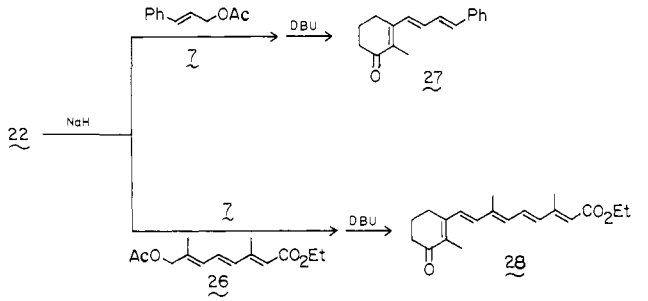
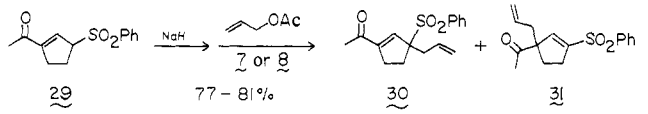
yield (from **22**). Similarly, palladium-assisted alkylative elimination with cinnamyl acetate and the triene acetate **26** gave the



desired products **27**[7,23] and **28**[7,24] in 71% and 49% (~65% by high-pressure liquid chromatography analysis) yields after crystallization. The latter represents a model approach for possible Vitamin A metabolites and canthaxanthin.[25,26]

In an ancillary study, we noted that the choice of ligands on palladium had a pronounced effect on the α to γ ratio in the alkylation of γ-sulfonyl-α,β-unsaturated ketones.[27] For example, reaction of the sulfone **29** with allyl acetate and **7** gave a 3:2 ratio



of **30** and **31**; however, use of **8** as catalyst improved this ratio to 4:1. This flexibility of manipulating the reaction template and thereby manipulating the γ to α ratio is a decided advantage of transition-metal-catalyzed alkylations.

The dual reactivity accorded allyl sulfones substantially increases the role they can play in organic synthesis. Furthermore, this reversal of reactivity afforded by the transition metal highlights the application of such catalysts to generate new rules of selectivity.

Acknowledgments. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their continuing support of our programs. We also are grateful for a generous gift of ethyl 3,7-dimethyl-8-oxoocta-2,4,6-trienoate from Dr. Michael Rosenberger of the Hoffmann-La Roche Laboratories.

(23) **27**: mp 110 °C; IR 1648, 1600, 1589 cm^{-1}; 270-MHz NMR δ 1.95 (3 H, s), 6.70-7.00 (4 H, m), 7.25-7.43 (5 H, m); ^{13}C NMR (15.1 MHz) 126.5, 128.0, 128.4, 128.8, 130.5, 131.8, 134.8, 135.8, 136.5, 149.1.

(24) **28**: mp 132-133.5 °C; IR 1700, 1648, 1598 cm^{-1}; 270-MHz NMR δ 1.96 (3 H, s), 2.05 (3 H, s) 2.36 (3 H, s), 5.78 (1 H, s), 6.34 (2 H, d, J = 13.4 Hz), 6.65 and 6.78 (2 H, AB, J = 15.4 Hz), 7.01 (1 H, dd, J = 13.4, 13.4 Hz); ^{13}C NMR (15.1 MHz) 120.2, 127.1, 130.1, 132.5, 134.5, 137.9, 138.6, 149.3, 151.8, 166.8.

(25) For allyl sulfones in Vitamin A, see ref 21a and earlier references cited therein: Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287. Fischli, A.; Mayer, H.; Simon, W.; Stotler, H. J. *Helv. Chim. Acta* **1976**, *59*, 397. Manchand, P. S.; Wong, H. S.; Blount, J. F. *J. Org. Chem.* **1978**, *43*, 4769.

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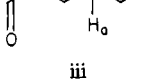
(27) Cf.: Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602.

(28) The failure of the simple base-catalyzed elimination in these cases compared to the many examples of such reactions apparently stems from the high acidity of H_a in iii, precluding the E_2 elimination.



iii

(29) NIH-NCI Postdoctoral Fellow, 1978-1980.

