method used for the 4 to 3 conversion:[11b] IR (neat) 3010 (m), 2940 (s), 2860 (m), 2830 (w), 1640 (w), 1460 (m), 770 (m), 685 (m); NMR ($CDCl_3$) δ 0.92 (d, 3 H, = 7.5 Hz), 1.5–1.8 (m, 6 H), 2.1 (m, 1 H), 2.3 (m, 1 H), 2.5 (m, 1 H), 5.16 (ddd, 1 H, J = 10, 2, 2, Hz), 5.77 (dddd, 1 H, J = 1 0, 6, 2, 1 Hz); mass spectrum, m/e (relative intensity) 122 (M^+, 40), 107 (27), 94 (32), 93 (100), 91 (21), 81 (38), 80 (33), 79 (98), 78 (20, 77 (29); exact mass calcd for C_9H_{14} 122.1092, found 122.1096. Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.05; H, 11.45. A sample of (1*R*,4*R*,5*S*)-(−)-**7** (93% optically pure) gave (1*S*,2*S*,5*R*)-(−)-**6** in 46% yield after purification by column chromatography on silica gel (pentane eluant) and preparative GC (10 ft × $^3/_8$ in 15% UCON 50-LB-2000 on Chromosorb P). Capillary GC (200 ft, UCON LB-550-X) showed the presence of 0.4% exo isomer (+)-**3** and 0.2% unidentified impurity. This sample had $[\alpha]^{25}_D$ −43.8° and $[\alpha]^{25}_{365}$ −173.1° (*c*, 1.1, $CHCl_3$). Assuming that the impurity is achiral and correcting for the exo isomer (+)-**3** gives a value of $[\alpha]^{25}_D$ −45.0° ($[\alpha]^{25}_{365}$ −177°). Therefore the calculated absolute rotation of **6** is $[\alpha]^{25}_D$ −48.5° ($[\alpha]^{25}_{365}$ −191°).

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE 77-09139).

Registry No. (+)-**1**-OH, 68629-26-5; (+)-**1**-OAc, 79027-20-6; (+)-**2**, 79027-21-7; (−)-**3**, 78965-86-3; (+)-**4**, 79027-22-8; (+)-**5**, 79027-23-9; (−)-**6**, 79027-24-0; (−)-**7**, 79027-25-1; (−)-**8**, 79027-26-2.

A Novel Synthesis of Benzo[1,2:4,5]dicyclobutene via a Dual Parham Cyclialkylation[1]

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Benzodicyclobutenes have attracted attention due to their unique strain effects, which have been the subject of several theoretical studies.[2] More recently these compounds have been used as intermediates for the preparation of aryl cyclophanes.[3]

The first preparation of the symmetrical benzo[1,2:4,5]dicyclobutene (**2**) was achieved by Cava via the thermal extrusion of sulfur dioxide from the disulfone (**1**; Scheme I).[4]

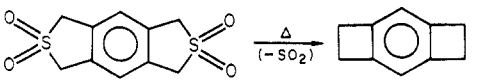
Other routes to **2**, recently reported,[2b,3a] entail lengthy syntheses and/or thermal extrusion reactions requiring special pyrolysis apparatus. These circumstances limit the amount of material that can be used in the reaction sequence and also place restriction on the type of functional groups that can be present.

From the success reported in using the Parham cyclialkylation reaction for the synthesis of benzocyclobutenes,[5-7] it seemed possible that benzo[1,2:4,5]dicyclobutene could be prepared by the action of 2 equiv of butyllithium at −100 °C on 2,5-dibromo-1,4-bis(2-bromoethyl)benzene (**3a**; Scheme II).

