# *gem*-Dialkyl Effect in the Intramolecular Diels–Alder Reaction of 2-Furfuryl Methyl Fumarates: The Reactive Rotamer Effect, Enthalpic Basis for Acceleration, and Evidence for a Polar Transition State[1]

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**Abstract:** Investigation of the rates of cyclization of a series of substituted 2-furfuryl methyl fumarates **1a–h** has allowed us to determine which of the two explanations for the *gem*-dialkyl effect is more important. Studies with compounds substituted with small-membered rings showed that the rate acceleration is due primarily to the reactive rotamer effect and not to angle compression ("Thorpe–Ingold effect"). For example, the cyclobutyl-substituted compound **1d** would experience a reactive rotamer effect similar to that of the dimethyl compound **1e** and thus should cyclize relatively rapidly if this effect were dominant. However, due to the small ring, **1d** would have a larger "internal" angle than other disubstituted derivatives and thus should cyclize even more slowly than the dihydrido compound **1a** if the angle compression effect were dominant. Since the cyclobutyl-substituted compound **1d** cyclizes in $CD_3CN$ at 25 °C 208 times faster than the dihydrido compound **1a**, we have concluded that the reactive rotamer effect outweighs angle compression in determining the rate of cyclization in this system. The activation parameters for the cyclization of **1a–f** in $CD_3CN$ have been calculated. These data show 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. For example, on going from the dihydrido **1a** to the monomethyl compound **1b**, the 1.3 kcal/mol decrease in the $\Delta G^{\ddagger}$ is almost entirely due to the 1.4 kcal/mol decrease in the $\Delta H^{\ddagger}$. Likewise, comparison of the dihydrido and dimethyl cases shows that the $\Delta\Delta G^{\ddagger}$ of 4.5 kcal/mol is due very largely to the 4.9 kcal/mol difference in the $\Delta H^{\ddagger}$ with little contribution from the entropy of activation ($\Delta S^{\ddagger}$). In fact, the entropy of activation is more negative for the more substituted cases (**1b** vs **1a** and **1e** vs **1a** or **1b**) and would, therefore, retard the rate rather than accelerate it, if it were not for the enthalpy change (an isokinetic relationship). The rate enhancements due to the *gem*-dialkyl effect in this system are much higher than those generally seen in other systems (normally no larger than a factor of 10 for the dimethyl case vs the dihydrido one, but here a ratio of 2100). This discrepancy in rate effects is almost certainly due to the presence of an oxygen atom in the tether of our system next to the affected carbon compared to the all carbon tethers in the other cases. Finally, examination of the effect of solvents on this reaction reveals a strong acceleration of the cycloaddition in polar solvents, with the reaction being slowest in toluene, faster in acetonitrile, and faster again in DMSO. The solvent effect can be quite large in certain cases, with $k_{rel}$ being as large as 3200. The results for the monomethyl compound **1b** in a wide variety of solvents indicate a better agreement with the dielectric constant of the solvent rather than other solvent polarity parameters, such as $E_T$. This solvent effect is explained by the rotation of the most stable conformation of the starting material, the s-trans ester conformation **5**, about the C–O bond to give the higher energy s-cis conformation **6**, which can then cyclize via the transition state **7** to the observed products, the lactones **2**. Since the s-cis conformation and the transition state derived from it have a net dipole due to the overlap of the dipoles of the ester, it is more polar than the starting material and thus would be expected to be stabilized by polar solvents. This is not the case for the intermolecular cycloaddition because the s-cis ester conformation is not required in the transition state. As additional evidence for this mechanistic rationale, the analogous tertiary amide **8**, which would not have this more polar transition state (relative to the starting material), shows essentially no solvent effect in several solvents under similar conditions.

## Introduction and Background

The *gem*-dialkyl effect is the name given to the acceleration of a cyclization due to the substitution of alkyl groups for hydrogen atoms on the carbons in the chain that links the two reactive centers. The effect has been known and studied for years, with several hypotheses having been put forth to explain the effect.[3] The first was postulated over 75 years ago by Beesley, Ingold, and Thorpe[4a] and later explained in detail by Ingold.[4b] The "Thorpe–Ingold effect", as this effect has been called, says that alkyl substitution on a central methylene causes compression of the internal angle (since alkyl groups take up more space than hydrogens).[5] This decrease in the internal angle causes the X and Y groups at the ends of the system to be moved somewhat closer (Figure 1). In 1961, Schleyer published an excellent study of intramolecular hydrogen bonding in 2-substituted 1,3-propanediols, which provided strong experimental evidence for the Thorpe–Ingold effect but concluded that it probably accounted for only a small portion of the *gem*-dialkyl effect.[6] An alternative explanation for the rate increase on substitution is that there is a higher population of reactive syn rotamers due to alkyl substituents on the chain connecting the reaction centers,[7] an effect that has been termed the "reactive rotamer effect". In order for a cyclization to occur between the reactive units X and Y in compound A (X and Y could be electrophile and nucleophile or diene and dienophile, for example), they must first get near each other, and that requires rotation about the central C–C bonds (two for the formation of a five-membered ring, three for a six-membered ring) from the most stable and, therefore, more highly populated anti conformation to the gauche (or syn-clinal) conformation, as shown in Figure 2. This is shown schematically for only one of the C–C bonds in A. However, if one of the two carbons of this C–C bond is substituted with one or two alkyl groups, the energetic picture changes since the anti form is now essentially equienergetic (depending on the sizes of the alkyl groups

(1) Gervay, J. Ph.D. Dissertation, UCLA, 1990.
(2) Winstein Dissertation Awardee, UCLA, 1989.
(3) For good reviews, see: (a) Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum: New York, 1976; Vol. 1, pp 43–75. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(4) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *Ibid.* **1921**, *119*, 305.
(5) Often this term and the "*gem*-dialkyl effect" are used interchangeably, but more correctly the "Thorpe–Ingold effect" refers specifically to the angle change on substitution, while the "*gem*-dialkyl effect" refers to the overall acceleration.
(6) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368.
(7) For one of the first examples of this explanation, see: Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.

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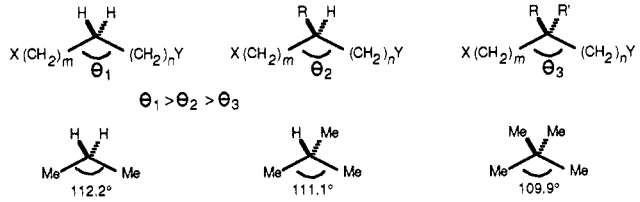



**Figure 1.** Thorpe–Ingold effect (angle compression).

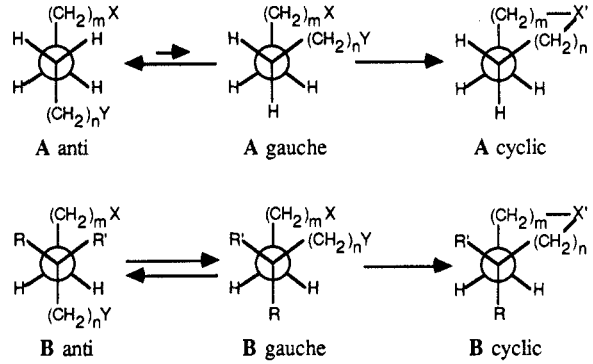
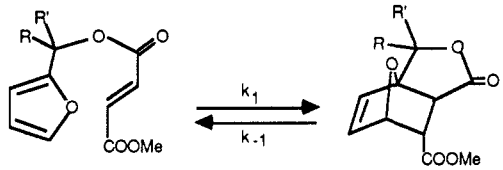



**Figure 2.** Reactive rotamer effect.

R and R′) to the gauche form as shown in B. Obviously, this conformational effect is felt about each C–C bond, although only one is shown schematically. Thus, the cyclization should be facilitated by a higher population of the reactive rotamer. The key effect is that 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.[8] We recently devised a system that allowed us to show that the reactive rotamer effect is the more important of these two hypotheses and now report the full details of our earlier work.[9] However, besides the determination of the physical reasons behind this effect, there has also been some question about the energetic basis of this effect, with a lowering of either the entropy or the enthalpy of activation being cited as the determining factor. In fact, it is a common assumption that the increased rate of cyclization is due primarily to a lowering of the activation entropy. We have determined the activation parameters for our intramolecular Diels–Alder reaction of the 2-furfuryl methyl fumarates **1a–f** to give the adducts **2a–f** and




| | | |
|---|---|---|
| **1a** | R = R′ = H | **2a** |
| **1b** | R = H R′ = Me | **2b** |
| **1c** | R, R′ = $(CH_2)_2$ | **2c** |
| **1d** | R, R′ = $(CH_2)_3$ | **2d** |
| **1e** | R = R′ = Me | **2e** |
| **1f** | R = H R′ = *t*-Bu | **2f** |
| **1g** | R, R′ = $(CH_2)_4$ | **2g** |
| **1h** | R = R′ = Et | **2h** |

now report that the remarkable rate enhancements in this system, i.e., the decrease in the free energy of activation ($\Delta G^{\ddagger}$), are nearly entirely due to a lowering of the enthalpy of activation ($\Delta H^{\ddagger}$) and not due to differences in the entropy of activation ($\Delta S^{\ddagger}$). Finally, we have investigated the reaction in several solvents, e.g., toluene, acetonitrile, and dimethyl sulfoxide (DMSO), and have uncovered

(8) For a slightly different explanation, see: Jung, M. E. *Synlett* **1990**, 186.
(9) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. (b) Jung, M. E.; Gervay, J. *Tetrahydron Lett.* **1988**, *29*, 2429.

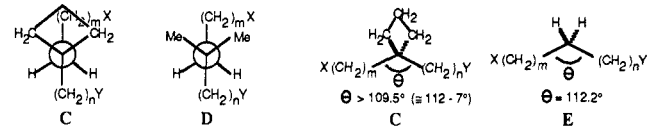



**Figure 3.** Effect of small ring on reactive rotamer and Thorpe–Ingold effects. The reactive rotamer effect of the cyclobutyl compound C would be similar to that of the dimethyl compound D, but the "internal" angle of C would be even larger than that of the dihydrido compound E.

a heretofore unseen but remarkable and very useful solvent effect on the cycloaddition. Polar solvents significantly accelerate the reaction, with $k_{rel}$ being as large as 3200. This polar solvent effect can be rationalized by realizing that the most stable conformation of the starting material, the s-trans ester conformation **5**, must rotate about the C–O bond to give the higher energy s-cis conformation **6**, which can then cyclize to the observed products, the lactones **2**. Since the s-cis conformation and the transition state **7** derived from it have a net dipole due to the overlap of the dipoles of the ester, it is more polar than the starting material and thus would be expected to be stabilized by polar solvents. These results and other related work are described in detail below.

