Medium 199 with 5% fetal bovine serum, penicillin (150 units/mL) and streptomycin (150 mcg/mL). When confluent monolayers were formed, the growth medium was removed and 250 mL of an appropriate dilution of virus was added to each well. Since the drugs must be present in this test during the adsorption phase, each aliquot of infectious virus was made up in the appropriate concentrations of drug before adding to the cell layer. After adsorption for 1 h at room temperature, the infected cell sheet was overlaid with equal parts of 1% agarose and 2X Medium 199 (2.5% FBS, penicillin, and streptomycin) containing varying concentrations of drug corresponding to those used during the adsorption phase. Cluster plates were incubated at 37 °C until the no drug control plates indicated optimum plaque size. A solution containing 10% formalin and 2% sodium acetate was added to each well to inactivate the virus and to fix the cell sheet to the plastic surface. The plaques were counted after staining the surrounding cell areas with crystal violet. Results from duplicate wells at each concentration were averaged and compared with control wells. The inhibition of plaque formation by 50% (IC_{50}) was estimated by plotting all results from 10 to 90% inhibition.

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Type III Intramolecular [2 + 2] Cycloadditions of Vinylketenes

Barry B. Snider,* Alban J. Allentoff, and Yashwant S. Kulkarni

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254

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Treatment of trans α,β-unsaturated acid chlorides with Et_3N in benzene at reflux gives a ca. 1:1 mixture of cis and trans α,β-unsaturated ketenes in excellent yield. If there is a second double bond in the side chain, the cis isomer undergoes a type III intramolecular cycloaddition to produce a bicyclo[3.2.0]hept-3-en-6-one and/or a bicyclo[3.1.1]hept-2-en-6-one in 30–50% yield from the acid chloride. The effect of substituents on the stereochemistry and regiochemistry of the cycloaddition is described.

Introduction

We[1] and others[2] have recently recognized that the stereospecific intramolecular cycloaddition of ketenes to alkenes provides a general method for the synthesis of polycyclic cyclobutanones. Although simple ketenes do undergo intramolecular [2 + 2] cycloaddition with some alkenes, satisfactory yields are not generally obtained unless activated ketenes are used. Excellent success has been obtained with alkoxyketenes,[1a,e] chloroketenes,[1f,k] arylketenes,[1l] and most significantly α,β-unsaturated ketenes.[1b,c,g-j,2a,b] Intramolecular [2 + 2] cycloadditions with α,β-unsaturated ketenes can be classified as type I, type II, and type III, depending on whether the tether containing the second double bond which adds to the ketene is attached to the unsaturated ketene at the ketene carbon, the α-carbon, or the β-carbon, respectively. We have reported detailed studies on type I and type II reactions and used these reactions for the synthesis of several bicyclo[3.1.1]heptane-containing mono- and sesquiterpenoids.[1] We report here studies on the scope and limitations of type III intramolecular cycloadditions.[3]

The general form of a type III intramolecular cycloaddition is shown in eq 1. Attachment of the tether to the β-carbon of the unsaturated ketene requires that the conjugated double bond be cis, complicating the synthesis of the ketene. However, once the ketene is formed, cycloaddition should be very facile since the presence of a cis double bond in the tether will decrease rotational freedom, resulting in a less negative entropy of activation. Early examples of this class of reaction were reported by Schiess and co-workers who prepared the ketenes by pyrolysis of 8-oxabicyclo[5.1.0]octa-2,4-dienes.[4] Complex

(1)

(1) (a) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (b) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809. (c) Kulkarni, Y. S.; Burbaum, B. W.; Snider, B. B. *Tetrahedron Lett.* **1985**, *26*, 5619. (d) Snider, B. B.; Kulkarni, Y. S. *Tetrahedron Lett.* **1985**, *26*, 5675. (e) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167. (f) Snider, B. B.; Kulkarni, Y. S. *J. Org. Chem.* **1987**, *52*, 307. (g) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568. (h) Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413. (i) Lee, S. Y.; Niwa, M.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 2356. (j) Lee, S. Y.; Kulkarni, Y. S.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848. (k) Snider, B. B.; Walner, M. *Tetrahedron*, in press. (l) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.

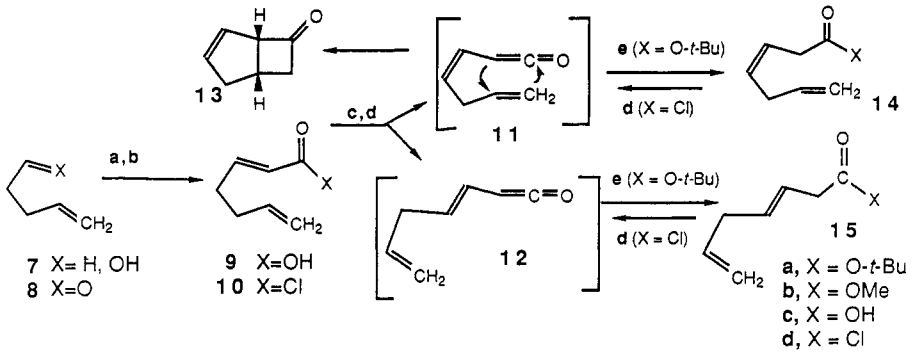
(2) (a) Markó, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192. (b) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339. (c) Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985**, *26*, 3535. (d) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1985**, *50*, 5177. (e) Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461. (f) Ghosez, L.; Marko, I.; Hesbain-Frisque, A.-M. *Tetrahedron Lett.* **1986**, *27*, 5211. (g) Oppolzer, W.; Nakao, A. *Tetrahedron Lett.* **1986**, *27*, 5471. (h) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1986**, *51*, 2145. (i) Arya, F.; Bouquant, J.; Chuche, J. *Tetrahedron Lett.* **1986**, *27*, 1913. (j) Brady, W. T.; Giang, Y. F.; Weng, L.; Dad, M. M. *J. Org. Chem.* **1987**, *52*, 2216. (k) Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229. (l) Yadav, J. S.; Joshi, B. V.; Gadgil, V. R. *Ind. J. Chem.* **1987**, *26b*, 399. (m) Brady, W. T.; Giang, Y.-s. F.; Marchand, A. F.; Wu, A.-h. *J. Org. Chem.* **1987**, *52*, 3457. (n) Hegmann, J.; Christl, M.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Tetrahedron Lett.* **1987**, *28*, 6429. (o) Corey, E. J.; Kang, M.-c.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649. (p) De Mesmaeker, A.; Veenstra, S. J.; Ernst, B. *Tetrahedron Lett.* **1988**, *29*, 459. (q) Funk, R. L.; Novak, P. M.; Abelman, M. A. *Tetrahedron Lett.* **1988**, *29*, 1493. (r) Brady, W. T.; Gu, Y.-Q. *J. Org. Chem.* **1988**, *53*, 1353. (s) Veenstra, S. J.; De Mesmaeker, A.; Ernst, B. *Tetrahedron Lett.* **1988**, *29*, 2303.

(3) A portion of this work has been published in preliminary form. See ref 1c.

(4) (a) Schiess, P.; Wisson, M. *Helv. Chim. Acta* **1974**, *57*, 1692; *Tetrahedron Lett.* **1971**, 2389. (b) Schiess, P.; Radimerski, P. *Helv. Chim. Acta* **1974**, *57*, 2583; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 288. (c) Schiess, P.; Fünfschilling, P. *Helv. Chim. Acta* **1976**, *59*, 1745. (d) Schiess, P.; Fünfschilling, P. *Ibid.* **1976**, *59*, 1756.

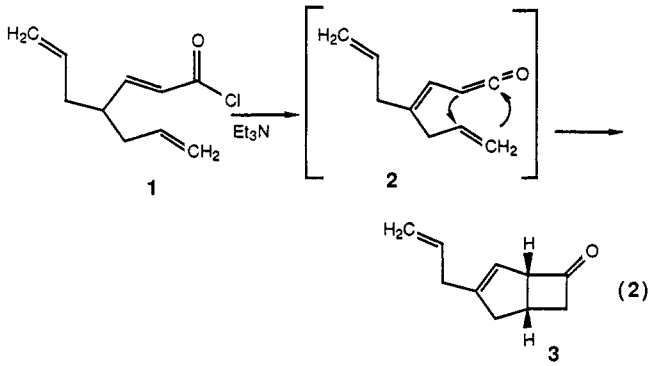
0022-3263/88/1953-5320$01.50/0

Scheme I[a]



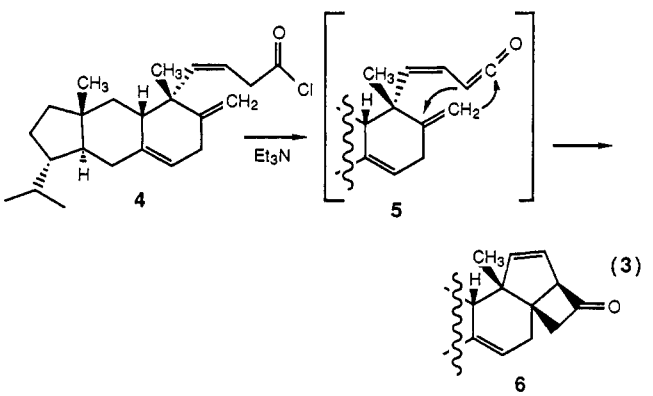
[a] (a) PCC; (b) pyridine, malonic acid; (c) oxalyl chloride; (d) Et_3N, 80 °C; (e) *t*-BuOH.

mixtures of products are produced in these pyrolyses. The first preparative examples of this class of cycloaddition are due to Ernst and Greuter who prepared cyclobutanone **3** in 83% yield via the intermediacy of ketene **2** by treatment of α,β-unsaturated acid chloride **1** with Et_3N (see eq 2).[2a]



(2)

The stereochemical problem was avoided by placement of two identical substituents on the β-position. Corey, Desai, and Engler used a type III cycloaddition as a key step in their synthesis of retigeranic acid (see eq 3).[2b] β,γ-Unsaturated acid chloride **4** was prepared by a Wittig reaction with the acid protected as a cyclic ortho ester, followed by introduction of the *exo*-methylene double bond. Treatment of **4** with Et_3N gave **6** in 80% yield via the intermediacy of ketene **5**. This procedure provides a general route to cis β,γ-unsaturated acid chlorides. Unfortunately, it is probably applicable only to α,α-disubstituted β,γ-unsaturated aldehydes, which cannot isomerize, and therefore could not be used, for instance, to prepare the unsubstituted example in eq 1.