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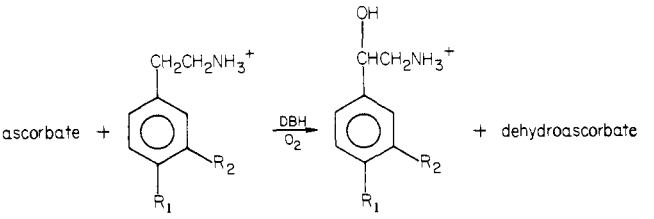
Asymmetric Sulfoxidation by Dopamine β-Hydroxylase, an Oxygenase Heretofore Considered Specific for Methylene Hydroxylation

Sir:

Dopamine β-hydroxylase (DBH) [EC 1.14.2.1], a copper-containing monooxygenase present in a variety of mammalian tissues,[1,2] catalyzes the conversion of dopamine to norepinephrine, thus playing a key role in the biosynthetic conversion of potent neurotransmitters and in the production of adrenaline.[3] Although a variety of 2-phenylethylamines substituted on either the aromatic ring or the alkyl chain have been examined as substrates, the only known oxygenase activity for this enzyme has been methylene hydroxylation at the benzylic position.[4] We now report that DBH stereoselectively catalyzes the conversion of phenyl 2-aminoethyl sulfides to the corresponding sulfoxides at a rate which is considerably higher than hydroxylation of the corresponding carbon analogues. To our knowledge, this is the first demonstration of sulfoxidation by an oxygenase which normally catalyzes only aliphatic hydroxylation.



Phenyl 2-aminoethyl sulfide (I), the prototype sulfide substrate, was synthesized by the method of Wehrmeister,[5] crystallized as the hydrochloride from EtOH/Et_2O, and characterized by NMR, plus mass spectral and elemental analysis [mp 162-163 °C (lit. 162-163 °C).[6] Anal. Calcd for $C_8H_{12}NSCl$: C, 50.65; H, 6.38; N, 7.38; S, 16.90. Found: C, 50.63; H, 6.38; N, 7.35; S, 16.89]. DBH was isolated and purified from bovine adrenals by using a modification of the method of Ljones et al.,[7] which is described elsewhere.[8] Incubation of I with highly purified DBH (sp act. 12-15 units/mg) in the presence of fumarate, copper,[9] and Fe(CN)$_6^{4-}$ or ascorbate as the electron donor results in an enzyme-dependent consumption of both electrons and O_2, in the

Table I. Stoichiometry of DBH-Catalyzed Oxygenation Reactions

oxygenated substrate	[Fe(CN)$_6^{4-}$]^a/[substrate] consumed	[O_2]^b/[substrate] Fe(CN)$_6^{4-}$	[O_2]^b/[substrate] ascorbic acid	[product]/[substrate]
phenyl 2-aminoethyl sulfide (I)	2.1	0.8	0.9	1.2^c
tyramine	2.1	1.0		*d*

^{a} Determined by measuring A_{420} under substrate-limiting conditions. See footnote *a*, Table II, for details. ^{b} Measured with an O_2-sensitive polarographic electrode under substrate-limiting conditions. See footnote *b*, Table II, for details. ^{c} Determined from UV analysis of the product isolated by ion-exchange chromatography as described in the text, after O_2 and electron consumption had ceased. ^{d} The stoichiometry of product formed per 2 equiv of Fe(CN)$_6^{4-}$ has been reported as 1:1.[7]

(1) Levin, E. Y.; Levenberg, B.; Kaufman, S. *J. Biol. Chem.* **1960**, *235*, 2080-2086.
(2) Friedman, S.; Kaufman, S. *J. Biol. Chem.* **1966**, *241*, 2256-2259.
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(8) Manuscript in preparation.

