was contaminated by a small amount of a compound that could be acetylated in acetic anhydride to give 1,2,4-trihydroxybutane triacetate. This by-product is probably a 1,2,4-trihydroxybutane diacetate.

Reaction of 8a with Pd/C. Formation of 13a. Compound **8a** (3.94 g) was refluxed with Pd/C (10%, 5.00 g) under N_2 in *p*-cymene (60 mL) for 24 h. The reaction mixture was filtered, concentrated, and treated with light petroleum (60–80 °C). The solid formed recrystallized from acetic acid, yielded **13a**, 1.32 g (49%), mp 142–143 °C (lit.[10] 143–144 °C) which was identical with an authentic sample.[9]

Detelluration of 8a with Triphenyltin Hydride. Compound **8a** (10 mmol) was refluxed with $(C_6H_5)_3SnH$ (50 mmol) under N_2 in toluene (150 mL) for 6 h, whereupon the solvent was removed and the residue distilled yielding 2-methyl-2,3-dihydrobenzofuran (84% yield).

Detelluration of 8a with Raney Nickel (W2). Compound **8a** (10 mmol) was refluxed with Raney nickel (ca. 20 g) under N_2 in dioxane (80 mL) for 6 h; GLC analysis of the reaction mixture revealed the formation of 2-methyl-2,3-dihydrobenzofuran and 2-propylphenol in the ratio 5:2.

Acknowledgment. Financial support by the Swedish Natural Research Council and Carl Tryggers Stiftelse is gratefully acknowledged. Dr. Jan Erling Bäckvall is also gratefully acknowledged for valuable discussions concerning interpretation of the NMR data. We also thank Dr. N. E. Stjernström, Uppsala, for the authentic sample of compound **13a**.

Studies on the Total Synthesis of Chlorothricolide: Stereochemical Aspects of the Intramolecular Diels–Alder Reactions of Methyl Undeca-2,8,10-trienoates

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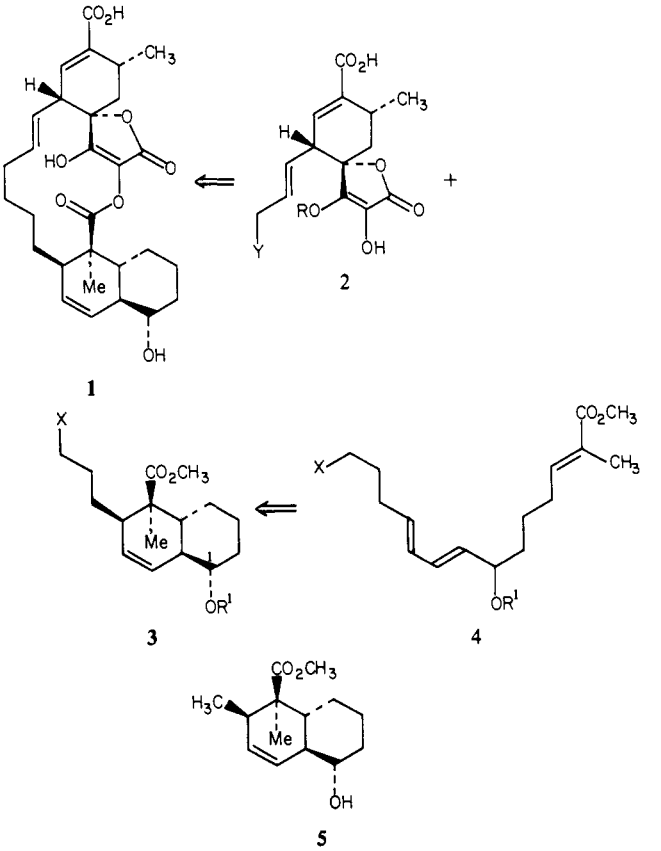
Abstract: The intramolecular Diels–Alder reactions of a series of methyl undeca-2,8,10-trienoates have been examined in connection with a planned synthesis of the bottom half **3** of chlorothricolide (**1**). The intramolecular Diels–Alder reactions of **11**, **18**, **19**, **22**, **23**, and **24** preferentially afford products possessing cis-ring fusions. In each case, the product distribution is independent of dienophile stereochemistry. Product ratios range from 62:38 to 81:19 (cis:trans). Trienes **20** and **21** afford essentially equal mixtures of cis- and trans-fused products. The intramolecular Diels–Alder reaction of trienone **46** shows reversed selectivity for the trans-fused product (65:35 trans:cis), but **47** isomerizes to **49** under the reaction conditions.

Chlorothricolide (**1**) is the aglycone of the antibiotic chlorothricin, which was isolated from *Streptomyces antibioticus* in 1969.[1] Chlorothricin is active against gram-positive bacteria, functioning as an inhibitor of pyruvate carboxylase and maleate dehydrogenase.[2] Chlorothricolide, a hydrolysis product of chlorothricin, retains some of the original activity of chlorothricin itself.[3] Recently, Ireland and Thompson have reported their progress on the total synthesis of chlorothricolide.[4]

Our original plan for the synthesis of **1** involved construction of the bottom half **3** by the intramolecular Diels–Alder reaction of **4**. This strategy was appealing since the cyclization **4** → **3**, an endo Diels–Alder reaction, would introduce each of the stereocenters in the cyclohexene ring in a single step. In addition, some element of stereochemical control of C(1) of **3** would be expected given the proper choice of hydroxyl-protecting group.[5] Of course, the success of such a route would depend on the degree to which the cyclizations of trienes such as **4** follow the endo rule. As a test of this strategy, we chose to attempt the synthesis of compound **5**, a model for the bottom half of chlorothricolide. These efforts led to the discovery of an unexpected reactivity pattern in the intramolecular Diels–Alder reactions of a series of methyl undeca-2,8,10-trienoates. We disclose herein the results of this study.



Synthesis and Cyclization of Model Triene 11. Condensation of sorbaldehyde **6** with the Grignard reagent prepared from 4-bromobutyraldehyde diethyl acetal[6] afforded acetal **7** in 93% yield.

(1) (a) Keller-Schierlein, W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. (b) Muntwyler, R.; Widmer, J.; Keller-Schierlein, W. *Ibid.* **1970**, *53*, 1544. (c) Muntwyler, R.; Keller-Schierlein, W. *Ibid.* **1972**, *55*, 2071. (d) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

(2) (a) Schindler, P. W.; Zachner, H. *Arch. Microbiol.* **1972**, *82*, 66; *Eur. J. Biochem.* **1973**, *39*, 591. (b) Prache, W.; Chapman, D. *Biochem. Biophys. Acta* **1972**, *255*, 348. (c) Schindler, P. W. *Eur. J. Biochem.* **1975**, *51*, 579.

(3) Schindler, P. W.; Scrutton, M. C. *Eur. J. Biochem.* **1975**, *55*, 543.

(4) Ireland, R. E.; Thompson, W. *J. Org. Chem.* **1979**, *44*, 3041; *Tetrahedron Lett.* **1979**, 4705. See also: Ireland, R. E.; Thompson, W. J.; Mandel, N. S.; Mandel, G. S. *J. Org. Chem.* **1979**, *44*, 3583.

(5) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008.

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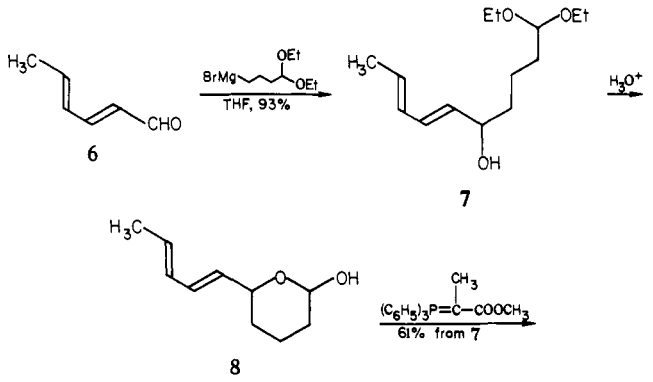
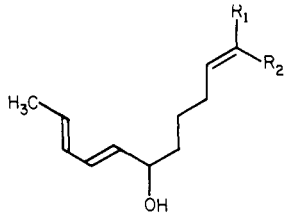
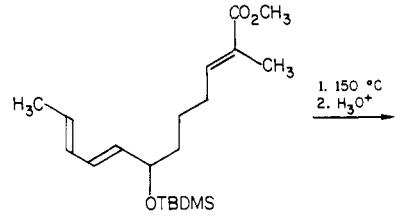


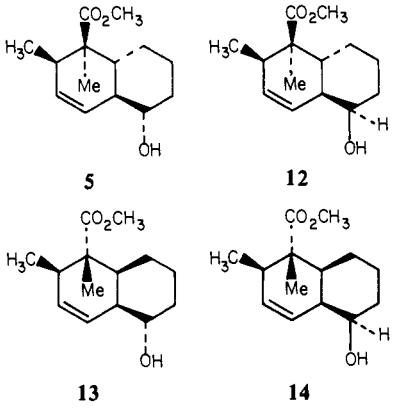


9, $R_1 = COOCH_3$, $R_2 = CH_3$
10, $R_1 = CH_3$, $R_2 = COOCH_3$

Hydrolysis of **7** followed by treatment of the crude hemiacetal **8** with (carbomethoxy)ethylidenetriphenylphosphorane[7] in refluxing C_6H_6 afforded the expected triene **9** in 61% overall yield. The hydroxyl group of **9** was protected as a *tert*-butyldimethylsilyl ether (85%)[8] and the resulting ether **11** was cyclized to afford 10%



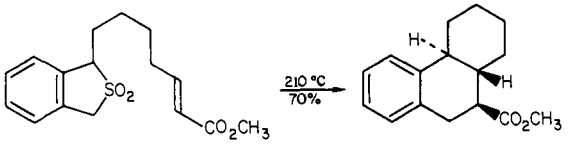
11



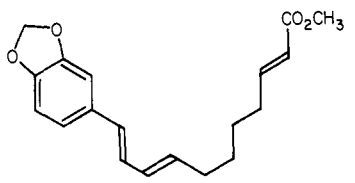
of recovered triene plus 90% of a 15:13:23:49 mixture of four cycloadducts. These compounds were most easily separated after deprotection. In this manner, pure samples of **5** (7%), **12** (3%), **13** (6%), and a 60:40 mixture **13–14** (35%) were obtained. Repeated chromatography of the latter mixture afforded a pure sample of **14**.

It was anticipated from the outset that the major product(s) of the Diels–Alder reaction of **11** would possess trans-ring fusions. However, double-irradiation experiments showed unambiguously that both **13** and **14** possess cis-ring fusions. Therefore, **13** and **14** must be exo rather than endo Diels–Alder adducts.[9] Isomer **12** was assigned a trans-ring fusion by NMR studies. The stereocenters at C(5) and C(6) were assigned on the basis of the chemical shifts of the two methyl groups (δ 1.16 and 0.89) which are consistent with these groups residing in axial and pseudoaxial positions, respectively, on the cyclohexenyl ring.[10] The stereochemistry of the final isomer **5** was assigned by comparison of the NMR spectrum of **5** to the NMR spectra of certain chlorothricolide degradation products.[11] Clearly, model compound **5** is a minor product of the cyclization of **11**, and **4** would therefore appear to be an unpromising precursor of the bottom half of chlorothricolide.

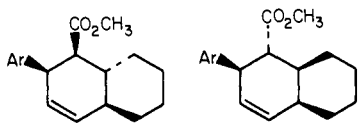
Stereochemistry of the Intramolecular Diels–Alder Reactions of Methyl Undeca-2,8,10-trienoates. Only a few examples of intramolecular Diels–Alder reactions of terminally activated 1,7,9-trienes have been studied.[12] Nicolaou et al.[12a] have reported that sulfone ester **15** cyclizes, presumably via an (*E*)-*o*-diquinomethane intermediate, with high selectivity to trans-fused **16**. The stereochemical outcome of this cyclization is in agreement with previous studies of unactivated dienophile–*o*-diquinomethane intramolecular cycloadditions, which are usually highly selective for the trans-fused product.[13] On the other hand, Joshi et al.[12b] reported that the cyclization of **17** affords a mixture of cyclo-



15 **16**



17



~1:2

(6) 4-Bromobutyraldehyde diethyl acetal was prepared in 62–67% yield by treatment of 4-bromobutyraldehyde (Vedejs, E.; Arnost, M.; Hagen, J. *J. Org. Chem.* **1979**, *44*, 3230) with EtOH, $(EtO)_3CH$, and a catalytic amount of NH_4Cl.

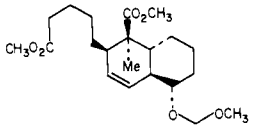
(7) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278.

(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

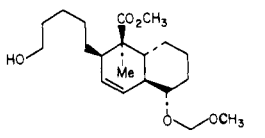
(9) Stereochemistry at C(5) and C(6) of **13** and **14** was assigned on the assumption that the olefin stereochemistry of **11** is preserved in the reaction products. There is no experimental evidence to suggest that the cis principle is violated by this reaction.

(10) Jackman, L. M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1972; pp 83–86.

(11) A sample of naturally derived i and the 90-MHz ^1H NMR spectrum



i



ii

of **ii** were kindly provided by Professor R. E. Ireland and Dr. W. J. Thompson. NMR data for i: δ 5.88 (d, J = 10.5 Hz, H_8), 5.65 (dd, J = 10.5, 4.5 Hz, H_7), 1.15 (s, 3 H). NMR of ii: δ 5.88 (d, J = 10.5 Hz, H_8), 5.75 (dd, J = 10.5, 4.5 Hz, H_7), 1.15 (s, 3 H).

(12) (a) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463. (b) Joshi, B. S.; Viswanathan, N.; Gawad, D. H.; Balakrishnan, V.; Philipsborn, W. v. *Helv. Chim. Acta* **1975**, *58*, 2295.