## Results and Discussion

**Reactive Rotamer Effect.** As mentioned above, we wanted to devise a system that would allow us to distinguish between the two possible reasons behind the *gem*-dialkyl effect, namely angle compression at the substituted carbon (Thorpe–Ingold effect) or the reactive rotamer effect. The problem with examining the importance of the two effects is that they are both active in the *gem*-dialkyl compound. Thus, dimethyl substitution, for example, on a central methylene should produce both the reactive rotamer effect *and* the angle compression, and thus it would be impossible to distinguish between the two. So it was necessary to devise a system that forced the two effects to be in opposition. This could be easily done with a small-membered ring as the dialkyl substituent, i.e., the cyclobutyl and cyclopropyl systems shown in Figure 3. As shown schematically, the cyclobutyl system C should experience at least in most part the reactive rotamer effect but should not show angle compression but rather an angle enlargement. Thus, if the reactive rotamer effect were more important, compound C should cyclize nearly as fast as the dimethyl analogue D, but if angle compression were the overriding effect, it should cyclize much more slowly, comparable to or even slower than the dihydrido compound E. The overall rates of cyclization would probably be somewhat slower than expected because of the increased strain in the product due to the presence of the small-membered ring, but we hoped that the numbers would still allow us to make a decision concerning the relative importance of the two effects.

As our system to study these effects, we chose the 2-furfuryl methyl fumarates **1a–h** for several reasons: (a) there was a longstanding interest in and familiarity with Diels–Alder reactions in the group; (b) all of the substituted substrates should be easily prepared from furan itself and 2-furylcarbonyl derivatives; and (c) only one stereoisomer of the product (lactone exo, ester endo) would be produced in the intramolecular Diels–Alder reaction, namely, **2a–h**, which would simplify the analysis significantly. However, in addition to these advantages, this system has the slight disadvantage of having an oxygen atom in place of a carbon as one of the central atoms of the tether, which might dilute or at least modify the rotamer effect somewhat. The 2-furfuryl methyl fumarates **1a–h** were all prepared by acylation of the corresponding alcohols **3a–h** with either the acid **4a** by a Mitsunobu process or

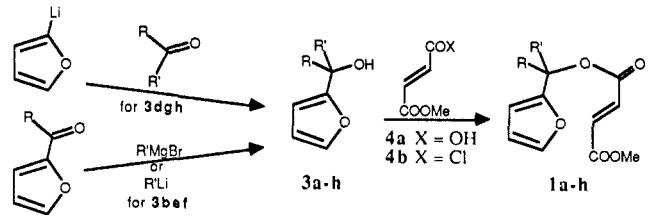


**Table I.** Rate Constants $k_1$ ($s^{-1}$) for the Cyclization of the Furfuryl Methyl Fumarates **1a–f** in $CD_3CN$

| 1a | | 1b | | 1c | | 1d | | 1e | | 1f | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $T^b$ | $10^6k_1$ | $T^b$ | $10^5k_1$ | $T^b$ | $10^5k_1$ | $T^b$ | $10^4k_1$ | $T^b$ | $10^4k_1$ | $T^b$ | $10^5k_1$ |
| 320 | 2.44[a] | 310 | 0.55 | 310 | 0.68 | 298 | 0.37 | 283 | 1.04 | 325 | 2.21 |
| 325 | 3.42 | 320 | 1.59 | 320 | 1.47 | 310 | 1.40 | 298 | 4.05 | 335 | 6.17 |
| 330 | 4.88[a] | 320 | 1.61[a] | 330 | 3.88 | 320 | 2.89 | 310 | 11.4 | 335[a] | 7.6 |
| 340 | 10.1[a] | 330 | 3.19 | 330 | 3.82[a] | 330 | 5.01 | | | 345 | 17.4 |
| 345 | 29.4 | 330 | 3.38[a] | 340 | 10.6 | 330 | 7.76 | | | 345[a] | 16.4 |
| 351 | 36.7[a] | 350 | 21.5 | 351 | 19.9 | | | | | 355 | 28.2 |
| | | 252 | 21.9[a] | | | | | | | | |

[a] The rate constant was derived from approaching the equilibrium from the reverse direction. [b] Kelvin.

the acid chloride **4b** in the presence of base. The alcohols **3a–h** either were commercially available themselves, e.g., **3a**, or were prepared by straightforward routes from commercially available furan derivatives. For example, several of the alcohols, e.g., **3d,g,h**, were prepared by addition of 2-furyllithium to the corresponding ketone (in yields of 69%, 63%, and 83%, respectively) while the cyclopropanol **3c** was prepared in 78% yield by addition of 2-furylmagnesium bromide to 1-ethoxycyclopropanol. Addition of methylmagnesium bromide to furfural and 2-acetylfuran afforded the alcohols **3b,e**, in yields of 81% and 74%, respectively. Finally the *tert*-butyl derivative **3f** was synthesized in 75% yield by addition of *tert*-butyllithium to furfural. The acylations of these alcohols to give the mixed fumarates **1a–h** are described in the Experimental Section. However, three fumarates were not readily available by this simple procedure, namely, the dimethyl, cyclopentyl, and diethyl compounds **1e,g,h**. In these cases, the intramolecular Diels–Alder reaction was so fast that the acyclic precursors **1e,g,h** could not be isolated and only the cycloadducts **2e,g,h** were isolated from the acylation reaction. The fumarates **1e,g,h** could be prepared and characterized by heating the cycloadducts **2e,g,h** in toluene-$d_8$ for a few minutes to set up an equilibrium of the adducts **2e,g,h** with the acyclic materials **1e,g,h** and then by quenching the equilibrium by rapidly cooling the sample in a dry ice–acetone bath. $^1H$ NMR allowed us to identify the educts **1e,g,h** although they could not be isolated pure, since the forward Diels–Alder reactions were just too fast. Because of this fact, we have not carried out extensive studies of the cyclopentyl and diethyl compounds **1g,h** but rather focused our efforts only on the dimethyl substrate **1e**. It should be pointed out, however, that there were no major differences in the rates of cyclization among these three compounds.

With these compounds in hand, an extensive investigation of their reactivities was undertaken. Initially the rate of cyclization was determined by monitoring the esters **1a–d** in deuterated acetonitrile ($CD_3CN$) at room temperature. Integration of the methyl ester singlets in the $^1H$ NMR quantified the relative amount of acyclic precursor A and cycloadduct C. With use of simple first-order kinetics (ln [A] versus time), the rates were obtained and the half-life of the reaction was determined.[9b] The cyclization rate for the disubstituted substrates could only be estimated, since the cycloaddition occurred during the acylation reaction. Since the retro Diels–Alder reaction is well documented, it became necessary to determine whether it was occurring here. The purified adducts **2a–d** were allowed to react with an excess of maleic anhydride in $CD_3CN$ at 25 °C for several hours. In no case was the adduct resulting from retro Diels–Alder reaction followed by intermolecular trapping of maleic anhydride detected. In addition, equilibration of the separated diastereomers of **2b** was not observed after several hours in $CD_3CN$. These experiments seemed adequate proof that the reverse reaction was not occurring. This, in fact, turned out not to be the case, and thus the half-lives we originally reported are incorrect.[9b] More careful examination of all the substrates **1a–h** showed that the reaction exhibited reversible kinetics. One source of our misunderstanding emanated from the fact that the reaction is so slow for the unsubstituted, monosubstituted, and cyclopropyl-substituted derivatives. The number of data points was limited, since at room temperature these required several days for reaction to become apparent. Furthermore, the inherent error in the early data points was large enough to merit eliminating them from the data set. So our initial

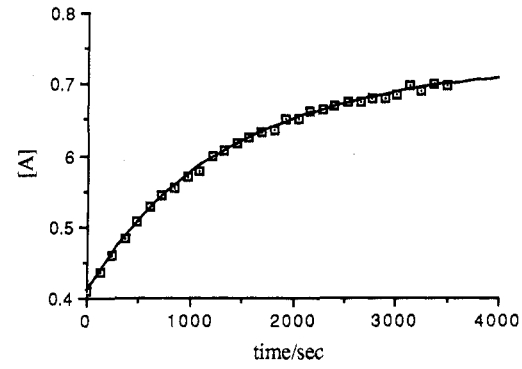



**Figure 4.** Moore plot: monomethyl furfuryl fumarate **1b** rate to equilibrium (352 K, $CD_3CN$).

results were found by taking the center of the curve, which was nearly linear for these substrates. However, by performing the reaction at higher temperatures, we found that the time to reach equilibrium was reduced and more data points were, therefore, available. When these data were fit to the equation for a reversible reaction (1), a linear relationship was demonstrated.

$$\ln \frac{[A] - [A]_\infty}{[A]_0 - [A]} = -(k_1 + k_{-1})t \qquad (1)$$

The time required to reach equilibrium at elevated temperatures allowed for the final concentration of the acyclic precursor ($[A]_\infty$) to be experimentally determined. However, a method for estimating $[A]_\infty$ was necessary for the lower temperature experiments. Of the several methods available,[10] we used that of Moore,[10d] which estimates both $[A]_0$ and $[A]_\infty$. This procedure was applied to the data obtained by $^1H$ NMR integration of the methyl ester singlets corresponding to the acyclic precursors **1a–f** and the cycloadducts **2a–f**. In the cases where $[A]_0$ and $[A]_\infty$ values could be experimentally determined, the approximated value was within experimental error. A typical Moore plot corresponding to the integration data is shown in Figure 4. To be consistent, the estimated values of $[A]_0$ and $[A]_\infty$ were used in solving eq 1 even when these values could be experimentally determined. The apparent rate, which is by definition the sum of the forward rate $k_1$ and the reverse rate $k_{-1}$, was obtained from the slope of these plots (Figure 5). In this way, the values of both the forward and reverse rates were determined.

A particularly appealing aspect of the reversible reaction kinetic expression (1) is that it is valid regardless of where monitoring begins along the reaction coordinate. For example, the apparent rate constant of **1a** at a given temperature should be the same whether the reaction begins with a greater percentage of A or C. The rate constants were determined at several temperatures and are listed in Table I. For those cases **1a–c,f** where cycloaddition was somewhat slower, the reaction could be monitored from both directions (from the fumarate or mainly from the cycloadduct). As shown in Table I, these rates correlated very well. The rapid retro Diels–Alder reaction and very large equilibrium constants

(10) (a) Guggenheim, E. A. *Philos. Mag.* **1926**, *2*, 538. (b) Kezdy, F. J.; Jaz, J.; Bruylants, A. *Bull. Soc. Chim. Belg.* **1958**, *67*, 687. (c) Swinbourne, E. S. *J. Chem. Soc.* **1960**, 2371. (d) Moore, P. *J. Chem. Soc., Faraday Trans. 1* **1972**, *68*, 1890.

