

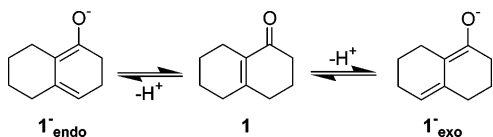
## Enolization of $\Delta^{9,10}$ -Octal-1-one: Relative Stabilities of s-Trans Exocyclic and s-Cis Endocyclic Dienolates

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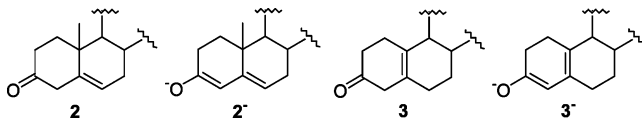


$\Delta^{9,10}$ -Octal-1-one (3,4,5,6,7,8-hexahydro-1(2*H*)-naphthalenone, **1**) can be deprotonated at either of its two  $\gamma$  positions to form the isomeric exocyclic (**1<sup>-exo</sup>**) and endocyclic (**1<sup>-endo</sup>**) dienolates. The rate of deuterium exchange for the  $\gamma_{\text{exo}}$  protons of **1** ( $1.6(\pm 0.1) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ) is 12-fold faster than that for those at the  $\gamma_{\text{endo}}$  position ( $1.38(\pm 0.08) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ). Assuming a Brønsted coefficient of 0.5, these results indicate that the exocyclic dienolate is 3.0 kcal/mol more stable than its endocyclic counterpart.

Formation of an enolate is a compulsory step in a variety of reactions, including many important enzymatic processes, and subsequently there has been considerable interest in understanding the factors that control the stabilities and rates of formation of these species. Numerous studies have demonstrated that  $\alpha$ -phenyl<sup>1,2</sup> and  $\alpha$ -vinyl<sup>3,4,5</sup> substituents can bring about substantial increases in enolate stability by extended conjugation in the enolate, and also indicate that such stabilization is strongly dependent on conformational factors (i.e., stereoelectronic effects). For example, molecular mechanics calculations,<sup>1b</sup> substituent effects,<sup>1d-f</sup> and <sup>13</sup>C NMR spectra of the enolates<sup>1c</sup> support the view that the greater acidity of the cyclic benzylc ketones 2-indanone ( $\text{p}K_{\text{a}} = 12.2$ )<sup>1a,b,2</sup> and 2-tetralone ( $\text{p}K_{\text{a}} =$

12.9)<sup>1a,b</sup> relative to benzyl methyl ketone ( $\text{p}K_{\text{a}} = \text{ca. } 16$ )<sup>2b,6</sup> results from the planarity of the cyclic enolates, the planar systems providing for greater delocalization of charge into the phenyl ring via more efficient p-orbital overlap.

The acidities of  $\Delta^5$ -3-ketosteroids show a marked dependence on the position of the  $\beta,\gamma$  double bond. 5-Androstene-3,17-dione (**2**,  $\text{p}K_{\text{a}} = 12.7$ )<sup>3a</sup> is of comparable acidity to 2-tetralone, suggesting that phenyl and vinyl groups could have similar intrinsic electronic effects on the stabilities of enolates. However, 5(10)-estrene-3-ones (**3**,  $\text{p}K_{\text{a}} > 14$ ),<sup>7</sup> as well as 3-cyclohexenone ( $\text{p}K_{\text{a}} = 15.2$ ),<sup>4</sup> are considerably less acidic. Examination of the structures of the corresponding enolates reveals a number of factors which could be responsible for the disparity in the acidities of these  $\beta,\gamma$ -unsaturated ketones. First, the double bonds of **2<sup>-</sup>** are in the s-trans conformation while those of **3<sup>-</sup>** and the dienolate of 3-cyclohexenone are s-cis. Second, **2<sup>-</sup>** has an exocyclic double bond that is absent in the dienolates of **3** and 3-cyclohexenone.<sup>8</sup> Differences in the degree of alkyl substitution of the  $\beta,\gamma$  double bond could also contribute to the relative stabilities of the dienolates. We now report the results of an investigation of the enolization of the  $\alpha,\beta$ -unsaturated, bicyclic ketone  $\Delta^{9,10}$ -octal-1-one (3,4,5,6,7,8-hexahydro-1(2*H*)-naphthalenone, **1**), which can form the s-cis, endocyclic (homoannular, **1<sup>-endo</sup>**) and s-trans, exocyclic (heteroannular, **1<sup>-exo</sup>**) dienolates, both of which have identical patterns of alkyl substitution at the  $\beta,\gamma$  double bond.



