(500 μg, 1.9 μmol), TBHP (4.0 M in CH_2Cl_2, 50 μL), benzene (1.0 mL), and subsequent purification by HPLC. The IR and 400-MHz ^1H NMR spectra and HPLC retention times of both sample were identical with those of the sample prepared by the step-by-step method.

Acknowledgment. We are grateful to Professor Etsuro Kurosawa and Dr. Teruaki Suzuki of Hokkaido University for the generous gift of a sample of natural teurilene (1) and for fruitful discussions.

Registry No. 1, 96304-92-6; **29**, 116216-69-4; **31**, 123908-75-8; **33**, 123908-76-9; **34**, 132298-82-9; **35**, 123908-77-0; (-)-**36**, 82188-73-6; **36** tosylate, 121401-06-7; (-)-**37**, 76985-25-6; **37** diol tosylate, 132341-93-6; (+)-**38**, 121400-91-7; **39**, 116216-77-4; **40**, 116216-78-5; **41**, 121429-28-5; **42**, 116216-79-6; **42** TBDMS ether, 121400-96-2; **43**, 121400-97-3; **43** aldehyde, 121400-98-4; **44**, 121400-92-8; **45**, 121400-99-5; **45** chloride, 121401-00-1; **46**, 121400-93-9; **47**, 121429-29-6; **48**, 132298-83-0; **49**, 121400-94-0; **50**, 121400-95-1; **51**, 121429-30-9; **52**, 121401-03-4; **53**, 121401-04-5; **54**, 121401-05-6; **55**, 109307-91-7; **55** THP ether, 132298-84-1; **56**, 132298-85-2; **56** aldehyde, 132298-86-3; (±)-**57**, 132341-94-7; (±)-**58**, 132298-87-4; (±)-**59**, 132298-88-5; **60**, 123908-78-1; **61**, 122554-78-3; **62**, 132298-89-6; **63**, 122554-81-8; **64**, 122554-82-9; **65**, 122554-84-1; **66**, 124018-82-2; $CH_3C(PPh_3)CO_2Et$, 5717-37-3; geraniol, 106-24-1.

Supplementary Material Available: ^1H NMR spectra of **1**, **33-38**, **43-49**, **51**, **52**, and **56-66** (30 pages). Ordering information is given on any current masthead page.

Stereoselectivities of Intramolecular Diels-Alder Reactions. Formation of the Taxane Skeleton

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The stereodirecting effect of an alkyl (Me) group on the diene and/or dienophile on the intramolecular Diels-Alder reaction leading to the formation of an eight-membered ring has been studied under both thermal and Lewis acid catalyzed cyclization conditions. The synthesis and cycloaddition reactions of tetraenes **2a-d**, leading to the formation of the taxane skeleton, is described. Selectivity is shown to vary under thermal conditions depending upon substitution pattern, while the catalyzed cycloaddition invariantly gives the cis-fused product.

Introduction

The taxane diterpenes[3] such as taxol (**1a**) and cephalomannine (**1b**) have received much attention over the past decade. These materials have shown significant anti-leukemic and tumor-inhibitory properties.[4] Structurally, the taxanes have posed may challenges to the organic chemist. The unusual tricyclic carbon framework that contains a bridgehead olefin, a sterically congested eight-membered ring system, and a bicyclo[5.3.1]undecene system trans fused to a cyclohexane ring has not yet yielded to a total synthesis of these complex molecules, although a synthesis of the simplest member of this family of compounds, taxusin, has appeared.[6f] Numerous synthetic approaches to the taxane skeleton ring system have been reported with the earliest entry dating back to 1974.[5a] The question of the construction of the basic carbon framework has been addressed via a biogenetical consideration, extensive chemical modifications of camphor,[6] a skeletal reorganization of the bicyclo[2.2.2]octane system via an anionic oxy-Cope reaction,[7] several photolysis processes,[8] novel rearrangements and fragmentation routes,[9] annulation strategies,[10] intercalation of enediol silyl eth-

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(2) (a) Carnegie-Mellon University. (b) University of Toledo. (c) 3M Company. (d) Louisiana State University. (e) University of California at Los Angeles.

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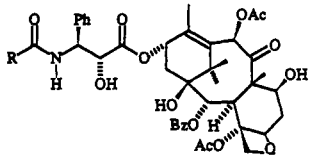
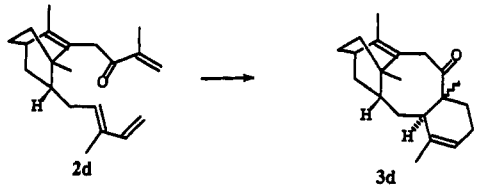
ers,[11] several unique cyclization methods,[12] and numerous intramolecular Diels–Alder (IMDA) approaches.[13] All of these methodologies can be further classified in a broad sense, namely, formation of the eight-carbon B ring indirectly via ring expansion or, conversely, via direct ring closure. This latter approach has proven to be difficult as is generally found for the formation of medium rings.[12a]



1a R = Ph
1b R = CMeCHMe

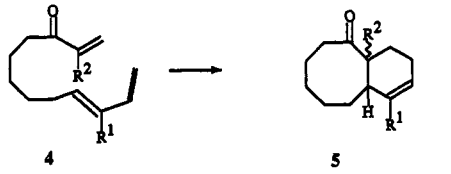
We have reported our systematic model studies of the Lewis acid catalyzed cycloadditions of internally activated trienes that show this to be a viable route for the stereoselective formation of systems containing seven-, eight-, and nine-membered rings.[14,15] Sakan has reported the synthesis of the taxane model system **3d** using this technology (eq 1).[13a,16] The thermal and catalyzed reactions



2d 3d (1)

of **2d** proceeded in high yield to give the trans- and cis-fused products, respectively. This result was surprising, since catalysis of the Diels–Alder reaction normally enhances but does not reverse stereoselectivity.

The stereodirecting effects of alkyl substituents located on the diene and dienophile have been investigated in simple systems leading to cyclooctanes **5** (eq 2).[15] In this



4 5 (2)

paper, we report an extension of this work to the taxane diterpene system. The effects of methyl substituents on the stereochemical outcome of the IMDA reaction of the four substrates **2a–d** under both thermal and Lewis acid catalyzed conditions have been investigated, and the results are described in the following text.

