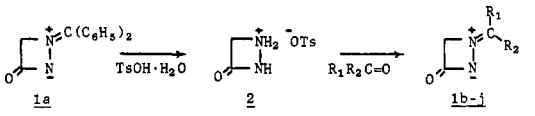
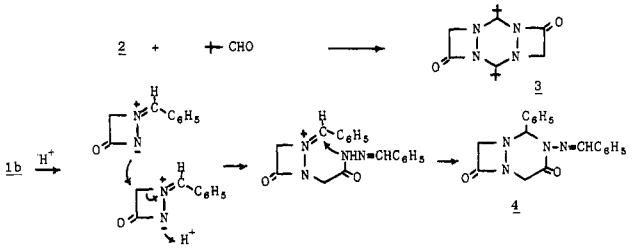
Scheme I



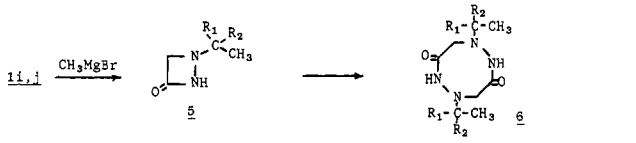
| 1 | $R_1$ | $R_2$ | mp, °C | Yield, % | E/Z ratio[a] |
|---|---|---|---|---|---|
| a | $C_6H_5$ | $C_6H_5$ | | | |
| b | H | $C_6H_5$ | 196-198 d | 57 | |
| c | H | $C_6H_4OCH_3$-p | 190-191 d | 71 | |
| d | H | $C_6H_4Cl$-p | 220 d | 77 | |
| e | H | $C_6H_4CH{=}CH$ | 199-200 d | 99 | |
| f | ~$CH_3$ | ~$C_6H_5$ | | 55 | 30/70 |
| g | $CH_2C_6H_5$ | $CH_2C_6H_5$ | 87-89 | 42 | |
| h | ~$CH_3$ | ~$CH(OCH_3)_2$ | | 36 | 85/15 |
| i | ~$CH_3$ | ~$CH_2CH(OCH_3)_2$ | | 68 | 50/50 |
| j | | $-C_5H_{10}-$ | 157-159 d | 90 | |

[a] As isolated from the reaction.

Scheme II

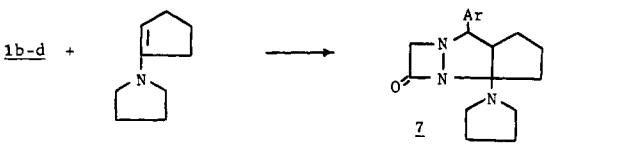


Scheme III



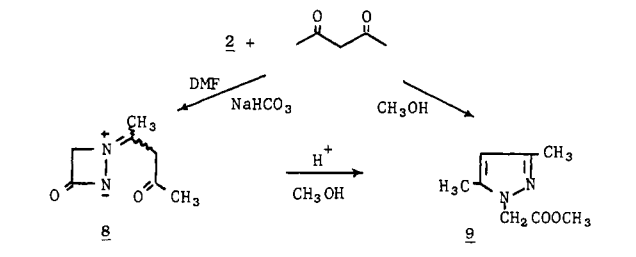
| $R_1$ | $R_2$ | mp, °C | Yield, % |
|---|---|---|---|
| $CH_3$ | $CH_2CH(OCH_3)_2$ | 149-151 | 53 |
| | $-C_5H_{10}-$ | 310-315 | 36 |

Scheme IV



| Ar | mp, °C | Yield, % |
|---|---|---|
| $C_6H_5$ | 138-140 | 97 |
| $C_6H_4OCH_3$-p | 117-119 | 90 |
| $C_6H_4Cl$-p | 136-137 | 91 |

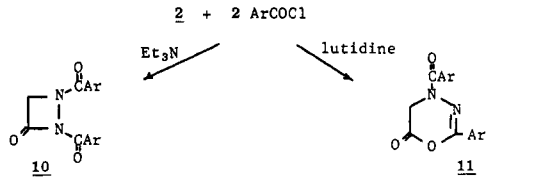
Scheme V



acidic methanol at room temperature (it is stable in neutral methanol).

It was not possible to monoacylate 3-oxo-1,2-diazetidinium tosylate (**2**) under a variety of reaction conditions. However, 1,2-diaroyl-1,2-diazetidinones (**10**) are formed on treatment of **2** with 2 equiv of an aroyl chloride in the presence of triethylamine in dichloromethane at −78 °C. When 2,6-lutidine is used as the base, ring expansion to 2-aryl-4-aroyl-4,5-dihydro-1,3,4-oxadiazin-6-ones (**11**) occurs. We are currently exploring the conversion of these now readily accessible heterocycles to 1,3,4-oxadiazin-6-ones, which should be of considerable interest as precursors to pyridazines, 2-pyrones, and unusually substituted acetylenes.

