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Type-II Intramolecular [2 + 2] Cycloaddition of Alkenes with Vinylketenes Prepared by the Regiospecific Deprotonation of β,β-Disubstituted α,β-Unsaturated Acid Chlorides

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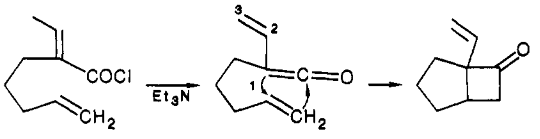
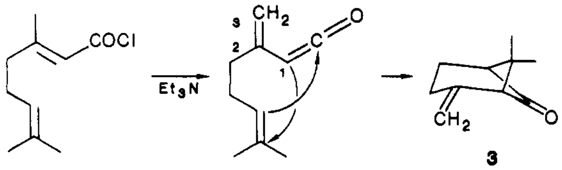
Treatment of β,β-disubstituted α,β-unsaturated acid chlorides with Et_3N in the presence of an alcohol leads to mixtures of vinylketenes, which were trapped as the β,γ-unsaturated ester. These studies establish that deprotonation occurs largely on the less substituted γ-carbon ($CH_3 > CH_2 > CH$) due to the greater kinetic acidity of protons on a less substituted alkyl group. The stereochemistry of the α,β-unsaturated acid chloride has no effect on the mixture of vinylketenes formed. This result is in marked contrast to the deprotonation of α,β-unsaturated esters, acids, and amides with lithium bases, which occurs regiospecifically on the γ-carbon syn to the carbonyl group. Vinylketenes **5**, **11**, **16**, and **21** undergo an intramolecular [2 + 2] cycloaddition with the terminal double bond to give adducts **6**, **12**, **17** and **18**, and **23** with an exocyclic double bond. In two cases, cycloadducts **14** and **25** with an endocyclic double bond were also isolated. These minor adducts, which were formed only in cases where cyclization should be slow, appear to be formed by interconversion of vinylketenes by protonation–deprotonation prior to cyclization.

The stereospecific cycloaddition of ketenes to alkenes provides an attractive route to cyclobutanones and is one of the few general methods for carbofunctionalization of alkenes. We[2] and others[3] have recently recognized that the intramolecular version of this reaction provides a general method for the synthesis of polycyclic cyclobutanones.[4] Although simple ketenes do react with some alkenes, satisfactory yields are not generally obtained unless activated ketenes are used. Excellent results have been obtained with alkoxyketenes,[2a,e,3a,d] chloroketenes,[2a,f] vinylketenes,[2b,c,g,3a-c,e,g] and keteniminium salts.[2a,e,3a,f] Vinylketenes are particularly attractive addends since the alkene-containing side chain can be attached to the vinylketene at three different positions (see eq 1-3), and the resulting vinylcyclobutanones are versatile synthetic intermediates.



(1)

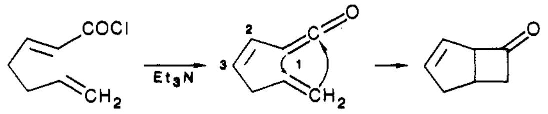
type I



(2)

1 **2** **3**

type II



(3)

type III

Vinylketenes[5] have been prepared from crotonyl chloride and dimethylacryloyl chloride by treatment of amine bases and trapped as cyclobutanone adducts with reactive alkenes such as enol ethers,[6] enamines,[7] and cyclopentadiene and other dienes.[8] Cyclobutanones can also be obtained with simple alkenes if an excess of alkene is used as solvent.[8d] Vinylketenes can also be prepared by electrocyclic ring opening of cyclobutenones.[5,8c] Vinylketenes used in intramolecular cycloadditions have been prepared unambiguously by the dehydrohalogenation of β,γ-unsaturated acid chlorides[3b,c] and α,β-unsaturated acid chlorides containing two identical β-substituents.[3a]

We have shown that vinylketenes of all three types, in which the side chain is attached to any of the three carbons of the vinylketene, can be efficiently prepared by treatment of readily available α,β-unsaturated acid chlorides with Et_3N. In particular, vinylketenes of type II (see eq 2) are prepared with excellent regioselectivity despite the possibility of deprotonation of the methylene group to give isomeric vinylketenes.[2b,c,g] For instance, treatment of geranoyl chloride (**1**) with Et_3N in toluene at reflux gives a 40–50% yield of **3** and only ≈5% of the isomer containing an endocyclic double bond. Adduct **3** has been

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[1] Camille and Henry Dreyfus Teacher-Scholar, 1982–1987.

[2] (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.

[3] (a) Marko, 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. G. *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.

[4] For earlier examples of intramolecular cycloadditions of ketenes, see ref 3 in ref 2e and the following: (a) Murray, R. K., Jr.; Goff, D. L.; Ford, T. M. *J. Org. Chem.* **1977**, *42*, 3870. (b) Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1977**, *42*, 2981.

[5] Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821 and references cited therein.

[6] Payne, G. B. *J. Org. Chem.* **1966**, *31*, 718.

[7] Hickmott, P. W.; Miles, G. J.; Sheppard, G.; Urbani, R.; Yoxall, C. T. *J. Chem. Soc., Perkin Trans.* **1973**, 1514.

[8] (a) Holder, R. W.; Freiman, H. S.; Stefanchik, M. F. *J. Org. Chem.* **1976**, *41*, 3303. (b) Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810. (c) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (d) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330. (e) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.

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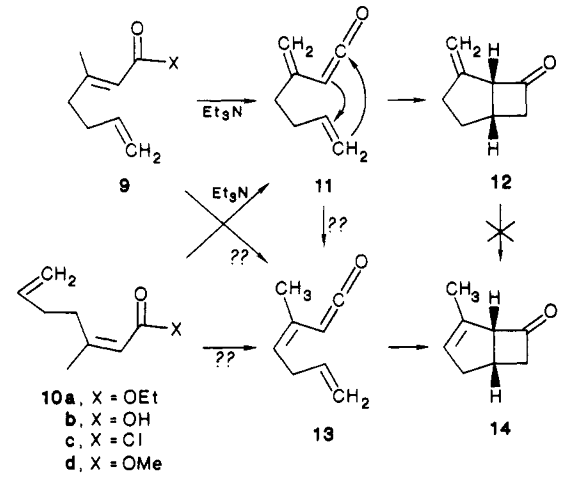
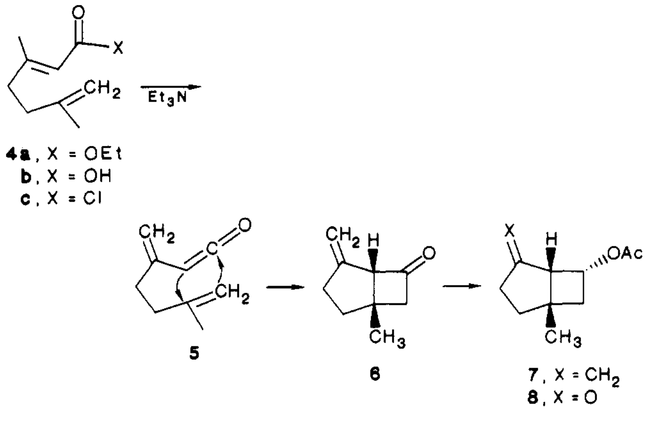
Scheme I



