Birch Reduction of [2.2]Paracyclophane-2-carboxylic Acid

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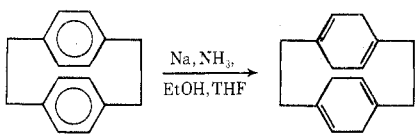
The Birch reduction of [2.2]paracyclophane-2-carboxylic acid (**3**) gives the tetrahydro product **4b** in which the double bonds of each deck are only partially overlapping; i.e., the Birch reduction proceeds in a manner previously observed for [2.2]paracyclophane (**1**) itself. This stereochemistry is demonstrated by reducing the pseudo-*gem*-deuterio derivative of **3**. The stereochemistry of the carboxylate group in **4b** is shown to be pseudo-equatorial. The system **4b** thus furnishes a unique NMR system for study in which a 1,4-dihydrobenzene ring is strongly puckered, the 1 substituent is not in the pseudo-axial orientation, and there exist two homoallylic protons to the 1 substituent.

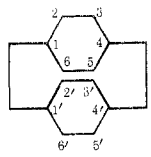
It has recently been shown[2] that the tetrahydro Birch reduction product of [2.2]paracyclophane (**1**) is *dl* (**2**) with the double bonds on each deck only partially overlapping.



1 **2**

This structure elucidation was accomplished by means of the proton NMR analysis of the tetraepoxide derivative of **2**. Because this analysis embodied a complex and involved argument, it seemed desirable to demonstrate that this stereochemistry[3] prevailed in another system which could be analyzed in a more straightforward fashion. Because of the ease of the Birch reduction of aromatic carboxylic acids and because of the synthetic availability of [2.2]paracyclophane-2-carboxylic acid (**3**), we chose to study the Birch reduction of **3**. An additional attractive feature of working with **3** would be the possibility of obtaining in the Birch reduction product a unique 1,4-dihydro-1-benzoic acid moiety forced into a puckered conformation and amenable to proton NMR analysis. In particular, if kinetic control would prevail, as expected, the approach of the hydrogen would occur from the top of **3** to force the carboxylate into a pseudo-equatorial orientation, contrasted with previous studies where the substituent was pseudo-axial.[4]

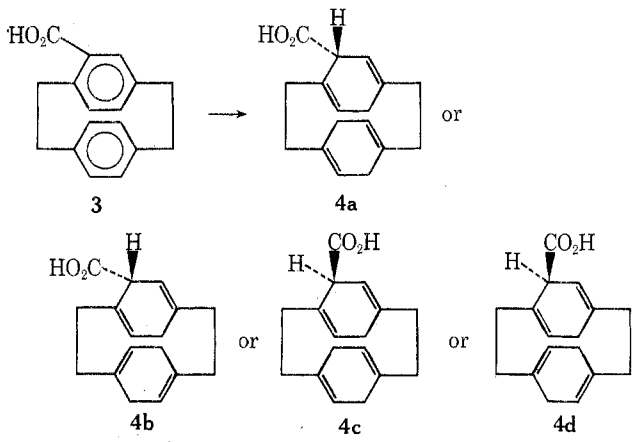
General Considerations. In this paper we shall use the numbering scheme shown by **1a**. This numbering scheme



1a

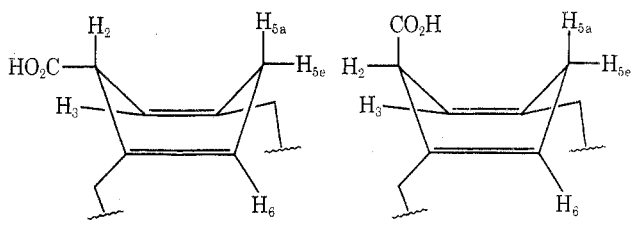
differs from that of Cram[5] in that our [2.2]paracyclophane-2-carboxylic acid would be named by his method [2.2]paracyclophane-4-carboxylic acid. This new numbering scheme was adopted so as to allow facile nomenclature involving stereochemical[3] comparison between the two decks. Assuming that the reduction of the top ring of **3** would go 1,4 to the carboxylate group, there would a priori exist four possible products (see **4a–d**). In **4a,b** the carboxylate group is pseudo-equatorial and in **4c,d** is pseudo-axial. In **4a** and **4c** the double bonds are "eclipsed" (i.e., the double bonds in the upper deck overlie those in the lower deck); in **4b** and **4d** the double bonds are "staggered" (i.e., the double bonds in the upper deck only partially overlap those of the lower deck).

