Synthesis of *in*,*out*-isomeric phosphite and phosphate cryptands

Ingmar Bauer,[a]* Gulnur G. Sergeenko,[b] Il'yas S. Nizamov,[b] Gabriele Theumer,[a] Roland Fröhlich[c], Alexander R. Burilov,[b] Vera I. Maslennikova[d], and Wolf D. Habicher[a]*

[a] *Institute of Organic Chemistry, University of Technology Dresden, 01062 Dresden (Germany)*
[b] *Arbuzov Institute of Organic and Physical Chemistry, RAS, Arbuzov str. 8, 420088 Kazan, Russia*
[c] *Institute of Organic Chemistry, University Münster, Corrensstrasse 40, D-48149, Münster, Germany*. [d] *Moscow Pedagogical State University, Nesvizhsky per. 3, Moscow, 119021, Russia*
E-mail: Ingmar.Bauer@chemie.tu-dresden.de; Wolf.Habicher@chemie.tu-dresden.de

Dedicated to Professor Alexander I. Konovalov on his 70th birthday

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Abstract

The reaction of $POCl_3$ with the trinuclear bisphenol **1** has been investigated. All three homeomorphic *in*,*out*-isomers of the phosphorus cryptand were isolated. Among them the *out*,*out*-isomer was the main macrobicyclic product obtained. The reaction of the previously described *in*,*in*-phosphite **2** with CuCl afforded an interesting complex containing two metal centers bridging the cavity of the cryptand together with a central chloride ion. This complex suggested the use of Cu(I) as a template for the formation of the formerly described *in*,*out*-phosphite cryptands. With this method it is now possible to carry out the reaction in higher concentrated solution to isolate larger quantities of the phosphorus macrobicycles.

Keywords: Cryptands, phosphites, phosphates, *in*,*out*-isomers, macrocycles

Introduction

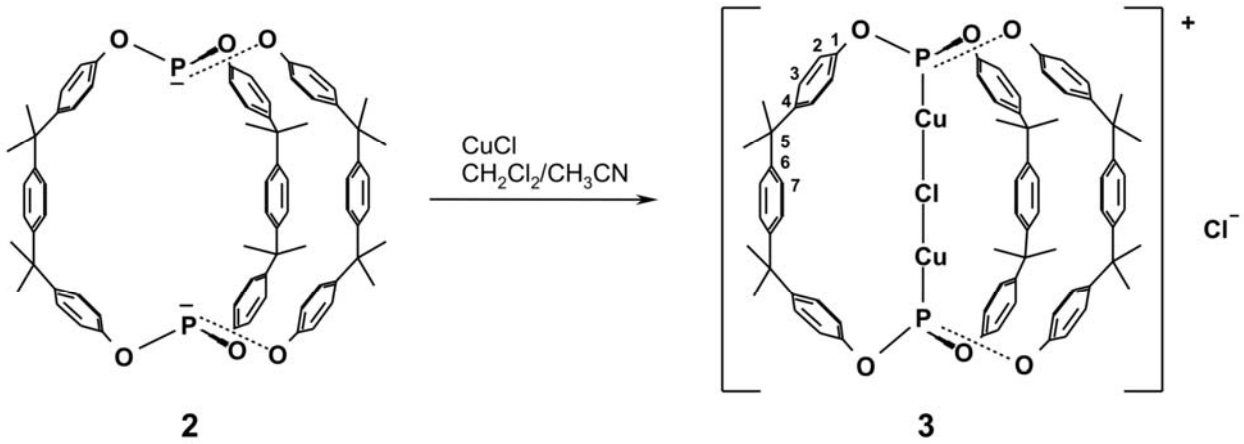
Phosphorus containing cryptands are interesting molecules with potential applications in various fields of chemistry. With trivalent phosphorus incorporated into a macrobicyclic skeleton, such structures can be potential ligands for the complexation of soft metals, a feature that makes them promising candidates for selective extraction of metal cations from aqueous solution or as catalysts in transition metal catalyzed reactions such as hydroformylation, Heck reaction, Suzuki coupling and others. Pentavalent phosphoryl compounds are interesting for complexation and separation of lanthanides and actinides. The macrocyclic framework can support the complexation and selectivity by either providing the appropriate size for a specific metal or