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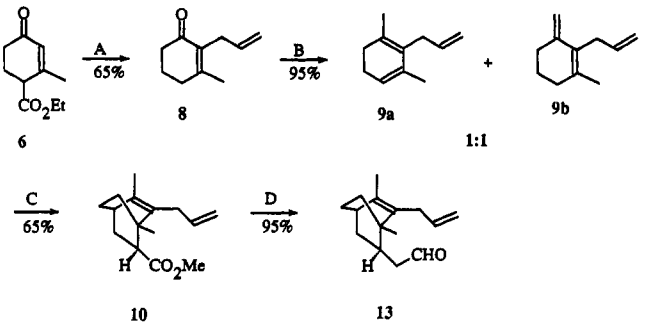
Scheme I[a]



[a] Key: A (1) NaOEt/EtOH, 25 °C, (2) CH_2CHCH_2Cl, 0 °C, (3) KOH/H_2O, 0 °C, (4) 10% KOH/ethylene glycol, 135 °C; B (1) $MeMgBr/Et_2O$, 0 °C, (2) $MgSO_4$/pentane; C $CH_3CO_2CHCH_2/AlCl_3/PhH$, 25 °C, D (1) LAH/THF, 0 °C, (2) $MsCl/Et_3N$/THF, −25 °C, (3) NaI/NaCN/DMSO, 73 °C, (4) $DIBAL/CH_2Cl_2$, −78 °C.

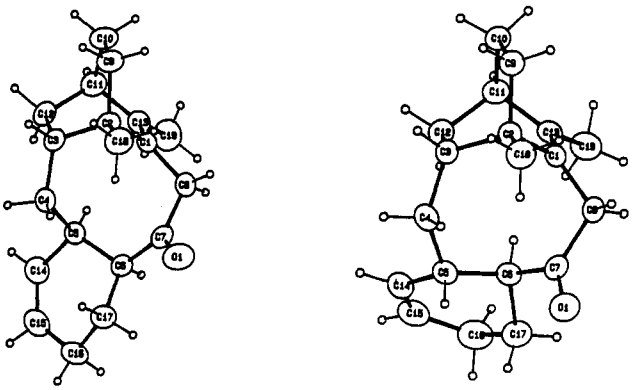


Figure 1. X-ray crystal structures of **3a**-*α*-*cis* and **3a**-*β*-*trans*.

Results and Discussion

A convenient starting material for the targeted tetraenes **2a–d** is the commercially available 4-carbethoxy-3-methyl-2-cyclohexen-1-one (**6**), cf. Scheme I.[13a,17,18] Treatment of **6** with sodium ethoxide in ethanol at room temperature followed by the addition of allyl chloride gave the *α*-alkylated keto ester, **7**. Saponification of the ester moiety in aqueous KOH at 0 °C and subsequent decarboxylation of the resultant acid using 10% KOH in ethylene glycol afforded the desired 2-allyl-3-methyl-2-cyclohexen-1-one (**8**) in 65% overall yield. A 1:1 mixture of 1-methyl-3-methylene-2-(2-propenyl)cyclohexene (**9a**) and its structural isomer cyclohexadiene **9b** was formed when ketone **8** was treated with methyl magnesium bromide at 0 °C followed by dehydration with anhydrous magnesium sulfate in pentane at room temperature. Attempts to convert the cyclohexene **9b** to **9a** under pyridine–tosylate conditions proved fruitless. The mixture of trienes **9a,b** was then dissolved in dry benzene and reacted with vinyl acetate in the presence of aluminum chloride to yield the bicyclo[2.2.2]octene ring system **10** in 60% overall yield from enone **8**.[17b] The 65% yield for the cycloaddition step is due to isomerization of the starting materials **9** during cycloaddition.

The reduction of ester **10** with lithium aluminum hydride in THF followed by activation of the primary alcohol provided the mesylate **11**, which underwent a Finkelstein-type reaction with sodium iodide. Displacement of the primary iodide with sodium cyanide in DMSO at 73

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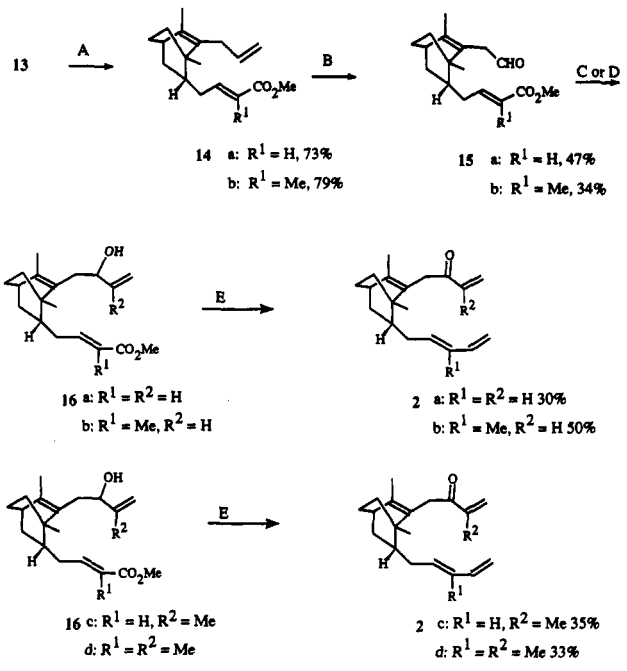
Scheme II[a]



[a] A $Ph_3PCR^1CO_2Me$/PhH/dark, 25 °C; B (1) OsO_4/THF, −60 → 28 °C, (2) H_2S/THF,) °C, (3) $NaIO_4$/3:1 MeOH/H_2O, 0 °C; C CH_2CHLi/THF, −78 → 25 °C; D $CH_2C(CH_3)MgBr$/THF, −78 °C; E (1) TBSCl/DMAP/dark, 25 °C, (2) DIBAL/CH_2Cl_2, −78 °C, (3) PDC/DMF, 0 °C, (4) *n*-BuLi/Ph_3PCH_3Br/THF, 25 °C, (5) *n*-Bu_4NF/THF, 25 °C, (6) (i) TFAA/DMSO/CH_2Cl_2, −78 °C, (ii) Et_2Ni-Pr, −78 → 0 °C.

°C gave the nitrile **12**. Treatment of **12** with DIBAL in dichloromethane gave aldehyde **13** in 95% yield from **10**.

At this stage, our route was set to diverge to produce the Diels–Alder substrates **2a–d**, which contain the various substitution patterns. These substrates incorporate the bicyclo[2.2.2]octene system in order to overcome entropic problems common to IMDA reactions in which the diene and dienophile are separated by a chain of five or more atoms by rigidly positioning C1, C2, C3, C4, and C8 (Figure 1).[13a,f,19] This locks the A-ring synthon into the boat conformation (which is known for the natural taxanes[20]) and eliminates free rotation about five single bonds. The bicyclooctane also serves as a masked C2 geminal methyl group, a structural feature that is expected to disfavor cyclization.[21] This system can be considered synthetically equivalent to the taxane A ring, provided appropriate functionality exists at either C9 or C10. The stereochemistry observed at C3 is correct for the natural product.