In any of the structures **4a–d**, the two decks would be expected to be puckered, for two reasons. (1) There would be a great deal of steric interaction between the two decks of **4**. (This steric interaction for [2.2]paracyclophane itself has been shown to be quite severe, leading to distortion of the aromatic rings.)[6] Inspection of models of **4a–d** suggests that this steric difficulty is greatly relieved by puckering, which increases the distance between the two decks. (2) NMR analysis of the tetraepoxide derivative of **2** shows[2] that at least in this compound the decks are indeed strongly puckered.



3 **4a** **4b** (found) **4c** **4d**

The puckered top deck of **4** is shown in **5a,b**. In **5a** the carboxylate group is pseudo-equatorial (corresponding to **4a,b**) and in **5b** is pseudo-axial (corresponding to **4c,d**).



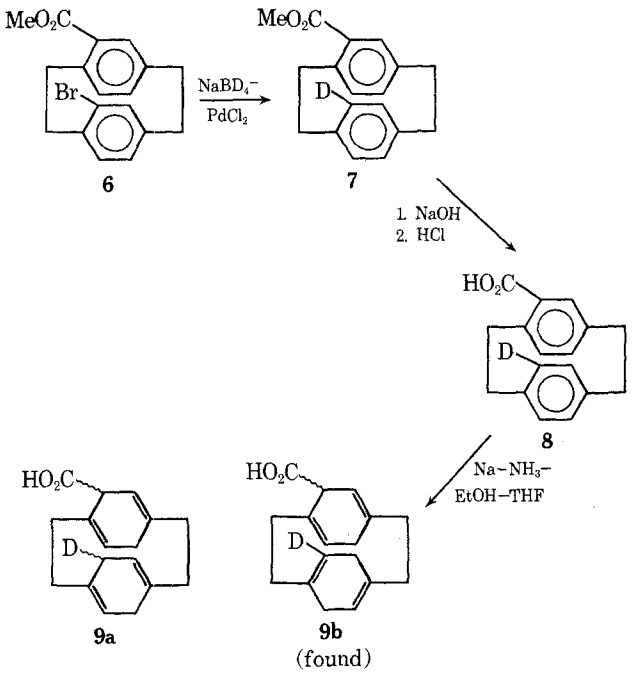
5a **5b**

Birch Reduction of 3 and Subsequent Structure Elucidation. The Birch reduction of **3** gave **4** in 85% yield, mp 158–159°; the elemental analysis and mass spectrum indicated that four hydrogens had been added, and the ultraviolet spectrum of **4** showed no conjugated chromophore (the uv spectrum was quite similar to that of **2**[7]). By catalytic dehydrogenation **4** could be reconverted to **3**. The only structures so far consistent with these data were **4a–d**.

The sharp melting point of **4** and the existence of only one methine (H_2) absorption in the proton NMR spectrum (δ 3.25) indicated that one isomer predominated.

In an attempt to elucidate the structure of **4** in a manner similar to that of **2**, the synthesis of an epoxide derivative

Scheme I



of 4 was attempted.[2] However, treatment of 4 under epoxidation conditions resulted only in oxidation back to **3**.