(3)

We therefore turned our attention to simple, general methods for the preparation of acid chlorides suitable for the preparation of cis α,β-unsaturated ketenes. We initially considered approaches for the construction of cis β,γ-unsaturated acids. This class of acids is remarkably difficult to prepare. The obvious approaches such as oxidation of homoallylic alcohols have been reported to proceed in very poor yield.[5] We therefore decided to examine the deprotonation of readily available trans α,β-unsaturated acid chlorides, which can give a mixture of trans and cis α,β-unsaturated ketenes. There is some justification to expect selectivity for the cis isomer, since deprotonation of trans α,β-unsaturated esters with lithium amide bases occurs with good selectivity for the *cis*-dienolate.[6]

Results and Discussion

Acid **9** was easily prepared by the literature procedure.[7] Oxidation of 4-penten-1-ol (**7**) with PCC gave crude 4-pentenal (**8**), which was condensed with malonic acid in pyridine to give acid **9** in 39% overall yield. While the yield of **9** is not high, purification is straightforward and the Knoevenagel condensation is insensitive to impurities present in the crude aldehyde. Acid **9** was converted to acid chloride **10** with oxalyl chloride in benzene at reflux. Addition of **10** to a solution of excess Et_3N in benzene at reflux gave a 38% yield of bicyclo[3.2.0]hept-3-en-6-one (**13**),[8] indicating that the desired *cis*-vinyl ketene **11** was formed as a significant component from the trans acid chloride **10** (Scheme I). The low yield could be due to either the high volatility of **13** and/or the concomitant formation of *trans*-ketene **12**.

To determine the stereochemistry of the double bond of the conjugated ketene, acid chloride **10** was added to a mixture of excess Et_3N and *tert*-butyl alcohol in benzene at 25 °C, a procedure known to trap the intermediate vinylketene.[9] Workup after 12 h gave a 72% yield of a 1:1 mixture of **14a** and **15a** as determined by the absorptions of the α-methylene group at δ 3.01 and 2.96, respectively.[6d,10] Similar isomer mixtures were obtained under all reaction conditions investigated. Reaction of **10** with Et_3N in benzene, in the absence of *tert*-butyl alcohol, at 25 °C gave **13** in only 20% yield. Since **14a** and **15a** are formed in good yield at 25 °C, it appears that the cycloaddition of **11** competes more effectively with side reac-

(5) Knight, J. A.; Diamond, J. H. *J. Org. Chem.* **1959**, *24*, 400.
(6) (a) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023. (b) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. (c) Ikeda, Y.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5181. (d) Alcock, S. G.; Baldwin, J. E.; Bohlmann, R.; Harwood, L. M.; Seeman, J. I. *J. Org. Chem.* **1985**, *50*, 3526. (e) Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1971**, *36*, 3290.
(7) Mamdapur, V. R.; Subramaniam, C. S.; Chadha, M. S. *Ind. J. Chem.* **1979**, *18B*, 75.
(8) Fleming, I.; Au-Yeung, B. W. *Tetrahedron Suppl. 1* **1981**, *37*, 13.
(9) Iwakura, Y.; Toda, F.; Iwata, R.; Torii, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 841. Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1995; **1967**, *40*, 1232.
(10) Mizugaki, M.; Hoshino, T.; Ito, Y.; Sakamoto, T.; Shiraishi, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1980**, 2347.

tions at higher temperatures. These results establish that deprotonation of α,β-unsaturated acid chlorides is not stereoselective, unlike the deprotonation of related esters with LDA.[6] However, the accessibility of the trans α,β-unsaturated acid chloride, the operational simplicity of this method, and the ease of separation of the desired cyclobutanone from the more polar byproducts makes this an attractive method well-suited for exploration of the scope and limitations of type III cycloadditions.

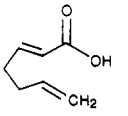
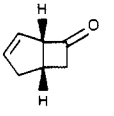
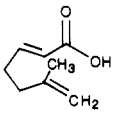
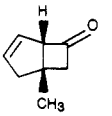
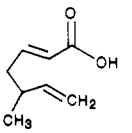
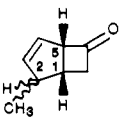
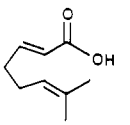
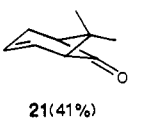
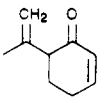
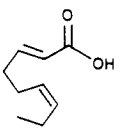
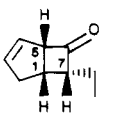
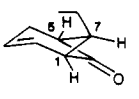
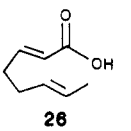
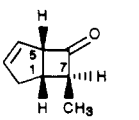
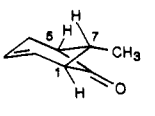
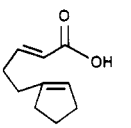
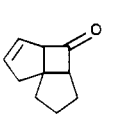
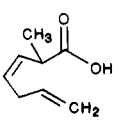
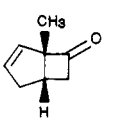
We have established that yield of **13** corresponds closely to the percentage of *cis*-ketene **11** formed from **10**. Ketene generation from **10** was carried out in benzene at relux in the presence of naphthalene as an internal standard and monitored by GC. The yield of **13** was 28% after 10 min, 39% after 40 min, and reached a maximum of 45% after 2 h. This suggests that **11** reacts to give **13** in very high yield and that **12** does not isomerize to **11** under the reaction conditions.

We have confirmed that ketenes **11** and **12** do not interconvert by preparing mixtures rich in either *cis*-ketene **11** or *trans*-ketene **12**. Deprotonation of methyl (*E*)-2,6-heptadienoate as described in the literature for related α,β-unsaturated esters[6] with LDA in THF/HMPA followed by careful protonation at −78 °C gave a 4:1 mixture of **14b** and **15b**. Careful hydrolysis with lithium hydroxide in aqueous DME[11] gave a 4:1 mixture of acids **14c** and **15c** (67% from the α,β-unsaturated ester), which were converted to the acid chlorides, which were reacted with Et_3N in benzene in reflux to generate ketenes **11** and **12**, respectively. GC analysis indicated that the yield of **13** was 72% after 10 min and reached a steady state of 80% after 20 min. The overall yield of **13** from methyl 2,6-heptadienoate from this multistep procedure is comparable to that obtained directly from **9** via **10**. Jones' oxidation of a 8.4:1 mixture of (*E*)- and (*Z*)-3,6-heptadienol[12] gave a 27% yield of a 1:8.4 mixture of acids **14c** and **15c**, which were converted to ketenes **11** and **12** as described above. GC analysis indicated that the yield of **13** was 8% after 10 min and reached a steady state of 10% after 20 min. These results convincingly establish that ketenes **11** and **12** do not interconvert in benzene at reflux.

We have shown that isomerization of α,β-unsaturated ketenes can occur prior to type II intramolecular cycloaddition.[1h] The likely mechanism for this isomerization is protonation on the β-carbon of the ketene by triethylammonium chloride to give a tertiary cation followed by loss of a proton to regenerate a ketene. Our results described above demonstrate that ketenes **11** and **12** do not interconvert. This is not inconsistent with our results obtained in type II cycloadditions[1h] since protonation of **11** or **12** will give an unstable secondary cation.

Eight examples of type III cycloadditions are shown in Table I. All of the acids except for **23** and **31** were prepared by Knoevenagel condensation[7] of malonic acid with the γ,δ-unsaturated aldehyde. The aldehyde precursors to **9**, **16**, **18**, and **26** were prepared by oxidation of the commercially available alcohols.[13] The aldehyde precursors to **20**[14] and **29**[15] were prepared by the literature procedure. Commercially available (2*E*,6*Z*)-nonadienal was oxidized to **23** in 91% yield by silver oxide. Acid **31** was prepared by deconjugative methylation of methyl (*E*)-2,6-heptadienoate,[6] followed by hydrolysis. Details are provided in the Experimental Section.

Table I. Type III Intramolecular Cycloadditions of Vinylketenes and Alkenes

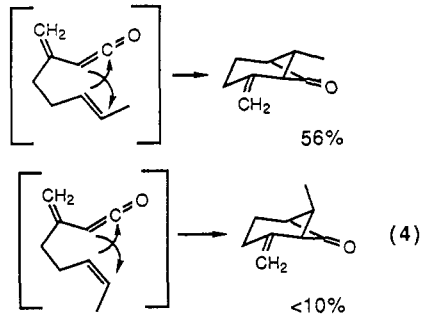
acid	cyclobutanone (yield)
 **9**	 **13**(38%)
 **16**	 **17**(43%)
 **18**	 **19a** (23%) β-Me **b** (7%) α-Me
 **20**	 **21**(41%)  **22**(16%)
 **23**	 **24**(36%)  **25**(7%)
 **26**	 **27**(38%)  **28**(9%)
 **29**	 **30**(50%)
 **31**	 **32**(48%)

The α,β-unsaturated acid was converted to the acid chloride as described above. Addition of the acid chloride to Et_3N in benzene at reflux gave the desired cyclobutanone. The yields range from 30% to 50%, suggesting that the yields based on the *cis*-ketene are from 70% to greater than 90%. The regiochemistry of the cycloaddition is controlled by the electronic effects of the substituents on the double bond.[1] The least substituted end of the double bond adds to the carbonyl group of the ketene. Introduction of a methyl group on the internal carbon of the double bond leads to bicyclo[3.2.0]heptanone **17** in slightly higher yield. If the double bond is present in a ring, as in acid **29**, then a tricyclic cyclobutanone **30**, a model for the synthesis of triquinane sesquiterpenes, is formed in 50% yield. Introduction of two methyl groups

