

**Figure 1.**  $^{13}\text{C}$  spectra of 0.5 M rifamycin S in  $\text{CDCl}_3$  recorded on an XL-200 Varian spectrometer at 23 °C: (A)  $^{13}\text{C}$  spectrum after irradiation of the phenolic hydroxyl proton, (B) as (A) but with the decoupler set "off" resonance. (C) difference spectrum (A - B). The presaturation selective pulse on the phenolic hydroxyl proton had a 10-s duration and 0.5-W power. During the acquisition of the FIDs the decoupler was on with a power of 4 W in the broad-band mode. The structure of rifamycin S is inset. Only those carbon atoms relevant to the discussion are numbered.

**Table I**

$C_n$	$\delta^a$	$\text{NOE}_{C_n}(\text{H}_8)$	$R_{C_n}^b$ $\text{s}^{-1}$	$r_{o-}^c$ (H-C $_n$ )	$r_{A-}^d$ (H $_8$ -C $_n$ )	$r_{B-}^e$ (H $_8$ -C $_n$ )
$C_1$	184.57	0.35	0.35	2.38A	2.27	2.30
$C_8$	166.59	0.89	0.17	2.02A		2.05
$C_7$	114.31	0.05	0.27	3.26A	3.01	3.05
$C_9$	110.51	0.34	0.23	2.54A	2.45	2.5

<sup>a</sup> ppm from external  $\text{Me}_4\text{Si}$ . <sup>b</sup>  $^{13}\text{C}$  spin-lattice relaxation rates obtained by using the inversion recovery method. <sup>c</sup> Proton-carbon internuclear distances calculated by computer modeling. <sup>d</sup> Proton-carbon internuclear distances calculated by using method A and  $r(\text{C}_8\text{-H}_8)$  as the calibration. <sup>e</sup> Proton-carbon internuclear distances calculated using method B and  $\tau_c = 1.7 \times 10^{-10} \text{ s}^{-1}$ . This value was evaluated from the dipolar contribution of the protonated  $\text{C}_3$  relaxation rate ( $R_{C_3} = 3.9 \text{ s}^{-1}$ ).

combination of NOE and  $^{13}\text{C}$  relaxation rate measurements yielded information on single proton-carbon distances since

$$\text{NOE}_{C_m}(\text{H}_n)R_{C_m} = (\gamma_{\text{H}}/\gamma_{\text{C}})/\delta_{mn} \quad (1)$$

The internuclear distance ( $r_{m-n}$ ) between the carbon atom ( $C_m$ ) and the  $\text{H}_n$  proton can be obtained by two independent methods.

Method A: When the saturation of  $\text{H}_n$  gives Overhauser effects on two or more carbon resonances, internuclear distances can be calculated from the following type of relationship:

$$\frac{\text{NOE}_{C_1}(\text{H}_n)R_{C_1}}{\text{NOE}_{C_2}(\text{H}_n)R_{C_2}} = \frac{r_{2-n}^6}{r_{1-n}^6} \quad (2)$$

In order to evaluate  $r$ 's from eq 2, a knowledge of correlation times is not required, but one of the two distances has to be used as a calibration one.

Method B: If both the correlation time and the cross-relaxation term are known, an absolute determination of  $r_{mn}$  is possible with use of eq 3.

$$r_{m-n}^6 = \frac{h^2\gamma_{\text{H}}^3\gamma_{\text{C}}}{10\text{NOE}_{C_m}(\text{H}_n)R_{C_m}} \left[ \frac{6\tau_c}{1 + (\omega_{\text{H}} + \omega_{\text{C}})^2\tau_c^2} - \frac{\tau_c}{1 + (\omega_{\text{H}} - \omega_{\text{C}})^2\tau_c^2} \right] \quad (3)$$

The use of either of the methods depends on the particular system being investigated, but it seems reasonable that, as in the present work, they can be used simultaneously, thus allowing a double check on calculated  $r$  values and hence the assumptions behind the data in Table I.

Registry No. Rifamycin S, 13553-79-2.