The <sup>1</sup>H NMR spectrum of **1** in 50% CD<sub>3</sub>OD/D<sub>2</sub>O (bottom spectrum of Figure 1) shows six signals, some of which can be unambiguously assigned on the basis of chemical shifts. The signal at 1.58 ppm (m, 4H, not shown) is assigned to the hydrogens at positions C-6 and C-7, those being the furthest removed from deshielding groups. The protons at position C-3,  $\beta$  to both the C=O and C=C groups, are assigned to the signal at 1.91 ppm (quintet, 2H), which is consistent with the observed coupling pattern. At the other end of the spectrum, the protons at C-2 are the most deshielded due to their proximity to the carbonyl group and are thus assigned to the signal at 2.38 ppm (t, 2H), a triplet due to coupling with the C-3 protons.

This leaves the protons at positions C-4, C-5, and C-8 to account for the signals at 2.08 (m, 2H), 2.23 (m, 2H), and 2.29 ppm (m, 2H). The COSY spectrum (not shown) shows coupling between the protons at 1.91 ppm (C-3 protons) and those at 2.38 (C-2 protons) and 2.29 ppm. Thus, the signal at 2.29 ppm is due to the protons at C-4. The COSY spectrum also correlates

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(7) This value is based upon the finding that no spectral changes attributable to a dienolate are observed for 5-estrene-3,17-dione in 1 M NaOH (ref 5). Fedor and co-workers (ref 7b) also suggest that the acidity of 17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-5-estrene-3-one is substantially less than that of 5-androstene-3,17-dione on the basis of their relative rates of isomerization in basic solution. (b) Perera, S. K.; Dunn, W. A.; Fedor, L. R. *J. Org. Chem.* **1980**, *45*, 2816–2821.

(8) As noted by a reviewer, these two factors are not independent; the s-trans geometry of **2<sup>-</sup>** requires the  $\beta,\gamma$ -double bond be exocyclic while the s-cis geometry of **3<sup>-</sup>** necessitates an endocyclic  $\beta,\gamma$ -double bond.

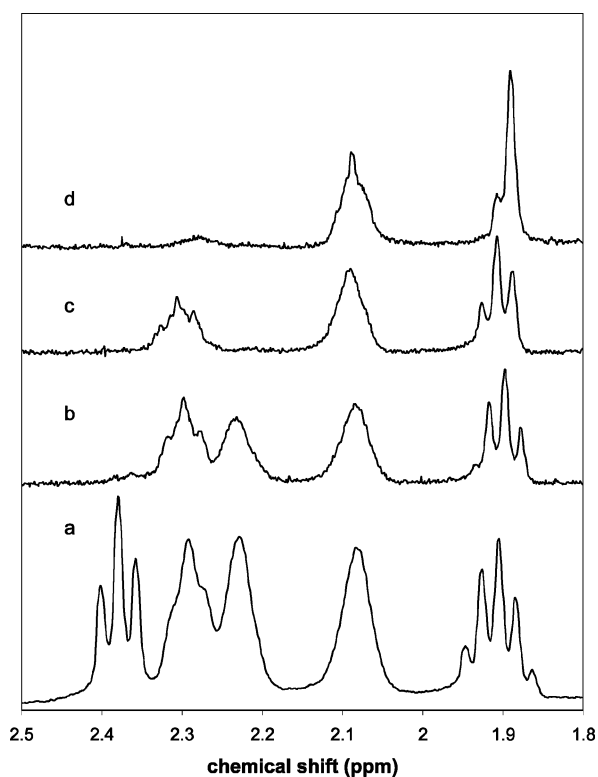
(1) (a) Ross, A. M.; Whalen, D. L.; Eldin, S.; Pollack, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 1981–1982. (b) Eldin, S.; Pollack, R. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 1344–1349. (c) Eldin, S.; Whalen, D. L.; Pollack, R. M. *J. Org. Chem.* **1993**, *58*, 3490–3495. (d) Nevy, J. B.; Hawkinson, D. C.; Blotny, G.; Yao, X.; Pollack, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 12722–12726. (e) Yao, X.; Gold, M. A.; Pollack, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 6220–6225. (f) Yao, X.; Pollack, R. M. *Can. J. Chem.* **1999**, *77*, 634–638.

