

product 5 exhibited a strong carbonyl infrared absorption at 1767 cm^{-1} and had a proton NMR spectrum consistent with the assigned structure.

Oxidation of 4 with *m*-Chloroperoxybenzoic Acid. To a solution of 1 g of 4 (0.003 mol) in 25 mL of dry methylene chloride was slowly added 0.63 g of *m*-chloroperoxybenzoic acid. The reaction temperature was maintained at 25 °C over the 30-min addition. After 1 h of additional stirring, the reaction was quenched with 20 mL of 10% sodium sulfite. The methylene chloride layer was separated and dried over anhydrous magnesium sulfate. After removal of solvent, the reaction mixture was distilled (bp₁₀ 64 °C) to yield 0.42 g (86%) of the 10:40 *exo*/*endo* isomeric mixture 1. There was no 5 found from this procedure.

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Registry No. *endo*-1, 93426-67-6; *exo*-1, 62255-25-8; 3 (isomer 1), 68378-82-5; 3 (isomer 2), 68378-83-6; 4, 93426-68-7; *exo*-5, 93426-69-8; *endo*-5, 93426-70-1.

A Method for the Stereoselective Synthesis of (*E*)-Methylstilbene Retinoids

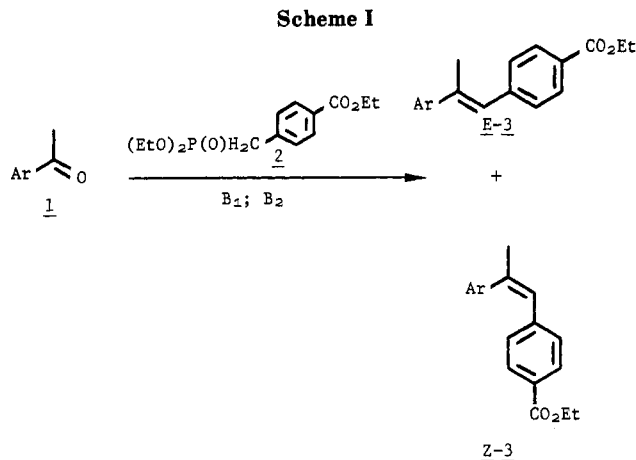
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The *E* isomers of stilbenes 3 are a new class of aromatic retinoids that has shown promising activity in controlling the differentiation of epithelial cells and, therefore, may have potential therapeutic value in the treatment of such proliferative diseases of the skin as cancer, psoriasis, and acne.¹⁻³ Highly stereoselective syntheses of (*E*)-3 are desirable because the *E* and *Z* isomers in this series are frequently difficult to separate. We have investigated the stereoselectivity of the Horner-Emmons olefination of aryl methyl ketone 1 with the anion of diethyl (4-carbethoxybenzyl)phosphonate (2) to form this bond system (Scheme I). The Horner-Emmons olefination is reported to be strongly dependent upon reaction conditions and the relative stability of the initially formed threo and erythro adducts generally leading to product mixtures in which the more stable *E* double-bond isomer predominates.^{4,5} Recent reports by Still and Gennari⁵ on the stereoselective synthesis of trisubstituted *Z* olefins using a Horner-Emmons olefination and by Ford and co-workers⁶ on the double-bond isomeric mixtures obtained using a Wittig olefination have prompted us to report our results.

In the reaction shown in Scheme I, two processes have been found to occur, namely, (a) the olefination leading to a kinetically controlled mixture of isomers (*E*)-3 and (*Z*)-3 and (b) the base-catalyzed isomerization of the mixture affording predominately the thermodynamically more stable (*E*)-3 isomer. The phosphonate anion required



