeling suggested that the cavity in (±)-**2** would be sufficiently deep to fully accommodate the tetracyclic scaffold of axially included hydrophobic steroids such as cholesterol. With its increased depth, the cavity of (±)-**3** was expected to additionally encapsulate parts of the hydrophobic side chain of cholesterol. Furthermore, low-energy structures of (±)-**3** generated by energy-minimizations with MacroModel showed the buta-1,3-diynediyl linkages in a twisted orientation. This twist, in return, enables the naphthalene moieties to orient in a cofacial fashion more readily, resulting in a substantial enlargement in width of the binding cavity in this receptor (*Fig. 4*). It will become clear, from the binding studies described below, that this difference in cavity width (cavity openings of 8 Å × 11 Å in

(±)-**2** and 9 Å × 12 Å in (±)-**3**) largely determines differences in substrate specificity between the two receptors. In view of the large size of the binding site apertures, steroids were expected to penetrate and exit the receptors without significant steric hindrance.

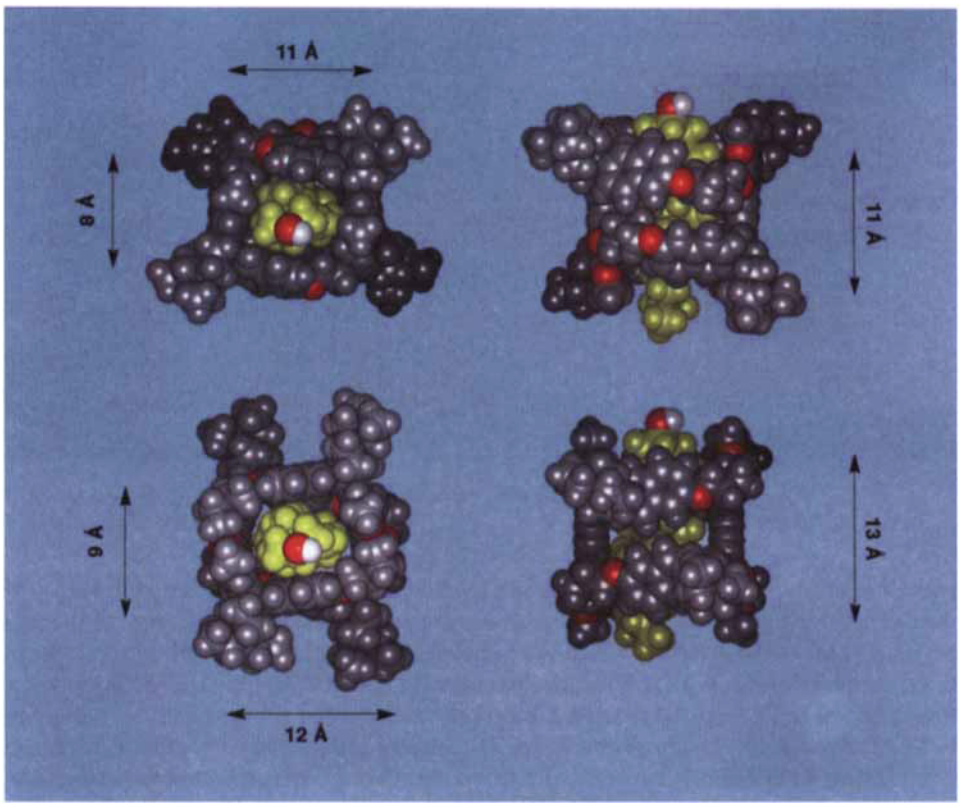


Fig. 4. *Comparison of two views of MacroModel-minimized structures of (±)-***2** (top) *and (±)-***3** (bottom) *complexed to cholesterol* (yellow). The views on the left show the greater width of the cavity of (±)-**3** (*ca.* 12 Å × 9 Å) as compared to (±)-**2** (*ca.* 11 Å × 8 Å). Dimensions were calculated at the cavity entrance; the larger distance is between the cofacial Ph rings, the smaller between the naphthalene H-atoms H–C(8). For numbering, see *Schemes 1* and *2*. The views on the right show the greater depth of the receptor cavity in (±)-**3** (*ca.* 13 Å) as compared to (±)-**2** (*ca.* 11 Å).

2.2.2. *Dissolution of Cholesterol in Aqueous Solution.* The complexation of some of the least H_2O-soluble steroids, cholesterol (**1**), testosterone (**41**), and progesterone (**42**) was evaluated using the solid-liquid extraction method (*Table 1*) [56]. The maximum solubility of cholesterol in pure H_2O is 4.7×10^{-6} M [57a]. Upon extraction of an excess of solid cholesterol with a 1.0 mM aqueous solution of (±)-**2**, a 8.5×10^{-4} M solution of cholesterol was obtained. This represents a complexation-mediated increase in solubility by a factor of 180. From these data, the binding free enthalpy for the (±)-**2** · cholesterol complex was calculated [56] as $\Delta G^\circ = -8.2$ kcal mol^{-1} (295 K). We had expected that receptor (±)-**3** would form an even more stable complex with cholesterol (**1**), since its

deeper cavity could accommodate not only the tetracyclic steroid frame but also parts of the hydrophobic side chain. Extraction of solid cholesterol with a 1 mM aqueous solution of (±)-**3**, however, only provided a 0.42 mM solution of the steroid, corresponding to a solubility increase by a factor of 90. Thus, the binding free enthalpy of the formed 1:1 complex amounts to $\Delta G^\circ = -7.1$ kcal mol^{-1}, corresponding to a difference in free enthalpy between the complexes formed by (±)-**2** and (±)-**3** of $\Delta(\Delta G^\circ)$ ((±)-**3** – (±)-**2**) = 1.1 kcal mol^{-1}.

Table 1. *Association Constants* K_a [l mol^{-1}] *and Complexation Free Enthalpies* ΔG° [kcal mol^{-1}] *for 1:1 Steroid Complexes of Receptors (±)-***2** *and (±)-***3** *as Determined at 295 K by Solid-Liquid Extraction in* H_2O[a])

Steroid	Receptor	K_a [l mol^{-1}]	ΔG° [kcal mol^{-1}]	Maximum aqueous solubility [mol l^{-1}] (300 K)
Cholesterol (**1**)	(±)-**2**	1.1×10^6	−8.2	4.7×10^{-6}[b])
Cholesterol (**1**)	(±)-**3**	1.5×10^5	−7.1	4.7×10^{-6}[b])
Testosterone (**41**)	(±)-**2**	6.8×10^4	−6.5	8.3×10^{-5}[c])
Progesterone (**42**)	(±)-**3**	1.5×10^5[d])	−7.1	2.9×10^{-5}[c])

[a]) Reproducibility of ΔG° in triplicate runs: ±0.4 kcal mol^{-1}. [b]) From [57a]. [c]) From [57b]. [d]) A 1:2 receptor-steroid stoichiometry cannot be fully ruled out; the given K_a and ΔG° values are only meaningful if a 1:1 complex forms exclusively.

To explain this finding, both receptors complexed to cholesterol (**1**) were modeled, and the energy-minimized structures were analyzed (*Fig. 4*). This procedure revealed that receptor (±)-**2** has 12 short C···C contacts below 3.7 Å with the bound steroid, whereas only 7 such contacts were observed in the complex of (±)-**3** [58]. Thus, the less wide cavity in the smaller receptor (±)-**2** has a higher complementarity for cholesterol (**1**), with its A-B ring segment flattened by the C(5)=C(6) bond, than the larger cavity in (±)-**3**.

Solid testosterone (**41**) was also extracted into H_2O through complexation by (±)-**2**, although, at $\Delta G^\circ = -6.5$ kcal mol^{-1}, the formed 1:1 complex is much less stable in comparison to the cholesterol complex. This can be readily explained by the higher affinity of the more polar testosterone to the aqueous phase, a fact that is reflected in its higher H_2O solubility (8.3×10^{-5} M) [57b] compared to cholesterol. Surprisingly, extraction of testosterone with a 1 mM solution of (±)-**3** provided a 1.09 ± 0.11 mM solution of testosterone in H_2O. Two interpretations of this result are possible: *i*) 1 equiv. of testosterone (**41**) is extracted into solution upon treatment with (±)-**3** because of very strong 1:1 complex formation ($\Delta G^\circ << -7.0$ kcal mol^{-1}), or *ii*) more than one molecule of testosterone is binding in the deep cavity. We favor the latter explanation since, with their flat cyclohexenone-type A rings, two testosterone molecules should be able to arrange themselves in the wide cavity of (±)-**3**. In previous work, we had shown that [2.2]- and [4.2]paracyclophanes, which contain two cofacially aligned benzene rings, can be incorporated into the cavity of a receptor which is structurally closely related to the two macrocycles that are linked by acetylenic bridges to form the binding sites in (±)-**2** and (±)-**3** [24b]. Energy minimizations of receptor (±)-**3** complexed with two testosterone molecules revealed that the cavity is sufficiently deep and broad to easily

accommodate two molecules of the steroidal substrate (*Fig. 5*). The two guests penetrate from opposite cavity sides, and their A rings are stacked in the center of the binding site; this way, their OH groups at C(17) are favorably oriented into the aqueous solution. Since the binding site in receptor (±)-**2** is significantly narrower than in (±)-**3**, testosterone forms only an inclusion complex with exclusive 1:1 stoichiometry with (±)-**2** in H_2O.

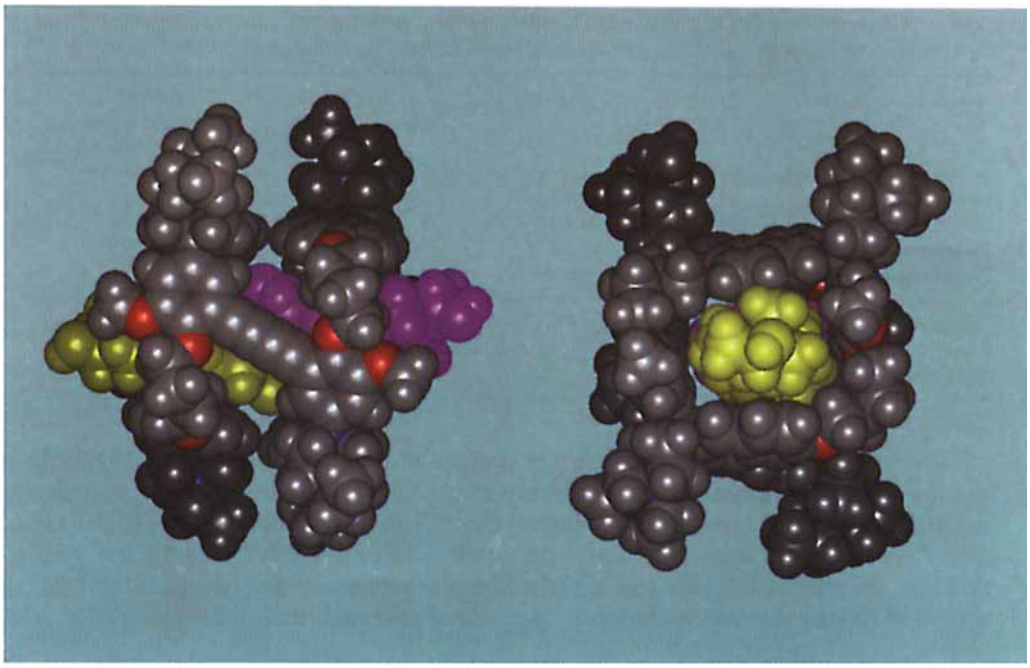


Fig. 5. *Views on the energy-minimized complex between receptor (±)-***3** *and two testosterone* (**41**) *molecules* (in yellow and purple colors) *showing the accommodation of the two substrates in the wide receptor cavity*

Extraction of solid progesterone (**42**) with a 1 mM solution of receptor (±)-**3** provided a 0.83 ± 0.04 mM solution of this steroid hormone, allowing calculation of $\Delta G^\circ = -7.1 \pm 0.4$ kcal mol^{-1} for formation of a 1:1 complex. If a 1:1 complex forms exclusively, its formation free enthalpy is the same than that of the complex formed between (±)-**3** and cholesterol (**1**). However, it cannot be ruled out that progesterone (**42**), like testosterone (**41**), also forms a complex with 1:2 receptor-substrate stoichiometry, although the bulkier MeCO side chain at C(17) could possibly provide steric hindrance to such an association mode. Computer simulations suggested that the cavity of (±)-**3** should indeed be able to incorporate two progesterone molecules in a geometry similar to that modeled for the complex with two testosterone guests. However, progesterone (O···O distance of *ca.* 12.5 Å) has a more extended structure than testosterone (O···O distance of 11.4 Å), and, in the case where two progesterone molecules are bound, a large part of the steroid is still in contact with the aqueous solution. The two

molecules cannot be completely encapsulated by the receptor. It should be noted that similar uncertainties about the host-guest stoichiometry are common for complexes formed between cyclodextrins and steroidal substrates [7].

A 1:2 stoichiometry of receptor-substrate association is certainly not possible for cholesterol: Both *Corey-Pauling-Koltum* (*CPK*) model examinations and computer simulations clearly show that the bulkier saturated A ring and the aliphatic side chain at C(17) prevent two cholesterol molecules from being incorporated together into the binding site of either receptor (±)-**2** or receptor (±)-**3**.

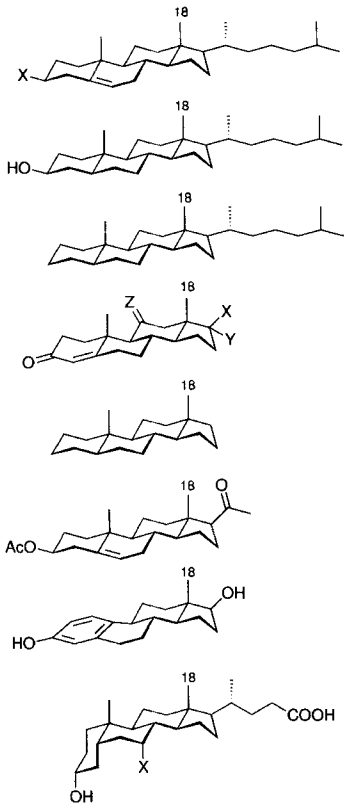
The binding behavior of testosterone (and possibly also of progesterone) in H_2O contrasts to that determined by ^{1}H-NMR binding assays in CD_3OD. *Job* plots [59] of the association of receptor (±)-**3** with testosterone (**41**), progesterone (**42**), and cholesterol (**1**) in CD_3OD clearly indicate that only 1:1 complexation takes place in the organic solvent. In H_2O, the much stronger hydrophobic effect [60] presumably forces the flat A rings of the two testosterone molecules (and possibly also of two progesterone molecules) inside the wide cavity of (±)-**3**, thus increasing the amount of steroid that is dissolved in the solid-liquid extraction.

2.2.3. *^{1}H-NMR-Spectroscopic Investigations into the Steroid-Binding Selectivity of Receptors (±)-2 and (±)-3 in CD_3OD.* A detailed analysis of the binding selectivity of the novel receptors and the principles that govern steroid recognition in apolar cavities was undertaken by ^{1}H-NMR binding titrations in CD_3OD (*Table 2*). In this solvent, 1:1 host-guest complexation was exclusively observed as demonstrated by the *Job* plots mentioned above (*Sect. 2.2.2*). The steroid concentration was held constant during the titrations, and the complexation-induced upfield shift of the steroidal Me(18) resonance were monitored and evaluated. The resonances of Me(18) in the two possible diastereoisomeric complexes between racemic receptor and enantiomerically pure steroid were not resolved; therefore, the association constants in *Table 2* give average values for both complexes. All considered steroids **1** and **41**–**53** (*Fig. 6*) formed homogenous solutions in the concentration ranges suitable for ^{1}H-NMR titrations, and, at the reduced overall association strength (as compared to H_2O), host-guest exchange kinetics was sufficiently fast, providing highly resolved signals of the binding partners during the titrations. Similarly accurate ^{1}H-NMR binding assays were not possible in D_2O due to low steroid solubilities, slow host-guest exchange kinetics, and too strong binding [61].

