Studies of an Intramolecular Diels–Alder Approach to the Nargenicins: Involvement of Boatlike Transition States in the Cyclizations of Substituted 1,7,9-Decatrien-3-ones[1]

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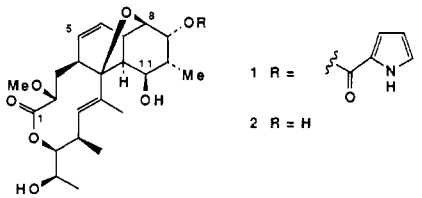
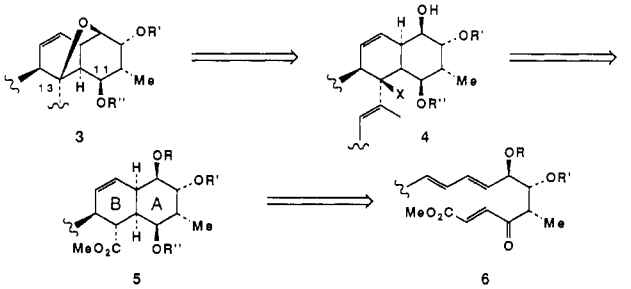
The intramolecular Diels–Alder reactions of a series of substituted decatrienones were examined in connection with a planned synthesis of the decalin framework of the nargenicin antibiotic family. The cyclization of triene **7** provided cis-fused cycloadduct **9** with very high diastereoselectivity through transition state $\mathbf{7B}_{boat}$ with a boatlike conformation of the connecting chain. The Diels–Alder reactions of trienes **19–23** generated mixtures of cycloadducts, but again a high preference for cyclization through boatlike transition states was observed. The involvement of boatlike transition states in decatrienone intramolecular Diels–Alder reactions appears to be general. A detailed analysis is presented that shows that, assuming the transition state is early as suggested by numerous other investigations, the boat decatrienone transition state is actually free of destabilizing eclipsing or other unfavorable nonbonded steric interactions. The boat transition state in the decatrienone cis-fused manifold is favored over the chairlike arrangement in part as a consequence of a stabilizing eclipsing sp^3–sp^2 interaction between the diene and the allylic C–H bond, a relationship that is absent from the chair transition state.

Introduction

Nargenicin A_1 (**1**) is a structurally novel antibiotic isolated from *Nocardia argentineneas*.[3] A closely related antibiotic, nodusmicin (**2**), is produced by the soil organism *Saccharopolyspora hirsuta*.[4] The structure and stereochemistry of nodusmicin was established by X-ray crystallographic studies,[4a] while the structural assignment for nargenicin A_1 was verified by its synthesis from nodusmicin.[5,6]

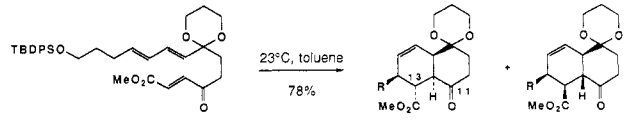


We have investigated an approach to the nargenicins in which an intramolecular Diels–Alder reaction (**6** → **5**) is used to establish the cis-fused decalin skeleton.[7-9] Trienes of general structure **6** were regarded as attractive precursors to **5** for several reasons. First, we envisiaged that the three asymmetric centers could be easily established in acyclic precursors, thereby minimizing manipulations of the decalin system after the cyclization event. Second, the Diels–Alder reaction was expected to proceed with excellent cis selectivity by analogy to the established behavior of simple 1,7,9-decatrien-3-ones.[10,11] Finally, the cycloadduct would possess handles for additional functionalization of C(13) as well as introduction of the required endo C(11) hydroxyl group.[12]



The major uncertainty at the inception of our studies was the issue of diastereoselectivity in the competing cis-fused transition states. Inspection of molecular models of possible cis-fused transition states, $\mathbf{6A}_{chair}$ and $\mathbf{6B}_{chair}$, suggested that $\mathbf{6A}_{chair}$, leading to the desired diastereomeric cycloadduct, should be favored as it contained fewer serious nonbonded interactions. Although the interaction of the axial C(10)-CH_3 with C(12)-H in $\mathbf{6A}_{chair}$ is potentially

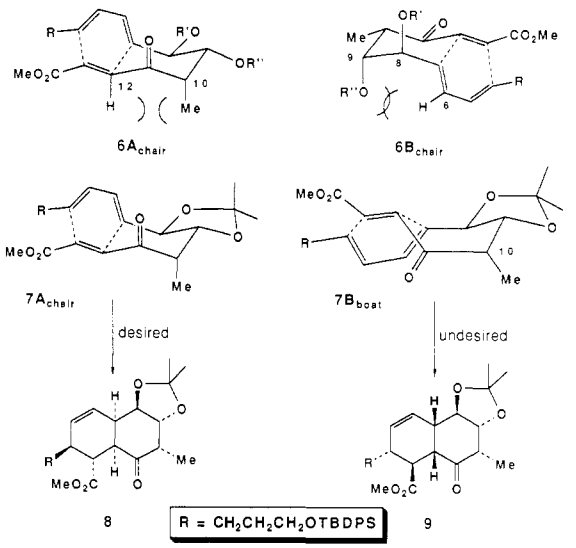
(1) Taken from the 1988 Ph.D. Thesis of J. W. Coe, Massachusetts Institute of Technology, Cambridge, MA 02139.
(2) Address correspondence to this author at Indiana University.
(3) Celmer, W. D.; Chmurny, G. N.; Moppet, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203.
(4) Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659.
(5) Magerlein, B. J.; Mizsak, S. A. *J. Antibiot.* **1982**, *35*, 111.
(6) The absolute configuration was assigned by using the nonempirical CD exciton method: Cane, D. E.; Yang, C.-C. *J. Antibiot.* **1985**, *38*, 423.
(7) (a) The first synthesis of a nargenicin, 18-deoxynargenicin A_1, was recently reported: Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041. For other synthetic studies, see: (b) Kallmerten, J. *Tetrahedron Lett.* **1984**, *25*, 2843. (c) Kallmerten, J.; Plate, D. J. *Heterocycles* **1987**, *25*, 145. (d) Jones, R. C. F.; Tunnicliffe, J. H. *Tetrahedron Lett.* **1985**, *26*, 5845.
(8) For recent reviews of the intramolecular Diels–Alder reaction: (a) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1.
(9) Interestingly, Cane has speculated that an intramolecular Diels–Alder reaction may be involved in the nargenicin biosynthesis: Cane, D. E.; Yang, C.-C. *J. Am. Chem. Soc.* **1984**, *106*, 784.
(10) (a) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002. (b) Gras, J. L.; Bertrand, M. *Tetrahedron Lett.* **1979**, *20*, 4549.
(11) (a) In preliminary work we established that triene i cyclized at 23 °C to provide a 13:1 mixture of the cis- and trans-fused isomers (described fully in ref 1).



(b) For a second but less selective example, see: Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.
(12) A C(3) chiral center is often an excellent stereochemical control element in intramolecular Diels–Alder reactions of functionalized 1,7,9-decatrienes. In the majority of cases, however, the C(3) substituent occupies an exo orientation in the transition state, opposite to what is required for C(11) of the nargenicins: (a) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696. (b) Marshall, J. A.; Grote, J.; Audia, J. E. *Ibid.* **1987**, *109*, 1186. (c) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180.

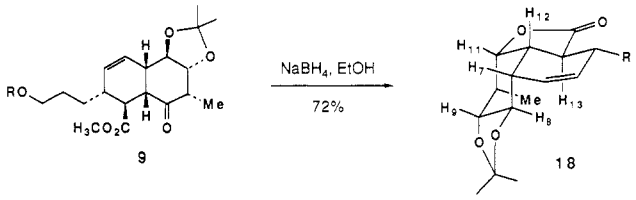
0022-3263/89/1954-0915$01.50/0

problematic, we viewed the interaction between H(6) and the axial C(9)-OR unit in $\mathbf{6B}_{chair}$ as more serious.[13] Greater discrimination between the competing transition states was considered possible if the C(8) and C(9) alkoxyl units were protected as an acetonide as in triene **7**. In this case, a chairlike transition state ($\mathbf{7B}_{chair}$) corresponding to $\mathbf{6B}_{chair}$ is inaccessible. Remaining, however, is transition state $\mathbf{7B}_{boat}$ in which the chain bridging the diene and dienophile is constrained in a boatlike arrangement. While we were aware of several reports suggesting that decatrienone intramolecular Diels–Alder reactions may proceed via boatlike conformations as in $\mathbf{7B}_{boat}$, convincing experimental evidence in those cases was lacking.[11b,14] Moreover, computational studies published after our work was initiated suggested that the chair conformations, at least in simple saturated systems, should be favored.[15] Consequently, we viewed **7** to be an ideal precursor to the nargenicin decalin nucleus and initiated work on its synthesis.[16]



Synthesis and Diels–Alder Cyclization of Triene 7. Our willingness to consider **7** as a synthetic intermediate was facilitated by knowledge that the three stereocenters could be introduced with high stereoselectivity by using the tartrate ester modified crotylboronate methodology developed in our laboratory.[17] Thus, the synthesis commenced with the reaction of D-glyceraldehyde acetonide (**10**) and the chiral (*E*)-crotylboronate (*S,S*)-**11** that provides **12** with 96% diastereoselectivity[17] (Scheme I). Treatment of **12** with catalytic *p*-toluenesulfonic acid in acetone provided an easily separated 10:1 mixture of **12** and **13**; after one recycle of recovered **12** the yield of isomerically pure **13** was 94%. Ozonolysis of **13** in methanol at −78 °C followed by reduction of the α-methoxy hydroperoxide with Me_2S (or PPh_3) generated a crude ω-hydroxy aldehyde that existed exclusively in the open chain form (no hemiacetal was detected). Without purification, this intermediate was oxidized to the corresponding acid by treatment with MCPBA.[18] Ester **14** was then obtained in 97% yield following diazomethane esterification and purification by silica gel chromatography. Introduction of the diene was performed in a nonstereoselective manner following Swern oxidation of **14** to aldehyde **15**.[19] Treatment of crude **15** with the ylide prepared from phosphonium salt **16** gave a mixture of diene isomers, which was then isomerized[20] by using catalytic I_2 in dry hexane to provide (*E,E*)-diene **17** in 76% overall yield from **14**. The isomeric purity of **17** was determined by ^1H NMR analysis to be >10:1.

Treatment of ester **17** with an excess of dimethyl (α-lithiomethyl)phosphonate in THF at −78 °C afforded a crude β-keto phosphonate that condensed with methyl glyoxal using mild Horner–Wadsworth–Emmons conditions[21] to provide (*E,E,E*)-triene **7** in excellent yield. A toluene solution of **7** was warmed to reflux for 22 h. Analysis of the reaction mixture by TLC and ^1H NMR spectroscopy revealed the presence of a single cycloadduct that was isolated in 78% yield overall from **17**. The stereochemistry of the Diels–Alder cycloadduct was determined following conversion to lactone **18**. Homonuclear decoupling experiments established the ring fusion to be cis ($J_{7,12}$ = 5.0 Hz). NOE difference experiments showed strong interactions between C(10)-CH_3, H(13), and H(8), indicating that all three are closely positioned in the concave cup of the molecule. The cis relationship of H(9), H(11), and H(12) was similarly determined by an NOE experiment [irradiation of H(11)]. These data, plus the large diaxial coupling between H(12) and H(13) ($J_{12,13}$ = 15.0 Hz), are uniquely consistent with structure **18**, *requiring that the intramolecular Diels–Alder cyclization of 7 proceeds through the boatlike transition state* $\mathbf{7B}_{boat}$.



Stereochemical Study of Intramolecular Diels–Alder Reactions of Substituted 1,7,9-Decatrien-3-ones. This result with **7** was most unexpected. With hope of uncovering the factors responsible for this result and also of discovering a stereoselective pathway to potential nargenicin precursors, we embarked on a study of the Diels–Alder reactions of a series of structurally related trienes (**19–23**). Our selection of these substrates was based on the following considerations.

First, we considered that the interaction between the axial C(10)-methyl group and C(8)-H and C(12)-H in $\mathbf{7A}_{chair}$ was more serious than originally anticipated, thus enabling $\mathbf{7B}_{boat}$ to become accessible. The magnitude of this effect could be assessed by studying the cyclization

(13) Interactions between C(8) substituents (e.g., Me, TMS, Br, etc.) and axial C(5)-H are believed to be highly destabilizing in chair, cis-fused 1,7,9-decatriene transition states: (a) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *10*, 6289. (b) Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560. (c) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. (d) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1986**, *26*, 4327. (e) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710.

(14) (a) Tabler, D. F.; Gunn, B. G. *J. Am. Chem. Soc.* **1979**, *101*, 3992. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. (c) For an example that was published while our work was in progress, see: Zschiesche, R.; Grimm, E. L.; Reissig, H.-V. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1086.

(15) (a) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297. (b) Marshall, J. A.; Audia, J. E.; Grote, B. G. *J. Org. Chem.* **1986**, *51*, 1155.

(16) A preliminary account of the synthesis and intramolecular Diels–Alder reaction of **7** has been published: Roush, W. R.; Coe, J. W. *Tetrahedron Lett.* **1987**, *28*, 931.

(17) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

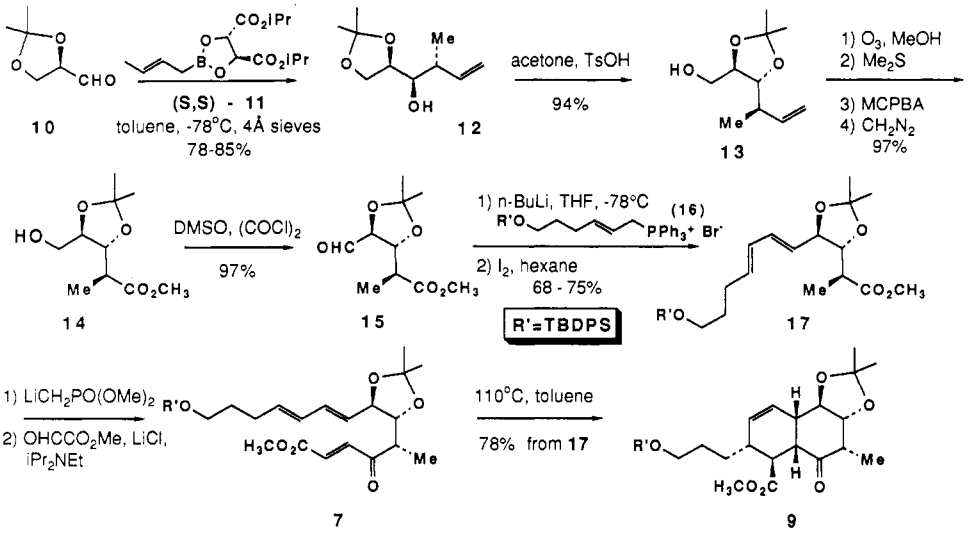
(18) (a) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914. (b) Koll, P.; Durrfeld, R.; Wolfmeier, U.; Heyns, K. *Tetrahedron Lett.* **1972**, 5081.

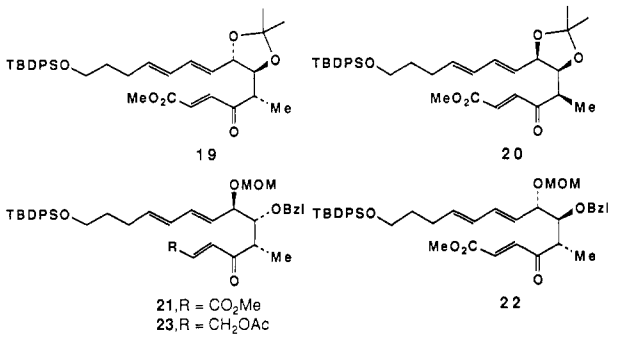
(19) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(20) (a) Alder, K.; Vogt, W. *Justus Liebigs Ann. Chem.* **1951**, *571*, 190. For recent examples see: (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (c) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.

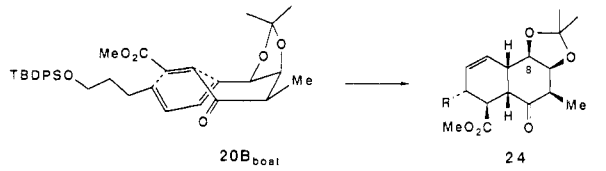
(21) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

Scheme I





of **19**, which was expected to cyclize through the chairlike transition state $\mathbf{19A}_{chair}$, analogous to $\mathbf{7A}_{chair}$. On the other hand, we expected triene **20**, the C(8) epimer of **7**, to exhibit an accentuated preference for cyclization through boatlike transition state $\mathbf{20B}_{boat}$, since the other possible cis-fused transition states $\mathbf{20A}_{chair}$, $\mathbf{20A}_{boat}$, and $\mathbf{20B}_{chair}$ would be sterically destabilized. In this way we hoped to exploit the preference for the boat transition state, as cycloadduct **24** could be used in a synthesis of nargenicin following inversion at C(8) (albeit in the enantiomeric series).



Second, the "strategically important" acetonide linkage may have introduced strain into transition state $\mathbf{7A}_{chair}$ that was relieved by cyclization through $\mathbf{7B}_{boat}$. Analysis of space-filling molecular models suggested that $\mathbf{7A}_{chair}$ experiences substantial strain in the region of C(7)–C(10), and such models nicely relax into the boatlike arrangement $\mathbf{7B}_{boat}$. This hypothesis would be tested by examining the Diels–Alder reactions of trienes **21** (cf. triene **6** of our original synthetic analysis) and **22**, an isomer in the same stereochemical series as **19** designed to provide further information concerning the role of the C(10)-methyl group on the stereochemical course of these reactions. Finally, **23** was studied to assess the role of secondary orbital interactions involving the carbomethoxyl group.