Olefin Stereochemistry[3] Elucidation. An umambiguous assignment of the stereochemistry[3] of the olefins of 4 was afforded by the Birch reduction of the pseudo-*gem*-deuterio derivative **8**. Scheme I shows the reasoning behind this approach. The compound 2′-bromo-2-carboxymethyl-[2.2]paracyclophane (**6**), prepared according to the procedure of Cram,[8] would be treated with sodium borodeuteride–palladium chloride according to the procedure of Bosin[9] to give **7**. Saponification of **7** would give **8**. The Birch reduction of **8** would give **9**, whose deuterium would be aliphatic in **9a** (the "eclipsed" isomer) or olefinic in **9b**, (the "staggered" isomer). Proton NMR spectroscopy would easily distinguish between **9a** and **9b**.

The product **7** actually obtained upon the indicated treatment of **6** indicated clean substitution of a deuterium at the 2′ position: the mass spectral analysis of **7** showed 97% d_1 deuterium incorporation and the NMR spectral pattern of **7** lacked a one-proton absorption that the methyl ester of **3** possessed at the highest field part of the aromatic region (the shielding cone of the carboxyl group would be most effective for the 2′ proton).[10] The aromatic NMR pattern of **8** was the same as that of **7**.

The Birch reduction of **8** gave **9** in 91% yield. The comparison of the NMR spectrum of **9** with that of the nondeuterated analog **4** is shown in Figures 1a and 1b. The aliphatic regions of the NMR spectra of **4** and **9** were virtually identical, whereas the olefinic regions were different: the olefin region of **4** showed three signals at δ 5.30, 5.45, and 5.75 integrating for 1:2:1 (within 5%) while that of **9** showed the same three regions integrating for 1:1:1 (within 5%). [The olefinic proton NMR assignments that appear in Figure 1 follow from consideration of the respective coupling patterns (vide infra).] Thus, the correct choice for **9** was **9b**; isomers **4a** and **4c** were eliminated from consideration; and it was concluded that the Birch reduction product **4** had the double bonds "staggered" (either **4b** or **4d**).

Choice of the Correct Epimer 4b or 4d. The two structures remaining as candidates for **4** were the epimers **4b** or **4d**. Choice of the correct epimer was possible by an NMR study of **4**, including selective decoupling experiments,

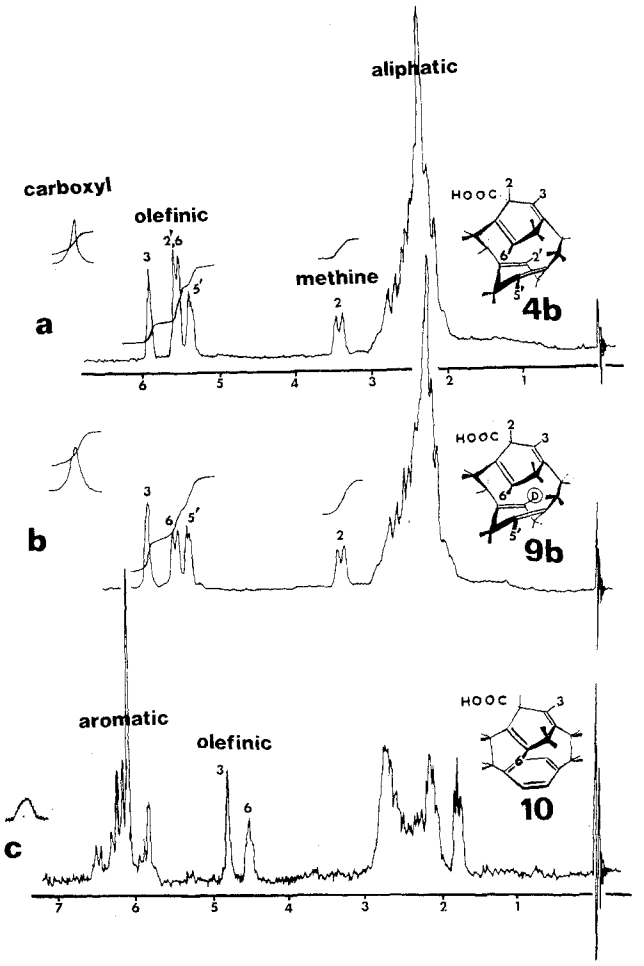
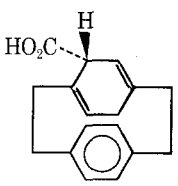


Figure 1. 100-MHz proton NMR spectra of various Birch reduction products of [2.2]paracyclophane-2-carboxylic acid: **4b** (a), **9b** (b), and **10** (c).

while using **5a** and **5b** as geometrical models for **4b** and **4d**, respectively. A ten-step argument follows that allows assignments for each of the olefinic signals appearing in Figure 1 and which allows unequivocal assignment of **4b** (**5a**) as the complete structure of **4**.

