Synthesis and Isolation of Homeomorphous Isomers of P-Containing Cryptands

Ingmar Bauer,*[a] Otto Rademacher,[b] Margit Gruner,[a] and Wolf. D. Habicher*[a]

Abstract: The novel isomeric phosphite cryptands **2**, **3**, and **4** could be synthesized by a simple one-pot tripod capping method starting from bisphenol **1** and PCl_3. The assembling of five components led to the formation of a macrobicyclic structure, which probably requires an appropriate preorganization of the reactants. In contrast to the NMR spectra of **2**, **3**, and **4** in solution, the X-ray structures of **2** and **3** reveal that these molecules have no C_3 symmetry in the solid state. In the ^{31}P NMR spectra, both *in*- and *out*-P atoms have remarkably different chemical shifts due to a distorted geometry around the *in*-phosphorus. Phosphorus atoms in the *in*-position have a decreased reactivity. They are, therefore, more slowly oxidized by cumene hydroperoxide than *out*-P atoms. A stepwise synthesis was developed for phosphite/phosphate-cryptands (**5**, **7**, **9**, and **15**) via the monoprotected bisphenol **11** and the phosphate **14**. In addition, the cylindrical macrotricycle **16** was isolated as a mixture of diastereomers from the crude product of this reaction.

Keywords: cryptands · macrocyclic ligands · NMR spectroscopy · phosphates

Introduction

Over the recent years phosphorus-containing cryptands have become of interest because of their complexation abilities.[1] This makes them attractive not only for metal extraction from aqueous solution, but also as potential ligands for transition metal catalyzed reactions in organic synthesis, such as hydroformylation, olefin metathesis, and hydration. The geometry and a possibly well-defined position of the complexing phosphorus atom could lead to outstanding catalyst complexes, which could have applications for enantioselective syntheses after a chiral modification of the cage compound.

Few macrobicycles that contain phosphorus as bridgehead atoms have been synthesized to date. The synthesis of P- and P(O)-cryptands and the complexing behavior of the latter toward hydrogen-donating neutral compounds was reported by Friedrichsen et al.[2] A bis(phosphotriester) bimacrocyclic polyether was published by Allan et al.,[3] who used this system for alkali metal complexation and found it to form more stable complexes than similarly sized nitrogen-bridgehead compounds. A number of phosphorhydrazide macrobicycles have been reported by Caminade et al.[4] We recently synthesized the *out*,*out*- and the *in*,*out*-isomers of a phosphite cage compound with P-bridgeheads.[5] However, the *in*,*in*-isomer was not obtained owing to steric hindrance induced by the *ortho*-methyl substitution of the bisphenol.

[a] Doz. Dr. W. D. Habicher, Dr. I. Bauer, Dr. M. Gruner
Institut für Organische Chemie der Technischen Universität Dresden, Mommsenstr. 13, 01062 Dresden (Germany)
Fax: +(49) 351-463-4093
E-mail: wolf.habicher@chemie.tu-dresden.de

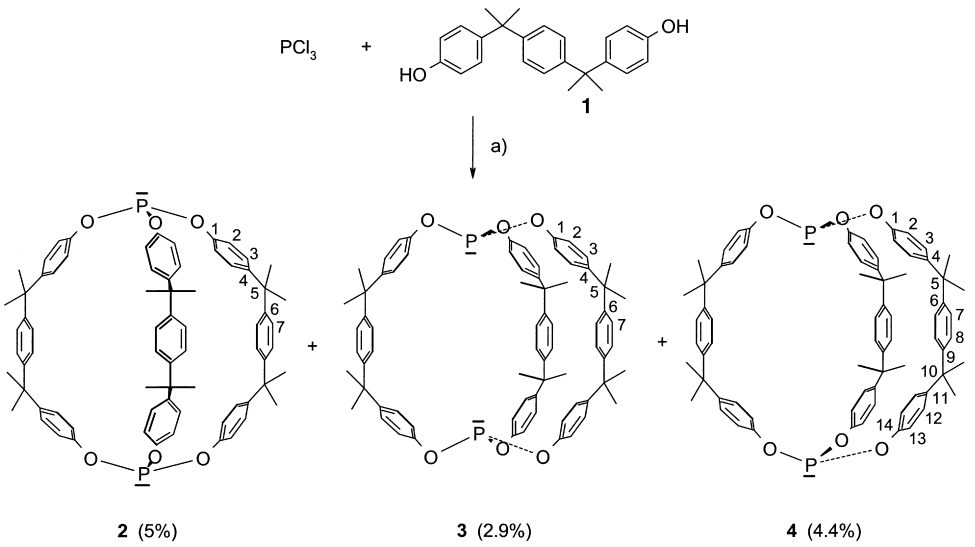
[b] Priv.-Doz. Dr. O. Rademacher
Institut für Anorganische Chemie der Technischen Universität Dresden, Mommsenstr. 13, 01062 Dresden (Germany)
Fax: +(49) 351-463-7287
E-mail: otto.rademacher@chemie.tu-dresden.de

Results and Discussion

One-step synthesis of P cryptands: The reaction of the non-hindered bisphenol **1** with PCl_3 was performed in the presence of triethylamine (TEA) in toluene at 25 °C by using high dilution conditions. In this case, all three possible homeomorphous isomers were formed in a 2:2:1 (**2**, **4**, **3**) ratio with a crude yield of 15 % (Scheme 1). This seems rather high for a one-step synthesis of such highly organized structures. Only few examples exist for the formation of macrobicyclic cages out of five components, the so-called tripod-capping method,[6] which generally affords products in very poor yields. Furthermore, the flexible arms should disfavor the formation of a macrobicycle. The astonishingly good yield can probably be attributed to an appropriate preorganization (self-assembly) of the reactants; this should be realized by hydrogen bonding of the partly dissolved bisphenol **1** in the non-polar solvent.

The three isomers **2**, **3**, and **4** could be isolated by column chromatography on silica gel by using *n*-pentane/toluene (1:1)

  0947-6539/00/0616-3043 $ 17.50+.50/0



Scheme 1. One-step synthesis of macrobicycles **2**, **3**, and **4**. The atom numbering is in accordance with the magnetic equivalence of protons and C atoms in solution; a) TEA, toluene, RT, 3 d.

as the eluent. The *out*,*out*-isomer **2** behaves as the most nonpolar compound and is eluted first, followed by *in*,*out*-isomer **4**, and lastly, the *in*,*in*-isomer **3**. Open-chain products and simple macrocycles bearing free OH groups remain on the column. The *in*,*in*-product **3** can also be eluted with chloroform as a single isomer from basic aluminum oxide, while the other by-products and isomeric cryptands remain on the column. The rationale could be an alkylation of the phosphorus compounds with chloroform to form polar phosphonium products, while **3** is inert to the alkylating agent as a result of the decreased availability of the P lone pairs inside the cryptand.

X-ray structure analyses: Colorless crystals of *out*,*out*-isomer **2** and *in*,*in*-isomer **3** were grown from $MeCN/CH_2Cl_2$. The crystal structures of **2** and **3** (Figure 1) reveal that the molecules have no C_3 symmetry in the P–P direction as might be assumed according to the images in Scheme 1. In addition, no internal symmetry is found for **2**, which crystallized in space group $P\bar{1}$ with half a CH_2Cl_2 molecule on statistically distributed and disordered positions. Two "arms" of the cage form a nearly planar macrocycle. The four phenyl groups A, C, A′, and C′ next to the oxygen are in a position that to some extent resembles the *cone*-conformation of a calix[4]arene. The two central phenyl rings B and B′, however, are twisted out of the cone with angles of 83.8°/70.3° and 87.8°/80.0° to the neighboring phenyl ring planes A/C and A′/C′, respectively. This shows that the molecule is flexible enough to evade a steric repulsion of aromatic hydrogens by distorting two neighboring phenyl groups almost 90° to each other.