(11) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.
(12) Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003.
(13) Cresson, P. *Bull. Soc. Chem. Fr.* **1964**, 2629.
(14) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *219*, 2095.
(15) (a) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153. (b) Cartaya-Marin, C. P. Ph.D. Thesis, Brandeis University, 1985.

on the terminal end of the double bond leads, as expected,[1] exclusively to the bicyclo[3.1.1]heptane apochrysanthenone (**21**)[16] and monocyclic enone **22**.[16]

Cycloaddition of the ketenes derived from acids **23** and **26** was examined to determine the regiochemistry of the cycloaddition with electronically unbiased 1,2-disubstituted alkenes. The reactions both proceed in good yield, assuming ≈50% conversion to cis α,β-unsaturated ketene. Both cycloadditions are stereospecific but lead to a mixture of regioisomers in which the bicyclo[3.2.0]heptanone predominates. This cycloaddition contrasts to related intramolecular cycloadditions of chloroketenes and type II vinyl ketenes with 1,2-disubstituted alkenes (see eq 4). In these

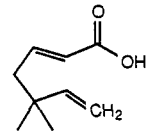


(4)

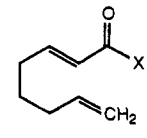
cases the trans isomer reacts rapidly and stereospecifically to give the expected bicyclo[3.1.1]heptan-6-one while the cis isomer gives a mixture of both bicyclo[3.1.1]heptanones in lower yield with the chloroketene and does not react with the type II vinylketene.[1k] Apparently, the presence of the double bond in the tether in the type III cycloaddition facilitates the cycloaddition so that both the cis and trans isomers react in good yield and favors the formation of the bicyclo[3.2.0]heptanone.

Acid **18** was examined since substituents on the δ-position have been shown to favor formation of the *trans*-dienolate in the deprotonation of conjugated esters.[6] A single methyl group in the δ-position increases the amount of *trans*-ketenes since the 30% yield of cyclobutanones **19a** and **19b** obtained is lower than the yield of cyclobutanone **13** obtained from **10**. The reaction was monitored by GC as described above. The yield of **19a** and **19b** was 10% after 10 min, 18% after 40 min, 31% after 2 h, and reached a maximum of 36% after 5 h. Since **13** was formed in a GC yield of 45%, deprotonation of the acid chloride derived from **18** gives, as expected, more of the *trans*-ketene. Generation of the ketene from the acid chloride derived from **18** in the presence of *tert*-butyl alcohol in benzene at 25 °C as described above gave a low yield of a mixture of cyclobutanones **19** and cis and trans β,γ-unsaturated ester, suggesting that a 2:3 mixture of *cis*- and *trans*-ketenes were formed. The low yield of ketene derived products formed from **18** at 25 °C and the longer time required for formation of **19** suggests that deprotonation of the acid chloride derived from **18** is slower than deprotonation of **10**.[2s]

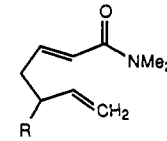
α,β-Unsaturated acid chlorides with two δ-substituents, such as that derived from acid **33**, should give only *trans*-ketene. The *cis*-ketene, if formed, should undergo facile cycloaddition since the presence of the geminal dimethyl group should favor cycloaddition. No cyclobutanone was obtained from acid **33**, confirming that the *trans*-ketene is formed selectively in the deprotonation. Fortunately, *cis*-ketenes of this type, which cannot be prepared from α,β-unsaturated acid chlorides should be readily available by a Wittig reaction on α,α-dialkyl β,γ-unsaturated aldehydes by the procedure of Corey.[2b]



33



34, X = OH
35, X = NMe_2



36, R = H
37, R = Me

Type III cycloadditions can also be carried out with keto ketenes. Acid **31** was prepared as a 3.3:1 *Z*–*E* mixture by alkylation of the α,β-unsaturated ester by the procedures of Pfeffer, Krebs, and Kende,[6] followed by hydrolysis. Conjugation of the double bond during hydrolysis did not occur. The isolated yield of cycloadduct was 48%, even though 77% of the desired *cis*-ketene should be obtained from the mixture of β,γ-unsaturated acid chlorides. GC analysis using naphthalene as an internal standard indicated the yield of **32** reached a steady state of 72% after 10 min. The 48% isolated yield is due to the high volatility of **32**.

Like many other intramolecular cycloadditions of ketenes,[1,2] the reaction fails with four carbon tethers. No cyclobutanone was obtained from the ketene prepared from acid **34**. Keteniminium salts have been used with good success with longer tethers.[2a] We therefore prepared amide **35** and converted it to the keteniminium salt.[17] No cyclobutanone was obtained from the keteniminium salt in this case either.

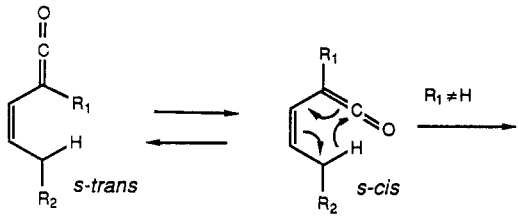
The cycloadditions of alkenes with keteniminium salts differ in several ways from the corresponding ketene cycloadditions. Firstly, different mixtures of cis and trans α,β-unsaturated keteniminium salts may be formed and secondly, different mixtures of stereoisomers of **19** should be obtained. The keteniminium salt derived from **36** gave a 23% yield of **13**. The keteniminium salt derived from **37** gave a 32% yield of a 1:1 mixture of **19a** and **19b**. Therefore type III intramolecular cycloadditions of vinyl keteniminium salts are slightly less effective than the ketene cycloadditions. There are significant differences in stereocontrol as we have previously noted with alkoxy-substituted ketenes and keteniminium salts.[1e]

A potentially serious side reaction in type III intramolecular cycloadditions of unsaturated ketenes such as **11** is a 1,5-sigmatropic hydride shift to give a conjugated dienal. This rearrangement has been observed at 400–600 °C by Schiess.[4b] We have previously found that unsaturated ketene **39** undergoes 1,5-sigmatropic hydride shift to give dienal **40** as the major product.[1j] No type I cycloaddition product is isolated. On the other hand, we have not obtained any dienal byproduct in any of these type III cycloadditions carried out at 80 °C. To our surprise, no 1,5-sigmatropic hydride shift to give a dienal occurs even in ketene **38** with a saturated side chain that cannot undergo an intramolecular cycloaddition. This indicates that intermolecular condensation reactions are faster than the 1,5-sigmatropic hydride shift for aldoketenes. The presence of an alkyl group (R_1) on the ketene carbon is apparently necessary for the 1,5-hydride shift leading to

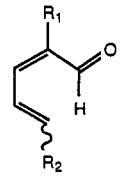
(16) (a) Catalan, C. A. N.; Merep, D. J.; de Delfini, M. L. T.; Retamar, J. A. *Riv. Ital. E.P.P.O.S.* **1981**, *63*, 209; *Chem. Abstr.* **1981**, *95*, 204163*b*. (b) Catalan, C. A. N.; de Iglesias, D. I. A.; Inigo, R. P. A.; Retamar, J. A. *Riv. Ital. E.P.P.O.S.* **1981**, *63*, 289; *Chem. Abstr.* **1982**, *96*, 69227*d*. (c) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *J. Chem. Soc., Perkin Trans 2* **1984**, 1351.

(17) (a) Ghosez, L.; Marchand-Brynaert, J. In *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; Part 1, pp 421–532. (b) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879.

dienals. Presumably, the introduction of the alkyl group increases steric hindrance in the s-trans conformer favoring the s-cis conformer necessary for the 1,5-hydride shift.



11, R_1 = H, R_2 = CH=CH_2
38, R_1 = H, R_2 = n-Pr
39, R_1 = 4-pentenyl, R_2 = Me

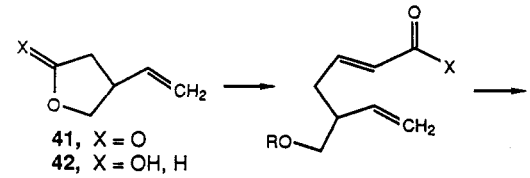


40, R_1 = 4-pentenyl, R_2 = Me

The ketene derived from **31** is a keto ketene, which could undergo a 1,5-hydride shift to give a trienal. Cyclobutanone **32** is the only volatile product obtained indicating that type III intramolecular cycloaddition is faster than the 1,5-hydride shift even for keto ketenes. The conversion of **39** to **40** indicates that the 1,5-hydride shift is faster than a type I cycloaddition. The presence of the double bond in the tether restricts rotational freedom making type III cycloadditions faster than type I cycloadditions.

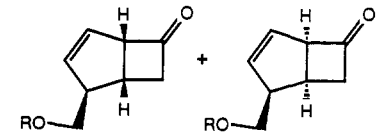
Synthesis of Prostaglandin Intermediates. Cycloaddition of the ketene derived from acid **18** gave a 3.4:1 mixture of exo and endo isomers **19a** and **19b**. Increasing the steric bulk of the alkyl substituent should lead to improved selectivity for the exo isomer. Use of alkoxymethyl substituents would allow simple modification of substituent size and was particularly attractive since (methoxymethyl)bicycloheptenone (**48**) has been prepared by Fleming and Au-Yeung as a prostaglandin intermediate by an intermolecular ketene cycloaddition.[8] Reduction of lactone **41**[18] with Dibal in THF at −78 °C gave lactol **42**. Reaction of **42** with (carbomethoxymethylene)triphenylphosphorane[19] gave *E* ester **43** in 63% yield from **41**. Methylation of **43** with silver oxide, methyl iodide, and anhydrous calcium sulfate[20] gave methyl ether **44**, which was hydrolyzed to give acid **45** in 73% yield from **43**. Conversion of **45** to the acid chloride and addition to Et_3N in benzene at reflux gave a 40% yield of a 5:1 mixture of cyclobutanones **48** and **50**. The increased bulk of the substituent increases the preference for the exo isomer **48** only slightly.

