Phosphorus macrocycles and cryptands*,**

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The reviews covers authors´ studies dealing with the synthesis of P^{III}- and P^{V}-containing macrocycles and cryptands. The separation, structural characterization, and the chemical properties of a number of homeomorphic compounds with *in*,*out* bridgehead phosphorus atoms are described. Modification of the *in*-positions in macrobicyclic compounds with bulky groups is described for the first time.

Key words: macrocycles, phosphites, cryptands, *in*,*out*-isomers, crystal structure, the Staudinger reaction.

Introduction

Phosphorus-containing macrocycles are attractive molecules with potential applications in supramolecular and synthetic organic chemistry. Although phosphorus macrocycles have been much less studied than their aza analogs, the chemistry of these compounds has already been surveyed,[1] in particular, their use as ionophores.[2] Crown ether analogs, phosphorous hydrazides, and cyclophosphazenes occupy the largest section in this field, apart from biochemical phosphorus-containing macrocycles such as cyclic DNA.[1]

Phosphorus macrobicycles with configurationally stable P-bridgehead atoms show an interesting feature, namely, *in*,*out*-isomerism*** with respect to their exocyclic residues.[3] Due to their special position inside the cavity, the *in*-isomers (directed inside the macrocycle cavity) are particularly attractive, as their micro environment can give rise to unusual properties. Only a few stable *in*-isomers have been isolated until now; these are mainly bicyclic compounds devoid of phosphorus. The bridgehead atoms are mostly amine or ammonium nitrogen atoms;[4—6] in a few cases, these are methine C atoms[7] or phosphine and phosphine oxide P atoms.[8,9] The largest *in*-substituent reported to date is the methyl group at the sp^3 bridgehead carbon atom.[10—13] A small *in*-fluorosilane has been reported.[14] However, the synthetic access to such *in*-functional groups with the aim of functionalization of macrobicyclic compounds has not yet been elaborated.

In this paper, we describe the synthesis of a number of phosphorus macrocycles and macrobicycles and their further modification. This includes the first examples for the introduction of bulky groups into *in*-positions of macrobicyclic compounds

Synthesis of phosphorus macrocycles

Phosphorous chloride method. The methods suitable for the formation of macrocyclic compounds have been classified by Lehn.[5] To construct phosphorus-containing macrocycles, we chose the so-called [2+2]-condensation using bisphenols and phosphodichloridites as building blocks.

As the first example, we performed the reaction of phosphodichloridite **2** with bisphenol **1** under moderate dilution conditions ($2.5 \cdot 10^{-3}$ mol L^{-1}), which furnished macrocycle **3** (Scheme 1) in 7% yield.[15,16] The *cis*- and *trans*-diastereomers of **3** are formed in 1 : 1 ratio, being

* Dedicated to Professor A. I. Konovalov on the occasion of his 70th birthday.

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*** *in*,*out*-Isomers (convex-concave) are isomers differing in the arrangement of the residues pointing either inwards (*in*) or outwards (*out*) with respect to the macrobicyclic system.

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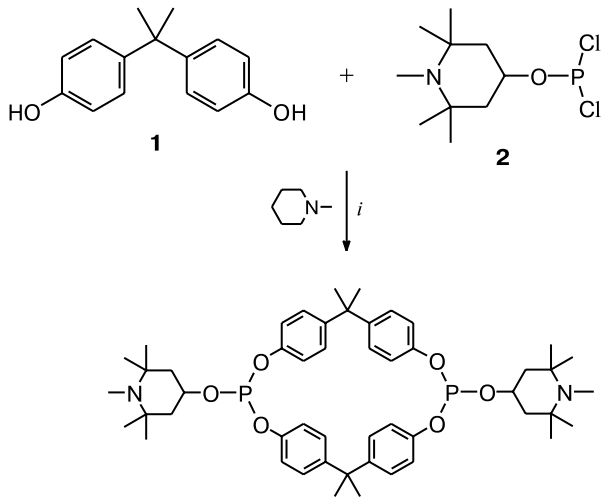
responsible for ^{31}P NMR signals at δ 136.8 and 137.2, respectively.

Scheme 1



cis-**3**, *trans*-**3** (1 : 1, 7%)

Conditions: *i*. Toluene, ~20 °C, 3 days

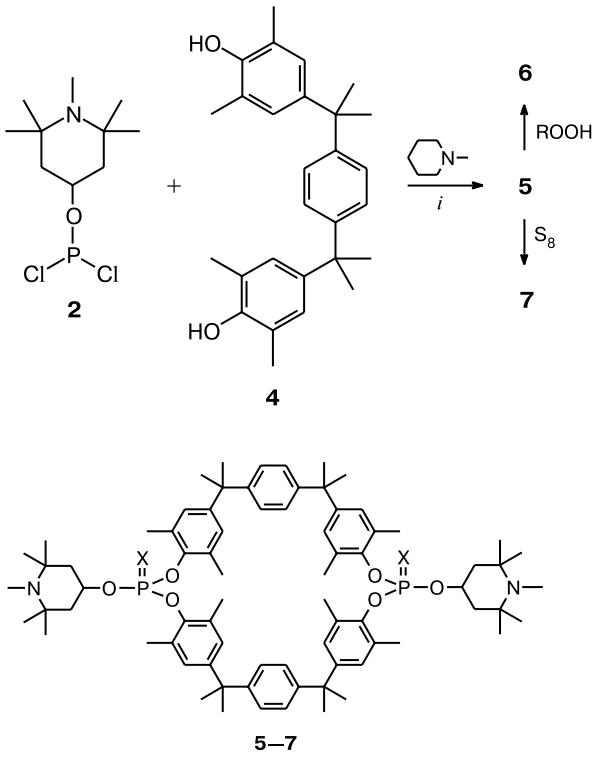
The reaction of phosphodichloridite **2** with bisphenol **4** affords the phosphite macrocycle **5** as a mixture of *cis*- and *trans*-diastereomers (Scheme 2).[15] In this case, the yield of macrocycle **5** (25%) was higher than that of compound **3**. This suggests that the pre-organization effect favors the ring closure rather than the formation of oligomeric products.

Oxidation of macrocycle **5** with cumene hydroperoxide gives the corresponding phosphate **6** in a quantitative yield (see Scheme 2). The addition of sulfur to product **5** affords a *cis*,*trans*-isomer mixture of macrocyclic thiophosphate **7** in a straightforward reaction.[15]

A comparative study of the synthesis of P-macrocycles starting from phosphodichloridite **8** and bisphenols of different shape and flexibility under identical conditions showed that the intrinsic structural information of the building blocks leads to macrocycles of different sizes, thus amplifying the structural differences in the starting materials.[17] The reaction was carried out in toluene at room temperature for 24 h in the presence of Et_3N as a base with a concentration of the starting materials of $4.5 \cdot 10^{-3}$ mol L^{-1}.

The reaction of bisphenol **9** with phosphodichloridite **8** afforded the corresponding P-macrocycle **10** in a moderate yield (46%) as a mixture of *cis*- and *trans*-isomers (Scheme 3).[17] This demonstrates that, as in the case of formation of macrocycle **5**, bisphenol **9** is well suited for this type of [2+2]-macrocyclocondensation, giving only minor amounts of oligomeric side products. The two isomers of **10** are formed in a 1 : 1 ratio, according to the

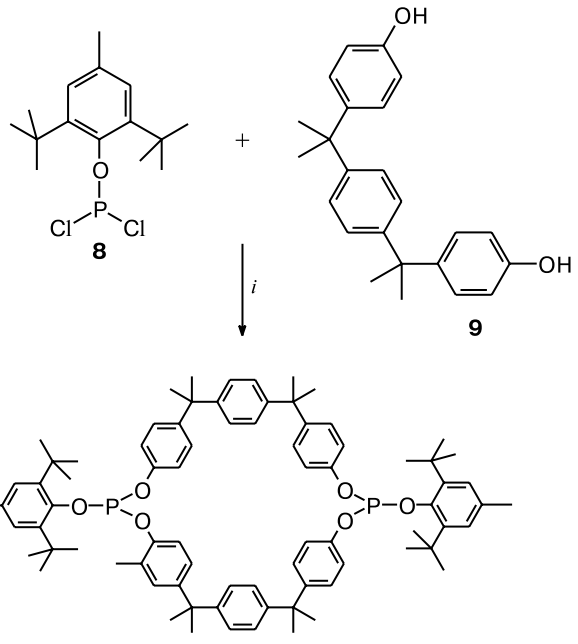
Scheme 2



5—7

Reagents, conditions, and product yields: *i*. toluene, 60 °C, 10 h; *cis*-**5**,*trans*-**5**: X is the lone electron pair, yield 25%; *cis*-**6**,*trans*-**6**: X = O, yield 100%; *cis*-**7**,*trans*-**7**: X = S, yield 100%.

