mg, 1.2 mmol) in 5 mL of CH_3CN, and the reaction mixture was stirred for 2 h at room temperature and then poured into 5% $NaHCO_3$. The aqueous suspension was extracted with $CHCl_3$, the $CHCl_3$ was dried and evaporated, and the residue was column chromatographed (97/3 $CHCl_3$/EtOH) to give 0.56 g, 84% yield, of **28**: ^1H NMR δ 4.50 (s, 2 H), 5.13 (s, 2 H), 5.47 (s, 2 H), 6.38 (t, 1 H, J = 7), 7.87 (s, 1 H); UV λ_{max} (nm (ϵ)) 257 (14 900), 269 (15 400). Anal. Calcd for $C_{33}H_{30}N_5O_8Cl$: C, 60.0; H, 4.6; N, 10.6. Found: C, 59.6; H, 4.5; N, 10.6.

Phosphate Coupling Reactions. General Procedure. The phosphate coupling reactions were performed as described.[13,15] The products were column chromatographed by using 5-10% EtOH or CH_3OH in $CHCl_3$ for elution, and the results are summarized in Tables I and II.

The 3'-3' dimers were prepared from phosphodioesters **16a,c** and the 5'-blocked monomers from **3b** and **28** with TPS-NT as above. The chlorophenoxyacetyl or benzyl carbonate groups were removed as described[32] without isolating the fully protected dimer.

5'-(CH_3O)TrTpC$^{4N\text{-}Cbz}$pA$^{6\text{-}N\text{-}Cbz}$pG$^{6\text{-}O\text{-}Bn,2\text{-}NCbz}$-3'-OH (42). To the fully protected tetramer **37** (66 mg, 0.027 mmol) in 1.0 mL of pyridine was added 50 mg of hydrazine hydrate in 1 mL of 3/2 pyridine/HOAc. The mixture was stirred at room temperature for 5 min, cooled to 0 °C, 2,4-pentanedione (0.5 mL) added, and the solution stirred for 15 min more. The mixture was added to 50 mL of rapidly stirring ether and 65 mg of precipitated product collected. This product was contaminated with low-molecular-weight byproducts and was purified by HPLC (4/96 EtOH/$CHCl_3$) to give pure **42**, 49 mg, 0.20 mmol, 74% yield, t_R (B, 1a) 9.8, 10.8 min.

Removal of *N*-(Benzyloxycarbonyl) and *O*-Benzyl Groups by Transfer Hydrogenolysis. General Procedure. To the catalyst (100 wt.% per Cbz and benzyl group) in a 16 × 3 cm test tube was added a solution (1/1 EtOAc/EtOH) of the substrate (10 mg/mL) and cyclohexadiene (0.5 mL per 30 mg of substrate), and the suspension was mixed with a Vibro Mixer under a nitrogen atomosphere for the time specified in Table I. Pd/C (10%, Engelhard) was used as is. Palladium hydroxide on carbon (Aldrich) was hydrogenated for 1 h (50 psi) in ethanol before use. Palladium black was freshly generated from palladium acetate (Engelhard) in water (50 psi H_2 for 1 h) and then washed twice with water and twice with ethanol. For the hydrogenolysis of **42**, 30 mg was treated in 6 mL of solvent with 0.5 mL of cyclohexadiene and palladium black from 120 mg of palladium acetate for 24 h. The resulting diastereomers (30 mg) were readily separated on HPLC (A, 1d).

p(T-C-A-G) (44). Removal of the 2-chlorophenyl groups from 30 mg of **43** was effected with *p*-nitrobenzaloximate as described.[13b] After 36 h, the solvent was evaporated, and the residue, which contained the (MeO)Tr-blocked tetramer, was dissolved in 10 mL of 80% HOAc and stirred at room temperature for 5 h to remove the (MeO)Tr group. The solvent was evaporated, and the tetramer **44** was freed of organic material by partitioning the residue between 0.01 M Et_3N/HOAc buffer (pH 7.0) and ether. The aqueous layer was lyophilized and the residue chromatographed (C, 2b). The tetramer thus obtained was pure by HPLC (A, 2a).

Enzymatic Digest of p(T-C-A-G) (44). The tetramer **44** (100 μg) was dissolved in 100 μL of 0.1 M NH_4OAc (pH 6.5), and one unit of spleen phosphodiesterase was added. The mixture was incubated at 37 °C for 18 h and then analyzed by HPLC (A, 3). A mixture of 5'-HOTp, 5'-HOdCp, 5'-HOdAp, and dG was obtained in a ratio of 1.1:0.9:1.1:0.9.

Stability of Pyrimidine Bases to Transfer Hydrogenation Conditions. When thymidine (**12a**) was subjected to the transfer hydrogenation conditions described above for 24 h, the thymidine was recovered unchanged. HPLC analysis (A, 4b) showed that no dihydrothymidine (**45**) was produced. Under these HPLC conditions, dihydrothymidine (**45**) is cleanly separated from thymidine **12a**. When 4-*N*-Cbz-dC was subjected to these reaction conditions for 24 h, 2'-deoxycytidine (**1a**) was isolated as the sole nucleosidic product, and no 2'-deoxydihydrouridine (**46**) was found to be present (HPLC system CA, 4a). When 2'-deoxycytidine was treated with hydrogen over 10% Pd/C in EtOAc/95% EtOH in a Parr apparatus, 2'-deoxydihydrouridine was isolated as the major product. The above HPLC separations were monitored at 220 or 230 nm.

Acknowledgment. This work was supported in part by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy, under Contract No. DE-AC03-76SF00098. Assistance in the preparation of intermediates was expertly provided by Wendy S. Jacks, undergraduate research participant.

Registry No. 1, 951-77-9; **2**, 82892-54-4; **3a**, 82892-55-5; **3b**, 82892-74-8; **4**, 82892-56-6; **5**, 958-09-8; **6**, 51549-32-7; 7, 82892-57-7; **8**, 961-07-9; **9**, 51549-35-0; **10**, 82892-58-8; **11**, 82892-59-9; **12a**, 50-89-5; **13b**, 82902-24-7; **13c**, 82892-60-2; **13d**, 82892-61-3; **15a**, 82892-62-4; **15c**, 82902-25-8; **16a**, 82892-63-5; **16c**, 82902-27-0; **17a**, 76512-73-7; **17c**, 82892-64-6; **17d**, 82902-28-1; **18b**, 82892-65-7; **18d**, 82902-29-2; **19d**, 82892-66-8; **20b**, 82892-67-8; **20d**, 82892-68-0; **21**, 82892-76-0; **22**, 82892-69-1; **23**, 82902-38-3; **24**, 82892-81-7; **25**, 82892-72-6; **26**, 82892-73-7; **27**, 82892-82-8; **28**, 82892-70-4; **29**, 82902-36-1; **30**, 82892-77-1; **31**, 82892-75-9; **32**, 82902-34-9; **33**, 82902-35-0; **34**, 82892-78-2; **35**, 82892-79-3; **36**, 82892-80-6; **37**, 82902-31-6; **38**, 82902-33-8; **39**, 82902-39-4; **40**, 82892-83-9; **41**, 82902-37-2; **42**, 82902-30-5; **43**, 82902-32-7; **44**, 82892-71-5; *N*-benzyloxy carbonyl imidazole, 22129-07-3; imidazole, 288-32-4; benzyl chloroformate, 501-53-1; triethyloxonium tetrafluoroborate, 368-39-8; 6-*N*-benzyloxycarbonyladenine, 82919-04-8.

(33) Arentzen, R.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1*, 1977, 445.

Applications of the Intramolecular Diels-Alder Reaction to the Formation of Strained Molecules. Synthesis of Bridgehead Alkenes[1]

Kenneth J. Shea,* Sean Wise, Lonnie D. Burke, Peter D. Davis, Jeffrey W. Gilman, and Arthur C. Greeley

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received June 18, 1981*

Abstract: The synthesis and thermolysis of a number of 2-alkenyl-1,3-butadienes are reported. In all cases studied, the dominant reaction manifold is intramolecular Diels-Alder cycloaddition, which results in formation of bicyclo[*n*.3.1] bridgehead alkenes. Electron-withdrawing substituents accelerate the reaction, thereby permitting synthesis of a variety of functionalized bridgehead olefins. These cycloadditions are found to be highly regio- and stereospecific. Kinetic studies permit evaluation of the effectiveness of various electron-withdrawing groups to accelerate the reaction, in addition to establishing the reaction's exo selectivity.