Ghosez has observed that much better stereocontrol is obtained with a (*tert*-butyldiphenylsilyl)oxy substituent than an acetoxy substituent in an intramolecular cycloaddition of a keteniminium salt.[2f] Conversion of alcohol **43** to the *tert*-butyldiphenylsilyl ether **46**,[21] followed by saponification gave acid **47** in 65% yield. Conversion of **47** to the acid chloride and addition to Et_3N in benzene at reflux gave a 39% yield of a 5:1 mixture of **49** and **51**. The increased bulk of the *tert*-butyldiphenylsilyl group is apparently too far removed from the ketene and alkene



41, X = O
42, X = OH, H

43, R = H, X = OMe
44, R = Me, X = OMe
45, R = Me, X = OH
46, R = Si-*t*-$BuPh_2$, X = OMe
47, R = Si-*t*-$BuPh_2$, X = OH



48 R = Me **50**
49 R = Si-*t*-$BuPh_2$ **51**

to affect the ratio of stereoisomers formed in the cycloaddition.

Structure of Cycloadducts. The structure of cycloadducts **13**,[8] **21**,[16] **17**,[4c] **32**,[4c] and **48**[8] were established by comparison with spectra of authentic samples. The stereochemistry of **19** was convincingly established by examination of the ^{13}C NMR spectra, as previously reported in related systems.[22,1h,j] the γ-gauche butane interaction of the methyl group with carbon 7 in the endo isomer **19b** results in upfield shifts of the methyl carbon (8.1 ppm), carbon 2 (6.1 ppm), carbon 1 (2.8 ppm), and carbon 7 (6.3 ppm) as compared to the exo isomer **19a**. The stereochemistry was confirmed by analysis of the ^1H and ^{13}C NMR spectra. The key coupling constants, $J_{1,2}$ = 0 and 8.4 Hz in **19a** and **19b**, respectively, agree well with the calculated[23] dihedral angles of 81° and 26°.

Similar analysis was used to assign the stereochemistry of **48**–**51**. The γ-gauche butane interaction of the methoxymethyl group with carbon 7 in the endo isomer **50** results in upfield shifts of the methylene carbon (4.3 ppm), carbon 2 (5.9 ppm), carbon 1 (0.9 ppm), and carbon 7 (6.2 ppm) as compared to the exo isomer **48**. The γ-gauche butane interaction of the [(*tert*-butyldiphenylsilyl)oxy]-methyl group with carbon 7 in the endo isomer **51** results in upfield shifts of the methylene carbon (4.1 ppm), carbon 2 (5.6 ppm), carbon 1 (0.6 ppm), and carbon 7 (5.9 ppm) as compared to the exo isomer **49**. $J_{1,2}$ = 0 Hz in the exo isomers **48** and **49**.

The regiochemistry of **24** and **27** was easily established by analysis of the ^1H NMR spectra. The methine proton between the carbonyl group and double bond in **24** and **27**, H_5, absorbs at δ 4.24 and 4.19, respectively, a value consistent with known bicyclo[3.2.0]hept-3-en-6-ones.[8,4c] The methine proton between the carbonyl and double bond in **25** and **28**, H_1, absorbs at δ 3.17 and 3.03, respectively, a value consistent with known bicyclo[3.1.1]-hept-2-en-6-ones.[1g,16]

The stereochemistry of these adducts could also be determined by analysis of coupling constants. In **24** the coupling constant $J_{1,7}$ = 9.4 Hz is consistent only with two hydrogens in a cis relationship.[24] In **27**, the coupling constant $J_{1,7}$ = 5.5 Hz is consistent only with two hydrogens in a trans relationship.[24] The stereochemistry of **25**

(18) Kondo, K.; Mori, F. *Chem. Lett.* **1974**, 741.
(19) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390.
(20) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806.
(21) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(22) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869; **1986**, *108*, 6343.
(23) MMX from Serena Software, 489 Serena Lane, Bloomington, Indiana, 47401 was used. An updated version of MODEL obtained from Prof. Steliou, University of Montreal, was used for structure input.
(24) Rey, M.; Roberts, S. M.; Dreiding, A. S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* **1982**, *65*, 703.

was assigned on the basis of the coupling constant $J_{1,7}$ = 5.2 Hz, a value consistent with previous observations[25] and the calculated[23] dihedral angle of 30°. The stereochemistry of **28** was assigned on the basis of the coupling constants $J_{1,7} \approx J_{5,7} \approx 0$ Hz, a value consistent with previous observations[25] and the calculated[23] dihedral angle of 100°.

Conclusions

These results establish that cis α,β-unsaturated ketenes can be prepared in ≈50% yield by elimination of hydrogen chloride from trans α,β-unsaturated acid chlorides and that type III intramolecular cycloadditions proceed in good yield to produce a variety of bicyclo[3.2.0]hept-3-en-6-ones and bicyclo[3.1.1]hept-2-en-6-ones.

Experimental Section

Materials and Methods. NMR spectra were recorded on Varian EM-390 and XL-300 spectrometers in $CDCl_3$. Chemical shifts are reported in δ, and coupling constants are reported in hertz. IR spectra were obtained on a Perkin-Elmer 683 spectrometer. Combustion analyses were performed by Galbraith Laboratories. All air-sensitive reactions were run under nitrogen in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.

Bicyclo[3.2.0]hept-3-en-6-one (13). A solution of acid **9**[7] (0.160 g, 1.25 mmol) in 3 mL of dry benzene was treated with oxalyl chloride (0.80 g, 6.30 mmol) at 0 °C. The solution was stirred at room temperature for 1 h and at reflux for 0.5 h. Excess oxalyl chloride and solvent were removed in vacuo to give the crude acid chloride as a light yellow oil. The acid chloride was dissolved in 10 mL of benzene and added dropwise to a stirred solution of Et_3N (0.45 g, 4.40 mmol) in 12 mL of benzene at reflux. The resulting mixture was heated at reflux for 8 h. The reaction solution was cooled and washed with saturated brine. The aqueous layer was extracted three times with ether. The combined organic layers were dried, and the solvent was removed to give a red oil. Purification by flash chromatography on silica gel (90:10 pentane–ether) gave 45 mg (38%) of pure **13**: ^{1}H NMR δ 5.90–5.98 (m, 1), 5.58–5.66 (m, 1), 4.22–4.31 (m, 1), 3.15–3.30 (m, 1), 2.70–2.90 (m, 3), 2.40–2.55 (m, 1); ^{13}C NMR δ 216.1, 133.5, 125.4, 73.7, 53.2, 40.4, 25.8; IR (neat) 3075, 1775, 1610 cm^{-1}. The spectral data agree with those previously reported.[8]

***tert*-Butyl (*Z*)- and (*E*)-3,6-Heptadienoate (14a, 15a).** Acid **9** (0.193 g, 1.53 mmol) was converted to the acid chloride as described above. A solution of the acid chloride in 2 mL of benzene was added dropwise to a stirred mixture of Et_3N (0.31 g, 3.06 mmol), *t*-BuOH (0.41 g, 5.54 mmol), and 3 mL of benzene at 25 °C. The reaction solution was stirred overnight at 25 °C. Normal aqueous workup and evaporation in vacuo gave 0.201 g (72%) of a crude 1:1 mixture of **14a** and **15a**: ^{1}H NMR δ 5.90–5.50 (m, 3), 5.04 (ddt, 1, *J* = 17.1, 1.9, 1.9), 5.00 (br d, 1, *J* = 10.2), 3.01 (d, 0.5 × 2, *J* = 6.1, **14a**), 2.96 (ddd, 0.5 × 2, *J* = 4.4, 1.0, 1.0, **15a**), 2.82 (m, 2), 1.47 (s, 0.5 × 9), 1.45 (s, 0.5 × 9).

(*E*)-6-Methyl-2,6-heptadienoic Acid (16). To a stirred solution of pyridinium chlorochromate (3.25 g, 15.1 mmol) and 200 mg of Florisil in 13 mL of methylene chloride was added 4-methyl-4-penten-1-ol (1.02 g, 10.1 mmol) in one portion. The dark brown solution was stirred for 2 h. The solution was then decanted, and the remaining gummy residue was washed well with ether. The combined solution was filtered through Florisil. Evaporation of the solvent gave 1.34 g of crude aldehyde[13] containing some residual solvent, which was used immediately for the next step.

A mixture of crude aldehyde (0.991 g), malonic acid (1.26 g, 12.1 mmol), and pyridine (0.67 mL) was stirred overnight at 25 °C. The solution was then heated at reflux for 4.5 h, cooled, and acidified to pH 1 with 10% hydrochloric acid. The solution was extracted three times with ether. The combined organic extracts were dried, and solvent was removed in vacuo. Flash chromatography on silica gel (75:15:10:0.2 hexane–EtOAc–CH_2Cl_2–HOAc) gave 0.340 g (25% from the alcohol) of pure **16**: ^{1}H NMR δ 7.09 (dt, 1, *J* = 15.6, 6.8), 5.85 (dt, 1, *J* = 15.6, 1.4), 4.77 (br s, 1), 4.71 (br s, 1), 2.39 (dtd, 2, *J* = 6.8, 7, 1.4), 2.18 (br t, 2, *J* = 7), 1.73 (br s, 3); ^{13}C NMR 172.1, 151.6, 144.0, 120.9, 110.9, 35.6, 30.3, 22.3; IR (neat) 1693, 1649, 1417, 1283, 884 cm^{-1}. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.90; H, 8.62.