Synthesis and Intramolecular Diels–Alder Reaction of 19. The stereochemistry of C(8)–C(10) of **19** represents a sequence that is difficult to access *directly* by using the tartrate (*Z*)-crotylboronate methodology.[17,22] Consequently, an indirect method was employed to establish this stereochemical triplet. The synthesis begins with the matched double asymmetric reaction[24] of (*R*,*R*)-DIPT modified (*Z*)-crotylboronate **25** and D-glyceraldehyde acetonide (**10**) that provides the 3,4-syn-4,5-anti diastereomer **26** with >99:1 stereoselectivity[22,23] (Scheme II). Deprotection of **26** in acidic methanol provided the triol that was selectively silylated to give **27**. Introduction of the acetonide protecting group followed by removal of the TBDMS ether afforded the "acetonide migration" product **28** in excellent yield. It should be noted that the one-step acid-catalyzed acetonide migration that was used to great advantage in the synthesis of triene **7** (e.g., **12** → **13**) is not applicable here because **28** contains a cis dioxolane and is less stable than **26**.

Oxidation of **28** by using a standard Swern protocol[19] provided a crude aldehyde that was immediately treated with methanolic K_2CO_3 to effect epimerization to the more stable trans dioxolane.[25] The mixture was then neutralized with acetic acid and treated with $NaBH_4$ to provide **29** in 69% yield. Elaboration of **29** to diene ester **30** proceeded smoothly by using the methodology described for the synthesis of **17** (54% yield overall). Finally, β-keto phosphonate **31** was obtained in 69% yield by treatment of **30** with dimethyl (α-lithiomethyl)phosphonate. A significant amount of a β-elimination product also was obtained (23%).

The condensation of **31** with methyl glyoxal provided **19** in 84% yield. The Diels–Alder reaction proceeded smoothly over a 4–5-h period in refluxing benzene, giving a mixture of three cycloadducts **32**, **33**, and **34** in a ratio of 0.8:1.2:1.0 (high-field ^1H NMR analysis of crude reaction mixtures). We subsequently found that cyclization occurs at 23 °C over a 6-day period to provide the same three products in slightly altered ratio: **32** (2.3):**33** (1.6):**34** (1.0).

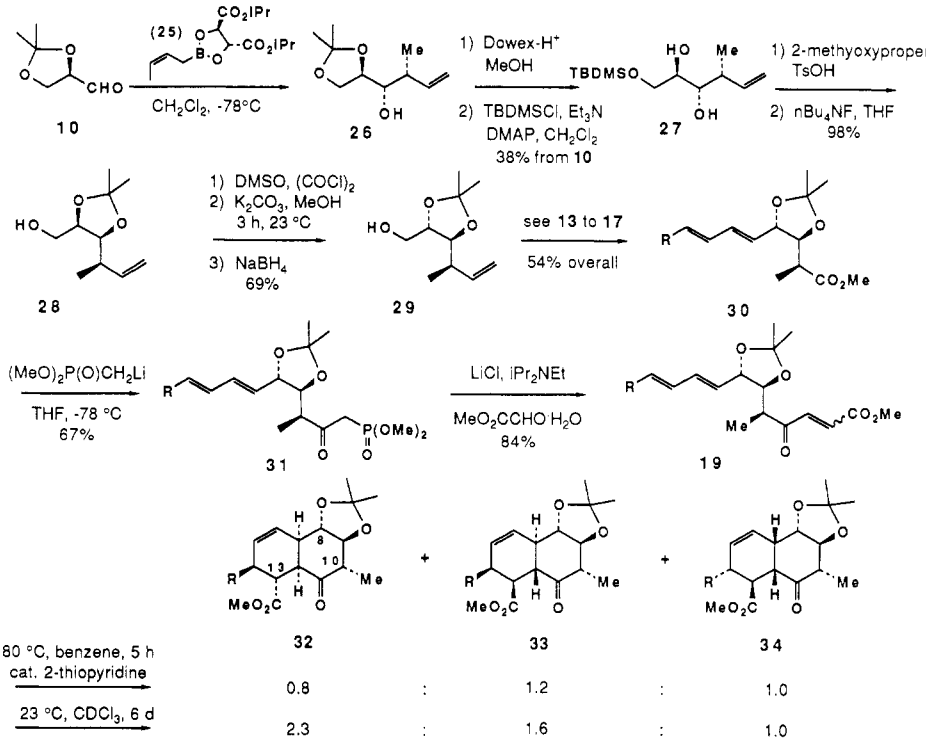
(22) The reaction of D-glyceraldehyde (**10**) with the chiral (*Z*)-crotylboronate (*R*,*R*)-**25** is a matched pair and provides diasteromer **26** with >99:1 stereoselectivity. Because the intrinsic diastereofacial selectivity of **10** is very great with (*Z*)-crotylboronates (ca. 20:1, see ref 23), the mismatched double asymmetric reaction with (*S*,*S*)-**25** fails to give useful selectivity for the 3,4-syn-4,5-syn diastereomer: Roush, W. R.; Halterman, R. L., unpublished research results.

(23) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

(24) For a review of double asymmetric synthesis, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(25) Lee, A. W. M.; Marten, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515.

Scheme II. Synthesis and Intramolecular Diels–Alder Reaction of 19



Unfortunately, isolation of pure samples of **32** and **33** proved difficult. Isomer **34** was separated with relative ease, but **32** and **33** coeluted with small amounts of residual, isomerically impure triene, making chromatographic purification extremely difficult. The residual triene, however, was removed by reaction with excess cyclopentadiene, allowing samples of the **32**/**33** mixture to be separated by exhaustive multiple elution chromatography. Attempts to promote cyclization of the residual isomerically impure **25** by using an in situ I_2 isomerization, as successfully applied in the case of **20** (vide infra), was less efficient owing to the slower rate of cyclization of **19**, thus enabling decomposition reactions of the triene and/or the Diels–Alder cycloadducts to become increasingly competitive.

The stereochemistry of cis-fused product **32** was assigned on the basis of the observed coupling constants: $J_{7,8}$ = 10.5 Hz, $J_{8,9}$ = 9.0 Hz, $J_{9,10}$ = 12.5 Hz, $J_{7,12}$ = 6.5 Hz, $J_{12,13}$ = 12.0 Hz. Structure elucidation of compound **33** follows from the similarities of many of the ^{1}H NMR resonances to those for **32**. Large diaxial relationships are observed for protons at C(7), C(8), C(9), and C(10). The H(12) resonance, an 11.5-Hz doublet of doublets (dd), and the broadened dd for H(7) ($J_{7,12} = J_{7,8}$ = 11.5 Hz) are indicative of a trans ring juncture.

The stereochemical assignment for cycloadduct **34** was also straightforward. H(9) appears as a dd ($J_{8,9}$ = 9.5 Hz, $J_{9,10}$ = 12.5 Hz), establishing the axial placement of H(8), H(9), and H(10). H(8) in **34**, however, differs from **32** and **33** in the coupling to the ring fusion proton ($J_{7,8}$ = 5.0 Hz), suggesting an equatorial placement of H(7). Finally, the ring fusion is cis as required by $J_{7,12}$ = 6.5 Hz.

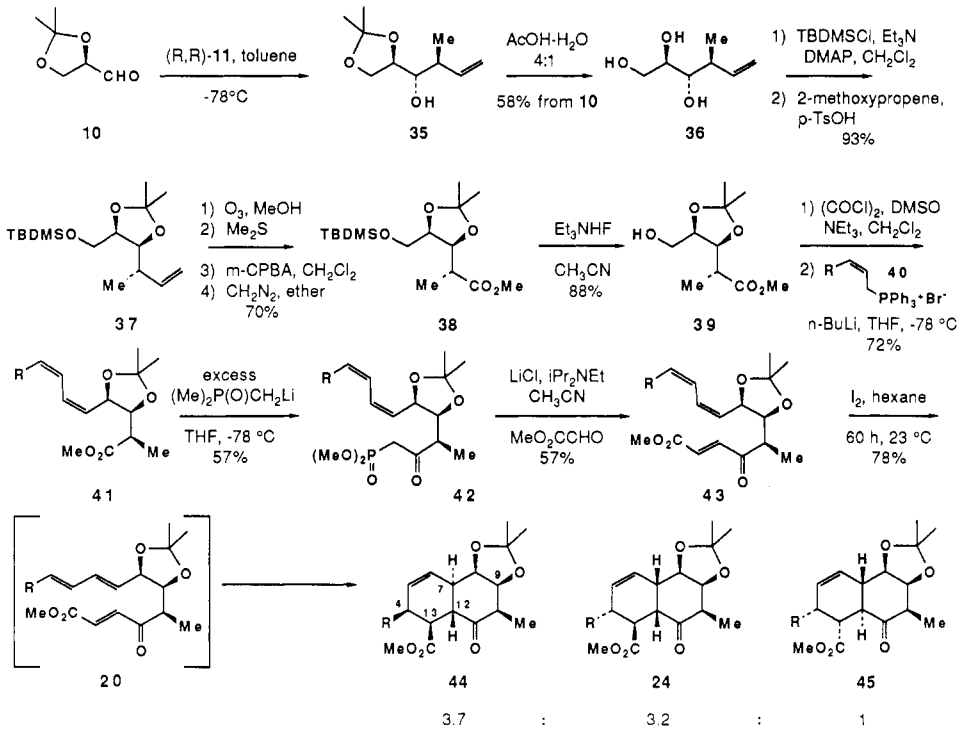
Synthesis and Intramolecular Diels–Alder Reaction of 20. Triene **20**, the (enantiomeric) C(8) epimer of **7**, was synthesized by a similar route initiated by the reaction of **10** and crotylboronate (*R,R*)-**11** that provides the 3,4-anti-4,5-anti diastereomer **35** with 87% diastereoselection[17] (Scheme III). As with **26**, it is not possible to effect an acid-catalyzed acetonide migration. Consequently, the acetonide protecting group was removed to give **36**, which was then selectively monosilylated. The acetonide unit was then reintroduced to give **37** in 54% overall yield (from **10**) by using conditions similar to those described for the preparation of **28**. The oxidative conversion of **37** to **38** proceeded smoothly (70%), and then the TBDMS ether was removed by using triethylammonium fluoride in acetonitrile to give hydroxy ester **39** in 88% yield.[26] Conversion of **39** to the (*Z,Z*)-diene ester **41** followed the method for synthesis of **17**, with the exception that the ylide prepared from (*Z*)-phosphonium salt **40** was used. In addition, the previously employed I_2-catalyzed diene isomerization was less efficient, leading to an inseparable 1:1 mixture of (*E,Z*)- and (*E,E*)-diene isomers. We opted, therefore, to postpone this step on the presumption that it could be performed under the same conditions as the intramolecular Diels–Alder reaction. If so, the Diels–Alder cyclization would drive the diene isomerization to completion.

The conversion of **41** to β-ketophosphonate **42** was complicated by competitive β-elimination of the C(9)-alkoxyl unit (acetone), and **42** was obtained only in 57% yield. Following introduction of the dienophile by using the standard HWE reaction with methyl glyoxal, the (*E,Z,Z*)-triene **43** was exposed to catalytic I_2 in hexane at 23 °C. Triene **20**, while never directly observed or isolated, presumably was formed transiently since smooth conversion to a mixture of three cycloadducts (**44**, **24**, and **45**) occurred over a 2.5-day period. The ratio of these products was 3.7:3.2:1 as determined by ^{1}H NMR analysis of the crude reaction mixture. The same mixture of products was obtained when (*E,E*)-**42** was used in this olefination/cyclization sequence (reaction time, <1 h, 23 °C). Pure samples of each cycloadduct were obtained by careful chromatography.

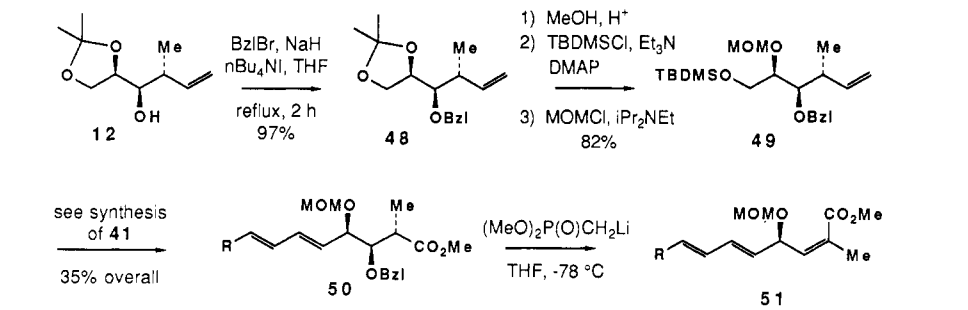
The stereochemical assignment for **44** is based on the following data. The large diaxial ^{1}H coupling of H(12) to H(7) and H(13) ($J_{7,12} = J_{12,13}$ = 12.5 Hz) and the smaller

(26) Hunig, S.; Wehner, G. *Synthesis* **1975**, 180.

Scheme III. Synthesis and Intramolecular Diels-Alder Reaction of 20



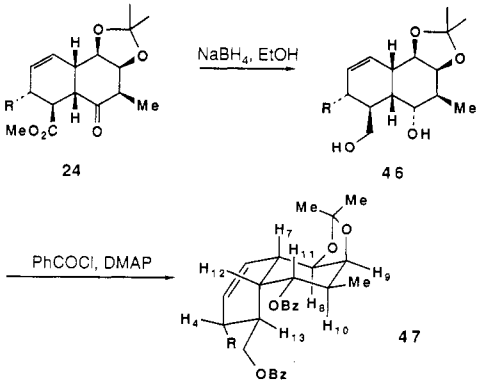
Scheme IV



gauche coupling of H(13) to H(4) ($J_{13,4}$ = 6.5 Hz) supports the expected half-chair conformation of the cyclohexene B ring, and defines the ring fusion to be trans. Less obvious is the conformation of the A ring, particularly since resonances for H(8) and H(9) overlap and $J_{7,8}$ and $J_{9,10}$ are very small (<2 Hz). MMX calculations comparing the ground-state conformational energy of structures containing chair and boat A rings show the boat conformation to be 3.14 kcal/mol more stable.[27]

Cycloadduct **45**, the minor component of this mixture, was identified as the other possible trans-fused cycloadduct. The resonance for H(7) appears as a broadened dd ($J_{7,12}$ = 12.0 Hz, $J_{7,8}$ = 10.5 Hz), requiring an equatorial placement of the C(8) oxygen atom. The 5.0-Hz dd for H(9) and the doublet of doublet for H(8) ($J_{8,7}$ = 10.5 Hz, $J_{8,9}$ = 5.0 Hz) support the assignment of a chair conformation in the A ring.

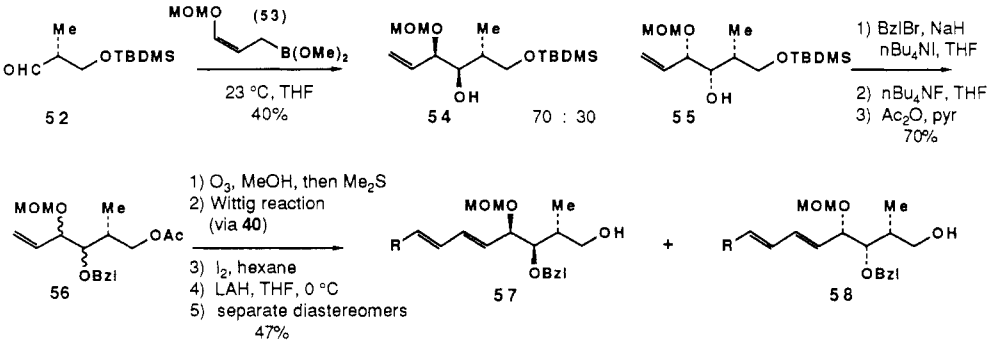
The stereochemistry of the third product, **24**, was assigned following conversion to dibenzoate **47**. The small couplings for H(12) ($J_{7,12}$ = $J_{11,12}$ = 4.0 Hz) define the ring fusion to be cis and also indicate that C(13) occupies an axial position with respect to the A ring. The large coupling involving H(11) ($J_{11,10}$ = 12.0 Hz) requires that the C(11)-OBz unit occupies an equatorial position, while the remaining coupling constants ($J_{7,8}$ = 9.0 Hz; $J_{8,9}$ = $J_{9,10}$ = 4.5 Hz) are uniquely consistent with the stereochemistry assigned to **24**/**47**.