(13) For leading references, see: (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (c) Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885. (d) Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1979**, 1119. (e) Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017. (f) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215. (g) Kametani, T.; Nemoto, H.; Tsubuki, M.; Nishiuchi, M. *Tetrahedron Lett.* **1979**, 27.

adducts among which the cis-fused product predominates. The product distribution realized in the latter case is in line with our results with **11**. As a consequence of the variation in these results, we decided to study a number of additional methyl undeca-2,8,10-trienoates in order to define the stereochemical parameters of these Diels–Alder reactions. We hoped that our efforts in this regard would lead to the development of a useful route to the bottom half of chlorothricolide.

Trienes **18–21** were synthesized by the methods described at the end of the Discussion. The results of the Diels–Alder reactions of these trienes are summarized in Scheme I.[14] Stereochemistry was assigned to the individual cycloadducts by a combination of spectroscopic and chemical methods, as discussed below.

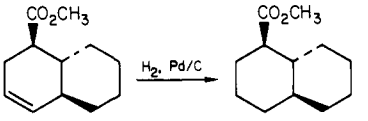
The major products **25a** and **25b** of the Diels–Alder reaction of **18** were initially assumed to be hydroxyl epimers as a consequence of the similarities of the ^{1}H NMR signals of C(5)–H, the proton α to the carbomethoxyl group, of the two isomers. In both isomers, this signal appears as a doublet of doublets with coupling constants of 10 and 12 Hz. These data require that the protons at C(4a), C(5), and C(6) occupy axial positions on the cyclohexenyl ring.[12b] The epimeric nature of these compounds was subsequently established by oxidation of either isomer with pyridinium chlorochromate (PCC)[15] to give the same ketone **39** in excellent yield (Scheme II). The ring fusions of **25a** and **25b** were shown to be cis by double irradiation experiments.

The structures of the major products **27a** and **27b** of the Diels–Alder reaction of **19** were assigned by correlation with **25a** and **25b**, respectively. Thus, treatment of **27b** with $NaOCH_3$ in CH_3OH at 80 °C followed by acid hydrolysis effected complete epimerization and deprotection to **25b** (79% yield). Contrathermodynamic epimerization of **25a** afforded **27c** (58%) along with recovered **25a** (31%). Alcohol **27c** was also prepared from Diels–Alder adduct **27a** by a mild acid hydrolysis. Treatment of **27c** with *p*-TsOH in refluxing benzene resulted in smooth lactonization to **40** (91% yield). This result provides unequivocal evidence that the ring fusions of **25a**, **25b**, **27a**, and **27b** are cis.

The structures of the minor products of the Diels–Alder reactions of **18** and **19** were assigned by analogous methods (Scheme II). Oxidation of either **28c** or **28d** (which were prepared from the corresponding silyl ethers **28a** and **28b** by acid hydrolysis) with PCC[15] afforded ketone **41** in high yield. The ring fusion stereochemistry of both **28c** and **28d** was shown to be trans by double-irradiation experiments; interestingly, this stereorelationship is preserved on oxidation of these alcohols to ketone **41**. The remaining stereocenters at C(5) and C(6) were assigned by analysis of the ^{1}H NMR signals for C(5)–H which appear as doublets, J = 3.5–4 Hz, for each isomer. The multiplicity of this signal is consistent only with structures in which an axial carbomethoxyl group is flanked by a pseudoaxial alkyl group at C(6). It is interesting to note that the C(5)–H signal of these compounds is very similar to the C(4)–H signal of stereochemically related perhydroindene intramolecular cycloadducts.[16]

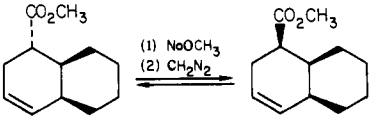
The structures of cycloadducts **26a** and **26b** were assigned on the basis of ^{1}H NMR spectroscopy and by their smooth PCC oxidation to trans-fused ketone **42**. The resonance for C(5)–H of these compounds appears as a doublet of doublets, with coupling constants of 10 and 5 Hz. These data leave little doubt about the stereochemical environment of C(5)–H, since these coupling constants are characteristic of trans-fused cycloadducts possessing equatorial carbomethoxyl groups flanked by a pseudoaxial alkyl group at C(6).[12b,16]

The structure of **30** was confirmed by hydrogenation to the



30 43

known ester **43**. The ^{13}C NMR spectrum of **43** so obtained was in good agreement with the spectrum previously reported for this compound.[17] Finally, adducts **29** and **31** were correlated by ester



29 31

~1:1

epimerization which afforded an approximate 1:1 mixture of these two isomers.

On the basis of the results summarized in Scheme I and in reference 14 we conclude the following.

(1) The unexpected product selectivity realized with **11** is general for trienes of this type, as cis-fused cycloadducts are the major products for each of the Diels–Alder reactions of **18–19** and **22–24**.

(2) Product selectivity is independent of dienophile stereochemistry.

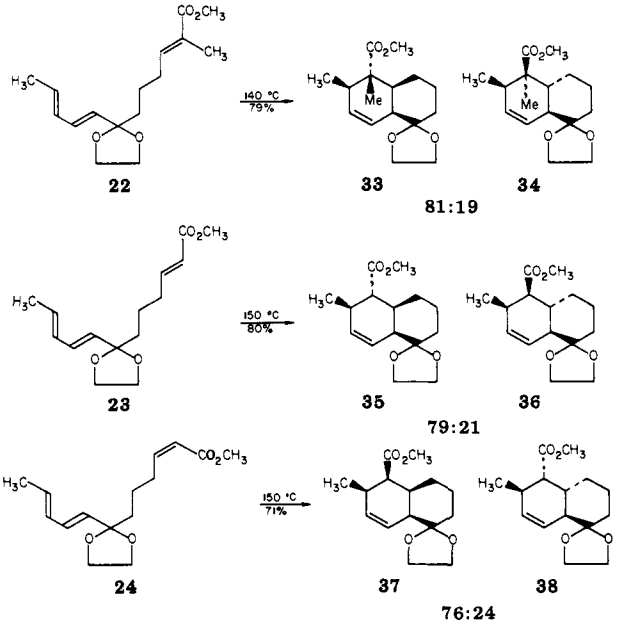
(3) Secondary orbital interactions do not control the stereochemical course of these Diels–Alder reactions.

In the case of trienes **11**, **18**, **19**, **22**, **23**, and **24**, the major

exo-**11**,**22**	R_1 = $COOCH_3$, R_2 = CH_3	*endo*-**11**,**22**
exo-**18**,**20**,**23**	R_1 = $COOCH_3$, R_2 = H	*endo*-**18**,**20**,**23**
endo-**19**,**21**,**24**	R_1 = H, R_2 = $COOCH_3$	*exo*-**19**,**21**,**24**

products arise via transition-state A. Clearly, the endo rule is violated by (*E*,*E*,*E*)-trienes **11**, **18**, **22**, and **23**. Although the major products of the Diels–Alder reactions of (*Z*,*E*,*E*)-trienes **19** and

(14) We have also studied the Diels–Alder reactions of **22–24**. These compounds were synthesized in order to assess the effect of the stereochemistry of the C(7) alkoxyl substituent on the cyclizations of **11**, **18**, and **19**. It is apparent from the results summarized below that the cyclizations of these



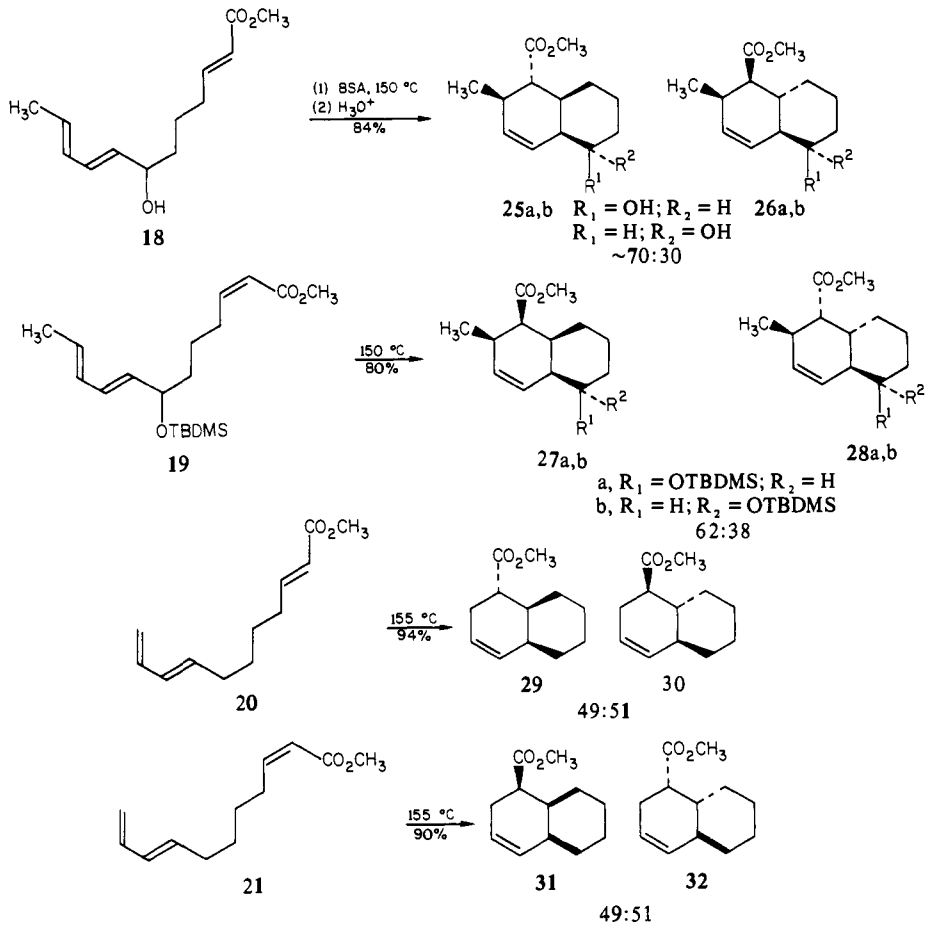
ketals are somewhat more selective for the cis-fused products than are the cyclizations of **11**, **18**, and **19**. Full experimental details for these cyclizations are reported in the Experimental Section.

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

(16) (a) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390. (b) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264. (c) Roush, W. R.; Gillis, H. R. *Ibid.* **1980**, *45*, 4283. (d) Roush, W. R.; Gillis, H. R. *Ibid.* **1980**, *45*, 4267.

(17) Gordon, M.; Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1973**, *51*, 2092.

Scheme I



24 are endo adducts, it is apparent that secondary orbital interactions are not the controlling factor for these cyclizations. To the extent that an endo transition state is stabilized by secondary orbital interactions, one expects to observe relatively more cis-fused product from the (*Z*,*E*,*E*)-trienes, and relatively more trans-fused product from the (*E*,*E*,*E*)-trienes. This tendency is not apparent in the data. In fact, (*E*,*E*,*E*)-trienes **18** and **23** afford slightly more cis-fused product than is obtained from the corresponding (*Z*)-dienophile isomers.

Control experiments established that each of the cyclizations reported in Scheme I is kinetically controlled.[18] It therefore follows that cis-fused transition-state A is somewhat lower in energy than trans-fused transition-state B (1.0–1.2 kcal mol^{-1} for **18**, **19**, and **22–24**). The results with **20** and **21** imply that the greater selectivity realized with the more highly functionalized trienes such as **11**, **18**, and **19** is related to the presence of substituents at C(7) (and possibly at C(11)). The precise nature of the factors responsible for the increased selectivity in these cases is, however, uncertain at present.

It is now apparent that intramolecular Diels–Alder reactions which occur at temperatures in excess of 100 °C are not governed by secondary orbital interactions.[19] We have previously shown that the intramolecular Diels–Alder reactions of a series of methyl (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-deca-2,7,9-trienoates preferentially afford *trans*-perhydroindene cycloadducts.[5,16] In many respects, the stereochemical parameters of these cyclizations parallel the results presented in Scheme I. In both cases, product selectivity is independent of dienophile stereochemistry; in both cases, product selectivity seems to be dominated by subtle steric and/or conformational factors; and, the parent, unsubstituted trienes are the least selective examples in each series. The principal difference between the two sets of reactions is that the decatrienoates afford primarily trans-fused products,[5,16] whereas the undecatrienes (Scheme I) afford predominantly cis-fused products.

The results reported by Joshi et al.[12b] for **17** are consistent with our data. With respect to the data published for **15**[12a] and other unactivated deca-1,7,9-trienes,[13,20] there is some evidence that the pronounced trans selectivity observed in many of these cases may derive in part from steric interactions between substituents at C(8) of the diene and an axial C(5)–H in the cis-fused transition state. Wilson and co-workers[20a,b] invoke such arguments to account for the different product selectivity realized with **44** and **45**. It is interesting to note that the majority of 1,7,9-trienes, including *o*-diquinomethanes,[13] which cyclize with high selectivity to trans-fused octahydronaphthalenes possess substituents at C(8) (as in **44**). Whether or not substituents at the corresponding position of trienes **18–21** will alter the stereochemical course of these cyclizations remains for determination.

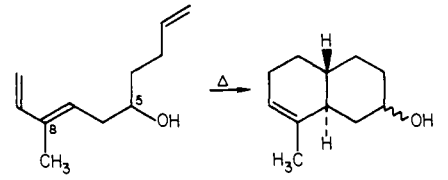
Attempts to improve the selectivity of the cyclizations summarized in Scheme I using Lewis acid catalysts[16d] have been unsuccessful. Attempts to catalyze the cyclizations of **9**, **11**, **20**, or **21** with a variety of Lewis acids such as $EtAlCl_2$, Et_2AlCl, and menthyloxy-$AlCl_2$ have led only to products of decomposition and/or butadiene polymerization.

Cyclization of Trienone Ester 46. Another factor well-known to influence the stereochemical course of intramolecular Diels–

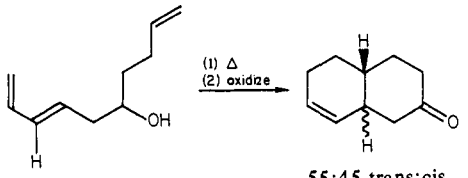
(18) The individual cycloadducts were resubjected to the Diels–Alder reaction conditions and were recovered unchanged (GC analysis).

