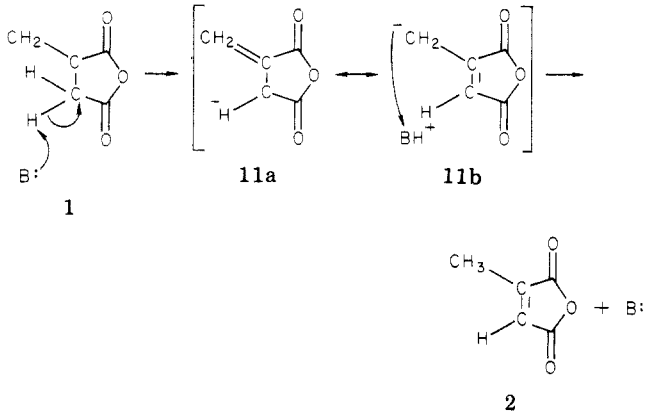
Scheme I[a]



[a] B: = N,N-diethylaniline, pyridine, or N,N-dimethylaniline.

isomerization mechanism for the amine-catalyzed reaction (Scheme I). Increases in either amine basicity or concentration would enhance the formation of the carbanion **11a**, resulting in higher conversion rates of ITA to CTA. Also, greater solvation of the carbanion intermediate probably occurs in more polar solvents which would account for the reaction rate increase in acetone compared to chloroform.

Registry No. 1, 2170-03-8; *N,N*-dimethylaniline, 121-69-7; pyridine, 110-86-1; *N,N*-diethylaniline, 91-66-7; chloroform, 67-66-3; acetone, 67-64-1; citraconic anhydride, 616-02-4.

Absolute Configuration of Glycerol Derivatives. 8.[1] 2-Hydroxy-3-(1-naphthoxy)propionic Acid, a Major Oxidative Metabolite of the β-Adrenergic Antagonist Propranolol

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Propranolol (**1**) is a β-adrenergic antagonist used extensively in the treatment of various cardiovascular disorders, including hypertension and angina pectoris, as well as in other situations.[2] In man, 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**; "propranolol lactic acid") is the major urinary metabolite resulting from multistep oxidative N-dealkylation of the propanolamine side chain.[3]

Because the β-adrenergic antagonist properties of the propranolol are retained almost exclusively by one of the enantiomers,[4] and evidence that the enantiomers of propranolol are metabolized to pharmacologically active and inactive products at different rates in rats,[5] dogs,[6] rabbits,[7] and in man,[8] we were interested in obtaining additional information concerning the enantioselectivity of the N-dealkylation process. Associated with a metabolic study of this nature was the need for more stereochemical information about this acid. In this paper we report a facile synthesis and resolution of **2** and establish the absolute stereochemistry of the enantiomers of **2**.

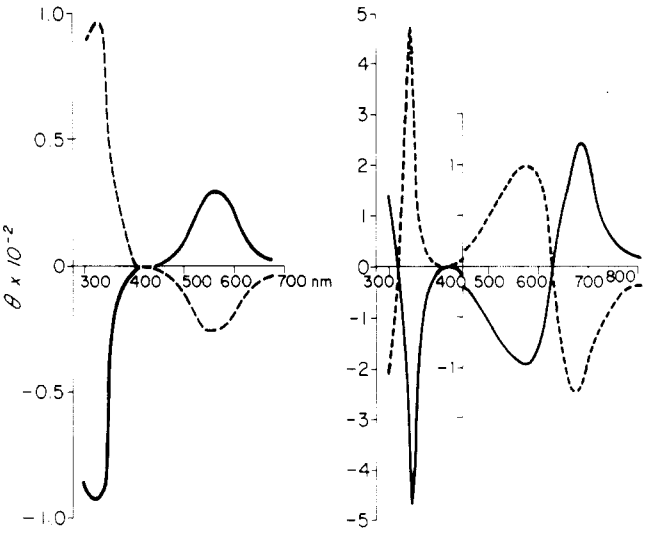
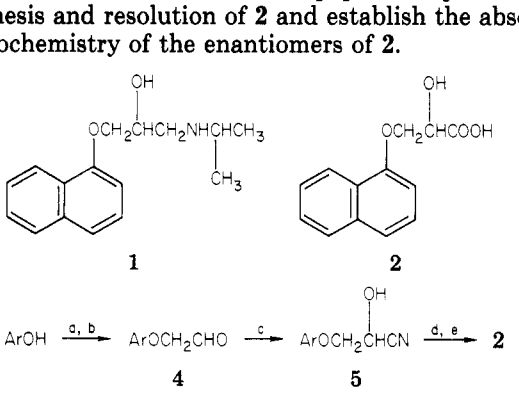


