The optically active monoester **6** was coupled in 65% yield by using the mixed phosphoric anhydride method (1 equiv of *n*-BuLi, THF, −78 °C; $(EtO)_2POCl$ to room temperature) with optically pure **10**, obtained from **1** by treatment with *t*-$BuMe_2SiCl$ (TBSCl) followed by *n*-butyllithium (Scheme II). The resulting diester **11** was deprotected with 5% aqueous HF in THF to give **12** (96%). This material was converted into the mesylate **3** ($MsCl/Et_3N/CH_2Cl_2$) and crude **3** was added over 3 h to excess $Bu_4N^+F^-\cdot 3H_2O$ in acetonitrile at 34 °C to effect ring closure to the monocrotaline acetal **4** (71% yield).

The possibility of using *d,l*-**6** in the coupling with **10** was explored briefly. Thus, *d,l*-**6** was converted into the mixed phosphoric anhydride as before and then treated with a deficiency of optically pure **10**. Although a modest 2:1 enantiomer differentiation in favor of the natural isomer **11** was observed, this procedure did not utilize the precursor **6** efficiently. Further experiments with **11** derived from *d,l*-**7** were restricted to demonstrating that this material could be cyclized to the *d,l* dilactone **4** via the desilylation of **3**.

Deprotection of **4** as described earlier affords **2**. Coupled with recent efforts in the synthesis of (±)- or (+)-retronecine,[8] this study completes the total synthesis of monocrotaline. Furthermore, the sequence confirms the generality of the nucleophilic cyclization method for synthesis of retronecine-derived dilactones. As in our earlier report,[2a] the 2-(trimethylsilyl)ethyl ester is converted in situ to a tetrabutylammonium carboxylate under dilution conditions which favor intramolecular displacement of mesylate. Attempts to extend this cyclization method to a relatively simple macrolide have not been promising,[9] but the procedure is remarkably effective in the case of pyrrolizidine alkaloids. There are now four successful examples of cyclization to 11-membered retronecine dilactones,[2a] as well as a recent extension to a 12-membered analogue.[2e]

Acknowledgment. This work was supported by the National Institutes of Health (CA17918; also RR0 2388-01 for the AM-500 NMR system).

Registry No. **2**, 315-22-0; (±)-**2**, 109525-74-8; (±)-**5**, 109391-24-4; (±)-**6**, 109391-25-5; (±)-**7**, 109391-26-6; (±)-**8**, 109391-27-7; (±)-**10**, 89710-47-4; (±)-**11**, 109432-25-9; (±)-**12**, 109391-29-9; (±)-2,3,4-trimethylcyclopent-2-enone, 109391-22-2; (±)-2,3-dihydroxy-2,3,4-trimethylcyclopentanone, 109391-23-3; (±)-3-methylheptane-2,5-dione, 109391-28-8; 3-methylbut-3-en-2-one, 814-78-8; propionaldehyde, 123-38-6; (±)-2,3,4-trimethyl-2,3-dihydroxycyclopentanone methylene acetal silyl enol ether, 109391-30-2; *d,l*-monocrotalic acid methylene acetal, 109494-78-2; (±)-9-*O*-(*tert*-butyldimethylsilyl)retrocene, 89617-46-9; 2-(trimethylsilyl)ethanol, 2916-68-9.

Supplementary Material Available: Experimental details and characterization data for **4–6**, **11**, and **12** (8 pages). Ordering information is given on any current masthead page.

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Kinetic and Product Hydrogen–Deuterium Isotope Effects in Ene Reactions: A Model for Understanding Apparently Anomalous Effects

Summary: Cases in which a concerted and a stepwise ene reaction show an apparently anomalous change in a product hydrogen–deuterium isotope effect with electrophilic activation of the eneophile are reported and shown to be consistent with a kinetic scheme in which a reaction intermediate can partition between the steps of reversal, equilibration of geometrically defined species, and conversion to product.

Sir: Comparisons of kinetic and product hydrogen–deuterium isotope effects have been a powerful tool for making choices between concerted and stepwise mechanisms of a number of formal ene reactions.[1,2] Equal kinetic and product isotope effects in inter- and intramolecular competitions usually are taken as evidence for concert in a single bond-making and bond-breaking step, although Orfanopoulous, Foote, and Smonou recently have made a qualitative suggestion that low isotope effects may be interpreted in terms of partially equilibrating reaction intermediates.[3a] Unequal kinetic and product isotope effects usually are taken to establish the presence of a reaction intermediate.[2-7] In this paper we report apparent anomalies in product isotope effects accompanying activation of the eneophile in both concerted and stepwise mechanisms of the ene reaction. We provide a framework for the interpretation of kinetic and product isotope effects and illustrate how such isotope effects can be quantitatively interpreted in terms of partitioning of a reaction intermediate.