for the olefination was generated by treatment of 2 with a variety of standard bases B₁ (*n*-BuLi/THF, NaH/15-crown-5/THF,⁷ NaCH₂SOCH₃⁸), which are listed in Table I. For example, by monitoring reaction aliquots by high-performance LC, we have found that the *Z* isomer predominated initially when NaH was used as the base, the amount of *E* isomer increased with time, and the rate of increase was dependent upon the base used. By using deuterated solvents and examining the product mixture by both ¹H NMR and GC-MS, we have found that the isomerization proceeded by deprotonation-protonation of the vinylic methyl group of both bond isomers of 3 by the base (Table II). The base isomerization method afforded a much higher *E*/*Z* isomeric ratio (9:1) than the photoisomerization method reported by Loeliger² for (*Z*)-3a, in which the *E*/*Z* ratio was 1:1. The isomerization was effected by a variety of strong bases B₂, including the anion of 2, dimsyl anion, hydride, and ethoxide, as long as the counteraction was complexed by the addition of a crown ether or by the solvent. The lithium salt of 2/THF, NaH/THF, and NaOEt/THF did not isomerize 3a at any appreciable rate but led to extensive side reactions with time. The sodium salt of 2/15-crown-5/THF, and NaCH₂SOCH₃/Me₂SO also caused side reactions that reduced the yield. The isomerization was found to be more rapid with ethoxide than with the phosphonate anion in Me₂SO. These results indicate that NaOEt/Me₂SO are the base and solvent of choice for the isomerization to the (*E*)-3 isomer after the initial olefination reaction. Optimal reaction conditions for this two-step one-pot procedure are reported in the Experimental Section. We have found that this method is applicable to the synthesis of other retinoids. Our results also suggest that the isomer ratios reported by others⁶ in the syntheses of retinoids and other trisubstituted olefins in which the double bond is in conjugation with an electron-withdrawing group may not be simply due to the thermodynamics of the olefination reaction but may in part be the result of further base-catalyzed equilibration of the olefinic products.

Experimental Section

Melting points were determined with a hot-stage microscope and are uncorrected. LC analyses were done on a Waters Associates ALC equipped with a RCM-100 module containing a Radialpak B cartridge. Detection was by a Schoeffel Instrument Model 770 variable wavelength UV monitor. Analyses were performed at 260 nm at ambient temperature. Preparative work was done on a Waters Associates Prep/LC System 500 instrument

(1) Bollag, W. *Cancer Chemother. Pharmacol.* 1981, 7, 27-29.

(2) Loeliger, P.; Bollag, W.; Mayer, H. *Europ. J. Med. Chem.* 1980, 15, 9-15.

(3) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L.-S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. J., *J. Med. Chem.* 1984, 27, 1516.

(4) Wadsworth, W. S. *Org. React. (N.Y.)* 1977, 25, 73-250.

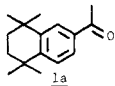
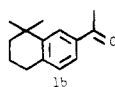
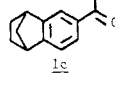
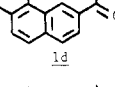
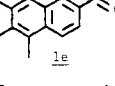
(5) Still, W. C.; Gennari, C. *Tetrahedron Lett.* 1983, 24, 4405-4408.

(6) Bernard, M.; Ford, W. T.; Nelson, E. C. *J. Org. Chem.* 1983, 48, 3164-3168.

(7) Baker, R.; Sims, R. J. *Synthesis* 1981, 117.

(8) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* 1965, 87, 1345-1353.

Table I. Horner-Emmons Olefination of Aryl Methyl Ketones 1a-e

ketone 1	base		solv	olefin 3	
	B ₁ ^a	B ₂		E/Z isomer ratio ^b	yield, %
	<i>n</i> -BuLi		THF	16/84 ^c	45
	NaH/15-C-5 ^d		THF	58/42	66
	NaH/15-C-5		THF	88/12	43
	NaCH ₂ SOCH ₃		Me ₂ SO	65/35	91
	NaCH ₂ SOCH ₃	NaCH ₂ SOCH ₃	Me ₂ SO	93/7	71
	NaCH ₂ SOCH ₃	NaOEt	Me ₂ SO	96/4	86
	NaCH ₂ SOCH ₃	NaOEt	Me ₂ SO	92/8	83
	<i>n</i> -BuLi		Me ₂ SO	33/67	51
	NaCH ₂ SOCH ₃	NaOEt	Me ₂ SO	88/12	85
	NaH/15-C-5		THF	50/50	82
	NaCH ₂ SOCH ₃	NaOEt	Me ₂ SO	85/15 ^c	76
	NaH/15-C-5		THF	40/60	61
	NaCH ₂ SOCH ₃	NaOEt	Me ₂ SO	98/2	93

^a Phosphonate anion generated from excess 2 and base B₁. ^b E/Z isomer ratio determined by comparison of ¹H NMR integrals for vinylic CH₃ and H signals for isomers and by LC peak areas (Radialpak B, 1–3% Et₂O/hexane, 1.0–3.0 mL/min, 260 nm). ^c Ratio determined by LC data only. ^d 15-Crown-5 (15-C-5).