Figure 1. (left) Circular dichroism spectra of the enantiomers of 3-(1-naphthoxy)propane 1,2-glycol (**6**) in Cupra A–MeOH (4:1), (2*R*)-(−)-**6** (solid line) and (2*S*)-(+)-**6** from (2*R*)-(−)-**2** (dotted line). (right) Circular dichroism spectra of the enantiomers of 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**), in Cupra A solution, (2*S*)-(+)-**2** (solid line) and (2*R*)-(−)-**2** (dotted line).



Ar = 1-naphthyl; a, $BrCH_2CH(OEt)_2/Na_2CO_3$; b, H_3O^+; c, KCN, $NaHSO_3$; d, MeOH/HBr, H_2O; e, $^-OH/H_2O$

A need for sufficient quantities of 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**) to effect a resolution prompted us to develop a practical synthesis for it.[9] Acid **2** was obtained from the cyanohydrin of 2-(1-naphthoxy)acetaldehyde (**4**). Conversion of the cyanohydrin to an α-hydroxy carboxylic acid ester, followed by alkaline hydrolysis, proved to be a more successful route to **2** than direct hydrolysis of the cyanohydrin (**5**). The "lactic acid metabolite" of the related β-adrenergic antagonist timolol

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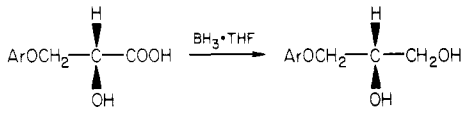
(9) Although several reports of the use of **2** as an analytical standard appear in the literature, we are not aware of reports of its synthesis.

0022-3263/82/1947-1574$01.25/0

has been prepared by a similar series of steps.[10]

Optical resolution was accomplished by crystallization of the diastereomeric salts formed with the enantiomers of α-methylbenzylamine. Decomposition of the salts afforded the enantiomers of **2** but did not establish their absolute configuration.

Absolute configuration was established by borane–tetrahydrofuran reduction of (−)-**2**, $[\alpha]_D^{20}$ −6.1°, to (2*S*)-(+)-3-(1-naphthoxy)propane-1,2-diol ((2*S*)-**6**) a compound of known absolute configuration, previously prepared from (2*S*)-3-(tosyloxy)propane-1,2-diol 1,2-acetonide.[11] This process establishes the absolute configuration of (−)-**2** as 2*R*, since it affords the 2*S* glycol. The change in configurational designation results from the priorities in the Cahn–Ingold–Prelog sequence rules.



(2*R*)-(−)-**2** (2*S*)-(+)-**6**

Ar = 1-naphthyl

Comparison of the Cupra A circular dichroism spectra was made. Spectral similarities between the enantiomers of (2*R*)-(−)- and (2*S*)-(+)-**6** and the enantiomeric acids, respectively, are noted (Figure 1). The chirality of the glycol obtained from (−)-**2** is established as 2*S* from its Cupra A CD spectrum. Its Cupra A circular dichroism spectrum is the mirror image of the spectrum of known (2*R*)-**6**. Chirally related enantiomers of the glycols and the acids provide long-wavelength transitions of the same sign in the 600–700-nm region, 550 nm for the glycols and 680 nm for the acids. The short-wavelength transitions in the 290–350-nm region are also of the same sign and are of greater intensity. The observed bands are at longer wavelength in the spectra of the acids and show a greater degree of complexity.

The Cupra A circular dichroism technique, previously applied to several closely related 1,2-diols and amino alcohols[11,12] might be applicable to some α-hydroxy carboxylic acids as well, since the spectra of chiral acids (2*R*)-**2** and (2*S*)-**2** and of the enantiomers of mandelic acid[13] correlate well. Considerable difficulties have been encountered in correlating chiroptical properties to absolute configuration in conformationally mobile α-hydroxyphenylacetic acids and their derivatives, e.g., the "lactic acid anomaly".[14] Further study is needed to determine whether the Cupra A circular dichroism technique is more generally applicable.

