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A triple layered helical chiral cyclophane — one-pot synthesis, enantiomer separation and chiroptical properties

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Abstract

The triple layered tetraazacyclophane **3a** was prepared in high yield by a fourfold bond connection in a one-pot reaction sequence. The helical chirality of **3a** results from the unique crossed *meta*/*meta*-cyclophane linkage. A racemisation process can only take place by breaking a covalent bond. The X-ray structure analysis of **3a** proved the constitution of the isomer, difficult to determine by spectroscopy, and revealed a *face to face* arrangement of the skeleton arene rings. Enantiomer separation was achieved by HPLC on a cellulose–tris(3,5-dimethylphenylcarbamate) column. The CD spectrum of **3a** was recorded and chiroptical properties are discussed.

1. Introduction

For several years we have been interested in the synthesis and chiroptical properties of small helical chiral cyclophanes[1] and helicenes.[2] Helical[3] and planar chiral[4] cyclophanes act as model substances for the systematic investigation of experimental structure/chiroptic correlations. Furthermore we have developed a new iterative[5] synthetic strategy for the preparation of multilayered azacyclophanes, which leads to nanometre-scaled molecular ribbons containing up to nine benzene rings in its backbone.[6]

Propeller-like cyclophane frameworks[7] have aroused particular interest. Twofold bridged or multilayered so called 'gyrochiral' cyclophanes have been synthesised by Misumi,[8] Nagazaki[9] and Chan.[10] The two *para* bridges spanning the inner benzene ring of **1** give rise to D_2- and C_2-symmetry, respectively. Misumi first developed a strategy to prepare oligolayered paracyclophanes like **1** (Fig. 1).[8] The aim of

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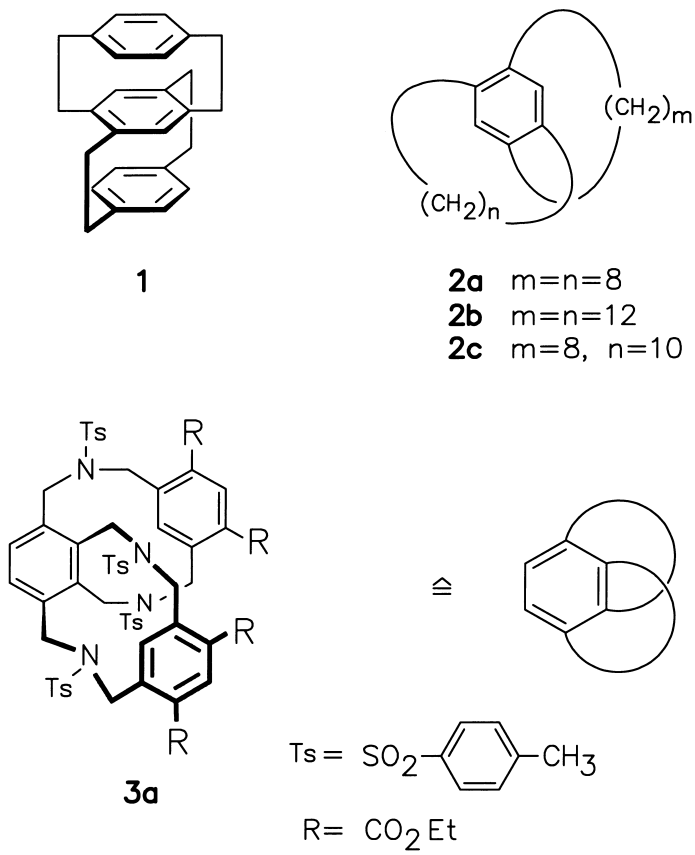

Fig. 1. Doubly bridged, chiral cyclophanes

his group was the investigation of their electronic properties and interaromatic charge transfer processes. Nagazaki et al. were interested in stereochemical aspects of multilayered [2.2]paracyclophanes and doubly bridged [*m*][*n*]paracyclophanes of type **2**. They synthesised optically active multilayered cyclophanes with predetermined absolute configurations[11] by the use of enantiomerically pure [2.2]paracyclophane carboxylic acid. In 1994 Chan and Leung[10] developed a new route to [*m*][*n*]paracyclophanes following standard cyclophane methodology.