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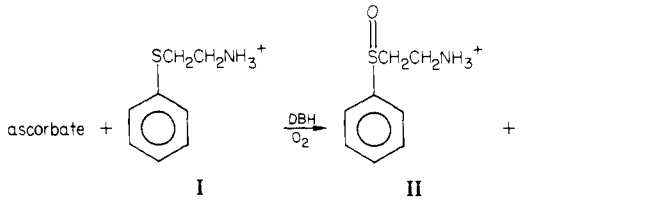
Table II. Kinetic Parameters of DBH Oxygenation Reactions

oxygenated substrate	electron donor: $Fe(CN)_6^{4-}$ [a] k_{cat}, s^{-1}	$Fe(CN)_6^{4-}$ [a] k_{cat}/K_m, M^{-1} s^{-1}	ascorbic acid [b] k_{cat}, s^{-1}	ascorbic acid [b] k_{cat}/K_m, M^{-1} s^{-1}
2-phenylethylamine	19	1.9×10^4	65	1.9×10^4
3-phenylpropylamine	1	2.0×10^3	12	1.0×10^3
phenyl 2-aminoethyl sulfide (I)	6	4.0×10^3	68	3.0×10^3

[a] The reaction system contains 5 μM $CuSO_4$, 10 mM sodium fumarate, and 2 mM $K_4Fe(CN)_6$ in 0.1 M Mes buffer, pH 6.0,[7] and varying amounts of substrate. The reaction was followed spectrophotometrically at 420 nm ($\Delta\epsilon$ 1100 M^{-1} cm^{-1}), and the cell compartment was thermostated at 37 °C. [b] The reaction system contains 5 μM $CuSO_4$, 10 mM sodium fumarate, 10 mM ascorbic acid, 200 μg/mL catalase, and varying amounts of substrate, in 0.1 M acetate buffer, pH 5.0. The reaction was followed by measuring O_2 uptake at 37 °C with a Clark polarographic electrode and a YSI Model 53 O_2 monitor. Details of the oxygen monitor assay will be published elsewhere.[8]

stoichiometry diagnostic for monooxygenase-catalyzed oxygenations. Comparative data for I and the commonly used DBH



substrate, tyramine, are presented in Table I. Initial identification of the enzymatic product as the sulfoxide was accomplished by subjecting enzymatic reaction mixtures to ion-exchange chromatography on a polymethacrylate resin (NH_4^+ form), followed by elution with 0.1 M NH_3. The product exhibited a UV spectrum characteristic of an aryl alkyl sulfoxide,[10] and the shape of the product spectrum corresponded precisely to that of an authentic sample of phenyl 2-aminoethyl sulfoxide [II (isolated as the hydrochloride salt): mp 158–159.5 °C (lit. 158.5–159.5 °C);[6] λ_{max} 235 nm (H_2O), log ϵ 3.6; sh, 265 nm, log ϵ 3.0; sh, 272 nm, log ϵ 2.7] prepared by periodate oxidation of I.[11] In other experiments, where I was present in excess, identification of the enzymatic product was accomplished by high-pressure liquid chromatography with a reverse-phase column. Positive indication of sulfoxide was also obtained by using the HCl, KI/starch color test,[12] which we find to be unreactive with the substrate (I).

Preparative scale experiments were carried out to allow direct spectral confirmation of the structure of the enzymatically produced sulfoxide, as well as a determination of its chirality. Typically, 25 mg of I was incubated with 30 units of partially purified DBH[13] in 10 mL of 0.2 M acetate, pH 5.0, which contained 50 mM ascorbate, 5 μM $CuSO_4$, and 7 mg of catalase. After 18 h of incubation in a rotary shaker at 35 °C, the precipitated protein was removed by centrifugation, and the reaction mixture was subjected to ion-exchange chromatography and eluted as described above. The pK_a shift which accompanies sulfoxidation[14] allowed for clean product separation from unreacted I. By UV analysis, we estimate that 8.7 mg of product was obtained, a yield of 30%. After $CHCl_3$ extraction, the NMR [δ ($CDCl_3$) 1.61 (s, 2 H), 2.91 (t, 2 H, J = 6 Hz), 3.16 (m, 2 H), 7.61 (m, 5 H)], IR [($CHCl_3$) strong S–O stretch at 1035 cm^{-1}], and mass spectral [molecular ion, m/e 169] data were examined and found to be identical with those of chemically synthesized II, thus unequivocally establishing enzymatic sulfoxidation. In control experiments where DBH was omitted, sulfoxide production was reduced by more than 98%, and was at the limit of detection. The ORD spectrum of the enzymatic product in ethanol exhibited a strong negative Cotton effect corresponding to the UV λ_{max}, with $[\alpha]^{25}_D$ −240°. By comparison, all phenyl alkyl sulfoxides of *R* configuration exhibit positive rotation,[10,22,23] and the $[\alpha]^{25}_D$ value for (*R*)-phenyl ethyl sulfoxide is +176.6° (ethanol). Thus, it is highly probable that the enzymatic product is entirely of the *S* configuration, but conditions for much greater scaleup will have to be developed to allow final confirmation of optical purity by NMR methods. DBH has been shown to be stereospecific in methylene hydroxylation, generating only the (*R*)-alcohol from 2-phenylethylamines.[15,16] We note that the (*S*)-sulfoxide from I has the same spatial arrangement of oxygen, phenyl, and amine functionalities as the (*R*)-phenylethanolamines, the opposite *R* and *S* designations arising from the altered priority sequence of the sulfur substituents (phenyl > aminoethyl).

