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MACROCYCLIC PARACYCLOPHANE SYNTHESIS

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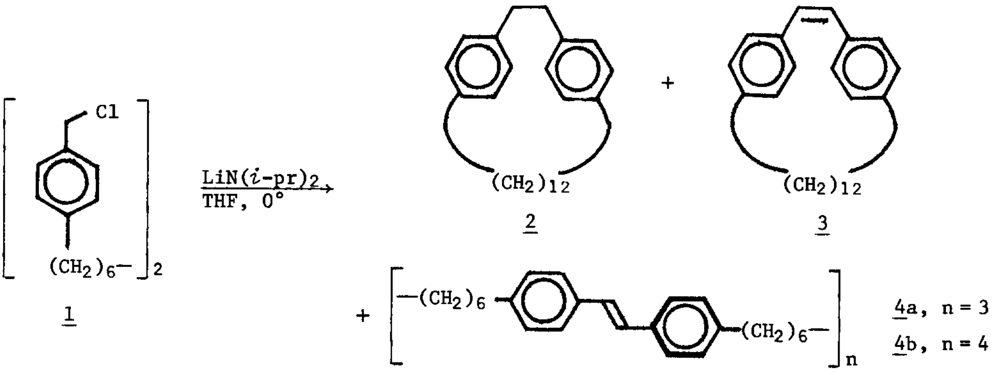
Abstract: Macrocyclic stilbene derivatives are prepared using strong base to couple the terminal carbons of 1,12-bis-[4-chloromethylphenyl]-dodecane and its homologs.

Although [2.2]-paracyclophane and its derivatives have been extensively investigated,[1] the [2.n]-homologs in which n > 10 remain relatively rare.[2] These macrocyclic paracyclophanes are ideal for use as enzyme mimics, especially if they encorporate a stilbene moiety.[3] Thus it is a pleasure to report a novel, convenient synthesis for this class of compounds from readily available starting materials.

Commencing from 1,12-*bis*-[4-chloromethylphenyl]-dodecane (1), which is obtained in four steps from toluic acid and 1,10-dibromodecane,[4] an easily separated mixture of paracyclophanes is obtained in a one-pot reaction using LDA as the base (see Scheme).



A mixture of [2.12]-paracyclophane (2) and *cis* [2.12]-paracyclophan-1-ene (3) are formed as the major products (~50%).[5] Modest yields of all *trans* trimer (4a) and all *trans* tetramer (4b) were also isolated.[6] No dimer was formed in isolable quantity. Separation of the saturated monomer 2 from the *cis* stilbene monomer 3 was achieved through bromination of the mixture of 2 and 3, separation of the dibromide (5) from [2.12]-paracyclophane (2), and debromination with Zn-dust/10% aqueous ethanol to yield pure 3 in 20.6% yield. Debromination using NaI/acetone failed.

Specifically, a 1000 mL three-necked flask equipped with a magnetic stirrer, a N_2 inlet tube, and a rubber septum, is charged with 3 g (7.2 mmol) of 1,12-bis-[4-chloromethylphenyl]-dodecane (1), 600 mL of anhydrous tetrahydrofuran (THF), and 2 mL (0.0143 mol) of diisopropylamine and cooled to 0° with stirring under a blanket of N_2. To the stirred solution is added 5.30 mL (0.0143 mol) of *n*-BuLi (2.5 M in hexane) over 10 min and the intense black solution is kept at 0° for 6 hr. Following the addition of 1 mL of water and evaporation of solvent the residue is chromatographed on alumina. The first fraction elutes with 10% CH_2Cl_2/20-40° petroleum ether, and contains ~1 g of a 6:7 mixture of 2 and 3. A second fraction elutes with 20% CH_2Cl_2/pet. ether and contains a 1:3 mixture of the trimer (4) and tetramer (5).[7] The mixture of 2 and 3 (0.95 g, 2.7 mmol) is dissolved in 10 mL of CH_2Cl_2 and treated with Br_2/CH_2Cl_2 until a faint color persists, and is then chromatographed on alumina. The first fraction eluted contains 0.4309 g (1.2 mmol) of pure saturated 2[8] (17.3% based on the dichloride 1). The second fraction, eluted with 10% CH_2Cl_2/pet. ether, contains 0.7596 g (1.5 mmol) of [2.12]-1,2-dibromoparacyclophane (5). Debromination of 0.1047 g (0.2 mmol) of 5 using 0.1075 g of Zn-dust in refluxing 10% ethanol for 1 hr gives 0.0709 g (0.2 mmol) of pure 3[9] (20.6% based on the dichloride 1). Hydrogenation of the mixture of 2 and 3 in ethanol, using 5% Pd/C, can be used to give pure 2. This route provides an easy access to [2.12]-paracyclophane in fair yield, and can be used to prepare higher homologs (e.g. [2.14]-paracyclophane[10]) as well, although the yield is somewhat lower.

Ready access to macrocyclic stilbenes of this type makes possible a number of experiments concerning the influence exerted by the long chains present in these molecules. Experiments designed to test the feasibility of forming derivatives encorporating *trans* stilbene and acetylene moieties in the macrocyclic ring are presently in progress.

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References and Notes:

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2. Potter, S.E.; Sutherland, I.O. *J. Chem. Soc. Chem. Comm.* 1973, 520-521; *also see* Keehn, P.M.; Rosenfeld, S.M., "Cyclophanes," Vol. 1&2, Academic Press, New York, NY, 1983.
3. Tirado-Rives, J.; Oliver, M.A.; Fronczek, F.R.; Gandour, R.D. *J. Org. Chem.* 1984, 49, 1627-1634.
4. Butcher, J.A., Jr.; Hinz, H.R.; Parsons, E.J.; Peyser, J. *Tetra. Lett.* (in this issue).
5. The *cis* configuration was evidenced by a characteristic absorption at 260-265 nm in the UV, and by a singlet at 6.62 ppm for the stilbene protons and a singlet in the aromatic region at 6.99 ppm of the nmr spectrum.
6. The *trans* configuration was indicated by a UV absorption at 285-290 nm which is characteristic for *trans* stilbenes, and confirmed by the nmr spectrum, which exhibited a singlet at 7.01 ppm for the stilbene protons and an AB pattern in the aromatic region (δ: 7.374 and 7.129).
7. This material was obtained as a white crystalline solid. Elemental analysis (Galbraith Labs, Inc., Knoxville, TN) was consistent with the empirical formula: $C_{26}H_{34}$. Calculated: C: 90.11%, H: 9.89. Found: C: 89.83%, H: 10.02. Molecular weight determination gave a molecular weight of 1270, which is consistent with the results from size exclusion chromatography (Waters 500 Å ultrastyragel) which revealed the presence of two components in a 1:3 ratio.
8. ^{1}H nmr ($CDCl_3$) δ: 6.90 and 6.75 (8H,AB); 2.90 (4H,s); 2.52 (4H,t); 1.55 (4H,bm); 1.25 (16H,s).
9. ^{1}H nmr ($CDCl_3$) δ: 6.99 (8H,s); 6.62 (2H,s); 2.59 (4H,t); 1.54 (4H,bm); 1.26 (16H,s).
10. The [2.n]-paracyclophanes obtained by this route are identical to the material obtained by standard procedures as shown by nmr, HPLC, and boiling point. Data for [2.14]-paracyclophane distilled at 255° @ 1.5 torr is typical. Calculated for $C_{28}H_{40}$: C: 89.30%, H: 10.70, MW: 376.62. Found: C: 89.32%, H: 10.81, MW: 376.

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