the different in vivo distributions exhibited by the two isomeric bleomycins, it is evident that metal coordination of this unidentified group has a dramatic affect on drug delivery. Work in progress on the behavior of the hydrolysis product at high pH and on the spectroscopic properties of the entact cobalt(III)bleomycins will more clearly define the coordination properties of the entact biologically active antibiotic.

Acknowledgment. We are especially indebted to C. J. Hawkins for helpful advice on several aspects of the work presented in the manuscript. We also wish to thank J. I. Legg, C. W. Storm, D. W. Margerum, and K. Hyde for helpful discussions. The help of Y. Kuroda of the Univeristy of Rochester NMR facility in obtaining the NMR data is also appreciated. Special thanks to F. S. Santillo and C. Randall for their help in obtaining the potentiometric titration and optical data for the complex. Finaly, we acknowledge the National Institutes of Health for support of this work (Grant CA 25112-01).

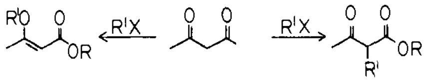
Palladium-Catalyzed 1,3-Oxygen-to-Carbon Alkyl Shifts. Basic Studies

Barry M. Trost* and Thomas A. Runge

Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received March 27, 1981*

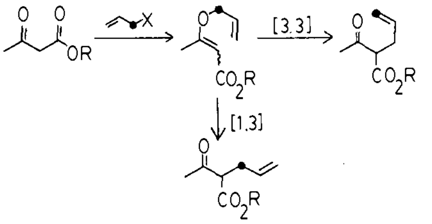
Abstract: [1-(Carbomethoxy)alkylidene]-5-vinyltetrahydrofurans which arise from preferential O-alkylation upon cyclization of β-keto esters smoothly rearrange to the desired C-alkylation products, 2-(carbomethoxy)-3-vinylcyclopentanones, with catalysis by Pd(0). With the methyl-substituted analogue, i.e., 2-(5-vinyltetrahydrofuran-2-ylidene)propionate, the major product is (*Z*)-2-(carbomethoxy)-2-methyl-3-vinylcyclopentanone. On the other hand, 1-(benzenesulfonyl)-1-(5-vinyltetrahydrofuran-2-ylidene)ethane rearranged to (*E*)-2-(benzenesulfonyl)-2-methyl-3-vinylcyclopentanone with high stereoselectivity. Conformational considerations account for these observations. This reaction constitutes the equivalent of a [1.3] rearrangement of an allyl vinyl ether and thus complements the normal [3.3] thermal rearrangement.

The chemistry of β-keto esters continues to play a major role in synthetic design. Unfortunately the major problem of O- vs. C-alkylation of such species plagues this important C–C bond-forming process (eq 1).[1] In the special case of allylating agents,



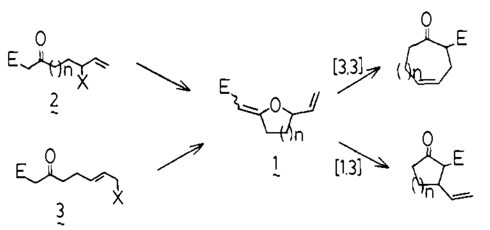
(1)

O-alkylation can be rectified by [3.3] sigmatropic rearrangement (eq 2).[2] Nevertheless, such a solution requires an allyl inversion.



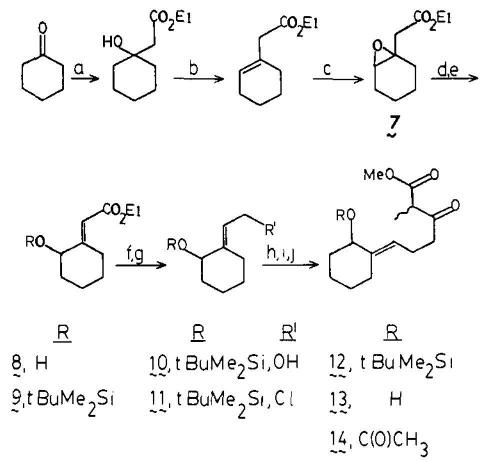
(2)

For substituted allyl systems, the substitution pattern of the product will be different, and most importantly, for intramolecular cases such as **1**, different ring sizes arise (eq 3).[3] This aspect is particularly troublesome since the problem of O- vs. C-alkylation is especially pronounced for substrates like **2** or **3** ($n = 1$) which lead exclusively to products of O-alkylation.[1,4]



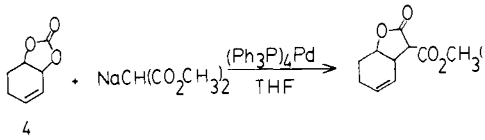
(3)

Scheme I. Synthesis of (*E*)-2-Acetoxy[[3-oxo-4-(carbomethoxy)pentyl]methylidene]cyclohexane



[a] Zn, $BrCH_2CO_2Et$, Et_2O/PhH, Δ_x, 1 h. [b] *p*TSA, Dean-Stark, 48 h, 76%. [c] MCPBA, CH_2Cl_2/0.5M $NaHCO_3$, 25 °C, 3 h, 80%. [d] *t*-BuOK, THF, −105 °C, 2 h. [e] *t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C, 2 h, 43% from 7. [f] *i*-Bu_2AlH, $PhCH_3$, −78–25 °C, 1.5 h, 96%. [g] HMPA, CCl_4, Et_2O, 0 °C, 1 h, 84%. [h] $CH_3COCH(CH_3)CO_2CH_3$, NaH, BuLi, 0.8M in THF, 0 °C, 1 h, 62%. [i] *n*-Bu_4NF, $PhCO_2H$, THF, 25 °C, 90 h. [j] AcCl, 4-DMAP, CH_2Cl_2, 25 °C, 1 h, 73% from **12**.

Work in our laboratories indicated the feasibility of vinyl carbonates such as **4** serving in palladium-catalyzed allylic al-



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(4)

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[1] E.g., Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. *Bull. Soc. Chim. Fr.* **1978**, *II*, 131. Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, 1602.

[2] Rhoads, S. J.; Raulins, N. R. *Org. React.* (*N.Y.*) **1975**, *22*, 1.

[3] Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 5813. Demole, E.; Enggish, P. *Chem. Commun.* **1969**, 264.

[4] Cf., Maxwell, E. N.; Titterington, D. *Tetrahedron Lett.* **1980**, 2123.

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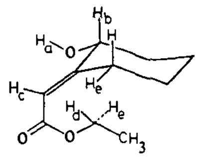
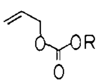
Table I. Eu(fod)$_3$-Induced ^{1}H NMR Shift Data (δ) for 8



	mol % Eu(fod)$_3$						total shift, Hz
	0	3.0	6.2	11.0	16.8	21.7	
H_a	2.36	3.80	6.24	10.05	14.75	18.98	1662
H_e	3.68	3.80	4.06	4.44	4.96	5.43	175
H_d	4.18	4.24	4.42	4.64	4.96	5.28	110
H_b	4.18	4.45	5.10	6.04	7.26	8.36	418
H_c	5.98	6.35	6.98	7.97	9.28	10.44	446

kylations.[5] The fact that palladium(0) complexes initiate the ionization of structures such as **5** suggested that vinylogous carbonates such as **6**, a structural feature embodied in **1**, may also serve as substrates for such complexes.[6] The regio- and stereocontrol offered by transition-metal templates stimulated our interest in pursuing such studies.[7-9]



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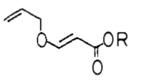
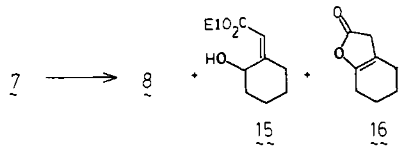


6

Preparation of Substrates. While the desired allylic acetates were expected to arise most readily from a secoalkylative four-carbon-chain extension procedure,[10] this methodology was in the early stages of development. It was deemed most efficient to concurrently synthesize the target molecules by more classical chemistry (Scheme I).

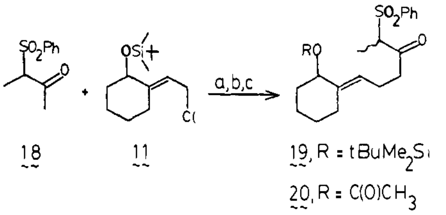
Synthesis of the epoxy ester **7** proceeded straightforwardly.[11,12] The stereoselective production of the allylic alcohol **8** proved troublesome (eq 5). Despite the investigation of a huge variety of different reaction conditions, the crude mixture was always contaminated with a small amount of the (*Z*)-allylic alcohol **15** and a significant amount of the lactone **16**. The latter appeared to be derived from alcohol **15**, since the ratio of **16**:**15** was directly proportional to the temperature and duration of the reaction. The optimum experimental conditions involved the addition of a solution of potassium *tert*-butoxide in tetrahydrofuran (THF) to a THF solution of epoxide **7** maintained at −105 °C with a liquid nitrogen–THF cooling bath. Allowing the mixture to warm to −90 °C permitted a maximum amount of alcohol **15** to convert to lactone **16** while still ensuring an optimum yield of the desired product **8**.



(5)

The mixture could be separated on a preparative scale by dry column chromatography, or thin-layer chromatography (TLC), to give pure **8** (40–45%). The stereochemistry as pictured was confirmed by a ^{1}H NMR study using Eu(fod)$_3$ (Table I). The olefinic proton (H_c) was shifted downfield to nearly the same extent (446 Hz) as the axial proton (H_b) (418 Hz, d of d, J = 10 and 4 Hz), indicating a similar interatomic distance from the site of complexation, the hydroxyl proton (H_a). The ester methylene proton (H_d) was shifted to a much lesser degree (110 Hz), approximately the same as the equatorial, allylic proton (H_e) (175 Hz, d of t, J = 12 and 5 Hz).

Scheme II. Synthesis of (*E*)-2-Acetoxy[(4-(benzenesulfonyl)-3-oxopentyl)methylidene]cyclohexane

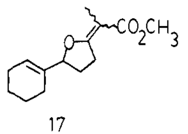


^{a} NaH, BuLi, 0.8 M in THF, 0 °C, 2.5 h, 60%. ^{b} n-Bu$_4$NF, PhCO$_2$H, THF, Δ_x, 48 h, 86%. ^{c} AcCl, 4-DMAP, CH$_2$Cl$_2$, 25 °C, 1 h, 91%.

On a large scale, the lactone **16** (26%) was distilled out of the crude reaction mixture from the opening of epoxide **7**. The remaining mixture of alcohols (54%, **8**:**15** = 85:15) was selectively protected with *tert*-butyldimethylchlorosilane and imidazole and distilled to yield pure **9** (43% from **7**). Reduction with i-Bu$_2$AlH at −78 °C and purification by distillation gave the pure allylic alcohol **10** (96%).

Conversion of **10** to the adduct **12** via the corresponding allylic bromide was unsuccessful due to the lability of the bromide. On the other hand, the corresponding chloride **11**, available by reacting the alcohol **10** with carbon tetrachloride and hexamethylphosphorus triamide[13] in 84% yield, was stable and easily handled. The alkylation involving **11** with the dianion of methyl methylacetoacetate[14] was highly concentration dependent. Because of insolubility of the initial sodium salt, a dilute THF solution was required for formation of the soluble lithio sodio dianion. Subsequently, the concentration was increased from 0.15 to 0.80 M with a stream of nitrogen. At this concentration, alkylation proceeded cleanly to give pure adduct **12** in 62% yield after 1 h at 0 °C.

So that protic hydrolysis conditions, which lead to competing formation of enol ether **17**, were avoided the silyl ether **12** was reacted with a large excess of anhydrous tetra-n-butylammonium fluoride (3–4 equiv) in the presence of benzoic acid for a prolonged period of time (60–90 h) at 25 °C to give the pure alcohol **13** (80%). Higher temperatures caused decarbomethoxylation. Acetylation of **13** using acetyl chloride with a stoichiometric amount of 4-(dimethylamino)pyridine in dichloromethane[15] on crude alcohol **13** yielded pure allylic acetate **14** (73% from **12** based on unrecovered starting material) after TLC.