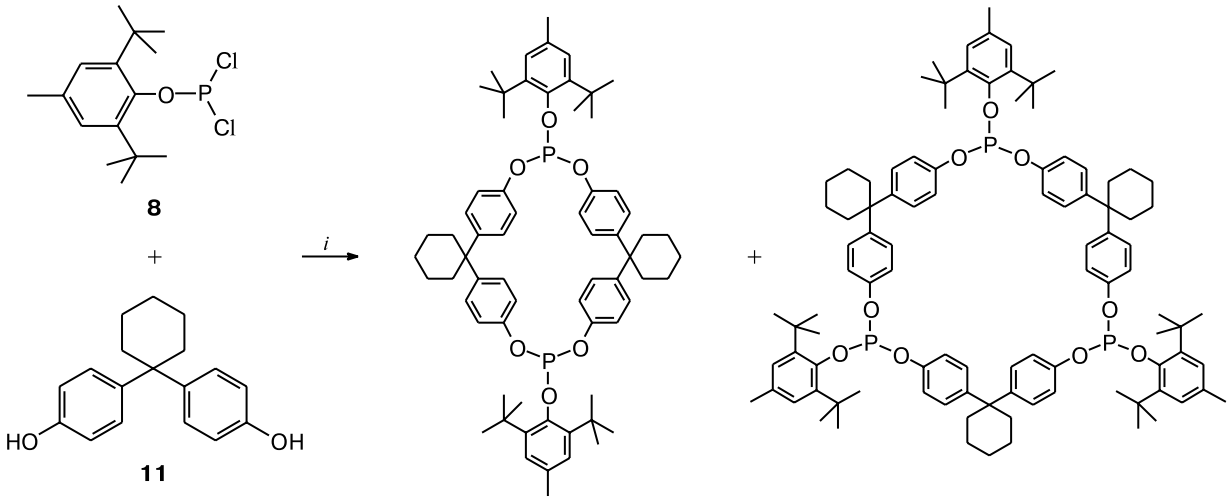
Scheme 3



cis-**10**, *trans*-**10** (1 : 1, 46%)

Conditions: *i*. Et_3N, toluene, ~20 °C, 24 h.

Scheme 4



cis-**12**, *trans*-**12** (1 : 1, 35%) *cis*,*cis*-**13** + *cis*,*trans*-**13** (31%)

Conditions: *i*. Et_3N, toluene, ~20 °C, 24 h.

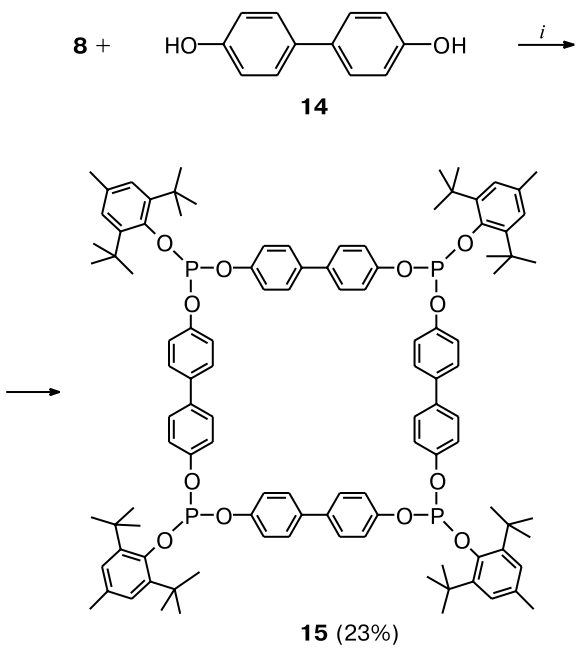
intensity of the ^{31}P NMR peaks at δ 137.2 and 136.9, respectively.

The large size of the macrocycle is probably responsible for the absence of any substrate-induced diastereoselectivity mediated by the first phosphite center formed, even though it bears a very bulky exocyclic substituent. Bisphenol **11** has been repeatedly used for the synthesis of macrocyclic products, as its cyclohexane-1,2-diyl unit forces the molecule into a curved shape, which seems to fit extremely well for the formation of macrocycles.[18] In the reaction of **11** with **8**, we obtained the corresponding dimeric macrocyclic product **12** as a 1 : 1 mixture of *cis*- and *trans*-isomers with ^{31}P NMR peaks at δ 141.4 and 141.2, respectively (Scheme 4).[17]

However, the trimeric product **13** was isolated in nearly the same yield. In the case of this macrocycle, two isomers (*cis*,*cis* and *cis*,*trans*) can be formed as well; this would give rise to three different peaks in the ^{31}P NMR spectrum of the reaction mixture. Since the ^{31}P NMR signals at δ 137.2 and 137.1 appeared in a 1 : 2 ratio, they were tentatively assigned to *cis*,*trans*-**13**. The c*is*,*cis*-isomer **13** is formed in only minor amounts.

According to its geometric features, 1,1′-biphenyl-4,4′-diol (**14**) is not expected to form macrocyclic compounds. In fact, one would expect the preferred formation of oligomeric compounds. However, even in this case, in the reaction with phosphorous dichloride **8**, we could isolate the tetrameric macrocycle **15** as a mixture of diastereomers (*rccc*, *rcct*, *rctt*, *rtct*, Scheme 5).[17] The finally isolated product **15** shows only one ^{31}P NMR signal at 138.4 ppm. However, this also might be a mixture of isomers with unresolved ^{31}P NMR signals.

Scheme 5

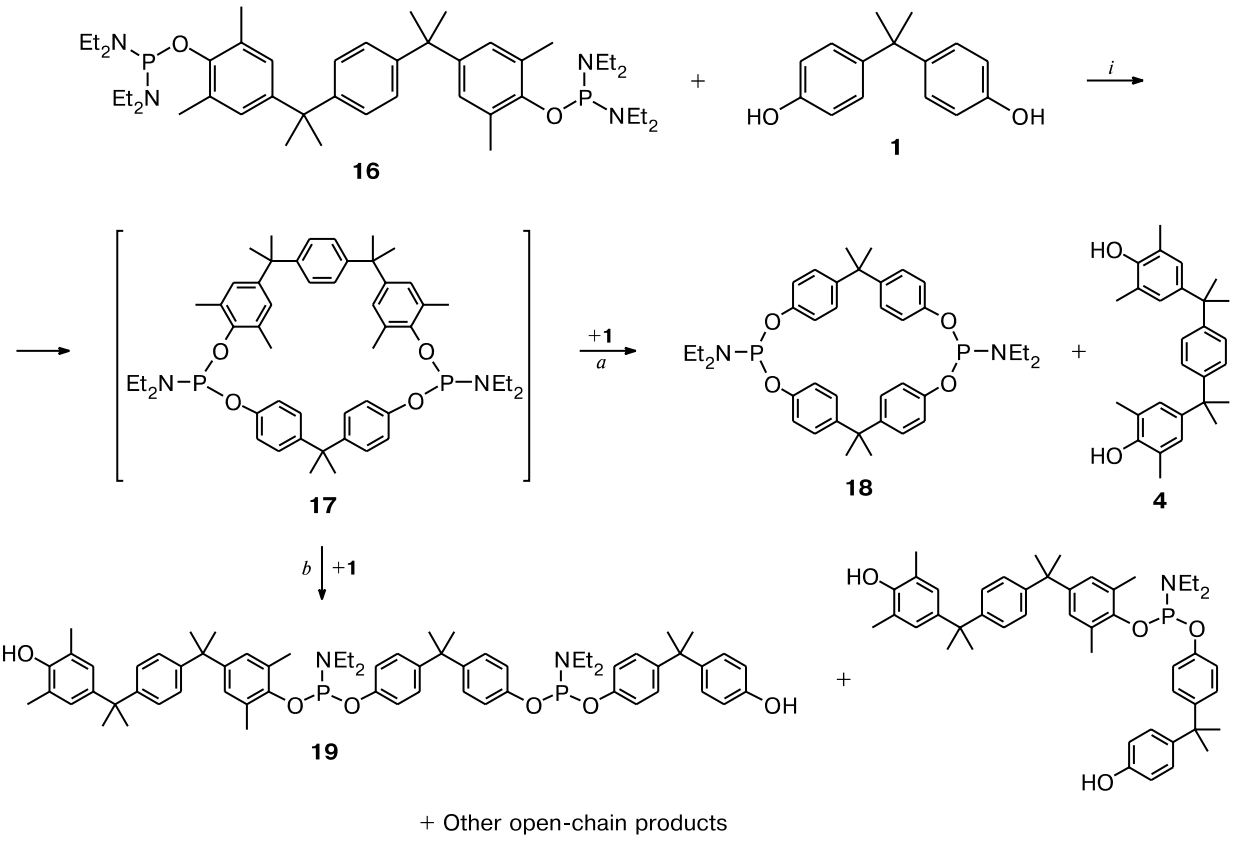


15 (23%)

Conditions and products: *i*. Et_3N, toluene, ~20 °C, 24 h; a mixture of *rccc*-, *rcct*-, *rctt*-, and *rtct*-isomers of **15**.

Phosphorous amide method. Phosphites can be synthesized not only from phosphorous chlorides reacting with alcohols or phenols but also from phosphorous amides. The advantage of this method is that the reaction can be carried out stepwise and the reactive intermediates are easier to handle.[19] However, the re-

Scheme 6



Conditions: *i*. Toluene, refluxing, 24 h.

action of bisphenol A (**1**) with the phosphorous amide obtained from the same bisphenol gave only open-chain and oligomeric products.[20,21] Cyclization was successful only for the reaction of bisphenols with phosphonous acid diamides to give macrocyclic phosphonites.[22–24]

While studying the reaction of phosphorous monoester diamide **16** with bisphenol **1** in boiling toluene, we could not obtain the expected asymmetric macrocycle **17** (Scheme 6).[25] In addition to the open-chain products, the reaction afforded symmetrical macrocycle **18** as a *cis*,*trans*-isomer mixture. This reaction pattern can be explained only in terms of transesterification that leaves the diethylamino group intact.[26] The desired asymmetrical macrocycle **17** probably appears as an intermediate, which is again attacked by remaining bisphenol **1**. If this attack occurs simultaneously on both sides of the molecule, the symmetrical macrocycle **18** is formed (Scheme 6, path *a*). In case of an attack on one phosphorus atom, the macrocyclic ring in **17** is cleaved to give open chain-product **19** (Scheme 6, path *b*).

