

A New Route to Optically Active [12][12]Paracyclophanes

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A novel strategy derived from sulfur-based cyclocoupling in conjunction with a modified Ramberg–Bäcklund reaction together with the utilization of (–)-menthol as the chiral auxiliary is presented for the synthesis of (+)- and (–)-[12][12]paracyclophanes.

The optical isomerism of cyclophanes arising from restricted rotation of the aromatic ring about single bonds has intrigued organic chemists for decades.¹ Lüttringhaus,² Cram³ and Blomquist⁴ first pioneered the synthesis and resolution of optically active [*n*]paracyclophanes. In 1977, Nakazaki adapted the benzene–furan ‘hybrid’ [2,2]paracyclophanes as the key intermediates in the synthesis of optically active [8][8] and [8][10]paracyclophanes.⁵ Nevertheless, this synthetic approach is limited in a sense that at least one of the two bridges must carry eight methylene units. As part of our continuing interest in designing effective methodology applic-

able for the synthesis of various types of cyclophanes, we wish to report a new approach to [*m*][*n*]paracyclophanes as demonstrated by the synthesis of optically active [12][12]paracyclophanes (**1a** and **b**). Our strategy, summarized in Scheme 1, evokes the iterative use of sulfur-based cyclocoupling⁶ in conjunction with a refined version⁷ of the Meyers’ modification⁸ of the Ramberg–Bäcklund reaction as the main reaction framework together with the utilization of (–)-menthol at mid stage as the chiral auxiliary to generate the requisite optically active precursors.

Cyclocoupling of dithiol **2** with 1,10-dibromodecane under moderately high dilution gave dithiacyclophane **3** in good yield. Oxidation of **3** with hydrogen peroxide in acetic acid led to bissulfone **4** which was further converted to the cyclic diene **5**, presumably the (*Z,Z*)-isomer, by using the modified Ramberg–Bäcklund reaction.⁷ Hydrogenation of diene **5** afforded the [12]paracyclophane **6** in nearly quantitative yield.

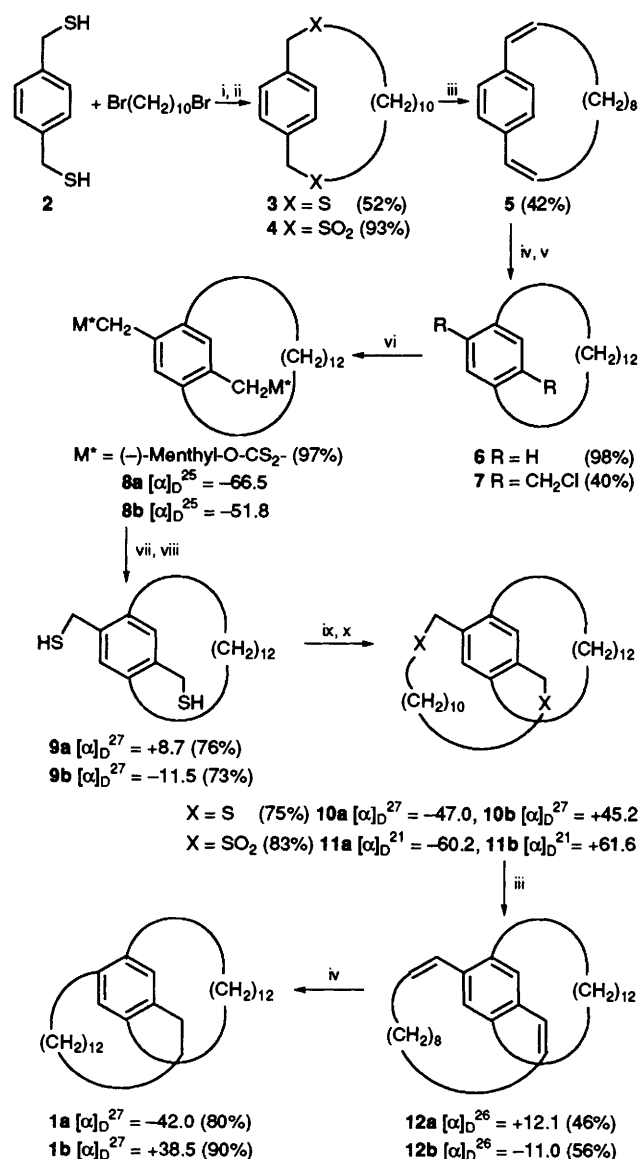
Bischloromethylation of [12]paracyclophane was best effected by chloromethyl methyl ether–stannic chloride⁹ to afford 14,17-bis(chloromethyl)[12]paracyclophane **7** in moderate yield. The racemic paracyclophane **7** was further converted, according to the general procedure reported by Isola,¹⁰ to a diastereoisomeric mixture of (–)-menthyl bisxanthates **8a** and **8b** which could be separated into diastereoisomerically pure entities by means of fractional crystallization from petroleum ether at –20 °C. When the solution of diastereoisomeric mixture of **8a** and **b** was allowed to cool at around –20 °C, the diastereoisomer with the smaller *R_f* value crystallized gradually. Further purification of this solid substance by repeated recrystallization from acetone until constant melting point and specific rotation furnished diastereoisomer **8b** as colourless needles with $[\alpha]_{\text{D}}^{25} = -51.8$ (*c* 4, C₆H₆).‡