The following conclusions could be drawn from the comprehensive binding data in *Table 2*:

i) Although the hydrophobic driving force for complexation is much weaker in CD_3OD than in D_2O, cholesterol (**1**) and its derivatives as well as a variety of other steroids form stable complexes with (±)-**2** and/or (±)-**3** in the organic solvent. Significant differences in binding selectivity are observed between the two receptors, and these can be largely explained with the differences in width and length of their binding cavities.

ii) In CD_3OD, like in H_2O, (±)-**2** is the more effective receptor for cholesterol (**1**) and its derivatives **43** and **44** by 0.2–0.4 kcal mol^{-1}. As suggested by the computer modeling in *Fig. 4*, the narrower cavity of (±)-**2** provides better *van der Waals* contacts to flatter unsaturated steroids, whereas the wider cavity in (±)-**3** has a better complementarity to fully aliphatic substrates. Thus, the presence of a C(5)=C(6) bond in steroids such as cholesterol lowers the affinity for receptor (±)-**3**. A comparison of the binding of (±)-**2**



		X
43	cholesteryl acetate	$OCOCH_3$
44	5-cholestene	H
1	cholesterol	OH
45	dihydrocholesterol	
46	5α-cholestane	

		X	Y	Z
42	progesterone	$COCH_3$	H	H_2
41	testosterone	OH	H	H_2
47	cortisone	$COCH_2OH$	OH	O
48	hydrocortisone	$COCH_2OH$	OH	α-H, β-OH
49	5α-androstane			
50	pregnenolone acetate			
51	β-estradiol			

		X
52	lithocholic acid	H
53	chenodeoxycholic acid	OH

Fig. 6. *Steroids investigated in ^{1}H-NMR binding studies with receptors (±)-**2**, (±)-**3**, and (±)-**4** in CD_3OD*

and (±)-**3** to the fully aliphatic substrate 5α-cholestane (**46**) ($\Delta(\Delta G^\circ)$ ((±)-**2** – (±)-**3**) = 0.7 kcal mol^{-1}) and other steroids indicates that unsaturation of the guest in 5,6-position is favorable by 0.8 kcal mol^{-1} ($\Delta(\Delta G^\circ)$((±)-**2**$_{44-46}$) for complexation by receptor (±)-**2** but unfavorable by 0.1 kcal mol^{-1} ($\Delta(\Delta G^\circ)$((±)-**3**$_{44-46}$) and ($\Delta(\Delta G^\circ)$((±)-**3**$_{1-45}$) for complexation by (±)-**3**. As mentioned in *Sect. 2.2.2*, modeling studies revealed more short intermolecular contacts (≤ 3.7 Å) in the cholesterol (**1**) complex with (±)-**2** than with (±)-**3**. In contrast, fully aliphatic 5α-cholestane (**46**) has seven such short C···C contacts in the energy-minimized complex with receptor (±)-**3**, but only six when bound to (±)-**2**.

iii) Side-chain complexation is promoted by the deeper cavity of receptor (±)-**3**. Comparison of the binding of 5α-cholestane (**46**) with 5α-androstane (**49**) ($\Delta(\Delta G^\circ)$ ((±)-**3**$_{46-49}$ = 1.2 kcal mol^{-1}) indicates that the side chain makes a 0.9 kcal mol^{-1}) higher contribution to the free enthalpy of complexation by receptor (±)-**3** than by receptor (±)-**2** ($\Delta(\Delta G^\circ)$((±)-**2**$_{49-46}$ = 0.3 kcal mol^{-1}). Evidence for significantly greater encapsulation of the steroidal side chain by receptor (±)-**3** was also obtained in the ^{1}H-NMR spectra of complexes of both receptors in CD_3OD (*Fig. 7*). When measured at equivalent degrees of complexation with both receptors, 5α-cholestane (**46**) exhibits

Table 2. *Association Constants* K_a *and Binding Free Enthalpies* ΔG° *from* ^{1}*H-NMR Titrations for 1:1 Steroid Complexes Formed by Receptors (±)-***2** *and (±)-***3** *in* CD_3OD *at 298 K.* Also shown are the maximum observed complexation-induced upfield shifts $\Delta\delta_{max\,obs}$ and the upfield shifts at saturation binding $\Delta\delta_{sat}$ of the steroidal Me(18) resonance, which was evaluated in the titrations.

Steroid		Receptor (±)-**2**			Receptor (±)-**3**		
		K_a [a] [mol l^{-1}]	ΔG° [kcal mol^{-1}]	$\Delta\delta_{max\,obs}$ ($\Delta\delta_{sat}$) Me(18)	K_a [a] [mol l^{-1}]	ΔG° [kcal mol^{-1}]	$\Delta\delta_{max\,obs}$ ($\Delta\delta_{sat}$) Me(18)
43	Cholesteryl acetate	4800	−5.0	−1.54 (−1.95)	2300	−4.6	−0.95 (−1.33)
44	5-Cholestene	3200	−4.8	−0.85 (−1.19)	2300	−4.6	−0.85 (−1.20)
1	Cholesterol	1500	−4.3	−1.14 (−1.70)	900	−4.1	−0.64 (−0.97)
45	Dihydrocholesterol	[b]			1200	−4.2	−0.67 (−0.93)
46	5α-Cholestane	870	−4.0	−0.90 (−1.57)	2700	−4.7	−0.81 (−1.10)
42	Progesterone	[b]			2600	−4.7	−1.30 (−1.63)
41	Testosterone	2100	−4.5	−1.25 (−1.69)	200	−3.1	−0.34 (−1.13)
47	Cortisone	160	−3.0	−0.36 (−1.52)	[b]		
48	Hydrocortisone	110	−2.8	−0.13 (−0.60)	[b]		
49	5α-Androstane	500	−3.7	−0.72 (−1.74)	370	−3.5	−0.51 (−1.16)
50	Pregnelonone acetate	[b]			2100	−4.5	−1.33 (−1.68)
51	β-Estradiol	390	−3.5	−0.81 (−2.04)	170	−3.0	−0.29 (−1.10)
52	Lithocholic acid	310	−3.4	−0.17 (−0.57)	[b]		
53	Chenodeoxycholic acid	40	−2.2[c]		[b]		

[a]) Association constants determined by nonlinear least-squares curve-fitting of 500-MHz ^{1}H-NMR-titrations. The resonances of Me(18) in the two possible diastereoisomeric complexes between racemic receptor and enantiomerically pure steroid were not resolved, and the association constants give an average value for both complexes. Reproducibility of K_a values: ± 10%. [b]) Not determined. [c]) Estimated upper limit.

diagnostic upfield shifts of the resonances assigned to the Me groups at the steroidal nucleus and the side chain. The weaker binding of receptor (±)-**2** (ΔG° = −4.0 kcal mol^{-1}) induces larger upfield shifts in the resonances of the Me groups at the steroidal nucleus (Me(18), Me(19)), whereas the stronger binding by receptor (±)-**3** (ΔG° = −4.7 kcal mol^{-1}) induces larger upfield shifts in the signals assigned to the Me groups of the steroidal side chain (Me(21), Me(26), Me(27)), indicating much more efficient encapsulation of this hydrophobic moiety.

iv) The difference in cavity width between the two receptors leads to a striking difference in binding affinity ($\Delta(\Delta G^\circ)$((±)-**3** − (±)-**2**) = 1.4 kcal mol^{-1}) for testosterone (**41**). Whereas (±)-**2** complexes testosterone strongly (ΔG° = −4.5 kcal mol^{-1}) in CD_3OD, a much weaker 1:1 complex (ΔG° = −3.1 kcal mol^{-1}) is formed by (±)-**3** with its wider cavity.

v) A remarkable difference in binding free enthalpy ($\Delta(\Delta G^\circ)$((±)-**3**)$_{41-42}$ = 1.6 kcal mol^{-1}) was measured for the complexation of testosterone (**41**) and progesterone (**42**) by (±)-**3**, which results from the difference of their substituents at C(17). The costs for partial desolvation of the OH group in **41** upon incorporation of the steroidal D ring into the deep receptor cavity may be higher than those for the partial desolvation of the MeCO group in **42**. Furthermore, the MeCO group of **42** may undergo favorable CH···π interactions with the aromatic receptor-binding site [62]. Such interactions may also be responsible for the increased binding affinity ($\Delta(\Delta G^\circ)$((±)-**2**)$_{44-43}$ =

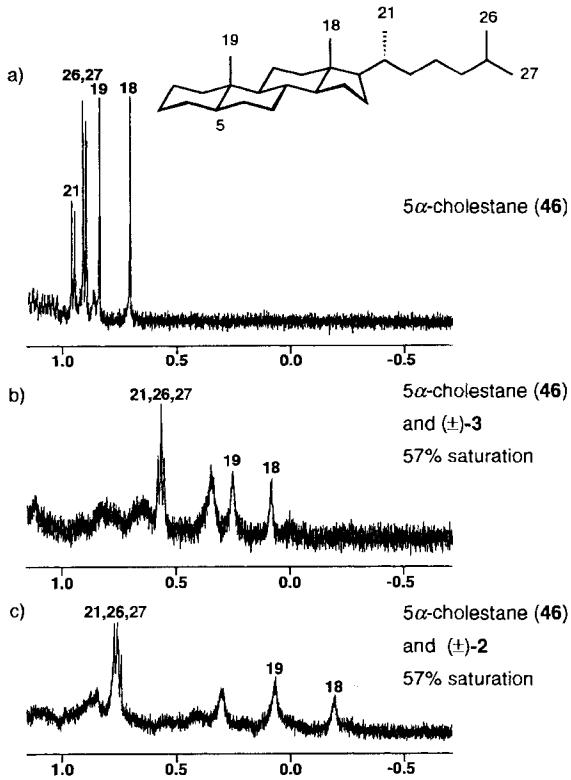


Fig. 7. *Receptor (±)-3 showing significantly greater side-chain encapsulation of 5α-cholestane* (**46**) *than receptor (±)-2*. The ^{1}H-NMR spectral regions (500 MHz) display the resonances of the Me groups on the side chain (Me(21), Me(26), Me(27)), the C–D ring junction (Me(18)), and the A-B ring junction (Me(19)). *a*) Free 5α-cholestane (**46**) at 0.25 mM. *b*) Receptor (±)-**3** (0.625 mM) and 5α-cholestane (0.25 mM), 57% degree of complexation. *c*) Receptor (±)-**2** (1.75 mM) and 5α-cholestane (0.25 mM), 57% degree of complexation. The stronger-binding receptor (±)-**3** induces the largest upfield shifts of the resonances of the side-chain Me groups, whereas the weaker-binding (±)-**2** induces larger upfield shifts of the Me resonances at the steroid nucleus.

0.2 kcal mol^{-1}) of receptor (±)-**2** for cholesteryl acetate (**43**) over the more hydrophobic 5-cholestene (**44**).

vi) Both receptors (±)-**2** and (±)-**3** are specific for aliphatic steroids. Flat aromatic hormones, such as β-estradiol (**51**) are even more weakly bound by the wider receptor (±)-**3** ($\Delta G^\circ = -3.0$ kcal mol^{-1}) than by (±)-**2** ($\Delta G^\circ = -3.5$ kcal mol^{-1}). Also, bile acids form weak complexes with (±)-**2**, presumably due to the less favorable *cis*-configuration of their A-B rings. Chenodeoxycholic acid (**53**) undergoes a particularly weak association since its OH group at C(7) will become desolvated upon incorporation into the hydrophobic receptor cavity. Unfavorable functional-group desolvation [24] upon incorporation into the host cavity might also be at the origin of the weak complexation of cortisone (**47**) and hydrocortisone (**48**) by (±)-**2**.

2.2.4. *Geometry of Receptor (±)-4 and ^{1}H-NMR Spectroscopic Investigations into Its Steroid-Binding Selectivity in CD_3OD.* Receptor (±)-**4** differs from the cylindrical

analogs (±)-**2** and (±)-**3** by its conical shape. Computer simulations showed that the cavity of (±)-**4** is *ca.* 11 Å deep with a wider rim opening of *ca.* 11 Å × 9.5 Å (distances between the centers of cofacial naphthalene and Ph rings, resp.) and a narrower rim opening of *ca.* 10 Å × 8 Å (distances between the centers of cofacial Ph rings). Receptor (±)-**4** had initially been conceived for selective complexation of aromatic steroids such as β-estradiol (**51**). It is composed of a larger cyclophane component capable of including alicyclic steroidal rings and a smaller one expected to preferentially encapsulate flat aromatic rings. The smaller macrocycle belongs to the family of [6.1.6.1]paracyclophanes which are well-known for their high affinity for flat benzene and naphthalene derivatives [19][36][55] as well as for being too narrow for encapsulation of alicyclic substrates of the size of cyclohexane rings. Thus, the flat aromatic A ring of β-estradiol was expected to bind within the cavity of the smaller macrocycle in (±)-**4** while the more spacious C and D rings of the hormone would be encapsulated by the larger cyclophane moiety. Aliphatic steroids, on the other hand, were expected to associate only weakly with (±)-**4** since the smaller [6.1.6.1]paracyclophane component would prevent a complete incorporation of their tetracyclic skeleton inside the binding cavity. ^{1}H-NMR binding studies, however, provided quite different results.

The stability of the complexes formed between (±)-**4** and cholesterol (**1**), testosterone (**41**), progesterone (**42**), and β-estradiol (**51**) was determined by ^{1}H-NMR binding titrations as described in *Sect. 2.2.3. Job* plots suggested 1:1 stoichiometry of the four complexes in the considered concentration ranges. In the titrations with testosterone and β-estradiol, only the shift of the Me(18) resonance could be followed, whereas in the titrations with cholesterol and progesterone, additional resonances (a total of 5 for **1** and 2 of **42**) could be monitored and evaluated, which led to the proposals of preferred host-guest binding geometries shown in *Fig. 8*. The resonance of Me(19) of both testosterone and progesterone could not be followed during the titrations due to strong broadening, presumably due to differences in the chemical shift of this resonance in the formed diastereoisomeric complexes.

The following conclusions were drawn from the NMR titration data (*Table 3*):

i) Receptor (±)-**4** does not preferentially bind aromatic steroids; on the contrary, β-estradiol (**51**) shows the weakest binding affinity among the four steroids considered.

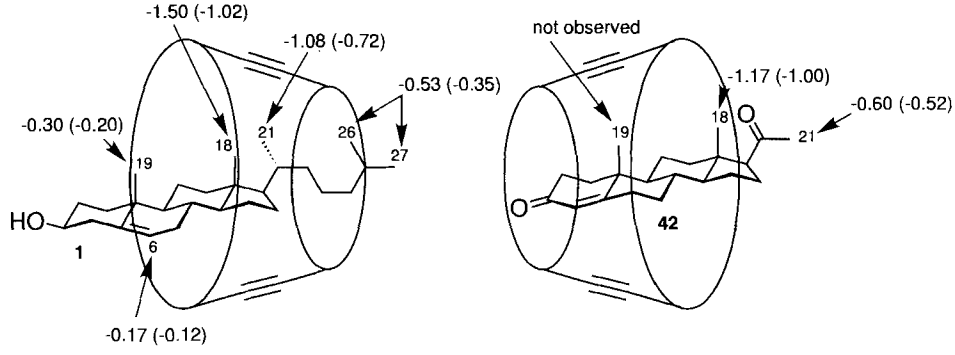


Fig. 8. *Schematic representations of the preferred binding modes of cholesterol* (**1**) (left) *and progesterone* (**42**) (right), *based on the depicted complexation-induced changes in chemical shift at saturation binding* ($\Delta\delta_{max}$) *and the maximum observed shift* ($\Delta\delta_{max\ obs}$; shown in parentheses)

Table 3. *Association Constants* K_a [l mol^{-1}] *and Complexation Free Enthalpies* ΔG° [kcal mol^{-1}] *for 1:1 Steroid Complexes of Receptor* (±)-**4** *in* CD_3OD (298 K). Also shown are the calculated and, in parenthesis, the maximum observed complexation-induced upfield shifts, $\Delta\delta_{sat}$ and $\Delta\delta_{max\ obs}$, of the steroidal Me(18) resonance which was evaluated during the titrations as well as the maximum solubilities of the steroids in MeOH.

