(s, 1, C=CH), 7.30 (m, 2, 7,8-H), 7.41 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.45 (d, J = 1 Hz, 1, 5-H), 8.04 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); UV (EtOH) λ_{max} 304 nm (ϵ 2.1 × 10^4).

Using the above described procedures benzoates **3b**, **3d**, and **3e** were prepared, isolated, and characterized. (*E*)-**3b** and (*E*)-**3e** were prepared by the second method and isolated by recrystallization. (*E*)-**3d** and (*Z*)-**3d** were prepared by the first method and purified by preparative LC using the recycle technique (3% Et_2O/hexane). (*E*)-**3c** and (*Z*)-**3c** were prepared from the lithium phosphonate of **2** in THF and isolated by preparative LC (1% Et_2O/hexane) before characterization.

Ethyl 4-[(*E*)-2-(1,1-dimethyl-1,2,3,4-tetrahydro-7-naphthyl)propenyl]benzoate ((*E*)-3b): mp 83–84 °C (hexane); LC (3% Et_2O/hexane, 1.0 mL/min) t_R 5.0 min (99.8%); IR ($CHCl_3$) 1705, 1610 cm^{-1}; 90-MHz ^1H NMR δ 1.33 (s, 6, $C(CH_3)_2$), 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 1.72 (m, 4, 2,3-H), 2.29 (d, J = 1.5 Hz, 3, CH_3C=C), 2.80 (m, 2, 4-H), 4.41 (q, J = 7 Hz, 2, CH_2CH_3), 6.79 (s, 1, C=CH), 7.0–7.55 (m, 5, 5,6,8-H, ArH meta to CO_2Et), 8.11 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); UV (95% EtOH) λ_{max} 233 nm (ϵ 1.4 × 10^4), 305 (2.6 × 10^4). Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.64; H, 8.25. The ^1H NMR spectrum for (*Z*)-**3b** displayed signals at δ 1.11 (s, 6, $C(CH_3)_2$), 1.37 (t, J = 7 Hz, 3, CH_2CH_3), 1.71 (m, 4, 2,3-H), 2.26 (d, J = 1.5 Hz, 3, CH_3C=C), 2.79 (m, 2, 4-H), 4.36 (q, J = 7 Hz, 2, CH_2CH_3), 6.53 (s, 1, C=CH), 6.8–7.2 (m, 5, 5,6,8-H, ArH meta to CO_2Et), and 7.87 (d, J = 8 Hz, 2, ArH ortho to CO_2Et).

Ethyl 4-[(*E*)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoate ((*E*)-3c): yellow oil; LC (2% Et_2O/hexane, 3.0 mL/min) t_R 5.0 (0.5%), 5.7 min (99.5%); IR (film) 1730, 1620, 1580 cm^{-1}; 300-MHz ^1H NMR δ 1.21 (d, J = 8 Hz, 2, endo-2,3-H), 1.56 (m, 1, anti-9-H), 1.77 (d, J = 8 Hz, 1, syn-9-H), 1.94 (d, J = 8 Hz, 2, exo-2,3-H), 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 2.29 (s, 3, CH_3C=C), 3.37 (s, 2, 1,4-H), 4.38 (q, J = 7 Hz, 2, CH_2CH_3), 6.81 (s, 1, C=CH), 7.16 (d, J = 8 Hz, 1, 7-H), 7.24 (d, J = 8 Hz, 1, 8-H), 7.35 (s, 1, 5-H), 7.40 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 8.03 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); UV (EtOH) λ_{max} 233 nm (ϵ 1.49 × 10^4), 308 (2.66 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1757.