Figure 1 shows the X-ray structure of the isolated symmetrical macrocycle *trans*-**18**. The independent neighboring aromatic rings are almost perpendicular to each other. The opposite aromatic rings are coplanar. Two of them form the walls of a molecular cavity with a distance from one side to the other of 766 pm.

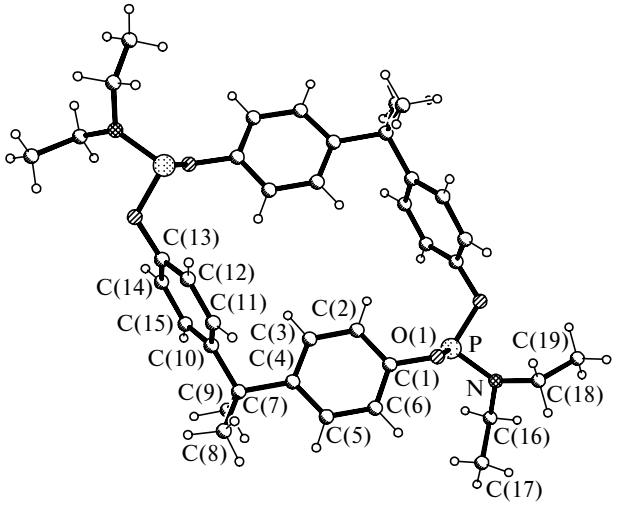


Fig. 1. Structure of *trans*-**18** in the solid state.

Synthesis of phosphorus macrobicycles

Double-capping route. For the synthesis of phosphite cryptands, we chose the so-called double-capping method.[5] One should expect a very low product yield for this reaction, as six bonds have to be formed in one step without control of any intermediates. Therefore, only few examples of double-capping or tripod-capping syntheses have been documented.[27—32] We reported a one-pot reaction of PCl_3 with bisphenol **4** under moderate dilution conditions ($2.5 \cdot 10^{-3}$ mol L^{-1}), resulting in homeomorphic cryptands **20** and **21** formed in low to medium yields (Scheme 7).[15] The products were isolated by column chromatography.

It is noteworthy that the ^{31}P NMR shifts for the *in*- and *out*-phosphorus atoms in compound **21** are extremely different (δ 147.2 (*in*) and δ 128.0 (*out*)). The ^{31}P NMR chemical shift of the *in*-phosphorus has the highest value among those observed for phosphites, whereas the ^{31}P NMR chemical shift for the *out*-phosphorus atom lies in the normal region for this type of compound.

The reaction of sterically nonhindered bisphenol **9** with PCl_3 in the presence of Et_3N in toluene at 25 °C under moderate dilution conditions affords all three possible homeomorphic isomers (*out*,*out* (**22**), *in*,*in* (**23**), and *in*,*out* (**24**)) in a 2 : 1 : 2 ratio, the total yield of the crude product being 15% (Scheme 8).[33]

The three isomers **22**, **23**, and **24** can be isolated by column chromatography on silica gel with a 1 : 1 *n*-pentane—toluene mixture as the eluent. The colorless crystals of the *out*,*out*-isomer **22** and the *in*,*in*-isomer **23** were grown from a MeCN—CH_2Cl_2 mixture. The crystal structures of **22** and **23** (Fig. 2) indicate that the molecules do not have C_3 symmetry, which might be expected for them according to the images shown in Scheme 8.

The *out*,*out*-compound **22** crystallizes in space group $P\bar{1}$ with half a CH_2Cl_2 molecule distributed statistically in disordered positions. Two "arms" of the cage form a nearly planar macrocycle. The four phenyl groups next to oxygen occupy a position resembling, to some extent, the *cone*-conformation of calix[4]arene. The third arm of the macrobicycle is attached to the macrocyclic plane as a bridge 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 from this side.

The crystal structure of the *in*,*in*-isomer **23** differs from that of **22**. The compound crystallizes in space group $C\bar{2}$, the unit cell containing two slightly different conformers (only one conformer is shown in Fig. 2) of the cage compound. In addition, each molecule crystallizes with one MeCN molecule and half a toluene molecule, the latter being located in statistical positions. The two conformers of **23** resemble more closely a C_3-symmetric structure than the T-shaped molecule of compound **22**.

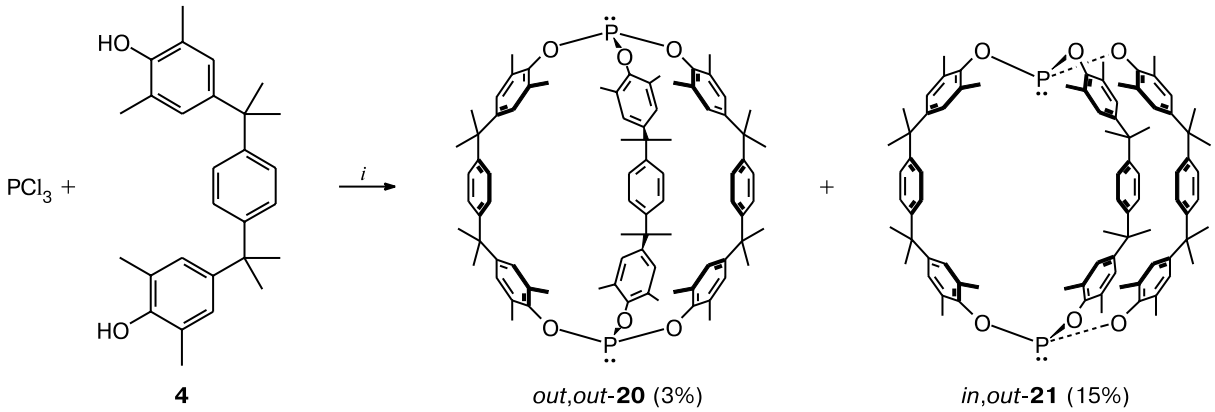
The distances between the phosphorus atoms in the two conformers of *in*,*in*-isomer **23** are nearly equal, 8.5 and 8.3 Å, respectively. As expected, these distances are markedly shorter than those in *out*,*out*-isomer **22** (10.5 Å).

The ^{31}P NMR chemical shifts of the *in*- and *out*-P atoms (**22**: δ 121.6 (*out*); **23**: δ 142.7 (*in*); **24**: δ 143.1 (*in*), 121.6 (*out*)) are also remarkably different, as has already been observed for compounds **20** and **21**. In **22** and **23**, the two sides of the molecule are equivalent, as illustrated by the ^{31}P, ^{1}H, and ^{13}C NMR spectra, which show only one signal for each corresponding pair of atoms, whereas in **24**, the *in*- and *out*-sides of the molecule are magnetically nonequivalent

The double-capping synthesis of phosphorus macrobicycles starting from the trinuclear *para*-*meta*-bridged bisphenol **25** and PCl_3 (Scheme 9, path *a*) has been described.[34] The reaction was carried out in toluene at room temperature for 24 h in the presence of Et_3N as a base.

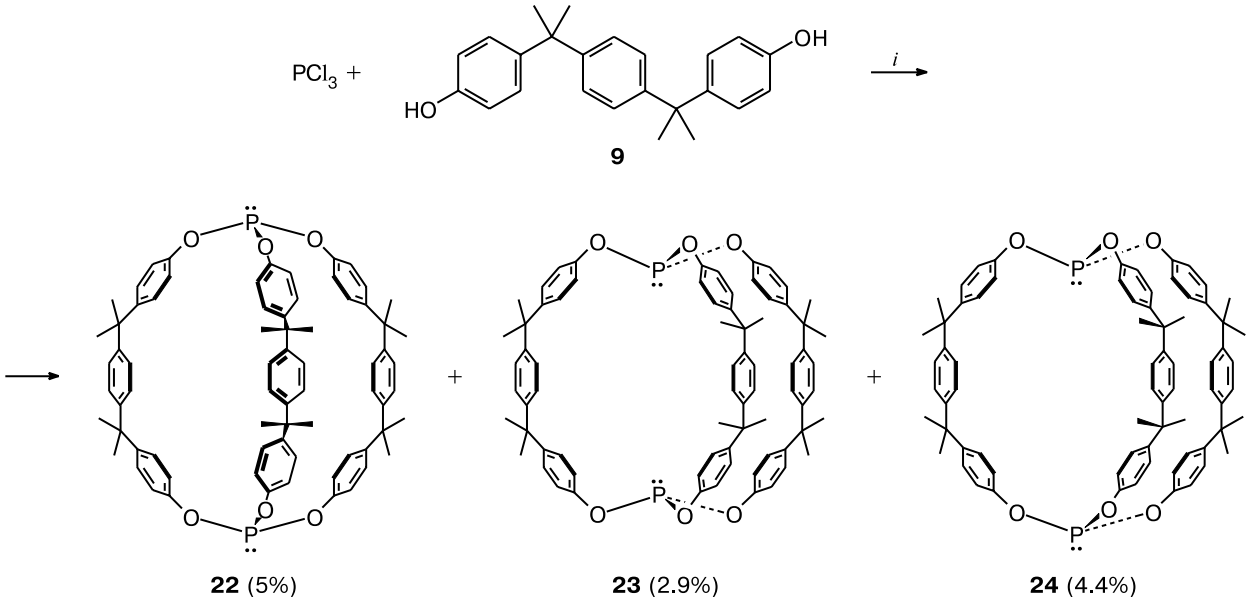
The product mixture contains three homeomorphic P cryptands **26—28** (the yields are ~6 (**26**), ~3 (**27**), and

Scheme 7



Reagents and conditions: *i*. Et_3N, toluene, ~20 °C, 3 days; [**4**] = $2.5 \cdot 10^{-3}$ mol L^{-1}.

