contaminated with a little **11**. Chromatography of the filtrate using hexane–benzene (1:1) as eluent gave 0.5 g of additional **20**. Recrystallization from methylene chloride gave 1.30 g (50%) of pure **20** as white needles, mp 423–424 °C; ^{1}H NMR δ 7.07–7.22 (m, 20 H); mass spectrum, m/e (relative intensity) 542 (21), 540 (47), 538 (20), 380 (38), 302 (45), 273 (21), 271 (47), 269 (21), 182 (100), 181 (97). Anal. Calcd for $C_{30}H_{20}Br_2$: C, 66.69; H, 3.72. Found: C, 66.40; H, 3.81.

Reaction of 1,4-Dibromo-2,3,5,6-tetrachlorobenzene with Phenylmagnesium Bromide. The typical procedure was followed, by using 5 mmol of **30**,[16] 40 mmol of phenylmagnesium bromide and a reaction time of 16 h at room temperature. The usual workup afforded 2.1 g of crude solid product which was chromatographed on silica gel to give first, with petroleum ether as the eluent, 0.66 g (61%) of 1,2,4,5-tetrachlorobenzene which was recrystallized from benzene, mp 138–140 °C (lit.[18] 139–140 °C). Further elution with benzene–petroleum ether (v:v = 40:60) gave 0.69 g (36%) of 1,2,4,5-tetraphenylbenzene with properties identical with those described above.

Reaction of Bromopentachlorobenzene (32) with Phenylmagnesium Bromide. The typical procedure was followed, using 1 mmol of **32**[19] suspended in 10 mL of THF added over 10 min to 8 mmol of phenylmagnesium bromide in 40 mL of THF, with a reaction time of 13 h at room temperature. The usual workup gave, after chromatography on silica gel with hexane as eluent, 225 mg (90%) of pentachlorobenzene. The product was recrystallized from benzene–ethanol to give white needles, mp 84–85 °C (lit.[20] 85–86 °C). No terphenyl was isolated on further elution of the silica gel column.

Data for New Compounds in Table I. 1,2,4,5-Tetra-*p*-tolylbenzene (12): ^{1}H NMR: δ 2.33 (s, 12 H), 7.02–7.12 (m, 16 H), 7.48 (s, 2 H); mass spectrum m/e (relative intensity) 440 (5), 439 (36), 438 (M^+, 100), 219 (5), 204 (13), 196 (16), 189 (16), 130 (18), 85 (20). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 93.15; H, 6.91. **1,2,4,5-Tetra-*m*-tolylbenzene (13)**: ^{1}H NMR: δ 2.27 (s, 12 H), 6.95–7.15 (m, 16 H), 7.50 (s, 2 H); mass spectrum, m/e (relative intensity) 440 (5), 439 (27), 438 (M^+, 100), 423 (4), 407 (4), 219 (9), 189 (50). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 92.91; H, 6.91. **1,2,4,5-Tetra-*o*-tolylbenzene (14)**: ^{1}H NMR δ 2.0–2.3 (very broad s, 12 H), 6.88–7.16 (m, 16 H), 7.26 (s, 2 H); at 275 K the methyl signal separates into five peaks and below 250 K into eight peaks;[10] mass spectrum, m/e (relative intensity) 440 (5), 439 (32), 438 (M^+, 100), 423 (4), 397 (2), 347 (4), 333 (4), 219 (40), 189 (16). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 92.94; H, 6.81. **1,2,4,5-Tetramesitylbenzene (15)**: ^{1}H NMR δ 1.99 (s, 24 H), 2.21 (s, 12 H), 6.73 (s, 8 H), 7.05 (s, 2 H); mass spectrum m/e (relative intensity) 552 (6), 551 (25), 550 (M^+, 88), 535 (12), 520 (3), 430 (3), 275 (4), 85 (100). Anal. Calcd for $C_{42}H_{46}$: C, 91.58; H, 8.42. Found: C, 91.56; H, 8.38. **1,2,4,5-Tetra-1′-naphthylbenzene (16)**: ^{1}H NMR δ 8.03–8.16 (m); mass spectrum, m/e (relative intensity) 584 (2), 583 (11), 582 (M^+, 23), 455 (1), 291 (5), 87 (32), 85 (100). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.66; H, 5.24. **1,2,4,5-Tetra-2′-naphthylbenzene (17)**: ^{1}H NMR δ 2.29 (dd, 4 H), 7.42–7.46 (m, 8 H), 7.59 (d, 4 H), 7.75–7.77 (m, 8 H), 7.85 (s, 2 H), 7.96 (s, 4 H); mass spectrum, m/e (relative intensity) 584 (7), 583 (27), 582 (M^+, 76), 491 (3), 455 (9), 415 (12), 291 (18), 126 (84), 40 (100). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.48; H, 5.23. **1,2,4,5-Tetra-*p*-biphenylylbenzene (18)**: ^{1}H NMR δ 7.32–7.72 (m); mass spectrum, m/e (relative intensity) 686 (M^+, 14), 44 (100). Anal. Calcd for $C_{54}H_{38}$: C, 94.42; H, 5.58. Found: C, 94.26; H, 5.69. **1,2,4,5-Tetra-*m*-biphenylylbenzene (19)**: ^{1}H NMR δ 7.37–7.63 (m, 36 H), 7.73 (s, 2 H); mass spectrum, m/e (relative intensity) 688 (5), 687 (20), 686 (M^+, 58), 595 (4), 143 (8), 77 (11), 57 (12), 55 (12), 44 (100). Anal. Calcd for $C_{54}H_{38}$: C, 94.42; H, 5.58. Found: C, 94.25; H, 5.73. **1,4-Dibromo-2,3,5,6-tetra-*m*-tolylbenzene (21)**: ^{1}H NMR δ 2.22 (s, 6 H), 2.23 (s, 6 H), 6.82–7.00 (m, 12 H), 7.02–7.12 (m, 4 H); mass spectrum, m/e (relative intensity) 598 (16), 596 (50), 594 (22), 436 (17), 420 (11), 218 (11), 210 (29), 203 (33), 202 (23), 201 (15), 200 (12), 195 (100), 188 (47), 187 (21), 182 (30), 163 (22). Anal. Calcd for $C_{34}H_{28}Br_2$: C, 68.47; H, 4.73. Found: C, 68.62; H, 4.74. **1,4-Dibromo-2,3,5,6-tetra-*o*-tolylbenzene (22)**: ^{1}H NMR (300 K) δ 2.11, 2.16, 2.19, 2.25, 2.28 (singlets of nonintegral intensity, 12 H), 6.85–7.15 (m, 16 H); in Me_2SO, 7 peaks are seen which change relative intensities but do not change in number up to 440 K;[10] mass spectrum, m/e (relative intensity) 598 (19), 596 (37), 594 (19), 437 (15), 436 (38), 252 (30), 163 (62), 91 (100). Anal. Calcd for $C_{34}H_{28}Br_2$: C, 68.47; H, 4.73. Found, C, 68.55; H, 4.76. **2,3,5,6-Tetra-*m*-anisylbenzene (23)**: ^{1}H NMR δ 3.63 (s, 12 H), 6.8–7.3 (m, 16 H), 7.56 (s, 2 H); mass spectrum, m/e (relative intensity) 504 (8), 503 (37), 502 (M^+, 100), 396 (2), 78 (8), 43 (9). Anal. Calcd for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02. Found: C, 81.19; H, 6.06.