(1) The 2′ proton was obviously one of the signals at δ 5.54, since this proton signal disappeared upon deuterium substitution (Figure 1b). (2) The methine proton (H_2) appeared as a doublet with J = 8.8 Hz (see Figure 1). If the correct choice of structures was **5b**, then this large coupling observed for H_1 should arise from the vicinal coupling between H_2 and H_3 (whose dihedral angle would approach 0°). However, irradiation of each of the olefin regions did not remove this coupling of 8.8 Hz (irradiation of the olefin signal at δ 5.91 *did* sharpen the doublet). This experiment established the carboxyl group as pseudo-equatorial. (3) Supporting the conclusion of 2, irradiation of the methine proton did not remove the large coupling of any of the olefin signals (but did sharpen the appearance of the δ 5.91 signal). (4) It thus appeared that the δ 5.91 signal was H_3 and that the dihedral angle of H_3 and H_2 was far from 0° and was closer to 90° (i.e., the correct structure was **5a**). One would in fact expect H_3, vicinal to the electronegative carboxylate group, to be the furthest downfield olefin signal. (5) The other olefinic protons of **4**, however, would each be eclipsing (at least approximately) a methylene proton and therefore would have large splitting. This is what was observed (see Figures 1a and 1b). (This argument assumes that the bottom deck is puckered also.). (6) To confirm that the large splittings of these three olefinic protons

were due to coupling with the methylene protons, various frequencies in the methylene region were irradiated. Indeed, irradiation at δ 2.4 collapsed the patterns at δ 5.37 and 5.54 to broad singlets. (7) This same irradiation at δ 2.4 collapsed H_2 to a singlet. Thus, this splitting was undoubtedly due to homoallylic coupling with one of the H_5 protons.[11] (8) To differentiate between the two remaining unassigned olefin signals (H_6 and $H_{5'}$) experiment 3 was repeated with special attention devoted to the signals at δ 5.54 and 5.37. The H_6 proton should engage in allylic coupling with H_2 whereas the $H_{5'}$ proton could not. When H_2 was irradiated, there was slight sharpening in the δ 5.54 region while the δ 5.37 region was unchanged. Thus, H_6 was assigned as one of the protons at δ 5.54 and $H_{5'}$ was assigned as the δ 5.37 signal. (9) Being closer to the carboxyl group, H_6 would be expected to be downfield from $H_{5'}$. These were in fact the assignments made in 8 immediately above. (The fact that the 2′ proton is no longer the highest field olefin proton suggests that the carboxyl group is rotated to a different orientation in **4** from that in **3**.) (10) When the dihydro Birch reduction product of **3** was made (see **10**)—the synthetic intermediate during the reduction of **3**



10

to produce **4**—it was observed in the proton NMR spectrum (see Figure 1c) that the downfield olefinic signal (H_3) was relatively sharp, again consistent with an approximately orthogonal relationship with H_2.

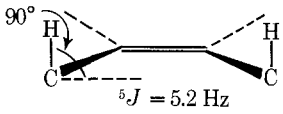
It had been originally hoped that a study of compound **10** would give more definitive stereochemical information. Unfortunately, the methine proton (H_2) had moved upfield and lay hidden under the broad aliphatic absorptions.

That the proton absorptions for H_2 and the olefinic protons H_3 and H_6 had all moved upfield suggested more severe steric compression[12] in **10** than in **4**; this is as expected, because the aromatic ring of **10** could not easily pucker.