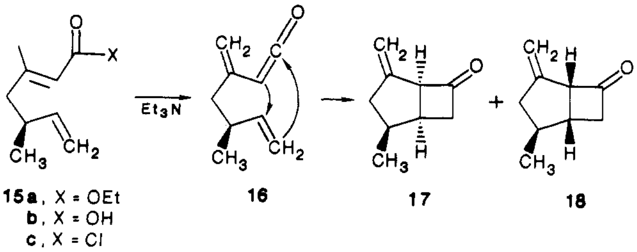
converted to chrysanthenone and β-pinene. In a similar manner, farnesoyl chlorides have been converted to the β-bergamotenes. We report here the origin of the regioselective deprotonation of α,β-unsaturated acid chlorides such as 1 and further studies indicating the scope and limitations of type II intramolecular cycloadditions of vinylketenes.[9]

Results and Discussion

The requisite acid chlorides were easily prepared from the corresponding ketone by a three-step sequence. Reaction of the ketone with the sodium salt of triethyl phosphonoacetate in DME gave the α,β-unsaturated ester as a mixture rich in the *E* isomer.[10] Hydrolysis of the ester with aqueous barium hydroxide at reflux gave the acid, which was converted to a mixture of acid chlorides rich in the *E* isomer by treatment with oxalyl chloride. Slow addition of a toluene solution of 4c[10–12] to a solution of Et_3N (3 equiv) in toluene at reflux followed by heating for 1 h at reflux gave 6 in 43% isolated yield. The yield may be significantly higher since the volatility of 6 makes isolation difficult. The formation of a bicyclo[3.2.0]heptanone rather than a bicyclo[3.1.1]heptanone such as 3 was expected since we have previously shown that electronic effects of substituents on the alkene, rather than the connectivity pattern, control the regiochemistry of the cycloaddition.[2]



Similar treatment of acid chloride 9c[11] gave a 58% yield of 12 and a 10% yield of 14 (Scheme I). This demonstrates the importance of the conjugated double bond in facilitating the cycloaddition since the intramolecular cycloaddition of the saturated ketene lacking the methylene group has been reported to give only a 3% yield of cycloadduct.[3a] Although this reaction gave a good yield of the expected product 12, a significant, and somewhat variable, amount of the unexpected adduct 14, with an endocyclic double bond, was also formed. Treatment of acid chloride 15c[12] with Et_3N gave a 39% yield of an inseparable 1.5:1 mixture of 17 and 18. Finally, treatment of 19c with Et_3N gave a 1.5:1 mixture of cycloadducts, which were separated to give a 33% yield of the expected anti adduct 23 and a 25% yield of the unexpected adduct 25 (Scheme II).



Vinylcyclobutanones 6, 12, 17, 18, 23, and 25 are relatively unstable. They can be purified chromatographically and stored under nitrogen, but undergo spontaneous Baeyer–Villiger reactions at room temperature in air.

The structures of the adducts were determined by analysis of the ^1H and ^{13}C NMR spectra. 4-Methylenebicyclo[3.2.0]heptan-6-ones and bicyclo[3.2.0]hept-3-en-6-ones are readily characterized by the NMR absorption of H_5 at δ 3.9–4.1 and the downfield absorption of $(CH_2)_7$ with a geminal coupling constant of 18 Hz. No similar absorptions occur in 2-methylenebicyclo[3.1.1]heptan-6-ones.[2g] The stereochemistry of 17 and 18 was easily assigned by examination of the ^{13}C NMR spectra. The methyl group and C_7 of the major isomer 17 absorb at δ 22.7 and 51.2, respectively. The corresponding carbons of the minor isomer in which the methyl group and C_7 are cis on the five-membered ring are shifted upfield to δ 14.1 and 45.1 by the γ-gauche effect.

The gross structures of 23 and 25 were easily assigned. However, the stereochemistry of 23 could not be determined by analysis of the NMR spectra, especially in the absence of the syn isomer 24. Fortunately the absorptions due to H_{6a} and $H_{6\beta}$ can be clearly distinguished and assigned in the 300-MHz ^1H NMR spectrum. Shift experiments with $Eu(fod)_3$ established that H_{6a} was shifted downfield by 0.76 ppm/mol of shift reagent while $H_{6\beta}$ was shifted downfield only 0.32 ppm. This result is consistent only with the anti isomer 23. $H_{6\beta}$ would be shifted further downfield than H_{6a} in the syn isomer 24.

Formal Synthesis of Lineatin. Reduction of 6 with L-Selectride (Aldrich Chemical Co.) at −78 °C for 0.5 h and 1.5 h at 0 °C followed by acetylation of the resulting alcohol with acetic anhydride in pyridine gave 7 in 68% overall yield. The NMR spectrum of 7 prior to purification indicated the presence of ≈10% of the epimeric acetate in the product. Ozonolysis of 7 followed by reduction of the ozonide with triphenylphosphine gave 8 in 97% yield. Keto acetate 8 is an intermediate in Mori's synthesis of lineatin.[13] The 90-MHz NMR and IR spectra of 8 are

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[9] Portions of this work have been published in preliminary form. See ref 2c.

[10] (a) Wadsworth, W. S., Jr. *Org. React.* (*N.Y.*) **1977**, *25*, 73. (b) Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 1292.

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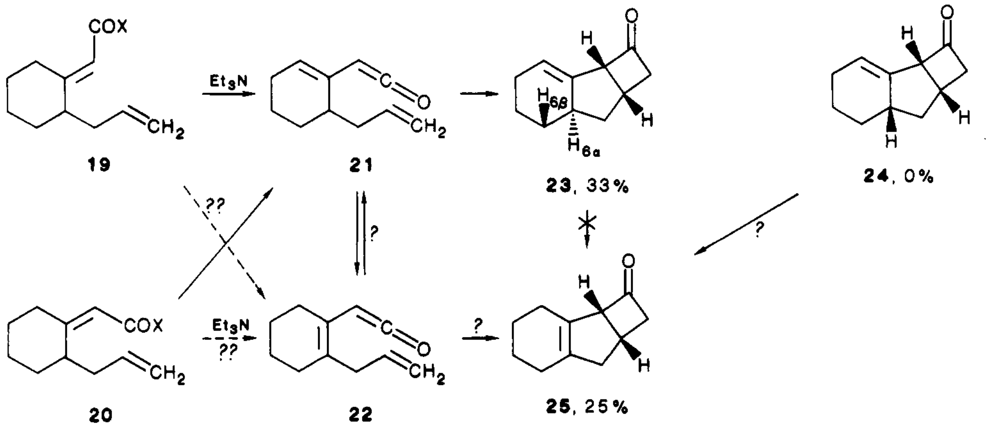
[13] (a) Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197. (b) Mori, K.; Uematsu, T. *Tetrahedron Lett.* **1982**, *23*, 1921. (c) Mori, K.; Uematsu, T. *Tetrahedron* **1983**, *39*, 1735. (d) Mori, K.; Sasaki, M. *Tetrahedron Lett.* **1979**, 1329.

Scheme II



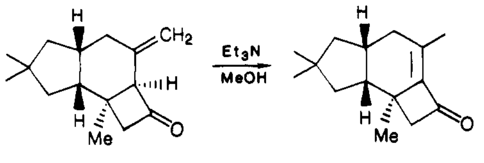
a, X = OEt; b, X = OH; c, X = Cl; d, X = OMe; e, X = O-*t*-Bu

identical with those provided by Mori.[14] The preparation of **8** therefore constitutes a formal synthesis of lineatin and provides a further structure proof of **6**.

Regiochemistry of Ketene Generation. These results raise two significant mechanistic questions. In general, the cycloadducts possess an exocyclic double bond and are obtained from the vinylketene derived from deprotonation of a methyl group syn to the acid chloride rather than a methylene group anti to the acid chloride. What is the origin of this selectivity? Secondly, why are products **14** and **25** with an endocyclic double bond obtained in addition to the expected adducts **12** and **23**.