The oily residue from the above fractional crystallization was purified by flash chromatography to afford a colourless oil which appeared as a single component, with a higher *R_f* value than that of **8b**, on TLC analysis. This oily component, which is referred to as **8a**, has $[\alpha]_{\text{D}}^{25} = -66.5$ (*c* 4, C₆H₆).‡

The purity of each diastereoisomer could also be determined by ¹H NMR. The ¹H NMR spectra of **8a** and **b** are nearly identical except for a small but discernible difference with respect to the shape as well as the chemical shift between the two sets of AB quartet at δ 4.3–4.5 for the benzylic protons adjacent to the xanthate groups.§ The conversion of **8a** and **b** into the corresponding 14,17-bis(mercaptomethyl)[12]paracyclophane enantiomers **9a** and **b**, respectively, was accomplished by morpholinolysis. Decomposition of **8a** by morpholine in benzene at reflux yielded **9a**, $[\alpha]_{\text{D}}^{27} = +8.7$ (*c* 3.5, C₆H₆).‡ Similarly, **8b** was transformed into the optically active dithiol **9b** with $[\alpha]_{\text{D}}^{27} = -11.5$ (*c* 4, C₆H₆).‡

The enantiomeric purity of **9a** and **b** prepared from morpholinolysis has not been determined with certainty. Nevertheless, the ready access to these nonracemic synthetic intermediates allowed us to proceed with the synthesis of our target compounds.

Cyclocoupling of the optically active dithiols **9a** and **b** with 1,10-dibromodecane under moderate dilution to 2',13'-dithia-[12][14]paracyclophanes **10a** and **b** was found to be most effectively accomplished by using NaOH as the base. Oxidation of the bissulfides **10a** and **b** with MCPBA led to bissulfones **11a** and **b** as colourless plates. Attempts to determine the absolute configuration of these highly crystal-



Scheme 1 Reagents and conditions: i, KOH, EtOH, C₆H₆; ii, H₂O₂, HOAc, heat; iii, CBr₂F₂, KOH, Bu^tOH; iv, H₂, Pd/C; v, MeOCH₂Cl, SnCl₄; vi, (–)-menthol, CS₂, NaOH; vii, resolution by fractional recrystallization and column chromatography; viii, morpholine in C₆H₆, reflux; ix, NaOH, EtOH, C₆H₆, Br₂(CH₂)₁₀Br; x, MCPBA

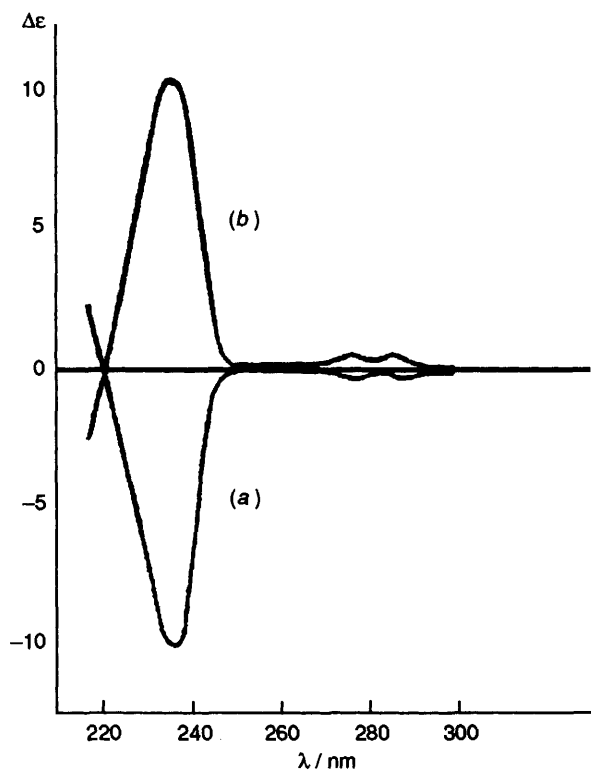


Fig. 1 CD spectra of (a) (+)-[12][12]paracyclophane (**1a**) and (b) (-)-[12][12]paracyclophane (**1b**) in methanol

line substances by X-ray crystallography were unsuccessful owing to a high degree of mobility of the methylene bridges. Extrusion of sulfur dioxide followed by catalytic hydrogenation of the resulting dienes **12a** and **b** completed the synthesis to afford optically active [12][12]paracyclophanes **1a** and **b**, respectively.