Acknowledgment. We are indebted to the National Institutes of Health GM15997 for financial support of this research. K.H. also thanks UBE Industries for a leave of absence. We also thank Mr. Chin-hahn Suh for performing preliminary experiments.

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Synthesis and Chiroptical Properties of 5,7-Dioxobicyclo[2.2.2]oct-2-ene and Bicyclo[2.2.2]octane-2,5-dione

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Received June 24, 1985

5,7-Dioxobicyclo[2.2.2]oct-2-ene (**5**) and its dihydro derivative **9** were obtained in racemic form by sequential Diels–Alder addition of maleic anhydride to hydroquinone, hydrolysis of the adduct to diacid **7**, oxidative decarboxylation of **7** with lead tetraacetate, and catalytic hydrogenation. Partial resolution of **7** with brucine or quinine afforded (−)-**5** in 80–86% enantiomeric purity. Ketalization of (±)-**5** with diethyl (*R,R*)-(+)-tartrate and subsequent chromatographic separation of the diastereomeric monoketals gave optically pure samples of both antipodes of the enedione. This substance was found to interact powerfully with plane and circularly polarized light. The Cotton effects observed in the ORD and CD spectra of (−)-**5** indicate that its absolute configuration is 1*S*,4*S* when analyzed by the generalized octant rule. It follows that (−)-**9**, its hydrogenation product, is 1*R*,4*R*.

Interest has continued to surround dissymmetric molecules that possess a C_n (Schoenfliess notation) axis of symmetry.[4] Well-known members of this class include spiro compounds (e.g., **1**),[5] allenes such as **2**,[6] and biphenyls

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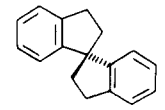
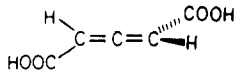
of type **3**.[7] Bicyclic 2,5-diones of general formula **4** also have this property. Although the bridgehead carbon at-



1



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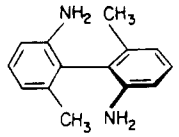
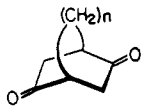


3



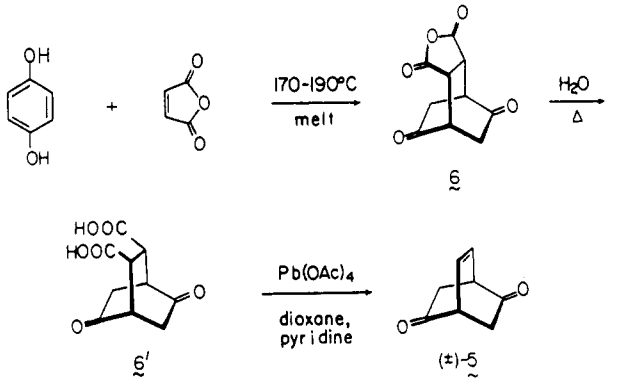
4

oms in **4** have four different groups attached to them and may appear to be asymmetric, their distribution in space engenders a C_2 axis that bisects the dihedral angle of the planes containing the bridgehead carbons and carbonyl groups. Thus, the point group is dissymmetric (C_2), not asymmetric (C_1), and the asymmetry is associated with the molecule as a whole.

