Helical thiaza[2.2]metacyclophanes. Synthesis, structure, circular dichroism, absolute configuration

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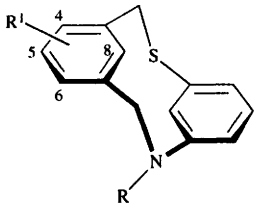
A series of helical-chiral 1-thia-10-aza[2.2]metacyclophanes 2–11 with different substituents at the nitrogen atom and at the aromatic ring have been synthesised and their chiroptical properties examined. These new *N*-substituted phanes are more suitable for the investigation of structure–chiroptics relationships than the already characterised *N*-tosylated aza[2.2]phanes. Their absolute configuration can be derived by comparison with the known parent compound 1 with free NH in the bridge. Chiral separations were achieved by HPLC, using a cellulose carbamate-coated, chiral column material. The secondary amine 1 has been derivatised at the nitrogen atom with various electrophiles. The X-ray structures of 1–4 give detailed information about deformation and distortion in the [2.2]metacyclophane skeleton. In the *N*-tosyl[2.2]metacyclophanes 8–11, containing stilbene chromophores, the UV absorption is shifted bathochromically. The disturbing influence of the tosyl chromophore in the CD spectra can be accounted for by the separation of the stilbene transitions. The synthetic method used is demonstrated to be more generally applicable to strained secondary amines by preparing the first chiral and even more strained thiaza[2.2]orthometacyclophane 15.

Introduction

Previous work reported in the area of chiral [2.2]cyclophanes[1] has demonstrated that these compounds are appropriate subjects for the investigation of stereochemical and spectroscopic questions, especially on account of experimental and theoretical correlation of structure and circular dichroism (CD).[1–4] Replacing the CH_2-units in the bridges by different hetero atoms results in helically distorted chiral molecules, the two aromatic chromophores being arranged in a screw orientation like propeller blades. In addition, electronic and steric factors, strain and deformation can be easily modified, *e.g.* varying the length and the substitution of the clamping bridges or by introducing further substituents at the aromatic ring[1,5] (Scheme 1).



	R	R1
1	H	H
2	$COCF_3$	H
3	$CSCF_3$	H
4	SO_2CF_3	H
5	NO	H
6	Bn	H
7	Tos	H
8	Tos	5–Styryl
9	Tos	8–Styryl
10	Tos	4–Styryl
11	Tos	6–Styryl

Scheme 1 1-Thia-10-aza[2.2]metacyclophanes with various substituents

Therefore, a number of tailored compounds of this type, bearing no stereogenic centre, have been prepared and characterised in order to study relationships between structure and spectroscopic properties (^{1}H NMR[6] and CD[2–5]). Furthermore, the small and compact [2.2]phanes are outstanding objects for quantum chemical considerations, for which the rigidity of the molecular framework is convenient; data obtained from the X-ray structural analysis are transferable to the solution and gas phases and only little conformational flexibility must be considered in the calculations.

Recently, the CD spectra for 1-thia- and 1-oxa-[2.2]-metacyclophane were calculated on a semi-empirical level by using a new method, showing remarkably good agreement with the experimental data.[2] Subsequently, this method has been extended successfully to planar-chiral adamantano- and [*n*]cyclophanes.[7] Yet the comparison of theoretical and experimental results so far has been hampered in the case of aza[2.2]metacyclophanes as these were hitherto only available preparatively with *N*-tosyl groups. The large tosyl substituent prevents detailed theoretical studies and interpretations of CD spectra. Nevertheless, the tosyl group seemed to be synthetically unavoidable, as it favours the intramolecular ring-closure to the strained ten-membered ring and decreases oligomerisation. Yields were improved remarkably in some cases by applying the dilution principle,[8] the caesium effect[9] and the choice of an ideal solvent.[10] A series of substituted [2.2]phanes of type **7** were prepared and investigated, but any attempt to obtain the free amine **1** by detosylation afterwards failed.[11]

As an alternative, we followed two strategies to avoid the disadvantages of the tosyl group: (1) preparation of aza[2.2]metacyclophanes **2** and **4** with other *N*-protecting and activating groups, which contained no further arene units and were easily removed; and (2) extension of one aromatic chromophore to a stilbene unit, which leads to a bathochromically shifted absorption, separable from the perturbing tosyl absorption.

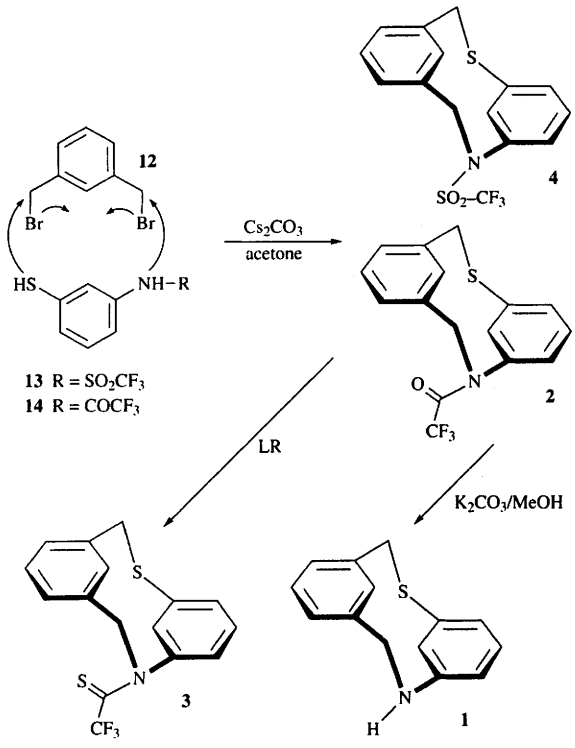
We describe here the first syntheses and properties of thiaza[2.2]cyclophanes **1–6** lacking any tosyl group at their nitrogen atom, as well as those of the 'stilbenophanes' **8–11**, containing stilbene units in different orientations.

