prior to use. All glassware was dried in an oven at 140 °C and purged with argon before titration.

***N*-Pivaloyl-*o*-toluidine (1).** In a 250-mL flask, *o*-toluidine (10 g, 0.093 mol) and Et_3N (9.41 g, 0.093 mol) were mixed together in CH_2Cl_2 (50 mL). The solution was cooled to 0 °C, and a solution of pivaloyl chloride (11.2 g, 0.093 mol) dissolved in CH_2Cl_2 (10 mL) was slowly added. On completion of the addition, the solution was stirred for $^1/_2$ h and then poured into water (200 mL). The organic layer was washed with water (3 × 100 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded a crude white solid, which after two recrystallizations from hot methylene chloride-/hexane (12/80 mL) afforded *N*-pivaloyl-*o*-toluidine as a white crystalline solid: yield 88%; mp 109–110 °C (lit.[11] mp 109–111 °C). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.36; H, 8.96; N, 7.32. Found: C, 75.62; H, 8.92; N, 7.24.

***N*-Pivaloyl-*o*-benzylaniline (2).** The same procedure as above was used. Recrystallization of the crude product from hot hexane (200 mL) afforded *N*-pivaloyl-*o*-benzylaniline as a white crystalline solid: yield 90%; mp 83 °C (lit.[11] mp 78–80.5 °C). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.14; H, 8.06; N, 5.19.

Titration of Organolithium Reagent. A 25-mL round-bottom flask fitted with a septum and containing a magnetic stirring bar was evacuated and flushed with argon or nitrogen. Approximately 250–380 mg (0.9–2.0 mmol) of the reagent 1 or 2 was charged into the flask. Anhydrous THF (5–10 mL) was added, and a white sheet of paper was placed behind the flask. The organolithium solution was added from a 1-mL Hamilton gas-tight syringe. The solution was rapidly stirred under argon. Triplicate analyses were performed in all cases.

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Registry No. 1, 61495-04-3; 2, 85864-33-1; BuLi, 109-72-8; *s*-BuLi, 598-30-1; *t*-BuLi, 594-19-4; MeLi, 917-54-4; PhLi, 591-51-5; *o*-toluidine, 95-53-4; pivaloyl chloride, 3282-30-2; *N*-pivaloyl-*o*-benzylaniline, 28059-64-5.

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Selective Synthesis and Hydrolysis of Dimethyl *cis,cis*-3-Halomuconates

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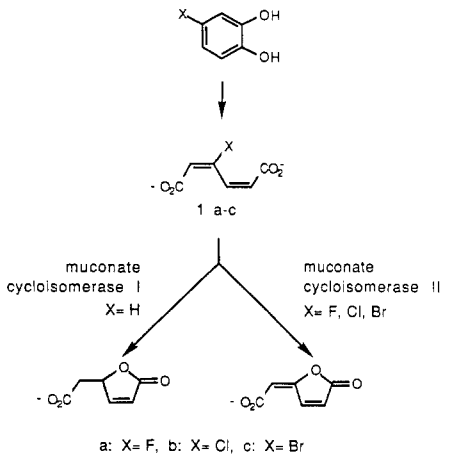
The microbial degradation of halogenated aromatic acids has received increased attention recently in light of its importance in the detoxification of environmental pollutants.[2] A key step in the degradation of 4-halocatechols is the lactonization and dehalogenation of the 3-halomuconates catalyzed by muconate cycloisomerase II (Scheme I).[3] A number of important questions concerning the chemical mechanism of this conversion have remained unresolved due to the lack of an unambiguous chemical synthesis of these substrates. Thus, we here report the synthesis of the dimethyl *cis,cis*-3-halomuconates[4] and their hydrolysis.

Scheme I



In reference to the three known isomers of unsubstituted muconic acid,[5,6] it has been established that only the cis,cis isomer is a substrate for muconate cycloisomerase I (Scheme I).[7] By analogy, it is generally accepted that only the cis,cis isomers of the 3-halomuconates **1a–c** are biologically active.[8,9] Detailed characterization of the geometry of the biological substrates, however, has been impaired by their instability in acidic media toward C-4, C-5 double bond isomerization and lactonization.[8,9]

The classical synthesis of *cis,cis*-muconic acid involves the oxidation of phenol[5,10] or catechol[11] with peracetic acid. This method has been applied to the synthesis of 3-chloromuconate,[9] yielding an unidentified mixture of isomers. In our hands the Fe(III)-catalyzed oxidation of 4-chlorocatechol with peracetic acid[11] produced only the cis,trans isomer **6b**. Several other reported methods for the synthesis of *cis,cis*-muconic acid or its derivatives[12] have not produced satisfactory results when applied to the synthesis of the title compounds.

