Synthesis and Stereochemistry of Metacyclophanes with Intraannular Substituents[1]

G. J. Kang and T. H. Chan*

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

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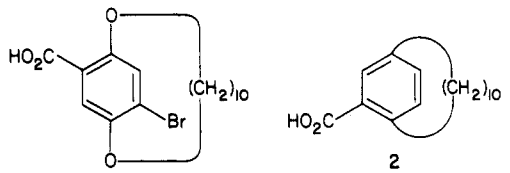
Two metacyclophanes with a morpholino substituent inside the cavity of the hydrocarbon ring are synthesized. These metacyclophanes possess planar chirality and are successfully resolved. A number of metacyclophanes with alkyl substituents at the intraannular position are synthesized. Depending on the ring size and the steric size of the alkyl group, some of them are also resolved. The rotation process of some of these metacyclophanes is studied through their temperature dependent ^1H NMR spectra.

The stereochemistry of paracyclophanes has been well investigated since the first successful resolution of compound **1** by Luttringhaus and his co-workers in 1941.[2] The carbocyclic analogue **2** as well as the [2,2]paracyclophane **3** were subsequently resolved.[3,4] In 1968, Gerlach and Huber prepared a series of parapyridinophanes **4** and found that the compound with $m = 9$ was resolvable.[5]



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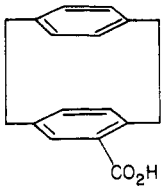

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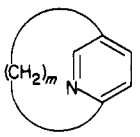

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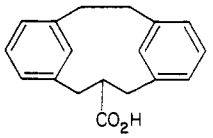
The enantiomerism of metacyclophanes was recognized as early as that of paracyclophanes by Luttringhaus. However no special effort was made to resolve the enantiomers of metacyclophanes. This was perhaps due to the fact that there was not a suitable compound available then.



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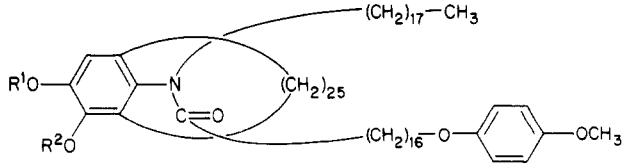
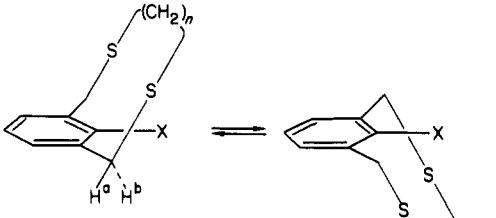


6, $R^1 = R^2 = H$
7, $R^1 = R^2 =$ —CH(C_2H_5)—

The existance of this type of enantiomerism was demonstrated by Griffin and Coburn in 1963 through the study of temperature dependent NMR spectroscopy on compound **5**,[6] but the resolution of this compound was not successful. This challenge was taken up again by Schill and his co-workers in 1966. In the attempt to synthesize catenanes, they obtained compound **6** which met the conditions for chirality. Compound **6** was chromatographed on cellulose-2,5-acetate but no optical activity was observed in the compound after chromatography. After this failure, the diastereomer **7** was prepared and again subjected to chromatography on cellulose-2,5-acetate. No optical activity of the chromatographed material was detected.[7]

In order to study the effect of different substituents, a number of metacyclophanes of type **8** were synthesized by Forster and Vögtle.[8] When the rotation process is restricted, H^a and H^b appear as AB quartet in the ^1H NMR spectra. In other words, the benzylic methylene protons are diastereotopic in **8**. The possibility of enantiomerism of metacyclophanes is thus demonstrated, even though **8** itself is not chiral.



8A **8B**

Successful resolution of several [2,2]metacyclophanes have been reported.[9]

Synthesis and Optical Resoltuion of Chiral Metacyclophanes Bearing a Morpholino Group on the Aromatic Ring. Most of the syntheses of cyclophanes start from an aromatic precursor and are followed by the construction of the macrocyclic ring.[10] A viable alternative

(1) Preliminary accounts of this work: Chan, T. H.; Kang, G. J. *Tetrahedron Lett.* **1983**, *24*, 3187.
(2) Luttringhaus, A.; Gralheer, H. *Liebigs Ann. Chem.* **1941**, *550*, 67. Luttringhaus, A.; Gralheer, H. *Liebigs Ann. Chem.* **1947**, *557*, 112. Lauttringhaus, A.; Eyring, G. *Liebigs Ann. Chem.* **1957**, PS604PS, 111. Luttringhaus, A.; Eyring, G. *Angew. Chem.* **1957**, *69*, 137.
(3) Blomquist, A. T.; Smith, B. H. *J. Am. Chem. Soc.* **1960**, *82*, 2073.
(4) Gram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1955**, *77*, 6289.
(5) Gerlach, H.; Huber, E. *Helv. Chim. Acta.* **1968**, *51*, 2027.
(6) Griffin, R. W., Jr.; Coburn, C. A. "Abstracts of Papers, 145th Meeting of the American Chemical Society, New York, 1963; American Chemical Society: Washington, DC, 1963; 20-Q.
(7) Schill, G. *Chem. Ber.*, **1966**, *99*, 2689. Also see: Schill, G. "Catenannes, Rotaxanes and Knots"; Academic Press: New York 1971; p 60.
(8) Vögtle, F.; Grutze, J.; Natscher, R.; Wieder, W.; Weber, E.; Grun, R. *Chem. Ber.* **1975** *108*, 1694. Forster, H.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429.
(9) (a) Anet, F. A. L.; Miura, S.; Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1419. (b) Wittek, M.; Vögtle, F.; Stühler, G.; Mannschreck, A.; Lang, B. M.; Irngartinger, H. *Chem. Ber.* **1983**, *116*, 207. (c) Vögtle, F.; Meurer, K.; Mannschreck, A.; Stühler, G.; Puff, H.; Roloff, A.; Sievers, R. *Chem. Ber.* **1983**, *116*, 2630. (d) Glotzmann, C.; Langer, E.; Lehner, H.; Schlogl, K. *Monatsh. Chem.* **1974**, *105*, 907.