Results and discussion

Synthesis

The preparation of strained heterocyclic [2.2]metacyclophanes requires special conditions to avoid the formation of the

kinetically favoured higher oligomers. A two-component high-dilution[8] reaction between a bis(bromomethyl)benzene unit like **12** and an *N*-protected 3-aminothiophenol like **13** or **14** (or the corresponding *N*-tosyl precursor[12]) according to Scheme 2 has



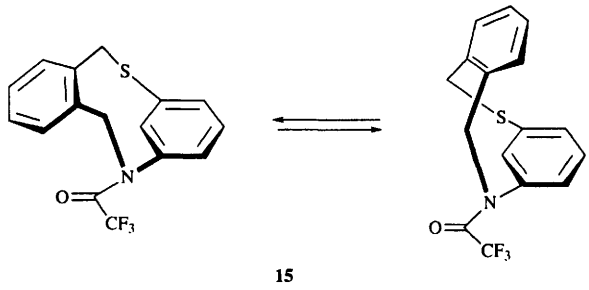
Scheme 2 Synthesis of *N*-substituted 1-thia-10-aza[2.2]metacyclophanes **1**–**4** (LR = Lawesson's reagent)

been applied successfully. The highest yields for **2** (32%) and **4** (48%) were obtained in boiling acetone with Cs_2CO_3 as base. Compared to other [2.2]cyclophane syntheses, these yields are rather good, especially if one takes into account the fact that these are not organometallic reactions, which usually lead to the highest yields in the cyclisation of strained cyclophanes. This means that these chiral phanes are now easily available, a circumstance that may increase their importance for further synthetic applications. Especially in the synthesis of **2**,[13] *O*-alkylation occurs as a side reaction (10%), but this can be suppressed by using the solvent combination acetone–DMF. The *N*-protected precursors **13** and **14** were obtained by reaction of 3-aminothiophenol **13** (R = H) with the corresponding acid anhydride.

The *N*-trifluoroacetyl phane **2** (TFA = trifluoroacetyl) was converted into the thioamide **3** by using Lawesson's reagent.[14]

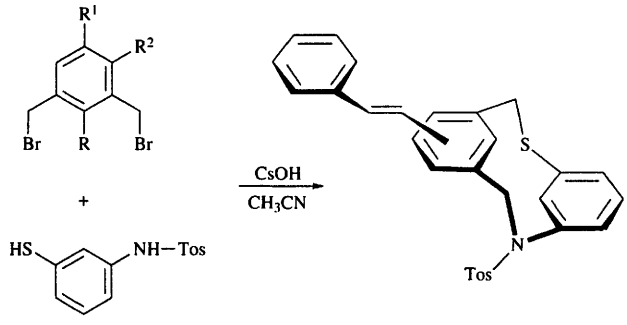
The advantage of the *N*-TFA group, in contrast to the tosyl group, is the possibility of easy removal to yield the corresponding amine **1**[13] under mild conditions by simple hydrolysis. The target parent [2.2]metacyclophane **1** with a free NH-bridge is available quantitatively without further chromatographic purification. This successful synthetic strategy—*N*-activation by a TFA group with subsequent hydrolysis to yield the free amine—was also extended to the even more strained [2.2]orthometacyclophane **15**, which is the first chiral representative of this cyclophane type (see Scheme 3). As expected, the yield is much lower (2%) than for **2**, presumably due to the increased strain in the skeleton of the nine-membered ring.[15]

The *N*-benzylthiaza[2.2]metacyclophane **6** was obtained by reaction of **1** with benzyl bromide and K_2CO_3 in refluxing acetonitrile, the decreased reactivity of the nucleophilic bridging nitrogen needing more drastic conditions. The *N*-nitroso derivative **5** could be prepared only by using ethyl nitrite as the nitrosating reagent; other methods failed.



Scheme 3 *syn*/*anti* Conformational process for the *N*-trifluoroacetyl-1-thia-10-aza[2.2]orthometacyclophane **15**

The preparation of the tosylated [2.2]metacyclophanes **8**–**11** with stilbene units were achieved by using a procedure described earlier.[10] The required styryl-substituted 1,3-bis(bromomethyl)benzenes **16**–**18** were obtained by selective bromination of the corresponding dimethylstilbenes with *N*-bromosuccinimide (see Scheme 4).



16 R = H, R[1] = Styryl, R[2] = H
17 R = H, R[1] = H, R[2] = Styryl
18 R = Styryl, R[1] = H, R[2] = H

8 5-Styryl[2.2]metacyclophane
9 8-Styryl[2.2]metacyclophane
10 4-Styryl[2.2]metacyclophane
11 6-Styryl[2.2]metacyclophane

Scheme 4 Synthesis of tosylated [2.2]metacyclophanes with stilbene units **8**–**11**

Surprisingly, the synthesis of the intra-annularly styryl-substituted compound **9**, which should be the most strained, proceeded with the highest yield. The reason for this unexpected result may lie in a 'template effect' by interaction of the superimposing arene units of the reactants, resulting in their pre-organisation during ring closure.[16] Attractive forces between benzene units are well documented.[17]

Structural characterisation

The thiaza[2.2]metacyclophanes **2**–**4** with the new *N*-substituents could be examined by X-ray analysis. Helicity angles, which were introduced in an earlier work, are well suited to describe the distortion of the [2.2]metacyclophane skeleton.[18]

Comparison shows similar values for the different *N*-substituted phanes **2**–**4**, due to the nitrogen substituents being nearly planar (trigonal) in all cases (Table 1). The angles in the parent compound **1** deviate from those in compounds **2**–**4**, which can be explained by a pseudo-tetrahedral arrangement at the nitrogen atom. All compounds **1**–**4** contain the characteristic boat-shaped benzene rings. This deviation of the benzene rings from planarity is due to the steric repulsion of the intra-annular hydrogen atoms as in the [2.2]metacyclophane hydrocarbon itself (Fig. 1).[1]

Remarkably, both amide groups in **2**[13] and in **3** have the same orientation in the solid state. This suggests an interaction between the amide oxygen (or sulfur) and one of the N–CH_2-hydrogen atoms, which may also be detected both in the ^1H NMR and in CD spectra (see below).

The ^1H NMR spectra of all [2.2]metacyclophanes are characteristic, due to their special rigid step-like structure. The intra-annular protons in **1**–**5** and in **7**–**11** are found at high field, and

the magnitude of this shift can serve as a certain indicator for strain and distortion in the molecule. As expected from the X-ray structures, there are no deviations within the series of the phanes bearing different *N*-substituents: the molecular framework is nearly identical.

The interaction in **2** and **3** between the chalcogen atoms and one of the NCH_2 hydrogen atoms leads to significant downfield shifted signals of the corresponding deshielded protons to 6.0 ppm for **2** and even 7.0 ppm for **3**, indicating that the larger and more polarisable sulfur interacts more strongly. In all other aza[2.2]phanes, this proton resonates at *ca.* 4.6 ppm.

The NH proton of **1** is exchangeable with deuterium in D_2O. Information on a nitrogen inversion process could be obtained from spectra recorded at −90 °C. In the stilbenophane **9** with the intra-annular styryl group, the olefinic AB-system is shifted remarkably to higher fields, and the difference between the A and the B signals increases from 0.3 ppm in **18** to 1.2 ppm in the phane **9**. This effect is caused by the influence of the benzene ring, facing the styryl group.