The enantioselectivity of the metabolic N-dealkylation of propranolol is under investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B spectrophotometer, ultraviolet spectra on an Aminco DW-2 UV–vis spectrophotometer, and NMR spectra on a Varian 360-A spectrophotometer using Me_4Si as an internal standard. Notations used in the descriptions are as follows: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were recorded on the HP-5985 GC-MS (electron-impact spectra) and on the VG-7070H mass spectrometer (chemical-ionization spectra). Optical rotations were obtained with a JASCO DIP-4 digital polarimeter. Circular-dichroism spectra were recorded on a Jobin Yvon Dichrograph III. Microanalyses were performed by Galbraith Laboratories Inc. (Knoxville, TN).

2-(1-Naphthoxy)acetaldehyde Diethyl Acetal (3). 1-Naphthol (46.8 g, 0.33 mol) was added to a solution contg. 63.0 g (0.32 mol) of α-bromoacetaldehyde diethyl acetal and 34.6 g (0.33 mol) of potassium carbonate in 480 mL of DMF. This mixture was stirred for 24 h at 125 °C, cooled, and added to 500 mL of 5% aqueous NaOH and extracted with ether (6 × 200 mL). The combined ether extracts were washed with 5% aqueous NaOH (2 × 200 mL) and water (2 × 200 mL), dried ($MgSO_4$), and evaporated to yield a brown viscous liquid. Vacuum distillation afforded 57.5 g (69%) of **3** as a yellow liquid: bp 147 °C (0.7 mm) [lit.[15] bp 207–208 °C (18 mm)]; IR (neat), 3050, 2975, 2940, 2875, 1640, 1600, 1580, 1510, 1460, 1400, 1275, 1245, 1140, 1110, 1080, 1020, 800, 780 cm^{-1}; NMR ($CDCl_3$) δ 8.40 (m, 1, Ar H-8), 7.70 (m, 1, Ar H-5), 7.30 (m, 4, Ar H-3, -4, -6, and -7), 6.60 (dd, *J* = 2, 6 Hz, 1, Ar H-2), 4.80 (t, *J* = 5 Hz, 1,$CH(CH_2CH_3)_2$, 4.05 (d, *J* = 5 Hz, 2, CH_2), 3.45 (m, 4, OCH_2CH_3), 1.15 (t, *J* = 7 Hz, 6, OCH_2CH_3; mass spectrum (EI), *m/z* 260 (M^+, 35), 169 (30), 143 (17), 127 (30), 115 (56), 103 (base peak), 75 (39). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.64; H, 7.58.

2-(1-Naphthoxy)acetaldehyde (4). 2-(1-Naphthoxy)acetaldehyde diethyl acetal (**3**; 54.0 g, 0.21 mol) was added to a solution of 91.4 mL of aqueous 2 N HCl (0.18 mol) in 350 mL of acetone. The resulting solution was refluxed for 4 h, cooled, and extracted with ether (4 × 200 mL). The combined ether extracts were washed with 5% aqueous potassium carbonate (2 × 300 mL) and water (300 mL), dried ($MgSO_4$), and evaporated to yield a yellow viscous liquid. Vacuum distillation afforded 33.2 g (85%) of **4**, bp 142 °C (0.5 mm), which solidified: mp 58–61 °C; IR (KBr), 3400, 3050, 2875, 2810, 1740, 1625, 1595, 1580, 1505, 1460, 1400, 1265, 1240, 1105, 795, 775 cm^{-1}; NMR ($CDCl_3$) δ 9.80 (t, *J* = 1 Hz, 1, CHO), 8.30 (m, 1, Ar H-8), 7.75 (m, 1, Ar H-5), 7.40 (m, 4, Ar H-3, -4, -6, -7), 6.50 (dd, *J* = 2, 8 Hz, 1, Ar H-2), 4.55 (d, J = 1 Hz, 2, CH_2); mass spectrum (EI), *m/z* 186 (M^+, base peak) 157 (43), 144 (26), 143 (48), 127 (58), 115 (91).

Oxime: mp 127–128 °C (EtOH) [lit.[15] mp 108 °C]. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51: N, 6.96. Found: C, 71.52; H, 5.61; N, 6.84.