Rotation of plane-polarized light occurs when the interaction of photons and electrons in a dissymmetric environment causes electric and magnetic moment changes that are not orthogonal.[8] Dextrorotation occurs if these effects are parallel and levorotation occurs if they are antiparallel. Usually these effects arise from structural features that impose a "twist" or helical activity to the motions of electrons in the molecule.[9] Right-handed helical motion results in dextrorotation at long wavelength.[9] Helical motion arising from σ electrons is usually small and difficult to predict accurately. Helical motion arising from π electrons is much larger and dominates the effects from σ electrons.[10] The best examples of these helical effects are the hexahelicenes, for example, hexahelicene $[\theta]_D = +12\,200°$ ($CHCl_3$).[11]

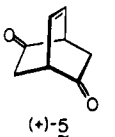
5,7-Dioxobicyclo[2.2.2]oct-2-ene (**5**) has three chromophores, two carbonyl groups symmetrically distributed (C_2 axis) about a double bond which is β,γ to both keto functions. Although the carbonyl groups are equivalent, they could conceivably interact with light either essentially independently or cooperatively through π transmission (homoconjugation) or as coupled oscillators. The rotations and Cotton effects should be large since this molecule represents a twisted π framework of almost maximum twist. In addition, it is known[10] that inherently dissymmetric chromophores have high molecular amplitudes in rotatory curves as opposed to asymmetrically perturbed chromophores such as 3-methylcyclohexanone, which have small to moderate molecular amplitudes. The original octant rule for cyclohexanones[12] was based on the idea of an asymmetrically perturbed symmetric chromophore. An extended octant rule has since been proposed[13] which

Scheme I



allows predictions of absolute configuration based on the sign of the long-wave Cotton effect for α,β-unsaturated ketones, 1,3-dienes, β,γ-unsaturated ketones, and 1,4-dienes.

On the latter basis, it can be predicted that (+)-**5** and (−)-**5** should have the absolute configurations shown. We can also forecast that the long-wave Cotton effect will be fine-structured and of high magnitude. Herein are de-



(+)-5

(−)-5

scribed the successful resolution of **5** into its antipodes and the chiroptical properties of this optically active bicyclic diketone. Until now the only report of optically active **5** was an experiment in which one enatiomer of **5** was generated in 3.5% optically purity by preferential photodestruction of the 1*S*,4*S* enantiomer by right circularly polarized light.[14]

Synthetic Considerations. The target molecule is available in racemic form via the three-step sequence outlined in Scheme I. Although the Diels–Alder cycloaddition between hydroquinone and maleic anhydride[15] proceeds in low yield (11% maximum), the starting materials are inexpensive, product purification is straightforward, and the reaction can be carried out on relatively large scale. The initially reported[16] lead tetraacetate oxidation of diacid **6′** gave low yields, and application of the Wolinski modification[17] did not noticeably improve matters. However, the procedure described by Jefford[18] repeatedly afforded (±)-**5** in approximately 30% yield.[19,20] Accompanying formation of the desired enedione in this latter reaction is 2-acetoxydioxane, which arises from oxidation of the solvent.

Our initial efforts to achieve resolution focused on separation of the diastereomeric quinine and brucine salts of **6′**. Although the necessary recrystallizations proceeded

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(2) The Ohio State University.
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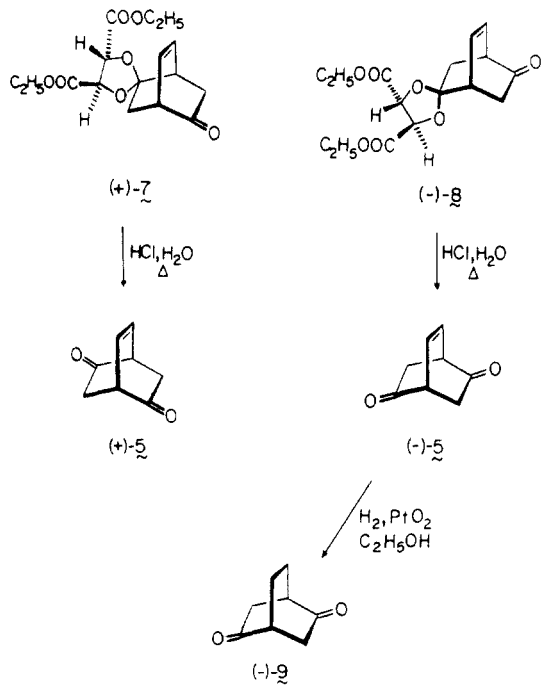
Scheme II



satisfactorily, difficulty was encountered in recovering the resolved diacid. However, this complication was conveniently circumvented by evaporation of the solvent following decomposition of the amine salt and direct $Pb(OAc)_4$ oxidation of the residue. Moreover, direct oxidation of the quinine or brucine salt could be applied to deliver optically active **5** in 15–20% yield.

The resolved enedione displayed the same high rotation whether prepared from the brucine ($[\alpha]^{30}_D$ −1030° (*c* 0.036, cyclohexane)) or quinine salt ($[\alpha]^{30}_D$ −1013° (*c* 0.032, cyclohexane)). Although these findings suggested that the optical purity of (−)-**5** was probably substantial, no knowledge of the precise % enantiomeric excess was in hand. An alternative protocol capable of providing this information was consequently devised.

To this end, racemic **5** was ketalized with an equimolar quantity of diethyl (*R,R*)-(+)-tartrate in refluxing xylene containing *p*-toluenesulfonic acid as catalyst.[21] Separation of monoketals **7**/**8** (Scheme II) from other contaminants was easily accomplished by medium-pressure liquid chromatography. The monoketals eluted first, followed in turn by a diastereomeric mixture of bisketals and finally (at higher solvent polarity) unreacted **5** and diethyl tartrate. The individual monoketals were less easily separated on a preparative scale. However, this could be accomplished by peak shaving techniques combined with resubmission to chromatography. The diastereomeric purities of **7** and **8** were confirmed as 100% by analytical HPLC on silica gel under conditions where base line separation between them was consistently realized. The optical rotations of the less polar ketal **8** and its diastereomer **7** were found to be $[\alpha]^{27.8}_D$ −308° (*c* 0.041, CH_3CN) and $[\alpha]^{27.8}_D$ +223° (*c* 0.093, CH_3CN).

