Substituent Effects in the Intramolecular Diels−Alder Reaction of 6-Furylhexenoates

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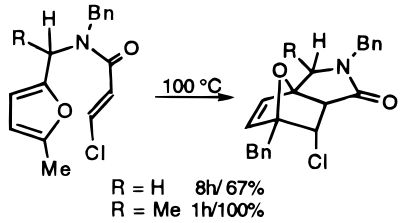
The series of furyl enone esters, **4a**−**c**, were synthesized from furan or furfural by straightforward routes. Their thermal intramolecular Diels−Alder reactions to give the tricyclic ketones **5a**−**c** were studied in acetonitrile and toluene at two temperatures and the kinetics of the reactions determined. A comparison of these data with that obtained for the corresponding esters **2** to give the lactones **3** indicates that the rate enhancements seen for the esters (rate of dimethyl 310 times that of monomethyl) are much larger than those seen for the ketones (rate of dimethyl 6.8 times that of monomethyl). Thus, this is additional evidence for the earlier hypothesis that the presence of the oxygen atom in the tether is a factor responsible for the larger than normal rate enhancements.

Introduction

Previous work in these laboratories has demonstrated that alkyl substitution on the tether of *N*-benzyl-*N*-furfuryl-*β*-chloroacrylamides appreciably accelerates the intramolecular Diels−Alder (IMDA) cyclization of these compounds.[1] Further extensive studies with furfuryl



fumarates have revealed unexpectedly large rate enhancements with geminal disubstitution of alkyl groups on the tether connecting the diene and dienophile.[2] The present work aims at a further understanding of the accelerating effect on the rates of IMDA reactions of alkyl substituents on the chain connecting the furan diene and the dienophilic unit.

The contributions of the Thorpe−Ingold effect, namely the effect of internal angle compression,[3] and the reactive rotamer effect to the overall observed rate acceleration in IMDA reactions of furan dienes were first determined by Jung and Gervay to be strongly in favor of the reactive rotamer effect.[2c] Thus, the compression of the central angle on alkyl substitution (Figure 1) was not as important as the reactive rotamer effect (Figure 2). In order for cyclization between the reactive units X and Y in compound A to occur, rotation about the central C−C bonds from the most stable and, therefore, more highly populated, anti conformation to the gauche conformation

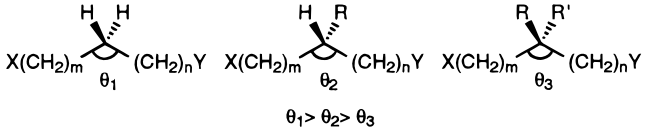


Figure 1. Thorpe−Ingold effect (angle compression).

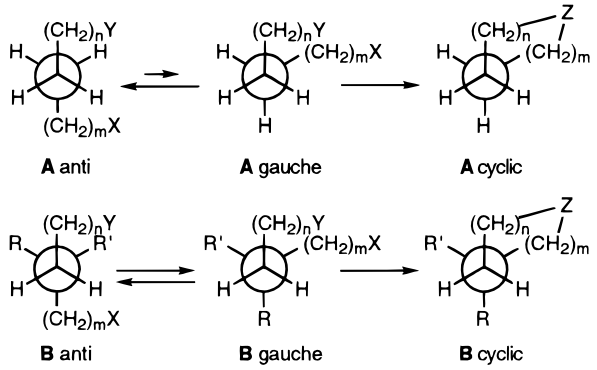


Figure 2. Reactive rotamer effect.

is required. But if one of the two carbons of this C−C bond is substituted with one or two alkyl groups, the energetic picture changes noticeably since the anti form is now essentially equienergetic to the gauche form as shown in **B**. Thus, the dialkyl-substituted cyclization substrate can more easily attain the required transition state for cyclization as compared to the unsubstituted substrate and therefore would be expected to cyclize more rapidly. With *gem*-dialkyl substitution, both the Thorpe−Ingold effect of angle compression and the reactive rotamer effect are operative. To distinguish between these two possible sources of rate enhancement, rate constants for the IMDA reaction of substituted furfuryl fumarates **2** were determined. The choice of substituents on the tether connecting diene and dienophile provided a range of angles (θ) at the substituted carbon that allowed for an analysis of the extent of the importance of the angle compression (Thorpe−Ingold effect) in this system.

(1) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327.
(2) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. (b) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (d) Jung, M. E. *Synlett* **1994**, 186.
(3) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.

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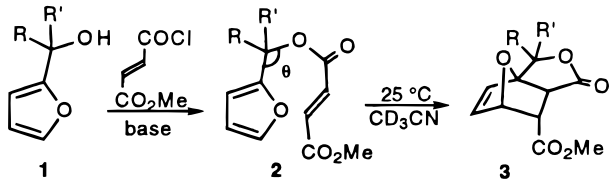
Scheme 1. Rates of Cyclization of Furfuryl Methyl Fumarates



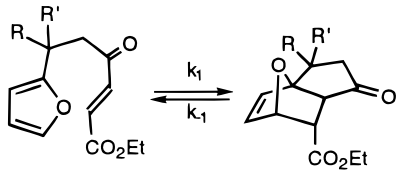
Substrate	Estimated Angle	k (sec^{-1})	k_{rel}
2a R = R' = H	112.2 °	1.94×10^{-7}	1
2b R = Me R' = H	110.5 °	1.62×10^{-6}	8
2c R = R' = Me	109.5 °	4.12×10^{-4}	2000
2d R = R' = $(CH_2)_3$	112.2 °	4.03×10^{-5}	200
2e R = R' = $(CH_2)_2$	114.6 °	2.03×10^{-6}	10

As shown in Scheme 1, the unsubstituted precursor **2a** cyclizes slowly and is the basis of comparison for other substrates. With the substitution of one methyl on the tether (**2b**), we observed a compression in the angle θ and an 8-fold increase in rate constant.