(19) This conclusion is not surprising since bimolecular Diels–Alder reactions of open-chain dienes and dienophiles obey the endo rule only at low temperatures. Reviews: (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 14. (b) Onishenko, A. S. "Diene Synthesis" (English Translation) 1964, Israel Program for Scientific Translation, Jerusalem. (c) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.

(20) (a) Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560. (b) Wilson, S. R.; Mao, D. T. *Ibid.* **1979**, *44*, 3093; *J. Am. Chem. Soc.* **1978**, *100*, 6289. (c) Naf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114. (d) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085. (e) Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1980**, *45*, 5079.



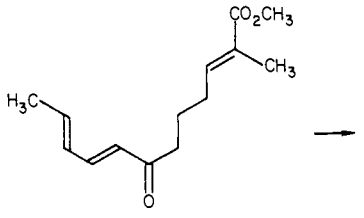
44 >95% trans fused



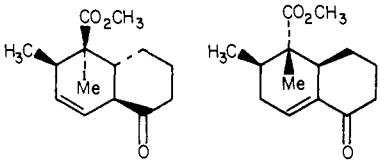
45 55:45 trans:cis

Alder reactions is the hybridization of the atoms of the chain separating the diene and dienophile.[21] Pioneering studies by Oppolzer have shown that sp^2-hybridized atoms at the position allylic to the diene prefer to remain coplanar to the diene in the reaction transition state, thereby maintaining orbital overlap along the reaction coordinate. In some cases, the stereochemical outcome of cyclizations of trienes bearing sp^2-hybridized atoms at the position allylic to the diene is opposite to the outcome realized with trienes bearing sp^3-hybridized allylic substituents.[21c] We therefore decided to study the Diels–Alder reaction of **46** in order to determine whether or not a carbonyl group at C(7) would alter the stereochemical course of the reaction in favor of the trans-fused product. Examination of Dreiding molecular models of **46** reveals that if the carbonyl group is constrained to remain coplanar to the butadiene, then bonding geometries are easily obtained only in the transition state that leads to the trans-fused product.

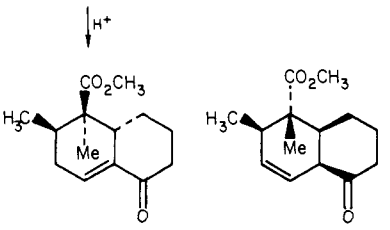
Accordingly, **46** was prepared by oxidation of **9** with



46

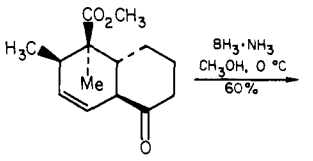


47 48

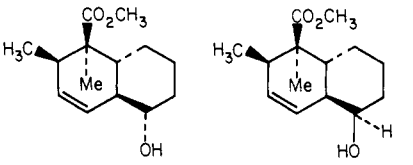


49 50

Ag_2CO_3–Celite.[22] Heating a solution of **46** in toluene at temperatures between 150 and 200 °C to 50–65% conversion afforded a mixture of cycloadducts among which **47** was the major product. Enones **48** and **49** were also present in variable amounts. Pure



47



5 12

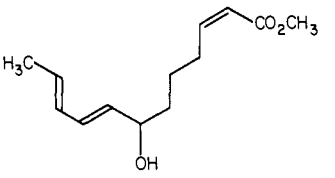
2:1

47 was isolated from one such mixture by chromatography. The stereochemistry assigned to **47** was confirmed by reduction of **47** with $BH_3 \cdot NH_3$[23] to a 2:1 mixture of alcohols **5** and **12**.

Attempts to increase the conversion of **46** to cyclization products led in general not to increased yields of **47** but rather to mixtures in which conjugated enones **48** and **49** were the major components. In one case, a 35:65 mixture of **48**:**49** was obtained in 82% combined yield. The structure of **49** was established by acid-catalyzed isomerization of **47**, which afforded **49** in 33% yield. We presume that **48** is the conjugated tautomer of exo Diels–Alder adduct **50**. To date, we have been unable to suppress the deleterious isomerization of **47** to **49**.[24]

Thus, the carbonyl group at C(7) influences the stereochemical course of this cyclization. With respect to our ultimate goal of achieving the total synthesis of chlorothricin, however, it would appear that sequences involving dienone cyclizations will not be useful unless the conjugation problem can be overcome. We are currently pursuing an alternate synthesis of the bottom half **3** of **1** and will report on these studies in due course.

Synthesis of Cyclization Substrates. Triene **18** was prepared from acetal **7** by hydrolysis to hemiacetal **8** followed by condensation of crude **8** with (carbomethoxy)methylenetriphenylphosphorane[25] (63% yield from **7**). Small quantities (6%) of the *cis*-dienophile isomer **18a** were also obtained.



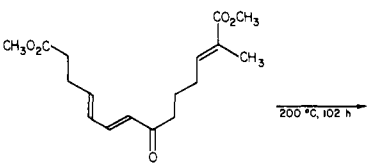
18a

(21) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (c) Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001. (d) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836.

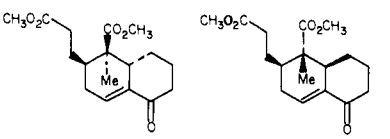
(22) Fetizon, M.; Golfier, M. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1968**, *267*, 900.

(23) Andrews, G. C.; Crawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 693.

(24) Similar results have been obtained with triene **iii**, which cyclizes to afford a 62:38 mixture of enones **iv** (δ 1.09 (s, 3 H)) and **v** (δ 0.92 (s, 3 H)), respectively.



iii

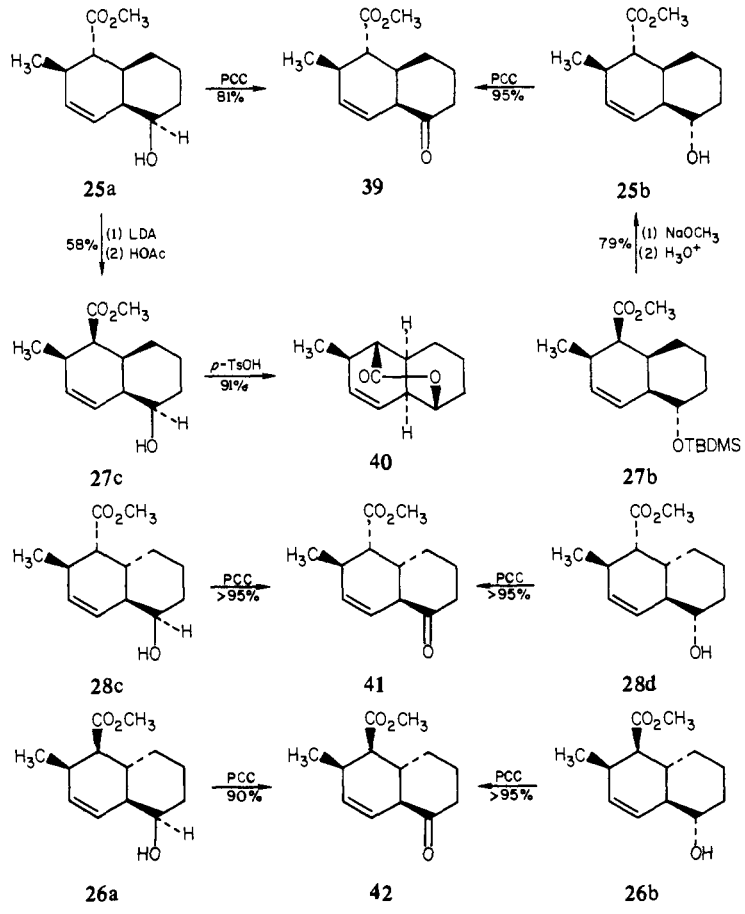


iv v

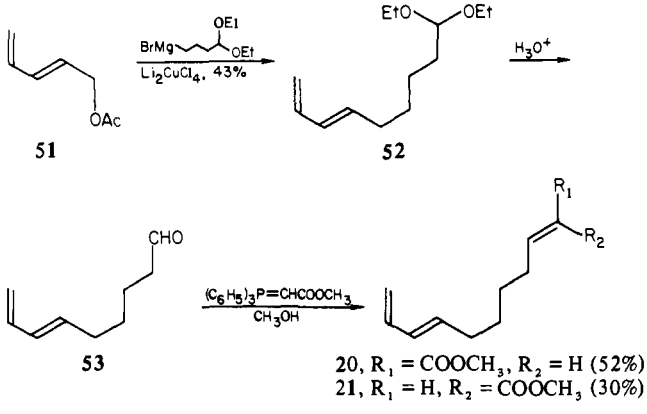
62:38

(25) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

Scheme II



Scheme III



Triene **19** was synthesized by the route described in a preliminary communication.[26] Full experimental details for this synthesis are provided in the Experimental Section.

Trienes **20** and **21** were prepared as outlined in Scheme III. Condensation of 2,4-pentadienyl acetate (**51**)[27] with the Grignard reagent prepared from 4-bromobutyraldehyde diethyl acetal in the presence of Li_2CuCl_4[28] afforded volatile acetal **52** in 43% yield. Hydrolysis of **52** afforded aldehyde **53** which, without purification, was treated with (carbomethoxy)methylenetriphenylphosphorane in CH_3OH[25] to give an easily separated mixture of **20** (52%) and **21** (30%).

(26) Roush, W. R.; Gillis, H. R.; Hall, S. E. *Tetrahedron Lett.* **1980**, *21*, 1023.
(27) Odia, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1990.
(28) (a) Samain, D.; Descoins, C.; Commeron, A. *Synthesis* **1978**, 388. (b) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82. (c) Preparation of Li_2CuCl_4: Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

Experimental Section

^1H NMR spectra were measured at 60 MHz on Perkin-Elmer R-24B and Varian T-60 instruments and at 250 MHz on a Bruker 250 instrument. Chemical shifts are reported in δ units relative to internal Me_4Si. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High-resolution mass spectra were provided by the Facility supported by NIH Grant RR0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high-resolution mass spectrometer equipped with an IBM 1800 computer system to process data recorded on photographic plates. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ. Si analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points were recorded on Fisher-Johns hot-stage melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried (120 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from sodium benzophenone ketyl; CH_2Cl_2 and Me_2SO were distilled from CaH_2; benzene was distilled from $LiAlH_4$; toluene was distilled from sodium metal. Preparative thin-layer chromatography (TLC) was performed by using 20 × 20 cm plates coated with 0.5- and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chromatography was performed by using activity I Woelm silica gel. Flash chromatography was performed as described by Still.[29] All chromatography solvents were distilled prior to use.

(*E*,*E*)-5-Hydroxy-6,8-decadienal Diethyl Acetal (7). To a vigorously stirred mixture of 1.76 g of Mg turnings (72.6 mmol) in 50 mL of dry, refluxing THF containing one crystal of I_2 was added, dropwise, a solution of 7.05 g of 4-bromobutyraldehyde diethyl acetal[6] (31.3 mmol) in 120 mL of dry THF over 2 h. The mixture was then refluxed for 20 min and cooled to 0 °C prior to the next step.

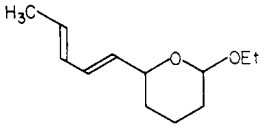
(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

A solution of 2.00 g (20.8 mmol) of sorbaldehyde (**6**)[30] in 10 mL of dry THF was added over 8 min with stirring. Twenty minutes later, the excess reagent was quenched by the addition of 1 mL of MeOH. The resulting solution was poured through a glass-wool plug into a separatory funnel containing 100 mL of ether and 100 mL of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with two additional 100-mL portions of ether. The combined extracts were concentrated in vacuo and dissolved in 50 mL of CH_2Cl_2. This solution was dried over Na_2SO_4 and Na_2CO_3, filtered, and then was concentrated in vacuo to give a yellow crude product. The crude product was purified by chromatography on 150 g of silica gel by using 1:2 ether–hexane as eluant, affording adduct **7**: 4.36 g (93%); NMR (neat) δ 5.2–6.3 (m, 4 H, vinylic H's), 4.37 (m, 1 H, $-CH(OEt)_2$), 3.97 (br q, 1 H, CH(OH), 3.46 (dq, J = 3, 6 Hz, 4 H, OCH_2), 2.80 (s, 1 H, OH), 1.72 (d, J = 6 Hz, 3 H, vinyl CH_3), 1.41 (br s, 6 H), 1.15 (t, J = 8 Hz, 6 H, CCH_3); IR (neat) 3435, 3030, 1665, 1447 cm^{-1}; mass spectrum, m/e 242 (parent ion).

1-Hydroxy-5-((*E*,*E*)-penta-1,3-dienyl)tetrahydropyran (8). To a stirred solution of 50 mL of 5% aqueous oxalic acid and 50 mL of THF was added a solution of 7.86 g of acetal **7** (32.5 mmol) in 30 mL of THF. The reaction vessel was placed in an ice bath to prevent warming of the solution during the addition. The ice bath was then removed and the flask purged with Ar. After being stirred for 21.5 h at room temperature, the reaction mixture was poured into a separatory funnel containing 100 mL of CH_2Cl_2 and 100 mL of saturated aqueous $NaHCO_3$. The CH_2Cl_2 layer was washed with 100 mL of saturated aqueous $NaHCO_3$. The combined aqueous extracts were extracted with two 100-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and Na_2CO_3, filtered, and concentrated in vacuo to give the crude product, 5.92 g. In practice, this crude product was not purified but taken on directly to the next step.

A sample of **8** was purified by PTLC (1:1 ether–hexane, 61% yield): NMR (CCl_4) δ 5.2–6.3 (m, 4 H, vinylic H's), 4.46 (m, 1 H, CH(OH)(OR), diastereomers), 4.00 (m, 1 H, C=CCHOR), 1.60 (m, 9 H, doublet in br s); IR (neat) 3400, 3023, 1663, 1440 cm^{-1}; mass spectrum, m/e 168 (parent ion); high-resolution mass spectrum calcd for $C_{10}H_{16}O_2$ 168.11503; found 168.11272.