Ethyl 4-[(*Z*)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoate ((*Z*)-3c): yellow oil; LC (2% Et_2O/hexane, 3.0 mL/min) t_R 5.0 (99%), 5.7 min (1.0 %); IR (film) 1730, 1620, 1580 cm^{-1}; 300-MHz ^1H NMR δ 1.10–1.20 (2 m, 2, endo-2,3-H), 1.35 (t, J = 7 Hz, 3, CH_2CH_3), 1.50 (d, J = 8 Hz, 1, anti-9-H), 1.74 (d, J = 8 Hz, 1, syn-9-H), 1.88 (m, 2, exo-2,3-H), 2.21 (s, 3, CH_3C=C), 3.25 and 3.34 (2 s, 2, 1,4-H), 4.34 (q, J = 7 Hz, 2, CH_2CH_3), 6.42 (s, 1, C=CH), 6.85 (d, J = 8 Hz, 1, 7-H), 6.94 (s, 1, 5-H), 6.95 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.06 (d, J = 8 Hz, 1, 8-H), 7.73 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); UV (EtOH) λ_{max} 239 nm (ϵ 1.67 × 10^4), 300 (1.68 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1741.

Ethyl 4-[(*E*)-2-(1,2-dimethyl-7-naphthyl)propenyl]benzoate ((*E*)-3d): pale yellow crystals, mp 94–95 °C (EtOAc/hexane); LC (2% Et_2O/hexane, 1.5 mL/min) t_R 6.6 min (100%); IR ($CHCl_3$) 1705, 1605 cm^{-1}; 300-MHz ^1H NMR δ 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 2.42 (d, J = 1 Hz, 3, CH_3C=C), 2.50 (s, 3, 2-CH_3), 2.64 (s, 3, 1-CH_3), 4.40 (q, J = 7 Hz, 2, CH_2CH_3), 6.98 (s, 1, C=CH), 7.29 (d, J = 8 Hz, 1, 3-H), 7.47 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.61 (d, J = 8 Hz, 1, 4-H), 7.62 (d, J = 9 Hz, 1, 6-H), 7.79 (d, J = 9 Hz, 1, 5-H), 8.07 (d, J = 8 Hz, 2, ArH ortho to CO_2Et), 8.12 (m, 1, 8-H); UV (EtOH) λ_{max} 220 nm (ϵ 3.6 × 10^4), 240 (2.7 × 10^4), 288 (2.9 × 10^4), 318 (2.7 × 10^4). Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69, H, 7.02. Found: C, 83.85; H, 7.20.

Ethyl 4-[(*Z*)-2-(1,2-dimethyl-7-naphthyl)propenyl]benzoate ((*Z*)-3d): white crystals, mp 88–88.5 °C (EtOAc/hexane); LC (2% Et_2O/hexane, 1.5 mL/min) t_R 6.2 min (100%); IR ($CHCl_3$) 1705, 1605 cm^{-1}; 300-MHz ^1H NMR δ 1.32 (t, J = 7 Hz, 3, CH_2CH_3), 2.34 (d, J = 1 Hz, 3, CH_3C=C), 2.46 (s, 6, 1,2-CH_3), 4.29 (q, J = 7 Hz, 2, CH_2CH_3), 6.59 (s, 1, C=CH), 7.02 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.18 (dd, J = 8 Hz, J = 2 Hz, 1, 6-H), 7.28 (d, J = 8 Hz, 1, 3-H), 7.58 (d, J = 8 Hz, 1, 4-H), 7.68 (d, J = 8 Hz, 1, 5-H), 7.72 (d, J = 8 Hz, 2, ArH ortho to CO_2Et), 7.86 (d, J = 1 Hz, 1, 8-H); UV (EtOH) λ_{max} 231 nm (ϵ 5.5 × 10^4), 287 (2.1 × 10^4). Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 84.00; H, 7.09.

Ethyl 4-[(*E*)-2-(1,2,3,4-tetramethyl-6-naphthyl)propenyl]benzoate ((*E*)-3e): pale yellow plates, mp 114–115 °C (EtOAc/hexane); LC (2% Et_2O/hexane, 1.0 mL/min) t_R 8.9 min (100%); IR ($CHCl_3$) 1715, 1605 cm^{-1}; 300-MHz ^1H NMR δ 1.42 (t, J = 7 Hz, 3, CH_2CH_3), 2.42 (d, J = 1 Hz, 3, CH_3C=C), 2.44 (s, 6, 2,3-CH_3), 2.64 and 2.67 (2 s, 6, 1,4-CH_3), 4.40 (q, J = 7 Hz, 2, CH_2CH_3), 7.00 (br s, 1, C=CH), 7.48 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.65 (dd, J = 9 Hz, J = 2 Hz, 1, 7-H), 8.03 (d, J = 9 Hz, 1, 8-H), 8.07 (d, J = 8 Hz, 2, ArH ortho to CO_2Et), 8.14 (d, J = 2 Hz, 1, 5-H); UV (EtOH) λ_{max} 224 nm (ϵ 3.3 × 10^4), 245 (2.8 × 10^4), 296 (3.4 × 10^4), 325 (2.7 × 10^4). Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 84.01; H, 7.64.

