Macrocycles

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Shape-Persistent Chiral Alleno-Acetylenic Macrocycles and Cyclophanes by Acetylenic Scaffolding with 1,3-Diethynylallenes**

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The chemistry of chiral allenes has attracted increasing interest in recent years due to the development of improved syntheses and their emerging use in pharmaceuticals.[1] While strained small-ring allenes have been investigated in greater detail for their theoretical properties and their limits of

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

stability and isolability,[2] macrocyclic allenes, in particular shape-persistent ones,[3] are nearly unknown.[4] The only such macrocycle known is a [3$_4$]cyclophane, reported by Krause and co-workers,[5] in which four *para*-phenylene moieties are bridged by four 1,3-dimethylallene-1,3-diyl linkers and which was isolated as a mixture of several stereoisomers. This absence of allenic macrocycles is rather surprising in view of the opportunities for creating new nonplanar, chiral topologies and for developing new chiral host molecules.

The recently described synthesis of the first stable 1,3-diethynylallenes[6] now opens up the way for acetylenic scaffolding, and here we report the preparation of the new chiral, unsaturated macrocycles **1** and **2** (Figure 1). Compound **1** is the first alleno-acetylenic macrocycle without aromatic rings in the backbone. It exists as seven stereoisomers, two pairs of enantiomers and three achiral diastereoisomers, which could be isolated as pure compounds. For one of the enantiomeric pairs, the relative configuration could be assigned unambiguously. Cyclophane **2** was prepared as a mixture of six stereoisomers, two pairs of enantiomers and two achiral diastereoisomers; remarkably, both racemates and the two achiral isomers could all be isolated and their relative configurations assigned.

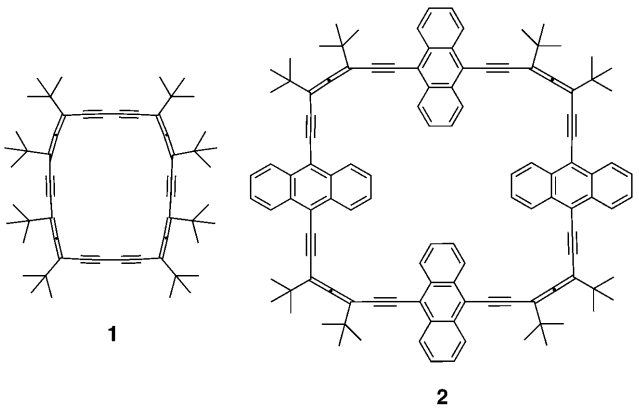
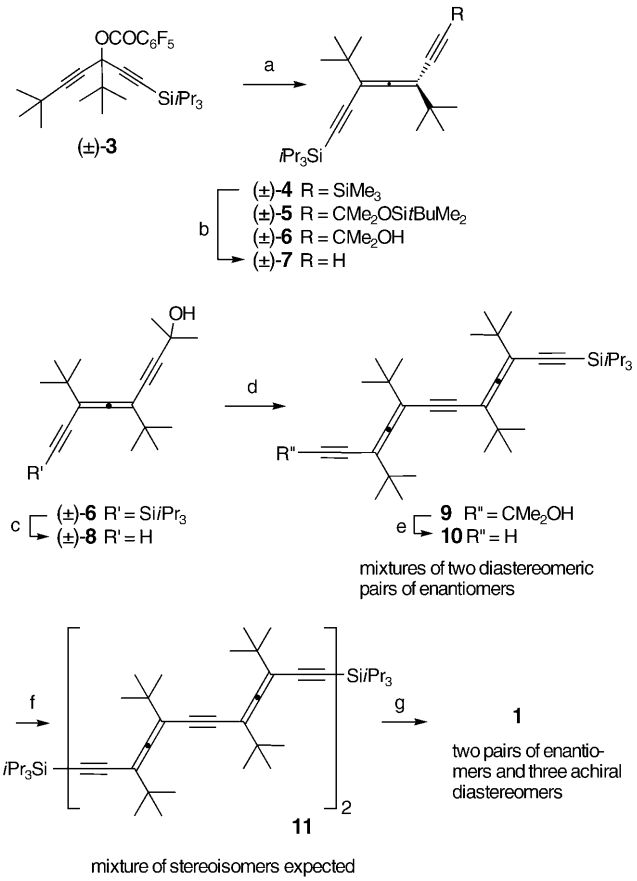


Figure 1. Two pairs of enantiomers and three achiral diastereoisomers are expected for macrocycle **1**; two pairs of enantiomers and two achiral diastereoisomer are expected for cyclophane **2**.