The thiaza[2.2]orthometacyclophane **15** exhibits the expected conformational behaviour, known from the corresponding hydrocarbon phane.[19] The CH_2 protons of the bridges appear as singlets, due to fast *syn*/*anti*-ring flip processes indicated in Scheme 3.[20] The conformers are not 'frozen' even at −50 °C.

The circular dichroism of the helical-chiral thiaza[2.2]metacyclophanes are suitable for systematic studies of structure–chiroptics relationships. The red-shifted Cotton effect of the stilbene unit is easy to distinguish from the other aromatic transitions, which overlap the absorption of the tosyl group [Fig 2(a)]. Here, the stilbene transition is asymmetrically disturbed by the helical skeleton and can therefore serve as an indicator for the chirality in the molecule.

Nevertheless, the chiral *N*-tosylthiaza[2.2]phanes are limited in their use for the interpretation of their chiroptical data. As shown in the CD spectra of the unsubstituted parent phane **1**, as well as in those of the derivatives **2**–**4** [Fig. 2(b)], the single Cotton effects are better resolved. Compared to the tosyl compound **7** [Fig. 2(a)], their Cotton effects exhibit more detailed structure.

The finer structure of the curves for **2** and **3** can be rationalised by the favoured amide conformation, which according to the ^1H NMR results is also predominant in solution, and therefore is responsible for the CD. In contrast to this predominant conformation, the *N*-tosyl[2.2]phanes like **7** have no favoured conformation in solution, all conformers caused by the free *N*-tosyl rotation being energetically similar; hence, they all give their different contributions to the CD. Therefore, the aromatic transitions cannot be investigated in detail, only a broad absorption band being observed here.

The possibility of calculating the CD theoretically allows identification of the characteristic transitions. The absolute configuration of the parent compound **1** was derived by anomalous X-ray dispersion[13] and agrees with the calculated CD.[3] The transitions responsible for single Cotton effects, identified by calculation, are similar for all 1-thia-10-aza[2.2]metacyclophanes. The absolute stereochemistry of all 1-thia-10-aza[2.2]metacyclophanes can therefore be predicted. These results are fully consistent with those for the monothia[2.2]phane[2] and for the *N*-tosylthiaza[2.2]metacyclophane, substituted with an SCH_3 group on the arene ring.[21] The prediction of the helicity and the interpretation of chiroptical data for hetera[2.2]metacyclophanes is therefore now possible by a combination of theoretical methods and experimental results. Even conformation processes like N-inversion in **1**, which is much too fast on the NMR time-scale to be investigated can, by integration of experimental results and theoretical CD data, the UV excitation being very short-lived,[3] be studied.

Conclusion

Although many *N*-substituted aza[2.2]phanes have been prepared and investigated in recent years, it was not possible to analyse accurately their spectroscopic properties and the reactivity of the fixed nitrogen; the *N*-tosyl group prevented this. The work presented here shows two possible ways to avoid this disadvantage: first, by shifting to longer wavelength the absorption of the compounds, so that they can be investigated separately, and second by avoiding the tosyl group altogether. The chiral thiaza[2.2]metacyclophanes described here with different *N*-substituents offer distinct advantages over the *N*-tosyl phanes (the only previously known thiaza[2.2]metacyclophanes). Such compounds allow the unambiguous interpretation of spectroscopic data, particularly circular dichroism. Structure–chiroptics relationships are quantitatively available now and by analysis of the CD spectra for the new phanes,

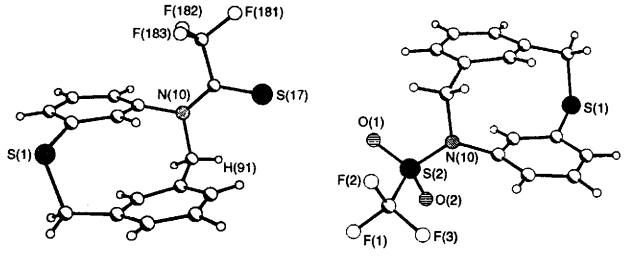


Fig. 1 X-Ray structures of the *N*-substituted cyclophanes **3** and **4**

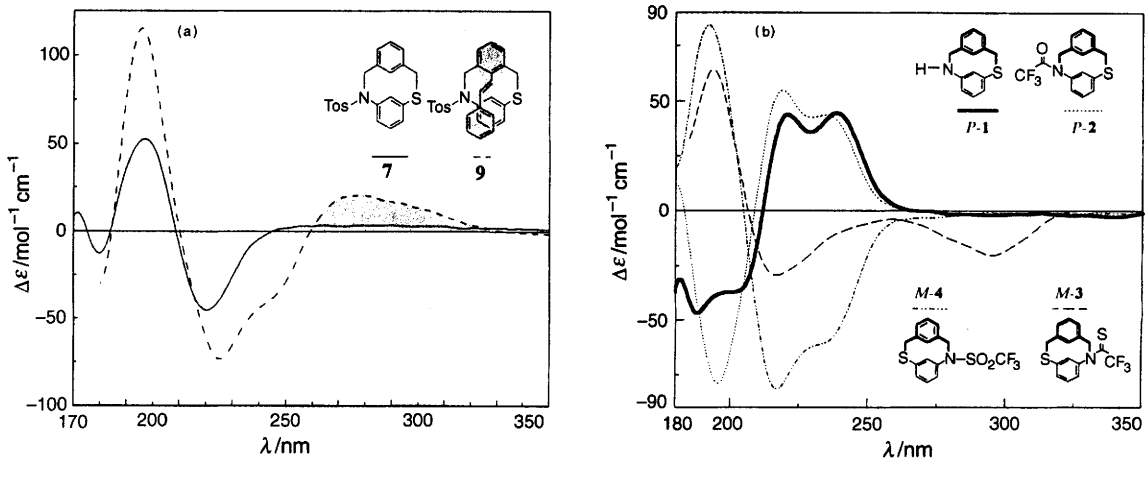


Fig. 2 (a) CD spectra of the stilbenophane **9**, compared to the unsubstituted compound **7**; solvent hexafluoropropan-2-ol; (b) CD spectra of the different *N*-derivatives; solvent hexafluoropropan-2-ol; **P-1** (——), **P-2** (····), **M-3** (---), **M-4** (–···–···)

Table 1 Helicity angles for the *N*-substituted compounds **1–4** and **7**[18]

Helicity angles (°)*	1	2	3	4	7
α′	1.2	3.3	3.2	2.3	0.4
β′	5.5	0.1	0.2	0.9	2.5
γ′	8.5	0.9	0.2	2.8	5.6
δ	8.9	10.2	8.8	4.3	5.4

* α′: defined as 'horizontal distortion' angle of both benzene planes; β′: defined as angle between 'twisted' benzene planes against each other; γ′: defined as deviation between both 'lines' of ethano bridges; δ: defined as angle between 'plane-normal' of both benzene units.

especially that of the parent compound **1**, the assignment of absolute stereochemistry for all thiaza[2.2]metacyclophanes so far investigated is possible. Extension of the synthetic strategy, by introduction of an *N*-trifluoroacetyl activating group with subsequent hydrolysis, to the more strained thiaza[2.2]ortho-metacyclophane, underlines the general utility of this method for the synthesis of strained amines.