Table II. Isomerization of Olefin 3

olefin	base ^a	solv	E/Z isomer ratio ^b		recovery, %
			initial	final	
3a	NaH/15-C-5	THF	100/0	85/15	42
3a	NaH/15-C-5	THF	65/35	85/15	41
3a	NaOEt	Me ₂ SO	100/0	93/7	58
3a	NaOEt	Me ₂ SO	65/35	94/6	74
3a	NaCD ₂ SOCD ₃	Me ₂ SO-d ₆	65/35	95/5	26
3b	NaCD ₂ SOCD ₃	Me ₂ SO-d ₆	92/8	92/8	49
3a	NaOEt	Me ₂ SO-d ₆	93/7	93/7	85

^a NaH was used to prepare NaOEt and NaCD₂SOCD₃ in Me₂SO-d₆. Isomerization in THF used 0.6 equiv of base and 0.1 equiv of crown ether for 16 h, when equilibrium was reached. Isomerization in Me₂SO used 0.2 equiv of base until equilibrium attained (0.5–4.0 h). ^b Determined by NMR and LC.

using Prep Pak 500/silica cartridges at a flow rate of 0.2 L/min. Detection was by refractive index. IR spectra were recorded with a Perkin-Elmer 710B infrared spectrophotometer. ¹H NMR spectra were obtained with a Varian 390, a JEOL FX90Q, or a 300-MHz Nicolet spectrometer, using Me₄Si as an internal standard (δ 0) and CDCl₃ as solvent. UV spectra were taken on a Perkin-Elmer 575 spectrophotometer. TLC analyses were performed on Analtech silica gel analytical plates. Merck silica gel was used for chromatography.

General Methods. Ketone 1a was obtained from BASF. Ketones 1b, 1c, and 1e were obtained from Friedel-Crafts acylation of the corresponding hydrocarbon with acetyl chloride and AlCl₃. Ketone 1d was prepared from reaction of (1,2-dimethyl-7-naphthyl)magnesium bromide with MeCHO followed by Collins oxidation. Solvents were dried or distilled before use. Where required, reactions were conducted with deoxygenated solvents and under inert gas (argon). NaH was used as a 60% suspension in mineral oil (Aldrich). NaOEt was used as a 2.0 M solution in EtOH, prepared from Na in anhydrous EtOH. A 1.0 M solution of NaCH₂SOCH₃ was prepared daily from NaH (65 °C, 1 h). The reactions reported in Tables I and II were generally run on a 0.5-mmol scale with magnetic stirring in a thermostated 24–25 °C bath. Reaction mixtures were worked up by pouring into 5% NaHCO₃ (100 mL), Et₂O extraction (5 × 30 mL), washing with brine (10 mL), and drying (MgSO₄). After removal of Et₂O, the residue was chromatographed (30 g of silica gel, 10% Et₂O/hexane, mixture applied in 1 mL of toluene) to afford a mixture of (E)-3 and (Z)-3 that showed no other components by TLC.

¹H NMR signals were assigned by comparison with those reported^{2,9–11} for similar compounds. Spectral signal designations are based on the naphthalene and benzonorbornene numbering systems. In all compounds in this series, the ¹H NMR signals for the vinylic methyl group and proton and the phenyl ring protons for the E isomer were shifted downfield relative to those of the Z isomer. In addition, the E isomer had the longer LC retention time.

Horner-Emmons Olefination Using NaH/15-Crown-5/THF. The method of Baker and Sims⁷ was modified. To a stirred suspension of 36 mg (1.5 mmol) of NaH in 1.0 mL of THF was added a solution of 300 mg (1.0 mmol) of 2, 44 mg (0.2 mmol) of 15-crown-5, and 115 mg (0.5 mmol) of 1a in 1.5 mL of THF. The reaction mixture gradually turned red-brown over a period of 0.5 h. After 16 h, the reaction mixture was quenched, and the product was isolated by chromatography to afford 80 mg (43%) of 3a as a colorless solid: TLC (10% Et₂O/hexane) R_f 0.43 ((Z)-3a), 0.46 ((E)-3a); LC (3% Et₂O/hexane, 1.0 mL/min) t_R 4.8 (12%, (Z)-3a), 5.4 min (88%, (E)-3a).