There are several ways that a diene and dienophile can be joined in the intramolecular Diels-Alder reaction. In the example illustrated in eq 1, the dienophile is joined at the 1-position of the diene (we refer to this as type 1 IDA). This variant has assumed

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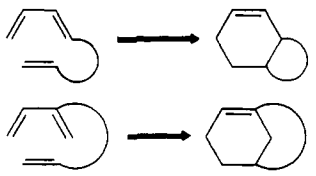
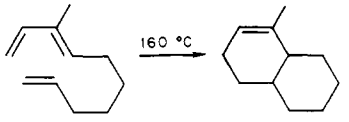


(1)

(2)

enormous importance in contemporary organic synthesis.[2] Recently we reported the first examiples of an intramolecular Diels–Alder reaction of the type illustrated by eq 2, where the dienophile is joined at the 2-position of the diene (type 2 IDA).[3] This reaction is distinguished by the fact that a bridgehead double bond is formed in the cycloaddition step. Unlike type 1 cycloadditions, which usually result in formation of relatively strain-free products, the strain energy associated with the bridgehead alkene manifests itself in the reaction conditions necessary for cycloaddition. For example, triene **1** undergoes cycloaddition at 160 °C[4] while triene **2** requires temperatures in excess of 400 °C before cycloaddition occurs at an appreciable rate.[3]



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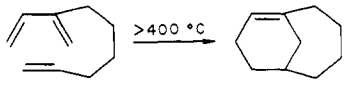

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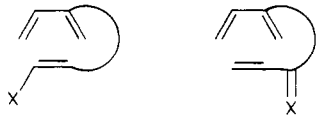
Under these harsh conditions for cycloaddition, the entropy of reaction ($\Delta S°_{Rxn}$), not an important factor in type 1 IDA reactions,[5] contributes significantly to the free energy and results in an unfavorable reaction equilibrium.[6] Since chemical reactivity in the Diels–Alder cycloaddition can be significantly modified by the appropriate choice of substituents, we have undertaken an investigation of the influence of electron-withdrawing groups on the reactivity of trienes of the general constitution shown in structures **3** and **4**. It was our hope that the activated dienophiles



3 4

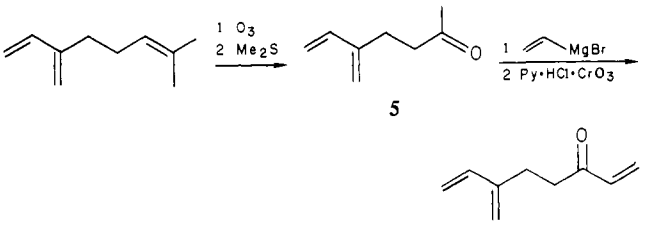
would result in milder conditions for these cycloadditions, which, in turn, would result in a more favorable reaction equilibrium.[6] It will be shown that the type 2 IDA offers a general, and in some cases a high yield, synthesis of functionalized bridgehead alkenes. Our studies also provide some preliminary kinetic and mechanistic information regarding this reaction.

Results

Synthesis. The syntheses of representative α,β-unsaturated ketones and esters are outlined in the schemes.

Starting material for trienone **6** is 4-methylene-5-hexenal (**5**), readily available from ozonolysis of technical grade myrcene.[7]

Scheme I



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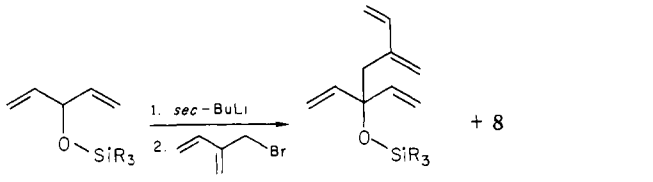
6



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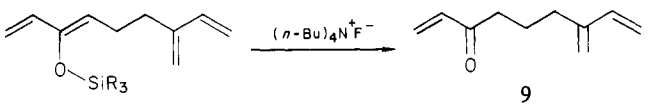

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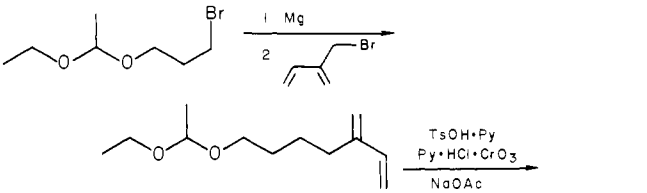
Scheme II



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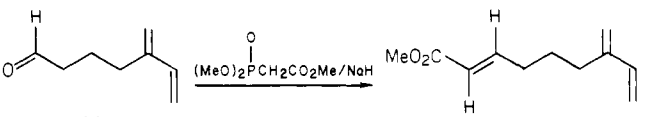
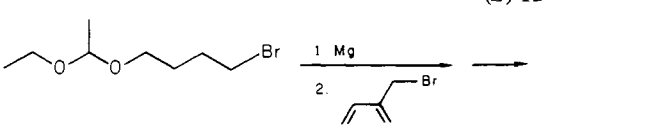
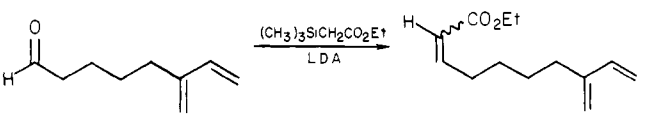


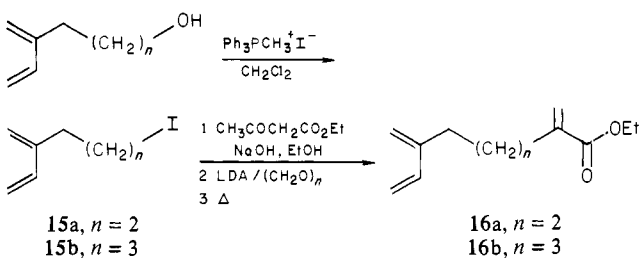
11 (*E*)-12





13 (*E*)-14 + (*Z*)-14

Scheme III



15a, $n = 2$ 16a, $n = 2$
15b, $n = 3$ 16b, $n = 3$

Addition of vinylmagnesium bromide to the dienal followed by oxidation of the resulting allylic alcohol affords the desired ketone (Scheme I).

Homologous trienone **9** is obtained by reaction of lithium 3-(*tert*-butyldimethylsiloxy)pentadienyl anion[8] with 2-(bromomethyl)-1,3-butadiene.[9] The mixture (20:80) of regioisomers **7**

(1) This work has appeared in preliminary form: Shea, K. J.; Wise, S. *Tetrahedron Lett.* **1979**, 1011.
(2) Recent reviews: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Carlson, R. G. *Annu. Rep. Med. Chem.* **1974**, *9*, 270. (c) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63.
(3) Shea, K. J.; Wise, S. *J. Am. Chem. Soc.* **1978**, *100*, 6519.
(4) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289.
(5) The entropy of activation for a "typical" bimolecular Diels–Alder reaction (isoprene dimerization, −41.0 eu)[5a] is significantly larger (more negative) than the intramolecular Diels–Alder cycloaddition of *N-tert*-butylpentadienylacrylamide (−14.4 eu).[5b] (a) Rimmelin, J.; Jenner, G. *Tetrahedron* **1974**, *30*, 3081. (b) Gschwend, H. W.; Lee, A. O.; Meier, H. *J. Org. Chem.* **1973**, *38*, 2169.
(6) This analysis is not intended to imply that equilibrium in either example has been achieved. We have observed an apparent equilibrium in the intramolecular Diels–Alder cycloaddition of 3-methylene-1,7-octadiene.[3] This observation has permitted a rough estimate of $\Delta G_{rxn}°$ for the type 2 IDA.
(7) Bertele, E.; Schudel, P. S. *Helv. Chim. Acta* **1967**, *50*, 2445.
(8) Oppolzer, W.; Snowden, R. L. *Tetrahedron Lett.* **1976**, *4187*.
(9) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281.

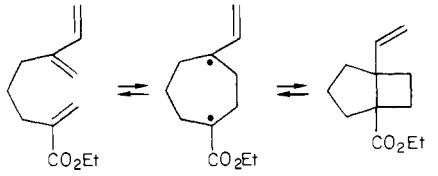
and **8** that result from α- and γ-alkylation is converted into the more stable γ isomer by heating for 1 h at 150 °C in xylene. Deprotection of **8** with tetra *n*-butylammonium fluoride gives the trienone **9**.

The synthesis of triene esters **12** and **14** is outlined in Scheme II. A three-carbon extension of 2-(bromomethyl)-1,3-butadiene with the protected Grignard reagent derived from 3-bromopropanol[10] gives diene **10**. Deprotection followed by oxidation affords dienal **11**. Treatment of **11** with the carbanion derived from trimethyl phosphonoacetate gives a 6:1 mixture of (*E*)- and (*Z*)-**12**. Homologous triene esters (*E*)-**14** and (*Z*)-**14** are prepared in a similar manner from THP-protected 4-bromobutanol[11] and 2-(bromomethyl)-1,3-butadiene. Treatment of dienal **13** with lithium(trimethylsilyl)acetate[12] gave a 57:43 mixture of (*E*)- and (*Z*)-**14** while treatment of **13** with sodium triethyl phosphonoacetate gave nearly pure (*E*)-**14**. The isomeric esters could be separated by column chromatography.

α-Methylene esters **16a** and **16b** are obtained by the method outlined in Scheme III. Ethyl acetoacetate is alkylated with diene iodide **15a** or **15b**. Deacylative condensation[13] of the anion derived from the alkylated ethyl acetoacetate by treatment with paraformaldehyde followed by thermolysis in refluxing tetrahydrofuran affords α-methylene esters **16a** and **16b**.

Thermolysis. The thermolysis of unsaturated ketones and esters was examined under several conditions. The flow pyrolysis method consists of passing neat samples of trienes down a hollow quartz pyrolysis tube under an inert atmosphere of dry, oxygen-free nitrogen. The pyrolyses were run at atmospheric pressure with the simple apparatus described in the Experimental Section. Pyrolysis products were collected in a −78 °C trap, diluted with dry pentane, and analyzed by VPC chromatography. The experimental variables with this apparatus are contact time (flow rate) and temperature. Solution-phase pyrolysis was carried out in sealed ampules in dilute (0.02–0.05 M) degassed xylene solution. For purposes of discussion, the triene precursors are divided into two groups, differentiated by the number of atoms joining diene and dienophile.