Control experiments indicated that **14** was not formed by isomerization of **12**, which could in principle occur by conjugation followed by deconjugation. No reaction occurred on heating a toluene solution of the cycloadduct **12** at reflux in the presence of either Et_3N, $Et_3N{\cdot}HCl$, or Et_3N and acetyl chloride. Cycloadduct **12** is also not isomerized by Et_3N in methanol. A similar series of experiments established that **23** does not isomerize to **25** under the reaction conditions. It is conceivable that **25** could be formed by isomerization of the syn adduct **24**. This could not be established since **24** was not available.

Oppolzer reported that treatment of **26** with Et_3N in methanol resulted in conjugation of the double bond to give **27**.[3g] On the other hand, conjugation of the double bond of **12** or **23** cannot be carried out under these or considerably harsher conditions. Molecular mechanics calculations suggest a thermodynamic rather than kinetic origin for this differing behavior due to the size of the ring fused to the cyclobutanone. Conjugation of the double bond is predicted to be favorable by 1 kcal/mol for 5-methylenebicyclo[4.2.0]heptan-7-ones such as **26** and unfavorable by 3 kcal/mol for 4-methylenebicyclo[3.2.0]-heptan-6-one (**12**).



26 **27**

The regiochemistry of deprotonation of α,β-unsaturated acids, esters, and amides with lithium amide bases has been studied extensively.[15-18] Katzenellenbogen and Crumrine suggested that kinetic deprotonation of β,β-disubstituted α,β-unsaturated acids occurs on the methyl rather than methylene group regardless of double bond geometry.[15] More recently, Harris and Weiler[17] and Snieckus et al.[18] showed, by the use of labeled substrates, that deprotonation occurs selectively on the group syn to an acid, ester, or amide function under kinetic conditions. This syn effect has been proposed to result from coordination of the lithium to the carbonyl oxygen. Since the predominant isomer of the acid chlorides is the *E* isomer (**4c**, **9c**, **15c**, and **19c**), either the syn effect and/or the greater kinetic acidity of the less substituted alkyl group could be responsible for the observed regioselectivity.

In order to distinguish between these two possibilities, the *Z* acid chlorides **10c** and **20c** were prepared from the ketone by using the Peterson olefination procedure, which has been shown to be selective for the *Z* isomer.[11,19] Treatment of **10c** with Et_3N in toluene at reflux gave a 60% yield of **12** and **14**, again as a ≈5:1 mixture. Similar treatment of **20c** gave a 51% yield of a 1.5:1 mixture of **23** and **25**. Thus, in both cases, identical mixtures of cycloadducts are obtained from either the *E*- or *Z* acid chloride.

These results establish that the position of deprotonation of β,β-disubstituted α,β-unsaturated acid chlorides with amine bases is controlled by the kinetic acidity of the substituents and that the syn effect is not applicable. These results do not, however, explain why significant amounts of adduct with an endocyclic double bond are obtained from **9c** but not from **4c** or **15c**. Furthermore, they do not explain why adduct **25**, which is derived from ketene **22** formed by abstraction of a methine proton, is formed almost as readily as adduct **23**, which is derived from ketene **21** formed by abstraction of a methylene proton.

We therefore turned our attention to the exploration of other methods that could be used to trap the ketene. Vinylketenes react with alcohols to give β,γ-unsaturated esters.[20,21] Reaction of α,β-unsaturated acid chlorides with

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[14] We thank Professor Mori for providing us with spectral data of 8.

[15] Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925; 1974, *96*, 5662.

[16] Cainelli, G.; Cardillo, G.; Contento, M.; Trapani, G.; Ronchi, A. U. *J. Chem. Soc., Perkin Trans. 1*, 1973, 400.

[17] Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939; 1984, *25*, 1333.

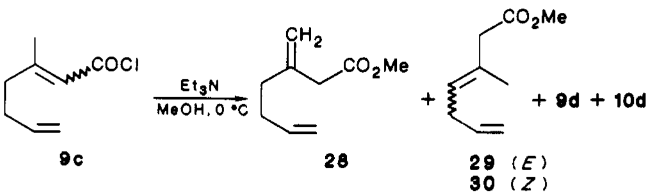
[18] Majewski, M.; Green, J. R.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 531.

[19] (a) Strekowski, L.; Visnick, M.; Battiste, M. A. *Tetrahedron Lett.* **1984**, *25*, 5603. (b) Visnick, M.; Strekowski, L.; Battiste, M. A. *Synthesis* **1983**, *284*.

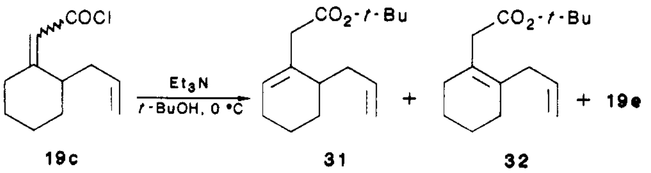
[20] Mayer, H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 500. Huisgen, R.; Mayer, H. *J. Chem. Soc., Chem. Commun.* **1976**, 55 and 57. Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6118.

Et_3N in the presence of alcohols gives mixtures of β,γ-unsaturated esters via addition of alcohol to the ketene and α,β-unsaturated esters via direct displacement.[20,21] Acylammonium salts, formed by displacement of the chloride with triethylamine, are probably intermediates in both the formation of the vinylketene and α,β-unsaturated ester. Use of an unhindered alcohol such as methanol favors formation of the α,β-unsaturated ester by direct displacement, while use of a hindered alcohol such as *tert*-butyl alcohol favors formation of the β,γ-unsaturated ester via the ketene. This reaction had in fact been used by Bedoukian and Wolinsky who trapped ketene **2** with methanol to produce methyl γ-geranoate.[22]

Since we have previously determined that either *E*- or *Z* acid chlorides give the same mixture of cycloadducts, the trapping experiments were performed on a mixture of stereoisomers. A 3.7:1 mixture of **9c** and **10c**, respectively, was treated with Et_3N and methanol to give, after normal workup, a 55:5:1:1:1 mixture of **28**, either **29** or **30**, either **30** or **29**, **9d**, and **10d**, respectively, as determined by analysis of the NMR spectrum. The selective formation of **28** is expected from Bedoukian and Wolinsky's results.[22]



A 4:1 mixture of the acyl chlorides **19c** and **20c**, respectively, when treated as described above, gave a 4:1 mixture of the α,β-unsaturated esters **19d** and **20d**, respectively. This result was puzzling, since we isolated the expected β,γ-unsaturated esters via trapping of the vinylketene intermedites **11** and **13**. After extensive experimentation, we concluded that the α,β-unsaturated esters were being formed by direct displacement without the intermediacy of a ketene. Since the use of hindered alcohols favors ketene formation at the expense of direct displacement,[21] the ketene trapping experiment with **19c** and **20c** was repeated with *tert*-butyl alcohol, which gave a 15:3:1 mixture of **31**, **19e**, and **32**, respectively. The conjugated ester **19e** was presumably formed by direct displacement of the acid chloride with *tert*-butyl alcohol without the intermediacy of a vinylketene.



The selective formation of **21** from the *Z* acid chloride **20c** was expected on mechanistic grounds. In fact, the syn effect should not be operative with any derivative of the *Z* acid **20**. Derivatives of *E* acid **19** exist in the conformation with an equatorial methyl group, leaving both syn and anti axial hydrogens exposed for deprotonation. Because of $A^{1,3}$ strain,[23] *Z* acid chloride **20c** exists as the conformer with an axial methyl group, leaving only the anti axial proton available for deprotonation. Thus, the *Z* acid chloride derived **20c** should undergo deprotonation exclusively from the anti axial methylene proton to give vinylketene **21**.