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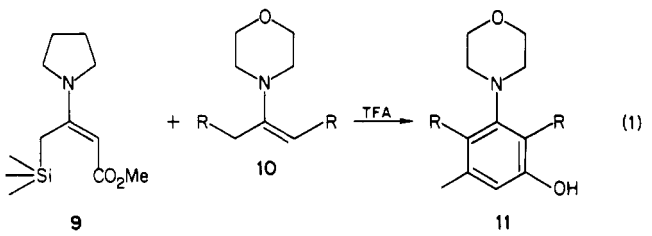
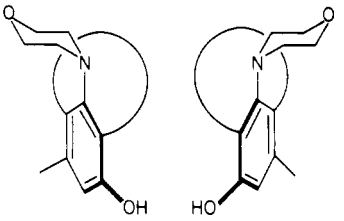
is to start with a macrocyclic precursor and then graft onto it an aromatic structure. Our recent studies on cycloaromatization reactions for the synthesis of phenolic and anilino compounds[11] led us to examine the possibility of preparing metacyclophanes by a cycloaromatization process.

We have recently reported that methyl 4-(trimethylsily)-3-pyrrolidinocrotonate (**9**) condenses with enamines of acyclic compounds **11** by a 3C + 3C combination (eq 1).[11] It seems to us that if the ketone enamine **10** is derived from a macrocyclic ring of sufficient size (say, larger than 9), the reaction represents an entry into the metacyclophane system.



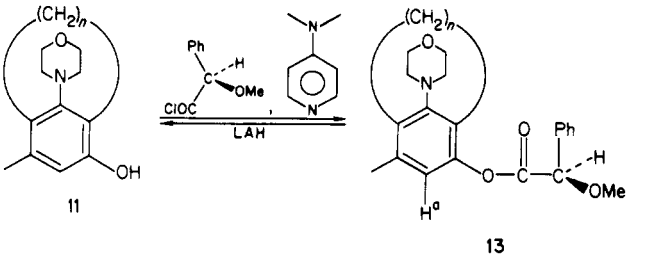
To test this, the morpholine enamine of cyclododecanone [**10a**, R, R = $(CH_2)_9$] was synthesized and then reacted with **9** in the presence of trifluoroacetic acid (TFA). The product **11a**, derived indeed by the 3C + 3C cyclization, was isolated in 51% yield. The reaction between **9** and **10b** [R, R = $(CH_2)_{12}$], the morpholine enamine of cyclopentadecanone, gave **11b** in 25% yield.

Examination of the molecular models of **11** shows that the hydrocarbon chain and the morpholine group are located in different faces of the aromatic plane because the cavity of the hydrocarbon ring is not large enough to accommodate the morpholino group. Since the aromatic ring is further substituted by two different groups (OH and CH_3), compounds **11a,b** are chiral. Such chiral metacyclophanes belong to a group in which the optical isomerism is caused by restricted rotation. A very important feature of this type of enantiomerism is the energy factor. The energy barrier of the rotation must be high enough to permit resolution of the enantiomers.



Compound **11a** possesses a hydroxy group and should be readily converted into diastereomeric compounds. Compound **11a** was allowed to react with (*R*)-(−)-α-methoxyphenylacetyl chloride (**12**) which was generated in situ from the corresponding acid with thionyl chloride. When pyridine was used as the base, no reaction took place. When (dimethylamio)pyridine (DMAP) was employed, the expected ester **13a** was obtained in 81% yield.

Compound **13a** existed as two diastereomers (α + β) which were clearly distinguishable in the ^1H NMR spectrum. The ratio of α-**13a** to β-**13a** was about 1:2 by ^1H NMR. The mixture of α-**13a** and β-**13a** was a colorless oil, and attempts at crystallization failed. They were finally separated by careful TLC mesh chromatography.[12] 200-MHz ^1H NMR showed that either α-**13a** or β-**13a** were more than 90% pure.



a, n=9, b, n=12

Reduction of α-**13a** with lithium aluminum hydride gave (−)-**11a** with $[\alpha]^{20}_D$ −30° (acetone). The ^1H NMR and IR spectra of (−)-**11a** were identical with those of the racemic compound. Similar reduction of β-**13a** with $LiAlH_4$ gave (+)-**11a**, $[\alpha]^{20}_D$ +26.4° (acetone).

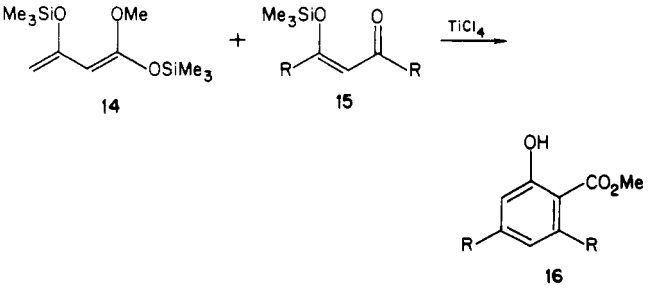
Successful resolution has also been achieved with compound **11b**. The yield of the esterification reaction was 87%. The ratio of the two isomers was also 1:2. Similar chromatography of **13b** (α + β) led to the separation of the two diastereomers. Either isomer was more than 95% pure as judged by ^1H NMR spectra (200 MHz).

Compounds α-**13b** and β-**13b** were each reduced with $LiAlH_4$. It was found that the α-diastereomer gave (−)-**11b**, $[\alpha]^{20}_D$ −17° (THF), and the β-diastereomer gave (+)-**11b**, $[\alpha]^{20}_D$ +11° (THF). Again, their ^1H NMR and IR spectra were identical with those of the racemic compound **11b**.

The successful resolution of compounds **11a,b** suggests that these metacyclophanes are indeed chiral. Furthermore, the energy barrier for the rotation of the hydrocarbon ring from one face of the benzene ring to the other face is sufficiently high that racemization does not take place at room temperature. In order to examine the dynamics of the restricted rotation process, one can either increase the hydrocarbon ring size, thus increase the size of the cavity, or diminish the size of the group inside the cavity. Since cycloketones of ring size larger than 15 members are not readily available, we have chosen the latter alternative.

Synthesis and Optical Resolution of Chiral Metacyclophanes Having the *o*-Salicylate Structure. The cycloaromatization reaction of enamines described above only allows us to synthesize those metacyclophanes with an amino group inside the hydrocarbon chain. Since even the smallest dialkylamino group will have a considerable steric size, we seek metacyclophanes with other structural features.