Nevertheless, all approaches to these interesting derivatives are multi-pot syntheses with more or less low overall yields. To our knowledge an access to doubly bridged helical chiral *meta*/*meta*-cyclophanes has not been reported so far.

In previous papers[5,6] we reported on the high cyclisation tendency of our new repetitive building block **5**, which leads to linear multilayered aza[3.3]cyclophanes in good yields. These molecular ribbons contain up to nine benzene rings and are the largest monodisperse cyclophanes known to date. These findings encouraged us to synthesise helical chiral or kinked multilayered cyclophanes such as **3a** starting from a central aromatic building block with a 1,2,3,4-substitution pattern. In this work we report on the expansion of our synthesis concept towards helical chiral azacyclophanes of C_2-symmetry.

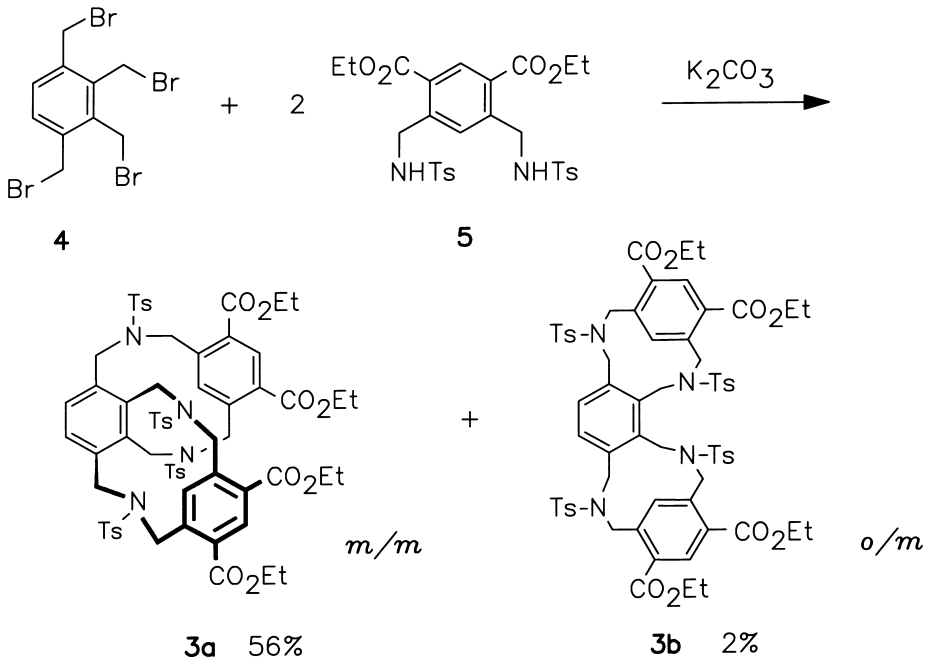

Fig. 2. Synthesis of the cyclophanes **3a** and **3b**

2. Results and discussion

Following our well-optimised preparation pathway we carried out the cyclisation procedure with the starting components **4**[12] and **5**[13] in DMF under high dilution conditions using potassium carbonate as base (Fig. 2). Recrystallisation and chromatography afforded two isomeric triple layered azacyclophanes. The major product (56% yield) **3a** was easily purified by recrystallisation from ethyl acetate while the non-chiral *ortho/meta*-connected cyclophane **3b** was only isolated as a crude oil in low yield after column chromatography (2% yield).[14] In contrast to further observations the yield-ratio of the two constitutional isomers is very different, possibly due to increased steric overcrowding in **3b**. The ^{1}H NMR spectra of **3a** and **3b** are similar and revealed a *syn/syn*-arrangement of the skeleton benzene rings in solution. The group of broad signals of the azamethylene bridges is due to a rapid motion of the cyclophane bridges carrying the tosyl groups. Nevertheless, 2-D NMR experiments allowed the assignment of all signals by characteristic long range couplings (H_6–H_9), but were not valuable for a determination of the exact constitution of **3** and **6**, which differ only in the connectivity of the four azamethylene bridges with the central aromatic ring.[15]

As a decisive method for the discrimination between isomeric triple layered azacyclophanes of this type we used X-ray crystal structure analysis. Crystals of **3a** were obtained from toluene solution without the inclusion of solvent molecules.