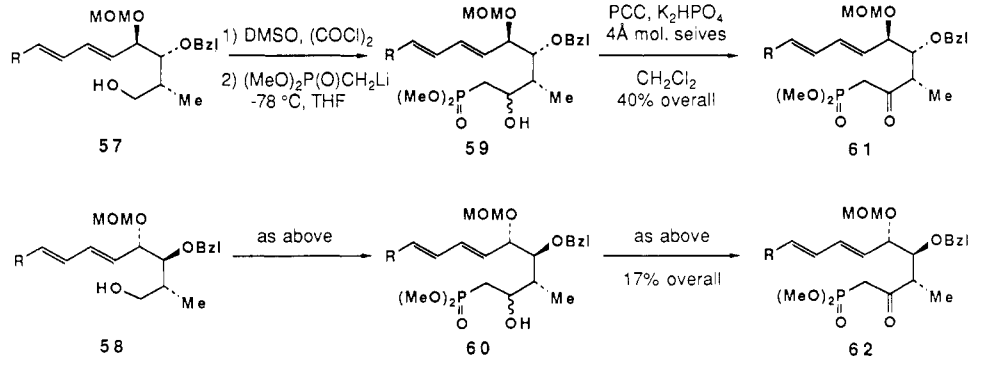
(27) Molecular mechanics calculations were performed by using the MMX PC modification of MM2: Gilbert, K. E.; Gajewski, J. J. Serena Software, P. O. Box 3076, Bloomington, IN 47402-3076. MMX is derived from MM2 (1977 version QCPE 395) with the VESCF π subroutines from MMP1 (QCPE 318) and includes an internally defined set of transition state atoms for modeling pericyclic transition states. The version of MMX used in this study has been updated with improved MM2 parameters for aldehydes and ketones (see ref 28).

(28) For a discussion of problems with the original MM2 parameters for ketones and the definition of improved parameters, see: (a) Bowen, J. P.; Pathiaseril, A.; Profeta, S., Jr.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 5162. (b) Goldsmith, D. J.; Bowen, J. P.; Qamhiyeh, E.; Still, W. C. *Ibid.* **1987**, *52*, 951.

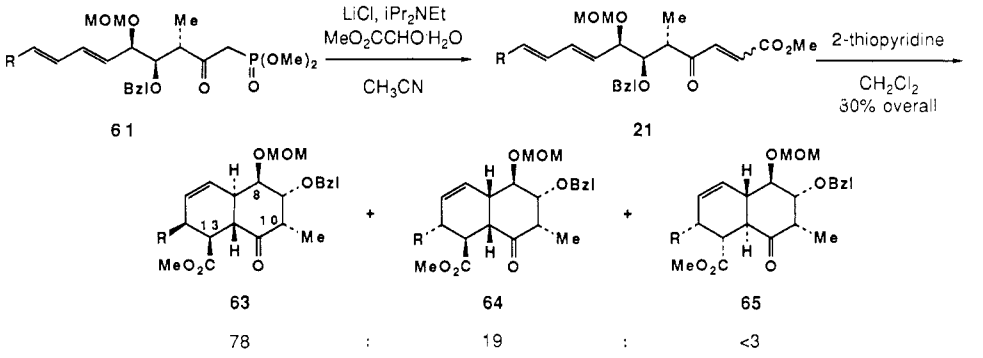
Scheme V



Scheme VI



Scheme VII



78 : 19 : <3

Synthesis and Diels–Alder Reactions of Trienes

21–23. We expected at the outset that **21** and **23** could be prepared from **12**. In the event, **12** was smoothly elaborated to **49** by a series of standard functional group manipulations, and then to diene **50** by using the Wittig and diene isomerization technology (Scheme IV). Unfortunately, all attempts to convert **50** to the desired β-keto phosphonate resulted in exclusive β-elimination to triene ester **51**. While the desired β-ketophosphonate could be prepared from **50** following conversion to the aldehyde (vide infra), this route was regarded as inefficient, and an alternative synthesis was explored.

The reaction of (*Z*)-γ-(methoxymethyl)allylboronate **53** and chiral aldehyde **52** was performed (Scheme V). This reaction, as with other aldehyde addition reactions of γ-alkoxyallylboronates,[29] proved to be rather sluggish and was performed at 23 °C. The diastereoselectivity, 70:30 favoring **54**, is comparable to that previously obtained in the reaction of **52** with pinacol (*Z*)-crotylboronate.[30] Although this reaction was relatively nonselective, it proved useful in the long run by providing access to diastereomer **55** from which triene **22** was prepared.

The conversion of **54** and **55** to dienes **57** and **58** was usually performed on the unseparated mixture. Separation of the diastereomers was easily accomplished by chromatography at this stage. Unfortunately, it proved necessary to switch protecting groups in the conversion of **54** and **55** to **56** since selective removal of the primary TBDMS ether following introduction of the diene resulted in competitive removal of the side chain TBDPS ether.

Completion of the syntheses of trienes **21–23** proceeded as outlined below. Addition of dimethyl α-lithiomethylphosphonate to the aldehydes prepared from **57** and **58** produced a mixture of diastereomeric β-hydroxy phosphonates that were unstable even to TLC analysis. This instability complicated the subsequent oxidation to the target β-ketophosphonates **61** and **62** and was a major contributor to the poor overall yields. Use of K_2HPO_4

(29) (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1982**, *23*, 845; **1981**, *22*, 5263. (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498. (c) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Justus Liebigs Ann. Chem.* **1985**, 2246. (d) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353. (e) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575. (f) For a chiral γ-alkoxyallyborane, see: Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *Ibid.* **1988**, *110*, 1535.

(30) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316.

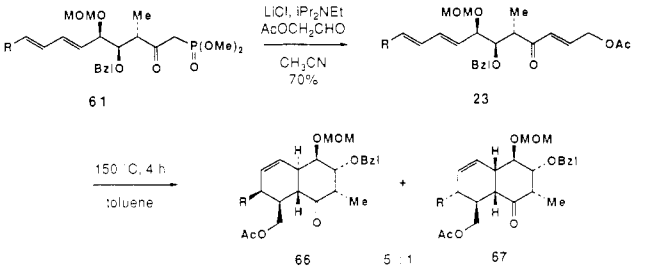
buffered PCC in the presence of 4-Å molecular sieves gave the most reproducible results in the oxidation step (Scheme VI).

Conversion of **61** to triene **21** proceeded smoothly, with the exception that the isomeric purity of the dienophile was poor. This was corrected by treatment of a CH_2Cl_2 solution of **21** with a catalytic amount of 2-thiopyridine.[31] A rapid cyclization ensued over 2–5 h at 23 °C, providing a 4:1 mixture of cycloadducts **63** and **64** in 80% overall yield from **61**. A third cycloadduct tentatively assigned structure **65** was also produced in <3% yield (Scheme VII).

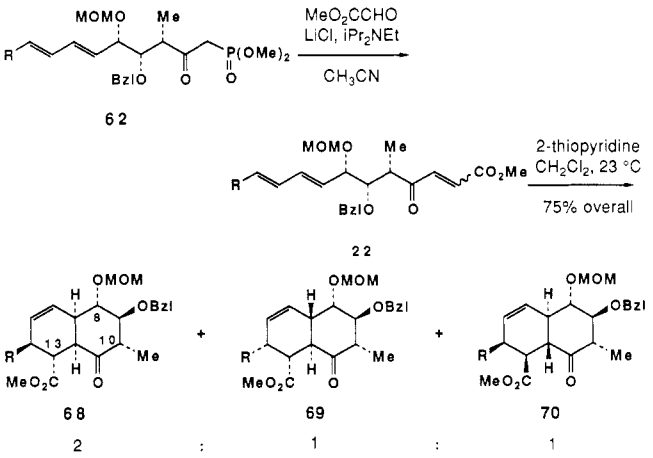
The stereochemistry of the major product, **63**, was assigned on the basis of the large coupling constants between H(7) and H(12), and H(12) and H(13) ($J_{7,12} = J_{12,13} = 12$ Hz), and small couplings ($J < 2$–3 Hz) between H(7)–H(8), H(8)–H(9), and H(9)–H(10). These data require that **72** possess a trans ring fusion and that the C(8) and C(9) alkoxyl groups occupy axial positions.

Cis-fused adduct **64** was identified with the aid of COSY 2D analysis and NOE difference techniques. The spectrum of **64** recorded in $CDCl_3$ shows the H(7), H(8), and H(9) signals possess small (<6 Hz) couplings to their neighbors. Unfortunately, unambiguous assignment of H(12), H(13), and H(10) was not possible, since they and H(7) appear in a narrow δ 3.10–2.90 window. In C_6D_6, the H(7) and H(10) signals collapse to a two proton multiplet, and H(12) and H(13) shift downfield but are obscured by the ester and MOM methoxyl signals. With CD_3OD as solvent all of these protons collapse to within a 0.1 ppm window. Satisfactory spectral dispersion was ultimately achieved in a mixed solvent system of 1:1 C_6D_6 and CD_3OD, in which H(7), H(12), H(13), and H(10) are free of overlap. COSY 2D analysis then provided a connectivity plot that shows H(13) to be the triplet at δ 3.23 ($J_{12,13} = J_{4,13} = 5.2$ Hz), and H(12) to be a doublet of doublets at δ 3.15 ($J_{12,13} = 5.2$ Hz, $J_{7,12} = 6.6$ Hz), clearly establishing that the ring fusion is cis. Finally, the cis relationship of H(10) and H(12) was established by difference NOE studies.

The predominance of a trans-fused cycloadduct in the cyclization of **21** prompted us to briefly examine the cyclization of **23** in order to probe the role of the CO_2Me group on the endo–exo stereoselectivity of these reactions. Thus, treatment of β-ketophosphonate **61** with acetoxyacetaldehyde under the usual Wadsworth–Horner–Emmons conditions provided **23** in 70% yield. This material was warmed to reflux in toluene for 18 h and then in a sealed tube at 150 °C for 4 h to give a 5:1 mixture of two cycloadducts **66** [trans-fused: $J_{7,12} = 11.0$ Hz; $J_{7,8} < 2$ Hz] and (presumably) **67** as indicated by ^{1}H NMR analysis. Unfortunately, all attempts to separate the two compounds were unsuccessful. Structure elucidation of **66** therefore rests on spectroscopic analysis of the mixture. Compound **67** could not be isolated in pure form and its structure remains unproven.



Triene **22** was prepared from **62** by the usual procedure. Solutions of crude **22** convert to cycloadducts within 1 h at 23 °C. Diels–Alder adducts **68** and **69** are readily separated from unreacted, geometrically impure triene by silica gel chromatography. The third product, **70**, coelutes with unconsumed, isomerically impure **22** and was isolated initially as a mixture. This fraction was briefly exposed to iodine (5 h) to consume residual triene and then rechromatographed to obtain a pure sample of **70**.



The stereochemistry of cycloadduct **68** was assigned with the aid of ^{1}H NMR double irradiation experiments that establish $J_{9,10} = 12.0$ Hz, $J_{8,9} = 9.0$ Hz, $J_{7,8} = 10.5$ Hz, and $J_{7,12} = 5.5$ Hz. The latter value defines the ring fusion to be cis. Diastereomer **70**, like **68**, possesses equatorial substituents at C(8), C(9), and C(10) [$J_{9,10} = 10.5$ Hz, $J_{8,9} = 9.0$ Hz, $J_{7,8} = 12.0$ Hz]. The ring fusion in this case, however, is trans as indicated by $J_{7,12} = 12.0$ Hz. The third cycloadduct was assigned structure **69** with a trans ring fusion on the basis of $J_{7,12} = 10$ Hz, $J_{12,13} = 10$ Hz, $J_{4,13} = 6$ Hz, and $J_{8,9} = J_{7,8} = \sim 2$ Hz.

Discussion

Although the Diels–Alder reactions of **19**–**23** failed to provide selective access to intermediates of potential use

(31) Asaoka, M.; Yanagida, N.; Sugimura, N. Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061.

(32) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1966; p 469–474.

(33) (a) Lowe, J. P. *Prog. Phys. Org. Chem.* **1968**, *6*, 1. (b) Krisher, L. C.; Saegebarth, E. *J. Chem. Phys.* **1971**, *54*, 4553. (c) Wilson, E. B. *J. Adv. Chem. Phys.* **1959**, *2*, 367.

(34) The true boat conformation of cyclohexanone is 5.6 kcal mol^{-1} higher in energy than the chair conformation and has two eclipsed ethane units. One of these, however, is eliminated as the system relaxes into the twist boat form. For a discussion, see ref 32.

(35) Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 5817.

(36) Recent experimental work using ultrasonic dispersion techniques has obtained values of conformational relaxation from the boat to chair form of cyclohexanone as follows: $\Delta G° = 0.82$, $\Delta H° = 2.37$ kcal/mol, and $\Delta S° = 4.53$ cal/mol/K. See: Reddy, B. A.; Gopal, K.; Rao, N. P. *Indian J. Pure Appl. Phys.* **1982**, *20*, 37.

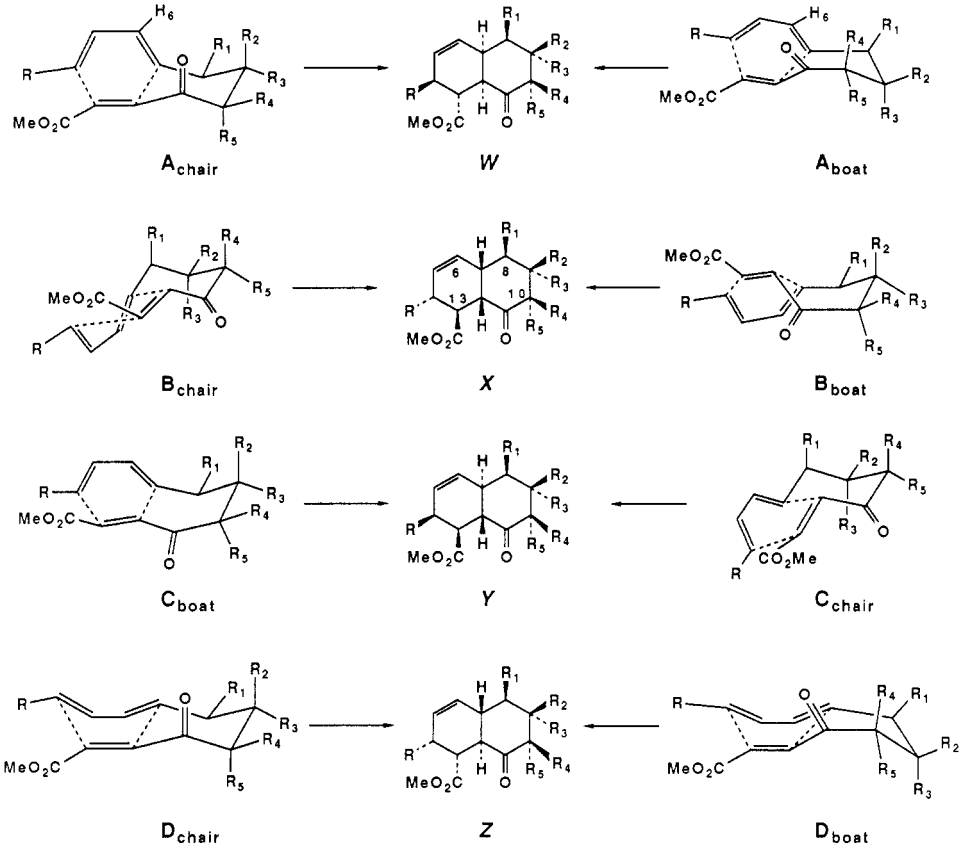
(37) (a) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5545. (b) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609. (c) For a recent summary of theoretical work on Diels–Alder transition states, see: Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

(38) For structure determination of 1-butene by physical methods, see: (a) Van Hemelrijk, D.; Van den Enden, L.; Geise, H. J.; Sellers, H. L.; Schafer, L. *J. Am. Chem. Soc.* **1980**, *102*, 2189. For theoretical treatment see: (b) Wiberg, K. B.; Schreiber, S. L. *J. Org. Chem.* **1988**, *53*, 783 (and ref 5 cited therein). (c) Tosi, C. *J. Mol. Struct. (Theochem)* **1984**, *110*, 23 and references cited therein.

(39) Each of the transition state structures (ii, iii, v, vi, viii, ix, xi, and xii) discussed in this section has been modeled by using MMX.[27] A table of torsional angles appears in the supplementary material that support the geometric arguments presented in text. These calculations show that the "eclipsed ethane" units present in decatriene transition states cis_{boat} (ii) and $trans_{boat}$ (viii) are not localized at C(3)–C(4) but are actually distributed over C(3)–C(5), much as the two eclipsed ethanes in twist-boat cyclohexane are not formally localized at specific C–C bonds.[32]

(40) Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269.

Scheme VIII. Transition States for Decatrienones 7 and 19–23



Trienes	Cycloadducts
7: R_1 and R_3 = $OC(Me)_2O$; R_5 = Me; R_2 = R_4 = H	X = 9
19: R_1 and R_3 = $OC(Me)_2O$; R_4 = Me; R_2 = R_5 = H	W = 34, X = 32, Z = 33
20: R_1 and R_2 = $OC(Me)_2O$; R_4 = Me; R_3 = R_5 = H	X = 24, Y = 44, Z = 45
21: R_1 = OMOM; R_3 = OBzl; R_5 = Me; R_2 = R_4 = H	X = 64, Y = 63, Z = 65
22: R_1 = OMOM; R_3 = OBzl; R_4 = Me; R_2 = R_5 = H	X = 68, Y = 69, Z = 70
23: substituents are the same as 21	X = 67, Y = 66

as nargenicin precursors, we were intrigued by the complexity of the results. Among several other unexpected observations, we were surprised that the high selectivity for cis octalin products exhibited by simple 1,7,9-decatriene-3-ones,[10,11] or even **7**, is not seen in the cyclizations of **19–23**, as we had assumed would be the case. From a detailed analysis of possible transition states (see Table I and Scheme VIII) we have identified several factors that contribute to these results. A near-complete stereochemical series has been examined, and consequently the effects of substituents on the various transition states can be determined with some certainty. As will be shown in the following discussion, boatlike transition states must be invoked to rationalize many of the results. We conclude that all other factors being equal, cis-fused boatlike transition states are the lowest energy pathway available in decatrien-3-one intramolecular Diels–Alder reactions.