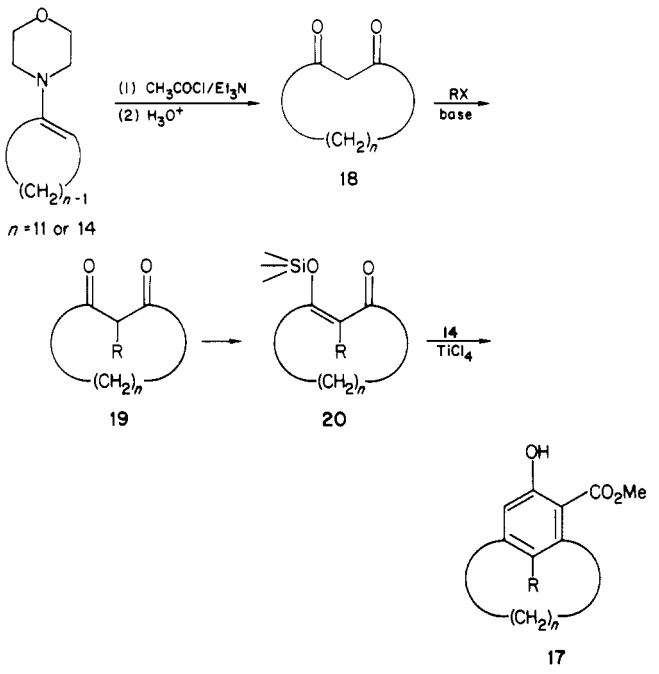
We have previously reported that the condensation of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene **14** with



4-(trimethylsiloxy)pent-3-en-2-one (**15**, R = R = CH_3) gives the aromatic compound **16** in good yield.[11] If we could synthesize the macrocyclic analogues of **15**, we would have in hand a way to synthesize metacyclophanes of *o*-salicylate

(10) For review, see: Keehn, P. M., Rosenfeld, S. M. Eds. "Cyclophanes"; Academic Press: New York, 1983.
(11) Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102* 3534. Chan, T. H.; Kang, G. J. *Tetrahedron Lett.* **1983**, *24*, 3051.
(12) Taler, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

Scheme I



a, n = 11, R = CH_2Ph; b, n = 11, R = CH_3; c, n = 11, R = H; d, n = 14, R = CH_3

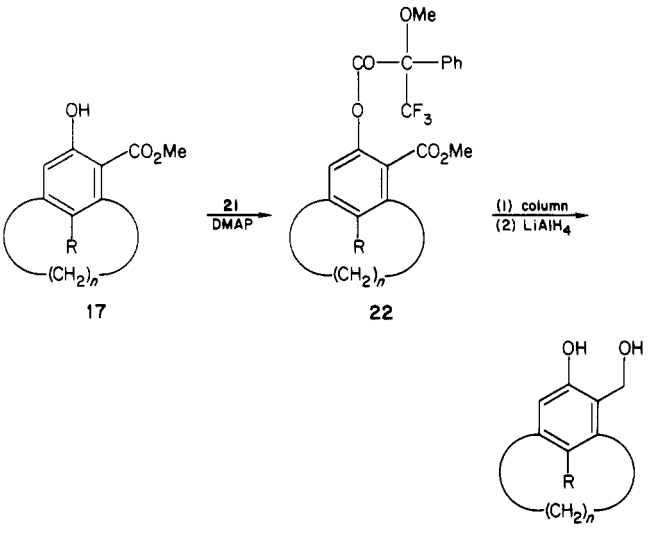
structures (**16**). This approach will also allow us to introduce substituent at the intraannular position of the metacyclophanes by starting from the appropriate precursor (Scheme I).

Compound **18** (n = 11) was prepared from the morpholino enamine of cyclododecanone following the method of Kirrmann and Wakselman.[13] The benzylation reaction of **18** was performed by Hermann's method[14] with 5% potassium hydroxide and benzyl bromide. Compound **18** was quantitatively converted to **19a** (n = 11, R = CH_2Ph). When the methylation reaction of **23** was first carried out by the same method used for its benzylation, the ^1H NMR spectrum showed that the product was a mixture of almost equal amount of C-alkylation and O-alkylation compounds. In 1977, Clark and Miller reported that with tetra-n-butylammonium fluoride,[15] the product of alkylation of acetylacetone was exclusively due to C-alkylation. Following their method, 2-methylcyclotetradecane-1,3-dione (**19b**, n = 11, R = CH_3) was obtained in 87% yield from **18**. When a slight modification was used, **19c** (n = 14, R = CH_3) was prepared from the morpholine enamine of cyclopentadecanone by the reaction of propanoyl chloride/triethylamine.

The silylation of **18** to the corresponding β-siloxy-α,β-unsaturated ketone **20** was performed by $Et_3N/ZnCl_2/Me_3SiCl$ with quantitative yield.[16] Compounds **20** were used to react with **14** under $TiCl_4$ conditions to give **16** in about 60% yields. When (R)-(−)-2-(methoxyphenyl)acetyl chloride was used in the resolution of **11(a,b)**, it was found that the ratio of the two diastereomeric esters was 2:1 for both **13(a,b)**. The hydrogen at the α-position in either the acid chloride or the product ester is quite acidic. Since (dimethylamino)pyridine is a reasonably strong base, we cannot exclude the possibility that epimerization by proton abstraction may have occurred. In the case of **13b**, after separation by column chromatography, both the α- and β-diastereomers were greater than 95% pure by 200-MHz ^1H NMR spectra. Yet, the specific rotations of the two reduced enantiomers of **11b** were found to be quite different: −17° for one and +11° for the other. We therefore looked for another resolving agent where such epimerization is not possible.

Optically pure α-(trifluoromethyl)-α-(methoxyphenyl)-acetyl chloride (**21**) has often been used to resolve racemic alcohols and amines or to determine their optical purities.[17] With **21**, epimerization is unlikely, at least under these reaction conditions. Another advantage of **21** is that it can be kept in a refrigerator for several months without apparent decomposition whereas **12** is unstable and must be prepared immediately prior to its use.

The esterification of **17a** with (S)-**21** was performed in the same manner with (dimethylamino)pyridine. A 1:1 mixture of diasteromeric esters α-**22a** and β-**22a** was obtained in essentially quantitative yield. The mixture of α-**22a** and β-**22a** was separated by chromatography on silica gel. They were more than 90% pure by ^1H NMR spectra. Both α-**22a** and β-**22a** were reduced by lithium aluminum hydride in ether. Compound (+)-**23a** was obtained from the α-diastereomer and had $[\alpha]^{20}_D$ +12.6° (acetone). Isomer (−)-**23a** was obtained from the β-diastereomer and had $[\alpha]^{20}_D$ −14.4° (acetone).



a, n = 11, R = CH_2Ph; b, n = 11, R = CH_3; c, n = 11, R = H; d, n = 14, R = CH_3

When either (+)-**23a** or (−)-**23a** were refluxed in hexane, no change in their specific rotations was observed.