1-Cyano-2-(1-naphthoxy)ethanol (5). To a solution of 2-(1-naphthoxy)acetaldehyde (**4**; 6.42 g, 30.5 mmol) in 100 mL of H_2O were added $NaHSO_3$ (5.0 g, 48 mmol) and KCN (3.0 g, 46 mmol). The reaction mixture was stirred at room temperature for 6 h. The white solid was removed by filtration and washed with cold H_2O to give 4.45 g (61%) of **5**. An analytical sample was purified by column chromatography on silica gel, eluting with $CHCl_3$–EtOAc–EtOH (95:5:1), affording **5** as a solid: mp 57–61 °C; IR (KBr) 3410, 3050, 2925, 1735, 1705, 1595, 1580, 1505, 1460, 1400, 1265, 1240, 1105, 795, 775 cm^{-1}; NMR (acetone-d_6) δ 8.35 (m, 1, Ar H-8), 7.80 (m, 1, Ar H-5), 7.45 (m, 4, Ar-3, -4, -6, -7), 6.90 (dd, *J* = 2, 8 Hz, 1, Ar H-2), 5.17 (t, *J* = 5 Hz, 1, CH), 4.40 (d, *J* = 5 Hz, 2, CH_2); mass spectrum *m/z* 213 (M^+, 91), 186 (73), 157 (63), 144 (70), 143 (46), 127 (57), 115 (base peak). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.26; H, 5.20; N, 6.57. Found: C, 73.33; H, 5.26; N, 6.51.

2-Hydroxy-3-(1-naphthoxy)propionic Acid (2). The procedure was adapted from the method of Morgan.[16] 1-Cyano-2-(1-naphthoxy)ethanol (**5**; 500 mg, 2.3 mmol) was dissolved in 0.30 mL (8.0 mmol) of CH_3OH and the mixture cooled to 0 °C. Gaseous HBr was then bubbled through the mixture for 30 min. The resulting light-brown imido ester salt which precipitated was converted to the methyl ester by adding 5 mL of water and stirring the mixture at room temperature for 30 min. The resulting solution was then added to a mixture of 10 mL of aqueous 20% KOH and 20 mL of ethanol, and the mixture was stirred at room temperature for 24 h. The ethanol was evaporated and the

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aqueous solution (pH >10) was washed with ethyl acetrate (50 mL), adjusted to pH 1.0 (concentrated HCl), and extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated to yield a tan precipitate. Crystallization from methanol–water yielded 380 mg (71%) of **2** as off-white flakes: mp 148.5–149.5 °C; IR (KBr) 3400, 3050, 2940, 1720, 1585, 1400, 1375, 1275, 1245, 1115, 1105, 795, 770 cm^{-1}; NMR (acetone-d_6) δ 8.25 (m, 1, Ar H-8), 7.80 (m, 1, Ar H-5), 7.40 (m, 4, Ar H-3, -4, -6, -7), 6.90 (m, J = 3, 6 Hz, 1, Ar H-2), 6.15 (s, 2, OH and COOH), 4.65 (t, J = 4 Hz, 1, CH), 4.45 (d, J = 4 Hz, 2, CH_2); UV (MeOH) λ_{max} 291 nm (log ϵ 3.64), 236 (log ϵ 3.91); mass spectrum (CI, methane), m/z 233 (QM) (93), 232 (M^+, 27), 215 (21), 187 (base peak), 169 (21), 145 (53), 144 (22). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.20. Found: C, 67.28; H, 5.42.

(2*S*)-(+)-2-Hydroxy-3-(1-naphthoxy)propionic Acid ((2*S*)-2). 2-Hydroxy-3-(1-naphthoxy)propionic acid (**2**: 3.0 g, 13 mmol) was added to 1.58 g (13 mmol) of (−)-α-methylbenzylamine in 40 mL of ethanol. Repeated fractional crystallization (ethanol) of the resulting diastereomeric salts yielded 490 mg (11%) of the (−) salt: mp 172–176 °C; $[\alpha]_D^{20}$ −31.0° (c 1.0, MeOH). The salt was then decomposed in acidic water (50 mL) and extracted with EtOAc (2 × 50 mL). The EtOAc extract was dried ($MgSO_4$) and evaporated to yield a tan solid. Crystallization from chloroform–hexane yielded 200 mg of (2*S*)-**2** as tan needles: mp 132–133 °C; $[\alpha]_D^{20}$ +6.0° (c 1.0, MeOH); circular dichroism (c 0.10, Cupra A), $[\theta]_{790}$ +50, $[\theta]_{675}$ +155, $[\theta]_{625}$ 0, $[\theta]_{565}$ −120, $[\theta]_{415}$ −10, $[\theta]_{320}$ −430, $[\theta]_{315}$ 0, $[\theta]_{295}$ +115; circular dichroism of methyl ester (c 0.10 MeOH), $[\theta]_{300}$ 0, $[\theta]_{285}$ +210, $[\theta]_{270}$ 0.