Transition-State Analysis. Analysis of the transition states available to trienes **7** and **19** is relatively straightforward since only four are possible (Scheme VIII). Inspection of these clearly reveals that the axial C(10)-methyl group destabilizes transition states $\mathbf{7A}_{chair}$ and $\mathbf{7D}_{chair}$, as originally suspected, since $\mathbf{19A}_{chair}$ and $\mathbf{19D}_{chair}$ with equatorial C(10)-methyl groups contribute 20% and 33% of the products in the cyclization of **19**. The absence of products from the trans-fused, boatlike "$\mathbf{C}_{boat}$" transition state in both series may reflect a steric interaction between H(6) and H(9)[13] or strain that would develop if the reaction were to proceed to the (unobserved) products. Analysis of molecular models of transition states $\mathbf{7C}_{boat}/\mathbf{19C}_{boat}$ suggests that considerable strain resulting from the trans dioxolane unit is translated into the connecting chain in orientations that provide optimal geometry for the

Table I. Intramolecular Diels–Alder Reactions of Trienes 7 and 19–23: Product Distribution as a Function of Transition State[a,b]

transition states	trienes, %					
	7	**19**	**20**	**21**	**22**	**23**
$\mathbf{A}_{chair}$	0	20	0	0	0	0
$\mathbf{A}_{boat}$	na[c]	na[c]	0	0	0	0
$\mathbf{B}_{chair}$	na	na	0	0	0	0
$\mathbf{B}_{boat}$	>95	47	40	19	50	17
$\mathbf{C}_{chair}$	na	na	0	*d*	0	*d*
$\mathbf{C}_{boat}$	0	0	47	78[d]	25	83[d]
$\mathbf{D}_{chair}$	0	33	13	3	25	0
$\mathbf{D}_{boat}$	na	na	0	0	0	0

[a] The intramolecular Diels–Alder reactions were performed in toluene or CH_2Cl_2. Reaction conditions are as follows: **7**, 110 °C, 22 h; **19**, 23 °C, 6 days; **20**, 23 °C, 60 h; **21**, 23 °C, 2 h; **22**, 23 °C, 1 h; and **23**, 150 °C, 4 h. [b] Product ratios were determined by ^1H NMR analysis of crude reaction mixtures. [c] Na indicates that the transition state is not accessible. The acetonide protecting group precludes cyclization from transition states with diaxial C(8) and C(9) alkoxy groups. [d] Transition states $\mathbf{C}_{boat}$ and $\mathbf{C}_{chair}$ both probably contribute to the production of **63** (from **21**) and **66** (from **23**); the percentages listed under "$\mathbf{C}_{boat}$" is thus the total product arising from this set of transition states. Molecular mechanics calculations of transition states with a 0.05 bond order, however, indicate that $\mathbf{21C}_{boat}$ is lower in energy than $\mathbf{21C}_{chair}$.

Diels–Alder reaction. In any event, the results with **19** provide a striking demonstration that a boatlike transition state ($\mathbf{19B}_{boat}$) is favored even in competition with relatively strain free chairlike arrangements ($\mathbf{19A}_{chair}$ and $\mathbf{19D}_{chair}$). In retrospect, the very high stereoselectivity realized in the cyclization of **7** is a consequence of the intrinsic preference for the boat transition state ($\mathbf{7B}_{boat}$) along with the fortuitous destabilization of transition states $\mathbf{7A}_{chair}$ and $\mathbf{7D}_{chair}$ by the axial methyl group.

Trienes **20–23** present a more complex analytical problem as eight, and not four, transition states must be considered. The absence of the acetonide unit permits transition states with trans-diaxial C(8) and C(9) alkoxyl groups in the cyclizations of **21–23** that were not possible with **7** and **19**. The presence of the cis dioxolane in **20** allows greater conformational flexibility, and here also chair and boat transition states must be considered for each potential product.

We begin with the cyclizations of **21** and **22** since this permits the role of the acetonide blocking group on the results for **7** and **19** to be assessed. In the case of **22**, it is most likely that the major product, **68** (50%), arises from boat transition state $\mathbf{22B}_{boat}$ since the alternative, $\mathbf{22B}_{chair}$, suffers from three destabilizing nonbonded interactions: those between C(9)-OBzl and C(6)-H,[13] between C(10)-Me and C(8)-OMOM, and between C(10)-Me and C(12)-H. Transition state $\mathbf{22C}_{chair}$ possesses similar destabilizing interactions involving C(10)-Me, and so it is probable that the second most abundant product, **69** (25% of total), arises from boatlike transition state $\mathbf{22C}_{boat}$. Thus, 75% of the products deriving from the cyclization of **22** likely arise from boat transition states. It is notable that the corresponding product was not produced from $\mathbf{19C}_{boat}$, suggesting indeed that the acetonide linkage strains transition states $\mathbf{7C}_{boat}/\mathbf{19C}_{boat}$ as previously suggested. The third product, **70**, most likely derives from transition state $\mathbf{22D}_{chair}$ since $\mathbf{22D}_{boat}$ has several serious steric interactions, including that between C(8)-OMOM and C(10)-Me and possibly also a flagpole interaction between C(12)-H and C(9)-OBzl.

The product distribution shifts substantially in the cyclization of **21** relative to **22**. Transition state $\mathbf{22D}_{chair}$, responsible for 25% of the product from **22**, is rendered almost totally inaccessible by the movement of the C(10)-Me to an axial position in $\mathbf{21D}_{chair}$; transition state $\mathbf{21D}_{boat}$ retains the destabilizing C(12)-H/C(9)-OBzl flagpole interaction and is probably not involved in the generation of **65**, which is a very minor product (3%) of this reaction. Considerably less product also arises from the "**B**" series transition states with **21** than **22**. This may be the consequence of a gauche interaction that develops in transition state $\mathbf{21B}_{boat}$ between the C(10)-Me and C(9)-OBzl that is absent in $\mathbf{22B}_{boat}$. Although the 1,3-diaxial interaction between the C(10)-Me and C(8)-OMOM, present in $\mathbf{22B}_{chair}$, is relieved in $\mathbf{21B}_{chair}$, this transition state still suffers from the unfavorable interaction between C(6)-H and the axial C(9)-OBzl group.[13] Consequently, it is likely that $\mathbf{21B}_{chair}$ contributes less to the production of **64** than $\mathbf{21B}_{boat}$. Finally, the "**C**" series transition states contribute substantially more product from **21** (78%) than **22** (25%). In this case, transition state $\mathbf{21C}_{chair}$ is more stable than $\mathbf{22C}_{chair}$ since the diaxial interaction between C(10)-Me and C(8)-OMOM present in $\mathbf{22C}_{chair}$ is relieved. It is likely that $\mathbf{21C}_{boat}$ and $\mathbf{21C}_{chair}$ both contribute to the production of **63** in this reaction, although MMX calculations with a 0.05 bond order (hence, a reactant like transition state) suggest that $\mathbf{21C}_{boat}$ is lower in energy.[41]

The predominance of trans-fused cycloadduct **63** in the cyclization of **21**, requiring that the CO_2Me group is positioned in an endo position with respect to the diene in both transition states $\mathbf{21C}_{boat}$ and $\mathbf{21C}_{chair}$, prompted us to examine briefly the cyclization of **23** in order to probe the role of the CO_2Me group on the stereoselectivity of this reaction. A 5:1 mixture of two products, **66** and (presumably) **67**, was obtained with the major one (**66**) deriving from transition states analogous to $\mathbf{21C}_{boat}$ and/or $\mathbf{21C}_{chair}$, in which the carbonyl activating group is positioned exo with respect to the diene. We conclude, therefore, that stabilizing endo interactions involving the CO_2Me group are not responsible for the predominant trans stereoselectivity of this reaction.

The final triene examined is **20**. While our original analysis was correct in predicting that **24** would be the only cis-fused cycloadduct formed (via transition state $\mathbf{20B}_{boat}$), we were misled in thinking that the high cis-fusion selectivity of simple decatrienones[10,11] would be general for more highly substituted systems. Trans-fused cycloadduct **44** undoubtedly derives from transition state $\mathbf{20C}_{boat}$, owing to the 1,3-interactions involving the axial C(10)-Me group that seriously destabilize the chair alternative $\mathbf{20C}_{chair}$, while the minor trans-fused product **45** most likely arises from transition state $\mathbf{20D}_{chair}$. This result again underscores the competitiveness of boatlike transition states (e.g., $\mathbf{20B}_{boat}$, $\mathbf{20C}_{boat}$) even when a seemingly superior trans-fused chair transition state is available (e.g., $\mathbf{20D}_{chair}$).

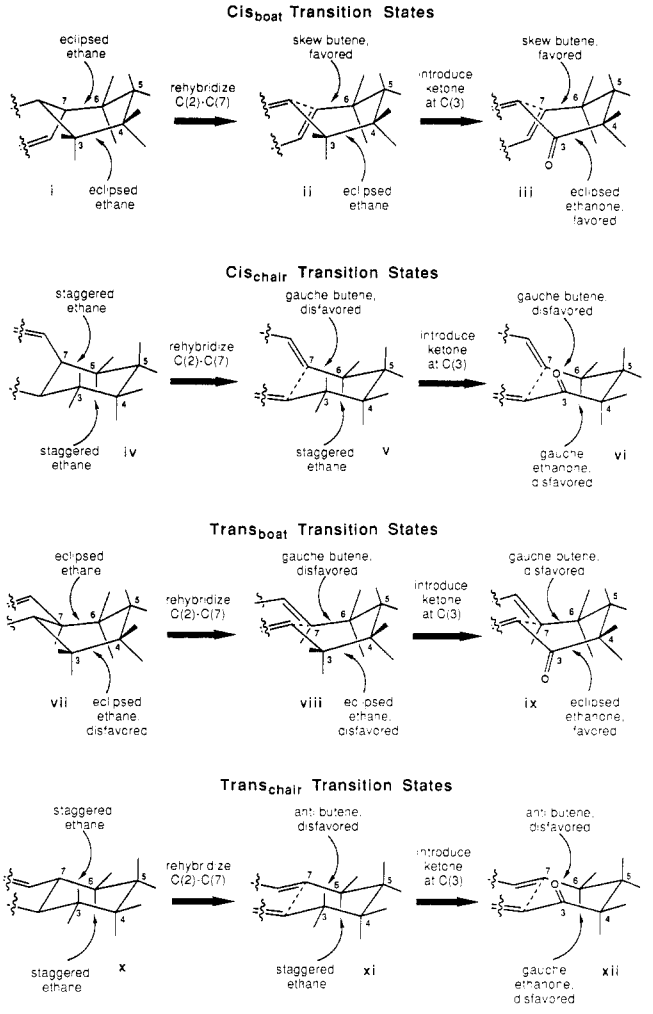
Rationalization of the Accessibility of Boat Transition States in Decatrienone Cyclizations. The cyclizations of trienes **7** and **19–23** provide firm evidence that boat transition states are highly competitive in decatrien-3-one cyclizations, as graphically illustrated by the data summarized in Table I. This conclusion conflicts with "conventional wisdom" that the chair transition states should be lower in energy than the boatlike arrangements. Thus, a detailed reexamination of the conformational and enthalpic features of these systems is warranted. We have developed a model, supportive of our experimental results, that suggests that in the absence of overriding steric or other nonbonded interactions the cis-fused, boatlike transition state should be favored in decatrienone cyclizations.

It is instructive to begin with a brief discussion of the destabilizing interactions in boat cyclohexane and cyclohexanone and then work backwards into the intramolecular Diels–Alder transition state, following the principle of microscopic reversibility, to assess the nature of any stabilizing or destabilizing interactions that may be present. The lowest energy twist-boat conformation of cyclohexane is 5.3 kcal mol^{-1} less stable than the chair conformation.[32] It is useful to think of the destabilization of boat cyclohexane as arising formally from two eclipsed ethane units.[32,33] Replacement of one of the methylene groups of cyclohexane with the carbonyl present in cyclohexanone stabilizes the boat conformation by replacing one of the eclipsed ethane units with a favorable eclipsed ethanone linkage.[34,35] The strain remaining in twist-boat cyclohexanone (ca. 3.0 kcal mol^{-1}, vide supra) is very close to the value of a single eclipsed ethane unit (i.e., 2.85 kcal mol^{-1}).[32,34]

Considerable evidence suggests that the Diels–Alder transition state is early, or reactant-like, rather than late.[15a,37] All possible boatlike conformations of the con-

(41) For related computational approaches to the analysis of intramolecular Diels–Alder transition states, see ref 37b and Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 2674.

Scheme IX



necting chain in the boatlike transition states therefore must be less strained than in ground-state boat cyclohexane or boat cyclohexanone since, if one moves backwards along the reaction coordinate from product to transition state, the C–C bonds formed in the reaction lengthen and the carbon atoms take on more p character. These reacting termini should exhibit conformational behavior reflective of sp^2 hybridization prior to Diels–Alder bond formation, a factor that undoubtedly has a pronounced effect on the stability of the various transition states (vide infra).

The picture that emerges for decatriene and decatrienone intramolecular Diels–Alder reactions is as follows. As the boatlike cis-fused product-conformer (i) rehybridizes into the boatlike decatriene transition state (ii), one of the destabilizing eclipsed ethane linkages (at C(6)–C(7)) is eliminated (Scheme IX). A preferred, skewed rotamer of this butene segment of the triene results.[38] One eclipsed ethane linkage remains in the decatriene transition state ii (formally localized at C(3)–C(4)),[39] destabilizing this structure by ca. 2.85 kcal mol^{-1}. This destabilization can be alleviated by rehybridization at C(3), such as in the decatrienone transition state iii, where the boatlike conformer now exhibits a favorable "eclipsed ethanone" alignment between C(3) and C(4).[35] Consequently, the destabilizing interactions of ground-state boat cyclohexanone are absent from transition state iii, which is devoid of any destabilizing eclipsing and nonbonded interactions. In this and all other decatrienone transition states, the C(4)–C(6) segment is nearly fully staggered.[39]

The stereochemically related cis-fused chairlike structures (i.e., iv) possess staggered relationships between all sp^3 atoms of the connecting chain in the decatriene and decatrienone transition states (v and vi, respectively), undoubtedly contributing to the arguments and assumptions commonly advanced supporting the inherent stability of chair transition states. However, when rehybridized into the transition state (v), the beneficial staggered orientations in the product (iv) are replaced by a less favorable gauche orientation of the C(6)–C(7) butene linkage in the decatriene transition state v. Although the conformation of the C(3)–C(4) segment is staggered (favored) in v, this unit is replaced by a less stable gauche ethanone linkage in the decatrienone transition state vi, where beneficial eclipsing between C(3) and C(4) is less easily attained. Thus, to the extent that the "eclipsed ethanone" and "skew butene" rotamers are able to stabilize a transition state, products should be observed from the cis-boat rather than cis-chair decatrienone arrangements.

While the cis-fused boatlike decatrienone transition state exhibits favorable sp^2–sp^3 conformational relationships at two sites, rotation of the diene into the trans-fused boatlike conformer eliminates the favored skew butene stabilization in the decatriene/decatrienone transition states viii and ix. The diene and the C(5)–C(6) bond now occupy a less favorable gauche relationship compared to the skew relationship in ii and iii. The C(3)–C(4) orientation again parallels that of the cis-fused boatlike system,[39] the eclipsed ethane unit destabilizing the decatriene transition state (viii) by ca. 2.85 kcal mol^{-1}, and the eclipsed ethanone unit providing overall stabilization to the dienophilic portion in the decatrienone transition state ix. The ability of the skew butene to stabilize a transition state is demonstrated in the cyclization of triene **22**, where a 2:1 mixture of cis- and trans-fused products were formed via boatlike conformations $\mathbf{22B}_{boat}$ (cis) and $\mathbf{22C}_{boat}$ (trans), respectively.

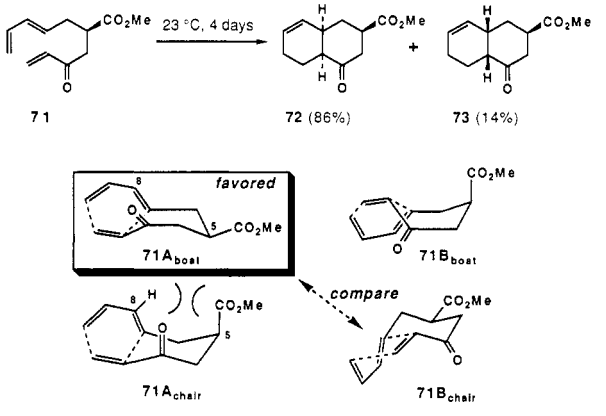
The final set of transition states to be considered are the trans-fused chairlike arrangements. As is the case in the cis-fused chair manifold, all sp^3 hybridized connecting chain atoms adopt staggered relationships with their neighbors in transition states xi and xii. Rehybridization of x into the decatriene transition state (xi) requires that the diene adopt a disfavored anti relationship with the C(5)–C(6) bond. It has been determined experimentally that cis-fused product formation is enthalpically favored by 0.3 kcal mol^{-1},[40] possibly reflecting the greater stability of the gauche relationship of the olefinic–dienylic position in the cis-fused, chair transition state v compared to the anti arrangement in xi. In decatrienone transition state xii both the sp^2–sp^3 linkages adopt unfavorable conformations, and one would expect this to be among the least accessible of the four decatrienone transition states.