With the addition of a second methyl (**2c**), we noted further compression of the angle to the normal tetrahedral value and another rate increase, this time by a factor of 2000. Thus far, all these results could be explained by the Thorpe−Ingold effect, although the magnitude of the rate increase for **2c** is decidedly larger than the reported enhancements due to angle compression. The other important results are the entries for compound **2d** and **2e**. Where the internal angle is approximately the same, as is the case for **2a** and **2d**, the Thorpe−Ingold effect would predict a similar rate of cyclization, but the results in Scheme 1 show a 200-fold increase for the cyclobutyl-substituted substrate **2d**. With the absence of angle differences, the only factor at work in this example would seem to be the reactive rotamer effect. Similarly, in the cyclopropyl case **2e**, where the angle is even larger than the unsubstituted case **2a**, the rate of cyclization is about 10 times faster. Clearly the widening of the angle does have a retarding effect (compare **2d**) but the net effect is one of acceleration relative to the unsubstituted case, which directly contradicts the Thorpe−Ingold postulate. These results argue strongly that angle compression is not an important factor in the *gem*-dialkyl effect in cyclizations giving five-membered rings. The major factor on cyclization must therefore be a conformational effect like the reactive rotamer effect. Jung and Gervay also reported activation parameters for the cyclization of **2a**−**2e**[2c] which indicated that the large rate acceleration seen in this system, namely the significant lowering of the $\Delta G^{\ddagger}$, is due almost entirely to a lowering of the enthalpy of activation ($\Delta H^{\ddagger}$) and not to a difference in the entropy of activation ($\Delta S^{\ddagger}$). These results are in accord with most of the studies of the *gem*-dialkyl effect,[4] although there is some disagreement.[5]

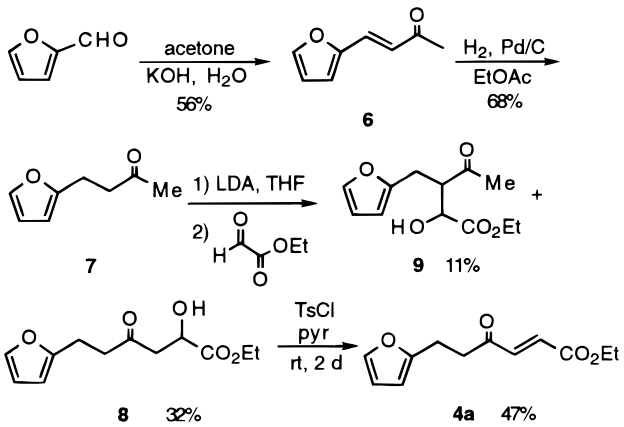
To determine the reason for the great acceleration observed in the case of furfuryl fumarates, we postulated a possible contribution from the presence of the oxygen in the connecting chain to the overall rate enhancement.

Scheme 2



4a R= R'= H **5a** R= R'= H
4b R= H, R'= Me **5b** R= H, R'= Me
4c R= R'= Me **5c** R= R'= Me

Scheme 3



Accordingly, the oxygen of the fumarate was replaced by a carbon, and the cyclization rates were determined for the unsubstituted and mono- and dimethyl-substituted derivatives **4a**−**c** to give **5a**−**c**. Comparison of the results of this kinetic experiment with those obtained by Gervay would clarify the role of oxygen in this unprecedented rate acceleration (Scheme 2). The work herein describes the kinetics of cyclization of the furylethyl keto esters **4a**−**c** to give the cyclized ketoesters **5a**−**c** and the effect of solvent and temperature on their IMDA reactions.

Results and Discussion

A. Synthesis. Compounds **4a**−**c** were prepared with the target 3-keto enoate **4a** being synthesized in four steps from furfural as shown in Scheme 3. The known (*E*)-butenone **6**,[6] prepared by condensation of furfural with acetone, was selectively hydrogenated using palladium on carbon to give the saturated ketone **7**. Aldol condensation of the ketone **7** with ethyl glyoxalate[7] gave the β-keto alcohol **8** as well as some starting material and the product **9** of trapping of the thermodynamic enolate with the glyoxalate. Tosylation and elimination of the aldol product **8** proceeded slowly over 2 days to afford our first precursor **4a** as well as some unreacted starting material.

The more challenging mono- and dimethyl substrates **4b,c** were synthesized as follows. Methyl β-(2-furanyl)-acrylate **10** was prepared in high yield from the reaction of furfural with trimethyl phosphonoacetate (Scheme 4). The subsequent cuprate addition proceeded in moderate yield to give the β-methyl ester **11**.[8] Reduction of this

(4) (a) Allinger, N. L.; Zalkow, V. J. *J. Org. Chem.* **1960**, *25*, 701. (b) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1361. (c) Bruice, T. C.; Pandit, K. P. *J. Am. Chem. Soc.* **1960**, *82*, 5858. (d) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275.

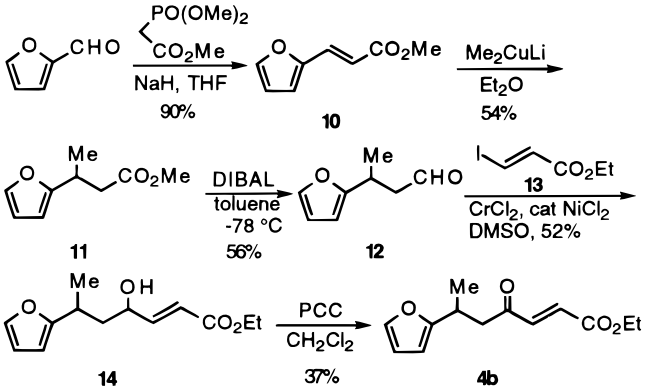
(5) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319.

(6) Leuck, G. J.; Cejka, L. *Organic Syntheses*; Wiley: New York, 1956: Collect. Vol. I, p 283.

(7) Jung M. E.; Shishido, K.; Davis, L. *J. Org. Chem.* **1982**, *47*, 891.

(8) Gustafsson, B.; Nilsson, M.; Ullenius, C. *Acta Chem. Scand. B* **1977**, *31*, 667.