17

A minor modification of this procedure provided an analogue to **14** in which the carbomethoxy substituent is replaced by benzenesulfonyl (Scheme II). Sodium benzenesulfinate was alkylated with ethyl iodide[16] in 60% and the resulting ethyl phenyl sulfone was acylated by sequential treatment with n-BuLi and

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(5) Masse, G., unpublished observations in these laboratories.

(6) For reviews on Pd chemistry, see: Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385; *Tetrahedron*, **1977**, *33*, 2615.

(7) For a preliminary report of a portion of this work, see: Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840.

(8) For related work, see: Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 3393, 1475.

(9) For a related independent Pt-catalyzed reaction, see: Balavoine, G.; Guibe, F. *Tetrahedron Lett.* **1979**, 3949. Balavoine, G.; Bram, G.; Guibe, F. *Nouv. J. Chim.* **1978**, *2*, 207.

(10) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910.

(11) Rathke, M. W. *Org. Reac. (N.Y.)* **1975**, *22*, 423. Shriner, R. L. *Ibid.* **1942**, *1*, 1.

(12) Falbe, J.; Schulze-Steinen, H. -H.; Korte, F. *Chem. Ber.* **1964**, *97*, 1096.

(13) Downie, I. M.; Lee, J. B.; Matough, M. F. S. *Chem. Soc., Chem. Commun.* **1968**, 1350.

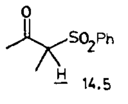
(14) Cf.; Sum, P. E.; Wieler, L. *Can. J. Chem.* **1977**, *55*, 996. Huckin, S. N.; Wieler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

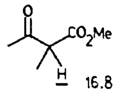
(15) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(16) Birnbaum, K.; Gaier, J. *Chem. Ber.* **1880**, *13*, 1274. Meek, J.; Fowler, J. *J. Org. Chem.* **1968**, *33*, 3422.

EtOAc[17] to give the β-keto sulfone **18** in 70% yield. Formation of the dianion, under identical conditions as were used on methyl methylacetoacetate, and alkylation with the allylic chloride **11** gave the adduct **19** in 60% yield as an inseparable mixture of diastereomers. The silyl ether **19** was converted to acetate **20** in 78% yield by treatment with 4 equiv of $(n\text{-Bu})_4NF{\cdot}PhCO_2H$ in refluxing THF for 48 h followed by acetylation with acetyl chloride and 4-(dimethylamino)pyridine in CH_2Cl_2.

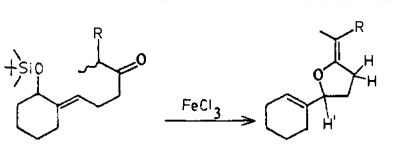
This 3-step procedure readily provided, in 47% overall yield from the common intermediate **11**, an analogue to ester **14** which possessed only slight electronic differences (pK_a = 14.5 vs. 16.8)[18]





but quite dramatic steric differences which can be estimated by the use of "*A* values" which are 1.2 for CO_2CH_3 and 2.5 for SO_2Ph.[19] Therefore, if the steric environment of the enolate carbon site is related to the stereochemistry of the alkylation, a substantial difference in results would be expected between the two systems.

The required alkylidenetetrahydrofurans **17** and **21** were most efficiently prepared from the allylic silyl ethers through the use of anhydrous $FeCl_3$ at 0 °C in Ac_2O (60%) or preferably CH_2Cl_2 (80%, eq 6). The dichloromethane avoids the side reaction of formation of the allylic acetate **20**. Ester **17** is produced as the pure *E* isomer in this reaction, but the alternate *Z* isomer was obtained in small amounts from attempted C-alkylation experiments (vide infra). The sulfone **21** was formed as an *E*:*Z* (86:14) mixture. In both cases, the *E*:*Z* mixture was easily separable by TLC, and the *Z* isomer was observed to thermally isomerize to the *E* isomer very readily. Therefore, for the *Z* isomers spectra were obtained and reactions were conducted as soon as possible following isolation.



(6)

12, R=CO$_2$Me 17, R=CO$_2$Me

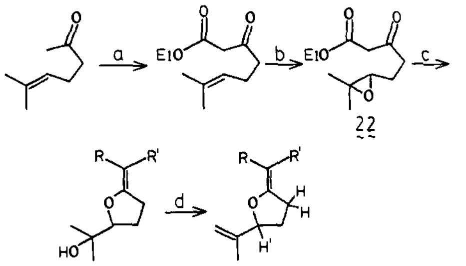
19, R=SO$_2$Ph 21, R=SO$_2$Ph

The assignment of the isomers is based on several key spectral features. In the 100-MHz ^1H NMR spectrum of (*Z*)-**17** the allylic methylene protons of the tetrahydrofuran ring resonate at δ 2.6 as a broad triplet, while in (*E*)-**17** they appear at δ 2.5–3.3 (m) due to the deshielding effect of the ester carbonyl. This effect is also observed in the expected opposite direction in the chemical shifts of the methine proton (H′) of the heteroatom ring: δ 4.6 in (*Z*)-**17** and δ 4.5 in (*E*)-**17**. A larger coupling constant between the vinyl methyl protons and the homoallylically related methylene protons when the groups are in a trans relationship (as in (*E*)-**17**, J = 1.0 Hz) compared to the cis orientation as in (*Z*)-**17** ($J \sim$ 0 Hz) further supports the assignment.

The 270-MHz ^1H NMR spectra of (*E*)- and (*Z*)-**21** shows the same trends. While the allylic methylene protons of (*Z*)-**21** occur as a pseudotriplet (δ 2.6), in (*E*)-**21** they are resolved and deshielded by the sulfone anisotropy: δ 3.05 (dt, 1 H, J = 17.5, 9.0 Hz) and 3.45 (ddd, 1 H, J = 17.5, 9.0, 4.0 Hz). The opposite shifts are found for H′ with δ 4.75 in (*Z*)-**21** and 4.52 in (*E*)-**21**. Finally, the homoallylic coupling of the vinyl methyl protons is observed only in (*E*)-**21** (1.0 Hz).

An alternate method of preparing the necessary alkylidene tetrahydrofuran skeleton is the intramolecular opening of an epoxide by a stabilized enolate to form the 5-membered ring and subsequent dehydration of the alcohol to form the olefin substituent. The desired substrate was prepared by means of chemistry initially explored by Trost and Vladuchick (Scheme III).[21] Commercially available 6-methyl-2-oxo-5-heptene was converted to the crude epoxide **22** which was cyclized with ethanolic sodium ethoxide to yield a readily separable mixture of the alcohols **23** (8%) and **24** (28%). Exclusive O-alkylation was observed in the formation of the 5-membered ring. Each alcohol was dehydrated separately to the corresponding olefins **25** and **26** by treatment with thionyl chloride in collidine. The reaction conditions were critical, since almost any other method gave a predominance of the internal, fully substituted olefin and even the furan derivative. This strategy did provide the required enol ethers **25** and **26** in four steps from an economical starting material and was quite adaptable to large scale.

Scheme III. Synthesis and Reaction of Ethyl [5-(Propen-2-yl)-tetrahydrofuran-2-ylidene]acetate

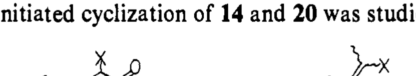


	R	R′	
23	CO$_2$Et	H	25
24	H	CO$_2$Et	26

[a] NaH, C(O)(OEt)$_2$, Et$_2$O, Δ_x, 7 h, 50%. [b] MCPBA, CH$_2$Cl$_2$, 0 °C, 1.5 h. [c] Na, EtOH, 25 °C, 0.5 h, 71% from olefin. [c] SOCl$_2$, collidine, 25 °C, 1 h, 18%.

Spectral proof of the isomeric assignments parallels that presented for **17** and **21**. While the allylic methylene protons of **25** are found at δ 2.6–2.9 as a triplet of multiplets, deshielding by the ester carbonyl in the *E* isomer **26** causes them to occur at δ 2.7–3.4 as a complex multiplet. The reverse effect is found for H′ with shifts of δ 4.9 in **25** and 4.7 in **26**. The shielding effect of the ring oxygen is seen in the shift of the vinyl methine of **25** (δ 4.67) as compared to **26** (δ 5.20). In addition, only compound **26** exhibits an allylic coupling between the vinyl methine and the allylic methylene (1.0 Hz), thereby demonstrating their trans relationship.

Initial Cyclization Studies. While attempts to cyclize substrates like **2** or **3** (eq 3) normally lead to O-alkylation, the effect of a transition-metal template might alter such a tendency. For that reason, palladium-initiated cyclization of **14** and **20** was studied.



(7)

14 X=CO$_2$CH$_3$ 17 X=CO$_2$CH$_3$

20 X=PhSO$_2$ 21 X=SO$_2$Ph

Nevertheless, the sodium or triethylammonium salts of **14** furnish only the products of O-alkylation with palladium(0) catalysts regardless of solvent (THF, Me_2SO, or toluene) or phosphine ligand. The sodium salt of **20** behaved similarly. This reaction constitutes an efficient preparation of these alkylidene tetrahydrofurans (**17** obtained in 87% yield as 46:54 *E*:*Z* mixture in toluene). Use of more covalent enolate derivatives such as the thallium (+) salt, the enol silyl ether, or the enol borinate still

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[17] Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1397.

[18] Extrapolated from the data of: Bordwell, F. G.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883.

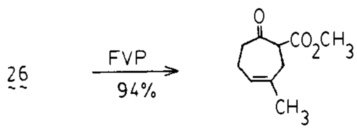
[19] (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 1990. (b) Also, see: Ozbal, H.; Zajac, Jr., W. W. *Tetrahedron Lett.* **1979**, 4821.

[20] Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.

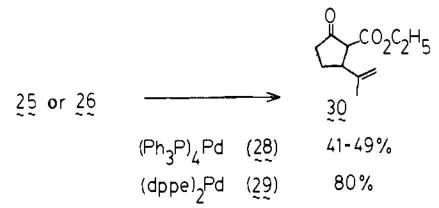
[21] Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148. Vladuchick, W. C. Ph.D. Thesis, University of Wisconsin, 1978.

produced only the product of O-alkylation. Thus a palladium leaving group does not alter the stereoelectronic bias for O-alkylation.

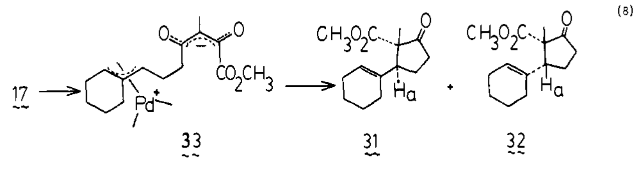
Rearrangement to 2-(Carboalkoxy)cyclopentanones. Reconstitution of **17** and **21** into cyclopentanones is a heretofore unknown process. Such allyl vinyl ethers normally undergo [3.3] sigmatropic rearrangement which, in the present case, produces 4-cyclohepten-1-ones (e.g., **27**), as is observed for **26**. The achievement of a 1,3 reorganization to cyclopentanones then would complement the more normal type of reactivity profile.



The leaving groups which have been demonstrated in the palladium-catalyzed allylic alkylation range from acetate[6] to benzenesulfonyl,[22] hydroxyl,[23,24] and phenoxy.[23] To the extent that the thermodynamic pK_a reflects the stability of the resultant anion from a conjugate acid and therefore the ability of such anion to serve as a leaving group, the fact that acetoacetic ester is less acidic by about 1–2 pK_a units than phenoxy[25] suggests that substrates such as **17** are on the borderline of reactivity. In the event, reaction of **25** or **26** with $(Ph_3P)_4Pd$ (**28**)[26] in refluxing DME led to an 88:12 *E*:*Z* mixture of the cyclopentanone **30**. With poorer leaving groups, the stability of the initial olefin–palladium(0) complex becomes more critical. A catalyst bearing sterically less demanding bidentate phosphine ligands such as **29**[27] dramatically improved the yield from ~50 to 80%.