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(3) (a) Pollack, R. M.; Zeng, B.; Mack, J. P. G.; Eldin, S. *J. Am. Chem. Soc.* **1989**, *111*, 6419–6423. (b) Zeng, B.; Pollack, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 3838–3842.

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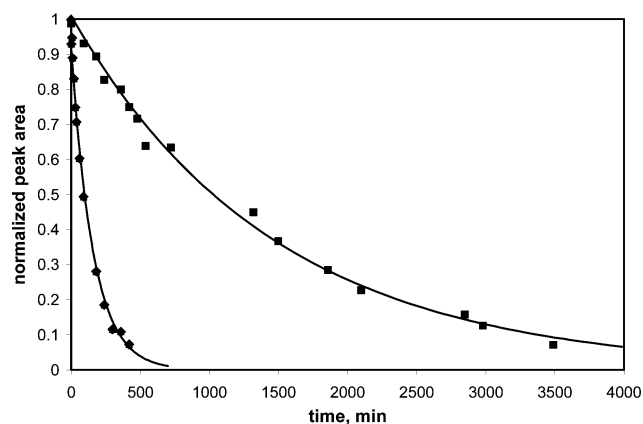
(5) Eldin, S.; Whalen, D. L.; Pollack, R. M. *J. Org. Chem.* **1993**, *58*, 7100–7105.



**FIGURE 1.**  $^1\text{H}$  NMR spectra of  $\Delta^{9,10}$ -octal-1-one (**1**) in 50%  $\text{CD}_3\text{OD}/\text{D}_2\text{O}$  containing 0.31 M NaOD at the following times (bottom to top): (a) before addition of NaOD, (b) 65 min, (c) 1180 min, and (d) 7200 min.

the signal at 1.58 ppm with those at 2.08 and 2.23 ppm. While these two signals must be due to the protons at C-5 and C-8, it is not possible to distinguish between these positions on the basis of the COSY spectrum.

Completion of the spectral assignments is possible by using spectra obtained under basic conditions, where the hydrogens at positions C-2, C-4, and C-5 exchange with solvent deuterium via proton abstraction by deuteroxide followed by protonation of the resulting enolate by solvent. Figure 1 shows  $^1\text{H}$  NMR spectra of **1** in 50%  $\text{CD}_3\text{OD}/\text{D}_2\text{O}$  containing 0.31 M NaOD at various time intervals. After about 1 h (Figure 1b), the signal at 2.38 ppm, assigned to the protons at C-2 (the  $\alpha$  protons), completely disappears from the spectrum. None of the other signals show substantial decrease in intensity during this time period, but the signal at 1.91 ppm (C-3 protons) collapses from a quintet to a triplet due to the exchange of the two C-2 protons. The second signal to vanish from the spectrum is that at 2.23 ppm (complete exchange within about 20 h (Figure 1c)). Since the C-5 position has the only set of exchangeable hydrogens not assigned above, the signal at 2.23 ppm must be due to those protons. This interpretation is further supported by the fact that the signal at  $\delta$  1.91 ppm (C-3 protons) remains a triplet while those at 2.23 ppm are exchanged; if the C-4 protons had exchanged during this period, the signal at  $\delta$  1.91 ppm would have collapsed to a singlet over this interval. At longer times (5 days, Figure 1d), the decay of the signal at  $\delta$  2.29 ppm (C-4 position) is accompanied by collapse of the signal at  $\delta$  1.91 ppm to a singlet. At this point, the only unassigned signal is that at 2.08 ppm, which thus must correlate to the C-8 protons.