Dual exchange of *p*-dibromobenzene with 2 equiv of butyllithium in a hydrocarbon solvent has been achieved by Gilman.[8] However, a dual halogen–lithium exchange reaction has not been attempted in the presence of reactive functional groups such as those that have been used by Parham et al.[5,9]

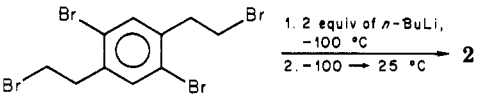
The tetrabromide **3a** was unknown but can be prepared in a straightforward manner from 1,4-bis(2-hydroxyethyl)benzene[10] (**6a**, Scheme III). Treatment of the diol

Scheme I



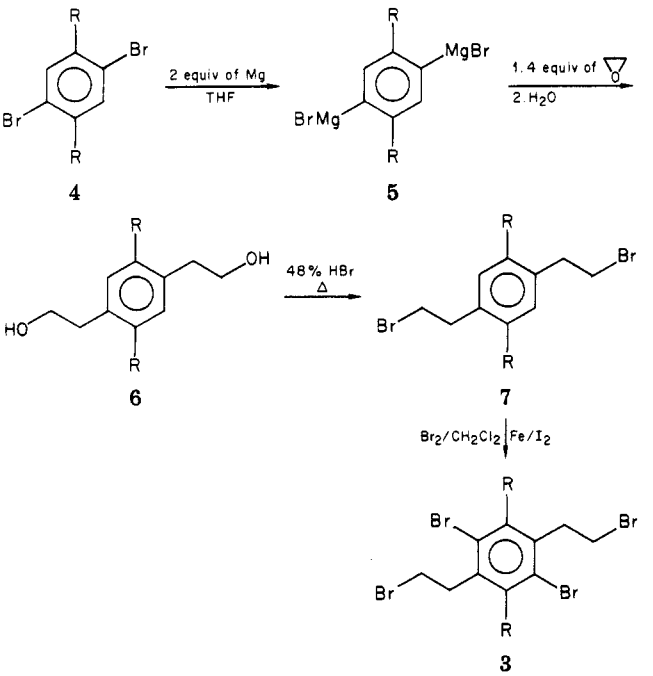
1 2

Scheme II



3a

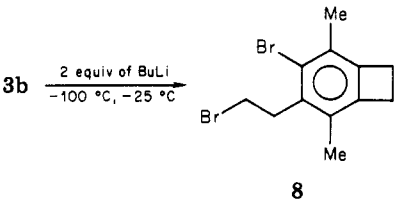
Scheme III[a]



4 5 6 7 3

[a] a, R = H; b, R = Me.

Scheme IV



8

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6 with hydrobromic acid, followed by ring bromination, afforded **3a** in 89% yield.

Selective bromine–lithium exchange of both the aromatic bromine atoms of **3a** took place readily at −100 °C.[11] When the reaction mixture was warmed to room temperature, the dual cyclialkylation occurred to yield benzo[1,2:4,5]dicyclobutene (**2**) in 64% yield (28% yield from *p*-dibromobenzene, **4a**).

Attempts to carry out bromine–lithium exchange on **3a** with 1 equiv of butyllithium yielded a mixture consisting of six products, by GLC analysis. This result was not unexpected in light of the findings of Gilman with regard to the exchange behavior in systems of approximately equal electronegativities.[12]

An attempt to extend this synthesis to the preparation of 3,6-dimethylbenzo[1,2:4,5]dicyclobutene failed. It proved possible to prepare the required 2,5-dibromo-3,6-dimethyl-1,4-bis(2-bromoethyl)benzene (**3b**), but even in the presence of 2 equiv of butyllithium at −100 °C only *one* of the two aromatically bound bromine atoms exchanged. The product (**8**), characterized by ^1H and ^{13}C NMR, as well as elemental analysis, proved to be a substituted benzocyclobutene derivative (Scheme IV). No trace of the expected 3,6-dimethyl-benzo[1,2:4,5]dicyclobutene[3a] was detected. An attempt to carry out bromine–lithium exchange by treatment of **8** with 1 equiv of butyllithium resulted in the recovery of the starting material. It has not been established why **8** fails to undergo bromine–lithium exchange.

Although the double cyclialkylation method appears limited in scope, it does provide a convenient route to benzo[1,2:4,5]dicyclobutene (**2**) with use of readily available apparatus.