Methyl (*E*,*E*,*E*)-7-Hydroxy-2-methyldodeca-2,8,10-trienoate (9). To a stirred solution of 2.40 g of crude **8** (14.3 mmol maximum) in 75 mL of dry benzene was added 5.15 g (14.8 mmol) of α-(carbomethoxy)-ethylidenetriphenylphosphorane.[7] The flask was flushed with N_2 and heated to reflux for 3 h. The cooled solution was concentrated in vacuo to afford the crude product. The resultant oil was immediately chromatographed on a 50-mm flash chromatography column[29] using 1:2 ether–hexane as eluant. This gave, after rechromatography of mixed fractions, 2.08 g of **9** (61% from **7**), 0.127 g (3%) of a mixture of **9** and a compound tentatively assigned structure **10**, and 0.297 g (12%) of mixed acetal **8a**. Acetal **8a** can be hydrolyzed in comparable yield to hemiacetal **8** by using the conditions described for the hydrolysis of **7**.



8a

9: NMR ($CDCl_3$, 250 MHz) δ 6.71 (tq, J = 7.3, 1.3 Hz, 1 H, H_3), 6.12 (dd, J = 14.5, 10.5 Hz, 1 H, H_9), 6.00 (m, 1 H, H_{10}), 5.67 (dq, J = 14.3, 7.0 Hz, 1 H, H_{11}), 5.50 (dd, J = 14.5, 7.0 Hz, 1 H, H_8), 4.07 (m, 1 H, H_7), 3.69 (s, 3 H, OCH_3), 2.16 (m, 2 H, allylic CH_2), 1.78 (d, J = 1.3 Hz, 3 H, C_2 methyl), 1.72 (d, J = 7.1 Hz, 3 H, vinyl CH_3), 1.50 (m, 4 H); IR (CCl_4) 3613, 3500, 3015, 1714, 1647 cm^{-1}; mass spectrum, m/e 238 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.

8a: NMR (CCl_4) δ 5.2–6.3 (m, 4 H, vinyl H's), 4.76 (b s, 1 H, CH(OR)(OEt)), 4.12 (m, 1 H, CH(OR)), 3.52 (m, 2 H, OCH_2), 1.76 (d, J = 6 Hz, 3 H, vinyl CH_3), 1.68 (b s, 6 H, $CH_2CH_2CH_2$), 1.20 (t, J = 6 Hz, 3 H, CH_3); IR (neat) 3020, 1660, 1438 cm^{-1}; mass spectrum, m/e 196 (parent ion); high-resolution mass spectrum calcd for $C_{12}H_{20}O_2$ 196.146 33, found 196.146 36.

(30) Commercial sorbaldehyde (**6**) is a mixture of diene isomers of which the (*E*,*E*)-isomer is the major component (~85%). The sorbaldehyde used in this study was prepared from isomerically pure sorbic acid (mp 134.5–135 °C; recrystallized two times from H_2O) by $LiAlH_4$ reduction (60%; Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548) to the alcohol which was oxidized to **6** with the reagent prepared from Me_2SO and oxalyl chloride (Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480). The crude aldehyde (>95% isomerically pure, 84% yield) obtained from this oxidation was used directly in the Grignard reaction.

Methyl (*E*,*E*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-methyldodeca-2,8,10-trienoate (11). To a solution of 103 mg (0.434 mmol) of **9** in 1.0 mL of dry DMF was added 76.8 mg (1.13 mmol) of imidazole and 86.1 mg (0.527 mmol) of *tert*-butyldimethylsilyl chloride.[8] This solution was stirred for 43 h at 23 °C under Ar. The reaction mixture was diluted with 15 mL of H_2O and was extracted with three 15-mL portions of hexane. The combined hexane extracts were washed once with 15 mL of H_2O, dried over $NaHCO_3$, and concentrated in vacuo to give 161 mg of crude product. Silyl ether **11** was purified by preparative TLC on one 0.5-mm silica gel gel plate by using 2.5% ether–hexane as eluant: 127 mg (83%); NMR (CCl_4) δ 6.73 (br t, J = 8.5 Hz, H_3), 5.2–6.2 (m, 4 H), 4.15 (m, H_7), 3.70 (s, 3 H), 1.8 (s and d, J = 7 Hz, vinyl CH_3's), 0.95 (s, 9 H, *tert*-butyl), 0.04 (s, 6 H, $SiMe_2$); IR (CCl_4) 3024, 1717, 1654 cm^{-1}; mass spectrum, m/e 352 (parent ion).

Cyclization of 11. Methyl 5α,6β-Dimethyl-1α-hydroxy-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (5), Methyl 5α,6β-Dimethyl-1β-hydroxy-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (12), Methyl 5β,6β-Dimethyl-1α-hydroxy-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (13), and Methyl 5β,6β-Dimethyl-1β-hydroxy-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (14). A solution of 104.1 mg (0.29 mmol) of **11** in 0.35 mL of tetrachloroethylene was degassed with Ar for 1 min before it was transferred to a thick-wall NMR tube. The tube was flushed with Ar, sealed, and placed in a 150 °C oil bath. The progress of the reaction was followed by NMR spectroscopy. Since there was little difference between the NMR spectra taken after 3 and 5 h, the reaction was terminated. The mixture was concentrated in vacuo to give 103.1 mg of crude product. GC analysis (20 ft 4% DC-QF-1, 165 °C, flow 10 mL/min) of this material showed the presence of four cyclization products in the ratio 15:13:23:49 (retention times 112, 122, 128, 136 min, respectively) plus uncyclized triene (retention time 148 min). Initial chromatography of 90 mg of this mixture on a 20-mm flash chromatography column gave three mixed fractions of cycloadducts (80.9 mg, 90%) and 8.8 mg of uncyclized trienes (10%). The mixtures of cycloadducts were separated, following deprotection (CH_3OH, 1 N HCl, 18 h, 23 °C), by repeated, careful chromatography (silica gel, 1:1 ether–hexane) to afford pure samples of **5** (7%), **12** (3%), **13** (6%), and a 60:40 mixture of **13**–**14** (35%). Repeated chromatography of a small portion of this mixture (15 mg of mixture was chromatographed twice on 0.25-mm silica gel plates, 1% MeOH–CH_2Cl_2, six developments) afforded a pure sample of **14**.

5: NMR ($CDCl_3$, 250 MHz) δ 5.92 (br d, J = 10 Hz, H_8), 5.61 (ddd, J = 10, 5, 2.0 Hz, H_7), 3.67 (s, 3 H), 3.35 (dt, J = 4, 10 Hz, H_1), 1.17 (s, 3 H), 0.86 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3620, 3440, 3025, 1733, 1654 cm^{-1}; mass spectrum, m/e 238 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1555.

12: NMR ($CDCl_3$, 250 MHz) δ 5.72 (ddd, J = 10.0, 4.8, 2.7 Hz, H_7), 5.42 (br d, J = 10.0 Hz, H_8), 4.09 (br s, H_1), 3.68 (s, 3 H), 2.21 (dt, J = 1.9, 11.4 Hz, H_{4a}), 1.16 (s, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), the ring fusion was shown to be trans by double-irradiation experiments ($J_{4a,8a}$ = 11.4 Hz); IR (CCl_4) 3603, 3012, 1731, 1655 cm^{-1}; mass spectrum, m/e 238 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1558.

13: NMR ($CDCl_3$, 250 MHz) δ 5.58 (m, 2 H), 3.80 (dt, J = 2.9, 6.2 Hz, H_1), 3.69 (s, 3 H), 2.87 (m, H_6), 2.41 (m, H_{4a}), 2.16 (m, H_{8a}), 1.16 (s, 3 H), 0.94 (d, J = 7.3 Hz, 3 H), double-irradiation experiments showed that the ring fusion is cis ($J_{4a,8a}$ = 5.8 Hz); IR (CCl_4) 3620, 3490, 3012, 1729, 1655 cm^{-1}; mass spectrum, m/e 238 (parent ion); high-resolution mass spectrum (parent ion not observed) calcd for $C_{14}H_{20}O_2$(P-H_2O) 220.1463, found 220.1439.

14: NMR ($CDCl_3$, 250 MHz) δ 5.68 (s, 2 H), 3.72 (m, H_1), 3.65 (s, 3 H), 2.97 (m, H_6), 2.34 (br s, H_{8a}), 2.03 (dt, J = 11, 4 Hz, H_{4a}), 1.22 (s, 3 H), 1.00 (d, J = 7.8 Hz, 3 H), double-irradiation experiments showed that the ring fusion of **14** is cis ($J_{4a,8a}$ = 4 Hz); IR (CCl_4) 3618, 3505, 3024, 1733, 1654 cm^{-1}; mass spectrum, m/e 238 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1540.

Cyclization of 18. Methyl 1β-Hydroxy-6β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (25a), Methyl 1α-Hydroxy-6β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (25b), Methyl 1β-Hydroxy-6β-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (26a), and Methyl 1α-Hydroxy-6β-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (26b). A solution of 2.03 (9.06 mmol) of **18** in 23 mL of dry toluene was added to a resealable Carius tube. The solution was purged with Ar for 10 min, and then bis(trimethylsilyl)acetamide (5.5 mL, 22.3 mmol) was added. The tube was sealed and the solution was stirred at room temperature for 24 h. The tube was opened, purged again with Ar, resealed, and heated in a 150 °C oil bath for 19 h. The cooled tube was opened, and then all volatile components were removed in vacuo. The crude

product, a mixture of Me_3Si ethers, was chromatographed on 350 g of silica gel, initially by using 1.5% ether–hexane as eluant. Four 225-mL fore fractions were taken and discarded. Thereafter, 25-mL fractions were collected. The solvent was changed at fraction 140 to 5% ether–hexane, at fraction 160 to 1:6 ether–hexane, and at fraction 175 to 1:2 ether–hexane. Fractions 56–140 afforded 1.02 g of a mixture of the Me_3Si ethers of **25a** and **26a**; fractions 160–203 afforded 0.05 g of a mixture of the Me_3Si ethers of **25b**, **26b**, and uncyclized **18**; and fractions 222–245 (125 mL each, 1:1 ether–hexane) afforded a mixture of **25b** and **26b** (desilylation occurred on the column). The mixed fractions of Me_3Si ethers were individually hydrolyzed with 1 N HCl in MeOH (23 °C, 1 h), and uncyclized triene was removed from the second mixture by hydrolysis in MeOH containing 1 N NaOH (23 °C, overnight). Repeated chromatography ("flash" chromatography, silica gel, 2:1 hexane–ether) of these fractions then afforded 452 mg (22%) of **25a**, 263 mg (13%) of **26a**, 208 mg (10%) of **26b**, and 842 mg (42%) of an approximate 70:30 mixture of **25b** and **26b**. A pure sample of **25b** was obtained by repeated chromatography of small (~15 mg) samples of this mixture.

25a: mp 79.5–80 °C; NMR ($CDCl_3$, 250 MHz) δ 5.79 (dt, J = 10.2, 1.6 Hz, 1 H, H_8), 5.55 (ddd, J = 10.2, 4.6, 2.4 Hz, 1 H, H_7), 3.81 (br d, J = 2.7 Hz, 1 H, H_1), 3.67 (s, 3 H, OCH_3), 2.86 (dd, J = 11.8, 9.9 Hz, 1 H, H_5), 2.48 (m, 1 H, H_6), 2.20 (m, 1 H, H_{8a}), 2.03 (m, 1 H, H_{4a}), 1.96 (m, 1 H, $H_{2\alpha}$), 1.75 (m, 1 H), 1.4 (m, 5 H), 0.97 (d, J = 7.3 Hz, 3 H, CH_3), the ring fusion was shown to be cis by double-irradiation experiments ($J_{4a,8a}$ = 3.5 Hz); IR (CCl_4) 3577, 3015, 1735, 1651 cm^{-1}; mass spectrum, m/e 224 (parent ion). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.88; H, 9.30.

26a: NMR ($CDCl_3$, 250 MHz) 5.77 (m, H_7), 5.49 (br d, J = 10.3 Hz, H_8), 4.02 (br s, $W_{1/2}$ = 7 Hz, H_1), 3.64 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H); IR (CCl_4) 3600, 3500, 3014, 1737, 1658 cm^{-1}; mass spectrum, m/e 224 (parent ion). The crystalline acetate prepared from **26a** was fully characterized: mp 80.5–81.0 °C; NMR ($CDCl_3$, 250 MHz) δ 5.62 (m, 1 H, H_7), 5.35 (br d, J = 10.5 Hz, 1 H, H_8), 5.14 (br s, $W_{1/2}$ = 6 Hz, 1 H, H_1), 3.66 (s, 3 H, OCH_3), 2.51 (m, 2 H), 2.01 (s, 3 H, OAc), 0.89 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3015, 1734, 1655 cm^{-1}; mass spectrum, m/e 266 (parent ion). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.96; H, 8.40.

26b: NMR ($CDCl_3$, 270 MHz) δ 5.95 (br d, J = 10.5 Hz, H_8), 5.64 (m, H_7), 3.68 (s, 3 H, OCH_3), 3.30 (dt, J = 4, 10 Hz, H_1), 2.62 (dd, J = 10, 5 Hz, H_5), 0.92 (d, J = 7 Hz, 3 H). The crystalline acetate prepared from **26b** was fully characterized: mp 52–53 °C; NMR ($CDCl_3$, 250 MHz) δ 5.60 (m, H_7), 5.53 (br d, J = 10.2 Hz, H_8), 4.48 (dt, J = 4.6, 10.8 Hz, H_1), 3.65 (s, 3 H, OCH_3), 2.59 (dd, J = 5.9, 11.3 Hz, H_5), 2.55 (m, H_6), 2.04 (s, 3 H), 0.86 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3033, 2940, 1740, 1660 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1532.

25b: mp 78–81 °C; NMR ($CDCl_3$, 250 MHz) δ 5.97 (m, H_7), 5.55 (dt, J = 10.1, 1.6 Hz, H_8), 3.69 (s, 3 H, OCH_3), 3.45 (dt, J = 5.0, 10.1 Hz, H_1), 2.53 (m, H_6), 2.30 (dd, J = 12, 10 Hz, H_5), 2.18 (m, H_{4a}), 1.95 (m, H_{8a}), 0.96 (d, J = 7 Hz, 3 H), the ring fusion was shown to be cis by double-irradiation experiments ($J_{4a,8a}$ = 3.5 Hz); IR (CCl_4) 3622, 3500, 3025, 1736, 1652 cm^{-1}; mass spectrum, m/e 224 (parent ion). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.80; H, 9.16.