Intramolecular cycloadditions of either **9c** or **10c** or mixtures of them gave identical ≈5:1 mixtures of **12** and **14**. Trapping of the vinylketenes (**11** and **13**) obtained from **9c** and **10c** with methanol indicated that they were formed in a ratio of greater than 10:1. Since **12** was not converted to **14** under the reaction conditions, vinylketene **11** was probably converted to **13** by protonation–deprotonation, followed by cyclization of **13** to give **14** (Scheme I). Vinylketene **11** was also presumably converted to the *E* isomer of **13** by protonation–deprotonation. However, the *E* isomer cannot undergo a cycloaddition and either dimerizes or polymerizes.

A similar hypothesis explains the discrepancy between formation of a 1.5:1 mixture of **23** and **25** from either **19c** or **20c** despite the formation of a 15:1 mixture of vinylketenes **21** and **22** as evidenced by trapping with *tert*-butyl alcohol. Presumably, the cyclization of **21** is slower than the cyclization of **22** and acyclic ketenes **5**, **11**, and **16**. Conversion of **21** to **22**, which cyclizes to **25**, can therefore compete more effectively.

Conclusion

These results establish that the regioselectivity of dehydrochlorination of unsaturated acid chlorides to give vinylketenes results solely from the relative kinetic acidity of the γ-protons. This is in marked contrast to the recent results of Weiler[17] and Snieckus[18] who found that deprotonation of α,β-unsaturated esters, acids, or amides with lithium amide bases occurred regioselectively on the group syn to the acid function under kinetic conditions. The regioselectivity in these cases has been proposed to result from coordination of the lithium to the carbonyl oxygen. Since complexation cannot occur in ketene formation from treatment of acid chlorides with Et_3N, the dichotomy is more apparent than real. In the absence of complexation effects, the relative kinetic acidity of the γ-proton would be expected to control the regiochemistry of dehydrochlorination.

The formation of α,β-unsaturated methyl esters on treatment of **19c** and **20c** with Et_3N in methanol, which was a major aggravation at the time, in retrospect confirms our analysis of the origin of the regioselectivity of deprotonation. Deprotonation of the methyl protons of **9c** and **10c** by Et_3N is faster than direct displacement of the chloride by methanol. On the other hand, deprotonation of the methylene protons of **19c** and **20c** by Et_3N is slower than direct displacement of the chloride by methanol. Since direct displacement should occur at the same rate in both cases, this result provides evidence of the importance of the relative kinetic acidity of the γ-protons ($CH_3 > CH_2 > CH$) in an inter- rather than intramolecular competition.

The less substituted vinylketene formed by kinetic deprotonation of the most acidic hydrogen atom can isomerize, presumably by protonation–deprotonation, to give the more substituted vinylketene, which cyclizes to give an adduct with an endocyclic double bond such as **14** and **25**. The formation of the unexpected minor cycloadduct **25** as 40% of the product mixture, while the *tert*-butyl alcohol-trapping experiment establishes that only traces of vinylketene **22** were formed on dehydrochlorination with Et_3N, unambiguously establishes that interconversion of vinylketenes can occur.

No ketene isomerization is observed with **5**, which cyclizes rapidly because of the more nucleophilic 1,1-disubstituted double bond. Similarly, ketene **16** cyclizes more rapidly because of the buttressing effect of the methyl

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[22] Bedoukian, R. H.; Wolinsky, J. *J. Org. Chem.* **1975**, *40*, 2154.

[23] Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

group. A small amount of isomerization is observed with **10**, while with **21** a substantial amount of isomerization to **22** occurs, presumably due to steric inhibition of the cycloaddition reaction by the cyclohexane ring.

These results indicate the scope of type II intramolecular cycloadditions of vinylketenes and indicate the factors responsible for regiospecific generation of vinylketenes from β,β-disubstituted α,β-unsaturated acid chlorides.

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. MPLC refers to medium-pressure liquid chromatography on a Merck Lobar silica gel column. Gas chromatography was performed with a Perkin-Elmer 8310 apparatus equipped with a flame ionization detector and a fused silica glass capillary column (25 m, 0.25 μm, bonded OV-225B). Temperature programing was as follows: first ramp from 60–100 °C at 10 °C/min, second ramp from 100–170 °C at 30 °C/min, and isothermal stage at 170 °C for 2 min. Flow rate was 25 mL/min. 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.

Preparation of Starting Materials. 5-Methyl-5-hexen-2-one and 4-methyl-5-hexen-2-one were prepared by oxidation[24] of the commercially available alcohols. Allylcyclohexanone was prepared by the literature procedure.[25] Mixtures of unsaturated esters rich in the E isomer were obtained by adding the ketone to a solution of the sodium salt of triethyl phosphonoacetate (prepared from NaH) in DME at 25 °C and heating the resulting solution for 30 min at reflux.[10] The desired α,β-unsaturated esters were obtained in 60–80% yield as a mixture containing 75–85% of the E isomer. Mixtures of unsaturated esters rich in the Z isomer were obtained by adding the ketone to a solution of the lithium salt of ethyl (trimethylsilyl)acetate (prepared from LDA) at −78 °C.[11,19] The resulting solution was stirred for 2 h at −78 °C, warmed to 25 °C, and worked up to give a 40–70% yield of a mixture containing 50–70% of the Z isomer. Partial separation of isomers could be effected by flash chromatography on silica gel with 95:5 pentane–ether as eluent. The Z isomer eluted first. The spectral data reported below are obtained from partially separated isomers. Hydrolysis of the ester was effected by heating at reflux an aqueous suspension of the ester with barium hydroxide for 12–24 h. The stereochemistry was easily determined by analysis of the ^{1}H and ^{13}C NMR spectra. The ester or acid deshields the protons on a *syn*-β-alkyl group[26] and shields the carbon of a *syn*-β-alkyl group.[27]

The spectral data for ethyl (E)-3-methyl-2,6-heptadienoate (**9a**)[11,12] are as follows: ^{1}H NMR δ 5.80 (m, 1, H$_6$), 5.67 (br, 1, H$_2$), 5.04 (d, 1, J = 17.1, H$_7$), 4.99 (d, 1, J = 10.2, H$_7$), 4.13 (q, 2, J = 7.1), 2.24 (br, 4), 2.20 (s, 3), 1.27 (t, 3, J = 7.1); ^{13}C NMR δ 158.9, 137.2, 115.9, 115.4, 59.4, 40.1, 31.5, 18.7, 14.3, the carbonyl carbon was not observed; GC t_R 6.9 min.

The spectral data for ethyl (Z)-3-methyl-2,6-heptadienoate (**10a**)[11,12] are as follows: ^{1}H NMR δ 5.83 (ddt, 1, J = 17.1, 9.9, 6.5, H$_6$), 5.67 (br, 1, H$_2$), 5.05 (dd, 1, J = 17.1, 1.4, H$_7$), 4.95 (dd, 1, J = 9.9, 1.2, H$_7$), 4.13 (q, 2, J = 7.3), 2.73 (t, 2, J = 7.7, H$_4$), 2.23 (dt, 2, J = 7.7, 6.5, H$_5$), 1.88 (d, 3, J = 1.3), 1.27 (t, 3, J = 7.3); ^{13}C NMR δ 166.1, 159.3, 137.8, 116.5, 114.7, 59.3, 32.5, 32.2, 25.0, 14.2; GC t_R 6.4 min.