Cycloaddition of trienes containing three atoms in the bridge joining diene and dienophile results in a bridgehead olefin containing a trans-cyclooctene ring. These strained, highly reactive compounds represent the current limits of isolatable bridgehead alkenes.[14] Thermolysis of trienes **6**, **12**, and **16a**, entries 2–5 in Table I, results in formation of bridghead olefins; in all cases examined, intramolecular Diels–Alder cycloaddition was the predominant reaction manifold. Most of the compounds isolated in this series exhibit the characteristic strong, unpleasant odor associated with strained double bonds. Several of the cycloadditions are accompanied by side reactions. For example, thermolysis of triene **16a** (entry **5**, Table I) also results in formation of a bicyclo[3.2.0]heptane derivative **23**. Structural confirmation of this product was secured by an independent synthesis. The product arises by a formal intramolecular 2 + 2 cycloaddition, eq 3. A similar ring closure has been reported[15] for 3,6-bis(methylene)-1,7-octadiene.



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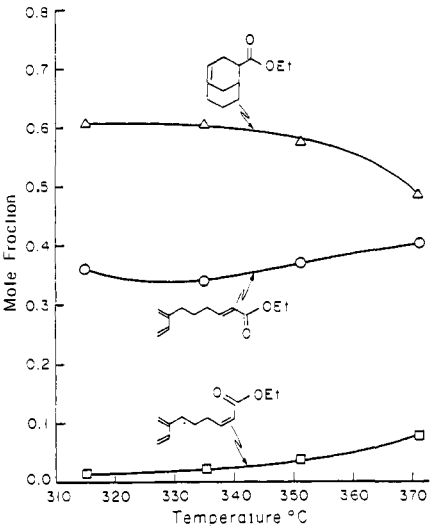


Figure 1. Gas-phase thermolysis of trienester (*E*)-**12**; contact time 12 s.

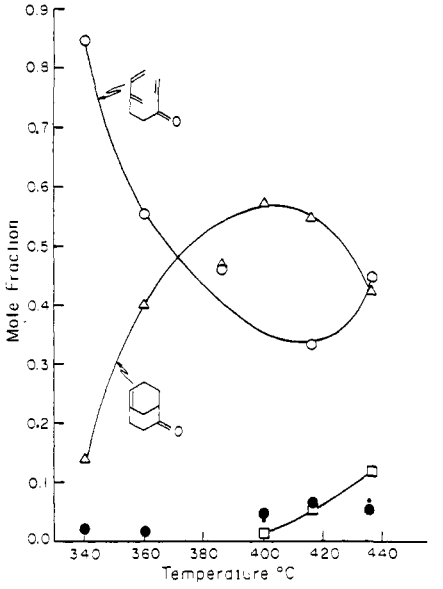


Figure 2. Gas-phase thermolysis of trienone **6**. (●, •, □) Unidentified side products; contact time 12 s.

An additional complication was noted during thermolysis of triene ester (*Z*)-**12**; recovered "unreacted" triene consisted of almost exclusively (*E*)-**12**. Since cis–trans isomerization occurs competitively with cycloaddition, it was impossible to establish the reaction stereochemistry. Both (*E*)-**12** and (*Z*)-**12** gave the same bridgehead olefin; the stereochemistry of the adduct is tentatively assigned as exo (vide infra).

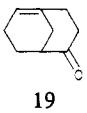
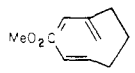
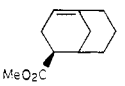
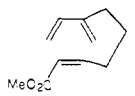
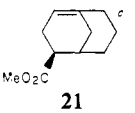
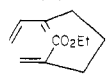
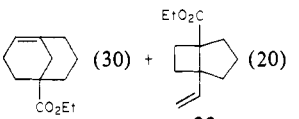
Included for comparison in Table I is the unsubstituted triene, 3-methylene-1,7-octadiene (**17**), entry 1. It should be noted that all of the substituted derivatives undergo cycloaddition at lower temperatures than the parent triene. The cycloaddition proceeds to higher conversions under these milder conditions; the percent conversions are approximately what one would expect for equilibrium mixtures of an isoenergetic series with diminished $T\Delta S°$ contribution to the free energy of reaction.[16]

An exception to this observation is trienone **6**. This compound is only slightly more reactive than the parent triene although the conversion to product is significantly higher. The very modest activation could be due to the poor overlap of the enone group in the Diels–Alder transition state. Inspection of molecular models

(10) Eaton, P. E.; Copper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947.
(11) Sih, C. J.; Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G.; Lee, L. F. H.; Lee, S. S. *J. Am. Chem. Soc.* **1975**, *97*, 865.
(12) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620.
(13) Veno, Y.; Setoi, H.; Okawara, M. *Tetrahedron Lett.* **1978**, *3753*.
(14) (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (b) Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978; (C) Kesse, R. *Angew. Chem., Int. Ed. Eng.* **1975**, *14*, 528. Kobrich, G. *Ibid.* **1973**, *12*, 464.
(15) Shea, K. J.; Wise, S. *Tetrahedron Lett.* **1978**, 2283.

(16) The analysis assumes equilibrium has been achieved; this has not been rigorously established for all examples in Table I.

Table I. Gas-Phase Thermolysis of Three Atom Bridged Triene Esters and Ketones

	starting material	conditions[a]	product (% conversion)[b]
1	 **17**	420 °C, 23 s	 (32) **18**
2	 **18**	395 °C, 18 s	 (72) **19**
3	 (*E*)-**12**	318 °C, 18 s	 (76) **20**
4	 (*Z*)-**12**	365 °C, 12 s	 [c] **21**
5	 **16a**	390 °C, 12 s	 (30) + (20) **22** **23**

[a] Pyrolysis oven temperature and contact time; for details, see Experimental Section. [b] Determined by VPC, based upon starting material remaining after pyrolysis. [c] Starting material underwent rapid isomerization to the *E* isomer under pyrolysis conditions. The cycloaddition product was identical with that obtained from (*E*)-**12**.

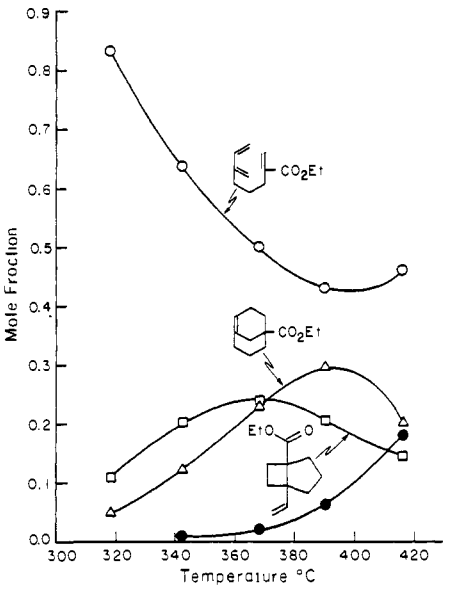
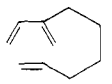
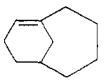
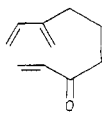
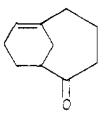
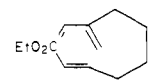
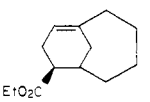


Figure 3. Gas-phase thermolysis of trienester **16a**. (●) Unidentified side product; contact time 12 s.

of **6** reveals simultaneous coplanarity of both diene and enone units in a conformation suitable for cycloaddition is difficult to accomplish. The higher conversion of **6** may be a manifestation of a more negative enthalpy of reaction, brought about by the introduction of a sp^2 center on the bicyclo[3.3.1]nonene skeleton.

A rough estimate of the relative reactivities of the trienes in Table I can be obtained from the flow pyrolysis data. Product composition is a function of both contact time and temperature. These variables were adjusted to optimize the cycloadduct composition; these optimized values are given in the table. Several plots of the temperature vs. product composition are given in Figures 1–3. The relative reactivity of the trienes can be established from the temperature at which the cycloaddition product

Table II. Gas-Phase Thermolysis of Four Atom Bridged Triene Esters and Ketones

	starting material	conditions[a]	product	% conversion[b]
1	 **2**	455 °C, 8 s	 **24**	55
2	 **9**	398 °C, 8 s	 **25**	85
3	 (*E*)-**14**	420 °C, 8 s	 **26**	80

[a] Pyrolysis oven temperature and contact time; for details, see Experimental Section. [b] Determined by VPC, percentages based upon starting material remaining after pyrolysis.

reaches a maximum (constant contact time). Triene ester (*E*)-**12** is clearly the most reactive; even at 315 °C, cycloadduct is the major component. α-Methylene ester **16a** is the considerably less reactive; a temperature in excess of 390 °C was required to optimize the cycloaddition product. Triene **6** proved to be the least reactive.

We have noted that in certain instances, i.e., Figure 3, a further increase of reaction temperature results in a falloff of the mole fraction of cycloadduct. Although certain side reactions begin to appear at these elevated temperatures, they alone do not account for product falloff; indeed, most of the loss in cycloadduct can be accounted for by a corresponding increase in starting material. This result suggests a shift in the position of equilibrium resulting from increasing importance of the entropy contribution to the free energy of reaction.

Our efforts at the condensed-phase cycloaddition of trienes **6**, **12**, and (*E*)-**16** have thus far been unsatisfactory. The solution-phase reactions are characterized by poor mass balances, due in part perhaps to the secondary reactions of the highly reactive cycloadduct formed in the reaction.