Horner-Emmons Olefination Using NaCH₂SOCH₃/NaOEt/Me₂SO. To 330 mg (1.1 mmol) of 2 was added 1.0 mL of 1.0 M NaCH₂SOCH₃ (1.0 mmol) in Me₂SO with stirring. After 0.5 h, the red-brown solution of phosphonate anion was added to 115 mg (0.5 mmol) of 1a in 1.5 mL of Me₂SO. The reaction mixture was stirred for 2–4 h, at which time LC indicated no 1a remained. Then 0.3 mL of 2.0 M NaOEt (0.6 mmol) in EtOH was added, and the red-brown reaction mixture was stirred for 2 h more, at which time LC analysis indicated that the amount of (E)-3a had been optimized. Workup and chromatography yielded 163 mg (86%) of 3a as a colorless solid: LC (3% Et₂O/hexane, 1.0 mL/min) t_R 4.8 (5%, (Z)-3a), 5.4 min (95%, (E)-3a). Crystallization afforded 148 mg (78%) of ethyl 4-[(E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-6-naphthyl)-propenyl]benzoate ((E)-3a): mp 96–97 °C (EtOH) (lit.² 99–99.5 °C); LC (2% Et₂O/hexane, 2.0 mL/min) t_R 4.2 min (100%); IR (CCl₄) 1715, 1605 cm⁻¹; 300-MHz ¹H NMR δ 1.30 and 1.33 (2 s, 6, C(CH₃)₂), 1.40 (t, J = 7 Hz, 3, CH₂CH₃), 1.70 (s, 4, 2,3-H), 2.29 (d, J = 1 Hz, 3, CH₃C=C), 4.38 (q, J = 7 Hz, 2, CH₂CH₃), 6.81

(9) Vetter, W.; Englert, G.; Rigassi, N.; Schwieter, U. In "Carotenoids"; Isler, O.; Gutmann, H.; Solms, U., Eds.; Birkhaeuser-Verlag: Basel, 1971; pp 216–225.

(10) Dawson, M. I.; Chan, R.; Hobbs, P. D.; Chao, W.; Schiff, L. J. J. Med. Chem. 1983, 26, 1282–1293.

(11) Tori, K.; Aono, K.; Hata, Y.; Muneyuki, R.; Tsuji, T.; Tanida, H. Tetrahedron Lett. 1966, 9–17.

(s, 1, C=CH), 7.30 (m, 2, 7,8-H), 7.41 (d, $J = 8$ Hz, 2, ArH meta to CO₂Et), 7.45 (d, $J = 1$ Hz, 1, 5-H), 8.04 (d, $J = 8$ Hz, 2, ArH ortho to CO₂Et); 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% Et₂O/hexane). (*E*)-**3c** and (*Z*)-**3c** were prepared from the lithium phosphonate of **2** in THF and isolated by preparative LC (1% Et₂O/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% Et₂O/hexane, 1.0 mL/min) t_R 5.0 min (99.8%); IR (CHCl₃) 1705, 1610 cm⁻¹; 90-MHz ¹H NMR δ 1.33 (s, 6, C(CH₃)₂), 1.40 (t, $J = 7$ Hz, 3, CH₂CH₃), 1.72 (m, 4, 2,3-H), 2.29 (d, $J = 1.5$ Hz, 3, CH₃C=C), 2.80 (m, 2, 4-H), 4.41 (q, $J = 7$ Hz, 2, CH₂CH₃), 6.79 (s, 1, C=CH), 7.0–7.55 (m, 5, 5,6,8-H, ArH meta to CO₂Et), 8.11 (d, $J = 8$ Hz, 2, ArH ortho to CO₂Et); UV (95% EtOH) λ_{\max} 233 nm (ϵ 1.4×10^4), 305 (2.6×10^4). Anal. Calcd for C₂₄H₂₈O₂: 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(CH₃)₂), 1.37 (t, $J = 7$ Hz, 3, CH₂CH₃), 1.71 (m, 4, 2,3-H), 2.26 (d, $J = 1.5$ Hz, 3, CH₃C=C), 2.79 (m, 2, 4-H), 4.36 (q, $J = 7$ Hz, 2, CH₂CH₃), 6.53 (s, 1, C=CH), 6.8–7.2 (m, 5, 5,6,8-H, ArH meta to CO₂Et), and 7.87 (d, $J = 8$ Hz, 2, ArH ortho to CO₂Et).