Similarly, when **17b** was treated with (S)-α-(trifluoromethyl)-α-methoxyphenylacetyl chloride and DMAP, **22b** was obtained. Again, the ^1H NMR spectrum of this ester showed two clearly distinguishable diastereomers. The diastereomeric mixture of **22b** was separated with similar column chromatography. Both isomers were more than 95% pure by ^1H NMR spectra. After standing in deuterated chloroform for 3 days at room temperature, their ^1H NMR were checked again and no change was observed at all. This means that there is no epimerization at room temperature.

The reduction of these two diastereomers gave (+)-**23b** and (−)-**23b**, respectively. Specific rotation for (+)-**23b** was $[\alpha]^{20}_D$ +6.3° (acetone) and for (−)-**23b**, $[\alpha]^{20}_D$ −8.0° (acetone). After (+)-**23c** was refluxed in hexane for about 5 min, its optical activity totally disappeared.

(13) Kirrmann, A.; Wakselman, C. *Bull. Soc. Chim. Fr.* **1967**, 3766.
(14) Stetter, H. *Angew. Chem.* **1955**, *67*, 769.
(15) Clark, J. H.; Miller, J. M. *J. Chem. Soc. Perkin Trans. 1* **1977**, *15*, 1743.
(16) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7808.
(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

On the other hand, when **17c** or **17d** was converted to the corresponding α-(trifluoromethyl)-α-methoxyphenyl acetate esters **22c** or **22d**, the ^1H NMR spectra of **22c** and **22d** showed only one set of signals for each case at room temperature. In other words, the two diastereomers either did not exist, or if they existed, they interconverted by rotation of the side chain at a rate faster than the NMR time scale. Optical resolution of compounds **17c** and **17d** were therefore not feasible. The effect of ring size and substituent on the stereochemistry of these metacyclophanes can thus be summarized as follows. For metacyclophanes with nine carbons on the cyclophane ring (n = 9), the compounds are resolvable when the intraannular substituent is either a benzyl or a methyl group but not when it is a hydrogen. The larger benzyl group confers greater optical stability to the system than the smaller methyl group. For compounds **22b** and **22d**, both having the same methyl substituent, only **22b** with the smaller hydrocarbon ring can be resolved into their optical antipodes at room temperature. These results establish quite clearly that the restricted rotation of the hydrocarbon ring to flip from one face of the benzene ring to the other face is the cause of chirality.

Dynamic NMR Studies. The rotation process of the hydrocarbon ring in these metacyclophanes can be studied by variable temperature NMR. Thus the temperature dependent ^1H NMR of **22c** was examined in CD_2Cl_2. Even at −70 °C the aromatic protons remained as distinct singlets. The chemical shift of the methyl ester group was shifted considerably and also broadened but nevertheless it remained a singlet.

The variable temperature ^1H NMR of **22d** was performed in a range of temperature from 20 to −90 °C by about 10 °C intervals in CD_2Cl_2 (see paragraph at the end of paper about supplementary material). At 20 °C, the aromatic proton H^a appeared as a singlet. At −70 °C and lower temperatures, it appeared as two signals. The coalescing temperature was determined to be at −49.6 °C. $\Delta\nu_{AB}$ was found to be 13.8 Hz for H^a at −85 °C. The activation energy of the rotation process for **22d** has thus been calculated to be 11.4 kcal/mol (47.9 kJ/mol).[18]

The temperature dependent ^1H NMR of **22b** was performed in a range of temperature from 20 to 200 °C in deuterated nitrobenzene ($C_6D_5NO_2$) (see paragraph at the end of paper about supplementary material). The aromatic proton coalesced at 132.7 °C, whereas the methyl ester still remained as two separate signals though with considerable broadening. A rotation barrier of $\Delta_G^{\ddagger}$ = 21.4 kcal/mol (89.9 kJ/mol) has been calculated for **22b**.

The results of these dynamic NMR studies are consistent with the optical resolution studies. For metacyclophanes with the same number of carbons on the hydrocarbon ring (n = 9), the larger benzyl group imposed a high energy barrier to the rotation of the ring so that no coalescence was observed at temperature up to 200 °C. On the other hand, when the substituent was hydrogen, there was no resolution of the NMR peaks at temperatures down to −70 °C. This suggests that either the ground state of the molecule has the hydrocarbon ring coplanar with the benzene moiety or that the barrier to rotation is sufficiently low. At the present time, it is not possible to make a distinction between the two possibilities, even though, recently, an X-ray crystallographic study of a metacyclophane in the solid state shows that the hydrocarbon ring is not coplanar with the benzene ring.[19] Finally, when the intraannular substituent is methyl, the energy barrier to the rotational process is dependent on the ring size. With the larger ring (n = 11), $\Delta G^{\ddagger}$ = 47.9 kJ/mol, and with the smaller ring (n = 9), $\Delta G^{\ddagger}$ = 89.9 kJ/mol can be deduced.

Concluding Remarks. This work clearly demonstrates that optical resolution of chiral metacyclophanes can be achieved. As for the determination of the absolute and the relative configurations of these compounds, X-ray diffraction and ORD–CD studies will be necessary. We are currently undertaking an investigation in this area.

Experimental Section

Unless otherwise stated, common reagents were commercial products and were reagent grade. Melting and boiling points are reported uncorrected. NMR spectra were taken on Varian T-60A or XL-200 NMR spectrometers. All ^1H and ^{13}C spectra are reported in chemical shift (δ) with tetramethylsilane as the reference. Infrared spectra were taken on a Perkin-Elmer Model 257 infrared spectrophotometer and were calibrated with the 1602 cm^{-1} band of polystyrene film. Mass spectra were obtained on a Dupont 21-492B mass spectrometer. Column chromatographs were done with silica gel unless otherwise specified. Chemical analyses were performed by Guelph Chemical Laboratories Ltd.

Separation of Diastereomers. All of the diastereomers were separated by a similar procedure of TLC mesh chromatography.[12] The ΔR_f values for the morpholine derivatives (**13a**, **13b**) was about 0.02 and for the alkyl derivatives (**22b**, **22c**) was 0 on analytical TLC. After separation, all the diastereomers were more than 90% diastereomerically pure as judged by 200-MHz ^1H NMR spectra. The recoveries were between 60–80%. A 20-mm column (internal diameter) was usually used for the separation of 100 mg of mixtures. The height of silica gel was between 7.5 and 9 in. If it was below 7 in., the separation was not efficient, whereas if it was above 9 in., the silica bed underwent distortion during elution.