The spectral data for (E)-3-methyl-2,6-heptadienoic acid (**9b**) are as follows: ^{1}H NMR δ 5.79 (m, 1, H$_6$), 5.70 (s, 1, H$_2$), 5.04 (d, 1, J = 17.1, H$_7$), 5.00 (d, 1, J = 8.9, H$_7$), 2.26 (m, 4), 2.17 (d, 3, J = 1.2); ^{13}C NMR δ 172.2, 162.5, 137.0, 115.5, 40.4, 31.4, 19.1, one carbon was not observed.

The spectral data for the (Z)-3-methylhepta-2,6-dienoic acid (**10b**) are as follows: ^{1}H NMR δ 5.83 (m, 1, H$_6$), 5.70 (br, 1, H$_2$), 5.07 (d, 1, J = 17.1, H$_7$), 5.00 (d, 1, J = 9.9, H$_7$), 2.77 (t, 2, J = 7.1, H$_4$), 2.23 (m, 2, H$_5$), 1.93 (s, 3).

The spectral data for a 6:1 mixture of ethyl (E)- and (Z)-3,6-dimethylhepta-2,6-dienoate (**4a**)[10b,11] are as follows: ^{1}H NMR δ 5.7 (br s, 1, H$_2$), 4.72 (br s, 2, H$_7$), 4.1 (q, 2, J = 7), 2.7 (m, 0.14 × 2, Z-H$_4$), 2.3 (m, 0.86 × 4 + 0.14 × 2), 2.2 (s, 0.86 × 3), 1.8 (s, 0.14 × 3), 1.7 (s, 3, Me), 1.2 (t, 3, J = 7).

The spectral data for a 6:1 mixture of (E)- and (Z)-3,6-dimethylhepta-2,6-dienoic acid (**4b**) are as follows: ^{1}H NMR δ 12.2 (br s, 1), 5.7 (br s, 2, H$_2$), 4.78 (br s, 1, H$_7$), 4.72 (br s, 1, H$_7$), 2.7 (m, 0.14 × 2, Z-H$_4$), 2.3 (m, 0.86 × 4 + 0.14 × 2), 2.2 (s, 0.86 × 3), 1.8 (s, 0.14 × 3), 1.7 (s, 3, Me).

The spectral data for a 6:1 mixture of ethyl (E)- and (Z)-3,5-dimethylhepta-2,6-dienoate (**15a**)[12] are as follows: ^{1}H NMR δ 5.6 (m, 2, H$_2$, H$_6$), 4.98 (br d, 1, J = 17, H$_7$), 4.92 (br d, 1, J = 10, H$_7$), 4.1 (q, 2, J = 7), 2.6–2.2 (m, 3), 2.16 (s, 0.86 × 3, E-Me), 1.8 (s, 0.14 × 3, Z-Me), 1.2 (t, 3, J = 7), 0.98 (d, 3, J = 7).

The spectral data for a 6:1 mixture of (E)- and (Z)-3,5-dimethylhepta-2,6-dienoic acid (**15b**) are as follows: ^{1}H NMR δ 9.3 (br s), 5.6 (m, 2, H$_2$, H$_6$), 4.98 (br d, 1, J = 17, H$_7$), 4.92 (br d, 1, J = 10, H$_7$), 2.6–2.2 (m, 3), 2.16 (s, 0.86 × 3, E-Me), 1.8 (s, 0.14 × 3, Z-Me), 0.98 (d, 3, J = 7).

The spectral data for ethyl (E)-[2-(2-propenyl)cyclohexylidene]acetate (**19a**) are as follows: ^{1}H NMR δ 5.65 (m, 1), 5.58 (d, 1, J = 1.2), 4.95 (m, 2), 4.13 (q, 2, J = 7.1), 3.00 (m, 1), 2.70 (m, 1), 2.4–2.1 (m, 4), 1.9–1.4 (m, 5), 1.27 (t, 3, J = 7.1); ^{13}C NMR δ 166.5, 165.3, 136.3, 116.0, 112.0, 59.2, 45.0, 36.3, 33.4, 28.1 (2), 23.5, 14.1; GC t_R 5.9 min.

The spectral data for ethyl (Z)-[2-(2-propenyl)cyclohexylidene]acetate (**20a**) are as folows: ^{1}H NMR δ 5.80 (m, 1), 5.63 (d, 1, J = 1.7), 5.06 (d, 1, J = 10), 4.97 (br d, 1, J = 17), 4.17 (q, 2, J = 7.1), 4.00 (m, 1, H$_2$), 2.33 (dd, 2, J = 7.2, 7.2), 2.2–1.4 (m, 8), 1.33 (t, 3, J = 7.1); ^{13}C NMR δ 166.5, 165.5, 136.9, 115.6, 114.1, 59.4, 36.5, 35.8, 33.5, 30.2, 28.2, 20.4, 14.2; GC t_R 5.6 min.

The spectral data for (E)-[2-(2-propenyl)cyclohexylidene]acetic acid (**19b**) are as follows: ^{1}H NMR δ 5.63 (s, 1), 5.33 (dddd, 1, J = 17.5, 9.9, 7.5, 6.0), 5.06 (d, 1, J = 17.5), 5.02 (d, 1, J = 9.9), 3.00 (m, 1), 2.70 (m, 1), 2.4–2.1 (m, 3), 1.9–1.3 (m, 5); ^{13}C NMR δ 172.8, 168.7, 136.4, 116.4, 111.6, 45.5, 36.5, 33.6, 28.5, 28.4, 23.6.

The spectral data for (Z)-[2-(2-propenyl)cyclohexylidene]acetic acid (**20b**) are as follows: ^{1}H NMR δ 5.75 (m, 1), 5.63 (s, 1), 5.00 (d, 1, J = 10), 4.91 (br d, 1, J = 17), 4.00 (m, 1, H$_2$), 2.70 (t, 1, J = 7.2), 2.1–1.4 (m, 8); ^{13}C NMR δ 172.4, 168.8, 136.7, 115.6, 113.7, 36.5, 35.7, 33.6, 30.2, 28.2, 20.3.

Preparation of 1-Methyl-4-methylenebicyclo[3.2.0]heptan-6-one (6). Oxalyl chloride (1.4 g, 11.6 mmol) was added to a solution of a 6:1 mixture of (E)- and (Z)-3,6-dimethyl-2,6-heptadienoic acid (**4b**) (0.358 g, 2.3 mmol) in 8 mL of benzene. The solution was heated to 78 °C for 0.5 h and cooled to 25 °C. The benzene was removed in vacuo, and the acid chloride **4c** was added in 25 mL of toluene over 10 min to a boiling solution of Et$_3$N (0.73 g, 7.0 mmol) in 125 mL of toluene. The solution was heated at 110 °C for 1 h and cooled to 25 °C. The solvent was evaporated, and the resulting gum was dissolved in pentane. Filtration and evaporation of the solvent gave 0.451 g (140%) of crude product. Flash chromatography (silica gel, 95:5 pentane–ether) gave 0.138 g (43%) of **6**, which was greater than 95% pure as determined by 300-MHz ^{1}H NMR: ^{1}H NMR δ 4.92 (br s, 1), 4.87 (br s, 1), 3.44 (m, 1), 2.95 (dd, 1, J = 2.4, 18.3), 2.84 (dd, 1, J = 4.4, 18.3), 2.52 (m, 2), 1.93 (ddd, 1, J = 2.5, 7.1, 13.0), 1.74 (ddd, 1, J = 8.1, 13.0, 13.0), 1.45 (s, 3); ^{13}C NMR δ 206.5, 147.8, 108.9, 75.4, 56.6, 39.3, 38.2, 33.3, 24.7; IR (neat) 3070, 2960–2900 (2940), 2850, 1772, 1650 cm^{-1}. Vinylcyclobutanones **6**, **12**, **17**, **18**, **23**, and **25** are relatively unstable and undergo spontaneous Baeyer–Villiger reactions in the presence of oxygen. This precluded obtaining accurate elemental analyses.