The free amine **1** is also appropriate as a starting material for further chiral phanes, as demonstrated by the preparation of some *N*-derivatives (*e.g.* **5**, **6**). Furthermore, the reduction of **5** leads to an NNH_2-containing chiral [2.2]phane, which can be considered as a helical-chiral RAMP/SAMP analogue.[22] This opens new perspectives for the chiral [2.2]phanes, which are no longer solely model compounds for spectroscopic studies. Preparative applications in synthetic chemistry are possible now, *e.g.* as chiral bases or auxiliaries.

Experimental

Materials and miscellaneous

All chemicals were of commercial reagent quality and used without further purification with the following exceptions: THF, toluene and diethyl ether were distilled over sodium. Silica gel used for chromatography was SiO_2 40 (0.040–0.063 μm), Macherey, Nagel & Co., Düren. Analytical thin layer chromatography was performed on commercial Merck plates coated with silica gel $60F_{254}$.

Spectroscopic data were obtained by means of ^1H and ^{13}C NMR: WM 250 (250 62.90 MHz, respectively), Bruker Physik AG. J Values are given in Hz. H_i refers to the intra-annular hydrogen atom. Mass spectra were obtained with an MS 50, A.E.I (EI, 70 eV). All chromatographic separations of enantiomers described were achieved with an HPLC column (HPLC equipment: Fa. Gilson Medical Electronics, Inc., USA) filled with the chiral stationary phase cellulose–tris(3,5-dimethylphenyl)carbamate (CHIRACEL OD®);[23] for the free amine **1**, a poly[2-pyridyl(diphenyl)methylmethacrylate]-coated phase [(Chiralpak OP(+)®] was used.[24] The separations were optimised by varying the hexane–propan-2-ol mixture as eluent first and flow afterwards.

Circular dichroism spectra were obtained by J-720, Jasco Spectropolarimeter, Jasco Labor- und Datentechnik GmbH, Germany.

N-Trifluoromethylsulfonyl-3-aminothiophenol 13

A solution of trifluoromethanesulfonic acid anhydride (5 ml, 30 mmol) in dry diethyl ether (45 cm^3) was added under an argon atmosphere to a stirred solution of 3-aminothiophenol (3.75 g, 30 mmol) in dry diethyl ether (150 cm^3) with the temperature maintained at <0 °C. After completion of the addition, the reaction mixture was allowed to warm to room temp. at which it was stirred for 3 h. It was then washed with water and saturated brine. The aqueous layer was back-extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated to give the liquid product **13** (6.65 g, 85%); δ_H(60 MHz, $CDCl_3$) 3.6 (s, 1 H, SH), 6.3 (s br, 1 H, NH) and 6.8–7.4 (m, 4 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 115.3 [q, ^1J(CF) = 285], 118.9, 119.1, 120.3, 120.4, 129.8 and 133.6 (Found: *m/z* 256.9791. $C_7H_6NO_2S_2F_3$ requires 256.9792); *m/z* 257 (M^+, 65%) and 124 ($M^+ - SO_2CF_3$, 100).

N-Trifluoroacetyl-3-aminothiophenol 14

A solution of trifluoroacetic acid anhydride (6.9 ml, 50 mmol) in dry THF (40 cm^3) was added slowly (30 min) at 0 °C under an argon atmosphere to a solution of 3-aminothiophenol (6.25 g, 50 mmol) in dry THF (80 cm^3). After completion of the addition, the mixture was allowed to warm to room temp. at which it was stirred for 2 h. The mixture was then evaporated and the residue taken up in dichloromethane. This solution was then washed with 1 M hydrochloric acid and water, dried (Na_2SO_4) and evaporated. The crude product was recrystallised from aqueous ethanol (8.3 g, 75%); mp 78–80 °C; δ_H(250 MHz, $CDCl_3$–[$^2H_6$]DMSO) 4.55 (s, 1 H, SH), 6.9–7.8 (m, 4 H, ArH) and 10.8 (s br, 1 H, NH); δ_C(62.9 MHz, $CDCl_3$) 115.5 [q, ^1J(CF) = 285], 154.7 [q, ^2J(CF) 39], 119.3, 119.5, 121.0, 122.9, 130.4 and 135.4 (Found: *m/z* 221.0120. $C_8H_6NOSF_3$ requires 221.0122); *m/z* 221 (M^+, 100%), 152 ($M^+ - CF_3$, 32) and 124 ($M^+ - COCF_3$, 15).

(*E*)-3,5-Bis(bromomethyl)stilbene 16

A solution of 3,5-dimethylstilbene (*E*/*Z*-mixture; 5.2 g, 25 mmol) in tetrachloromethane (500 cm^3) was heated under reflux and irradiated with a 500 W lamp. A suspension of *N*-bromosuccinimide (12.8 g, 0.6 mol) and of azoisobutyronitrile (AIBN) (15 mg) in tetrachloromethane (200 cm^3) was then added slowly in small portions over a period of 1 h to the solution. The mixture was heated for an additional 6 h, after which it was cooled and filtered. The filtrate was washed with sat. aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. The residue was dissolved in ethanol and the solution stored at 0 °C to give the product as a precipitate. This was recovered and recrystallised from ethanol (2.3 g, 25.1%); mp 121 °C; δ_H(250 MHz, $CDCl_3$) 4.5 (s, 4 H, CH_2Br), 7.03 [d, 1 H, ^3J(HH) 16.4, ArCH=CHAr (*E*)], 7.15 [d, 1 H, ^3J(HH) 16.4, ArCH=CHAr (*E*)] and 7.25–7.6 (m, 8 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 32.8 (CH_2Br), 116.3, 118.2, 118.9, 119.0, 124.7, 125.7, 128.0, 128.2, 128.9 and 132.9 (Found: *m/z* 365.9441. $C_{16}H_{14}Br_2$ requires 365.9442); *m/z* 366 (M^+, 65%), 286 (M^+ − Br, 92) and 206 (M^+ − 2Br, 100).