The third arm of the macrobicycle is attached to the macrocyclic plane like a bridging handle, leading to a sort of T-shaped conformation of the molecule. This keeps one side of the cage open and makes the inner part of the cryptand accessible on this side.

The crystal structure of the *in*,*in*-isomer **3** gives a different picture (Figure 1). It contains two slightly different conformers (**3a** and **3b**) of the cage compound in space group *C*2, both generated by a two-fold rotation axis from their halves. Moreover, each molecule crystallized with one molecule of acetonitrile and half a molecule toluene, the latter on statistically distributed positions. Compound **3** also consists of two macrocyclic arms, which are identical in this case due to the symmetry of the molecule and gives a "cone-like" conformation, and a "handle", which has two identical halves. The two outer phenyl rings (D) of the handle are placed in a co-planar position to each other. In comparison to the T-shaped compound **2**, the conformers **3a** and **3b** are more similar to a C_3 symmetric structure.

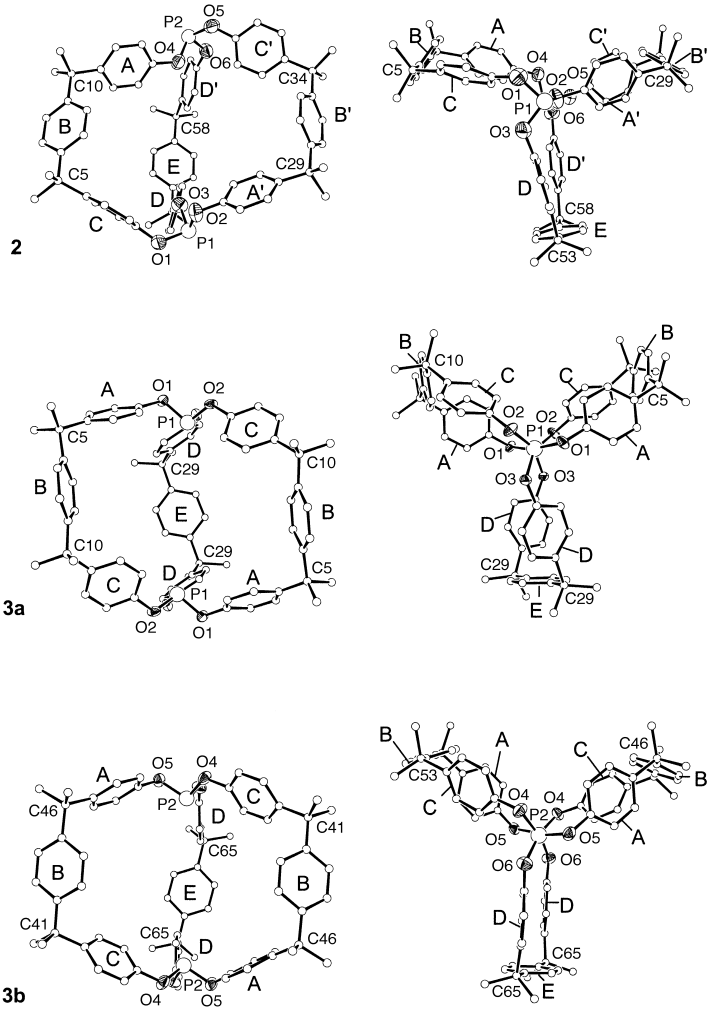


Figure 1. Structures of **2**, **3a**, and **3b** in the solid state. Hydrogen atoms and solvent molecules are omitted for clarity. Left: view into the cavity with the "handle" arms pointing to the back. Right: view along the P–P axis with the "handle" arms pointing downwards.

0947-6539/00/0616-3044 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 16

The shape of the molecules, referred to as "T-shaped" and "C_3 resembling", is reflected by the size of the angles between the P atoms and the first neighboring C atoms of the phenyl groups (Table 1). In the *out*,*out*-isomer **2**, the angles between the two arms of the "conelike" macrocyclic ring are about 110°, whereas in the *in*,*in*-conformers **3a** and **3b**, the angles are only 80° and 85°, respectively. In contrast, the angles between the "conelike" arms and the "handle" arm in **2** also are about 110° or slightly smaller; in **3a** and **3b**, however, these values vary from about 110° to 130°.

Table 1. Selected angles [°] for **2**, **3a**, and **3b**.

	2	**3a**	**3b**	remark[a]
C1-P1-C25	111.76			c-c
C14-P2-C38	113.58			c-c
C1-P1-C14		84.87		c-c
C37-P2-C50			79.65	c-c
C1-P1-C49	100.42			c-h
C25-P1-C49	98.60			c-h
C14-P2-C62	113.58			c-h
C38-P2-C62	93.12			c-h
C1-P1-C25		109.12		c-h
C14-P1′-C25′[b]		129.92		c-h
C37-P2-C61			114.64	c-h
C50-P2″-C61″[b]			125.21	c-h
O1-P1-O2	103.09	97.33		c-c
O4-P2-O5	98.02		97.70	c-c
O1-P1-O3	96.65	96.14		c-h
O2-P1-O3	98.13	95.10		c-h
O4-P2-O6	96.28		95.40	c-h
O5-P2-O6	101.79		96.20	c-h
Ø O-P-O	98.99	96.19	96.43	
C4-C5-C6 C40-C41-C42	111.1	108.0	111.2	c c
C9-C10-C11	109.5	110.3		c
C45-C46-C47			107.8	c
C28-C29-C30	109.7	106.9		c
C64-C65-C66			108.8	h
C33-C34-C35	108.3			c
C52-C53-C54	110.0			h
C57-C58-C59	109.5			h
Ø CPh-CiPr-CPh	109.7	108.4	109.3	
	Ø (**3a**,**3b**) 108.8			

[a] c = "conelike" macrocyclic arm; h = "handle"arm. [b] Symmetry transformations: ′: $-x+1, y, -z+2$; ″: $-x+2, y, -z+1$.

The distances between the phosphorus atoms in the *in*,*in*-isomer **3** are almost the same (within 8.5 Å for **3a** and 8.3 Å for **3b**), but as expected they are markedly shorter than that of the *out*,*out*-isomer **2** (10.5 Å). In contrast, the corresponding O–O and C–C distances within the "conelike" macrocyclic arms and the "handle" arm are smaller in *out*,*out*-isomer **2** in comparison to both *in*,*in*-conformers **3a** and **3b**, thus avoiding a strong compressing effect of the short P–P distance in **3** on the bridging arms (Table 2).

Compared with the *out*,*out*-isomer **2**, the C(Ph)–C(iPr)–C(Ph) angles are slightly smaller in *in*,*in*-isomer **3** and also slightly smaller than a tetrahedral angle; this reveals that the molecule is somewhat compressed caused by the configuration of the *in*-P atoms. Although this effect is only very weak, it was also observed in solution by NOESY measurements as discussed below. Even more evident are the smaller averaged O–P–O angles in **3a** and **3b** relative to **2** (values and further selected structural details are summarized in Table 1 and Table 2). This means that the pyramid formed by the *in*-P and the oxygen atoms is more pointed than the pyramid around the *out*-P. This distortion strongly influences the chemical shifts of the *in*-P atoms in the ^{31}P NMR spectra.

Table 2. Selected bond lengths [Å] and atom distances of **2**, **3a**, and **3b**.

	2	**3a**	**3b**	remark[a]
P–P	10.507	8.485	8.257	
P1–O1	1.602	1.640		c
P1–O2	1.625	1.632		c
P1–O3	1.625	1.627		h
P2–O4	1.621		1.645	h
P2–O5	1.609		1.630	h
P2–O6	1.638		1.643	h
O1–O4	10.12			c
O2–O5	9.69			c
O1–O2		10.35		c
O5–O6			10.00	c
O3–O6	8.97			h
O3–O3′[b]		9.79		h
O6–O6″[b]			9.93	h
C1–C14	8.99	9.20		c
C25–C38	8.74			c
C37–C50			8.91	c
C49–C62	8.22			h
C25–C25′[b]		8.68		h
C61–C61″[b]			8.80	h

[a] c = "conelike" macrocyclic arms; h = "handle" arm. [b] Symmetry transformations: ′: $-x+1, y, -z+2$; ″: $-x+2, y, -z+1$.