Cyclization of 19. Methyl 1β-Hydroxy-6β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5β-carboxylate (27c), Methyl 1α-Hydroxy-6β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5β-carboxylate (27d), Methyl 1β-Hydroxy-6β-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylate (28c), and Methyl 1α-Hydroxy-6β-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylate (28d). A solution of 396 mg (1.17 mmol) of **19** in 8.0 mL of dry toluene in a resealable Carius tube was cyclized (150 °C, 17 h) by using the procedure described for **22**. GC analysis of the crude product showed four products (in order of increasing retention time) in the ratio 22:42:16:20 (**28a**:**27b**:**28b**:**27a**). The crude product was chromatographed (40 g silica gel, 1.2% ether–hexane) giving six fractions, none of which was homogeneous, which yielded a total of 317 mg (80%) of cycloadducts. Repeated chromatography of the mixed fractions gave samples of each of the four Diels–Alder adducts. These compounds were characterized as the free alcohols, which were prepared from the silyl ethers by mild acid hydrolysis (1 N HCl, CH_3OH, 23 °C, 24 h).

Alcohol **27c** (from **27a**): mp 112–113 °C (softening point, 90 °C); NMR ($CDCl_3$, 250 MHz) δ 5.70 (m, 2 H, H_7, H_8), 3.74 (m, 1 H, H_1), 3.67 (s, 3 H), 2.83 (dd, J = 7.2, 2.7 Hz, H_5), 2.73 (m, 1 H, H_6), 1.00 (d, J = 7.2 Hz, 3 H); IR (CCl_4) 3620, 3450, 3025, 1738, 1648 cm^{-1}; mass spectrum, m/e 224 (parent ion). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.80; H, 9.07.

Alcohol **27d** (from **27b**): mp 83.5–85 °C; NMR ($CDCl_3$, 250 MHz) δ 5.63 (dt, J = 10.2, 3.2 Hz, H_7), 5.36 (br d, J = 10.2 Hz, H_8), 3.94 (br s, $W_{1/2}$ = 9 Hz, H_1), 3.67 (s, 3 H, OCH_3), 2.69 (m, 2 H, H_5, H_6), 2.44 (m, 1 H), 2.35 (m, 1 H), 1.02 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3622, 3480, 3017, 1740, 1647 cm^{-1}; mass spectrum, m/e 224 (parent ion). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.81; H, 9.27.

Alcohol **28c** (from **28a**): NMR ($CDCl_3$, 250 MHz) δ 5.73 (m, H_7), 5.50 (br d, J = 10.0 Hz, H_8), 4.03 (br d, J = 2.2 Hz, H_1), 3.62 (s, 3 H, OCH_3), 2.44 (m, 1 H, H_6), 2.38 (d, J = 3.7 Hz, H_5), 2.21 (m, 1 H, H_{8a}), 1.96 (m, 1 H, H_{4a}), 1.08 (d, J = 7.2 Hz, 3 H), double-irradiation experiments showed that the ring fusion was trans ($J_{4a,8a}$ = 12.5 Hz); IR (CCl_4) 3593, 3012, 1737, 1650 cm^{-1}; mass spectrum, m/e 224 (parent ion); high-resolution mass spectrum calcd for $C_{13}H_{20}O_3$ 224.14124, found 224.14101.

Alcohol **28d** (from **28b**): NMR ($CDCl_3$, 250 MHz) δ 5.98 (br d, J = 10.2 Hz, H_8), 5.63 (m, H_7), 3.63 (s, 3 H, OCH_3), 3.18 (m, H_1), 2.47 (m, H_6), 2.41 (d, J = 3.5 Hz, H_5), 1.98 (m, 1 H), 1.91 (tq, J = 10.2, 1.9 Hz, H_{8a}), 1.06 (d, J = 7.2 Hz, 3 H); the ring fusion was determined to be trans by double-irradiation experiments ($J_{4a,8a}$ = 10.2 Hz); IR (CCl_4) 3620, 3500, 3027, 1739, 1648 cm^{-1}; mass spectrum, m/e 206 (parent – H_2O); high-resolution mass spectrum calcd for $C_{13}H_{20}O_3$ 224.141 24, found 224.143 92.

Cyclization of 20. Methyl 1,2,3,4,4aα,5,6,8aα-Octahydronaphthalene-5α-carboxylate (29) and Methyl 1,2,3,4,4aβ,5,6,8aα-Octahydronaphthalene-5β-carboxylate (30). Triene **20** (210 mg, 1.08 mmol) was cyclized in toluene (8 mL, resealable Carius tube, 155 °C, 45 h) by using the procedure described for **22**. GC analysis (10 ft 4% SE-30, 110 °C) of the crude product (198 mg, 94%) showed that this material consisted of 8% of uncyclized triene and 92% of a 49:51 mixture of **29** (R_t 61.2 min) and **30** (R_t 55.2 min). Attempts to separate this mixture by TLC were unsuccessful. A small portion of this mixture was separated by preparative GC (12-ft 15% SE-30 on Chromosorb A column), giving pure samples of the two cycloadducts.

29: NMR ($CDCl_3$, 250 MHz) δ 5.56 (br s, 2 H), 3.68 (s, 3 H), 2.72 (dt, J = 5, 7.3 Hz, H_5), 2.4 (m, 2 H, $H_{2\alpha}$, $H_{2\beta}$); IR (CCl_4) 3027, 2929, 1740, 1685, 1659 cm^{-1}; mass spectrum, m/e 194 (parent ion).

30: NMR ($CDCl_3$, 250 MHz) δ 5.67 (m, H_7), 5.41 (br d, J = 10 Hz, H_8), 3.67 (s, 3 H, OCH_3), 2.33 (m, 1 H); IR (CCl_4) 3022, 2928, 1740, 1684, 1655 cm^{-1}; mass spectrum, m/e 194 (parent ion).

A high-resolution mass spectrum was measured on the mixture of **29** and **30**. Calcd for $C_{12}H_{18}O_2$: 194.130 68. Found: 194.130 37.

Cyclization of 21. Methyl 1,2,3,4,4aα,5,6,8aα-Octahydronaphthalene-5β-carboxylate (31) and Methyl 1,2,3,4,4aβ,5,6,8aα-Octahydronaphthalene-5α-carboxylate (32). Triene **21** (109 mg, 0.56 mmol) was cyclized by using the procedure described for **22** (5.0 mL of toluene, resealable Carius tube, 155 °C, 45 h). The crude product (98.5 mg, 90%), a mixture of **31** and **32**, could not be separated by TLC or GC (10-ft 4% SE-30 and 20-ft 4% DC-QF-1 columns). The ratio of these two isomers was determined to be 49:51 (**31**:**32**) by integration of the carbomethoxyl signals in the 250-MHz NMR spectrum. Isomer **31** was identified by comparison of the NMR spectrum of this mixture to the spectrum of the product of epimerization of **29**.

Spectroscopic data of mixture: NMR ($CDCl_3$, 250 MHz) δ 5.72 (m, H_7 of **31**, H_7 of **32**), 5.45 (br d, J = 10 Hz, H_8 of **32**), 5.36 (br d, J = 10 Hz, H_8 of **31**), 3.67 (s, OCH_3 of **31**), 3.64 (s, OCH_3 of **32**); IR (CCl_4) 3024, 2925, 1728, 1640 cm^{-1}; mass spectrum, m/e 194 (parent ion); high-resolution mass spectrum calcd for $C_{12}H_{18}O_2$ 194.130 68, found 194.130 61.

Cyclization of 22. Methyl 5β,6β-Dimethyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalen-1-one-5α-carboxylate Ethylene Glycol Ketal (33) and Methyl 5α,6β-Dimethyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalen-1-one-5β-carboxylate Ethylene Glycol Ketal (34). A solution of 86.8 mg (0.31 mmol) of **22** in 2.0 mL of dry toluene was transferred to a resealable Carius tube and purged with dry Ar for 15 min. The sealed tube was then heated in a 140 °C oil bath for 16 h. The reaction mixture was cooled, and approximately 0.25 mL was removed for GC analysis. The remainder was concentrated in vacuo to give 80 mg of crude product. GC analysis (10-ft 4% SE-30, 165 °C) showed that the crude product consisted of 87% of an 81:19 mixture of **33** and **34**, plus 12% of uncyclized triene. This mixture was separated by preparative TLC (0.5-mm silica gel plate, 2:1 hexane–ether), giving 50.2 mg (64%) of **33** (R_f 0.33) and 28.2 mg of a mixture of **34** and **22** (R_f 0.44). The latter mixture was treated with 0.25 mL of 1 N NaOH in 1.0 mL of MeOH for 24 h at room temperature to saponify residual **22**. This mixture was worked up in the usual manner to give 25 mg of crude product which was chromatographed (half of a 0.25-mm silica gel plate, 2:1 hexane–ether) to give 10.1 mg of the carboxylic acid corresponding to **22** and 12.3 mg (15%) of **34**.

33: NMR ($CDCl_3$, 250 MHz) δ 5.68 (dt, J = 10.2, 3.2 Hz, H_7), 5.55 (dq, J = 10.2, 1.3 Hz, H_8), 3.93 (m, 4 H, OCH_2CH_2O), 3.67 (s, 3 H), 2.95 (m, H_6), 2.30 (dt, J = 12.1, 4.0 Hz, H_{4a}), 2.13 (m, $W_{1/2}$ = 11.2 Hz, $J_{4a,8a}$ = 4.0 Hz (ring fusion), H_{8a})), 1.25 (s, 3 H), 1.03 (d, J = 7.8 Hz, 3 H); IR (CCl_4) 3030, 1732, 1651 cm^{-1}; mass spectrum, m/e 280 (parent

ion); high-resolution mass spectrum calcd for $C_{16}H_{24}O_4$ 280.167 46, found 280.166 55.

34: NMR ($CDCl_3$, 250 MHz) δ 5.61 (br s, 2 H), 3.95 (m, OCH_2CH_2O), 3.64 (s, 3 H), 1.13 (s, 3 H), 0.86 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3031, 1730, 1660 cm^{-1}; mass spectrum, m/e 280 (parent ion); high-resolution mass spectrum calcd for $C_{16}H_{24}O_4$ 280.167 46, found 280.164 62.

Cyclization of 23. Methyl 6β-Methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalen-1-one-5α-carboxylate Ethylene Glycol Ketal (35) and Methyl 6β-Methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalen-1-one-5β-carboxylate Ethylene Glycol Ketal (36). Triene **23** (88.6 mg, 0.33 mmol) was cyclized in 2 mL of toluene (150 °C, 18 h) by using the procedure described for the cyclization of **22**. GC analysis (10 ft 4% SE-30, 160 °C) of the crude product indicated that this mixture consisted of 12% of uncyclized triene and 88% of a 79:21 mixture of **35** and **36**. Uncyclized **23** was removed in the usual way by saponification (1 N NaOH, CH_3OH, 23 °C, 24 h), and the mixture of cycloadducts was separated by chromatography (0.5-mm silica gel plate, 2:1 hexane–ether, two developments), giving 51.8 mg (60%) of **35** and 17.0 mg (20%) of **36**.

35: mp 83.0–83.5 °C; NMR ($CDCl_3$, 250 MHz) δ 5.67 (ddd, J = 10.0, 4.6, 2.4 Hz, H_7), 5.54 (dt, J = 10.0, 1.6 Hz, H_8), 3.83 (m, 4 H, OCH_2CH_2O), 3.66 (s, 3 H), 2.84 (dd, J = 11.6, 9.4 Hz, H_5), 2.43 (m, H_6), 2.35 (m, $J_{4a,8a}$ = 4.5 Hz (ring fusion), H_{8a}). 2.15 (dt, J = 11.6, 4.5 Hz, H_{4a}), 0.95 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3025, 1733, 1655 cm^{-1}; mass spectrum, m/e 266 (parent ion). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.73; H, 8.66.

36: mp 120–121 °C; NMR ($CDCl_3$, 250 MHz) δ 5.66 (br s, 2 H), 3.94 (m, OCH_2CH_2O), 3.65 (s, 3 H), 2.56 (dd, J = 11.3, 5.9 Hz, H_5), 2.06 (br d, J = 10.7 Hz (ring fusion), H_{8a}), 0.90 (d, J = 7.2 Hz, 3 H); IR (CCl_4) 3030, 1740, 1655 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1531.

Cyclization of 24. Methyl 6β-Methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalen-1-one-5β-carboxylate Ethylene Glycol Ketal (37) and Methyl 6β-Methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalen-1-one-5α-carboxylate Ethylene Glycol Ketal (38). A solution of 11.1 mg (0.042 mmol) of **24** in 1.5 mL of dry toluene was cyclized (150 °C, 19 h) in a resealable Carius tube by using the procedure described for **22**. GC analysis (10 ft 4% SE-30, 160 °C) of the crude product indicated that this material consisted of 15% of uncyclized triene and 85% of a 76:24 mixture of **37** and **38**. These isomers were separated by preparative TLC (0.25-mm silica gel plate, 2:1 hexane–ether, two developments) and uncyclized triene was removed by the usual selective saponification procedure. In this manner, pure **37** (5.0 mg, 47%) and a 90:10 mixture of **38**:**37** (2.6 mg, 24%) was obtained.

37: NMR ($CDCl_3$, 250 MHz) δ 5.67 (dt, J = 10.5, 3.0 Hz, H_7), 5.59 (dq, J = 10.5, 1.3 Hz, H_8), 3.93 (m, OCH_2CH_2O), 3.67 (s, 3 H), 2.77 (dd, J = 7.3, 3.0 Hz, H_5), 2.69 (m, H_6), 2.39 (m, H_{4a}), 2.29 (br s, H_{8a}), 1.01 (d, J = 7.5 Hz, 3 H), double-irradiation experiments showed that the ring fusion was cis ($J_{4a,8a}$ = 4 Hz); IR (CCl_4) 3027, 1743, 1649 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.151 81, found 266.151 94.