The monoketals were hydrolyzed to the enantiomerically pure enediones by heating in 10% hydrochloric acid. The white crystalline solids were isolated by sublimation. Levorotatory ketal **8** afforded (−)-**15**, $[\alpha]^{29.5}_D$ −1257° (*c* 0.0015, cyclohexane). Likewise, dextrorotatory ketal **7** produced (+)-**5**, $[\alpha]^{29.5}_D$ +1252° (*c* 0.0012, cyclohexane).

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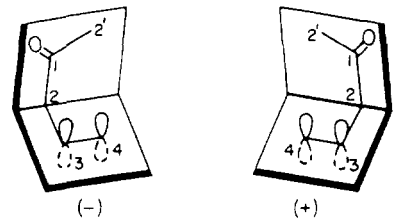


Figure 1. Geometries applicable to utilization of the extended octant rule.

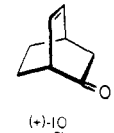
Optical rotation measurements on carbon tetrachloride solutions also gave large values for these diketones. The samples produced by resolution of diacid **7** were therefore of 80–86% enantiomeric purity.

The melting points of (+)-**5** and (−)-**5** were identical (88–89.5 °C) but depressed from that reported for the racemic material (97–99 °C).[16] The 300-MHz ^1H NMR spectra of the optical isomers matched that of the original racemic **5**. Hydrogenation of (−)-**5** over platinum oxide at 15 psi afforded (−)-**9** quantitatively. The absolute configuration of this saturated compound, whose maximum rotation at the D line in cyclohexane is −49.7°, follows from that of (−)-**5**.

Chiroptical Properties. The levorotatory enedione was observed to exhibit a negative Cotton effect of high magnitude (ORD molecular amplitude of 90 400 and CD molecular ellipticity of 55 800 in cyclohexane).[22] The long-wave carbonyl absorption displayed the enhanced intensity characteristic of β,γ-unsaturated ketones, reflecting a strengthened n,π^* transition. The four absorptions near 283, 292, 312, and 322 nm have previously been identified as characteristic of the strengthened n,π^* transitions in β,γ-benzo ketones.[23]

The sign of the Cotton effect was used to determine the absolute configuration of homoconjugated ketone **5** by applying the generalized octant rule. As seen in Figure 1, the two planes are defined by the groups $O–C_1–C_2$ and $C_2–C_3–C_4$, which intersect at an angle greater than 90° (120° for **5**). The first dissymmetric conformation shown should give rise to a negative Cotton effect and its mirror image to a positive one. This analysis correctly predicts the absolute configuration of dehydrocamphor ($[\alpha]_D$ −735° (C_2H_5OH)), which was established independently by its hydrogenation[24] to (+)-camphor.[25]

The molecular amplitude (Figure 2) and molecular ellipticity (Figure 3) of (−)-**5** correlate well with values determined for (−)-bicyclo[2.2.2]oct-5-en-2-one (**10**; molecular amplitude = 5.2×10^4 and $[\alpha]_{max} = 3.35° \times 10^4$).[26,27] The



(+)-10

absolute configuration of (+)-**10** has been independently assigned by Walborsky[28] and by Berson[29] and appears ironclad. Relevantly, (−)-**5** has approximately twice the

(22) Samples of (−)-**5** prepared by resolution of diacid **7** were utilized for these measurements.

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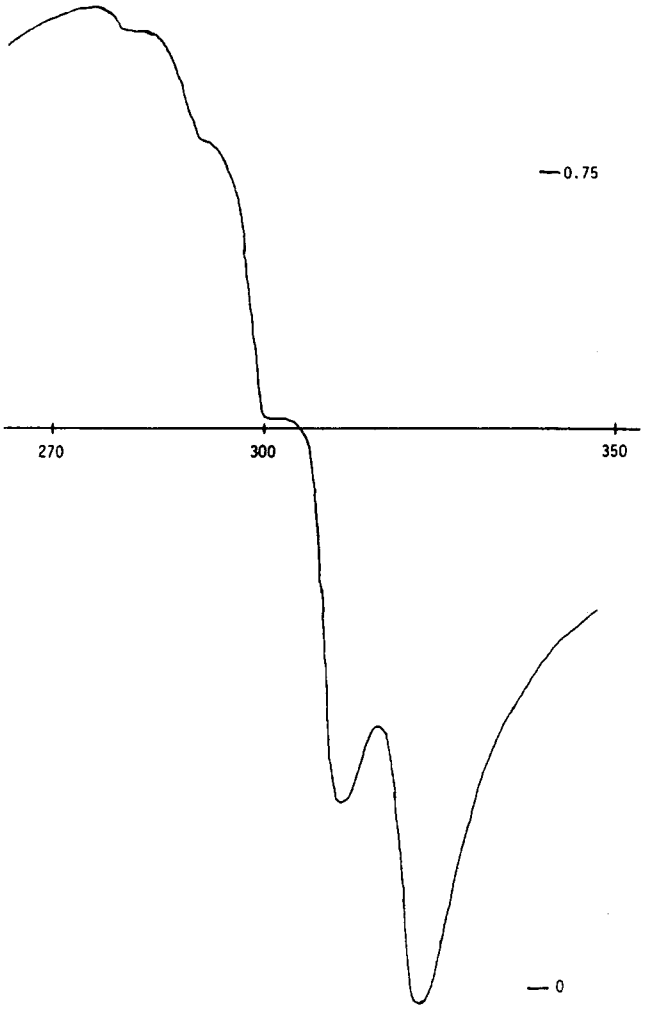

Figure 2. ORD of (−)-**5** (*c* 0.0056 in cyclohexene), 0.4° full scale.

optical rotation of (+)-**10**, and its ORD curve is enantiomeric with that of (+)-**10**, as fully anticipated.