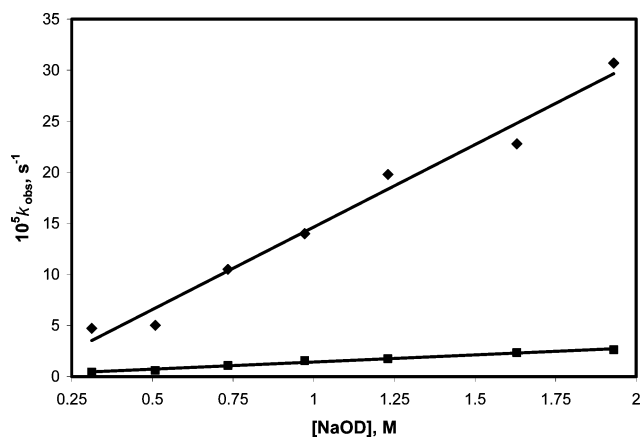
**FIGURE 2.** Plot of the normalized  $^1\text{H}$  NMR peak area against time for exchange of the  $\gamma_{\text{exo}}$  (C-5,  $\blacklozenge$ ) and  $\gamma_{\text{endo}}$  (C-4,  $\blacksquare$ ) protons of  $\Delta^{9,10}$ -octal-1-one (**1**) with solvent deuterium in 50%  $\text{CD}_3\text{OD}/\text{D}_2\text{O}$  containing 0.31 M NaOD at 25  $^\circ\text{C}$ .

**TABLE 1.** Pseudo-First-Order Rate Constants for Deuterium Exchange of the  $\gamma_{\text{endo}}$  and  $\gamma_{\text{exo}}$  Protons of  $\Delta^{9,10}$ -Octal-1-one (**1**) at 25  $^\circ\text{C}$  (50%  $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ )

[NaOD], M	$10^5 k_{\text{endo}}^{\text{obs}}, \text{s}^{-1}$	$10^4 k_{\text{exo}}^{\text{obs}}, \text{s}^{-1}$
0.312	$0.447 \pm 0.008$	$0.473 \pm 0.005$
0.509	$0.62 \pm 0.02$	$0.50 \pm 0.01$
0.734	$1.09 \pm 0.02$	$1.05 \pm 0.02$
0.972	$1.59 \pm 0.03$	$1.40 \pm 0.05$
1.23	$1.75 \pm 0.05$	$1.98 \pm 0.03$
1.63	$2.35 \pm 0.07$	$2.28 \pm 0.08$
1.93	$2.6 \pm 0.2$	$3.07 \pm 0.05$

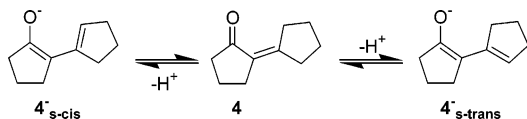
As described above, protons at the three enolizable positions of **1** exchange with solvent deuterium at greatly different rates, with the  $\alpha$  protons (2.38 ppm; C-2) exchanging the fastest, followed by the  $\gamma_{\text{exo}}$  protons (2.23 ppm; C-5), and the  $\gamma_{\text{endo}}$  protons (2.29 ppm; C-4) exchanging the slowest. First-order rate constants for exchange of the  $\gamma$ -hydrogens with solvent deuterium were determined by monitoring the decrease in area of the corresponding  $^1\text{H}$  NMR signals as a function of time. Following addition of NaOD, spectra were recorded at numerous time intervals over a period of 3–4 half-lives for the exchange. Peak areas of the exchangeable protons were integrated and normalized against the peak areas of the nonexchangeable protons. Figure 2 shows a plot of normalized peak area vs time for exchange of the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  protons at  $[\text{NaOD}] = 0.31$  M. Fitting the normalized peak areas to a first-order rate equation by nonlinear least-squares regression gives the pseudo-first-order rate constants for exchange of the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  hydrogens with solvent deuterium ( $k_{\text{exo}}^{\text{obs}}$  and  $k_{\text{endo}}^{\text{obs}}$ , respectively). Standard deviations of the rate data from the theoretical curve ranged from 1.1% to 5.7%. The pseudo-first-order rate constants for the exchange at several  $[\text{NaOD}]$  are listed in Table 1.