The *m*/*m*-isomer **3a** possesses C_2-symmetry.[16] As expected the conformation of **3a** in the solid state is *syn*/*syn*. On the right side in Fig. 3, the substituents are omitted to show the intertwined connectivity of the cyclophane bridges. The angles between the three benzene rings A (C4 to C9), B (C13 to C18) and C (C22 to C27) and the distances between the centers are shown in Table 1. The rings A and B are nearly coplanar, while the angles between B and C, and A and C respectively are wide caused by the intertwined cyclophane skeleton of **3a**.

The new helical chiral cyclophane **3a** can be separated into its (P) and (M) enantiomers

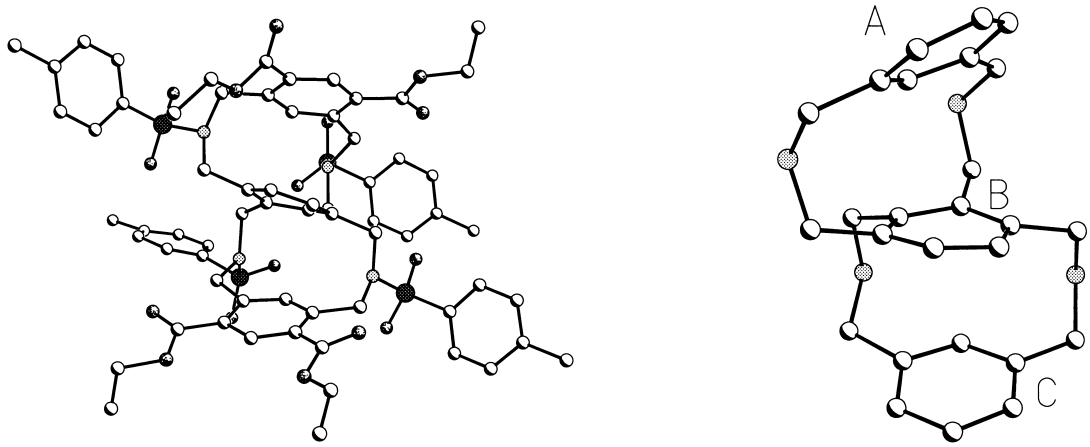

Fig. 3. Molecular structure of **3a**

Table 1
Distances between the centers of the skeleton benzene rings and angles between the rings

ring	distance [pm]	ring	angle [°]
$C_A \cdots C_B$	336	A···B	19
$C_C \cdots C_B$	373	B···C	36
$C_A \cdots C_C$	701	A···C	46
		$C_A \cdots C_B \cdots C_C$	168

by high performance liquid chromatography on a chiral stationary phase (cellulose–tris(3,5-dimethyphenylcarbamate)[17] leading to a baseline separation with the separation parameters α=2.3 and R=0.28, see experimental part). The specific rotation values measured at several wavelengths[18] in dichloromethane increase with shorter wavelengths. The CD spectrum of **3a** is rather complex due to the number of different chromophores, especially the four mobile tosyl groups and the ester functions (Fig. 4). We observed seven Cotton effects in the range between 190 and 282 nm. For this reason a reasonable theoretical discussion and calculation of the CD spectrum for an assignment of the absolute configuration was not possible. Calculations of theoretical CD spectra of a hypothetical molecule in which ester and tosyl functions were omitted were not helpful for a determination of absolute configuration.[19]

3. Conclusion

Taking advantage of the high cyclisation tendency of the bis-tosylaza compound **5** the first synthesis of significant amounts of a functionalised gyrochiral molecule **3a** was achieved in one pot. The unique chiral framework of the triple layered cyclophane **3a** with a 1,2,3,4-substitution pattern of the central building block was proven by X-ray structure analysis and subsequent HPLC-separation (CD spectrum). Following our optimised iterative procedure for elongation of azacyclophanes[5,6] it should be possible to get to a whole family of optically active multilayered cyclophanes especially five-layered derivatives in a three step procedure starting with compound **3a**.