The isotope effects for the thermal and catalyzed ene reactions of methylenecyclohexane (**1**), 2,2-dideuteriomethylenecyclohexane (**1**-d_2), and 2,2,6,6-tetradeuterio-

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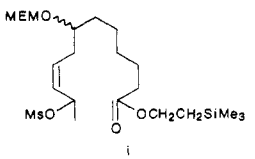
(9) We were unable to isolate a macrolide from attempted cyclization of structure i:[10]



i

(10) Vedejs, E.; McClure, C. K., unpublished results.

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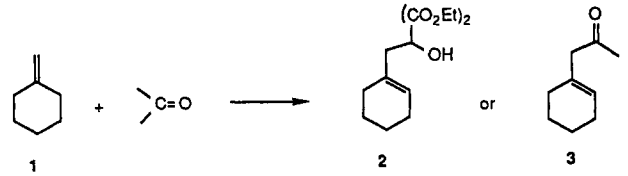
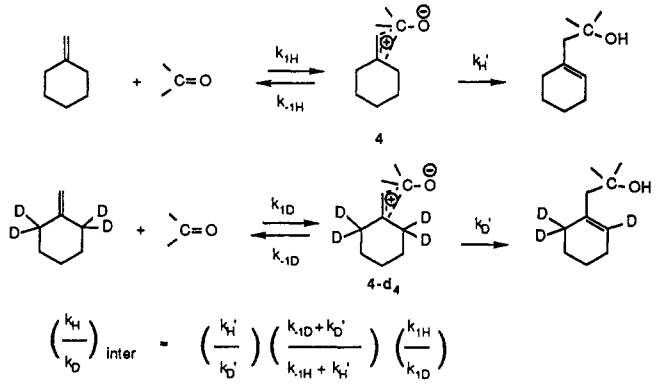
Table I. Isotope Effects for the Ene Reactions of Methylenecyclohexane



entry	eneophile reagents	k_H/k_D[a] 1 vs. 1-d_4	1-d_2	product
1	$(EtO_2C)_2C{=}O$, 130 °C[b]	2.8 ± 0.6	2.4 ± 0.2	2
2	$(EtO_2C)_2C{=}O$, $SnCl_4$, 5 °C, PhH[c]	1.1 ± 0.1	1.2 ± 0.1	2
3	$(CH_3CO)_2O$, $ZnCl_2$[d]	1.0 ± 0.3	3.2 ± 0.7	3
4	$CH_3C{\equiv}O^+SbCl_6^-$, −78 °C, CH_2Cl_2[b]	1.1 ± 0.2	1.1 ± 0.1	3
	$CH_3O{\equiv}O^+SbCl_6^-$, −40 °C, CH_2Cl_2	1.1 ± 0.1	1.1 ± 0.2	3

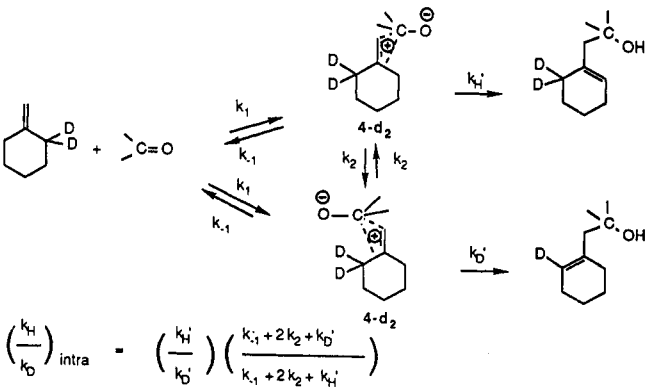
[a] For calculations of k_H/k_D values, see ref 4. [b] Molar ratio of olefin (d_0, d_4, or d_2) to enophile was 5:5:1 and 5:1. [c] Molar ratio of olefin (d_0, d_4, or d_2) to enophile to $SnCl_4$ was 5:5:1:0.1 and 5:1:0.1; see ref 3 and 6 for similar isotope effects. [d] Reference 4; solvent is acetic anhydride; 1-d_2 gives 2.1 ± 0.2 in nitromethane.