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Registry No. **1a**, 17610-21-8; **1b**, 53326-65-1; **1c**, 4228-39-1; **1d**, 93184-82-8; **1e**, 34163-24-1; **2**, 71441-08-2; (*E*)-**3a**, 71441-09-3; (*Z*)-**3a**, 75078-90-9; (*E*)-**3b**, 93184-83-9; (*Z*)-**3b**, 93184-84-0; (*E*)-**3c**, 91587-20-1; (*Z*)-**3c**, 91587-21-2; (*E*)-**3d**, 93184-85-1; (*Z*)-**3d**, 93184-86-2; (*E*)-**3e**, 93184-87-3; (*Z*)-**3e**, 93184-88-4; CH_3CHO, 75-07-0; 1,1-dimethyl-1,2,3,4-tetrahydronaphthalene, 1985-59-7; 1,4-methano-1,2,3,4-tetrahydronaphthalene, 4486-29-7; 1,2,3,4-tetramethylnaphthalene, 3031-15-0; 7-bromo-1,2-dimethylnaphthalene, 93184-89-5.

Reaction of Lithium *o*-Lithiophenoxide with Carbonyl Compounds

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The usefulness of the regioselective ortho deprotonation of aromatic ethers by strong bases, such as *n*-butyllithium, has been widely recognized by synthetic chemists.[1] Metal–halogen exchange of *o*-bromophenyl ethers with *n*-butyllithium is also a useful method for the preparation of these lithium salts.[2] The ortho-lithiated aryl ethers have been treated with a wide variety of electrophiles to produce adducts in good to excellent yields. We were in need of a general method for the preparation of a number of α,α-disubstituted 2-hydroxybenzyl alcohol derivatives of the general formula **4a** (R = H). We were able to prepare adducts of ketones and aldehydes with the lithium salt of anisole[3] **3b** in good yields. Due to the extreme acid sensitivity of the benzylic alcohol functionality all attempts to demethylate the adducts with a number of reagents were unsuccessful. While there are a number of basic reagents available for the deprotection of aryl methyl ethers,[4] the high temperatures and vigorous reaction conditions required rendered them unsuitable for the present purposes. Even the more labile *o*-methoxymethylphenol adducts[5] **4c** suffered appreciable decomposition upon attempted deprotection.

While the preparation of lithium *o*-lithiophenoxide has been known for some time,[6] its reaction with carbonyl

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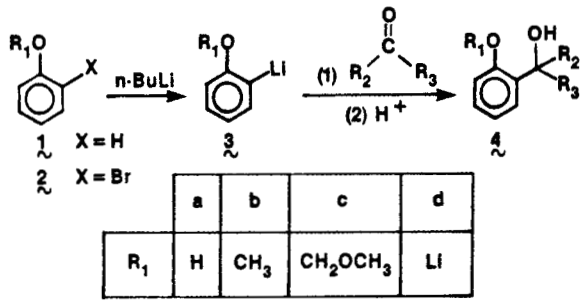

	a	b	c	d
R_1	H	CH_3	CH_2OCH_3	Li

compounds has not been exploited. We found that the dianion **3d** condensed with a number of enolizable and nonenolizable ketones and aldehydes to produce the desired adducts **4a** in good yields. The dianion **3d** was conveniently prepared in high yield by treatment of an etheral solution of *o*-bromophenol with 2 equiv of *n*-butyllithium at 0 °C for 2–3 h.

