Synthesis of *trans*-2,3-Dihydroxy-2,3-dihydrobenzoic Acid and Related Substances from 4-Carbo-*tert*-butoxyoxepin[1]

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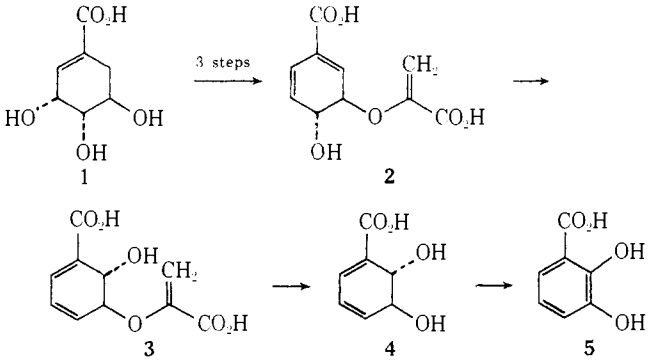
Abstract: The synthesis of 4-carbo-*tert*-butoxyoxepin (**10**) is described. Reaction of **10** with methoxide ion afforded *tert*-butyl *trans*-2-methoxy-3-hydroxy-2,3-dihydrobenzoate (**14**) that was converted to its acetate derivative **15**. Esters **14** and **15** were converted to the corresponding carboxylic acids **16** and **17**. The thermal stability of **15** is described. Irradiation of **15** affords hexatriene **21**. Reaction of **10** with hydroxide ion in *tert*-butyl alcohol–H_2O provided a synthesis of racemic *trans*-2,3-dihydroxy-2,3-dihydrobenzoic acid (**4**).

The main pathway for the biosynthesis of aromatic amino acids and growth factors in bacteria and presumably higher plants[2,3] involves conversion of shikimic acid (**1**) to chorismic acid (**2**) and a subsequent highly branched sequence that includes several *trans*-2,3-disubstituted-2,3-dihydro- and *trans*-3,4-disubstituted-3,4-dihydrobenzoic acid derivatives. *trans*-2,3-Dihydroxy-2,3-dihydrobenzoic acid (**4**), the immediate precursor to the growth factor 2,3-dihydroxybenzoic acid (**5**), is formed enzymically from **2** *via* isochorismic acid (**3**) as indicated in Scheme I.[2,4,5] As part of a

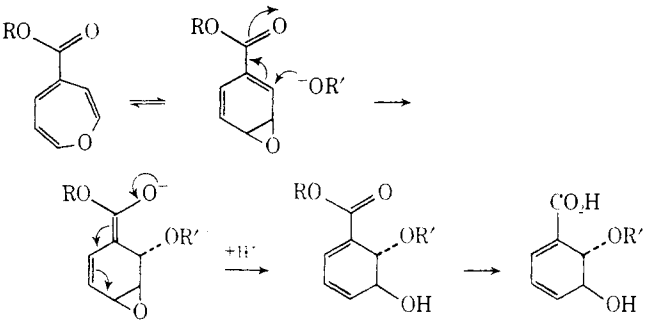
Scheme I



program concerned with the biosynthesis of aromatic amino acids and growth factors in bacteria, methods of synthesis of substituted dihydrobenzoic acids are under investigation. Reported herein are the synthesis and properties of **4** and related substances.

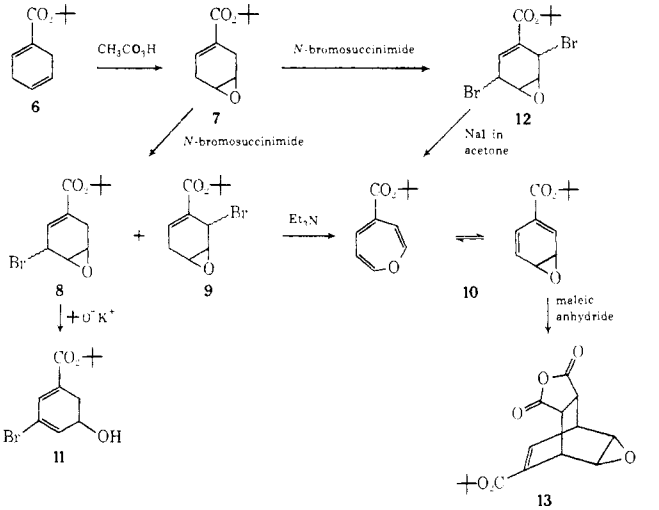
In view of the relatively low reactivity of oxepin–benzene oxide toward oxygen nucleophiles,[6] a reasonable approach to **4** and the corresponding 2-alkoxy derivatives, as indicated in Scheme II, involves Michael addition of hydroxide or alkoxide to the carboalkoxy-substituted oxepin–benzene oxide and subsequent conversion of the ester to the carboxylic acid. The *tert*-butyl ester derivative of oxepin–benzene oxide (**10**) was chosen for the study in order to effect conversion to the carboxylic acid with CF_3CO_2H or HF in ether.

Scheme II



The synthesis of **10** was accomplished through application of Vogel's procedures[7,8] for the parent system (Scheme III). Diene **6** was epoxidized with peracetic acid in $CHCl_3$ to give **7** (80%). Allylic bromination of **7** with *N*-bromosuccinimide in CCl_4 gave a mixture of allylic bromides consisting of approximately equal amounts of the pairs of epimers **8** and **9** (estimated from the nmr spectrum). Treatment of the bromide mixture

Scheme III



(1) Financial support from the National Institutes of Health, Grant No. 1RO1-GM19103, and from Hoffmann-La Roche, Inc., Nutley, N. J., is gratefully acknowledged.