(2*R*)-(−)-2-Hydroxy-3-(1-naphthoxy)propionic Acid ((2*R*)-2). From 3.0 g (13 mmol) of **2** and 1.58 g (13 mmol) of (+)-α-methylbenzylamine fractional crystallization (EtOH) afforded 570 mg (12%) of the (+) salt: mp 170–172 °C; $[\alpha]_D^{20}$ +31.0° (c 1.0, MeOH). Conversion of the salt to the free acid afforded 250 mg of (2*R*)-**2** as tan needles: mp 132–133 °C; $[\alpha]^{20}_D$ −6.1° (c 1.0, MeOH); circular dichroism (c 0.10, Cupra A), $[\theta]_{790}$ −30, $[\theta]_{680}$ −160, $[\theta]_{630}$ 0, $[\theta]_{565}$ +115, $[\theta]_{415}$ 0, $[\theta]_{325}$ +460, $[\theta]_{315}$ 0, $[\theta]_{295}$ −140; circular dichroism of methyl ester (c 0.10 MeOH), $[\theta]_{300}$ 0, $[\theta]_{285}$ −230, $[\theta]_{270}$ 0.

(2*S*)-(+)-3-(1-Naphthoxy)-1,2-propanediol ((2*S*)-6). Borane (18 mg, 0.66 mmol, 0.66 mL of a 1.0 M solution in THF) was added dropwise at −15 °C to a solution of 100 mg (0.44 mmol) of (2*R*)-2-hydroxy-3-(1-naphthoxy)propionic acid ((2*R*)-**2**) in 1.0 mL of THF in a Reactivial. The container was sealed. The solution was allowed to warm to room temperature and stirred for 24 h. Excess diborane was destroyed by the addition of 2 mL of a 1:1 THF–H_2O mixture. The aqueous layer was saturated with K_2CO_3, the THF layer removed, and the aqueous layer extracted with ether (3 × 5 mL). The THF and ether extracts were combined, dried ($MgSO_4$), and evaporated to yield a white solid. Crystallization from benzene yielded 50 mg (50%) of (2*S*)-**6** as white flakes: mp 108–109 °C (lit.[11] mp 108–110 °C); $[\alpha]_D^{20}$ +6.9° (c 1.0 MeOH); IR (KBr) 3225, 2970, 1575, 1500, 1450, 1400, 1265, 1240, 1110, 1080, 985, 785, 770 cm^{-1}; NMR (acetone-d_6) δ 8.25 (m, 1, Ar H-8), 7.80 (m, 1, Ar H-5), 7.45 (m, 4, Ar H-3, -4, -6, -7), 6.90 (m, 1, Ar H-2), 4.20 (m, 1, CHOH), 4.00 (br s, 2, OH), 3.80 (m, 2, CH_2OH); $[\alpha]_D^{20}$ +6.9° (c 1.0, EtOH); circular dichroism (c 0.10, Cupra A–MeOH, 4:1), $[\theta]_{780}$ 0, $[\theta]_{550}$ −20, $[\theta]_{400}$ 0, $[\theta]_{330}$ +95, $[\theta]_{325}$ 0.

(2*R*)-(−)-3-(1-Naphthoxy)-1,2-propanediol ((2*R*)-6). This compound was prepared from (2*R*)-3-(tosyloxy)propane-1,2-diol acetonide as previously reported:[11] mp 108–110 °C (lit.[11] mp 109–111 °C); IR (KBr) 3250, 1590, 1465, 1410, 1295, 1255, 1115, 1080, 1005, 780 cm^{-1}; $[\alpha]_D^{20}$ −8.1°; circular dichroism (c 0.11, Cupra A–MeOH, 4:1), $[\theta]_{780}$ 0, $[\theta]_{555}$ +30, $[\theta]_{360}$ 0, $[\theta]_{325}$ −90, $[\theta]_{320}$ 0.

Acknowledgment. We acknowledge support of this work by the U.S. Public Health Service by Research Grant GM-25373 and by National Research Service Award GM-07750.

Registry No. (2*R*)-**2**, 80789-57-7; (2*R*)-**2** (+)-α-methylbenzylamine salt, 80789-58-8; (2*S*)-**2**, 80789-59-9; (2*S*)-**2** (−)-α-methylbenzylamine salt, 80789-60-2; (±)-**2**, 80844-62-8; **3**, 80789-61-3; **4**, 60148-34-7; **4** oxime, 80789-62-4; (±)-**5**, 80789-63-5; (2*R*)-**6**, 61248-78-0; (2*S*)-**6**, 56715-19-6; 1-naphthol, 90-15-3; α-bromoacetaldehyde diethyl acetal, 2032-35-1.