As is evident from Table II, the k_{cat} for I is about six times greater than that for the analogous hydroxylated substrate, 3-phenylpropylamine. This relationship holds for both ascorbic acid and $Fe(CN)_6^{4-}$ supported oxygenations, despite the large difference in absolute rates between the two systems. I is as active a substrate as 2-phenylethylamine, when ascorbate is the electron donor; thus, sulfoxidation by DBH is clearly a facile process, and the mechanistic implications of this finding will be discussed elsewhere in greater detail.[8]

The data presented here represent the first demonstration of sulfoxidation activity by a specific hydroxylase, and since purified enzyme preparations were used in these experiments, catalysis by DBH, as well as product structure, is unequivocally established. By comparison, there have been reports of sulfoxidation by crude liver microsomal systems,[17,18] where it might be presumed that cytochrome P-450, a highly nonspecific monooxygenase,[19] is involved. In related work, microsomal amine monooxygenase has been shown to form sulfinic acids from substituted thioureas.[20,21] The high stereoselectivity demonstrated here for DBH sulfoxidation is particularly noteworthy and is consistent with the known course of methylene hydroxylation. In sharp contrast, it has been reported that microsomal sulfoxidation results in only a very slight enrichment (~1%) in (*R*)-sulfoxide[22] while microbes which effect stereospecific sulfoxidation have been evaluated for synthetic applications by using whole cell systems.[23] The implications of our findings in terms of the mechanism of action of

(9) Standard reaction solutions contained 10 mM fumarate and 5 μM $CuSO_4$. Omission of fumarate decreased the reaction rate by 60%. Examination of the copper dependence of the DBH reaction revealed an approximate 15-fold stimulation, with the optimal copper concentration being 3–5 μM. Both the fumarate and copper effects for I parallel those observed with DBH-catalyzed hydroxylation.

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(13) DBH used in these experiments was purified through the PEG precipitation step, using the procedure of Ljones et al.[7]

(14) The pK_a for I was found to be 9.2, by potentiometric titration of the hydrochloride salt with NaOH, while that for II was found to be 8.1.

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DBH and the design of novel neurotransmitter analogues are currently under investigation.

Acknowledgments. Partial support of this work by the Biomedical Research Support Program of NIH is gratefully acknowledged.

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(24) Alfred P. Sloan Foundation Research Fellow, 1977-1979.

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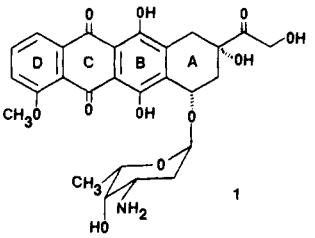
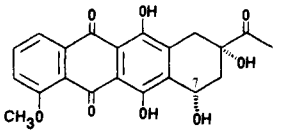
An Efficient, Regiospecific Synthesis of (±)-Daunomycinone

Sir:

The efficacy of adriamycin (**1**) as an agent for the treatment of a broad spectrum of human cancers has precipitated a deluge of activity directed toward anthracycline total synthesis.[1,2] Central