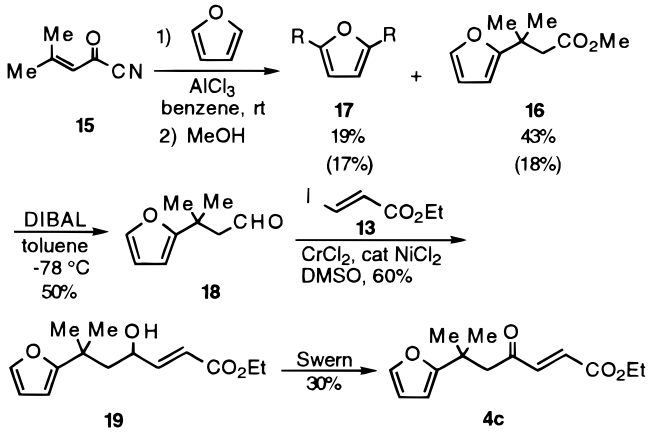
Scheme 4



ester with diisobutylaluminum hydride (DIBAL) at low temperature gave the desired aldehyde **12** as well as some starting material and some of the corresponding alcohol due to overreduction. The iodoalkene **13** was prepared by addition of hydroiodic acid to propiolic acid to form the corresponding acid, followed by esterification with ethanol in benzene.[9] The initially formed cis acid was thermally isomerized to the desired trans isomer in the presence of a catalytic amount of iodine.[10] Coupling of the iodoolefin **13** with the aldehyde **12** in DMSO under the Nozaki conditions[11] afforded allylic alcohol **14** in 52% yield. The presence of nickel(II) chloride in catalytic amounts was essential to the success of the reaction as noted both by Nozaki and Kishi.[12] PCC oxidation of the alcohol **14** resulted in the formation of the target monomethyl substrate **4b**.

In preparing the third cyclization substrate, we used the findings of Hoffmann and Ismail,[13] who reported that tertiary alkyl groups could be introduced on to furans via a Friedel−Crafts alkylation. Specifically, 4-methyl-2-oxo-3-pentenenitrile (**15**) was shown to react successfully with furan in the presence of aluminum trichloride to give a mixture of the mono- and dialkylated products **16** and **17** as shown in Scheme 5. The acyl cyanide intermediate formed after the first step could be isolated on treatment with water and quick extraction with ether. For our purposes, however, the more stable ester would be more useful. The acyl cyanide (**15**) was prepared in good yield (85%) from the corresponding commercially available acyl chloride by heating with cyanotrimethylsilane (TMSCN) in the presence of catalytic zinc iodide. Following the procedure outlined by Hoffmann and Ismail, furan and the acyl cyanide **15** were reacted in benzene to give, after workup and distillation, the two products **17** and **16** in a 1:1 ratio, each in a maximum 18% yield. This alkylation step was incorporated into the synthesis despite its low yield because the starting materials were inexpensive. Reduction of the ester **16** to the aldehyde **18** proceeded in 50% yield. Aldehyde **18** was joined to the iodoolefin **13** by a Nozaki coupling in a manner similar to that described for the monomethyl

Scheme 5



precursor and furnished the alcohol **19** in 60% yield. Finally, Swern oxidation afforded the dimethyl heptenoate **4c**, the final cyclization substrate. With these three cyclization substrates in hand, the kinetic study of the IMDA reaction could be undertaken.

B. Kinetics. The kinetic experiments were conducted in sealed 5 mm NMR tubes containing known concentrations of the substrates **4a**−**c**. For each substrate, the experiment was carried out in deuterioacetonitrile and deuteriotoluene, both at 25 and at 80 °C. The progress of the reactions in the NMR tubes was monitored at irregular intervals by high-field proton NMR. The samples for high-temperature experiments were kept in an 80 °C oil bath with the exception of substrate **4c** for which the entire high-temperature kinetic experiments were performed in a preheated (80 °C) 500 MHz NMR probe. The ratio of integrals for the shrinking furan peak (δ 6.0 ppm) in the starting material and the growing H-6 peak in the product (δ 5.1 ppm) were used to determine the rate constants.

The reversible nature of IMDA reactions of this type was previously determined by Gervay[2c] and our findings confirmed this observation, since reduction of the product to starting material ratio was observed in several experiments where the sample was heated after having been initially kept at room temperature. To determine the rate constants for these reactions, we made use of eq 1,

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}$$

$$\ln \frac{[\mathrm{A}_t] - [\mathrm{A}_{eq}]}{[\mathrm{A}_o] - [\mathrm{A}_{eq}]} = k_{app} t \qquad (1)$$

the rate expression for reversible first-order reactions. The k_{app} refers to the apparent rate constant, and $[A_o]$ and $[A_{eq}]$ are the initial and equilibrium concentrations of the acyclic starting material **A**, respectively. The initial concentration $[A_o]$ was known, and the concentration of the acyclic compound at selected times t ($[A_t]$) could be calculated from the ratio of the integral (in the proton NMR spectra) of the indicated peaks of the product vs those of the starting material and the initial-concentration of the starting material, $[A_o]$ (eq 2). The

$$[\mathrm{A}_o] = [\mathrm{A}_t] + [\mathrm{C}_t]$$

$$[\mathrm{C}_t] = [\mathrm{A}_o] - [\mathrm{A}_t]$$

(9) (a) Bowden, K.; Price, M. J. *J. Chem. Soc. B* **1970**, 1466. (b) Jung, M. E.: Hagenah, J. A.: Zeng, L.-M. *Tetrahedron Lett.* **1983**, *24*, 3973.
(10) Topek, K.; Vsetecka, V.; Prochazka, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2395.
(11) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.
(12) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644 and references therein.
(13) Ismail, Z. N.; Hoffmann, H. M. R. *Angew. Chem.* **1983**, *95*, 737.

$$\frac{[C_t]}{[A_t]} = \frac{[A_o] - [A_t]}{[A_t]} = R$$

(experimentally determined ratio of integrals)

$$[A_o] - [A_t] = [A_t]R$$

$$[A_o] = [A_t](R + 1)$$

$$[A_t] = \frac{[A_o]}{(R + 1)} \text{ where } R = \frac{[C_t]}{[A_t]} \qquad (2)$$

equilibrium concentration $[A_{eq}]$, however, could not be determined experimentally since in most cases the reaction times were long and equilibrium was not achieved during the experiment time. Therefore, we needed a method for estimating $[A_{eq}]$. There are several available for this purpose, the most commonly used one being the Guggenheim approximation.[14] For our purposes, the method published by Moore in 1972[15] was particularly appealing since it did not require data collection at regular intervals and allowed for estimation of $[A_o]$ if this concentration was not accurately known. Given that eq 1 is not a linear equation, solution by the method of least squares required an iterative procedure starting from approximate values of unknown parameters. Since use of the experimentally known concentration for $[A_o]$ allowed for no error in this value, the problem was treated as a three-parameter problem, and the three normal equations involved were solved for $\delta k_{app,}$ $\delta[A_o]$, and δ-$[A_{eq}]$, using estimated values for $k_{app,}$ $[A_o]$, and $[A_{eq}]$. The improved values for the three parameters above were obtained by adding the δ values to the previous values (eq 3). The improved values were then used to solve the

$$k(\text{improved}) = k(\text{previous}) + \delta k \qquad (3)$$

three normal equations for the second set of δ values, which were once again added to the previous parameters. This process was continued until the δ values were small enough and no improvement in the value of the unknown parameters could be achieved. Values thus obtained for $[A_o]$ and $[A_{eq}]$ were used to graphically determine k_{app} from the slope of a plot of eq 1. A representative plot is shown in Figure 3.