(2) F. Lingens, *Angew. Chem.*, **80**, 384 (1968); *Angew. Chem., Int. Ed. Engl.*, 7, 350 (1968), and references cited therein.

(3) I. G. Young, F. Gibson, and C. G. MacDonald, *Biochim. Biophys. Acta*, **192**, 62 (1969).

(4) I. G. Young, L. M. Jackman, and F. Gibson, *Biochim. Biophys. Acta*, 177, 381 (1969); **148**, 313 (1967).

(5) I. G. Young and F. Gibson, *Biochim. Biophys. Acta*, **177**, 348 (1969).

(6) A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, unpublished manuscript.

(7) E. Vogel and H. Gunther, *Angew. Chem.*, **79**, 429 (1967); *Angew. Chem. Int. Ed. Engl.*, **6**, 385 (1967).

(8) The transformations described in Scheme III have been reported in preliminary form: R. M. DeMarinis and G. A. Berchtold, *Chem. Commun.*, 810 (1971).

with Et_3N at room temperature resulted in selective elimination of HBr from epimers **9** to give **10** (41% yield from bromide mixture). Although **8** did not react with Et_3N, it was isomerized to dihydrophenol **11** with potassium *tert*-butoxide.[9] Dihydrophenol **11** was relatively unstable. Both **11** and its acetate derivative decomposed readily to *tert*-butyl *m*-bromobenzoate.

Oxepin **10** could also be obtained in approximately the same overall yield by treatment of **7** with 2 equiv of *N*-bromosuccinimide to form the epimeric dibromide mixture **12** and subsequent elimination with NaI in acetone. The former procedure, however, is more reliable. Purification of **10** by distillation and low-temperature recrystallization gave the oxepin valence isomer as orange needles. Although the nmr spectrum (see Experimental Section) indicated **10** to exist predominantly in the oxepin form in solution, the presence of the benzene oxide valence isomer was demonstrated by formation of the Diels–Alder adduct **13** and from reactions with nucleophiles described later. Treatment of **10** with hot, aqueous acid formed *m*-hydroxybenzoic acid as the major product and only a trace of the para isomer as expected on the basis of stability of the carbonium ion obtained from ring opening of the protonated benzene oxide isomer.

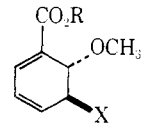
Reaction of **10** with methoxide ion proceeded as indicated in Scheme II to produce methoxy alcohol **14** (56%) that was surprisingly stable. It could be purified by glpc on a neutral 6-ft 20% SE-30 column at 175°. Acetic anhydride in pyridine converted **14** to acetate **15** that was recovered in analytical purity from glpc at 150°. Acetate **15** underwent slow elimination of acetic acid in refluxing xylene to *tert*-butyl *o*-methoxybenzoate thereby establishing the position of the methoxy group. The spectral data of **14** and **15** also confirm the structure (see Experimental Section).

The stereochemistry of **15**, and consequently **14**, was assigned trans on the basis of nmr double resonance experiments from which it is concluded that $J_{2,3} = 1$ Hz and $J_{2,6}$ and $J_{3,5} \sim 0$ Hz. The absence of allylic coupling of 1–3 Hz indicates neither H_2 nor H_3 is quasiaxial and therefore the CH_3O– and AcO– substituents are quasiaxial. The twist conformation of **15** results in a H_2–C–C–H_3 dihedral angle of ~65° and consequently $J_{2,3}$ is small.[10,12]

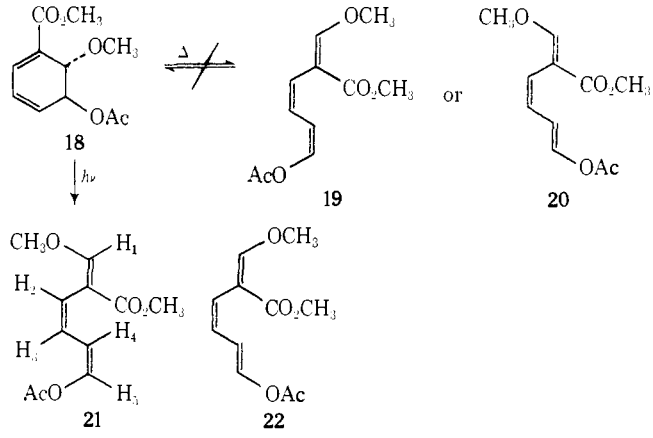
Reaction of **14** and **15** with CF_3CO_2H at room temperature produced the stable, crystalline carboxylic acids **16** (64%) and **17** (70%), respectively. Anhydrous HF in ether also converted **15** to **17**, but the yield was lower.