**Table II.** Activation Parameters for the Intramolecular Diels–Alder Reaction of the Furfuryl Methyl Fumarates **1a–f** at 298 K in $CD_3CN$

| substrate | $k_{298}$ ($s^{-1}$) | $k_{rel}$ | $E_{act}$ (kcal/mol) | $\Delta H^{\ddagger}_{298}$ (kcal/mol) | $\Delta S^{\ddagger}_{298}$ (cal/mol·deg) | $\Delta G^{\ddagger}_{298}$ (kcal/mol) |
|---|---|---|---|---|---|---|
| **1a** | $1.94 \times 10^{-7}$ | 1 | 20.5 ± 2.1 | 19.8 ± 2.1 | −22.7 ± 6.4 | 26.6 ± 2.8 |
| **1b** | $1.62 \times 10^{-6}$ | 8.35 | 19.1 ± 0.5 | 18.4 ± 0.5 | −23.2 ± 1.6 | 25.3 ± 0.7 |
| **1c** | $2.03 \times 10^{-6}$ | 10.5 | 17.9 ± 0.5 | 17.3 ± 0.5 | −26.6 ± 1.5 | 25.2 ± 0.7 |
| **1d** | $4.03 \times 10^{-5}$ | 208 | 16.9 ± 1.8 | 16.3 ± 1.8 | −23.9 ± 5.6 | 23.4 ± 2.5 |
| **1e** | $4.12 \times 10^{-4}$ | 2123 | 15.5 ± 0.4 | 14.9 ± 0.4 | −24.0 ± 1.5 | 22.1 ± 0.6 |
| **1f** | $1.61 \times 10^{-6}$ | 8.32 | 19.8 ± 1.7 | 19.1 ± 1.7 | −21.0 ± 5.1 | 25.4 ± 2.3 |

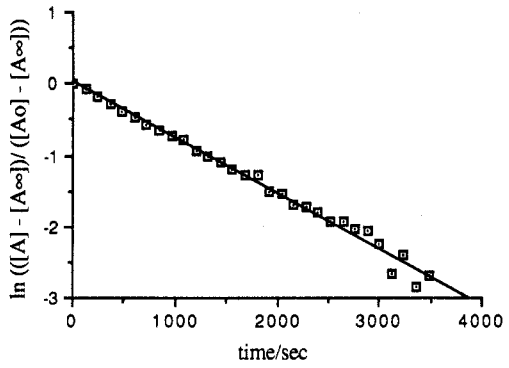



**Figure 5.** Reversible first-order: **1b** rate to equilibrium (352 K, $CD_3CN$).

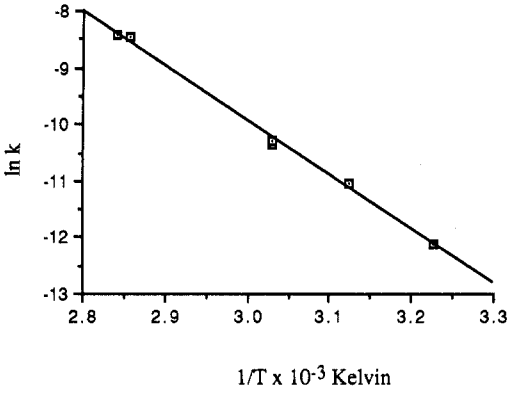



**Figure 6.** Arrhenius plot: monomethyl **1b** activation energy ($CD_3CN$).

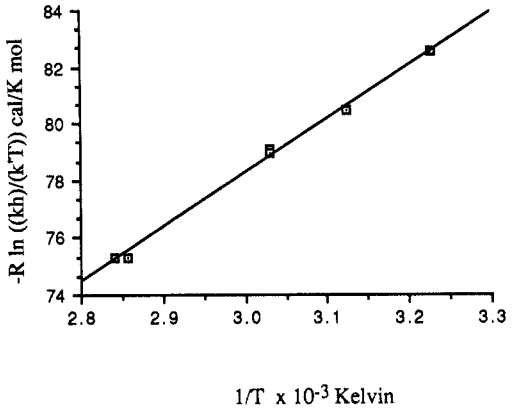



**Figure 7.** Eyring plot: monomethyl **1b** activation entropy and enthalpy ($CD_3CN$).

precluded bidirectional monitoring of the cyclobutyl **1d** and dimethyl **1e** derivatives. The cycloaddition of **1e** was further complicated by competing elimination (to 2-(α-methylvinyl)furan and the fumaric acid by an E1 mechanism) and, therefore, could be monitored only at relatively low temperatures (283–310 K). In this temperature range, the reverse reaction was negligible and simple first-order kinetics were observed.

From the data in Table I, one can estimate the relative importance of the two possible reasons behind the *gem*-dialkyl effect, namely, the reactive rotamer effect or angle compression. The key comparison is that of the rates of cyclization of the cyclobutyl system **1d** with those of the dihydrido and monomethyl substrates **1a,b**. The rate of cyclization of the cyclobutyl substrate **1d** is more than 100 times that of the dihydrido compound **1a** and nearly 20 times that of the monomethyl compound **1b**, although the angle between the diene and dienophile in **1d** should be significantly larger than that in both **1a,b**. Thus, this result argues strongly that angle compression is not an important factor in the *gem*-dialkyl effect, at least for cyclizations giving five-membered rings.[11] The major effect on cyclization must arise from some conformational effect like the reactive rotamer effect, although the exact source of the large rate accelerations is still not totally clear.

**Enthalpic Basis for the Acceleration.** While we have not been able to describe precisely the physical reasons behind the *gem*-dialkyl effect, we have shown that angle compression is a minor point, at least for our five-membered ring cyclizations. It would be extremely useful in trying to understand this effect to know if the large rate enhancements seen, i.e., the significant lowering in the $\Delta G^{\ddagger}$, are due to a lowering in $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, or a mixture of the two. Therefore, we decided to calculate the kinetic activation parameters for the cyclization of the series of mixed fumarates **1a–f**. As it turned out, we could do this for the entire series only in $CD_3CN$ since the cyclization of the dihydrido compound **1a** was too slow in toluene-$d_8$ and that of the dimethyl compound **1e** in DMSO-$d_6$ was too fast to allow us to easily measure the activation parameters.

The rate constants of Table I were used in the Arrhenius equation (2) (Figure 6) to determine the activation energy ($E_{act}$), while the Eyring equation (3) (Figure 7) was used to determine $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$, respectively. $\Delta G^{\ddagger}$ was calculated from these values. The kinetic activation parameters are given in Table II. The rate data listed in Table II were obtained by extrapolation of the Arrhenius plots back to 298 K.

$$\ln k = \ln [A] - E_{act}/RT \quad (2)$$

$$-R \ln (kh/kT) = -\Delta S^{\ddagger} + \Delta H^{\ddagger}/T \quad (3)$$

Inspection of these values reveals a significant rate enhancement upon alkyl substitution. The source of the rate acceleration, i.e., the lowering of the $\Delta G^{\ddagger}$, is clearly, in $\Delta H^{\ddagger}$ and not in $\Delta S^{\ddagger}$. For example, on going from the dihydrido **1a** to the monomethyl compound **1b**, the 1.3 kcal/mol decrease in the $\Delta G^{\ddagger}$ is almost entirely due to the 1.4 kcal/mol decrease in the $\Delta H^{\ddagger}$. Likewise, comparison of the dihydrido and dimethyl cases shows that the $\Delta\Delta G^{\ddagger}$ of 4.5 kcal/mol is due very largely to the 4.9 kcal/mol difference in the $\Delta H^{\ddagger}$ with little contribution from $\Delta S^{\ddagger}$. In fact, the entropy of activation is more negative for the more substituted cases (**1b** vs **1a** and **1e** vs **1a** or **1b**) and would, therefore, retard the rate rather than accelerate it, if it were not for the enthalpy change.[12] However, the variation in the entropy of activation is fairly small within this series, with all of the values being about

(11) One would anticipate that the angle compression effect would be much more important in the formation of smaller membered rings, especially three- and four-membered rings, where angle strain of the rings is much more important, although that might be experimentally difficult to test.

(12) This linear relationship between $\Delta\Delta H^{\ddagger}$ and the $\Delta\Delta S^{\ddagger}$ ($\Delta\Delta H^{\ddagger} = \rho\Delta\Delta S^{\ddagger}$, where $\rho$ is positive) is quite common and is sometimes called the isokinetic relationship. For a discussion, see: (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; pp 324–342. (b) Linert, W.; Jameson, R. F. *Chem. Soc. Rev.* **1989**, *18*, 477. Interpretation of this relationship in physical terms is that the addition of substituents to the carbon atom causes conformational changes to occur such that the molecule can more easily reach the transition state (therefore, the $\Delta H^{\ddagger}$ is lowered); however, this movement toward the transition-state geometry is countered by a loss in degrees of freedom (thus, the $\Delta S^{\ddagger}$ is lowered too).

−23 eu except for the cyclopropyl derivative **1c**, which is about 3 eu more negative (−26.6 eu), and thus the entropy change has little effect on the overall rate. The cyclopropyl and cyclobutyl compounds **1c,d** have lower $\Delta G^{\ddagger}$ than the dihydro or monomethyl cases as expected from the reactive rotamer effect but not as low as the dimethyl case **1e** due to the additional strain of the cycloadducts **2c,d** compared to that of **2e**. The relative rates ($k_{rel}$) show that the addition of one methyl group to the dihydrido substrate increases the rate of cyclization by a factor of about 8 (rate of **1a** vs that of **1b**), while the addition of a second methyl group (**1e**) increases the rate by over 250 vs the monomethyl and by over 2100 vs the dihydrido compound. It is also interesting that, in this fumarate series, the *tert*-butyl compound **1f** cyclizes at essentially the same rate as the monomethyl compound **1b**, namely, about 8 times faster than the dihydrido compound **1a**. This is in sharp contrast to the results of De Clercq,[13] who reported that in a related all-carbon system substitution of a *tert*-butyl group caused a rate enhancement of 240, roughly 30 times higher than the effect in our system. This difference is probably due to the presence of an oxygen atom $\alpha$ to the substituted carbon atom in our system, which eliminates some of the nonbonded interactions that may provide the driving force for cyclization in De Clercq's system.