Since hydrogenation of (−)-**5** has given rise to (−)-**9**, it becomes possible to check for consistency by applying the restricted octant rule for cyclohexanones to predict the sign of the Cotton effect for **9**. Contributions can be seen in the lower left rear and upper right rear octants. Both of these octants induce negative Cotton effects, in full support for the absolute configurational assignment to (−)-**9**. The ORD and CD curves are reproduced in Figures 4 and 5. Also, the maximum rotation of this saturated diketone ($[\alpha]_{589}$ −49.7°) agrees well with the specific rotation of norcamphor (+31°).[26]

We note in passing that since the C_2 axis in **5** and **9** produces equivalent carbonyl groups, a chiral shift reagent study would be nonproductive. This technique requires enantiotopic groups to be successful.[30]

Enedione **5** holds the interesting prospect of serving as a direct precursor to optically active barrelenes, thus opening up this system to chiroptical investigation. Studies in this direction have been initiated.

Experimental Section

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (6). A number of runs were made, the lowest yield obtained being 3.6% and the highest 11.4%; the average yield was about 8%. A typical run is described below.

Maleic anhydride (500 g, 5.2 mmol) was placed in a 3-L flask equipped with a reflux condenser, mechanical stirrer and provision for addition of a solid, i.e., an Erlenmeyer flask attached by Gooch tubing. The flask was gently heated under nitrogen until all of the maleic anhydride had melted. Hydroquinone (330.33 g, 3 mol) was added in small portions when the temperature had reached 140 °C, and the temperature was kept below 170 °C until addition was complete and then raised to 190 °C and kept constant for 6 h. The reaction mixture was allowed to cool to about 60 °C, and then 300 mL of ethyl acetate and 700 mL of ether were added and kept at reflux for 30 min. After cooling, the insoluble anhydride (46.9 g) mp 265–270 °C, was collected by filtration: IR (KBr) 2960, 1870, 1800, 1720, 1400, 1330, 1305, 1215, 1185, 1100, 1080, 1040, 960, 920, 865, 810, 775, 740, 720, 695 cm^{-1}. An NMR spectrum was difficult to obtain, as **6** resists dissolution in the common NMR solvents. A spectrum was finally obtained in

(30) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1.

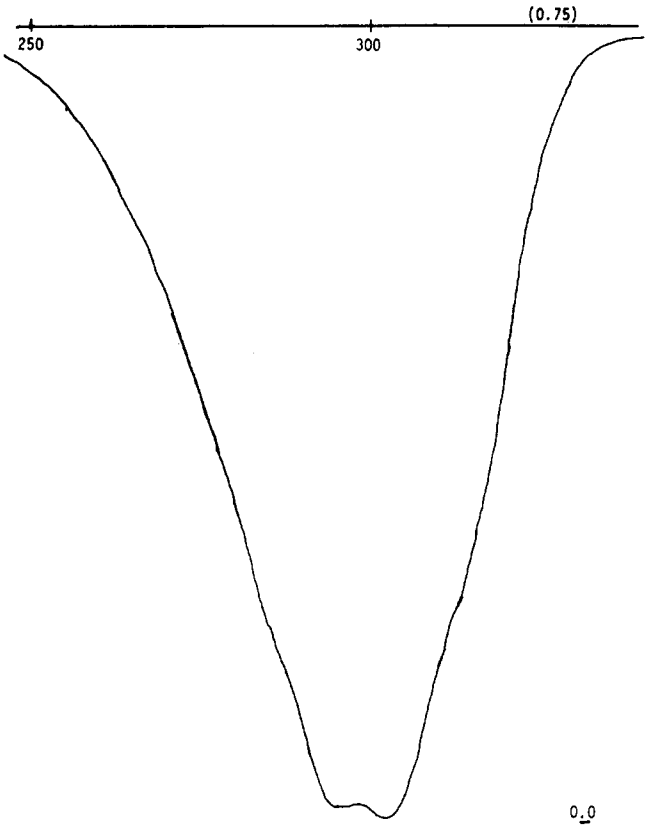

Figure 3. CD of (−)-**5** (*c* 0.036 in cyclohexane), 2° full scale.

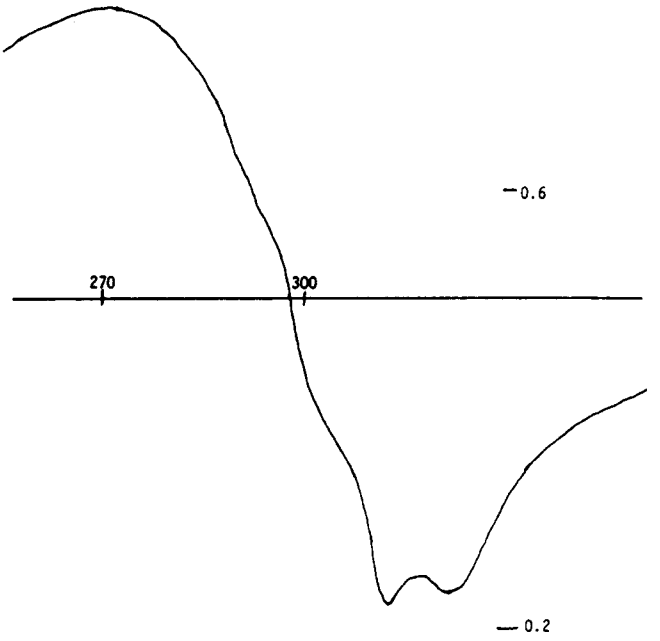

Figure 4. ORD of (−)-**9** (*c* 0.45 in cyclohexane), 2° full scale.