Preparation of Enamines. The following enamines were prepared by the water-separator method.[20] Methyl 3-pyrrolidinocrotonate: yield, 88%; bp 116–118 °C (2.5 mm); methyl 3-morpholinocrotonate: yield, 79%; bp 131–132 °C (4 mm). The following enamines were made by the procedure of White and Weingarten.[21] 1-Morpholinocyclododecene: yield, 90%; bp 132–135 °C (0.1 mm) (lit.[13] 128–130 °C (0.05 mm)); 1-morpholinocyclopentadecene: yield, 91%; bp 158–161 °C (0.1 mm) (lit.[13] 163–164 °C (0.2 mm)).

Methyl 4-(Trimethylsilyl)-3-pyrrolidinocrotonate (9). Under N_2 at 0 °C, to a solution of dry diisopropylamine (3.4 mL, 24 mmol) in THF (50 mL) was added n-BuLi (16 mL of 1.5 M in hexane, 24 mmol), followed by TMEDA (3.2 mL). The solution was cooled to −78 °C and methyl 3-pyrrolidinocrotonate (3.38 g, 20 mmol) was added. The reaction mixture was stirred for 0.5 h and then quenched with trimethylchlorosilane (4 mL). The reaction mixture was allowed to warm to 0 °C and concentrated on the rotary evaporator. The residue was triturated with dry hexane (100 mL) and filtered. The filtrate was concentrated (finally under high vacuum) to give **9** as a yellowish oil: yield, 4.43 g (92%), >95% pure by ^1H NMR; bp 132–135 °C (1 mm); ^1H NMR ($CDCl_3$) 0.1 (s, 9 H), 1.80–2.03 (m, 4 H), 2.73 (s, 2 H), 3.20–3.43 (m, 4 H), 3.60 (s, 3 H), 4.47 (s, 1 H); ^{13}C NMR ($CDCl_3$) −1.7, 21.6, 25.0, 48.0, 49.5, 81.0, 163.0, 169.3; IR (film, cm^{-1}) 1665, 1550, 1150; MS, m/z (relative intensity) 241 (M+, 26), 226 (39), 210 (33), 168 (77), 138 (84), 110 (100).

11-Hydroxy-13-methyl-15-morpholino[9]metacyclophane (11a) (Method A). To a mixture of 2.57 g of 1-morpholinocyclododecene (10 mmol) and 1.20 g of **9** (5 mmol) was added 1.14 g of TFA (10 mmol) dropwise at 0 °C with stirring. The mixture was warmed to room temperature and stirred for 10 min and then heated to 80 °C. It was stirred for 1 day at 80 °C. To the cooled reaction mixture was added 300 mL of ether. The ether solution was washed with aqueous acid (1.5 N HCl) and water, dried

(18) Line shape analysis was not used. For a discussion on the relative merits of the various methods of kinetic evaluation of NMR spectra, see Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219.

(19) Effenberger, F.; Schonwalder, K-H.; Stezowski, J. J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 871.

(20) Hunig, S.; Benzing, E.; Lucke, E. *Chem. Ber.* **1957**, *90*, 2833.

(21) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

($MgSO_4$), and filtered. The filtrate was concentrated to give 2.45 g of brown oil, which was purified by flash chromatography (eluted with petroleum ether and ethyl acetate, 9:1) to give **11a**: mp 174–177 °C; 51% yield; ^1H NMR ($CDCl_3$) 0.24–0.44 (m, 2 H), 0.70–1.20 (m, 8 H) 1.48–1.74 (m, 4 H), 2.20 (s, 3 H), 2.56–3.16 (m, 4 H), 3.18–3.30 (m, 4 H), 3.72–3.87 (m, 4 H), 4.68 (s, 1 H), 6.44 (s, 1 H); IR (KBr, cm^{-1}) 3290, 1590, 1440, 1100, 850; MS, *m/z* (relative intensity) 317 (M^+, 91), 260 (36), 249 (100), 204 (62), 176 (90), 149 (77). Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.71; H, 9.78. Found: C, 75.76; H, 9.78.

14-Hydroxy-16-methyl-18-morpholino[12]metacyclophane (11b). The reaction was performed according to the procedure above but with 1-morpholinocyclopentadecene as the starting material. The [12]metacyclophane **11b** was obtained in 25% yield: mp 210–214 °C; ^1H NMR ($CDCl_3$) 0.76–1.34 (m, 16 H), 1.50–1.84 (m, 4 H), 2.20 (s, 3 H), 2.42–3.54 (m, 8 H), 3.70–3.84 (m, 4 H), 4.48 (s, 1 H), 6.46 (s, 1 H); IR (KBr, cm^{-1}) 3300, 1595, 1150; MS, *m/z* (relative intensity) 359 (M^+, 100), 316 (22), 302 (46), 149 (44).

The Preparation and Separation of Diastereomers 13a (Method B). (*R*)-(−)-α-Methoxyphenylacetic acid (116 mg, 1 mmol) was dissolved in a 10-fold excess of thionyl chloride. The solution was refluxed for about 10 min in an oil bath and then cooled to room temperature. Thionyl chloride was removed from the mixture by water aspirator and then under high vacuum for 30 min. The crude acid chloride was diluted with 10 mL of dry THF. To the mixture was added a solution of 158 mg of **11a** in 10 mL of THF, followed by 122 mg of (dimethylamino)pyridine under vigorous stirring and N_2. The reaction mixture was stirred for 30 min at room temperature and overnight at 50 °C. To the cooled reaction mixture was added 100 mL of ether. This solution was washed with 5% HCl, saturated sodium carbonate solution, and then water. The ether solution was dried with $MgSO_4$ and filtered and the filtrate was concentrated by rotary evaporator to give 204 mg of yellow oil. Purification by flash chromatography, eluted with petroleum ether and ethyl acetate, gave 188 mg of colorless oil. A ^1H NMR spectrum of this oil showed a 1:2 mixture of α-**13a** and β-**13a**. This mixture was separated by TLC mesh chromatography (eluted with pentane, ethyl acetate, and acetonitrile, 20:1:1): ^1H NMR ($CDCl_3$) α-**13a** 0.1–1.9 (m, 14 H), 2.15 (s, 3 H), 2.40–3.00 (m, 4 H), 3.00–3.10 (m, 4 H), 3.51 (s, 3 H), 3.64–3.74 (m, 4 H), 4.96 (s, 1 H), 6.54 (s, 1 H), 7.32–7.54 (m, 5 H); β-**13a** 0.1–1.9 (m, 14 H), 2.15 (s, 3 H), 2.50–3.10 (m, 4 H), 3.10–3.20 (m, 4 H), 3.48 (s, 3 H), 3.64–3.74 (m, 4 H), 4.96 (s, 1 H), 6.62 (s, 1 H), 7.32–7.54 (m, 5 H).