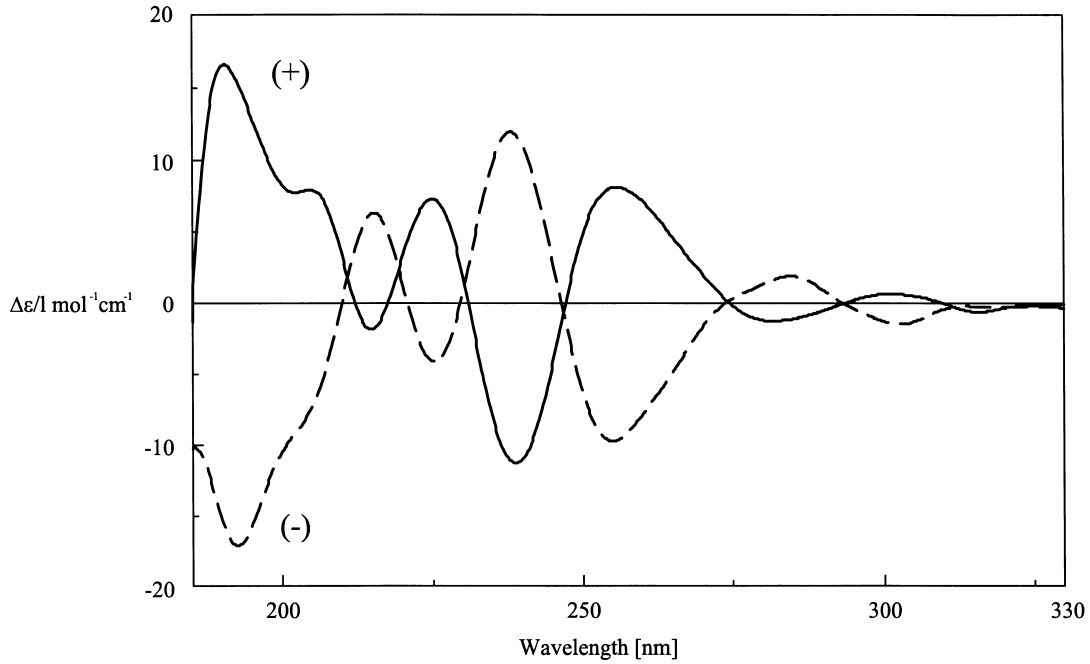

Fig. 4. Circular dichroism of **3a** (in acetonitrile as solvent)

4. Experimental section

*4.1. Cyclisation procedure for the cyclophanes **3a** and **3b***

2,4-Bis[(4-tolylsulfonylamino)methyl]benzene-1,5-dicarboxylic acid diethylester **5** (1.1 g, 1.86 mmol) and 1,2,3,4-tetrakis(bromomethyl)benzene **4** (0.4 g, 0.94 mmol) were dissolved in 50 ml of dry DMF. The solutions were added dropwise and synchronously to a suspension of 2.8 g of powdered potassium carbonate in 600 ml of dry DMF under argon over 42 h at room temperature. After addition the mixture was stirred for another 10 h. The solvent was evaporated in vacuo and the remaining pale yellow solid was dissolved in dichloromethane. The dichloromethane solution was washed three times with brine and dried (Na_2SO_4). Evaporation of the solvent and recrystallisation from ethyl acetate yielded 1.35 g (56%) of cyclophane **3a**. Workup of the remaining ethyl acetate solution by column chromatography (SiO_2: 40–63 μm, trichoromethane:acetone=100:1, R_f=0.21) supplied a small amount of the *m*/*o*–*o*/*m*-cyclophane **3b**. Single crystals from **3a** were yielded from a toluene solution by slow evaporation.