Using the values obtained for $k_{app,}$ $[A_o]$, and $[A_{eq}]$, the forward and reverse rate constants k_1 and k_{-1} could be easily determined using eqs 4 and 5.

$$k_{app} = k_1 + k_{-1} \qquad (4)$$

$$K_{eq} = \frac{k_1}{-1} = \frac{[C_{eq}]}{[A_{eq}]} = \frac{[A_0] - [A_{eq}]}{[A_{eq}]} \qquad (5)$$

Table 1 lists the rate constants calculated for cyclization of compounds **4a**–**c** at 25 °C in acetonitrile and for **4c** in toluene at both 25 and 80 °C and in acetonitrile at 80 °C. For the reasons given below, additional kinetic studies for the cyclizations of **4a** and **4b** could not be carried out.

The IMDA reaction of the unsubstituted precursor **4a** at room temperature was extremely slow, and after months only negligible amounts of the cyclized material could be detected. The first entry in Table 1 is based solely on two data points and, therefore, is no more than an approximation of the rate constant. At 80 °C, the cyclization was slightly faster for **4a** but was accompanied by simultaneous isomerization of the olefin from the *E*- to the *Z*-isomer. Indeed, in all cases, this isomerization was observed, but for the instances listed in Table 1, the data points were collected before noticable quantities of the isomerized alkene were observed. The isomerized alkene also underwent a Diels–Alder cyclization as indicated by the appearance of a second peak for the bridgehead (H-6) proton of that adduct in the 5 ppm region. Thus, the kinetic picture is more complex than that of a simple unimolecular process. As shown in Figure 4, there are three equilibria occurring simultaneously, the cyclization of the trans substrate, its isomerization to its stereoisomers, and the cyclization of the cis substrate. This series of reversible reactions and their corresponding forward and reverse rate constants complicated the process of kinetic analysis for these experiments beyond the scope of our study. It is worth mentioning, however, that isomerization of the olefin was consistently faster in toluene than acetonitrile for all three substrates at both temperatures.

Comparison of the rate constants for the cyclization of the keto substrates **4a**–**c** with those for the IMDA reaction of the furfuryl fumarates obtained by Gervay[2c] is outlined in Table 2. The absolute values for the forward rate constants of the fumarate series are larger, as expected, but the relative increase in rate of cyclization with substitution of one or two methyls is similar for the

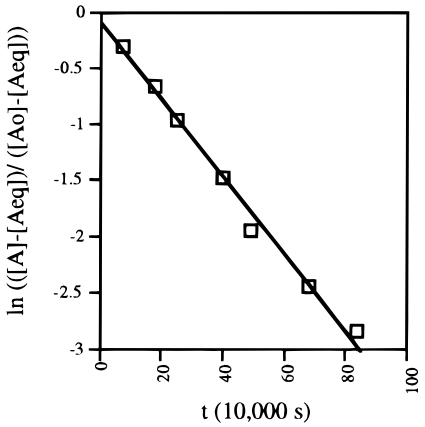


Figure 3. Cyclization of **4b** at 25 °C in acetonitrile.

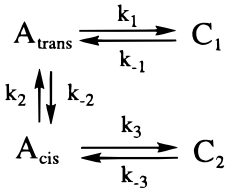


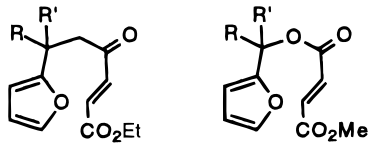
Figure 4.

Table 1

substrate	solvent	T (°C)	k_{app}	k_1 (s^{-1})	k_1 (s^{-1})
4a	acetonitrile	25	$\sim 1.6 \times 10^{-6}$	$\sim 4.8 \times 10^{-9}$	$\sim 1.6 \times 10^{-6}$
4b	acetonitrile	25	3.4×10^{-6}	7.5×10^{-7}	2.6×10^{-6}
4c	acetonitrile	25	6.2×10^{-6}	5.1×10^{-6}	1.1×10^{-6}
4c	toluene	25	4.9×10^{-6}	3.0×10^{-6}	1.9×10^{-6}
4c	acetonitrile	80	5.0×10^{-3}	1.8×10^{-3}	3.2×10^{-3}
4c	toluene	80	4.0×10^{-3}	8.0×10^{-4}	3.2×10^{-3}

(14) Guggenheim, E. A. *Philos. Mag.* **1926**, *2*, 528.
(15) Moore, P. *J. Chem. Soc., Faraday Trans. 1* **1972**, *68*, 1890.

Table 2. Comparison of Forward Rate Constants in Acetonitrile at 25 °C



4a R= R' = H **2a** R = R' = H
4b R= Me R' = H **2b** R = Me R' = H
4c R= R' = Me **2c** R = R' = Me

substrate	k_1	k_1 (rel)	substrate	k_1	k_1 (rel)
4a	4.8×10^{-9}	1	**2a**	2.0×10^{-7}	1
4b	7.5×10^{-7}	156	**2b**	1.1×10^{-6}	5.5
4c	5.1×10^{-6}	1062	**2c**	3.4×10^{-4}	1700

two series as compared to the desmethyl compounds **2a** and **4a**. The rate increase for the monomethyl precursor **4b** is somewhat larger than the fumarate counterpart **2b**, while for the dimethyl substrate the relative increase is greater in the fumarate series (**2c**) than in the keto series (**4c**). However, given the inaccuracy of the rate constant measured for **4a**, it is not reasonable to compare the increases on methyl substitution to **4b** or **4c** with those in the ester series **2a**−**c**. But the rate increase in going from monomethyl to dimethyl is reliable in both systems and therefore can be compared. Here, the increase in the keto series (going from **4b** to **4c**) is 6.8, while the corresponding increase in the ester series (going from **2b** to **2c**) is 310. This is a significant difference and lends further evidence to our earlier hypothesis,[2c] namely that the presence of the ring oxygen is the major factor responsible for the great rate enhancement observed in IMDA reaction of these furan dienes with *gem*-dimethyl substitution on the tether. Further experiments on similar substrates not containing a furan will have to be carried out to verify the importance of this specific diene on the rate.