38 (data obtained on 90:10 mixture): NMR ($CDCl_3$, 250 MHz) δ 5.73 (br d, J = 10.2 Hz, H_8), 5.63 (m, H_7), 3.95 (m, OCH_2CH_2O), 3.63 (s, 3 H), 2.42 (m, 2 H), 1.09 (d, J = 7.3 Hz, 3 H); IR (CCl_4) 3027, 1739, 1655 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.151 81, found 266.149 76. The stereochemistry of **38** could not be assigned by ^1H NMR as a consequence of the complexity of the spectrum. The structure of **38** was confirmed by equilibration with **36**, as described in a subsequent epimerization experiment.

Methyl 6β-Methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalen-1-one-5α-carboxylate (39). To a stirred solution of 27.5 mg (0.122 mmol) of **25a** in 1.0 mL of dry CH_2Cl_2 was added 3.5 mg (0.043 mmol) of NaOAc and 39.9 mg (0.185 mmol) of pyridinium chlorochromate.[15] The mixture was stirred for 2 h at 23 °C, and then 2 mL of ether was added. The resulting solution was filtered through a small pipet containing Florisil. The residue remaining in the reaction flask was rinsed with four 1–2 mL portions of ether, which were passed through the plug of Florisil. The combined ether extracts were concentrated in vacuo to give 22.0 mg of **39** (81%), which was unstable to chromatography on silica gel: NMR (CCl_4) δ 5.6 (m, 2 H), 3.64 (s, 3 H), 0.95 (d, J = 6 Hz, 3 H); IR (CCl_4) 3032, 1736, 1720, 1655 cm^{-1}; mass spectrum, m/e 222 (parent ion).

Using a similar procedure, 43.9 mg of **25b** was oxidized to give 41.2 mg of **39** (95% yield).

Epimerization and Deprotection of 27b. A solution of 36.7 mg (0.108 mmol) of **27b** in 2.0 mL of dry methanol was prepared and transferred to a resealable Carius tube. The solution was thoroughly degassed with Ar, and then 192 μL of 2 N $NaOCH_3$ (0.39 mmol) in methanol was added. The tube was sealed and heated in a 100 °C oil bath for 24 h. The cooled reaction mixture was quenched with 52 μL (0.40 mmol) of glacial HOAc. The solvent was removed in vacuo, giving 40.0 mg of crude product. This material was directly chromatographed on a 0.5-mm silica gel plate using 5% ether–hexane as eluant (two developments), giving 31.6 mg (86%) of the TBDMS ether of **25b**. A solution of this compound in 1.5 mL of CH_3OH was treated with 0.3 mL of 1 N HCl. The resultant mixture was vigorously stirred at room temperature for 80 min. Saturated $NaHCO_3$ (1.5 mL) was then added to quench the reaction. The solution was diluted with 10 mL of water and was extracted with three 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo to give 21.0 mg of crude product. Purification of this material was effected by PTLC (0.5-mm silica gel, 1:1 ether–hexane), giving 19.2 mg (91%; 79% overall from **27b**) of **25b**.

Epimerization of 25a. To a solution of 0.16 mL (1.13 mmol) of diisopropylamine in 5 mL of dry THF at −78 °C was added 0.48 mL (1.05 mmol) of 2.18 M n-BuLi solution in hexane. Thirty minutes later a solution of 64.7 mg (0.31 mmol) of **25a** in 3 mL of THF was added. After being stirred at −78 °C for 90 min, this solution was warmed to 0 °C over a 90-min period. The solution was recooled to −70 °C, and the enolate was then quenched with a solution of 1.0 mL of glacial acetic acid in 1.0 mL of dry THF. The reaction mixture was warmed to room temperature and was poured into a separatory funnel containing 15 mL each of ether and 1 N HCl. The ether layer was washed once with 15 mL of 1 N HCl. The combined aqueous extracts were extracted with an additional 10-mL portion of ether. The combined ether extracts were dried over $NaHCO_3$, filtered, and concentrated in vacuo to give 70.1 mg of crude product. The mixture of products was separated by PTLC (0.5-mm silica gel plate, 1:1 ether–hexane, two developments), giving 41.0 mg (58%) of **27c**, along with 21.3 mg (31%) of recovered **25a**.

1β-Hydroxy-6β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid δ-Lactone (40). To a solution of 10.6 mg (0.047 mmol) of hydroxyester **27c** in 3.0 mL of benzene was added one small crystal of p-TsOH·H_2O. The resulting solution was refluxed for 5 h. The cooled solution was directly applied to a 10 × 20 cm 0.25-mm silica gel plate, which was then developed with 2:1 hexane–ether. The major band was isolated, giving 8.3 mg (91%) of lactone **40**: mp 93.5–94.5 °C; NMR ($CDCl_3$, 250 MHz) δ 5.73 (ddd, J = 9.4, 5.1, 2.4 Hz, H_7), 5.63 (dt, J = 9.4, 0.8 Hz, H_8), 4.45 (m, H_1), 2.68 (m, 1 H), 2.53 (dd, J = 5.4, 0.8 Hz, 1 H), 2.15 (m, 3 H), 1.06 (d, J = 7.5 Hz, 3 H); IR (CCl_4) 3030, 1725, 1645 cm^{-1}; mass spectrum, m/e 192 (parent ion). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.07; H, 8.31.

Methyl 6β-Methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalen-1-one-5α-carboxylate (41). Alcohols **28c** and **28d** were oxidized by using the procedure described for **39**. In each case, a quantitative yield of **41** was obtained: mp 89–91 °C (hexane); NMR ($CDCl_3$, 250 MHz) δ 6.07 (dt, J = 10.3, 1.5 Hz, H_8), 5.70 (m, 1 H, H_7), 3.70 (s, 3 H), 3.29 (br d, $J_{4a,8a}$ = 9.5 Hz (ring fusion), H_{8a}), 1.10 (d, J = 7.0 Hz, 3 H); IR (CCl_4) 3033, 1737, 1715, 1652 cm^{-1}; mass spectrum, m/e 222 (parent ion). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.25; H, 8.27.

Methyl 6β-Methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalen-1-one-5β-carboxylate (42). Alcohols **26a** and **26b** were oxidized by using the procedure described for **39**. Ketone **42** was obtained from **26a** in 90% yield and from **26b** in essentially quantitative yield. This compound is unstable to silica gel chromatography: mp 92–96 °C; NMR ($CDCl_3$, 250 MHz) δ 5.93 (br d, J = 10.0 Hz, H_8), 5.69 (m, H_7), 3.67 (s, 3 H, OCH_3), 2.80 (br d, $J_{4a,8a}$ = 12.5 Hz (ring fusion), H_{8a}), 0.84 (d, J = 7.3 Hz, 3 H); IR (CCl_4) 3027, 1736, 1720, 1657 cm^{-1}; mass spectrum, m/e 222 (parent ion); high-resolution mass spectrum calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1263.

Epimerization of 36. A solution of 2.4 mg (0.009 mmol) of **36** in 1.0 mL of dry methanol was prepared in a resealable Carius tube. The solution was thoroughly degassed with Ar, and then 3.0 mg (0.055 mmol) of $NaOCH_3$ was added. The tube was sealed and heated in a 100 °C oil bath for 25 h. The cooled reaction mixture was neutralized with 10 μL (0.10 mmol) of glacial HOAc. The solution was concentrated in vacuo, and the residue was treated with excess ethereal CH_2N_2. The product was extracted with ether–H_2O to remove salts, and the extracts were dried (Na_2SO_4) and concentrated in vacuo. GC analysis (10 ft 4% SE-30, 160 °C) showed that the crude product (2.3 mg) was a 30:70 mixture of **38**:**36**.

Epimerization of 29. A solution of 6.4 mg (0.033 mmol) of **29** in 1.0 mL of dry methanol was prepared in a resealable Carius tube. The solution was thoroughly degassed with Ar, and then 5.5 mg (0.10 mmol) of $NaOCH_3$ was added. The sealed tube was heated at 90 °C for 23 h, and the reaction was worked up by essentially the procedure described above for **36**. Analysis of the crude product (6.0 mg) by 250-MHz ^1H NMR spectroscopy showed it to be a ~1:1 mixture of **29** and **31**.

Hydrogenation of 29 and 30. Hydrogenation of the mixture of **29** and **30** is the preferred method for preparation of **43** since mixtures of **43** and

dihydro **29** are more easily separated than mixtures of **29** and **30**.

To a solution of 82.5 mg (0.44 mmol) of a 49:51 mixture of **29** and **30** in 1.0 mL of MeOH was added 38.0 mg of 5% Pd/C. The flask was thoroughly flushed with H_2 (several vacuum-purge cycles), and then the mixture was stirred for 44 h under an atomosphere of H_2. At this point, GC analysis (10 ft 4% SE-30, 110 °C) of the reaction mixture showed that the hydrogenation had gone to completion (R_t (**43**) 50 min; R_t (dihydro-**29**) 61 min). The catalyst was removed by filtration, and solvent was removed in vacuo, giving a mixture of **43** and dihydro-**29**. These isomers were separated by preparative GC (0.25 in. × 12 ft 15% SE-30, 80 °C (10 min) to 130 °C (rate of temperature increase: 3 °C/min)).

43: NMR ($CDCl_3$, 250 MHz, ^1H) δ 3.63 (s, 3 H, OCH_3), 2.02 (ddd, J = 12.1, 10.7, 3.2 Hz, 1 H, H_1); NMR ($CDCl_3$, 62.8 MHz, ^{13}C) δ 176.8, 51.2, 50.2, 44.5, 41.9, 34.0, 33.4, 31.3, 30.2, 26.3, 26.3, 25.3; IR (CCl_4) 2928, 2854, 1734 cm^{-1}; mass spectrum, m/e 165 (parent - OCH_3).

Dihydro-**29**: NMR ($CDCl_3$, 250 MHz) δ 3.64 (s, 3 H, OCH_3), 2.61 (br t, J = 10 Hz, 1 H, H_1); IR (CCl_4) 2928, 2864, 1736 cm^{-1}; mass spectrum, m/e 196 (parent ion).

Hydrogenation of pure **30** (obtained by preparative GC as described in the procedure for cyclization of **20**) afforded **43**.

Methyl (*E*,*E*,*E*)-2-Methyl-7-oxododeca-2,8,10-trienoate (46). To a stirred solution of 501 mg (2.10 mmol) of **9** in 100 mL of benzene was added 10.15 g (17.8 mmol) of Ag_2CO_3 on Celite.[22] Benzene (~30 mL) was distilled from the mixture, and the remaining suspension was refluxed for an additional 30 min. The mixture was filtered to remove the spent reagent, and the filtrate was concentrated in vacuo to give 483 mg of crude product (97%). This material was of sufficient purity to use directly in the ketalization reaction (see procedure for preparation of **22**). The material used in the intramolecular Diels–Alder reaction was purified either by PTLC (silica gel 1:2 ether–hexane, 70% yield) or, preferably, by bulb-to-bulb distillation (150–160 °C (0.1 mm)). In one case 231 mg of crude **46** prepared from 238 mg of **9** was distilled to give 215 mg of nearly colorless **46** (91%): NMR ($CDCl_3$, 250 MHz) δ 7.06 (m, 1 H, H_9), 6.67 (t, J = 7 Hz, 1 H, H_3), 6.11 (m, 2 H, H_{10}, H_{11}), 6.00 (d, J = 15.6 Hz, 1 H, H_8), 3.75 (s, 3 H, OCH_3), 2.51 (t, J = 7 Hz, 2 H, $COCH_2$), 2.16 (q, J = 7 Hz, 2 H, allylic CH_2), 1.82 (d, J = 6 Hz, 3 H, C_{11} methyl), 1.77 (m, 5 H); IR (CCl_4) 3022, 1711, 1636, 1592 cm^{-1}; mass spectrum, m/e 236 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{20}O_3$ 236.141 25, found 236.140 81.

Cyclization of 46. Methyl 5β,6β-Dimethyl-1,2,3,4,4aα,5,6,7-octahydronaphthalen-1-one-5α-carboxylate (48) and Methyl 5α,6β-Dimethyl-1,2,3,4,4aβ,5,6,7-octahydronaphthalen-1-one-5β-carboxylate (49). A solution of 9.2 mg (0.039 mmol) of **46** in 1.5 mL of dry toluene was added to a resealable NH_3-washed Carius tube. The solution was purged with dry Ar for 15 min and 0.1 mg of Na_2CO_3 was added. The tube was then sealed and placed in a 200 °C oil bath. After 102 h the tube was removed and cooled. The reaction mixture was concentrated in vacuo to give 9.1 mg of crude product. Analysis of this material by 250-MHz NMR spectroscopy indicated that the mixture consisted mostly of a 65:35 mixture of **49**:**48** as determined by integration of the olefinic signals of the two isomers. The crude product was chromatographed on half of a 0.5-mm silica gel preparation plate by using 1:1 ether–hexane as eluant. In this manner there was obtained 3.8 mg (41%) of **49**, and 3.8 mg (41%) of a 4:1 mixture of **48** and **49**.

49: NMR ($CDCl_3$, 250 MHz) δ 6.72 (m, H_8), 3.69 (s, 3 H, OCH_3), 2.95 (m, 1 H), 2.59 (m, 1 H), 2.52 (m, 1 H), 1.09 (s, 3 H, tert CH_3), 0.78 (d, J = 7.2 Hz, 3 H, secondary CH_3): IR (CCl_4) 2946, 1730, 1691, 1619 cm^{-1}; mass spectrum, m/e 236 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{20}O_3$ 236.141 25, found 236.143 84.

48 (spectral data measured on 4:1 mixture of **48**:**49**): NMR ($CDCl_3$, 250 MHz) δ 6.85 (m, H_8), 3.71 (s, 3 H, OCH_3), 2.92 (m, 1 H), 2.56 (m, 1 H), 0.91 (s, 3 H, tert CH_3), 0.80 (d, J = 7 Hz, 3 H, secondary CH_3); IR (CCl_4) 2932, 1731, 1693, 1619 cm^{-1}; mass spectrum, m/e 236 (parent ion); high-resolution mass spectrum calcd for $C_{14}H_{20}O_3$ 236.141 25, found 236.140 42.