It must be stressed that as the boatlike Diels–Alder reactions progress the product will become fully destabilized by the eclipsed ethane interactions that develop. Because the transition state is early, however, this destabilization should have only minor effect on the course of the reaction. The reaction exothermicity (ΔH ~−34 kcal/mol) provides a driving force that should greatly outweigh the destabilization experienced after the reactive centers rehybridize from sp^2 to sp^3. In other words, bond formation during a Diels–Alder reaction should be unaffected by a 2–3 kcal/mol eclipsed ethane interaction experienced only after the majority of bonding has occurred. Thus, the destabilization that develops in the boat conformation of the product as more sp^3 character develops during the bond-forming process is inconsequential when the diene and dienophile are still primarily sp^2 hybridized early along the reaction coordinate.

These arguments provide a qualitative basis for understanding the involvement of boat transition states in the cyclizations of 7 and 19–23. These reactions, however, are very complex, and the difference in energy between competing transition states is too small in most cases to justify a detailed discussion of relative stabilities (e.g., $\mathbf{19A}_{chair}$ or $\mathbf{19B}_{boat}$ vs $\mathbf{19D}_{chair}$; $\mathbf{20B}_{boat}$ vs $\mathbf{20C}_{boat}$; $\mathbf{22C}_{boat}$ vs $\mathbf{22D}_{chair}$; etc.). Clearly, nonbonded interactions such as those already enumerated, or additional ones such as the possible H(6)–H(9) interaction in $\mathbf{19A}_{chair}$, may influence the stability of an individual transition state and tip the balance such that a chair or a boat may be favored, depending on the exact stereochemical makeup of the system.

Nevertheless, a very significant conclusion of this analysis is that in the absence of overriding nonbonded interactions a boatlike decatrienone cyclization transition state should be favored over the more usually invoked chairlike arrangement. This statement is supported by the greater stability of $\mathbf{19B}_{boat}$ over $\mathbf{19A}_{chair}$ and of $\mathbf{20C}_{boat}$ relative to $\mathbf{20D}_{chair}$. The comparable stability of transition states $\mathbf{22C}_{boat}$ and $\mathbf{22D}_{chair}$ is also notable. Moreover, decatrienone cis-fused transition states should be favored over trans-fused ones, since each of the cis-fused structures has a greater number of stabilizing sp^2–sp^3 interactions than the corresponding trans-fused isomer.

A striking illustration of these arguments is provided by the cyclization of 71 that gives a 86:14 mixture of cis-fused cycloadducts 72 and 73.[14c] Undoubtedly, the major product 72 arises from boatlike transition state $\mathbf{71A}_{boat}$ since the alternative chairlike arrangement, $\mathbf{71A}_{chair}$, is significantly destabilized by interactions between C(8)-H and C(5)-CO_2Me.[13] The minor product, 73, derives either from the chair transition state $\mathbf{71B}_{chair}$, containing an equatorial CO_2Me group, or from the boat transition state $\mathbf{71B}_{boat}$ with an axial CO_2Me unit. Ordinarily, of course, one would assume that $\mathbf{71B}_{chair}$ would be lower in energy than $\mathbf{71A}_{boat}$. That it is not attests to the validity of the arguments that favorable eclipsing sp^2–sp^3 interactions are stabilizing to those transition states that possess them.



Summary

The involvement of boatlike transition states in decatrienone intramolecular Diels–Alder reactions appears to be general. In the absence of overriding substituent effects, the boat transition state is free of destabilizing eclipsing or other unfavorable nonbonded steric interactions. In such cases the boat transition state in the cis-fused manifold is favored over the chairlike arrangement as a consequence of a stabilizing eclipsing sp^3–sp^2 interaction between the diene and the allylic C–H bond that is absent in the chair. While the factors that govern absolute levels of selectivity for cis- vs trans-fused products in these reactions are not obvious, it is clear that interactions involving substituents on the chain linking the diene and dienophile can tip the balance in either direction. One interaction that is highly destabilizing in chairlike decatrienone transition states is the placement of a methyl, or presumably any other bulky group, in an axial position at C(4) [C(10) in the nargenicin numbering system].

Our analysis also indicates that chair transition states should be favored over the boatlike arrangements in decatriene cyclizations since the boat transition state structures are destabilized by one eclipsed ethane unit. The difference in energy between the chair and boat transition states, however, is small enough (ca. 3 kcal mol^{-1}) that involvement of boat transition states may be observed in cases where a trans-fused transition state is sufficiently destabilized by nonbonded steric interactions. Based on our analysis of the diene–dienylic rotamer situation, we would expect the involvement of boatlike transition states to be more likely in the cis-fused manifold.

Experimental Section

General Procedures. Proton (^{1}H) NMR chemical shifts are reported in δ units using the 7.24 ppm resonance of residual chloroform as internal reference or the 7.15 ppm resonance of residual C_6D_6 as internal standard in mixed solvent systems.

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, benzene, and toluene were distilled from sodium benzophenone ketyl. Hexane was distilled from sodium benzophenone ketyl in the presence of tetraglyme (Aldrich). Methylene chloride was distilled from CaH_2.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.5-mm thickness of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid, or *p*-anisaldehyde/H_2SO_4 or by staining with iodine vapor. Unless noted otherwise, all compounds purified by chromatography are sufficiently pure (≥95% by ^{1}H NMR analysis) for use directly in subsequent preparative reactions.

Synthesis of 12. A solution of the chiral crotylboronate (*S,S*)-11 (20 g, crude preparation, theoretically 67 mmol)[17] in toluene (220 mL) was treated with powdered 4-Å molecular sieves (10 g, Aldrich) at 23 °C for 30 min, and then the dispersion was cooled to −78 °C. D-Glyceraldehyde acetonide 10 (5.25 g, 40 mmol, prepared by $NaIO_4$ cleavage of mannitol diacetonide in aqueous THF)[42] was added as a solution in toluene (10 mL) from a dropping funnel over a 30-min period. The reaction was allowed to stir for an additional 1.5 h at −78 °C. The cooling bath was removed, and the mixture was saponified by the addition of aqueous 1 N NaOH (135 mL) to the cold reaction mixture. After ambient temperature was reached, the mixture was stirred for an additional 20 min. The toluene layer was separated and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo (50 mmHg, 50 °C). The combined aqueous extracts were extracted with ether (3 × 100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), concentrated, and combined with the toluene extracts. The crude product was chromatographed on silica gel (a 2.5 × 7-in. column packed with 70–230 mesh silica gel) to provide 12 (5.78 g, 78%, >95% purity by GC), that was identical in all respects with authentic material.[17,23]

Acetonide Isomer 13. To a 1 M solution of 12 (4.0 g, 21.5 mmol) in dry acetone (K_2CO_3 dried) under argon was added

(42) Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841.

p-TsOH (2.0 mg, 0.05%). This solution was stirred for 48 h at 23 °C, $NaHCO_3$ (10 mg) was introduced, and the acetone was removed in vacuo. Purification of the crude product by chromatography on silica gel yielded homogeneous **13** (3.0 g, 75%) and 1.0 g of a mixed fraction that was resubjected to the original reaction conditions, yielding additional **13** (0.75 g, 19%): R_f 0.30 (5:2 hexane–ether); $[\alpha]^{20}_D$ +29.6° (c = 1.19, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$ + D_2O) δ 5.83 (ddd, J = 8.0, 11.0, 17.0 Hz, 1 H, H_5), 5.06 (d, J = 11.0 Hz, 1 H, H_{6Z}), 5.04 (d, J = 17.0 Hz, 1 H, H_{6E}), 3.87 (m, 1 H, H_2), 3.78 (m, 2 H, $H_{1A,3}$), 3.55 (dd, J = 5.0, 12.0 Hz, 1 H, H_{1B}), 2.37 (m, 1 H, H_4), 1.39 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.07 (d, J = 7.0 Hz, 3 H, methyl); IR (neat) 3445, 3075, 2980, 2930, 2875, 1635, 1453, 1370, 1240, 1215, 1040, 905, 850 cm^{-1}; mass spectrum, m/e 171 ($M^+ - CH_3$). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.47; H, 9.74. Found: C, 64.39; H, 10.01.

Hydroxy Ester 14. Alkene **13** (3.0 g, 16.1 mmol) was dissolved in 40 mL of dry methanol and cooled to −78 °C under a stream of dry O_2. Ozone was introduced until the solution became gray-blue. After removal of excess ozone, Me_2S was introduced (1.5 mL), and the cooling bath was removed. After 1–2 h the solution was negative to starch–KI paper, and the methanol was removed in vacuo to provide a crude aldehyde that was used without purification in the next step: ^1H NMR (250 MHz, $CDCl_3$) δ 9.76 (d, J = 3.0 Hz, 1 H, H_1), 4.10 (dd, J = 7.0, 8.0 Hz, 1 H, H_3), 3.98 (ddd, J = 8.0, 4.5, 4.0 Hz, 1 H, H_4), 3.85 (AB dd, J = 12.5, 4.0 Hz, 1 H, H_{5A}), 3.73 (AB dd, J = 12.0, 4.5 Hz, 1 H, H_{5B}), 2.60 (m, 1 H, H_2), 1.40 (s, 6 H, acetonide), 1.16 (d, J = 7.0 Hz, 3 H, methyl).

The above aldehyde (4.3 g, theoretically 16.1 mmol) was azeotropically dried from CH_2Cl_2 (3 × 30 mL) and then dissolved in 40 mL of CH_2Cl_2. Treatment of this solution with MCPBA (6.64 g, 85% purity, 32.7 mmol) was initially exothermic. The resulting mixture was stirred vigorously until no aldehyde remained (1 h, TLC analysis, *p*-anisaldehyde stain). The slurry was then cooled to 0 °C, filtered to remove *m*-chlorobenzoic acid, and treated directly with ethereal CH_2N_2 until a yellow color persisted. Acetic acid was added dropwise to consume excess CH_2N_2, and then the mixture was concentrated in vacuo to give an oily white solid. This material was purified by chromatography (silica gel, 3:2 ether–hexane to remove methyl chlorobenzoate followed by 100% ether to elute product), yielding 3.4 g (97%) of pure **14**: R_f 0.25 (2:1 ether–hexane); $[\alpha]^{23}_D$ +24.8° (c = 1.36, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 4.10 (t, J = 8.0 Hz, 1 H), 4.00 (m, 1 H), 3.78 (dd, J = 12.0, 6.0 Hz, 1 H), 3.71 (s, 3 H, ester), 3.62 (m, 1 H), 3.54 (m, 1 H), 2.76 (m, 1 H, H_2), 1.39 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.18 (d, J = 8.0 Hz, 3 H, methyl); IR (neat) 3450, 2982, 2945, 2880, 1725, 1380, 1370, 1258, 1210, 1055 cm^{-1}; mass spectrum, m/e 171 ($M^+ - CH_3$); high-resolution mass spectrum for $C_9H_{15}O_3$ calcd 203.0919, found 203.0919.

Aldehyde 15. To a −78 °C solution of $(COCl)_2$ (2.0 mL, 23 mmol) in dry CH_2Cl_2 (20 mL) under argon was added DMSO (2.6 mL, 36.7 mmol). After 5 min, a −78 °C solution of **14** (2.0 g, 9.2 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The resulting white slurry was stirred for 10 min, and then Et_3N (6.4 mL, 46 mmol) was introduced dropwise over 3 min. The solution, containing a thick white precipitate, was diluted with an additional 20 mL of CH_2Cl_2, and the cooling bath was removed. After ambient temperature was reached, the mixture was diluted with water (20 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (4 × 75 mL) and dried by filtration through cotton. Concentration in vacuo yielded crude **15** (1.98 g, ~100%) that was used in the next step without purification: ^1H NMR (250 MHz, $CDCl_3$) δ 9.73 (d, J = 2.0 Hz, 1 H, H_5), 4.35 (t, J = 7.0 Hz, 1 H, H_3), 4.19 (dd, J = 2.0, 7.0 Hz, 1 H, H_4), 3.73 (s, 3 H, ester), 2.82 (m, 1 H, H_2), 1.50 (s, 3 H, acetonide), 1.41 (s, 3 H, acetonide), 1.22 (d, 3 H, J = 6.0 Hz, methyl).

Diene 17. A stirred slurry of phosphonium salt **16** (1.39 g, 2.05 mmol) in dry THF (25 mL) at −78 °C under argon was treated with *n*-BuLi (1 equiv in hexane). The cooling bath was removed, and the mixture was warmed to 0 °C and maintained until a homogeneous blood red solution resulted (~15 min). The solution was recooled to −78 °C, and then a precooled solution of **15** (435 mg, 2.0 mmol) in THF (2 mL) was added via cannula to generate a yellow mixture that was allowed to warm to 23 °C. Hexane (30 mL) was added, and the reaction mixture was filtered through a 2-in. plug of silica gel with use of 50% ether/hexane (100 mL) as eluent. The concentrated filtrate (950 mg, 89%) was chromatographed on silica gel to yield a clear oil (747 mg, 70%) that was a 7:1 mixture of (*Z*,*E*):(*E*,*E*) dienes as determined by ^1H NMR analysis.

The geometrically impure diene was azeotropically dried from THF (30 mL) and then dissolved in dry hexane (20 mL) under argon. I_2 (7 mg) was added, and the purple solution was stirred for 1–2 days at 23 °C. The reaction was quenched by rapid addition into a vigorously stirred mixture of ether, saturated aqueous $NaHCO_3$, and saturated aqueous $Na_2S_2O_3$ (20 mL each). The aqueous layer was separated and extracted with ether (50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to give (*E*,*E*)-diene **17** (725 mg, 68% yield from **15**). The isomeric purity of **17** so obtained was ~10:1 (*E*,*E*):(*E*,*Z*) as determined by ^1H NMR analysis. This material was used as such in the following reaction: R_f 0.42 (2:1 hexane–ether); $[\alpha]^{23}_D$ +14.4° (c = 2.85, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 6.24 (dd, J = 10.5, 15.0 Hz, 1 H, H_6), 6.04 (dd, J = 10.5, 15.0 Hz, 1 H, H_5), 5.69 (dt, J = 15.0, 7.0 Hz, 1 H, H_4), 5.47 (dd, J = 8.0, 15.0 Hz, 1 H, H_7), 4.24 (t, J = 8.0 Hz, 1 H, H_8), 3.91 (t, J = 8.0 Hz, 1 H, H_9), 3.66 (s, 3 H, ester), 3.65 (t, J = 6.0 Hz, 2 H, H_1), 2.72 (m, 1 H, H_{10}), 2.15 (m, 2 H, H_3), 1.62 (m, 2 H, H_2), 1.39 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 1.14 (d, J = 7.0 Hz, 3 H, methyl), 1.04 (s, 9 H, *tert*-butyl); IR (neat) 3068, 2982, 2933, 2855, 2741, 1660, 1580, 1428, 1380, 1168, 1110, 990, 700 cm^{-1}; mass spectrum, m/e 479 ($M^+ - C_4H_9$). Anal. Calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26. Found: C, 71.89; H, 8.03.

Triene 7. A −78 °C solution of dimethyl methylphosphonate (735 μL, 7.0 mmol) in dry THF (15 mL) under argon was treated with *n*-BuLi (5.73 mmol in hexane). This mixture was stirred for 40 min, and then a solution of **17** (1.0 g, 1.74 mmol) in THF (4.0 mL) was added dropwise over 5 min. TLC analysis indicated that the reaction was complete within 10 min. Saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was warmed to 23 °C. It was then diluted with CH_2Cl_2 (100 mL) and extracted with saturated aqueous $NaHCO_3$ (50 mL). The organic extracts were filtered through a cotton plug and concentrated in vacuo to give a yellow oil. High-vacuum removal of excess dimethyl methylphosphonate gave the crude β-ketophosphonate (1.12 g, 97%) that was used in the next step without purification: R_f 0.26 (EtOAc); $[\alpha]^{23}_D$ 28.4° (c = 2.1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 6.25 (dd, J = 10.5, 15.0 Hz, 1 H, H_6), 6.04 (dd, J = 10.5, 15.0 Hz, 1 H, H_5), 5.70 (dt, J = 15.0, 7.0 Hz, 1 H, H_4), 5.46 (dd, J = 8.0, 15.0 Hz, 1 H, H_7), 4.18 (dd, J = 8.0, 6.0 Hz, 1 H, H_8), 3.77 (d, J_P = 11.0 Hz, 6 H, methoxyls), 3.70 (m, 1 H, H_9), 3.63 (t, J = 6.0 Hz, 2 H, H_1), 3.38 (dd, J_{AB} = 13.5 Hz, J_P = 21.5 Hz, 1 H, H_{12}), 3.15 (dd, J_{AB} = 13.5 Hz, J_P = 21.5 Hz, 1 H, H_{12B}), 3.05 (m, 1 H, H_{10}), 2.17 (m, 2 H, H_3), 1.65 (m, 2 H, H_2), 1.40 (s, 3 H, acetonide), 1.35 (s, 3 H, acetonide), 1.01 (s, 9 H, *tert*-butyl), 1.01 (d, J = 6.0 Hz, 3 H, methyl); IR (neat) 3070, 2930, 2855, 1715, 1630, 1585, 1465, 1430, 1380, 1250, 1110, 1030, 705 cm^{-1}; mass spectrum, m/e 628 (parent ion). Anal. Calcd for $C_{34}H_{49}O_7PSi$: C, 64.95; H, 7.85. Found: C, 64.73; H, 8.00.