NMR spectroscopy: The chemical shifts of the *in*- and *out*-P atoms in ^{31}P NMR [**2**: $\delta = 121.6$ (*out*); **3**: $\delta = 142.7$(*in*); **4**: $\delta =$ 143.1 (*in*), 121.6 (*out*)] are remarkably different. This can be attributed to the different geometries around the P atoms. The assignment of the *in*- and *out*-P atoms in ^{31}P NMR was confirmed by the crystal structures of **2** and **3**. The solid state structures also confirmed that the averaged O–P–O angles in **3** are smaller than in the *out*,*out*-isomer **2**; this means that the pyramidal geometry is somewhat stretched in **3**. This could be the reason for the low-field shift of the ^{31}P NMR signal in **3**. Interestingly, a ^2J(P,C) coupling between *in*-P and *ipso*-C could be observed (**3** and **4**), but not between *out*-P and *ipso*-C (**2** and **4**). However, the ^3J(P,C) coupling between *in*- or *out*-P and the *ortho*-carbon (C-2 or C-13) could be observed in both cases.

The nonequivalence of the two sides of **4** is reflected in the ^{1}H, ^{13}C, and two-dimensional NMR spectra. The ^{1}H NMR spectrum shows different signals each for 2-H and 13-H, 3-H and 12-H, and 5-Me and 10-Me. The same is true for the ^{13}C NMR spectrum. All pairs of corresponding carbon atoms from the two non-equivalent sides of the molecule give two signals each.

In compounds **2** and **3**, however, both sides of the molecule are equivalent; this is demonstrated by the ^{31}P, ^{1}H, and ^{13}C NMR spectra, which contain only one signal for each corresponding pair of atoms.

The asymmetric conformation found for the structures of **2**, **3a**, and **3b** in the solid state with regard to the three arms referred to as "conelike" macrocycle and "handle" is not fixed in solution. According to the NMR results the three arms of the cage are equivalent. The "handle" arm can be transformed

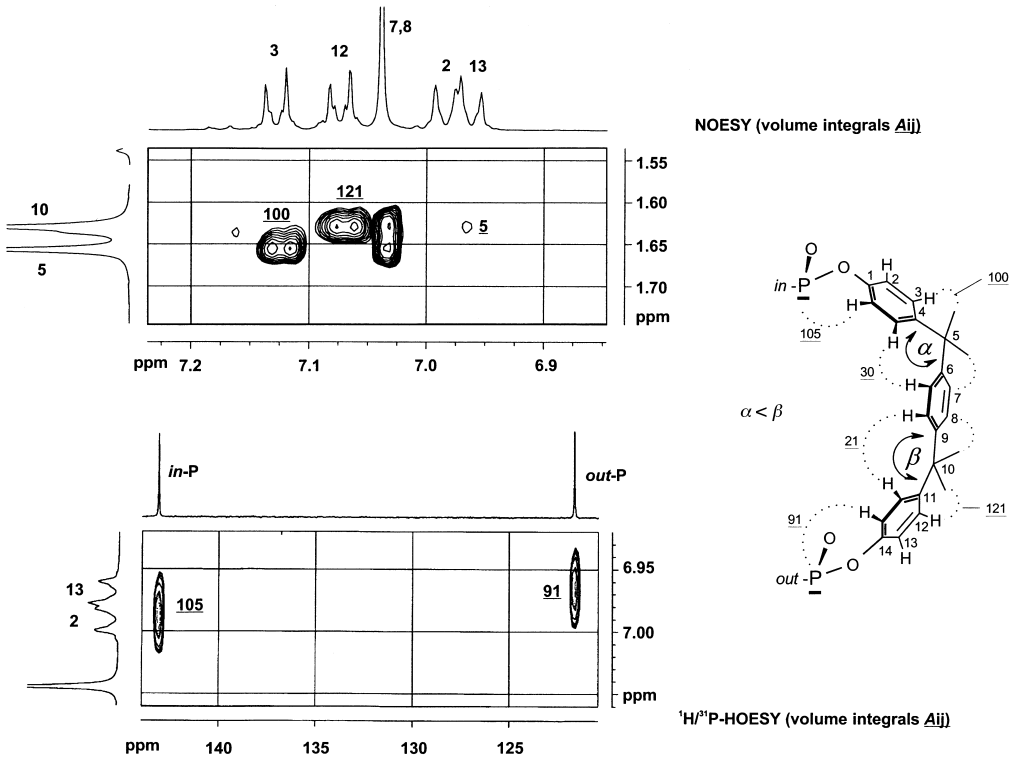


Figure 2. Part of the NOESY- and HOESY-spectra of *in*,*out*-cryptand **4** with values of volume integrals.

into a macrocyclic arm and vice versa. This conformational change is fast enough on the NMR timescale to give only one signal for corresponding protons and carbon atoms on different arms; for the atom numbering of non-equivalent carbon atoms see Scheme 1.

The exact assignment of the proton and carbon NMR signals for compound **4** can be attained by starting from two-dimensional ^{31}P NMR experiments. The assignment of 2-H and 13-H, respectively, to the neighboring *in*-P and *out*-P atom was obtained by ^{1}H/^{31}P HMBC and by ^{31}P/^{1}H HOESY correlation,[7] which considers the heteronuclear NOEs between these nuclei (see example for ^{31}P/^{1}H HOESY in ref. [2a]). The intensities of the ^{31}P/^{1}H HOESY spectrum of **4** (Figure 2) demonstrate that the averaged distance between *in*-P and 2-H in solution is smaller than that between *out*-P and 13-H.

The signals for 2-H and 13-H can be used for the identification of 3-H and 12-H by their COSY peaks. These two protons give NOESY peaks of differing intensities with 7-H and 8-H, respectively. This can be attributed to the different size of the angles α and β (Figure 2). The proton pair 8-H/12-H has a lower NOESY intensity than 7-H/3-H; this is a result of the smaller angle α. The corresponding NOE intensities of 3-H and 12-H with 5-Me and 10-Me, respectively, support this statement. In addition, the 3-H/5-Me NOE interaction is smaller than those of 12-H/10-Me. This is in accordance with the results from the crystal structures of *out*,*out*-isomer **2** and *in*,*in*-isomer **3a**/**3b**. Although the side arms in both **2** and **3a**/**3b** are not equivalent in the solid state and almost all C(Ph)-C(iPr)-C(Ph) angles in one molecule are different, the average of these angles in **2** is slightly larger than in **3** (Table 2). As the C(Ph) – C(iPr) – C(Ph) angles in *out*,*out*-isomer **2** should correspond to the angle β in **4** and the corresponding angles in *in*,*in*-isomer **3a**/**3b** to angle α in **4**, this can be taken as a confirmation for the assignment of the relative size of α and β angles obtained from the NOESY results above.

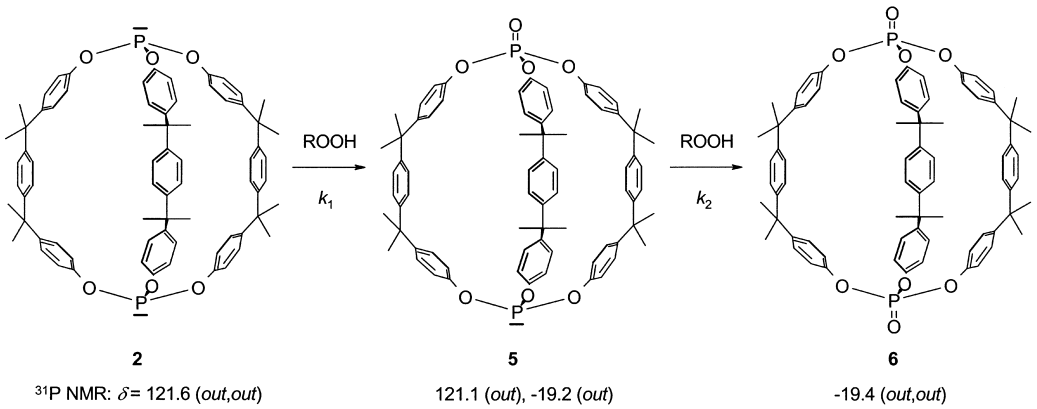
The complete assignment of all signals in the ^{1}H and ^{13}C NMR spectra of **4** to the individual atoms was achieved by ^{1}H/^{13}C correlated HSQC and HMBC spectra.