Quenching an etheral solution of the dianion with D_2O produced *o*-deuteriophenol in 90% isolated yield. That complete conversion of *o*-bromophenol to the dianion had occurred was confirmed by gas chromatographic analysis of the crude product mixture. The extent of ortho-deuteration was essentially quantitative as determined by proton magnetic resonance spectroscopy and mass spectrometry.

We believe there are several aspects of this process that merit emphasis. The condensation product of the readily available deuterioacetone and the dianion was obtained in good yield. Synthesis of this product by the more conventional method[7] would have required condensation of methyl salicylate with the vastly more expensive CD_3MgI. Since all the chemistry takes place in one pot, the process is quick and operationally simple. The need for masking and unmasking of the phenol has been eliminated by this method. We have also found that the dianion of substituted 2-bromophenol derivatives such as 2-bromo-4-methoxyphenol are easily prepared in a similar manner.[8]

Experimental Section

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Microlab MX-250 instrument as neat liquids, solutions in chloroform, or as KBr disks. Proton and carbon magnetic resonance spectra were recorded on Varian EM-390 and Varian XL-200 spectrometers, respectively, as solutions in deuteriochloroform. High-resolution and field-desorption mass spectra were recorded on a MAT 731 mass spectrometer. Analytical VPC was performed on a Varian 3700 FID or Varian 6000 FID-equipped instrument with a 10 ft × $^1/_8$ in. 3% OV 101 column. Medium-pressure liquid chromatography was performed on 0.032–0.063 mm ICN silica gel in Michael-Miller columns. Components were detected at 280 nm by an ISCO Model UA-5 detector. Flash chromatography[9] was carried out on the aforementioned silica gel using hexane–ethyl acetate as eluant. Thin layer chromatography (TLC) was performed on Whatman glass plates (0.25 mm) with silica gel; the components were visualized with phosphomolybdic acid. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane and chloroform were distilled from P_2O_5 and stored over activated 4-Å molecular sieves. All other solvents used were the highest purity available and used as received.

2-(2-Hydroxyphenyl)-2-hydroxytricyclo[3.3.1.1]decane. A Typical Example. To a solution of *n*-butyllithium (8.2 mL, 13 mmol, 1.55 M in hexane) in ether cooled to 0 °C was added *o*-bromophenol (1.127 g, 6.5 mmol). After being stirred at room temperature for 2 h, the solution was cooled to −78 °C and adamantanone (0.978 g, 6.50 mmol) in 20 mL of ether was added dropwise over a period of 10 min. The solution was allowed to warm to 0 °C (ca. 1 h) and then quenched by the dropwise addition of saturated aqueous ammonium chloride solution. The phases were separated, the aqueous phase was extracted with ether, and the combined ethereal layer was washed with sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude solid was purified by recrystallization from toluene–hexane: mp 165–166 °C; 1.31 g (82%); ^1H NMR ($CDCl_3/Me_4Si$) δ 1.62 (m, 1 H), 1.76 (m, 5 H), 1.87 (m, 3 H), 2.13 (s, 1 H, exchanges with D_2O), 2.40 (m, 1 H), 2.56 (m, 3 H), 6.68 (dd, 2 H, J = 7 Hz, J = 1 Hz), 7.78 (s, 1 H, exchanges with D_2O); ^{13}C NMR ($CDCl_3/Me_4Si$) 26.84 (d), 27.09 (d), 33.16 (t), 35.57 (t), 35.76 (d), 37.84 (t), 78.70 (s), 118.25 (d), 119.26 (d), 127.11 (d), 128.80 (d), 130.68 (s), 156.37 ppm (s); IR (KBr) 3442 cm^{-1} (OH); mass spectrum calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1451.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.7; H, 8.3.

9-(2-Hydroxyphenyl)-9-hydroxy[3.3.1]nonane, isolated in 55% yield after recrystallization from toluene and hexane: mp 164–165 °C; ^1H NMR ($CDCl_3/Me_4Si$) δ 1.40–2.60 (m, 15 H), 1.98 (s, 1 H, exchanges with D_2O), 6.67–7.34 (m, 4 H), 7.79 (s, 1 H, exchanges with D_2O); ^{13}C NMR ($CDCl_3/Me_4Si$) 20.08 (t), 20.65 (t), 27.58 (t), 30.22 (t), 35.56 (d), 77.89 (s), 118.14 (d), 119.33 (d), 127.34 (d), 128.76 (d), 131.07 (s), 156.40 ppm (s); IR (KBr) 2248 cm^{-1} (OH); mass spectrum calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1461.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.6; H, 8.8.