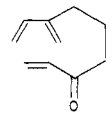
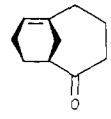
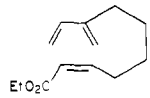
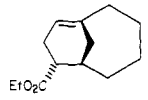
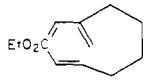
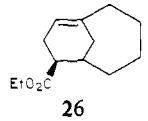
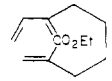
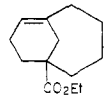
Cycloaddition of trienes containing four atoms in the bridge joining diene and dienophile results in a bridgehead alkene containing a *trans*-cyclononene ring. The strain energy in the resulting bridgehead alkene is expected to be somewhat less than in the cyclooctene series.[17]

Results of the gas-phase thermolysis of trienes **9** and (*E*)-**14** are given in Table II. The parent hydrocarbon, 3-methylene-1,8-nonadiene (**2**), is also included for comparison. In all cases, the activated trienes undergo intramolecular cycloaddition to bridgehead alkene. These reactions occur at lower temperatures and higher conversions than the parent triene **2**. The flow pyrolysis conditions in Table II have not been optimized since it was soon discovered that the solution-phase reactions offered a more convenient and higher yield method of cycloaddition. The solution-phase results are summarized in Table III. The cycloadditions can be carried to completion; in most cases, the cycloadducts were the only volatile reaction products observed. Since many of the reactions proceed to completion, one can isolate the product simply by concentration of the reaction mixture and trap-to-trap distillation. This was in fact accomplished from the thermolysis of triene ester (*E*)-**14** (0.35 g); the bridgehead olefin **26** was isolated in 91% yield (>99% pure by VPC).

Reaction Stereospecificity. Special note should be made of entries 2 and 3 in Table III. Cycloaddition of triene esters (*Z*)-**14**

(17) The difference in strain energy between *trans*-cyclononene and *trans*-cyclooctene is 2.3 kcal/mol. Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3654.

Table III. Solution-Phase Thermolysis of Triene Esters and Ketones

	starting material	conditions[a]	product	% yield[b]
1	 9	201 °C 15 min	 25	57
2	 (Z)-14	232 °C 4 h	 27	65
3	 (E)-14	206 °C 2 h	 26	80 (91)[c]
4	 16b	220 °C 3 h	 28	63

[a] Reactions were performed in dilute (0.04-0.09 M) xylene solution. [b] Yields are calculated by VPC by reference to an internal standard. [c] Isolated yield.

Table IV. Relative Rates of Cycloaddition (201 °C)

compd	k_{rel}[a]	$t_{1/2}$, min
(Z)-14	(1)	205
16b	2.4	86
(E)-14	13.0	16
6	33.6	6

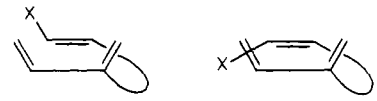
[a] 0.05 M xylene, 201 °C.

and (*E*)-**14** results in formation of isomeric bridgehead olefins (**26** and **27**). The two isomers are readily distinguished by both physical (VPC retention times) and spectroscopic means. Their interconversion was accomplished by epimerization of the endo isomer (**27**) (LDA:THF:−78 °C/H^+). The proton α to the ester carbonyl in *endo*-**27** is located at 2.9 ppm (deuterium labeling). In *exo*-**26**, this proton is shifted upfield by more than 0.4 ppm and is buried in the aliphatic region of the NMR spectrum. The upfield shift in *exo*-**26** is attributed to the proximity of the proton to the shielding region of the bridgehead double bond. Careful inspection of the pyrolysate from (*Z*)-**14** and (*E*)-**14** did not reveal any isomeric contamination. These results establish that for the isomeric series (*Z*)- and (*E*)-**14**, the type 2 IDA is stereospecific at the dienophile.

Kinetic Studies. Reactivity in Diels–Alder chemistry is best understood in terms of frontier orbital interactions. In the absence of steric factors, the rates of many cycloadditions can be correlated with the energy gap of the pertinent HOMO–LUMO's.[18] The intramolecular variant is amenable to such analysis although these reactions are particularly sensitive to conformational effects that influence the orientation of diene and dienophile in the transition state. An estimate of the solution-phase rates of cycloaddition was obtained in order to quantitatively delineate the influence of activating groups. These results, obtained at 201 °C, are summarized in Table IV. Ketone **9** reacts fastest of all four trienes, a result not surprising since ketones are usually more reactive than esters in the Diels–Alder reaction.[19] It is interesting that trans ester (*E*)-**14** undergoes cyclization faster than methylene ester **16b**, since it is known that methacrylate esters react faster than crotonate esters in bimolecular Diels–Alder reactions.[20] The cis ester, (*Z*)-**14**, was the least reactive.

The overall spread in reactivity is rather small; rates of cyclization for the entire series differ by only a factor of 33. This compressed scale of reactivity may, in part at least, be due to the reaction's lowered exothermicity. The latter transition state would be expected to diminish the importance of frontier orbital interactions on chemical reactivity.

Rate studies of the isomeric esters (*Z*)-**14** and (*E*)-**14** permit a direct measure of the endoselectivity for the intramolecular Diels–Alder reaction. The constraints imposed upon type 2 IDA cycloadditions permit only the transition states illustrated by structures **29** and **30** for the *E* and *Z* isomers of **14**, respectively.



29, exo **30**, endo

The relative rate of cycloaddition $k_{(Z)\text{-}14(exo)}/k_{(E)\text{-}14(endo)} = 13$ (201 °C); we conclude that secondary orbital interactions are not important in determining the stereoselectivity of type 2 intramolecular Diels–Alder cycloadditions.

The scope of the intramolecular Diels–Alder cycloaddition has been extended to permit synthesis of a wide variety of functionalized bridgehead alkenes. We are currently developing new extensions of this reaction and exploring the application of bridgehead alkenes to organic synthesis.

Experimental Section

General Information. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. ^1H NMR spectra were obtained at either 60 MHz (Varian EM-360) or at 90 MHz (Bruker WH 90 D). ^{13}C NMR spectra were recorded at 22.6 MHz (Bruker WH 90 D). ^1H and ^{13}C NMR chemical shifts are reported in δ units (ppm) relative to internal Me_4Si (δ 0).

Low-resolution mass spectra were recorded on a Finnigan 4000 GC mass spectrometer; high-resolution mass spectra were determined at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE.

Purity of all new compounds was >98%, as established by chromatographic (VPC, TLC) techniques.

Analytical vapor-phase chromatography (VPC) was performed on a Hewlett-Packard 5710A gas chromatograph equipped with a flame ionization detector. Analyses were obtained by using a 4 ft × $^1/_8$ in. stainless steel column packed with 8% DC-550 on 80/100 Gas Chrom Q.

A Varian Aerograph Model 920 gas chromatograph equipped with a thermal conductivity detector was used for preparative VPC. Glass inserts were used to line the injection port. The preparative work employed a 5 ft × $^1/_4$ in glass column packed with 3% SP-2100 on 80/100 Supelcoport.

6-Methylene-1,7-octadien-3-one (6). 3-Hydroxy-6-methylene-1,7-octadiene. 4-Methylene-5-hexenal (**5**)[7] (0.82 g, 7.25 mmol) in tetrahydrofuran (10 mL) is added to a solution of vinylmagnesium bromide (10.9 mmol) in tetrahydrofuran (20 mL) at −10 °C. The reaction mixture is stirred for 15 min at −10 °C and then quenched with saturated NH_4Cl solution. The aqueous layer is separated and washed with ether (10 mL), and the combined organics are washed with dilute HCl (10 mL), $NaHCO_3$ (10 mL), and brine (15 mL) and dried (Na_2SO_4). The solvent is removed and the residue chromatographed on silica gel (pentane–ether, 2:1) to yield 0.50 g of alcohol (50%): NMR ($CDCl_3$) δ 1.4–1.9 (m, 3 H), 2.0–2.6 (m, 2 H), 3.9–4.3 (m, 1 H), 4.8–5.4 (m, 6 H), 5.90 (ddd, J = 6, 10, 17 Hz, 1 H), 6.44 (dd, J = 10, 17 Hz, 1 H); IR (neat) 3380 (br s), 3095 (s), 3015 (m), 2990 (s), 2950 (s), 2870 (s), 1645 (mw), 1635 (mw), 1595 (s), 989 (s), 940 (m), 917 (s), 893 (vs) cm^{-1}. The unstable allylic alcohol was immediately oxidized according to the procedure described below.

Oxidation of 3-Hydroxy-6-methylene-1,7-octadiene. To a rapidly stirred suspension of pyridinium chlorochromate[21] (1.08 g, 5.0 mmol) and NaOAc (0.82 g, 1.0 mmol) in dichloromethane (20 mL) is added 3-hydroxy-6-methylene-1,7-octadiene (0.46 g, 3.5 mmol). After stirring

(18) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 781. (b) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 779.

(19) Gouesnard, J. P.; Normant, H. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1974**, *278*, 797.

(20) Wasserman, A. "Diels-Alder Reactions"; Elsevier: New York, 1965.

(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

for 2 h, the reaction mixture is diluted with ether (20 mL) and the organic solution decanted from the black gum. The residue is thoroughly washed with 3 × 5 mL portions of anhydrous ether. The combined organics are passed through a short plug of Florisil and concentrated to yield ketone **6** (0.37 g, 86%): NMR ($CDCl_3$) δ 2.3–2.9 (m, 4 H), 4.8–5.4 (m, 5 H), 5.6–6.7 (m, 3 H); IR (CS_2, 0.051 mm) 3095 (m), 3060 (w), 3015 (mw), 2985 (m), 2940 (m), 1702 (vs), 1683 (vs), 1614 (m), 985 (s), 960 (m), 950 (s), 897 (s), 865 (w) cm^{-1}, mass spectrum, *m/e* (EI, relative percent) 136 (M^+, 11) 121 (9), 108 (30), 93 (39), 81 (75), 67 (26), 55 (100); UV λ_{max} 217, 222 nm; M_r $C_9H_{12}O$ requires 136.0888, found 136.0884.