Experimental Section

General Procedures. All reactions involving organolithium reagents were conducted under an atmosphere of nitrogen. Tetrahydrofuran was distilled from either lithium aluminum hydride or calcium hydride. Reaction temperatures of −100 °C were achieved with a liquid nitrogen–diethyl ether bath. All organic residues were dried over anhydrous magnesium sulfate. ^1H NMR data were obtained from the following: (a) a JEOL Model JNM-MH-100 100-MHz spectrometer, (b) Varian Model EM-360 60-MHz spectrometer, and (c) a Varian Model T-60 60-MHz spectrometer, all employing 1–2% tetramethylsilane as an internal standard. ^{13}C NMR data were obtained from a JEOL Model FX-60 15-MHz Fourier transform spectrometer with $CDCl_3$ lock and employing 1–2% tetramethylsilane as an internal standard. IR data were obtained from a Perkin-Elmer Model 297 spectrometer. Microanalyses were performed by MHW Laboratories, Phoenix, AZ. All melting points were obtained from a Mel-Temp heating block apparatus and are uncorrected.

1,4-Bis(2-hydroxyethyl)benzene (6a) was prepared in 49% yield by the method of Clark and O'Reilly:[10] mp 82–83.5 °C (lit.[10] mp 85 °C); IR (KBR) 3315 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (br s, 2 H, exchangeable OH), 2.79 (t, 4 H, CH_2), 3.79 (t, 4 H, benzylic CH_2), 7.12 (s, 4 H, ArH).

1,4-Bis(2-bromoethyl)benzene (7a). A suspension of 17.73 g of **6a** in 250 mL of 48% hydrobromic acid was refluxed and stirred for 15 h. The mixture was extracted with methylene chloride, and the extracts were dried, filtered, and concentrated under vacuum to yield 29.75 g of brown solid. Recrystallization from hexane afforded 27.48 g (88%) of dihalide **7a** as pale yellow needles: mp 70–71 °C (lit.[13] mp 73 °C); ^1H NMR ($CDCl_3$) δ 3.14 (t, 4 H, CH_2), 3.58 (t, 4 H, benzylic CH_2), 7.12 (s, 4 H, ArH).

2,5-Dibromo-1,4-bis(2-bromoethyl)benzene (3a). To 9.30 g (31.8 mmol) of **7a** in 200 mL of methylene chloride were added 0.5 g of iron filings and 0.10 g of iodine, followed by the dropwise addition of 11.18 g (69.9 mmol) of bromine. The mixture was stirred at room temperature for 114 h.

The mixture was then filtered, washed with 15% sodium thiosulfate solution, dried, and concentrated under reduced pressure. The off-white solid (13.73 g) obtained was recrystallized from hexane, affording 13.42 g (94%) of colorless needles: mp 106.5–108.5 °C; ^1H NMR ($CDCl_3$) δ 3.23 (t, 4 H, CH_2), 3.57 (t, 4 H, benzylic CH_2), 7.43 (s, 2 H, ArH).

Anal. Calcd for $C_{10}H_{10}Br_4$: C, 26.67; H, 2.22; Br, 71.11. Found: C, 26.89; H, 2.46; Br, 70.94.

Benzo[1,2:4,5]dicyclobutene (2). To the usual low temperature reaction apparatus[5] were added 2,5-dibromo-1,4-bis(2-bromomethyl)benzene (10.00 g, 22 mmol), dry tetrahydrofuran (125 mL), and hexane (30 mL), and the mixture was cooled to −100 °C. Butyllithium (17.78 mL, 0.044 mol, 2.5 M in hexane) was added at such a rate as to maintain the temperature below −95 °C. A sample[11] was taken after 15 min at −100 °C and revealed that exchange was complete.

The mixture was then allowed to warm to room temperature and was quenched in water (200 mL). The organic phase was separated and the aqueous phase was extracted with ether (3 × 125 mL). The combined organics were then dried, filtered, and concentrated (rotary evaporation) to yield 2.65 g of a yellow solid, which was recrystallized from ethanol to yield pure benzo[1,2:4,5]dicyclobutene (**2**): 1.83 g (64%) as colorless plates; mp 100–101 °C (lit.[14] mp 101 °C); IR (KBr) 2925, 1445, 1315, 1205, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 8 H, cyclobutene CH_2), 6.76 (s, 2 H, ArH).