## Origin of the Rate Acceleration in the Ireland-Claisen Rearrangement

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The synthetically useful,<sup>1</sup> mechanistically intriguing<sup>2</sup> aliphatic Claisen rearrangement (thermal [3,3]-sigmatropic shift of allyl vinyl ethers to  $\gamma,\delta$ -unsaturated carbonyl compounds) is a concerted reaction which proceeds via a transition state that is chairlike, as revealed from stereochemical studies,<sup>3</sup> that more resembles reactant than product, and that resembles an oxallyl radical-allyl radical pair than a 2-oxacyclohexane-1,4-diyl, as revealed from secondary deuterium kinetic isotope effects (2° DKIEs).<sup>4</sup>

Trimethylsilyloxy substitution at C-2 of the parent ether lowers the activation free energy by roughly 9 kcal/mol relative to that of allyl vinyl ether itself.<sup>5</sup> Despite the qualitative rationalization by Carpenter,<sup>6</sup> the magnitude of the effect is not well understood. Significantly, the rate-accelerating effect is not observed in the 3,3-rearrangement of 2-(trimethylsilyloxy)-3-methyl-1,5-hexadiene, which requires heating to 210 °C to achieve a 2-h half-life,<sup>7</sup> so the effect of  $\text{Me}_3\text{SiO}$  substitution is not universal. The mechanistic question therefore is which of the two "perpendicular" alternatives,<sup>8</sup> 2-oxacyclohexane-1,4-diyl or oxallyl-allyl radical pair, is stabilized by 2- $\text{Me}_3\text{SiO}$  in the aliphatic Claisen rearrangement.

Table I records the DKIEs for the 3,3-shift of 2-(trimethylsilyloxy)-3-oxa-1,5-hexadiene obtained from the kinetics of rearrangement in carbon tetrachloride of the vacuum-distilled ketene acetals. The reaction rates are independent of solvent polarity ( $k(\text{CH}_3\text{CN}) = 1.33k(\text{CCl}_4)$ ); thus, mechanistic interpretation must focus on a neutral transition state and not on the effect of solvents including that of THF, the usual solvent for the reaction.

The KIEs provide a measure of the progress along the two structural coordinates, O,C-4 bond breaking and C-1,C-6 bond making, assuming the linear free energy relationship,  $\text{KIE} = \text{EIE}^d$ , where the EIEs are the H/D fractionation factors between  $\text{O}-\text{CH}_2(\text{D}_2)-\text{C}$  and  $\text{C}=\text{CH}_2(\text{D}_2)$  and  $\text{C}=\text{CH}_2(\text{D}_2)$  and  $\text{C}-\text{C}-\text{H}_2(\text{D}_2)-\text{C}$ , respectively.<sup>9,10</sup> This assumes that the factors af-

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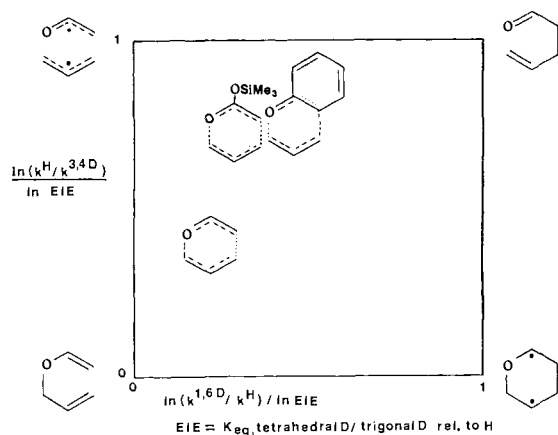
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Table I. Deuterium Effects and  $d$  Values for Bond Making and Breaking

compound	$t, ^\circ\text{C}$	C-6			C-4		
		$k^H/k^{D_2}$	EIE <sup>c</sup>	$d$ BM <sup>d</sup>	$k^H/k^{D_2}$	EIE <sup>c</sup>	$d$ BB <sup>d</sup>
3-oxa-1,5-hexadiene	160.3 <sup>a</sup>	1/1.025	1/1.16	0.17 (0.04)	1.09	1.23	0.42 (0.02)
2-(trimethylsiloxy)-1,5-hexadiene	25.0 <sup>b</sup>	1/1.09 (0.03)	1/1.35	0.29 (0.10)	1.48 (0.06)	1.59	0.85 (0.07)

<sup>a</sup> Gas phase. <sup>b</sup> In  $\text{CCl}_4$ . <sup>c</sup> Reference 4:  $\log K^{H/D_2} = (291.6/(2.3RT)) - 0.0818$ . <sup>d</sup> Std dev in parentheses, from std dev in KIE. <sup>e</sup> From correlation of EIEs of all Claisen rearrangements studied by IEs and Shiner's unpublished FFs:  $\log K^{H/D_2} = (500.1/(2.3RT)) - 0.1621$ .

fecting the ground-state-transition-state isotopic fractionation are the same as those affecting the EIE, which appears to be the case in the Cope rearrangement.<sup>4</sup> A More O'Ferrall-Jencks diagram



provides a useful pictorial description of the transition state in each of the Claisen rearrangements examined to date.

