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

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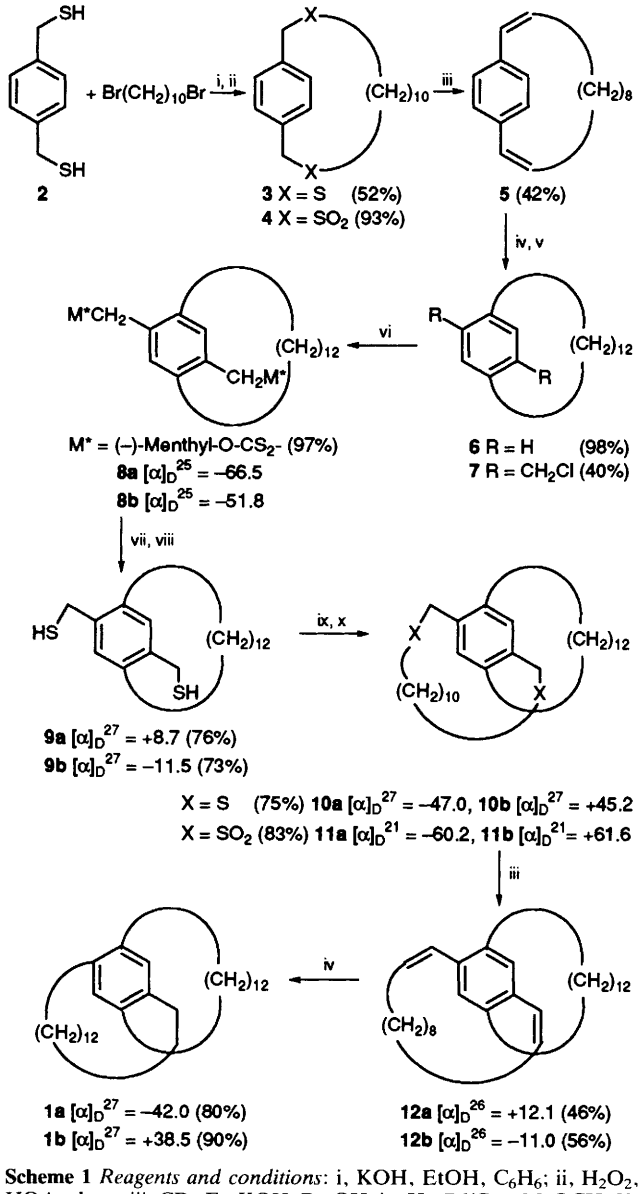
A novel strategy derived from sulfur-based cyclocoupling in conjunction with a modified Ramberg–Bäcklund reaction together with the utilization of (−)-menthol as the chiral auxiliary is presented for the synthesis of (+)- and (−)-[12][12]paracyclophanes.

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] Cram[3] and Blomquist[4] 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 applicable 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 cyclocoupling[6] in conjunction with a refined version[7] of the Meyers' modification[8] of the Ramberg–Bäcklung 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.



Scheme 1 *Reagents and conditions*: i, KOH, EtOH, C_6H_6; ii, H_2O_2, HOAc, heat; iii, CBr_2F_2, KOH, Bu^{t}OH; iv, H_2, Pd/C; v, $MeOCH_2Cl$, $SnCl_4$; vi, (−)-menthol, CS_2, NaOH; vii, resolution by fractional recrystallization and column chromatography; viii, morpholine in C_6H_6, reflux; ix, NaOH, EtOH, C_6H_6, $Br_2(CH_2)_{10}Br$; x, MCPBA

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 chloride[9] 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 $[\alpha]_D^{25} = -51.8$ (*c* 4, C_6H_6).‡

The oily reside 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 $[\alpha]_D^{25} = -66.5$ (*c* 4, C_6H_6).‡

The purity of each diastereoisomer could also be determined by ^{1}H NMR. The ^{1}H 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**, $[\alpha]_D^{27} = +8.7$ (*c* 3.5, C_6H_6).‡ Similarly, **8b** was transformed into the optically active dithiol **9b** with $[\alpha]_D^{27} = -11.5$ (*c* 4, C_6H_6).‡

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-

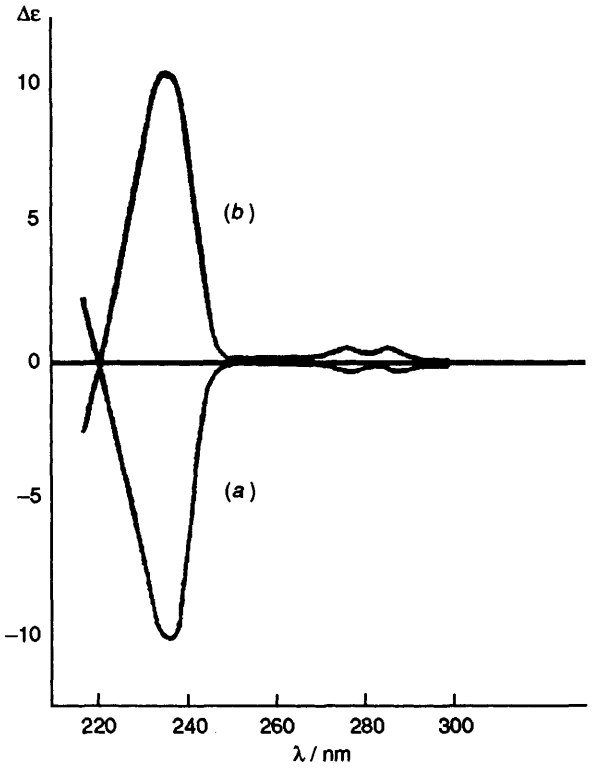


Fig. 1 CD spectra of (*a*) (+)-[12][12]paracyclophane (**1a**) and (**b**) (−)-[12][12]paracyclophane (**1b**) in methanol

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 afforded 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.

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Footnotes

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‡ The specific optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

§ ^{1}H 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 (2H, m, -$SCSOHR_2$), 7.26 (2H, s, ArH). All *J* in Hz.

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