2,5-Bis(2-hydroxyethyl)-1,4-dimethylbenzene (6b). A Grignard reagent was prepared from 73.29 g (278 mmol) of 2,5-dibromo-1,4-dimethylbenzene (**4b**)[15] in dry tetrahydrofuran (200 mL) essentially as described by Clark et al.[10] for the preparation of (**6a**), and the reagent was allowed to react with 48.93 g (1.11 mol) of ethylene oxide in tetrahydrofuran. Worked up as in the case of the homologue **6a**, the product was obtained as a brown oil, which on trituration with hexane afforded a yellow solid, which on crystallization from benzene yielded 23.20 g (43%) of **6a** as colorless needles: mp 108–109.5 °C; IR (KBr) 3320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 7 H, CH_3, OH), 2.90 (t, 4 H, CH_2), 3.97 (t, 4 H, benzylic CH_2), 6.93 (s, 2 H, ArH).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.23; H, 9.28. Found: C, 74.47; H, 9.46.

2,5-Bis(2-bromoethyl)-1,4-dimethylbenzene (7b). By use of a procedure analogous to that used in the preparation of **7a**, 3.87 g (20 mmol) of the dihydroxy compound **6b** was converted to the dibromide **7b**: 5.80 g (91%) of small tan needles; mp 128–130 °C; ^1H NMR ($CDCl_3$) δ 2.12 (s, 6 H, CH_3), 3.16 (t, 4 H, CH_2), 3.56 (t, 4 H, CH_2), 7.08 (s, 2 H, ArH).

3,6-Dibromo-2,5-bis(2-bromoethyl)-1,4-dimethylbenzene (3b). Following the procedure described for the preparation of **3a**, 5.62 g (35.2 mmol) of **7b** was brominated in methylene chloride to afford a yellow solid, which on recrystallization from hexane gave 8.18 g (97%) of small colorless needles: mp 132–133 °C; ^1HNMR ($CDCl_3$) δ 2.52 (s, 6 H, CH_3), 3.47 (s, 8 H, CH_2).

Anal. Calcd for $C_{12}H_{14}Br_4$: C, 30.16; H, 2.95; Br, 66.89. Found: C, 30.47; H, 2.95; Br, 66.62.

4-Bromo-3,6-dimethyl-5-(2-bromoethyl)benzocyclobutene (8). The reaction of **3b** (2.52 g, 5.27 mmol) with butyllithium (4.58 mL, 10.5 mmol) was carried out as previously described in the preparation of benzo[1,2:4,5]dicyclobutene (**2**) and yielded 1.40 g (84%) of virtually pure **8** as colorless needles from methanol: mp 73–74.5 °C; ^1H NMR ($CDCl_3$) δ 2.14 (s, 6 H, CH_3), 2.99 (s, 4 H, cyclobutene CH_2), 3.43 (s, 4 H, side chain CH_2); ^{13}C NMR ($CDCl_3$) δ 14.68, 18.06, 27.16, 27.35, 29.82, 37.49, 126.44, 130.47, 131.18, 135.60, 142.42, 143.33.

Anal. Calcd for $C_{12}H_{14}Br_2$: C, 45.28; H, 4.40; Br, 50.32. Found: C, 45.45; H, 4.45; Br, 50.26.

In a separate experiment a sample of the dibromo compound (**8**; 1.25 g, 3.93 mmol) was subjected to the action of butyllithium (3.93 mmol, in hexane) under conditions similar to those used

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in the cyclization of **3a**. The starting material (1.19 g, 95%) was recovered unchanged.

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Synthesis of Porphinedipropionic Acid and Dealkylated Protoporphyrin Analogues