(−)-11-Hydroxy-13-methyl-15-morpholino[9]metacyclophane (11a) (Method C). To 5 mL of dry THF was added 20 mg of lithium aluminum hydride followed by the addition of 40 mg of α-**13a** in 5 mL of THF dropwise with stirring. The reaction mixture was stirred overnight at 50 °C. The cooled reaction mixture was diluted with 50 mL of ether, acidified with 1.5 N HCl, washed with water, and dried with $MgSO_4$. After filtration, the filtrate was concentrated by rotary evaporator to give 72 mg of crude product. Purification of this crude product by flash chromatography (eluted with petroleum ether and ethyl acetate, 7:1) gave 29 mg of (−)-**11a** (67% yield). Its NMR and IR spectra were identical with those of racemic **11a**. It had $[\alpha]^{20}_D$ −30.0° (*c* 0.010 g/mL, acetone).

(+)-11-Hydroxy-13-methyl-15-morpholino[9]metacyclophane (11a). A quantity of 70 mg of β-**13a** was reduced by method C to give 33 mg of (+)-**11a**. Its NMR and IR spectra were identical with those of racemic **11a**. It had $[\alpha]^{20}_D$ +26.4° (0.005 g/mL, acetone).

Preparation and Separation of Diastereomers 13b. A quantity of 190 mg of racemic **11b** was converted to **13b** by method B described above. The reaction gave 225 mg of **13b** which was a 1:2 mixture of α-**13b** and β-**13b** by ^1H NMR. The above mixture (150 mg) was separated by TLC mesh chromatography (eluted with pentane, acetonitrile, and ethyl acetate 20:1:1) to give 47 mg of α-**13b** (95% pure) and 72 mg of β-**13b** (90% pure). ^1H NMR ($CDCl_3$): α-**13b** 0.80–1.60 (m, 20 H), 2.23 (s, 3 H), 2.16–3.46 (m, 8 H), 3.46 (s, 3 H), 4.94 (s, 1 H), 6.66 (s, 1 H), 7.34–7.60 (m, 5 H); β-**13b** 0.8–2.0 (m, 20 H), 2.23 (s, 3 H), 2.44–3.40 (m, 8 H), 3.46 (s, 3 H), 4.94 (s, 1 H), 6.66 (s, 1 H), 7.34–7.60 (m, 5 H).

(−)-14-Hydroxy-16-methyl-18-morpholino[12]metacyclophane (11b). A quantity of 40 mg of α-**13b** was reduced by method C to give 23 mg of (−)-**11b** (82% yield). Its ^1H NMR and IR spectra were identical with those of racemic **11b**. It had $[\alpha]^{20}_D$ −17.3° (*c* 0.015 g/2 mL, THF).

(+)-14-Hydroxy-16-methyl-18-morpholino[12]metacyclophane (11b). A quantity of 36 mg of β-**13b** was reduced by method C to give 19 mg of (+)-**11b** (75% yield). Its ^1H NMR and IR spectra were identical with those of racemic **11b**. It had $[\alpha]^{20}_D$ 10.8° (*c* 0.007 g/mL, THF).

1,3-Bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (14). Compound **14** was prepared by a literature[11] method in 92% yield. Its ^1H NMR was identical with that reported.

Cyclotetradecane-1,3-dione (18). Compound **18** was prepared by a literature method[13] in 28% yield: mp 30–32 °C (lit.[13] mp 31–31 °C).

2-Benzylcyclotetradecane-1,3-dione (19a). To a solution of 1.12 g of **18** in 5 mL of 5% potassium hydroxide was added 0.86 g of bezyl bromide dropwise with stirring. The reaction mixture was stirred for 2 h at room temperature and then acidified with 2.5 N HCl and extracted with ether. The ether extract was dried with $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporator. The residue was purified by flash chromatography on silica gel, eluted with petroleum ether and ethyl acetate (20:1), to give 1.47 g of **19a** (94% yield): mp 81–83 °C; ^1H NMR ($CDCl_3$) 1.0–1.8 (m, 18 H), 2.2–2.6 (m, 4 H), 3.66 (d, 2 H, J = 7 Hz), 3.93 (t, 1 H, J = 7 Hz), 7.07 (s, 5 H); IR (KBr, cm^{-1}) 1690, 740, 695; MS, *m/z* (relative intensity) 314 (M^+, 42), 286 (92), 159 (71), 146 (67), 55 (100).

2-Methylcyclotetradecane-1,3-dione (19b). Compound **19b** was prepared from compound **18** by the literature method.[15] The yield was 81%: mp 35–37 °C (lit.[13] mp 35–37 °C).

2-Methylcycloheptadecane-1,3-dione (19d). Compound **19c** was prepared by a literature method[13] in 62% yield: mp 39–40 °C.

2-Alkyl-3-(trimethylsiloxy)cycloalk-2-enone (20a–d). Compounds **20a–d** were prepared by the following method[16] in quantitiative yield from **19a–d**. In 2 mL of dry triethylamine was added 0.1 g of $ZnCl_2$. The mixture was stirred vigorously for 1 h under N_2. Compound **19** (3 mmol in 15 mL of dry benzene) was added and followed by 0.7 mL of Me_3SiCl. The reaction mixture was stirred overnight. The solvent was removed by rotary evaporator. To the residue was added 100 mL of dry hexane and the solution was filtered. The filtrate was concentrated by rotary evaporator to give **20**.

20a: ^1H NMR ($CDCl_3$) 0.13 (s, 9 H), 0.4–2.7 (m, 24 H), 3.43 (s, 2 H, CH_2Ph, major isomer), 3.60 (s, 2 H, CH_2Ph, minor isomer), 7.04 (s, 5 H); IR (film, cm^{-1}) by 1670, 1600, 1450, 840.