The synthesis of allenes (±)-**4** through (±)-**6** (Scheme 1) by Pd-catalyzed cross-coupling of ester (±)-**3** with the corresponding alkynes followed the previously described protocol;[6] however, a considerable improvement in reaction yields was obtained by using pentafluorobenzoate as the leaving group.[7] Removal of the silyl groups from (±)-**4** and (±)-**6** afforded the free terminal alkynes (±)-**7** and (±)-**8**, respectively. A second cross-coupling of (±)-**3** with (±)-**8** provided diallene **9** in 71% yield as a mixture of two diastereoisomeric pairs of enantiomers as evident from the ^{13}C NMR spectrum (125 MHz, C_6D_6). All attempts to separate the two diastereoisomeric pairs by HPLC failed.[8] The acetonide protecting group in **9** was removed with KOH in hot benzene to give the free alkyne **10**. Subsequent oxidative homocoupling under Hay conditions[17] yielded tetraallene **11** in high yield (91%). The formation of different stereoisomers



Scheme 1. Synthesis of the allene–alkyne macrocycle **1**. Reagents and conditions: a) R-C≡CH, [Pd(PPh$_3$)$_4$], CuI, *i*Pr$_2$NEt, (CH$_2$Cl)$_2$, 50°C; 74% ((±)-**4**), 53% ((±)-**5**), 69% ((±)-**6**); b) K$_2$CO$_3$, MeOH/THF, 20°C; 90%; c) *n*Bu$_4$NF, THF, 0°C; 67%; d) (±)-**3**, [Pd(PPh$_3$)$_4$], CuI, (CH$_2$Cl)$_2$, Cy$_2$NMe, 60°C; 71%; e) KOH, C$_6$H$_6$, 80°C; 65%; f) CuCl, TMEDA, (CH$_2$Cl)$_2$, 50°C; 91%; g) 1. *n*Bu$_4$NF, *ortho*-nitrophenol, THF, 20°C; 2. CuCl, CuCl$_2$, pyridine, [**11**] ≈ 10^{-4} M; 80% total yield of seven stereoisomers. Cy = cyclohexyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

was expected, but the spectroscopic data did not give precise information on the composition of the mixture and HPLC analyses showed mainly one peak. Deprotection of **11** with *n*Bu$_4$NF in THF in the presence of *ortho*-nitrophenol provided the crude free terminal bis(alkyne) which, after a filtration through SiO$_2$, was subjected directly to the final ring closure under high dilution (10^{-4} M). The Eglinton–Galbraith conditions[9] proved to be the most effective, providing a total yield of 80% of the macrocyclic tetraallene **1**: higher molecular weight products were not detected by analytical gel permeation chromatography (GPC) after filtration through SiO$_2$ (for experimental details see the Supporting Information).

The individual detection of the expected stereoisomers (two racemates and three achiral diastereoisomers) was possible by analytical HPLC on SiO$_2$ (see the Supporting Information).[10] The increased rigidity of the formed macrocycles **1**, compared to the flexible acyclic precursors **11**, most likely had beneficial effects on the separation. Preparative separation was hampered by the highly apolar nature and the

reduced solubility (despite the *tert*-butyl groups) of the compounds. The five stereoisomeric products were finally isolated with the aid of two different preparative HPLC separations on "Buckyclutcher 1" and Kromasil columns.[11] The detected ratio of the stereoisomers roughly corresponded to the values of 1:1:4:1:1 expected for an unselective ring closure. The formation of racemic, C_1-symmetric (*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**1** (Figure 2)[12] is statistically favored over the formation of the other isomers.