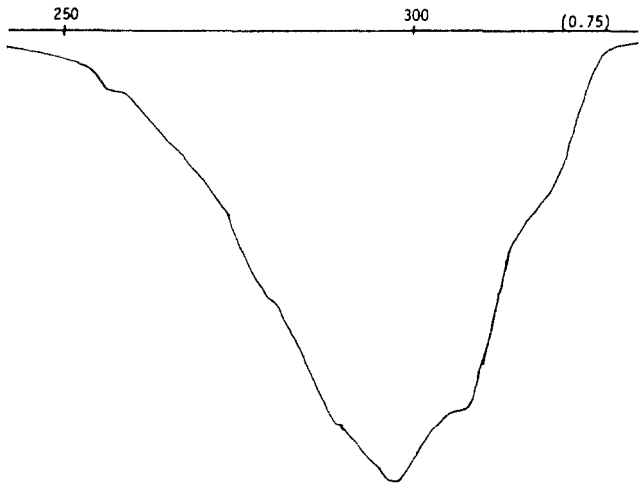

Figure 5. CD of (−)-**9** (*c* 0.45 in cyclohexane), 2° full scale.

dichloroacetic acid after heating to 140 °C to achieve dissolution. Three broad absorptions were observed at δ 4.1, 3.6, and 2.9 in a ratio of 2:2:4.

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Acid (6′). Recrystallization of **6** from hot water gave the *cis*-diacid **6′** in 90–95% yield: mp 264–266 °C (lit.[15] mp 272–273 °C); IR (KBr) 3300–2800, 1740, 1705, 1420, 1390, 1255, 1220, 1200, 1090, 915, 870 cm^{-1}. The diacid was only slightly soluble in ordinary NMR solvents. For this reason, its dimethyl ester was prepared.[15] Its ^1H NMR in $CDCl_3$ showed only one OCH_3 peak at δ 3.7 which integrated for six protons. This observation would appear more consistent with trans stereochemistry for these substances. That the actual configuration is cis was demonstrated by ^{13}C NMR spectroscopy which revealed four carbonyl absorptions at 207.51, 207.14, 172.46, and 170.51 ppm downfield from internal Me_4Si. Thus, the original methoxy singlet appears to be an example of fortuitous chemical shift equivalence.

(±)-5,7-Dioxobicyclo[2.2.2]oct-2-ene (5). A solution of **6′** (22.6 g, 0.1 mol) and lead tetraacetate (88 g, 0.2 mol) in 220 mL of dioxane was purged by bubbling nitrogen through the solution for 15 min while stirring, and placed in a water bath at 12–15 °C. The nitrogen flow was increased, 210 mL of pyridine was added dropwise, and the mixture was placed in a water bath at 60 °C for 10 min. The contents were rapidly cooled, poured into 1 L of 2 N nitric acid, and extracted with chloroform (8 × 100 mL). The extracts were washed with saturated sodium bicarbonate (2 × 75 mL) and brine solutions (1 × 75 mL) prior to drying. Removal of solvent left 6.5 g of a brown oil. High-pressure liquid chromatography (Waters Prep 500) on silica gel (elution with 20% ethyl acetate in petroleum ether) gave 4.0 g (30%) of racemic **5**: mp 95–99 °C (lit.[16] mp 97–99 °C); IR (film) 2955, 2875, 1720 (split), 1390, 1330, 1290, 1050, 930, 870, 730, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54–6.50 (m, 2 H), 3.45 (s, 2 H), 2.47–2.30 (m, 4 H).

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.93. Found: C, 70.72; H, 6.00.

Also isolated was 1.8 g of a water-white liquid tentatively identified as 2-acetoxy-1,4-dioxane: ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1 H), 4.07–3.53 (series of m, 6 H), 2.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) 169.4, 89.1, 67.5, 65.8, 61.6, 20.8 ppm; mass spectrum, *m/z* ($M^+ - CH_3CO$) calcd 103.0396, obsd 103.0391.

Resolution of 6′. A. Use of Brucine. Brucine (50 g of brucine–$4H_2O$ and 10 g of brucine, 0.133 mol) and **6′** (29 g, 0.128 mol) were heated at gentle reflux for 4 days in 700 mL of methanol and cooled. The solid was collected by filtration to give 23.18 g of brucine salt: mp 215–217 °C; $[\alpha]^{27}_D$ −46° (*c* 2.75, Me_2SO). Two recrystallizations from methanol did not alter the melting point, and the brucine salt thus recovered (12 g) was decomposed with sodium carbonate and extracted with chloroform. After acidification of the aqueous layer with 6 N hydrochloric acid, the diacid did not precipitate. Water was removed, and the solid residue was treated directly with the theoretical amount of lead tetraacetate.

B. Use of Quinine. Quinine (72 g, 0.22 mol) and **6′** (45.2 g, 0.2 mol) were heated at gentle reflux for 3 days in 500 mL of methanol, and the quinine salt was collected by filtration; mp 187–187.5 °C; $[\alpha]^{26}_D$ −126.6° (*c*, 1.92, Me_2SO). Three recrystallizations from methanol gave 25 g of quinine salt with a constant mp of 194–195 °C, $[\alpha]^{35}_D$ −59.35° (*c* 1.68, Me_2SO). The quinine salt (12 g) was decomposed with sodium bicarbonate and extracted with chloroform. After acidification of the aqueous layer with 6 N hydrochloric acid, the diacid did not precipitate. Water was removed, and the residue was treated directly with the theoretical amount of lead tetraacetate.