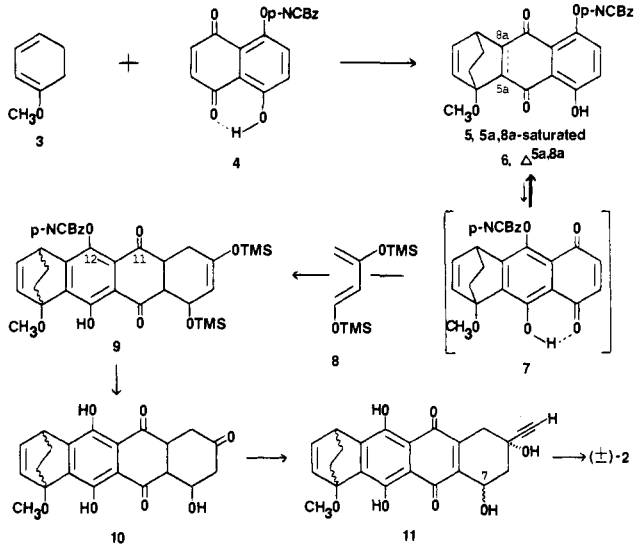


1



2

Scheme I[4]



to the synthetic[2] problem has been the challenge posed by aglycones such as daunomycinone (**2**).[3] Numerous aglycone syntheses have been achieved.[2] Nonetheless, the goal of developing an efficient, regiospecific route that is potentially amenable to large-scale operation and sufficiently flexible to provide at least putative access to a diversity of analogues has been elusive.

We now report a ten-step regiospecific synthesis of (±)-**2** from commercially available starting materials which proceeds in 36% overall yield (Scheme I).

Thus, Diels-Alder reaction between *p*-nitrocarbobenzoxy (*p*-NCBz) naphthazarin[5] (**4**, prepared from naphthazarin[6] by treatment with *p*-NCBzCl[6] and CaH_2 in THF)[7] and **3**[8] (20 °C, CH_2Cl_2) gives **5** regiospecifically, as anticipated[9] on the basis of earlier studies. Oxidation of **5** (≤1 equiv of KH, excess PbO_2, THF) affords **6**. Although NMR data indicate that **6** exists almost

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(2) For a comprehensive review of synthetic studies published through early 1979, see: (a) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288. For more recent synthetic contributions, see inter alia: (b) Walker, T. E.; Baker, R. *Carbohydr. Res.* **1978**, *64*, 266. (c) Horton, D. *J. Antibiot.* **1979**, *32*, S-145; and unpublished work of J. Swenton, D. Jackson, and W. Weckerle cited therein. (d) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. (e) Braun, M. *Tetrahedron Lett.* **1979**, 2885. (f) Savard, J.; Brassard, P. *Ibid.* **1979**, 4911. (g) Krohn, K.; Rösner, A. *Liebigs Ann. Chem.* **1979**, 2018. (h) Krohn, K.; Behnke, B. *Ibid.* **1979**, 2011. (i) Krohn, K.; Ostermeyer, H.-H.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 2640. (j) Krohn, K.; Tolkiehn, K. *Ibid.* **1979**, *112*, 3453. (k) Iwataki, I.; Nakamura, Y.; Takahashi, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. (l) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596. (m) Carrupt, P. -A.; Vogel, P. *Tetrahedron Lett.* **1979**, 4533. (n) Sih, C. J.; Massuda, D.; Corey, P.; Gleim, R. D.; Suzuki, F. *Ibid.* **1979**, 1285. (o) Oda, N.; Nagai, S.-I.; Ito, I. *Chem. Pharm. Bull.* **1979**, *27*, 2229. (p) Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. M.; Watanabe, T.; Glick, M. D. *J. Org. Chem.* **1979**, *44*, 4396. (q) Wiseman, J. R.; Pendery, J. J.; Otto, C. A.; Chiong, K. G. *Ibid.* **1980**, *45*, 516. (r) Chandler, M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1007. (s) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1980**, *45*, 1149. (t) Barton, D. H. R.; Dawes, C. C.; Franceschi, G.; Foglio, M.; Ley, S. V.; Magnus, P. D.; Mitchell, W. L.; Temperelli, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 643. (u) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802. (v) Whitlock, B. J.; Whitlock, H. W. *J. Org. Chem.* **1980**, *45*, 12. (w) Parker, K. A.; Kallmerten, J. *Ibid.* **1980**, *45*, 2614, 2620. (x) Rama Rao, A. V.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1980**, *21*, 2661. (y) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Ibid.* **1980**, *21*, 2509. (z) Terashima, S.; Tanno, N.; Koga, K. *Ibid.* **1980**, *21*, 2749, 2753. (aa) Penco, F.; Angelucci, F.; Ballabio, M.; Vigevani, A.; Arcamone, F. *Ibid.* **1980**, *21*, 2253. (bb) Bridson, J. N.; Bennett, S. M.; Butler, G. *J. Chem. Soc., Chem. Commun.* **1980**, 413. (cc) Fronza, G.; Fuganti, C.; Grasselli *Ibid.* **1980**, 442. (dd) *Tetrahedron Lett.* **1980**, *21*, 2999. (ee) Tolkiehn, K.; Krohn, K. *Chem. Ber.* **1980**, *113*, 1575. (ff) Fariña, F.; Primo, J.; Torres, T. *Chem. Lett.* **1980**, 77. (gg) Amarco, A.; Carreno, M. C.; Fariña, F. *Tetrahedron Lett.* **1979**, 3983. (hh) Jew, S.-s.; Terashima, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2351. See also ref 9g-l.