In one of the earliest theoretical treatments of the *gem*-dialkyl effect, Allinger and Zalkow[14] calculated the thermodynamic parameters for the cyclization of hexane and substituted hexanes to the corresponding cyclohexanes and stated that their arguments should carry over directly to the corresponding activation parameters. Their findings were that the large effect on the equilibrium ($\Delta G$ more negative by about 1.8 kcal/mol per methyl group) was due to both an enthalpy and an entropy effect, a view that has been cited in other papers on the *gem*-dialkyl effect.[15] However, quite often the *gem*-dialkyl effect is assumed to be due almost completely to entropy,[16] even though a higher population of reactive rotamers is almost certainly due in great part to a favorable enthalpic change. In the few cases where the activation parameters for a *gem*-dialkyl effect have been calculated, both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ contribute in a nonlinear way to the decrease in $\Delta G^{\ddagger}$ on going from the dihydrido to the monomethyl to the dimethyl substrate.[17-19] For example, Eberson[17] showed that, for the cyclization of succinic acids to the anhydrides, $\Delta\Delta H^{\ddagger}$ was negative on going from dihydrido to monomethyl but positive from monomethyl to dimethyl, even though the $\Delta\Delta G^{\ddagger}$ was uniformly negative. Likewise in a case very similar to ours, the Claisen rearrangement of aryl propargyl ethers to chromenes via *o*-allenylphenols, Harfenist and Thom[18] showed that in several cases the $\Delta\Delta H^{\ddagger}$ was positive when an additional methyl group was added to a substrate, although the $\Delta\Delta G^{\ddagger}$ was always negative. Thus, our case is a rare example where the $\Delta\Delta H^{\ddagger}$ is uniformly negative on going from dihydrido to monomethyl to dimethyl and shows clearly that in this system there is a strong enthalpic basis for the *gem*-dialkyl effect rather than an entropic one.

One final point concerns the size of the rate enhancement of cyclization upon substitution. In general, the *gem*-dialkyl effect gives only modest rate increases on going from dihydrido to dimethyl, on the order of 0–10,[13,16a,20] although the use of bulkier alkyl groups (ethyl, propyl, *tert*-butyl) can give larger effects.[13,20,21]

**Table III.** Solvent Effects on Cycloaddition of **1** To Give **2**

| compd | R | R′ | $k_1$ ($s^{-1}$) toluene-$d_8$ | $CD_3CN$ | $Me_2SO$-$d_6$ |
|---|---|---|---|---|---|
| **1a** | H | H | $\sim 10^{-9}$ [a] | $2 \times 10^{-7}$ | $3.2 \times 10^{-6}$ |
| **1b** | H | Me | $3.0 \times 10^{-8}$ | $1.1 \times 10^{-6}$ | $6.6 \times 10^{-6}$ |
| **1c** | $(CH_2)_2$ | | $2.5 \times 10^{-7}$ | $1.3 \times 10^{-6}$ | $6.5 \times 10^{-6}$ |
| **1d** | $(CH_2)_3$ | | $3.4 \times 10^{-6}$ | $3.6 \times 10^{-5}$ | $1.3 \times 10^{-4}$ |
| **1e** | Me | Me | $1.3 \times 10^{-4}$ | $3.4 \times 10^{-4}$ | $\sim 10^{-3}$ [b] |

[a] Estimated since $K_{eq}$ too small to determine rate. [b] Estimated since $K_{eq}$ too large to determine rate.

**Table IV.** Relative Rate Constants for the Cycloaddition of **1** To Give **2**

| compd | R | R′ | $k_{rel}$ toluene | acetonitrile | $Me_2SO$ |
|---|---|---|---|---|---|
| **1a** | H | H | 1 | ~200 | ~3200 |
| **1b** | H | Me | 1 | 36.7 | 220 |
| **1c** | $(CH_2)_2$ | | 1 | 5.2 | 26 |
| **1d** | $(CH_2)_3$ | | 1 | 10.6 | 38.2 |
| **1e** | Me | Me | 1 | 2.6 | 7.7 |

**Table V.** Rate of Cyclization of **1b** in Relation to Solvent Polarities

| solvent | dielectric const | $E_T$ | $k_1$ ($s^{-1}$) | $k_{-1}$ ($s^{-1}$) |
|---|---|---|---|---|
| $Me_2SO$-$d_6$ | 48.9 | 45.0 | $6.6 \times 10^{-6}$ | $7.7 \times 10^{-7}$ |
| $CD_3CN$ | 37.9 | 46.0 | $1.1 \times 10^{-6}$ | $2.0 \times 10^{-7}$ |
| acetone-$d_6$ | 20.5 | 42.2 | $5.5 \times 10^{-7}$ | $1.6 \times 10^{-7}$ |
| $CD_2Cl_2$ | 8.9 | 41.1 | $3.0 \times 10^{-7}$ | $2.7 \times 10^{-7}$ |
| $CDCl_3$ | 4.7 | 39.1 | $4.3 \times 10^{-7}$ | $4.1 \times 10^{-7}$ [a] |
| toluene-$d_8$ | 2.38 | 33.9 | $3.0 \times 10^{-8}$ | $2.6 \times 10^{-7}$ |

[a] Both the forward and reverse reactions may be larger than expected due to catalysis by trace amounts of HCl inthe $CDCl_3$ (even after passage through alumina).

However, as the $k_{rel}$'s of Table II indicate, our system is much more susceptible to substitution since the dimethyl compound cyclizes more than 2100 times faster than the dihydrido. The reason for this discrepancy in rate effects is almost certainly due to the presence of an oxygen atom in the tether of our system next to the affected carbon compared to the all carbon tethers in the other cases.[22] We are currently investigating the theoretical basis for this heightened *gem*-dialkyl effect due to the heteroatom in the tether and will report on it in due course.

Thus, the large rate enhancements of cyclization due to substitution in our 2-furfuryl methyl fumarates are due nearly entirely to a lowering of the enthalpy of activation.

**Evidence for a Polar Transition State.** A large body of theoretical and experimental evidence has been produced to show that the Diels–Alder reaction proceeds via the concerted but nonsynchronous formation of the two new $\sigma$ bonds.[23] For this reason, a large degree of charge separation is not developed in the transition state, and therefore these cycloadditions are relatively in-

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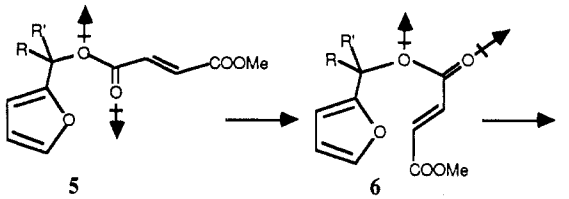
(21) In special cases, where an additional alkyl group is used to lock a system in a reactive conformation (Cohen's "trialkyl lock" in substituted *o*-hydroxyhydrocinnamic acid lactonizations), the rate enhancements can be incredibly large (up to $10^{11}$), nearing enzyme-catalyzed rates. Milstien, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1143; *J. Am. Chem. Soc.* **1972**, *94*, 9158. Borchardt, R. T.; Cohen, L. A. *Ibid.* **1972**, *94*, 9166, 9175.
(22) Harfenist and Thom reported rate enhancements of 200–1400 on going from dihydrido to dimethyl in their system, which also has an oxygen atom in the tether.
(23) (a) For an excellent review of the mechanistic aspects on the Diels–Alder reaction, including solvent effects, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) For earlier work, see: Wassermann, A. *Diels-Alder Reactions*; Elsevier: Amsterdam, 1965. (c) For a recent excellent review of solvent effects, see: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1988. (d) For an older review on solvent parameters, see: Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 29.

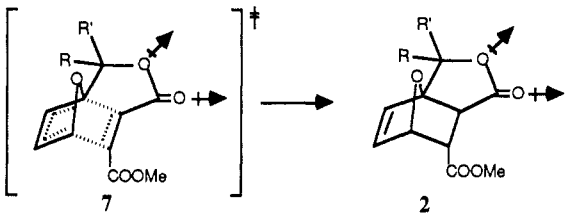
sensitive to changes in solvent polarity.[23] In fact, Berson and co-workers developed a parameter to measure solvent polarity ($\Omega$), which was based on the difference in the endo/exo product ratio of the intermolecular Diels–Alder reaction of methyl acrylate with cyclopentadiene in various solvents.[24] However, the overall rates for the cycloadditions did not differ greatly with solvent polarity.[24] There have been several reports of very large accelerations in the Diels–Alder reaction upon changing solvents,[25] but usually these are due to some special effects. We have observed significant rate enhancements of the intramolecular Diels–Alder reaction of our 2-furfuryl methyl fumarates **1** by the use of polar solvents, which we believe are due to the fact that an ester group is part of the chain connecting the diene and dienophile.[9a]

As shown in Table III, the rate constants for the forward Diels–Alder reaction ($k_1$) increase with increasing alkyl substitution, as expected because of the *gem*-dialkyl effect described above. However, the rates of cyclization are significantly faster in acetonitrile than in toluene and faster still in $Me_2SO$, as shown by the rate constants for the forward reaction ($k_1$) in Table III. A comparison of the relative rate constants for each substrate (not comparable down the columns) is given in Table IV. As shown, this solvent effect can be quite large in certain cases, with $k_{rel}$ being as large as 3200. The rate enhancements are largest for the least reactive substrate, the dihydrido compound **1a**, and smallest for the most reactive substrate, the dimethyl compound **1e**. The cycloaddition of the monomethyl compound **1b** was also examined in several additional solvents, including ones of intermediate polarity, with the results shown in Table V. The increase of the rate constants with increasing solvent polarity agrees better with the dielectric constant of the solvent than with the $E_T$ parameter for solvent polarity,[23c,d] although the agreement is not perfect with either parameter. As Table V indicates, the rate of the cycloreversion reaction ($k_{-1}$) is relatively insensitive to changes in polarity, with all the rate constants being roughly $2 \times 10^{-7}$ $s^{-1}$, with the exception of $Me_2SO$-$d_6$, in which the rate constant is somewhat higher.