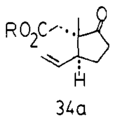
Surprisingly, initial attempts to rearrange **17**, purified only by TLC, failed due to the noticeable decomposition of the catalyst. Hypothesizing that catalyst decomposition was initiated by imperceptible ferric chloride impurities that survived the TLC purification, we purified by distillation substrate **17**, which successfully rearranged to the desired cyclopentanones **31** and **32** (77% yield) upon treatment with 6 mol % of **28** in Me_2SO at 120 °C. The reaction time decreased by a factor of 4 by use of the alternate catalyst **29**. The *Z* isomer of **17** rearranged approximately twice as fast as the *E* isomer to give the same product ratio. The dependence of the reaction rate on the olefin stereochemistry of the starting material shows the rate-determining step is the oxidative addition to the Pd(0) complex. The common zwitterionic intermediate **33**, depicted in the *E*,*E* conformation expected in a solvent such as Me_2SO and in the absence of an alkali metal cation (eq 8),[28] is formed more rapidly from the isomer of higher ground state energy. The facile isomerization of (*Z*)- to (*E*)-**17** (vide supra) identifies the former as the less stable. The stereochemistry of **31** and **32** follows from the ^1H and ^{13}C NMR spectra. The *E* isomer **31** shows the absorptions for the methyl group (^1H δ 1.04, ^{13}C δ 13.7) at significantly higher field than those for the corresponding *Z* isomer **32** (^1H δ 1.38, ^{13}C δ 20.5) due to steric compression. A similar trend had been reported for **34a,b**.[29,30] Another notable feature of **31** and **32** is the downfield shift of the methine proton (H_a) in **31** (δ 3.27) compared to that in **32** (δ 2.7), which can be attributed to the deshielding by the *cis*-carbomethoxy group in **31**.



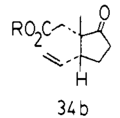
(8)

Table II. Solvent Effects on Rearrangement of **35** with $(dppe)_2Pd$ Catalyst

solvent	catalyst, mol %	temp, 0 °C	time, h	yield, %	*E*:*Z*
Me_2SO	6	50	5	79	22:78
Me_2SO/pyr	17	50	5	79	27:73
DMF	17	110	27	44–54	33:67
CH_3CN	15–37	81	22–27	57–79	33:67
$PhCH_3$	19	111	27	NR	
THF	28	66	7	NR	

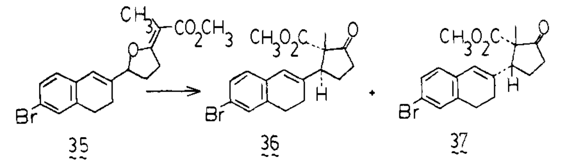


34a



34b

A similar mixture of stereoisomers (i.e., **36** and **37**) resulted in 79% yield from the rearrangement of **35**,[10] which required use of **29** as the catalyst. ^1H and ^{13}C spectra confirm the stereochemical assignments here, too. In analogy to the above cases, the quaternary methyl group of **36** (^1H δ 1.05, ^{13}C δ 14.0) appears at higher field than the corresponding absorptions for **37** (^1H δ 1.45, ^{13}C δ 19.8). In this example, the carbomethoxy groups exhibited sufficiently large differences to be useful with an expected converse relationship. Thus, the ^1H absorption for the protons of methyl ester (δ 3.72) and the ^{13}C absorption for the ester carbonyl carbon atom (δ 172.8) in **36** appear at lower field than the corresponding absorptions in **37** (δ 3.56 and 170.7, respectively).



Surprisingly, in each of these cases, the major product was the *Z* isomers **32** and **37**. To determine whether the geometry of the intermediate (π-allyl)palladium complex was the controlling factor, we conducted the rearrangement of **35** under conditions that accelerated the rate of syn–anti interconversion by ligating to palladium and thereby facilitating the π to σ palladium interconversion.[31-40] For example, use of Me_2SO as solvent[36] or

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[22] Trost, B. M.; Schmuff, N.; Miller, M. *J. Am. Chem. Soc.* **1980**, *102*, 5979.

[23] Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230.

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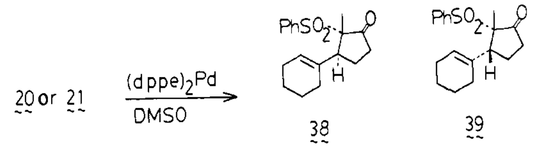
addition of pyridine,[40b] two conditions known to favor syn–anti interconversion, led to no significant difference in the E:Z ratio as summarized in Table II.

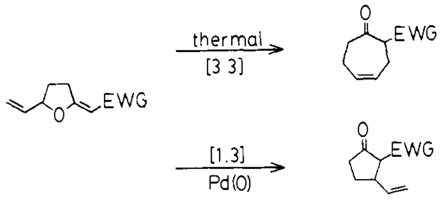
To determine whether the geometry of the intermediate anion was a factor in the observed stereochemistry, we conducted the rearrangement of (E)-**17** in the presence of several Lewis acid salts, and the composition of the reaction mixture was analyzed by GC (Table III). Without exception this caused a drastic decrease in the reaction rate and a corresponding increase in the predominance of the (Z)-cyclopentanone **32**. If the rate-determining step is, indeed, the oxidative addition (vide supra), this rate decrease would seem to be caused by Lewis acid–Lewis base complex formation between the added salt and the coordinatively unsaturated Pd species resulting in a loss of catalytic activity.

Dramatically different results were obtained when the carbomethoxy group was replaced by the much more bulky benzenesulfonyl group. Reaction of crystalline **21** with (dppe)$_2$Pd in Me$_2$SO at 130 °C gave the E-isomer **38** as the overwhelmingly major product (92%), with a small amount (8%) of the Z-isomer **39**, in 74% yield. Furthermore, the allylic acetate **20** could be directly transformed in a "one-pot" procedure to the C-alkylation products. Treatment of **20** with NaH in Me$_2$SO at 25 °C followed by addition of 6 mol % (dppe)$_2$Pd and raising the temperature to 130 °C gave **38** and **39** directly in the same ratio via the intermediacy of **21** as detected by both TLC and NMR analysis. One recrystallization of the crude reaction product from ethanol gave a sharp melting product which was enriched to a 98:2 E:Z ratio as determined by 270-MHz ^{1}H NMR spectroscopy. The stereochemical assignment rests upon the higher field absorptions in the ^{1}H and ^{13}C NMR spectra for the quaternary methyl group in the E series (^{1}H δ 1.11, ^{13}C δ 15.8) compared to the Z series (^{1}H δ 1.44, ^{13}C δ 21.1). To ensure that these reactions require palladium catalysis, we performed a control experiment by heating **21** in Me$_2$SO-d_6 at 130–140 °C and observing no change by NMR spectroscopy.



Discussion

The results demonstrate the ability of a transition metal to reorder the reactivity profile as shown in eq 9. While the nature of the electron-withdrawing group (EWG) remains to be defined, both carbomethoxy and benzenesulfonyl are excellent. Thus, the utility of 2-alkylidene-5-vinyltetrahydrofurans as synthetic intermediates increases substantially, these being precursors to both cycloheptenones and cyclopentanones.



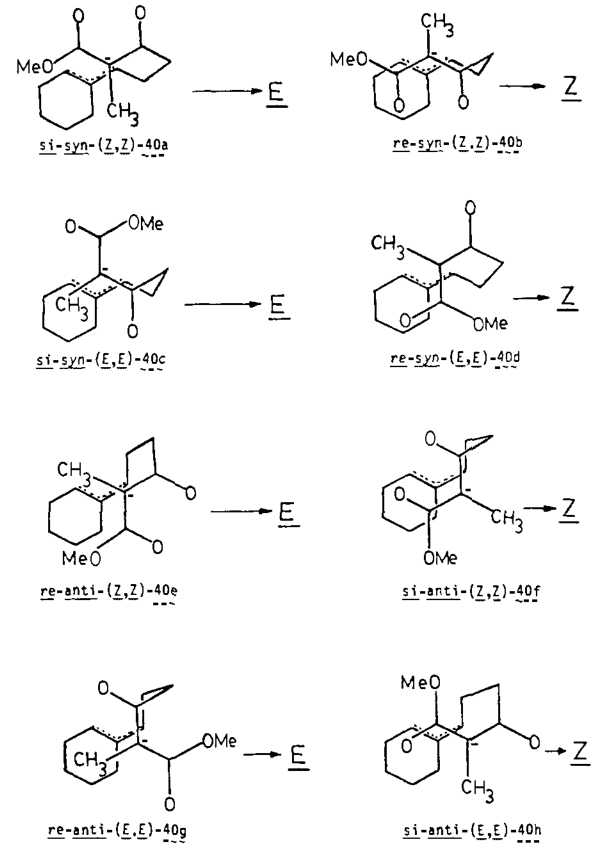
(9)

The unusual ring stereochemistry can be understood in terms of the possible transition states for the rearrangement. Scheme IV illustrates all of the possible transition states for formation of **31** and **32**. The Pd atom and its ligands have been omitted for clarity but lie below the plane of the π-allyl moiety. There are three variables in the selection of a transition state: (1) the geometry of the β-keto ester enolate, (2) the geometry of the (π-allyl)palladium complex, and (3) the orientation of the enolate relative to the π-allyl moiety. Study of Scheme IV reveals that the third variable is the controlling factor in the stereochemistry.

Table III. Reaction of (E)-17 with 6% (Ph$_3$P)$_4$Pd and 1.0 Equiv Lewis Acid Salt

				GC product analysis, %		
salt	solvent	temp, °C	time, h	(Z)-**17**	**31** (E)	**32** (Z)
	Me$_2$SO	120	40		39	39
	DMF	120	120	31	27	42
LiBF$_4$	Me$_2$SO	110	20	77	7	16
LiOAc	Me$_2$SO	120	44	55	16	29
LiOAc	CH$_3$CN	82	67	71	9	20
ZnCl$_2$	CH$_3$CN	82	20	100		
ZnCl$_2$	DMF	100	94	22	17	60
ZnCl$_2$	HMPA	100	94	different products		

Scheme IV. Transition States for Formation of **31** and **32**



Consideration of the first four structures, **40a–d**, demonstrates the relative insignificance of the enolate geometry. Alkylation of the *si* face of the (Z,Z)-enolate (**40a**) and of the *si* face of the (E,E)-enolate (**40c**) both result in (E)-**31**. Alternately, either of the two possible enolates may give rise to (Z)-**32** via **40b** and **40d**. Furthermore, when the three-dimensional steric requirements of the substituents at the α position of the β-keto ester are taken into account, it can be seen that **40b** is kinetically preferred over **40a** and **40d** which, in turn, is preferred over **40c**. The preferred conformation is the one which places the larger group (CH$_3$, A = 1.7) in a less sterically crowded position (i.e., away from the cyclohexene ring) than the smaller group (CO$_2$Me, A = 1.2).[19a] Thus, alkylation of either the (Z,Z)- or (E,E)-enolates are expected to give rise preferentially to (Z)-**32**. This is exactly the result observed experimentally since rearrangement in Me$_2$SO alone would be expected to involve the (E,E)-enolate almost exclusively, while reaction with an equivalent amount of Lewis acid salt added should involve mostly alkylation via the (Z,Z)-enolate.