Discussion

Stereochemistry[3] of Double Bonds. In the stepwise reduction of **3**, one would expect that the top ring would be reduced first, since the carboxylate group would activate this ring to Birch reduction. Indeed, by using less sodium in the Birch reduction of **3**, the 2,5-dihydro product **10** was isolated. In the mechanistic steps from **10** to **4**, the carboxylate groups should now not influence the sterochemical course of the reduction, since the carboxylate group is now no longer conjugated with the π system. Thus, further reduction of **10** should proceed just as it would without the carboxylate group, and the final product **4** should have the same olefinic stereochemistry[3] as the Birch reduction product **2** of [2.2]paracyclophane (**1**). Indeed, CNDO/2 calculations based on likely intermediates during the reduction of **1** suggested[2] that the "staggered" arrangement should result, and this "staggered" stereochemistry[3] was concluded to prevail in the Birch reduction of both **1** and **3**. The conclusions of the present work thus corroborate those of the previous paper.

Homoallylic Coupling. Barfield and Sternhell have recently shown[13] that in homoallylic coupling (^5J HC–C=C–CH) an angular dependence should be observed whereby this coupling should increase as the H–C bonds become more nearly parallel to the p orbitals of the olefin. Examples **11** and **12** demonstrate the calculated extremes in $|^5J^{\pi}|$ for a cis olefin.



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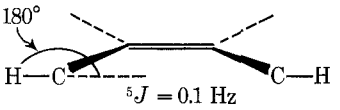
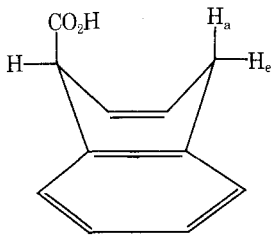
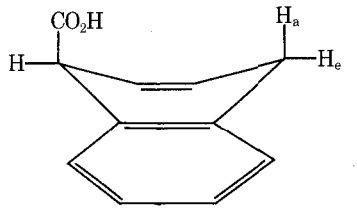


12

For a 1,4-cyclohexadiene, a double homoallylic path is possible and even larger ^5J values may be observed, but the same steric dependence should prevail. In view of this expectation, the homoallylic J values of 1,4-dihydronaphthoic acid[4] (**13**) appear anomalous: the NMR data strongly indicate a preference of the carboxylate group for a pseudo-axial conformation, but a pseudo-equatorial H_1 proton in a strongly puckered system (**13a**) should couple to an insignificant extent (<1 Hz) with the H_4 protons. Even in a "flattened boat" conformation (**13b**) the calculated ^5J

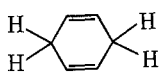


13a



13b

values are only about 1 Hz. The ^5J values actually observed for **13** are 3.8 and 4.4 Hz. Furthermore, for simple 1,4-dihydrobenzene derivatives (**14**), which apparently are flat,[14]



14

one would again predict a ^5J somewhat less (~5 Hz)[15] than the >8 Hz actually observed. One is thus faced with the choice that (1) the theoretical treatment is qualitatively correct for 1,4-cyclohexadienes but underestimates the ^5J values; or (2) for 1,4-cyclohexadienes an entirely new treatment is necessary. There is a priori no reason to believe that possibility 2 is correct. Thus, it would be desirable to obtain homoallylic ^5J values in 1,4-cyclohexadienes whose conformation would definitely predict a small ($\ll$1 Hz) coupling. The present study gives such an example.

As discussed above, the methine (H_2) NMR absorption of **4b** was a doublet of 8.75 Hz. Close inspection of this doublet at expanded scale and a careful LAOCOON III[16] study placed an upper limit of 1 Hz of the other couplings involving H_2. Considering the vicinal couplings involving H_2, that $^3J_{23}$ < 1 Hz indicates that the involved dihedral angle is very close to 90° and that the ring is definitely puckered with the carboxylate group pseudo-equatorial—compare this ^3J value with the analogous value in **13** (a "flattened boat"), 2.4 Hz, and in **14** (which is flat), 3.1 Hz.[14] This puckered conformation as shown in **5a** would from Barfield's treatment predict (1) $J_{2,5e}$ should be small (<1 Hz); (2) $J_{2,5a}$ (in **4b**) > ^5J (in **14**) > ^5J (in **13**). These predictions are in fact what are observed.

