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Synthesis of a chiral macrocyclic tetraphosphine – 1,9-di-*R*,*R*(and *S*,*S*)-α-methylbenzyl-3,7,11,15-tetramesityl-1,9-diaza-3,7,11,15-(*RSSR*)-tetraphosphacyclohexadecane

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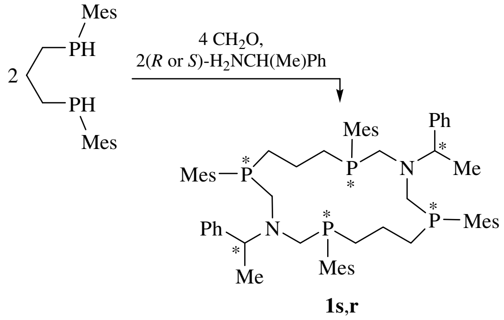
Two enantiomers of the title compound containing six chiral atoms have been synthesised *via* stereoselective covalent self-assembly of two diphosphinopropane, four formaldehyde and two primary amine molecules.

Chiral macrocyclic species are important selective molecular recognition participants and asymmetric catalysts.[1,2] The number of the chiral macrocyclic phosphines, as well as their applications in catalysis, are limited only by several examples.[3,4] An insufficient attention is explained by difficulties in the preparation of macrocyclic phosphines (template reactions[5] or high dilution conditions[3,6]) and the separation of stereoisomers.[7]

The stereoselective formation of a single isomer of 1,9-dibenzyl-3,7,11,15-tetramesityl-1,9-diaza-3,7,11,15-(*RSSR*)-tetraphosphacyclohexadecane has been revealed.[8] The high-yield synthesis of the macrocyclic compound has been explained in terms of a self-assembly process.[8,9]

Here, we report the synthesis of optically active 1,9-diaza-3,7,11,15-tetraphosphacyclohexadecanes **1s** and **1r**.

The reaction of a diastereomeric mixture of 1,3-bis(mesitylphosphino)propane,[8,10] formaldehyde (30% in H_2O) and (*S*)- or (*R*)-α-methylbenzylamine proceeded stereoselectively giving only one isomer of desired chiral macrocycles **1s** and **1r** in a good yield.[†]



1s,r

Scheme 1

The ^{31}P NMR spectroscopic monitoring of the reaction mixture showed that the concentration of **1s** grew from 30% towards to all products after 1 h, since the beginning of the reaction, to 47% in 24 h. Pure **1s** was obtained in 73% yield, possibly, due to the relatively fast equilibrium between intermediates and products of the reaction.

Compounds **1s** and **1r** are air-stable and readily soluble in organic solvents ($CHCl_3$, CH_2Cl_2, C_6H_6 and toluene). ^{31}P, ^{1}H and ^{13}C NMR spectroscopic data and elemental analysis confirm the formation of chiral 1,9-diaza-3,7,11,15-tetraphosphacyclohexadecanes **1s** and **1r**. The investigation of the structural peculiarities conditioned by a presence in **1s** and **1r** of six chiral atoms was carried out by NMR correlations (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC).

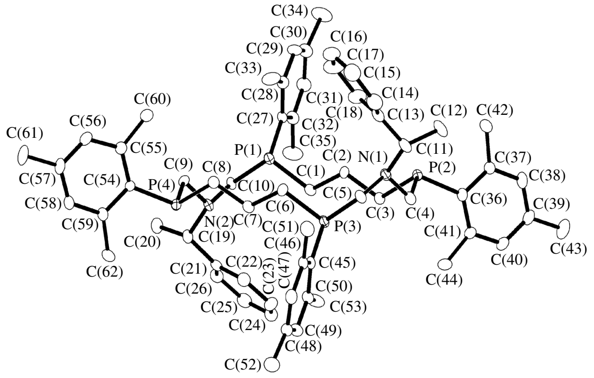


Figure 1 X-ray crystal structure of macrocycle **1s**.

The structure of **1s** was determined by X-ray analysis.[‡] The configurations of four phosphorus atoms correspond to the *RSSR*-stereoisomer of desired di-1,9-(*S*,*S*)-α-methylbenzyl-3,7,11,15-tetramesityl-1,9-diaza-3,7,11,15-tetraphosphacyclohexadecane. The macrocycle conformation is similar to that described for 1,9-dibenzyl-3,7,11,15-tetramesityl-1,9-diaza-3,7,11,15-(*RSSR*)-tetraphosphacyclohexadecane.[8]

The presence of chiral units at the nitrogen atoms in **1s** leads to some distortion of a 16-membered ring and the whole macromolecule of **1s** is asymmetrical.