Alkyl-substituted 1,2-benzoquinones are known to undergo oxidation with lead tetraacetate in the presence of methanol to give the alkyl-substituted dimethyl *cis,cis*-muconates.[13,14] We were able to obtain the title com-

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(4) To simplify the discussion of the various isomers we use the trivial nomenclature, where the cis,cis or cis,trans prefix refers to the orientation of the hexadienedioate carbon skeleton. The systematic name of these compounds is (2*E*,4*Z*)-dimethyl 3-halo-2,4-hexadienedioate.
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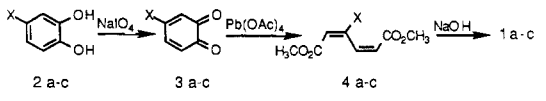
Scheme II



a: X= F, b: X= Cl, c: X= Br

pounds from the 4-halocatechols in moderate yields by this method (Scheme II). Oxidation of the catechols **2a–c** with sodium periodate in CH_2Cl_2/H_2O in the presence of tetrabutylammonium bromide as phase-transfer catalyst yielded the 1,2-benzoquinones **3a–c**.[15] Since **3a–c** decompose upon exposure to light and air at room temperature in ~1 h, they were immediately oxidized with lead tetraacetate. The dimethyl muconates **4a–c** were thus obtained in yields ranging from 25 to 75% as light yellow oils.

The cis,cis geometry of the hexadienedioate skeleton in **4a–c** was established by comparison of ^1H NMR data of the cis,cis and the cis,trans isomers. The vicinal coupling constant of H_4 and H_5 in known dimethyl *cis,cis*-muconates shows a typical value of $J_{H4,H5}$ = 12.1 Hz.[14,16] The corresponding C-4,C-5 trans isomers display a characteristically larger coupling constant of $J_{H4,H5}$ = 16.0 Hz.[14,16] Conversion of the title compounds **4a–c** to their cis,trans isomers **5a–c** by UV irradiation in $CHCl_3$ at room temperature increased their H_4,H_5 coupling constant in the same fashion (Scheme III). The geometry of the C-2,C-3 double bond can be inferred from the characteristically large downfield shift of the H_4 proton upon UV isomerization of **4a–c** to **5a–c**. This shift difference, ranging from $\Delta\delta$ = 0.75 ppm (**4a** to **5a**) to $\Delta\delta$ = 1.55 ppm (**4c** to **5c**), has also been observed during the isomerization of dimethyl *cis,cis*-3-methylmuconate ($\Delta\delta$ = 1.47 ppm) by Jaroszewski and Ettlinger.[14] It arises from the steric interaction of H_4 with two adjacent ester groups in compounds **5** versus one ester group in compounds **4**.

The dimethyl muconates **4a–c** were hydrolyzed to the disodium *cis,cis*-3-halomuconates **1a–c** with NaOH. These proved to be unstable to purification conditions either by recrystallization or anion-exchange chromatography. The hydrolysis products **1a–c** display vicinal coupling constants similar to those of their dimethyl precursors. Hydrolysis of the dimethyl *cis,trans*-3-halomuconates **5a–c** provides the *cis,trans*-3-halomuconic acids **6a–c** (Scheme III). In contrast to their cis,cis isomers, acids **6a–c** are stable to acidic solutions and can be well characterized. The study of the isomerization of muconates **1a–c** at various pHs and their reaction with muconate cycloisomerases is in progress.

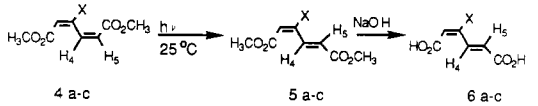
Experimental Section

NMR spectra were recorded on an IBM AF 400(FT) or an IBM AM 200(FT) instrument, as indicated. Chemical shifts of ^{19}F spectra are reported relative to trifluoroacetic acid (TFA) as an external standard. Mass spectra were recorded on a VG 7070H instrument. All melting points are uncorrected.