Therefore, the present work supports previous work[14] suggesting that 1,4-cyclohexadiene is not normally puckered and indicates that with highly puckered 1,4-cyclohexadienes significant homoallylic coupling will not occur with the pseudo-equatorial protons. The present work further supports qualitatively the theoretical homoallylic work of Barfield and Sternhell with regard to 1,4-cyclohexadienes.

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 237 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Jelco JNM-PS-100, with tetramethylsilane as an internal standard reference, utilizing field sweep internal lock mode. Elemental analyses were performed by C. F. Geiger, Ontario, Calif.

[2.2]Paracyclophane-2-carboxylic acid (3) was prepared according to the procedure of Cram.[5]

Birch Reduction of 3. Preparation of 2,5,3′,6′-Tetrahydro-[2.2]paracyclophane-(e)-2-carboxylic Acid (4b). Compound **3** (218 mg, 0.865 mmol) was dissolved in dry tetrahydrofuran in a 250-ml three-necked flask equipped with a mechanical stirrer. Liquid ammonia (75 ml) was distilled into the flask. Over a period of 1 hr, 400 mg of sodium in small pieces and 4 ml of absolute ethyl alcohol dropwise were added. After 3 hr of further stirring, the blue-brown color had disappeared. Ammonium chloride (1.5 g) was cautiously added followed by 60 ml of water. After standing overnight, the reaction mixture was mixed with 130 ml of ice–water and very carefully acidified to a pH of 4 with dilute hydrochloric acid. The tetrahydrofuran solvent was removed under vacuum, and the resulting residue was filtered, dissolved in chloroform, dried (magnesium sulfate), and concentrated to give 187 mg of white crystals (85%), mp 155–158°. Recrystallization from petroleum ether gave an analytical sample: mp 158–159°; ir (KBr) 795 cm^{-1}; NMR ($CDCl_3$) δ 2.1–2.9 (14 H, $-CH_2-$), 3.45 (d, J = 8.75 Hz, 1 H, H_2), 5.37 (m, 1 H, H_3), 5.54 (d, J = 8 Hz, 2 H, $H_{2'}$ and H_6), 5.91 (m, 1 H, $H_{5'}$), 10.1 (s, 1 H, CO_2H); mass spectrum m/e 256 (M^+); uv, end absorption to 240 nm. NMR is shown in Figure 1.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.30; H, 8.14.

Dehydrogenation of 4b. Compound **4b** (300 mg) was refluxed in 100 ml of dry benzene with 290 mg of 10% palladium on charcoal to give after filtering 250 mg (84%) of **3**, mp 190–195°, ir, NMR, and mass spectrum identical with those of authentic samples. Recrystallization from acetic acid gave a pure sample, mp 221–222° (lit. mp 222.5–224°), mmp 221–222°.

2′-Bromo-2-carboxymethyl[2.2]paracyclophane (6) was prepared according to the procedure of Cram[8] in 52% yield.

2′-Deuterio-2-carboxymethyl[2.2]paracyclophane (7). To a stirring mixture of 700 mg of **6**, 50 ml of methanol-*O*-*d*, and 720 mg of predried palladium chloride, held at 40°, was added 849 mg of sodium borodeuteride in portions over a period of 15 min. After a subsequent 1 hr of stirring, the stirring mixture was immersed in a constant-temperature water bath at 80° for 5 min. Immediately after, the stirring mixture was immersed in an ice–water bath and 70 ml of 0.7 N hydrochloric acid was added. The alcohol was removed under vacuum and the product was dissolved in chloroform. This chloroform solution was dried (magnesium sulfate) and concentrated under vacuum to give 490 mg (90%) of **7**, mp 135–138° (lit. mp of nondeuterated compound, 139–140°).[8] The mass spectrum indicated 97% deuterium incorporation. The NMR was complex but lacked a signal integrating for 1 H that existed at the highest field portion of the aromatic region in the nondeuterated compound.