additional cooperative functions such as π-donating aromatic moieties. Both types of phosphorus compounds can also play an important role in supra-molecular chemistry for molecular recognition of charged and neutral organic substrates especially also for those of biological interest. Despite of their interesting properties the number of phosphorus containing macrocycles and macrobicycles is, contrary to their aza analogues, still limited but has continuously grown during the last two/three decades.[1] If the phosphorus occupies bridgehead positions, *in*,*out*-isomers regarding the position of the exocyclic rest at the phosphorus in respect to the cavity, are possible. The phenomenon of *in*,*out*-isomerism has been summarized by Alder.[2] A review on *in*,*out*-isomerism of phosphorus bridgehead compounds is also available.[3] Especially *in*-groups might be interesting as their exceptional position inside the cavity provides a defined micro environment which can pronouncedly differ from the bulk solution and which can be predicted as the macrobicyclic framework is relatively rigid and has less degrees of freedom than open chain skeletons. So far, only a small number of stable *in*-isomers has been isolated. Bridging atoms therein have mainly been methines,[4] amines and ammonium[5] ions and in very few cases phosphorus atoms.[6] Largest *in*-group reported so far is a methyl group at a sp^3-C-bridgehead centre by Vögtle and coworkers.[7] We were able to successfully employ a *double-capping* method for the synthesis of the *out*,*out*- and *in*,*out*-isomers of a sterical hindered, flexible phosphorus containing cryptand.[8] Reacting two non-hindered bisphenols with PCl_3 each, we could even isolate all three homeomorphic isomers of the corresponding phosphite cage compounds in reasonable yields.[9] The corresponding phosphate cryptands have been observed but not isolated in most cases by treating the phosphite cryptands with cumene hydroperoxide. *In*-positions are therein much less reactive than *out*-phosphites. It was interesting to see whether the corresponding *in*,*out*-phosphates and *in*,*out*-thiophosphates can be obtained directly by the same *double-capping* method as employed for the phosphite cryptands. The product distribution of the corresponding *in*,*out*-isomers will be discussed in the present paper.

Results and Discussion

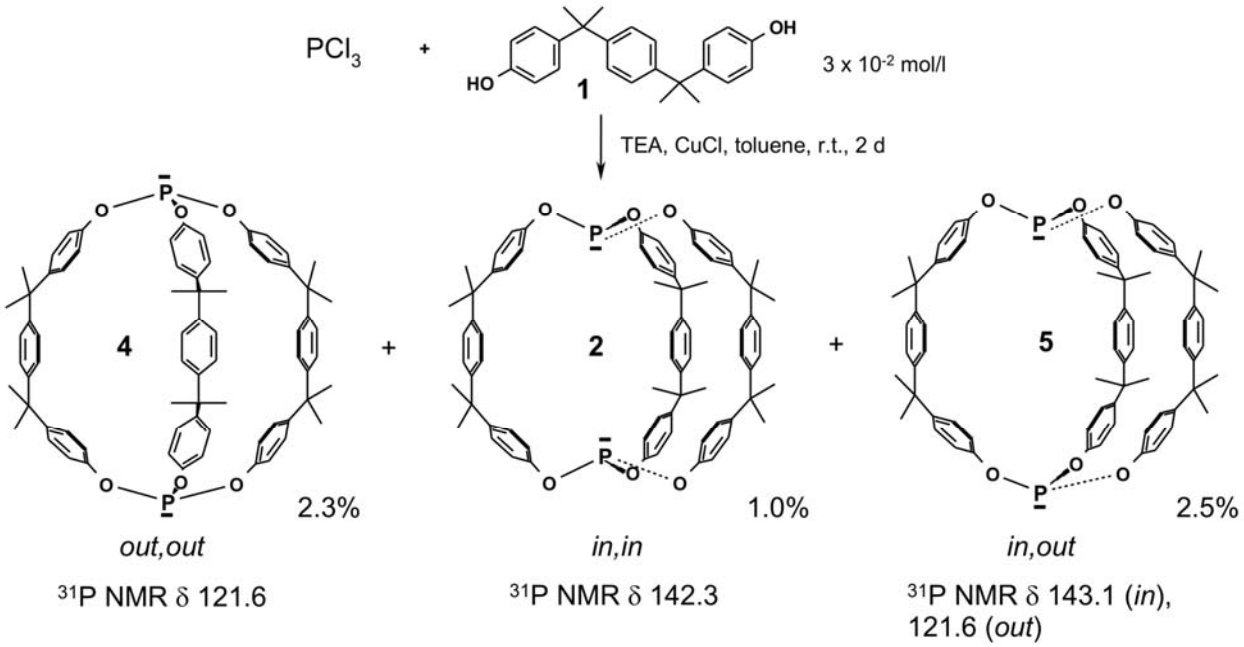
The *double-capping* reaction of PCl_3 with bisphenol **1**, we reported earlier, required rather diluted conditions (5×10^{-3} mol/l of the bisphenol) to obtain 12% of a mixture of all three homeomorphic isomers.[9a] It seems obvious to study a templated version of this reaction to improve the yield of the cryptands and in particular those of *in*,*in*-phosphite **2**. As Cu(I) ions should be readily complexed with phosphite functions, we reacted *in*,*in*-phosphite **2** with CuCl to investigate the structure of such complexes. A solution of CuCl in moist CH_3CN was slowly added to a toluene solution of the cryptand. After a few minutes crystals separated at the phase interface. They have been investigated by ^{31}P, ^{1}H, ^{13}C NMR, MALDI TOF MS and elemental analysis. However, we were not able to obtain an X-ray structure of them so that we can only tentatively assign structure **3** to them (Scheme 1). It shows an interesting complex cation of the *in*,*in*-macrobicyclic framework with two Cu(I) centers and a central chloride atom. These three