(3) The conversion of (±)-**2** into the natural antipode of **1** has been achieved.[1,2a,c]

(4) The structures of all single compounds in Scheme I are supported by spectral data and combustion analyses. In the case of most mixtures of stereoisomers (e.g., **10**), the individual isomers have been isolated and characterized by spectral and analytical data. Full experimental details are available upon request.

(5) The choice of the *p*-NCBz group arose from the finding that the Grignard reaction (**10** → **11**) fails completely when the C-12 oxygen in **10** is "protected" as an ester or carbonate (we believe that the C-11 carbonyl in such compounds is preferentially attacked by HC≡CMgBr and that deprotonation of the C-11 OH, as well as that at C-6, in **10** suppresses Grignard addition at the neighboring carbonyl). Due to the *pronounced* tendency for **9** and **10** to suffer A-ring aromatization, severe constraints are imposed on the reaction conditions employable for deprotection. "Directing" groups other than *p*-NCBz which were examined and found wanting, for one or more reasons, include pivaloyl, acetyl, CBz, *t*-BOC, *tert*-butyldimethylsilyl, chloroacetyl, and *o*-nitrobenzoyl.

(6) Available from Fluka/Tridom.

(7) On the basis of unrecoverable naphthazarin, the yield is quantitative; conversion is 62%.

(8) The technical grade of **3** available from Aldrich is satisfactory. We thank Dr. Max Brinkman of Heico for a generous sample of 1-methoxycyclohexa-1,4-diene.

(9) (a) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5513. For related studies from this laboratory, see: (b) Kelly, T. R.; Goerner, R. N., Jr.; Gillard, J. W.; Prazak, B. K. *Tetrahedron Lett.* **1976**, 3869. (c) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr. *Ibid.* **1976**, 3873. (d) Kelly, T. R. *Ibid.* **1978**, 1387. (e) Kelly, T. R.; Tsang, W.-G. *Ibid.* **1978**, 4457. (f) Kelly, T. R.; Montury, M. *Ibid.* **1978**, 4309, 4311. (g) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798. For recent relevant papers from other laboratories, see: (h) Manning, W. B. *Tetrahedron Lett.* **1979**, 1661. (i) Russell, R. A.; Collin, G. J.; Sterns, M.; Warrener, R. N. *Ibid.* **1979**, 4229. (j) Takano, S.; Hatakeyama, S.; Ogasawara, K.; Kametani, T. *Heterocycles* **1979**, *12*, 1163. (k) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548, 3554. (l) Boeckman, R. K.; Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098. We do not entirely concur with the generalizations put forward in the last cited paper.