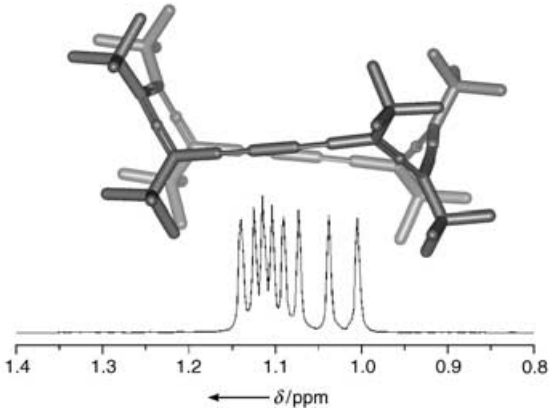
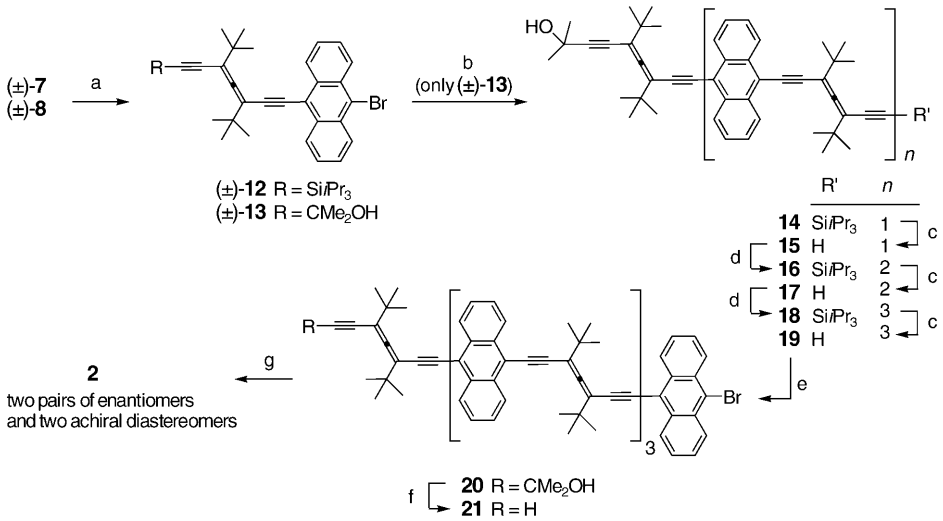


Figure 2. Tube model and ^{1}H NMR spectrum (300 MHz, $C_6D_5CD_3$) of twisted, C_1-symmetric (*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**1**. The conformation of the (*M*,*P*,*P*,*P*) isomer was optimized by AM1 calculations using Spartan Pro.[12]

The assigned relative configuration of (*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**1** was clearly proven spectroscopically. In the ^{1}H NMR spectrum in deuterated benzene or toluene, all eight expected resonances of the eight nonequivalent *tert*-butyl groups were clearly separated (Figure 2). Furthermore, the ^{13}C NMR spectrum showed four signals for the four nonequivalent cumulenic C atoms of the four allene moieties. The relative configuration of the other isolated stereoisomers could not be assigned based on symmetry considerations. For the second racemate, D_2-symmetric (*M*,*M*,*M*,*M*)/(*P*,*P*,*P*,*P*)-**1**, and the three achiral isomers, C_{2h}-symmetric (*M*,*M*,*P*,*P*)-**1** and (*M*,*P*,*P*,*M*)-**1**, and C_{2v}-symmetric (*M*,*P*,*M*,*P*)-**1**, two magnetically different *tert*-butyl groups and one signal for the central C atom of the four allene moieties was expected and observed in the ^{13}C NMR spectra (see the Supporting Information).

The synthesis of anthracenophane **2** started with the Sonogashira cross-coupling[13] of (±)-**7** and (±)-**8** with 9,10-dibromoanthracene to give (±)-**12** and (±)-**13**, respectively (Scheme 2). A series of four Sonogashira cross-couplings alternating with three deprotection steps afforded, after acetonide cleavage, the linear tetraallene , the precursor to cyclophane **2**, as a mixture of stereoisomers (15% overall yield starting from (±)-**13**), which were not separated. Macrocyclization with one equivalent of [Pd(PPh$_3$)$_4$] and CuI provided **2** in 60% yield as a mixture of two racemates and two achiral diastereoisomers, which were separated by preparative HPLC ("Buckyclutcher 1"; for experimental details see the Supporting Information).[11]

In the case of cyclophane **2**, the relative configuration of all the stereoisomers could be assigned. Thanks to its symmetry the major product was identified by ^{1}H NMR spectroscopy (300 MHz, $CDCl_3$) as C_2-symmetric (*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**2** with four magnetically different *tert*-butyl groups (Figure 3a). On the other hand, the spectrum of the achiral C_{2h}-symmetric (*M*,*M*,*P*,*P*)-**2** features only two different *tert*-butyl resonances (Figure 3b). The ^{1}H NMR spectra of the other two products display only one *tert*-butyl signal as expected as a result of their higher symmetry (D_4 and D_{2d}, respectively). Fortunately, the structure of D_4-symmetric (*P*,*P*,*P*,*P*)/(*M*,*M*,*M*,*M*)-**2** could be assigned unambiguously by an X-ray crystal structure analysis of moderate resolution (Figure 3c; for further details of the crystal structure see the