The asymmetry of macrocycles **1r** and **1s** is also seen in ^{1}H, ^{13}C and ^{31}P NMR spectra (two sets of signals). The 2D ^{1}H–^{13}C HMBC NMR spectrum of **1r** indicates that the atoms of both non-equivalent parts of the macromolecule are covalently bonded through methylene chains. Hence, the spectral signals were attributed to P*(*S*)CH$_2$NC*(*S*)CH$_2$P*(*S*) (A) and P*(*R*)CH$_2$NC*(*S*)CH$_2$P*(*R*) (A′) parts of the molecules. An equivalence of PCH$_2$ fragments in each subunit (A or A′) is due to the fast exchange between twisted conformations with simultaneous inversion of nitrogen configuration. The chemical shift of the methyl group of CH**Me* on side A′ is strongly downfield shifted ($\Delta\delta\,^{1}$H 0.43 ppm and

$\Delta\delta^{13}$C 8.68 ppm) relative to Me on side A. An opposite is observed for other nuclei [*e.g.*, *o*-Ph (^{1}H) and *ipso*-Ph (^{13}C)]. Such a low field shift of C*H*Me*$^{\mathrm{A'}}$ is due to a close vicinity with phosphorus lone pair at P(*R*)P(*R*) side, while on the P(*S*)P(*S*) side the similar effects for nuclei of C*Ph$^{\mathrm{A}}$ are seen. This hypothesis is supported by the chemical shift calculations for simple model systems, and an inspection of X-ray and MM minimised structures.[§]

Thus, the structure asymmetry for **1s** and **1r** was established by NMR correlations (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC) in a solution.[§,11]

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[†] All manipulations were carried out with standard high-vacuum and dry-nitrogen techniques. The NMR experiments were carried out with an Avance 600 (Bruker) specrtometer. ^{31}P NMR (242.97 MHz), external 85% H_3PO_4; ^{1}H NMR (600.13 MHz), internal solvent; ^{13}C NMR (150.90 MHz), internal solvent. The melting points were determined on a Boetius apparatus and are uncorrected. Specific rotation was determined on a Perkin–Elmer Model 341 polarimeter at 589 nm. Bis(mesitylphosphino)propane was synthesised according the method described previously.[8,10]