For examination of the effect of the geometry of the π-allyl complex on the stereochemical outcome, another set of four structures should be examined, e.g., **40a,b,e,f**. But first, it must

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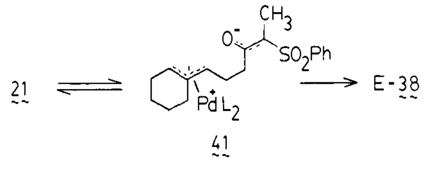
(40) (a) Faller, J. W.; Incorvia, M. J.; Thomson, M. E. *J. Am. Chem. Soc.* **1969**, *91*, 518. (b) Faller, J. W.; Thomson, M. E.; Mattina, M. J., *Ibid.*, **1971**, *93*, 2642. (c) Faller, J. W.; Mattina, M. J. *Inorg. Chem.* **1972**, *11*, 1296.

be noted that the syn conformation of the (π-allyl)palladium complex is normally considered to be favored. However, the presence of a 2-substituent on the allyl group (a C–C bond of the cyclohexene ring in **40**) offsets this preference by introducing an unfavorable eclipsing interaction between the enolate side chain and the C–C bond of the cyclohexene ring in *syn*-**40**.[40] Therefore, the thermodynamic preference of this particular (π-allyl)palladium complex is difficult to know, and it is likely that both conformations are populated to a significant degree.

Regardless, Scheme IV shows that alkylation of the *si* face of the (*Z*,*Z*)-enolate by the syn complex (**40a**) has approximately the same steric interactions as alkylation of the *re* face of the (*Z*,*Z*)-enolate by the anti complex (**40e**), and both transition states give rise to (*E*)-**31**. Alternately, either of the two possible complexes may give rise to (*Z*)-**32** by the sterically similar **40b** and **40f**. Thus, even if one complex were preferred greatly over the other, it would still be the third variable, the orientation of the enolate relative to the complex, which determined the product composition, and this orientation is dictated by the steric differences between the two substituents α to the carbonyl group, i.e., methyl and carbomethoxy.

The synthesis and rearrangement of the analogue to **17** where SO_2Ph replaces CO_2Me (i.e., **21**) was conceived as a way to further prove all of the previous steric arguments. It was reasoned that this compound would undergo the 1,3-O-to-C Pd-catalyzed rearrangement via a transition state, **41**, with opposite steric preferences from that of **40** (eq 10). This assumption is based



(10)

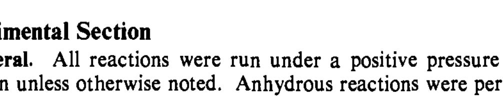
on the fact that the "*A* value" of SO_2Ph is 2.5,[19] which is significantly larger than that for CH_3 ($A = 1.7$). Indeed, the almost exclusive formation of the *E* isomer in this case nicely confirmed these predictions.

The success of the rearrangement of **35** is particularly noteworthy. Because of the well-known and facile oxidative addition of aryl bromides to Pd(0) complexes (eq 11),[41] ionization of the

$$ArBr + L_4Pd \rightarrow ArPdBrL_2 \qquad (11)$$

allylic system might have been circumvented by a more rapid insertion into the aryl–bromine bond. In main group chemistry, such metal–halogen exchanges are normally much faster than even carbonyl addition. Nevertheless, a high chemoselectivity is seen, and only the isomerization products can be detected.

The sulfone case is particularly intriguing because of the utility of β-keto sulfones in synthesis.[42] One particularly useful aspect with respect to control of ring stereochemistry is regio- and stereocontrolled alkylation at the α position, as illustrated in eq 12. Further implications of this basic new process in synthesis are considered in the accompanying manuscript.



(12)

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen unless otherwise noted. Anhydrous reactions were performed in flame-dried glassware which was cooled under nitrogen. Anhydrous solvents were transferred by oven-dried syringe. Solvents were distilled before use: hexamethylphosphoric triamide (HMPA), dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), pyridine (pyr), benzene (C_6H_6), hexane (C_6H_{14}), and pentane (C_5H_{12}) from calcium hydride; diethyl ether (Et_2O), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), 1,4-dioxane, and toluene ($PhCH_3$) from sodium benzophenone ketyl; *N*-methylpyrrolidinone (NMP) from barium oxide; thionyl chloride ($SOCl_2$) from triphenyl phosphite; acetone from K_2CO_3; methanol (MeOH) from magnesium. Solvents for use in $(dppe)_2Pd$-catalyzed reactions were deoxygenated by flushing with argon for 20–30 min. All palladium(0) catalysts were transferred under nitrogen atmosphere. Other reagents were used as obtained commercially. The term "in vacuo" refers to the removal of solvent on a Buchi-Brinkman Rotoevaporator at water aspirator pressure followed by evacuation of the flask (0.1 mm) for 15–30 min, except as noted otherwise for volatile compounds. Silica gel (Macherey-Nagel PNV_{254}) was used for analytical and all preparative (1.5 mm thick) thin-layer chromatography (TLC) and activated before use by heating at 120 °C for 2 h. Precoated, high-resolution analytical plates (Macherey-Nagel Nano-Plates SIL-$20UV_{254}$) were also employed. Typical loadings on preparative plates were as follows: up to 80 mg on 20 × 10 cm; 80–200 mg on 20 × 20 cm; 200–450 mg on 20 × 40 cm. Column chromatography was accomplished with Grace (grade 62, 60–200 mesh) silica gel and Fisher (60–100 mesh) Florisil adsorbent. Removal of the material from silica gel was accomplished by successive washings with ethyl acetate (EtOAc). High-pressure liquid chromatography (HPLC) was performed analytically (up to 2 mg) on a Waters M6000 instrument with a μ-Porasil silica gel column (10 μm, Waters p/n 27477) or preparatively on a Waters Prep 500 instrument with a self-packed, semiprep (2.5 × 30 cm, μ-Porasil, 37–75 μm, 2–500 mg) silica gel column and a PrepPak-500 silica gel column (75 μm, 1–10 g). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are uncorrected. Gas chromatography was performed on a Varian Aerograph, Model 90P.

Proton (^1H) NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) instrument unless otherwise noted that a Bruker WH-270 (270 MHz) spectrometer was used. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (Me_4Si). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; b or br, broad. Coupling constants are reported in hertz (Hz). Infrared spectra (IR) were determined in the indicated solvent in 1-mm-thick solution cells on a Perkin-Elmer 267 or a Beckman AccuLab 7 instrument and are reported in cm^{-1}. Carbon (^{13}C) NMR spectra were determined on a Jeolco FX-60 (15.4 MHz) or a Jeolco FX-200 (50.1 MHz) spectrometer. Chemical shifts are reported in δ units, and splitting patterns are designated as with ^1H NMR. Mass spectra (MS) were obtained on an AEI-902 instrument at an ionizing current of 98 mA and an ionizing voltage of 70 eV unless otherwise noted. Data are reported as *m*/*e* (%). Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

Preparation of (*E*)-[(Carboethoxy)methylidene]-2-hydroxycyclohexane (8). Due to the very low temperatures required for this reaction, the procedure was repeated several times on a smaller scale to avoid localized heating. The combined products were then purified.

To a vigorously stirred solution of the epoxide 7 (10.08 g, 0.55 mol), obtained in 61% overall yield from cyclohexanone in 115 mL of dry THF maintained under nitrogen at −109 °C with a THF–liquid nitrogen cooling bath was added a solution of potassium *tert*-butoxide (6.22 g, 0.55 mol) in 25 mL of dry THF in dropwise fashion. The solution was maintained at −107 to −103 °C during addition and for 1 h afterwards, allowed to warm to −88 °C over 30 min, maintained there for 30 min, and poured rapidly into a mixture of ether (100 mL) and saturated aqueous ammonium chloride solution (100 mL) maintained at 0 °C. The aqueous layer was extracted with ether (50 mL), and the combined organic phases were washed with brine (100 mL) and dried over sodium sulfate. The solvent was removed in vacuo to yield a clear, pale yellow oil (8.99 g), which NMR spectroscopy showed to be a mixture of the lactone **16** (23%) and the allylic alcohols **8** and **15** (77%, $E{:}Z = 88{:}12$). The crude products from all of the runs were combined, and the lactone was distilled away (28.5 g, 26%, 34–53 °C (0.01–0.02 mm)), leaving a yellow oil (49 g, 54%) which NMR showed to be only the two alcohols ($E{:}Z = 85{:}15$).

TLC separation using 33% ethyl acetate in hexane (v/v) gave pure **8** (46%, R_f 0.25): NMR (CCl_4) 1.3 (t, 3 H, $J = 7$ Hz), 1.2–2.2 (m, 7 H), 2.9 (bs, 1 H), 3.62 (d of m, $J = 12$ Hz), 4.1 (q, 2 H, $J = 7$ Hz), 4.1 (m, 1 H), 5.84 (s, 1 H); NMR ($CDCl_3$, 11 mol % $Eu(fod)_3$) 0.7 (bs, 3 H, fod), 1.42 (t, 3 H, $J = 8$ Hz), 1.8–3.4 (m, 7 H), 4.44 (d of t, 1 H, $J = 12$, 3 Hz, H_e), 4.64 (q, 2 H, $J = 8$ Hz, H_d), 6.04 (d of d, 1 H, $J = 10$, 4 Hz, H_b), 7.97 (s, 1 H, H_c), 10.05 (bs, 1 H, H_a); IR (CCl_4) 3600, 3550–3300, 1715, 1655 cm^{-1}; MS (all-glass, heated inlet) 184 (43), 166 (59), 155 (14), 139 (56), 138 (100), 127 (26), 110 (34), 109 (35), 99 (27), 93 (49), 81 (42), 67 (44), 55 (56), 41 (52), 29 (42), 28 (31), 18 (90) (calcd for $C_{10}H_{16}O_3$, 184.1099; found, 184.1094). Anal. Calcd for

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(41) Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Commun.*, **1968**, 6. Fitton, P.; McKeon, J. E.; Ream, B. C., *Ibid.*, **1969**, 370. Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287. Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146; *Org. React.* (*N.Y*), in press.

(42) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363; *Acc. Chem. Res.* **1978**, *11*, 453. Magnus, P. *Tetrahedron*, **1977**, *33*, 2019.

$C_{10}H_{16}O_3$: C, 65.18; H, 8.76; mol wt, 184.1099. Found: C, 65.22; H, 8.71; mol. wt, 184.1094.

Preparation of (*E*)-2-(*tert*-Butyldimethylsiloxy)[(1-carboethoxy)-methylidene]cyclohexane (9). To a stirred solution of **8**:**15** (47 g, 0.25 mol, 85:15) and imidazole (36.44 g, 0.53 mol) in 70 mL of dry dimethylformamide (DMF) at 25 °C under nitrogen was added *tert*-butylchlorodimethylsilane (43.0 g, 0.28 mol) under a stream of nitrogen. The mixture was stirred 2 h and partitioned between water (50 mL) and pentane (100 mL). The aqueous phase was extracted with pentane (50 mL), and the combined organic layers were washed with water (5 × 20 mL) and dried over magnesium sulfate. The solvent was removed in vacuo, and reduced-pressure distillation yielded pure **9** (61.66 g, 81%, 43% from **7**, 84–88 °C (0.03–0.05 mm)): NMR (CCl_4) 0.00 (s, 6 H), 0.87 (s, 9 H), 1.20 (t, 3 H, J = 7 Hz), 1.1–2.1 (m, 7 H), 3.47 (d of m, 1 H, J = 12 Hz), 4.02 (q, 2 H, J = 7 Hz), 4.0 (m, 1 H), 5.72 (bs, 1 H); IR (CCl_4) 1725, 1655 cm^{-1}; MS (all-glass, heated inlet) 298 (1.5), 284 (1.1), 283 (5.2), 253 (29), 241 (43), 213 (33), 195 (58), 167 (18), 151 (17), 121 (49), 103 (53), 93 (11), 91 (12), 85 (15), 77 (19), 75 (100), 72 (64), 59 (18), 45 (17), 41 (18), 36 (25), 29 (22), 28 (62), 27 (33), 18 (12), 15 (3.7) (calcd for $C_{16}H_{30}Si$, 298.1964. Found, 298.1947).