atoms form a fourth bridge between the phosphorus bridgeheads of the ligand through the inside of the cavity. The structure is topologically reminiscent of a propellane compound. It formally represents a type of ligand stabilized $[Cu_2Cl]^+$ cation.



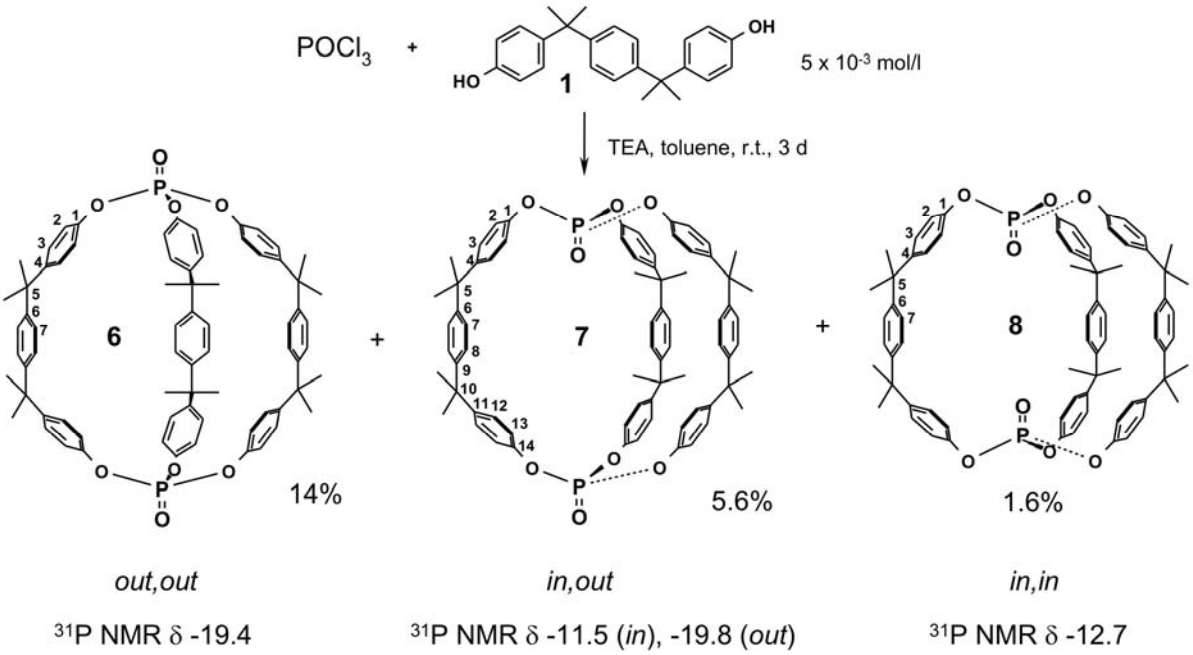
Scheme 1

The ^{31}P NMR spectrum of **3** shows a broad peak at 112.1 ppm which is in accordance with ^{31}P NMR shifts for other P-Cu complexes.[10] Its ^{1}H and ^{13}C NMR spectra are very simple and reflect the C_{3v} symmetry of the molecule. Most convincing, however, is the MALDI TOF peak at 1258 Da for the complex cation. An exact elemental analysis for the proposed compound was achieved. With these data in mind we expected a favorable template effect for the reaction of PCl_3 with bisphenol **1** in the presence of CuCl to form larger quantities of *in*,*in*-phosphite **2** compared to the non-templated reaction reported by us earlier.[9a] The reaction was accordingly carried out in toluene in the presence of triethylamine and CuCl, but with a one order of magnitude higher concentration of the educts compared to the previously reported reaction. The initially formed amino Cu(I) complex is destroyed in the course of the reaction as the amine is protonated by HCl released from the esterification reaction. Instead a phosphite Cu(I) complex is formed as was observed by following the reaction by ^{31}P NMR giving a broad peak at 110 ppm. The crude product of the reaction was washed with ammonia solution to decompose the complex. The finally obtained product mixture after filtration through silica with toluene/CH_2Cl_2 is in terms of ratio of homeomorphic *in*,*out*-isomers more or less identical with those of the non-templated reaction. Enrichment of *in*,*in*-product **2** was not achieved. However, the yield does not dramatically decrease when the reaction solution is more concentrated as was observed for the non-templated reaction. In fact even a concentration of 3×10^{-2} mol/l of the bisphenol **1**, one order of magnitude higher than for the non-templated reaction, still led to yields of 6.6% for the total of all phosphorus cryptand isomers, which allowed us to isolate about half a gram of *out*,*out*-isomer **4** and *in*,*out*-isomer **5** and 200 mg of *in*,*in*-isomer **2** in one batch (Scheme 2). The analytical data for compounds **2**, **4** and **5** are in agreement with those described by us earlier.[9a]