(2-Hydroxyphenyl)diphenylmethanol, isolated in 88% yield after recrystallization from aqueous methanol: mp 135.5–138.5 °C (lit. mp 140–141 °C); ^1H NMR ($CDCl_3/Me_4Si$) δ 3.67 (s, 1 H, exchanges with D_2O), 6.70–7.33 (m, 15 H), 8.37 (s, 1 H, exchanges with D_2O); ^{13}C NMR ($CDCl_3/Me_4Si$) 84.73 (s), 117.54 (d), 119.13 (d), 127.79 (d), 127.87 (d), 128.14 (d), 129.53 (d), 129.99 (d), 130.13 (s), 144.89 (s), 155.88 ppm (s); IR (KBr) 3350 cm^{-1} (OH); mass spectrum calcd for $C_{19}H_{16}O_2$ 276.1150, found: 276.1151.

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.28; H, 5.82. Found: C, 82.3; H, 5.9.

α,α-Dimethyl-2-hydroxybenzyl alcohol, isolated in 80% yield after recrystallization from *n*-hexane: mp 44.5–45.5 °C (lit.[8] mp 41–44 °C); ^1H NMR ($CDCl_3/Me_4Si$) δ 1.62 (s, 6 H), 2.94 (s, 1 H, exchanges with D_2O), 7.00 (m, 4 H), 9.17 (s, 1 H, exchanges with D_2O); IR (KBr) 3350 cm^{-1} (OH).

α-Phenyl-2-hydroxybenzyl alcohol, isolated in 88% yield after recrystallization from *n*-hexane: mp 87–89 °C (lit.[11] mp 84–85 °C); ^1H NMR ($CDCl_3/Me_4Si$) δ 3.08 (br s, 1 H, exchanges with D_2O), 5.92 (s, 1 H), 6.80–7.40 (m, 9 H), 7.86 (s, 1 H, exchanges with D_2O); IR (KBr) 3330 cm^{-1} (OH).

α,α-Bis(trideuteriomethyl)-2-hydroxybenzyl alcohol, isolated in 80% yield after recrystallization from *n*-hexane: mp 45–47 °C; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.00 (s, 1 H, exchanges with D_2O), 7.05 (m, 4 H), 8.52 (s, 1 H, exchanges with D_2O); ^{13}C NMR ($CDCl_3/Me_4Si$) 29.14 (sept, J = 19.4 Hz), 117.27 (d), 119.62 (d), 125.24 (d), 128.73 (d), 131.00 (s), 155.20 ppm (s); IR (KBr) 3340 cm^{-1} (OH); mass spectrum calcd for $C_9H_6D_6O_2$ 158.1214, found 158.1215.

2-Deuteriophenol, isolated in 90% yield after sublimation at 15 mm at room temperature: mp 40.0–41.5 °C; ^1H NMR ($CDCl_3/Me_4Si$) δ 4.83 (br s, 1 H, exchanges with D_2O), 6.87 (m, 2 H), 7.27 (m, 2 H), proton decoupled at 50.3-MHz ^{13}C NMR ($CDCl_3/Me_4Si$) 155.04 (C-1, s), 115.03 (C-2, t, J = 25 Hz), 129.54 (C-3, d), 102.86 (C-4, d), 129.63 (C-5, d), 115.30 ppm (C-6, d); IR (KBr) 3400 cm^{-1} (OH); mass spectrum M^+ 95, fragmentation pattern indicated deuterium on the ring.

Salicylaldehyde, prepared in 70% yield: bp 195 °C; ^1H NMR and IR spectra identical with those of an authentic sample.