Preparation of (*E*)-2-(*tert*-Butyldimethylsiloxy)[(hydroxymethyl)-methylidene]cyclohexane (10). To a stirred solution of **9** (51.17 g, 0.17 mol) in 95 mL of dry toluene at −78 °C under nitrogen was added a solution of diisobutylaluminum hydride in hexane (0.88 M, 430 mL, 0.38 mol) over 35 min. The mixture was stirred at −78 °C for 1 h, warmed to 25 °C, and stirred for 30 min. After cooling to −78 °C, the reaction was carefully quenched with methyl alcohol (22 mL) and warmed to 25 °C. Upon recooling to 0 °C, the aluminum salts were precipitated by careful addition of saturated aqueous sodium sulfate solution (40 mL). Ether (600 mL) and anhydrous sodium sulfate was added, and the mixture was stirred 20 min, filtered, and dried over sodium sulfate. The solvents were removed in vacuo, and Kugelrohr distillation gave pure **10** (42.20 g, 96%, 95–105 °C (0.005 mm)) as a viscous, colorless oil: NMR (CCl_4) 0.00 (s, 6 H), 0.85 (s, 9 H), 1.3–2.0 (m, 7 H), 2.05 (bs, 1 H), 2.3–2.6 (m, 1 H), 3.9–4.05 (m, 1 H), 4.02 (d, 2 H, J = 7 Hz), 5.46 (t, 1 H, J = 7 Hz); IR (CCl_4) 3620, 3580–3260 cm^{-1}; MS (20 eV) 256, 255 (0.2), 254 (0.6), 241 (1.3), 226 (1.7), 225 (9), 201 (14), 200 (14), 199 (81), 198 (10), 197 (35), 181 (22), 171 (2), 167 (3), 157 (3), 155 (4), 131 (14), 123 (5), 117 (5), 109 (18), 107 (25), 105 (14), 79 (25), 75 (100), 73 (12), 67 (10), 57 (6) (calcd for $C_{14}H_{28}O_2Si$, 256.1858; found, 256.1853).

Preparation of (*E*)-2-(*tert*-Butyldimethylsiloxy)[(chloromethyl)-methylidene]cyclohexane (11). To a stirred solution of **10** (2.69 g, 10.50 mmol) and distilled carbon tetrachloride (2.42 g, 15.76 mmol) in 40 mL of dry ether at 0 °C under nitrogen was added distilled hexamethylphosphorus triamide (1.89 g, 11.56 mmol) dropwise. The mixture was stirred 1.5 h, gradually warmed to 25 °C, added to water (40 mL), separated, and extracted with ether (40 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL) and dried over magnesium sulfate. The solvent was removed in vacuo, and Kugelrohr distillation yielded pure **11** (2.42 g, 84%, 80–90 °C (0.15 mm)): NMR (CCl_4) 0.05 (s, 6 H), 0.93 (s, 9 H), 1.3–2.1 (m, 7 H), 2.4–2.7 (m, 1 H), 4.03 (m, 2 H, J = 8 Hz), 5.6 (t, 1 H, J = 8 Hz); IR (CCl_4) 1660, 1455, 1440 cm^{-1}; MS (all-glass, heated inlet) 276 (0.4), 274 (1.4), 240 (2.6), 239 (13), 219 (25), 218 (13), 217 (63), 181 (7), 175 (8), 151 (14), 149 (36), 135 (6), 125 (6), 123 (11), 109 (9), 108 (8), 103 (39), 95 (14), 93 (33), 91 (14), 81 (17), 79 (62), 75 (100), 73 (60), 67 (14), 59 (14), 57 (25), 47 (11), 45 (18), 43 (10), 41 (26), 39 (10), 29 (18), 28 (28), 27 (11), 18 (44) (calcd for $C_{14}H_{27}OClSi$, 274.1520; found, 274.1514).

Preparation of (*E*)-2-(*tert*-Butyldimethylsiloxy)[(4-(carbomethoxy)-3-oxopentyl)methylidene]cyclohexane (12). To a manually stirred slurry of sodium hydride (63% oil dispersion, 0.34 g, 9.06 mmol) in 17 mL of dry THF at 0 °C under nitrogen was slowly added methyl methylacetoacetate (1.01 g, 7.75 mmol). The thick grey slurry was stirred 30 min, and a solution of *n*-butyllithium in hexane (1.57 M, 5.4 mL, 8.48 mmol) was added. The clear, yellow solution was stirred 30 min, and the solvent was evaporated with a stream of nitrogen over 60 min at 0 °C. Dry THF (2 mL) was added, and the allylic chloride **11** (1.00 g, 3.64 mmol) was added to the stirred mixture at 0 °C under nitrogen. The mixture was stirred 45 min, and saturated aqueous ammonium chloride solution (10 mL) was cautiously added. The mixture was partitioned between ether (20 mL) and water (10 mL) and extracted with ether (20 mL). The combined organic layers were washed with water (3 × 20 mL) and dried with sodium sulfate. Preparative TLC, using 20% ethyl acetate in hexane (v/v), yielded pure **12** (0.83 g, 62%, R_f 0.5): NMR (CCl_4) −0.05 (s, 3 H), −0.02 (s, 3 H), 0.86 (s, 9 H), 1.2 (d, 3 H, J = 7 Hz), 1.1–2.05 (m, 8 H), 2.1–2.3 (m, 2 H), 2.3–2.5 (m, 2 H), 3.35 (q, 1 H, J = 7 Hz), 3.64 (s, 3 H), 3.92 (bm, 1 H), 5.17 (t, 1 H, J = 7 Hz); IR (CCl_4) 3030, 2940, 2870, 1740, 1720, 1450, 1360, 1330, 1250, 1220, 1130, 1110, 1090, 1050, 1030, 910, 840, 670 cm^{-1}; MS (50 eV) 368, 367 (0.03), 337 (7), 311 (46), 279 (10), 251 (6), 223 (10), 205 (8), 188 (28), 187 (55), 173 (8), 159 (16), 131 (12), 121 (15), 107 (54), 91 (16), 89 (27), 79 (31), 75 (100), 73 (81), 59 (28), 57 (18), 43 (10), 41 (22), 39 (6) (calcd for $C_{20}H_{36}O_4Si$, 368.2383; found, 368.2372).

Preparation of (*E*)-2-Hydroxy[(4-(carbomethoxy)-3-oxopentyl)-methylidene]cyclohexane (13). To a stirred mixture of silyl ether **12** (104.9 mg, 0.28 mmol) and benzoic acid (122.5 mg, 1.00 mmol) in 0.4 mL of dry THF at 0 °C under nitrogen was added a solution of tetra-*n*-butylammonium fluoride (240.0 mg, 0.92 mmol) in 0.4 mL of dry THF. The mixture was stirred at 25 °C for 90 h and partitioned between ether (15 mL) and saturated aqueous sodium bicarbonate solution (15 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. The solvent was removed in vacuo to yield a clear, pale yellow oil (66.6 mg, 92%) which NMR showed to be a mixture of starting material (10%) and product **13** (90%). TLC purification using 12% ether in chloroform (v/v) gave **13** (70%, R_f 0.3): NMR (CCl_4) 1.15 (d, 3 H, J = 7 Hz), 1.1–1.9 (m, 8 H), 2.0–2.3 (m, 2 H), 2.3–2.55 (m, 2 H), 2.52 (bs, 1 H), 3.3 (q, 1 H, J = 7 Hz), 3.58 (s, 3 H), 3.78 (bm, 1 H), 5.09 (t, 1 H, J = 7 Hz); IR (CCl_4) 3630, 3600–3300, 1745, 1720, 1655, 1620 cm^{-1}; MS 254 (2), 237 (10), 236 (77), 205 (10), 156 (12), 149 (49), 148 (62), 144 (20), 143 (18), 131 (20), 130 (71), 125 (72), 124 (76), 122 (19), 121 (100), 120 (20), 115 (48), 112 (24), 111 (47), 109 (11), 107 (36), 106 (19), 98 (43), 97 (21), 95 (18), 93 (19), 91 (13), 88 (32), 83 (19), 81 (34), 80 (13), 79 (36), 69 (14), 67 (38), 59 (23), 57 (23), 56 (20), 55 (66), 43 (33), 41 (20) (calcd for $C_{14}H_{22}O_4$, 254.1518; found, 254.1514).

Preparation of (*E*)-2-Acetoxy[(4-(carbomethoxy)-3-oxopentyl)-methylidene]cyclohexane (14). To a stirred mixture of crude **13** (66.6 mg, 0.26 mmol, **13**:**12** = 90:10) and 4-(dimethylamino)pyridine (32.6 mg, 0.27 mmol) in 0.2 mL of dry dichloromethane at 25 °C under nitrogen was added acetyl chloride (26.1 mg, 0.37 mmol). The mixture was stirred 1 h, partitioned between ether (10 mL) and 3 N aqueous hydrochloric acid solution (10 mL), and extracted with ether (10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (2 × 10 mL) and brine (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo. TLC, using 40% ethyl acetate in hexane (v/v), gave pure silyl ether **12** (9 mg, 9%, R_f 0.75) and pure acetate **14** (56.2 mg, 73% from **12** based on unrecovered starting material, R_f 0.5): NMR (CCl_4) 1.1 (d, 3 H, J = 7 Hz), 1.2–1.7 (m, 6 H), 1.83 (s, 3 H), 1.95–2.55 (m, 6 H), 3.25 (q, 1 H, J = 7 Hz), 3.67 (s, 3 H), 4.97 (bm, 1 H), 5.12 (t, 1 H, J = 7 Hz); IR (CCl_4) 1750–1720, 1650 cm^{-1}; MS 296 (0.09), 278 (1.8), 254 (6), 237 (22), 221 (4), 205 (8), 178 (7), 177 (6), 158 (10), 149 (24), 148 (22), 143 (6), 135 (9), 131 (11), 125 (10), 124 (42), 121 (48), 120 (13), 115 (16), 111 (15), 109 (10), 107 (23), 106 (16), 95 (10), 93 (22), 91 (24), 81 (10), 79 (49), 77 (19), 67 (33), 65 (11), 59 (33), 57 (23), 56 (11), 55 (42), 53 (16), 45 (10), 43 (100), 42 (11), 41 (45), 39 (22), 29 (25), 28 (31), 27 (27), 15 (36) (calcd for $C_{16}H_{24}O_5$, 296.1624; found, 296.1612).

Preparation of Methyl (*E*)-2-[5-(cyclohex-1-en-1-yl)tetrahydrofuran-2-ylidene]propionate (17). Anhydrous ferric chloride was prepared by heating in vacuo (70 °C (0.2 mm)) overnight. To a stirred solution of silyl ether **12** (60.9 mg, 0.17 mmol) in 0.4 mL of acetic anhydride at 0 °C under nitrogen was added dry ferric chloride (3.0 mg, 0.02 mmol) under a stream of nitrogen. The mixture was stirred 35 min, partitioned between ether (10 mL) and 3 N aqueous hydrochloric acid solution (10 mL), and washed with saturated aqueous sodium bicarbonate solution (2 × 10 mL). The combined aqueous phases were extracted with ether (10 mL). The combined organic layers were washed with brine (10 mL) and dried over magnesium sulfate. The solvent was removed in vacuo, and TLC, using 25% ethyl acetate in hexane (v/v), yielded **17** (21.9 mg, 56%, R_f 0.5) as a clear, yellow oil. Microdistillation (80 °C (0.005 mm)) gave pure **17** as a colorless oil: NMR (CCl_4) 1.3–1.7 (m, 4 H), 1.62 (t, 3 H, J = 1 Hz), 1.7–2.1 (m, 6 H), 2.5–3.3 (m, 2 H), 3.51 (s, 3 H), 4.5 (bt, 1 H, J = 7 Hz), 5.55 (bm, 1 H); IR (CCl_4) 1700, 1635, 1440 cm^{-1}; MS 236 (38), 205 (16), 204 (19), 189 (6), 187 (5), 177 (19), 176 (16), 159 (9), 149 (12), 148 (13), 141 (18), 131 (7), 123 (11), 133 (19), 121 (18), 115 (72), 109 (21), 107 (31), 105 (10), 97 (10), 95 (12), 93 (23), 91 (25), 85 (16), 83 (46), 81 (37), 80 (12), 79 (50), 77 (23), 69 (19), 68 (16), 67 (28), 65 (12), 59 (22), 57 (13), 56 (10), 55 (47), 53 (28), 51 (10), 45 (10), 44 (14), 43 (100), 42 (16), 41 (64), 40 (10), 39 (35) (calcd for $C_{14}H_{20}O_3$, 236.1412; found, 236.1412). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.07; H, 8.54.