Oxidation experiments: The *in*- and *out*-P atoms have different reactivities toward oxidizing agents. Addition of an excess of cumene hydroperoxide to the solution of a mixture of **2**, **3**, and **4** in $CDCl_3$ in an NMR tube leads to a rapid decrease of the *out*-phosphite peaks in favor of the corresponding *out*-phosphate peaks. The *in*-P atoms are more slowly oxidized. This is additional proof for the assignment of the ^{31}P NMR peaks in the *in* and *out* position.

In compound **2**, the oxidation of the first P atom proceeds faster than the oxidation of the second (Scheme 2, Figure 3, Table 3, $k_1 > k_2$). This suggests that the primarily oxidized P atom influences the oxidation rate of the second one. As an electronic effect is unlikely over a distance of many bonds, the influence must be of steric nature, probably mediated by a conformational change after the first oxidation that makes the second P-lone pair less available.

The reaction of **4** with cumene hydroperoxide leads to fast oxidation of the *out*-P to give intermediate **7**, followed by a much slower oxidation of the *in*-position to afford *in*,*out*-phosphate **8** (Scheme 3, Figure 4, Table 3, $k_3 \gg k_4$). The difference of the rate constants is about one order of magnitude. Moreover, k_3 is also smaller than the comparable k_1 of the oxidation of **2**. This again shows that the nature of

  0947-6539/00/0616-3046 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 16



Scheme 2. Oxidation of **2** by cumene hydroperoxide.

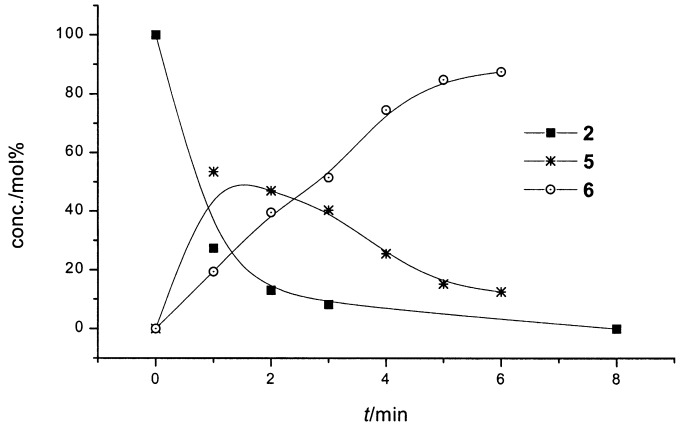


Figure 3. Relative concentrations of P cryptands during the oxidation of **2** with cumene hydroperoxide.

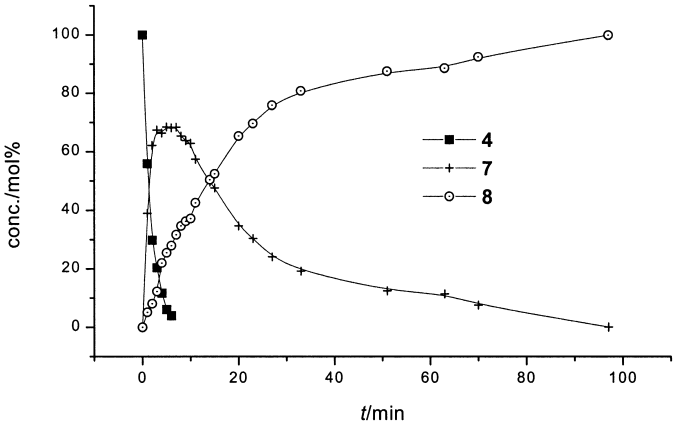


Figure 4. Relative concentration of P cryptands during the oxidation of **4** with cumene hydroperoxide.

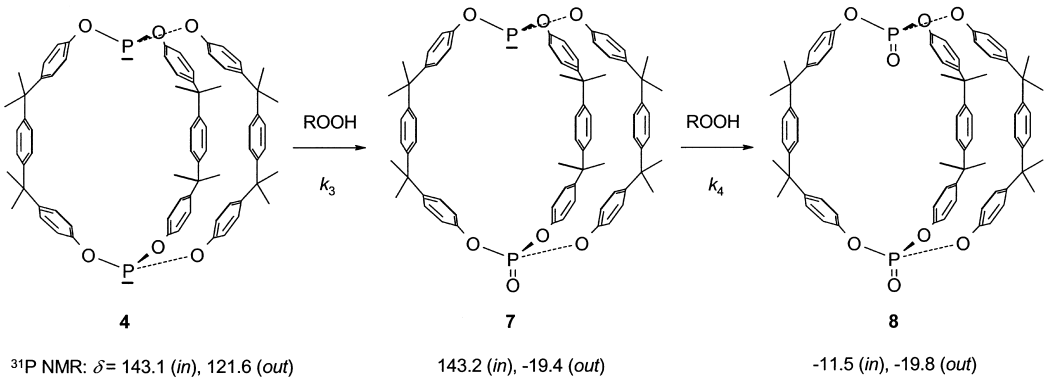
Table 3. Rate constants of the oxidation of **2**, **3**, and **4**.

	k_{ox} [s^{-1}] (298 K)
k_1 (*out*)	13.7×10^{-3}
k_2 (*out*)	7.5×10^{-3}
k_3 (*out*)	9.0×10^{-3}
k_4 (*in*)	8×10^{-4}
k_5 (*in*)	15×10^{-4}
k_6 (*in*)	3×10^{-4}

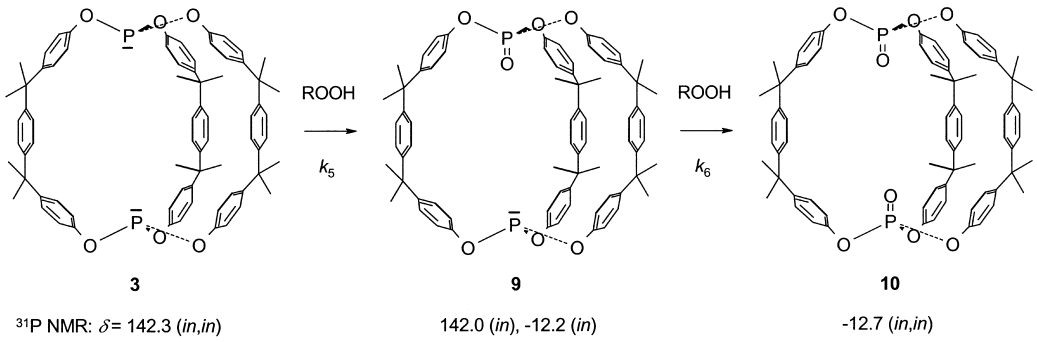
one phosphorus atom can influence the oxidizability of the phosphorus atom on the other side of the cryptand, probably through a conformational change of the whole molecule.

The *in*,*in*-isomer **3** is most slowly oxidized. After the oxidation of the first P atom (k_5) to give intermediate **9**, the further oxidation (k_6) is very slow due to the hindrance of the bulkier phosphate group pointing inwards (Scheme 4, Figure 5, Table 3).

In summary, comparison of the oxidation rate constants of all six P atoms of the three isomeric cage compounds **2**, **3**, and **4** by cumene hydroperoxide resulted in the following sequence (Table 3): $k_1 > k_2 \approx k_3 \gg k_5 > k_4 > k_6$.