*4.1.1. 5,7,23,25-Tetrakis(ethoxycarbonyl)-2,11,20,29-tetrakis(4-tolylsulfonyl)-2,11,20,29-tetraaza-[3.3](1,3)(1,3)[3.3](2,4)(1,3)cyclophane **3a***

Mp 279–280°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.29 (t, ^3J=7.1 Hz, 6H, CH_2CH_3), 1.34 (t, ^3J=7.1 Hz, 6H, CH_2CH_3), 2.44 (s, 12H, Ts–CH_3), 4.24 (q, ^3J=7.1 Hz, 4H, CH_2CH_3), 4.33 (q, ^3J=7.1 Hz, 4H, CH_2CH_3), 3.40–5.5 (group of broad signals, 16H, $ArCH_2N$), 5.90 (br s, 2H, H_{ar}), 6.75 (s, 2H, H_{ar}), 7.74 (s, 2H, H_{ar}), 7.39, 7.77 (AB q, ^3J=8.2 Hz, 8H, Ts–H_{ar}), 7.43, 7.98 (AB q, ^3J=8.2 Hz, 8H, Ts–H_{ar}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.16 ($2CH_2CH_3$), 14.25 ($2CH_2CH_3$), 21.66 (4Tos–CH_3), 49.82 ($2ArCH_2N$), 52.10 ($2ArCH_2N$), 52.51 ($2ArCH_2N$), 53.33 ($2ArCH_2N$), 61.44 ($2CH_2CH_3$), 61.50 ($2CH_2CH_3$), 127.81 ($2CH_{ar}$), 127.84 ($2CH_{ar}$), 130.16 (8 CH_{ar}), 130.26 (8 CH_{ar}), 131.17 ($2CH_{ar}$), 134.18 ($4Cq_{ar}$), 138.02 ($2Cq_{ar}$), 139.11 ($4Cq_{ar}$), 144.01 (6 Cq_{ar}), 144.12 ($4Cq_{ar}$),

166.28 (2CO), 166.42 (2CO); MS (positive-FAB, *m*-NBA): *m*/*z*=1303.4 ($M^+[C_{66}H_{70}N_4O_{16}S_4]$+H), 1147.4 (1303.4-Ts), DC (SiO_2): R_f=0.29 (trichloromethane:acetone=50:1); $C_{66}H_{70}N_4O_{16}S_4$: (1303.54); CHN analysis calcd (found) C: 60.81 (60.55), H: 5.41 (5.35), N: 4.19 (3.71). Enantiomer separation by HPLC. Column: cellulose–tris(3,5-dimethylphenylcarbamate) (CDMPC), 250×10 mm. Eluent: *n*-hexane:2-propanol=70:30, 2.0 ml min^{-1}. Injection of 25 μl portions of a 4×10^{-3} molar solution of **3a** in dichloromethane. Pressure: 47 bar. Temperature: 20°C. Detection: UV, λ=254 nm; t_0=7.33 min; $t_r[(+)_D]$=21.75 min; $t_r[(-)_D]$=40.50 min; $k'[(+)_D]$=1.97 min; $k'[(-)_D]$=4.53 min; α=2.30; R=0.28; $[\alpha]_{578}^{20}$=412 (c=1.5×10^{-3}; l=10; CH_2Cl_2) polarimeter Perkin–Elmer 341. CD-measurement: JASCO-spectropolarimeter J 700, 1.3×10^{-4} mol/l solution in acetonitrile, 1 mm cell.

*4.1.2. 5,7,23,25-Tetrakis(ethoxycarbonyl)-2,11,20,29-tetrakis(4-tolylsulfonyl)-2,11,20,29-tetraaza[3.3](1,3)(1,2)[3.3](3,4)(1,3)cyclophane **3b***

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.20–1.5 (m, 12H, CH_2CH_3), 2.41 (s, 12H, Ts–CH_3), 4.05–4.51 (m, 8H, CH_2CH_3), 3.40–5.00 (group of broad signals, 16H, $ArCH_2N$), 4.82 (br s, 2H, H_{ar}), 7.29–7.90 (m, 20H, H_{ar}); MS (positive-FAB, *m*-NBA): *m*/*z*=1303.4 ($M^+[C_{66}H_{70}N_4O_{16}S_4]$+H), 1147.4 (1303.4-Ts), DC (SiO_2): R_f=0.21 (trichloromethane:acetone=50:1); $C_{66}H_{70}N_4O_{16}S_4$ (1303.54).