20b: ^1H NMR ($CDCl_3$) 0.27 (s, 9 H, trimethylsilyl of one isomer), 0.30 (s, 9 H, trimethylsilyl of the other isomer), 1.35 (m, 18 H), 1.80 (s, 3 H, Me, major isomer), 1.87 (s, 3 H, Me, minor isomer), 2.2–2.7 (m, 4 H); IR (film, cm^{-1}) 1680, 1250, 840.

20c: ^1H NMR ($CDCl_3$) 0.07 (s, 9 H, trimethylsilyl, minor isomer), 0.20 (s, 9 H, trimethylsilyl, major isomer), 0.90–1.90 (m, 18 H), 2.06–2.93 (m, 4 H), 5.42 (s, 1 H, vinyl, minor isomer), 5.50 (s, 1 H, vinyl, major isomer); IR (film, cm^{-1}) 1675, 1580, 1250, 840.

20d: ^1H NMR ($CDCl_3$) 0.2 (s, 9 H, trimethylsilyl, major isomer), 0.24 (s, 9 H, trimethylsilyl, minor isomer), 0.77–1.90 (m, 24 H), 1.77 (s, 3 H, Me, major isomer), 1.83 (s, 3 H, Me, minor isomer), 2.33–2.73 (m, 4 H); IR (film, cm^{-1}) 1670, 1610, 1250, 840.

13-(Methoxycarbonyl)-14-hydroxy-17-benzyl[11]metacyclophane (17a) (Method D). To a mixture of 0.77 g of **20a** (2 mmol) and 0.78 g of **14** (3 mmol) in 30 mL of dry CH_2Cl_2 was added 0.22 mL of $TiCl_4$ (2 mmol) under N_2 at −23 °C. The reaction mixture was stirred for 8 h at −23 °C and then overnight at room temperature. Concentrated sodium bicarbonate solution was added until the mixture was basic. The mixture was extracted with ether and dried with $MgSO_4$. It was filtered and the filtrate was concentrated to give 0.71 g of a yellowish solid. Purification of this solid by flash chromatography on silica gel gave 0.54 g of **17a** (69% yield): mp 112–114 °C; ^1H NMR ($CDCl_3$) 0.4–2.0 (m, 18 H), 2.06–3.70 (m, 4 H), 3.84 (s, 3 H), 4.20 (s, 2 H), 6.63 (s, 1 H), 6.70–7.27 (m, 5 H), 10.90 (s, 1 H); IR (KBr, cm^{-1}) 3470, 1650, 1240; MS, */z* (relative intensity) 394 (M^+, 11), 362 (39), 314 (35), 286 (100), 159 (94), 91 (100). Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.19; H, 8.63. Found: C, 79.23; H, 8.67.

13-(Methoxycarbonyl)-14-hydroxy-17-methyl[11]metacyclophane (17b). Compound **17b** was synthesized from **20b** by method D in 63% yield: mp 89–91 °C; ^1H NMR ($CDCl_3$)

0.4–1.8 (m, 18 H), 2.27 (s, 3 H), 2.1–3.5 (m, 4 H), 3.93 (s, 3 H), 6.63 (s, 1 H), 10.07 (s, 1 H); IR (KBr, cm^{-1}) 3420, 1660, 1220; MS, m/z (relative intensity) 318 (M^+, 49), 287 (49), 286 (100), 189 (33).

13-(Methoxycarbonyl)-14-hydroxy[11]metacyclophane (17c). Compound **17c** was obtained from **20c** by method D in 59% yield: mp 69–71 °C; ^1H NMR ($CDCl_3$) 0.62–1.90 (m, 18 H), 2.40–2.67 (m, 2 H), 2.80–3.03 (m, 2 H), 3.83 (s, 3 H), 6.43 (s, 2 H), 10.70 (s, 1 H); IR (KBr, cm^{-1}) 3410, 1660, 1560, 1250; MS, m/z (relative intensity) 304 (M^+, 54), 273 (47), 272 (100), 91 (19).

16-(Methoxycarbonyl)-17-hydroxy-20-methyl[14]metacyclophane (17d). Compound **17d** was prepared from **20d** by method D in 54% yield: mp 102–105 °C; ^1H NMR ($CDCl_3$) 0.70–1.90 (m, 24 H), 2.17 (s, 3 H), 2.43–3.20 (m, 4 H), 3.85 (s, 3 H), 6.54 (s, 1 H), 10.30 (s, 1 H); IR (KBr, cm^{-1}) 3410, 1650, 1430; MS, m/z (relative intensity) 360 (M^+, 71), 329 (60), 328 (100), 302 (22).

(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl Chloride (21). Compound **21** was prepared by a literature method[17] in 81% yield: bp 67–68 °C (2 mm) (lit.[17] bp 54–55 °C (1 mm)).

Preparation and Separation of the Diastereomers 22a. Compound **17a** was quantitatively converted into diastereomers **22a** with **21** by method B. The ratio of the two diastereomers was 1:1. They were separated by TLC mesh chromatography (eluted with petroleum ether and ethyl acetate, 35:1). From 180 mg of the mixture were obtained 66 mg of α-**22a** and 75 mg of β-**22a**: ^1H NMR ($CDCl_3$, 200 MHz) α-**22a** 0.66–1.76 (m, 18 H), 2.20–3.00 (m, 4 H), 3.66 (s, 6 H), 4.25 (ABq, 2 H, J = 3 Hz), 6.82 (s, 1 H), 6.92–7.64 (m, 10 H); β-**22a** 0.66–1.76 (m, 18 H), 2.20–3.00 (m, 4 H), 3.58 (s, 3 H), 4.25 (ABq, 2 H, J = 3 Hz), 6.85 (s, 1 H), 6.92–7.64 (m, 10 H).

(+)-13-(Hydroxymethyl)-14-hydroxy-17-benzyl[11]metacyclophane (23a). Compound α-**22a** was reduced by method C to give (+)-**23a**: mp 138–139 °C; $[\alpha]^{20}_D$ 12.6° (*c* 0.012 g/2 mL acetone); ^1H NMR ($CDCl_3$) 0.37–1.90 (m, 18 H), 2.0–3.1 (m, 4 H), 4.16 (s, 2 H), 4.93 (s, 2 H), 6.50 (s, 1 H), 6.80–7.5 (m, 5 H); IR (KBr, cm^{-1}) 3415, 1600, 1080; MS, m/z (relative intensity) 366 (M^+, 12), 350 (100), 348 (88), 91 (99); exact mass calcd for $C_{25}H_{34}O_2$ 366.2559, found 366.2521.