Scheme VI



| | Ar | mp, °C | Yield, % | mp, °C | Yield, % |
|---|---|---|---|---|---|
| a | $C_6H_5$ | 111-113 | 42 | 91-93 | 35 |
| b | $C_6H_4NO_2$-p | 110 d | 21 | 158 d | 43 |
| c | $C_6H_4OCH_3$-p | 142 d | 23 | 125-127 | 64 |
| d | $C(CH_3)_3$ | 70-70.5 | 70 | ref. 7 | |

## Stereochemistry of an Alkoxide-Accelerated [1,3] Migration

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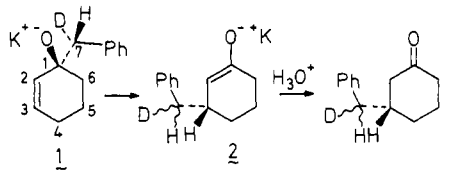
*Received August 28, 1981*

In 1975 Evans and Golob[1] reported the dramatic acceleration of a [3,3]-sigmatropic rearrangement caused by an alkoxide substituent. Subsequently it was found that similar rate enhancements occur for [1,3][2-6] and [1,5][7] migrations. In this communication we turn our attention to the stereochemistry of the alkoxide-accelerated [1,3] rearrangement **1** → **2**.



Recent work by Evans et al.[8] has shown that the potassium alkoxide substituent does not alter the stereochemistry of a [3,3]-sigmatropic migration. However, at the inception of the present study we had reason to believe that this constancy of mechanism upon substitution need not be universally true and that the [1,3]-sigmatropic shift might be a case where the rate acceleration would be accompanied by a change in stereochemistry.

The basis for this belief was a simple model for substituent effects on pericyclic reactions that we had found to be useful for interpreting a number of experimental observations[9,10] including

(1) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
(2) Franzus, B.; Scheinbaum, M. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976**, *98*,, 1241–1247.
(3) Thies, R. W.; Seitz, E. P. *J. Chem. Soc., Chem. Commun.* **1976**, *846*–847.
(4) Wilson, S. R.; Mao, D. T. *J. Chem. Soc., Chem. Commun.* **1978**, 479–480.
(5) Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2033–2048.
(6) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443–2446.
(7) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972–3974.
(8) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774–782.

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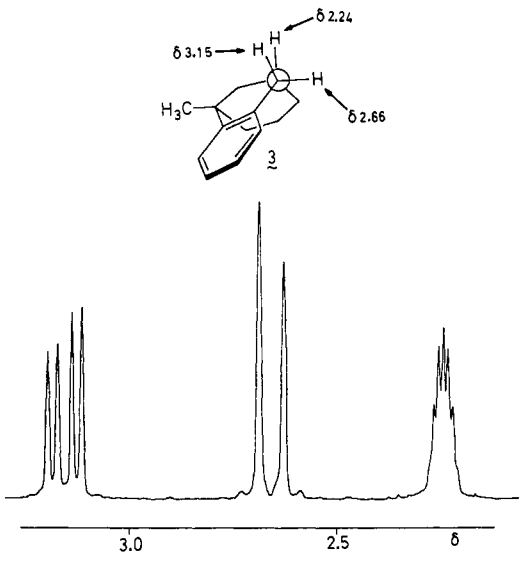
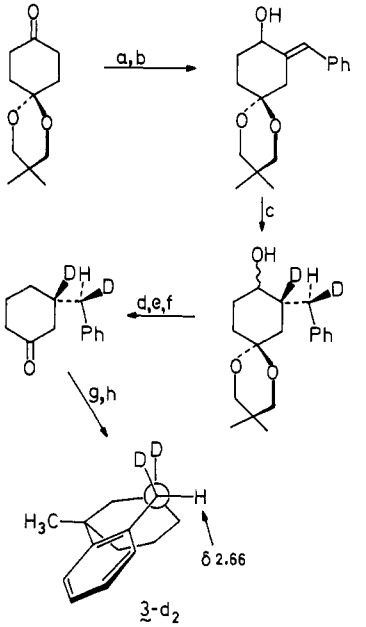



**Figure 1.** Part of the 300-MHz $^1$H NMR spectrum of **3** ($CDCl_3$; chemical shifts in ppm downfield from $Me_4Si$).