Scheme 2

In order to obtain the corresponding phosphate cryptands, the reaction of $POCl_3$ with bisphenol **1** was carried out in toluene in the presence of triethyl amine. After stirring for 3 days at room temperature a product mixture containing all three homeomorphic *in*,*out*-isomers was obtained. A subsequent column chromatography on silica gel with CH_2Cl_2/EtOAc (40:1) afforded the three isomers in a pure state. The main cryptand obtained was the *out*,*out*-isomer **6** with 14% yield followed by the *in*,*out*-isomer **7** with 5.6% and *in*,*in*-isomer **8** which could be obtained only in 1.6% yield (Scheme 3).



Scheme 3

All isomers have been characterized by ^{31}P, ^{1}H and ^{13}C NMR, MALDI-TOF MS and elemental analysis. All of them have melting points higher than 360°C. *In*,*in*-isomer **8** has already been described by us earlier by oxidation of *in*,*in*-phosphite **2** with cumene hydroperoxide. The ^{31}P NMR shifts of **6** and **7** have also been reported therein, without isolation of the corresponding products.[9a] The ^{31}P NMR chemical shifts for *in*- and *out*-positions are different but not as pronounced as for the corresponding phosphites. Again the signals for the *in*-phosphorus atoms are shifted to low field, namely -11.5 ppm for *in*,*out*-compound **7** and -12.7 ppm for *in*,*in*-cryptand **8**. The chemical shifts for the *out*-positions are more or less in a region where open chain aryl phosphates would be expected, in particular -19.4 ppm for *out*,*out*-compound **6** and -19.8 ppm for *in*,*out*-cryptand **7**. The ^{1}H and ^{13}C NMR spectra reflect the high symmetry of the products in solution. *Out*,*out*-compound **6** and *in*,*in*-compound **8** have C_{3v} symmetry. Both halves of the molecule are magnetically equivalent which leads to a single ^{31}P NMR peak for each of them and very simple ^{1}H and ^{13}C spectra. *In*,*out*-compound **7** is only C_3 symmetric giving different signals for corresponding atoms on the two sides of the molecule.