In the event, Wittig reaction of aldehyde **13** with either methyl (triphenylphosphoranylidene)acetate or ethyl (triphenylphosphoranylidene)acetate in dry benzene gave the olefinic products **14a** (R^1 = H) or **14b** (R^1 = Me) in 73 and 79% yield, respectively (Scheme II). Osmylation of the C1 allyl moiety followed by periodate cleavage of the resultant diol gave the aldehydes **15a** (47%) and **15b** (34%).

(19) The rigid group principle states that incorporation of torsionally rigid groups into acyclic precursors encourages the formation of medium rings for statistical reasons. For examples, refer to: (a) Baker, W.; Banks, R.; Lyon, D. R.; Maim, F. G. *J. Chem. Soc.* **1945**, 27. (b) Baker, W.; McOmie, J. F. W.; Ollis, W. D. *J. Chem. Soc.* **1951**, 200. (c) Vogtle, F.; Neumann, P. *Synthesis* **1973**, 85.

(20) (a) Woods, M. C.; Chiany, H. C.; Nakadana, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 522. (b) Castellono, E. E.; Hodder, O. J. R. *Acta Crystallogr., Sect. B.* **1973**, *B29*, 2566.

(21) Boeckman, R.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033 and references therein.

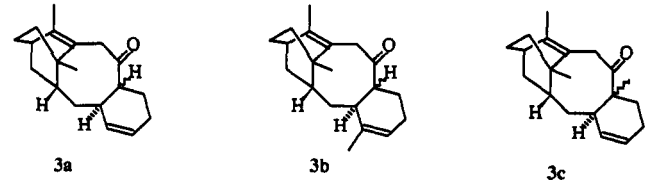
Table I. Stereochemical Outcome of the Cycloadditions of 2 and 4[a]

		α-trans	α-cis	α-trans/α-cis	β-trans	β-cis	α/β
2a	thermal	17	64	0.27	19	9	4.26
	catalyzed[b]	0	97		0	0	
2b	thermal	36	49	0.73	15	0	5.67
	catalyzed[b]	0	97		0	0	
2c	thermal	38	27	1.40	12	13.5	2.57
	catalyzed	0	80		0	15[c]	
2d	thermal[d]	70					
	catalyzed	0	85		0	0	
4a[e,f]	thermal	19	34	0.56			
	catalyzed	0	69				
4b[e,f]	thermal	11.4	8.6	1.33			
	catalyzed	7	55	0.13			

[a] Values given are in absolute percent yield; ratios are untiless. [b] Only one cycloaddition product was observed. [c] The structural assignment of this product is tentative. [d] An unidentified minor product accounted for 15–20% of the total yield of this reaction. See text for a discussion. [e] Reference 15. [f] The designations α and β have no meaning for these compounds.

Chain extension on the C7 aldehyde function was accomplished by treatment with vinyllithium or allylmagnesium bromide in THF to yield an epimeric mixture of allyl alcohols **16a–d**. Protection of the C7 alcohol as its silyl ether followed by DIBAL reduction of the C4 ester moiety, PDC oxidation, and Wittig olefination with methyltriphenylphosphonium bromide gave the conjugated diene system of **17a–d** in 46% overall yield from **15a–b**. Deprotection of the C7 silyl ether with tetrabutylammonium fluoride followed by oxidation using trifluoroacetic anhydride in DMSO/CH_2Cl_2 provided the C7 keto tetraenes **2a–d** in 60% yield with the appropriate substitution patterns at C6 and C14.

The cycloaddition studies using **2a–d** were carried out under both thermal and Lewis acid catalyzed conditions. The stereochemical outcome of these reactions is summarized in Table I. With one exception (**3c**-β-*cis*, vida infra), each product was isolated in pure form and resubjected to the reaction conditions employed; adducts were found to be configurationally stable. Each product obtained had the taxane skeleton. This was not unexpected, since (1) cycloaddition of the diene to the activated, α,β-unsaturated ketone is more likely than the cycloaddition to the inactivated tetrasubstituted olefin of the bicyclo[2.2.2]octene system and (2) the preferred regioselectivity of the reaction between 1-alkyl or 1,2-dialkylbutadienes with electron-deficient alkenes unites the unsubstituted termini of the two reactants.[22] We have classified the four possible stereoisomers of the products **3** as α or β, depending on whether the hydrogen originating at the internal diene terminus (H5) is down or up, respectively, and as cis or trans, according to the nature of the B/C ring fusion in the taxanes. By use of this nomenclature, naturally occurring taxanes have the α-trans stereochemistry.



3a 3b 3c

Cycloaddition of 2a (R^1 = R^2 = H). The reaction of **2a** in benzene at 140 °C gave a quantitative yield of three products in a ratio of 64:19:17.[23a] Comparison of the ^1H

(22) Fleming, I. *Frontier Orbitals and Organic Chemistry Reactions*; John Wiley & Sons: New York, 1976; pp 86–181.

NMR signals assigned to H8 and H8′ was diagnostic. Under catalyzed conditions ($AlCl_3$ or Me_2AlCl, benzene, room temperature) a single product idential with the major thermal product was formed quantitatively.[23a]

The structures of the two major components from the thermal reaction were determined by single-crystal X-ray analysis (Figure 1). The predominant product had the **3a**-*α-cis* stereochemistry, while the second most abundant thermal product was **3a**-*β-trans*. The least abundant product was determined to be **3a**-*α-trans* by base-catalyzed interconversion with the major product. Since H6 (cf. Figure 1) is the only epimerizable proton, the major and minor products must have the same stereochemistry at C5. An equilibrium ratio of 39:61 for **3a**-*α-cis*/**3a**-*α-trans* was obtained upon treatment of either compound with NaOMe in MeOH.[23b] While the cis isomer is formed more readily during the cycloaddition, the trans-fused product is thermodynamically favored by 0.3 kcal mol^{-1}. This parallels our earlier results (Table I).[14,15] ^1H NMR data obtained at 300 and/or 600 MHz were obtained for all three thermal reaction products and were of assistance for the structure determination of the more highly substituted analogues described in the following text.