Scheme 8



Reagents and conditions: *i*. Et_3N, toluene, ~20 °C, 3 days; [**9**] = $6 \cdot 10^{-3}$ mol L^{-1}.

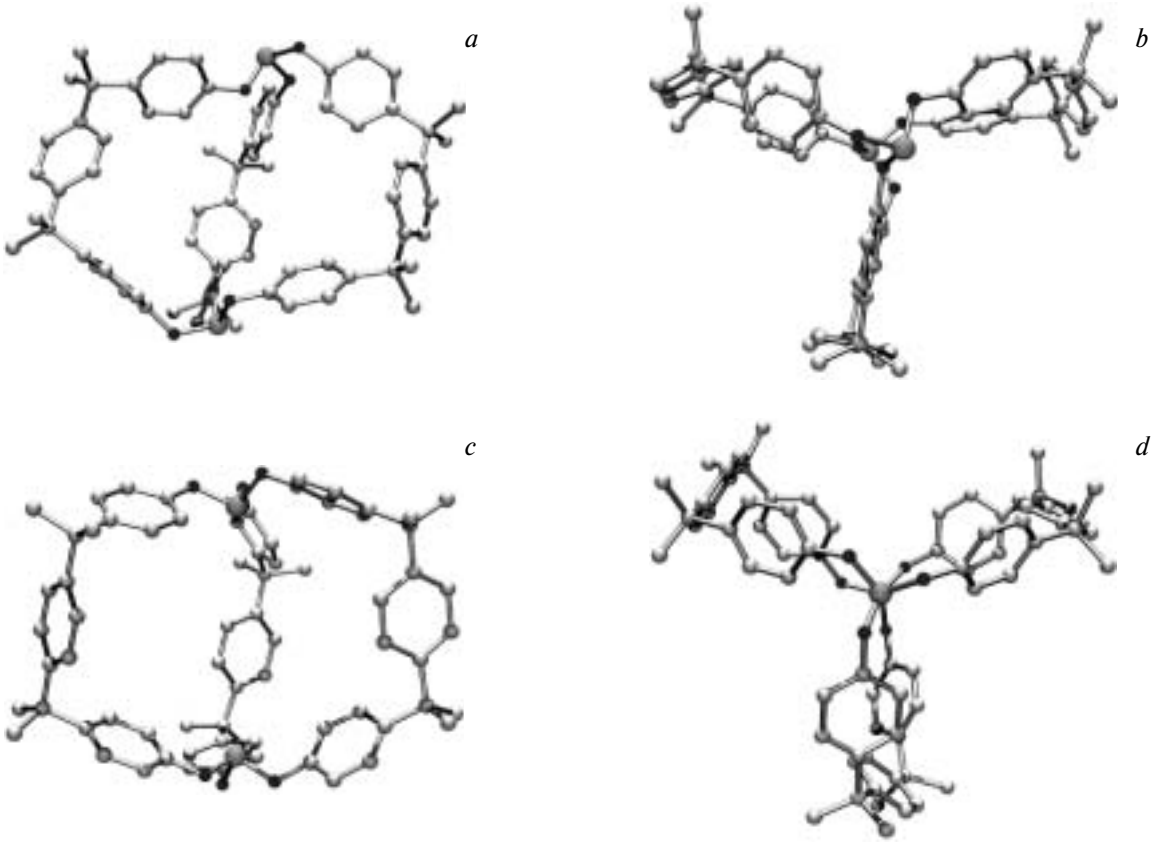
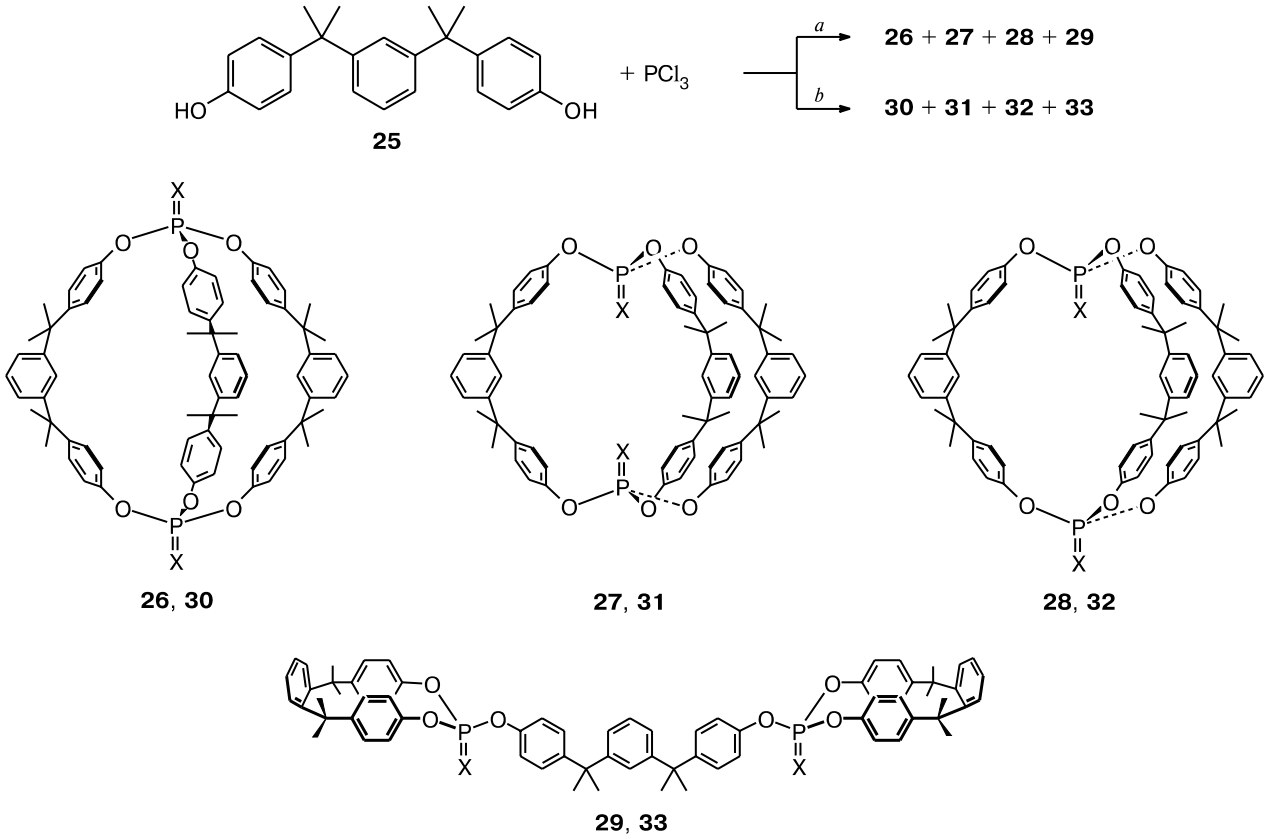


Fig. 2. Crystal structures of molecules **22** (*a*, *b*) and **23** (*c*, *d*). The hydrogen atoms and the solvent molecules are omitted for clarity (*a*, *c*, view into the cavity; *b*, *d*, view along the P—P axis).[33]

Scheme 9



Conditions, products, and yields: *a*. Et_3N, toluene, ~20 °C, 24 h; *b*. (1) Et_3N, toluene, ~20 °C, 24 h, (2) cumene hydroperoxide, ~20 °C, 1 h; **26—29:** X is the lone pair, yield 6% (**26**), 3% (**27**), 10% (**28**), 35% (**29**);
30—33: X = O, the yields of all compounds are quantitative, **33** is a mixture of conformers; the *syn*,*syn*-conformer of **33** was isolated.

~10% (**28**)) and compound **29** as the major product formed in a yield of ~35% according to ^{31}P NMR. The yields of macrobicycles **26—28** lie in the same range as the yields of macrobicycles **22—24** in the reaction of the corresponding *p*-phenylenebisphenol **9** with PCl_3.

However, a stronger curvature of the bisphenolic component permits a competitive reaction, namely, intramolecular ring closure in an intermediate phosphorous chloride leading to compound **29**. This reaction is very much favored, so that **29** proves to be the major product even though the resulting P heterocycles in **29** are slightly strained. An analogous reaction with the corresponding *p*-phenylenebisphenol **9** did not take place. The homeomorphic macrobicycles **26** and **27** and compound **29** were isolated by column chromatography on silica gel and characterized by NMR spectroscopy and MALDI-TOF mass spectrometry; compounds **26** and **27** were additionally characterized by X-ray diffraction (Fig. 3).

The *in*,*in*-isomer **27** crystallizes as two different conformers, like the corresponding 1,4-phenylene-*in*,*in*-cryptand **23**.

Both homeomorphic isomers **26** and **27** represent highly crumpled molecules containing almost no cavity due to the short distance between the opposite parts of the molecules. For this reason, no solvent molecules are complexed inside the cavity but only outside the macrobicycles.