2-Methyl-5-*tert*-butylcyclohexane-1,3-dione and Related 2-Alkylcyclohexane-1,3-diones from 1,3-Dimethoxybenzenes

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In connection with vitamin D analogue syntheses and studies on the mechanism of asymmetric aldol condensation reactions, we required a facile preparation of 2-methyl-5-*tert*-butylcyclohexane-1,3-dione (**1a**,[2] Chart I). We report its preparation as well as that of 2-alkylcyclohexane-1,3-diones **2a–c** needed in related ongoing studies. Rather than directly preparing 2-unsubstituted cyclohexane-1,3-diones and then alkylating, a sequence known to proceed with modest efficiency at best,[3] we extended the method of Piers and Grierson[4] for incorporating the alkyl group between the two carbonyl moieties.

The 5-*tert*-butyl derivatives **1a** and **1b** were synthesized from the cyclohexadiene **3a**. Alkylation[4] of **3a** (*tert*-butyllithium in THF, −78 °C, 10 min; CH_3I, −78 °C to room temperature; 93% distilled yield) afforded **4a**, which upon hydrolysis (1 M HCl) gave **1a** in essentially quantitative yield. Direct hydrolysis of **3a** afforded the dione **1b**.[2] A recent report[5] described the sequence **5** → **6** → **7** → **8** in which the R group is introduced in the first step by using a tertiary carbinol. Rather than utilizing **8a** for the reduction, we have found that exhaustive Birch reduction (Li, *t*-BuOH, NH_3–THF) of the previously unreported **7** (R = *t*-Bu)[5] afforded **3a** directly in 82% yield.

Similar Birch reduction of **8b**[6] and **8c**[4] afforded **3b** and **3c**, respectively. Alkylation of **3b** (methyl iodide), **3c** (ethyl iodide), and **3c** (isopropyl bromide) as above for **3a** afforded **4b–d**, which upon hydrolysis gave the known diketones **2c**[3d] (80% based on **3b**), **2a**[2b] (78% based on **3c**), and **2b**[3e,7] (64% based on **3c**).

(1) (a) Universidad de Santiago. (b) University of California, Riverside.

(2) The title diketone **1a** appears to be unknown, but the demethyl compound **1b** has been reported: Dunkelblum, E.; Levene, R.; Klein, J. *Tetrahedron* **1972**, *28*, 1009–1024. The isomeric 2-*tert*-butylcyclohexane-1,3-dione has also been synthesized: Newkome, G. R.; Montelaro, R. C.; Sauer, J. D.; Wander, J. D. *J. Chem. Soc., Chem. Commun.* **1972**, 905.

(3) (a) Methylation of cyclohexane-1,3-dione proceeds in 54–56% yield. Mekler, A. B.; Ramachandra, S.; Swaminathan, S.; Newman, M. S. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5 V, pp 743–746. A typical yield in our hands was about 51%. (b) ethylation of cyclohexane-1,3-dione proceeds in ~30% yield, a result reproducible in our hands. Smith, H. *J. Chem. Soc.* **1953**, 803–810. Newkome, G. R.; Roach, L. C.; Montelaro, R. C.; Hill, R. K. *J. Org. Chem.* **1972**, *37*, 2098–2101. Coke, J. L.; Williams, H. J.; Natarajan, S. *Ibid.* **1977**, *42*, 2380–2382. (c) Methylation of dimedone is reported to proceed in 70% yield, although our yields have averaged 53%. Clark, R. D.; Ellis, J. E.; Heathcock, C. H. *Synth. Commun.* **1973**, *3*, 347–354. (d) Methylation of 5-methylcyclohexane-1,3-dione affords 48% of product. Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098–1106. The first crop yield with this procedure was 21–35% (three trials) in this laboratory. (e) The isopropyl derivative **2b** has been prepared by the classical Claisen route: Newkome's improved route[3b] and ref 7.

(4) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755–3757. In our hands, we were unable to improve our yields significantly using hexamethylphosphoramide as co-solvent in the alkylation step.

(5) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344–346. For a related study, see also: Focella, A.; Teitel, S.; Brossi, A. *Ibid.* **1977**, *42*, 3456–3457.

(6) Birch, A. J.; Rickards, R. W. *Aust. J. Chem.* **1956**, *9*, 241–243.

(7) Bhattacharyya, P. C. *J. Indian Chem. Soc.* **1965**, *42*, 467–469. Newkome's paper[3b] gives a melting point of 150–151 °C for **2b**.

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