1-Methylbicyclo[3.2.0]hept-3-en-6-one (17). Acid **16** (0.161 g, 1.14 mmol) was converted to the acid chloride as described above and added to Et_3N in benzene at reflux. The reaction mixture was heated at reflux for 15 h and worked up. Flash chromatography on silica gel (97:3 pentane–ether) gave 53.5 mg (43%) of pure **17**: ^{1}H NMR δ 5.88 (dddd, 1, *J* = 5.2, 2, 2, 2), 5.57 (dddd, 1, *J* = 5.2, 2, 2, 2.7), 3.80 (m, 1), 3.04 (dd, 1, *J* = 17.7, 2.7), 2.86 (dd, 1, *J* = 17.7, 4.7), 2.65 (dddd, 1, *J* = 17.4, 3.6, 2, 2), 2.57 (dddd, 1, *J* = 17.4, 2, 2, 2); ^{13}C NMR 133.9, 125.9, 77.8 (C_5), 58.9 (C_7), 47.4 (C_2), 34.7 (C_1), 24.0 (CH_3), (the carbonyl carbon was not observed); IR (neat) 3030, 1775, 1603, 710 cm^{-1}. The spectral data agree with those previously reported.[4]

(*E*)-5-Methyl-2,6-heptadienoic Acid (18). 3-Methyl-4-penten-1-ol (2.71 g, 26.8 mmol) was converted to 2.74 g of crude aldehyde[13] as described above. Acid **18** was prepared from crude aldehyde (2.19 g), malonic acid (2.78 g, 26.8 mmol), and pyridine (1.42 mL) as described above. Normal workup and flash chromatography on silica gel (80:20:0.2 hexane–EtOAc–AcOH) gave 0.659 g (34% from the alcohol) of pure **18**: ^{1}H NMR δ 7.04 (dt, 1, *J* = 15.2, 7.3), 5.83 (dt, 1, *J* = 15.2, 1.1), 5.73 (ddd, 1, *J* = 17.2, 10.2, 6.9), 5.02 (ddd, 1, *J* = 17.3, 1.5, 1.5), 4.98 (ddd, 1, *J* = 10.2, 1, 1), 2.29 (m, 1), 2.25 (dd, 2, *J* = 7, 7.3), 1.04 (d, 3, *J* = 6.6); ^{13}C NMR δ 171.9, 150.4, 142.8, 121.9, 113.6, 39.2, 36.8, 19.7; IR (neat) 1694, 1646, 1416, 977, 908 cm^{-1}. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.64.

***exo*- and *endo*-2-Methylbicyclo[3.2.0]hept-3-en-6-one (19a, 19b).** Acid **18** (0.313 g, 2.23 mmol) was converted to the acid chloride, which was added to Et_3N at reflux as described above. Normal workup followed by flash chromatography on silica gel (96:4 pentane–ether) gave 73.2 mg (30%) of a 3.8:1.0 mixture of **19a** and **19b** as a clear volatile oil. Pure samples of **19a** and **19b** were obtained by preparative GC (0.375 in. × 7 ft, 10% XF-1150 on Chromosorb PAW 60/80 mesh) at 120 °C. Anal. Calcd for $C_8H_{10}O$: 122.0732. Found: 122.0735.

The data for **19a**: ^{1}H NMR δ 5.89 (m, 1), 5.56 (m, 1), 4.27 (m, 1, H_5), 3.91 (ddd, 1, *J* = 4.4, 9.1, 18.1, $H_{7\beta}$), 2.82 (ddd, 1, *J* = 3.2, 5.6, 18.1, $H_{7\alpha}$), 2.75 (m, 1, H_2), 2.42 (ddd, 1, *J* = 5, 5.8, 9.1, H_1), 1.05 (d, 3, *J* = 7.1); ^{13}C NMR δ 139.4 (C_4*), 124.3 (C_3*), 72.9 (C_5), 52.2 (C_7), 48.1 (C_2), 33.3 (C_1), 21.5 (CH_3) (the carbonyl carbon was not observed); IR ($CDCl_3$) 1773, 1600 cm^{-1}; t_R 15.9 min. Decoupling experiments established that $J_{1,7\alpha}$ = 5.6, $J_{1,7\beta}$ = 9.1, $J_{1,2}$ = 0, $J_{1,5}$ = 5, $J_{5,7\alpha}$ = 3.2, and $J_{5,7\beta}$ = 4.4.

The data for **19b**: ^{1}H NMR δ 5.60 (m, 1), 5.50 (m, 1), 4.19 (m, 1, H_5), 3.23 (ddd, 1, *J* = 17.4, 5.9, 3.2, $H_{7\alpha}$), 3.21 (m, 1, H_2), 2.93 (dddd, 1, *J* = 8.8, 5.9, 8.4, 4.6, H_1), 2.82 (ddd, 1, *J* = 17.4, 4.4, 8.8, $H_{7\beta}$), 1.18 (d, 3, *J* = 7.4); ^{13}C NMR δ 139.5 (C_4), 124.9 (C_3), 73.8 (C_5), 45.9 (C_7), 42.0 (C_2), 30.5 (C_1), 13.4 (CH_3) (the carbonyl carbon was not observed); IR ($CDCl_3$) 1777, 1606 cm^{-1}; t_R 20.1 min. Decoupling experiments established that $J_{1,7\alpha}$ = 5.9, $J_{1,7\beta}$ = 8.8, $J_{1,2}$ = 8.4, $J_{1,5}$ = 4.6, $J_{5,7\alpha}$ = 3.2, and $J_{5,7\beta}$ = 4.4.

7-Methyl-2,6-octadienoic Acid (20). A mixture of 5-methyl-4-hexenal[14] (1.55 g, 13.8 mmol), malonic acid (1.73 g, 16.6 mmol), and pyridine (0.91 mL) were allowed to react overnight at 25 °C and at reflux for 12 h as described above. Normal workup and flash chromatography on silica gel (75:25:0.2 hexane–EtOAc–AcOH) gave 1.43 g (70%) of pure acid **20**: ^{1}H NMR δ 7.09 (dt, 1, *J* = 15.7, 6.5), 5.83 (dt, 1, *J* = 15.7, 1.4), 5.10 (m, 1), 2.26 (m, 2), 2.17 (m, 2), 1.70 (br s, 3), 1.61 (br s, 3); ^{13}C NMR δ 172.3, 152.0, 132.9, 122.6, 120.8, 32.5, 26.4, 25.6, 17.7; IR (neat) 1698, 1651, 1420, 1285, 974 cm^{-1}. The data agree with those previously reported.[26]

7,7-Dimethylbicyclo[3.1.1]hept-2-en-6-one (21) and 6-(1-Methylethenyl)-2-cyclohexen-1-one (22). To a stirred mixture of NaH (0.162 g, 60% dispersion, washed twice with hexanes, 4.04 mmol) in 7.6 mL of benzene was added acid **20** (0.208 g, 1.35 mmol) dropwise at 0 °C. The reaction mixture was stirred for 10 min at 25 °C. The solution was then treated with oxalyl chloride as

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described above and stirred at room temperature for 2 h. Excess oxalyl chloride and solvent were removed in vacuo to give the acid chloride, which was added to Et_3N in benzene at reflux. The solution was heated for 12 h and worked up to give a mixture of **21**, **22**. Flash chromatography on silica gel (90:10 pentane–ether) gave 67.3 mg (41%) of pure **21** and 25.9 mg (15.8%) of **22**.

The data for **21**: ^1H NMR δ 5.87 (br dd, 1, J = 9, 7.4), 5.68 (ddd, 1, J = 9.1, 2.7, 2.7), 2.83 (dd, 1, J = 7.4, 7.4), 2.77 (m, 2), 2.60 (ddd, 1, J = 7.4, 2.9, 2.9), 1.24 (s, 3), 1.22 (s, 3); ^{13}C NMR δ 129.8, 126.4, 63.4, 63.0, 35.0, 27.3, 14.9 (the carbonyl and quaternary carbon were not observed); IR (neat) 3017, 1780, 1680, 665 cm^{-1}. The spectral data agree with those previously reported.[16]

The data for **22**: ^1H NMR δ 6.97 (dt, 1, J = 10.1, 3.6), 6.05 (dt, 1, J = 10.1, 2.0), 4.97 (dd, 1, J = 1.5, 1.5), 4.77 (s, 1), 3.05 (dd, 1, J = 5.1, 10.9), 2.40 (m, 2), 2.10 (m, 2), 1.77 (br s, 3); ^{13}C NMR δ 149.0, 130.0, 113.6, 54.9, 27.9, 25.3, 20.6 (the carbonyl and quaternary carbon were not observed); IR (neat) 1681 cm^{-1}. The spectral data agree with those previously reported.[16]

(2*E*,6*Z*)-2,6-Nonadienoic Acid (23). To a stirred mixture of silver nitrate (4.8 g, 28.0 mmol) in water (10 mL) was added a solution of sodium hydroxide (2.25 g, 56.0 mmol) in water (10 mL). The resulting solution was stirred for 5 min after which (2*E*,6*Z*)-2,6-nonadien-1-al (2.76 g, 20.0 mmol) was added in one portion. The reaction solution was then stirred for 1 h at 25 °C and filtered. The residue was washed with water. The combined aqueous layers were washed with ether, cooled to 0 °C, and acidified with 10% hydrochloric acid. The solution was then saturated with sodium chloride and extracted with several portions of ether. The combined ether layers were dried and concentrated in vacuo. Flash chromatography of the residue on silica gel (85:15:0.2 hexane–EtOAc–AcOH) gave 2.80 g (91%) of pure acid **23**: ^1H NMR δ 7.15 (dt, 1, J = 6.5, 16.0), 5.90 (br d, 1, J = 16.0), 5.30–5.70 (m, 2), 1.95–2.50 (m, 6), 1.03 (t, 3, J = 7.5); IR (neat) 1700, 1650, 1420 cm^{-1}. The spectral data agree with those previously reported.[27]

***endo*-7-Ethylbicyclo[3.2.0]hept-3-en-6-one (24) and *syn*-7-Ethylbicyclo[3.1.1]hept-2-en-6-one (25).** A solution of acid **23** (0.770 g, 5.00 mmol) in benzene, was treated with oxalyl chloride to give the acid chloride, which was added to Et_3N in benzene at reflux as described above. The mixture was heated at reflux for 1 h followed by normal workup to give a crude mixture of **24** and **25**. Medium-pressure liquid chromatography on silica gel (99:1 hexane–EtOAc) gave 230 mg (36%) of pure **24** and 50 mg (7%) of pure **25**. Ketone **25** was found to decompose within days, even when kept in hexane at −20 °C.