7-Methylene-1,8-nonadien-3-one (9). A 100-mL oven-dried flask, equipped with additional funnel, magnetic stirrer, and N_2 bubbler, was charged with *O*-(*tert*-butyldimethylsilyl)-1,4-pentadien-3-ol[8] (1.0 g, 5.04 mmol) in tetrahydrofuran (20 mL) then cooled to −78 °C. To this solution was added dropwise a hexane solution of *sec*-butyllithium (3.61 mL, 5.04 mmol, Aldrich). The solution was stirred for 1.5 h, and then treated dropwise over 30 min with a tetrahydrofuran solution (10 mL) of freshly distilled 2-(bromomethyl)-1,3-butadiene[9] (0.79 g, 5.04 mmol). Stirring was continued at −78 °C for 0.5 h, then at room temperature for 1.5 h. Pentane (75 mL) was added and the reaction quenched with saturated NH_4Cl. The organic layer was washed (H_2O, 3×), dried (Na_2SO_4), and concentrated to yield 1.30 g (98%) of crude product. VPC analysis revealed two major peaks in a ratio of 20:80. These intermediates were isolated by preparative VPC and characterized as the α- and γ-alkylation products, respectively. α isomer **7**: NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.95 (s, 9 H), 2.57 (d, *J* = 0.8 Hz, 2 H), 4.99–5.39 (m, 8 H), 6.02 (dd, *J* = 16.6, 10.0 Hz, 2 H), 6.40 (dd, *J* = 17.3, 10.6 Hz, 1 H). γ isomer **8**: NMR ($CDCl_3$) δ 0.16 (s, 6 H), 1.04 (s, 9 H), 2.35 (s, m, 4 H), 4.86–5.43 (m, 7 H), 6.21 (dd, *J* = 16.6, 10.0 Hz, 1 H), 6.43 (dd, *J* = 17.9, 10.6 Hz, 1 H).

A xylene solution (50 mL) of the α- and γ-alkylation products (0.539 g, 2.04 mmol) was heated at 150 °C for 1 h. Solvent was removed in vacuo, and the pale yellow residue was passed through a short column of silica gel (petroleum ether). Removal of solvent left a colorless oil (0.493 g, 91.5%) shown by VPC and ^1H NMR spectroscopy to be pure **8**. A solution of *tert*-butyldimethylsiloxy tetraene **8** (0.30 g, 1.13 mmol) in tetrahydrofuran (25 mL) containing $(n\text{-Bu})_4NF$[22] (0.90 g, 3.44 mmol) was stirred at room temperature for 6 h. Pentene (50 mL) and H_2O (25 mL) were added, and the organic layer was separated, washed with saturated $NaHCO_3$, H_2O, and brine, and then dried (Na_2SO_4). Removal of solvent afforded an oil (0.30 g) shown by VPC to contain trienone **9** and a *tert*-butyldimethylsiloxy compound.

Samples of pure **9** were obtained by preparative VPC. Compound **9**: NMR $CDCl_3$) δ 1.67–1.88 (m, 2 H), 2.03–2.18 (m, 4 H), 4.90–5.30 (m, 5 H), 5.71–6.48 (m, 2 H); IR (CS_2, 0.052 mm) 3050 (m), 2960 (m), 2940 (m), 1680 (s), 1640 (s), 1600 (m), 1580 (m), 970 (s), 935 (m), 875 (s); mass spectrum, *m/e* (CI, isobutane, relative percent) 151 (MH^+, 63), 133 (80), 123 (29), 121 (17), 117 (10), 109 (47), 81 (100).

Methyl 7-Methylene-2,8-nonadienoate ((*E*)-12, (*Z*)-12). 5-Methylene-6-hepten-1-ol. Magnesium turnings (1.95 g, 37.4 mmol) are covered with tetrahydrofuran (10 mL), and 3 mL of a solution of ethyl 3-bromopropyl acetaldehyde acetal[10] (7.17 g, 34.0 mmol) in 25 mL of tetrahydrofuran is added. Dibromomethane is added to initiate Grignard formation, and the reaction mixture warms from 24 to 29 °C. The flask is cooled with a water bath, and the remainder of the bromoacetal is added at such a rate that the temperature never exceeds 30 °C. When the addition is complete, the reaction is stirred for 1 h at room temperature. The Grignard reagent is carefully added via syringe to a solution of 2-(bromomethyl)-1,3-butadiene[9] (4.0 g, 27.2 mmol) in tetrahydrofuran (20 mL) at −10 °C over a 30-min period. After addition the reaction is stirred for 20 min at −10 °C (negative Gilman test). The reaction is quenched with saturated NH_4Cl (5 mL) and water (5 mL). The aqueous layer is separated and extracted with ether (50 mL), and the combined organic layers are washed with saturated NH_4Cl (2 × 20 mL), dried (Na_2SO_4), and then concentrated. The residue is dissolved in 70 mL of EtOH and pyridinium *p*-toluenesulfonate[23] (170 mg, 0.68 mmol) is added. The mixture is stirred at 55 °C for 3 h, concentrated in vacuo and chromatographed on silica gel (pentane–ether, 1:1) to yield 5-methylene-6-hepten-1-ol (2.24 g, 65%): NMR ($CDCl_3$) δ 1.3–1.9 (m, 7 H), 2.0–2.4 (br t, *J* = 10, 17 Hz, 1 H); IR (neat) 3360 (s), 3095 (m), 3015 (w), 2940 (s), 2875 (s), 1633 (w), 1595 (s), 989 (s), 892 (vs), 827 (w) cm^{-1}; C_8H_{12} (M − H_2O) requires 108.0939, found 108.0936.

5-Methylene-6-heptenal (11). 5-Methylene-6-hepten-1-ol (0.65 g, 5.15 mmol) was oxidized with pyridinium chlorochromate[21] (1.65 g, 7.7 mmol) in dichloromethane with sodium acetate buffer as described above. The aldehyde was isolated in 81% yield (0.52 g): NMR ($CDCl_3$) δ 1.4–2.6 (m, 6 H), 4.8–5.3 (m, 4 H), 6.43 (dd, *J* = 11, 17 Hz, 1 H), 9.9 (t, *J* = 2 Hz, 1 H); IR (neat) 3430 (w), 3090 (m), 2890 (s), 2460 (s), 1728 (vs), 1596 (s), 990 (s), 898 (vs), 730 (w), 698 (w) cm^{-1}; $C_8H_{12}O$ requires 124.0888, found 124.0887.

Conversion of 11 to (*E*)-12 and (*Z*)-12. A stirred suspension of sodium hydride (0.377 g, 50% dispersion in oil, 8.0 mmol) in tetrahydrofuran (30 mL) at 0 °C is treated with trimethyl phosphonoacetate[24] (1.50 g, 8.22 mmol) over a 5-min period. After 15 min at 0 °C, 5-methylene-6-heptenal (0.33 g, 2.74 mmol) in tetrahydrofuran (5 mL) is added over a 5-min period. After addition, the reaction is allowed to warm to room temperature and then stirred for 20 h. The reaction is concentrated to a thick paste, filtered through a short plug of silica gel (pentane–ether, 1:1), and concentrated. Chromatography of the crude material, silica gel (pentane–ether, 1:1), yields 260 mg (52%) of a 1:6 mixture of *Z* and *E* α,β-unsaturated esters. (*Z*)-**12**: NMR ($CDCl_3$) δ 1.3–1.9 (m, 2 H), 1.9–2.4 (br t, *J* = 6 Hz, 2 H), 2.6 (q, *J* = 6 Hz, 2 H), 3.65 (s, 3 H), 4.8–5.4 (m, 4 H), 5.7 (d, *J* = 12 Hz, 1 H), 5.9–6.7 (m, 2 H); IR (neat) 3090 (m), 3035 (m), 2985 (m), 2955 (s), 1739 (vs), 1648 (s), 990 (m), 894 (s), 815 (s), 662 (m) cm^{-1}; mass spectrum, *m/e* (EI, relative percent) 180 (5), 180 (5), 148 (20), 121 (20), 105 (25), 100 (32),, 91 (28), 81 (73), 68 (89), 53 (100). (*E*)-**12**: NMR ($CDCl_3$) δ 1.4–1.9 (m, 2 H), 2.0–2.5 (m, 4 H), 3.7 (s, 1 H), 4.8–5.4 (m, 1 H), 5.88 (dt, *J* = 15, 1 Hz, 1 H), 6.45 (dd, *J* = 10, 17 Hz, 1 H), 7.05 (dt, *J* = 15, 7 Hz, 1 H); IR (CS_2, 0.051 mm) 3090 (m), 2990 (m), 2950 (m), 1730 (vs), 1660 (s), 1260 (s), 1190 (s), 1170 (s), 1130 (s), 982 (m), 970 (m), 898 (s), 890 (s), 710 (w) cm^{-1}; mass spectrum, *m/e* (EI, relative percent) 180 (3.2), 148 (16), 121 (13), 105 (27), 91 (27), 79 (54), 68 (100); $C_{11}H_{16}O_2$ requires 180.1151, found 180.1148. UV (hexane) λ_{max} = 217, 222 sh nm.