General Procedure for the Synthesis of *o*-Quinones. To a stirred solution of the catechol (8 mmol) in methylene chloride (30 mL) were added a solution of sodium periodate (2 g, 9.3 mmol) in water (20 mL) and tetra-*n*-butylammonium bromide (5–10 mg). After the mixture was stirred at room temperature for 10 min, the layers were separated and the organic layer was dried with sodium sulfate and evaporated.

4-Chloro-1,2-benzoquinone (3b) was obtained in 77.5% yield (880 mg): ^1H NMR ($CDCl_3$, 90 MHz) δ 6.9 (dd, 1 H, J = 9-10 Hz, J = 2 Hz), 6.55 (d, 1 H, J = 2 Hz), 6.3 (d, 1 H, J = 10 Hz).

Scheme III



a: X= F, b: X= Cl, c: X= Br

The red compound decomposed in the solid state after approximately 30 min to a yellow material.

4-Bromo-1,2-benzoquinone (3c) was obtained as a dark red solid that was immediately employed for the synthesis of dimethyl 3-bromo-*cis,cis*-muconate.

4-Fluoro-1,2-benzoquinone (3a) was obtained as a dark solid that was immediately employed for the synthesis of dimethyl *cis,cis*-3-fluoromuconate.

General Procedure for the Synthesis of Dimethyl *cis,cis*-3-Halomuconates. A solution of the *o*-quinone (8.0 mmol) in 1/1 benzene/methanol (75 mL) was cooled to 0 °C. Solid lead tetraacetate (4.3 g, 9.7 mmol) was added, and the mixture was stirred at 0 °C in the dark for 1 h. After evaporation the mixture was repeatedly extracted with ether, and the combined extracts were filtered through a short silica column (1 × 3 cm) and evaporated. Prolonged exposure to silica gel causes extensive isomerization.

Dimethyl *cis,cis*-3-fluoromuconate (4a) was obtained as a light yellow oil in 75% yield (1.128 g): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.31 (dd, 1 H, $J_{H,F}$ = 25 Hz, J = 12.5 Hz), 6.15 (d, 1 H, J = 12.5 Hz), 5.76 (d, 1 H, $J_{H,F}$ = 19 Hz), 3.79 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.31, 166.09, 163.15 (d, J = 176.1 Hz), 126.92, 124.72 (d, J = 18.8 Hz), 104.21 (d, J = 27.2 Hz), 51.9, 51.55; ^{19}F NMR ($CDCl_3$, 376 MHz, TFA as external standard) δ −31.1 (ddd, J = 28 Hz, J = 18 Hz, J = 2 Hz). Anal. Calcd for $C_8H_9FO_4$: C, 51.07; H, 4.82. Found: C, 51.27; H, 4.87. CI mass spectrum (isobutane), m/e 189 (M + 1), 157 ($M^+ - OCH_3$), 129 ($M^+ - COOCH_3$).

Dimethyl *cis,cis*-3-chloromuconate (4b) was obtained as a light yellow oil in 50% yield (815 mg): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.08 (dd, 1 H, J = 12 Hz, J = 1.8 Hz), 6.23 (m, 1 H), 6.07 (d, 1 H, J = 12 Hz), 3.75 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.23, 164.23, 144.65, 136.12, 124.36, 120.99, 51.80. Anal. Calcd for $C_8H_9ClO_4$: C, 46.96; H, 4.43. Found: C, 46.73; H, 4.54.

Dimethyl *cis,cis*-3-bromomuconate (4c) was obtained as a light yellow oil in 25% yield (500 mg): ^1H NMR ($CDCl_3$, 200 MHz) δ 6.99 (dd, 1 H, J = 12 Hz, J = 2 Hz), 6.48 (d, 1 H, J = 2 Hz), 5.95 (d, 1 H, J = 12 Hz), 3.75 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.71, 164.15, 139.44, 134.87, 124.39, 122.73, 51.71. Anal. Calcd for $C_8H_9BrO_4$: C, 38.58; H, 3.64. Found: C, 38.28; H, 3.59.

General Procedure for the Hydrolysis of the Dimethyl *cis,cis*-Muconates. The dimethyl muconate was stirred with equimolar NaOH per ester group in water (5 mL) for 30 min. The mixture was extracted with ether, and the aqueous phase was evaporated at 3 Torr. Attempted purification of the muconates by anion-exchange chromatography (Dowex 1 formate equilibrated with potassium carbonate), 0–1 M potassium carbonate, resulted in extensive isomerization. Attempted recrystallization from various solvent systems resulted in the isolation of isomerized compounds.