(*E*)-2,4-Bis(bromomethyl)stilbene 17

Compound **17** (2.05 g, 20.1%) was prepared from 2,4-dimethylstilbene in a fashion similar to that described for compound **16**; mp 98 °C; δ_H(250 MHz, $CDCl_3$) 4.48 (s, 2 H, CH_2Br), 4.62 (s, 2 H, CH_2Br), 7.10 [d, 1 H, ^3J(HH) 16, ArCH=CHAr (*E*)], 7.45 [d, 1 H, ^3J(HH) 16, ArCH=CHAr (*E*)] and 7.3–7.5 (m, 8 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 31.4 (CH_2Br), 32.7 (CH_2Br), 118.1, 118.4, 119.0, 121.1, 121.3, 122.8, 123.0, 125.2, 126.1, 126.1, 128.9 and 130.1 (Found: *m/z* 365.9441. $C_{16}H_{14}Br_2$ requires 365.9442); *m/z* 366 (M^+, 45%), 286 (M^+ − Br, 100) and 205 (M^+ − 2Br, 62).

(*E*)-2,6-Bis(bromomethyl)stilbene 18

Compound **18** (3.6 g, 39%) was prepared from 2,6-dimethylstilbene in a fashion similar to that described for compound **16**; mp 84 °C; δ_H(250 MHz, $CDCl_3$) 4.58 (s, 4 H, CH_2Br), 7.02 [d, 1 H, ^3J(HH) 16, ArCH=CHAr (*E*)], 7.34 [d, 1 H, ^3J(HH) 16, ArCH=CHAr (*E*)], 7.3–7.6 (m, 8 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 32.7 (CH_2Br), 115.1, 117.9, 118.0, 119.2, 120.1, 121.9, 122.5, 124.7, 124.8, 129.1 and 130.1 (Found: *m/z* 365.9442. $C_{16}H_{14}Br_2$ requires 365.9442); *m/z* 366 (M^+, 22%), 286 (M^+ − Br, 26) and 205 (M^+ − 2Br, 100).

Synthesis of the stilbenophanes 8–11

General procedure. A three-necked flask fitted with two precision dropping funnels was charged with acetonitrile (2500 cm^3) and kept under an argon atmosphere. One dropping funnel con-

tained one of the appropriate bromides **16**–**18** (5 mmol, 1.83 g) in acetonitrile (250 cm^3) whilst the other was filled with a solution of *N*-tosyl-3-aminothiophenol (1.45 g, 5 mmol)[12] in ethanol (245 cm^3) together with a solution of CsOH (1.5 g, 10 mmol) in water (5 cm^3). The two components were added simultaneously over a period of 8 h to the refluxing solvent. After completion of the addition the reaction mixture was kept at reflux for 4 h and then evaporated. The resulting residue was taken up in trichloromethane and the solution dried (Na_2SO_4). Product isolation was by column chromatography.

5-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 8. Yield 180 mg (8%); mp 232 °C; δ_H(250 MHz, $CDCl_3$) 2.3 (s, 3 H, CH_3), 3.33 [d, 1 H, ^2J(HH) = 12.1, SCH], 3.8 [d, 1 H, ^2J(HH) 13.1, NCH], 3.93 [d, 1 H, ^2J(HH) 12.1, SCH], 4.55 (t, 1 H, H_l), 4.82 (t, 1 H, H_l), 5.33 [d, 1 H, ^2J(HH) 13.1, NCH], 7.0–7.6 (m, 14 H, ArH), 7.25 [d, ^3J(HH) 16, 1 H, ArCH=CHAr] and 7.4 [d, ^3J(HH) 16, 1 H, ArCH=CHAr]; δ_C(62.9 MHz, $CDCl_3$) 21.5 ($ArCH_3$), 45.7 (CH_2S), 59.1 (CH_2N), 126.1, 126.6, 127.0, 127.6, 128.0, 128.9, 129.7, 129.7, 130.7, 130.8, 130.9, 132.7, 133.0, 135.5, 135.9, 136.1, 137.1, 138.1, 138.1, 139.6, 143.7 and 145.5 (22 C_{arom}) (Found: *m/z* 483.1328. $C_{29}H_{25}NO_2S_2$ requires 483.1326); *m/z* 483 (M^+, 42.7%) and 328 ($M^+ - SO_2 - Ar - CH_3$, 100).

8-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 9. Yield: 520 mg (21%); mp 72 °C; δ_H(250 MHz, $CDCl_3$) 2.41 (s, 3 H, CH_3), 3.73 [d, 1 H, ^2J(HH) 12.2, SCH], 4.10 [d, 1 H, ^2J(HH) 12.2, SCH], 4.45 [d, 1 H, ^2J(HH) 13.3, NCH], 4.49 (t, 1 H, H_l), 4.73 [d, ^3J(HH) 16, 1 H, ArCH=CHAr], 5.14 [d, 1 H, ^2J(HH) 13.3, NCH], 5.97 [d, ^3J(HH) 16, 1 H, ArCH=CHAr] and 6.9–7.8 (m, 15 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 21.6 ($ArCH_3$), 41.3 (CH_2S), 55.4 (CH_2N), 115.3, 118.9, 119.7, 119.9, 127.0, 127.1, 127.1, 127.6, 128.3, 129.8, 129.9, 130.1, 131.2, 132.3, 132.8, 134.1, 135.1, 136.0, 138.9, 140.4, 144.1 and 144.9 (22 C_{arom}) (Found: *m/z* 483.1312. $C_{29}H_{25}NO_2S_2$ requires 483.1326); *m/z* 483 (M^+, 17%), 328 ($M^+ - SO_2 - Ar - CH_3$, 5) and 205 ($C_{14}H_{13}$, 100).

4-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 10. Yield: 98 mg (5%); mp 145 °C; δ_H(50 MHz, $CDCl_3$) 2.3 (s, 3 H, CH_3), 3.28 [d, 1 H, ^2J(HH) 12.2, SCH], 3.75 [d, 1 H, ^2J(HH) 13, NCH], 4.05 [d, 1 H, ^2J(HH) 12.2, SCH], 4.49 (t, 1 H, H_l), 4.9 (t, 1 H, H_l), 5.28 [d, 1 H, ^2J(HH) 13, NCH] and 7.0–7.8 (m, 16 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 21.4 ($ArCH_3$), 45.6 (CH_2S), 58.9 (CH_2N), 118.3, 119.5, 119.6, 120.2, 125.9, 126.6, 127.2, 128.3, 128.3, 128.8, 129.6, 130.9, 131.7, 133.3, 133.7, 134.9, 134.95, 136.3, 137.9, 138.9, 143.4 and 144.1 (22 C_{arom}) (Found: *m/z* 483.1325. $C_{29}H_{25}NO_2S_2$ requires 483.1326); *m/z* 483 (M^+, 32.7%) and 328 ($M^+ - SO_2 - Ar - CH_3$, 100).