1-(2-Hydroxyphenyl)-2-propen-1-ol, isolated in 88% yield,

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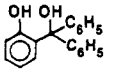
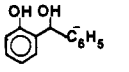
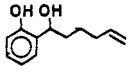
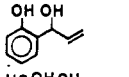
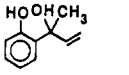
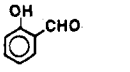
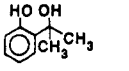
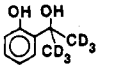
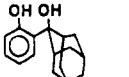
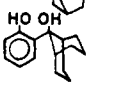
Table I. Adducts of Lithium o-Lithiophenoxide with Carbonyl Compounds

Substrate	Product	Yield[a]	mp (bp) °C	lit. mp °C ref
$C_6H_5CC_6H_5$ (O)		75	135.5-138.5	140-141[10]
C_6H_5CHO		88	87-89	84-85[11]
$CH_2=CH(CH_2)_3CHO$		82	oil	oil[12,13]
$CH_2=CH-CHO$		88	oil	25-30[12]
$CH_2=CH-C(=O)-CH_3$		80	oil	25-30[12]
$C_6H_5N(CHO)-CH_3$		68	(195)	(b)
CH_3CCH_3 (O)		80	44.5-45.5	41-45[7]
CD_3CCD_3 (O)		80	46-47	
		82	165-166	
		55	163-165	

[a] Isolated yield of purified product. [b] Identical with an authentic sample.

after purification by medium-pressure liquid chromatography using 6:1 hexane/ethyl acetate: oil (lit.[12] oil); ^1H NMR ($CDCl_3/Me_4Si$) 1.20 (s, 1 H, exchanges with D_2O), 5.00–5.30 (m, 3 H), 5.97 (ddd, 1 H, J = 14 Hz, J = 10 Hz, J = 5.5 Hz), 6.70–7.30 (m, 4 H), 8.30 (s, 1 H, exchanges with D_2O); IR (neat liquid) 3380 cm^{-1} (OH).

2-(2-Hydroxyphenyl)-3-buten-2-ol, isolated in 80% yield after purification by flash chromatography using 6:1 hexane/ethyl acetate: oil (lit.[12] oil); ^1H NMR ($CDCl_3/Me_4Si$) δ 1.00–2.28 (m, 6 H), 1.24 (s, 1 H, exchanges with D_2O), 4.68 (d, 1 H, J = 8 Hz), 4.80–5.10 (m, 2 H), 5.71 (ddt, 1 H, J = 17 Hz, J = 10 Hz, J = 6 Hz), 6.76–7.30 (m, 4 H), 8.00 (s, 1 H, exchanges with D_2O); IR (neat liquid) 3320 cm^{-1} (OH).

Acknowledgment. We wish to thank Dr. Elizabeth Williams and Mr. Paul Donahue for obtaining carbon NMR spectra, Mr. Steve Dorn for mass spectral data, and Lynn Heidrich Hendrickson for preparing this manuscript.

Registry No. **2a**, 95-56-7; **3d**, 55274-02-7; (2-hydroxyphenyl)diphenylmethanol, 6326-60-9; 2-phenyl-2-hydroxybenzyl alcohol, 40473-50-5; 1-(2-hydroxyphenyl)-5-hexen-1-ol, 38865-45-1; 1-(2-hydroxyphenyl)-2-propen-1-ol, 38865-40-6; 2-(2-hydroxyphenyl)-3-buten-2-ol, 38865-41-7; salicylaldehyde, 90-02-8; α,α-dimethyl-2-hydroxybenzyl alcohol, 3045-32-7; α,α-bis(trideuteriomethyl)-2-hydroxybenzyl alcohol, 93085-30-4; 2-(2-hydroxyphenyl)-2-hydroxytricyclo[3.3.1.1]decane, 93085-31-5; 9-(2-hydroxyphenyl)-9-hydroxybicyclo[3.3.1]nonane, 93085-32-6; 2-deuteriophenol, 23951-01-1; benzophenone, 119-61-9; benzaldehyde, 100-52-7; 5-hexenal, 764-59-0; 2-propenal, 107-02-8; 3-buten-2-one, 78-94-4; *N*-methyl-*N*-phenylformamide, 93-61-8; 2-propanone, 67-64-1; 2-propanone-d_6, 666-52-4; 2-adamantanone, 700-58-3; bicyclo[3.3.1]nonan-9-one, 17931-55-4; water-d_2, 7789-20-0; *n*-butyllithium, 109-72-8; hexane, 110-54-3.