Preparation of 4-Methylenebicyclo[3.2.0]heptan-6-one (12) and 4-Methylbicyclo[3.2.0]hept-3-en-6-one (14). A solution of (E)- and (Z)-3-methyl-2,6-heptadienoyl chloride (**9c** and **10c**) (792.5 mg, 5 mmol), obtained from a 3.7:1 mixture of **9b** and **10b** as described above, in 30 mL of toluene was added dropwise over 15 min to a boiling solution of Et$_3$N (1.96 g, 19.4 mmol) in 80 mL of toluene. The resulting mixture was heated at reflux for 1 h, cooled, and treated with 40 mL of water. The aqueous layer was

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[24] Ratcliffe, R. W. *Org. Synth.* **1976**, *55*, 84.

[25] Howard, W. L.; Lorette, N. B. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 25 and 292.

[26] See ref 19a and ref 7 therein.

[27] For assignment of the ^{13}C NMR spectra of 3-methyl-2-butenoic acid and cyclohexylideneacetic acid, see: *Carbon-13 NMR Collection*; Sadtler Research Laboratories; spectra 1964C and 5516C.

separated and extracted twice with pentane. The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo to give 903 mg of crude product, which consisted of a 5.2:1 mixture of 4-methylenebicyclo[3.2.0]heptan-6-one (**12**) and 4-methylbicyclo[3.2.0]hept-3-en-6-one (**14**), respectively, as determined by analytical GC. Purification of a portion of the crude product (380 mg) by flash chromatography (silica gel, 95:5 pentane–ether) gave 25 mg of unidentified product, 24.4 mg (10%) of **14**, and 150.5 mg (58%) of **12**, which was greater than 95% pure as determined by 300-MHz ^{1}H NMR. Elution with ether gave 99 mg of a brown, unidentified mixture of products.

The spectral data for 4-methylbicyclo[3.2.0]hept-3-en-6-one (**14**) are as follows: ^{1}H NMR δ 5.46 (br, 1, H_3), 4.02 (br, 1, H_5), 3.21 (ddd, 1, $J \approx 18, 9, 5$, H_7), 2.81 (m, 3), 2.36 (m, 1), 1.76 (s, 3); ^{13}C NMR δ 135.0, 126.6, 76.1, 53.4, 40.2, 26.6, 15.3, the carbonyl carbon was not observed; GC t_R 4.0 min.

The spectral data for 4-methylenebicyclo[3.2.0]heptan-6-one (**12**) are as follows: ^{1}H NMR δ 4.98 (br, 1), 4.95 (br, 1), 3.92 (m, 1, H_5), 3.25 (ddd, 1, $J = 18.4, 9.0, 5.0$, H_7), 3.05 (m, 1, H_1), 2.76 (ddd, 1, $J = 18.4, 5.1, 3.1$, H_7), 2.48 (m, 1), 2.30 (br dd, 1, $J = 15.0, 7.5$), 1.99 (dddd, 1, $J = 12.8, 12.8, 7.5, 6.5$), 1.83 (br ddd, 1, $J = 12.8, 7.5, 2.5$); ^{13}C NMR δ 207.3, 147.6, 108.8, 70.9, 51.3, 31.8 (2 C), 29.8; IR 3080, 2950, 2860, 1778, 1650; GC t_R 4.5 min.

Preparation of 2-Methyl-4-methylenebicyclo[3.2.0]heptan-6-one (17 and 18). The acid chloride **15c** prepared as described above from a 6:1 mixture of (*E*)- and (*Z*)-**15b** (0.206 g, 1.3 mmol) was added in 25 mL of toluene over 30 min to a boiling solution of Et_3N (1.38 g, 13.4 mmol) in 250 mL of toluene. The solution was heated at 110 °C for 7.5 h. The solution was cooled to 25 °C, the solvent was evaporated at 20 Torr and 0 °C, and the resulting gum was dissolved in pentane. Filtration through Celite and evaporation of the solvent gave 0.266 g of crude product. Medium-pressure chromatography (silica gel, 99.6:0.4 pentane–ethyl acetate) gave 0.058 g (39%) of an inseparable 1.5:1 mixture of **17** and **18**: ^{1}H NMR (**17**) δ 5.01 (s, 2), 3.94 (m, 1, H_5), 3.21 (ddd, 1, $J = 4.7, 9.3, 18.6$, $H_{7\beta}$), 2.92 (m, 1, H_1), 2.77 (ddd, 1, $J = 3.2, 5.2, 18.6$, $H_{7\alpha}$), 2.44 (br dd, 1, $J = 6, 14$, H_3), 2.20 (m, 1, H_2), 2.09 (m, 1, H_3), 0.95 (d, 3, $J = 7.0$), (**18**) δ 4.94 (br s, 1), 4.92 (br s, 1), 3.94 (m, 1, H_5), 3.21 (ddd, 1, $J = 4.7, 9.3, 18.6$, $H_{7\beta}$), 2.92 (m, 1, H_1), 2.77 (ddd, 1, $J = 3.2, 5.2, 18.6$, $H_{7\alpha}$), 2.68 (m, 1, H_3), 2.62 (m, 1, H_3), 2.36 (br dq, 1, $J = 6, 7$, H_2), 1.08 (d, 3, $J = 6.3$); ^{13}C NMR (**17**) δ 216.0, 146.6, 110.4, 70.3, 51.2, 38.8, 37.3, 31.9, 22.7, (**18**) δ 216.0, 146.9, 109.3, 71.8, 45.1, 39.3, 36.7, 34.7, 14.1; IR (neat) 2940, 2850, 1772, 1650 cm^{-1}.

Preparation of 1,2a,4,5,6,6a,7,7a-Octahydro-(7a*β*,2a*β*,6a*α*)-2*H*-cyclobut[*a*]inden-2-one (23) and 1,2a,3,4,5,6,7,7a-Octahydro-(7a*β*,2a*β*)-2*H*-cyclobut[*a*]inden-2-one (25). Hexane washed sodium hydride (0.06 g, 1.6 mmol) was treated with 2 mL of dry THF, and the suspension was cooled to 0 °C. Acid **19b** (0.263 g, 1.5 mmol) was added to the flask in 4 mL of toluene. After 5 min, oxalyl chloride (0.93 g, 7.3 mmol) was added to the solution. After the addition was complete, one drop of pyridine was added, and the reaction mixture was warmed to 60 °C and stirred for 2.5 h. The reaction mixture was cooled to 25 °C and filtered under airless conditions, and the solvent was evaporated in vacuo. The resulting acid chloride **19c** was added in 30 mL of toluene over 30 min to a boiling solution of Et_3N (1.45 g, 14.6 mmol) in 250 mL of toluene. The solution was heated at 110 °C for 2.75 h. The solution was cooled to 25 °C, the solvent was evaporated at 20 Torr and 0 °C, and the residual gum was dissolved in pentane. The solution was filtered through Celite to remove $Et_3N{\cdot}HCl$ and evaporated to give 0.265 g (140%) of crude oil containing mineral oil. Gas chromatographic analysis indicated that a 1.5:1 mixture of **23** and **25** had been formed. Medium-pressure chromatography of 0.234 g (silica gel, 99.6:0.4 pentane–ethyl acetate) gave 0.041 g (25%) of **25** followed by 0.055 g (33%) of **23**. Both isomers were greater than 90% pure as determined by 300-MHz ^{1}H NMR.