Ethyl 8-Methylene-2,9-decadienoate ((*E*)-14, (*Z*)-14). 6-Methylene-7-octen-1-ol. Magnesium turning (0.85 g, 3.5 mmol) in a 50-mL three-necked round-bottomed flask equipped with a magnetic stir bar, thermometer, reflux condenser, and constant pressure addition funnel are treated with 3 mL of a solution of the tetrahydropyran-protected ether of 4-bromo-1-butanol[11] (6.9 g, 29.1 mmol) in tetrahydrofuran (20 mL). Dibromoethane (50 μL) is added to initiate the reaction, and the temperature rises to 40 °C. The remainder of the bromide is added at a rate sufficient to maintain the temperature at 40 °C. After addition is complete, the Grignard is stirred for 2 h at room temperature. The reaction mixture is transferred via syringe to an addition funnel and then added to a stirred solution of 2-(bromomethyl)-1,3-butadiene (4.0 g, 27.2 mmol) in tetrahydrofuran (10 mL) at −10 °C over a 40-min period. The mixture is stirred for 3 h at −10 °C and then quenched with 5 mL of saturated NH_4Cl and 5 mL of water. The reaction mixture is extracted with ether (50 mL), and the organic layer is washed with water (20 mL) and brine (2 × 20 mL) and dried (Na_2SO_4). The solvent is removed in vacuo to yield 6.2 g of crude product. The crude product is dissolved in 150 mL of ethanol containing pyridinium *p*-toluenesulfonate (0.15 g, 0.59 mmol). The mixture is heated to 55 °C for 3 h and then concentrated. The residue is chromatographed on silica gel (pentane–ether, 1:1) to yield 2.09 g (55%) of pure alcohol in addition to 0.72 g of a mixture of alochol and tetrahydrofuran-protected alcohol. NMR ($CDCl_3$) δ 1.2–2.0 (m, 7 H), 2.0–2.5 (m, 2 H), 3.6 (m, 2 H), 4.8–5.4 (m, 4 H), 6.45 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3350 (br s), 3095 (m), 3010 (w), 2940 (s), 2865 (s), 1065 (s), 1044 (s), 1010 (m), 985 (s), 955 (w), 890 (s) cm^{-1}; mass spectrum, *m/e* (CI, isobutane, relative percent) 141 (MH^+, 5), 123 (M^+ − H_2O, 78); C_9H_{14} (M − H_2O) requires 122.1096, found 122.1099.

6-Methylene-7-octenal (13). To a rapidly stirred suspension of pyridinium chlorochromate (1.65, 7.7 mmol) and sodium acetate (1.26 g, 1.54 mmol) in anhydrous dichloromethane (15 mL) is added 6-methylene-7-octen-1-ol (0.72 g, 5.13 mmol) in 5 mL of dichloromethane. After stirring for 2 h, the reaction mixture is diluted with ether (25 mL) and the organic solution decanted from the black gum. The residue is thoroughly washed with 3 × 5 mL portions of ether. The combined organics are passed through a short plug of Florisil and concentrated to yield 0.61 g (86%) of product: NMR ($CDCl_3$) δ 1.3–1.95 (m, 4 H), 1.95–2.7 (m, 4 H), 4.8–5.4 (m, 4 H), 6.4 (dd, *J* = 10, 17 Hz, 1 H), 9.9 (t, *J* = 2 Hz, 1 H); IR (neat) 3090 (m), 3020 (w), 3005 (w), 2940 (s), 2865 (s), 2815 (m), 2710 (m), 1725 (vs), 1642 (w), 1632 (w), 1595 (s), 988 (s), 890 (s), 725 (w) cm^{-1}; mass spectrum, *m/e* (CI, isobutane, relative percent) 139 (MH^+, 13), 121 (100).

Conversion of 13 to (*E*)-14 and (*Z*)-14. Ethyl(trimethylsilyl)acetate[12] (0.57 g, 3.57 mmol) in tetrahydrofuran (2.5 mL) is added dropwise to lithium dicyclohexylamide (3.57 mmol) in tetrahydrofuran (18 mL) at −65 °C. The mixture is stirred for 10 min, and 6-methylene-7-octenal (**13**) (0.30 g, 2.17 mmol) in tetrahydrofuran (2 mL) is added. The mixture is stirred for 1 h at room temperature and then quenched by

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addition of powdered sodium bisulfate monohydrate (0.4 g, 2.9 mmol). After stirring for 10 min, the solution is decanted, diluted with water (10 mL), and extracted with ether (15 mL) and ethyl acetate (2 × 15 mL). The combined extracts are dried (Na_2SO_4) and concentrated. The oily product is chromatographed on silica gel (hexane–ethyl acetate, 4:1) to yield 0.36 of product which is 80% pure by GC (10 ft, 10% carbowax 1540, 140 °C); product yield is 64%, which consists of a mixture of (*Z*)-**14** and (*E*)-**14** (43:57). (*Z*)-**14**: NMR ($CDCl_3$) δ 0.9–1.9 (m, 7 H), 1.9–2.4 (m, 2 H), 2.4–2.9 (m, 2 H), 4.15 (q, *J* = 7 Hz, 2 H), 4.8–5.4 (m, 4 H), 5.83 (d, *J* = 13 Hz, 1 H), 6.0–6.8 (m, 2 H); IR (neat) 3092 (w), 3040 (w), 2980 (w), 2935 (m), 2861 (m), 1723 (s), 1642 (m), 991 (w), 895 (m), 819 (m) cm^{-1}; mass spectrum, *m/e* (CI, relative percent) 208 (0.41), 179 (3), 162 (4), 135 (26), 114 (24), 99 (24), 95 (34), 86 (44), 79 (49), 67 (100); $C_{12}H_8O_2$ (methyl ester) requires 194.1307, found 194.1302; UV λ_{max} 216, 222 (sh) nm; (*E*)-**14**: NMR ($CDCl_3$) δ 0.9–1.7 (m, 7 H), 1.7–2.4 (m, 4 H), 4.0 (q, *J* = 7 Hz, 2 H), 4.8–5.4 (m, 4 H), 5.7 (d, *J* = 16 Hz, 1 H), 6.4 (dd, *J* = 10, 17 Hz, 1 H), 6.85 (dt, *J* = 16, 6 Hz, 1 H); IR (neat 3092 (w), 3000 (w), 2982 (m), 2938 (s), 2860 (m), 1724 (vs), 1659 (m), 1597 (m), 985 (m), 895 (m), 850 (w), 663 (w) cm^{-1}; UV λ_{max} 216, 223 (sh) nm; mass spectrum, *m/e* (EI, relative percent) 208 (0.2), 179 (2), 162 (4), 135 (24), 93 (29), 79 (40), 68 (100); UV λ_{max} 216, 223 (sh) nm.

Ethyl 8-Methylene-(*E*)-2,9-decadienoate ((*E*)-14). Sodium hydride (0.52 g of a 50% dispersion in oil, 10.2 mmol) is weighed into 100-mL round-bottom flask and washed with tetrahydrofuran (3 × 5 mL). The hydride is suspended in 35 mL of tetrahydrofuran, cooled to 0 °C, and treated with triethyl phosphonoacetate[24] (2.54 g, 11.3 mmol). The mixture is stirred for 30 min at 0 °C, and 5-methylene-6-octenal (**13**) (0.5 g, 3.6 mmol) in tetrahydrofuran (10 mL) is added over 8 min. The reaction is stirred overnight at room temperature, concentrated, filtered through a short plug of silica gel (pentane–ethyl acetate, 4:1), and concentrated. The product is chromatographed on silica gel (pentane–ether, 10:1). Two fractions are collected: the first 0.14 g, is 83% *E* and 17% *Z* ester; the second, 0.40 g, is pure *E* ester. The yield is 0.54 g (70%, 96% (*E*)-**14**, 4% (*Z*)-**14**).

Ethyl 2,7-Dimethylene-8-nonenoate (16b). 1-Iodo-5-methylene-6-heptene. Triphenyl phosphite methiodide[25] (4.52 g, 10.0 mmol) in 12 mL of dichloromethane is treated with a dichloromethane (3 mL) solution of 5-methylene-6-hepten-1-ol (0.70 g, 5.0 mmol). The reaction is heated to reflux for 20 min, cooled, and diluted with 2 volumes of ether (precipitate formation). The mixture is extracted with cold 0.1 N NaOH (3 × 10 mL), water (10 mL), and brine (10 mL) and then dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on silica gel to yield iododiene (1.03 g, 86% yield): NMR ($CDCl_3$) δ 1.3–2.0 (m, 4 H), 2.22 (br t, *J* = 6 Hz, 2 H), 3.2 (t, *J* = 6 Hz, 2 H), 4.8–5.4 (m, 4 H), 6.45 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3095 (m), 3010 (m), 2984 (m), 2948 (m), 2948 (s), 1642 (w), 1632 (w), 1596 (s), 992 (s), 898 (s), 720 (w) cm^{-1}; mass spectrum, *m/e* (CI, isobutane, relative percent) 109 ($M^+ - I$, 100), 95 (20), 85 (28).

8-Methylene-3-carbethoxy-9-decen-2-one. Ethyl acetoacetate (1.2 g, 9.2 mmol) is treated with sodium ethoxide (0.39 g, 7.5 mmol) in 15 mL of anhydrous ethanol. The mixture is heated to reflux and 1-iodo-5-methylene-6-heptene (1.0 g, 4.23 mmol) in EtOH (3 mL) is added. Reflux is continued for 3 h, and the reaction mixture is cooled and then neutralized to pH 6 (concentrated HCl). The ethanol is removed in vacuo and the residue taken up in ether. The ethereal solution is washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and then concentrated. The residue is chromatographed on silica gel (pentane–ether, 4:1) to yield β-keto ester (0.71 g, 70%): NMR ($CDCl_3$) δ 1.1–2.3 (m, 11 H), 2.25 (s, 3 H), 3.45 (t, *J* = 6 Hz, 1 H), 4.25 (q, *J* = 6 Hz, 2 H), 4.8–5.4 (m, 4 H), 6.45 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3430 (w), 3090 (m), 2940 (s), 2964 (m), 1738 (vs), 1710 (vs), 1642 (w), 1631 (w), 988 (w), 950 (w), 892 (s), 853 (w) cm^{-1}.