In a separate experiment, a solution of 103.6 mg (0.439 mmol) of **46** in 2.0 mL of dry toluene was heated at 160–165 °C for 138 h in a presilylated (the reaction vessel was pretreated with bis(trimethylsilyl)-acetamide at 120 °C) resealable Carius tube. Analysis of the crude product (108 mg, obtained by evaporation of all volatile components in vacuo) by 90-MHz ^1H NMR spectroscopy indicated that this material consisted mainly of **47** together with smaller amounts of enones **48** and **49**. An 11-mg sample of the crude product was chromatographed (0.5-mm silica gel plate, 2:1 hexane–ether) to give 5.7 mg of unconjugated ketone **47** (52%). Treatment of **47** with *p*-TsOH in refluxing toluene afforded 33% of **49** following silica gel chromatography. Alternatively, reduction of **47** with $BH_3{\cdot}NH_3$[23] in CH_3OH at 0 °C afforded 60% of a 2:1 mixture of **5**:**12** following silica gel chromatography.

47: NMR ($CDCl_3$, 250 MHz) δ 5.87 (br d, J = 10.5 Hz, H_8), 5.66 (ddd, J = 2.4, 4.6, 10.5 Hz, H_7), 3.67 (s, 3 H, OCH_3), 2.76 (br d, $J_{4a,8a}$ = 12.1 Hz (ring fusion), H_{8a}), 1.24 (s, 3 H, tert CH_3), 0.82 (d, J = 7.0 Hz, secondary CH_3); IR (CCl_4) 2954, 1734, 1630 cm^{-1}; high-resolution mass spectrum calcd for $C_{14}H_{20}O_3$ 236.141 25, found 236.139 12.

Methyl (*E*,*E*,*E*)-7-Hydroxydodeca-2,8,10-trienoate (18). To a stirred solution of 4.08 g of crude **8** (from 21.7 mmol of **7**) in 150 mL of dry benzene was added 15.10 g (45.0 mmol) of (carbomethoxy)methylenetriphenylphosphorane.[25] The flask was flushed with N_2 and heated to reflux for 2 h. The solution was cooled and concentrated in vacuo to give a semicrystalline product. The crude product was purified by chromatography on 260 g of silica gel by using 1:3 ether–hexane as eluant, followed by rechromatography of mixed fractions. This gave 3.05 g of **18** (63% from **7**), 0.312 g of **18a** (6%), and 0.796 g of mixed acetal **8a** (20%).

18: NMR (250 MHz, $CDCl_3$) δ 6.96 (dt, J = 7.0, 15.6 Hz, H_3), 6.17 (ddd, J = 14.8, 10.2, 0.8 Hz, H_{10}), 6.04 (m, H_{11}), 5.82 (dt, J = 15.8, 1.6 Hz, H_2), 5.71 (ddd, J = 14.8, 8.1, 0.5 Hz, H_9), 5.54 (dd, J = 14.5, 7.0 Hz, H_8), 4.12 (m, H_7), 3.73 (s, 3 H, OCH_3), 2.24 (m, 2 H, $CH_2C{=}CCO_2Me$), 1.77 (d, J = 7.0, 3 H, vinyl CH_3), 1.56 (m, 4 H); IR (neat) 3440, 3025, 1720, 1659, 1440 cm^{-1}; mass spectrum, m/e 224 (parent ion). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.22; H, 9.06.

18a: NMR (CCl_4) δ 5.3–6.5 (m, 6 H, vinyl H's), 4.1 (m, 1 H, CH(OR)), 3.7 (s, 3 H, OCH_3), 2.7 (m, 3 H, allylic CH_2 and OH), 1.77 (d, J = 6 Hz, 3 H, CH_3), 1.5 (b s, 4 H, CH_2CH_2). This compound was further characterized as the ketone precursor of ketal **24**.

Synthesis of 19.[26] **(a) (*E*,*E*)-6-Hydroxyundeca-7,9-dien-1-yne (54).** To a vigorously stirred mixture of 1.22 g of Mg turnings (50.3 mmol) in 50 mL of dry THF was added a small crystal of I_2. The mixture was heated to reflux and, when the I_2 color dissipated, a solution of 3.98 g of 1-(5-bromo-1-pentynyl)trimethylsilane[31] (18.2 mmol) in 50 mL of dry THF was added dropwise. On this scale, the addition required 2 h. The mixture was refluxed for an additional 15 min after the addition was complete. The Grignard reagent was then cooled to 0 °C, and 1.43 mL of sorbaldehyde[30] (13.0 mmol) was added. The resulting solution was stirred for 15 min before being quenched with 1 mL of MeOH. The reaction mixture was poured through a glass-wool plug into a separatory funnel containing 110 mL of ether and 110 mL of saturated NH_4Cl. The ether layer was extracted once with 110 mL of saturated NH_4Cl. The combined aqueous extracts were then extracted twice with 110-mL portions of ether. The ether extracts were combined and concentrated in vacuo. The wet residue was dissolved in CH_2Cl_2, filtered through a cotton plug, and concentrated in vacuo to give 3.55 g of crude product.

To a solution of 15.05 g of KF (260 mmol) in 40 mL of distilled H_2O and 100 mL of DMF[32] was added over 8 min a solution of 3.05 g of the crude Grignard addition product (11.2-mmol maximum) in 10 mL of DMF with vigorous stirring. After being stirred for 41 h at 23 °C, the reaction mixture was poured into a separatory funnel containing 450 mL of distilled H_2O and 150 mL of 1:4 ether–hexane. The aqueous layer was extracted thrice with 150-mL portions of 1:4 ether–hexane. The combined organic extracts were concentrated in vacuo and dissolved in a minimal amount of CH_2Cl_2. This solution was filtered through a cotton plug and concentrated in vacuo to give 2.17 g of crude product. Purification of this material was affected by bulb-to-bulb distillation (80 °C (0.1 mm)), giving 1.54 g of **54** (84% based on sorbaldehyde): NMR (CCl_4) δ 5.3–6.3 (m, 4 H, vinyl H's), 4.07 (m, 1 H, CH(OR)), 3.33 (b s, OH), 2.20 (m, 2 H, $CH_2C{\equiv}C$), 1.79 (d, J = 5 Hz, CH_3), 1.58 (m, 4 H, CH_2CH_2); IR (neat) 3305, 3020, 2123, 1659 cm^{-1}; mass spectrum, m/e 164 (parent ion); high-resolution mass spectrum calcd 164.120 11, found 164.120 43. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 79.75, 79.92; H, 9.90, 10.03.

(b) Methyl (*E*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)dodeca-8,10-dien-2-ynoate (55). To a solution of 0.917 g of **54** (5.59 mmol) in a 5 mL of dry DMF was added 1.09 g of *tert*-butyldimethylsilyl chloride[8] (7.27 mmol) and 0.957 g of imidazole (14.1 mmol). This solution was stirred for 43 h at 23 °C. The reaction mixture was poured into a separatory funnel containing 50 mL of distilled H_2O and 50 mL of hexane. The aqueous layer was washed twice with 50-mL portions of hexane. The combined hexane extracts were washed once with 50 mL of distilled H_2O, dried over Na_2CO_3, and concentrated in vacuo to give 1.66 g of crude product, which was used in the next step without purification.

A solution of 1.46 g of the crude silyl ether (5.26 mmol) in 17 mL of dry THF was cooled to −78 °C. To this solution was added 2.55 mL of

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(32) Drouin, J.; Leyendecker, F.; Conia, J. M. *Tetrahedron Lett.* **1975**, 4053.

a 2.4 N *n*-butyllithium solution in hexane (6.12 mmol). This mixture was stirred at −78 °C for 20 min, and then 0.84 mL of methylchloroformate (13.2 mmol) was added. After an additional 30 min at −78 °C the solution was allowed to warm to 0 °C and then was quenched with 25 mL of saturated aqueous $NaHCO_3$. This two-phase mixture was stirred for 4 h (in other runs, this step was performed for only 30 min). The resulting mixture was poured into a separatory funnel containing 100 mL each of distilled H_2O and CH_2Cl_2. The organic layer was washed twice with 100 mL of H_2O, filtered through a cotton plug, and concentrated in vacuo to give 1.79 of crude product. This material was purified by chromatography on 30 g of silica gel by using 5% ether in hexane as eluant. This gave 1.48 g of **55** (84% from **54**): NMR (CCl_4) 5.1–6.3 (m, 4 H, vinyl H's), 4.13 (m, 1 H, CH(OR)), 3.68 (s, 3 H, OCH_3), 2.35 (b s, 2 H, $CH_2C{\equiv}C$), 1.76 (d, J = 5 Hz, 3 H, CH_3), 1.60 (m, 4 H, CH_2CH_2), 0.92 (s, 9 H, *tert*-butyl), 0.04 (s, 6 H, $SiMe_2$); IR (neat) 3024, 2244, 1720, 1660 cm^{-1}; mass spectrum, m/e 336 (parent ion); high-resolution mass spectrum calcd 336.212 07, found 336.211 09. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.56; Si, 8.34. Found: C, 67.90; H, 9.85; Si, 8.29.

(c) Methyl (*Z*,*E*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)dodeca-2,8,10-trienoate (19). A solution of 0.679 g of **55** (2.02 mmol) in 6 mL of dry toluene was hydrogenated at 23 °C over 68.0 mg of Lindlar catalyst (5% $Pd/CaCO_3$, lead poisoned).[33] The progress of the reaction was monitored by H_2 uptake and by analytical TLC (2% ether–hexane, two developments: R_f (**55**) 0.45; R_f (**19**) 0.60). When **55** could no longer be detected by analytical TLC (UV analysis, 6.5 h in this case), the catalyst was removed by filtration and the toluene was removed in vacuo to give 0.673 g of crude **19**. This material was purified by chromatography on 40 g of silica gel using 1.5% ether–hexane as eluant, giving 0.567 g of triene **19** (83%, 91% based on unrecovered **55**), 0.051 g of recovered **55** (8%), and 0.035 g (5%) of an unidentified overreduction product.

19: NMR (CCl_4) δ 5.2–6.4 (m, 6 H, vinylic H), 4.12 (m, 1 H, CH(OR)), 3.63 (s, 3 H, OCH_3), 2.64 (m, 2 H, allylic CH_2), 1.77 (d, J = 6 Hz, 3 H, CH_3), 1.52 (b s, 4 H, CH_2CH_2), 0.89 (s, 9 H, *tert*-butyl), 0.02 (s, 6 H, $SiMe_2$); IR (neat) 3020, 1726, 1656, 1644 cm^{-1}; mass spectrum, m/e 338 (parent ion). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12; Si, 8.29. Found: C, 67.44; H, 10.23; Si, 7.96.

Synthesis of 20 and 21. (a) (*E*)-Nona-6,8-dienal Diethyl Acetal (52). To a solution of 3.23 g (25.6 mmol) of 2,4-pentadienyl acetate[27] in 125 mL of dry THF was added 10.14 mL (1.01 mmol) of 0.1 M Li_2CuCl_4 in THF.[28] This mixture was cooled to −15 °C, and 245 mL (38.3 mmol maximum) of 0.16 M $BrMg(CH_2)_3CH(OEt)_2$ in THF (see procedure for preparation of **7**) was added dropwise over 63 min. During the addition, the solution changed color from orange to faint purple. Following the addition of the Grignard reagent, the solution was stirred vigorously at 0 °C for 3 h before being quenched with 100 mL of saturated aqueous NH_4Cl. The mixture was then transferred to a separatory funnel containng 100 mL of saturated aqueous NH_4Cl and 200 mL of ether. The aqueous phase was diluted with 50 mL of H_2O (to dissolve all solids) and was extracted with three 100-mL portions of ether. The combined ether extracts were dried over Na_2SO_4 and concentrated in vacuo to give 9.93 g of crude product. Acetal **52** was separated from other byproducts by flash chromatography (two 50-mm columns, 10:1 hexane–ether). In this manner, 2.33 g (43%) of acetal **52** along with 0.25 g of a mixture of **52** and $(EtO)_2CH(CH_2)_6CH(OEt)_2$, and 0.65 g (38%) of a mixture of reductive coupling products of 2,4-pentadienyl acetate (NMR (CCl_4, 60 MHz) δ 5.0–7.0 (m, 5 H), 2.2 (m, 2 H)) was obtained.

52: NMR ($CDCl_3$, 250 MHz) δ 6.27 (dt, J = 16.6, 10.2 Hz, H_6), 6.01 (m, H_7), 5.66 (m, H_8), 5.04 (br d, J = 16.6 Hz, H_9), 4.92 (br d, J = 10.2 Hz, H_9), 4.44 (t, J = 5.8 Hz, $CH(OR)_2$), 3.53 (m, 4 H, OCH_2R), 2.06 (br q, J = 6.7 Hz, allylic CH_2), 1.58 (m, $CH_2CH(OEt_2)$), 1.38 (m, 4 H), 1.17 (t, J = 7.3 Hz, CH_3); IR (CCl_4) 3085, 3035, 1648, 1603 cm^{-1}; mass spectrum, m/e 213 (parent ion + 1); high-resolution mass spectrum (parent ion not observed) calcd for $C_{13}H_{24}O_2$ − OEt 167.1436, found 167.1431.

(b) 6(*E*),8-Nonadienal (53). A solution of 0.900 g (4.24 mmol) of acetal **52** in 6.0 mL of THF and 4 mL of 5% aqueous oxalic acid was stirred vigorously at 23 °C for 36.5 h. The reaction mixture was poured into a separatory funnel containing 15 mL of CH_2Cl_2 and 10 mL of H_2O. The CH_2Cl_2 layer was washed once with 10 mL of H_2O. The combined aqueous layers were washed once with 10 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $NaHCO_3$, filtered through a cotton plug, and concentrated in vacuo to give 0.626 g of crude product which was shown by 250-MHz NMR to be nearly pure: NMR ($CDCl_3$, 250 MHz) δ 9.72 (d, J = 1.5 Hz, H_1), 6.26 (dt, J = 16.9, 10.2 Hz, H_6), 6.01 (m, H_7), 5.64 (m, H_8), 5.05 (d, J = 16.9 Hz, H_9), 4.93 (d, J = 10.3 Hz, H_9), 2.40 (dt, J = 1.5, 7.0 Hz, CH_2CHO), 2.07 (q, J = 7.0 Hz, allylic CH_2), 1.64 (m, 2 H), 1.42 (m, 2 H); IR (CCl_4) 3088, 3035, 2715, 1725, 1650, 1603 cm^{-1}; mass spectrum, m/e 138 (parent ion); high-resolution mass spectrum calcd for $C_9H_{14}O$ 138.1045, found 138.1040.