The surprising thermal stability of **15** raised the question whether it underwent thermal disrotatory ring opening to the substituted hexatriene and subsequent disrotatory ring closure on cooling with preservation of stereochemistry. To establish whether such ring opening was occurring, acid **17** was partially resolved with (+)-α-methylbenzylamine to give approximately 5% enrichment of the (−) isomer as determined by chiral lanthanide shift reagent analysis.[14] The partially resolved acid was converted to the chiral methyl ester **18** with 1-methyl-3-*p*-tolyltriazene. Thermolysis of **18** under the glpc conditions or in refluxing xylene and recovery of **18** did not lead to loss of optical activity. Consequently, **18** does not undergo thermal equilibration between the optical antipodes *via* a planar conformation of triene **19** or **20** under the conditions studied. Irradiation of **18** in methanol with a 3000-Å source for 12 hr (77% reaction) yielded the conrotatory ring-opened triene **21** whose structure was assigned on the basis of spectral data (see Experimental Section). Diene **18** recovered from the irradiation mixture showed no loss in optical activity, and irradiation of **21** resulted in polymerization. Failure to observe reversibility in the photochemical reaction may be due to the inability of excited **21** to adapt the proper conformation for ring closure. The stereoselectivity in the photochemical ring opening of **18** to **21** rather than **22** parallels that observed for *trans*-1,5,6-triphenylcyclohexa-1,3-diene[15] and *trans*-1,4-diphenyl-5,6-dimethylcyclohexa-1,3-diene[16] where it is concluded that secondary steric factors control the bond reorganization.

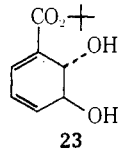
Reaction of **10** with hydroxide ion in aqueous dioxane gave *tert*-butyl *trans*-2,3-dihydroxy-2,3-dihydrobenzoate (**23**) as a viscous oil that decomposed to



14, R = Me_3C; X = OH
15, R = Me_3C; X = OAc
16, R = H; X = OH
17, R = H; X = OAc



18 19 20 21 22



23

(9) See ref 8 for a more detailed discussion.

(10) The nmr analysis is in excellent agreement with the nmr spectral data for **3**[11] and **4**.[4]

(11) I. G. Young, T. J. Batterham, and F. Gibson, *Biochim. Biophys. Acta*, 177, 389 (1969).

(12) The H_2–H_3 coupling constant is 4.5 Hz in the maleic anhydride adduct of **15** and is consistent only with trans stereochemistry.[13] We thank Dr. W. W. Schloman for preparation of the Diels–Alder adduct.

(13) D. T. Gibson, M. Hensley, H. Yoshioka, and T. J. Mabry, *Biochemistry*, **9**, 1626 (1970); L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 288, and references cited therein.

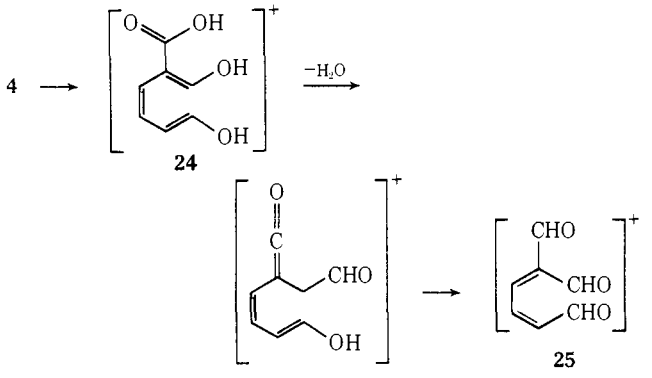
(14) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **95**, 1038 (1973). We are indebted to Mr. M. D. McCreary for this determination.

(15) A. Padwa, L. Brodsky, and S. Clough, *J. Amer. Chem. Soc.*, **94**, 6767 (1972).

(16) P. Courtot and R. Rumin, *Tetrahedron Lett.*, 1849 (1970).

tert-butyl *m*-hydroxybenzoate on attempted purification by molecular distillation. Treatment of **23** with CF_3CO_2H or HF in ether effected aromatization. Cleavage of the *tert*-butyl ester of the bistrifluoroacetate derivative of **23** followed by hydrolysis of the trifluoroacetate groups with aqueous bicarbonate gave impure **4**. Pure **4** could be prepared in 21% yield from the two-phase reaction of **10** with KOH in *tert*-butyl alcohol–H_2O. Other reaction products include **23** (5%), *tert*-butyl *m*-hydroxybenzoate (5%), *m*-hydroxybenzoic acid (20%), *p*-hydroxybenzoic acid (20%), and unreacted **10** (25%) from which **4** is readily separated and purified *via* the tristrimethylsilyl derivative. The spectral properties of racemic **4** are in agreement with those reported for (−)-*trans*-2,3-dihydroxy-2,3-dihydrobenzoic acid isolated from cultures of *Aerobacter aerogenes* grown in an iron deficient medium to suppress the 2,3-dihydroxybenzoate synthesizing system.[4]

The mass spectrum of **4** shows the most intense peak at *m/e* 138 corresponding to loss of water from the parent ion.[4] Although the major thermal decomposition product of **4** is 3-hydroxybenzoic acid, further fragmentation of the *m/e* 138 ion from **4** does not correspond to the fragmentation pattern observed for 3-hydroxybenzoic acid. The loss of water from the molecular ion of **4** is followed by three successive losses of 28 and 29 mass units to give ions of high intensity at *m/e* 110, 109, 82, 81, and 53.[4] The fragmentation pattern suggests electron impact involves cleavage of the C_2–C_3 bond to form the hexatrienyl molecular ion **24** that readily loses water to form an ion (such as **25**) from which the successive loss of CO and CHO units would be expected.



Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrometer. Proton nmr spectra were taken on Varian T-60 or Perkin-Elmer R-20 spectrometers, and chemical shift data are reported in parts per million downfield from tetramethylsilane as an internal standard at 0.00. Mass spectra were run on a Hitachi-Perkin-Elmer RMU-6D mass spectrometer with an ionizing potential of 80 eV and are expressed in per cent relative to the most intense peak. High resolution mass spectra were run on a CEC-21-110B spectrometer.[17] Melting points were taken on a Thomas-Hoover "Uni Melt" and are corrected. Gas chromatographic analyses and isolations were carried out with either a Hewlett-Packard Model 5750 gas chromatograph with thermal conductivity detectors or a Varian Aerograph Model 2100 gas chromatograph equipped with flame ionization detectors in an all glass system. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark or Galbraith Microanalytical Laboratories, Knoxville, Tenn.

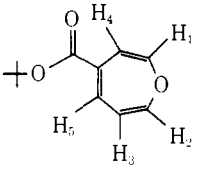
tert-**Butyl 2,5-Dihydrobenzoate (6).** A solution of 40 g (0.32 mol) of *tert*-butyl propiolate,[18] 100 g (1.85 mol) of butadiene, and 100 ml of benzene was heated in a steel bomb for 48 hr at 95–105°. The excess butadiene was allowed to evaporate and the benzene solution was washed with saturated Na_2CO_3 solution. The organic layer was separated, dried (Na_2CO_3), filtered, and evaporated to give a yellow oil that was distilled from a small amount of Na_2CO_3 to give 40.5 g (70%) of **6** as a colorless oil: bp 49–51° (0.2–0.3 mm); ir ($CHCl_3$) 2970, 2920, 2870, 1705, 1670, 1635, 1475, 1410, 1390, and 1370 cm^{-1}; nmr ($CDCl_3$) δ 6.85 (m, 1 H), 5.70 (m, 2 H), 2.83 (broad s, 4 H), and 1.50 ppm (s, 9 H); *m/e* 180 (1), 165 (1), 124 (9), 123 (76), 122 (40), 107 (40), 79 (45), 78 (11), 77 (25), 57 (100), 41 (25).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.40; H, 8.87. Found: C, 73.36; H, 8.82.

tert-**Butyl 3,4-Oxo-2,5-dihydrobenzoate (7).** To a slurry of 25 g (0.139 mol) of **6**, 25 g of anhydrous NaOAc, and 200 ml of $CHCl_3$ stirred at 0° was added dropwise 39.5 g (0.180 mol) of 40% peracetic acid. After the addition was complete, the mixture was allowed to warm to room temperature and was stirred for 18 hr. The mixture was washed with 100 ml of water, 50 ml of saturated aqueous Na_2CO_3, and 50 ml of saturated aqueous NaCl. It was dried (Na_2CO_3), filtered, and evaporated to give a yellow oil that was distilled from a small amount of Na_2CO_3 to give 21.9 g (81%) of **7** as a colorless oil: bp 80–83° (0.3–0.4 mm); ir ($CHCl_3$) 2970, 2920, 2890, 1705, 1660, 1390, and 1360 cm^{-1}; nmr ($CDCl_3$) δ 6.60 (m, 1 H), 3.25 (m, 2 H), 2.63 (m, 4 H), and 1.52 ppm (s, 9 H); *m/e* 196 (1), 181 (1), 141 (10), 140 (16), 124 (12), 123 (80), 105 (45), 77 (20), 57 (100), 56 (43), 41 (41).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.34; H, 8.16. Found: C, 67.29; H, 8.19.

4-Carbo-*tert*-**butoxyoxepin (10).** (a) *Via* **the Monobromide Derivative of 7.** To a solution of 3.0 g (15.3 mmol) of **7** in 20 ml of CCl_4 was added a finely ground mixture of 3.5 g (20 mmol) of *N*-bromosuccinimide and 100 mg of AIBN. The mixture was heated under reflux and irradiated for 0.5 hr after which time it was cooled, filtered, and evaporated to yield 4.3 g of the bromide mixture **8** and 9 as a yellow viscous oil. The crude bromide mixture was dissolved in 25 ml of ether and 2.0 g (20 mmol) of triethylamine was added in one portion. The solution was stirred at room temperature overnight. The solution was filtered from the precipitated hydrobromide salt and was washed with 20-ml portions of water and 5% aqueous NaOH. It was dried (Na_2CO_3), filtered, evaporated, and distilled to yield 1.2 g (41%) of a bright red oil, bp 80–90° (0.3–0.5 mm). The product crystallized in the freezer and was recrystallized from petroleum ether at −20° to give orange needles of **10**: mp 37–39°; uv max (CH_3OH) 300 nm (ϵ 1140) trailing >400 nm; ir ($CHCl_3$) 2980, 2930, 1700, 1660, 1570, 1390, and 1365 cm^{-1}; *m/e* 195 (4), 194 (30), 139 (10), 138 (100), 121 (56), 93 (11), 69 (22), 68 (13), 65 (10), 57 (37), 41 (19); nmr (220 MHz, CS_2)[19]



	δ, ppm	J, Hz
H_1	5.36	$J_{1,4} = 5.35$; $J_{1,5} = 0.7$, $J_{1,2} = 0.4$
H_2	5.52	$J_{2,3} = 5.25$; $J_{2,5} = 0.85$
H_3	5.59	$J_{3,5} = 6.6$; $J_{3,4} = 0.4$
H_4	6.01	$J_{4,5} = 1.1$
H_5	6.89	
$(CH_3)_3C$	1.47	

Oxepin **10** formed a 1:1 adduct (**13**) in 60% yield with maleic anhydride in refluxing benzene. It was crystallized from $CHCl_3$–hexane as white flakes: mp 164.5–166°; ir ($CHCl_3$) 2980, 1860, 1785, 1705, 1630, 1380, and 1360 cm^{-1}; nmr ($CDCl_3$) δ 6.75 (d of d, 1 H, J = 7 Hz, 2 Hz) 4.20 (m, 1 H), 3.78 (m, 1 H), 3.40 (m, 4 H), and 1.50 ppm (s, 9 H).