(−)-(1*S*,4*S*)-5,7-Dioxobicyclo[2.2.2]oct-2-ene (5) via Decarboxylation. Lead tetraacetate oxidation, as previously described, of the residues obtained from the quinine and brucine resolutions gave almost identical results; (−)-**5** from quinine, $[\alpha]^{30}_D$ −1013° (*c* 0.032, cyclohexane); (−)-**5** from brucine, $[\alpha]^{30}_D$ −1030° (*c* 0.036, cyclohexane); ORD (*c* 0.0056, cyclohexene) (a) (nm) −1030 (589), −37 500 (322), −24 286 (312), 0 (302), +19 286 (292), +26 420 (283), +29 000 (275); CD (*c* 0.0056, cyclohexane) $[\psi]_{303}$ −41 100, $[\psi]_{295}$ −40 500, $[\theta]_{max}$ 55 800.

Ketalization of (±)-5 with Diethyl (*R*,*R*)-(+)-Tartrate. A solution containing 1.36 g (10 mmol) of racemic **5**, 2.10 g (10 mmol) of diethyl (*R*,*R*)-(+)-tartrate, and 0.22 g of *p*-toluenesulfonic acid monohydrate dissolved in dry xylenes (30 mL) was heated at reflux for 81 h under a Dean–Stark trap and nitrogen atmosphere. Upon cooling, the reaction mixture was taken up in ether (200 mL), washed with water (3 × 100 mL), and dried. The solvents were subsequently removed under vacuum. The residual brown syrup was subjected to MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether). There was obtained 2.14 g (66%) of a mixture of monoketals **7** and **8**.

The monoketals were obtained in optically pure conditions by peak shaving and recycling of the shavings. The first pass was made through two Merck silica gel columns in series (elution with 30% ethyl acetate in petroleum ether), and the second pass was carried out through three identical columns in series (identical solvent system).

(+)-**7**: IR (neat) 3060, 2980, 2940, 1760, 1730, 1612, 1468, 1445, 1405, 1370, 1355, 1338, 1215, 1125, 1080, 1045, 1015, 955, 899, 888, 850, 765, 715, 653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (br dt, *J* = 1.20, 7.80 Hz, 1 H), 6.29 (br t, *J* = 6.70 Hz, 1 H), 4.76 (d, *J* = 4.65 Hz, 1 H), 4.71 (d, *J* = 4.65 Hz, 1 H), 4.24 (q, *J* = 7.18 Hz, 2 H), 4.21 (q, *J* = 7.11 Hz, 2 H), 3.15–3.08 (m, 1 H), 3.07–2.98 (m, 1 H), 2.42 (dd, *J* = 1.79, 18.56 Hz, 1 H), 2.38 (dd, *J* = 2.02, 14.86 Hz, 1 H), 2.05 (dd, *J* = 3.48, 14.86 Hz, 1 H), 1.96 (dd, *J* = 3.51, 18.56 Hz, 1 H), 1.30 (t, *J* = 7.17 Hz, 3 H), 1.27 (t, *J* = 7.17 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) 209.57 (s), 169.55 (s), 168.72 (s), 134.45 (d), 129.47 (d), 116.74 (s), 77.32 (d), 76.95 (d), 61.69 (t), 49.17 (d), 42.08 (d), 37.61 (t), 34.56 (t), 13.97 (q), 13.94 (q) ppm; mass spectrum, *m/z* calcd (M^+) 324.1209, obsd 324.1212; $[\alpha]^{27.8}_D$ +223.0° (*c*, 0.093, acetonitrile, α +20.791).

(−)-**8**: IR (neat) 3060, 2980, 2945, 1755, 1730, 1612, 1465, 1443, 1405, 1370, 1355, 1338, 1215, 1160, 1125, 1080, 1045, 1015, 955, 902, 889, 850, 765, 715, 655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (dt, *J* = 1.62, 6.47 Hz, 1 H), 6.32 (br dt, *J* = 1.16, 6.56 Hz, 1 H), 4.81 (d, *J* = 4.50 Hz, 1 H), 4.76 (d, *J* = 4.50 Hz, 1 H), 4.26 (q, *J* = 7.05 Hz, 2 H), 4.25 (q, *J* = 7.12 Hz, 2 H), 3.20–3.09 (m, 1 H), 3.09–2.98 (m, 1 H), 2.58 (dd, *J* = 1.93, 18.67 Hz, 1 H), 2.33 (dd, *J* = 3.35, 14.83 Hz, 1 H), 2.18 (dd, *J* = 2.17, 14.83 Hz, 1 H), 2.02 (dd, *J* = 3.44, 18.67 Hz, 1 H), 1.31 (t, *J* = 6.93 Hz, 3 H), 1.29 (t, *J* = 7.05 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) 210.07 (s), 169.68 (s), 134.22 (d), 130.02 (d), 117.11 (s), 77.52 (d), 77.37 (d), 62.01 (t), 49.42 (d), 42.32 (d), 37.99 (t), 35.06 (t), 14.07 (q) ppm; mass spectrum *m/z* calcd (M^+) 324.1209, obsd 324.1212; $[\alpha]^{27.8}_D$ −308.4° (*c* 0.041, acetonitrile, α −12.675).

General Procedure for Monoketal Hydrolysis. A mixture of (+)-**7** (104 mg, 0.321 mmol) and 10% hydrochloric acid (7 mL) was refluxed gently for 12 h, after which a light yellow solution was obtained. This solution was extracted with chloroform (3 × 10 mL), and the combined extracts were dried and evaporated to afford an oily solid. Sublimation [68 °C (0.25 torr)] gave optically pure (+)-**5** (37 mg, 85%) as a white solid. The identical procedure with (−)-**8** (117 mg) produced (−)-**5** (42 mg, 84%).