A solution of the crude β-ketophosphonate (1.12 g, 1.68 mmol) in dry CH_3CN (15 mL) was treated with LiCl (85 mg, 2.0 mmol) and diisopropylethylamine (314 μL, 1.8 mmol). Methyl glyoxal hydrate[43] (200 mg, 1.9 mmol) in CH_3CN (2 mL) was then introduced. The resulting slurry was stirred for 5 min and then concentrated to a gummy oil that was dissolved in MeOH (1 mL) and applied to a 1-in. pad of silica gel. Elution with 25% ether/hexane (100 mL) and concentration of the eluent gave triene **7** as a homogeneous yellow oil (960 mg, 99%). This material was used in the following experiment without further purification. Only a single C-12,C-13 geometric isomer was observed: R_f 0.43 (3:1 hexane–ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 7.22 (d, J = 15.5 Hz, 1 H, H_{13}), 6.70 (d, J = 15.5 Hz, 1 H, H_{12}), 6.25 (dd, J = 10.5, 15.0 Hz, 1 H, H_6), 6.00 (dd, J = 10.5, 15.0 Hz, 1 H, H_5), 5.72 (dt, J = 15.0, 7.0 Hz, 1 H, H_4), 5.48 (dd, J = 8.0, 15.0 Hz, 1 H, H_7), 4.20 (t, J = 8.0 Hz, 1 H, H_8), 3.90 (t, J = 8.0 Hz, 1 H, H_9), 3.81 (s, 3 H, ester),

3.65 (t, J = 6.5 Hz, 1 H, H_1), 2.98 (m, 1 H, H_{10}), 2.18 (m, 2 H, H_3), 1.63 (m, 2 H, H_2), 1.38 (s, 3 H, acetonide), 1.10 (d, J = 7.0 Hz, 3 H, methyl), 1.05 (s, 9 H, *tert*-butyl). Anal. Calcd for $C_{35}H_{46}O_6Si$: C, 71.15; H, 7.85. Found: C, 70.89; H, 8.12.

Intramolecular Diels–Alder Reaction of 7. A solution of **7** (840 mg, 1.46 mmol) in toluene (10 mL) was heated to reflux for 22 h under argon. The solution was cooled and concentrated in vacuo to give the crude product. Analysis of this material by TLC and ^1H NMR spectroscopy showed a single cycloadduct, **9**, contaminated only by minor amounts of geometrically impure triene. The crude product was then chromatographed on silica gel (45 g, 230–400 mesh), giving pure **9** as an oil (654 mg, 78% from **17**): R_f 0.19 (5:1 hexane–ether); $[\alpha]^{23}_D$ −10.7° (c = 1.05, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 5.86 (d with fine splitting, $J_{6,5}$ = 11.0 Hz, 1 H, H_6), 5.75 (d, J = 11.0 Hz, 1 H, H_5), 3.92 (dd, $J_{9,10}$ = 6.0 Hz, $J_{9,8}$ = 9.5 Hz, 1 H, H_9), 3.64 (s, 3 H, ester), 3.70–3.60 (m, 3 H, $H_{1,8}$), 3.00 (m, 2 H, $H_{10,12}$), 2.67 (br d, $J_{4,13}$ = 10.5 Hz, 1 H, H_4), 2.57 (t, J = 10.5 Hz, 1 H, H_{13}), 2.50 (m, 1 H, H_7), 1.62 (m, 4 H, $H_{2,3}$), 1.48 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.22 (d, J = 7.0 Hz, 3 H, methyl), 1.03 (s, 9 H, *tert*-butyl); IR (neat) 3070, 2985, 2935, 2860, 1738, 1712, 1590, 1428, 1380, 1230, 1110, 1090, 735, 700 cm^{-1}; mass spectrum, m/e 533 ($M^+ - C_4H_9$). Anal. Calcd for $C_{35}H_{46}O_6Si$: C, 71.15; H, 7.85. Found: C, 70.98; H, 7.85.

Lactone 18. To a solution of **9** (148 mg, 0.26 mmol) in EtOH (2 mL) was added a solution of $NaBH_4$ in EtOH (0.5 mL, 1.0 M). The reaction was monitored by TLC. After the lactonization of the initially formed alcohol (R_f 0.15 (1:1 ether–hexane)) was complete (~20 min), saturated aqueous NH_4Cl solution (2.0 mL) was added carefully, and the mixture was extracted with ether (3 × 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and then dried ($MgSO_4$). Concentration of the extracts and chromatography of the crude product on silica gel afforded pure **18** as an oil (106 mg, 72%): R_f 0.38 (1:1 ether–hexane); $[\alpha]^{23}_D$ 18.0° (c = 2.50, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 5.88 (ddd, $J_{6,5}$ = 9.0 Hz, $J_{6,7}$ = 4.0 Hz, $J_{6,4}$ = 2.0 Hz, 1 H, H_6), 5.73 (d, $J_{5,6}$ = 9.0 Hz, 1 H, H_5), 4.70 (t, J = 7.0 Hz, 1 H, H_{11}), 3.70 (t, J = 10.0 Hz, 1 H, H_8), 3.65 (t, J = 8.0 Hz, 1 H, H_1), 3.52 (dd, $J_{9,8}$ = 10.0 Hz, $J_{9,10}$ = 5.0 Hz, 1 H, H_9), 2.92 (ddq, $J_{10,9}$ = 5.0 Hz, $J_{10,11}$ = 7.0 Hz, $J_{10,Me}$ = 8.0 Hz, 1 H, H_{10}), 2.54 (ddd, $J_{12,7}$ = 6.5 Hz, $J_{12,11}$ = 7.0 Hz, $J_{12,13}$ = 15.0 Hz, 1 H, H_{12}), 2.45 (m, 1 H, H_4), 2.25 (m, 1 H, H_7), 2.08 (dd, $J_{13,12}$ = 15.0 Hz, $J_{13,4}$ = 10.5 Hz, 1 H, H_{13}), 1.67 (m, 4 H, $H_{2,3}$), 1.45 (s, 3 H, acetonide), 1.43 (s, 3 H, acetonide), 1.05 (d, J = 8.0 Hz, 3 H, methyl), 1.04 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradiation of δ 4.70 causes δ 2.92 to simplify to dq ($J_{10,9}$ = 5.0 Hz, $J_{10,Me}$ = 8.0 Hz) and δ 2.54 to simplify to dd ($J_{12,13}$ = 15.0 Hz, $J_{12,7}$ = 6.5 Hz); irradiation of δ 3.52 causes δ 3.65 and δ 2.92 to simplify; irradiation of δ 2.92 causes δ 4.70 to collapse to a doublet ($J_{11,12}$ = 7.0 Hz), and δ 3.52 to collapse to a doublet ($J_{9,8}$ = 10.0 Hz); NOE difference experiments, irradiation of δ 4.70 (H_{11}) causes enhancement of δ 3.52 (3.2%, H_9), 2.92 (13.5%, H_{10}), and 2.54 (10.3%, H_{12}); irradiation of δ 1.05 (methyl) causes enhancement of δ 3.70 (1.7%, H_8), 2.92 (1.9%, H_{10}), and 2.08 (1.1%, H_{13}); IR (neat) 3060, 2930, 2855, 1773, 1590, 1425, 1370, 980, 680, 630 cm^{-1}; mass spectrum, m/e 503 ($M^+ - C_4H_9$). Anal. Calcd for $C_{34}H_{44}O_5Si$: C, 72.82; H, 7.91. Found: C, 72.53; H, 8.13.

Triene 19. β-Ketophosphonate **31** (57 mg, 0.091 mmol) was converted to a mixture of triene isomers (~1:1, TLC analysis, isomeric in the dienophile) following the procedure described for the preparation of **7**. Conversion of this mixture to a sample highly enriched in the *E,E,E* isomer was accomplished by treatment with 2-thiopyridine[31] (~1 mg) in CH_2Cl_2 (1 mL) at 23 °C for 1.5 h. The thiol was then removed by filtering the mixture through a silica pad with 1:1 ether–hexane as the eluant. Concentration of the filtrate afforded triene **19** (44 mg, 84% yield) as an 11:1:1 mixture of (*E,E*)-, (*Z,E*)-, and (*E,Z*)-diene isomers that was used directly in the next step: R_f 0.63 (1:1 ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, aromatic), 7.40 (m, 6 H, aromatic), 7.21 (d, $J_{13,12}$ = 16.0 Hz, 1 H, H_{13}), 6.69 (d, $J_{12,13}$ = 16.0 Hz, 1 H, H_{12}), 6.21 (dd, J = 10.0, 15.0 Hz, 1 H, H_5), 6.00 (dd, J = 10.0, 15.0 Hz, 1 H, H_6), 5.70 (dt, J = 15.0, 6.5 Hz, 1 H, H_4), 5.43 (dd, J = 8.0, 15.0 Hz, 1 H, H_7), 4.17 (dd, J = 8.0, 8.0 Hz, 1 H, H_8), 3.96 (dd, J = 8.0, 5.0 Hz, 1 H, H_9), 3.80 (s, 3 H, OMe), 3.66 (t, J = 6.5 Hz, 2 H, H_1), 3.01 (m, 1 H, H_{10}), 2.18 (m, 2 H, H_3), 1.64 (m, 2 H, H_2), 1.41 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 1.22 (d, J = 7.0 Hz, 3 H, methyl), 1.05.

Intramolecular Diels–Alder Reaction of 19. A solution of triene **19** (43.8 mg, 0.76 mmol) in benzene (5 mL) was refluxed for 4 h. Proton NMR analysis indicated the presence of a mixture of three cycloadducts, **32**, **33**, and **34**, in a ratio of 0.8:1.2:1.0, respectively, along with residual, geometrically impure **19** (unreactive diene isomers). Cycloadduct **34** was separated from the other isomers by preparative TLC (2:1 hexane–ether). The remaining material was collected as a single fraction, dissolved in benzene, and treated with freshly prepared cyclopentadiene (0.5 mL) for 20 h to consume remaining **19**. Cycloadducts **32** and **33** were then separated from the cyclopentadiene adduct of **19** and purified by exhaustive preparative TLC (0.5-mm preparative plate, seven elutions, 8:1 hexane–ether).

In a separate experiment, triene **19** was allowed to cyclize in $CDCl_3$ at 23 °C over 6 days, giving a mixture of **32**, **33**, and **34** in the ratio of 2.3:1.6:1.0. The following spectroscopic data were obtained on samples of ≥95% purity (NMR analysis).

Data for **32**: R_f 0.46 (40% ether–hexane); $[\alpha]^{23}_D$ +33.3° (c = 0.42, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 7.81 (m, 4 H, aromatic), 7.28 (m, 6 H, aromatic), 5.90 (m, 1 H, H_6), 5.52 (d, $J_{5,6}$ = 10.5 Hz, 1 H, H_5), 3.71 (dd, $J_{8,9}$ = 9.0 Hz, $J_{8,7}$ = 10.5 Hz, 1 H, H_8), 3.62 (t, J = 6.0 Hz, 1 H, H_1), 3.41 (s, 3 H, OMe), 3.06 (dd, $J_{9,8}$ = 9.0 Hz, $J_{9,10}$ = 12.5 Hz, 1 H, H_9), 2.88 (dd, $J_{12,7}$ = 6.5 Hz, $J_{12,13}$ = 12.0 Hz, 1 H, H_{12}), 2.79 (dq, $J_{10,9}$ = 12.5 Hz, J = 6.5, 1 H, H_{10}), 2.72 (m, 1 H, H_9), 2.62 (dd, $J_{13,12}$ = 12.0 Hz, $J_{13,4}$ = 10.5 Hz, 1 H, H_{13}), 2.17 (m, 1 H, H_7), 1.65–1.40 (m, 4 H, $H_{2,3}$), 1.43 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.32 (d, J = 6.5 Hz, 3 H, methyl), 1.20 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradiation of δ 3.06 causes δ 3.71 to collapse to a doublet, $J_{8,7}$ = 10.5 Hz, and δ 2.79 to simplify; irradiation of δ 2.17 causes δ 5.90 to simplify, δ 3.71 to collapse to a doublet, $J_{8,9}$ = 9.0 Hz, and δ 2.88 to collapse to a doublet, $J_{12,13}$ = 12.0 Hz; IR (CH_2Cl_2) 3070, 3030, 2990, 2950, 2930, 2890, 2860, 1740, 1712, 1590, 1470, 1455, 1435, 1428, 1380, 1370, 1360, 1305, 1290, 1230, 1220, 1190, 1165, 1130, 1110, 1070, 1028, 1005, 962, 935, 920, 850 cm^{-1}; mass spectrum, m/e 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2352.

Data for **33**: R_f 0.48 (40% ether–hexane); $[\alpha]^{23}_D$ +104.6° (c = 0.39, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H, aromatic), 7.41 (m, 6 H, aromatic), 5.84 (d, $J_{5,6}$ = 10.0 Hz, 1 H, H_5), 5.80 (m, 1 H, H_6), 3.72 (dd, $J_{8,7}$ = 11.5 Hz, $J_{8,9}$ = 8.5 Hz, 1 H, H_8), 3.66 (s, 3 H, ester), 3.60 (m, 2 H, H_1), 3.14 (dd, $J_{9,8}$ 8.5 Hz, $J_{9,10}$ = 11.5 Hz, 1 H, H_9), 2.90 (m, 2 H, $H_{10,13}$), 2.69 (t, $J_{12,13}$ = $J_{12,7}$ = 11.5 Hz, H_{12}), 2.55 (m, 1 H, H_4), 2.21 (br t, J = 11.5 Hz, 1 H, H_7), 1.52 (s, 3 H, acetonide), 1.72–1.35 (m, 4 H, $H_{2,3}$), 1.43 (s, 3 H, acetonide), 1.15 (d, J = 6.0 Hz, 3 H, methyl), 1.03 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradiation of δ 3.14 causes δ 3.72 to collapse to a doublet, $J_{8,7}$ = 11.5 Hz, and δ 2.90 to simplify; irradiation of δ 2.90 causes δ 3.14 to collapse to a doublet, $J_{9,8}$ = 8.5 Hz, and δ 2.69 to collapse to a doublet, $J_{12,7}$ = 11.5 Hz; irradiation of δ 2.69 causes δ 2.21 to collapse to a doublet, $J_{7,8}$ = 11.5 Hz, and δ 2.90 to simplify; irradiation of δ 2.21 causes δ 2.69 to collapse to a doublet, $J_{12,13}$ = 11.5 Hz, and δ 3.72 to collapse to a doublet, $J_{8,9}$ = 8.5 Hz; IR (CH_2Cl_2) 3070, 3030, 2990, 2950, 2930, 2890, 2855, 1737, 1722, 1651, 1590, 1470, 1452, 1435, 1381, 1371, 1360, 1318, 1230, 1195, 1175, 1133, 1110, 1072, 1025, 1005, 995, 980, 965, 910, 895, 840, 820 cm^{-1}; mass spectrum, m/e 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2358.

Data for **34**: R_f 0.40 (40% ether–hexane); $[\alpha]^{23}_D$ −3.2° (c = 0.34, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4 H, aromatic), 7.42 (m, 6 H, aromatic), 5.79 (s, 2 H, $H_{5,6}$), 4.04 (dd, $J_{8,7}$ = 5.0 Hz, $J_{8,9}$ = 9.5 Hz, 1 H, H_8), 3.70 (m, 2 H, H_1), 3.68 (s, 3 H, OMe), 3.56 (br s, 1 H, H_{13}), 3.46 (dd, $J_{9,8}$ = 9.5 Hz, $J_{9,10}$ = 12.5 Hz, 1 H, H_9), 3.21 (m, 1 H, H_7), 2.99 (br d, $J_{12,7}$ = 6.5 Hz, 1 H, H_{12}), 2.63 (m, 1 H, H_4), 2.51 (dq, $J_{10,9}$ = 12.5 Hz, J = 6.0 Hz, 1 H, H_{10}), 1.72 (m, 2 H, H_3), 1.54 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.40 (m, 2 H, H_2), 1.20 (d, J = 6.0 Hz, 3 H, methyl), 1.08 (s, 9 H,

(43) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3529.

tert-butyl); homonuclear decoupling experiments, irradiation of δ 4.04 causes δ 3.46 to collapse to a doublet, $J_{9,10}$ = 12.5 Hz, and δ 3.21 to simplify; irradiation of δ 3.46 causes δ 4.04 to collapse to a doublet, $J_{8,7}$ = 5.0 Hz; irradiation of δ 2.99 causes δ 3.21 to simplify; IR (CH_2Cl_2) 3070, 3030, 2990, 2950, 2930, 2860, 1727, 1712, 1590, 1470, 1455, 1435, 1428, 1380, 1370, 1290, 1230, 1200 1175, 1155, 1110, 1090, 1050, 1005, 995, 965, 840 cm^{-1}; mass spectrum, *m/e* 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2349.

(*Z*,*Z*,*E*)-Triene 43. β-Ketophosphonate **42** (396 mg, 0.69 mmol, a 5:1 mixture of (*Z*,*Z*)- and (*E*,*Z*)-diene isomers) was converted to **43** following the procedure described for synthesis of **7**. Triene **43**, a mixture of diene isomers, but otherwise pure, was isolated by chromatography on silica gel eluted with 4:1 hexane–ether (191 mg, 57%).