Cycloaddition of 2b (R^1 = Me, R^2 = H). The cycloaddition reactions were carried out under conditions identical with those used for **2a**. The thermal reaction again provided a quantitative yield of three compounds in a ratio of 49:36:15.[23a] The catalyzed reaction formed a single product quantitatively, identical with the major thermal product. This compound was identified as **3b**-*α-cis* by comparison of the ^1H NMR spectrum to the spectra of the cycloadducts **3a**. The assignment was confirmed by chemical correlation with **3d**-*α-cis*[13a,16] as follows. Treatment of **3b**-*α-cis* with KO*t*-Bu in THF followed by methyl iodide provided **3d**-*α-cis*, identical by ^1H NMR and TLC with an authentic sample. Treatment of **3b**-*α-trans*, described in the following text, under identical conditions resulted only in recovery of starting material. Presumably, proton abstraction by the bulky base is not possible due to steric hindrance in this isomer. This issue is being addressed as part of ongoing molecular modeling studies.

The second most abundant thermal cycloadduct was shown to be epimeric with **3b**-*α-cis* by NaOMe-catalyzed epimerization. The equilibrium ratio of 68:32 for **3b**-*α-cis*/**3b**-*α-trans* shows a reversal of the relative stabilities of cis and trans compounds compared to the all-hydrogen **3a**. Interestingly, this increased relative stability of **3b**-*α-cis* is not reflected by a faster rate of formation. The ratio of **3b**-*α-cis*/**3b**-*α-trans* is 58:42 from the thermal cycloaddition and 68:32 from equilibration, whereas the corresponding ratios for **3a** are 79:21 and 39:61, respectively.[23b] This again parallels the results observed for the formation of the bicyclo[6.4.0]dodecene system.[14,15]

The structure of the least abundant thermal cycloadduct was shown to be **3b**-*β-trans* by partial elucidation of the single crystal structure (Figure 2). Crystals are monoclinic, $P_{21/c}$, with two independent molecules in the asymmetric unit. One molecule is disordered, and at the present state of refinement, R = 0.23, a satisfactory model has not been found. The second molecule appears well-ordered, and this portion establishes the stereochemistry of the compounds.

Cycloaddition of 2c (R^1 = H, R^2 = Me). The most complex results were obtained from **2c**. This compound is less reactive than **2a** or **2b**,[24] the thermal cycloaddition

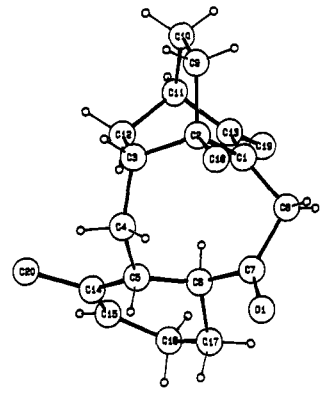


Figure 2. X-ray crystal structure of **3b**-*β-trans*.

was carried out at 160 °C in toluene containing 5 equiv of trimethyl borate to suppress byproduct formation.[13a] A 90% yield of four cycloadducts was obtained from the thermal reaction in a ratio of 42:30:15:13,[23c] while the Me_2AlCl-catalyzed reaction proceeded in 95% yield to give an 84:16 ratio[23a] of two products. The two predominant products of the thermal reaction were readily identified by ^1H NMR as **3c**-*α-trans* (42%) and **3c**-*α-cis* (30%). Coupling patterns and selective decoupling of the olefin protons were also used to assign the least abundant product as **3c**-*β-trans*. The fourth product, which was unstable after isolation, was tentatively assigned as **3c**-*β-cis* on the basis of its 600-MHz ^1H NMR spectrum.

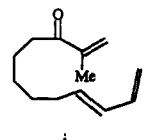
The major product of the catalyzed reaction was **3c**-*α-cis*. This was chemically correlated by independent synthesis from **3a**-*α-cis* by treatment with KO*t*-Bu in THF followed by methyl iodide. Again, treatment of the *α*-trans epimer under these conditions gave only recovered starting material. The minor catalyzed product was identical by ^1H NMR and TLC with the tentatively assigned **3c**-*α-cis*.

Cycloaddition of 2d (R^1 = R^2 = Me). As described earlier,[13a,16] the thermal cycloaddition of **2d** gave a 4:1 mixture of products from which **3d**-*α-trans* was isolated in 70% yield while the catalyzed reaction provided **3c**-*α-cis* in 85% with just a trace (i.e., <5%) of minor product observed by 300-MHz ^1H NMR. In neither case was the minor product isolated or identified.

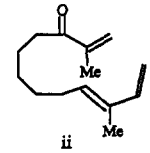
Trends in Cycloaddition Stereoselectivity. Table I summarizes the cycloaddition reaction results. Under thermal cyclization conditions, placement of a methyl group on the conjugated diene of **2** increases the selectivity for *α* over *β* slightly and doubles the *α*-trans to *α*-cis ratio (cf. **2a** to **2b** and **2c** to **2d**). This is in qualitative agreement with the effect observed during formation of the bicyclo[6.4.0]dodecene system **5** (cf. eq 2). Placement of a methyl group on the diene of **4** increases the trans selectivity slightly (cf. **4a** to **4b**). Methyl group substitution on the dienophile of **2** (cf. **2a** to **2c** and **2b** to **2d**) decreases formation of *α* relative to *β* products by 40%. However, the selectivity for *α*-trans over *α*-cis increases significantly; the

(23) (a) Determined by ^1H NMR at 300 MHz. (b) The equilibrium ratio was determined by integration of the well-resolved multiplets assigned to olefinic proton H15. (c) Determined by isolation.

(24) Similarly, substrates leading to the bicyclo[6.4.0]dodecene system **5** containing a bridgehead methyl group were also less reactive. Neither i nor ii gave any intramolecular cycloadduct under thermal conditions, while Lewis acid catalysis required a temperature of 50–55 °C in order to proceed at an appreciable rate.



i



ii

trans/cis ratio is more than five times greater than for the unsubstituted system. Substitution of a methyl group on both the diene and dienophile has a synergistic effect.

There is no trend to analyze in the catalyzed cases. With the exception of a minor product obtained from **2c**, all the catalyzed reactions give exclusively products with α-cis geometry. This is in contrast to the bicyclo[6.4.0]dodecene series, in which substitution of a methyl group for a hydrogen on either the diene or dienophile caused an increase in the amount of trans-fused product formed.[15] In these cases, the position of the methyl substituent made little difference to the change in stereoselectivity, and the combined effect of the two substituents was additive, not synergistic. The high cis selectivity of Lewis acid catalyzed intramolecular Diels–Alder reactions of internally activated dienophiles has been documented.[13a,14-16,25]

The preference for H5 α stereochemistry appears to be a unique feature of the skeleton of **3**. Molecular mechanics studies are in progress and will be reported in due course.