Preparation of (*E*)-2-(*tert*-Butyldimethylsiloxy)[(4-(benzenesulfonyl)-3-oxopentyl)methylidene]cyclohexane (19). To a stirred slurry of NaH (283.5 mg, 11.81 mmol) in 20 mL of dry THF at 0 °C was carefully added *β*-keto sulfone **18** (2.26 g, 10.67 mmol). The cloudy yellow solution was stirred at 25 °C for 2 h and cooled to 0 °C, and a solution of *n*-butyllithium in hexane (1.5 M, 7.5 mL, 11.25 mmol) was added. The deep orange-red, heterogeneous mixture was stirred at 0 °C for 1 h, and the solvent was evaporated with a stream of nitrogen over

90 min at 25 °C. The resulting red solid was stirred at 0 °C with 7 mL dry THF, and the allylic chloride **11** (2.45 g, 8.93 mmol) was added. The viscous, orange-red solution was stirred 2.5 h, and saturated aqueous NH_4Cl solution (20 mL) was cautiously added. The mixture was partitioned between ether (40 mL) and H_2O (20 mL) and extracted with ether (40 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (40 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. Column chromatography, using 10% EtOAc in hexane (v/v), yielded **19** (2.28 g, between 1000 and 1300 mL, 57%) which was pure by analytical TLC and shown to be a diastereomeric mixture by NMR: (CCl_4) -0.07 (s, 3 H), -0.05 (s, 3 H), 0.85 (s, 9 H), 1.2 (d, 3 H, *J* = 7 Hz), 1.0–3.0 (m, 12 H), 3.9 (m, 1 H), 4.0 (q, 1 H, *J* = 7 Hz), 5.0 (bt, 0.15 H, *J* = 7 Hz), 5.2 (bt, 0.85 H, *J* = 7 Hz), 7.35–7.75 (m, 5 H); IR (CCl_4) 1720, 1590, 1470, 1460, 1450, 1330, 1310, 1250, 1220, 1200, 1150, 1110 cm^{-1}; MS 436 (0.7), 396 (13), 394.5 (100), 310 (5), 270 (29), 252 (50), 201 (13), 200 (72), 178 (27), 160 (20), 144 (11), 136 (31), 170.5 (51), 97.5 (12), 79 (16), 75 (71), 73 (35), 57 (12) (calcd for $C_{24}H_{38}O_4SiS$, 450.2260; found, 450.2265).

Preparation of (*E*)-2-Hydroxy[(4-(benzenesulfonyl)-3-oxopentyl)-methylidene]cyclohexane. To a stirred mixture of silyl ether **19** (205.2 mg, 0.46 mmol) and benzoic acid (223.6 mg, 1.83 mmol) in 1.4 mL of dry THF at 25 °C, was added *n*-Bu_4NF (494.0 mg, 1.88 mmol). The mixture was refluxed 21 h, neutralized with saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with ether (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Preparative TLC, using two elutions with 40% acetone in hexane (v/v), yielded the alcohol (131.6 mg, R_f 0.4, 86%) as a clear, pale yellow oil, which was pure by analytical TLC and shown to be a diastereomeric mixture by NMR: (CCl_4) 0.9–3.0 (m, 16 H), 3.6–3.9 (m, 1 H), 4.0 (bq, 1 H), 4.85 (bt, 0.2 H, *J* = 7 Hz), 5.1 (bt, 0.8 H, *J* = 7 Hz), 7.1–7.9 (m, 5 H); IR (CCl_4) 3600, 3600–3300, 1715, 1445, 1320, 1150 cm^{-1}; MS (30 eV) 336 (0.2), 318 (1), 305 (1), 273 (1), 252 (1), 235 (1), 226 (1), 212 (14), 195 (21), 194 (29), 177 (100), 176 (13), 159 (10), 151 (13), 149 (11), 143 (14), 135 (22), 133 (17), 126 (14), 125 (86), 124 (54), 121 (29), 111 (87), 109 (16), 107 (14), 105 (12), 98 (18), 97 (47), 96 (12), 95 (12), 93 (20), 91 (16), 84 (24), 81 (35), 79 (16), 77 (12), 71 (16), 69 (18), 67 (25), 57 (70), 55 (35), 43 (55) (calcd for $C_{18}H_{24}O_4S$, 336.1395; found, 336.1395).

Preparation of (*E*)-2-Acetoxy[(4-(benzenesulfonyl)-3-oxopentyl)-methylidene]cyclohexane (20). To a stirred mixture of the above alcohol (128.1 mg, 0.38 mmol) and 4-(dimethylamino)pyridine (57.7 mg, 0.47 mmol) in 0.25 mL of dry CH_2Cl_2 at 0 °C was added acetyl chloride (36.0 mg, 0.46 mmol). The mixture was stirred at 25 °C for 1 h, partitioned between ether (20 mL) and 3 N aqueous HCl solution (15 mL), and extracted with ether (20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Preparative TLC, using 40% acetone in hexane (v/v), yielded pure **20** (130.5 mg, R_f 0.6, 91%) which was pure by analytical TLC and shown to be a diastereomeric mixture by NMR: (CCl_4) 1.25 (d, 3 H, *J* = 7 Hz), 1.3–1.9 (m, 6 H), 2.0 (s, 3 H), 2.1–2.4 (m, 4 H), 2.5–3.1 (m, 2 H), 4.16 (bq, 1 H, *J* = 7 Hz), 5.17 (m, 1 H), 5.32 (bt, 1 H, *J* = 7 Hz), 7.4–7.8 (m, 5 H); IR (CCl_4) 1735, 1730, 1450, 1370, 1320, 1150 cm^{-1}; MS 291 (0.1), 270 (1), 207 (0.3), 181 (9), 180 (2), 177 (2), 149 (18), 123 (8), 121 (98), 119 (100), 117 (99), 107 (11), 86 (43), 84 (79), 82 (68), 77 (11), 67 (12), 60 (10), 57 (19), 55 (15), 49 (35), 47 (78), 45 (16), 43 (37), 41 (18), 40 (10), 38 (37), 36 (86), 35 (27) (calcd for $C_{20}H_{26}O_5S$, 378.1501; found, 378.1490).

Preparation of (*E*)- and (*Z*)-1-(Benzenesulfonyl)-1-[5-(cyclohex-1-en-1-yl)tetrahydrofuran-2-ylidene]ethane (21). To a stirred solution of silyl ether **19** (499.8 mg, 1.11 mmol) in 4.4 mL of dry CH_2Cl_2 at 0 °C was added anhydrous $FeCl_3$(12.0 mg, 0.07 mmol). The mixture was stirred for 4 h, partitioned between hexane (40 mL) and water (20 mL), and extracted with hexane (40 mL). The combined organic layers were washed with H_2O (2 × 5 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL). The organic phase was dried over Na_2SO_4, concentrated in vacuo, and purified by preparative TLC, using two elutions with 40% acetone in hexane (v/v), to yield (*Z*)-**21** (39.8 mg, R_f 0.5, 11%), which isomerized to (*E*)-**21** over 3 days at 25 °C, and (*E*)-**21** (246.6 mg, R_f 0.6, 70%) which were pure by analytical TLC and NMR. Data for (*E*)-**21**: NMR (270 MHz, $CDCl_3$) 1.2–2.3 (m, 10 H), 1.86 (t, 3 H, *J* = 1.0 Hz), 3.05 (dt, 1 H, *J* = 17.5, 9.0 Hz), 3.45 (ddd, 1 H, *J* = 17.5, 9.0, 4.0 Hz), 4.52 (bt, 1 H, *J* = 7 Hz), 5.56 (bs, 1 H), 7.4 (m, 3 H), 7.65 (m, 2 H); IR (CCl_4) 1645, 1450, 1315, 1220, 1190, 1170, 1150, 1130 cm^{-1}; MS 318 (4), 197 (5), 178 (13), 177 (100), 176 (94), 159 (21), 134 (23), 121 (15), 119 (22), 109 (11), 107 (41), 105 (12), 97 (14), 93 (13), 91 (15), 81 (25), 79 (26), 77 (22), 69 (10), 67 (14), 57 (44), 55 (13), 43 (14) (calcd for $C_{18}H_{22}O_3S$, 318.1289; found, 318.1288).

Further purification of (*E*)-**21** (203.7 mg) by semipreparative HPLC (15% EtOAc in hexane (v/v), 50 mL/min) gave 118.6 mg white plates (t_R = 8.5 min, mp 82–84.5 °C). Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S, 10.07. Found: C, 67.91; H, 6.96, S, 10.04.

Preparation of (*Z*)- and (*E*)-Ethyl [5-(2-Hydroxyprop-2-yl)tetrahydrofuran-2-ylidene]acetate (23 and 24). To a stirred solution of ethyl 7-methyl-3-oxo-7-octenoate (16.09 g, 81.0 mmol) in 380 mL of dry CH_2Cl_2 at 0 °C under nitrogen was added 85% *m*-chloroperbenzoic acid (17.85 g, 89.0 mmol) in portions under a stream of nitrogen. The mixture was stirred for 90 min, and sufficient 2 N aqueous sodium hydroxide solution was added to dissolve the precipitated *m*-chlorobenzoic acid. Water (200 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (2 × 100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo to give a pale yellow oil (18.13 g) which spectral data showed to be nearly pure epoxide **22**: NMR (CCl_4) 1.04 (s, 6 H), 1.07 (t, 3 H, *J* = 7 Hz), 1.2–1.9 (m, 2 H), 2.3–2.6 (m, 2 H), 3.2 (s, 1.7 H), 3.95 (q, 2 H, *J* = 7 Hz), 4.8 (s, 0.3 H); IR (CCl_4) 1745, 1725, 1650 cm^{-1}. To a stirred solution of the unpurified epoxide (7.58 g, 35.0 mmol) in 90 mL of dry ethanol at 25 °C under nitrogen was added dropwise a solution of clean sodium metal (1.61 g, 70.0 mmol) in 45 mL of dry ethanol. The mixture was stirred 30 min, and saturated aqueous ammonium chloride solution (15 mL) was added. The ethanol was removed in vacuo, saturated aqueous ammonium chloride solution (25 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo to give a pale yellow oil (7.03 g). Dry column (600 g, 4.5 × 90 cm) chromatography, using 50% ether in chloroform (v/v), yielded the pure *Z* isomer **23** (1.16 g, 15% from olefin, R_f 0.4) and the *E* isomer **24** (4.27 g, 56% from olefin, R_f 0.6), the latter being contaminated by approximately 40% of a dimeric product. A previous TLC purification afforded pure **24**. Compound **24**: NMR (CCl_4, 270 MHz) 1.18 (s, 3 H), 1.26 (t, 3 H, *J* = 7.2 Hz), 1.30 (s, 3 H), 1.86 (bs, 1 H), 1.9–2.1 (m, 2 H), 2.92 (d of t of d, 1 H, *J* = 18.2, 9.5, 2.1 Hz), 3.36 (d of d of d of d, 1 H, *J* = 18.2, 9.2, 3.7, 1.5 Hz), 4.12 (q, 2 H, *J* = 7.2 Hz), 4.23 (d of d, 1 H, *J* = 8.8, 6.8 Hz), 5.32 (m, 1 H); IR (CCl_4) 3610, 3600–3300, 1710, 1645, 1470, 1450, 1380, 1360, 1120, 1050, 960, 890 cm^{-1} Compound **23**: NMR (CCl_4, 100 MHz) 1.04 (s, 3 H), 1.15 (t, 3 H, *J* = 7 Hz), 1.18 (s, 3 H), 1.85 (t, 2 H, *J* = 8 Hz), 2.6 (t, 2 H, *J* = 8 Hz), 3.58 (bs, 1 H), 3.95 (q, 2 H, *J* = 7 Hz), 4.2 (bt, 1 H, *J* = 7 Hz), 4.6 (s, 1 H); IR (CCl_4) 3620, 3600–3300, 1705, 1645 cm^{-1}