Data for (*Z*,*Z*,*E*)-**43** (prepared from pure (*Z*,*Z*)-**42**): R_f 0.48 (2:1 hexane–ether); $[\alpha]^{23}_D$ −34.0° (*c* = 0.73, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, aromatic) 7.40 (m, 6 H, aromatic), 7.18 (d, *J* = 16.0 Hz 1 H, H_{13}), 6.71 (d, *J* = 16.0 Hz, 1 H, H_{12}), 6.34 (dd, *J* = 14.0, 10.5 Hz, H_5), 6.18 (t, *J* = 10.5 Hz, 1 H, H_6), 5.80 (dt, *J* = 14.0, 6.5 Hz, H_4), 5.35 (t, *J* = 10.5 Hz, 1 H, H_7), 5.01 (dd, *J* = 10.5, 6.0 Hz, 1 H, H_8), 4.26 (dd, *J* = 6.0, 10.0 Hz, 1 H, H_9), 3.82 (s, 3 H, ester), 3.66 (t, *J* = 6.0 Hz, 2 H, H_1), 2.23 (m, 2 H, H_3), 1.66 (m, 2 H, H_2), 1.44 (s, 3 H, acetonide), 1.30 (s, 3 H, acetonide), 1.05 (s, 9 H, *tert*-butyl), 0.95 (d, *J* = 7.0 Hz, 3 H, methyl); IR (CH_2Cl_2) 3070, 3030, 2990, 2950, 2930, 2890, 2860, 1728, 1700, 1650, 1620, 1590, 1470, 1435, 1478, 1380, 1370, 1305, 1220, 1170, 1110, 1040, 995, 950, 905, 865, 820 cm^{-1}.

Intramolecular Diels–Alder Reaction of 20. Isomerically impure triene **43** (191 mg, 0.32 mmol) was stirred at 23 °C in dry hexane (15 mL) under N_2. I_2 (2 mg, 0.008 mM) was added, and the reaction was stirred for 5 h at which time additional I_2 (2 mg) was added. Additional I_2 (2 mg) was added again after 18 h, and stirring was continued for a total of 48 h. Solid $Na_2S_2O_3 \cdot 2H_2O$ (500 mg) was added, and the mixture was stirred for 0.5 h before ether (20 mL) and half-saturated aqueous $NaHCO_3$ (15 mL) were introduced. The mixture was stirred vigorously, and acetone (1 mL) was added to dissolve iodinated residues. The layers were separated, and the aqueous layer was extracted with ether (50 mL) and dried ($MgSO_4$). ^1H NMR analysis of this crude product mixture revealed three products in the ratio of 3.7:3.2:1 (**44**:**24**:**45**, respectively). This material was applied to two 0.5-mm preparative TLC plates (silica gel). Elution with 1:1 ether–hexane allowed for the separation of unreacted trienes (32 mg, 17%), the major trans-fused adduct **44** (61 mg, 32%), and a band containing **24** and **45** (55 mg, 29%). The latter mixture was separated by preparative TLC (two 0.5-mm plates, two elutions, 2:1 hexane–ether), yielding homogeneous samples of **24** (32 mg, 17%) and **45** (10 mg, 5%).

Data for **44**: R_f = 0.26 (1:1 ether–hexane); $[\alpha]^{23}_D$ +71.0° (*c* = 0.42, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, aromatic), 7.38 (m, 6 H, aromatic), 5.93 (m, 1 H, H_6), 5.62 (d, $J_{5,6}$ = 10.0 Hz, 1 H, H_5), 4.54 (br s, 2 H, $H_{8,9}$), 3.70 (s, 3 H, ester), 3.58 (m, 2 H, H_1), 3.10 (t, *J* = 12.5 Hz, 1 H, H_{12}), 2.72 (dd, $J_{13,12}$ = 12.5 Hz, $J_{13,4}$ = 6.5 Hz, 1 H, H_{13}), 2.47 (m, 1 H, H_4), 2.40 (br q, *J* = 7.5 Hz, 1 H, H_{10}), 2.28 (br d, $J_{7,12}$ = 12.5 Hz, 1 H, H_7), 1.80–1.45 (m, 4 H, $H_{2,3}$), 1.47 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.28 (d, *J* = 7.5 H_2, 3 H, methyl), 1.01 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradition of δ 4.54 causes δ 2.40 to sharpen to a quartet, *J* = 7.5 Hz; irradiation of δ 3.10 causes δ 2.72 to simplify to a doublet, $J_{13,4}$ = 6.5 Hz and δ 2.28 to collapse to a broad singlet; irradiation of δ 2.72 causes δ 3.10 to collapse to a doublet, $J_{12,7}$ = 12.5 Hz; irradiation of δ 2.28 causes δ 3.10 to collapse to a doublet, $J_{12,13}$ = 12.5 Hz and δ 5.93 to simplify to a doublet of doublets, ($J_{6,5}$ = 10.0 Hz, $J_{6,4}$ = 4.5 Hz); IR (CH_2Cl_2) 3070, 3020, 2990, 2950, 2930, 2860, 1735, 1716, 1590, 1470, 1450, 1435, 1425, 1420, 1415, 1382, 1372, 1360, 1318, 1210, 1195, 1170, 1130, 1110, 1090, 1020, 995, 935, 892, 880 cm^{-1}; mass spectrum, *m/e* 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2368.

Data for **24**: R_f 0.47 (1:1 ether–hexane); $[\alpha]^{23}_D$ −81.5° (*c* = 0.41, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.40 (m, 6 H, aromatic), 5.74 (ddd, *J* = 9.5, 4.0, 3.0 Hz, 1 H, H_6), 5.65 (d, $J_{5,6}$ = 9.5 Hz, 1 H, H_5), 4.49 (br s, 2 H, $H_{8,9}$), 3.66 (s, 3 H, ester), 3.49 (m, 2 H, H_1), 3.33 (m, $W_{1/2}$ = 6 Hz, 1 H, H_{13}), 3.01 (m, $W_{1/2}$ = 10 Hz, 1 H, H_{12}), 2.81 (m, 2 H, $H_{7,10}$), 2.57 (m, 1 H, H_4), 1.60 (m, 2 H, H_2), 1.35–1.10 (m, 2 H, H_3), 1.39 (s, 3 H, acetonide), 1.33 (s, 3 H, acetonide), 1.10 (d, *J* = 6.0 Hz, 3 H, methyl), 1.03 (s, 9 H, *tert*-butyl); IR (CH_2Cl_2) 3070, 3050, 3020, 2990, 2950, 2930, 2860, 1730, 1715, 1590, 1470, 1455, 1425, 1382, 1365, 1330, 1235, 1210, 1165, 1110, 1045, 1000, 950, 930, 895, 880, 820 cm^{-1}; mass spectrum, *m/e* 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2361.

Data for **45**: R_f 0.53 (1:1 ether–hexane); $[\alpha]^{23}_D$ −87.4° (*c* = 0.41, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H, aromatic), 7.42 (m, 6 H, aromatic), 5.85 (s, 2 H, $H_{5,6}$), 4.60 (t, $J_{9,10}$ = $J_{9,8}$ = 5.0 Hz, 1 H, H_9), 4.00 (dd, $J_{8,9}$ = 5.0 Hz, $J_{8,7}$ = 10.5 Hz, 1 H, H_8), 3.68 (s, 3 H, ester), 3.64 (m, 2 H, H_1), 2.90 (m, 2 H, $H_{10,13}$), 2.63 (dd, $J_{12,13}$ = $J_{12,7}$ = 12.0 Hz, 1 H, H_{12}), 2.54 (m, 1 H, H_4), 2.33 (br dd, $J_{7,8}$ = 10.5 Hz, $J_{7,12}$ = 12.0 Hz, 1 H, H_7), 1.75–1.25 (m, 4 H, $H_{2,3}$), 1.44 (s, 3 H, acetonide), 1.39 (s, 3 H, acetonide), 1.22 (d, *J* = 7.0 Hz, 3 H, methyl), 1.06 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradiation of δ 4.00 causes δ 4.60 to collapse to a doublet, $J_{9,10}$ = 5.0 Hz, and δ 2.33 to collapse to a doublet, $J_{7,12}$ = 12.0 Hz; irradiation of δ 2.90 causes δ 4.60 to collapse to a doublet, $J_{9,8}$ = 5.0 Hz, and δ 2.63 to collapse to a doublet, $J_{12,7}$ = 12.0 Hz; irradiation of δ 2.63 causes δ 2.33 to collapse to a doublet, $J_{7,8}$ = 10.5 Hz, and δ 2.90 to simplify; irradiation of δ 2.33 causes δ 4.00 to collapse to a doublet, $J_{8,9}$ = 5.0 Hz, and δ 2.63 to collapse to a doublet, $J_{12,13}$ = 12.0 Hz; irradiation of δ 1.22 causes δ 2.90 to simplify; IR (CH_2Cl_2) 3070, 3020, 2990, 2950, 2930, 2860, 1725, 1590, 1470, 1450, 1425, 1380, 1365, 1330, 1320, 1240, 1220, 1200, 1075, 1035, 1110, 1030, 995, 938, 895, 865, 820 cm^{-1}; mass spectrum, *m/e* 533 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{31}H_{37}O_6Si$ calcd 533.2360, found 533.2350.

Structure Assignment for 24: Preparation of Dibenzoate 47. Cycloadduct **24** (22 mg, 0.038 mmol) was dissolved in EtOH (3 mL) at 0 °C and treated with $NaBH_4$ (5 mg, 0.13 mmol). After 1.5 h saturated aqueous NH_4Cl solution (10 mL) was introduced, and the resulting mixture was stirred for 20 min. The organic phase was separated, dried ($MgSO_4$), and concentrated in vacuo to give the crude product mixture that was separated by preparative TLC (silica gel), providing pure samples of a hydroxy ester [R_f 0.54 (2:1 ether–hexane); IR (CH_2Cl_2) 1728 cm^{-1}]; the corresponding lactone [R_f 0.61 (2:1 ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H, aromatic), 7.39 (m, 6 H, aromatic), 6.01 (d with fine splitting, $J_{6,5}$ = 9.5 Hz, 1 H, H_9), 5.71 (d, $J_{5,6}$ = 9.5 Hz, 1 H, H_5), 4.50 (dd, $J_{11,10}$ = 9.8 Hz, $J_{11,12}$ = 6.8 Hz, 1 H, H_{11}), 4.14 (t, $J_{9,10}$ = $J_{9,8}$ = 4.0 Hz, 1 H, H_9), 3.89 (dd, $J_{8,9}$ = 4.0 Hz, $J_{8,7}$ = 7.5 Hz, 1 H, H_8), 3.71 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H_1), 2.57–2.32 (m, 3 H), 2.07 (m, 1 H), 1.94 (dd, *J* = 14.5, 10.0 Hz, 1 H, H_1), 1.75–1.50 (m, 4 H, $H_{2,3}$), 1.47 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.34 (d, *J* = 7.0 Hz, 3 H, methyl), 1.09 (s, 9 H, *tert*-butyl); IR (CH_2Cl_2) 2930, 2850, 1773, 1110 cm^{-1}; mass spectrum, *m/e* 503 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{30}H_{35}O_5Si$ calcd 503.2252, found 503.2254]; and diol **46** [R_f 0.38 (2:1 ether–hexane)] in a ~1:1:3 ratio.

Diol **46** was treated with DMAP (25 mg, 0.20 mmol) and benzoyl chloride (0.02 mL, 0.17 mmol) in dry CH_2Cl_2 (1 mL). After 18 h, the crude reaction was applied directly to a 0.5-mm preparative TLC plate and eluted with 1:1 ether–hexane to obtain pure **47**: R_f 0.62 (1:1 ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.20–7.08 (20 H, aromatic), 6.07 (d with fine splitting, $J_{6,5}$ = 10.0 Hz, 1 H, H_6), 5.64 (dd, $J_{5,6}$ = 10.0 Hz, $J_{5,4}$ = 2.0 Hz, 1 H, H_5), 5.34 (dd, $J_{11,12}$ = 4.0 Hz, $J_{11,10}$ = 12.0 Hz, 1 H, H_{11}), 4.53, 4.49 (AB of ABX, 2 H, H_{14}), 4.31 (dd, $J_{9,8}$ = $J_{9,10}$ = 4.5 Hz, 1 H, H_9), 3.96 (dd, $J_{8,9}$ = 4.5 Hz, $J_{8,7}$ = 9.0 Hz, 1 H, H_8), 3.64 (t, $J_{1,2}$ = 6.0 Hz, 2 H, H_1), 2.79 (ddd, $J_{12,13}$ = 12.0 Hz, $J_{12,7}$ = $J_{12,11}$ = 4.0 Hz, 1 H, H_{12}), 2.53 (m, 2 H, $H_{10,7}$), 2.36 (m, 1 H, H_4), 1.82 (br dd, $J_{13,12}$ = $J_{13,4}$ = 12.0 Hz, 1 H, H_{13}), 1.80–1.40 (m, 4 H, $H_{2,3}$), 1.45 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.25 (d, *J* = 7.0 Hz, 3 H, methyl), 1.03 (s, 9 H, tert-butyl); homonuclear decoupling experiments, irradiation of δ 5.34 causes δ 2.79 to simplify to a doublet of doublets ($J_{12,13}$ = 12.0 Hz, and $J_{12,7}$ = 4.0 Hz); irradiation of δ 4.51 causes δ 1.82 to sharpen; irradiation of δ 3.96 causes δ 4.31 to collapse to a broad singlet and δ 2.53 to simplify; irradiation of δ 2.79 causes δ 5.34 to collapse to a doublet, $J_{11,10}$ = 12.0 Hz, δ 2.53 to simplify, and δ 1.82 to collapse to a broad doublet, $J_{13,4}$ = 12.0 Hz; irradiation of δ 2.53 causes δ 6.07 to collapse to a doublet, $J_{6,5}$ = 10.0

Hz, causes both δ 4.31 and δ 3.96 to collapse to doublets, $J_{8,9}$ = $J_{9,8}$ = 4.5 Hz, and causes δ 2.79 to collapse to a broad doublet, $J_{12,13}$ = 12.0 Hz; irradiation of δ 1.82 causes δ 2.79 to collapse to a broad singlet and δ 2.36 to sharpen; IR (CH_2Cl_2) 3070, 3020, 2990, 2950, 2930, 2850, 1718, 1600, 1582, 1450, 1428, 1380, 1368, 1310, 1215, 1175, 1110, 1070, 1035, 1025, 990, 895, 865, 820 cm^{-1}; mass spectrum, *m/e* 757 ($M^+ - CH_3$), 715 ($M^+ - C_4H_9$).

Intramolecular Diels–Alder Reaction of Triene 21. β-Keto phosphonate **61** (86 mg, 0.12 mmol) was converted to a mixture of trienes **21*E*** and **21*Z*** by using the procedure described for the preparation of **7**. This mixture was dissolved in CH_2Cl_2 (1 mL) at 23 °C and treated with 2-mercaptopyridine (1 mg). The isomerization of **21*Z*** to **21*E*** was complete after 2 h, and the solution was allowed to stand overnight (18 h). During this time the cyclization of (*E,E,E*)-**21** to cycloadducts **63**, **64**, and **65** went to completion. A small amount of (*Z,E*)-diene isomers, however, remained. Partial purification of this mixture, care being taken not to separate cycloadducts from residual triene, was performed by preparative TLC eluted with 2:1 hexane–ether. The material so obtained was dried azeotropically (CH_2Cl_2, 3 × 20 mL), dissolved in dry hexane (5 mL) and then treated with a crystal of I_2. Complete conversion of residual triene to cycloadducts was observed (TLC analysis) over 5 h. The reaction was worked up in the usual fashion (see **15** to **17**), affording a mixture of cycloadducts (69.5 mg, 85% from β-ketophosphonate **61**). Analysis of this mixture by ^1H NMR indicated the presence of **63** and **64** in a 4:1 ratio (cycloadduct **65** was detectable only by TLC analysis). The three cycloadducts were then separated by careful preparative TLC (1:1 ether–hexane), giving homogeneous samples of each: **63** (42.6 mg, 49%), **64** (10.6 mg, 12%), and **65** (1.8 mg, 2%).

Data for **63**: R_f 0.50 (1:1 ether–hexane); $[\alpha]^{23}_D$ +104.2° (*c* = 0.95, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4 H, aromatic), 7.33 (m, 6 H, aromatic), 5.78 (ddd, $J_{6,5}$ = 10.0 Hz, $J_{6,7}$ = 4.8 Hz, $J_{6,4}$ = 2.8 Hz, 1 H, H_6), 5.55 (d, $J_{5,6}$ = 10.0 Hz, 1 H, H_5), 4.64 (s, 2 H), 4.56 (A of AB d, *J* = 11.8 Hz, 1 H, H_A), 4.50 (B of AB d, *J* = 11.8 Hz, 1 H, H_B), 3.86 (m, 2 H, $H_{8,9}$), 3.64 (s, 3 H, ester), 3.58 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H_1), 3.33 (s, 3 H, OMe), 3.19 (t, $J_{12,7}$ = $J_{12,13}$ = 12.2 Hz, 1 H, H_{12}), 3.03 (m, 1 H, H_{10}), 2.86 (dd, $J_{13,12}$ = 12.2 Hz, $J_{13,4}$ = 6.0 Hz, 1 H, H_{13}), 2.56 (br d, $J_{7,12}$ = 12.2 Hz, 1 H, H_7), 2.47 (m, 1 H, H_4), 1.70–1.20 (m, 4 H, $H_{2,3}$), 1.04 (d, *J* = 6.8 Hz, 3 H, methyl), 1.01 (s, 9 H, *tert*-butyl); IR (CH_2Cl_2) 3055, 3025, 2995, 2950, 2930, 2890, 2830, 1736, 1720, 1590, 1470, 1455, 1435, 1428, 1390, 1360, 1220, 1195, 1175, 1145, 1110, 1045, 1005, 915, 895, 820 cm^{-1}; mass spectrum, *m/e* 684 (parent ion). Anal. Calcd for $C_{41}H_{52}O_7Si$: C, 71.90; H, 7.66. Found: C, 72.29; H, 7.48.