The P—P distance varies from 4.47 to 5.33 Å for the two *in*,*in*-conformers, whereas the P—P distance in *out*,*out*-isomer **26** is 4.94 Å, which is surprisingly not longer than those in the *in*,*in*-isomers. This is due to the distinct distortion from an ideal *out*-geometry, as expressed by the "*out*-ness" of the substituents,[3] which can be described by the angle θ between the substituent (lone electron pair), the bridgehead atom bearing the substituent, and the other bridgehead atom (Fig. 4). In the case of *in*,*in*-conformer **27A**, the lone pair—P(1)—P(2) angle (θ = 9.4°) is almost ideal for an *in*-substituent; however the angle at P(2) is 67.1°, indicating that this *in*-position is substantially distorted towards 90°. For the *in*,*in*-conformer **27B**, this distortion is even more pronounced, θ = 50.0° for one side and θ = 83.8° for the other side. In

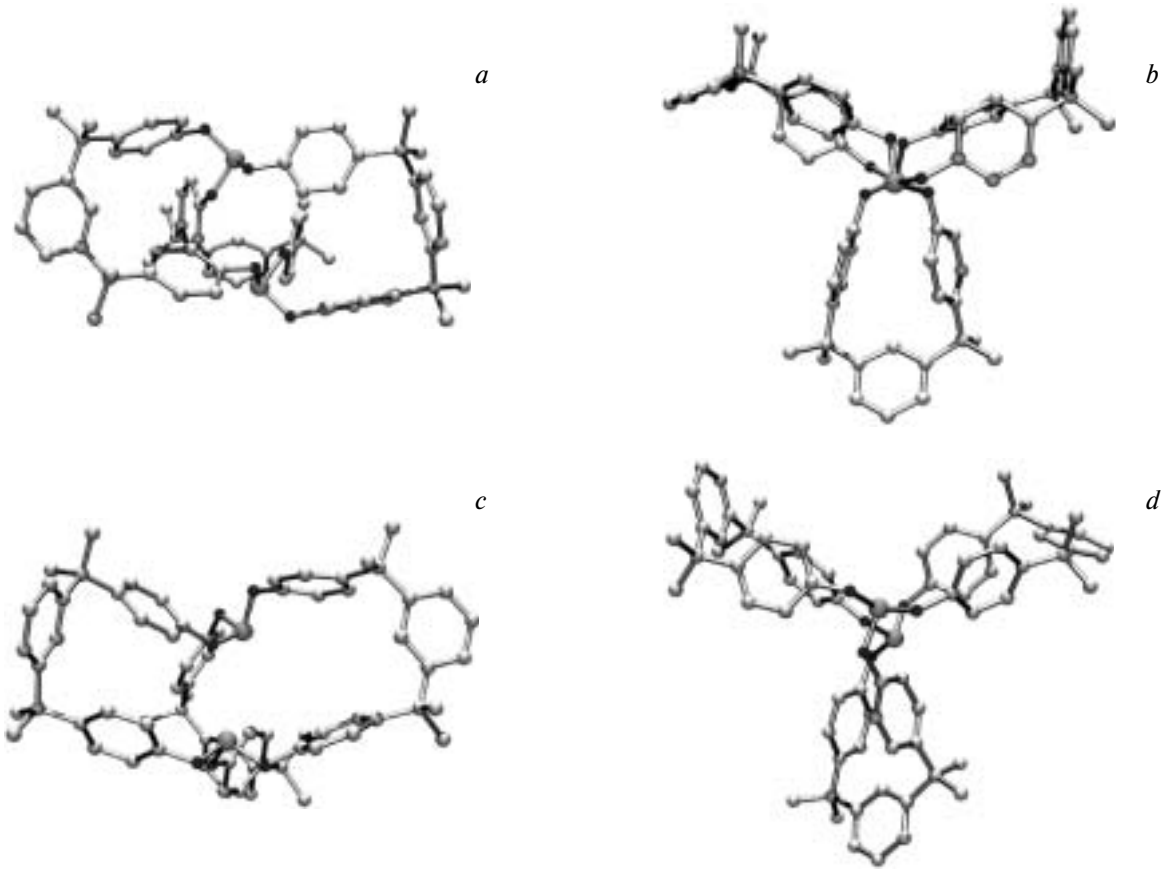
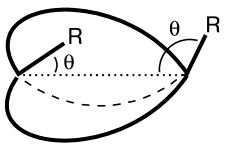


Fig. 3. Structures of *out*,*out*-isomer **26** (*a*, *b*) and one conformer (**A**) of *in*,*in*-isomer **27** (*c*, *d*) in the solid state. The hydrogen atoms and the solvent molecules are omitted for clarity (*a*, *c*, view into the cavity; *b*, *d*, view along the P—P axis).[34]



in-R: $0° \le \theta \le 90°$, *out*-R: $90° \le \theta \le 180°$

Fig. 4. Schematic image of the *in*,*out*-isomers of bicyclic compounds. The θ angle characterizes the *in*- and *out*-positions in bicyclic compounds.[3]

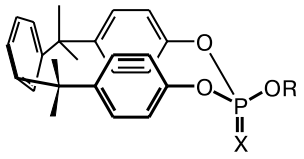
fact, this conformer can hardly be regarded as an *in*,*in*-conformer, because at least one of the angles is close to 90°. However, the most pronounced deviation from the ideal *in*- or *out*-position is found for the *out*,*out*-isomer **26** with $\theta = 92.1°$ and $\theta = 103.3°$. This means that the lone pairs are almost perpendicular with respect to the P—P axis.

Cage compounds **26—28** are hydrolytically less stable than 1,4-phenylene macrobicycles **22—24**. Thus they were found to be completely hydrolyzed in a standard NMR solvent, $CDCl_3$, after several days. As opposed to cage compounds **22—24**, they do not incorporate solvent guest molecules, as was proved by NMR spectroscopy and X-ray diffractometry. This is due to the crumpled shape of these molecules forming almost no cavity.

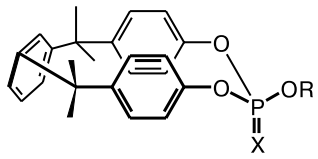
In order to improve the hydrolytic behavior of **29** for some structural investigations, we carried out the double-capping reaction of **25** with PCl_3 with immediate subsequent oxidation of the mixture by an excess of cumene hydroperoxide. After 1 h, the oxidation was complete. The corresponding homeomorphic macrobicylic phosphates **30** and **31** were separated, as well as compound **33** formed as the major product (Scheme 9, path *b*).[34] The oxidation of all phosphorus moieties including the *in*-phosphorus atoms with cumene hydroperoxide proceeds relatively fast. This result is rather surprising, as macrobicycles **22** and **23** obtained earlier did not show such a fast oxidation for the *in*-positions. The reason for this rapid oxidation of the *in*-positions, which are normally less accessible, is the pronounced distortion of an ideal *in*-geometry (Fig. 4) with the average $\bar{\theta} = 52.6°$ over the four *in*-positions in the two *in*,*in*-conformers. This implies that the lone pairs point more or less outside the cavity, which increases their reactivity towards oxidizing agents.

Compounds **29** and **33** include a narrow macrocyclic ring. According to ^1H NMR measurements, the rotation

of the *para*-phenylene rings is hindered at room temperature. Moreover, the central *m*-phenylene ring also occupies a fixed position outside the macrocyclic plane. The different arrangements of this ring relative to the P—OR group gives rise to conformational *syn*- and *anti*-atropoisomers **A** and **B**.



A



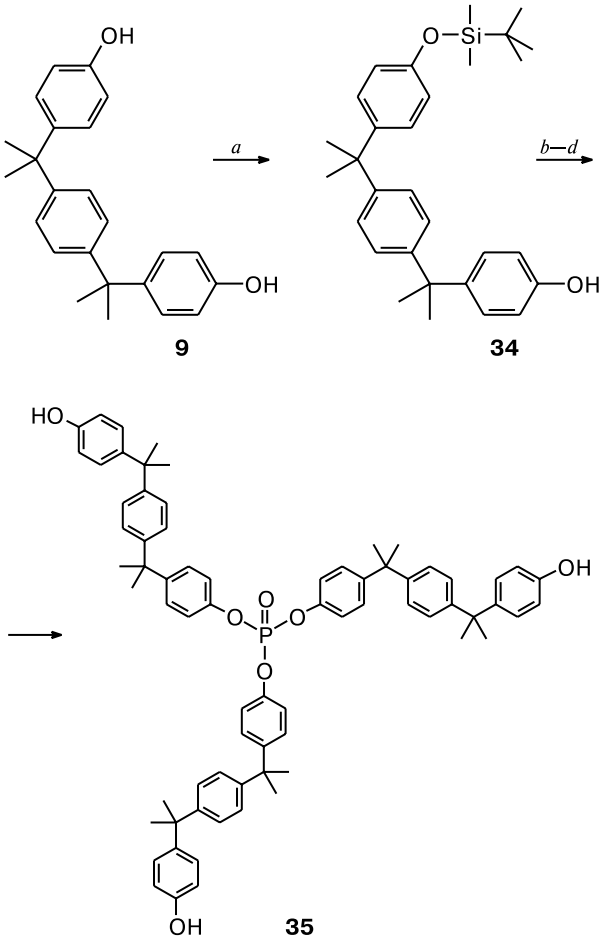
B

Three conformers would be possible for compounds **29** and **33**, namely, *syn*,*syn*, *syn*,*anti*, and *anti*,*anti* conformers, which should be responsible, in total, for four ^{31}P NMR signals in a mixture. We isolated the *syn*,*syn*-atropisomer of **33** whose structure was confirmed by single crystal X-ray diffraction (Fig. 5).