Ethyl 4-[(*E*)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoate ((*E*)-3c**):** yellow oil; LC (2% Et₂O/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, CH₂CH₃), 2.29 (s, 3, CH₃C=C), 3.37 (s, 2, 1,4-H), 4.38 (q, $J = 7$ Hz, 2, CH₂CH₃), 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 CO₂Et), 8.03 (d, $J = 8$ Hz, 2, ArH ortho to CO₂Et); UV (EtOH) λ_{\max} 233 nm (ϵ 1.49×10^4), 308 (2.66×10^4); MS calcd for C₂₃H₂₄O₂ 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% Et₂O/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, CH₂CH₃), 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, CH₃C=C), 3.25 and 3.34 (2 s, 2, 1,4-H), 4.34 (q, $J = 7$ Hz, 2, CH₂CH₃), 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 CO₂Et), 7.06 (d, $J = 8$ Hz, 1, 8-H), 7.73 (d, $J = 8$ Hz, 2, ArH ortho to CO₂Et); UV (EtOH) λ_{\max} 239 nm (ϵ 1.67×10^4), 300 (1.68×10^4); MS calcd for C₂₃H₂₄O₂ 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% Et₂O/hexane, 1.5 mL/min) t_R 6.6 min (100%); IR (CHCl₃) 1705, 1605 cm⁻¹; 300-MHz ¹H NMR δ 1.41 (t, $J = 7$ Hz, 3, CH₂CH₃), 2.42 (d, $J = 1$ Hz, 3, CH₃C=C), 2.50 (s, 3, 2-CH₃), 2.64 (s, 3, 1-CH₃), 4.40 (q, $J = 7$ Hz, 2, CH₂CH₃), 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 CO₂Et), 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 CO₂Et), 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 C₂₄H₂₄O₂: 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% Et₂O/hexane, 1.5 mL/min) t_R 6.2 min (100%); IR (CHCl₃) 1705, 1605 cm⁻¹; 300-MHz ¹H NMR δ 1.32 (t, $J = 7$ Hz, 3, CH₂CH₃), 2.34 (d, $J = 1$ Hz, 3, CH₃C=C), 2.46 (s, 6, 1,2-CH₃), 4.29 (q, $J = 7$ Hz, 2, CH₂CH₃), 6.59 (s, 1, C=CH), 7.02 (d, $J = 8$ Hz, 2, ArH meta to CO₂Et), 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 CO₂Et), 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 C₂₄H₂₄O₂: 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% Et₂O/hexane, 1.0 mL/min) t_R 8.9 min (100%); IR (CHCl₃) 1715, 1605 cm⁻¹; 300-MHz ¹H NMR δ 1.42 (t, $J = 7$ Hz, 3, CH₂CH₃), 2.42 (d, $J = 1$ Hz, 3, CH₃C=C), 2.44 (s, 6, 2,3-CH₃), 2.64 and 2.67 (2 s, 6, 1,4-CH₃), 4.40 (q, $J = 7$ Hz, 2, CH₂CH₃), 7.00 (br s, 1, C=CH), 7.48 (d, $J = 8$ Hz, 2, ArH meta to CO₂Et), 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 CO₂Et), 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 C₂₆H₂₈O₂: 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; CH₃CHO, 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 anisole³ **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 adducts⁵ **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

- (1) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* 1979, 26, 1.
- (2) Wife, R. L.; van Oort, A. B.; van Doorn, J. A.; van Leeuwen, W. N. *M. Synthesis* 1983, 71.
- (3) Shirley, D. A.; Hendrix, J. P. *J. Organomet. Chem.* 1968, 11, 217.
- (4) Green, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981; Chapter 3.
- (5) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* 1981, 3923.