Ethyl 2,7-Dimethylene-8-nonenoate (16b).[13] β-Keto ester (0.69 g, 2.9 mmol) in tetrahydrofuran (3 mL) is added dropwise over 10 min to lithium diisopropylamide (3.15 mmol) in tetrahydrofuran (19 mL) at −78 °C. The mixture is stirred at −78 °C for 10 min and then warmed to room temperature before paraformaldehyde (0.5 g, 16.6 mmol) is added. The mixture is stirred for 45 min at room temperature followed by 4.5 h at reflux. The cooled solution is filtered and concentrated and the residue stirred with 15 mL of saturated $KHCO_3$ solution. The product is extracted with dichloromethane (2 × 15 mL), and the organic layer is washed with brine (10 mL) and dried (Na_2SO_4). Concentration and chromatography on silica gel (pentane–ether, 4:1) yields α-methylene ester **16b** (0.40 g, 66%): NMR ($CDCl_3$) δ 1.1–2.0 (m, 7 H), 2.0–2.5 (m, 4 H), 4.20 (q, *J* = 5 Hz, 2 H), 4.8–5.4 (m, 4 HO), 5.5 (s, 1 H), 6.2 (s, 1 H), 6.4 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3090 (m), 2990 (m), 990 (m), 940 (m), 895 (s), 817 (m) cm^{-1}; mass spectrum, *m/e* (EI, relative percent) 208 (0.8), 179 (1), 162 (s), 174 (s), 135 (18), 119 (9), 107 (11), 95 (39), 79 (52), 67 (100), 53 (45); mass spectrum, *m/e* (CI, isobutane, relative percent) 209 (MH^+, 2) 163 (22), 135 (100), 107 (24).

Ethyl 2,6-Dimethylene-7-octenoate (16a). 7-Methylene-3-carbethoxy-8-nonen-2-one. 4-Methylene-1-ido-5-hexene (1.13 g, 5.50 mmol) is treated with the sodium salt of ethyl acetoacetate (10 mmol) as described above to yield 0.78 g of β-keto ester (69%): NMR ($CDCl_3$) δ 1.1–2.4 (m, 9 H), 2.25 (s, 3 H), 3.4 (t, *J* = 7 Hz, 1 H), 4.2 q, *J* = 6 Hz, 2 H), 4.8–5.4 (m, 4 H), 6.45 (dd, *J* = 10, 1m Hz, 1 H); IR (neat) 3095 (m), 2990 (s), 2955 (s), 2880 (m), 1742 (vs), 1715 (vs), 1642 (m), 988 (s), 950 (w), 895 (s), 852 (w) cm^{-1}.

Ethyl 2,6-Dimethylene-7-octenoate (16a). β-Keto ester (0.76 g, 3.4 mmol) is converted to the α-methylene ester (**16a**) (0.42 g, 62%) in the manner described above: NMR ($CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 3 H), 1.45–1.95 (m, 2 H), 1.95–2.5 (m, 4 H), 4.20 (q, *J* = 7 Hz, 2 H), 4.8–5.4 (m, 4 H), 5.5 (s, 1 H), 6.2 (s, 1 H), 6.45 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3420 (w), 3092 (m), 2984 (s), 2940 (s), 2870 (m), 1720 (vs), 1632 (s), 1596 (s), 990 (s), 940 (s), 895 (vs), 817 (s) cm^{-1}; mass spectrum, *m/e* (CI, isobutane, relative percent) 195 (MH^+, 3) 149 (19), 121 (100); UV λ_{max} 217, 223 nm.

1-Carbethoxy-5-vinylbicyclo[3.2.0]heptane (23). 1,5-Dicarbomethoxybicyclo[3.2.0]heptane[26] (5.9 mmol) in ether (25 mL) is cooled to −70 °C and treated with sodium bis(2-methoxyethoxy)aluminum hydride (1.8 mL 70% hexane solution, 5.9 mmol) for 24 h. To this solution is added methylenetriphenylphosphorane (11.9 mmol) in ether (35 mL) at −70 °C. The reaction mixture is slowly warmed to −10 °C (3 h), maintained for 45 min, and then quenched with 1.5 mL of water and stirred 30 min; then 11 mL of 18% sulfuric acid was added with cooling and stirring for 15 min at 0 °C. The reaction mixture is diluted with pentane (20 mL) and the aqueous fraction removed. The organic layer is washed with bicarbonate (2 × 10 mL), water (3 × 10 mL), and brine (10 mL) and then dried ($MgSO_4$). The solvent is removed from a small portion of the reaction mixture, and an NMR is taken of the crude product.

NMR spectroscopy reveals the presence of an aldhyde, an ester, and a compound containing a vinyl group. Half the reaction mixture is concentrated and chromatographed on silica gel, eluting first with pentane to isolate the hydrocarbon fraction and then with ether:pentane (1:1) to isolate an oxygenated fraction.

The second fraction contains 1-vinyl-5-carbomethoxybicyclo[3.2.0]-heptane, which is also further purified by VPC: NMR ($CDCl_3$) δ 1.0–3.0 (m, 10 H), 3.65 (s, 3 H), 4.8–5.2 (m, 2 H), 6.0 (dd, *J* = 11, 18 Hz, 1 H); IR (neat) 3080 (w), 3010 (w), 2950 (s), 2870 (m), 1725 (vs), 1677 (w), 1658 (w), 1640 (w), 1630 (m) cm^{-1}. The methyl ester was converted to the ethyl ester by transesterification. Approximately 10 mg of methyl ester is added to a stirred solution of sodium ethoxide in ethanol (prepared by adding a small piece of sodium to 2 mL of anhydrous ethanol). The reaction is monitored by VPC; after 3 h at 60 °C the reaction is complete. The reaction mixture was diluted with hexane, washed with water and brine, and dried (Na_2SO_4). The product is isolated by preparative VPC. The ^1H NMR ($CDCl_3$) spectrum is identical with that of the minor product isolated from the thermolysis of triene ester **16a**. Compound **23**: NMR ($CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 3 H), 1.5–2.7 (m, 10 H), 4.12 (q, *J* = 7 Hz, 2 H), 4.9–5.2 (m, 2 H), 5.91 (dd, *J* = 10, 17 Hz, 1 H); IR (neat) 3090 (w), 2990 (s), 2960 (s), 2880 (m), 1725 (vs), 1642 (w), 1630 (m), 903 (m) cm^{-1}.

Gas-Phase Flow Pyrolysis Apparatus. A gas-phase flow pyrolysis system consisting of a 30 cm × 10 mm hollow quartz tube heated by a cylindrical tube furnace was employed for all the high-temperature work. The alkenes are introduced neat or as concentrated cyclohexane solutions in a three-neck flask fitted via a 14/20 ground-glass joint to the horizontally mounted pyrolysis tube. Warming of the three-neck flask was often required to expedite transfer of the trienes. The alkenes are swept through the hot zone by a stream of dry, oxygen-free nitrogen at atmospheric pressure. The pyrolysate is trapped at −78 °C and then analyzed by VPC. Contact time in the hot zone was estimated by measuring the flow of nitrogen at room temperature, doubling this value to correct for expansion, and then dividing the volume of the tube (23 cm^3) by the corrected flow rate.

Solution Phase—General Information. All reactions were carried out in sealed ampules. All kinetics and most preparative pyrolyses were done in xylene (distilled). The samples were freeze–thaw degassed 3 times, pyrolyzed, cooled, and then opened. The pyrolysate was analyzed (Hewlett-Packard 5710A), and the products were isolated (Varian 920) by VPC. The concentration in preparative-scale reactions was 0.05–0.1 M. Kinetics were carried out by pyrolyzing the trienes at 201 °C in dilute xylene (0.02–0.05 *m*) up to approximately 50% conversion in the

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presence of an internal standard. Half-lives were calculated by assuming a zero intercept. The results are presented in Table IV.

Solution-Phase Pyrolysis of (*E*)-14. Triene ester (370 mg) in cyclohexane (20 mL) is placed in a Carius tube, freeze–thaw degassed, and then pyrolyzed for 165 min at 200 °C. The NMR and GC analyses show only bridgehead olefin **26**. The pyrolysate is concentrated to yield 0.338 g of crude product. Kugelrohr distillation (100 °C, 0.3 mm) yields bridgehead olefin (0.309 g, 91%), which is 99% by VPC analysis.

Spectral Data of Bridgehead Olefins. 6-Oxobicyclo[3.3.1]-1(2)-nonene (19). NMR (C_6D_4) δ 1.6–2.7 (m, 11 H), 5.5 (m, 1 H); IR (CS_2, 0.052 mm) 3022 (m), 2952 (s), 2925 (s), 2886 (s), 2862 (s), 1712 (vs), 1630 (w), 1414 (w), 1343 (w), 1308 (w), 1279 (w), 1269 (w), 1240 (m), 1199 (m), 1161 (m), 1124 (w), 1070 (s), 1063 (s), 1040 (w), 980 (w), 949 (mw), 931 (w), 910 (w), 838 (m), 797 (s), 770 (w), 660 (w) cm^{-1}; UV (hexane) λ_{max} 193 nm; mass spectrum, *m/e* (EI, relative percent) 136 (29), 118 (3), 107 (6), 93 (40), 79 (100), 67 (14), 53 (18).