(17) The high-resolution mass spectra required in this work were provided by the Facility supported by National Institutes of Health Grant RR00317 (Principal Investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.

(18) F. Sondheimer, N. Sternstrom, and D. Rosenthal, *J. Org. Chem.*, **24**, 1280 (1959).

(19) We thank Dr. H. J. C. Yeh, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Md., for the spectrum.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.48. Found: C, 61.58; H, 5.66.

(b) Via the Dibromide Derivative of 7. To a solution of 5.0 g (25.8 mmol) of **7** in 35 ml of CCl_4 was added 10.5 g (60 mmol) of *N*-bromosuccinimide and 100 mg of AIBN. The mixture was stirred under reflux and irradiated for 12 hr. It was cooled, filtered, and evaporated to give 9.8 g of crude dibromide **12** as a viscous oil. The oil was dissolved in 50 ml of acetone and 55 ml of 1 *M* NaI was added dropwise with stirring. After addition was complete the solution was stirred at room temperature for 4.5 hr, poured into excess aqueous $Na_2S_2O_3$, and extracted with ether. The ether layer was washed with 25-ml portions of saturated aqueous $Na_2S_2O_3$, 5% aqueous NaOH, water, and saturated aqueous NaCl. The ether layer was dried (Na_2CO_3), filtered, and evaporated to give a red oil that was distilled to yield 2.3 g (45%) of **10**.

tert-Butyl **3-Hydroxy-5-bromo-2,3-dihydrobenzoate (11).** To a suspension of 2.4 g (20 mmol) of potassium *tert*-butoxide in 50 ml of ether maintained at −78° was added dropwise a solution of 2.76 g (10 mmol) of the mixture of bromides **8** and **9** in 10 ml of ether. After the addition was complete, the mixture was stirred at −78° for 0.5 hr. It was hydrolyzed by the cautious addition of 10 ml of water and allowed to warm to room temperature. The ether layer was separated, washed with water, dried, filtered, and evaporated to give 1.37 g (49%) of crude **11** as a yellow oil: ir (neat) 3440, 3060, 2980, 2930, 1705, 1625, 1575, 1480, 1455, 1390, 1365, 1300, 1250, 1160, 840, 740, and 705 cm^{-1}; nmr ($CDCl_3$) δ 7.0 (m, 1 H), 6.2 (m, 1 H), 4.4 (m, 1 H), 3.6 (m, 1 H), 2.8 (m, 2 H), and 1.55 ppm (s, 9 H).

Product **11** could also be prepared from bromide **8** isolated from the reaction of **8** and **9** with triethylamine described above in the synthesis of **10** in which only isomer **9** reacts. Bromide **8**, bp 115–124° (0.4–0.8 mm), under similar conditions gave crude **11** in 84% yield. Short path distillation at 90° (0.1 mm) gave **11** in >90% purity that contained small amounts of *tert*-butyl benzoate and *tert*-butyl *m*-bromobenzoate. Alcohol **11** could not be purified further without decomposition. Treatment of **11** with acetic anhydride in pyridine gave the acetic derivative (52%) that could be short path distilled but contained the same impurities. Thermal decomposition of **11** or its acetate derivative yielded *tert*-butyl *m*-bromobenzoate.

Reaction of 4-Carbo-*tert*-butoxyoxepin (10) with Acid. A mixture of 150 mg of **10**, 5 ml of water, and 4 drops of H_2SO_4 was stirred under reflux for 1 hr. The solution was cooled, made basic with solid Na_2CO_3, and extracted with ether. The ether was discarded, and the aqueous layer was acidified with H_2SO_4 and extracted with ether. The ether was dried, filtered, and evaporated to give 67 mg (63%) of *m*-hydroxybenzoic acid that was characterized as its methyl ester by comparison with an authentic sample. Analysis by glpc showed the methyl *m*-hydroxybenzoate to contain less than 5% of the para isomer.

tert-Butyl *trans*-**2-Methoxy-3-hydroxy-2,3-dihydrobenzoate (14).** To a solution of 400 mg (2.0 mmol) of **10** in 6 ml of CH_3OH was added a solution of 72 mg (3.0 mmol) of LiOH in 2 ml of water. The solution was stirred for 0.5 hr at 60°, cooled, diluted with 15 ml of water, and extracted with two 25-ml portions of ether. The combined ether extracts were washed with 10 ml of cold 5% aqueous NaOH, dried (Na_2CO_3), filtered, and evaporated to give 251 mg (56%) of **14** as a viscous oil: ir ($CHCl_3$) 3600, 3380, 2980, 2930, 2820, 1700, 1650, 1590, 1450, 1390, and 1365 cm^{-1}; nmr ($CDCl_3$) δ 7.2 (m, 1 H), 6.4 (m, 2 H), 4.4 (broad s, 3 H), 3.6 (s, 3 H), and 1.6 ppm (s, 9 H); *m/e* 226 (1), 224 (1), 208 (11), 194 (18), 152 (47), 139 (11), 138 (100), 135 (50), 123 (48), 122 (10), 121 (63), 105 (36), 93 (17), 92 (14), 77 (21), 65 (17), 57 (67), 56 (42), 55 (18), 41 (86), 39 (41). Product **14** could be obtained in analytical purity by glpc on a neutral 6-ft 20% SE-30 column at 175°.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.86; H, 7.96.