6-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 11. Yield: 120 mg (3%); mp 132 °C; δ_H(250 MHz, $CDCl_3$) 2.3 (s, 3 H, CH_3), 3.2 [d, 1 H, ^2J(HH) 12.1, SCH], 3.85 [d, 1 H, ^2J(HH) 13.1, NCH], 3.9 [d, 1 H, ^2J(HH) 12.1, SCH], 4.6 (t, 1 H, H_l), 4.95 (t, 1 H, H_l), 5.35 [d, 1 H, ^2J(HH) 13.1, NCH], 6.8–7.7 (m, 14 H, ArH), 7.25 [d, ^3J(HH) 16, 1 H, ArCH=CHAr] and 7.4 [d, ^3J(HH) 16, 1 H, ArCH=CHAr]; δ_C(62.9 MHz, $CDCl_3$) 21.5 ($ArCH_3$), 44.9 (CH_2S), 59.3 (CH_2N), 117.2, 117.9, 118.7, 120.2, 125.9, 127.0, 127.05, 127.3, 128.1, 128.8, 130.9, 131.0, 131.1, 132.7, 132.8, 133.2, 133.8, 135.0, 139.9, 140.2, 142.6 and 143.8 (22 C_{arom}) (Found: *m/z* 483.1326. $C_{29}H_{25}NO_2S_2$ requires 483.1326); *m/z* 483 (M^+, 37%) and 328 ($M^+ - SO_2 - Ar - CH_3$, 100).

_N_-Trifluoroacetyl-1-thia-10-aza[2.2]orthometacyclophane 15
To a stirred suspension of oxygen-free acetone (2500 cm^3) and Cs_2CO_3 (3.91 g, 12 mmol) heated under reflux under an argon atmosphere were added over 10 h, by use of a perfusor with two injectors, solutions of 1,2-bis(bromomethyl)benzene (2.32 g, 5 mmol) and *N*-trifluoroacetyl-3-aminothiophenol **14** (1.1 g, 5 mmol), each in acetone (50 cm^3). After the mixture had been refluxed for 4 h it was evaporated and the residue was subjected to column chromatography to give the product (40 mg, 2.4%); mp 93–95 °C; δ_H(250 MHz, $CDCl_3$) 4.1 (s, 2 H, SCH_2), 4.3 (s, 2 H, NCH_2) and 7.1–7.4 (m, 8 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 34.2 (CH_2S), 39.9 (CH_2N), 115.2 [q, ^1J(CF) 285, CF_3], 154.7 [q, ^2J(CF) 39, CO], 117.38, 120.08, 127.15, 127.16, 128.26, 128.32, 128.7, 130.41, 133.99, 134.4, 136.43 and 139.32 (12 C_{arom}) (Found: *m/z* 323.0595. $C_{16}H_{12}NOSF_3$ requires 323.0591); *m/z* 323 (M^+, 100%), 290 ($M^+ - CF_3$, 43), 226 ($M^+ - COCF_3$, 25) and 104 ($C_8H_8^+$, 10).

_N_-Trifluoroacetyl-1-thia-10-aza[2.2]metacyclophane 2
Solutions of 1,3-bis(bromomethyl)benzene **12** (2.64 g, 10 mmol) and *N*-trifluoroacetyl-3-aminothiophenol **14** (2.21 g, 10 mmol), each dissolved in acetone (50 cm^3), were added over a period of 8 h to a boiling suspension of oxygen-free acetone (2500 cm^3) and Cs_2CO_3 (20 mmol) under an argon atmosphere. After completion of the addition, the mixture was refluxed for 4 h. It was then evaporated and the resulting residue was subjected to column chromatography to give the product (1.03 g, 32%); mp 122 °C; δ_H(250 MHz, $CDCl_3$) 3.36 [d, 1 H, ^2J(HH) 12.1, SCH], 3.48 [d, 1 H, ^2J(HH) 12.7, NCH], 3.98 [d, 1 H, ^2J(HH) 12.1, SCH], 4.6 (t, 1 H, H_l), 4.75 (t, 1 H, H_l), 6.0 [d, 1 H, ^2J(HH) 12.7, NCH] and 7.26–7.8 (m, 6 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 45.7 (SCH_2), 57.1 (NCH_2), 116.3 [q, ^1J(CF) 288.9, CF_3], 155.7 [q, ^2J(CF) 35, CO], 128.2, 128.9, 129.2, 130.6, 131.1, 133.3, 133.5, 134.5, 136.0, 136.6, 136.7 and 144.2 (12 C_{arom}) (Found: *m/z* 323.0593. $C_{16}H_{12}NSOF_3$ requires 323.0592); *m/z* 323 (M^+, 65%), 254 ($M^+ - CF_3$, 73), 226 ($M^+ - COCF_3$, 35) and 104 ($C_8H_8^+$, 100).

_N_-Trifluorothioacetyl-1-thia-10-aza[2.2]metacyclophane 3
A solution of *N*-trifluoroacetyl-1-thia-10-aza[2.2]metacyclophane **2** (161 mg, 0.5 mmol) and Lawesson's reagent[14] (111 mg, 0.28 mmol) in dry toluene (50 cm^3) was stirred and heated to 80 °C under a nitrogen atmosphere for 4 h. After completion of the reaction (TLC control), the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated. The resulting residue was subjected to column chromatography to give the product as a yellow solid (135 mg 80%); mp 104–105 °C; δ_H(250 MHz, $CDCl_3$) 3.41 [d, ^2J(HH) 12.2, 1 H, CH_2S], 3.65 [d, ^2J(HH) 12.6, 1 H, CH_2N], 4.05 [d, ^2J(HH) 12.2, 1 H, CH_2S], 4.6 (t, 1 H, H_l), 4.75 (t, 1 H, H_l), 7.04 [d, ^2J(HH) 12.6, 1 H, CH_2N] and 7.3–7.8 (m, 6 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 45.8 (CH_2S), 63.6 (CH_2N), 117.5 [q, ^1J(CF) 281, CF_3], 184.6 [q, ^2J(CF) 34, C=S], 127.5, 128.3, 129.2, 129.4, 130.4, 136.5, 136.7, 143.1, 133.0, 133.4, 137.3 and 139.6 (12 C_{arom}) (Found: *m/z* 339.0364. $C_{16}H_{12}NS_2F_3$ requires 339.0363); *m/z* 339 (M^+, 68%), 270 ($M^+ - CF_3$, 100) and 226 ($M^+ - CSCF_3$, 80).