Data for **64**: R_f 0.43 (1:1 hexane–ether); $[\alpha]^{23}_D$ +28.6° (*c* = 0.85, CH_2Cl_2); ^1H NMR (300 MHz, 2:1 C_6D_6–$CDCl_3$) δ 7.74 (m, 4 H, aromatic), 7.25 (m, 11 H, aromatic), 5.67 (dt, $J_{6,5}$ = 10.3 Hz, $J_{6,7}$ = $J_{6,4}$ = 2.6 Hz, 1 H, H_6), 5.58 (dt, $J_{5,6}$ = 10.3 Hz, $J_{5,4}$ = $J_{5,7}$ = 2.6 Hz, 1 H, H_5), 4.62 (s, 2 H, CH_2OMe), 4.53 (A of AB, *J* = 12.0 Hz, 1 H, H_A), 4.31 (B of AB, *J* = 12.0 Hz, 1 H, H_B), 3.93 (dd, $J_{8,9}$ = 3.1 Hz, $J_{8,7}$ = 4.2 Hz, 1 H, H_8), 3.74 (dd, $J_{9,8}$ = 3.1 Hz, $J_{9,10}$ = 2.3 Hz, 1 H, H_9), 3.69 (t, *J* = 6.1 Hz, 2 H, H_1), 3.54 (s, 3 H, OMe), 3.28 (s, 3 H, methoxyl), 3.23 (t, $J_{13,12}$ = $J_{13,4}$ = 5.2 Hz, 1 H, H_{13}), 3.15 (dd, $J_{12,13}$ = 5.2 Hz, $J_{12,7}$ = 6.6 Hz, 1 H, H_{12}), 3.06 (br m, 1 H, H_7), 2.84 (m, 1 H, H_{10}), 2.57 (br m, 1 H, H_4), 1.70 (m, 4 H, $H_{2,3}$), 1.14 (s, 9 H, *tert*-butyl), 1.05 (d, *J* = 6.9 Hz, 3 H, methyl); ^1H NOE difference spectrum, irradiation of the resonance at δ 2.84 (H_{10}) causes an enhancement of δ 3.74 (8%, H_9) and δ 3.23 (6%, H_{13}); the expected enhancement at δ 1.05 was not recorded; IR (CH_2Cl_2) 3062, 3050, 3025, 2950, 2930, 2890, 2858, br 1720, 1670, 1590, 1495, 1472, 1455, 1435, 1428, 1390, 1360, 1195, 1170, 1150, 1110, 1035, 915, 895, 820 cm^{-1}; mass spectrum, *m/e* 627 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{37}H_{43}O_7Si$ calcd 627.2778, found 627.2777.

Partial data for **65**: R_f 0.31 (1:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 3.17 (dd, *J* = 12.0, 12.0 Hz, 1 H, H_{12}), 3.00 (dd, *J* = 12.0, 12.0 Hz, 1 H, H_7).

Intramolecular Diels–Alder Reaction of Triene 23. A solution of β-ketophosphonate **61** (29 mg, 0.040 mmol) in CH_3CN (2 mL) was treated with LiCl (10 mg, 0.24 mmol) and diisopropylethylamine (20 μL, 0.14 mmol). α-Acetoxyacetaldehyde (10 mg, 0.1 mmol) was added, and the mixture was stirred for 0.5 h. The reaction mixture was filtered through a silica gel plug and eluted with ether (10 mL). The filtrate was concentrated, and the crude product was purified by preparative TLC (0.5-mm preparative plate, 2:1 hexane–ether), providing homogeneous triene **23** (19.6 mg, 67%): R_f 0.36 (2:1 hexane–ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (m, 4 H, aromatic), 7.30 (m, 11 H, aromatic), 6.80 (dt, *J* = 16.5, 6.0 Hz, 1 H, H_{13}), 6.38 (d, *J* = 16.5 Hz, 1 H, H_{12}), 6.21 (dd, *J* = 10.0, 15.5 Hz, 1 H, H_6), 5.99 (dd, *J* = 10.0, 15.5 Hz, 1 H, H_5), 5.68 (dt, *J* = 15.5, 6.5 Hz, 1 H, H_4), 5.41 (dd, *J* = 8.0, 15.5 Hz, 1 H, H_7), 4.70–4.37 (3 AB's, m, 6 H), 4.23 (dd, *J* = 3.0, 8.0 Hz, 1 H, H_8), 3.67 (m, 3 H, $H_{1,9}$), 3.38 (m, 4 H, H_{10}, methyl), 2.00 (m, 2 H, H_3), 2.08 (s, 3 H, OAc), 1.62 (m, 2 H, H_2), 1.08 (d, *J* = 7.0 Hz, 3 H, methyl), 1.02 (s, 9 H, *tert*-butyl).

A solution of **23** (9.6 mg, 0.013 mmol) in toluene (1 mL) was heated to reflux for 18 h and then was transferred to a sealed tube and heated to 150 °C for 4 h. The apparent single product (TLC analysis) was purified by preparative TLC (0.25-mm silica gel preparative plate, 3:2 hexane–ether). This material was determined by ^1H NMR analysis to be comprised of two cycloadducts **66** and **67** in the ratio of 5:1. The ratio of these materials appeared unchanged from that observed in the NMR spectrum of the crude reaction product.

Data for **66** (obtained on the 5:1 mixture containing **67**): R_f 0.42 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4 H, aromatic), 7.30 (m, 11 H, aromatic), 5.84 (m, 1 H, H_6), 5.51 (d, $J_{5,6}$ = 10.5 Hz, 1 H, H_5), 4.66 (dd, $J_{14e,14a}$ = 12.0 Hz, $J_{14e,13}$ = 6.0 Hz, 1 H, H_{14e}), 4.62 (s, 2 H), 4.57 (AB, J_{AB} = 12.0 Hz, 1 H, H_A), 4.50 (AB, J_{BA} = 12.0 Hz, 1 H, H_B), 3.95 (dd, $J_{14a,14e}$ = 12.0 Hz, $J_{14a,13}$ = 12.0 Hz, 1 H, H_{14a}), 3.82 (m, 2 H, $H_{8,9}$), 3.63 (m, 2 H, H_1), 3.32 (s, 3 H, methoxyl), 2.91 (m, 1 H, H_{10}), 2.83 (dd, $J_{12,7}$ = $J_{12,13}$ = 11.0 Hz, 1 H, H_{12}), 2.72 (br d, $J_{7,12}$ = 11.0 Hz, 1 H, H_7), 2.40 (m, 1 H, H_{13}), 2.23 (m, 1 H, H_4), 1.92 (s, 3 H, OAc), 1.70–1.10 (m, 4 H, $H_{2,3}$), 1.00 (m, 12 H, *tert*-butyl, methyl); homonuclear decoupling experiments, irradiation of δ 3.95 causes δ 4.66 to collapse to a doublet, $J_{14e,13}$ = 6.0 Hz; irradiation of δ 2.91 causes δ 3.82 to simplify; irradiation of δ 2.40 causes δ 2.83 to collapse to a doublet, $J_{12,7}$ = 11.0 Hz, and causes δ 4.66 and δ 3.95 to simplify.

Intramolecular Diels–Alder Reaction of 22. A stirred solution of β-ketophosphonate **62** (17 mg, 0.024 mmol), LiCl (20 mg, 0.48 mmol), and diisopropylethylamine (10 μL, 0.072 mmol) in acetonitrile (1 mL) at 0 °C was treated with methyl glyoxal (10 mg, 0.096 mmol). Salts immediately precipitated. TLC analysis after 5 min showed the presence of both dienophile isomers (**22*Z***, R_f 0.26; **22*E***, R_f 0.32, 40% ether–hexane). 2-Mercaptopyridine (1 mg, 0.005 mmol) was introduced, and the reaction mixture was stirred at 0 °C for 20 min, at which time TLC analysis indicated complete isomerization of **22*Z*** to **22*E*** had occurred. NH_4Cl solution (3 mL) was introduced, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were filtered through cotton and concentrated, affording 12.1 mg (75%) of a mixture of **22** and cycloadducts **68**–**70**. This mixture was allowed to stand in CH_2Cl_2 (1 mL) at 23 °C for 1 h to allow complete cyclization of **22**. ^1H NMR analysis of the crude product indicated a mixture of three cycloadducts were produced in a ratio of 2:1:1. These were separated on a 0.25-mm preparative TLC plate eluted with 40% ether–hexane. Cycloadducts **68** and **69** were obtained in pure form. The least polar cycloadduct **70** coeluted with unreacted, geometrically impure triene isomers. This fraction was dried, dissolved in dry hexane (2 mL), and treated with I_2 (0.1 mg). After 12 h at 23 °C, a crystal of $Na_2S_2O_3 \cdot 2H_2O$ was added. TLC analysis indicated the presence **68**, **69**, and **70**, which were separated as before.

Data for **68**: R_f 0.22 (40% ether–hexane); $[\alpha]^{23}_D$ −25.3° (*c* = 0.33, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.35 (m, 11 H, aromatic), 5.96 (m, 1 H, H_6), 5.71 (d, $J_{5,6}$ = 10.0 Hz, 1 H, H_5), 4.94 (A of AB d, J_{AB} = 6.5 Hz, 1 H, H_A), 4.80 (A′ of A′B′ d, $J_{A'B'}$ = 11.0 Hz, 1 H, $H_{A'}$), 4.75 (B of AB d, J_{BA} = 6.5 Hz, 1 H, H_B), 4.61 (B′ of A′B′ d, $J_{B'A'}$ = 11.0 Hz, 1 H, $H_{B'}$), 3.80 (dd, $J_{8,7}$ = 10.5 Hz, $J_{8,9}$ = 9.0 Hz, 1 H, H_8), 3.63 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H_1), 3.57 (s, 3 H, methoxyl), 3.40 (s, 3 H, methoxyl), 3.22 (dd, $J_{9,8}$ = 9.0 Hz, $J_{9,10}$ = 12.0 Hz, 1 H, H_9), 2.95 (dq, $J_{10,9}$ = 12.0 Hz, $J_{10,Me}$ = 6.5 Hz, 1 H, H_{10}), 2.72 (dd, $J_{12,7}$ = 5.5 Hz, $J_{12,13}$ = 12.0 Hz, 1 H, H_{12}), 2.64 (m, 2 H, $H_{13,4}$), 2.39 (m, 1 H, H_7), 1.65–1.25 (m, 4 H, $H_{2,3}$), 1.14 (d, *J* = 6.5 Hz, 3 H, methyl), 1.02 (s, 9 H, *tert*-butyl); homonuclear decoupling experiments, irradiation of δ 5.96 causes δ 2.39 to simplify to (dd, $J_{7,12}$ = 5.5 Hz, $J_{7,8}$ = 10.5

Hz) and δ 2.39 to simplify; irradiation of δ 3.22 causes δ 3.80 to collapse to a doublet, $J_{8,7}$ = 10.5 Hz, and δ 2.95 to simplify; irradiation of δ 2.95 causes δ 3.22 to collapse to a doublet, $J_{9,8}$ = 9.0 Hz; irradiation of δ 2.39 causes δ 2.72 to collapse to a doublet, $J_{12,13}$ = 12.0 Hz, and δ 3.80 to collapse to a doublet, $J_{8,9}$ = 9.0 Hz; IR (CH_2Cl_2) 3090, 3070, 3030, 2995, 2950, 2900, 2860, 1741, 1712, 1610, 1590, 1472, 1455, 1435, 1428, 1390, 1360, 1320, 1210, 1190, 1155, 1110, 1025, 920, 895 cm^{-1}; mass spectrum, *m/e* 627 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{37}H_{43}O_7Si$ calcd 627.2777, found 627.2777.

Partial data for **69**: R_f 0.30 (40% ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.65 (m, 11 H, aromatic), 5.73 (br d, $J_{6,5}$ = 11.0 Hz, 1 H, H_6), 5.66 (d with fine coupling, $J_{5,6}$ = 11.0 Hz, 1 H, H_5), 4.72 (AB, J_{AB} = 12.0 Hz, 1 H, H_A), 4.51 (s, 2 H), 4.50 (AB, J_{BA} = 12.0 Hz, 1 H, H_B), 3.90 (dd, *J* = 2.0, 2.0 Hz, 1 H, H_8), 3.71 (s, 3 H, methoxyl), 3.63 (m, 3 H, H_1 and probably H_9), 3.28 (m, 1 H, H_{10}), 3.25 (s, 3 H, methoxyl), 3.02 (dd, $J_{12,7}$ = $J_{12,13}$ = 10.0 Hz, 1 H, H_{12}), 2.60 (dd, $J_{13,12}$ = 10.0 Hz, $J_{13,4}$ = 6.0 Hz, H_{13}), 2.60 (m, 1 H), 2.28 (m, 1 H)8, 1.75–1.30 (m, 4 H, $H_{2,3}$), 1.10 (d, *J* = 7.0 Hz, 3 H, methyl), 1.02 (s, 9 H, *tert*-butyl).

Data for **70**: R_f 0.26 (40% ether–hexane); $[\alpha]^{23}_D$ +42.1° (*c* = 0.11, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.70 (m, 11 H, aromatic), 5.92 (d, *J* = 11.0 Hz, 1 H, H_5), 5.83 (m, 1 H, H_6), 4.99 (AB, *J* = 6.5 Hz, 1 H, H_A), 4.79 (A'B', *J* = 11.0 Hz, 1 H, $H_{A'}$), 4.76 (AB, *J* = 6.5 Hz, 1 H, H_B), 4.63 (A'B', *J* = 11.0 Hz, 1 H, $H_{B'}$), 3.66 (s, 3 H, methoxyl), 3.67–3.57 (m, 3 H, H_1, H_8), 3.46 (s, 3 H, methoxyl), 3.24 (dd, $J_{9,8}$ = 9.0 Hz, $J_{9,10}$ = 10.5 Hz, 1 H, H_9), 2.87 (dd, $J_{13,12}$ = 12.0 Hz, $J_{13,4}$ = 6.5 Hz, 1 H, H_{13}), 2.80 (m, 1 H, H_{10}), 2.71 (t, *J* = 12.0 Hz, 1 H, H_{12}), 2.53 (m, 1 H, H_4), 1.98 (br t, *J* = 12 Hz, 1 H, H_7), 1.70–1.20 (m, 4 H, $H_{2,3}$), 1.15 (d, *J* = 6.5 Hz, 3 H, methyl), 1.03 (s, 9 H, *tert*-butyl); IR (CH_2Cl_2) 3070, 3060, 3050, 3030, 2995, 2950, 2930, 2890, 2860, 1736, 1722, 1610, 1590, 1472, 1438, 1428, 1390, 1360, 1350, 1325, 1200, 1178, 1110, 1025, 935, 920 cm^{-1}; mass spectrum, *m/e* 627 ($M^+ - C_4H_9$); high-resolution mass spectrum for $C_{37}H_{43}O_7Si$ calcd 627.2777, found 627.2777.

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Supplementary Material Available: A table of torsional angles for MMX-generated transition states ii, iii, v, vi, viii, ix, xi, and xii and experimental procedures for synthesis of β-keto phosphonates **31**, **42**, **61**, and **62** and phosphonium salts **16** and **40** (15 pages). Ordering information is given on any current masthead page.

Scope and Stereochemistry of the Tandem Intramolecular Cyclopropanation/Cope Rearrangement Sequence

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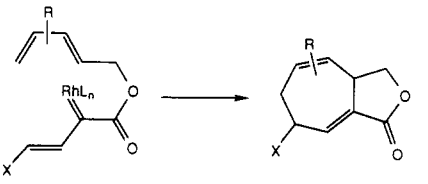
A stereoselective synthesis of a series of fused seven-membered carbocycles was achieved by a formal intramolecular 3 + 4 cycloaddition between vinylcarbenoids, generated by rhodium(II) acetate catalyzed decomposition of vinyldiazomethanes, and dienes. The products are formed by a tandem cyclopropanation/Cope rearrangement sequence rather than a concerted process.

Introduction

Highly functionalized cycloheptanes are present in a variety of important natural products, and consequently, new procedures for their formation have been actively sought.[1] As part of a general program aimed at developing new synthetic methodology based on carbenoid intermediates, we have been investigating the scope of formal 3 + 4 cycloadditions between vinylcarbenoids and dienes.[2] We have previously reported that [3.2.1] bicyclic systems are readily formed on reaction of rhodium(II)-stabilized vinylcarbenoids with furans[2a,b] or cyclopentadiene.[2c] In this paper we describe how the reaction can be extended to intramolecular systems,[2d] leading to fused cycloheptadienes of predictable stereochemistry, as shown in Scheme I.

Scheme I



Our initial studies into the formal 3 + 4 cycloaddition between vinylcarbenoids and dienes revealed that a concerted mechanism is not involved.[2c] Instead, the reaction proceeds through a two-step sequence with initial cyclo-

(1) For examples of other 3 + 4 cycloaddition sequences for the synthesis of seven-membered rings, see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (b) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (c) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483.

(2) (a) Davies, H. M. L.; Clark, D. M.; Smith, T. K. *Tetrahedron Lett.* **1985**, *26*, 5659. (b) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265. (c) Davies, H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853. (d) Davies, H. M. L.; Oldenburg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Henretta, J. P.; Romines, K. R. *Tetrahedron Lett.* **1988**, *29*, 975. (e) A related tandem cyclopropanation/Cope rearrangement sequence using a Fischer-carbene complex has been reported recently: Wulff, W. D.; Yang, D. C.; Murray, C. K. *J. Am. Chem. Soc.* **1988**, *110*, 2653.

0022-3263/89/1954-0930$01.50/0