The data for **24**: ^1H NMR δ 5.92 (dddd, 1, J = 2.1, 2.4, 2.4, 5.7), 5.60 (dddd, 1, J = 2.1, 2.1, 3.0, 5.7), 4.24 (dddd, 1, J = 2.1, 3.0, 3.3, 8.0), 3.21 (dddd, 1, J = 3.3, 7.2, 8.0, 9.6), 3.11 (dddd, 1, J = 2.5, 8.0, 9.1, 9.6), 2.46–2.65 (m, 2), 1.66 (ddq, 1, J = 7.2, 7.5, 14.1), 1.52 (ddq, 1, J = 7.5, 8.7, 14.1), 0.92 (t, 3, J = 7.5); ^{13}C NMR δ 211.0, 134.7, 125.3, 71.5, 63.2, 32.6, 30.2, 20.9, 12.9; IR (neat) 1772, 1610, 1455 cm^{-1}. Decoupling experiments established that $J_{1,7}$ = 9.6.

The data for **25**: ^1H NMR δ 5.77 (dd, 1, J = 7.3, 7.3), 5.66 (ddd, 1, J = 3.0, 3.0, 7.3), 3.17 (ddd, 1, J = 5.2, 7.3, 7.3), 3.01 (m, 1), 2.78 (m, 1), 2.71 (m, 1), 2.12 (m, 1), 1.64 (m, 2), 0.93 (t, 3, J = 7.3); ^{13}C NMR δ 216.2, 127.0, 126.1, 57.5, 56.7, 33.3, 32.4, 15.3, 12.8; IR (neat) 2965, 2930, 2880, 1773 cm^{-1}. Decoupling experiments established that $J_{1,7}$ = 5.2.

(2*E*,6*E*)-2,6-Octadienoic Acid (26). (*E*)-4-Hexen-1-ol (2.51 g, 25.1 mmol) was converted to 3.07 g of the crude aldehyde[13] as described above. Crude aldehyde (2.10 g), malonic acid (2.67 g, 25.7 mmol), and pyridine (1.36 mL) were allowed to react as described above. Normal workup followed by flash chromatography on silica gel (90:10:0.2 hexane–EtOAc–AcOH) gave 0.463 g (24% from the alcohol) of pure **26** as a waxy white solid: mp 44–46 °C; ^1H NMR δ 7.08 (dt, 1, J = 15.6, 6.7), 5.83 (dt, 1, J = 15.6, 1.9), 5.50 (dq, 1, J = 15.0, 5.9), 5.39 (dtq, 1, J = 15.0, 5.4, 1), 2.29 (br dd, 1, J = 6.7, 7.8), 2.16 (br dd, 1, J = 5.4, 7.8), 1.65 (br d, 3, J = 5.9); ^{13}C NMR δ 172.1, 151.7, 129.4, 126.3, 120.9, 32.3, 30.8, 17.9; IR ($CDCl_3$) 1695, 1653, 1420, 1285, 963 cm^{-1}. The spectral data agree with those previously reported for the methyl ester.[28]

***exo*-7-Methylbicyclo[3.2.0]hept-3-en-6-one (27) and *anti*-7-Methylbicyclo[3.1.1]hept-2-en-6-one (28).** Acid **26** (0.197 g, 1.40 mmol) was converted to the acid chloride as described above which was added to Et_3N in benzene at reflux. Heating at reflux for 1.5 h followed by normal workup and flash chromatography on silica gel (85:15 pentane–ether) gave 41.2 mg (31%) of pure **27** followed closely by 23.1 mg (17%) of an inseparable 1:1 mixture of **27** and **28**.

The data for **27**: ^1H NMR δ 5.89 (dddd, 1, J = 5.3, 2, 2, 2), 5.66 (dddd, 1, J = 5.3, 2, 2, 2.7), 4.19 (m, 1), 3.00 (ddq, 1, J = 5.5, 3.3, 7.6), 2.83 (ddddd, 1, J = 17.7, 7.7, 2, 2, 2), 2.56 (br d, 1, J = 17.7), 2.40 (br ddd, 1, J = 7.7, 5.5, 6.9), 1.20 (d, 3, J = 7.6); ^{13}C NMR δ 133.4 (C_4*), 126.2 (C_3*), 71.3 (C_5), 60.3 (C_7), 40.3 (C_2), 35.1 (C_1), 13.2 (CH_3) (the carbonyl carbon was not observed); IR (neat) 1779, 1604, 1455, 1215, 912, 729 cm^{-1}. Decoupling experiments established that $J_{1,7}$ = 5.5.

The data for **28** were determined from the mixture: ^1H NMR δ 6.09 (ddd, 1, J = 8.0, 5.0, 3.4), 5.56 (ddd, 1, J = 8.1, 2.8, 2.8), 3.03 (m, 1), 2.85 (m, 2), 2.82 (m, 1), 2.12 (q, 1, J = 6.8), 1.14 (d, 3, J = 6.8); ^{13}C NMR δ 133.2, 124.9, 63.5, 60.8, 38.4, 33.3, 17.7 (the carbonyl carbon was not observed); IR ($CDCl_3$) 1770, 1603, 1245 cm^{-1}. Decoupling experiments established that $J_{1,7} = J_{1,5} = 0$.

(*E*)-5-(1-Cyclopentenyl)-2-pentenoic Acid (29). The acid was prepared from crude 1-cyclopentene-1-propanal[15] (0.783 g), malonic acid (0.786 g, 7.55 mmol), and pyridine (0.41 mL) as described above. Normal workup followed by flash chromatography on silica gel (90:10:0.2 hexane–EtOAc–AcOH) gave 0.223 g (71%) of pure **29** as a white solid: mp 80–81 °C (hexane); NMR 7.10 (dt, 1, J = 15.7, 6.9), 5.84 (dt, 1, J = 15.7, 1.6), 5.37 (br t, 1, J = 1.4), 2.40 (dt, 2, J = 7.5, 7.5), 2.34–2.11 (m, 6), 1.87 (tt, 2, J = 7.5, 7.5); ^{13}C NMR δ 172.3, 152.0, 142.9, 124.4, 120.7, 35.1, 32.4, 30.5, 29.3, 23.3; IR (neat) 1684, 1648, 1427 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.03; H, 8.67.

Tricyclo[5.3.0.0^{1,5}]dec-3-en-6-one (30). A mixture of acid **29** (0.184 g, 1.10 mmol) and NaH (0.1320 g, 60% dispersion, washed twice with hexanes, 3.30 mmol) in benzene was treated with oxalyl chloride as described above and stirred at room temperature for 2 h. Excess oxalyl chloride and solvent were removed in vacuo to give the acid chloride, which was added to Et_3N in benzene at reflux. The solution was heated for 12 h and worked up. Flash chromatography on silica gel (96:4 pentane–ether) gave 67.9 mg (50%) of pure **30** as a light yellow oil with a camphoraceous smell: ^1H NMR δ 5.93 (dddd, 1, J = 5.6, 2.2, 2.2, 2.2), 5.57 (dddd, 1, J = 5.6, 2, 2, 2.7), 3.73 (m, 1), 3.21 (br dd, 1, J = 8.2, 3.2), 2.73 (dddd, 1, J = 17.9, 2, 2, 2), 2.63 (dddd, 1, J = 17.9, 4.0, 2, 2), 2.07 (m, 1), 1.93 (m, 2), 1.68 (m, 3); ^{13}C NMR δ 134.4, 125.2, 75.1, 69.1, 47.2, 43.1, 35.4, 30.1, 26.9, (the carbonyl carbon was not observed); IR (neat) 3032, 1783, 1609, 1263, 786, 686 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.31; H, 8.30.

Methyl (*E*)-2,6-heptadienoate was prepared from acid **9** by the procedure of Grundy et al.[29] To a stirred mixture of potassium carbonate (0.61 g, 4.47 mmol), acetone (8 mL), and acid **9** (0.513 g, 4.06 mmol) was added dimethyl sulfate (0.42 mL, 4.47 mmol) in one portion. The mixture was heated at reflux for 2 h. The reaction solution was cooled and then poured into 50 mL of water. The aqueous layer was separated and extracted three times with ether. The combined organic layers were dried, and the solvent was removed to give 0.450 g (80%) of the methyl ester: ^1H NMR δ 7.08 (dt, 1, J = 6.5, 16.0), 5.82 (br d, 1, J = 16.0), 5.58–6.05 (m, 1), 5.06 (br d, 1, J = 17.0), 3.63 (s, 3), 2.10–2.50 (m, 4); IR (neat) 1730 cm^{-1}.

Methyl (*Z*)-2-methyl-3,6-heptadienoate was prepared by the procedures of Kende and Krebs.[6] To a stirred solution of diisopropylamine (0.180 g, 1.78 mmol) in THF (13 mL) at 0 °C was added *n*-BuLi (0.71 mL of a 2.5 M solution in hexane, 1.78 mmol) dropwise. The solution was stirred at 0 °C for 0.5 h and was then cooled to −78 °C. HMPA (0.35 g, 1.96 mmol) was then added, and the solution was stirred at −78 °C for an additional 0.5 h. Methyl 2,6-heptadienoate (0.227 g, 1.62 mmol) was then added dropwise, and the solution acquired a yellow-orange color. The reaction solution was stirred at −78 °C for 1 h, and methyl iodide (0.30 g, 2.11 mmol) was added slowly. The solution was stirred

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at −78 °C for 1.5 h, during which time the color changed to light yellow. Water (15 mL) was added, and the two layers were separated. The aqueous layer was extracted three times with ether. The combined organic layers were washed twice with 10% hydrochloric acid and then with water and were dried. Evaporation of the solvent followed by flash chromatography on silica gel (95:5 hexane–EtOAc) gave 0.144 g (62%) of the methyl ester as a 3.3:1 *Z*–*E* mixture: ^{1}H NMR δ 5.81 (ddt, 1, *J* = 17.1, 10.1, 6.3), 5.51 (m, 2), 5.05 (ddt, 1, *J* = 17.0, 1.7, 1.7), 5.00 (ddt, 1, *J* = 10.1, 1.7, 1.5), 3.67 (s, 3), 3.44 (ddq, 1, *J* = 7.2, 1.0, 7.1), 2.85 (m, 0.77 × 2), 2.78 (0.23 × 2), 1.24 (d, 3, *J* = 7.1); ^{13}C NMR (*Z* isomer) δ 175.3, 136.1, 129.7, 128.6, 115.1, 51.8, 37.9, 31.6, 17.9; IR (neat) 1743, 1667, 1645, 1460, 1439, 1195, 1170, 915 cm^{-1}.