Steroid	K_a [l mol^{-1}]	ΔG°[a]) [kcal mol^{-1}]	$\Delta\delta_{sat}$ ($\Delta\delta_{max\ obs}$) Me(18)	Maximum Solubility in MeOH [mM]
Cholesterol (**1**)	600	−3.8	−1.50 (−1.02)[b])	14.5–18.3
Testosterone (**41**)	1100	−4.1	−0.72 (−0.53)	450–770
Progesterone (**42**)	2600	−4.6	−1.17 (−1.00)[b])	220
β-Estradiol (**51**)	400	−3.6	−1.84 (−1.47)	102–119

[a]) Uncertainties in ΔG°: ± 0.1 kcal mol^{-1}. The resonances in the two possible diastereoisomeric complexes between racemic receptor and enantiomerically pure steroid were not resolved, and the association constants give an average value for both complexes. [b]) Additional resonances were evaluated; the K_a and ΔG° values reported are averages from those calculated from the changes in chemical shift of several steroidal resonances; see *Fig. 8*.

Computer modeling actually showed that the bridging with the larger cyclophane widens the cavity of the smaller [6.1.6.1]paracyclophane moiety in (±)-**4** substantially, thus reducing its selectivity for inclusion of flat aromatic rings. The observed binding selectivity is clearly dictated by steric host-guest complementarity and not simply by differences in solubility of the free steroid. There exists no correlation between steroid solubility and host-guest association strength; thus testosterone (**41**) binds by 0.5 kcal mol^{-1} more strongly than β-estradiol (**51**), although it is *ca.* five times more soluble in MeOH.

ii) The two steroids **41** and **42** with a flat cyclohexenone moiety as A ring exhibit the strongest binding. We propose that they penetrate the cavity from the side of the wider rim and orient their flat A ring into the narrower section of the binding site of (±)-**4** which is shaped by the smaller [6.1.6.1]paracyclophane moiety (*Fig. 8*). Examinations of CPK and computer models of the receptor clearly show that this part of the macrotricyclic cavity is suitable for incorporation of a cyclohexenone ring.

iii) Cholesterol (**1**) penetrates the binding cavity with its hydrophobic side chain from the wider rim. This way, the side chain, with a large computed hydrophobic *van der Waals* surface of 132 Å^2 occupies the cavity section shaped by the smaller [6.1.6.1]-paracyclophane while the A ring (108 Å^2 hydrophobic *van der Waals* surface) protrudes with its OH group at C(3) into the solvent on the wider cavity side. Such a geometry is strongly supported by the small upfield shift of the ^{1}H-NMR signal of Me(19) at the A-B ring junction and by the large upfield shifts of the Me(18) resonance at the C-D ring junction and of all three Me groups (Me(21), Me(26), Me(27)) of the steroidal side chain (*Fig. 8*). This geometry was also greatly favored by MacroModel simulations (1000-step MC search of conformational space, AMBER* force field, GB/SA water solvation model). The experimentally supported inclusion geometry schematically shown in *Fig. 8* was found to be preferred by 8 kcal mol^{-1} over the alternative one, in which the A ring penetrates the binding site of (±)-**4** from the wider rim to occupy the cavity of the smaller cyclophane moiety, while the steroidal side chain is sticking into the solvent.

3. Conclusions. – Efficient artificial receptors for steroid recognition in aqueous or methanolic solution were prepared by synthetic sequences in which key C–C bond forming reactions were accomplished by Pd^0-catalyzed cross-coupling reactions such as the *Stille* and *Hiyama* coupling. This modern synthetic methodology increasingly provides versatile access to the construction of complex functional molecular architecture for applications at the interfaces of chemistry to both biology and materials sciences [63].

The comprehensive binding studies with the three receptors (±)-**2**, (±)-**3**, and (±)-**4** nicely complement the X-ray investigations on biological steroid complexes in enhancing the understanding of the principles governing selective molecular recognition of steroids. With their highly preorganized, betwen 11- and 13-Å deep apolar cavities, they can fully include all four rings, A, B, C, and D, of steroidal substrates. Thus, these novel double-decker cyclophane receptors resemble most closely some of the deep apolar pockets found in steroid-binding antibodies, proteins, and enzymes. In particular, the comparative studies between the cylindrical receptors (±)-**2** and (±)-**3** clearly revealed the different binding characteristics of fully aliphatic and flatter, partially unsaturated steroids. Cholesterol (**1**) and derivatives with a C(5)=C(6) bond prefer being incorporated into the shallower cavity of (±)-**2**, whereas fully aliphatic derivatives such as 5α-cholestane prefer complexation in the deeper and wider cavity of (±)-**3**. These experimental steroid-binding selectivities could be nicely reproduced in computer simulations.

Unprecedented information on the contributions from the complexation of the isoprenoidal side chain of the steroidal substrates to the overall stability of the formed inclusion complexes was obtained. Thus, 5α-cholestane (**46**) with such a side chain is bound by $\Delta(\Delta G^\circ) = 1.2$ kcal mol^{-1} more strongly by receptor (±)-**3** in CD_3OD than 5α-androstane (**49**) without such side chain. Large complexation-induced upfield shifts of the side-chain Me-group resonances in the ^{1}H-NMR spectra of solutions of (±)-**3** and **46** provided strong evidence for the efficient incorporation of at least parts of the steroidal side chain into the shielding receptor cavity. Similarly, ^{1}H-NMR data revealed that the conical receptor (±)-**4** prefers incorporation of the steroidal side chain of cholesterol into the narrowing section of its cavity, whereas its A ring protrudes into the solvent. These structural data illustrate a distinct advantage of cyclophane receptors over cyclodextrins: As a result of the anisotropic effects of the aromatic cavity walls on the chemical shifts of protons in bound steroids, molecular-recognition studies with cyclophane receptors provide extensive information on the geometries of the inclusion complexes formed. In contrast, cyclodextrin receptors without aromatic rings affect the chemical shifts of protons in bound substrates only weakly and structural information, therefore, is limited.

Receptors (±)-**2** and (±)-**3** are the first fully synthetic receptors capable of efficient solubilization of cholesterol in H_2O, a property previously reserved to cyclodextrins and derivatives. The development of highly specific, tight-binding steroid receptors could provide new strategies for interfering with biologically important steroids *in vivo* and potentially lead to a new class of pharmacological agents. Receptors specific for cholesterol may offer an alternative pharmacological strategy for the dissolution of cholesterol deposits such as those in atherosclerotic plaque. Many of the pharmacological objectives such as steroid solubilization, enhanced steroid transport and delivery, and steroidal drug stabilization, which had previously been exclusively targeted with cyclodextrins, might be approached in the future with tailor-made synthetic receptors, which are tunable in their

properties by design and molecular construction. Furthermore, developments in steroid analytics, sensorics, and separations should benefit from the enhanced insight into steroid molecular-recognition principles provided by studies with artificial receptors such as those described in this paper.

Experimental Part

General. Reagents and solvents were reagent-grade commercials and were used without further purification. THF and Et_2O were freshly distilled from sodium benzophenone ketyl; CH_2Cl_2 was distilled over CaH_2. Evaporation *in vacuo* was done at H_2O aspirator pressure; if not indicated otherwise, drying of solids and viscous oils was done at 5×10^{-5} Torr/r.t. Column chromatography (CC) and flash chromatography (FC): SiO_2 *60* (230–400 mesh, 0.040–0.063 mm) from *E. Merck* and *Fluka*. TLC: plastic sheets pre-coated with SiO_2-*G* UV_{254} from *Macherey-Nagel* and glass-backed SiO_2-*60* F_{254} from *Merck* and *Fluka*, visualization by UV light. M.p.: *Büchi Smp-20*; uncorrected. IR Spectra (cm^{-1}): *Perkin-Elmer 1600-FT IR*. NMR Spectra: *Bruker AMX 500* or *AMX 400*, and *Varian Gemini 300* or *200* at 296 or 300 K, with Me_4Si or solvent peaks as reference. MS (%, *m/z*): EI: *VG TRIBRID* spectrometer at 70 eV; FAB: *VG ZAB2-SEQ* spectrometer with 3-nitrobenzyl alcohol (NOBA) as matrix; MALDI-TOF: *Bruker REFLEX* spectrometer with 2-(4-hydroxyphenylazo)benzoic acid (HABA) or sinapic acid as matrix, positive-ion mode; ESI: *Finnigan TSQ 7000* spectrometer; 10^{-5} M sample conc. in MeCN or MeOH, 25 µl/min flow, nebulizer gas N_2, polarity + 4.5 kV, capillary temp. 473 K, gas pressure 50 psi. Elemental analyses were performed by the *Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich*. Compounds were named either with the computer program *Beilstein Autonom 1.1* or by *Chemical Abstracts Service*, 2540 Olentangy River Road, P. O. Box 3103, Columbus, OH 43210, USA.

Computer Modeling. For the simulations of (±)-**2** and (±)-**3** and their macrotricyclic precursors, Version 4.0 of MacroModel [29] was used, whereas Versions 5.0 and 5.5 were applied in the simulations of receptor (±)-**4** and related compounds as well as of model compound **35**, which were prepared at a later stage. For the simulations of (±)-**3** and its precursor (±)-**15**, the AMBER* force field in MacroModel V. 4.0 was modified to include buta-1,3-diyne (–C≡C–C≡C–) parameters. For this purpose, an X-ray crystal structure of 1,4-diphenylbuta-1,3-diyne [64] provided values for bond lengths and angles, whereas stretching and bending force constants were adapted from AMBER*-supplied $C(sp^2)$–C≡C–(sp^2) parameters. To estimate the energetic difference between the possible diastereoisomeric macrotricyclic structures in the syntheses of (±)-**2**, (±)-**3**, and (±)-**4**, molecular dynamics (MD) simulations were performed. Equilibration of the two structures for 500 ps (AMBER* force field [30], 300 K, GB/SA solvation model for $CHCl_3$ [31]) was followed by minimization of the lowest-potential-energy structures obtained, and repeated 200-ps simulations on low-energy minimized structures were carried out, until convergence of total energies was reached. To determine the surface of **35**, which is buried by dimerization in the X-ray crystal structure, the solvent-accessible surface area (solvent radius 1.4 Å) [54] of the dimer was compared to the corresponding area of both molecules separated using MacroModel V. 5.5.

Optical Resolutions by Anal. HPLC. The resolution of (±)-**16** was conducted by Dr. *C. Welch* at *Regis Technologies Inc.*, 8210 Austin Ave., P.O. Box 519, Morton Grove, IL 60053, USA. The stationary phase was a *S,S-Whelk-O1* column (24 × 0.4 cm) with CH_2Cl_2/MeOH 20:1 as the eluent. The flow rate was 1 ml min^{-1} with UV detection at 254 nm. By on-line polarimetric detection, it was shown that the (–)-enantiomer was eluted first (retention time t_R = 8.12 min), followed by the (+)-enantiomer (t_R = 10.25 min) (*J. Brice*, research group of Prof. *W. H. Pirkle* at the *University of Illinois*, Urbana-Champaign, in conjunction with *Regis Technologies Inc.*). The enantiomers of (±)-**25** were separated at the *ETH* also on the (*S,S*)-*Whelk-O1* column using the conditions described above. The faster eluting enantiomer had t_R = 5.24 min, the other t_R = 5.95.

Critical Aggregation Concentration (CAC) of the Receptors in D_2O. The CAC of (±)-**2** and (±)-**3** was determined by the absence of significant changes in ^{1}H-NMR chemical shift upon diluting a D_2O soln. from 2.0 mM ((±)-**2**) or 1.7 mM ((±)-**3**) to 0.5 mM at 295 K. For more details, see [56].

Determination of Steroidal Solubilities in CD_3OD. Solid steroid in excess of its maximum solubility was sonicated for 10 min in MeOH. The sat. soln. was equilibrated by standing for 1 h in a thermostat and centrifuged. The supernatant was filtered, diluted, and the concentration of steroid was determined by UV/VIS on a *Varian Cary-5* spectrophotometer at λ = 210 nm (**1**), 309 nm (**41**), 310 nm (**42**), and 298 nm (**51**). The molar extinction coefficients at these wavelengths were determined from solns. of known concentrations.

Solid-Liquid Extractions to Determine Binding Free Enthalpies in Aq. Soln. Solns. of (±)-**2** or (±)-**3** (1–2 mM) in H_2O were sonicated for 45 min in the presence of excess of solid steroid and allowed to equilibrate at 295 K for 2 h. Centrifugation of the suspension was followed by filtration of the supernatant liquid through a 0.45 µm

cellulose acetate filter. Removal of H_2O under reduced pressure was followed by addition of CD_3OD, which allowed determination of percent steroid extracted by ^{1}H-NMR integration. For the calculation of K_a, see [56]. The association constants are average values of two diastereoisomeric complexes which are of similar stability, and data shown in *Table 1* are averaged over triplicate runs. The reproducibility of the ΔG° values was $\pm$ 0.4 kcal mol^{-1}. The solubilization of progesterone by (±)-**2** was not studied.

^{1}H-NMR Binding Titrations in CD_3OD. Association constants were determined by nonlinear least-squares curve fitting of 500-MHz ^{1}H-NMR titration data (298 K) using the program Associate V. 1.6 [65]. In these titrations, the steroid concentration was held constant (usually 0.25 mM) and the receptor concentration varied (usually between 0.2 mM and 2 mM) to provide between 10 and 90% of saturation binding. The complexation-induced change in chemical shift of the steroidal Me(18) resonance was monitored and evaluated in all titrations with (±)-**2** and (±)-**3**, and additional steroidal resonances were followed in titrations with (±)-**4**. Association constants shown are an average value for the two diastereoisomeric complexes that form between the racemic receptor and the enantiomerically pure steroidal substrates. This approximation is justified by the absence of any significant differential complexation-induced shifts for the resonances of the diastereoisomeric complexes, indicating similar complex geometries and stabilities. Only one set of resonances is observed for host and guest during the titrations. Reproducibility of K_a values: ± 10%.

1′,1″,1‴,1⁗-Tetraacetyl-25,26,51,52-tetradehydro-6,7,8,9,42,43,44,45-octahydro-4,22,29,47-tetramethoxytetraspiro[19H,32H-23,2:28,49-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:27,31:33,37:36,40-hexamethenodibenzo[g,k][1,6,13,18]tetraoxacyclooctatetracontin-19,4′:32,4″:53,4‴:86,4⁗-tetrapiperidine] ((±)-**7**). *Method A from* **5**: A soln. of **5** (2.00 g, 1.91 mmol), bis(tributylstannyl)acetylene (1.152 g, 1.91 mmol), 2,6-di(*tert*-butyl)-*p*-cresol (70 mg, 0.32 mmol), and [Pd(PPh$_3$)$_4$] (440 mg, 0.381 mmol) in DMF (200 ml) was deoxygenated with Ar, sealed in a medium-pressure bottle, and heated to 110° for 2 d. After cooling, 2M HF · pyridine (10 ml) was added and the mixture stirred at r.t. for 16 h. Addition of CH_2Cl_2 (400 ml) and conc. aq. NH_3 was followed by separation of the org. layer, washing with sat. aq. NaCl soln. (200 ml), and drying (Na_2SO_4). Evaporation of CH_2Cl_2 *in vacuo* and addition of Et_2O/pentane 1:1 to the residual DMF soln. led to the precipitation of crude product. Plug filtration (SiO_2 (25 g), CH_2Cl_2/MeOH 20:1) followed by FC (SiO_2 (100 g), CH_2Cl_2/MeOH 100:3) provided (±)-**7** (244 mg, 14%).