Preparation of Ethyl (*E*)-[5-(Propen-2-yl)tetrahydrofuran-2-ylidene]acetate (26). To a stirred solution of alcohol **24** (256.8 mg, 1.20 mmol) in 4.0 mL of collidine (distilled from KOH) at 25 °C under nitrogen was slowly added distilled thionyl chloride (from $(PhO)_3P$). The mixture was stirred 20 min, diluted with water (10 mL), and extracted with ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous cupric nitrate solution (2 × 10 mL) and brine (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to give a yellow-brown oil (331.6 mg). Column chromatography through Florisil adsorbent (11 g, 2 × 10 cm), using 10% ethyl acetate in hexane (v/v), yielded a pale yellow oil (120.2 mg, 51%, collected in first 50 mL) which NMR showed to be a mixture of olefin products. Medium-pressure liquid chromatography (Woelm silica gel, 0.032–0.063 mm, 2 × 20 cm, 60 psi), using 10% ethyl acetate in hexane (v/v) collected in 15-mL fractions yielded pure **26** (42 mg, 18%, fractions 6 and 7): NMR (CCl_4) 1.23 (t, 3 H, *J* = 7 Hz), 1.73 (s, 3 H), 1.5–2.35 (m, 2 H), 1.65–3.45 (m, 2 H), 4.03 (q, 2 H, *J* = 7 Hz), 4.7 (bt, 1 H, *J* = 7 Hz), 4.85 (bs, 1 H), 4.98 (bs, 1 H), 5.2 (bs, 1 H); IR (CCl_4) 1715, 1650, 1450 cm^{-1}; MS 196 (51), 151 (48), 150 (16), 135 (12), 115 (46), 109 (19), 95 (21), 87 (81), 81 (40), 79 (15), 69 (100), 67 (51), 55 (38), 53 (20), 44 (47), 43 (44), 41 (53), 40 (32), 39 (37), 31 (24) (calcd for $C_{11}H_{16}O_3$, 196.1100; found, 196.1103).

Preparation of (*Z*)-Ethyl [5-(Propen-2-yl)tetrahydrofuran-2-ylidene]acetate (25). In a procedure exactly analogous to the preparation of *E*-isomer **26**, the alcohol **23** (1.95 g, 9.10 mmol) was reacted with thionyl chloride (1.62 g, 13.65 mmol) in 24 mL of collidine at 25 °C under nitrogen for 1 h. Workup gave a red-brown, viscous oil (1.6 g). Column chromatography through Florisil (33 g, 2 × 30 cm), using 10% ethyl acetate in hexane (v/v), afforded crude *E*-olefin **26** (50% of 150 mg, 4% collected in first 70 mL). Further elution with 20% ethyl acetate in hexane (v/v) yielded **25** (340 mg, 19%) as a clear oil which NMR showed to be greater than 95% pure: NMR (CCl_4) 1.2 (t, 3 H, *J* = 7 Hz), 1.75 (s, 3 H), 1.55–2.4 (m, 2 H), 2.57–2.88 (m, 2 H), 4.02 (q, 2 H, *J* = 7 Hz), 4.67 (s, 1 H), 4.8–5.0 (m, 1 H), 4.86 (bs, 1 H), 5.03 (bs, 1 H); IR (CCl_4) similar to **26**; MS 196 (12), 151 (25), 135 (10), 115 (22), 109 (16), 95 (11), 87 (52), 83 (10), 81 (26), 79 (17), 69 (100), 67 (44), 55 (34), 53 (30), 44 (20), 43 (41), 41 (60), 40 (29), 39 (43), 31 (21) (calcd for $C_{11}H_{16}O_3$, 196.1100; found, 196.1103).

Palladium-Catalyzed Cyclization of (*E*)-2-Acetoxy[(4-(carbomethoxy)-3-oxopentyl)methylidene]cyclohexane. To a stirred mixture of allylic acetate **14** (48.3 mg, 0.16 mmol) and distilled triethylamine (18.2

mg, 0.18 mmol) in 0.73 mL of dry THF at 25 °C under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (**28**) (7.0 mg, 0.006 mmol) under a stream of nitrogen. The mixture was stirred for 1.5 h at 25 °C and 1 h at reflux before the catalyst precipitated from solution as palladium black. Additional catalyst **28** (7.7 mg, 0.007 mmol) and triphenylphosphine (1.2 mg, 0.005 mmol) were added, and the mixture was stirred 1.5 h at reflux. The mixture was diluted with ether and filtered through Celite. The solvent was removed in vacuo to give a yellow oil, which NMR showed to contain none of the desired cyclopentanone. TLC, using two elutions with 33% ethyl acetate in hexane (v/v), yielded pure enol ether **17** (17.5 mg, 45%).

Preparation of 2-(Carboethoxy)-4-methylcyclohept-4-enone (27). The enol ether **26** (32.9 mg, 0.17 mmol) was distilled at reduced pressure (0.007 mm) through a horizontally mounted quartz tube (prerinsed with *O,N*-bis(trimethyl)silylacetamide and hexane, inside diameter = 5 mm) preheated to 610 °C. The product condensed into a collecting bulb which was cooled to −78 °C. After cooling, the entire tube was thoroughly rinsed with ether, and the combined rinsings were concentrated in vacuo to yield **27** (30.8 mg, 94%) as a clear, colorless oil. Preparative TLC purification, using 30% acetone in hexane (v/v), gave pure **27** (21.1 mg, R_f 0.6, 64%) with spectral characteristics identical with those of the crude material: NMR (270 MHz, CDCl$_3$) 1.27 (t, 3 H, J = 7 Hz), 1.57 (bs, 3 H), 2.14–2.81 (m, 6 H), 3.83 (dd, 1 H, J = 10.6, 3.7 Hz), 4.20 (q, 1 H, J = 7 Hz), 4.21 (q, 1 H, J = 7 Hz), 5.60 (bt, 1 H, J = 0.5 Hz); IR (CCl$_4$) 1750, 1715, 1650, 1445 cm^{-1}; MS 197 (6), 196 (71), 151 (39), 150 (81), 135 (20), 123 (39), 122 (51), 121 (13), 115 (18), 109 (15), 108 (33), 107 (14), 105 (20), 96 (16), 95 (98), 94 (60), 93 (25), 91 (14), 87 (35), 82 (28), 81 (86), 80 (56), 79 (100), 77 (30), 69 (23), 68 (16), 67 (68), 66 (12), 65 (15), 55 (83), 53 (50), 51 (13), 45 (23), 44 (19), 43 (87), 40 (13), 39 (70) (calcd for C$_{11}$H$_{16}$O$_3$, 196.1099; found, 196.1102).

Preparation of 2-(Carboethoxy)-3-(propen-2-yl)cyclopentanone (30). Method A. To a stirred solution of E-olefin **26** (193.9 mg, 0.99 mmol) in 3.2 mL of dry DME at 25 °C under nitrogen was added catalyst **28** (73.6 mg, 0.06 mmol) under a stream of nitrogen. The mixture was refluxed 14 h, stirred an additional 6 h, and filtered through Celite with ether (20 mL). Reaction progress was monitored by gas chromatography (20% DC710 on Chromosorb W, 60–80 mesh, 3.7 m × 0.9 cm, T = 220 °C), as TLC proved unsatisfactory. The solvent was removed in vacuo to give a brown oil (260.1 mg) which was dissolved in ether (10 mL), cooled to 0 °C, and extracted rapidly with 13 °C, 4 N aqueous potassium hydroxide[21] solution (2 × 10 mL). The base extracts were added immediately to a 0 °C, stirred mixture of ethyl acetate (20 mL) and 3 N aqueous hydrochloric acid solution (26.5 mL), and the pH was adjusted to 5. The mixture was separated and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. The solvent was removed in vacuo, and Kugelrohr distillation gave pure **30** (94.8 mg, 49%, 65–75 °C (0.5 mm)) as a colorless oil which NMR showed to be a mixture (trans:cis = 88:12) of stereoisomers: NMR (CCl$_4$) 1.32 (t, 3 H, J = 8 Hz), 1.5–1.95 (m, 1 H), 1.82 (s, 3 H), 1.95–2.8 (m, 3.2 H), 2.95–3.28 (m, 1.8 H), 4.2 (q, 2 H, J = 8 Hz), 4.68 (bs, 0.24 H), 4.85 (bs, 1.76 H); IR (CCl$_4$) 3600–3400, 1752, 1725, 1650 cm^{-1}; MS 197 (9), 196 (80), 155 (21), 151 (39), 150 (74), 135 (24), 124 (17), 123 (100), 122 (43), 113 (14), 109 (68), 95 (38), 94 (11), 81 (21), 79 (16), 69 (14), 67 (20), 55 (33), 53 (16), 43 (17), 41 (39), 40 (15), 39 (21), 29 (43) (calcd for C$_{11}$H$_{16}$O$_3$, 196.1100; found, 196.1099). Anal. Calcd for C$_{11}$H$_{16}$O$_3$: C, 67.32; H, 8.22. Found: C, 67.45; H, 8.16.

Method B. To a mixture of the enol ether **26** (44.4 mg, 0.23 mmol) and catalyst **29** (13.8 mg, 0.015 mmol) in a dry NMR tube at 25 °C was added 0.6 mL of dry Me$_2$SO-d_6 (previously deoxygenated by bubbling argon through it). The mixture was heated at 50–60 °C and agitated periodically over 5 h. Preparative TLC purification, using two elutions with 25% acetone in hexane (v/v), yielded pure **30** (34.2 mg, R_f = 0.6, 80%) as a clear, colorless oil which NMR proved to be an E:Z (88:12) mixture.

Method C. In a procedure exactly analogous to the preparation of **30** from the (E)-isomer **26**, the Z-olefin **25** (90.0 mg, 0.46 mmol) was reacted with catalyst **28** (41.0 mg, 0.04 mmol) in 1.8 mL of dry DME under identical conditions. Workup and base extraction/purification, followed by Kugelrohr distillation, yielded pure **30** (35.2 mg, 39%, 65–75 °C (0.5 mm)) as a colorless oil (NMR showed E:Z = 88:12).