*Di-1,9-(*S,S*)-α-methylbenzyl-3,7,11,15-tetramesityl-1,9-diaza-3,7,11,15-(*RSSR*)-tetraphosphacyclohexadecane* **1s**. A solution of (*S*)-α-methylbenzylamine (0.25 g, 2.0 mmol) in 5 ml of benzene was slowly added to a solution of bis(mesitylphosphino)propane (0.71 g, 2.0 mmol) and formaldehyde (4.3 mmol, 0.33 ml of 30% formaline) in 5 ml of benzene for 5 min at 40 °C. After seven days, the reaction mixture was evaporated and a white crystalline product was recrystallised from DMF. The resulting crystals were collected by filtration and dried in a vacuum. Yield 0.74 g (74%), mp 148–150 °C. ^{31}P NMR (C_6D_6) δ: –41.91, –41.75. ^{1}H NMR (C_6D_6, δ 7.15) δ: 1.06 (d, 3H, Me$^{\mathrm{A}}$, $^3J_{\mathrm{HH}}$ 6.8 Hz), 1.49 (d, 3H, Me$^{\mathrm{A'}}$, $^3J_{\mathrm{HH}}$ 7.0 Hz), 1.80–2.50 (m, 12H, $\mathrm{PCH_2CH_2CH_2P^{(A+A')}}$), 2.08 (s, 6H, *p*-Me$^{\mathrm{A\ or\ A'}}$), 2.09 (s, 6H, *p*-Me$^{\mathrm{A\ or\ A'}}$), 2.55 (s, 12H, *o*-Me$^{\mathrm{A\ or\ A'}}$), 2.61 (partly covered by *o*-Me$^{\mathrm{A'}}$, P–$\mathrm{CH_2^{A'}}$–N), 2.64 (s, 12H, *o*-Me$^{\mathrm{A\ or\ A'}}$), 3.03 (dd, 2H, P–$\mathrm{CH_2^{A}}$–N, $^2J_{\mathrm{HH}}$ 12.8 Hz, $^2J_{\mathrm{HP}}$ 10.0 Hz), 4.01 (d, 2H, P–$\mathrm{CH_2^{A}}$–N, $^2J_{\mathrm{HH}}$ 12.8 Hz), 4.09 (d, 2H, P–$\mathrm{CH_2^{A'}}$–N, $^2J_{\mathrm{HH}}$ 13.0 Hz), 4.72 (m, 1H, C*H$^{\mathrm{A'}}$), 4.80 (m, 1H, C*H$^{\mathrm{A}}$), 6.75 (s, 8H, *m*-H in Mes), 6.98 (dd, 1H, *p*-H$^{\mathrm{A'}}$, $^3J_{\mathrm{HH}}$ 7.4 Hz, $^3J_{\mathrm{HH}}$ 7.4 Hz), 7.05 (dd, 2H, *m*-H$^{\mathrm{A'}}$ in Ph, $^3J_{\mathrm{HH}}$ 7.4 Hz, $^3J_{\mathrm{HH}}$ 7.4 Hz), 7.12–7.20 (*o*-H$^{\mathrm{A'}}$ and *p*-H$^{\mathrm{A}}$ overlapped with the C_6D_6), 7.29 (dd, 2H, *m*-H$^{\mathrm{A}}$ in Ph, $^3J_{\mathrm{HH}}$ 7.5 Hz, $^3J_{\mathrm{HH}}$ 7.5 Hz), 7.49 (d, *o*-H, $^3J_{\mathrm{HH}}$ 7.5 Hz). ^{13}C{H} NMR (C_6D_6, δ 128.02) δ: 11.94 (s, Me$^{\mathrm{A}}$), 20.62 (s, Me$^{\mathrm{A'}}$), 20.93 (s, *p*-Me), 23.85 (d, *o*-Me$^{\mathrm{A\ or\ A'}}$, $^3J_{\mathrm{PC}}$ 18.8 Hz), 23.97 (d, *o*-Me$^{\mathrm{A\ or\ A'}}$, $^3J_{\mathrm{PC}}$ 18.3 Hz), 29.40–29.90 (m, P*C*$\mathrm{H_2CH_2}$*C*$\mathrm{H_2P}$), 29.60 (s, $\mathrm{PCH_2}$*C*$\mathrm{H_2CH_2P}$), 52.36 (d, P–$\mathrm{CH_2^{A\ or\ A'}}$–N, $^1J_{\mathrm{PC}}$ 9.7 Hz), 52.43 (d, P–$\mathrm{CH_2^{A\ or\ A'}}$–N, $^1J_{\mathrm{PC}}$ 9.2 Hz), 58.76 (t, C*H$^{\mathrm{A}}$, $^3J_{\mathrm{PC}}$ 8.9 Hz), 59.33 (t, C*H$^{\mathrm{A'}}$, $^3J_{\mathrm{PC}}$ 8.7 Hz), 126.87 (s, *p*-C$^{\mathrm{A}}$ in Ph), 127.05 (s, *p*-C$^{\mathrm{A'}}$ in Ph), 128.00–128.54 (*o*-C$^{\mathrm{(A+A')}}$ in Ph overlapped with C_6D_6), 128.59 (s, *m*-C$^{\mathrm{A}}$ in Ph), 128.76 (s, *m*-C$^{\mathrm{A'}}$ in Ph), 129.95 (s, *m*-C$^{\mathrm{A\ or\ A'}}$ in Mes), 130.00 (s, *m*-C$^{\mathrm{A\ or\ A'}}$ in Mes), 131.27 (d, *ipso*-C$^{\mathrm{A\ or\ A'}}$ in Mes, $^1J_{\mathrm{CP}}$ 20.4 Hz), 131.32 (d, *ipso*-C$^{\mathrm{A\ or\ A'}}$ in Mes, $^1J_{\mathrm{CP}}$ 21.4 Hz), 138.64 (s, *p*-C$^{\mathrm{A\ or\ A'}}$ in Mes), 138.67 (s, *p*-C$^{\mathrm{A\ or\ A'}}$ in Mes), 141.06 (s, *ipso*-C$^{\mathrm{A'}}$ in Ph), 144.69 (d, *o*-C$^{\mathrm{A\ or\ A'}}$ in Mes, $^2J_{\mathrm{PC}}$ 14.2 Hz), 144.75 (d, *o*-C$^{\mathrm{A\ or\ A'}}$ in Mes, $^2J_{\mathrm{PC}}$ 14.2 Hz), 145.45 (s, *ipso*-C$^{\mathrm{A}}$ in Ph). $[\alpha]_{\mathrm{D}}^{20}$ +29 (*c* 0.001, C_6H_6). Found (%): C, 75.6; H, 8.1; N, 2.9; P, 12.4. Calc. for $C_{62}H_{82}P_4N_2$ (979) (%): C 76.0, H 8.4, N 2.8, P 12.6.

1r was obtained analogously. Yield 0.65 g (36%), mp 148–150 °C. $[\alpha]_{\mathrm{D}}^{20}$ –29 (*c* 0.001, C_6H_6). Found (%): C, 75.8; H, 8.1; N, 2.6; P, 12.3. Calc. for $C_{62}H_{82}P_4N_2$ (979) (%): C, 76.0; H, 8.4; N, 2.8; P, 12.6.

[‡] *Crystallographic data for* **1s**: $C_{62}H_{82}N_2P_4$; $M = 979.18$, triclinic, space group $P\bar{1}$, $a = 9.6643(9)$, $b = 12.7047(11)$ and $c = 13.2562(11)$ Å, $\alpha = 66.297(9)°$, $\beta = 87.254(10)°$, $\gamma = 74.928(10)°$, $V = 1436.1(3)$ Å^3, $Z = 1$, $d_{\mathrm{calc}} = 1.132$ mg cm^{-3}; $T = 173$ K, μ(MoKα) = 0.170 mm^{-1}; 13824 reflections measured, 12026 independent reflections. Final $R_1 = 0.0374$, $R_{\mathrm{w}} = 0.0816$ for 7852 reflections with $I \geq 2\sigma(I)$, and $R_1 = 0.0563$, $R_{\mathrm{w}} = 0.0853$ for all reflections.

CCDC 680561 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

[§] Details of NMR experiments, as well as calculation data will be published later in a separate paper.