Scheme 3. Oxidation of **4** by cumene hydroperoxide.



Scheme 4. Oxidation of **3** by cumene hydroperoxide.

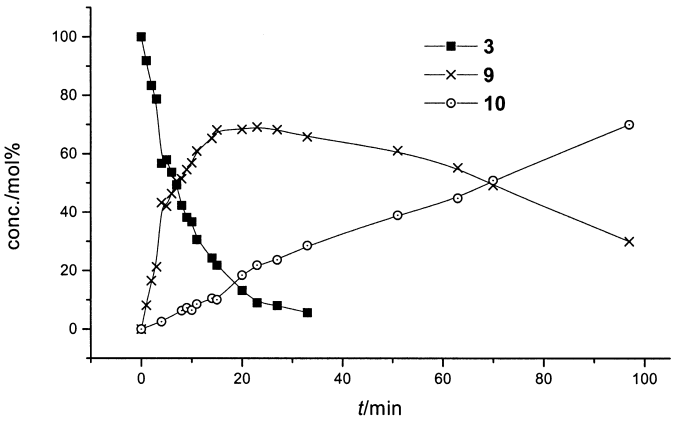
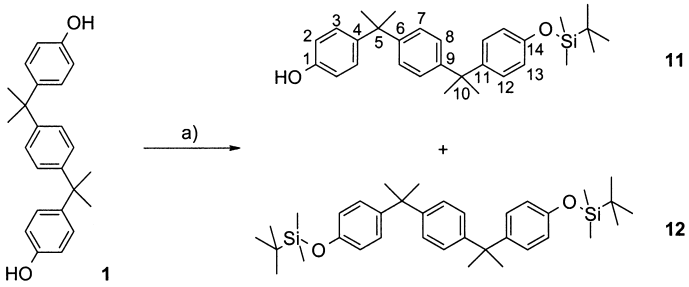


Figure 5. Relative concentrations of P cryptands during the oxidation of **3** with cumene hydroperoxide.

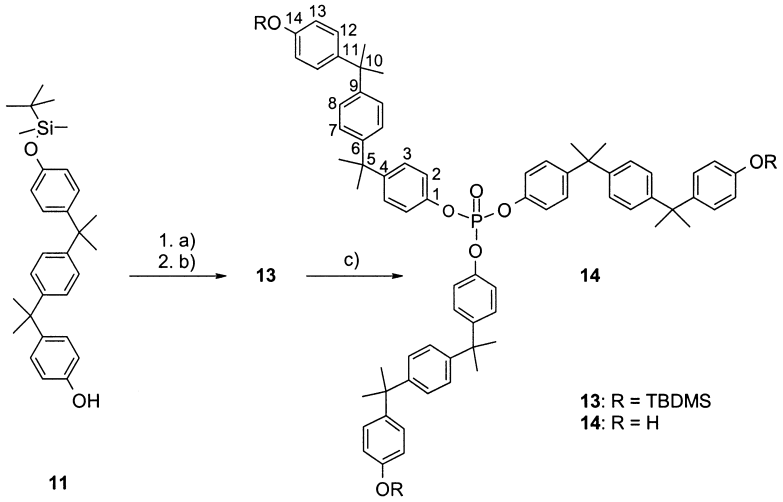


Scheme 5. Monoprotection of bisphenol **1**; a) TBDMSCl, imidazole, CH_2Cl_2, RT, 24 h, 36 %.

The identity of the ^{31}P NMR peaks of the fully oxidized products was confirmed by the oxidation of the single isomers. Oxidation of **3** was also carried out by using an H_2O_2/urea complex to give *in*,*in*-phosphate **10**. This reaction turned out to be faster than the oxidation with cumene hydroperoxide, although in general the H_2O_2/urea complex is less reactive.

Multi-step synthesis of P cryptands: As an alternative to the one-step synthesis (tripod-capping method) of these types of cryptands, we have developed a stepwise synthesis. In the first step, the bisphenol **1** was monoprotected with *tert*-butyldimethylsilyl chloride (TBDMSCl) with a 1:1 ratio of the reactants to give **11** (Scheme 5). The fully protected **12** was formed as a byproduct. The separation of **11** from **12** by column chromatography turned out to be complicated. As **12** is inert to the following reaction conditions, the two compounds can also be applied as a mixture, and compound **12** can be removed at a later stage.

In the second step, the mixture of **11** and **12** was treated with PCl_3 (Scheme 6). In contrast to the trimethylsilyl (TMS) protecting group, which is readily split by treatment with PCl_3 to form phosphorous esters, the TBDMS protecting group is inert to PCl_3. The phosphite formed from the reaction of PCl_3 with the unprotected OH group is immediately oxidized with cumene hydroperoxide to afford the corresponding TBDMS-protected phosphate **13**. This compound can be deprotected by using TBAF in acetic acid according to Ogilvie et al.[8] to give **14**, but only in low yield in our case. In the absence of acetic acid the increased nucleophilicity of F^- also leads to the cleavage of the phenyl phosphate function. This behavior is used in some DNA syntheses to remove the protecting phenyl groups from phosphates without affecting the internucleoside linkage (alkyl phosphates).[8] The cleavage of phenyl phosphites by F^- is even faster than those of phenyl



Scheme 6. Synthesis of cage compound precursor **14**; a) PCl_3, TEA, toluene, RT, 15 h; b) cumene hydoperoxide, toluene, RT, 2 h, 16 %; c) TBAF, AcOH, RT, 24 h, 11 %.

0947-6539/00/0616-3048 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 16

phosphates. Therefore, it is not possible to remove the TBDMS protecting group selectively in the presence of a phosphite function.[9] The low yield is attributed to a partial cleavage of the P–O bond by the F^- ion.

Phosphate **14** can be cyclized with PCl_3 to form P-bridged cage compounds (Scheme 7). Four diastereomers (**5**, **7**, **9**, and **15**) are possible, with the phosphorus lone pair or the phosphate oxygen in the *in* or the *out* position. All four possible isomers could be detected in the crude product by ^{31}P NMR spectroscopy. Isomers **5** and **7** are the main products, while isomers **15** and **9** were observed as traces only. After chromatography, a mixture of **5** and **7** were isolated as one fraction.