Scheme 2. Synthesis of anthracenophane **2**. Reagents and conditions: a) 9,10-dibromoanthracene, [PdCl$_2$(PPh$_3$)$_2$], CuI, TMEDA, toluene, 110°C; 56% ((±)-**12**), 73% ((±)-**13**); b) (±)-**7**, [PdCl$_2$(PPh$_3$)$_2$], CuI, TMEDA, toluene, 110°C; 83%; c) *n*Bu$_4$NF, THF, 20°C; 95% (**15**); 96% (**17**); 86% (**19**); d) (±)-**12**, [PdCl$_2$(PPh$_3$)$_2$], CuI, TMEDA, toluene, 110°C; 63% (**16**); 65% (**18**); e) 9,10-dibromoanthracene, [PdCl$_2$(PPh$_3$)$_2$], CuI, TMEDA, toluene, 110°C; 64%; f) NaOH, C_6H_6, 90°C, 85%; g) [Pd(PPh$_3$)$_4$], CuI, *i*Pr$_2$NEt, toluene, 110°C, 2 h, then air, CH_2Cl_2, 20°C, 24 h; 60%.

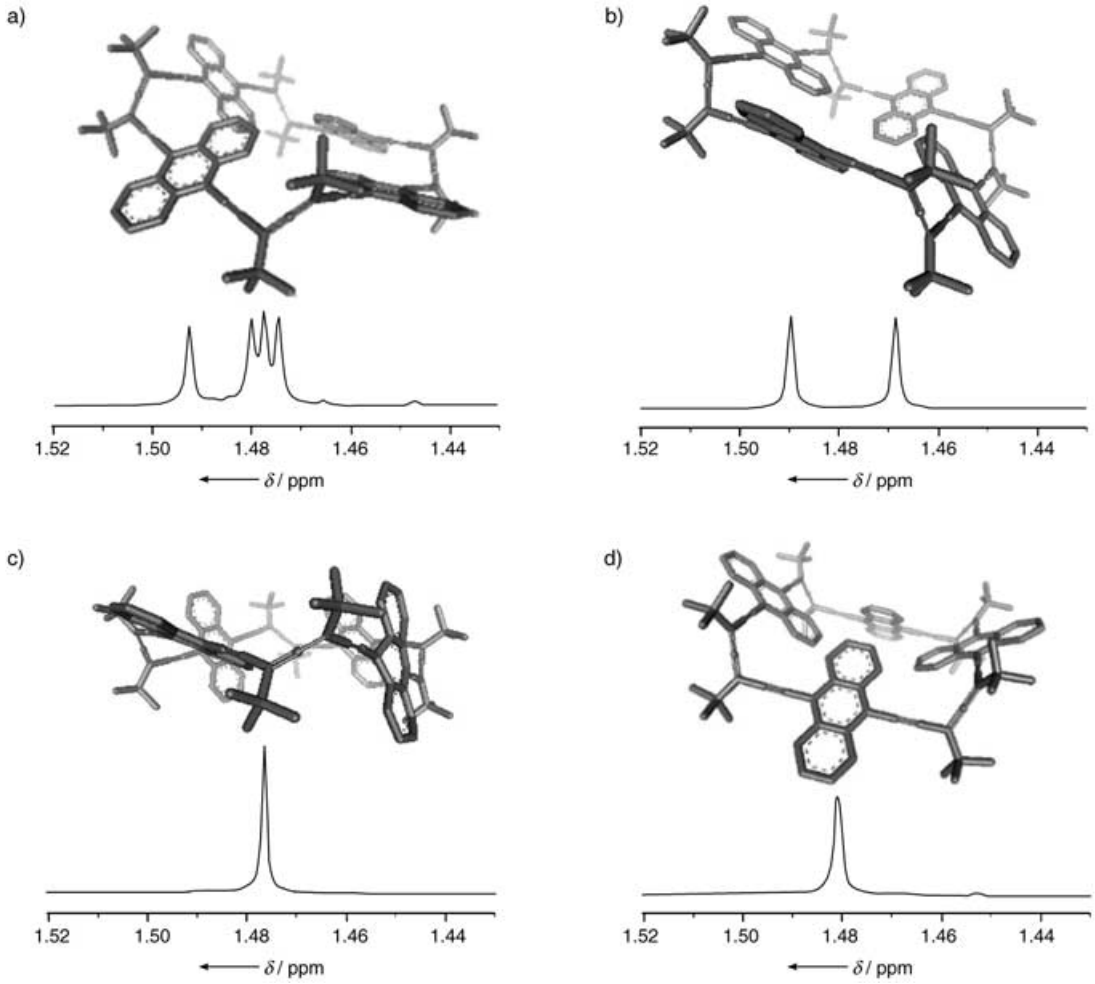


Figure 3. Tube models and ^{1}H NMR spectra of a) C_2-symmetric (*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**2**, ((*P*,*M*,*M*,*M*) isomer shown), b) C_{2h}-symmetric (*M*,*M*,*P*,*P*)-**2**, c) (*P*,*P*,*P*,*P*)/(*M*,*M*,*M*,*M*)-**2**, and d) D_{2d}-symmetric (*M*,*P*,*M*,*P*)-**2**. ^{1}H NMR spectra in $CDCl_3$. The models in (a), (b), and (d) show conformations optimized by AM1 calculations.[12] The X-ray crystal structure of (*M*,*M*,*M*,*M*)-**2** is shown in (c). (Note that in the crystal structure the actual symmetry is C_1 in contrast to the observation from NMR spectroscopy; for further details see the Supporting Information.)

Supporting Information and ref. [14]). Finally, the structure of the last isomer, D_{2d}-symmetric (*M*,*P*,*M*,*P*)-**2**, was assigned by exclusion (Figure 3d).

Macrocycle **1** and cyclophane **2** differ substantially in their properties. While the isomers of **1** are colorless solids, those of **2** are brown-colored. All compounds are stable for weeks upon storage in the air at ambient conditions, when protected from light. The characteristic anthracene bands in the visible region of the electronic absorption