the alkoxide-induced rate enhancements.[9] The model attributes these rate enhancements to a stabilizing resonance interaction between a $p_\pi$ orbital on the substituent and the pericyclic array of orbitals on the skeletal atoms in the transition state for the reaction. This stabilizing interaction is not present in the reactant if the substituent is attached to an $sp^3$ hybridized atom, and so the net result is a reduction in $\Delta H^\ddagger$. According to this model the stabilizing effect is the same for anionic, radical, or cationic substituents provided that the skeletal atoms form an even-membered, uncharged ring in the transition state.[9] There is substantial evidence that this feature of the model is correct.[9,11] A second prediction of particular importance for the present work is that the substituent will invariably interact more strongly with the transition state for a forbidden[12] reaction than with that for an allowed[12] reaction. This is because the forbidden transition state suffers an antiaromatic destabilization which can be alleviated by increasing or decreasing the electron density in the ring. The substituent provides a means of achieving this end.[13] If the model is correct one can therefore make the general statement: *any substituent will accelerate a forbidden pericyclic reaction more than it accelerates the corresponding allowed reaction.*[14,15] An interesting corollary, leading us to the present study, is that the differential stabilization of the forbidden transition state might sometimes exceed the energy gap between allowed and forbidden pathways for the parent (unsubstituted) system. Under such circumstances the rate enhancement caused by the substituent would be accompanied by a change in stereochemistry.[15]

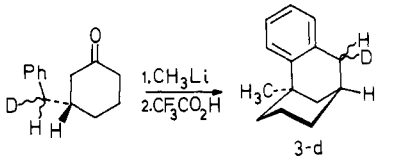
Scheme I[a]




[a] (a) NaOH/PhCHO; (b) $NaBH_4$; (c) $D_2$/Pd, C; (d) $CH_3SO_2Cl$/py; (e) $LiEt_3BH$; (f) $H_3O^+$; (g) $CH_3Li$; (h) $CF_3CO_2H$.

We selected the [1,3]-sigmatropic migration as a possible candidate to exhibit this behavior because, while it does normally follow the allowed suprafacial inversion pathway[16,17] (of particular relevance to the present study being the work of Lown et al.[18] showing ≥95% inversion in a suprafacial [1,3]-benzyl migration), there is good reason to believe that the suprafacial retention mechanism is accessible.[16,17] Our goal was to determine whether one could cause the suprafacial retention mechanism to become competitive through an electronic substituent effect.

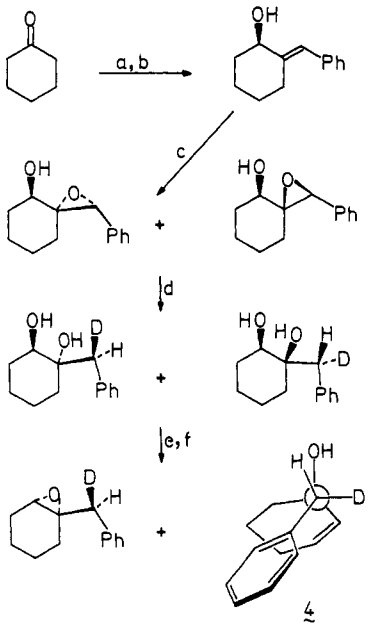
Since the stereochemical relationship between C1 and C7[19] in **1** was determined by synthesis (vide infra) and that between C1 of **1** and C3 of **2** fixed by the cyclohexene ring (for an intramolecular migration), it was necessary only to determine the relationship between C3 and C7 in **2** to deduce the overall stereochemistry of the rearrangement. This could be achieved by conversion of the 3-benzylcyclohexanone product to 1-methylbenzobicyclo[3.3.1]non-2-ene-4-*d* (**3**-*d*).




The $^1$H NMR spectrum of unlabeled 1-methylbenzobicyclo[3.3.1]non-2-ene (**3**) showed clearly resolved resonances for the two benzylic hydrogens and the bridgehead hydrogen (Figure 1). The near 90° dihedral angle between $H_b$ and the bridgehead hydrogen in **3**, combined with the lack of vicinal coupling between one of the benzylic hydrogens and the bridgehead hydrogen, led us to assign the δ 2.66 resonance to $H_b$ and the δ 3.15 resonance to $H_a$. However, the relative chemical shifts so deduced for $H_a$ and $H_b$ were reversed from those found in a derivative of **3**,[20] and so we sought an independent method of assignment. This was achieved by synthesis of the stereospecifically deuterated compound **3**-$d_2$, as shown in Scheme I. The observation of a resonance at