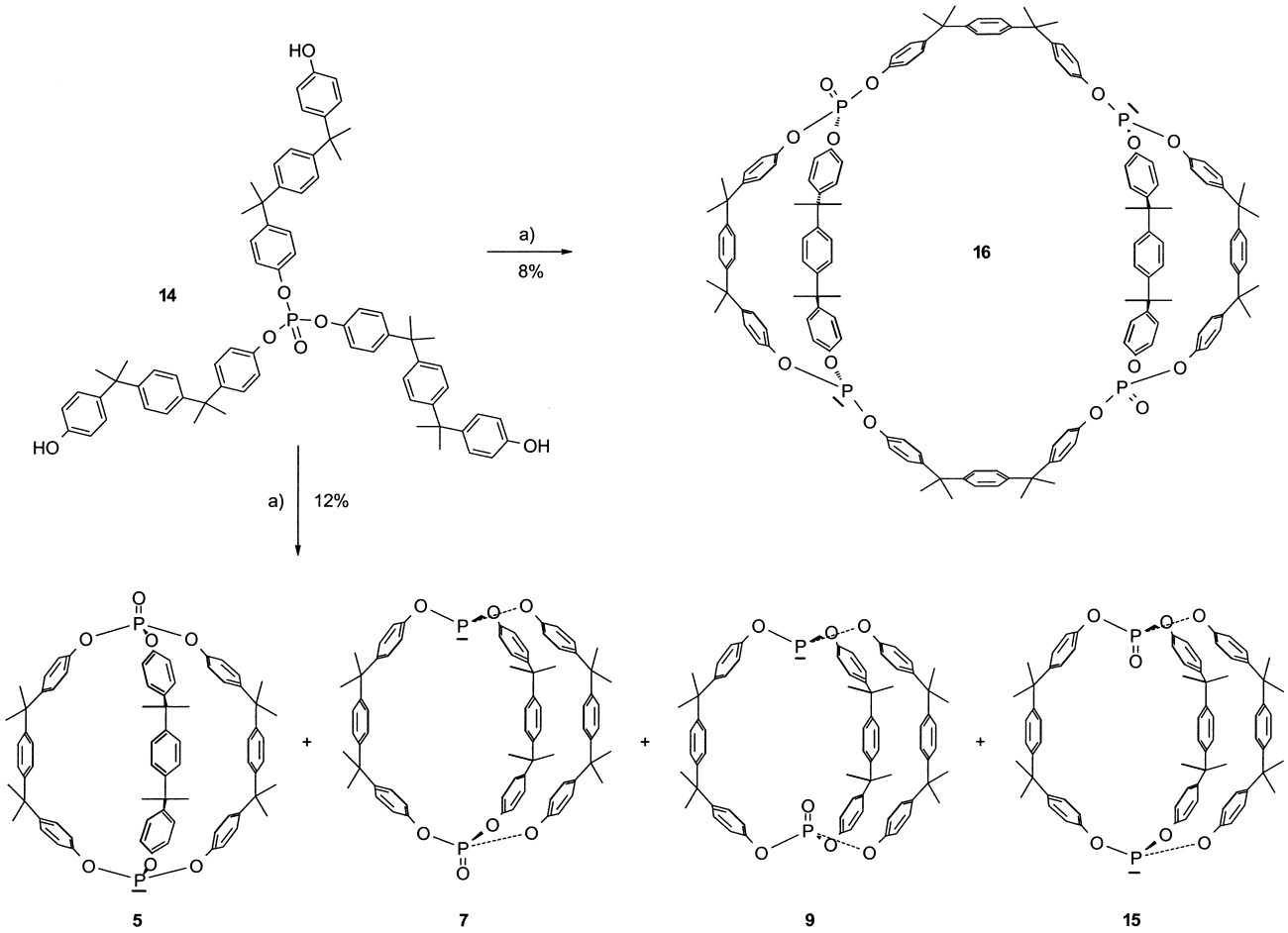
Interestingly a second fraction was obtained that gave a single MALDI-TOF mass peak at 2226 Da. It was therefore tentatively assigned to an isomeric mixture of the cylindrical macrotricycle **16**. The analogous pyramidal product with the same molecular mass cannot be formed owing to the pre-set structure of reactant **14**. The ^{31}P NMR peaks of **16** do not have the characteristic difference between the *in* and the *out* position as observed for **5**, **7**, **9**, and **15**. They give two groups of signals around $\delta = 128$ and $\delta = 127$, besides those due to the phosphate groups at $\delta = -17.1$ and -17.4. This is in the same region as for corresponding open-chain products. This seems plausible as the steric stress is diminished in the large macrotricycle in contrast to the macrobicycles **5**, **7**, **9**, and **15**.

Experimental Section

General: Melting points were determined on a Boëtius melting point apparatus. ^1H NMR (TMS internal reference), ^{13}C NMR (TMS internal reference) and ^{31}P NMR spectra (85% H_3PO_4 external reference) were recorded on a Bruker AC200 P, AC300 and a DRX-500 spectrometer. Exact assignment of ^1H and ^{13}C NMR spectra was carried out by two-dimensional NMR techniques (COSY, $^1H/^{13}C$ correlated HSQC, $^1H/^{13}C$ correlated HMBC, NOESY, $^1H/^{31}P$ correlated HMBC, $^{31}P/^1H$ correlated HOESY) for **4**, **11**, and **14**. The assignment of ^1H and ^{13}C NMR spectra for **2**, **3**, **10**, and **13** was done in accordance with those of **4**, **11**, and **14**, respectively. IR spectra were performed on a Nicolet 250 FT-IR spectrometer. The mass spectra were recorded on a Finnigan MAT 95-A spectrometer and MALDI-TOF mass spectra were measured on a Kratos Kompact MALDI II (Shimadzu Europa GmbH, Duisburg, Germany) with an N_2 laser source ($\lambda = 337$ nm), a positive polarity, and 20 kV acceleration voltage. The microanalyses were recorded on a CHN-S analyzer (Fa. Carlo Erba). Solvents were purified by conventional methods.

Phoshite cryptands 2, 3, and 4: Bisphenol **1** (4.00 g, 11.5 mmol) and TEA (3.00 g, 29.6 mmol) were dissolved in toluene (1.8 L) in a flame-dried 2 L flask under argon atmosphere (bisphenol **1** is only partly soluble). Under vigorous stirring, PCl_3 (1.06 g, 7.7 mmol) was added dropwise by syringe. The solution was stirred for 3 d at 25 °C. The hydrochloride formed was removed, and the solvent was evaporated. A partially crystallizing viscous oil was obtained. Chromatography on silica gel with *n*-pentane/toluene (1:1) afforded *out*,*out*-cryptand **2** (210 mg, 5.0%), *in*,*out*-cryptand **4** (185 mg, 4.4%), and *in*,*in*-cryptand **3** (125 mg, 2.9%) as white solids. The latter could also be isolated in a pure state by chromatography of the crude product on basic aluminum oxide with $CHCl_3$.

***Out*,*out*-isomer 2**: M.p. 289–293 °C; $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): $\delta = 121.6$; ^1H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J = 8.7$ Hz, 12H; 3-H),



Scheme 7. Cyclization of **14** with PCl_3; a) PCl_3, TEA, toluene, RT, 2 d.

7.06 (s, 12H; 7-H), 6.94 (d, $J = 8.6$ Hz, 12H; 2-H), 1.63 (s, 36H; 5-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.1$ (C-1), 147.5 (C-7), 146.5 (C-4), 127.8 (C-3), 126.2 (C-7), 120.2 (d, ^3J(P, C) = 6.0 Hz; C-2), 42.0 (C-5), 30.6 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxy-anthracene): *m/z*: 1093 $[M+H]^+$, 1115 $[M+Na]^+$, 1132 $[M+K]^+$; elemental analysis (%) calcd for $C_{72}H_{72}O_6P_2$ (1095.24): C 78.95, H 6.63; found C 78.58, H 7.01.

***In,in*-isomer 3**: M.p. 313–316 °C; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta =$ 142.3; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 8.6$ Hz, 12H; 3-H), 7.02 (s, 12H; 7-H), 6.99 (d, $J = 8.6$ Hz, 12H; 2-H), 1.65 (s, 36H; 5-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.4$ (d, ^2J(P, C) = 10.7 Hz; C-1), 147.8 (C-6), 146.6 (C-4), 128.1 (C-3), 126.1 (C-7), 119.8 (d, ^3J(P, C) = 8.5 Hz; C-2), 42.0 (C-5), 30.6 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 1094 $[M+H]^+$; elemental analysis (%) calcd for $C_{72}H_{72}O_6P_2$ (1095.24): C 78.95, H 6.63; found C 78.74, H 6.91.

***In,out-isomer* 4**: M.p. 290–294 °C; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta =$ 143.1 (*in*), 121.6 (*out*); ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.13$ (d, $J =$ 8.6 Hz, 6H; 3-H), 7.08 (d, $J = 8.7$ Hz, 6H; 12-H), 7.04 (s, 12H; 7-H, 8-H), 6.99 (d, $J = 8.6$ Hz, 6H; 2-H), 6.98 (d, $J = 8.7$ Hz, 6H; 13-H), 1.66 (s, 18H; 5-Me), 1.63 (s, 18H; 10-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.5$ (d, ^2J(P, C) = 10.9 Hz; C-1), 149.2 (C-14), 147.6 (C-6, C-9), 146.6 (C-4), 146.4 (C-11), 128.0 (C-3), 127.9 (C-12), 126.3 (C-8), 126.1 (C-7), 120.0 (d, ^3J(P, C) = 6.0 Hz; C-13), 119.7 (d, ^3J(P, C) = 8.7 Hz; C-2), 42.1 (C-10), 41.9 (C-5), 30.7 (10-Me), 30.4 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 1094 $[M+H]^+$; elemental analysis (%) calcd for $C_{72}H_{72}O_6P_2$ (1095.24): C 78.95, H 6.63; found C 78.45, H 6.83.