Method B from **6**: In a flame-dried *Schlenk* flask under N_2 a mixture of **6** (2.18 g, 1.91 mmol), bis(tributylstannyl)acetylene (1.0 ml, 1.15 g, 1.91 mmol), [Pd(PPh$_3$)$_4$] (0.131 g, 0.113 mmol, 6 mol%), and 2,6-di(*tert*-butyl)-*p*-cresol (70 mg, 0.32 mmol) in DMF (200 ml) was degassed by freeze-pump-thaw cycles and subsequently heated to 90° for 2 d. Workup as described for *Method A* yielded (±)-**7** (210 mg, 12%). White powder. M.p. 160–162° (dec.; Et_2O/CH_2Cl_2 20:1). IR (KBr): 3433*m*, 2926*s*, 2867*s*, 1717*w*, 1646*s*, 1600*s*, 1572*s*, 1448*s*, 1260*s*, 1217*s*, 1167*m*, 1150*m*, 1117*m*, 1094*m*, 1028*m*, 989*m*, 950*w*, 844*w*, 806*m*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 400 K): 1.90–2.06 (br. *m*, 16 H); 1.98 (*s*, 12 H); 2.32–2.52 (2 br. *m*, 16 H); 3.38–3.77 (3 br. *m*, 16 H); 3.79 (*s*, 12 H); 4.07–4.18 (2 br. *m*, 16 H); 6.87–6.89 (*m*, 4 H); 6.89 (*dd*, *J* = 8.9, 2.5, 4 H); 7.03 (br. *s*, 8 H); 7.05 (*dd*, *J* = 8.8, 2.1, 4 H); 7.32 (*d*, *J* = 8.8, 4 H); 7.42 (*d*, *J* = 9.2, 4 H); 7.47 (br. *s*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$, 300 K): 21.36, 25.78; 26.20; 36.85 (2×); 38.49; 43.50; 44.68; 56.10; 67.20; 72.53; 89.93; 106.16; 111.97; 118.02; 119.13; 124.13; 125.69 (2×); 127.16; 128.38; 129.43; 132.60; 141.00; 141.77; 147.41; 152.49; 156.91; 168.79 (set of peaks for one conformer). HR-FAB-MS: 1825.9070 (MH^+; calc. for $^{13}C^{12}C_{115}H_{121}N_4O_{16}^+$: 1825.8777).

25,26,51,52-Tetradehydro-1′,1″,1‴,1⁗-tetraethyl-6,7,8,9,42,43,44,45-octahydro-4,22,29,47-tetramethoxytetraspiro[19H,32H-23,2:28,49-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:27,31:33,37:36,40-hexamethenodibenzo[g,k][1,6,13,18]tetraoxacyclooctatetracontin-19,4′:32,4″:53,4‴:86,4⁗-tetrapiperidine] ((±)-**9**). $LiAlH_4$ (1M in Et_2O, 10 ml, 10 mmol) was added to (±)-**7** (204 mg, 0.112 mmol) under Ar, and the white suspension was stirred for 16 h at r.t. For workup, MeOH (10 ml) was carefully added, followed by CH_2Cl_2 (100 ml), and the mixture was extracted with 1M aq. NaOH soln. (3 × 100 ml) and sat. aq. NaCl soln. (100 ml). Evaporation *in vacuo* afforded a white solid which was purified by FC (SiO_2 (75 g), CH_2Cl_2/NEt_3 20:1) to give (±)-**9** (116 mg, 59%). White powder. M.p. 239–241° (dec.; hexane/CH_2Cl_2 10:1). ^{1}H-NMR (500 MHz, $CDCl_3$; for numbering, see *Scheme 1*): 1.08 (*t*, *J* = 7.1, 4 *Me*CH_2N); 1.94–2.18 (3 br. *m*, 4 CH_2CH_2); 2.38 (*q*, *J* = 7.1, 4 MeCH_2N); 2.41–2.75 (3 br. *m*, 8 ArAr′CCH_2CH_2N); 3.78 (*s*, 4 MeO); 4.05–4.07 (*m*, 4 PhOCH_2); 4.16 (*t*, *J* = 6.6, 4 NaphOCH_2); 6.85 (*s*, 4 H–C(3′)); 6.87 (*s*, 4 H–C(5′)); 6.92 (*s*, 4 H–C(5)); 6.96–6.98 (*m*, 4 H–C(3), 4 H–C(7)); 7.27 (br. *s*, 4 H–C(4)); 7.35 (*d*, *J* = 8.2, 4 H–C(8)); 7.45 (*s*, 4 H–C(1)). ^{13}C-NMR (125 MHz, $CDCl_3$, 300 K): 12.26; 25.64; 26.30; 35.74; 36.47; 44.52; 50.15; 50.25; 52.44; 56.12; 67.11; 72.39; 90.04; 106.15; 112.24; 119.01; 120.31; 124.38; 124.65; 126.25; 126.98; 127.91; 129.48; 132.49; 142.74 (2×); 147.01; 152.30; 156.81. HR-FAB-MS: 1769.9758 (MH^+; calc. for $^{13}C^{12}C_{115}H_{129}N_4O_{12}^+$: 1769.9606).

25,26,51,52-Tetradehydro-1′,1′,1″,1″,1‴,1‴,1⁗,1⁗-octaethyl-6,7,8,9,42,43,44,45-octahydro-4,22,29,47-tetramethoxytetraspiro[19H,32H-23,2:28,49-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:27,31:

33,37:36,40-hexamethenodibenzo[g,k][1,6,13,18]tetraoxacyclooctatetracontin-19,4':32,4'':53,4''':86,4''''-tetrapiperidinium] Tetrachloride ((±)-**2**). A soln. of (±)-**9** (50 mg, 0.028 mmol) in dry $CHCl_3$ (15 ml) was washed with 1M aq. NaOH soln. (15 ml) and dried (Na_2SO_4). Freshly distilled EtI (15 ml) was added and the mixture stirred in the dark under Ar at r.t. for 4 d. Evaporation *in vacuo* provided a white powder which was eluted through an ion-exchange column (*Dowex* Cl^-, $MeOH/H_2O$ 1:1). Recrystallization (Et_2O/MeOH 50:1) and drying (1 Torr, 75°) provided (±)-**2** (44.5 mg, 78%). Hygroscopic white solid. M.p. 250–252° (dec.). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 400 K): 1.22–1.33 (*m*, 24 H); 1.92–2.05 (2*m*, 16 H); 2.55–2.91 (3 br. *m*, 16 H); 3.13–3.52 (5 br. *m*, 32 H); 3.88 (*s*, 12 H); 4.08–4.14 (2*m*, 16 H); 6.86–6.88 (*m*, 8 H); 7.06 (br. *s*, 4 H); 7.14 (br. *s*, 4 H); 7.21 (br. *s*, 4 H); 7.39–7.48 (*m*, 8 H); 7.49–7.63 (*m*, 4 H). ^{13}C-NMR (125 MHz, CD_3OD, 300 K): 7.27; 7.51; 7.83; 7.90; 26.90; 27.67; 29.82; 30.72; 44.61; 52.78; 56.85; 59.04; 68.68; 74.05; 91.16; 107.44; 112.88; 119.51; 120.44; 124.32; 125.24; 126.09; 129.01; 130.16; 130.75; 134.61; 141.68 (2×); 148.95; 154.51; 158.58. MALDI-TOF-MS (sinapic acid): 2029 (M^+; calc. for $^{13}C^{12}C_{123}H_{148}{}^{37}Cl_2{}^{35}Cl_2N_4O_{12}$: 2029). Anal. calc. for $C_{124}H_{148}Cl_4N_4O_{12} \cdot 8\,H_2O$ (2172.52): C 68.56, H 7.61, N 2.58; found: C 68.65, H 7.72, N 2.90.

1-Acetyl-4-{2-[6-(4-chlorobutoxy)]naphthyl}-4-(3-iodo-4-hydroxy-5-methoxyphenyl)piperidine (**11**). To a soln. of **10** (82.0 g, 170 mmol) in CH_2Cl_2 (2000 ml) was added at 0° NEt_3 (30 ml, 21.78 g, 215 mmol) under N_2. After slow addition of a soln. of ICl (29.5 g, 170 mmol) in CH_2Cl_2 (200 ml), the dark mixture was stirred for 3.5 h at 0° and then quenched by addition of conc. AcOH (17.5 ml), sat. aq. $Na_2S_2O_3$ soln. (600 ml), and H_2O (1000 ml). The separated aq. layer was extracted with AcOEt (2 × 1000 ml), the combined org. layers were washed with sat. aq. NaCl soln. (2 × 1200 ml), dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to give, after recrystallization (CH_2Cl_2 (100 ml)), pure **11**. The mother liquor was chromatographed (SiO_2 (600 g), CH_2Cl_2/MeOH 20:1) and recrystallized (CH_2Cl_2), adding to a combined yield of 66.4 g (64%). Off-white powder. M.p. 186–188°. IR (KBr): 3456*w*, 2922*m*, 2867*m*, 1611*s*, 1561*m*, 1456*s*, 1400*s*, 1350*m*, 1267*s*, 1033*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.00–2.04 (*m*, 4 H); 2.10 (*s*, 3 H); 2.35–2.49 (2 br. *m*, 4 H); 3.50–3.78 (3 br. *m*, 4 H); 3.64 (*t*, *J* = 6.2, 2 H); 3.75 (*s*, 3 H); 4.11 (*t*, *J* = 5.7, 2 H); 5.99 (*s*, 1 H); 6.63 (*d*, *J* = 2.3, 1 H); 7.08 (*d*, *J* = 2.3, 1 H); 7.15 (*dd*, *J* = 8.9, 2.3, 1 H); 7.22 (*d*, *J* = 2.3, 1 H); 7.22 (*dd*, *J* = 8.8, 1.9, 1 H); 7.64 (*d*, *J* = 8.8, 1 H); 7.65 (*s*, 1 H); 7.71 (*d*, *J* = 8.9, 1 H). EI-MS: 607.1 (100, M^+). Anal. calc. for $C_{28}H_{31}ClINO_4$ (607.92): C 55.32, H 5.14, N 2.30; found: C 55.61, H 5.28, N 2.28.

1,1''-Diacetyl-18,37'-diiodo-40',44'-dimethoxydispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo[34.2.2.2^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaene-21',4''-piperidine] (**6**). To a stirred suspension of Cs_2CO_3 (32.5 g, 99.7 mmol) in MeCN (2600 ml) was added **11** (12.0 g, 19.7 mmol), and the mixture was heated to reflux under N_2 for 3 d. The inorg. salts were removed by filtration, washed with CH_2Cl_2 (2 × 100 ml), and the soln. was evaporated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (700 ml), and the resulting soln. was washed with 50% sat. aq. NaCl soln. (2 × 500 ml), dried (Na_2SO_4), and evaporated *in vacuo*. CC (SiO_2, CH_2Cl_2/MeOH 35:1) and recrystallization (CH_2Cl_2/EtOH 1:1) afforded **6** (5.38 g, 48%). White powder. M.p. 257°. IR (KBr): 2933*m*, 2878*w*, 1643*s*, 1602*m*, 1446*m*, 1267*s*, 1217*m*, 1173*m*, 1027*s*, 952*m*, 852*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.00–2.03 (*m*, 8 H); 2.09 (*s*, 6 H); 2.29–2.47 (2 br. *m*, 8 H); 3.48–3.96 (3 br. *m*, 8 H); 3.56 (*s*, 6 H); 3.90–3.96 (*m*, 4 H); 4.19 (*t*, *J* = 6.4, 4 H); 6.53 (*d*, *J* = 2.3, 2 H); 7.01 (*d*, *J* = 2.3, 2 H); 7.09 (*dd*, *J* = 8.7, 2.1, 2 H); 7.10 (*dd*, *J* = 8.9, 2.5, 2 H); 7.22 (*d*, *J* = 2.1, 2 H); 7.52 (*d*, *J* = 8.9, 2 H); 7.63 (*s*, 2 H); 7.63 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.98; 24.98; 25.14; 35.10; 35.99; 38.09; 43.07; 44.03; 55.45; 66.34; 71.39; 92.44; 105.87; 111.90; 119.07; 124.06; 125.68; 127.07; 128.12; 128.88; 132.50; 139.58; 144.76; 145.99; 151.83; 156.88; 168.47. FAB-MS: 1142.9 (100, MH^+). Anal. calc. for $C_{56}H_{60}I_2N_2O_8$ (1142.92): C 58.85, H 5.29, N 2.45, I 22.21; found: C 58.82, H 5.45, N 2.60, I 22.03.

1,1''-Diethyl-18,37'-diiodo-40',44'-dimethoxydispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo[34.2.2.2^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaene-21',4''-piperidine] (**12**). To a soln. of **6** (1.00 g, 0.875 mmol) in dry CH_2Cl_2 (100 ml) at 0° was slowly added under Ar DIBAL-H (20 ml, 1M in CH_2Cl_2) *via* syringe, and the mixture was stirred at 0° for 1 h. After careful addition of MeOH (25 ml), followed by 1M aq. NaOH soln. (100 ml), the org. layer was separated, washed with sat. aq. NaCl soln. (100 ml), dried (Na_2SO_4), and evaporated *in vacuo* to yield a white crude product. Plug filtration (SiO_2 (100 g), CH_2Cl_2/NEt_3 20:1) afforded **12** (800 mg, 82%). White powder. M.p. 265° (dec.; hexane/CH_2Cl_2 20:1). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.06 (*t*, *J* = 7.2, 6 H); 2.00–2.04 (*m*, 4 H); 2.09–2.12 (*m*, 4 H); 2.34 (*q*, *J* = 7.2, 4 H); 2.44 2.62 (3 br. *m*, 16 H); 3.56 (*s*, 6 H); 3.95 (*t*, *J* = 6.2, 4 H); 4.19 (*t*, *J* = 6.2, 4 H); 6.57 (*d*, *J* = 2.2, 2 H); 7.02 (*d*, *J* = 2.2, 2 H); 7.09 (*dd*, *J* = 8.8, 2.3, 2 H); 7.11 (*dd*, *J* = 8.6, 1.8, 2 H); 7.26 (*d*, *J* = 2.3, 2 H); 7.52 (*d*, *J* = 8.6, 2 H); 7.64 (*d*, *J* = 8.8, 2 H); 7.65 (*s*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.24; 25.27; 25.50; 36.17; 44.36; 50.15; 52.39; 55.75; 66.69; 71.61; 92.62; 106.27; 112.54; 119.14; 124.88; 126.59; 127.00; 128.52; 128.99; 129.28; 132.67; 141.32; 145.88; 146.38; 151.95; 157.05. HR-FAB-MS: 1115.3289 (MH^+; calc. for $^{12}C_{56}H_{65}I_2N_2O_6^+$: 1115.2936).

1,1''-Diethyl-18',37'-dimethoxy-40',44',bis[(trimethylsilyl)ethynyl]dispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo[34.2.2.2^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaene-21',4''-piperidine] (**13**). A medium-pressure bottle was charged with **12** (1.225 g, 1.099 mmol), $[PdCl_2(PPh_3)_2]$ (0.397 g, 0.566 mmol), and $NHEt_2$ (150 ml). The suspension was thoroughly deoxygenated by bubbling Ar through, then $Me_3SiC{\equiv}CH$ (1.111 g, 11.3 mmol) and CuI (cat. amount) were added. After a subsequent brief deoxygenation (Ar), the vessel was sealed and heated to 100° for 18 h. After cooling to ambient temp., the yellow soln. was decanted from the formed solid salts and filtered. The salts were dissolved in CH_2Cl_2 (20 ml), then re-precipitated with Et_2O (100 ml). The Et_2O soln. was filtered, the filtrate combined with the yellow $NHEt_2$ soln., and the solvent was evaporated *in vacuo*. FC (SiO_2 (75 g), hexane/CH_2Cl_2/NEt_3 50:50:5) provided **13** (1.07 g, 92%). White powder. M.p. 248–250° (hexane/CH_2Cl_2 100:1). IR (CCl_4): 2956*s*, 2815*m*, 2154*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.27 (*s*, 18 H); 1.06 (*t*, *J* = 7.2, 6 H); 1.91–1.96 (*m*, 4 H); 2.05–2.10 (*m*, 4 H); 2.34 (*q*, *J* = 7.2, 4 H); 2.48–2.56 (br. *m*, 16 H); 3.58 (*s*, 6 H); 4.09 (*t*, *J* = 6.3, 4 H); 4.13 (*t*, *J* = 6.6, 4 H); 6.59 (*d*, *J* = 2.2, 2 H); 6.99 (*d*, *J* = 2.2, 2 H); 7.03 (*d*, *J* = 2.4, 2 H); 7.07 (*dd*, *J* = 9.0, 2.4, 2 H); 7.10 (*dd*, *J* = 8.8, 1.8, 2 H); 7.48 (*d*, *J* = 8.8, 2 H); 7.64 (*d*, *J* = 9.0, 2 H); 7.66 (*d*, *J* = 1.8, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −0.02; 12.23; 25.42; 25.78; 36.01; 44.29; 50.16; 52.36; 55.88; 66.92; 72.16; 97.76; 101.94; 106.10, 113.38; 117.14; 119.06; 123.69; 124.31; 126.64; 126.88; 128.47; 129.22; 132.58; 142.15; 143.46; 147.75; 152.25; 156.91. HR-FAB-MS: 1055.6146 (MH^+; calc. for $^{12}C_{66}H_{83}N_2O_6Si_2^+$: 1055.5789).