spectra of the isomers of **2** are retained but red-shifted by nearly 100 nm (see the Supporting Information). Similar to anthracene, the macrocycles show fluorescence ($\Phi = 0.2$; $\lambda_{max} = 478$–481 and 510–515 nm at $\lambda_{exc} = 315$ nm). The isomers of **2** undergo two reversible $2e^-$ oxidation and one reversible $4e^-$ reduction steps under cyclovoltametric conditions.[15] Whereas the isomers of **1** are stable upon irradiation, photoisomerization of the allene moieties in **2** occurs. The different stereoisomers interconvert slowly upon irradiation (within days under sunlight or within hours under xenon-lamp irradiation, 450 W; $\lambda_{exc} = 300$ nm or 463 nm) to finally reach the photostationary state with an isomeric ratio of 10:5:1:5 (C_2/C_{2h}/D_4/D_{2d}). This ratio differs slightly from the statistically expected ratio of 4:2:1:2. Photoisomerization of **2** but not of **1** is probably a result of the anthracene moieties, which can act as intramolecular sensitizers.[16]

In summary, we have prepared, separated, and characterized the first members of a new class of unsaturated allenoacetylenic macrocycles as well as four new cyclophanes which undergo photoisomerization. The three-dimensional shapes and symmetries of these novel hydrocarbons are intriguing, and the preparation of optically pure derivatives with potentially promising chiroptical properties is being pursued. Furthermore, the host–guest complexation properties of **2** and related macrocycles, which are obtained by Diels–Alder reaction of the anthracene moieties, are now under investigation.

Experimental Section

(*M*,*P*,*P*,*P*)/(*P*,*M*,*M*,*M*)-**1**: A solution of **11** (216 mg, 0.203 mmol) and *ortho*-nitrophenol (43 mg, 0.31 mmol) in THF (100 mL) was treated with nBu$_4$NF (0.30 mL of a 1M solution in THF, 0.30 mmol). After the