Experimental Section[26]

All reactions were performed in oven-dried glassware under dry argon. The solvents benzene, toluene, and tetrahydrofuran were distilled from benzophenone ketyl and methylene chloride from calcium hydride immediately prior to use. R_f values refer to TLC, carried out on 0.25-mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. Ultraviolet light, iodine vapor, and 5% phosphomolybdic acid in 95% ethanol were used to visualize compounds. Chromatographic separations were performed by using flash columns with Merck Kieselgel 60 (230–400 mesh) silica gel.[27] Yields reported are for isolated, purified materials. NMR spectra were recorded on an IBM NR-80 (^{1}H, 80-MHz), a Bruker WH-300 (^{1}H, 300-MHz), or the Carnegie-Mellon University 600 (^{1}H, 600-MHz) spectrometer. Spectra were taken in $CDCl_3$, using the residual solvent peak at 7.24 ppm as the internal standard unless otherwise noted. Chemical shifts are reported in ppm, coupling constants in hertz. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad).

2-Allyl-3-methyl-2-cyclohexen-1one (8). A mixture of ethanol (150 mL) and sodium (5.4 g, 0.23 mol) was refluxed under argon until all of the sodium had been consumed. The resulting solution was cooled to 0 °C (ice–water), and Hagemann's ester[21] (**6**; 36.4 mL, 0.22 mol) was added dropwise. The reaction was warmed to room temperature and stirred for 30 min. The dark enolate anion solution was then cooled to 0 °C (ice–water), and allyl chloride (26 mL, 0.32 mol) was added dropwise. The reaction was allowed to warm slowly to ambient temperature and stirred for 25 h. TLC (petroleum ether/ether (1:1), R_f 0.72) indicated complete consumption of **6**. The reaction was cooled to ice temperature and saponified with 5 N KOH (50 mL) and stirred 3.5 h. The mixture was diluted with water (250 mL) and extracted into $CHCl_3$ (4 × 50 mL). The aqueous layer was made acidic (pH ~1) by the addition of concentrated HCl (20 mL) and then extracted with $CHCl_3$ (3 × 100 mL). The combined organic washings were dried over Na_2SO_4, filtered, and concentrated. TLC (10% MeOH/$CHCl_3$) of the crude acid showed one spot with R_f 0.38. The acid was then taken up in ethylene glycol (35 mL), and powdered KOH (4 g, 0.07 mol) was added. The mixture was heated under argon for 2 h at 135 °C at which time TLC (petroleum ether/ether (3:1), R_f 0.53) indicated complete reaction. The reaction was diluted with water (100 mL) and extracted into a solvent mixture of 1:2 CH_2Cl_2/petroleum ether (3 × 100 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica left 21.4 g (65%) of **8**.

1-Methyl-3-methylene-2-(2-propenyl)cyclohexene (9b) and 1,3-dimethyl-2-(2-propenyl)-1,3-cyclohexadiene (9a). A solution of enone **8** (3.87 mL, 25 mmol) in ether (50 mL) was treated with methylmagnesium bromide (11.5 mL, 2.3 M) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h at which time TLC (petroleum ether/ether 2:1) indicated product formation. The reaction was cooled to ice temperature and quenched with aqueous sodium tartrate (0.5 mL). The crude addition product was extracted into 2:1 CH_2Cl_2/petroleum ether (3 × 50 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was then taken up in pentane (200 mL) and treated with anhydrous $MgSO_4$. The mixture was stirred at room temperature for 10 h after which time TLC (petroleum ether, R_f 0.91) indicated complete dehydration. The solution was filtered to remove the magnesium sulfate, and the filtrate was concentrated to leave 3.5 g (95%) of **9a** and **9b** in a 1:1 product ratio.

Bicyclo[2.2.2]octene 10. To a benzene (140 mL) solution of vinyl acetate (5 mL, 54 mmol) and 0.183 N $AlCl_3$ in ether (7.5 mL) stirring at room temperature under argon was added a solution **9a** and **9b** (4.26 g, 28.7 mmol) in benzene (16 mL) over 5 h. The reaction was stirred for 18 h until TLC (petroleum ether/ether (10:1), R_f 0.65) indicated complete consumption of **9a,b**. The reaction was quenched by the addition of aqueous sodium tartrate, and the crude product **10** was extracted into petroleum ether (2 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica (petroleum ether/ether (30:1)) left 4.38 g (65%) of **10**.

Preparation of Aldehyde 13. To stirred solution of **10** (3.76 g, 16.1 mmol) in THF (70 mL) at 0 °C was added lithium aluminum hydride (1.0 M, 20 mL). The reaction was stirred at ice temperature for 30 min at which time the disappearance of **10** was noted by TLC (petroleum ether/ether (1:1), R_f 0.61). Celite (6 g) was added to the reaction followed by the addition of aqueous Na_2SO_4. The resulting mixture was stirred at ambient for 15 min, and the insoluble inorganics were removed by vacuum filtration. The filter pad was exhaustively washed with THF until no product was observed in the washes by TLC. The combined filtrates were concentrated and the residue azeotroped twice with toluene (ca. 10 mL each). The resultant crude alcohol was obtained in quantitative yield and taken up in THF (70 mL). The THF solution was cooled to −25 °C and treated with triethylamine (4.6 mL, 33 mmol) followed by methanesulfonyl chloride (1.37 mL, 17.7 mmol). The reaction was complete within 10 min as judged by TLC (petroleum ether/ether (2:1)) and quenched with water. The insoluble precipitates were removed by filtration, and the organic fitrate was dried over Na_2SO_4, filtered, and concentrated to leave crude mesylate **11**.

To a solution of mesylate **11** in DMSO (39 mL) was added NaI (1.2 g 8.0 mmol) and NaCN (7.7 g, 0.16 mol). The reaction was then heated in the dark at 73 °C for 44 h. The reaction was cooled to room temperature and diluted with water (300 mL) and the product extracted with petroleum ether (3 × 150 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated to leave 3.36 g (95% overall from **10**) of the crude nitrile **12**. Analysis of **12** by TLC (petroleum ether/ether (10:1), R_f 0.43) showed one single spot. A dichloromethane (80 mL) solution of **12** (3.36 g 15.6 mmol) was treated with DIBAL (1 N, 16 mL) at −78 °C. The reaction was slowly warmed to ambient temperature and TLC (petroleum ether/ether (10:1)) indicated complete reaction after 2 h. The reaction was then cooled to ice temperature, and aqueous NH_4Cl was added dropwise to the vigorously stirred solution. The quenched reaction was stirred at 0 °C for 1 h and then acidified with 1 N HCl. The solution was transferred to a separatory funnel and extracted with petroleum ether (2 × 100 mL). The organic layer was then washed with aqueous $NaHCO_3$, water, and saturated brine and then dried over Na_2SO_4, filtered, and concentrated to leave 3.38 g (quantitative) of aldehyde **13**.