(9) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877–1884.
(10) (a) Wilcox, C. F., Jr.; Carpenter, B. K.; Dolbier, W. R., Jr. *Tetrahedron* **1979**, *35*, 707–711. (b) Wilcox, C. F., Jr.; Carpenter, B. K. *J. Am. Chem. Soc.* **1979**, *101*, 3897–3905.
(11) (a) For additional cation-accelerated rearrangements, see: Itô, S.; Itoh, I.; Yutaka, F.; Nakatsu, T.; Senkler, C. A.; Schleyer, P. v. R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2379–2390. Schipper, P.; de Haan, J. W.; Buck, H. M. *J. Chem. Soc., Perkin Trans. 2* **1981**, 457–463. (b) For an interesting comparison of carbanion and radical-accelerated cyclobutene ring openings, see: Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 1256–1258. Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970–974.
(12) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/Bergstr, 1970.
(13) An alternative statement of the same phenomenon would be to say that the substituent can interact strongly with either the high-lying HOMO or low-lying LUMO that all antiaromatic structures possess. We thank Professor David Lemal (Dartmouth) for this interpretation.
(14) Our theoretical model strictly applies to potential-energy changes. These will usually be well approximated by $\Delta\Delta H^\ddagger$[10b] but not necessarily by $\Delta\Delta G^\ddagger$. Prediction of a rate acceleration thus presumes that a reduction of $\Delta H^\ddagger$ is not completely counterbalanced by a reduction in $\Delta S^\ddagger$.
(15) Epiotis has arrived at a similar but more restricted conclusion using a more sophisticated theoretical model: Epiotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 1206–1214.
(16) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406–414.
(17) Roth, W. R.; Friedrich, A. *Tetrahedron Lett.* **1969**, 2607–2611.
(18) Lown, J. W.; Akhtar, M. H.; McDaniel, R. S. *J. Org. Chem.* **1974**, *39*, 1998–2006.
(19) IUPAC numbering is not used for the carbon atoms of **1** but is used in the naming of all compounds.
(20) Shapiro, B. L.; Shapiro, M. J. *J. Org. Chem.* **1976**, *41*, 1522–1529.

Scheme II[a]



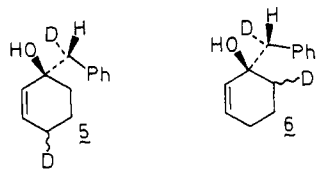
[a] All compounds shown are racemic but single diastereomers. (a) NaOH/PhCHO; (b) $NaBH_4$; (c) *m*-$ClC_6H_4CO_3H$; (d) $LiAlD_4$; (e) $CH_3SO_2Cl$/py; (f) DBU.

$\delta$ 2.66 but none at $\delta$ 3.15 in the $^1H$ NMR spectrum of **3**-$d_2$ confirmed our assignments for **3**. This experiment also showed that the **2** → **3**-*d* conversion would preserve stereochemical information at the benzylic carbon.

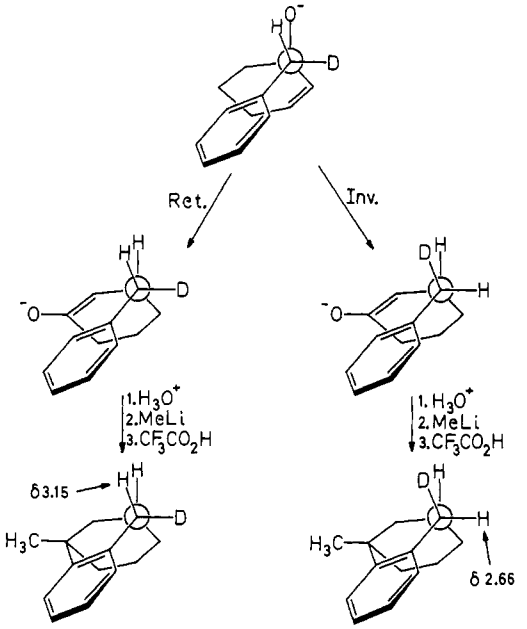
The synthesis of the alcohol precursor to **1** was achieved by the route shown in Scheme II.[21]

When **4** was treated with potassium hydride in HMPA at 22 °C it underwent a [1,3] migration to afford **2** which, in turn, gave **3**-*d* after the reaction sequence outlined above. The $^1H$ NMR spectrum of **3**-*d* showed an integral ratio of (1.60 ± 0.04):1 for the resonances at $\delta$ 3.15 and 2.66. Mass spectral analysis showed that **1**, which had been 99.0% $d_1$, gave **3**-*d* which was 98.4% $d_1$. Integration of the $\delta$ 2.66 and 3.15 resonances in the $^1H$ NMR spectrum against the bridgehead resonance at $\delta$ 2.24 also confirmed that essentially no deuterium had been lost from the benzylic position. As shown in Scheme III, the NMR data indicate a 1.60:1 retention to inversion ratio in the rearrangement.