Conclusion

In conclusion, the three cyclization substrates **4a**−**c** have been prepared from furan derivatives. The IMDA reaction of these substrates in toluene and acetonitrile both at 25 and at 80 °C have been studied. Comparison of the calculated rate constants for substrates **4a**−**c** at 25 °C in acetonitrile with the rate constants reported by Jung and Gervay for the IMDA reaction of furfuryl fumarates **2a**−**c** under the same conditions indicates that the oxygen in the tether of the fumarate is a factor responsible for the uncharacteristically large rate enhancements observed for the cyclization of the mono- and dimethyl substrates.

Experimental Section

General Methods. All reactions were carried out under argon with the exclusion of moisture. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, benzene, and toluene from calcium hydride, and triethylamine from potassium hydroxide. Flash column chromatography was carried out in the indicated solvent system (in the percentage of volume) on 230−400 mesh silica gel.

The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 200 or 400 MHz (as noted), and the carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. Spectra were taken in the indicated solvent at ambient temperature unless otherwise specified, and the chemical shifts are reported in parts per million relative to the lock of the solvent used. The infrared (IR) spectra were recorded on an FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Autospec instrument.

4-(2-Furanyl)-2-butanone (7). A solution of the enone **6**[6] (3.4 g, 25.0 mmol) in ethyl acetate (150 mL) containing 5% palladium on carbon (150 mg) was hydrogenated at atmospheric pressure until the reaction was complete (TLC). The suspension was filtered through Celite and concentrated under reduced pressure. Flash column chromatography on silica gel (hexane/ethyl acetate 2:1) yielded the desired product **7** as a colorless oil (2.36 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (1H, dd, J = 1.8, 0.6 Hz), 6.27 (1H, dd, J = 3.1, 1.9 Hz), 5.99 (1H, dd, J = 3.1, 0.8 Hz), 2.91 (2H, t, J = 7.3 Hz), 2.78 (2H, t, J = 7.3 Hz), 2.16 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.33, 154.51, 141.10, 110.22, 105.20, 41.70, 29.94, 22.18. FT-IR (neat): 2920.6, 1720.7, 1363.8, 1165.1, 1008.9 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 138.1 ([M]$^+$, 65), 123.10 (10), 95.1 (66). High-resolution EI MS (*m*/*z*): 138.0683, calcd for $C_8H_{10}O_2$ 138.0681.

Ethyl 6-(2-Furanyl)-2-hydroxy-4-oxohexanoate (8). Lithium diisopropylamide was prepared as follows: to a solution of diisopropylamine (0.76 mL, 6.6 mmol) in tetrahydrofuran (40 mL) at −78 °C was added dropwise *n*-butyllithium (3.02 mL, 1.82 M). After 30 min, a solution of the furylbutanone **7** (0.69 g, 5.00 mmol) in THF (5 mL) was added via syringe over 10 min. After the reaction stirred for 1 h, ethyl glyoxalate[7] (1.02 g, 10 mmol) was added, and after 20 min aqueous ammonium chloride (40 mL) was added. The organiclayer was separated and the aqueous layer extracted twice with ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. Purification by flash chromatography (hexane/ethyl acetate 2:1) on silica gel yielded the desired product **8** (0.39 g, 32%) as well as the diastereomeric aldol products **9**, resulting from the thermodynamic enolate (0.138 g, 11%) and unreacted starting material. Major Product (**8**). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (1H, m), 6.26 (1H, dd, J = 3.0, 1.9 Hz), 5.99 (1H, dd, J = 3.1, 0.7 Hz), 4.48 (1H, dd, J = 5.3, 4.9 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.17 (1H, d, J = 5.3 Hz), 2.94 (4H, m), 2.83 (2H, m), 1.28 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.79, 173.66, 154.15, 141.17, 110.25, 105.35, 66.97, 67.98, 45.96, 41.50, 21.84, 14.13. FT-IR (neat): 3489.7, 1736.2, 1720.7, 1097.6 cm^{-1}. MS (EI) *m*/*z* (rel intensity) 240.1 ([M]$^+$, 100), 222.1 (8), 94.0 (66). High-resolution EI MS (*m*/*z*): 240.0997, calcd for $C_{12}H_{16}O_5$ 240.0998. Minor Product (**9**). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35 (0.28 H, br s), 7.30 (0.72 H, br s), 6.25−6.31 (1H, m), 6.11−6.13 (0.28 H, m), 6.0−6.04 (0.72 H, m), 4.14−4.44 (2H, m), 2.74−3.38 (4H, m), 2.17 (2.16 H, s), 2.12 (0.84 H, s), 1.29 (2.16 H, t, J = 7.3 Hz), 1.28 (0.84 H, t, J = 7.2 Hz).

(*E*)-Ethyl 6-(2-Furanyl)-4-oxo-2-hexenoate (4a). The β-keto alcohol **8** (0.39 g, 1.62 mmol) and *p*-toluenesulfonyl chloride (0.62 g, 3.24 mmol) were stirred in pyridine (10 mL) for 2 d. The reaction mixture was poured onto ice−water and extracted twice with ether (2 × 10 mL). The organic extracts were washed successively with two portions of 50% hydrochloric acid and water (3 × 5 mL). After drying over $MgSO_4$ and rotary evaporation of the solvent, the brown residue was subjected to flash chromatography to give the desired elimination product **4a** (170 mg, 47%) along with unreacted starting material **8** (111 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (1H, m), 7.10 (1H, d, J = 16.0 Hz), 6.73 (1H, d, J = 16.0 Hz), 6.31 (1H, br d, J = 3.1 Hz), 6.05 (1H, br d, J = 3.1 Hz), 4.31 (2H, q, J = 7.1 Hz), 3.04 (4H, br s), 1.36 (3H, t, J = 7.1 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.06, 165.32, 153.81, 141.12, 138.87, 131.01, 110.13, 105.38, 61.34, 39.44, 21.87, 13.99. FT-IR (neat): 2922.5, 2851.1, 1724.6, 1703.4, 1367.7, 1304.0, 1184.4 cm^{-1}. MS (EI) *m*/*z* (rel intensity): 222.1 ([M]$^+$, 62), 193.0 (53), 149.1 (57), 95.0 (59). High-resolution EI MS (*m*/*z*): 222.0889, calcd for $C_{12}H_{14}O_4$ 222.0892.