tert-Butyl *trans*-**2-Methoxy-3-acetoxy-2,3-dihydrobenzoate (15).** Alcohol **14** (251 mg, 1.11 mmol) was dissolved in 3 ml of anhydrous pyridine and 1 ml of acetic anhydride was added. The solution was stirred at room temperature overnight. It was poured into 25 ml of ice–water, and the mixture was extracted with two 25-ml portions of ether. The combined ether extracts were washed with water, dried (Na_2CO_3), filtered, and evaporated to give 258 mg of a tan oil. Distillation at 110° (0.05 mm) gave 208 mg (69%) of **15** as a colorless oil: ir (CCl_4) 3050, 2980, 2930, 2820, 1740, 1705, 1650, 1590, 1480, 1460, 1390, 1370, 1290, 1240, 1170, 1080, 1020, 950, 905, 880, and 840 cm^{-1}; uv max (CH_3OH) 225 nm (ϵ 2460), 278 (7380); nmr ($CDCl_3$) δ 7.05 (d of d, 1 H, J = 5 Hz, J = 1 Hz), 6.20 (m, 2 H), 5.40 (d of d, 1 H, J = 5 Hz, J < 1 Hz), 4.20 (d, 1 H, J < 1 Hz), 3.42 (s, 3 H), 2.05 (s, 3 H), and 1.50 ppm (s, 9 H); *m/e* 268 (2), 236, (1), 227 (1), 226 (3), 212 (4), 208 (5), 196 (5), 195 (5), 194 (5), 171 (4), 170 (40), 163 (11), 153 (9), 152 (48), 139 (9), 138 (74), 135 (30), 124 (21), 123 (53), 121 (17), 110 (20), 109 (12), 105 (38), 95 (10), 94 (16), 81 (11), 79 (34), 65 (16), 60 (10), 57 (100), 56 (20), 53 (10), 51 (15), 47 (19), 45 (19), 43 (83), 41 (56), 39 (28).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46. Found: C, 62.76; H, 7.79.

trans-**2-Methoxy-3-hydroxy-2,3-dihydrobenzoic Acid (16).** Four hundred milligrams of ester **14** was dissolved in 2 ml of 100% trifluoroacetic acid and allowed to stand at room temperature for 15 min. The excess acid was evaporated and the residue taken up in 25 ml of ether. The ether was extracted with 25 ml of 5% sodium hydroxide and the aqueous phase allowed to stand at room temperature for 6 hr. It was warmed on a steam bath for several minutes, cooled, and acidified to pH 1–2 with 25% sulfuric acid. The acidified aqueous phase was washed with an equal volume of ether and the ether discarded. The aqueous phase was continuously extracted with ether for 18 hr. The extract was dried ($MgSO_4$), filtered, and evaporated to give 192 mg (64%) of a pale yellow gum which crystallized upon standing. It could be crystallized from a small amount of ether to give white cubes: mp 129–133° (softening 121°); ir (KBr) 3500–2500 (broad), 1700, 1645, 1585, 1450, 1410, 1385, 1290, 1240, 1060, 1010, 945, 935, and 735 cm^{-1}; nmr (acetone-d_6) δ 7.15 (d of d, 1 H, J = 5, J = 1.5 Hz), 6.25 (m, 1 H), 5.25 (broad, 2 H), 4.25 (m, 1 H), 3.38 ppm (s, 3 H); *m/e* 170 (6), 167 (3), 152 (7), 149 (8), 138 (8), 138 (52), 124 (12), 123 (21), 122 (54), 121 (30), 110 (28), 109 (27), 105 (100), 95 (10), 94 (12), 93 (22), 92 (20), 82 (30), 81 (37), 79 (11), 78 (15), 77 (98), 76 (11), 74 (20), 73 (50), 68 (12), 66 (36), 65 (50), 64 (14), 63 (26), 62 (10), 61 (22), 55 (20), 54 (11), 53 (43), 52 (17), 51 (73), 50 (43), 45 (17), 43(10), 41 (20), 40 (12), 39 (74), 38 (25), 37 (10).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.88. Found: C, 56.41; H, 5.98.

trans-**2-Methoxy-3-acetoxy-2,3-dihydrobenzoic Acid (17).** Acetate **15** (239 mg, 90 mmol) in 2 ml of trifluoroacetic acid was stirred at room temperature for 15 min and the solvent was removed under vacuum. The residue was taken up in ether, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil that partially crystallized on standing. It was washed with CCl_4, and the supernatant liquid was drained off to yield 115 mg (60%) of **17** as cubic crystals. The CCl_4 washings were evaporated to yield a yellow oil that was resubmitted to the reaction conditions and work-up to yield an additional 22 mg (10%) of **17**. The product could be recrystallized from benzene–hexane: mp 120–123° dec; ir ($CHCl_3$) 2950 (broad), 1735, 1690, 1650, 1590, 1430, 1380, 1240, 1080, 1015, and 920 cm^{-1}; uv max (CH_3OH) 278 nm (ϵ 6580); nmr ($CDCl_3$) δ 11.30 (broad s, 1 H), 7.40 (m, 1 H), 6.40 (m, 2 H), 5.50 (m, 1 H), 4.30 (finely split s, 1 H, J < 1 Hz), 3.42 (s, 3 H), 2.02 ppm (s, 3 H); *m/e* 213 (1), 212 (11), 171 (6), 170 (60), 152 (22), 139 (12), 138 (100), 124 (15), 123 (25), 122 (14), 121 (19), 110 (28), 109 (17), 105 (25), 92 (10), 82 (13), 78 (10), 77 (26), 44 (27), 43 (80), 41 (65).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.68. Found: C, 56.81; H, 5.70.