1,1''-Diethyl-18',37'-diethynyl-40',44'-dimethoxydispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo[34.2.2.2^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaene-21',4''-piperidine] (**14**). A mixture of **13** (960 mg, 0.909 mmol) and K_2CO_3 (250 mg, 1.809 mmol) in THF/MeOH 1:1 (150 ml) was stirred for 3 h at 20° under Ar. After evaporation *in vacuo*, FC (SiO_2 (75 g), hexane/CH_2Cl_2/NEt_3 50:50:5) provided **14** (0.780 g, 94%) which, for anal. purposes, was recrystallized from hexane/CH_2Cl_2 10:1. White powder. M.p. 258–260°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.05 (*t*, *J* = 7.2, 6 H); 1.93–1.97 (*m*, 4 H); 2.05–2.09 (*m*, 4 H); 2.33 (*q*, *J* = 7.2, 4 H); 2.46–2.60 (3 br. *m*, 16 H); 3.07 (*s*, 2 H); 3.63 (*s*, 6 H); 4.07 (*t*, *J* = 6.2, 4 H); 4.14 (*t*, *J* = 6.7, 4 H); 6.70 (*d*, *J* = 2.0, 2 H); 6.89 (*d*, *J* = 2.0, 2 H); 6.98 (*d*, *J* = 2.5, 2 H); 7.06 (*dd*, *J* = 9.0, 2.5, 2 H); 7.11 (*dd*, *J* = 8.7, 1.7, 2 H); 7.49 (*d*, *J* = 8.7, 2 H); 7.63 (*d*, *J* = 9.0, 2 H); 7.65 (*d*, *J* = 1.7, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.23; 25.34; 25.70; 36.12; 44.43; 50.17; 52.40; 55.85; 66.95; 72.37; 80.53; 80.58; 106.27; 112.97; 116.22; 119.06; 124.22; 124.77; 126.64; 126.99; 128.53; 129.29; 132.66; 141.56; 144.15; 147.85; 152.29; 157.00. FAB-MS: 911.3 (MH^+). Anal. calc. for $C_{60}H_{66}N_2O_6$ (911.20): C 79.09, H 7.30, N 3.07; found: C 78.86, H 7.48, N 2.93.

25,26,27,28,53,54,55,56-Octadehydro-1,1'1'',1'''-tetraethyl-6,7,8,9,44,45,46,47-octahydro-4,22,31,49-tetramethoxytetraspiro[19H,34H-23,2:30,51-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:29,33:35,39:38,42-hexamethenoidibenzo[g,m][1,6,15,20]tetraoxacyclodopentacontin-19,4':34,4'':57,4''':90,4''''-tetrakispiperidine] ((±)-**15**). A dark-green mixture of **14** (0.700 g, 0.768 mmol), CuCl (1.52 g, 0.0154 mol), and TMEDA (1.785 g, 0.0154 mol) in dry CH_2Cl_2 (500 ml) was stirred at r.t. for 16 h in dry air. After addition of conc. aq. NH_4OH soln. (300 ml) and phase separation, the org. layer was washed with H_2O (200 ml), sat. aq. NaCl soln. (200 ml), dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. FC (SiO_2 (75 g), CH_2Cl_2/NEt_3 20:1) afforded (±)-**15** (0.291 g, 42%). White powder. M.p. 270° (dec.; hexane/CH_2Cl_2 20:1). ^{1}H-NMR (500 MHz, $CDCl_3$; for numbering, see *Scheme 2*): 0.98 (*t*, *J* = 7.1, 4 *Me*CH_2N); 1.96–2.55 (5 br. *m*, 56 H, CH_2CH_2, MeCH_2N, ArAr'CCH_2CH_2N); 3.73 (*s*, 4 MeO); 4.10–4.46 (3 br. *m*, 16 H, PhOCH_2, NaphOCH_2); 6.74 (*s*, 4 H–C(5')); 6.79 (br. *s*, 4 H–C(3'), 4 H–C(3)); 7.15 (*dd*, *J* = 8.9, 2.3, 4 H–C(7)); 7.24 (br. *s*, 4 H–C(5)); 7.57 (*d*, *J* = 8.7, 4 H–C(4)); 7.67 (*s*, 4 H–C(1)); 7.69 (br. *s*, 4 H–C(8)). ^{13}C-NMR (125 MHz, $CDCl_3$, 300 K): 12.08; 25.10; 25.35; 35.16; 36.88; 44.76; 49.76; 49.96; 52.22; 55.84; 66.21; 72.19; 77.32; 79.16; 106.03; 112.95; 115.77; 119.12; 124.07; 126.48; 126.91; 127.55; 128.39; 129.26; 132.61; 142.79; 143.41; 148.49; 152.39; 157.23. HR-FAB-MS: 1818.0666 (MH^+; calc. for $^{13}C^{12}C_{119}H_{129}N_4O_{12}^+$: 1817.9606).

25,26,27,28,53,54,55,56-Octadehydro-1,1,1',1'1'',1'',1''',1'''-octaethyl-6,7,8,9,44,45,46,47-octahydro-4,22,31,49-tetramethoxytetraspiro[19H,34H-23,2:30,51-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:29,33:35,39:38,42-hexamethenodibenzo[g,m][1,6,15,20]tetraoxacyclodopentacontin-19,4':34,4'':57,4''':90,4''''-tetrakispiperidinium] Tetrachloride ((±)-**3**). A soln. of (±)-**15** (250 mg, 0.137 mmol) in dry $CHCl_3$ (50 ml) was washed with 1M aq. NaOH soln. (50 ml) and dried (Na_2SO_4). Freshly distilled EtI (50 ml) was then added, and the mixture was stirred in the dark under Ar at r.t. for 4 d. Evaporation *in vacuo* provided a white powder which was eluted through an ion-exchange column (*Dowex* Cl^-, MeOH/H_2O 1:1). Recrystallization from Et_2O/MeOH 50:1 and drying (1 Torr, 75°) afforded (±)-**3** (250 mg, 88%). M.p. 260° (dec.). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 400 K): 1.19–1.27 (br. *m*, 24 H); 1.89–1.99 (2 br. *m*, 16 H); 2.60–2.89 (3 br. *m*, 16 H); 3.07–3.48 (4 br. *m*, 32 H); 3.80–3.87 (br. *m*, 12 H); 4.08–4.24 (4*m*, 16 H); 6.81–6.86 (*m*, 4 H); 7.05–7.14 (br. *m*, 12 H); 7.19 (br. *s*, 4 H); 7.51–7.60 (*m*, 4 H); 7.62–7.78 (br. *m*, 8 H). MALDI-TOF-MS (HABA): 2076 (M^+; calc. for

$^{13}C^{12}C_{127}H_{148}{}^{37}Cl_2{}^{35}Cl_2N_4$: 2075). Anal. calc. for $C_{128}H_{148}Cl_4N_4O_{12} \cdot 7\,H_2O$ (2202.55): C 69.74, H 7.50, N 2.54; found: C 69.89, H 7.81, N 2.91.

1,1',1'',1'''-Tetraacetyl-25,26,27,28,53,54,55,56-octadehydro-6,7,8,9,44,45,46,47-octahydro-4,22,31,49-tetramethoxytetraspiro[19H,34H-23,2':30,51-bis(epoxybutanoxy[2,6]naphthalenomethano)-11,15:14,18:20,24:29,33:35,39:38,42-hexamethenodibenzo[g,m][1,6,15,20]tetraoxacyclodopentacontin-19,4'':34,4''':57,4'''':90,4''''-tetrakispiperidine] ((±)-**16**). A medium-pressure bottle was charged with **6** (2.00 g, 1.75 mmol), $[PdCl_2(PPh_3)_2]$ (0.246 g, 0.350 mmol), and $NHEt_2$ (100 ml). The suspension was thoroughly deoxygenated by bubbling Ar through, then $Me_3SiC{\equiv}CH$ (0.430 g, 4.38 mmol) and CuI (cat.) were added. After a subsequent brief deoxygenation, the vessel was sealed and heated to 100° for 18 h. After cooling to r.t., the yellow soln. was decanted from formed solid salts and filtered. The salts were dissolved in CH_2Cl_2 (10 ml), then re-precipitated with Et_2O (100 ml). The Et_2O soln. was filtered, the filtrate combined with the yellow $NHEt_2$ soln., and the solvent was removed *in vacuo*. Plug filtration (SiO_2 (25 g), $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 50:1) afforded **17** (1.855 g) as a gold-colored crude product to which were added K_2CO_3 (200 mg, 1.45 mmol), THF (100 ml), and MeOH (100 ml). After stirring at r.t. for 3.5 h, the mixture was evaporated *in vacuo*, CH_2Cl_2 (100 ml) and H_2O (100 ml) were added, and the separated org. layer was washed with sat. aq. NaCl soln. (100 ml) and dried (Na_2SO_4). Evaporation provided **18** as a brownish crude product which was dried thoroughly *in vacuo*, then vigorously stirred together with dry CH_2Cl_2 (1.5 l), dry acetone (1.5 l), CuCl (3.052 g, 0.031 mol), and TMEDA (1.785 g, 0.0154 mol) at r.t. in dry air for 16 h. After addition of conc. aq. NH_4OH soln. (500 ml), the separated org. layer was washed with H_2O (500 ml), then sat. aq. NaCl soln. (500 ml), dried (Na_2SO_4), and evaporated *in vacuo*. FC (SiO_2 (100 g), CH_2Cl_2/MeOH 25:1) followed by recrystallization (hexane/CH_2Cl_2 20:1) afforded (±)-**16** (0.315 g, 19% over three steps). White powder. M.p. 270° (dec.). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 375 K): 1.80–2.06 (3 br. *m*, 16 H); 1.89 (*s*, 12 H); 2.33–3.65 (8*m*, 32 H); 3.78 (*s*, 12 H); 4.07–4.28 (3*m*, 16 H); 6.80 (*s*, 4 H); 7.04–7.06 (*m*, 8 H); 7.15 (*d*, *J* = 9.2, 4 H); 7.21 (br. *s*, 4 H); 7.57 (*d*, *J* = 8.5, 4 H); 7.65 (*s*, 4 H); 7.76 (*d*, *J* = 9.2, 4 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$, 400 K): 20.14; 24.86; 25.24; 33.70; 35.51; 43.91 (2×); 56.03; 66.98; 72.35; 76.14; 78.91; 106.73; 114.31; 114.59; 118.31; 123.37; 124.62; 125.45; 126.34; 127.91; 128.82; 131.97; 141.52; 141.60; 148.15; 151.91; 156.28; 167.35; a ^{13}C-NMR spectrum in $CDCl_3$ indicated that one signal (36.04 ppm) was obscured by the Me_2SO peak. HR-FAB-MS: 1873.9881 (MH^+; calc. for $^{13}C^{12}C_{119}H_{121}N_4O_{16}^+$: 1873.8777).

1-Acetyl-4-hydroxy-4-(4-methoxyphenyl)piperidine (**20**). A soln. of 4-bromoanisol (2.20 ml, 3.28 g, 0.018 mol) in THF (40 ml) and a catal. amount of I_2 were added to Mg (8.6 g, 0.354 mol), and the mixture was heated to reflux under N_2. After the formation of the *Grignard* reagent had started, 4-bromoanisol (42.1 ml, 62.9 g, 0.336 mol) in THF (800 ml) was slowly added while reflux was maintained, and stirring was continued for 1 h at r.t. The mixture was cooled to 0°, and a soln. of 1-acetylpiperidin-4-one (50.0 g, 0.354 mol) in THF (370 ml) was added. After stirring for 2 h at r.t., the mixture was quenched with sat. aq. NH_4Cl soln. (500 ml) in an ice bath and stirred overnight. Evaporation *in vacuo* afforded a yellow solid which was filtered, washed with H_2O and Et_2O, and dried (60°, 100 mbar) to provide **20** (49.3 g, 56%). M.p. 127–129° (i-PrOH). IR (KBr): 3398*m*, 2948*w*, 1896*w*, 1616*s*, 1513*m*, 1460*m*, 1357*m*, 1305*m*, 1276*m*, 1212*m*, 1174*m*, 1027*m*, 995*m*, 830*m*, 626*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.74–1.99 (*m*, 4 H); 2.11 (*s*, 3 H); 3.09 (*dt*, *J* = 12.8, 2.9, 1 H); 3.52–3.78 (*m*, 2 H); 3.80 (*s*, 3 H); 4.52 (*dm*, *J* = 13.2, 1 H); 6.89 (*dm*, *J* = 8.9, 2 H); 7.38 (*dm*, *J* = 8.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.40; 37.78; 37.80; 38.89; 42.81; 55.28; 70.77; 113.71; 125.71; 140.07; 158.69; 168.90. EI-MS: 249 (10, M^+), 231 (100, $[M - H_2O]^+$). Anal. calc. for $C_{14}H_{19}NO_3$ (249.31): C 67.45, H 7.68, N 5.62, O 19.25; found: C 67.22, H 7.60, N 5.61, O 19.39.

1-Acetyl-4-(4-hydroxyphenyl)-3,4-dehydropiperidine (**21**). To a soln. of **20** (12.96 g, 52 mmol) in CH_2Cl_2 (500 ml) was carefully (!) added BBr_3 (25 ml, 65 g, 260 mmol) under N_2. The brownish-orange suspension was heated to reflux for 3 h, then cooled to 0°, and quenched by addition of MeOH (100 ml). After evaporation *in vacuo*, the remaining brown solid was washed with H_2O (2 × 50 ml) and Et_2O (2 × 50 ml), then dried to yield **21** (11.18 g, 98%). Light-brown solid. M.p. 186–188° (EtOH). IR (KBr): 3200*s*, 2933*m*, 2867*m*, 1889*w*, 1617*s*, 1511*s*, 1450*s*, 1433*s*, 1356*m*, 1261*m*, 1222*s*, 1178*m*, 972*m*, 839*m*, 800*s*, 733*s*. ^{1}H-NMR (200 MHz, CD_3OD): 2.11, 2.15 (2*s*, 3 H); 2.45–2.49, 2.53–2.57 (2*m*, 2 H); 3.69, 3.75 (2*t*, *J* = 5.9, 2 H); 4.12–4.16 (*m*, 2 H); 5.93, 5.94 (2*t*, *J* = 3.5, 1 H); 6.74 (*dm*, *J* = 8.7, 2 H); 7.24 (*dm*, *J* = 8.7, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 21.16, 21.57; 26.37, 27.13; 37.50, 41.33; 42.66, 44.98; 115.0; 117.59, 118.11; 125.68, 125.70; 130.61, 130.66; 133.97, 134.33; 156.61, 156.64; 168.17, 168.33 (2 conformers). EI-MS: 217 (100, M^+), 174 (65, $[M - MeCO]^+$). Anal. calc. for $C_{13}H_{15}NO_2$ (217.27): C 71.87, H 6.96, N 6.45, O 14.73; found: C 71.62, H 7.05, N 6.43, O 14.49.