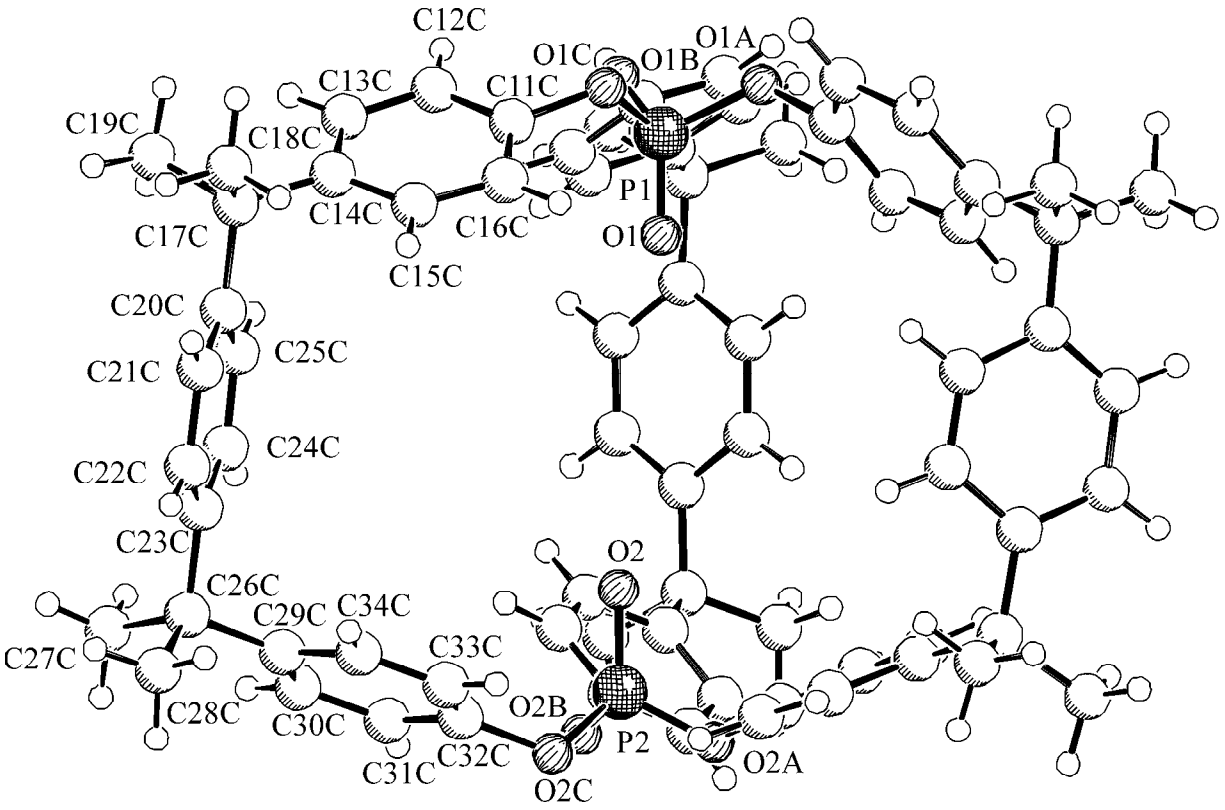


Figure 1

We were able to grow crystals of *in*,*in*-phosphate **8** from CH_2Cl_2/CH_3CN. The X-ray structure of it is presented in Figure 1. However, the small size of the crystals and a high content of solvent molecules leading to a low diffracting power, allows us only to confirm the *in*,*in*-

phosphate structure but not to discuss geometrical details. The crystal contains a large number of solvent molecules namely one molecule of CH_2Cl_2, four molecules of CH_3CN and half a molecule of hexane per unit cell, which are located both inside and outside the cavity. The solvent molecules have been omitted in Figure 1 for clarity. The distance between the two *in*-oxygen atoms is approximately 5 Å.