The ^{31}P NMR spectra of homeomorphic phosphite macrobicyles **26—28** show a characteristic pattern similar to that observed for compounds **22—24**. The signals of all *in*-phosphorus atoms are shifted downfield compared to the normal values at around δ 128. The *in*,*in*-phosphite **27** exhibits a ^{31}P NMR peak at δ 133.0, while the *in*-P atom of the *in*,*out*-phosphite **28** is responsible for a signal at δ 131.2. The *out*-P atoms are shifted upfield to δ 123.3 in *out*,*out*-phosphite **26** and to δ 124.6 in *in*,*out*-phosphite **28**. The ^{1}H and ^{13}C NMR measurements for both *out*,*out*-phosphite **26** and *in*,*in*-phosphite **27** reflect the C_3-symmetry of these molecules in solution.

In compounds **29** and **33**, the phosphorus atoms are incorporated into a slightly strained heterocyclic ring, which results in a distorted geometry around the P atom. This is reflected by an upfield shift of the ^{31}P NMR signal, which occurs at δ 121.1 for phosphite **29** and δ −18.5 for phosphate **33**. These peaks correspond to single isolated conformers, which are, however, equilibrated after a certain period of time, giving rise to varying amounts (up to 20%) of the second conformer.

Scheme 10



Reagents and conditions: *a*. Bu^{t}Me$_2$SiCl, imidazole, CH_2Cl_2, ~20 °C, 24 h; *b*. PCl_3, Et_3N, toluene, ~20 °C, 15 h; *c*. cumene hydroperoxide, toluene, ~20 °C, 2 h; *d*. Bu$^{n}_4$NF, AcOH, ~20 °C, 24 h.[33]

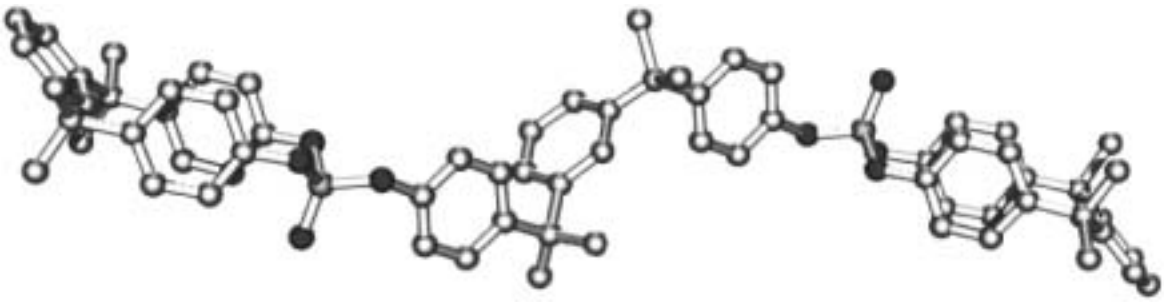


Fig. 5. Structure of bis(phosphate) **33**. The hydrogen atoms and the solvent molecules are omitted. Side view of subunits of the macrocycle demonstrating the *syn*-arrangement of the 1,3-phenylene ring and the P—OR substituent.[34]

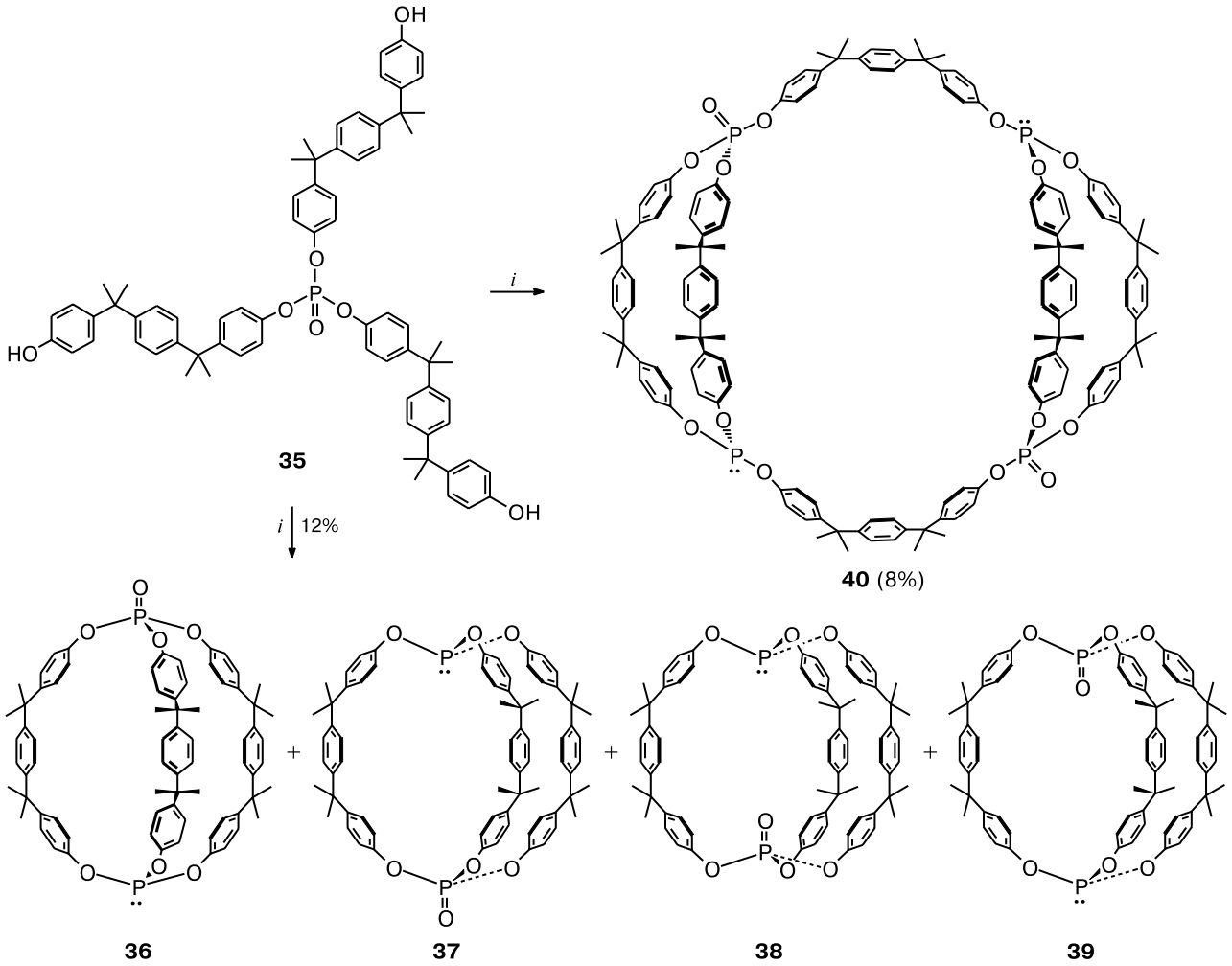
Multistep synthesis of P-cryptands (single-capping method). As an alternative to the one-step synthesis (double-capping method) of such type of cryptand, we developed a stepwise synthesis.[33] In the first step, bisphenol **9** was protected at one phenolic group by reaction with Bu^tMe_2SiCl using a 1 : 1 ratio of the reagents to give compound **34** (Scheme 10).

In the second step, compound **34** was treated with PCl_3. In contrast to the Me_3Si protecting group, which is readily split off on treatment with PCl_3 to form phosphites, the Bu^tMe_2Si group is inert with respect to PCl_3. The phosphite formed upon the reaction of PCl_3 with the unprotected OH group is immediately oxidized with cumene hydroperoxide to afford the corresponding Bu^tMe_2Si-protected phosphate. This compound can be deprotected using Bu^n_4NF in AcOH to give phosphate **35**.

Phosphate **35** can be cyclized on treatment with PCl_3 to form P-bridged cage compounds (Scheme 11).[33] In this case, four homeomorphic isomers **36—39** having the phosphorus lone pair or the phosphate oxygen atom in either *in*- or *out*-position can exist. All four isomers can be detected in the crude product by ^{31}P NMR spectroscopy. Compounds **36** and **37** are the major components, while compounds **38** and **39** are formed in only trace amounts. After chromatography, a mixture of **36** and **37** is isolated as a single fraction.

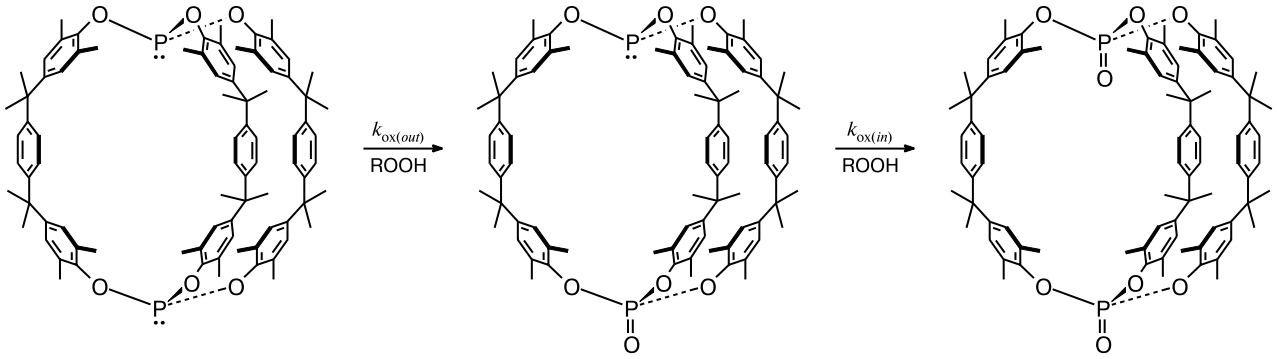
Interestingly, a second fraction responsible for a single peak at 2226 Da in the MALDI-TOF mass spectrum can be obtained. Thus, this fraction was tentatively identified as an isomeric mixture of the cylindrical macrotricycle **40**. An analogous pyramidal product having the same molecular mass cannot be formed due to structural features of compound **35**.