Preparation of Aldehyde 15a. A solution of aldehyde **13** (1.69 g, 7.7 mmol) in benzene (40 mL) was treated with methyl (tri-

(25) Ciganek, E. *Organic Reactions*; John Wiley & Sons: New York, 1984; pp 1–374.

(26) Due to the untimely death of the principle investigator, the subsequent dispersion of the remaining researchers, and the amount of time elapsed since the bulk of this synthetic work was accomplished, we have been unable to locate all of the pertinent spectroscopic and analytical data for the compounds described herein. We feel, however, and Professor Heathcock has concurred, that because of the divergent nature of this synthesis and the availability of NMR and crystallographic data for the cycloaddition substrates and products, that the identity of the synthetic intermediates has been sufficiently established to meet the criteria of this journal.

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

phenylphosphoranylidene)acetate (3.63 g, 10.8 mmol) and stirred in the dark at room temperature for 2 days. The reaction was concentrated and the residue taken up in CH_2Cl_2 (ca. 2 mL). The dichloromethane solution was then passed through a small column of silica (CH_2Cl_2 as eluent) to remove the polar byproducts. The collected fractions were concentrated, and the crude Wittig olefin was purified by flash chromatography (using a solvent gradient of petroleum ether/ether (30:1 to 10:1)) to leave 1.56 g (73%) of ester olefin **14a** as an oil. Olefin **14a** was further purified by Kugelrohr distillation (bp 70 °C; 0.3 mmHg) to leave 1.52 g (97% recovery). To olefin **14a** (1.49 g, 5.45 mmol) in THF (30 mL) at −60 °C was added OsO_4 (1.24 g, 4.91 mmol). The resulting mixture was allowed to stand at −28 °C for 5 days. The reaction was quenched by bubbling H_2S through the solution and stirring at ice temperature for 1 h. The resulting black precipitate was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (2.5% MeOH/$CHCl_3$) to leave 850 mg (51%) of the desired diol. The diol (850 mg, 2.75 mmol) in MeOH (35 mL) and water (11 mL) was treated with $NaIO_4$ (625 mg, 2.92 mmol) at 0 °C. TLC (5% MeOH/$CHCl_3$) showed complete reaction after 20 min, and the reaction was quenched with the addition of saturated brine (70 mL). The crude aldehyde **15a** was extracted into 2:1 petroleum ether/CH_2Cl_2 (3 × 100 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica (petroleum ether/ether (3.5:1)) left 634 mg (83%) of aldehyde **15a**. Overall yield from **13** was 31% over 3 steps.

Preparation of Aldehyde 15b. Following the procedure outlined previously, aldehyde **13** (1.69 g, 7.7 mmol) when treated with ethyl 2-(triphenylphosphoranylidene)propionate (4.88 g, 13.5 mmol) left 1.74 g (79%) of ester olefin **14b** after purification by flash chromatography (petroleum ether/ether (30:1)). Treatment of **14b** (1.7 g, 5.89 mmol) with OsO_4 (1.35 g, 5.30 mmol) left 820 mg (43%) of pure diol after flash chromatography (1.5% MeOH/$CHCl_3$). Sodium metaperiodate (575 mg, 2.68 mmol) cleavage of the diol (820 mg, 2.54 mmol) left, after flash chromatography (petroleum ether/ether (4:1)), 520 mg (70%) of pure aldehyde **15b**. Overall yield from **13** was 24%.

Preparation of Tetraene 2a. To a solution of aldehyde **15a** (367 mg, 1.33 mmol) in THF (24 mL) stirring at −78 °C was added dropwise a solution of vinyllithium in THF (0.94 M, 1.7 mL). The reaction was allowed to warm slowly to room temperature and stirred for 45 min, at which time TLC (petroleum ether/ether (3:1), R_f 0.27) indicated consumption of **15a**. The reaction was diluted with petroleum ether (50 mL) and quenched with aqueous $NaHCO_3$. The layers were separated, and the organic layer was washed once with saturated brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to leave the crude allylic alcohol **16a**. Purification by flash chromatography (petroleum ether/ether (3:1)) left 241 mg (60%) of **16a**. To allylic alcohol **16a** (241 mg, 0.79 mmol) in DMF (7.5 mL) was added DMAP (290 mg, 2.37 mmol) and *tert*-butyldimethylsilyl choride (180 mg, 1.19 mmol) at room temperature. The reaction was stirred in the dark for 35 h until TLC (petroleum ether/ether (10:1), R_f 0.55) indicated product formation. The reaction as quenched with the addition of water (4 drops) and stirred for 15 min. The reaction was diluted with pentane (100 ML) and water (25 mL), and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purifed by flash chromatography (petroleum ether/ether (15:1)) to leave 280 mg (84%) of the desired silyl ether. The silyl ether (280 mg, 0.67 mmol) in CH_2Cl_2 (18 mL) was treated with DIBAL (1 M, 1.47 mL) at −78 °C. The reaction was stirred for 30 min at which time TLC (petroleum ether/ether (10:1)) indicated consumption of the starting material. The reaction mixture was quenched with aqueous sodium tartrate and extracted with CH_2Cl_2 (75 mL). The layers were separated and the organic layer dried over Na_2SO_4, filtered, and concentrated to leave the crude allylic alcohol, which was taken up in DMF (3.5 mL) and treated with pyridinium dichromate (600 mg, 1.59 mmol) at ice temperature for 30 min. TLC (petroleum ether/ether (10:1), R_f 0.47) indicated complete reaction. The inorganic salts were removed by filtration, and the filtrate was concentrated to leave the crude allylic aldehyde. A solution of methyltriphenylphosphonium bromide (480 mg, 1.34 mmol) in THF (10 mL) was treated with *n*-BuLi (1.6M, 0.74 mL). The resulting ylide was then reacted with the allylic aldehyde dissolved in THF (ca. 3 mL) at room temperature. The reaction was instantaneous by TLC (petroleum ether/ether (10:1)) and quenched with aqueous NH_4Cl. The crude product was extracted with CH_2Cl_2 (70 mL) and washed with water. The layers were separated and the organic layer dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/petroleum ether (1:2.5)) left 201 mg (79% from the silyl ether) of the tetraene **17a**.