In summary, application of $POCl_3$ compared to PCl_3 in the *double-capping* reaction with bisphenol **1** leads to a higher fraction of the *out*,*out*-isomer in comparison to the *in*,*in*-isomer. This can be attributed to the higher sterical demand of the phosphoryl oxygen in the *in*-position. It will be interesting to investigate whether the corresponding reaction with $PSCl_3$ continues this trend and probably does not form the *in*,*in*-isomer at all. However, it is possible to place two sulfur atoms inside the cavity as the *in*,*in*-thiophosphate cryptand has already been described by us as a side product of a Staudinger reaction of *in*,*in*-phosphite **2** with a thiophosphoryl azide.[11]

Experimental Section

General Procedures. The melting points were determined on a Boëtius melting point apparatus. ^{1}H NMR (TMS internal reference), ^{13}C NMR (TMS internal reference) and ^{31}P NMR spectra (85% H_3PO_4 external reference) were recorded on Bruker AC-300 and DRX-500 spectrometers. MALDI-TOF mass spectra were measured on a Kratos Kompact MALDI II (Shimadzu Europa GmbH, Duisburg, Germany) using a N_2-laser source (λ = 337 nm), a positive polarity and 20 kV acceleration voltage. The microanalyses were recorded on a CHN-S analyzer (Carlo Erba). Solvents were purified by conventional methods.

Cu(I)-complex (3). To a solution of 50 mg of *in*,*in*-phosphite **2** (0.046 mmol) in 5 ml of CH_2Cl_2 was slowly added a solution of 9 mg (0.091 mmol) of CuCl in moist CH_3CN. After a short period of about 30 min, crystals of **3** precipitated and were separated by filtration; Yield: 39 mg (65%), decomp. ~360°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 112.1 (br.); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.06 (2d*, 24H, 2,3-H), 7.01 (s, 12H, 7-H), 1.65 (s, 36H, 5-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.4 (C-1)$^{\#}$, 147.7 (C-6) $^{\#}$, 147.2 (C-4) $^{\#}$, 128.2 (C-3)†, 126.2 (C-7)†, 120.2 (d, ^3J(P,C) = 6.2 Hz, C-2), 42.0 (C-5), 29.9 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxy-anthracene): *m*/*z*: 1258 [*M*-Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{72}H_{72}O_6P_2Cu_2Cl_2$ (1293.23): C 66.87, H 5.61, Cl 5.48; found C 66.64, H 5.64, Cl 5.95.

* Coupling constant not determined, because signals are very close together to appear as one singlet.

$^{\#,\dagger}$ Signals assigned in accordance with those of *in*,*in*-phosphite **2**,[9a] which have been proven by various 2D NMR techniques including ^{1}H/^{31}P correlated HMBC and ^{31}P/^{1}H correlated HOESY.

Reaction of 1 with PCl_3 in the presence of CuCl. Biphenol **1** (20.0 g, 57.7 mmol) and TEA (15.0 g, 148.2 mmol) were dissolved in toluene (2.0 L) in a flame-dried 2 L flask under argon atmosphere (**1** is only partly soluble). Anhydrous CuCl (3.8 g, 38.4 mmol) was added and the

solution was stirred at room temperature for 10 min. Under vigorous stirring PCl_3 (5.3 g, 38.6 mmol) was added dropwise by syringe within 10 min. The solution was stirred for 2 d at 25°C. The hydrochloride formed was removed by filtration and the solvent was concentrated in vacuum to 400 ml. Subsequently it was washed three times with 40 ml concentrated ammonia solution each until the color of the washing solution did not turn blue. After the first washing procedure a white solid precipitated which was filtered and disposed. The organic layer was dried over $MgSO_4$ and further concentrated to 40 ml. Subsequently it was filtered through silica gel with toluene/CH_2Cl_2 (4:1) as eluent. After evaporation of the solvent mixture 1.40 g (6.6%) of a white solid were obtained, which contained a mixture of the three homeomorphic isomers **2**, **4** and **5.** They could be separated by column chromatography on silica gel with cyclohexane/toluene (2:1) to afford *out*,*out*-macrobicycle **4** (480 mg, 2.3%, compound partly hydrolyzes on the column), *in*,*out*-phosphite **5** (530 mg, 2.5%) and *in*,*in*-phosphite **2** (210 mg, 1.0%,), as white solids. The analytical data of **2**, **4** and **5** are in accordance with those described in the literature.[9a]

Reaction of 1 with $POCl_3$. Biphenol **1** (1.00 g, 2.9 mmol) and TEA (0.75 g, 7.4 mmol) were dissolved in toluene (500 mL) in a flame-dried 1 L flask under argon atmosphere (**1** is only partly soluble). Under vigorous stirring $POCl_3$ (0.30 g, 1.95 mmol) was added dropwise by syringe within 10 min. The solution was stirred for 3 d at 25°C. The hydrochloride formed was removed by filtration and the solvent was evaporated in vacuum to yield a viscous oil containing a mixture of **6**, **7**, and **8** and some non-cyclic and simple macrocyclic byproducts according to ^{31}P NMR. Chromatography on silica gel with CH_2Cl_2/EtOAc (40:1) afforded *out*,*out*-macrobicycle **6** (152 mg, 14.0%), *in*,*out*-phosphate **7** (61 mg, 5.6%) and *in*,*in*-phosphate **8** [9a] (17 mg, 1.6%) as white solids.