reaction mixture had been stirred for 1 h at 20 °C, the solvent was removed under reduced pressure. The orange oil was taken up in cyclohexane/CH_2Cl_2 and filtered through a plug of SiO_2 (eluent: cyclohexane/EtOAc 20:1). After concentration, the residue was dissolved in pyridine (0.30 L) and added to a degassed solution of CuCl (1.50 g, 15.1 mmol) and $CuCl_2$ (0.20 g, 1.51 mmol) in pyridine (1.20 L). The green mixture was degassed with Ar and stirred for 3 d at 20 °C. Pyridine was removed under vacuum until a volume of about 100 mL remained, and cyclohexane and toluene were added. The Cu salts were extracted with aq NH_4Cl solution (3×) and aq EDTA (0.2 M) solution. The organic layer was dried over $MgSO_4$ and concentrated. The residual brown solid was filtered twice through SiO_2 and eluted with toluene and cyclohexane successively to give a light brown solid (160 mg). Analytical HPLC analysis (Kromasil, hexane, 1 mL min^{-1}) showed roughly a 1:1:4:1:1 mixture of stereoisomers. Isolation of the most abundant C_1-symmetric isomer (≈60 mg) on preparative scale was successful on a "Buckyclutcher 1" column (eluent: hexane, 10 mL min^{-1}). White solid. M.p. >290 °C (decomp); ^{1}H NMR (300 MHz, $C_6D_5CD_3$): $\delta = 1.007$ (s, 9H), 1.040 (s, 9H), 1.075 (s, 9H), 1.093 (s, 9H), 1.106 (s, 9H), 1.116 (s, 9H), 1.127 (s, 9H), 1.142 ppm (s, 9H); ^{13}C NMR (75 MHz, $C_6D_5CD_3$): $\delta = 29.51$, 29.54, 29.56, 29.62, 29.73, 29.75, 29.80, 29.84, 36.01 (2×), 36.06 (2×), 36.18, 36.21, 36.34, 36.43, 76.43, 76.49 (3×), 78.86, 78.93, 79.11, 79.21, 87.52, 87.64, 88.06, 88.16, 104.04, 104.13, 104.24, 104.44, 105.43, 105.47, 105.60 (2×), 214.56, 215.07, 215.20, 215.46 ppm; UV/Vis (hexane): λ_{max} (ε) = 237 (126700), 266 (sh, 48800), 281 (sh, 32500), 295 (sh, 21300), 321 nm (12800); MALDI-MS (%): $m/z = 783.53$ (19, $[M+K]^+$), 767.55 (34, $[M+Na]^+$), 745.57 (100, $[M+H]^+$), 689.50 (22, $[M+H-t\mathrm{Bu}]^+$); HR-MALDI-MS: $m/z = 745.5694$ ($[M+H]^+$, $C_{56}H_{73}^+$; calcd 745.5707).

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[14] X-ray crystal structure of (*P,P,P,P*)/(*M,M,M,M*)-**2**: Crystal data at 220(2) K for $C_{116}H_{104} \times 4\,CH_3OH \times 4\,H_2O$. $M_r = 1698.22$. Triclinic, space group $P\bar{1}$ (no. 2), $\rho_{calcd} = 0.997$ g cm^{-3}, $Z = 2$, $a = 11.2927(2)$, $b = 13.4550(3)$, $c = 37.9436(8)$ Å, $\alpha = 83.672(1)$, $\beta = 89.873(1)$, $\gamma = 80.841(1)°$, $V = 5656.4(2)$ Å^3. Bruker-Nonius Kappa-CCD diffractometer, $Mo_{K\alpha}$ radiation, $\lambda = 0.7107$ Å, $\mu = 0.061$ mm^{-1}. A yellow crystal of (*P,P,P,P*)/(*M,M,M,M*)-**2** (linear dimensions ca. 0.25 × 0.15 × 0.13 mm) was obtained by slow evaporation of a CH_2Cl_2/CH_3OH solution. It was mounted at low temperature to prevent evaporation of enclosed solvent. The numbers of measured and unique reflections are 15697 and 11184, respectively ($R_{int} = 0.030$). The structure was solved by direct methods (SHELXS-97; G. M. Sheldrick, SHELXS-97 Program for the Solution of Crystal Structures, University of Göttingen, Germany, **1997**) and refined by full-matrix least-squares analysis (SHELXL-97; G. M. Sheldrick, SHELXL-97 Program for the Refinement of Crystal Structures, University of Göttingen, Germany, **1997**), using an isotropic extinction correction. The subunit C(88)–C(102) is disordered over two orientations (for arbitrary atom numbering, see the Supporting Information). For C(91)–C(98), C(100), and C(101), two sets of atomic parameters with population parameters of 0.5 were refined. The derived solvents exhibit static and dynamic disorder. All heavy atoms were refined anisotropically, H atoms of the ordered part isotropically, whereby H-atom positions are based on stereochemical considerations. Final $R(F) = 0.138$, $wR(F^2) = 0.325$ for 1277 parameters and 7418 reflections with $I > 2\sigma(I)$ and $2.93 < \theta < 21.01°$ (corresponding *R*-values based on all 11184 reflections are 0.185 and 0.347 respectively). CCDC-271068 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.

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