1-Acetyl-4-[4-(4-chlorobutoxy)phenyl]-3,4-dehydropiperidine (**22**). A suspension of **21** (35.5 g, 0.164 mol), K_2CO_3 (113.3 g, 0.820 mol), and 1,4-dichlorobutane (207.5 g, 1.64 mol) in MeCN (700 ml) was heated to reflux for 28 h. The mixture was filtered, the isolated solid was washed with EtOH (3 × 100 ml), and the combined filtrates were concentrated. The product was precipitated by addition of ice-cold hexane (420 ml), filtered, washed

with Et_2O (2 × 175 ml) and dried to yield **22** (32.7 g, 74%). Anal. pure material was obtained by CC (SiO_2, CH_2Cl_2/MeOH 19:1) followed by recrystallization (EtOH). White solid. M.p. 86–87°. IR (KBr): 2924*w*, 2869*w*, 1618*s*, 1513*s*, 1438*s*, 1362*w*, 1278*m*, 1234*s*, 1183*m*, 1134*w*, 1052*w*, 972*w*, 839*m*, 804*m*, 656*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.91–2.01 (*m*, 4 H); 2.14, 2.16 (2*s*, 3 H); 2.51–2.57 (*m*, 2 H); 3.62 (*t*, *J* = 6.2, 2 H); 3.65, 3.81 (2*t*, *J* = 5.6, 2 H); 4.00 (*t*, *J* = 5.6, 2 H); 4.11, 4.21 (2*d*, *J* = 2.8, 2 H); 5.90–5.94, 5.96–6.00 (2*m*, 1 H); 6.86 (*d*, *J* = 8.6, 2 H); 7.30 (2*dm*, *J* = 8.6, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.47, 21.87; 26.66; 27.14, 27.96; 29.32; 38.35; 42.15, 43.42; 44.73, 45.82; 67.04; 114.39; 117.63, 119.38; 126.01, 126.04; 132.85, 132.93; 134.21, 136.11; 158.34, 158.44; 169.24, 169.42 (2 conformers). EI-MS: 307 (100, M^+), 264 (39, $[M - Me]^+$). Anal. calc. for $C_{17}H_{22}ClNO_2$ (307.82): C 66.33, H 7.20, N 4.55, O 10.40, Cl 11.52; found: C 66.36, H 7.49, N 4.51, O 10.55, Cl 11.78.

1-Acetyl-4-[4-(4-chlorobutoxy)phenyl]-4-(4-hydroxy-3-methoxyphenyl)piperidine (**23**). To a soln. of **22** (6.03 g, 19.59 mmol) in CH_2Cl_2 (60 ml) under Ar was slowly added $BF_3 \cdot OEt_2$ (17.2 ml, 19.5 g, 137.12 mmol), then guaiacol (14.59 g, 117.54 mmol), and the mixture was stirred for 9 d at r.t. After addition of MeOH (30 ml), the mixture was poured into H_2O (250 ml), and the product was extracted with AcOEt (2 × 300 ml). Drying ($MgSO_4$) of the org. layer and evaporation *in vacuo* was followed by distillation to remove excess guaiacol (0.1 Torr, 100°). CC (SiO_2 (350 g), CH_2Cl_2/MeOH 19:1, then SiO_2 (700 g), CH_2Cl_2/Et_2O 1:1) and recrystallization (EtOH) gave **23** (5.24 g, 68%). White solid. M.p. 158–159°. IR (KBr): 3044*m*, 2944*s*, 2855*m*, 2789*m*, 1611*s*, 1589*s*, 1517*s*, 1440*s*, 1375*m*, 1245*s*, 1181*s*, 1133*s*, 1037*s*, 1002*m*, 971*m*, 942*m*, 839*m*, 776*w*, 638*w*, 597*w*, 550*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.90–2.00 (*m*, 4 H); 2.08 (*s*, 3 H); 2.28–2.35 (*m*, 4 H); 3.60 (*t*, *J* = 6.3, 2 H); 3.45–3.53, 3.63–3.72 (2*m*, 4 H); 3.80 (*s*, 3 H); 3.96 (*t*, *J* = 5.8, 2 H); 5.65 (*s*, 1 H); 6.66 (*d*, *J* = 2.2, 1 H); 6.72 (*dd*, *J* = 8.3, 2.2, 1 H); 6.81 (*dm*, *J* = 8.9, 2 H); 6.83 (*d*, *J* = 8.3, 1 H); 7.13 (*dm*, *J* = 8.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.43; 26.68; 29.34; 36.17; 37.12; 38.67; 43.66; 44.21; 44.73; 55.92; 66.92; 109.73; 114.23; 114.43; 119.71; 127.97; 138.58; 138.70; 143.92; 146.59; 157.03; 168.89. EI-MS: 431 (M^+). Anal. calc. for $C_{24}H_{30}ClNO_4$ (431.96): C66.73, H 7.00, N 3.24, O 14.82, Cl 8.21; found: C 66.64, H 7.11, N 3.22, O 14.60, Cl 8.21.

1-Acetyl-4-[4-(4-chlorobutoxy)phenyl]-4-(4-hydroxy-5-iodo-3-methoxyphenyl)piperidine (**24**). A soln. of **23** (4.0 g, 9.26 mmol) and NEt_3 (1.54 ml, 1.12 g, 11.11 mmol) in CH_2Cl_2 (100 ml) was cooled to 0° under N_2. After dropwise addition of ICl (1.29 g, 10.19 mmol) in CH_2Cl_2 (20 ml), the mixture was stirred for 2 h and subsequently conc. AcOH (1 ml), sat. aq. $Na_2S_2O_3$ soln. (20 ml), and H_2O (50 ml) were added. The aq. layer was extracted with AcOEt (250 ml), and the combined org. layers were washed with sat. aq. NaCl soln. (2 × 100 ml), dried ($MgSO_4$), and evaporated *in vacuo*. CC (SiO_2 (200 g), CH_2Cl_2/Et_2O 1:1) followed by recrystallization (EtOH) provided pure **24** (3.26 g, 63%). White solid. M.p. 166° (dec.). IR (KBr): 3420*w*, 2926*m*, 2867*m*, 1617*m*, 1569*m*, 1513*m*, 1461*m*, 1406*s*, 1350*m*, 1240*s*, 1190*s*, 1144*m*, 1043*s*, 993*m*, 843*m*, 794*m*, 652*m*, 600*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.90–2.02 (*m*, 4 H); 2.08 (*s*, 3 H); 2.19–2.28, 2.31–2.38 (2*m*, 4 H); 3.41–3.46, 3.50–3.55, 3.73–3.76 (3*m*, 4 H); 3.61 (*t*, *J* = 6.3, 2 H); 3.78 (*s*, 3 H); 3.97 (*t*, *J* = 5.9, 2 H); 6.04 (*s*, 1 H); 6.59 (*d*, *J* = 2.1, 1 H); 6.83 (*dm*, *J* = 8.9, 2 H); 7.12 (*dm*, *J* = 8.9, 2 H); 7.15 (*d*, *J* = 2.1, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.41; 26.67; 29.32; 36.06; 36.98; 38.54; 43.54; 44.04; 44.74; 56.21; 66.95; 81.47; 109.99; 114.58; 127.98; 128.61; 137.61; 140.82; 144.08; 146.02; 157.19; 168.91. EI-MS: 557 (M^+). Anal. calc. for $C_{24}H_{29}ClINO_4$ (557.86): C 51.67, H 5.24, N 2.51, O 11.47, Cl 6.36, I 22.75; found: C 51.47, H 5.29, N 2.50, O 11.51, Cl 6.22, I 22.54.

1,1''-Diacetyl-5',20'-iodo-33',37'-dimethoxydispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**19**). A suspension of **24** (5.00 g, 8.96 mmol) and Cs_2CO_3 (14.6 g, 44.82 mmol) in MeCN (1875 ml) and *p*-xylene (250 ml) was heated to reflux for 3 d. After cooling to r.t. and filtration, the filtrate was concentrated to yield a residue which was dissolved in CH_2Cl_2 and was washed with H_2O and sat. aq. NaCl soln. CC (SiO_2 (100 g), CH_2Cl_2/MeOH 20:1, then SiO_2 (250 g), CH_2Cl_2/MeOH 30:1) afforded **19** (2.03 g, 43%). White solid. M.p. 291° (dec.; EtOH/CH_2Cl_2 1:1). IR (KBr): 2953*m*, 1649*s*, 1608*m*, 1514*s*, 1471*s*, 1394*m*, 1258*s*, 1187*s*, 1140*w*, 1072*w*, 1027*m*, 990*m*, 973*m*, 812*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.99–2.03 (*m*, 8 H); 2.07 (*s*, 6 H); 2.16–2.24, 2.30–2.41 (2*m*, 8 H); 3.58 (*s*, 6 H); 3.36–3.40, 3.53–3.56, 3.86–3.98 (3*m*, 12 H); 4.08 (*t*, *J* = 6.1, 4 H); 6.52 (*d*, *J* = 2.1, 2 H); 6.83 (*dm*, *J* = 8.8, 4 H); 7.09 (*dm*, *J* = 8.8, 4 H); 7.13 (*d*, *J* = 2.1, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.41; 25.39; 25.74; 35.71; 36.62; 38.50; 43.50; 44.01; 55.88; 66.96; 72.05; 92.86; 112.11; 114.99; 127.92; 128.50; 136.70; 145.52; 146.39; 152.18; 157.44; 168.85. FAB-MS: 1043 (100, MH^+). Anal. calc. for $C_{48}H_{56}I_2N_2O_8$ (1042.79): C 55.29, H 5.41, N 2.69, O 12.27, I 24.34; found: C 55.15, H 5.35, N 2.66, O 12.56, I 24.37.

1,1''-Diacetyl-18,37'-dimethoxy-40',44'-bis[(trimethylsilyl)ethynyl]dispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo[34.2.2.2.^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaen-21',4''-piperidine] (**17**). To a suspension of **6** (400 mg, 0.35 mmol) and $[PdCl_2(PPh_3)_2]$ (97 mg, 0.138 mmol) in $NHEt_2$ (50 ml), which was thoroughly deoxygenated by freeze-pump-thaw cycles, $Me_3SiC{\equiv}CH$ (0.5 ml, 3.5 mmol) and CuI (10 mg, 0.053 mmol) were added and, after another deoxygenating cycle,

the mixture was heated to reflux for 14 h. The residue obtained by evaporation *in vacuo* was dissolved in CH_2Cl_2, washed with 1M aq. HCl soln. and sat. aq. NaCl soln., and dried (Na_2SO_4). CC (SiO_2, THF/CH_2Cl_2 1:5) followed by precipitation from CH_2Cl_2/hexane yielded **17** (270 mg, 71%). Yellowish solid. M.p. 282–286° (dec.) (Et_2O). IR (KBr): 3422*w*, 2954*m*, 2152*w*, 1631*s*, 1455*s*, 1263*s*, 1087*s*, 845*s*, 759*m*, 474*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.26 (*s*, 18 H); 1.90–1.98 (*m*, 4 H); 2.05 (*t*, *J* = 6.6, 4 H); 2.08 (*s*, 6 H); 2.31–2.48 (*m*, 8 H); 3.50–3.68, 3.72–3.79 (2*m*, 8 H); 3.56 (*s*, 6 H); 4.02–4.09 (*m*, 4 H); 4.13 (*t*, *J* = 6.6, 4 H); 6.53 (*d*, *J* = 2.2, 2 H); 6.98 (*d*, *J* = 2.4, 2 H); 6.99 (*d*, *J* = 2.2, 2 H); 7.07 (*m*, 4 H); 7.49 (*d*, *J* = 8.7, 2 H); 7.62 (*s*, 2 H); 7.63 (*d*, *J* = 8.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 0.00; 21.38; 25.47; 25.82; 35.54; 36.44; 38.63; 43.60; 44.53; 55.99; 66.97; 72.29; 98.36; 101.62; 106.16; 113.17; 117.49; 119.46; 123.18; 124.11; 126.26; 127.37; 128.48; 129.26; 132.88; 140.82; 142.32; 148.26; 152.60; 157.22; 168.94. FAB-MS: 1083 (100, *M*H$^+$). Anal. calc. for $C_{66}H_{78}N_2O_8Si_2 \cdot H_2O$ (1101.53): C 71.97, H 7.32, N 2.54; found: C 72.16, H 7.15, N 2.51.

1,1''-Diacetyl-18,37'-diethynyl-40',44'-dimethoxydispiro[piperidine-4,2'-[11,16,30,35]tetraoxaheptacyclo-[34.2.2^{17,20}.1^{3,7}.1^{6,10}.1^{22,26}.1^{25,29}]hexatetraconta[3,5,7(46),8,10(45),17,19,22,24,26(42),27,29(41),36,38,39,43]hexadecaen-21',4''-piperidine] (**18**). To a soln. of **17** (500 mg, 0.461 mmol) in THF/MeOH 1:1 (50 ml) was added K_2CO_3 (637 mg, 4.61 mmol), and the resulting suspension was stirred for 3 h at r.t. and subsequently concentrated. The residue was suspended in CH_2Cl_2 (50 ml) and washed with H_2O (40 ml). The org. layer was dried (Na_2SO_4), and the solvent was evaporated. Recrystallization (CH_2Cl_2/Et_2O) gave pure **18** (385 mg, 90%). White powder. M.p. 194° (dec.). IR (KBr): 3439*m*, 3284*m*, 2938*m*, 2103*w*, 1640*s*, 1603*s*, 1574*m*, 1452*s*, 1265*s*, 1172*m*, 1080*m*, 995*m*, 956*m*, 852*m*, 681*w*, 475*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.92–1.96, 2.05–2.12 (2*m*, 8 H); 2.07 (*s*, 6 H); 2.30–2.38, 2.42–2.49 (2*m*, 8 H); 3.11 (*s*, 2 H); 3.45–3.60, 3.82–3.88 (2*m*, 8 H); 3.62 (*s*, 6 H); 4.02–4.09 (*m*, 4 H); 4.14 (*t*, *J* = 6.5, 4 H); 6.63 (*d*, *J* = 2.1, 2 H); 6.89 (*d*, *J* = 2.1, 2 H); 6.98 (*d*, *J* = 2.1, 2 H); 7.09–7.12 (*m*, 4 H); 7.50 (*d*, *J* = 8.8, 2 H); 7.62 (*s*, 2 H); 7.62 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.40; 25.40; 25.73; 35.55; 36.50; 38.57; 43.57; 44.60; 55.95; 66.97; 72.50; 80.29; 80.98; 106.27; 112.78; 116.57; 119.42; 123.75; 124.44; 126.18; 127.44; 128.52; 129.30; 132.92; 140.25; 142.92; 148.32; 152.58; 157.26; 168.88. FAB-MS: 939 (100, *M*H$^+$). Anal. calc. for $C_{60}H_{62}N_2O_8 \cdot 2\,H_2O$ (975.19): C 73.90, H 6.82, N 2.87; found: C 73.94, H 6.76, N 2.84.

1',1'',1''',1''''-Tetraacetyl-25,26,47,48-tetradehydro-6,7,8,9,32,33,34,35-octahydro-4,22,30,44-tetramethoxytetraspiro[19H,41H-45,28-(epoxybutanoxy[1,4]benzenomethano)-23,2-(epoxybutanoxy[2,6]naphthalenomethano)-37,40-etheno-11,15:14,18:20,24:42,46-tetramethenodibenzo[g,a$_1$][1,6,21,26]tetraoxacyclotetratetracontin-19,4':41,4'':62,4''':80,4''''-tetrakispiperidine] ((±)-**25**). To a degassed soln. of **17** (100 mg, 0.0923 mmol), **19** (96 mg, 0.0923 mmol), and [Pd(PPh$_3$)$_4$] (9 mg, 0.0078 mmol, 8 mol%) in abs. THF (200 ml) in flame-dried glassware was added TAS-F (141 mg, 0.462 mmol) under N_2 at −78°. The mixture was slowly warmed to r.t. (2–3 h) and was then heated to reflux for 24 h. After cooling to r.t., 1M aq. Na_2CO_3 soln. (20 ml) was added and, after stirring for several min, H_2O (100 ml) was added, and the product was extracted with CH_2Cl_2 (200 ml). The org. layer was washed with sat. aq. NaCl soln. (100 ml), dried (Na_2SO_4), and concentrated. CC (SiO_2, CH_2Cl_2/MeOH 30:1) gave (±)-**25** (32.3 mg, 20%). M.p. 259° (dec.; CH_2Cl_2/Et_2O/hexane). IR (KBr): 3446*w*, 2946*s*, 2867*m*, 1647*s*, 1606*s*, 1576*s*, 1511*s*, 1449*s*, 1355*m*, 1256*s*, 1184*s*, 1123*m*, 1033*m*, 993*m*, 950*m*, 850*w*, 806*w*, 475*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 400 K): 1.80–2.65 (br. *m*, 32 H); 1.99 (*s*, 6 H); 2.02 (*s*, 6 H); 3.20–3.95 (br. *m*, 16 H); 3.73 (*s*, 6 H); 3.85–3.92, 4.08–4.16, 4.17–4.25, 4.25–4.32 (4*m*, 16 H); 3.88 (*s*, 6 H); 6.40–6.48 (*m*, 4 H); 6.75–6.77 (*m*, 4 H); 6.80 (br. *s*, 2 H); 6.85 (br. *s*, 2 H); 6.90 (br. *s*, 2 H); 6.91–6.97 (*m*, 2 H); 7.17 (br. *s*, 6 H); 7.51 (br. *d*, *J* = 8.5, 2 H); 7.57 (br. *s*, 2 H); 7.61 (br. *d*, *J* = 8.5, 2 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 13.90; 21.29; 21.99; 24.81; 25.23; 25.37; 25.93; 26.12; 30.89; 34.14; 34.70; 35.13; 35.51; 36.15; 38.10; 43.05; 43.59; 44.68; 55.93; 56.09; 66.55; 67.51; 72.33; 72.60; 89.42; 89.65; 106.54; 112.61; 112.76; 114.02; 116.62; 117.06; 118.45; 122.04; 123.86; 126.07; 127.01 (2×); 128.09; 128.13; 128.72; 129.42 (2×); 132.40; 138.92 (2×); 141.00; 141.23; 142.42; 142.59; 146.48; 146.81; 152.16; 152.29; 156.29 (2×); 168.11. FAB-MS: 1725.6 (100, *M*H$^+$). Anal. calc. for $C_{108}H_{116}N_4O_{16} \cdot 2\,H_2O$ (1762.15): C 73.61, H 6.86, N 3.18, O 16.34; found: C 73.69, H 7.01, N 3.12, O 16.06.