We have put forward a novel hypothesis to explain the polar solvent effect in this system and its absence in the corresponding intermolecular reactions. The starting material **1** should exist primarily in the conformation **5** with the *Z* or s-trans conformation about the ester bond, since it is well-known that esters are more stable in this conformation for several reasons, one of which is to minimize overall dipole effects.[25] In order to cyclize, there must be a rotation about this ester bond to give the *E* or s-cis conformer **6**, which then can achieve the transition state **7**. Both the s-cis



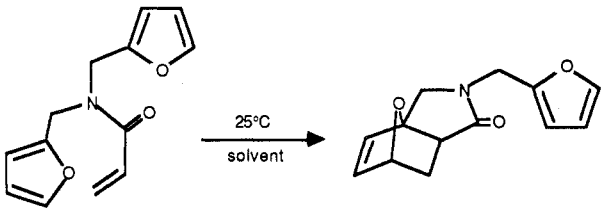

5 6




7 2

conformer **6** and the transition state **7**, due to the overlap of dipoles in the s-cis conformation, now have a larger dipole moment than the starting s-trans material **5**. Therefore, the transition state **7** is more polar than the starting material and thus should be stabilized more by polar than nonpolar solvents. Since the transition state for the corresponding intermolecular reactions of dienes with methyl acrylate, for example, does not require an s-cis ester conformation, it would more resemble the starting material in polarity and thus should experience no major solvent effects. The absence of significant change in $k_{-1}$ as the polarity of the solvent is varied (Table V) lends support for this mechanistic hypothesis, since the cycloreversion of **2** would not be expected to involve major changes in polarity in reaching the transition state **7**, since both have similar cisoid ester conformations.

If this argument of a polar transition state due to the s-cis ester conformation is correct, then one would expect a similar intramolecular cycloaddition that lacks this special polar transition state to be relatively insensitive to solvent polarity. For example, cyclization of the corresponding tertiary amide **8** to give the lactam **9** should have a relatively nonpolar transition state (due to the

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lack of strong dipole effects in tertiary amides) and should not experience similar solvent effects. This is indeed the case. Cyclization of the amide **8** in various solvents (toluene-$d_8$, $CD_2Cl_2$, $CDCl_3$, acetone-$d_6$, $CD_3CN$, $Me_2SO$-$d_6$) at 25 °C produced the expected lactam **9** at essentially the same rate, irrespective of solvent.

It is interesting to point out that by changing two experimental parameters that have essentially nothing to do with the HOMO and LUMO of the diene and dienophile, namely the substituents on the connecting chain and the solvent, we can achieve a rate enhancement of $10^6$ (the dihydrido **1a** in toluene-$d_8$ vs the dimethyl **1e** in $Me_2SO$-$d_6$)!

This solvent effect has several important implications, one of which is that the cyclization of any compound having two reactive centers connected by an ester linkage should experience a polar solvent effect if the ester unit must rotate into the s-cis conformation in order to arrive at the transition state. We are currently testing this concept and have preliminary results, which indicate that other reactions such as the ene reaction do indeed show polar solvent effects similar to those reported above. Finally we have just completed a detailed NMR study, which shows conclusively that polar aprotic solvents stabilize the *E* or s-cis conformer of esters relative to the *Z* or s-trans conformer.[26]

**Conclusion.** Our results indicate that the *gem*-dialkyl effect is caused not by angle compression but by some other effect of dialkyl substitution at a central methylene on the linking chain, namely the reactive rotamer effect. The large decrease in the free energy of activation for the cyclization on substitution is due nearly completely to a lowering of the enthalpy of activation and not the entropy of activation. Therefore, enthalpy changes are responsible for the large increases seen in our system. Finally, a quite useful but unusual acceleration of the intramolecular Diels–Alder reaction of our mixed fumarates due to polar solvents has been uncovered and explained by a novel conformational argument that predicts that other cyclizations of analogous compounds having reactive centers joined by an ester linkage will also experience similar effects.

## Experimental Section

**General Procedure.** The proton nuclear magnetic resonance spectra ($^1H$ NMR) were recorded on a Bruker AF-200 spectrometer operating at 200.132 MHz, a Bruker AM-360 spectrometer operating at 360.134

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MHz, or a Bruker AM-500 spectrometer operating at 500.134 MHz and are so indicated. $^{13}C$ NMR spectra were also recorded on the AF-200, AM-360, and AM-500 operating at 50.323, 90.556, and 125.760 MHz, respectively, and are so indicated. Spectra were recorded in the indicated solvent. Chemical shifts are reported in parts per million relative to the lock of the solvent used. Resonance patterns are reported with the following notations: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). If not stated otherwise, the spectra were recorded at 25 °C. The infrared spectra (IR) were recorded on a Perkin-Elmer 1310 spectrometer as a liquid film (neat), a Nujol mull, or a solution in the indicated solvent. Polystyrene was used as a standard, and the spectra are reported in reciprocal centimeters. The Fourier transform infrared spectra (FTIR) were recorded on a Perkin-Elmer spectrometer as a liquid film. High-resolution mass spectra (MS) were recorded on a double-focusing instrument (AEI Model MS-902) and are reported in $m/e$ units for the most abundant peaks. The elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard 5790A series gas chromatograph with an SE-30 cross-linked methyl silicone gum column (12 m × 0.2 mm × 0.33 mm film thickness). All ultraviolet spectra were recorded on a Hewlett-Packard diode array spectrometer 8450A at 25 °C in quartz cells unless otherwise indicated. Analytical thin-layer chromatography (TLC) was conducted on E. Merck silica gel 60 $F_{254}$ 0.2-mm precoated plates. Visualization was accomplished with ultraviolet light or ceric sulfate (1.5 g) and ammonium molybdate (1.0 g) in 10% aqueous sulfuric acid (100 mL). Flash column chromatography (FCC) was carried out according to the normal method in the solvent system indicated on Merck silica gel 230–400 mesh. Reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. The following solvents and reagents were distilled from the indicated agent under dry nitrogen: tetrahydrofuran (THF), diethyl ether, benzene, and toluene from sodium benzophenone ketyl; methylene chloride, pyridine, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), and diisopropylethylamine from calcium hydride.

**1-(2-Furanyl)cyclopropanol (3c).** 2-Furyllithium was generated by reaction of furan (6.4 mL, 88 mmol) in 50 mL of diethyl ether and 13.3 mL of TMEDA with *n*-butyllithium (37 mL of 2.37 M in hexanes, 88 mmol) at 0 °C. In a separate reaction vessel, magnesium bromide was prepared by reaction of 1,2-dibromoethane (7.6 mL, 88 mmol) with magnesium metal (2.2 g, 91 mmol) in 50 mL of diethyl ether. This was added to the 2-furyllithium at 0 °C and the solution brought to reflux. 1-Ethoxycyclopropanol (3 g, 29 mmol) was added dropwise at reflux and stirring continued for 2 h after addition was complete. The reaction mixture was cooled and then quenched by pouring into 50 mL of saturated $NH_4Cl$. The organic layer was separated and the aqueous layer extracted with 3 × 25 mL of diethyl ether. The combined organic layers were washed with 3 × 25 mL of saturated $NaHCO_3$ and 1 × 25 mL of brine solution and then dried over $MgSO_4$. Evaporation of the solvent left 9.7 g of crude material. Fractional distillation through an 8-in. Vigreaux column at 85–95 °C (20 mmHg) provided the pure alcohol **3c** as a colorless oil in 78% yield (8.5 g). Decomposition did occur at 25 °C over several days; however, the alcohol could be stored under argon at −20 °C for several weeks. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.27 (1 H, d, $J$ = 2.0 Hz), 6.29 (1 H, dd, $J$ = 3.0, 2.0 Hz), 6.18 (1 H, d, $J$ = 3.0 Hz), 3.65 (1 H, br), 1.1 (2 H, m), 1.03 (2 H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 156.67, 141.27, 110.37, 104.76, 52.05, 15.07. IR (neat): 3500, 3120, 1580, 1320 cm$^{-1}$. High-resolution MS ($m/e$): 124.0528, calcd for $C_7H_8O_2$ 124.0524.

**1-(2-Furanyl)cyclobutanol (3d).** 2-Furyllithium was prepared by addition of *n*-butyllithium (6 mL of 2.6 M in hexanes, 15.7 mmol) to furan (1.15 mL, 15.7 mmol) in 50 mL of tetrahydrofuran and 2.4 mL of TMEDA (15.7 mmol) at 0 °C and the solution stirred for 30 min. Cyclobutanone (1 g, 14.3 mmol) was then added, the reaction warmed to 25 °C, and the mixture stirred overnight. The reaction was quenched by the addition of 25 mL of water and extracted with 2 × 50 mL of diethyl ether. The combined organic layer was washed with 2 × 25 mL of $NaHCO_3$ and dried over $MgSO_4$. Evaporation left a brown oil, which was purified by FCC with 4/1 hexanes–ethyl acetate as eluent to afford 1.5 g of the desired alcohol **3d** as a yellow oil (69% yield). $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.50 (1 H, m), 6.45 (1 H, m), 6.39 (1 H, m), 2.9 (1 H, br s), 2.7–2.3 (4 H, m), 2.1–1.5 (2 H, m). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 158.21, 142.16, 110.10, 104.91, 72.24, 35.66, 12.71. IR (neat): 3346 (OH), 2991, 2945, 1506, 1251, 1159, 1134, 1081, 1008, 922 cm$^{-1}$. High-resolution MS ($m/e$): 138.0670, calcd for $C_8H_{10}O_2$ 138.0681.

**α-(1,1-Dimethylethyl)furan-2-methanol (3f).** Furfural (500 mg, 5.2 mmol) was diluted in 25 mL of diethyl ether and the mixture cooled to 0 °C. *tert*-Butyllithium (3.8 mL of 1.5 M in hexanes, 5.7 mmol) was then added and the reaction mixture stirred for 1 h at 0 °C before being quenched by the addition of saturated $NH_4Cl$ and extracted with 3 × 25 mL of diethyl ether. The combined organic extracts were washed with 4 × 25 mL of water and then dried over $MgSO_4$. Distillation through an 8-in. Vigreaux column at 87 °C (15 mmHg)[27] afforded 600 mg (75% yield) of the pure alcohol **3f** as a clear liquid. $^1H$ NMR ($CDCl_3$, 360 MHz): $\delta$ 7.31 (1 H, dd, $J$ = 1.6, 0.6 Hz), 6.29 (1 H, dd, $J$ = 1.8, 1.6 Hz), 6.17 (1 H, br d, $J$ = 1.8 Hz), 4.32 (1 H, s), 2.28 (1 H, br s), 0.92 (9 H, s). $^{13}C$ NMR ($CDCl_3$, 90 MHz): $\delta$ 155.74, 141.15, 109.84, 106.83, 60.33, 35.63, 32.53.