Deuterium exchange with solvent involves proton abstraction by deuteroxide followed by protonation of the resulting enolate by solvent (eq 1). Since the concentration of  $\text{D}_2\text{O}$  is much greater than that of HOD,  $k_2[\text{D}_2\text{O}]$  will be much greater than  $k_{-1}[\text{HOD}]$ , and the steady-state rate law predicts that the observed rates of deuterium exchange will show a linear dependence on  $[\text{DO}^-]$  (eq 2). Figure 3 show plots of the observed pseudo-first-order rate constants for deuterium exchange at the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  positions ( $k_{\text{exo}}^{\text{obs}}$  and  $k_{\text{endo}}^{\text{obs}}$ ) against  $[\text{NaOD}]$ . The apparent second-order rate constants for proton abstraction by deuteroxide at the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  positions,

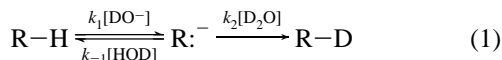


**FIGURE 3.** Plot of  $k_{\text{obs}}^{\text{exo}}$  (◆) and  $k_{\text{obs}}^{\text{endo}}$  (■) against [NaOD] for exchange of the  $\gamma$  protons of  $\Delta^{9,10}$ -octal-1-one (**1**) with solvent deuterium in 50%  $\text{CD}_3\text{OD}/\text{D}_2\text{O}$  at 25 °C.

#### SCHEME 1



obtained by fitting the data of Table 1 by linear least-squares regression, are  $k_{\text{exo}} = 1.6(\pm 0.1) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{\text{endo}} = 1.38(\pm 0.08) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ .



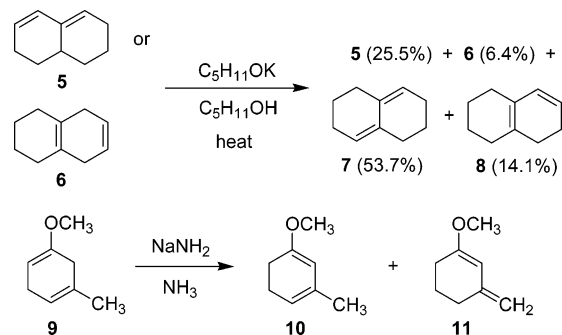
$$k_{\text{obs}} = k_1[\text{DO}^-] \quad (2)$$

The 12-fold faster rate of deprotonation at the  $\gamma_{\text{exo}}$  position indicates that the transition state for formation of the exocyclic, s-trans dienolate is 1.5 kcal/mol lower in energy than that for the endocyclic, s-cis dienolate. An estimation of the relative stabilities of the dienolic species can be made by using the Brønsted catalysis law (eq 3). Using a  $\beta$  coefficient of 0.5, the value obtained from studies of the general base-catalyzed conjugation of 3-cyclopentenone and 3-cyclohexenone,<sup>9</sup> the above rate ratio leads to a  $\Delta pK_a$  of  $2.2 \pm 0.3$  (assuming 10% uncertainty in  $\beta$ ), corresponding to a  $3.0 \pm 0.4$  kcal/mol difference in stability between the two dienolates.

$$\Delta \log k = \beta(\Delta \log K_a) \quad (3)$$

Pollack and co-workers<sup>5</sup> addressed the relative stabilities of s-cis and s-trans dienolates by studies of the enolization of 2-cyclopentylidenecyclopentanone (**4**, Scheme 1). From the rates of solvent deuterium exchange at the  $\gamma$  positions and the distribution of deuterium in **4** when an equilibrium solution of the dienolates was rapidly quenched in  $\text{D}_2\text{O}$ , it was estimated that the energy of the transition state for formation of the s-cis dienolate (**4**<sub>s-cis</sub>) was 0.8 kcal/mol higher than that for the s-trans dienolate (**4**<sub>s-trans</sub>). From these results it was estimated that the s-trans dienolate is ca. 1.7 kcal/mol more stable than the s-cis dienolate ( $\Delta pK_a = 1.2$ ). Since the difference in energies of the s-cis and s-trans dienolates of **4** was insufficient to explain

#### SCHEME 2



the greater acidity of **2** compared with **3** and 3-cyclohexenone, it was argued that greater strain energy in the homoannular cyclohexadienyl ring system played a major role in determining the stabilities of the cyclic dienolates.