In order to determine whether any of the products had been formed by fragmentation of **1** to cyclohexenone and a benzyl anion, followed by readdition in a 1,4 fashion, we carried out a double labeling experiment. 2-Cyclohexenone was converted to cyclohexanone-2,3-$d_2$ by treatment with $D_2$ and $Rh(Ph_3P)_3Cl$ and then to cyclohexanone-3-*d* by repeated washing with aqueous $NaHCO_3$. The cyclohexanone-3-*d* was converted to a 1:1 mixture of **5** and **6** by following the sequence of reactions outlined in Scheme II. The mixture of **5** and **6** (86.2 mg) was the combined with unlabeled 3-benzyl-3-cyclohexenol (94.6 mg) and treated with KH in HMPA.



Scheme III. Relationship between [1,3]-Migration Stereochemistry and Chemical Shift of Benzyl Proton in **3**-*d*



The products were converted to their respective 1-methylbenzobicyclo[3.3.1]non-2-enes and analyzed first for the retention/inversion ratio. This time $^2H$ NMR spectroscopy was used because the presence of >50% unlabeled material would have reduced the precision of any data determined by $^1H$ NMR spectroscopy. We were gratified to find that the $^2H$ NMR integration confirmed the 1.6:1 retention/inversion ratio found in the earlier experiment.

The 1-methylbenzobicyclo[3.3.1]non-2-enes were then subjected to mass spectrometry (MS) at 14-eV ionization energy. This showed a ratio of 49.6:26.1:23.3:1.0 $d_0/d_1/d_2/d_3$ products. Since the mixture of **5** and **6** had been 97% $d_2$, 2% benzyl-$d_1$ and 1% ring-$d_1$, the MS results indicated loss of 19.0% of the deuterium. The earlier experiment using 3-*d* had shown no D loss from the benzyl position, and so one can deduce that 38.7% of the ring deuterium had been lost. This result is not surprising when one considers that **6** rearranges to a ketone with an $\alpha$ deuterium atom. Allowing for the deuterium loss, one can calculate that the $d_0/d_1/d_2$ ratios should be 52.8:19.0:28.2 for a completely intramolecular mechanism and 38.0:48.7:13.4 for a completely intermolecular (fragmentation/recombination) mechanism. The observed values are best fit by a reaction that is 75% intramolecular and 25% intermolecular, leading to a calculated ratio of 49.1:26.4:24.5 $d_0/d_1/d_2$.

Given that the intermolecular reaction must (presumably) proceed with a 1:1 retention/inversion ratio, it follows that *the intramolecular [1,3] rearrangement of* **1** → **2** *occurs with at least*[22] *65% retention of configuration.*

The experimental results lead us to two main conclusions:

(1) Unlike the [3,3]-sigmatropic rearrangement,[8] the [1,3] migration (**1** → **2**) experiences a change in mechanism associated with introduction of an alkoxide substituent.

(2) The observation of predominant retention of configuration in the intramolecular rearrangement is consistent with the theoretical prediction, although, as usual, one cannot rule out fragmentation/recombination within a solvent cage as a contributor to the intramolecular reaction.

**Acknowledgment.** Support of this work by the NIH (Grant GM 27022) is gratefully acknowledged.

(21) The benzyl hydrogens of the unlabeled *trans*-diol exhibited an AB coupling pattern in the $^1H$ NMR spectrum. $^1H\{^2H\}$ and $^2H\{^1H\}$ NMR spectra of the corresponding deuterated compound showed the epoxide ring opening to be stereospecific within the limits of detection. We assume that the *cis*-diol was also formed stereospecifically but cannot prove it because of the diastereotopic benzyl hydrogens have coincidentally identical chemical shifts for this compound and **4**.

(22) The value of 65% retention is a lower limit because the stereochemistry of the reactant (**1**) might have been partially scrambled by fragmentation and recombination in a 1,2 sense. Such a process would have been undetectable in reisolated **4** owing to overlap of the two benzylic hydrogen resonances in the $^1H$ NMR spectrum.[21]