_N_-(Trifluoromethylsulfonyl)-1-thia-10-aza[2.2]metacyclophane 4
To a boiling suspension of acetone (2000 cm^3) and Cs_2CO_3 (6.74 g, 21 mmol) were added 1,3-bis(bromomethyl)benzene **12** (2.11 g, 8 mmol) and *N*-trifluoromethylsulfonyl-3-aminothiophenol **13** (2.06 g, 8 mmol), each in acetone (50 cm^3), over a period of 6 h. The mixture was then evaporated and the residue taken up in dichloromethane and the solution dried (Na_2SO_4). Further purification was achieved by column chromatography to give the product (1.37 g, 48%); mp 166 °C; δ_H(250 MHz, $CDCl_3$) 3.33 (d, ^2J 12.2, 1 H, CH_2S), 3.96 (d, ^2J 12.2, 1 H, CH_2S), 3.94 (d, ^2J 13.2, 1 H, CH_2N), 4.62 (t, 1 H, H_l), 4.90 (t, 1 H, H_l), 5.08 (d, ^2J 13.2, 1 H, CH_2N) and 7.36–7.75 (m, 6 H, ArH); δ_C(62.89 MHz, $CDCl_3$) 45.8 (CH_2S), 61.4 (CH_2N), 120.0 [q, ^1J(CF) 322, CF_3], 128.4, 129.7, 130.1, 130.95, 131.0, 133.2, 133.6, 134.7, 136.7, 137.0, 137.7 and 145.6 (12 C_{arom}) (Found: *m/z* 359.0253. $C_{15}H_{12}NO_2S_2F_3$ requires 359.0264); *m/z* 359 (M^+, 90%) and 226 ($M^+ - SO_2 - CF_3$, 100).

1-Thia-10-aza[2.2]metacyclophane 1
To a solution of compound **2** (323 mg, 1 mmol) in methanol (100 cm^3) was added K_2CO_3 (2 g) and the mixture was refluxed for 1 h. After completion of the reaction (TLC control), the

mixture was evaporated and the residue taken up in dichloromethane. The solution was washed with water, dried (Na_2SO_4) and evaporated to afford the product; this was recrystallised from hexane (190 mg, 84%); mp 137 °C; δ_H(250 MHz, $CDCl_3$) 2.80 (br, 1 H, NH), 3.28 [d, 1 H, ^2J(HH) 11.9, SCH_2], 3.47 [d, 1 H, ^2J(HH) 11.9, NCH_2], 3.95 [d, 1 H, ^2J(HH) 11.9, SCH_2], 4.32 [d, 1 H, ^2J(HH) 12.1, NCH_2], 4.35 (t, 1 H, H_i), 4.65 (t, 1 H, H_i) and 7.1–7.5 (m, 6 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 46.1 (SCH_2), 60.8 (NCH_2), 125.4, 126.9, 127.8, 130.3, 130.6, 131.8, 132.2, 135.5, 136.2, 137.0, 141.8 and 146.8 (12 C_{arom}) (Found: *m/z* 227.0764. $C_{14}H_{13}NS$ requires 227.0769); *m/z* 226 ($M^+ - H$, 75%), 190 (23) and 105 (100).

N-Benzyl-1-thia-10-aza[2.2]metacyclophane 6

A mixture of K_2CO_3 (24 mg, 0.17 mmol) and 1-thia-10-aza[2.2]metacyclophane **1** (40 mg, 0.17 mmol) in acetonitrile (50 cm^3) was refluxed under an argon atmosphere whilst a solution of benzyl bromide (20 μl, 17 mg, 0.17 mmol) in acetonitrile (10 cm^3) was added. After the mixture had been heated for 2 h, it was evaporated and the resulting residue was dissolved in hexane. The solution was dried (Na_2SO_4), filtered and evaporated to give the product; this was recrystallised from methanol (54 mg, 90%); mp 134 °C; δ_H(250 MHz, $CDCl_3$) 3.38 [d, 1 H, ^2J(HH) 11.95, SCH_2], 3.38 [d, 1 H, ^2J(HH) 11.98, NCH_2], 3.93 [d, 1 H, ^2J(HH) 13.85, NCH_2Ph], 3.97 [d, 1 H, ^2J(HH) 11.95, SCH_2], 4.14 [d, 1 H, ^2J(HH) 11.98, NCH_2], 4.17 [d, 1 H, ^2J(HH) 13.85, NCH_2Ph], 4.44 (t, 1 H, H_i), 4.93 (t, 1 H, H_i) and 7.1–7.5 (m, 11 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 46.3 (SCH_2), 55.9 (NCH_2), 64.5 (NCH_2Ph), 125.0, 127.1, 127.5, 128.3, 128.4, 128.8, 129.0, 130.2, 132.3, 132.4, 134.3, 136.2, 136.8, 139.0, 140.9 and 149.8 (16 C_{arom}) (Found: *m/z* 317.1236. $C_{21}H_{19}NS$ requires 317.1238); *m/z* 317 (M^+, 100%), 224 (50), 105 (48) and 91 (55).

N-Nitroso-1-thia-10-aza[2.2]metacyclophane 5

Ethyl nitrite (15% solution in ethanol; 5 ml) was added *via* a syringe to a stirred solution of the phane **1** (40 mg, 0.17 mmol) in dry THF (50 cm^3) under an argon atmosphere at 0 °C. The mixture was then allowed to warm to room temp. when it was stirred overnight. When the reaction was complete (monitored by TLC), the mixture was evaporated and the residual yellow oil was purified by chromatography (40 mg, 92%); mp >45 °C (decomp.); δ_H(250 MHz, $CDCl_3$) 3.33 [d, 1 H, ^2J(HH) 12.1, SCH_2-*anti*], 3.35 [d, 1 H, ^2J(HH) 12.0, SCH_2-*syn*], 3.35 [d, 1 H, ^2J(HH) 13.1, NCH_2-*syn*], 3.96 [d, 1 H, ^2J(HH) 12.1, SCH_2-*anti*], 4.0 [d, 1 H, ^2J(HH) 12.0, SCH_2-*syn*], 4.53 [d, 1 H, ^2J(HH) 13.0, NCH_2-*anti*], 4.51 (t, 1 H, H_i-*anti*), 4.8 (t, 1 H, H_i-*syn*), 4.48 (t, 1 H, H_i-*anti*), 4.91 (t, 1 H, H_i-*syn*), 6.15 [d, 1 H, ^2J(HH) 13.0, NCH_2-*anti*], 6.48 [d, 1 H, ^2J(HH) 13.0, NCH_2-*syn*] and 7.1–7.8 (m, ArH); *syn*:*anti* ratio 60:40 (by ^1H NMR). The exact assignment of *syn*/*anti* was secured from a 250 MHz-^1H,^1H-COSY-NMR spectrum; δ_C(62.9 MHz, $CDCl_3$) 45.7/46.7 (2 SCH_2) and 52.4/61.8 (2 NCH_2); *m/z* 257 (M^+ + H, 5%).