Scheme 11



Reagents and conditions: *i*. PCl_3, Et_3N, toluene, ~20 °C, 2 days.

Scheme 12



Modification of phosphorus macrobicycles

in,*out*-Compound **21** was oxidized directly in the NMR tube with an excess of cumene hydroperoxide at room temperature (Scheme 12).[15] This proves that the *in*-phosphorus atom in **21** is much less reactive (about 3000 times) than the *out*-phosphorus atom. The *out*-phosphorus was completely oxidized within 25 min to give a phosphate peak in the ^{31}P NMR spectrum of compound **41**. Conversely, the oxidation rate of the *in*-phosphorus atom in compound **21** is unusually low. Only half of the phosphite is converted into the completely oxidized phosphate **42** after ten days. The isomer **20** is completely oxidized at the same rate as the *out*-phosphorus atom in **21** to give the corresponding *out*,*out*-cryptand.

The addition of excess cumene hydroperoxide to a solution of a mixture of **22**, **23**, and **24** in $CDCl_3$ directly in the NMR tube leads to a rapid decrease of the *out*-phosphite peaks, which are replaced by the corresponding *out*-phosphate peaks.[33] The rate of oxidation of the *in*-P atoms is much lower. However, the difference is less pronounced than for compound **21** (Scheme 13).

In compound **22**, the oxidation of the first P atom proceeds somewhat faster than the oxidation of the second atom (see Scheme 13, Table 1, $k_1 > k_2$).

This suggests that the primarily oxidized P atom influences the oxidation rate of the opposite counterpart. Since transmission of electronic effects over a large number of bonds is unlikely, the influence must be mediated by an allosteric effect caused by the first oxidation, which makes the lone pair of the second phosphorus atom less accessible.

Table 1. Oxidation rates of **22**, **23**, and **24** [33]

k_n	k_{ox}/s^{-1} (298 K)	k_n	k_{ox}/s^{-1} (298 K)
$k_{1(out)}$	$13.7 \cdot 10^{-3}$	$k_{4(in)}$	$3 \cdot 10^{-4}$
$k_{2(out)}$	$7.5 \cdot 10^{-3}$	$k_{5(out)}$	$9.0 \cdot 10^{-3}$
$k_{3(in)}$	$15 \cdot 10^{-4}$	$k_{6(in)}$	$8 \cdot 10^{-4}$

The *in*,*in*-isomer **23** is oxidized most slowly. After the first P atom (k_3) is oxidized to give intermediate **38**, further oxidation (k_4) occurs very slowly due to the hindrance caused by the bulkier phosphate group pointing inwards (see Scheme 13 and Table 1).

The reaction of compound **24** with cumene hydroperoxide leads to fast oxidation of the *out*-P atom to give intermediate **37** followed by much slower oxidation of the *in*-position resulting in *in*,*out*-phosphate **45** (see Scheme 13, Table 1, $k_5 \gg k_6$). The difference between the rate constants is about an order of magnitude

In order to introduce larger groups in the *in*-positions, we treated the *in*,*in*-isomer **23** with an excess (1 : 3 ratio) of thiophosphoryl azide **46** in boiling THF according to the Staudinger reaction pattern[35–38] (Scheme 14).[39] This gave P=N—P=S-containing compounds, similar to cryptands and dendritic structures described previously.[40–43]

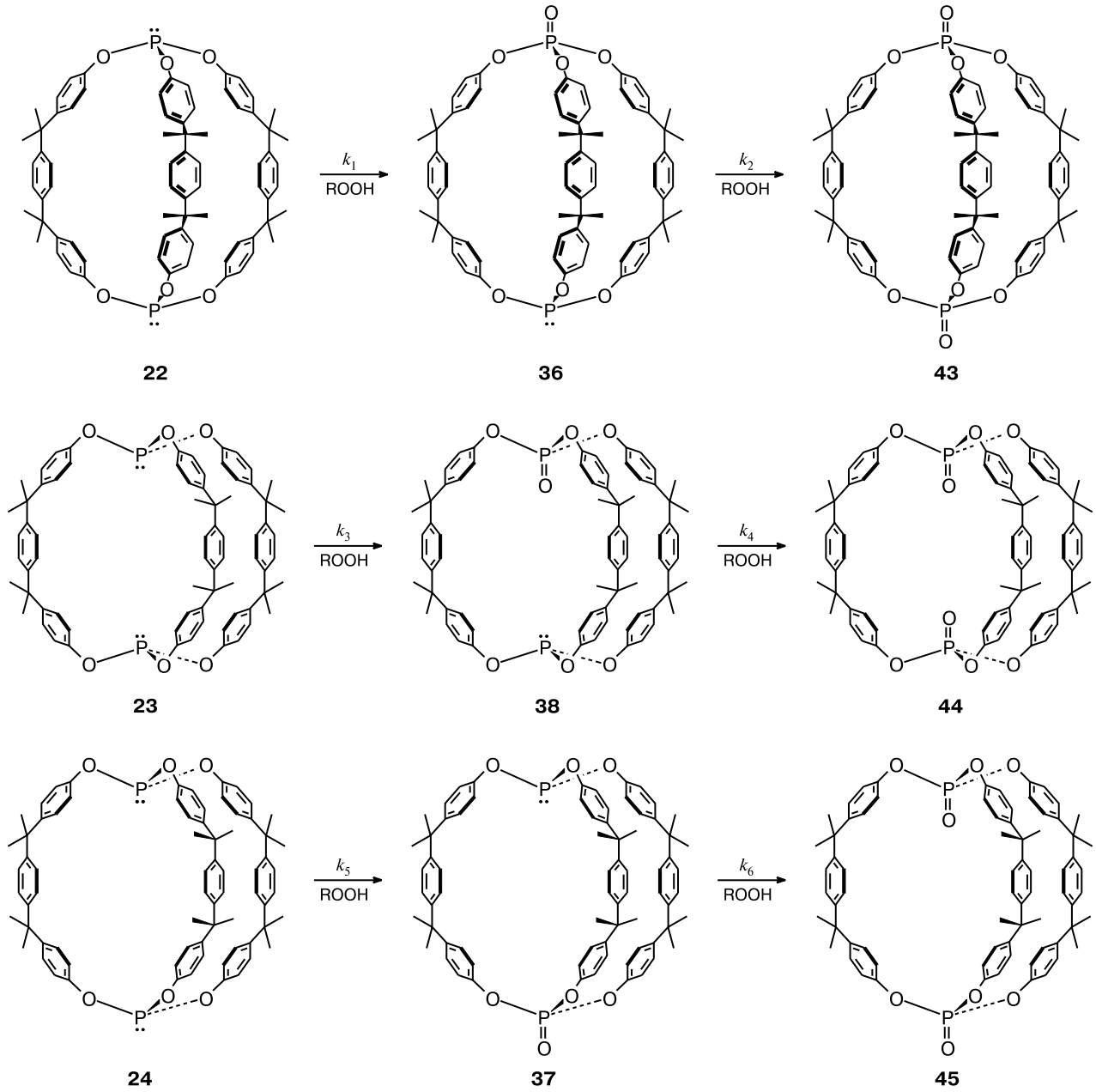
In a side reaction, the phosphite positions were partly thiolated by the thiophosphoryl azide **46**. This led to the formation of *in*,*in*-thiophosphate **47** which could be isolated in 28.8% yield.

The cavity of *in*,*in*-phosphite **23** is too small to allow a reaction of **46** at both *in*-positions. Therefore, the formation of monosubstituted compound **48** was expected; this product was obtained in 51.6% yield. The synthesis of compound **48** is the first example of a successful functionalization of *in*-bridgehead positions in macrobicycles.

The ^{31}P NMR spectrum of **48** contains three signals located at δ 142.5 (P_c), 39.2 (P_b), and –22.5 (P_a). The position of benzaldehyde groups inside the cage was proven by NOESY and ROESY interactions of their protons with those of the macrocyclic arms, in particular, with the protons of the central phenylene rings.