Scheme I



$$\left(\frac{k_H}{k_D}\right)_{inter} = \left(\frac{k_H'}{k_D'}\right)\left(\frac{k_{1D}+k_D'}{k_{1H}+k_H'}\right)\left(\frac{k_{1H}}{k_{1D}}\right)$$

Scheme II



$$\left(\frac{k_H}{k_D}\right)_{intra} = \left(\frac{k_H'}{k_D'}\right)\left(\frac{k_{-1}+2k_2+k_D'}{k_{-1}+2k_2+k_H'}\right)$$

methylenecyclohexane (1-d_4) with diethyl oxomalonate and with the equivalent of the acetylium ion to give **2** and **3**, respectively, are compared in Table I. The isotope effects for the first and third entries show these reactions of methylenecyclohexane to be, respectively, a concerted reaction with 2-oxomalonate and a stepwise reaction with acetic anhydride–zinc chloride, consistent with previous reports.[4,6] The second and fourth entries describe ene reactions with activated eneophiles, which provide the same products as the above entries, but show a different pattern of isotope effects. The interesting result is that for each of the limiting mechanisms of the ene reactions, concerted and stepwise, activation of the eneophile leads to low kinetic *and product* isotope effects. While a low kinetic isotope effect might be expected for the intermolecular competition between 1 and 1-d_4 by a faster first step, the low product isotope effect with the intramolecular competition afforded by 1-d_2 is more remarkable in both cases.[3-8]

An analysis is provided in Scheme I for the effect of reversible formation of a structurally defined intermediate **4** on the intermolecular competition between 1 and 1-d_4.[3] A similar analysis is provided in Scheme II for the effect of equilibration and reversibility of **4** on the intramolecular competition within 1-d_2. Under this analysis for 1 and 1-d_4 in Scheme I with an isotope effect for hydrogen removal, k_H'/k_D', of 3, no isotope effect on the first step, $k_{1H} = k_{1D}$, and partial reversal in the formation of **4** with $k_{-1H} = k_{-1D} = 0.5\ k_D'$, the observed kinetic isotope effect $(k_H/k_D)_{inter}$ would be 1.3.[9] Application of the same limits to 1-d_2 in Scheme II with no equilibration between the isomers of 4-d_2, $k_2 = 0$, also would provide an observed product isotope effect of $(k_H/k_D)_{intra}$ of 1.3. If the first step was irreversible under Scheme I an isotope effect of $(k_H/k_D)_{inter} = (k_{1H}/k_{1D}) > 1$ would result from 1 and 1-d_4.[9] With 1-d_2 under Scheme II, if the first step was irreversible, $k_{-1} \ll k_H'$, k_D', and there was partial equilibration between the isomers of 4-d_2 with $k_2 = 0.25k_D$, a true isotope effect, k_H'/k_D', of 3.0 would give a $(k_H/k_D)_{intra}$ of 1.3.

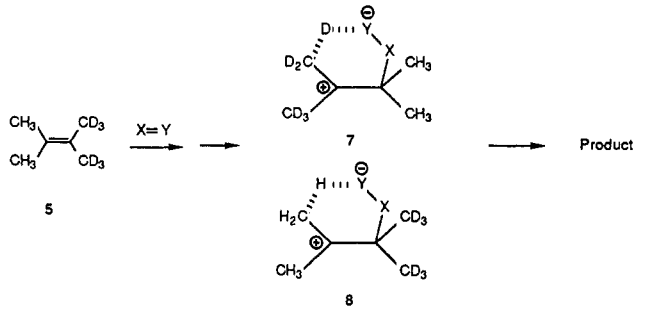
The value of $(k_H/k_D)_{intra}$ would be relatively unaffected by any secondary isotope effects[9] so low intramolecular isotope effects can be attributed to partial reversal in formation of the intermediate and/or equilibration between different isomers of the intermediate. These calculations then illustrate quantitatively how observed kinetic and product isotope effects can be substantially lower than the isotope effects for hydrogen removal due to partitioning of an intermediate. These values do not provide a unique fit to the experimental data but demonstrate the value of this model for understanding ap-

(8) The rationale that an activated eneophile reacts by a concerted mechanism with bent and/or unsymmetrical carbon hydrogen bond breaking is plausible but vague and in detailed formulation becomes problematic.

(9) In the intermolecular competition the assumption of $k_{1H} = k_{1D}$ and $k_{-1H} = k_{-1D}$ ignores the secondary isotope effects which would, in fact, make these rates unequal. However, if it is also assumed $k_{-1H} = 0.9k_{-1D}$ and $k_{1H} = 1.1k_{1D}$ the resulting $(k_H/k_D)_{inter}$ would be 1.5. Secondary isotope effects clearly will contribute to the $(k_H/k_D)_{inter}$ differences discussed. However, for $(k_H/k_D)_{intra}$ the only affect would be on the ratio of (k_H'/k_D') and this should be small.

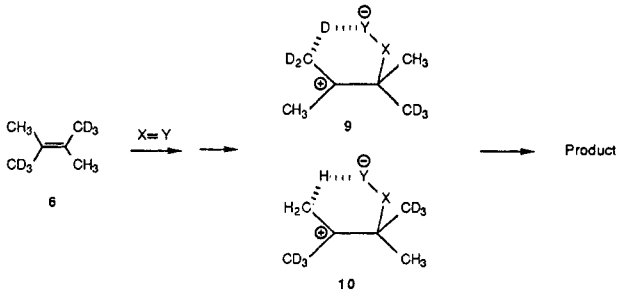
parently anomalous isotope effects.