***In,in*-phosphate cryptand 10**: Compound **3** (21.8 mg, 0.02 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Urea/H_2O_2 complex (9 mg, 0.10 mmol) was added to the solution, which was then stirred at 25 °C for 3 d. Subsequently the precipitate was filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel with toluene/*n*-pentane 1:1 as the eluent, to obtain **10** (18.7 mg, 83%) as a white solid. M.p. > 380 °C; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = -12.7$; ^{1}H NMR (300.1 MHz, $CDCl_3$,): $\delta = 7.07$ (d, $J = 8.9$ Hz, 12H; 2-H or 3-H), 7.01 (d, $J = 9.0$ Hz, 12H; 2-H or 3-H), 6.96 (s, 12H; 7-H), 1.57 (s, 36H; 5-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 148.3$ (d, ^2J(P, C) = 6.5 Hz; C-1), 147.8 (C-6 or C-4), 147.4 (C-6 or C-4), 128.2 (C-3), 126.3 (C-7), 119.7 (d, ^3J(P, C) = 4.8 Hz; C-2), 42.1 (C-5), 30.5 (5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene); *m/z*: 1129 $[M+H]^+$, 1151 $[M+Na]^+$; elemental analysis (%) calcd for $C_{72}H_{72}O_8P_2$ (1127.24): C 76.71, H 6.44; found C 76.32, H 6.77.

Oxidation of cryptands 2, 3 and 4 with cumene hydroperoxide: The experiment was carried out directly in the NMR tube and monitored by means of ^{31}P NMR spectroscopy. A mixture of **2**, **3**, and **4** (30 mg, 0.027 mmol) was placed in an NMR tube and dissolved in $CDCl_3$ (1 mL). An excess of cumene hydroperoxide (50 μL, 0.338 mmol) was added. The temperature was kept at 25 °C by air-flow thermostatting. At the beginning of the reaction, spectra were recorded every 60 s. At a later stage of the reaction the periods were extended according to the reaction rate. The degree of conversion was determined by the ratio of the ^{31}P NMR peak heights to the total of all peak heights.

Monoprotected bisphenol 11: Bisphenol **1** (30.0 g, 86.6 mmol), TBDMSCl (21.0 g, 139.3 mmol) and 15.2 g (223.3 mmol) imidazole were dissolved in dry CH_2Cl_2 (200 mL). The solution was stirred for 3 d at 25 °C. Subsequently, the solution was washed three times each with saturated NaCl, $CuSO_4$, and water. After drying over $MgSO_4$ the solvent was removed. The crude product was eluted through silica gel with *n*-pentane/diethyl ether (2:1). The resulting product still contained the fully protected bisphenol **12** as a byproduct. This mixture, however, was used for the following reaction with PCl_3. Pure **11** (14.4 g, 36.1%) can be obtained by fractional crystallization from *n*-hexane. M.p. 97.5–99.5 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 8.6$ Hz, 2H; 3-H), 7.08 (s, 4H, 7-and 8-H), 7.06 (d, $J = 8.6$ Hz, 2H; 12-H), 6.71 (d, $J = 8.6$ Hz, 2H; 2-H), 6.71 (d, $J = 8.6$ Hz, 2H; 13-H), 4.36 (s, 1H; O*H*), 1.62 (s, 6H; 5-Me), 1.61 (s, 6H; 10-Me), 0.96 (s, 9H; *t*Bu), 0.18 (s, 6H; Si–Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 153.3$ (C-14), 153.2 (C-1), 148.0 (C-9), 147.8 (C-6), 143.4 (C-11), 143.3 (C-4), 128.0 (C-3), 127.7 (C-12), 126.3 (C-7), 126.2 (C-8), 119.2 (C-13), 114.7 (C-2), 41.93 (C-5 or C-10), 41.90 (C-5 or C-10), 31.0 (5-Me or 10-Me), 30.9 (5-Me or 10-Me), 25.7 (*t*Bu-Me), 18.2 (C-*t*Bu), −4.4 (Si-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 458 $[M+H]^+$; elemental analysis (%) calcd for $C_{30}H_{40}SiO_2$ (460.71): C 78.21, H 8.75; found C 78.25, H 8.95.

Phosphate 13: Monosilylated bisphenol **11** (29.2 g, 63.4 mmol; contains bisilylated product **12**) and TEA (15 mL, 108.4 mmol) were dissolved in toluene (600 mL). PCl_3 (2.91 g, 21.1 mmol) was added under stirring. The mixture was stirred at 25 °C for 15 h. Cumene hydroperoxide (5 mL, 33.8 mmol) was added, and the solution stirred for another 2 h at 25 °C. The hydrochloride was filtered, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel with toluene as the eluent. Phosphate **13** was obtained as a colorless oil (4.86 g, 16.1%). (The signals marked * could not be exactly distinguished; the coupling constant for the doublet marked ∔ could not be determined.) ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): $\delta = -17.08$; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.2$–7.05 (m, 30H), 6.73 (d, $J = 8.7$ Hz; 6H, 13-H), 1.64 (s, 18H; 5-Me or 10-Me), 1.63 (s, 18H; 5-Me or 10-Me), 0.99 (s, 27H; *t*Bu), 0.20 (s, 18H; Si-Me); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 153.3$ (C-14), 148.3*, 148.2*, 147.0, (C-4, C-6, C-9), 148.2* (d*, ^2J(P,C); C-1), 143.2 (C-11), 128.2, 127.7 (C-3, C-12), 126.3, 126.2 (C-7, C-8), 119.4 (d, ^3J(P,C) = 5.2 Hz; C-2), 119.2 (C-13), 42.2, 41.9 (C-10, C-5), 30.9, 30.8 (10-Me, 5-Me), 25.7 (*t*Bu-Me), 18.1 (C-*t*Bu), −4.4 (Si–Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 1424 $[M+H]^+$; elemental analysis (%) calcd for $C_{90}H_{117}O_7Si_3P$ (1426.08): C 75.80, H 8.27; found C 75.38, H 8.53.

Phosphate 14: Phosphate **13** (4.86 g, 3.41 mmol) was dissolved in ethanol (250 mL), then TBAF · 3H_2O (20 g, 63.4 mmol) was added. The solution was stirred for 24 h at room temperature. After the addition of water, a white solid precipitated, which was filtered and dissolved in toluene. The toluene solution was dried with $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography with CH_2Cl_2/MeOH (10:1) as the eluent. Phosphate **14** (418 mg, 11.3%) was obtained as a white solid. M.p. 98–103 °C; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = -17.18$; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 8.8$ Hz, 6H; 3-H), 7.08 (d, $J = 8.6$ Hz, 6H; 2-H), 7.08 (d, $J = 8.6$ Hz, 6H; 8-H), 7.07 (d, $J = 8.75$ Hz, 6H; 12-H), 7.05 (d, $J = 8.55$ Hz, 6H; 7-H), 6.70 (d, $J = 8.65$ Hz, 6H; 13-H), 4.90 (br s, 1H; O*H*), 1.61 (s, 36H; 5-Me and 10-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 153.2$ (C-14), 148.3 (d, ^2J(P, C) = 7.9 Hz; C-1), 148.2 (C-4 and C-6), 147.2 (C-9), 143.0 (C-11), 128.2 (C-3), 127.9 (C-12), 126.3 (C-8), 126.2 (C-7), 119.4 (d, ^3J(P, C) = 4.6 Hz; C-2), 114.6 (C-13), 42.2 (C-5), 41.9 (C-10), 30.9 (10-Me or 5-Me), 30.8 (10-Me or 5-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 1084 $[M+H]^+$, 1106 $[M+Na]^+$; elemental analysis calculated (%) for $C_{72}H_{75}O_7P$ (1083.29): C 79.82, H 6.98; found C 79.51, H 7.13.