Acknowledgements

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References

1. (a) K. P. Meurer, F. Vögtle, *Top. Curr. Chem.* **1985**, *127*, 1; (b) D. Müller, M. Böhme, M. Nieger, K. Rissanen, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2937; (c) S. de la Moya Cerero, M. Böhme, M. Nieger, F. Vögtle, *Liebigs Ann./Recueil* **1997**, 1221; (d) F. Vögtle, *Cyclophane-Chemistry*, Wiley, Chichester 1993.
2. (a) I. Pischel, S. Grimme, S. Kotila, M. Nieger, F. Vögtle, *Tetrahedron: Asymmetry* **1996**, *7*, 109; (b) S. Grimme, I. Pischel, M. Nieger, F. Vögtle, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2771; (c) M. S. Newman, D. Lednicer, *J. Am. Chem. Soc*. **1956**, *78*, 4765; (d) M. S. Newman, W. B. Lutz, D. Lednicer, *J. Am. Chem. Soc*. **1955**, *77*, 3420; (e) R. H. Martin, *Angew. Chem*. **1974**, *86*, 727; *Angew. Chem. Int. Ed. Engl*. **1974**, *13*, 649; (f) W. H. Laarhoven, W. J. C. Prinsen, *Top. Curr. Chem*. **1984**, *125*, 63; (g) E. C. Constable, *Angew. Chem*. **1991**, *103*, 1482; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 1450; (h) L. Owens, C. Thilgen, F. Diederich, C. B. Knobler, *Helv. Chim. Acta* **1993**, *76*, 2757; (i) R. H. Janke, G. Haufe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc*. **1996**, *118*, 6031–6035; (j) A. William, *Chem. Eur. J*. **1997**, *3*, 15.
3. (a) S. Grimme, S. D. Peyerimhoff, S. Bartram, F. Vögtle, A. Breest, J. Hormes, *J. Chem. Phys. Lett*. **1993**, *213*, 32; (b) K. Meurer, F. Vögtle, A. Mannschreck, G. Stühler, H. Puff, A. Roloff, *J. Org. Chem.* **1984**, *49*, 3484; (c) F. Vögtle, K. Mittelbach, J. Struck, M. Nieger, *J. Chem. Soc., Chem. Commun.* **1989**, 65; (d) F. Vögtle, A. Ostrowicki, P. Knops, P. Fischer, H. Reuter, M. Jansen, *J. Chem. Soc., Chem. Commun.* **1989**, 1757; (h) F. Vögtle, P. Knops, A. Ostrowicki, *Chem. Ber.* **1990**, *123*, 1859; (i) P. Knops, P.-M. Windscheif, F. Vögtle, A. Roloff, M. Jansen, M. Nieger, E. Niecke, Y. Okamoto, *Chem. Ber.* **1991**, *124*, 1585; (j) K. Rissanen, A. Ostrowicki, F. Vögtle, *Acta Chem. Scand.* **1990**, *44*, 268.
4. (a) F. Vögtle, K. Meurer, A. Mannschreck, G. Stühler, H. Puff, A. Roloff, R. Sievers, *Chem. Ber.* **1983**, *116*, 2630; (b) R. Lemmerz, S. Grimme, F. Vögtle, *Chem. Ber*. **1994**, *127*, 1147.
5. (a) S. Breidenbach, S. Ohren, M. Nieger, F. Vögtle, *J. Chem. Soc., Chem. Commun.* **1995**, 1237; (b) S. Breidenbach, S. Ohren, R. Herbst-Irmer, S. Kotila, M. Nieger, F. Vögtle, *Liebigs Ann*. **1996**, 2115; (c) N. Feuerbacher, F. Vögtle, *Top. Curr. Chem*. **1998**, *197*, in press.
6. S. Breidenbach, S. Ohren, F. Vögtle, *Chem. Eur. J.* **1996**, 2, 832.
7. X. Qiao, D. H. Ho, R. A. Pascal Jr., *Angew. Chem*. **1997**, *109*, 1588; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1531.