The ^{1}H and ^{13}C NMR spectra are consistent with a C_3-symmetric structure. This indicates that the inner benz-

Scheme 13

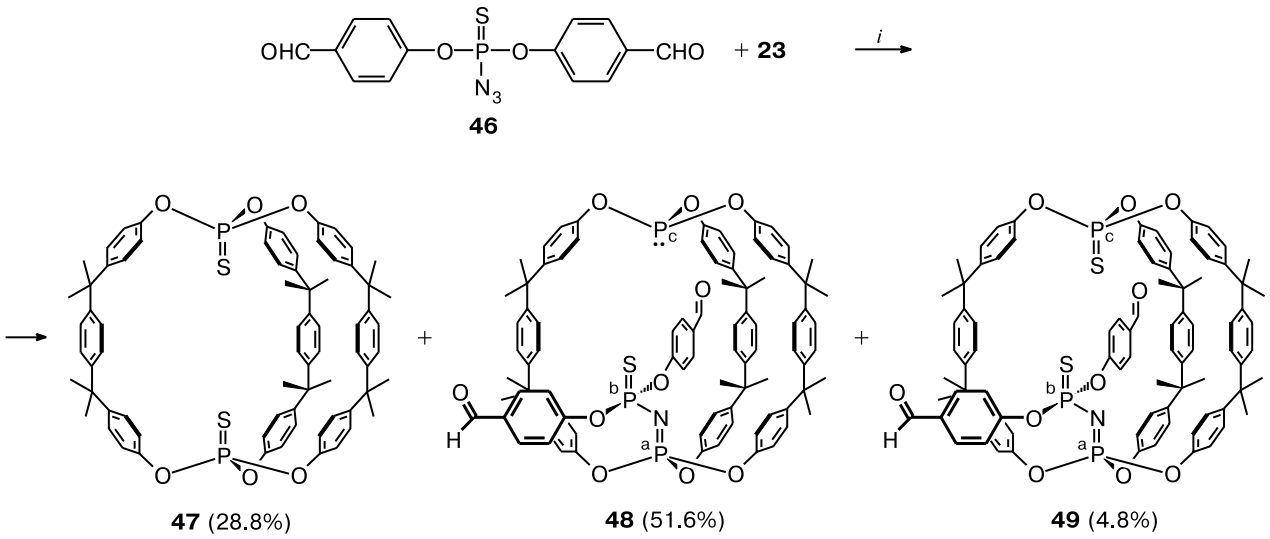


aldehyde groups are not long enough to be permanently fixed between the cage bars, but they can freely rotate from one gap to the other. Apparently, the rotation is not horizontal; the benzaldehyde groups have to move up, passing in the vicinity of the opposite bridgehead phosphorus.

As an additional fraction, compound **49** was isolated from the reaction mixture in 4.8% yield. In this case, one of the *in*-phosphite groups was thionated, whereas the other was converted into the expected imidophosphate. Figure 6 shows two views of the X-ray structure of **49**. The *in*-positions of the bridgehead P atoms are clearly seen in Fig. 6, *a*. The thiophosphoryl substituent points inside the cavity. The angle θ equal to 7.0° implies almost an ideal *in*-position.[3] The benzaldehyde fragments on the opposite side are located between the macrocyclic arms and jut out of the cage bars. The distance between the bridgehead P atoms is 8.76 Å; hence, it is only slightly larger than that for free phosphite **23** where these distances are 8.5 and 8.3 Å (two conformers).

The ^{31}P NMR spectrum of **49** shows three signals with δ 62.2 (P_c), 37.6 (P_b), and −20.0 (P_a).

Scheme 14



Reagents and conditions: *i*. THF, refluxing, 11 days.

The signal for P_c is shifted downfield; as in the case of compound **23**, this may imply an *in*-position of the bridgehead atom. Conversely, the signal for P_b is shifted upfield inside the cage molecule. The protons of the *in*-benzaldehyde groups exhibit NOESY and ROESY interactions with the protons of the central phenylene rings of the macrocyclic arms, thus proving their *in*-arrangement.

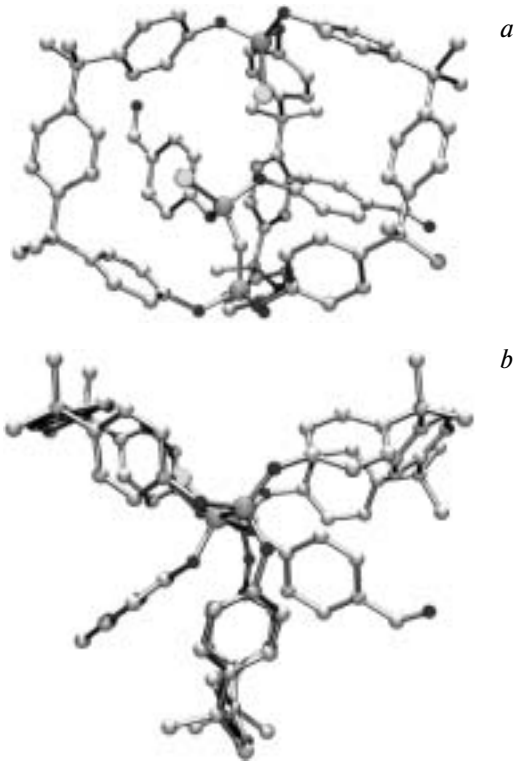


Fig. 6. Structure of *in*,*in*-compound **49** in the crystal. The hydrogen atoms and the solvent molecules are omitted (*a*, view into the cavity; *b*, view along the P—P axis of the macrobicycle).[39]

The ^1H and ^{13}C NMR spectra of compound **49** indicate only C_s symmetry for this structure rather than C_3. Two of the macrocyclic bridges are equivalent, but the third one gives additional signals. This is due to fixing of the *in*-benzaldehyde functions between the macrocyclic arms, in contrast to those in *in*-phosphite **48**. Therefore, one macrocyclic bridge adjoins two benzaldehyde groups, whereas each of the other two bridges have only one such neighboring group. The movement of the benzaldehyde groups from one gap of the cage to another is hindered by the *in*-sulfur atom at the opposite bridgehead phosphorus, in contrast to the lone pair in compound **48**.

However this process is not fully suppressed but only retarded, as indicated by the exchange signals between benzaldehyde protons and the protons of the macrocyclic arms in the NOESY spectrum.

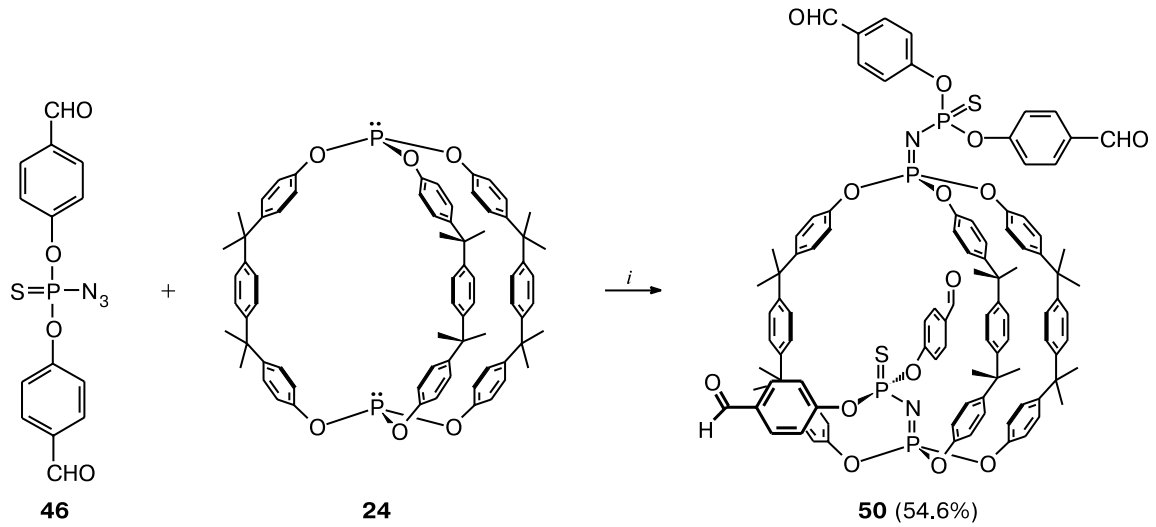
Only elongation of the *in*-moieties could result in total fixing of these groups between the cage bars.

The reaction of *in*,*out*-phosphite **24** with thiophosphoryl azide **46** (Scheme 15)[39] proceeded much faster than the same reaction of *in*,*in*-phosphite **23**. The *in*-position in **24** is more easily accessible than that in **23**, due to a greater volume of the cavity resulting from the *out*-position of the opposite group. The disubstituted *in*,*out*-isomer **50** was isolated in 54.6% yield

The ^{31}P NMR spectrum of **50** shows two doublets for each of the nonequivalent sides of the molecule at δ 46.05 (*out*)/−20.26 (*out*) and δ 39.17 (*in*)/−22.03 (*in*), respectively.

The inner protons of the benzaldehyde groups exhibit NOESY interactions with the phenylene protons of the

Scheme 15



46 **24** **50** (54.6%)

Reagents and conditions: *i*. THF, refluxing, 3 days.

macrocyclic arms, and especially with those of the central phenylene rings. No such interactions can be observed for the outer benzaldehyde moieties. Similarly to *in,in*-phosphite-imidophosphate **48** and unlike *in*,*in*-thiophosphate-imidophosphate **49**, all macrocyclic arms in **50** are equivalent, indicating a free rotation of the inner benzaldehyde groups. This is possible because the opposite *out*-bridgehead atom offers even more space for such a movement than the *in*-arranged lone pair in **48** and, the more so, than the *in*-sulfur atom in compound **49**.

In the synthesis of compounds **48**—**50**, the attachment of bulky groups to the *in*-positions of macrobicyclic compounds was achieved for the first time. This opened up the way for specific modification of the cavity of macrobicyclic compounds and can be used to accomplish specific adjustment of macrobicyclic hosts to specific substrates for molecular recognition or to design ligands for metal-catalyzed reactions with a specified microenvironment.

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