Disodium *cis,cis*-3-fluoromuconate (1a) was obtained in 89% yield (130 mg): ^1H NMR (D_2O/NaOD, 200 MHz) δ 6.60 (dd, 1 H, $J_{H,F}$ = 33 Hz, J = 12.8 Hz), 6.11 (d, 1 H, J = 12.8 Hz), 5.55 (d, 1 H, $J_{H,F}$ = 22 Hz).

Disodium *cis,cis*-3-chloromuconate (1b) was obtained in 72% yield (95 mg): ^1H NMR (D_2O/NaOD, 200 MHz) δ 6.65 (d, 1 H, J = 12.7 Hz), 6.09 (s, 1 H), 5.99 (d, 1 H, J = 12.7 Hz).

Disodium *cis,cis*-3-bromomuconate (1c) was obtained in 78% yield (217 mg): ^1H NMR (D_2O/NaOD, 200 MHz) δ 6.65 (dd, 1 H, J = 12.6 Hz, J = 1 Hz), 6.38 (d, 1 H, J = 1 Hz), 5.95 (dd, 1 H, J = 12.6 Hz, J = 0.7 Hz).

General Procedure for the Isomerization of the Dimethyl *cis,cis*-3-Halomuconates. The dimethyl *cis,cis*-3-halomuconate (2.5 mmol) was dissolved in $CHCl_3$ (10 mL). The solution was irradiated for 1 h with a 250 W UV sun lamp at room temperature. The products were purified by silica gel TLC (1/1 hexane/$CHCl_3$).

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Dimethyl *cis,trans*-3-fluoromuconate (5a) was obtained as a colorless oil in 93% yield (438 mg): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.17 (dd, 1 H, $J_{H,F}$ = 18.7 Hz, J = 15.9 Hz), 6.48 (d, 1 H, J = 15.9 Hz), 5.84 (d, 1 H, $J_{H,F}$ = 17.9 Hz), 3.82 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.46 (d, J = 143.7 Hz), 165.01 (d, J = 23.9 Hz), 164.54, 131.31 (d, J = 20.0 Hz), 125.83 (d, J = 5.7 Hz), 105.96 (d, J = 29.0 Hz), 52.08, 51.92; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −30.57 (dd, $J_{H,F}$ = 17.9 Hz, $J_{H,F}$ = 27.1 Hz); EI mass spectrum, m/e 188 (M^+), 157 ($M^+ - OCH_3$), 129 ($M^+ - COOCH_3$), 97 ($M^+ - HOCH_3 - COOCH_3$), 70 ($M^+ - COOCH_3 - COOCH_3$); HRMS calcd for $C_8H_9FO_4$ 188.0485, found (m/e) 188.0494.

Dimethyl *cis,trans*-3-chloromuconate (5b) was obtained as a colorless oil in 84% yield (428 mg): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.57 (d, 1 H, J = 15.3 Hz), 6.57 (d, 1 H, J = 15.3 Hz), 6.33 (s, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (CDCl, 50 MHz) δ 165.85, 163.70, 145.21, 135.95, 128.01, 123.55, 52.00; EI mass spectrum, m/e 206 (M + 2), 204 (M^+), 175 (M + 2 − OCH_3), 173 ($M^+ - OCH_3$), 147 (M + 2 − $COOCH_3$), 145 ($M^+ - COOCH_3$); HRMS, calcd for $C_8H_9ClO_4$ 204.0189, found (m/e) 204.0185.

Dimethyl *cis,trans*-3-bromomuconate (5c) was obtained as a colorless solid in 88% yield (548 mg): mp 58 °C (hexane/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.52 (d, 1 H, J = 15.5 Hz), 6.60 (s, 1 H), 6.52 (d, 1 H, J = 15.5 Hz), 3.81 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.57, 163.52, 136.95, 136.78, 130.27, 122.66, 51.82; EI mass spectrum, m/e 250 (M + 2), 248 (M^+), 235 (M + 2 − CH_3), 233 ($M^+ - CH_3$), 219 (M + 2 − OCH_3), 217 ($M^+ - OCH_3$), 191 (M + 2 − $COOCH_3$), 189 ($M^+ - COOCH_3$), 169 (M^+ − Br); HRMS calcd for $C_8H_9BrO_4$ 247.9684, found (m/e) 247.9691.

