collected with a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination) and mass spectra with a Varian MAT CH5 instrument (70 eV, 250 °C ion source temperature). Melting points (Thermopan hot stage, Reichert) are uncorrected. TLC was performed on silica gel 60 F-254 plates (Merck) with dichloromethane as the mobile phase.

1-[(4-Nitro-1*H*-inden-1-ylidene)methyl]pyrrolidine (9). A solution of 1[1] (450 mg, 2.33 mmol) in *N,N*-dimethylformamide (3 mL), *N,N*-dimethylformamide dimethyl acetal (0.375 mL, 2.82 mmol), and pyrrolidine (0.225 mL, 2.70 mmol) was heated under a nitrogen blanket in an oil bath (125 °C) for 18 h. The mixture was concentrated in a rotary evaporator at a bath temperature of 90 °C under aspirator vacuum and the resulting residue chromatographed on a column of silica gel (LiChroprep Si 60; E. Merck) with dichloromethane as the mobile phase. The dark red solids which were obtained after solvent evaporation were recrystallized from dichloromethane/methanol to give dark magenta prisms: 240 mg (42.5%); mp 151-152 °C; TLC R_f 0.75; UV (EtOH) λ_{max} 209 nm (ϵ 34 200), 240 (sh, 9500), 276 (5900), 352 (31 500), 369 (sh, 21 700), 448 (9000); NMR ($CDCl_3$) δ 2.04 (s, CH_2CH_2), 3.63 (s, CH_2NCH_2), 7.12 (t, H6, $J_{5,6} = J_{6,7} = 8$ Hz), 7.21, 7.54 (AB, H2 and H3, $J_{2,3} = 5$ Hz),[2] 7.70 (s, CH), 7.79 (d, H7, $J_{6,7} = 8$ Hz), 8.06 (d, H5, $J_{5,6} = 8$ Hz); EI mass spectrum, m/z (relative intensity) 242 ($M^{+\cdot}$, 100), 225 (M - OH, 14), 195 (M - HO - NO, 45).

Anal. Calcd for $C_{14}H_{14}N_2O_2$ (mol wt 242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.63; H, 6.04; N, 11.44.

Crystallographic Analysis. The crystal was of space group $P\bar{1}$ with unit cell dimensions a = 9.262 (2) Å, b = 11.056 (3) Å, c = 12.980 (3) Å, α = 66.66 (2)°, β = 80.73 (2)°, and γ = 82.74 (2)°, and d_{calcd} = 1.339 g cm^{-3} for $Z = 4$.

A crystal of the approximate dimensions 0.10 × 0.12 × 0.30 mm served for the collection of data which were not corrected for absorption [μ(Cu Kα) = 7.5 cm^{-1}]. Of the 3222 independent reflections for $\theta < 57°$, 2513 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[3] and was refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.047 and R_w = 0.054 for the 2513 observed reflections. The final difference map has no peaks greater than ±0.2 e Å^{-3}.

1-[(4-Nitro-1*H*-inden-1-ylidene)methyl]morpholine. The procedure used for the synthesis of **9** was followed, but morpholine was substituted for pyrrolidine. TLC indicated only a little product after 18 h at 125 °C. Thus, the bath temperature was increased to 150 °C and the mixture again heated overnight. Although an appreciable amount of starting material still remained, additional product was formed. The mixture was worked up as described to furnish the title compound in 25% yield as dark magenta prisms: mp >204 °C dec; TLC R_f 0.35; NMR ($CDCl_3$) δ 3.76 and 3.90 (2 m, $N(CH_2CH_2)_2O$), 7.21 (t, H6, $J_{5,6} = J_{6,7} = 8$ Hz), 7.29, 7.63 (AB, H2 and H3, $J_{2,3} = 5.5$ Hz),[2] 7.46 (s, CH), 7.83 (d, H5, $J_{5,6} = 8$ Hz), 8.09 (d, H7, $J_{6,7} = 8$ Hz); EI mass spectrum, m/z (relative intensity) 258 ($M^{+\cdot}$, 100), 241 (M - OH, 14), 228 (M - NO, 6), 212 (M - NO_2, 16), 211 (M - OH - NO, 23).

***N,N*-Dimethyl(4-nitro-1*H*-inden-1-ylidene)methanamine.** The described procedure leading to **9** was repeated without pyrrolidine, yielding the title compound as dark magenta crystals: 5% yield; mp > 173 °C dec; TLC R_f 0.72; NMR ($CDCl_3$) δ 3.34 (s, $N(CH_3)_2$), 7.16 (t, H6, $J_{5,6} = J_{6,7} = 8$ Hz), 7.32, 7.58 (AB, H2 and H3, $J_{2,3} = 5.5$ Hz), 7.53 (s, CH), 7.82 (d, H7, $J_{6,7} = 8$ Hz), 8.07 (d, H5, $J_{5,6} = 8$ Hz); EI mass spectrum, m/z (relative intensity) 216 ($M^{+\cdot}$, 100), 199 (M - OH, 6), 186 (M - NO, 6), 170 (M - NO_2, 23), 169 (M - OH - NO, 19).