Diene **17a** (201 mg, 0.52 mmol) was treated with a THF solution of *n*-Bu_4NF (0.75 N, 2 mL) at room temperature. The reaction was stirred for 15 min, and TLC (petroleum ether/ether (4:1), R_f 0.5) indicated loss of the silyl moiety. The reaction was concentrated and purified by flash chromatography (petroleum ethr/ether (5:1)) to leave 140 mg (99%) of allylic alcohol. To a solution of TFAA (108 mL, 0.76 mmol) in CH_2Cl_2 (11 mL) was added DMSO (75 mL, 1.05 mmol) at −78 °C. A solution of allylic alcohol (140 mg, 0.51 mmol) in CH_2Cl_2 (ca. 2 mL) was added to the oxidation solution at −78 °C followed by the addition of Hunig's base (300 μL). The reaction temperature was allowed to slowly warm to 0 °C until TLC (petroleum ether/ether (4:1)) indicated complete oxidation. The reaction was quenched with aqueous NH_4Cl and diluted with petroleum ether (100 mL). The organic layer was then treated with 1 N NaOH and vigorously stirred at room temperature for 3 h. The layers were separated and the organic layer dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (petroleum ether/ether (15:1)) left 106 mg (76%) of tetraene **2a**.

Preparation of Tetraene 2b. In a similar fashion to that of aldehyde **15a**, reaction of **15b** (242 mg, 0.83 mmol) left 235 mg (89%) of allylic alcohol **16b**. Treatment of **16b** (235 mg, 0.74 mmol) with *tert*-butyldimethylsilyl chloride (180 mg, 1.19 mmol) afforded 300 mg (94%) of the desired silyl ether. The silyl ether (300 mg, 0.69 mmol) was treated with DIBAL (1M, 1.53 mL) to leave the allylic alcohol in quantitative yield. Oxidation with PDC (600 mg, 1.59 mmol) followed by Wittig olefination (500 mg, 1.37 mmol) left 257 mg (93%) of tetraene **17b**. Deprotection of **17b** (257 mg, 0.64 mmol) with *n*-Bu_4NF (0.75 N, 0.5 mL) left 180 mg (98%) of allylic alcohol, which when treated with TFAA (132 μL) left 115 mg (65%) of tetraene **2b**.

Preparation of Tetraene 2c. A solution of **15a** (181 mg, 0.66 mmol) in THF (14 mL) left 127 mg (60%) of allylic alcohol **16c** when treated with allylmagnesium bromide (1.1 M, 0.60 mL). Treatment of **16c** (127 mg, 0.40 mmol) with *tert*-butyldimethylsilyl chloride (89 mg, 0.58 mmol) afforded 148 mg (86%) of the desired silyl ether. The silyl ether (316 mg, 0.73 mmol) was treated with DIBAL (1M, 216 mL) to leave the allylic alcohol in quantitative yield. Oxidation with PDC (1.0 g, 2.65 mmol) followed by Wittig olefination (580 mg, 1.59 mmol) left 317 mg (>95%) of tetraene **17c**. Deprotection of **17c** (317 mg, 0.79 mmol) with *n*-Bu_4NF (0.75 N, 5.0 mL) left 214 mg (95%) of allylic alcohol. Treatment of the allylic alcohol (39 mg, 0.14 mmol) with TFAA (29 μL) left 29 mg (74%) of tetraene **2c**.

Preparation of Tetraene 2d. In an analogous manner to that of aldehyde **15a**, a solution of **15b** (188 mg, 0.65 mmol) in THF (14 mL) left 172 mg (80%) of allylic alcohol **16d** when treated with allylmagnesium bromide (1.1 M, 0.60 mL). Treatment of **16d** (172 mg, 0.52 mmol) with *tert*-butyldimethylsilyl chloride (150 mg, 0.98 mmol) afforded 196 mg (68%) of the desired silyl ether. The silyl ether (196 mg, 0.44 mmol) was treated with DIBAL (1M, 0.97 mL) to leave the allylic alcohol in quantitative yield. Oxidation with PDC (400 mg, 1.06 mmol) followed by Wittig olefination (315 mg, 0.86 mmol) left 123 mg (67%) of tetraene **17d**, which upon deprotection with *n*-Bu_4NF (0.75 N, 1.5 mL) left 81 mg (89%) of allylic alcohol. Treatment of the allylic alcohol (40 mg, 0.13 mmol) with TFAA (29 μL) left 28 mg (70%) of tetraene **2d**.

Cycloaddition Reactions of Substituted Tetraenes 2a–d. Method A. Thermal Cycloaddition of Tetraene 2a. A solution of **2a** (35 mg, 0.129 mmol) in dry benzene (30 mL) was added to an oven-dried ampule. The solution was then treated with BHT (15 mg, 0.068 mmol) and degassed three times (liquid N_2) under high vacuum. The ampule was sealed under vacuum and immersed in a 120 °C oil bath for 4 days followed by a 140 °C oil bath for 1 day. The crude reaction mixture was purified by column chromatography on silica with petroleum ether followed by a

solvent gradient of petroleum ether/ether (20:1 and 10:1) to leave pure cycized **3a**-α-*cis* (64%), **3a**-α-*trans* (17%), and **3a**-β-*trans* (19%). **3a**-α-*cis* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.53 (1 H, m), 5.31 (1 H, m), 3.51 (1 H, d, J = 14.1 Hz), 3.15 (1 H, dq, J = 14.1, 1.1 Hz), 2.81 (1 H, m, $J_{3/8}$ = 5.9 Hz), 2.45 (1 H, m), 2.34 (1 H, m), 1.86 (3 H, d, J = 1.1 Hz), 0.97 (3 H, s). **3a**-β-*trans* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.49 (1 H, m), 5.45 (1 H, m), 3.29 (1 H, d, J = 14.7 Hz), 3.00 (1 H, d, J = 14.7 Hz), 2.69 (1 H, ddd, J = 14.0, 11.0, 3.7 Hz), 2.39 (1 H, m, $J_{3/8}$ = 13.9 Hz), 2.36 (1 H, quint), 1.85 (3 H, s), 1.00 (3 H, s). **3a**-α-*trans* (300-MHz) ^{1}H NMR ($CDCl_3$): 5.56 (1 H, m), 5.18 (1 H, m), 3.50 (1 H, d, J = 14.9 Hz), 3.13 (1 H, d, J = 14.9 Hz), 3.13 (1 H, ddq, J = 14.9, 1.7, 1.2 Hz), 2.55 (1 H, m, $J_{3/8}$ = 9.7 Hz), 2.42 (1 H, dddd, J = 11.4, 9.7, 3.6, 1.7 Hz), 2.31 (1 H, m), 1.80 (3 H, d, J = 1.2 Hz), 1.09 (3 H, s).