Methyl 3-(2-Furanyl)propenoate (10). Sodium hydride (0.84 g, 21 mmol) was suspended in dry THF and the mixture cooled to 0 °C. Trimethyl phosphonoacetate (3.82 g, 21 mmol)

was added to the suspension with vigorous stirring. The white gelatinous mixture was next treated with a THF (25 mL) solution of freshly distilled furfural (1.92 g, 20 mmol). The reaction was shown to be complete in 10 min by TLC, and then saturated aqueous ammonium chloride solution (15 mL) was added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 30 mL). The combined organic materials were dried over $MgSO_4$, and the solvent was evaporated. Vacuum distillation (bp 95−98 °C, 2 mmHg) afforded the α,β-unsaturated ester **10** as a yellow oil (2.74 g, 90%). The spectral data for this compound were consistent those reported in the literature.[16] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.18 (1H, d, J = 15.8 Hz), 7.00 (1H, br s), 6.35 (1H, d, J = 3.3 Hz), 6.21 (1H, dd, J = 3.4, 1.8 Hz), 6.06 (1H, d, J = 15.8 Hz), 3.53 (3H, s).

Methyl 3-(2-Furanyl)butanoate (11). This compound was synthesized from the furylpropenoate **10** and lithium dimethylcuprate following the procedure of Gustafsson and coworkers.[8] To a suspension of copper(I) iodide (2.36 g, 12.4 mmol) in anhydrous ether (4 mL) cooled to 0 °C was added methyllithium (27.7 mL, 0.9 M). After the solution stirred for 30 min at this temperature, a solution of the enoate **10** (1.39 g, 9.14 mmol) in ether (7 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. A solution of saturated ammonium chloride (15 mL) was then added to the reaciton. The two layers were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (hexane/ether 5:1) gave the desired product **11** as a colorless oil (843 mg, 54%). The spectral data for this compound were consistent with those reported in the literature.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (1H, dd, J = 1.8, 0.7 Hz), 6.27 (1H, dd, J = 1.8, 3.2 Hz), 6.01 (1H,br d, J = 3.2 Hz), 3.67 (3H, s), 3.36 (1H,-br sextet, J = 7.1 Hz), 2.73 (1H, dd, J = 15.4, 6.4 Hz), 2.46 (1H, dd, J = 15.4, 8.2 Hz), 1.30 (3H, d, J = 6.9 Hz).

3-(2-Furanyl)butanal (12). The methyl ester **11** (112 mg, 0.67 mmol) was dissolved in anhydrous toluene (3 mL) and cooled to −78 °C. A solution of diisobutylaluminum hydride (0.74 mL, 1.0 M in hexanes) was added dropwise. After 30 min, an additional amount of hydride (0.1 mL) was added to reduce the residual ester. After 2 h, 2 N HCl (3 mL) was added, and then the reaction was diluted with ether. The organic layer was separated and the aqueous layer extracted with ether (2 × 3 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The colorless oil was purified by flash chromatography on silica gel (hexane/ether 4:1) to give the slightly impure aldehyde **12** (52 mg, 56%) along with some starting material and another more polar product (possibly the corresponding alcohol). The aldehyde proved unstable to purification and was carried on as crude material in later experiments. The spectral data for this compound were consistent with the literature data.[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (1H, t, J = 1.9 Hz), 7.31 (1H, br s), 6.28 (1H, dd, J = 3.2, 1.9 Hz), 6.02 (1H, d, J = 3.2 Hz), 3.43 (1H, br sextet, J = 7.0 Hz), 2.80 (1H, ddd, J = 16.8, 6.6, 1.9 Hz), 2.59 (1H, ddd, J = 16.8, 7.2, 1.9 Hz), 1.32 (3H, d, J = 6.9 Hz).

(*E*)-3-Iodopropenoic Acid. A mixture of propiolic acid (1.01 g, 14.4 mmol) and aqueous hydriodic acid (47%, 3.92 g, 14.4 mmol) was heated to 90 °C for 4 h. Evaporation of the water under reduced pressure gave a yellow oil that crystallized on cooling. This crude cis iodoolefin was dissolved in dioxane (10 mL) and treated with a few crystals of iodine. The solution was heated to 60 °C and was monitored by ^{1}H NMR. After the solution was heated for 6 h, the heat was removed and a 10% solution of $Na_2S_2O_3$ (5 mL) was added. This aqueous mixture was extracted with dichloromethane(4 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated. The title compound was obtained as white crystals (2.56 g, 90%). The spectral data for this compound were consistent with those reported in the literature.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, d, J = 14.8 Hz), 6.87 (1H, d, J = 14.8 Hz).

(*E*)-Ethyl 3-Iodopropenoate (13). (*E*)-3-Iodopropenoic acid (2.56 g, 12.9 mmol) was dissolved in a 3:1 mixture of absolute ethanol and benzene (40 mL) and treated with a catalytic amount (two drops) of concentrated sulfuric acid. The solution was refluxed for 14 h. A solution of saturated sodium bicarbonate (20 mL) was added, and the mixure was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were dried and evaporated to give the desired ethyl ester **13** as a pale yellow oil (2.44 g, 84%) that was used without further purification. The spectral data for this compound were consistent with the literature data.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (1H, d, J = 14.8 Hz), 6.87 (1H, d, J = 14.8 Hz), 4.20 (2H, q, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz).