The existence of such intermediates also can provide a framework for understanding of other interesting product isotope effects in ene reactions. The trans- and *gem*-substituted olefins **5** and **6** would be expected to give the same isotope effects in an ene reaction. In fact these compounds provide a ratio of $(k_H/k_D)_5/(k_H/k_D)_6$ of ca. 1.5 with a number of enophiles.[3,7] The actual isotope effect for hydrogen removal from **5** will be determined by the free energy difference in the transition structures **7** and **8**. The



5 7 8

corresponding isotope effect from **6** will arise from the free energy difference between **9** and **10**. To the extent the



6 9 10

charge can be considered localized in these structures the secondary isotope effect of the trideuteriomethyl group on the adjacent position will enhance the isotope effect for **5** and depress it for **6**.[10] While the magnitude of the effect is uncertain and would be modified by the partitioning noted above, this apparently anomolous effect is consistent with the partitioning of an intermediate between competitive transition structures in accord with precedented effects.

In summary, we provide a general scheme to explain a range of kinetic isotope effects in ene reactions, including those which have appeared anomalous. We emphasize the quantitative values chosen are illustrative only and further work will be needed to determine the viability of the proposed scheme. This work further demonstrates the advantage of combined kinetic and product isotope effects in mechanistic studies.

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Registry No. 1, 1192-37-6; D_2, 7782-39-0; diethyl oxomalonate, 609-09-6.

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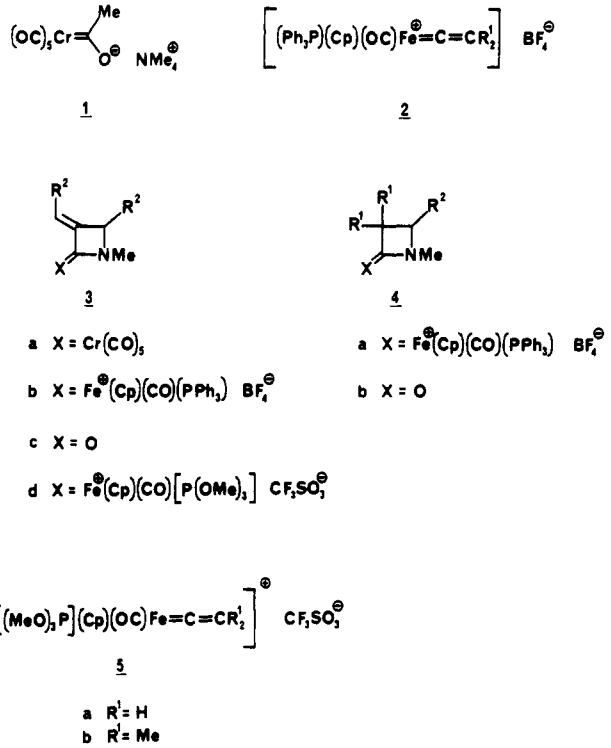
Cationic Iron Vinylidene Complexes in Bicyclic β-Lactam Synthesis

Summary: The iron vinylidene complex $[(Cp)[(MeO)_3P](CO)Fe{=}C{=}CMe_2]^+CF_3SO_3^-$ reacted in a stepwise manner with the imines PhCH=NMe, 2-thiazoline, ethyl 2-thiazoline-4-carboxylate, and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate to produce the corresponding [2 + 2] azetidinylidene cycloadducts (66%, 82%, 72%, 51%).

Sir: Recently we reported that the chromium carbene complex **1**[1] and the cationic iron vinylidenes **2** (R^1 = H, Me)[2] are useful in the preparation of the azetidinylidene complexes **3a** (R^2 = aryl; 6–25%), **3b** (R^2 = Ph; 52%), and **4a** (R^1 = Me, R^2 = aryl, PhCH=CH; 31–52%). Subsequent oxidation of these materials gave the corresponding β-lactams **3c** (68–100%) and **4b** (R^1 = Me, R^2 = Ph; 19%).



1 2 3 4 5

In principle the complexes **3a**, **3b**, and **4a** may have arisen via formal [2 + 2] cycloaddition reactions with the intermediacy of $(OC)_5Cr{=}C{=}CH_2$[3] in the chromium case. In order to improve the synthetic versatility of this ketene surrogate chemistry, we have examined several alternative cationic vinylidene systems.[4] Herein we report a preliminary account of the preparation and reactions of complexes **5a** and **5b**. Vinylidene **5b** is especially useful for the preparation of bicyclic azetidinylidene complexes in high yield.

The preparation of **6b** via double methylation of **6a** was inefficient due to competitive Cp lithiation.[5] However, reaction of $Cp(CO)_2Fe$-*i*-Pr[6] with trimethyl phosphite[7]

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