Phosphite/phosphate cryptands 5, 7, 9, and 15: Phosphate **14** (290 mg, 0.27 mmol) and TEA (200 mL, 1.4 mmol) were dissolved in toluene (250 mL). PCl_3 (36.9 mg, 0.27 mmol) from a prediluted solution in toluene was added. The solution was stirred for 2 d at 25 °C. Subsequently, the hydrochloride was filtered and the solvent was removed in vacuo. Column chromatography on silica gel with toluene/Et_2O (9:1) as the eluent gave a mixture of phosphite/phosphate-cryptands **5**, **7**, and traces of **15** (total yield 36 mg, 12%) as a white solid. Another fraction afforded a diastereomeric mixture of macrotricycle **16** (24 mg, 8%) as a white solid (m.p. 328–335 °C). Mixture of isomers **5**, **7**, and **15**: M.p. 312–323 °C; MALDI-TOF-MS matrix: 1,8,9-trihydroxyanthracene): *m/z*: 1112 $[M+H]^+$, 1134 $M+Na]^+$, 1151 $[M+K]^+$; elemental analysis calculated (%) for $C_{72}H_{72}O_7P_2$ (1111.24): C 77.82, H 6.53; found C 77.32, H 6.90. The following ^{31}P NMR peaks have been assigned from the mixture of isomers according to the peaks obtained from the oxidation experiment of **2**, **3**, and **4** and the relative peak intensities in the crude product.

***Out,out*-phosphite/phosphate cryptand 5**: ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = 121.1$ (*out*), −19.2 (*out*).

***In,out*-phosphite/phosphate cryptand 7**: ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = 143.2$ (*in*), −19.3 (*out*).

***In,in*-phosphite/phosphate cryptand 9**: ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$,): $\delta = 141.9$ (*in*), −12.3 (*in*).

***Out,in*-phosphite/phosphate cryptand 15**: ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = 121.9$ (*out*), −11.7 (*in*).

Macrotricyclic phosphite/phosphate cryptand 16: ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): $\delta = 128.2$, 128.1, 127.6, 127.5, 127.3, 127.2 [P-phosphite (*in* and *out* position in different isomers)], −17.1, −17.4 [P-phosphate (*in* and *out* position in different isomers)]; MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): *m/z*: 2226 $[M+H]^+$; elemental analysis calculated (%) for $C_{144}H_{144}O_{14}P_4$ (2222.47): C 77.82, H 6.53; found C 78.20, H 6.99.

0947-6539/00/0616-3050 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 16

Table 4. Crystallographic details for the X-ray analysis of **2** and **3**.

	2	**3**
empirical formula	$C_{72.5}H_{73}O_6P_2Cl$	$C_{77.5}H_{79}O_6P_2N$
formula	$C_{72}H_{72}O_6P_2 \cdot 0.5\,CH_2Cl_2$	$C_{72}H_{72}O_6P_2 \cdot C_2H_3N \cdot 0.5\,C_7H_8$
crystal system	triclinic	monoclinic
space group	$P\bar{1}$	$C2$
a [Å]	12.3316(7)	21.033(4)
b [Å]	15.5292(8)	13.409(3)
c [Å]	18.8975(10)	25.001(5)
α [°]	78.2929(10)	90
β [°]	77.5780(10)	103.66(3)
γ [°]	66.7520(10)	90
V [Å^3]	3219.0(3)	6852(2)
Z	2	4
ρ_{calcd} [g cm^{-3}]	1.174	1.146
μ [mm^{-1}]	0.160	0.115
crystal size [mm]	$0.50 \times 0.43 \times 0.11$	$2.1 \times 1.4 \times 0.7$
index range	$-12 \le h \le 12$	$-27 \le h \le 27$
	$-16 \le k \le 13$	$-17 \le k \le 15$
	$-18 \le l \le 19$	$-32 \le l \le 32$
$2\theta_{max}$ [°]	21.5	27.5
completeness to 2θ [%]	99.7	88.6
reflections measured	12380	10487
unique reflections	7359	10486
observed reflections	6023	8782
refinement method	full matrix least-squares on F^2	
data/restraints/parameters	7359/7/770	
goodness-of-fit on F^2	1.090	1.142
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0555$ $wR2 = 0.1660$	$R1 = 0.0796$ $wR2 = 0.1983$
R indices (all data)	$R1 = 0.0683$ $wR2 = 0.1750$	$R1 = 0.0987$ $wR2 = 0.2190$
largest diff. peak [e Å^{-3}]	0.731	1.545
largest diff. hole [e Å^{-3}]	−0.217	−0.471

X-ray measurement: X-ray structure analysis data for **2** were collected at 298 K with a BRUKER axs SMART diffractometer system with a CCD detector, and for **3** at 238 K with a NONIUS KAPPA CCD diffractometer system; in both cases $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, was used. The structures were solved and refined by using a SHELXS and SHELXL program package. See Table 4 for crystallographic details. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-136952 for **2** and CCDC-136951 for **3**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +(44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgement

We thank Dr. M. Ruf from BRUKER axs Karlsruhe for repeating the measurement of the X-ray reflection data of compound **2** and Dr. H. Goerls (Friedrich-Schiller-University Jena) and Dr. M. Adam (NONIUS GmbH, Delft) for the X-ray measurement of compound **3**. The authors gratefully acknowledge the financial support of this work by the DFG.

[1] a) A. M. Caminade, J. P. Majoral, *Chem. Rev.* **1994**, *94*, 1183–1213; b) A. M. Caminade, J. P. Majoral, *Synlett* **1996**, 1019–1028.
[2] a) B. P. Friedrichsen, H. W. Whitlock, *J. Am. Chem. Soc.* **1989**, *111*, 9132–9134; b) B. P. Friedrichsen, R. P. Powell, H. W. Whitlock, *J. Am. Chem. Soc.* **1990**, *112*, 8931–8941.
[3] C. B. Allan, L. O. Spreer, *J. Org. Chem.* **1994**, *59*, 7695–7700.
[4] a) F. Gonce, A. M. Caminade, F. Boutonnet, J. P. Majoral, *J. Org. Chem.* **1992**, *57*, 970–975; b) J. Mitjaville, A. M. Caminade, R. Mathieu, J. P. Majoral, *J. Am. Chem. Soc.* **1994**, *116*, 5007–5008; c) J. Mitjaville, A. M. Caminade, J. P. Majoral, *J. Chem. Soc. Chem. Commun.* **1994**, 2161–2162;
[5] I. Bauer, W. D. Habicher, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *139*, 89–105.
[6] a) B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, **1992**; b) F. Vögtle, G. Hohner, E. Weber, *J. Chem. Soc., Chem. Comm.* **1973**, 366–367; c) G. R. Newkome, V. K. Majestic, F. R. Fronczek, *Tetrahedron Lett.* **1981**, *22*, 3035–3038; d) G. R. Newkome, V. K. Majestic, F. R. Fronczek, J. L. Atwood, *J. Am. Chem. Soc.* **1979**, *101*, 1047–1048; e) J. Jazwinski, J.-M. Lehn, D. Lilienbaum, R. Ziessel, J. Guilhem, C. Pascard, *J. Chem. Soc. Chem. Comm.* **1987**, 1691–1694.
[7] C. Yu, G. C. Levy, *J. Am. Chem. Soc.* **1984**, *106*, 6533–6537.
[8] K. K. Ogilvie, S. C. Beaucage, D. W. Entwistle, *Tetrahedron Lett.* **1976**, *16*, 1255–1256.
[9] G. Kumar, M. S. Poonian, *J. Org. Chem.* **1984**, *49*, 4905–4912.

Received: January 26, 2000 [F2260]