Preparation of 2-(Carbomethoxy)-3-(cyclohex-1-en-1-yl)-2-methylcyclopentanone (31 and 32). To a stirred solution of distilled enol ether **17** (198.3 mg, 0.84 mmol) in 3.2 mL of dry Me$_2$SO at 25 °C under nitrogen was added catalyst **28** (62.6 mg, 0.05 mmol) under a stream of nitrogen. The mixture was degassed by alternating vacuum with nitrogen and heated to 120 °C. Reaction progress was monitored by gas chromatography (20% DC710 on Chromosorb W, 60–80 mesh, 3.7 m × 0.9 cm, T = 280 °C), as TLC proved unsatisfactory. After 19 h at 120 °C, reaction had apparently ceased short of completion. Additional catalyst (27.3 mg, 0.02 mmol) was added, but further heating at 120 °C (21 h) produced little change. The mixture was cooled, partitioned between ether (20 mL) and water (10 mL), and extracted with ether (2 × 10 mL). The combined organic layers were washed with water (4 × 5 mL) and brine (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo, and TLC, using four elutions with 12% ethyl acetate in hexane (v/v), gave a 1:1 mixture of **31** and **32** (152.8 mg, 77%, R_f 0.6). This material was separated by preparative gas chromatography (20% DC710 on Chromosorb W, 60–80 mesh, 3.7 m × 0.9 cm, T = 225 °C, flow rate ~ 120 cm^3/min), and stereochemical assignments were made on the basis of the following spectral data: Peak 1 (**32**, t_R 12.8 min); ^{1}H NMR (270 MHz, CDCl$_3$) 1.38 (s, 3 H), 1.48–2.71 (series of m, 12 H), 3.61 (s, 3 H), 5.55 (m, 1 H); ^{13}C NMR (PhH-d_6) 214.0, 171.0, 135.7, 123.5, 59.8, 56.3, 51.2, 37.6, 28.9, 25.7, 23.9, 23.4, 22.7, 20.5 (q). Peak 2 (**31**, t_R 14.6 min): ^{1}H NMR (270 MHz, CDCl$_3$) 1.04 (s, 3 H), 1.45–2.47 (series of m, 11 H), 3.27 (m, 1 H), 3.73 (s, 3 H), 5.50 (m, 1 H); ^{13}C NMR PhH-d_6: 213.3, 173.3, 135.4, 123.1, 59.3, 52.0, 51.7, 37.4, 29.1, 25.5, 23.1, 22.9, 22.7, 13.7 (q); IR (mixture, CCl$_4$) 1765, 1745, 1450 cm^{-1}; MS (**32**) 237 (10), 236 (66), 208 (21), 205 (22), 204 (56), 189 (10), 178 (12), 177 (99), 176 (85), 161 (16), 159 (12), 149 (68), 148 (57), 147 (21), 141 (11), 135 (13), 134 (20), 133 (16), 131 (14), 122 (15), 121 (32), 120 (15), 119 (21), 117 (11), 115 (62), 112 (22), 109 (22), 108 (22), 107 (82), 106 (18), 105 (39), 97 (12), 95 (16), 94 (11), 93 (51), 92 (18), 91 (80), 88 (37), 83 (36), 81 (52), 80 (20), 79 (95), 78 (24), 77 (59), 69 (14), 67 (54), 65 (24), 59 (29), 55 (63), 53 (45), 51 (12), 44 (14), 43 (31), 41 (100), 39 (42) (calcd for C$_{14}$H$_{20}$O$_3$, 236.1412; found, 236.1415); MS (**31**): 237 (4), 236 (36), 205 (20), 204 (16), 189 (12), 178 (12), 177 (100), 176 (44), 149 (18), 148 (18), 121 (11), 115 (27), 107 (20), 105 (12), 93 (13), 91 (21), 81 (15), 79 (25), 77 (15), 67 (12), 55 (18), 53 (12), 41 (25), 40 (30), 39 (12) (found, 236.1412).

Preparation of 2-(Carbomethoxy)-2-methyl-3-(3-bromo-5,6-dihydronaphth-7-yl)cyclopentanone (36 and 37). To a mixture of enol ether **35** (19.2 mg, 0.05 mmol) and catalyst **29**[27] (3.3 mg, 0.003 mmol) in a dry NMR tube at 25 °C under argon was added dry Me$_2$SO-d_6 (0.35 mL, previously deoxygenated by flushing with argon). The heterogeneous mixture was heated to 50 °C, shaken mildly to give a clear, homogeneous yellow solution, maintained at 50 °C for 5 h, and purified by TLC, using three elutions with 33% acetone in hexane (v/v), to yield a 22:78 mixture of **36** and **37** (15.1 mg, R_f 0.7, 79%) as shown by ^{1}H and ^{13}C NMR. A larger scale reaction with crude enol ether **35** (131.4 mg, 0.36 mmol) was performed in Me$_2$SO (2.3 mL) with catalyst **29** (37.6 mg, 0.04 mmol) at 115 °C for 12 h, and the mixture was concentrated in vacuo and purified by TLC to yield **36** and **37** (80.4 mg, 61%). The E:Z mixture was preparatively inseparable. HPLC analysis on a C$_{18}$ μ-Bondapak reverse-phase column showed two peaks with retention times of 9.9 (major) and 11.2 (minor) min eluting with 65% methanol in water: ^{1}H NMR (CDCl$_3$) 1.05 (s, 0.66 H), 1.45 (s, 2.34 H), 2.0–2.6 (m, 7 H), 2.74 (bt, 2 H, J = 8 Hz), 7.2 (m, 2 H); IR (CDCl$_3$): 1755, 1735, 1640, 1590, 1480, 1460 cm^{-1}; ^{13}C NMR (**37**, CDCl$_3$) 214.5, 170.7, 139.1, 137.0, 132.9, 130.0, 129.3, 127.2, 123.6, 120.0, 59.9, 55.9, 51.8, 37.4, 27.8, 26.7, 23.5, 19.8; (**36**, CDCl$_3$) 213.8, 172.8, 139.1, 136.6, 132.9, 130.0, 129.3, 127.2, 123.3, 120.0, 59.2, 52.5, 51.2, 37.4, 27.6, 27.1, 22.8, 14.0. MS: 364 (75), 362 (75), 333 (12), 332 (31), 331 (16), 330 (29), 305 (90), 304 (89), 303 (100), 302 (76), 276 (11), 274 (12), 235 (11), 234 (37), 233 (8), 232 (36), 208 (61), 206 (62), 168 (29), 167 (34), 166 (21), 165 (13), 154 (22), 153 (22), 141 (20), 130 (11), 128 (40), 115 (53), 98 (32), 97 (15), 83 (40), 59 (12), 55 (12), 43 (14), 41 (18), 36 (30) (calcd for C$_{18}$H$_{19}$^{79}BrO$_3$, 362.0518; found, 362.0516). Anal. Calcd for C$_{18}$H$_{19}$BrO$_3$: C, 59.52; H, 5.27; Br, 22.00. Found: C, 59.39; H, 5.31; Br, 21.93.

Preparation of 2-(Benzenesulfonyl)-3-(cyclohex-1-en-1-yl)-2-methylcyclopentanone (38). Method A from 21. To a stirred solution of HPLC-purified enol ether **21** (94.4 mg, 0.30 mmol) in 1.4 mL of dry Me$_2$SO (previously deoxygenated by flushing with argon) at 130 °C under argon was added catalyst **29**[27] (27.1 mg, 0.03 mmol). The mixture was stirred at 130 °C for 3 h and black solid precipitated, leaving a clear orange solution which was concentrated in vacuo and filtered through Florisil (5 × 0.5 cm) with EtOAc (20 mL). Concentration in vacuo and preparative TLC purification, using three elutions with 20% acetone in hexane (v/v), yielded a 92:8 mixture of **38** and **39** (70.1 mg, R_f 0.7, 74%) as an off-white solid. Recrystallization from absolute EtOH gave white needles (mp 97.5–99 °C) of a 98:2 E:Z ratio: ^{1}H NMR (270 MHz, CDCl$_3$) 1.11 (s, 2.94 H), 1.44 (s, 0.06 H), 1.5–2.8 (m, 12 H), 3.75 (bt, 1 H, J = 7 Hz), 5.32 (bs, 0.01 H), 5.62 (bs, 0.97 H), 5.82 (bs, 0.02 H), 7.61 (m, 5 H); IR (CDCl$_3$) 2930, 2860, 2840, 1740, 1590, 1450, 1405, 1380, 1305, 1185, 1145, 1080, 1000, 840; MS 318 (0.2), 197 (0.4), 186 (0.3), 178 (16), 177 (74), 176 (100), 161 (12), 149 (14), 148 (20), 147 (14), 135 (22), 134 (62), 133 (26), 120 (13), 119 (30), 110 (12), 107 (22), 106 (16), 105 (32), 93 (37), 92 (12), 91 (39), 81 (38), 79 (43), 78

(15), 77 (26), 69 (10), 67 (31), 55 (25), 43 (12), 41 (20) (calcd for $C_{18}H_{22}SO_3$, 318.1289; found, 318.1285); ^{13}C NMR (PhH-d_6) 211.0, 136.8, 136.7, 134.0, 131.2, 128.8, 126.7, 75.8, 47.7, 38.1, 28.5, 25.6, 24.2, 23.1, 22.5, 15.8 (q). Anal. Calcd for $C_{18}H_{22}SO_3$: C, 67.89; H, 6.96; S, 10.07. Found: C, 67.74; H, 6.98; S, 10.07.

The mother liquor provided a second crop of crystals, and the resulting mother liquor showed a 59:35 *E*:*Z* ratio. Partial spectra: ^{1}H NMR (270 MHz, $CDCl_3$) 5.83 (bs, 0.06 H), 5.62 (bs, 0.59 H), 5.32 (bs, 0.35 H), 1.44 (s), 1.26 (s), 1.11 (s); ^{13}C NMR (67.9 MHz, PhH-d_6) 22.5 (q), 21.1 (q), 15.8 (q).

Method B from 20. To a stirred solution of acetate **20** (85.1 mg, 0.23 mmol) in 1.1 mL of dry Me_2SO (previously deoxygenated by flushing with argon) at 25 °C under argon was cautiously added NaH (5.2 mg, 0.22 mmol). The mixture was stirred for 2 h to give a clear, orange-yellow solution. Catalyst **29** (12.8 mg, 0.014 mmol) was added, and the mixture was heated to 130 °C over 15 min. After 45 min at 130 °C the deep red-brown solution was cooled to 25 °C, concentrated in vacuo, and filtered through Florisil (5 × 0.5 cm) with EtOAc (20 mL). Concentration in vacuo and preparative TLC purification, using three elutions with 20% acetone in hexane (v/v), yielded the same product as above (35.8 mg, 52%) as an off-white solid, the physical and spectral characteristics of which were identical with those of the material obtained from reaction of the enol ether. The progress of the reaction can be followed by analytical TLC or NMR, and it clearly proceeds through the intermediacy of the enol ether **21**.

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Palladium-Catalyzed 1,3-Oxygen-to-Carbon Alkyl Shifts. A Cyclopentanone Synthesis

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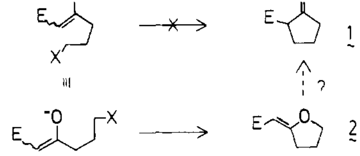
Abstract: A cyclopentanone synthesis emerges from the Pd(0)-catalyzed isomerization of 5-vinyl-2-alkylidenetetrahydrofurans. Four routes into such species were developed. First, cyclization of β-keto esters leads to O- rather than C-alkylation. Second, olefination of 4-vinyl lactones produced such substrates. The availability of such vinyl lactones from carbohydrates translates into a chiral synthesis of cyclopentanones. Third, 1-(arylthio)cyclopropanecarboxaldehyde served as a conjunctive reagent to convert ketones into the requisite substrates. Fourth, methyl 6-oxo-2-hexynoate converts vinyl organometallics into 5-vinyl-2-alkylidenetetrahydrofurans. In connection with this last conjunctive reagent, the intramolecular addition of a nucleophile to an ynoate is considered. The ability to direct the rearrangement to cyclopentanone or cycloheptenone formation [i.e., Pd(0)-catalyzed [1.3] vs. [3.3] rearrangement] is considered. The application of this method to the synthesis of steroids and prostaglandins is presented.

The discovery of natural products that contain five-membered rings has flourished in the last two decades. While prostaglandins and their metabolic relatives and the rethrolones, representatives of monocyclic systems, provided a major stimulus, polycondensed cyclopentanoids such as the hirsutanes,[1] capnellanes,[2] pentalanes,[3] zizaanes,[4] isocomanes,[5] and [3.3.3]propellanes[6] provided an even greater challenge. Natural products that contain one five-membered ring as part of a more complex ring system are numerous. The vetivanes[7] and steroids, which fall into this category, have stimulated much innovative work.

Among the most strategically innovative approaches have been the use of the intramolecular Alder ene reaction,[8] the vinylcyclopropane–cyclopentene rearrangement,[9] and photochemical cycloadditions.[10] Of the more classical approaches, one of the most useful would be intramolecular alkylation, as shown in eq 1. The thwarting of this approach due to the preference for O- rather than C-alkylation derives from stereoelectronic considerations.[11,12] The particular flexibility associated with a β-keto ester (i.e., **1** when E = CO_2CH_3) for structural elaboration imparts special importance to devise a route to achieve this transformation.[13] Since bond-energy considerations suggest that **1** is more



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