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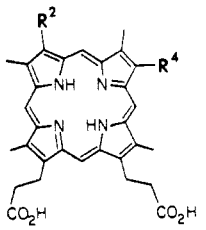
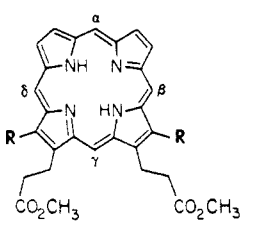
Hemoproteins, composed of an iron porphyrin active site and the apoprotein, exhibit an amazingly broad spectrum of functions including oxygen transport, electron transport, hydrogen peroxide decomposition, and oxidation of organic substrates. The variation in heme function among hemoproteins depends upon specific interactions between the heme prosthetic group and the apoprotein. An obvious method of probing the heme–protein relationship is to investigate structural modifications in the heme group and to relate these to alterations in the functional properties of hemoproteins reconstituted with these hemes.[2] The heme derivatives studied in previous reconstitution experiments invariably involved those hemes derived directly from protoporphyrin IX (1) with modification of the substituents at position 2 and 4 of the porphyrin ring, i.e., deutero, meso, diacetyl, and formyl derivatives.[3,4] However, the electronic effect and the steric effect of the side chains in such compounds have been altered simultaneously, and this blending of the two effects has made the interpretation of the results very ambiguous. For differentiation of these two effects, more synthetic hemes are required. We have previously prepared a hexamethyl porphyrin **2** and reconstituted the heme into hemoglobin[5] as well as peroxidase.[6] We now report the synthesis of two demethylated analogues **3** and **4**. Hemes of such porphyrins deprived of side chains should have greater freedom inside the protein pocket and therefore would exhibit properties approaching those of an unstrained system.



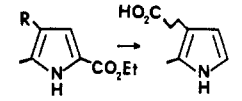
1) $R^2 = R^4$ = vinyl
2) $R^2 = R^4$ = Me



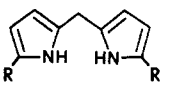
3) R = H
4) R = Me

Porphyrin Synthesis via the *a,c*-Biladiene Routes

The most convenient synthesis for porphyrin **3** is probably the *a,c*-biladiene route, using copper(II) salts for ring closure.[7,8] The required pyrrolepropionic acid **8** was synthesized from pyrrole **5**[9] via the acrylic ester **7**.[10] Condensation of (5,5′-diformyl-2,2′-dipyrryl)methane (**10**), prepared as previously described,[11] and 2 mol of the decarboxylated **9** in 40% HBr in acetic acid afforded a 75% yield of the *a,c*-biladiene dihydrobromide **12**. This tetrapyrrole was cyclized, using copper acetate in pyridine, to give the copper porphyrin, which was demetalated in sulfuric acid and esterified with methanol to give porphyrin **3**. The yield was very low (<2% from **12**) and the main product was an insoluble black powder. Since variations of the cyclization conditions failed to improve the yield, it was decided to try this method on different tetrapyrroles.

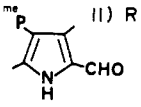


5) R = H
6) R = CHO
7) R = CH=CH$_2$CO$_2$Et
8) R = CH$_2$CH$_2$CO$_2$Et

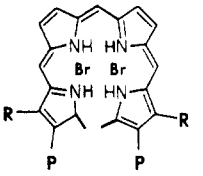


9)

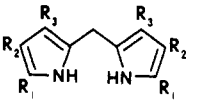
10) R = CHO
11) R = H



14)



12) R = H
13) R = Me



15) R_1 = H R_2 = Me R_3 = Me
16) R_1 = CHO R_2 = Me R_3 = CH$_2$CH$_2$CO$_2$Me
17) R_1 = H R_2 = Me R_3 = CH$_2$CH$_2$CO$_2$H
18) R_1 = CO$_2$Et R_2 = H R_3 = CH$_2$CH$_2$CO$_2$Et
19) R_1 = CO$_2$Et R_2 = H R_3 = Me

Condensation of **11** and 2 mol of **14** in HBr–HOAc afforded 82% of the biladiene **13** dimethyl ester, which was then treated with copper(II) chloride in hot DMF. After demetalation and esterification, porphyrin **4** was obtained again in less than 2% yield. Previously this copper cyclization method has been shown to give satisfactory yields (>20%) of porphyrins from fully substituted tetrapyrroles.[7,8] Indeed, when (3,3′,4,4′-tetramethyl-2,2′-dipyrryl)methane (**15**)[12] was condensed with **14**, subsequent ring closure under identical conditions provided 22% of the hexamethyl porphyrin **2**. It appears, therefore, that the cause of the poor yield is associated with the unsubstituted *a,c*-biladienes.

Porphyrin Synthesis by the MacDonald Procedure

Porphyrins like **3** and **4**, having a C_{2v} symmetry, can be prepared by condensation of two symmetric dipyrrylmethanes (north–south direction) via formyl groups.[13] Thus the condensation of (5,5′-dipyrryl)methane **16**[11] and

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