(*Z*)-2-Methyl-3,6-heptadienoic Acid (31). To a solution of barium hydroxide octahydrate (0.516 g, 1.64 mmol) in water (20 mL) was added the methyl ester (0.126 g, 0.820 mmol) in one portion. The solution was heated at reflux for 1.5 h and was then cooled. The solution was washed with pentane, acidified to pH 1 with 10% hydrochloric acid, and extracted three times with ether. The combined organic layers were dried and evaporated to give 92.9 mg (81%) of **31** as a 3.3:1 *Z*–*E* mixture: ^{1}H NMR δ 5.81 (ddt, 1, *J* = 17.1, 10.1, 6.3), 5.51 (m, 2), 5.05 (ddt, 1, *J* = 17.0, 1.7, 1.7), 5.00 (ddt, *J* = 10.1, 1.7, 1.5), 3.46 (ddq, 1, *J* = 7.2, 1.0, 6.8), 2.85 (m, 2), 1.27 (d, 3, *J* = 6.8); ^{13}C NMR δ 181.3, 136.0, 129.3, 129.0, 115.3, 37.9, 31.7, 17.8; IR (neat) 1708, 1642, 1632, 1455, 1413, 1279, 1217, 908 cm^{-1}.

5-Methylbicyclo[3.2.0]hept-3-en-6-one (32). Acid **31** (0.129 g, 0.92 mmol) was treated with oxalyl chloride to give the acid chloride as described above. The acid chloride was added to Et_3N in benzene at reflux, and heating was continued for 1.5 h. Normal workup followed by flash chromatography on silica gel (95:5 pentane–ether) gave 41.3 mg (48%) of pure **32**: ^{1}H NMR δ 5.84 (ddd, 1, *J* = 5.4, 2.4, 2.4), 5.46 (ddd, 1, *J* = 5.4, 2.7, 2.7), 3.18 (dd, 1, *J* = 17.8, 8.7), 2.94 (dddd, 1, *J* = 17.5, 7.7, 2.7, 2.4), 2.75 (dd, 1, *J* = 17.8, 5.8), 2.45 (br d, 1, *J* = 17.5), 2.41 (m, 1), 1.28 (s, 3); ^{13}C NMR δ 132.1, 131.2, 79.8, 50.0, 40.3, 33.1, 10.7 (the carbonyl was not observed); IR (neat) 1776, 1450, 1390, 1103, 1013, 733, 708 cm^{-1}. The spectral data agree with those previously reported.[4]

4-Ethenyltetrahydrofuran-2-ol (42). Diisobutylaluminum hydride (59.2 mL of a 1.0 M solution in hexanes, 59.2 mmol) was added dropwise over 10 min to a solution of lactone **41**[18] (3.61 g, 29.6 mmol) in 40 mL of dry THF stirred at −78 °C. The solution was stirred at −78 °C for 1 h and was then slowly poured into a mixture of 30 g of ice and 4 mL of acetic acid. The two layers were then separated, and the aqueous layer was extracted three times with ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated to give 2.92 g of crude lactol **42** as a 1:1 mixture of diastereomers, which was used immediately for the next step: ^{1}H NMR δ 5.84 (ddd, 1 × 0.5, *J* = 17.1, 10.2, 8.1), 5.72 (ddd, 1 × 0.5, *J* = 17.1, 10.1, 8.0), 5.12 (ddd, 1 × 0.5, *J* = 17.1, 1.1, 1.1), 5.10 (ddd, 1 × 0.5, *J* = 17.1, 1.1, 1.1), 5.03 (br d, 1, *J* = 10.2), 4.19 (dd, 1 × 0.5, *J* = 8.2, 8.2), 3.97–3.72 (m, 2), 3.56 (dd, 1 × 0.5, *J* = 8.1, 8.1), 3.32 (br s, 1), 3.16 (ddddd, 1 × 0.5, *J* = 8, 8, 8, 8, 8), 2.87 (ddddd, 1 × 0.5, *J* = 8, 8, 8, 8, 8), 2.35 (ddd, 1 × 0.5, *J* = 14.3, 8.3, 5.4), 2.14–1.64 (m, 1 + 1 × 0.5); IR (neat) 3400, 2950, 1649, 1510, 1232, 1055, 995, 917 cm^{-1}.

Methyl (*E*)-5-(Hydroxymethyl)-2,6-heptadienoate (43). To a stirred solution of (carbomethoxymethylene)triphenylphosphorane (8.82 g, 26.4 mmol) in 30 mL of CH_2Cl_2 at room temperature was added a solution of lactol **42** (2.53 g, 22.0 mmol) in 12 mL of CH_2Cl_2.[19] The reaction was stirred overnight at room temperature. Evaporation of solvent followed by flash chromatography on silica gel (60:40 ether–hexane) gave 0.460 g (32% from **41**) of a fraction containing a 9:1 mixture of **43** and the *Z* isomer, followed immediately by 0.317 g (31% from **41**) of pure **43**: ^{1}H NMR δ 6.93 (dt, 1, *J* = 15.6, 7.2), 5.86 (dt, 1, *J* = 15.6, 1.5), 5.66 (ddd, 1, *J* = 17.1, 10.5, 7.8), 5.19 (dd, 1, *J* = 10.5, 1.0), 5.16 (ddd, 1, *J* = 17.1, 1.0, 1.0), 3.73 (s, 3), 3.61–3.52 (m, 2), 2.45–2.36 (m, 2), 2.27 (ddtt, 1, *J* = 1.5, 8, 8, 8, 8), 1.73 (br s, 1); ^{13}C NMR δ 166.8, 146.8, 138.1, 122.5, 117.7, 65.0, 51.4, 45.4, 33.5; IR (neat) 3433, 2946, 1723, 1658, 1437, 1203, 1170, 1040, 916 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.37; H, 8.28.

(*E*)-5-(Methoxymethyl)-2,6-heptadienoic Acid (45). To a stirred mixture of silver(I) oxide (0.973 g, 4.2 mmol), anhydrous calcium sulfate (1.14 g, 8.4 mmol), and methyl iodide (14.3 g, 101.0 mmol) was added alcohol **43** (0.358 g, 2.10 mmol).[20] The reaction solution was heated at 60 °C in the dark for 48 h. The solution was then cooled, diluted with CH_2Cl_2, and filtered. Evaporation of the solvent gave 0.389 g of **44** as a clear oil, which was used directly for the next step.

A mixture of barium hydroxide octahydrate (1.22 g, 3.87 mmol), ester **44** (0.356 g, 1.93 mmol), and 50 mL of water was heated at reflux for 2 h. The reaction solution was cooled, washed with pentane, and acidified to pH 1 with 10% hydrochloric acid. The solution was then extracted three times with ether. The combined organic layers were dried, and the solvent was evaporated to give 0.323 g of crude acid **45**. Flash chromatography on silica gel (60:40:0.2 hexane–EtOAc–AcOH) gave 0.234 g (73.5% from **43**) of pure **45**: ^{1}H NMR δ 7.04 (ddt, 1, *J* = 15.6, 7.3), 5.85 (dt, 1, *J* = 15.6, 1.5), 5.68 (ddd, 1, *J* = 16.7, 7.8, 11.0), 5.12 (ddd, *J* = 11.0, 1.0, 1.0), 5.11 (ddd, 1, *J* = 16.7, 1.0, 1.0), 3.35 (s, 3), 3.36–3.32 (m, 2), 2.55–2.42 (m, 2), 2.27 (ddtt, 1, *J* = 7.7, 1.4, 7.7, 7.7); ^{13}C NMR δ 171.1, 149.8, 138.1, 122.1, 116.6, 75.3, 58.8, 42.8, 34.1; IR (neat) 2920, 1697, 1652, 1421, 1283, 1112, 982, 915 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.39.

***exo*- and *endo*-2-(Methoxymethyl)bicyclo[3.2.0]hept-3-en-6-one (48, 50).** Acid **45** (0.192 g, 1.13 mmol) in 6.3 mL of benzene was treated with oxalyl chloride (0.727 g, 5.65 mmol) to give the acid chloride which was added dropwise to Et_3N (0.45 g, 4.49 mmol) in benzene at reflux as previously described. The mixture was heated at reflux for 10 h followed by normal workup to give a crude mixture of **48** and **50**. Flash chromatography on silica gel (75:25 pentane–ether) gave 58.1 mg (39.8%) of an inseparable mixture of **48** and **50** as a light yellow oil. Analysis by capillary GC (Bonded OV-225B, 0.25 mm × 25 M) showed that a 5:1 mixture of **10** and **11** was present: IR (neat) 2926, 1781, 1602, 1385, 1192, 1105, 911, 728 cm^{-1}.

The data for **48**: ^{1}H NMR δ 5.88–5.87 (m, 1), 5.74–5.68 (m, 1), 4.31–4.20 (m, 1, H_5), 3.36 (s, 3), 3.40–3.34 (m, 1), 3.26 (ddd, 1, *J* = 18.4, 9.1, 4.6, $H_{7\beta}$), 3.16 (dd, 1, *J* = 7.8, 9.1), 3.01–2.91 (m, 1, H_2), 2.84 (ddd, 1, *J* = 18.4, 5.7, 3.2, $H_{7\alpha}$), 2.69 (ddd, 1, *J* = 9.1, 5.7, 6.1, H_1); ^{13}C NMR δ 207.2 (C=O), 134.2 (C_4), 127.2 (C_3), 75.8 (CH_2O), 73.0 (C_5), 58.9 (OCH_3), 54.0 (C_2), 52.3 (C_7), 29.2 (C_1); t_R 8.10 min. The spectral data agree with those previously reported.[8]

The data for **50**: ^{1}H NMR δ 5.88–5.87 (m, 1), 5.79–5.68 (m, 1), 4.31–4.20 (m, 1, H_5), 3.60 (dd, 1, *J* = 6.7, 9.3), 3.51 (dd, 1, *J* = 9.3, 9.3), 3.38 (s, 3), 3.29–2.26 (m, 4); ^{13}C NMR δ 134.4 (C_4), 127.2 (C_3), 73.6 (C_5), 71.5 (CH_2O), 58.9 (OCH_3, 48.1 (C_2), 46.1 (C_7), 28.3 (C_1) (the carbonyl carbon was not observed); t_R 8.70 min.