(*E*)-Ethyl 6-(2-Furanyl)-4-hydroxy-2-heptenoate (14). The furyl aldehyde **12** (76 mg, 0.55 mmol) and the trans iodoolefin **13** were dissolved in dry dimethyl sulfoxide (13 mL) with careful exclusion of moisture under an atmosphere of argon. Chromium(II) chloride (405 mg, 3.3 mmol) and nickel(II) chloride (0.4 mg, 0.003 mmol) were added, and the resulting deep green solution was stirred under argon for 2 d. To the reaction were then added chloroform and saturated ammonium chloride solution (10 mL each). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. Flash chromatography on silica gel (hexane/ether 4:1) provided the desired allylic alcohol **14** as a colorless oil (68 mg, 52%). Note that a 1:1 mixture of diastereomers is formed. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (0.5 H, dd, J = 1.8, 0.8 Hz), 7.31 (0.5 H, dd, J = 1.8, 0.8 Hz), 6.92 (1H, dd, J = 15.6, 5.1 Hz), 6.90 (1H, dd, J = 15.6, 5.1 Hz), 4.32−4.36 (0.5 H, m), 4.17−4.22 (0.5 H, m), 4.20 (1H, q, J = 7.1 Hz), 4.19 (1H, q, J = 7.1 Hz), 3.12−3.16 (0.5 H, m), 3.03 (0.5 H, sextet, J = 7.1 Hz), 1.97 (0.5 H, dt, J = 13.9, 7.7 Hz), 1.88 (0.5 H, ddd, J = 13.9, 10.1, 3.6 Hz), 1.79 (0.5 H, d, J = 4.8 Hz), 1.70−1.77 (1H, m), 1.65 (0.5 H, d, J = 4.8 Hz), 1.29 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.47 (2 C's), 159.38, 159.02, 149.97, 149.64, 141.09, 140.98, 120.41, 120.00, 110.05 (2 C's), 104.46, 104.01, 69.39, 69.24, 60.48, 60.45, 42.89, 42.64, 29.87, 29.79, 20.07, 19.22, 14.24 (2 C's). FT-IR (neat): 3440.5, 2971.7, 1719.8, 1701.0, 1278.0 cm^{-1}. MS (EI) *m*/*z* (rel intensity): 238.1 ($[M]^+$, 19), 220.1 (31), 191.1 (38), 130.1 (40), 95.0 (100). High-resolution EI MS (*m*/*z*): 238.1214, calcd for $C_{13}H_{18}O_4$ 238.1205.

(*E*)-Ethyl 6-(2-Furanyl)-4-oxo-2-heptenoate (4b). The allylic alcohol **14** (114 mg, 0.48 mmol) was added to a suspension of Celite (200 mg) and pyridinium chlorochromate (207 mg, 0.96 mmol) in dichloromethane (4 mL), and the dark suspension was stirred overnight. Upon completion of the reaction (TLC), the mixture was diluted with ether and filtered through a pad of silica gel using dichloromethane (20 mL) to wash the solids. After evaporation of the solvent, the yellow oil was flash chromatographed on silica gel (hexane/ether 4:1) to afford the pure product **4b** as a clear oil (42 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (1H, dd, J = 1.8, 0.8 Hz), 7.02 (1H, d, J = 16.0 Hz), 6.65 (1H, d, J = 16.0 Hz), 6.26 (1H, dd, J = 3.2, 1.8 Hz), 6.00 (1H, dd, J = 3.2, 0.7 Hz), 4.26 (2H, q, J = 7.1 Hz), 3.46 (1H, m), 3.07 (1H, dd, J = 16.6, 6.0 Hz), 2.77 (1H, dd, J = 16.6, 7.8 Hz), 1.30 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.23, 165.50, 158.36, 141.11, 139.29, 131.01, 110.07, 104.16, 61.43, 47.00, 28.98, 18.87, 14.13. FT-IR (neat): 2972.7, 2936.0, 1726.5, 1703.4, 1298.3, 1184.4 cm^{-1}. MS (EI) *m*/*z* (rel intensity): 236.1 ($[M]^+$, 46), 128.0 (73), 95.0 (100). High-resolution EI MS (*m*/*z*): 236.1048, calcd for $C_{13}H_{16}O_4$ 236.1048.

4-Methyl-2-oxo-3-pentenenitrile (15). To the suspension of dry zinc iodide (13 mg, 0.042 mmol) in cyanotrimethylsilane (843 mg, 8.5 mmol) at room temperature was added 3-methyl-2-butenoyl chloride (1.00 g, 8.5 mmol) all at once. The mixture was refluxed under argon for 2 h. Vacuum distillation of the solution (bp 64−67 °C, 21 mmHg) afforded the desired acyl cyanide **15** as a clear liquid (787 mg, 85%). The spectral data

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for this compound were consistent with the literature data.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.05 (1H, s), 2.18 (3H, s), 1.98 (3H, s).

Methyl 3-(2-Furanyl)-3-methylbutanoate (16). This ester was prepared by an application of the method of Hoffmann and Ismail.[13] A solution of the acylnitrile **15** (560 mg, 5.14 mmol) was dissolved in anhydrous benzene (15 mL) and treated with aluminum trichloride (171 mg, 1.28 mmol). After the solution stirred at room temperature for 30 min, furan (384 mg, 5.65 mmol) was added all at once. A gummy precipitate was formed. The reaction mixture was stirred at room temperature for 14 h and then treated with methanol (15 mL). The amber-colored solution was stirred at room temperature overnight. The solution was next diluted with ether (20 mL) and washed successively with water, saturated sodium bicarbonate solution, and water again (20 mL each). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. Flash column chromatography on silica gel (hexane/ether 9:1) gave the desired alkylated furan **16** (172 mg, 18%) as well as the dialkylated product **17** (274 mg, 18%). The spectral data for these compounds were consistent with the literature data.[13] Compound **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (1H, dd, J = 1.8, 0.8 Hz), 6.26 (1H, dd, J = 3.2, 1.8 Hz), 6.00 (1H, dd, J = 3.2, 0.8 Hz), 3.58 (3H, s), 2.61 (2H, s), 1.39 (6H, s). Compound **17.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 (2H, s), 3.58 (6H, s), 2.58 (4H, s), 1.39 (12H, s).