***exo*-4-Carbomethoxybicyclo[3.3.1]-1(2)-nonene (22).** NMR (C_6D_4) δ 1.0–2.2 (m, 9 H), 2.42 (complex t, J = 6.0 Hz, 2 H), 2.80 (m, 1 H), 3.34 (s, 3 H), 5.55 (t, J = 6.6 Hz, 1 H); IR (CS_2, 0.052 mm) 3010 (w), 2945 (s), 2925 (s), 2860 (m), 1733 (vs), 1622 (w), 1425 (m), 1340 (m), 1275 (m), 1245 (w), 1220 (nw), 1182 (s), 1170 (s), 1150 (ms), 1118 (w), 1085 (w), 1032 (w), 972 (w), 928 (w), 862 (w), 850 (w), 750 (w) cm^{-1}; UV (hexane) λ_{max} 207 nm; mass spectrum, *m/e* (EI, relative percent) 180 (24), 148 (30), 121 (45), 105 (46), 100 (29), 91 (77), 79 (100), 68 (47), 53 (39).

5-Oxobicyclo[4.3.1]-1(9)-decene (25). NMR (C_6D_6) δ 1.2–2.6 (m, 13 H), 5.36 (m, 1 H); IR (CS_2, 0.052 mm) 3030 (w), 2935 (s), 2880 (m), 2855 (m), 1705 (vs), 1335 (w), 1318 (w), 1259 (m), 1195 (w), 1180 (w), 1100 (m), 1020 (m), 930 (w), 893 (w), 808 (m), 615 (w) cm^{-1}; UV (hexane) λ_{max} 193, 233 sh, nm; mass spectrum, *m/e* (EI, relative percent) 150 (26), 135 (7), 122 (10), 107 (17), 93 (34), 79 (100), 67 (18), 55 (32).

***exo*-7-Carbethoxybicyclo[4.3.1]-1(9)-decene (26).** NMR ($CDCl_3$) δ 1.0–2.45 (m, 17 H), 4.14 (q, J = 7 Hz, 2 H), 5.57 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.14, 142.64, 123.80, 60.27, 47.41, 38.77, 35.35, 33.95, 31.21, 27.41, 25.82, 21.92, 14.28; IR (CS_2, 0.052 mm) 3038 (w), 2980 (m), 2932 (s), 2852 (m), 1731 (vs), 1651 (w), 1433 (m), 1370 (w), 1341 (w), 1300 (w), 1258 (m), 1239 (w), 1213 (w), 1173 (m), 1160 (m), 1142 (m), 109 (m), 1061 (w), 1038 (m), 855 (w), 812 (m), 791 (m) cm^{-1}; UV (hexane λ_{max} 199 nm; mass spectrum, *m/e* (EI, relative percent) 208 (7), 179 (2), 163 (4), 134 (100), 119 (25), 105 (28), 91 (91), 74 (74), 67 (60), 55 (43).

***endo*-7-Carbethoxybicyclo[4.3.1]-1(9)-decene (27).** NMR ($CDCl_3$) δ 0.9–2.8 (m, 16 H), 2.95 (t, J = 7 Hz, 1 H), 4.11 (q, J = 7 H, 2 H), 5.55 (m, 1 H); IR (CS_2, 0.052 mm) 3040 (w), 2980 (m), 2929 (s), 2858 (m), 1733 (vs), 1653 (s), 1435 (m), 1366 (m), 1333 (w), 1321 nw), 1252 (w), 1212 (w), 1100 (s), 1149 (s), 1097 (w), 1057 (w), 1021 (m), 966 (w), 910 (w), 851 (w), 818 (w), 792 (w) cm^{-1}; UV (hexane) λ_{max} 197 nm; mass spectrum, *m/e* (EI, relative percent) 208 (11), 179 (2), 163 (10), 134 (73), 120 (20), 105 (31), 93 (100), 79 (82), 67 (55), 55 (50).

6-Carbethoxybicyclo[4.3.1]-1(9)-decene (28). NMR ($CDCl_3$) δ 1.1–1.9 (m, 9 H), 1.9–2.4 (m, 6 H), 4.14 (q, J = 5 Hz, 2 H), 5.68 (t, J = 5 Hz, 1 H); IR (CS_2, 0.052 mm) 3035 (w), 2978 (m), 2930 Is), 2848 (m), 1728 (vs), 1652 (w), 1367 (w), 1299 (w), 1246 (s), 1237 (m), 1200 (m), 1175 (s), 1148 (w), 1104 (w), 1093 (w), 1070 (m), 1055 (m), 794 (m) cm^{-1}; UV (hexane) λ_{max} 198 nm; mass spectrum, *m/e* (CI, 2-methylpropane, relative percent) 209 (MH^+, 100), 163 (7), 161 (7), 135 (87), 134 (53), 133 (36).

Epimerization and Deuterium Labeling of *endo*-7-Carbethoxybicyclo-[4.3.1]-1(9)-decene (27). Bridgehead olefin ester **27** (0.005 g, 0.24 mmol) is added to LDA (0.26 mmol) in THF (5 mL) at −78 °C. The reaction mixture is stirred at −78 °C for 1 h and then quenched with 1 mL of ethanol-*d*. After 15 min at −78 °C, the reaction is warmed, diluted with water, and extracted with ether (2 mL). The organic layer is washed with brine (2 × 11 mL) and dried (Na_2SO_4). The mixture is concentrated and analyzed by VPC. The product is predominantly exo ester **26** (97%) with a small amount (3%) of endo ester **27**. GC–MS analysis reveals that the exo diastomer has 11% deuterium incorporation while the endo had 83% deuterium incorporated. The endo ester, isolated by preparative VPC, has an ^1H NMR ($CDCl_3$) spectrum that is identical with nondeuterated *endo*-**27** except that the absorption at 2.9 ppm is absent.

Acknowledgment. Support of this work by the National Science Foundation is gratefully acknowledged. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF instrumentation grants.

Registry No. 1, 68695-14-7; **5**, 17844-21-2; **6**, 71304-43-3; 7, 82865-49-4; **8**, 82865-50-7; **9**, 71304-44-4; **11**, 71304-41-1; (*E*)-**12**, 71304-45-5; (*Z*)-**11**, 82865-51-8; **13**, 71304-42-2; (*E*)-**14**, 71304-46-6; (*Z*)-**14**, 71304-51-3; **15b**, 82865-52-9; **16a**, 82865-53-0; **16b**, 82865-54-1; **1m**, 68695-13-6; **18**, 17530-61-9; **19**, 71304-49-9; **20**, 71304-48-8; **22**, 82865-55-2; **23**, 82865-56-3; **2**, 61764-75-8; **25**, 71304-50-2; **26**, 71328-42-2; **27**, 71304-47-7; **28**, 82865-57-4; 3-hydroxy-6-methylene-1,7-octadiene, 82865-58-5; vinyl bromide, 593-60-2; *O*-(*tert*)-butyldimethylsilyl)-1,4-pentadien-3-ol, 82865-59-6; 2-(bromomethyl)-1,3-butadiene, 23691-13-6; ethyl 3-bromopropyl acetaldehyde acetal, 34399-67-2; 2-(bromomethyl)-1,3-butadiene, 23691-13-6; 5-methylene-6-hepten-1-ol, 74785-37-8; trimethylphosphonoacetate, 5927-18-4; 6-methylene-7-octen-1-ol, 82865-60-9; 4-bromo-1-butanol THP, 31608-22-7; ethyl (trimethylsilyl)acetate, 4071-88-9; triphenylphosphite methyliodide, 2065-66-9; methyl acetoacetate sodium salt, 34284-28-1; 8-methylene-3-carboethoxy-9-decen-2-one, 82865-61-0; formaldehyde, 50-00-0; 4-methylene-1-iodo-5-hexene, 17844-24-5; 7-methylene-3-carboethoxy-8-nonen-2-one, 82865-62-1; 1,5-dicarbomethoxybicyclo[3.2.0]heptane, 31947-23-6; 1-vinyl-5-carbomethoxybicyclo[3.2.0]heptane, 82865-63-2.

Synthesis and Chemistry of a Bridgehead Enol Lactone

Kenneth J. Shea* and Eiji Wada

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received December 9, 1981*

Abstract: Intramolecular Diels–Alder cycloaddition of ethyl 1-methylene-2-methyl-2-propenyl hex-2-enedioate (**6**) results in formation of bridgehead enol lactone **7** in high yield. The bridgehead enol lactone is a stable crystalline solid. Under mild acidic and basic conditions, the lactone bridge is cleaved to produce an enol or enolate ion in a high-energy boat conformation. Product stereochemistry of the cleavage reaction under basic or mildly acidic conditions reveals a rapid conformational relaxation to a low-energy chair conformer that undergoes highly stereoselective protonation. At higher Brønsted acidities, the apparent stereoselectivity of this protonation step diminishes. This is believed to be due to the onset of competing AS_E2 carbon–carbon double bond protonation, a process that results in formation of a product epimeric with that of the lactone cleavage reaction under milder acidic or basic conditions.

The intramolecular Diels–Alder reaction occupies a prominent position in contemporary organic synthesis.[1] Recently the scope of this reaction has been extended to include the synthesis of bicyclic bridgehead olefins.[2] This intramolecular cycloaddition reaction has proven to be sufficiently flexible to permit synthesis of a wide variety of functionalized bridgehead alkenes.[3] These compounds are of interest not only for providing an opportunity

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0002-7863/82/1504-5715$01.25/0 © 1982 American Chemical Society