25,26,47,48-Tetradehydro-1',1'',1''',1''''-tetraethyl-6,7,8,9,32,33,34,35-octahydro-4,22,30,44-tetramethoxytetraspiro[19H,41H-45,28-(epoxybutanoxy[1,4]benzenomethano)-23,2-(epoxybutanoxy[2,6]naphthalenomethano)-37,40-etheno-11,15:14,18:20,24:42,46-tetramethenodibenzo[g,a$_1$][1,6,21,26]tetraoxacyclotetratetracontin-19,4':41,4'':62,4''':80,4''''-tetrakispiperidine] ((±)-**32**). A soln. of $LiAlH_4$ (1M in Et_2O, 6.4 ml, 6.4 mmol) was added to (±)-**25** (123 mg, 0.0713 mmol) at 0°, and the resulting white suspension was stirred overnight at r.t. under N_2. Quenching of the reaction by careful addition of i-PrOH, EtOH, then MeOH was followed by addition of 1M aq. KOH soln. (75 ml) and extraction of the product with CH_2Cl_2 (100 ml). The org. layer was washed with 1M aq. KOH soln. (2 × 75 ml) and sat. aq. NaCl soln. (75 ml), then dried (Na_2SO_4), and concentrated. CC (SiO_2, CH_2Cl_2/NEt_3 20:1), followed by uptake of the product in CH_2Cl_2 (50 ml), washing with 1M aq. KOH soln.

(2 × 30 ml), and precipitation from CH_2Cl_2/Et_2O/hexane afforded (±)-**32** (78 mg, 65%) as a white powder. M.p. 208°. IR (KBr): 3440*m*, 2934*s*, 2811*m*, 2767*w*, 1604*m*, 1576*m*, 1511*m*, 1470*m*, 1381*m*, 1350*m*, 1250*s*, 1183*m*, 1006*m*, 950*w*, 848*w*, 650*w*, 550*w*. ^{1}H-NMR (500 MHz, $CDCl_3$, 313 K; for numbering, see *Scheme 4*): 1.06, 1.08 (2*t*, *J* = 7.2, 4 *Me*CH_2N); 1.80–1.95 (br. *m*, 2 C(1'')–OCH_2CH_2); 1.88–2.00, 2.04–2.14 (2*m*, 2 C(7')–OCH_2-CH_2); 1.95–2.10 (br. *m*, 2 C(1')–OCH_2CH_2); 2.03–2.13, 2.19–2.25 (2*m*, 2 C(6)–OCH_2CH_2); 2.33, 2.37 (2*q*, *J* = 7.2, 4 MeCH_2N); 2.26–2.30, 2.70–2.78 (4*m*, 8 NCH_2CH_2); 3.71 (*s*, 2 C(2'')–OMe); 3.80–3.88 (*m*, 2 C(7')–OCH_2); 3.86 (*s*, 2 C(2')–OMe); 3.89–3.95, 4.12–4.18 (2*m*, 2 C(1'')–OCH_2); 4.15–4.19, 4.24–4.28 (2*m*, 2 C(1')–OCH_2); 4.19–4.25, 4.32–4.38 (2*m*, 2 C(6)–OCH_2); 6.42 (br. *d*, *J* = 8.4, 4 H–C(8')); 6.69 (br. *s*, 2 H–C(3'')); 6.71 (br. *d*, *J* = 8.4, 4 H–C(9')); 6.86 (*d*, *J* = 2.0, 2 H–C(5')); 6.87 (br. *d*, *J* = 1.7, 2 H–C(5'')); 6.94 (br. *d*, *J* = 8.7, 2 H–C(7)); 7.01 (*d*, *J* = 2.0, 2 H–C(3')); 7.06 (*d*, *J* = 8.8, 2 H–C(3)); 7.06 (br. *s*, 2 H–C(5)); 7.45 (*d*, *J* = 8.8, 2 H–C(4)); 7.49 (*d*, *J* = 8.7, 2 H–C(8)); 7.52 (br. *s*, 2 H–C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.26; 25.43; 26.19; 26.41; 26.66; 35.51; 35.96; 36.40; 36.69; 43.64; 44.83; 50.08; 50.14; 50.29; 52.41; 52.47; 56.06; 56.36; 66.63 (2×); 68.06 (2×); 72.43; 73.14; 89.82 (2×); 90.17; 106.66; 112.31; 114.03; 117.67; 118.25; 119.02; 123.72; 124.39; 125.62; 126.40; 127.02; 127.47; 128.53; 129.51; 132.67; 142.29; 143.20; 147.03; 147.13; 152.20; 156.55; 156.85. HR-ESI-MS: 1669.9301 (MH^+; calc. for $C_{108}H_{125}N_4O_{12}$: 1669.9293).

*25,26,47,48-Tetradehydro-1',1',1'',1'',1''',1''',1'''',1''''-octaethyl-6,7,8,9,32,33,34,35-octahydro-4,22,30,44-tetramethoxytetraspiro[19*H,41H*-45,28-(epoxybutanoxy[1,4]benzenomethano)-23,2-(epoxybutanoxy[2,6]naphthalenomethano)-37,40-etheno-11,15:14,18:20,24:42,46-tetramethenodibenzo[*g,a_1*][1,6,21,26]tetraoxacyclotetratetracontin-19,4':41,4'':62,4''':80,4''''-tetrakispiperidinium] Tetrachloride* ((±)-**4**). A soln. of (±)-**32** (231 mg, 0.042 mmol) and EtI (20 ml) in $CHCl_3$ (20 ml) was stirred for 5 d at r.t. in the dark. The product obtained after concentration and drying was transformed by ion-exchange chromatography (*Dowex* Cl^- (8 g), MeOH/H_2O 1:1) and recrystallization (MeCN/acetone) into hygroscopic ((±)-**4**) (198 mg, 70%). White powder. M.p. 250–255° (dec.). IR (KBr): 3418*s*, 2933*s*, 1628*m*, 1600*m*, 1572*m*, 1505*m*, 1467*s*, 1378*m*, 1350*m*, 1260*s*, 1183*s*, 1106*s*, 1028*m*, 806*w*, 561*w*, 472*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 403 K): 1.20–1.28 (*m*, 24 H); 1.78–2.02 (*m*, 16 H); 2.52–2.88 (*m*, 16 H); 3.20–3.65 (br. *m*, 32 H); 3.77, 3.78 (2*s*, 6 H); 3.81–3.95, 4.07–4.31 (2*m*, 16 H); 3.93 (*s*, 6 H); 6.49–6.51 (*m*, 4 H); 6.78 (br. *s*, 4 H); 6.84–6.92 (br. *m*, 6 H); 6.93 (br. *s*, 2 H); 7.15 (br. *s*, 2 H); 7.22, 7.24 (2 br. *s*, 4 H); 7.55 (br. *d*, *J* = 8.4, 2 H); 7.61 (br. *d*, *J* = 8.5, 2 H); 7.66 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, CD_3OD): 7.51; 7.91; 26.70; 27.27; 27.83; 29.85; 30.99; 44.02; 44.97; 56.64; 56.93; 57.07; 57.11; 59.17; 66.82; 68.24; 69.42; 73.83; 74.49; 91.00; 107.92; 113.04; 115.99; 119.07; 119.68; 120.69; 123.0; 125.52; 126.57; 128.37; 129.15; 130.14; 130.90; 134.79; 141.7; 148.99; 154.47; 158.61; 158.92. ESI-MS: 446.5 (100, $[M - 4\,Cl^-]^{4+}$), 607.3 (53, $[M - 3\,Cl^-]^{3+}$), 928.5 (4, $[M - 2\,Cl^-]^{2+}$). Anal. calc. for $C_{116}H_{144}Cl_4N_4O_{12} \cdot 4\,H_2O \cdot 2\,HCl$ (2073.25): C 67.20, H 7.49, N 2.70, O 12.35, Cl 10.26; found: C 67.42, H 7.57, N 2.69, O 12.06, Cl 9.97.

1-Iodo-2,3-dimethoxybenzene (**28**) [66]. To a soln. of 1,2-dimethoxybenzene (9.2 ml, 10.0 g, 72 mmol) in abs. Et_2O (100 ml) in a flame-dried flask under N_2 was slowly added BuLi (50 ml, 1.6M in hexane, 79.2 mmol), and the mixture was refluxed for 5 h. After cooling to r.t., a soln. of I_2 (20.1 g, 79.2 mmol) in abs. Et_2O (200 ml) was added, and the resulting dark-brown mixture was stirred for 1 h at r.t. under N_2. The mixture was poured into sat. aq. $Na_2S_2O_3$ soln. (200 ml). The aq. layer was extracted with Et_2O (250 ml), and the combined org. layers were washed with sat. aq. $Na_2S_2O_3$ soln. (150 ml), H_2O (200 ml), and sat. aq. NaCl soln. (200 ml), and dried ($MgSO_4$). Evaporation *in vacuo* and drying yielded **28** as a brown oil (17.25 g, 90%). Anal. pure material was obtained by recrystallization from hexane. Brown crystals. M.p. 32° ([66]: 43–43.5°). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.84 (*s*, 3 H); 3.86 (*s*, 3 H); 6.76–6.93 (*m*, 2 H); 7.32–7.38 (*m*, 1 H). EI-MS: 264 (100, M^+). Anal. calc. for $C_8H_9IO_2$ (264.06): C 36.39, H 3.44; found: C 36.51, H 3.46.

[(2,3-Dimethoxyphenyl)ethynyl]trimethylsilane (**30**). To a soln. of **28** (2.0 g, 7.573 mmol) and $[PdCl_2(PPh_3)_2]$ (265 mg, 0.379 mmol, 5 mol%) in $NHEt_2$ (40 ml) in a pressure tube, which was degassed by 3 freeze-pump-thaw cycles, were added CuI (72 mg, 0.379 mmol, 5 mol%) and $Me_3SiC{\equiv}CH$ (2.08 ml, 1.49 g, 15.146 mmol), and, after another degassing cycle, the tube was sealed and the mixture heated to 90° for 6 h. After cooling to r.t., filtration through *Celite* and concentration yielded a residue which was dissolved in Et_2O (400 ml) and washed with 1M aq. HCl soln. (200 ml) and sat. aq. NaCl soln. (200 ml). Drying ($MgSO_4$), evaporation *in vacuo*, and CC (SiO_2, hexane/AcOEt 20:1) yielded **30** (1.39 g, 78%). Distillation (bulb-to-bulb) gave anal. pure material as a colorless oil. B.p. 100–105°/0.4 Torr. IR (neat): 2959*m*, 2836*w*, 2151*m*, 1574*m*, 1470*s*, 1425*s*, 1307*m*, 1268*s*, 1171*m*, 1081*s*, 1007*m*, 940*m*, 844*s*, 787*m*, 759*m*, 716*m*, 638*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.26 (*s*, 9 H); 3.84 (*s*, 3 H); 3.94 (*s*, 3 H); 6.87 (*dd*, *J* = 8.1, 1.7, 1 H); 6.94 (*dd*, *J* = 8.1, 7.8, 1 H); 7.01 (*dd*, *J* = 7.8, 1.7, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −0.09; 56.03; 60.76; 98.75; 101.01; 113.23; 117.77; 123.64; 125.45; 150.95; 152.65. EI-MS: 234 (100, M^+). Anal. calc. for $C_{13}H_{18}O_2Si$ (234.37): C 66.62, H 7.74; found: C 66.36, H 7.68.

1-Ethynyl-2,3-dimethoxybenzene (**31**). A suspension of K_2CO_3 (590 mg, 4.27 mmol) and **30** (200 mg, 0.853 mmol) in MeOH/THF 1:1 (2 ml) was stirred for 4 h at r.t. After evaporation *in vacuo*, the residue was

suspended in hexane and filtered, and evaporation of the filtrate, followed by drying, yielded pure **31** (128 mg, 92%). Colorless oil. IR (neat): 3286*s*, 2935*s*, 2837*m*, 2572*w*, 2105*w*, 1980*w*, 1574*s*, 1468*s*, 1305*s*, 1266*s*, 1175*s*, 1072*s*, 1004*s*, 911*m*, 787*m*, 746*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.27 (*s*, 1 H); 3.87 (*s*, 3 H); 3.95 (*s*, 3 H); 6.92 (*dd*, *J* = 8.0, 1.9, 1 H); 7.00 (*dd*, *J* = 8.0, 7.7, 1 H); 7.06 (*dd*, *J* = 7.7, 1.9, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 55.99; 61.03; 79.84; 81.14; 113.49; 116.84; 123.86; 125.57; 151.11; 152.72. EI-MS: 162 (100, M^+), 147 (31, $[M - CH_3]^+$). Anal. calc. for $C_{10}H_{10}O_2$ (162.19): C 74.06, H 6.21; found: C 73.92, H 6.18.

Tributyl[(2,3-dimethoxyphenyl)ethynyl]stannane (**29**). To a soln. of **31** (100 mg, 0.616 mmol) in CH_2Cl_2 (1.5 ml) were added molecular sieves (4 Å) and $(Bu_3Sn)_2O$ (164 µl, 191 mg, 0.308 mmol), and the mixture was stirred for 3 h under N_2. Filtration, evaporation *in vacuo*, and drying yielded **29** (225 mg, 81%) as a colorless oil. CC (SiO_2, hexane/AcOEt 4:1) provided anal. pure material. IR ($CHCl_3$): 3007*w*, 2958*s*, 2931*s*, 2872*m*, 2853*m*, 2127*w*, 1594*w*, 1573*m*, 1468*s*, 1425*m*, 1377*w*, 1306*w*, 1266*s*, 1170*w*, 1078*s*, 1004*m*, 926*w*, 692*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.1, 9 H); 1.06 (*t*, *J* = 7.9, 6 H); 1.30–1.48, 1.55–1.68 (2*m*, 12 H); 3.83 (*s*, 3 H); 3.93 (*s*, 3 H); 6.83 (*dd*, *J* = 7.9, 2.0, 1 H); 6.94 (*dd*, *J* = 7.9, 7.6, 1 H); 7.02 (*dd*, *J* = 7.6, 2.0, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 10.94; 13.41; 26.71; 28.64; 55.70; 60.38; 97.88; 105.26; 112.18; 118.41; 123.29; 125.37; 150.38; 152.38. EI-MS: 452 (1, M^+), 395 (67, $[M - Bu]^+$), 266 (68), 162 (10, $[M - SnBu_3 + H]^+$), 41 (100). Anal. calc. for $C_{22}H_{36}O_2Sn$ (451.24): C 58.56, H 8.04; found: C 58.76, H 8.10.