3-(2-Furanyl)-3-methylbutanal (18). The methyl ester **16** (460 mg, 2.53 mmol) was taken up in toluene (10 mL) and cooled to −78 °C. A solution of diisobutylaluminum hydride (2.78 mL, 1.0 M in hexanes) was added slowly via syringe. After the solution stirred for 2 h at −78 °C, 1 *N* HCl (5 mL) was added. The organic layer was separated and the aqueous layer extracted with ether (2 × 5 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL) and dried over $MgSO_4$. After evaporation of the solvents, the residue was subjected to flash chromatography to give the desired aldehyde **18** as a colorless oil (190 mg, 50%). The aldehyde proved unstable and was used in the next step promptly. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (1H, t, J = 2.4 Hz), 7.34 (1H, dd, J = 1.4, 0.5 Hz), 6.29 (1H, dd, J = 2.5, 1.5 Hz), 6.04 (1H, dd, J = 2.5, 0.5 Hz), 6.21 (2H, d, J = 2.4 Hz), 1.40 (6H, s).

(*E*)-Ethyl 6-(2-Furanyl)-4-hydroxy-6-methyl-2-heptenoate (19). In a manner analogous to that used in the preparation of compound **14**, the furyl butanal **18** (100 mg, 0.66 mmol) was coupled to the vinyl iodide **13** (447 mg, 1.98 mmol) using chromium(II) chloride (489 mg, 3.98 mmol) and catalytic nickel(II) chloride (0.5 mg, 0.004 mmol). After workup and flash column chromatography (hexane/ether 3:1), the desired allylic alcohol **19** was obtained as a slightly impure colorless oil (100 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (1H, dd, J = 1.8, 0.6 Hz), 6.78 (1H, dd, J = 15.6, 4.8 Hz), 6.28 (1H, dd, J = 3.2, 1.9 Hz), 6.06 (1H, dd, J = 3.2, 0.6 Hz), 5.93 (1H, dd, J = 15.6, 1.7 Hz), 4.27 (1H, m), 4.17 (2H, q, J = 7.1 Hz), 1.87 (2H, m), 1.52 (1H, d, J = 4.1 Hz), 1.37 (3H, s), 1.34 (3H, s), 1.27 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.58, 161.57, 150.25, 141.25, 119.58, 110.11, 104.13, 68.86, 60.35, 48.61, 35.02, 27.78, 27.23, 14.25. FT-IR (neat): 3445.3, 2970.7, 1709.8, 1705.3, 1279.0, 1159.4 cm^{-1}. MS (EI) m/z (rel intensity): 252.1 ([M]$^+$,17), 109.1 (100). High-resolution EI MS (m/z): 252.1361, calcd for $C_{14}H_{20}O_4$ 252.1361.

(*E*)-Ethyl 6-(2-Furanyl)-4-oxo-6-methyl-2-heptenoate (4c). Oxalyl chloride (69 μL, 0.79 mmol) was dissolved in dichloromethane (3 mL) and cooled to −78 °C. Dimethyl sulfoxide (0.11 mL, 1.59 mmol) was added to this mixture as a solution in dichloromethane (1 mL). After the solution was stirred for 15 min at this temperature, a solution of the allylic alcohol **19** (100 mg, 0.40 mmol) in dichloromethane was added slowly. After the solution was for 50 min, triethylamine (0.44 mL, 3.18 mmol) was added. The mixture was stirred at −78 °C for an additional 5 min and was then allowed to gradually warm to room temperature. Sodium bisulfate (3 mL) was added to the organic mixture, and the whole mixture was extracted with ether (4 × 3 mL). The ethereal extracts were dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (hexane/ether 3:1) afforded a mixture of the desired product **4c** and an unknown compound. A second chromatography (hexane/ether 15:1) afforded the pure enone **4c** (30 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (1H, dd, J = 1.8, 0.8 Hz), 6.68 (1H, d, J = 15.9 Hz), 6.43 (1H, d, J = 15.9 Hz), 6.24 (1H, dd, J = 3.2, 1.8 Hz), 5.98 (1H, dd, J = 3.2, 0.8 Hz), 4.21 (2H, q, J = 7.1 Hz), 2.89 (2H, s), 1.38 (6H, s), 1.29 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.78, 165.56, 160.34, 140.97, 139.54, 130.07, 110.14, 104.09, 61.21, 52.39, 35.60, 26.98, 14.12. FT-IR (neat): 2963.0, 2924.5, 1728.4, 1695.6 cm^{-1}. MS (EI) m/z (rel intensity): 250 ([M]$^+$, 27), 222.1 (6), 127.0 (17), 109.1 (100). High-resolution EI MS (m/z): 250.1202, calcd for $C_{14}H_{18}O_4$ 250.1205.

(±)-(4*R*,6*S*,7*S*,7a*S*)-Ethyl 2,3,3a,6,7,7a-Hexahydro-3,3-dimethyl-3a,6-epoxy-1-oxoindene-7-carboxylate (5c). Known amounts of the enoate **4c** were placed in four NMR tubes. Acetonitrile-d_3 (0.5 mL) was added to two of the tubes, while toluene-d_8 (0.5 mL) was added to the other two. The NMR tubes containing solutions of the enoate were then sealed under vacuum. One each of the samples containing acetonitrile and toluene was stored at room temperature and monitored periodically by proton NMR. Each of the other two samples was placed in a preheated (80 °C) NMR probe and monitored by scanning at regular intervals. The integration data thus obtained was processed using an Excel spread sheet program. After the conclusion of the kinetic experiment, the sealed tubes were reopened and the material in them combined and evaporated. Upon chromatography, the cyclized Diels−Alder product **5c** was obtained as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (1H, d, J = 5.9 Hz), 6.33 (1H, dd, J = 5.9, 1.5 Hz), 5.19 (1H, dd, J = 5.0, 1.5 Hz), 4.11 (2H, q, J = 7.1 Hz), 3.40 (1H, dd, J = 5.0, 3.1 Hz), 2.85 (1H, br d, J = 3.1 Hz), 2.48 (1H, d, J = 18.9 Hz), 2.36 (1H, dd, J = 18.9, 1.1 Hz), 1.36 (3H, s), 1.24 (3H, t, J = 7.1 Hz), 1.21 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.31, 170.58, 135.66, 133.96, 101.12, 80.03, 61.12, 55.37, 52.40, 51.11, 35.90, 26.76, 22.91, 14.21. FT-IR (neat): 2965.0, 1742.0, 1194.1 cm^{-1}. MS (EI) m/z (rel intensity) 250.1 ([M]$^+$, 18), 109.1 (100). High-resolution EI MS (m/z): 250.1209, calcd for $C_{14}H_{18}O_4$ 250.1205.

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