**1-(2-Furanyl)cyclopentanol (3g).** 2-Furyllithium was generated by reaction of furan (6 mL, 78 mmol) with *n*-butyllithium (33 mL of 2.37 M in hexanes, 78 mmol) in 75 mL of diethyl ether and TMEDA (12 mL, 78 mmol) at 0 °C and the reaction mixture warmed to 25 °C for 30 min. The temperature was reduced to 0 °C before addition of the cyclopentanone (6 g, 71 mmol). The mixture was warmed to 25 °C and stirred overnight. We quenched the reaction by pouring the mixture into ice water and extracting with 3 × 50 mL of diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Evaporation left a brown oil, which was purified by vacuum distillation through an 8-in. Vigreaux column at 107–109 °C (17 mmHg) to afford 7.5 g (63% yield) of the pure alcohol **3g**. $^1H$ NMR ($CD_3CN$, 200 MHz): $\delta$ 7.35 (1 H, m), 6.28 (1 H, m), 6.17 (1 H, m), 3.24 (1 H, br), 2.1–1.5 (8 H, m). $^{13}C$ NMR ($CD_3CN$, 50 MHz): $\delta$ 161.02, 142.33, 110.93, 104.97, 79.64, 40.19, 24.23. IR (neat): 3500, 3000, 2900, 1600, 1500, 1460, 1180, 1000 cm$^{-1}$. High-resolution MS ($m/e$): 152.0832, calcd for $C_9H_{12}O_2$ 152.0838.

**α,α-Diethylfuran-2-methanol (3h).** In an analogous procedure to that for **3d**, 2-furyllithium (41.2 mmol) was reacted with 3-pentanone (3.95 mL, 37.5 mmol) in 100 mL of THF and TMEDA (6.25 mL, 41.2 mmol). Distillation through an 8-in. Vigreaux column at 94 °C (15 mmHg) afforded the pure alcohol **3h** in 83% yield (4.8 g) (lit.[27] bp 92–95 °C (14 mmHg)).

**(*E*)-(2-Furanyl)methyl Methyl 2-Butenedioate (1a).** Furfuryl alcohol (**3a**) (500 mg, 5.1 mmol), (*E*)-β-carbomethoxyacrylic acid (**4a**)[28] (663 mg, 5.1 mmol), and triphenylphosphine (1.34 g, 5.1 mmol) were diluted in 50 mL of THF under an argon atmosphere, and the mixture was cooled to 5 °C. Diethyl azodicarboxylate (DEAD) was added via syringe pump over a 25-min period. As the addition continued, the solution became slightly yellow. When addition was complete, the reaction mixture was allowed to come to room temperature and stirred for 2 h. The solvent was then removed in vacuo, leaving a viscous yellow oil. FCC on a 9 cm × 4 cm bed of silica with 400 mL of a 3/1 hexanes–ethyl acetate solvent system afforded 1 g (95% yield) of the desired product **1a** as a slightly yellow oil. TLC: $R_f$ = 0.32 (3/1 hexanes–ethyl acetate), phosphomolybdic acid stain (PMA). $^1H$ NMR (toluene-$d_8$, 360 MHz): $\delta$ 6.92 (1 H, d, $J$ = 1.1 Hz), 6.72, 6.68 (2 H, ABq, $J$ = 15.6 Hz), 6.09 (1 H, d, $J$ = 3.2 Hz), 5.91 (1 H, dd, $J$ = 3.2, 1.1 Hz), 4.75 (2 H, s), 3.15 (3 H, s). $^{13}C$ NMR ($CS_2$, 90 MHz): $\delta$ 164.33, 163.68, 149.23, 143.31, 133.58, 133.12, 111.41, 111.08, 58.58, 51.99. IR (neat): 3110, 3090, 2950, 1715, 1640, 1500, 1440, 1360, 970, 910, 880, 820, 750 cm$^{-1}$. High-resolution MS ($m/e$): 210.0528, calcd for $C_{10}H_{10}O_5$ 210.0528.

**(*E*)-1-(2-Furanyl)ethyl Methyl 2-Butenedioate (1b).** In an analogous manner to the preparation of **1a**, **3b** (520 mg, 4.6 mmol) was reacted with (*E*)-β-carbomethoxyacrylic acid (**4a**) (664 mg, 5.1 mmol), triphenylphosphine (1.33 g, 5.1 mmol), and DEAD (0.8 mL, 5.1 mmol) to produce **1b** in 92% yield. TLC: $R_f$ = 0.27 (3/1 hexanes–ethyl acetate), PMA. $^1H$ NMR (toluene-$d_8$, 360 MHz): $\delta$ 6.90 (1 H, d, $J$ = 1.4 Hz), 6.75, 6.71 (2 H, ABq, $J$ = 15.7 Hz), 6.08 (1 H, d, $J$ = 3.2 Hz), 5.97 (1 H, q, $J$ = 6.7 Hz), 5.93 (1 H, dd, $J$ = 3.2, 1.4 Hz), 3.14 (3 H, s), 1.33 (3 H, d, $J$ = 6.7 Hz). $^{13}C$ NMR ($CD_3CN$, 50 MHz): $\delta$ 166.03, 164.84, 154.03, 143.88, 134.31, 134.19, 111.37, 109.18, 67.05, 52.85, 18.40. IR (neat): 3150, 3110, 3090, 3000, 2955, 2840, 1720, 1640, 1520, 1500, 1435, 1370, 920, 880, 850, 820, 750 cm$^{-1}$. High-resolution MS ($m/e$): 224.0683, calcd for $C_{11}H_{12}O_5$ 244.0685.

**(*E*)-1-(2-Furanyl)cyclopropyl Methyl 2-Butenedioate (1c).** 1-(2-Furanyl)cyclopropanol (**3c**) (700 mg, 5.6 mmol) was diluted in 20 mL of pyridine and cooled to 0 °C. (*E*)-β-Carbomethoxyacryloyl chloride (**4b**)[29] (1.5 g, 10.2 mmol) was added dropwise and the mixture slowly warmed to 25 °C and stirred for 12 h. The reaction was quenched by filtration through a plug of Celite followed by FCC with 3/1 hexanes–ethyl acetate to afford 1 g (78% yield) of the pure mixed ester **1c** as a colorless oil. TLC: $R_f$ = 0.30 (3/1 hexanes–ethyl acetate), PMA. $^1H$ NMR (toluene-$d_8$, 360 MHz): $\delta$ 6.89 (1 H, d, $J$ = 1.5 Hz), 6.75, 6.71 (2 H, ABq, $J$ = 15.7 Hz), 6.38 (1 H, d, $J$ = 3.2 Hz), 5.97 (1 H, dd, $J$ = 3.2, 1.5 Hz), 3.16 (3 H, s), 0.99 (4 H, m). FTIR (neat): 2950, 1720,

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(28) Spatz, S. M.; Stone, H. *J. Org. Chem.* **1958**, *23*, 1559.
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1440, 1300, 1150, 970 $cm^{-1}$. High-resolution MS (*m/e*): 236.0685, calcd for $C_{12}H_{12}O_5$ 236.0685.

**(*E*)-1-(2-Furanyl)cyclobutyl Methyl 2-Butenedioate (1d).** Furan (260 μL, 3.6 mmol) and TMEDA (54 μL, 3.6 mmol) in 15 mL of THF were cooled to 0 °C before addition of *n*-butyllithium (1.6 mL of 2.3 M in hexanes, 3.6 mmol). The mixture was warmed to 25 °C for 30 min and then cooled to 0 °C before addition of magnesium bromide (3.9 mmol) and cyclobutanone (250 mg, 3.6 mmol). Stirring was continued at 0 °C for 30 min. Then the THF was evaporated and 15 mL of toluene added followed by pyridine (15 μL, 1.8 mmol). Finally, (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (1.16 g, 7.14 mmol) was added at −20 °C. The reaction continued for 2 h, during which time the reaction temperature was allowed to slowly warm to 25 °C. Filtration through a plug of Celite and FCC with 3/1 hexanes–ethyl acetate afforded 612 mg (68% yield) of the pure diester **1d** as a slightly yellow oil. TLC: $R_f$ = 0.25 (3/1 hexanes–ethyl acetate), PMA. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 6.95 (1 H, d, *J* = 1.4 Hz), 6.73, 6.69 (2 H, ABq, *J* = 16.0 Hz), 6.42 (1 H, d, *J* = 3.2 Hz), 6.01 (1 H, dd, *J* = 3.2, 1.4 Hz), 3.17 (3 H, s), 2.01 (4 H, m), 1.5–1.3 (2 H, m). FTIR (neat): 2954, 1724, 1437, 1310, 1264, 1010 $cm^{-1}$. High-resolution MS (*m/e*): 250.0850, calcd for $C_{13}H_{14}O_5$ 250.0841.

**(*E*)-1-(2-Furanyl)-1-methylethyl Methyl 2-Butenedioate (1e).** The cycloadduct **2e** was diluted in toluene-$d_8$ and placed in an NMR tube. The tube was placed in an oil bath at 95 °C for 5 min and then immediately placed in a dry ice–acetone bath to quench the reaction. The reaction mixture was then filtered through a plug of potassium carbonate. The acyclic diester **1e** was observed by $^1$H NMR; however, it was not isolable as the Diels–Alder reaction was too fast. At this temperature a 10/1 ratio of **2e** to **1e** was obtained. An alternative method utilized flash vacuum pyrolysis. A 0.01 M solution of **2e** in deuterated benzene was injected into a 1 × 16 cm Pyrex tube containing 5-mm Pyrex balls. The temperature of the tube was typically 350–400 °C, and the pressure was at 5 mmHg. The reaction mixture was collected at the end of the tube and filtered through a plug of potassium carbonate. Normally a 2/1 ratio of **2e** to **1e** was obtained. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 6.93 (1 H, m), 6.79, 6.75 (2 H, ABq, *J* = 15.9 Hz), 6.10 (1 H, d, *J* = 2.9 Hz), 6.02 (1 H, dd, *J* = 2.9, 1.7 Hz), 3.31 (3 H, s), 1.72 (6 H, s).

**(*E*)-2,2-Dimethyl-1-(2-furanyl)propyl Methyl 2-Butenedioate (1f).** 2,2-Dimethyl-1-(2-furanyl)propanol (**3f**) (200 mg, 1.3 mmol) was diluted in 25 mL of diethyl ether and cooled to 0 °C before the addition of *n*-butyllithium (1.3 mL of 2.4 M in hexanes, 1.3 mmol). The mixture was stirred at 0 °C for 30 min, and then (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (290 mg, 1.95 mmol) was added. The reaction continued for 1 h, at which time TLC showed complete conversion of the starting material. The reaction was filtered through a Celite plug and the solvent evaporated, leaving a black residue. FCC with 3/1 hexanes–ethyl acetate afforded 280 mg (81% yield) of the pure diester **1f** as a slightly yellow oil. TLC: $R_f$ = 0.28 (3/1 hexanes–ethyl acetate), PMA. $^1$H NMR ($CD_3CN$, 360 MHz): δ 7.44 (1 H, dd, *J* = 1.7, 0.7 Hz), 6.91 (2 H, s), 6.41 (1 H, dd, *J* = 3.1, 1.7 Hz), 6.37 (1 H, dd, *J* = 3.1, 0.7 Hz), 5.58 (1 H, s), 3.75 (3 H, s), 0.97 (9 H, s). FTIR (neat): 2959, 2974, 1725, 1646, 1437, 1300, 1261, 1226, 1156, 1010, 981, 746 $cm^{-1}$. High-resolution MS (*m/e*): 266.1169, calcd for $C_{14}H_{18}O_5$ 266.1154.