The spectral data for **23** are as follows: ^{1}H NMR δ 5.59 (br s, 1, H_3), 3.93 (br s, 1, H_{2a}), 3.22 (ddd, 1, $J = 18.3, 8.9, 4.6$, $H_{1\beta}$), 2.95 (m, 1, H_{7a}), 2.73 (ddd, 1, $J = 18.3, 5.1, 3.2$, $H_{1\alpha}$), 2.50 (br s, 1, H_{6a}), 2.05 (m, 4), 1.77 (br s, 1), 1.49 (m, 2), 1.07 (dddd, 1, $J = 12.4, 12.4, 10.5, 2.7$, $H_{6\beta}$); ^{13}C NMR δ 209.4, 140.0, 121.9 (CH), 70.9 (CH), 51.4, 39.4, 37.0 (CH), 28.8, 28.4 (CH), 25.3, 22.2; IR 1763, 1650, 1440 cm^{-1}; GC t_R 6.1 min. Experiments using $Eu(fod)_3$ as a shift reagent gave the following shifts per mole of Eu: H_3, 0.68; H_{2a}, 1.56; $H_{1\beta}$, 1.46; H_{7a}, 0.76; $H_{1\alpha}$, 1.50; H_{6a}, 0.76; $H_{6\beta}$, 0.32.

The spectral data for **25** are as follows: ^{1}H NMR δ 4.04 (br s, 1, H_{2a}), 3.11 (ddd, 1, $J = 18, 10, 5$, $H_{1\beta}$), 2.73 (m, 3), 2.28 (m, 1), 2.01 (br s, 4, $H_{3,6}$), 1.63 (br s, 4, $H_{4,5}$); ^{13}C NMR δ 208.3, 137.7, 129.4, 75.8, 53.1, 43.7, 26.2, 25.0, 24.7, 22.8, 22.6; IR 2930, 2840, 1770, 1645, 1445, 1250 cm^{-1}; GC t_R 5.7 min.

Preparation of 1-Methyl-4-methylene-6-acetoxybicyclo[3.2.0]heptane (7). Ketone **6** (0.117 g, 0.85 mmol) in 10 mL of THF was added to a solution of L-Selectride (2.6 mL, 1 M in THF, 2.6 mmol) at −78 °C. After 10 min, the solution was warmed to 0 °C and stirred for 1.5 h. The reaction was slowly quenched with 3 mL of H_2O and slowly oxidized with 3 mL of 30% H_2O_2, and the mixture was warmed to 25 °C. The product was extracted from the aqueous layer three times with methylene chloride. The organic layer was washed with sodium thiosulfate and saturated sodium bicarbonate, dried (Na_2SO_4), and concentrated to give 0.138 g (116%) of crude alcohol containing some *sec*-butyl alcohol. The unpurified alcohol (0.119 g, 0.85 mmol) was added to pyridine (5 mL) and acetic anhydride (0.15 g, 1.5 mmol), and the reaction mixture was stirred at 25 °C overnight. The reaction was quenched with 3 mL of cold water. The aqueous layer was extracted three times with ethyl ether. The combined organic layers were washed three times with saturated $CuSO_4$ solution, dried (Na_2SO_4), and concentrated to give 0.148 g (96%) of crude **7**. Medium-pressure chromatography of 0.106 g (silica gel, 99.8:0.2 pentane–ethyl acetate) gave 0.076 g (68%) of **7**, which was greater than 95% pure as determined by 300-MHz ^{1}H NMR: ^{1}H NMR δ 4.99 (ddd, 1, $J = 7.7, 7.7, 7.7$, H_6), 4.92 (s, 1, =CH), 4.63 (s, 1, =CH), 2.95 (br d, 1, $J = 7.7$, H_5), 2.56 (m, 1, H_3), 2.31 (dd, 1, $J = 7.7, 16.0$, H_3), 2.09 (ddd, 1, $J = 2.9, 9.0, 16.0$, H_7), 1.96 (m, 1, H_7), 1.95 (s, 3, OAc), 1.57 (dd, 1, $J = 7.6, 12.5$, H_2), 1.38 (ddd, 1, $J = 7.7, 12.5, 12.5$, H_2), 1.19 (s, 3, Me); ^{13}C NMR δ 170.4, 150.7, 109.6, 64.9, 54.6, 41.1, 39.9, 36.4, 34.0, 25.3, 20.9; IR ($CDCl_3$) 2930, 2840, 1720, 1650, 1440, 1420, 1365, 1250, 1235, 1045 cm^{-1}.

Preparation of 5-Methyl-7-acetoxybicyclo[3.2.0]heptan-2-one (8). Alkene **7** (0.020 g, 0.11 mmol) was dissolved in 15 mL of dry methylene chloride and cooled to −78 °C. Ozone was bubbled into the solution until it became lavender colored. Nitrogen was then bubbled into the solution until it became colorless. Triphenylphosphine (0.06 g, 0.22 mmol) was added, and the reaction mixture was stirred at 25 °C overnight. Evaporation of the solvent followed by medium-pressure chromatography of the residue (silica gel, 99:1 pentane–ethyl acetate) gave 0.020 g (97%) of pure **8**. The 90-MHz ^{1}H NMR and IR spectra were identical with data provided by Professor Mori.[14] 300-MHz ^{1}H NMR δ 5.19 (ddd, 1, $J = \approx 9, 9, 9$, H_7), 2.74 (br d, 1, $J = 9.1$, H_1), 2.65 (ddd, 1, $J = 8.9, 12.7, 18.8$, H_3), 2.49 (m, 1, H_3), 2.41 (m, 1, H_6), 2.22 (dd, 1, $J = 7.8, 13.1$, H_6), 2.01 (s, 3, OAc), 1.97 (m, 1, H_4), 1.74 (ddd, 1, $J = 8.8, 12.7, 12.7$, H_4), 1.35 (s, 3, Me); ^{13}C NMR δ 217.2, 170.1, 62.4, 55.9, 39.3, 38.0; 37.6, 35.7, 25.3, 20.8; IR (neat) 2940, 2860, 1735, 1450, 1410, 1370, 1230, 1040 cm^{-1}.

Preparation of Methyl 3-Methylenehept-6-enoate (28).[21] A 3.7:1 mixture of (*E*)- and (*Z*)-3-methyl-2,6-heptadienoic acid (**9b** and **10b**) (364 mg, 2.6 mmol) was converted to a mixture of acid chlorides **9c** and **10c** in the normal manner. A solution of this mixture in 1 mL of benzene was added dropwise at 0 °C to a solution of Et_3N (305 mg, 3 mmol) and methanol (301 mg, 9.4 mmol) in 1 mL of benzene. The resulting mixture was maintained at 0 °C and allowed to stir for an additional 1 h. The solvent was removed in vacuo, and the product was purified by flash chromatography (silica gel, 9:1 pentane–ether) to yield 229 mg (58%) of an inseparable 55:5:1:1:1 mixture of methyl 3-methylenehept-6-enoate (**28**), either methyl (*E*)-3-methylhepta-3,6-dienoate (**29**) or methyl (*Z*)-3-methylhepta-3,6-dienoate (**30**), either **30** or **29**, methyl (*E*)-3-methylhepta-2,6-dienoate (**9d**), and methyl (*Z*)-3-methylhepta-2,6-dienoate (**10d**), respectively, as determined by analysis of high-field ^{1}H NMR spectra and analytical GC data.