Partial Resolution of 17. Racemic **17** (1.00 g, 4.73 mmol) was dissolved in 5.0 ml of absolute ethanol and 675 mg (5.60 mmol) of (+)-α-methylbenzylamine was added to the solution with stirring. After 1 hr solvent was removed and the resulting yellow oil partially crystallized after 0.5 hr at 4°. It was washed with ether and dried to give 1.24 g (79%) of white crystals: mp 119–122°; ir ($CHCl_3$) 2950 (broad), 1730, 1650, and 1550 cm^{-1}; $[\alpha]^{25}D$ + 2.00°. The salt was dissolved in 4.0 ml of ethanol and kept at room temperature overnight. The fine white needles that formed were filtered and dried: 574 mg; $[\alpha]^{25}D$ +0.02°. A second crystallization from 1.5 ml of ethanol gave 413 mg of salt, $[\alpha]^{25}D$ −0.60°. The partially resolved salt was dissolved in 10 ml of water and concentrated HCl was added to pH 1–2. The aqueous solution was extracted with three 10-ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 232 mg of partially resolved **17**, $[\alpha]^{26}D$ −12.7°. The acid displayed a plain negative ORD curve over the range examined (365–589 nm) and was estimated to be resolved to the extent of ~5% based on analogous systems and corroborated by chiral lanthanide shift reagent analysis.[14]

Methyl *trans*-**2-Methoxy-3-acetoxy-2,3-dihydrobenzoate (18). (Racemic and Partially Resolved).** To 295 mg (1.39 mmol) of **17** in 5 ml of ether was added 520 mg (3.50 mmol) of 1-methyl-3-*p*-tolyltriazene in 5 ml of ether. The reaction mixture was gently refluxed until N_2 evolution ceased (2 hr). The resulting solution was washed with two 5-ml portions of 10% aqueous HCl and two 5-ml portions of 10% aqueous Na_2CO_3, dried ($MgSO_4$), filtered, and

evaporated to give 280 mg (90%) of **28** as an oil: ir (CCl_4) 3040, 2980, 2940, 2820, 1740, 1720, 1650, 1590, 1460, 1440, 1400, 1380, 1330, 1290, 1230, 1190, 1090, 1020, and 950 cm^{-1}; uv max (C_2H_5OH) 278 nm (ϵ 7380); nmr (CCl_4) δ 7.10 (m, 1 H), 6.30 (m, 2 H), 5.40 (m, 1 H), 4.20 (broad s, 1 H), 3.80 (s, 3 H), 3.40 (s, 3 H), and 2.00 ppm (s, 3 H); *m/e* 226 (5), 195 (3), 194 (2), 184 (29), 166 (21), 152 (46), 135 (47), 133 (20), 124 (28), 123 (12), 121 (18), 105 (22), 93 (10), 92 (15), 79 (10), 77 (38), 75 (20), 65 (13), 59 (15), 58 (10), 51 (15), 45 (14), 44 (20), 43 (100), 39 (13).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.39; H, 6.25. Found: C, 58.42; H, 6.21.

Chiral **18** was prepared from partially resolved **17** by the same procedure. It displayed a plain negative ORD curve virtually superimposable on that of the acid.

Thermolysis of Partially Resolved 18. Compound **18** was recovered with no sign of decomposition on a 6-ft SE-30 glpc column at 200° with an injection port temperature of 240°. When the temperature of the injection port was increased to 350°, approximately 10% of **18** underwent acetate pyrolysis to yield methyl *o*-methoxybenzoate. Recovered **18** showed no loss in optical activity.

When 101 mg of **18** in 3 ml of *m*-xylene was refluxed under N_2 for 12 hr, 40% of **18** decomposed. Recovered **18** showed no loss in optical activity.

Triene 21 from Photolysis of 18. A solution of 99.7 mg of partially resolved **18** and 37.9 mg of C_{13} internal standard in 2 ml of CH_3OH (distilled from Mg turnings and degassed with N_2 for 1 hr prior to use) was irradiated in a Rayonet Reactor, Model RPR 100 (Southern New England Ultraviolet Co.) fitted with 3000-Å lamps, and the reaction was monitored by glpc. After 100 hr, 80% of **18** had undergone reaction. Recovered **18** showed no loss in optical activity. A new peak appeared on glpc that increased up to 24 hr and then leveled off as secondary photoproducts appeared. It was collected as a yellow, viscous oil that polymerized on exposure to the atmosphere for several hours. The oil was assigned structure **21** on the basis of the following data: ir (CCl_4) 3100, 2940, 1760, 1640, 1430, 1370, 1210, 1140, 1100, and 1030 cm^{-1}; nmr (CCl_4) δ 7.30 (s, 1 H, H_1), 7.10 (d, 1 H, J = 6 Hz, H_5), 6.40 (t, 1 H, J = 10 Hz, H_3), 5.80 (d, 1 H, J = 10 Hz, H_2), 5.40 (d of d, 1 H, J = 6 Hz, 10 Hz, H_4), 3.90 (s, 3 H), 3.70 (s, 3 H), and 2.10 ppm (s, 3 H). Irradiation of the doublet at 7.10 ppm caused the doublet of doublets at 5.40 ppm to collapse to a doublet, J = 10 Hz. Irradiation of the doublet of doublets at 5.40 ppm caused the doublet at 7.10 ppm to collapse to a singlet; uv max (C_2H_5OH) 235 nm (ϵ 30,000) and 275 (15,000).