Registry No. 1, 79172-35-3; 9, 79172-36-4; pyrrolidine, 123-75-1; 1-[(4-nitro-1*H*-inden-1-ylidene)methyl]morpholine, 79172-37-5; morpholine, 110-91-8; *N,N*-dimethyl(4-nitro-1*H*-inden-1-ylidene)-methanamine, 79172-38-6.

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Supplementary Material Available: Tables containing atomic coordinates and anisotropic thermal parameters for **9** (3 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of 3,5-Dihydroxy-4-methylbenzoic Acid

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In connection with our synthesis and elucidation of molecular mechanism of serotonin neurotoxins[1] we needed access to 3,5-dihydroxy-4-methylbenzoic acid (1). This benzoic acid, in various modified forms, is a component of a number of natural products including long-chain phenols[2] (of cashew nutshell liquid), fungal[3,4] and lichen[5,6] metabolites (e.g., depsidones), and the antitumor antibiotic sibiromycin.[7] This compound has been used as a starting material, for example, in the synthesis of sclerotiorin group of fungal metabolites and their numerous degradation products,[8] long-chain resorcinols,[2] and in the total synthesis efforts toward sibiromycin.[9] However, this relatively simple benzoic acid is not available commercially and is extremely inaccessible by the procedures described in early literature.[10-12] More recently, a relatively simple five-step synthesis of 1 from 3,4,5-trimethoxybenzoic acid was described,[13] although the overall yield was low. We now report an operationally simple and high yielding three-step synthesis of 1 from readily available starting material, 3,5-dihydroxybenzoic acid (2).

Our approach involved selective protection of C-2 and C-6 of 2 followed by introduction of a methyl group equivalent on C-4 and finally removal of the protecting groups and generation of the methyl function both in one step.[14] Thus, addition of bromine (in slight excess of 2

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(14) Reference 9 described failure to introduce a methyl group on C-4 by way of iodination or formylation of 2 or its methyl ester, respectively.

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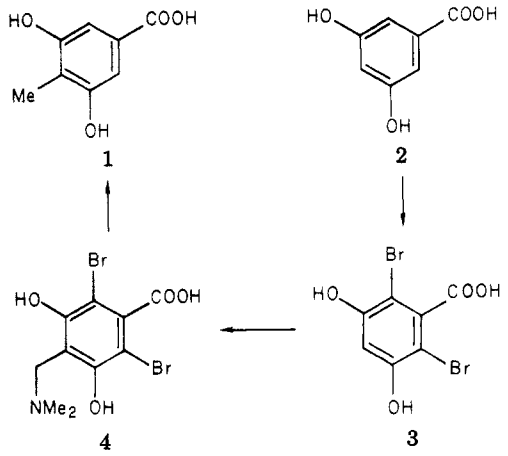
equiv) in chloroform to a suspension of **2** in chloroform at room temperature produced the dibromoresorcylic acid (**3**) in 97% yield. As the product precipitated from the reaction mixture, isolation was greatly simplified and entailed only filtration. Only trace amounts of the tribromo derivative of **2** were formed (as detected by mass spectrometry) presumably because of the insolubility of **3** in chloroform.



Next we considered the introduction of methyl group equivalents such as CH_2OH, CH_2Cl, or CH_2NMe_2 on C-4 of **3**, which would allow simultaneous generation of the methyl function and removal of bromines by, for example, catalytic hydrogenolysis. Attempts to hydroxymethylate or chloromethylate **3** were not successful, leading in each case to the formation of intractable products. However, when **3** was treated with 2 equiv of a mixture containing aqueous formaldehyde and aqueous dimethylamine in ethanol–acetic acid at toom temperature for 24 h, the Mannich base **4** precipitated and was isolated by filtration quantitatively. Similar results were obtained when morpholine was used as the amine. Presence of the (dimethylamino)methyl group in **4** could be easily detected by ^1H NMR. Treatment of **4** in 3 N NaOH with about equal weight of Raney nickel alloy at 25–30 °C resulted in the isolation of the desired benzoic acid **1** by extractive workup in 70% yield. Its physical properties were identical with those described in literature.[13] In addition, its ^1H NMR spectrum displayed, as expected, sharp singlets at δ 2.16 and 7.18 due to methyl and H-2 and H-6, respectively.