The results of the current study are consistent with the above interpretation. The ratio of rates of solvent deuterium exchange for the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  protons of **1** ( $k_{\text{exo}}/k_{\text{endo}} = 12 \pm 1$ ) is 5-fold greater than for the  $\gamma_{\text{s-trans}}$  and  $\gamma_{\text{s-cis}}$  protons of **4** ( $k_{\text{s-trans}}/k_{\text{s-cis}} = 2.4 \pm 0.2$ ), indicative of a greater difference in the stabilities of the corresponding dienolates of the former. Assuming a Brønsted  $\beta$  value of 0.5 for both systems, the calculated energy difference for the cyclic dienolates **1**<sup>-exo</sup> and **1**<sup>-endo</sup> is 1.3 kcal/mol greater than that for the “acyclic” s-trans and s-cis dienolates of **4**. In addition, the calculated  $\Delta pK_a$  for the  $\gamma_{\text{exo}}$  and  $\gamma_{\text{endo}}$  protons of **1** ( $\Delta pK_a = 2.2$ ) is comparable to the difference in acidity of **2** compared with **3** and 3-cyclohexenone.

The thermochemical calculations of Pollack et al.<sup>10</sup> provide compelling support for the notion that strain plays a major role in determining the acidifying effect of the vinyl group in cyclic  $\beta,\gamma$ -unsaturated ketones. The preference for formation of cyclohexadienes containing exocyclic double bonds over the corresponding homoannular dienes has also been experimentally demonstrated in base-catalyzed isomerizations of dienes (Scheme 2). Upon heating **5** or **6** at 184 °C for 24 h in potassium *tert*-pentoxide/*tert*-pentanol, the resulting equilibrium mixture of hexahydronaphthalenes contained greater than 75% of the exocyclic dienes **5** and **7**.<sup>11</sup> From the product ratios, the major isomer (**7**), with structure analogous to that of dienolate **1**<sup>-exo</sup>, was calculated to be 1.85 kcal/mol more stable than the homoannular diene **8**. Likewise, Birch et al. observed a preference for formation of exocyclic systems during base-catalyzed isomerization of 1-methoxy-5-alkyl-1,4-cyclohexadienes.<sup>12</sup> Treatment of **9** with sodamide ( $\text{NaNH}_2$ ) in liquid ammonia initially (reaction times of 3 min and 1 h) gave a mixture of the endocyclic (**10**) and exocyclic (**11**) dienolic ethers, but after reaction with base for 24 h, **11** was the exclusive product.

(10) Pollack and co-workers (ref 5) addressed the relative stabilities of isomeric s-cis, endocyclic (homoannular) and s-trans, exocyclic (heteroannular) dienolates via molecular mechanics calculations of the heats of formation of  $\beta,\gamma$ -unsaturated ketones and the corresponding dienolates. In all cases, introduction of a second endocyclic double bond into a 6-membered ring, yielding a homoannular dienolate, involved a substantially greater increase in energy (8.8–11.3 kcal/mol) than for the corresponding heteroannular dienolates. These calculations were supported by evaluation of the energetics for isodesmic interconversion of a homoannular–heteroannular diene pair using literature values for the heats of formation.

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## Experimental Section

$\Delta^{9,10}$ -Octal-1-one (**1**). *cis*-Decahydro-1-naphthol was oxidized with PCC<sup>13</sup> and the resulting ketone converted to **1** as reported by House and Thompson (chlorination with SO<sub>2</sub>Cl<sub>2</sub> followed by heating under N<sub>2</sub> with LiCl in DMF).<sup>14</sup> Following vacuum distillation (7 mmHg, bp 115–118 °C), GCMS analysis indicated two isomeric products, presumably  $\Delta^{8,9}$ -octal-1-one<sup>14</sup> in addition to **1** (major isomer), in a ca. 10:1 ratio. Further purification by column chromatography (7:1 petroleum ether:EtOAc) and a second vacuum distillation (2.5 mmHg, bp 93–95 °C) gave a single

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compound by GCMS. MS: *m/z* (%) 150 (M, 57), 135 (27), 122 (75), 94 (30), 79 (100). IR (neat): includes 2934, 2863, 1665, 1634 cm<sup>-1</sup>. The <sup>1</sup>H NMR of **1** is described in detail in the text.

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**Supporting Information Available:** General experimental information and the complete <sup>1</sup>H NMR spectrum of **1** (1–8.5 ppm) in 50% CD<sub>3</sub>OD–D<sub>2</sub>O. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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