(−)-**5**: IR ($CDCl_3$) 3080, 3000, 2960, 2920, 1731, 1611, 1402, 1345, 1302, 1222, 1086, 1062, 970, 942, 780, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55–6.47 (m, 2 H), 3.47–3.37 (m, 2 H), 2.40 (dd, *J* = 2.16, 18.73 Hz, 2 H), 2.30 (dd, *J* = 3.03, 18.73 Hz, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) 207.37, 132.07, 49.81, 34.93 ppm; mass spectrum *m/z* calcd (M^+) 136.0524, obsd 136.0516; $[\alpha]^{29.5}_D$ −1257° (*c* 0.0015,

cyclohexane, α −1.949), $[\alpha]^{29.5}_D$ −1235° (c 0.0057, carbon tetrachloride, α −7.103).

(+)-5: $[\alpha]^{29.5}_D$ +1252° (c 0.0012, cyclohexane, α +1.502), $[\alpha]^{29.5}_D$ +1222° (c 0.0063, carbon tetrachloride, α +7.700).

(±)-Bicyclo[2.2.2]octane-2,5-dione (9). A solution of (±)-5 (136 mg, 1 mmol) in 10 mL of ethanol was hydrogenated using 10% Pd/C catalyst at atmospheric pressure until the theoretical amount of hydrogen had been taken up. Filtration and removal of solvent gave 133 mg of crude product. ^{1}H NMR analysis indicated that hydrogenation was incomplete. Recrystallization from benzene gave 110 mg of racemic 9 (80%); mp 203–205 °C (lit.[16] mp 203–205 °C); IR (film) 2910, 2875, 2840, 1720 (split), 1450, 1430, 1380, 1280, 1230, 1070, 920, 850, 840, 785 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.8 (br s, 2 H), 2.55 (d, 4 H), 2.08 (br s, 4 H).

(−)-Bicyclo[2.2.2]octane-2,5-dione (9). Hydrogenation of (−)-5, $[\alpha]^{30}_D$ −1030°, in ethanol over PtO_2 for 30 min in a Parr shaker at 15 psi gave (−)-9 in quantitative yield: mp 201–203 °C; $[\alpha]^{30}_D$ −40.7° (c 0.45, cyclohexane); ORD (c 0.45, cyclohexane) −40.7 (589), −1210 (322), −1250 (312), 0 (297), +1190 (272); CD (c 0.45, cyclohexane) $[\psi]_D$ −1555, $[\psi]_{297}$ −1870, $[\theta]_{max}$ −2581.

Acknowledgment. We thank the National Science Foundation for their financial support of this work.

Aflatoxin Precursors: Total Synthesis of (±)-Averufin and (±)-Nidurufin

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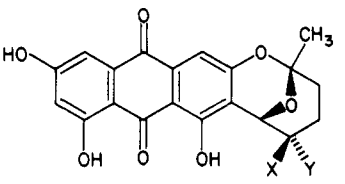
Received June 18, 1985

A practical, improved synthesis of 1,3,6,8-tetrahydroxyanthraquinone is described. The latter compound has been used as the starting material in new syntheses of the racemic forms of the *Aspergillus* metabolites averufin and nidurufin. The 2′-endo epimer of nidurufin was also synthesized regiospecifically.

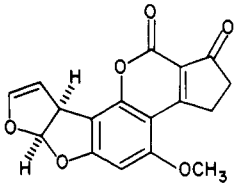
The aflatoxins are a group of mycotoxins produced by certain strains of the mold *Aspergillus*. Aflatoxin B_1 (3), the most widely produced member of this group, is acutely hepatotoxic and carcinogenic. The importance of aflatoxin mycotoxicoses on both animals and in man has spurred intensive studies of the biosynthesis of these compounds.[2] The anthraquinone derivatives averufin[3] and versiconal acetate[4] have been firmly established as intermediates along the complex pathway of aflatoxin biosynthesis.

Until very recently, the minor *Aspergillus* metabolite nidurufin[5] (**2a**) seemed to be a most likely intermediate between averufin (1) and versiconal acetate (4). Model rearrangement studies indirectly supported this view, as did synthetic studies leading to the reassignment of the stereochemistry of nidurufin.[6] Although nidurufin has now been shown to be only poorly incorporated into aflatoxin,[7] the most recent biosynthetic results still point to an as yet unknown intermediate which must be very close structurally and stereochemically to nidurufin.

Both averufin and nidurufin may be regarded as structurally elaborated derivatives of 1,3,6,8-tetrahydroxyanthraquinone. In this paper, we describe an improved, practical synthesis of this important intermediate and its elaboration into both (±)-averufin and (±)-nidurufin[8] as well as (±)-2′-*epi*-nidurufin (**2b**). The general synthetic scheme was patterned after our earlier synthesis of the model substance 6,8-dideoxynidurufin.[6]



1, X=Y=H
2a, X=OH; Y=H
2b, X=H; Y=OH



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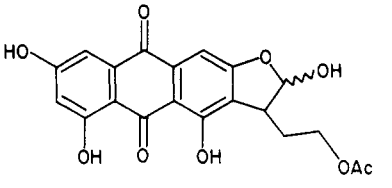

4

Results and Discussion

Synthesis of 1,3,6,8-Tetrahydroxyanthraquinone (6). A number of syntheses of 1,3,6,8-tetrahydroxyanthraquinone have been described in the literature.[9] In general, none of these procedures affords a convenient means of obtaining multigram quantities of this compound for further study. The best synthesis reported is that of Brassard and co-workers.[9a] This procedure involves the

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