Anal. (molecular ion) Calcd for $C_{11}H_{14}O_5$: 226.08412. Found: 226.08240.

Irradiation of triene **21** in CH_3OH with the 3000-Å source gave only polymerization.

***tert*-Butyl *trans*-2,3-Dihydroxy-2,3-dihydrobenzoate (23).** To a solution of 1.35 g (6.9 mmol) of **10** in 15 ml of dioxane was added in one portion a solution of 165 mg (6.9 mmol) of LiOH in 9 ml of water. The mixture was stirred for 1 hr in an oil bath maintained at 60° It was cooled and diluted with ice to 50 ml. The aqueous phase was extracted with two 50-ml portions of pentane, and the pentane layers were discarded. The aqueous phase was extracted with four 50-ml portions of ether. The ether extracts were combined, dried (Na_2CO_3), filtered, and evaporated to give 445 mg (30%) of **23** as a light brown viscous oil: ir ($CHCl_3$) 3580, 3400, 2970, 2920, 2860, 1695, 1640, 1590, 1475, 1450, 1390, 1365, 1300, 1250, 1160, 1115, 1070, 940, 885, 870, and 840 cm^{-1}; nmr ($CDCl_3$) δ 7.00 (m, 1 H), 6.25 (m, 2 H), 3.50–5.00 (broad, 4 H), and 1.55 ppm (s, 9 H).

Further attempts to purify **23** led to complete conversion to *tert*-butyl *m*-hydroxybenzoate.

***trans*-2,3-Dihydroxy-2,3-dihydrobenzoic Acid (4).** To a solution of 1.02 g (5.25 mmol) of **10** in 15.5 ml of *tert*-butyl alcohol was added a solution of 0.35 g (5.25 mmol) of KOH in 7.8 ml of water. The two-phase mixture was stirred vigorously at 65° for 3 hr. The mixture was cooled and 20 ml of water was added. The solution was extracted with one 20-ml and one 15-ml portion of pentane to remove unreacted **10** (25%). The aqueous mixture was extracted with three 20-ml portions of ether to remove *tert*-butyl *m*-hydroxybenzoate (5%) and **23** (5%). Nitrogen was bubbled through the aqueous phase to remove residual ether and the solution was brought to pH 2 with 5% aqueous HCl and filtered. The filtrate was applied to a 10 × 1 cm column of XAD-2 resin (Mallinckrodt) at a rate of 1 ml/min. An additional 15 ml of distilled water (adjusted to pH 2 with HCl) was applied to the column at 1 ml/min. The combined eluents were evaporated under vacuum to give a residue that was suspended in 5 ml of anhydrous CH_3OH. The solution was filtered and the solvent evaporated under vacuum to give 175 mg (21%) of **4** as a pale yellow extremely hydroscopic material. The product gave one spot, R_f 0.44, on silica gel thin layer with methanol–ethyl acetate (1:4) and the spectral data were identical with that of purified material described below. Elution of the XAD-2 with CH_3OH gave *m*-hydroxybenzoic acid (20%) and *p*-hydroxybenzoic acid (20%).

Further purification of **4** was effected by the following procedure. To a solution of 37 mg of **4** in 300 μl of anhydrous pyridine was added 150 μl of bis(trimethylsilyl)trifluoroacetamide and 15 μl of trimethylchlorosilane. The solution was kept at room temperature overnight, the volatile components were removed under aspirator pressure, and the trimethylsilyl *trans*-2,3-bis(trimethylsilyloxy)-2,3-dihydrobenzoate was distilled, 70° (0.02 mm), as a clear, colorless oil: 43 mg (49%); ir (CCl_4) 3040, 2950, 2895, 1685, 1645, 1585, 1405, 1325, 1265, 1170, 1055, 1010, 970, and 865 cm^{-1}; nmr (CCl_4) δ 7.00 (m, 1 H), 6.12 (m, 2 H), 4.52 (d, 1 H, J = 2 Hz), 4.05 (m, 1 H), 0.42 (s, 9 H), 0.24 (s, 9 H), and 0.21 ppm (s, 9 H). The oil was dissolved in ether, a stoichiometric amount of CH_3OH and 5% aqueous HCl was added, the solution was kept at room temperature for 30 min, and the solvent was evaporated. After standing overnight in ether, **4** was obtained as a white, hydroscopic powder that was dried under vacuum, mp 130–132° dec. The spectral data (uv, nmr, and mass spectra) of racemic **4** were identical with those reported for (−)-**4** isolated from cultures of *Aerobacter aerogenes*.[5]

Anal. (molecular ion) Calcd for $C_7H_8O_4$: 156.0423. Found: 156.0428.