General Procedure for the Synthesis of *cis,trans*-3-Halomuconic Acids. The dimethyl *cis,trans*-3-halomuconate (0.5 mmol) was dissolved in methanol (2 mL). An equal volume aqueous NaOH (10%) was added, and the mixture was stirred at room temperature for 1.5 h. The solution was acidified with aqueous HCl (20%) and chilled (5 °C) for several hours. The white precipitate was recrystallized from methanol/water.

***cis,trans*-3-Fluoromuconic acid (6a)** was obtained in 92% yield (74 mg): mp 222–224 °C dec; ^{1}H NMR (acetone-d_6, 200 MHz) δ 8.22 (dd, 1 H, $J_{H,F}$ = 29.3 Hz, J = 16.1 Hz), 6.45 (dd, 1 H, J = 16.1 Hz, J = 0.6 Hz), 5.97 (d, 1 H, $J_{H,F}$ = 18.7 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 168.40, 167.02 (d, J = 262.4 Hz), 167.38 (d, J = 23.5 Hz), 132.45 (d, J = 20.4 Hz), 126.97 (d, J = 5.4 Hz), 107.63 (d, J = 28.0 Hz); ^{19}F NMR (methanol-d_4, 376 MHz) δ −28.96 (dd, $J_{H,F}$ = 18.9, $J_{H,F}$ = 29.3); EI mass spectrum, m/e 160 (M^+), 140 (M^+ − HF), 123 (M^+ − HF − OH), 115 (M^+ − COOH), 97 (M^+ − COOH − H_2O), 69 (M^+ − COOH − HCOOH); HRMS calcd for $C_6H_5FO_4$ 160.0172, found (m/e) 160.0173.

***cis,trans*-3-Chloromuconic acid (6b)** was obtained in 98% yield (86 mg): mp 229–231 °C dec; ^{1}H NMR methanol-d_4, 400 MHz) δ 8.59 (dd, 1 H, J = 15.3 Hz, J = 0.6 Hz), 6.49 (dd, 1 H, J = 15.3 Hz, J = 0.6 Hz), 6.39 (t, 1 H, J = 0.6 Hz); ^{13}C NMR (methanol-d_4, 100 MHz) δ 168.58, 166.07, 145.57, 137.42, 129.33, 126.22; EI mass spectrum, m/e 178 (M + 2), 176 (M^+), 141 (M^+ − Cl), 133 (M + 2 − COOH), 131 (M^+ − COOH), 95 (M^+ − COOH − HCl); HRMS calcd for $C_6H_5ClO_4$ 175.9876, found (m/e) 175.9874.

***cis,trans*-3-Bromomuconic acid (6c)** was obtained in 72% yield (80 mg): mp 223 °C dec; ^{1}H NMR (methanol-d_4, 200 MHz) δ 8.57 (dd, 1 H, J = 15.1 Hz, J = 1.0 Hz), 6.71 (dd, 1 H, J = 0.6 Hz, J = 1.0 Hz), 6.45 (dd, 1 H, J = 15.1 Hz, J = 0.6 Hz); ^{13}C NMR (methanol-d_4, 100 MHz) δ 166.36, 164.59, 138.17, 136.99, 131.37, 129.78; EI mass spectrum, m/e 222 (M + 2), 220 (M^+), 177 (M + 2 − COOH), 175 (M^+ − COOH), 141 (M^+ − Br), 95 (M^+ − COOH − HBr); HRMS calcd for $C_6H_5BrO_4$ 219.9371, found (m/e) 219.9357.

Acknowledgment. We thank the National Institutes of Health (Grant GM 37210) for support of this research.

Registry No. **1a**, 118070-97-6; **1b**, 118071-02-6; **1c**, 118102-33-3; **2a**, 367-32-8; **2b**, 2138-22-9; **2c**, 17345-77-6; **3a**, 118070-98-7; **3b**, 31222-02-3; **3c**, 90965-63-2; **4a**, 118070-99-8; **4b**, 118071-00-4; **4c**, 118071-01-5; **5a**, 118071-03-7; **5b**, 118071-04-8; **5c**, 118071-05-9; **6a**, 118071-06-0; **6b**, 118071-07-1; **6c**, 118071-08-2.