Thermal Cycloaddition of Tetraene 2b. By use of the procedure outlined previously, **2b** gave **3b**-α-*cis* (49%), **3b**-α-*trans* (36%), and **3b**-α-*trans* (15%) after purification by column chromatography on silica. **3b**-α-*cis* (300-MHz) ^{1}H NMR ($CDCl_3$): 5.25 (1 H, bs), 3.50 (1 H, d, J = 14.6 Hz), 3.15 (1 H, dq, J = 14.6, 1.3 Hz), 2.61 (1 H, m, $J_{3/8}$ = 4.9 Hz), 2.32 (1 H, dddd, J = 11.9, 4.9, 2.4 Hz), 2.31 (1 H, m), 1.81 (3 H, d, J = 1.3 Hz), 1.59 (3 H, bs), 0.93 (3 H, s). **3b**-β-*trans* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.36 (1 H, bs), 3.30 (1 H, d, J = 15.1 Hz), 3.01 (1 H, d, J = 15.1 Hz), 2.79 (1 H, ddd, J = 14.0, 10.6, 3.7 Hz), 2.37 (1 H, quint), 2.33 (1 H, m, $J_{3/8}$ = 14.0 Hz), 1.84 (3 H, s), 1.66 (3 H, b s), 1.04 (3 H, s). **3b**-α-*trans* (300-MHz) ^{1}H NMR ($CDCl_3$): 5.48 (1 H, bd, J = 6.4 Hz), 3.30 (1 H, d, J = 13.1 Hz), 3.19 (1 H, d, J = 13.1 Hz), 2.78 (1 H, b quint), 2.27 (1 H, m), 1.72 (3 H, s), 1.50 (3 H, b s), 1.31 (3 H, s).

Thermal Cycloaddition of Tetraene 2c. In an analogous manner to that above, thermal cycloaddition of **2c** yielded after purification **3c**-α-*cis* (27%), **3c**-α-*trans* (38%), **3c**-β-*cis* (13.5%), and **3c**-β-*trans* (12%). **3c**-β-*cis* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.55 (1 H, m), 5.48 (1 H, m), 3.54 (1 H, d, J = 13.2 Hz), 3.22 (1 H, d, J = 13.6 Hz), 2.82 (1 H, b s), 2.22 (1 H, bs), 1.80 (3 H, s), 1.40 (3 H, s), 1.17 (3 H, s). **3c**-α-*cis* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.40 (1 H, m), 5.29 (1 H, m), 3.85 (1 H, d, J = 14.3 Hz), 3.05 (1 H, dq, J = 14.3, 1.1 Hz), 2.37 (1 H, b t), 2.34 (1 H, b q), 1.92 (3 H, d, J = 1.1 Hz), 1.12 (3 H, s), 0.99 (3 H, s). **3c**-β-*trans* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.55 (1 H, m), 5.17 (1 H, m), 3.58 (1 H, d, J = 15.1 Hz), 3.15 (1 H, dq, J = 15.1, 1.5 Hz), 2.65 (1 H, m), 2.28 (1 H, m), 1.85 (3 H, d, J = 1.5 Hz), 1.08 (3 H, s), 1.03 (3 H, s). **3c**-α-*trans* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.47 (1 H, m), 5.15 (1 H, m), 3.68 (1 H, d, J = 16.2 Hz), 3.15 (1 H, m), 3.09 (1 H, dq, J = 16.2, 1.8 Hz), 2.31 (1 H, quint, J = 2.9 Hz), 1.82 (3 H, d, J = 1.8 Hz), 1.10 (3 H, s), 0.94 (3 H, s).

Thermal Cycloaddition of Tetraene 2d. In a similar fashion to that above, **2d** afforded **3d**-α-*trans* (70%) after purification. **3d**-α-*trans* (300-MHz) ^{1}H NMR ($CDCl_3$): 5.16 (1 H, m), 3.85 (1 H, d, J = 14.4 Hz), 3.05 (1 H, dq, J = 14.4, 1.4 Hz), 2.33 (1 H, q, J = 2.9 Hz), 2.14 (1 H, b d, J = 6.0 Hz), 1.90 (3 H, d, J = 1.4 Hz), 1.60 (3 H, b s), 1.06 (3 H, s), 0.98 (3 H, s).

Method B. Lewis Acid Cycloaddition of Tetraene 2d. A solution of **2d** (40 mg, 0.145 mmol) in dry benzene (25 mL) was treated slowly with dimethylammonium chloride (1.0 M, 0.15 mL, 0.145 mmol) at room temperature. After the addition was complete, TLC (80:7 petroleum ether/ether) indicated complete consumption, and the reaction was quenched with saturated $NaHCO_3$ (5 mL). After 30 min, the reaction was diluted with petroleum ether (ca. 15 mL) and transferred into a separatory funnel. The organic layer was separated and the aqueous portion further extracted with petroleum ether (5 × 5 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel (80:7 petroleum ether/ether) provided pure **3d**-α-*cis* (85%). **3d**-α-*cis* (600-MHz) ^{1}H NMR ($CDCl_3$): 5.33 (1 H, b s), 3.70 (1 H, d), 3.09 (1 H, dq), 3.04 (1 H, b s), 2.31 (1 H, quint), 1.82 (3 H, d), 1.64 (3 H, m), 1.11 (3 H, s), 0.97 (3 H, s).

Epimerization Studies on Cycloadducts 3a-α-*cis* and 3a-α-*trans*. A methanolic solution of pure or enriched mixtures of **3a**-α-*cis* or **3a**-α-*trans* were treated with 1 M NaOMe at 58 °C for 18 h. The reaction was cooled to ambient temperature and diluted with petroleum ether (20 mL). The organic mixture was quenched with saturated $NaHCO_3$ and the layers separated. The organic phase was then washed with brine, dried over Na_2SO_4, and concentrated. The crude reaction was examined by proton NMR to determine the product ratios.

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Supplementary Material Available: X-ray experimental procedures and coordinates for hydrogen and non-hydrogen atoms, anisotropic thermal parameters, bond distances and angles, and torsion angles for **3a**-α-*cis* and **3a**-β-*trans*; approximate coordinates for the ordered molecular **3b**-β-*trans* (16 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of (*S*)-Zearalenone Dimethyl Ether, an Orsellinic Acid Type Macrolide

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The synthesis of (*S*)-zearalenone dimethyl ether is described. The chiral part of the molecule was obtained by asymmetric synthesis monitored by a chiral sulfoxide group and introduced in the very last steps of the synthesis.

Zearalenone (**1a**) is a naturally occuring 14-membered orsellinic acid type macrolide[1] with anabolic and uterotropic activity. Several total syntheses of racemic zearalenone were carried out during the last 20 years,[2] and a chiral synthesis from a natural product was recently published.[2j]

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