Bis(2,3-dimethoxyphenyl)acetylene (**27**). *Method A*: A soln. of **30** (100 mg, 0.426 mmol) and $(Bu_3Sn)_2O$ (130 µl, 0.256 mmol) in abs. THF (10 ml) was treated with Bu_4NF (19 µl, 1M in THF, 0.019 mmol), and the mixture was stirred for 1 h at r.t. under N_2 in a pressure tube. Activated molecular sieves (4 Å) were added, and stirring was continued for 18 h. $[Pd(PPh_3)_4]$ (45 mg, 0.039 mmol) and **28** (122 mg, 0.461 mmol) were added, and the mixture was heated to 90° for 17 h. After cooling to r.t., the soln. was decanted from inorg. salts, HF · pyridine 70:30 (0.5 ml) was added, and the mixture was stirred at r.t. for 18 h. The solvent was removed by distillation, and CC (SiO_2, hexane/AcOEt 4:1) afforded **27** (85 mg, 67%).

Method B: A soln. of $[Pd(PPh_3)_4]$ (20 mg, 0.017 mmol) and **29** (230 mg, 0.510 mmol) in abs. THF (12 ml) in a pressure tube was degassed by freeze-pump-thaw cycles. After addition of **28** (146 mg, 0.550 mmol) and further degassing, the tube was sealed and the mixture was heated to 80°. After cooling to r.t., HF · pyridine 70:30 (1.0 ml) was added and the mixture was stirred for 18 h. Workup as described for *Method A* yielded **27** (118 mg, 77%). Slightly yellow solid. M.p. 70–71° (hexane). IR (KBr): 2932*w*, 1572*m*, 1475*s*, 1422*m*, 1332*w*, 1266*s*, 1231*m*, 1171*w*, 1095*s*, 1003*m*, 787*m*, 749*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 4.03 (*s*, 3 H); 6.90 (*dd*, *J* = 8.1, 1.7, 1 H); 7.02 (*dd*, *J* = 8.1, 7.8, 1 H); 7.12 (*dd*, *J* = 7.8, 1.7, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 55.98; 56.03; 60.97; 61.05; 89.66; 112.86; 118.12; 123.81; 125.02; 150.44; 152.75. EI-MS: 298 (100, M^+). Anal. calc. for $C_{18}H_{18}O_4$ (298.34): C 72.47, H 6.08; found: C 72.36, H 5.92.

1-Acetyl-4-(4-methoxyphenyl)-3,4-dehydropiperidine (**37**). A soln. of **20** (9.3 g, 37.0 mmol) and TsOH (0.6 g, 2.9 mmol) in toluene (47 ml) was heated to reflux for 2 h under N_2. After cooling and washing with 1M aq. NaOH soln. (250 ml) and sat. aq. NaCl soln. (250 ml), evaporation and drying yielded **37** (7.4 g, 87%). Yellow solid. M.p. 106–107° (hexane). IR (KBr): 3427*w*, 3009*w*, 2958*w*, 2927*w*, 2900*w*, 2834*m*, 1627*s*, 1517*s*, 1430*s*, 1366*m*, 1344*m*, 1320*w*, 1277*s*, 1262*m*, 1250*s*, 1183*s*, 1115*w*, 1033*s*, 983*w*, 971*m*, 840*m*, 825*s*, 813*m*, 803*m*, 779*w*, 717*w*, 641*m*, 632*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.14, 2.17 (2*s*, 3 H); 2.50–2.58 (*m*, 2 H); 3.66, 3.80 (2*t*, *J* = 5.6, 2 H); 3.82 (*s*, 3 H); 4.11–4.15, 4.20–4.24 (2*m*, 2 H); 5.91–5.95, 5.97–6.01 (2*m*, 1 H); 6.89 (*dm*, *J* = 8.7, 2 H); 7.31 (*dm*, *J* = 8.7, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.53, 21.94; 27.20, 28.02; 38.37, 42.21; 43.49, 45.90; 55.41; 114.04; 117.87, 119.62; 126.24, 126.27; 133.13, 134.47; 136.36; 159.45; 169.50 (2 conformers). EI-MS: 231.1 (100, M^+). Anal. calc. for $C_{14}H_{17}NO_2$ (231.29): C 72.70, H 7.41, N 6.06; found: C 72.91, H 7.61, N 6.02.

1-Acetyl-4-(3-methoxy-4-hydroxyphenyl)-4-(4-methoxyphenyl)piperidine (**38**). A soln. of $BF_3 \cdot OEt_2$ (7.5 ml, 60 mmol) and **37** (5.4 g, 23 mmol) in guaiacol (7.6 ml, 69 mmol) was heated to 85° under N_2 for 2 h. After addition of MeOH (35 ml), the mixture was poured into H_2O (300 ml), the product was extracted with AcOEt (350 ml), and the org. layer was washed with sat. aq. NaCl soln. (300 ml), dried ($MgSO_4$), and concentrated until the product precipitated. After standing overnight, the solid was filtered and dried to give **38** (6.2 g, 75%), which was recrystallized twice (toluene, then i-PrOH) for anal. characterization. White crystals. M.p. 182–185°. IR (KBr): 3162*m*, 2958*m*, 2834*w*, 1605*s*, 1509*s*, 1480*m*, 1455*s*, 1369*m*, 1201*s*, 1254*s*, 1188*m*, 1133*w*, 1118*m*, 1057*w*, 1031*s*, 993*m*, 942*w*, 927*w*, 888*w*, 874*w*, 848*m*, 764*w*, 713*w*, 643*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.11 (*s*, 3 H); 2.29–2.38 (*m*, 4 H); 3.48–3.54, 3.64–3.72 (2*m*, 4 H); 3.80 (*s*, 3 H); 3.82 (*s*, 3 H); 5.63 (*s*, 1 H); 6.69 (*d*, *J* = 2.1, 1 H); 6.75 (*dd*, *J* = 8.3, 2.1, 1 H); 6.86 (*dm*, *J* = 8.3, 1 H); 6.86 (*dm*, *J* = 8.7, 2 H); 7.17 (*dm*, *J* = 8.7, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.50; 36.24; 37.19; 38.73; 43.75; 44.30; 55.33; 55.99; 109.90; 114.12; 114.41; 119.93; 128.19; 138.74; 139.00; 144.15; 146.83; 158.01; 169.22. EI-MS: 355.2 (100, M^+). Anal. calc. for $C_{21}H_{25}NO_4$ (355.43): C 70.96, H 7.09, N 3.94; found: C 70.72, H 7.17, N 4.03.

1-Acetyl-4-(3-methoxy-4-hydroxy-5-iodophenyl)-4-(4-methoxyphenyl)piperidine (**36**). To a soln. of **38** (2.8 g, 7.9 mmol) and NEt_3 (1.3 ml, 9.4 mmol) in CH_2Cl_2 (85 ml) at 0° under N_2 was slowly added ICl (0.4 ml, 1.1 g, 8.6 mmol) in CH_2Cl_2 (16 ml), and the mixture was stirred at 0° for 2 h. Conc. AcOH (0.9 ml), sat. aq. $Na_2S_2O_3$ soln. (20 ml), and H_2O (40 ml) were added, the layers were separated, and the aq. layer was extracted with AcOEt (200 ml). The combined org. layers were washed with sat. aq. NaCl soln. (2 × 80 ml), dried ($MgSO_4$), and evaporated to yield, after CC (SiO_2 (200 g), CH_2Cl_2/MeOH 100:1) and recrystallization (i-PrOH), **36** (1.9 g, 47%). White crystals. M.p. 205–207°. IR (KBr): 2880*m*, 2800*m*, 1718*w*, 1600*s*, 1564*s*, 1514*s*, 1497*s*, 1456*s*, 1403*s*, 1357*m*, 1262*s*, 1182*s*, 1147*m*, 1104*m*, 1065*w*, 1030*s*, 997*s*, 976*m*, 919*w*, 850*m*, 812*s*, 732*m*, 694*w*, 641*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.10 (*s*, 3 H); 2.22–2.40 (*m*, 4 H); 3.37–3.61 (*m*, 4 H); 3.79 (*s*, 3 H); 3.80 (*s*, 3 H); 5.98 (*s*, 1 H); 6.60 (*d*, *J* = 1.9, 1 H); 6.86 (*dm*, *J* = 8.7, 2 H); 7.15 (*dm*, *J* = 8.7, 2 H); 7.17 (*d*, *J* = 1.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.48; 36.14; 37.08; 38.60; 43.62; 44.13; 55.36; 56.30; 81.5; 110.19; 114.28; 128.21; 128.83; 137.79; 141.12; 144.32; 146.28; 158.17; 169.21. EI-MS: 481.1 (100, M^+). Anal. calc. for $C_{21}H_{24}NO_4I$ (481.33): C 52.40, H 5.03, N 2.91; found: C 52.25, H 5.25, N 3.14.

1-Acetyl-4-(3,4-dimethoxy-5-iodophenyl)-4-(4-methoxyphenyl)piperidine (**39**). A mixture of **36** (1.50 g, 3.0 mmol), MeI (0.4 ml, 6.1 mmol), and K_2CO_3 (0.60 g, 4.2 mmol) in acetone (60 ml) was heated to reflux for 3 h. After cooling to r.t., H_2O (4 ml), AcOEt (100 ml), and 2M aq. NaOH soln. were added, followed by separation of the layers. The org. layer was dried ($MgSO_4$) and concentrated to yield a yellow oil which was dissolved in CH_2Cl_2. Precipitation with hexane, followed by recrystallization, yielded **39** (0.90 g, 61%). Yellow crystals. M.p. 164–166°. IR (KBr): 3447*w*, 3001*w*, 2960*m*, 2931*m*, 2867*w*, 1718*w*, 1684*w*, 1632*s*, 1608*m*, 1586*m*, 1552*m*, 1515*m*, 1483*s*, 1438*s*, 1396*m*, 1373*m*, 1357*w*, 1295*m*, 1255*s*, 1191*m*, 1138*m*, 1049*m*, 1032*m*, 994*m*, 948*m*, 859*w*, 844*m*, 814*m*, 732*w*, 647*w*, 620*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.08 (*s*, 3 H); 2.20–2.40 (*m*, 4 H); 3.40–3.58 (*m*, 4 H); 3.75 (*s*, 3 H); 3.78 (*s*, 3 H); 3.79 (*s*, 3 H); 6.65 (*d*, *J* = 2.2, 1 H); 6.86 (*dm*, *J* = 8.7, 2 H); 7.15 (*dm*, *J* = 8.7, 2 H); 7.21 (*d*, *J* = 2.2, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.95; 33.52; 34.44; 36.06; 41.04; 41.67; 52.82; 53.58; 57.96; 90.24; 109.82; 111.76; 125.70; 126.4; 134.74; 142.96; 144.96; 150.10; 155.66; 166.64. EI-MS: 495.2 (100, M^+). Anal. calc. for $C_{22}H_{26}INO_4$ (495.36): C 53.34, H 5.29, N 2.83; found: C 53.36, H 5.03, N 3.05.

Bis[(1-acetyl-4-(3',4'-dimethoxyphenyl)-4-(4''-methoxyphenyl)piperidine-5-yl)]acetylene (**35**). A soln. of **39** (500 mg, 1.0 mmol), bis(tributylstannyl)acetylene (300 mg, 0.5 mmol), and $[Pd(PPh_3)_4]$ (100 mg, 0.075 mmol) in abs. THF (15 ml) in a flame-dried pressure tube was degassed and subsequently heated in the sealed tube to 80° for 2 d. After cooling to r.t., HF · pyridine 70:30 (0.25 ml, 10 mmol) was added and the mixture was stirred for 2 h, then evaporated *in vacuo*. CC (SiO_2 (50 g), CH_2Cl_2/MeOH 50:1) and recrystallization (hexane/toluene) yielded **35** (102 mg, 27%). White crystals. M.p. 222–225°. IR (KBr): 3447*m*, 2934*m*, 1718*w*, 1638*s*, 1576*s*, 1512*s*, 1452*s*, 1355*m*, 1252*s*, 1185*s*, 1152*m*, 1132*m*, 1118*m*, 1065*m*, 1032*m*, 1000*m*, 833*m*, 806*w*, 789*w*, 766*w*, 731*w*, 649*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.09 (*s*, 6 H); 2.28–2.38 (*m*, 8 H); 3.45–3.75 (*m*, 8 H); 3.77 (*s*, 6 H); 3.79 (*s*, 6 H); 3.96 (*s*, 6 H); 6.68 (br. *s*, 2 H); 6.86 (*dm*, *J* = 8.9, 4 H); 7.00 (*d*, *J* = 2.2, 2 H); 7.16 (*dm*, *J* = 8.9, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.45; 35.87; 36.82; 38.58; 43.58; 44.30; 55.31; 56.22; 61.14; 90.10; 90.14; 112.55; 114.20; 117.66; 123.36; 123.39; 128.08; 128.14; 137.90; 137.98; 142.92; 142.98; 148.93; 152.87; 158.11; 169.21. FAB-MS: 761.4 (100, MH^+). Anal. calc. for $C_{46}H_{52}N_2O_8 \cdot 0.5\ H_2O$ (769.94): C 71.76, H 6.94, N 3.64, O 17.66; found: C 71.93, H 7.04, N 3.62, O 17.48.

Bis[(1-acetyl-4-(3',4'-dimethoxyphenyl)-4-(4''-methoxyphenyl)piperidine-5-yl)]ethane (**40**). To a soln. of **35** (99 mg, 0.13 mmol) in MeOH (20 ml) in a pressure hydrogenator was added PtO_2 (4 mg, 0.12 mmol), and the mixture was stirred for 24 h under H_2 (5 bar). Filtration through *Celite* and evaporation *in vacuo* afforded a crude product which was dissolved in CH_2Cl_2 and re-precipitated with Et_2O to yield **40** (80 mg, 80%). White powder. M.p. 134–135°. IR (KBr): 3430*w*, 2935*m*, 1645*s*, 1600*m*, 1584*m*, 1512*s*, 1480*m*, 1445*s*, 1356*w*, 1251*s*, 1184*m*, 1145*m*, 1080*m*, 1032*m*, 1009*m*, 835*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.10 (*s*, 6 H); 2.24–2.34 (*m*, 8 H); 2.82–2.88 (*m*, 4 H); 3.38–3.50 (*m*, 4 H); 3.55–3.63 (*m*, 4 H); 3.74, 3.78, 3.80 (3*s*, 18 H); 6.55 (br. *s*, 2 H); 6.62 (br. *s*, 2 H); 6.85 (*dm*, *J* = 8.7, 4 H); 7.15 (*dm*, *J* = 8.7, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.24; 30.27; 34.82; 35.74; 37.9; 42.99; 43.39; 54.05; 54.59; 59.39; 108.35; 112.83; 119.27; 126.87; 134.12; 137.26; 141.03; 144.39; 151.54; 145.70; 167.87. FAB-MS: 765.4 (100, MH^+). Anal. calc. for $C_{46}H_{56}N_2O_8 \cdot 0.5\ H_2O$ (773.97): C 71.39, H 7.42, N 3.62; found: C 71.37, H 7.66, N 3.36.

X-Ray Crystal Structure of **35**. Crystal Data of 293 ± 2 K for $C_{46}H_{52}N_2O_8 \cdot CHCl_3 \cdot 0.5\ H_2O$, M_r 888.26: monoclinic space group *P*2(1)/*n*, $\rho_{calc.} = 1.309$ g/cm^{-3}, $Z = 8$, $a = 21.469(11)$, $b = 17.281(9)$, $c = 24.760(12)$ Å, $\beta = 101.03(3)°$, $V = 9016(8)$ Å^2. *Picker-Stoe* diffractometer, CuK_α radiation, $\lambda = 1.54178$ Å. Single crystals were obtained by diffusion of Et_2O into a $CHCl_3$ soln. The structure was solved by direct methods (SHELXS-86) and refined by full-matrix least-squares analysis (heavy atoms anisotropic, H-atoms fixed, whereby H-positions are based on stereochemical considerations) using an isotropic extinction correction. Final $R(F) = 0.0798$, $wR(F) = 0.2188$ for 1091 variables and 9252 observed reflections with $I > 2\sigma(I)$. Further details of the crystal

structure investigations are available on request from the Director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK.

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