(c) Methyl (*E*,*E*)-Undeca-2,8,10-trienoate (20) and Methyl (*Z*,*E*)-Undeca-2,8,10-trienoate (21). To a solution of 0.529 g (3.83 mmol) of crude aldehyde **53** in 7 mL of CH_3OH was added 1.60 g (4.79 mmol) of (carbomethoxy)methylidenetriphenylphosphorane.[25] The resulting solution was stirred for 22 h at 23 °C. The solvent was removed in vacuo and the residue was chromatographed on a 40-mm flash column to remove reaction byproducts. This gave 0.705 g (95%) of a mixture of **20** and **21**. Separation of these isomers was effected by flash chromatography (40 mm, 5% ether–hexane) to give 0.386 g (52%) of **20**, 0.035 g (5%) of a 1:2 mixture of **20**:**21** and 0.225 g (30%) of **21**.

20: NMR ($CDCl_3$, 250 MHz) δ 6.92 (dt, J = 15.6, 7.0 Hz, H_3), 6.26 (dt, J = 16.4, 10.2 Hz, H_8), 6.00 (dd, J = 16.4, 10 Hz, H_9), 5.78 (dt, J = 15.6, 1.6 Hz, H_2), 5.63 (m, H_{10}), 5.08 (ddd, J = 16.9, 1.1, 0.5 Hz, H_{11}), 4.92 (ddd, J = 10.2, 1.1, 0.5 Hz, H_{11}), 3.68 (s, 3 H), 2.16 (dq, J = 1.6, 7.0 Hz, $CH_2C{=}CCO_2R$), 2.05 (q, J = 6.5 Hz, diene allylic CH_2), 1.41 (m, 4 H); IR (CCl_4) 3085, 3030, 1724, 1657, 1600 cm^{-1}; mass spectrum, m/e 194 (parent ion); high-resolution mass spectrum calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1316.

21: NMR ($CDCl_3$, 250 MHz) δ 6.22 (m, H_8, H_3), 6.01 (dd, J = 15.0, 10.2 Hz, H_9), 5.74 (dt, J = 1.7, 11.6 Hz, H_2), 5.65 (m, H_{10}), 5.05 (dd, J = 16.8, 1.3 Hz, H_{11}), 4.91 (br d, J = 10.6 Hz, H_{11}), 3.67 (s, 3 H), 2.61 (m, $CH_2C{=}CCO_2R$), 2.07 (m, diene allylic CH_2), 1.42 (m, 4 H); IR (CCl_4) 3086, 3040, 1722, 1644, 1602 cm^{-1}; mass spectrum, m/e 194 (parent ion); high-resolution mass spectrum calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1294.

Methyl (*E*,*E*,*E*)-2-Methyl-7-oxododeca-2,8,10-trienoate Ethylene Glycol Ketal (22). To a stirred solution of 104 mg of crude **46** (0.44 mmol) in 2.0 mL of dry THF was added 0.15 mL of 2-methoxy-1,3-dioxolane (1.59 mmol), 0.26 mL of ethylene glycol (4.67 mmol), and one small crystal of *p*-TsOH·H_2O.[34] The progress of the reaction was monitored by analytical TLC (silica gel, 1:2 ether–hexane (R_f(**46**) 0.33; R_f(**22**) 0.51). When complete (19 h in this case), the reaction mixture was poured into a separatory funnel containing 5 mL of saturated $NaHCO_3$ and 10 mL of CH_2Cl_2. The CH_2Cl_2 extract was washed once with a 5 mL portion of saturated $NaHCO_3$. The combined aqueous extracts were then extracted twice with 10-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were filtered through a cotton plug and concentrated in vacuo to give 148 mg of crude product. This material was purified by PTLC (one 0.5-mm silica gel plate, 1:2 ether–hexane), giving 3.4 mg (3%) of recovered **46** and 88.0 mg of **22** (71%): NMR ($CDCl_3$, 250 MHz) δ 6.70 (tq, J = 7.5, 1.3 Hz, H_3), 6.23 (dd, J = 15.2, 10.5 Hz, H_9), 5.99 (m, H_{10}), 5.72 (dq, J = 15.1, 6,7 Hz, H_{11}), 5.36 (dd, J = 15.2, 0.5 Hz, H_8), 3.85 (m, 4 H, OCH_2CH_2O), 3.69 (s, 3 H, OCH_3), 2.14 (q, J = 7 Hz, 2 H, allylic CH_2), 1.77 (d, J = 1.3 Hz, CH_3), 1.72 (dd, J = 6.5, 1.3 Hz, 3 H, CH_3), 1.51 (m, 2 H); IR (CCl_4) 3023, 1716, 1650 cm^{-1}; mass spectrum, m/e 280 (parent ion); high-resolution mass spectrum calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1678.

Methyl (*E*,*E*,*E*)-7-Oxododeca-2,8,10-trienoate Ethylene Glycol Ketal (23). Alcohol **18** (175 mg, 0.78 mmol) was oxidized with Ag_2CO_3 on Celite (5.1 g, 8.85 mmol, 40 mL of benzene)[22] by using the procedure described above for **46**. The crude ketone (169 mg, 98%) was sufficiently pure for preparation of **23**. On one occasion, this material was purified by bulb-to-bulb distillation (140–150 °C (0.1 mm), 85% yield) to give a nearly colorless liquid which crystallized on refrigeration (mp 20–30 °C): NMR (250 MHz, $CDCl_3$) δ 7.09 (m, H_9), 6.91 (dt, J = 15.7, 7.0 Hz, H_3), 6.17 (m, 2 H, H_{10}, H_{11}), 6.02 (d, J = 15.3 Hz, 1 H, H_8), 5.80 (dt, J = 15.7, 1.6 Hz, H_2), 3.69 (s, 3 H, OCH_3), 2.54 (t, J = 7.3 Hz, 2 H, $COCH_2$), 2.20 (m, 2 H, allylic CH_2), 1.83 (d, J = 5.4, 3 H, CH_3), 1.76 (m, 2 H, CH_2); IR (CCl_4) 3030, 1728, 1693, 1663, 1640, 1598 cm^{-1}; mass spectrum, m/e 222 (parent ion); high-resolution mass spectrum calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1238.

The ethylene glycol ketal was prepared by the procedure described above for **22**. To a solution of 159 mg of crude ketone (0.715 mmol) in 3 mL of dry THF was added 0.23 mL of 2-methoxy-1,3-dioxolane,[34] 0.4 mL of ethylene glycol, and one small crystal of *p*-TsOH·H_2O. This solution was stirred at 23 °C, and the progress of the reaction monitored by analytical TLC (silica gel, 1:2 ether–hexane: R_f (ketone) 0.35; R_f(**23**) 0.50). When complete (13 h in this case), the reaction was worked up in the usual manner. The crude product was purified by preparative TLC (one 0.5-mm silica gel plate using 1:2 ether–hexane as eluant), giving 136.0 mg of **23** (72% from **18**): NMR (250 Hz, $CDCl_3$) δ 6.91 (dt, J

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= 15.6, 7.0 Hz, H_3), 6.24 (dd, J = 10.5, 15.3 Hz, H_9), 6.00 (m, H_{10}), 5.75 (m, 2 H, H_2, H_{11}), 5.37 (d, J = 15.3 Hz, H_8), 3.86 (m, 4 H, OCH_2CH_2O), 3.68 (s, 3 H, OCH_3), 2.18 (m, 2 H, allylic CH_2), 1.72 (dd, J = 6.8, 1.3 Hz, CH_3), 1.66 (m, 2 H), 1.54 (m, 2 H); IR (CCl_4) 3022, 1723, 1660 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1519.

Methyl (*Z*,*E*,*E*)-7-Oxododeca-2,8,10-trienoate Ethylene Glycol Ketal (24). Triene **18a** (49.1 mg, 0.22 mmol) was oxidized with Ag_2CO_3 on Celite (0.923 g, 1.62 mmol, 10 mL of benzene)[22] as described for **46**, giving 50 mg of crude product. This material was partially purified by bulb-to-bulb distillation (150 °C (0.1 mm)), giving 45.7 mg of methyl (*Z*,*E*,*E*)-7-oxododeca-2,8,10-trienoate (94%). The distilled product still contained a small amount of impurities which were removed by preparative TLC on a 10 × 20 cm 0.25-mm silica gel plate eluted with 1:1 ether–hexane. This gave 31.0 mg (64%) of pure ketone: mp 34–37 °C; NMR ($CDCl_3$, 250 MHz) δ 7.09 (m, H_9), 6.21 (m 3 H, H_3, H_{10}, H_{11}), 6.02 (d, J = 15.1 Hz, 1 H, H_8), 5.76 (dt, J = 11.6, 1.6 Hz, H_2), 3.66 (s, 3 H, OCH_3), 2.64 (dq, J = 1.6, 7.5 Hz, 2 H, allylic CH_2), 2.56 (t, J = 7.2 Hz, 2 H, $COCH_2$), 1.83 (d, J = 5.1 Hz, CH_3), 1.74 (m, 2 H); IR (CCl_4) 3024, 1720, 1685, 1667, 1636, 1593 cm^{-1}; mass spectrum, m/e 222 (parent ion); high-resolution mass spectrum calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1236.

Ketal **24** was prepared by using the procedure described for **22**. To a solution of 17.8 mg of the ketone described in the previous paragraph (0.08 mmol) in 0.5 mL of dry THF at 23 °C was added 0.4 mL of 2-methoxy-1,3-dioxolane (0.42 mmol), 0.3 mL of ethylene glycol (0.54 mmol), and one small crystal of p-$TsOH \cdot H_2O$.[34] The reaction was monitored by analytical TLC (1:2 ether–hexane: R_f(ketone) 0.31; R_f(**24**) 0.47). When complete (18 h in this case), the reaction was worked up in the usual manner. The crude product was purified by PTLC (one 0.5-mm silica gel plate, 1:2 ether–hexane), giving 14.1 mg of ketal **24** (68%): NMR ($CDCl_3$, 250 MHz) δ 6.0–6.4 (m, 3 H, H_3, H_9, H_{10}), 5.74 (m, 2 H, H_{11}, H_2), 5.39 (d, J = 15.1 Hz, H_8), 3.87 (m, 4 H, OCH_2CH_2O), 3.67 (s, 3 H, OCH_3), 2.64 (dq, J = 1.6, 7.5 Hz, 2 H, allylic CH_2), 1.74 (dd, J = 6.7, 1.3 Hz, 3 H, CH_3), 1.50 (m, 2 H); IR (CCl_4) 3023, 1729, 1644 cm^{-1}; mass spectrum, m/e 266 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1529.

Acknowledgment. Acknowledgment is made to the NIH (Grant No. GM26782), to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for support of this research. We are grateful to Dr. Catherine Costello for measurement of high-resolution mass spectra.

Reagent Design and Study of *p*-Benzoquinone Derivatives as Highly Reactive Electron-Attracting Dienophiles.[1] A Promising Class of Reagents (Synthons) for Cycloaddition

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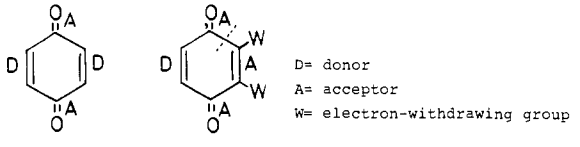
Abstract: *p*-Benzoquinone-2,3-dicarboxylic anhydride (**4**) and *N*-phenylimide (**5**) were prepared by oxidation of the corresponding hydroquinones. Compounds **4** and **5** are found to have high reactivities toward electron-rich dienes and trienes such as norbornadiene, 6,6-dimethylfulvene, and cycloheptatriene; the selectivities are discussed in terms of frontier molecular orbital theory, indicating that both compounds are powerful electron-attracting dienophiles for the cycloadditions. The stereochemistry of the adducts was determined by spectral inspections and chemical transformation leading to the cage compounds.

Interest in strained cage molecules[3] has accelerated greatly during the past decade, since these compounds continue to play an important role in the understanding of many aspects of organic chemistry. Thus, synthetic efforts in this area have been extensive. One of the general methods used to prepare such systems involves a photochemical intramolecular [2 + 2] cycloaddition of *p*-benzoquinone (**1**) to cyclic dienes.[4] *However, p-benzoquinone behaves only as a weak dienophile in the Diels–Alder reaction and is rather inert to homodienes, conjugated medium-ring polyenes such as norbornadiene, cycloheptatriene, and tropone even under drastic conditions. Therefore, it appears worthwhile to attempt to use this versatile p-benzoquinone derivative as a dienophile component in the Diels–Alder reactions.*

Results and Discussion

Theoretical Expectations. On the basis of the concept of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) relationship of the frontier-controlled pericyclic reactions,[5] we considered that introduction of strong electron-attracting substituents in *p*-benzoquinone would cause a lowering of the LUMO energy. This would result in enhancement of the reactivity of *p*-benzoquinone which would accelerate the pericyclic reaction to the polyenes. These ideas are also applicable to variations of the olefinic reactants in the pericyclic reactions. Since the $_{\pi}4_s + _{\pi}2_s$ transition state of the cycloaddition of an electron-rich butadiene and an electron-poor ethylene is isoconjugate to a substituted benzene, the reaction proceeds via aromatic transition states and the aromaticity is not destroyed by substituents.[6,7]

Chart I



Recently, Inagaki et al.[8] proposed the degree of cyclic electron delocalization to be a function of the mode of the donor–acceptor

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