***Out,out*-phosphate (6).** m.p. >360°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = -19.3; ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.13 (d, ^3J(H,H) = 8.8 Hz, 12H, 2-H), 7.06 (s, 12H, 7-H), 7.05 (d, ^3J(H,H) = 8.5 Hz, 12H, 3-H), 1.64 (s, 36H, 5-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.3 (d, ^2J(P,C) = 8.7 Hz, C-1), 148.1, 147.4 (C-4, C-6), 129.2, 127.1 (C-3, C-7), 119.2 (d, ^3J(P,C) = 4.6 Hz, C-2), 42.2 (C-5), 29.7 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m*/*z*: 1128 $[M+H]^+$; elemental analysis calcd (%) for $C_{72}H_{72}O_8P_2$ (1127.28): C 76.71, H 6.44; found C 76.38, H 6.67.

***In,out*-phosphate (7).** m.p. >360°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = -11.5 (*in*), -19.6 (*out*); ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.20-7.07 (m, 24H, 2,3,12,13-H), 7.03 (s, 12H, 7,8-H), 1.65, 1.60 (s, 18H each, 5,10-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.4 (d, ^2J(P, C) = 8.6 Hz, C-1 or C-14), 148.3 (d, ^2J(P, C) = 6.2 Hz, C-1 or C-14), 148.0, 147.6, 147.4, 147.3 (C-4, C-11, C-6, C-9), 128.12, 128.10 (C-3, C-12), 126.3, 126.2 (C-8, C-7), 119.6 (d, ^3J(P, C) = 4.7 Hz, C-13 or C-2), 119.2 (d, ^3J(P, C) = 4.7 Hz, C-13 or C-2), 42.2, 42.0 (C-5, C-10), 30.8, 30.3 (5-Me, 10-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m*/*z*: 1128 $[M+H]^+$; elemental analysis calcd (%) for $C_{72}H_{72}O_8P_2$ (1127.28): C 76.71, H 6.44; found C 76.22, H 6.72.

***In, in*-phosphate (8).** Analytical data are in agreement with those in the literature.[9a]

Crystal data for 8. formula $C_{72}H_{72}O_8P_2$ * 4 C_2H_3N * CH_2Cl_2 * 0.5 C_6H_{14}, *M* = 1419.46, colorless crystal 0.20 x 0.15 x 0.05 mm, *a* = 16.016(1), *b* = 16.085(1), *c* = 18.422(1) Å, α =

71.00(1), β= 64.44(1), γ = 75.40(1), V = 4015.8(4) Å^3, ρ_{calc} = 1.174 g cm^{-3}, μ= 1.76 cm^{-1}, no absorption correction (0.966 ≤ T ≤ 0.991), Z = 2, triclinic, space group P1bar (No. 2), λ= 0.71073 Å, T = 198 K, ω and φ scans, 16867 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.54Å^{-1}, 10441 independent (R_{int} = 0.066) and 5849 observed reflections [$I \geq 2\ \sigma\ (I)$], 828 refined parameters, R = 0.160, wR^2 = 0.381, max. residual electron density 1.31 (-0.9) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. Structure analysis was only done to prove the presence of the *in*,*in*-isomer. Due to the small crystal size and the high content of solvent molecules the diffracting power is very low. Even a long data-collection time with the generator at highest possible power resulted in data set only usable up to 2θ of 45°. All solvent molecules are refined with isotropic thermal parameters only, disorder could not be refined due to the limited amount of observed reflections. Three of the four acetonitriles are refined with the first one as a geometrical model (SAME instruction). The remaining electron density could not be assigned in chemical meaningful way. Data set was collected with a Nonius Kappa CCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[12] structure solution SHELXS-97,[13] structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, 1997).

Supplementary Information

Crystallographic data (excluding structure factors) for structure **8** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-251947. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

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