**(*E*)-1-(2-Furanyl)cyclopentyl Methyl 2-Butenedioate (1g).** The cycloadduct **2g** (25 mg, 0.09 mmol) was diluted in 1 mL of toluene-$d_8$ and placed in an oil bath at 70 °C for 15 min. We quenched the reaction by placing the NMR tube in a dry ice–acetone bath. The acyclic diester **1g** was not isolable as cycloaddition was too fast. At this temperature, a 7/1 ratio of **2g** to **1g** was obtained. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 6.94 (1 H, d, *J* = 1.6 Hz), 6.80, 6.76 (2 H, ABq, *J* = 15.7 Hz), 6.23 (1 H, d, *J* = 3.0 Hz), 6.02 (1 H, dd, *J* = 3.0, 1.6 Hz), 3.31 (3 H, s), 2.01–1.75 (8 H, m).

**(*E*)-1-(2-Furanyl)-1-ethylpropyl Methyl 2-Butenedioate (1h).** The cycloadduct **2h** (25 mg, 0.09 mmol) was diluted in 1 mL of toluene-$d_8$ and placed in an oil bath at 95 °C for 10 min. We quenched the reaction by placing the NMR tube in a dry ice–acetone bath. The acyclic diester **1h** was not isolable as cycloaddition was too fast. At this temperature, a 6.5/1 ratio of **2h** to **1h** was obtained. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 6.97 (1 H, m), 6.86, 6.81 (2 H, ABq, *J* = 15.8 Hz), 6.12 (1 H, m), 6.05 (1 H, m), 3.27 (3 H, s), 2.24 (4 H, q, *J* = 7.5 Hz), 0.66 (6 H, t, *J* = 7.5 Hz).

**(±)-(3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-Tetrahydro-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate (2a).** The 2-furfuryl methyl fumarate (**1a**) (25 mg, 0.12 mmol) was diluted in 1 mL of $Me_2SO$-$d_6$ and the mixture reacted at 25 °C for several days. The entire reaction mixture was placed on a 2 × 4 cm bed of flash silica gel and chromatographed with 3/1 hexanes–ethyl acetate to give 3 mg (12% yield) of the desired lactone and 20 mg of recovered starting material. It was usually a mixture of the acyclic precursor **1a** and **2a**, since the retro Diels–Alder reaction occurs during isolation. TLC: $R_f$ = 0.17 (3/1 hexanes–ethyl acetate), PMA. Mp: 94–97 °C. $^1$H NMR ($Me_2SO$-$d_6$, 200 MHz): δ 6.41 (1 H, d, *J* = 3.9 Hz), 6.36 (1 H, dd, *J* = 3.9, 1.5 Hz), 5.30 (1 H, dd, *J* = 4.7, 1.5 Hz), 4.85, 4.55 (2 H, ABq, *J* = 10.9 Hz), 3.66 (3 H, s), 3.42 (1 H, dd, *J* = 4.7, 3.5 Hz), 3.11 (1 H, d, *J* = 3.5 Hz). IR (neat): 2953, 1774, 1730, 1431, 1322, 1267, 1207, 1147, 995, 859 $cm^{-1}$. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.12; H, 4.80. Found: C, 57.31; H, 4.80.

**(±)-(3*RS*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-Tetrahydro-3-methyl-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate (2b).** 1-(2-Furanyl)ethyl methyl fumarate (**1b**) (25 mg, 0.1 mmol) was diluted in $Me_2SO$-$d_6$ and the mixture reacted for several days at 25 °C until an equilibrium mixture was obtained. The entire reaction mixture was then placed on a 2 × 4 cm bed of flash silica gel and chromatographed with 3/1 hexanes–ethyl acetate. Isolation of the adduct is complicated by retro Diels–Alder reaction, which occurs during purification, but under optimum conditions 5 mg (20% yield) of the desired lactone could be obtained as a yellow solid in a 1/1.1 ratio of the diastereoisomers. TLC: $R_f$ = 0.15 (3/1 hexanes–ethyl acetate), PMA. Mp: 105 °C dec.

**Data for the Major Isomer.** $^1$H NMR ($CDCl_3$, 200 MHz): δ 6.53 (1 H, d, *J* = 5.9 Hz), 6.38 (1 H, dd, *J* = 5.9, 1.5 Hz), 5.29 (1 H, dd, *J* = 5.4, 1.5 Hz), 5.07 (1 H, q, *J* = 6.6 Hz), 3.67 (3 H, s), 3.56 (1 H, dd, *J* = 5.4, 3.4 Hz), 3.34 (1 H, d, *J* = 3.4 Hz), 1.45 (3 H, d, *J* = 6.6 Hz).

**Data for the Minor Isomer.** $^1$H NMR ($CD_3CN$, 360 MHz) δ: 6.53 (1 H, m), 6.38 (1 H, m), 5.27 (1 H, m), 5.91 (1 H, q, *J* = 6.5 Hz), 3.69 (3 H, s), 3.56 (1 H, m), 3.36 (1 H, m), 1.52 (3 H, d, *J* = 6.5 Hz).

**Data for the Mixture.** FTIR (neat): 2955, 1777, 1733, 1439, 1311, 1267, 1180, 1036, 982, 930 $cm^{-1}$. High-resolution MS of mixture (*m/e*): 224.0683 calcd for $C_{11}H_{12}O_5$ 224.0685.

**(±)-(3′a*R*,6′*S*,7′a*S*)-Methyl 1′,6′,7′,7′a-Tetrahydro-1′-oxospiro[cyclopropane-1,3′-[3*H*-3a′,6a′]-epoxyisobenzofuran]-7′-carboxylate (2c).** 2-Furanylcyclopropyl methyl fumarate (**1c**) (25 mg, 0.11 mmol) was diluted in 1 mL of $Me_2SO$-$d_6$ and the mixture reacted at 25 °C for several days. FCC of the entire reaction mixture on a 2 × 4 cm column of gel afforded 5 mg (20% yield) of the pure lactone **2c** as a slightly yellow solid. TLC: $R_f$ = 0.20 (3/1 hexanes–ethyl acetate), PMA. Mp: 110–111 °C. $^1$H NMR ($CD_3CN$, 360 MHz): δ 6.76 (1 H, d, *J* = 5.8 Hz), 6.42 (1 H, dd, *J* = 5.8, 4.8 Hz), 5.33 (1 H, dd, *J* = 4.8, 1.5 Hz), 3.62 (3 H, s), 3.52 (1 H, dd, *J* = 3.7, 1.5 Hz), 3.30 (1 H, d, *J* = 3.7 Hz), 1.5–1.15 (4 H, m). FTIR (neat): 2954, 2851, 1782, 1736, 1438, 1305, 1265, 1214, 1189, 1104, 1025, 980, 937, 714 $cm^{-1}$. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.59; H, 5.60.

**(±)-(3′a*R*,6′*S*,7′*S*,7′a*S*)-Methyl 1′,6′,7′,7′a-Tetrahydro-1′-oxospiro-[cyclobutane-1,3′-[3*H*-3a′,6a′]-epoxyisobenzofuran]-7′-carboxylate (2d).** 2-Furanylcyclobutanol (163 mg, 1.2 mmol) was treated with *n*-butyllithium (0.5 mL of 2.5 M in hexanes, 1.32 mmol) in THF at 0 °C and the mixture then reacted for 30 min before addition of pyridine (0.2 mL, 2.4 mmol). Finally, (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (350 mg, 2.4 mmol) was added and the reaction mixture stirred for 18 h. The reaction was quenched by filtration through a plug of Celite followed by FCC with 3/1 hexanes–ethyl acetate to provide 200 mg (68% yield) of the pure lactone **2d** as a white solid. TLC: $R_f$ = 0.15 (3/1 hexanes–ethyl acetate), PMA. Mp: 135–136 °C. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 5.78 (2 H, m), 4.75 (1 H, dd, *J* = 4.9, 1.2 Hz), 3.42 (1 H, dd, *J* = 4.9, 3.2 Hz), 3.09 (3 H, s), 2.96 (1 H, d, *J* = 3.2 Hz), 1.90 (1 H, m), 1.80 (1 H, m), 1.7–1.4 (4 H, m). FTIR (neat): 3075, 2998, 2943, 1773, 1734, 1437, 1321, 1288, 1261, 1244, 1178, 947, 925 $cm^{-1}$. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.48; H, 5.61.

**(±)-(3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-Tetrahydro-3,3-dimethyl-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate (2e).** A 50% mixture of sodium hydride and mineral oil (247 mg, 5.2 mmol) was washed with 3 × 10 mL portions of THF and then suspended in 30 mL of THF. 2-(2-Furanyl)propan-2-ol (**3e**) (500 mg, 4 mmol) was added and the slurry stirred for 30 min at 25 °C. The THF was evaporated and then replaced with 30 mL of toluene, the mixture cooled to −20 °C, and pyridine (0.2 mL, 2 mmol) added. Finally, (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (1.2 g, 8 mmol) was added and the mixture allowed to slowly warm to 25 °C. The reaction was continued for 2 h before being quenched by filtration through a plug of Celite. FCC on a 3 × 4 cm bed of silica gel with 3/1 hexanes–ethyl acetate afforded 524 mg (55% yield) of the pure lactone **2e** as a white solid. TLC: $R_f$ = 0.13 (3/1 hexanes–ethyl acetate), PMA. Mp: 138.5–139 °C. $^1$H NMR ($CD_3CN$, 200 MHz): δ 6.65 (1 H, d, *J* = 5.9 Hz), 6.44 (1 H, dd, *J* = 5.9, 1.5 Hz), 5.28 (1 H, dd, *J* = 4.8, 1.5 Hz), 3.76 (3 H, s), 3.47 (1 H, dd, *J* = 4.8, 3.4 Hz), 3.23 (1 H, d, *J* = 3.4 Hz), 1.64 (3 H, s), 1.40 (3 H, s). FTIR (neat): 3095, 2983, 2957, 1771, 1740, 1462, 1437, 1392, 1376, 1290, 1214, 1177, 1103, 978, 942, 860 $cm^{-1}$. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92. Found: C, 60.20; H, 5.94.