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An Internal Imino-Diels-Alder Route to a Tetrahydroisoquinoline

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The internal Diels–Alder reaction of benzocyclobutenes (via quinodimethanes) has been exploited for heterocyclic systems on numerous occasions,[1] as has been the imino-Diels–Alder reaction,[2] but the generation of both reactive intermediates at the same time (e.g., **9**) has not yet been attempted. Construction of an appropriate precursor for the application of this route to the synthesis of Praziquantel (**1**), a well-known drug for the treatment of schistosomiasis,[3] was accomplished in a straightforward manner.

Our first choice for the leaving group on the oxymethylamide moiety, an acetoxy group (**7**), proved too labile, and the compound decomposed (to amide **6**). However, the less labile methoxy group **8** worked reasonably well and was easily prepared directly from the acetoxy intermediate. Pyrolysis of the precursor in various solvents was unavailing, but was successfully accomplished in the gas phase.

The only poor step in the sequence was the alkylation of the primary amine **3** with chloroacetamide (38%). No real attempt was made to optimize the yield; however, the alternative synthesis of amine **4** by reductive amination with glycineamide (30%, also unoptimized) appears to be more promising despite the lower yield.

Experimental Section

Melting points (uncorrected) were determined in open capillaries in a Thomas-Hoover Uni-melt apparatus. Routine proton spectra were obtained with a Varian EM360 nuclear magnetic resonance spectrometer, in deuteriochloroform, with tetramethylsilane as the internal standard. Infrared spectra were recorded on a Perkin-Elmer IR598 instrument. Elemental analyses were performed by the Galbraith Analytical Laboratories, Knoxville, TN. We offer thanks to Dr. Joseph W. Depenbusch for the authentic sample of (racemic) Praziquantel.

Hydrogenation[5] of Cyanobenzocyclobutene. Cyanobenzocyclobutene (**2**;[4] 8.0 g, 0.062 mol) was added to 300 mL of ethanol saturated with ammonia, followed by a slurry of 0.5 g of Raney nickel (W-2) in water (pH 10). The mixture was shaken in an atmosphere of hydrogen at 25–30 psi until no further hydrogen was absorbed (6–8 h) and then filtered through Celite and concentrated to give 8.5 g of crude product. This was distilled under vacuum to give (benzocyclobutenyl)methylamine (**3**) (7.96 g, 96%) as a colorless liquid: bp 35–40 °C (0.05 mm); ^1H NMR δ 7.15 (4 H, m, ArH), 3.75–2.60 (5 H, m), 1.30 (2 H, s, exchangeable D_2O, NH_2). IR 3640, 3360, 2915, 2845, 1590, 1580, 1570, 1455, 1445, 870 cm^{-1}. Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.90; H, 8.32; N, 10.34.

Condensation of Amine 3 with Chloroacetamide. A mixture of amine **3** (8.0 g, 0.06 mol) and 6.0 g (0.064 mol) of chloroacetamide in 50 mL of absolute ethanol was refluxed under nitrogen for 6 h. After about 4 h the initially clear solution began to deposit white crystals. The hot mixture was suction filtered, and the crystalline product was washed with warm ethanol and dried under vacuum, affording hydrochloride **4** (5.2 g, 38%): mp 246–248 °C dec; ^1H NMR 9.40 (2 H, br s, exchangeable D_2O, NH_2^+), 8.07 and 7.60 (2 H, each br s, exchangeable D_2O, $CONH_2$), 7.26 (4 H, m, ArH), 3.77 (2 H, s, CH_2CO), 4.10–2.90 (5 H, m); IR 3380, 3200, 2920, 3880, 2760, 2623, 2415, 1780, 1642, 1455, 1415, 1318, 730 cm^{-1}. Anal. Calcd for $C_{11}H_{15}N_2OCl$: C, 58.28; H, 6.67; N, 12.35; Cl, 15.64. Found: C, 58.40; H, 6.86; N, 12.37; Cl, 15.71.

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