Enantiomer separations[23,24]

5-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 8. Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane–propan-2-ol 99:1; flow 0.8 ml min^{-1}; eluate 1.5 ml, $c < 0.1$ mg ml^{-1}; t_R (retention time) 33.2 (P-**8**) and 34.9 min (M-**8**).

8-Styryl-*N*-tosyl-1-thia-10-aza[2.2]metacyclophane 9. Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane–propan-2-ol (90:10); flow 0.6 ml min^{-1}; eluate 1 ml, c 1 mg ml^{-1}; t_R 29.8 (P-**9**) and 38.9 min (M-**9**).

***N*-Trifluoromethylsulfonyl-1-thia-10-aza[2.2]metacyclophane 4.** Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane–propan-2-ol (99.5:0.5); flow 0.7 ml min^{-1}; eluate 0.5 ml, c 0.2 mg ml^{-1}; t_R 29.8 (P-**4**) and 36.9 min (M-**4**).

***N*-Trifluoroacetyl-1-thia-10-aza[2.2]metacyclophane 2.** Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane; flow 0.4 ml min^{-1}; eluate 0.25 ml, c 1 mg ml^{-1}; t_R 85 (P-**2**) and 97 min (M-**2**).

***N*-Trifluoroacetyl-1-thia-10-aza[2.2]metacyclophane 3.** Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane–propan-2-ol (99.5:0.5); flow 0.7 ml min^{-1}; eluate 1 ml, c 0.2 mg ml^{-1}; t_R 29.8 (P-**3**) and 36.9 min (M-**3**).

1-Thia-10-aza[2.2]metacyclophane 1. Stationary phase poly[2-pyridyl(diphenyl)methylmethacrylate] (Chiralpak OP(+)®, Fa. Daicel), dimensions 20 cm × 5 mm; eluent hexane–propan-2-ol (95:5); flow 0.4 ml min^{-1}; eluate 0.5 ml, c 1 mg ml^{-1}; t_R 23.4 (M-**1**) and 26.1 min (P-**1**).

***N*-Benzyl-1-thia-10-aza[2.2]metacyclophane 6.** Stationary phase cellulose–tris[(3,5-dimethylphenyl)carbamate] (Chiracel OD®, Fa. Daicel), dimensions 50 cm × 4 mm; eluent hexane–propan-2-ol (99.5:0.5); flow 0.35 ml min^{-1}; eluate 10 μl, c 0.5 mg ml^{-1}; t_R 32.4 (P-**6**) and 33.9 min (M-**6**).

Crystallographic data for 3 and 4

Crystal data 3.[25] $C_{16}H_{12}F_3NS_2$, $M_r = 339.37$, monoclinic, space group $P2_1/n$ (no. 14), $a = 5.402(1)$, $b = 16.791(3)$, $c = 17.115(2)$ Å, $\beta = 99.36(2)°$, $V = 1531.7(7)$ Å^3, $Z = 4$, $D_c = 1.472$ g cm^{-3}, $F(000) = 696$, $T = 296 \pm 1$ K.

Data collection and reduction. Data collected for a colourless crystal 0.20 × 0.25 × 0.30 mm were recorded with a SYNTEX $P2_1$ diffractometer using graphite monochromatised Cu-Kα radiation [λ(Cu-Kα) = 1.5418 Å] and ω scan mode to $2\theta = 113°$ ($h = -5 \rightarrow 5$, $k = 0 \rightarrow 18$, $l = 0 \rightarrow 18$). Of the total 2417 collected reflections 1948 were unique ($R_{int} = 0.030$), 1241 with $I > 3\sigma I$ were used for refinement. No absorption correction [μ(Cu-Kα) = 33.6 mm^{-1}] was applied, but instead an extinction correction was done [extinction correction factor 38.6(46)].

Structure solution and refinement. The structure was solved by direct methods[25a] and subjected to full-matrix refinement.[25b] All non-hydrogen atoms were refined anisotropically and the H-atom isotropically. The F_o/parameter ratio = 5.02 and the final R value was 0.043 and $R_w = 0.048$ for 247 parameters: {$w = w'$ $[1.0 - (\Delta F/6 - \sigma F)^2]^2$, where w' = Chebychev polynomial for F_c with three coefficients (0.572, 0.288, 0.153). $S = 1.16$, convergence, max. shift/error < 0.01. A final difference map displayed no electron density higher than 0.31 e Å^{-3}.

Crystal data 4.[26] $C_{15}H_{12}F_3NO_2S_2$, $M_r = 359.4$, monoclinic space group $P2_1/n$ (No. 14), colourless crystals, $a = 5.300(1)$, $b = 16.026(1)$, $c = 17.901(1)$ Å, $\beta = 95.55(1)°$, $V = 1513.2(3)$ Å^3, $D_c = 1.58$ g cm^{-3}, $Z = 4$, μ(Cu-Kα) = 3.54 mm^{-1}, $T = 293$ K, 2223 symmetry independent reflections, of which 2033 with $F > 4\sigma(F)$ were used for the structure solution (direct methods) and refinement (full-matrix least-squares on F, 210 parameters), non-hydrogen atoms were refined anisotropically, H-atoms localised by difference electron density and refined using a 'riding model'. $R_w = 0.043$, $w^{-1} = \sigma^2(F) + 0.0002\ F^2$. Extinction and semi-empirical absorption correction (ψ-scans) were applied. Full crystallographic results for compounds **3** and **4** have been deposited at the Cambridge Crystallographic Data Centre.† Any request for this material should be accompanied by a full bibliographic reference together with the following reference no: CCDC 207/65.

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† For details of this scheme, see Instructions for Authors (1996), *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.

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