(−)-13-(Hydroxymethyl)-14-hydroxy-17-benzyl[11]metacyclophane (23a). Compound β-**22a** was reduced by method C to give (−)-**23a**: mp 138–140 °C; $[\alpha]^{20}_D$ 14.4° (*c* 0.006 g/2 mL acetone). Its ^1H NMR and IR spectra were identical with those of (+)-**23a**.

Preparation and Separation of Diastereomers 22b. Compound **17b** was converted into the diastereomeric esters **22b** in 90% yield by method B with compound **21**. The two diastereoisomers were separated by TLC mesh chromatography on silica gel (eluted with petroleum ether and ethyl acetate, 35:1): ^1H NMR ($CDCl_3$) α-isomer, 0.46–1.80 (m, 18 H), 2.32 (s, 3 H), 2.36–3.18 (m, 4 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 6.76 (s, 1 H, 7.44–7.65 (m, 5 H); β-isomer 0.46–1.80 (m, 18 H), 2.32 (s, 3 H), 2.31–3.18 (m, 4 H), 3.58 (s, 3 H), 6.80 (s, 1 H), 7.44–7.65 (m, 5 H).

(+)-13-(Hydroxymethyl)-14-hydroxy-17-methyl[11]metacyclophane (23b). The reduction of α-**22b** by method C gave (+)-**23b**: mp 123–158 °C; $[\alpha]^{20}_D$ +6.3° (*c* 0.036 g/2 mL, acetone); ^1H NMR ($CDCl_3$) 0.3–1.9 (m, 18 H), 2.30 (s, 3 H), 2.40–3.30 (m, 4 H), 4.90 (s, 2 H), 6.53 (s, 1 H); IR (KBr, cm^{-1}) 3610, 3400, 3200, 1600, 960; MS, m/z (relative intensity) 290 (M^+, 9), 274 (99), 272 (82), 257 (33), 136 (100). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.62; H, 10.34. Found: C, 78.71; H, 10.32.

(−)-13-(Hydroxymethyl)-14-hydroxy-17-methyl[11]metacyclophane (23b). Compound β-**22b** was similarly reduced to (−)-**23b**. Its ^1H NMR and IR spectra were identical with those of (+)-**23b**: mp 123–125 °C; $[\alpha]^{20}_D$ −8° (*c* 0.024 g/2 mL acetone).

Preparation of 22c. Compound **22c** was prepared from **17c** by method B in 92% yield: ^1H NMR ($CDCl_3$) 0.67–2.00 (m, 18 H), 2.50–2.87 (m, 4 H), 3.63 (s, 6 H), 6.80 (s, 1 H), 7.07 (s, 1 H), 7.33–7.73 (m, 5 H); IR (CCl_4, cm^{-1}): 205 (42.3), 189 (100); exact mass calcd for $C_{29}H_{35}F_3O_5$ 520.2437, found 520.2425.

Preparation of 22d. Compound **17d** was converted to **22d** in 90% yield by method B: ^1H NMR ($CDCl_3$) 0.70–1.80 (m, 24 H), 2.27 (s, 3 H), 2.53–2.90 (m, 4 H), 3.60 (s, 6 H), 6.77 (s, 1 H), 7.23–7.70 (m, 5 H); IR (film, cm^{-1}) 3420, 1665, 1220; MS, m/z (relative intensity) 576 (M^+, 4), 545 (3), 374 (30), 189 (100).

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Registry No. **9**, 87565-80-8; **11a**, 87968-80-7; (−)-**11a**, 87968-82-9; (+)-**11a**, 87968-83-0; **11b**, 87968-84-1; (−)-**11b**, 87968-86-3; (+)-**11b**, 87968-85-2; **12**, 34713-98-9; **13a** (isomer 1), 88034-40-6; **13a** (isomer 2), 87968-81-8; **13b** (isomer 1), 94294-14-1; **13b** (isomer 2), 94346-88-0; **14**, 67609-52-3; **17a**, 94294-21-0; **17b**, 94323-81-6; **17c**, 94323-82-7; **17d**, 94294-22-1; **18**, 3725-27-7; **19a**, 94294-15-2; **19b**, 3725-25-5; **19c**, 3725-27-7; **19d**, 94294-16-3; **20a**, 94294-17-4; **20b**, 94294-18-5; **20c**, 94294-19-6; **20d**, 94294-20-9; (*S*)-**21**, 20445-33-4; **22a** (isomer 1), 94294-23-2; **22a** (isomer 2), 94346-89-1; **22b** (isomer 1), 94294-26-5; **22b** (isomer 2), 94346-90-4; **22c**, 94294-29-8; **22d**, 94294-30-1; (+)-**23a**, 94294-24-3; (−)-**23a**, 94294-25-4; (+)-**23b**, 94294-27-6; (−)-**23b**, 94294-28-7; methyl 3-pyrrolidinocrotonate, 15424-17-6; (*R*)-(−)-α-methoxyphenylacetic acid, 3966-32-3; 1-morpholinocyclododecene, 3725-39-1; 1-morpholinocyclopentadecene, 3804-59-9.

Supplementary Material Available: Temperature dependent ^1H NMR spectra of compounds **22b** and **22d** (2 pages). Ordering information is given on any current masthead page.

Nuclear Spin–Spin Coupling via Nonbonded Interactions. 4. F–F and H–F Coupling in Substituted Benzo[*c*]phenanthrenes[1]

Frank B. Mallory,* Clelia W. Mallory, and Wendella M. Ricker

Department of Chemistry, Bryn Mawr College, Bryn Mawr, Pennsylvania 19010

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NMR measurements of the F–F coupling constants for a series of 4-substituted 1,12-difluorobenzo[*c*]-phenanthrenes are reported. The results provide further support for earlier generalizations that intramolecular "through-space" F–F coupling, in contrast to its "through-bond" counterpart, is essentially insensitive to the electronic character of substituents even though they cause significant perturbations in the ^{19}F chemical shifts. The large magnitude "through-space" H–F coupling between H-12 and F-1 for several 4- and 9-substituted 1-fluorobenzo[*c*]phenanthrenes shows a similar insensitivity to substituents. This is consistent with the notion that "through-space" H–F and F–F coupling have analogous origins in nonbonded overlap interactions.

Pairs of fluorine atoms that are crowded against one another intramolecularly are well documented to exhibit unusually large nuclear spin–spin coupling constants as measured by ^{19}F NMR spectroscopy.[2,3] Such F–F cou-

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