The spectral data for **28** are as follows: ^{1}H NMR δ 5.81 (dd, 1, $J = 17.0, 10.3$, H_6), 4.99 (m, 2, H_7), 4.93 (m, 2, =CH_2), 3.69 (s, 3), 3.08 (s, 2, H_2), 2.17 (m, 4, $H_{4,5}$); GC t_R 2.6 min.

Characteristic ^{1}H NMR peaks for **29** or **30** are as follows: 5.40 (m, 1, H_4), 5.07 (m, 2, H_6), 3.02 (br, 3, H_2), 2.80 (m, 2, H_5), 1.80 (dt, 3, $J = 1.3, 1.3$, C_3-*Me*); GC t_R 3.0 min.

Characteristic ^{1}H NMR peaks for **30** or **29** are as follows: 5.32 (m, 1, H_4), 3.02 (br, 2, H_2), 2.80 (m, 2, H_5), 1.70 (dt, 3, $J = 1.3, 0.8$, C_3-*Me*).

Characteristic ^1H NMR peaks for **9d** are as follows: 5.68 (br, 1, H_2), 2.17 (d, 3, $J = 1.4$, C_3-*Me*).

Characteristic ^1H NMR peaks for **9e** are as follows: 5.68 (br, 1, H_2), 1.89 (d, 3, $J = 1.3$, C_3-*Me*).

Compounds **30**, **9d**, and **10d** had the following GC data: t_R 3.3, 3.4, or 3.6 min. It was not possible to correlate the peaks to the compounds.

Attempted Preparation of Methyl [2-(2-Propenyl)cyclohexylidene]acetate. A 10:1 mixture of (*E*)- and (*Z*)-[2-(2-propenyl)cyclohexylidene]acetic acid (**19b** and **20b**) (136 mg, 0.76 mmol) was converted to a mixture of acid chlorides in the normal manner. The resulting 4:1 mixture of **19c** and **20c** in benzene (1 mL) was added dropwise to a solution of Et_3N (106 mg, 1.05 mmol) and methanol (39 mg, 1.21 mmol) in benzene (0.5 mL) at 0 °C. The solution was stirred for 1 h at 0 °C. Normal workup gave 88.7 mg of a ca. 4:1 mixture of **19d** and **20d** as determined by analysis of the 300-MHz ^1H and ^{13}C NMR spectra. The data given below were obtained from that mixture.

The spectral data for methyl (*E*)-[2-(2-propenyl)cyclohexylidene]acetate (**19d**) are as follows: ^1H NMR δ 5.7 (m, 1), 5.61 (d, 1, $J = 1.2$), 5.0 (m, 2), 3.68 (s, 3), 3.0 (m, 1), 2.7 (m, 1), 2.5–1.3 (m, 8); ^{13}C NMR δ 171.7, 166.0, 136.1, 116.5, 111.3, 50.7, 45.5, 36.4, 33.6, 28.4, 28.3, 23.5.

Characteristic peaks for methyl (*Z*)-[2-(2-propenyl)cyclohexylidene]acetate (**20d**) are as follows: ^1H NMR δ 5.7 (m, 1), 5.59 (br, 1), 5.0 (m, 2), 4.0 (m, 1), 3.67 (s, 3); ^{13}C NMR δ 136.3, 115.9, 113.5, 51.6, 36.2, 35.7, 33.4, 30.1, 28.1, 20.2, 2 carbons were not observed.

Preparation of *tert*-Butyl [6-(2-Propenyl)cyclohex-1-enyl]acetate (31). A ca. 3:1 mixture of (*E*)- and (*Z*)-[2-(2-propenyl)cyclohexylidene]acetic acid (**19b** and **20b**) (220 mg, 1.2 mmol) was converted to the acid chloride in the normal manner. The resulting 3:1 mixture of **19c** and **20c** was treated with Et_3N (152.5 mg, 1.51 mmol) and *t*-BuOH (125.8 mg, 1.7 mmol) at 0 °C for 1 h. Normal workup gave 147.7 mg (55%) of crude product, which consisted of a chromatographically inseparable 15:3:1 mixture of *tert*-butyl [6-(2-propenyl)cyclohexenyl]acetate (**31**), *tert*-butyl (*E*)-[2-(2-propenyl)cyclohexylidene]acetate (**19e**), and *tert*-butyl [2-(2-propenyl)cyclohexenyl]acetate (**32**) as determined by ^1H and ^{13}C NMR spectral analysis.

The spectral data for **31** are as follows: ^1H NMR δ 5.75 (dddd, 1, $J = 17.5, 9.9, 7.5, 6.0$), 5.58 (dddd, 1, $J = 3.8, 3.8, 2.3, 1.5$, H_2), 5.0 (m, 2), 3.01 (ddddd, 1, $J = 15.2, 2.2, 2.2, 1.3, 0.9$, CH_2CO_2R), 2.83 (ddddd, 1, $J \approx 15.2, 0.7, 0.7, 0.7, 0.7$, CH_2CO_2R), 2.4–2.1 (m, 5), 2.0 (br m, 4), 1.45 (s, 9); ^{13}C NMR δ 171.6, 137.4 (CH), 134.3 (C), 126.9 (CH), 115.9 (CH_2), 80.2, 42.5, 37.0, 36.4 (C_6), 28.0 (3 C), 27.1, 25.5, 19.0.

Characteristic peaks for **19e** are as follows: ^1H NMR δ 5.61 (ddd, $J = 0.9, 0.9, 0.9$, $=CHCO_2R$); ^{13}C NMR δ 171.8, 162.2 (C_1), 111.3 ($=CHCO_2R$).

Characteristic peaks for **32** are as follows: ^1H NMR δ 3.04 (br d, 1, $J = 13.3$, CH_2CO_2R), 2.87 (dd, 1, $J = 13.3, 0.8$, CH_2CO_2R); ^{13}C NMR δ 171.8, 136.1.

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Stereochemical Studies of Type-II Intramolecular Ene Reactions of δ,ϵ-Unsaturated Aldehydes

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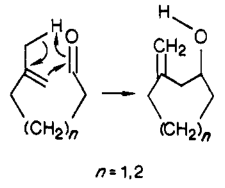
Intramolecular Lewis acid catalyzed ene reaction of aldehyde **3** gives the (*E*)-ene adduct **18** with 85–90% selectivity. Intramolecular ene reactions of aldehydes **6**, **10**, and **13** proceed with 88–100% selectivity for the isomer with an equatorial methyl group and an axial hydroxyl group. Intramolecular type-II ene reaction of allenic aldehyde **17** occurs either thermally or with Lewis acid catalysis to give a mixture of the expected ene adduct, bis exocyclic diene **26**, and diene **27**.

Introduction

Oppolzer and Snieckus have classified intramolecular ene reactions into three types based on the connectivity of the ene and enophile.[1] Type-II reactions, which produce alkylidene cycloalkanes, proceed through a highly ordered bridged bicyclic transition state with considerable potential for control of stereochemistry (see eq 1). These



(1)

reactions have been much less studied than type-I ene reactions and stereochemical constraints are less well understood. The majority of studies have involved Lewis acid catalyzed ene reactions with either aldehydes or ketones as enophiles.[2-5] These reactions, which can be considered to be intramolecular Prins reactions, can only be used to produce cyclohexanols or cycloheptanols.[2i] Cyclohexanols are produced exclusively with an axial alcohol group as expected from either a concerted reaction or stepwise re-

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