It is clear that 2-Me<sub>3</sub>SiO substitution results in a transition state with much more bond breaking than that in the parent rearrangement. The remarkable facility of the Ireland-Claisen reaction therefore is not due to "greater concert" but to the enhanced stability of the 2-(trimethylsiloxy)-1-oxaallyl moiety resulting in alteration in transition-state structure and energy to resemble this species.

The experimental fact can be rationalized by thermochemical kinetic considerations<sup>11</sup> and the activation free energy response surface equations developed to correlate the rates of [3,3]-sigmatropic shifts<sup>12</sup> provided that the siloxy group can be treated like a methoxy group. The heats of formation (in kcal/mol) of the allyl radical and the  $\cdot\text{CH}_2\text{COOMe}$  radical are known to be 40.6 and -51 (4),<sup>13</sup> respectively, and that of allyl methyl ketene acetal can be estimated to be -48.3 from Benson group contributions, assuming that the two oxygens of the ketene acetal are each treated like a vinyl ether oxygen. The difference in heats of formation is only 38 kcal/mol, which is 15 kcal/mol less than the corresponding difference in the cleavage of allyl vinyl ether itself. This difference is probably the difference in the ester resonance energy in the 2-methoxy-1-oxaallyl radical and the additional resonance energy of the ketene acetal. The implication here is that the additional oxygen is not stabilizing the free electron but the  $\pi$  bond associated with this highly unsymmetrical oxaallyl species. There is the further implication that any substituent that conjugates strongly with a carbonyl group will strongly stabilize the bond-breaking alternative when substituted on C-2 of an allyl vinyl ether, a fact borne out by the rearrangements of lithioallyl acetate,<sup>5</sup> 2-fluoroallyl vinyl ethers,<sup>14</sup> and perhaps even O-allyl amide acetals<sup>15</sup> and S-allyl thioamide acetals.<sup>16</sup>

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With reasonable estimates of the relative free energies of the two allyl species, of 1-(trimethylsiloxy)-2-oxacyclohexane-1,4-diyl, and of the product silyl ester, 35, 60, and -28 kcal/mol, respectively, the 3,3-shift correlation equation of ref 12 predicts an activation free energy of 26 (2) kcal/mol at 25 °C for the allyl methyl ketene acetal rearrangement, a value within experimental error of that observed for the Ireland-Claisen rearrangement.

A further demonstration of the transition-state structure in this reaction is provided by the rates of rearrangement of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -phenylallyl trimethylsiloxy ketene acetal relative to the parent: >77, 4.3, and 1, respectively. The  $\alpha$ -phenyl derivative has a half-life of less than 5 min at room temperature indicating substantial radical character at C- $\alpha$ . The small effect of  $\beta$ -phenyl indicates little radical, cationic, or anionic character at this site. The lack of effect at C- $\gamma$  appears to be consistent with radical stabilizing groups being counterbalanced by the same effects prevalent in Diels-Alder and polymerization reactions. These rates above are also correlated by the equations of ref 12. Given the success of the correlation equations in Claisen rearrangements, it should be noted that unless electron-withdrawing groups stabilize radicals or destabilize  $\pi$  bonds, our model predicts that these groups should have no effect on Claisen rearrangements despite the predictions of the Carpenter model. Thus the success of the Carpenter model with cyano groups may be attributable to the radical stabilization associated with cyano not necessarily its negative inductive effect. Indeed, examination of Claisen rearrangements substituted with trifluoromethyl groups might assess the strengths of the two models unless Carpenter's model does not apply to  $\sigma$ -inductive substituents as suggested by a referee.

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### Total Synthesis of 5(S),15(S)-Dihydroxy-6,13-trans-8,11-cis-eicosatetraenoic Acid (5,15-DiHETE) and 8(S),15(S)-Dihydroxy-5,11-cis-9,13-trans-eicosatetraenoic Acid (8,15-DiHETE): Two Novel Metabolites of Arachidonic Acid

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5(S),15(S)-Dihydroxy-6,13-trans-8,11-cis-eicosatetraenoic acid (5,15-DiHETE, 1)<sup>1,2</sup> and 8(S),15(S)-dihydroxy-5,11-cis-9,13-

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