Methyl (*E*)-5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,6-heptadienoate (46). To a mixture of imidazole (0.461 g, 6.77 mmol) and *tert*-butyldiphenylsilyl chloride (0.928 g, 3.38 mmol) in 25 mL of dry DMF was added the alcohol **43** (0.524 g, 3.07 mmol).[21] The reaction mixture was stirred at 25 °C overnight and was poured into 20 mL of water. The layers were separated, and the aqueous layer was extracted one time with ether. The combined organic layers were then washed once with water and dried. Evaporation of solvent followed by flash chromatography on silica gel (80:20 hexane–AcOEt) gave 0.860 g (72%) of pure silyl ether **46**: ^{1}H NMR δ 7.64 (dd, 4, *J* = 7.8, 1.6), 7.46–7.34 (m, 6), 6.92 (dt, 1, 15.7, 7.3), 5.83 (dt, 1, *J* = 15.7, 1.5), 5.67 (ddd, 1, *J* = 17.1, 10.6, 7.9), 5.06 (br d, 1, *J* = 10.6), 5.03 (ddd, 1, *J* = 17.1, 1.0, 1.0), 3.72 (s, 3), 3.63 (dd, 1, *J* = 10.0, 5.2), 3.56 (dd, 1, *J* = 10.0, 6.5), 2.54 (dddd, 1, *J* = 14.4, 7.3, 5.1, 1.5), 2.40 (br dtt, 1, *J* = 7.9, 5, 5), 2.26 (dddd, 1, *J* = 14.4, 7.3, 7.0, 1.5), 1.05 (s, 9); ^{13}C NMR δ 166.9, 147.6, 138.3, 135.6 (4 C), 133.5 (2 C), 129.6 (2 C), 127.6 (4 C), 122.2, 116.5, 66.4, 51.3, 45.3, 33.7, 26.8 (3 C), 19.3; IR (neat) 3072, 2929, 2850, 1726, 1660, 1427, 1261, 1110, 698 cm^{-1}. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.58; H, 8.04.

(*E*)-5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,6-heptadienoic Acid (47). A mixture of anhydrous lithium hydroxide (0.413 g, 17.2 mmol), DME (22 mL), water (9 mL), and ester **46** (0.704 g, 1.72 mmol) was stirred at 25 °C for 20 h.[11] The mixture was washed with pentane and was then carefully acidified to pH 2 with 10% hydrochloric acid. The solution was then extracted three times with ether. The combined organic layers were washed once with water and then with saturated brine and dried. Evaporation of the solvent gave 0.607 g (89%) of acid **47**: ^{1}H NMR δ 7.65 (dd, 4, *J* = 7.7, 1.6), 7.46–7.35 (m, 6), 7.03 (dt, 1, *J* = 15.6, 7.3), 5.83 (dt, 1, *J* = 15.6, 1.3), 5.67 (ddd, 1, *J* = 17.1, 7.9, 10.5), 5.08 (br d, 1, *J* = 10.5), 5.04 (ddd, 1, *J* = 17.1, 1.0, 1.0), 3.64 (dd,

1, J = 10.0, 5.2), 3.56 (dd, 1, J = 10.0, 6.6), 2.57 (dddd, 1, J = 14.4, 7.3, 5.1, 1.5), 2.41 (br dtt, 1, J = 7.9, 5, 5), 2.31 (dddd, 1, J = 14.4, 7.3, 7.0, 1.5), 1.06 (s, 9); ^{13}C NMR δ 171.7, 150.4, 138.2, 135.6 (4 C), 133.5 (2 C), 129.6 (2 C), 127.7 (4 C), 122.0, 116.6, 66.4, 45.3, 33.8, 26.9 (3 C), 19.3; IR (neat) 3066, 2926, 2851, 1698, 1654, 1428, 1110, 736, 698 cm^{-1}.

***exo*- and *endo*-2-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]bicyclo[3.2.0]hept-3-en-6-one (49, 51).** Acid **47** (0.276 g, 0.700 mmol) was treated with oxalyl chloride (0.444 g, 3.50 mmol) in benzene (4 mL) to give the acid chloride, which was added dropwise to Et_3N in benzene as described above. The reaction solution was heated at reflux for 5 h followed by normal workup to give crude **49** and **51**. Flash chromatography on silica gel (92:8 pentane-ether) gave 91.5 mg (39%) of an inseparable mixture of **49** and **51** as a viscous oil. Analysis of NMR data showed a 5:1 mixture of **49** and **51**: IR (neat) 3070, 2924, 2854, 1783, 1428, 1111, 821, 734, 698 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_2Si$: 376.1859. Found: 376.1874.

The data for **49**: ^{1}H NMR δ 7.65 (dd, 4, J = 7.7, 1.6), 7.43-7.35 (m, 6), 5.86 (br ddd, 1, J = 5.5, 2, 2, H_4), 5.70 (ddd, 1, J = 5.5, 1.9, 2.9, H_3), 4.26-4.14 (m, 1, H_5), 3.65 (dd, 1, J = 10.0, 5.6), 3.48 (dd, 1, J = 10.0, 6.7), 3.23 (ddd, 1, J = 17.9, 9.0, 4.3, $H_{7\beta}$), 2.94-2.87 (m, 1, H_2), 2.82 (ddd, 1, J = 17.9, 5.7, 3.1, $H_{7\alpha}$), 2.71 (ddd, 1, J = 9.0, 5.7, 5.9, H_1), 1.05 (s, 9); ^{13}C NMR δ 207.6, 135.5 (4 C), 134.6 (C_4), 133.6 (2 C), 129.7 (2 C), 127.6 (4 C), 127.2 (C_3), 73.2 (C_5), 66.7 (CH_2O), 56.3 (C_2), 52.2 (C_7), 28.9 (C_1), 26.8 (3 C), 19.2.

The data for **51**: ^{1}H NMR δ 7.73-7.57 (m, 4), 7.43-7.35 (m, 6), 5.87-5.78 (m, 1, H_4), 5.76-5.62 (m, 1, H_3), 4.26-4.14 (m, 1, H_5), 3.91 (dd, 1, J = 10.1, 6.6), 3.77 (dd, 1, J = 10.1, 9.0), 3.70-2.66 (m, 4), 1.05 (s, 9); ^{13}C NMR δ 135.5 (4 C), 134.4 (C_4), 133.6 (2 C), 129.7 (2 C), 127.6 (4 C), 126.9 (C_3), 73.5 (C_5), 62.6 (CH_2O), 50.7 (C_2), 46.3 (C_7), 28.3 (C_1), 26.8 (3 C), 19.2 (the carbonyl carbon was not observed).

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Palladium-Catalyzed C-Alkylations of the Highly Acidic and Enolic Triacetic Acid Lactone. Mechanism and Stereochemistry[1]

Marcial Moreno-Mañas,* Jordi Ribas, and Albert Virgili

Departamento de Química, Universidad Autónoma de Barcelona, Bellaterra, 08193 Barcelona, Spain

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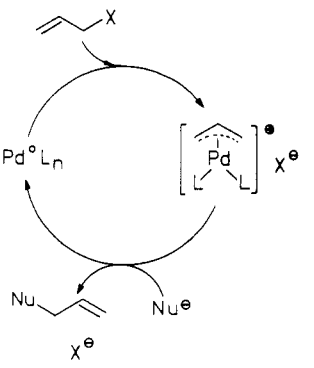
4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone) (**1**) is efficiently alkylated at C-3 with primary and secondary allylic substrates under thermodynamic control by using palladium(0) catalysts. Controlled hydrogenation of the resulting allylated derivatives affords pyrones with saturated chains at C-3. Allylic alkylations occur with retention of configuration at the allylic center, probably through a reversible kinetically favored O-alkylation.

Alylation of proton-active substrates with allylic systems under palladium catalysis is a well established synthetic methodology and some excellent reviews are available.[2] The acidities of the most frequently used proton-active compounds are in the range pK_a = 10-24. The mechanism involves nucleophilic attack of the conjugate bases of the proton-active substrates on a cationic (π-allyl)palladium complex formed in situ from an allylic derivative and zerovalent palladium stabilized by ligands, generally phosphines. The general features of the mechanism are represented in Scheme I. A great variety of leaving groups X have been used, although acetates and alkoxy carbonates have met with the most general acceptance.

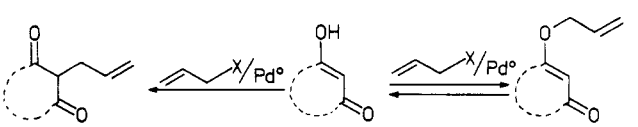
The situation is not so general when nucleophiles of high acidity (p$K_a \leq 10$) are considered. There are some examples of allylic alkylations of nitro acetates and nitro sulfones (p$K_a \sim 5.7$).[3] These nitro substrates do not contain appreciable quantities of alternative tautomers.

Cyclic β-diketones and β-keto esters are substrates having pK_a values around 5 and a high enol content (frequently >99%) which are particularly difficult to alkylate at the central carbon atom due to competition from O-alkylation. We reasoned that C-alkylation of these substrates could be achieved if the reactions were performed under reversibility conditions in order to permit the slow alkylation at carbon to predominate under thermodynamic control. Palladium-catalyzed alkylation with allylic reagents should fit the above conditions since the enol ether initially formed under kinetic control ought to act as an alkylating agent itself in which the leaving group, the enolate anion, is the conjugate base of an acid as strong as acetic acid. In other words, alkylation at oxygen must

Scheme I



Scheme II



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