**(±)-(3*RS*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-Tetrahydro-3-(1,1-dimethylethyl)-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate (2f).** 2,2-Dimethyl-1-(2-furanyl)propyl methyl fumarate (**1f**) (25 mg, 0.09 mmol) was diluted in 1 mL of $Me_2SO$-$d_6$ and the mixture reacted at 25

°C for 10 days. FCC of the entire reaction mixture on a 2 × 4 cm column of gel afforded 10 mg (40% yield) of the pure lactone **2f** as a white solid. The $^1$H NMR spectrum showed a mixture of diastereoisomers in approximately a 20/1 ratio. Due to the small amount of the minor isomer, the splitting pattern was not resolved. TLC: $R_f$ = 0.20 (3/1 hexanes–ethyl acetate), PMA. Mp: 168–170 °C.

**Data for the Major Isomer.** $^1$H NMR ($CD_3CN$, 200 MHz): δ 6.75 (1 H, d, $J$ = 5.8 Hz), 6.49 (1 H, dd, $J$ = 5.8, 1.7 Hz), 5.41 (1 H, dd, $J$ = 3.4, 1.7 Hz), 4.65 (1 H, s), 3.55 (3 H, s), 3.30 (1 H, dd, $J$ = 3.6, 3.4 Hz), 3.10 (1 H, d, $J$ = 3.6 Hz), 0.90 (9 H, s).

**Data for the Minor Isomer.** $^1$H NMR ($CD_3CN$, 200 MHz): δ 6.75 (1 H, m), 6.49 (1 H, m), 5.38 (1 H, m), 4.50 (1 H, s), 3.56 (3 H, s), 3.33 (1 H, m), 3.01 (1 H, m), 1.30 (9 H, s).

**Data for the Mixture.** FTIR (neat): 1779, 1737, 1646, 1310, 1266, 1210, 668 cm$^{-1}$. High-resolution MS ($m/e$): 266.1147, calcd for $C_{14}H_{18}O_5$ 266.1154.

**(±)-(3′a*R*,6′*S*,7′*S*,7′a*S*)-Methyl 1′,6′,7′,7′a-Tetrahydro-1′-oxospiro[cyclopentane-1,3′-[3*H*-3a′,6a′]-epoxyisobenzofuran]-7′-carboxylate (2g).** In an analogous procedure to that used for **2e**, 2-furanylcyclopentanol (**3g**) (1 g, 6.6 mmol) was reacted with sodium hydride (350 mg, 7.2 mmol) and (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (2.14 g, 13.2 mmol) and the mixture stirred for 2 h. FCC with 3/1 hexanes–ethyl acetate afforded 1.1 g (63% yield) of the pure lactone **2g** as a white solid. TLC: $R_f$ = 0.15 (3/1 hexanes–ethyl acetate), PMA. Mp: 114–116 °C. $^1$H NMR ($CD_3CN$, 200 MHz): δ 6.53 (1 H, d, $J$ = 5.9 Hz), 6.37 (1 H, dd, $J$ = 5.9, 1.5 Hz), 5.27 (1 H, dd, $J$ = 4.9, 1.5 Hz), 3.76 (3 H, s), 3.27 (1 H, dd, $J$ = 4.9, 3.3 Hz), 3.12 (1 H, d, $J$ = 3.3 Hz), 2.05–1.20 (8 H, m). FTIR (neat): 2954, 2877, 1773, 1734, 1437, 1327, 1266, 1239, 975, 958, 711 cm$^{-1}$. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.61; H, 6.11. Found: C, 63.65; H, 6.15.

**(±)-(3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-Tetrahydro-3,3-diethyl-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate (2h).** In a procedure analogous to that used for **2e**, 3-(2-furanyl)pentan-3-ol (**3h**) (500 mg, 3.2 mmol) was reacted with sodium hydride (171 mg, 3.6 mmol) and (*E*)-β-carbomethoxyacryloyl chloride (**4b**) (713 mg, 4.8 mmol) and the mixture stirred for 2 h. FCC with 3/1 hexanes–ethyl acetate afforded 494 mg (58% yield) of the pure lactone **2h** as a white solid. TLC: $R_f$ = 0.17 (3/1 hexanes–ethyl acetate), PMA. Mp: 138–138.5 °C. $^1$H NMR (toluene-$d_8$, 360 MHz): δ 6.57 (1 H, d, $J$ = 5.9 Hz), 6.31 (1 H, dd, $J$ = 5.9, 1.6 Hz), 5.28 (1 H, dd, $J$ = 4.9, 1.6 Hz), 3.67 (3 H, s), 3.52 (1 H, dd, $J$ = 4.9, 3.4 Hz), 3.30 (1 H, d, $J$ = 3.4 Hz), 1.97 (4 H, m), 1.09 (3 H, t, $J$ = 7.4 Hz), 0.86 (3 H, t, $J$ = 7.4 Hz). FTIR (neat): 2950, 2912, 1776, 1737, 1263, 1216, 1182, 1100, 1005, 976, 943, 919 cm$^{-1}$. High-resolution MS ($m/e$): 266.1157, calcd for $C_{14}H_{18}O_5$ 266.1154.

***N*,*N*-Bis(2-furanylmethyl)propenamide (8).** The known *N*-(2-furanylmethyl)carboxamide[30] was prepared as follows. To 2-furoic acid (5 g, 45 mmol), 2-furfurylamine (3.94 g, 45 mmol), and DMAP (504 mg, 4.5 mmol) in dry dichloromethane in an argon atmosphere at 0 °C was added DCC (12 g, 59 mmol). The reaction mixture was then warmed to 25 °C and stirred overnight. Filtration through Celite and concentration of the filtrate afforded the crude amide, which was purified by FCC on a 6 × 5 cm bed of silica gel with 2/1 diethyl ether–petroleum ether eluent. The yield was quantitative. TLC: $R_f$ = 0.2 (2/1 diethyl ether–petroleum ether). Mp: 109–111 °C. $^1$H NMR ($CDCl_3$, 360 MHz): δ 7.35 (2 H, m), 7.06 (1 H, m), 6.55 (1 H, br, NH), 6.42 (1 H, m), 6.24 (2 H, m), 4.53 (2 H, d, $J$ = 5.8 Hz). FTIR (neat): 3307, 1651, 1595, 1572, 1527, 1474, 1302, 1183, 1013 cm$^{-1}$. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.81; H, 4.75. Found: C, 63.02; H, 4.75. The known *N*-(2-furanylmethyl)-2-furanmethanamine[31] was prepared as follows. *N*-Furfuryl-2-furanamide (1g, 5.23 mmol) was added to a slurry of lithium aluminum hydride (250 mg, 6.59 mmol) in dry diethyl ether at 0 °C under an argon atmosphere. When addition was complete, the reaction temperature was increased to 25 °C and the reaction mixture stirred for 2 h when TLC indicated complete conversion of the starting material. The reaction was quenched by the addition of 1 mL of water, 1 mL of 10% NaOH, and finally 3 mL of water. The aluminum salts were removed by filtration through a fritted-disk filter, and evaporation of the solvent afforded a 3/1 mixture of the desired amine and starting material. FCC on a 6 × 3 cm bed of silica gel with 2/1 diethyl ether–petroleum ether as eluent yielded 465 mg of the di-2-furfurylamine in a 62% yield (quantitative based on recovered starting material). TLC: $R_f$ = 0.3 (2/1 diethyl ether–petroleum ether). $^1$H NMR ($CDCl_3$, 200 MHz): δ 7.40 (2 H, m), 7.10 (2 H, m), 6.46 (3 H, m), 4.57 (4 H, d, $J$ = 3.7 Hz). FTIR (neat): 3500, 2987, 2925, 2771, 2791, 2580, 2361, 1577, 1497, 1456, 1223, 1151, 1007 cm$^{-1}$. The di-2-furfurylamine (1 g, 5.6 mmol) was reacted with acryloyl chloride (0.5 ml, 6.2 mmol) in the presence of diisopropylethylamine (1.2 ml, 6.8 mmol) in 50 mL of THF at −78 °C. The reaction mixture was allowed to slowly warm to 25 °C. The reaction was quenched by filtration through a plug of Celite. Evaporation of the filtrate afforded 1.4 g of the desired amide **8** as a yellow oil in quantitative yield. $^1$H NMR ($Me_2SO$-$d_6$, 200 MHz): δ 7.59 (1 H, br s), 7.56 (1 H, br s), 6.90 (1 H, dd, $J$ = 16.6, 10.3 Hz), 6.45 (2 H, br s), 6.38 (2 H, br s), 6.15 (1 H, dd, $J$ = 16.6, 2.4 Hz), 5.72 (1 H, dd, $J$ = 10.3, 2.4 Hz), 4.58 (2 H, br s), 4.53 (2 H, br s). FTIR (neat): 2924, 1651, 1615, 1505, 1441, 1378, 1353, 1281, 1251, 1190 cm$^{-1}$. High-resolution MS ($m/e$): 231.0906, calcd for $C_{13}H_{13}NO_3$ 231.0932.

**(±)-(3a*R*,6*R*,7a*S*)-2-(2-Furanylmethyl)-1,6,7,7a-tetrahydro-3*H*-3a,6-epoxyisoindol-1-one (9).** *N*,*N*-Di-2-furfurylacrylamide (**8**) (25 mg, 0.1 mmol) was diluted in 1 mL of toluene-$d_8$ and refluxed overnight. The solvent was evaporated and the crude product subjected to FCC on a 2 × 2 cm column of silica gel eluting with 2/1 diethyl ether–petroleum ether. The desired cycloadduct **9** was obtained in 75% yield (19 mg) as a yellow oil. $^1$H NMR ($CD_2Cl_2$, 360 MHz): δ 7.60 (1 H, br s), 6.49 (1 H, m), 6.46 (1 H, m), 6.31 (1 H, m), 6.28 (1 H, m), 4.98 (1 H, m), 4.46, 4.35 (2 H, ABq, $J$ = 15.6 Hz), 3.97 (1 H, d, $J$ = 11.6 Hz), 3.51 (1 H, d, $J$ = 11.6 Hz), 2.42 (1 H, dd, $J$ = 8.8, 3.5 Hz), 1.87 (1 H, m), 1.42 (1 H, dd, $J$ = 11.6, 8.8 Hz). FTIR (neat): 2932, 1687, 1474, 1360 cm$^{-1}$. High-resolution MS ($m/e$): 231.0917, calcd for $C_{13}H_{13}NO_3$ 231.0932.

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