The CD spectra of (+)- and (-)-[12][12]paracyclophanes (Fig. 1) show clearly antipodal patterns. Unfortunately, the observed Cotton effects from these spectra alone are not strong enough to allow assignment of the absolute configurations.

In summary, this synthetic approach provides a flexible entry to various optically active [*m*][*n*]paracyclophanes with the readily available 1,4-bis(mercaptomethyl)benzene as the starting material. The reactions involve neither expensive reagents nor complicated operations. The preparation of other non-racemic [*m*][*n*]paracyclophanes on the basis of this synthetic approach are under way in other laboratory.

We thank the Department of Chemistry, CUHK for financial support and Mr D. Z. Huang of the Shanghai Institute of Organic Chemistry, Academia Sinica for assistance in CD measurements.

Received, 16th May 1994; Com. 4/02873B

Footnotes

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‡ The specific optical rotations are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$.
§ ^1H NMR, **8a**: δ_{H} (CCl_4 , 250 MHz) 0.8–1.15 and 1.5–2.3 (56 H, two groups of unresolved broad peaks, nonbenzylic aliphatic protons at 2–11 positions and those on the menthyl moiety), 2.44–2.58 and 2.85–2.94 (4 H, two sets of m, ArCH_2 at 1 and 12 positions), 4.32 and 4.47 (4 H, AB quartet, ArCH_2S , J_{gem} 13.0), 5.45–5.54 (2 H, m, SCSOHR_2), 7.29 (2 H, s, ArH); **8b**: δ_{H} (CCl_4 , 250 MHz) 0.8–1.15 and 1.50–2.30 (56 H, two groups of unresolved broad peaks, nonbenzylic aliphatic protons at 2–11 positions and those on the menthyl moiety), 2.44–2.53 and 2.85–2.94 (4 H, two sets of m, ArCH_2 at 1 and 12 positions), 4.30 and 4.40 (4 H, AB quartet, ArCH_2S , J_{gem} 13.0), 5.46–5.55 (2 H, m, $-\text{SCSOHR}_2$), 7.26 (2 H, s, ArH). All *J* in Hz.

References

- (a) R. H. Mitchell, *Cyclophanes Vol. 1*, ed. P. M. Keehn and S. M. Rosenfeld, Academic, New York, 1983, 240 and refs. cited therein; (b) F. Vögtle, A. Ostrowicki, P. Knops, S. Billen and K. Mittelbach, *Pure Appl. Chem.*, 1990, **62**, 505.
- (a) A. Lüttringhaus and H. Gralheer, *Ann.*, 1947, **557**, 108, 112; (b) A. Lüttringhaus and G. Eyring, *Angew. Chem.*, 1957, **69**, 139; *Ann.*, 1957, **604**, 111.
- (a) D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, 1958, **77**, 6289; (b) D. J. Cram, R. J. Wechter and R. W. Kierstead, *J. Am. Chem. Soc.*, 1955, **80**, 3126.
- A. T. Blomquist, R. E. Stahl, Y. C. Meinwald and B. H. Smith, *J. Org. Chem.*, 1961, **26**, 1687.
- M. Nakazaki, K. Yamamoto, M. Ito and S. Tanaka, *J. Org. Chem.*, 1977, **42**, 3468.
- (a) T. Otsubo and S. Misumi, *Synth. Commun.*, 1978, **8**, 285; (b) V. Boekelheide, *Acc. Chem. Res.*, 1980, **13**, 65 and refs. cited therein.
- T.-L. Chan, S. Fong, Y. Li, T.-O. Man and C.-D. Poon, *J. Chem. Soc., Chem. Commun.*, 1994, 1771.
- C. Y. Meyers, W. S. Matthews, L. L. Ho, V. M. Kolb and T. E. Paraday, in *Catalysis in Organic Synthesis*, ed. G. V. Smith, Academic, New York, 1977, 197.
- (a) L. D. Taylor and R. B. Davis, *J. Org. Chem.*, 1963, **28**, 1713; (b) S. H. Pines, R. F. Czaja and N. L. Abramson, *J. Org. Chem.*, 1975, **40**, 1920; (c) G. A. Olah, D. A. Beal and J. A. Olah, *J. Org. Chem.*, 1976, **41**, 1627.
- M. Isola, E. Ciuffarin and L. Sagromora, *Synthesis*, 1976, 326.