8. (a) S. Misumi, *Mem. Inst. Sci. Ind. Res., Osaka Univ*. **1991**, *48*, 9; (b) S. Misumi in: *Cyclophanes*, Vol. II (P. M. Keehn, S. M. Rosenfeld, Ed.), New York 1983, see references therein.
9. (a) M. Nagazaki, K. Yamamoto, S. Tanaka, M. Ito, *Tetrahedron Lett*. **1971**, 341.
10. T. Chan, C. Hung, T. Man, M. Leung, *J. Chem. Soc., Chem. Commun.* **1994**, 1971.
11. (a) M. Nagazaki, K. Yamamoto, S. Tanaka, *J. Chem. Soc., Chem. Commun.* **1972**, 433; (b) M. Nagazaki, K. Yamamoto, *Chem. Lett*. **1974**, 1051; (c) M. Nagazaki, K. Yamamoto, S. Tanaka, H. Kametani, *J. Org. Chem*. **1977**, *42*, 287.
12. E. Giovannini, H. Vuillemier, *Helv. Chim. Acta* **1977**, *60*, 1452.
13. See Refs. 5 and 6; S. Breidenbach, PhD Thesis, University of Bonn, 1995.
14. In all further preparations of comparable multilayered azacyclophanes and also in this case possible *meta*/*para*-isomers were not detected.
15. A differentiation between the isomers by ^{1}H NMR spectroscopy was not possible. The azacyclophanes exhibit neither significant shifts of the aromatic backbone protons (*syn*/*syn*-conformation) nor useful nuclear-Overhauser-effects.
16. X-Ray structure of **3a**: Crystal data: $C_{66}H_{70}N_4O_{16}S_4$, MW 1303.5 g mol^{-1}, colourless plates, dimensions 0.18×0.10×0.10 mm, $d_{calc.}$=1.35 Mg m^{-3}, triclinic, space group $P\bar{1}$ (No. 2), *a*=9.753(1), *b*=14.419(1), *c*=24.608(2) Å, α=78.40(1)°, β=86.78(1)°, γ=71.45(1)°, V=3213.7(5) Å^3, Z=2, F(000)=1372. A total of 9104 reflections (2Θ=113.5°) were recorded on an Enraf-Nonius CAD4 diffractometer (graphite monochromator, λ (CuK_α)=1.54178 Å), μ (CuK_α)=1.955 mm^{-1}, T=293 K). Of these, 8580 independent reflections were used for the structure solution (SHELXTL-Plus) and refinement (811 parameter and 1052 restraints, SHELXL-93). Non-hydrogen atoms were refined anisotropically (full matrix least squares refinements on F^2); H atoms were refined using using a riding model, wR2=0.227 (R for I>2 σ(I)=0.068), largest difference peak 0.535 eÅ^{-3}. G. M. Sheldrick, SHELXTL-Plus, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1989. G. M. Sheldrick, SHELXL-93, University of Göttingen, 1993.
17. (a) P. Knops, P.-M. Windscheif, F. Vögtle, A. Roloff, M. Jansen, M. Nieger, E. Niecke, Y. Okamoto, *Chem. Ber.* **1991**, *124*, 1585; (b) Y. Okamoto, K. Suzuki, K. Ohta, Hatada, Y. Yuki, *J. Am. Chem. Soc.* **1979**, *101*, 4763; (c) H. Yuki, Y. Okamoto, I. Okamoto, *ibid.* **1980**, *102*, 6356; (d) Y. Okamoto, S. Honda, I. Okamoto, H. Yuki, S. Murata, R. Noyori, H. Takaya, *ibid.* **1981**, *103*, 6971; (e) F. Vögtle, T. Dünnwald, R. Jäger, *J. Am. Chem. Soc.* **1997**, *119*, 10547–10548.
18. Optical rotation value measured in dichloromethane: $[\alpha]^{20}_{589}$=374; $[\alpha]^{20}_{578}$=412; $[\alpha]^{20}_{546}$=480; $[\alpha]^{20}_{436}$=956; $[\alpha]^{20}_{365}$=1601; (c=1.5×10^{-3}; l=10).
19. Examples of theoretical methods of CD calculation and following assignment of absolute configurations: (a) D. Wortmann-Saleh, S. Grimme, B. Engels, D. Müller, F. Vögtle, *J. Chem. Soc., Perkin Trans. 2*, **1995**, 1185; (b) see also Refs. 1b, 3a, 3g and 4b.