2′-Deuterio[2.2]paracyclophane-2-carboxylic Acid (8). Compound **7** (400 mg) was refluxed in 100 ml of 0.25 N sodium hydroxide in 5:1 methanol–water for 4 hr. The mixture was cooled and dilute hydrochloric acid was added to precipitate the product **8**. The product was collected by filtration and recrystallized from acetic acid to give 361 mg (95%) of **8**, mp 220–222° (lit. mp of nondeuterated compound, 222.5–224°).[5] The NMR was virtually identical with that of **7** in the aromatic region.

2′-Deuterio-2,5,3′,6′-tetrahydro[2.2]paracyclophane-2-carboxylic Acid (9b). The procedure used to reduce **8** to give **9** was identical with that for the nondeuterated (**3** → **4**) compounds. In such a manner was obtained 320 mg (91%), mp 156–158.5°. The NMR lacked an olefinic signal that existed for **4** (see Figure 1); mass spectrum m/e 257 (M^+).

2,5-Dihydro[2.2]paracyclophane-2-carboxylic Acid (10). Compound **3** was reduced in a manner identical with that to obtain **4** except that only 9% the sodium was used as for **4** (only the reactive carboxyl aromatic ring is reduced here, and accordingly only a small amount of sodium is required). In such a manner was obtained 177 mg (86%): mp 152–153.5°; NMR ($CDCl_3$) δ 1.75–2.95 (13 H, $-CH_2-$ and H_2), 4.59 (m, 1 H, H_6), 4.85 (broad s, 1 H, H_3), 9.65 (s, 1 H, CO_2H); mass spectrum m/e 254 (M^+).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.34. Found: C, 80.31; H, 7.56.

Attempted Epoxidation of 4b. The same procedure was used as for **2**.[2] In such a manner was obtained a 80:20 mixture of **4b:3**.

Acknowledgments. The authors gratefully acknowledge the financial support of the Robert A. Welch Foundation, Grant No. B-325, and of North Texas State University Faculty Research.

Registry No.—**3**, 18931-39-0; **4b**, 54844-44-9; **6**, 24417-98-9; **7**, 54910-36-0; **8**, 54910-37-1; **9b**, 54910-38-2; **10**, 54844-45-0.

References and Notes

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(2) J. L. Marshall and B.-H. Song, *J. Org. Chem.*, **39**, 1342 (1974).
(3) As a referee pointed out, there is a question whether "stereochemistry" or "structure" is correct here. We prefer "stereochemistry", because in principle the two possible double bond arrangements—"eclipsed" (**4a** or **4c**) and "staggered" (**4b** or **4d**)—can be introconverted by rotation of one of the decks. For an example, see G. C. Whitesides, B. A. Pawson, and A. C. Cope, *J. Am. Chem. Soc.*, **90**, 639 (1968).
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(11) The only other possibility would be a four-bonded coupling of H_2 with a bridging methylene proton. However, this is not a reasonable possibility because (1) such a large $^4J_{HH}$ value is unprecedented; (2) the geometry is wrong anyway (ref 10, p 143).
(12) There is some question whether this effect is from steric compression directly or from the shielding effect of the aromatic ring currents (ref 10, p 65). We prefer the former explanation, because the protons in question are on the *periphery* of the ring. In any case, that protons become shielded as the rings in [*m,n*]paracyclophanes approach one another is well established: D. J. Cram and L. A. Singer, *J. Am. Chem. Soc.*, **85**, 1084 (1963); D. J. Cram and R. C. Helgeson, *ibid.*, **88**, 3515 (1966).
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(15) This approximate value is obtained by assuming a normal tetrahedral H_4–C–H_4 angle of 110°, by then taking the calculated $^5J_{HH}$ value for this geometry, and by then doubling to account for the two olefins.
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