Experimental Section

2,6-Dibromo-3,5-dihydroxybenzoic Acid (3). To a stirred suspension of 3,5-dihydroxybenzoic acid (Aldrich, 97%, 38.1 g, 240 mmol) in 400 mL of chloroform was added from a pressure-equalizing dropping funnel a solution of bromine (80 g, 500 mmol) in 100 mL of chloroform at 25 °C over a period of 1.5 h. (A trap system leading from the top of the addition funnel was provided to trap evolving hydrogen bromide.) The mixture was then stirred at 25 °C for 5 h and filtered. The filter cake was washed with chloroform (3 × 100 mL) and then with ice cold water (1 × 200 mL). The precipitate was dried under vacuum over NaOH overnight to give 72.6 g (97%) of **3** as a white powder: mp 256 °C dec; ^1H NMR (acetone-d_6) δ 6.80 (s, H-4, after exchange of OH protons with D_2O); mass spectrum (EI), *m/e* (relative intensity) 314 (54, $M^+ + 4$), 312 (100, $M^+ + 2$), 310 (53, M^+).

Anal. Calcd for $C_7H_4Br_2O_4$: C, 26.95; H, 1.29. Found: C, 27.07; H, 1.33.

2,6-Dibromo-3,5-dihydroxy-4-[(dimethylamino)methyl]benzoic Acid (4). To a stirred mixture of 37% aqueous formaldehyde (76.8 g, 960 mmol), absolute ethanol (160 mL), and glacial acetic acid (320 mL) was added 40% aqueous dimethylamine (108 g, 960 mmol) in portions with cooling, keeping the temperature at ~25 °C. The cooling bath was removed and powdered 2,6-dibromo-3,5-dihydroxybenzoic acid (**3**; 149.8 g, 480 mmol) was added over a period of 2 min. The mixture became homogeneous and darkened slightly, and after ~5 min a white solid began to appear. The mixture was stirred at 25 °C for 24 h and then at 0 °C for 2 h (to complete precipitation of product) and filtered. The precipitate was washed with cold acetone (2 × 200 mL), dried under suction briefly (prolonged exposure to air darkens the product), and then under vacuum to give 173.6 g (98%) of **4** as a white powder: mp 210 °C dec; ^1H NMR (dimethyl-d_6 sulfoxide) δ 2.48 (s, 6 H, NMe_2), 4.00 (s, 2 H, CH_2), 5.50 (br s, OH, exchanged with D_2O); mass spectrum (EI), *m/e* (relative intensity) 371, (10, $M^+ + 4$), 369 (19, $M^+ + 2$), 367 (11, M^+).

Anal. Calcd for $C_{10}H_{11}Br_2NO_4$: C, 32.55; H, 3.00; N, 3.80. Found: C, 32.51; H, 3.35; N, 3.48.

3,5-Dihydroxy-4-methylbenzoic Acid (1). To a stirred solution of 2,6-dibromo-3,5-dihydroxy-4-[(dimethylamino)-methyl]benzoic acid (**4**; 73.8 g, 200 mmol) in 500 mL of 3 N NaOH (1500 mmol) under nitrogen was added with cooling, keeping the temperature at 25–30 °C, in 3–4-g portions 69 g of Raney nickel alloy (Grace, No. 2813 Raney Nickel Catalyst Powder) over a period of 4 h. The mixture was then stirred at 25 °C for 12 h and filtered through a pad of Celite covered with a thin layer of glass wool. The filter cake was washed with water (2 × 100 mL), and the combined filtrates were acidified to pH 1 with concentrated HCl to give a clear pale yellow or light purple solution. The solution was extracted with ethyl acetate (4 × 75 mL), and the combined organic extracts were washed with 10% NaCl solution (2 × 30 mL), dried (Na_2SO_4), and evaporated in vacuo to dryness to give 23.24 g (70%) of **1** as a white solid: mp 264–265 °C (lit.[13] mp 264–265 °C); ^1H NMR (acetone-d_6) δ 2.16 (s, 3 H, CH_3), 5.35 (br s, OH, exchanged with D_2O), 7.18 (s, 2 H, H-2, H-6). Benzylation ($PhCH_2Cl/K_2CO_3$/DMF, 95 °C, 4 h) of **1** gave known benzyl 3,5-(dibenzyloxy)-4-methylbenzoate: mp 118–119 °C (lit.[9] mp 118–119 °C). The ^1H NMR of this benzoate was identical with that described in literature.[9]

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Registry No. **1**, 28026-96-2; **2**, 99-10-5; **3**, 79200-80-9; **4**, 79200-81-0; benzyl 3,5-(dibenzyloxy)-4-methylbenzoate, 76447-15-9.

$S_{RN}1$ Reactions of *o*-Dibromobenzene with Ketone Enolate Ions[1]

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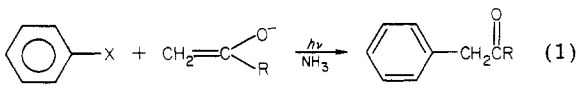
Under irradiation, ketone enolate ions in ammonia solution are phenylated by reaction with halobenzenes[3-5] (eq 1). There is evidence that these reactions occur by the radical-chain $S_{RN}1$ mechanism.[6]



(1)

Several other nucleophiles also react with simple halobenzenes under photostimulation.[6]

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